A REVIEW OF BIOLOGICAL IMPORTANCE OF HETEROCYCLIC COMPOUNDS

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Abstract

Synthetic as well as natural heterocyclic compunds are biologically active and are used as drugs in clinics. They are widely used in pharmaceuticals, agrochemicals, sensitizers, antioxidants, copolymers, as corrosion inhibitors, dyes etc... Natural products occur in minimum quantities and are difficult to extract and utilize them. Synthetic Organic Chemistry is an excellent solution, which provides an alternative path to synthesize drugs which are mimics of natural medicines. In that regard this paper gives a review on the biological importance of heterocyclic compounds.

Keywords: first keyword, second keyword, third keyword (Provide 4–6 keywords most relevant to your research topic)

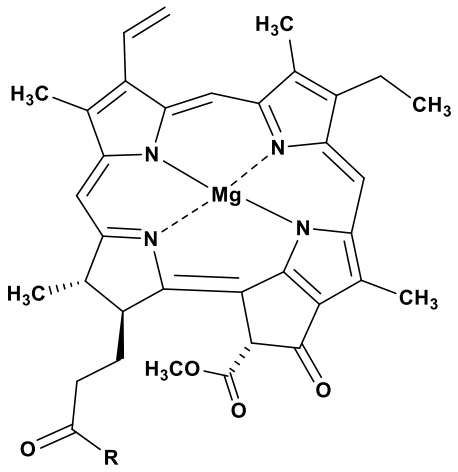
1. INTRODUCTION

1.1.heterocyclic chemistry:

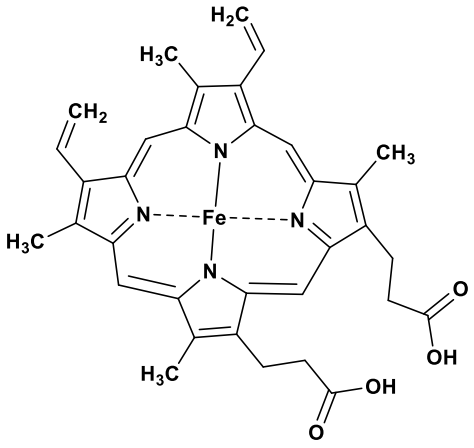
Heterocyclic compounds are major class of organic compounds characterized by the presence of ring structure and at least one heteroatom in their ring, which give them distinct physical and chemical properties compared their all-carbon-ring analogs. They incorporate the functional group either as a subsituent or as a part of the ring itself. Commonly the heterocycles have 5 or 6 membered heterocyclic rings with heteroatoms (N, O or S). Pyridine, pyrrole, furan and thiophene are few examples. These heterocycles are found naturally available, are vital in living cell's metabolism and therefore essential to life. Synthetic as well as natural heterocyclic compunds are biologically active and are used as drugs in clinics. They are widely used in pharmaceuticals, agrochemicals, sensitizers, antioxidants, copolymers, as corrosion inhibitors, dyes etc...
Natural antibiotics such as cephalosporin, morphine, reserpine, penicillin are heterocyles. Fundamental importance of heterocyclic compunds is that they are found as a key component in biological processes (**Table 1.1).**

Table 1.1: Role of natural heterocycles in living systems

S.No	HETEROCYCLIC COMPOUND	FUNCTION
1	Pyrimidines and purines	Genetic material DNA, antibiotics
2	Adenine, guanine and pyrimidine, namely thymine, cystosine	mechanism of replication
3	Chlorophyll and heme	photosynthesis in higher plants
4	Thiamine	Vitamin-B_1
5	Riboflavin sodium phosphate	Vitamin-B_2
6	Pyridoxol	Vitamin-B_6
7	Niacinamide	Vitamin-B_3
8	L-Ascorbic acid	Vitamin-C
9	Amino acids in proteins	histidine, proline and tryptophan



Chlorophyll

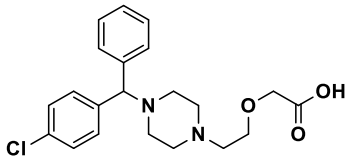


Heme in haemoglobin

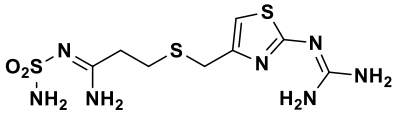
Natural products occur in minimum quantities and are difficult to extract and utilize them. Synthetic Organic Chemistry is an excellent solution, which provides an alternative path to synthesize drugs which are mimics of natural medicines. Antibacterial agents based on the β-lactam structure of pencillin, amoxicillin, clavuanic acid, amoxicillin etc.., many of the pharmaceuticals are heterocyclic compunds which are synthesised in laboratories and industries.

Table 1.2: Synthetic heterocyclic compounds and their applications

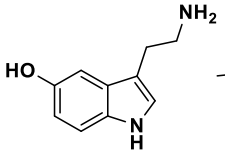
S.No	HETEROCYCLIC COMPOUND	FUNCTION
1	Cetrizine, chlorpheniramine, Pantoprazole and imidazole	histamine H_2 receptor antagonist-medicine for peptic ulcers
2	Famotidine	inhibits gastroesophageal reflux disease
3	Zidovudine	reverse transcriptase inhibitor
4	Acyclovir	treatment of herpes simplex
5	Ganciclovir	treatment of cytomegalovirus infections
6	Cladribine	treatment of multiple sclerosis contraction of blood platelet-helps rapid healing
7	Serotonin	mood regulator-helps to overcome anxiety, depression constrictor of arteries in the brain and is implicated in migraine, alters mood and appetite
8	Ptilomycalin A	antiviral activity
9	Latrunculins	actin-binding activity



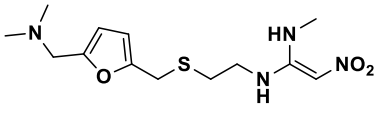
Cetrizine



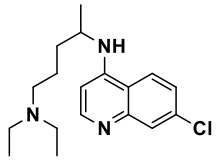
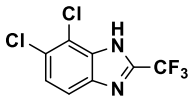
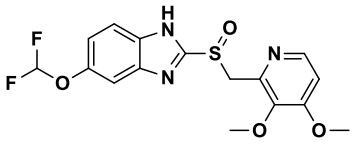
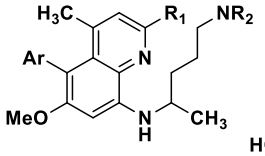
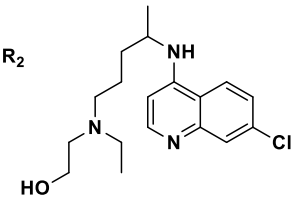
Famotidine



Serotonin



Ranitidine

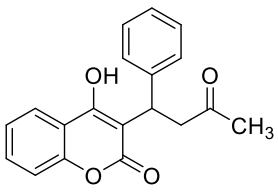
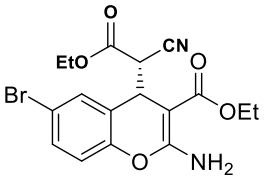
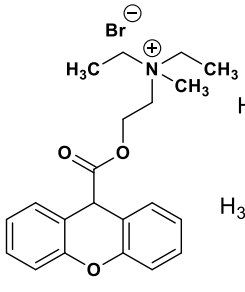
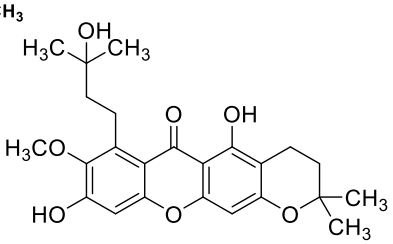






Chloroquine **Chlorflurazole** **Pantoprazole** **8-aminoquinoline** **Hydroxychloroquine**

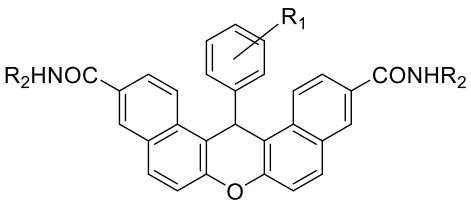
Thus the synthetic methodologies for the development of heterocyclic syntheses are utilized during drug discovery in the pharmaceutical industry. The aim of collaborations between industry and academia in developing innovative synthetic approaches to functionalized heterocycles of greatest pharmaceutical interest is achieved by synthetic organic chemistry[1]. Kwa Clovis Dze and Fayad Samad discussed in detail about the various heterocycles, the different synthetic strategies and their applications. Heterocyclic compounds are obtained by inserting heteroatoms like N, S or O into their aromatic ring systems so that they remain conjugated and isoelectronic with the original hydrocarbon (eg: – CH=CH- structural unit is replaced by –CH=N-, -N=N-, -O-, -S- and -NR- units). Heterocycles containing more than one hetero atom are called poly heterocycles and occur in natural products like plant alkaloids, nucleic acids, vitamins, flavones, haem pigment, chlorophyll, carbohydrates and proteins[2].

1.2. biological importance of dibenzo xanthenetetraone core:

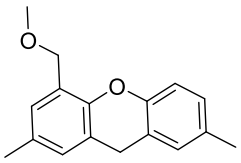
Xanthenes are a class of heterocycles with oxygen atom incorporated in their cores and are important structural subunits widely available in natural products as well as in synthesized drugs. Their enhanced physical, chemical properties and biological applications are well correlated with their structure. The versatility of this xanthene nucleus made it play key role in many neuroprotector, antitumor, antimicrobial, antifungal, antibacterial, anti-inflammatory, analgesic activities, antidiabetic, antioxidant, antihistaminic, antipsychotic, anticonvulsant activity, antiviral agents[3]. Aryl or heteroaryl dibenzo xanthenes exhibited significant anti-viral activity against tobacco mosaic virus[4]. *Bis*-dibenzo-xanthenes posses medicine like properties such as antiviral, antidepressants, antinociceptives in addition to the applications in the field of laser technology and anti-coagulants[5]. Some of the medicines in usage with Xanthenes are been described below. Warfarin is used in prevention blood clots formation, HA14-1 is utilized for inducing apoptosis and selective modulator for anticancer drugs, Methantheline is used in the treatment of intestinal and stomach ulcers disease, 3-Isomangostin Hydrate is an traditional medicine used for treating suppuration, diarrhea, abdominal pain, dysentery, wound infections, chronic ulcer and wound infections.

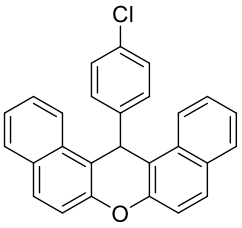
Warfarin **HA14-1** **Methantheline** **3-Isomangostin Hydrate**



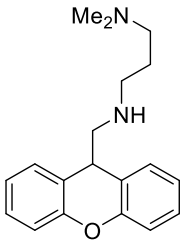
Anticancer



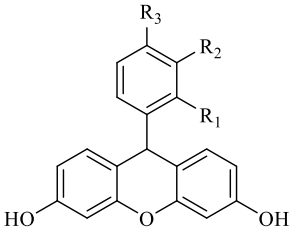
Antimicrobial



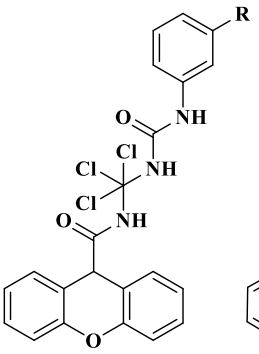
Antiviral



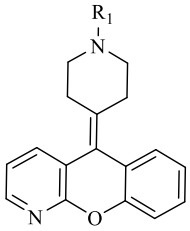
Antimalarial



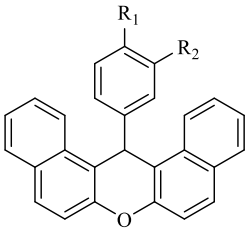
Antiinflammatory and Analgesic



Antidiabetic



Antihistaminic and Bronchodilator



DPPH and ABTS scavengers

Dibenzoxanthenes possessed showed high cytotoxic activities on BEL(7402), HeLa(A549) and MG[63] cancer cells[6]. Indole-xanthendione moieties have shown cytotoxicity against PBMCs and)ER-∝ dominant T47D BC cell lines[7]. Aryldibenzo Xanthenes possessed anti-bacterial activity against gram negative bacteria such as *E. coli* & *P. aeruginosa* as well as Antifungal activity against *A. niger and F. moniliforme*[8]. Dibenzoxanthene derivatives have shown anti-tumor activity against Eca-109, HepG2 and SGC-7901 cell lines[9]. Spiro [fluorene-9,9′-xanthene] exhibited electroluminescence performance[10]. Organo-soluble polymers were prepared with spiro[fluorene-9,9′-xanthenes[11]. Hydroxyspiro[indoline-3,9-xanthene]trione were proved to be butyrylcholinesterase inhibitors[12]. Xanthenes have shown better steric projections, H-bond interactions and binding affinity towards ATP of Human-(PIM1) kinase receptor[13]. Hydroxyxanthenones have shown better antiproliferative activity against several tumor cell lines HeLa, HepG2, SW620 and A549[14].

1.3: biological importance of tetrahydrobenzo quinoline

NATURAL SOURCES WITH QUINOLINE MOEITY	MEDICINAL ACTIVITIES
Cinchona alkaloids from *Cinchona* bark	Antimalarial and antiarrhythmic drugs
Camptothecin from stem of Happy tree [*Camptotheca acuminata* -Camptotheca]	Cancer treatment
Cryptolepine isolated from *Cryptolepis* sp.	Potential antimalarial, antiplasmodial activiity
Lunasiaamara extract Skokusagine	Anti- *tuberculosis[*H37Rv] Activity was significant
Dictamnine isolated from roots of *Zanthoxylumwutaiense*	Exhibited antitubercular activity
Extracts from *Chelidonium majus*- Papaveraceae	Exhibited Antimicrobial action
C. Albicans of chelerythrine	Antifungal activity was *Strong*
Leaves or trunk bark extract- *Chimanines A, B, C and D* from medicinal plant- *Galipea longiflora* [*Rutaceae*]	Antileishmanial and antitrypanosomal activity, activity Chagas disease
A Lycopodium alkaloid obtained from Trev. plants *Huperzia serrata*	acetylcholinesterase inhibitory action against Alzheimer's disease highly active

Cryptolepis sanguinolenta plant's root extract	cytotoxic activition against adenocarcinoma-colon cells
quinolone alkaloids	inhibits T. cruzi. - antichagasic agents
quinazoline alkaloids extracted from *Peganum harmala* plant-*Vasicine, Vasicinone*	*bronchodilatory, bronchoconstrictory and an antianaphylactic action*
cuspareine, angustureine, galipeine, galipinine (tetrahydroquinolines) extracted from *G. officinalis*	highlt active against antimalarial activity *P. falciparum.*
Streptonigrin isolated from an actinomycete strain	Potential action against *human neuroblastoma* SH-SY5Y
huajiaosimuline and zanthosimuline-pyranoquinoline alkaloids-root, bark extracts of *Zanthoxylum simulans*	Cytotoxic activity

Table 1.4: BIOLOGICAL IMPORTANCE OF QUINOLINE

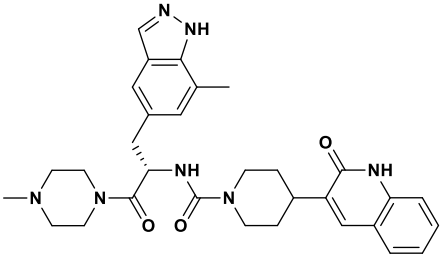
QUINOLINE BASED APPROVED DRUGS	MEDICINAL ACTIVITIES
Gemifloxacin	antibacterial agent treatment chronic bronchitis and pneumonia
Neratinib	HER2-cancer treatment
Carteolol	beta-adrenergic antagonist-anti-arrhythmia agent
Delafloxacin-fluoroquinolone	antibiotic
Amsacrine- derivative of aminoacridine	Potential antineoplastic agent
Hydroxychloroquine	Treatment of coronavirus-2019 (COVID-19)
Gemifloxacin- quinolone	antibacterial, treatment of bronchitis as well as pneumonia
Ivacaftor	a drug for Cystic Fibrosis
Camptothecin-Irinotecan	treatment of pancreatic cancer
Indacaterol	inhibitor of Hepatitis-C-Virus{ NS3/4A protease}
Aripiprazole lauroxil	antipsychotic drug for schizophrenia treatment
Amsacrine	antineoplastic agent
Lisuride	dopamine agonists
Oxamniquine	Schistosomicidal, anthelmintic activity
Brexpiprazole	serotonin-dopamine activity modulator (SDAM)
Tasquinimod	anti-angiogenic agent, taxotere, anti- cancer, tasquinimod, androgen ablation.
Pavinetant	treatment of Schizophrenia
Pelitinib	anticancer agent-EKB-569-irreversible inhibits EGFR [epidermal growth factor receptor].
Laquinimod	Immune modulator
Talnetant	antagonist for neurokinin 3 receptor -SB-223,412
Acridine carboxamide	topoisomerase inhibitor-chemotherapatic agent in treatment of cancer
Pyrazoloacridine	treatment of metastatic, lung, breast cancer and skin cancer
Fluoroquinolones	treatment of HIV infection
amphotericin B	anti-protozoal activity
4-anilinoquinolines	antimalarial activity
benzo-[h] quinoline	DNA-intercalating agents
4-alkynyl-quinoline	anti-proliferative and PI3Kα inhibitory activities
4-thiophenyl quinolones	inhibits HMG-CoA reductase and hypocholesterolemic
Tetrahydroquinolines	inhibits cardiovascular activity.

3-aminoquinoline	NK3 antagonist
quinoline-2-carbaldehyde hydrazone	in vitro antioxidant activity
5-alkoxy triazoloquinoline	anticonvulsant activity
4,7-trifluoromethylquinolines	analgesic activity was excellent
4-triazole thiols containing 2-chlorofromyl quinoline	antibacterial, anti-inflammatory and antifungal activities
4-arylquinolines	anthelmintic activity
Trifluoromethyl quinoline	inhibits ZIKV replication

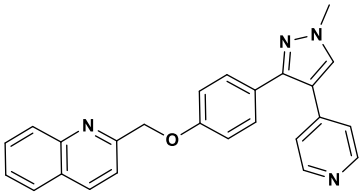
Quinoline (C_9H_7N) is a bicyclic (benzene ring fused with pyridine), hetero-aromatic, plannar compound with 10 delocalised π electrons which is an important core in medicinal chemistry field[15]. They have therapeutic activity for chronic leukaemia [malaria] treatment, solid tumours, in treatment of lung cancer, cardiotonic, inflammations, bacterial and antifungal infections[16].

Few drugs with Quinoline moiety and their applications were discussed below

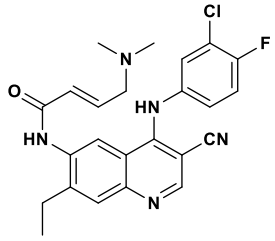
- Vazegepant is used in treatment of migraine, pulmonary inflammation and COVID-19.
- Mardepodect is used in schizophrenia treatment.
- Pelitinib (EKB-569) is an anticancer agent, utilized in treatment of EGFR.
- 6-desfluoroquinolones is used in HIV treatment.
- Cliioquinol is involved in treating skin infections.
- 7-chloro quinolones is used in treatment of pathogens that are multidrug-resistant.
- Pyrano[2,3-b] quinoline dicarboxyhydrazides is involved in treatment of tuberculosis.



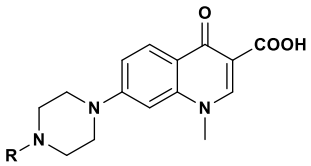
Vazegepant



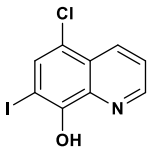
Mardepodect



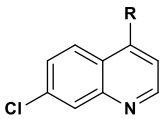
Pelitinib (EKB-569)



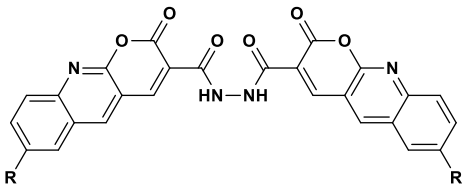
6-desfluoroquinolones



Cliioquinol



7-chloro quinolones



Pyrano[2,3-b] quinoline dicarboxyhydrazides

Molecules with Quinoline core have potential antidepressant and antifungal activity[17]. Benzo[f]quinolinium salts have antimicrobial drug properties[18]. Heteroaryl dioxobenzothiadizin hydroxyl quinolinones inhibits (NS5B polymerase)-hepatitis C virus[19]. Thioxo-pyrrolo quinolone posess antiproliferative activity on various human cancer cell-lines in colon, liver and breast regions[20]. Benzo quinolines were found to have anti-cancer activity[21]. Antitumor [DNA intercalating] - Tetrahydrobenzo quinolines have high cytotoxicity over few Human cancer cell lines[22]. Cytotoxic activity of

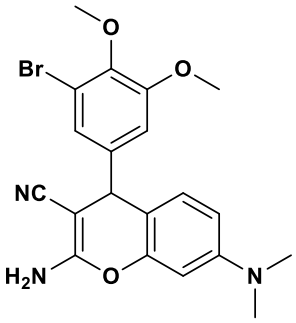
benzoquinoline carboxamide derivatives against human tumor cell lines such as Human Cervix Adenocarcinoma, Acute Promyelocytic Leukemia and Human Hepatocellular Carcinoma cells was prominent[23]. Good *In vitro* antimicrobial activity results of pyrano quinolin cyanoethane-thioates against *Escherichia coli, Micrococcus roseus* and *Staphylococcus aureus* were obtained[24]. Benzoquinolines have inhibitory activity against Ebola virus replication[25]. Heteroaryl quinolinones were found to have potential inhibitory action on Hepatitis-C Virus[26]. Tetrahydro-isoquinolines have shown multipotent pharmacological activities against various neurodegenerative diseases and pathogens[27]. Benzoquinolines inhibits proline-rich ligand interaction with that of Src-SH3 domain[28]. Inhibitory activities of Indolo-quinolinediones against Cytotoxic Leukemia Topoisomerase-I were studied by structure cum mutagenicity relationship[29]. mTOR Inhibitory Docking Score of tetrahydroquinoline was studied[30].

1.4 biological importance of benzoindenochromene:

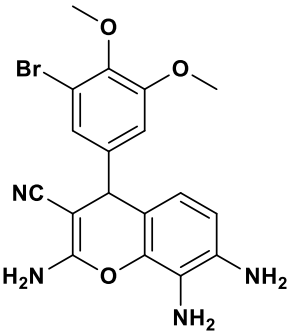
Chromenes were naturally extracted from bark of Tabebuia sp. Aminophenyl-benzo chromene carbonitrile have shown anticancer activities six human carcinogenic cell lines[31].

Some of the medicines with Chromene core, their structures and biological functions were described

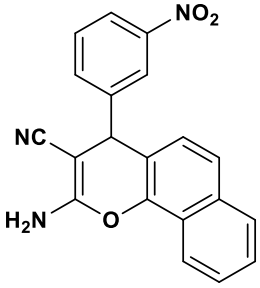
- MX58151 is used as cell proliferation inhibitors and caspase activators.
- EPC2407 (Cirobulin) is used to treat psoriasis, relieves itching, redness, and swelling of skin, to remove dead worn-out cells of skin and helps in skin softening.
- LY29018 is utilized in retarding the growth of xenograft tumors.
- Tioclomarol is used as rodenticide and anticoagulant.
- Dicoumarol has been utilized in treatment of blood clots and thrombosis at deep veins.



MX58151



EPC2407 Cirobulin



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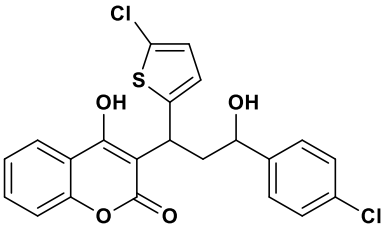
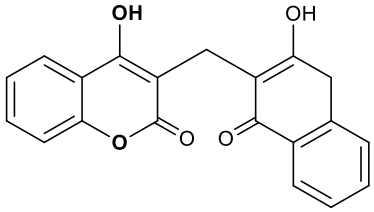
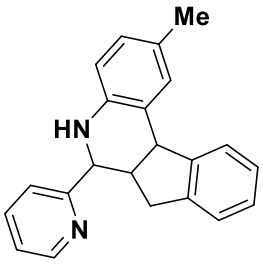
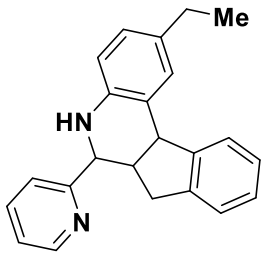


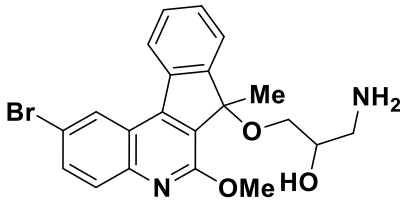
Tioclomarol

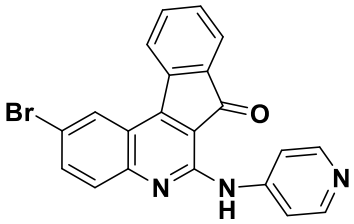


Dicoumarol









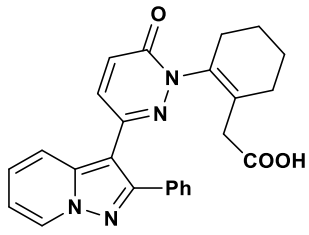
Indeno[2,1-c]quinoline with antitrypanosomal properties

Benzo[h]chromenes with aggregation-induced-emission (AIE) property were used to detect sulfite (SO_3^{2-}) and bisulfite (HSO_3^-) ions[32]. Antioxidant activities of Aryldihydrobenzo chromene triones were established[33]. *4H* chromenes and benzo chromeno-phenazines having fluorescence were found to sense metal ions such as Fe^{3+}& Cu^{2+} ions[34]. Chromenes have biological applications like anticancer, AChE inhibition, anti-proliferative, anti-inflammatory, antimicrobial, antiviral and antioxidant activities[35]. Indeno[1,2,-*c*]chromenes can be used as solar cell materials as they are proved to be good electron push subunits[36]. Rhinacanthin O extracted from Rhinocanthus nasutus, bark of Tabebuia sp, pyranokunthone from a marine frenolicin and actinomycete are few natural sources of chromenes[37]. Biological studies revealed that dihydro-indeno[2,1-c]chromene-3inhibited the thrombin, ADP-induced platelet and collagen aggregation[38]. Natural benzo[g]chromenes with antitumor activity were ∝-xiloidone, pyranokunthone, β-lapachone and lambertellin[39]. Benzo[f]chromenes have shown predominant anticoagulant-based medicines[40]. Indenochromenes shows antidiuretic and antagonism activity[41]. Benzochromene carbonitriles shown biologically activities and was prepared using Lawsone[42].

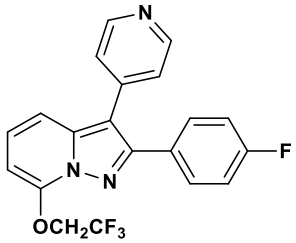
1.5 biological importance of tetrahydrodipyrazolopyridine:

Several drugs containing pyrazolopyridine core and their medicinal usages were discussed below.

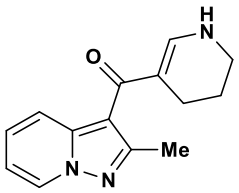
- Roscovitine is used in in cell cycle regulation, to treat cancer, apoptosis and in neurobiology studies.
- Cartazolate is tested in human clinical trials for anxiety treatment.
- Etazolate (EHT-0202) is a GABAA modulator for treating senile psychosis.
- Tracazolate- used as an anticonvulsant.

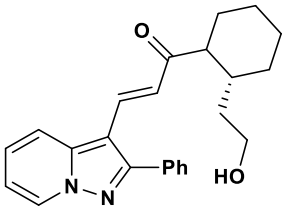


Antagonist for Adenosine AntagonistforDiureticAdenosineA1 Receptor

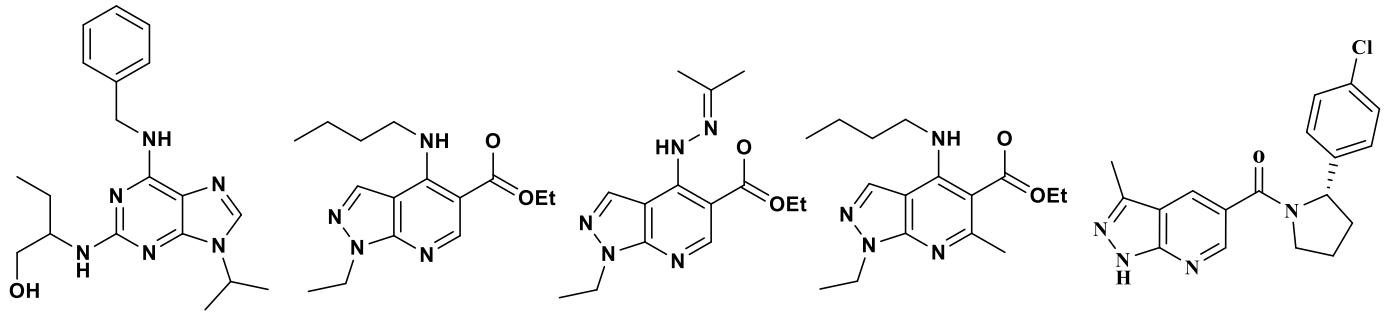


Inhibitor of P38-Kinase





Anti Tubercullosis



Roscovitine **Cartazolate** **Etazolate** **Tracazolate** **CDK8 Inhibitor**

Thiadiazolo-pyranopyrazoles exhibited antifungal, antibacterial activity against *A. flavus*, *A. niger*, *S. aureus*, *B. subtilis*, *P. vulgaris* and *E. coli*[43]. Pyrazolo-pyridine carboxylate inhibits Synucleinopathy {*C. elegans* }[44]. Pyrazolopyridines were inhibitors of CREBBP- cancer {AML}[45]. *Staphylococcus aureus* [Gram+ve] and *Escherichia coli* [Gram-ve] bacterium were inhibited by pyrazolopyridin-cyanomercapto-acrylamides[46]. K562 cancer cells were subjected to apoptotic cell death and at the same time, PBMCs {peripheral blood mononuclear cells} of healthy blood from donors were unaffected which proved the differential toxicity of amino-pyrazolopyridines[47]. Pyrazolothieno-pyridine's have shown anticancer activity against cancer cells [MCF-7, P C-3 and HepG-2][48]. Pyrazolopyridines potentially inhibits CDK2, MCF7 and HepG2 cancer cells[49]. Inhibition of proliferation of tumor, pim-1 kinase by pyrazol[3,4-b]pyridines were studied[50]. Pyrazolopyridines exhibited DNA-binding affinity, antimicrobial and antitumor activity with good oral absorption [51]. Pharmaceutical importance of heterocycles with pyrazolopyridine cores inhibits–CDK1, HIV, chemokine receptor, xantine oxidases, protein kinase inhibitors, vasodilator and anxiolytic[52].They also have shown analgesic[53], FGFR-Kinase Inhibitory action[54] and inhibits Tubulin polymerization[55], DYRK1A and 1B[56], PD-1/PD-L1 interaction[57] and inhibits *Staphylococcus aureus*-ATCC-19433 & *Bacillus subtilis*-ATCC-6633, *Proteus vulgaris*-ATCC-29213, *Escherichia coli*-ATCC-8739, *Aspergillus flavus*-MTCC1884, *Aspergillus niger*-MTCC1881 [58], inhibits COX-1 and COX-2 enzymes[59], *Rhizoctonia solani*[60], *Fusarium solani* [soilborne fungi][61] and PI3Kδ [62].

2.CONCLUSION:

Heterocyclic compounds are of high pharmaceutical importance. Each and every heterocycle got its own medicinal activity. Most of the heterocycles are naturally occurring. Extracting and purifying them are really hectic process. Synthezing heterocyclic compounds via one pot multicomponent reactions are the best alternate for prevailing challenges.

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