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Pharmacological Significance of Synthetic Heterocycles Scaffold: A Review

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Abstract: Heterocyclic chemistry offers an example for the lack of distinct demarcations; in fact, it pervades the plurality of the other chemical disciplines. Heterocycles are inextricably woven into the life processes. The vital interest of the pharmaceutical and agrochemical industries in heterocycles is often connected with their natural occurrence. Synthetic chemistry provides cornucopia of heterocyclic systems. More than 90% of new drugs contain heterocycles and the interface between chemistry and biology, at which so much new scientific insight, discovery and application is taking place is crossed by heterocyclic compounds. This review article covers the most active heterocycles that have shown considerable biological actions such as antibiotic, antifungal, anti-inflammatory, antiviral, anticancer, anticonvulsant, anthelmintic,antihistamine, antidepressant activities.

Key words: Heterocycles · Antibacterial · Antifungal · Pharmacological activities

INTRODUCTION

Two hundred years ago, the chemical science was an undivided field; around 1900 a division into inorganic, organic and physical chemistry became necessary. The increase of factual material enforced a progressive segmentation into sub disciplines. A map shows countries and regions neatly separated; similarly, the uninformed observer may regard chemistry as a side-by-side of numerous disciplines and specialties. The comparison is fallacious, however, because broad overlap is thwarting clear divisions.

Heterocycles form by far the largest of classical divisions of organic chemistry and are of immense importance biologically and industrially. The majority of pharmaceuticals and biologically active agrochemicals are heterocyclic while countless additives and modifiers used in industrial applications ranging from cosmetics, reprography, information storage and plastics are heterocyclic in nature. One striking structural features inherent to heterocycles, which continue to be exploited to great advantage by the drug industry, lies in their ability to manifest substituents around a core scaffold in defined three dimensional representations. For more than a century, heterocycles have constituted one the largest areas of research in organic chemistry. They have contributed to the development of society from a biological and industrial point of view as well as to the understanding of life processes and to the efforts to improve the quality of life. 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 electronics, biology, optics, pharmacology, material sciences and so on is very well known. Between them, sulfur and nitrogen-containing heterocyclic compounds have maintained the interest of researchers through decades of historical development of organic synthesis [1]. However, heterocycles with other heteroatoms such as oxygen [2], phosphorus [3] and selenium [4] also appears. Many natural drugs [5-8] such as papaverine, theobromine, quinine, emetine, theophylline, atropine, procaine, codeine, reserpine and morphine are heterocycles. Almost all the compounds we know as synthetic drugs such as diazepam, chlorpromazine, isoniazid, metronidazole, azidothymidine, barbiturates, antipyrine, captopril and methotrexate are also heterocycles. Some dyes (e.g. mauveine), luminophores, (e.g. acridine orange), pesticides (e.g. diazinon) and herbicides (e.g. paraquat) are also heterocyclic in nature. All these natural and synthetic heterocyclic compounds can and do participate in chemical reactions in the human body. Furthermore, all

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biological processes are chemical in nature. Such fundamental manifestations of life as the provision of energy, transmission of nerve impulses, sight, metabolism and the transfer of hereditary information are all based on chemical reactions involving the participation of many heterocyclic compounds, such as vitamins, enzymes, coenzymes, nucleic acids, ATP and serotonin [9]. Why does nature utilize heterocycles? The answer to this question is provided by the fact that heterocyles are able to get involved in an extraordinarily wide range of reaction types. Depending on the pH of the medium, they may behave as acids or bases, forming anions or cations. Some interact readily with electrophilic reagents, others with nucleophiles, yet others with both. Some are easily oxidized, but resist reduction, while others can be readily hydrogenated but are stable toward the action of oxidizing agents. Certain amphoteric heterocyclic systems simultaneously demonstrate all of the above-mentioned properties. The ability of many heterocycles to produce stable complexes with metal ions has great biochemical significance. The presence of different heteroatoms makes tautomerism ubiquitous in the heterocyclic series. Such versatile reactivity is linked to the electronic distributions in heterocyclic molecules. Evidently, all the natural products and the synthetic drugs mentioned above are good examples of nature's preference for heterocycles whose biological activity cannot be determined by one or a combination of two or three of the above mentioned properties.

Synthetic heterocycles have widespread therapeutic uses such as antibacterial, antifungal, antimycobacterial, trypanocidal, anti-HIV activity, antileishmanial agents, genotoxic, antitubercular, antimalarial, herbicidal, analgesic, antiinflammatory, muscle relaxants, anticonvulsant, anticancer and lipid peroxidation inhibitor, hypnotics, antidepressant, antitumoral, anthelmintic and insecticidal agents [10-16].

The are larger number of synthetic heterocyclic compounds with other important applications such as fungicides, herbicides, anticorrosive agents, photostabilizers, agrochemicals, dyestuff, copolymer,photographic developers, fluorescent whiteners, sensitizers, booster agent, antioxidant in rubber and flavouring agent [17-22].

Pyrimidine(cytosine, thymine and uracil) and purine (adenine and guanine) derivatives are monocyclic and bicyclic heterocycles with two and four nitrogen atoms, respectively. They are key components of the deoxyribonucleic acid (DNA) molecules and participate directly in the encoding of genetic information. They also pass information to the related ribonucleic acid (RNA) molecules that control, in protein synthesis, the sequence of amino acids [23-24]. The need for minute quantities of accessory dietary factors, the vitamins is well-known. Vitamins in the B group thiamine, folic acid, riboflavin, cyanocobalamine, are nitrogen-containing heterocycles [25] and function either as coenzymes or their precursors. Other vitamins such as ascorbic acid (vitamin C) [26] and α-tocopherol (vitamin E) are oxygen heterocycles[27].

The essential amino acid proline, histidine and tryptophan [28], photosynthesizing pigment chlorophyll; the oxygen transporting pigment haemoglobin [29], the hormones kinetin, heteroauxin, cytokinins [30], neurotransmitter serotonin, histamine respectively are successful application of heterocyclic compounds.

In conclusion, it can be questioned why it is specifically appropriate to emphasize the role of heterocycles, since analogies to the roles of other classes of organic compounds are easily found. In fact, dyes, luminophores, herbicides, pesticides and drugs do not necessarily have to be heterocyclic in structure. In a similar fashion there are many common features in chemistry and physics between such related compounds as pyrrole and aniline, or between pyridine and nitrobenzene. Nevertheless, nature selected the heterocycles pyrrole and pyridine and not the homocycles aniline and nitrobenzene, as the basis of most essential biological systems. We now know the reason for this: the introduction of a heteroatom into a cyclic compound imparts new properties. Heterocycles are chemically more flexible and better able to respond to the many demands of biochemical systems. The constantly accelerating rate of research and development in heterocyclic chemistry suggested that enormous numbers of heterocyclic systems are well known and this number is increasing very rapidly.

Heterocycles in the Service of Humankind

Antibiotics: The word "antibiotics" comes from the Greek anti ("against") and bios ("life"). Antibiotics are drugs that either destroy bacteria or prevent their reproduction. Antibiotics that kill bacteria are called "bactericidal" and the ones that stop the growth of bacteria are called "bacteriostatic".

Antibacterial antibiotics can be categorized based on their target specificity: "narrow-spectrum" antibiotics target particular types of bacteria, such as Gram-negative

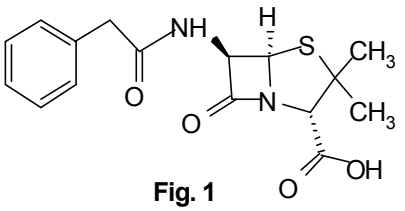


Fig. 1

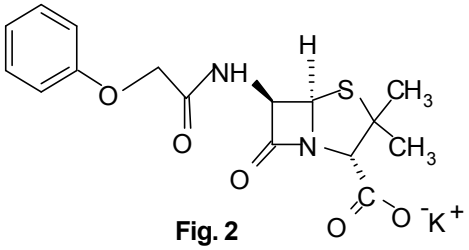


Fig. 2

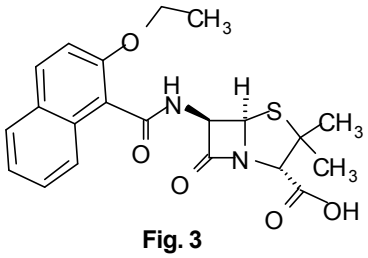


Fig. 3

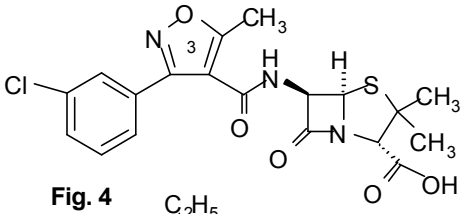


Fig. 4

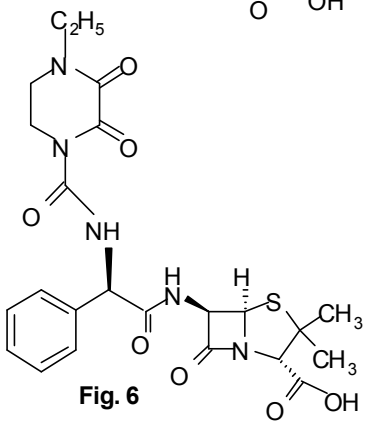


Fig. 6

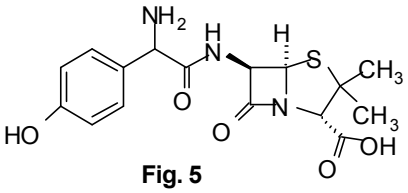


Fig. 5

or Gram-positive bacteria, while broad-spectrum antibiotics affect a wide range of bacteria. Antibiotics which target the bacterial cell wall [31] (penicillins, cephalosporins), or cell membrane [32] (polymixins), or interfere with essential bacterial enzymes (quinolones, sulfonamides) usually are bactericidal in nature. Those which target protein synthesis such as the aminoglycosides, macrolides and tetracyclines are usually bacteriostatic [33].

β-Lactam Antibiotics: β-lactam antibiotics are useful and frequently prescribed an antimicrobial agent that shares a common structure and this class includes penicillin G (Fig 1) and VK (Fig 2), which are active against susceptible gram–positive cocci. Penicillins work by binding to specific penicillin-binding proteins (PBPs) in the bacterial cell wall and inhibiting the final stage of bacterial cell wall synthesis, resulting in autolysis of the bacterial cells by autolysin enzymes.

Penicillinase-resistant penicillins such as nafcillin (Fig 3) and cloxaciilin (Fig 4) which are active against penicillinase-producing Staphylococcus aureus; Amoxicillin (Fig 5) and other agents with an improved gram negative spectrum, especially when combined with a β-lactamase inhibitors; and extended–spectrum penicillins with activity against Psuedomonas aeruginosa,such as piperacillin (Fig 6) are reported [34-37].

β-lactam antibiotics also include cephalosporin antibiotics [38-39], which are classified by generation: First generation cephalosporins includes cefradine (Fig 7) and cefadroxil (Fig 8) tend to be broad-spectrum antibiotics that are effective against gram-positive and gram-negative bacteria, including Staphylococcus, Streptococcus, Escherichia coli and Klebsiella pneumoniae; second generation cephalosporins includes cefaclor (Fig 9) and cefprozil (Fig 10), third generation agents ceftizoxime (Fig 11) and ceftriaxone (Fig 12) tend to be more effective against gram-negative bacterial species that are resistant to the first-generation cephalosporins. Second-generation cephalosporins have proven effective against gonorrhea, Haemophilus influenzae and the abscesses caused by *Bacteroides fragilis*; fourth generation cephalosporins includes cefepine (Fig. 13). They also have a greater resistance to beta-lactamases than the third-generation cephalosporins.

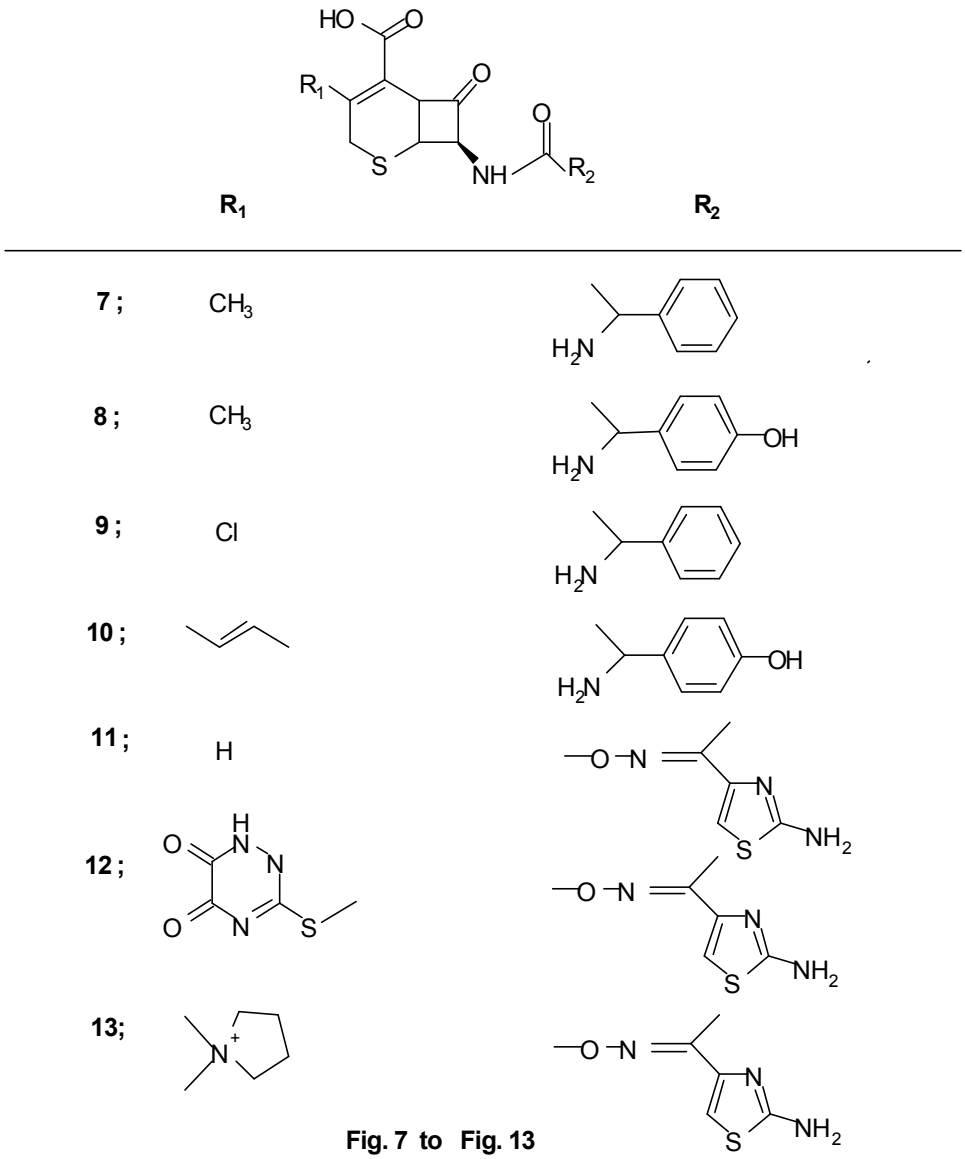


Fig. 7 to Fig. 13

Other β-Lactam Antibiotics: Important therapeutic agents with β-Lactam structure that are neither penicillins nor cephalosporins have been developed. Carbapenems such as Imipenem, meropenem and ertapenem (Fig 14) are β-lactam that contains β-lactam ring and a five membered ring system that differs from penicillins in being unsaturated and containing a carbon atom instead of the sulphur atom, have the broadest antimicrobial spectrum of any antibiotic,whereas the monobactams aztreonam (Fig 15) has gram-negative spectrum resembling that of the aminoglycosides [40, 41].

Clavulanic acid (Fig 16) produced by Streptomycin clavuligenus has a chemical structure similar to some β-lactam, e.g. penicillin. It has little or no intrinsic antibacterial activity of its own; instead, it is used to enhance the activity of antibiotics by blocking bacterial beta-lactamases. [42, 43].

Macrolide Antibiotics: Macrolides exert their antibiotic effect by binding irreversibly to the 50S subunit of bacterial ribosomes and they are thought to do this by preventing peptidyltransferase from adding the peptidyl attached to tRNA to the next amino acid as well as inhibiting ribosomal translocation during translation, the macrolides are a group of drugs whose activity stems from the presence of a *macrolide ring*, a large macrocyclic lactone ring to which one or more deoxy sugars, usually cladinose and desosamine, may be attached. The lactone rings are usually 14, 15 or 16-membered. Macrolides belong to the polyketide class of natural products.

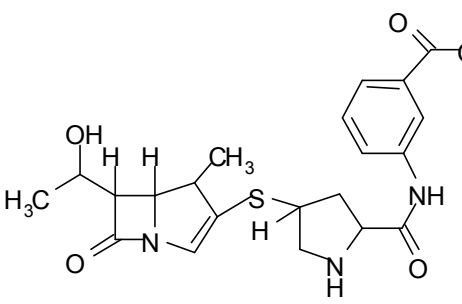


Fig. 14

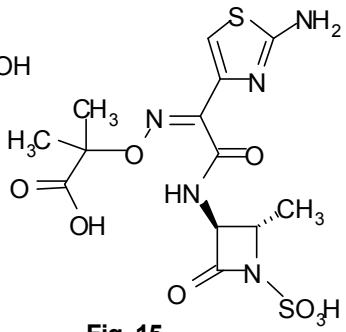


Fig. 15

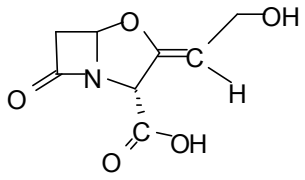


Fig. 16

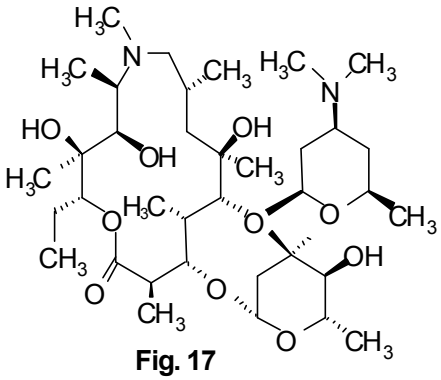


Fig. 17

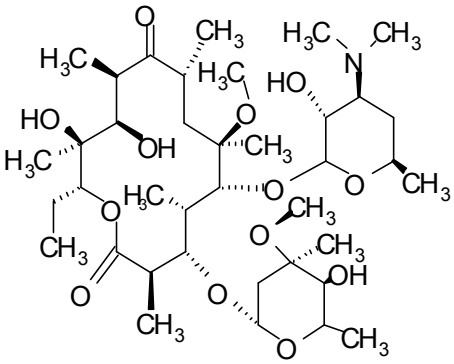


Fig. 18

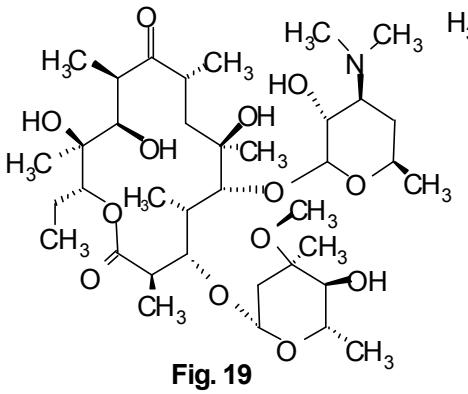


Fig. 19

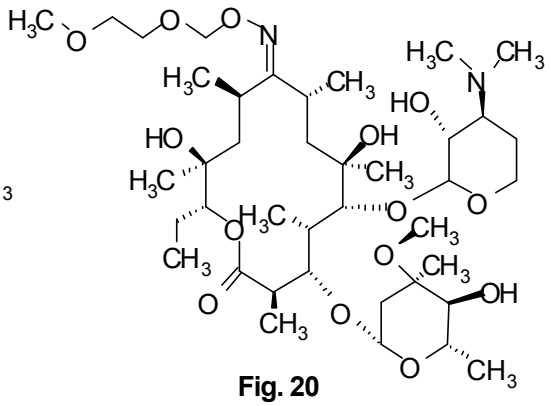


Fig. 20

Among the antibiotics [44-46] azithromycin (Fig 17), clarithromycin (Fig 18), erythromycin (Fig 19) and roxithromycin (Fig 20) are macrolide antibiotics.

Ketolides [47] (telithromycin) (Fig 21) dalfopristin (Fig 22), quinupristin (Fig 23) and linezolid (Fig 24) are other bacteriostatic protein synthesis inhibitors that binds the 50s ribosomal subunit [48,49]. Ketolides are derived from erythromycin by substituting the cladinose sugar with a keto-group and attaching a cyclic carbamate group in the lactone ring.

Lincomycin (Fig 25) is an antibiotic classified as a constituent of the lincosamide group which typically feature a 6,8-dideoxy-6-aminooctose lincosamine and has an antibacterial spectrum similar to macrolide. There is another lincosamide antibiotic called clindamycin which usually used to treat infections with anaerobic bacteria but can also be used to treat some protozoal diseases, such as malaria. It is a common topical treatment for acne and can be useful against some methicillin-resistant Staphylococcus aureus infections [50, 51].

Glycopeptides for example vancomycin (Fig 26) and teicoplanin (Fig 27) and lipopeptides for example daptomycin (Fig 28) inhibits the synthesis of the cell wall by binding with high affinity to the D-alanyl–D alanine terminus of cell wall precursor units and active only against gram positive bacteria [52, 53].

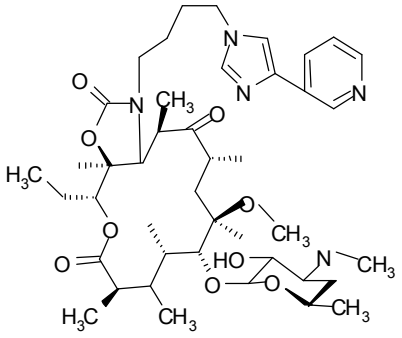


Fig. 21

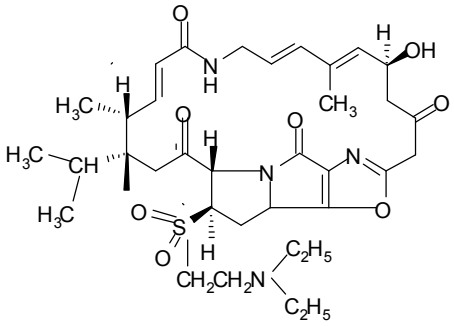
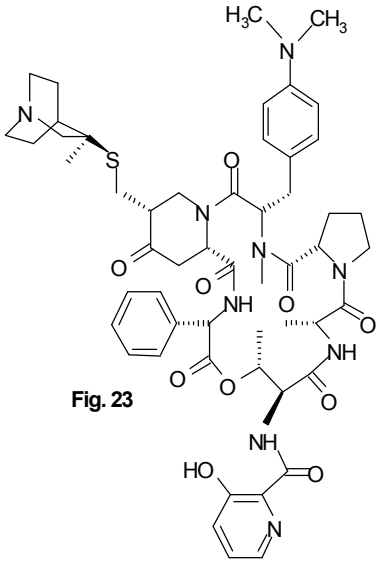


Fig. 22



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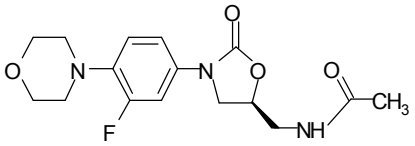


Fig. 24

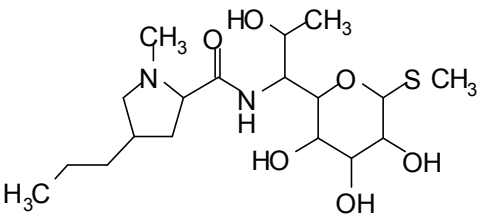


Fig. 25

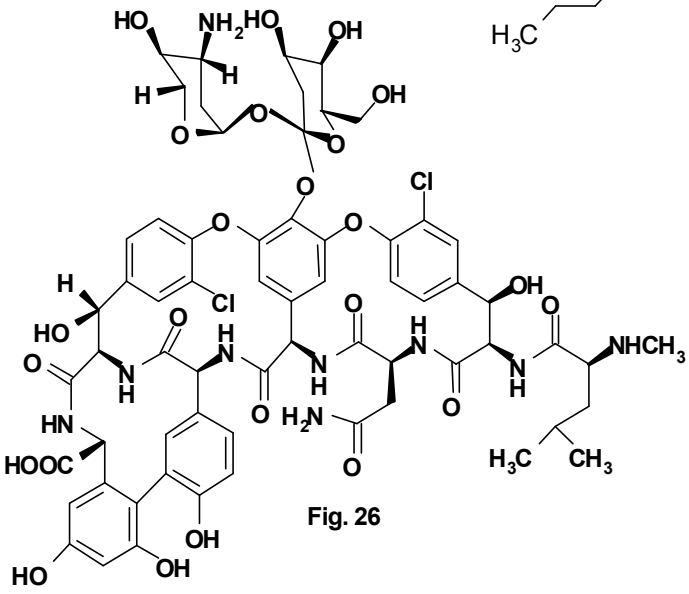


Fig. 26

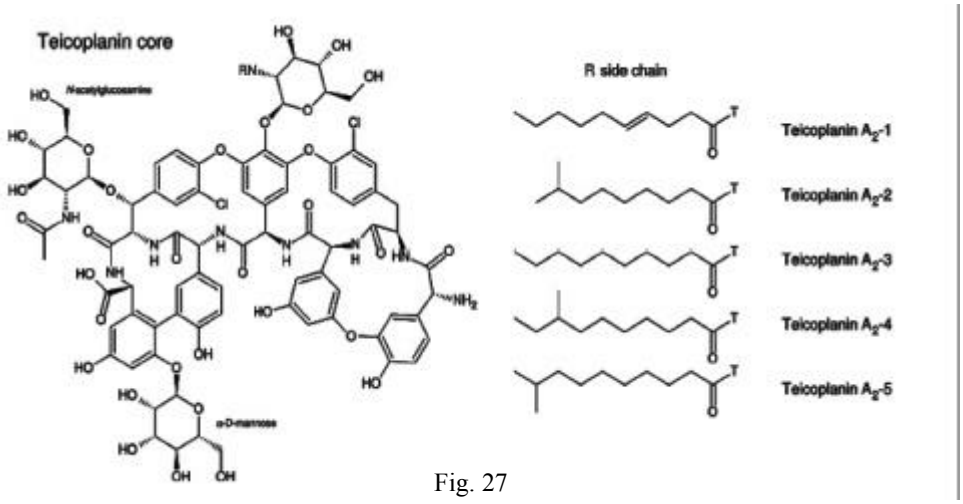


Fig. 27

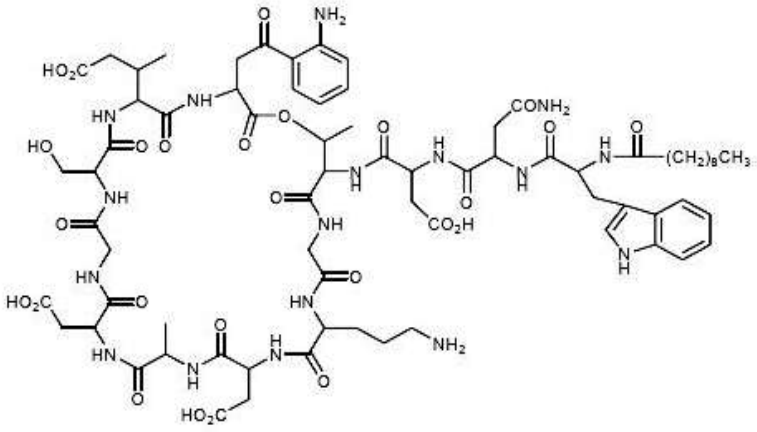


Fig. 28

Quinolone Antibiotics: The quinolones are a family of synthetic broad-spectrum antibiotics. The quinolones are divided into generations based on their antibacterial spectrum. The first generation of the quinolones begins with the introduction of nalidixic acid (Fig 29) in 1962 for treatment of urinary tract infections in humans [54]. The drugs most frequently prescribed today consist of ciprofloxacin (Fig 30), moxifloxacin (Fig 31), prulifloxacin (Fig 32), ofloxacin (Fig 33) and gemifloxacin (Fig 34).

Fluoroquinolones antibiotics inhibit the bacterial DNA gyrase or the topoisomerase IV enzyme, thereby inhibiting DNA replication and transcription. Quinolones can enter cells easily via porins and therefore are often used to treat intracellular pathogens such as Legionella pneumophila and Mycoplasma pneumoniae. [55].

Sulphonamide Antibiotics: Sulphonamides are synthetic antibiotics also called sulpha drug that act as competitive inhibitors of the enzyme dihydropteroate synthetase (DHPS). DHPS catalyses the coversion of para-aminobenzoate to dihydropteroate, a key step in folate synthesis [56]. Folate is necessary for the cells to synthesize nucleic acids and in its absence cells will be unable to divide. Hence the sulfonamide antibacterials exhibit a bacteriostatic rather than bactericidal effect. Sulphonamides do not affect mammalian cells by this mechanism because they require preformed folic acid and cannot synthesize it. Sulfonamides have broad spectrum activity against both gram-positive and gram-negative bacteria. Resistance to sulfonamide antibiotics is also common and they are frequently used in combination with trimethoprim which blocks two steps in folic acid metabolism and thus helps to prevent the emergence of strains of bacteria resistant to sulfa drugs. These compounds include sulphadiazine (Fig 35) sulphamethazine (Fig 36), sulphamethoxazole (Fig 37), sulphamethizole (Fig 38), sulphathiazole (Fig 39) and sulfafurazole (Fig 40). They have a common core chemical structure, p-aminobenzenesulphonamide [57-59].

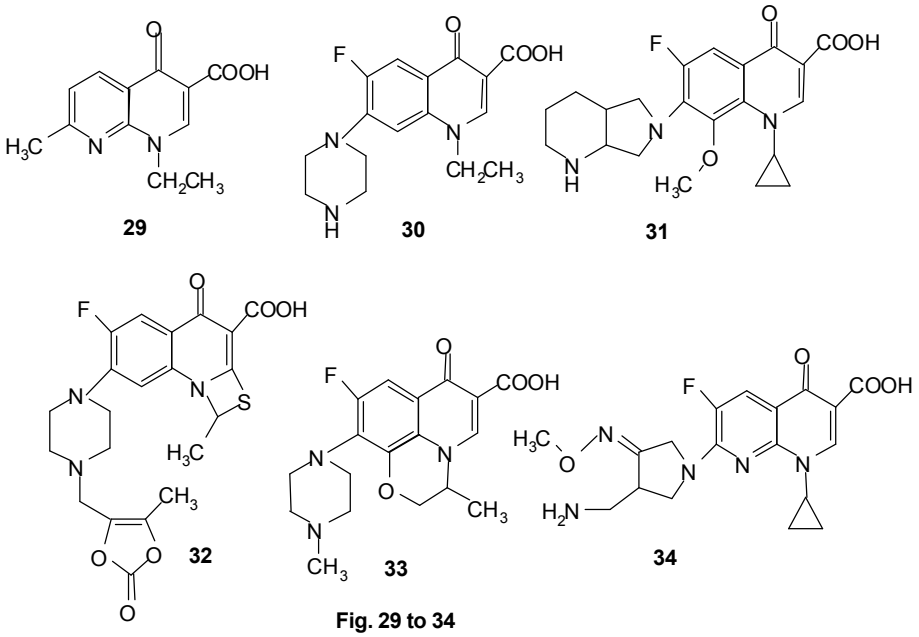


Fig. 29 to 34

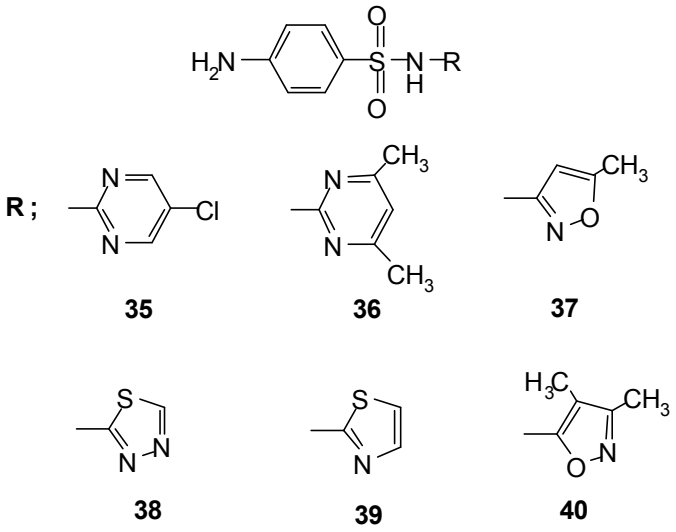


Fig.35 to 40

Antiviral Drugs: Antiviral drugs are a class of medication used specifically for treating viral infections. Most of the antiviral now available are designed to deal with HIV, herpes viruses, hepatitis B and C viruses which can cause liver cancer and influenza A and B viruses. Ritonavir (Fig 41) and nelfinavir (Fig 42) are antiretroviral drug from the protease inhibitor class used to treat HIV infection and AIDS [60, 61].

Nevirapine (Fig 43) and delavirdine (Fig 44) are non-nucleoside reverse transcriptase inhibitor used to treat HIV-1 infection and AIDS [62, 63].

Ribavirin (Fig 45) is a trizole carboxamide member of the nucleoside antimetabolite drugs that interfere with duplication of viral genetic material [64, 65].

Antifungal Drug: An antifungal drug is a medication used to treat fungal infections such as athlete's foot, ringworm, candidiasis, serious systemic infections such as cryptococcal meningitis and others. The azole antifungals include two broad classes, imidazoles and triazoles which inhibit the cytochrome P 450 - dependent enzyme 14-α-steroldemethylase. This enzyme converts lanosterol to ergosterol and is required in fungal cell

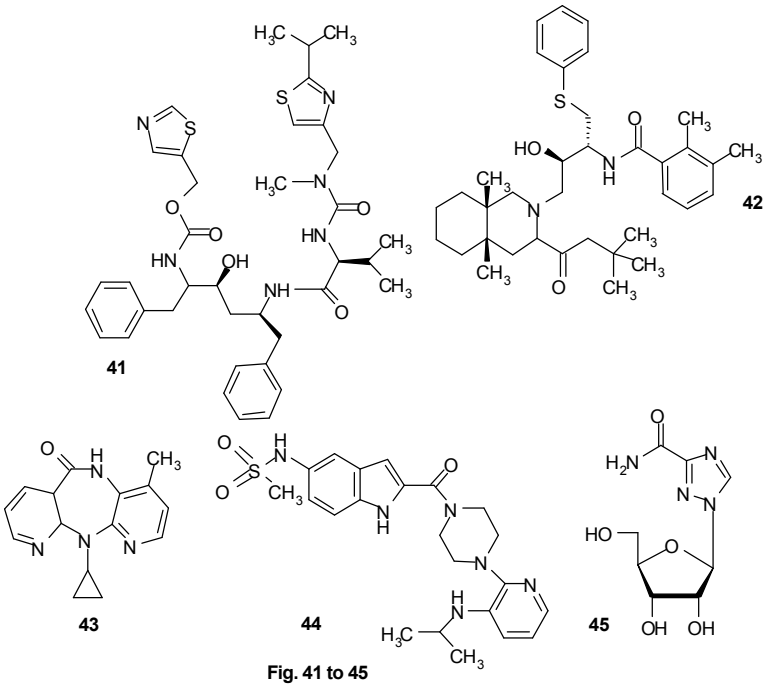


Fig. 41 to 45

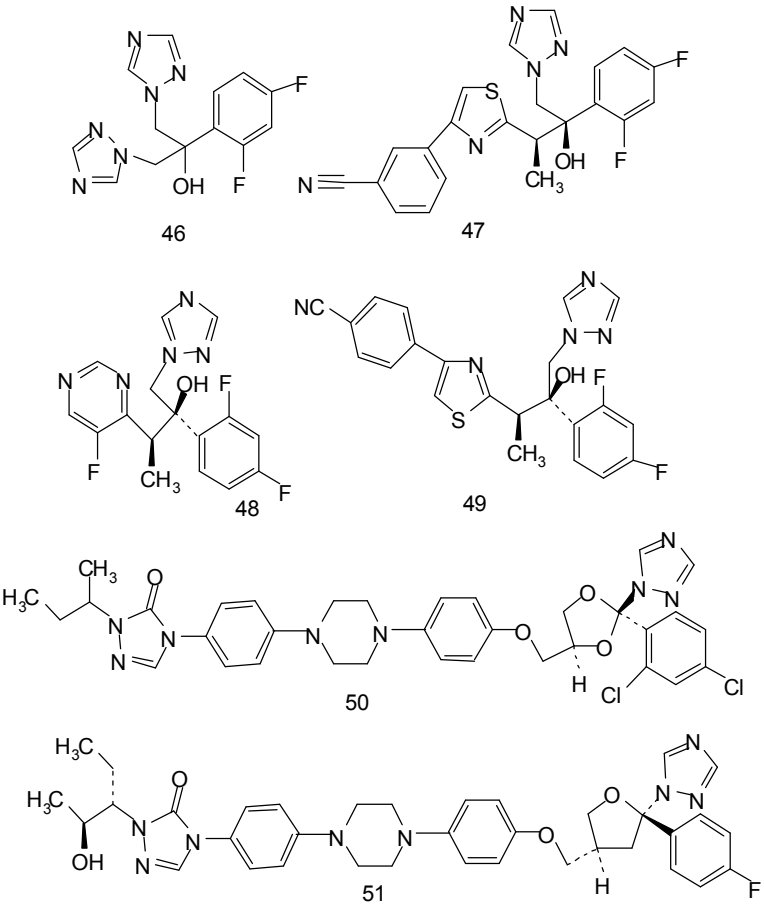


Fig. 46 to 51

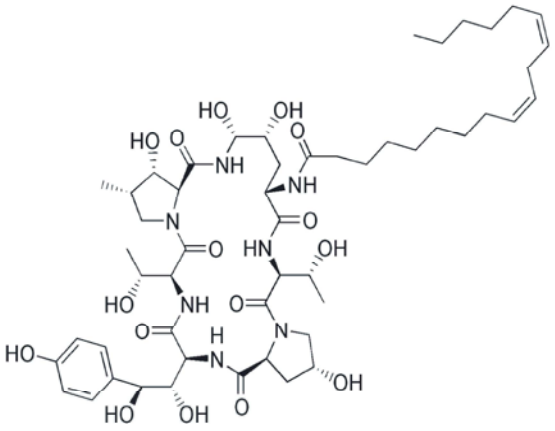


Fig. 52

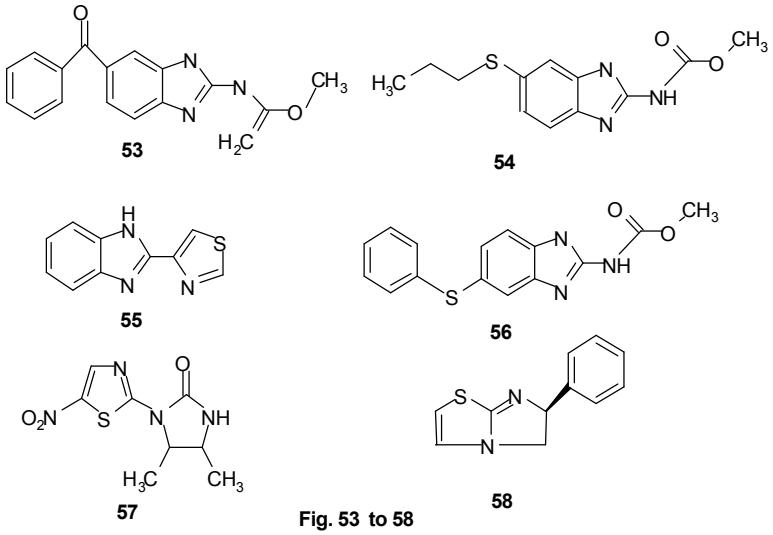


Fig. 53 to 58

membrane synthesis [66]. These drugs also block steroid synthesis in humans and thus inhibiting growth of fungi. Several heterocyclic analogues of trizole [67-71] used as antifungal are fluconazole (Fig 46), isavuconazole (Fig 47), voriconazole (Fig 48), ravuconazole (Fig 49) itraconazole (Fig 50) and posaconazole (Fig 51).

Echinocandin [72, 73] are a new and unique class of antifungal agents that act on the fungal cell wall by way of noncompetitive inhibition of the synthesis of 1,3-glucans.Caspofungin, micafungin, pneumocandins, cilofungin and anidulafungin belongs to this class. Echinocandin B (Fig 52) consists of a cyclic hexapeptide whose N-terminus is acylated with linoleic acid.

Antihelmintics: Infections with parasitic helminthes and protozoa are important causes of morbidity and mortality worldwide. Anthelminthics can act by causing narcosis or paralysis of worm, or by damaging its cuticle, leading to partial digestion or to ejection by immune mechanism. Mebendazole (Fig 53), albendazole (Fig 54), thiabendazole (Fig 55) and fenbendazole (Fig 56) are broad spectrum agents and constitute one of main groups of antihelmintics used clinically [74-76].

The thiazole derivatives niridazole (Fig 57) and levamisole (Fig 58) are used as antihelmintic drugs [77, 78].

Anticonvulsants: The anticonvulsants are a diverse group of pharmaceuticals used in the treatment of epileptic seizures. Anticonvulsants are also increasingly being used in the treatment of bipolar disorder, since many seem to act as mood stabilizers [79].

The heterocyclic compounds mostly used as anticonvulsants are barbexaclone (Fig 59), phenobarbital (Fig 60) nimetazepam (Fig 61), lorazepam (Fig 62). Oxcarbazepine (Fig 63) and rufinamide (Fig 64) are carboxamide type anticonvulsant widely used for the control generalized myoclonic seizures [80-85].

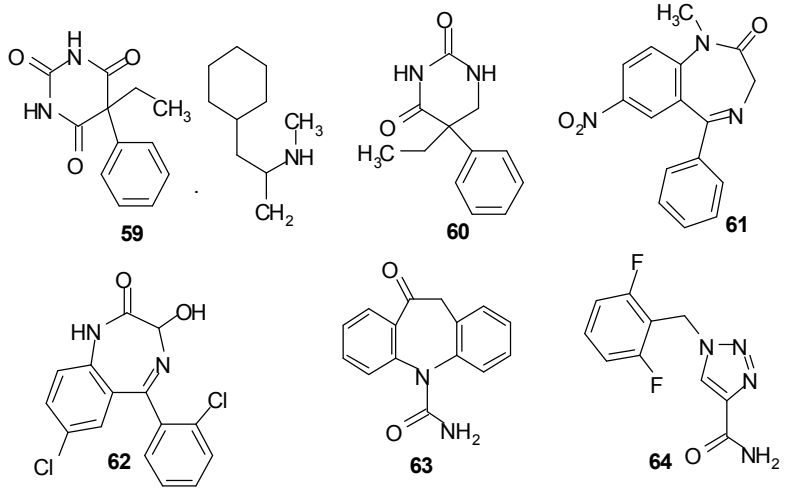


Fig. 59 to 64

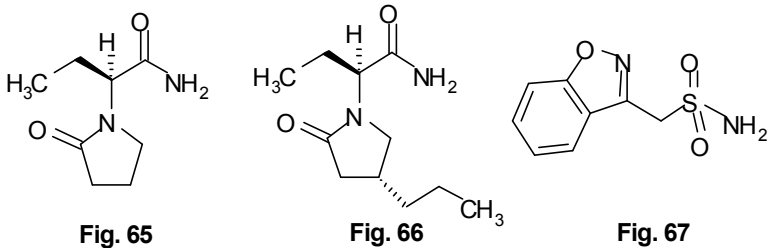


Fig. 65 Fig. 66 Fig. 67

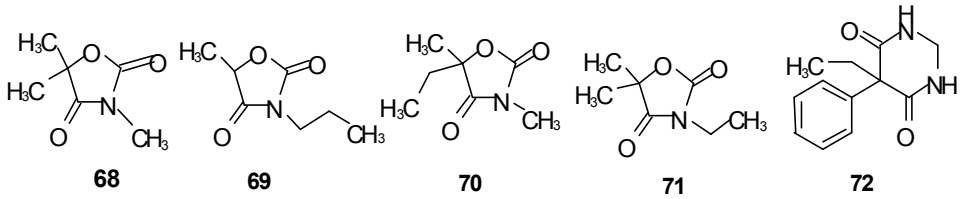


Fig. 68 to 72

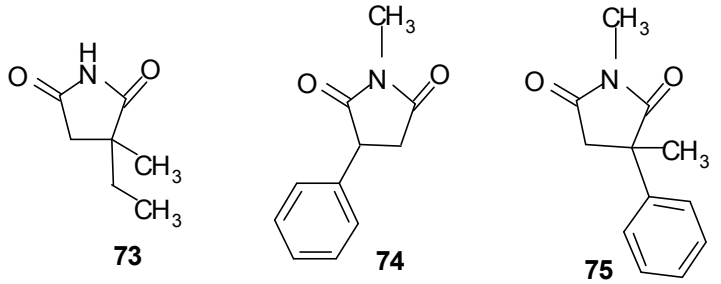
The pyrrolidines [86] derivatives such as levetiracetam (Fig 65) and brivaracetam (Fig 66) are used in epilepsy. Levetiracetam has potential benefits for other psychiatric and neurologic conditions such as tourette syndrome, autism and anxiety disorder. Zonisamide (Fig 67) is a sulfonamide anticonvulsant approved for use as an adjunctive therapy in adults with partial-onset seizures [87].

Oxazolidine-2, 4-diones which are used in petitmal epilepsy [88], includes troxidone (Fig 68), aloxidone, (Fig 69), paramethadione (Fig 70) and ethadione (Fig 71). Primidone (Fig 72) is a pyrimidinedione class anticonvulsant which is used to treat the disorder of movement such as tremor [89].

The succinimide derivatives [90] such as ethosuximide (Fig 73) are one of the best drugs for petitmal epilepsy. Other succinimides used are phensuximide (Fig 74) and methsuximide (Fig 75). New anticonvulsants lamotrigine (Fig 76) was approved in late 1994 thought to act by blockade of sodium channels; useful in partial seizures and also in primarily generalised seizures. Tiagabine (Fig 77) is an anticonvulsive medication which enhanced the activity of gamma aminobutyric acid, the major inhibitory neurotransmitter in the central nervous system [91].

Antipyretics and Non-steroidal Antiinflammatory Drugs: Non-steroidal antiinflammatory drugs are the drugs with analgesic, antipyretic and, in higher doses, with antiinflammatory effects. The term "non-steroidal" is used to distinguish these drugs from steroids which have a similar eicosanoid-depressing antiinflammatory action.

The NSAIDs covered in this section include pyrazolone derivatives, [92,93] phenazone (Fig 78), metamizole (Fig 79),aminophenazone (Fig 80), phenyl butazone (Fig 81) and apazone (Fig 82). Most NSAIDs act



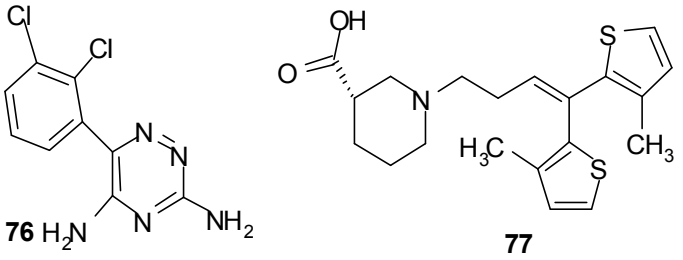


Fig.73 to 77

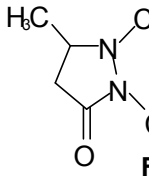


Fig. 78

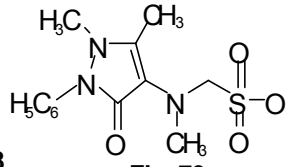


Fig. 79

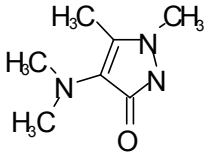


Fig. 80

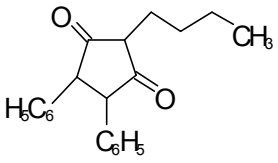


Fig. 81

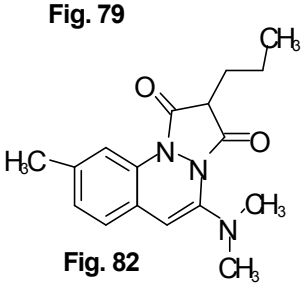


Fig. 82

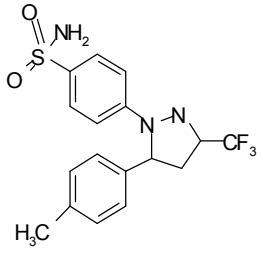


Fig. 83

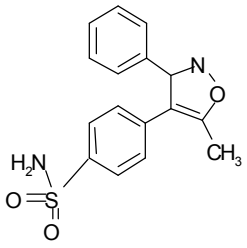


Fig. 84

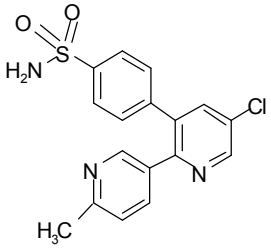


Fig. 85

as non-selective inhibitors of the enzyme cyclooxygenase, inhibiting both the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes. Cyclooxygenase catalyzes the formation of prostaglandins act as messenger molecules in the process of inflammation [94].

Celecoxib(Fig 83), valdecoxib (Fig 84), etoricoxib (Fig 85) are licensed for use in osteoarthritis, rheumatoid arthritis, acute pain, painful menstruation and menstrual symptoms and to reduce the number of colon and rectal polyps in patients with familiar adenomatous polyposis [95].

Indole derivatives [96] were examined as antiinflammatory agents because of speculation of the very potent drug indomethacin (Fig 86). A number of simpler aryl and heteroaryl-acetic acid and propionic acid have been introduced as nonsteroidal antiinflammatory

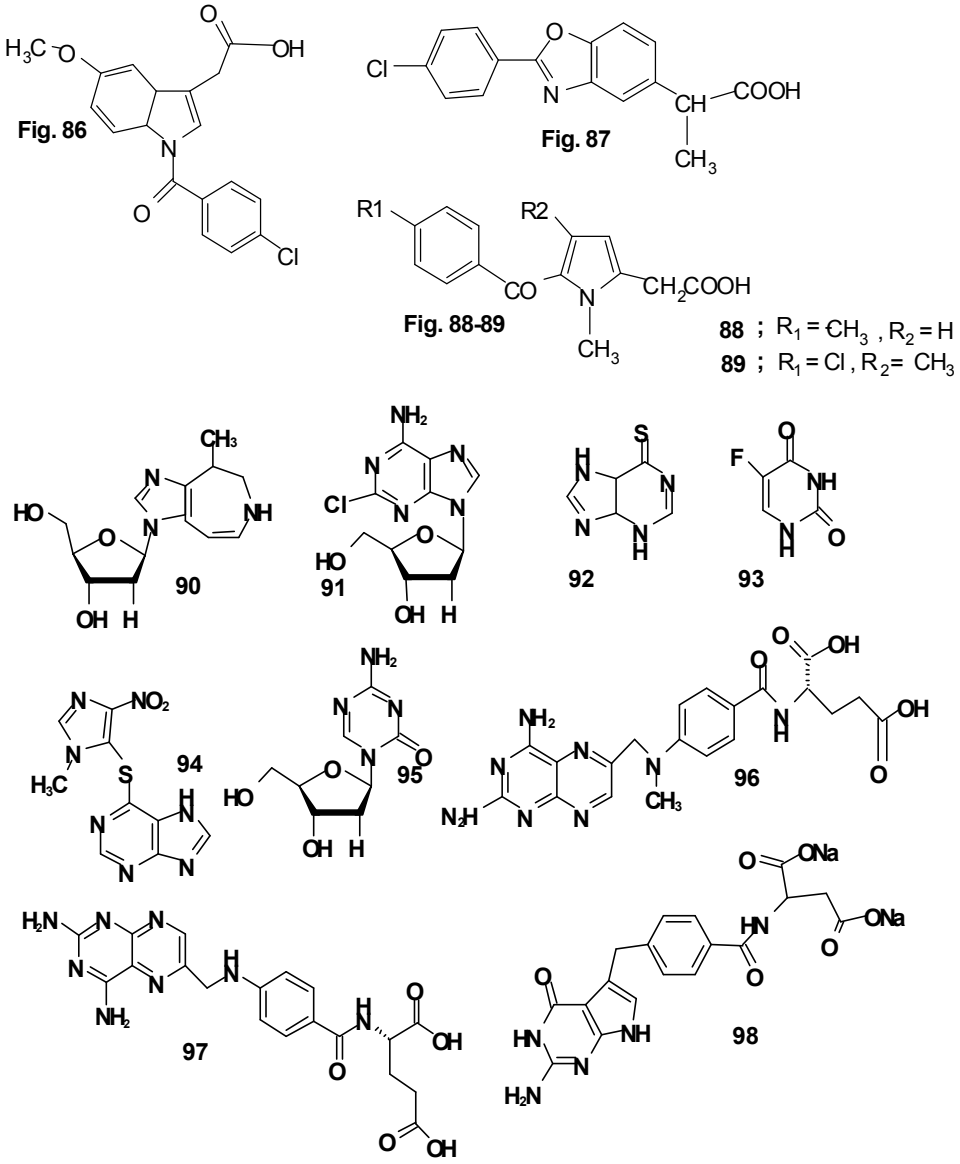


Fig. 90 to 98

agents. They include benoxaprofen (Fig 87), tolmetin (Fig 88) and zomepirac (Fig 89).They are used primarily to reduce hormones that cause pain, swelling, tenderness and stiffness in conditions such as osteoarthritis and rheumatoid arthritis, including juvenile rheumatoid arthritis [97].

Cytostatic Drugs: Cytostatic drugs, also known as antineoplastic agents, are the pharmaceutical used to treat various forms of cancer. Some cytostatic drugs are also used to treat autoimmune diseases and to suppress transplant rejections. There are a number of classes of cytostatic drugs such as alkylating agents, anti-metabolites, alkaloids and antitumor antibiotics. The majority of these drugs interfere with mitosis (cell division) to selectively kill fast growing tumor cell through a number of mechanisms such as inhibition of DNA synthesis. Cytostatic drugs are cytotoxic by nature as well as potentially carcinogenic and genotoxic. The cytostatic drugs reviewed here include three antimetabolites: (i) Purine analogues-pentostatin (Fig 90), cladridine (Fig 91) and mercaptopurine(Fig 92) mimics the nucleoside adenosine and thus inhibits the enzyme adenosine deaminase, interfering with the cell's ability to process DNA [98] (ii) Pyrimidine analogues [99] -5-fluorouracil (Fig 93), azathioprine (Fig 94) and azacitidine (Fig 95) and (iii) Antifolates [100]-methotrexate, (Fig 96) aminopterin (Fig 97)and pemetrexed (Fig 98).

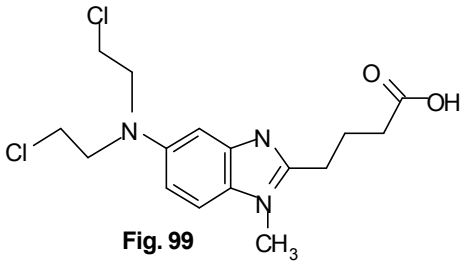


Fig. 99

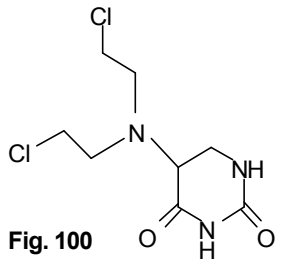


Fig. 100

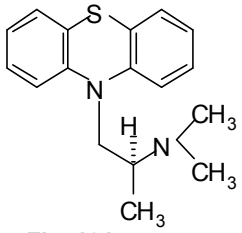


Fig. 101

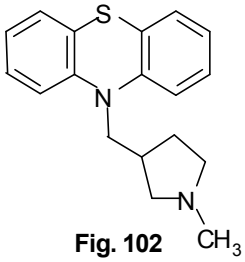


Fig. 102

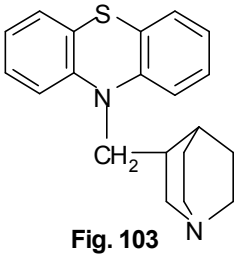


Fig. 103

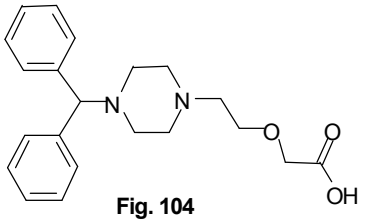


Fig. 104

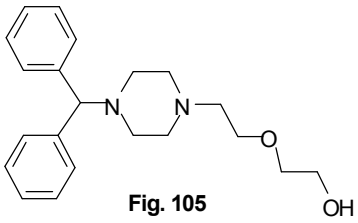


Fig. 105

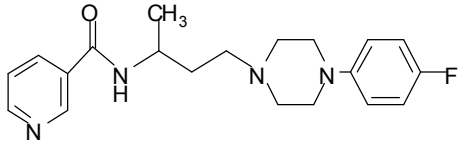


Fig. 106

Alkylating antineoplastic [101] agents includes nitrogen mustards, bendamustine (Fig 99) and uramustine (Fig 100). As the name suggests, alkylating agents are cytostatic drugs capable to covalently modify electronegative groups of DNA and thus interfere DNA replication in tumor cell [102].

Anti-Histamine: Antihistamine can be used to describe any histamine antagonist that act upon the H_1 histamine receptor. It has been discovered that these H_1-antihistamines are actually inverse agonists at the histamine H_1-receptor and are used to treat urticaria, anaphylaxis, asthma and allergic rhinitis [103]. The heterocyclic compounds most used as histamine antagonist are phenothiazine derivatives, promethazine (Fig 101), methdilazine (Fig 102) and mequitazine (Fig 103) [104, 105].

Piperazine analogues such as levocetirizine (Fig 104), hydroxyzine (Fig 105) and niaprazine (Fig 106) act as a sedating antihistamine [106, 107].

Heterocyclic analogues include diphenylpyraline (Fig 107),clemastine (Fig 108) and meclizine (Fig 109) are potent antihistamines with antiemetic activity useful in the treatment of motion sickness [108].

Chlorphenramine (Fig 110), desloratadine (Fig 111) azatadine (Fig 112) are used in the prevention of the symptoms of allergic conditions such as rhinitis and urticaria [109].

Cyproheptadine (Fig 113) which is also a serotonin antagonist, used as an antipruritic and antihistaminic. It has also been used in the treatment of pituitary-dependent hyperadrenocorticism. Ketotifen (Fig 114) and clobenzepam (Fig 115) are prophylactic agent to be used medication in the chronic treatment of mild atopic asthmatic children [110].

Zolamine (Fig 116), thonzyl amine (Fig 117), methapyrilene (Fig 118), chloroten (Fig 119) and nydiamine (Fig 120) are useful as an antihistamine as well as a topical local anaesthetic [111].

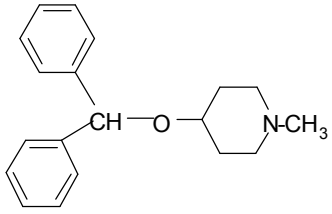


Fig. 107

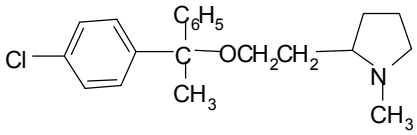


Fig. 108

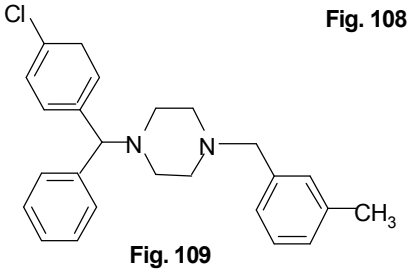


Fig. 109

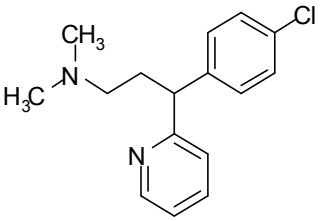


Fig. 110

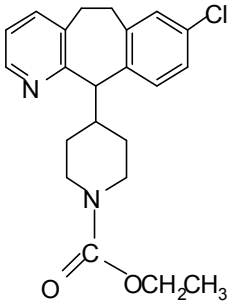


Fig. 111

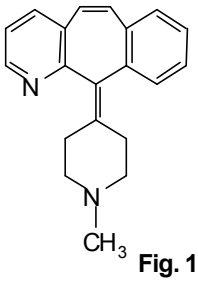


Fig. 112

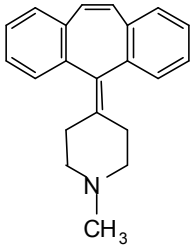


Fig. 113

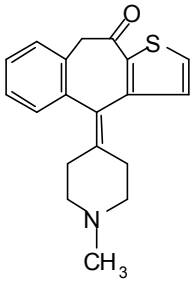


Fig. 114

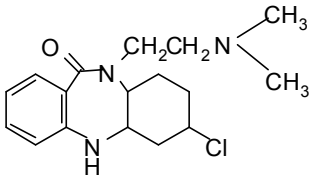
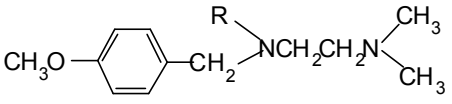
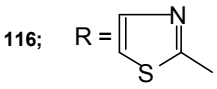


Fig. 115





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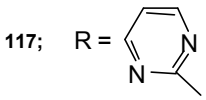

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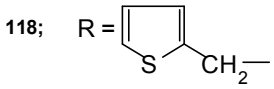

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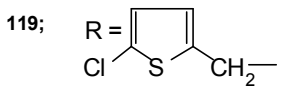

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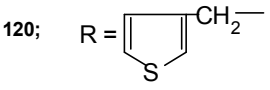

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Fig. 116 to Fig. 120

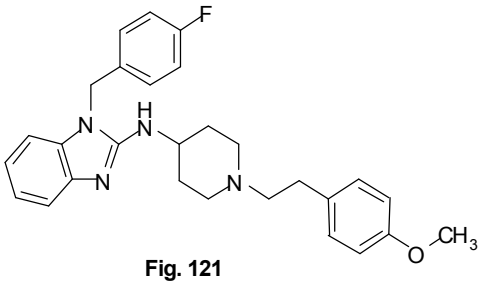


Fig. 121

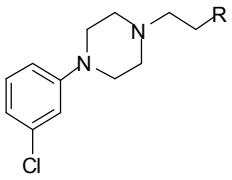
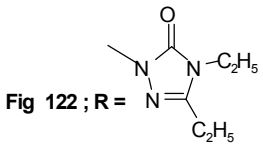


Fig 122 ; R =



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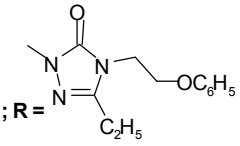
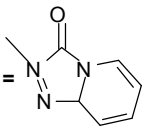


Fig 124 ; R =



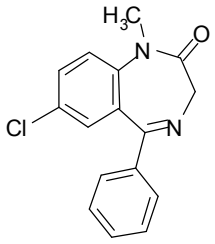


Fig. 125

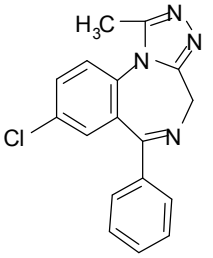


Fig. 126

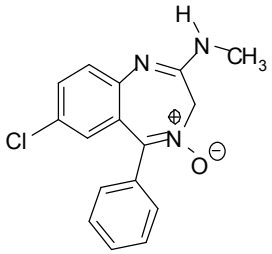


Fig. 127

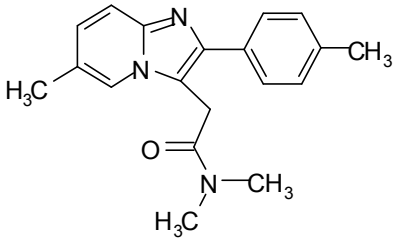


Fig. 128

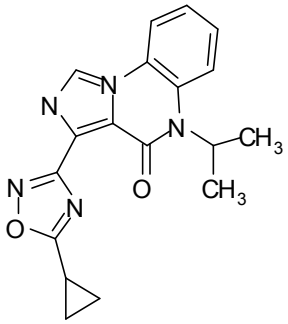


Fig. 129

Astemizole (Fig 121) is a histamine H_1-receptor antagonist. It is structurally similar to terfenadine and haloperidol possessing anticholinergic and antipruritic effects [112].

Psychoactive Drug: A psychoactive drug or psychotropic substance is a chemical substance that acts primarily upon the central nervous system where it alters brain function, resulting in temporary changes in perception, mood, consciousness and behavior. There are five major classes of psychiatric medications: antidepressants, anxiolytics, stimulants, antipsychotic and depressants. The chlorophenylpiperazine derivative etoperidone (Fig 122), nefazodone (Fig 123) and trazodone (Fig 124) are effective antidepressant active compound and acts primarily as a potent antagonist at the 5-HT_2 receptors. [113].

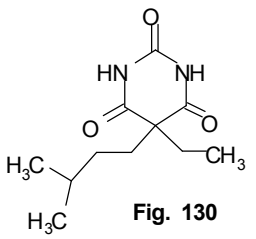


Fig. 130

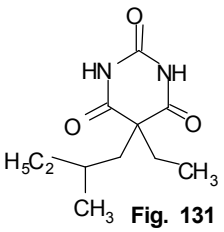


Fig. 131

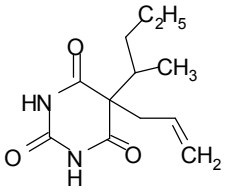


Fig. 132

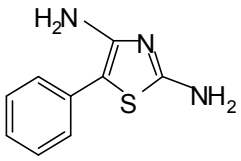


Fig. 133

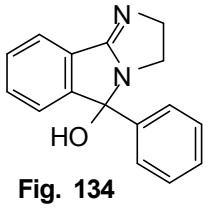


Fig. 134

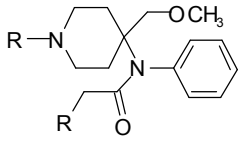


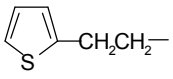
Fig 135; R = 

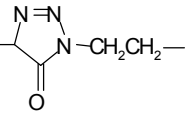
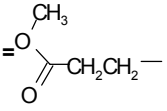
Fig 136; R = 

Fig 137; R = 

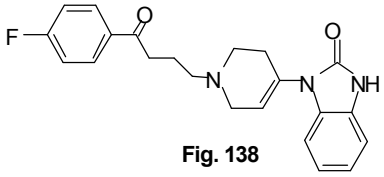


Fig. 138

Anxiolytics are generally divided into two groups, benzodiazepines and non-benzodiazepines. Benzodiazepines include diazepam (Fig 125), alprazolam (Fig 126), chlordiazepoxide (Fig 127) etc. possesses anxiolytic, anticonvulsant, hypnotic, sedative anskeletal muscle relaxant properties [114].

Non-benzodiazepines include zolpidem (Fig 128) and panadiplon (Fig 129) with anxiolytic properties and relatively little sedative or amnestic effect. [115].

Amobarbital (Fig 130), pentobarbital (Fig 131) and secobarbital (Fig 132) are barbiturate derivatives have sedative-hypnotic and analgesic properties.

Amiphenazole (Fig 133) and mazindol (Fig 134) are effective antidepressant active compound [116].

Sufentanil (Fig 135), alfentanil (Fig 136) and remifentanil (Fig 137) have properties of sedation and this makes it a good analgesic component of anaesthetic regimen during surgery [117].

Droperidol (Fig 138) is an antidopaminergic drug used as an antiemetic and antipsychotic [118]. Droperidol is also often used for neuroleptanalgesic anesthesia and sedation in intensive-care treatment.

Antihypertensive Drugs: The control of blood pressure requires a constant adjustment of cardiac output and peripheral vascular resistance. Antihypertensive Drugs are a class of drugs that are used in medicine and pharmacology to treat hypertension [119].

Chlorothiazide (Fig 139), flumethiazide (Fig 140), trichloromethiazide (Fig 141) and polythiazide (142) are diuretic drug of the thiazide class that acts by inhibiting the kidneys' ability to retain water [120]. This reduces the volume of the blood, decreasing blood return to the heart and thus cardiac output is believed to lower peripheral vascular resistance. Indapamide (Fig 143) and furosemide (Fig 144) are non-thiazide sulphonamide diuretic drug which are generally used in the treatment of hypertension as well as decompensate cardiac failure [121, 122].

Merbaphen (Fig 145) also had a strong diuretic property [123].

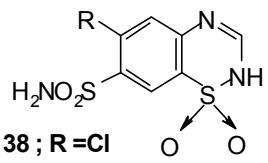
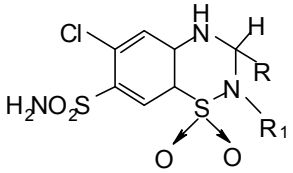


Fig. 138 ; R =Cl

Fig. 139 ; R =CF_3



141; R = -$CHCl_2$, R_1 = -H

142; R = -$CH_2SCH_2CF_3$: R_1 = - CH_3

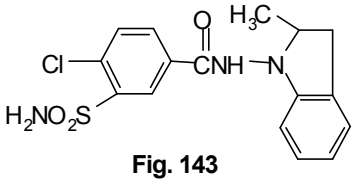


Fig. 143

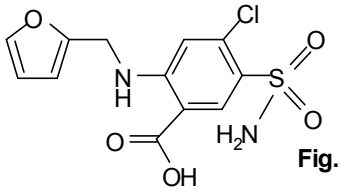


Fig. 144

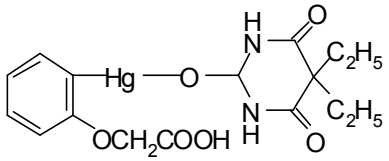


Fig. 145

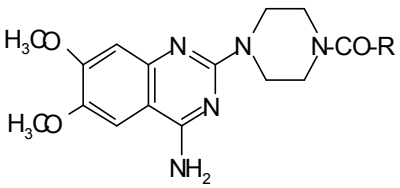


Fig. 143 ; R=

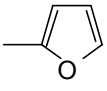
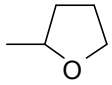


Fig. 144 ; R=



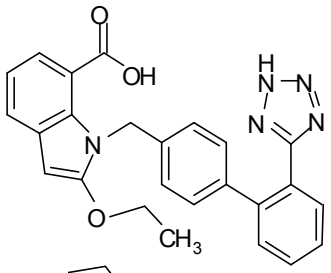


Fig. 148

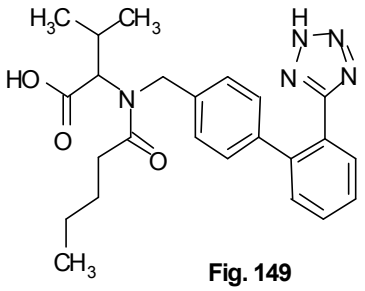


Fig. 149

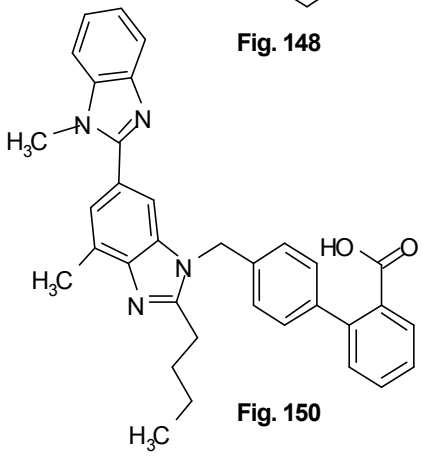


Fig. 150

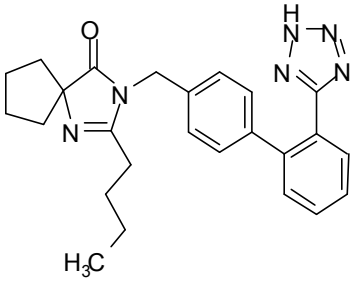


Fig. 151

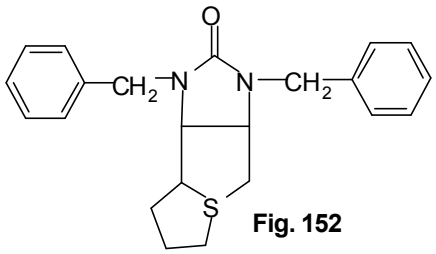


Fig. 152

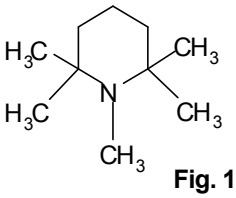


Fig. 153

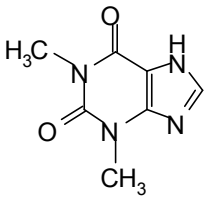


Fig. 154

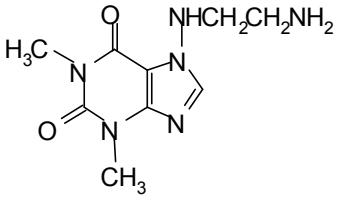


Fig. 155

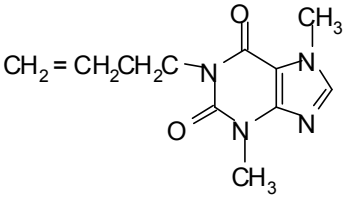


Fig. 156

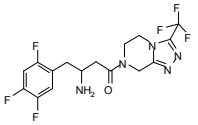
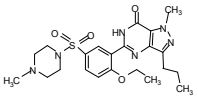
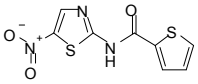
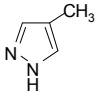
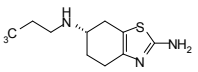
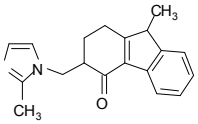
Prazosin (Fig 146) and terazosin (Fig 147) belongs to the class of alpha-adrenergic blockers which lower blood pressure by relaxing blood vessels [124].

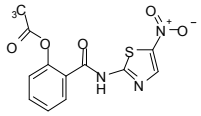
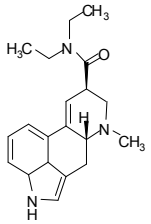
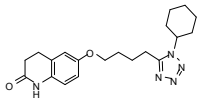
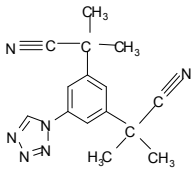
Candesartan (Fig 148), telmisartan (Fig 149), valsartan (Fig 150) and irbesartan (Fig 151) are an angiotensin II receptor antagonist used for the treatment of high blood pressure [125].

Trimethaphan (arfonad) (Fig 152) and pempidine (Fig 153) are reported to have ganglionic blockers with antihypertensive properties [126].

Theophylline (Fig 154) is the most widely used though generally as a derivative for example amino phylline (Fig 155) and theobryl (Fig 156) are soluble derivative of theobromine and are more powerful diuretic than theophyline [127].

Pharmacological Activity of Some Clinically Used Heterocyles

S. No.	Name of drug	Activity	Chemical structure
1.	Sitagliptin	Antidiabetic	
2.	Sildenafil	Erectile dysfunction	
3.	Tenonitrozole	Antiprotozoal	
4.	Fomepizole	Antidote	
5.	Pramipexole	Antiparkinson	
6.	Ondansetron	Antiemetic	

7.	Nitazoxanide	Antidiarrhoeal	
8.	Lysergic acid diethylamide	Psychedelic drug	
9.	Cilostazol	Antiplatelet drug	
10.	Anastrozole	Aromatase inhibitor	

CONCLUSION

The heterocyles nucleus is one of the most important and well known heterocycles which is a common and integral feature of a variety of natural products and medicinal agents. Heterocyles nucleus is present as a core structural component in an array of drug categories such as antimicrobial, anti-inflammatory, analgesic, antiepileptic, antiviral, antineoplastic, antihypertensive, antimalarial, local anaesthetic, antianxiety, antidepressant, antihistaminic, antioxidant, antitubercular, anti-Parkinson's, antidiabetic, antiobesity and immunomodulatory agents, etc.This review reflects the contribution of heterocyles to the development of society from a biological point of view as well as to the understanding of life processes and to the efforts to improve the quality of life. 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. 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. Between them, sulfur and nitrogen-containing heterocyclic compounds have maintained the interest of researchers through decades of historical development of organic synthesis. The grounds of this interest were their biological activities and unique structures that led to several applications in different areas of pharmaceutical and agrochemical research or, more recently, in material sciences. The present paper is an attempt to review the pharmacological activities reported for heterocyles in the current literature with an update of recent research findings on this nuclei.

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