Chapter I

Introduction and literature review of Quinazolines, Azetidin-2-Ones, Thiazolidin-4-One, Tetrazoles, 1,2,4 Tri azoles, 1, 3, 4 Oxa Di Azoles and its derivatives
Section I:
1.0 INTRODUCTION
1.1. GENERAL INTRODUCTION

In the past decades the tools available to the medicinal chemist to identify, design and test drugs have increased dramatically, both in quantity and sophistication. Computational methods, combinatorial chemistry, biotechnologies and high-throughput screening are among the many powerful techniques that have been harnessed to bring an element of rationality to the search for new drugs. In particular synthetic organic chemistry will continue to play a fundamental role in academic research and in the research and development departments of drug companies of the third millennium.

The role of organic synthesis in drug research and development nowadays and over the next decades was discussed at the 11th Camerino – Noordweijkerhout symposium (11-15 may 1997), in a section dedicated to New Developments in synthetic Medicinal Chemistry. Organic synthesis has made so much progress that it appears as a nature science, ready to face any synthetic problem, however difficult that problem may appear. The mechanistic advance in understanding organic chemistry has made prediction possible of the reactivity of organic compounds towards different reagents, and also to take on more and more complicated synthetic tasks. Retrosynthetic analysis has taught us to disconnect strategic bonds in order to dissect target molecules and identify useful synthetic strategies.

During the past 30 years, many milestones have been attained in the synthesis of natural products with pharmacological interest. The synthesis of prostaglandins, started by Corey in the 1960s and which continued with outstanding results for years; the synthesis of vitamin B12 realized by Woodward in the 1970s; the synthesis of the 64-chiralcenters palytoxin, performed by kishi in the 1980s, and the achievement, almost at the same time, of the synthesis of the much-sought taxol by two different teams in the present era. From the Medicinal Chemistry point of view, it must be stressed that total syntheses, even if not of practical use for commercial production of the drugs, are however very useful in opening the way to analogous and simpler molecules that may help to establish SARs and to design easier to obtain compounds.
Synthesis of bioactive heterocyclic compounds functionalized Multi Walled Carbon Nano Tubes in the field of organic chemistry received significant attention resulting in substantial advances both in the synthetic and medicinal aspects. Generally nitrogen containing heterocycles have been the object of considerable focus because they are structural components of many bioactive natural products such as vitamins, hormones, antibiotics, alkaloids, glycosides and many more compounds which are of significance for human and animal health. There are several generic drugs available in the market contains Quinazolines, tetrazoles, pyrimidines and oxazoles, Tri azoles as their main core of the structure.

1.2. Introduction about Heterocyclic chemistry:

Literature survey revealed that the history of Heterocyclic chemistry began in the 1800's, in step with the development of organic chemistry. Heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly and economically useful as therapeutic agents. Heterocyclic compounds are cyclic compounds containing at least one atom of carbon and at least one element other than carbon. A ring with only heteroatom is called homocyclic compound and heterocycles are the counter parts of monocyclic compounds. Thus incorporation of oxygen, nitrogen, sulphur or an atom of a related element into an organic ring structure in place of a carbon atom gives rise to a heterocyclic compounds.

Heterocyclic compounds are organic compounds containing at least one element other than carbon, such as sulphur, oxygen or nitrogen within a ring structure. In addition to that, a variety of atoms such as N, O, S, Se, P, Si, B are also incorporated in to ring structures. The name comes from the Greek word “heteros” which means “different.” By far the most numerous and most important heterocyclic systems are those of five and six members.

Heterocyclic chemistry is a very important branch of organic chemistry accounting for nearly one-third of modern publications. In fact two thirds of organic compounds are heterocyclic compounds. A cyclic organic compound containing all carbon atoms in ring formation is referred to as a carbo cyclic compound. If at least one atom other than carbon forms a part of the ring system then it is designated as a heterocyclic compound. Nitrogen, oxygen and sulfur are the most common hetero atoms but heterocyclic rings
containing other hetero atoms are also widely known. An enormous number of heterocyclic compounds are known and this number is increasing rapidly. Accordingly the literature on the subject is very vast. Heterocyclic compounds may be classified into aliphatic and aromatic. The aliphatic heterocyclics are the cyclic analogues of amines, ethers, thio ethers, amides, etc. Their properties are particularly influenced by the presence of strain in the ring. These compounds generally consist of small (3- and 4-membered) and common (5 to 7 membered) ring systems. The aromatic heterocyclic compounds, in contrast, are those which have a heteroatom in the ring and behave in a manner similar to benzene in some of their properties. Furthermore, these compounds also comply with the general rule proposed by Huckel. Besides the vast distribution of heterocycles in natural products, they are also the major components of biological molecules such as DNA and RNA. DNA is without doubt the most important macromolecule of life. Nucleotides, the building blocks of our genes are derivatives of pyrimidine and purine ring structures. Chlorophyll and heme, the oxygen carriers in plants and animals respectively are derivatives of large porphyrin rings.

Heterocycles are an important class of compounds, making up more than half of all known organic compounds. Heterocycles are present in a wide variety of drugs, most vitamins, many natural products, biomolecules, and biologically active compounds, including antitumor, antibiotic, anti-inflammatory, antidepressant, antimalarial, anti-HIV, antimicrobial, antibacterial, antifungal, antiviral, antidiabetic, herbicidal, fungicidal, and insecticidal agents. Also, they have been frequently found as a key structural unit in synthetic pharmaceuticals and agrochemicals. Some of these compounds exhibit a significant solvate chromic, photochromic, and biochemi-luminescence properties. Most of the Heterocycles possess important applications in materials science such as dyestuff, fluorescent sensor, brightening agents, information storage, plastics, and analytical reagents. In addition, they have applications in supra molecular and polymer chemistry, especially in conjugated polymers. Moreover, they act as organic conductors, semiconductors, molecular wires, photovoltaic cells, and organic light-emitting diodes (OLEDs), light harvesting systems, optical data carriers, chemically controllable switches, and liquid crystalline compounds. Heterocycles are also of considerable interest because of their synthetic utility as synthetic intermediates, protecting groups, chiral auxiliaries, organ catalysts, and metal ligands in asymmetric catalysts inorganic synthesis. Therefore,
substantial attention has been paid to develop efficient new methods to synthesize heterocycles.

The alkaloids form a major group of naturally occurring heterocyclic compounds having varied biological activity. Most alkaloids contain basic nitrogen atoms.

1.2.1 Introduction about Quinazolines:

The name Quinazoline (I) is universally used today to denote the 1,3-benzodiazine ring system. The name quinazoline (German chinazolin) was first proposed at the University of Leipzig in 1887 by Widdige on observing that his compounds were isomeric with the known cinnoline (II) and quinoxaline (III) derivative. Quinazoline isomers The class of bicyclic aromatic ring structures comprising a benzene ring linked to two-nitrogen containing aromatic ring such as pyridazine, pyrimidine, pyrazine are known in four isomers with the structural formulas as shown in figure (1). These isomers, also called as diazanaphthalenes are identified by the position of nitrogen in the heterocyclic ring. Quinazoline is a compound made up of two fused six-membered simple aromatic rings, a benzene ring and a pyrimidine ring. Phthalazine, also called benzo-orthodiazine or benzopyridazine bears a benzene ring and a pyrazidine ring. Quinoxaline, also called a benzopyrazine, consists of a benzene ring and a pyrazine ring. Cinnoline is a heterocyclic double-ring structure compound containing a benzene ring and a pyridazine ring.

![Quinazolines Isomers](image1)

Heterocycles have a central position in medicinal as well as in organic chemistry and considerable attention has been focused on their synthesis. Nitrogen Heterocycles in particular exhibit diverse biological and pharmacological activities due in part to the similarities with many natural and synthetic molecules with known biological activity. Moreover, Quinazolines are of the most extensively studied classes of heterocyclic compounds, and have received much attention from synthetic organic as well as medicinal chemists, because of the diverse range of their biological activities. Quinazolines are
classes of fused Heterocycles that are of considerable interest because of the diverse range of their biological properties.

Many substituted quinazoline derivatives possess a wide range of bioactivities such as antimalarial, anticancer, antimicrobial, antifungal, antiviral, antiprotozoan, anti-inflammatory, diuretic, muscle relaxant, antitubercular, antidepressant, anticonvulsant, acaricidal, weedicide and many other biological activities.

Heterocyclic compound containing quinazoline and quinazolinone nucleus plays most important role in the field of medicinal chemistry. It shows wide range of activities for medication purpose. A large number of Quinazoline compounds have been synthesized and evaluated for their different biological activities. Some marketed quinazoline and Quinazolinone nucleus containing drugs have different types of pharmacological activities.

The Quinazoline and Quinazolinone based pharmaceuticals are becoming very important class of therapeutic agents and are likely to replace many obtainable organic based pharmaceuticals in the very near future. The Quinazoline and Quinazolinone based pharmaceuticals will be created on a large scale by different research development processes and will become available commercially for therapeutic uses. The biological profiles of this new generation of quinazoline and Quinazolinone represent much progress with regard to the older compounds. This study gets an efficient way of understanding about the target pharmacophore relationship which can further aid the process of drug design developments. This study may also accelerate the designing processes to generate a larger number of therapeutically active molecules. The molecular treatment of potentially lead molecules is still a major line of approaches for the discovery and development of new drug molecules.

Quinazoline compounds are also used in preparation of various functional materials for synthetic chemistry and also present in various drugs molecules. The Quinazoline is present in a variety of biologically active compounds among these are several marked drugs such as Afatinib, Dacomitinib, Barasertib, Alfuzosine Hydrochloride, Prazosin hydrochloride, Doxazosine mesylate, Terazosine hydrochloride (adrenergic blocker/Prostate disorders), Dacomitinib, Verubulin, Sotrastaurin, Letermovir.
### Table-1.1  Quinazoline compounds and their uses

<table>
<thead>
<tr>
<th>S.NO</th>
<th>Quinazoline Derivative</th>
<th>Chemical structure</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Afatinib</td>
<td><img src="image" alt="Afatinib Structure" /></td>
<td>Antifungal activity</td>
</tr>
<tr>
<td>2</td>
<td>Alfuzocin</td>
<td><img src="image" alt="Alfuzocin Structure" /></td>
<td>Anti Cancer activity</td>
</tr>
<tr>
<td>3</td>
<td>Barasertib</td>
<td><img src="image" alt="Barasertib Structure" /></td>
<td>Acute myeloid leukemia</td>
</tr>
<tr>
<td>4</td>
<td>Cediranib</td>
<td><img src="image" alt="Cediranib Structure" /></td>
<td>Heamatological cancer,Liver metastases</td>
</tr>
<tr>
<td>5</td>
<td>Letermovir</td>
<td><img src="image" alt="Letermovir Structure" /></td>
<td>Human cytomegalovirus</td>
</tr>
<tr>
<td>#</td>
<td>Drug Name</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>-----------------</td>
<td>-------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Sotrastaurin</td>
<td>Psoriasis, ulcerative colitis.</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Tandutinib</td>
<td>Glioblastoma.</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Varlitinib</td>
<td>Anticancer drug.</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Verubulin</td>
<td>Anticancer drug.</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Dacomitinib</td>
<td>Antifungal</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Alfuzosine</td>
<td>Anticancer</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Prazosin</td>
<td>High blood pressure Treatment</td>
<td></td>
</tr>
</tbody>
</table>
Several structural modifications have been made to the quinazoline nucleus to enhance the biological activities like analgesic, anti-inflammatory, anticonvulsant, antibacterial, antifungal, antitubercular and antihistaminic activity, which attracted the attention of medicinal chemists.

A brief account on hydroxyl quinolines and various methods for the synthesis of Quinazolines are discussed and presented in the following few pages.

1.2.2 Synthesis:

The synthetic studies of the quinazoline derivatives discussed in this section are based upon the following substitution patterns of the ring system:

- 2-Substituted-quinazolines.
- 4-Substituted-quinazolines.
- 2, 4-Disubstituted-quinazolines.

1.2.3 2-Substituted-quinazolines

Erba et al employed a three-component reaction to form 2-alkylquinazolines from the reaction of amidines with ammonia [1]. In the first step, an aldehyde is reacted with morpholine and, subsequently, with an aryl azide to afford the triazolines 3 in acceptable yields, Scheme 1. On exposure to a saturated ethanolic solution of ammonia in a sealed vessel at 150°C or, alternatively, in ammonium acetate in boiling toluene, the triazolines 3 were converted into the desired quinazoline products 4 in approximately 30 min. The procedure is characterized by the use of readily available starting materials for the synthesis of 2-substituted-quinazolines that bear electron-withdrawing groups.
1.2.4 Reaction of Amidines with 2-fluorobenzaldehyde

Kotsuki et al developed a condensation of cyano- and nitro- activated o-fluorobenzaldehydes with amidines 5 to give a variety of quinazoline derivatives 6 in good yields [2]. The method involves tandem imine formation with the aldehyde function and an intramolecular nucleophilic aromatic substitution at the fluorine-substituted carbon centre, Scheme 2. The reaction was carried out in refluxing acetonitrile with potassium carbonate in the presence of powdered molecular sieves, and the crude product is purified by chromatography.

1.2.5 4-Substituted-quinazolines

4-Substituted quinazolines can be obtained by the following methods.
1.2.6 Derivatisation of 4(3H)-quinazolinones:

The introduction of chlorine, bromine or thiomethyl substituent at the 4-position in the quinazoline skeleton to activate the pyrimidine ring towards nucleophilic substitution is the basis of reaction. Chlorination of 4(3H)-quinazolinones is more often achieved through Phosphorus oxychloride [3] or thionyl chloride [4,5]. The 4-chloroquinazolines were further subjected to amination by various aromatic or aliphatic amines to afford 4-substitutedquinazolines. 4-Chloroquinazolines, for example, compound 7, are important synthetic intermediates as they can be derivatised further through nucleophilic attack at the C-4 position. This is illustrated in the synthesis of 8, an intermediate in the synthesis of AX7593, a quinazoline-derived photo affinity probe for epithelial growth factor receptor (EGFR), Scheme 3.

![Scheme 3](attachment:image.png)

1.2.7 Reaction of anilines with 2-aminobenzonitrile:

The reaction of 2-aminobenzonitrile with anilines in presence of anhydrous aluminum chloride, Scheme 4 [6,7] an optimal yield of amidines 9 was obtained using an excess of the required aniline and aluminum chloride. The formation of these amidines is, however, limited by the aromatic substitution pattern on the aniline. No reaction was observed with 3,4-dichloroanilines or with nitroanilines, possibly due to the reduced nucleophilicity of the amino group in each case. 2-amino-N-arylbenzamides 9 furnished the 4-arylaminoquinazolines 10 in good yields (70-92%) when heated with 85% formic acid, Scheme 4. The reaction can only be applied to the synthesis of 2-unsubstituted 4-arylaminoquinazolines.
1.2.8 Reaction of anilines with 2-amidinobenzonitriles

Tsou et al. reported a method for the synthesis of 4-anilinoquinazolines. 5-Nitroanthranilonitrile 11 when condensed with DMF acetal to yield (12) [8].

Heating compound 12 with 3-bromoaniline in acetic acid afforded the desired quinazoline 13 in excellent yield, Scheme 5. An advantage of this approach is the formation of the quinazoline ring and the incorporation of the 4-anilino group in one step. Yoon et al. reported the reaction of N,N-dimethylamidinobenzamide 14 with benzylamine 15 to give 4-aminoquinazoline 16 under the conditions of microwave (MW) irradiation, Scheme 6 [9].
1.2.9.0 2, 4-Disubstituted Quinazolines

1.2.9.1 Polymer-supported synthesis of 2,4-diaminoquinazolines

The solid-phase synthesis reported by Wilson enabled the preparation of 2,4-diaminoquinazolines 17 in good yields and purities [10]. This was accomplished using an acyl isothiocyanate resin 18 with functionalized 2-aminobenzonitriles 19 and amines 20 as the key building blocks in the synthesis, Scheme 7. This approach enabled the synthesis of the α-1 antagonist prazosin 21 in good yield and purity.

1.2.9.2 2-Substituted-4-aminoquinazolines by microwave irradiation:

Seijas et al. reported a microwave-promoted synthesis of 4-aminoquinazolines 23 by reacting cyano aromatic compounds with anthranilonitrile 22 (X=H) in a domestic microwave oven, Scheme 8 [11] A dramatic reduction in reaction time, the absence of solvents and the use of only a catalytic amount of base are appealing features of this approach.
1.2.9.3 Quinazoline formation by thermal ring contraction and rearrangement:

A few examples of quinazoline ring synthesis by ring contraction have also been reported. Sashida et al. studied the thermolysis of 5-methoxy- and 5-diethylamino-(3H)-1,4-benzodiazepines to give 4-methoxy- and 4-diethylaminoquinazolines by a ring contraction mechanism, Scheme 9 [12]. On heating 5-methoxy-(3H)-1,4-benzodiazepines 24 in diphenyl ether at 160-170°C for 6h, 4-methoxyquinazolines 25 were furnished as the sole products in moderate yields (41-46%). Similarly, 5-diethylamino-(3H)-1,4-benzodiazepines 26 were treated with sodium methoxide at room temperature to give the corresponding 4-diethylaminoquinazolines 27 in acceptable yields, Scheme 9 and 10.
Szczepankiewicz et al. showed that readily available 5,5-diaryl-4,5-dihydro-1,2,4-oxadiazoles 29 in boiling acetic anhydride transform into 4-arylquinazolines via 4,4-diaryl-1,3-diaza-1,3-butadiene derivatives 30, which undergo thermal electrocyclization to form the 1,8 a bond of the quinazoline system 31 Scheme 11.

1.2.13. From 2-Aminobenzylamine.

The 2-aminobenzylamine 32 reacts with butyrolactone 33 which involves forming intermediate compound 34 and further condensed with O-Chloro benzaldehyde to give 3-(2-chlorobenzylidene)-1,2,3,9-tetrahydropyrrolo-2quinazoline 35 (see Scheme 12).

1.2.14 Reactivity of 2,4-dichloroquinazolines:

Strekowski et al. reported that the reaction of organolithium reagents with 2,4-dichloroquinazoline 32 was regioselective, resulting in predominant substitution at the 4-position, Scheme 13 [13]. The reaction of 4-chloroquinazoline 33 with phenyllithium resulted in the formation of 2-[(benzylidene)amino]benzonitrile 34 as the minor product and 2-[diphenylmethyl]-amino]benzonitrile 35 as the major product, Scheme 14. This indicates that the addition of a lithium reagent to the un substituted 2-position is favored over substitution at the 4-chloro substituent. Similarly, the reaction of 2-chloro-4-phenylquinazoline 36 with 1 equiv of phenyl lithium gave a complicated mixture of products,
Scheme 15. The expected 2,4-diphenylquinazoline was not formed, possibly as a result of ring opening of the pyrimidine ring system.

The 2-chloro substituent can, however, be replaced by both alkoxides and amines to give the corresponding 2,4-disubstituted quinazolines in 60-80% yields. Indeed, this substitution can be carried out selectively depending on the conditions.

2,4-Dichloroquinazolines synthesized by chlorinating quinazoline-2,4-dione using phosphorousoxychloride or thionyl chloride can be regiospecifically substituted by simply treating with a nucleophile. Substitution at the position-4 can be achieved by treating 2,4-dichloroquinazoline with a nucleophile. This is illustrated in the course of several syntheses. A Stille coupling resulted in exclusive reaction at the 4-chloro substituent in 2,4-dichloro Quinazoline derivatives 37, since this position is the most electrophilic, Scheme 15. Substitution at the remaining 2-position by both Organo tin and Organozinc reagents was possible using similar cross-coupling methodology, producing 38a and 38b.
Alcohols, thiols or amines in the presence of sodium hydroxide could also be used to replace the 2-chloro substituent, to produce 38 (a-c) in yields of 50-90%, Scheme 16.

1.2.15 Chemical Properties of Quinazolines:

The chemistry of quinazoline was reviewed by Williamson in 1957 and then by Lindquistin 1959 and brought up to date by Armaregoin 1963.

Quinazolines is stable in cold dilute acid and alkaline solutions, but it is destroyed when these solutions are boiled. O-Aminobenzaldehyde, ammonia, and formic acid are formed when quinazoline is boiled with hydrochloric acid.

1.2.16 Hydrolysis, Oxidation, and Reductions:

Oxidation of quinazoline in dilute aqueous acid with two equivalents of hydrogen peroxide at room temperature gave 3,4-dihydro-4-oxo quinazoline. In alkaline medium, the anhydrous neutral species of quinazoline were predominantly undergo oxidation with KMnO4 and yielded 3,4-dihydro-6 4-oxo quinazoline.

Scheme 17
1.2.17 Reductions.

Reduction with sodium amalgam gave 1,2,3,4-tetrahydroquinazoline. Lithium aluminum hydride and sodium borohydride gave 3,4-dihydro and 1,2,3,4 Tetra hydro quinazoline (Scheme 18).

1.2.18. Nucleophilic and Electrophilic Substitution Reactions.

The two known nucleophilic substitution reactions of Quinazoline are sodamide and hydrazine most probably proceed via the intermediate addition products, and gave 4-amino and 4 hydrazinequinazoline (see Scheme 19).

1.2.19 Electrophonic Substitution Reaction of Quinazolines

Nitration is the only known electrophilic substitution reaction of quinazoline. The expected order of reactivity is at positions 8 > 6 > 5 > 7 > 4 > 2. Quinazoline gives 6nitroquinazoline with fuming nitric acid in concentrated H₂SO₄. No oxidation of the Heterocyclic ring can occur under these conditions because the hydrated cation is not present (see Scheme 20).
1.2.20 Addition Reactions.

Quinazoline is highly reactive towards anionic reagents which attack on position 4. Sodium bisulphate, hydrogen cyanide, acetone, 2-butanone, acetophenone, and cyclohexanone add across the 3,4-double bond of quinazoline. Methyl, ethyl, isopropyl, benzyl, t-butyl, and phenyl magnesium halides and phenyl lithium also add across the 3,4-double bond to give the corresponding 4-substituted 3,4-dihydroquinazolines.

1.2.21 Biological Significance:

The Quinazoline scaffold is present in many classes of biologically active compounds. Quinazolines are classes of fused Heterocycles that are of considerable interest because of the diverse range of their biological properties, for example, anticancer, diuretic, anti-inflammatory, anticonvulsant and antihypertensive activities [14].

Table 1.2 Biologically potent Quinazoline derivatives

<table>
<thead>
<tr>
<th>S.NO</th>
<th>Compound</th>
<th>Activity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td><img src="image1.png" alt="Compound Image" /></td>
<td>antitumor</td>
<td>J. He et al [15]</td>
</tr>
<tr>
<td>02</td>
<td><img src="image2.png" alt="Compound Image" /></td>
<td>antitumor</td>
<td>H.-Q. Li et al [16]</td>
</tr>
<tr>
<td>03</td>
<td><img src="image" alt="Structural formula" /></td>
<td>EGFR inhibitors</td>
<td>C. Fernandes et al [17]</td>
</tr>
<tr>
<td>----</td>
<td>-----------------------------</td>
<td>----------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>04</td>
<td><img src="image" alt="Structural formula" /></td>
<td>ErbB-1/ErbB-2 tyrosine kinase inhibitor</td>
<td>K. G. Petrov et al [18]</td>
</tr>
<tr>
<td>05</td>
<td><img src="image" alt="Structural formula" /></td>
<td>Antibacterial</td>
<td>P. M. S. Bedi et al [19]</td>
</tr>
<tr>
<td>06</td>
<td><img src="image" alt="Structural formula" /></td>
<td>Antifungal</td>
<td>G.-F. Xu et al [20]</td>
</tr>
<tr>
<td>07</td>
<td><img src="image" alt="Structural formula" /></td>
<td>Anti mutagenic</td>
<td>D. Kohli et al [21]</td>
</tr>
<tr>
<td>08</td>
<td><img src="image" alt="Structural formula" /></td>
<td>Analgesic</td>
<td>A. M. Alafeefy et al [22]</td>
</tr>
<tr>
<td>09</td>
<td><img src="image" alt="Structural formula" /></td>
<td>Anti plasmodial</td>
<td>Y. Kabri et al [23]</td>
</tr>
</tbody>
</table>
Thus, the important role displayed by quinazoline and its derivatives for various therapeutic and biological activities prompted us to synthesize some azetidinones, thiazolidinones, tetrazoles, Tri Azoles and oxadiazole derivatives bearing Quinazoline centroid nucleus. The main objective of the present investigation was to synthesize a Quinazoline derivative with a broad spectrum of biological activity. The results were reported in the experimental chapters.

Section II: Introduction and literature review of Azetid-2-Ones:

1.3. AZETIDIN-2-ONES:

Azetidin-2-one [1] is a four member cyclic amide with four atoms in its ring. β-lactams are the generic descriptors for penicillin family antibiotics. 2-Azetidinones, formally known as β-lactams are well-known heterocyclic compounds among organic and medicinal chemists. The azetidin-2-ones have medicinal as well as chemical significance. (Fig:2)

\[
\text{\textbf{1}}
\]

(Fig:2 Structure of Azetidin-2-one)

The chemistry of β-lactams has occupied an important place in organic chemistry after the discovery of Penicillin by Sir Alexander Fleming in 1928 and shortly thereafter Cephalosporin which were discovered as successful antibiotics. The β-lactam antibiotics attract the much attention of scientists and researchers. Besides antibiotic activity, β-lactam possesses cholesterol inhibition, antithrombotic, antiviral and antifungal activities.

β-lactam synthon method was stated by Ojima [25,26] according to which azetidin-2ones can be utilized as useful building blocks in organic synthesis. The cyclic 2-azetidinone skeleton has been extensively used as a template for the development of new
Studies on Quinazolines

chemical entities of pharmaceutical importance by utilizing the chirality and fictionalisation of the β-lactam nucleus as a stereo controlling element. A number of broad spectrum β-lactam antibiotics including penicillins (2), cephalosporins (3), carbapenems (4), nocardicinA (5) and monobactams attributed to have the 2-azetidinone (β-lactam) ring as common structural core. All the above mentioned drugs are extensively used as chemotherapeutic agents to treat microbial diseases and bacterial infection. (Fig:3)

(Fig: 3 β-lactam antibiotics)

The β-lactam antibacterial drugs mediate the final step of cell wall biosynthesis [27,28] by forming covalent adducts with membrane bound bacterial transpeptidases, a group of transpeptidases anchored within the bacterial cell membrane which are also known as penicillin binding proteins (PBPs). β-lactam antibiotics prevent the construction of cell wall and eventually lead to cell lysis and death. Due to their β-lactamase inhibitory action heterocycles having 2-azetidinones represent an attractive target of contemporary organic synthesis [29].

Azetidinones are very important class of compounds possessing wide range of biological activities such as antimicrobial [30-46], pesticidal [47], antitumor [48], antitubercular [49], anticancer [50] cytotoxic [51-53], enzyme inhibitors [54], elastase inhibitors [55] & cholesterol absorption inhibitors [56]. Many β-lactam drugs had been reported in the literature. Heterocycles possessing azetidin-2-one ring were found to show various types of biological activities [57-70].
Some important β-lactam drugs reported in the literature were shown in the following Table-1.3.

**Table-1.3 Biologically potent azetidin-2-one derivatives**

<table>
<thead>
<tr>
<th>S.NO.</th>
<th>Compound</th>
<th>Activity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Compound 1" /></td>
<td>Antibacterial</td>
<td>Sinh et al [71]</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Compound 2" /></td>
<td>Antifungal, Anti inflammation and anti tubercular</td>
<td>Rajasekaran et al [72]</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Compound 3" /></td>
<td>Antimicrobial</td>
<td>Dhakad et al [73]</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4.png" alt="Compound 4" /></td>
<td>Antimicrobial</td>
<td>Mulwad and Mir [74]</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5.png" alt="Compound 5" /></td>
<td>Anti tubercular</td>
<td>Patel et al [75]</td>
</tr>
<tr>
<td>No.</td>
<td>Structure</td>
<td>Activity</td>
<td>Reference</td>
</tr>
<tr>
<td>-----</td>
<td>------------</td>
<td>-------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6.png" alt="Structure 6" /></td>
<td>Antimicrobial</td>
<td>Nagaraja et al [76]</td>
</tr>
<tr>
<td>7</td>
<td><img src="image7.png" alt="Structure 7" /></td>
<td>Antimicrobial</td>
<td>Desai and Desai [77]</td>
</tr>
<tr>
<td>8</td>
<td><img src="image8.png" alt="Structure 8" /></td>
<td>Antimicrobial</td>
<td>Naik and Desai et al [78]</td>
</tr>
<tr>
<td>9</td>
<td><img src="image9.png" alt="Structure 9" /></td>
<td>Antifungal, antibacterial</td>
<td>Khatri et al [79]</td>
</tr>
<tr>
<td>10</td>
<td><img src="image10.png" alt="Structure 10" /></td>
<td>Antimicrobial</td>
<td>Halve et al [80]</td>
</tr>
<tr>
<td>11</td>
<td><img src="image11.png" alt="Structure 11" /></td>
<td>Antibacterial</td>
<td>Patel et al [81]</td>
</tr>
<tr>
<td>12</td>
<td><img src="image12.png" alt="Structure 12" /></td>
<td>Anti-microbial</td>
<td>Vasoya et al [82]</td>
</tr>
<tr>
<td>No.</td>
<td>Chemical Structure</td>
<td>Activity</td>
<td>Reference</td>
</tr>
<tr>
<td>-----</td>
<td>-------------------</td>
<td>--------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>13</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>Anti convulsing</td>
<td>Rajashekaran et al [83]</td>
</tr>
<tr>
<td>14</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>Antibacterial</td>
<td>Pawar et al [84]</td>
</tr>
<tr>
<td>15</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>Antibacterial</td>
<td>Desai et al [85]</td>
</tr>
<tr>
<td>16</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>Antifungal, antibacterial</td>
<td>Padmakant et al [86]</td>
</tr>
<tr>
<td>17</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>Anti bacterial</td>
<td>K. N. Jayaveeera et al [87]</td>
</tr>
<tr>
<td>18</td>
<td><img src="image6" alt="Chemical Structure" /></td>
<td>Antibacterial</td>
<td>G. Madhu et al [88]</td>
</tr>
</tbody>
</table>
Section III: Introduction and literature review of Thiazolidin-4–One:

1.4. Thiazolidin-4–Ones:

Thiazolidin-4-one (6) is a derivative of thiazolidine (7) with a carbonyl group at 4th position which belongs to an Important class of Heterocyclic compounds (Fig:4).

\[
\begin{align*}
R &= -\text{OCH}_3, -\text{CF}_3 \\
X &= -\text{CH}_2, -\text{O}, -\text{S}, -\text{NCH}_3
\end{align*}
\]

(Fig:4 Structure of Thiazolidinone)

Thiazolidin-4-one attacks an Electrophilic center due to the nucleophilic activity of methylene carbon atom at fifth position [90]. Variety of heterocyclic products including drugs [91,92], dyes and intermediates such as thiazol yellow, thioflavin T., thidiazuron [93], herbicides [94], insecticides [95,96] etc attributable to possess thiazolidin-4-one. Besides the above applications, thiazolidinones moiety is also associated with broad spectrum of biological activities including antibacterial [97-99], antifungal [100], anti-inflammatory [101-103], hypnotic, anticonvulsant, antitubercular [104], antiviral [105,106], antihistaminic [107], anthelmintic, cardiovascular and anticancer [108]. A number of 4 thiazolidinone derivatives were screened for their inhibitory effects on the oxidation of the substrates of the tricarboxylic cycle and β-hydroxybutyrate by rat brain homogenates for respiratory activity [109]. Heterocycles bearing thiazolidin-4-one nucleus were found to possess various types of biological activities [110-124].

Some important thiazolidin-4-one derivatives reported in the literature were shown in the following Table-1.4.
### Table-1.4 Biologically potent thiazolidin-4-one derivatives

<table>
<thead>
<tr>
<th>S.No</th>
<th>Compound</th>
<th>Activity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Compound 1" /></td>
<td>Antimicrobial</td>
<td>Bhambi et al [125]</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Compound 2" /></td>
<td>Antibacterial</td>
<td>Khan SA et al [126]</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Compound 3" /></td>
<td>Antifungal</td>
<td>Patel et al [127]</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Compound 4" /></td>
<td>Antimicrobial</td>
<td>Kumar et al [128]</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Compound 5" /></td>
<td>Anticonvulsant</td>
<td>Gursoy et al [129]</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6" alt="Compound 6" /></td>
<td>Antihistaminic</td>
<td>Agrawal et al [130]</td>
</tr>
<tr>
<td>No.</td>
<td>Chemical Structure</td>
<td>Activity</td>
<td>Authors</td>
</tr>
<tr>
<td>-----</td>
<td>--------------------</td>
<td>----------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>7</td>
<td><img src="image1.png" alt="Chemical Structure" /></td>
<td>Anti microbial</td>
<td>Jaju et al [131]</td>
</tr>
<tr>
<td>8</td>
<td><img src="image2.png" alt="Chemical Structure" /></td>
<td>Antimycobacterial</td>
<td>Kucukguze et al [132]</td>
</tr>
<tr>
<td>9</td>
<td><img src="image3.png" alt="Chemical Structure" /></td>
<td>Anti-psychotic</td>
<td>Kaur et al [133]</td>
</tr>
<tr>
<td>10</td>
<td><img src="image4.png" alt="Chemical Structure" /></td>
<td>Anticonvulsant</td>
<td>Shiradkar et al [134]</td>
</tr>
<tr>
<td>11</td>
<td><img src="image5.png" alt="Chemical Structure" /></td>
<td>Anti inflammatory</td>
<td>Ottana et al [135]</td>
</tr>
<tr>
<td>12</td>
<td><img src="image6.png" alt="Chemical Structure" /></td>
<td>Antibiotic</td>
<td>Bondock et al [136]</td>
</tr>
<tr>
<td>13</td>
<td><img src="image7.png" alt="Chemical Structure" /></td>
<td>Antibacterial</td>
<td>Gaikwad et al [137]</td>
</tr>
</tbody>
</table>
### Section IV: Introduction and literature review of Tetrazoles:

**1.5. Tetrazoles:**

Tetrazoles are class of Five-member Heterocyclic compounds with four nitrogen and one carbon atom besides hydrogen. Tetrazole was the simple molecule among its derivatives with molecular formula CN₄H₂. It is white to pale yellow crystalline solid with weak characteristic odour, soluble in alcohol and water. The presence of four nitrogen atoms imparts acidic nature to the tetrazole. Numbering of tetrazoles is as shown below. (Fig:5)
In general tetrazoles are explosive heterocyclic compounds. Nature of tetrazoles was unknown. Tetrazole is used as gas generating agent for air bags. Several tetrazoles are used as pharmaceutical agents. They undergo electrophilic as well as nucleophilic substitution reactions. Tetrazoles can act as pharmacophore for the carboxylate group. This property increases their activity. Tetrazoles and its derivatives are associated with a variety biological activities such as antifungal [142], antinociceptive [143,144], anti convulsant[145], antidiabetic [146], cyclo-oxygenase inhibitors [147], hypoglycaemic[148], antibacterial[149] and anti-Inflammatory [150] activities. Tetrazoles are used as catalysts in the synthesis of phosphonates.

Some important tetrazole derivatives reported in the literature were shown in the following Table-1.5

Table-1.5 Biologically potent tetrazole derivatives

<table>
<thead>
<tr>
<th>S.No</th>
<th>Compound</th>
<th>Activity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="N=\text{N}" /> R=H,O,Me,ClCF_3,Br,ClH</td>
<td>Anti-proliferative</td>
<td>Gundugola A.S. et al [151]</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="N=\text{N}" /> Ar</td>
<td>Anti hyperglycemic</td>
<td>Ashoke Sharon et al [152]</td>
</tr>
<tr>
<td>Studies on Quinazolines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>3</strong> Anti hypertensive</td>
<td>Sharma M.C. et al [153,154]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>4</strong> Anti cancer</td>
<td>Bhaskar V.H. et al [155]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>5</strong> Anticonvulsant</td>
<td>Xian-Yu Dun et al [156]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>6</strong> Analgesic</td>
<td>Rajasekaran A. et al [157]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>7</strong> Antifungal</td>
<td>Upadhyaya R.S. et al [158]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>8</strong> Microbial and</td>
<td>Adnan A. Bekhit et al [159]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti inflammatory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>9</strong> Antibacterial and</td>
<td>Hari N. Patil et al [160]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antifungal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>10</strong> Antimicrobial</td>
<td>Mosaad Sayed Mohamed et al [161]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Section V: Introduction and literature review of 1, 3, 4 Oxa Di Azoles:

1.6 1, 3, 4 Oxa Di Azoles:

Oxadiazole is a five-membered heterocyclic, aromatic chemical compound having two carbons, two nitrogens, and one oxygen atom with two double bonds having general formula C₂H₂ON₂. There are four isomers of oxadiazole- 1,2,4-oxadiazole, 1,2,5-oxadiazole, and 1,3,4-oxadiazole are known, but the 1,2,3-isomer is unstable and reverts to the diazoketone tautomer. (Fig: 6)

(Fig:6 Structures of Isomeris Oxa di azoles )

1, 3, 4-Oxadiazole is a thermally stable molecule. Oxadiazole is a very weak base due to the Inductive effect of the extra Heteroatom. The 1, 3, 4-oxadiazole undergoes number of reactions including electrophilic substitution, nucleophilic substitution, thermal and photochemical. The electrophilic substitution in oxadiazole ring is extremely difficult at the carbon atom because of the relatively low electron density on the carbon atom which can be attributed to electron withdrawing effect of the nitrogen atom. If oxadiazole ring is substituted with electron releasing groups then the attack of electrophiles occurs at nitrogen. Oxadiazole ring is generally resistant to nucleophilic attack.
Heterocyclic compounds have attracted the attention of medicinal chemists because of having broad spectrum of pharmacological activities and hence It continues to yield new medicinal agents one such heterocyclic nucleus of medicinal importance is oxadiazole nucleus. 1,3,4-oxadiazole nucleus are known to exhibit Unique anti-inflammatory activity [164-167], differently substituted oxadiazole moiety has been found to have other interesting activities such as analgesic [168,169], antitubercular [170], anticonvulsant [171], antimicrobial [172], anti cancer [173], ulcerogenic [174], hypolipidemic [175], anti fungal [176] activities.

Some important 1,3,4 Oxa Di Azole derivatives reported in the literature were shown in the following Table-1.6

<table>
<thead>
<tr>
<th>S.NO</th>
<th>Compound</th>
<th>Activity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>anti-inflammatory</td>
<td>Radha et al [177]</td>
</tr>
<tr>
<td>02</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>Hypoglycemic</td>
<td>Yale et al [178]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>03</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>Anticancer</td>
<td>Aboraia et al. [179]</td>
</tr>
<tr>
<td>04</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>antitumor</td>
<td>Zhang et al [180]</td>
</tr>
<tr>
<td>05</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>Anti-inflammatory</td>
<td>Palaska et al. [181]</td>
</tr>
<tr>
<td>06</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>Anti Tumor</td>
<td>S.Bondock et al [182]</td>
</tr>
<tr>
<td>07</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>Anti-tubercular</td>
<td>S. R.Pattan et al [183]</td>
</tr>
<tr>
<td>08</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>Antituberculosis</td>
<td>F. Macaev et al [184]</td>
</tr>
<tr>
<td>09</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>Anticonvulsant</td>
<td>Y. Mohammad and W. MohdAkhter et al [185]</td>
</tr>
<tr>
<td>10</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>Analgesic</td>
<td>A.Husain and A. Mohammed et al [186]</td>
</tr>
</tbody>
</table>

**Section VI: Introduction and literature review of 1, 2, 4-Triazoles:**

**1.7 1, 2, 4-Triazoles:**

1,2,4-Triazole is one of a pair of Isomeric chemical compounds with molecular formula \( \text{C}_2\text{H}_3\text{N}_3 \), called Tri azoles (Fig:7), which have a five-membered ring of two carbon atoms and three nitrogen atoms. 1,2,4-Triazole is a basic aromatic Hetero cycle. 1,2,4-Triazole derivatives find use in a wide variety of applications, most notably as Antifungals such as Flucanazole and Itraconazole (Fig:8).

![1,2,4 Triazole](image6)
Triazolic nucleus is now a day’s considered an important moiety in the design and synthesis of bioactive compounds that are associated with numerous biological activities [187] such as antibacterial, antifungal [188], anti-inflammatory [189], anticonvulsant [190], anti-HIV [191], antineoplastic, and antiproliferative [192-199]. Additionally, there are review studies that indicate the fact that 1,2,4-triazoles occupy a distinctive place in the field of medicinal and pharmaceutical chemistry [200,201], as well as in industry [202]. Also, synthesis and complete characterization by both spectroscopic and thermal techniques were reported in literature for numerous derivatives bearing 1,2,4- triazole moieties [203-206].

1.8 DATA

Melting points

Melting points are determined in open capillary tubes using a cintex melting point apparatus and are uncorrected (in degree Celsius).

Infrared Spectra

The Infrared spectra of the compounds were recorded in KBr discs on Perkin–Elmer FT–IR (Spectrum ONE) spectrophotometer (ν max in cm⁻¹).

¹HNMR spectra
The $^1$H NMR spectra were recorded on a JOEL (300 MHz) and DRX-300 MHz Bruker spectrophotometer using TMS as an internal standard (chemical shifts in $\delta$).

$^{13}$CNMR spectra

The $^{13}$CNMR Spectra were recorded on a Brucker 75MHz spectrophotometer using TMS as an internal standard (chemical shifts in $\delta$).

Mass Spectra

The Mass spectra were recorded on varian MATCH-7 mass spectrometer at 70ev instrument (m/z in %).

Analysis

Elemental analyses were carried out on a carloerba 106 and Perkin-Elmer analyser. Calculated percentage of C, H and N are given in parenthesis (in %).
REFERENCES


Studies on Quinazolines


**Studies on Quinazolines**
166. Kamble RR and Sudha BS;Synthesis and Pharmacological Screening of 5- methyl-3-[p-(6'aryl-2'-thioxo-1',2',5',6'- tetrahydropyrimidin-4'-yl)phenyl]-3H-2-oxo- A4-1,3,4-oxadiazoles. *India. Pharm. Sci.*, 2006; 68, 249.


188. P. Zoumpoulakis, C. Camoutsis, G. Pairas et al., “Synthesis of novel sulfonamide-1,2,4-triazoles, 1,3,4-thiadiazoles and 1,3,4-oxadiazoles, as potential antibacterial and antifungal agents. Biological evaluation and conformational analysis studies,” *Bioorganic and Medicinal Chemistry*, vol. 20, no. 4, pp. 1569–1583, 2012.


