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Synthetic aspects and Biological Studies of some Heterocycles

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Abstract: Heterocyclic chemistry is a key branch of chemistry dealing with synthesis, properties and applications of heterocycles. Heterocycles have enormous potential as the most promising lead molecules for the design of new drugs. It plays a vital role in biological processes and are wide spread as natural products. Our article is emphasized on synthesis and biological activity of nitrogen, sulphur and oxygen containing heterocyclic moieties- benzothiazole, thiazolidine, azetidine and chromene derivatives which shall be the milestones of conjunction based drug concept in synthetic chemistry.

Keywords: Heterocyclic Chemistry, Benzothiazole, Thiazolidine, Azetidine and Chromene

1. INTRODUCTION

Heterocyclic chemistry is one of the intriguing branch of organic chemistry and heterocyclic compounds constitute the largest and most varied family of organic compounds. Heterocyclic compounds[1] offer a high degree of structural diversity and have enormous potential as the most promising molecules as lead structures for the design of new drugs. They are organic compounds containing at least one atom of carbon and at least one element other than carbon, such as sulfur, oxygen or nitrogen etc. within a ring structure. Since in heterocycles, non-carbons replace carbon atoms and are called heteroatom e.g. different from carbon and hydrogen. These structures **(Fig.1)** may comprise either simple aromatic rings or non-aromatic rings. The heterocyclic compounds possess usually a stable ring structure which does not readily hydrolyze or depolymerize.

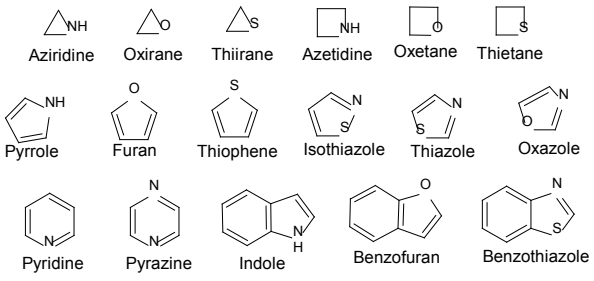


Fig.1 Structure and names of some common heterocycles

They are widely distributed in nature[2] and are essential to life as they play a pivotal role in the metabolism of all living cells. For example proteins, hormones, photosensitizing pigment chlorophyll, oxygen transporting pigment haemoglobin, hormones like kinetin, heteroauxin, serotonin and histamine together with most of the sugars. The pyrimidine and purine bases found in RNA and DNA are heterocycles, (**Fig. 2)** as are the sugars that in combination with phosphates provide the backbones and determine the topology of the nucleic acids.

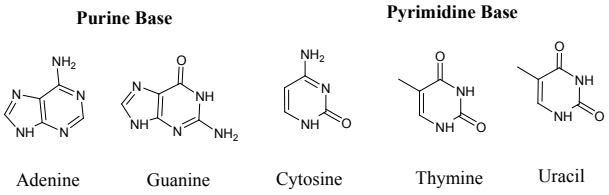


Fig. 2 Heterocycles in DNA & RNA

Three out of twenty natural amino acids are heterocyclic, which are essential amino acids proline, histidine and tryptophan. Many essential vitamins **(Fig. 3)** such as Thiamin (Vitamin B_1), Riboflavin (Vitamin B_2), Nicotinamide (Vitamin B_3), Pyridoxal (Vitamin B_6) and Ascorbic acid (Vitamin C) are heterocyclic compounds[3,4] too.

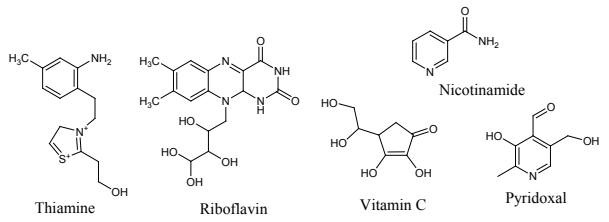


Fig. 3 Essential vitamins

They are found abundantly in nature particularly in plant alkaloids, anthocyanins and flavones. The alkaloids form a major group of naturally occurring heterocyclic compounds having varied biological activity. Ergotamine, the indole based alkaloid exhibits antimigraine activity**.** Cinchonine and Quinine (a quinolone class of alkaloid) show antimalarial activity**.**

Heterocycles are common structural units in marketed drugs and in medicinal chemistry targets in the drug discovery process. Medicinal chemistry occupies an important position to establish a relationship between pharmacological activity and chemical structure. They serve as useful tools to manipulate lipophilicity, polarity, and hydrogen bonding capacity of molecules, which may lead to improved pharmacokinetic, pharmacological, toxicological, and physicochemical properties of drug candidates and ultimately drugs. During the period of 1930 to 1970, a large number of important drugs have been introduced and this period is regarded as "Golden Period" of new drug discovery. The modern concept of drug discovery started in 1933 by Gernand Dogmak with his finding of "protonsil red" a compound responsible for the antibacterial activity. Over 80% of top small molecule drugs contain at least one heterocyclic fragment in their structures.

These are some of the specific examples representing new therapeutics-

Name of drugs year usages

Sulfa drugs	1933	First antibacterial drug
Penicillin	1940	Antibiotics
Chloroquine	1945	Antimalarial
Methyldopa	1950	Antidiabetic
Chlorthiazide	1957	Diuretic
Adrenergic betablockers	1958	Coronary Vasodilatory
Semi synthetic penicillins	1960	Antibacterial
Trimethoprim	1965	Antimicrobial
Disodium Chromoglycoate	1967	Antiallergic

Synthetically produced heterocycles[5], designed by organic chemists are used for instance as

agrochemicals and pharmaceuticals which play an important role in human life. An isoxazolyl group is found in many antibiotics, such as cloxacillin, dicloxacillin and flucloxacillin. Sumatriptan, an indole group heterocycle is the first antimigrain drug**,** in which replacement of sulfonamide moiety with 1, 2,4-triazole**,** which is also a potent 5-HT1D receptor agonist**.** Chloroquinine, the main drug among the 4-aminoquinoline class, is one of the most successful antimalarial agents ever produced. They are present in a wide variety of drugs, many natural products, biomolecules and biologically active compounds, including anticancer[6,7], antibiotic, anti-inflammatory[8], antidepressant[9], antimalarial[10], anti-HIV[11,12], antidiabetic[13], antimicrobial[14], antibacterial[15], antifungal, antiviral, , herbicidal, fungicidal and insecticidal agents[16]. Some of these compounds exhibit a significant solvatochromic, photochromic and biochemiluminescence properties. Most of the heterocycles possess important applications in material science such as dyestuff, fluorescent sensor, brightening agents, information storage, plastics and analytical reagents. In addition, these have applications in supra molecular and polymer chemistry, especially in conjugated polymers. Moreover, they act as organic conductors, semiconductors, molecular wires, photovoltaic cells and organic light-emitting diodes, optical data carriers, light harvesting systems, chemically controllable switches and liquid crystalline compounds.

They have enormous potential as the most promising molecules as lead structures for the design of new drugs because of the unique ability of the compounds to imitate the structure of peptides and to bind reversibly to proteins. They are also of considerable interest because of their synthetic utility as protecting groups, synthetic intermediates, chiral auxiliaries, organic catalysts and metal ligands in asymmetric catalysts inorganic synthesis. Therefore, significant attention has been paid to develop proficient new methods to synthesize heterocycles.

2. **Benzothiazole**

Benzothiazole (**Fig. 4)** is a privileged heterocyclic scaffold belongs to the family of bicyclic heterocyclic compounds sharing benzene nucleus fused with five-membered ring thiazole. Sulphur and nitrogen atoms comprise the core structure of thiazole and numerous pharmacologically and biologically active compounds. Benzothiazoles have promising biological profile and are easy to access which makes this pharmacophore an interesting moiety for experimental drug designing.

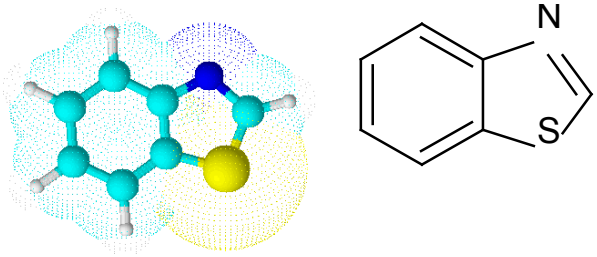
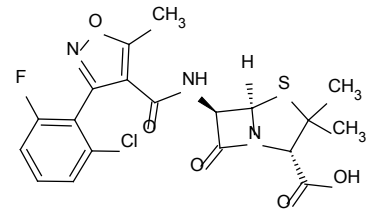
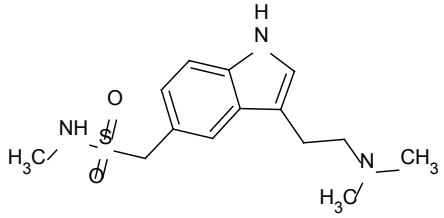
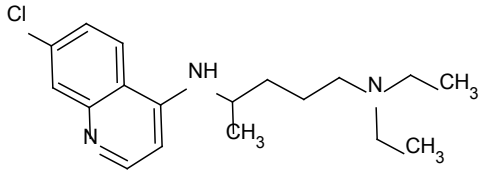
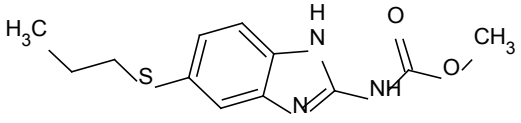
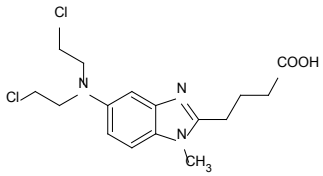
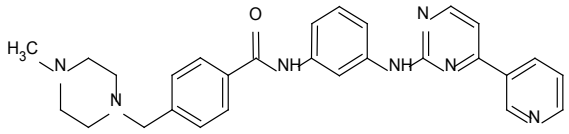
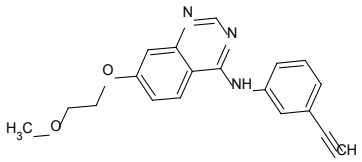
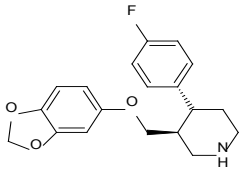


Fig. 4

In the 1950s, a number of 2-aminobenzothiazoles were intensively studied as central muscle relaxants. After then, medicinal chemists have not taken active interest in this family. Biologist's attention was drawn to this series when the pharmacological profile of Riluzole was discovered. Riluzole (6-trifluoromethoxy-2-benzothiazolamine, Rilutek) was found to interfere with glutamate neurotransmission in biochemical, electrophysiological, and behavioral experiments. Afterwards benzothiazole derivatives have been studied broadly and found to have diverse chemical reactivity and broad spectrum of biological activity[17-19].

Benzothiazole derivatives find use in various chemical researches, for instance, in dyes, drugs, polymer chemistry, vulcanization

SOME BIOLOGICALLY ACTIVE HETEROCYCLIC SCAFFOLDS

S. No.	Name of Drug	Activity	Chemical Structure
1	Flucloxacillin	Antibiotic	
2	Sumatriptan	Antimigrain drug	
3	Chloroquinine	Antimalarial	
4	Albendazole	Antihelminitic	
5	Bendamustine or Nitrogen mustard	Antineoplastic agent	
6	Imatinib	Chronic myelogenous leukemia	
7	Erlotinib	Tyrosine Kinase inhibitor	
8	Paroxetine	Antidepressant	

accelerators, corrosion inhibitor for steel and clothing textile in industry, antifreeze, cooling liquids, as a substitute for chlorophenols in wood preservation and leather production. It serves as an interesting terrestrial and marine natural product too.[20]

The structural framework of this scaffold have proved to be an important class of privileged bicyclic substructures owing to their potent use in research as a starting material for the synthesis of bioactive structures. It play a vital role in the manufacture of various biologically active marketed drugs as Riluzole, Thioflavin, Pittsburgh compound B, Ethoxzolamine, Pramipexole, Dimazole, Flutemetamol and Dithiazanine Iodide.

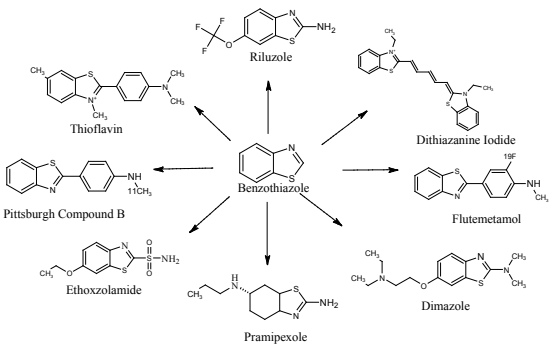
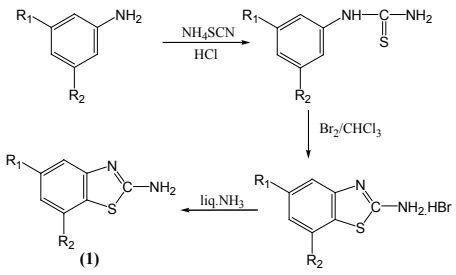


Fig. 5 Benzothiazole containing drugs

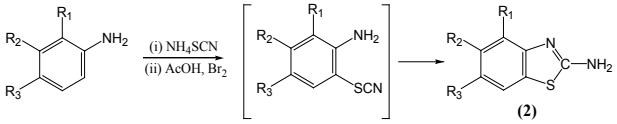
2.1 Synthetic aspects

Mukherji *et al.*[21] prepared 2-amino-5,7-disubstituted benzothiazole **(1)** by cyclization through suitable substituted aniline with ammonium thiocyanate and bromine **(Scheme 1)**



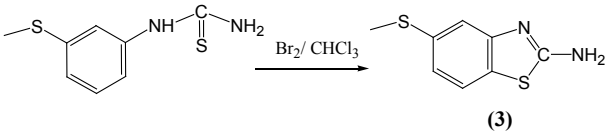
(Scheme 1)

Patel and coworkers[22] synthesized various 4,5,6-trisubstituted-2-aminobenzothiazoles **(2)** by reaction of the corresponding substituted anilines with ammonium thiocyanate followed by oxidative cyclizations of the resultant thiocyanate with bromine. **(Scheme 2)**



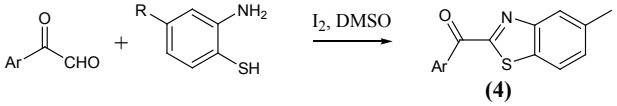
(Scheme 2)

Johanson and coworkers[23] prepared 2-amino-6-ethylmercaptobenzothiazole **(3)** by oxidation of 4- Methylmercaptophenylthiourea with bromine as a catalyst. **(Scheme 3)**



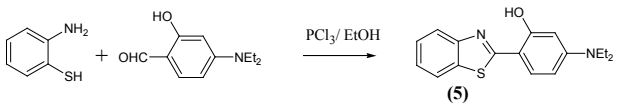
(Scheme 3)

Zhu *et al.*[24] synthesized 2-acylbenzothiazoles **(4)** by condensation of aryl substituted glyoxal with various *ortho*-aminothiophenol in one-pot metal-free reaction. **(Scheme 4)**



(Scheme 4)

Condensation of ortho-aminothiophenol and 4-(diethylamino)-2-hydroxybenzaldehyde using PCl_3 as a catalyst in ethanol (EtOH) resulted 2- substitutedbenzothiazole **(5)** and was reported by Padalkar *et al.*[25] **(Scheme 5)**

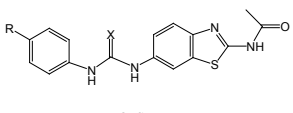


(Scheme 5)

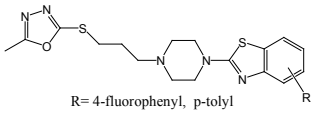
2.2 Medicinal aspects

Benzothiazole is one of the most important heterocycles that has received overwhelming response owing to its diversified molecular design and remarkable biological properties like anticancer[26], antibacterial[27], anticonvulsant[28,29], antidiabetic[30], anti-HIV[31], antimalarial[32], diuretic activity[33], antifungal[34], anti-inflammatory[35], antileishmanial[36], antitubercular[37]etc.

2.2.1 Anticancer activity Synthesis of the series of 2, 6-disubstituted benzothiazole derivatives **(6)** have been done by Sadhasivam *et al.*[38] and their anti-cancer activities were evaluated *in vitro* and have shown cytotoxic effects on all the three (MCF-7, HeLa, and MG63) cell lines. Murty *et al.*[39] synthesized piperazinyl benzothiazole derivatives **(7)** associated with1,3,4-oxadiazole-2-thiol and their anticancer activity was tested against five human cancer cell lines, namely breast, cervical, skin, lung, colon and liver cell lines.

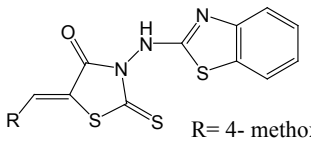


(6)



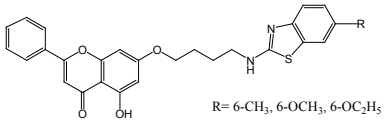
(7)

Antitumor screening of various novel 4-thiazolidinones containing benzothiazole moiety has been synthesized by Havrylyuk *et al.*[40] 2-{2-[3-(benzothiazol-2-ylamino)-4-oxo-2-thioxothiazolidin-5-ylidenemethyl]-4-chlorophenoxy}-N-(4-methoxyphenyl)-acetamide **(8)** has been synthesized by Knoevenagel condensation and have shown inhibition activity against all human tumor cells, melanoma, colon, prostate, CNS, ovarian, leukemia, renal, lung, and breast cancers cell lines.

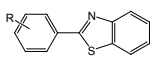


(8)

Mistry *et al.*[41] reported compounds **(9)** which were synthesized by combination of 7-(4-Bromobutoxy)-5-hydroxy-2-phenyl-4H-chromen-4-one and a broad range of 6-substituted 2-aminobenzothiazoles and showed antioxidant and anticancer activity against ovarian cancer cell lines and cervical cancer cell lines(HeLa and CaSki). Racane *et al.*[42] synthesized 6-amino-2-phenylbenzothiazoles **(10)** and were found to display antitumor activity and were screened on the human malignant cell lines: colon, laryngeal carcinoma, cervical, breast and normal human fibroblast cell lines.



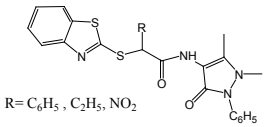
(9)



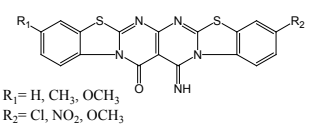
(10)

2.2.2 Antimicrobial activity

Karali *et al.*[43] synthesized a series of benzothiazole derivatives of pyrazole. 2-(1,3-benzothiazole-2-ylmercapto)-N-(1,5-dimethyl-2-phenyl-3-oxo-2,3-dihydro-1H-pyrazole-4-yl)-acylamine **(11)** have been prepared and showed *in vitro* antimicrobial activity against *S. aureus, S. epidermidis, E. coli, K. pneumonia, P. aeruginosa, S. typhi, S. flexneri, C. albicans*. Baheti *et al.*[44] performed the synthesis of novel heterocyclic system possessing six ring, 15-iminobenzothiazolo[2,3-b] pyrimido[5,6-e] pyrimido[2,3-b]-benzothiazol-14(*H*)-one **(12)** and further evaluated for their antibacterial activity against gram- positive species *B. subtilis, S. aureus* and gram negative species *S. typhi* and *E coli* .



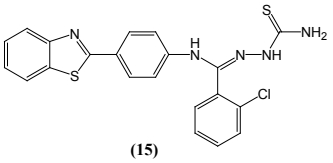
(11)



(12)

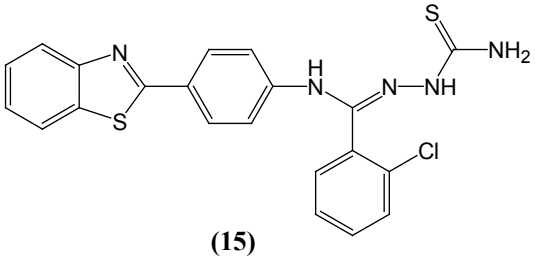
A series of novel pyrazole imine benzothiazole derivatives **(13)** have been synthesized by Mistry *et al.*[45] under both conventional heating method and microwave technique and were

screened for their antibacterial activity against *S. aureus, B. subtilis, E. coli* and *S. typhi*. Patel *et al.*[46] described the synthesis of 6-substituted-2-benzothiazolylimino-5-piperazinyl-4-thiazolidinones **(14)** and these compounds were screened as potent inhibitors of the growth of Gram-positive (*S. aureus and B. subtilis*) and Gram- negative bacteria (*E. coli and P. aeruginosa*) and a fungus (*C. albicans*).



(15)

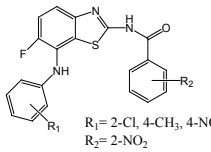
Singh and coworkers[47] focused on the development of new therapeutically active antibacterial agents of substituted benzothiazole derivatives **(15)** containing semicarbazone and thiosemicarbazone as building blocks and broad range of activity with MIC values against Gram-positive as well as Gram-negative bacterial strains.



(15)

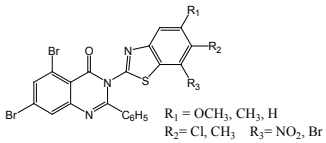
2.2.3 Anti-inflammatory activity

Fluorine substituted benzothiazole have received considerable attention due to their effective bioactivities. Gupta and coworkers[48] synthesized N-{6-fluoro-7-[(4-methoxyphenyl)-amino] 1, 3-benzothiazole-2-yl}-4-nitro benzamides **(16)** and the compounds showed anti-inflammatory activity that was performed on wistar albino rats of sex weighing using carrageenin induced rat hind paw edema method. A series of 2-Phenyl-3-(4-6-dimethylbenzothiazol-2-yl)quinazolin-4(3*H*)-one **(17)** was synthesized by Laddha and coworkers[49] and were screened for their anti-inflammatory activity against carrageenan-induced paw edema in rats and evaluated for their *in vitro* antimicrobial activity against *E. coli* and *P. aeruginosa*, *S. aureus*, *E. faecalis* and *C. albicans*.



R_1= 2-Cl, 4-CH_3, 4-NO_2, 3-OH
R_2= 2-NO_2

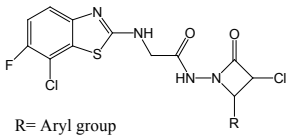
(16)



R_1 = OCH_3, CH_3, H
R_2= Cl, CH_3 R_3= NO_2, Br

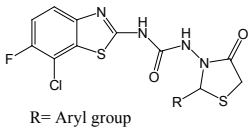
(17)

Kumar *et al.*[50] synthesized compounds 2-[(7-chloro-6-fluoro-benzothiazol-2-yl) amino]-N-[2-aryl-4-oxothiazolidin-3-yl] acetamide **(18)** and 2-[(7-chloro-6-fluoro-benzothiazol-2-yl)amino]-N-[4-aryl-3-chloro-2-oxoazetidene-1-yl) acetamide **(19)** and screened them for anti-inflammatory activity by using inhibition of albumin denaturation technique.



R= Aryl group

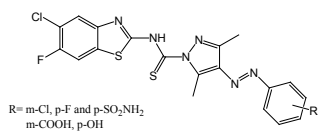
(18)



R= Aryl group

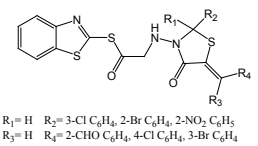
(19)

1-(5-chloro-6-fluoro-1,3-benzothiazole-2-yl) thiocarbamoyl-3,5-dimethyl-4-[(substituted phenyl) diazenyl] pyrazoles **(20)** was synthesized by Hussain *et al.*[51] and further investigated for their analgesic, antibacterial, anti-inflammatory, ulcerogenic, antifungal, lipid peroxidation activity. Yadav and coworkers[52] described the synthesis of thiazolidine clubbed benzothiazole derivatives **(21)** and evaluated their antimicrobial activity and anti inflammatory activity at a dose of 50 mg/kg body weight in albino rats.



R= m-Cl, p-F and p-SO_2NH_2
m-COOH, p-OH

(20)

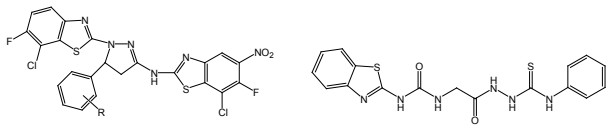


R_1= H R_2= 3-Cl C_6H_4, 2-Br C_6H_4, 2-NO_2 C_6H_5
R_3= H R_4= 2-CHO C_6H_4, 4-Cl C_6H_4, 3-Br C_6H_4

(21)

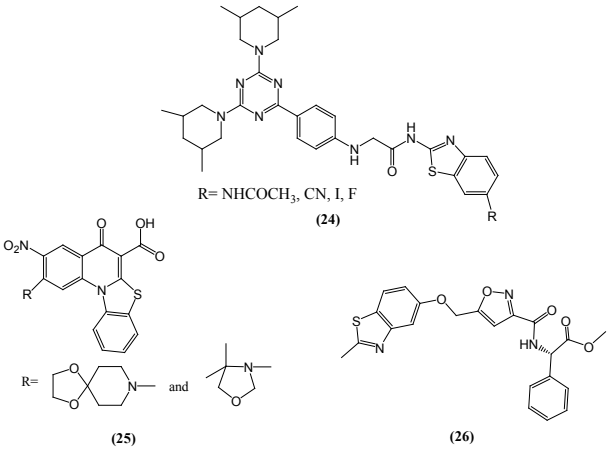
2.2.4 Antitubercular activity

Hazra *et al.*[53] synthesized fluoronitrobenzothiazolopyrazolines **(22)** and tested them for antitubercular activity and cytotoxicity against THP-1 cell lines. A series of regioisomers of fluoronitrobenzothiazolopyrazoline was synthesized and evaluated for their antitubercular activity on *Mycobacterium tuberculosis* $H_{37}Rv$ strain. Benzothiazoles-urea and thiourea derivatives **(23)** were prepared by Abdel-Rahman *et al.*[54] and evaluated them for their in vitro cytotoxicity, antitubercular activity against MCF-7 breast cancer cells, *Mycobacterium tuberculosis* $H_{37}Rv$ and antimicrobial activity against *S. aureus*, *E. coli,* and *C. albicans* respectively.



(22) (23)

Patel *et al.*[55] described N-benzothiazolyl acetamide-based **(24)** analogs which displayed inhibition against *Mycobacterium tuberculosis* H37Rv in Mycobacteria Growth Indicator Tubes (MGIT) and Lowenstein and Jensen method. Dinakaran *et al.*[56] synthesized 3-nitro-2-(sub)-5,12-dihydro-5-oxobenzothiazolo [3,2-a]-1,8-naphthyridine-6-carboxylic acids **(25)** and showed effective antitubercular activities against *M. tuberculosis* $H_{37}Rv$ and multi-drug resistant *M. tuberculosis*. Huang and co-workers[57] described the synthesis of benzothiazole-isoxazole carboxamide derivatives **(26)** and were found effective against antitubercular agents (Mtb) $H_{37}Rv$ and have also shown antiprotozoal activities against protozoan parasites (*Plasmodium falciparum*).



(24) (25) (26)

2. Thiazolidines

Thiazolidines **(fig. 6)** are a class of heterocyclic organic compounds having a five membered saturated system comprising of three carbon atoms, one sulfur atom at position 1, and one nitrogen atom at position 3 and is of considerable interest in different areas of medicinal chemistry.

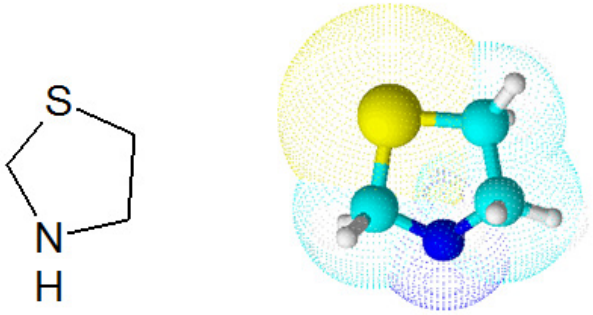
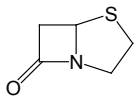


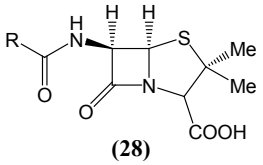
Fig. 6

Its derivatives belong to the most frequently studied moieties and its presence in penicillin was the first recognition of its occurrence in nature. Antibiotics contain basic structural units; penam **(27)** which include powerful antibiotics; penicillins **(28)** include penicillin G, benzathine penicillin, penicillin V and procaine penicillin. Penicillin antibiotics are historically significant because they are the first drugs that were effective against many diseases, such as

syphilis, and infections.



(27)



(28)

Thiazolidinones are the derivatives of thiazolidines which belong to an important group of heterocyclic compounds containing thiazole with carbonyl group. The medication class of thiazolidinediones (also called as "glitziness") was introduced in late 1990's as an adjunct therapy for Type II diabetes mellitus and related diseases. The drug Pioglitazone contains a thiazolidine ring usually indicated in cases of Type II diabetes for decreasing blood sugar. It also decreases triglycerides and C-reactive protein levels, lowers blood pressure and increases levels of HDL (high-density lipoproteins).

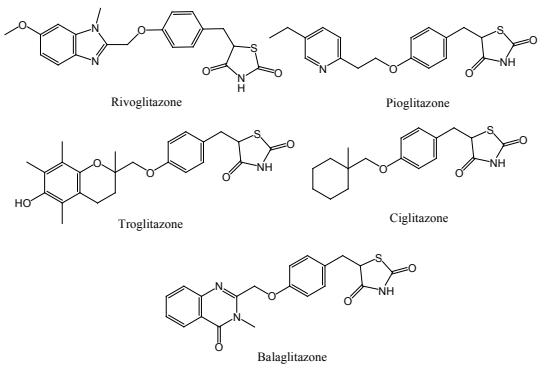
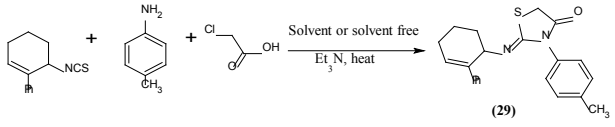


Fig. 7 Thiazolidine containing drugs

3.1 Synthetic aspects

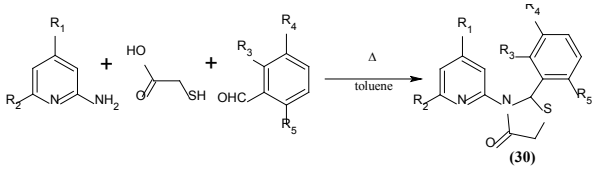
One-pot multicomponent regio/stereoselective synthesis of 2-iminothiazolidin-4-ones **(29)** under solvent /scavenger-free conditions using triethylamine was given by Murugan *et al.*[58] **(Scheme 6)**



(29)

(Scheme 6)

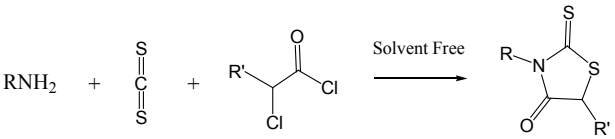
Rao *et al.*[59] described the synthesis of 2,3-diaryl-1,3-thiazolidin-4-ones **(30)** by reacting aromatic aldehydes with an equimolar amount of heteroaromatic amine in the presence of mercaptoacetic acid. **(Scheme 7)**



(30)

(Scheme 7)

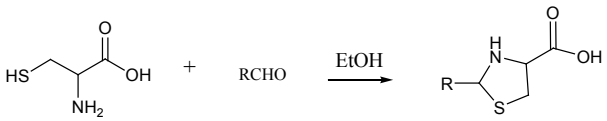
Nasiria *et al.*[60] described the reaction of a primary amine and carbon disulfide at room temperature in the presence of chloroacetyl chloride or 2-chloro-2-phenylacetyl chloride and afforded 3-alkyl-2-thioxo-1,3-thiazolidine-4-one derivatives **(31)** in high yields. **(Scheme 8)**



(31)

(Scheme 8)

Under normal conditions, reaction of L-cysteine with various aldehydes gave acid derivatives of thiazolidines **(32)** and was described by Gududuru and coworkers[61] **(Scheme 9)**

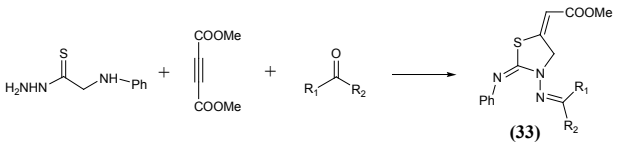


(32)

(Scheme 9)

4-Phenylthiosemicarbazide reacted with dimethyl acetylenedicarboxylate in the presence of aldehydes or ketones under solvent free conditions to produce highly functionalized thiazolidine-4-ones **(33)** and was shown by

Yavari *et al*.[62] **(Scheme 10)**



(33)

(Scheme 10)

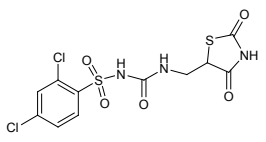
3.2 Biological significance

Thiazolidine derivatives have been studied extensively and found to have diverse chemical reactivities and broad spectrum of biological activities as antifungal[63], antioxidant[64], anti-inflammatory[65], anti YFV (yellow fever virus) activity[66], antitubercular[67], anti HIV[68], anticancer[69-71], antidiabetic[72], antimalarial[73], anticonvulsant[74], antiparasitc[75], antihyperlipidemic[76], CNS activity[77], antimicrobial activity[78] etc.

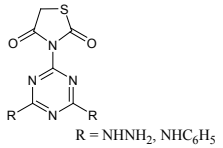
3.2.1 Antidiabetic activity

Dhanaji *et al.*[79] described a series of 2,4-thiazolidinediones with aryl sulfonylurea moieties by condensing various substituted sulfonamides and 5-(isocyanatomethyl) thiazolidino-2,4-dione and the synthesized compounds **(34)** were evaluated for *in vivo* antihyperglycemic activity in sucrose loaded rat model and compared with standard antidiabetic drug metformin.

A novel series of 1,3,5-triazine-thiazolidine-2,4-diones have been synthesized by Shrivastava *et al.*[80] and characterized them with the aid of numerous analytical and spectroscopic techniques and were screened for in vitro inhibition of dipeptidyl peptidase-4, where synthesized compounds **(35)** showed most prominent inhibition.

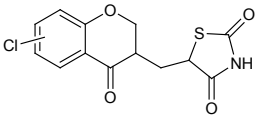


(34)

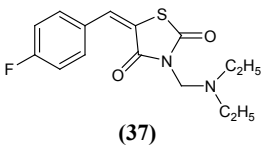


(35)

Nazreenand and co-workers[81] synthesized conjugates of chromones and 2,4-thiazolidinedione by Knoevenagel condensation followed by reduction using hydrogen gas and Pd/C as a catalyst. Synthesized compounds **(36)** were most effective in lowering the blood glucose level comparable to standard drug Pioglitazone. Novel 5-Benzylidene-[3-(diethyl amino) methyl] thiazolidine-2, 4- dione derivatives **(37)** was synthesized by Shyam *et al.*[82] in the presence of formaldehyde and DMF and compounds were assayed for anti diabetic activity by using animal models (male wistar rats).



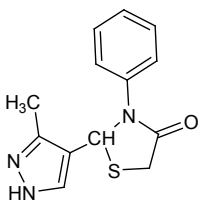
(36)



(37)

3.2.2 Antioxidant activity

Sen and coworkers[83] synthesised 2-(3-methyl-1*H*-pyrazol-4-yl)-3-phenylthiazolidin-4-one **(38)** which showed higher antioxidant activity than the standard ascorbic acid, due to the presence of strong electron donating group. Kilcigil and coworkers[84] synthesized and examined the antioxidant properties of 2-[2-(4-chlorophenyl)benzimidazole-1-yl]-N-(4-oxo-2-aryl-thiazolidine-3-yl)acetamide **(39)** derivatives. The free radical scavenging properties of the compounds were also examined *in vitro* by determining the interaction of 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical.



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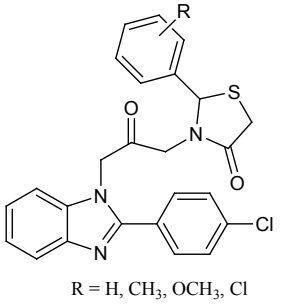
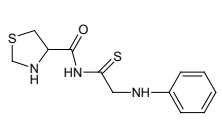
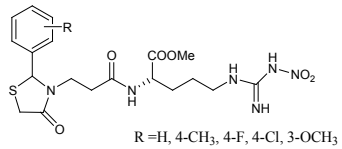


(39)

Thiazolidine compounds **(40)** containing a thiourea moiety was prepared by Silva *et al.*[85] using boric acid as a coupling agent in a multicomponent methodology and evaluated the antioxidant activity as reflected by free radical scavenging. New thiazolidine-4-one derivatives **(41)** of nitro-l-arginine methyl ester (NO_2-Arg-OMe) have been synthesized by Panzariu *et al.*[86] and biologically evaluated in terms of antioxidant and antibacterial/ antifungal activity. The antioxidant potential was investigated using in vitro methods based on ferric/phosphomolybdenum reducing antioxidant power and DPPH/ABTS radical scavenging assay.



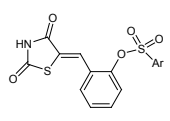
(40)



(41)

3.2.3 Anticancer activity

Chen and coworkers[87] synthesized 2-arenesulfonyloxy-5-benzylidene-thiazolidine-2,4-diones **(42)** followed by nucleophilic substitution with 5-[2'-hydroxybenzylidene]-2,4-thiazolidinone and arylsulfonyl chlorides and were examined for their antiproliferative effects on a panel of carcinoma cell lines (SKHep, H460, SW620, BT474, PC-3). New 5-(4-alkylbenzylidene) thiazolidine-2,4-dione derivatives **(43)** have been synthesized by Laxmi *et al.*[88] and evaluated for anticancer and antimicrobial activities using DNA cleavage studies. An *in vitro* study on anticancer activity was done against the full panel of human tumor cell lines (Leukemia, Colon cancer, CNS cancer, Melanoma, Ovarian cancer, Renal cancer).



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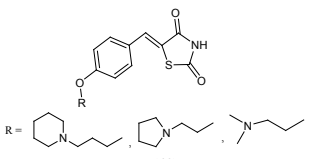
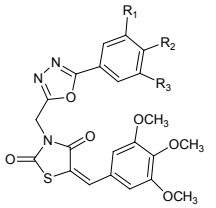
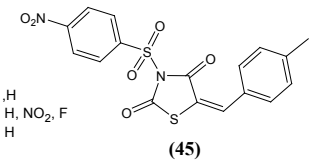


(43)

A series of new substituted (*E*)-3-{[5-(aryl)-1,3,4-oxadiazol-2-yl]methyl}-5-(3,4,5-trimethoxybenzylidene)thiazolidine-2,4-diones **(44)** have been synthesized by Ashok *et al*.[89]. The products have been characterized by their IR, ^{1}H NMR, ^{13}C NMR, and mass spectral properties and evaluated for anticancer activity against four human cancer cell lines: A549, A375, MCF-7, and HT-29. Nguyen *et al*.[90] reported the synthesis of a series of 5-(4-methyl-benzylidene)-thiazolidine-2,4-dione **(45)** derivatives. The antiproliferative effects of the synthesised compounds were tested against viable human skin fibroblast cell line and carcinoma cell lines namely HeLa cells, MCF-7cells, HT-29 cells, HepG-2 cells using MTT assay by adopting positive and negative control.



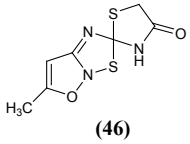
(44)



(45)

3.2.4 Antimicrobial activity

A new synthetic strategy for novel 6-methyl-3-aryl spiro[isoxazolo[2,3-*b*][1,2,4]thiadiazole-2,2'-thiazolidin]-4-ones **(46)** was described by Eligeti *et al.*[91] and compound showed significant antimicrobial activity against all the standard strains Gram-negative bacteria *P. aeruginosa*, *K. aerogenes*, *C. violaceum*, and Gram-positive bacteria *B. subtilis*, *B. sphaericus*, and *S. aureus.* A series of 2-(2-chloroquinolin-3-yl)-5-((aryl) benzylidene)-3-(4-oxo-2-phenylquinazolin-3(4H)-yl)thiazolidin-4-ones **(47)** have been synthesized by Desai *et al.*[92] and compounds exhibited promising antibacterial activities against *E. coli, S. aureus, P. aeruginosa* and *S. pyogenus*. Some of them exhibited very good antifungal activity against *C. albicans, A. niger* and *A. clavatus.*



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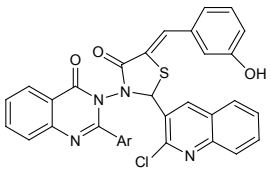
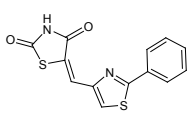


(47)

5-((2-phenylthiazol-4-yl)methylene) thiazolidine-2,4-dione **(48)** and 5-(2,6-dichloro-benzylidene)thiazolidine-2,4-dione **(49)** were synthesized by Stana *et al.*[93] and their antimicrobial activities were assessed *in vitro* against Gram-positive (*S. aureus, B. cereus,* and *E. fecalis*) and Gram-negative (*E. coli* and *S. typhimurium*) bacteria and one fungal strain (*C. albicans*) as growth inhibition. A series of 2-aryl/heteryl-3-(5-phenyl[1,2,4]triazolo[4,3-c] quinazolin-3-yl)-1,3-thiazolidin-4-ones **(50)** was prepared by Reddy *et al.*[94] and antifungal activity was evaluated against four fungal strains (*C. albicans, A. fumigatus, T. rubrum, T. mentagrophytes*).



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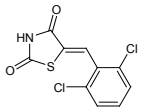

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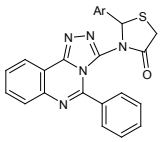
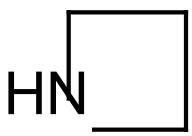


(50)

3. Azetidine

Azetidine (**Fig. 8**) is a four membered heterocyclic compound containing one nitrogen atom. The 2-carbonyl derivative of 4-membered heterocyclic ring with nitrogen atom is designated as 2-azetidinone. It is also called as β-lactam. Azetidine derivatives occupy a central place among medicinally important compounds due to their diverse and interesting antibiotic properties and biological activity[95-98].



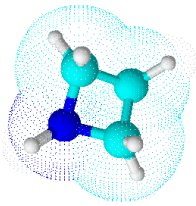
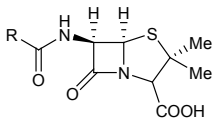
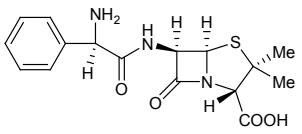


Fig. 8

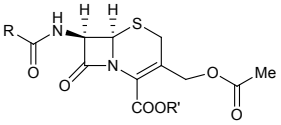
They act as versatile intermediates for the synthesis of aromatic β-amino acids and their derivatives, peptides, polyamines, polyamino alcohols, amino sugars and polyamino ethers. Azetidine containing various drugs e.g. penicillin (antibacterial), pyrazinamide (antitubercular), indinavir, ritonavir. (Protease inhibitors as anti-AIDS) etc. The azetidine based antibiotics are still the most prescribed antibiotics used in medicine. They are considered as a significant contribution of science to humanity. The most widely used antibiotics such as the penicillins, Ampicillins, Cephalosporins, Thienamycine, Aztreonam, Carumonam, and the Nocardicins contain β-lactam (azetidin-2-one) ring. After the spectacular world-wide recognition and tremendous success of the penicillins, the best known family of β-lactams is termed as cephalosporins, wherein the β-lactam ring is strategically fused to a 6-membered dihydrothiazine ring system. Following are the structures of several β-lactam antibiotics that have been applied clinically. **(Fig. 9)**



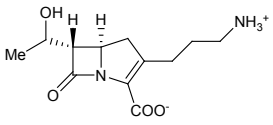
Penicillin



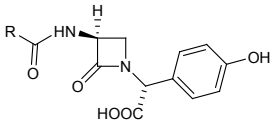
Ampicillin



Cephalosporin



Thienamycin



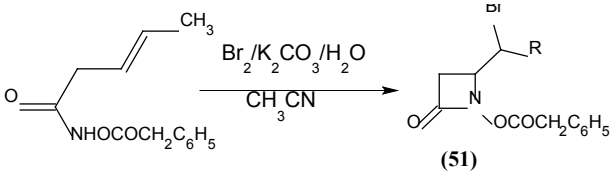
Nocardicin

Fig. 9 Azetidine containing antibiotics

4.1 Synthetic aspects

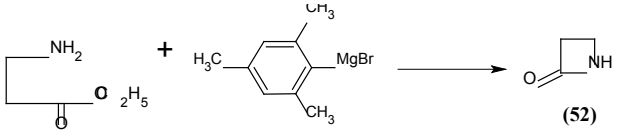
The bromine induced cyclization of *o*-acyl-β

hydroxamates via the formation of bromonium ion intermediate for the synthesis of β-lactams **(51)** was given by Rajendra *et al.*[99] **(Scheme 11)**



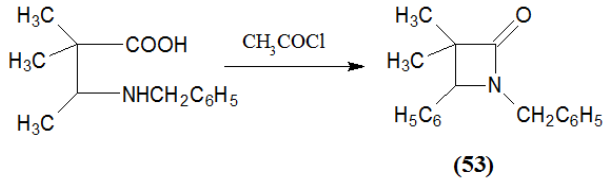
(Scheme 11)

Kunieda *et al.*[100] synthesized azetidinones **(52)** by the reaction of β-amino esters with Grignard reagents via the formation of *N*-anion. **(Scheme 12)**



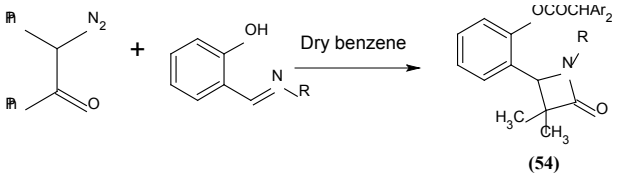
(Scheme 12)

Staudinger and coworkers[101] described the most common method for the synthesis of 2-azetidinones **(53)** by the Staudinger ketene imine cycloaddition, in which the reaction of imines with acid chloride in the presence of a tertiary base. **(Scheme 13)**



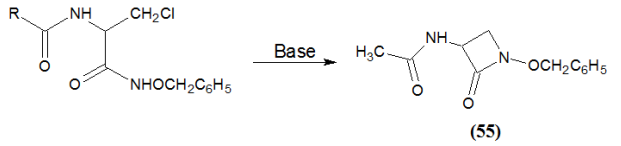
(Scheme 13)

Singh *et al.*[102] synthesized 2-azetidinones **(54)** by the reaction of *N*-salicylideneamines and equivalent) α-diazocarbonyl compounds. **(Scheme 14)**



(Scheme 14)

N-substituted β-halo amides are cyclized in the presence of a base producing β-lactams **(55)** via an intermediate was described by Wasserman and coworkers[103] **(Scheme 15)**



(Scheme 15)

4.2 Pharmacological significance

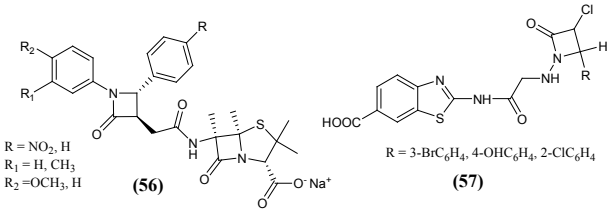
Azetidinones are very important class of compounds possessing wide range of biological activities such as anti-inflammatory[104], antihyperlipidemic[105], CNS activity[106], tryptase inhibitory[107], human leukocyte elastase inhibitory[108], antihyperglycemic[109], vasopressin V1a antagonist[110], and anticancer activity[111], antimicrobial[112], antitubercular[113], cytotoxic[114], and cholesterol absorption inhibitors[115].

4.2.1 Antimicrobial activity

Novel semi-synthetic β-lactam compounds **(56)** containing an azetidinone moiety clubbed with the (+)-6-aminopenicillanic acid (6-APA) as new antibacterial agents was reported by Rosa *et al.*[116] and it displayed good antimicrobial activity against all tested *S. aureus S. epidermidis, E. coli, Salmonella, P. fluorescens and P. aeruginosa.*

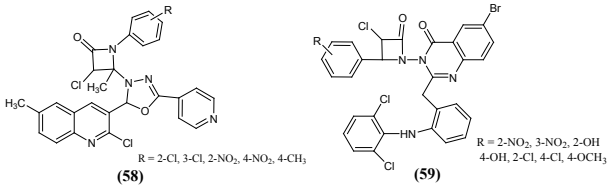
Chavan *et al.*[117] synthesized 2-{2-[3-chloro-2-(aryl)-4-oxoazetidin-1-ylamino]-acetylamino}

benzothiazole-6-carboxylic acids **(57)** and screened them for their antibacterial activity against four microorganisms: *S. aureus, B. subtilis, P. aeruginosa* and *E. coli* and three different fungi such as *C. tropicans*, *A. niger* and *F. heterosporium* by filter paper disc technique.



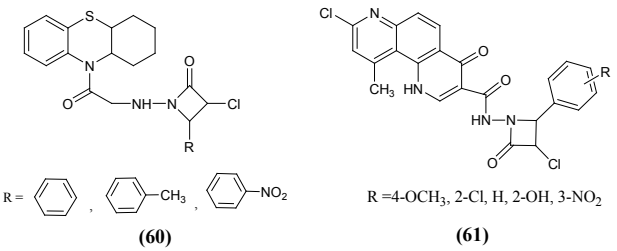
A series of quinoline nucleus containing 1,3,4-oxadiazole and 2-azetidinone derivatives **(58)** have been synthesized by Desai *et al.*[118] and compounds were screened for their antibacterial activity against four different strains like *E. coli, P. aeruginosa, S. aureus and S. pyogenes,* and antifungal activity against three different strains like *C. albicans, A. niger* and *A. clavatus*.

Patel and coworkers[119] synthesized a series of 2-oxo-azetidinyl-quinazolin-4(3*H*)-ones **(59)** from Schiff bases and the antibacterial activity was screened against two gram positive bacteria (*S. aureus and B. subtilis*) and two gram negative bacteria (*P. aeruginosa and E. coli*) and antifungal activity against fungi *C. albicans*.

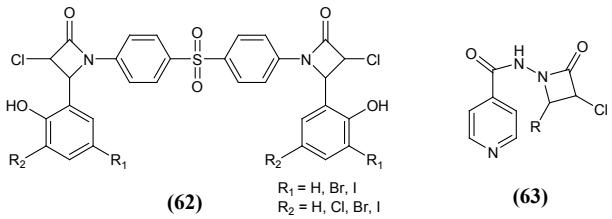


4.2.2 Antitubercular activity

Rajasekaran *et al.*[120] synthesized azetidinones derivatives **(60)** by cyclocondensation of various Schiff bases of phenothiazine with chloroacetyl chloride in presence of triethylamine and screened for antitubercular activity against *Mycobacterium tuberculosis* H37Rv strain using Lowenstein-Jensen medium method. Patel *et al.*[121] synthesized pyridoquinolones containing azetidinones derivatives **(61)** and the synthesized compounds were screened against *Mycobacterium tuberculosis* $H_{37}Rv$.



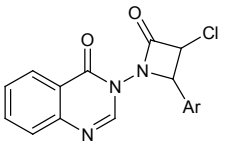
A series of 2-azetidinone of 4,4'-sulfonyldianiline **(62)** has been synthesized by Bhusnure *et al.*[122] under microwave irradiation and conventional heating and screened them for their anti-tubercular activity against the human strain using Lowenstein-Jensen medium method. A series of novel azetidinone derivatives **(63)** was synthesized by Elumalai *et al.*[123] and the synthesized compounds were preliminarily assayed against freshly isolated clinical strains, *Mycobacterium fortuitum* and *Mycobacterium tuberculosis*, as per the dilution method in agar.



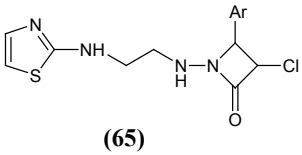
4.2.3 Antiinflammatory activity

Dhingra and coworkers[124] synthesized quinazolone fused azetidine analogs **(64)** to find compounds with promising anti-inflammatory activity using carrageenan-induced rat paw edema model taking aspirin as standard drug. A new series of 3-chloro-4-(substituted phenyl)-1-{[2-(2-thiazolylamino)ethyl]amino}-2-azetidinone **(65)** has been synthesized by Samadhiya *et al.*[125] Here, the carageenan-induced rat paw edema method was employed for evaluating the anti-inflammatory activity of the compounds using phenylbutazone as the

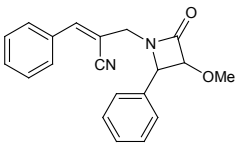
standard drug.



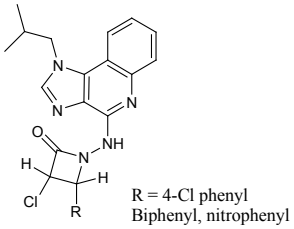
(64)



(65)

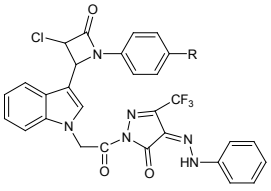


(68)

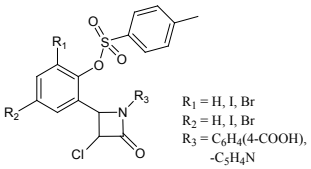


(69)

Muralikrishna *et al.*[126] synthesized 4-oxazetidine derivatives **(66)** bearing indole moiety and the compounds showed better anti-inflammatory activity and equipotent analgesic activity than standard drug phenyl butazone at the dose of 25, 50 and 100 mg/kg . Kendre *et al*.[127] synthesized azetidin-2-one derivatives containing aryl sulfonate moiety, 2-(3-Chloro-1-(4-carboxyphenyl)-4-oxoazetidin-2-yl) phenyl 4-methyl benzene sulfonate **(67)** and has shown good anti-inflammatory activity compared with standard drugs.



(66)



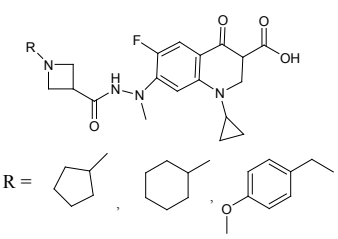
(67)

4.2.4 Anticancer activity

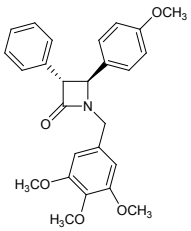
Geesala and coworkers[128] synthesized a series of twenty-five 2-azetidinone (*β*-lactam) derivatives **(68)** and evaluated them for anti-cancer properties against breast cancer, MCF-7 and MDA-MB-231 using (3–4, 5–dimethylthiazol–2–yl)–2, 5–diphenyltetrazolium bromide (MTT) assay. Novel imidazoquinoline based 2-azetidinones derivatives **(69)** were synthesized by Kayarmar *et al.*[129] and the anticancer activity was performed against the cancer cell lines, HeLa by employing the Trypan blue exclusion method.

A series of nine new N-(substituted azetidine-3-carbonyl)-N-methyl-hydrazino derivatives **(70)** was synthesized by Rajulu *et al.*[130] which displayed good growth inhibition against (MCF-7) breast carcinoma, (HCT-116) colon carcinoma and (A549) lung adenocarcinoma cell lines.

Boyle and coworkers[131] described the structure-activity relationship of antiproliferative β-lactams, doing modifications at the 4-position of the β-lactam ring. The antiproliferative activity was assessed in MCF-7 cells, where the 4-(4-ethoxy) phenyl substituted compounds **(71)** displayed the most potent activity.



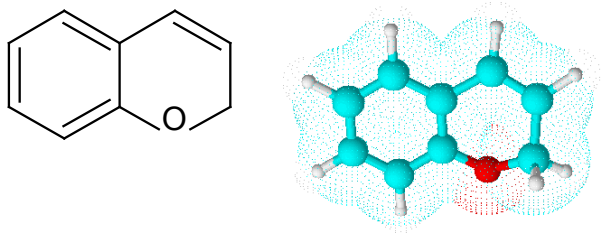
(70)



(71)

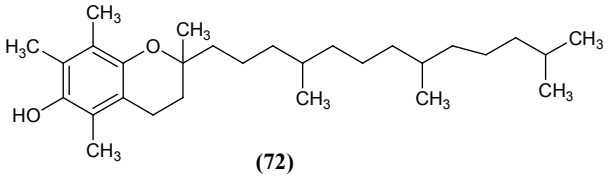
4. Chromene

Chromene **(Fig.10)** are heterocyclic compounds with a benzene ring fused to a pyran nucleus. Chromene is a common motif in a variety of naturally occurring and synthetic molecules with interesting biological activities. The benzopyran nucleus includes some structural skeletons such as chromane, 2*H*-chromene and 4*H*-chromene.



(Fig.10)

Chromene and its derivatives have also been recognized as 'privileged medicinal scaffolds' due to their unique pharmacological and biological activities[132-135]. Chromene constitute the basic backbone of various types of polyphenols and widely found in natural alkaloids, tocopherols, flavonoids, and anthocyanins. Vitamin E **(72)** was an evident example for the naturally occurring chromane, possessing antioxidant activity.



(72)

Currently, a number of drug molecules bearing chromene unit are biologically active natural products and promising synthetic compounds in the field of medicinal, agrochemical, cosmetics pigment industries and in the treatment of various ailments such as hypertension, asthma, ischemia and urinary incontinence. The naturally and synthetic occurring available bioactive chromene heterocycles are as **(Fig. 11, 12)**

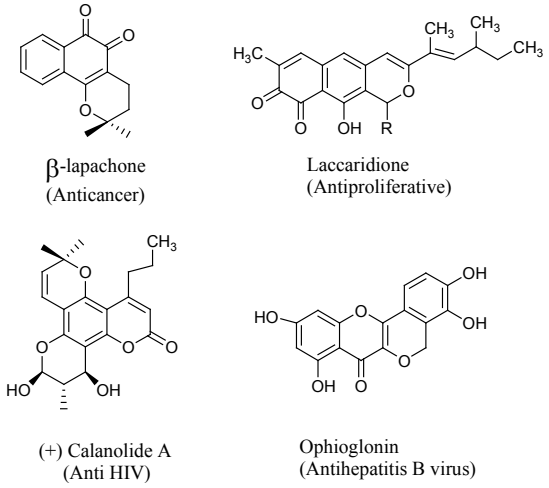


Fig. 11 Naturally occurring potent bioactive chromene heterocycles

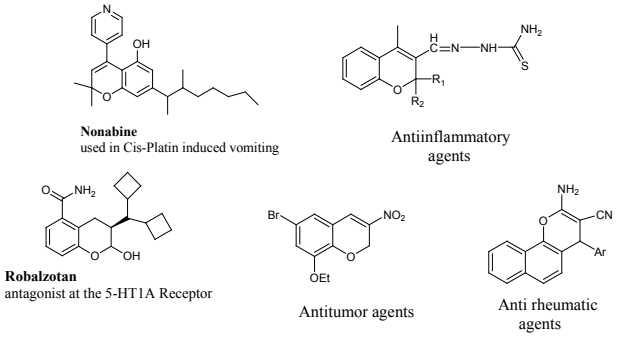
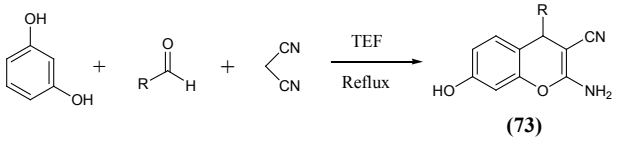


Fig. 12 Synthetically important drug-like chromene heterocycles

Synthetic aspects

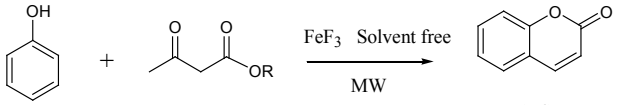
S. Khoksar *et.al.*[136] synthesized one-pot three component regioselective synthesis of 2-amino-3-cyano-4*H* chromene derivatives **(73)** with good yields by annulation of aldehydes, malononitrile, and resorcinol under reflux conditions in 2,2,2-trifluoroethanol without the use of a catalyst or any other additive. **(Scheme 16)**



(73)

(Scheme 16)

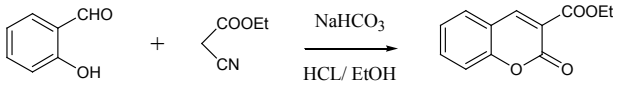
Vahabi *et al.*[137] described one-pot synthesis of coumarin derivatives **(74)** via the von Pechmann condensation of phenols with ethyl acetoacetate using FeF_3 as an acid catalyst under Microwave irradiation. **(Scheme 17)**



(74)

(Scheme 17)

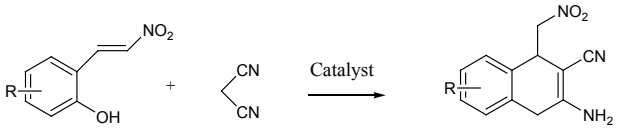
Brufola *et al.*[138] synthesized ethyl coumarin-3-carboxylate **(75)** by the Knoevenagel reaction of o-salicylaldehyde with ethyl cyanoacetate using sodium bicarbonate followed by hydrolysis of carbonitrile group with hydrochloric acid in ethanol with 87% yield. **(Scheme 18)**



(75)

(Scheme 18)

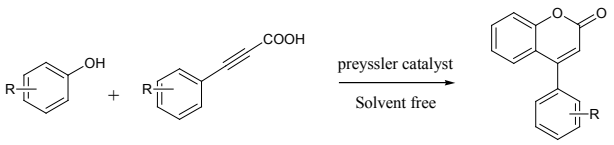
Gao and coworkers[139] developed organocatalytic Michael addition–cyclization of malononitrile to nitroalkenes for the direct synthesis of chiral 2-amino-4*H*-chromene-3-carbonitrile **(76)** derivatives. **(Scheme 19)**



(76)

(Scheme 19)

4-phenylcoumarins **(77)** were prepared by Escobar *et al.*[140], followed by direct esterification of phenols with phenylpropiolic acid, using Preyssler structure as heterogeneous catalyst under solvent-free reaction conditions. **(Scheme 20)**



(77)

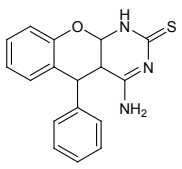
(Scheme 20)

5.2 Biological importance:

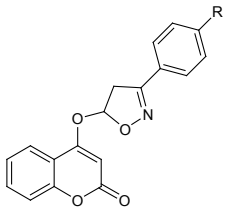
It is known that chromene derivatives possess certain natural and synthetic chromene derivatives and important biological activities such as antitumor[141], antivascular[142], antimicrobial[143], TNF-α inhibitor[144], antifungal[145], anticoagulant[146], estrogenic[147], antiviral[148], anti-helminthic[149], anticancer[150], anti-inflammatory[151], antimalarial[152], anticonvulsant[153] etc.

5.2.1 Antimicrobial activity

Kamdar *et al.*[154] described the synthesis of 4*H*-Chromeno[2,3-d]pyrimidines **(78)** and the antimicrobial activity was performed against four species of bacterial strains: *S. aureus and S. pyogenes* as Gram-positive, *E. coli and P. aeruginosa* as Gram-negative; and one species of fungal strain *A. niger*. New series of 4-((3-aryl-4,5-dihydroisoxazol-5-yl)methoxy)-2H-chromen-2-ones **(79)** was prepared by Zghab *et al.*[155] and screened them for their antibacterial activity against two Gram-negative bacteria (*E. coli and P. aeruginosa*) and two other Gram-positive bacteria (*S. aureus and E. faecalis*). The obtained data revealed that most of the compounds showed moderate to excellent activities against the used microorganisms.



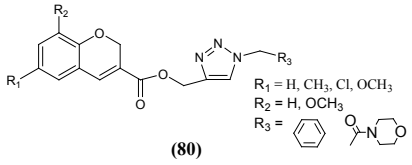
(78)



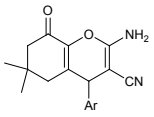
(79)

Reddy and co-workers[156] synthesized 1,4 disubstituted (1-alkyl-1H-1,2,3-triazol-4-yl) methyl-2*H*-chromene-3-Carboxylates **(80)** and screened them against antibacterial strain *B. subtilis* (Gram-positive), *S. aureus* (Gram-positive), *P. aeruginosa* (Gram-negative) and antifungal strain *A. niger*, *R. solani* and *A. terreus*.

Jain *et al.*[157] described one-pot synthesis of heteroaryl substitued dihydropyrano(c) chromenes **(81)** via initial Knoevenagel, subsequent Micheal and final heterocyclization reactions and the compounds have shown good antimicrobial activity against different microbial strains (*E. Coli, S. typhi, K. pneumonia, P. aeruginosa*).



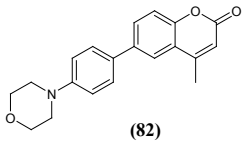
(80)



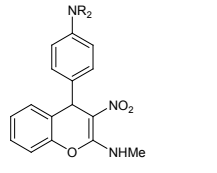
(81)

5.2.2 Antiproliferative activity

Rao *et al.*[158] synthesized 4-Methyl-6-(41-morpholinophenyl)-2*H*-chromen-2-one **(82)** by using Suzuki–Miyara cross coupling reaction and compounds were tested for antiproliferative activity against different human cancer cell lines (SiHa, MDAMB-231, and PANC-1). A new series of C4-N,N-dialkylaniline-substituted 4-aryl-4H-chromenes **(83)** was synthesized by Parthiban *et al.*[159] and their antiproliferative properties were evaluated against human cancer cell lines, namely, laryngeal carcinoma (Hep2), lung adenocarcinoma (A549), and cervical cancer (HeLa).

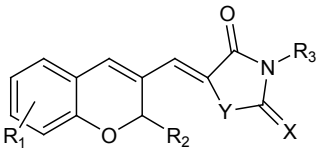


(82)



(83)

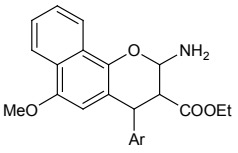
A variety of (Z)-[(2*H*-chromen-3-yl)methylene] azolidinones **(84)** bearing thiazolidine-2,4-dione, rhodanine or hydantoin scaffolds were designed and synthesized by Azizmohammadi *et al.*[160] as potential anticancer agents against A549 (human alveolar basal epithelial adenocarcinoma), K562 (human chronic myelogenous leukemia), MCF-7 (human breast adenocarcinoma), and MOLT-4 (human acute lymphoblastic leukemia) cancer cell lines.



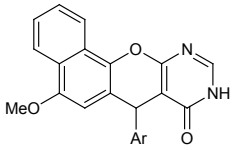
X = O,S Y = S, NH, NMe
R_1 = H, Br, OMe
R_2 = H, Me
R_3 =H, Me, Et, CH_2COOH

(84)

Novel derivatives of 4*H*-benzo[h]chromene **(85)** and 7*H*-benzo[h]chromeno[2,3-d]pyrimidine **(86)** were prepared by El-Agrody *et al.*[161] and were evaluated them for their anti-proliferative activity against three human tumor cell lines breast adenocarcinoma (MCF-7), human colon carcinoma (HCT-116) and hepatocellular carcinoma (HepG-2) in comparison with the standard drugs Doxorubicin.



(85)

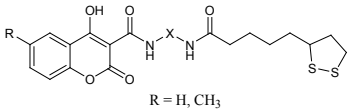


(86)

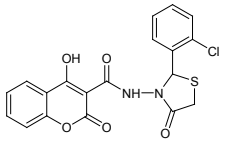
5.2.3 Anti-inflammatory activity

A series of novel coumarin-3-carboxamides **(87)** and their hybrids with the alpha-lipoic acid were designed and synthesized by Melagraki *et al.*[162] and in vivo anti-inflammatory effects of the tested coumarins were assessed by using the functional model of carrageenin-induced rat paw edema. Indulatha and co-workers[163] synthesized *N*-[2-(2-substituted aryl / heteryl)-4-oxo-1,3-thiazolidin-3-yl]-2-oxo-

2*H*-chromene-3-carboxamide **(88)** derivatives and evaluated them for their anti inflammatory activity by Hind paw oedema method using the standard drug Aspirin.

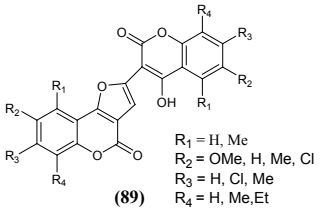


(87)

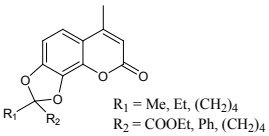


(88)

Elenkov *et al.*[164] designed series of variously substituted furochromenes **(89)** and evaluated their anti-inflammatory activity in PMA induced ear edema in CD1 mice, with potency equal in comparison with zileuton as the reference compound. Fylaktakidou *et al.*[165] reported several 6,7 or 7,8-fused dioxolane coumarins **(90)** and evaluated them for their antioxidant and anti-inflammatory potential. All compounds displayed anti-inflammatory potential against carrageenan-induced paw edema, showing a higher activity than the reference drug, indomethacin.



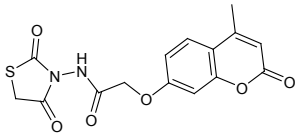
(89)



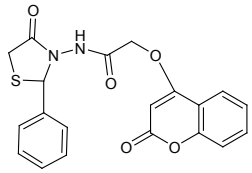
(90)

5.2.4 Antioxidant activity

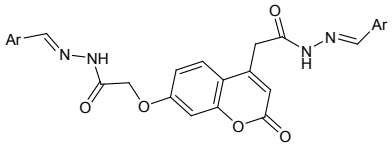
Cacic *et al.*[166] described synthesis of novel N-(2-(substituted phenyl)-4-oxo-thiazolidin-3-yl)-2-(4-methyl-2-oxo-2*H*-chromen-7-yloxy) acetamides **(91)** and the antioxidant activity of tested coumarin derivatives was evaluated by the phosphomolybdenum method and have shown better antioxidant activity in comparison with ascorbic acid. Kadhum *et al.*[167] studied *N*-(4-oxo-2-phenylthiazolidin-3-yl)-2-(2-oxo-2*H*-chromen-4-yloxy)acetamide **(92)** with the 1,1-diphenyl-2-picryhydrazyl (DPPH), hydrogen peroxide and nitric oxide radical methods and compared them with the known antioxidant ascorbic acid. Molnar and coworkers[168] synthesized a series of coumarin Schiff bases (7-(arylidenehydrazinocarbonyl methoxy)-2-oxo-2*H*-chromen-4-yl]acetic acid arylidene hydrazide) **(93)** and evaluated them for their antioxidant activity using scavenging of 1,1-diphenyl-2-picryhydrazyl (DPPH) radical and phosphomolybdenum method.



(91)



(92)



(93)

5. Conclusion

This review gives an overview of the advances of different heterocycles in the synthesis of conjunction based novel heterocyclic compounds. These compounds possess enormous significance in the field of drug discovery process. Substituted benzothiazoles, thiazolidine, azetidine, chromene and their analogues have been used as precursors for the synthesis of various biologically dynamic molecules. Our review covers the synthetic and medicinal applications of heterocyclic moieties containing nitrogen, oxygen and sulfur atoms which have much significance that impinge on almost all aspects of modern organic chemistry, medicinal chemistry and biochemistry.

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