Chapter-II
Literature Survey
**LITERATURE SURVEY**

**PART-[A]: STUDIES ON ADAMENTAN BASED THIAZOLES AND THIAZOLIDINE DERIVATIVES**

**Introduction:**

**Properties of Adamantane Derivatives**

Adamantane (1) is the proprietary name of the hydrocarbon tricycle [3.3.1.1] decane. It occurs as white crystalline powder with characteristic aromatic odour. It exists as a minor constituent of petroleum oil.

Adamantane is a highly lipophilic compound, it is readily soluble in organic solvents, sublimes at 209-212°C, crystallizes at –30°C and melts in sealed tubes at 268°C. Adamantine nucleus was first built up by Prelog and Seiwerth in 1941 via aluminum chloride-catalyzed isomerization of tetrahydrodicyclopentadiene, [1] this chemical synthesis was latterly improved via catalytic hydrogenation of dicyclopentadiene in the presence of aluminum chloride.[2]
Due to the high lipophilicity of adamantane, the incorporation of the adamantyl moiety into several molecules results in compounds with relatively high lipophilicity, which in turn can modify the biological availability of these molecules. After the discovery of amantadine in 1960 as antiviral and anti-parkinsonian drug, adamantane derivatives attracted the attention of several scientists as potential chemotherapeutic agents. As a result of this intensive search, thousands of adamantane derivatives were synthesized and tested for several biological activities. This resulted in the discovery of several drugs which are now available in market. Among the major biological activities displayed by adamantane derivatives, the antiviral, antibacterial, antifungal, anti-inflammatory, central nervous and 11 β-HSD1 inhibitory activities are the most important ones.

Adamantane, 1-aminoadamantane, has been found to display anti-Influenza A properties in 1964. While in these early days the target protein was not known, many studies dealing with structural modifications of the aminoadamantane pharmacophor have been undertaken. Indeed, more active compounds like rimantadine have been identified that also are valuable to combat other viruses and are advantageous due to reduced side effects. Tromantadine could be marketed for the combat of Herpes simplex (HSV). More important is, however, the finding, that simple amino adamantane derivatives have pronounced activities in disorders related with the central nervous system (CNS). Most important in this respect are the fortuitous finding that Amantadine also improves the symptoms of Parkinson’s disease (PD) and the identification of Memantine (1-amino-3,5-dimethyladamantane hydrochloride) as a mild, non-competitive NMDA receptor antagonist valuable in the treatment of Alzheimer’s disease.
As an introduction to the research this thesis is dealing with, the history of Adamantane derivatives used in medicinal chemistry is summarized. The complexity of the substances studied has obviously increased, from the simple amino adamantanes to Vildagliptin and Saxagliptin, two novel dipeptidyl peptidase inhibitors that are about to enter the multi-billion dollar market of diabetes treatment.

**Antiviral Adamantane Derivatives**

Adamantane hydrochloride (2) (1-adamantanamine hydrochloride, Symmetrel®) is the first adamantane derivative to be introduced in medicine as effective therapy against Asian A2 influenza viruses.[3-5] The pronounced central nervous stimulant and cardiovascular effects of Adamantane [6] necessitated the search for newer more potent and less toxic agents for the control of pandemic influenza viruses. Rimantadine (3) (methyl-1-adamantanemethylamine hydrochloride, Flumadine®) [7] was further developed as more potent and less toxic alternative to amantadine.[8]
Amantadine and rimantadine inhibit the viral replication during the early stages of infection by blocking the ion channel formed by the trans membrane domain of the M2 protein.[9-10] Although both Adamantane and rimantadine are orally active and well absorbed, Adamantane is excreted unchanged by the kidney while rimantadine is metabolized in the liver by hydroxylation before excretion giving rise to the metabolites 4a-c.[11] The three metabolites of rimantadine were found to be active *in vitro* against the wild type influenza A viruses (H3N1 and H1N1) and inactive against influenza B viruses.

Phenotypic resistance to Adamantane was detected shortly after its discovery,[12] and subsequent studies showed the ease of selecting resistant variants *in vivo*.[13] The study of the genetic basis of resistance, ultimately shown to be linked to single nucleotide changes and corresponding single amino acid substitution in the trans-membrane of the M2 ion channel protein, this was critical to understand Adamantane mechanism of action.[14] As a result, influenza A viruses have the ability to undergo changes and new evolving strains were developed causing serious threat to the human population. Thus pandemic influenza A viruses appeared in Spain in 1918 (H1N1), Asia in 1957 (H2N2), Hong Kong in 1968 (H3N2) and recently the most fatal pandemic in 1997 (H5N1),[15] which occurred in several far Eastern countries and extended during late 2003 and early 2004 to the Middle East region, infecting both
human and birds. Despite the viral resistance of the newly developed mutants (H5N1) to the M2 inhibitors as Adamantane and rimantadine, recent reports revealed that the combination therapy of M2 inhibitors with the newly developed neuraminidase inhibitors as zanamivir (5) (Relenza®) [16] and oseltamivir (6) (Tamiflu®) [17] is a good option for the control of resistant influenza viral infections till the exploration of other novel drugs.[18]

\[
\begin{align*}
&\text{(5)} \\
&m&
\end{align*}
\]

As a result of extensive search based on Adamantane and rimantadine, tromantadine (7) (ViruMerz®) was introduced in 1971 as a potent antiviral drug for the treatment of viral skin diseases as Herpes Simplex (HSV).[19] The drug was not approved for systemic use due to its adverse side effects.

\[
\begin{align*}
&\text{(7)} \\
&m&
\end{align*}
\]

The 1-(1-adamantyl) thio urea derivatives (80), prepared in 1969, were found to possess good activity against Herpes Simplex viruses (HSV-1).[20] In addition, the antiviral activity of 1-(1-adamantly)-3-[(4-aminophenyl)sulfonyl] thiourea (9) compared favorably with that of Adamantane in mice infected with A2/Asian/J305 virus. [21] Meanwhile, the 1-adamantyl secondary and tertiary amines of the general structures (10) were proved to exhibit potent activity against several strains of pathogenic viruses.[22]
Danilenko *et al.* reported the synthesis and antiviral activity of a series of arylamides of adamantane carboxylic acids of the structure (11).[23] The derivative (n = 0, R = 3-OCH3) was the most effective against A2 influenza virus.

The adamantyl thiosemicarbazones (12) and (13), prepared by Sallay and Childress, were found to be useful antagonists of Herpes Simplex and vaccinia viruses. [24]
Several adamantane spiro compounds were synthesized and tested for antiviral activity against influenza viruses, of these, the adamantane spiro-3' pyrrolidines (14) which were found superior to amantadine in level and spectrum of activity. [25] The adamantane spiro sultone (15) also showed marked antiviral activity. [26]

![Diagram](image)

R = H, Me, Allyl, n-Hexyl, Benzyl, CH2CH2OH

The adamantane spiro-2'-pyrrolidines (16) were reported to exhibit potent activity against influenza A H2N2 strains which are not sensitive to adamantane. The structure-activity relationship studies revealed that the 5-methyl substitution was optimal for antiviral activity. [27]

![Diagram](image)

The cyclic rimantadine analogues (17), (18) and (19) were recently prepared and tested for activity against the resistant strains of influenza a viruses. It was observed that the pyrrolidine analogue (19) is the most potent, as it was 9-fold more potent than rimantadine and 27-fold more potent than Adamantane. [28]
Although the classical adamantane derivatives adamantane and rimantadine did not inhibit the replication of human immunodeficiency viruses (HIV), the causative agent of acquired immunity deficiency syndrome (AIDS), several adamantane derivatives were proved to possess marked inhibitory activity. \(N\)-(1-Adamantyl)-4-aminophthalimide (20), produced good inhibitory effect against both HIV-1 and HIV-2 in CEM cell cultures. [29]

**Antimicrobial Adamantane Derivatives**

Several adamantane derivatives have long been known to possess bactericidal and fungicidal activities. The \(N\)-(dialkylaminoalkyl) adamantane-1-carboxamides (21) were proved to exhibit antibacterial and antifungal activities, in addition to anti-inflammatory, antiprotozoal and antialgal activities. [30] Isosteric replacement of the amide function NH with O or S to get the esters and thioesters (22), resulted in improving the antibacterial, antifungal and anti-inflammatory activities. [31]
Anti-inflammatory Adamantane Derivatives

Several compounds were reported to possess anti-inflammatory activity as the main biological activity. The adamantane spiro tetrahydroxazinone (23) was reported to elicit 30% reduction of the carrageen in induced paw oedema in rats.[32]

CNS Activity of Adamantane Derivatives

As a result of the high lipophilicity of adamantane molecule, high lipophilicity is reflected on several adamantane-containing derivatives. The lipophilicity of the adamantane derivatives enables them to pass through the blood brain barriers leading to the existence of high levels of these derivatives in the central nervous system. After the approval of Adamantane and rimantadine in the treatment and prophylaxis of influenza infection, the use of these drugs suffered from the undesirable CNS stimulant side effects such as insomnia, nervousness and diminished concentration, in addition to the undesirable cardiovascular effects.[33] The
therapeutic efficacy of Adamantane in the symptomatic treatment of Parkinson's disease was discovered serendipitically in 1969, and Adamantane is still in use as anti-Parkinsonian drug for more than 30 years.[34] The complete mechanism of action of Adamantane still remains elusive. Adamantane is a dopaminergic, noradrenergic and serotonergic substance with neuroprotective properties.[35] Adamantane is known to increase the synthesis, release and uptake of dopamine in the striatum, which is consistent with its amphetamine-like action.[36] Adamantane was found to act as blocker of brain monoamine oxidase A and as non-competitive \(N\)-methyl-D-aspartate (NMDA)-receptor antagonist thereby influencing the dopamine transmission.[37]

Klimova et al. introduced a polar hydroxyl group to some adamantly amines, the derivatives (24) and (25) were found to possess anticataleptic activity, without the undesirable psychomotor-stimulation activity shown by adamantane. [38]

\[
\text{(24)} \quad \text{(25)}
\]

Miscellaneous Activities of Adamantane Derivatives

Other biological activities were also observed for some adamantine derivatives. The hypoglycemic potency of the adamantyl analog of tolbutamide, \(N\)-\((p\text{-tolylsulphonyl})\)-\(N'\)-(1-adamantyl)urea (26) was found to be five times as of tolbutamide, in addition to its rapid onset of action.[39]
Antitumour activity was also reported for some adamantane derivatives, of these, the (S)-1-(3- and 4-pyridyl)ethyl adamantane-1-carboxylate (27) and (28) which characterized by potent inhibitory activity towards 17-hydroxylase and C17,20-lyase activities of human testicular cytochrome P45017α. In addition, these derivatives were found to be resistant to degradation by esterases.

**Introduction of Thiazole**

Last decade’s problem of chemistry and pharmacology of 4-thiazolidones and related eterocyclic systems that have been of interest for the pharmaceutical science since the beginning of the 20th century, is in principle now undergoing new development. A series of fundamental reviews have been dedicated to 4-thiazolidones.[40-42] But considering the remoteness of these publications from the 60’s till 80’s, they give a true view of the current condition of the research in this area. It is worth to mention, that during last years the interest in 2,4-thiazolidinedion derivatives has been heightened markedly, because of their development as a new class of antidiabetic (insulin-sensitising) drugs (Troglitazone, Pioglitazone, Ciglitazone and Darglitazone).

4-oxo-thiazolidines have been shown to have various important biological activities such as antibacterial, antifungal, antiviral, diuretic, antituberculostatic, anti-HIV, antihistaminic, anticancer, anticonvulsant, anti-inflammatory and analgesic properties.[43-48] A series of 5-
arylidene-4-oxo-thiazolidines is under clinical trials as potential thyromimetic, antimicrobial, antiviral, anti-ischaemic, cardiovascular, anticancer, thrombolytic drugs.

**Chemistry of Thiazolidines**

Thiazolidines have been found important structurally as well as pharmacologically. To exploit the properties of the system, several Thiazolidines have been prepared wherein the presence of >N-C-S linkage imparts activity to the structure.

![Thiazolidine structures](image)

Thiazolidine (29) with a carbonyl group at 4-position is known as 4-thiazolidone (30) or 4-oxo-thiazolidines. Substituent at position 2, 3 and 5 are known and such a group can form alkyl, aryl or aryl-alkyl thiazolidone (31). The oxygen attached to C-2 would make 2,4-thiazolidone (32).[49] These compounds were screened for antitubercular activity and maximum activity has been observed when R1 = H, R = 2-hydroxy phenyl.[50]

In some cases, the Schiff bases were prepared in the same solvent and when the calculated amount of water was separated, 2-sulfanyl acetic acid was added and refluxing was continued.[51] This reactive nitrogen attacks on the carbonyl carbon, which has positive charge thus eliminating hydroxy group and forming the thiazolidone ring (33). The hydroxyl group and the hydrogen atom released combines together to give a water molecule.

![Thiazolidine cycle construction](image)

**Method of Thiazolidine cycle construction**
The synthetic methods leading to the Thiazolidines ring can be divided into three groups:

a) [2,3]-cyclocondensation,

b) synthesis of 4-oxo-thiazolidines from similar heterocycles and

c) Ring transformation of some heterocycles into the 4-oxo-thiazolidine ring.

a) Reaction of [2, 3]-cyclocondensation

In any analogy of mentioned method the substitution of CS$_2$ to COS yield 2,4-thiazolidinedione (34b) derivatives.[52-53] Krus and co-workers [54] have applied the dithiocarbamate method of rhodanines synthesis (35) using chloroacetyl chloride, which reacted with N-alkyl(aryl)dithiocarbaminic acid salt in the present of triethylamine. Use of unsaturated carboxylic acid derivatives instead of chloroacetic acid derivatives in the last step is an interesting modification of this method. Reaction of maleimides [55] or aroylacrylic acids [56-57] with dithiocarbaminates yields amide of rhodanine-5-acetic acids (36) and 5-arylmethylenephodanines (37) accordingly. Similarly DMAD reacts with alkylammonium N-alkylthiocarbamates in methanol at room temperature giving 5-[(methoxycarbonyl)methylidene]-3-R-2, 4-thiazolidinediones (10). [58]
Reaction of chloroacetamides and potassium ethylxanthogenate in the system CS$_2$ – sodium tert-butylate in DMF at 10°C yields the corresponding 3-alkylrhodanines (39).[59] 2,4-Thiazolidinediones (41) are synthesized by the condensation of alkyl(aryl) thiocarbamates
(xanthogenamides) (40) with α-helogenacarboxylic acids in EtOH or AC₂O.[60]

\[
\begin{align*}
\text{R}^+\text{N}^+\text{C}^+\text{Cl}^- & \quad \xrightarrow{\text{H}_3\text{C}^+\text{O}^-\text{SNa}^-} \quad \text{R}^-\text{N}^-\text{C}^-\text{CH}_3^- \quad \xrightarrow{\text{t-BuNa CS}_2^-} \quad \text{O}^-\text{N}^-\text{S}^-\text{S}^-\text{N}^-\text{Ar}^- (\text{Alk}) \\
\text{Alk}^-\text{N}^-\text{O}^-\text{Alk}^- & \quad \xrightarrow{\text{Hal}^-\text{COOH}} \quad \text{R}^+\text{N}^+\text{O}^-\text{Ar}^- (\text{Alk}) \\
\end{align*}
\]

(b) Synthesis of following the transformation among related heterocycles

For example, this approach was demonstrated for the synthesis of some antihyperglycemic thiazolidinediones using α-halogenonitriles (42) as an equivalent of the dielectrophilic synthon [C₂]²⁺.[61-63]

\[
\begin{align*}
\text{H}_2\text{N}^-\text{C}^-\text{NH}_2^- & \quad \xrightarrow{\text{Hal}^-\text{C}^-\text{N}} \quad \text{O}^-\text{N}^-\text{S}^-\text{S}^-\text{N}^-\text{R}^-\text{H}^+ \quad \xrightarrow{\text{H}^+ \quad \text{H}_2\text{O}} \quad \text{O}^-\text{N}^-\text{S}^-\text{S}^-\text{N}^-\text{R}^-\text{H}^+ \\
\end{align*}
\]

A more recent study proposed a one-pot synthesis of 2, 4-thiazolidinedione 44.[64] 2,4-thiazolidinedione-5-acetic acid (45) and 5,5'-bis-2,4-thiazolidinedione (46)[65] that include heterocyclisation and acid hydrolysis.
Heating of 5-arylidenerhodanines (47) with dimethyl sulphate without solvent and further hydrolysis by dilute ethanol is effective for the preparation of 5-arylidine-2, 4-thiazolidinediones (48).[66]

(c) Reaction of ring transformation in 4-oxo-thiazolidines synthesis.
As logical development of rhodanines dethionation methods would be action of chloroacetic acid on 3-(S-thiocarbamoylthio) propionic acids (49) [67] and 2-thioxo-1,3-thiazanones-4 (50). 2-thioxo-1,3-thiazanones-4 undergo ring transformation yielding 2,4-thiazolidinediones (51).[68]
Method of 4-oxo-thiazolidine cycle modification

In 5-position of 4-oxo-thiazolidines the methylene group is active enough,[69-70] which is why one of the most studied reactions of 4-thiazolidones is the modification of the mentioned position.

Synthesis of annulated systems on the base of 4-oxothiazolidines

The formylation of 2, 4-thiozolidinedione according to Vilsmeier-Haack leading to 4-chloro-5-formyl-4-thiazolinone-2 (54) is interesting and important for the synthesis of various annulated heterocyclic systems.[71]

Subsequent reaction of (54) with binucleophiles (thioamides, thiourea, o-aminophenols, o-phenyldiamines, 2-aminothiazoles and etc.) was developed as an approach to synthesis of condensed thiazoles.[72]
Thiazolidone ring breaking reactions

Following the hydrazinolysis of 2,4-thiazolidinedione, as well as rhodanines 4-mercaptoacetylsemicarbazide is obtained, that is converted into triazolone (61). [73] 5-Arylidene-2,4-thiazolidinediones under action of hydrazine yield pyrazoline derivatives.

Pharmacological features of 4-oxo-thiazolidines and possible aspects of their clinical use: 4-Oxo-thiazolidine derivatives are powerful sources of biologically active substances as potential drugs. Even the simplest representatives, such as 2,4-thiazolidinedione, are recommended to be used as radioprotective agents. [75] Mashelkar and Rane et al [76] synthesized compound (62) and studied antibacterial and antitubercular activity. Desai N C et al [77] have synthesized (63) several 4-oxo-quinazoline and thiazolidine derivatives and tested them for their anti AIDS, anticancer and antitubercular activities.
Quinazolinone derivatives having thiazolidone (64), benzoxazole derivatives were introduced by several research workers [78-80] and studied their CNS activity. Shanker and coworkers synthesized several quinazolines (65) as potential anti-inflammatory agents.[81]

Panamkant and Saksena [82] synthesized 2-phenyl-3-p-(2´-methyl-3´-aryl- 4´-oxo-thiazolin-2´-yl) phenylquinazolin-4-ones who studied their antimicrobial activity. Paola Vicini et al [83] synthesized new 2-thiazolylimino-5- arylidene-4-oxo-thiazolidines (66) and assayed for their *in vitro* antimicrobial activity against Gram positive & Gram negative bacteria, yeasts and mould. The compounds were very potent towards all tested Gram positive and Gram negative and other microorganisms.
In 1982 research workers at Takeda [84-94] reported a series of 5-(4-alkoxybenzyl)-2,4-
thiaolidinediones (Ciglitazone) as antihyperglicaemic agent of a new type, which reduces insulin 
resistance in genetically obese and diabetic animal model. After 1997 various drugs like 
Troglitazone (67), Ciglitazone (68), Englitazone (69), Rosiglitazone (70) and Pioglitazone (71) 
are undergoing second phase of clinical trials. Thiazolidinediones have become a separate 
pharmacological group used for the treatment of type 2 Diabetes Mellitus.
During biological anticancer assays in National Cancer Institute (Bethesda, Maryland, USA) of combinatorial library of 4-thiazolidine derivatives and related heterocycles, synthesized in Lviv National Medical University, group of active compounds with low cytotoxicity were selected. [95-96]

**Chemistry of Thiazole**

Thiazole or 1, 3-Thiazole is a five member ring, in which two of the vertices of the ring are nitrogen and sulfur, and the other three are carbons. Thiazoles are a class of organic compounds related to azoles with a common thiazole functional group. Thiazoles are aromatic. The structure of thiazole has been approached using various theoretical methods. [97] Best set of numerical values introduce in to simple Hückel-type MO calculation. Thiazole substituted in 2-, or 4-position by XH groups \((XH = NHR, OH, SH)\) is susceptible to protomerism.
Thiazoles are structurally similar to imidazoles. Like imidazoles, thiazoles have been used to give N-S free carbenes [98] and transition metal carbene complexes. Penicilline are also very important naturally occurring thiazolidine derivative.

2-Aminothiazole derivatives are widely used as pharmaceuticals. For example, Talipexole [99-102] and Pramipexole [103-105] with a 2-aminothiazole moiety are used as antiparkinsonian drugs and dopamine agonists. Pramipexole is a medication indicated for treating Parkinson’s disease and restless legs syndrome (RLS). It is also sometimes used off-label as a treatment for cluster headache or to counteract the problems with low libido experienced by some users of SSRI antidepressant drugs. Pramipexole (72) and Talipexol (73) are fused thiazole derivative having 2-amino functional group.

Thiazole derivatives are widely used in antibacterial drugs like Cefditoren pivoxil [106] is a third-generation oral cephalosporin with a broad spectrum of activity against pathogens, including both Gram-positive and -negative bacteria, and is stable to hydrolysis by many common [beta]-lactamases. 4-Methyl-5-formylthiazole (74) is a key intermediate for the synthesis of cefditoren pivoxil [107], which was first synthesized in 1939[108].
Synthetic methods of Thiazoles

The numerous synthesis of thiazoles are classified according to the nature of the components which join to form the ring system, following the scheme proposed by Sprague and Land [109] in case of thizole, thiazolines and thiazolidines the syntheses are classified as shown below.

(iii) Reaction with thiourea and substituted thiourea

Of all the methods described for the synthesis of thiazole compounds, the most efficient involves the condensation of equimolar quantities of thiourea and α-halo ketones or aldehyde yield the corresponding 2-aminothiazoles (75)[110-111]

Applications of Thiazolederivative

Natural occurance:

The most important naturally occuring thiazole derivative is thiamine (Vitamin B1). Other natural antibiotics such as althiomycin [112-116]. Or micrococcin [117] contain thiazole ring as do many metabolic products of living organism such as 2-amino-4-(4-carboxy thiazol-2-yl) butyric acid (10). which has been isolated from the fungus Xerocomus subtomentosus [118] or aeruginoic acid which has been isolated from the culture medium of Pseudomonas aeruginosa and has the structure 2-o-hydroxyphenylthiazole-4-carboxylic
Luciferin, a natural product responsible for the bioluminescence and chemiluminescence of fireflies, has structure involving both benzothiazole and a thiazoline ring.[120]

\[
\begin{align*}
\text{Penicillin G} & \quad (76) \\
\text{HO} & \quad \text{COOH} \\
\text{NHCOCH}_2\text{Ph} & \\
\text{HMe} & \\
\text{Me} & \\
\text{H} & \\
\text{COOH} & \\
\text{NH}_2 & \\
(77)
\end{align*}
\]

A large number of natural flavors and aroma of foods contain the thiazole nucleus [121].

\[
\begin{align*}
\text{(78)} & \\
(79) & \\
(80) & \\
(81)
\end{align*}
\]

**Pharmaceutical features of the Thiazoles and their clinical applications**

Thiazole is one of important class of five member heterocyclic moiety in pharmaceutical industry. More recently a large number of thiazole derivative have been found to exhibit pharmacological activity.[122-132] More specifically, 2-(p-chlorophenyl) thiazol-4-ylacetic acid (82) possesses anti-inflammtory properties [133]. ‘Thiabendazole’ or 2-(4-thiazolyl) benzimidazole (83) is widely used as an anthelmintic and fungicide. Other derivative such as 3-substituted 4-aminothiazoline-2-thiones (85) possed anti fungul activity, inhibiting in \textit{in-vivo} the growth of \textit{Xanthomonas oryza}.[134].
Yufu Sagara et al [135], synthesized a novel class of 2-Aminothiazole-4-carboxamides derivative (86) having Muscarinic M3 Selective Antagonists, which is target for treatment of pulmonary urinary diseases.

Shigeo Ueda et al [136] synthesized a series of 2-amino thiazole (87) for Inducible Nitric Oxide Synthesis Inhibitors,
The chemistry and pharmacology of thiazole derivative have been of great interest to medicinal chemistry because thiazole derivatives have wide range of pharmacological properties like anti-inflammatory [137] antibacterial Antiviral [138], anticancer [139].

Number of molecules having thiazole moiety as a core are in market for different therapeutic category (chart 1). Also number of molecules having thiazole moiety as a core are in different clinical trials.

[Images of chemical structures of Dasatinib, Meloxicam, Cefotiam, Pramipexole, Famotidine, and Riluzole with their respective uses]
Nitazoxanide (Romark Laboratories)
Viral replication inhibitor; Antibacterial

Mivotilate (Yuhan Corp)
Hepatitis B virus infection

Drugs available in market having thiazole moiety

Acotiamide (Phase 3)
Gastric motility disorder

Lu-AA47070 (Phase 1)
Parkinsons disease

Mirabegron (Phase 3)
Non-insulin dependent diabetes

Tetomilast (Phase 3)
Inflammatory bowel disease
BMS-582949 (Phase 2)
Rheumatoid arthritis

BMS (Discovery)
Anticancer

PRA-027 (Phase 1)
Progesterone receptor modulator

ER-24161 (Phase 1)
Fungal infection
PART-[B]: STUDIES ON ISO-QUINOLINE BASED 1, 2, 4-TRIAZOLES DERIVATIVES

Introduction

Triazole is a class of five-membered nitrogen heterocyclic ring compounds containing at least one other non-carbon atom of nitrogen, sulfur, or oxygen and its importance in medicinal chemistry. 1, 2, 4 trizoles are important as heterocyclic components of many natural products, drugs, and biologically active molecules. Consequently, new efficient methodologies for the preparation of triazole derivatives provide a valuable tool to synthetic organic chemists.


![Triazole Structure](image)

(88)

The triazoles are numbered to indicate the relative positions of the nitrogen atoms, tetrazole and pentazole are unambiguous names. 1,2,3-triazoles are surprisingly stable, when one considers that they contain three directly-linked nitrogen atoms, but on flash vacuum pyrolysis at 500°C they do lose nitrogen to give 2H-azirines, probably via the 1H-isomers.[164-165]
The stability of 1, 2, 4-triazole nucleus is an inherent property of its aromatic nature. An aromatic sextet is formed by contribution of one $\pi$ electron from each atom joined by double bonds and the remaining two electrons from a nitrogen atom. Such a system is stabilized by resonance and though the triazole nucleus may be represented by tautomeric forms,[166-168] each tautomer is capable of extended resonance and its structure is more correctly represented as a hybrid to which the following canonical forms[169-171] contribute.

It is also necessary to consider the tautomeric form where the imino hydrogen atom is at the 4-position. The canonical forms that contribute to this resonance hybrids.[172] are given below.
This representation makes the assumption that the triazole nucleus actually consists of two hybrid structures,[173] each representing an individual tautomeric form. In modern theories such a view is incorrect. A more suitable expression is to regard 1, 2, 4-triazoles as a true aromatic system,[174] stabilized by resonance and represented below.

It is not intended to represent the charges on a nitrogen atom and on the hydrogen atom as separate,[175-177] complete charges but merely as a slight, overall negative charge on the ring, balanced by a corresponding positive charge on the hydrogen atom.[178]

**Amphoteric nature**

1,2,4-Triazoles are amphoteric in nature, [179] forming salts with acids as well as bases.

**Tautomerism in triazoles**

Tautomerism is possible in both the structural isomers of triazoles.

A. **Tautomerism in 1,2,3-triazoles**

1,2,3-Triazoles have two tautomeric forms, $1H$-1,2,3-triazole (91) and $2H$-1,2,3-triazole (92).
B. Tautomerism in 1,2,4-triazoles

1, 2, 4-Triazoles exhibit two tautomeric forms namely $[4H]-1, 2, 4$-triazoles (93) and $[1H]-1, 2, 4$-triazoles (94).

\[
\text{N} \quad \text{N} \\
\text{NH} \quad \text{N} \\
(93) \quad (94)
\]

The higher stability for tautomer (94) is indicated by temperature coalescence studies,[179-181] x-rays studies, basicity measurements, dipole moment studies, NMR-spectra and theoretical methods.

C. Tautomerism in substituted-1,2,4-triazoles

Among the substituted 1,2,4-triazoles, 3-mercapto-1,2,4-triazoles exist in two tautomeric forms, because the labile hydrogen may be attached either to the nitrogen or the sulfur atom. It exhibits thione-thiol tautomeric forms shown below. This compound exists predominantly in thione (95) form.[182]

\[
\text{N} \quad \text{N} \\
\text{NH} \quad \text{N} \\
R \quad S \\
1 \quad 2 \\
(95) \quad (96)
\]

Chloro-1,2,4-triazoles exist as 3-chloro-$1H$-1,2,4-triazole (97a), 3-chloro-$4H$-1,2,4-triazole (97b) and 5-chloro-$1H$-1,2,4-triazole (97c). These tautomers have the stability order; 97a > 97c > 97b according to physical and theoretical calculations 6. In case of bromo-1,2,4-triazoles, the possible tautomeric forms are, 3- bromo-$1H$-1,2,4-triazole (98a), 3-bromo-$4H$-1,2,4-triazole (98b) and 5-bromo- $1H$-1,2,4-triazole (98c). According to physical and theoretical calculations,
the tautomer (98a) and (98c) are of similar energy and the most stable tautomer is (98c). These calculations agree with the results of Flammang et al.[183]

\[
\text{X} \quad \text{N} \quad \text{H} \\
\text{N} \quad \text{X} \\
\text{N} \quad \text{N} \\
\]

D. Spectroscopic evidence of Tautomerism

Generally, the mixtures of tautomers are formed by the compounds having free NH group. In the dominant isomer, the position of NH proton in NMR spectra is generally unknown but sometimes spectroscopic comparison with alkylated compounds is beneficial. It has been shown that alkylation and acylation of 1,2,4-triazole leads to 1-substituted compounds and in the absence of other information, the tautomeric mixtures are represented by 1-\(H\) form in both 1,2,3-triazoles and 1,2,4-triazoles.

Spectroscopy of 1,2,4-triazole

Ultraviolet, infrared and nuclear magnetic resonance spectroscopic studies are very informative about the structure of 1, 2, 4-triazoles and their derivatives.

Ultraviolet spectroscopy

The unsubstituted 1, 2, 4-triazole (99) shows a very weak absorption at 205 nm in the ultraviolet absorption spectrum. Bathochromic shift occurs in N-acetyl- 1, 2, 4-triazole (100), with the absorption band being located at 221.5 nm. A similar shift in the absorption maximum of 3,5-dimethyl-1,2,4-triazole (101) Appears on conversion into N-acetyl-3,5-dimethyl-1,2,4-triazole (102).
Cyclopentadiene has an absorption maximum at 238.5 nm and by replacing carbon-carbon unsaturation with carbon-nitrogen unsaturation, a known hypsochromic shift occurs, therefore, the lower value obtained for 1,2,4-triazoles is understandable.

A large hyperchromic effect occurs on the acetylation of triazole and its derivatives which may be compared qualitatively to the similar effect observed in passing from benzene to acetophenone. In case of 5-substituted-3-mercapto-1,2,4-triazoles, the thione-thiol tautomeric forms can also be differentiated by UV spectroscopy. The ultraviolet spectra of an ethanolic solution of 5-aryl-3-mercapto-1,2,4-triazoles usually show two absorption maxima at 252-256 nm and 288-298 nm. The absorption at 288-298 nm is due to the presence of the chromophoric C=S group.[184-187]

Infrared spectroscopy

The infrared spectroscopy is also very useful in characterization of triazole ring. The absorptions in the region of 1570-1550 cm\(^{-1}\) due to N=N and in the region of 1640-1560 cm\(^{-1}\) due to C=N functions are the diagnostic features. 4-Amino-1,2,4-triazoles show the characteristic strong N–H stretching of a primary amine at 3400-3200 cm\(^{-1}\).

In 5-substituted-3-mercapto-1,2,4-triazoles, the thione-thiol tautomeric forms can also be differentiated in the IR spectra by the presence of C=S absorption band at about 1325-1300 cm\(^{-1}\) for thione and by characteristic SH absorption band at about 2600-2550 cm\(^{-1}\) for thiol forms.

The N–H stretching vibrations at 3165 cm\(^{-1}\) and 3450 cm\(^{-1}\) have also been found supportive of thione-thiol equilibrium. 4-Amino-1,2,4-triazoles have been characterized by the appearance of N–H bands in the regions of 3200-3100 cm\(^{-1}\). For NH\(_2\) group, the absorption bands appear at about 3400- 3300 cm\(^{-1}\).

NMR and mass spectrometry
$^{13}$C NMR is a powerful tool to characterize 1,2,4-triazol-3-ones. In the spectrum of 1,2,4-triazol-3-ones two values for chemical shifts are obtained, one at about 164-173 ppm for imine (C=N) and the other at 150-160 ppm for carbonyl (C=O) carbon.

In EIMS of 1,2,4-triazoles, a strong molecular ion peak is always observed and the cleavage of bonds between N1–N2 and N4–C5 has been observed usually. The triazole ring also undergoes N1–N2 and C3–N4 cleavage.[188]

**Applications and biological activities**

1,2,4-Triazole and its derivatives are an important class of compounds which possess diverse agricultural, industrial and biological activities [189], including anti-microbial [190-192], anticonvulsant [193], antifungal [194], anticancer [195-196], diuretic [197], hypoglycemic [198], sedative[199], antitubercular [200] anti-inflammatory[201], antibacterial [202-205], and. In recent years, the synthesis of these heterocyclic compounds has received considerable attention. This wide range of applications has been covered by more than sixty papers in the literature, many in the form of patents.

**Agricultural applications**

In the plant protection technology, the research has been promoted to discover more efficient pesticides to tackle new challenging problems. In order to selectively control the growth of weeds, a whole range of azole herbicides has been developed exhibiting high levels of activity, application flexibility crop tolerance and low levels of toxicity to mammals. Triazoles play an important role among this classes of heterocycles. A series of 1, 2, 4-triazole derivatives have been patented and extensively employed [206]

**Pharmacological applications**

Over the last few decades, the biological and pharmaceutical properties of 1,2,4-triazoles have created considerable interest in their synthesis and characterization [207]. 1,2,4-Triazole and its derivatives possess widely differing activities e.g., bacteriostate[208], bactericide [209], antifungal, sedative, anticarcinogen, tuberculostatic, anti-inflammatory,diuretic, antiviral, muscle relaxant and antihuman immunodeficiency virus (HIV) [210-211]. Three major fungal infections in immuno-compromised individuals are candidosis, aspergillosis and cryptococcosis [212]
Whereas the most widespread human superficial and cutaneous fungal infections are dermatomycoses such as, toenails and tinea pedis. The common antifungal agents currently used in clinic are azoles (such as fluconazole, ketoconazole, and itraconazole), polyenes (such as amphotericin B) nystatin [213], echinocandins (such as caspofungin and micafungin) [214] and allyl amines [215]. In antifungal chemotherapy, azoles having fungistatic and broad-spectrum activities are used widely against most yeasts and filamentous fungi. Fluconazole is preferred as first line antifungal chemotherapy with relatively low toxicity but is not effective against avasive aspergillosis and has suffered severe drug resistance [216].

Glycosylated triazole derivatives like 1-β-D-ribofuranosyl-[1H]-1, 2, 4- triazole-3-carboxamide (Virazo) [217] belong to the highly potent drugs against DNA- and RNA-viruses [80]. Moreover, this compound shows antitumor activity just as the anomeric 1-(2,3,4,6-tetra-O-acetyl-D-glucopyranosyl)-5-nitro- [1H]-1,2,4-triazole. The therapeutic use of non-steroidal anti-inflammatory drugs (NSAIDs) which are used in treatment of a number of arthritic diseases such as rheumatoid arthritis and osteoarthritis is limited because of their side effects, such as, gastrointestinal haemorrhage and ulceration [218]. So, new drugs having potent anti-inflammatory activity with minimum side effects have been developed.

INDUSTRIAL APPLICATIONS

A. Chemical Industry

Some selected triazoles have been used as light emitting diodes (Electroluminescent devices) [219]. Some triazole systems have extensive use in the separation of silver from other metal cations in liquid membrane systems [220].

In addition, these compounds are used as synthetic dyes and bleaching agents [221]. Moreover, the inks having smooth writing properties also contain triazole derivatives e.g, 3-amino-5-mercapto-1,2,4-triazole. These 155 compounds have also been reported as inhibitors of corrosion of copper, brass, aluminium and steel in marine environment [222] and inhibit fog formation in photographic emulsions [223], plant growth inhibitors [224] and herbicides.[225]

B. Textile industry
The triazole derivatives have many applications in textile industry e.g., sodium salt of a sulphonated triazole derivative possesses good detergent action and N-benzylated aminotriazoles (103) have useful properties in inhibiting the acid fading of dyestuff [226].

C. Cotton industry

In the cotton industry, 3-amino-1,2,4-triazole under its trade name Amizol, has been used as a commercial defoliant for a number of years [227].

Synthetic approaches towards 1, 2, 4-triazoles

The early methods of preparation of 1,2,4-triazoles were simple and low yields were obtained but they made the nucleus available for study within a year of the original discovery by Bladin. These have now been replaced by later modifications and by more efficient methods [228].

From semicarbazides

A method of practical importance involves synthesis of 1-aryltriazoles from 1-arylsemicarbazides. This is illustrated by the formation of 3-hydroxy-1-phenyl-1,2,4-1H-triazole (104) from 1-phenylsemicarbazide and boiling anhydrous formic acid. By heating (104) to over 200°C with phosphorus pentasulfide103, 1-phenyl-1,2,4-1H-triazole (105) is obtained in 80% yield.
From Triazine

The reaction of $s$-triazine with a substituted hydrazine salt\textsuperscript{104} gives substituted 1,2,4-triazoles. For example, from phenyl hydrazine hydrochloride 1-phenyl-1,2,4-$1H$-triazole is obtained in 83% yield. The reaction proceeds by the formation of a substituted formamidrazone as a result of ring cleavage of $s$-triazine, which reacts immediately with another molecule of triazine to yield the substituted triazole.

\[
\begin{align*}
\text{HN} & \text{-N} & \text{-NH}_2 \\
\text{HN} & \text{-NHCl} & \text{NH}_2 \text{Cl}
\end{align*}
\]

From Thiosemicarbazides with Benzoyl chloride

Thiosemicarbazide with benzoyl chloride in boiling pyridine or alkali undergo benzoylation and cyclization resulting in the formation of 4-benzoyl-3-phenyl-$\Delta^2$-5-mercapto-1,2,4-triazoline (106) \textsuperscript{[229]}.

\[
\begin{align*}
\text{S} & \text{-HN} & \text{-NH}_2 \\
\text{S} & \text{-HN} & \text{-NH}_2 \\
\text{O} & \text{-Cl} & \text{pH}>7
\end{align*}
\]
The intuitive statistical argument from two ‘hydrazinic’ N centers against one ‘amine’ N favours the less symmetrical $1H$ rather than the symmetrical $4H$ structure for $1,2,4$-triazole. On the evidence of X-ray diffraction analysis the solid parent triazole has a planar structure with hydrogen bridges between N-1 and N-4 of neighboring rings;[230] of the two N-H bond lengths implied, only that leading to N-1 is of the order required by covalent bonding. Confirmation from similar studies carried out at $160^\circ$C proves the molecular dimensions as shown in following table for one unit of a pleated sheet linked by hydrogen bridges. Slightly different values are obtained at room temperature or in substituted aromatic triazoles.[231]

Molecular Geometry of $1, 2, 4$-triazole$^a$ at $160^\circ$C

<table>
<thead>
<tr>
<th>Angle (°)</th>
<th>Bond</th>
<th>Bond length (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-1-4</td>
<td>110.2</td>
<td>1-2</td>
</tr>
<tr>
<td>1-2-3</td>
<td>102.1</td>
<td>2-3</td>
</tr>
<tr>
<td>2-3-4</td>
<td>114.6</td>
<td>3-4</td>
</tr>
<tr>
<td>3-4-5</td>
<td>103.0</td>
<td>4-5</td>
</tr>
<tr>
<td>4-5-1</td>
<td>110.1</td>
<td>5-1</td>
</tr>
<tr>
<td>N(1)-H</td>
<td>103.0</td>
<td></td>
</tr>
<tr>
<td>C(3)-H</td>
<td>93.0</td>
<td></td>
</tr>
<tr>
<td>C(5)-H</td>
<td>93.0</td>
<td></td>
</tr>
</tbody>
</table>

$^a$The numbering refers to annular centers in $1H$–$1,2,4$-triazole.

**Different routes for synthesis of triazoles**

[A] Synthesis of triazole rings from acyclic compounds.

i. Methods employing hydrazine derivatives

The ease of forming C-N and C=N bonds as compared with difficulty of N-N formation practically prescribes the use of hydrazines in the synthesis of 1, 2, 4-triazoles. In addition to hydrazine, acylhydrazine, amidrazone or acylamidrazone can also be used for the synthesis of triazole analogues.
ii. Nitrilimine methods

Huisgen’s studies of 1,3-dipolar cyclo additions leading to a great variety of heterocyclic systems are applicable to the synthesis of triazoles and derivatives. Nitrilimines (5) formed by dehydrohalogenation of C-halobenzyl idenephynyl hydrazones (4) react with C≡N, C=N (as in CNO) to afford triazoles and triazolines.[232]
Synthesis of triazole rings from other heterocyclic systems

Transformation of other heterocycles into triazoles implies one or more of the following operations:

i. Destruction of non-triazole rings

Methods of this type are best considered as reactions of the fused ring systems. The example illustrated in the given scheme is of potential interest in pharmacology. The conversion of the 1-aminoadenosine (112) into the imidazolyltriazole (113) amounts to triazole formation from an amidrazone intermediate and a formyl group derived from the pyrimidine moiety.

\[
\begin{align*}
\text{(112)} & \quad \xrightarrow{\text{OH}^-} \quad \text{(113)} \\
\text{Where } R &= \text{D 1-ribosyl}
\end{align*}
\]

ii. Cleavage and recyclization of non-triazole rings

Following scheme summarizes the overall reaction much used for the conversion of 1,3,4-oxadiazoles (X=O) (114) and thia-diazoles (X=S) (114) to triazoles (115a) and (115b).

\[
\begin{align*}
\text{(114)} & \quad \xrightarrow{\text{R'},R''} \quad \text{(115a)} \\
\text{Where } X &= \text{O,S} \\
R',R'' &= \text{H,Alk,Ar} \\
\text{(115 b)} & \quad \text{R''=H}
\end{align*}
\]

Nitrilimines derived from non-triazole rings
Nitrilimines for the preparation of triazoles are often generated from tetrazoles or from 1,3,4-oxadiazoline (116) derivatives, which themselves are obtainable by thermolysis of tetrazoles.

\[ \text{Ar} \quad \text{O} \quad \text{Ph} \quad \text{OMe} \quad \text{D} \quad \rightarrow \quad \text{ArC} \quad \text{N} \quad \text{NPh} \quad \text{triazoles} \]

\( (116) \)

[D] Introduction and modification of functions on the triazole ring

Specific functions in specified positions of the triazole ring are available in three ways (a) constituent portions of the ring to be formed carry the functions (b) the preformed triazole ring is substituted and (c) existing functions are modified.

i. Alkyl and aryl groups

Alkyl and aryl triazolium compounds are formed mostly by quaternization of preformed triazoles, more rarely by rearrangement of oxadiazoles proceeding through acylamidrazzone intermediates. An unusual method is the addition of the alkoxydiazonium fluoroborate (117) to the Schiff base (118) to form the triazolium salt (119) through a mechanism that may involve a triazolidine intermediate.

\( (117) \quad \rightarrow \quad (118) \quad \rightarrow \quad (119) \)
ii. Halo groups

The application of the amidrazone method is limited. Most of the other published preparations are equally divided between electrophilic halogenation, nucleophilic displacement of halogen or nitro groups, and displacement of diazo or nitrosamino groups.

iii. Carbonyl functions

The two major techniques for the preparation of triazolecarboxylic acids are the amidrazone method and transformations of replacements of existing functions. In the former case one can introduce the carboxylic acid through starting materials such as (120). Alternatively, cyclization of other amidrazone can be accomplished with derivatives of oxalic acid, e.g. by converting the acylamidrazone (121) into the amide (122) from which the acid may be liberated by hydrolysis.

![Chemical structures]

[E] Intramolecular condensations [233]

i. Ring closures in alkaline media

Ring closure of acyl derivatives of semicarbazides, thiosemicarbazides, or aminoguanidines in alkaline solutions is a method widely applied for the preparation of s-triazoles. Gehlen [234] reported that 3-hydroxy-5-alkyl–s-triazoles (123) are produced in 40-50% yield by this method.

![Chemical structure]

R' = H, C₆H₅

ii. Ring closures in acidic media
In concentrated hydrochloric acid, thiourazole (124) has been obtained from carbamylthiosemicarbazide [235] (125, R=H), but phenylcarbamyl-thiosemicarbazide (125, R=C6H5) apparently is changed into 2-amino-5-hydroxythiadiazoles.[236] From (126) in concentrated hydrochloric acid, 4-aminodithiourazole is obtained.[237]

iii. Oxidative ring closures in the presence of peroxide

From the S-methylthiosemicarbazone of benzaldehyde, 3-phenyl–5-methyl–thio-1,2,4-triazole is obtained in an unspecified good yield by peroxide oxidation.[238]

iv. Thermally induced ring closure

Several acyl derivatives of semicarbazides, thiosemicarbazides, and aminoguanidines change into s-triazoles when heated.

[F] Molecular rearrangements

Hydroxy-s-triazoles are obtained on pyrolysis of hydrazones of pyruvylhydroxamic acids, the Gastaldi reaction.[239] In an illustration of the reaction, 1-phenyl-3-methyl–5-hydroxy-
1,2,4-triazole is obtained from the phenylhydrazone of pyruvylhydroxamic acid in propionic anhydride.

\[
\text{HO-} \quad \begin{array}{c}
\text{N} \\
\text{C} \\
\text{H}_2 \text{CO} \text{O} \\
\end{array} \\
\text{N} \\
\text{H} \\
\text{N} \\
\text{O} \\
\text{HO} \\
\text{N} \\
\text{H} \\
\text{N} \\
\text{C} \\
\text{H}_2 \text{CO} \text{O} \\
\end{array} \\
\rightarrow \\
\begin{array}{c}
\text{HO} \\
\text{N} \\
\text{C} \\
\text{H}_2 \text{CO} \text{O} \\
\end{array} \\
\text{N} \\
\text{O} \\
\text{HO} \\
\text{N} \\
\text{H} \\
\text{N} \\
\text{C} \\
\text{H}_2 \text{CO} \text{O} \\
\end{array} \\
\]

(129) \quad (130)

[G] Unclassified methods

Certain examples of s-triazole preparations appear unrelated to other methods and have remained undeveloped. In one instance, a triazolotriazole (132) obtained from benzalizine (131) and cyanic acid has been transformed into 1-benzyl-3-phenyl-5-hydroxy-1, 2, 4-triazole (133), identical with the product obtained on oxidation of the benzaldehyde derivative of 2-benzylsemicarbazide.[240]

\[
\begin{array}{c}
\text{HOCN} \\
\end{array} \quad \begin{array}{c}
\text{HO} \\
\text{N} \\
\text{C} \\
\text{H}_2 \text{CO} \text{O} \\
\end{array} \\
\text{N} \\
\text{O} \\
\text{HO} \\
\text{N} \\
\text{H} \\
\text{N} \\
\text{C} \\
\text{H}_2 \text{CO} \text{O} \\
\end{array} \\
\rightarrow \\
\begin{array}{c}
\text{HO} \\
\text{N} \\
\text{C} \\
\text{H}_2 \text{CO} \text{O} \\
\end{array} \\
\text{N} \\
\text{O} \\
\text{HO} \\
\text{N} \\
\text{H} \\
\text{N} \\
\text{C} \\
\text{H}_2 \text{CO} \text{O} \\
\end{array} \\
\]

(131) \quad (132) \quad (133)

Literature survey

Khosrow Zamani et al [241] and Monika Wujec et al [242] synthesized some new 3,5-disubstituted-1,2,4-triazoles (135) and their derivatives through the intramolecular cyclization of 1,4-disubstituted thiosemicarbazides (134).
Bahittin Kahveci et al [243] and Shirodkar P Y et al [244] synthesized different kinds of 1, 2, 4-triazole derivatives and screened for their antitumor activity and found to be weakly cytotoxic. Haydar Yuksek et al [245] synthesized 4-arylamino-4,5-dihydro-1H-1,2,4-triazole-5-one derivatives and checked acidic properties of these new potential biologically active compounds.

Among the triazole, studies for Loreclezole (135) have shown anticonvulsant [246] GABA agonist that binds allosterically to the GABA receptor [247] and also showed antiepileptic [248] activity. Gadaginamath G S et al [249] synthesized triazoles (136) and were found to exhibit a wide spectrum of biological activities. [250-256] They have synthesized some bio-dynamic heterocyclic systems at position-5 linked through methoxy bridge with a view to prepare biheterocycles to enhance biological activities.
Xu Pengfei Y X et al.[257-264] have synthesized thiosemicarbazides, triazoles, thiadiazoles and oxadiazoles with 6-nitrobenzimidazoles \((137)\) in one framework. Jingde Wu et al [265] synthesized novel derivatives of 4-amino-3-(2-furyl)-5-mercapto-1,2,4-triazole \((138)\) as potential HIV-1. Currently non-nucleoside reverse transcriptase inhibitors (NNRTIs) have found to be widespread use in HIV therapy in multidrug treatment regimes and in highly active antiretroviral therapy (HAART). [266]

![Chemical structures](137) ![Chemical structures](138)

Svensson [267] et al synthesized 2, 4-dihydro-[1,2,4]triazole-3-thione \((139)\). These compounds are inhibitors of the enzyme myeloperoxidase (MPO) and are thereby particularly useful in the treatment of prophylaxis of neuroinflammatory disorders. Hardtmann G E et al [268] have prepared tricyclic 1,2,4-triazoloquinazolines \((140)\) and tested them for antibacterial activity. The synthesized compounds were also tested for anti-inflammatory activity at 3-200 mg/kg, tranquilizer at 5-200 mg/kg and virucidal against pot viruses at 0.01-10 µg/ml.
Where $W = H, CH_3,F,OH,CH_2OH,Ph$

$X = O,CH_2,NR_3$. $R_3 = H,CH,6$ ALKYL

$Y = $phenyl,napthyl

Udupi R.H. et al [269] synthesized different kinds of 1,2,4-triazole derivatives by treating acid hydroxide with alcoholic KOH/CS$_2$ and further with acid hydroxide and tested them for anti-inflammatory and analgesic activities.

R.R. Kamble et al [270] have developed a 3’-substituted-2-aryl-5-methyl-5’-thiox-[4,4’-bi-4H-1,2,4-triazol]-3(1’H,2H)-ones (141) and found intresing properties, such as antinociceptive [271-275], anticancer [276] and plant growth regulative activities. Some 1, 2, 4-triazole derivatives also exhibit bacteriostatic,[277] hypoglycemic [278-282] and antiviral activities.Kane J.M. et al [283] synthesized 1,2,4-triazole derivatives (142) as potential antitumor agents.

Goknur Aktay et al [284] have synthesized 3-[1-(4-(2-methylpropyl) phenyl)ethyl]-1,2,4-triazole-5-thione (143) and its bicyclic condensed derivatives 6-benzylidenethiazolo[3,2-b]-
1,2,4-triazole-5(6H)-ones (144) and demonstrated that they possess moderate anti-inflammatory activity against carrageenan induced mice paw edema.

\[
\text{NHN} \quad \text{N} \quad \text{N}
\]

Where \( R = 4-\text{Cl},3-\text{CH}_3,4-\text{CH}_3,2-\text{OCH}_3 \)

(144)

Mhasalkar M Y et al [285] synthesized some 5-substituted, 4-(substituted aryl), 3-mercapto 1,2,4-triazoles (145) which showed antifungal activity. Similarly 5(p-sec-amylphenyl) methoxy-3-mercapto1,2,4-triazole (146) showed good antifungal activity.

\[
\text{N} \quad \text{N} \quad \text{R}
\]

\[
\text{SH} \quad \text{O} \quad \text{HN} \quad \text{N} \quad \text{SH}
\]

Where \( R = \text{Aryl} \ R' = \text{Alkyl} \)

(145) (146)

**Importance of 1,2,4-triazoles as analytical reagents [284]**

Substituted 1,2,4-triazoles find many useful applications. Some of them are used as analytical reagents for determination of boron, antimony and cobalt. Other triazoles find many synthetic uses as halogenating agents [286] or as activating polymeric reagents. Now 1,2,4-triazoles derivatives are widely used as biocides and as antifungal agents. [287] Several 1,2,4-triazoles derivatives find applications as photographic reagents.
Commercially available 1,2,4-triazoles as antimicrobial agents

Although dozens of 1,2,4-triazoles have been synthesized and reported, the most notable ones being developed, or used, as a medicine worldwide include Fluconazole, Ribavirin, Triazolam, Itraconazole, Viramidine, Voriconazole and Terconazole.
Looking to the pharmaceutical applications of 1,2,4-triazoles derivatives, in this section we have synthesized some biologically active heterocyclic compounds which contain triazole moiety.

**Introduction of Iso-quinoline**

The Quinoline and Isoquinoline nucleus is found to be very important in pharmacy field. In recent years, a lot of synthetic drugs have been synthesized in different yield. Isoquinoline and quinoline are benzopyridines, which are composed of a benzene ring fused to a pyridine ring. In a broader sense, the term isoquinoline is used to make reference to isoquinoline derivatives. 1-Benzylisoquinoline is the structural backbone in naturally occurring alkaloids including papaverine and morphine. The isoquinoline ring in these natural compound derives from the aromatic amino acid tyrosine.[288]
Isoquinoline, a structural isomer of quinoline is benzopyridine composed of a benzene ring fused to a pyridine ring. The numbering system of the isoquinoline nucleus is Shown in structure.

![Isoquinoline](image)

**General structure and numbering system of isoquinoline nucleus**

Isoquinoline is a colorless hygroscopic liquid at room temperature with a penetrating, unpleasant odor. Impure samples can appear brownish, as is typical for nitrogen heterocycles. It crystallizes platelets that have a low solubility in water but dissolve well in ethanol, acetone, diethyl ether, carbon disulfide, and other common organic solvents. It is also soluble in dilute acids as the protonated derivative.

Several isoquinoline synthetic methods have been developed due to its skeleton represent as a key intermediate for synthesis of many aporphine alkaloids. The synthetic approaches toward isoquinoline alkaloids and derivatives can be divided systematically into different types relying on the mode of formation of the heterocyclic ring [289] and the homocyclic ring, where the dashed lines indicate bonds being formed. Type 6, 8 and 14 are cycloaddition, while type entails a rearrangement (Grethe, 1981).
Type 1 Type 2 Type 3 Type 4
Type 5 Type 6 Type 7 Type 8
Type 9
Type 10
Type 11
Type 12
Type 13
Type 14
Type 15

**Isoquinoline alkaloid synthetic approaches**

The classical and important methods of isoquinoline synthesis are the Bischler-Napieralski reaction, the Pictet-Spengler reaction, and the Pomeranz-Frisch reaction. Bischler-Napieralski reaction and Pictet-Spengler reaction belong to type 1 synthesis, involving ring closure between the benzene ring and the carbon atom that forms C-1 of the resulting isoquinoline ring. In addition, the Pomeranz-Fritsch reaction, the ring closing between C-4 and C-4a of the isoquinoline nucleus, is type 5 synthesis.

**The Bischler-Napieralski reaction**

The Bischler-Napieralski reaction is the most valuable and frequently used for the synthesis of isoquinoline compounds. It involves the cyclodehydration of an acyl derivatives of β-phenethylamides [290] in the presence of a Lewis acid such as phosphoryl chloride or phosphorus pentoxide in dry inert solvent to afford a 3,4-dihydroisoquinoline [291]
The cyclization of Bischler-Napieralski reaction could be occurred in more than one direction. For instance, cyclization of m-methoxy-β-phenylethylamine [292] may be led to either 6-methoxy- or 8-methoxy-3,4-dihydro isoquinoline, depending on the direction of ring closure. When the para position to the methoxy group has no substituent, cyclization preferentially occurs at the para to give a 6-methoxy-isoquinoline derivative. When the para position is blocked, cyclization will proceed to the otho position to the methoxy group.

If the both available positions are activated to a similar extent, a mixture of both cyclized products is obtained, as in case of cyclization of N-(3-benzyloxy-4,5-dimethoxyphenethyl)-4-benzyloxy-3-methoxyphenylacetamide (152) to the 8-benzyloxy-6,7-dimethoxy- (153) and 6-benzyloxy-7,8-dimethoxy-3,4-dihydroisoquinoline derivative (154).
The Pictet-Spengler reaction

The Pictet-Spengler reaction, one of the special cases of the Mannich reaction, is the condensation of a β-arylethylamine with a carbonyl compound to yield 1,2,3,4-tetrahydroisoquinoline.

In 1911, Pictet and Spengler reported the condensation of phenylethylamine (155) with a dimethoxymethane in the presence of concentrated hydrochloric acid to form 1,2,3,4-tetrahydroisoquinoline (157).

In nature, the use of concentrated hydrochloric acid as a catalyst in preparing tetrahydroisoquinoline was not reasonable, so the condensation under possible physiological condition was examined. In 1934, Schöpf and Bayerle achieved Pictet-Spengler reaction under the same condition in plants. The reaction of β-(3,4-dihydroxyphenyl)ethylamine (158) with homopiperonal (159) gave 1,2,3,4-tetrahydro-6,7-dihydroxy-1-piperonylisoquinoline (160) at pH 6 and 25°C.
ISOQUINOLINE FROM O-ALKYNYL-ARALDEHYDE IMINES:

\[ 
\text{o-ido araldehyde imine} \xrightarrow{\text{DMF,Pd(oAC)\textsubscript{2} Na\textsubscript{2}CO\textsubscript{3}}} \text{PhCH\textsubscript{2}COOEt} \xrightarrow{100^\circ C} \text{Isoquinoline} 
\]

ISOQUINOLINE ETHANEAMIDES

The Pomeranz-Fritsch reaction

This reaction, first reported by Pomeranz and Fritsch, has been utilized in the synthesis of a variety of isoquinoline derivatives. Cyclization of benzal aminoacetals (169) under acid-catalyzed condition resulted in the formation of the expected isoquinoline (164) (Pomeranz, 1893; Fritsch, 1893).

This reaction is carried out in 2 steps: 1) aryl aldehyde is condensed with amino acetal to form an aryl-aldimine. 2) aldimine is cyclized by treatment with strong acids.
The process is carried out in two stages; the first involves the formation of the benzalminoacetal (163), and the second entails the acid-catalyzed cyclization. In the first step, the Schiff base is formed by the condensation of aromatic aldehyde (162) and an aminoacetal (161), and the product can be used in the cyclization step either with or without purification. In the cyclization step, sulfuric acid has been used in concentrations ranging from fuming acid to approximately 70% sulfuric acid or in a mixture with other acidic reagents such as gaseous hydrogen chloride, acetic acid, phosphorous pentoxide and phosphoryl chloride.
PART-[C]: STUDIES ON CHROMEN BASED THIAZOLIDIN DERIVATIVES

Introduction

Heterocycles are one the most important compounds in organic chemistry. Among them, sulfur and nitrogen-containing heterocyclic compounds have been the focus of interest among researchers because of their biological activities [293-295].

Thiazole or 1, 3-Thiazole is a five member ring, in which two of the vertices of the ring are nitrogen and sulfur, and the other three are carbons. Thiazoles are a class of organic compounds related to azoles with a common thiazole functional group. Thiazoles are aromatic. The structure of thiazole has been approached using various theoretical methods. Best set of numerical values introduce in to simple Hückel-type MO calculation. Thiazole substituted in 2-, or 4-position by XH groups (XH = NHR, OH, SH) is susceptible to protomerism.

Fused Thiazolidine continue to attract considerable attention because of their great practical usefulness, primarily, due to a very wide spectrum of biological activities. This is evident, in particular, from publications of regular reviews on the chemistry of systems where the Thiazolidine ring is fused to various heterocycles, such as purines,[296-302],pteridines,[303] quinazolines,[304-306] pyridopyrimidines,[307-311] triazolopyrimidines,[312-317] pyrazolopyrimidines,[318] pyrimidoazepines,[319] furopyrimidines, Thiazolidine, and pyrrolopyrimidines.[320] Thienopyrimidines occupy a special position among these compounds. Along with some other pyrimidine systems containing an annulated five-membered heteroaromatic ring, thienopyrimidines are structural analogs of biogenic purines and can be considered as potential nucleic acid antimetabolites. Earlier, various aspects of the chemistry and biology of isomeric thienopyrimidines have been reviewed.[321-329]

Thiazolidine nucleus, especially the 4-thiazolidinone moiety is an important chemical scaffold that possesses diverse biological properties.
Thiazolidine Ring                     Thiazolidine-4-one Ring

There are several published reports on the biological activities of thiazolidin-4-one derivatives [330-331]. These include anti-hyperglycaemic, anti-inflammatory, anti-bacterial, anti-fungal, anti-cancer, anti-convulsant activity, anti-hypertensive activities etc. Thiazolidine ring is also present in the PPAR γ agonists (anti-diabetic drugs).

**Anti-oxidant moiety / hindered phenolic group**

Oxidative stress plays an important role in the development of atherogenesis, diabetes and many conditions. Oxidative stress is the cause of the inflammation that originates in adipose tissue which results in insulin resistance.[323-333] Excess reactive oxygen species (ROS) generated by the mitochondria contributes to the oxidative burden of the cell. In the case of atheroma, the oxidative modification of deposited LDL cholesterol makes it resistant to degradation. So presence of an anti-oxidant moiety in the molecule was thought to be useful in maintaining the oxidant-anti-oxidant balance. Moreover, studies on thiazolidine derivatives with hindered phenolic groups/ antioxidants (for e.g. butylated hydroxyl toluene (BHT)) had produced compounds which exhibited hypolipidaemic and hypoglycaemic activities with ability to inhibit lipid peroxidation.[334]

The initial few molecules had a hindered phenolic group in their structure attached to C-2 of thiazolidinone ring (e.g. NAT1 has para methoxy phenyl group and NAT-2 has BHT) but later on derivatives without any hindered phenolic (anti-oxidant) group in their structure (e.g. NAT-3 has toluyl group and NAT-4 has para chloro phenyl group) were prepared.

**Synthesis of the Thiazolidine -4 one derivatives**

Thiazolidine derivatives are prepared by cyclization reactions. Though there are many cyclization reactions reported in the synthesis of thiazolidinone derivatives,[335] but the compounds synthesized in our laboratory involved the reaction between a Schiff base and an α-mercaptoalkonic acid.[336-337]
There are numerous biologically active molecules which contain various heteroatoms such as nitrogen, sulphur and oxygen, always drawn the attention of chemist over the years mainly because of their biological importance. Thiazolidinones are thiazolidine derivatives and have an atom of sulfur at position 1, an atom of nitrogen at position 3 and a carbonyl group at position 2, 4, or 5. However, its derivatives belong to the most frequently studied moieties and its presence in penicillin was the first recognition of its occurrence in nature.[338-339] Similarly 1,3-thiazolidin-4-ones are heterocyclic nucleus that have an atom of sulfur and nitrogen at position 1 and 3, respectively and a carbonyl group at position 4 have been subjected to extensive study in the recent years. The 4-thiazolidinone scaffold is very versatile and has featured in a number of clinically used drugs. They have found uses as antitubercular, antimicrobial, anti-inflammatory and as antiviral agents, especially as anti-HIV agents. It has been extensively reported that presence of arylazo,[340] sulfamoyl phenylazo,[341] or phenylhydrazono[342] moieties at different positions of the thiazolidione ring enhanced anti-microbial activity and its antibacterial activity may be due to its inhibitory activity of enzyme Mur B which is a precursor acting during the biosynthesis of peptidoglycan.[343] Numerous reports have appeared in the literature which highlight their chemistry and pharmacological uses.[344-346]

In the present review, emphasis is given on diverse pharmacological properties associated with substituted thiazolidinones and structurally related thiazolidines. The review covers advances made in the last twelve years and provides a detailed discussion on SAR.

**Preparation of Thiazolidinones**

Several methods for the synthesis of 4-thiazolidinones are widely reported in the literature. The main synthetic routes to 1,3-thiazolidin-4-ones involve three components that is an amine, a carbonyl compound, and a mercapto-acid. The classical synthesis reported can be either a one-pot three-component condensation or a two-step process. The reactions begin by
formation of an imine (the nitrogen of amine attacks the carbonyl of aldehyde or ketone), which undergoes attack by generated sulfur nucleophile, followed by intramolecular cyclization on elimination of water.[347-349]

Common synthetic route for the synthesis of 4-thiazolidinone derivatives.

Eltsov et al. reported an convenient one-step cyclization reaction protocol wherein the reaction of ethyl 5-phenylthioureido- 3H-imidazole-4-carboxylate with bromoacetic acid to
afforded (imidazolylimino)thiazolidinones. The cyclization reaction proceeds by one of the nitrogen atoms of the nucleophilic centers in derivatives of 5-thioureido-3H-imidazole-4-carboxylic acid give the desired thiazolidinone.[350]

Furthermore, novel route to the synthesis of 2-isopropyl-3-benzyl-1,3-thiazolidin-4-ones and 2-phenyl-3-isobutyl-1,3-thiazolidin-4-ones by using 1:1:3 mole ratio of valine, arene aldehyde and mercaptoacetic acid was reported by Cunico et al.[351] and suggested that the insertion of strong withdrawing group, NO₂, present on benzaldehydes favored the synthesis of hetero-cycle 1 in good yields, whereas the methoxy and fluoro groups produces the type 2 thiazolidinones. In continuation of research, authors reported solvent-free synthesis of five-membered heterocyclic thiazolidinones from phenylhydrazine and 2,4-dinitrophenylhydrazine as the amino cores.[352] Pratap et al.[353] have reported another method of synthesis of 2,3-diaryl-4-thiazolidinones (147) wherein Saccharomyces cerevisiae (baker’s yeast) that contained enzyme lipase was used as a catalyst which accelerated the formation of imines as well as cyclocondensation of the aryl aldehydes, amines, and thioglycolic acid.

Various quinazolinyl azomethines 148 on treatment with mercaptoacetic acid in the presence of silica chloride that was used as a heterogeneous catalyst to accelerate the intra-molecular cyclocondensation under solvent-free condition, yield 4-thiazolidinones 149.[354]
Furthermore, the reaction of aryl or alkyl isothiocyanate (150) with a primary amine furnished the corresponding thiourea derivative, (151) which was directly cyclized by treating with halo acetic acid to the corresponding two isomeric 2-imino-thiazolidin-4-ones of the general structures (152) and (153). [355]

Also, coupling reaction between α-chloro amide derivatives (155) with isothiocyanate in the presence of a mild base afforded the iminothiazolidinone derivatives. (156) [356]

\[
\text{Ar} \xrightarrow{\text{NH}_2} \xrightarrow{\text{O}} \xrightarrow{\text{X}} \text{Ar} \xrightarrow{\text{HN}} \xrightarrow{\text{O}} \xrightarrow{\text{X}} \text{Ar' NCS} \\
\xrightarrow{\text{K}_2\text{CO}_3} \xrightarrow{\text{CH}_3\text{CN}} \text{Ar} \xrightarrow{\text{N}} \xrightarrow{\text{Ar'}} \text{N}_{\text{SSN}}
\]

(154) (155) (156)

Where: X- Cl, Br, I

**Biological activity of 4-thiazolidinones**

The thiazolidinones ring has been incorporated into a broad range of known biologically active compounds, either as a substitutent group or as a replacement of another ring inspired researchers to synthesize several compounds containing this moiety. There are several reports in the literature describing the thiazolidinone derivatives for their various biological activities and some of them are covered in this review.

The known approaches to the synthesis of thienopyrimidines can be divided into two main groups: construction of the pyrimidine ring by intramolecular cyclization of thiophene derivatives and thiophene ring closure in pyrimidine derivatives.

**Introduction**

**Chromen**

Chromen is a derivative of benzopyran with a substituted keto group on the pyran ring. It is an isomer of coumarin. Derivatives of chromone are collectively known as chromones. Most, though not all, chromones are also phenylpropanoids. Chromones constitute one of the major classes of naturally occurring compounds, and interest in their chemistry continues unabated because of their usefulness as biologically active agents.
Chromen (157) is a chemical compound found in many plants, notably in high concentration in the tonka bean (Dipteryx odorata), vanilla grass (Anthoxanthum odoratum), woodruff (Galium odoratum), and sweet grass (Hierochloe odorata). The name comes from a French word, coumarou, for the tonka bean. It has a sweet scent, readily recognised as the scent of newly-mown hay, and has been used in perfumes since 1882.

Some of the biological activities attributed to chromone derivatives include cytotoxic (anticancer), neuroprotective, HIV-inhibitory, antimicrobial, antifungal and antioxidant activity. Due to their abundance in plants and their low mammalian toxicity, chromone derivatives are present in large amounts in the diet of humans.

Chromen [357] have been the subject of the considerable chemical interest in the past decades. They occur widely in nature and exhibit important biological as well as pharmacological activities.[358] They are photochemically very active and lead to the generation of some exotic heterocyclic compounds.[359] Flavonoids [360] are the chromones that are also most abundantly distributed in nature. Peucenin,[361] eugenitol [362] and isoeugenitol [363] are some commonly occurring chromones. The chromones are also well known for their antioxidant,[364] biocidal,[365] wound healing,[366] anti-inflammatory,[367] antiulcer,[368] and immune-stimulatory [369] activities. Recently, some chromones are also reported as anti-HIV agents.[370] Khellin [371] (158) and 2,4-thiazolidinedione [372] (159) are the chromones that are used as antispasmodic agent, in the treatment of anginapectoris and antidiabetic agent that improve peripheral insulin resistance in type-II diabetic patients respectively.
These pharmacological activities have been the major incentives behind the synthesis of the chromones and their derivatives. As chromones are present in all parts of the plant kingdom, they are exposed to sun light for longer durations of time that make them liable to undergo some photo-structural transformations. As chromones are bichromophoric substrates that contain double bond as well as C=O group as the chromophoric units which can undergo photoexcitation either in isolation or in conjugation.

Chromones are known to undergo photocycloaddition, photodimerisation, photoisomerisation, photorearrangement, photooxidation-reduction and photocyclisation reactions involving both n→π* and π→π* transitions.

**Photocycloaddition reactions**

Photocycloaddition reactions of chromones with different olefins and related compounds are known to provide the products both through [3+2] and [2+2]π cycloaddition reactions. [2+2]π photocycloaddition reactions are extensively studied by Hanifin and Cohen.[373] These photoaddition reactions involve an electrophilic attack by C-3 of chromone involving n→π* triplet excitation with the fact that only phosphorescence is observed and no fluorescence is observed. It is consistent with the idea that intersystem crossing from n→π* singlet to triplet should be rapid when singlet to triplet energy gap is small.[374] Singlet- triplet energy gap for chromone in 2M THF is only about 5-kcal/mol.
Irradiation of a solution of chromen (161) with 1,1-dimethoxyethylene (162) gave photoproducts (163) and (164). But further studies have shown that (164) was a secondary photolysis product arising from (163).

Large-coupling constant for these photocycloaddition products by [2+2] π addition revealed the cis orientation.[375] The mechanism of cyclobutane formation is probably best described as an unsensitized [376] and electrophilic attack by $C_α$ of the $n→π^*$ chromone triplet on the most nucleophilic carbon atom of the olefin to give a 1,4-diradical intermediate such as (165) followed by formation of cyclobutane ring. Competition reaction might be depending upon the olefin used for initial H-abstraction.

**If α attack**

More stable

More stable
The Chromen ring (2-phenyl-chromen-4-one) system is of considerable interest due to several biological effects including antibacterial [377] and antifungal activity. [378-379] A survey of the literature provides information that chromen containing methylenedioxy group (–O–CH2–O–) widely occur in natural plant pigments.[380] The flavonoids are an group of natural products founds in fruits, vegetables, nuts, seeds and flowers as well as in teas and wines, and are an important constituent of human diet. They have been demonstrated to possess many biological and pharmacological activities such as antibacterial, antifungal, antiviral, antioxidant, anti-inflammatory, antimutagenic and antiallergic activities and inhibitory activities on several enzymes.[381-382] Our previous articles [383-384] have reported the antibacterial and antifungal effects of the chromen ring system (2-phenyl-chromen-4-one) containing furan, prenyl, methoxyl and hydroxyl group in various positions. This paper reports the syntheses of two derivatives of 2-phenyl-chromen-4-one (flavone) containing methylenedioxy group from their corresponding chalcones by using different DMSO/I2, diphenyl sulphide and DDQ as oxidizing agents. Both the flavones and their corresponding chalcones were screened in vitro for their antibacterial and antifungal activity against four human pathogenic bacteria, viz., Sarcina lutea(G+), Bacillus subtilis (G+), Shigella dysenteriae (G–), Pseudomonas aeruginosa (G–) and five plant and mould fungi, viz. Colletotrichum gloeosporioides Penz., Candida albicans, Aspergillus niger, Aspergillus flavus and Penicillium sp. Some of the biological activities attributed to chromone derivatives include cytotoxic (anticancer),[385-387] 2-4 neuroprotective,[388] HIV-inhibitory,[389] antimicrobial,[390-391], antifungal [392] and antioxidant activity.[393] Due to their abundance in plants and their low mammalian toxicity, chromone derivatives are present in large amounts in the diet of humans.[394]

The synthesis of chromone derivatives is a research field of great interest and long history.[395] In general, chromones are synthesized by the cyclodehydration of 1-(o-hydroxyaryl)- 1,3- diketones or equivalent intermediates catalyzed by strong acids or strong
bases (Vilsmeier-Haack reaction).[396] They have been prepared on a large scale by the Allan-Robinson synthesis involving acylation-rearrangement, and subsequent cyclization.[397] This methodology has been followed in the synthesis of chromone derivatives[398] with quaternary ammonium functionalities which show not only activity of cosmetic interest but also for hair sustainability, as well as in the asymmetric synthesis of optically active 4-chromone derivatives. In the Baker-Venkatakrishnan synthesis, internal Claisen condensation of 2-aryloxy-1-acetylene is employed as a key step. More recently the synthesis[399] of chromone derivatives was accomplished by intramolecular ester carbonyl olefination or Pd-catalyzed regiospecific carbonylative annulation of o-iodophenol acetates and acetylenes.[391] 3-Cyanochromones have been synthesized in a mild and facile method from oximes derived from 3-formyl chromones using dimethyl formamide/thionyl chloride complex.[392] As for aminochromones, useful for the prevention of allergic and asthmatic reactions in mammals, as indicated by tests in rats, they have been synthesized either by rearrangement of isoxazoles [393] or from chlorinated salicylic acids and malononitrile in aqueous NaOH or NaH.[394]

During the last few years we have been involved in the one-step synthesis of heterocycles [395-396] employing N-hydroxybenzotriazole esters of α-amino or α-hydroxy acids as acylating agents of active methylene compounds to produce a wide variety of γ-amino [397] or γ-hydroxy butenoates,[398] which can be converted to five-membered heterocycles with biological interest.[399] As a consequence, we employed the N-hydroxybenzotriazole methodology[400] in the synthesis of 4-hydroxycoumarins by using a number of substituted acetyl salicylic acids as the precursors.[401]

The chroman structural unit is found in a large number of drugs and natural products.[402] Chroman derivatives exhibit various useful biological activities,[403] such as antioxidant,[404] antiestrogen,[405] anticonvulsions,[406] and neuroprotection.[407] Many synthetic methods for chromans have been developed.[408] One of the efficient pathways is based on the transformation of 2H-chromenes, including oxidation,[409-410] reduction[411] and conjugate addition.[412] The coumarin (2H-chromen-2-one) moiety is often found in natural products. In view of the ubiquity of this fragment in a variety of biologically active compounds, the synthesis of various 2H-Chromen-2-one analogues are important in gauging their potential as a source of chemotherapeutics.
2H-1-Benzopyrans, commonly known as 2H-benzopyrans or 2H-chromenes, are key structural units of a variety of biologically important compounds, many of which are pharmaceutically significant. The 2H-benzopyran daurichromenic acid is known to exhibit anti-HIV properties,[413] while coutareagenin possesses antidiabetic activity.[414] Derivatives of 3, 4-diphenylchromans are known to have estrogenic activity.[415] Numerous derivatives of 2H-benzopyrans are useful for the treatment of proliferative skin disorders and microbial infections[416] and show potent antifungal activity.[417] Derivatives of 2H-benzopyrans, like 2, 4-diphenyl-2H-benzopyran and 2, 2, 4-triphenyl-2H benzopyran, have been studied for their photochromic behavior.[418] Owing to their biological and pharmaceutical importance, there has been a constant research in the development of new methodologies for the synthesis of 2H-chromene derivatives. To contribute to this area of research, we are interested in developing a methodology that provides facile access to 2H-chromene derivatives.[419]

During the last twenty years, the study of the biological activities of chromene derivatives has been the aim of many scientists [420-429] recently, the anticoagulant, antibacterial, anti-helminthic, hypothermal and vasodilatory properties of chromene has been reviewed. Fused chromenes are interesting due to their significant antibacterial,[430-434] and novobiocin [435-436] activities.

Theodore O. Johnson et.al reported [437] the structure-based design of a parallel synthetic array directed toward the discovery of irreversible inhibitors of human rhinovirus 3c protease (165).

Utilizing the tools of parallel synthesis and structure-based design, a new class of Michael acceptor-containing, irreversible inhibitors of human rhinovirus 3C protease (HRV 3CP) was discovered. These inhibitors are shown to inhibit HRV-14 3CP with rates of inactivation ranging from 886 to 31400 M-1 sec-1. These inhibitors exhibit antiviral activity when tested against
HRV-14 infected H1-HeLa cells. Raimund Mannhold et.al reported [438] the 6-sulfonyl chromenes (169) as highly potent kATP-channel openers.

1-[(4-Chloro-2, 2-dimethyl-2H-chromen-3-yl) methylene] thiosemicarbazide, 1-[(4-chloro spiro-2H-chromen (2,1) cyclo hexane-3-l) Methylene] thiosemi carbazide and 1-[(4-chloro-2-ethyl-2-methyl-2H-chromen-3-yl) methylene] thiosemicarbazide were found to be potent anti-inflammatory agents comparable to indomethacin. On the other hand, they show no ulcerative activity and higher LD50 values than indomethacin. The thiosemicarbazide group at position 3 of the pyrane ring might be responsible for these activities. Ahmed M.M; El-Saghier et.al reported the synthesis and antibacterial activity of some new fused chromenes.

The chromenes obtained were preliminarily evaluated for their \textit{in vitro} antibacterial activity, against a narrow spectrum of bacterial species procured from the laboratory of microbial
biochemistry.

\[
\text{CNCH2COOEt} \\ \text{ETHANOL/PIP}
\]

(175) \[\rightarrow\] (176)

B. Rajitha et.al reported [439] the synthesis and biological activity of \textit{meso}-tetrakis (2, 10-dioxo-2\(H\), 10\(H\)-pyrano [2, 3-\(f\)] chromene-9-yl) porphyrins. Compounds were evaluated for their antiviral activity against HEL, Hela and Vero cell cultures. The cytotoxicity was verified in mock-infected HEL, Hela and Vero cells. The antiviral activity assays were based on inhibition of virus-induced cytopathicity. The activity of these compounds was compared with that of standard Brivudin, Ribavirin, Acyclovir and Ganciclovir. Microliter plates were inoculated with 100 CC1D50 of virus, ICC1D50 being the virus dose required to infect 50% of the cell cultures. The compounds were screened for antitumor activity against L1210 murine leukemia cells as well as human T-lymphocyte cells molt 4/C8 and CEM/0. Etoposide was used as a standard drug.

\textbf{Literature survey}

Mailavaram Raghu Prashad et al [440] synthesized some novel 6-Substituted-2,3,4-trihydropyrimido[1,2-c]9,10,11,12-tetrahydrobenzo[b]thieno[3,2-e]pyrimidines (184) and their derivative by microwave assisted cyclization of amino ester derivative (180).

MD. Mosharef Hossain Bhuiyan et al [441] and Wangat W. Wardakhani et al [442] synthesized some fused pyrimidines for antimicrobial activity. [1,2,4]Triazolo[4,3-c]thieno-[3,2-
Pyrimidine (188) derivatives were prepared by initial treatment of o-aminonitrile (185) with carbon disulfide, followed by methylation with methyl iodide and subsequent reaction with benzhydrazide and thiosemicarbazide. Some of these derivatives exhibited pronounced activity.

Thienylthiourea derivatives were prepared by condensation of the amino ester derivative (185) with alkyl or aryl isothiocyanates, either by heating at reflux or under microwave irradiation.

Scheme 15 Where R= Methyl, Ethyl, Benzyl, Phenyl, Pyridyl.

Irradiation; [444-446] Cyclization of (191) using alcoholic KOH gave the mono potassium salts of the corresponding 3-substituted-2-thioxo-4,5-disubstituted-thieno[2,3-d]pyrimidin-4-ones (192). Alkylation of (192) with alkyl halides gave 2-alkylthio-derivatives (193).
V. Alagarsamy et al [447] synthesized dimethylthieno [2,3-\textit{d}] pyrimidin-4(3\textit{H})-ones as analgesic, Anti-Inflammatory and Antibacterial Agents. The key intermediate 3-amino-2-mercapto-5,6-dimethylthieno[2,3-\textit{d}] pyrimidin-4(3\textit{H})-one (197) was prepared by treating carbon disulfide and...
sodium hydroxide solution to 2-amino-3-carbethoxy-4,5-dimethyl thiophene (194) in dimethyl sulfoxide; the sodium salt of dithiocarbamic acid obtained was methylated with dimethyl sulfate to get methyl N-(3-carbethoxy-4,5-dimethylthienyl) dithiocarbamate (196). The compound (196) and hydrazine hydrate when refluxed in ethanol yielded the desired 3-amino-2-mercapto-5,6-dimethylthieno[2,3-d] pyrimidin-4(3H)-one (197). The (2-methylthio-4-oxo-3H-5,6-dimethylthieno[2,3-d]pyrimidin-3-yl) dithiocarbamic acid methyl ester (200) was prepared by treating carbon disulfide and sodium hydroxide solution to (198) in dimethyl sulfoxide; the sodium salt of dithiocarbamic acid obtained was methylated with dimethyl sulfate to yield (200). Compound (200) was treated with secondary amine in ethanol to give compound (201).
Yujia Dai et al [448] synthesized a series of novel thienopyrimidine-based receptor tyrosine kinase inhibitors. Investigation of structure-activity relationships at the 5- and 6-positions of the thienopyrimidine nucleus led to a series of \(N,N\)-diaryl ureas that potently inhibit all of the vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptor tyrosine kinases. A number of compounds have been identified as displaying excellent in vivo potency.

![Structural formula of compound](image)

Mailavaram Raghu Prasad et al [449] synthesized a new series of 5-alkyl/aryl-8,9-dimethyl/8,9,10,11-tetrahydro[1]benzothieno[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine-3(2H)-thiones (203) through a facile cyclization reaction. The affinities of these compounds for adenosine \(A_1/A_2A\) receptors were determined at 1 \(\mu\)M concentration.[450] Some of the compounds have shown \(K_i\) values in the range of 1.0–4.0 \(\mu\)M.

![Structural formula of compound](image)

Looking to the pharmaceutical applications of thienopyrimidine derivatives, in this section we have synthesized some biologically active heterocyclic compounds which contain thienopyrimidine moiety.