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A REVIEW ON NOVEL APPROCHES OF HETEROCYCLIC COMPOUNDS

Dr. Debopratim Dasgupta, Kamallochan Barman*

Student, GIPS, Guwahati Assam India 781346.

***Corresponding Author: Kamallochan Barman**
Student, GIPS, Guwahati Assam India 781346.

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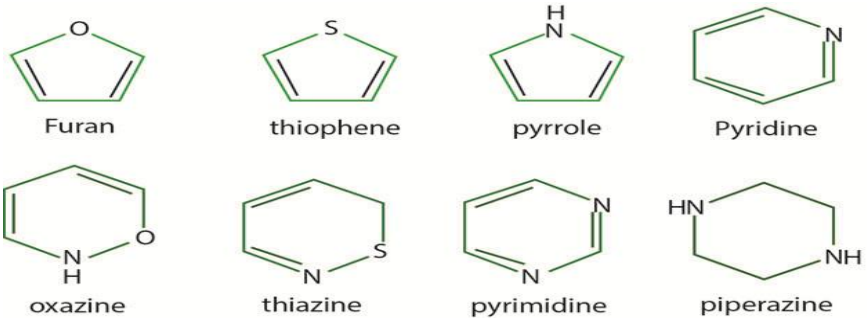
ABSTRACT
The heterocyclic compound like Quinine shows antimalarial activity and the substitution quinine shows more potent activities in compound like chlorquinine, primaquinine etc. Research shows that ferroquinone and aminoquinone shows high activity against chloroquinone-resistant malaria parasites. The quinazoline derivative drugs like erlotinib, and lapatinib are also important tyrosine kinase inhibitors. And the research studies shows that Crizotinib has an aminopyridine structure, and functions as a protein kinase inhibitor by competitive binding within the ATP-binding pocket of target kinases. Lastly the compounds which are SND approved in 2018 having heterocyclic ring. The compounds are Cefditoren pivoxil, Eltrombopag Olamine tablets, Alectinib capsule, Bendamustine Hydrochloride injection, Methotrexate injection prefilled syringe, Sildenafil powder for oral suspension, Febuxostat tablets and Posaconazole injection. They are not only pivotal in the synthesis of drugs, but also form part of the structure of a diversity of drugs, vitamins, natural products and biomolecules. The compounds shows activities like anti malarial, anti neoplastic activity and the compounds that are approved in 2018 have different heterocyclic compound for potency of the compound.

KEYWORDS: Heterocyclic compounds, Pharmaceuticals, heterocyclic ring.

INTRODUCTION
Heterocyclic chemistry is a very important branch of organic chemistry accounting for nearly one-third of modern publications. In fact two thirds of organic compounds are heterocyclic compounds. Heterocyclic compounds constitute the largest and most varied family of organic chemistry, after all every carboxylic compound i.e. any group of organic compound that contain carbon in all ring atom; regardless the structure and functionally may converted into a heterocyclic analogue by replacing one or more of the ring carbon atom with different elements. The oxygen, nitrogen and sulfur (the most common heterocyclic element), are the numerous replacement of the ring carbon. The best known of the simple heterocyclic compounds are pyridine, pyrrole, furan, and thiophene. A molecule of pyridine contains a ring of six atoms—five carbon atoms and one nitrogen atom. Pyrrole, furan, and thiophene molecules each contain five member rings, composed of four atoms of carbon and one atom of nitrogen, oxygen, or sulfur, respectively.

A large number of heterocyclic compounds follow the Huckel's rule of aromaticity. Heterocyclic compound in pharmaceuticals play an important role. Because the human body made up of the six elements: carbon, hydrogen, nitrogen, calcium and phosphorous. It is 99% of mass of human body. Only 0.85% is composed of another five element i.e. potassium, sulfur, chlorine, sodium and magnesium. This 11 element are necessary for life. And other elements are called are trace element. As the heterocyclic compounds contain this element in carbocyclic compound so it maintains our body elements as a medicine.



Different Activities of Heterocyclic Compound

Heterocycles are present in a wide variety of drugs, most vitamins, many natural products, bio molecule, and biologically active compound, including antitumor, antibiotic, anti-inflammatory, antidepressant, ant malarial, anti-HIV, antimicrobial, antibacterial, antifungal, anti viral, anti diabetic, herbicidal, fungicidal, and insecticidal agents. Also, they have been frequently found as a key structural unit in synthetic pharmaceuticals and agrochemicals. Some of these compounds exhibit a significant solvate chromic, photo chromic, and biochemical-luminescence properties.

Most of the heterocycles possess important applications in materials science such as dyestuff, fluorescent sensor, brightening agents, information storage, plastics, and analytical reagents. In addition, they have applications in supra molecular and polymer chemistry, especially in conjugated polymers. Moreover, they act as organic conductors, semiconductors, molecular wires, photovoltaic cells, and organic light-emitting diodes (OLEDs), light harvesting systems, optical data carriers, chemically controllable switches, and liquid crystalline compounds.

Heterocycles are also of considerable interest because of their synthetic utility as synthetic intermediates, protecting groups, chiral auxiliaries, organ catalysts, and metal ligand in asymmetric catalysts inorganic synthesis. Therefore, substantial attention has been paid to develop efficient new methods to synthesize heterocycles.

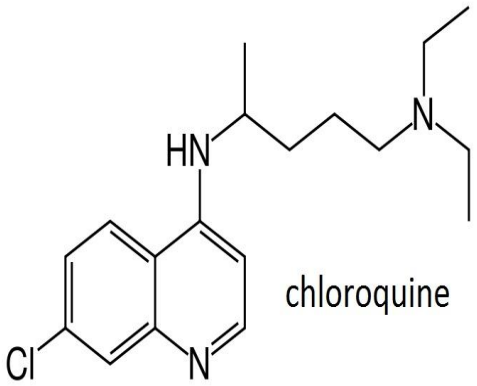
Heterocyclic Compounds as Anti Malarial

Malaria is one of the most serious, complex and refractory malady facing humanity this century. Some 300-500 million of world's population are infected by the disease, presenting 120 million clinical cases annually.

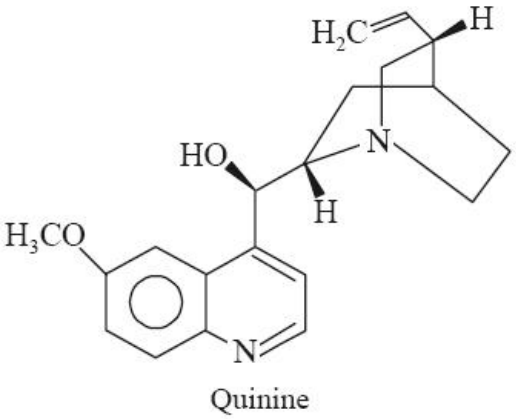
Quinine may be claimed, without exaggeration, as the drug to have relieved more human suffering than any other inhibitors**.**

Chloroquinine, the main drug among the 4-aminoquinoline class, is one of the most successful anti malarial agents ever produced.

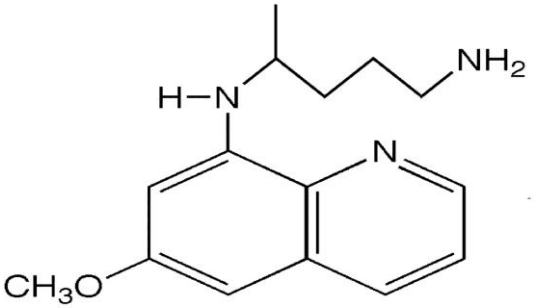
Primaquinine is the drug of 8-aminoquinoline class, which is connected to amino acids by forming peptide bond to the amino group. These amino acid derivatives are known for higher activity and lower toxicity.



chloroquine



Quinine



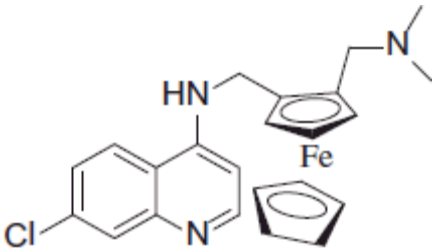
Primaquine

Novel Approches for Anti Malarial Drugs

- **Novel ferroquine-based antimalarials**

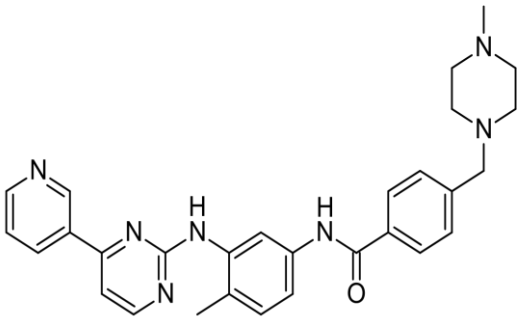
Ferroquine (FQ), a ferrocene-containing 4-aminoquinoline derivative, has potent *in vitro* efficacy against Chloroquinone(CQ)-resistant *P. falciparum* and CQ-sensitive *P. vivax*. FQ showed tremendous activity against CQ-sensitive and -resistant *P. falciparum* and *P. vivax*(median 50% inhibitory concentrations, there was significant cross-susceptibility with the quinoline-based drugs CQ, amodiaquine and piperaquine (for *P. falciparum.* The observed *ex vivo* cross-susceptibility is likely to reflect similar mechanisms of drug uptake/efflux and modes of drug action of this drug class. However, the potent activity of FQ against resistant isolates of both *P. falciparum* and *P. vivax* highlights a promising role for FQ as a lead antimalarial against CQ-resistant *Plasmodium* and a valuable partner drug for artemisinin-based combination therapy.

Marfurt et al. synthesized the 4-aminoquinoline FQ, an unusual **ferrocene** moiety which is inserted into the side chain. FQ shows high activity against CQ-resistant malaria parasites. In a dose-ascending study, FQ was generally well tolerated up to 1600 mg as single dose and up to 800 mg as repeated dose in an asymptomatic young male with *falciparum* infection.

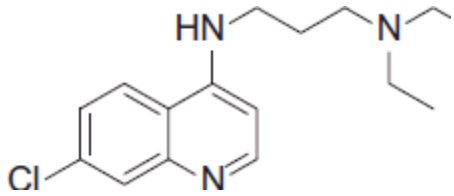


- **Novel 4-aminoquinoline analogs as antimalarials**

O'Neill et al. synthesized the 4-aminoquinoline which is a short side-chain analogue of CQ, since it shows high activity against CQ-resistant strains of *P.falciparum.*



Imatinib



It has already undergone **Phase I** clinical trials, which indicate a similar profile to CQ. Dose adjustment is required because of increased clearance compared with CQ.

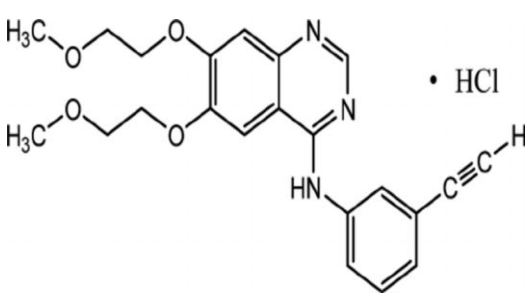
Heterocyclic Compounds as Antineoplastic Agents

Cancer is a major human health problem worldwide and is the second leading cause of death in United States**.** Systematic chemotherapy began in the 1940's and 1950's with nitrogen mustards developed from war gases and with antimetabolites developed from early knowledge of DNA metabolism. Compounds that alkylated DNA have long been of interest as anticancer drugs. Different types of antineoplastic agents are developed, which include nitrogen mustards (Bendamustine), tyrosine kinase inhibitors, 26S proteasome inhibitors etc.

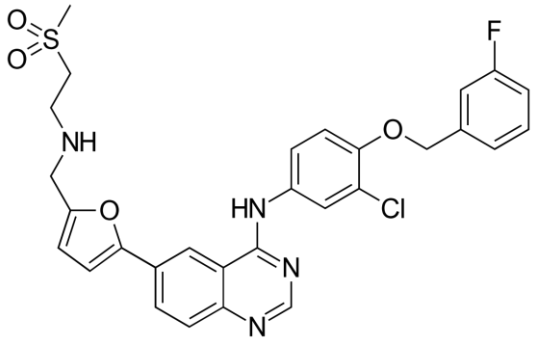
Quinozoline and pyrimidine derivatives are used as tyrosine kinase inhibitors. A series of substituted 2-(aminopyridyl)-and 2-(aminopyrimidinyl) thiazole-5-carboxamides was identified as potent Src/Abl kinase inhibitors with excellent antiproliferative activity against hematological and solid tumor cell lines**.** Chronic Myelogenous Leukemia (CML) is a myeloproliferative disorder that is characterized by hyper proliferation of stem cells, followed by their subsequent differentiation into peripheral white blood cells.

Imatinib, is the block buster drug used for the treatment of Chronic Myelogenous Leukemial (CML)**.**

Imatinibmysilate is marketed under brand name Gleevec. The quinazoline derivative drugs like erlotinib, and lapatinib are also important tyrosine kinase inhibitors.



Erlotinib

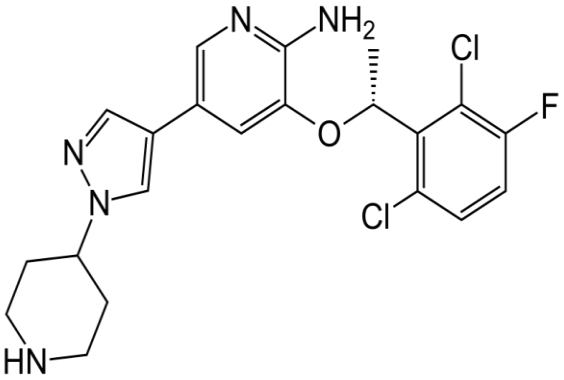


Lapatinib

Novel Approches for Antineoplastic Agents

Crizotinib

It is approved for marketing in 2017. Crizotinib has an aminopyridine structure, and functions as a protein kinase inhibitor by competitive binding within the ATP-binding pocket of target kinases.



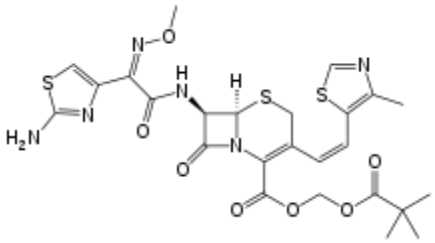
Crizotinib is an anti-cancer drug acting as an ALK (anaplastic lymphoma kinase) and ROS1 (c-ros oncogene 1) inhibitor, approved for treatment of some non-small cell lung carcinoma (NSCLC) in the US and some other countries, and undergoing clinical trials testing its safety and efficacy in anaplastic large cell lymphoma, neuroblastoma, and other advanced solid tumors in both adults and children.

Some of the biological properties of some heterocyclic compunds, known in literature are summarized as: Anti-viral, Anti-fungal, Anti-protozoal, Anti-tumor, Cytotoxic, Analgesic, Anti-convulsion, Anti-depression, Antioxidant, Anti-diabetes, Muscle relaxant.

2018 SND Approved Drugs

Manufacturing and marketing permission issued from SND division from 01-01-2018 to 20-04-2018. It has been seen that out of 11 compounds, 8 compounds contain different substituted or manipulated heterocyclic group with different activities. New drug products of a different therapeutic class for new indication, new strength, new routes as they are modified.

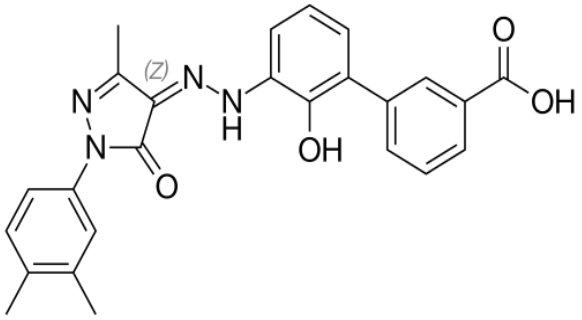
Cefditoren Pivoxil Dry Powder for Suspension



Date of approval: 04-01-2018

It conatin thiazole compound in structure. Cefditoren pivoxil is used to treat uncomplicated skin and skin structure infections, community acquired pneumonia, acute bacterial exacerbation of chronic bronchitis, pharyngitis, and tonsillitis.

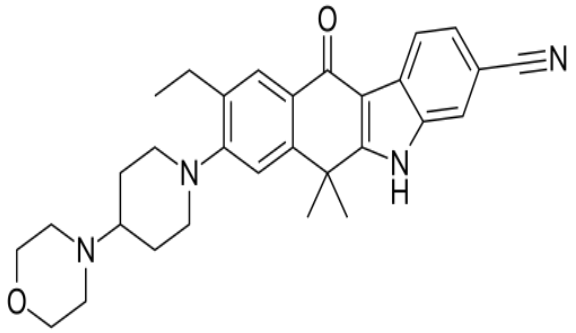
Eltrombopag Olamine Tablets



Date of approval:06-02-2018

It conatin pyrazole ring. It is used to treat chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients aged 1 year and above who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). It is indicated in adult patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy. It is indicated in adult patients with acquired severe aplastic anaemia (SAA) who were either refractory to prior immunosuppressive therapy or heavily pretreated and are unsuitable for haematopoietic stem cell transplantation.

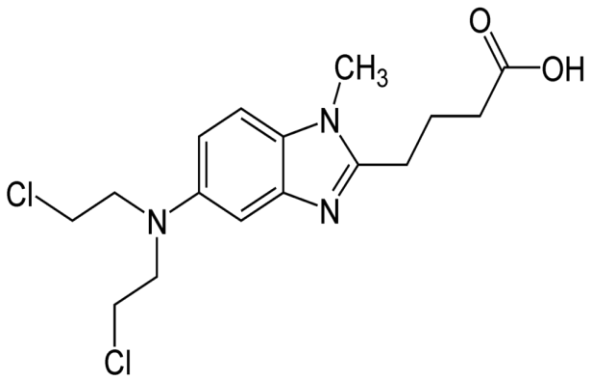
Alectinib Capsule



Date of approval: 05-03-2018.

It conatian pyrroline, piperidine and morpholin compound as heterocyclic ring. **Alectinib** is an oral drug that blocks the activity of anaplastic lymphoma kinase (ALK) and is used to treat non-small-cell lung cancer(NSCLC).

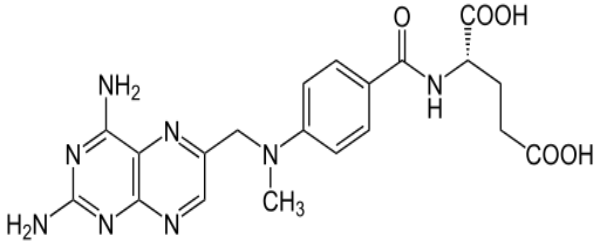
Bendamustine Hydrochloride Injection



Date of approval: 23-03-2018

It conatin benzimidazole ring as heterocycles. Bendamustine HCl is a parenterally administered alkylating agent used alone and in combination with other antineoplastic agents in the treatment of chronic lymphocytic leukemia and refractory forms of non-Hodgkin lymphoma. Bendamustine therapy is associated with minor transient serum enzyme elevations during treatment and to rare instances of clinically apparent liver injury, with jaundice generally arising as a part of a generalized hypersensitivity syndrome. Bendamustine also has potent immunosuppressive activity and can cause reactivation of chronic hepatitis B that can be severe and even fatal.

Methotrexate Injection Prefilled Syringe



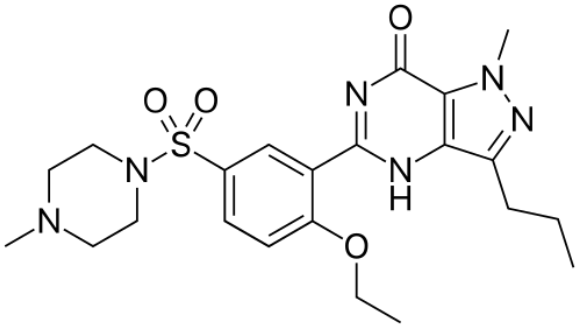
Date of approval:09-03-2018

It contain pteridine ring as heterocyclic compound.

Methotrexate, formerly known as amethopterin, is a chemotherapy agent and immune system suppressant. It is used to treat cancer, autoimmune diseases, ectopic pregnancy, and for medical abortions. Types of cancers it is used for include breast cancer, leukemia, lung cancer, lymphoma, and osteosarcoma. Types of autoimmune diseases it is used for include psoriasis, rheumatoid arthritis, and Crohn's disease. It can be given by mouth or by injection.

It is used as a disease-modifying treatment for some autoimmune diseases, including rheumatoid arthritis.

Sildenafil Powder for Oral Suspension

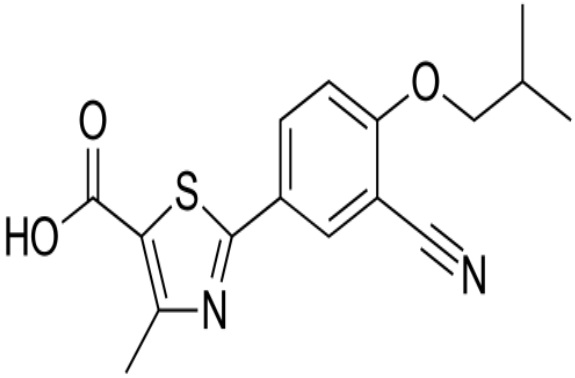


Date of approval: 20-03-2018

It contains piperazine and purine rings as heterocycles.

Sildenafilis a medication used to treat erectile dysfunction and pulmonary arterial hypertension. Its effectiveness for treating sexual dysfunction in women has not been demonstrated.

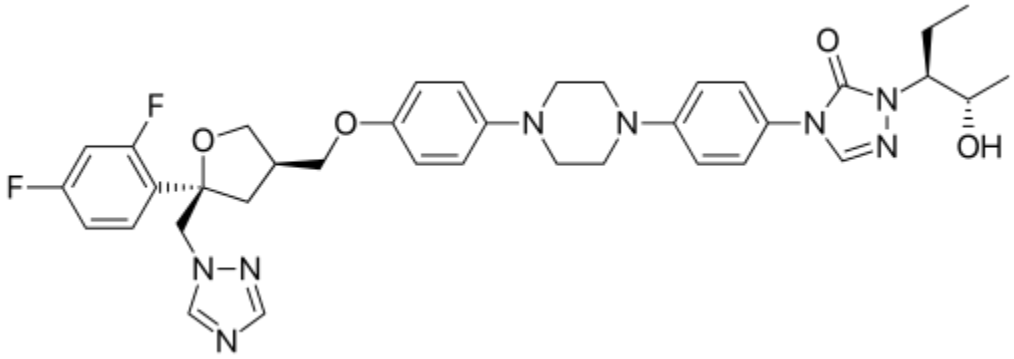
Febuxostat Tablets



Date of approval:06-04-2018.

It contain thiazole ring as heterocycles. Febuxostat is a medication used in the treatment of chronic gout and hyperuricemia. There are concerns about more heart related deaths with febuxostat compared to allopurinol. It inhibits xanthine oxidase, thus reducing production of uric acid in the body.

Posaconazole Injection



Date of approval:13-04-2018

It conatain triazole and piperazine ring as hetrocycle.

Posaconazole is used to treat invasive aspergillosis and candidiasis and fungal infections caused by Scedosporium and Fusarium species, which may occur in immune compromised patients. It is also used for the treatment of oropharyngeal candidiasis (OPC), including OPC refractory to itraconazole and/or fluconazole therapy.

DISCUSSION

The antimalerial activity of Quinine shows more potent when heterocyclic moiety substituted activities in compound like chlorquinine, primaquinine etc. The novel approaches of chloroquine sensitive D10 strain of Plasmodium falciparum of a series of N,N-diethyl-N-(4-quinolinyl)-1,2-ethanediamines with 11 different substituent at the 7-position on the quinoline ring have been investigated in vitro. Electron-withdrawing groups at the 7-position have been shown to lower the pKa of both the quinoline ring nitrogen atom and the tertiary amino nitrogen in the alkyl side chain. The quinoline nitrogen pKa ranges from 6.28 in the nitro derivative to 8.36 in the amino derivative, while the tertiary amino nitrogen has a pKa ranging between 7.65 in the trifluoromethyl derivative and 10.02 in the amino derivative. Calculation suggests that the resulting pH trapping of these compounds in the parasite food vacuole ranges between about 7% of that observed in chloroquine for the NO2 derivative and 97% in the amino derivative. A direct proportionality between antiplasmodial activity normalized for pH trapping and β-hematin inhibitory activity was observed. Activity could not be correlated with any other observed physical parameter. The β-hematin inhibitory activity of these derivatives appears to correlate with both the hematin−quinoline association constant and the electron-withdrawing capacity of the group at the 7-position (Hammett constant). For the compounds under investigation, the hematin association constant is in turn influenced by the lipophilicity of the group at the 7-position.

The antineoplastic activity of Quinozoline and pyrimidine derivatives show by tyrosine kinase inhibitors. A novel 2-amino-5-aryl-3-benzyloxypyridine series was created to more effective. In the novel series, the 2-aminopyridine core allowed a 3-benzyloxy group to reach better ligand efficiency (LE). Further optimization of the lead series generated the clinical candidate crizotinib, which demonstrated potent in vitro and in vivo (Mesenchymal–Epithelial Transition Factor)c-MET kinase and ALK inhibition, effective tumor growth inhibition, and good pharmaceutical properties.

The compounds which are SND approved in 2018 having heterocyclic ring. The compounds are Cefditoren pivoxil, Eltrombopag Olamine tablets, Alectinib capsule, Bendamustine Hydrochloride injection, Methotrexate injection prefilled syringe, Sildenafil powder for oral suspension, Febuxostat tablets and Posaconazole injection.

CONCLUSION

Heterocyclic chemistry is vastly expanding, because of the enormous amount of research work being done in this area. The majority of known molecules are heterocyclics. Heterocyclic compounds dominate the field of biochemistry, medicinal chemistry, dyestuff, photographic sciences and are of increasing importance in many other areas including polymers, adhesives and molecular engineering.

The challenges of discovering new heterocyclic systems and of understanding their properties also continue to stimulate research in the area as the heterocyclic compounds are versatile and they can easily manipulated the structure to have different biological as well as pharmacological activities.

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nice guidance and providing all the necessary information for developing a good system.

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