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The chemistry and biological significance of imidazole, benzimidazole, benzoxazole, tetrazole and quinazolinone nucleus

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ABSTRACT

The imidazole, benzimidazole, benzoxazole, tetrazole and quinazolinone are heterocyclic aromatic organic compounds. It is an important pharmacophore and privileged structure in medicinal chemistry. It plays a very important role with plenty of useful therapeutic activities such as antiulcers, antihypertensives, analgesic, anti-inflammatory, anti-virals, antifungals, anticancer, antidepressant activity, antilishmanial activity, anticonvulsant activity, antitubercular activity, antitumor activity, cyclooxygenase-2 inhibiting activity, DNA Topoisomerase inhibiting activity, antileukemic activity, antimalarial activity, antioxidant activity, antileishmanial activity and antihistaminics. The review of the literature shows that the imidazole, benzimidazole, benzoxazole, tetrazole and quinazolinones derivatives are outstandingly effective compounds and a large number of reviews available for biochemical and pharmacological studies conformed that their molecules are useful against a wide variety of micro-organisms. Because of their importance, the methods for their synthesis have become a focus of synthetic organic chemists. Therefore in the present review we tried to compile the chemistry of different derivative of substituted imidazole, benzimidazole, benzoxazole, tetrazole and quinazolinones as well as various pharmacological activities and some of the important methodologies used for the synthesis.

INTRODUCTION

Research in the field of pharmaceutical chemistry has its most important task in the development of new and better drugs and their successful introduction into clinical practice. The word 'drug' is derived from the French word 'drogue' which means a dry herb. In general way, a drug may be defined as a substance used in the prevention, diagnosis, treatment or cure of disease in man or other animals. The basis of understanding in the medicinal chemistry lies in awareness of the relation between the chemistry of a particular compound or group of compounds and their interactions with the body, which is known as structure activity relation and the mechanism by which the compound influences the biological system, is known as its mode of action.

Human health is impacted by a large variety of chemical substances, including those essential to human life, such as vitamins and nutrients and medicines. Natural substances are intrinsically exhibit superior properties with regard to efficacy and safety in matters related to human health. As it is difficult to meet the worldwide demand of the requirement of the natural products due to their low abundance in nature, it is essential to produce synthetic substances in large quantities. This can extend to so-called nature identical materials that are natural substances produced synthetically in an identical or with slight modification of the molecular form, in order to increase the biological activity of the molecule. Heterocycles are among the most frequently encountered scaffolds in drugs and pharmaceutically relevant substances. The remarkable ability of heterocyclic nuclei to serve both as biomimetics and reactive pharmacophores has largely contributed to their unique value as traditional key elements of numerous drugs. The development of heterocycles as scaffolds, containing a high degree of diversity has become a leading focus in modern drug discovery. In this research program the derivatives of various diverse classes of heterocycles

e.g., imidazole, benzimidazole, benzoxazole, tetrazole, and quinazolinone were developed. Certain possible modifications on the heterocyclic ring by the addition of diverse substituents may lead to new products with better biological profiles. As a result of the biological activity exhibited by the heterocyclic molecules, the development of new chemical entities (NCEs) is the focus of intense activity in pharmaceutical industry. Various types of newly synthesized molecules may be very good at blocking the action or killing the pathogens without harming the human cells so as to prevent or cure the disease. The nitrogen, oxygen and sulphur heterocycles are an attractive source of compounds for the identification of new biological probes. The main aim is to design and synthesize molecules involving the use of structural motif commonly found in majority of well-established drug molecules. The research work is mainly concentrated on the above points.

1.1 Heterocycles

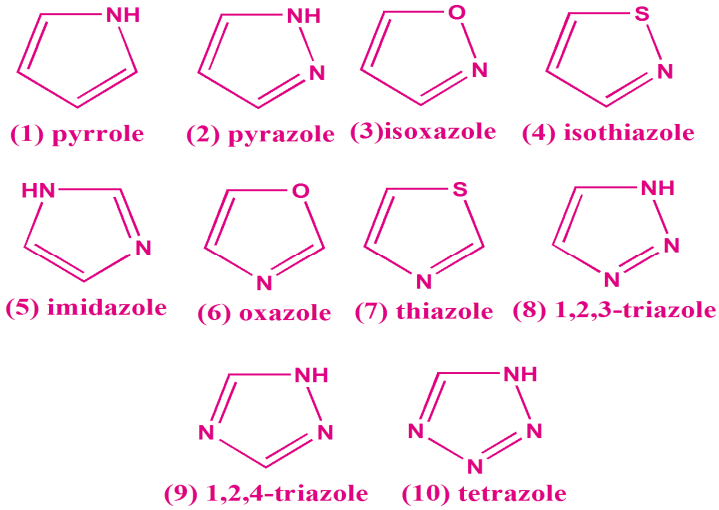
Heterocycles are organic compounds containing at least one atom of carbon, and at least one element other than carbon, such as sulfur, oxygen or nitrogen within a ring structure Eicher *et al.*, (**2003**)[1]. Heterocyclic chemistry is the branch of chemistry dealing with synthesis, properties, and applications of heterocycles. The history of heterocyclic chemistry began in the 1800's, in step with the development of organic chemistry. Some noteworthy developments: Campaigne *et al*.,(**1986**)[2] **1818**: Brugnatelli isolates alloxan from uric acid; **1832**: Dobereiner produces furfural (a furan compound) by treating starch with sulfuric acid; **1834**: Runge obtains the pyrrole ("fiery oil") by dry distillation of bones; **1906**: Friedlander synthesizes indigo, allowing synthetic chemistry to displace a large agricultural industry; **1936**: Treibs isolates chlorophyll derivatives from crude oil, explaining the biological origin of petroleum; **1951**: Chargaff's rules are described, highlighting the role of heterocyclic compounds (purines and pyrimidines) in the genetic code. Heterocycles form by far the largest of the classical divisions of organic chemistry and are of immense importance biologically, industrially, and indeed to the functioning of any developed human society. For more than a century, heterocycles have constituted one of the largest area of research in organic chemistry. Among the approximately 20 million chemical compounds identified by the end of the second millennium, more than two-thirds are fully or partially aromatic, and approximately half are heterocyclic. The presence of heterocycles in all kinds of organic compounds of interest in biology, pharmacology, optics, electronics, material sciences, and so on is very well known. The majority of pharmaceuticals and biologically active agrochemicals are heterocyclic. There are countless heterocyclic additives and modifiers used in industries as varied as cosmetics, information storage, and plastics. Heterocycles play an important role in biochemical processes because the side groups of the most typical and essential constituents of living cells, DNA and RNA, are based on aromatic heterocycles Balaban, *et al.,(***2004**)[3].

Heterocyclic systems occur in a wide variety of natural and synthetic compounds and are essential to life in various ways. Certain derivatives are produced in nature by various animals and plants. Frequently, the naturally occurring heterocycles are structurally complex. Most of the sugars and their derivatives including vitamin-C exist largely in the form of five membered (furan) or six membered (pyran) rings containing one oxygen atom. Cinchona bark has been used for several hundred years as treatment for malaria. The active constituent is quinine. Many quinolines were synthesized in the hope of finding a better antimalarial than quinine e.g. Plasmoquine, Pentaquine and Chloroquine. Caffeine (1,3,7-trimethylxanthine) is the major stimulant in tea and coffee. The most of the alkaloids which are nitrogenous bases occurring in plants contains heterocyclic ring system. Camphothecin (an alkaloid) has attracted much interest as an anticancer agent. The powerful antibiotics penicillins and cephalosporins contain a β–lactam unit. Heterocycles are of great importance in the metabolic activities. Among these few compounds are thiamin, riboflavin, nicotinic acid, pyridoxine folic acid, biotin, vitamin E, chlorophyll, haemoglobin, adenine, purine, pyrimidine, hormones etc. Many natural drugs such as quinine, papaverine, emetine, theophylline, atropine, procaine, codeine, morphine and reserpine are heterocycles.

The synthetic heterocyclic drugs are still more numerous and include most of the hypnotics, anticonvulsants, analeptics, antihistaminics, antithyroid drugs, also many antiseptics, fungicides, vasopressor modifiers. Most of the compounds we know as synthetic drugs such as diazepam, chlorpromazine, isoniazid, metronidazole, azidothymidine, barbiturates, antipyrine, captopril and methotrexate are heterocycles. Many pesticides are heterocyclic e.g. the weed-killers paraquat, diquat and simazine, and the insecticides such as rotenome, diazinon and minazon. Heterocyclic rings constitute a large number of synthetic dyes e.g. mauveine. Many commercially available dyestuffs are compounds with quinoline ring. Some of the cyanine dyes are of immense importance in photography. Heterocycles also act as important constituent in plastic and resins such as melanin and cumarone are polymerized to yield useful plastics and resins. Antioxidant piperidine is used in rubber industry. Heterocycles are also used as important analytical reagents. These include o-phenanthroline, dipyridyl oxine and nitrone. The ready availability of furfural from agricultural wastes has resulted in its becoming one of the most valuable industrial sources of many aliphatic compounds which can be formed from it by simple chemical processes.

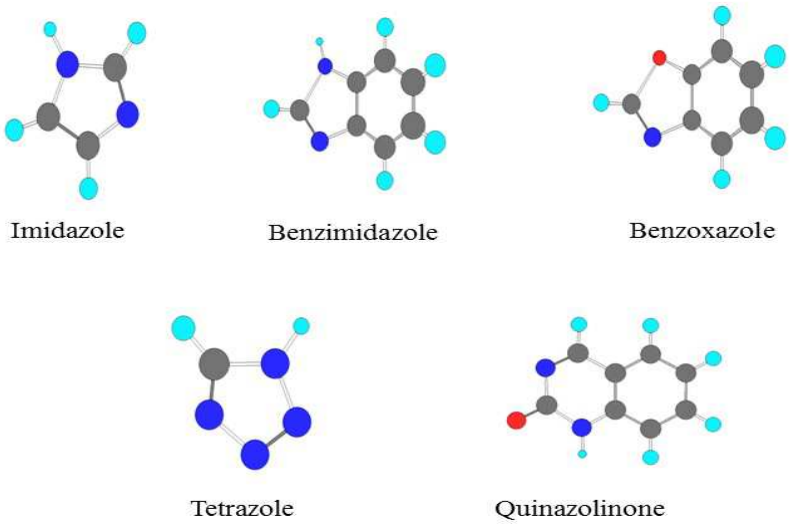
1.2 Azoles

Five membered heterocyclic compounds containing one or more heteroatoms, at least one of which must be nitrogen are termed as azoles. The simplest azole, pyrrole (**1**) contains one nitrogen atom. The ring containing two nitrogen atoms; one oxygen and one nitrogen atom; one sulphur and one nitrogen atom in 1, 2-position are designated as pyrazole (**2**), isoxazole (**3**) and isothiazole (**4**) respectively. When both the heteroatoms are represent in a 1,3-relationship then they are referred as imidazole (**5**), oxazole (**6**) and thiazole (**7**) respectively. A five membered ring containing three nitrogen atoms is known as triazole such as 1, 2,3-triazole (**8**) and 1,2,4-triazole (**9**). While a five membered ring containing four nitrogen atoms is known as tetrazole (**10**). Azoles are found widely in natural sources and there are several drugs available which contain azole ring in their molecular framework.



Heterocyclic compounds are a very wide and an expanding area of chemistry as well as pharmacology. Aromatics and heteroaromatic thiocyanato compounds are useful intermediates in the synthesis of heterocycles such as imidazole, benzimidazole, benzoxazole, benzothiazoles, thiazines etc. Thiocyanation of aromatics and hetero aromatics is an important carbon-hetero atom bond formation in organic synthesis Roberto *et al.,* (**2000**)[4]. Thiocyanation approach is the most beneficial process for direct induction of sulphur atom into the organic molecules Kelly *et al.,* (**1993**)[5]. In addition, the thiocyanate group shows a significant functionality in several anticancer agents Rajendra et al., (**1995**)[6].

Synthesis of various substituted imidazole ,benzimidazole, benzoxazole, tetrazole and quinazolinones from aryl thiocyanates have received considerable attention during the last two decades as they are endowed with a variety of biological activities and have a wide range of therapeutic properties.



1.3 Thiocyanate

The thiocyanate radical has a close similarity in its chemical property to halogens, which may be named "pseudo halogen". Thiocyanate shares its negative charge approximately equally between sulfur and nitrogen. As a consequence, thiocyanate can act as a nucleophile at either sulfur or nitrogen as it is an ambidentate ligand.

Thiocyanate is the anion [SCN] ¯. It is the conjugate base of thiocyanic acid. Common derivatives include the colourless salts potassium thiocyanate and sodium thiocyanate. Organic compounds containing the functional group SCN are also called thiocyanates. Mercury(II) thiocyanate was formerly used in pyrotechnics Conner *et al.,* (**2006**)[7].

1.4 Imidazole

Imidazole is a planar five-membered heterocyclic ring system with three carbon and two nitrogen atoms at the 1st and 3rd positions. Imidazole represents an important class of compound being the main component of many naturally occurring products, as well as synthetic derivatives. Imidazole ring has been of great interest for organic chemist due to their useful biological and pharmacological aspects. Imidazole derivatives have occupied a unique place in the field of medicinal chemistry. It is the constituent of several natural compounds like histamine, histamine, biotin, alkaloids and nucleic acid and a very important class among the medicinal compounds. Large number of imidazole derivatives have been are being developed for different therapeutic actions, Imidazole is an entity which is being synthesized in many of its derivative form from past few years; the entity is major source of interest for many of medicinal chemist to explore its various pharmacological potentials Satyanarayana *et al.,* (**2010**)[8].

1.5 Benzimidazole

Benzimidazole is an important pharmacophore and a privileged structure in medicinal chemistry. This compound is bicyclic in nature which consists of the fusion of benzene and imidazole. The most prominent benzimidazole compounds in nature is N-ribosyl-dimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin B12 Benzimidazole is a heterocyclic aromatic organic compound Shalini *et al.,* (**2010**)[9]. This bicyclic compound consists of the fusion of benzene and imidazole. Heterocyclic compounds are occupied prominent place among various class of aromatic organic compounds. Benzimidazole are having a variety of therapeutic uses including antitumor, antifungal, antiparasitic, analgesics, antiviral, antihistamine, as well as use in cardiovascular disease, neurology, endocrinology, and ophthalmology Day A R *et al.,* (**1950**)[10]**.**

1.6 Benzoxazole

Benzoxazole is an aromatic organic compound with a benzene fused oxazole ring structure. Substituted benzoxazole derivatives and their analogues such as benzimidazoles and benzothiazoles have been the aim of many researchers for many years, because they constitute an important class of heterocyclic compounds. The structural variations of these compounds are that different substituents can be incorporated on the benzene ring and diverse heterocycles and other active groups can be introduced at the 2-position in order to create good biological activity. The substitution at second position in benzoxazole skeleton is influential for the biological activity of the molecule Jauhari *et al.,* (**2008**)[11]. Benzoxazole derivatives are biologically significant compounds and known to exhibit various biological activities such as anticancer, antimicrobial, anti HIV and dopamine D4 agonists Kumar *et al.,* (**2002**)[12]. Benzoxazoles are also interesting fluorescent probes which show high Stokes shift and present thermal and photophysical stability due to an excited state intramolecular proton transfer mechanism Holler *et al.,* (**2002**)[13].
Since they interfere with biosynthesis of coloured carotenoids by inhibiting the enzyme phytoene desaturase, they are studied as potential bleaching herbicides Laber *et al.,* (**1999**)[14]. Benzoxazoles can be considered as structural bioisosteres of naturally occurring nucleotides such as adenine and guanine, which allow them to interact easily with the biopolymers of a living system. They have shown low toxicity in warm-blooded animals Dunwell *et al.,* (**1977**)[15]. Benzoxazoles have a number of optical applications such as photoluminescents Claussen, *et al.,* (**1981**)[16], whitening agents and dye laser Reser, *et al.,* (**1972**)[17]. Benzoxazoles have found applications as intermediates for organic synthesis Fery-Forgues *et al.,* (**1993**)[18].

1.7 Tetrazole

Tetrazole is a 5-membered ring containing 4 nitrogens and 1 carbon. Due to its energetic potential and structural similarity to carboxylic acids, this ring system has a wide number of applications. Tetrazoles are used in the pharmaceutical industry in modern anti-hypertensive medications. While this field is fairly developed, the energetic applications for tetrazoles are fairly unexplored. Throughout this thesis, tetrazole derivatives were synthesized and investigated as potential energetic materials or components of energetic materials. In most cases, these compounds were an acceptable substitute for the problematic azido derivatives common in many energetic compounds Mohite P.B. *et al.,* (**2011**)[19].

Specifically, azido groups are unstable because they react with a variety of compounds. In energetic binders, they react with the cure catalysts and introduce charges along the polymer chains. The synthesis of tetrazoles is inherently dangerous because of the explosive and toxic nature of sodium azide. One of the initial goals of this research was to design a safe and efficient synthesis of tetrazoles.

1.8 Quinazolinone

Quinazoline are classes of fused heterocycles that are of considerable interest because of the diverse range of their biological properties, for example, anticancer, diuretic, anti-inflammatory, anticonvulsant and antihypertensive activities. Quinazolinone will be classified into the following five categories, based on the substitution patterns of the ring system. Out of the three quinazolinone structures, 4(3H)-quinazolinones are most prevalent, either as intermediates or as natural products in many proposed biosynthetic pathways. This is partly due to the structure being derived from the anthranilates (anthranilic acid or various esters, isatoicanhydride, anthranilamide and anthranilonitrile) while the 2(1H)-quinazolinone is predominantly a product of anthranilonitrile or benzamides with nitriles. Quinazolinone moiety is a building block for approximately 150 naturally occurring alkaloids. Luotonin A, Bouchardatine1, and Febrifugine as naturally occurring alkaloids have quinazolinone skeleton. Methaqualone, the most well-known synthetic quinazolinone drug synthesized for the first time in 1951, has sedative–hypnotic effects Rakhi Rajput *et al.,* (**2012**)[20].

In the most common approach for the synthesis of quinazolinone compounds, 2-aminobenzoic acid or its derivatives, 2-aminobenzamide, 2-aminobenzonitrile, isatoic anhydride, 2-carbomethoxyphenylisocyanate, *N*-arylnitrilium salts, and 4*H*-3,1-benzoxazinones as appropriate precursors were used. Other methods involve the reaction of anthranilic acid and the appropriately substituted imidate in a facile one-pot procedure, cycloaddition of anthranilic acid iminoketene to methylbutyrolactam (via sulfonamide anhydride), reactions of anthranilic acid derivatives with a wide range of substrates including imidates and imino halides, and microwave-promoted reaction of anthranilic acid with amines and formic acid (or its ortho ester) and isatoic anhydride.

2. BIOLOGICAL ACTIVITIES

2.1 Medicinal Chemistry

During the pre-scientific period, natural products were used for medicinal purposes, including arrow poisons and cosmetics. Some notable examples are opium, belladonna, cinchona bark and squill. The science of medicinal chemistry did not develop until anatomy and physiology reach the status of science.

Now-a-days, the research findings in various science fields, including molecular biology, pharmacology and enzymology, are applied to the field of medicinal chemistry. Wolff and Coadjutors have pointed out that the present situation would definitely continue for some more time, before physical measurements and mathematical calculations would convert medicinal chemistry into an exact science.

2.2 Pharmacotherapeutics

The development of modern pharmacology as a science is fairly recent and this science took shape only after the invention of screening procedures. Till that period, the treatment was only empirical and experience alone played a dominant role. A good knowledge of the mode of action of the drug is necessary for the rational treatment of diseases. Pharmacology, being considered a branch of biology, provides the required scientific data in both animals and humans. The science of pharmacology includes some allied fields too, such as pharmacognosy, pharmacy, pharmacodynamics, pharmacokinetics, therapeutics, toxicology and chemotherapy. Pharmacognosy is a science of identification of drugs, whereas pharmacy is considered as a science of identification, selection, preservation, compounding and dispensing of drugs. The quantitative biological and therapeutic effects of drugs, and drug action-chemical structure relation are studied in pharmacodynamics. However, pharmacokinetics describes the absorption, distribution, metabolism and excretion of drugs. The word"Therapeutics" refers to "To nurse" and this branch of medicine deals with the cure of diseases. The science of toxicology deals with the detection and measurement of poisons. Hemotherapy is a science, concerned with the effect of drug on microorganisms and parasites Helen.P.Kavitha *et al.,* (**2000**)[21].

2.3 Drug Administration

A drug may be applied locally or it may be administered either orally or by injection. The term local application refers to the application of a material, such as a dusting powder, paste, ointment, lotion or plaster on the surface of the body. Oral or eternal route is normally the most commonly followed route for drug administration, because it is safe, convenient and economical. However, this method is not suitable for administering irritant and unpalatable drugs.

2.4 Toxicity Studies in Animals

Toxicity studies are normally conducted in animals, including mice, rat, guinea pigs, dogs and monkeys with a view to assess the safety of a drug. The tests, normally carried out, are classified into three types, viz., acute toxicity tests, chronic toxicity tests and special tests for teratogenecity, mutagenecity and carcinogenecity.

2.5 Acute Toxicity Tests

The purpose of acute toxicity tests is the same, regardless of the chosen route of exposure. That is, they are undertaken to investigate the potential adverse effects arising from exposure to a given chemical over a short period of time. There are many different types of acute effects that could be studied, but the one acute effect, or end-point, which all chemicals will demonstrate is lethality and it is this which is therefore used as the end-point in this type of study. The results from acute toxicity tests are graphically represented as a dose-response curve which is often converted to a straight line plot as it makes the data easier to handle and interpret Laura Robinson *et al*., (**2005**)[22].

2.6 Lethal Dose, LD_{50}

The term LD_{50} refers to a dose which is effective in producing a certain expected response in 50% of the animal group. There is another term, known as, ED_{50} which is useful in understanding the potency of the drug with respect to a reference standard. The value of ED_{50} can be calculated by determining the graded response shown by the drug. However, when the response is quantal or all-or-none, ED_{50} is considered to be equal to LD_{50}.

The safety of a drug can be understood based only on the values of both LD_{50} and ED_{50}. The term therapeutic index refers to the ratio of LD_{50} to ED_{50}. The greater the therapeutic index, the safer is the drug. It has been suggested Kulkarni *et al*., (**1993**)[23] that the therapeutic index of a drug, having a low margin of safety, has been found to be close to unity. It is of interest to determine a dose that is effective in most of the animals, namely, ED_{50} and least toxic to most of the animals of a group, viz., LD_{50}. The graphical method is normally employed to calculate these values.

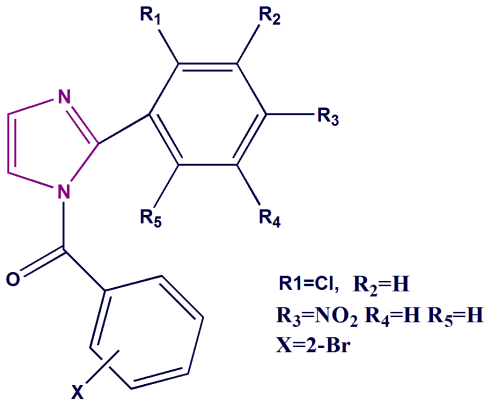
Several methods are available to calculate the LD_{50} value. One among them is acute toxic class method which follows the OECD 423 guidelines. It is a stepwise procedure with the use of 3 animals of a single sex per step. Depending on the mortality and/or the moribund status of the animals, on an average 2-4 steps may be necessary to allow judgment on the acute toxicity of the test substance. This procedure is reproducible and uses very few animals. The method as adopted in 1996 was extensively validated *in vivo* against LD_{50} data obtained from the literature, both nationally and internationally Christina Ruby Stella.P *et al.*, (**2013**)[24].

3. Medicinal Chemistry of Imidazole

Medicinal chemistry is the discipline concerned with determing the influence of chemical structure on biological activity and in the practice of medicinal chemistry developed from an empirical one involving organic synthesis of new compound based largely on the modification of structure and then identifies their biological activity Williams.D.A. *et al.*, (**2002**)[25]. Medicinal chemistry concerns with the discovery, development, interpretation and the identification of mechanism of action of biologically active compounds at the molecular level. Various biologically active synthetic compounds have five-membered nitrogen-containing heterocyclic ring in their structures Lednicer D *et al.*, (**1997**)[26].

3.1 Antifungal and anti-bacterial activity

Deepika Sharma *et al.*, (**2009**)[27] **(1)** have synthesized 2-(substituted phenyl)-1H-imidazole and (substituted phenyl)-[2-(substituted phenyl)-imidazol-1-yl]-menthanone analogues and screened for antimicrobial activity against gram positive, gram negative, and fungal species. Norfloxacin used as standard and following compound is the most potent.



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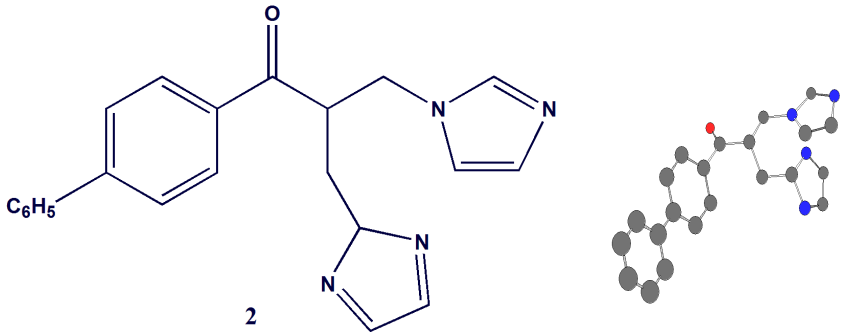
Daniele Zampieri *et al.*, (**2007**)[28] **(2)** synthesized bis-imidazole derivatives and screened for antifungal and anti-mycobacterial activity. All compounds showed moderate to good activity against *Candida albicans* and *Candida glabrata*. Miconazole was used as reference drug.



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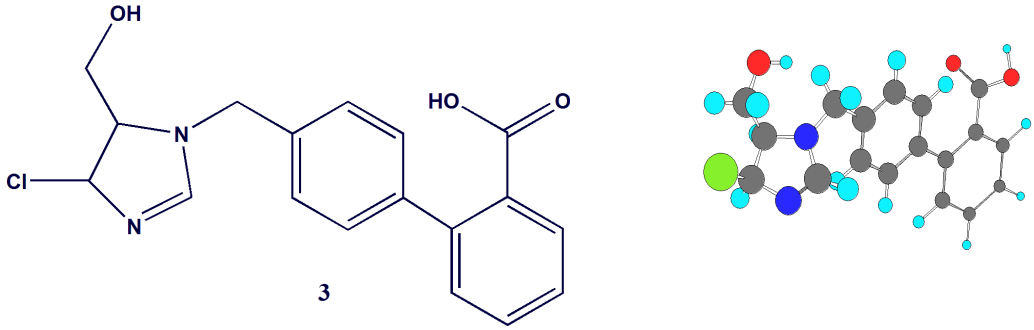
Shreenivas.M.T *et al.,* (**2011**)[29] **(3)** Compounds were screened for their in-vitro antibacterial activity against *S. aureus* and *B. Subtilis* employing cup-plate method at the concentration of 100µg/ml in nutrient agar media and also for in-vitro antifungal activity against *C. albicans* and A. Niger by cup plate method at 100µg/ml. concentration using sabouraud-dextrose agar. DMSO was used as solvent control for antimicrobial activity. Streptomycin was used as standard for antimicrobial activity. The area of inhibition of zone was measured in cm.



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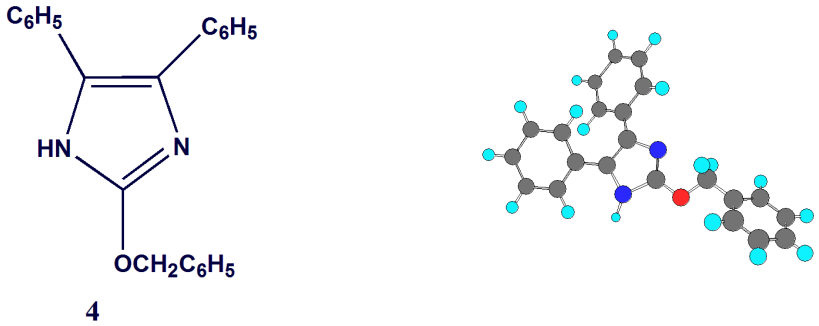
3.2 Anti -inflammatory and analgesic activity

Puratchikody.A *et al.,* (**2007**)[30] studied on **(4)** 2-substituted-4, 5-diphenyl-1H-imidazoles and checked the anti-inflammatory activity based on Carrageenan-induced paw edema method. This compound shows maximum activity and indomethacin was used as reference drug.



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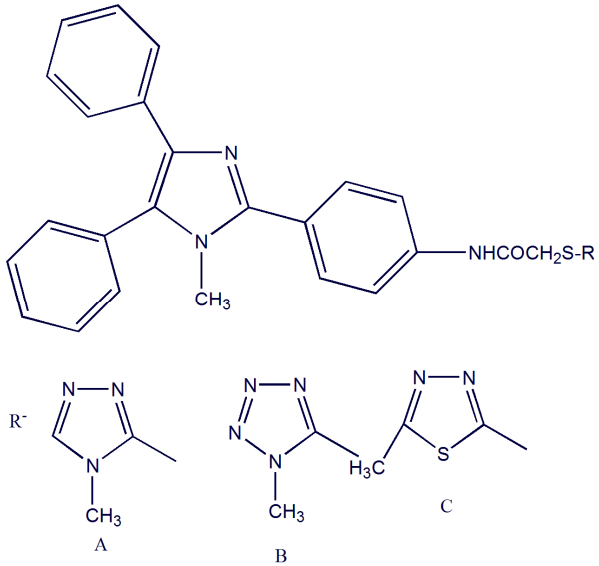
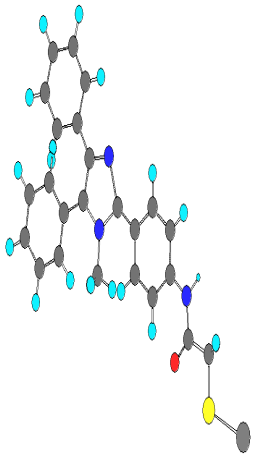
3.3 Anticancer activity

Yusuf Ozkay *et al.,* (**2010**)[31] synthesized many novel **(5)** imidazole-(Benz) azole and imidazole epiperazine derivatives in order to investigate the anticancer activity. Anticancer activity screening results revealed that these were the most active compounds in the series. Cisplatin was used as reference drug.





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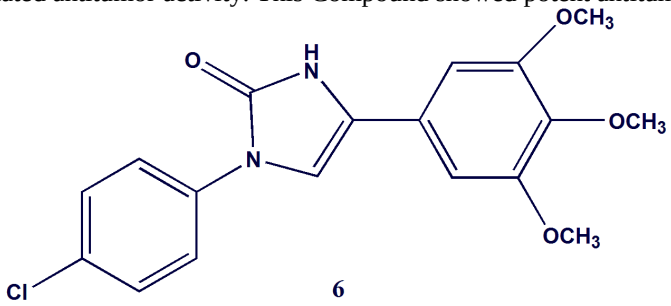
Cenzo congiu *et al.*, (**2008**)[32] synthesized a series of **(6)** 1, 4-diarylimidazole-2(3H)-one derivatives and their 2-thione analogues and evaluated antitumor activity. This Compound showed potent antitumor activity.



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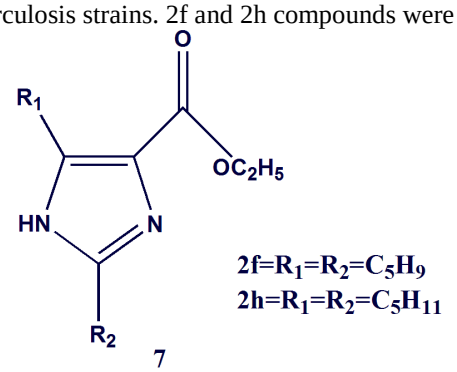
Preeti Gupta *et al.*, (**2004**)[33] described anti-mycobacterium tuberculosis activities of ring substituted **(7)** 1H imidazole-4-carboxylic acid derivatives and 3-(2-alkyl-1H-imidazole-4-yl)-propionic acid derivatives against durg-sensitive and durg- resistent M. tuberculosis strains. 2f and 2h compounds were the most potent compounds.



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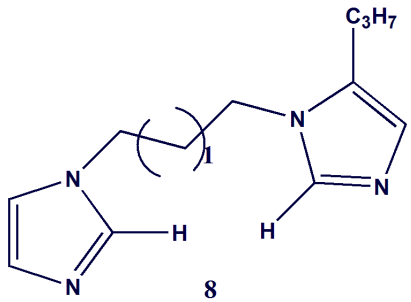
Jyoti Pandey *et al.*, (**2009**)[34] synthesized a series of **(8)** imidazole derivatives and compounds were screened against tuberculosis where this compound showed good antitubercular activity.



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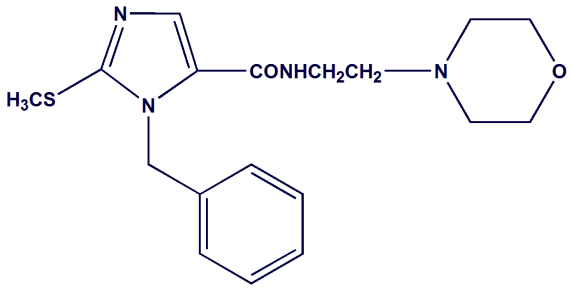
3.4 Antidepressant activity

Farzin Hadizadeh *et al.*, (**2008**)[35] synthesized **(9)** moclobemide analogues by replacing moclobemide phenyl ring with substituted imidazole and studied for the antidepressant activity using forced swimming test. Analogues 7a-c was found to be more potent than moclobemide.



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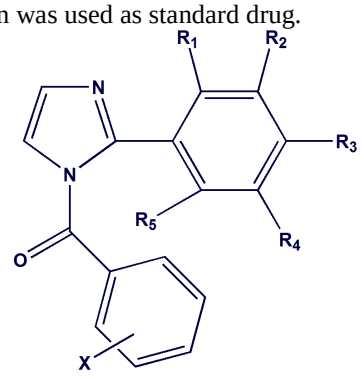
3.5 Antiviral activity

Sharma.D *et al.*, (**2009**)[36] synthesized imidazole derivatives and the antiviral screening of **(10)** (substituted phenyl) -[2-(substituted phenyl)-imidazol-1-yl]-methanones against viral strains indicated that compounds A selected as the most potent antiviral agents. Ribavirin was used as standard drug.

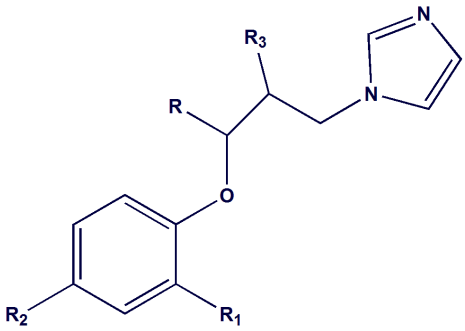


R_1=H,R_2=H,R_3=Cl,NO_2,R_4=H,R_5=H,X=4-NO_2

10

3.6 Antilishmanial activity

Kalpana bhandari *et al.*, (**2010**)[37] synthesized a series of **(11)** substituted aryloxy alkyl and aryloxy aryl alkyl imidazole and evaluated in vitro as antileishmanial against Leshmania donovani. Among all compounds exhibited 94–100% inhibition.

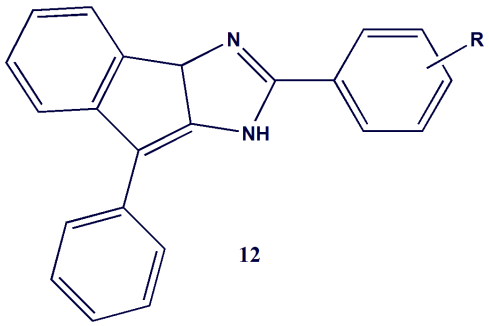


R=CH_3,R_1=H,R_2=$NO_2$$R_3$=H

11

3.7 Anticonvulsant Activity

Bhragual *et al.*, (**2010**)[38] evaluated the anticonvulsant activity by Maximal Electroshock Method (MES). Substitution of chloro and nitro group at 2nd position in the substituted ring **(12)** showed significant anticonvulsant activity without neurotoxicity while hydrogen and 4-nitro substitution did not show the anticonvulsant activity.



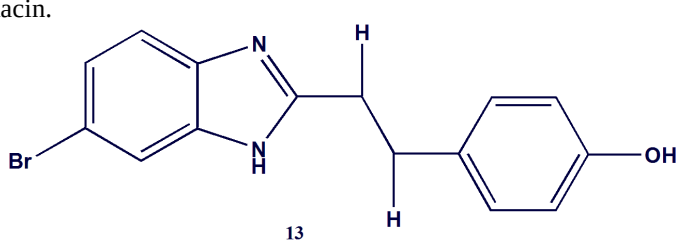
12

4. Medicinal Chemistry of Benzimidazole

Benzimidazoles are regarded as a promising class of bioactive heterocyclic compounds that exhibit a range of biological activities. Specifically, this nucleus is a constituent of vitamin-B12. Several benzimidazoles are commercially available as pharmaceuticals. Benzimidazoles are the most widely studied drugs as anthelmintic. Recent studies have established that benzimidazole carbamates such as Albendazole (1), mebendazole (2), flubendazole (3), and fenbendazole (4) inhibit the in vitro growth of Trichomonas vaginalis and G. lamblia. Clinical reports have shown that albendazole is as effective as metronidazole, the choice drug for the treatment of giardiasis. Benzimidazole carbomates, well known therapeutic agents used mainly as anthelmintics, have a broad antiparasitic spectrum of activity, low toxicity and have been used successfully to treat gastrointestinal helminthic infections Sivakumar.R *et al.,* (**2011)**[39].

4.1 Antibacterial activity

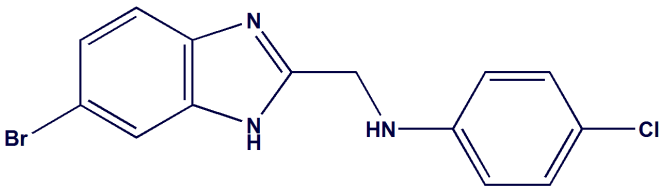
Ramya.V *et al.,* (**2009)**[40] **(13)** synthesized a series of novel 5-(nitro/bromo)-styryl-2-benzimidazole derivatives and tested for the antibacterial activity against *Staphylococcus aureus*, Escherichia coli, *Enterococcus faecalis*, and *Klebsiella pneumoniae* and anti-fungal activity against *Candida albicans* and *Aspergillus fumigates*. This was comparable with ciprofloxacin.



13

4.2 Analgesic and anti-inflammatory activities

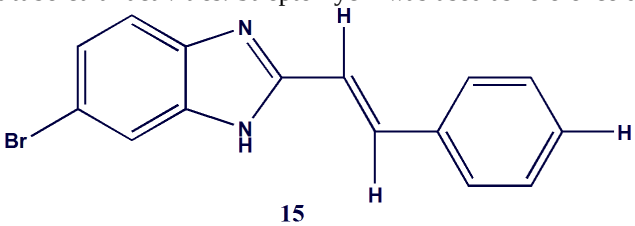
Achar.K.C.S *et al.,* (**2010)**[41] have synthesized a series of **(14)** 2-methylaminibenzimidazole derivatives and newly synthesized compounds were screened for analgesic and anti-inflammatory activities. This compound showed analgesic activity and compared with standard nimesulide drug.



14

4.3 Antitubercular activity

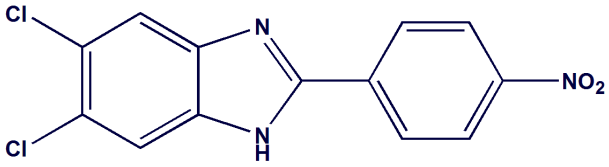
Shingalapur.R.V *et al.,* (**2009)**[42] synthesized series of novel **(15)** 5-(nitro/bromo)-styryl-2-benzimidazoles (1–12) derivatives and screened for in vitro anti-tubercular activity against Mycobacterium tuberculosis, and these compounds showed good antitubercular activities. Streptomycin was used as reference drug.



15

4.4 Anti-viral activity

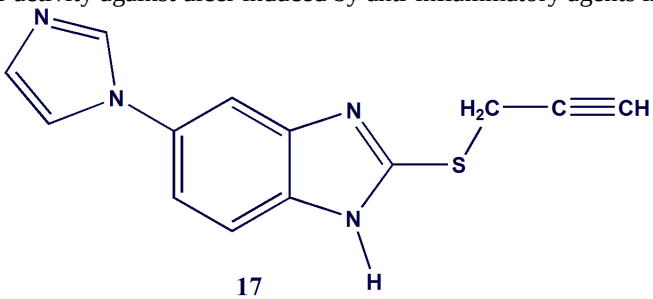
Michele Tonelli *et al.,* (**2010**)[43] synthesized seventy six 2-phenylbenzimidazole derivatives and evaluated for cytotoxicity and anti-viral activity against a panel of RNA and DNA viruses. **(16)** Compound ([5,6-dichloro-2-(4-nitrophenyl) benzimidazole]) exhibited a high activity Resulting more potent than reference drugs mycophenolic acid and 6-azauridine.



16

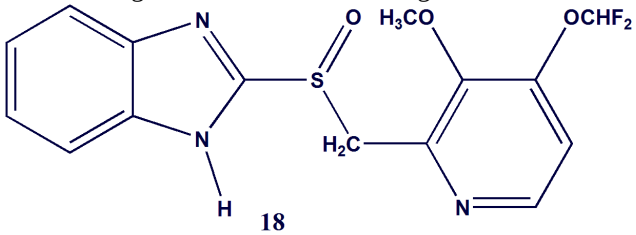
4.5 Antiulcer activity

Brumagniez *et al.,* (**1990**)[44] **(17)** reported the synthesis of 2-(thiopropyne)-5-(imidazol-1-yl) benzimidazole which exhibited moderate antiulcer activity against ulcer induced by anti-inflammatory agents in rats orally.



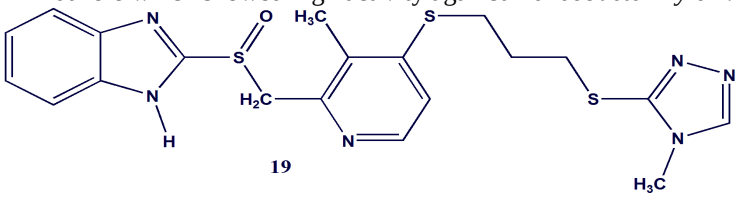
17

Braendstroem *et al.,* (**1991**)[45] **(18)** reported the synthesis of 2-[(3,4 dimethoxy, 2-pyridyl) methyl, sulfinyl]5-acetyl, 6-methyl benzimidazole which inhibited gastric acid secretion in dogs.



18

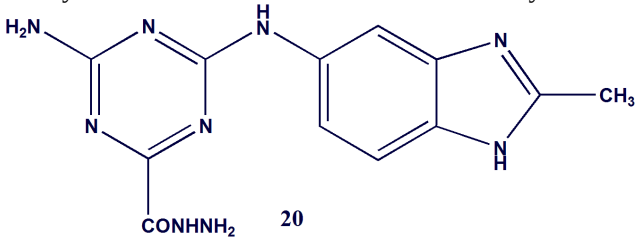
Kohli.P *et al.,* (**2007**)[46] **(19)** reported the synthesis of 2-[3-methyl, 4(N-methyl-1, 2, 4 triazol-3-yl)1,3-dithiane]methyl thio benzimidazole which showed high activity against *Helicobacter Pylori*.



19

4.6 Antiviral activity

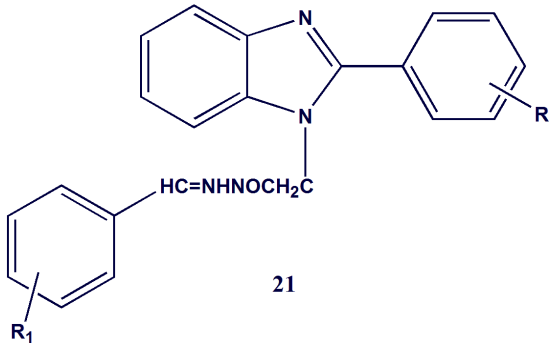
Laila *et al.,* (**2008**)[47] **(20)** have reported the synthesis of 4-amino-6-(2-methyl-iH-benzimidazol-5-ylamino)-[1,3,5]triazine-2-carboxylic acid hydrazide which showed the antiviral activity.



20

4.7 Antitumor activity

Balram Soni1 *et al.,* (**2012**)[48] synthesised and invitro antitumor activity of benzimidazole derivatives **(21).**



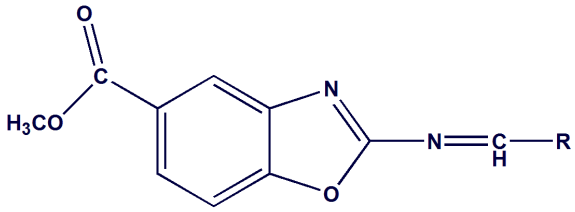
21

5. Medicinal Chemistry of Benzoxazole

The majority of pharmaceuticals and biologically active agrochemicals are heterocyclic, while countless additives and modifiers used in industrial application ranging for cosmetics, reprography, information storage and plastics are heterocyclic in nature. The heterocyclic ring comprises of very core of the active moiety or the pharmacophore. Several Benz-fused hetero, bicyclic ring systems as indole, benzothiazole, benzimidazole, benzoxazole, have been studied and found to be possessing interesting pharmacological activities. Biologically active benzoxazole derivatives have been known for long time, since they are the isosters of naturally occuring cyclic nucleotides and they may easily interact with the biopolymers of the organisms Manish Kumar Gautam *et al.,* (**2012**)[49].

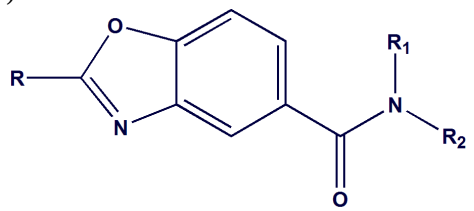
5.1 Anti-inflammatory activity

VidyaSagar.J *et al.,* (**2010**)[50] have synthesized methyl-2-(arylideneamino) benoxazole-5-carboxylate derivatives **(22)** by reaction of methyl-2-aminobenzoxazole-5-carboxylate and appropriate aromatic aldehydes with absolute alcohol. Synthesized compounds were screened for their anti-inflammatory activity using carrageenan induced paw oedema method. The synthesized derivatives showed moderate to potent anti-inflammatory activity when compared to standard drug Diclofenac sodium.



22

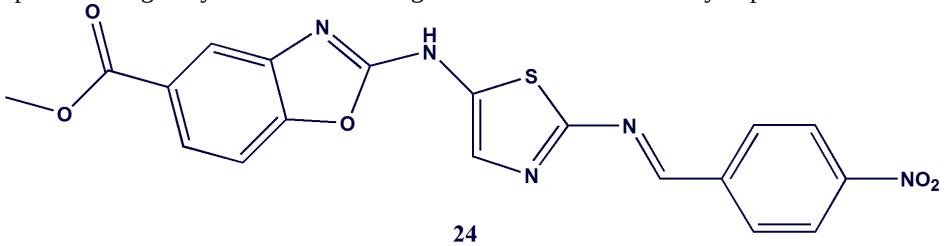
Reena *et al.,* (**2010**)[51] **(23)** showed the anti-inflammatory activity of 2-substituted-[(N, N-disubstituted)-1,3-benzoxazole]-5-carboxamide (49).



R=H,-CH_3,-C_2H_5 ; R_1=CH_3,-C_2H_5,-C_6H_5 ;R_2=CH_3,-C_2H_5,-C_6H_5

23

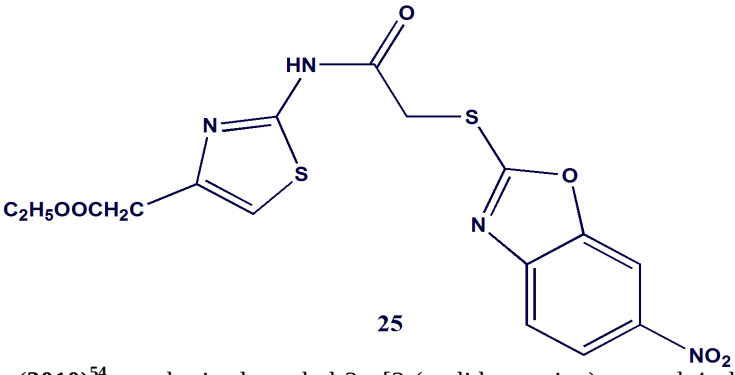
Srinivas.A *et al.,* (**2010**)[52] **(24)** reported the increased anti-inflammatory activity of the compound that is attributed to the presence of pharmacologically active thiazole ring on the benzoxazole moiety at position-2.



24

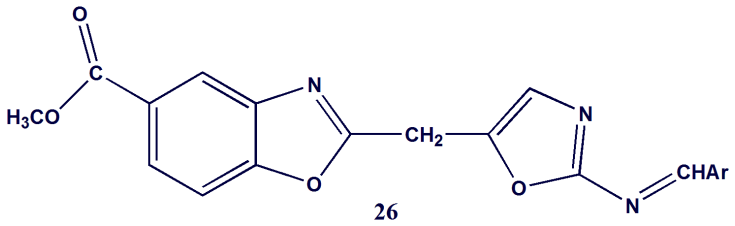
5.2 Anti-microbial activity

Zafer Asim *et al.,* (**2004**)[53] **(25)** proved the significant antimicrobial activity of benzoxazole.



25

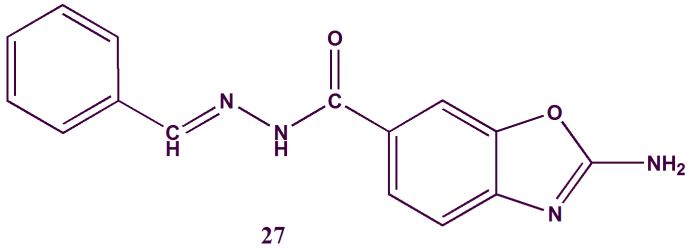
Dayakar Gadhe *et al.,* (**2010**)[54] synthesized methyl-2- [2-(arylideneamino) oxazol-4-ylamino] benzoxazole-5-carboxylate derivatives **(26)** by the reaction of Methyl-2-(2-aminoxazol-4-ylamino) benzoxazole-5-carboxylate and appropriate aromatic aldehydes by dissolving in alcohol and finally washed with 1% sodium bicarbonate solution. The synthesized benzoxazole-5-carboxylate derivatives showed excellent antibacterial activity against *Bacillus subtilis, E.coli* etc.



26

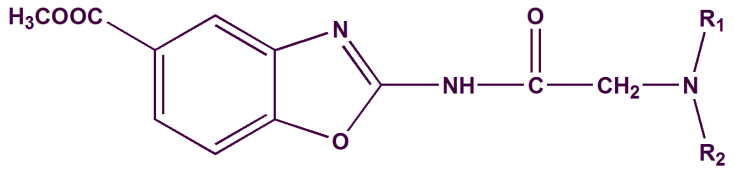
5.3 Cyclooxygenase-2 inhibiting activity

Garrepalli *et al.,* (**2011**)[55] **(27)** proved that 2-amino-N-(substituted arylidene) benzoxazole-5-carbohydrazide serve as an excellent candidate for selective COX-2 inhibition.



27

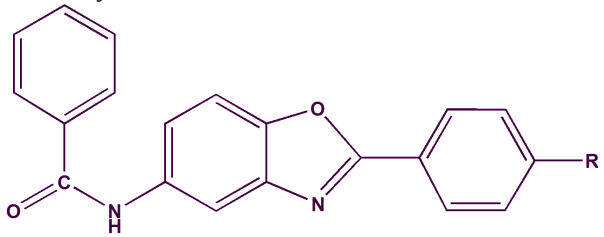
Srinivas A *et al.,* (**2010**)[56] have synthesized methyl-2- [2-(disubstituted amino) acetamido] benzoxazole-5-carboxylates **(28)** by the reaction of a solution of Methyl 2-(2 chloroacetamido) benzoxazole-5-carboxylate in dry acetone and N, N-dialkylamine. All the synthesized benzoxazole derivatives were shown good to moderate activity. Some compounds shown the IC50 values of 12.69, 20.13, 23.85 and 21.09 respectively.



28

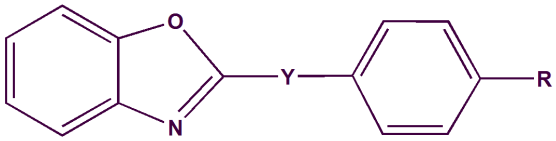
5.4 DNA Topoisomerase inhibiting activity

Akbay Aysogul *et al.,* (**2003**)[57] **(29)** have synthesized 5-phenylacetamidosubstituted-2-phenylbenzoxazole which inhibits reverse transcriptase activity.



R=H,-C_2H_5 29

Emine Oksuzoglu *et al.,* (**2008**)[58] **(30)** and team members investigated the DNA Topoisimerase II inhibitory effects of 5-methyl-2-substituted benzoxazole.



R=NHCH$_3$, -CH$_3$, -Br ; Y=CH$_2$, C$_2$H$_4$,CH$_2$O

30

Since DNA Topoisomerases are considered as important targets for cancer chemotherapy, the present findings may provide future opportunities to design and develop new chemotherapeutic agents.

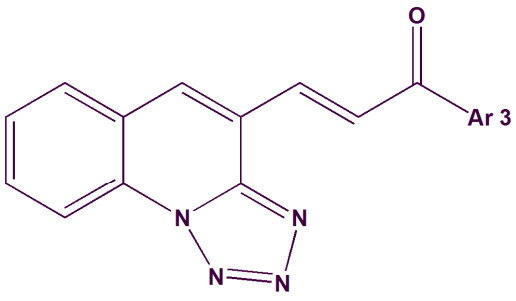
6. Medicinal Chemistry of Tetrazole

Tetrazole and its derivatives have attracted much attention because of their unique structure and applications as antihypertensive, antiallergic, antibiotic and anticonvulsant agents. Synthesis of tetrazole derivatives is obviously an important task in modern medicinal chemistry. Although a number of synthetic methods are available, there still exists a demand for improved protocol which allows an effective transformation in the presence of a wide range of functional groups. The development of tetrazole chemistry has been largely associated with wide scale of applications of these classes of compounds in medicine, biochemistry, agriculture and also a large number of medicinally important tetrazole heterocyclic incorporated drugs approved by the FDA. The tetrazole functionality plays an important role in medicinal chemistry, primarily due to its ability to serve as bioequivalent (bioisosteres) of the carboxylic acid group. Heterocyclic derivative is the first approved treatment for the partial agonist of dopamine D2 receptors; and also heterocyclic derivatives are widely used as antibacterial agents in human and veterinary medicines. Some of tetrazole containing compounds have been used both as anticancer and antimicrobial agents.

1-Substituted tetrazole derivatives are used as antibiotics and optically active tetrazole containing antifungal preparations of azole type. There is always a need for new and effective antifungal and antibacterial agents with broad spectrum antibacterial and antifungal activities. It was decided to exploit this interest by ascertaining the molecules features essential for activity and utilizing them to develop a new class of drugs. Prompted by the various biological activities of tetrazole and its substituted derivatives, we envisioned our approach towards the synthesis of a novel series of 1- substituted tetrazole derivatives and study their biological activities. The objective of the present study was to synthesize new substituted tetrazole derivatives and to evaluate their antibacterial and antifungal properties Dhayanithi Varadaraji *et al.,* (**2010)**[59]**.**

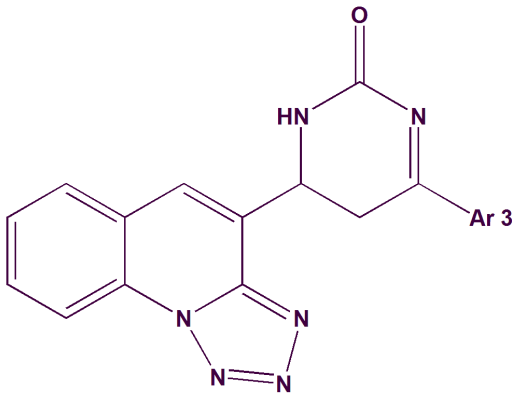
6.1 Antibacterial activity

Adnan. A *et al.,* (**2011)**[60] **(31 and 32)** reported tetrazolo [1,5a] quinoline as a potential promising new scaffold for the synthesis of novel anti-inflammatory and antibacterial agents. The four compounds were proved to be active anti-inflammatory agents against indomethacin.



Ar3=C$_6$H$_5$,p-BrC$_6$H$_4$,p-ClC$_6$H$_4$

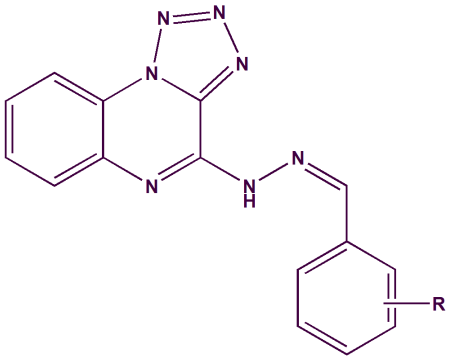
31



Ar3=C$_6$H$_5$,p-BrC$_6$H$_4$,p-ClC$_6$H$_4$

32

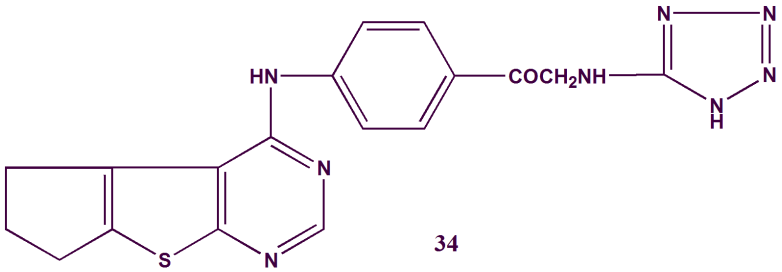
Umarani Natrajan *et al.,* (**2010)**[61] **(33)** reported a facile design and efficient synthesis of Schiff's bases of tetrazolo [1,5-*a*] quinoxalines as potential anti-inflammatory and anti-microbial agents and few of them exhibited promising activity.



R= 5a=2-OHC$_6$H$_4$ 5b=3-OHC$_6$H$_4$ 5c=4-OHOHC$_6$H$_4$ 5d=2-NO 2C$_6$H$_4$

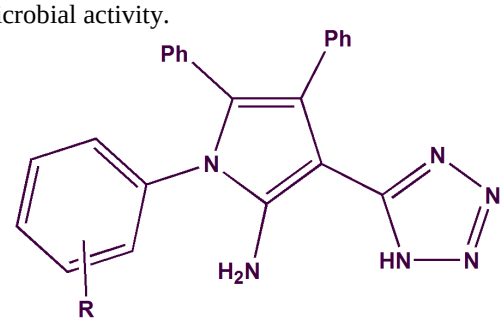
33

Md Salahuddin *et al.,* (**2009**)[62] **(34)** reported the synthesis of some novel Benzo Thieno [2, 3-d] pyrimidines and synthesized compounds are active against the bacteria like *Bacillus subtilis, Bacillus pumilis, Escherichia coli and Staphylococcus aureus but the* Thieno [2, 3-d] pyrimidine derivative containing tetrazole ring shows moderate antibacterial activity.



34

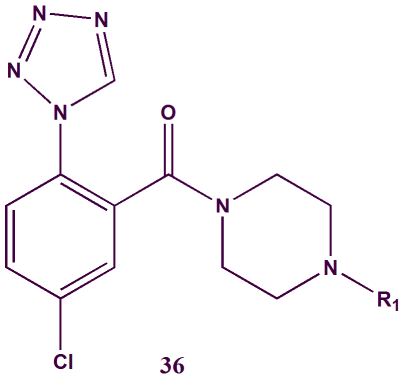
Mosaad Sayed Mohamed *et al.,* (**2009**)[63] **(35)** reported the synthesis of *N*-(3-cyano-1-(3-methylphenyl)-4,5-diphenyl-1*H*-pyrrol-2-yl)-acetamides (**5c**), 2-amino-1-(4-methoxyphenyl)-4,5-diphenyl-3-tetrazolo-1*H*pyrroles(**5d**) and found to possess potent antimicrobial activity.



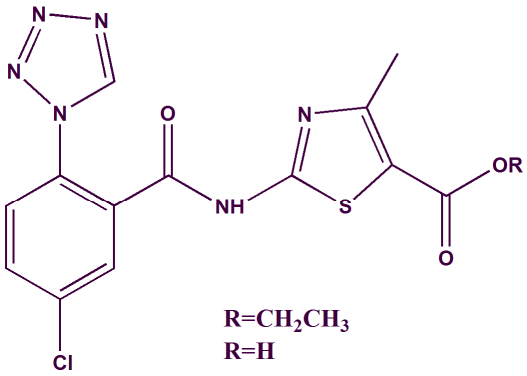
R=H,2-CH$_3$,3-CH$_3$,4-OCH$_3$

35

Hari N. Patil *et al.,* (**2010**)[64] **(36, 37 and 38)** have reported synthesis and evaluation of a series of 1-substituted tetrazole derivatives as antimicrobial agents a series of novel 1-substituted tetrazole derivatives were synthesized and evaluated for their antibacterial and antifungal activity**.** All the derivatives were efficiently synthesized by four steps process. In this study, thiazole attached tetrazole derivatives were most active than the piperazine attached tetrazole derivatives.

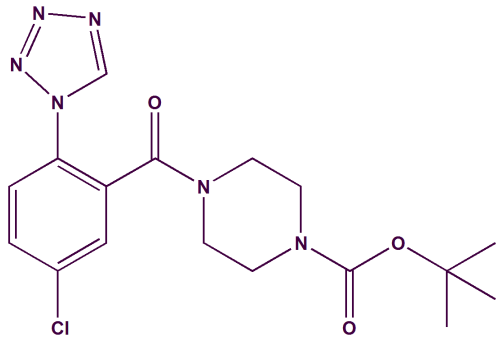


36



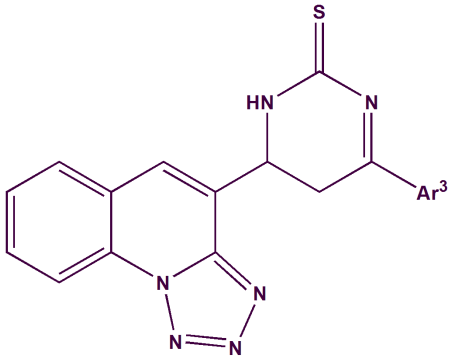
R=CH_2CH_3
R=H

37



38

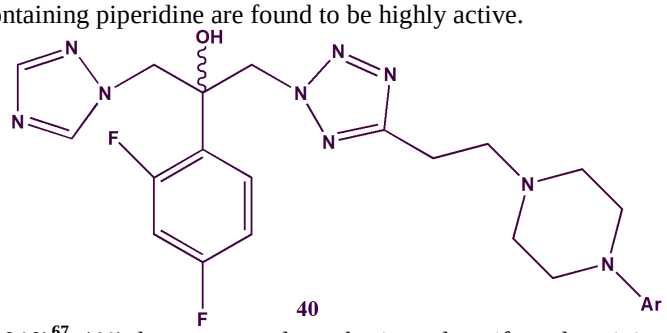
Adnan A Bekhit *et al.*, (**2004**)[65] **(39)** have synthesised three series of tetrazolo [1,5-*a*]quinoline derivatives. The newly synthesized compounds were evaluated for their anti-inflammatory and antimicrobial activities. Four compounds were proved to be as active as indomethacin in animal models of inflammation.



39

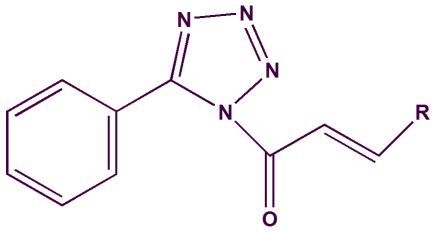
6.2 Antifungal activity

Ram Shankar Upadhayaya *et al.*, (**2004**)[66] **(40)** reported **s**ynthesis of novel substituted tetrazoles having antifungal activity. The derivatives containing piperidine are found to be highly active.



40

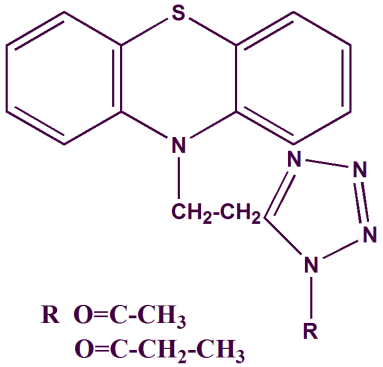
Movie Popat. B *et al.*, (**2010**)[67] **(41)** have reported synthesis and antifungal activity of 3-aryl 1-(5-phenyl-1*H*-tetrazol-1-yl)prop-2-en-1-one and evaluated for antifungal activity using cup and plate method in which compounds containing chloro group are highly active.



41

6.3 Analgesic activity

Rajasekaran A *et al.,* (**2004**)[68] **(42)** have reported on synthesis and analgesic evaluation of some 5-[b-(10-phenothiazinyl) ethyl]-1-(acyl)-1, 2, 3, 4-tetrazoles.

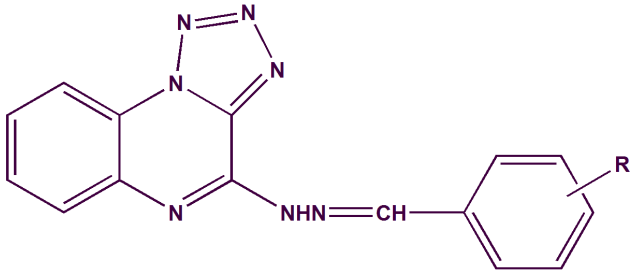


R **O=C-CH$_3$**
O=C-CH$_2$-CH$_3$

42

6.4 Anti-inflammatory activity

Ilango Kaliappan *et al.,* (**2010**)[69] **(43)** reported, a novel synthetic methodology of Schiff's bases incorporating tetrazolo quinoxalines .All the newly synthesized heterocycles have been screened for their *in vitro* antimicrobial and anti-inflammatory activities. Few of them exhibited promising activity. The ambient conditions, excellent product yields and easy work up procedures make this synthetic strategy a better protocol for the synthesis of newer Schiff's derivatives.



43

7. Medicinal Chemistry of Quinazolinone

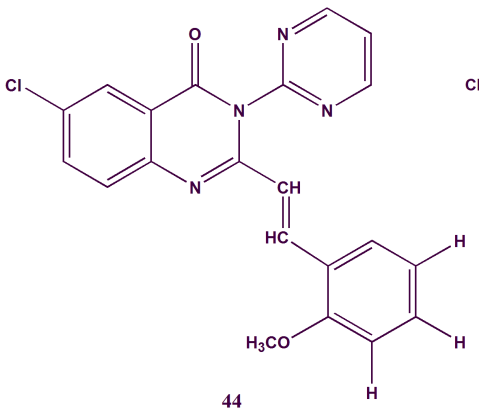
The quinazolinone skeleton is a frequently encountered heterocycles in medicinal chemistry literature with applications including antibacterial, analgesic, anti-inflammatory, antifungal, antimalarial, CNS depressant, anticonvulsant, anticoccidial, anti-parkinsonism, and cancer activities. Little number of quinazolinones was reported as potent chemotherapeutic agents in the treatment of tuberculosis. For example 3-aryl-6, 8-dichloro-2H-1, 3-benzoxazine-2, 4(3H) - diones and 3-arylquinazoline-2, 4(1H, 3H)-diones as anti-mycobacterial agents, quinazolinone derivatives as antitubercular agents.

Compounds of both synthetic and natural origin comprising a diverse group of chemical structure have been reported as antileishmial agents. These include mostly nitrogen heterocyclic such as quinolines, purine, pyrimidine, acidine, phenothiazines, bisbenzamides, pyrazolol, pyridine, benzothiazole and imidazolines Rakhi Rajput *et al.,* (**2012**)[70]**.**

7.1 Antileukemic activity

Raffa *et al.,* (**2004**)[71] synthesized 3-(3-Methylisoxazol-5-yl) and 3-(pyrimidin-2-yl)-2 styrylquinazolin-4(3H)-ones **(44 and 45)** by refluxing in acetic acid the corresponding 2-methylquinazolinones with the benzoic aldehyde for 12

h and tested for their in vitro antileukemic activity against L-1210 (murine leukemia), K-562 (human chronic myelogenous leukemia) and HL-60 (human leukemia) cell lines showing in some cases good activity.



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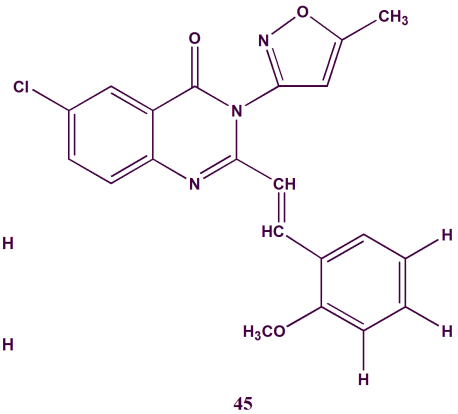
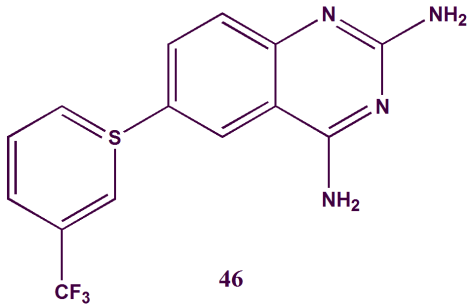


45

7.2 Antimalarial activity

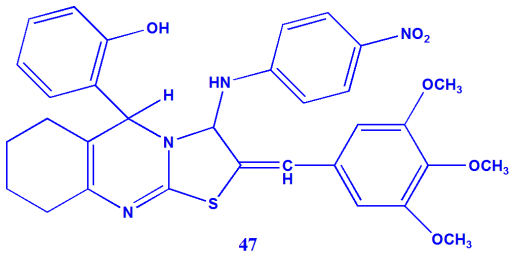
Werbel *et al.*, (**1987**)[72] synthesized a variety of analogues of 2, 4-diamino-6-[(aryl) thio] quinazolines with known antimalarial properties wherein the 4-amino group was replaced by hydrazine and hydroxyamino moieties and they found that such changes reduce markedly the antimalarial properties of this series. The compound **(46)** was tested against a normal drug-sensitive strain of Plasmodium berghei in mice by the parenteral route.



46

7.3 Antioxidant activity

Selvam *et al.*, (**2010**)[73] synthesized a series of novel thiazole quinazoline derivatives by condensation of different aromatic aldehydes with 4-nitro aniline and chemical structures of the synthesized compounds were confirmed by means of IR, ^{1}H-NMR, mass spectroscopy and elemental analyses and screened for antioxidant activity by DPPH radical assay, nitric oxide scavenging activity and hydrogen peroxide scavenging activity and reported that synthesized compounds **(47, 48 and 49)** were found to have the most potent anti-oxidant activity.



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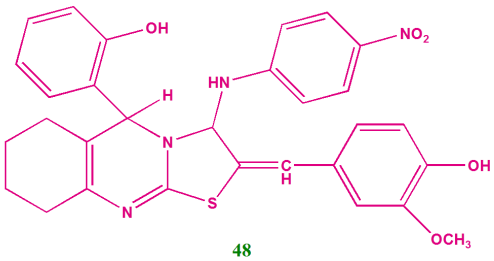

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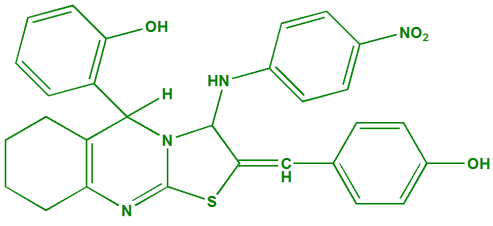
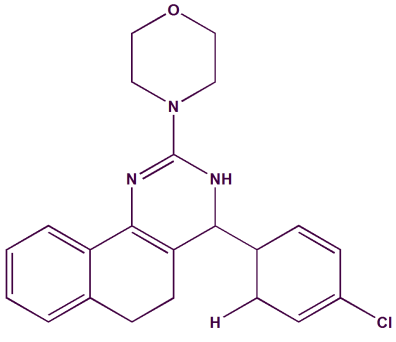


49

7.4 Antileishmanial activity

Agarwal KC *et al.*, (**2009**)[74] synthesized 4-(Substituted-benzylidine)-2-substituted-5, 6 dihydrobenzo[h]quinazoline and 4-(substitutedbenzylidine) - 2-substituted-3, 4, 5, 6 tetrahydrobenzo[h]quinazoline from 2-(substituted-

benzylidine)tetralone-1 and several substituted guanidine sulfates and evaluated for their in vitro antileishmanial activity and they reported that compounds **(50,51 and 52)** show promising antileishmanial activity against Leishmania donovani.



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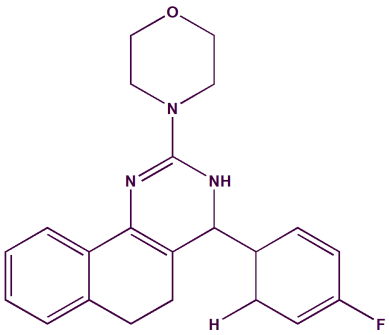

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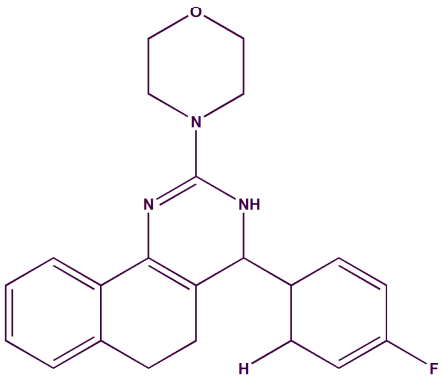
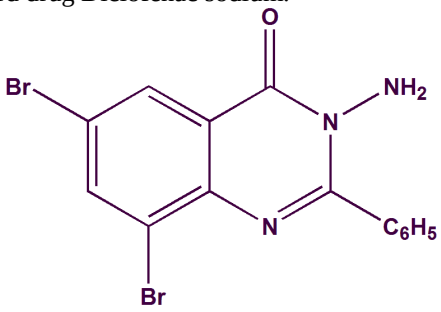


52

7.5 Analgesic activity

Hemlatha *et al.*, (**2011**)[75] synthesized a series of some novel 2, 3-disubstituted quinazolinone derivatives by condensing 2-methyl/2-phenyl/6-bromo-2-methyl/6-bromo-2-phenyl/6, 8-dibromo-2-methyl/ 6, 8-dibromo-2-phenyl benzoxazines with compounds containing amino group were confirmed by IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectral data and evaluated for their analgesic activity and they reported that compound **(53)** show promising analgesic activity compared to standard drug Diclofenac sodium.



53

CONCLUSION

The above mentions clearly shown that the structurally simple imidazole, benzimidazole, benzoxazole, tetrazole and quinazolinone ring plays an important role in medicinal chemistry and the related research has been being unusually active subjects. A large amount of work has been made toward imidazole, benzimidazole, benzoxazole, tetrazole and quinazolinone medicinal chemistry. Numerous outstanding achievements revealed that imidazole, benzimidazole, benzoxazole, tetrazole and quinazolinone compounds possess extensively potential application as medicinal drugs, diagnostic agents, and pathologic probes. In particular, a large number of imidazole, benzimidazole, benzoxazole, tetrazole and quinazolinone compounds as clinical anticancer, antibacterial, antifungal, antineuropathic, antihypertensive, antihistaminic, antiparasitic agents, and so on have been successfully developed, marketed, and extensively used in the clinic in preventing and treating various types of diseases with low toxicity, high bioavailability, and good biocompatibility and curative effects. An expanding effort from all over the world has been

directly focusing on imidazole, benzimidazole, benzoxazole, tetrazole and quinazolinone compounds for possible clinical application in the diagnosis and treatment of various types of diseases. Excitingly, an increasing number of imidazole, benzimidazole, benzoxazole, tetrazole and quinazolinone derivatives have been becoming clinical drug candidates in actively ongoing research and developments. All these have strongly suggested the infinite potentiality of imidazole, benzimidazole, benzoxazole, tetrazole and quinazolinone derivatives in medicinal field.

Convincingly, with the continuous efforts directly toward imidazole, benzimidazole, benzoxazole, benzothiazole, tetrazole and quinazolinone medicinal chemistry and the progress in other disciplines such as cell biology, molecular biology, pharmacology, and materials science. A growing number of imidazole, benzimidazole, benzoxazole, tetrazole and quinazolinone drugs with better efficacy, lower toxic and superior pharmacokinetic characteristics, and effective diagnostic agents and pathologic probes will be used in the clinic and make remarkable contributions for the protection of human health.

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