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REVIEW ARTICLE
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A REVIEW ARTICLE ON IMPORTANCE OF HETEROCYCLIC COMPOUNDS

SOURAV DE*[1], NIRANJAN BABU M[2], SUNEEL BABU T[3], BHAVYA SREE R[3], SAI KIRAN A[3], K SUNIL KUMAR REDDY[3]

[1]Assistant Professor, Department of Pharmaceutical Chemistry, Seven Hills College of Pharmacy, Venkatramapuram, Tirupati-517561, Andhra Pradesh.[2] Professor & Principal, Seven Hills College of Pharmacy, Tirupati – 517561, Andhra Pradesh, India.[3] Seven Hills College of Pharmacy, Venkatramapuram, Tirupati-517561, Andhra Pradesh. **Email:** mpharmsourav@rediffmail.com

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ABSTRACT

Heterocyclic compounds are of very much interest in our daily life. Heterocyclic compounds have one or more heteroatoms in their structure. They may be cyclic or non-cyclic in nature. Heterocyclic compounds have a wide range of application. They are predominantly used as pharmaceuticals, agrochemicals, and veterinary products. They also find applications as sanitizers, developers, antioxidants, corrosion inhibitors, copolymers, dyestuff. They are used as vehicles in the synthesis of other organic compounds. Some of the natural products e.g. antibiotics such as penicillin's, cephalosporin; alkaloids such as vinblastine, morphine, reserpine etc. have heterocyclic moiety. 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.

Keywords: Heterocycles, Synthesized compounds, Biological activities.

INTRODUCTION

Compounds classified as heterocyclic probably constitute the largest and most varied family of organic compounds. After all, every carbocyclic compound, regardless of structure and functionality, may in principle be converted into a collection of heterocyclic analogs by replacing one or more of the ring carbon atoms of a different element. Even if we restrict our consideration to oxygen, nitrogen, and sulfur (the most common heterocyclic elements), the permutations and combinations of such a replacement are numerous.

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 feature 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. Between them, sulfur and nitrogen-containing heterocyclic compounds have maintained the interest of researchers through decades of historical development of organic synthesis [1-8]. Synthetic heterocycles have widespread therapeutic uses such as antibacterial, antifungal, anti-mycobacterial, trypanocidal, anti-HIV activity, antileishmanial agents, genotoxic, antitubercular, antimalarial, herbicidal, analgesic, anti-inflammatory, muscle relaxants, anticonvulsant, anticancer and lipid peroxidation inhibitor hypnotics, antidepressant, antitumor, anthelmintic and insecticidal agents [9-15].

Heterocyclic aromatic compounds may be of natural origin (e.g. alkaloids), but high environmental concentrations mainly result from human activities. The higher polarity and water solubility of the heterocyclic substances is based on the substitution of one carbon atom by nitrogen, sulfur or oxygen (NSO-HET) [16]. These chemical properties lead to increased bioavailability and mobility as compared to the homologous polycyclic aromatic hydrocarbons (PAH). Several studies using the concept of effect-directed analysis and mass balance calculations concluded that NSO-HET contributes significantly to the ecotoxicological hazard of water, sediment and soil samples [17-19]. Heterocyclic aromatic compounds are known to show a large range of ecotoxic effects, e.g. acute toxicity, developmental and reproductive toxicity, cytotoxicity, photoinduced toxicity, mutagenicity, and carcinogenicity [20-22].

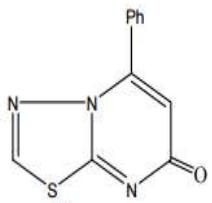
PHARMACOLOGICAL ACTIVITY

Literature survey shows that a number of heterocyclic compounds having condensed ring system possess various types of physiological activities. Condensed triazolo- pyrimidines and N-benzylidene derivatives exhibits antifungal [23-26], anti-inflammatory [27-34], antibacterial [35-42], anticonvulsant [43-46], anti-allergic [47-55], herbicidal [56-63]. Anticancer activity [64-67].

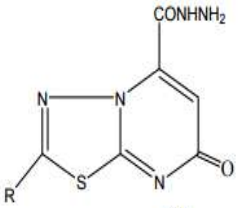
ANTIFUNGAL ACTIVITY

Fungi are heterotropic microorganisms that are distinguished from algae by the lack of photosynthetic ability. Fungi includes both yeast and moulds.The formers are spherical, oval and mucosid colonies in agar medium and the latter consists of elgonated cells that usually reproduce by budding and forming branches of cells.

a) F. Russo et al have synthesized thiadiazolopyrimidines (i) and their hydrazine (ii) R=$CF_3C_6H_4$, 2-$OEtC_6H_4$ and 4-$NO_2C_6H_4$.

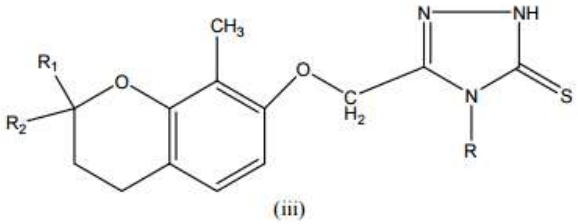


(i)



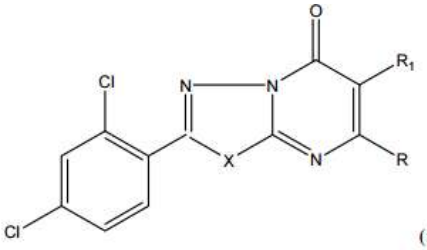
(ii)

b) Ahluwalia et al have synthesized 5-(3',4'-dihydro-2',2',8'-trimethyl-2'H-1'-benzopyran-7-yloxymethyl)-4-phenyl-1,3,4-triazole-3(4H)- thiol (III) which shows significant antifungal activity.R=C_6H_5,mcl-C_6H_4, pcl-C_6H_4,m-or pCH_3- C_6H_4, pCH_3O-C_6H_4.R1=CH_3, C_6H_5,R2=H,CH_3.



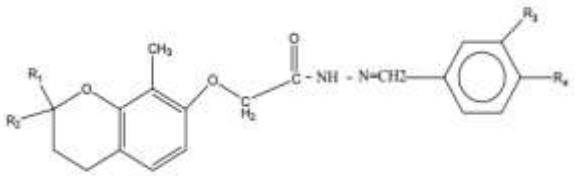
(iii)

c).Gogia et al have synthesized 1,3,4-oxa / thiadiazolo –(3,2-a)pyrimidin-5-one (iv) which shows antifungal activity.x=O,S.



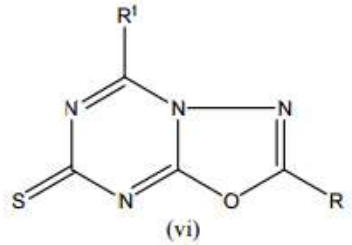
(iv)

d).Ahluwalia et al have studied the N-benzylidene-3, 4-dihydro-2,2,8-trimethyl-2H-1-benzopyran-7-yloxyacetie acid hydrazide (v) and found antifungal R1=R2=CH_3,C_6H_5,R3=R4=H,CH_3.



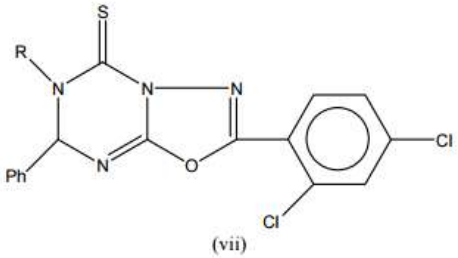
(v)

e).Singh et al have synthesized 1,3,4-oxadiazolo-(3,2-a)-s-triazin-7-thione(vi).and found antifungal.In compound(v), R= C_6H_5 CH_2-,C_6H_5,$OClC_6H_4$,m-MeC_6H_4,p-MeC_6H_4;R1 =C_6H_5,O- ClC_6H_4



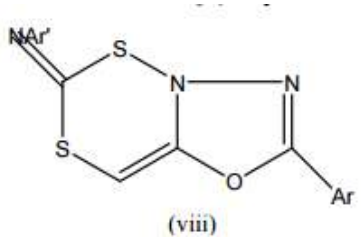
(vi)

f) Dutta et al have synthesized 2-substituted 1,3,4-oxadiazolo-[3,2-a]-1,3,5-triazin-5-(6H,7H)-thione derivatives(vii).and found antifungal.In compound (vii), R= C_6H_5 ,4-BrC_6H_4,4-ClC_6H_4,2-ClC_6H_4,3- ClC_6H_4,2-$No2C_6H_4$; 3-$No2C_6H_4$



(vii)

g) Dhar et al have synthesized 1,3,4-oxadiazolo-[3,2-a]- 1,3,4-dithiazines (viii). and found antifungal.In compound (viii) Ar=2-ClC_6H_4, Ar'=2- $ClC_6H_4OCH_2$.

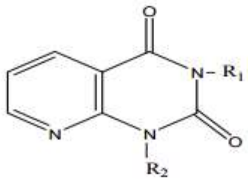


(viii)

ANTI-INFLAMMATORY

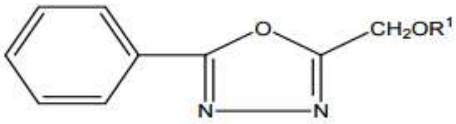
Anti-inflammatory drugs make up about half of analgesics, remedying pain by reducing inflammation as opposed to opioids, which affect the CNS. Non-steroidal anti-inflammatory drugs (NSAIDs), Some common examples of NSAIDs are aspirin, ibuprofen, and naproxen. The newer specific COX-inhibitors - although, it is presumed, sharing a similar mode of action - are not classified together with the traditional NSAIDs. Long-term use of NSAIDs can cause gastric erosions, which can become stomach ulcers and in extreme cases can cause severe hemorrhage, resulting in death. The risk of death as a result of the use of NSAIDs is 1 in 12,000 for adults aged 16–45. Other dangers of NSAIDs are exacerbating asthma and causing kidney damage. Apart from aspirin, prescription, and over-the-counter NSAIDs also, increase the risk of myocardial infarction and stroke.

a) J.A. Beres and Coworkers have synthesized the compound associated with anti-inflammatory activity. Pyrido [2, 3, - d] pyrimidinone derivatives have been found to possess anti-inflammatory activities. In compound (I), R1 =H, halo, alkyl, R2 =Ph, Cyclohexyl, alkyl, OH.



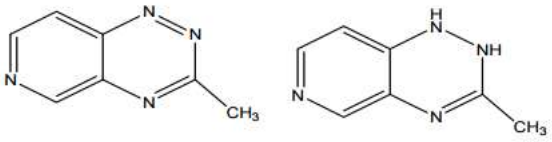
(ix)

b) Thomas et al have synthesized 2-(hydroxymethy1)- 5-pheny1-1, 3, 4-oxadiazoles (x) and found that these show antiinflammatory activities in mice , rats, and guineapigs. In compound (x), R1 =H, $CONH_2$ OR CONHMe.



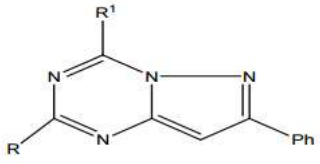
(x)

c) Lewis et al have synthesized 3-Subtstituted - Pyrido-[3, 4-e]-as-triazines (xi), (xii). These compounds showed antiinflammatory activity.



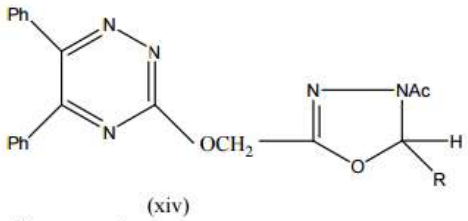
(xi) (xii)

d) Kim et al have reported 7-phenyl pyrazolo-[1, 5-a]-1, 3, 5-triazine derivatives as anti-inflammatory agents (xiii) where R= Thia alkyl, R1 =Substituted amino, N-heterocycloalkyl.

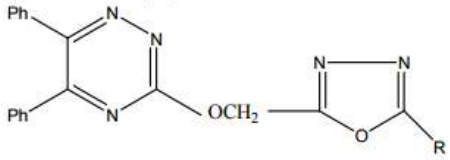


(xiii)

e).Abdle et al have synthesized some novel 1,3,4-oxadiazole derivatives (xiv), (xv). In compound xv R=4-ClC_6H_4, 4-$MeOC_6H_4$, 3, 4- $(MeO)_2$ C_6H_3, 4-$(Me_2N)C_6H_4$

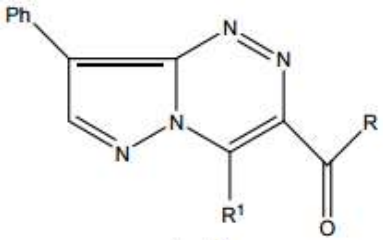


(xiv)



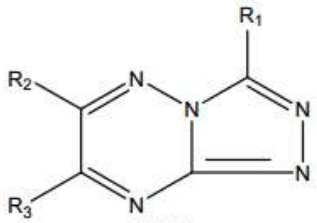
(xv)

f) Joshi et al have synthesized some fluorine containing pyrazolo [5, 1,-C]- 1, 2, 4-triazine (xvi) whereR=3,4-ClFC$_6$H$_3$



(xvi)

g) Heilman et al have synthesized 1,2,4-triazolo [4, 3-b]-1, 2, 4-triazines (xvii) where R1 =H,alkyl,alkoxyalkyl,haloalkyl,R2 = H, alkyl, pyridyl, R3 = alkyl, pyridyl,haloalkyl

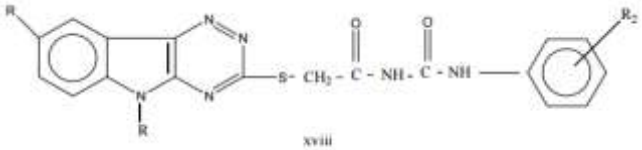


(XVII)

ANTIBACTERIAL

Bacteria are the simplest and smallest unicellular organisms found individually or in clusters. The multitude of highly effective and relatively non-toxic drugs available for the treatment of bacterial infections has provided tough competition for the medicinal chemist, attempting a synthesis of new antibacterial agents.

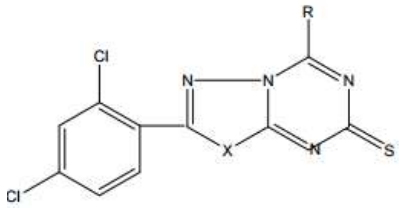
a) Sen Gupta et al has synthesized (xviii), some triazine derivatives and found antibacterial agents.



xviii

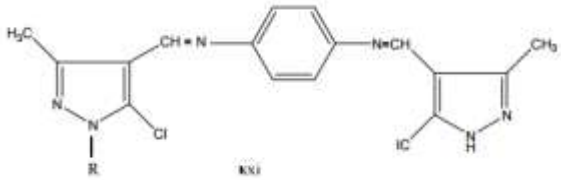
b) Desai et al have synthesized (xix), 2, 4-bis (4-methoxy-anilino)-6-(N-aryl-thiourido-N-amino-acyl)-1, 3, 5- triazine derivatives and found antibacterial agents.

c) Dutta et al have synthesized 2, 5-disubstituted-1, 3, 4-oxadiazolo/ thiadiazolo -[3,2-a]-S-triazine-5-7-thiones (xx).and found antibacterial agents.In compound (xx),

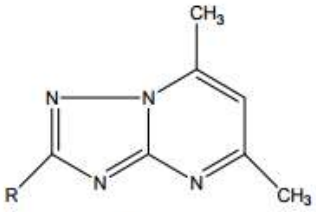


XX

d) Pawar et al have synthesized 6-hydroxy-3-methyl-1-phenylpyrazolo [5,4-d] pyrimidine. (xxi), found antibacterial agents.

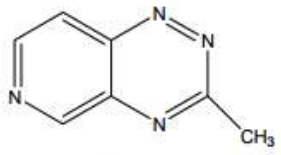


e) Novinson et al have synthesized substituted triazolo-pyrimidine derivatives and found antibacterial activity.In compound (xxii), R= pyridyl

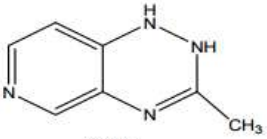


XXII

f) Lewis et al have synthesized 3-substituted pyrido [3,4-e]-as-triazine (xxiii) & (xxiv) and found antibacterial useful agents

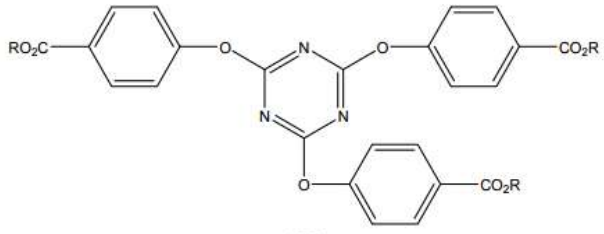


XXIII



XXIV

g) Saeki et al have synthesized triazine derivatives (xxv), where R=alkyl, Ph. and found antibacterial useful agents.

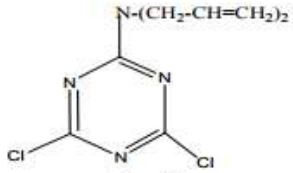


XXV

ANTICONVULSANT

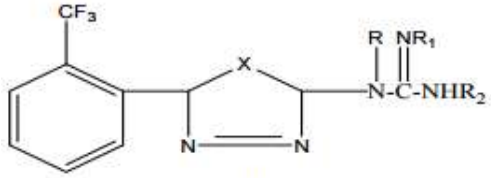
These are defined as the agents that prevent the severity of convulsive seizures.

a) Kreutzberger et al have synthesized 2,4-dichloro-6-dialkylamino-1,3,5- triazine derivatives(xxvi) and found anticonvulsant useful agent



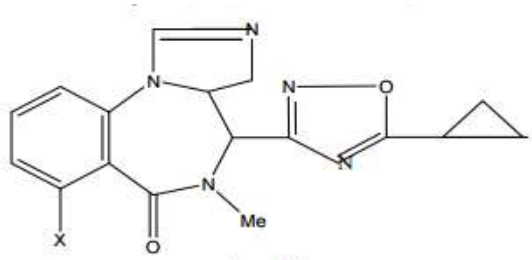
(xxvi)

b) Chapleo et al have synthesized some substituted-1,3,4- thia/ oxadiazoles (xxvii).) and found anticonvulsant useful agent.X=O, S, R=H, Me, R1=R2=H,alkyl,Ph-CH_2.



(xxvii).

c).Waetzen et al have synthesized oxadiazolylimidazobenzodiazepines (xxviii) which have useful anticonvulsant activity in mice. In compound (xxviii) X=Br, Cl, F, Me, CF_3 ,CN.

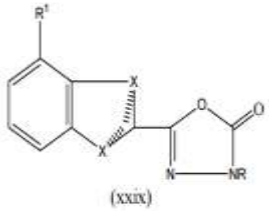


(xxviii).

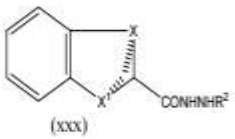
ANTI-ALLERGIC

A number of heterocyclic compounds have shown the antiallergic activity.

a) Musser et al have synthesized 2-(2, 3-dihydro-2-oxo-1, 3,4-oxadiazol-5-yl) benzo heterocycles (xxix), (xxx). In compound xxix X=O, NMe, CCl, CH, CMe; X'=N, S, CH_2, NH; R=H, Ac, CO_2Et, Me etc. R'=H, 5-Cl', 5-(CO_2Me), 5-CO_2Et and in compound xxx R2 =H, CO_2ET

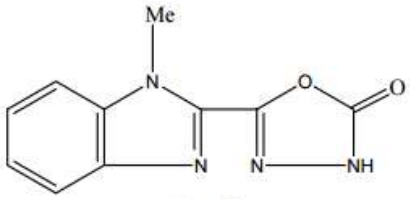


(xxix)



(xxx)

b) Khandwala et al have synthesized 1-menthyl-2-[1,3,4-oxadiazol-2(3H)-one-5-yl] benzimidazole(xxxi)and related compounds as antiallergic agents.

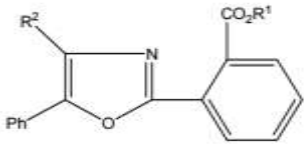


(xxxi)

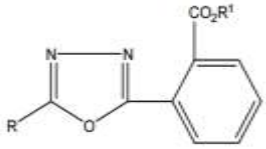
HERBICIDAL ACTIVITY

These are the drugs which destroy the unwanted plants along with some grasses without affecting the food crops.

a) Brouwer, et al have synthesized oxazole and Oxadiazole benzoic acid derivatives (xxxii &xxxiii) as herbicides. In compound xxiii R'=H, R2 =H, Me; R'=Et, Bu; R2 =H and in compound XXIV r=Ph, substituted phenyl, (3-pyridyl), Me, R'=H, Me, Et, Propyl, Butyl, Octyl, Dodecyl.

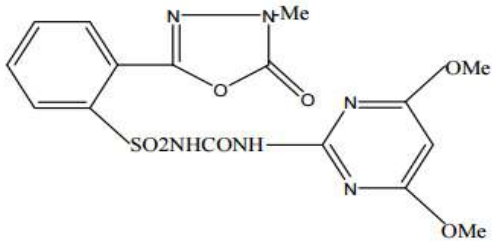


xxxii



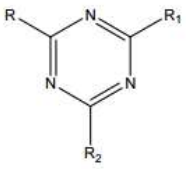
xxxiii

b) Rorer and coworkers have synthesised phenyl-2-[3-methyl-1,3,4-oxdiazol-2-(3H)-one] sulfonylpyrimidyl urea (xxxiv).



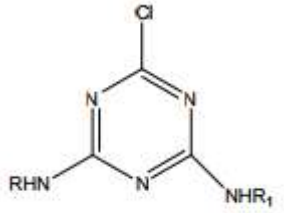
xxxiv

c). Bandarenko et al have synthesized –s-triazines (xxxv), a new series of biologically active compounds. In these compounds R, R1,R2= Cl, MeO,-NH_2, NMe_2,$NHCHMe_2$, SH, Sme, SEt.. Some of these show herbicidal activity.



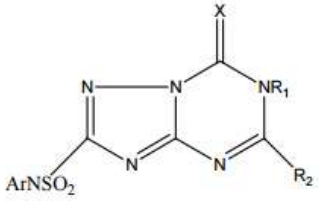
XXXV

d). Two well-known herbicides such as simazine (xxxvi) R=R1= ethyl and atrazine R=ethyl; R1=isopropyl are persistent soil acting herbicides which can be applied n large concentration (5-10/ha) as a total weed killer.



XXXVI

e) Westerman et al have prepared 6,7-dihydro-1,3,4-triazolo[1,5-a]-1,3,5-triazin-2-Sulfonamides (xxxvii) and found them as agents with herbicidal and plant growth regulating activity. In compound xxxvii Ar=(un) / substituted Ph, naphthyl, pyridyl; R=H, acyl, alkyl,phenyl alkyl,(un) substituted carbonyl etc.R1,R2= phenyl; X=O,S.

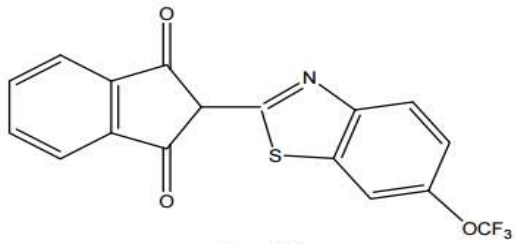


xxxvii

ANTICANCER ACTIVITY

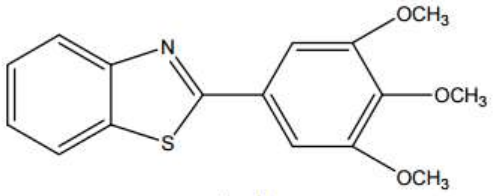
Anticancer refers to a group of disease caused by several agents like as chemical compound, radiant energy. Cancer is characterized by an abnormal & uncontrolled division of cell exhibiting varying the degree of malignancy which produces tumor & invades adjacent normal tissue. These agents are used for the treatment of cancer or either kill cancer cells or modify their growth.

a) Stanton HLK, et al have synthesized (xxxviii) benzothiazole containing phthalimide and studied their anti-cancer activity on human carcinoma cell lines



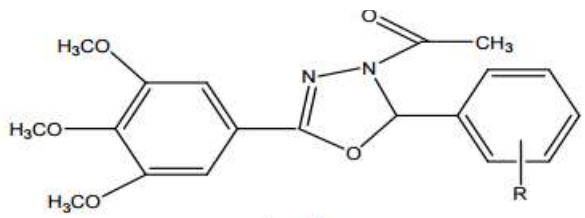
(xxxviii)

b) Wang M et al have(xxxix) synthesized carbon 11 labeled fluorinated2-aryl benzothiazoles used for protein emission tomography(PET) to image tyrocinekinese in cancer



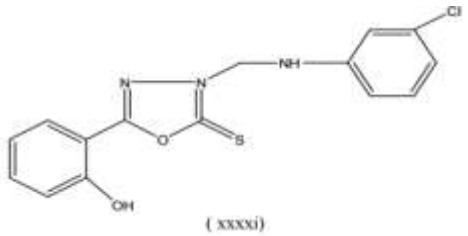
(xxxix)

c) Aboraia S. Ahmed et al have synthesized 3-acetyl-2-substituted phenyl -5-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1,3,4-oxadiazole derivatives and these compound were screened for their in vitro antitumor activities against PC_3, BGC823, & Bcap-37 by MTT method



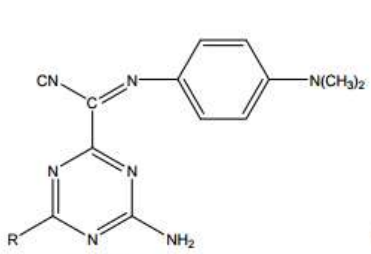
(xxxx)

d) Jin Jiang Chen et al have synthesized a new series of 5-(2-hydroxyphenyl)-2-substituted -2,3-dihydro-1,3,4- oxadiazole-2-thione derivatives The promising anticancer activities were reported.



(xxxxi)

e) Sączewski F et al have Synthesized(xxxxii) and (xxxxiii) and reported anticancer activity of novel 2,4-diamino-1,3,5-triazine derivatives and of a novel alkenyl -1,3,5-triazine derivatives, it showed growth inhibitory activity in low micromolar concentrations against renal cancer A498 cell line and colon cancer cell line COLO 205.



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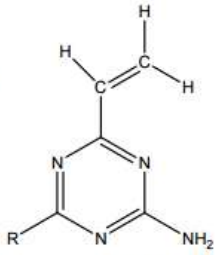
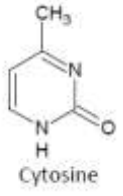


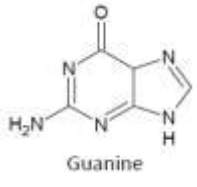
(xxxxii)

Heterocyclic compounds are of fundamental importance to living systems. It is striking how often a heterocyclic compound is found as a key component in biological processes. For example the nucleic acid bases, which are derivatives of the purine, namely adenine, guanine and pyrimidine, namely thymine, cytosine as being crucial to the mechanism of replication. Some purine and pyrimidines can act as antibiotics, by interference with DNA synthesis. *Puromycin* is an example of such an antibiotic.



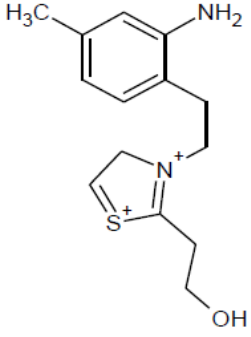
Cytosine

Thymine

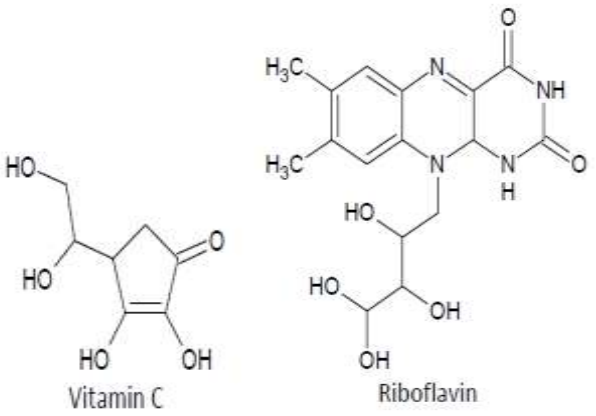


Guanine

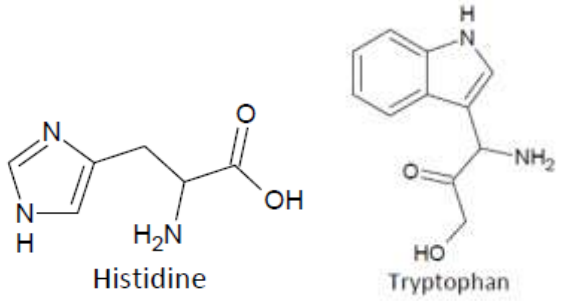
Chlorophyll and heme, which are derivatives porphyrin ring system are the components required for the photosynthesis and for oxygen transport in higher plants and in animal. Essential diet ingredients such as thiamin (vitamin B1), riboflavin (vitamin B2), pyridoxol (vitamin B6), nicotinamide (vitamin B3) and ascorbic acid (vitamin C) are heterocyclic compounds.



Thiamine



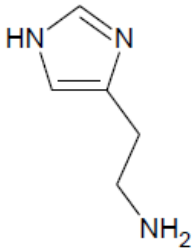
Of the twenty amino acids commonly found in different proteins, three, namely histidine, proline, and tryptophan, are heterocyclic.



Many of the pharmaceuticals and most of the other heterocyclic compounds with practical applications are nor extracted from natural sources but are synthesized. The origins of organic chemistry do however lie in the study of natural products. These have formed the basis for the design of many of the useful compounds developed subsequently: examples are the early development of vat dyes based on the structure of indigo and the continuing invention of new antibacterial agents based on the β-lactam structure of penicillin. Some examples of drugs having β-lactam moiety are cephalosporin C**,** amoxicillin, clavulanic acid, penicillin etc.

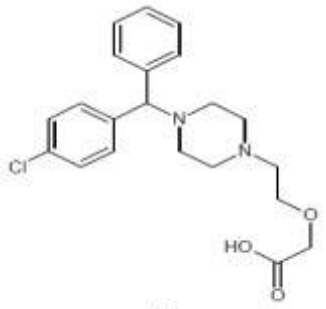
Pharmaceuticals related to Histamine

Histamine, a monosubstituted imidazole, is derived *in vivo* from the amino acid histidine by decarboxylation by enzyme histidine decarboxylase. Histamine, [2] a biogenic amine involved in local immune responses and also acts as a neurotransmitter [68]. It is involved in allergic reactions and is liberated from skin cells on injury and also participates in the regulation of gastric acid secretion.



(2)

From the 1940s onwards several synthetic drugs became available that can act as histamine antagonists. Two different types of histamine receptor were distinguished in the body; these were labeled as H1 and H2 receptors. Cetirizine [3], chlorpheniramine [4] etc act as blockers of H1 receptors.



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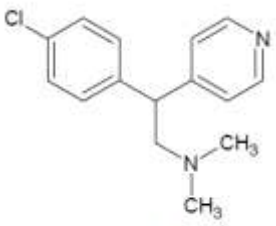
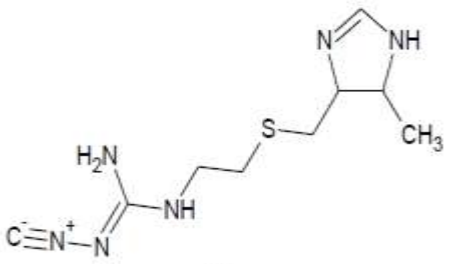


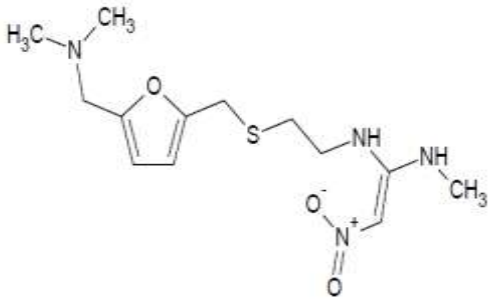
(4)

Although it took a long period to discover active compounds, the work eventually resulted in 1976 was the introduction of a drug, cimetidine an imidazole derivative for the treatment of peptic ulcers [69-70]

The success of cimetidine [5] has prompted the introduction of other drugs having structures that are closely related but with the replacement of imidazole ring by other heterocycles. Rantidine [6] containing a furan ring, is also an important and successful drug for the treatment of peptic ulcer [71-72]. Another drug, Famotidine having thiazole moiety, inhibits stomach acid production and gastro esophageal reflux disease [73] (GERD).

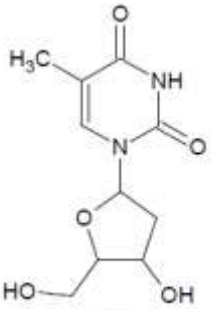


(5)



(6)

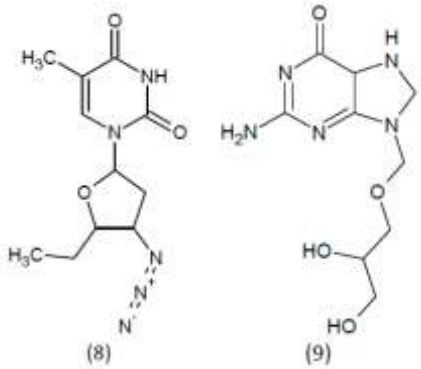
Nucleoside Analogues: A logical starting point in the search for drugs to combat cancer and viruses is the structure of DNA. One of the approaches that have been intensively explored is to investigate the use of analogues [74-75] of the nucleosides. These nucleic acid fragments consist of a heterocyclic nitrogenous base (a purine or a pyrimidine) linked to a sugar; for example 2'deoxythymidine [7].

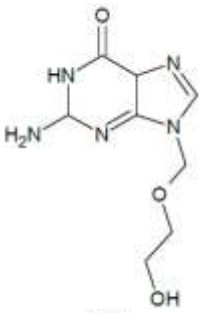


(7)

Some important drugs of this type have been produced. Zidovudine/azidothymidine (AZT) [8] (also called ZDV) is a nucleoside analog reverse transcriptase inhibitor [76-78] (NRTI), an a type of antiretroviral [79-80] drug used in the treatment of AIDS, is an analogue of 2'-deoxythymidine. Acyclovir (ACV) [9] is an analogue of 2'-deoxyguanosine, in which the acyclic side chain part mimics the sugar in the natural nucleoside.

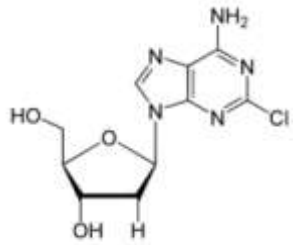
It is a useful drug for the treatment of herpes simplex [81] and herpes zoster viral infections due to high selectivity [82] and low cytotoxicity. Ganciclovir [10] is a structurally related antiviral agent that has been used for the treatment of cytomegalovirus infections [83-84] in AIDS patient and in recipients of organ transplants





(10)

Cladribine (Leustatin) [85] [11] and Pentostatin [86] [12] are drugs, used to treat hairy cell leukemia (leukemic reticuloendotheliosis) and multiple sclerosis.



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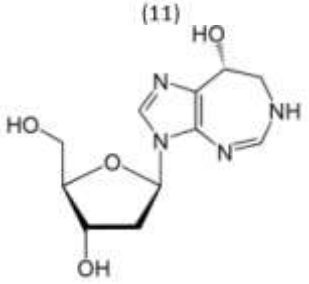
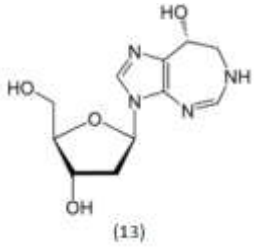


(12)

Compounds related to Serotonin

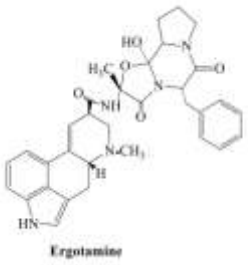
Natural products often occur in small quantities and, therefore, difficult to investigate if the compounds have to be extracted from the natural source. Organic chemists can provide a solution to the problem by devising practical laboratory synthesis. An example is provided by serotonin [13] (commonly called 5-hydroxy tryptamine or 5-HT). This compound is widely distributed in nature but occurs only in low concentration. It is derived in nature from the amino acid tryptophan, by the short pathway including two enzymes, tryptophan hydroxylase, and amino acid decarboxylase.



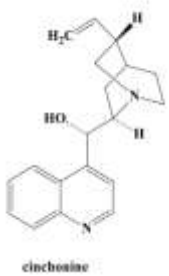
(13)

It acts as a constrictor of arteries in the brain and is implicated in a migraine [87]. Changes in serotnin concentration in the brain also alter mood [88-91] and appetite. However, it is too rapidly metabolized to have any potential as a pharmaceutical agent.

Ergotamine, the indole-based alkaloid exhibits antimigraine activity [92] .Cinchonine, a quinolone class of alkaloid shows antimalarial activity [93]

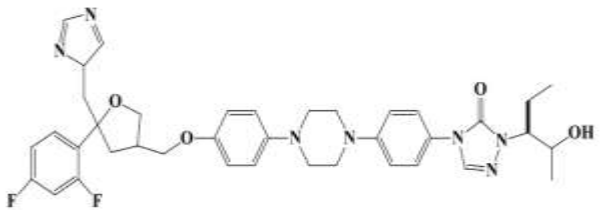


Ergotamine



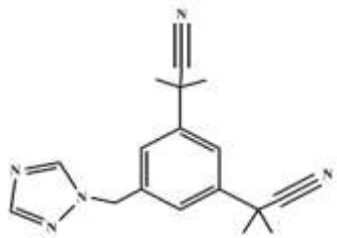
cinchonine

Posaconazole is a triazole antifungal drug [94] . It is active against the following microorganism candida, aspergillus, Zygomycetes.



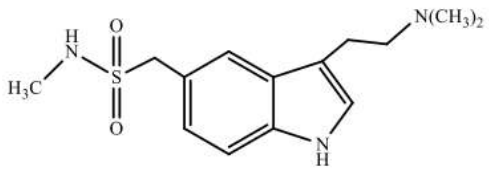
Posaconazole

Anastrozole is an aromatase-inhibiting drug approved for the treatment of breast cancer after surgery, as well as for metastasis in both pre and postmenopausal women. The severity of breast cancer is increased by estrogen, as sex hormones cause hyperplasia, and differentiation at estrogen receptor sites [95-96] .Anastrozole works by inhibiting the synthesis of estrogen.



Anastrozole

Sumatriptan, a heterocyclic compound is the first antimigraine drug [97] , replacement of sulfonamide moiety in sumatriptan with 1, 2,4-triazole (A), which is also a potent 5-HT1D receptor agonist [98] .



Sumatriptan

CONCLUSION

According to our study heterocyclic compounds and their derivatives known to exhibit anti fungal, anti inflammatory, anti convulsant, anti bacterial, anti allergic, anti herbicidal, anti-cancer activity. There is still a lot to known about the heterocyclic compounds. On further study, we will get to know about heterocyclic compound and pharmacological activity.

ACKNOWLEDGEMENT

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