CHAPTER – 1

GENERAL

INTRODUCTION
1. GENERAL INTRODUCTION:

Before the twentieth century, medicines consisted mainly of herbs and potions. It was not until the mid-nineteenth century that the first serious efforts were made to isolate and purify the active principles of these remedies (i.e. the pure chemicals responsible for the medicinal properties). Since then, many naturally occurring drugs have been obtained and their structures were determined (e.g. morphine from opium, cocaine from coca leaves, and quinine from the bark of the cinchona tree). These natural products sparked off major synthetic effort, where chemists made literally thousands of analogues in an attempt to improve on what nature had provided. Much of this work was carried out on a trial and error basis, but the results obtained revealed several general principles behind drug design. The success of these efforts led to the birth of many pharmaceutical companies worldwide. An overall pattern for drug discovery and development also evolved, but there was still a higher element of trial and error involved in the process.

In recent years, medicinal chemistry has undergone revolutionary change. Rapid advances in the biological sciences have resulted in a much better understanding of how the body functions at the cellular and molecular level. As a result most research projects in the pharmaceutical industry or university sector now begin by identifying a suitable target in the body and designing a drug to interact with that target. Today, many medicines are synthesized in industries, but due to lower cost and shorter shelf life of the drugs, the trend is diverted to biotechnology. Now a day, virtual screening emerged as an important tool in our quest to access novel drug like compounds. There are a wide range of comparable and contrasting methodological protocols available in screening databases for the identification of lead compounds. The number of molecular simulation and modeling methods utilizes several software packages such as GOLD, Zinc, Gaussian, FLEX, ORISIS, etc., which employ the target and ligand based virtual screening, are increasing at a rapid pace.

The chemistry of heterocyclic compounds has evoked keen interest and considerable attention owing to the wide spread applications they possess. More than half of the compounds produced by nature have heterocyclic rings incorporated in their structures. A large number of alkaloids derived from heterocyclic molecules are used as drugs. The influence of these heterocycles in day-to-day life has been convincingly established. Moreover, pharmaceutical and agrochemical industries have made rapid and significant progresses to quench the quest of organic chemists in discovering and developing suitable heterocyclic compounds for the benefits of mankind. It is well known that the majority of antibiotics are most effective drugs. However, majority of drugs are generally synthesized products and most of them are heterocyclic compounds.
Among the different class of compounds, the chemistry of nitrogen and sulphur atoms containing heterocycles has undergone remarkable advances in the last couple of decades, ever since their initial use in agriculture commenced nearly a century ago.

Among the wide variety of nitrogen heterocycles that have been explored for developing pharmaceutically important molecules, 4(3H)-quinazolinone is the most frequently encountered heterocyclic compound in medicinal chemistry, possessing a wide range of pharmacological properties like anticonvulsant, CNS depressant, anti HIV, antimalarial, antitubercular, anti-inflammatory and anticancer activities. Substituents like methyl, styryl, aromatic rings, heterocyclic rings, sulfonamides etc. have been tried successfully by various scientist at 2nd and 3rd position of the 4(3H)-quinazolinone to obtain potentially bioactive analogues.

Moreover, sulfonamide is the first synthetic bacterial discovered and has been extensively utilized scaffold in the medicinal chemistry. Numerous derivatives possessing sulfonamide (-SO₂NH-) group with a variety of substitutions have been synthesized, by several groups of scientists to obtain potent analogues of parent sulfanilamide, which have exhibited a wide range of pharmacological effects such as antitumor, antimalarial, anti-inflammatory activities, apart from anti-infective, diuretic, specific enzyme inhibition, hormone regulations, etc. activities.

Amino acids are the important molecules found in the back-bone component of molecular structure of any living species. The synthesis of peptides and proteins involves the α-amino acids as precursors. However, their contribution in the synthetic organic and heterocyclic chemistry are of great interest mainly as a starting material for the synthesis of compounds (unnatural or natural products) is due to their easy availability, natural source of chirality, broad range of reactivity and multifunctional character.

Looking to the aforesaid importance of the quinazolinone, sulfonamide and amino acids, it was of great interest to obtain newer quinazolinone-sulfonamide molecules having these moieties in their molecular framework with anticipated biological activity. Hence, it is proper to review the background and significance of quinazolinone derivatives, especially 2,3-disubstituted-4(3H)-quinazolinones. This chapter also throws light on the amino-acids and sulfonamides as well as on the literature reports for the incorporation of amino-acids and sulfonamide as substitutions in the backbone of 4(3H)-quinazolinone derivatives at position-2 or -3 respectively. This chapter also highlights on the structural hybridization approach applied to devise the new molecules in a single molecular framework and on the microwave technology in organic synthesis as well.
1.1 INTRODUCTION TO QUINAZOLINONE DERIVATIVES:

Quinazoline (1) is a member of fused bicyclic heterocyclic compound, which was earlier known as benzo-1,3-diazine and was first prepared in the laboratory by Gabriel S.[1] Although one of its derivative was known much earlier.[2]

For this compound, the name quinazoline was first coined by Weddige,[3] on observing that this was isomeric with the compounds cinnoline (2) and quinoxaline (3). Paal and Bush, who suggested the numbering of quinazoline ring system (Figure 1.1.1), and which is used currently.[4] The other less commonly used names for this ring systems are 5,6-benzopyrimidine and phenmiazine. However, quinazoline is now universally accepted.

Quinazoline which contains hydroxyl group substituent at position-2 or position-4 are known as 2-/4-ketoquinazoline or 2-/4-quinazolones or 2(1H)-/4(3H)-quinazolinone respectively. Although, both of these type of compounds are known to exhibit tautomeric properties of both, the keto and enol forms (as shown in Figure 1.1.2), however, they mainly exist in the keto form in solid state as well as in the solution. [5-8].

As the present thesis deals with synthesis of various 4(3H)-quinazolinone derivatives, especially, 2,3-disubstituted 4(3H)-quinazolinones, therefore a brief review on the some aspects of 2,3-disubstituted 4(3H)-quinazolinones is discussed under the following heads.
1.1.1 SYNTHETIC METHODS OF 4(3H)-QUINAZOLINONES:

The first derivatives of quinazolinone was synthesized in the late 1860s by P. Griess from anthranilic acid and cyanogen in ethanol to give 2-cyanoquinazolin-4(3H)-one (4a) and 2-ethoxy-4(3H)-quinazolinone (4b) as shown in Figure 1.1.3.[9] Since then, a remarkable number of quinazolinone syntheses have been carried out, and for more detailed information on the chemistry, many literature reviews and monographs about the synthesis of quinazolinone are available.[10-14]

![Figure 1.1.3](image-url)

Many of the reports about synthetic methods for the elaboration of this simple ring structure are, however, time consuming, tedious and often low yielding.[15-18] The new and improved methods for the construction of the 4(3H)-quinazolinone derivatives have been described, with a particular emphasis on 2,3-disubstituted-4(3H)-quinazolinone, some of these procedures have clear technical advantages over older methods in terms of yield and versatility, but do not employ new chemistry in the construction of the ring systems. The use of combinatorial synthesis, microwave-induced protocols and new catalytic methodologies for the preparation of these heterocycles is a clear indication that significant advancement has been made in recent years.

1.1.1.1 Niementowski quinazolinone synthesis:

The only name reaction for the preparation of 4(3H)-quinazolinone derivatives is known as Niementowski quinazolinone synthesis, which was named after its discoverer Stefan von Nimentowski.[19] His original work was published in 1895,[20] and the utility of this reaction have been reviewed by various researchers.[21-24]. This method involves the condensation or fusion of anthranilic acids (5) with appropriate amides (6) at elevated temperature to give corresponding quinazolinone derivatives (7).

![Scheme 1.1.1](image-url)
Mayer and Wagner subjected modification of this reaction and suggested alternative starting materials of methyl anthranilate or isatoic anhydride with substituted amides or amidines in the formation of 3-substituted-4-keto-3,4-dihydroquinazolines or 3-substituted amides or amidines.[25] A detailed mechanistic examination was established, that it proceeds in discrete steps and the steps indicated several possibilities in terms of yield improvement in the reaction. Patel and Patel studied Niementowski reaction and modified its mechanism which has increased its applicability.[26] This reaction continues to be used in development of modern synthetic procedures including microwave irradiation.[27-31]

1.1.1.2 Intramolecular coupling of azides to carbonyl groups:

A milder and efficient route for the synthesis of fused [2,1-b]quinazolinone was reported by Kamal and co-workers.[32] The procedure employs an intramolecular azido-reductive cyclization for the preparation of the pyrrolo[2,1-b]quinazolinone ring system (9) in high yield (85-97%), as shown in Scheme 1.1.2. This was exploited in the synthesis of deoxyvasicinone, which is a precursor for vasicinone, a known bronchodilator.[33] The FeCl₃/NaI combination had not previously been investigated for the reduction of the azide functionality and the role of NaI could be attributed to the in situ formation of FeI₃.

![Scheme 1.1.2](image)

Eguchi et al. have undertaken the synthesis of optically active L-vasicinone, a known pyrrolo[2,1-b]quinazolinone alkaloid by using intramolecular aza-Wittig reaction as a key step in the construction of quinazolinone ring with a 97% ee isomer (Scheme 1.1.3).[34]

![Scheme 1.1.3](image)

Hernández et al. reported the use of an Eguchi aza-Wittig reaction to fashion the 2,3-disubstituted quinazolinone skeleton in the synthesis of (−)-5-N-acetylardeemin analogues.[35] Recently, a polyethylene glycol (PEG) supported aza-Wittig reaction was published for the synthesis of various 4(3H)-quinazolinones by Ding and co-workers [36].
1.1.1.3 Formation of pyrrole substituted quinazolinones from benzodiazepines:

Fabis et al. showed that aromatic system of pyrrolo[2,1-c]-1,4-benzodiazepine was reactive towards nucleophiles like hydrazine hydrate, leading to the formation of 3-aminoo-2-(pyrrol-2-yl)quinazolinones as a rearrangement product in 60% yield (Scheme 1.1.4).[37]

![Scheme 1.1.4](image)

1.1.1.4 Formation of 2,3-disubstituted quinazolinone from benzoxazepinediones:

Uskokovic et al. have reported the synthesis of 2-(α-hydroxyalkyl)-3-N-methylquinazolinones (17) from 4,1-benzoxazepine-2,5(1H,3H)-diones (16).[38] The ring closure of 15 to form the benzoxazepines (16) was achieved in acceptable yield by refluxing in DMF. The formation of 17 was achieved in methanol in the presence of methylamine over a period of a week, as shown in Scheme 1.1.5.

![Scheme 1.1.5](image)

1.1.1.5 Formation of disubstituted quinazolinones via benzoxazinones:

3,1-Benzoxazin-4-ones are the most common intermediates used for the synthesis of various 2,3-disubstituted quinazolinones. Erred et al. have extensively studied the reaction of primary amine with acetanthranil and established the plausible mechanistic pathways for the synthesis of 2,3-disubstituted-4-quinazolones.[39-40] However, the early work with this reaction was done in the 1900s by Heller, Bogert, and other investigators, who reported that o-acylamidobenzamides, and/or corresponding quinazolones, were the major products (Scheme 1.1.6(a)).[39] Párkányi and Schmidt have synthesized the 2,3-disubstituted quinazolinones from chloro-substituted anthranilic acid and acetic anhydride.[42] In a study, similar work was reported by Jiang et al. for the synthesis of 2,3-disubstituted 4-quinazolinone derivatives, and is shown in Scheme 1.1.6(b).[43]
A similar approach was explored by Kumar et al. in the synthesis of 2-methyl-3-(2-methyl-1H-indol-3-yl)quinazolin-4(3H)-one (21) as shown in Figure 1.1.4.[44]

Figure 1.1.4

Recently, Zhou et al. [45] demonstrated the synthesis of a range of quinazolinone derivatives bearing the sulfonamides at position-3 with a variety of substitutions by using this solid phase method to introduce acyclic N-substituents (Scheme 1.1.7).

During the course of investigation for this reaction, some open chain product 28 (o-acylaminoanthranilamide) was isolated as shown in Scheme 1.1.8. In order to test the hypothesis that this reaction preceded via an open chain intermediate, equivalent amounts of 25 and benzenesulfonyl hydrazide (26) were dissolved in anhydrous DMF, and by stirring the reaction mixture at room temperature (for 22 hrs.) afforded 28 as a major product and 5% of the cyclized product 27. Heating this mixture subsequently furnished 27 in 78% yield following chromatographic purification, supporting the idea of an acyclic intermediate.
Benzoxazinones continued to be used for the preparation of 4-quinazolinones till date.[46-48] Liu J.F. has devised a novel, one-pot, highly efficient approach to 2,3-disubstituted-4-quinazolinones using microwave technology and applied this methodology to the total syntheses of several of quinazolinone containing natural products.[50]

1.1.1.6 Formation of 2,3-disubstituted quinazolinones from N-acylanthranilic acids:

Another approach for the formation of 2,3-disubstituted-4(3H)-quinazolinones involve the heterocyclization of N-acylanthranilic acids as shown in scheme 1.1.9a.

This general heterocyclization method was established by Grimmel et al. for the preparation of 4-quinazolones (30) from the N-acylanthranilic acids by heating them at elevated temperature with a range of substituted aniline in toluene or xylene in the presence of dehydrating agent such as phosphorous trichloride, phosphorous oxychloride or thionyl chloride. This method became more common and simpler method in the quinazolinone synthesis.[51] An illustrative example of this method is shown in Scheme 1.1.9b.

The modification and optimization of Grimmel’s conditions was investigated by Xue et al., for the synthesis of C2, N3-disubstituted quinazolin-4-ones by changing the reaction conditions, solvents, and amount of reagent, to improve the reaction time and
When the same optimized methodology was applied to o-chloroaniline (31) and substituted anthranilic acid (32), a small amount of 33 (10%) was observed. Subsequent experimentation led to the isolation of 34, which was proposed as being a possible intermediate in the formation of quinazolinone product (Scheme 1.1.10.)

![Scheme 1.1.10](image)

Virgil et al. employed benzenesulfonyl chloride as a coupling agent for asymmetric catalysis in the synthesis of monodentate atropisomeric ligands (37) (Scheme 1.1.11).[53]

![Scheme 1.1.11](image)

Giri et al. developed a novel and efficient strategy to synthesize benzoazinones and quinazolinones from N-acylanthrancacid (Scheme 1.1.12).[54] Two key intermediates, a mixed anhydride and benzoazinones, formed by reductive elimination from organometallic [Ar(CO)Pd(II)−OTs] species, provides mechanistic evidence for a dual-reaction pathway.

![Scheme 1.1.12](image)

1.1.1.7 Quinazolinones via palladium-catalyzed cyclocarbonylation:

Larksarp and Alper developed a palladium acetate/diphenylphosphinoferrocene (dppf) catalyst system for cyclocarbonylation of o-iodoanilines (41) with hetero-cumulenes (42) to afford the corresponding 4(3H)-quinazolinone derivatives (43) as shown in Scheme 1.1.13.[55] Carbodiimides and keteniminines were employed in this synthesis and the reactions were conducted at 100 °C (for 24 hrs.) under carbon monoxide pressure.
A further extension of this methodology utilized the ketenimines (44) rather than carbodiimides in the reaction with o-iodoaniline (41) and CO as shown in Scheme 1.1.14. An equimolar amount of the ketenimine was employed under a carbon monoxide pressure using Pd(OAc)$_2$ and dppf catalysis to afford 2-alkyl-4(3H)-quinazolinones (45) in good to excellent yields. Alper and Zheng have reported the Pd(OAc)$_2$ catalyzed cyclocarbonylation of o-iodoanilines with imidoyl chlorides for the synthesis of quinazolin-4(3H)-ones.[56]

Langer and Döring have elaborated the preparation of quinazolinones (48) by the reaction of anthranilic acid (46) with oxalic acid bis(imidoyl)chloride (47), and achieved the moderate to good yields in 3 days at 60 °C (Scheme 1.1.15). Keith Jones and co-workers have developed an efficient three step synthetic route to 2,3-diaryl-(3H)-quinazolin-4-ones via imidoyl chlorides using microwave-assisted condensation with aryl amine.[58]

Kundu and Chaudhuri have developed a novel Cu-catalyzed hetero-annulation to prepare (E)-2-(2-arylviny)-quinazolinone derivatives from alkynes in good yields (Scheme 1.1.16).[59] The conversion of the alkylnyl-aminobenzenamides into the disubstituted alkynes occurred via a Sonogashira–Hagihara coupling, followed by a rearrangement to the allene intermediate 51. The amide nitrogen takes part in nucleophilic attack on the terminal carbon.
of the allene with concomitant ring closure gave the substituted quinazolin-4-one derivatives (52) with predominant E-stereochemistry at the vinylic group. This is the first reported synthesis of quinazolinones employing a copper-catalyzed cyclization. The method is very mild, requires inexpensive starting materials and is experimentally undemanding.

\[
\text{Raid A.J. et al. have also reported a copper iodide (CuI) catalyzed synthesis of 2-substituted quinazolinones in good yield by condensation of anthranilamide with aryl, alkyl or heteroaryl aldehydes in refluxing ethanol.}[60]\] Fu Hua et al. also reported a simple and efficient approach to prepare quinazolinones under copper catalyzed milder condition [61].

1.1.1.10 Quinazolinone formation using Appel’s salt:

Kim et al. [62] developed a facile approach to synthesize 3-methyl-2-cyano-4(3H)-quinazolinone (56) (R = Me) using 4,5-dichloro-1,2,3-dithiazolium chloride (Appel’s salt) (54) as shown in Scheme 1.1.17. The cyano-group of 3-substituted-2-cyano-4-quinazolin-(3H)-ones can be readily displaced by various nucleophiles to give corresponding 2-substituted analogues in good to excellent yields. This approach allows a rapid and efficient synthesis of newer quinazolinone derivatives.

Gong Y.D. and co-workers have reported the solid-phase synthesis of 2-cyanoquinazolin-4(3H)-one by using the same approach. [64] Pereira D.F. reported a two-step process using Appel’s salt (54) for the synthesis of 1-imino-2,3-dihydro-(1H)-pyrazino[2,1-b]quinazoline-5-ones in acceptable yields. [63] Gong Y.D. and co-workers have reported the solid-phase synthesis of 2-cyanoquinazolin-4(3H)-one by using the same approach. [64]
1.1.1.11 Quinazolinone formation using 1-acetyl-1-methylhydrazine:

Peet et al. [65] demonstrated a simple and efficient procedure for the synthesis of 2,3-disubstituted-4(3\(^H\))-quinazolinones (61). The desired product in a respectable yield could be prepared by the cyclization of \(N^1\)-acetyl-2-amino-\(N^1\)-methylbenzohydrazide (60) under acidic condition as shown in Scheme 1.1.18.

![Scheme 1.1.18](image)

1.1.1.12 Formation of quinazolinones from polymer-bound anthranilamides:

Makino et al. have synthesized a series of 4(3\(^H\))-quinazolinones (64) by the cyclocondensation of anthranilamides (63) on solid supports in \(N\)-methylpyrrolidine (NMP) with a variety of orthoformates (Scheme 1.1.19).[66] The reaction proceeded smoothly under mild acidic condition and the product obtained exhibited excellent purity.

![Scheme 1.1.19](image)

Zhang et al. reported the effective solid-phase method for the synthesis of 2-alkyl and 2-aryl-3-substituted quinazolinones (65), which employ reagents with a lower oxidation state than orthoformates as shown in Scheme 1.1.20.[67] However, an oxidation step was required and it is not applicable for the synthesis of molecules which are susceptible to oxidation. Although, Makino’s route is limited by the commercial availability of the fewer orthoformates, it is superior to the solid-phase synthesis reported by Zhang et al. due to products obtained were not of high purity.
Kamal A. and co-workers have reported the solid-phase synthesis of some fused [2,1-b]quinazolinone alkaloids using polymer supported anthranilic acid derivatives.[68]

1.1.1.13 Chemoselective lithiation of quinazolinone derivatives:

Smith et al. reported the reaction of 3-(acylamino)-2-unsubstituted quinazolinone systems (66) with alkyl lithium, which gave the corresponding 1,2-addition product 67, rather than lithiation at the 2nd position (Scheme 1.1.21, Route A). The reactions were completed within 5 min. period and very good yields of the addition products were achieved.[69] It was later discovered that chemoselective lithiation at the 2nd position of 3-(pivaloylamino)- and 3-(acylamino)-4(3H)-quinazolinones (66a and 66b) was possible using lithium diisopropylamide (LDA) at low temperature to furnish a range of 2-substituted products 68 (Scheme 1.1.21, Route B). This direct lithiation is a facile, practical and regioselective process, enabling the synthesis of a range of derivatives including those that are not easily accessed by other routes. The ease of removal of the acylamino group affords the 3-amino analogues under basic or acidic conditions.

Srinivasan K.V. et al. applied an efficient protocol for the synthesis of quinazolin-4-one based alkaloids, tryptanthrin and deoxyvasicinone in good yields using similar regioselective lithiation strategy for intramolecular electrophilic reaction as a key-step [70].

A subsequent discovery showed that 3-amino-2-methylquinazolin-4(3H)-ones (69) could be lithiated readily using 2.2 equivalent of n-butyl-lithium at low temperature in THF and then quenched by a series of electrophiles in high yield.[71] Interestingly, attack by the...
The addition of n-BuLi at the carbonyl group or the imine functionality of the quinazolinone ring did not occur (Scheme 1.1.22; Route A). Based on the success observed using alkyl lithiurns, this method was transferred to the 3-amino-2-ethylquinazolin-4(3H)-ones (74), although only low yields were obtained. However, increased yields were achieved by using lithium diisopropylamide (LDA) at low temperature (Scheme 1.1.22; Route B). This new approach obviates need for protecting groups and simple procedure provides direct access to aminoquinazolinones, those were only previously available with difficulty.

Scheme 1.1.22

1.1.1.14 Combinatorial approach to access quinazolinones:

Houghten et al. developed a novel and chemoselective approach for the synthesis of 2-arylamino substituted quinazolinones with the possibility of manipulation at position-3, which demonstrates a traceless approach for parallel solid-phase synthesis of o-arylamino substituted quinazolinones from common precursors such as 2-aminobenzoic acids (R₁), aryl isocyanates (R₂) and amines (R₃) (as shown in Scheme 1.1.23).[72] The literature on the solid-phase approaches in the synthesis of quinazolines and quinazolinones has recently been reviewed by Vögtle and Marzinzik [73].
1.1.2 BIOLOGICAL IMPORTANCE OF QUINAZOLINONES:

It is important to note that the quinazolinone alkaloids are a member of a class of quinazoline natural compounds. Quinazolin-4-one is a building block for approximately 150 naturally occurring alkaloids isolated till date from a number of families of the plant kingdom, from animals and from microorganisms and possess a wide range of biological activities.[74] The chemistry of the quinazolinone alkaloids with very diverse structures along with their pharmacological importance is well documented in a number of comprehensive reviews and monographs,[14, 75-76] and is continuously updated in Natural Product Reports.[77-78] The quinazolinone natural products isolated so far has been reviewed in the reviews published by Johne S. in 1984,[79] has covered the literature of all the quinazolinone natural products isolated till 1983, which has been updated time to time by various groups and recently by Mhaske S.B. in 2006,[74] and Liu, J.-F. in 2007.[80]

The first quinazoline alkaloid to be isolated was vasicine (peganine) (80a) in 1888, produced by Indian medicinal tree *Adhatoda vasica*, and later isolated from other species along with the related pyrrolo[2,1-b]quinazolinone alkaloids, vasicinone (80b) and deoxyvasicinone (80c) [81-83].

![Figure 1.1.5](image.png)

**80a** \( X = H_2, R = OH \) (-)-vasicine

**80b** \( X = O, R = OH \) (-)-vascinone

**80c** \( X = O, R = H \) deoxyvascinone

Interest in the medicinal chemistry of quinazolinone derivatives was stimulated in the early 1950s with the elucidation of a quinazolinone alkaloid, febrifugine (81) from an Asian plant *Dichroa febrifuga*, which is an ingredient of a traditional Chinese herbal remedy, effective against malaria.[84] Another derivative isofebrifugine (82), which is analogue of febrifugine with antimalarial property. These two compounds are potent and potential antimalarial drugs, whose stereochemistry has been revised recently.[85-88] Therefore, they are perhaps the most interesting quinazolinone alkaloids of all, but unfortunately they were toxic to human. Apart from the medicinally important alkaloids, (-)-Vasicinone and febrifugine, some other alkaloids such as luotonin A, rutaecarpine, ardeemin, and (-)-asperlicin are the important quinazolinone natural products from a structural and therapeutic point of view.

The structural diversity of fungal quinazolinones has been broadened with the discovery of asperlicin (83), isolated from the fungus *Aspergillus alliaceus*, which is a
potent cholecystokinin (CCK) antagonist. Asperlicin has 300-400 fold more affinity for pancreatic, gastrointestinal, and gallbladder CCK receptors than proglumide, a standard agent of this class.[89-91]

A few alkaloids have been the object of synthetic work by Bergman and co-workers. Among them rutaecarpine (84) [92, 93] is one of the several quinazolinocarboline alkaloids isolated from various plants of the *rutacea* family (e.g. *citrus* belongs). Chrysogine (85) (isolated from molds) [92-95] and a derivative of auranthine (86) (a benzo-diazepine alkaloid, *vide infra*) [96, 97] have been synthesized by members of the group. Several other quinazolinone derivatives have been isolated, characterized and synthesized.

The quinazolinone alkaloid, luotonin A (87) was triggered considerable interest among synthetic chemists and pharmacists because it is strikingly reminiscent of the cytotoxic alkaloid, camptothecin, the derivatives of which are clinically useful anti-cancer agents [98]. Cagir *et al.* recently increased the importance of these findings by demonstrating that, despite the lack of A-ring functionality; luotonin A stabilizes human DNA topoisomerase-I dependent cytotoxicity in intact cells.[99]

*N*-Acetylardeemin (88) having the pyrazinoquinazoline substructure, isolated from *Aspergillus fischeri*,[100] and is known as one of the most potent multidrug resistance (MDR) inhibitor.[101, 102] These class of alkaloids often exhibit very interesting biological properties and have drawn considerable interest of synthetic chemists.[103]

Interest in the medicinal chemistry of quinazolinone derivatives was stimulated in the early 1950s with the elucidation of a quinazolinone alkaloid (febriufugine) effective against malaria. In a quest to find additional potential quinazolinone-based drugs, various substituted quinazolinones have been synthesized, which led to synthesis of the derivative, 2-methyl-3-o-tolyl-4(3H)-quinazolinone (89). Methaqualone (89) was synthesized for the first time in 1951,[104] and it is the most well-known synthetic quinazolinone drug, famous for its sedative–hypnotic effects.[105] The introduction of methaqualone and its discovery as a hypnotic triggered the research activities toward the synthesis, and studies on the pharmacological properties of the quinazolinones and related compounds. The other analogs of methaqualone such as Diproqualone (90), Etaqualone (91), Methymethaqualone (92), Mecloqualone (93), Mebroqualone (94), Cloroqualone (95) etc. having similar pharmacological activity were also marketed during 1960s to 1980s.[106-110] However, its’ analogue Afloqualone (96) was marketed as centrally acting muscle relaxant.[111-113] Zaroxolyn (metolazone) (97) is a drug which belongs to quinazolinone class,[21] which is currently available in the market, having diuretic, saline and antihypertensive potency.
Several quinazolinones from natural or synthetic origin are known to give a wide variety of biological responses, which has stimulated the preparation and pharmacological evaluation of a great number of quinazolinone derivatives. Hence, intensive research in the field of quinazolinone area is still in active progress. Like the benzodiazepines the quinazolinones are considered to be a “Privileged structure” for drug development.[114] Many of the quinazolinone derivatives were available for clinical trials and the treatments with a wide variety of biological activities. This topic has been very well reviewed in the literature.[14, 79, 105, 115-118] Some of natural and unnatural quinazolinone derivatives (80-102) of the pharmaceutical importance are provided in Table 1.1.1.

Table 1.1.1 Natural/Synthetic quinazolinones of therapeutic importance:

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Natural/Synthetic Quinazolinones</th>
<th>Therapeutic Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>80b</td>
<td>(-) - Vasicinone</td>
<td>Anti-tumor, Hypotensive, Bronchodilator, Antienthelmintic, Anti-anaphylactic; Used as remedy in India (Ayurveda) for rheumatism, cold, cough, bronchitis asthma, and Phthisis.</td>
</tr>
<tr>
<td>81</td>
<td>Febribugine</td>
<td>Anti-malarial ingredient found in a traditional Chinese herbal remedy.</td>
</tr>
<tr>
<td>82</td>
<td>Isofebrugine</td>
<td>Anti malarial.</td>
</tr>
<tr>
<td>83</td>
<td>(-) Asperlicin</td>
<td>300-400 fold more affinity for Gastrointestinal, Pancreatic and Gallbladder CCK receptors; Highly selective for Peripheral CCK receptors relative to Brain and Gastrin Receptor.</td>
</tr>
<tr>
<td>84</td>
<td>Rutacearpine</td>
<td>Strong Analgesic, Anti-emetic, Anti-hypertensive, Anti-inflammatory, COX-2 inhibitor.</td>
</tr>
</tbody>
</table>
Chapter-1

85

\[
\text{Chrysogine}
\]

Cytostatic (antileukemic).

86

\[
\text{Aurathine}
\]

Anti-cancer, antiproliferative.

87

\[
\text{Luotonin A}
\]

Anti-tumor cytotoxic towards the murine Leukemia P-388 cell line, Naturally occurring human DNA topoisomerase-I, poison, Activity like Camptothecin.

88

\[
\text{(-)-5-Acetyldedehydramine}
\]

Reversed Multiple drug resistance (MDR) in human Tumor Cell lines and Sensitized cells to the Anti-cancer agent, Vinblastine.

89

\[
\text{Methaqualone}
\]

Sedative - hypnotic.

90

\[
\text{Diproqualone}
\]

Sedative - hypnotic.

91

\[
\text{Ftaqualone}
\]

Sedative - hypnotic.

92

\[
\text{Methylmethaqualone}
\]

Sedative - hypnotic.
Sedative - hypnotic.

Mecloqualone

Sedative - hypnotic.

Mebroqualone

Sedative - hypnotic.

Chloroqualone

Centrally acting Muscle Relaxant.

Afloqualone

Diuretic, Saluratic, Antihypertensive.

Metolazone

Anti-fertility.

Canthine-6-one

Antibiotic; Highly active against drug sensitive and drug-resistant M. tuberculosis.

Tryptanthrin

A triazole antifungal with potential broad-spectrum antibacterial activity.

Albacnazole (UR-9825)
Partial peroxisome proliferator-activated receptor-gamma (PPAR-γ) agonist; excellent antidiabetic and hypolipidemic properties, but less adipogenic activity.

Inhibitor of the delta isoform of phosphoinositide 3'-kinase (PI3-kinase) delta (p110delta) for the treatment of hematological cancer.

Due to the aforementioned medicinally important natural or unnatural derivatives of pharmaceutical interest, 4(3H)-quinazolinone derivatives have continuously attracted a wide spread interest for a long time of synthetic and medicinal chemists. Further, research has been continued to produce a wide variety of structural variation in this core area which possessed a diverse pharmacological activity spectrum, such as antibacterial,[119, 120] antifungal,[121,122] antitubecular,[123,124] antimalarial,[125-127] antinflammatory,[128-130] antitumor,[131-135] antihyperglycemic,[136,137] broncho-dilatory,[138,139] and several others,[97,140] including inhibitory activity of various enzymes like acetyl-choline esterase inhibitor,[141,142] antifolate synthase inhibitor,[143,144] or thymidate synthase inhibitor,[145,146] protein kinase inhibitor,[147-149] among others.[80,145]

The high degree of protection against seizures can be positive signs for further investigation of quinazolinone derivatives as anticonvulsants. The activity of quinazolinone as antitubercular compounds and their potent anthelmintic activity are promising. The broad spectrum antibacterial and antifungal activity of these compounds could lead to a new series of antimicrobials. The quinazolinone derivatives have demonstrated significant antiviral and anticancer activities also. The enzymes and receptor agonist or antagonist action of these derivatives further shows their biological importance. Thus, quinazolinone scaffold is not only synthetically important, but also possesses a wide range of promising biological activities. Hence, future investigations of this scaffold could give some more encouraging results.
1.2 INTRODUCTION TO SULFONAMIDES:

Considerable progress had been made before 1930 to develop extremely applicable bactericides, but most bactericides that could be administered internally having reasonable safety margin, and unfortunately lost their activity in presence of blood serum. There were limited agents available for the treatment of most diseases of bacterial origin. Large numbers of organic compounds have been synthesized on the basis of model molecule, which might have useful antibacterial activity for the treatment of local, systemic, and/or urinary tract infections. A chemical class of compounds, such as synthetic antibacterial agents, includes sulfonamides, sulfones, phenols, many heterocycles like quinolones, etc.

In chemistry, sulfonamide or sulphonamide is a \(-\text{S}(=\text{O})_2\text{-NH}\)- functional group containing compounds, \textit{i.e.} an amide of sulfonyl and amine group. The derivatives of sulfonamide form an important class of sulphur containing compounds having general general formula as shown in Figure 1.2.1, where \(R\) and \(R_1\) is some organic group usually alkyl, aryl or heterocyclic substitutions, and \(R_2\) is usually H-atom. Any sulfonamide can be considered as derived from a sulfonic acid or sulfonyl halide by replacing a hydroxyl or halide group respectively with an amine group.[150]

\[
\begin{align*}
\text{(1')} & : \text{Sulfonamide (Sulphonamide) functional group} \\
\text{(2')} & : \text{Sulfonamide (Sulphonamide) functional group} \\
\text{(3')} & : \text{Sulfonamide (Sulphonamide) functional group}
\end{align*}
\]

Sulfonamides have been discovered in early 1930s as the first synthetic antibacterial agents, although their applications have been extended as therapeutic agents over the last seven decades to treat other diseases. Diseases like pneumonia, meningitis, dysentery, etc., could not be treated effectively until epoch-making discovery of sulpha or sulfa drugs. The discovery and development of sulphonamides as an antibacterial agents, were one of the most fascinating and informative field in the medicinal chemistry, highlighting the roles of skillful planning and serendipity in drug research.[151] Carefully observed effects in pharmacological and clinical studies of sulfonamides revealed new unanticipated activities; successful exploitation of these leads opened up new areas in chemotherapy, such as anti-diabetics, carbonic anhydrase inhibitors, and diuretics.[151]

In medicine, sulfonamides or sulphonamides is the general term and is the basis of several classes of drugs. The generic name of a “sulphonamide” is built up by adding the prefix “sulpha-” to an abbreviated form of the chemical name of the \(N^1\)-residue. This is
done in two ways: either the amido nitrogen is taken as a part of the “sulpha” residue, as in case of $N^1$-heterocyclic sulphonamides, e.g., Sulphapyridine, or the amido nitrogen is taken as a part of $N^1$-residue as in Sulphaguanidine. The term "sulfonamide" is sometimes used as a synonym for “sulfa” drugs, a derivative or variation of Sulfanilamide. In general, it is a generic term that is used to describe three different cases, as shown in Figure 1.2.2.[152]

1. Aniline-substituted sulfonamides, i.e. sulfanilamides.

2. Prodrugs that react to generate active sulfanilamides, i.e. Sulfasalazine like prodrug obtained from Sulfapyridine and $p$-aminosalicylic acid, etc.

3. Non-aniline sulfonamides. i.e. mafenide, mafenideacetate, etc.

![Diagram of sulfonamides](image)

Figure 1.2.2 General structure of Sulfonamides (Sulphonamides) or Sulfa drugs

Sulphanilamide ($\text{SF}; R_1=R_4=H$) is considered as a model compound for this class of compounds. The core structure of sulphonamide cannot be modified, if it is to be effective competitive “mimic” for 4-aminobenzoic acid. Essential structural features are the benzene ring with two substituents para- to each other: an amino group at position-4; and a singly substituted sulphonamido group. It must be noted that the ortho- and meta- isomers are therapeutically valueless, and any substitution on aromatic ring either destroys or reduces the activity of the sulpha drug. Many structural modifications of Sulphanilamide were made at $R_1$ by the substitution of heterocyclic aromatic nuclei, which have yielded highly potent compounds, and the substitution of another hydrogen atom is comparatively rare.[151, 152]

### 1.2.1 HISTORICAL BACKGROUND OF SULFONAMIDES:

Sulfonamides were the first effective agents against most Gram-positive and many Gram-negative organisms, as well as employed systematically for the prevention and cure of bacterial infections.[151, 152] The prototype compound, 4-aminobenzenesulphonamide, known as sulphanilamide, was first synthesized by Gelmo, in 1908, which was widely used as an intermediate in the formation of azo-dyes in the dye-making industry.[153] It occurred surprisingly many years before its therapeutic value was actually ascertained. Domagk G.,
in 1910, screened number of these azo dyes for their antibacterial effects and observed their activity against *staphylococci*, *streptococci* and other Gram-positive bacteria. In 1932, a German firm prepared 4-sulphonyl-chrysoidine or 4-sulphonamide-2',4'-diaminobenzene – a red dye. After three years, Domagk suggested its significant disease curative properties and named it as Prontosil.[154] In 1935, Trefouel *et al.* at the Pasteur Institute, found the active substance within Prontosil was sulphanilamide. Prontosil on metabolic cleavage produces sulphanilamide (Scheme 1.2.2).[155] Prontosil is highly inactive *in vitro*, but it posses excellent activity *in vivo*, where it metabolizes to give the active agent sulphanilamide and it can interfere with the process of bacteria and act as potent bacteriostatic agent.

\[
\text{Prontosil Rubrum/Red} \xrightarrow{\text{Metabolic Cleavage}} \text{Sulphanilamide}
\]

**Scheme 1.2.1**

Due to the inability of bacteria to acquire dihydrofolic acid from their environment, as part of bacteria’s DNA biosynthesis, inhibition of *dihydropteroate synthase* enzyme inhibits the formation of *dihydrofolinic acid* poses a desirable target for bacteriostatic agents. Inhibition of this enzyme has been achieved with early sulfonamides such as sulphanilamide. The formation of dihydrofolinic acid is initiated by coupling pteridine diphosphate with *p*-aminobenzoic acid, which can then undergo amide coupling with glutamic acid to form dihydrofolinic acid. Sulphanilamide displays similar core structure to that of *p*-aminobenzoic acid and act as a competitive inhibitor (as shown in Scheme 1.2.2). Dihydrofolinic acid formation is blocked during the second step; due to a lack of acidic terminal available to couple with glutamic acid, and hence dihydrofolinic acid formation is interrupted. This action arrests the bacterial growth and cell division. The competitive nature of sulfonamides action means that the drugs do not permanently damage to a microorganism; hence, they are bacteriostatic and not bactericidal.[151, 152, 156]
The first structural analogue of sulphanilamide, i.e. Sulphapyridine was prepared in 1937,[157] which was indeed proved a tremendous success in curing pneumonia. This magnificent discovery in fact, paved the way for the synthesis and screening of thousands of derivatives of sulphanilamide by 1945,[158] but only few have gained the glory of being potent medicinal compound. Discovery of sulpha drugs gave mankind its first armour against infections. Thus, sulpha drugs are said to be miracle drug- a real “magic bullet” of Paul Ehrlich. For the pioneering work in the chemotherapy by G. Domagk, he was awarded the Nobel Prize in medicine & physiology in 1938.[152]

Till date, many thousands of sulphonamide derivatives, analogues, and related compounds have been synthesized.[159,160] This has lead to the discovery of many useful drugs, which are effective as antimicrobial agents as well as diuretics, anti-diabetic, antimalarial, antileprotic, antithyroid agents, and several other agents.[151, 152, 160]

1.2.2 GENERAL METHODS FOR THE SYNTHESIS OF SULPHONAMIDES:

Due to the broad applicability of sulfonamides, it is desirable to find general and effective methods of synthesis. Although, a comprehensive review of this is not provided, following section provides several of most common methods for the synthesis of sulfonamides.

The classical and general method for the synthesis of sulfonamides or sulfanilamides (sulfa drugs) is via the coupling of appropriate sulfonyl chloride with amine, which could involves one of the fairly straightforward routes (as shown below).[162] The preferred intermediate in the synthesis of sulfonamides is sulfonyl chlorides, which could be prepared from appropriate precursors such as acetanilide, aryl sulfonic acids, thiols, etc.

4-Acetamidobenzenesulfonyl chloride (ASC), which is a reactive and versatile starting material for the preparation of most of sulphanilamides, and ASC could be prepared by chlorosulfonation of acetanilide.[163] Reaction of ASC with an appropriate amine in presence of base gives the intermediate, which upon hydrolysis in either acid or base leads to the sulfanilamides.[164,165] In the another approach, the amide (sulfonamide) formation is performed on p-nitrobenzenesulfonyl chloride. Reduction by either chemical or catalytic methods affords directly the desired product.[166] Alternatively, the required sulfonyl chloride is normally prepared from the corresponding sulfonic acids by using SOCl₂, PCl₅ or POCl₃,[167] followed by reaction with amines give desired sulfonamides.
Scheme 1.2.3

A method for the synthesis of sulfonamides from thiols, require in situ formation of a sulfonyl chloride by bubbling a chlorine gas through thiols. Recent report involved an aqueous acid, sodium hypochlorite (commercial bleach), mediated oxidation of thiols.[168]

Scheme 1.2.4

A one-pot method to furnish sulfonamides was developed to prepare aliphatic- and aromatic-sulfonyl chloride in situ by using trichlorocyanuric acid (TCCA) and benzyl-trimethyl ammonium chloride in water to generate a controlled amount of chlorine into aprotic solvent (MeCN).[169]

The combination of H₂O₂ and SOCl₂ is a highly reactive reagent for direct oxidative conversion of thiols to the corresponding sulfonyl chlorides through oxidative chlorination. Upon reaction with amines in pyridine, the corresponding sulfonamides were obtained in high yields in very short reaction times under microwave conditions.[170] In situ preparation of sulfonyl chlorides from thiols by oxidation with NCS, tetrabutylammonium chloride, and water followed by reaction with amine or sodium azide enables a convenient synthesis of sulfonamides and sulfonyl azides.[171]

A one-pot synthesis of sulfonamides from aromatic and heteroaromatic halides was established to increase diversity on sulphur by using Grignard reagent, which then attack sulfur dioxide to form sulfinic acid salt. Subsequent, chlorination of which using sulfuryl chloride (SO₂Cl₂) generates sulfonyl chloride, and aminolysis with amines furnishes sulfonamides.[172]

Scheme 1.2.5
The stable colorless solid charge-transfer complex generated from the combination of DABCO and sulfur dioxide, i.e. DABSO, can replace gaseous sulfur dioxide in organic synthesis. Reactions with Grignard reagents form sulfinates, which can then be converted to sulfonyl chloride in situ to form sulfonamides. Alternatively, reaction with anilines and iodine leads to the formation of a series of sulfonamides. [173]

However, many of these methods require excess oxidant and/or aqueous acids, and are not compatible with acid sensitive substrates.[160, 174] Even though, a wide variety of sulfonamides can be generated from these procedures, several steps are required. Furthermore, the fairly harsh conditions and functional group compatibility are therefore a point of major restriction. It would appear that some general limitations to sulfonamide synthesis exist including (1): excessive amount of highly toxic chlorinating agents (CISO$_2$H, SO$_2$Cl$_2$, PCl$_5$ and POCl$_3$) and (2): organolithium and Grignard reagents are incompatible with several functional groups (-OH, -SH and -COOH) while aqueous acids (ClSO$_2$H and H$_2$SO$_4$), and are not compatible with acid sensitive substrates.

Alternatively, aromatic, heterocyclic and aliphatic sulfonyl chlorides prepared in optimal yield in situ, by using trichloroacetonitrile-triphenylphosphine complex (Cl$_3$CCN: PPh$_3$: sulfonic acid) in a ratio 3:3:1 in dichloromethane, which upon treatment with amines in the presence of 4-picoline resulted sulfonamide formation.[175]

![Scheme 1.2.6](image)

Recently, a novel approach to sulfonamide synthesis was developed by utilizing aliphatic or aromatic sulfonic acids and isonitrides (R–N≡C) under aqueous conditions.[176]

![Scheme 1.2.7](image)

An innovative approach of sulfonamides synthesis is illustrated by Greenbaum et al. in the synthesis of 6-uracilsulfonamide, which is reasonably and effectively oxidized from 6-uracilsulfenamide using KMnO$_4$ with 64% yield.[177] A similar methodology was used in the synthesis of 6-ethoxybenzothiazole-2-sulfonamide as a potential carbonic anhydrase inhibitor (Scheme 1.2.8).[178] Alternatively, mild and selective oxidants, m-CPBA, have also been utilized for the conversion of sulfenamides into sulfonamides (e.g. pyrimidine-4-sulfonamide).[179]
The aforementioned methods do have some limitations in as much as they do not allow diversification of substituents on sulfur or nitrogen. Transition-metal catalyzed C–N bond formation has been studied extensively, where the most well known, palladium catalyzed N-arylation is the Buchwald-Hartwig reaction.[180] However, there are few reports explored the N-arylation on sulfonamides.

Alternative approach is to carry out synthetic modification of primary sulfonamide, unfortunately, this method led to only modest yield of N-arylsulfonamides. The palladium catalysed N-arylation of sulfonamides under microwave irradiation described the effect of modifying the ligands, bases and solvents, and identified optimal reaction conditions under microwave heating at 180 °C for 10 minutes (Scheme 1.2.9).[181]

The first example of transition-metal catalyzed C–N bond formation is Chan-Lam reaction, which used cupric acetate and arylboronic acid to give N-arylsulfonamide.[182] An effective protocol was described using 0.1 equivalent of copper(II) acetate and TEMPO under milder conditions, to give quantitative yield of N-arylsulfonamide (Scheme 1.2.9).

A range of sulfonamides have been synthesized using Cu(I) catalysed coupling using aryl bromide/iodide (Scheme 1.2.11). During the optimization process, it was found that use of amino acid as a ligand introduces advantage of its easy removal after the reaction. After screening several amino acids, they found that N-methylglycine and N, N-
dimethyl-glycine were the most effective with Cu(I). Together with K$_3$PO$_4$ as a base, and DMF as the solvent, all desired $N$-arylsulfonamides can be generated up to 99% yield.[183]

\[
\text{Ar}-X + R-S-\text{N}-R' \xrightarrow{\text{Cu(I)}} \text{N-arylsulfonamides}
\]

Scheme 1.2.11

Recently, pentafluorophenyl (PFP) sulfonate esters have been introduced to replace sulfonyl chloride for the preparation of sulfonamides. The use of PFP sulfonate esters may introduce several advantages such as reduced toxicity, enhanced shelf stability, makes them desirable as precursors.[184,185] The aminolysis of sulfonates in refluxing THF can be used as an effective method for the synthesis of sulfonamides in good to excellent yield. It was further shown that a range of amines (primary, secondary, aromatic, and aliphatic) could undergo reaction with PFP sulfonate esters to produce a wide range of sulfonamides (Scheme 1.2.12). Another advantage of PFP sulfonate esters over sulfonyl chlorides is that they can readily be employed under aqueous conditions.

\[
\text{R}^+\text{SO}_2\text{OPFP} \xrightarrow{\text{NHR}R^+\text{u}} \text{R}^+\text{SO}_2\text{NRR}^+\text{u}
\]

Scheme 1.2.12

Due to the high cost of pentafluorophenol, a cheaper and even less toxic alternative was sought. Trichlorophenol (TCPOH), a household antiseptic, was employed in the formation of sulfonate esters, and found to be a good leaving group during subsequent aminolysis. Aminolysis of TCP sulfonate esters with primary amines in the presence of TEA in NMP later furnished sulphonamides up to 94% yield. However due to high stability of TCP, the reactivity is noticeably reduced in comparison with that of PFP, therefore an increase in reaction time is needed as well as more forcing condition.[186]

The numerous sulphonamides have been prepared by various synthetic methods, however the most common method for the synthesis of wide range of sulphonamides especially sulphanilamides follow the traditional method described in the very beginning, which involves the condensation of appropriate sulfonyl chlorides with primary amines in the presence of organic bases or inorganic bases in a variety of solvents.[160]
1.2.3 CLINICAL IMPORTANCE OF SULPHONAMIDES:

The sulfonamides are well known motifs in medicinal chemistry, forming a large family of antibacterial agents as well as being found in numerous other drugs. A sulfonamide is any compound with an -SO₂NH(R)- moiety. The major difference between sulfonamide antimicrobials and other sulfonamide-containing medications such as diuretics, antiviral, anti-HIV, anticonvulsant, anti-glaucoma, etc, is that sulfonamide antimicrobials contain an aromatic amine group at the N⁴-position. This allows for division of the sulfonamides into two major groups: aromatic amines (i.e., sulfonamide antimicrobials such as sulfanilamides and their prodrugs) and non-aromatic amines (i.e. Mafenide, Furosemide, Celecoxib, Sildenafil, etc.) as shown in Figure 1.2.2. In addition to this, sulfonamide antimicrobials contain a substituted ring usually heterocyclic ring at the N¹-position; this group is not found with non-aromatic amine-containing sulfonamides. However, this position is predominant to impart majority of structural variations to obtain more potent analogs than a parent sulfanilamide.[152, 160, 162]

The derivatives of sulphonamides have been classified in many different ways, apart from which it was mentioned earlier. The one based on absorption and half-life appears to be the most logical and clinically relevant classification, as shown in Table 1.2.1. Sulphonamide derivatives that have a half-life of less than 10 hours are termed as short acting; between 10 to 24 hours are considered to be medium acting, and longer than 24 hours are long acting. “Long-acting” denotes slow excretion and/or re-absorption of the drug into the system from the excretory route and is to be differentiated from the depository form. In the later case, the drug is formulated in such a way that it is stored in the body in a form in which the total quantity is not available all at once, but is gradually released.

Table 1.2.1 Clinical Classification based on absorption and half-life.

<table>
<thead>
<tr>
<th>Class</th>
<th>Common Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poorly absorbed, locally acting</td>
<td>Phthalylsulphacetamide; Phthalylsulphathiazole;</td>
</tr>
<tr>
<td>Well absorbed, rapidly excreted</td>
<td>Sulphamethizole (Sulphamethylthiadiazole); Sulphacarbamide (Sulphanilylurea);</td>
</tr>
<tr>
<td></td>
<td>Sulphapyridine; Sulphanilamide</td>
</tr>
<tr>
<td>Rapidly absorbed, medium rate of excretion</td>
<td>Sulphaphenazole; Sulphamethoxazole</td>
</tr>
<tr>
<td>Readily absorbed, slowly excreted</td>
<td>Sulphamethyldiazine; Sulphadimethoxine</td>
</tr>
</tbody>
</table>
1.2.3.1 PRESENT STATUS IN THERAPEUTICS:

Sulphonamides now available provide a broad range of pharmacokinetic properties and antimicrobial spectrum. The sulfonamides have an established a place in therapeutics even after several decades of their first introduction. Combination therapy with DHFR inhibitors has greatly increased their usefulness. Clinical indications for sulphonamide therapy have been carefully assessed, and their relative merits are reasonably well-known. In assessing the overall clinical usefulness of a sulphonamide apart from its antimicrobial activity, other factors such as solubility, protein binding, half-life, and metabolism are taken into consideration. Thus, best sulphonamide is one that combines the optimum values for most of these properties. However, antibiotic resistance has emerged as an important factor that severely limits the clinical use of sulfonamides.[187, 188] Currently, sulfonamides are still in use for the effective treatment of a variety of infectious disease (Table 1.2.2).

### Table 1.2.2 Combination of sulfonamides and its Therapeutic Uses.

<table>
<thead>
<tr>
<th>Combination of Sulfonamides</th>
<th>Therapeutic Usages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethoprim-Sulfamethoxazole</td>
<td>Treatment and prophylaxis of pneumonia; First attack of urinary infection</td>
</tr>
<tr>
<td>Pyrimethamine-Sulfadiazine</td>
<td>Treatment and prophylaxis of cerebral toxoplasmosis</td>
</tr>
<tr>
<td>Silver Sulfacetamine</td>
<td>Prevention/ treatment of bacterial infection for burn patients</td>
</tr>
<tr>
<td>Sodium Sulfacetamide</td>
<td>Conjunctivitis and related superficial ocular infections</td>
</tr>
<tr>
<td>Sulfadoxine and Sulfalene in combination with Quinine</td>
<td>Chloroquine-resistant malarial treatment</td>
</tr>
</tbody>
</table>

Since discovery, the sulfonamido group has been found as a key structural motif shared by a large number of bioactive compounds, spanning a wide variety of biological effects, such as, specific enzyme inhibition, hormone regulation, and several others.[189] Apart from the commercialized application as antibacterial/antibiotic agents, various sulfonamides such as Celecoxib and Valdecoxib (COX-2 inhibitor), Darunavir, Tipranavir and Fosamprenavir (Protease Inhibitors), Probenecid (PBN), Sulfasalazine (SSZ), Sumatriptan (SMT) among others. are also known to inhibit several enzymes.[190] Moreover, the widespread potential value of sulfonamides, have led to the discovery of several pharmaceutical agents for various other therapeutic applications such as anti-cancer and antiviral agents,[191] a large number of diuretic agents (Acetzolamide, Bumetanide, Chlorthalidone, Clopamide, Furosemide, Hydrochlorothiazide, Indapamide, Mefruside, Metolazone, Xipamide), anticonvulsants (Acetzolamide, Ethoxzolamide, Sultiam, Zonisamide), and dermatologicals (Mafenide), anti-impotence agent (Sildenafil) and several others.[152, 192]
Due to the aforementioned pharmaceutical application of sulfonamide analogues, the sulfonamide core has also to be considered as a “Privileged structure” for drug development like the other organic scaffolds, *viz.* benzodiazepines, quinazolinones, etc.[114] Moreover, the intensive research to develop new agents with sulphonamide backbone is still in active progress.[161, 165, 193-195]

1.3 SULFONAMIDE LINKED QUINAZOLINONE DERIVATIVES:

In continuation of our interest in the synthesis of 4-quinazolinone and sulfonamide derivatives of biological interest, it is thought worthwhile to link both the moiety together in a single molecular framework. The 4(3H)-quinazolinone ring would offer different positions to produce sulfonamide-linked-quinazolinone derivatives. There are fewer reports available wherein sulfonamide-linked-quinazolinone molecules of various interests have been explored, of which some important molecules have been highlighted.

The most interesting example of sulfonamide-linked-quinazolinone include fewer intermediates for the diuretic drugs of 1,2,3,4-tetrahydroquinazolinone-6-sulfonamide class such as QS1, QS2, and QS3.

A diuretic and antihypertensive agent, 7-chloro-2-ethyl-1,2,3,4-tetrahydro-4-oxo-6-quinazolinesulfonamide, (Quinethazone, QS1) was prepared by the reduction of 3,4-dihydro-4-oxoquinazoline intermediate, the later was resulted by the reaction of 5-amino-sulfonyl-4-chloroantranilamide and propionyl chloride using POCl3.[196] A thiazide-like diuretic with saluretic and hypocalciuric activity, 7-chloro-1,2,3,4-tetrahydro-4-oxo-2-phenyl-6-quinazolinesulfonamide (Fenquizone, QS2) was prepared by the condensation of 2-amino-4-chloro-5-sulfamoylbenzamide and benzaldehyde.[197] 7-Chloro-1,2,3,4-tetrahydro-2-methyl-3-(2-methylphenyl)-4-oxo-6-quinazolinesulfonamide (Metolazone, QS3) was prepared by the reaction of 6-sulfamoyl-7-chloro-isotoic anhydride with 2-toluidine to gave intermediate, which upon treatment with acetaldehyde dimethyl acetal gave metolazone.[198] Clinical evaluations of it was reported as diuretic in chronic renal disease,[199a] hypertension,[199b] and congestive heart failure diseases.[199c]
Apart from this type of quinazolinone-sulfonamide derivatives, the incorporation of sulfonamides (or sulfanilamides) in 4(3H)-quinazolinone ring structure at position-3 as well as at position-2 to produce variety of quinazolinone-linked-sulfonamide derivatives have been found in the literature reports, which is highlighted as shown under.

Anwar et al. reported reaction of p-toluenesulfonyl chloride with 2-phenyl-3-methylamino-4-quinazolinone to produce corresponding QS4.[200]

![QS4](image)

Gupta et al. have prepared newer quinazolinone derivatives, and showed that quinazolinone with sulphonamide at position-3 (QS5) was an anthelmintic agent.[201]

![QS5](image)

Ammar, Y.A. has reported reactions of 6-chloro-2-methyl-3,1-benzoxazin-4-one with some amino compounds, e.g. p-chlorobenzenesulfonylhydrazide to yield the corresponding quinazolinone derivative (QS6).[202]

![QS6](image)

Gaur, V.B. et al. have reported the synthesis of various alkyl or aryl or aminomethyl or cinnamyl substituted-3-p-sulfonamidophenyl-4(3H)-quinazolinone derivatives (QS7a, QS7b and QS7c).[203]

![QS7a](image)  ![QS7b](image)  ![QS7c](image)

Where: R = -Ph, 2-MeC₆H₄, 3-MeC₆H₄, 4-MeC₆H₄ etc.
R₁ = 2-NO₂C₆H₄, 3-NO₂C₆H₄, 4-NO₂C₆H₄, 2-ClC₆H₄, 3-ClC₆H₄, 4-ClC₆H₄ etc.
El-Naser, O.A.R. *et al.* have reported the synthesis of some newer derivatives of 3-\((p\text{-sulfomylbenzene})\)-4(3\(H\))-quinazolinone (QS8) and all the prepared compounds were screened for their anticonvulsant activity.[204]

![Chemical Structure of QS8](image)

Where:
- \(R_1 = \text{alkyl}\)
- \(R_2 = \text{H}, \text{-CH}_3, \text{Halogen}\)
- \(R_3 = \text{H}, \text{-Cl}, \text{-NO}_2\)
- \(R_4 = \text{H}, \text{Halogen}\)

Zahran, M.A. has reported the synthesis of some quinazolino-quinoxalines having sulfonamide substituent at position-3 of the quinazolinone ring (QS9), using quinoxaline-2,3-dicarboxylic acid anhydride.[205]

![Chemical Structure of QS9](image)

Barakat, S.S. has synthesized a series of new 4(3\(H\))-quinazolinone analogues (QS10) and screened for their potential hypoglycemic activity.[206]

![Chemical Structure of QS10](image)

Where:
- \(R_1 = \text{-CH}_3, \text{-Et}, \text{-Pr}, \text{-CH}_2\text{-C}_6\text{H}_4\)
- \(R_2 = \text{H}, \text{-Br}, \text{-Cl}, \text{-CH}_3\)
- \(R_3 = \text{H}, \text{-Cl}\)

Selvam, P. *et al.* have reported synthesis of a series of 6-bromo-2-(methyl or phenyl)substituted-4(3\(H\))-quinazolinonone derivatives (QS11a, QS11b) by condensing sulfanilamides (Sulfamoxole and Sulfadimidine) with 2-substituted-4-benzoazinones. The synthesized compounds were screened for antimicrobial and antiviral activity, and exhibited comparable antibacterial activity with that of standard sulfonamides.[207]
Zhou, Y. et al. have developed a general method to synthesize a class of $N$-(4-oxo-2-
substituted-4$H$-quinazolin-3-yl)substituted sulfonamide derivatives (QS12) in moderate to
good yield. About 90 compounds were reported using this method. This new method can be
applied in both, single compound and parallel fashion synthesis. [208]

Abdel, R. and Taha, M. have reported the reactivity of 3-amino-4-quinazolinone
derivatives towards some electrophilic and nucleophilic reagents. They subsequently used a
product (QS13) in the building of some interesting heterocycles as anticancer agent.[209]

Liu J.-F. et al. have reported the synthesis of 2,3-disubstituted quinazolin-4(3$H$)-one
derivatives (QS14). It involved the microwave promoted one-pot, two-step reaction
sequence by combining anthranilic acids, carboxylic acids, and amines.[210]

Radadia, V.R. et al. have prepared some new $N$-4-oxoquinazolin-3-yl sulfonamides
or aryl amide (QS15); and the products screened for their antimicrobial activity by
comparison with standard drugs were shown to have moderate activity.[211]
Morsy, J.M. has prepared newer heterocyclic derivatives of 2-(substituted-vinyl)-quinazoline-4-one (16) from the corresponding intermediate 4H-3,1-benzoaxazinone. [212]

![QS16](image)

Where:
- \( R \) - COOH, - NHAc, - Cl
- \( R_1 \) - CH\(_3\), - OCH\(_3\), - NO\(_2\), - Cl
- \( R_2 \) - OAc, - Cl, - OH

Patel, N.B. and co-workers have recently reported the synthesis and antimicrobial studies of several quinazolin-4(3H)-ones bearing (4-oxo-thiazolidinyl)sulfonamide derivatives (QS17), where \( R_6 = H \), \( R_6 = Cl \), and \( R_6 = Br \) with different aryl substitutions.[213]

![QS17](image)

Guryn, R. has synthesized six 1,4-diazepano[2,1-b]quinazolines as the title compounds I (\( R = Me, PhCH\(_2\), Ph, 4-MeC\(_6\)H\(_4\)SO\(_2\) (QS18), PhCH\(_2\)OCH\(_3\), H) in good yields by cyclocondensation reaction of thiolactams II (\( R = Me, PhCH\(_2\), Ph, 4-MeC\(_6\)H\(_4\)SO\(_2\), R\(_1\)R\(_2\) = bond, R\(_3\) = SMe) with 2-H\(_2\)NC\(_6\)H\(_4\)COOH in MeOH.[214]

![QS18](image)

Where:
- \( R = Me, PhCH\(_2\), Ph, 4-MeC\(_6\)H\(_4\)SO\(_2\) (QS18), PhCH\(_2\)OCH\(_3\), H) in good yields by cyclocondensation reaction of thiolactams II (\( R = Me, PhCH\(_2\), Ph, 4-MeC\(_6\)H\(_4\)SO\(_2\), R\(_1\)R\(_2\) = bond, R\(_3\) = SMe)

Singh, P. has reported the synthesis of some 2-alkyl-3-aryl-4(3H)-quinazolinone derivatives including QS19 as possible antitumor agents (nitrogen mustards).[215]

![QS19](image)
Venkataraman, S. et al. have designed a method for the preparation of quinazolinone derivatives (QS20) as the target compounds by the reaction of 4H-3,1-benzoxazin-4-one derivatives with sulfonamide. The title compounds were evaluated for antimicrobial activity against Gram-positive bacteria and Gram-negative bacteria in comparison with Lincomycin and Cefatazidime. These compounds were also evaluated for their anti-inflammatory activity in a carrageenan-induced rat paw edema model. It was found that they displayed as antimicrobial and anti-inflammatory as well.[216a] In another report, Muthumani, P. et al. have reported an efficient 2-step synthesis for the preparation of some novel quinazolinone derivatives (QS20). In the step-1, various 2-substituted 3,1-benzoxazin-4-one derivatives were formed by the reaction of anthranilates and Ac₂O or BzCl or (EtCO)₂O. In the step-2, the 3,1-benzoxazin-4-ones were condensed with sulfonamide (Valdecoxib).[216b]

Ukhin, L.Y. and Kuz'mina, L.G. have reported a synthesis of some newer 3,4-dihydroquinazolin-4-one and 1,2,3,4-tetrahydroquinazolin-4-one (QS211,b) derivatives, and studied the reactions of hydrazide, mesylhydrazide, succinylhydrazide, and maleylhydrazide of anthranilic acid with carbonyl compounds to prepare QS21.

Luhashi, A.B.N. et al. have reported the use of iminophosphoranes in intramolecular aza-Wittig reactions of (azidobenzoyl)oxobenzoisothiazoline dioxide with P(EtO)₃ to prepare fused quinazolinone such as oxobenzoisothiazoloquinazoline dioxide (QS21).[218]
Abdel-Aleem, A.M. et al. have reported certain derivatives of 3-aryl-2-(β-aryl-sulfonylhydrazinomethyl)-4(3H)-quinazolinone derivatives (QS22) of etiological interest, which were prepared by the treatment of appropriate 2-chloromethyl-4-quinazolinones with 4-R, C₆H₄SO₂NHNH₂, and evaluation of its antibacterial activity have shown the bactericidal activity less than that of Sulfanilamide.[219]

![Chemical Structure of QS22]

R₁ = H, Me, NH₂, Ac, Br, Cl, NO₂
R₂ = C₆H₄, 4-MeC₆H₄, 3-MeOC₆H₄, 4-BrC₆H₄, 3-ClC₆H₄, 4-ClO₂C₆H₄

Bossio, R. et al., during their studies on isocyanides and related compounds, have reported a synthesis of 3-substituted-2-arylsulfonylamino-3,4-dihydro-4-oxoquinazolines (QS23) via a novel three-component reaction approach. The reaction between isocyanides, methyl anthranilate, and chloramine T or chloramine B occurred easily in the presence of benzyltriethylammonium chloride to give the guanidines, which, upon heating, underwent a ring-closure reaction to afford the title compounds QS23. The authors have reported that in some cases, after an induction period, the reaction took place violently.[220]

![Chemical Structure of QS23]

Brzozowski, Z. et al. have reported synthesis of 4-chloro-N-(4-oxopyrimidin-2-yl)-2-mercaptobenzenesulfonamide derivatives including a 4-quinazolinone (QS24a), and the synthesized compounds were evaluated for their anti-HIV-1 integrase, and cytotoxic activities.[221a] Brzozowski, Z. and Saczewski, F. have synthesized some N-(3-amino-3,4-dihydro-4-oxopyrimidin-2-yl)-4-chloro-2-mercapto-5-methylbenzenesulfonamide derivatives including 2,3,6,8-tetrasubstituted-4-quinazolinone (QS24b), and all the prepared compounds were evaluated for their anti-HIV activity.[221b]
Rao, D.A. et al. have reported biological activities of certain derivatives of 3-aryl-4(3H)-quinazolinones (QS25) from corresponding 2-chloromethyl-3-aryl-4-quinazolin-(3H)-ones, which were obtained by cyclo-condensation of N-chloroacetylanthranilic acids with appropriate amines (R₁NH₂) in presence of PCl₃. All the synthesized compounds were screened for antifungal activity, some compound have shown total control of C. lunata and F. oxysporum.[222]

Where;
- R H; Br
- R₁ 4-MeC₆H₄, 2-MeC₆H₄, 4-O₂NC₆H₄, 2-O₂NC₆H₄
- R₂ NMe₂, NEt₂, N(CH₂CH₂OH)₂, piperidino, morpholino, 4-AcNH₂C₆H₄SO₂, etc.
- R₂ Cl (intermediate)

El-Sharief, A.M. Sh. and co-workers have published the synthesis of naphtho-fused azirino-pyrazolo- and 1,4,5-oxadiazepinoquinazolinones by oxidation of corresponding 3-aminoquinazolinones (QS26) with lead tetraacetate (Pb(OAc)₄) in DMC.[223]

Zia-ur-Rehman, M. et al. have reported the synthesis of bio-active 2-(4-hydroxy-1,1-dioxido-2H-1,2-benzothiazin-3-yl)quinazolin-4(3H)-one (QS27) by condensation of respective 4-hydroxy-1,2-benzothiazine-1,1-dioxide derivatives with anthranilamide followed by cyclization. Some of the assayed compounds showed marked antibacterial activity against B. subtilis amongst the various bacterial species tested.[224]

Goldfarb, D.S. has patented a method using lifespan-altering compounds for altering the lifespan of eukaryotic organisms, and screening for such compounds. In which, he had reported method for producing lifespan-altering compounds such as QS28.[225]
Recently, our group has reported the microwave assisted synthesis of various 4-(acetamido or amino)-N-(4-o xo-2-(alkyl or aryl)-substituted-4H-quinazolin-3-yl)-benzenesulfonamides (QS29) using heterocyclization approach via N-acylanthranilic acids under modified Grimmel's conditions and 4-(acetamido or amino)-N-(4-oxo-2-styryl substituted-4H-quinazolin-3-yl)-benzenesulfonamide derivatives (QS30) using cyclo-condensation approach via appropriate 2-styryl-4-benzoaxinones.[226]

\[ \text{QS29 (R}_6 = \text{R}_6 = \text{H/Cl/Br, R}_2 = \text{Alkyl, Aryl)} \]
\[ \text{QS30 (R}_6 = \text{R}_6 = \text{H/Cl/Br, R}_2 = \text{styryl)} \]

From the above literature survey, it was observed that several quinazolinone-linked-sulfonamide derivatives could be synthesized, which would have a variety of chemical or biological significances. However, there are very fewer reports on the synthesis of substitution of benzenesulfonamide (especially sulfanilamides) at position-2 of 4(3H)-quinazolinone ring respectively. Therefore, it was planned to produce some quinazolin-4(3H)-one derivatives linked with 4-aminobenzenesulfonamide at position-2 of this heterocyclic ring system, and the approaches to achieve such structurally diverse compounds is discussed in the subsequent sections.

### 1.4 INTRODUCTION TO AMINO ACIDS:

Amino acids form an important class of organic molecules,[227] that possess a basic amino group (-NH$_2$) and an acidic carboxyl group (-COOH) in their structure, that are attached by an organic chain. The key elements found in amino acids are carbon, hydrogen, oxygen, and nitrogen. Depending upon position of amino group from carboxylic acid, amino acids can be classified as alpha-, beta-, gamma-, delta- and so on. As well as depending on the source of availability they are classified as natural/unnatural amino acids.

### 1.4.1 ALPHA-AMINO ACIDS AND THEIR STRUCTURAL FEATURES:

Alpha-amino acids are the compounds having generic formula H$_2$N-CH(R)-COOH, (Figure 1.3.1), where R is a specific side chain substituent and the amino group is attached to the carbon atom adjacent to the carboxylate group (the alpha–carbon). All alpha-amino acids differ in which side-chain (R-group) is attached to their alpha carbon, and can vary in
size from just one hydrogen atom in glycine to a large heterocyclic group in tryptophan. These are the most common form found in nature. Depending upon side chain they are further subdivided in four small groups (neutral nonpolar, neutral polar, acidic and basic)

\[
\text{H}_2\text{N} - \text{C} - \text{H} \quad \text{R} \quad \text{H}_2\text{N} - \text{C} - \text{O} - \text{H}
\]

**Figure 1.3.1a** General structure of alpha-amino acids

The amine and carboxylic acid functional groups found in amino acids allow them to have amphiprotic properties. Carboxylic acid groups (\(-\text{CO}_2\text{H}\)) can be deprotonated to become negative carboxylate ions (\(-\text{CO}_2^-\)), and \(\alpha\)-amino groups (\(\text{NH}_2^-\)) can be protonated to become positive \(\alpha\)-ammonium ions (\(\text{NH}_3^+\)). At pH between 2.2 to 9.4, the predominant form adopted by \(\alpha\)-amino acids contains a negative carboxylate and a positive \(\alpha\)-ammonium group, ionized structure (Figure 1.3.1a), so has net zero charge. This molecular state is known as a zwitter-ion, from the German, Zwitter meaning *hermaphrodite* or *hybrid*. Isoelectric point is the pH values, at which the zwitter-ion predominates, but coexists in dynamic equilibrium with small amounts of net negative and net positive ions.

Depending upon need for the human development, amino acids can be classified as essential and non-essential amino acids. The amino acids regarded as essential for humans are phenylalanine, valine, threonine, tryptophan, isoleucine, methionine, leucine, lysine, and histidine. The amino acids arginine, cysteine, glycine, glutamine, histidine, proline, serine and tyrosine are considered conditionally essential in humans.

Most active bio-molecules (only one enantiomer is bio-active) are chiral where L-amino acids, are utilized as building blocks for bio-synthesis. The \(\alpha\)-C is a chiral centre for \(\alpha\)-amino-acids. The chiral centre gives rise to two stereoisomers. These two isomers are mirror images of each other. Such molecules, called enantiomers, cannot be superimposed on each other. The physical properties of enantiomers are identical except that they rotate plane-polarized light in opposite directions. Molecules that possess this property are called optical isomers ((+\(d\)) and (−\(l\))). The isomer is termed L or D depending on the position of non-hydrogen group around a molecule’s chiral carbon to the chiral carbon in either of glyceraldehyde isomers, where the molecule is placed with the more oxidized group on top, and the two lateral groups projected towards the front. Alternatively, “\(S\)” and “\(R\)” designators are used to indicate absolute stereochemistry. Almost all amino acids in proteins are “\(S\)” at the \(\alpha\)-carbon, with cysteine being “\(R\)” and glycine is not chiral.
Figure 1.3.1b Structure of common protenogenic amino acids depending upon side-chains
Other types of amino acids can also exist, when the carbon atom to which the amino group attached is separated from the carboxylate group by two or more carbon atoms (β- or γ-carbon), and these are therefore referred to as beta-amino acids (e.g. β-alanine) or gamma amino acids (e.g. β-aminobutyric acid). In addition to this, depending upon the involvement in the metabolic pathways they are classified as glucogenic and ketogenic amino acids.

1.4.2 HISTORY OF AMINO ACIDS:

The first few amino acids were discovered in the early 19th century. The first amino acid was discovered, in 1806, by the French chemists Vauquelin L.-N. and Robiquet P.J., who isolated a compound in asparagus that was subsequently named as asparagine.[228] Another amino acid that was discovered in 1810, was cystine,[229] although its monomer, cysteine,[230] was discovered much later, in 1884. Glycine and leucine were also discovered around this time, in 1820.[231] From 1898, the term “amino acid” in the English language is used.[232] Proteins were found to yield amino acids after enzymatic digestion or acid hydrolysis. In 1902, Emil Fischer and Franz Hofmeister proposed that proteins are the result of the formation of bonds between the amino group of one amino acid with the carboxyl group of another in a linear structure which Fischer termed peptide.[233] For this leading discovery in the biochemistry, Emil Fischer was awarded the Nobel Prize in 1903.

1.4.3 AMINO ACIDS TO HETEROCYCLIC COMPOUNDS:

Naturally-occurring α-amino acids, building blocks of proteins, constitute important materials in all disciplines of biology, medicine, biochemistry, and chemistry. The α-amino acids have great potential as chiral building blocks for synthesis of optically active materials; polyfunctional unusual amino acids, amino-polyols, and peptide mimics like enzyme inhibitors, amino-sugar antibiotics, and sympatho-mimetic amines.[234] Numerous efforts subjected to develop syntheses of optically pure amino acids: asymmetric derivatization of glycine, electrophilic amination of enolates, nucleophilic amination of α-substituted acids, asymmetric Strecker synthesis, asymmetric hydrogenation of dehydro-amino acids, and enzymatic syntheses of α-amino acids.[235] The synthesis of efficient assembly of complex molecules from readily available building blocks is an important task for organic chemists.[236] The proteinogenic amino acids possess limited but significant number of functional groups, which facilitate synthetic operation with protection deprotection-activation chemistry is thoroughly documented,[237] and they are readily available commercially, usually in both enantiomeric forms.
Researchers in this field have relied heavily on enantiospecific processes proceeding from the chiral pool to gain access to this broad class of compounds. Of all the members of the physiologically active compounds, amino acids, due to their versatility, have been the most extensively used for the synthesis of enantiomerically pure heterocycles. [238]

The proteinogenic α-amino acids can serve as precursors to a wide range of other naturally occurring heteroaromatic substances including alkaloids, antibiotics and peptides.[239] However, the great diversity of heterocycles alongside their chemical, biological, and technological relevance justifies a permanent effort to devise efficient synthetic procedures for their preparation. Further, special attention has been devoted to the development of methodologies for the synthesis of optically active heterocyclic compounds, due to their biological importance. In this context, proteinogenic α-amino acids are the most extensively used precursors for the synthesis of enantiomerically pure heterocycles, because they constitute a natural source of optical activity (chirality) that is readily available and display a multifunctional character that facilitates synthetic transformations.[240]

The proteinogenic alpha-amino acids as optically pure starting materials for the synthesis of heterocyclic compounds, provides additional information on the utility of the products in selected synthetic transformations, and focuses mainly on synthetic methods of general applicability to different amino acids. The diverse synthetic approaches have been organized according to the nature of the reactions that the α-amino acid functional groups undergo to generate the heterocyclic skeleton (i.e., intramolecular or intermolecular cyclizations and cycloaddition reactions).[241] The ease of access to α-amino acids in optically pure forms, their diversity, and their multifunctional character makes them extremely valuable starting materials for the asymmetric synthesis of complex molecules by means of stereoselective transformations. In this context, we have tried to provide a general perspective, rather than an exhaustive revision due to the vast literature in the field of the applicability of α-amino acids for the asymmetric synthesis of heterocycles. The synthetic methodologies have been organized according to the type of cyclization that the α-amino acid undergoes to assemble the heterocycles (intramolecular or intermolecular cyclizations and cycloadditions). In this way, it is easy to realize the potential behind the α-amino acid functional moieties to generate a great diversity of heterocyclic systems.[240-242]

In continuing search for the compounds producing interesting biological activities, the N-heterocycles especially 4-quinazolinone is of our interest would provide an excellent starting point for further investigation. Applications of amino acids in the synthesis of quinazolinones will provide elegant entry in marshalling the newer quinazolinone entities.
1.5 QUINAZOLINONE CORE DERIVED FROM AMINO ACIDS:

In addition, a large number of research groups have reported a variety of synthetic approaches to biologically active natural/synthetic quinazolinone alkaloids isolated so far, which have been included in the published literature reviews.[74, 79, 80] Due to the unique structural features and pharmaceutical relevance of quinazolinone class of compounds, much attention has been devoted for the development of an efficient synthesis of quinazolinone natural products and a library based on these scaffolds as well.[14]

The use of several natural and unnatural \(\alpha\)-amino acids in combination for the design of natural, pseudo-natural, and synthetic hybrid quinazolinone derivatives with tailored properties is the most challenging task, while the applications of \(\beta\)-amino acids in the synthesis of quinazolinones will provide an elegant entry to new quinazolinone entities.[74] Therefore, some representative approaches that utilize the functionalization of amino acids in the synthesis of quinazolinone especially unnatural quinazolinone derivatives published recently are discussed in this section.

Mhaske S.B. and Argade N.P. have reviewed the chemistry of recently isolated naturally occurring quinazolinone alkaloids along with their bioactivity.[74] The combination of unique structural features, extensive functionalization, and very high biological activity found in the quinazolinone alkaloids have presented an elegant challenge to the synthetic chemists to design these molecules in a shorter and smarter fashion. All the important synthetic approaches to the quinazolinone alkaloids isolated as natural products and their analogues, in the different categories according to their structural features and further depending on their substitution pattern, have been illustrated and are discussed in detail in this review.[74]

Perusal of this literature review revealed that the closure of the quinazolinone ring is a critical step in all of these syntheses. From the synthetic chemistry point of view, there are some important protocols developed during the synthesis of quinazolinones to effect the cyclization.[243, 244] One approach employs isomerisation of intermediate 4-imino-4\(H\)-3,1-benzoxazines into quinazoline-4-ones under basic or acidic conditions,[243b] which was discovered by Mazurkiewicz [243a] and modified by Ganesan [243c]. This transformation has been used in the stereoselective synthesis of fumiquinazolines A,[243g,k] B,[243g,k] C,[243j,k] E,[243j,k] F,[243f] G,[243c,d,f] H,[244j,k] I,[244g,k] and others. Another widely used cyclization method is an aza-Wittig cyclization of imines (Eguchi protocol).[244] This protocol has been successfully applied to the stereoselective synthesis of amauromine and 5-\(N\)-acetylardeemin,[245] fumiquinazoline G and its dehydro-
derivative,[246] glyantrypine, fumiquazoline F, and other 2,4-dihydro-1H-pyrazino-
[2,1-b]quinazoline-3,6-diones,[247] as well as asperlicin,[248a] and benzomalvin A,[248b]
natural products. To date, the Ganesan protocol provides the best conditions for the
dehydration of diamides to form a quinazolinone moiety, though it proceeds through the
intermediate benzoxazine–amidine. Hence, efficient reagent and reaction conditions to
effect the direct transformation to the quinazolinone are presently in need of discovery.
Still, a more detailed investigation is needed for the development of reaction conditions that
would facilitate the condensation of benzoxazinones with aliphatic/aromatic amines, which
is otherwise difficult or low yielding.[74]

Zhichkin, P. and co-workers have developed an efficient three-step synthesis of 2,3-
disubstituted 3H-quinazoline-4-one derivatives (AQ1) from Boc-protected amino acids, and
2-nitrobenzoic acids or anilides (or benzylamide) as commercial starting materials.[249]
The reaction of imidoyl chloride of 2-nitrobenzoic acids with α-amino acid followed by
reductive cyclization affords enantiomerically pure (ee >93%) quinazoline-4-ones in good
overall yield (Scheme 1.3.1). However, somewhat lower yields in the case of Boc-L-serine
are the result of side reactions of the OH-group. Alternatively, synthesis of hindered
quinazolinones was achieved by employing KHMDS in the reaction. A comparison with the
existing approaches has indicated that this method could be superior for hindered substrates.

Scheme 1.3.1

When Zhichkin, P. et al. have applied the 4-imino-4H-3,1-benzoxazinone approach
following the Mazurkiewicz-Ganesan protocol,[243a,c] afforded 4-quinazolinones (AQ1)
with high purity products (Scheme 1.3.2). However, the overall yield was disappointing
(14% from 2-amino-N-benzamide).

Scheme 1.3.2
Further, Zhichkin, P. et al. have examined Egichi protocol,[244] which employ reaction of amides with 2-azidobenzoyl chloride, was not successful (Scheme 1.3.3), as no reaction of amides with acid chloride was observed in the presence of either NaHMDS or NEt$_3$, DMAP. A likely explanation for this failure is the decreased reactivity of both the amide nitrogen and the acid chloride carbonyl resulting from their ortho-substitution.

![Scheme 1.3.3](image)

Kshirsagar, U.A. and co-workers have demonstrated hexamethyldisilazane-iodine (HMDS/I$_2$) induced the intramolecular dehydrative cyclization of diamides as a simple and efficient general approach to access various quinazolinone scaffolds, including peptide-mimetic examples.[250] The protecting groups –Boc, –Fmoc and –Cbz tolerated the present reaction conditions to produce corresponding 4-quinazolinones (AQ2) from various amino acids without any racemisation, as shown in Scheme 1.3.4. The present protocol has also been used as a key step for the efficient four-step syntheses of the naturally occurring quinazolinones, such as sclerotigenin, (-)-circumdatin-F and (-)-fumiquinazoline-F.

![Scheme 1.3.4](image)

Brunton, S.A. et al. reported a synthesis of small family of 3-phenylsubstituted quinazolinone ureas (AQ3a,b) as potent modulators of Hedgehog protein function, which was derived by the functionalisation of N-Cbz-glycine.[251] Preliminary SAR studies of the urea substituent led to a nanomolar Hedgehog antagonist.
Na, Y.H. and co-workers have reported novel quinazolinone derivatives as 5-HT7 receptor ligands.[252] The library of quinazolinone (AQ4) was designed and synthesized in good yields by an efficient three component one-pot reaction from anthranilic acids, anilines, and N-Boc-glycine. The quinazolinone library of total 85 compounds possessed with three building blocks, anthranilic acids, aromatic rings, arylpiperazinyllalkanoic acids, each of which has different substituents (X, Y, R₁, and R₂) on the aromatic rings and different carbon chain length. The binding affinities of all the synthesized compounds were obtained by radio-ligand binding assay for the 5-HT7 receptor. Among the 85 compounds, 24 compounds show very good binding affinities with IC₅₀ values below 100 nM. During in vivo animal study, some synthesized compounds really have the antidepressant activity in the forced swimming test in mice.

Hirota, S. et al. have reported an efficient synthesis of imidazo- and pyrimido-[1,2-b]benzo-1,2,4-thiadiazine-1,1-dioxides by the tandem aza-Wittig reaction/intramolecular NH-nucleophilic addition or NH-nucleophilic substitution cyclization methodology.[253] Various quinazolinone derivatives (AQ5a) were synthesized through the aza-Wittig reaction–tandem cyclization strategy (Scheme 1.3.5). One of two amino acid esters employed, i.e. (L)-alanine methyl ester was incorporated as a building block into the corresponding iminophosphorane starting materials, and obtained optically active entitled imidazo[2,1-b]quinazolinones (AQ5b).

![Scheme 1.3.5](image-url)
Meyyanathan, S.N. et al. reported a design and synthesis of a new series of 2-methyl-3H-quinazolin-4-one derivatives (AQ6a-d) substituted with amino acids, such as glycine, L-lysine, L-cysteine, and L-glutamic acid, and aryl amine at the position-3.[254] Further, the compounds were screened for their in vivo antimalarial activity using the rodent malaria parasite *P. yoelii* (N-67) with the Swiss mice model. The compounds were also tested for their antibacterial activity. Some of the compounds have shown better bio-activity.

![AQ6a](image1.png) ![AQ6b](image2.png) ![AQ6c](image3.png) ![AQ6d](image4.png)

Jankowski, F. et al. have developed a general method for the synthesis of 1,3-disubstituted-imidazo[1,5-a]quinazolin-5-(4H)-one derivatives (AQ7a).[255] This process involves initial microwave-assisted synthesis of quinazolinone derivatives (AQ7b) by the reaction between anthranilamide and N-(Boc or acyl)-derivatives of amino acids, viz glycine, alanine, Leucine and phenyl alanine, followed by intramolecular cyclodehydration under acidic conditions. In case of 3-monosubstituted-imidazo-quinazolinones (R1=H), the procedure needs the formation of formamide derivatives by deprotection and formylation of the Boc-intermediates.

![AQ7a](image5.png) ![AQ7b](image6.png)

Where: R1, R2 = H, Me, iPr, Bn, tBu, CH3, OtBu, H, Ph

Recently, W. Xu and H. Fu have reported amino acids as the nitrogen-containing motifs in copper-catalyzed domino synthesis of *N*-heterocycles.[256] A Cu-catalyzed domino method for synthesis of quinazolinones (AQ8) was developed using readily available α-amino acids as the nitrogen-containing motifs (Scheme 1.3.6). The domino process underwent Ullmann-type *N*-arylation, decarboxylation, aerobic oxidation, and intramolecular addition. The protocol used cheap and readily available CuBr as the catalyst, substituted 2-halobenzenamides and α-amino acids as the starting materials, and economical and environmentally friendly air as the oxidant, and the corresponding quinazolinones were obtained in moderate to good yields. This method provided a new and useful strategy for construction of *N*-heterocycles.
Mayer J.P. and co-workers have reported a solid-phase synthesis of substituted 4(3H)-quinazolinone derivatives. In addition, diversity at position-3 was realized by employing Fmoc-N-amino acid derivatised polymer support. Anthranilamide precursors and aldehydes were combined under acidic conditions to furnish 1,2-dihydro-quinazolinone skeletons (Scheme 1.3.7). Dehydrogenation of this skeletons using KMnO4 followed by trifluoroacetic acid cleavage afforded the desired quinazolinone compounds (such as AQ10) in acceptable yields and purities. An advantage of this approach is that the Fmoc-amino acid and anthranilamide derivatised Wang resins could be derived from either nitrobenzoic acids or isatoic anhydrides, allowing a range of aromatic substitution patterns to be accessed.

Recently, Liu, J.F. has published a review on rapid syntheses of biologically active quinazolinone natural products using microwave technology. A highly efficient three component one-pot reaction sequence, was developed that allows in situ construction of key intermediates from the simplest and easily available precursors (anthranilic acids and amino acids), and utilize only a single reagent (P(PhO)3) to complete the total synthesis of quinazolinone natural products, such as (i) natural products with pyrazino[2,1-b]quinazoline-3,6-dione core scaffold, such as glyantipine, fumiquazolines F and G, ficalin B, alantripinione, fumiquazolines H, and ardeemin; (ii) natural products with quinazolinobenzodiazepine core scaffold, such as Sclerotigenin, Circumdatins A-G,
Asperlicin C, asperlicin E, Benzomalvin A; and (iii) pyrrolo[2,1-b]quinazoline type of alkaloids,[258d] such as deoxyvasicinone, 8-hydroxydeoxyvasicinone, vasicinone, Isaindigotone, Luotonin A, pyrroloquinazoline alkaloid and Rutaecarpine belongs to the quinazolino-carboline type of alkaloids[258c] and (iv) 4-oxy-linaric acid, a quinazolinone analogue of the newly isolated natural product, linaric acid. One critical hurdle faced was the identification of an appropriate protecting group for α-amino acids. The ideal protecting group needed to be compatible with the microwave reaction conditions for the formation of benzoxazinones and quinazolinone. To establish the forward synthetic route, formation of quinazolinones was first examined by employing amino acids with standard protecting groups such as Boc, Cbz, Bn, and Fmoc. Boc-amino acids were identified as the optimal performers under the reaction conditions.[80]

Perusal of this literature review revealed that various amino acids could be incorporated at the position-2 or position-3 or at both the positions of this heterocyclic ring skeleton to produce (2 or 3)-monosubstituted or 2,3-disubstituted quinazolinone derivatives (AQ10), and is shown below by a general reaction pathway (Scheme 1.3.8).

![Scheme 1.3.8](image)

The protocol established by Liu et al. has been employed by Leca, D. et al.[259] and Watanabe, T. et al.[260] for the synthesis quinazolinones and pyrazino[2,1-b]-quinazoline-3,6-diones leading to natural products of this class as shown in Scheme 1.3.9.

![Scheme 1.3.9](image)

Leca, D. et al. have reported acid-catalyzed aza-diels-alder reactions for the total synthesis of (±)-Lapatin B, wherein the intermediate pyrazino[2,1-b]quinazoline-3,6-dione was prepared by using Boc-alanine as a starting material and glycine methyl ester was utilized as a substituent at position-3 of quinazolinone ring (AQ11a, R=Me).[259]
Watanabe, T. and co-workers have disclosed synthesis of alantrypinone derivatives and their antagonist activity toward insect GABA receptors.[260] In an attempt to obtain compounds with greater activity, a series of racemic alantrypinone derivatives were systematically synthesized using hetero Diels–Alder reactions of intermediate pyrazino[2,1-b]quinazoline-3,6-diones, and total 34 compounds were examined for their ability to inhibit specific binding of [3H]40-ethynyl-4-N-propylbicycloorthobenzoate, a high-affinity non-competitive antagonist, to housefly-head membranes. The assay results showed that (i) there is no significant difference between the potencies of natural (+)-alantrypinone and its synthetic racemate; (ii) amide of amines at two positions are important for high activity. The preparation involved initial formation of quinazolinones as similar to AQ11a.[260]

Previously, Zinc triflate-catalyzed synthesis of pyrazino[2,1-b]quinazoline-3,6-diones was reported by Tseng, M.-C. and Chu, Y.H., which was conveniently achieved in only three steps, starting from the amino acid-bound Wang resin.[261] Using zinc triflate, the direct one-pot double cyclodehydration of linear tripeptides {open-chain tripeptides such as (Gly-Abz-L-Phe, L-Ala-Abz-L-Ala, and D-Ala-Abz-L-Ala)}, where anthranilic acid (Abz) can be at the C-terminal, the N-terminal in to the total synthesis of pyrazino[2,1-b]-quinazoline-3,6-diones on solid support was achieved with good overall yields in short reaction time as shown in Scheme 1.3.10. The formation of desired compounds would have been formed via corresponding quinazolinone derivatives (AQ11a, R1= appropriate side-chain). They have also investigated the formation of ring-expanded target molecules [1,4]-diazepino[7,1-b]-quinazoline-2,11-diones from their linear tripeptide precursors, Gly-Abz-β-Ala and L-Phe-Abz-β-Ala, using Zn(OTf)2. In these cases, β-Ala was used rather than α-amino acid. Following cyclodehydration and cyclazive cleavage, low amounts of the desired products were isolated.
1.6 QUINAZOLINONE–SULFONAMIDE HYBRIDS DERIVED FROM AMINO ACIDS:

There is limited number of reports on the quinazolinone derivatives, derived from amino acids, and having sulfonamide motif in their backbone at either position-2. Hence, significance of work has been highlighted as under.

Liu, J.-F. et al. have disclosed the preparation of quinazolinone derivatives (AQ12a) useful in the treatment of proliferative diseases and cancer.[262] Desired compounds (AQ12a) and quinazolinone-sulfonamides (AQS1a-d) were prepared using one-pot methodology in good yield from amino-acids to gave corresponding amino-quinazolinone intermediate followed by NH₂-deprotection and amidation with acid/acyl chloride/sulfonyl chloride. In bioassays for antitumor activity, AQ12b was found to possess an IC₅₀ value of 0.028 mM against HsEg5 ATPase, and 0.36 mM and 0.42 mM in MTS assay using NCI H460 and NCI A549 cell line, respectively. Hence, AQ12a and their pharmaceutical compounds are useful for the treatment of a cell proliferative disorder, such as a cancer.

Johnson, M. et al. have described the synthesis of a series of quinazolinone-amide derivatives (AQ13), by one-pot approach using 2-aminobenzoic acid and Boc-amino acid, as antagonists of CXCR3 (a chemokine receptor).[263] The quinazolinone-sulfonamides (AQS2a,b) was achieved by treatment of corresponding amino compound with the sulfonyl chlorides in pyridine. However, replacement of the amide by an amine (alkyl chain) or a sulfonamide resulted in significant loss of activity.
Lemoine, R.C. and co-workers have explored the discovery of a series of quinazolinone-based fungal efflux pump inhibitors by high-throughput screening for potentiation of fluconazole in *C. albicans*. Synthesis of screening hits from sulfonamide compound (ASQ3) led to the discovery of an analogue with greatly improved physical properties and activity against clinically-relevant *Candida spp.*[264]

Watkins, W.J. and co-workers has systematically extended the earlier work by exploration of SARs of a novel series of fungal efflux pump inhibitors with respect to potentiation of the activity of fluconazole against strains of *Candida albicans* and *Candida glabrata* over-expressing ABC-type efflux pumps.[265] Some quinazolinone-sulfonamide hybrid molecules (ASQ4) were found to be less active among the other variants of urea moiety, which have shown potent activity.

Richard, M. and co-workers have disclosed a preparation and pharmaceutical compositions of quinazolinone amide compounds (AQ14), including several quinazolinone-sulfonamide derivatives like AQS5 as modulators of nuclear receptors, particularly farnesoid X receptor (FXR) and/or orphan nuclear receptors.[266]

El-Sharief, A.M. Sh. and co-workers have employed amino acids for the first time in the synthesis of heterocyclic systems for the preparation of 3-amino-quinazolinone derivatives (AQS) from various N-(tosyl)amino acids, which upon nucleophilic interaction with different reagents resulted some novel triazinoquinazolinones, triazepinoquinazolinones and triazocinoquinazolinones of potential biological interest. Some of the products showed mild to moderate antimicrobial and antifungal activities.[267]
Recently, IUPAC has placed a similar method in to the practice for the preparation of similar compounds under the same experimental procedure using the same starting materials (n=1).[268]

![ASQ5](image)

Where:
- \( R_2 = \text{H; CH}_3; \text{CH}_2\text{CH}_3; \text{H (n=2); CH}_3(\text{CH}_3)_2; \text{CH}_2\text{CH}(\text{CH}_3)_2 \)
- \( R_4 = \text{H (n=1); CH}_3 \)

Gao, Y. has patented the compositions containing \( N \)-aminoquinazolinones (AQ15a) and \( N \)-hydroxyquinazolinones (AQ15b) and methods for preparing combinatorial libraries which find use in synthesis of combinatorial libraries. The disclosed method include synthesis of 3-hydroxy- and 3-amino-4(3H)-quinazolinones performed on a solid support or in solution at ambient temperature, especially via the reaction of various Fmoc-protected amino acids with appropriate 2-aminobenzamide compounds, using PyBrOP in DMAC as the condensing agent. The resulting products were deprotected with piperidine and reacted with several acid chlorides and fewer sulfonyl chlorides and treated with TFA to cleave the resin, yielding a library of different 3-(hydroxyl-/amino-)quinazolin-4-ones (AQ16a,b) including corresponding 3-(hydroxyl-/amino-)quinazolinone-sulfonamides (AQSa and AQSb), which were stored for further bioassay.[269]

![AQ15a,b](image)

- a: \( R = -\text{CH}_3 \)
- b: \( R = -\text{NH}_2 \)

- \( R_1 = \text{H; Me; MeO; halo; NO}_2; R_2 = \text{amino acid side-chain; } R_3 = \text{sidechain forming a carbamate, sulfonamide, or urea group; } R_4 = \text{alkyl, substituted phenyl group} \)

There are very fewer reports for the synthesis of quinazolinone-linked-sulfonamides which utilize amino acids especially arylsulfonl amino acids as starting material to tolerate the linkage at position-2.[267-269] Further, these reports include synthesis of such 2,3-substituted-4-quinazolinones having amino-group at position-3.

Perusal of the above literature survey revealed that there are no specific report appear in which quinazolinone-sulfonamide derivatives have utilized amino acids as an initial precursor for the construction of linkage between quinazolinone ring and sulfonamide moiety especially sulfanilamide at position-2, as well as various substitutions at position-3.
1.7 HYBRID MOLECULES BY STRUCTURAL HYBRIDIZATION APPROACH:

One of the main goal of organic synthesis in its inception has been search for new compounds that exhibit novel physical, chemical and biological properties.[270] In this quest, human hunch and leads from nature have played a pivotal role. Nature makes natural products of mystifying diversity and complexity and these are generally derived through specific biosynthetic pathways like, shikimate, polyketide or mevalonate, leading to a particular class of compounds.[271] Many biologically active natural products are also derived through mixed biosynthesis. This may involve either integration of the different biosynthetic pathways to generate complex structures or eventuate in covalent linkage between components derived through different pathways, e.g. indole alkaloids, strychnine.

Many of the natural products arising through such mixed biosynthesis have been found to exhibit unusual properties and biological activity as different molecular segments act jointly to control and modulate conformation, recognition, communication, transport and solubility among other properties. These promising features of molecules of mixed biosynthetic origin perhaps led to the idea of generating novel molecular entities by rationally or by senendipty combining two or more different classes of compounds of natural or synthetic origin. The underlying expectation being that combination of structural features of two or more active substances into one molecule or their covalent coupling may either enhance or modulate the desired characteristics of individual components or lead to new types of properties. An appealing feature of this approach is that it may provide many possibilities for generating a diverse array of new types of molecules for application in biology and material science.

During the past two decades design of such entities has been receiving increasing attention and these have been referred as ‘hybrid molecules’ or ‘conjugates’ or ‘chimeras’ or even ‘mermaids’ in the literature.[272] Although, in strict terms ‘hybrid molecules’ refers to structural motifs derived through domain integration of two or more entities, in present thesis it has been used in an all inclusive sense.

Such entities can be derived either through integration of structural features or through covalent linkage of two or more natural or unnatural mlecules. The main aim to craft such systems has been to either amplify certain characteristics, particularly the therapeutic spectrum based on natural product leads. Synthesis of such entities can either involve complicated synthetic manipulations for structural integration or straightforward connectivity through functional groups.[272]
Hybrid molecules are also defined as chemical entities with two or more than two structural domains having different biological functions (chimeric structure is also a possible naming, but the use of hybrid is preferred) and multiple activity indicates that a hybrid molecule can acts as distinct pharmacophores.[273] Both entities of hybrid molecule are not necessarily acting on the same biological target. These hybrid molecules should be confused with prodrugs. When a drug candidate has a weak bioavailability, prodrug strategy is highly useful to correct the pharmacokinetic and pharmacodynamic profiles of a valuable lead.[274] The hybrid molecule strategy is different than the fragment-based lead discovery as well. The fragment-based approach in drug design is the improvement of the biological activity of a molecule fragment by the addition of chemical functions able to bind to adjacent regions of the active site when the protein target is known.[275]

The design of new drugs with better physiochemical properties, adequate absorption, distribution, metabolism, and excretion, effective pharmacological potency and low toxicity remains is a challenge. Actually, there are four main different routes which can be explored to elaborate affordable and efficient drugs: (i) a drastic reduction of the production costs of biological drugs, (ii) improvements of drug discovery via “computer-assisted combinatorial methods”, (iii) going back to an extensive exploration of natural products as drug sources, and (iv) drug discovery by manbrain- a human inspiration, including serendipity, rational-drug design, and bio-inspired design.[273] These last two items are fascinating areas for researchers in universities and pharmaceutical companies. Molecular manipulation of a known drug to isolate or enhance a single pharmacological property, from a drug's pharmacological profile is a common “trick of the trade” in medicinal chemistry.[276]

Molecular hybridization is a molecular modification approach to obtain multiple ligands or compounds with pharmacokinetic advantages over concomitant administration of two different drugs.[277] The term “multiple ligands”, proposed by Morphy et al., applies to drugs that recognize more than one receptor. The advantages of multiple ligands are their ability: (1) to activate different targets by a single molecule, thereby increasing therapeutic efficacy and (2) to change the bioavailability profile in the cell and be effectively eliminated after exerting their effects.[278] The hybridization process is closely related to the strategy of obtaining a mutual prodrug, with the main difference being that the prodrug action is dependent on its in vivo cleavage while hybrid compounds can also act “per se” at their specific receptors or targets (Figure 1.5.1). Hybrid compounds can be constructed by linking pharmacophore subunits directly or with spacer agents. The simple association of two distinct active principles can also be considered a hybrid compound.
Molecular hybridization— a structural hybridization approach is a new concept in drug design and development based on the combination of pharmacophoric moieties of different bioactive substances to produce a new hybrid compound with improved affinity and efficacy, when compared to the parent drugs.[279] Additionally, this strategy can result in compounds presenting modified selectivity profile, different and/or dual modes of action and reduced undesired side effects. Several examples of this rather recent approach for drug design, discovery and pharmaco-modulation focused on new innovative hybrid compounds with unprecedented bioactivity such as anti-inflammatory, platelet anti-aggregating, analgesic, anti-infectious, anticancer, antimalarial, anti-microbial, cardio- and neuroactive properties has been well-documented in literature.[272, 273, 278, 280, 281] Although the examples of hybrid molecules are plenty, herein we wish to highlight some of the recently crafted quinazolinone systems apart.

The antimicrobial activity associated with both quinazolines and nalidixic acid moieties prompted Grover and Kini to synthesise some nalidixic acid derivatives carrying biodynamic heterocyclic systems (quinazolones) at position-3 with an objective to obtain biheterocycles of enhanced biological activities.[282] The compounds (Hybrids H1) so obtained were screened for antifungal and antibacterial activities. Almost all the synthesised hybrids have displayed enhanced antimicrobial activity in comparison to pure nalidixic acid.
Liu, J.-F. and co-workers have designed and synthesized a focused natural product-templated library, i.e. hybrid chemical series of natural products, mackinazolinone and isaindigotone.[283] The 44-membered library of hybrid (H2) was screened in a search for the biochemical target. The tubulin assay suggested that this class of compounds are antimitotic agents and exert their action through the inhibition of tubulin polymerization.

Kumar P. and co-workers have reported design and synthesis of some novel 2-(substituted)-3-[(substituted]amino]quinazolin-4(3H)-one hyrids (H3) with the objectives to utilize molecular hybridization of Methaqualone, having quinazolin-4(3H)-one nucleus and 4-(aryloxy) phenyl semicarbazones and replacement of methyl group at position 2 of synthesized compounds by phenyl and n-propyl group, as well as to study their effect on anticonvulsant activity.[284]

Structural hybridizations presumably impart new physico-chemical and biological properties, and at a standstill is the major line approach to graft a diverse molecular backbone by means of the structural variation of a various lead molecules. Apart from these, several structural modifications in the 4(3H)-quinazolinone nucleous and sulfonamide motif are published in direct/indirect manner. Some important work reported for the structural hybridization in quinazolinone nucleous has been discussed earlier.
1.8 MICROWAVES IN ORGANIC SYNTHESIS:

Heating chemical reactions by microwave energy continues to be a popular theme in the organic and medicinal chemistry community. It has been known since the first published reports in 1986 by groups of Gedye and Giguere, on the use of microwave irradiation to carry out organic chemical transformations, numerous articles have been published in this fast moving and exciting field, generally referred to as microwave assisted organic synthesis (MAOS).[285] This “non-conventional” synthetic method has shown broad applications as a very efficient way to accelerate the course of many organic reactions, producing high yields and higher selectivity, lower quantities of side products and, consequently, easier work-up and purification of the products. MAOS is considered as a “green” technology, principally since many organic reactions can be carry out in solvent-free conditions.[286]. Therefore, the growing interest in academic and industrial research laboratories is not surprising and is reflected in an exponential increase in the productivity of scientific papers, books,[287] and reviews [288] related to the use of this technology.

In recent years, researchers have applied microwave as a tool in order to diminish reaction time, avoid side products, increase yield and simplify the course of reactions for combinatorial chemistry.[289]

A brief introduction of microwave assisted organic synthesis is given below:

1.5.2.1 INTRODUCTION TO MICROWAVE:

Microwaves are electromagnetic waves, which contain electric and magnetic field components. The microwave region of the electromagnetic spectrum lies between 1 cm-1 m (0.3 to 300 GHz) and in order to avoid interfering with radar and telecomunication activity which operate within this region, the frequencies allotted for microwave dielectric heating (also referred as microwave heating or dielectric heating) are 918 MHz and 2.45 GHz, among this the latter frequency being used most often. The latter is also applied in domestic microwave ovens. These frequencies correspond to respective wavelengths of 33.3 and 12.24 cm, which are in the region between the infrared and radiowave wavelengths in the electromagnetic spectrum.

The energy of the microwave photon in this frequency region (0.0016 eV) is too low to break chemical bonds and is also lower than the energy of Brownian motion. It is therefore clear that microwaves cannot initiate chemical reactions but it enhances the rate of chemical reaction.[290-293]
### 1.5.2.2 BACKGROUND AND THEORY:

Microwave heating (dielectric heating) is a very efficient process because microwave couple directly with the molecules that are present in the reaction mixture, leading to a fast rise in temperature, faster reactions and cleaner chemistry. The two fundamental mechanisms for transferring energy from microwaves to the substance are dipole rotation and ionic conduction. Dipole rotation is an interaction in which polar molecules try to align themselves with the rapidly changing electric field of the microwave. Ionic conduction mechanism consists in the instantaneous superheating of the ionic substance due to the ionic motion generated by the electric field. When the temperature increases, the transfer of energy becomes more efficient. Since their ionic character, ionic liquids absorb microwave irradiation extremely well and transfer energy quickly by ionic conduction. The MW theory and how the MW increase reactions rate has been recently discussed in details by several authors [287, 288, 290, 291].

If two samples containing water and dioxane respectively are heated in single mode microwave cavity at a fixed radiation power and for a fixed time the final temperature will be higher in the water sample (Figure 1.5.2).

![Figure 1.5.2](image)

**Figure 1.5.2** Temperature increases of water and dioxane respectively, at 150 W MWI. The upper curve represents water and the lower plot represents dioxane.

In order to understand why this phenomenon occurs, it is necessary to know the underlying mechanisms of microwave-dielectric heating. As with all electromagnetic radiation, microwave radiation can be divided into an electric field component and a magnetic field component. The former component is responsible for the dielectric heating, which is effected via two major mechanisms.
**Dipolar polarization mechanism:** One of the interactions of the electric field component with the matrix is called the dipolar polarization mechanism. For a substance to generate heat when irradiated with MWs it must possess a dipole moment, as has a water molecule. A dipole is sensitive to external electric fields and will attempt to align itself with the field by rotation (Figure 1.5.3).

![Figure 1.5.3](image) Dipolar molecules which try to align with an oscillating electric field.

Under low frequency irradiation, molecule will rotate in phase with the oscillating electric field. The molecule gains some energy by this behavior, but the overall heating effect by this full alignment is small. Alternatively, under the influence of a high frequency electric field the dipoles do not have sufficient time to respond to the oscillating field and do not rotate. Since no motion is induced in the molecule no energy transfer takes place and therefore no heating occurs. In the microwave radiation region, the frequency of the applied irradiation is low enough so that the dipoles have time to respond to the alternating electric field and therefore rotate. The frequency is, however, not high enough for the rotation to precisely follow the field. Therefore, as the dipole re-orientates to align itself with the electric field, the field is already changing and generates a phase difference between the orientation of the field and that of the dipole. This phase difference causes energy to be lost from the dipole by molecular friction and collisions, giving rise to dielectric heating.

**Conduction mechanism:** If two samples containing distilled water and tap water respectively are heated in a single mode microwave cavity at a fixed radiation power and for a fixed time the final temperature will be higher in the tap water sample (Figure 1.5.4).

![Figure 1.5.4](image) Temperature increases of distilled and tap water respectively at 150 W MWI. The upper curve represents tap water and the lower plot represents distilled water sample.
This phenomenon is due to the second major interaction of electric field component with the sample, the conduction mechanism. A solution containing ions or even a single isolated ion with a hydrogen bonded cluster in the sample, the ions will move through the solution under the influence of an electric field resulting in expenditure of energy due to an increased collision rate converting the kinetic energy to heat (Figure 1.5.5).

![Charged particles in a solution will follow the applied electric field.](image)

**Figure 1.5.5** Charged particles in a solution will follow the applied electric field.

The conductivity mechanism is a much stronger interaction than dipolar mechanism with regard to the heat-generating capacity. In the above example, the heat generated by the conduction mechanism due to the presence of ions adds to the heat produced through the dipolar mechanism resulting in a higher temperature of the tap water.

**Loss angle:**

In order to be able to compare the abilities of different solvents to generate heat from microwave irradiation, their capabilities to absorb microwave energy and to convert the absorbed energy into heat must be taken into account. These factors may be considered using the loss angle, $\delta$, which is usually expressed in the form of its tangent (Equation 1).
temperature dependent and decreases as the temperature is increased. Since both $\varepsilon'$ and $\varepsilon''$ are dependent on $\tau$, the ability of a solvent to convert microwave energy into heat will be dependent not only on the frequency, but also on the temperature. Consequently, an organic solvent with a relaxation time $>65$ ps irradiated at 2.45 GHz will have a loss tangent that increases with temperature. The heating rate for these solvents will increase during MW dielectric heating, most probably by limiting the formation of ‘boiling nuclei’.[295] This phenomenon is described as superheating and may result in the boiling points of solvents being raised up to 26 °C above their conventional values.[293, 295]. In a pure solvent, the higher boiling point can be maintained as long as the microwave irradiation is applied. Substrates or ions present in the solvent will, however, aid the formation of ‘boiling nucleuses’ and the temperature will eventually return to that of the normal boiling point of the solvent. The superheating phenomenon is widely believed to be responsible for many of the rate increases which often accompany solution phase microwave assisted organic reactions at atmospheric pressure.[296]

### 1.5.2.3 SOLVENTS IN MICROWAVE ASSISTED ORGANIC SYNTHESIS:

Since the frequency for most types of microwave apparatus is set at 2.45 GHz, the dielectric constant can only change with temperature. When a solvent is heated, the dielectric constant decreases as the temperature increases. Water has a dielectric constant which decreases from 78 at 25 °C to 20 at 300 °C, the latter value being comparable to that of solvents such as acetone at ambient temperature.[297]. Water can, therefore, behave as a pseudo-organic solvent at elevated temperatures, but this property is only valid in pressurized systems. It was mentioned earlier that non polar solvents are not heated under microwave irradiation. The addition of small amounts of a polar solvent with a large loss tangent, however, usually leads to higher heating rates for the whole mixture. The energy transfer between the polar molecules that couple with the microwave radiation and the non polar solvent bulk is rapid. This method provides an effective means of using non-polar solvents in microwave organic synthesis. Another way of increasing heating rate is the addition of salts to the solvent. Unfortunately, a solubility problem in many organic solvents results in heterogeneous mixtures. In microwave assisted synthesis, a homogeneous mixture is preferred to obtain a uniform heating pattern.

Ionic liquids have recently been reported as novel environmentally friendly and recyclable alternatives to dipolar aprotic solvents for organic synthesis.[297, 298] The excellent dielectric properties of these ionic liquids offer large advantages when used as solvents in microwave assisted organic synthesis. Ionic liquids absorb microwave
irradiation in a very efficient manner and, moreover, they exhibit a very low vapour pressure, thereby enhancing their suitability even further for microwave heating. Despite ionic liquids being salts, they dissolve to an appreciable extent in a wide range of organic solvents as compared to water and alcohols.[298, 299] Some ionic liquids are also soluble in many non-polar organic solvents and can therefore be used as microwave coupling agents when microwave transparent solvents are employed.

1.5.2.4 **Why does microwave irradiation speed up chemical reactions?**

Since the introduction of MAOS in 1986, the main debate has dealt with the question of what actually alters the outcome of the synthesis. Is it merely an effect of the thermal heat generated by the microwaves or is it an effect specific for microwave heating?

In order to be able to make this distinction, the term ‘specific microwave effect’ should be defined. Historically, ‘specific microwave effects’ have been claimed, when the outcome of a synthesis performed using microwave heating differs from its thermally heated counterpart. Some of the earlier reports have, in later experiments not been reproduced,[296] while some are definitely debatable and others are hard to explain.[300] The main advantage of using microwave assisted organic synthesis is the shorter reaction time. The rate of the reaction can be described by the Arrhenius Equation (2).
Since the reaction vessels employed are typically made out of (nearly) microwave-transparent materials, such as borosilicate glass, quartz or teflon, an inverted temperature gradient results compared to conventional thermal heating. The very efficient internal heat transfer results in minimized wall effects (no hot vessel surface) which may lead to the observation of so-called specific microwave effects, for example, in the context of diminished catalyst deactivation.[304, 305]

Microwave assisted organic synthesis continues to affect synthetic chemistry significantly by enabling rapid, reproducible and scalable chemistry development.[287, 288, 306] Further, MAOS can facilitate the discovery of new reactions and reduce cycle time in optimization of reactions. In addition, it serves to expand chemical space in compound library synthesis.[307-309]. Moreover, in a near future, the use of adapted reactants and techniques offering operational, economic and environmental benefits, over conventional methods, will be crucial in the preparation and development of molecules with biological activity.[310] Recently, the use of clean and more efficient technologies, like microwaves, has become a major stimulus for both industry and academia.[311-315]

Numerous reactions have been explored under microwave conditions,[316-318] among which the formation of heterocyclic rings by cyclocondensation reactions are studied in great extent, mostly for molecules with pharmaceutical interest.[319-322] A number of reports describing the synthesis of 4(3H)-quinazolinone derivatives under microwave irradiation are published in last decade and some of the important works have been discussed earlier.

1.9 OBJECTIVES:

Perusal of the above literature survey reveals that the 4(3H)-quinazolinone skeleton, particularly, 2,3-disubstituted-4-quinazolinone is found in a number of biologically active molecules, and derivatives of sulfonamide motif have played vital role in pharmaceutical chemistry. Further, amino acids are of enormous synthetic interest as a precursor, which display versatile reactivities with multi-functional character to facilitate various transformation. Moreover, modern approaches like structural hybridization and microwave assisted organic synthesis serves to expand chemical space in compound library synthesis. Therefore, it has been thought worthwhile to unite active sulphonamide moiety with 4(3H)-quinazolinone moiety in a single molecular framework, and to derive resulting quinazolinone-sulfonamide hybrid heterocyclic system from various amino acids under appropriate reaction conditions, which have not been reported so far.
Hence, against this background and keeping in mind the pivotal role of above class of compounds, the objectives of the present work are:

- To synthesize quinazolinone-sulfonamide clubbed hybrid molecules using amino acids under conventional and microwave heating.
- To characterize so-called synthesized compounds by using physico-chemical analyses, spectroscopic investigations like ESI-MS, FT-IR, $^1$H-NMR and $^{13}$C-NMR.
- *In silico* screening of the above synthesized compounds to understand the behavior of produced compounds in terms of bioactivities.
- *In vitro* evaluation of the selected hits (screened compounds) to study the effect of structural variations on biological activity.

### 1.10 PRESENT WORK:

In a view of the above objectives, research work carried out has been devided in to the following chapters of the present thesis:

The detailed synthesis of quinazolinone-sulfonamide clubbed hybrid molecules from amino acids using conventional and microwave irradiation method followed by the experimental protocols and data of synthesized compounds are described in the **Chapter-2**.

The biological activity of entitled compounds is included in the **Chapter-3**. The content of this chapter is subdivided in to the two sections. *In silico* screening of all the synthesized compounds, and *in vitro* evaluations of the screened compounds, are described in **Section A** and **Section B** respectively.

A summary of all the investigations carried out for the present thesis entitled “*Conventional and Microwave Assisted Synthesis of Quinazolinone-Sulfonamide Linked Hybrid Molecules derived from Amino Acids and their Biological Studies*” is outlined in Chapter-4.
1.11 REFERENCES


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