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BIOLOGICAL AND SYNTHETIC STUDIES OF FOUR, FIVE AND SIX MEMBERED HETEROCYCLES

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ABSTRACT
The largest of classical divisions of organic chemistry are formed by heterocycles and are of immense importance biologically and industrially. In the area of research, for more than a century the largest area is being occupied by heterocyclic compounds. An enormous number of heterocyclic compounds are known and this number is increasing rapidly. It is well known in literature that nitrogen and sulfur containing compounds are essentially used in medical purpose for the treatment of different kinds of fungal and bacterial infections along with treatment of gastric ulcer, cancer etc. In this review, we emphasize on overview of heterocyclic active compounds like- azetidinone, imidazole, pyrimidine and 2-amino benzenethiol families and their main applications in medicine.

KEYWORDS: Azetidinone, Imidazole, Pyrimidine, 2-amino benzenthiol

1. INTRODUCTION

1.1 AN OVERVIEW OF HETEROCYCLIC COMPOUNDS:

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. The heterocyclic compounds are organic compounds containing at least one atom of carbon and at least one element other than carbon, such as sulfur, oxygen or nitrogen within a ring structure. They are widely distributed in nature. It is striking how often a heterocyclic compound is found as a key component in biological processes. The aliphatic heterocycles are the cyclic analogues of amines, ethers, thio ethers, amides etc. Their properties are particularly influenced by the presence of strain in the ring. These compounds generally consist of small (3- and 4-membered), common (5 to 7 membered) ring systems and fused ring systems **(fig.1)**. The aromatic heterocyclic compounds behave in a manner similar to benzene in some of their properties. Furthermore, these compounds also comply with the general rule proposed by Huckel. Besides the vast distribution of heterocycles in natural products, they are also the major components of biological molecules such as DNA and RNA.

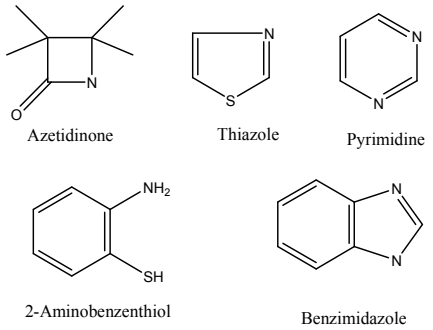


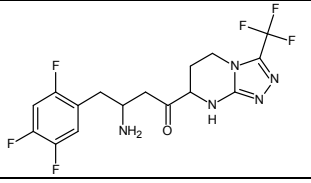
Fig 1 : Structure and name of some heterocycles

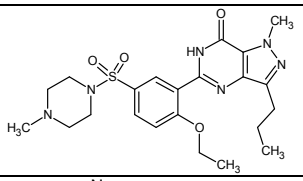
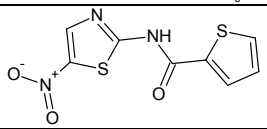
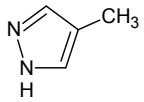
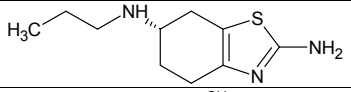
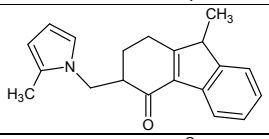
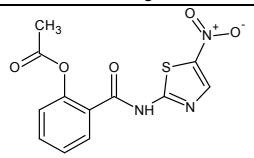
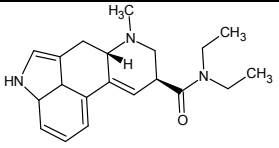
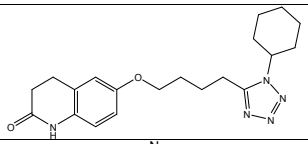
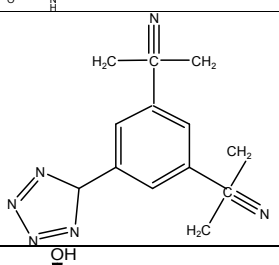
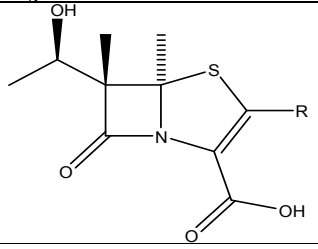
Heterocycles form by far the largest of classical organic divisions of organic chemistry and are of immense importance biologically and industrially. The majority of pharmaceuticals and biologically active agrochemicals are heterocycles while countless additives and modifiers used in industrial applications ranging from cosmetics reprography, information storage and plastics are heterocycles in nature. One striking structural features inherent to heterocycles, which continue to be of 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, 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 heterocycles. 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.

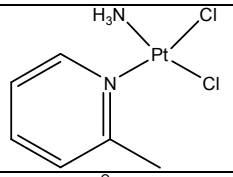
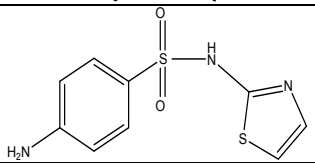
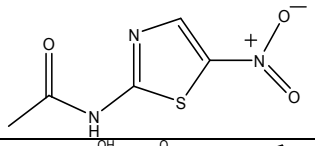
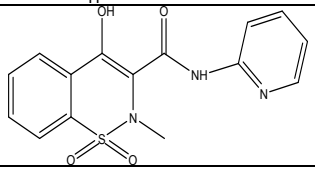
Medicinal chemistry is a chemistry-based discipline, involving aspects of biological, medical and pharmaceutical sciences. It is concerned with the invention, discovery, design, identification and preparation of biologically active compounds, the study of their metabolism, the interpretation of their mode of action at the molecular level and the construction of structure-activity relationships (SARs). It includes synthetic and computational aspects of the study of existing drugs and agents in development in relation to their biological activities. Pharmaceutical chemistry is focused on quality aspects of medicines and aims to assure fitness for purpose of medicinal products.

Compounds used as medicines are most often organic compounds, which are often divided into the broad classes of small organic molecules (e.g., atorvastatin, fluticasone, clopidogrel) and "biologics" (infliximab, erythropoietin, insulin glargine), the latter of which are most often medicinal preparations of proteins (natural and recombinant antibodies, hormones etc).

Pharmacological Activity of Some Clinically Used Heterocyles

S No	Name of Drug	Activity	Chemical Structure
1.	Sitagliptin	Antidiabetic	

S No	Name of Drug	Activity	Chemical Structure
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.	Cilostazole	Antiplatelet drug	
10.	Anastrozole	Aromatase inhibitor	
11.	Penem	Antibiotic drug	

S No	Name of Drug	Activity	Chemical Structure
12.	Picoplatin	Antineoplastic drug	
13	Sulfathiazole	Antimicrobial drug	
14	Acinitrazole	Prophylactic drug	
15.	Piroxicam	Anti-inflammatory drug	

2. AZETIDINONE

Natural and synthetic azetidinone derivatives occupy a central place among medicinally important compounds due to their diverse and interesting antibiotic activities. Even though they have a long history of development starting from the discovery of Penicillin in 1928 the quest for new synthetic methods and refinement of those already known remains appealing, as does the research into the application of these methods in synthesising novel biologically active azetidinone derivatives. The utility of azetidinones as synthons for various biologically active compounds, as well as their recognition as cholesterol absorption inhibitors and enzyme inhibitors, has given impetus to these studies. In the late 1990s, several groups reported novel methodologies for the synthesis of azetidinones. Since then, a plethora of work has appeared in the literature. It would therefore be useful to review the work done in this area more frequently. The synthetic methods are described under four headings— Staudinger reaction and related methods (cycloaddition), cyclisation (amino acids, amino esters, etc.) and other methods, chemical transformations in azetidinone ring containing compounds and, finally, the synthesis of 3-azetidinones.

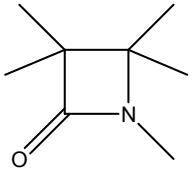
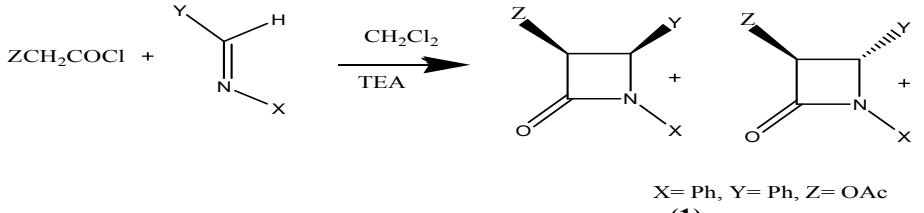


Fig. 2 : Structure of azetidinone

2.1 SYNTHETIC ASPECTS OF AZETIDINONE

Staudinger's ketene–imine reaction is the most common method for the synthesis of azetidinones and it has been reviewed recently by Palomo *et al*.[9] The reaction is carried out thermally or photochemically using acid chlorides in the presence of triethylamine or 2-

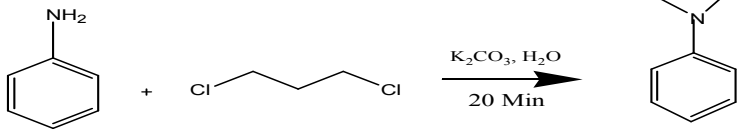
diazoketones as ketene precursors. The previous decade has also seen the use of microwave radiation in synthesizing azetidinone. **(Scheme-1)**



(1)

Scheme-1

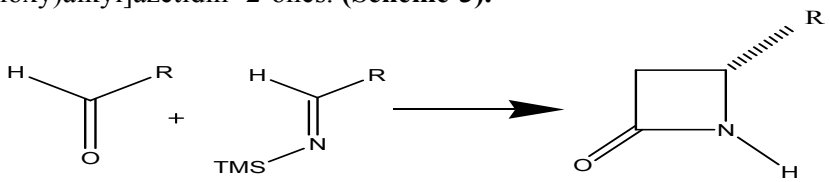
Alberto *et al.*[10] synthesized via cyclization of aniline with 1,3-dichloropropane in water by the assistance of microwaves (80-100 W), affording N-Ph-azetidine. **(Scheme-2)**



(2)

Scheme-2

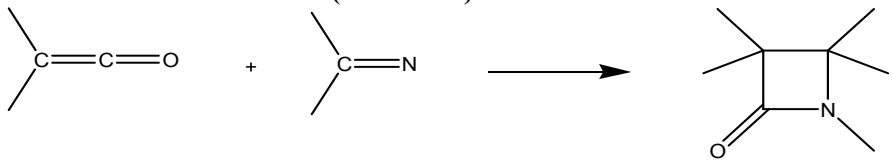
Elisa *et al.*[11] utilized 2-aza-1,3-dienes for preparation of the *α*-lactam ring. They reported a trans-stereoselective synthesis of 3-halo-4-arylazetidin 2-ones and 3-halo-4-[1-(triialkylsilyloxy)alkyl]azetidin- 2-ones. **(Scheme-3).**



(3)

Scheme-3

Singh *et al.*[12] reported highly stereoselective photochemical reactions of diazoketones derived from suitably protected amino acids with the imines leading to trans-arranged 4-aryl cinnamoyl-substituted azetidinones. **(Scheme-4)**



(4)

Scheme-4

2.2 MEDICINAL SIGNIFANCE OF AZETIDINONE

Even more than 70 years after the discovery of penicillin, β-lactam antibiotics remain as one of the most important contributions of science to humanity. The β-lactam skeleton is the common structural element of the widely used penicillins, cephalosporins, thienamycin, nocardicins, aztreonam and carumonam. The 2-azetidinone derivatives have been reported to possess a wide range of biological activities *i.e.* antimicrobial, anticancer, antitubercular, anti-inflammatory, anticonvulsant, antidiabetic, antiviral, cholesterol absorption inhibitor, tryptase and chymase inhibitor, vasopressin via antagonists and fatty acid amide hydrolase.

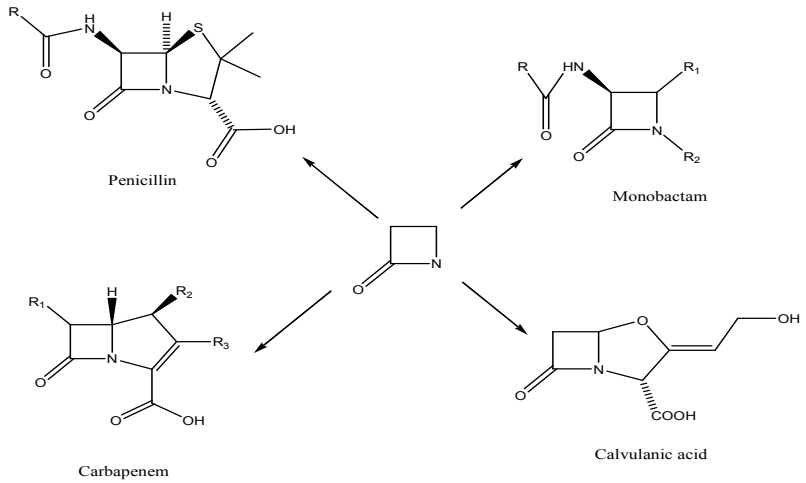
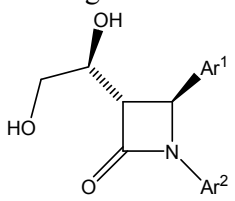


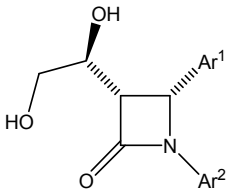
Fig. 3 : **Azetidinone containing drugs**

Guangzhong *et al.*[13] developed novel one-step diastereo- and enantioselective formation of trans-azetidinones **(5 and 6**) and its application to the total synthesis of cholesterol absorption inhibitors**.** Recently, trans azetidinones have been found to be potent cholesterol absorption inhibitors (CAI) and have shown efficacy in clinical trials in reducing cholesterol levels. Various synthetic methods have been developed to establish the two chiral centers on the *α*-lactam ring.



Trans

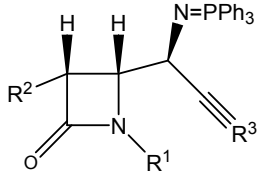
(5)



Cis

(6)

Benito *et al.*[14] synthesized optically pure highly functionalized γ-Lactams via 2-azetidinone-tethered iminophosphoranes**(7).** Despite the versatility of the 2-azetidinone ring, synthetic routes to monocyclic *β*-lactams from *γ*-lactams have been scarcely reported. The Carbonyl *γ*-lactams were used as chiral templates and recently have shown their manipulation to a variety of potentially bioactive products. Palomo *et al.*[15] explained the construction of quaternary stereogenic centers via cycloaddition reactions. They synthesized homochiral 4,4-disubstituted 2-azetidinones derivatives **(8)** containing *β*-lactam nucleus and tested its in vitro for their antimicrobial activity.

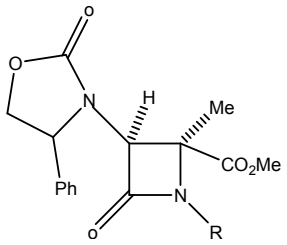


R^1= Propenyl

$R^{2 = }$ OPh

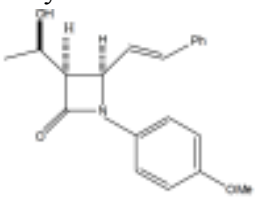
R^3 = Ph

(7)

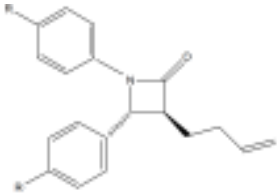


(8)

Georg *et al.*[16] developed metal directed stereoselective synthesis of S-1-Hydroxyethyl 2-azetidinone derivatives **(9)** from methyl 3-hydroxybutyrate and evaluated its antihyperglycemic activity against alloxan–induced diabetes in rats and Sharma *et al.*[17] developed convenient trans diastereoselective synthesis of 3-butadienylazetidinones **(10)** and their Diels-Alder cycloaddition reactions. The importance and structural diversity of biologically active *α*-lactam antibiotics led to the development of many novel methods for the construction of appropriately substituted azetidin-2-ones with attendent control of functional groups and stereochemistry. In recent years several natural monocyclic *β*-lactams were found to exhibit high activity against Gram negative organisms, suggesting that a suitably substituted monocyclic β-lactam ring might perhaps be the minimum requirement for biological activity.

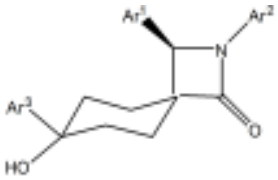


(9)



(10)

Guangzhong *et al.*[18] reported catalytic asymmetric synthesis of a spirofused azetidinone **(11)** and its role as a cholesterol absorption inhibitor. The recent discovery of potent cholesterol absorption inhibition by this class has stimulated significant synthetic interests in developing asymmetric processes. Mattingly *et al.*[19] have reported synthesis and bactericidal property of different 2-azetidinones **(12).**

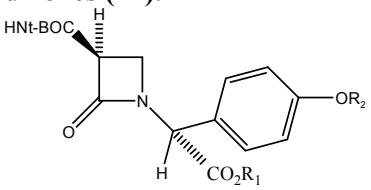


Ar_1= $BnoC_6H_4$

Ar_2= FC_6H_4

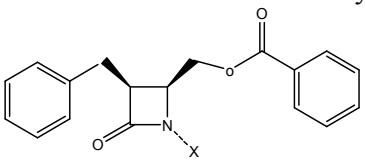
Ar_3 = ClC_6H_4

(11)

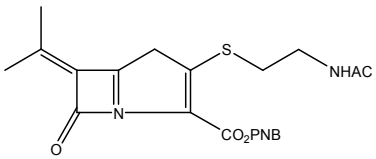


(12)

Benito *et al.*[20] discussed the stereoselective synthesis of 3-substituted 4-(formyloxy)-2-azetidinones (**13)** by the unusual Baeyer-villiger reaction of β-Lactam aldehyde and robert Adlington *et al.*[21] discussed the active site binding analysis of monocyclic 2-azetidinone **(14)** derivatives and screened its antiviral activity**.**



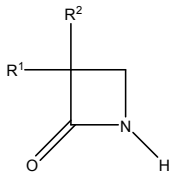
(13)



(14)

Mckittrick *et al.*[22] explained synthesis of C_3 heteroatom-substituted azetidinones **(15)** that display potent cholesterol absorption inhibitory activity. Alcaide *et al.*[23] synthesized highly substituted lactam rings derivatives **(16)** which possess diverse biological activity,

and much attention was focused on excitatory amino acid chemistry, to better understand CNS function in mammalian systems.



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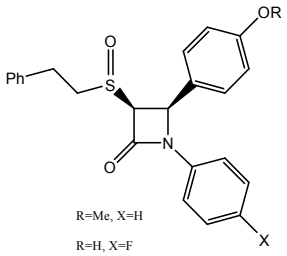


(16)

3. IMIDAZOLE

Imidazole ring is an important five-membered aromatic heterocycle widely present in natural products and synthetic molecules. The unique structural feature of imidazole ring with desirable electron rich characteristic is beneficial for imidazole derivatives to readily bind with a variety of enzymes and receptors in biological systems through diverse weak interactions, thereby exhibiting broad bioactivities. The related research and developments of imidazole-based medicinal chemistry have become a rapidly developing and increasingly active topic.

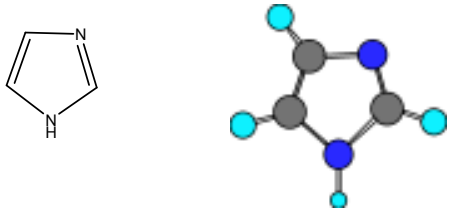
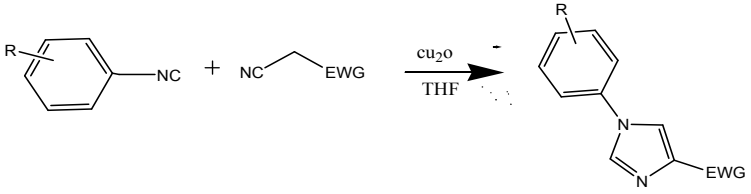


Fig. 4

The imidazole ring has also been identified as an attractive isostere of triazole, oxazole, pyrazole, thiazole, tetrazole, amide etc., and extensively used to design and develop various bioactive molecules.

3.1 SYNTHETIC ASPECTS OF IMIDAZOLE

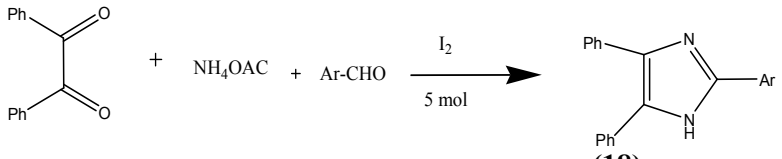
Chikashi *et al.*[24] synthesized copper-catalyzed cross-cycloaddition between arylisocyanides and isocyanides by 1,4- disubstituted imidazoles in very high yields **(Scheme-5).**



(17)

Scheme -5

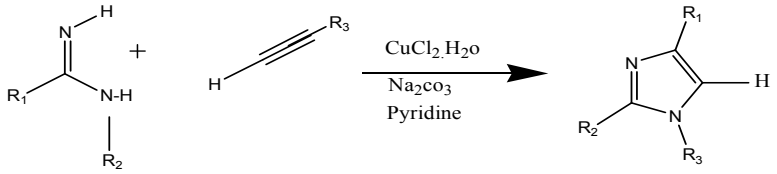
Mazaahir *et al.*[25] synthesized iodine facilitated diamine intermediate (I), which under mild acid catalysis of iodine condenses further with the carbonyl carbon of 1,2 diketone followed by dehydration to afford the iso-imidazole (II), which rearranges via [1,5] sigmatropic shift to the required imidazoles **(Scheme-6).**



(18)

Scheme- 6

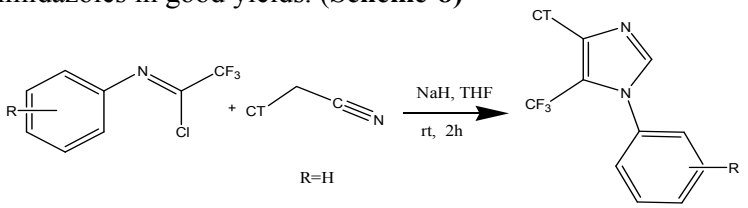
Jihui *et al*.[26] have synthesized 1,2,4-tri substituted Imidazoles**(Scheme-7)**.



(19)

Scheme- 7

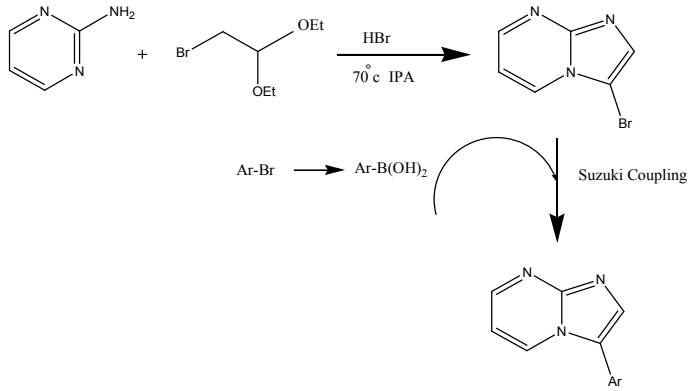
Bunev *et al*.[27] synthesized a new series of 1,4,5-trisubstituted imidazoles containing trifluoromethyl group i.e. using van Leusen reaction, which incorporate two-component condensation reaction-trifluoroacetimidoyl chlorides with tosylmethylisocyanide. This protocol provide a novel and improved method for obtaining trifluoromethyl containing 1, 4, 5-trisubstituted imidazoles in good yields. (**Scheme-8)**



(20)

Scheme -8

Wenjie *et al.*[28] prepared 3-arylimidazo[1,2-*a*]pyrimidines as intermediates for synthesizing pharmaceutically active compounds. Their initial approach involved bromination at the 3-position of imidazo[1,2-*a*]pyrimidine which was prepared using Suzuki coupling with arylboronic acids to give the desired product. **(Scheme-9)**



(21)

Scheme- 9

3.2 MEDICINAL SIGNIFICANCE OF IMIDAZOLE

Particularly, numerous imidazole-based compounds as clinical drugs have been extensively used in the clinic to treat various types of diseases with high therapeutic potency, which have shown the enormous development value. This work systematically gives a comprehensive review in current developments of imidazole-based compounds in the whole range of medicinal chemistry as anti-inflammatory[29-30], anti-viral[31-32], antidiabitic[33-34], anticonvulsant[35-42], antineuropathic[43-44], antibacterial, antitubercular, antihypertensive, antihistaminic, antiparasitic, antiobesity, and other medicinal agents, together with their potential applications in diagnostics and pathology.

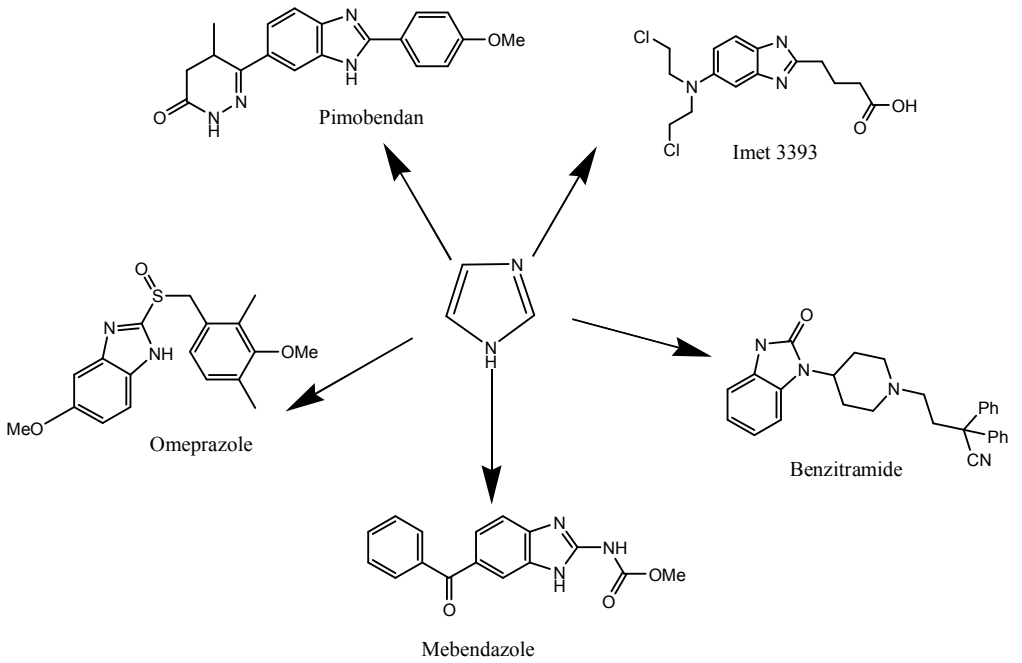
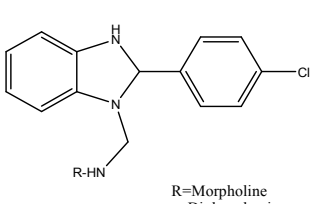


Fig. 5 : Some imidazole containing drugs

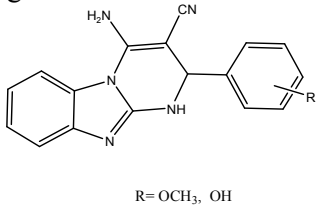
3.2.1 Anti-infammatory activity

Synthesis and anti-inflammatory activity of phenyl benzimidazole **(22)** was reported by Leonardo *et al*.[29] Compounds were screened for anti-inflammatory activity and they showed significant inhibition at 50 mg/kg dose and some compound showed maximum (54.6%) inhibition of paw edema and synthesis of 2, 3, 4,-trisubstituted-1, 2-dihydropyrimido[1,2-a]benzimidazole **(23)** derivatives was reported by Deshmukh *et al*.[30] The compounds were tested for their fungicidal activities against *Aspergillus niger* MTCC-2255 and *Penicillium chrysogenum*-NCIM-723 using Greiseofulvin as control.



R=Morpholine
Diphenylamine
Dimethylamine
Imidazole

(22)

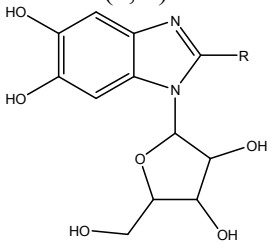


R= OCH_3, OH

(23)

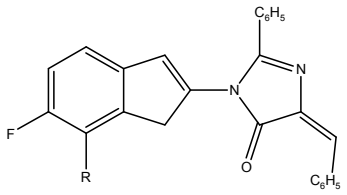
3.2.2 Antiviral activity

Synthesis of 2-(benzylthio)-5, 6-dichloro-1-(β-D-ribofuranosyl) benzimidazoles **(24)** was reported by Devivar *et al*.[31] Compounds performed antiviral activity against HSV-1 and HCMV and some compounds showed maximum activity at 90% inhibitory concentration (μM) and Sathe *et al*.[32] synthesized by using 4-Fluoro-3-chloroanilline, which when treated with potassium thiocyanate in presence of glacial acetic acid and bromine, was converted into 2-amino-6-fluoro-7-chlorobenzothiazole resulting into 2-amino benzothiazole. The synthesized compounds (25) in presence of 2-phenyl-4-benzylidine-5-oxazolinone when refluxed in pyridine gave 2- (2- Phenyl - 4 - benzylidenyl - 5 - oxo - imidazolin - 1 - ylamino) - 6 - fluoro -7-substituted (1, 3) benzothiazoles as products.



R= SCH_3, SO_2CH_3, $SO_2C_6H_5$

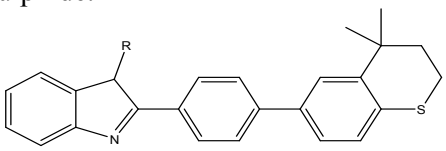
(24)



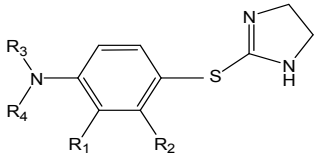
(25)

3.2.3 Anti-diabetic activity

A series of functionalized benzimidazole derivatives were reported by Kumar *et al*.[32] Compounds showed anti-diabetic activity against DPP-IV and PTP-IB. Compound **(26)** showed inhibitory activity against PTP-IB (1.64 %, 2.42 %) at 30μM doses and inhibitory activity against DPP-IV (3%) at 0.3 μM doses. Stella *et al*.[33] (27) reported an efficient and practical synthesis of imidazolyl derivatives through thiocyanation of aniline derivatives to gave the intermediate followed by the reaction with ethylene diamine in the presence of carbondisulphide.



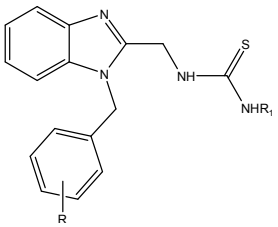
(26)



(27)

3.2.4 Anticonvulsant activity

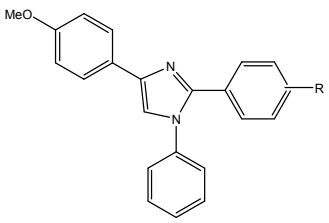
Siddiqui *et al*.[33] synthesized a number of new 1-[(1-(2-substituted benzyl)-1Hbenzo[d]imidazol-2-yl) methyl]-3-arylthiourea compounds **(28)**. All the newly synthesized compounds were screened for their anticonvulsant activity in ip MES and sc PTZ model, were compared with the standard drug Phenytoin. Majority of the compounds exhibited significant activity against both the animal models however, some compounds displayed promising activity. Husain *et al.*[34] reported a series of 1,2,4-trisubstituted-1 *H*-imidazoles (29) were synthesized by the 2,4-disubstituted-1 *H*-imidazoles and these compounds showed anticonvulsant activity.



R= H, Cl

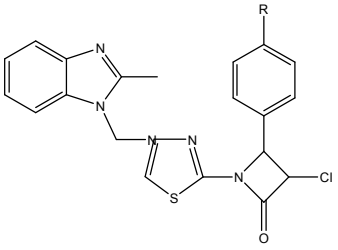
R_1= C_6H_5, $CH_3C_6H_5$, $OCH_3C_6H_5$

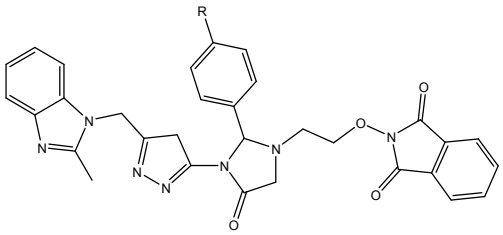
(28)



(29)

Monika *et al*.[34] have reported the synthesis of ethoxyphthalimido derivatives, thiadiazole assembled imidazolidinone and chloroazetidinone **(30 and 31**) systems from common intermediate Schiff's bases and also evaluated their anticonvuslant activity.

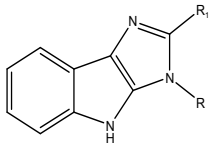


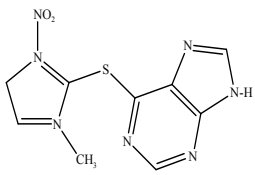


R= H, Cl, OCH_3, $N(CH_3)_2$

(30) **(31)**

Toshikazu *et al*.[35] synthesized 4-(2-hydroxy phenyl)imidazo [4,5-b] pyrrole -3(4H)-yl studied and sequence-specific DNA-of alkylating pyrrole-imidazole polyamide derivatives **(32)** used them anticancer agents. DNA-binding moiety of Py-Im polyamides can be made by solid-phase synthesis. These two functional moieties are then linked with chemically stable indole linker. The present alkylating Py-Im polyamides can be synthesized on a large scale, which would allow for future animal studies for the development of antitumor agents targeting the expression of specific genes responsible for cancer cell growth. Zhang *et al*.[36] suggested current developments of imidazole derivatives **(33**) as anticancer agents. Cancer is one of the most serious threats to human health, which has drawn unusual attention all over the world. Extensive research has been devoted to the development of effective anticancer therapeutics, involving an integrated employment of surgical techniques, radiation therapy, and chemotherapy.



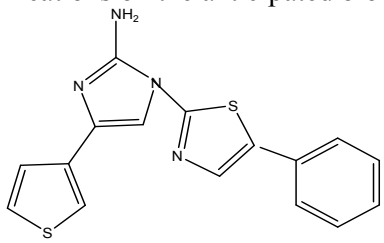


(32) **(33)**

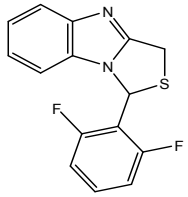
Groessl *et al*.[37] described SAR of imidazole, indazole, 1,2,4-triazole, 4-amino-1,2,4-triazole and 1-Methyl-1,2,4-triazole). Ruthenium(III) complexes **(34)** are among the most intensively studied alternatives to platinum compounds in cancer chemotherapy. Aquation, protein binding, and activation by reduction are regarded as important steps with respect to their mode of action. In the present study, NAMI-A was compared to a representative number of analogous compounds with varying azole ligands in terms of stability in aqueous solution, interaction with the most important plasma proteins, redox potentials, and antiproliferative activity.

(34)

Shameer H *et al.*[38] synthesized novel *N*- substituted-5-oxa imidazole **(35)** derivatives. In search for new biodynamic potent molecules, it was thought worthwhile to incorporate some additional heterocyclic moieties in the imidazole nucleus and study of their biological and pharmacological activity. Substituted fluorobenzothiazole, imidazole compounds were synthesized and screened for anti-inflammatory activity. Samia *et al*.[39] suggested some novel benzimidazole derivatives (**36**) for evaluation of in vitro anti HIV, anticancer and antimicrobial activities. The above mention findings prompted us to continue our investigation of benzofuran derivatives in an attempt to generate new lead compounds for future development as anti- HIV, antitumor or antimicrobial agents. In this work , a new series of benzofuran that comprise the benzofuran nucleus directly linked at C-2 to various substituted heterocyclic ring systems was synthesized in order to investigate the effect of such structural modifications on the anticipated biological activity.



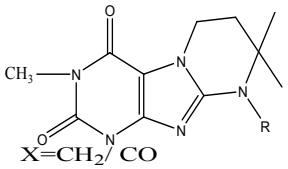
(35)



(36)

3.2.5 CNS Activity

Pawłowski *et al*.[40] synthesized tricyclic theophylline **(37)** derivatives. The potency of sedative action depends significantly on the kind of N-substituted basic side chain. Variation of the alkylamino substituents confirmed unequivocally that the most apparent CNS activity was exerted by the compounds with phenylpiperazinopropyl- or phenylpiperazinobutyl-substituents. Nagia *et al*.[41] synthesized fused imidazole derivatives, since it was found that bornano[1,2,3]triazine **(38)** showed a strong central nervous system (CNS) stimulant activity, a series of isomeric bornano[1,2,4]triazines and 5,8-methanoquinazolines fused with five and six-membered heterocycles was synthesized in order to investigate the structure activity relationship.

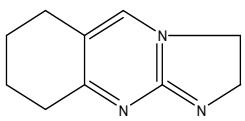


X=CH_2/ CO

R=Benzyl

R_1,R_2=Alkyl

(37)



(38)

4. PYRIMIDINE

The name pyrimidine (combination of words pyridine and amidine) was first applied by Pinner. Pyrimidines are the most important six membered heterocycles containing 2 nitrogen atoms at position 1 and 3. It is isomeric with two other forms of diazene.

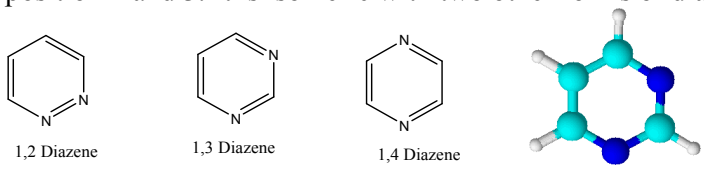


Fig. 6 : Pyrimidine

Pyrimidine and its derivatives are present in many of the bioactive aromatic compounds that are of wide interest because of their diverse biological and clinical applications. Pyrimidines and their fused analogues form a large group of heterocyclic compounds which share in building of nucleic acids, DNA and RNA. Nucleic acid hydrolysis produces several pyrimidines (uracil, thymine and cytosine). Of the 2 types of nucleic acid DNA and RNA, cytosine is found present in both DNA and RNA, while uracil is present only in RNA and thymine only in DNA.

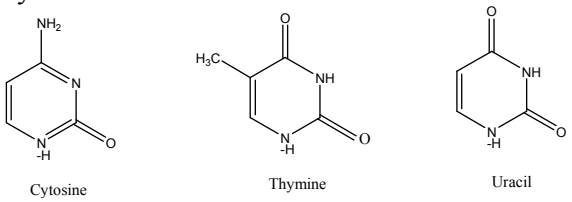


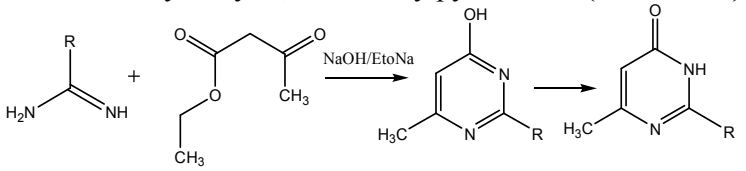
Fig. 7 : Pyrimidine containing bases

Pyrimidine derivatives occupy an extremely important role in the field of pharmaceutical and medicinal chemistry since they display a fascinating array of pharmacological properties *viz*. antitumour, antimicrobial, antihypertensive, anti-inflammatory, antineoplastic A_2A and A_3 adenosine receptors antagonists, cardiovascular, diuretic etc. Furthermore, pyrimidines are compounds that *in-vitro* possess biological activity against a wide spectrum of unrelated viruses, such as poliovirus, herpes virus and HIV.

Some of the analogues of pyrimidine have been used as active ingredients in major drugs like trimethoprim as antibacterial, flucytosine as antifungal, urzamustine as antineoplastic, pyrantel embonate as antihelmintic and dipyridamole as vasodilators.

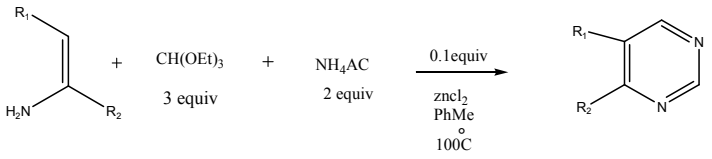
4.1 SYNTHETIC ASPECTS OF PYRIMIDINES:

Pyrimidines are generally prepared by the condensation between a three carbon compounds and compounds having the amidine structure where R = OH (urea), SH or SR (thiourea or its s-derivative) in the presence of catalyst sodium hydroxide or sodium ethoxide. This general reaction may be illustrated by the condensation of acetamidine with ethylacetoacetate to form 4- hydroxyl-2, 6- dimethylpyrimidine. **(Scheme-10)**



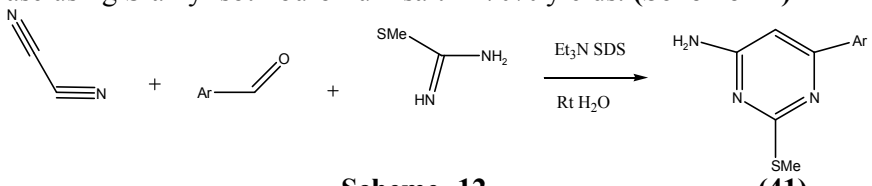
Scheme- 10 **(39)**

A novel three-component condensation reaction of functionalized enamines, triethyl orthoformate and ammonium acetate was reported by Konakahara *et al.*[45] They found that zinc chloride effectively catalyzes the reaction to produce 4, 5-disubstituted pyrimidine derivatives in moderate yields in single step. **(Scheme-11)**



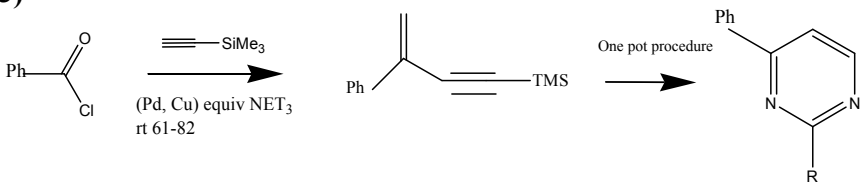
Scheme 11 **(40)**

Tao *et al*.[46] have described the synthesis of 2-alkylthiopyrimidine derivatives in aqueous phase using S-alkylisothiouronium salt in 70% yields. **(Scheme-12)**



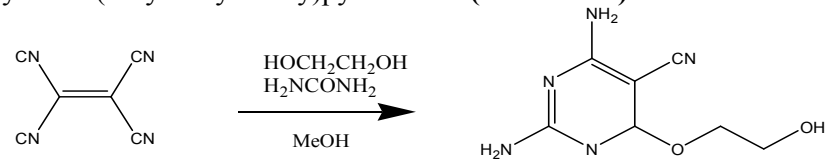
Scheme -12 **(41)**

Karpov *et al***.**[47] explained TMS-ynones are versatile synthetic equivalents of *β*-keto aldehydes and can be readily synthesized by coupling (hetero)aryl chlorides and (TMS)-acetylene with only one equivalent of triethylamine under Sonogashira conditions. This mild ynone synthesis is also a suitable entry to 2,4-disubstituted pyrimidines in the sense of a one-pot three-component reaction, i.e. a coupling-addition- cyclocondensation sequence. **(Scheme-13)**



Scheme- 13 **(42)**

Hockova *et al*.[48] selected 2,4 diamino cyano[2(diisopropoxyphosphory lmetho xy)ethoxy] pyrimidine as a suitable compound for the creation of its intermediate 2,4-diamino-5-cyano-6-(2-hydroxyethoxy)pyrimidine. **(Scheme-14)**



Scheme-14 **(43)**

4.2 MEDICINAL SIGNIFICANCE OF PYRIMIDINE:

The Pyrimidine scaffold being an integral part of DNA and RNA, occupy a unique and distinctive role in medicinal chemistry. In the past few years, fluorinated heterocyclic systems have been incorporated into drug discovery research to improve the drug physico-chemistry. properties. Pyrimidine derivatives possess several interesting biological activities such as antitumour, anticancer, antitumor and anti inflammatory activities etc.

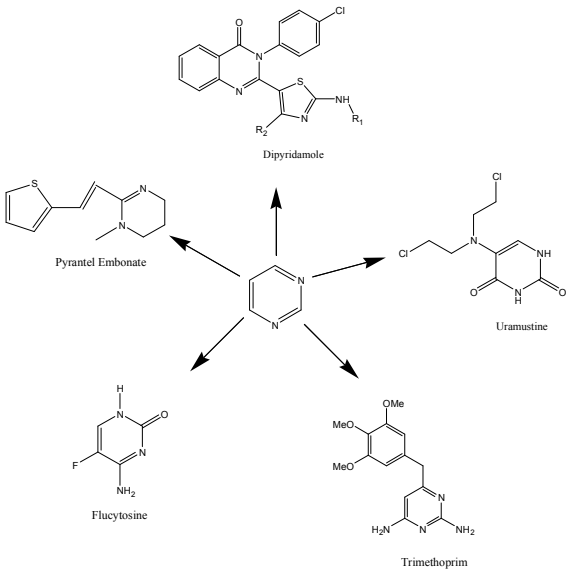
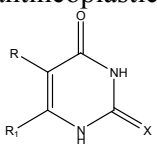


Fig. 8 Pyrimidine containing drugs

4.2.1 Anticancer activity

There are a large number of pyrimidine-based antimetabolites. One of the early metabolites prepared was 5-fluorouracil (5-FU), a pyrimidine derivative. 5-Thiouracil **(44)** also exhibits some useful antineoplastic activities.

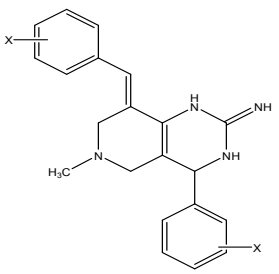


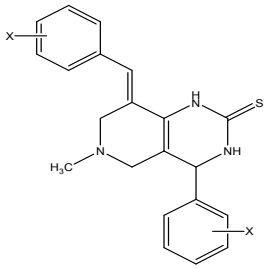
(44)

X = O, R = F, R^1 = H, 5-fluorouracil

X = O, R = SH, R^1 = H, 5-thiouracil

Mohamed *et al*.[49] synthesized newly pyridopyrimidine derivatives and were evaluated in vitro antitumor activities using different human tumor cell lines, representing cancers of CNS, ovary, renal, breast, colon, lung, leukemia, and melanoma, prostate as well as kidney. The compounds **(45 and 46)** with –NH group exhibited greater in vitro antitumor activities at low concentrations against the human tumor cell lines.



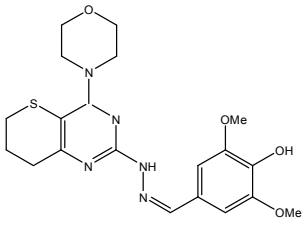


X= F, Cl, Br, H

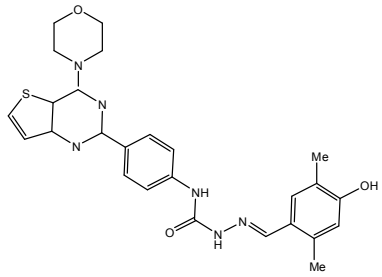
(45) **(46)**

Wufu *et al*.[50] have synthesized series of 7,8-dihydro-5H-thiopyrano[4,3-d]pyrimidine derivatives **(47)**. All the compounds were evaluated for the inhibitory activity against mTOR kinase at 10 μM level. The most promising compound showed strong antitumor activities. A

series of novel thieno[3,2-d]pyrimidine derivatives **(48)** possessing diaryl semicarbazone scaffolds were designed, synthesized and evaluated for their anticancer activity by Zijian *et al*.[51] In this study, a promising compound was identified, which showed the most potent antitumor activitiy.



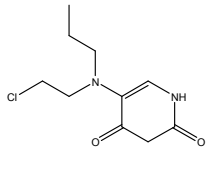
(47)



(48)

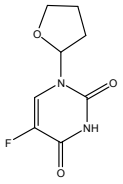
4.2.2 Antineoplastic drugs

Cancer is a major human health problem worldwide and is the second leading cause of death in United States**.** Systematic chemotherapy began with nitrogen mustards developed from war gases and with antimetabolites developed from early knowledge of DNA metabolism. DNA have long been of interest as anticancer drugs. Gueiffier *et al.*[52] synthesized different types of antineoplastic agents were developed, which include nitrogen mustards (Bendamustine), tyrosine kinase inhibitors, proteasome inhibitors etc.



Uramustine

(49)

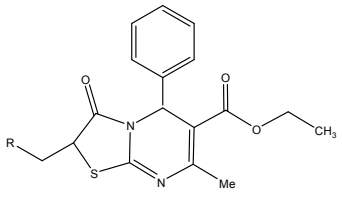


Tegafur

(50)

4.2.3 Antimicrobial activity

Mannich bases of ethyl 5-(2-chlorophenyl)-7-methyl-3-oxo3,5-dihydro-2H-thiazolo [3,2-a]pyrimidine-6-carboxylate derivatives **(51 and 52)** have been prepared by Vishant *et al*.[53] Evaluation of the title compounds as antimicrobacterial agent indicate that synthesized compounds have shown promising antimicrobacterial activity against both bacterial and fungal microorganisms.



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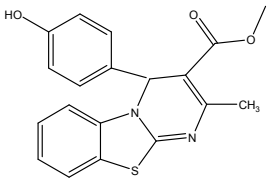
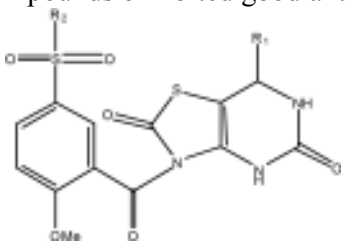


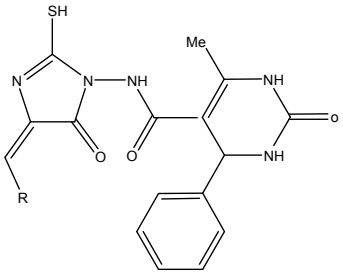
(52)

A new class of thiazolopyrimidine-based sulphonamides **(53)** has been synthesized by Navin *et al*.[54] All synthesized compounds were evaluated for in vitro antimicrobial activity against certain bacterial and fungal strains using the broth microdilution method as well as antitubercular activity against H37Rv using Lowenstein-Jensen agar method. Desai *et al*.[55] have described the novel approach for the synthesis and exploration of hybrid molecules containing pyrimidine-based imidazole scaffolds as potent antimicrobial agents. The targeted compounds **(54)** [R = Ph, $4FC_6H_4$, $2\text{-}MeOC_6H_4$ etc.] were achieved by the Knoevenagel condensation of a key precursor with different aldehydes in good yields, showing moderate to

excellent antimicrobial activity. The structural identification of final products was carried out by IR, ^{1}H NMR, ^{13}C NMR, and mass spectra. The obtained data indicated that the majority of the tested compounds exhibited good antibacterial activity over antifungal activity.



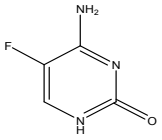
(53)



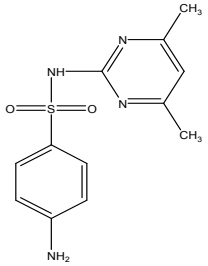
(54)

4.2.4 Antifungal drugs

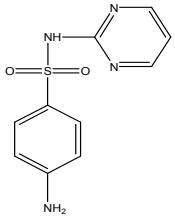
Wahab *et al*.[56] studied, antifungal, anti-hemolytic and cytotoxic evaluation of new imidazole-based drugs. Antifungals work by exploiting differences between mammalian and fungal cells to kill the fungal organism with fewer adverse effects to the host. Unlike bacteria, both fungi and humans are eukaryotes. Thus, fungal and human cells are similar at the biological level. This makes it more difficult to discover drugs that target fungi without affecting human cells.



Flucytosine
(55)



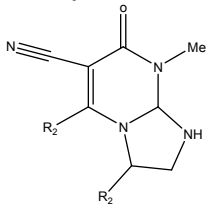
Sulfamethazine
(56)



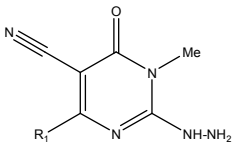
Sulfadiazine
(57)

4.2.5 Anti-inflammatory activity

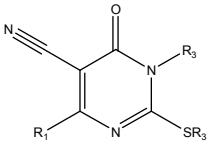
The synthesis of triazolopyrimidines **(59, 60 and 61)** was reported by Chetan *et al*.[57] Among the tested compounds, compounds **(59)** showed the most potent antioxidant and anti-inflammatory activity.



(58)

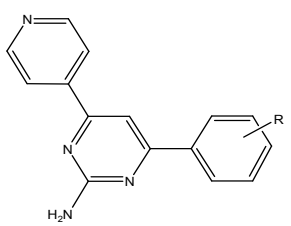


(59)

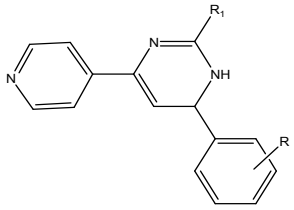


(60)

An attempt has been made by Monica *et al*.[58] to synthesize chalcones by the reaction of 4-acetylpyridine with various aromatic and heteroatom aldehydes. Further, chalcones derivatives were cyclized to pyrimidine analogs **(61)** (R = Cl, F, CH_3, CHO, 3,4(OCH_3)$_2$) and **(62)** (R^1 = OH, SH)by using thiourea, urea and guanidine hydrochloride. The newly synthesized pyrimidine derivatives were evaluated for their anti-inflammatory, antioxidant, antitubercular and antibacterial activities.

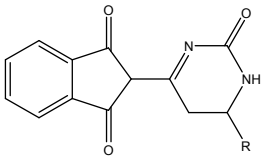


(61)

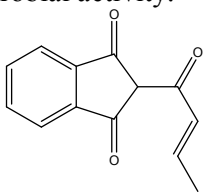


(62)

A new group of pyrimidine derivatives of indane-1,3-dione was synthesized by Giles *et al*.[59] aiming at the synthesis of new compounds acting as analgesic, anti-inflammatory, and antimicrobial activity. The title compounds **(63 and 64)** were synthesized from chalcone derivatives of indane-1,3-dione through cyclization with urea. The synthesized compounds were characterized by FT-IR, H^1NMR, mass spectral data, elemental analysis and were evaluated for anti-inflammatory, analgesic, antibacterial, and antifungal activities. The most active compound was evaluated for its ulcerogenicity. Good anti-inflammatory property was observed for this compdound. It mainly binds with Pro 218 of 1CX2, and the ligand could have caused much more conformational changes in the protein structure than other derivatives. It also exhibits good analgesic and antimicrobial activity.



(63)



(64)

5. 2-AMINOBENZENETHIOL

2-Aminobenzenethiol have attracted considerable attention because of their typical chemical and biological properties. 2-Aminothiophenol is an organosulfur compound with the formula C_6H_7NS. It is a colorless oily solid, although impure samples can be deeply colored. It is soluble in organic solvents and in basic water. It is a precursor to benzothiazoles, some of which are bioactive or are dyes. Isomers of aminothiophenols include 3-aminothiophenol and 4-aminothiophenol**.** 2-aminothiophenol is a versatile intermediate used extensively in industry as raw material for the production of medicines, agrochemicals, dyes and a variety of heterocyclic derivatives of synthetic importance. It is largely used as precursor for several biologically active molecules such as piperazine derivatives, which find therapeutic applications in many cardiovascular diseases, namely eschemic heart, thrombus, hypertension, etc. Similarly, benzothiazole derivatives (herbicide) and azophenothiazine, a valuable precursor for various pharmaceutically active substances, are prepared from 2-aminothiophenol. Thiazepines also derived from 2-aminothiophenol, are important ingredients for agricuitural and horticultural fungicides apart from being antihypertensive and antiviral agents.

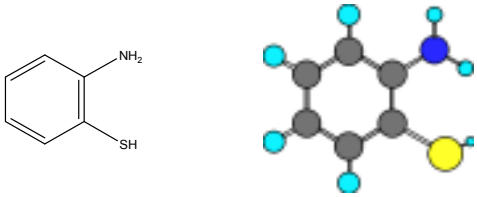


Fig. 9

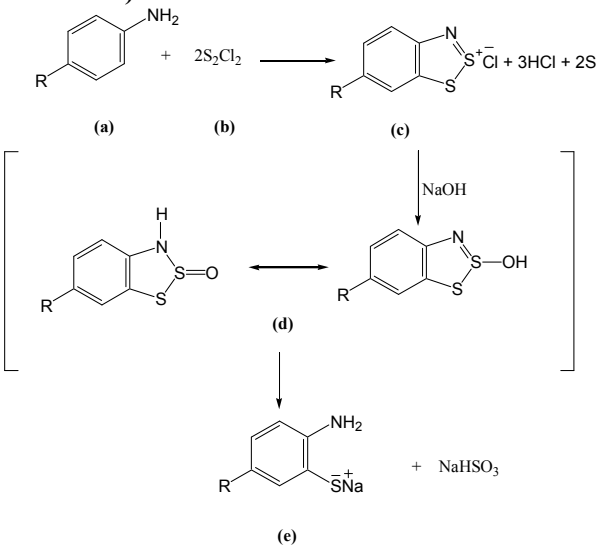
5.1 SYNTHETIC ASPECTS OF 2-AMINOBENZENTHIOL

A number of general and efficient methods for the preparation of this kind of compounds have been developed.

1. Herz method

It involves the condensation of substituted arylamines (having occupied para position) with sulfur monochloride (S_2Cl_2) resulting in the formation of Herz compound i.e. thiazothiolium chloride. Its alkaline hydrolysis produces sodium salt of the corresponding 2-aminobenzenethiol.

The hydrolysis of Herz compound involves the replacement of chlorine by hydroxyl group and opening of five membered ring in the presence of an alkali yielding sodium salt of 2-aminobenzenethiol. **(Scheme-15)**



(65)

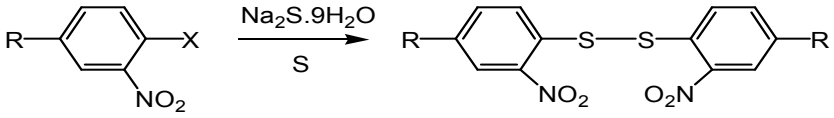
Scheme-15

2. Reduction of bis(*o*-nitrophenyl) disulfides

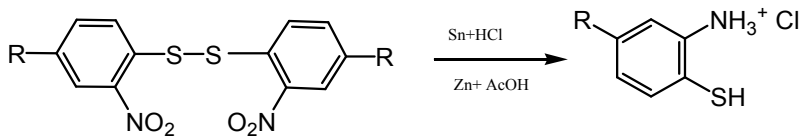
This method involves two steps.

1. In the first step, substituted *o*-halonitrobenzenes are treated with sodium polysulfide to get bis-(*o*-nitrophenyl) disulfide.
2. In the second step, products of first step are reduced with zinc and acetic acid or tin and hydrochloric acid to zinc salt or hydrochloride of 2-aminobenzenethiols. **(Scheme-16)**

Step 1



Step 2



(66)

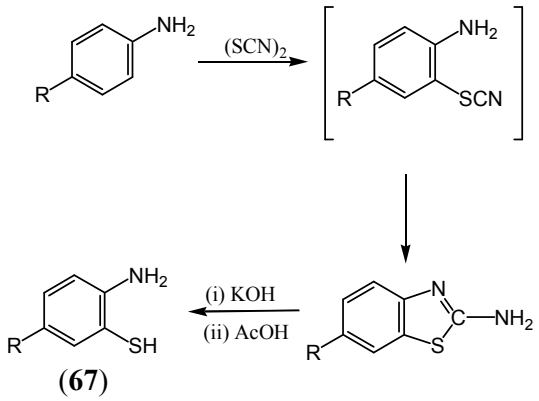
X = Cl, Br

R = alkyl/alkoxy/halo group

Scheme-16

3. Thiocyanogenation

This is the most widely used method for the preparation of 2-aminobenzenethiols which involves the hydrolytic cleavage of 2-aminobenzothiazoles which in turn, are prepared by the thiocyanogenation of arylamines. Thiocyanogenation is carried out by thiocyanogen gas, generated in situ by the reaction of cupric chloride and sodium thiocyanate or bromine and ammonium/potassium thiocyanate. Alkaline hydrolysis of 2-aminobenzothiazoles results 2-aminobenzenethiols. **(Scheme-17)**



(67)

Scheme-17

5.2 MEDICINAL SIGNIFICANCE OF 2- AMINOBENZENETHIOL

The importance of 2-aminobenzenethiol nucleus as chemotherapeutic agents has been well proved as illustrated by a large number of patents available on it. A number of biological activities associated with 2-aminobenzenethiol are as anti-inflammatory[81-82], anti-oxidant[83-84], antipsychotic[85-86], antifungal and antibacterial[87-88,] antimalarial[88-89], anticancer[90-91,] antihypertensive[92-95] antiasthemic[96-100], analgesics[101-104], anti-HIV[105-110], cardiovascular, vasodilating, ntidiabetic, cardioprotective, platelets aggregation inhibitor calcium antagonist.

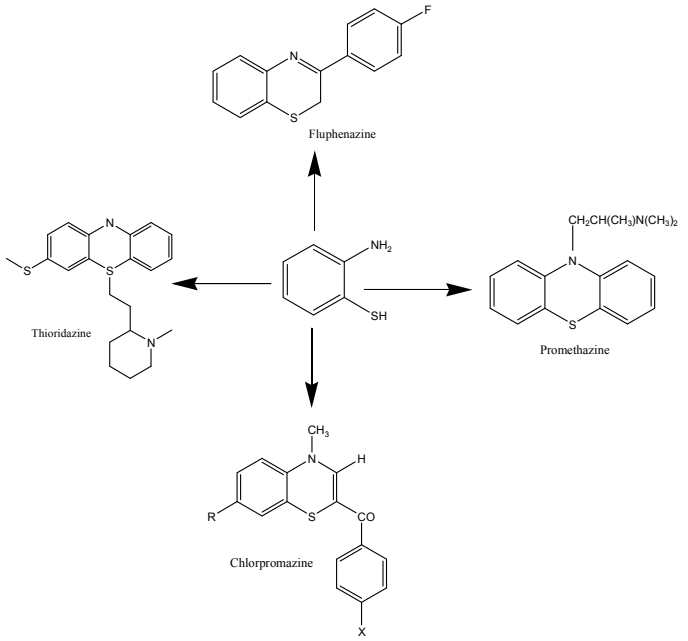
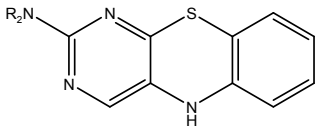


Fig. 10 2-Aminobenzenethiol containing drugs

5.2.1 Lipoxygenase inhibitors

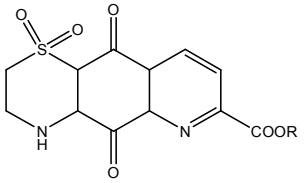
Bakavoli *et al.*[80] synthesized a series of 2-substituted pyrimido[4,5-*b*][1,4]benzothiazines evaluated their enzyme inhibitory activity on 15-lipoxygenase. The derivatives act as potential 15-lipoxygenase inhibitors. The enzyme 15-lipoxygenase (15-LO) is associated to cardiovascular complications since it is known to participate in oxidative modification of low density lipoproteins (LDL) which led to the development of atherosclerosis.



(68)

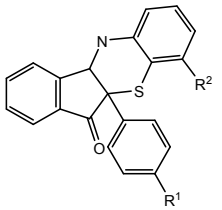
5.2.2 Anti-inflammatory activity

Pearce *et al.*[81] isolated tricyclic thiazine-containing quinolinequinone alkaloid and from the New Zealand ascidian *Aplidium* species which are found to display potent and selective inhibition of neutrophil superoxide production and hence used as antiinflammatory drugs.



R= H, CH_3

(69)

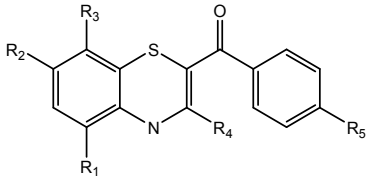


(70)

5.2.3 Antioxidant activity

Gautm *et al.*[83] synthesized a series of 4-(1-oxo-2-cyclopentenyl)-1,4-benzothiazine derivatives and screened them for their antioxidant properties through *in vitro* and *in vivo*

studies in Swiss albino mice. The synthesized compounds were found to exhibit mixed radical scavenging and antioxidant activity.



R_1=F, Cl

R_2& R_3= H, Br

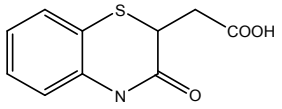
R_4= CH_3,C_6H_5

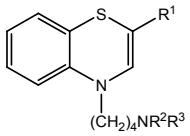
R_5= CF_3

(71)

5.2.4 CNS depressant activity

Krapcho and Yale *et al*.[85] found that ataractic and antispasmodic properties are associated with the salt of *N*-aminoalkyl benzothiazine derivatives. These are also found useful in the treatment of Parkinson's disease.



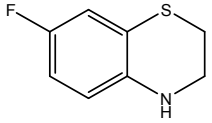


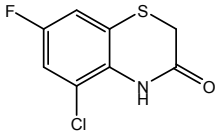
R^1&R^2= alkyl
R^3= Halogen

(72) **(73)**

5.2.5 Antibacterial and antifungal activity

Armenise *et al*.[86] synthesized a series of 7-fluoro-3,4-dihydro-2*H*-1,4-benzothiazine and 7-fluoro-2*H*-1,4-benzothiazin-3(4*H*)-one analogues and evaluated them for their *in vitro* antibacterial and antifungal activities against representative bacterial strains and fungal species. The compounds exhibited most promising results. Khairnar *et al*.[87] synthesized a series of 5-(3-methyl-7-substitued-4*H*-1,4-benzothiazin-2-yl)-*N*–aryl-1,3,4-oxadiazol-2-amines and reported them to possess potent *in vitro* antibacterial and antifungal activities against bacterial strains and fungal species.

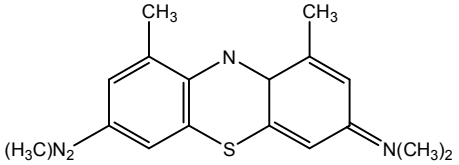




(74) **(75)**

5.2.6 Antimalarial activity

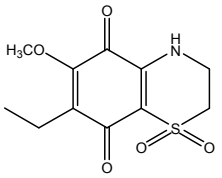
Guttmann and Ehrlich *et al*.[88] first to report high antimalarial potency of the famous thiazine dye methylene blue (**76**) and Vennerstrom *et al*.[89] further reported its high selectivity as antimalarial agent.



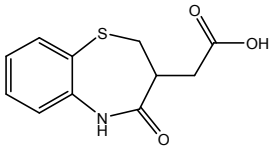
(76)

5.2.7 Anticancer activity

Aielllo *et al*.[90] have synthesized a series of structurally related thiazinoquinone derivatives using aplidinone as lead structure and investigated their antitumour activity. Naturally occurring aplidinone (**77**), thiazinoquinone isolated from Mediterranean ascidian *Aplidium conicum* is cytotoxic and pro-apoptotic agent. Although all the synthesized analogues exhibited better bioactivity but the compound (**78**) was found to be the most potent pro-apoptotic agent.



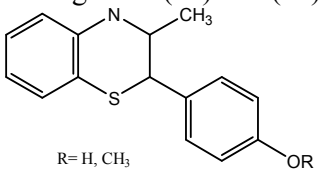
(77)



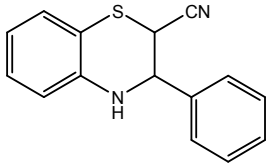
(78)

5.2.8 Antihypertensive activity

Chihara *et al.*[91] reported that benzothiazine derivatives are potent antihypertensive agents. Cecchetti *et al.*[92] synthesized a series of compounds having piperazine moiety variously linked to benzothiazine nucleus and evaluated for their *in vitro* α-adrenoreceptor affinity by radioligand receptor binding assays. Some of the benzothiazine derivatives bearing oxyalkyl-(2-methoxyphenyl) piperazine side chain were found to be good α-adreno receptor ligands and among them (**79**) and (**80**) were most effective.

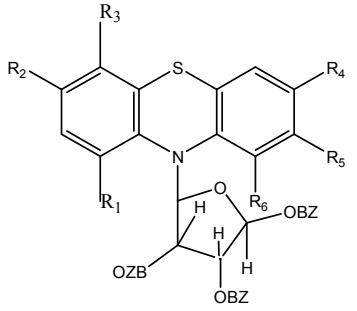


(79)



(80)

Gautam *et al.*[93] synthesized 10*H*-phenothiazines and evaluated their oxidative properties with their ribofurnanosides. These prepared ribofuranosides too possess similar chemotherapeutic activities and were evaluated for their antiradical & antioxidative properties.



(81)

CONCLUSION

This review gives an idea about different synthetic pathways of heterocyclic moieties and their pharmaceutical activities. The versatile synthetic applicability & biological activity of these heterocyclic compounds will help the medicinal chemists to plan organize & implement new approaches towards discovery of novel derivatives of different moieties. In this review we have focused our attention on heterocyclic scaffolds such as azetidinone imidazole, pyrimidine and 2-amino benzenethiol. This article helps to find potential future directions on the development of more potent and specific analogues of heterocyclic moieties for various biological targets.

6. REFERENCES

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