Medicinal Chemistry & Heterocyclic Compounds:

Drugs are the versatile molecules used as medicines or as components in medicines to diagnose, cure, mitigate, treat, or prevent disease [1].

Medicinal chemistry is the science that deals with the discovery and design of new therapeutic chemicals and their development into useful medicines. The discovery of a new drug not only requires a design process but also the synthesis of the drug, a method of administration, the development of tests and procedures to establish how it operates in the body and its safety assessment. Drug discovery may also require fundamental research into the biological and chemical nature of the diseased state. These and other aspects of drug design and discovery require input from specialists from many other fields and so medicinal chemists need to have outline knowledge of the relevant aspects of these fields.

An early definition of medicinal chemistry was given by an IUPAC specialized commission [2] that “Medicinal Chemistry concerns the discovery, the development, the identification and the interpretation of the mode of action of biologically active compounds at the molecular level.”

The medicinal chemistry deals mainly with organic medicinal substance which may be of natural or synthetic origin. The drugs obtained from natural sources are many alkaloids, glycosides, vitamins, hormones and antibiotics. Some of these prepared synthetically, e.g. vitamins and hormones and some are obtained economically from natural sources, such as alkaloids, glycosides, many antibiotics and some hormones like insulin. There are also drugs can be prepared semi-synthetically by involving simple or more complex modifications of the structure or the natural drugs, e.g. semi-synthetic penicillin. It has been possible to prepare many new analgesics, local anesthetics, sympathomimetics, etc. by caring out changes in the structures of natural and synthetic drugs. However, there are drugs such as barbiturates, antihistamines, certain antihypertensives etc. which are of pure synthetic origin.

Medicinal chemistry covers the following stages:

(i) In the first stage, new active substances or drugs are identified and prepared from natural sources, organic chemical reactions or biotechnological processes. They are known as lead molecules.
The second stage is the optimization of lead structure to improve potency, selectivity and less toxicity.

The third stage is the development stage which involves the optimization of the synthetic route for bulk production and modification of pharmacokinetic and pharmaceutical properties of active substance to render it’s chemically applicability.

Heterocyclic chemistry deals exclusively with the synthesis, properties and applications of heterocyclic especially vital to drug design. A cyclic organic compound containing all carbon atoms in ring formation is referred to as a carbocyclic compound. If at least one atom other than carbon forms a part of the ring system then it is designated as a heterocyclic compound [3]. Nitrogen, oxygen and sulfur are the most common hetero atoms but heterocyclic ring containing other hetero atoms are also widely known. A large number of heterocyclic compounds are known and this number is increasing rapidly.

The chemistry of heterocyclic compounds is as logical at that of aliphatic or aromatic in character, depending on their electronic constitution. Their study is of great interest both from the theoretical as well as practical standpoint. Heterocyclic compounds are very widely distributed in nature and are essential to life in various ways. Compounds such as alkaloids, antibiotics, essential amino acids, vitamins, hemoglobin, hormones and a large number of synthetic drugs and dyes contain heterocyclic ring systems. A knowledge of heterocyclic chemistry is useful in biosynthesis and as well as in drug metabolism.

There are also a large number of synthetic heterocyclic compounds with other important practical applications as dyestuffs, copolymers, solvents photographic sensitizer and developers, antioxidants and vulcanization accelerators, and many are valuable intermediates in synthesis.

Heterocyclic compounds have a great applicability as drugs because,

(i) They have specific chemical reactivity and

(ii) They provide convenient building blocks to which biologically active substituents can be attached.
MESOIONIC COMPOUNDS:

Mesoionic compounds are distinct type of heterocycles which belong to the class of non-benzenoid aromatics. Mesoionic compounds are structurally very different from benzenoid compounds but they fulfill most of the criteria of aromaticity and form a part of a variety of aromatic compounds. Mesoionic heterocycles contain two or more heteroatom with an exocyclic heteroatom (oxygen, nitrogen, sulfur). One feature of special interest of mesoionic compound is that they possess a wide range of biological activities [4].

According to the original definition, the term mesoionic was defined as: “A five or six-membered heterocycle which cannot be represented satisfactorily by any one covalent or polar structure and possesses a sextet of electrons in association with the atoms comprising heterocyclic ring”. But the term mesoionic has been restricted to the five-membered heterocycles and the definition of mesoionic heterocycle has been modified as:

“A five-membered heterocycle which cannot be represented satisfactorily by any one covalent or polar structure and possesses a sextet of electrons in association with the five atoms comprising the ring” [5].

The term mesoionic (mesomeric + ionic) was first introduced by Baker and Ollis [6] in 1949 to describe the structure of N-phenylsydnone (4) as a resonance hybrid of the dipolar resonating structures (1–3).

Resonating structure of N-phenyl sydnone

Compounds now classified as mesoionic have been known for more than a century [7]. Since that time both the concept of mesoionic compounds and methods for synthesizing them have undergone extensive changes and modifications. Following important papers by Schonberg [8], Baker and Ollis [9],

Representation of mesoionic heterocycles
Ollis and Ramsden [10] and Potts [11] put forward broadly similar definitions of mesoionic compounds. In particular, they stated or implied that they are aromatic compounds. Structure (5) corresponds to these definitions.

A ± symbol was adopted to represent electronic distributions for mesoionic compounds [13].

In 1953, Baker and Ollis, formalized the rules such that, in order to be considered as mesoionic, a molecule must: (a) contain a fully delocalized positive and negative charge in the molecule (b) be planar and contain a five-membered heterocyclic ring with an exocyclic atom or group capable of bearing a considerable amount of negative charge density, and (c) possess a considerable resonance energy. These three characteristics allowed mesoionic systems to be clearly distinguished from related dipolar species such as betaines, ylides and zwitterions. These other species have some degree of charge fixation whereas in the mesoionic systems the charges are delocalized.

At present the most frequently used is probably the ‘mesoionic’ structure of sydnone (7) proposed by Baker and Ollis [14].

Mesoionic compounds are heterocyclic betaines that are very useful in medicinal chemistry because of their well-known range of pharmacological activities and low toxicity. Their anticancer activity is especially remarkable because of very promising in vivo results [15-17]. The chemistry of mesoionic rings, especially their use as masked dipoles, has been a fruitful area of research since the late 1950s.
SYDNONE:

A significant portion of the research in heterocyclic chemistry has been devoted to sydnones containing different moieties, as evident from the literature [18-20]. Sydnones have played a crucial role in the development of theory in heterocyclic chemistry and have been used extensively as synthons in organic synthesis. Sydnone are unique, dipolar, heteroaromatic member of the general class of mesoionic compound [21]. Their derivatives are associated with an array of physiological activities. It is also reported that the ionic resonance structures of the heterocyclic ring of sydnones promote significant interactions with biological molecules [22], which also fulfill many of the spatial and electronic requirements ascribed to their biological activities [23].

Towards the end of the nineteenth century, Emil Fisher [7] reported the formation of an orange crystalline compound, dehydrodithizone, from the oxidation of dithizone. As more information on the chemical and physical properties became available it was evident that the bicyclic structure (8) which he proposed initially was incompatible. The structure that was deemed acceptable was a resonance stabilized monocyclic, mesomeric, ionic dipolar species (9). The supporting evidence for the existence of mesomeric ionic (mesoionic) structures was provided by Baker, Ollis and Poole [6, 14] in their articles published in the late 1940s and early 1950s.

Sydnones were first synthesized in Sydney, Australia in 1935. When Earl and Mackney [24] treated N-nitroso-N-phenylglycine with acetic anhydride, they obtained a neutral anhydro derivative to which they assigned a bicyclic structure (11; R=H, R₁=Ph). Due to the general utility of the reaction a variety of analogous compounds were prepared and given the name “sydnone” (due to their preparation in Sydney, Australia). Name, Sydnone came from first four words of Sydney and last three words of lactone. (SYDNey + LactONE = SYDNONE).

Baker, Ollis and Poole [25] showed that the assigned structure (11) for sydnones was incorrect and that it was actually monocyclic, dipolar oxadiazolone derivatives with many resonance forms.
Various methods of synthesis of sydnones have been found; these include heating in acetic anhydride or thionyl chloride, treatment with phosphorus pentoxide or the use of trifluoroacetic anhydride (TFAA) [26]. The most widely used method is the cyclization with trifluoroacetic anhydride (TFAA). It is rapid (<15 minutes), 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.

It is not possible to write a covalent structure for sydnones without separating the positive and negative charges [27]. The resonance in sydnone can be depicted by structures as in (12).

The aromaticity of the ring is explained by the classical sextet theory. 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 circle indicates the delocalization of six electrons which is detected as ring current by $^1$H-NMR spectroscopy. This polarization of charges is evidenced by large dipole moments (4-6 D) for the mesoionic rings. The ring will be positively charged, balanced by the negatively charge present on the exocyclic atom.
Two main types, depending formally upon the origin of the electrons in the system, have been identified, they are exemplified by structure (14) and (15).

In structure (14), the nitrogen and oxygen atoms, 1,3 to each other, are shown as donating two electrons each other to the total of eight electrons in the whole π systems, where as in structure (15) the two middle nitrogen atoms, 1,2 to each other, are the two electron donors.

The term “satisfactorily” in the definition refers to the fact that the charge in the ring cannot be associated exclusively with one ring atom. Thus these compounds are in sharp contrast with other dipolar structures, such as ylides (16), and such compounds are not considered mesoionic. Mesoionic compounds are most commonly represented as compound (14) as structure (17) and compound (15) as structure (18). The circle represents six π electrons, the positive charge is shared by all the rings atoms.

Sydnones are stable compounds of considerable polarity. Arylsydrones are generally solid crystals where as 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. In water they are generally insoluble but their solubility is enhanced when a polar functional group is present within the molecule.

Sydnone ring itself is sensitive to acids, bases and heat [28]. Hence the synthesis must be carried out with careful consideration of temperature, reaction path, the order of addition of reagents etc. Sydnone compounds are sometimes decomposed during reaction and/or work up. Sydnones on acid hydrolysis yield the corresponding monosubstituted hydrazines [29].

\[
\begin{align*}
\text{3-aryl sydnone} & \quad \xrightarrow{\text{HCl}} \quad \triangle \quad \text{mono substitute hydrazine} \\
\text{(19)}
\end{align*}
\]

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 [30] conducted a decomposition analysis, which demonstrated a large exotherm at 180°C, presumably due to the formation of pyrrolidinehydrazine and CO₂ (20).

\[
\begin{align*}
\text{sydnone} & \quad \xrightarrow{\text{heat}} \quad \text{hydrazine} \\
\text{(20)}
\end{align*}
\]

A general method for the introduction of heteroatoms to the 4th-position of a sydnone ring was developed by Fuchigami et al [31]. 4th-position of sydnone ring undergoes substitution with a wide variety of electrophiles, with retention of the ring, typical of aromatic substrates. No method to introduce electron releasing groups such as amino, hydroxyl and alkoxyl groups in to the 4th-position of the sydnone ring has been found. It seems to be possible to substitute the 4th-position by electron releasing groups in interposition of a methylene group [32].

Sydnone derivatives showed variety of biological properties, such as anti-malarial [33], anti-inflammatory [17], analgesic [22], anti-bacterial [34,35], anti-fungal [19], anti-tumor [36], anti-oxidant activity [37], etc. Kier and Roche [38]
had reviewed in detail the biological importance of various mesoionic compounds. Sydnones show liquid crystalline properties [39,40] and also used in battery applications [41, 42]. For e.g. N-methyl sydnones having a high dielectric constant was used as a solvent for lithium battery electrolyte.

A large number of derivatives of the penicillin [43- 45] and cephalosporin [46, 47] types have been prepared with N-acyl residues containing mesoionic heterocyclic groups, having general structure (21) and (22) shown below respectively. They posses antistreptococcal and anti-staphylococcal activities in vivo and other antimicrobial activities.

\[
\text{Kalluraya et al [48] discovered 3-Aryl-4-((6'-carbethoxy-5'-arylcyclohex-2'-enone-3'-yl)sydnones (23) which was prepared by Robinson’s annelation method where chalcones and ethylacetoacetate in the presence of potassium carbonate is grinded under solvent-free conditions.}
\]
Kalluraya et al [49] also prepared a novel 3-substituted-6-(3-arylsydnonyl)-8-aryl-1,2,4-triazolo[3,4,b][1,2,4] thiadizepines (24) and evaluated their pharmacological activities.

Rai et al [50] synthesized a novel series of 1,1a-dihydro-1-aryl-2-(3-arylsydnone-4-yl)-azirino[1,2-a] quinoxalines (25) were prepared in a one-pot reaction of 2,3-dibromo-1-(3-arylsydnone-4-yl)-3-arylpropan-1-one with o-phenylenediamine employing triethylamine in ethanol.

![Chemical structure of 25](image)

(25)

Shinge et al [51] have synthesized 4-arylazo-1,2-dihydro-pyrazol-3-one (26) derivatives from 3-arylsydnones. All the newly synthesized compounds exhibited antimicrobial activity greater than the reference drugs.

![Chemical structure of 26](image)

(26)

Mallur et al [52] converted 3-aryl sydnone in to the corresponding 3-aryl-5-methyl-1,3,4-oxadiazolin-2-ones (27) by a single step reaction with bromine in acetic anhydride. In the preliminary screening of all these compounds, the halogen substituted derivatives have shown antimicrobial activity equal to those of the standard drugs used.
Halila et al [53] had shown an important antitumour effect of SYD-1 (3-[4-chloro-3-nitro phenyl]-1,2,3-oxadiazolium-5-olate). They reported the effects of this mesoionic compound on mitochondrial metabolism. Their results showed that SYD-1 depresses the efficiency of electron transport and oxidative phosphorylation, suggesting that these effects may be involved in its antitumoural effect.

Kalluraya et al [54] synthesized a series of 4-[5-(4,6-disubstituted-2-thiomethylpyrimidyl)-4'-amino-1,2,4-triazol-3'-yl]thioacetyl-3-aryl sydnones (28) by the reaction of 5-(4,6-disubstituted-2-thiomethylpyrimidyl)-4-amino-3-mercapto-1,2,4-triazoles with 3-aryl-4-bromoacetyl sydnones in an ethanol medium. The newly synthesized compounds were screened for their antibacterial activity.

Asundaria et al [55] have synthesized 3,3′-(methylene-1,4-phenylene)bis (4-substituted aminosulfonyl)sydnones (29) and evaluated their antimicrobial activity.

Satyanarayana et al [56] have synthesized 4-[5-(substitutedaryl)-4,5-dihydro-1H-pyrazol-3-yl]-3-phenylsydnone (30) using 4-[1-oxo-3(substitutedaryl)-2-propenyl]-3-phenyl sydnone and hydrazine. From the synthesized compounds four compounds have shown anti-inflammatory activity and six compounds have shown analgesic activity while two compounds have shown antiarthritic activity.
Kamblea et al. [57] synthesized and evaluated benzophenone oximes appended with sydnone (31) and evaluated as Inhibitors of Secretory Phospholipase A$_2$ (PLA$_2$) with anti-inflammatory activity.

Srivastava et al. [58] have synthesized green synthesis of a series of 4-acetyl-3-(4-substituted) phenyl sydnones (32) by using Friedel-Craft reaction with an excellent yield under microwave irradiation. The results are compared with the conventional method.

Deshpande et al. [59] have synthesized a sydnone derivatives containing styryl ketone moiety, 4-[1-oxo-3-(substitutedaryl)-2-propenyl]-3-(4-methylphenyl)sydnones (33). The synthesized compounds have been screened for antibacterial and analgesic activities. The chloro and nitro derivatives showed good antibacterial activity against both gram positive and gram negative bacteria while the chloro and furyl derivatives exhibited highest analgesic effect among the series.
R. Stein [60] synthesized 3-[2-(dimethylamino)-2-phenylethyl]-N-[(phenyl amino) carbonyl] - sydnone imine (34) act as a CNS stimulant.

Where, $R_1 = R_2 = \text{hydrogen, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, halo, perfluoroalkyl of 1 to 3 carbon atoms.}$

$R_3 = \text{hydrogen, halo, nitro or alkanoyl of 2 to 4 carbon atoms.}$

$R_4 = \text{hydrogen, halo, nitro or perfluoroalkyl of 1 to 3 carbon atoms.}$

$R_5 = R_6 = \text{hydrogen or methyl atoms.}$

$R_7 = R_8 = \text{alkyl of 1 to 4 carbon atoms.}$

Asundaria et al [61] have synthesized novel 3-[4-(diethylamino phenyl)-4-(substituted-1-ylsulfonyl)sydnones (35). Compound 3-[4-(Diethylamino) phenyl]-4-(piperazin-1-ylsulfonyl)sydnones and 3-[4-(Diethylamino)phenyl]-4-[(4-methylpiperazin-1-yl)sulfonl]sydnone had exhibited highest activity against all tested microorganisms. Some compounds were found effective active against tested organisms.
QUINAZOLINE:

The ortho-fusion of benzene nucleus with pyrimidone ring (36) gives rise to a class of heterocyclic compounds containing 1, 3-benzodiazone ring system (37). As early as 1869, Griess [62] built up this ring system (38) for the first time by reaction of cyanogens with anthranilic acid to give a compound named as ‘bicyanoamidobenzene’ and used until 1885 when structure was known with some certainty.

Later on the name ‘Quinazoline’ was proposed by Weddige et al [63]. He was carried out systematic quinazoline synthesis following the observation that the formyl and acetyl derivatives of anthranilamide loose water on heating. He correctly interpreted this to be as a cyclization reaction and was first to realize the possibility of tautomerism in the oxoquinazolines. The preparation of parent quinazoline came many years later, when Bischler and Lang [64] obtained it by decarboxylation of the 2-carboxy derivatives. A more satisfactory synthesis of quinazoline was subsequently devised by Gabriel [65] who studied its properties and those of its derivatives in greater detail.

Numbering System of Quinazolinone

The nomenclature of the quinazolinone ring system is as follows:

Quinazolinone is also known as phenmiazine, benzylene-amidine, 1,3-diazanaphthalene or benzo-1,3-diazone or 5,6-benzo-pyrimidine. The term
phenmiazine was used by Wildman [66]. The numbering shown in the structure (40) was suggested by Paal and Busch [67], and is one in the current use [68,69].

Nientowaski quinazolinone synthesis was discovered (41) by Stefan Nientowaski (1866-1925) [70], from condensation of anthranilic acid and amides. The original work was published in 1895 [71], and the utility of the reaction has been reviewed [72]. The reactions have been modified to use anthranilic acid esters and isatoic anhydride [73], as well as anthranilicanides as starting materials. The reaction is still used in the modern development of synthetic procedures [74,75].

\[
\begin{array}{c}
\text{COOH} \\
\text{NH}_2 \\
\end{array} + \begin{array}{c}
R^1 \\
R^2 \\
\end{array} \rightarrow \begin{array}{c}
\text{O} \\
R^2 \\
R^1 \\
\end{array} - 2\text{H}_2\text{O}
\]

\text{Nientowaski quinazolinone synthesis (41)}

In the recent years, the chemistry of quinazolinone and their derivatives has received considerable attention owing to their synthetic and effective biological importance. Quinazolinone is one of the most frequently encountered heterocyclic compound in medicinal chemistry with wide applications including anti-hypertensive [76], CNS depressants [77], analgesic [78], anti-histaminic [79,80], anti-coccidial [81], anti-hyperten [82], anti-folates inhibitor [83,84], anti-cancer [85,86], anthelmintic agent [87], antiprion agent [88], anti-bacterial [89,90], anti-malarial activity [91], anti-fungal [92], anti-tubercular [93,94], anti-inflammatories [95], anti-proliferative activity [96], anti-convulsant [97], anti-HIV [98,99], antagonists [100-103] and several other useful and interesting properties [104].

Quinazoline having a hydroxyl group in the 2 or 4 position are tautomeric with the corresponding keto-dihydroquinazolines. Thus 4-hydroxyquinazoline, tautomeric [105] with 4-keto-3,4-dihydroquinazoline, is commonly named 4(3H)-quinazolone, or simply 4-quinazoline. It was further simplified that 4- hydroxyl quinazoline (42) and 4-quinazoline or 4(3H)-quinazoline (43) is a tautomeric mixture of the lactum and the lactim form. Various data [106,107] indicate that 4-hydroxyquinazoline exists as an equilibrium mixture of (42) and (43) in which the form (42) is the most favored. Because of tautomerism the quinazolones are high melting insoluble solid, extremely stable to heat, light and air and resistant to chemical oxidation, reduction, hydrolysis
and substitution on the benzene ring. They are readily soluble in alkali and form stable salt [108].

![Chemical structure of compounds](image)

The most important class of compounds containing the quinazoline nucleus is composed of those compounds, which have hydroxyl group in the 2 or 4 positions in the quinazoline ring, adjacent to a heterocyclic nitrogen atom. Also considered in this class are those compounds having a functional group, which is easily derived on converted to hydroxyl group like alkoxy, aryloxy, chloro, amino, thioethers and seleno etc. are included in this class.

The first quinazolone based drugs methaqualone (44) was prepared in a straightforward fashion by fusion of anthranilamide with toluidine. A catalyst POCl₃ or PCl₅ were used to facilitate the reaction more smoothly [109].

![Chemical reaction](image)

Ye et al [110] designed and synthesized a series of 3-[2-(2-methoxyphenyl)-2-oxoethyl]quinazolinone derivatives (45) as anticoccidial agents by modifying the quinazoline ring of febrifugine. All the compounds were biologically evaluated according to the ACI method, and four of them exhibited anticoccidial activity against Eimeria tenella in the chicken at a dose of 9 mg/kg. These data suggested that some compounds possesses high anticoccidial activity and may serve as a lead compound for the development of anticoccidial drugs in the future.
Kumar et al [111] synthesized a new series of 3-(benzylideneamino)-2-phenylquinazoline-4(3H)-ones (46) were prepared through Schiff base formation of 3-amino-2-phenyl quinazoline-4(3H)-one with various substituted carbonyl compounds. The synthesized compounds were screened for their cytotoxicity and antiviral activity. Compound (46, where R-H, R'-OH) showed better antiviral activity against the entire tested virus.

Chen et al [112] evaluated the selective effects of 2-isopropyl-3-butyl-8-(4-fluorophenylamino)-3H-imidazo[4,5-g]quinazoline (47), a member of a series of quinazolines, on the cell survival and growth of the non-small cell lung cancer (NSCLC) cell line A549 in vitro and in vivo.

Alafeefy et al [113] synthesized two series of some new 2,4,6-trisubstituted-quinazoline derivatives (48) and screened for their analgesic, anti-inflammatory activity and acute toxicity. Four compounds were more potent analgesic agents than the reference drug Indomethacin and thirteen compounds showed significant anti-inflammatory activity. Seven compounds showed combined ability to inhibit both pain and inflammation. Compounds tested for acute toxicity showed no toxic symptoms or mortality rates 24hrs post-administration implying their good safety margin.

Salahuddin et al [114] synthesized a series of novel 3-(6-substituted-1,3-benzothiazole-2-yl)-2-[(4-substitutedphenyl)amino]methyl]quinazolines-4(3H)-ones
Synthesized quinazolines-4(3H)-ones derivative were investigated for their anti-inflammatory and antibacterial activity.

Chandregowda et al [115] synthesized a series of 6,7-dialkoxy-4-anilinoquinazolines (50) by substituting different heterocycles on 6-position and a variety of anilines on 4-position of the quinazoline. Synthesized quinazolines-4-one derivative were investigated for their in vitro antitumor activities.

Song et al [116] developed a simple, efficient, and general method for the synthesis of various 3-alkylquinazolin-4-one derivatives (51) from quinazolin-4-one treated with alkyl bromides under phase transfer catalysis condition. Compound 6-bromo-3-propylquinazolin-4-one was found to possess good antifungal activity.

Khabazzadeh et al [117] have developed an efficient methodology for the preparation of 2-aryl-4H-3,1-benzoxazine-4-one (53) from an opportune N-acyl anthranilic acid derivative (52), under solvent free conditions, recyclable and eco friendly catalyst and shorten experimental time and good to excellent yields.
Suthakaran et al [118] have synthesized 6,8-dihalo-substituted-3-[2-(7-substituted-oxy-4-methyl-2-oxoquinolin-1(2H)-yl)ethyl]-2-(substituted)quinazolin-4(3H)-one (54) by three steps procedure. The title compounds were characterized by spectral data and were subjected to anti-oxidant, anti-histaminic activity, anti-inflammatory and anti-tumor activity. Some of the reported compounds have shown moderate to good activities.

Kumar et al [119] have synthesized 3-[4′-(p-chlorophenyl)-thiazol-2′-yl]-2-[(4″-oxo-2″-substituted phenyl-3″-chloroazetidin-1″-yl)aminomethyl]-6-bromoquinazolin-4-ones (55) and 3-[4′-(p-chloro phenyl)-thiazol-2′-yl]-2-[(4″-oxo-2″-substitutedphenyl-thiazolidin-3″-yl)aminomethyl]-6-bromo-quinazolin-4-ones (56). All the compounds have been screened for their anti-inflammatory and analgesic activities. Compound 2-(4′-Oxo-2′-(o-chlorophenyl)-thiazolidin-3′-ylaminomethyl)-3-[4″-(p-chlorophenyl)-thiazol-2″-yl]-6-bromoquinazolin-4-one showed maximum anti-inflammatory (38.35%) and analgesic (37.36%) activities.
Manfred et al. [120] have synthesized quinazolone derivatives (57) by reaction of anthranilamide and \( p \)-methoxy benzoyl chloride were stirred for an hour in pyridine and possess good fungicidal activity.

Narala et al. [121] have synthesized novel quinazoline derivative 4-(3'-bromo-4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline (58) exhibit significant cytotoxicity against V373 and V87 human glioblastoma cell lines, causing apoptotic cell death at micromolar concentrations.
Chandrika et al [122] have synthesized a series of novel 2,4,6-trisubstituted quinazoline derivatives and evaluated their antibacterial and cytotoxic activity against THP-1, HL-60 and A375 cell lines.

Li et al [123] have reported a series of quinazolinones (59) as orally active and specific matrix metalloproteinase-13 inhibitors were discovered for the treatment of osteoarthritis.

![Image of quinazolone (59)](image)

Bhanage et al [124] have reported an efficient protocol for the synthesis of quinazoline-2,4(1H,3H)-diones derivatives (60) from 2-amino benzonitriles with carbon dioxide using catalytic amount of cesium carbonate.

![Image of reaction](image)

Gwaltney et al. [125] have described structure-based design and optimization of alogliptin and related quinazolinone-based DPP-4 inhibitors (61) and also reported these noncovalent inhibitors provide sustained reduction of plasma DPP-4 activity and a lowering of blood glucose in animal models of diabetes.
Hour et al [126] have reported 6-pyrrolidinyl-2-(2-substituted phenyl)-4-quinazolinones (62) and they were assayed for their cytotoxicity *in vitro* against six cancer cell lines, including human monocytic leukemia cells (U937), mouse monocytic leukemia cells (WEHI-3), human hepatoma cells (HepG2, Hep3B) and human lung carcinoma cells (A549, CH27).
COUMARIN:

The study of coumarins began more than 200 years ago. The word “coumarin” is derived from “Coumarouna odorata Aube (Dipteryx odorata)”, from which it was isolated, for the first time [127]. Coumarin is a widely occurring as secondary metabolite that occurs naturally in several plant families and essential oils, and has been used as a fragrance in food and cosmetic products (63). The coumarin nucleus corresponds to benzo-α-pyrone(2H-1-benzopiran-2-one) whose systematic nomenclature was established by IUPAC [128].

Coumarin, as a central core for the source of simple coumarins. (63)

Over and above the discoveries made by isolation of coumarins from the hundreds of species of plants and other organisms. They are the derivatives of synthetic origin which significantly increases the number of coumarin structures known till today. Coumarins have been synthesized by several methods including Pechmann [129,130], Perkin [131], Knoevenagel [132,133], Reformatsky [134] and Wittig [135,136] reactions.

Hydroxy derivatives of 4-methyl coumarin are important group of coumarin derivatives showing medicinal as well as other applications. Pechmann reaction is a
well-known simple method and has been widely used to synthesize coumarins from activated phenols, mostly \( m \)-substituted phenols and acetoacetic esters or an unsaturated carboxylic acid in presence of an acid catalyst [129,130]. Besides the use of various conventional homogeneous acids such as \( \text{H}_2\text{SO}_4 \), \( \text{H}_3\text{PO}_4 \), \( \text{CF}_3\text{COOH} \), \( p \)-toluene sulfonic acid, \( \text{P}_2\text{O}_5 \), \( \text{POCl}_3 \) and metal halides, different solid acid catalysts [137-142] have also been studied for the synthesis of the hydroxy derivatives of 4-methyl coumarin. However, to obtain high yield with solid acid catalysts longer reaction times are required.

Synthesis of coumarins and their derivatives has attracted considerable attention from organic and medicinal chemists for many years as a large number of natural products contain this heterocyclic nucleus. Coumarins are extremely variable in structure, due to the various types of substitutions in their basic structure, which can influence their biological activity. The heterocycles derived from these intermediates have also been tested for their potential as anti-HIV [143], anti-inflammatory [144], anti-convulsant [145], anti-viral [146], anti-coagulant [147], anti-oxidant [148], anti-bacterial [149], anti-fungal [150], anti-carcinogenic material [151] and anti-histamine [152]. Apart from this, it is attracting considerable attention of chemists as it is widely used in fragrances, pharmaceuticals [153], optical brighteners [154] and molecular photonic devices [155] despite the importance of these intermediates, the methodologies available for the synthesis were generally target specific and restrictive in their scope.

Wanare \textit{et al} [156] have synthesized \( \alpha \)-pyranochalcones and pyrazoline analogs to discover chemically diverse antimalarial leads. Compounds were tested for antimalarial activity by evaluation of the growth of malaria parasite in culture using the microtiter plate based SYBR-Green-I assay. The (E)-3-(3-(2,3,4-trimethoxyphenyl)-acryloyl)-2\( H \)-chomen-2-one (64) turned out to be the most potent analog of the series, showing IC50 of 3.1 µg/ml against chloroquine sensitive (3D7) strain and IC50 of 1.1 µg/ml against chloroquine-resistant field isolate (RKL9) of \textit{Plasmodium falciparum}.
Fatunsin et al [157] have synthesized 9-hydroxy-6H-benzo[c]chromen-6-ones derivatives (65) based on the cyclocondensation of 1,3-bis(silyloxy)-1,3-butadienes with 4-chloro-2-oxo-2H-chromene-3-carbaldehyde.

(i) TiCl₄, CH₂Cl₂, 78-20°C, 16 hrs; (ii) HCl (10%).

Mandhane et al [158] have developed a mild and efficient method for condensation of substituted phenol with β-ketoester in the presence of catalytic amount of ammonium metavanadate (10 mol%) at ambient temperature to afford the corresponding substituted 4-methyl-2H-chromen-2-one (66) in high yields under mild conditions. Utilization of commercially available inexpensive catalyst makes this manipulation very interesting from an economic perspective.

Kotresh et al [159] have synthesized 3-aryl-[(1-isocyano-4-methyl-7-hydroxycoumarin)]-5-methyl-1,3,4-triazoline-2-one and its substituents (67) by the condensation of amino group of mono and disubstituted derivatives of 3-methyl-5-oxo-1,2,4-triazoles with 8-formyl-7-hydroxy-4-methylcoumarin in alcohol. The results indicate that the compounds may serve as better fungicides when compared to bactericides. The
synthesized compounds have turned to be the wonder compounds possessing antimicrobial properties.

Chaudhari et al [160] have synthesized 4-coumarin-6-yl(amo)(-5-coumarine-3-yi-3-phenyl-1,2,4-oxadiazolines (68,69) by the reaction with Schiff base and hydrazones with benzhydroxamoyl chloride respectively. The title compounds have been screened for their antibacterial activity.

Bhat et al [161] have synthesized a series of 3-(4-acetyl-5-methyl-5-substitutedphenyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2H-chromene-2-ones (70) and evaluated for anticonvulsant activity and neurotoxicity. A majority of the compounds were active in MES tests. Compound 3-(4-Acetyl-5-methyl-5-p-nitrophenyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one was found to be potent and had activity at lower dose of 30 mg/kg in MES-test. All the compounds were less toxic as compared with the standard drug phenytoin.
Tyagi et al [162] have studied the microwave assisted solvent free synthesis of hydroxy derivatives of 4-methyl coumarin by Pechmann reaction. The catalyst showed good activity for activated m-hydroxy phenol substrate viz., phloroglucinol and pyrogallol with ethyl acetoacetate for the synthesis of 5,7-dihydroxy-4-methyl coumarin and 7,8-dihydroxy-4-methyl coumarin, respectively, showing significant yields ranging from 78 to 85% within 5–20 min at 130°C. However, the less activated phenol and m-methyl phenol was observed to be inactive for the synthesis of 4-methyl coumarin and 4,7-dimethyl coumarin, respectively, under the studied experimental conditions.

Liu et al [163] have studied antimicrobial activity of an endophytic Xylaria sp.YX-28 and identification of its antimicrobial compound 7-amino-4-methylcoumarin(71).

Shinge et al [164] have synthesized 4-arylazo-2-(7-hydroxy-4-methyl-2-oxo-2H-chromen-8-ylmethyl)-5-methyl-1,2-dihydro-pyrazol-3-ones (72) from 3-[(7-acetoxy-4-methyl-8-methylene)coumaryl]sydnone. In this reaction 3-arylsydnones are used as masked hydrazines. All the newly synthesized compounds exhibited antimicrobial activity greater than the reference drugs used.

Khan et al [165] have synthesized 7-hydroxy-4-methyl-2H-chromen-2-one, 7-hydroxy-4, 5-dimethyl-2H-chromen-2-one and their some derivatives, and screened for their biological screening. The compounds (73) and (74) had shown high degree of cytotoxic activity. Three compound (73; R= i. -C₃H₅, ii. -C₅H₁₁) and (74) showed high degree of bactericidal activity amongst the present series.
Rajitha et al [166] have synthesized coumarin derivatives (75), using dipyridine copper chloride catalyzed via pechmann condensation under conventional heating and microwave irradiation in excellent yields with good purity.

Rao et al [167] have synthesized a series of 6-chloro-3-[2-(substitutedanilino)-1,3-Thiazol-4-yl]-2H-1-benzopyran-2-ones (76). The title compounds were subjected to in vitro antibacterial activity screening using four strains of organisms viz. B. subtillis, S. aureus, E. coli and K. pneumonia by agar cup plate method. Out of the compounds tested, some of the molecules with different substituents showed significant antibacterial activity when compared to standard Streptomycin and Ampicillin.

Manojkumar et al [168] have synthesized a series of new thiazolidine-4-ones (77), 5-carboxymethyl-4-thiazolidinones (78) by the condensation of 4-methylcoumarinly-7-oxyacetic acid[(substituted phenyl)methylene]hydrazides, with thioglycolic acid and thiomalic acid respectively. The title compounds were screen for their antibacterial activity against S. aureus and B. subtillis bacteria.
Rajanarendar et al [169] have synthesized new isoxazolyl coumarins (79) by pechmann condensation of isoxazolyl phenols with $\beta$-ketoester, dipyridine cobalt chloride is used as a catalyst. The method is simple, cost-effective and at ambient temperature gives good yield.
ACRIDINE:

Acridines have yielded much of technical and scientific interest since 1871 when Graebe [170] discovered acridine in a high-boiling of coal tar. They have provided a long series of orange and yellow basic dyestuffs and red and purple vat dyestuffs. Acridines have also provided important chemotherapeutic drugs which range in complexity from the simple mono and di-aminoacridines to the more complex acridines which have proved to be specific for malaria and lambliaisis (e.g., quinacrine and acranil). Finally, a number of miscellaneous uses have been found for acridines, from the inhibition of corrosion to their use as reagents in the preparation of certain enzymes and the analytical determination of particular groups.

Numbering system of Acridine:

At least seven different numbering systems have been used for the simple acridine ring system. At present only two systems of numbering (80) and (81) are significantly used for acridine derivative.

![Numbering system of Acridine](image)

In 1893, Graebe [171], suggested a numbering system (80) based on the accepted numbering used for anthracene, xanthenes etc. In 1900, however, method (81) was suggested by Richte [172]. This method of numbering gained some popularity. Among these two numbering system, Graebe's numbering system is still used in the majority of publication.

Synthesis of Acridine:

In 1970, Graebe and Caro reported the isolation of a new basic material acridine, from the anthracene fraction of coal tar. It was isolated as it dichromate and series of salts prepared. There is no general method of synthesis which can be used for most acridines.

a. Synthesis of Acridine from Acridone:

In 1880, Graebe and Caro [173] have synthesized acridine (82) from the readduction of acridone by distillation with zinc dust. Other example of the reaction,
which gives variable yield and is only suitable for the synthesis of acridines which can be distilled from the reaction mixture and is well reported [174].

The Zn-distillation reaction tends to become uncontrollable on a large scale and is of little use for preparative purposes. The most commonly used synthesis of acridine is the reduction [175] of the appropriate acridone to the 9,10-dihydroacridine, or acridan, followed by oxidation [176] to the acridine.

b. Acridine from 9-chloro acridine (McFadyen Reaction):

9-chloro acridine reacts with \( p \)-toluenesulphonyl hydrazide to give the corresponding acridly derivative [177]. Treatment of the later with sodium hydroxide [178] gives acridine and sodium \( p \)-toluene sulphonate.
c. Synthesis of Acridine by cyclation of Diphenylamine-2-aldehydes and Ketones:

(i) Aldehyde Cyclization:

Diphenylamine-2-aldehyde can be made in two ways by an extension of the Ullmann reaction [179].

(ii) Ketone Cyclization:

Diphenylamine-2-alkyl or aryl ketones have also been prepared in a similar way to the aldehydes and on treatment with acids to cyclize to the corresponding 9-substituted acridines [180].

The cyclization of aldehydes and ketones almost certainly proceeds through the addition of a proton to the carbonyl group followed by cyclization and dehydration as in the case of anthracence [181].
d. The Brenthsen reaction:

This reaction is one of the earliest used methods for the synthesis of acridines and consists of heating a mixture of an aromatic or aliphatic carboxylic acid with diphenylamine and zinc chloride (1.5-3.0 mole) in the absence of a solvent to 200-270°C [182].

\[
\begin{align*}
\text{Ar-CONH} & \quad \text{R-COOH} \quad \text{ZnCl}_2 \\
\text{Ar-NH} & \quad \text{Ar} \\
\end{align*}
\]

(88)

e. Synthesis of 9-chloro acridine by using Ullmann reaction conditions:

The most useful general method for the synthesis of 9-chloro acridine is the cyclization of the appropriate diphenylamine-2-carboxylic acid.

(i) Preparation of diphenylamine-2-carboxylic acids:

Diphenylamine-2-carboxylic acids (89) are mostly prepared by the Ullmann reaction [179]. The preparations of diphenylamine-2-carboxylic acid are necessary as they are essential intermediates in the preparation of many acridine and acridone.

\[
\begin{align*}
\text{Type 1} & \quad \text{COOH} \\
\text{Type 2} & \quad \text{NH}_2 \\
\end{align*}
\]

[High boiling alcohols are n-butanol, cyclohexanol, amyl alcohol]

The Ullmann reaction consists of essentially the interaction of halogen substituted benzene with aniline to give a diphenylamine, a carboxyl group being in the ortho position to either the halogen or to the amino group. Two types of reactions are therefore possible.

The reaction is probably ionic in character. If partial coordinate bond is formed between the halogen and the catalyst, which may be a cuprous compound
[183], attack of the (anionoid) amine at the carbon adjacent to the halogen will be facilitated, and the reaction can proceed (90).

\[ \text{Attack of anionoid amine at halogen adjacent carbon} \]

(ii) Cyclization of diphenylamine-2-carboxylic acid with POCl₃:

Lensnianski [184] discovered the general method for the cyclization of diphenylamine-2-carboxylic acid, where the acid is refluxed with an excess of the phosphorous oxychloride. Gleu et al [185] have suggested the following reaction (91) for the reaction between diphenylamine-2-carboxylic acid and phosphorous oxychloride.

\[ \text{Reaction between diphenylamine-2-carboxylic acid and POCl₃} \]

Although Drozdov [186] agreed that 9-chloroacridine dichlorophosphate was the primary product of the reaction between acridone and phosphorus oxychloride. Drozdov also suggested a reaction (92) which differs essentially from the previous reaction (91). The product is not an acridine dichlorophosphate. Other interpretations of these reactions are not excluded by the experimental results.

\[ \text{Reaction suggested by Drozdov} \]

Acridine and its derivatives, well known as DNA intercalates, have been widely studied from a variety of viewpoints, such as synthesis [187], physicochemical properties [188], structural requirements [189] and biological activities [190]. Due to a polycyclic planar structure, acridine moiety interacts with DNA by intercalation.
between base pairs and interferes with essential metabolic processes [191]. Acridines are known to be biologically versatile compounds possessing several pharmacological activities, including anti-cancer [192,193], anti-tumor [194,195], anti-viral [196], anti-microbial [197-199], anti-malarial [200], analgesic and anti-inflammatory [201] etc.

Maurice et al [202] have designed the synthesis and biological evaluation of novel acridine-polyamine conjugates against prostate cancer. This trifunctional compound and related derivatives were synthesized and tested against androgen dependent and androgen independent prostate cancer cell lines and they have demonstrated to be cytotoxic at the micromolar concentrations.

Rogness et al [203] have synthesized substituted acridines (93) by the [4 + 2] annulation of arynes and 2-aminoaryl ketones.

\[
\text{R}_1 \text{R}_2 \text{NH}_2 + \text{R}_3 \text{OTf} \rightarrow \text{Fluoride} \rightarrow \text{R}_1 \text{R}_2 \text{R}_3
\]

(93)

Nagarajan et al [204] have synthesized a new series of 6-(substitutedacridin-9-ylamino)-2,3-dihydro-3-thioxo-[1,2,4]triazolo[4,3-f][1,2,4]triazin-8(5H)-one (94) from the reaction of 9-chloro acridine and 6-amino-2,3-dihydro-3-thioxo-[1,2,4]triazolo[4,3-f][1,2,4]triazin-8(5H)-one. The structures of the compounds were confirmed by IR, \(^1\)H NMR, mass and elemental analysis. These compounds were evaluated for analgesic and diuretic activity.

Tlegenov [205] have synthesized 9-aminoacridine azomethines (95) by condensation of 9-aminoacridine with \(p\)-substituted aromatic aldehydes. It was found
to have *in vitro* antituberculous activity against *Mycobacterium tuberculosis* H₃₇Rv at a concentration of 6.25 µg / ml.

![Chemical structure](image)

**R-CHO**

Goodell *et al* [206] have synthesized a series of substituted 9-aminoacridines (96-99) are evaluated for antiproliferative activity toward pancreatic cancer cells. They concluded that the drug DNA complex formed are blocks of topoisomerase II binding and activity leading to catalytic inhibition of the enzyme and the induction of apoptosis and programmed cell death.

![Chemical structures](image)

Sondhi *et al* [207] have synthesized variety of N-[4-phenyl-3-(2',3',4'-substituted phenyl)thiazol-2(3H)-ylidene]-2,4-substituted acridin-9-amine (100) and
CHAPTER 1

INTRODUCTION

1-{(2,4-substituted acridin-9-yl)-3-[4-phenyl-3-(2’,3’,4’-substituted phenyl)thiazol-2(3H)-ylidene]}isothiourea (101) derivatives. These compounds were screened for antiinflammatory, analgesic and kinase (CDK1, CDK5 and GSK3) inhibition activities. Some compounds exhibited good anti-inflammatory (25–32%) and potent analgesic (50–75%) activities, at 50 mg/kg. A compound, 100 (Where; R₁ = H, R₂= OCH₃, R₃= CH₃, R₄= CH₃, R₅= H) exhibited moderate CDK1 (IC₅₀ = 8.5 lM) inhibition activity.

Mosher et al [208] have synthesized structure-activity relationships for the 9-(Pyridin-2’-yl)-aminoacridines (102).

Sondhi et al [209] have synthesized anti-inflammatory, analgesic and kinase inhibition activities of some acridine derivatives (103,104).
BENZIMIDAZOLE:

The benzimidazoles contain a phenyl ring fused to an imidazole ring, as indicated in the structure for benzimidazole (105).

(105)

The benzimidazoles are also known as benzoglyoxalines. This tautomerism is analogous to that found in the imidazoles and amidines. The benzimidazoles, in fact, may be considered as cyclic analogs of the amidines [210].

(106)

In 1872, the first benzimidazole was prepared by Hoebrecker [211], who obtained 2,5(or 2,6)-dimethylbenzimidazole by reduction of 2-nitro-4-methylacetanilide (107).

(107): The Hoebrecker's method for synthesis of benzimidazole
Generally, the benzimidazole is prepared from the reaction of o-phenylenediamines with most carboxylic acids in the presence of strong acid to give 2-substituted benzimidazoles.

The benzimidazole has been of considerable interest since it was noted that benzimidazole inhibits the growth of certain yeasts and bacteria. The discovery of 5,6-dimethylbenzimidazole as a unit in vitamin B\textsubscript{12} has increased this interest. A number of alkyl benzimidazoles have been tested and found to have some anti-vitamin B\textsubscript{12} activity and some have been reported to have anti-viral activity also [212]. That structural modifications can produce marked effects on physiological activity which has been shown by the test data on the substituted benzimidazoles (108) [213].

\begin{center}
\includegraphics[width=0.4\textwidth]{human-anthelmintic}
\includegraphics[width=0.35\textwidth]{psychoparmacological-agent}
\end{center}

(108) Biologically relevant benzimidazoles

Nitrogen containing heterocycles have always played a major role in the pharmaceutical and agrochemical industries because of their often potent physiological properties, which have resulted in numerous applications [214]. Benzimidazoles are an important class of heterocyclic compounds with a wide spectrum of biological activity [215-218]. Substituted benzimidazole derivatives have found applications as in diverse therapeutic agents including antiulcer, anti-helmintic, anti-hypertensive, anti-coagulant, anti-allergic, analgesic, anti-inflammator, anti-pyretic, anti-bacterial, anti-fungal, anti-viral, anti-parasitic, anti-oxidant, anti-cancer and anti-anxiolytic. [219,220]

Sharma \textit{et al} [221] designed and synthesized a series of heterocyclic benzimidazole derivatives bearing of novel 5,6-substituted-1-[2\textsuperscript{'}-(1\textit{H}-tetrazol-5-yl)-biphenyl-4-ylmethyl]-2-trifluoromethyl-1\textit{H}-benzoimidazol (109) for their potential antihypertensive agents. The majority of the compounds were found active in the
biological screening. The efforts were also made to establish structure activity relationships among synthesized compounds.

B. Reddy [222] have synthesized 1, 2- disubstituted benzimidazole deratives (110) by different carboxylic acids using Mannich base.

Gowda et al [223] have synthesized a series of 2-substituted-1-[(5-substituted phenyl-1,3,4-oxadiazole-2-yl)-methyl]-1H-benzimidazole (111). The newly synthesized compounds have been tested for their antifungal and antibacterial activity.

Rohini et al [224] have synthesized a series of 6-arylbenzimidazo-[1,2-c]quinazoline (112) by the condensation of 2-(o-aminophenyl)benzimidazole with different arylaldehydes, followed by oxidative cyclisation of the resulting 2-o-arylideneaminophenyl benzimidazoles. The antimicrobial activities of all compounds against three Gram-positive (S. aureus, B. subtilis, S. pyogenes), three
Gram-negative (*S. typhimurium, E. coli, K. pneumonia*) bacteria and three fungal strains (*A. niger, C. albicans, T. viridae*) were evaluated. Some of these compounds showed most potent inhibitory action against test organisms.

Yar *et al* [225] have synthesized pyrazoline and phenyl pyrazoline derivatives of benzimidazole (113,114) by the reaction of 1-(1H-benzimidazol-2-yl)-3-(substituted phenyl)-2-propen-1-one with hydrazine hydrate and phenyl hydrazine respectively. All the compounds entered for screening at the Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF) for their *in vitro* antibacterial activity against *Mycobacterium tuberculosis* H$_37$R$_v$ strain (ATCC 27294) using Microplate Alamar Blue Assay (MABA) susceptibility test.

Saberi *et al* [226] have synthesized a simple, fast, efficient and environmentally friendly synthesis of benzimidazole and its 2-alkyl, aryl and heteroaryl substituted derivatives (115) was developed using zeolite HY.

Sharghi *et al* [227] have synthesized a highly selective synthesis of 2-substituted benzimidazole derivatives (116) from the reaction of *o*-phenylenediamine derivatives and aromatic aldehydes in the presence of an organic salt, NH$_4$OAc, in absolute ethanol is presented.
Bahrami et al [228] have synthesized a new, convenient method for the synthesis of 2-substituted benzimidazole and benzothiazole (117). The main advantages of this procedure are short reaction times, large-scale synthesis, easy and quick isolation of the products, excellent chemo selectivity, and excellent yields.

Freeman et al [229] have synthesized 2-substituted-5,6-dichlorobenzimidazol-2'-isonucleosides (118). The newly synthesized compounds have been tested for their antiviral activity.

Jat et al [230] have synthesized 5-substituted(amino)-2-phenyl-1-(2'-carboxy biphenyl-4-yl)benzimidazoles (119). The newly synthesized compounds have been tested for their anti-hypertensive agents.
Tewari et al [231] have synthesized N-substituted-2-substituted-benzimidazole deratives (120). All the compounds were tested for their antiviral activities. These compounds have been screened for *Tobacco mosaic viruses* and *Sunhemp rosette viruses* and showed significant activities.

Vinodkumar et al [232] have synthesized a series of novel substituted benzimidazole derivatives by the condensation of *o*-phenylenediamine (OPDA) with 4-bromobenzoic acid and subsequent reactions of the benzimidazole with different electrophilic reagents are reported. The latter compounds were reacted with styrene and tert-butyl acrylate following Heck Coupling gives N-substituted-2-(4-styrylphenyl)-1*H*-benzimidazole (121) and N-substituted-3[4-(1*H*-benzimidazole-2-yl)-phenyl]-acrylic acid tert-butyl ester respectively (122). All the compounds synthesized were screened for their potential anti-bacterial, anti-asthmatic and anti-diabetic properties, which exhibited some promising results towards testing organism in vivo.