

HETEROCYCLIC COMPOUNDS

Literature survey revealed that the history of heterocyclic chemistry began in the 1800's, in step with the development of organic chemistry [1-5]. After World War II, there was an enormous explosion research in the field of heterocycles. About one half of over six million compounds recorded in *Chemical Abstracts* are heterocyclic. Heterocyclic chemistry is one of the most complex and intriguing branch of organic chemistry and heterocyclic compounds constitute the largest and most varied family of organic compounds. Many broader aspects of heterocyclic chemistry are recognized as disciplines of general significance that impinge on almost all aspects of modern organic chemistry, medicinal chemistry and biochemistry. Heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly and economically useful as therapeutic agents.

Heterocyclic compounds are organic compounds containing at least one atom of carbon and at least one element other than carbon, such as sulfur, oxygen or nitrogen within a ring structure [6]. Since in heterocycles non-carbons usually are considered to replace carbon atoms, they are called heteroatoms e.g. different from carbon and hydrogen. A ring with only heteroatoms is called homocyclic compound and heterocycles are the counterparts of homocyclic compounds. Thus incorporation of oxygen, nitrogen, sulfur or an atom of a related element into an organic ring structure in place of a carbon atom gives rise to a heterocyclic compound. These structures may comprise either simple aromatic rings or non-aromatic rings. The heterocyclic compounds usually possess a stable ring structure which does not readily hydrolyzed or depolymerized. Heterocycles with three atoms in the ring are more reactive because of ring strain. Those containing

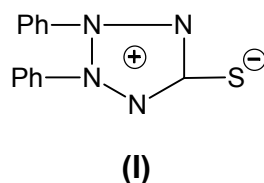
one heteroatom are in general, stable. Those with two heteroatoms are more likely to occur as reactive intermediates.

Heterocyclic compounds played a vital role in biological processes and are wide spread as natural products. They are widely found in nature particularly in nucleic acids, plant alkaloids, anthocyanins and flavones as well as in haem and chlorophyll. Additionally some vitamins, proteins, hormones contain aromatic heterocyclic system. Synthetically produced heterocycles designed by organic chemists are used for instance as agrochemicals and pharmaceuticals and play an important role in human life. Heterocycles have enormous potential as the most promising molecules as lead structures for the design of new drugs [7-10].

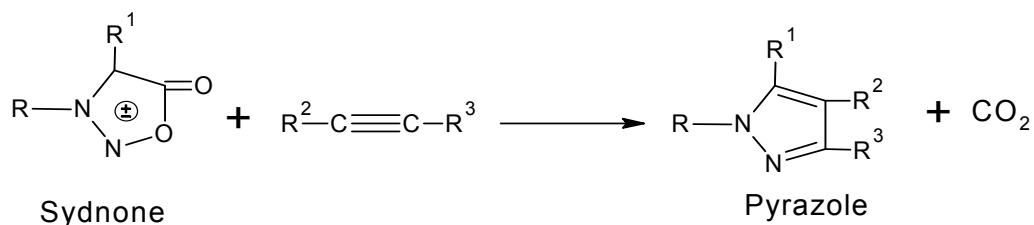
In short, heterocyclic chemistry is the branch of chemistry dealing with synthesis, properties and applications of heterocycles.

SYDNONES

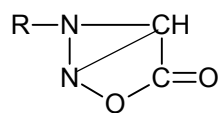
In 1882, Fischer and Besthorn [11] described the preparation of dehydrodithizone (**I**) and thus provided the first example of a mesoionic compound.



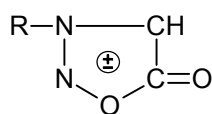
This initial contribution was soon followed by the pioneering work of Max Busch who, during the period 1895-1905, described the preparation and chemical properties of a number of mesoionic heterocycles. Considerable attention has recently been paid to finding applications of the mesoionic compounds in synthesis and pharmacology. The mesoionic compounds possess structural features which have been of considerable interest to medicinal chemists. A variety of monocyclic mesoionic compounds are known in chemistry. Among them sydnone ring is the most extensively studied and have gained significant interest because of ease of its synthesis from primary amines and also it is the only mesoionic ring which undergoes a wide variety of chemical reactions of synthetic utility and having useful biological properties. Sydnones act as useful and novel precursors for pyrazoles through cycloaddition with alkynes (**II**) [12-14].



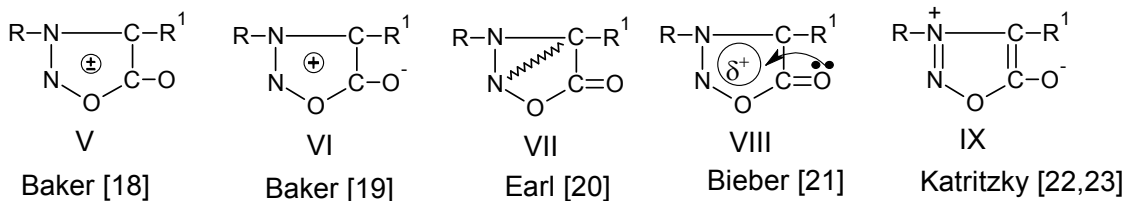
In 1935, Earl and Mackney [15] found that treating *N*-nitroso-*N*-phenylglycine with acetic anhydride gave an anhydro compound on intramolecular dehydration. A fused ring structure **(III)** was proposed and the name ‘Sydnone’ was suggested in honour of University of Sydney (Sydney + Lacton) where the study was performed first time. The original cyclodehydration used by Earl and Mackney made use of acetic anhydride at room temperature for six days.

**(III)**

Later on in 1949, Baker *et al.* [16] found structure **(III)** to be unsound in the light of the properties of sydnone and considered the sydnone to be resonance hybrid of a number of dipolar and tetrapolar ionic structures. Simpson [17] designated compounds of this type by the symbol \pm and therefore general adjective “mesoionic” (mesomerie + ionic) was introduced. Thus, the term “mesoionic” was first suggested by Simpson to describe this type of molecule. In this usage 3-phenylsydnone is presented by structure **(IV)**.

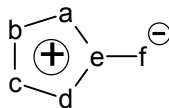
**(IV)**

Since that time both the concept of mesoionic compounds and methods for synthesizing them have undergone extensive changes and modifications. Many alternate representations of sydnes have been proposed by many scientists are depicted in structure **(V-IX)**.



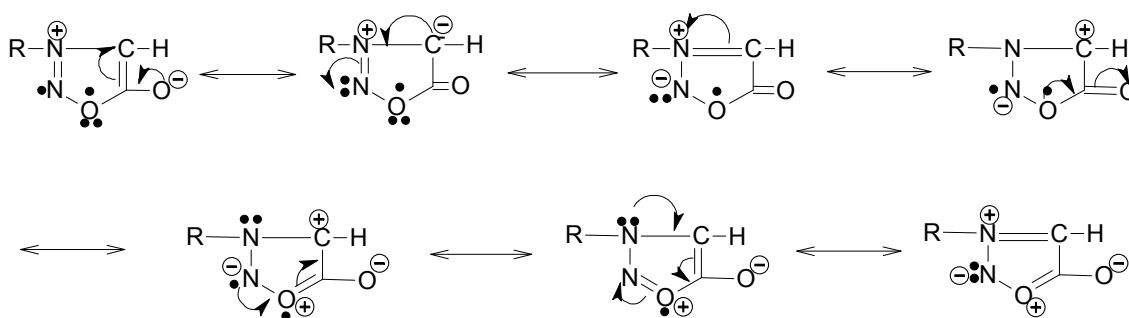
Variations to method of synthesis of sydnone have been found however and these include; heating in acetic anhydride or thionyl chloride, treatment with phosphorus pentoxide or the use of trifluoroacetic anhydride (TFAA). The most widely used method is the cyclization with trifluoroacetic anhydride (TFAA). It is rapid (< 15 minutes), is achievable at low temperatures (-5°C to 0°C) and affords high yields (> 90% for *N*-phenylsydnone). The only setback is the high cost of trifluoroacetic anhydride in comparison to other reagents.

Numerous works have been focused on the chemistry of mesoionic compounds. The sydnone ring is a nonbenzenoid heterocyclic aromatic five membered ring and possesses some unusual characteristics. It can be regarded as a mesoionic system with positive and negative charges distributed around the ring depending on their resonance forms [24]. A completely uncharged structure cannot be written therefore mesoionic compounds cannot be represented satisfactorily by any one mesomeric structure. The formal positive charge is associated with the ring atoms and the formal negative charge is associated either with ring atoms or an exocyclic atom. They are known as a subclass of betaines. Mesoionic compounds of the general formula (**X**), where a-f are suitably substituted carbons or heteroatoms, are an interesting family of heterocycles because of their unique structure, reaction behavior and pharmaceutical activity.

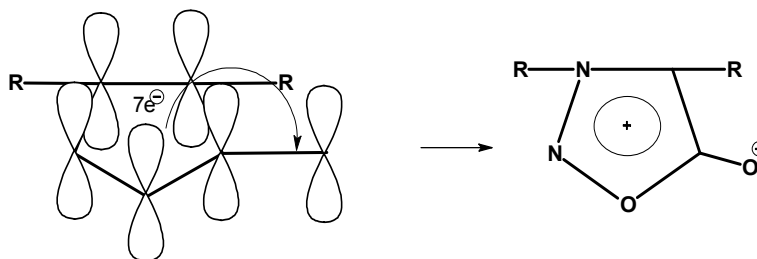


(X)

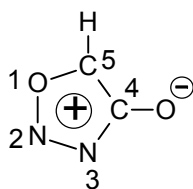
It is not possible to write a covalent structure for sydnones without separating the positive and negative charges. The resonance in sydnone can be depicted by structures as in (XI) [25].

**Resonance in sydnone (XI)**

The aromaticity of the sydnone is explained by the classical sextet theory. A total of seven 2p_z electrons are contributed by the five atoms of the ring with one 2p_z electron on the exocyclic atom. A sextet of electrons will be obtained when one of the seven 2p_z electrons is paired with the single electron on the exocyclic atom. The ring will be positively charged, balanced by the negative charge on the exocyclic atom.

**Overlap of p-orbitals in sydnone ring (XII)**

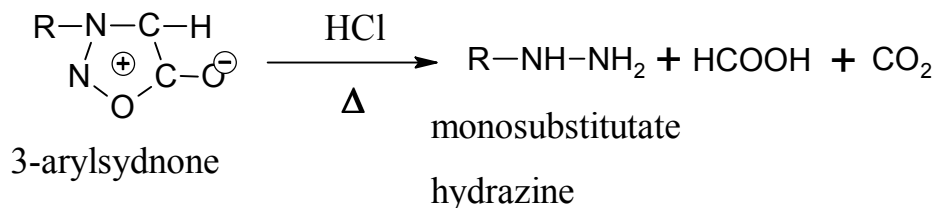
Numbering in sydnone ring generally given as represented in structure (XIII).



In general it is believed that C(4) possesses negative character and N(2) is positive in sydnone ring, based on their orientation and calculations [26,27]. Therefore the C(4) position of a sydnone ring is both acidic and nucleophilic. Sydnone is dipolar, pseudo-aromatic heterocycle with a unique variation in electron density around the ring.

Many sydnones are isolated as crystalline solids. They are stable compounds of considerable polarity. Aryl sydnones are generally solid crystals whereas alkylsydnones are usually either low melting point solids or liquids and can be distilled in *vacuo* without appreciable decomposition. They readily dissolve in polar organic solvents but are insoluble in nonpolar solvents like hexane and ether. They are generally insoluble in water but their solubility is enhanced when a polar functional group is present within the molecule. Sydnone can be stored at room temperature, although a few have been known to degrade in the presence of light.

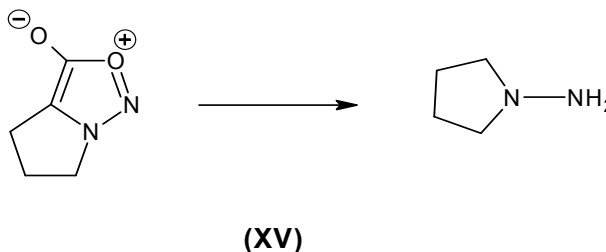
Concentrated acids can also cause degradation of sydnones, yielding the hydrazine derivatives with loss of CO₂. [28]



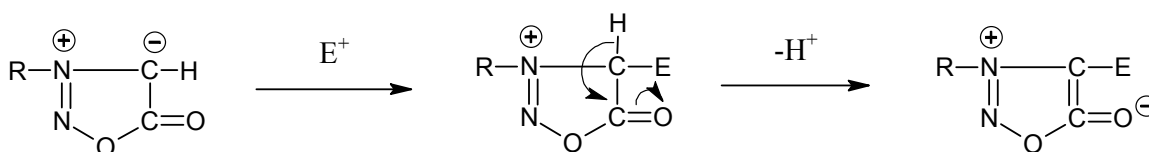
Degradation of sydnone ring (XIV)

Though aromatic, sydnone ring is readily cleaved by hydrochloric acid and as dipolarophile undergoes 1,3-dipolar cycloaddition reaction with unsaturated systems. This acid hydrolysis of 3-arylsydnone has been used in an approach to one-pot synthesis of pyrazoles, indoles and tetrahydrocarbazoles.

Heat can also cause degradation of the mesoionic ring system. Therefore reactions of sydnone must be carried out carefully in this manner. Nikitenko *et al.* [29] conducted a decomposition analysis, which demonstrated a large exotherm at 180 °C, presumably due to the formation of pyrrolidinehydrazine and CO₂ (XV).



Sydnone unsubstituted at 4th position undergoes substitution with a wide variety of electrophiles, with retention of the ring, typical of aromatic substrates.



Substitution reactions in sydnones (XVI)

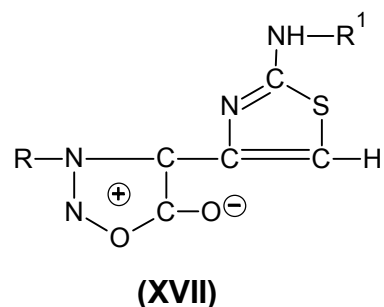
Some fundamental aromatic reactions such as bromination [30,31], nitration [32], acylation [33,34] and sulfonation [35] occur at the 4th position of the sydnone ring (XVI) and this position of sydnone ring also functionalized by various functional groups, such as phosphino, silyl, alkyls, halides etc [36,37].

Sydnone derivatives showed variety of biological properties, such as antimalarial [38], antiinflammatory [39], analgesic [40], antibacterial [41,42], antifungal [43] antitumor [44], antioxidant activity [45] etc. Kier and Roche [46] had reviewed in detail the biological importance of various mesoionic compounds. Sydnones show liquid crystalline properties [47,48] and also used in battery applications [49]. The *N*-methyl sydnones having a high dielectric constant was used as a solvent for lithium battery electrolyte [50].

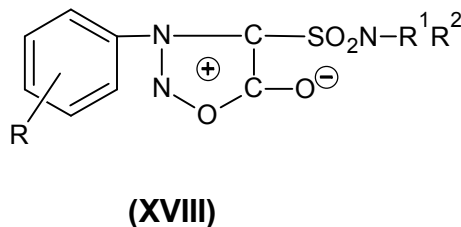
Thus, the synthetic strategies mediated by sydnones as synthons offer alternate efficient routes, for the synthesis of a wide variety of 1,5-diazapentamembered heterocycles from primary amines. Sydnone ring can also be utilized as masked hydrazine, and it is perhaps the only aromatic heterocycle which can be used as a source of hydrazine. Moreover, sydnone ring undergoes tandem reactions which are powerful avenues for convergent synthetic routes. These characteristics have encouraged extensive study of the chemical, physical, and biological properties of sydnones, as well as their potential applications.

Various substituted sydnone derivatives have been synthesized and characterized in our laboratory and found to possess good antibacterial activity [51-55]. To continue our work, the present investigation describes the synthesis and characterization of some new heterocyclic compounds bearing sydnone moiety as potential antimicrobial agents.

Upadhy *et al.* [56] have synthesized various 3-substituted-4-(4'-thiazolyl)sydnes (**XVII**) and evaluated for their antiinflammatory activity.



Pattanashetti *et al.* [57], Upadhy *et al.* [58] have synthesized various 3-phenylsydnone-4-sulfonamides (**XVIII**) and evaluated for their antiinflammatory and antibacterial activity.

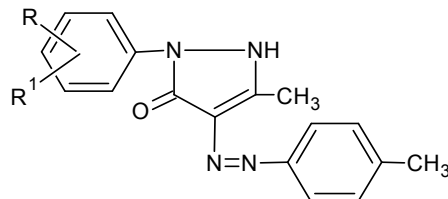


Ugarkar *et al.* [59] have synthesized and characterized different sulfonamide and sulfonate derivatives of 3-phenylsydnone.

Recently new approaches and aspects in the chemistry of sydnes have been developed and studied by various scientists [60-65].

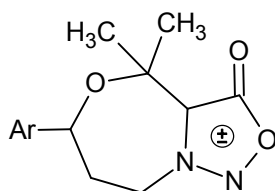
Shinge *et al.* [66] synthesized different 4-(4-chlorophenylazo)-5-methyl-2-aryl-1,2-dihydro-pyrazol-3-ones (**XIX**) from reacting 3-arylsydnes with 2-(4-chlorophenyl)-hydrazono-3-oxo-butyric acid ethyl

ester. The 3-arylsydnonones are used as masked hydrazines in this reaction. All the newly synthesized compounds exhibited antimicrobial activity greater than the reference drugs used.



(XIX)

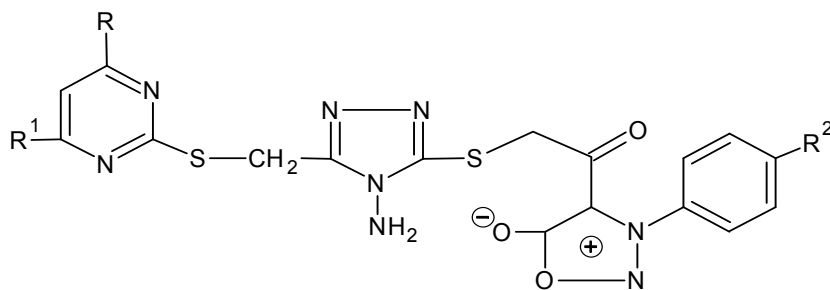
Zhang, Wu and Yin [67] have synthesized different derivatives containing fused sydnone rings (XX) using acetone in presence of $\text{BF}_3\text{-Et}_2\text{O}$.



(XX)

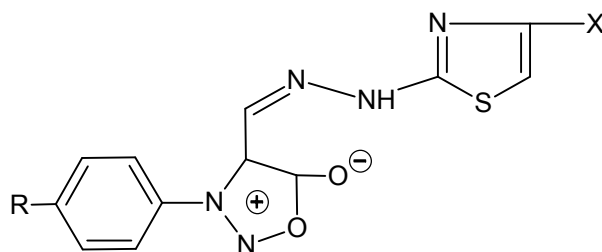
Ar = C_6H_5 , $4\text{-CH}_3\text{C}_6\text{H}_4$, $4\text{ClC}_6\text{H}_4$, $4\text{-BrC}_6\text{H}_4$, $4\text{-NO}_2\text{C}_6\text{H}_4$, 2-naphthyl

Kalluraya *et al.* [68] have synthesized 4-[5-(4,6-disubstituted-2-thiomethylpyrimidyl)-4'-amino-1,2,4-triazol-3'-yl]thioacetyl-3-arylsydnonones (XXI) by the reaction of 5-(4,6-disubstituted-2-thiomethylpyrimidyl)-4-amino-3-mercapto-1,2,4-triazoles with 3-aryl-4-bromoacetyl sydnonones in ethanol. Newly synthesized compounds were screened for their antibacterial activity and antifungal activity.



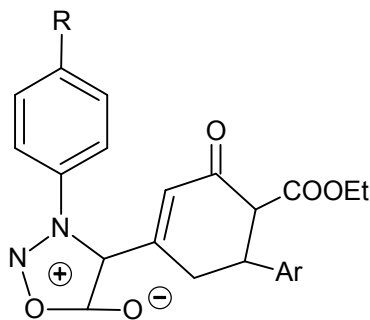
(XXI)

Kalluraya and Rai [69] have synthesized 4-substituted-3-(3-substituted sydnyldine-4-hydrazono)thiazoles (**XXII**) under solvent free conditions by grinding the reactants in a mortar with a pestle.



(XXII)

Kalluraya and Rai [70] have prepared 3-Aryl-4-(6'-carbethoxy-5'-arylcyclohex-2'-enone-3'-yl)sydnes (**XXIII**) by grinding chalcones and ethylacetoacetate in the presence of potassium carbonate under solvent-free conditions.



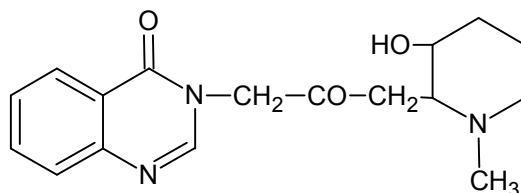
(XXIII)

R = H, CH₃

Ar = Phenyl, 4-anisyl,
3,4-methylenedioxyphenyl

QUINAZOLINES

Until 1960, there was only fragmentary information about biological importance of quinazoline derivatives. The alkaloid Febrifugine (**XXIV**) was isolated from the Chinese plant “chan-shan” (*Dichroa febrifuga* Lour) towards the end of 1940s, showed hundred times greater antimalarial activity than quinine but has not received practical use, since it proved to be 300 times as toxic as quinine alkaloids [71]. Due to its side effects, intensive study of the properties of febrifugine has been hindered for decades. As seen from (**XXIV**), these alkaloids contain the 4(3*H*)-quinazolinone aromatic moiety.



Febrifugine (XXIV)

However, work with Febrifugine served as the basis for searches for new antimalarial agents in the series of quinazoline derivatives and increased interest in seeking new quinazoline drugs not only with respect to malaria, but also in sicknesses caused by other bacteria or viruses. Large number of publications about the pharmacological activities of quinazolines began to appear in 1960s and 1970s [72-79]. More than twenty quinazoline drugs which had chemotherapeutic action came in to medical practice during these years. The availability of quinazoline derivatives, ease of synthesis and their biological activities are even today attracting considerable attention of the chemists. After 1970 vigorous development of the chemistry of the quinazoline begin. Recently various approaches and aspects in the chemistry

of quinazolines have been developed and studied by various scientists [80-84].

Quinazolines are made up of two fused six member simple aromatic rings. Quinazoline ring is an aromatic benzopyrimidine system. The recent literature contains much information concerning the synthesis and pharmacological activity of the quinazolines. The quinazolinone skeleton is a building block for the preparation of natural purine base, alkaloids [85], many biologically active compounds and intermediates in organic synthesis [86].

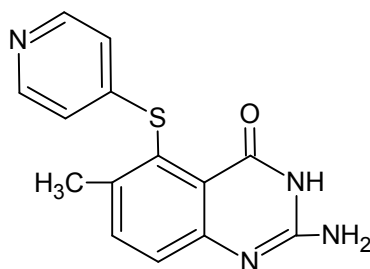
Several derivatives of quinazoline have been cited as useful hypnotics [87,88], antimalarial [89,90], antitumor [91,92], antibacterial [93,94], antiHIV [95,96], anti-inflammatory [97,98], antifungal [99,100], analgesic [101,102], anticonvulsant [103,104] etc. In addition to their diverse biological activity, the quinazolinone nucleus is also a key component in a relatively varied range of colored products [105,106].

Compounds containing a fused quinazoline ring belong to a broad class of compounds which have received a considerable attention over the past years due to their wide range of biological activities. Some of aminoquinazoline derivatives were found to be cardiac stimulants [107], they were also found as inhibitors of the tyrosine kinase [108] or dihydrofolate reductase enzymes [109] so they work as potent anticancer agents. They are also used to work out medicines against hypertension, malaria and to fight infections involving AIDS.

Aromatic quinazolines have been shown to possess tyrosine kinase inhibiting effect, useful to inhibit tumor growth [110]. Besides biological activity, quinazolines have O and N donor atoms, so they can act as good chelating agents [111].

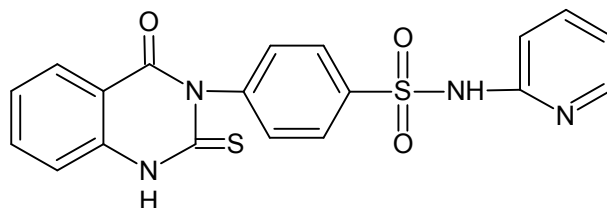
Many efforts have been focused on the modification of structure of quinazoline for development of clinically suitable compounds [112-119].

Chen and Wan [120] have synthesized 2-amino-6-methyl-5-(pyridin-4-ylsulfanyl)-3*H*-quinazolin-4-one (**XXV**) via three different synthetic routes and established best route which is a straightforward route via 2-guanidino-5-bromo-6-methyl-quinazolin-4-one.



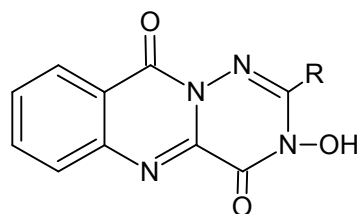
(XXV)

M. M. Aly [121] have synthesized novel quinazoline derivatives (**XXVI**) from sulfapyridine and characterized the compounds by elemental analyses and spectral data.



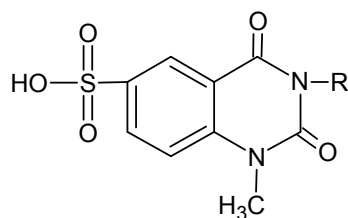
(XXVI)

Shemchuk *et al.* [122] developed new synthetic preparation method for [1,2,4]triazino[6,1-b]-quinazoline-4,10-diones (**XXVII**) using isatoic anhydride, carboxylic acids hydrazides, ethyl oxalyl chloride and hydroxyl amine.

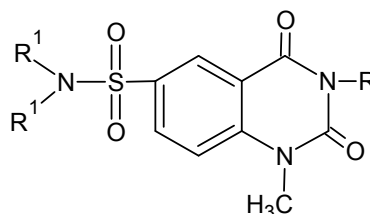


(XXVII)

Kuryazov *et al.* [123] have synthesized various sulfonic acid (XXVIII) and amide (XXIX) derivatives of 6-chlorosulfonylquinazoline-2,4-diones by the reactions of 1-methylquinazoline-2,4-dione and its 3-alkyl-substituted derivatives with chlorosulfonic acid.



(XXVIII)

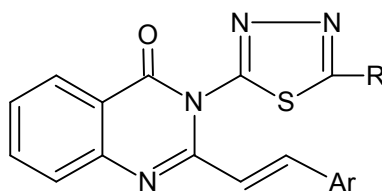


(XXIX)

Kuryazov *et al.* [124] investigated that treatment of quinazoline-2,4-dione and its symmetrical 1,3-dialkyl derivatives with chlorosulfonic acid gave the corresponding 6-chlorosulfonylquinazoline-2,4-diones which on reaction with nucleophilic agents gave the corresponding free 2,4-dioxoquinazoline-6-sulfonic acids, 6-sulfamidoquinazoline-2,4-diones and 2,4-dioxoquinazoline-6-sulfonic acid amides.

Jatav *et al.* [125] have synthesized 3-[5-substituted phenyl-1,3,4-thiadiazole-2-yl]-2-styrylquinazoline-4(3*H*)-ones (XXX) and evaluated for their antibacterial and antifungal activity and revealed that synthesized 2-styryl-quinazoline-4(3*H*)-one exhibited better antibacterial than antifungal

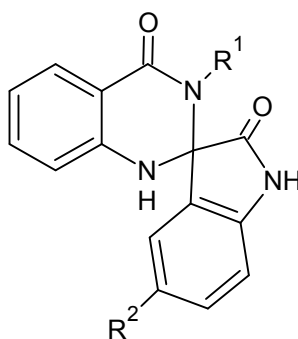
activity. Some of the compounds exhibited activity comparable to reference drug Norfloxacin.



(XXX)

Lichitsky *et al.* [126] have synthesized 12-aryl-1-oxo-1,2,3,4,5,12-hexa-hydroindolo[2,1-*b*]quinazoline-6-carbonitriles and studied the structure of the quinazoline derivative by X-ray diffraction analysis.

Dabiri *et al.* [127] have investigated efficient and direct procedure for the synthesis of spiro [isoindoline-1,2'-quinazoline]-3,4'(3'H)-dione derivatives (XXXI) and characterized the compounds by spectral analysis.

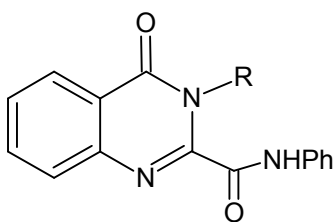


(XXXI)

Karpenko *et al.* [128] have synthesized different derivatives of 2-thio[1,2,4]triazolo[1,5-*c*]quinazoline and studied by X-ray diffraction analysis.

Samarov *et al.* [129] studied reaction of different quinazoline alkaloids with electrophilic reagents and established the structures by X-ray diffraction and crystallographic parameters.

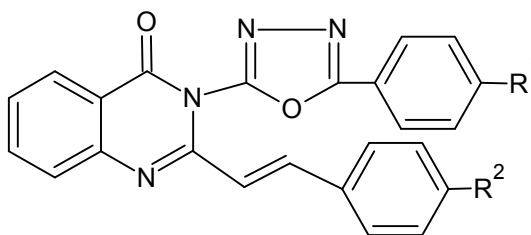
Zavarzin *et al.* [130] have synthesized and characterized various quinazoline derivatives (**XXXII**) from monothiooxamides.



(XXXII)

R= -CH₂Ph, NH₂, NHPH

Gupta *et al.* [131] have synthesized various 3-[5-(4-substituted)phenyl-1,3,4-oxadiazole-2-yl]-2-styrylquinazoline-4(3H)-one (**XXXIII**) and screened for antibacterial and antifungal activity and found that styryl moiety at the second position of 4(3H)-quinazolinone marginally increased the biological activity and exhibited better antibacterial than antifungal activities.

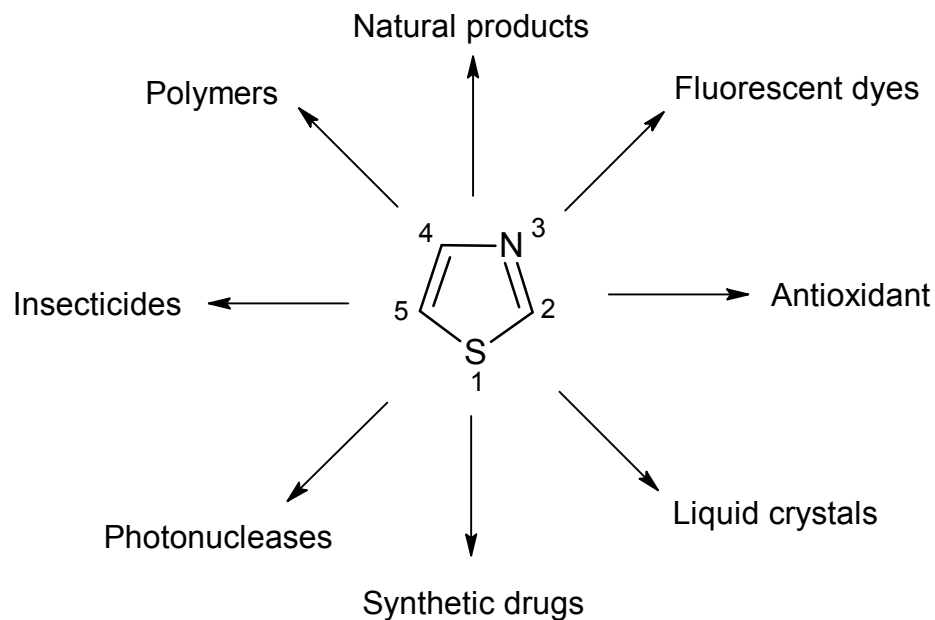


(XXXIII)

THIAZOLES

Molecules that possess sulfur atoms are important in living organisms. In this context, one important class of heterocyclic compound that contains one sulfur atom is known as thiazole. Five membered aromatic rings occupy a position of particular significance in the enormous field of heterocyclic chemistry. Thiazole is one of the important member of this family and thus merits a comprehensive study.

Thiazole derivatives were first reported by Hantzsch and Weber [132] in 1887, although benzothiazoles had been described in 1879. The importance of thiazole ring system was enhanced in the 1930's, when Williams and Cline [133] showed that thiamin (vitamin B₁) contained a thiazole ring and latter in 1939, one of the major sulfa drugs, sulfathiazole was produced. The class of heterocyclic compounds known as thiazole is found in many natural and synthetic products with a wide range of pharmacological activities. In the case of natural products, thiazole is present as a subunit in a large number of terrestrial and marine compounds, with different biological activities that represent a very important field in drug discovery. The depiction of various applications of thiazoles is described in figure (XXXIV).



Various applications of thiazoles (XXXIV)

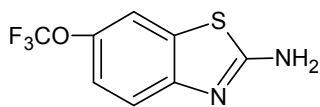
Due to the importance of this nucleus, many scientists have focused their research on thiazoles. Commercial significant thiazoles include mainly dyes [134,135] and fungicides [136,137]. Thiazoles are widely used as accelerators in rubber vulcanization [138,139] and as antioxidants [140,141]. A large number of dyes are derived from thiazololium salts.

2-Aminothiazoles have been used in varieties of applications, which cover the fields of agriculture, pharmacy, photography or related activities [142]. Various thiazole derivatives have found to possess antibacterial [143,144], fungicide [145,146], antiinflammatory [147,148], antihelmintics [149], antitubercular [150,151], anti-HIV [152,153], herbicides [154,155] etc. They are also among one of the key building blocks in drug discovery that can be well illustrated by the large number of drugs in the market containing this function group. Thiazole ring also finds applications in other fields, such as polymers [156-159], liquid crystals [160-162], photonucleases

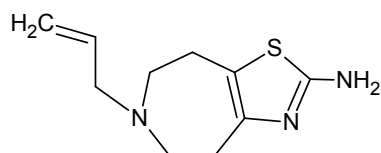
[163,164], fluorescent dyes [165,166], insecticides [167,168] and antioxidant [169,170]. Thiazole rings are planar and aromatic. In recent years thiazole based chemisensors have been investigated and showed to be successfully applicable in biological systems.

2-Aminothiazoles and their derivatives have been long used as precursors for the synthesis of biologically active molecules. Because of the wide spectrum of activity shown by the thiazole moiety, numerous thiazoles substituted with different groups at various positions have been prepared. 2-Amino-4-substituted-1,3-thiazoles, in the presence of various reagents, undergo different types of reactions to yield other heterocyclic compounds. Several 2-amino-1,3-thiazole derivatives are known as synthetic intermediates and therapeutic agents. For example, 5-alkyl-2-phenylalkylcarbonylamino-1,3-thiazoles are known as protein kinase-C inhibitors [171], 5-arylthio-2-acylamino-1,3-thiazoles are known as antitumor agents [172], phenylacetamidothiazole derivatives are known as anticancer agents [173] and 2-(arylmethyl-carbonylamino)-1,3-thiazole derivatives are known as cyclin-dependent kinase inhibitors [174].

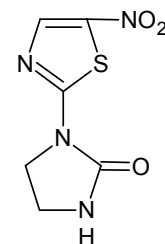
There are more than 500 structures containing the 2-aminothiazole moiety reported in the Derwent World Drug Index [175]. Therefore, it is of interest to synthesized compounds containing 2-aminothiazoles.



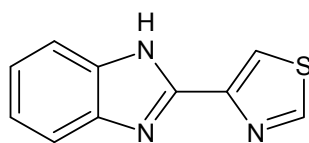
Riluzole
(anticonvulsant)



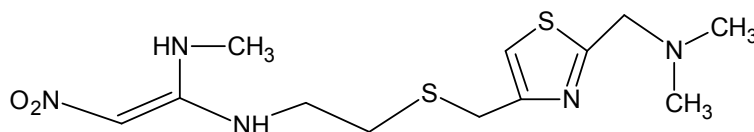
Talipexole
(antiparkinsonian)



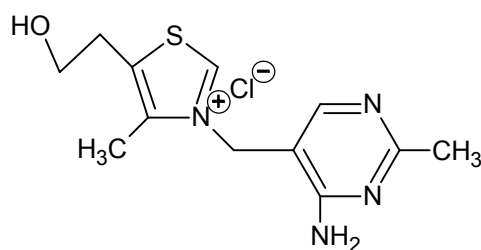
Miridazole
(antischistosomal)



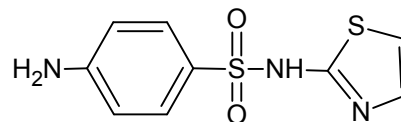
Tiabendazole
(anthelmintic)



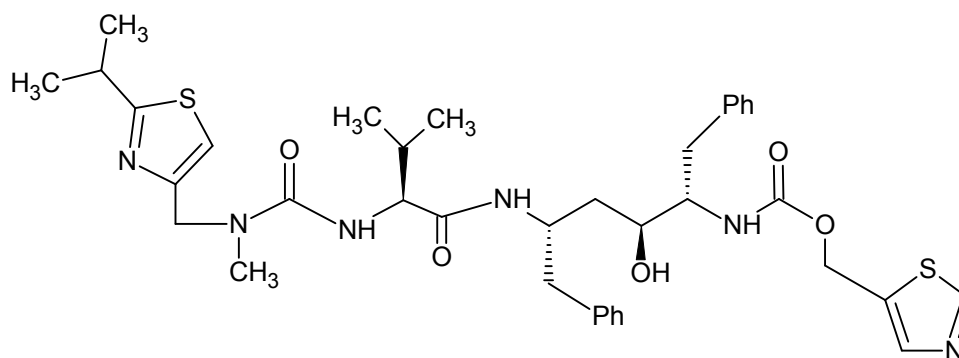
Alizatidine
(ulcer therapeutic, H₂ receptor antagonist)



Thiamine
Vitamin B₁



Sulfathiazole
(antibacterial)

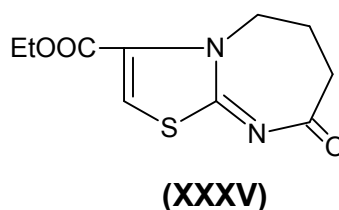


Ritonavir
(antiviral)

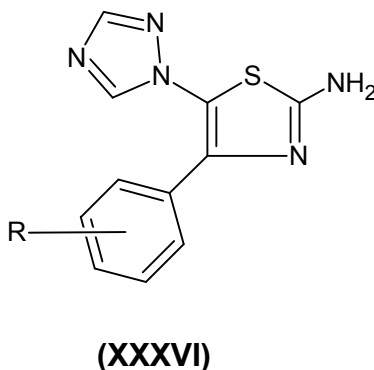
Natural and synthetic products containing thiazole (XXXV)

Wardakhan and Elkholy [176] have synthesized several thiazole derivatives from pyridazin-3-hydrazidic acids and reported the reactivity of these compounds toward amines, aldehydes, and hydroxyl amine.

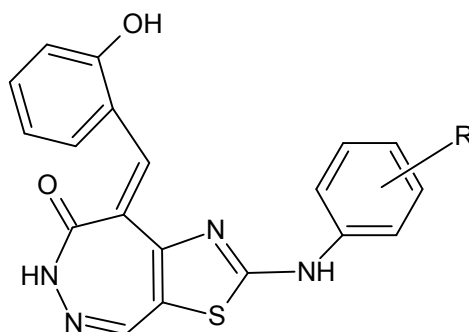
El-Subbagh *et al.* [177] have synthesized ethyl-8-oxo-5,6,7,8-tetrahydro-thiazolo[3,2-a][1,3]diazepin-3-carboxylate (**XXXV**) which is a member of a new generation of ultra-short acting hypnotics with no noticeable side effects.



Ling *et al.* [178] have synthesised 2-amino-4-aryl-5-(1H-1,2,4-triazol-1-yl)thiazole derivatives (**XXXVI**) from the reaction of α -bromo substituted acetophenone and thiourea and characterized by elemental analysis, ^1H NMR and single crystal X-ray diffraction analysis.

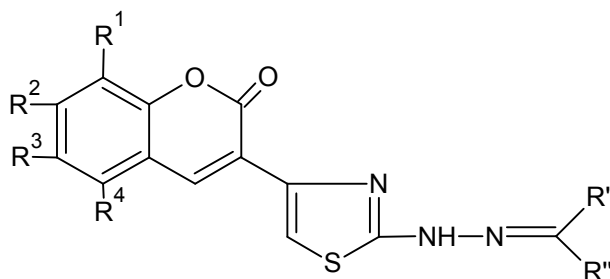


Koti *et al.* [179] have synthesized thiazole-fused diazepinones (**XXXVII**) by the application of intramolecular hydrazonolysis, wherein 2-arylamino-4-coumarinyl-5-formyl thiazoles were treated with hydrazine hydrate in refluxing ethanol to yield the rearranged products via an interesting ring-opening and cyclization process.



(XXXVII)

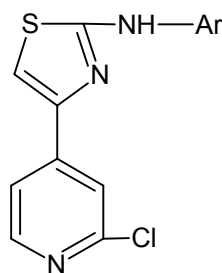
Rao *et al.* [180] synthesized different [3-(2-hydrazino-4-thiazolyl)coumarino]dimethylmethine (XXXVIII) and 3-substituted-7*H*-6-(6 or 8 or 6,8-disubstituted-3-coumarino)-*s*-triazolo[3,4-*b*][1,3,4]thiadiazines (XXXIX) derivatives.



For (XXXVIII) $R' = R'' = \text{CH}_3$

(XXXIX) $R' = \text{H}$, $R'' = \textit{p}$ -dimethylaminophenyl

Narayana *et al.* [181] synthesized 4-(2-chloropyridin-4-yl)-*N*-aryl-1,3-thiazol-2-amines (XL) have been prepared by reacting (4-bromoacetyl)-2-chloropyridine with thiourea and substituted thioureas and characterized by analytical and spectral data. Almost all the compounds were found to possess excellent antifungal and antibacterial activities.

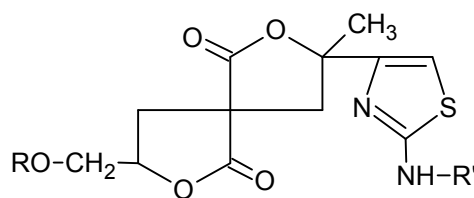
**(XL)**

Rangnekar and Maladkar [182] described synthesis of 2-amino-8-nitronaphtho[1,2-d]thiazole and its utilization a range of heterocyclic azo disperse dyes. These arylazo dyes were studied with respect to their color and constitution relationship. These dyes were applied on polyester fibre and their fastness properties were evaluated.

Kaplancikli *et al.* [183] synthesized various 1-(4-aryl-2-thiazolyl)-3-(2-thienyl)-5-aryl-2-pyrazoline derivatives by reacting substituted 3-(2-thienyl)-5-aryl-1-thiocarbamoyl-2-pyrazolines with phenacyl bromides in ethanol. Structures of the synthesized compounds were confirmed by elemental analyses, IR, $^1\text{H-NMR}$ and MS-FAB^+ spectral data. Their antimicrobial activities against important bacterial species.

Metwally [184] synthesized fused thiopyrano[2,3-*d*]thiazole derivatives by a stereoselective hetero Diels-Alder reaction of 5-(2,4-dihydroxy-benzylidene)-4-thioxo-thiazolidine derivatives with acrylonitrile, ethyl acrylate, *N*-phenylmale-imide, ω -nitrostyrene and *N*-phenyl-1,3,4-triazole-2,5-dione and discussed their structures and conceivable mechanisms.

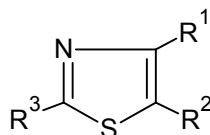
Kochikyan *et al.* [185] developed a method for obtaining derivatives of 3-methyl-3-(3'-amino[or substituted amino]thiazol-4-yl)-8-alkoxymethyl-2,7-dioxaspiro[4,4]nonane-1,6-diones **(XLI)** and evaluated their antibacterial and antitumor properties.



(XLI)

Kaplancikli *et al.* [186] synthesized various 2-[[[(benzoxazole/benzimidazol-2-yl)sulfanyl]acetylamino}thiazoles derivatives by reacting 4-substituted-2-(chloroacetylamino)thiazoles with benzoxazole/benzimidazole-2-thioles in acetone and in the presence of K₂CO₃ and elucidated their structure by IR, ¹H-NMR, and FAB⁺-MS spectral data. The compounds were found to possess significant level of antibacterial activity.

Liu *et al.* [187] investigated liquid phase synthesis of thiazoles (XLII) from poly(ethylene glycol) supported sulfonyl chloride.

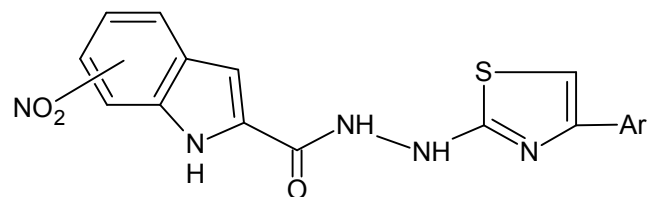


(XLII)

Zimenkovskii *et al.* [188] synthesized and studied antimicrobial activity of 2,4-dioxothiazolidine-5-acetic acid amides and their 3-substituted analogs.

Ashalatha *et al.* [189] synthesized 4-/5-/6-/7-nitro-N²-(4-aryl-1,3-thiazol-2-yl)-1*H*-indole-2-carbohydrazides (XLIII) by treating respective nitroindole thiosemicarbazide with aromatic acylbromides. The newly synthesized compounds were characterized by analytical and spectral data.

The compounds were also screened for antifungal and antibacterial activity. Some of these compounds exhibited promising antimicrobial activity.

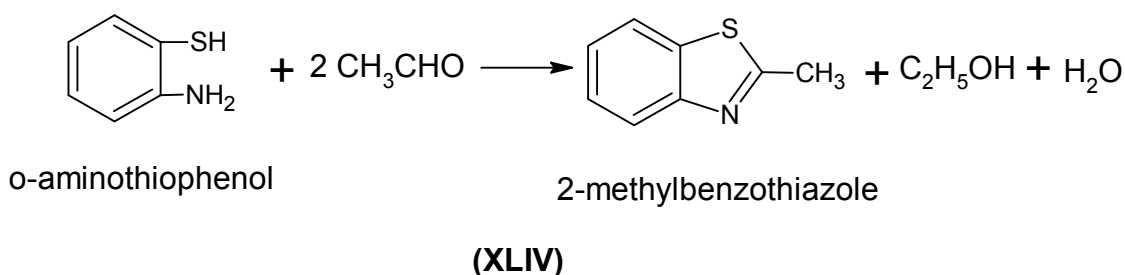


(XLIII)

BENZOTHAZOLES

Thiazoles are found in a variety of specialized products, often fused with benzene derivatives, are so-called benzothiazoles. Thus, benzothiazoles are a large family of compounds and their chemical structure containing a benzene ring fused with a thiazole ring is rather stable and is quite recalcitrant towards microorganisms and direct photolysis.

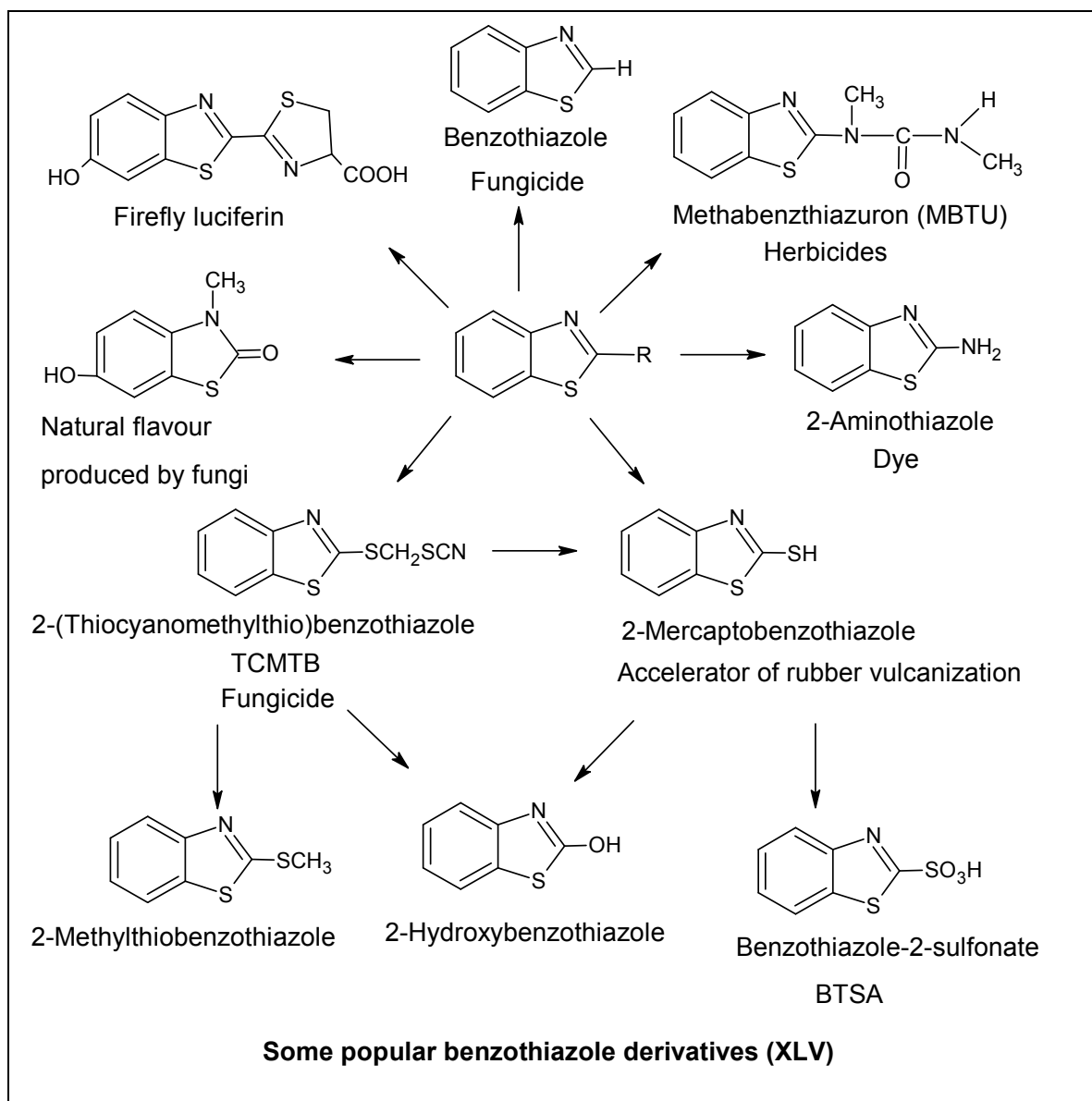
Benzothiazole derivatives were first reported by Hofmann [190] by the action of acids, acid chlorides and acid anhydrides upon o-aminothiophenol shown as in (XLIV).



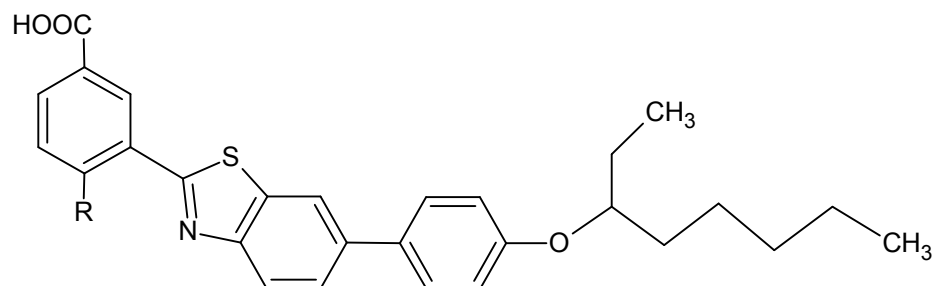
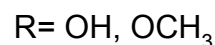
Benzothiazoles rarely occur as natural products. They form part of the structure of firefly luciferin and are also known as aroma constituents of tea leaves and cranberries or flavor compounds produced by the fungi *Aspergillus clavatus* and *Polyporus frondosus*. Being a heterocyclic compound, benzothiazole derivatives find use in various branches of chemical research e.g. in polymer chemistry [191-193], dyes [194-196], drugs [197-199] etc. Benzothiazolium salts have been used in silver photography, essentially as sensitizing dyes [200]. 2-Benzothiazole derivatives constitute a large group of xenobiotics which are manufactured worldwide for a variety of applications [201,202]. Benzothiazoles are worldwide manufactured for a wide variety of applications as shown in (XLV). The simplest member of the family, benzothiazole is a fungicide [203]. Methabenzthiazuron (MBTU) is used as herbicide in winter corn

crops and is an active ingredient of two commercially available formula Tribunil and Ormet [204]. Slimicides in the paper and pulp industry [205]. 2-Aminobenzothiazole is used in the manufacture of some disperse azo dye [206]. Riluzole (2-amino-6-trifluoromethoxybenzothiazole) is marketed by Rhône-Poulenc (Rilutek) for treatment of amyotrophic lateral sclerosis [207]. 2-(4-aminophenyl)benzothiazole presents antitumor properties [208]. Benzothiazole derivatives catalyse the formation of sulfide linkages (reticulation) between unsaturated elastomeric polymers in order to obtain a flexible and elastic crosslinked material. 2-Mercaptobenzothiazole (MBT/BTSH) is the main used rubber accelerator in certain specialty products and even in the tire production [209].

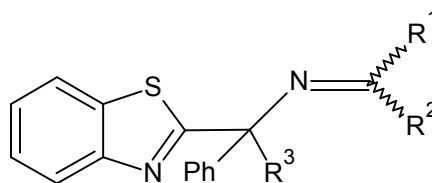
The formation of benzothiazole ring system has been reported by many procedures like oxidative photocyclization of thiobenzanilide [210] or *N*-phenylthiourethane [211], irradiation of *o*-halothioacetanilide [212], directed lithiation of 2,2-dimethyl-*N*-(3-halophenyl)propanethioamides or *N*-(3-halophenyl)-*tert*-butylthionocarbamates [213], thiocyanation of anilines [214], reaction of 2-aminophenol with the corresponding ortho-esters [215] etc.



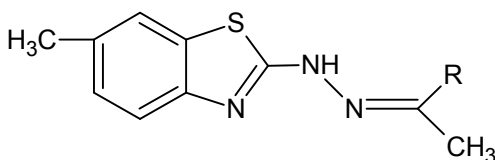
Nah *et al.* [216] have synthesized various lanthanide complexes with benzothiazole derivatives (**XLVI**) and investigated their photophysical properties.

**(XLVI)**

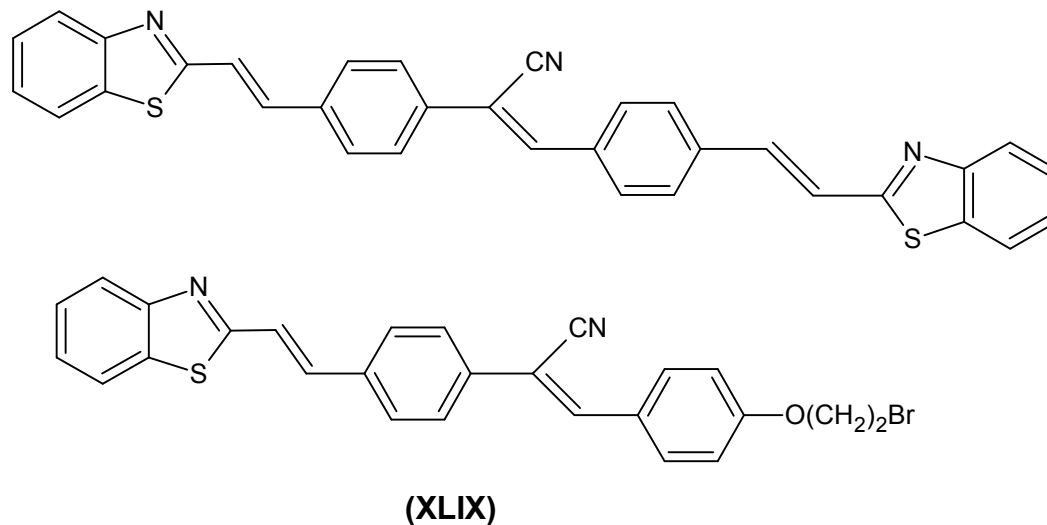
Alajarín *et al.* [217] synthesized benzothiazoles by cyclization of ketenimines bearing sulfenylimine fragments. The processes involve the formation of a new C–S bond and the concomitant migration of the imino group from the sulfur atom of the sulfenylimine fragment to the terminal carbon atom of the ketenimine function.

**(XLVII)**

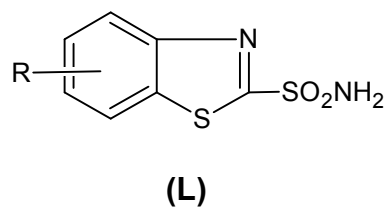
Alang *et al.* [218] synthesized different benzothiazole derivatives (**XLVIII**) and evaluated their antibacterial activity.

**(XLVIII)**

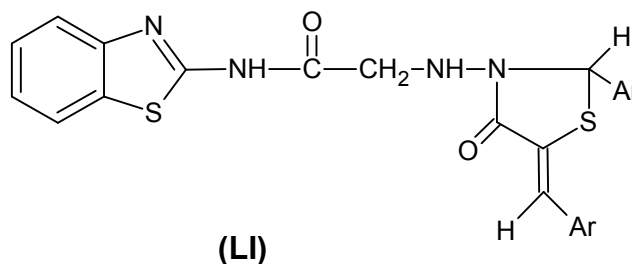
Reddy *et al.* [219] synthesized cyano substituted benzothiazole derivatives (**XLIX**) which possess an extended conjugated system and studied their absorption and fluorescence properties.



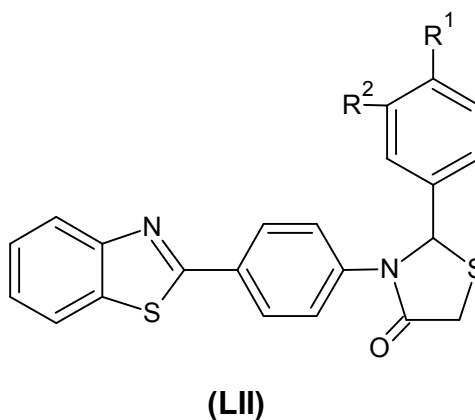
J. Korman [220] synthesized number of aryl substituted benzothiazole-2-sulfonamides (**L**) all of which are potent carbonic anhydrase inhibitors. Among these compounds 6-ethoxybenzothiazole-2-sulfonamide found to be clinically useful diuretics.



Srivastava and Sen [221] synthesized 2-aminobenzothiazole derivatives (**LI**) and evaluated their antibacterial and antifungal activity.

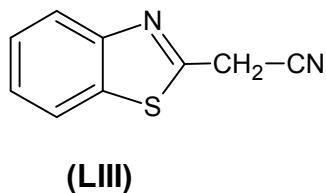


Nagarajan *et al.* [222] synthesized thiazolidinone derivatives (**LII**) and evaluated their antibacterial activities.



Moghaddam *et al.* [223] investigated facile and efficient one-pot protocol for the synthesis of benzoxazole and benzothiazole derivatives using molecular iodine as catalyst.

Y. Hassan [224] studied important reactions of 2-cyanomethyl-1,3-benzothiazole (**LIII**) and evaluated their antitumor activity.



Fadda *et al.* [225] reviewed various methods for the preparation of 2-cyanomethylbenzothiazole, its chemical reactivity towards different electrophiles and nucleophiles and its use for the synthesis of heterocyclic compounds. Its biological activity and applications were also reported.

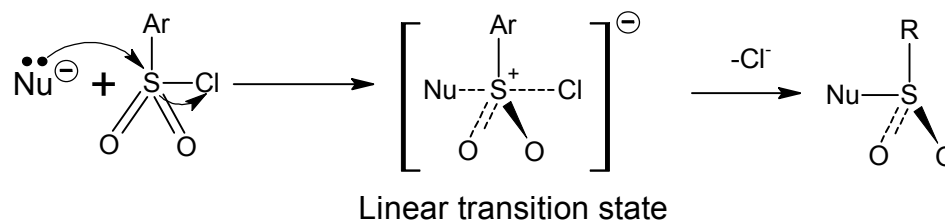
CHLOROSULFONATION

The use of chlorosulfonic acid for the synthesis of organic sulfonyl chlorides has been reviewed. The work before 1943 is described with extensive references by Suter [226], by Jackson [227] and, specifically for aromatic hydrocarbons, by Suter and Weston [228].

Fluorosulfonic acid readily dissociates into sulfur trioxide and hydrogen fluoride and consequently is not a very useful sulfonating agent. In contrast, chlorosulfonic acid is more stable, versatile and is a valuable sulfonating agent. Chlorosulfonic acid is a more powerful sulfonating agent than sulfuric acid [229] and sulfonation consequently generally occurs under mild conditions. In short chlorosulfonic acid is a versatile laboratory reagent which plays a key role in promoting several different types of reaction, such as alkylation, halogenation, rearrangement, cyclization and polymerization. In many of these reactions, chlorosulfonic acid functions as a powerful acid catalyst and dehydrating agent.

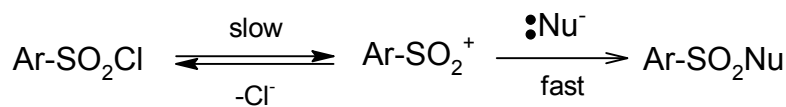
Less mechanistic studies have been carried out with chlorosulfonic acid than with sulfuric acid and generally the precise nature of the electrophilic species involved remains uncertain and appears to vary with the nature of the substrate and the reaction conditions.

The mechanism of the reaction of arylsulfonyl halides with nucleophilic reagents has been widely studied and reviewed [230-232]. The majority of kinetic and other evidence indicates that the reactions of an arylsulfonyl chloride with a nucleophile (Nu^-) generally follow the concerted bimolecular $\text{S}_{\text{N}}2$ -type mechanism as depicted in equation (LIV) with a linear bipyramidal transition state which is similar to the $\text{S}_{\text{N}}2$ (acyl) pathway established for acyl halides [233].

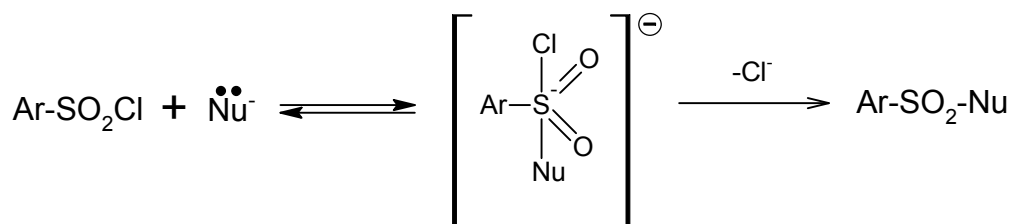


S_N2 mechanism (LIV)

Various other scientists have proposed alternative reaction mechanisms, namely the unimolecular (S_N1) and the stepwise addition-elimination pathway ($S_A N$) (LV and LVI respectively).

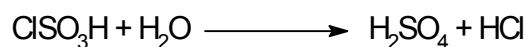


S_N1 mechanism (LV)



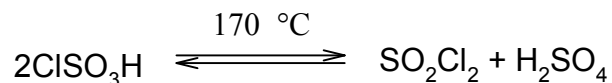
$S_A N$ reaction (LVI)

Chlorosulfonic acid is a powerful acid with a relatively weak sulfur-chlorine bond. It fumes in moist air producing pungent clouds of hydrogen chloride and sulfuric acid shown as under.

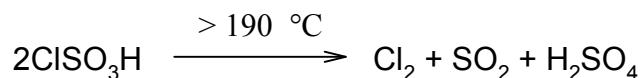


When chlorosulfonic acid is heated it partially decomposes into sulfuryl chloride (SO_2Cl_2), sulfuric acid, sulfur trioxide, pyrosulfuric acid

(H₂S₂O₇), hydrogen chloride, pyrosulfuryl chloride (Cl₂S₂O₅) and other compounds. At 170 °C, there is equilibrium between chlorosulfonic acid, sulfuryl chloride and sulfuric acid shown as under.

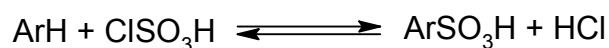


Sulfur dioxide and chlorine are not observed when chlorosulfonic acid is heated between 170-190 °C, but do appear at higher temperatures or when it is heated in a sealed tube shown as under.



When chlorosulfonic acid is treated with powerful dehydrating agents like phosphorus pentoxide, it is converted into its anhydride, pyrosulfuryl chloride (Cl₂S₂O₅).

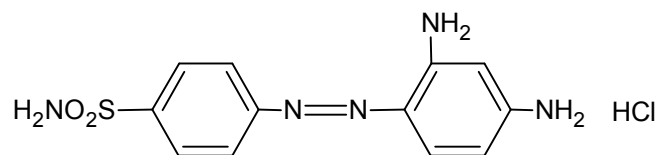
Chlorosulfonic acid is extremely useful reagent for sulfonation and chlorosulfonation of aromatic compounds shown as under.



Chlorosulfonation is essentially an electrophilic substitution reaction, consequently the reaction is facilitated by the presence of electron-donor groups like alkyl, alkoxy and hydroxy, when it proceeds under relatively mild conditions, e.g. the minimum excess of the reagent, temperatures of -5 °C to 25 °C and an inert diluent such as chloroform. On the other hand, when electron-withdrawing groups, e.g. nitro, carbonyl or carboxy are present, the reaction requires more drastic conditions, e.g. a large excess of the reagent and heating to 100-150 °C

SULFONAMIDES

Sulfonamides are oldest antimicrobial agents. Their mode of action, efficacy, safety and pharmacological properties are well known. Many thousands of molecules containing the sulfanilamide structure have been created since their discovery, yielding improved formulations with greater effectiveness and less toxicity. Prontosil, **(LVII)** the first commercially available antibacterial antibiotic was developed by a research team at the Bayer Laboratories of the I.G. Farben conglomerate in Germany. The discovery and development of this first sulfonamide drug opened a new era in medicine.



(LVII)

Sulfonamide is the basis of several groups of drugs. The original antibacterial sulfonamides (sulfa drugs) are synthetic antimicrobial agents that contain the sulfonamide group. Some sulfonamides are also devoid of antibacterial activity. Sulfonamides are among the most widely used antibiotics in the world. They have been in clinical use since 1968. In primary care medicine, sulfonamides are used mainly to treat urinary tract as well as upper respiratory tract infections [234, 235]. These drugs have remained popular because they are well tolerated by patients, and they are relatively inexpensive. Sulfa allergies are common; hence medications containing sulfonamides are prescribed carefully. Sulfa drugs are still widely used for conditions such as acne and urinary tract infections, and are receiving renewed interest for the treatment of infections caused by bacteria

resistant to other antibiotics. In 2008 there were 112 marketed drugs in the United States that contained a sulfonamide group [236].

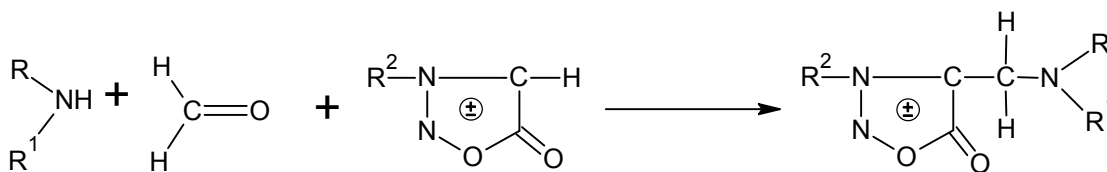
It is important to make a distinction between sulfa drugs and other sulfur containing drugs and additives, such as sulfates and sulfites, which are chemically unrelated to the sulfonamide group, and do not cause the same hypersensitivity reactions seen in the sulfonamides.

Thus, sulfonamide derivatives have proved fruitful area of research and subject of much interest due to their importance for various applications and their widespread potential and proven biological and pharmacological activities.

MANNICH REACTIONS

Mannich reaction is named after Chemist Carl Mannich [237]. Mannich reaction is an organic reaction which consists of an amino alkylation of an acidic proton placed next to a carbonyl functional group with formaldehyde and any primary or secondary amine. The final product is a β -amino-carbonyl compound known as a Mannich base. The Mannich reaction is an example of nucleophilic addition of an amine to a carbonyl group followed by dehydration to the Schiff base. The Mannich reaction is also considered a multi-component condensation reaction.

The mannich reaction of sydnones is depicted as under (fig. LVIII).



(LVIII)

In Mannich reaction, ammonia or primary or secondary amines are employed for the activation of formaldehyde. Mannich reaction is not possible with tertiary amine because tertiary amines lack an N-H proton to form the intermediate imine.

Mannich Reaction is employed in the organic synthesis of natural compounds such as peptides, nucleotides, antibiotics and alkaloids (e.g. tropinone). This reaction is also utilized in agro chemicals (e.g. plant growth regulators), paint and polymer chemistry, catalysts and crosslinking. Mannich reaction is also used in the synthesis of medicinal compounds e.g. rolitetracycline (Mannich base of tetracycline), fluoxetine (antidepressant), tramadol and tolmetin (anti-inflammatory drug).

Various mannich bases from 3-morpholinosydnone, 3-dimethylaminosydnone, 3-isopropylsydnone, 3-cyclohexylsydnone have been reported by various scientists [238,239].

PIPERAZINES

Piperazine is an organic compound that consists of a six member ring containing two opposing nitrogen atoms. Piperazines were originally named because of their chemical similarity with piperidine, a constituent of piperine in the black pepper plant (*Piper nigrum*). However, piperazines are not derived from Piper plants. Basically piperazine is the corresponding azine of piperidine.

Piperazine was originally developed for the treatment of gout. It was first synthesised in 1944 by the Wellcome Research Laboratories as a potential antihelminthic agent for livestock. Its use for this purpose declined due to poor efficacy and adverse effects such as seizures. Piperazine derivatives have been extensively investigated by the organic chemists due to their close association with various types of biological activities. Piperazine derivatives which contain piperazine functional group are class of synthetic drug that includes anticancer [240,241], antihistamine [242], antitumor [243], antibacterial [244,245], antimalarial [246,247], antipsychotic [248,249], HIV protease inhibitor [250,251], antidepressant [252,253] etc. Piperazines are also used in the manufacture of plastics, resins, pesticides, brake fluid and other industrial materials [254,255]. Simple piperazine is also used as a fluid for CO₂ and H₂S scrubbing in association with methyl diethanolamine (MDEA) [256]. Piperazines can cause unpredictable and serious toxicity and the true health consequences of their widespread availability are beginning to emerge with numerous reports of hospitalisations and even fatalities. Although, piperazines are commonly taken in combination with other illicit drugs, such as amphetamine and MDMA and the involvement of these, in cases of toxicity or fatality can not always be ruled out. The popularity of piperazines is still growing due to

their legal status in some jurisdictions, weak psychoactive effects and perceived safety compared to illicit drugs. Piperazine is still a very important starting material in the pharmaceutical industry.

Literature work revealed that bisheterocyclic compounds displayed much better antibacterial activity than heterocyclic compounds [257]. Our research is focused on search for novel potent antibacterial compounds, we herein report the synthesis and characterization of sydnones sulfonamide and methylene derivatives substituted with thiazole, benzothiazole, quinazoline and piperazine heterocycles.
