CHAPTER-1

INTRODUCTION

1 Introduction

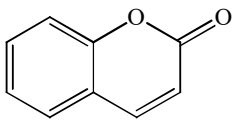
1.1 General introduction

Heterocyclic chemistry is one of the most complex and intriguing branch of modern organic chemistry. Either naturally occurring or chemically synthesized heterocyclic compounds have been a major field of scientific endeavour for over a century. The synthetic organic chemistry has significantly served pharmaceutical science by creating number of bio-active molecules.[1]The exploration of heterocycles as privileged structures in drug discovery is beyond doubt, one of the major areas in medicinal chemistry. Heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly and economically useful as therapeutic agents. These privileged structures represent a class of molecules that acts as ligands for various biological receptors with a high degree of binding affinity. Heterocyclic compounds play a vital role in biological processes and are wide spread as natural products. Synthetically produced heterocycles designed by organic chemists are used for instance as agrochemicals and pharmaceuticals and play key role in human life. Problems of drug resistant microorganisms have reached on alarming level in many countries around the world. A number of recent clinical reports explain the increasing occurrence of 'Meticillin' resistant *S aureous*, penicillin-resistant *Streptococcus Pneumoniae,* vancomycin-resistant *entercocci*, multi-resistant *Mycobacterium Tuberculosis* and other antibiotic resistant human pathogenic microorganisms in United States and European countries. Infections caused by those microorganisms pose serious challenges to the organic chemists and medical community. In most of the cases chemists have specific reasons for synthesizing particular compounds based on theoretical considerations, medicinal chemistry, biological mechanisms or a combination of all three and ultimately a need for an effective therapy has led them to a search for novel antimicrobial agents. Aromatic heterocycles are

of significant interest due to their presence in advanced pharmaceutical agents. Exploration of these agents should allow us to discover new biologically active compounds across broad range of therapeutic areas in a short time. For example Lipitor, that lowers cholesterol level and Plavix, a block buster drug used in the treatment of vascular diseases[2]. The use of these type of "wonder drugs" has led to a dramatic drop in deaths from diseases that were previously widespread, untreatable and frequently fatal. Recent trends suggest that the currently available compounds for screening programs are rather unsuitable for new target classes. Some diseases will have no effective therapies within the next ten years. So, there is an urgent requirement to develop new replacement drugs which are effective against resistant bacteria having lesser toxicity as well as economical also.[3]

Almost unlimited combinations of carbon, hydrogen and heteroatom like oxygen, nitrogen and sulphur can be designed, to have most diverse antimicrobial properties. It is therefore the development of new nitrogen, oxygen and sulphur hetero atoms containing heterocyclic systems as biologically active compounds will be an interesting area of research in medicinal chemistry.

1.2 Coumarin



Coumarin

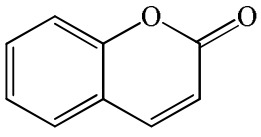
Coumarin is an aromatic heterocyclic organic compound. It is a bicyclic structure, consisting of a six-membered benzene ring fused to six-membered oxygen containing heterocyclic ring (benzopyrone). Coumarins are the best known aromatic lactones. Coumarin compounds represent an important type of naturally occurring and synthetic oxygen containing heterocycles with typical benzopyrone framework. This type of special benzopyrone structure enables its derivatives readily interact with a diversity of enzymes and receptors

in organisms through weak bond interactions, thereby exhibit wide potentiality as medicinal uses.

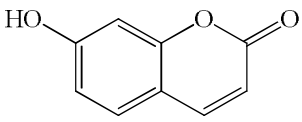
The principal sources have been classified in major a family from which most of the coumarin is isolated.

Major Families	**Examples**
Rutaceae	Bergamot fruit, Lime grass plant, Cloves, Common rue
Umbelliferae	Parsley, Parsnip, Celery, Ammi majus, Angelica archangelic
Moraceae	Ficus Carica
Leguminosae	Psoralea Corylifolia, Xanthoxylum Flavum

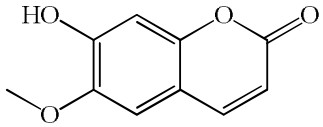
Some important naturally occurring coumarin derivatives are shown below. Coumarin **1** found in tonka beans with white clover. Umbelliferone **2** is 7-hydroxy coumarin. Scopoletin **3** is 7-hydroxy-6-methoxy coumarin, found in bark of the wild cherry. Fraxetin **4** is 7, 8- dihydroxy-6-methoxy coumarin and Isofraxetin **5** is 5, 6-dihydroxy-7-methoxy coumarin.



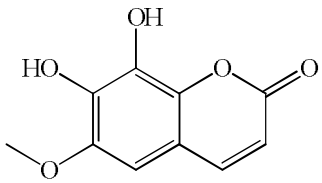
chromen-2-one
or coumarin **1**



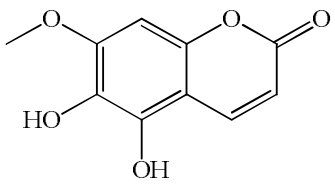
7-hydroxy coumarin
or umbelliferone **2**



7-hydroxy-6-methoxy coumarin
or scopoletin **3**

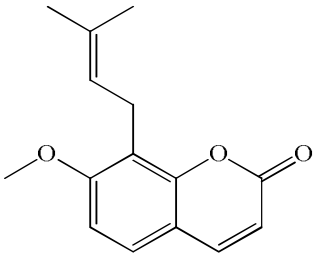


7,8-dihydroxy-6-methoxy coumarin
or fraxetin **4**

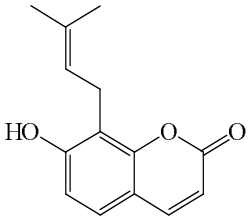


5,6-dihydroxy-7-methoxy coumarin
or isofraxetin **5**

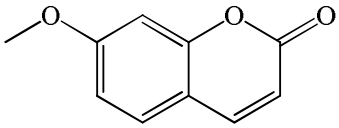
Some naturally occurring alkylated hydroxyl coumarins are Osthol and Osthanol. Osthol **6** is 7-methoxy-8-(3-methylbut-2-enyl) coumarin and Osthenol **7** is 7-hydroxy-8-(3-methylbut-2-enyl) coumarin. Herniarin **8** is 7- methoxy coumarin. Scoparone **9** (6, 7-dimethoxycoumarin) has been obtained from the Chinese herb *Artemisia scoparia*[3a].



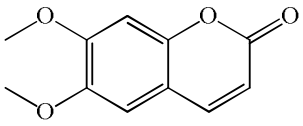
7-methoxy-8-(3-methylbut-2-enyl)coumarin
or osthol **6**



7-hydroxy-8-(3-methylbut-2-enyl)coumarin
or osthenol **7**

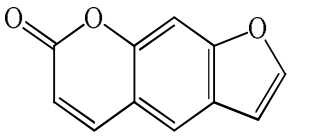


7-methoxy coumarin
or herniarin **8**

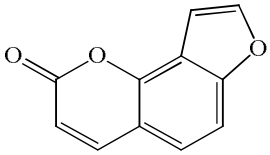


6,7-Dimethoxy coumarin
or scoparone **9**

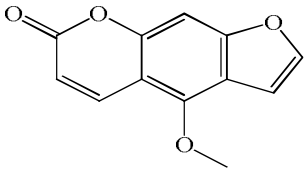
Some interesting naturally occurring coumarin derivatives like furocoumarins are; Psoralen **10**, Angelicin **11**, Bergapten **12**, Xanthotoxin **13**, Pimpinellin **14**, Isopimpinellin **15**, Aseculetin **16** Daphnetin **17** and Ayapin **18** are few members of this group[3b].



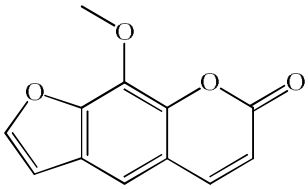
furo[3,2-*g*] coumarin or furocoumarin
or psoralene **10**



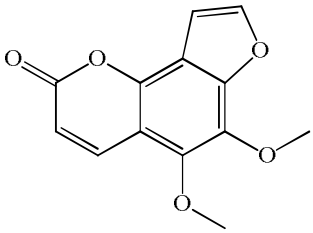
furo[2,3-*h*] coumarin
or angelicin **11**



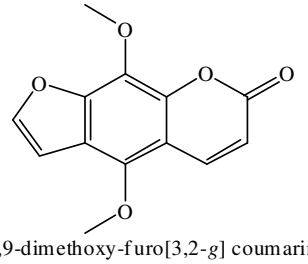
5-methoxy-furo[3,2-*g*] coumarin
or bergapten **12**



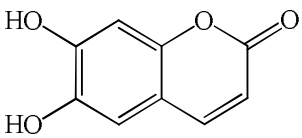
9-methoxy-furo[3,2-*g*] coumarin
or xanthotoxin **13**



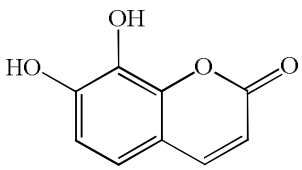
5,6-dimethoxy-furo[2,3-*h*] coumarin
or pimpinellin **14**



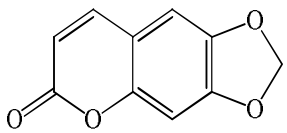
4,9-dimethoxy-furo[3,2-*g*] coumarin
or isopimpinellin **15**



6, 7-dihydroxy coumarin
or aesculetin **16**

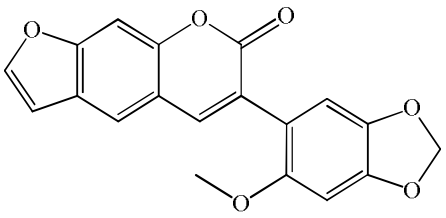


7, 8-dihydroxy coumarin
or daphnetin **17**

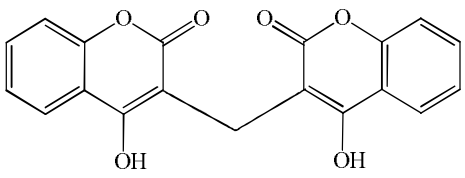


6H-[1, 3]dioxolo[4, 5-g] coumarin
or ayapin **18**

Pachyrrhizin **19** is a naturally occurring 3-Phenylcoumarin derivative. Dicoumarol **20** is 3-alkyl-4-hydroxy coumarin derivative used as anticoagulant drug and will become as a parent of a second group of drug [3C].

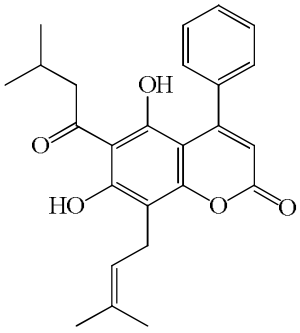


6-(6-methoxybenzo[*d*][1,3]dioxol-5-yl)-7*H*-furo[3,2-*g*] coumarin
or pachyrrhizin **19**



dicoumarol
20

Recently Coumarin Mammiesin[4] **21** is also one of the naturally occurring isolated compound from the Kielmeyera Genere.



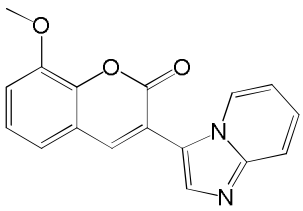
Mammeisin **21**

1.2.1 Therapeutic Potential

Coumarin has fungicidal as well as pesticidal[5] properties. Several natural products with a coumarin moiety have been reported to have multiple biological activities.[6-9a] Many naturally occurring and Synthetic coumarins are reported to be cytotoxic agents.[10] Intercalation between two base pairs of DNA takes place when coumarin reacts with DNA. During this intercalation they form cross linkage between two chains of DNA molecule, which is responsible for the mutagenic and carcinogenic effects.

Coumarin based selective estrogens receptor modulators (SERMs) and coumarin-estrogen conjugates had been described as potential anti breast cancer agents[11]. P.V.Kumar et al[12] have synthesized 3-indolizin-2-yl-chromen-2-one **22** as an ant tubercular, antiviral and anticancer agent.

1, 4-diaza-bicyclo-(3, 3, 1) nonane coumarin derivatives **23** were found to be useful for the treatment of disease of nervous system, disorders related to smooth muscle contraction, endocrine diseases, disorders related to neurodegeneration, inflammation and pain.[13]



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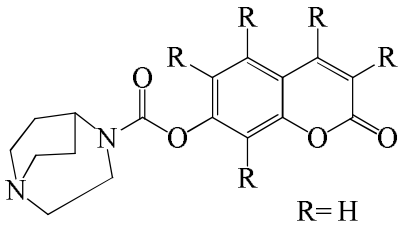

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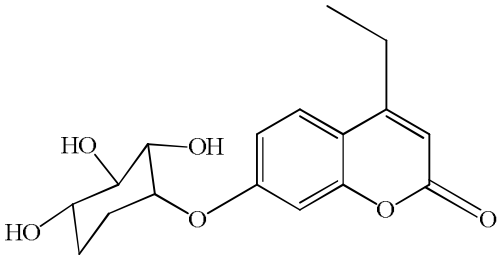
Carboxyglycosides of 4-ethyl-2-oxo-2-benzopyran-7-yl **24** as nonhydrolysable orally active venous antithrombotic agents has been synthesized by Vogel and co-workers[14]



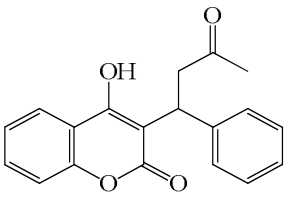
24

Coumarin can reduce tissue edema and inflammation. Its 7-hydroxy derivative inhibited prostaglandin biosynthesis.[15] 7-Hydroxy-4-methylcoumarin conjugated with paclitaxel through an ester linkage, selectively inhibited growth of ovarian and nasopharyngeal tumour cells.[16] 7-Hydroxy-4-methyl coumarin nucleus with different secondary amines through two carbon spacing showed affinities for both dopamine and 5-HT receptors.

It shows dopaminergic antagonistic activity.[17] Free 6-OH in the coumarin nucleus has been found to be important for antifungal activity; while the free hydroxyl group at 7th position is important for antibacterial activity.

Many flavour enhancers contains 6-methylcoumarin and 7-hydroxycoumarin which are used in sunscreens. It has been shown that 4-hydroxycoumarin and 7-hydroxycoumarin inhibited cell proliferation in a gastric carcinoma cell lines.[18] Naphthopyrone showed various biological activities like non steroidal human progesterone receptor agonists[19] and antimicrobial activity.[20] Prasad *et al.*[21] synthesized 3-[1-oxo-3-(2, 4, 5-trimethoxyphenyl) - 2-propenyl]-2*H*-1-benzopyran-2-ones that showed significant antimicrobial activity against *B. subtilis, B. pumilis* and *E. coli* when tested at a concentration of 1000 µg/ml. Number of the amino substituted coumarin derivatives have been reported as the inhibitors of DNA gyrase as potential antibacterials.[22]

Warfarin **25** is a popular anticoagulant drug in market which can be ingested or injected, depending on the needs of the patient.



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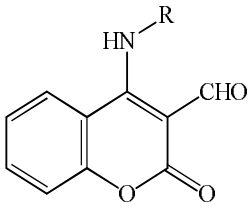
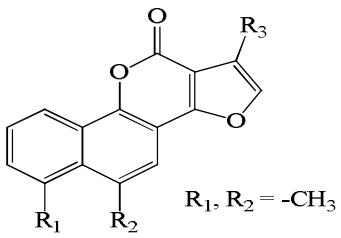


26

R = different hetero aryl substitutes
4-heteroaryl-coumarin-3-carbaldehydes



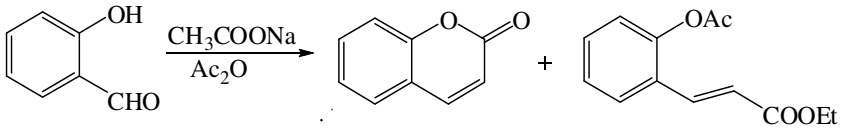
27

S. Govori et al [23] has synthesized various 4-Heteroaryl –coumarin-3-carbaldehydes **26** and corresponding hetero aryl amines that showed promising antimicrobial activity. Lee *et al*[24] reported a coumarin derivative neo-tanshinlactone, **27** with inhibition for two ER+ human breast cancer cell lines with 20 fold more potency compared to Tamoxifen.

1.2.2 General methods for synthesis of Coumarin and its derivatives

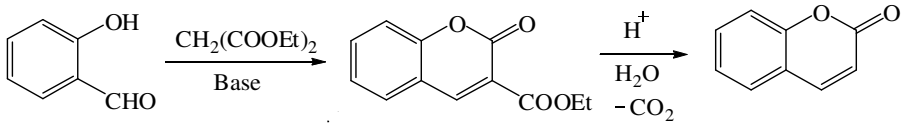
1. Perkin Condensation

Reaction of salicylaldehyde with acetic anhydride in the presence of sodium acetate to give coumarin and acetyl cinnamic acid[25].



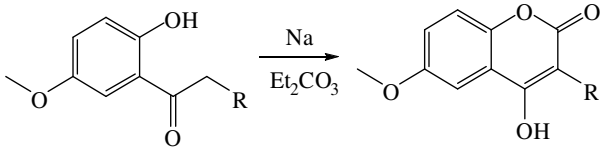
2. Knoevenagel Reactions

Salicylaldehyde in the presence of reactive methylene compound[26] like diethyl malonate in presence of pyridine and piperidine gives coumarin.



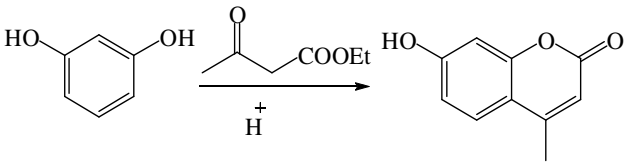
3. Hauben-Hosch Condensation

4-Hydroxy coumarin is prepared in good yield by condensation[27] of ortho-hydroxy phenyl ketone with diethyl carbonate and pulverized sodium.

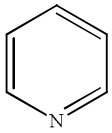


4. Pechmann Condensation

Coumarin derivatives are prepared from β–ketoester[28] by condensation with phenol in the presence of H_2SO_4.



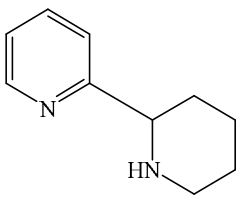
1.3 Pyridine



Pyridine is a heterocyclic organic compound with the chemical formula C_5H_5N. It is structurally related to benzene, with one CH group replaced by a nitrogen atom. It is used as a precursor to agrochemicals and pharmaceuticals and is also an important solvent and reagent.[29] Pyridine was first isolated and characterized by Anderson in 1846. It was obtained from bone oil and from coal tar. The cyclic nature of pyridine was recognized by Korner and Dewar in 1869.[30] In many enzymes of living organisms it is the prosthetic pyridine nucleotide ($NADP^+$) that is involved in various oxidation–reduction processes. Other evidence of the potent activity of pyridine in biological systems is its presence in the important vitamins such as niacin and pyridoxine (vitamin B_6) and also in highly toxic alkaloids such as nicotine.

In the pharmaceutical industry, pyridine forms the nucleus of over 7000 existing drugs. Pyridine ring system is very widely distributed in nature, especially in plant kingdom. Many important alkaloids atropine from Atropa belladonna, deadly nightshade contains saturated pyridine nucleus. In ancient times woman have used the fluid of leaves of the deadly nightshade to dilate pupils of eyes (mydriatic properties).[31]

Pyridine and its analogous are commonly called Pyridine bases. The pyridine alkaloid anabasine act as an insecticide, nicotine used as anthelmintic and ricinine used in the biosynthesis.



Anabasine

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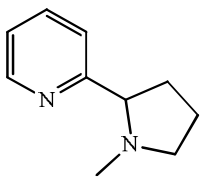
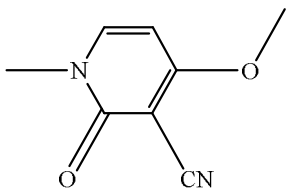


Nicotine

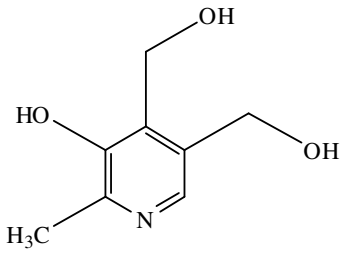
29



Ricinine

30

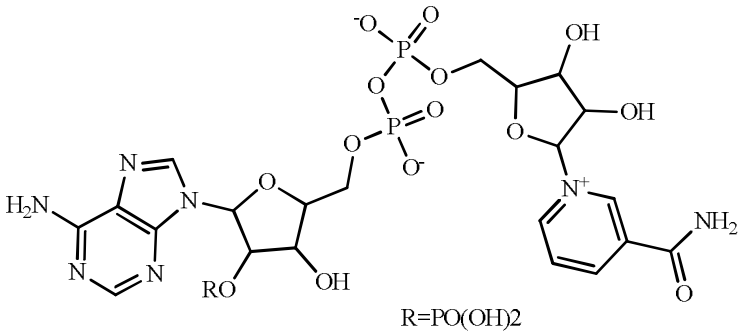
Pyridine nucleus has been extensively explored for its application in the field of medicine, agriculture and industrial chemistry. Alkaloids like quinine and morphine contain pyridine ring. Pyridoxol (vitamin B_6) **31** occurs in yeast and wheat germ is an important food additive.



Pyridoxol

31

Pyridine-3-carboxamide occurs as a component of the structure of the important coenzymes $NADP^+$ **32** one of the B_2 complexes of vitamin, occurs in red blood corpuscles and participates in biochemical redox reaction.



32

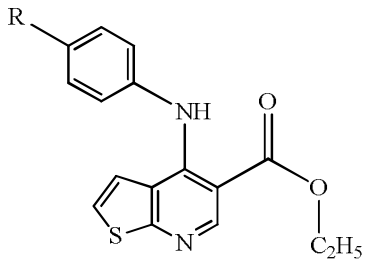
1.3.1 Therapeutic importance

Pyridine ring plays vital role in fundamental metabolism in two ways:

(i) As in reaction of amino acids, including racemisation, decarboxylation trans amination and elimination or replacement of substitution on the β –and γ-carbon atoms.

(ii) As a coenzyme, nicotinamide adenine dinucleotide, it is playing role in biological redox reactions.

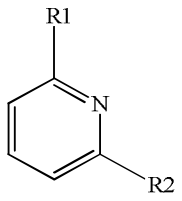
Bernardino *et al* synthesized new pyridine derivatives **33**, which showed inhibitory activity against Herpes simplex virus type 1 (HSV-1). Derivatives of 4-(phenyl amino)-1H-pyrazolo [3,4-b]pyridine show biological activities, such as anti-HIV-1.[32]



R=H,CH_3,OCH_3,NO_2,F

33

Jong-Keun Son *et al* synthesized 2, 6-diaryl-substituted pyridines **34** having cytotoxicity against several human cancer cell lines[33].

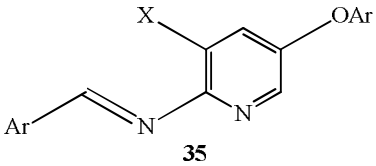


34

Bioisosteres of terpyridine

Where R1=Phenyl, furyl, thienyl or pyridyl

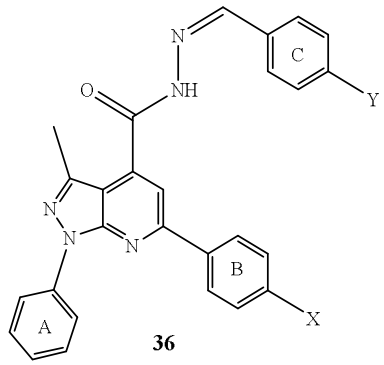
Bhatia *et al* synthesized a series of 5-substituted (aryl ethylene) pyridin-2-amine **35** by condensing various 5-substituted pyridyl-2-amines with various aromatic aldehydes. All the compounds were screened for their antibacterial activities[34].



35

Where X= H,NO_2

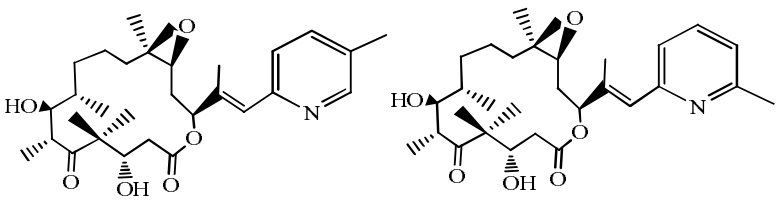
Chagas disease (American Trypanosomiasis) is caused by Trypanosoma cruzi, a parasite with a large zoonotic reservoir in Central and South America. Its endemy keeps 100 million people at risk and about 20 million people chronically infected with T. cruzi. Dias *et al* synthesized 1H-pyrazolo [3,4-b]pyridine **36** series compounds having antichagasic activity[35].



36

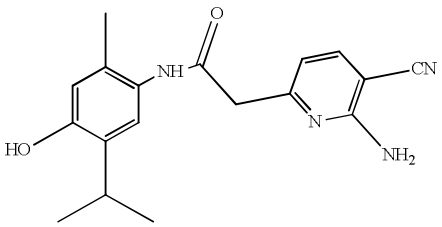
Where X=H,CN,NO_2,Cl,OCH_3,OC_2H_5, Y= H, F, OH, NO_2

Nicolaou *et al* synthesized pyridine epothilones **37** exhibiting cytotoxic properties against a number of human cancer cell lines. The compounds showed the importance of nitrogen atom at ortho position with the effect of methyl substitution on pyridine ring at 4- or 5-positions[36].



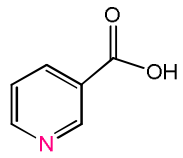
37

J M Desai and Co workers have reported the antibacterial and antifungal activity of 2-amino-3-cynano-6-substituted pyridines **38** [37]



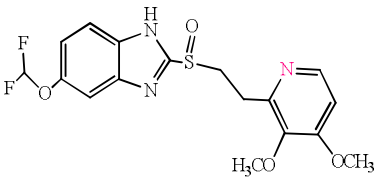
38

1.3.2 Some commercially available drugs having Pyridine moiety



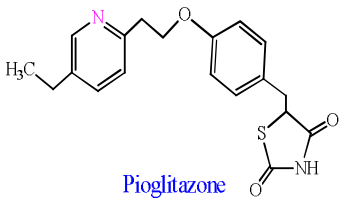
Niacine

39



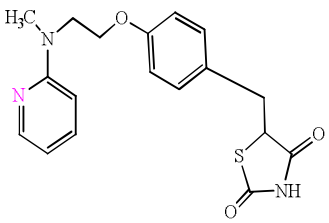
Pentoprazole

40



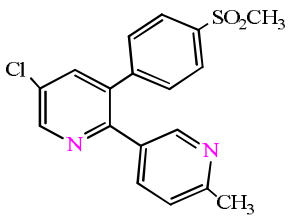
Pioglitazone

41



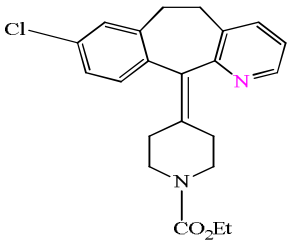
Rosiglitazone

42



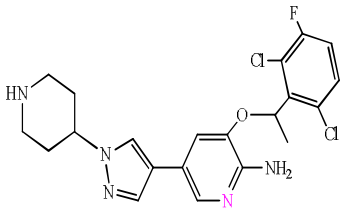
Etricoxib

43



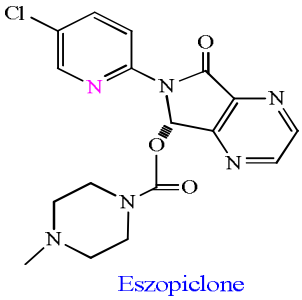
Loratidine

44



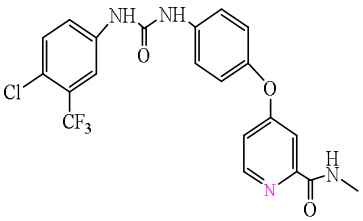
Crizotinib

45



Eszopiclone

46

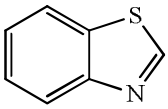


Sorafanib

47

The 3rd position substitution on pyridine ring system is rarely discussed class of heterocycles.

1.4 **Benzothiazole**



A heterocyclic compound is one which possesses a cyclic structure with at least one hetero atom in the ring. Nitrogen, oxygen, and sulphur are the most common heteroatoms, present in heterocyclic compounds. Benzthiazole\

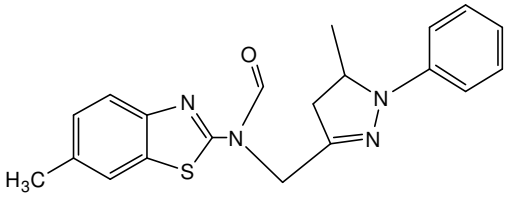
is an organosulphur heterocyclic compound, weakly basic in nature. It is a fused ring system having both sulphur and Nitrogen hetero atom. [38] A large number of therapeutic agents are synthesized with the help of benzothiazole nucleus. The simple benzothiazol nucleus that present in number of compounds possess interesting biological activities like- antimicrobial, antitubercular, antitumor, antimalarial, anticonvulsant, anthelmintic, analgesic and anti-inflammatory activity.[39-40] A number of 2-aminobenzothiazoles have been studied as central muscle relaxants and are found to interfere with glutamate neurotransmission in biochemical, electrophysiological and behavioural experiments.[41] Benzothiazol derivatives have been studied and found to have various biological activities such as anti-viral, anti-bacterial, anti-microbial and fungicidal activities.[42] Benzothiazol nucleus containing molecules are also reported as anti-allergic,[43] anti-diabetic,[44] antitumor,[45]anti-inflammatory, anti-helmintic, and anti-HIV agents. 2- aryl substituted benzothiazol show antitumor activity[46-47]. 2- Amino benzothiazole scaffold is one of privileged structure in medicinal chemistry [48-49] and also reported as cytotoxic to cancer cells. The combination of 2-aminobenzothiazoles with other heterocyclic rings is a well known approach to design new chemical entities for diverse physiological applications. In view of the biological importance of the benzothiazole nucleus containing compounds, we have designed and synthesized some substituted benzothiazole derivatives.

1.4.1 Therapeutic Importance

Antimicrobial activity:

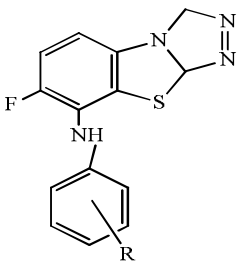
Microbes are the causative agents for various types of diseases like pneumonia, ameobiasis, typhoid, malaria, common cough, cold and various infections and cause some severe diseases like tuberculosis, influenza, syphilis, and AIDS etc. Benzothiazol show an antimicrobial activity and a considerable amount of work has been done on the synthesis of new potent antibacterial and antifungal benzothiazol.

Ojha K G et al[50] have reported some substituted 2-amino benzothiazol **48** compounds for their anti-bacterial activity against *Bacillus subtilis*, *Salmonella typhi* and *S. Dysentery* [50]



48

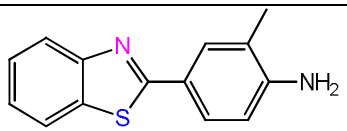
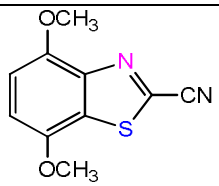
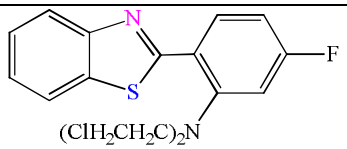
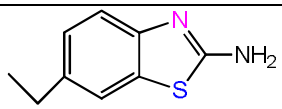
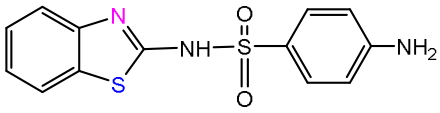
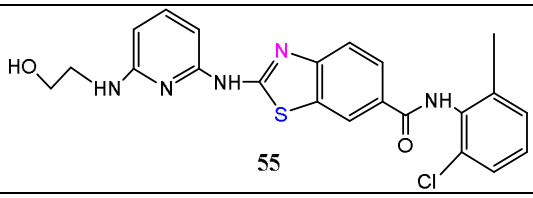
Trapani, V. et al[51] have reported various benzothiazolyl carboxamido pyrazoline derivatives **49** and studied their anti-microbial activity.



R= Cl,CH_3

49

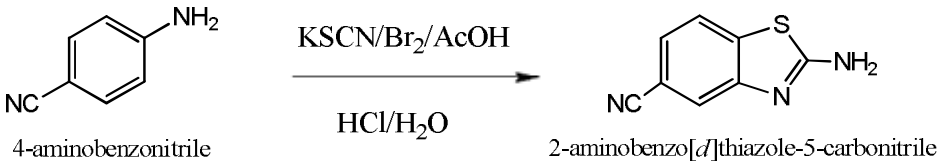
1.4.2 Various biological activities of reported benzothiazole derivatives

Activity	Structure	IC_{50}(µM) OR MIC value	Workers
Antitumor activity[51a]	 **50**	IC_{50}=0.001 µM	Kashiyama E et al.
Antitumor activity[51b]	 **51**	IC_{50}=20.6µM	Besson T et al.
Anticancer activity[52]	 **52**	81% cell Death	Kini. S et al.
Anticonvulsant activity[52b]	 **53**		P I Monet et al.
Antimicrobial Activity[53]	 **54**		Ghoneim K.M.et al
LCK inhibitor[54]	 **55**	IC_{50}=0.5nM (hLCK)	Das, J et al

1.4.2 Synthetic Aspect

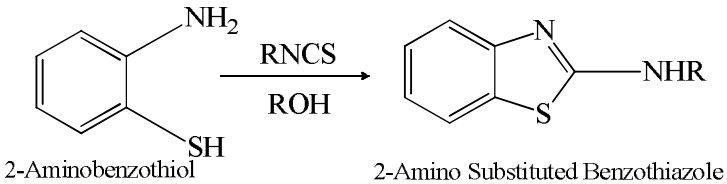
Synthesis of 2-amino benzothiazol (Reported methods)

(1) Irena, C. A. et al. have reported one step process for synthesis of 2-aminobenzothiazole using substituted aniline, potassium thiocyanate and bromine in acidic condition at low temperature (0-5°C). For the acidic media acetic acid as solvent have been is used for the synthesis of 2-aminobenzothiazole.[55]



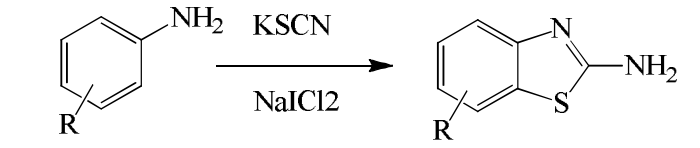
4-aminobenzonitrile — 2-aminobenzo[*d*]thiazole-5-carbonitrile

(2) Tweit, R. C. et al. have reported the synthesis of 2-aminobenzothiazole using alkyl isothiocyanate and 2-aminobenzothiol as starting material in the presence of alcohol as a solvent at reflux.[56]



2-Aminobenzothiol — 2-Amino Substituted Benzothiazole

(3) Telvekar, V. N. et al. have recently reported the simple, mild and efficient method for the synthesis of 2-amino benzothiazol[57]

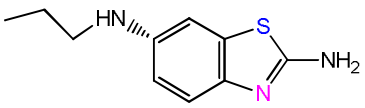


Substituted Aniline — Substituted 2-Amino Benzothazole

HRV (human rhinovirus) cause approximately one-half of all cases of respiratory tract infection (colds). Several 2-alkoxy and 2-alkylthio-benzothiazol derivatives showed excellent anti HRV activity[58].

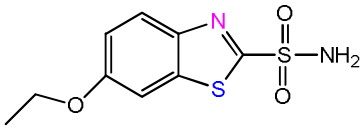
Owing to their importance in pharmaceutical utilities as mentioned above, the synthesis of various compounds from 2-amino benzothiazol moiety has charming considerable interests.

1.4.2 Some commercially available drugs based on benzothiazole moiety



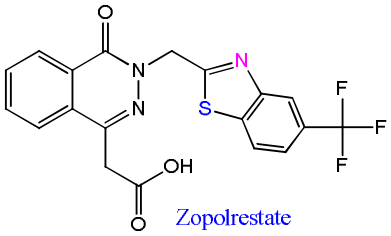
Premipexole

56



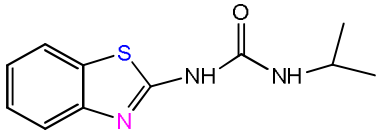
Ethoxazolamide

57



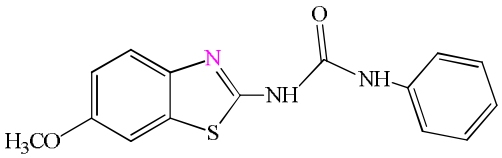
Zopolrestate

58



Bentaluron

59



Frentizole

60

1.5 References:

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