Keshav Lalit Ameta *Editor*

S-Heterocycles

Synthesis and Biological Evaluation

Springer

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Foreword

Sifting through the intricate web of chemical diversity, the S-Heterocycles emerge as crucial structural building block within many bioactive frameworks, offering an engaging journey into the rapidly expanding field of medicinal chemistry and its applications.

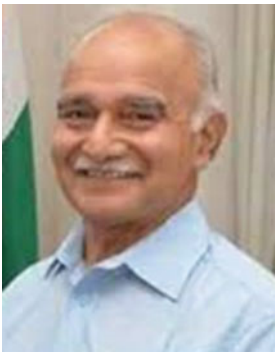
Within the pages of *S-Heterocycles*, we embark on an intellectual voyage into a realm where sulphur-containing bioactive heterocyclic systems compose distinctive biological applications in symphonies. The collaborative efforts of outstanding researchers and academicians who have committed their time and knowledge to uncovering the mysteries of S-heterocycles moieties are showcased in this edited collection.

The chapters in this book are thought-provoking excursions by researchers who comprehend the complexity of synthesis, characterization, and biological investigation of differentially substituted S-Heterocycles. They are not just lists of facts or collections of data. The writers have skilfully created a timeline that defies conventional thinking and pushes the boundaries of human comprehension, starting with fundamental concepts and ending with cutting-edge discoveries.

I am deeply appreciative of the individuals who have generously given their experience, turning this book into a treasure trove of knowledge. I hope this book inspires readers to keep going on their own knowledge quests by igniting fresh ideas.

With great pleasure, I invite you to delve into the world of *S-Heterocycles* and transcend conventional understanding in an intriguing tale of molecular exploration in which the sulphur-containing heterocyclic framework plays the lead role. All of this is conducted in the spirit of science.

Wishing you a reading experience as joyful as it is enlightening, and may your scientific pursuits be as abundant and fulfilling as the substances found within these pages.



Prof. (Dr.) Rama Shankar Dubey
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Preface

Heterocycles containing sulphur have been a crucial component of FDA-approved medications and pharmaceutically significant chemicals for many years to come. Scholars' focus has turned from nitrogen heterocycles to other heterocycles, particularly S-heterocycles, because of the extensive study of these compounds in medicinal chemistry. They are found in several kinds of physiologically active heterocyclic frameworks, and their skeleton is significantly widespread. Physio-chemical and biological aspects of the compounds are influenced by the presence of one or more sulphur atoms in the heterocyclic ring.

Thus, several attempts have been made to synthesize a variety of new sulphur-containing compounds with high medicinal value and low toxicity profile, in comparison to previous N-Heterocycles. Nowadays, S-Heterocycle-containing compounds have been largely reported as anticancer, antidiabetic, antimicrobial, antihypertension, antiviral, anti-inflammatory, etc.

Due to the significance and usefulness of S-Heterocycles in the drug discovery process, the purpose of the present book is to provide a succinct summary of methods for the synthesis of various natural products to inspire S-Heterocycle scaffolds and their biological evaluation. I trust that both undergraduate and graduate students, researchers and faculties will find in these pages an interesting guide and an updated state of the art on the enormous S-Scaffold.

Gandhinagar, India — Prof. Keshav Lalit Ameta

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Chapter 1
Synthesis and Biological Evaluation of Thiophene and Its Derivatives

Binoyargha Dam and Bhisma Kumar Patel

1.1 Introduction

Thiophene is a sulfur-containing aromatic heterocyclic compound that possesses a monocyclic five-member ring with sulfur as a heteroatom at position 1. Its chemical formula is C_4H_4S, and 2nd, 4th and 3rd, 5th positions are equivalent (Fig. 1.1) in an unsubstituted system. The chemical name of thiophene is thiacyclopentadiene. The word thiophene is derived from the Greek word *theion* meaning sulfur and *phaino* meaning shinning.

At room temperature, thiophenes are simple colorless liquids that are flammable having a sweet aroma reminiscent of benzene. They occur in coal tars and are discovered as contaminants in benzene. Thiophene and its derivatives are said to have various uses and properties. They are used in material science and industrial chemistry as corrosion inhibitors. They have prominent roles in the advancement of organic semiconductors [1] and the fabrication of organic light-emitting diodes (OLEDs) [2]. They also possess many pharmacological activities like anti-inflammatory [3], antimicrobial [4], antihypertensive [5] activities, etc. Structures of some thiophene moieties having medicinal activities are shown in Fig. 1.2.

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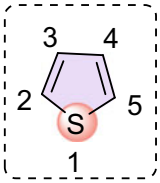
Fig. 1.1 Thiophene



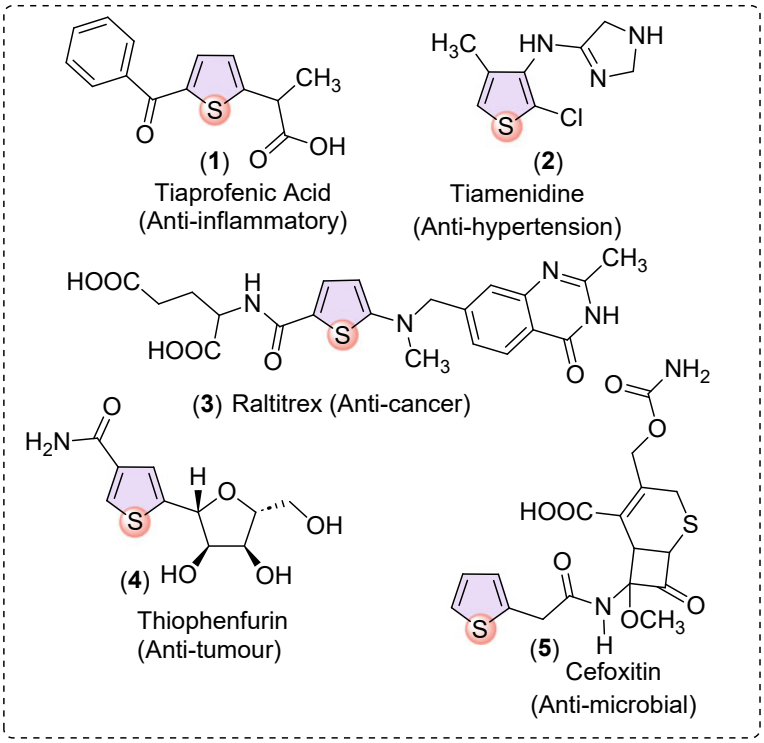
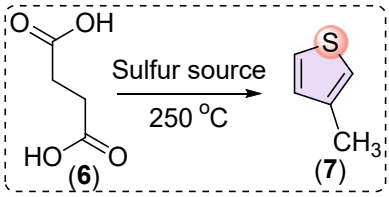


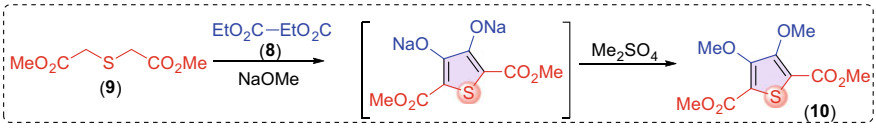
Fig. 1.2 Structures of a few medicinally active drugs containing thiophene moiety

1.2 General Approaches to Thiophene Ring Synthesis

Because of the various biological importance of thiophenes, this moiety has been classically synthesized in various ways. A few of these methods include Paal Knorr synthesis, Hinsberg synthesis, Fiessellmann synthesis, etc. In Paal Knorr synthetic procedure [6], 1,4-dicarbony1 compounds (**6**) were reacted with a sulfur surrogate to give thiophene derivatives (**7**) (Scheme 1.1). Traditionally used sulfur-based compounds are phosphorus sulfides, Lawesson's reagent, etc.

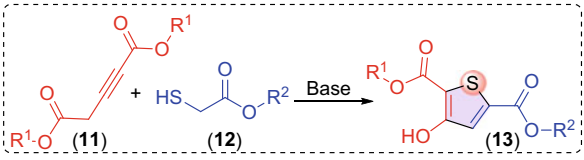
Scheme 1.1 Synthesis of thiophene derivatives by Paal Knorr method





Scheme 1.2 Hinsberg synthesis of thiophene derivatives

Scheme 1.3 Fiesselmann synthesis of thiophene derivatives



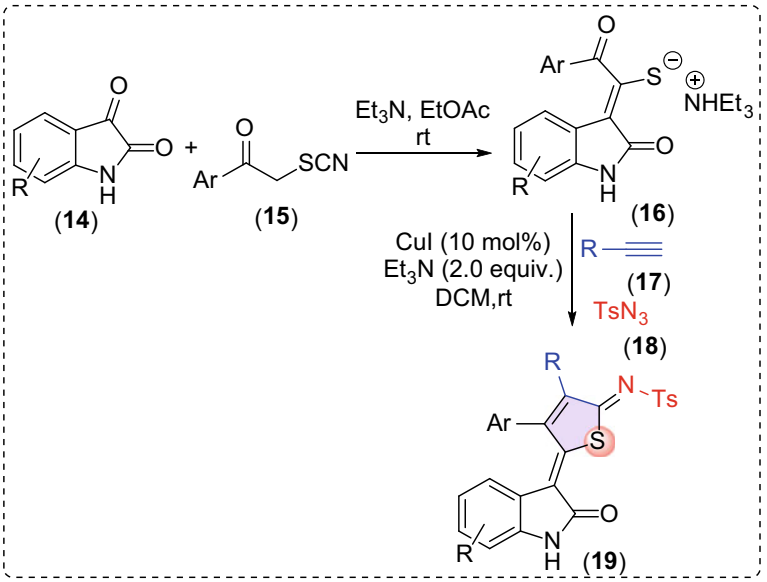
In Hinsberg synthesis [7], condensation of α-dicarbonyl compounds (**8**) and thioglycolic acid esters (**9**) in the presence of sodium alkoxide was carried out to yield thiophene-2,5-dicarboxylic acid derivatives (**10**) (Scheme 1.2).

In Fiesselmann synthesis [8], condensation of methyl thioglycolate (**12**) was carried out with dimethyl but-2-ynedioate (**11**) in the presence of a base to provide 3-hydroxy-2,5-thiophene carboxylate derivatives (**13**) (Scheme 1.3).

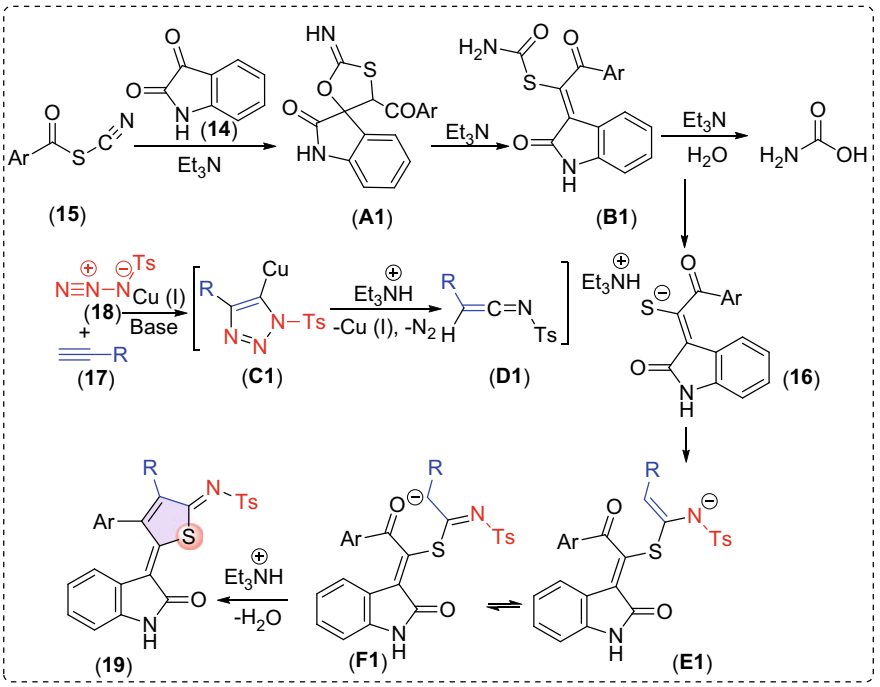
Aforementioned procedures are well-known classical methods for the synthesis of thiophene moieties. Because of many biological importance of thiophene derivatives, this moiety remains the subject of interest for many chemists and biologists. For this reason, scientists throughout the world are still focusing on the synthesis of this biologically relevant heterocycle. Some of the very latest reports are discussed herein in this chapter.

Li and co-workers used readily accessible triethylammonium 1-(2-oxoindolin-3-ylidene)-2-aroylethanethiolates (**16**) to synthesize diversely substituted thiophene derivatives (**19**) by copper(I)-catalyzed reaction of terminal alkynes (**17**) and *N*-sulfonyl azides (**18**) (Scheme 1.4) [9]. This reaction installed carbon–nitrogen, carbon–sulfur, and carbon–carbon bonds simultaneously, allowing the synthesis of functionalized thiophenes with a wide variety of substituents in one pot. A plausible mechanism for this domino process has been proposed as shown in Scheme 1.5.

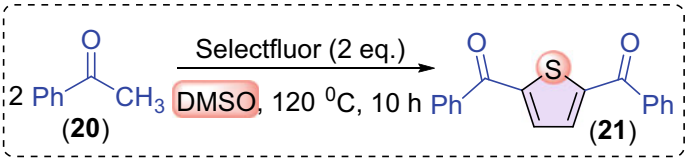
Firstly, triethyl amine-promoted [3 + 2]-between (**14**) and (**15**) leads to the formation of spiroindole (**A1**), which gives compound (**16**). Following that, the intermediate (**D1**), which is formed from copper-catalyzed cycloaddition of terminal alkynes (**17**) and *N*-sulfonyl azides (**18**), reacts with (**16**) to give anionic intermediate (**E1**).



Scheme 1.4 Synthesis of substituted thiophene derivatives (**19**) from (**16**)



Scheme 1.5 Reported mechanism for the synthesis of thiophene derivatives by Li and co-workers



Scheme 1.6 Selectfluor-promoted synthesis of thiophene moiety (**21**)

After tautomerization (**E1**) gives (**F1**), which underwent intramolecular nucleophilic addition to yield desired thiophene derivatives (**19**) [9] (Scheme 1.5).

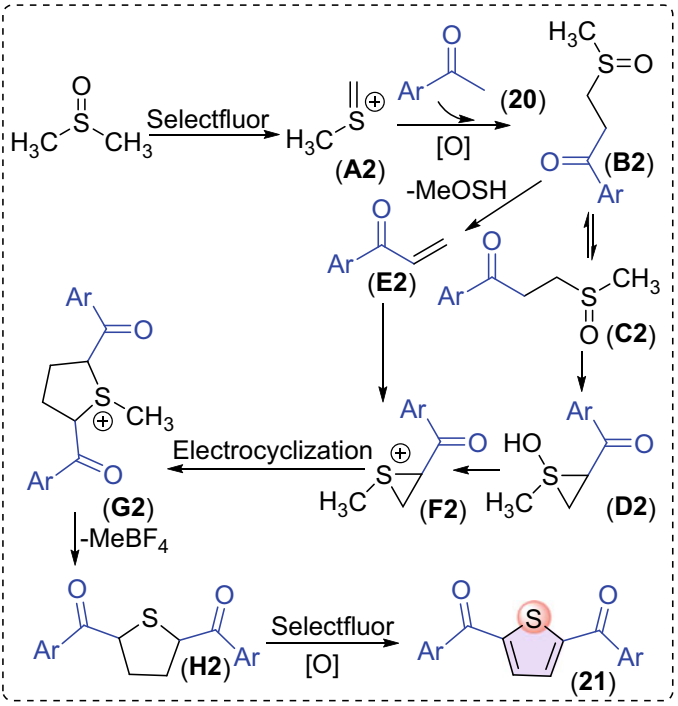
Recently, in the year 2023, Qiu and co-workers reported the synthesis of diacylthiophenes (**21**) from dimethyl sulfoxide (DMSO) and aryl methyl ketones (**20**) through selectfluor-promoted cyclization by simple solvent modification (Scheme 1.6) [10]. This method leads to the creation of new C–S and C–C bonds. Outstanding chemoselectivity, usage of easily available starting materials, and wide functional group tolerance were some added features of this protocol.

Scheme 1.7 shows a most probable mechanism as proposed by the authors [10]. Primarily, DMSO in the presence of select fluor gets converted to sulfonium cation (**A2**). Sulfonium cation then reacts with ketone (**20**) to form intermediate (**B2**). Following that, the intermediate (**B2**) underwent enol exchange to give intermediate (**D2**). The intermediate (**B2**) also eliminated MeOSH to give chalcone (**E2**). The intermediate (**D2**) gave (**F2**), which underwent intermolecular cycloaddition with (**E2**) to give intermediate (**G2**). Removal of methyl cation from (**G2**) leads to the formation of (**H2**), which underwent oxidative aromatization by selectfluor to yield desired thiophene (**21**).

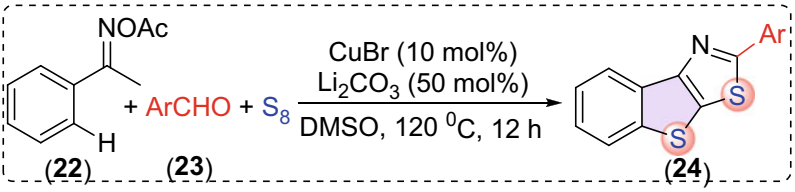
Deng and co-workers in the year 2018 reported a simplistic copper-catalyzed method to synthesize fused thieno[3,2-*d*]thiazole moieties (**24**) from methyl aromatic ketoxime acetates (**22**), aromatic aldehydes (**23**), and elemental sulfur (Scheme 1.8) [11]. The usefulness of this protocol was highlighted by the significant simplicity in one-pot organic transformations, high yield of products, application in gram-scale conditions, and potential applications in post-synthetic modifications.

Very recently, Li *and* co-workers developed a visible-light mediated method for the synthesis of 3-halobenzo[*b*]thiophenes (**27**). 2-Alkynylthioanisoles (**25**) and alkyl halides (**26**) were used as starting materials to synthesize diverse range of thiophene derivatives (Scheme 1.9) [12]. Reaction went smoothly in the presence of 10W blue LEDs at room temperature. THF was used as the solvent for this reaction. Further, after completion of reaction the synthesized product was subjected to many successful organic transformations.

Two separate mechanisms for bromo and iodocyclization were proposed by the research group as shown in Scheme 1.10. For bromocyclization, [**25** gets excited to (**25***)] and acted as a photosensitizer. This underwent an energy-transfer pathway with (**26**) to give (**26***), and the ground state (**25**) was regenerated. Bromide radical then gets formed from homolytic cleavage of (**26***). This bromide radical then reacted

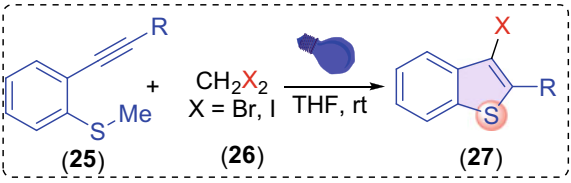


Scheme 1.7 Plausible mechanism for selectfluor-promoted synthesis of thiophene moiety



Scheme 1.8 Synthesis of fused thieno[3,2-*d*]thiazole moieties (**24**)

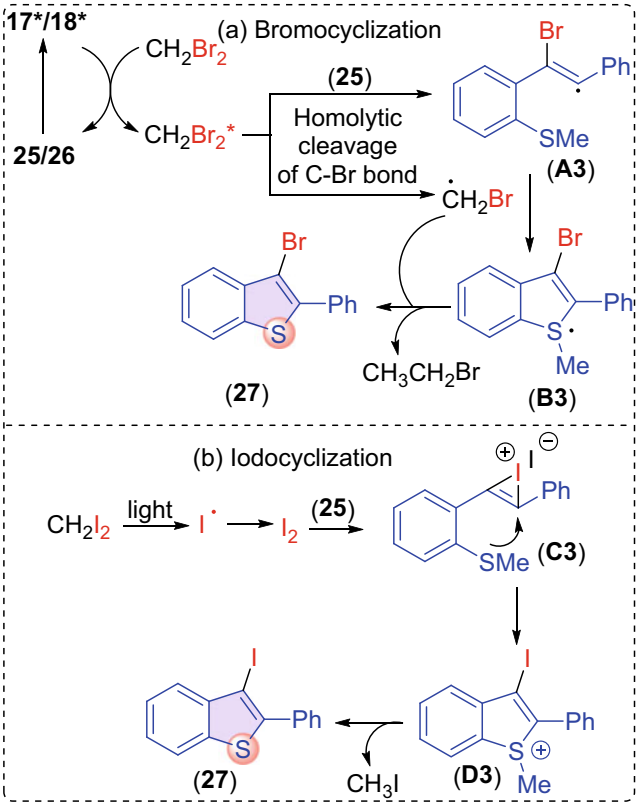
Scheme 1.9 Visible-light mediated synthesis of 3-halobenzo[*b*]thiophene derivatives (**27**)



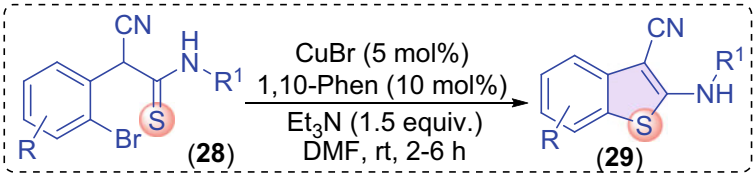
with alkynyl in (**25**) to generate intermediate (**A3**) in high regioselectivity. Consequently, this in situ generated radical reacted with the SMe part via intramolecular cyclization to give (**27**), which is the final product, along with the conversion of methyl radical into bromoethane. For iodocyclization, primarily, visible-light mediated homolytic cleavage of the C–I bond leads to the formation of an electrophilic iodine species (I_2) in situ, which then gets captured by the C–C triple bond in (**25**) to form an intermediate (**C3**). Following the intramolecular sulfur portion attack, the cationic intermediate (**D3**) was formed. Ultimately, the methyl group gets released to give the anticipated product (**27**) [12] (Scheme 1.10).

Peruncheralathan and research group reported the syntheses of various functionalized 2-aminobenzo[*b*]thiophenes (**29**) at room temperature by Ullmann coupling reaction (Scheme 1.11) [13]. Reaction was carried out using CuBr (5 mol%) and 1,10-phen (10 mol%). Further post-synthetic modification of newly synthesized thiophenes was carried out to synthesize quinolines in the presence of triflic acid.

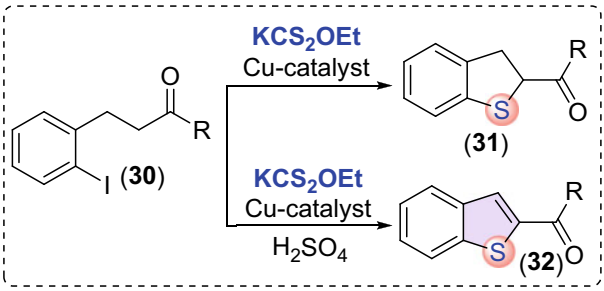
An efficient domino process was developed by Sekar et al. in the year 2020 for the syntheses of thiophenes (**31**) from 2-iodoketones (**30**) by using a copper catalyst



Scheme 1.10 Probable mechanism for visible-light mediated synthesis of (**27**)



Scheme 1.11 Synthesis of (**29**) by Ullmann coupling reaction

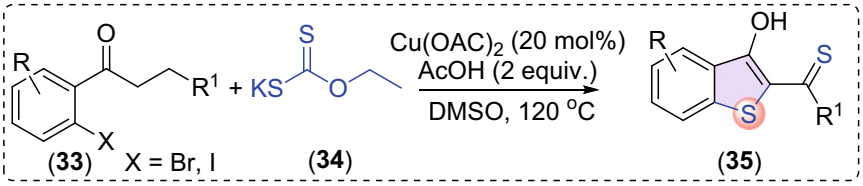


Scheme 1.12 Synthesis of (**31**) and (**32**)

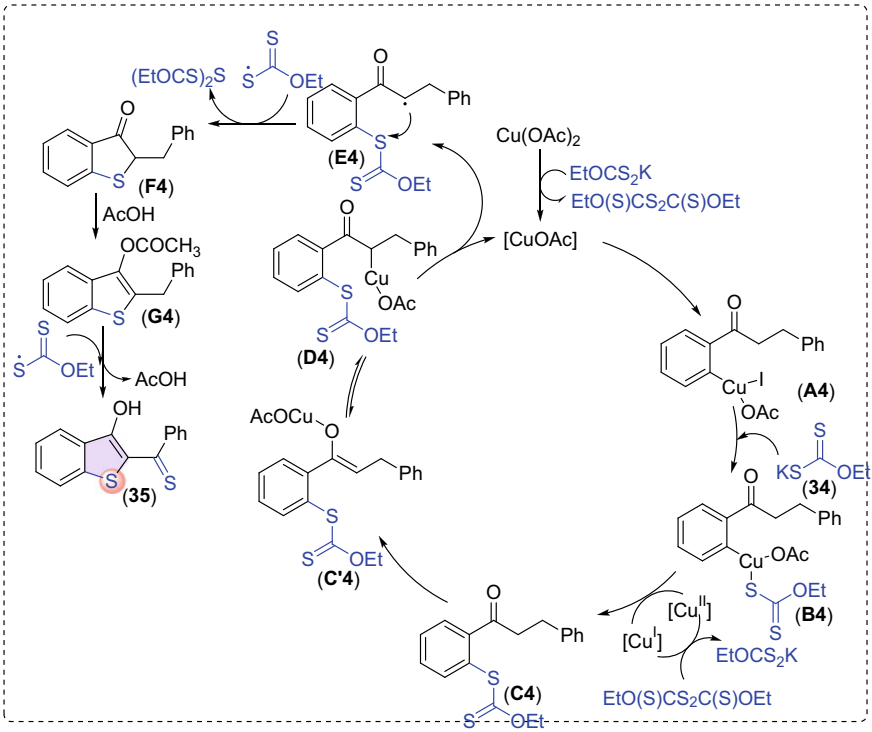
and xanthates the sulfur source. The process was also extended for the synthesis of 2-acylbenzo[*b*]thiophenes (**32**) using the in situ generated iodine from by product KI (Scheme 1.12) [14].

Sekar and research group again in the year 2021, reported a copper-catalyzed domino synthesis of thiophene derivatives (**35**) through radical cyclization of 2-iodophenyl ketones (**33**) and xanthate (**34**) as a sulfur surrogate (Scheme 1.13). After controlled experiments and literature survey, a probable mechanism was proposed by authors (Scheme 1.14). According to that, at first, 1-(2-iodophenyl)-3-phenylpropan-1-one (**33**) underwent oxidative addition in the presence of Cu(I) to form intermediate (**A4**), which then led to the formation of intermediate (**B4**) by ligand exchange with potassium ethyl xanthate (**34**). Reductive elimination of intermediate (**B4**) gave Cu(I) and xanthate ester. This Cu(I) gets oxidized to Cu(II) by the xanthate dimer, which reacts with the keto group of the xanthate ester and gives intermediate (**C4**). This (**C4**) underwent keto–enol tautomerism and gave (**D4**). Ultimately, (**D4**) underwent homolytic fission to give the radical intermediate (**E4**). Then, thiyl radical was generated through fission of the xanthate ester by in situ generated xanthate radicals which underwent cyclization to form (**F4**) (Scheme 1.14). Following that, a stable aromatic intermediate (**G4**) got formed from (**F4**), which eventually leads to the formation of desired thiophene moiety (**35**) [15].

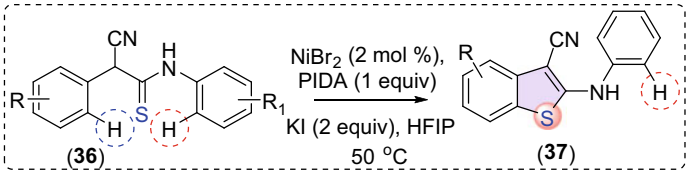
A catalytic site selective intramolecular C–S bond forming reaction has been reported by S. Peruncheralathan and his research group in the year 2018 (Scheme 1.15) [16]. The C–H bond functionalization of α-aryl-thioacetanilides (**36**) was resourcefully catalyzed by $NiBr_2$, resulting in (**37**).



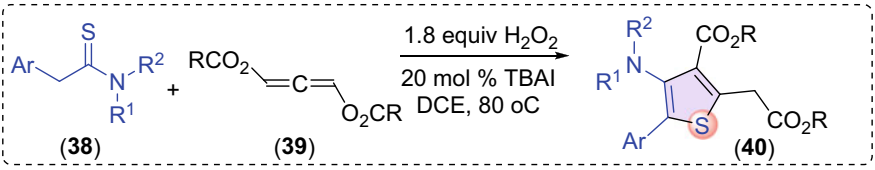
Scheme 1.13 Copper-catalyzed synthesis of thiophene derivatives (**35**)



Scheme 1.14 Plausible mechanism for domino synthesis of thiophene derivatives

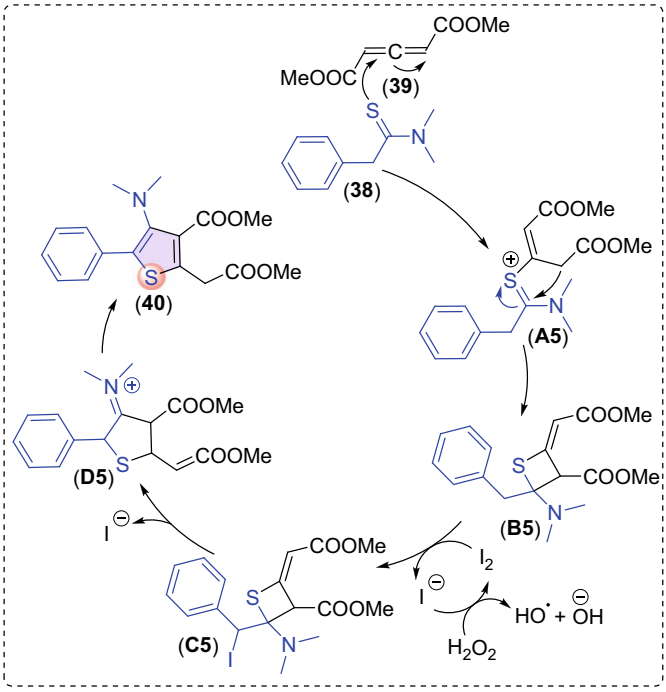


Scheme 1.15 $NiBr_2$-catalyzed synthesis of (**37**)



Scheme 1.16 TBAI-catalyzed synthesis of polyfunctionalized thiophenes (**40**)

Luo group in the year 2018 described a TBAI-catalyzed tandem thio-Michael addition/oxidative annulations reaction for the synthesis of substituted thiophene molecules (**40**) (Scheme 1.16). Thioamides (**38**) and allenes (**39**) were used as starting materials. This report discussed about a transition metal free oxidative cyclization procedure through 1,2-sulfur migration transformation protocol. Based on literature reports, a plausible mechanism was proposed as shown in Scheme 1.17. Primarily, arylthioamide (**38**) reacted with allene (**39**) to give intermediate (**A5**), this is then followed by an intramolecular nucleophilic ring closing reaction to give intermediate (**B5**). Following that, iodination of (**B5**) forms intermediate (**C5**), which underwent 1,2-sulfur migration to form intermediate (**D5**). At last, the intermediate (**D5**) underwent aromatization/oxidation to give thiophene derivatives (**40**) [17].



Scheme 1.17 Plausible mechanism for TBAI-catalyzed synthesis of polyfunctionalized thiophenes

1.3 Biological Activities of Thiopene Molecules

Heterocyclic compounds are known to play an important role in the exploration of biologically active molecules. In this regard, thiophene and its derivatives have been spotlighted of curiosity for almost two decades. Thiophene derivatives own extraordinary properties like anti-inflammatory, antianxiety, antifungal, antimicrobial, anticancer, and antipsychotic properties. Several marketed drugs like Olanzapine, Sertaconazole, Benzocyclidine, Tipepidine, Ticlopidine, Tioconazol, Clopidogrel, Tiquizium Bromide, Pasugrel, Timepidium, and Citizolam contain a thiophene nucleus in them. Structures of few of these medicinally active thiophene moieties are shown in Fig. 1.3.

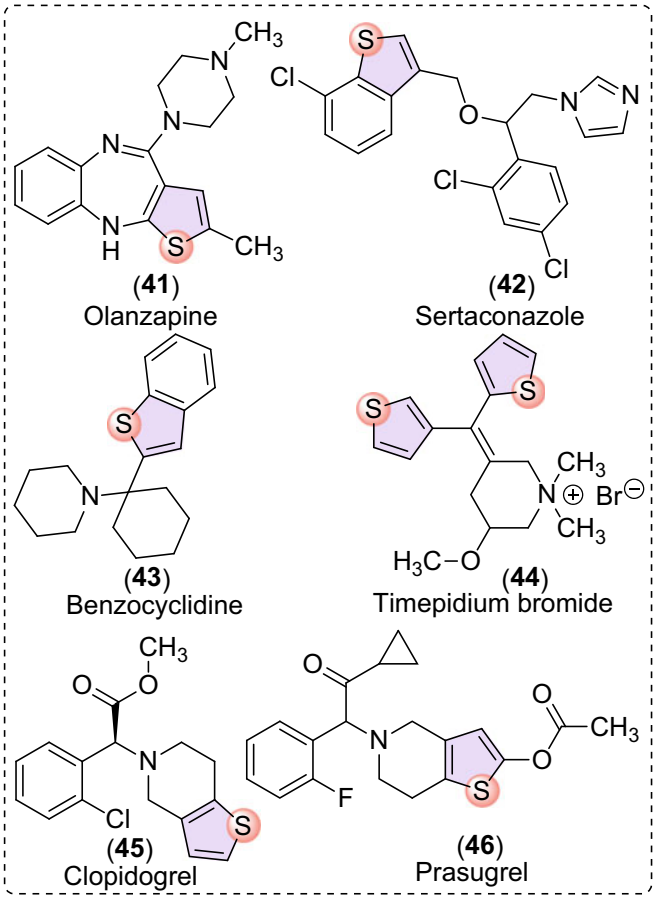


Fig. 1.3 Structures of Olanzapine, Sertaconazole, Benzocyclidine, Tiquizium Bromide, and Pasugrel

1.3.1 Anti-inflammatory Activity

Tiaprofenic acid (**1**), tenidap (**47**), tinoridine (**48**), and zileuton (**49**) (Fig. 1.4) are few examples of commercially available anti-inflammatory drugs with thiophene ring as pharmacophoric group. Tiaprofenic acid and tinoridine act as cyclooxygenase (COX) inhibitors [18, 19], whereas first three are non-steroidal anti-inflammatory drugs. Zileuton is a lipooxygenase (LOX) inhibitor [19].

COX enzymes are found in three forms. COX1 regulates various functions like platelet adhesiveness, produces prostaglandins from arachidonic acid, and is found in normal tissues [20, 21]. COX-2 are present in certain tissues like prostate, kidneys, and uterus. When a tissue gets damaged, their level enhances in body [22]. COX-3 are found in central nervous systems and are linked to the antipyretic effect of paracetamol [23–25].Other enzymes which are involved in inflammatory process are lipooxygenases (LOX). Several thiophenic molecules were being described as potential inhibitors of these enzymes. Filali and research group discovered that compound (**50**) (Fig. 1.5) presents inhibitory activity with an IC50 of 29.2 μM for 5-lipoxygenase [26]. Authors described that these potent activities were related to the presence of methoxy and methyl radicals in its structure. After a few years, Chiasson and co-workers synthesized a few compounds having benzothiophene moieties and phenolic acid fraction. Compounds (**51**) and (**52**) (Fig. 1.5) showed the best activities against polymorphonuclear leukocytes and HEK293 cells. This activity may correspond to the presence of methoxy and hydroxy group in the molecule [27].

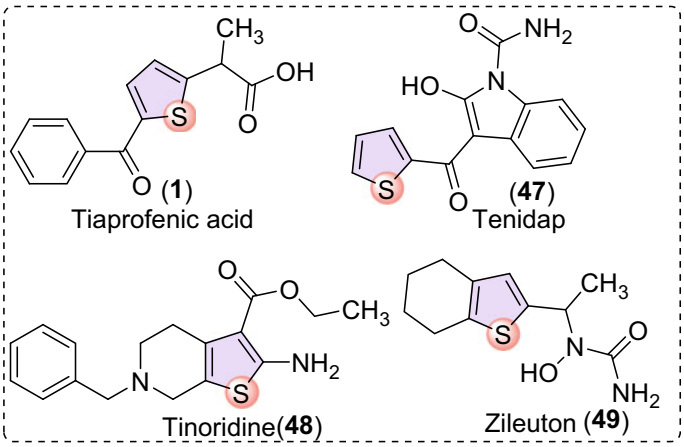


Fig. 1.4 Structures of few anti-inflammatory thiophene drugs

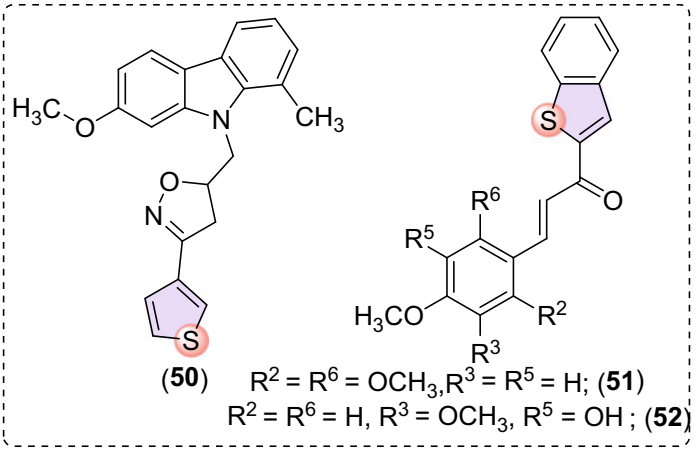


Fig. 1.5 Thiophene compounds possessing inhibitory activities against 5-lipoxygenase, polymorphonuclear leukocytes and HEK293 cells

1.3.2 Anticancer Activity

Cancer is a lethal disease accountable for growing death rate worldwide. It causes uncontrolled reproduction and multiplication of anomalous forms of the body's own cells. 2-Butylthiophene (**53**) had already been employed as a raw material in the synthesis of anticancer agents. Gunda and co-workers [28] synthesized a few new derivatives of thiophene and studied their in vitro cytotoxicity activities against colorectal adenoma cell line and breast cancer cell line. Among series of compounds synthesized by the researchers, compound (**54**) which had phenyl substituent showed the best anticancer activity (Fig. 1.6). Mohareb and research group in their work synthesized few thiophene derivatives, which were found to be active against breast adenocarcinoma cell, NCI-H460 (non-small lung cancer cell) and SF-268 (CNS cancer cells) [29]. Among various compound synthesized, compound (**55**) (Fig. 1.6) was found to contain higher cytotoxicity because of the presence of a chloro group.

1.3.3 Antioxidant Activity

A class of substituted thiophene derivatives was synthesized by Madhavi and research group, which were assessed for in vitro antioxidant activity by scavenging nitric oxide and 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radicals at 100 μM concentration [30]. Compound (**56**) (Fig. 1.7) was found to have maximum antioxidant activities as free radical scavengers in both the models.

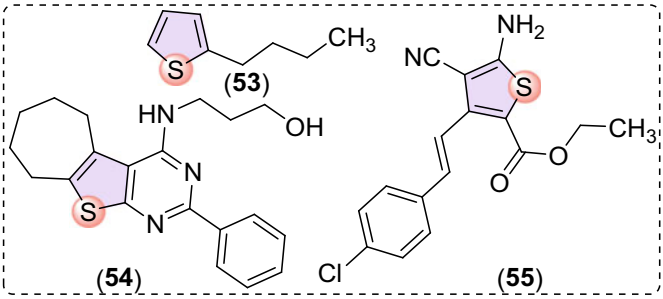
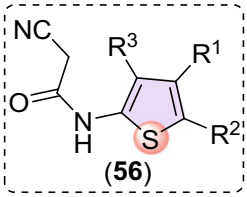


Fig. 1.6 Structures of 2-butylthiophene (**53**) and structures of two thiophene moieties (**54**, **55**) having anticancer activities

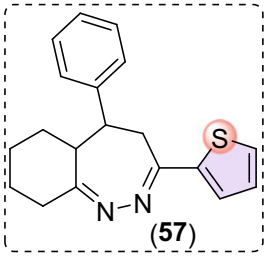
Fig. 1.7 Structure of a thiophene-based compound (**56**) found to have antioxidant activity



1.3.4 Antimicrobial Activity

Thiophene moieties are found to show high antimicrobial activities against several microbial infections. A series of thiophene analogues of chalcones were synthesized by Mazimba et al. [31] Synthesized compounds (**57**) (Fig. 1.8) were monitored for in vitro antimicrobial activities against *E. coli*, *C. Albicans*, *B. subtilis*, *S. Aureus,* and *P. Aeruginosa* using dilution method. Compounds were found to show superior antifungal and antibacterial activities.

Fig. 1.8 Structure of a thiophene-based compound (**57**) found to have antimicrobial activities



1.4 Conclusion

Since thiophene is of outmost importance for medicinal science, progress in the novel development for thiophene and their derivatives is a major concern among scientists. Some very recent and prominent strategies involved in constructing thiophene rings are discussed herein this chapter. Although the preparation of thiophenes has been widely studied, the synthesis of highly functionalized thiophenes needs special attention and is one of the challenges of organic chemistry. Some of the biological importance of the synthesized moieties is also discussed in this chapter.

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Chapter 2
Synthesis and Biological Evaluation of 4-Thiazolidinone Scaffold: A Versatile Chemistry and Diverse Biological Applications in the Drug Discovery and Development

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2.1 Introduction

Since many decades, causes of death due to health issues have tremendously increased and still increasing. Deaths due to non-communicable diseases increase in India. According to recent data, it will reach nearly 70% for the year 2022 which needs high attention of the chemists. This is the reason to boost research on medicinal important drugs. Many drugs have been discovered to cure various diseases. There are several biologically active motifs that contain heterocyclic compounds containing sulfur, oxygen, and nitrogen. Researchers have paid attention to these motifs because of their biological importance, and this is the reason, why it is one of the most important and prominent scaffolds to cure various diseases. It is a member ring and derivative of thiazolidine which contains a sulfur atom at the first position, nitrogen at the third position and has a >C=O (carbonyl group) on one of the remaining positions [1]. The most active area of modern heterocyclic chemistry is 4-thiazolidinone derivative

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chemistry [2]. It has been used as a moiety of choice because it possesses a wide range of pharmacological activities against different targets [3]. The 4-thiazolidinone core represents a major source for structurally new bioactive molecules that possess antibacterial, antifungal, antimalarial, antitubercular, anticancer, anti-inflammatory, anti-HIV, antidiabetic and so on [4, 5].

The scaffold's biological response profile has captured the attention of experts worldwide, who want to explore it further [6]. The broad pharmacological spectrum of structural fragments of the thiazolidinone paradigm is advantageous in modern medicinal chemistry. One of the privileged structural components in contemporary medicinal chemistry with a wide range of medical applications is the thiazolidinone template [7]. In this chapter we are going to discuss some important activities like antimicrobial [8–19], antimalarial [20–24], antitubercular [25–32], anticancer [33–37], anti-inflammatory [38–43], anti-HIV [44–50] and antidiabetic [51–53]. Many drugs are commercially available which contain thiazolidinone moiety. Penicillin is a prime drug that contains thiazolidinone scaffolds and has been discussed numerous times due to its prominent biological activity. It is used to treat certain infections caused by bacteria. Clinically important drugs having thiazolidinone moiety in their skeleton are darbufelone (**1**) and CI-987 (**2**) used as dual COX/LOX inhibitors, actithiazic acid (**3**) used as an antibiotic, ralitoline (**4**) as an antileptic agent, etozoline (**5**) as antihypertensive drug and pioglitazone (**6**) as hypoglycemic agents. In the current chapter, significance is given to various medicinal activities of synthesized thiazolidinone analogs (Fig. 2.1).

2.2 Synthesis of Thiazolidinone

Many routes have been reported by various research groups to synthesize thiazolidinone derivatives which we have discussed below. For the synthesis of thiazolidinones, there are mainly substituted amine, carbonyl compounds and mercapto acetic acid. The common synthetic route is given below to synthesize thiazolidinone (**7**) (Scheme 2.1).

Desai et al. [54] reacted phenylacetyl hydrazine and aromatic aldehyde in ethanol and piperidine to synthesize hydrazone. Hydrazone then reacted with thioglycolic acid and thiomalic acid to get two different scaffolds of 4-thiazolidinone (**8**). Further, Shiradkar et al. [55] synthesized thiourea derivatives with ethyl chloroacetate in absolute alcohol to get 4-thiazolidinone (**9**) (Scheme 2.2).

Shawky et al. [56] synthesized 7-cyano-6-(2-ethyl-4-oxothiazolidin-3-yl)-N-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxamide (**10**) from the reaction of 6-amino-7-cyano-N-phenyl-2,3-dihydro-1*H*-pyrrolizine-5-carboxamide with propionaldehyde and mercaptoacetic acid, while Ansari et al. [57] used thiosemicarbazide/3-methyl-thiosemicarbazideand DMAD in ethanol (99.5%) to prepare thiazolidinone conjugates (**11**). The reaction was heated at 70 °C (Fig. 2.2, Scheme 2.3).

Rahim et al. [58] synthesized aryl hydrazide bearing 4-thiazolidinone (**12**) by reacting Schiff bases with thioglycolic acid, and Salian et al. [59] synthesized

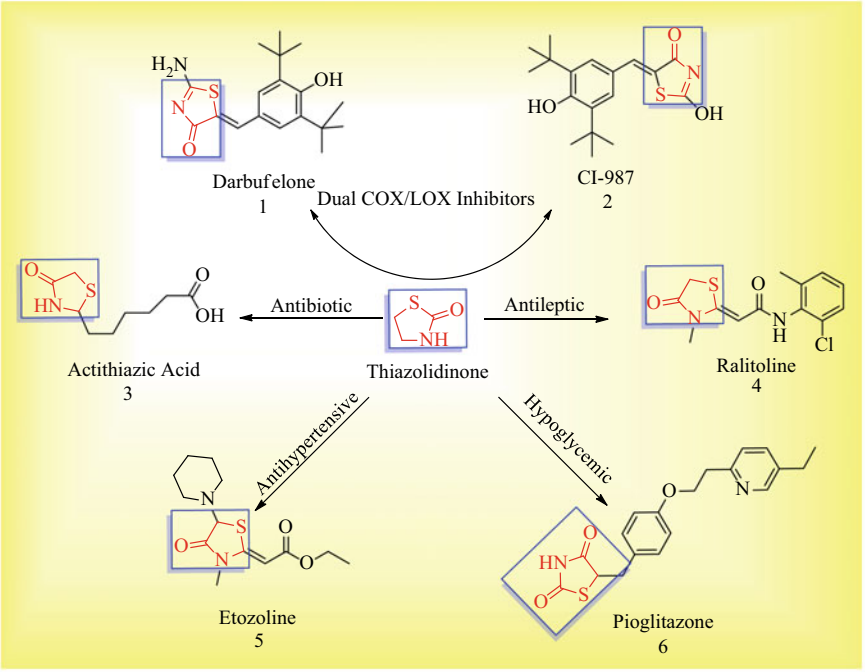
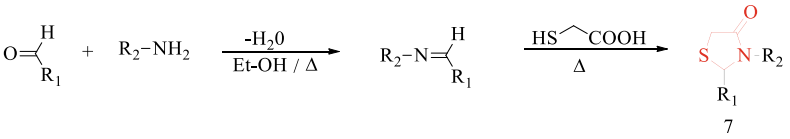
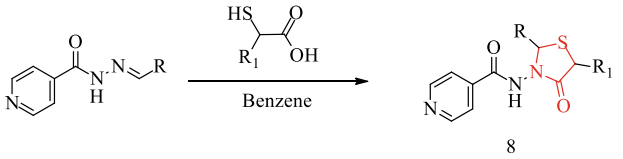


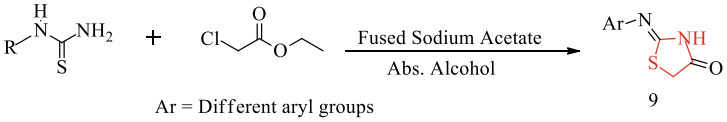
Fig. 2.1 Structures of commercially available drugs in the market



Scheme 2.1 Synthesis of thiazolidinones using substituted amine, carbonyl compounds and mercapto acetic acid



R_1 = -H and -CH_2COOH



Ar = Different aryl groups

Scheme 2.2 Synthesis of thiazolidinones using hydrazone with thioglycolic acid and thiomalic acid

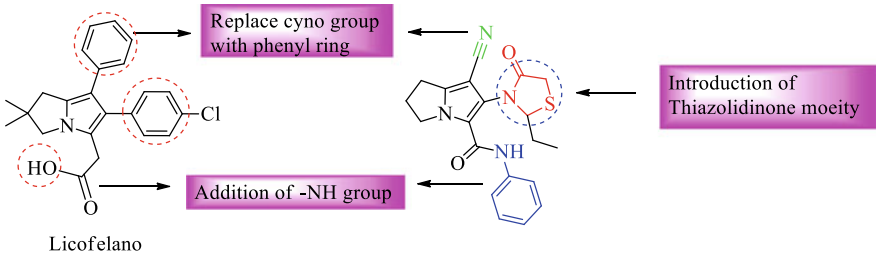
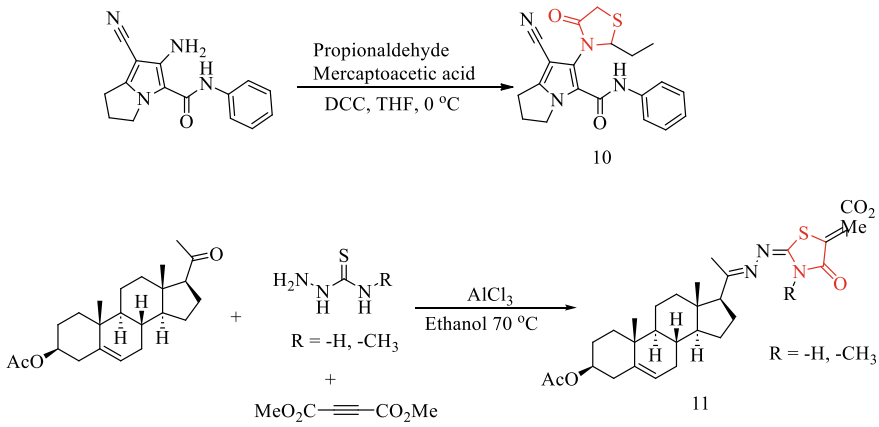


Fig. 2.2 Design of synthesized molecules from licofelano



Scheme 2.3 Synthesis of thiazolidinones using hydrazone with thioglycolic acid and thiomalic acid

appropriate 4-thiazolidione (**13**) by reacting 3-(4-chlorophenyl)-5-[4-(propan-2-yl)phenyl]-4,5-dihydro-1*H*-pyrazole-1-carbothioamide and ethyl chloroacetate in DMF at 25 °C for 24 h. Ansari et al. [60] synthesized 4-thiazolidinone (**14**) reacting 1-phenyl-3-(pyridine-4-ylmethyl)thiourea with chloroacetic acid by using ethanol as solvent (Fig. 2.3, Scheme 2.4).

In 2013, Kumar et al. [61] have synthesized 2,3-diphenylthiazolidin-4-one (**15**) by one-pot process. This reaction involves an aldehyde, an amine, a thioglycolic acid and different protic acids as a catalyst. Due to the nature of aldehydes, amines and protic acids yield of the thiazolidinone varies by different percentages. Protic acid which was used as a catalyst in this one-pot synthesis is SiO_2, Al_2O_3, $HClO_4$–SiO_2, K10, KSF, Amberlite and zeolite. The yield of this reaction was obtained between 36 and 85%. The lowest practical yield for this reaction was achieved by utilizing Amberlite as a protic acid catalyst, and the highest yield was achieved by using $HClO_4$–SiO_2 (230–400) as a protic acid catalyst (Scheme 2.5).

In 2012, Prasad et al. [62] synthesized 2-(4-chlorophenyl)-3-(3,4-difluorophenyl)thiazolidin-4-one (**16**) by the one-pot process. The advantage

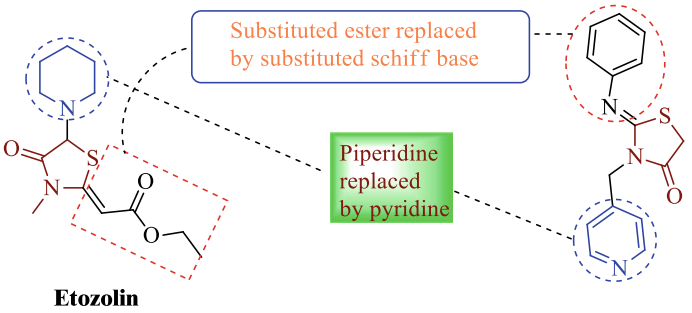
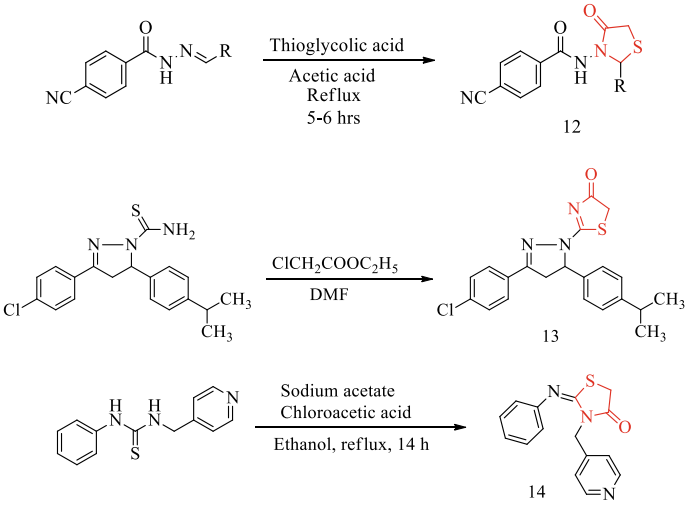
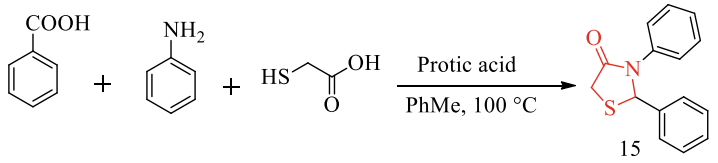


Fig. 2.3 Design of synthesized molecules from etozolin



Scheme 2.4 Synthesis of thiazolidinones using Schiff base and thioglycolic acid



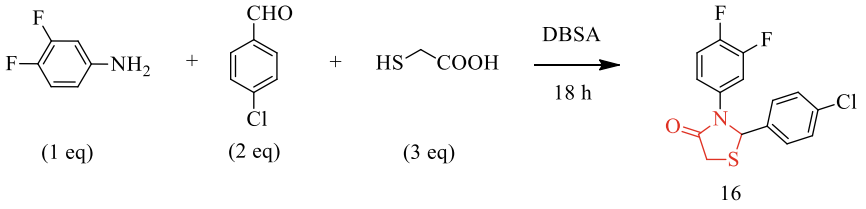
Protic acid = TfOH, $HClO_4$, H_2SO_4, p-TsOH, MsOH, HBF_4, TFA, AcOH, TfOH-SiO_2, $HClO_4$-SiO_2, p-TsOH-SiO_2, MsOH-SiO_2, HBF_4-SiO_2, TFA-SiO_2, AcOH-SiO_2

Scheme 2.5 Synthesis of thiazolidinones using aldehyde, an amine, thioglycolic acid and different protic acids as a catalyst

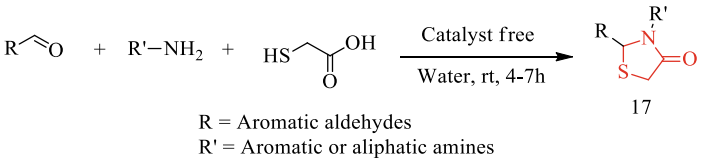
of this procedure is that water has been used as a solvent; in other words we can also say that this reaction proceeds under an aqueous medium. Dodecylbenzenesulfonic acid (DBSA) is used as a catalyst in this one-pot synthetic route. For water-sensitive reactions, DBSA is an efficient Bronsted acid-surfactant-combined catalyst. Although the reaction is carried out in aqueous medium product results in very good yields between 60 and 91% (Scheme 2.6).

In 2016, Thakare et al. [63] synthesized different thiazolidinone derivatives (**17**) via a one-pot reaction process. As the greener route of synthetic reaction, this process was very effective as it does not contain any catalyst or heating. Another advantage of this reaction was that it proceeds in an aqueous medium using water as a solvent in good yields. It was the best solvent-free and catalyst-free synthesis of thiazolidinone (Scheme 2.7).

In 2016, Subhedar et al. [64] synthesized a hybrid of tetrazoloquinoline–thiazolidinone (**18**) using DBU acetate as a catalyst. It is a one-pot synthesis process to prepare thiazolidinone (Fig. 2.4, Scheme 2.8).



Scheme 2.6 One-pot synthesis of thiazolidinones using aldehyde, an amine, thioglycolic acid and dodecylbenzenesulfonic acid (DBSA) as a catalyst



Scheme 2.7 Green synthesis of thiazolidinones via one-pot reaction process

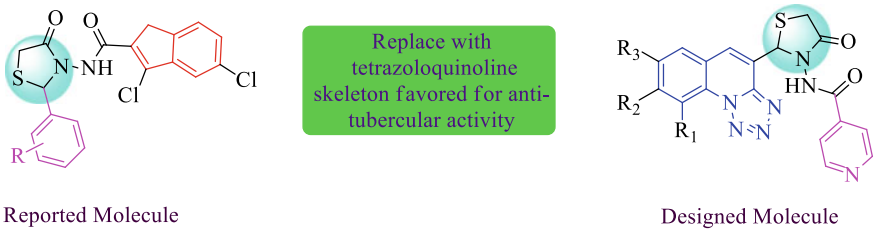
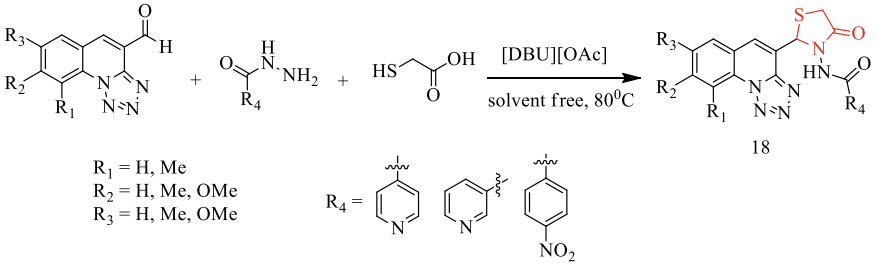


Fig. 2.4 Design of synthesized molecules from potent antitubercular molecule

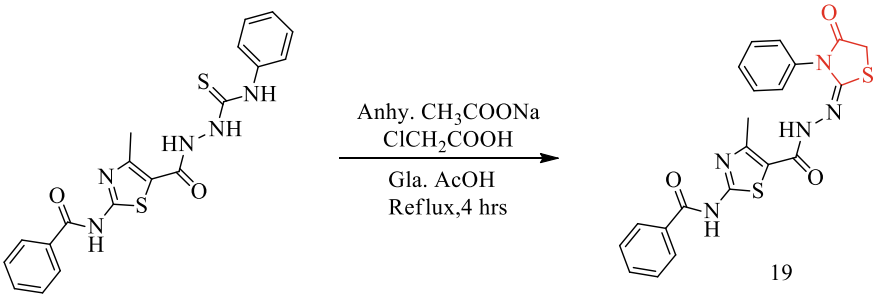


Scheme 2.8 One-pot synthesis of thiazolidinones using DBU acetate catalyst

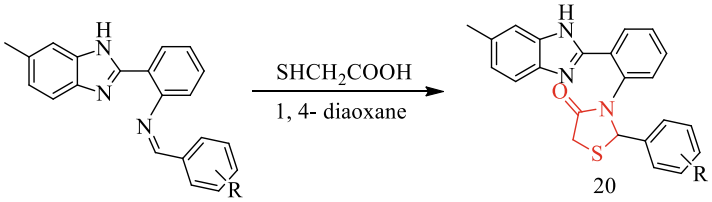
In 2012, Desai et al. [65] discovered a route to the formation of 4-thiazolidine. To synthesize ethyl 2-benzamido-4-methylthiazole-5-carboxylate, ethyl 2-amino-4-methylthiazole-5-carboxylate is agitated with benzoyl chloride in pyridine. After that, hydrazinehydrate is refluxed with it to yield N-(5-(hydrazinecarbonyl)-4-methylthiazol-2-yl)benzamide. Moreover, it formed *N*-(4-methyl-5-(2-(phenylcarbamothioyl) hydrozinecarbonyl) thiazol-2-yl)benzamide when it reacted with phenyl isothiocyanate in pyridine. The obtained product is further converted into *N*-(4-methyl-5-(2-(4-oxo-3-phenylthiazolidin-2-ylidene)hydrazinecarbonyl)thiazol-2-yl)benzamide (**19**) which on treatment with monochloro acetic acid and anhydrous sodium acetate in acetic acid (Scheme 2.9).

In 2012, Desai et al. [66] stabilized the new route of synthesis of 4-thiazolidinone. Then 2-amino benzoic acid and 4-methylbenzene-1, 2-diamine were reacting to form 2-(6-methyl-1*H*-benzo[*d*]imidazol-2-yl) aniline. Thus obtain amine reacting with different aldehydes to form Schiff bases. *N*-arylidene-2-(6-methyl-1*H*-benzo[*d*]imidazol-2-yl) anilines were refluxing with mercapto acetic acid in 1, 4-dioxane to produce 4-thiazolidinone derivatives (**20**) (Scheme 2.10).

In 2011, Pratap et al. [67] innovated a pot three-component synthesis of 4-thiazolidinone conjugates (**21**), using Saccharomyces cerevisiae (baker's yeast) as a catalyst for the formation of final products. Different aldehydes and amines are soluble in THF. Then, added TGA in the presence of Saccharomyces cerevisiae



Scheme 2.9 Synthesis of thiazolidinones using hydrazinecarbonylbenzamide and monochloro acid and acetic acid as a catalyst

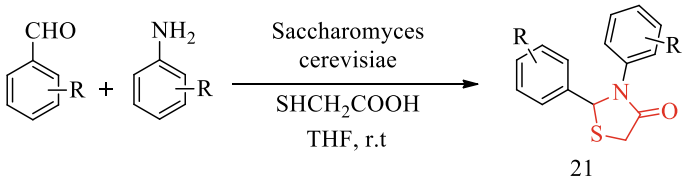


Scheme 2.10 Synthesis of thiazolidinones using amine and mercapto acetic acid

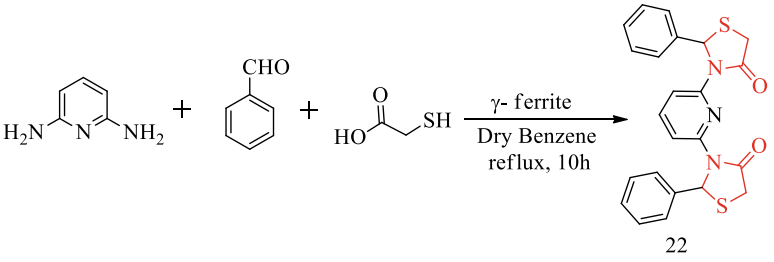
(baker's yeast) was at room temperature. After 40 h, the final product occurs with a good percentage of yields (Scheme 2.11).

In 2011, Shrivastava et al. [68] discovered a new path of synthetic derivatives of 4-thiazolidinone (**22**) with one-pot three-component condensation reaction. The difference from other reactions to the formation of 4-thiazolidinone is using γ-ferrite (anhydrous Fe_2O_3) as a catalyst. The formation way of 4-thiazolidinone uses dry benzene as a solvent. The reaction time is 10 h, which is monitored by TLC (Scheme 2.12).

In 2014, a new route for the synthesis of 4-thiazolidinones was discovered by Benmohammed et al. [69]. In the presence of anhydrous sodium acetate, the reaction was carried out by using various phenyl thiosemicarbazones and ethyl 2-bromoacetate to produce a novel class of thiazolidinones (**23**). The whole reaction mass is taken with ethanol (95%) (as solvent) and reflux for 1–3 h (Fig. 2.5, Scheme 2.13).



Scheme 2.11 One-pot three-component synthesis of 4-thiazolidinones using Saccharomyces cerevisiae (baker's yeast) as a catalyst



Scheme 2.12 One-pot three-component synthesis of 4-thiazolidinones using γ-ferrite (anhydrous Fe_2O_3) as a catalyst

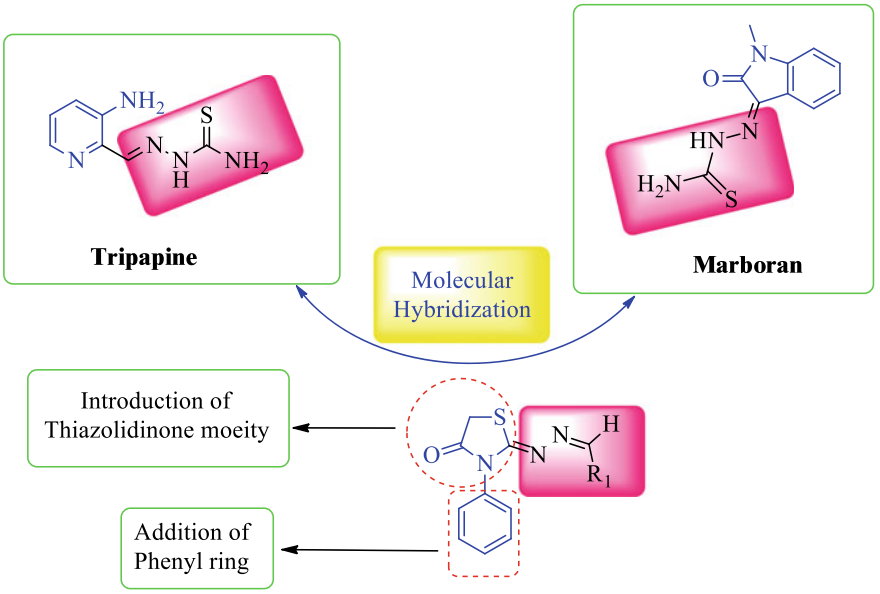
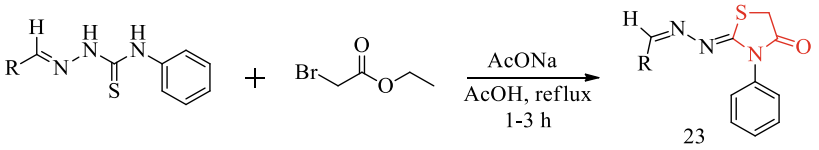
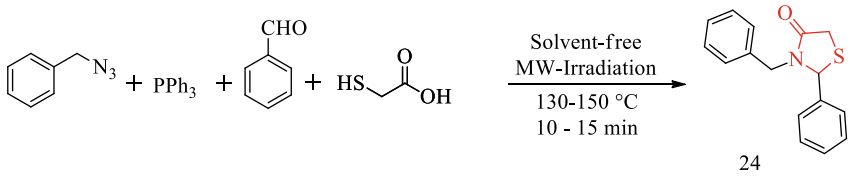


Fig. 2.5 Design of synthesized molecules from Triapine and Marboran using molecular hybridization



Scheme 2.13 Synthesis of 4-thiazolidinones from phenyl thiosemicarbazones and ethyl 2-bromoacetate using anhydrous sodium acetate

In 2014, the excellent method for the one-pot, three-component, solvent-free, microwave-accelerated synthesis of 4-thaizolidinone was provided by Shanmugavelan et al. [70]. It is the efficient and environmentally friendly method of producing 3-benzyl-2-phenylthiazolidin-4-one (24) with a high yield from organic azides, triphenylphosphine and aldehyde using mercaptoacetic acid through a tandem one-pot, solvent-free, three-component procedure that is microwave-accelerated (Scheme 2.14).



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Scheme 2.14 Microwave-assisted one-pot synthesis 4-thiazolidinones from organic azides, triphenylphosphine, aldehyde with mercaptoacetic acid

2.3 Pharmaceutical Profile of Thiazolidinones

The 4-thiazolidinone hybrids were found to have various pharmacological activities such as antimicrobial, antitubercular, antidiabetic, anticancer, antimalarial, anti-inflammatory, anti-HIV, antioxidant, antiparasitic, antihepatitic, antidepressant and anti-Alzheimer activity. Various thiazolidinone hybrids having different pharmaceutical profiles were shown in Fig. 2.6.

2.3.1 Antimicrobial Activity

Since many decades mankind has been suffering from various diseases. Microbes are one of the most common reasons that are affecting mankind. To get rid of it, it was needed to do research and find new and effective antimicrobials. To prevent the proliferation of undesirable microorganisms, antimicrobials are indispensable compounds [71]. Numbers of heteromoieties are effective as antimicrobial agents, and thiazolidinone is one of them. Thiazolidinone has a very important place in the field of heterocyclic scaffolds. Many researchers have found the significance of thiazolidinone moiety as an antimicrobial agent and synthesized several compounds that have shown prominent antimicrobial activity [72].

El-Gaby et al. [73] prepared several new compounds having 4-thiazolidinone moiety, and they were evaluated against different strains for antifungal and antibacterial activities. The activity data revealed that the bioactive molecuels which were tested against different pathogens had weak activity compared to standard drug ampicillin and mycostatine for their antibacterial and antifungal activities. Compounds (**25**)**,** (**26**) and (**27**) exibited very good activity against *Bacillus cereus,* while compound (**28**) exhibited remarkable efficacy against *Penicillium chrysogenum Thom* compared to other synthetic compounds (Fig. 2.7).

Omar et al. [74] reported a novel class of compounds known as 4-adamantyl-2-thiazolylimino-5-arylidene-4-thiazolidinones **(29)** that demonstrated moderate to remarkable inhibition of the growth of fungus, bacteria and Gram-positive and Gram-negative bacteria. Gram-positive bacteria *B. cereus* were the most susceptible species for the compounds of the test, whereas *Protius mirabilis* was the least resistant Gram-negative species. The majority of the compounds had the lowest action against *A.*

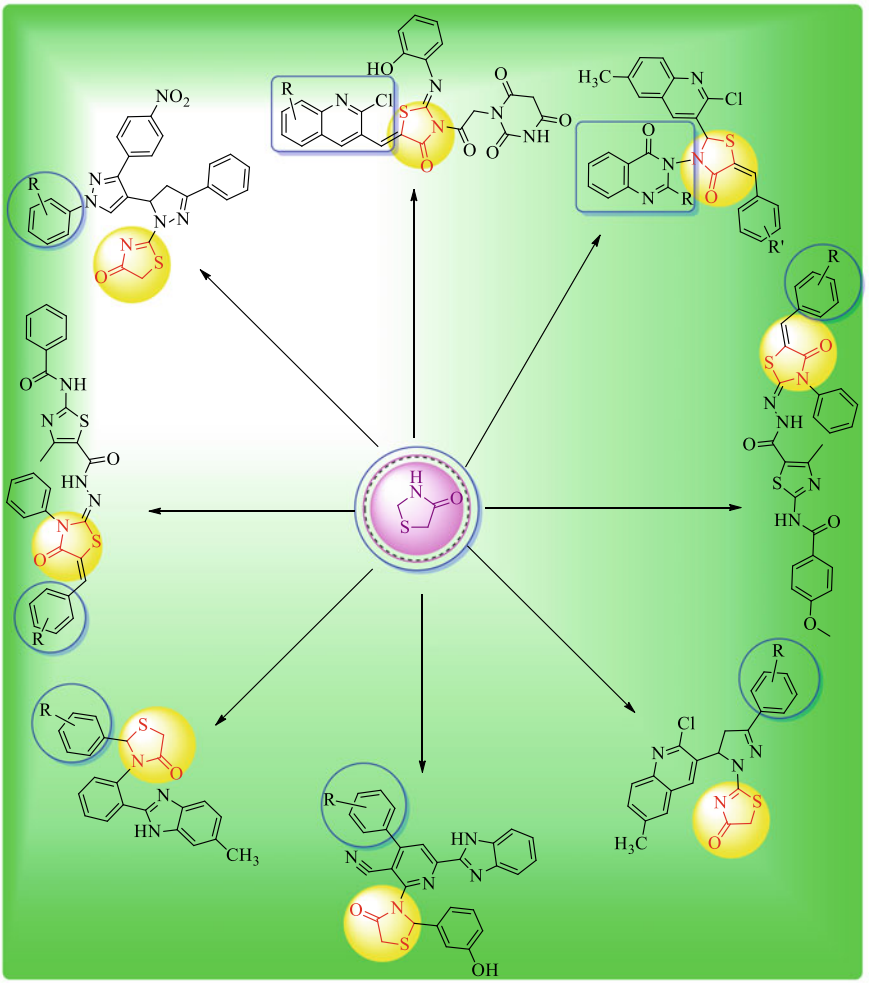
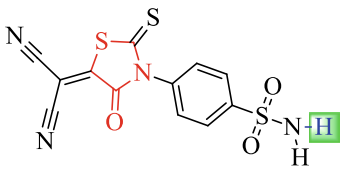


Fig. 2.6 Some synthesized molecules containing thiazolidinone nucleus possess various biological activities

versicolor, but *F. flavum* is the most sensitive fungus. It should be taken into account that all molecules had significantly better activity than the reference commercial antibacterial drugs and a more effectiveness than ketoconazole (Fig. 2.8).

A new series of thiazolidinone moiety clubbed with thiazole was synthesized by Pitt et al. [75]. Antimicrobial activity was examined for the synthesized compounds. All synthetic compounds showed good or promising activity against several strains. Of all the compounds, compound **(30)** showed exceptional antibacterial and antifungal properties. *L. monocytogenes* was the most resistant bacterial species to the compounds under evaluation, whereas *S. typhimurium* and *M. flavu* were among those most susceptible. Anticipating all the fungi to be tested, *A. ochraceus* turned



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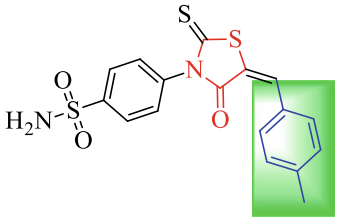

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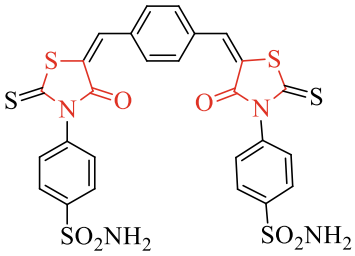

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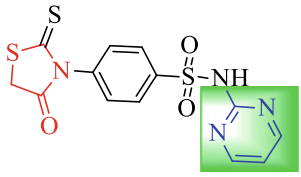

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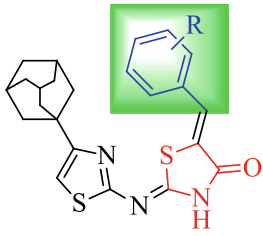
Fig. 2.7 4-thiazolidinone hybrids as potent antifungal and antibacterial agents

Fig. 2.8 Adamantane and thiazole-based 4-thiazolidinone hybrids as potent antifungal and antibacterial agents



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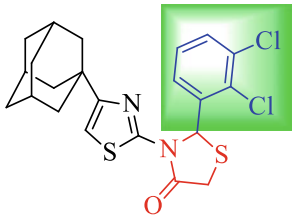
out to be the prone species, whereas *C. albicans* showed to be the most resistant (Fig. 2.9).

Fig. 2.9 Adamantane and thiazole-based 4-thiazolidinone hybrids as potent antimicrobial agents



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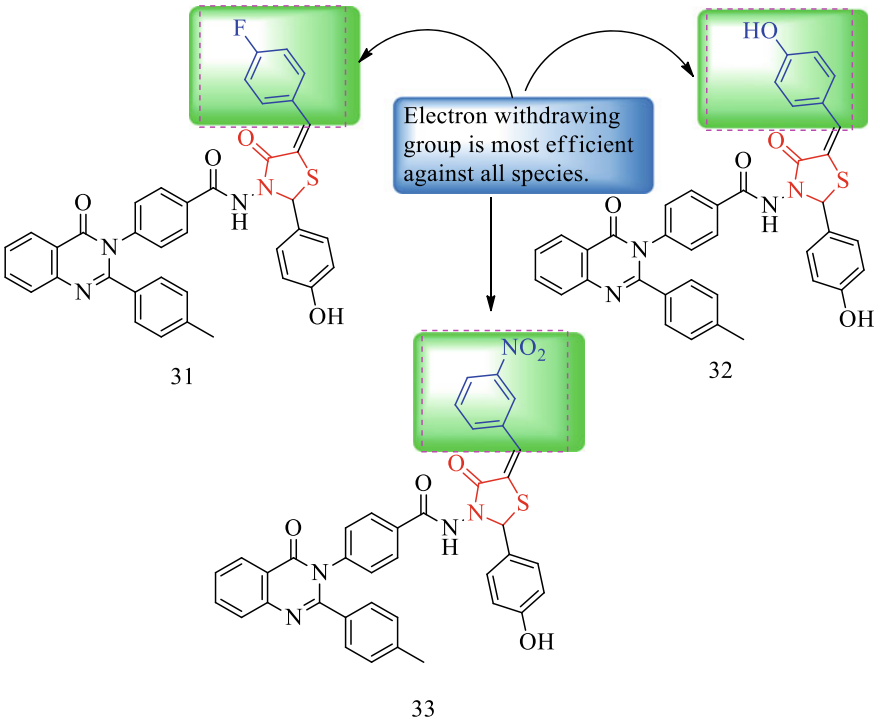
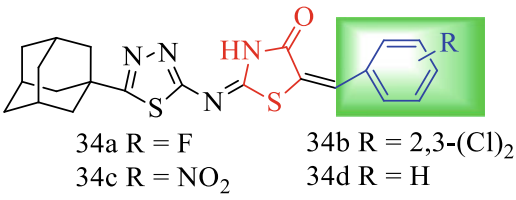


Fig. 2.10 Thiazolidinone containing quinazoline with antimicrobial potency

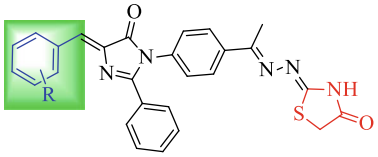
Desai et al. [76] synthesized a novel series of thiazolidinone containing quinazoline moiety. Novel compounds tested for various antimicrobial species exhibited very good activity. Compounds (**31**), (**32**) and (**33**) were most active against all species. We can conclude that electron-withdrawing displayed excellent activity among all tested compounds (Fig. 2.10).

The antibacterial activity of newly synthesized compounds of thiazolidinone has been studied by Fesatidou et al. [77]. Newly synthesized 2{[5-(adamantan-1-yl)-1,3,4-thiadiazol-2-yl]-imino}-5-arylidene-1,3-thiazolidin-4-ones were screened for antimicrobiac activity. A wide range of Gram-positive and Gram-negative bacteria and fungi showed inhibition of growth. Except for compounds containing derivatives of **(34a)** and **(34b)**, all compounds had antibacterial activity that was either better than or at par with that of the standard antibiotic ampicillin. Furthermore, when compared to streptomycin, several of the compounds had potencies that were either higher or equivalent; the compound with the nitro group in position four was the most powerful. It was found that *S. typhimirium* was the Gram-negative bacterium that was most sensitive to the compounds under evaluation, whereas *Escherichia coli* was the most resistant. It was found that *L. monocytogenes* was the most resistant Gram-positive bacteria, whereas *Staphylococcus aureus* was the most sensitive. Compounds with a derivative of the **(34c)** group were promising, followed by the **(34d)** derivative,



34a R = F
34b R = 2,3-$(Cl)_2$
34c R = NO_2
34d R = H

Fig. 2.11 Adamantane and thiadiazole-based 4-thiazolidinone hybrids as potent antimicrobial agents



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R = -H, -2-Cl, -4-Cl, -2-F, -4-F, -2-NO_2, -4-NO_2, -2-OH, -3-OH, -4-OH, -2-CH_3, -3-CH_3, -4-CH_3, -2-OCH_3, -4-OCH_3

Fig. 2.12 Antimicrobial potential of imidazole-based 4-thiazolidinones

when it applies to fungi as well. Of all the compounds examined, *A. ochraceus* and *T. viride* were the most resistant to the substances, and the most sensitive one was *A. fumigates* (Fig. 2.11).

Desai et al. [78] synthesized a novel series of 2-((1-(4-(4-(arylidene)-5-oxo-2-phenyl-4,5-dihydro-1*H*-imidazol-1-yl)phenyl)ethylidene)hydrazono)thiazolidin-4-ones (**35**). All synthesized compounds showed poor to promising activity against all strains. Ampicillin and griseofulvin were taken as reference drugs for the screening of all synthesized compounds. Data revealed that electron-donating groups like methyl, methoxy and hydroxy derivatives exhibited promising activity against antibacterial and antifungal strains for tested compounds. Moreover, based on structural-activity relationship studies, it should be noticed that the substituent at 2nd and 4th positions on the benzene ring of the imidazole ring influenced antimicrobial potency (Fig. 2.12).

Abo-Ashour et al. [79] have worked on a newly synthesized compound containing indole and thiazolidinone conjugates and their antibacterial activity. They have tested Gram-positive bacteria: *S. aureus* (RCMB 010028, Sa), Gram-negative bacteria: *Pseudomonas aeruginosa* (RCMB 010043, Pa) and *E. coli* (RCMB 010052, Ec). They used ciprafloxacin as standard, and strains used for antifungal activity were *A. fumigates* and *C. albicans,* while Amphotericin B was standard drug. Compounds (**36**) and (**37**) exhibited very good antibacterial and antifungal activities compared to others (Fig. 2.13).

Desai et al. [80] synthesized a novel series of thiazolidinone derivatives of pyridyl benzimidazoles. All substance was examined for antimicrobial activity. Compounds **(38)**, **(39)** and **(40)** demonstrated outstanding activity against bacterial pathogens, whereas compounds **(40)**, **(41)** and **(42)** showed promising efficacy against fungal strains (Fig. 2.14).

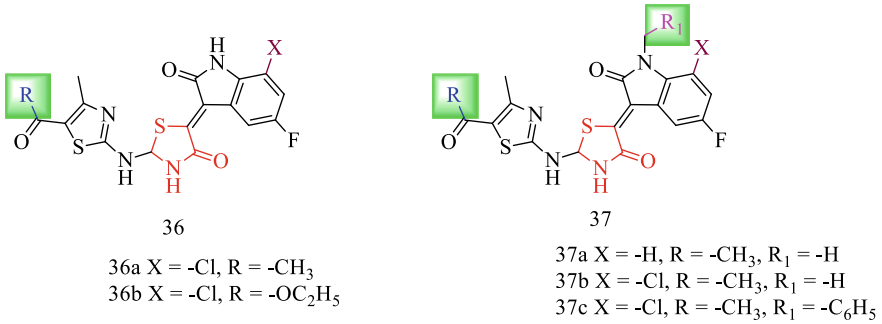


Fig. 2.13 Indole and thiazolidinone conjugates as antibacterial agents

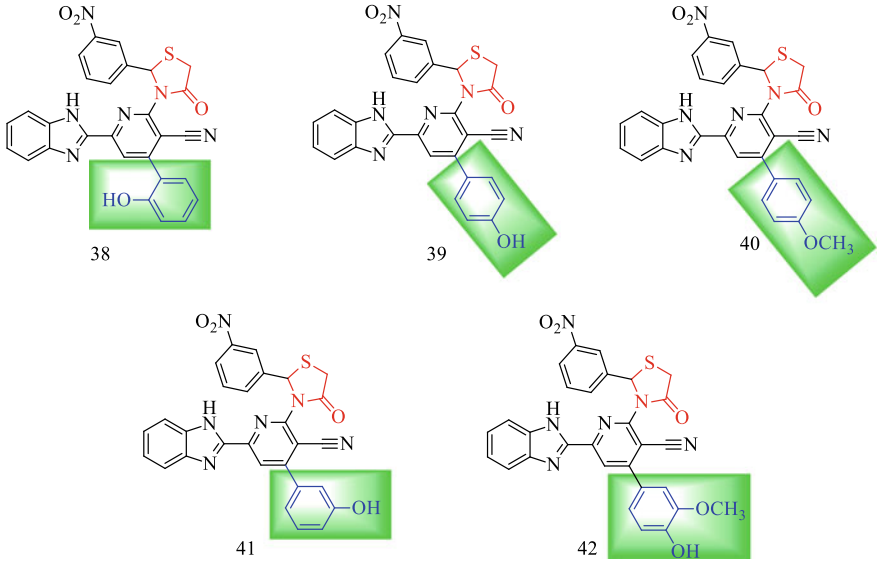


Fig. 2.14 Pyridine and benzimidazole-based 4-thiazolidinones with antimicrobial potency

Desai et al. [81] synthesized some novel compounds containing quinazoline and thiazolidinone and screened their antibacterial activity. Newly synthesized compounds exhibited very good antibacterial activity. Among all analogs, *N*-(2,5-bis(4-fluorophenyl)-4-oxothiazolidin-3-yl)-4-(4-oxo-2-(*p*-tolyl)quinazolin-3(4*H*)-yl)benzamide (**43**) and *N*-(5-(2-chlorophenyl)-2-(4-fluoro- phenyl)-4-oxothiazolidin-3-yl)-4-(4-oxo-2-(*p*-tolyl)quinazolin-3(4*H*)-yl)benzamide (**44**) showed prominent antibacterial activity against *E. coli, P. aeruginosa* and *S. pyogenes.* *N*-(2-(4-fluorophenyl)-5-(3-nitrophenyl)-4-oxothiazolidin-3-yl)-4-(4-oxo-2-(*p*-tolyl)quinazolin-3(4*H*)-yl) benzamide (**45**) showed a very good activity against *S. aureus.* We can conclude that electron-withdrawing groups are prominent against different antibacterial strains (Fig. 2.15).

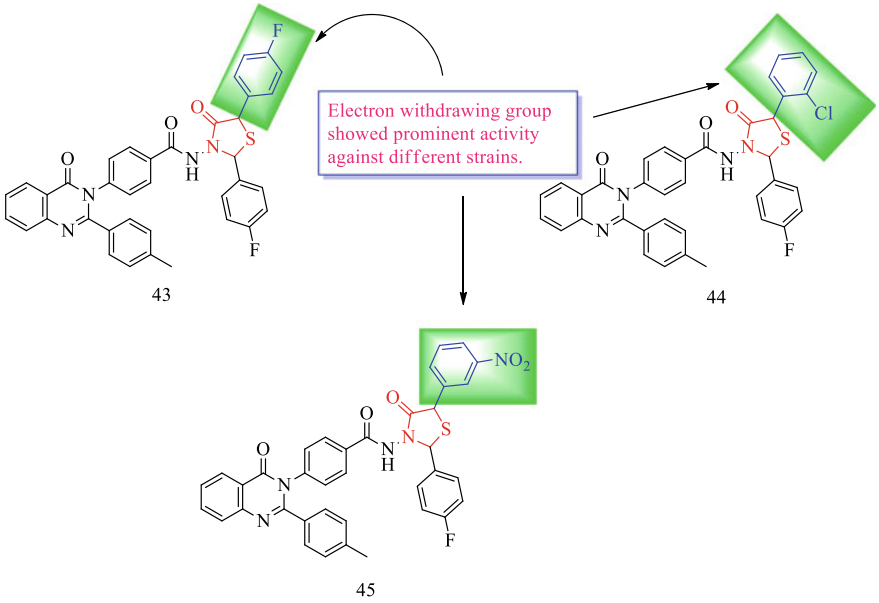


Fig. 2.15 Potent antibacterial quinazoline based 4-thiazolidinones

Desai et al. [82] have worked on the synthesis and antibacterial screening of quinoline-based quinazolinone-4-thiazolidinone heterocycles. The screening data showed very good activity of different synthesized compounds against different bacterial strains like *E. coli, P. aeruginosa, S. pyogenes* and *S. aureus* and antifungal strains like *C. albicans, A. niger* and *A. clavatus.* Compounds (**46**) and (**47**) showed prominent activity against the above-mentioned strains (Fig. 2.16).

Desai et al. [83] synthesized novel C-5 and N-3 substituted derivatives of 4-thiazolidinone containing quinoline and barbitone heterocycles. All newly synthesized compounds were tested for their antibacterial and antifungal activity. Compounds (**48**), (**49**), (**50**) and (**51**) exhibited excellent activity for antibacterial and

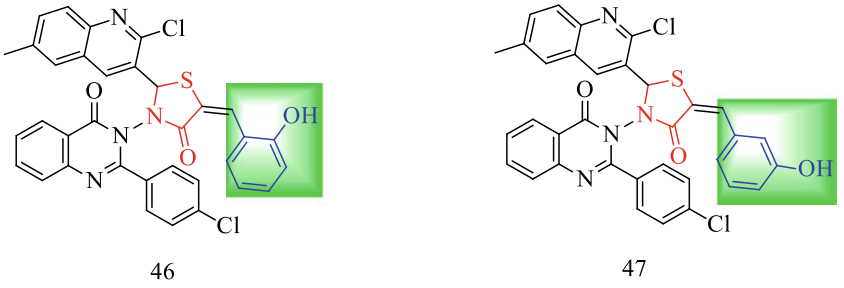


Fig. 2.16 Quinoline and quinazoline-based 4-thiazolidinones heterocycles as antimicrobial agents

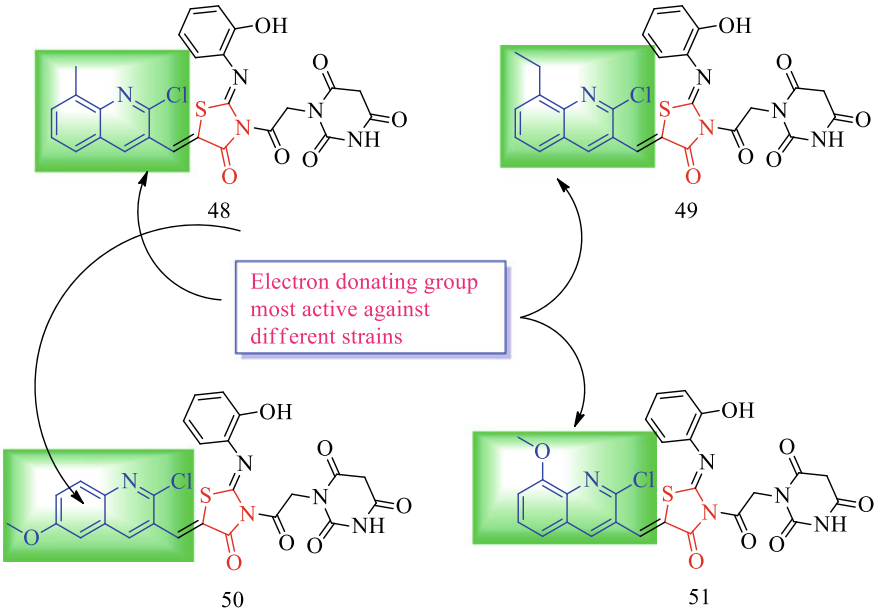


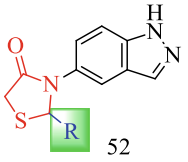
Fig. 2.17 4-thiazolidinone containing quinoline and barbitone as potential antimicrobial agents

antifungal as well. Mentioned compounds having electron-donating groups (methyl, methoxy and ethyl) at 6th and 8th position on quinoline moiety exhibited maximum antibacterial and antifungal activities (Fig. 2.17).

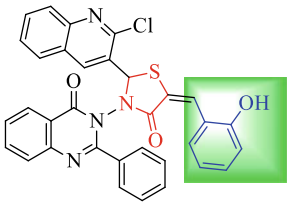
Works on antimicrobial screening of newly synthesized derivatives of indazole-4-thiazolidinone were done by Angapelly et al. [84]. Ciprofloxacin is taken as a standard drug. Compounds (**52a**), (**52b**) and (**52c**) showed very good activity against different strains of bacteria and fungi. Based on results we may coverlid that compounds containing electron-withdrawing groups are most active (Fig. 2.18).

A novel series of 2-(2-chloroquinolin-3-yl)-5-((aryl)benzylidene)-3-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)thiazolidin-4-ones was synthesized by Desai et al. [85]. Synthesized compounds were evaluated for their antimicrobial screening. Different types of strains are used for antibacterial and antifungal screening for synthesized compounds. Compounds (**53**) and (**54**) exhibited very good activity against both antibacterial and antifungal strains (Fig. 2.19).

Fig. 2.18
Indazole-4-thiazolidinones with antimicrobial activity



52a R = 4-CF_3
52b R = 3-CF_3
52c R = 4-OCH_3



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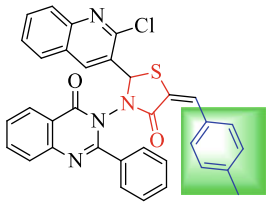
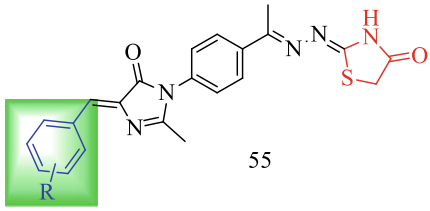


54

Fig. 2.19 Potent antimiocrobial agents based on quinoline and quinazoline based 4-thiazolidinones

Fig. 2.20 Imidazole-based thiazolidin-4-ones as bioactive agents



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Desai et al. [86] developed a novel series of 2-((1-(4-(4-arylidene-2-methyl-5-oxo-4,5-dihydro-1*H*-imidazol-1-yl)phenyl)ethylidene)hydrazono)thiazolidin-4-ones. Synthesized compounds contain two promising bioactive entity. Activity data revealed that compound (**55**) has an electron-donating group that exhibited promising activity against both antibacterial and antifungal strains (Fig. 2.20).

A novel series of 3-(2-(1*H*-benzo[*d*]imidazol-2-yl)phenyl)-2-arylthiazolidin-4-ones was synthesized by Desai et al. [87]. Synthesized compounds were screened for their antibacterial and antifungal activities against different strains. Screening results showed that due to the presence of methyl group at the third position of the phenyl ring, 3-(2-(1*H*-benzo[*d*]imidazol-2-yl)phenyl)-2-(*m*-tolyl)thiazolidin-4-one (**56**) was most active against *E. coli* and *P. aeruginosa* compared to standard drug gentamycin. The 3-(2-(1*H*-benzo[d]imidazol-2-yl)phenyl)-2-(4-fluorophenyl) thiazolidin-4-one (**57**) and 3-(2-(1*H*-benzo[d]imidazol-2-yl)phenyl)-2-(*p*-tolyl)thiazolidin-4-one (**58**) were found to be most active against *C. albicans* among all compounds due to the presence of methyl and fluorine groups at fourth position of phenyl ring compared to standard drug K. Nystatin (Fig. 2.21).

Desai et al. [88] synthesized thiazolidinone derivatives containing two phenyl rings. All novel compounds were screened against Gram-positive and Gram-negative bacteria. Also 2-(4-chlorophenyl)-*N*-(2-(4-hydroxy-3-methoxyphenyl)-4-oxothiazolidin-3-yl)acetamide (**59**) was most active against Gram-negative strain *E. coli,* while 2-(4-chlorophenyl)-*N*-(2-(2-hydroxyphenyl)-4-oxothiazolidin-3-yl)acetamide (**60**) was most active against Gram-positive strain *S. aureus* (Fig. 2.22).

A novel series of compounds containing 4-thiazolidinone was synthesized by Desai et al. [89]. All compounds were screened against *E. coli* and *S. aureus*

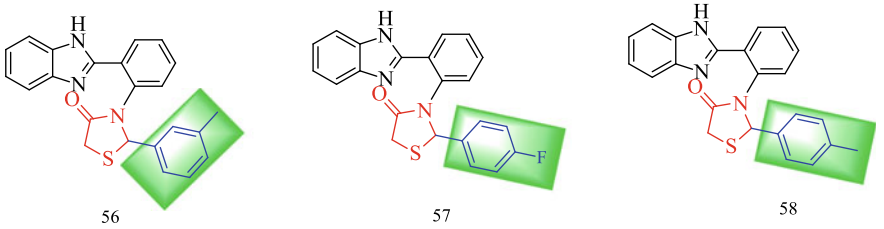


Fig. 2.21 Potent antimiocrobial agents based on benzimidazole and thiazolidin-4-ones

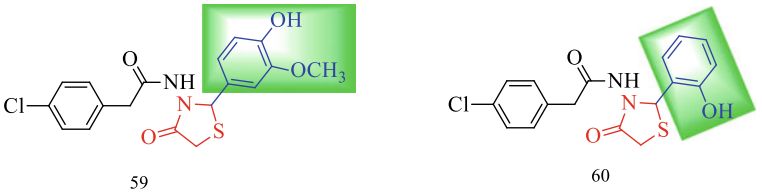


Fig. 2.22 Thiazolidinone derivatives containing two phenyl ring as antibacterial agents

strains. *N*-(2-(4-(benzyloxy)phenyl)-4-oxothiazolidin-3-yl)-3-nitrobenzamide (**61**) showed excellent activity against *E. coli,* while *N*-(2-(4-(benzyloxy)phenyl)-4-oxothiazolidin-3-yl)-4-methylbenzamide (**62**) exhibited good activity against *S. aureus*. It shows that the electron-withdrawing group was active against Gram-positive strain and the electron-donating group was active against Gram-negative strain (Fig. 2.23).

Desai et al. [90] synthesized a novel series of *N*-(5-(2-(5-(arylidene)-4-oxo-3-phenylthiazolidin-2-ylidene)hydrazinecarbonyl)-4-methylthiazol-2-yl)-4-methoxybenzamides. All novel compounds were tested against different bacterial and fungal strains. Compounds (**63**), (**64**) and (**65**) were most active against all tested strains and showed much stronger activity than the reference drug ciprofloxacin and griseofulvin (Fig. 2.24).

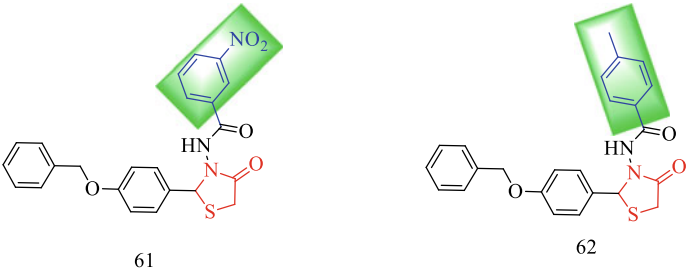


Fig. 2.23 Thiazolidinone derivatives containing (benzyloxy)benzene as antibacterial agents

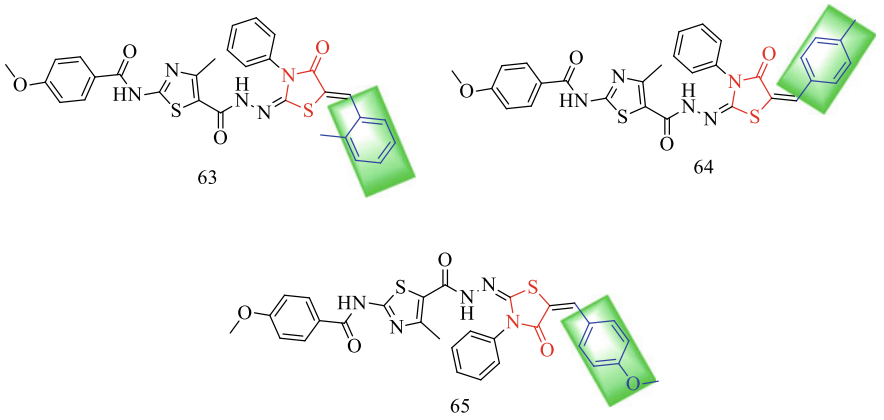


Fig. 2.24 Thiazole and thiazolidinone derivatives with antimicrobial potency

Desai et al. [91] synthesized a novel series of compounds containing 4-thiazolidinone, quinoline and barbitone. Synthesized compounds were evaluated for in vitro activity against different antifungal and antibacterial strains. Compounds having methyl (**66**), ethyl (**67**) and methoxy (**68**, **69**) groups at the 6th and 8th position of quinoline moiety exhibited excellent activity against all tested strains (Fig. 2.25).

A novel series of 6-(1*H*-benzo[*d*]imidazol-2-yl)-2-(2-(aryl)-4-oxothiazolidin-3-yl)-4-(3-methoxyphenyl)nicotinonitrile derivatives was synthesized by Desai et al. [92]. Synthesized compounds were tested against different antibacterial and antifungal strains. Evaluation of tested compounds revealed that 6-(1*H*-benzo[*d*]imidazol-2-yl)-2-(2-(3-hydroxyphenyl)-4-oxothiazolidin-3-yl)-4-(3-methoxyphenyl)nicotinonitrile (**70**) emerged as antibacterial agent and 6-(1*H*-benzo[*d*]imidazol-2-yl)-2-(2-(3-hydroxyphenyl)-4-oxothiazolidin-3-yl)-4-(4-methoxy- phenyl)nicotinonitrile (**71**) emerged as antifungal agent (Fig. 2.26).

Dincel et al. [93] have designed and synthesized some novel hydrazine carbothioamide, 4-thiazolidinone and 1,2,4-triazole-3-thione derivatives to assess their antimicrobial potential. The results of this study suggest that the newly synthesized compounds, including hydrazine carbothioamide, 4-thiazolidinone and 1,2,4-triazole-3-thione derivatives, have promising antibacterial and antifungal activities against a range of microbial strains (*S. aureus*, *E. coli*, *P. aeruginosa*, *C. albicans*, *C. krusei*, *C. parapsilosis*, *M. gypseum*, *T. mentagrophytes* var. erinacei and *T. tonsurans*). Among the tested compounds, (**72**) showed the most potent activity against the tested microorganisms. These findings suggest that these compounds could be further developed as potential drug candidates for the treatment of bacterial and fungal infections (Fig. 2.27).

Reddy et al. [94] have synthesized fused 4-thiazolidinone thiopyrimidine derivatives to evaluate their antimicrobial activity. The compounds were assessed for their in vitro antibacterial activity against four species of bacteria (Gram-positive *Bacillus*

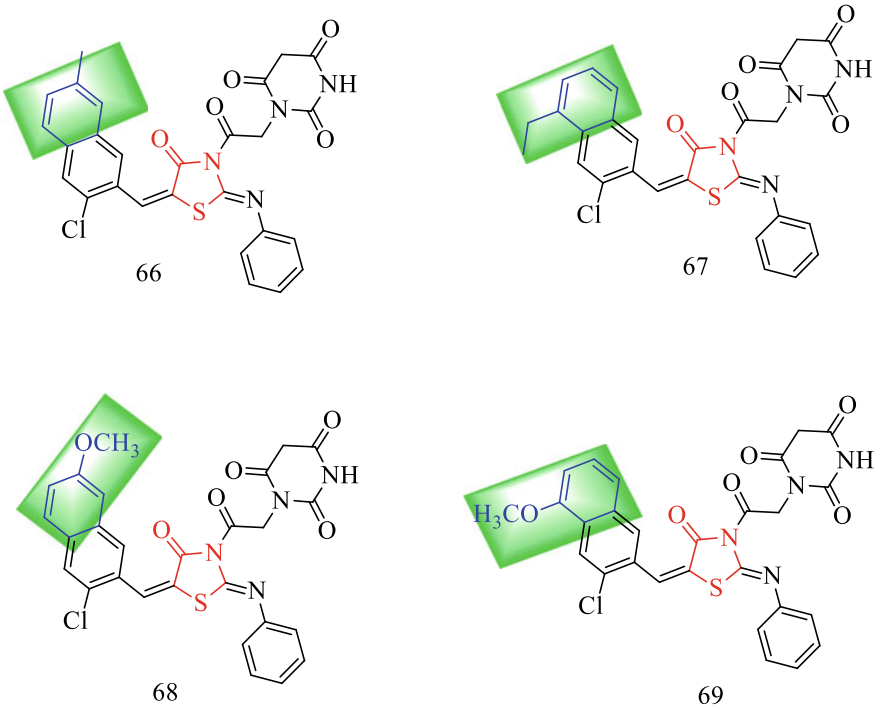


Fig. 2.25 4-thiazolidinones with quinoline and barbitone as antimicrobial activity

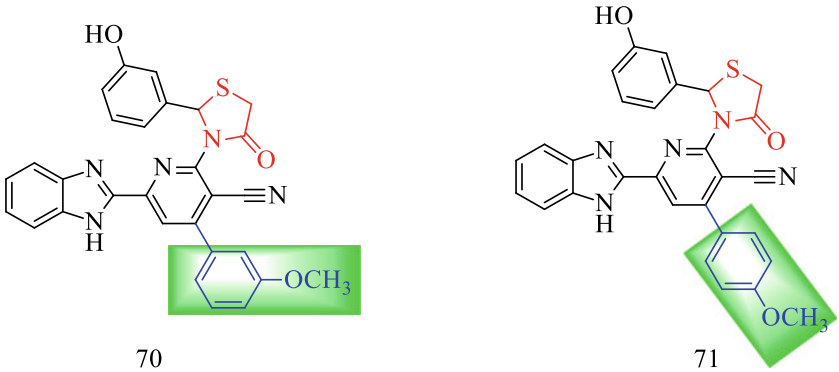
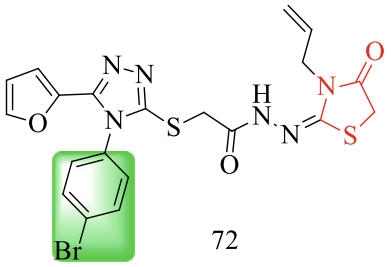


Fig. 2.26 Benzo[*d*]imidazole and pyridine-based thiazolidinones as antibacterial and antifungal agents



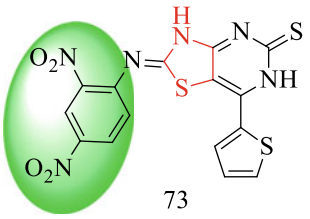
72

Fig. 2.27 1,2,4-triazole and 4-thiazolidinones as antimicrobial agents

subtilis and *S. aureus* and Gram-negative *E. coli* and *P. aeruginosa* bacteria), out of which two newly synthesized compounds showed moderate in vitro antibacterial activity against all the tested strains, except compound (**73**) that showed the highest antibacterial activity against Gram-positive and Gram-negative bacteria. The study also found that the compounds containing the nitro group (–NO_2) exhibited a higher zone of inhibition against antibacterial compared to the compounds that contain the ester group. The active compounds in this study were (**73**) and (**74**) (Fig. 2.28).

Ghoneim and Zordok [95] have designed and synthesized fluoroquinolones linked to 4-thiazolidinone moieties. The synthesized compounds were evaluated for their antimicrobial activity against Gram-positive (*S. aureus* and *S. epidermidis*) and Gram-negative (*P. aeruginosa*) microorganisms. The results showed that compounds (**78**), (**79**) and (**76**) exhibited outstanding antibacterial activity against *S. aureus*, while compounds (**78**) and (**77**) showed good potency for the inhibition of the growth of *P. aeruginosa.* The bioactivity score of the organic molecules indicated that compounds (**78**) and (**79**) exhibited the highest percentage of inhibition. The drug-likeness scores showed that 4-thiazolidinone targets (**75**), (**76**) and (**79**) had the maximum drug-likeness (Fig. 2.29).

Desai et al. [96] have designed and synthesized some 4-thiazolidinone hybrids bearing coumarin and pyridine moieties. The outcome of this research showed that the newly synthesized compounds exhibited promising antimicrobial activity against a representative panel of bacteria and fungi. Compound (**84**) was identified as the most potent component, possessing 50 μg/mL (minimum inhibitory concentration [MIC] value) against *S. aureus* and 250 μg/mL (MIC value) against *C. albicans* strains. Moreover, compounds (**80**), (**81**), (**82**), (**83**) and (**85**) were found to possess prominent



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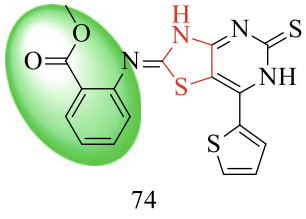
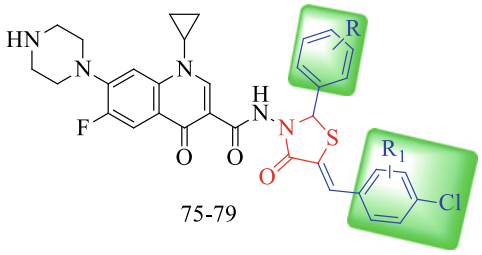


74

Fig. 2.28 4-thiazolidinone fused thiopyrimidine derivatives as antimicrobial agents



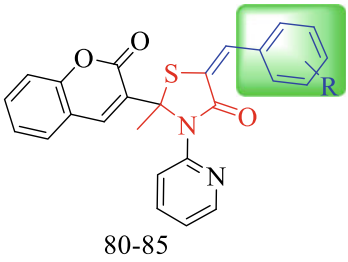
Where
R = H, R_1 = -4-Cl (75)
R = -4-CH_3, R_1 = -4-CH_3 (76)
R = -3-OCH_3, R_1 = -3-OCH_3 (77)
R = -2-NO_2, R_1 = -2-NO_2 (78)
R = -4-Cl, R_1 = -2-NO_2 (79)

Fig. 2.29 Fluoroquinolones linked to 4-thiazolidinones as antimicrobial agents

activity against *S. pyogenes*, *P. aeruginosa*, *E. coli* and *S. aureus*, respectively, having 62.5 μg/mL (MIC value). The data of biological activities revealed results on bacteria and fungi which were in comparison with reference drugs (griseofulvin) (Fig. 2.30).

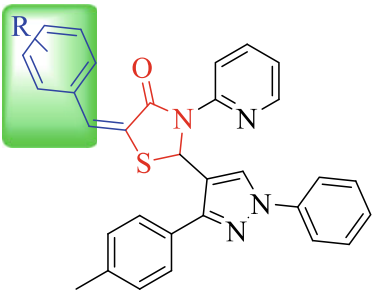
Desai and Jadeja [97] synthesized novel pyrazole-pyridine containing 4-thiazolidinone hybrids. The synthesized compounds were tested against various bacterial and fungal strains, and the results showed promising antimicrobial activity for some of the compounds. Compounds having electron-donating groups (–H, –4-OH, –4-OCH_3) (**86, 87, 88**) and electron-withdrawing groups (–2-Cl, –2-NO_2) (**89, 90**) were found to be most active against *C. albicans* fungal strain, showing MIC value of 250 μg/mL, which is twofold of standard drug griseofulvin. Compounds having –Br in 2nd position (**91**), –OH (**87**) and –NO_2 (**92**) groups each in 4th position were most active against Gram-negative strain *E. coli* having MIC value of 62.5 μg/mL, while –4-F (**93**) derivative was found to be most active against Gram-positive strain *S. aureus* having MIC value of 62.5 μg/mL (Fig. 2.31).

Benzimidazole containing 4-thiazolidinone-based 5-arylidene derivatives were synthesized by Desai et al. [98] to access their antimicrobial potential. The compounds were tested on various Gram-positive and Gram-negative bacterial strains as well as fungal strains. The results showed that compound (**94**) exhibited the highest potency against all Gram-positive strains with a minimum inhibitory concentration (MIC) in the range of 25–50 μg/mL. It also showed moderate activity against Gram-negative strains with a MIC value of 62.50 μg/mL. Compound (**95**) was found to



Where
R = -3-Cl (80)
R = -3-OCH_3 (81)
R = -4-OCH_3 (82)
R = -2-CH_3 (83)
R = -4-NO_2 (84)
R = -2,3-$(CH_3)_2$ (85)

Fig. 2.30 Antimicrobial activity of 4-thiazolidinone hybrids bearing coumarin and pyridine moieties



where
R = -H (86)
R = -4-OH (87)
R = -4-OCH_3 (88)
R = -2-Cl (89)
R = -2-NO_2 (90)
R = -2-Br (91)
R = -4-NO_2 (92)
R = -4-F (93)

Fig. 2.31 Pyrazole-pyridine containing 4-thiazolidinone hybrids as antimicrobial agents

be the most active against fungal strains with a MIC value of 250 μg/mL. Other compounds also showed good to moderate activity against the tested strains. The most active compound is referred to as (**94**) (Fig. 2.32).

Furan-based pyrimidine-thiazolidinones were designed and synthesized by Desai et al. [99] for the evaluation of their antimicrobial activity. The results of the study indicate that all the newly synthesized compounds exhibit notable in vitro antimicrobial activity. The compounds with electron-donating and electron-withdrawing groups on the arylidene ring are active against both bacterial and fungal strains. The structure–activity relationship (SAR) study revealed that compounds (**96**), (**97**), (**98**), (**101**) and (**102**) containing electron-withdrawing groups and compounds (**99**) and (**100**) containing electron-donating groups demonstrated effectiveness against bacterial strains. Compounds (**97**) and (**98**), which contain electron-withdrawing groups, both displayed antifungal activity **(99)** in arylidene substituents against various fungi strains (Fig. 2.33).

Desai et al. [100] designed and synthesized pyridine-based thiazolidine-4-one **(101)** and its 5-arylidene derivatives **(102)** to assess their antimicrobial potential.

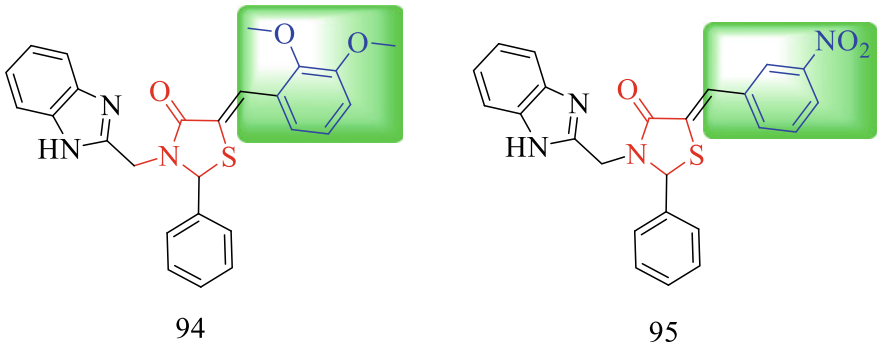
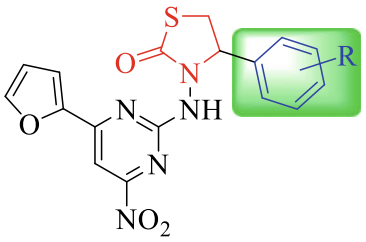


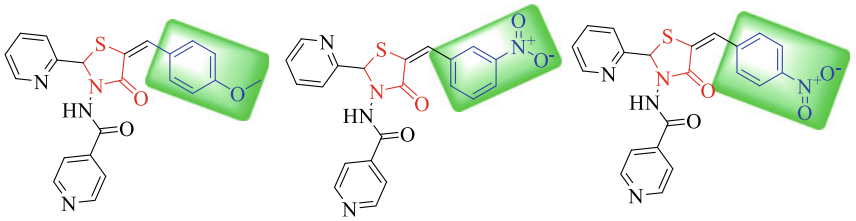
Fig. 2.32 Antimicrobial activity of benzimidazole containing 4-thiazolidinone-based 5-arylidene derivatives



96-102

Where
R = -H (96)
R = -3-F (97)
R = -4-F (98)
R = -4-OH (99)
R = -3,4-$(OCH_3)_2$ (100)
R = -3-NO_2 (101)
R = -4-NO_2 (102)

Fig. 2.33 Furan-based pyrimidine-thiazolidinones with antimicrobial activity



103 104 105

Fig. 2.34 Pyridine-based thiazolidine-4-one and its 5-arylidene derivatives as antimicrobial agents

Results furnished that compounds (**103**) (–4-OCH_3), (**104**) (–3-NO_2) and (**105**) (–4-NO_2) demonstrated excellent activity against the tested strains. Standard drugs, such as ciprofloxacin and chloramphenicol, were used to assess the biological activity of newly synthesized compounds against various bacterial strains (Fig. 2.34).

Desai et al. [101] designed and synthesized 1,2,4-triazole-thiazolidin-4-one hybrids to assess their antimicrobial potential. Results showed that several compounds demonstrated moderate to significant activity against the tested bacterial and fungal strains. For example, compounds (**106**) and (**107**) were effective against *S. pyogenus*. Compound (**108**), which has the electron-donor substituents –OCH_3 at the 2nd and 3rd positions of the benzylidene ring, was found to be the most effective against both Gram-negative strains. Compound (**106**), having the –OCH_3 group in the 4th position, showed significant activity against Gram-positive bacteria. Compound (**107**) with the electron-acceptor –NO_2 substituent in the benzylidene moiety exhibited moderate antibacterial and antifungal activities (Fig. 2.35).

Design and synthesis of thiophene-, piperazine- and thiazolidinone-based hybrids were done by Desai et al. [102] for the development of antimicrobial agents. Compound (**109**) depicted antibacterial efficacy against *E. coli*, *P. aeruginosa* and *S. pyogenes* and was superior to the standard drug ampicillin. It also showed promising antifungal effectiveness against *C. albicans* and *A. niger*. Compound (**110**) showed excellent antibacterial efficacy against *P. aeruginosa*, with an MIC of 50 μg/mL. Compound (**112**) showed similar potency against *S. aureus* as compound (**113**) did against *E. coli*. Compound (**113**) showed outstanding antibacterial activity against

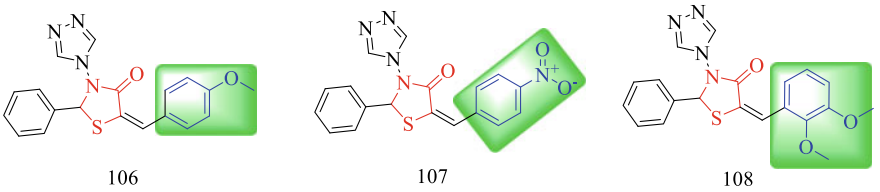


Fig. 2.35 1,2,4-triazole-thiazolidin-4-one hybrids with antimicrobial activity

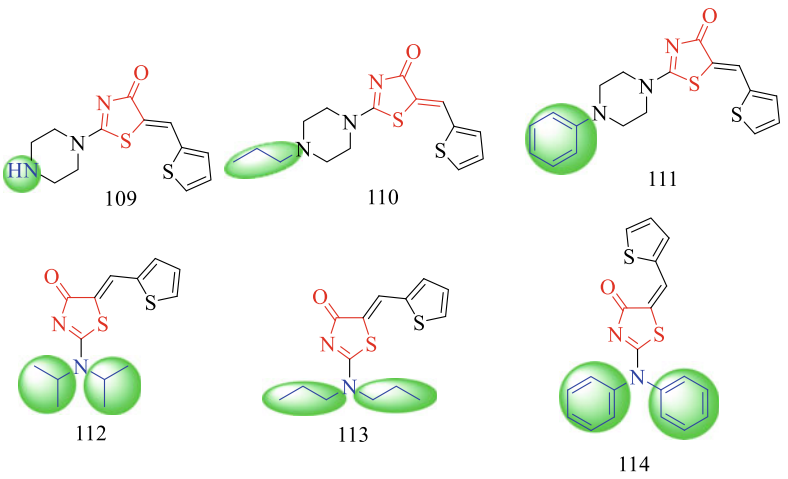


Fig. 2.36 Thiophene, piperazine and thiazolidinone-based with antimicrobial potential

E. coli, with a MIC twofold more than the standard antibiotic ampicillin. It also had considerable antibacterial activity against *P. aeruginosa.* Compound (**111**) had excellent antifungal efficacy against *C. albicans* and *A. niger*, with an MIC of 50 μg/mL. Compound (**114**) showed promising antifungal effectiveness against *C. albicans* and *A. niger* and was superior to the standard drug nystatin (Fig. 2.36).

2.3.2 Anticancer Activity

After cardiac disease cancer is the second largest threat to mankind. According to the report of WHO in the year 2018, 9.6 million people died due to cancer all over the world. Some of the major classes of these diseases are lung cancer, breast cancer, colorectal cancer, prostate cancer, skin cancer (non-melanoma) and stomach cancer [103]. It is caused by the rapid creation of abnormal cells which can affect any part of the human body. Due to these threats, it is necessary to design and synthesize some new molecules that can be helpful to overcome this disease [104]. In the search for active entities, it was found that thiazolidinone is useful in stopping the growth of

these abnormal cells. Many thiazolidinone containing hybrid molecules are tested for anticancer activity. Analysis of these results has confirmed that thiazolidinone is an active scaffold for cancer cells. There are some examples given below that will prove that hybrid molecules containing thiazolidinone moiety are effective in cancer treatment [105].

Tumor has been one of the most genuine maladies hugely pulverizing human well-being throughout the entire existence of human turn of events. Chemotherapy is fundamental for malignancy treatment; however customary chemotherapeutic medications show helpless selectivity among tumor and ordinary cells and therefore produce cytotoxicity to the human body. The frequency of multidrug opposition (MDR) and related extreme symptoms take steps to expand the mortality of malignancy patients fundamentally. Along these lines, it is basic to create novel anticancer operators. The advancement of focused anticancer operators has developed as one of the most encouraging procedures to keep away from extreme symptoms, improve the selectivity of chemotherapeutic specialists and beat tranquilize opposition [106–116].

Effect of various electron-donating and electron-withdrawing functional groups on phenyl ring in potent anticancer thiazolidinone compounds was described in Fig. 2.37.

Havrylyuk et al. [117] had prepared benzothiazole clubbed 4-thiazolidinone derivatives which showed moderate to excellent anticancer activity. The synthesized 5-arylidene-3-(benzothiazol-2-ylamino)-2-thioxo-4-thiazolidones (**115**) and 5-arylidene-2-(6-methyl benzothiazol-2-ylimino)-4-thiazolidinones (**116**) shown low to moderate activity on the evaluated cell lines in the in vitro screen. Several cancer cell lines had been subjected to the selective action of certain compounds. Compound I (3-OCH_3–4-OH–C_6H_5) was highly active on renal cancer RXF 393 cell line (GP = −0.71%), compounds II (4-NEt_2–C_6H_4) and II (4-Cl–C_6H_4) were highly active on the CNS cancer SF-295 cell line (GP = 22.52 and 4.01%, respectively), and I (2-(4-OMe-$C_6H_4NHCOCH_2O$)-5-Cl-C_6H_3 on the leukemia RPMI-8226 cell line (GP = 20.02%) (Fig. 2.38).

Isloor et al. [118] have synthesized some novel triazole-based 4-thiazolidinones for the treatment of breast cancer against MCF-7 cells. From the study, it has been proven that three thiazolidin-4-ones, compounds (**117**), (**118**) and (**119**) exhibited excellent cytotoxic activity in MCF-7 cell lines with low IC_{50} values (Fig. 2.39).

Eldehna et al. [119] have synthesized novel 4/3-((4-oxo-5-(2-oxoindolin-3-ylidene)thiazolidin-2-ylidene)amino)benzenesulfonamides. Investigations of the antiproliferative activity against MCF-7 indicated that compounds (**120**) and (**121**), only, displayed good activity with IC_{50} values of 3.96 ± 0.21 and 11.3 ± 0.77 μM (Fig. 2.40).

Several new 5-enamine-4-thiazolidinone derivatives have been synthesized by Holota et al. [120] to assess their anticancer potential. With an average GI_{50} value of 2.57 μM, compound **(122)** inhibited the growth of all fifty-nine human tumor cell lines. It should be noted that the nature of the enamine fragment in the C_5 position of the thiazolidinone core has a substantial impact on both action (anticancer). Such 5-enamine-4-thiazolidinones may provide more effective compounds that are

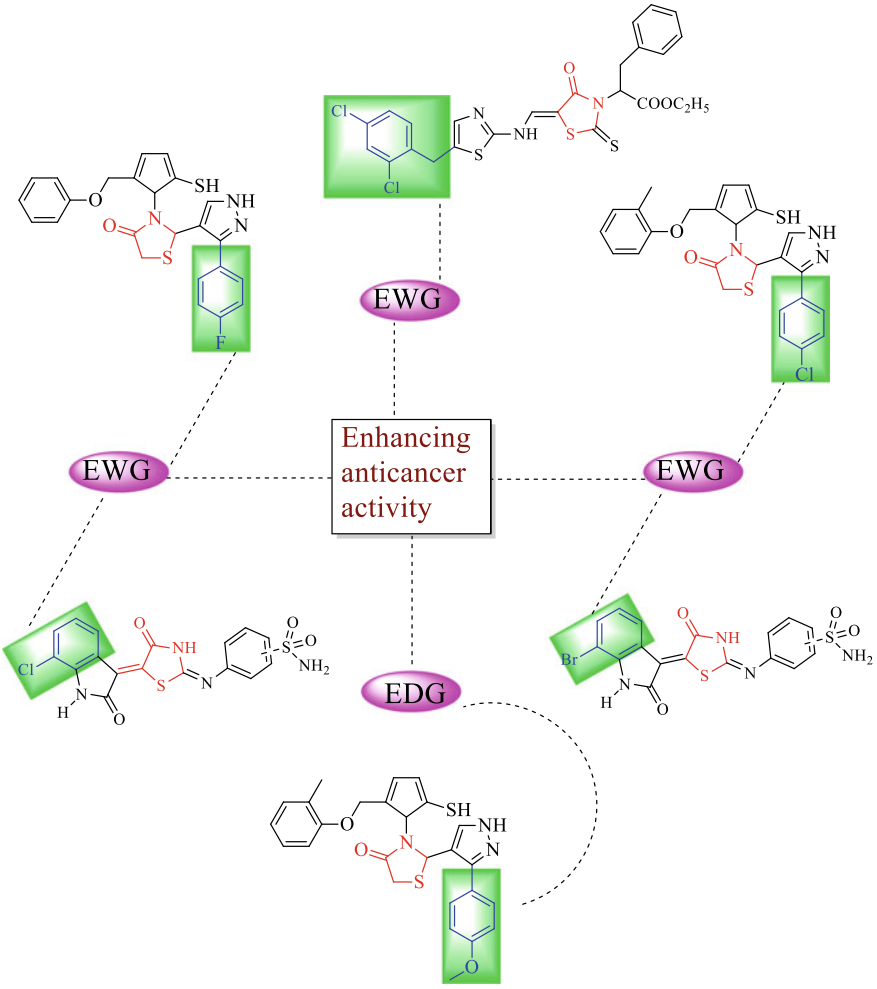
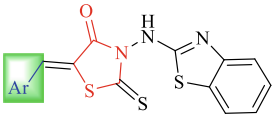


Fig. 2.37 Effect of various functional groups on biological activity



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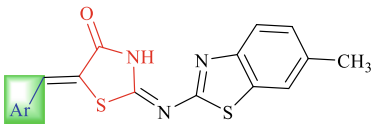
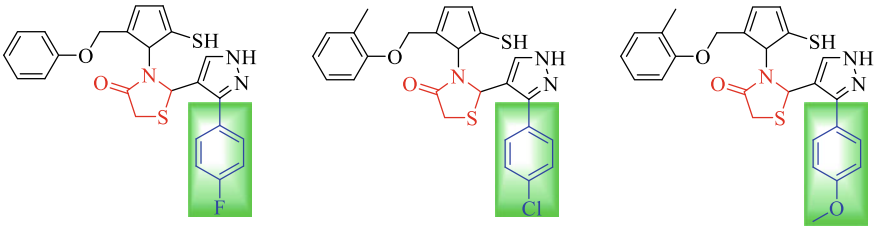


116

72a Ar = 3-OCH_3-4-OH-C_6H_5
72b Ar = 2-(4-OMe-$C_6H_4NHCOCH_2O$)-5-Cl-C_6H_3

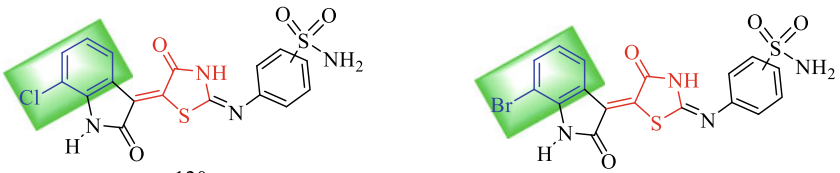
73a Ar = 4-NEt_2-C_6H_4
73b Ar = 4-Cl-C_6H_4

Fig. 2.38 Benzothiazole clubbed 4-thiazolidinone derivatives with anticancer activity



117 118 119

Fig. 2.39 Novel triazole-based 4-thiazolidinones for the treatment of breast cancer against MCF-7 cells



120 121

Fig. 2.40 Oxoindoline-based thiazolidinones with antiproliferative activity

good candidates for developing of novel antitrypanosomal and cancer therapies upon further research (Fig. 2.41).

Sharma et al. [121] have synthesized novel thiazolidinone derivatives using a K10 montmorillonite catalyst in which some compounds pursued anticancer activity. MTT essay of 2-(3,4-dimethoxyphenyl)-3-((S)-6-(2-oxobutyl)-4,5,6,7-tetrahydrobenzo[*d*]thiazol-2-yl)thiazolidin-4-one (**123**) showed excellent anticancer activity (Fig. 2.42).

Bakht et al. [122] have synthesized an isatin-thiazolidine (**124**) hybrid using a graphene oxide catalyst in a deep eutectic solvent in which the below compound has shown greater anticancer activity (Fig. 2.43).

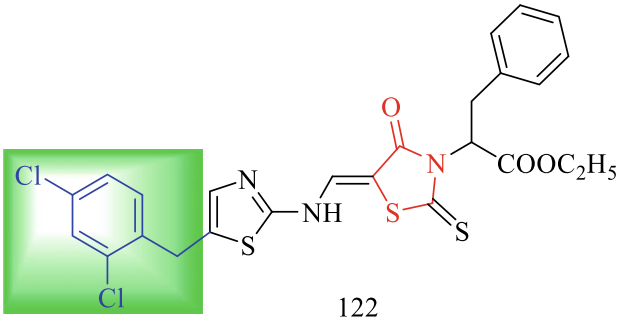


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Fig. 2.41 Thiazole-based 5-enamine-4-thiazolidinone derivatives with anticancer potential

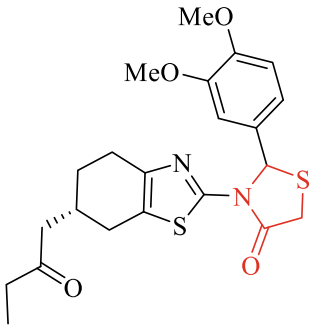

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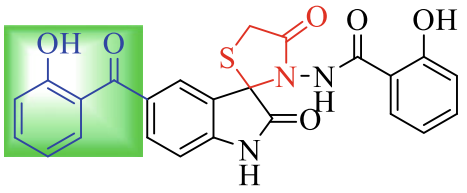
Fig. 2.42 Benzothiazole-based 4-thiazolidinone derivatives as anticancer agents



124

Fig. 2.43 Anticancer activity of isatin-thiazolidine

Iqbal et al. [123] have synthesized imidazopyridine-linked thiazolidinone as potential anticancer agent. The outcomes showed that three different compounds have remarkably broad-spectrum in vitro anticancer action. It may also be stated that the most successful approach to fight MCF-7 was to substitute a hydroxyl group at the para-position of the phenyl ring in substances. Results revealed that three compounds exhibited a remarkable and broad-spectrum in vitro anticancer activity. Furthermore, it was shown that the most effective way to replace the hydroxyl group at the para-position of the phenyl ring in compounds was to use it against the cancer cell lines MCF-7 (3.2 and 4.4 μM), A549 (10.9 and 8.4 μM) and DU145 (36.8 and 47.4 μM), **(125)**, **(126)**, as well as **(127)** (Fig. 2.44).

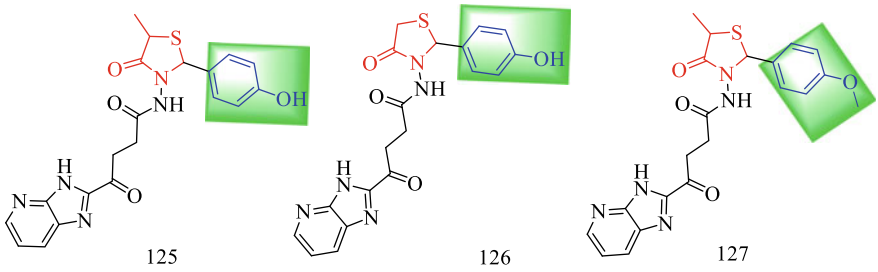


Fig. 2.44 Imidazopyridine-linked thiazolidinone as potential anticancer agent

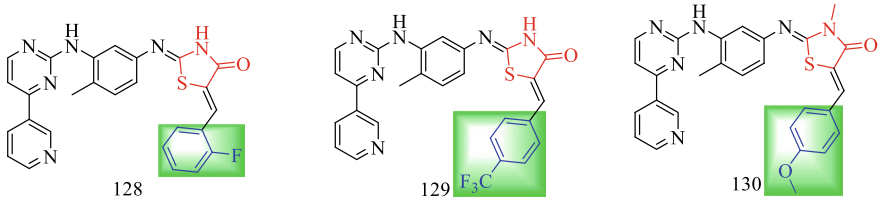
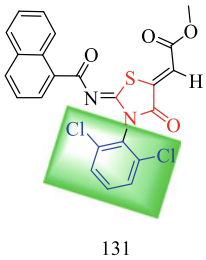


Fig. 2.45 Novel 4-thiazolidinone-phenylaminopyrimidine with anticancer activity

Fig. 2.46 2-(naphthoyl) iminothiazolidin-4-ones with anticancer activity



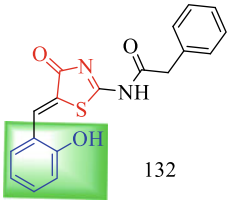
Türe et al. [124] have synthesized novel 4-thiazolidinone-phenylaminopyrimidine hybrids to evaluate anticancer activity which showed greater anticancer activity. IC_{50} values were found as 5.26, 3.52 and 8.16 μM for compounds (**128**), (**129**) and (**130**), respectively (Fig. 2.45).

Potential anticancer agents, 2-(naphthoyl) iminothiazolidin-4-ones, have been synthesized by Ashraf et al. [125]. Biological activity and SAR data suggested that **(131)** had more potency in comparison with 2-ITZDs substituted with trifluromethyl, fluoro and methoxy (Fig. 2.46).

Ibrahim et al. [126] have synthesized new phenolic compounds and biological evaluation as antiproliferative agents. Compound (**132**) displays sub-micromolar activity against the HOP-92 cell line with IC_{50} values of 0.81 μM, respectively (Fig. 2.47).

In 2023, Finiuk et al. [127] synthesized pyrrolidinedione-thiazolidinone hybrids. The study of the effects of three pyrrolidinedione-thiazolidinone derivatives on human tongue squamous carcinoma cells of the SCC-15 line (Les-6287, Les-6294 and 6328) has been carried out. The findings demonstrated that the synthesized compounds had a significant cytotoxic impact on SCC-15 cells, which may be related

Fig. 2.47 Thiazolidin-4-ones with anticancer activity



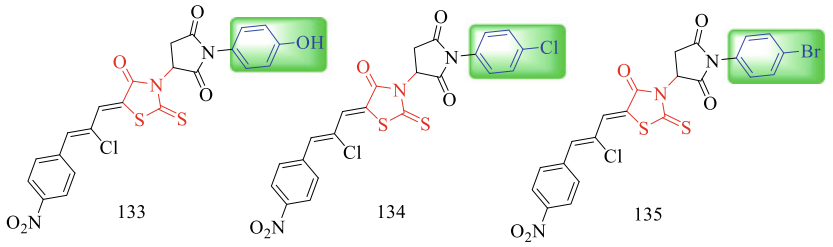


Fig. 2.48 Pyrrolidinedione-thiazolidinone hybrids with anticancer activity

to an increase in caspase-3 activity and an impairment of the cells' metabolic activity. The article suggests that studies of synthesized compounds may work as a potential for future cancer treatments; simultaneously further research is needed to fully understand their mechanism of action and side effects. The active compounds effective against cancer cell lines were (**133**), (**134**) and (**135**) (Fig. 2.48).

In 2023, Khan et al. [128] synthesized pyrimidine-based thiazolidinone derivatives to assess their anticancer activity. The synthesis, biological evaluation and molecular docking evaluation of thiazolidinone derivatives based on pyrimidines as possible anti-urease and anticancer drugs are discussed in the paper. Several of the synthetic scaffolds have inhibitory capability against cancer cell lines, according to the study. The minimum inhibitory concentration (MIC) in the presence of a standard drug (tetrandrineb) was used to calculate the inhibitory potential. Scaffolds (**136**), (**137**), (**138**) and (**139**), among the other compounds evaluated, had strong effects on cancer cell lines (Fig. 2.49).

In 2022, Bar et al. [129] synthesized new 4-thiazolidinone-based molecules to assess their anticancer activity. The study examined the cytotoxic effects of two 4-TZD-based derivatives, (**140**) and (**141**) on BJ and SCC-15 cells using metabolic activity, LDH release and caspase-3 activity assays. Compound (**140**) increased NF-κB gene expression but decreased PPARγ and KI67 expression. Compound (**141**) increased PPARγ and NF-κB mRNA expression but decreased KI67 mRNA expression in BJ cells. The LC_{50} indicated cell loss after treatment. Cytotoxicity in SCC-15 cells was observed only at high concentrations, suggesting limited drug potential. Further research was needed to investigate lower concentrations and other tumor cell types (Fig. 2.50).

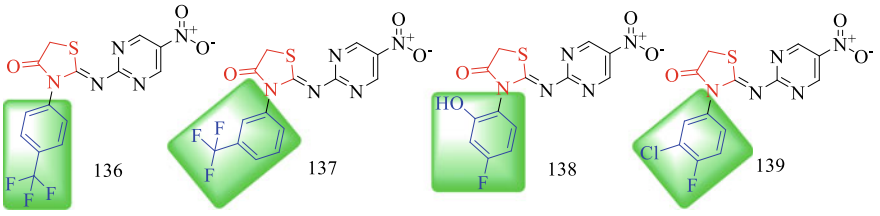
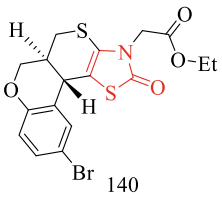


Fig. 2.49 Pyrimidine-based thiazolidinone derivatives as anticancer agents



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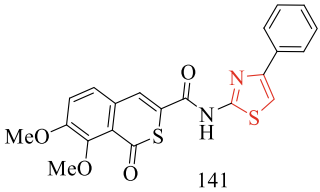

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Fig. 2.50 4-thiazolidinone-based molecules as anticancer agents

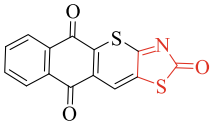

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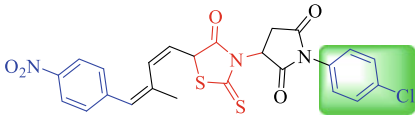
Fig. 2.51 4-thiazolidinone-based derivatives with anticancer profile

In 2021, Szychowski et al. [130] have synthesized 4-thiazolidinone-based derivatives. The study showed all compounds examined the expression of the genes Dlk1, Fabp4, Vegfa, Pai-1, resistin, adiponectin and Pparγ, but none of them cause symptoms similar to rosiglitazone or pioglitazone. Compound (**142**) decreases Pparγ, resistin, Vegfa and Fabp4 mRNA expression, but increases Dlk mRNA expression. Color ORO demonstrated that rosiglitazone and pioglitazone induced lipid accumulation in the 3T3-L1 cell line, a marker of adipocyte maturation. Only one rosiglitazone increased Pparγ protein expression after 14 days of differentiation treatment (Fig. 2.51).

In 2022, Finiuk et al. [131] synthesized novel hybrid pyrrolidinedione-thiazolidinones to assess their anticancer potential. The synthesized compounds were evaluated for their cytotoxicity, apoptosis and DNA damage effects. The study found that 1-aryl-3-(4-oxo-2-thioxothiazolidin-3-yl)pyrrolidin-2,5-diones with the bulky 5-ene substituents of thiazolidinone core showed the most effective anticancer properties. Specifically, compounds (**143**) and (**144**) were identified as hit compounds possessing sub-micromolar cytotoxic activity toward leukemia, colon cancer, CNS and ovarian cancer cell lines. These compounds also showed low toxicity to mitogen-activated lymphocytes from the peripheral blood of healthy human donors, as well as normal human keratinocytes of the HaCaT line (Fig. 2.52).



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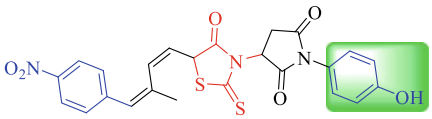

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Fig. 2.52 Pyrrolidinedione-thiazolidinones having anticancer potential

2.3.3 Antimalarial Activity

Malaria is the most common and dangerous disease that has been fought by mankind for many decades. It is very well known that *Plasmodium falciparum* and *Plasmodium vivax* are the species that are responsible for the malarial disease [132]. In 2015 according to the report of WHO, 212 million new cases of malaria were registered. This number is increasing daily. As the malarial parasites are developing resistance to common and basic drugs, it has been necessary to develop new hybrid molecules that could enhance antimalarial activity [133]. By this idea, a five-membered active pharmacophore thiazolidinone has been selected to synthesize new hybrids of quinoline and its derived drugs. The information given below is about thiazolidinone hybrids with different active components. There are some examples of novel synthesized hybrids that prove that thiazolidinone is an active entity for malarial disease [134]. The substantial cost demanded by jungle fever is not just aggravated by the developing issue of parasite protection from engineered tranquilizers yet in addition fueled by expanding bug spray opposition of mosquito vectors. Artemisinin-based mix treatment and boundless utilization of impregnated bed nets have decreased the horribleness and mortality because of malaria. Be that as it may, parasite protection from the current arms stockpile of preventive and treatment drugs joined with the way that the expense of the current antimalarial drugs is restrictive in helpless settings and legitimizes the squeezing need to describe new antimalarial operators that are less expensive and more compelling. It is additionally critical to find new drugs with less harmfulness and reactions [135–147].

Enhancement in antimalarial activity of thiazolidinone compounds was due to presence of various electron-donating and electron-withdrawing functional groups on phenyl ring (Fig. 2.53).

Fernando et al. [148] have synthesized some novel heterocyclic hybrids of chloroquine and thiazolidinone scaffolds and evaluated their antimalarial activity. Chloroquine is used as a reference standard for all of the above compounds (**145**) and (**146**) which showed in vitro antimalarial activity. They were effective 80–100% against parasites. The compounds were further screened for in vivo analysis, out of which compound **(146)** had shown promising antimalarial activity (Fig. 2.54).

Aguiar et al. [132] have synthesized novel primaquine-thiazolidinone hybrids (**147 to 151**) and evaluated their antimalarial activity. These derivatives of the primaquine-thiazolidinone hybrids have completely blocked the malaria sporogonic cycle of *P. berghei* in *An. stephensi* mosquitoes compared to the control mosquitos. The 4-OCH_3 derivative had reduced *P. gallinaceum*s porogony at lower doses of 50 and 25 mg/kg. It also reduced the number of EEFs in hepatoma cells and mice (Fig. 2.55).

Jain et al. [133] have synthesized novel arylidene derivatives of quinoline-based thiazolidinones for the evaluation of antimalarial activity. The 2-(4-chlorophenyl)-5-(4-methylbenzylidene)-3-((4-methylquinolin-2-yl)amino)thiazolidin-4-one (**152**) had shown excellent activity against 3D7 and RKL-9 strains of *P. falciparum.* Further evaluation of the compound may be useful as a lead compound for malarial disease (Fig. 2.56).

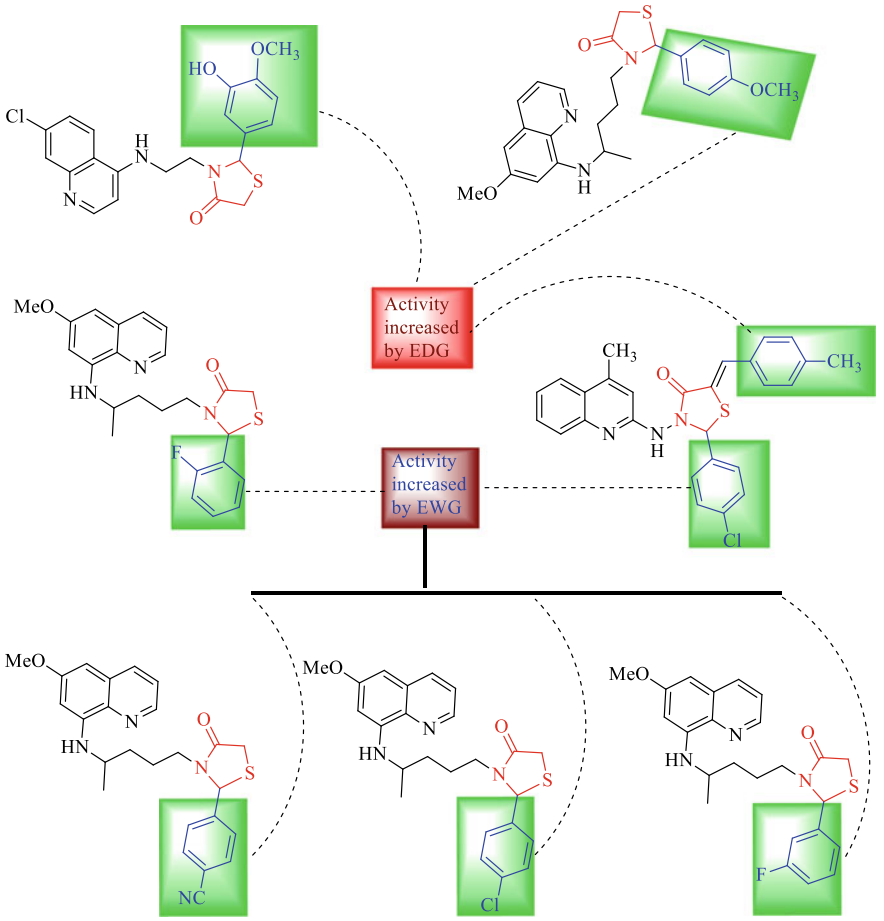
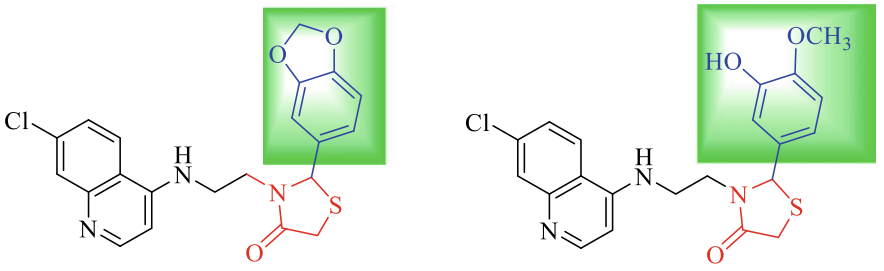
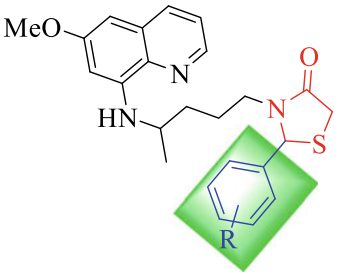


Fig. 2.53 Effect of substitutions on phenyl ring on the antimalarial activity



145 146

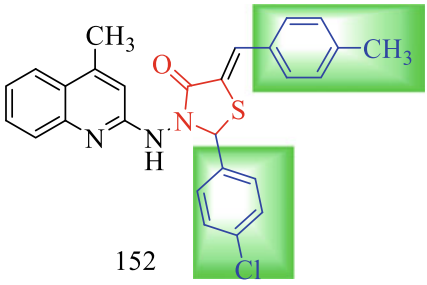
Fig. 2.54 Chloroquine and thiazolidinone scaffolds with antimalarial activity



R = 2-F (147)
R = 3-F (148)
R = 4-Cl (149)
R = 4-OCH_3 (150)
R = 4-CN (151)

Fig. 2.55 Antimalarial activity of primaquine-thiazolidinone hybrids

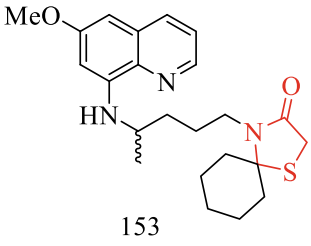
Fig. 2.56 Novel arylidene derivatives of quinoline-based thiazolidinones for the evaluation of antimalarial activity



Neuenfeldt et al. [149] have synthesized novel primaquine-thiazolidinone (**153**) derivatives via multicomponent reactions. They have studied the antimalarial activity of all the novel synthesized compounds in which they found very promising activity of these hybrids. Seventeen new primaquine-thiazolidinone derivatives were readily synthesized in moderate to good yields by a one-pot cyclo-condensation reaction. The synthesized compounds are an excellent place to start for developing new lead antimalarials. Discovering new antimalarials to replace primaquine is an urgent need, and it would be especially helpful if they could also successfully fight the deadly *P. falciparum* parasite's blood stages (Fig. 2.57).

All the above studies have confirmed that thiazolidinone scaffold is an active entity in malarial disease. Different hybrids of thiazolidinone with active antimalarial

Fig. 2.57 Novel primaquine-thiazolidinone as antimalarial agent



entities had shown promising antimalarial activity in both in vitro and in vivo analyses.

2.3.4 Anti-inflammatory Activity

Asthma, psoriasis, infections, arthritis and other ailments are all caused by inflammation, which is a natural process [150–153]. Non-steroidal anti-inflammatory drugs (NSAIDs), which function as selective or non-selective COX inhibitors, are one of the traditional treatment approaches for cyclooxygenase isoenzymes (COX-1, COX-2), which develop prostaglandins that are important in inflammation [154–156]. Almost all of them interact with the arachidonic acid cascade, which results in several undesirable, frequently severe adverse effects. For higher potency and in the avoidance of side effects innovative drugs are useful [157]. Nowadays all are interested in the synthesis of dual COX/LOX inhibitors that could provide several therapeutic advantages in terms of anti-inflammatory activity, improved gastric protection and safer cardiovascular profile compared to conventional NSAIDs [158].

COX-2 is highly inspired in settings of inflammation by cytokines and inflammatory mediators or physiological stress. The prostaglandins (PGs) produced by COX-2 play a major role in inflammatory reactions which are responsible for the characteristic inflammatory symptoms (redness, pain, fever, etc.) [159]. COX-3 is a recently identified splice variant/isoenzyme of COX-1 and, more suitably, may have been named COX-1b [160].

Naproxen and ibuprofen which belong to non-steroidal anti-inflammatory inhibit COX enzyme which catalyzes the biosynthesis of prostaglandins and tromboxane from arachidonic acid. These drugs have some undesirable side effects like GIT and renal toxicities [161].

Electron-donating groups on phenyl ring in thiazolidinone hybrids enhance activity against COX-1 and LOX enzyme, while electron-donating groups on phenyl ring enhance inhibition against COX-2 enzyme (Fig. 2.58).

The pyrazolo[3,4-*d*]pyrimidine-fused thiazolidinone moiety was synthesized by Tageldin et al. [162]. Newly synthesized compounds were assessed for their in vitro COX-1 and COX-2 inhibitory test assay. After demonstrating potential COX-2 selectivity, compounds were further tested for anti-inflammatory properties in vivo utilizing tests for formalin-induced paw edema (an acute model) and cotton-pellet-induced granuloma (a chronic model), with diclofenac sodium and celecoxib serving as reference drugs. Compounds (**154** and **155**) were considered to be promising candidates for managing both acute and chronic inflammation with a safe gastrointestinal margin (Fig. 2.59).

Omar et al. [163] developed 5-alk/arylidene as dual inhibitors based on thiazolidinone. The study on the new design of dual inhibitors of COX-2 and 15-LOX was based on combining 2-amino-1,3,4-thiadiazole and 4-thiazolodine. In vitro COX-1/COX-2 inhibition study indicates that compound (**156**) showed the highest inhibitory activity against COX-2 with an IC_{50} value of 70 μM. Additionally, a study on

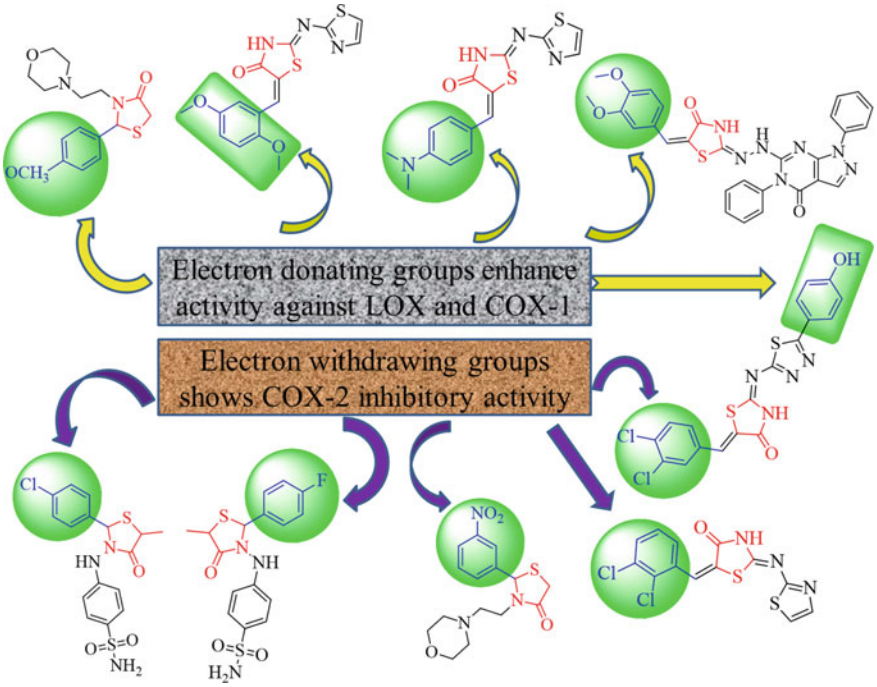


Fig. 2.58 4-thiazolidinones associated with anti-inflammatory activity

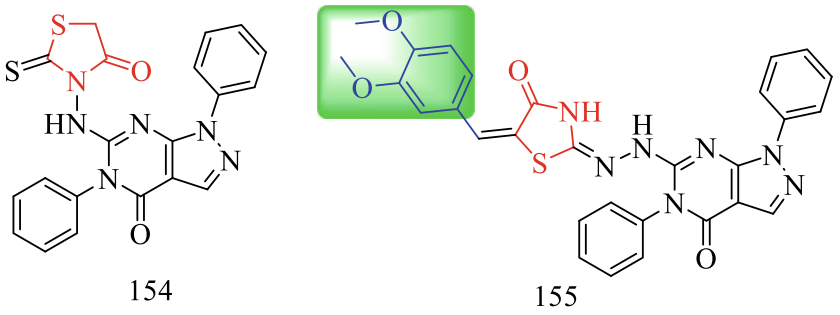
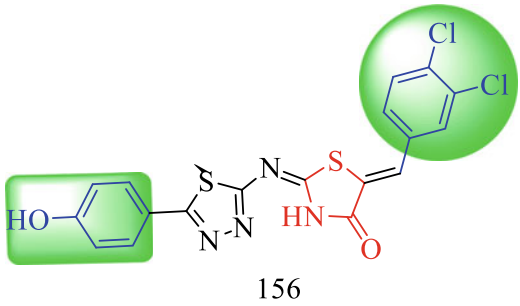


Fig. 2.59 Pyrazolo[3,4-*d*]pyrimidine-fused thiazolidinones as COX-1 and COX-2 inhibitors

the active ingredient revealed good GIT response and LOX inhibitory efficacy that was greater in vitro than zileuton. Consequently, the synthesized compounds' anti-inflammatory properties in vivo and in vitro may serve as a base for developing of novel anti-inflammatory drugs (Fig. 2.60).

In Gouvea et al. [164] new 4-thiazolidinones linking with morpholino moiety were easily designed by one-pot synthesis of 4-(2-aminoethyl)morpholine (2-morpholinoethylamine), arene aldehydes and mercaptoacetic acid. They study on



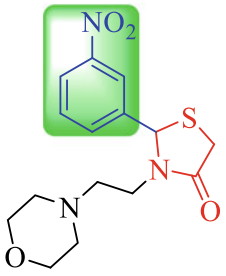
156

Fig. 2.60 1,3,4-thiadiazole and 4-thiazolodine as COX inhibitors

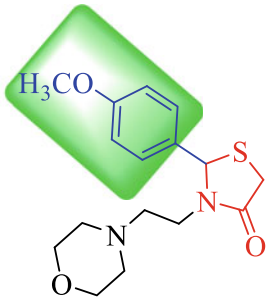
in vivo anti-inflammatory activities was based on the croton oil-induced ear edema model of inflammation in BALB C mice. Among them, two compounds (**157**) and (**158**) give tremendous results when compared to the standard drug indomethacin. Additionally, an investigation was conducted on the in vitro cytotoxicity activity of thiazolidin-4-ones against Vero cells, and it was shown that four compounds had a lower degree of toxicity at 500 μg/mL (Fig. 2.61).

Ali et al. [165] developed new 2-imino-4-thiazolidinone derivatives. In biological importance view, two compounds (**159**) and (**160**) exhibited in vivo anti-inflammatory activity (81.14 and 78.80%) and effect on ex-vivo COX-2 and TNF-α expression (70.10 and 68.43%). The anti-inflammatory activity of both compounds was compared with standard drugs indomethacin and celecoxib. Both of the two compounds caused a reduction in LPO concentration and did not cause any damage to the stomach lining. Compounds may be used for the development of new and safe anti-inflammatory agents (Fig. 2.62).

Abdellatif et al. [41] prepared 4-thiazolidinones derivatives, which react with 4-hydrazinobenzene sulfonamide hydrochloride with 4-substituted-aldehydes in the presence of sodium acetate to form hydrazones, which combine excess thiolacti-cacid under solvent-free conditions to form the 4-thiazolidinone derivatives. All the synthesized compounds were evaluated for their in vitro COX-2 selectivity and



157



158

Fig. 2.61 4-thiazolidinones linking with morpholino moiety as anti-inflammatory agents

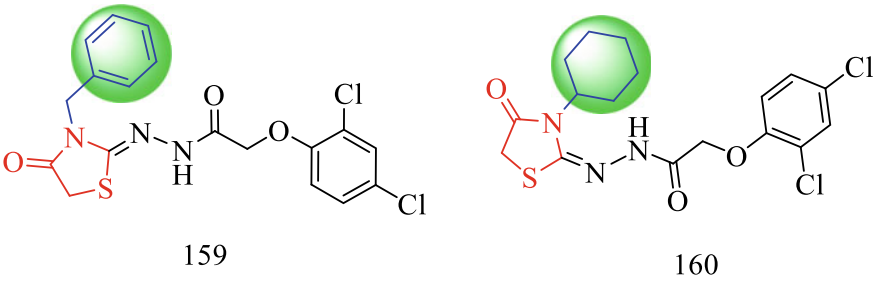


Fig. 2.62 New 2-imino-4-thiazolidinone derivatives with in vivo anti-inflammatory activity

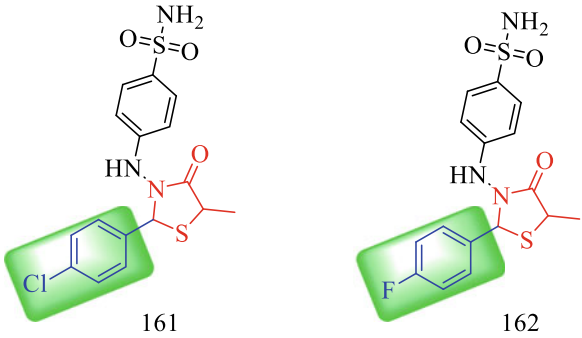
in vivo anti-inflammatory activity. Two compounds (**161**) and (**162**) have given COX-2 inhibitory activity (IC_{50} = 1.9 and 2.3 μM, respectively) and selectivity indexes (S.I. = 4.56 and 5.68, respectively) which are close to celecoxib. ED_{50} was calculated for the most potent compounds that showed the highest in vitro and in vivo results (Fig. 2.63).

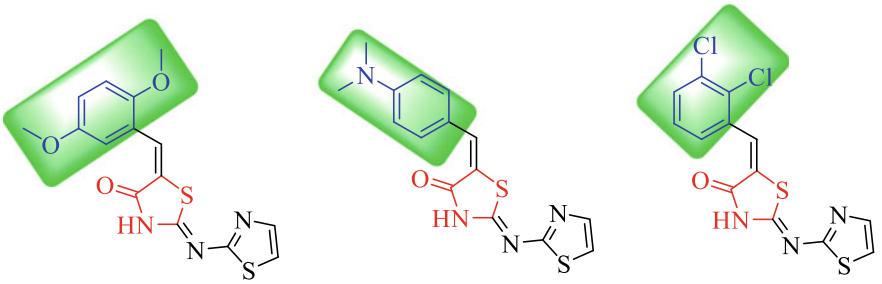
Apostolidis et al. [166] report the synthesis of novel 5-arylidene-2-(1,3-thiazol-2-ylimino)-1,3-thiazolidin-4-ones, which are being developed as dual antimicrobial/anti-inflammatory drugs. The inhibitory actions of COX-1/LOX were identified. Compound **(164)** exhibits 50% COX-1 inhibition and the best anti-inflammatory efficacy, whereas compound **(163)** is the most powerful LOX inhibitor. This compound **(165)** is the strongest inhibitor of COX-1. The influence of lipophilicity is not well documented (Fig. 2.64).

Decanoic acid [2,5-disubstituted-4-oxothiazolidin-3-yl]amides have been synthesized by Kumar et al. [167]. The preparation of novel thiazolidinones was synthesized with cyclo-condensation of Schiff's bases with thioglycolic acid. 4-thiazolidinones were tested for biological activities like anti-inflammatory, analgesic, and hydrogen peroxide scavenging activity. Compound (**166**) exhibited 44.84% inhibition of inflammation and was the most potent anti-inflammatory agent (Fig. 2.65).

Abdellatif et al. [168] synthesized two novel series of thiazolidine compounds with pyrazole cores, which were assessed for their anti-inflammatory and COX inhibitory

Fig. 2.63 COX inhibitory 4-thiazolidinones derivatives

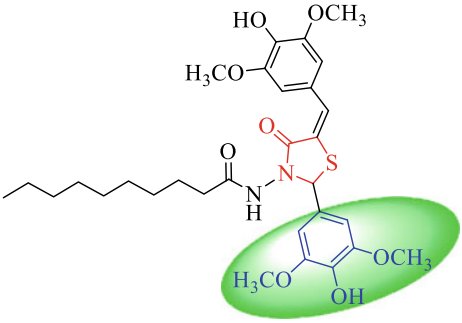




163 164 165

Fig. 2.64 5-arylidene-2-(1,3-thiazol-2-ylimino)-1,3-thiazolidin-4-ones as anti-inflammatory agents

Fig. 2.65 Decanoic acid [2,5-disubstituted-4-oxothiazolidin-3-yl]amides as potent anti-inflammatory agent



166

properties. Pharmacological investigations and the acquisition of structure–activity data showed that all substances were greater COX-2 inhibitors than COX-1. Four of these, compounds **167** to **170**, had higher COX-2 S.I. (8.69–9.26) than the COX-2 selective drug celecoxib (COX-2 S.I. = 8.60) (Fig. 2.66).

Hu et al. [169] synthesized four types of thiazolidinone derivatives and assessed their anti-inflammatory properties. Most of the synthetic compounds have shown noteworthy inhibitory effects against the synthesis of IL-6 and TNF-α produced by LPS. Among the most effective compounds are **(171)** and **(172)**, which are members of the pyrimidine-thiazolidinone series. Of these, 111 demonstrated anti-inflammatory properties in a dose-dependent manner with comparatively low IC_{50} values (Fig. 2.67).

Koppireddi et al. [170] synthesized a novel 2, 4-thiazolidinedione- 5-acetamides of 4-aryl-1, 3-thiazol-2-amines and 6-substituted-benzothiazol-2-amines. Among them below three compounds were given anti-inflammatory and antioxidant activities (**173**) to (**175**). The benzothiazole moiety has demonstrated strong anti-inflammatory properties and promising antioxidant properties (Fig. 2.68).

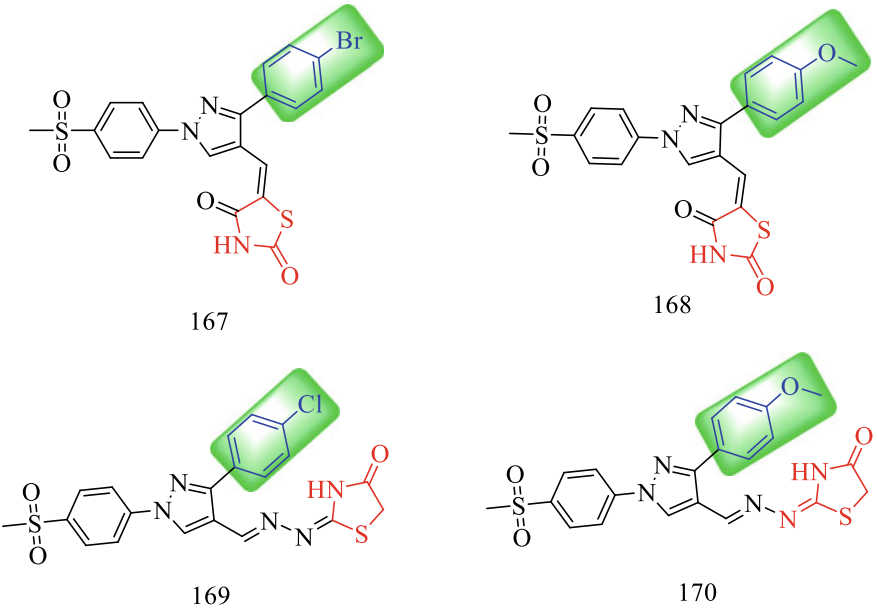


Fig. 2.66 Thiazolidine compounds with pyrazole cores as anti-inflammatory agents

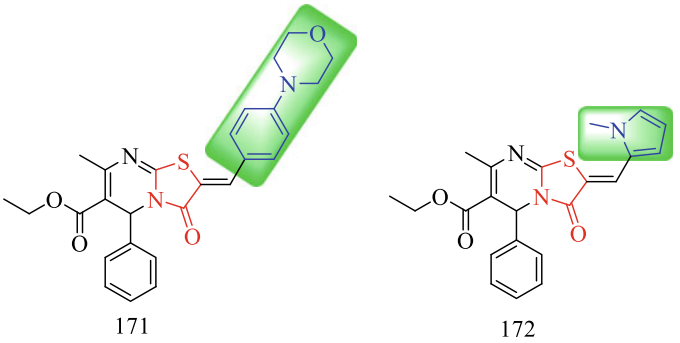


Fig. 2.67 Anti-inflammatory properties of pyrimidine-thiazolidinones

Maccari et al. [171] synthesize new series of 4-thiazolidine derivatives which differ by substitutions at N-3 and C-2 positions as well as at 5-arylidene moiety. In vitro, aldose reductase (AR) inhibitory activity indicated that the 2-thioxo-4-thiazolidinone core is more favorable for the AR affinity in comparison with the 2, 4-thiazolidinedione isosteric ring. Some representative AR inhibitors (**176**) to (**180**) were assayed in cultures of human keratinocytes to evaluate their capability to reduce NF-kB activation and iNOS expression (Fig. 2.69).

Two new series of pyrrolizine-5-carboxamides were developed by Shawky et al. [172] and tested for cytotoxicity and anti-inflammatory activities. The novel

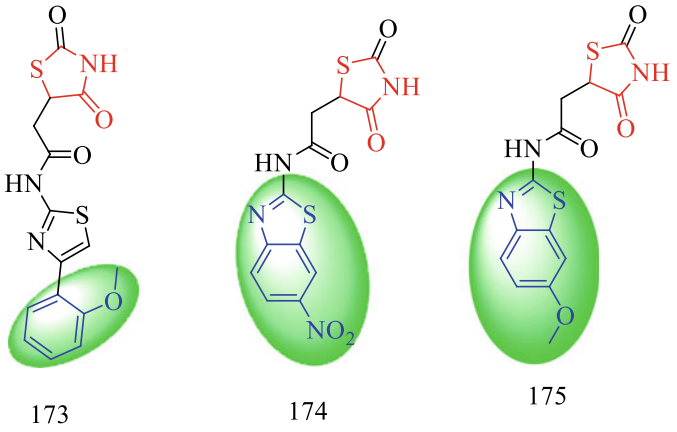


Fig. 2.68 Benzothiazole-based 4-thiazolidinediones with anti-inflammatory and promising antioxidant properties

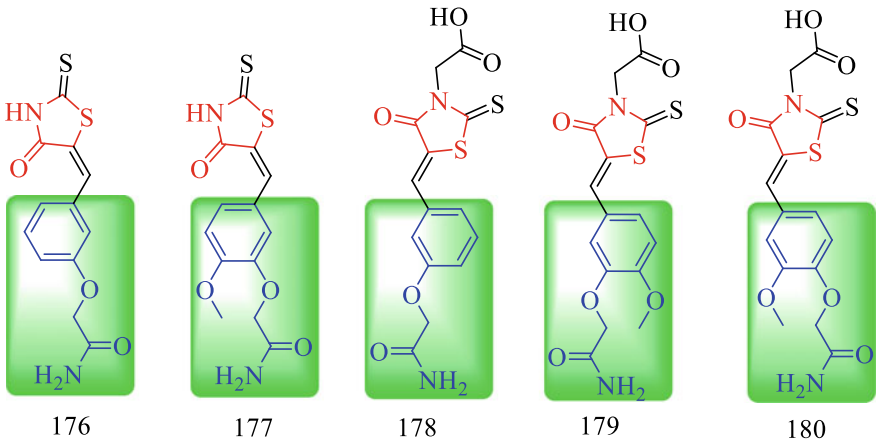
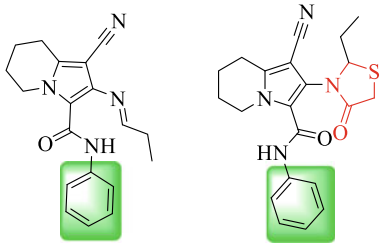


Fig. 2.69 4-thiazolidine derivatives which differ by substitutions at N-3 and C-2 positions as well as at 5-arylidene moiety having aldose reductase (AR) inhibitory activity

compounds demonstrated considerable anti-inflammatory action (18.13–44.51% inhibition of inflammation), which was mediated by COX-1/2 inhibition with a preference for COX-2 inhibition. The IC_{50} values for compounds (**181**) and (**182**) against COX-2 ranged from 0.6 to 56.1 μM. Nevertheless, compared to celecoxib and indomethacin, all of the test substances had lower activity. The investigation of SAR showed that the aliphatic side chain and 4-thiazolidinone moiety at C6 of the pyrrolizine nucleus produced excellent cytotoxic results, while the aromatic side chain boosted anti-inflammatory effects. The novel compounds showed a good fit into COX-1/2 and a stronger affinity for COX-2 in the docking research (Fig. 2.70).



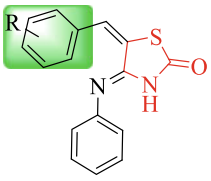
181 182

Fig. 2.70 Pyrrolizine-5-carboxamide-based 4-thiazolidinone as COX inhibitor

Several 4-phenylimino-thiazolidin-2-one derivatives were evaluated for their anti-inflammatory activities using an effective synthesis technique reported by Chulovska et al. [173]. The screening results revealed that some compounds had anti-inflammatory effects that were less potent than those of the reference drug. The anti-inflammatory effects of three compounds were carried out i.e., 37.7% (**183**), 41.5% (**184**) and 40.3% (**185**), respectively. They are nearly equal to the standard drug ibuprofen. The results of the anti-inflammatory activity evaluation demonstrated that synthetic compounds have potent anti-inflammatory capabilities, and some of them are comparable to or more potent than ibuprofen (Fig. 2.71).

In an attempt to continue developing anti-inflammatory agents that have minimal ulcerogenic potential, Elzahhar et al. [174] developed and synthesized a new class of pyrazolyl thiazolones as dual COX-2/15-LOX inhibitors with potential anti-inflammatory activity. According to biological screening results, all of them exhibited significant in vivo anti-inflammatory activity that was comparable to celecoxib and diclofenac in the acute inflammatory paradigm. In the chronic model, compounds (**186**) and (**189**) outperformed celecoxib and diclofenac in terms of anti-inflammatory efficacy. Compounds (**187**) and (**188**) showed strong inhibitory effects on monocyte-to-macrophage differentiation, a crucial and early stage in the inflammatory process, with the more specific capacity to prevent differentiation into the pro-inflammatory M1 polarization (Fig. 2.72).

Allawi et al. [175] studied to enhance the anti-inflammatory effectiveness of the 4-thiazolidinone clubbed ketoprofen. According to the ADME study, compounds (**190**), (**191**) and (**192**) encountered the Lipinski rule. All synthesized compounds that were absorbed by the GIT were tested in vivo for their ability to reduce inflammation as well as their in silico selectivity for COX-2 through molecular docking. Based on



183-185

Where
R = -4-Br (183),
R = -3-Cl (184),
R = -4-Cl (185)

Fig. 2.71 4-phenylimino-thiazolidin-2-one derivatives with anti-inflammatory activities

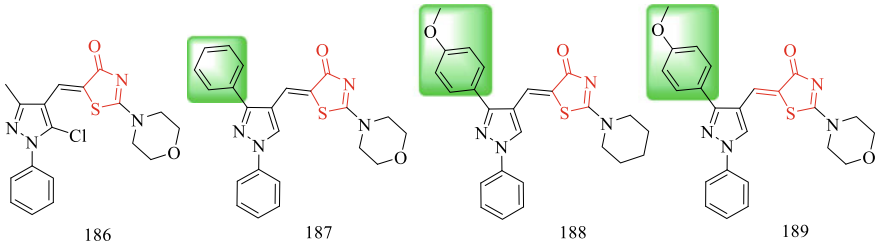
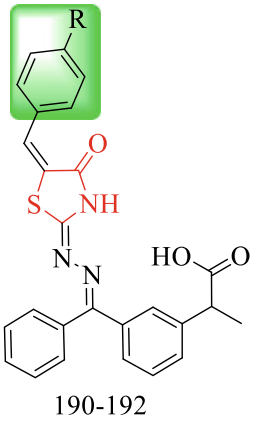


Fig. 2.72 Anti-inflammatory activity of pyrazolyl thiazolones

initial screening results of anti-inflammatory efficacy, compound (**192**) has a stronger anti-inflammatory effect as compared to other compounds combined (Fig. 2.73).

Borisova et al. [176] developed novel (–)-amphoteric aldehyde derivatives which include the pharma-core fragments thiazolidin-4-one, thiazinan-4-one and thiazolidine-4-dione. Compounds (**193**) and (**194**) have also shown anti-inflammatory effectiveness against histamine-induced inflammatory edoema (Fig. 2.74).

Fig. 2.73 Anti-inflammatory effectiveness of the 4-thiazolidinone clubbed ketoprofen



Where
R = -Cl (190),
R = -OH (191),
R = -$N(CH_3)_2$ (192)

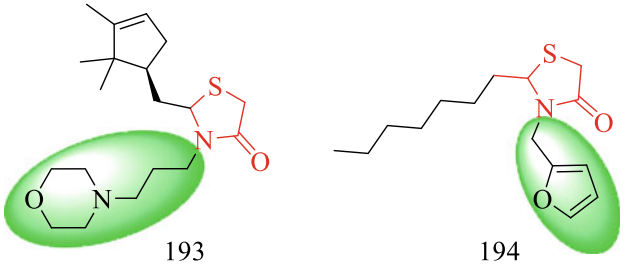
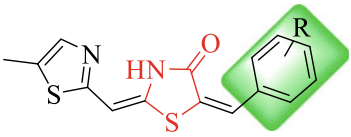


Fig. 2.74 Anti-inflammatory activity of furan and morpholine-based 4-thiazolidinone



195-202

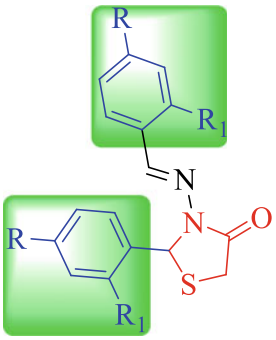
Where
R = H (195), R = 4-OCH_3 (196),
R = 2-NO_2 (197), R = 4-NO_2 (198),
R = 4-F (199), R = 4-Cl (200),
R = 2,3-$(Cl)_2$ (201), R = 3-Br (202)

Fig. 2.75 Anti-inflammatory activity of thiazole-based 4-thiazolidinones

Thiazole-based thiazolidinones were synthesized by Haroun et al. [177], and their biological activity and docking studies were used to predict their potential. It was discovered that compounds bring protection of up to 57.8%, with compounds (**198**), (**200**), (**201**) and (**202**) showing the greatest promise. Four other compounds (**195**), (**196**), (**197**) and (**199**) were equally effective as the reference drug. Three of the most potent compounds were tested in vitro for their ability to inhibit COX-1/COX-2 and LOX. The results showed that these compounds are effective COX-1 inhibitors with IC_{50} values that are better than those of the standard drug naproxen ($IC_{50} = 40.10$ M) (Fig. 2.75).

Thaizolidinone derivatives were developed by Ramkumar and Ramarajan [178] having more effective workup. Compared to standard diclofenac sodium, compounds (**203**), (**204**), (**205**), (**206**) and (**207**) had superior anti-inflammatory potential. Compound (**204**) was shown to have the most potent anti-inflammatory effects out of all of the compounds. Additionally, molecular docking analysis showed that each of the synthesized compounds enhanced the binding energy and inhibition constant with three different proteins. The potential medicinal value of the synthesized compounds was further evaluated by ADMET tests and Lipinski's five rules (Fig. 2.76).

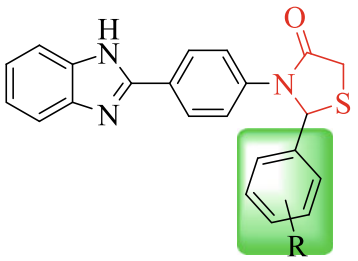
Soni [179] used a three-step procedure for the synthesis of eight substituted 4-thiazolidinone derivatives. The entire series of developed compounds had an anti-inflammatory activity that ranged from moderate to good, comparable with the



203-207

Where
R = Cl, R_1 = Cl (203),
R = Br, R_1 = H (204),
R = Cl, R_1 = H (205),
R = H, R_1 = Br (206),
R = H, R_1 = Cl (207)

Fig. 2.76 Anti-inflammatory activity of some 4-thiazolidinones

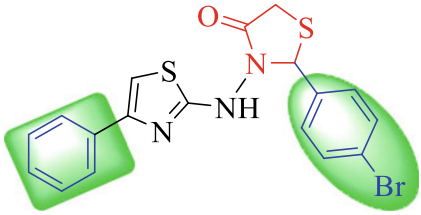


208-211

R = 3-OH, 4-OCH_3 (208),
R = 2-NO_2 (209),
R = 3-NO_2 (210),
R = 4-F (211)

Fig. 2.77 Benzimidazole-based 4-thiazolidinones with anti-inflammatory potential

Fig. 2.78 2-phenyl-3-((4-phenylthiazol-2-yl)amino)thiazolidin-4-one as anti-inflammatory agent



212

standard drug indomethacin (10 mg/kg, p.o.). Based on the results of the experiment, compounds (**208**) and (**210**) displayed greater anti-inflammatory activity, i.e., 66.7 and 64.3%, respectively, which is higher than the indomethacin standard drug (61.9%). After the third hour, the anti-inflammatory effects of compounds (**211**) and (**209**) were significantly demonstrated (54.3% and 57.1%, respectively). The synthesized derivatives also show a better binding profile, with COX-1 and COX-2 proteins showing higher binding energy values (Fig. 2.77).

Five novel 2-phenyl-3-((4-phenylthiazol-2-yl)amino)thiazolidin-4-one compounds have been synthesized by Mudgil et al. [180]. Compound (**212**) was identified as the most effective anti-inflammatory agent, with an IC_{50} value of 1.27 μg/mL and a percentage inhibition value of 57.24% at a concentration of 500 μg/mL (Fig. 2.78).

2.3.5 Anti-HIV Activity

HIV-1, also known as the human immunodeficiency virus type 1, is a pathogenic retrovirus that causes AIDS. One of the essential enzymes for making HIV-1 functional is HIV-1 RT. Both NRTIs and NNRTIs are inhibitors of HIV-1 RT. NNRTIs attach to a region of the enzyme that is not associated with the active site. As a result, computational chemistry plays a significant role in rational drug design [181].

Within the class of non-retroviral therapeutics (NRTIs), there is a group of inhibitors known as thiazolidinone derivatives that produce a quantitative association between chemical structure and biological activity according to quantitative structure–activity relationship (QSAR) modeling [46]. HIV-1 enzymes involved in HIV replication and maturation, as well as cellular receptor interactions between CD4, heparan sulfate and HIV-1 gp120 at the point of entry, are major targets for anti-HIV treatment [182]. However, most of drug-resistant mutations are found in the RT region since RT inhibitors compose a significant fraction of antiretrovirals currently in treatment. This suggests that to overcome this important target, novel strategies must be sought [183]. Additionally, the necessity to develop additional anti-HIV drugs with novel modes of action that can block drug-resistant HIV-1 is made apparent by the advent of escape mutations, the persistence of viral reservoirs, severe side effects and inadequate patient adherence [184] (Fig. 2.79).

Bielenica et al. [185] synthesis and evolution of thiourea derivative based 1,3-thiazolidin-4-ones. They reported thaizolidinone cytotoxicity against human leukemia/lymphoma- and solid tumor-derived cell lines and of their antiviral activity against HIV-1. The 2-benzothiazol-2-ylimino-3-(*p*-tolyl)thiazolidin-4-one (**213**) showed an interesting activity against HIV-1 wild type and against variants carrying clinically relevant mutations. Its mechanism of action as a non-nucleoside reverse transcriptase inhibitor was made clear using a colorimetric enzyme immunoassay (Fig. 2.80).

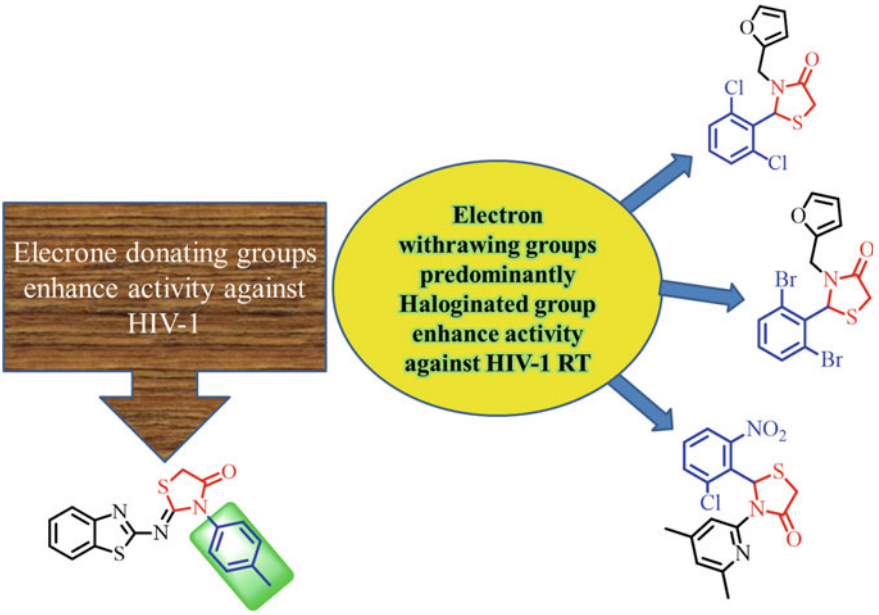
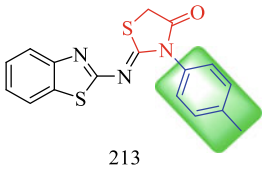


Fig. 2.79 Effect of phenyl ring having halodenated functional group on anti-HIV activity

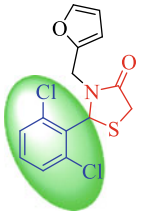


213

Fig. 2.80 2-benzothiazole-based thiazolidin-4-one as antiviral agent against HIV-1

It was designed and synthesized by Rawal et al. [186] to produce 2-aryl-3-heteroaryl-2-ylmethyl-1,3-thiazolidin-4-ones by reacting heteroaryl-2-ylmethyl amine with different 2, 6-dihalo-substituted benzaldehydes and mercaptoacetic acid. They assessed the inhibitory activity of HIV-1 reverse transcriptase (RT). Compounds **(215)** and **(214)** were shown to be less cytotoxic in acutely infected human T-lymphoid CEM cells and to be efficient inhibitors of HIV-1 reverse transcriptase enzyme at micromolar doses, according to the results of in vitro experiments. The below compounds are more active against MT-4 cells (Fig. 2.81).

Suryawanshi et al. [187] designed new molecules against HIV drug-resistant strains that are utmost essential. Based on the anti-HIV-1 activity, they observed 4-thiazolidinone derivatives and studied their interaction with reverse transcriptase (RT) from a panel of 10 clinical isolates using in silico methods and inhibition patterns using in vitro cell-based assays. Based on binding affinity observed in silico analysis against HIV-1 drug-resistant strains, 2-(2-chloro-6-nitrophenyl)-3-(4, 6-dimethylpyridin-2-yl)thiazolidin-4-one (**216**) is most active (Fig. 2.82).



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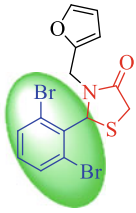

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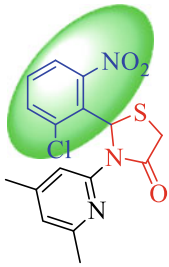
Fig. 2.81 Furan-based thiazolidin-4-one as antiviral agent against HIV-1



216

Fig. 2.82 Pyridine-based thiazolidin-4-one with anti-HIV-1 activity

Balzarini et al. [188] synthesized a series of thiazolidinone using adamantane-1-carbaldehyde. Among them 2-adamantan-1-yl-3-(4,6-dimethyl- pyridin-2-yl)-thiazolidin-4-one is most active. The 2-adamantyl-substituted thiazolidin-4-ones were prepared one-pot two-step methodology involving the formation of imines of adamantane-1-carbaldehyde 1 and different aliphatic, aromatic and heteroaromatic amines, followed by condensation of resulting Schiff bases, with mercaptoacetic acid. All compounds were evaluated for activity against HIV-1 and HIV-2 in CEM cell cultures. Nevirapine and ddI were included as reference compounds. Compound (**217**) showed the best anti-HIV activity (Fig. 2.83).

By using an aromatic amine, aromatic aldehyde and α-mercaptoacetic acid in a three-component one-pot synthesis, Chen et al. [189] synthesized 2,3-diaryl thiazolidin-4-ones. We synthesized the C-5 substituted compounds and assessed their ability to inhibit HIV-RT. The anti-HIV-RT activity of compounds **(218)**, **(219)** and **(220)** was found to be moderate. All of the methyl or alkyl acyloxy groups on thiazolidin-4-one's C-5 decreased the inhibitory effects of HIV-RT (Fig. 2.84).

Eighteen novel (4/6-halogen/MeO/EtO-substituted benzo[d]thiazol-2-yl)thiazolidin-4-ones were synthesized by Pitta et al. [190] and tested for anti-HIV-1 RT inhibitory action, among them four derivatives exhibited IC_{50} values lower than 3.4 μM (1.39 μg/ml) and two of them showed much better inhibition than the reference compound, nevirapin. Evaluation of HIV-1 RT inhibitory action, halogen or alkoxy-substituent at positions *meta* or *para* of the benzyl ring of

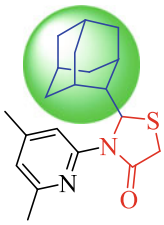


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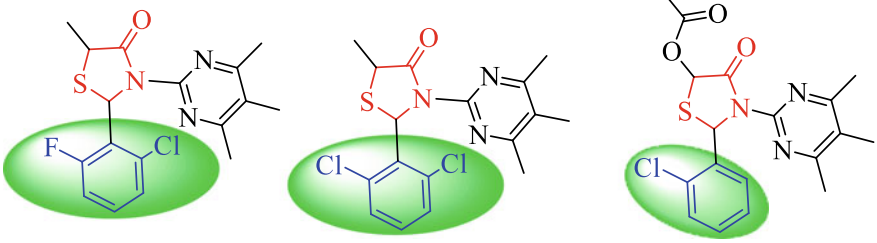
Fig. 2.83 Adamantane-based thiazolidinone as antiviral agent



218 219 220

Fig. 2.84 Pyrimidine-based thiazolidin-4-ones as antiviral agents

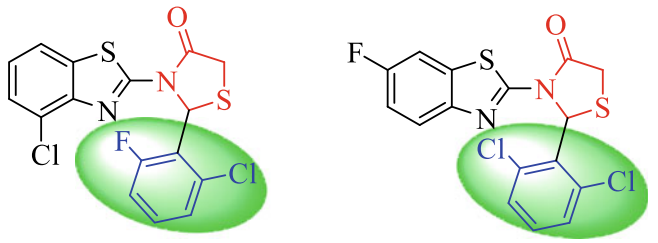


Fig. 2.85 Antiviral benzo[d]thiazol-2-yl)thiazolidin-4-ones

the benzothiazolyl moiety may convert a practically inactive non-substituted derivative to a relatively strong inhibitor. Two halogen substituted derivatives, the 3-(4-chloro-benzo[*d*]thiazol-2-yl)-2-(2-chloro-6-fluorophenyl)thiazolidin-4-one (**221**) ($IC_{50} = 0.04$ μM) and the 3-(6-fluoro-benzo[*d*]thiazol-2-yl)-2-(2,6-dichlorophenyl)thiazolidinone-4-one (**222**) ($IC_{50} = 0.25$ μM), were the most active compounds (Fig. 2.85).

The 5-((arylfuran/1*H*-pyrrol-2-yl)-methylene)-2-thioxo-3-(3-(trifluoromethyl)phenyl)thiazolidin-4-ones were synthesized by Jiang et al. [191]. Suzuki–Miyaura cross-coupling and then Knoevenagel condensation reaction were carried out. All of the compounds had anti-HIV-1 action, but compounds **(223)** and **(224)** are particularly effective in preventing HIV-1-mediated cell–cell fusion and exhibiting strong resistance to infection by primary and laboratory-adapted HIV-1 strains with EC_{50} values at low nanomolar levels (Fig. 2.86).

Tatar et al. [192] developed some novel 2-[2-(benzoylamino)-3-methylbutyrylhydrazono]-3-alkyl-/arylalkyl-5-non-substituted/methyl-1,3-thiazolidinones and evaluated their antiviral activity. Utilizing an MT-4/MTT-based test, anti-HIV and cytotoxicity results were also obtained with the compounds using

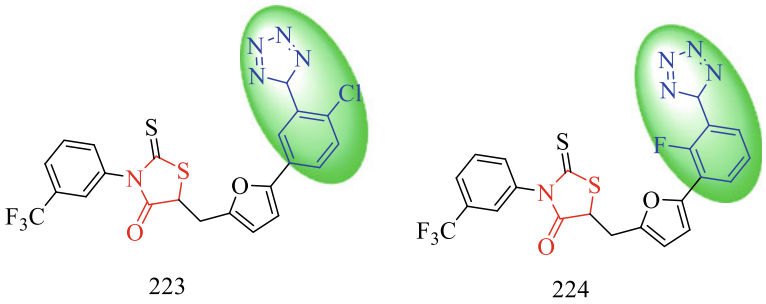


Fig. 2.86 5-((arylfuran/1*H*-pyrrol-2-yl)-methylene)-2-thioxo-3-(3-(trifluoromethyl)phenyl)thiazolidin-4-ones as potent antiviral agents

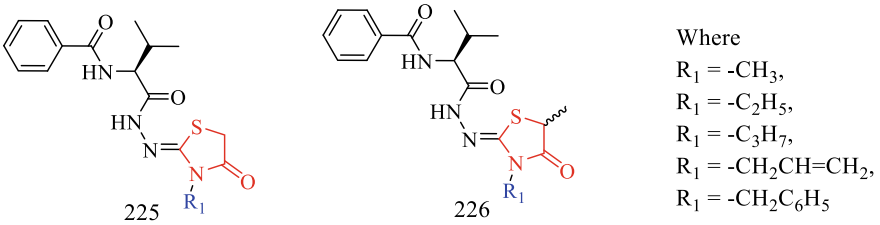


Fig. 2.87 2-[2-(benzoylamino)-3-methylbutyrylhydrazono]-3-alkyl-/arylalkyl-5-non-substituted/methyl-1,3-thiazolidinones as antiviral agents

the strains of HIV-1 (IIIB) and HIV-2 (ROD). Compounds (**225**) and (**226**) showed moderate antiviral activity at subtonic concentrations (Fig. 2.87).

By using Suzuki–Miyaura cross-coupling and Knoevenagel condensation, Katritzky et al. [193] designed and synthesized a series of new 2-aryl 5-(4-oxo-3-phenethyl-2-thioxothiazolidinylidenemethyl) furans. These compounds showed highly potent anti-HIV-1 activity. With selectivity measures ranging from 330 to 440, three compounds **(227)**, **(228)** and **(229)** inhibited the replication of primary and laboratory-adapted HIV-1 strains at <100 nM and demonstrated good activity with the lowest EC_{50} (70–74 nM). These findings suggest that these compounds may serve as a lead for the development of novel small molecule HIV fusion/entry inhibitors, which could be used to treat HIV/AIDS patients who have not responded to existing antiretroviral therapies (Fig. 2.88).

A novel series of imidazo[2,1-*b*]thiazoles with 4-thiazolidinone moieties have been synthesized by Güzeldemirci et al. [194]. Based on screening, a few compounds were shown to exhibit activity against a variety of RNA viruses (cytotoxic concentrations ranging from 100 to 20 μM). Additionally, the authors had thiazolidinone-fused imidazo[2,1-b]thiazoles that synthesized to increase the antiviral potency. Phytochemical analysis revealed that compounds (**230**) and (**231**) have antagonistic effects

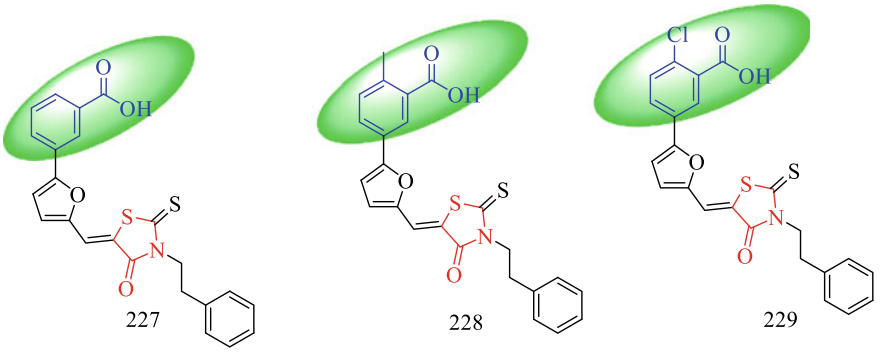
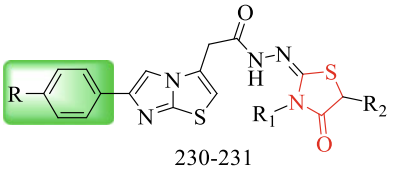


Fig. 2.88 Anti-HIV activity of -aryl 5-(4-oxo-3-phenethyl-2-thioxothiazolidinylidenemethyl) furans



Where
R = H, R_1 = CH_2=CH-CH_2, R_2 = CH_3 (230)
R = Cl, R_1 = CH_3, R_2 = CH_3 (231)

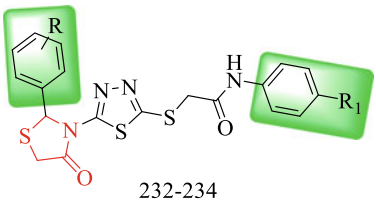
Fig. 2.89 Imidazo[2,1-*b*]thiazoles with 4-thiazolidinones as antiviral agents

on vesicular stomatitis virus in HeLa cells [antiviral EC_{50} values of 9 (cytotoxicity 100 μM) and 2 μM (cytotoxicity 20 μM), respectively] (Fig. 2.89).

A 3-(1,3,4-thiadiazol-2-yl)thiazolidin-4-one derivative has been designed, synthesized and biologically evaluated by Buemi et al. [195]. The derivatives (**232**), (**233**) and (**234**) with IC_{50} values of 19.17, 11.83 and 15.75 μM, respectively, were emerged and the most promising molecules among the two synthesized series. In MT-4 cell culture, all the proposed compounds had moderate anti-HIV activity. The results of biological studies showed that the arylacetamide moiety enhances the RT enzymatic inhibition. Docking studies also confirmed this evidence, proving that ligands made contact with residues involved in the recognition process inside the enzymatic cavity (Fig. 2.90).

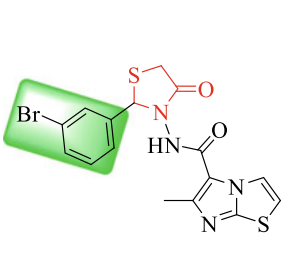
A multistep synthesis, İsaoğlu and Cesur [196] synthesized 4-thiazolidinone derivatives containing imidazo[2,1-b][1,3]thiazole moiety from 2-aminothiazole and ethyl 2-chloroacetoacetate. In vitro, antiviral and cytotoxic activities of 4-thiazolidinones were assessed against various types of DNA- and RNA viruses. According to appropriate cell culture models, compounds (**235**) and (**236**) exhibit antiviral activity against different types of viruses (Fig. 2.91).

An effective and straightforward chemical approach is used by Mandal et al. [197] to demonstrate the utility and synthesis of a series of 1,3-thiazolidin-4-one sulfonyl derivatives. The antiviral and antimicrobial effects of the target molecules have been assessed. When the antiviral efficacy of eleven final derivatives was studied, compound (**237**) demonstrated antiviral action against HIV-1 (strain IIIB) and HIV-2 (strain ROD), while other compounds only had moderate inhibitory activity against a variety of DNA and RNA viruses (Fig. 2.92).



Where
R = 3-Cl, R_1 = SO_2NH_2 (232)
R = 2-Cl, R_1 = SO_2CH_3 (233)
R = 3-Cl, R_1 = SO_2CH_3 (234)

Fig. 2.90 3-(1,3,4-thiadiazol-2-yl)thiazolidin-4-one derivative possessed antiviral agents



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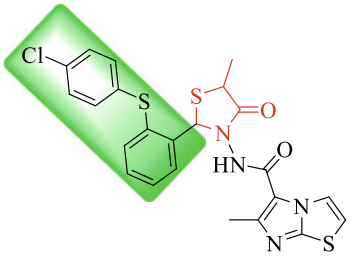

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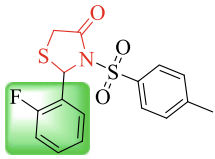
Fig. 2.91 4-thiazolidinone derivatives containing imidazo[2,1-b][1,3]thiazole as potent antiviral agents

Fig. 2.92 Anti-HIV activity of 1,3-thiazolidin-4-one sulfonyl derivatives



237

2.3.6 Antitubercular Activity

Approximately 10 million people worldwide are afflicted with tuberculosis, which is a leading cause of mortality when it matures into a single infectious disease. *Mycobacterium tuberculosis* is the causative agent of tuberculosis (TB), a chronic necrotizing bacterial infection that causes a wide range of symptoms and is responsible for approximately three million deaths globally each year. The World Health Organization (WHO) estimates that 30 million individuals will get infected with the Bacillus over the next 20 years if control measures are not further enhanced, accounting for approximately one-third of the world's population now afflicted with the infection. Thiazolidinone and its derivatives play a key role to biological activity. The WHO has declared TB a worldwide public health catastrophe due to rising circumstances [198–201]. Thiazolidinone is a useful therapeutic drug, and several of its classes have shown promise in combating tuberculosis [202].

Effect of various electron-donating and electron-withdrawing functional groups on phenyl ring of 4-thiazolidinone derivatives on antitubercular activity against *M. tuberculosis* and *M. bovis* is described in Fig. 2.93.

Mistry and Jauhari [203] synthesized a new class of thiazolidinone bioactive agents based on quinoline nucleus. The 2-chloroquinoline-3-carbaldehyde reacted with various substituted amines to form the corresponding Schiff base intermediates. They have derived final azetidinone and thiazolidinone analogs from Schiff bases using chloroacetyl chloride and 2-mercaptoacetic acid, respectively. The newly synthesized compounds were examined for their *M. tuberculosis* strain $H_{37}Rv$ to develop a novel class of bioactive agents. They performed biological screening for

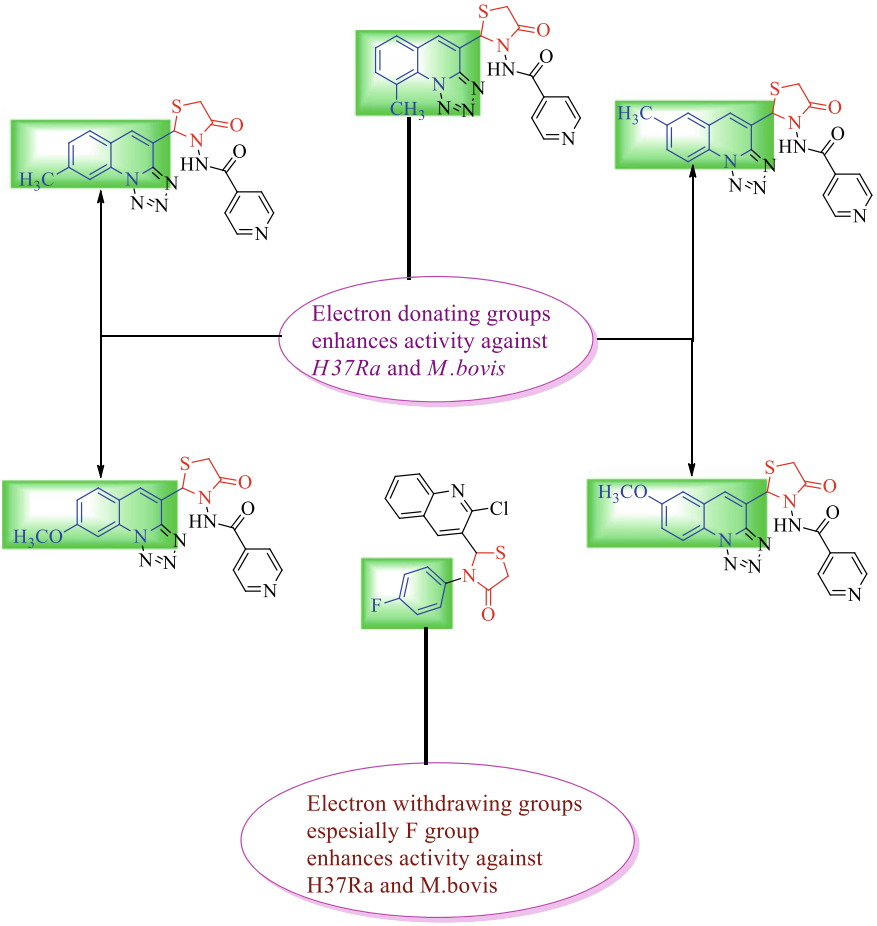
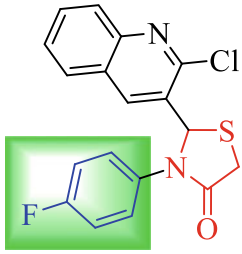


Fig. 2.93 Effect of various functional groups on phenyl ring of 4-thiazolidinone derivatives having antitubercular activity

antimycobacterial using the Lowenstein–Jensen (L–J) MIC method, and it is worthwhile to note that compound (**238**) with electron-withdrawing and strong electronegative fluoro substituent within the thiazolidinone class exhibited good inhibitory potential at 12.5 μg/mL of MIC against $H_{37}Rv$ strain (Fig. 2.94).

A new series of 4-thiazolidinones containing pyrazinyl and thiazolyl entities was synthesized by Dhumal et al. [204], and their antitubercular efficacy is described. Using pyrazinamide as a starting material and five consecutive stages, the title 4-thiazolidinones, *N*-(pyrazinyl substituted thiazoloylamino)-2-aryl-4-thiazolidinones, have been synthesized for the first time. Using solutions containing varying concentrations of the compounds, an antitubercular screening of the novel 4-thiazolidinones was conducted on Mycobacterium TB $H_{37}Rv$ and *Mycobacterium*

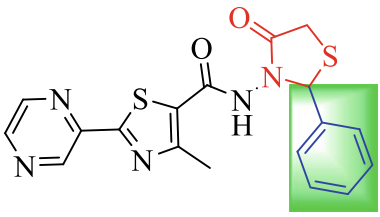


238

Fig. 2.94 Bioactive agents based on thiazolidinone and quinoline

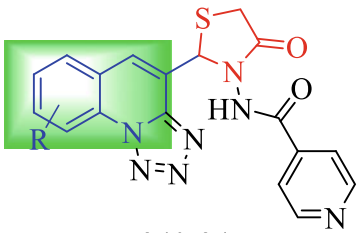
BCG. The screening outcomes are reported. Compound **239** has demonstrated significant antitubercular properties (Fig. 2.95).

A new way to synthesize a novel 4-thiazolidinone derivatives was developed by Subhedar et al. [205], a one-pot multicomponent cyclo-condensation of different tetrazoloquinoline aldehydes, acid hydrazides and thioglycolic acid in the presence of [DBUH]ijOAc] as a catalyst in high yields. All synthesized derivatives were tested with antimycobacterial activity against MTB $H_{37}Ra$ and *M. bovis* BCG strains (**240**) to (**245**) and showed excellent activity against MTB $H_{37}Ra$ and *M. bovis* BCG strains with MIC values ranging from 0.99–13.55 μmol mL^{-1} to 0.14–20.11 μmol mL^{-1}, respectively (Fig. 2.96).



239

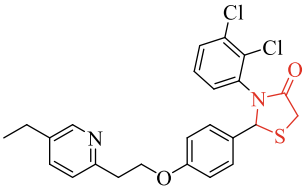
Fig. 2.95 4-thiazolidinones containing pyrazinyl and thiazolyl entities with antitubercular activity



240-245

Where
R = -H (240),
R = -8-CH_3 (241),
R = -7-CH_3 (242),
R = -6-CH_3 (243),
R = -7-OCH_3 (244),
R = -6-OCH_3 (245)

Fig. 2.96 4-thiazolidinones containing pyridine and quinoline as antitubercular agents



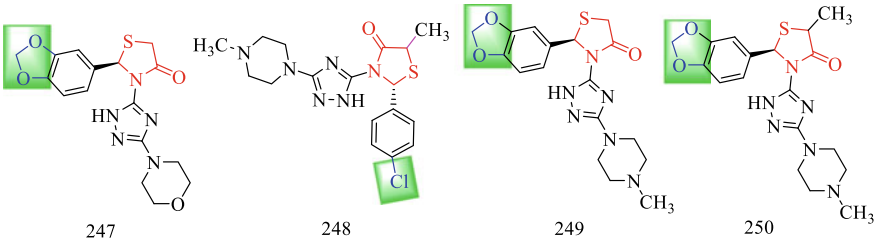
246

Fig. 2.97 Pyridine-based 4-thiazolidinone with antitubercular activity

Patel et al. [206] synthesize new thiazolidinones prepared from Schiff bases and thioglycolic acid in the presence of $ZnCl_2$ from 4-[2-(5-ethylpyridin-2-yl)ethoxy]benzaldehyde. These active compounds impelled us to study their antitubercular activity. Thiazolidinone (**246**) displayed *M. tuberculosis* MIC at 25 μg/mL, which is a better antitubercular agent compared to rifampicin (Fig. 2.97).

In Bialy et al. [207], synthesis of a series of 2-aryl 3-[1,2,4]triazol-5-yl 4-thiazolidinones was synthesized by a *domino* reaction of 5-amino-1*H*-[1,2,4]triazoles 3, aromatic aldehydes and α-mercaptoacids in boiling toluene in the presence of molecular sieves 4 Å. In this series, twenty novel 3-[1,2,4]triazol-5-yl 4-thiazolidinone derivatives were prepared, out of which compounds (**247**) to (**250**) displayed MICs of 4 μg/mL or less versus *M. tuberculosis.* All compounds were screened against *Candida albicans.* Compounds (**248**) and (**249**) gave MICs of 1 μg/mL or less and were fungicidal. Finally, in all of them, compound (**249**) was evaluated against an expanded fungal panel and showed good activity against *Cryptococcus neoformans.* In addition, compound (**249**) also appeared to be fungicidal against *Aspergillus arrhizus*, with MIC < 1 μg/mL (Fig. 2.98).

Shelke et al. [208] synthesize 5-(substituted benzylidene)-2-((substituted phenyl)amino)thiazol-4(5*H*)-one analogs with antitubercular activity. They synthesized compounds with excellent yields and tested their antimycobacterial activity in vitro against strains of *Mycobacterium bovis BCG* and *M. tuberculosis MTB H*$_{37}$*Ra.* Among all the synthesized compounds, in particular, compounds (**251**) to (**255**) exhibited MIC_{50} values 20, 5.5, 7.5, 8.9 and 15 μg/mL, respectively, against *MTB H*$_{37}$*Ra*, which shows that these are marginal antitubercular agents. In structure–activity relation electron-withdrawing groups showed more antitubercular activity (Fig. 2.99).



247 248 249 250

Fig. 2.98 2-aryl 3-[1,2,4]triazol-5-yl 4-thiazolidinones as antimycobacterial agents

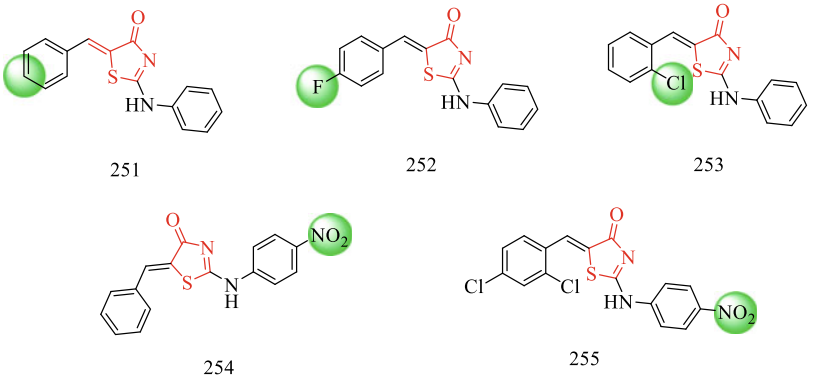
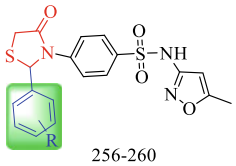


Fig. 2.99 5-(substituted benzylidene)-2-((substituted phenyl)amino)thiazol-4(5*H*)-one analogs with antitubercular activity

Fig. 2.100 Sulfamethaoxazole incorporated 4-thiazolidinone hybrids as antitubercular agents



Where
R = 4-F (256)
R = 4-Cl (257)
R = 4-CF_3 (258)
R = 2-Cl (259)
R = 2-F (260)

Bhat et al. [209] synthesized a sulfamethaoxazole incorporated 4-thiazolidinone hybrids, and this newly synthesized derivative was screened for their in vitro antitubercular activity against *M. Bovis BCG* and *M. tuberculosis* $H_{37}Ra$ *(MTB)* strains. Compounds (**256**) to (**260**) exhibit promising antimycobacterial activity against *M. Bovis* and *MTB* strains with IC_{90} values in the range of 0.058–0.22 and 0.43–5.31 μg/mL, respectively (Fig. 2.100).

Zhang et al. [210] designed and synthesized novel quinoxaline-1,4-di-*N*-oxides containing a thiazolidinone moiety and evaluated their antimycobacterial activities. The compounds that exhibited the most antimycobacterial activity against *Mycobacterium TB* strain $H_{37}Rv$ (minimal inhibitory concentration MIC = 1.56 μg/mL) were **(261)**, **(262)**, **(263)** and **(264)**. In these novel compounds, 12 out of the 26 compounds had active antimycobacterial activity, with an MIC ≤ 6.25 μg/mL and SI > 10 (Fig. 2.101).

In in vitro study of antitubercular activity against *M. tuberculosis* $H_{37}Rv$, Üstündağ et al. [211] synthesized and designed a novel series of compounds, noting that 4-thiazolidinone derivatives **(265)** to **(268)** and **(269)** to **(271)** demonstrated significant antituberculosis activity, showing 99% inhibition at MIC = 6.25 to 25.0 μg/ml. These compounds, (**265**) to (**268**) and (**269**) to (**271**) demonstrated anti-TB activity at concentrations tenfold lower than those cytotoxic for the mammalian cell lines (Fig. 2.102).

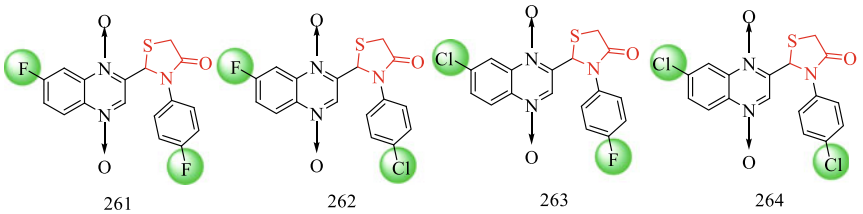


Fig. 2.101 Quinoxaline-1,4-di-*N*-oxides containing a thiazolidinone moiety with antimycobacterial activities

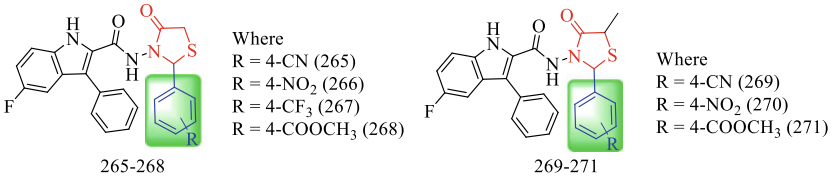


Fig. 2.102 Indole-based thiazolidinone as antitubercular agents

2.3.7 Antidiabetic Activity

Nowadays diabetes mellitus is considered to be one of the most dangerous health catastrophes in the world, and this is a major metabolic disorder [212]. Thiazolidinone is a very important class of drugs that cure diabetes mellitus [213]. The research of heterocyclic compounds is vital in the field of medicine. These substances have a significant role in a biological system. Numerous therapeutic candidates, including those with antibiotic, anti-tumor, anti-inflammatory, antiviral, antimicrobial, antifungal and antidiabetic properties, also depend on heterocyclic scaffolds [41, 214–225]. Thiazolidinone's wide spectrum of therapeutic effects results in the most dominating heterocyclic ring. Studies across thiazolidinone's nucleolus continue to develop new, biologically active substances. Thiazolidinedione is widely useful in the synthesis of antidiabetic compounds, and nowadays it is a license to give oral therapy for glycaemic control [225]. Thiazolidinone derivatives displayed important biological activities out of which antidiabetic activity has been widely executed, and a remarkable number of drugs are marketable such as rosiglitazone, pioglitazone, lobeglitazone and troglitazone. Diabetes mellitus (DM) is a deep-rooted metabolic disorder and is major disorder that is approaching pandemic proportions worldwide. DM is characterized by expanded levels of blood glucose/impaired insulin secretion/liver or peripheral insulin resistance. In this section, we discussed important novel synthetic compounds that exhibit antidiabetic activity [226]. Antidiabetic activity of some 4-thiazolidinones and effect of electron-withdrawing groups on activity are shown in Fig. 2.103.

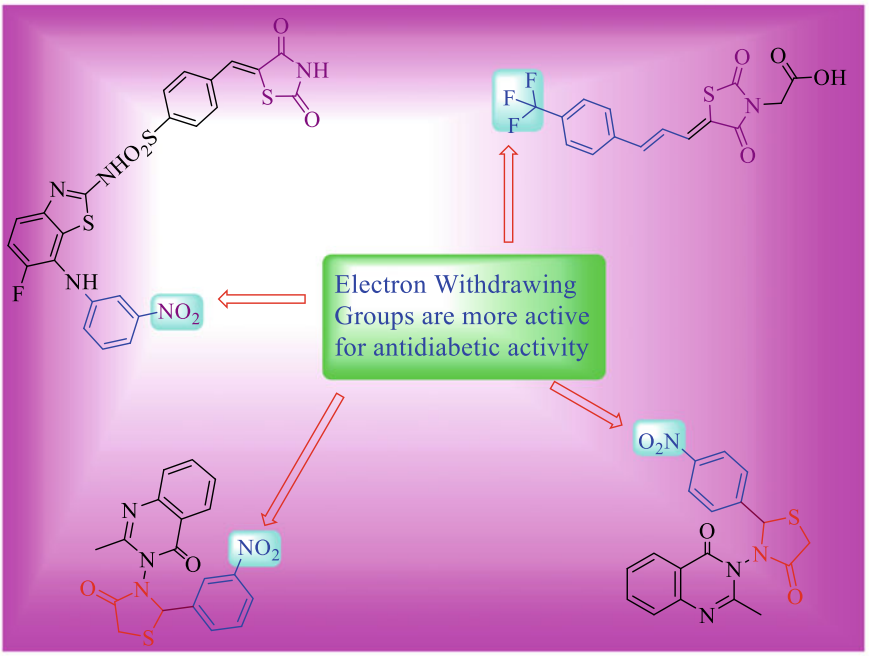
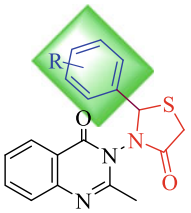


Fig. 2.103 Antidiabetic activity of some 4-thiazolidinones and effect of EWG on activity

Jangam and Wankhede [227] prepared one-pot multicomponent reaction using DMF media, a new set of 3-(2-substituted)-4-(oxothiazolidin-3-yl)-2-methylquinazolin-4(3*H*)-ones compounds via hybridization process of 3-amino-2-methylquinazolin-4(3*H*)-one with substituted benzaldehyde, thioglycolic acid and *N*,*N*-dicyclohexylcarbodiimide. All synthesized compounds are tested for antidiabetic activity against streptozotocin-induced diabetic rats at a dose of 200 mg/kg compared with standard pioglitazone (15 mg/kg). In all synthetic compounds containing thiazolidinone moiety, (**272**) to (**275**) showed promising antidiabetic activity and lower activity than the standard drug. Promising compounds that are appraised in vitro are tested for serum insulin, cholesterol, triglycerides, total protein, lipoprotein and enzyme factors. Compounds (**272**) to (**275**) are tested for biochemical parameters like lipid profile, HbA_1C, alkaline phosphatase (ALP), ALT, AST, insulin as well as total protein level that showed to be good. In the studies of molecular docking, the binding energies should be in the range of −8.95 to −11.46 kcal/mol, with peroxisome proliferator-activated receptor γ (PPAR γ) receptors (PDB ID: 4PRG). In these four active compounds, (**275**) showed excellent binding affinity. In all above, collected data is useful and helpful for synthesizing thiazolidinone containing hybrid molecules as oral antidiabetic active drugs (Fig. 2.104).

Abeed et al. [228] synthesized 1,3-diphenyl-1*H*-pyrazol-4-carboxaldehyde with different nucleophiles and a new series of compounds were obtained. Synthesized compounds were tested for their antihyperglycemic and renoprotective activities.



272-275

Where
R = 4-OH (272)
R = 4-NO_2 (273)
R = 3-NO_2 (274)
R = 3,4-$(OCH_3)_2$ (275)

Fig. 2.104 3-(2-substituted)-4-(oxothiazolidin-3-yl)-2-methylquinazolin-4(3*H*)-ones as antidiabetic agents

In synthesized compounds, three compounds demonstrate significant antidiabetic activity, and the other five compounds showed promising renoprotective activity. All compounds were tested for various biological evolution. Compound (**276**) was tested for serum glucose, and it showed a similar effect as compared to the reference drug gliclazide (Glic). In serum cholesterol and triglyceride levels (**276**) were observed to decrease remarkably. Among all these synthesized derivatives, compound (**276**) showed promising antidiabetic activity (Fig. 2.105).

Ottana et al. [229] presented a new series of (**277**), (**278**) and (**279**) suitably substituted derivatives that were explored. Thiazolidinedione particularly in acetic acid (**278a**) and (**278b**) is convinced to be a significant antioxidant agent as well as an active inhibitor of the enzyme that is capable of neutralizing the oxidative stress associated with both diabetic complications and other pathologies. The study of this paper noted that 5-arylidene-2,4-thiazolidinediones (**277**), (**278**) and 2-phenylimino analogs (**279**) inhibit aldose reductase (ALR2). Study of SARs, a series of acetic acids (**278**) exhibits more fabulous inhibitors than *N*-unsubstituted derivatives (**277**). Compound (**278**) also showed admirable antioxidant activity. As paintable note in this paper, thiazolidinone and thiazolidinedione also exhibit excellent antidiabetic activity (Fig. 2.106).

Thiazolidinone and thiazolidinedione are widely useful for antidiabetic activity. When the thiazole ring is recognized, the first parent compounds are thiazolidine and thiazolidinediones. Pattan et al. [230] synthesized a novel

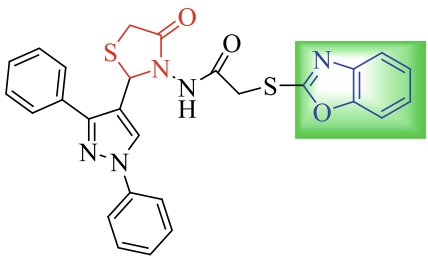


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Fig. 2.105 Pyrazole and benzazole-based thiazolidinone as antidiabetic agent

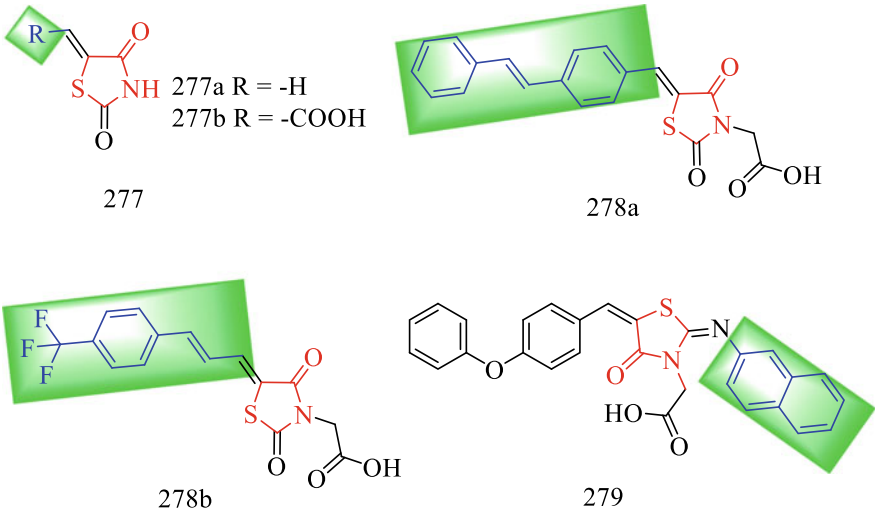


Fig. 2.106 Antidiabetic activity of 5-arylidene-2,4-thiazolidinediones

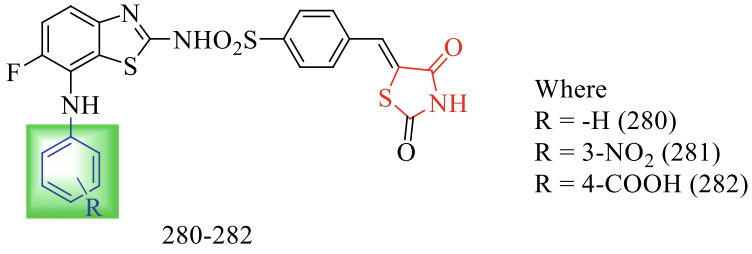


Fig. 2.107 Thiazolidinone based on benzothiazole as antidiabetic agents

series of 2-amino[5'(4-sulphonylbenzylidine)-2,4-thiazolidinedione]-7-chloro-6-fluorobenzothiazoles. In this synthesized series some compounds like (**280**), (**281**) and (**282**) showed excellent antidiabetic activity (Fig. 2.107).

2.3.8 Antioxidants Activity

Antioxidants are substances that help protect cells and tissues from oxidative damage caused by free radicals, which are highly reactive molecules that can harm DNA, proteins and lipids in the body. Oxidative stress is implicated in various diseases and aging processes, making antioxidants a crucial area of research in the quest for improved health and longevity.

The 4-thiazolidinone scaffold, on its own, does not exhibit antioxidant effects. However, research has demonstrated that when this structural element is combined

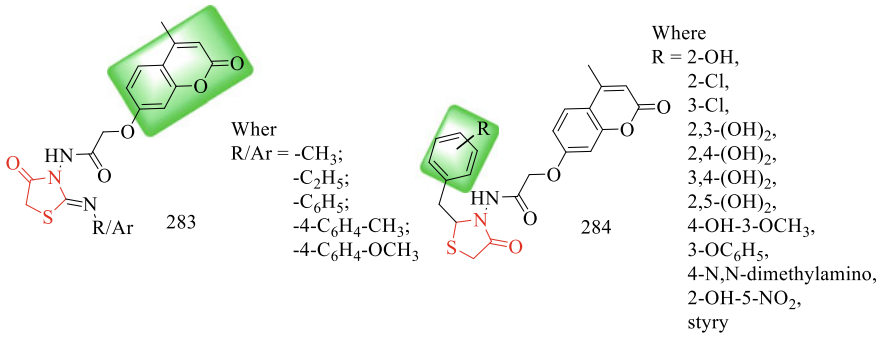
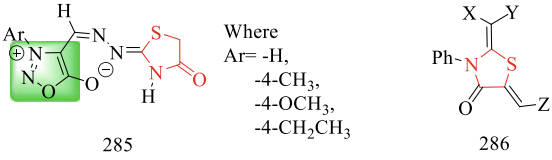


Fig. 2.108 Coumarin-based 1,3-thiazolidine-4-ones as antidiabetic agents

with other antioxidant compounds, it enhances their overall antioxidant potential. For instance, 7-hydroxy-4-methylcoumarins are well-known antioxidants, but when they are modified by attaching thiosemicarbazide and 4-thiazolidinone groups at position 7 (**283**), their antioxidant activity is significantly improved [231]. Additionally, a group of researchers synthesized derivatives containing both the coumarin moiety and the 1,3-thiazolidine-4-one scaffold (**284**), and among these derivatives, three compounds (A, B and C) exhibited superior antioxidant activity compared to ascorbic acid [232] (Fig. 2.108).

Combining sydnone derivatives with thiazolidinones (**285**) has been found to result in compounds with notable antioxidant activity [233]. Structure–activity relationship (SAR) studies have revealed that substituting the N-3 position of the 4-thiazolidinone scaffold with a phenyl group enhances antioxidant potential. The presence of two electron-donating hydroxyl (–OH) groups on the phenyl ring, with one located at the ortho position and the other at any other position on the ring, contributes to increased antioxidant activity. To assess antioxidant activity, thirty different 4-thiazolidinone derivatives (**286**) were synthesized and evaluated for their ability to scavenge 1,1-diphenyl-2-picrylhydrazyl radicals, using Vitamin E as a reference. Notably, 1,1-diphenyl-2-picrylhydrazyl radicals have an unpaired electron, resulting in strong absorption at a wavelength of 517 nm. When these radicals combine with electrons from antioxidant derivatives, the absorption decreases proportionally based on the number of electrons neutralized [234] (Fig. 2.109).

Fig. 2.109 Sydnone derivatives with thiazolidinones with antioxidant activity



2.3.9 *Antiparasitic Activity*

The parasite like helminths, amoeba, ectoparasites, parasitic fungi and protozoa was the causative for parasitic diseases in the host. Antiparasitic drugs were used to treat such parasitic diseases like pneumocystis, trypanosomiasis, scabies and malaria. Globally more than 2 billion people are affected by parasitic diseases, and it causes substantial morbidity and mortality [235]. Nowadays misuse and overuse of the available antiparasitic drugs are the main factor for antimicrobial resistance. The development of novel antiparasitic agents with different structures and mechanisms of action became a need of society. Some derivatives containing thiazolidinone core structure were found to have antiparasitic potential and can emerge as novel hybrids.

Havrylyuk et al. [236] developed novel pyrazoline-thiazolidinone hybrids that possessed trypanocidal activity. The derivatives were screened against *Trypanosoma brucei gambiense* (Feo strain) for inhibitory activity. Compounds (**287**), (**288**), (**289**), (**290**) and (**291**) have significant antiparasitic activity at 10 μg/mL concentration. Compounds (**287**) and (**289**) possessed IC_{50} values of 0.6 and 0.7 μM, respectively, against *T. brucei gambiense*. These both compounds were sixfold more potent than the standard drug nifurtimox (IC_{50} value is 4.4 μM). Compounds (**288**), (**290**) and (**291**) possessed significant trypanocidal properties, with IC_{50} values of 1.1, 1.2 and 1.2 μM, respectively (Fig. 2.110).

de Oliveira-Filho et al. [237] synthesized and studied 4-thiazolidinones against *Trypanosoma cruzi*. The thiazolidinone hybrids were found to have significant antiparasitic activity. The derivatives (**292**), (**293**) and (**294**) possessed IC_{50} values of 4.2, 2.9 and 1.7 μM, respectively, against *T. cruzi* at the concentration of 50 μg/

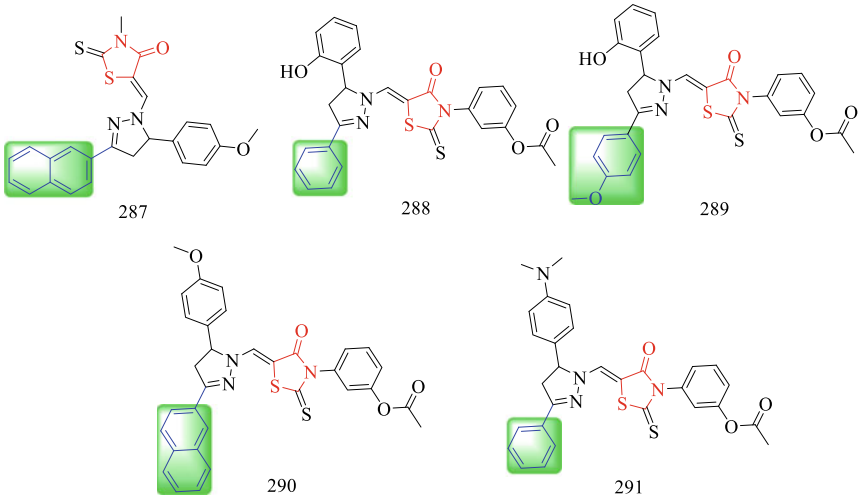


Fig. 2.110 Pyrazoline-thiazolidinone hybrids as trypanocidal agents

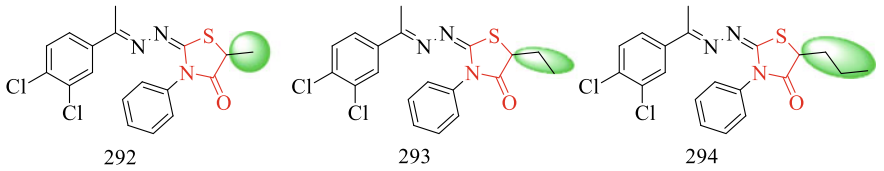


Fig. 2.111 4-thiazolidinones as antiparasitic agents against *Trypanosoma cruzi*

mL. These compounds were more potent than the standard drug benznidazole (IC_{50} = 10.6 μM) (Fig. 2.111).

Havrylyuk et al. [238] developed novel pyrazoline-based hybrids as potential antiparasitic agents. The synthesized compounds were screened for antitrypanosomal activity against *Trypanosoma brucei brucei* (Tbb) and *Trypanosoma brucei gambiense* (Tbg). The result indicated moderate potency of compounds (**295**), (**296**) and (**297**) with IC_{50} values against Tbb in the range of 5.43–13.87 μM and Tbg in the range of 2.53–6.66 μM, respectively (Fig. 2.112).

The 5-enamine-4-thiazolidinone derivatives containing trypanocidal activity were developed by Holota et al. [221] and screened for antitrypanosomal activity against *Trypanosoma brucei brucei* (Tbb) and *Trypanosoma brucei gambiense* (Tbg). The result indicated significant activity of compounds (**298**), (**299**) and (**300**) with IC_{50} values against Tbb in the range of 0.091–3.916 μM and Tbg in the range of 0.027–1.936 μM, respectively (Fig. 2.113).

Shepeta et al. [239] developed thiazolidinone-diclofenac hybrid molecules as potential antiparasitic agents. The in vitro antitrypanosomal activity of compounds (**301**) and (**302**) against *Trypanosome brucei brucei* (Tbb) indicated potency with IC_{50} values of 4.8 and 7.06 μM, respectively (Fig. 2.114).

Molina et al. [240] developed new 4-thiazolidinones possessed anti-toxoplasma activity. The derivatives (**303**), (**304**) and (**305**) possessed IC_{50} values of 0.46, 0.20 and 0.66 μM, respectively, against *Toxoplasma gondii* at the concentration of 10 μM (Fig. 2.115).

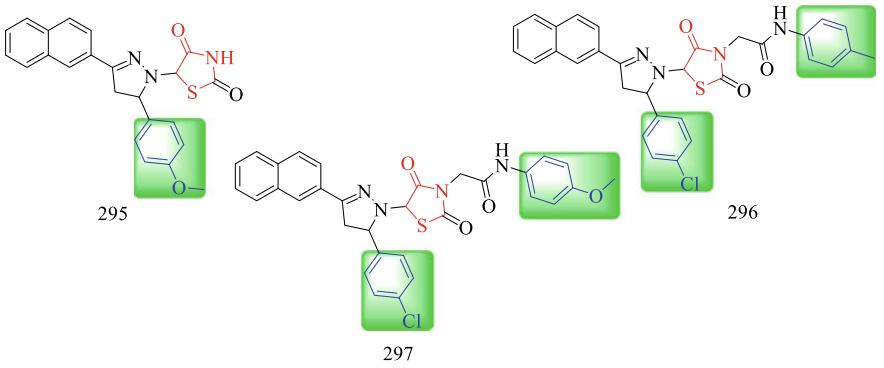


Fig. 2.112 Pyrazoline-based hybrids as potential antiparasitic agents

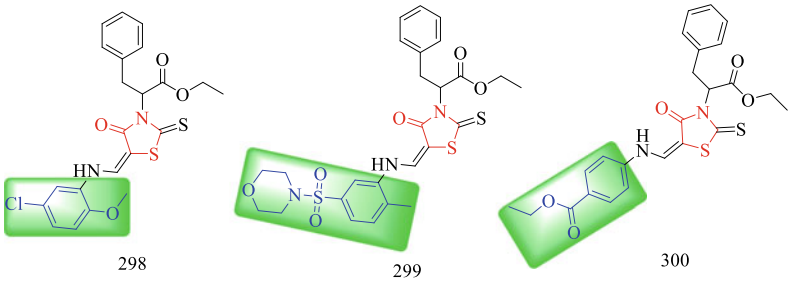


Fig. 2.113 5-enamine-4-thiazolidinone derivatives as potential antiparasitic agents

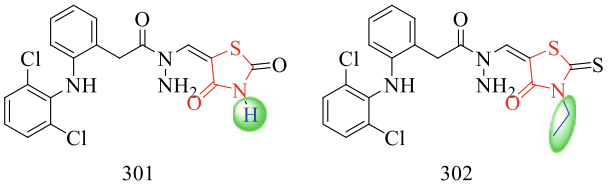


Fig. 2.114 Thiazolidinone-diclofenac hybrid molecules as potential antiparasitic agents

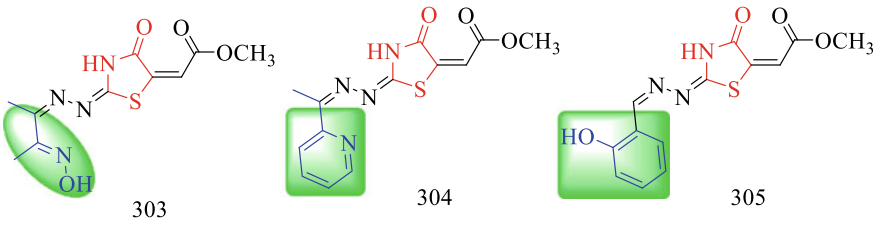


Fig. 2.115 4-thiazolidinones as potential anti-toxoplasma agents

Haroon et al. [241] synthesized 1,3-thiazole and 4-thiazolidinone ester derivatives as potential trypanocidal agents. Compound (**306**) possessed an IC_{50} value of 8.45 μM against *Trypanosoma cruzi*. The reference drug benzodiazepine possessed IC_{50} value of 34.5 μM (Fig. 2.116).

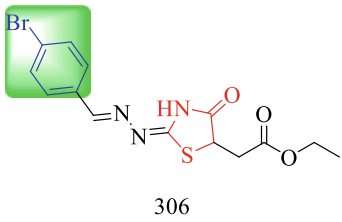


Fig. 2.116 4-thiazolidinone ester derivative as potential trypanocidal agents

Kryshchyshyn et al. [242] synthesized a novel class of antitrypanosomal agents based on thiazolidinone/thiazole hybrids. Novel compounds were screened on *Trypanosoma brucei gambience* and *Trypanosoma brucei brucei*. Compounds (**307**), (**308**) and (**309**) were inhibited growth of more than 90% of these parasites at the concentration of 10 μg/mL. Compounds (**310**), (**311**) and (**312**) containing indole hybrid in the structure possessed IC_{50} values of 0.03, 0.17 and 0.06 μM, respectively, against *Trypanosoma brucei brucei* (Fig. 2.117).

Pizzo et al. [243] synthesized 2-hydrazolyl-4-thiazolidinones as potential antiparasitic agents against *Trypanosoma cruzi*. The results indicated that compounds (**313**), (**314**) and (**315**) showed cruzipain inhibition at 75%, 65% and 71%, respectively, at the concentration of 100 μM (Fig. 2.118).

A novel class of 5-pyrazoline substituted 4-thiazolidinones was synthesized by Havrylyuk et al. [244], and evaluation of antitrypanosomal activity was carried out against *Trypanosoma brucei brucei* (Tbb) and *Trypanosoma brucei gambience* (Tbg). Compounds (**316**), (**317**) and (**318**) were found moderately active against both parasites with IC_{50} values in the range of 5.43–13.87 μM and 2.53–6.66 μM, respectively (Fig. 2.119).

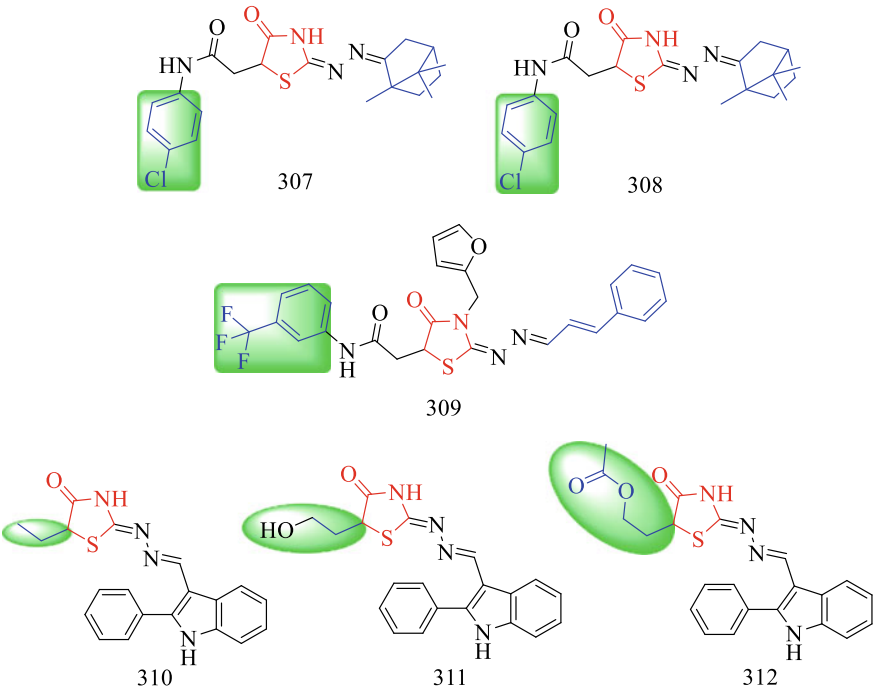


Fig. 2.117 Antitrypanosomal agents based on thiazolidinone hybrids

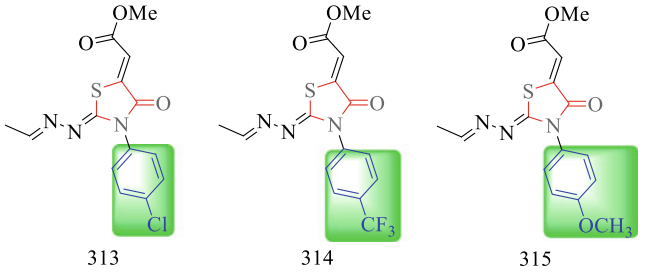


Fig. 2.118 2-hydrazolyl-4-thiazolidinones as potential antiparasitic agents against *Trypanosoma cruzi*

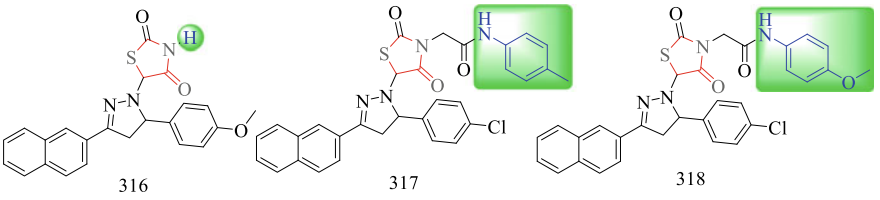


Fig. 2.119 5-pyrazoline substituted 4-thiazolidinones as potential antiparasitic agents

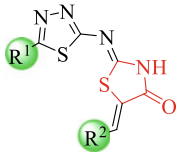
2.3.10 Miscellaneous Activity

2.3.10.1 Antihepatitic Activity

Inflammation of liver tissue known as hepatitis is caused mainly by *hepatovirus* A, B, C and D, and E. Hepatitis was both symptomatic and asymptomatic. Symptomatic hepatitis generally develops symptoms like jaundice, poor appetite, tiredness, diarrhea, vomiting and abdominal pain. Acute hepatitis was treated within six months, but chronic hepatitis lasts longer and may cause cirrhosis, liver cancer and liver failure. In 2019, chronic hepatitis B virus infection occurred in 296 million people and chronic hepatitis C virus infection occurred in 58 million people [245]. Each year 1.5 million new cases of each virus are found globally. Thiazolidinone derivatives that have antihepatitic activity were discussed here.

Çakır et al. [246] synthesized novel 4-thiazolidinones derivatives as non-nucleoside inhibitors of hepatitis C virus. The derivatives were screened for anti-HCV activity. The derivatives (**319**) to (**330**) were found to have IC_{50} values in the range of 25.3–54.1 μM. The arylidene derivative (**322**) was most potent with an IC_{50} value of 25.3 μM (Fig. 2.120).

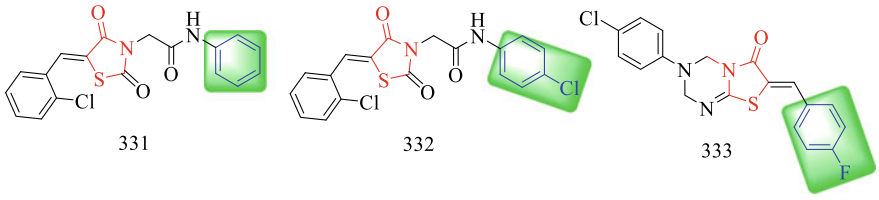
Hassan et al. [247] synthesized novel thiazolidinone and thiazolotriazine derivatives as potential NS5B polymerase inhibitors and studied for anti-hepatitis-C virus activity. The most active compounds (**331**), (**332**) and (**333**) possessed HCV antiviral activity with EC_{50} values of 3.80, 6.47 and 6.58 μM, respectively (Fig. 2.121).



319-330

Where
R^1 and R^2 = 319, R^1= 3-Pyridyl, R^2 = 3-Fluorophenyl,
320, R^1= 2-Fluorophenyl, R^2 = 3-Fluorophenyl,
321, R^1= 3-Fluorophenyl, R^2 = 3-Fluorophenyl,
322, R^1= 2-Chloro-6-fluorophenyl, R^2 = 3-Fluorophenyl,
323, R^1= 2,6-Dichlorophenyl, R^2 = 3-Fluorophenyl,
324, R^1= 3-Pyridyl, R^2 = 2,6-Dichlorophenyl,
325, R^1= 2-Fluorophenyl, R^2 = 2,6-Dichlorophenyl,
326, R^1= 3-Fluorophenyl, R^2 = 2,6-Dichlorophenyl,
327, R^1= 2-Chlorophenyl, R^2 = 2,6-Dichlorophenyl,
328, R^1= 2-Chloro-6-fluorophenyl, R^2 = 2,6-Dichlorophenyl,
329, R^1= 2,4-Dichlorophenyl, R^2 = 2,6-Dichlorophenyl,
330, R^1= 2,6-Dichlorophenyl, R^2 = 2,6-Dichlorophenyl

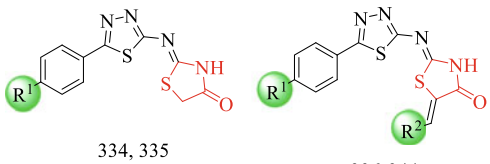
Fig. 2.120 4-thiazolidinones derivatives as non-nucleoside inhibitors of hepatitis C virus



331 332 333

Fig. 2.121 Thiazolidinone and thiazolotriazine derivatives and its potential anti-hepatitis-C virus activity

Küçükgüzel et al. [248] synthesized novel 2-heteroarylimino-5-arylidene-4-thiazolidinone derivatives as potential HCV NS5B polymerase inhibitors. Among the derivatives, eleven compounds (**334**) to (**344**) were found to have HCV NS5B inhibition with IC_{50} values in the range of 19.8–64.9 μM. Compound (**344**) was the most active among the series with an IC_{50} value of 5.6 μM (Fig. 2.122).



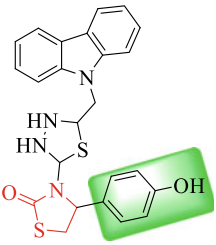
334, 335

Where
R^1= F (334),
R^1= Cl (335)

336-344

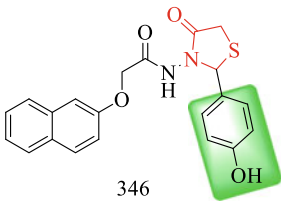
Where
R^1= F, R^2 = 2-Fluorophenyl (336),
R^1= F, R^2 = 3-Fluorophenyl (337),
R^1= F, R^2 = 2-Chlorophenyl (338),
R^1= F, R^2 = 2,6-Dichlorophenyl (339),
R^1= Cl, R^2 = 2-Fluorophenyl (340),
R^1= Cl, R^2 = 3-Fluorophenyl (341),
R^1= Cl, R^2 = 2-Chloro-6-fluorophenyl (342),
R^1= Cl, R^2 = 2-Chlorophenyl (343),
R^1= Cl, R^2 = 2,6-Dichlorophenyl (344)

Fig. 2.122 2-heteroarylimino-5-arylidene-4-thiazolidinone derivatives as potential HCV NS5B polymerase inhibitors



345

Fig. 2.123 4-thiazolidinone-carbazole derivatives with antipsychotic and anticonvulsant activities



346

Fig. 2.124 Naphthalene 4-thiazolidinone scaffolds and evaluated antidepressant activity

2.3.10.2 Antidepressant Activity

Kaur et al. [249] have prepared a novel series of 4-thiazolidinone-carbazole derivatives and screened their antipsychotic and anticonvulsant activities. In this study, 4-thiazolidinone heterocycle derivatives have potent antipsychotic and anticonvulsant properties. Among these, compound (**345**) exhibits a very beneficial interaction with psychotic illnesses, where it showed a favorable response to stereotyped behavior brought on by amphetamine (Fig. 2.123).

Dhar et al. [250] synthesized 4-thiazolidinone scaffolds and evaluated their antidepressant activity through a forced swim test (**FST**). The effectiveness of antidepressants is typically assessed using this test. When compared to imipramine, which had an immobility time of 74.6 s, the results demonstrated that compound (**346**) had a superior antidepressant effect with a duration of 88.8 s (Fig. 2.124).

2.3.10.3 Anti-Alzheimer Activity

Kumar et al. [251] have prepared a novel series of 4-thiazolidinone motifs and screened for their anti-Alzheimer activity. While comparing the BACE1 inhibitory potency of some of the produced analogs to that of the common donepezil drugs, compound (**347**) showed the most potent BACE1 inhibitory action. The binding affinity of TBT11 was found to be −10.4 kcal/mol (Fig. 2.125).

Sadashiva et al. [252] synthesized novel derivatives of 4-thiazolidinone containing morpholine moieties as muscarinic receptor 1 agonists in Alzheimer's dementia models. To determine their suitability for treating dementia, the synthesized compounds went through in vivo pharmacological evaluation of memory and

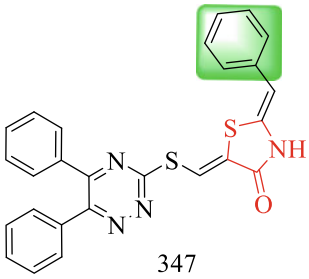


Fig. 2.125 1,2,4-triazine based 4-thiazolidinone motifs with anti-Alzheimer activity

learning in male Wistar rats (rodent memory evaluation and plusmaze studies) and in vitro muscarinic receptor binding studies using male Wistar rat brain membrane homogenate. Among all the synthesized compounds, four derivatives (**348**), (**349**), (**350**) and (**351**) exhibited increased efficacy and affinities for the M1 receptor (Fig. 2.126).

Using donepezil as the standard drug through an Ellman's method spectrophotometer, Aggarwal et al. [253] synthesized 4-thiazolidinone containing 1,3,4-thiadiazole derivatives and studied the in vitro acetylcholinesterase inhibitory efficacy of these synthesized compounds. Compounds **(352)** and **(353)**, out of all the synthesized compounds, are potent inhibitors of the AChE enzyme (Fig. 2.127).

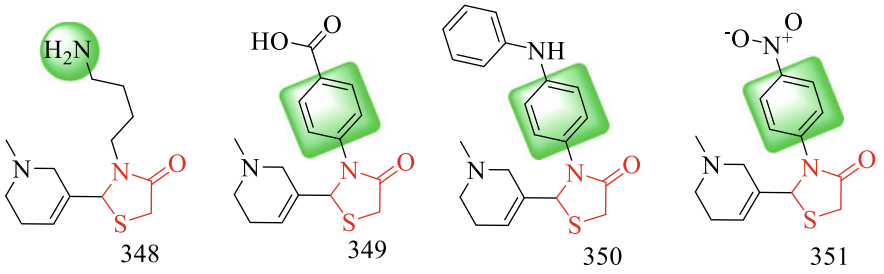


Fig. 2.126 4-thiazolidinone containing morpholine with anti-Alzheimer activity

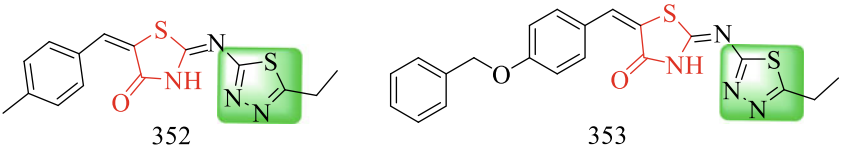
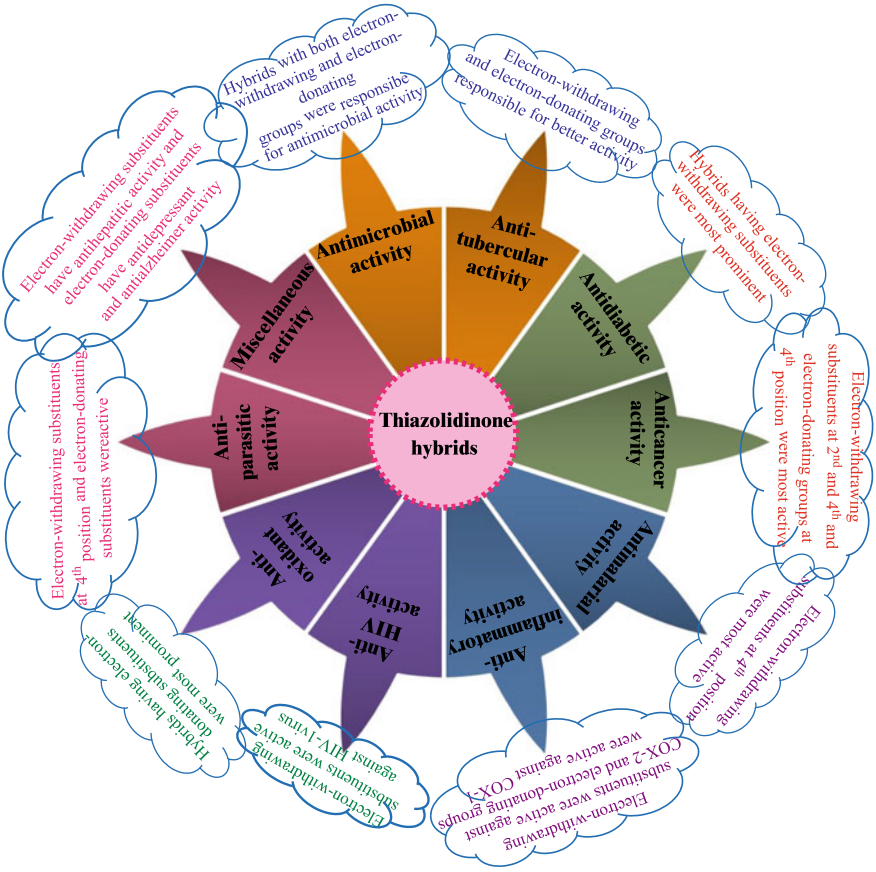


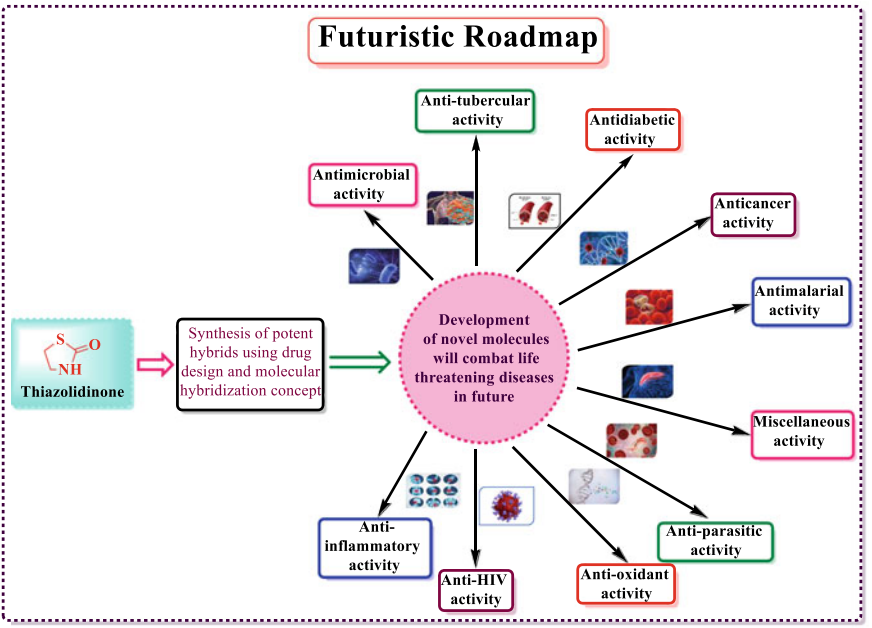
Fig. 2.127 4-thiazolidinones containing 1,3,4-thiadiazole derivatives having acetylcholinesterase inhibitory efficacy

2.4 Conclusion

Based on the above-mentioned studies we can conclude that thiazolidinone is an active pharmacophore against various microbial species. The combination of thiazolidinone moiety with other heterocyclic rings and phenyl rings containing different electron-withdrawing and electron-donating groups showed excellent activity against various diseases.



Futuristic Roadmap



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Chapter 3
Synthesis and Biological Evaluation of Thiazoline, Thiophene and Thiazole Scaffolds

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3.1 Introduction

The synthesis and biological study of S-heterocycles, such as thiazoline, thiophene and thiazole scaffolds, have garnered significant care because of their versatile possessions and possible uses in medicinal chemistry. These sulfur-containing heterocycles exhibition an extensive variety of biological activities, creation them crucial targets for drug finding. In this article, we delve into the synthesis strategies and evaluations of these intriguing compounds.

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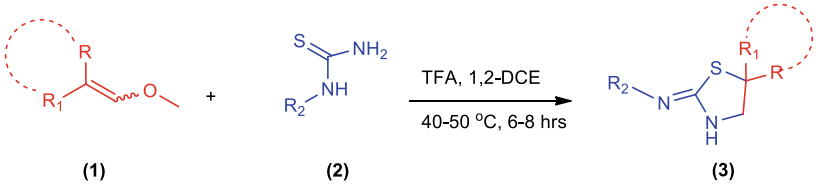
3.2 Thiazoline Derivatives

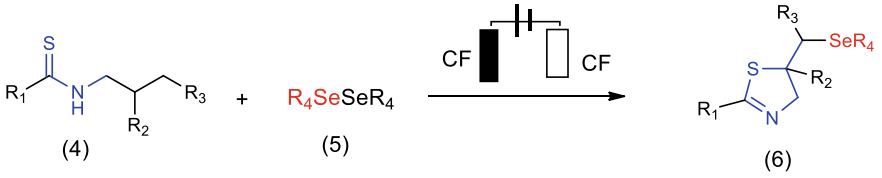
Jena et al. informed synthesis of substituted thiazoline (3) through condensation of different enol ether derivatives (1) with substituted thiourea (2) in presence of trifluoracetic acid (TFA) under 1,2-DCE solvent at 40–50 °C temperature to variable time in between 6 and 8 h [1]. Authors have monitored various catalysts and solvents to varied temperature range; also it was observed excellent product yields to TFA catalyst and 1,2-DCE (Scheme 3.1).

Chao et al. studied the synthesis selenium-containing 2-thiazolines (6) via electrochemical cyclization of diselenides (5) with thioamide (4) in presence of $LiClO_4$ and acetonitrile solvent. Equipped flask attached to both carbons felt anode and cathode with continuous existing flow at room temperature. It is greenery synthetic technique [2] (Scheme 3.2).

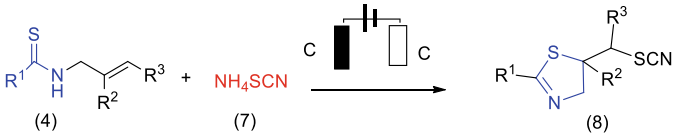
Zhang et al. have stated synthesis of thiocyanato substituted thiazoline (8) from electrochemically regioselective thiocyanothiocyclization (7) of *N*-allylthioamides (4). Such reaction was carried out without catalyst preservative and oxidant-free circumstances below without flexible current power at room temperature [3] (Scheme 3.3).



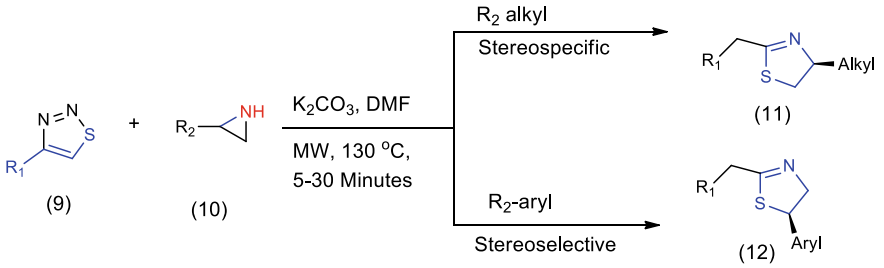
Scheme 3.1 Synthesis of thiazoline derivatives via condensation substituted thiourea and various substituted enol ethers



Scheme 3.2 Synthesis of electrochemical selenylation thiazoline derivatives



Scheme 3.3 Synthesis of thiocyanato substituted thiazoline



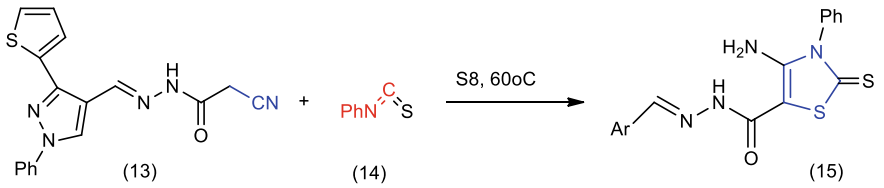
Scheme 3.4 Synthesis of stereospecific 4-alkylthiazolidenes and stereoselective 5-arylthiazolidenes

Wu et al. stated synthesis of stereospecific 4-alkylthiazolidenes (11) via ring expansion of 2-alkylaziridines (10) through intramolecular substitution. And stereoselective 5-arylthiazolidenes (12) via tandem ring cleavage of 4-substituted 1,2,3-thiazoles (9) under basic condition. Reactions were supported out in occurrence of K_2CO_3 in microwave at 130 °C temperature, 5–30 min using DMF solvent [4] (Scheme 3.4).

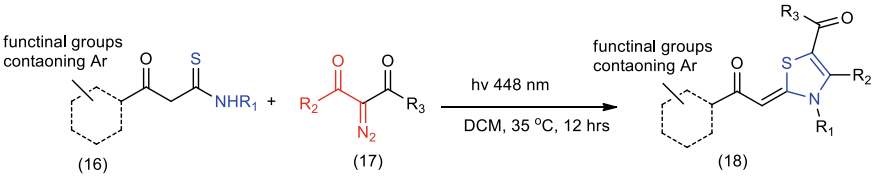
El-Helw et al. have prepared 4-amino-*N*-(argiomethylene)-3-phenyl-2-thioxo-2,3-dihydrothiazole-5-carbohydrazide (15) through continuous stirring of reaction mixture (nitrile derivatives (13), phenyl isothiocynate (14) and elemental sulfur) at 60 °C heat for 2 h. Reaction combination was filtered; residues was collected. Recrystallization by fractionation technique in ethanol/dioxane (1:1) afforded insoluble compound again recrystallized from dioxane, to produce compound (15) [5] (Scheme 3.5).

Prepared compound (15) displayed in vitro anti-tumor action in contradiction of two dissimilar humanoid tumor cell lines counting breast *adenovarcinoma* (MCF-7) (23.53) and (*hepatocellular liver carcinoma* (HepG2) (21.65). The standard doxorubicin showed 4.17 for MCF7 cell line and 4.50 for HepG2 cell line. Synthesized thiazoline derivatives displayed excellent anti-tumor activity in contradiction of both cell lines.

Ansari et al. studied synthesis of substituted thiazolines (18) from β-ketothioamines (16) and α-diazo 1,3-diketones (17) using observable bright under moderate temperature in open air condition. This synthesis was carried out from



Scheme 3.5 Synthesis of (*E*)-4-amino-*N*-(argiomethylene)-3-phenyl-2-thioxo-2,3-dihydrothiazole-5-carbohydrazide



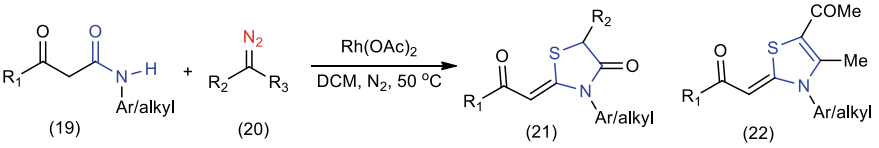
Scheme 3.6 Synthesis of substituted thiazoline from β-ketothioamines and α-diazo 1,3-diketones

α-diazo 1,3-diketones (electrophilic carbenes) (17) through little vigor (448 nm) and connection with nucleophilic β-ketothioamines (16) to provide product (18). Such synthesis has been proved ecofriendly [6] (Schemes 4.6, 3.6).

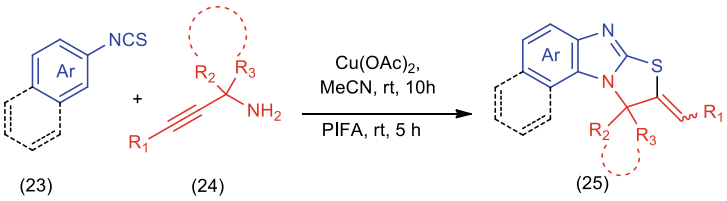
In present study, synthesis of highly functionalized thiazoline (22) and thiazolidine-4-ones (21) via one-pot multicomponent by Ansari and co-workers. Such molecule prepared from Rhodium(II) acetate catalyzed connection of substituted β-ketothioamide (19) through diazo (20) derivatives through mild reaction conditions. Multifunctionalization of diazo compounds becomes through S-alkylation, further intramolecular N-cyclization at normal temperature [7] (Scheme 3.7).

The research conducted by Wang and colleagues, studied synthesis of benzimidazo [2,1-b]thiazoline byproducts (25). Compound (25) has been discovered via cyclization oxidative coupling strategy under room temperature in presence of Cu (II) catalyst, benzimidazo [2,1-b]thiazoline scaffold (25) formed from aryl isothiocyanate (23) treated with propargylic amine (24) in attendance of $Cu(OAc)_2$ and PIFA under rt. (Scheme 3.8).

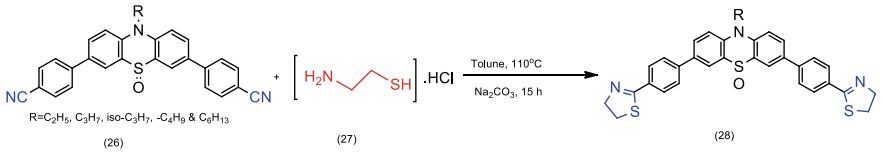
Researchers studied, Choudhary and co-workers have been developed novel method for successfully synthesized compound (28) based accepter contributor acceptor type of pull push molecule. These molecules were chromogenic sensing



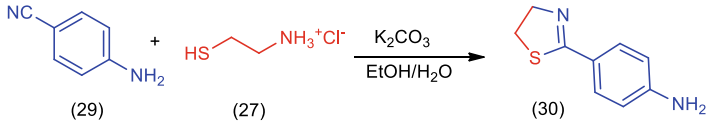
Scheme 3.7 Synthesis of highly functionalized thiazoline and thiazolidine-4-ones



Scheme 3.8 Synthesis of benzimidazo[2,1-b]thiazoline derivatives



Scheme 3.9 Synthesis of 3,7-bis(4-(4,5-dihydrothiazol-2-)phenyl)-10-alkyl-10*H*-phenothiazine-5-oxide



Scheme 3.10 Synthesis of *N*-[4-(thiazolin-2-yl)-phenyl]-amides

reply with TFA and HCl. Compound (28) prepared by refluxing of 4,4′-(5-oxido-10*H*-phenothiazine-3,7-dil)dibezonitrile (26) and cysteamine hydrochloride (27) in presence of Na_2CO_3 in toluene solvent. All prepared compounds showed good to excellent yield [8] (Scheme 3.9).

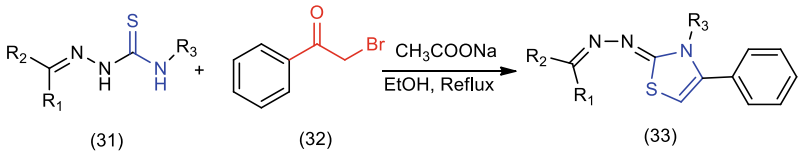
Fuentes-Gutierrez and colleagues have been efficiently synthesis of compound (30) from condensation of 4-amino benzonitrile (29) and cysteamine hydrochloride (27) in presence of K_2CO_3 under EtOH: H_2O (1:1) solvent [9] (Scheme 3.10).

Synthesized product (30) displayed excellent activity of *Quorum-sensing* inhibitors.

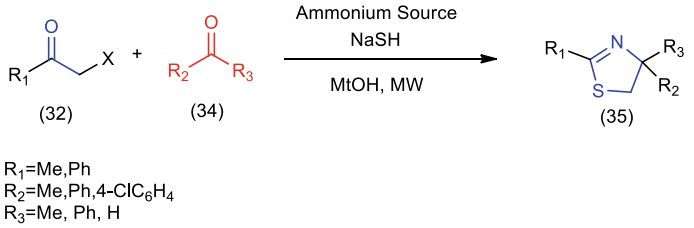
Synthesis of substituted hydrazonothiazoline (33) by Shehzad and co-workers, compound (33) prepared from cyclization of thiosemicarbazones (31) with phenacyl bromide (32) in attendance of sodium acetate using EtOH under reflux at 6–10 h. The product of yield was excellent [10] (Scheme 3.11).

The substituted thiazoline (33) is dynamic pharmacophore of this sequence that interrelate with the energetic side of enzyme of urease. Alkyl substituted (R_1, R_2 and R_3) favorably underwrite in such action. The high molecular groups at R_3 might drop their action because of crowding interferences. The interactive suitable or not interactive suitable drugs sites confirm by docking study.

Gordillo-Cruz et al. have published the green synthesis of compounds (35) through a singer reaction. Compounds (35) prepared from handling of various aldehyde/



Scheme 3.11 Synthesis of substituted hydrazonothiazoline



Scheme 3.12 Synthesis of 2,4-disubstituted thiazolines

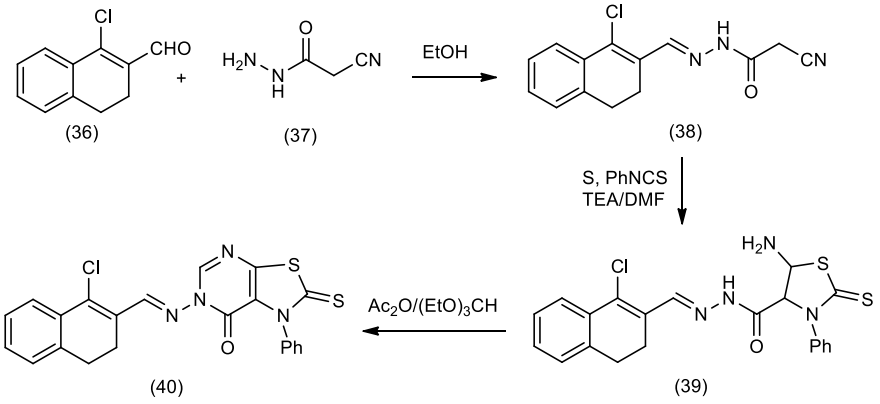
ketones and 1-Mercaptopropan-2-one, in and ammonia under MW irradiation. Most of reactions were carried out on room temperature under MW [11] (Scheme 3.12).

Bondock et al. have been studied, synthesis of intermediate Product (38) formed from condensation of 1-chloro-3,4-dihydronapthalene-2-carbaldehyde (36) in ethanol. Intermediate (38) refluxed with sulfur, thriethylamine, phenyl isothiacyanate at ethanol solvent. Finally, intermediate (39) heated under the reflux with mixture of acetic anhydride and thriethylorthoformate for 3 h, product (40) cool and wash with ethanol to scaffold the compound (40) [12] (Scheme 3.13).

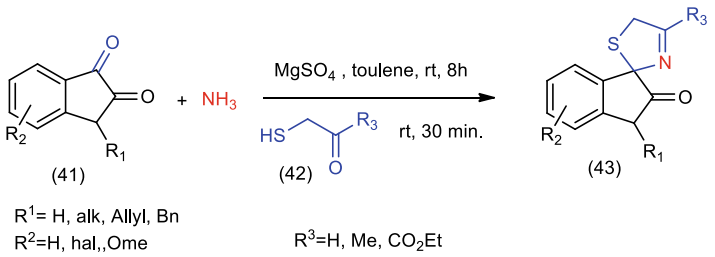
The product (40) displayed excellent anti-bacterial (Gram-positive—*B. subtilis* and *B. megaterium*) (Gram-negative stain *E. coli*) and anti-fungal activities against *A. niger and A. oryae.*

The research has carried by Rainoldi and co-workers, one-pot Asinger type, multicomponent synthesis of spirooxindole-fused 3-thiazoline derivatives (43) from treatment of isatin derivatives (41) with 1-mercaptopropan-2-one (42) presence of $MgSO_4$ in toluene at r.t. [13] (Scheme 3.14).

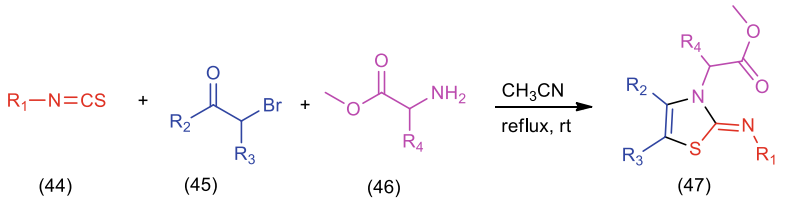
Preparation of iminothiazoline derivatives (47) without basic conditions by Barve and colleagues, 2-iminothiazoline derivatives (47) synthesized via multicomponent



Scheme 3.13 Synthesis of 6-{[(1-chloro-3,4-dihydronapthalene-2-yl)-methylene]amino}-1-phenyl-2-thioxo-1,6-dihydro[1,3]thiazolo[5,4-d]pyrimidin-7(2H)-one



Scheme 3.14 Synthesis of spirooxindole-fused 3-thiazoline derivatives



Scheme 3.15 Synthesis of 2-iminothiazoline derivatives

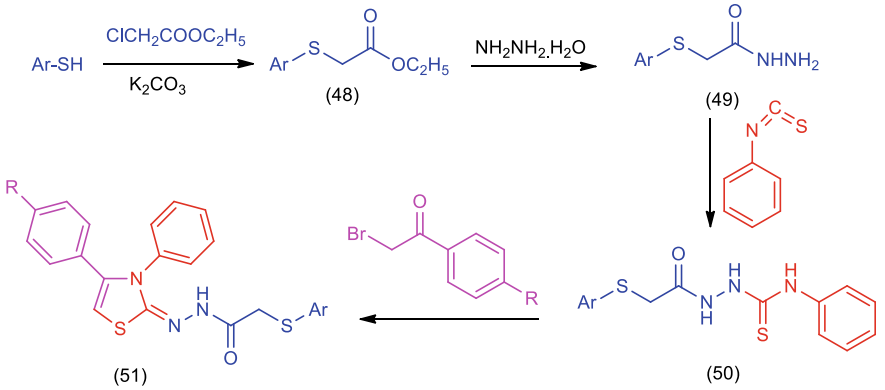
reaction using isothiocyanate (44), α-bromoketone (45) and chiral amino esters (46), stirred at r. t. in acetonitrile [14] (Scheme 3.15).

Altintop and co-workers have studied the efficient synthesis compound (51) with its monitored anti-microbials and anti-cancer (NIH/3T3 cell) activities. Such compound prepared by multistep reactions, in first, synthesis of substituted ethyl 2-[(aryl)thio]acetate (48) prepared from condensation of thiols with ethyl chloroacetate in attendance of K_2CO_3. The condensation of substituted ester with hydrazine hydrate to cheap compound (49), 1-(arylthioacetyl)-4-phenyl thiosemicarbazides (50) obtained from treatment of hydrazides with substituted phenyl isothiocyanates. In last step, cyclization of thiosemicarbazide and 2-bromoacetophenone to afforded target compound (51) [15] (Scheme 3.16).

Anticancer activity done by given two cell like NIH/3T3 and C6, most of compound (51) derivatives displayed anticancer activity using NIH/3T3 cell and C6 cell. All derivatives (51) showed excellent antimicrobial activity.

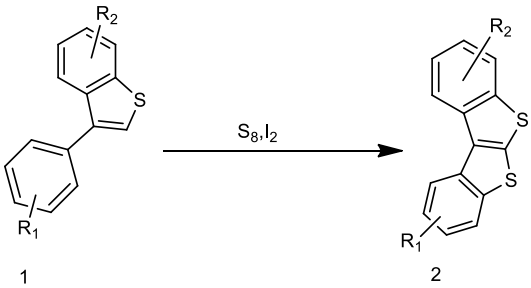
3.3 Thiophene

Kazuki Ito and co-worker [16] reported compound **(2)** by reaction of compound **(1)** and elemental sulfur and iodine. The advantages of this protocol are no side product in the present reaction, procurement BTBTs in great produce and great cleanliness (Scheme 3.17).



Scheme 3.16 Synthesis of Substituted *N′*-(3,4-diarylthiazol-2(3H)-ylidene)-2-(arylthiol)acetohydrazides

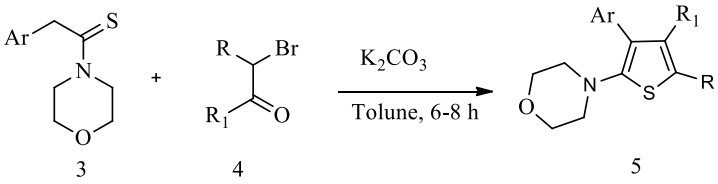
Scheme 3.17 Synthesis of [1]Benzothieno[2,3-b][1]benzothiophenes from 3-Arylbenzo[b]thiophenes through Iodine-Mediated sulphur Insertion Reaction



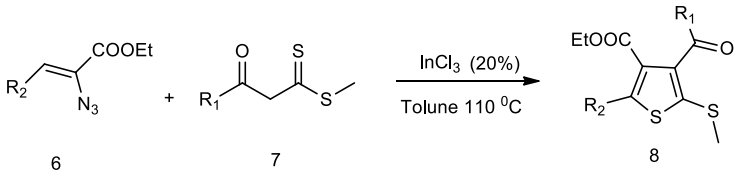
Moghaddam and Bionee [17] reported synthesis of an effective single step method for the synthesized extremely relieved derivation of substituted thiophenes **(5)** by using thiomorpholides and α-haloketones **(4)** (Scheme 3.18).

Zhang et al. [18] reported efficient preparation of thiophene scaffold **(8)** by β-oxodithioeters (6) and vinyl azydes (7) cyclized. Such method is extremely well-organized and obtained moderate to good yields (Scheme 3.19).

Sowmya et al. [19] described the novel the synthesis of polymers based on thiophene-containing bis-chalcone, compound (PTCA) (11), was achieved through



Scheme 3.18 Synthesis of highly substituted thiophenes from thiomorpholides and α-haloketones has been developed



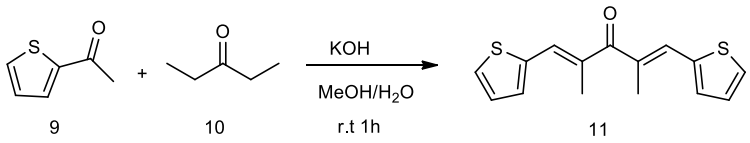
Scheme 3.19 Synthesis of thiophene derivatives through $InCl_3$-catalyzed cyclization of β-oxodithioesters with vinyl azides

oxidative coupling polymerization using $FeCl_3$. Confirmation of polymer formation was conducted through FT-IR and UV-DRS analyses. A kinetic study revealed that the adsorption of iodine onto the polymers followed a kinetic reaction of pseudo second order, exhibiting a high coefficient of correlations ($R_2 > 0.99$), indicative of the chemisorptive nature of adsorption. Remarkably, the polymers demonstrated efficient recyclability, retaining their iodine uptake capacity even after five cycles without a significant decline. This investigation presents an avenue for designing similar long-chain compounds with diverse heteroatomic functional groups (see Scheme 3.20).

Prim and Kirsch [20] reported simple method to synthesis of 2-alkylthiophenes **(12)** addition by reaction 1,4 diketone followed by subsequent S-alkylation of a carbanion to carbon disulfide (Scheme 3.21).

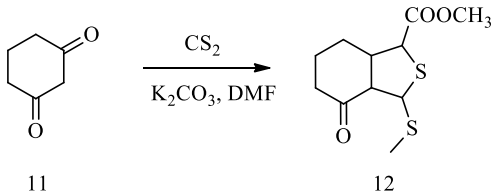
Wynberg and Kooreman [21] have been synthesized thiophene derivative **(14)** by two successive condensations (aldol) among a diethy1 thiodiacetates and 1,2-dicarbony derivatives (13). The yields were better to outstanding; the procedure was fast (Scheme 3.22).

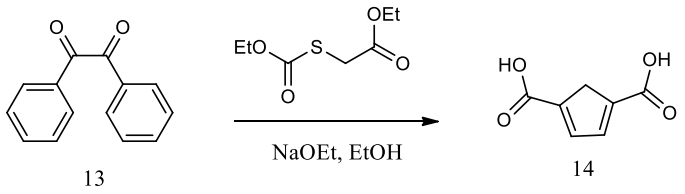
Balakit et al. [22] reported the new thiophenes scaffold (16) by reaction of aromatic amine and 3-bromo-4-methylcyclopenta-1,3-dienecarbaldehyde (15) under the microwave condition. This reaction was carried out using 5 ml MeOH. All the



Scheme 3.20 Design and synthesis of thiophene containing bis-chalcone-based mesoporous polymers for volatile iodine capture

Scheme 3.21 Synthesis of 2-alkylthiophenes





Scheme 3.22 Synthesized thiophene derivative by two consecutive aldol condensations

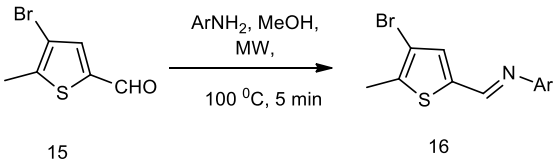
synthesized compound was established through FT-IR, ^{13}CNMR, ^{1}HNMR and mass characterization techniques (Scheme 3.23).

Mancuso et al. [23] have been devolved the efficient Biodegradable alkali free prepared derivatives (18) by iodoheterocyclization of compound (17) in under solvent Emim $EtSO_4$. The chief benefit of this method is that greater yields, littler reaction times and a simple investigational technique (Scheme 3.24).

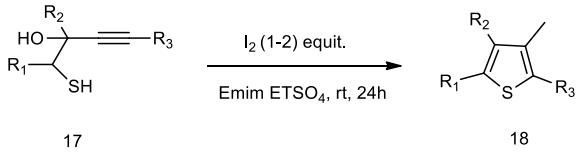
A proficient and high-yielding convention for Synthesis of compound (**21**) by iodocyclization of compound (**19**) further which was achieved by oxidation of 20 [24]. Synthesized compounds have been gained in enough to outstanding yields. The yields were good to excellent, less reaction time (Scheme 3.25).

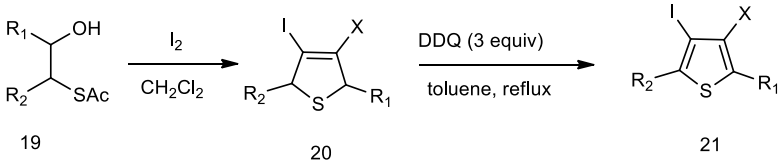
Yang et al. reported that [25] reported that 3,4-diiodothiophenes (**23**) have been synthesis by iodocyclization compound (**24**) by nitro methane, for 5 h at room temperature (Scheme 3.26).

Scheme 3.23 Synthesis of new Thiophene derivatives



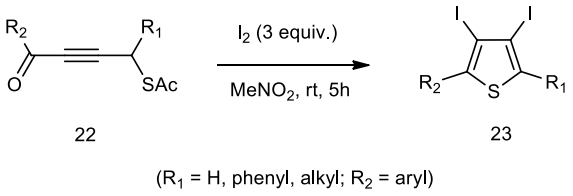
Scheme 3.24 Recyclable and base-free synthesis of thiophene derivative





Scheme 3.25 Synthesis of 3,4-dihalodihydrothiophenes

Scheme 3.26 Synthesis of 3,4-diiodothiophenes by iodocyclization of S-4-oxobut-2-ynylethanethioates



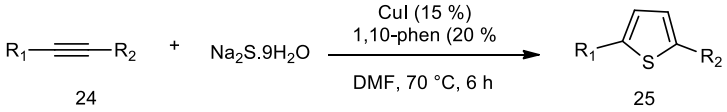
22 23

(R_1 = H, phenyl, alkyl; R_2 = aryl)

Jiang et al. [26] and co-worker developed new approach to synthesized 2,5-disubstituted thiophenes (24). Synthesized compound was prepared from starting material (sodium sulfite (5 equivalent and 1-bromoalkyls in presence of cupper iodine (15 mol %) with 1,10-phenanthroline 20 mol % using DMF for (Scheme 3.27).

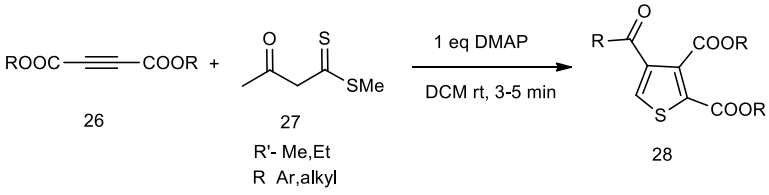
Nandi et al. [27] reported efficient protocol for synthesis of Thiophene (28) by cyclocondensation 2,3-dicarboalkoxy-4-aroyl under (DMAP) (26) using dichloromethane solvent for 4 to 5 min at room temperature. Such protocol authorization a spotless and unapproachable and synthetically. Advantageous of this protocol was less time and high yield (Scheme 3.28).

Gabriele et al. [28] reported the efficient synthesis of thiophenes derivative by cyclization of compound (30) by using catalyst PdI_2 and KI under solvent MeOH. They used the $BMIMBF_4$ as solvent allows the reprocessing of the catalyst (Scheme 3.29).



24 25

Scheme 3.27 Synthesis of thiophenes 25 from 1-bromoalkynes 24 and Na_2S by CuI

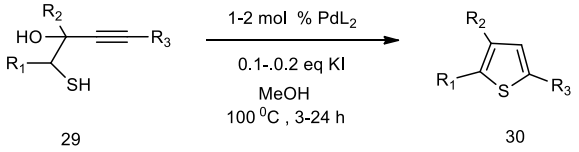


26 27 28

R'- Me,Et
R Ar,alkyl

Scheme 3.28 Synthesis of one-pot two-component [3 + 2] cycloaddition/annulation protocol for the synthesis of highly functionalized thiophene derivatives

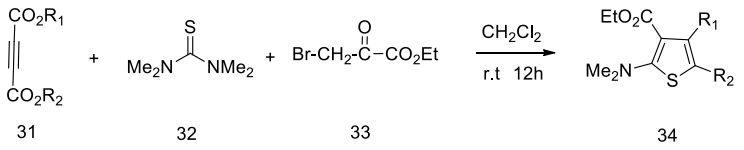
Scheme 3.29 Recyclable and base-free synthesis of thiophene derivative



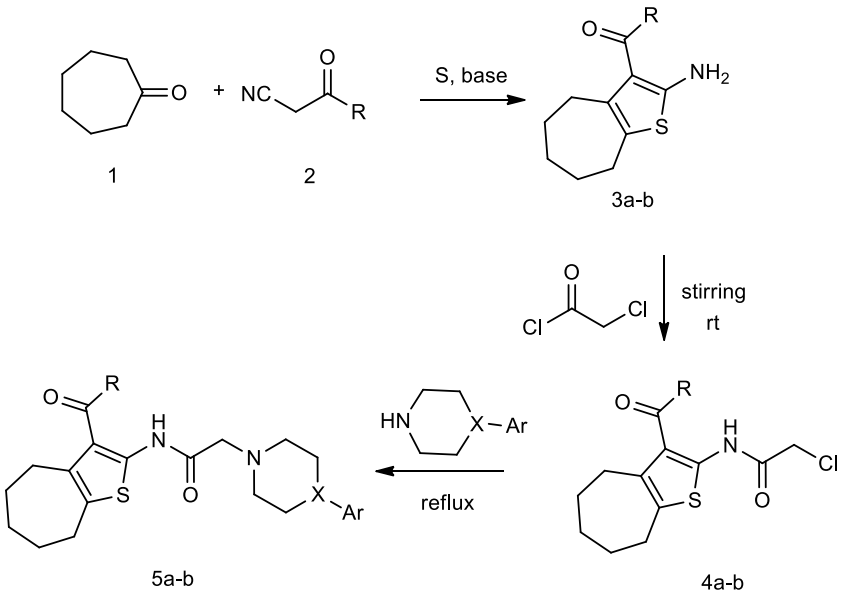
29 30

Yavari et al. [29] A have developed protocol for synthesis of preparation of derivatives (35) using multicomponent way. This synthesis involves reacting acetylenic esters (compound 31), ethyl bromopyruvate (compound 32) and compound (33) in CH_2Cl_2 solvent at room temperature for 12 h. The described protocol exhibits distinct advantages, including minimal environmental impact, high yield and a straightforward work-up procedure, as illustrated in Scheme 3.30.

The author Ismail M. M. et al. (Scheme 3.31) stated that a set of novel thiophene derivatives was synthesized through the Gewald protocol. The embarrassment activity against acetylcholinesterase was assessed using Ellman's method, with donepezil serving as a standard reference. Notably, certain compounds demonstrated higher inhibitory potency than the reference compound. Specifically, the compound (IIId) exhibited a 60% inhibition rate, surpassing the 40% reserve observed with donepezil [30].



Scheme 3.30 Multicomponent synthesis of ethyl 2-(2-(dimethylamino)thiophen-3-yl)-2-oxoacetate derivatives



Scheme 3.31 Thiophene derivatives

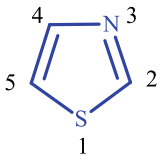
3.4 Thiazole Derivatives

Thaizole, also known as 1,3-thiazole, is a flammable liquid that is perfect to light yellow in color and has a pyridine-like fragrance. It is a 5-membered ring with nitrogen and sulfur as two of the vertices and three carbon atoms as the remaining three. The numbering scheme used to name thiazole derivatives is displayed in Fig. 3.1.

Due to significant therapeutic qualities of little ring, heterocycles with 'N' and 'S' have been studied for a very long time. Thiazole, also known as thiazole (1,2 positions), perfect to the azole family and has an sulfur atom and an atom of nitrogen in positions 1 and 3, respectively. One of the most lengthily investigated heterocycles, the thiazole nucleus theatres a crucial role in many biologically active chemicals [31]. Analgesic, anti-inflammatory, neuroprotective, anticancer, anticonvulsant, antioxidant and anti-HIV properties were among the properties exhibited by thiazoles.

Furthermore, the thiazole scaffold is current in a number of naturally occurring compounds, including penicillin (an antibiotic), bacitracin, epothilone (an anticancer medication) and thiamine (a vitamin B1). Moreover, the thiazole moiety is a crucial constituent of many synthetic commercial drugs available on the market, including the antifungal drug thiabendazole, the antisulfa-drug sulfathiazole, the antisulfa-drug niridazole, the anticancer drug tiazofurin, the anti-ulcer drug famotidine and the non-steroidal anti-inflammatory drug meloxicam, as shown in Fig. 3.2.

Fig. 3.1 1,3 Thiazole



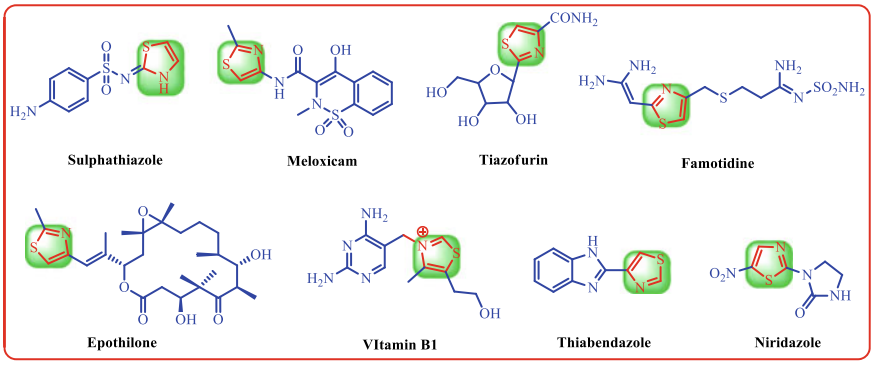


Fig. 3.2 Thiazole moiety containing synthetic commercial drugs available in the market

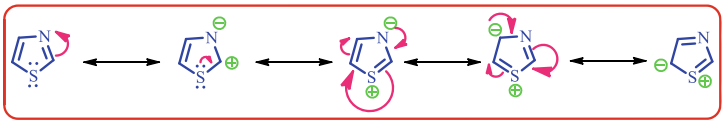


Fig. 3.3 Resonating structure of thiazole

Thiazole exhibits aromaticity through the presence of nitrogen containing electron accepting functional group and sulphur electrodonating functional group. The aromatic character of thiazole arises from non-bonding pair electrons delocalization and originally comes from S atom, ensuring satisfaction of the empty 6π e^- required to meet Huckel's Rules (Fig. 3.3).

Synthetic Approach of Thiazole Derivatives

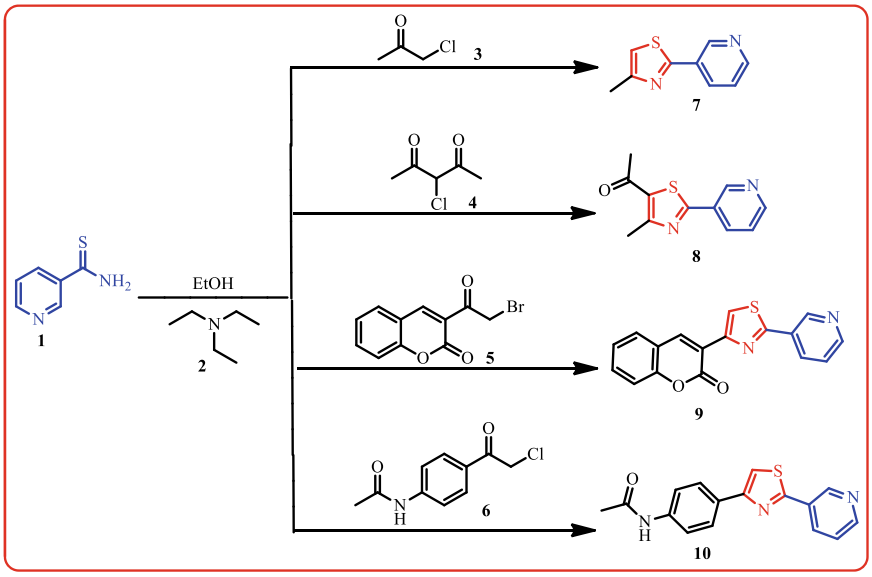
Because of its numerous applications, thiazole derivative research has become a significant area of study over time. The most alluring feature is that a straightforward synthesis process may synthesize the derivatives with a better yield from the preliminary reactant. Due to the special structure and importance of thiazole compounds, a wider range of environments, catalysts and techniques have been used in the process.

Hantzsch Synthesis

Thiazole synthesis via Hantzsch technique, developed in 1887 by a chemist of German of the same name, is the most famous technique for synthesizing thiazoles [32] This technique makes use of the summarizing reaction among nucleophile containing α-haloketones like thiourea, ammonia thio-carbonate and dithiocarbamate compounds [33] Furthermore, it was proposed that the most effective technique for synthesizing thiazole derivatives was Hantzsch thiazole synthesis [34] reaction of Hantzsch for thionicotinamide with 4 various forms-3-choloacetylacetate, α-haloketones-choroacetate, 3-bromoacetylcoumarin and *para*-chloroacetylacetanilide. four thiazole derivatives were produced using this approach using triethylamine as a catalyst. The reaction scaffold 2-(3-pyridyl) thiazole compounds (9–12) (Scheme 3.32).

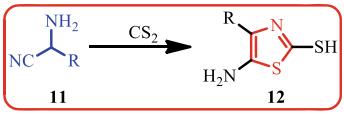
Cook–Heilbron Synthesis

Furthermore, α-aminonitriles or α-aminoamides can also be used to synthesize thiazole rings, with carbon disulfide serving as the reactant. This process, known as Cook–Heilbron synthesis, was exposed by Cook and Heilbron [36] under mild conditions, the Cook–Heilbron method produced 5-aminothiazoles, where substituted at two position due to the mixture of reaction of salt with ammonionitril, thioacids ester, disulfide of carbon/iso-thiocyanates [37]. Scheme 3.33 shows α-aminonitriles (**11**) react with carbon disulfide gives corresponding 5-amino-2-mercaptothiazole (**12**) in excellent yield.



Scheme 3.32 Reaction synthesis of 2-(3-pyridyl) thiazole derivatives [35]

Scheme 3.33 The Cook-Heilbron thiazole synthesis

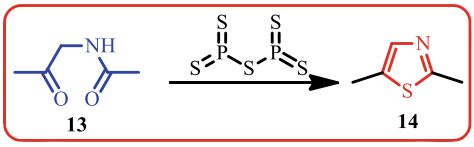


Synthesis of Gabriel

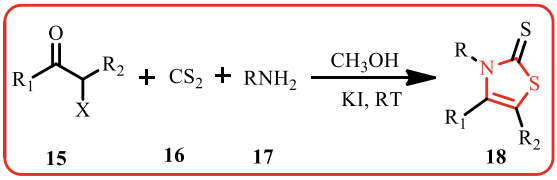
Gabriel route for thiazole derivatives. In this process by reacting acylamino-ketone (**13**) with phosphorus pentasulfide, with the goal of closing the thiazole ring produces 2,5-disubstituted thiazole derivatives (**14**) [38] Kotadiya [39] sponsored this investigation, in which the required molecule was synthesized by heat applying to Acylamino derivatives (phosphorous pentasulfide and *N*-(2-oxopropyl) acetamide) as indicated in Scheme 3.34

Nevertheless, Gabriel preparation, Cook–Heilbron, Cyclization of Hantzsch protocol possess significant disadvantages with their lengthy processes and inadequate yield percentages. As a result, numerous studies have enhanced the approach.

Scheme 3.34 Synthesis of thiazole compound via Gabriel reaction



Scheme 3.35 Synthesis of thiazole derivatives



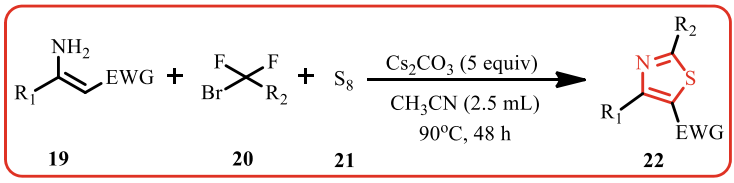
Safaei-Ghomi et al. [40] have developed a straightforward, gentle and practical method for producing 3,4,5-trialkyl-1,3-thiazole-2(3*H*)-thione compounds (**18**) using a single-pot multicomponent involving a α-haloketone (**15**), CS_2 (16) and primary amine (**17**) KI as a catalyst for room temperature (Scheme 3.35).

Production of isothazole and thiazoles, achieved Song et al. [41] by the use of three components: aminoesters (**19**), fluorodibromoiamides/ester (**20**) and sulfur (**21**). Breaking of two carbon-Florine bond, produced the thiazoles (**22**) and isothiazoles in addition to carbon–sulfur, carbon–nitrogen and nitrogen-sulfur bonds, respectively (Scheme 3.36).

Thiazoles (4,5-disubstituted) preparation (**25**) is made possible by base-induced cyclization of methyl arene-hetarenecarbodithioates (**23**) with methylene isocyanide actively (**24**) (ethyl isocyanoacetate, tosylmethyl isocyanide, arylmethyl isocyanides). This synthesis is quick, easy and frequently does not require purification stages (Scheme 3.37) [42].

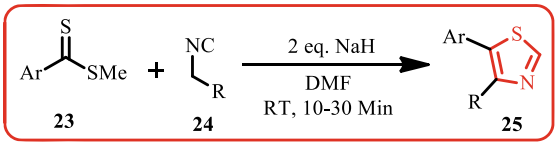
5-Arylthiazoles (**27**) are produced in good yield when triethylamine and phosphorous pentasulfide are treated with *N, N*-diformylaminomethyl (26) and arylketones using chloroform. 5-aryl-1,3-thiazole core of two position have functionalized to produce a 5-aryl-2-arylsulfonyl-1,3-thiazole wide variety in two processes (Scheme 3.38) [43].

A list of thiazoles (**29**) and selenothiazoles was prepared using product (**28**) insolation of chemistry catalyzed by *Ir. Fanetizole*, an anti-inflammatory medication, and a drug fragment containing thiazole this is bind to peptidyl t-RNA hydrolase in *N.*

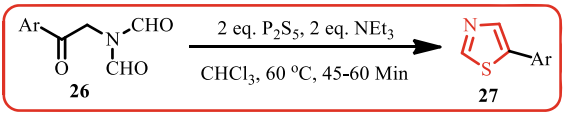


Scheme 3.36 Synthesis of thiazole derivatives

Scheme 3.37 Synthesis of thiazole derivatives



Scheme 3.38 Synthesis of thiazole derivatives

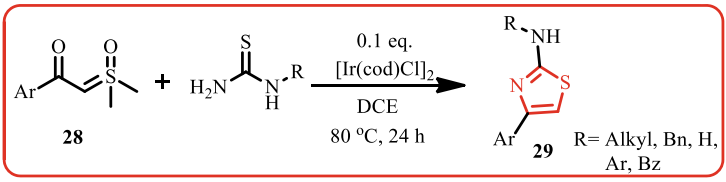


gonorrhoeae bacterial stain were both synthesised using this method (Scheme 3.39) [44].

4-Methylthio-5-acylthiazoles are obtained by cyclizing α-oxodithioesters with tosylmethyl isocyanide using potassium hydroxide while 4-ethoxycarbonyl-5 acyl thiazoles (**32**) are formed by cyclizing α-oxodithioesters (**30**) with Ethylcynoacetate (**31**) using DBU/ethanol (Scheme 3.40) [45].

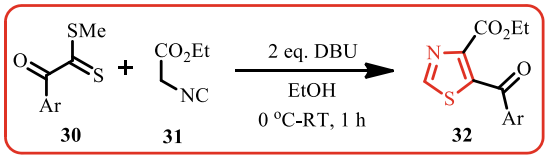
Enaminones (**33**), elemental sulfur (**21**) and cyanamide (**34**) are cyclized in one pot using three components in a cascade fashion to produce 2-amino-5-acylthiazoles (**35**) with good derivatives and tolerance of functional group. Such protocol provides a practical means of obtaining useful and possibly beneficial 2-amino-5-acylthiazole derivatives (Scheme 3.41) [46].

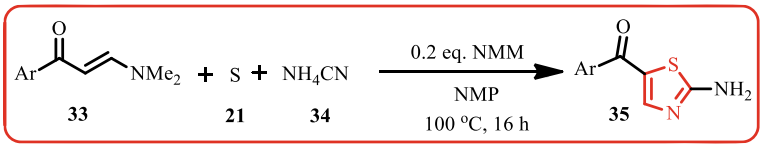
Using simple amines (**36**), aldehydes (**37**) and element sulfur (**21**) as starting materials-(Oxidative cupper catalyzed, carbon SP3 Hydrogen Multiple bond breakage methods synthesize thiazoles (**38**) under molecular oxygen condition) (Scheme 3.42) [47].



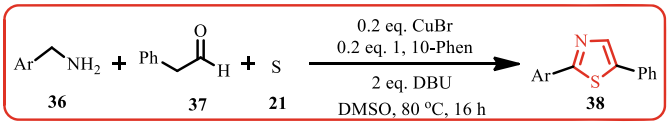
Scheme 3.39 Synthesis of thiazole derivatives

Scheme 3.40 Synthesis of thiazole derivatives



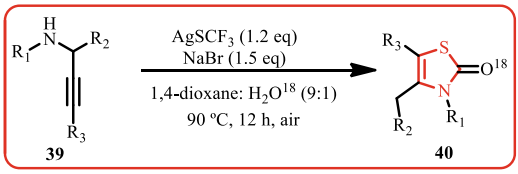


Scheme 3.41 Synthesis of thiazole derivatives



Scheme 3.42 Synthesis of thiazole derivatives

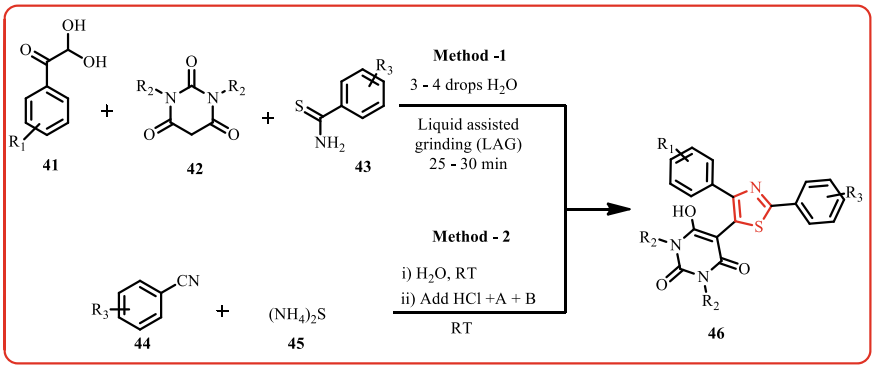
Scheme 3.43 Synthesis of thiazole derivatives



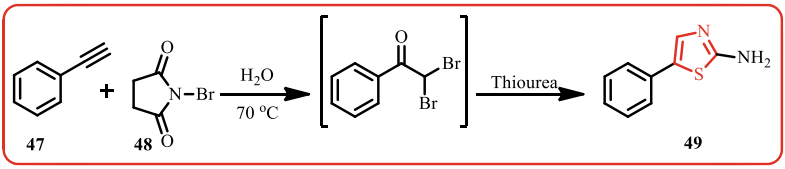
An effective approach for producing 2 and 3 position substituted thiazol 2—(3H)-one (40) by n-propargylamines (39), Silver (I) tribromomethanethiolate in high percent of product have been devised by Behera et al. [48]. The reaction goes through [3,3] *N*-propargylamines undergo – rearrangement of sigma-tropic/ five exo-dig cyclization (Scheme 3.43).

Mahata et al. [49] used widely available starting ingredients to create two catalyst-free procedures to create a series of hybrids barbituric acid linked diphenyl-1,3-thiazoles (**46**). Within 30 min, the treatment of arylglyoxal (**41**), barbituric-acid (**42**), aryl thioamides (**43**) using liquid aided grinding (LAG) and three to four drops of water yields matching tri-substituted moiety barbituric acid with thiazoles. On the other way, aryl nitriles (**44**), ammonium sulfide (**45**), arylglyoxal and barbituric acids in a water medium in water median aryl nitriles (44), ammonium sulfide (45), barbituric acid and arylglyoxal were combined to create a serially two-step single-pot procedure (Scheme 3.44).

Water is a solvent that can be used to develop of greenery chemical route since it is an environmentally acceptable solvent, non-toxic and economically viable.



Scheme 3.44 Synthesis of thiazole derivatives



Scheme 3.45 Synthesis of thiazole derivatives

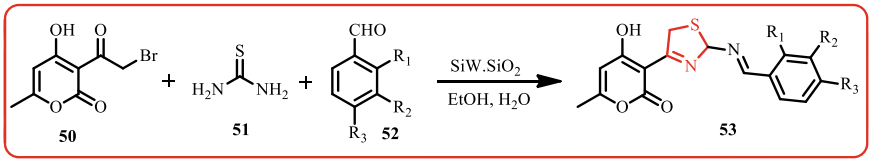
A three-component reaction has been carried out of phenyl acetylene (47), N-bromosuccinimide (48) using thiourea in presence of water as solvent to prepare thiazole derivatives (**49**) with an excellent yield (Scheme 3.45) [50].

A new single flask multicomponent technique for the preparation of substituted Hantzsch thiazole compounds (**53**) to produced, they are environmentally friendly route. Under normal heating or ultrasonic irradiation, silica-supported tungstosilicic acid catalyzed synthesis of 3-(bromoacetyl)-4-hydroxy-6-methyl-2H-pyran-2-one (50) treated with thiourea (51) and benzaldehyde derivatives (52) (Scheme 3.46) [51].

In positions 2 and 5, Sanz-Cervera et al. [52] created a limited library of molecules with thiazole scaffolds and structural variety. When a protected glycine is double-acylated, intermediate α-amido-β-ketoesters (**54**) are produced. These subsequently prepare 1,3 position thiazoles (55) from Lawesson's reagent (Scheme 3.47).

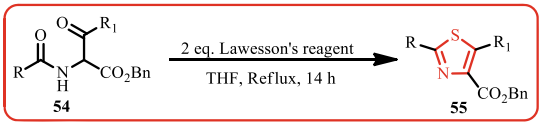
Zhu et al. [53] developed efficient single-pot multicomponent reaction involving α-nitro epoxides (56), KSCN and primary position Amine as an additional method for synthesizing polysubstituted 2-aminothiazoles (**57**). This technique produces good yields and is very efficient (Scheme 3.48).

Chen et al. [54] to produce, Pd (II) acetate catalyzed synthesis of 4 position substituted aminothiazoles via condensation of vinyl azides (58) with KSCN (59), whereas $FeBr_3$ was used to create 5-thioccyano-2-aminothiazoles of 4 position substituted (**60**) (Scheme 3.49).

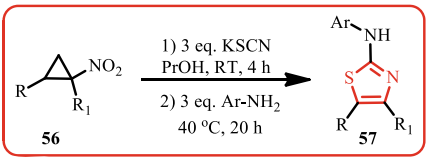


Scheme 3.46 Synthesis of thiazole derivatives

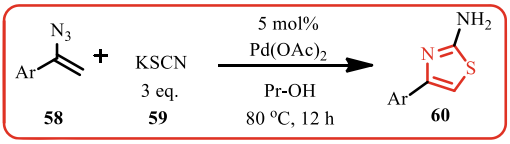
Scheme 3.47 Synthesis of thiazole derivatives



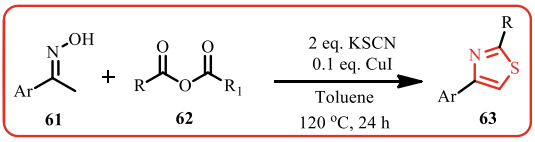
Scheme 3.48 Synthesis of thiazole derivatives

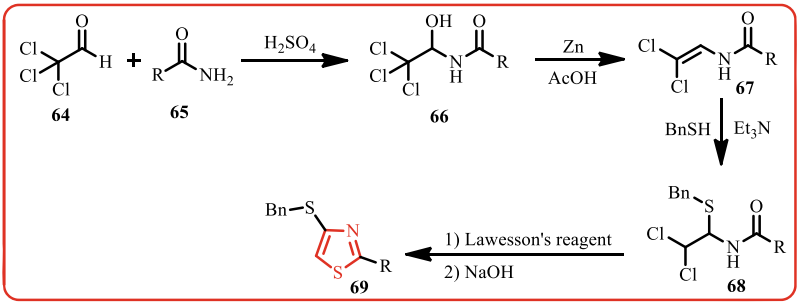


Scheme 3.49 Synthesis of thiazole derivatives



Scheme 3.50 Synthesis of thiazole derivatives





Scheme 3.51 Synthesis of thiazole derivatives

Tanh et al. [55] produced 5-position substituted arylthiazoles (63) from (3 + 1 + 2) condensation between oximes (61), anhydrides (62), KSCN (59) using cupper catalyst (Scheme 3.50).

Demydchuk et al. [56] industrialized a modest technique for making thiazole with 2-alkyl or aryl substituents (**69**), which were previously unavailable. Thiazole that has been synthesised shows great potential as building blocks for high-throughput synthesis of screening chemicals and medicinal chemistry (Scheme 3.51).

3.5 Biological Claim of Thiazole Scoffed

Biological Application of thiazole scoffed are shown below.

3.6 Anticancer Activity

Part of the structure of many biologically active chemical molecules includes thiazole fragments. Many natural compounds, including the secondary metabolites of marine creatures, contain thiazoles. These natural products' biological activities have been assessed and investigated as potential models for the development of novel pharmaceuticals. For instance, biological measurements show that latrunculin A (**70–72**, Fig. 3.4) derivatives suppress prostate tumors and activate HIF-1 in breast tumors [57].

The thiazole derivatives were created and synthesized by Mamidala et al. [58] using a microwave-assisted multicomponent process. All of the synthesized compounds were tested in contradiction of breast cancer cell lines in order to determine them in vitro cytotoxic activities. A compound **73** with strong action vs MDA-MB-231/ATCC cell line was used (Fig. 3.4).

A report on the preparation of phthalimido-bis-1,3-thiazoles (**74**, Fig. 3.4) has been made by Oliveira et al. [59] The cytotoxicity of each synthesised chemical was assessed in contradiction of several tumor cell stains.

Dawood et al. [60] conducted the synthesis of a range of bis-thiazoles, 5 cancer cell stains monitored of cytotoxic effects—2 cell line of breast cancer (MCF-7 and MDA-MB-231), 2 cell ovarian cancer cell stains (A2780 and KF28) and 1-cervical cancer cell line (*HELA*). The results demonstrated significant cytotoxicity against the KF-28 and (HeLa) Cell stain, respectively, 2 derivatives examined (**75**, **76**, Fig. 3.4) shown strong cytotoxic effects with high IC50 values of 0.6 and 6 nm. When combined, the investigated substances showed exceptional cytotoxic effects on the examined cancer cell lines, inducing apoptosis by blocking Pim-1 kinase. As a result, chemicals **75** and **76** merit more in vivo testing in the hopes of creating chemotherapeutic anti-cancer drugs.

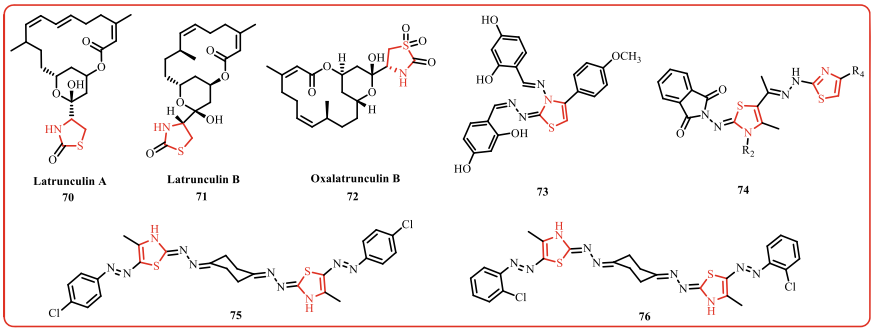


Fig. 3.4 Reported anticancer agents having an active thiazole nucleus

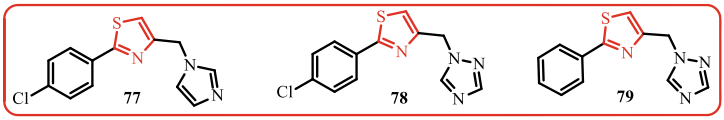
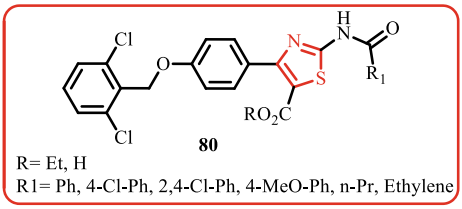


Fig. 3.5 Reported anticonvulsant agents having an active thiazole nucleus

Fig. 3.6 Reported antitubercular agents having an active thiazole nucleus



3.7 Anticonvulsant Activity

When the anticonvulsant activity was assessed in mice using the maximum electroshock (MES) and pentylenetetrazole (PTZ) paradigms, the compounds (**77–79**, Fig. 3.5) showed strong anticonvulsant action [61].

3.8 Antitubercular Activity

Lu and co-workers have been developed thiazole derivatives of ester compounds (**80**, Fig. 3.6), displayed antituberculosis activity using (*M. tubercular* H37Rv and *S. pneumonia*) [62]. The minimum inhibitory attentiveness standards were originating to be between 1.0–61.2 and 0.117–0.131 μM. The compound and an ethyl ester and a 4-Cl phenyl group connected to amide group were determined the active among the synthesized compounds, with a MIC value of 1.0 Mm.

3.9 Anti-inflammatory Activity

The way that organisms react to different stimuli is through inflammation. Many chronic or recurrently treated disorders like psoriasis, asthma and arthritis are related to inflammation. The most commonly used medications for treating provocative diseases are anti-inflammatory activity of non-steroidal medicines (NSAIDs), they are react pain, inflammation and fever, both intensely and chronically.

Though, prolonged scientific use of these drugs is linked to serious side effects, including bleeding and nephrotoxicity [63], renal disease [64], severe cardiovascular events [65] and gastrointestinal (GI) issues [63, 66].

The primary target is still cyclooxygenase (COX), an enzyme that is engaged in the initial phase of converting arachidonic acid to prostaglandins (PGs). Two isoforms (COX-1), they are broadly spoken on greatest tissues and catalyses prepared PG complex with regulation of physiological cellular tests, are inhibited by classical NSAIDs like indomethacin; COX-2 is primarily encouraged by a diversity of stimuli including mitogens, inflammatory endotoxins sides and cytokines [63, 67]. Therefore, the primary action of mechanism these drugs is the reduction of pro-inflammatory PGs generated by COX-2, while the cause of their adverse effects is the suppression of the constitutive COX-1 isoform.

Khloya et al. [68] studied the anti-inflammatory effect of a new series of pyrazolylthiazolecarboxylates, and their equivalent acid derivatives were evaluated in vivo by means of the carrageenan-encouraged rat paw *edema* technique [69]. With inhibitory percentages ranging from 93.66 to 89.59%, **81**, **82a** and **82b** (Fig. 3.7) were the most active compounds. Ester compounds appear to have more potency than acid derivatives.

Thiazole derivatives have been developed and synthesised from substituted 1,3-thiazole compound (**83a–c**, Fig. 3.8) by Abu-Melha et al. [70] The antioxidant activity of each synthetic molecule was assessed. When compared to the standard, the chemicals listed below (Fig. 3.8) demonstrated strong antioxidant activity.

The synthesis of new the substituted 1,3-thiazole compound has been described by Jaishree et al. [71]. Antioxidant properties in vitro were assessed for each synthesised molecule. A few of the compounds (**84**) had strong antioxidant capabilities (Fig. 3.8).

Due to the well-established biological activity of the thiazole moiety, extensive research has been dedicated to travelling thiazole derivatives as potential antimicrobial agents. These compounds have also been investigated as candidates for antibacterial drugs, given the growing concern about antibiotic resistance in bacterial strains. The introduction of various substituted to the primary molecular structure of thiazole has demonstrated positive responses from tested bacterial strains [72]. A considerable amount of research has focused on enhancing the chemical antibacterial result for thiazoles compounds. Notably, the chemical trichlorophenyl thiazole has exhibited significant inhibitory effects on a range—gram positive and negative stains,

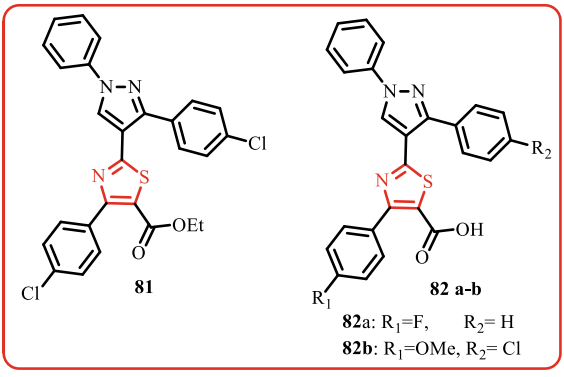


Fig. 3.7 Reported anti-inflammatory agents having an active thiazole nucleus

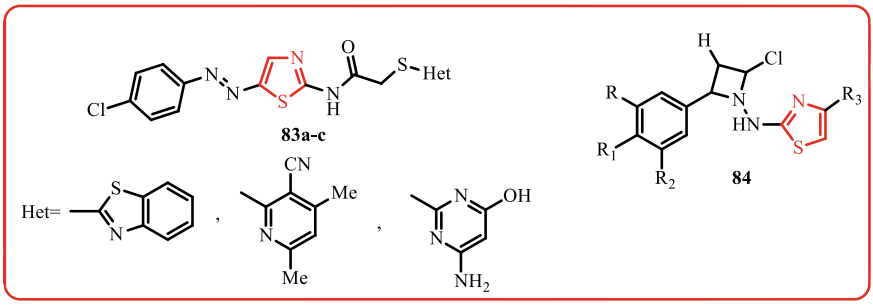


Fig. 3.8 Reported antioxidant agents having an active thiazole nucleus

involving *E. coli, B. subtilis and S. aureus P. fluorescens* [36]. A sequence of substituted thiazole derivatives with several *in-vitro* anti-bacterial test was produced by the prolonged synthesis of active antimicrobial agents [73].

Compound **85** displayed MIC 4.51, 4.60 and 4.32 μM/ml, while the synthesised analogues of **86** and **87** (Fig. 3.9), which had phenyl substituents nitro group, displayed active outcomes in contradiction of *B. subtilis*, *S. aureus* and *E. coli* with MIC values of 3.92–4.01, 3.39–4.11 and 3.59–4.23 μM/mL, correspondingly. This is because the tested microorganisms' amino acid residue produces a strong H bond with nitro moisturize present to *p*-position. Thus, it can be said that both the optimization of the substituent at the ring and the inhibition of microorganism activity were significantly aided by the thiazole ring containing nitro at position 4 [74].

The thiazole's –C = N spacer was found to be beneficial to the compounds antifungal activity in a different investigation. The compounds **88** and **89** (Fig. 3.9),

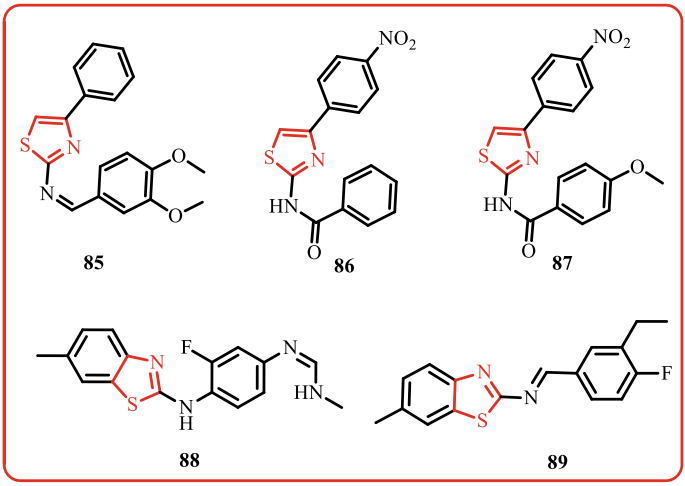


Fig. 3.9 Reported antimicrobial agents having an active thiazole nucleus

which were synthesised, showed significant antifungal action against *P. striiformis* and *U. tritici* [74].

3.10 Conclusion

In this chapter, we conclude that synthesis as well as biological study of S-heterocycles, such as thiazoline, thiophene and thiazole scaffolds, has garnered significant consideration because of their versatile possessions and possible claims in medicinal chemistry. These heterocycles containing sulfur show a comprehensive range of living effects, rendering them pivotal in drug discovery endeavors. This article explores the synthesis methods and biological assessments of these captivating compounds. Thiazoline, a sulfur and nitrogen containing five member ring, is commonly produced through cyclization reactions involving suitable amine and thiol precursors. Thiophene, a saturated five-membered ring with sulfur, can be synthesized through techniques such as ring-closing reactions of dienes or cyclization of thiolactones. Thiazole, another five-membered ring with sulfur and nitrogen, can be efficiently created through condensation reactions between amines and thioamides. These synthetic pathways offer a variety of derivatives for exploration in structure–activity relationships. Researchers have shown significant interest in the biological properties of thiazoline, thiophene and thiazole derivatives. Thiazoline derivatives have demonstrated potential in antimicrobial, antiviral and anticancer activities, owing to their structural resemblance to natural amino acids, facilitating effective interaction with biological targets. Thiazole derivatives, renowned for their antimicrobial, antitubercular and antiparasitic properties, have been utilized as scaffolds for the development of diverse therapeutic agents.

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Chapter 4
Synthesis and Biological Evaluation of Thiirane and Its Derivatives

Jagannath S. Godse, Suresh U. Shisodia, Bhawna P. Pingle, Santosh B. Gaikwad, Sanjay B. Ubale, and Rajendra P. Pawar

4.1 Introduction

Thiiranes are heterocyclic three-membered rings having two carbon and one sulfur atoms. Combining "thio" with "cyclopropane," which refer to the sulfur-containing molecule and three-membered ring structure, gets "thiirane". Thiiranes have oxygen instead of sulfur, unlike epoxides. To make three-membered saturated heterocycles, substitute one carbon atom in cyclopropane and cyclopropene rings with a heteroatom like sulfur. The bond angle distortion and ring strain affect the molecules' physical and chemical characteristics. In fully saturated three-membered heterocycles, carbon and heteroatoms hybridize Sp^3 show in Fig. 4.1 [1]. Thiirane's orbital has more "*s*" character than usual. This orbital has a pair of unbonded electrons. Tiny ring heterocycles have more "*p*" characters in internal bonds due to reduced bond angles. Due to the larger abundance of surface hybrid orbitals with "*s*" properties, outer bonds are more basic [1].

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Fig. 4.1 Thiirane

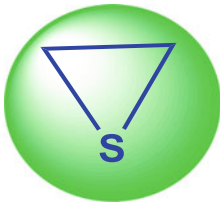
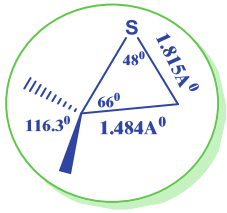


Fig. 4.2 Shape and bond angle thiirane



Thiiranes (Fig. 4.1) are more reactive than aryl and alkyl sulfides due to their sulfur atoms in three-membered rings. Thiiranes differ from aryl and alkyl sulfides. Fused ring thiiranes will be the focus of this chapter. Some thiiranes have spiro structures, depending on the structure's three aliphatic rings. Episulfidation with alkenes that are under strain due to cyclic endo-structures and alkenes with four substituents that are located on the outside of the molecule can synthesis thiiranes from alkenes.

In 1916, Sraudinger and Pfinninger were the first to successfully synthesize thiirane. This heterocycle, a three-membered saturated sulfur molecule, goes under several different names. Some of these names include episulfide and thiacyclopropane. This ring shape appears in a wide range of natural substances, both in its solitary forms and in their synthesized representations. Because of the smaller ring size and bigger atomic radius of the sulfur atoms, the molecule's shape is very similar to that of an acute angle triangle.

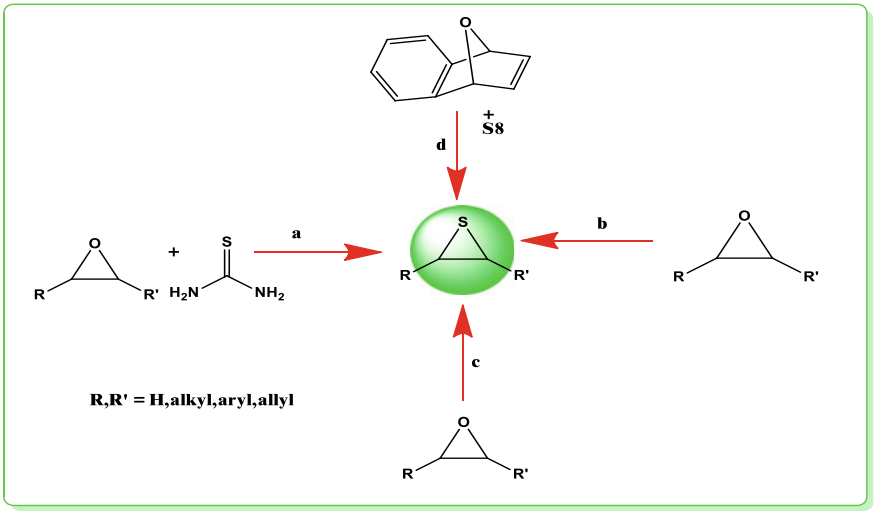
The thiirane ring is under tremendous stress because of bond angle compression and the ring opening potential of nucleophiles and electrophiles via carbon sulfur bond cleavage. On the other hand, sulfuric acid and carbon have severely compressed binding angles of 48 and 66° respectively. In contrast, the hydrogen–carbon bond has an angle of 116.30°, putting it roughly in the midway of the triagonal 120° shape and the tetrahedral 108°28′ shape show in Fig. 4.2 [1–3].

4.2 Synthesis of Thiirane

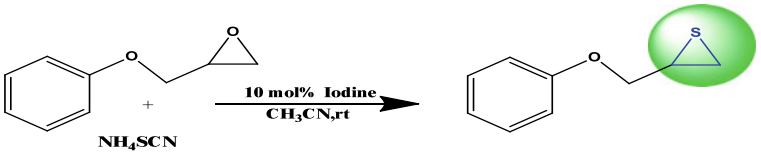
The immense biological significance of molecules based on thiirane has resulted in the publication of many synthetic techniques for the synthesis of numerous thiirane derivatives over the course of the past years. Using a green catalyst known as chitosan–silica sulfate nano hybrid (CSSNH) and water, it is possible to convert

epoxides 1 and thiourea 2 at room temperature, which will lead to the development of thiirane-derived products by Behrouz et al. in 2018 [4]. A different approach to the production the participation of thiirane derivatives was implicated converting oxiranes 1 to thiiranes in a solvent-free environment for a period of one and a half hours with a high percentage yield by making use of graphite oxide (GO), an acid catalyst, and sodium thiocyanate (NaSCN) by Mirza-aghayan et al. in 2015 [5]. In addition, the utilization of a green reagent known as alumina/thiourea for the conversion of epoxides 1 at room temperature makes it possible to manufacture thiiranes without the requirement of a solvent's presence by R. Eisavi et al. in 2016 [6]. The catalysis was facilitated by a rhodium complex ($RhH(PPh_3)_4$) synthesis combining sulfur and 7-oxabenzonorbornadiene 3 is reacted in the presence of dppe (1,2-Bis(diphenylphosphino)ethane), 4-ethynyltoluene, and acetone for three hours is another technique for generating thiirane derivatives by Arisawa et al. in 2015 [7]. This reaction takes place that is in the presence of acetone (Scheme 4.1).

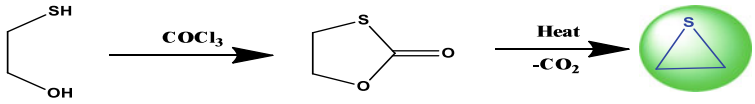
A method that is both effective using oxiranes as a starting point for the production of thiiranes more effectively was developed by making use of I_2 in a catalytic amount by Yadav et al. in 2008. Several salient features of this procedure include key factors to consider are achieving high conversion rates, using mild reaction conditions, ensuring economic feasibility of the reagents, minimizing reaction durations, simplifying experimental product isolation techniques, and ensuring compatibility with various moieties. These characteristics combine to make this process advantageous and appealing for the formation of a variety of thiiranes. This study presents a method that is gentle, effective, and practical for synthesizing thiiranes



Scheme 4.1 Synthesis of thiirane using multiple route **a** CSSNH (3.2 mmol), H_2O, r.t, 6 min, **b** NaSCN/GO (1 mmol), Solvent-free, 1.5 h, **c** NH_2CSNH_2 (2 mmol)/Al_2O_3, Solvent-free, grinding, r.t, 10 min, **d** 5 mol% $RhH(PPh_3)_4$, 10 mol% dppe, 50 mol% 4-ethynyltoluene, acetone, reflux, 3 h



Scheme 4.2 Synthesis of thiiranes with oxiranes and NH_4SCN



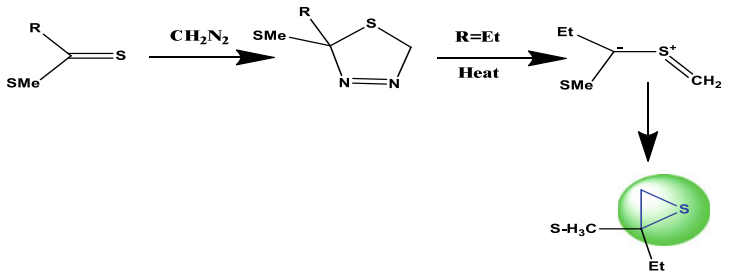
Scheme 4.3 Synthesis of thiiranes with 2-sulfanylethanol

with oxiranes and NH_4SCN. The process involves using molecular iodine as a catalyst. This is in continuation with the interest that has been shown in the application of elemental iodine as a catalyst. In the beginning, an attempt was made to perform 2-(phenoxymethyl) oxirane's interaction with NH_4SCN by utilizing 10 mol% of elemental iodine in CH_3CN at room temperature. In a time span of 2.5 h, the reaction brought about the formation of thiirane with a yield of 94% (Scheme 4.2) [8].

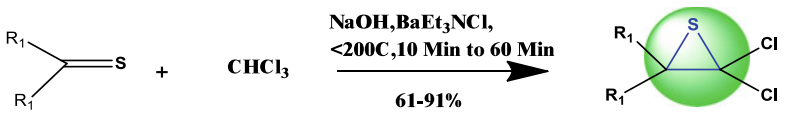
A reaction between the halothiols and the bases resulted in the synthesis of the thiiranes. This reaction was analogous to the production of oxirane. Under conditions that were very comparable, the beta-acetoxythiols were also able to produce thiiranes. Following the reaction of 2-sulfanylethanol combined with phosgene when pyridine is present, the 1,3-oxathiolan-2-one was heated to 200 °C for the purpose of decarboxylation, which resulted in the production of thiirane (Scheme 4.3) [9].

Among the few ways that may be utilized to produce S-containing dipolar intermediates, the most common method as a result of reacting with C=S dipolarophiles, diazomethane, which is then subsequent to nitrogen removal. The in situ produced reactive 1,3-dipoles (thiocarbonyl ylides) may be captured by several electron-deficient dipolarophiles. However, aromatic thioketones exhibited the highest reactivity. Dithioesters, compared with thioketones, have been utilized as substrates for sulfomethanides. (thiocarbonylides) a significantly lower percentage of the time. The synthesis of thiiranes, on the other hand, has described the process beginning with methyl propanedithioate. A thermal cleavage was performed on the intermediate, which resulted in the generation of thiocarbonyl S methanides. It was then necessary to rearrange these thiocarbonyl S methanides intramolecularly, which resulted in the production of thiirane. Furthermore, the formation of the 1,3-dithiolane isomers that were more hindered sterically occurred as a result of the regioselective trapping of intermediate compounds formed by the reaction of thiocarbonyl compounds with methyl dithioesters. It has been proposed that the thiocarbonyl S-methanide may serve as a reactive intermediary in these activities (Scheme 4.4) [10].

Using the dichlorocarbene, the imines and alkenes that were transformed into dichloroaziridines and dichlorocyclopropane. Nonenolizable dichlorocarbene and



Scheme 4.4 Synthesis of thiiranes with methyl propanedithioate

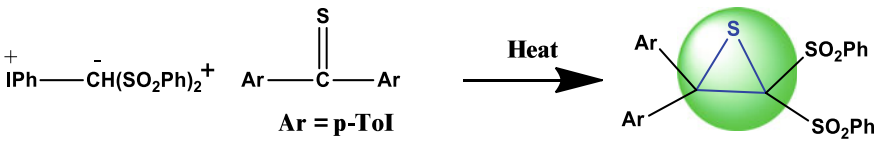


Scheme 4.5 Synthesis of 2,2-dichlorothiiranes

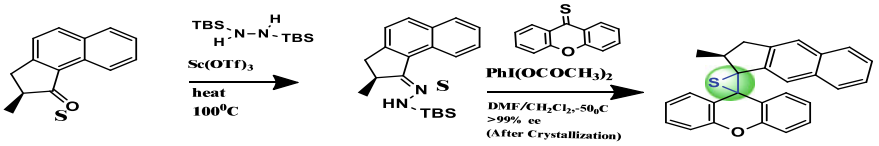
thioketones were used in the preparation of 2,2-dichlorothiiranes (Scheme 4.5). All these compounds were sterically characterized [10].

The [2 + 1]-cycloaddition, which entailed the incorporation of carbenes into the CS linkage in diarylthiones, led to the generation of thiiranes. Organomercury compounds, diazo compounds, and phenyliodonium bis- (alkyl- or aryl-sulfonyl) methylides are all examples of chemicals to consider are all potential source materials for the preparation of the carbene species. Scheme 4.6 illustrates the utilization of thiobenzophenones, albeit with low yields, and the results included the acquisition of a great deal of by-products, including benzothiophenes [10].

Through the utilization of 1,2-bis(*t*-butyldimethylsilyl) hydrazine, the conversion of ketone into TBS (*t*-butyldimethylsilyl hydrazone) was identified resulted in a significantly reduced degree of racemization. Furrow and Myers documented the conversion of a range of aldehydes and ketones into *t*-butyldimethylsilylhydrazones under reasonably mild conditions served as the foundation for this work. This work was founded upon their comprehensive analysis. The racemization that occurred under these conditions was because the deprotonation with NH_3NH_3 at the alpha site led to the creation of planar enolate, subsequently nonstereoselective deprotonation. The inclusion of bulky *t*-butyldimethylsilyl groups in the 1,2-bis(*t*-butyldimethylsilyl)hydrazine greatly hindered its ability to act as a base, resulting



Scheme 4.6 Synthesis of thiirane into the CS linkage in diarylthiones



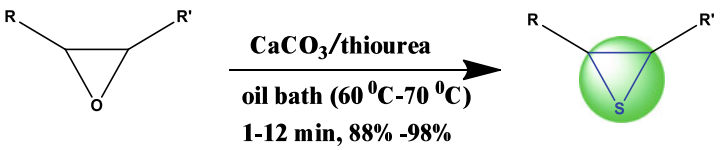
Scheme 4.7 Synthesis of thiirane with 1,2-bis(*t*-butyldimethylsilyl) hydrazine

in a decreased level of racemization. The compound's strong reactivity toward the production of *t*-butyldimethylsilyl hydrazone can be attributed to both the presence of a Lewis acid catalyst and the creation of a silicon–oxygen bond during the reaction, the nucleophilicity of the compound was hindered by the presence of the bulky *t*-butyldimethylsilyl groups. During the first stage of the process, the enantiopure (S)-ketone was transformed into *t*-butyldimethylsilyl hydrazone. The *t*-butyldimethylsilyl hydrazone being rapidly reacted with [bis(acetoxy)iodo] benzene, leading to a reaction that oxidized to a diazo molecule. Subsequently, the thioxanthone was introduced (Scheme 4.7) [10]. During the workup process, a significant quantity of crystals was formed by pouring the reaction mixture into water. These crystals were investigated and discovered to be constituted of enantiomerically pure (S)-episulfide. Isolating the small amount of episulfide that did not crystallize throughout the workup procedure indicated that it was completely racemic. At first glance, the racemization was only to a limited degree.

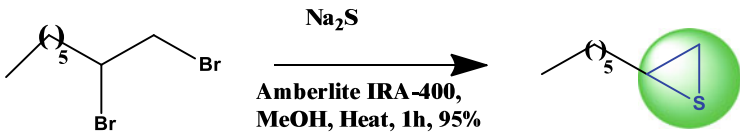
With the help of thiourea supported by $CaCO_3$ and conditions for an oil bath (60–70 °C), Zeynizadeh et al. in 2011 were able to successfully produce thiiranes through a process that is both environmentally friendly and practical. This method allows for the process of thiirane synthesis from epoxides without the need of any solvent (Scheme 4.8) [11].

Alkyl halides and metal sulfides reacted to produce symmetrical sulfides with different substituents. A comprehensive investigation on the transformation of organic functional groups looked at this technique, and no more research was found on catalyst-free interactions between metal sulfides and alkyl halides. This method worked well for producing higher yields of cyclic sulfides throughout their synthesis as well (Scheme 4.9) [12].

There are two ways to make thiirane oximes. Using a combination of sodium acetate, ethanol, and water, a ketone reacted with hydroxylammonium chloride to



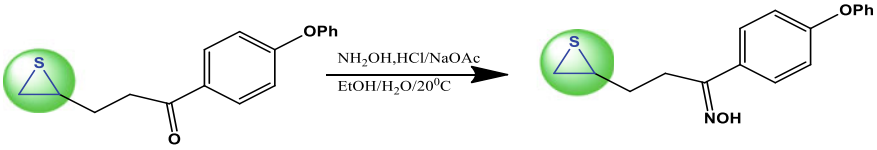
Scheme 4.8 Synthesis of thiirane with epoxide without solvent



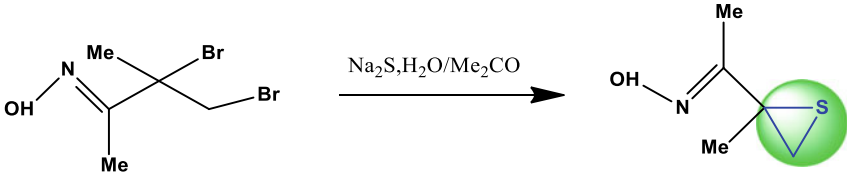
Scheme 4.9 Synthesis of cyclic sulfides with alkyl halides and metal sulfides

originally form the thiirane oxime (Scheme 4.10) [13]. 3,4-dibromo-3-methyl-2-hydroxyiminobutane reacted with $Na_2S{\cdot}H_2O$ in $(CH_3)_2CO$ to give the chemical 2-(α-hydroxyiminoethyl)-2-methylthiirane in a 40% yield (Scheme 4.11) [14].

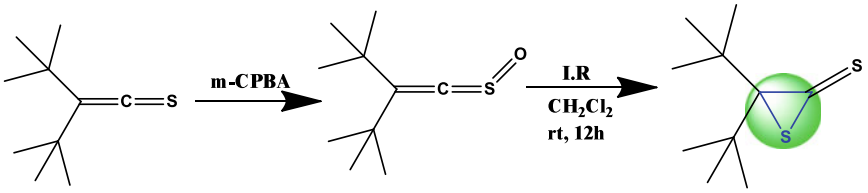
The production of thioketene-s-oxide comes about as a result of the oxidation of thioketene with m-chloroperoxybenzoic acid. Following a reaction with Lawesson's the reagent within dichloromethane for a period of twelve hours at the temperature of the room, the resultant thioketene-s-oxide gave rise to dithiolactone, a ringed compound with three members (Scheme 4.12) [15–17].



Scheme 4.10 Synthesis of thiirane oxime



Scheme 4.11 Synthesis of 2-(α-hydroxyiminoethyl)-2-methylthiirane



Scheme 4.12 Synthesis of thiirane with thioketene-s-oxide

4.2.1 *Derivatives of Thiirane*

The researchers of thiirane derivatives as gelatinase inhibitors by Fabrie et al. in 2014 was a result of the utilization of click chemistry. There is evidence that gelatinases, namely matrix metalloproteases (MMP-2 and MMP-9), play a significant role in the development and advancement of cancer and inflammatory diseases. As a result, MMPs are considered to be a major target in the field of cancer research. The zinc binding group and the ability to attach to the S1 pocket, sometimes referred to as the selectivity pocket, in MMPs are two characteristics that are typically associated with MMP inhibitors. SB-3CT, which has a thiirane ring, was identified as the initial gelatinase inhibitor in scientific literature. However, it suffered from the drawback of being poorly soluble in water [18]. Subsequently, a different group developed novel gelatinases inhibitors that possessed significant activity and contained azide, the compound contains a triazole group and hydroxamate group that binds to zinc [19]. The hydroxamate group is substituted with a thiirane moiety, which serves as a zinc binding group. This moiety undergoes ring opening when acted upon by gelatinase, resulting in zinc–thiol interactions. Additionally, an azide fragment is attached to different alkynes, which is responsible for interacting with the S1 pocket of gelatinases, furthermore selective inhibitors were developed. These inhibitors were developed because of these results. According to the findings of the MMPs inhibition assay, the compound exhibited a significantly higher IC50 value of 0.62 μM in comparison to other compounds. Studies involving molecular simulation and docking, on the other hand, have shown that the more extended and stiff P1 fragment in compound is responsible for its decreased stability. As a result, more attention ought to be paid to the P1 fragment in order to achieve the development of more powerful thiirane derivatives as gelatinase inhibitors (Fig. 4.3) [18].

Butkevich et al. [20] with the synthesis Among the *N*-aryl-*N*-(thietan-3-yl)cyanamides 2a-k that are the objective, with yields ranging from modest to good, the N-arylcyanamides 1a-k are subjected to alkylation using (chloromethyl)thiirane in an aqueous solution of potassium hydroxide a period of 48 h resulted in the formation of the latter (Scheme 4.13) [20].

With the use of tetrabutylammonium chloride and acyl group transfer (AGT), Schuetz et al. in 2013 are working on the process of polymerizing thiiranes using TZD to create larger rings. Indicating the acyl group are the rectangles in gray, which

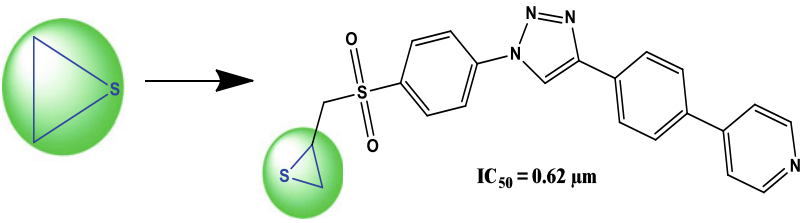
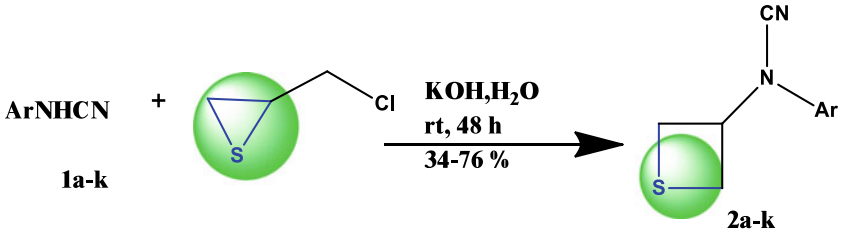
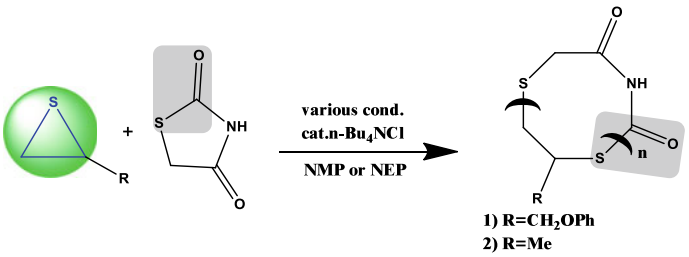


Fig. 4.3 Thiirane-based molecule reported as gelatinase inhibitor



a Ar=Ph, **b** Ar=2,6-$Me_2C_6H_3$,**c** Ar=4-$MeOC_6H_4$, **d** Ar = 1-naphthyl , **e** Ar=2-ClC_6H_4
f Ar=4-ClC_6H_4, **g** Ar=4-BrC_6H_4, **h** Ar=3-FC_6H_4, **i** Ar=2-$O_2NC_6H_4$,**j** Ar =3-$O_2NC_6H_4$
k Ar=4-$O_2NC_6H_4$

Scheme 4.13 Synthesis *N*-aryl-*N*-(thietan-3-yl)cyanamides



Scheme 4.14 Ring-expansion polymerization of thiiranes

remains intact following the introduction of the monomer and, as a result, functions as an active site, resulting in a regulated polymerization characteristic (Scheme 4.14) [21].

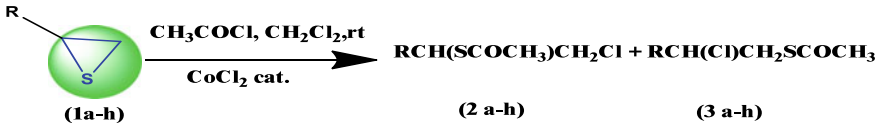
Iranpoor et al. in 2003, the propensity for thiiranes to readily polymerize, the investigation of the ring-opening reactions of this specific group of compounds is generally not pursued. It is only possible for thiiranes to undergo a reaction with primary alcohols when acids (BF_3, HCl, or H_2SO_4) that act as catalysts, are present. This reaction takes place at a high temperature and involves significant polymerization, which results in the production of b-alkoxy mercaptans with poor yields.

This study's objective is to document the process of producing β-chlorothioesters by reacting thiiranes with anhydrous $CoCl_2$ from Co(II). Initially, the responses of styrene sulfide (1a) and epichlorohydrin (1f) with acetyl chloride were examined as illustrations of activated and deactivated thiiranes. The reactions were performed using different Lewis acids as catalysts, as well as without any catalysts. In the absence of a catalyst, the reaction between styrene episulfide (1a) and acetyl chloride occurred in CH_2Cl_2 at room temperature. After six hours, a mixture of 2a and 3a was obtained, with a ratio of 88:12, accounting for 60% of the total product. In these conditions, the reaction between epichlorohydrine (1f) and acetyl chloride did not yield any product.

The subsequent phase consisted of doing research into the catalytic influence that a number of different Lewis acids had on these processes. The data presented in and demonstrate that the inclusion of $CoCl_2$ among the catalysts investigated in this work not only enhances the reaction's yield and regioselectivity between styrene oxide (1a) and acetyl chloride, However, it also exerts a substantial influence on the duration of the reaction. The reaction of epichlorohydrine (1f) is another example that brings to light the importance of catalyst in this transformation. With an absolute chemoselectivity of 0/100, this epoxide is unreactive towards acetyl chloride. When there is no catalyst present, reacts when there is 0.05 mol equivalents of anhydrous Co(II) chloride present. With an 81% yield, the process produces the equivalent thioacetates (2f/3f) (Scheme 4.15) [22].

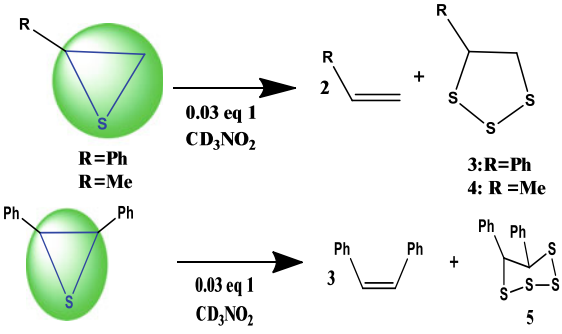
The researcher Sauve et al. in 2002, when compared to the reaction of styrene sulfide with the inequality of the disubstituted stilbene sulfide, which resulted in a different stoichiometry, the stoichiometry of the product was different. Under conditions regarded as equivalent, the overall reaction of styrene sulfide was six times faster than the reaction that occurred of cis-stilbene sulfide. This was the case throughout the entire reaction (Scheme 4.16) [23].

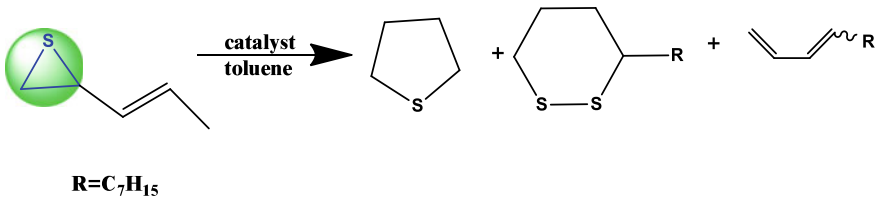
Erik Rogers et al. in 2007 and colleagues demonstrated that copper(II) hexafluoroacetyl-acetonate, in particular, was preferable because it was able to successfully suppress both diene (Scheme 4.17) [24] A synthetic method can be employed to separate the tetrahydrothiophene molecule from ethyl 6-heptenoate, which is readily obtainable in the market. Although the initial endeavor to produce



Scheme 4.15 Synthesis of β-chlorothioesters

Scheme 4.16 Disproportion reactions of styrene and propylene sulfides catalyzed CD_3NO_2 and disproportion reactions of cis-stilbene sulfides catalyzed CD_3NO_2





Scheme 4.17 Copper-catalyzed ring expansion of vinyl thiiranes

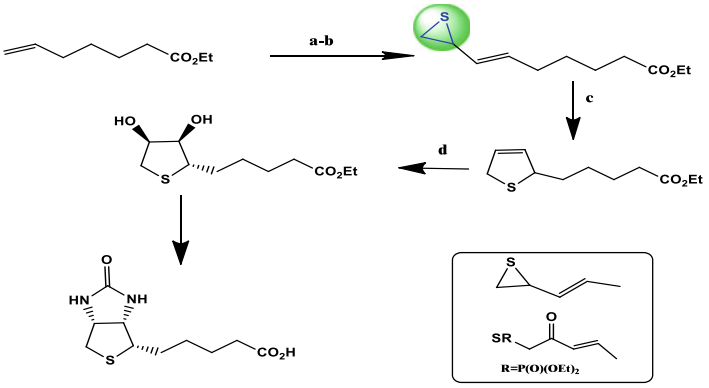
vinyl thiirane in one step through the cross-metathesis of ethyl 6-heptenoate with vinyl thiirane was unsuccessful, a subsequent cross-metathesis with enone thiophosphate, followed by selective reduction using $NaBH_4$ and in situ cyclization, yielded vinyl thiirane in a high amount. During our primary synthetic procedure, we rearranged vinyl thiirane to produce the necessary 2-substituted 2,5-dihydrothiophene. This compound then underwent a chemoselective and substrate-controlled dihydroxylation, resulting in the formation of a diol [25]. This diol serves as an intermediate in Ohrui's biotin synthesis [26] and can be obtained in just four steps starting from an ester (Scheme 4.18) [24]. (Scheme 4.19) [24] the several steps required to reach the fused heterocyclic core via copper-catalyzed vinyl thiirane rearrangement. An initial step was to preserve the amino group, and a single step was required to transform the aldehyde into an epoxide. The resulting epoxide was then thiiranated using potassium thiocyanate. Under the influence of $Cu(tfacac)_2$, the thiirane ring grew to form 2,5-dihydrothiophene. One byproduct of the sulfuryl chloride oxidation process was fused thiophene. Upon deprotection compound was generated from this product [27]. Plavix evolved from this synthetic chemical component with the incorporation of an additional synthesis step.

When potassium hydroxide is dissolved in water, the responses of several distinct N-substituted sulfonamides number and chloromethylthiirane number resulted in the formation of the corresponding 3-sulfonamidothietanes with yields ranging from low to moderate (Scheme 4.20) [28].

Under basic circumstances, the reactions of a number of different *N*-arylcyanamides and chloromethylthiirane, the reaction resulted in the formation of the corresponding *N*-aryl-*N*-(thietane-3-yl)cyanamides, with yields ranging from moderate to good. (Scheme 4.21) [29].

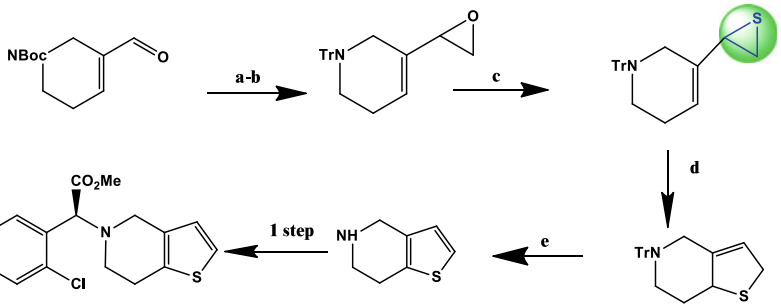
As nucleophiles, azaheterocycles, including 2-chloro-5(6)-nitrobenzimidazole [30], 3,5-dibromo-1,2,4-trizaole [31], pyrimidine-2,4(1H,3H)-diones [32], and isatins [33] used to initiate a reaction with chloromethylthiirane, it ultimately led to the development of the N-thietan-3-ylazahterocycles that corresponded to it (Scheme 4.22).

The thietane ring was designed as a prospective contender for protecting the NH group of heterocycles. Alkylation of azaheterocycles with chloromethylthiirane was a simple method that allowed for its introduction. Thietane is oxidized to thietane 1,1-dioxide by utilizing peroxide from hydrogen in acetic acid, the thietane protecting group was removed with the application of sodium alkoxide as a later treatment.



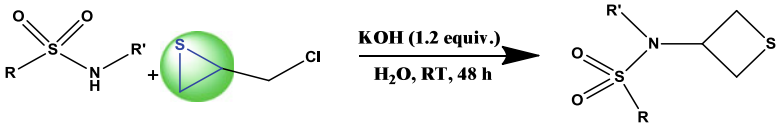
Conditions: a) 16, Grubbs second, CH_2Cl_2, 40 ^{0}C ,70 % b) $NaBH_4$, MeOH,10^{0}C,83 %
c) 5% Cu(hfacac)$_2$, benzene,120^{0}C,1.5h,0.01M,80%
d)AD-mix ,t-BuOH, H_2O, RT,50% (80% based on recovered starting material)

Scheme 4.18 Synthesis of biotin. Conditions: **a** 16, Grubbs second, CH_2Cl_2, 40 °C, 70%, **b** $NaBH_4$, MeOH,10 °C, 83%, **c** 5% Cu(hfacac)$_2$, benzene, 120 °C, 1.5 h, 0.01 M, 80%, **d** AD-mix ∝, t-BuOH, H_2O, RT,50% (80% based on recovered starting material)



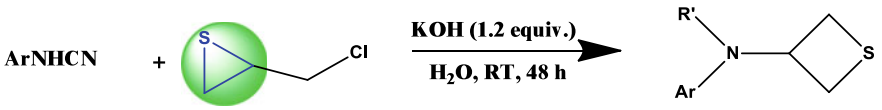
Condition: a) TFA, CH_2Cl_2, RT, then TrCl, Et_3N, RT,93 % b) $ClCH_2I$, n-BuLi, THF, -78 ^{0}C to RT c)KSCN, Et_3N, CH_2Cl_2-MeOH, RT (40% two Steps) d)5 mol% Cu(tfacac)$_2$, C_6H_6,100^{0}C,52% e) SO_2Cl_2, Et_3N, CH_2Cl_2,0^{0}C, then 1M HCl, THF, RT,65%

Scheme 4.19 Synthesis of thiophene core of plavix. Condition: **a** TFA, CH_2Cl_2, RT, then TrCl, Et_3N, RT, 93%, **b** $ClCH_2I$, n-BuLi, THF, − 78 °C to RT, **c** KSCN, Et_3N, CH_2Cl_2-MeOH, RT (40% two Steps), **d** 5 mol% Cu(tfacac)$_2$, C_6H_6,100 °C,52%, **e** SO_2Cl_2, Et_3N, CH_2Cl_2, 0 °C, then 1M HCl, THF, RT, 65%



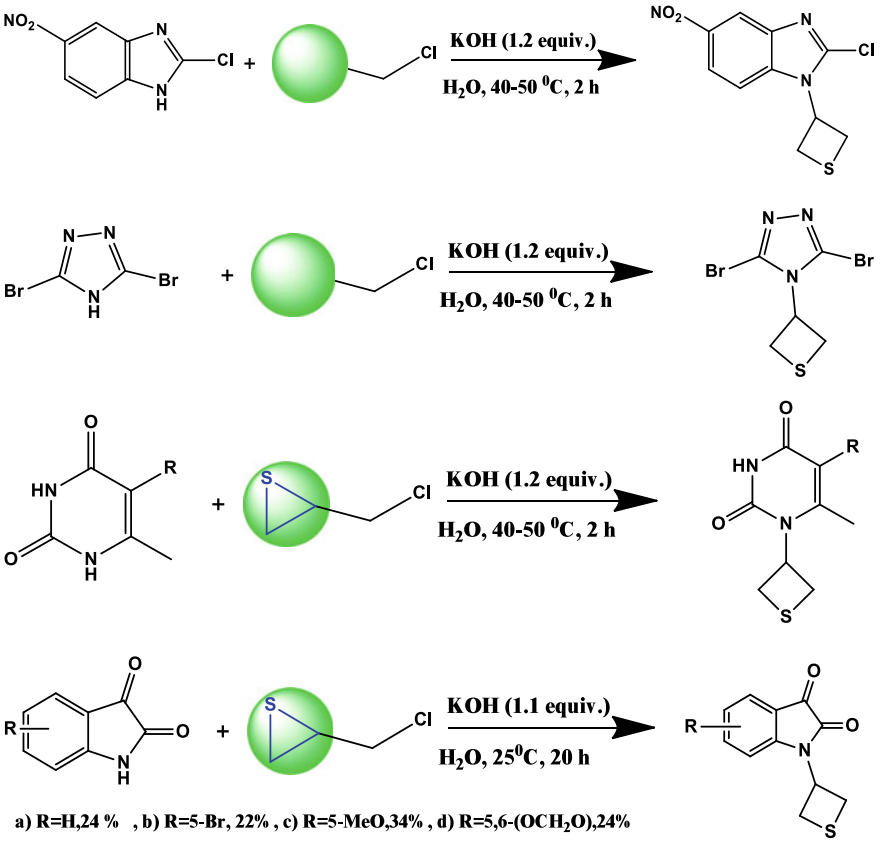
R=Ph, a) R' = 4-MeOC$_6$H$_4$, 62% ; b) R' = Bn, 5% c) R' =H, 25% ;
d) R' = 4-O$_2$NC$_6$H$_4$,30%
R=Me, e) R' =4-MeOC$_6$H$_4$, 56% f) R'= Napth-1-yl,25%

Scheme 4.20 Synthesis of 3-sulfonamidothietanes



a) Ar = Ph, 72 % : b) Ar = 2,6-$Me_2C_6H_3$,34% :, c) Ar=4-MeC_6H_4,59% ,
d) Ar=Naphth-1-yl,38% : e) Ar= 2-ClC_6H_4,63 % : f) Ar=4-ClC_6H_4, 76% :
g) Ar=4-BrC_6H_4,69% : h) Ar=3-FC_6H_4,74% : i) Ar= 2-$O_2NC_6H_4$, 44% :
j) Ar=3-$O_2NC_6H_4$, % 9% : k) Ar=4-$O_2NC_6H_4$,38%

Scheme 4.21 Synthesis of *N*-aryl-*N*-(thietane-3-yl)cyanamides



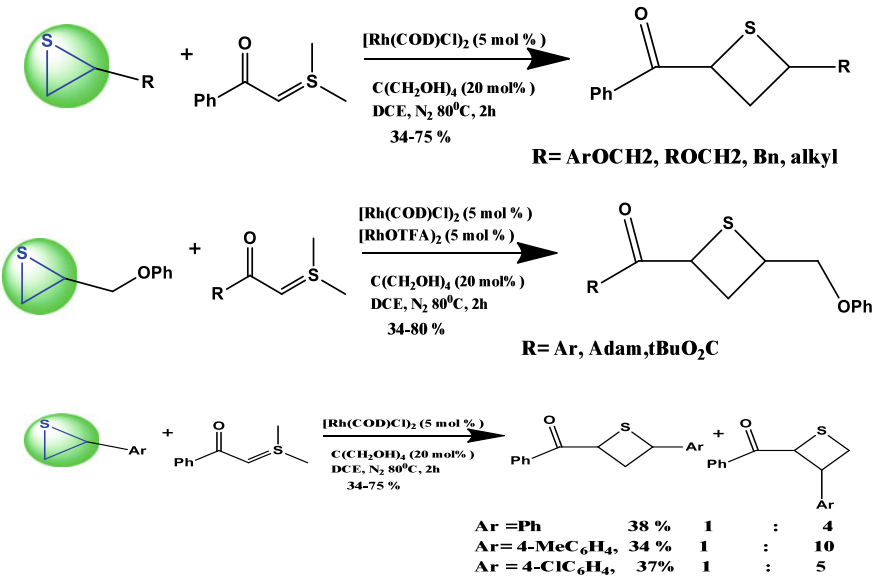
a) R=H,24 % , b) R=5-Br, 22% , c) R=5-MeO,34% , d) R=5,6-(OCH_2O),24%

Scheme 4.22 Synthesis of N-thietan-3-ylazahterocycles

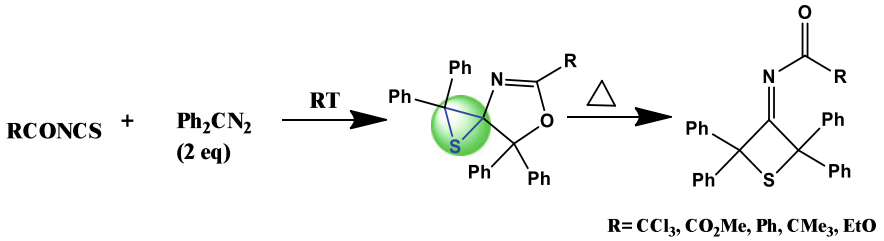
Owing to the fact that they have a low nucleophilicity, the sulfur ylides that lacked electrons could not expand their rings when combined with thiiranes, which would have resulted in the formation of the equivalent functionalized thietanes. Nevertheless, rhodium catalyzed the transformation of electron-deficient sulfur ylides into electrophilic metallocarbenes. Following their reaction with the sulfur atom in thiiranes, which is rich in electrons, these metallocarbenes underwent an electrophilic ring expansion of thiiranes, resulting in the production of thietanes. The reaction between sulfur acyl ylides and 2-alkylthiiranes resulted in the production of 2-acyl-4-alkylthietanes with yields ranging from moderate to good. However, they engaged with 2-arylthiiranes to generate mixtures of 2-acyl-4-arylthietanes and 2-acyl-3-arylthietanes in proportions varying from 1:4 to 1:10 (Scheme 4.23) [34]. In the process of ring expansion, alkyl and arylthiiranes and exhibited regioselectivity that was distinct from that of the process of nucleophilic ring-opening of thiiranes [35].

At room temperature, a reaction took place between acyl isothiocyanates RCONCS and two equivalents of diphenyldiazomethane. The production of 4,5-dihydro-1,3-oxazole-4-spiro-2'-thiiranes was the consequence of this reaction, this resulted in the formation of 3-iminothietanes by the process of heat isomerization (Scheme 4.24) [36].

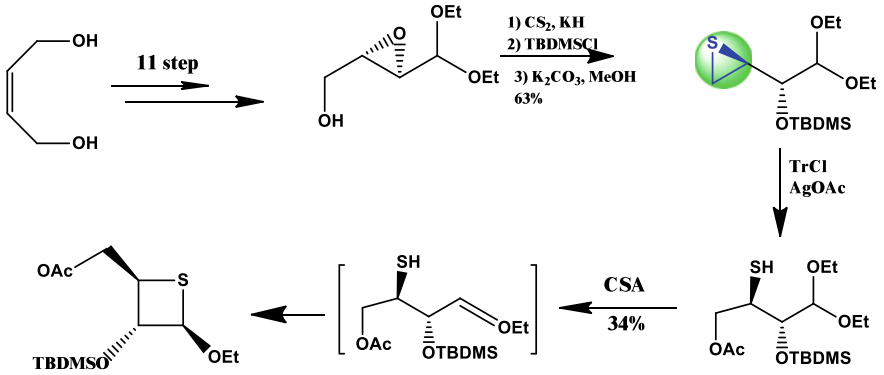
A de novo synthesis of a thietane derivative, namely a four-membered ring thiosugar, was performed by using cis-but-2-ene-1,4-diol. The sharpless asymmetric epoxidation was responsible for the generation of the first two asymmetric centers. Through the use of a cyclic xanthate intermediate that was produced as a result of the



Scheme 4.23 Synthesis of 2-acyl-4-arylthietanes and 2-acyl-3-arylthietanes



Scheme 4.24 Synthesis of 3-iminothietanes



Scheme 4.25 Synthesis of trans-trans substituted thietane

procedure including the use of CS_2 and KH, the epoxide was transformed into the equivalent thiirane. After the secondary hydroxyl group was preserved, the xanthate was methanolyzed to produce the target thiirane with a total yield of 63%. Regioselective ring-opening of thiirane by AgOAc led to the production of thiol. Subsequently, the thiol was converted into 1-O-ethyl-thietanoside through an acid-catalyzed elimination reaction involving the removal of ethanol, which was then the addition of the nucleophile of thiol with CSA in benzene that was in a refluxing state. The extremely stereoselective conversion was carried out by means of an oxocarbenium intermediate, which finally led to the formation of the trans–trans substituted thietane derivative, which is favorable from a thermodynamic standpoint (Scheme 4.25) [37].

4.3 Conclusion

Thiirane consists of a category of aliphatic saturated three-membered thia heterocycles that are considered to be the most important. Not only do they serve as fundamental medicinal cores and structural motifs of some biological substances, but they also serve as important and flexible synthetic intermediates in the field of

organic chemistry. Despite the fact that there are not a large deal of naturally occurring thiirane derivatives, they are extremely important. In recent years, a number of notable synthetic methods for thiiranes generated from heterocycles with three members have been the subject of research and development. The reactions discussed involve intramolecular cyclizations, nucleophilic and electrophilic ring expansions of thiiranes. These reactions mostly consist of nucleophilic ring openings of aliphatic three-membered heterocycles, along with ring expansion. In the future, I anticipate that these newly established synthetic processes will showcase several uses in creating sulfur-containing molecules with biological activity, as well as organic structures containing sulfur.

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Chapter 5
Synthesis and Biological Evaluation of 1,3,5-Dithiazinanes: Synthesis, Stereochemistry and Applications

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5.1 Introduction

S,N-containing heterocyclic subunits are commonly used compounds. Low-molecular heterocycles (300–500 Da) to be directly used in the form of ready-made substances in biological systems or as *building blocks* for further transformations are of special interest in this case [17, 69]. Over the years, application of a multi-component approach (multicomponent reactions MCR) has proved its high efficiency in the construction of these heterocyclic systems. Here we should mention some generally accepted varieties of these reactions in the synthesis of heterocycles with proven efficacy: domino (tandem) or *one-pot* reactions, *pseudo*-multicomponent reactions, as well as multicomponent cascade processes commonly applied in high-tech screening of bioactive molecules [2, 37, 53]. In fact, MCRs proceed as a *one-pot* process without isolating intermediate products. At the same time, the methodology of diversity-oriented synthesis (DOS) based on reagents similar in reactivity but different in structure is advancing in the search for new bioactive low molecular weight heterocycles with functional and stereochemical diversity [46].

Intensification of both approaches is impossible without using the conceptual issues of green chemistry [5] in terms of not only sustainable development processes and environmental safety, but also the influence of global economic and social challenges [45]. The approaches combining chemical synthesis with atomic precision

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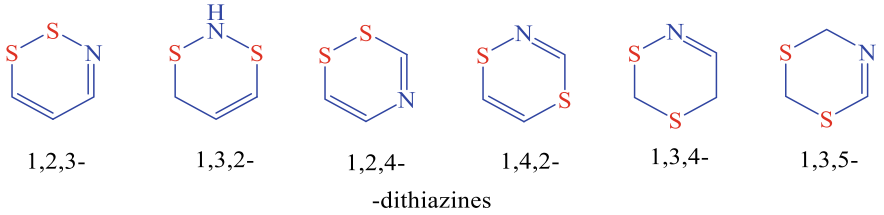


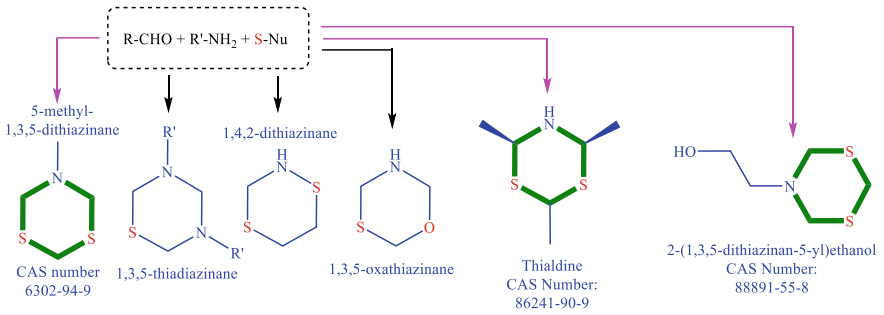
Fig. 5.1 Representatives of isomeric dithiazinane systems

and development of new chemical probes of high degree of binding to the biological target, hitting the "ideal" molecule, are essential for pharmacological marketing [19].

Among the many representatives of S,N-containing heterocycles, a class of six-membered heterocycles, dithiazines and their derivatives, in particular, should be highlighted. Taking into account the set of heteroatoms in a six-membered heterocycle with two sulfur atoms and one nitrogen atom, six isomeric dithiazine systems are possible: 1,2,3-, 1,3,2-, 1,2,4-, 1,4,2-, 1,3,4- and 1,3,5-dithiazines (Fig. 5.1):

To date, the most studied and promising are perhydro-1,3,5-dithiazines, 1,4,2-dithiazines and 1,3,5-oxathiazines (Scheme 5.1) [47] owing to the ease of design, high practical significance and unique chemical properties [8]. Perhydro-dithiazines are called dithiazinanes. Some representatives such as 2,4,6-trimethyl-1,3,5-dithiazinane (thialdine) and 5-methyl-1,3,5-dithiazinane are currently commercial products applied in food industry as flavor enhancers [72].

One of the recognizable structure of this class of heterocycles is thialdine (CAS No 638–17-5) synthesized by Justus von Liebig and Friedrich Wöhler in 1847 [82]. Thialdine has been identified among other compounds in cooked beef and can be used as an agent to impart the flavor of grilled meat, popcorn or shrimp. Another representative, monomeric 2-(1,3,5-dithiazinan-5-yl)ethanol (Scheme 5.1), being a commercially available reagent, is formed as the main undesirable product in the technology of chemical purification gas/oil from hydrogen sulfide using reagent N,N′,N″-tri(oxyethyl)-hexahydro-1,3,5-triazine. When isolated from aqueous solutions, this monomer partially polymerizes to form an insoluble solid, resulting in



Scheme 5.1 The family of six-membered *S,N*-containing saturated heterocycles

deposits or fouling on machine parts [83]. This is the contrast of 1,3,5-dithiazinanes as chemical compounds.

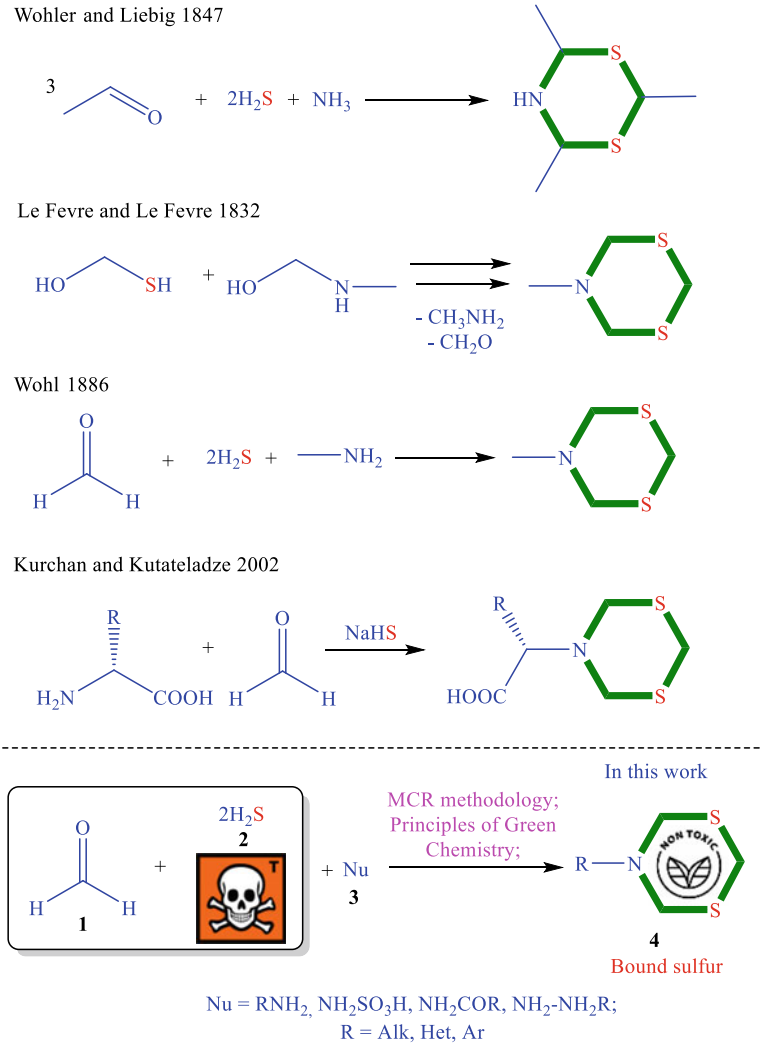
Convenient MCRs have been developed for the synthesis of 1,3,5-dithiazinanes. The vast majority of the approaches for their constructing are based on the cyclothiomethylation reaction of amines applying formaldehyde and various sulfur-containing reactants (H_2S, NaSH, Na_2S) [31]. It is noteworthy that formaldehyde has received a new developmental extension in terms of C-1 synthon in organic synthesis [52, 54]. As a result of the cyclothiomethylation reactions, new –NCH_2S– and –SCH_2S– bonds are formed with water as a by-product. It should be mentioned that the above condensation reaction subsequently appeared as aminomethylation (thiomethylation) of hydrogen sulfide according to Mannich in some publications [18]. A systematization by reagents of this reaction is described in a number of publications [10, 13, 47].

The evolution of the design of the 1,3,5-dithiazinane backbone is presented in Scheme 5.2. The cyclothiomethylation of methylamine, formaldehyde and hydrogen sulfide to form *N*-methyl-1,3,5-dithiazinane was first reported by A. Wohl and dates back to 1886 [81]. Later, applying the Le Fevre method in two stages, *N*-methyl-1,3,5-dithiazinane was obtained, called "methylthioformaldine" by Wohl with a gross formula of $C_4H_9NS_2$ [51]. The synthesis of 1,3,5-dithiazinane heterocycles can be currently considered as one of the possible ways of binding toxic hydrogen sulfide (a powerful nerve gas) into significant condensation products [7]. This chapter reviews the latest advances in the synthesis and modification of 1,3,5-dithiazinanes, and their structural features, complexing and biological activity over the past twenty years.

5.2 Multicomponent Cyclothiomethylation of Amines as a Methodology for the Synthesis of 1,3,5-Dithiazinanes

The synthesis of 1,3,5-dithiazinanes is conventionally carried out by the cyclothiomethylation reaction of primary amines with CH_2O and NaSH. Na_2S or H_2S, obtained in-situ under laboratory conditions by the action of mineral acids on alkali metal sulfides, have been directly used as effective S-nucleophiles.

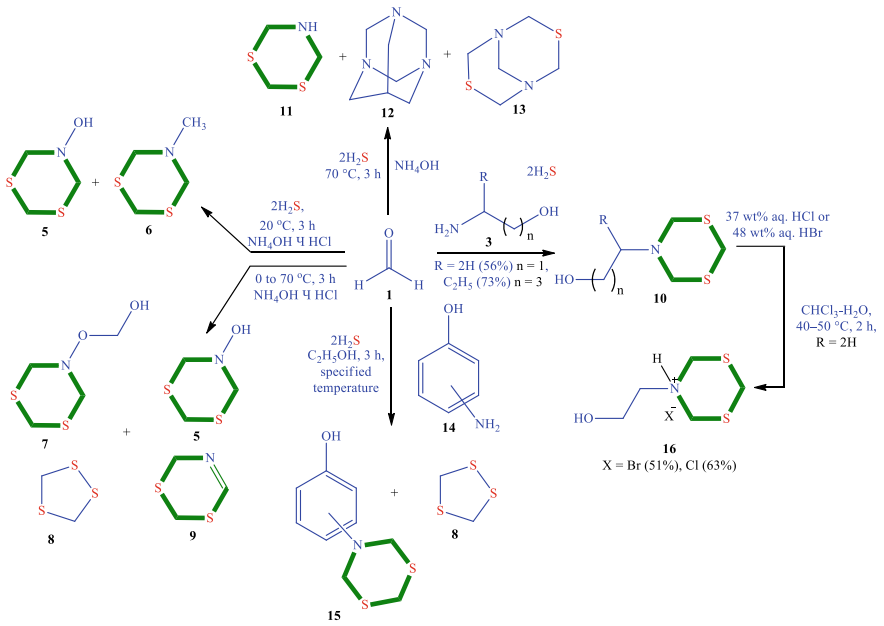
Cyclothiomethylation of bifunctional amines containing a hydroxyl group (hydroxylamine, ethanolamine, *R*-(-)-2-aminobutanol, 2-aminobutanol) was described in [12]. Heterocyclization under three-component condensation conditions using hydroxylamine or amino alcohols, H_2S and CH_2O in a 1:2:3 ratio gives *N*-hydroxy(hydroxyalkyl)-1,3,5-dithiazinanes in 47–73% yield. Predominantly, reactions occur at the amino group, except for when the OH-group of the amino alcohol is involved in the reaction with the "CH_2O–H_2S" reagent (4:3) to form (1,3,5-dithiazinan-5-yl)oxy-methanol **7** in a 56% yield. The authors point out that a further increase in the concentration of the thiomethylating "CH_2O–H_2S" reagent



Scheme 5.2 Evolution of synthetic approaches for the creation of *N*-substituted 1,3,5-dithiazinanes **4**

brings about a decrease in the selectivity of the reaction and formation of such by-products as 4*H*-1,3,5-dithiazine **9** and 1,2,4-trithiolane **8** (Scheme 5.3).

Based on the X-ray diffraction data, the crystal structure of the 1,3,5-dithiazinane molecule **5** has two independent forms (Fig. 5.2a) in a chair conformation and an axial arrangement of the OH-group, but with different geometric parameters [12]. Heterocycles with NCS bonds have an axial arrangement of *N*-substituents due to the anomeric effect. In the crystal, molecules **5A** and **5B** make *H*-dimers due to the O–H…O hydrogen bond. It should also be noted that there is an intramolecular bond



Scheme 5.3 MCR thiomethylation of amino alcohols using reagent CH_2O–H_2S

between the hydrogen atom and the sulfur atom H…S in molecule **5B**, which further stabilizes the conformation of the dithiazinane ring. *H*-Dimers are combined into zigzag chains because of the specific dipole–dipole S…S interaction with a distance of 3.530 Å (Fig. 5.2b).

The use of an aqueous solution of ammonia (NH_4OH) under the developed conditions and at a temperature of 70 °C gave a mixture of cyclocondensation products **11–13**, a minor among which was the target 1,3,5-dithiazinane **11** (9% yield). The main products were methenamine **12** and 3,7-dithia-1,5-diazabicyclo[3.3.1]nonane **13** with a total yield of ~ 60% (Scheme 5.3).

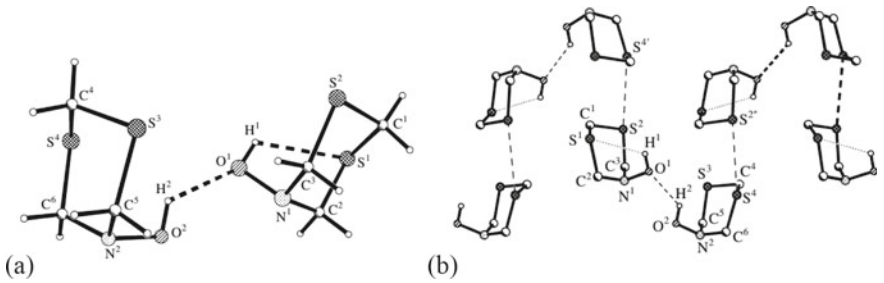


Fig. 5.2 **a** General view of two independent molecules **5A** and **5B** according to X-ray diffraction analysis. **b** Intermolecular bonds in a crystal

Isomeric aminophenols **14** react differently in the cyclothiomethylation reaction. Indeed, the MCR of *m*-aminophenol, CH_2O and H_2S (ratio 1:2:1) produced a mixture of products, including sulfur-containing cyclophane [9]. Meanwhile, the *o*- and *p*-isomers of aminophenol react with the thiomethylating «CH_2O–H_2S» reagent (3:2) to form 2- and 4-[4*H*-1,3,5dithiazin-5(6*H*-yl]phenols **15** in 86% and 71% yield, respectively (Scheme 5.3). The product of cyclocondensation of CH_2O and H_2S, 1,2,4-trithiolane **8**, is formed as an impurity. X-ray diffraction analysis of 5-(4-hydroxyphenyl)dihydro-1,3,5-dithiazine showed that the heterocyclic ring has a chair conformation with an axially located hydroxyphenyl group at the nitrogen atom. Molecular packaging is a collection of molecules forming macrochains due to the intermolecular hydrogen O–H…S bond (Fig. 5.3).

To obtain water-soluble derivatives, the reaction of 5-hydroxyethyldithiazinane with Bronsted acids (HCl or HBr) was carried out to form the adducts 5-(2-hydroxyethyl)-1,3,5-dithiazinan-5-ium chloride and bromide **16** with a yield of more than 50% [23] (Scheme 5.3). According to X-ray diffraction data, the dithiazinane ring has a distorted chair conformation with N(1)–C(1)–S(1)–C(2) and N(1)–C(3)–S(2)–C(2) torsion angles of − 61.7(2) and 63.0(2)°, respectively (Fig. 5.4).

Primary screening of compounds **10** (R = 2H, n = 1) and its hydrochloride **16** for fungicidal activity showed that 1,3,5-dithiazinane **10** at concentrations of 0.1, 0.2 and 0.5% did not affect the development of *B. sorokiniana, F. oxysporum*, but

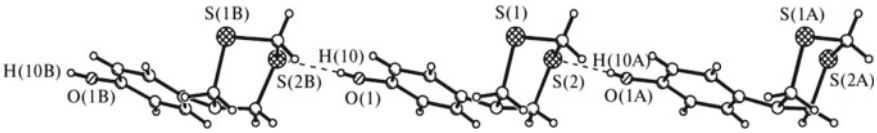


Fig. 5.3 Formation of OH…S hydrogen bonds in the macromolecular structure packing of 5-(4-hydroxyphenyl)dihydro-1,3,5-dithiazinanes **15**

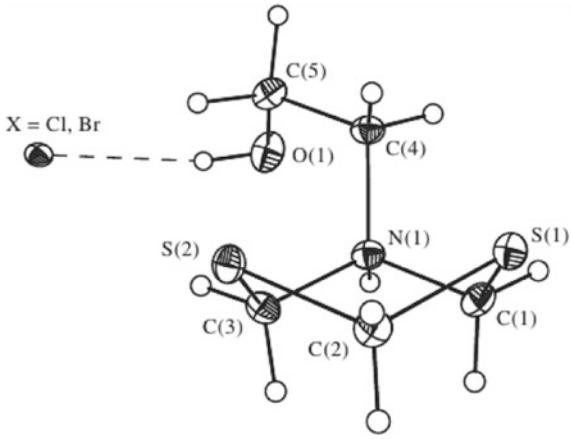


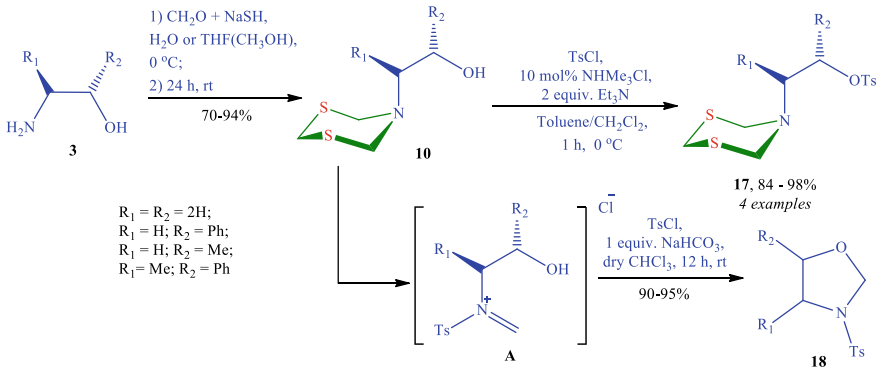
Fig. 5.4 Crystal structure of **16**, hydrogen bonded by OH…X with halogen cations (X = Cl, Br) (CCDC 713877 and 713878) [23]

completely inhibited the growth of *R. solani*. Meanwhile, a water-soluble adduct with hydrochloride **16** at a concentration of 0.5% inhibits the growth of *B. sorokiniana, F. oxysporum* and *R. solani* phytopathogenic fungi [6].

A convenient and effective reagent for the thiomethylation reaction is a CH_2O–NaSH mixture. This approach has a distinct advantage over using hydrogen sulfide gas as S-nucleophile. For instance, a method involving various derivatives of monoethanolamine **3** in the aminomethylation reaction (Scheme 5.4) was suggested in the work [34]. Subsequent functionalization at the primary hydroxyl groups of the resulting products **10** with tosyl chloride in a solvent mixture of toluene-methylene chloride selectively gave O-tosylated derivatives of 1,3,5-dithiazinane **17**. Meanwhile, dithiazinanes **10** under mild conditions can be easily transformed into 3-tosyl-1,3-oxazolidines **18** via *N*-tosyl-imine intermediate **A** (Scheme 5.4). The structure of compounds **18** ($R_1 = R_2 = H$ and $R_1 = Me$, $R_2 = H$) was proven by X-ray diffraction (Fig. 5.5). In this case, the oxazolidine ring has an envelope conformation with the oxygen atom moving out of the plane of the molecule. The study of intermolecular interactions revealed that the oxygen atoms of the tosyl group and neighboring hydrogen atoms in the unit cell form polymer-like structures.

The multicomponent cyclothiomethylation reaction with a formaldehyde-H_2S mixture occurs in different directions in aromatic amines, depending on the reaction conditions and the nature of *para*-substituted anilines [11]. For example, dithiazinanes **19** are selectively formed exclusively at the amino group under MCR conditions of *para*-sulfamido-substituted aniline **14** in a neutral environment, whereas in an acidic environment, amino and sulfamido groups participate in heterocyclization to form *bis*-dithiazinane **20** (Scheme 5.5). In the case of 4-aminobenzoic acid esters, cyclothiomethylation at room temperature occurs with the predominant formation of dithiazinanes **21**. 1,3-Thiazitidine **23** and 1,3,5-thiadiazinane **24**, which are usually formed at low temperatures, were isolated as by-products.

The approach based on the transamination reaction of *N*-methyl-1,3,5-dithiazinane **6** with primary arylamines **14** in the presence of 5 mol% $Sm(NO_3)_3$



Scheme 5.4 Synthesis of optically active 1,3,5-dithiazinanes **10**, their O-tosylated derivatives **17** and 3-tosyl-1,3-oxazolidines **18**

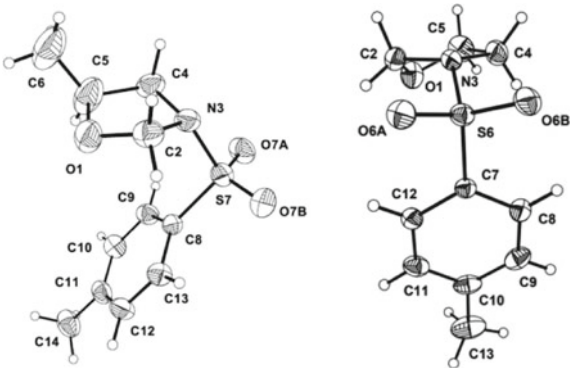
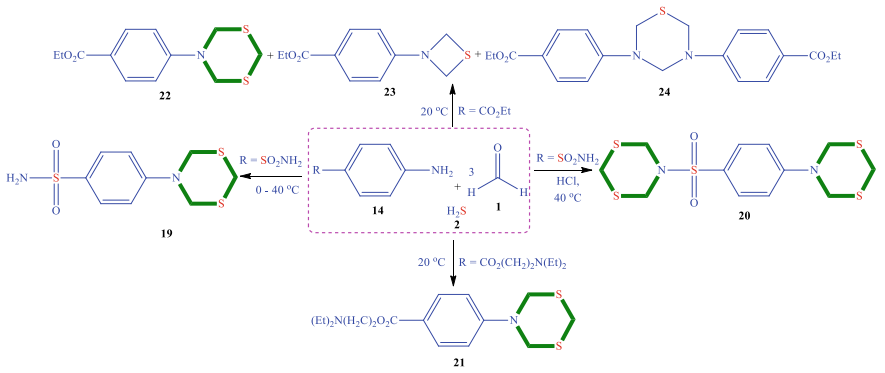


Fig. 5.5 Molecular structure of compounds **18** ($R_1 = R_2 = H$ and $R_1 = Me$, $R_2 = H$) in crystal (CCDC 236640 and 236642) [34]

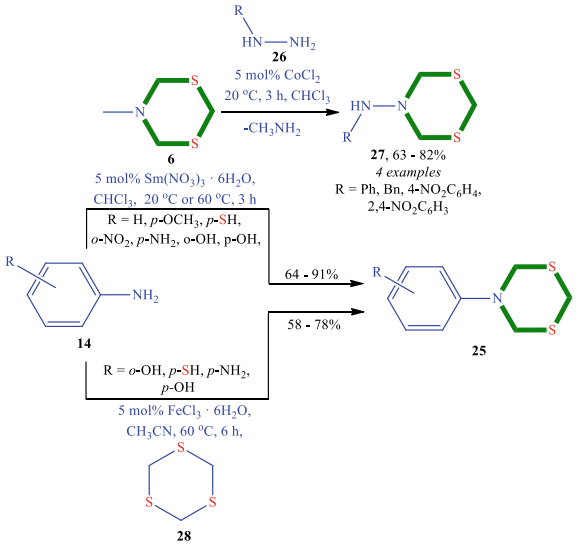


Scheme 5.5 MCR of *para*-substituted anilines **14** with formaldehyde and hydrogen sulfide

· $6H_2O$ as a catalyst (Scheme 5.6) offers a promising technique for the construction of saturated *N*-substituted dithiazinanes **25.** The authors demonstrate the advantage of the method in using *N*-methyl-1,3,5-dithiazinane **6** as a synthetic equivalent, compared to classical reactants based on gaseous H_2S and CH_2O in the aminomethylation reaction. It should be noted that *p*-phenylenediamine (conditions 20 °C, 3 h, DMF) entered into the thiomethylation reaction at only one amino group [61]. In the case of using *o*- and *p*-aminophenols with *N*-methyl-1,3,5-dithiazinane **6**, the transamination reaction is effectively carried out in a solvent mixture of EtOH–$CHCl_3$ to obtain 2- and 4-(1,3,5-dithiazinan-5-yl)phenols **25** with a yield of 72% and 91%, respectively [64]. The transamination of *N*-methyl-1,3,5-dithiazinane **6** with hydrazines **26** is realized similarly under catalysis of 5 mol% $CoCl_2$ at room temperature with the selective formation of 1,3,5-dithiazinan-5-amines **27** with a yield of more than 60% [61]. The disadvantage of the above technique for the synthesis of heterocycles **25** and **27** by transamination reaction is the preliminary preparation of 5-methyl-1,3,5-dithiazinane **5.**

Another universal preparative methodology is the one based on the catalytic synthesis of *N*-aryl-1,3,5-dithiazinanes **25** starting from 1,3,5-trithiane **28** and

Scheme 5.6 Scheme for the synthesis of *N*-aryl-1,3,5-dithiazinanes **26** and **28**

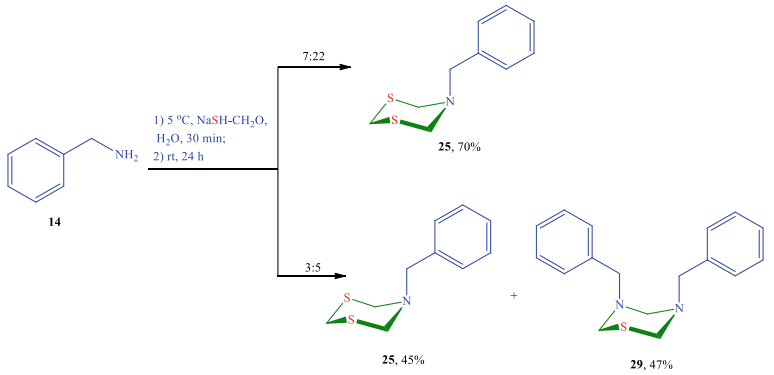


aromatic amines **14**. In the developed method, $FeCl_3 \cdot 6H_2O$ in acetonitrile at 60 °C proved to be an effective catalyst. The choice of solvent is obviously related to the limited solubility of 1,3,5-trithiane **28** in alcohol [64].

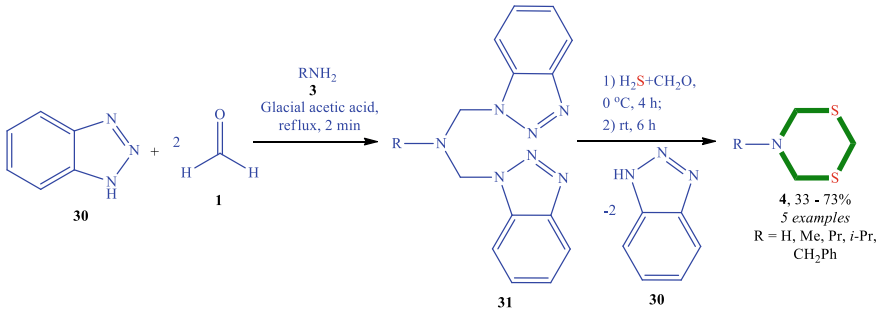
The authors of the work [29] once again demonstrated the high efficiency of using aromatic amines on the example of obtaining 5-benzyl-1,3,5-dithiazinane **25** in a 70% yield (Scheme 5.7). The thiomethylation reaction of benzylamine with five moles of formaldehyde and three moles of sodium hydrosulfide produces a mixture of the products N-benzyldithiazinane **25** and *N*-benzylthiadiazinane **29** in a ratio of ~ 1:1. Moreover, the use of a threefold excess of formaldehyde increases the selectivity of the reaction. Under otherwise equal conditions, condensation occurs under mild conditions, but over a longer period of time.

A two-stage synthesis of a series of N-substituted dithiazinanes **4** (5 examples) is carried out by aminomethylation reactions of primary amines with formaldehyde and benzotriazole **30** in glacial acetic acid to give the diaminomethyl derivative **31** [62]. At the second stage, compound **31** undergoes nucleophilic substitution of amino groups with sulfide groups under the influence of the "H_2S–CH_2O" system to form the target dithiazinanes **4** in yields of up to 73%. Benzotriazole **30** is eliminated and can be reused in the first stage of the presented approach (Scheme 5.8).

Replacing hydrogen sulfide gas **2** with sodium sulfide in the cyclothiomethylation reaction greatly simplifies the procedure. Still, despite the availability and convenient preparative properties of sodium hydrosulfide and sulfide, their use as starting reagents for the preparation of valuable heterocyclic compounds, including 1,3,5-dithiazinanes and 1,3,5-thiadiazinanes remains limited. The work [48] describes the reaction of 9-aqueous sodium sulfide with formalin (40% aqueous solution of formaldehyde **1**) and primary amines **3** at a reagent molar ratio of 2:3:1 in a chloroform-water mixture at room temperature to form 1,3,5-dithiazinanes **4** and



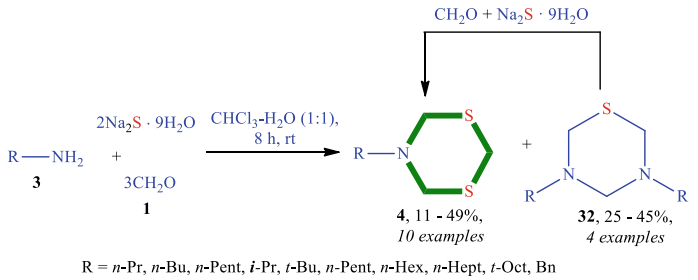
Scheme 5.7 Preparation of 1,3,5-dithiazinane **25** and 1,3,5-thiadiazinane **29** by condensation of *N*-benzylamine **14**, sodium hydrosulfide and formaldehyde at different ratios of the starting reactants



Scheme 5.8 Two-stage synthesis of dithiazinanes through the stage of aminomethylation of primary amines with formaldehyde and benzotriazole

1,3,5-thiadiazinanes **32** within 8 h (Scheme 5.9). The pH of the reaction medium is alkaline (pH ~ 13) under these conditions, unlike previous method with H_2S. The mixture is neutralized with a solution of hydrochloric acid at the end of the reaction. The chemoselectivity of thiomethylation under these conditions depends on the structure of the amines: primary linear alkylamines give predominantly thiadiazinanes with a yield of about 50%, while branched and cyclic amines form dithiazinanes. It is noteworthy that thiadiazines **32** can be converted into 1,3,5-dithiazinanes **4** under the action of a thiomethylating mixture.

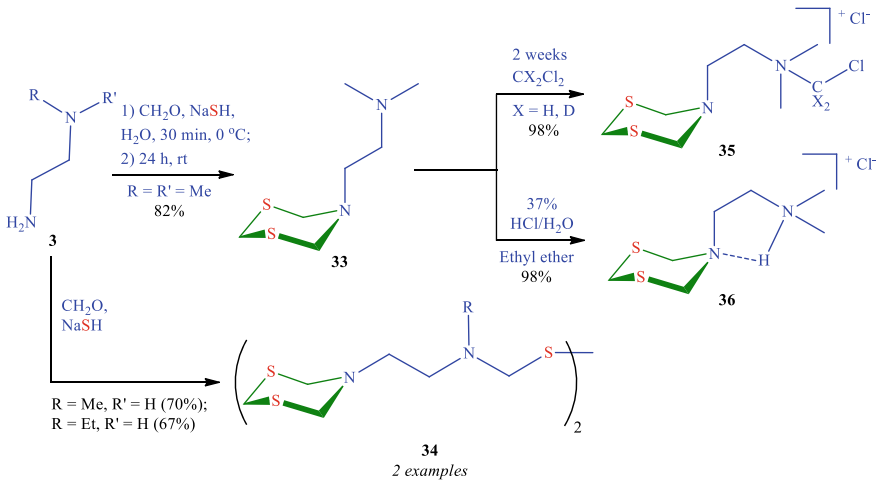
The use of NaSH as a thiomethylene reagent has proven to be effective when using *N*-substituted ethylene-diamines **3** (*N,N*-dimethyl-ethylene-diamine, *N*-methyl-ethylene-diamine and *N*-ethyl-ethylene-diamine) as nucleophiles [28]. Moreover, the reaction is carried out in an aqueous medium to give unsymmetrical 1,3,5-dithiazinane **33** with a yield of 82% (Scheme 5.10). The use of a twofold excess of thiomethylating reactants and bifunctional diamine under the developed conditions



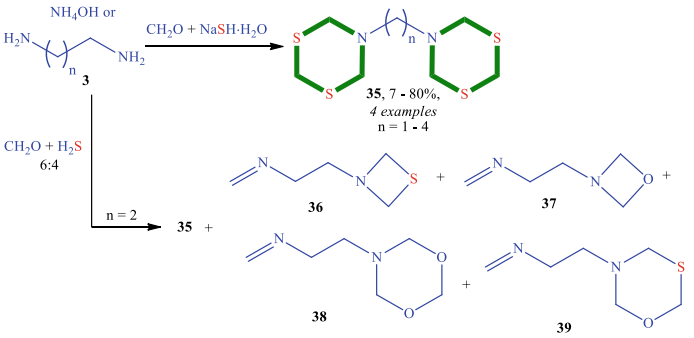
Scheme 5.9 Cyclothiomethylation of amines with the "CH_2O–Na_2S" system

led to the formation of *bis*(1,3,5-dithiazinanes) **34**. Dissolution of the starting dithiazinane **33** in methylene chloride and withstanding for two weeks gives *N*-{2-(1,3,5-dithiazinan-5-yl)-ethylene}-*N*-chloromethyl-*N,N*-dimethylammonium chloride **35** with a yield of 98%. In this case, the chloromethylene group quaternized the exocyclic nitrogen atom. In the presence of an aqueous solution of HCl, protonation of the amine occurs, which competes with the alkylation of nitrogen to form compound **35**.

The synthesis of *bis*(1,3,5-dithiazinanes) **35** is possible using NaSH monohydrate as a source of *S*-nucleophile (Scheme 5.11). For example, to obtain a methylene bridge between two heterocycles the use of NH_4OH in the condensation reaction is necessary. The authors found that the signal of the methylene group in the ^{13}C NMR spectrum is shifted to a high field of $\delta = 64.76$ ppm (theoretical ~ 89 ppm) as a result of each exocyclic N–C bond being a staggered conformation and the dithiazinane rings being in perpendicular planes. To extend the alkyl chain between heterocycles under the developed conditions, bifunctional amines



Scheme 5.10 MCR for the preparation of dthiazinane **33** and *bis*-dithiazinanes **34** containing *N*-ethyldiamine substituted



Scheme 5.11 Synthesis of *bis*(1,3,5-dithiazinanes) using NaSH or H_2S as the *S*-nucleophile

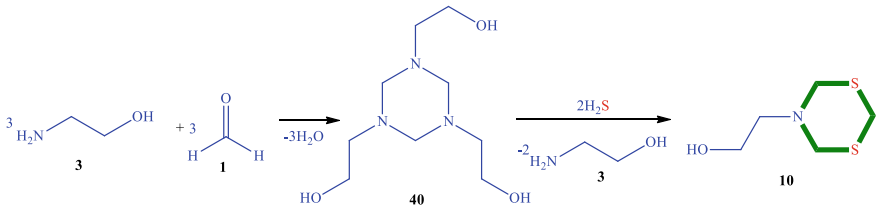
3 (1,2-ethylenediamine, 1,3-propanediamine, 1,4-butanediamine) were involved. The structure of the compounds 1,3-*bis*[5-(perhydro-1,3,5-dithiazinyl)]propane and 1,4-*bis*[5-(perhydro-1,3,5-dithiazinyl)]butane was proven by X-ray diffraction [24].

Another experiment to obtain symmetrical *bis*(1,3,5-dithiazinanes) **35** was implemented in [49]. In this approach, a mixture of "CH_2O–H_2S" was involved as a thiomethylating agent, obtained by preliminary bubbling formaldehyde with hydrogen sulfide for 2 h (Scheme 5.11). The authors of the work note that sequential mixing of formalin and amine (stirring for 2 h) is preferable to direct bubbling of hydrogen sulfide and formalin as by-products **38** and **39** are formed. In this case, reaction products **37–39** were identified based on GC–MS data.

5.3 Recyclization of 1,3,5-Hexahydrotriazines in the Synthesis of 1,3,5-Dithiazinanes

The development of high-sulfur oil through desulfurization is well known. Sulfur and sulfur compounds are often toxic (for example, hydrogen sulfide) to the environment and humans, flammable and bring damage to the equipment causing corrosive processes [1]. The most common technology for removing sulfur compounds is based on the hydrotreating of petroleum fractions, resulting in the formation of hydrogen sulfide (mercaptans) and additional amounts of hydrocarbons. The subsequent technological solution is oxidation to elemental sulfur (Claus process), while chemisorption using mono-, di- and triethanolamines is used for small H_2S impurities.

An economical and effective approach to remove hydrogen sulfide in the oil industry today is application of chemical absorbents. One of the common neutralizers and absorbers of low-concentration hydrogen sulfide from natural gas and oil is triazinans. Despite the ease of preparation of a variety of triazinane bases [16], the commonly applied scavenger is the one based on hexahydro-1,3,5-tris-(-2-hydroxyethyl)-s-triazine **40** (monoethanolamine triazine or MEA-triazine). The

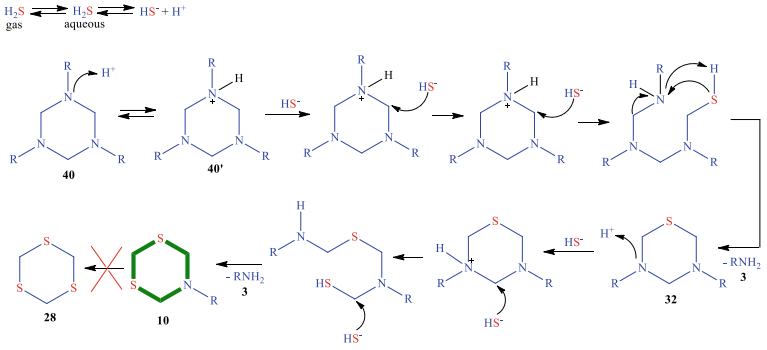


Scheme 5.12 Two-stage synthesis of 2-(1,3,5-dithiazinan-5-yl)ethanol as a technological method for purifying gas/oil from hydrogen sulfide

availability of formaldehyde **1** and 2-aminoethanol **3** played an important role in this regard. The method is based on the irreversible process of obtaining organic sulfides, namely the chemical reaction of the absorbent with H_2S to form a new –C–S– bond [70]. The process is presented in Scheme 5.12.

The authors of the work [66] offered a mechanism based on experimental data from the reaction of nucleophilic substitution of sulfur in the ring (Scheme 5.13). At the first stage of the interaction of H_2S and triazinane **40**, the nitrogen atom in the heterocyclic ring is protonated according to an acid–base reaction. As a result of further attack by the HS-(bisulfide anion), the ring opens and the exocyclic nitrogen binds to the hydrogen atom of the thiol group, while the sulfur atom attacks the carbon, eliminating one molecule of amine **3**. The recent research work [67] proved bisulfide anion to be the predominant form of H_2S in basic aqueous scavenger solutions. Furthermore, the concentration of HS- affects the purification process and high pH values contribute to inhibition of the reaction.

The resulting neutral thiadiazine molecule **32** is similarly protonated with ring opening. At the last stage, the sulfur atom binds to the electron-deficient carbon atom eliminating amine **3**. Further, the process is followed by the closure of the cycle to produce the final product dithiazinane **10**. The authors point out that formation of tritiane **28** as the final product is not observed in this case due to the subsequent



Scheme 5.13 The mechanism of the reaction of nucleophilic substitution of nitrogen atoms with a sulfur atoms in triazines **40**

polymerization reaction of dithiazinane **10** to form an amorphous product. DFT calculations of the energy profile of the reaction mechanism for trapping H_2S using 1,3,5-hexahydrotriazine **40** showed that the energy barrier for this reaction makes 24.49 kcal/mol. Meanwhile, the study of the anti-corrosion properties of dithiazinanes as products of spent absorbers in the work [73] revealed that 5-hydroxyethyl dithiazinane **10** is the most effective corrosion inhibitor.

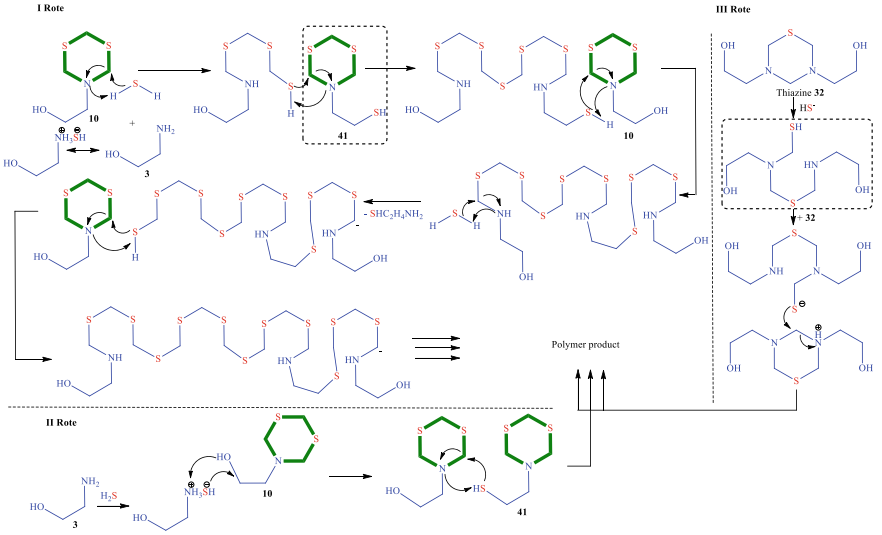
The bisulfide anion was observed to be the key chemical in initiating this chain reaction. This bisulfide anion is formed by the reaction of H_2S with ethanolamine **3** released in the sulfur insertion reaction carried out by *tris*(2-hydroxyethyl)-hexahydro-s-triazine **40**. This process was artificially induced by the reaction of monomeric or crystalline 5-hydroxyethyl dithiazinane **10** and hydrosulfide ethanolammonium.

The use of monoethanolamine triazine **40** is followed by a number of side effects, namely the precipitation of dithiazine in mains, distribution pipelines and structures, valves and filters [79]. This largely owes to the parent monomeric 5-(2-hydroxyethyl)-hexahydro-1,3,5-dithiazinane **10**; when isolated from aqueous solution it polymerizes to form an insoluble solid [83]. Meanwhile, 5-hydroxyethyldithiazinane **10** has a crystalline structure [71]. This solid product is called amorphous polymeric 5-(2-hydroxyethyl)hexahydro-1,3,5-dithiazinane. The process of a polymer product formation is presented in Scheme 5.14. In this case, the presence of a terminal hydroxyl group plays a crucial role in initiating the polymerization reaction of the corresponding dithiazinane **10**. The formation of 5-thioethyldithiazine **41** as a result of the reaction of 2-(1,3,5-dithiazinan-5-yl)ethanol **10** with bisulfide is noteworthy as well (Scheme 5.14, rote II). This stage is believed to be the key point in the polymerization process [74].

Furthermore, it is described in the work [32], based on DFT calculations, that formation of tritiane is not possible owing to the lower electrophilicity of the carbon atom in the –S–CH_2–N– fragment and, as a consequence, the high barrier to the activation energy of capture of the third molecule of H_2S. In this case, formation of a high molecular weight substance is possible as a result of nucleophilic cleavage of the 1,3,5-thiadiazinane ring, to form a sulfanylmethyl adduct (Scheme 5.14, rote III). Complete assignment of vibrational modes associated with 1,3,5-thiadiazinane and 1,3,5-dithiazinane is performed in the research work [63] by comparing the Raman spectra of pure samples with the DFT calculations.

Recently, [68] presented a spectral description of the previously considered intermediate compound 3,5-bis(2-hydroxyethyl)hexahydro-1,3,5-thiadiazinane **32**, confirming its formation under the reaction of removing hydrogen sulfide from the aqueous phase using MEA-triazine **40**. The calculated rate constants of the first and second purification reactions made 0.435 and 0.004 L mol^{-1} s^{-1} at 25 °C, while the activation energies were 68 and 57 kJ mol^{-1}, respectively.

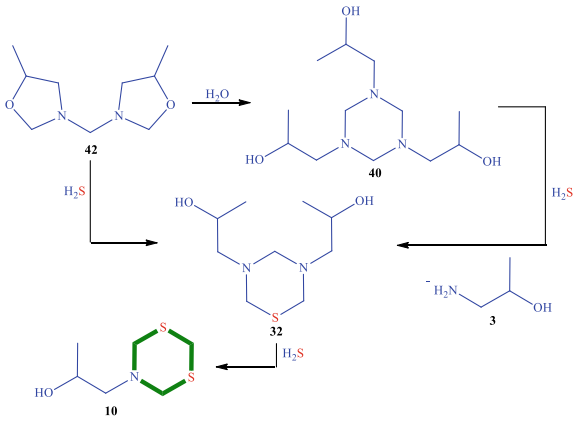
Hydrothermal oxidation unit was suggested to solve the problem of wastewater pollution when removing H_2S containing mainly unreacted triazinane **40** (unspent absorbent), monoethanolamine and dithiazine (spent absorbents). As a result of the purification process, complete transformation of organic nitrogen to ammonium and organic sulfur to sulfates was registered [56].



Scheme 5.14 Formation of polymethylene sulfide by polymerization of 5-(2-hydroxyethyl)hexahydro-1,3,5-dithiazinane

Another subgroup of hydrogen sulfide scavengers based on the ability to release formaldehyde *in-situ* are the oil-soluble bisoxazolidines **42** (Scheme 5.15). It should be noted that the latter is synthesized exclusively in anhydrous media involving monoethanolamine **3** and paraformaldehyde **1** to form the five-membered heterocyclic compound **42** [84]. The authors suppose hexahydrotriazine **40** to be the key component in the transformation of the oxazolidine ring upon binding of hydrogen sulfide.

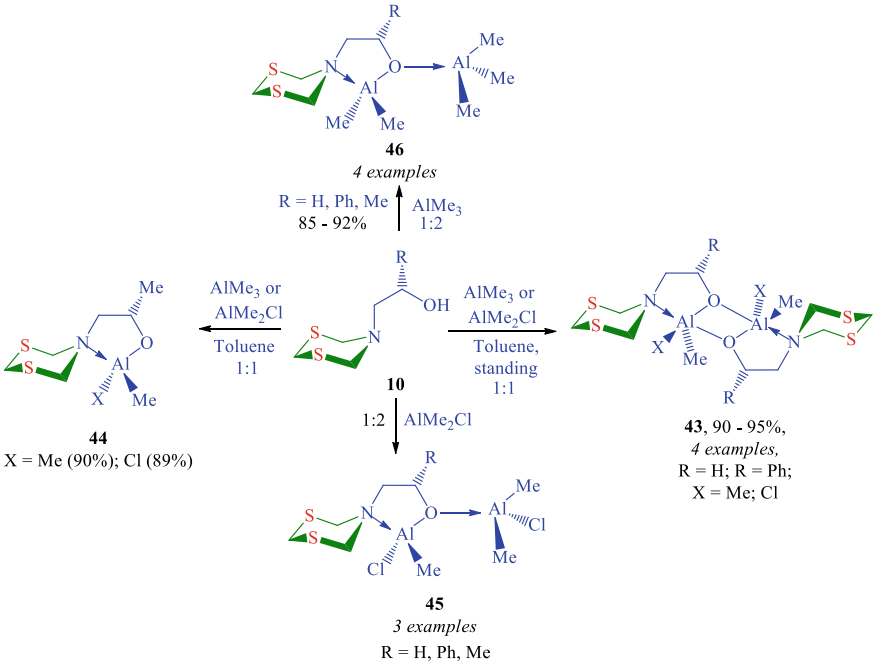
Scheme 5.15 Proposed mechanism for the formation of dithiazinanes **10** from *bis*-oxazolidines **42**



5.4 1,3,5-Dithiazinanes as S,N-Containing Polydentate Ligands

5.4.1 Complexation with Lewis Acids

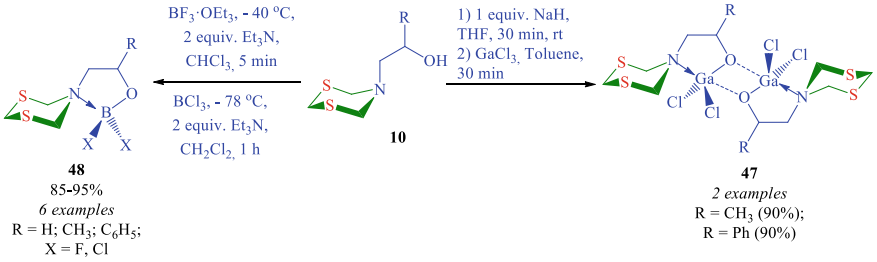
1,3,5-Dithiazinanes are valuable ligands capable of coordinating the nitrogen atom to the backbone group with various Lewis acids. For example, the work [40] details the synthesis of organometallic aluminum compounds on the basis of 2-(1,3,5-dithiazinan-5-yl)ethanol **10** as a polydentate ligand. Thus, 1,3,5-dithiazinane **10** coordinates with $AlMe_3$ or $AlMe_2Cl$ taken in equimolar amounts in toluene. The result is a dimeric complex **43** containing pentacoordinated aluminum atoms with the nitrogen and oxygen atoms of the ligand (Scheme 5.16). The application of 2-(1,3,5-dithiazinan-5-yl)ethanol **10** with a methyl substituent in the ethyl fragment of the ligand under the developed conditions produces monometallic compounds with tetracoordinated aluminum atoms of the type O-(AlMeY)-2-(1,3,5-dithiazinan-5-yl)ethanolates **44**. In the case of involving a twofold excess of aluminum reagents, tetracoordinated dialuminum complexes **45** and **46** were obtained. The structure of all the organometallic compounds of aluminum was proven by the X-ray diffraction method.



Scheme 5.16 Complex compounds of 2-(1,3,5-dithiazinan-5-yl)ethanol **10** with $AlMe_3$ and $AlMe_2Cl$

As shown in Scheme 5.17, ethanol dithiazinanes **10** proved to be effective chelating ligands with $BF_3{\cdot}OEt_2$, $BCl_3{\cdot}DMS$ and $GaCl_3$, forming the corresponding nitrogen-coordinated complexes N → $GaCl_2O$ **47**, N → BF_2O and N → BCl_2O **48** [41]. The gallium complex **47** is pentacyclic with two six-membered rings in a chair conformation, two five-membered rings in an envelope conformation, and one four-membered ring. Gallium is coordinated to the nitrogen atom of the dithiazinane ring in the equatorial position, while the ethanol moiety is coordinated in the axial position (Fig. 5.6).

The synthesis of tripodal ligand precursors is based on the preparation of enantiomerically pure 5-((*S*)-2-chloro-1-propyl)-1,3,5-dithiazinane **49** starting from (*S*)-1-chloropropylamine hydrochloride **48** (Scheme 5.18). Dithiazinane **49** is formed in a mixture with 3,5-di[(*S*)-2-chloro-1-propyl]-1,3,5-thiadiazinane in a 2:1 ratio, separated by column chromatography on silica gel. In order to obtain hindered conformations of the dithiazinane ring, borane addition was carried out to form *N*-adducts **50.** The borane group was found to fix the propyl group of the complex as well and have



Scheme 5.17 Complexes of gallium **47** and boron **48** with 2-(1,3,5-dithiazinan-5-yl)-ethanol derivatives **10**

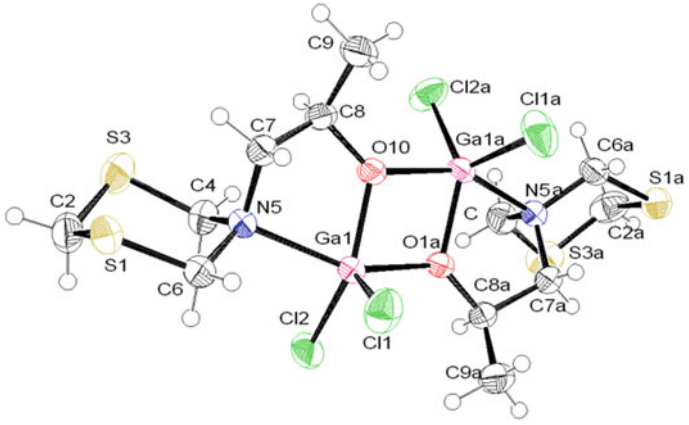
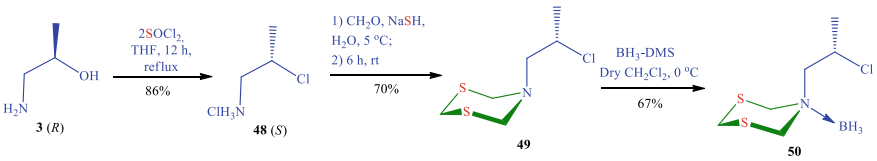


Fig. 5.6 Dimer structure of the gallium **47** (R=CH_3) chelate complex in crystal (CCDC 653944) [41]

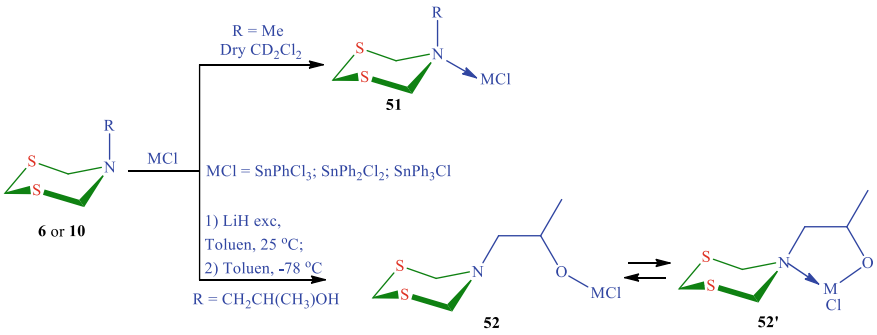


Scheme 5.18 Synthesis of 5-((*S*)-2-chloro-1-propyl)-1,3,5-dithiazinane **49** and its *N*-adduct with BH_3 **50**

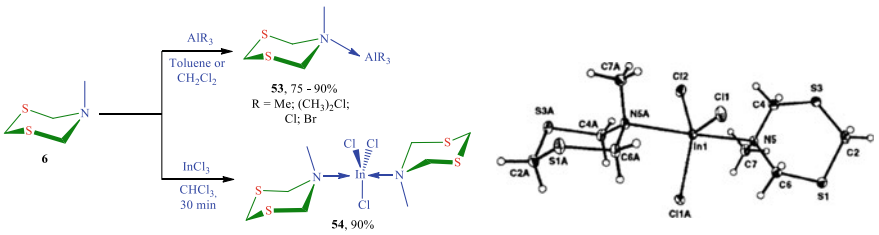
g- and *ε*-shielding electronic effects on protons. The authors of the work observe the adducts with BH_3 to be more reactive to reduction reactions [85].

Less stable complexes were observed in the experiments of mixing in an inert environment an equimolar amount of 5-methyl-1,3,5-dithiazinane **6** with $SnPh_3Cl$, $SnPh_2Cl_2$ and $SnPhCl_3$ in CD_2Cl_2 medium (Scheme 5.19). Complexation results in the formation of mononuclear tin(IV) N-adducts **51**, with the strength of the N → Sn coordination bond depending on the acidity and steric hindrance of chlorophenyltin [59]. Tin complexes with (*R*-2-hydroxy-prop-1-yl-[1,3,5]-dithiazinane **10** form O-tin(IV) adducts **52** and are in equilibrium between the open and spirane structures **52′**. Moreover, the equilibrium shifts toward a closed structure owing to an increase in the acidity of tin and a decrease in volume.

The study of 5-methyl-1,3,5-dithiazinanes **6** with $Al(CH_3)_3$, $Al(CH_3)_2Cl$, $AlCl_3$, $AlBr_3$ was carried out in Refs. [38, 39]. Mixing the starting components in toluene (or CH_2Cl_2) at 4 °C was found to give exclusively mono-N-adducts (Scheme 5.20). NMR spectroscopy and XRD studies revealed that the dithiazinane rings are present in a chair conformation. ^{27}A1 NMR confirmed the presence of characteristic signals in the range of δ = 110–183 ppm in the resulting adducts **53**. It is noteworthy that the equimolecular interaction of 5-methyl-1,3,5-dithiazinane **6** with $InCl_3$ in toluene at room temperature produces an In(III) complex with *bis*-N-ligands **54**, the structure of which was analyzed by X-ray diffraction. Likewise, dithiazinane rings maintain a chair conformation with the methyl group in the axial position.



Scheme 5.19 Tin complexes with nitrogen-containing 1,3,5-heterocyclohexanes **6** and **10**



Scheme 5.20 Mono- and *bis-N*-adducts **53**, **54** with 5-methyl-1,3,5-dithiazinane **5.** Molecular structure of indium(III) complex **54** in crystal (CCDC 217489) [38, 39]

The use of boron adducts as starting ligands for the synthesis of multipodal (one C2 proton of the heterocycle is replaced) (5-methyl-1,3,5-dithiazin-2-yl)silanes **55**–**57** and stannanes **58, 59** was implemented in the work [36]. A number of mono-, di- and tri-N-borane adducts based on 1,3,5-dithiazinan-silanes and -stannanes have been obtained (Fig. 5.7). The NMR spectroscopy data indicated that addition of borane to di- and tridithiazinyl compounds has an additive and systematic effect on the central Si-Me or Sn-Me groups. It should be noted that the resulting complexes are sensitive to moisture. The original result was provided by X-ray diffraction analysis of diborane adduct **55**. It was found that the N-adduct has a folded conformation, providing chemically identical S···S interactions between the four sulfur atoms, thereby making the sulfur atoms more positive and increasing the stability of the interactions (Fig. 5.8).

The synthesis of bipodal ligands *bis*(5-methyl-[1,3,5]-dithiazinan-2-yl)sulfide and *bis*(5-methyl-[1,3,5]-dithiazinan-2-yl)selenide **61** was carried out through the preliminary tripodal *tris*(5-methyl-1,3,5-dithiazinan-2-yl)stibine **60** with the metalloid as the central atom (Scheme 5.21).

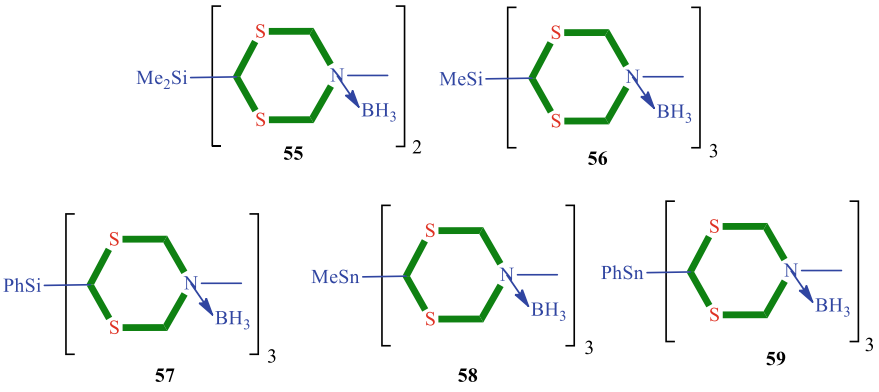


Fig. 5.7 Structures of N-adducts of BH_3 with (1,3,5-dithiazin-2-yl)silanes **55**–**57** and stannanes **58**, **59**

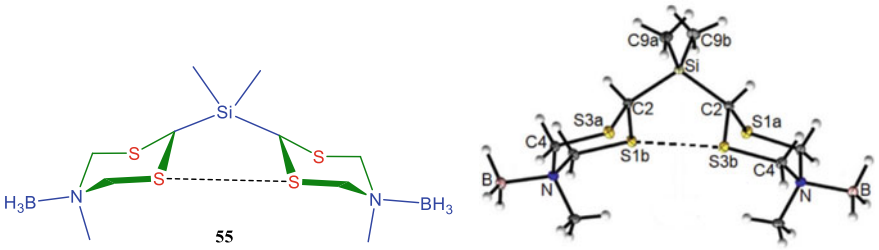
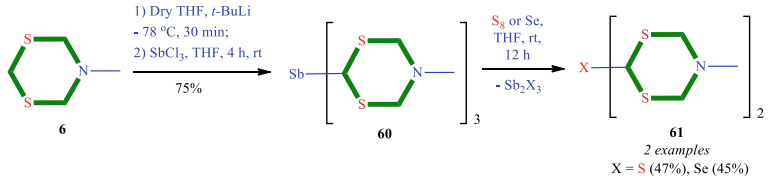


Fig. 5.8 Structure of compound **55** obtained from a single-crystal (CCDC 1993974) [36]

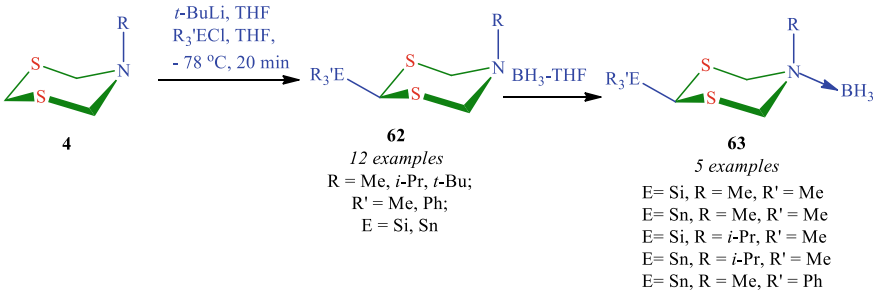


Scheme 5.21 Synthesis of *tris*(5-methyl-1,3,5-dithiazinanyl)stibine **60** and bipodal chalcogens **61**

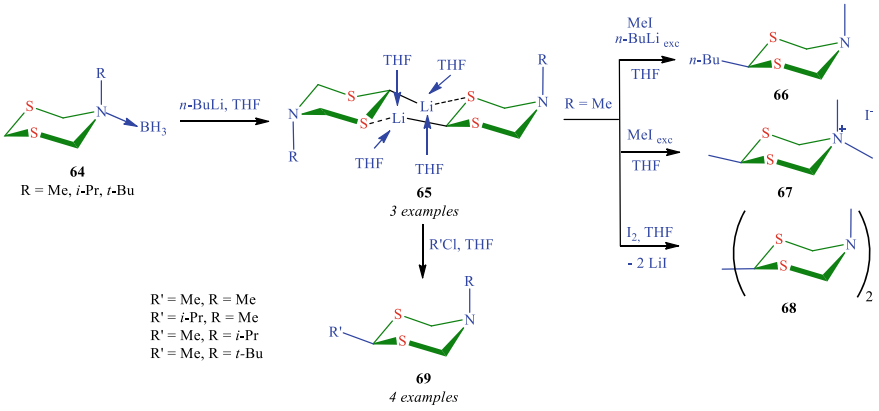
The synthesis of the latter was carried out by the interaction of 5-methyl-1,3,5-dithiazinane **6** with $SbCl_3$ in THF. The resulting chalcogen derivatives are stable products with the presence of many heteroatoms bearing lone pairs and separated by acidic methylene groups in the structure. Based on X-ray diffraction analysis, the presence of bonds Sb···S, Se···S and S···S was determined, and tricentric interactions S···S···S and S···Se···S were discovered in sulfides and selenides **61**, respectively [77]. These compounds are promising for complexation with boranes.

There are studies on the reaction of 1,3,5-dithiazinanes **4** with triorganylsilanyl- or triorganylstannyl—groups at the C-2 position of the heterocycle in order to stabilize ring inversion (Scheme 5.22). The dithiazinane ring was found to be in a chair conformation in the crystal of compound **62** with the N–R group in the axial position and 2-substituents in the equatorial position. Further experiments on the preparation of N-BH_3 adducts **63** with 1,3,5-dithiazinanes **4** lead to a blocked conformation and a configuration with retention of the ring chair conformation. Moreover, N-borane groups have an equatorial position even in the presence of N-bulky substituents [27].

N-Borane adducts of mono- and dialkyl-1,3,5-dithiazinanes proved to be effective for multipodal coordination at the C-2 position, through the *in-situ* synthesis of lithium adducts **65** (Scheme 5.23). As a result of the reaction of the latter with iodine, a dimeric structure **68** is formed, with a central ethylene group bearing four sulfur atoms. The crystal of the compound contained *syn*- and *anti*-conformations of C2–C2 bonds. The reaction with an excess of methyl iodide induces methylation of the C-2 position with quaternization of the tertiary amine **67** as well. The reaction with three equivalents of *n*-BuLi, and then one equivalent of methyl iodide in THF, produces dithiazinane **66** with the *n*-Bu group at C-2 position of the heterocycle. A similar reaction with methyl iodide or isopropyl chloride gives compounds **69** [35].



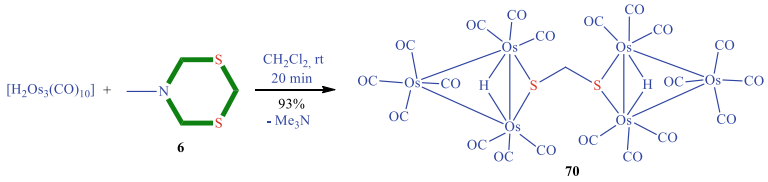
Scheme 5.22 Synthesis of 2-triorganylsilyl- and 2-triorganylstannyl derivatives of 1,3,5-dithiazinanes **62** and their N–BH_3 adducts **63**



Scheme 5.23 Synthesis of mono- and dimeric dialkyl-1,3,5-dithiazinanes **66–69** by alkylation through *N*-borane adducts and organolithium derivatives

5.4.2 *Complexation with $[H_2Os_3(CO)_{10}]$*

The complexing ability of 1,3,5-dithiazinane **6** with respect to the osmium metal complex $[H_2Os_3(CO)_{10}]$ has been studied (Scheme 5.24). The reaction results in the opening of the dithiazinane ring with the cleavage of the C–S, C–N and C–H bonds and formation of a connected cluster **70** with bridging fragments S–C and S–C–N, while the sulfur atoms form metal–metal bonds. The authors suggest that when the dithiazinane heterocycle is coordinated with one or more metal atoms, a change in the polarity of the endocyclic carbon atoms occurs, contributing to the attack of one of the hydride groups of the cluster [65].

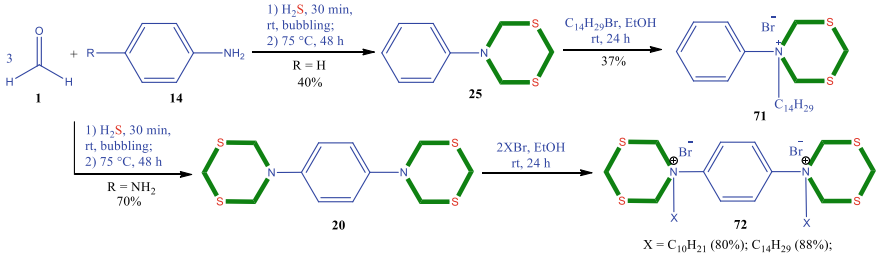


Scheme 5.24 Reaction of $[H_2Os_3(CO)_{10}]$ with *S*,*N*-containing six-membered heterocycle **6**

5.4.3 Complexes with Alkyl Halides

Dimeric quaternary ammonium salts are known to be an innovative class of multifunctional materials that can be applied as corrosion inhibitors including good biocidal properties as well [22]. Recently, the authors of the work [14] proposed the synthesis of a quaternary ammonium salt based on 5-phenyl-1,3,5-dithiazinane **25** in this regard (Scheme 5.25). The resulting compounds **25** and **71** were tested as potential corrosion inhibitors of carbon steel (C 95) in 2 M hydrochloric acid by the Tafel polarization method. 5-Phenyl-5-tetradecyl-1,3,5-dithiazinan-5-bromide **71** was found to act as a mixed type inhibitor and at a concentration of 0.005 M, the greatest effect was observed for carbon steel. Obviously, the combination of a heterocyclic fragment and a quaternary ammonium salt in a molecule provides the maximum anti-corrosion effect. It should be mentioned that the compounds did not exhibit antimicrobial activity against gram-negative *Staphylococcus epidermis* and gram-positive *Escherichia coli* bacteria.

Further research included the synthesis of *bis*(1,3,5-dithiazinanes) **20** and its heterocyclic cations **72** by the same group of authors [15]. In this case, the chosen strategy for the synthesis of molecules proved to be successful due to the enhancement of both anti-corrosion and antimicrobial properties in salts **72** (Scheme 5.25).

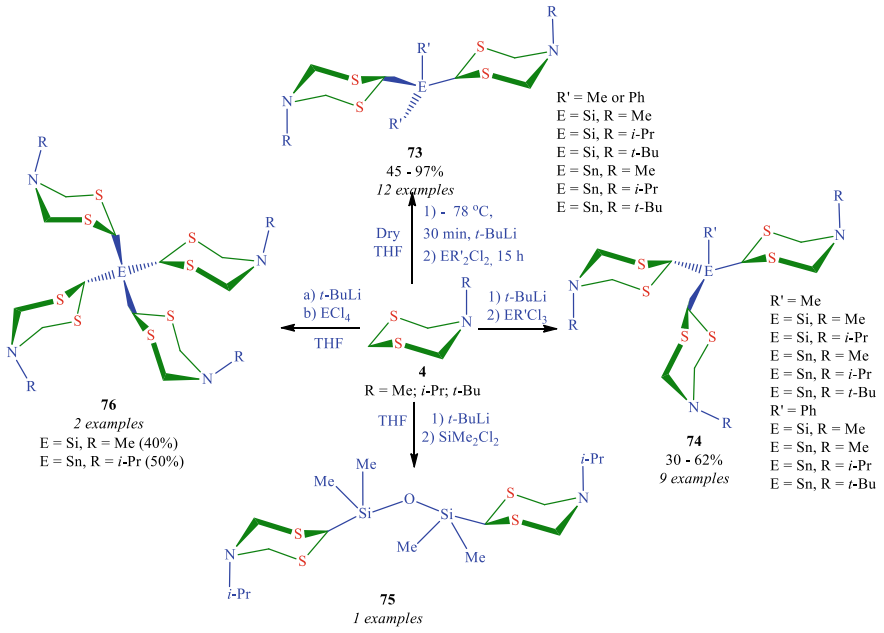


Scheme 5.25 One-pot synthesis of dithiazinanes **20**, **25** and their alkylation in the synthesis of cationic salts **71** and **72**

5.5 Synthesis of Organoelement Derivatives of 1,3,5-Dithiazinanes

Modification of 1,3,5-dithiazinanes **4** in the synthesis of organoelement derivatives gave *bis-, tris- and tetrakis*(1,3,5-dithiazinano)silicon and tin **74–76** (Scheme 5.26). The point is that 1,3,5-dithiazinanes **4** exhibit CH-acid properties at the second position and form 2-lithium-1,3,5-dithiazinanes under the action of the strong base *t*-BuLi at -70 °C, transformed from $R_2Si(Sn)Cl_2$ to *bis*-(dithiazinan-2-yl)dialkyl silanes or stannanes. Accordingly, the use of reagents $RSi(Sn)Cl_3$ or $Si(Sn)Cl_4$ produces *tris- and tetrakis*-derivatives of silicon and tin. The work also describes siloxane reagents effective in the synthesis of *bis*[(5-isopropyl-1,3,5-dithiazinan-2-yl)dimethylsilyl ether **75** [57].

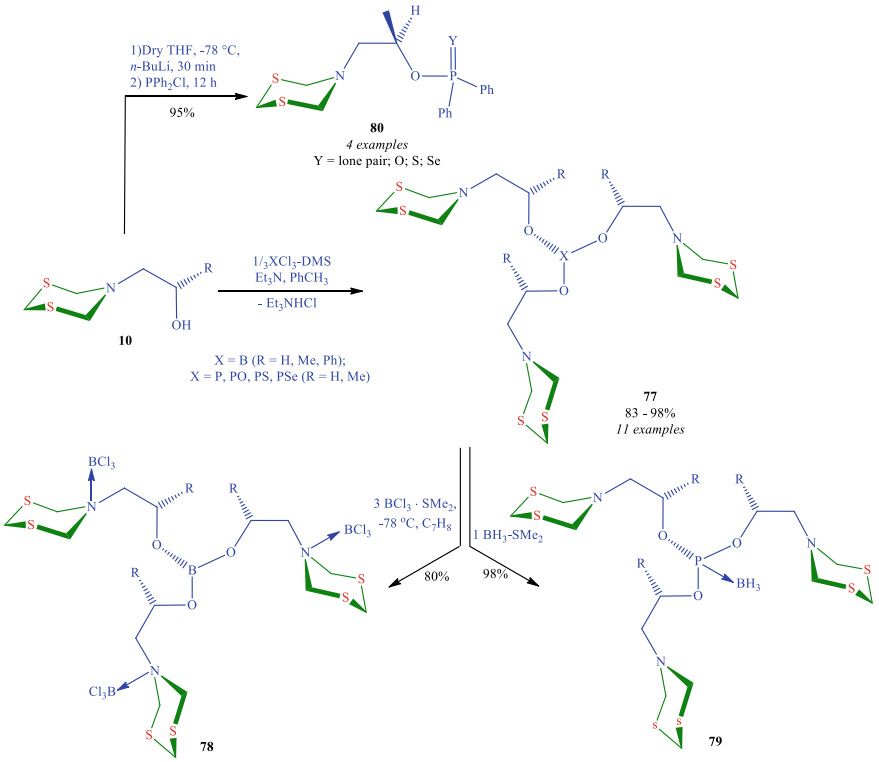
The synthesis of tripodal compounds based on ethanol dithiazinanes including fragments of planar tricoordinated boron esters, phosphites, phosphates, thiophosphates and selenophosphates is presented in [30]. Further studies on the reaction of boric acid ester with $BCl_3 \cdot SMe_2$ revealed that all three nitrogen atoms readily coordinated with the Lewis acid in N → BCl_3 manner (Scheme 5.27). This experiment confirmed the spatial accessibility of amino groups for coordination and the conformational equilibrium of the dithiazinane rings. Indeed, mixing an equimolar amount of phosphite **77** with $BH_3 \cdot SMe_2$ produces a single adduct **78** coordinated at the P → BH_3 atom, proving phosphorus to have sufficient space for coordination



Scheme 5.26 Synthesis of organoelement derivatives of 1,3,5-dithiazinane **74–76**

as well. The preparation of 1,3,5-dithiazinanes substituted at the β-position by N-propyl groups with $OP(Y)Ph_2$ moiety bearing chalcogenide atoms (O, S and Se) has been recently reported. Phosphinites **80** are obtained in good yield by the reaction of **10** with *n*-BuLi followed by the introduction of PPh_2Cl in THF at − 78 °C. The resulting compounds were sensitive to moisture [86].

Under similar conditions, a series of compounds based on N-methyl-1,3,5-dithiazinane at the C-2 position of the heterocycle were prepared: (5-methyl-1,3,5-dithiazinan-2-yl)diphenylphosphine and its oxide, sulfide and selenide, *bis*(5-methyl-1,3,5-dithiazinan-2-yl)phenylphosphine and its sulfide and selenide, *tris*(5-methyl-1,3,5-dithiazinan-2-yl)phosphine and its sulfide and selenide **81–83** [58]. The authors of the work demonstrate that chalcogen pulls back the density of phosphorus in phosphorus oxides, stabilizing the supply of intracycle sulfur and phosphorus, thereby ensuring the stability of these molecules (Fig. 5.9).



Scheme 5.27 Selective synthesis of mono- and tripodal compounds based on ethanol dithiazinanes, with fragments of boron and phosphorus esters

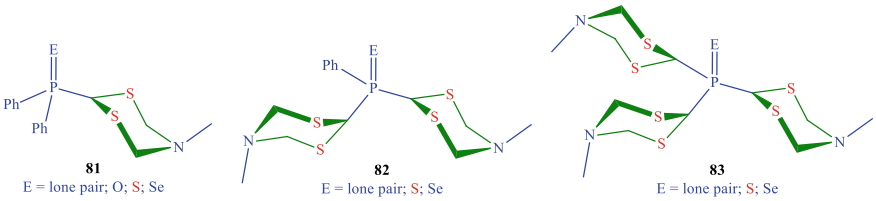
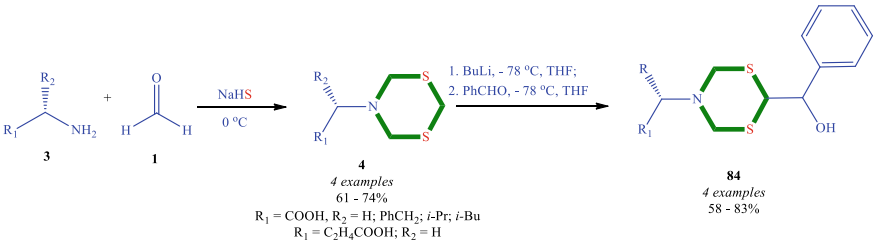


Fig. 5.9 Structures of (5-methyl-1,3,5-dithiazinan-2-yl)phosphines and their P = S and P = Se analogues

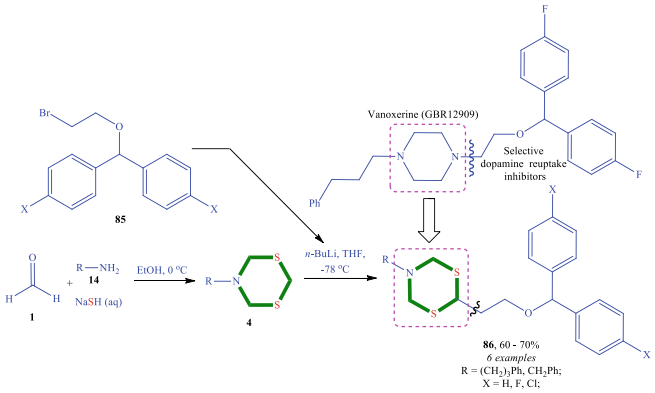
5.6 C2 Functionalization of 1,3,5-Dithiazinanes

Initially, sodium hydrosulfide and formaldehyde were used in the reactions with amines in a stoichiometric ratio of amine-formaldehyde-NaHS equal to 1:3:2 to form 1,3,5-dithiazinane rings **4** (Scheme 5.28). 1,3,5-Dithiazinanes **4** exhibit CH-acid properties at the second position. Thus, under the influence of strong organic bases, they form organometallic compounds, easily transformed with electrophiles into the C2 function. The authors suggest a two-stage synthesis of 2,5-disubstituted 1,3,5-dithiazinanes **84** based on the MCR of aliphatic and aromatic amines **3** with a thiomethylating mixture "CH_2O-NaHS" in ethanol at 0 °C, followed by alkylation of the heterocycle **4** to the second position involving benzaldehyde in the presence of the reaction activator *n*-BuLi at − 78 °C [50].

Similar strategy for the synthesis of the Vanoxerine analogue (12,909) with the structure of 2,5-disubstituted dithiazinanes **86** has been detailed [80]. Initially, the corresponding amine **14** was condensed with formaldehyde **1** in absolute ethyl alcohol (Scheme 5.29). Then, an aqueous solution of sodium hydrogen sulfide was introduced at 0 °C. Heterocycles, piperazine and 1,3,5-dithiazinane, having 1,4- and 2,5-substituents are ligands of the selective dopamine transporter of high affinity. The synthesis of 1,3,5-dithiazinane derivatives GBR 12,909 was carried out through the alkylation of 5-(3-phenylpropyl)-1,3,5-dithiazinane **4** with substituted 1-bromo-2-[*bis*(4-phenyl substituted)-methoxy]ethane **85**. Further, analogues with benzyl substituents were prepared. Benzyl analogues turned out to be more



Scheme 5.28 Two-step synthesis of 2,5-disubstituted dithiazinanes **84** with the participation of sodium hydrosulfide



Scheme 5.29 Strategy for the synthesis of Vanoxerine analog (GBR12909) with the structure of 2,5-disubstituted dithiazinanes **86**

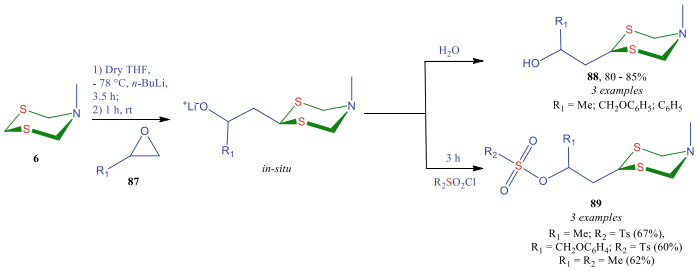
selective for dopamine transporters. The synthesis of 1,5-(3-phenylpropyl)-1,3,5-dithiazinane and 5-benzyl-1,3,5-dithiazinane **4** applying established procedures from 3-phenylpropylamine and benzylamine **14**, respectively, in the presence of *n*-BuLi bases in THF, is presented in Scheme 5.29.

This stable interest in 5-methyl-1,3,5-dithiazinane is caused by the ability to form multipodal compounds obtained by substituting a proton at the C-2 position of the heteroatom [77]. These molecules exhibit weak intramolecular nonclassical interactions due to the soft nature of the sulfur atoms. As a result, the ability to invert the polarity (umpolung) of organic functions is acquired, which is more typical for dithiane groups [78].

Preparation of new 1,3,5-dithiazinane derivatives **88** and **89**, functionalized at the C2 position with groups such as β-propanol, γ-phenoxy-β-propanol, β-phenyl-β-ethanol, β-(4-methylbenzenesulfonate)-propyl and β-methanesulfonate-propyl, is detailed in [78]. The synthesis methodology is based on the preparation of an intermediate lithium β-alcoholate, subsequently hydrolyzed to form hydroxyl derivatives of 1,3,5-dithiazinane **88**. Lithium methyl- and phenoxy-β-alcoholates reacted with *p*-toluenesulfonyl chloride or methylsulfonyl chloride to give corresponding sulfonate and methylsulfonate derivatives **89** (Scheme 5.30).

5.7 Original Approaches to the Synthesis of 1,3,5-Dithiazinanes

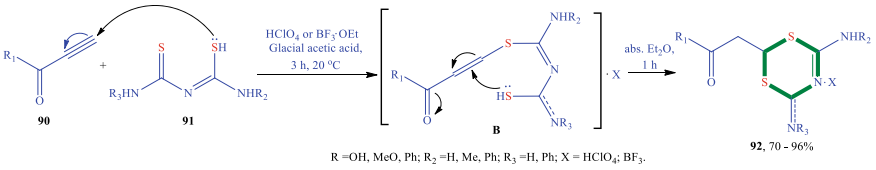
An original synthesis of unsaturated S,N-heterocycles **92** in good yield and selectivity was suggested by the authors of the work [43]. The approach is based on the reaction of activated acetylenes **90** with ambident nucleophiles based on dithiobiurets **91** in AcOH in the presence of $HClO_4$ or $BF_3 \bullet OEt$ (Scheme 5.31). It is noteworthy that



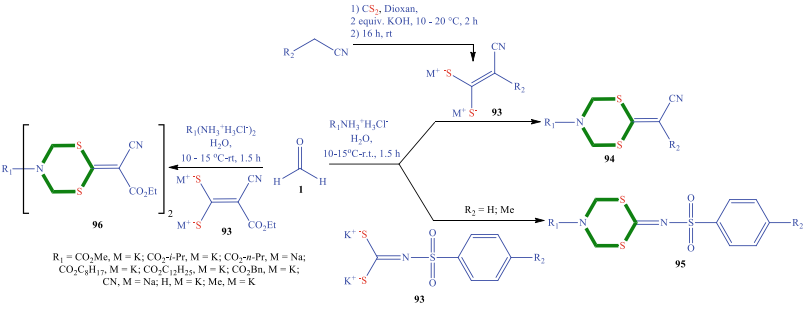
Scheme 5.30 Synthesis of 1,3,5-dithiazinanes **88** and **89** containing β-alcohol or β-sulfonate fragments at the C2 position

an additional *in-situ* stirring of the reaction mass in absolute diethyl ether causes formation of powdered 2-substituted perchlorates or trifluoroborates of 4-amino-6-imino-1,3,5-dithiazinium **92** with a yield of more than 70%.

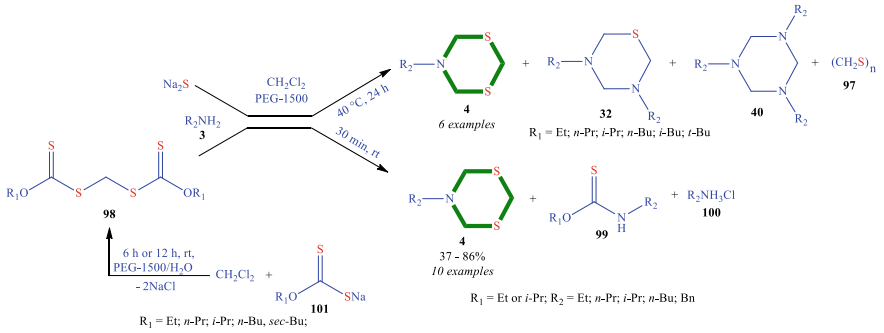
Another unusual technique for the preparation of C2-functionalized 1,3,5-dithiazinanes is based on the heterocyclization of dithiolate synthons containing SCSC chains in the molecule. Thus, there is an example of the synthesis of 5,6-dihydro-*4H*-1,3,5-dithiazines **94–96** starting from alkali metal dithiolates **93** (Scheme 5.32). Multicomponent condensation is based on the Mannich reaction of dithiolates **93** with formaldehyde **1** and primary amine hydrochlorides in water at room temperature [44].



Scheme 5.31 Synthesis of tetrahydro 1,3,5-dithiazinine derivatives **92**



Scheme 5.32 MCR of alkali metal dithiolates **93** with formaldehyde **1** and amines in the synthesis of 5,6-dihydro-4*H*-1,3,5-dithiazines **94–96**



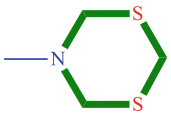
Scheme 5.33 Reactions of dichloromethane with thioanions (sodium sulfide or *bis*(alkoxythiocarbonylthio)methane) and monoalkylamines

An original approach for the preparation of dithiazinane heterocycles **4** was described in [75]. The synthesis method is based on the use of methylene chloride as a C-1 reagent and solvent for the reaction mixture. The reaction is carried out by mixing sodium sulfide and monoalkylamines **3** in the presence of 5 mol% polyethylene glycol (PEG-1500) at 40 °C for 24 h at the optimal molar ratio of RNH_2:Na_2S:NaOH:PEG = 0.8:0.4:0.4:0.02 (Scheme 5.33). The addition of sodium hydroxide is necessary to neutralize the hydrochloric acid resulting from aminolysis of CH_2Cl_2 and increase of the conversion of Na_2S. The formation of by-products included 1,3,5-thiadiazinane **32**, 1,3,5-triazinane **40** and polymethylene sulfide **97**. A more selective reaction was achieved while using *bis*(alkoxythiocarbonylthio)methane **98** as a reagent, obtained by catalyzed by PEG-1500 reaction of sodium O-alkyldithiocarbonates **101** in water with dichloromethane [21, 25].

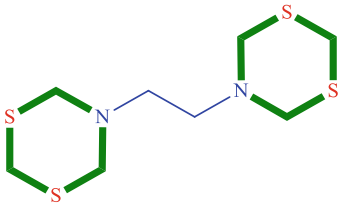
Still, these approaches have not found wide application for the preparation of dithiazinane heterocycles in practice because of the low selectivity of the reaction, the use of specific starting reagents, low temperatures and absolute solvents. Meanwhile, the yields of target heterocycles ranging from satisfactory to high and the *one-pot* methodology for obtaining substituted heterocycles can offer new prospects for the application of these reactions.

5.8 Practical Application of 1,3,5-Dithiazinanes

S,N-containing heterocycles, being polydentate ligands, are of interest as potential complexing agents, sorbents and extractants of noble and heavy metals [3, 4, 60]. The high affinity of mercury ions for sulfur (considering the LMCO principle) is essential in the development of novel adsorption materials for the extraction of Hg(II) ions from polluted environments [76]. The same principle applies to non-toxic (pharmaceutical) sulfur-containing chelating agents used to remove toxic metal ions from the



6
(Au) (Chanturia et al. 2015)



35
(Pd, Ag, Hg), (Anpilogova et al. 2011);
(Au) (Chanturia et al. 2015)

Fig. 5.10 Examples of 1,3,5-dithiazinanes **6** and **35** as *S*,*N*-containing chelating agents

intracellular or extracellular spaces of the body, thereby eliminating bioaccumulation with severe toxic consequences [33].

Thus, the sorption properties of weakly basic *bis*(1,3,5-dithiazinan-5-yl)-ethane **35** in relation to Pd(II), Ag(I) and Hg(II) ions at room temperature (Fig. 5.10) have been studied [20]. The presence of four thioether-electron-donating sulfur atoms in the reagent provides high sorption affinity for soft metal ions. The reagent effectively sorbs palladium(II) from 2 to 5 M HCl solutions (the maximum static sorption capacity is 7.8 mmol/g), from a 0.1 M HNO_3 solution silver(I) (27.4 mmol/g) and mercury(II) (19.0 mmol/g).

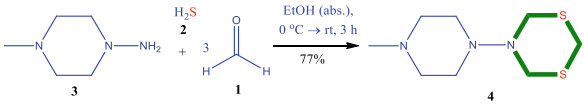
The authors made the assumption that the first stage of sorption interaction is based on the formation of ionic associates through the anion exchange mechanism. Unlike ion exchange resins, the sorption of the studied metals occurs irreversibly in this case accompanied by the destruction of the reagent:

$$2\mathrm{LH} + \mathrm{Cl}^{-}_{(s)} + \mathrm{PdCl}^{2-}_{4(s)} \leftrightarrow \left(\mathrm{LH}^{+}\right)_2\mathrm{PdCl}^{2-}_{4(s)} + 2\mathrm{Cl}^{-}_{(aq)}$$

LH ligand.

The studies confirming the high sorption efficiency of dithiazinane bases containing donor tertiary nitrogen and sulfur atoms separated by alkyl fragments have been reported (Fig. 5.10). On the example of two heterocycles, perhydro-1,3,5-dithiazin-5-yl-methane **6** and *bis*-perhydro-1,3,5-dithiazin-5-yl-ethane **35**, the efficiency of complex formation in an aqueous medium was demonstrated for gold extraction from difficult-to-process raw materials to flotation tests on ores with the study of the surface conditions of pyrite with artificially deposited gold (FeS_2Au) [26]. The authors classify the resulting compounds to hazard class III–IV in terms of toxicity. Meanwhile, laboratory tests showed that introduction of the *bis*-perhydro-1,3,5-dithiazine reagent **35** to butyl xanthate made it possible to increase the recovery of gold in the main and middling flotation concentrates by 15.9 and 4%, respectively (the degree of Au recovery was 81.66%). The most optimal ratio for the flotation of gold-bearing raw materials turned out to be the ratio of a mixture of xanthate and 1,3,5-dithiazin-5-yl-methane of 25–50% when used as a complexing agent, contributing to the improvement of technological performance [42].

Scheme 5.34 Synthesis of 5-(4-methylpiperazin-1-yl)-1,3,5-dithiazinane **4** with anti-corrosion properties



The authors of the work [55] conducted a targeted synthesis of potential metal corrosion inhibitors containing a piperazine fragment in the molecule. It is noteworthy that when synthesizing the target dithiazinane **4** by mixing 1-amino-4-methylpiperazine **3** with the thiomethylating reagent "$H_2S–CH_2O$," the yield of the target product **4** did not exceed 20% (Scheme 5.34). In this case, changing the sequence of mixing the starting amine **3** with formaldehyde **1** for 2 h at a temperature of 0 °C and subsequent bubbling with hydrogen sulfide **2** made it possible to increase the yield of 5-(4-methylpiperazin-1-yl)-1,3,5-dithiazinane **4** to 70%. The screening of anti-corrosion properties under conditions of immersion of N-80 carbon steel samples for 5 h in a 0.5 M HCl solution at 25 °C demonstrated that 1,3,5-dithiazinane **4** forms a protective film on metal surfaces as a result of adsorption and chemisorption with a degree of inhibition efficiency of 88.15%.

5.9 Conclusion

The development of research in the field of synthesis of sulfur-containing heterocycles, including 1,3,5-dithiazinanes, was largely facilitated by the availability and low prices of the raw materials H_2S and its salts NaHS, Na_2S, CS_2, as well as the variety of applied properties of the synthesized heterocycles. Considering the principles of green chemistry, the MCR cyclothiomethylation of amines seems to be a technological approach for the synthesis of 1,3,5-dithiazinanes, as well as catalytic transamination reaction of N-methyl-1,3,5-dithiazinane and 1,3,5-tritiane by aromatic amines. Other synthetic approaches are still few in number and require refinement of reactions to increase the selectivity. Currently, 1,3,5-dithiazinanes are applied as food additives imitating the flavor of grilled meat, nuts, seafood and also as sorbents of metals, especially gold and mercury. The high affinity of the soft thioether groups of the dithiazinane framework for heavy metals makes them suitable for chelation therapy, binding toxic metal ions to form structures thereby facilitating their effective removal from biological environments. Another aspect of application is acid and microbiological corrosion inhibitors. Based on the experiences, 1,3,5-dithiazinane derivatives proved to be promising inhibitors of the development of pathogenic microorganisms (viruses, bacteria, fungi) that are capable of developing resistance to traditional drugs. Obviously, it exposes research chemists to new experiences in the field of pharmaceuticals. The most important area worthy of a thorough research study is synthesis of dithiazinane complexes with transition metals and aluminum and boron salts. On the one hand, such compounds can be metal-complex catalysts with many aspects still to be explored. On the other hand, dithiazinane compounds, like thiolate

complexes of metalloenzymes, may have the ability to inhibit biological targets when creating targeted agents.

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Chapter 6
Synthesis and Biological Evaluation of Benzothiazepine, Benzothiazole, and Benzothiophene Derivatives

Kishor R. Desai, Vedant Patel, Misha Patel, Bhavin R. Patel, and Anand J. Patel

6.1 Introduction

One of the most varied families of organic molecules, heterocycles have a wide range of biological functions and are highly valued by the pharmaceutical, agrochemical, cosmetic, and other sectors [1].

Heterocycles are significant pharmacophores that are vital for forming unique chemical compounds with physiological properties. Broad-spectrum therapeutic medicines contain five-membered heterocyclic compounds that include nitrogen, sulphur, and oxygen as heteroatom. These compounds are highly essential to the processes of drug development and discovery [2].

Medium-sized benzo fused N and S heterocycle (Fig. 6.1) syntheses have attracted the interest of synthetic and medicinal chemists for over a century because their scaffolds are important components of many bioactive natural alkaloids and synthetic drugs with intriguing physiological properties [3–5]. Because of the broad range of applications along with their adaptable chemical properties, N-heterocycles play a significant role in many scientific, industrial, and medical fields [6]. These compounds which contain a nitrogen atom in ring structure are essential to fields of materials science, agro-chemistry, and medicine [7]. Heterocyclic compounds containing sulphur find applications as drugs and therapeutics due to their significant biological activity [8]. Sulphur drug, which contains a sulphur-containing ring, is essential for treating bacterial infections. Certain sulphur-containing heterocycles are also used as fundamental compounds in the pharmaceutical industry, enabling them into various medicines, including antibiotic and antiviral treatments [9].

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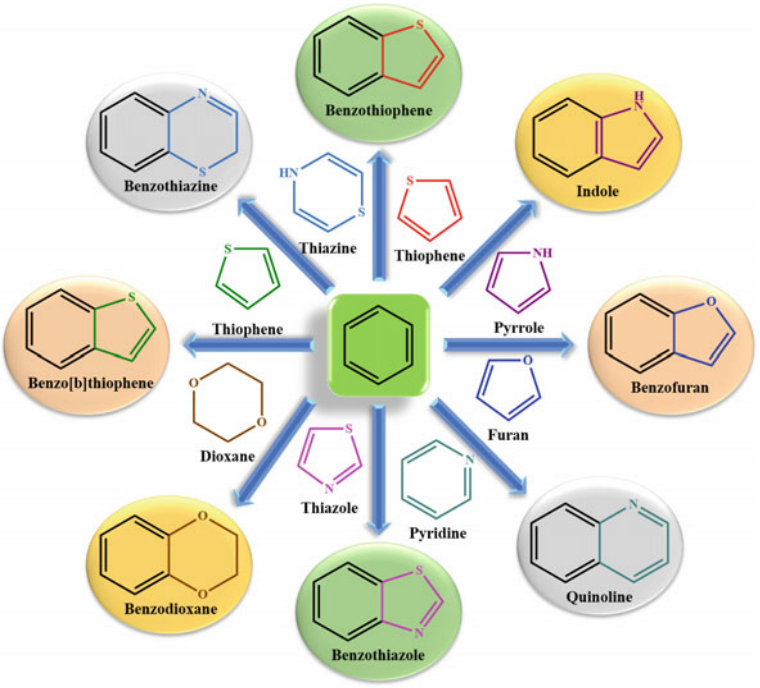


Fig. 6.1 Integration of heterocyclic ring systems with benzene rings [1–9]

Heterocycles containing sulphur and nitrogen are crucial to medicinal chemistry because they have specific pharmaceutical characteristics that affect how molecules interact with biological targets [8]. They are added to a variety of medications, such as antibiotics and antiviral therapies, to improve their efficacy and selectivity. A heterocyclic ring fused to a benzene ring is significant because it can give the resulting molecule unique and enhanced properties that affect its chemical and biological activity [10]. A hybrid structure is created that combines the different reactivities and electronic properties of the heterocyclic ring with the aromatic stability of benzene [11]. This structural configuration often results in molecules with altered physical and chemical properties, which can have important implications in several scientific areas [12].

6.2 Benzothiazepines

Benzothiazepines constitute a class of compounds in which thiazepine ring fused to a benzene ring. These scaffolds have garnered a great deal of interest in medicinal chemistry because of their exceptional pharmacological significance and variety of synthesis methods [13]. The importance of different synthetic approaches lies in

the ability to modulate the structure of benzothiazepines, resulting in compounds with different pharmacological properties, significant impact on various scientific areas [14]. In addition, benzothiazepines have been studied for their antimicrobial properties. This group of compounds has demonstrated antibacterial and antifungal properties, suggesting that it holds promise in treating infectious diseases [15].

A derivative of benzothiazepine used as a calcium channel blocker is called diltiazem (Fig. 6.2). It is frequently given to treat angina and hypertension [16].

Amongst the dibenzothiazepine class of medications is Quetiapine and Clothiapine, a typical antipsychotic (Fig. 6.3) [17].

Benzodiazepines are a diverse class of chemicals with a broad spectrum of pharmaceutical effects. Current research focuses on optimizing their pharmacokinetic properties and discovering new therapeutic applications for these molecules [15] 1,4-, 4,1-, and 1,5-benzothiazepines are the three different classes they have been classified into (Fig. 6.4). 1,5-Benzothiazepines have been extensively studied for the synthesis of novel therapeutic molecules [13].

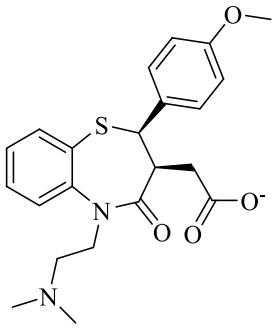


Fig. 6.2 Derivative of benzothiazepine used as a calcium channel blocker [16]

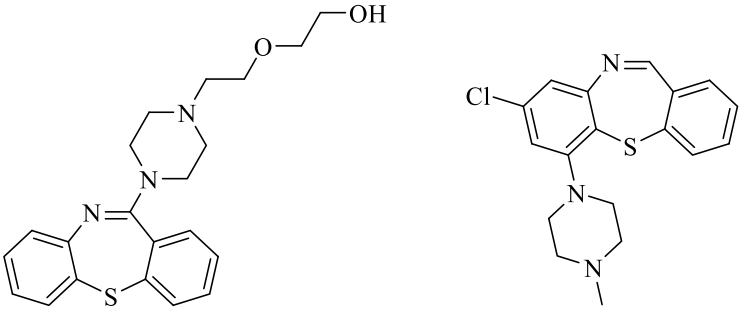


Fig. 6.3 Derivative of benzothiazepine used as an a typical antipsychotic [17]

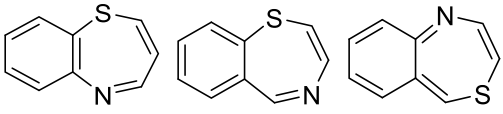


Fig. 6.4 The arrangements of benzothiazepines at the 1,5-, 4,1-, and 1,4-positions [13]

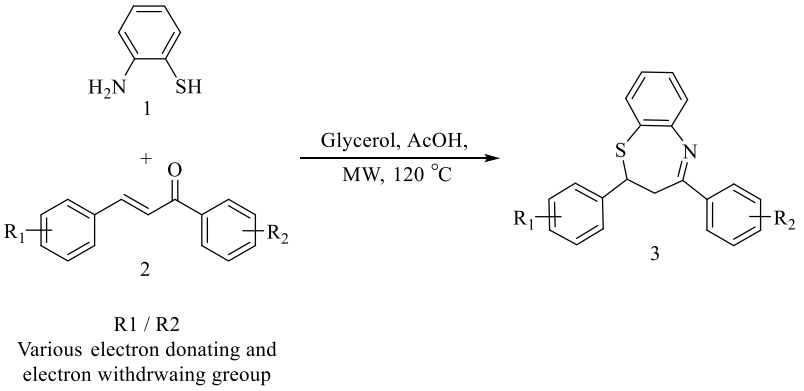
6.2.1 *Different Synthetic Approach for Benzothiazepines*

Kotalwar and colleagues have devised an ecologically conscious approach for the generation of pharmaceutically significant 2,3-dihydro-1,5-benzothiazepines by means of microwave irradiation in a more sustainable reaction medium. The procedure entails the condensation of α,β-unsaturated carbonyl moiety with o-amino thiophenol utilizing glycerol as the reaction medium (Scheme 6.1). Prominent attributes of this method comprise its environmentally friendly conditions, short reaction durations, and impressive yield [18].

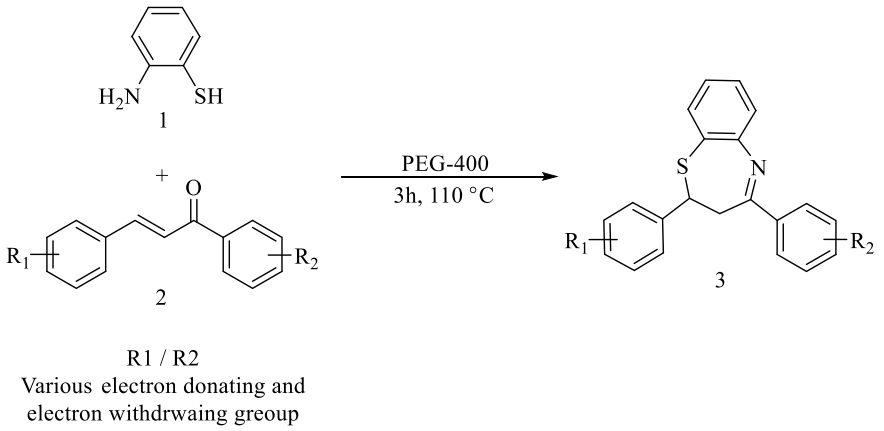
Lingampalle and colleagues have devised an eco-friendly one-step procedure for the production of 1,5-benzothiazepines from 1,3-diarylpropen-1-ones and o-amino thiophenol (Scheme 6.2). Through a comparative investigation, the traditional synthesis route was contrasted with the novel approach. Remarkably, it was observed that the latter methodology exhibited superior efficacy in retrieving the final compounds post-purification, thereby showcasing its commendable environmental advantages [19].

Chandrashekhar et al. developed a sustainable method for 1,5-benzothiazepines synthesis using ultrasound irradiation. The process involved the cyclo condensation of chalcone derivatives with o-amino thiophenol in presence of polyethylene glycol (PEG-400) as a medium (Scheme 6.3). The environmental friendliness, short response time, easy separation of product, and reusability of PEG-400 were significant characteristics of the methodology [20].

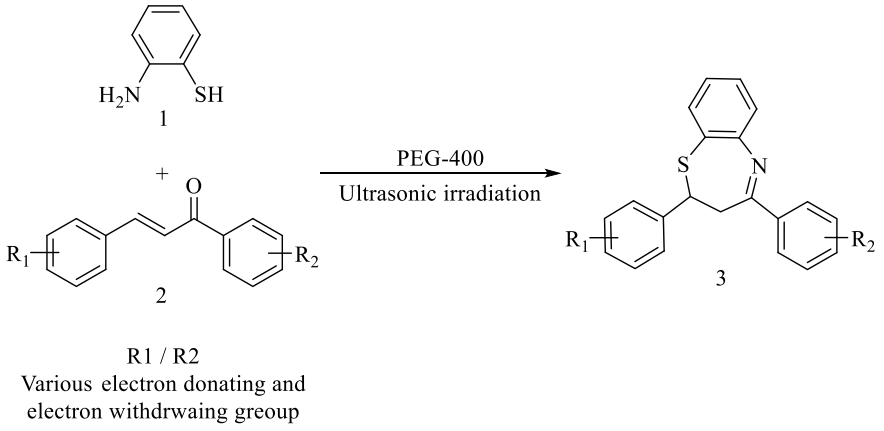
Sakirolla and colleagues have devised di-cationic ionic liquid catalyzed an environmentally conscious approach to producing 1,5-benzothiazepines from o-amino thiophenol and chalcones (Scheme 6.4). The investigation revealed that IL-C demonstrated superior performance in terms of reaction time and desired yield of the product. Additionally, the authors explored the substrate range and reusability of



Scheme 6.1 Microwave-induced synthesis of benzothaizepine from chalcones using glycerol as reaction medium [18]



Scheme 6.2 PEG-400 mediated synthesis of benzothaizepine from chalcones [19]

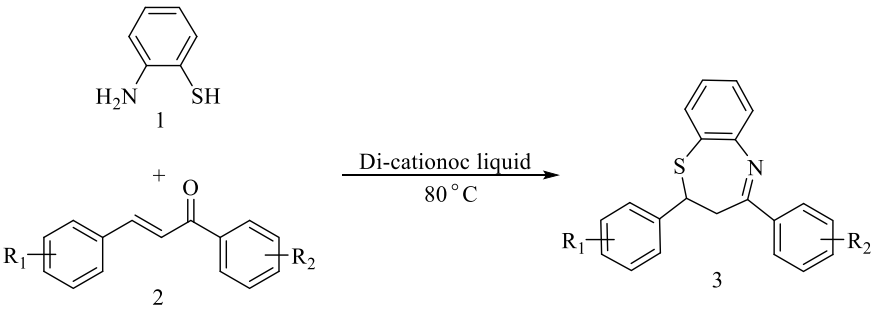


Scheme 6.3 Sonochemical synthesis of benzothaizepine from chalcones using PEG-400 [20]

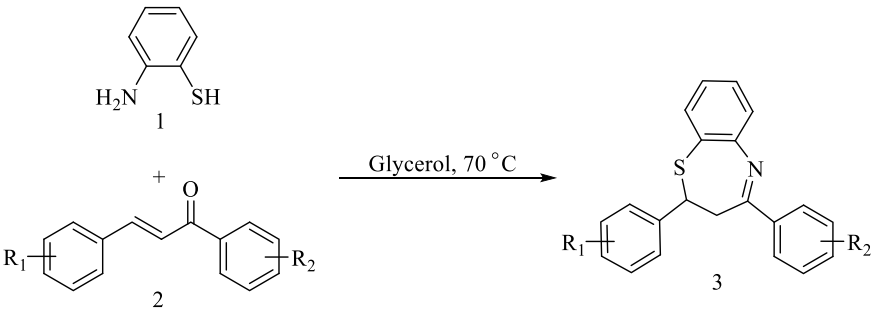
the catalyst, proposing a reaction mechanism involving a 1,4-conjugated Michael addition followed by a cyclo condensation reaction [21].

Yadav and co-workers developed a clean and efficient one-pot strategy for 2,3-dihydro-1,5-benzothiazepines synthesis from o-amino thiophenol and chalcone in glycerol (Propane-1,2,3,-triol) as a biodegradable medium (Scheme 6.5). The study examined the influence of temperature, catalyst, and solvent on the results of protocol. The best-optimized conditions were 70 °C without a catalyst and with a wide substrate range. Key features included environmentally friendly solvents, mild reaction conditions without catalyst, cheap reactants, good yields, ease of operation, and easy product isolation [22].

Domenico and group investigated a new, eco-friendly, and high-yielding two-component domino process for 2,3-dihydro-1,5-benzothiazepines synthesis. The



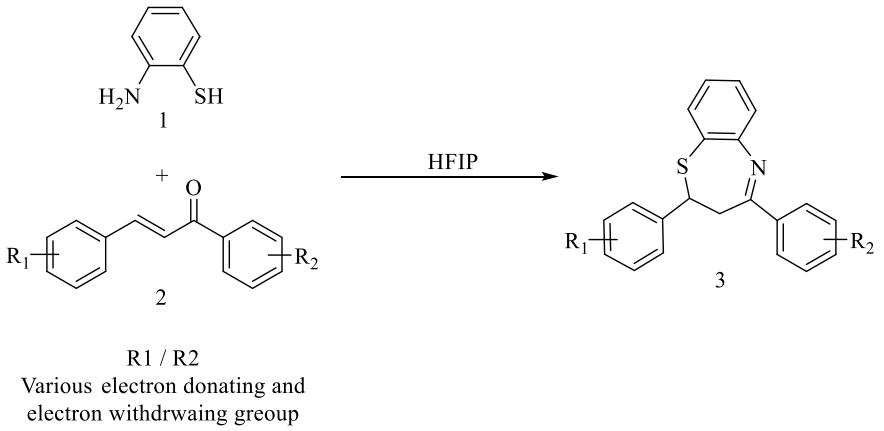
Scheme 6.4 Benzothaizepine synthesis from chalcones using di-cationic liquid at 80 °C [21]



Scheme 6.5 Benzothaizepine synthesis from chalcones using glycerol at 70 °C [22]

process includes the condensation of o-amino thiophenol with chalcones in a mildly acidic solvent, hexafluoro-2-propanol (HFIP) (Scheme 6.6). It was observed that other solvents such as acetone, DCM, DMF, and dioxane resulted in lower yields. Key features of the protocol include solvent reusability and higher yields under mildly acidic conditions, ensuring smooth reactions under optimized conditions [23].

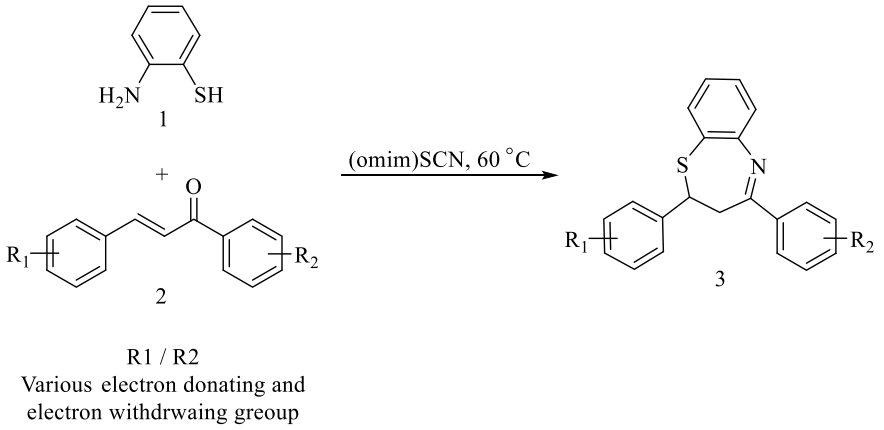
Sharifia et al. developed a clean, environmentally friendly, chemoselective, ionic liquid mediated, and catalyst-free method for 1,5-benzothiazepines synthesis using 2-amino thiophenol and chalcones (Scheme 6.7). The optimization of reaction was done concerning solvent, temperature, and amounts of amino thiophenol. The method provided satisfactory products with satisfactory yields using 1 mmol of chalcone



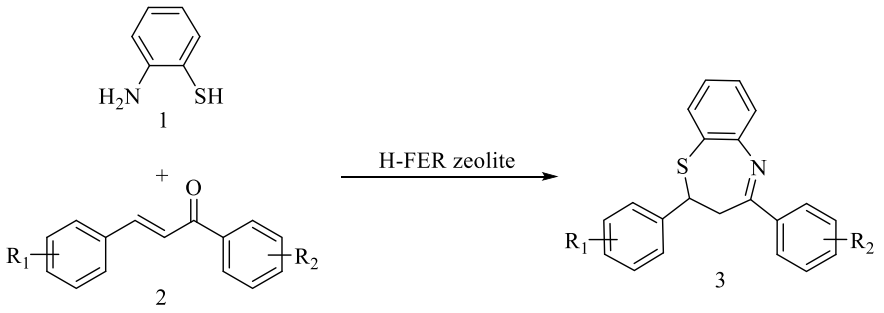
Scheme 6.6 Benzothaizepine synthesis from chalcones using hexafluoro-2-propanol [23]

and 1.5 mmol of amino thiophenol in 1-octyl-3-methylimidazolium thiocyanate or [omim] SCN at 60 °C (Scheme 6.7) [24].

Farghaly et al. developed a method to synthesize 1,5-benzothiazepines using substituted chalcones and o-amino thiophenol in a high-yield, solvent-free reaction (Scheme 6.8). The Michael adduct intermediate was formed, which was dehydrated and cyclized to produce the desired compounds. The process was further expanded to include the synthesis of 1,2,4-triazolo benzothaizepines through the condensation of o-nitro thiophenol and chalcones in Na_2CO_3/THAC. In terms of substrate selection, atom economy, and catalyst reusability, the process was determined to be effective and economical [25].



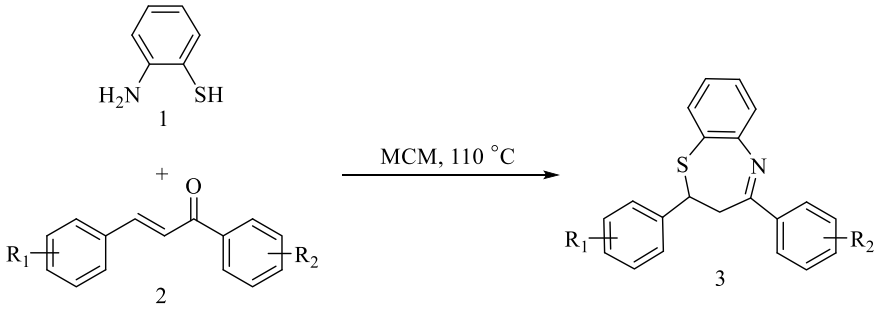
Scheme 6.7 Ionic liquid mediated synthetic method for benzothaizepine from chalcones [24]



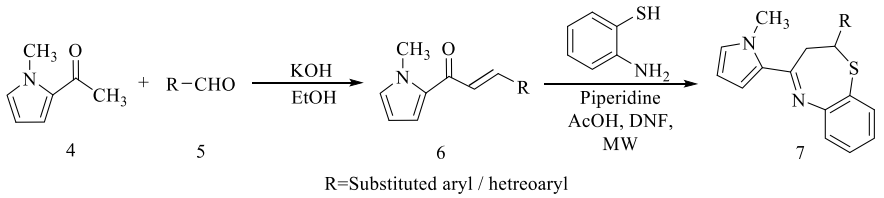
Scheme 6.8 Benzothaizepine synthesis from chalcones using H-FER zeolite [25]

A one-pot solid-phase protocol for the synthesis of 2,3-dihydro-1,5-benzothaizepines from the cyclocondensation of chalcones was developed by Climent and co-workers. Basic catalyst Al–Mg mixed oxide was employed for the preparation of intermediate chalcones. The synthesized chalcones were then treated with 2-amino thiophenol in presence of MCM-41 acid catalyst to give the final products (Scheme 6.9). The protocol was efficient in both batch and continuous modes and resulted in good to excellent yields [26].

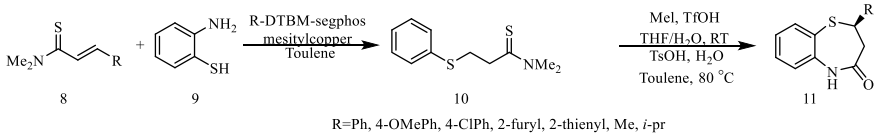
Microwave-induced synthesis of some pyrrole-bound 1,5-benzothiazepine scaffolds was reported by Yenupuri et al. The intermediate chalcones were prepared by condensation between 2-acetyl-1-methylpyrrole and aromatic/heteroaromatic aldehydes in ethanol according to Claisen–Schmidt condensation reaction. The mixture



Scheme 6.9 Benzothaizepine synthesis from chalcones using MCM-41 acid catalyst [26]



Scheme 6.10 Microwave-induced synthesis of some pyrrole-bound 1,5-benzothiazepine scaffolds [27]



Scheme 6.11 Chiral 1,5-benzothaizepinone synthesis [28]

of chalcone and 2-amino thiphenol was irradiated under microwaves with acetic acid and piperidine as co-catalysts in DMF, resulting in satisfactory to good yields of the titled products (Scheme 6.10) [27].

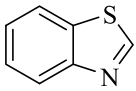
Mesityl copper/(R)-DTBM-Segphos, a Cu-based catalyst, was used by Ogawa and co-workers to synthesize enantioenriched 1,5-benzothiazepinones. Thiol was added asymmetrically to α- and β-unsaturated thioamides. The ideal parameters were 0.25 mol% of the catalyst and 1.2 equivalents of o-aminothiophenol. This intermediate enabled the enantioselective generation of the C−S bond in a THF/water system when treated with methyl iodide in the presence of TfOH, leading to good to excellent yields of titled products (Scheme 6.11). After studying the electrical potential of the substrate, the reaction could be effectively scaled to the gramme range without sacrificing stereoselectivity [28].

6.3 Benzothiazole

The fused ring structure of benzothiazole, an organic heterocyclic molecule, consists of a thiazole ring fused with benzene ring (Fig. 6.5). A nitrogen atom, a sulphur atom, and four-carbon atoms form the five-membered thiazole ring itself. Due to its structural configuration, benzothiazole has special chemical properties that make it an important substance in medicinal and pharmaceutical chemistry as well as a versatile building block in organic synthesis [29, 30].

The diverse uses of benzothiazole in drug development contribute to its importance in the pharmaceutical industry. Derivatives of benzothiazoles exhibit a varied range of biological effects, such as antibacterial, anticancer, anti-inflammatory, and anti-tumour [31]. In order to produce and synthesize a variety of active medicinal

Fig. 6.5 Structure of benzothiazole [29]



Benzothiazole

compounds, these materials serve as necessary building blocks, which aids in the development of novel medications with enhanced therapeutic efficacy [32].

The biological activity of benzothiazole derivatives can be explained by how they interact with biological macromolecules such as DNA and enzymes to influence cellular pathways and processes. Structure–activity relationship studies help in understanding and optimizing their pharmacological effects. Due to certain structural properties, benzothiazoles can bind to biological targets [33]. Using computational and experimental methods, rational drug design modifies these structures to increase medical efficacy and bioavailability and minimize negative effects [34].

Due to their special chemical properties and wide range of applications, benzothiazole and its derivatives are important in a variety of fields, including materials science and medicine. Scientific studies combine computer modelling, molecular biology, synthetic chemistry, and other methods to understand and exploit their potential [35].

When compared to the common medication Etoposide, the thiourea-containing benzothiazole derivative (Fig. 6.6) showed the strongest antiproliferative effect against the U-937 cell line [31].

A benzothiazole derivative containing cyanophenyl group showed impressive anti-tumour properties (Fig. 6.7) [36].

The dichloro phenyl-containing chloro-benzothiazole (Fig. 6.8) exhibited robust anticancer properties against nine different cancer cell lines, as indicated by its GI50 values spanning from 1.60 to 71.8 nM [31].

Benzothiazole is a structurally different substance with a broad spectrum of possible applications, especially in the pharmaceutical field as well as in chemical synthesis, photophysical properties, as corrosion inhibitor and as agrochemicals (Table 6.1). Its value as a fundamental ingredient in the development of therapeutically relevant compounds is highlighted by its adaptability in drug development and a varied range of biological potency. Research on benzothiazole and its properties is

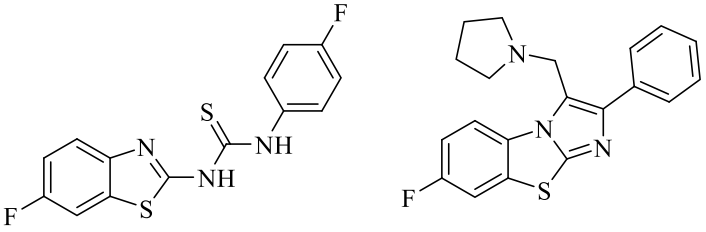


Fig. 6.6 Benzothiazole derivative used as an antiproliferative [31]

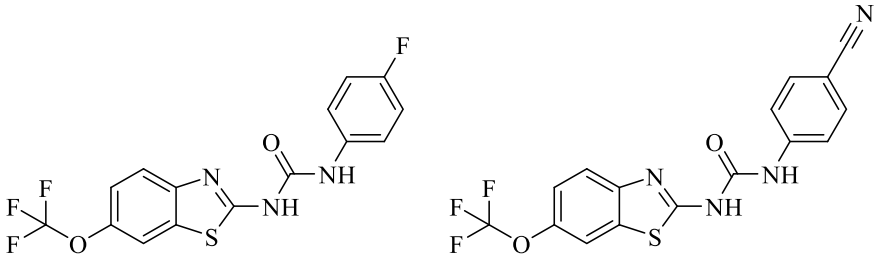


Fig. 6.7 Benzothiazole derivative used as an anti-tumour [36]

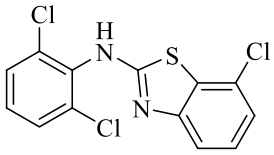


Fig. 6.8 Benzothiazole derivative exhibited anti-cancer properties [31]

ongoing, which promotes pharmaceutical research and leads to the development of novel drugs [37].

Table 6.1 The multidimensional significance of benzothiazole derivatives: a comprehensive overview [38–43]

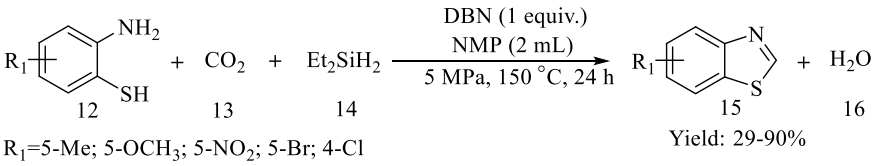
S. no	Aspect	Importance
1	Biological significance	The biological effects of benzothiazole derivatives are different, some derivatives showed antibacterial, antiviral, and anticancer effects, making them relevant for pharmaceutical research and drug development
2	Medicinal application	Benzothiazole are essential structural element used in the manufacture of many different medications. Some benzothiazole derivatives are used to treat neurological diseases, particularly ALS. Rizole is one such derivative
3	Chemical synthesis	A flexible basic component for organic synthesis is benzothiazole. Its derivatives are often used to construct complex organic molecules, supporting the development of novel substances and materials
4	Photophysical properties	Derivatives of benzothiazole often exhibit fascinating photophysical properties such as fluorescence. For this reason, they can be used to produce fluorescent dyes and probes for imaging applications in chemistry and biology
5	Corrosion inhibition	Some benzothiazole derivatives have the ability to suppress corrosion, making them useful in the production of corrosion inhibition to protect metals in a variety of industries, including oil and gas
6	Agrochemicals	Certain benzothiazole derivatives are used in the production of agrochemicals that contribute to the development of fungicides and insecticides that protect crops

6.3.1 *Different Synthetic Approach for Benzothiazole Derivatives*

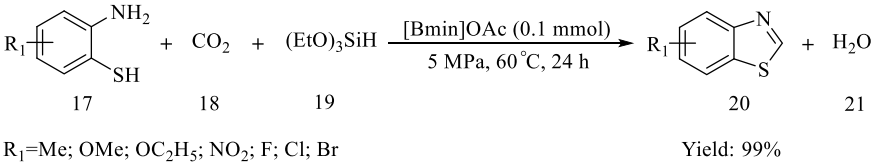
The article by Gao et al. [44] presents a report on benzothiazole synthesis from *o*-amino thiophenols, CO_2, and diethylsilane through a cyclization process. This process was conducted in the presence of diethyltoluene, under the effect of DBN (Scheme 6.12). The researchers were able to achieve excellent yields of various benzothiazole derivatives. The results of this investigation show how important hydrocyane is to the synthesis of benzothiazoles, as it effectively prevents the formation of benzothiazolones as unwanted byproducts. Overall, this approach offers an environmentally sustainable method for synthesizing benzothiazoles and their derivatives [44].

Furthermore, Gao and colleagues [45] employed a highly efficient catalyst, specifically an ionic liquid derived from acetate, to facilitate the cyclization of *o*-amino benzenethiols with CO_2 in the presence of Tris(trimethylsilyl)silane (Scheme 6.13). For the synthesis of a range of benzothiazoles, the researchers also investigated the impact of different temperatures, pressures, and catalyst types on this reaction. Notably, the reaction with [Bmim] [OAc] at 60 °C yielded excellent outcomes. Additionally, it was determined that [Bmim] [OAc] exhibited environmentally friendly characteristics, and even after being utilized five times, the yield of benzothiazole remained consistently high. This innovative process represents a potential breakthrough in utilizing CO_2 as a raw material for the synthesis of benzothiazoles within a mild and metal-free environment [45].

Chun et al. [46] conducted a study wherein they developed a reaction involving the utilization of 2-aminobenzenethiols, CO_2, and phenylsilane. This reaction was conducted in the presence of DBU and resulted in the synthesis of benzothiazoles with excellent yields (Scheme 6.14). The researchers observed a comprehensive range of



Scheme 6.12 DBN catalyzed synthesis of benzothiazole from 2-aminothiophenols [44]

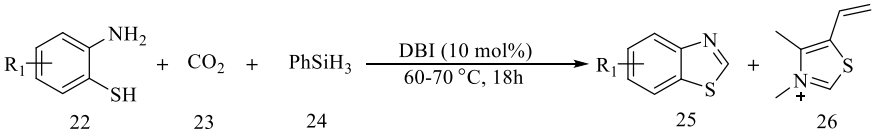


Scheme 6.13 Ionic liquid mediated synthesis of benzothiazole from 2-aminothiophenol [45]

substrates and noted the resistance of various functional groups towards this reaction. Additionally, they found that the pre-catalyst salt could be recycled multiple times without any loss in its activity [46].

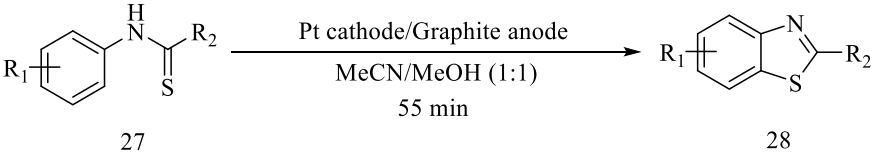
Folgueiras and colleagues [47] discovered that benzothiazoles can be synthesized through an electrolyte-free electrochemical and catalyst-free process using a flow electrochemical reactor (Scheme 6.15). This method yields moderate to good results and exhibits high current performances when aryl-thioamides are used as starting materials. Furthermore, the scalability of this reaction greatly improves the existing methodologies for benzothiazole production in this particular process [47].

According to Rey et al. [48], the cyclization of thioformanilides in the presence of toluene and 1,2-dichloroethane at 83.5 °C temperature proved to be a highly effective approach for 2-substituted benzothiazole synthesis (Scheme 6.16). This reaction pathway is straightforward to monitor and results in the formation of easily isolable compounds, with yields ranging from low to high [48].



R_1=F; Cl; Br; I; Me; OMe; C_2H_5; OC_2H_5; OCF_3 Yield: 33-90%

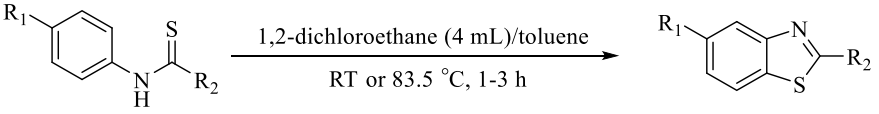
Scheme 6.14 Conversion of 2-aminobenzenethiols to benzothiazoles in the presence of DBU [46]



R_1=H; SCH_3; OCF_3; OCH_3
R_2=Ph

Yield:35-97%

Scheme 6.15 Electrochemical synthesis of benzothiazoles [47]



R_1=H; OCH_3
R_2=Ph; *t*-Bu; 4-C_6H_4-Z(z-t-Bu; CH_3)

Yield:5-80%

Scheme 6.16 Radical cyclization of thioformanilide [48]

6.4 Benzothiophene

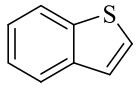
A benzene ring that fused with a thiophene ring results in the formation of a heterocyclic compound known as benzothiophene (Fig. 6.9). The thiophene ring, which comprises four-carbon atoms and one Sulphur atom, possesses an typical and fragrant configuration [49]. Due to the distinctive characteristics bestowed upon it by this particular chemical arrangement, benzothiophene serves as a noteworthy molecule that finds extensive applications in both scientific and industrial domains [50].

Due to its numerous applications in the realm of medicinal chemistry and pharmaceutical research, benzothiophene holds great significance within the pharmaceutical industry. Scientists and researchers have acknowledged and utilized benzothiophene derivatives as fundamental components in the development of bioactive compounds [51]. By virtue of its heterocyclic and aromatic nature, benzothiophene exhibits favorable pharmacological properties that enable its integration into therapeutic molecules, thereby enhancing their precision and effectiveness [52].

The medicinal advantages of benzothiophene derivatives have been explored extensively across diverse medical conditions. These compounds frequently manifest a broad spectrum of biological potency, including anticancer, antibacterial, and anti-inflammatory. Furthermore, benzothiophene-containing compounds are frequently employed as frameworks for the development of pharmacological agents that specifically target particular enzymes or receptors [53–55].

Qunilone fused benzothiophene derivatives were evaluated for their antiproliferative potential (Fig. 6.10) [49]. It shows DNA intercalation activity, when quinolone ring nitrogen was substituted with imidazolinyl ring.

Aleksic et al. [56] synthesized benzothiophene carboxanilide (Fig. 6.11). Through a 3D-QSAR analysis, it was found that the compound can bind to DNA as a binder and has high cytotoxicity against various cancer cell lines [56].



Benzothiophene

Fig. 6.9 Structure of benzothiophene [50]

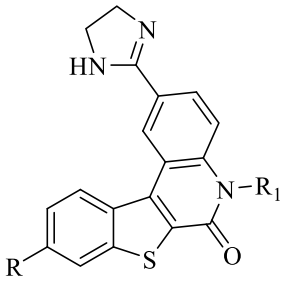


Fig. 6.10 Derivative of benzothiophene showing anti-proliferative DNA intercalation potential [49]

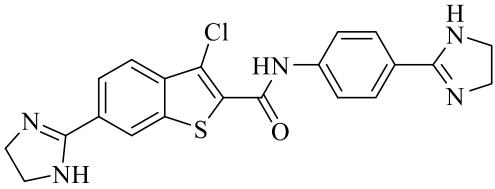


Fig. 6.11 Derivative of benzothiophene having high cytotoxicity [56]

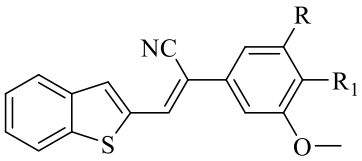


Fig. 6.12 Derivative of benzothiophene showing strong anticancer effects [57]

Pethana et al. synthesized benzothiophene acrylonitrile analogues and tested for their biological activity (Fig. 6.12). On evaluation it was found, strong anticancer effects are exhibited by benzothiophene acrylonitrile analogues, which work by interfering with tubulin polymerization [57].

In summary, the unique configuration of benzothiophene renders it an advantageous foundational component in the realm of pharmaceutical exploration and advancement (Table 6.2). The extensive array of pharmacological activities it exhibits and its adaptability as a framework exemplify its significance in the quest for innovative and potent therapeutic agents [58]. Ongoing investigations into derivatives of benzothiophene continue to contribute to the advancement of pharmaceutical science and the discovery of unprecedented treatments [59].

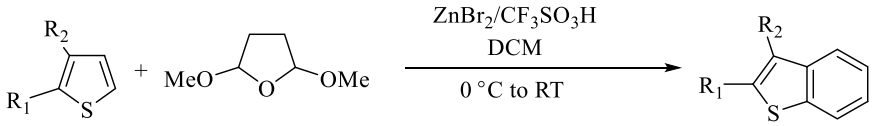
6.4.1 Different Synthetic Approach for Benzothiophene Derivatives

In the year 2014, Mohanakrishnan and colleagues successfully created dibenzothiophene and its derivatives using Lewis's acid/Brönsted acid-mediated cyclization. To carry out this reaction, a four-carbon synthon known as 2,5-Dimethoxytetrahydrofuran was employed, which then reacted with thiophene and benzothiophene via a cyclization reaction that took place at room temperature (Scheme 6.17) [65].

The functionalized derivatives of dibenzothiophene, as depicted in, arise from an anionic cyclization that occurs on an aryl lithium intermediate tethered to a benzyne moiety. This phenomenon was documented by the Fananas group in the year 2006. By treating 2-fluorophenyl 2-iodophenyl thioether with 3.3 equivalents of t-BuLi, the aforementioned reaction was initiated (Scheme 6.18). Subsequently, the resulting product proceeded to partake in further reactions with specific electrophiles [66].

Table 6.2 Numerous uses for benzothiophene: an important ingredient in chemical structure, biological activity, environment impact, scientific significance [53, 60–64]

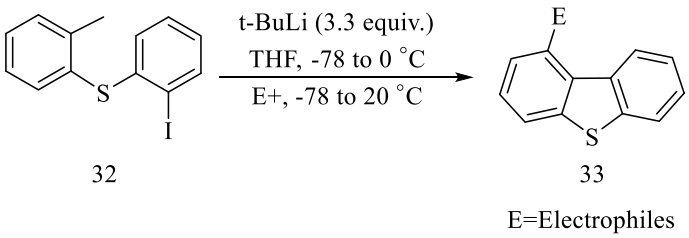
S. no	Aspect	Importance
1	Chemical structure	The heterocyclic compound benzothiophene is created when a thiophene ring is joined with a benzene ring. The distinctive properties of this substance are a result of its unique molecular arrangement
2	Application	Pharmaceuticals: Derivatives derived from benzothiophene play a crucial role in the development of pharmaceuticals and serve as fundamental constituents in the formulation of novel medicinal compounds
		Agrochemical: In the production of various pesticides and herbicides, it functions as a preliminary substance
		Material Science: Solar cells and organic light-emitting diodes (OLEDs) are illustrations of electrical devices that employ benzothiophene as a means to fabricate organic semiconductors [61]
3	Biological activity	The intriguing attributes of numerous benzothiophene derivatives in terms of biological activity have captured the attention of medicinal chemists. Ongoing research is currently underway to explore their potential application as antiviral, anticancer, and anti-inflammatory agents
4	Environment impact	The comprehension of benzothiophene's characteristics, a substance existing in crude oil, is essential due to its connection to the creation of sulphur-based contaminants when fossil fuels undergo combustion. This understanding aids in the facilitation of environmental control and surveillance
5	Scientific significance	Synthetic chemistry: It is an effective synthetic intermediate, allowing for the creation of a broad range of molecules that have different functions
		Drug development: The development of new medicines with improved medicinal properties is facilitated by the study of benzothiophene derivatives
		Material engineering: In the area of science materials, benzothiophene derivatives are used to create sophisticated materials with electronic uses



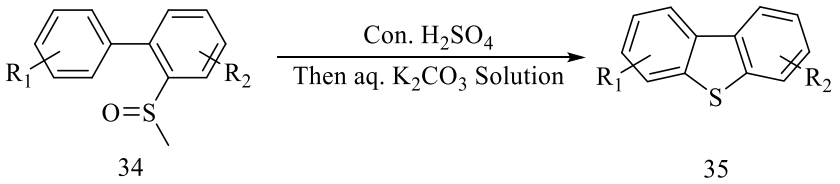
31 32 33

R1, R2=H, BrAlkyl, Aryl, Heteroaryl, 1,4-butan-1,3-diethyl, 5,6-diemthylenecyclohexa-1,3-dienyl

Scheme 6.17 Synthesis of dibenzothiophene through benzo-annulation of thiophene mediated by Lewis's acid and Brönsted acid [65]



Scheme 6.18 Organo lithium catalyzed synthesis of dibenzothiophene via anionic cyclization [66]

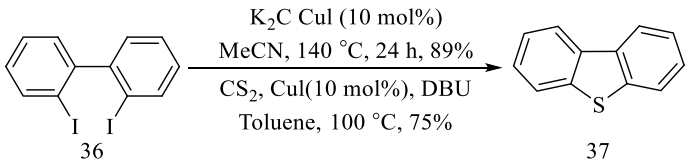


Scheme 6.19 The synthesis of dibenzothiophenes through acid-mediated intramolecular cyclization [67]

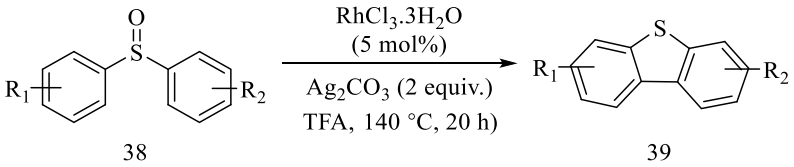
Depicts the practical and efficient technique introduced by the Patel research group in 2012 for synthesizing unsymmetrical dibenzothiophene derivatives. The utilization of Sulphuric acid in the intramolecular cyclization of biaryl sulfoxides facilitates the generation of dibenzothiophenes at reduced temperatures and with a remarkably short reaction time (Scheme 6.19). Notably, this method permits the incorporation of substituents at various positions on the dibenzothiophene molecule. Specifically, this approach simplifies the preparation of 1-substituted dibenzothiophene, which is traditionally challenging to achieve through direct substitution processes [67].

In 2010, the Xi group presented a comprehensive report on the utilization of the 2,2'-iodo-substituted biphenyl and K_2S Cu-catalyzed Ullmann process in the synthesis of dibenzothiophene, which was conducted at a temperature of 140 °C (Scheme 6.20). Subsequently, their investigation extended into 2013, where they sought to devise an alternative one-pot approach for the efficient production of dibenzothiophene. This particular method holds promise for the development of cyclic Sulphur-containing molecular structures, as it harnesses the cost-effective nature of CS_2 as a Sulphur source whilst employing the 2,2'-iodine-Substituted biphenyl as the substrate (Scheme 6.20) [68].

In 2015 Lin et al. reported a study on the utilization of rhodium catalyst for the synthesis of dibenzothiophene derivatives through diaryl sulfoxide cyclization (Scheme 6.21). The mechanism includes an intramolecular cross-dehydrogenative coupling process followed by deoxygenation. Regrettably, the presence of strong electron-attracting functional groups or atoms, such as fluoro, nitro, etc., in the substrates hinders their reactivity during this particular process [69].



Scheme 6.20 The synthesis of dibenzothiophenes through Ullmann reaction [68]



Scheme 6.21 Rh-catalyzed synthesis of dibenzothiophenes [69]

6.5 Conclusion

In conclusion, this chapter has explored various synthetic protocols and pharmaceutical significance of Benzothiazepines, Benzothiazole, and Benzothiophene derivatives. Through a comprehensive review of synthetic methodologies, a wide range of synthetic pathways have been elucidated, providing researchers with valuable tools for the efficient synthesis of these important heterocyclic compounds. The pharmaceutical significance of Benzothiazepines, Benzothiazole, and Benzothiophene derivatives has been underscored by their diverse pharmacological activities.

All things considered, the synthesis and medicinal importance of benzothiazepine, benzothiazole, and benzothiophene derivatives constitute a dynamic field of study with important ramifications for drug discovery, providing chances for the creation of innovative therapeutic agents to meet unmet medical needs in a range of disease areas. Further research in this field holds promise for the advancement of pharmaceutical science and the improvement of human health.

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Chapter 7
Synthesis and Biological Evaluation of Some Fused Pyrrolothiazoles, Pyrazolothiazoles, and Imidazothiazoles

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7.1 Introduction

Heterocyclic compounds play significant part in the cellular metabolism of whole living organisms, with a majority of fused heterocyclic compounds comprising five-membered rings exhibiting significant biological activity. Thiazole-fused heterocycles hold paramount importance in drug discovery due to their varied pharmacological profile and structural versatility. These compounds, which incorporate the thiazole ring as a core moiety, demonstrated a far-reaching range of medicinal activities, viz. antimicrobial, anticancer, anti-inflammatory, and antiviral effects [1, 2]. Thiazole-fused heterocycles also play a fundamental role in the development of pharmaceutical agents, serving as key structural motifs in many drugs [2–4]. Moreover, their unique structural features enable scientists to design and synthesize novel compounds with improved pharmacokinetic and pharmacodynamic profiles [5, 6]. By exploring the synthetic pathways and pharmacological activities of thiazole-fused heterocycles, researchers aim to discover new therapeutic agents to combat various diseases and address unmet medical needs [7]. Therefore, the study and development of thiazole-fused heterocycles represent a significant area of research in modern pharmaceutical sciences, offering promising avenues for the advancement of medicine and healthcare.

In this lieu, several moieties were fused with thiazole scaffold such as pyrrolothiazole, imidazothiazole, benzothiazole, pyrazolothiazole, and pyridazinothiazole, etc. (Fig. 7.1). These compounds exhibit diverse pharmacological activities and are

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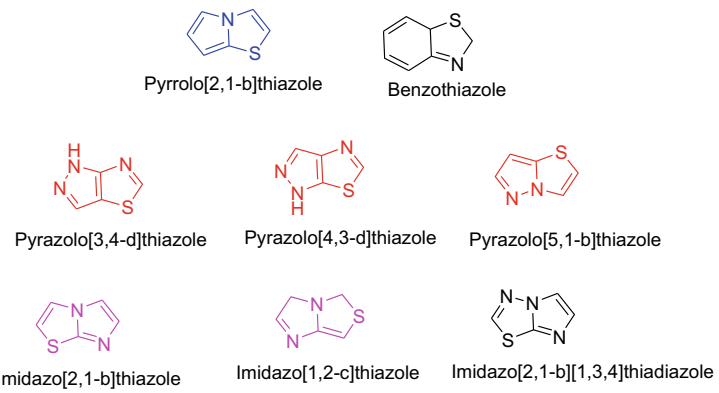


Fig. 7.1 Several thiazole-fused molecules

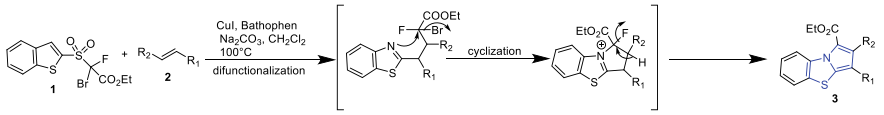
utilized in medicinal chemistry for drug development. Thiazole-fused rings are found in various natural and synthetic compounds, serving as key structural motifs in drug molecules.

This chapter discusses different synthetic aspects that have been employed for pyrrolo[2, 1-b]thiazole, imidazo[2, 1-b]thiazole, and pyrazolo[3, 4-d]thiazole molecules.

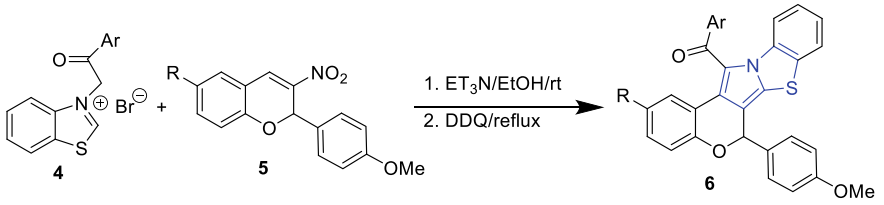
7.2 Synthesis of Pyrrolothiazole

The compounds bearing pyrrolothiazole were found to exhibit excellent pharmacological activities such as anticonvulsant [8], hepatoprotective [9], antitumor [10], anti-inflammatory, antipsychotic, antidiabetic [11], and so on [12]. So, there is an urgent need for advancement of effective synthetic protocols for the synthesis of this molecule. These compounds are commonly synthesized by either creating the bicyclic structure from existing pyrrole or thiazole rings using alkylation and dipolar cycloaddition reactions or by synthesizing them from acyclic precursors.

Numerous pyrrolo[2, 1-b]thiazoles **(3)** have been developed using a reaction of different kinds of alkenes **(2)** with a heterocyclizing reagent using CuI as a catalyst with bathophen as a ligand and Na_2CO_3 as a base in DCM solvent at 100 °C. The reaction involved radical-mediated heteroaryl migration, initiated by single electron transfer (SET) between Cu(I) and the C–Br bond of compound **1**, forming an intermediate and driving the conversion forward. Following the addition of reactant **1** to the alkene, a series of steps including ipso-heteroaryl shift and SO_2 removal occur, resulting in the formation of a radical species. This radical may subsequently abstract a chlorine (Cl) or bromine (Br) atom, further influencing the reaction pathway [13] (Scheme 7.1).



Scheme 7.1 Synthesis of diverse pyrrolo[2, 1-b]thiazoles using CuI as a catalyst



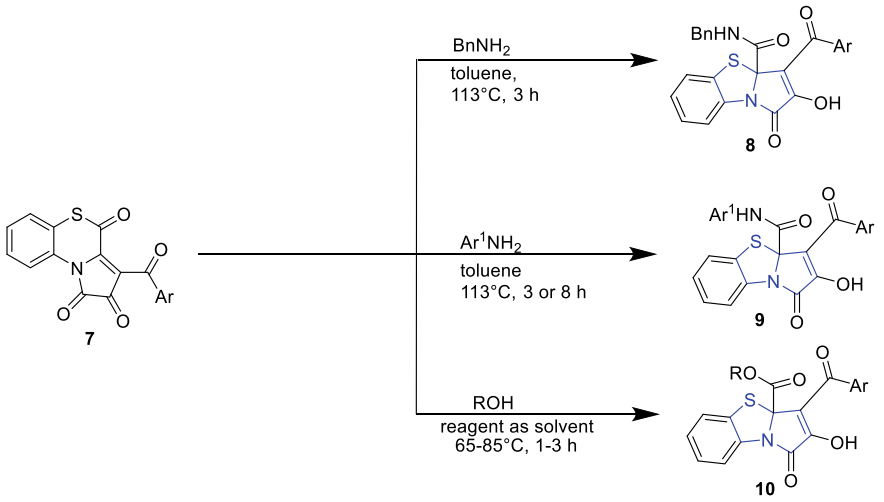
Scheme 7.2 Synthesis of benzo[d]chromeno[3′,4′:3,4]pyrrolo[2, 1-b]thiazoles

A novel two-step pathway has been introduced for the synthesis of benzo[d]chromeno[3′,4′:3,4]pyrrolo[2, 1-b]thiazoles **(6)** using triethylamine-assisted 1,3-dipolar cycloaddition reaction of 3-nitrochromenes **(5)** with 2-phenacyl- or 2-alkoxycarbonylmethylbenzothiazolium bromides **(4)** in ethanol (EtOH) medium at room temperature (RT) followed by sequential oxidation with DDQ at reflux. The reaction was advanced through endo-[3 + 2] cycloaddition of the cyclic dipolarophiles to the in situ generated anti-form ylides [14] (Scheme 7.2).

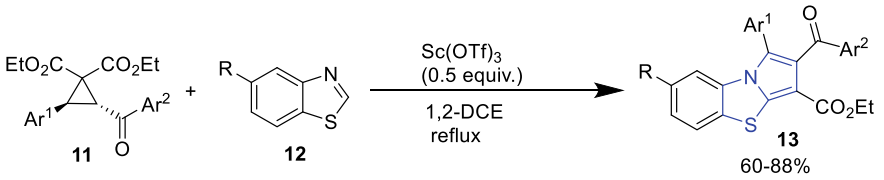
A new approach has been explored for the synthesis of pyrrolo[2, 1-b][1, 3]benzothiazoles **(8, 9 and 10)** through the nucleophile-caused ring contraction of 1,4-benzothiazine. The reaction involved the mixing of several nucleophiles such as arylamine, benzylamines, and alkanols, with 3-aroylpyrrolo[2, 1-c][1, 4]benzothiazine-1,2,4-triones **(7)** and the reaction progressed through cleavage of C-S bond of **7** in the influence of nucleophile to obtain 1-(2-thiophenyl)pyrrole analogs that underwent intramolecular cyclization to furnish the final molecule [15] (Scheme 7.3).

The synthesis of benzo[d]pyrrolo[2, 1-b]thiazoles **(13)** involved a (3 + 2) annulation process in which benzothiazoles **(12)** were reacted with donor − acceptor cyclopropanes substituted with aroyl **(11)**, facilitated by catalytic amount of $Sc(OTf)_3$ in 1,2-dichloroethene (1,2-DCE) at reflux condition. The annulation process resulted in the generation of dearomatized (3 + 2) adducts. Following this, there was an unforeseen occurrence of dehydrogenative and decarbethoxylative rearomatization, leading to the formation of complete aromatized products. This distinct reactivity is ascribed to the existence of an additional aroyl group within the donor − acceptor cyclopropanes [16] (Scheme 7.4).

A two-stage procedure was used to create the pyrrolo[2, 1-b][1, 3]benzothiazoles **(18)**. The first step produced a 92% product yield by employing microwave (MW) irradiation for 10 min at 40 °C to synthesize 2-cyano-methyl-1,3-benzothiazole **(16)**. The compound **16** was then subjected to MW irradiation with several aldehydes at



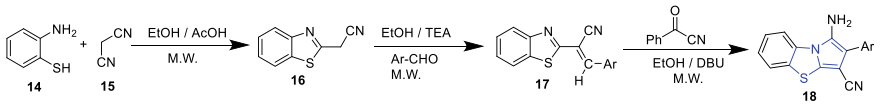
Scheme 7.3 Synthesis of pyrrolo[2, 1-b][1, 3]benzothiazoles through the nucleophile-caused ring contraction



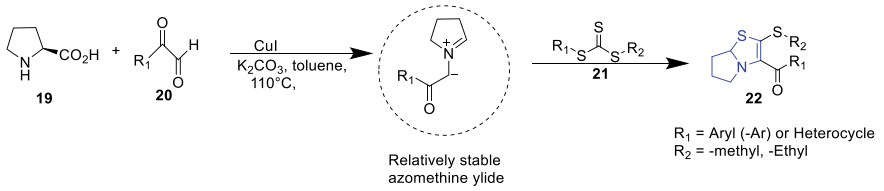
Scheme 7.4 Synthesis of benzo[d]pyrrolo[2, 1-b]thiazoles via (3 + 2) annulation

60 °C in the second phase. This process produced the target compounds **(18)** with higher yields than traditional heating techniques. The two steps of the synthesis were a base-catalyzed Knoevenagel condensation among aldehydes and 2-cyanomethyl-1,3-benzothiazole, which produced 2-arylidenecyanomethyl 1,3-benzothiazoles **(17)** as first step and [4 + 1] cycloaddition of **17** to benzoyl cyanide as the second step [17] (Scheme 7.5).

A different technique produced 5,6,7,8a-tetrahydropyrrolo[2, 1-b]thiazoles **(22)** by decarboxylating proline **(19)** and its analogues to form azomethine ylide in the presence of K_2CO_3 and phenyl glyoxal **(20)**. This was followed by an oxidative [3



Scheme 7.5 Synthesis of the pyrrolo[2, 1-b][1, 3]benzothiazole derivatives via [4 + 1] cycloaddition

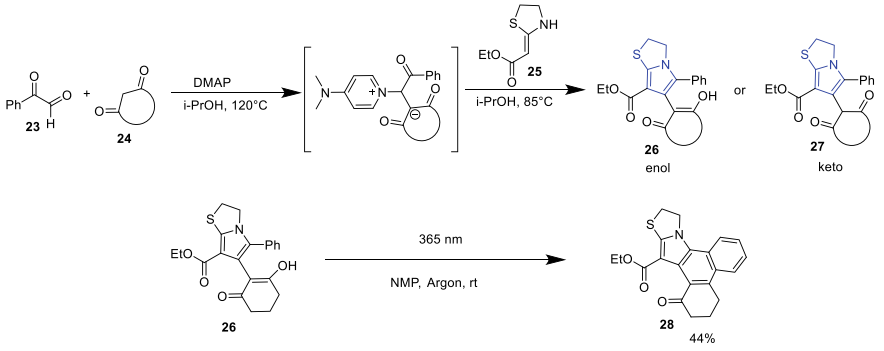


Scheme 7.6 Synthesis of 5,6,7,8a-tetrahydropyrrolo[2, 1-b]thiazoles via azomethine ylide intermediate

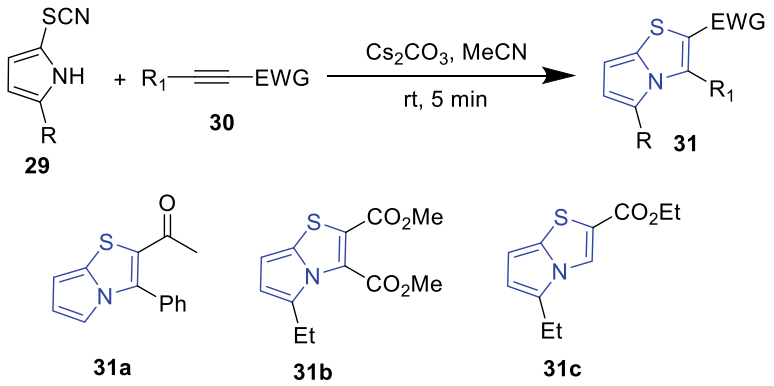
+ 2] cycloaddition reaction with dialkyl trithiocarbonate **(21)**. CuI catalyst acted as the catalyst for this reaction, which had high regiospecificity. This was probably because Cu(I) catalyst was involved in a delayed, symmetry-controlled transition state. Additionally, the reaction demonstrated exceptional tolerance to several proline substitutions, including pipecolinic acid, thiazolidine-4-carboxylic acid, and 4-hydroxyproline, yielding outstanding product yields [18] (Scheme 7.6).

In a two-step, one-pot approach supported by DMAP, 2,3-dihydropyrrolo[2, 1-b]thiazoles were synthesized using ethyl 2-(thiazolidin-2-ylidene)acetate **(25)** as a substrate. This substrate was mixed with several cyclic 1,3-dicarbonyl molecules **(24)**, and phenyl glyoxal **(23)** to produce pyrrolo[2, 1-b]thiazole derivatives, in moderate to excellent yield. Interestingly, pyrrolo[2, 1-b]thiazole **(26)** showed a conjugated benzene diene molecule in its enol form. Moreover, an attempt has been made to create a polyheteroaromatic core using photochemical cyclization. This endeavor led to the formation of the anticipated polyheterocycle **(28)**, achieving a 44% yield when exposed to ultraviolet (UV) irradiation at 365 nm [19] (Scheme 7.7).

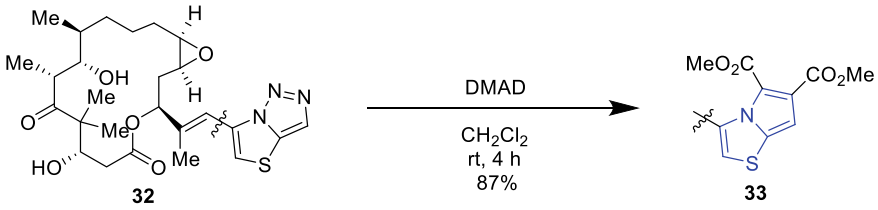
The synthesis of pyrrolothiazoles entailed the interaction between amphiphilic dithioloimines **(29)** and arynes or alkynes **(30)** featuring electron-withdrawing groups. Under standard conditions, the reaction employed Cs_2CO_3 in acetonitrile at RT, resulting in favorable yields of the targeted pyrrolothiazoles **(31)**



Scheme 7.7 Synthesis of 2,3-dihydropyrrolo[2, 1-b]thiazoles using ethyl 2-(thiazolidin-2-ylidene)acetate



Scheme 7.8 Synthesis of pyrrolothiazoles using dithioloimines



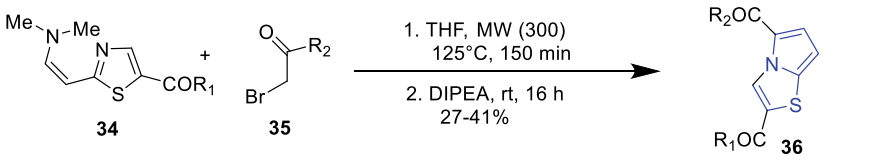
Scheme 7.9 Synthesis of pyrrolo[2, 1-b]thiazole-5,6-dicarboxylate

[20] (Scheme 7.8). In different method, synthesis of pyrrolo[2, 1-b]thiazole-5,6-dicarboxylate **(33)** was achieved through the reaction of triazoloepothilone **(32)** with dimethyl acetylenedicarboxylate (DMAD) in DCM at RT with 87% yield [21] (Scheme 7.9).

By using an innovative synthesis approach, pyrrolo[2, 1-b]thiazoles attached with a protected carbohydrate moiety have been obtained in which MW irradiation helped with the N-alkylation step. A two-step method has been developed to synthesize pyrrolo[2, 1-b]thiazoles substituted with a protected carbohydrate moiety using substituted thiazoles as a starting material. To generate target compounds **(36)**, DIPEA was added after MW irradiation in THF initially mediated the N-alkylation phase [22] (Scheme 7.10).

7.3 Synthesis of Pyrazolothiazoles

Pyrazolothiazoles comprise molecules with a fused structure of pyrazole and thiazole rings. Currently, three systems within this category have been explored in scientific literature, depicted as pyrazolo[4, 3-d]thiazoles, pyrazolo[3, 4-d]thiazoles and pyrazolo[5, 1-b]thiazoles (Fig. 7.2). Research indicates that pyrazolothiazoles



Scheme 7.10 Synthesis of pyrrolo[2, 1-b]thiazoles substituted with a protected carbohydrate moiety

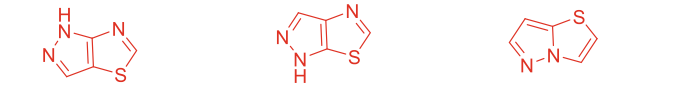


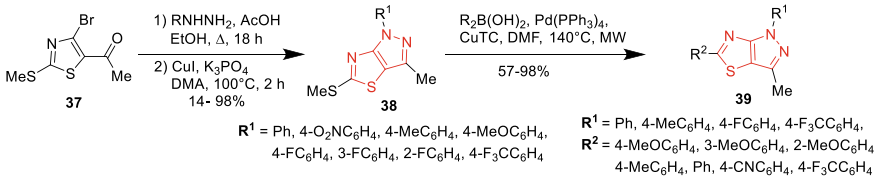
Fig. 7.2 Different kinds of pyrazolothiazoles

possess varied biological functionalities, including their role as an antagonist of the corticotropin-releasing factor 1 [CRF(1)] receptor [23], anti-tubercular activities [24], antimicrobial [25] and protein kinase modulators for cancer [26], and other medical conditions.

Generally, two methods have been employed for synthesizing these types of molecules. One approach involves annulating the pyrazole ring around an existing thiazole molecule, while the other entails annulating the thiazole ring around an existing pyrazole ring. It's noteworthy that the formation of the pyrazole ring around the thiazole ring is more commonly utilized in synthesis [27]. This section describes various procedures that have been developed for the synthesis of pyrazolothiazole moiety in recent times.

*7.3.1 Synthesis of Pyrazolo[3,4-*d*]thiazoles*

The reaction of hydrazines with 1,3-difunctional electrophilic precursors is recognized to be the primary method for producing functionalized and fused pyrazoles. By using this approach, pyrazolo[3, 4-d]-thiazoles **(38)** were created by condensation of 5-acyl-4-bromo-2-(methylsulfanyl)thiazole **(37)** with arylhydrazine or hydrazine to form the pyrazole ring, which was then followed by an intramolecular cyclization catalyzed by copper [28].Then the synthesized compounds were functionalized by reacting with several monosubstituted aromatic boronic acids via Liebeskind–Srogl cross-coupling reaction, using palladium complex as a catalyst under MW irradiation [29] (Scheme 7.11).



Scheme 7.11 Synthesis of pyrazolo[3, 4-d]-thiazoles and their post-functionalization

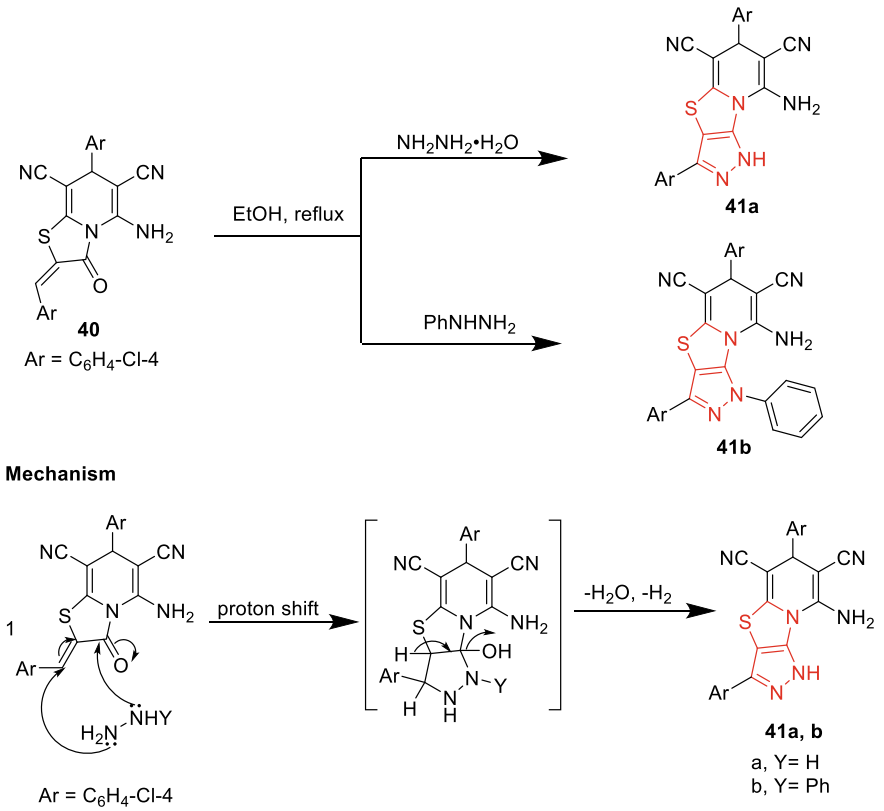
A 5-aminothiazolo[3, 2-a]pyridine derivative **(40)** was effectively converted into pyrazolo[3,4:4,5]thiazolo[3, 2-a]pyridine **(41a, b)** by reacting with hydrazine or aryl-hydrazine in EtOH solvent at reflux condition via intramolecular cyclocondensation followed by the oxidation of cycloadduct [30] (Scheme 7.12). In other study, the pyrazole ring was annulated on thiazolo[3, 2-a]pyrimidine ring structure through reacting phenyl hydrazine with arylidine compounds **43a-e** in EtOH solution under reflux condition using piperidine as a catalyst [31] (Scheme 7.13).

In another approach, two pyrazolo[3, 4-d]-thiazoles **(46a and b)** were synthesized by reacting chalcone **45** with phenyl hydrazine ($PhNHNH_2$) and hydrazine hydrate (NH_2NH_2) using EtOH as a solvent and hydrochloric acid as a catalyst [32] (Scheme 7.14). In a study, first thiazole ring derivatives **(52)** were synthesized by reacting various aldehydes with 4-(1*H*-benzo[d]imidazol-2-yl)thiazol-2-amine **(51)** using EtOH as a solvent and glacial acetic acid (AcOH) as a catalyst afforded compound **(52)** which again reacted with thioglycolic acid and several aldehydes in the presence of zinc chloride in 1,4-dioxane solvent under reflux. Then, the pyrazole ring was annulated on thiazole ring by the condensation of **53** with hydrazine hydrate using glacial AcOH and anhydrous sodium acetate at reflux. In this reaction, **51** was synthesized by condensation of **47** and **48** followed by oxidation of synthesized compound **49** into compound **50** that further reacted with thiourea and yielded **51** [33] (Scheme 7.15).

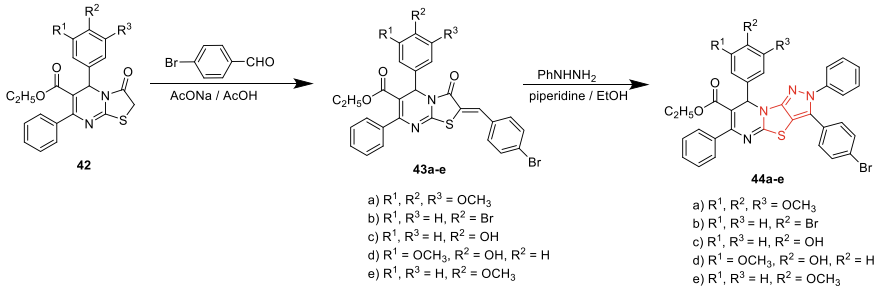
The pyrazolo[3, 4,d]thiazoles **(59)** were synthesized using the condensation of thiazol-2-yl possessing 2-imino-thiazolidin-4-ones **(57)** with various aldehydes in EtOH and sodium acetate that further cyclized with NH_2NH_2 in AcOH [34] (Scheme 7.16). The pyrazolo[3, 4,d]thiazoles **(61a-c)** were synthesized through the reaction of 4-((5-((dimethylamino)methylene)-4-oxo-4,5-dihydrothiazol-2-yl)amino) benzene sulfonamide **(60)** with either $PhNHNH_2$, hydrazinecarbothioamide or NH_2NH_2 in EtOH medium in the presence of Et_3N under reflux condition followed by cyclization and aromatization [35] (Scheme 7.17).

Hantzsch reaction was used for the synthesis of pyrazolo[3, 4-d]thiazole-5-thione analogs **(63)** through annulation of thiazole ring by reaction of 3-methyl-1-tosyl-1*H*-pyrazol-5(4*H*)-one **(62)** and methyl/phenylisothiocyanate with elemental sulfur in the solvent system of dimethylformamide (DMF)/EtOH using influence of Et_3N as a catalyst at reflux conditions [36] (Scheme 7.18).

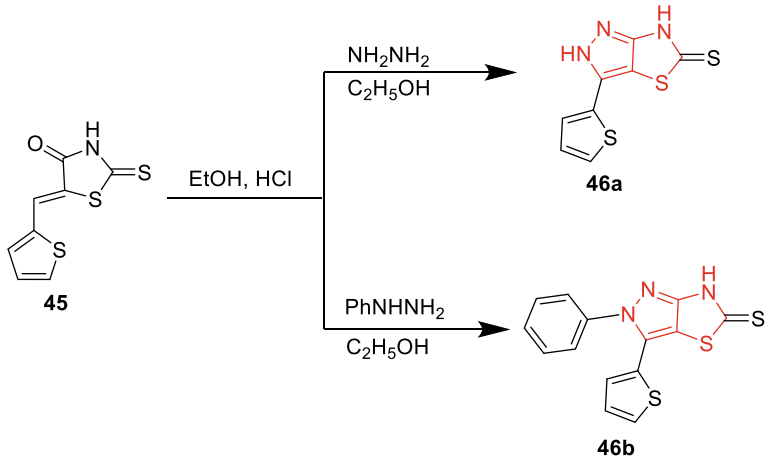
The annulation of thiazole moiety for the synthesis of 3-(pyridin-3-yl)-1-*p*-tolyl-1*H*-pyrazolo [3, 4-d]thiazol-5-amine **(65)** was achieved through reacting KSCN with 3-(pyridin-3-yl)-1-*p*-tolyl-1*H*- pyrazol-5-amine **(64)** in the influence of glacial AcOH



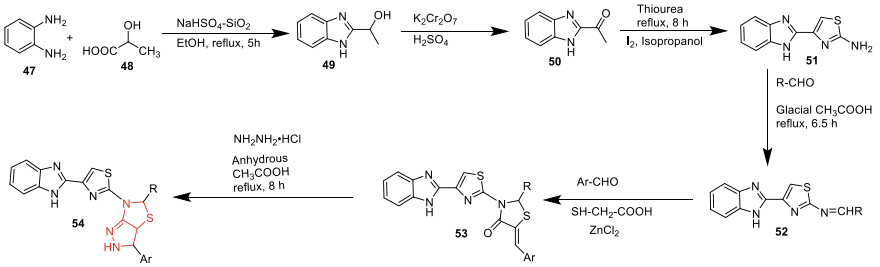
Scheme 7.12 Synthesis and plausible mechanism of synthesis of pyrazolo[3,4:4,5]thiazolo[3, 2-a]pyridine



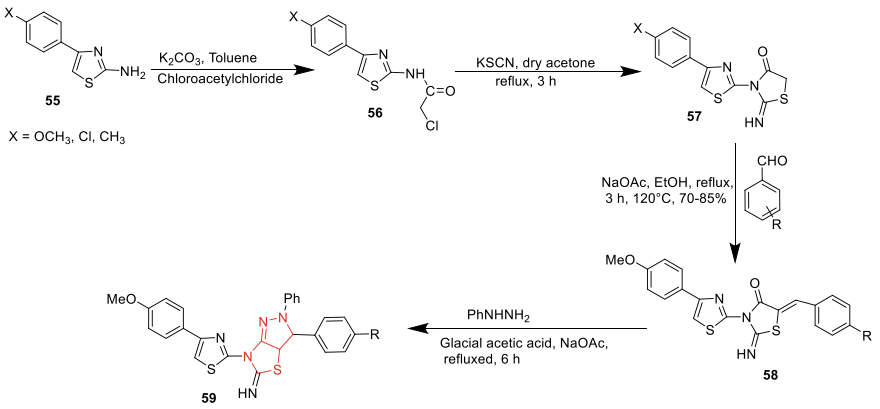
Scheme 7.13 Synthesis of pyrazolo[3, 4-d]-thiazoles via pyrazole ring annulation



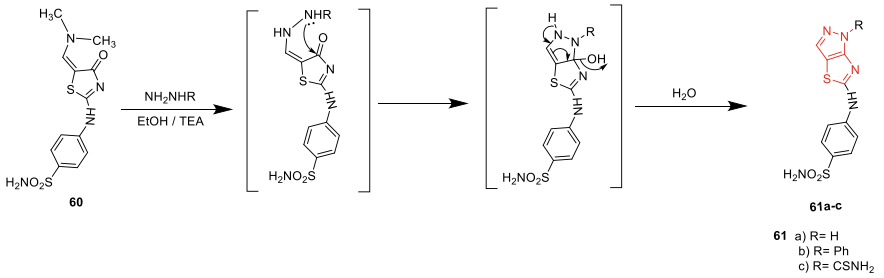
Scheme 7.14 Synthesis of chalcone-substituted pyrazolo[3, 4-d]-thiazoles



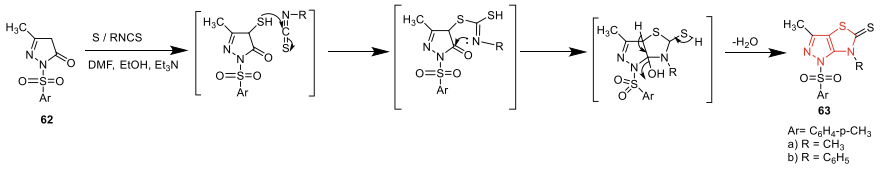
Scheme 7.15 Schematic synthesis of pyrazolo[3, 4-d]-thiazoles using 4-(1*H*-benzo[d]imidazol-2-yl)thiazol-2-amine



Scheme 7.16 Synthesis of pyrazolo[3, 4,d]thiazoles by condensation of thiazol-2-yl-substituted 2-imino-thiazolidin-4-ones



Scheme 7.17 Synthesis of pyrazolo[3, 4,d]thiazoles by condensation of 4-((5-((dimethylamino)methylene)-4-oxo-4,5-dihydrothiazol-2-yl)amino) benzene sulfonamide



Scheme 7.18 Synthesis of pyrazolo[3, 4-d]thiazole-5-thione derivatives

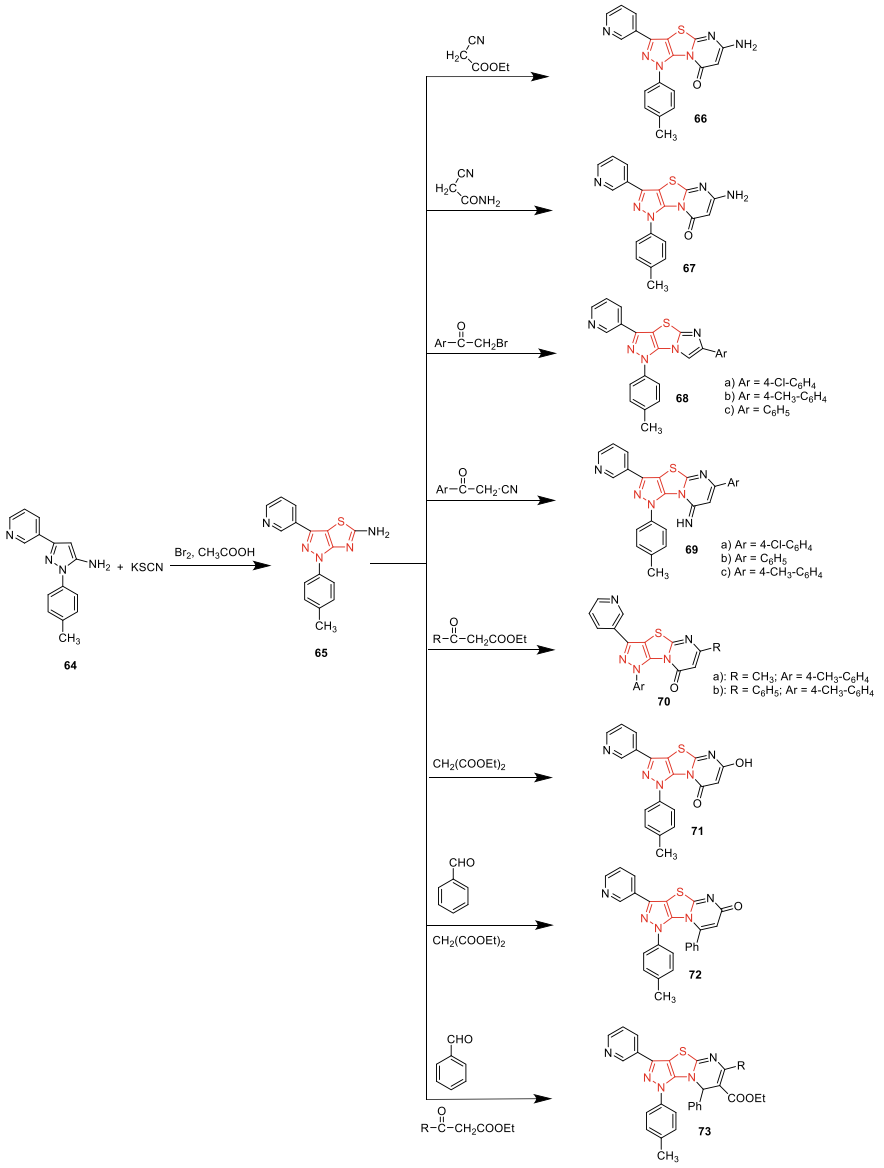
and bromine. Then, 3-(pyridin-3-yl)-1-*p*-tolyl-1*H*-pyrazolo[3, 4-d]thiazol-5-amine **(65)** was employed as versatile precursor for the synthesis of novel fused heterocyclic moieties containing imidazoles or pyrimidines **(66–73)** [37] (Scheme 7.19).

*7.3.2 Synthesis of Pyrazolo[4,3-*d*]thiazoles*

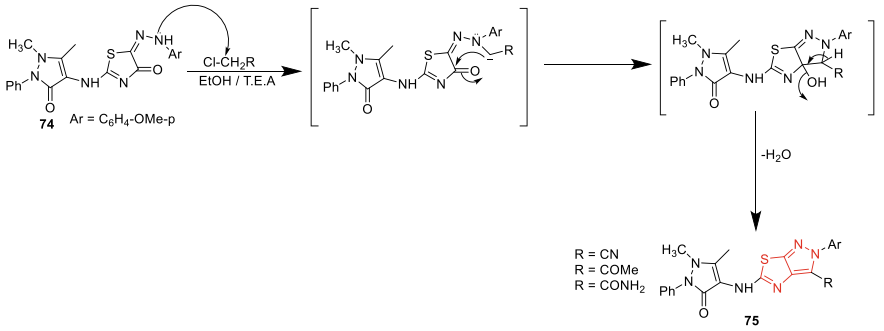
Pyrazolo[4, 3-d]thiazole derivatives **(75)** were synthesized by the condensation of hydrazone derivative **(74)** with different halo compounds such as chloroacetone, chloroacetamide, or chloroacetonitrile using EtOH as a solvent and triethylamine as a catalyst under reflux condition followed by cyclization and tautomerism to form pyrazole ring [38] (Scheme 7.20).

*7.3.3 Synthesis of Pyrazolo[5,1-*d*]thiazoles*

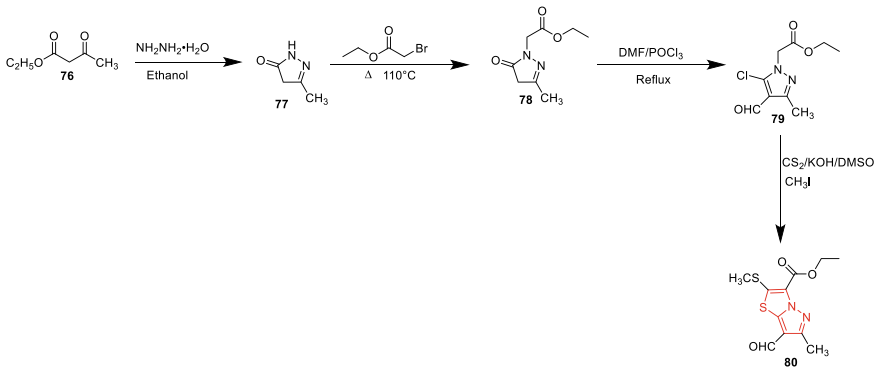
Fused pyrazolo[5, 1-b]thiazole aldehyde **(80)** were synthesized by multiple step reactions that include synthesis of 3-methylpyrazolone **(77)** from the condensation of ethyl acetoacetate with hydrazine hydrate in EtOH that again reacted at 110 °C with ethyl bromoacetate and obtained pyrazolone-acetate **(78)**. Further, pyrazolone-acetate underwent formylation via Vilsmeier–Haack reaction using DMF and phosphorus oxychloride and afforded pyrazolone-acetate-substituted aldehyde **(79)**. At



Scheme 7.19 Synthesis of 3-(pyridin-3-yl)-1-*p*-tolyl-1*H*-pyrazolo [3, 4-d]thiazol-5-amine and their post-functionalization



Scheme 7.20 Synthesis of pyrazolo[4, 3-d]thiazole derivatives



Scheme 7.21 Synthesis of fused pyrazolo[5, 1-b]thiazole aldehyde

last, prepared aldehyde was reacted with potassium hydroxide and CS_2 in DMSO solvent in the presence of iodomethane furnished the fused pyrazolo[5, 1-b]thiazole aldehyde **(80)** [39] (Scheme 7.21).

7.3.4 Synthesis of Imidazothiazole

The imidazothiazole core demonstrates versatile therapeutic applications, including antihelminthic [40, 41], antitumor [42–45], anti-inflammatory [46], cardiotonic [47], antiviral [48], antiparasitic [49], anti-hypertensive [50], fungicidal [51–53], antibacterial [54–56], and antioxidant properties [57]. Notably, Levamisole, a crucial imidazothiazole derivative, is extensively utilized in cancer therapy (Fig. 7.3). Additionally, imidazothiazoles serve as potent IDO1 inhibitors, aiding in cancer treatment [57]. Furthermore, derivatives of imidazothiazoles (imidazo[2, 1-b]thiazole and

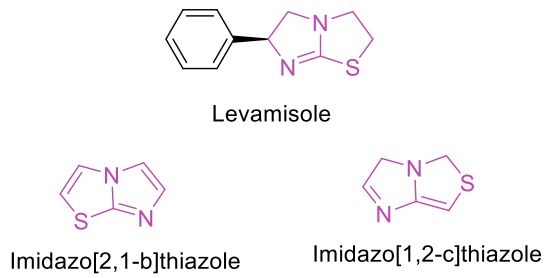


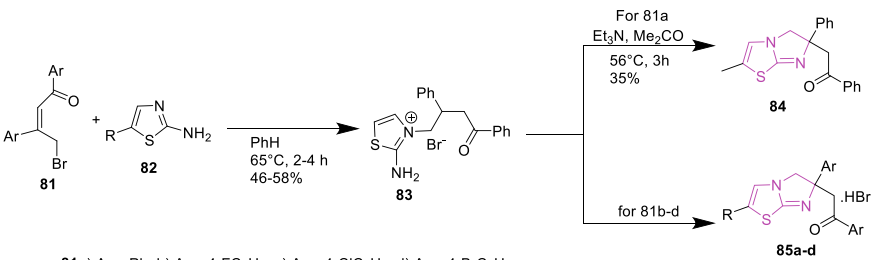
Fig. 7.3 Different kinds of imidazothiazole and biologically active compounds

imodazo[1, 2-c]thiazole (Fig. 7.3) exhibit potential as HIV-1 RT inhibitors, emphasizing their significance in medicinal chemistry [59]. These diverse pharmacological roles underscore the usefulness of imidazothiazole moieties in drug discovery. Consequently, the synthesis of these moiety holds predominant importance in organic chemistry. This section presents several approaches that have been incorporated for the development of imidazothiazole analogs.

An effective approach has been explored for the synthesis of imidazo[2, 1-b][1, 3]thiazole compounds **(84 and 85)** by condensation of (2Z)-1,3-diaryl-4-bromobut-2-en-1-one analogs **(81)** with 2-aminothiazoles **(82)** in the presence of base. The reaction underwent through Michael addition via cyclization using base as a catalyst [60] (Scheme 7.22).

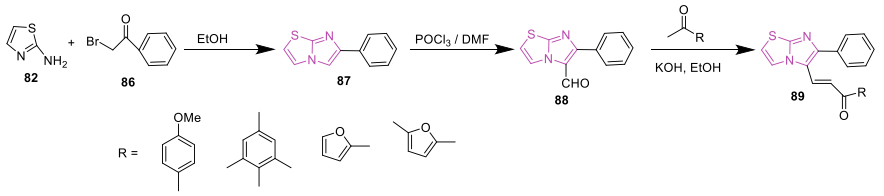
In a different work, aldehyde with various methyl ketone was subjected to Claisen–Schmidt condensation to create derivatives of imidazothiazoles replaced with chalcone. Through cyclocondensation of 2-aminothiazole **(82)** and an α-halogenated carbonyl molecule **(86)** in the presence of EtOH, imidazo[2, 1-b]thiazole **(87)** was produced. Imidazo[2, 1-b]thiazole carbaldehyde **(88)** was produced using the Vilsmeier–Haack reaction with the resultant product **87** in phosphoryl chloride ($POCl_3$) and DMF. Further, the chalcone derivatives **(89)** were synthesized by the reaction of aromatic aldehyde **88** and different methyl ketones in the presence of KOH and EtOH [61] (Scheme 7.23).

In order to synthesize imidazothiazole derivatives, α-bromo-3(4)-methoxyacetophenone **(90)** was cyclized with 2-amino-thiazole **(82)** in EtOH

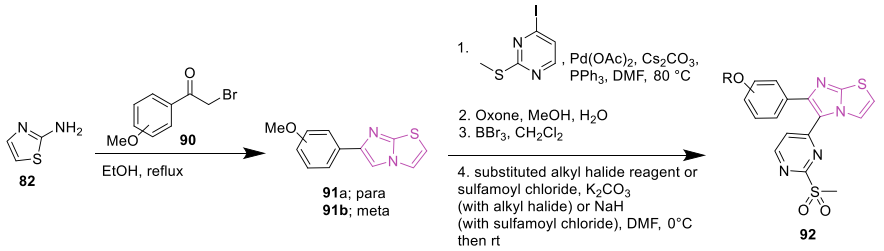


81a) Ar = Ph, b) Ar = 4-FC_6H_4, c) Ar = 4-ClC_6H_4, d) Ar = 4-BrC_6H_4;
85a) Ar = 4-FC_6H_4, R = H; b) Ar = 4-FC_6H_4, R = Me; c) Ar = 4-ClC_6H_4, d) Ar = 4-BrC_6H_4, R = H

Scheme 7.22 Synthesis of imidazo[2, 1-b] [1, 3] thiazoles



Scheme 7.23 Synthesis of imidazo[2, 1-b]thiazole by cyclocondensation between 2-aminothiazole and an α-halogenated carbonyl compound



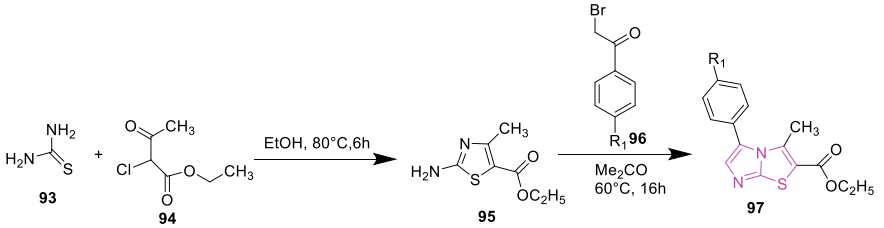
Scheme 7.24 Synthesis of imidazo[2, 1-b]thiazole by cyclization of α-bromo-3(4)-methoxyacetophenone with 2-amino-thiazole

at reflux to produce intermediates **(91)**. These intermediates were then reacted with 4-iodo-2-(methylthio)pyrimidine in the influence of caesium carbonate, triphenylphosphine as a ligand, and palladium (II) acetate as a catalyst to form compounds. Oxone was used to produce the methylsulfide's subsequent oxidation to sulfone. The next step was to use boron tribromide to remove the methoxy group from molecules, which produced the equivalent hydroxyl counterparts. The required target derivatives **(92)** were obtained in the last stage by adding alkyl halide or sulfamoyl chloride using potassium carbonate or sodium hydride, respectively [62] (Scheme 7.24).

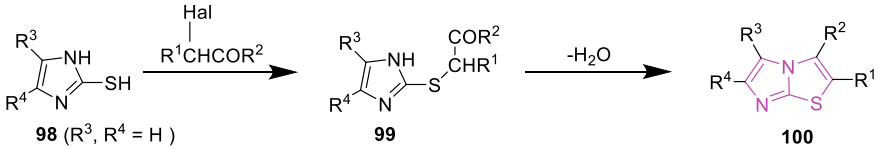
3-Methyl-imidazo[2, 1-b]thiazole-based analogs **(97)** were prepared in two steps, initially precursor 2-amino-4-methylthiazole-5-carboxylate **(95)** was synthesized by the reaction of thiourea **(93)** with 2-chloroacetoacetate **(94)** in EtOH medium at reflux, then it was reacted with different 2-bromo-1-(4-substituted phenyl)ethanone analogs **(96)** at 60 °C in acetone solvent and yielded the target compounds **(97)** [63] (Scheme 7.25).

When 2-mercaptoimidazole **(98)** underwent reaction with aliphatic alpha-halogenoketones in EtOH or butanol in the absence of alkali, it led to a cyclization reaction, resulting in the production of imidazo[2, 1-b]thiazoles **(100)** [64] (Scheme 7.26).

For the synthesis of triazole-substituted imidazothiazole analogs **(106)**, a multi-step reaction strategy was employed. The process initiated with the treatment



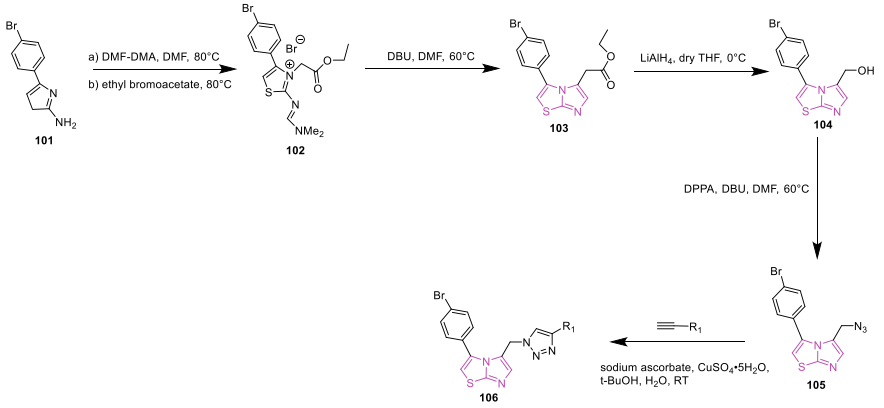
Scheme 7.25 Synthesis of 3-methyl-imidazo[2, 1-b]thiazole-based analogs



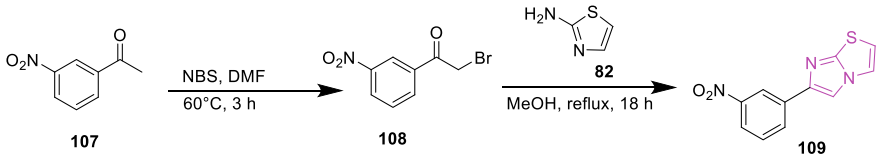
R^1 = H, Ac: R^2 = Alk, Ar: R^3 = H, Ar: R^4 = H, Ar

Scheme 7.26 Synthesis of imidazo[2, 1-b]thiazoles using 2-mercaptoimidazole

of 4-(4-bromophenyl)thiazol-2-amine **(101)** using ethyl bromoacetate and DMF-dimethylacetamide (DMA), leading to the formation of intermediate **102**. Subsequently, intermediate **102** underwent an intramolecular cyclization, followed by reduction, resulting in the formation of compound **103**. This compound, in turn, reacted with DPPA to yield azide **105**. Expanding the scope, alkynes were carefully selected, and target compounds **(106)** were synthesized through the utilization of click chemistry reactions under classical conditions. The comprehensive approach provides insights into the systematic and controlled synthesis of these specialized imidazothiazoles [58] (Scheme 7.27).



Scheme 7.27 Synthesis of triazole-substituted imidazothiazoles



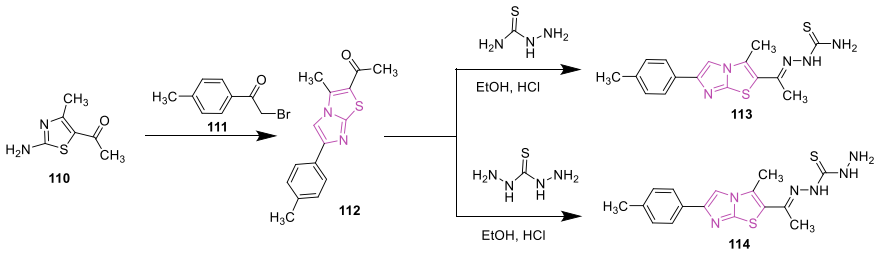
Scheme 7.28 Synthesis of imidazothiazole derivatives using 3′-nitroacetophenone

When 3′-nitroacetophenone **(107)** reacts with N-bromosuccinamide in DMF, α-bromination takes place, yielding compound **107.** Subsequently, compound **108** underwent reflux with 2-aminothiazole **(82)** in MeOH, resulting in the formation of compound **109**. This synthetic pathway outlines the stepwise conversion of 3′-nitroacetophenone into the targeted compound **109** through controlled chemical reactions [65] (Scheme 7.28).

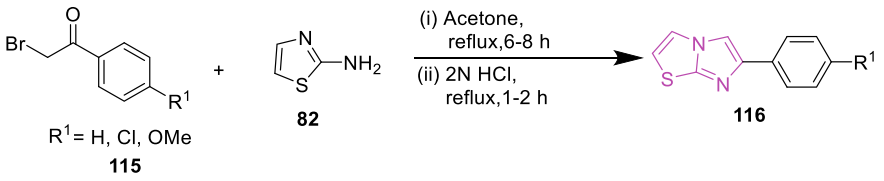
2-Acetyl-(3-methyl-6-(substituted)-imidazo[2, 1-b]thiazoles **(113 and 114)** were synthesized by the cyclization of phenacylbromide derivative **(111)** with 5-acetyl-2-amino-4-methylthiazole **(110)**, which further underwent condensation with thiosemicarbazide and thiocarbohydrazide in refluxing EtOH/HCl, respectively [66] (Scheme 7.29).

In a different approach, imidazo[2, 1-b]thiazoles **(116)** were synthesized through reacting 2-aminothiazole **(82)** with 2-bromoacetophenone **(115)** in acetone under reflux followed by addition of HCl [67] (Scheme 7.30).

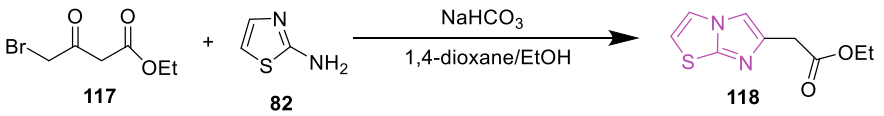
In another study, 2-aminothiazole **(82)** reacted with ethyl 4-bromoacetoacetate **(117)** in the influence of sodium bicarbonate as a catalyst and mixture of 1,4-dioxane



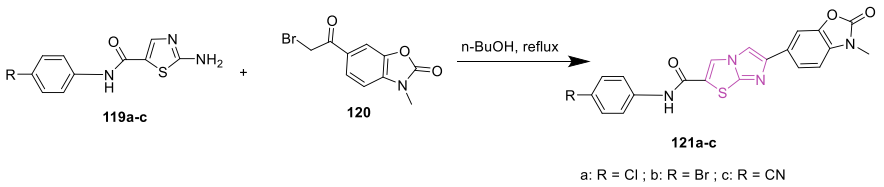
Scheme 7.29 Synthesis of 2-acetyl-(3-methyl-6-(substituted)-imidazo[2, 1-b]thiazole



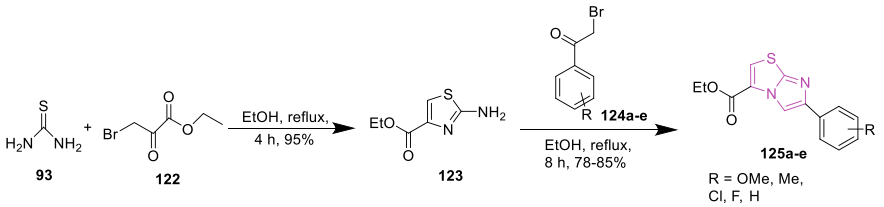
Scheme 7.30 Synthesis of imidazo[2, 1-b]thiazoles



Scheme 7.31 Synthesis of ethyl imidazo[2, 1-b] thiazole-6-yl acetate



Scheme 7.32 Synthesis of benzoxazole-substituted imidazo[2, 1-b][1, 3]thiazole-2-carboxamides



Scheme 7.33 Synthesis of imidazothiazole derivatives via two-step approach

and EtOH as solvent system afforded the ethyl imidazo[2, 1-b] thiazole-6-yl acetate **(118)** in significant yield [68] (Scheme 7.31).

A series of benzoxazole-substituted imidazo[2, 1-b][1, 3]thiazole-2-carboxamide derivatives **(121a-c)** were synthesized by the condensation of 1,3-thiazole-5-carboxamides **119a-c** with benzoxazole **120** in n-butanol at reflux condition followed by cyclization [69] (Scheme 7.32).

Imidazothiazole derivatives were synthesized in two-step reaction in which initially thiourea **(93)** was condensed with ethyl bromopyruvate **(122)** in EtOH under reflux which afforded ethyl-2-aminothiazole-4-carboxylate **(123)** as an intermediate, which further reacted with several phenacyl bromides **(124a-e)** in EtOH medium and underwent cyclization reaction to obtain the desired compounds **(125a-e)** [70] (Scheme 7.33).

7.3.5 Conclusion

The synthesis of fused pyrollothiazole, pyrazolothiazole, and imidazothiazole compounds represents a significant advancement in heterocyclic chemistry with profound implications for drug discovery and development. Through innovative

synthetic methodologies, researchers have successfully accessed these complex heterocyclic scaffolds, paving the way for the exploration of their diverse pharmacological properties.

The biological significance of these compounds is underscored by their therapeutic potential across various diseases, including cancer, infectious diseases, inflammation, and neurological disorders. Leveraging the synthetic versatility of these frameworks, medicinal chemists can tailor molecular structures to optimize drug-like properties and enhance biological activity, thereby accelerating the development of novel therapeutics.

Moreover, computational modeling and mechanistic studies have provided invaluable insights into reaction pathways and structure–activity relationships, facilitating rational design strategies for the synthesis of next-generation analogs with improved pharmacokinetic profiles and target selectivity.

In conclusion, the synthesis of fused pyrollothiazole, pyrazolothiazole, and imidazothiazole derivatives represents a dynamic field at the intersection of organic synthesis and medicinal chemistry, offering exciting opportunities for the discovery of therapeutically relevant compounds with enhanced efficacy and safety profiles.

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Chapter 8
Synthesis and Biological Evaluation of Some Dithiazines

Vidya S. Dofe, Sunil U. Tekale, Sandip S. Dhotre, and Rajendra P. Pawar

8.1 Introduction

The present chapter deals with the chemistry of heterocyclic compounds possessing one nitrogen as part of the six-membered ring and two sulfur atoms (dithiazines). A literature survey reveals that dithiazines and related compounds possess a diverse range of biological and pharmacological activities. Dithiazine derivatives are in clinical use, and many dithiazines exhibit antiviral, antiprotozoal, fungicidal, and bactericidal potential [1–3], most probably by the presence of the toxophoric (–N = C–S) group. In addition, dithiols and dithiazines have been patented as synthetic flavor compounds [4, 5] and in photographic development by a diffusion transfer process [6]. The dithiazine heterocyclic moiety is analogous to the six-membered benzene ring comprising of three carbons replaced by two sulfur and one nitrogen atom [7]. Many pharmaceutical products are heterocyclic and resemble natural molecules with biological activities [8]. Thus, the present chapter focuses attention on the synthesis of dithiazines and biological activity.

8.2 Synthesis and Biological Activity

Substituted dithiazines **(3)** can be synthesized from N-[2-(furan-2-yl)-1-(3-nitrophenyl)-4- oxoazetidin-3-yl]-N-substituted dicarbanodithioimidic **(1)** and phenylisocyanodichloride **(2)** and were found to possess in vitro antioxidant activity using the 1,1-diphenylpicrylhydrazyl (DPPH) radical scavenging assay Fig. 8.1 [9].

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K. L. Ameta (ed.), *S-Heterocycles*, https://doi.org/10.1007/978-981-97-4308-7_8

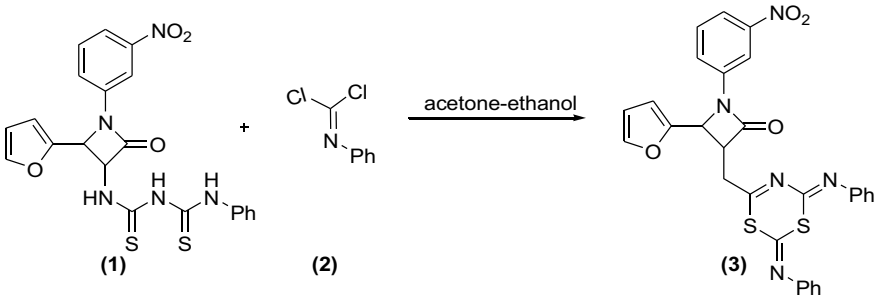


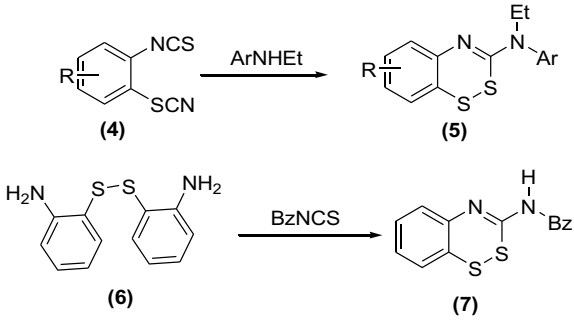
Fig. 8.1 Synthesis of 3-(((2Z,4Z)-2,4-bis(phenylimino)-4H-1,3,5-dithiazin-6-yl)methyl)-4-(furan-2-yl)-1-(3-nitrophenyl)azetidin-2-one

The synthesis of 3-anilino-1,2,4-benzodithiazines **(5)** involved the condensation of N-ethylaniline or 4-bromo-N-ethylaniline with substituted o-thiocyanatophenylisothiocyanates **(4)**, [10a], whereas more recently, another benzo-fused analog **(7)** was isolated from the reaction of 2,2′-diamino diphenyl disulfide **(6)** with N-benzoyl thiocyanate [10]. It is noteworthy that di- and tetrahydro-1,2,4-dithiazines are more common in possessing diverse biological activities [11]. Bridged analogs of 3,6-dihydro-1,2,4-dithiazin-5-ones are found in various natural products and exhibit interesting biological potential including antibacterial (such as hyalodendrin) [12], antiviral (such as aranotin) [13], and antitumor (such as gliotoxin) [14] Fig. 8.2 [15].

These molecules show cooperative intermolecular hydrogen-bonding interactions, leading to a two-dimensional layer-packing motif. It was found that the layers were built up from seven component entities via extensive intermolecular hydrogen bonding of 6-chlorothieno[2,3-e]-1,4,2-dithiazine-3(2H)-thione-1, 1-dioxide anions **(12)**, water molecules, and ammonium cations Fig. 8.3 [16].

Two pyrrolidino1,3,5-dithiazines—namely 2-ethyl-4-methyl and 2-isopropyl-4-methyl derivatives **(16)**, were reported as pork flavor Fig. 8.4 [17].

Fig. 8.2 Synthesis of benzo-fused 1,2,4-dithiazine



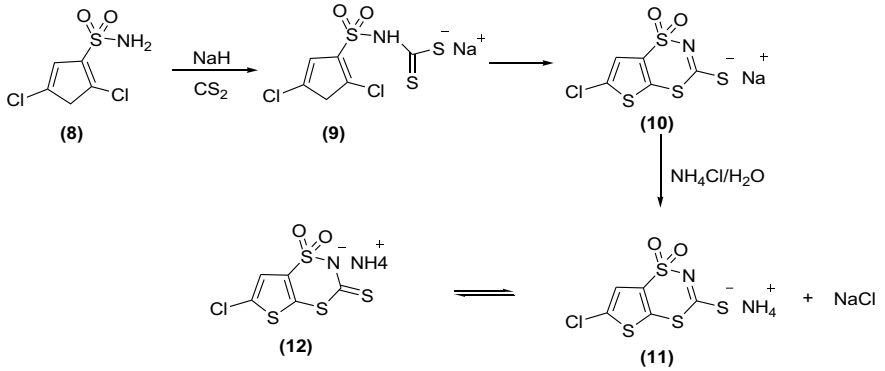


Fig. 8.3 Synthesis of ammonium 6-chloro-3-thioxothieno[2,3-e][1,4,2]dithiazin-2-ide 1,1-dioxide

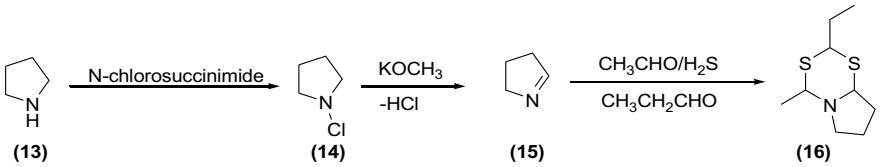


Fig. 8.4 Synthesis of 2-ethyl-4-methyltetrahydro-4H-pyrrolo[2.1-d]-1,3,5-dithiazine

1,4,2-Benzodithiazines can be used as antitumoral as well as antiviral agents. The compound **(17)** has shown in vitro antitumoral activity. Also, in some in vitro studies, benzodithiazine **(18)** has shown anticarcinogenic activity [18, 19] Fig. 8.5.

2-(1,3,5-Dithiazin-5-yl)acetic acid **(19)** and 2-hydroxy-1-perhydro-[1,3,5-dithiazin-5-yl] ethane **(20)** can be used in petroleum industry as growth-suppressor agents of sulfate-reducing bacteria. The 1,3,5-dithiazines showed activity as organic absorbents for the extraction of metals such as Ag, Au, and Pt in solution [20–22] Fig. 8.6.

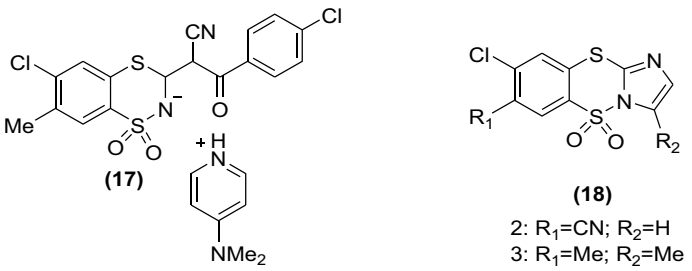
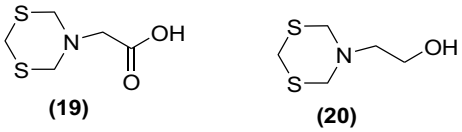


Fig. 8.5 Synthesis of 1,4,2-benzodithiazines

Fig. 8.6 Synthesis of 1,3,5-dithiazines



The derivatives of 8-chloro-7-imidazo[1,2-b][1,4,2]benzodithiazine 5,5-dioxide **(23)** were synthesized as potential antitumor or anti-HIV agents. The in vitro antitumor and anti-HIV-1 activities of these compounds were studied in cell lines and were found to be effective ineffective in leukemia, melanoma, ovarian, lung, and renal cancer cells with 1–2 μM values of GI_{50} [23] Fig. 8.7.

Some novel 3-methylthio-1,1-dioxo-1,4,2-benzodithiazines **(27)** were prepared as outlined in Fig. 8.8 and were studied for in vitro antitumor activity of the compounds [24] Fig. 8.8.

1,2,4-Dithiazine ring system is present in epidithiodioxopiperazine system **(28)**, which is commonly present in several fungal metabolites, such as gliotoxin **(29)**, and

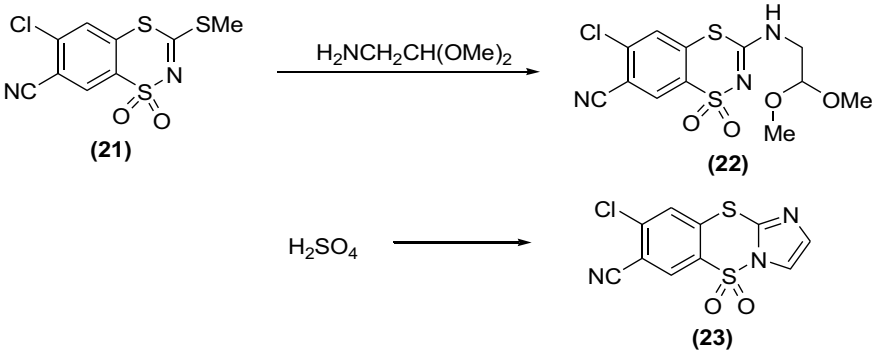


Fig. 8.7 Synthesis of 8-chlorobenzo[e]imidazo[1,2-b][1,4,2]dithiazine-7-carbonitrile-5,5-dioxide

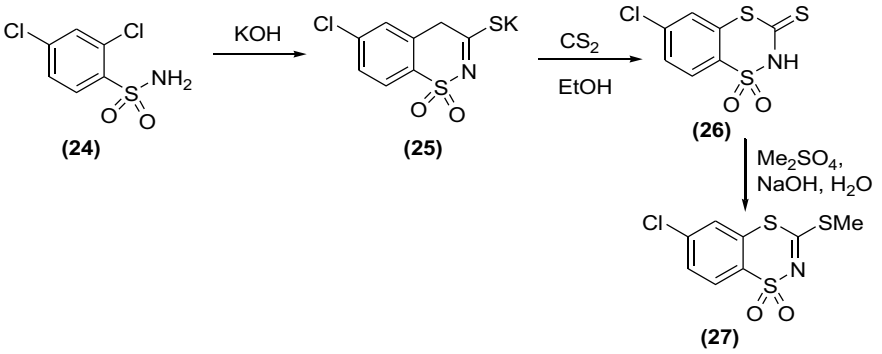


Fig. 8.8 Synthesis of 6-chloro-3-(methylthio)benzo[e][1,4,2]dithiazine-1,1-dioxide

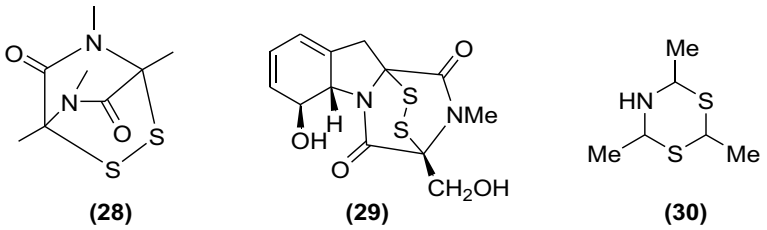
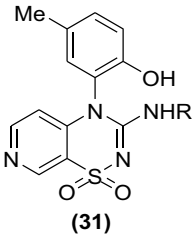


Fig. 8.9 Structure of biologically active dithiazine compounds

Fig. 8.10 Structure of 3-(R-amino)-4-(2-hydroxy-5-methylphenyl)-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides

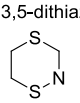


is a reason for potent antiviral, antibacterial, and antifungal activities. The compounds are probably better considered as diketopiperazines rather than 1,2,4-dithiazines. Thialdine **(30)**, a 1,3,5-dithiazine, has been identified as responsible for the flavor of beef broth, and after this discovery, other 1,3,5-dithiazines have been proposed as flavor enhancement agents [25] Figs. 8.8, 8.9 and 8.10.

All six of the possible dithiazines (Table 8.1) have been described in the literature although the rarer 1,3,2- and 1,5,2-isomers are only known as the fully oxidized tetraoxides.

3-(R-amino)-4-(2-hydroxy-5-methylphenyl)-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides **(31)** were synthesized and were found to be effective in vitro anticancer agents [26]

Table 8.1 Dithiazines

Ring system	Comments
 1,2,3-dithiazine	Rare System-6 thione known
 1,2,4-dithiazine	Few examples of 5,6-dihydro derivative
 1,3,2-dithiazine	Rare System-1,1,3,3-tetraoxide only
 1,3,5-dithiazine	Common System
 1,4,2-dithiazine	Common System, especially 1,1-dioxide
 1,5,2-dithiazine	Rare System-1,1,5,5-tetraoxide only

8.3 Conclusion

Nitrogen and sulfur-containing heterocyclic compounds and their clinical therapeutic uses are a growing area of research. The present chapter focuses attention on several synthetic aspects and the biological potential of various dithiazine derivatives. We believe that the present chapter will be useful for researchers in synthetic and medicinal chemistry.

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Chapter 9
Synthesis and Biological Evaluation of Some Sulfur-Containing Spiro Compounds

Aakash Singh and Ruby Singh

9.1 Introduction

Spiro compounds are cyclic compounds in which two cyclic rings are combined through a single carbon atom, and in 1900, Adolf von Baeyer created the first spiro compound spiran. Since the beginning of the twentieth century, several chemists have struggled to create diverse spirocyclic molecules [1]. The main concern in spirocyclic structures appears not only from their structural features, but also from their potent biological activities and presence in a wide variety of naturally occurring products obtained from different sources [2].

Heterocyclic scaffolds are organic compounds that have a ring-like structure with one or more heteroatoms. Heterocyclic compounds containing a sulfur atom represent a major component in FDA-approved medications and therapeutically active structures. Sulfur atom-containing heterocycles are flavoring agents commonly used in culinary products such as meat, vegetables, peanuts, coffee, and cocoa [3]. Heterocycles with sulfur atom, such as clopidogrel, raloxifene, and rosiglitazone, are FDA-approved drugs used to treat peripheral artery disease, breast cancer, and diabetes, respectively [4]. Similarly, ritonavir is a famous antiviral agent [5] and thiabendazole as an antifungal agent. Aside from that, various drugs containing sulfur heterocycles have been approved by the FDA and are used to treat a wide range of medical conditions [6–8].

The development of creative synthetic methods for producing novel analogs of bioactive heterocyclic skeleton is a key challenge in the fields of synthetic and medicinal chemistry. Reactions that yield fresh C–C, C–O, C–N, and C–S bonds, while

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maximizing molecular complexity with minimal operations, are not only notable but also essential for constructing heterocyclic molecular frameworks. Keeping in view of unique properties of spiro derivatives and diverse biological activities associated with sulfur-containing heterocyclic compounds, in the present chapter, we summarize the synthesis of a variety of spiro compounds by annulations of sulfur-containing ring at another heterocyclic moieties.

9.2 Construction of Five-Member Sulfur-Containing Rings

9.2.1 Construction of Thiophene Ring Annulated Spiro Compounds

Tetrahydrothiophenes, which are distinct sulfur-containing heterocycles, have garnered substantial consideration due to their intriguing conformational properties and a broad range of biological activities. These activities encompass antibacterial, [9] antimicrobial, [10] and antifungal properties, [11], antitumor effects [12] anti-inflammatory [13] characteristics, acetyl-CoA carboxylase (ACC) inhibition [14], and the inhibition of human telomerase [15]. Furthermore, polysubstituted tetrahydrothiophenes are integral components of numerous natural products and pharmaceutical agents, including the essential coenzyme biotin [16] with critical biological functions, chiral organocatalysts, [17] potential HIV, [18] inhibitors, glucosidase inhibitors, [19] antitumor natural products, [12], and human A3 adenosine receptor ligands [20]. Drawing from these precedents and previously reported literature on the synthesis of simple and poly spirotetrahydrothiophenes, these compounds can serve as foundational scaffolds for drug design (Fig. 9.1).

The advancement of procedures for the stereoselective formation of chiral spirocyclic tetrahydrothiophene offshoots has become a current issue in synthetic chemistry. A diversity of spirotetrahydrothiophene frameworks fastened to different skeletons has been designated in the literature over the last decade. Rapid use of diverse ranging organocatalyst as a potent green catalyst is another commanding artificial implementation for the grounding of multifaceted molecular and structural designs from simple starting materials. This is fundamentally acknowledged for constructing the organocascade approach, a process that consists of two or more consecutive reactions initiated by an organocatalyst, with each subsequent reaction being the outcome of the functionality created in the previous reaction [21]. Thiophene scaffolds, in addition to their somewhat partially reduced 2,3- or 2,5-dihydrothiophene or the thoroughly reduced tetrahydrothiophene ring structures, are exceptional sulfur encompassing heterocycles that have paying attention, predominantly for the reason that their distinctive place as natural product construction blocks.

To bridge the concept of green and sustainable chemistry in heterocyclic synthesis, Nagaraju et al. [22] have been established a green and resourceful method for

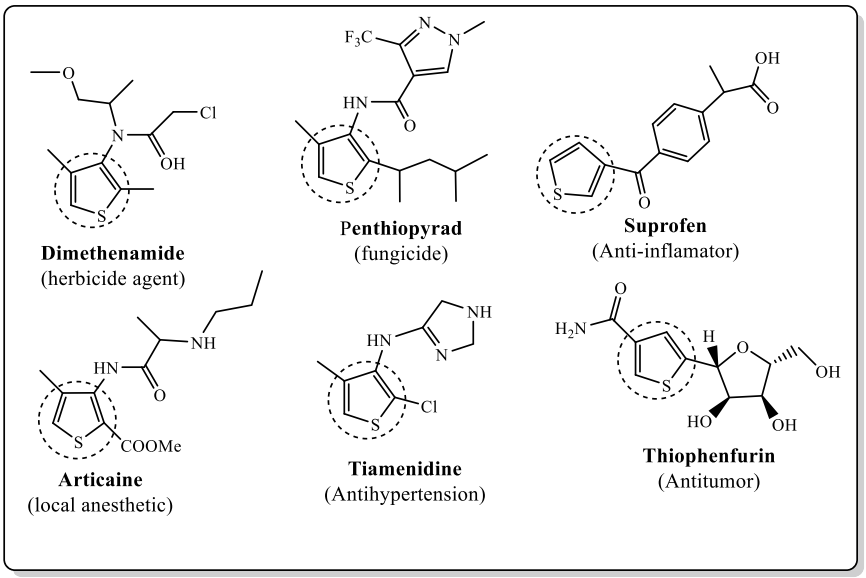
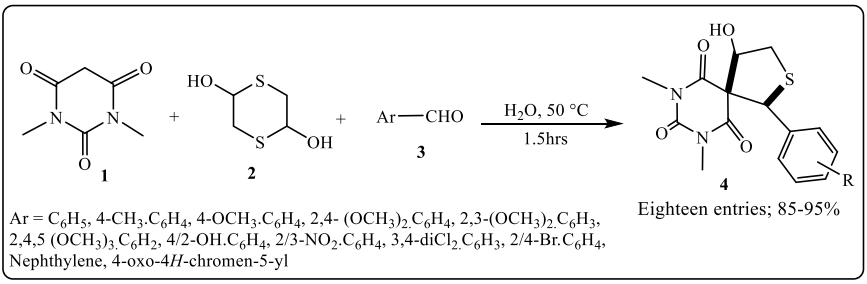


Fig. 9.1 Examples of some thiophene-containing drugs

the blending of quaternary centered and library of eighteen compounds of spiro-barbiturate-tetrahydrothiophene hybrids **4** via one-pot reactions of barbituric acid **1**,1,4-dithiane-2,5-diol **2** and aldehydes **3** under green reaction conditions using water as efficient reaction media with a catalyst-free propagation (Scheme 9.1).

The associated reaction mechanism involves subsequent the Knoevenagel condensation, 1,4-thia-Michael, and intramolecular aldol reactions for synthesis of desired spiro compounds **4.** The role of water plays a vital role in step forward reaction due to hydrophobic effect of water by which the all reactants are aggregating and interacted to each other in hydrogen-bonded water setup. These non-covalent interactions encourage the conjugation of reactive components together to give Knoevenagel adduct **A** which further react with the in situ created monomeric

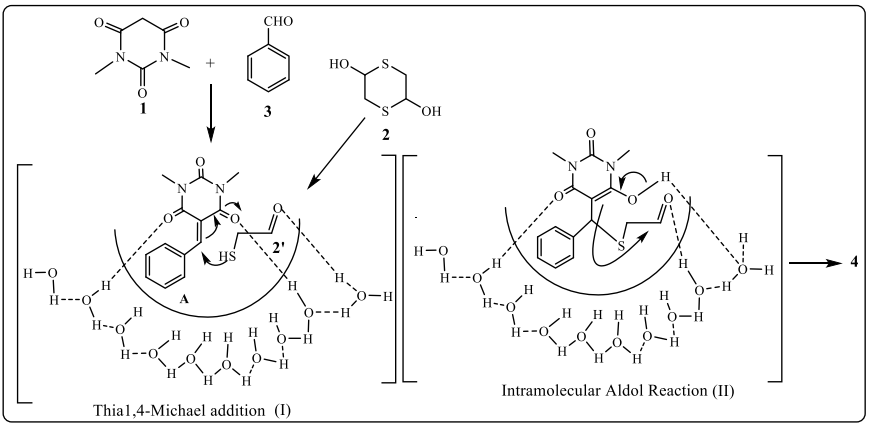


Scheme 9.1 Synthesis of spiro-barbiturate-tetrahydrothiophene hybrids **4**

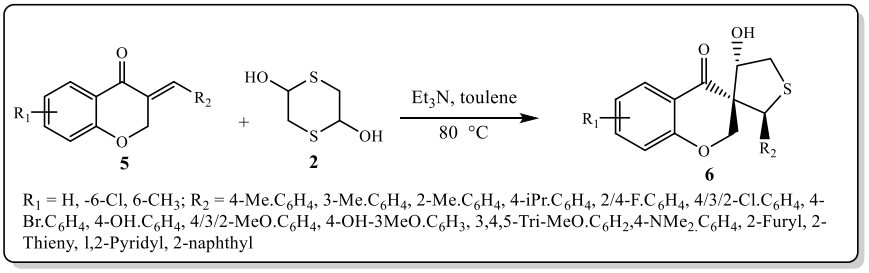
mercaptaldehyde **2′** by means of active transition state I which assisted the sulfa-1,4-Michael followed by intramolecular aldol reactions II to provide the final spiro-barbiturate-tetrahydrothiophene (Scheme 9.2).

Hu et al. [23] have developed a new library of functionalized spirochromanone-tetrahydrothiophenes **6** having three adjacent stereocenters with better diastereoselective fashion via reaction of (E)-3-arylidenechroman-4-ones **5** with 1,4-dithiane-2,5-diol **2** followed by intramolecular sulfa-Michael/aldol cascade reaction using trimethylamine as base and toluene as reaction media at 80 °C temperature. A series of twenty-seven spiro adducts with a good to excellent yield range of 85–99% were synthesized successfully. The diastereoselectivity of synthesized product was established by single crystal X-ray spectroscopy of one of the representative compounds (Scheme 9.3).

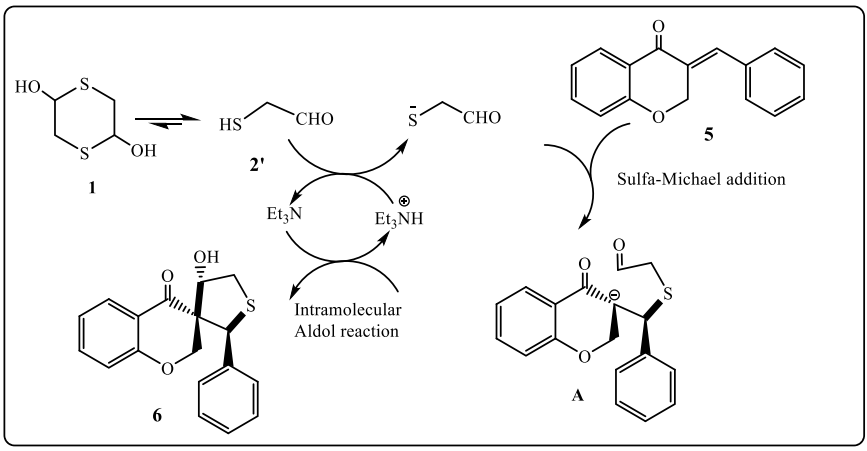
To better explain the reaction pathway, authors have proposed a cascade reaction mechanism, and according to that, in situ generated 2-mercaptoacetaldehyde



Scheme 9.2 Possible reaction mechanism for synthesis of spiro-barbiturate-tetrahydrothiophenes **4**



Scheme 9.3 Synthesis of spirochromanone-tetrahydrothiophenes **6**



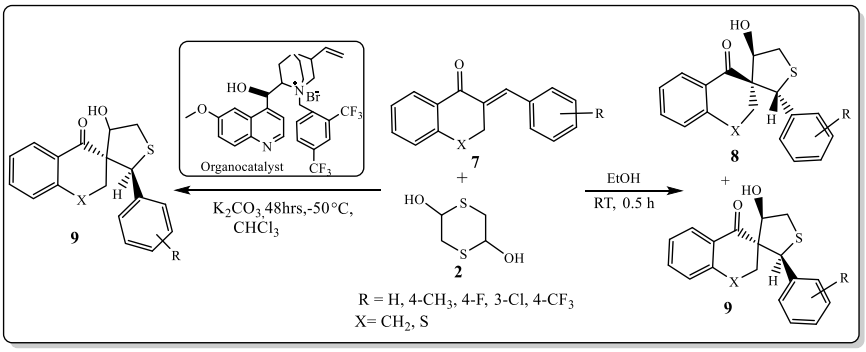
Scheme 9.4 Possible mechanism for synthesis of spirochromanone-tetrahydrothiophenes **6**

2′ from 1,4-dithiane-2,5-diol **2** undergoes the intramolecular sulfa-Michael addition to 3-benzylidenechroman-4-one **5** to generate an enolate-based intermediate **A** which is consequently followed by intramolecular aldol condensation converted to spirochromanone-tetrahydrothiophene **6** (Scheme 9.4).

Liang et al. [24] have published the synthesis of series of polyheterocyclic spirotetrahydrothiophene derivatives as mixture of two diastereoisomers **8** and **9** in reasonable to excellent total yields under catalyst-free sulfa-Michael/aldol cascade reaction of chalcones **7** and commercially available 1,4-dithiane-2,5-diol **2** using ethanol as solvent in 0.5 h.

Furthermore, there is a significant desire for a new synthetic technique that allows for the straightforward production of chiral spirotetrahydrothiophene derivatives with good feasibility for assembling different substitution patterns. For that, Liang group has successfully achieved the synthesis of asymmetric chiral spirotetrahydrothiophene derivatives via sulfa-Michael/aldol cascade reaction of chalcones **7** with 1,4-dithiane-2,5-diol **2** with reasonable to fine enantioselectivities, under optimized reaction conditions using readily available chiral quaternary ammonium salts as organocatalysts and K_2CO_3 in $CHCl_3$ at − 50 °C for 48 h (Scheme 9.5).

Kowalczyk et al. [25] have been reported enantioselective synthesis of benzofuran-3(2*H*)-one containing crystalline scaffold of spiro cyclictetrahydrothiophenes **11** in a cascade approach followed by thio-Michael–aldol reaction of 2-arylidenebenzofuran-3(2*H*)-ones **10** and in situ generated 2-thioacetaldehyde, from 1,4-dithiane-2,5-diol **2**. For optimization of reaction conditions and to get best results in regard to enantio and diastereoselectivity, one of the selected reactions has been studied in using simple cinchona alkaloids catalyst quinine or cinchonidine and other bifunctional catalysts, derived from cinchona alkaloids. Catalysts having either a thiourea or squaramide moiety enhance the enantioselectivity with its low diastereoselectivity. The incorporation of a strong H-bonding unit in the catalyst structure was

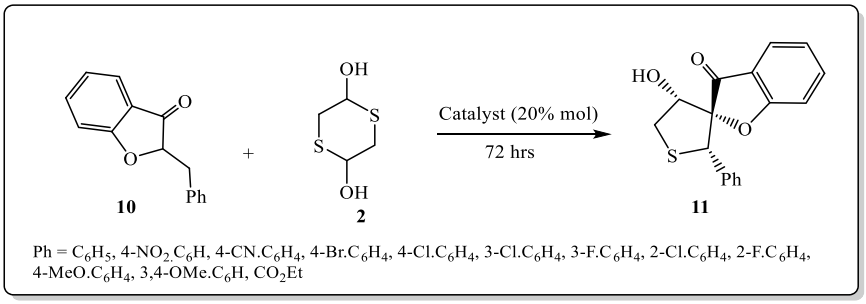


Scheme 9.5 Synthesis of polyheterocyclic spirotetrahydrothiophenes

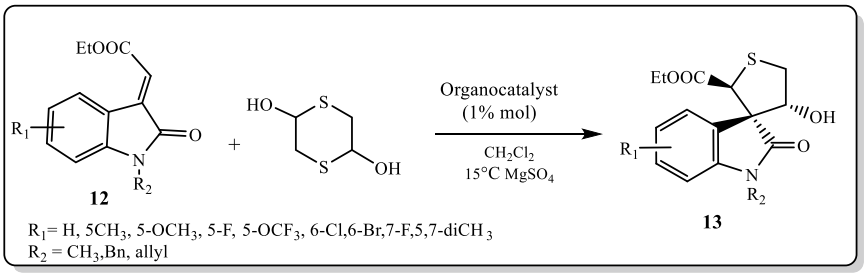
discovered to be advantageous for the stereochemical outcome. It was noticed that the reaction occurred smoothly with wide variety of 2-arylidenebenzofuran-3(2*H*)-ones **10** with electron-withdrawing and electron-releasing substituents on arylidene moiety. A library of fourteen differently substituted tetrahydrothiophene derivatives was synthesized in a good to be excellent yield range of 87–99% (Scheme 9.6).

Duan et al. [26] have established an competent organocatalyzed Michael–aldol cascade reaction for construction of a new enantio enriched family of tetrahydrothiophene-fused spirooxindoles **13** bearing three consecutive stereogenic centers via one-pot multicomponent reaction of (E)-ethyl 2-(1-methyl-2-oxoindolin-3-ylidene) acetate **12** and 1,4-dithiane-2,5-diol **2** catalyzed by organocatalyst cinchonidine-derived squaramide (1% mol) and $MgSO_4$ (10% mol) as base catalyst under mild solvent CH_2Cl_2 media for 30 min at very less temperature 15 °C. They have synthesized a series of twelve compounds having efficient and economic yields of 74–96% (Scheme 9.7).

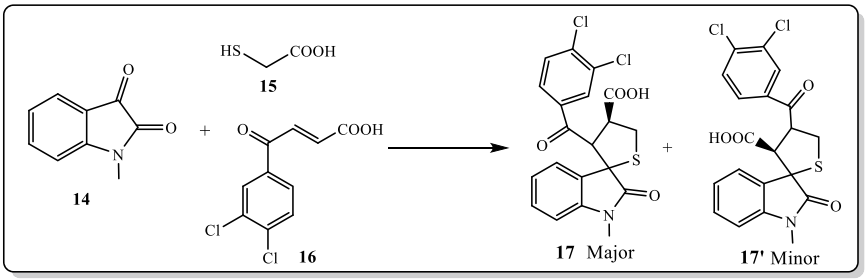
Rizk et al. [27] have been established a synthetic approach for the synthesis for regioselective synthesis of spiroindoline-3,2′-tetrahydrothiophene **17** using one-pot multicomponent 1,3-dipolar cycloaddition reaction of isatins **14**, thioglycolic acid **15,**



Scheme 9.6 Synthesis of spiro cyclictetrahydrothiophenes derivatives **11**



Scheme 9.7 Synthesis of tetrahydrothiophene-fused spirooxindoles



Scheme 9.8 Synthesis of spiroindoline-3,2′-tetrahydrothiophene **17**

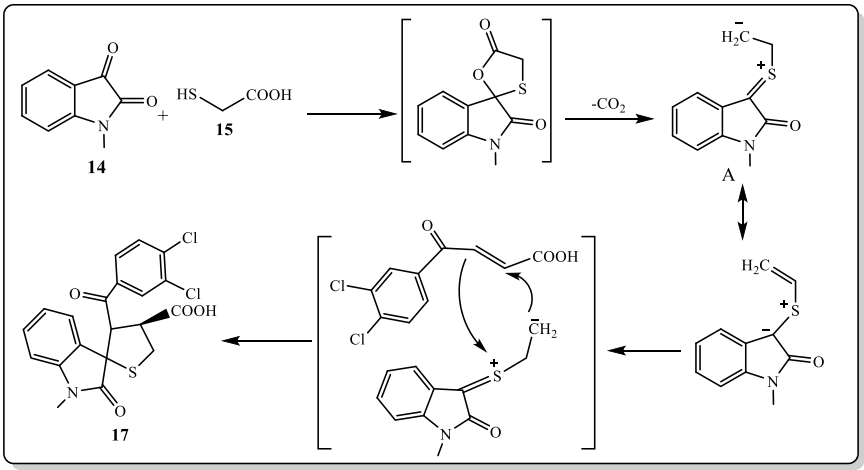
and 4-aryl-4-oxo-but-2-enoic acids **16** to afford the spirooxindoles **17** in reasonable to good yields using ethanol as reaction media (Scheme 9.8).

The anticipated mechanism of present reaction involves the in situ generation of thia-methine ylides **A**, via decarboxylative condensation of isatin **14** and thioglycolic acid **15** which in next step undergoes 1,3-dipolar cycloaddition reaction with dipolarophile 4-aryl-4-oxo-but-2-enoic acids to furnish the preferred product **17** with preferred regio and diastereoselective manner (Scheme 9.9).

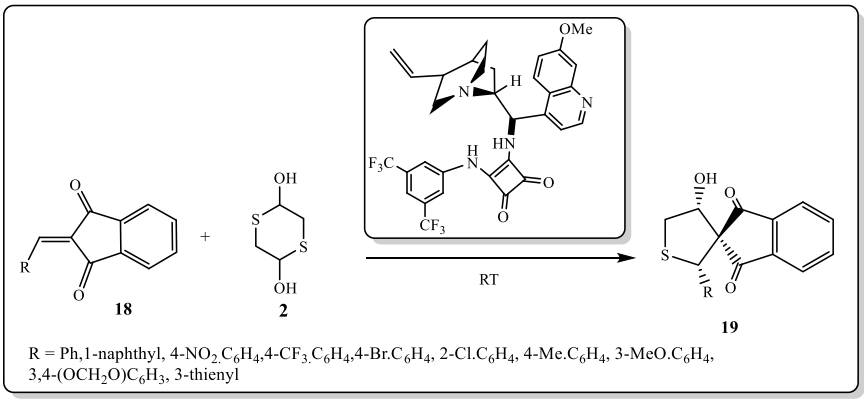
Some of synthesized compounds exhibited the preeminent cytotoxic activity against MCF-7 and Wl-38 cells and showed strong cytotoxicity with very good IC50 values.

Mahajan et al. [28] have developed a rapid excess report for synthesis of a new asymmetric domino sulfa-Michael/aldol reaction of 1,4-dithiane-2,5-diol **2** with 2-arylidene-1,3-indandiones **18** for synthesis of spirotetrahydrothiophene-indan-1,3-dione **19** catalyzed by a quinidine-derived squaramide with moderate to good diastereo- and enantioselectivities (Scheme 9.10).

Kumar et al. [29] accomplished a sustainable and synthetically economical technique in aqueous medium in the presence of base catalyst triethylamine for the stereoselective synthesis of novel spiro[indene-2,3′-thiophen]-1(3*H*)-ones **21** from the domino reactions of a series of (*E*)-2-benzylidene-2,3-dihydro-1*H*-inden-1-ones **20**



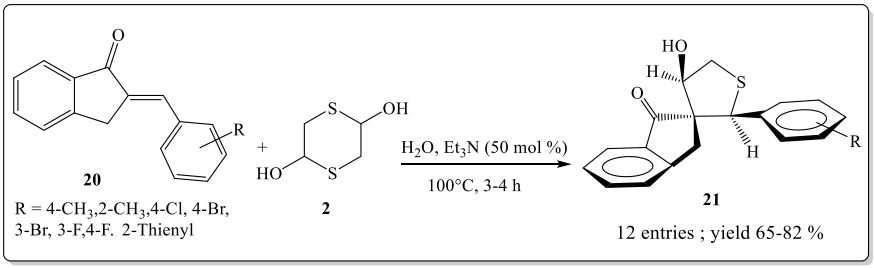
Scheme 9.9 Mechanism for synthesis of spiroindoline-3,2′-tetrahydrothiophenes **17**



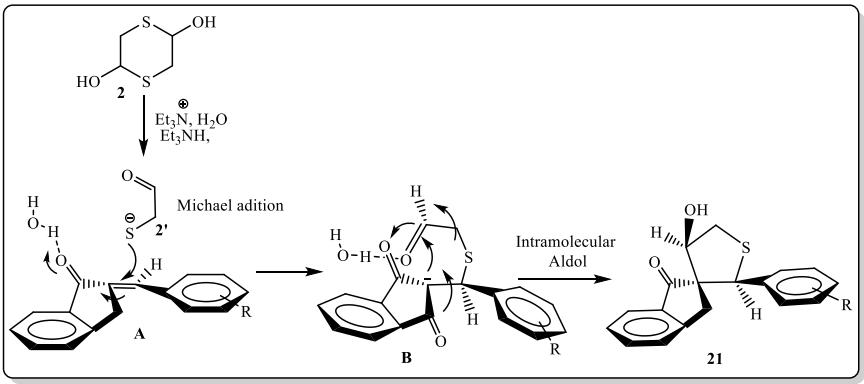
Scheme 9.10 Synthesis of spirotetrahydrothiophene-indan-1,3-dione **19**

with 1,4-dithiane-2,5-diol **2** in good yields. This conversion is 100% atom-economic, and reaction proceeds under green reaction conditions (Scheme 9.11).

A plausible mechanism for the formation of spiro[indene-2,3′-thiophen]-1(3*H*)-one **21** involves the generation of 2-mercaptoacetaldehyde **2′** from the reaction of 1,4-dithiane-2,5-diol **2** with triethylamine. This thiolate anion **2′** reacts with (*E*)-2-(aryl)-2,3-dihydro-1*H*-inden-1-ones **20** via Michael addition to give intermediate **A** which subsequent through intramolecular aldol reaction afford exclusively one diastereomer of **21** with highly stereoselective manner. The trans-relationship between the indanone carbonyl and either the aryl ring connected to the tetrahydrothiophene ring



Scheme 9.11 Synthesis of novel spiro[indene-2,3′-thiophen]-1(3*H*)-ones **20**

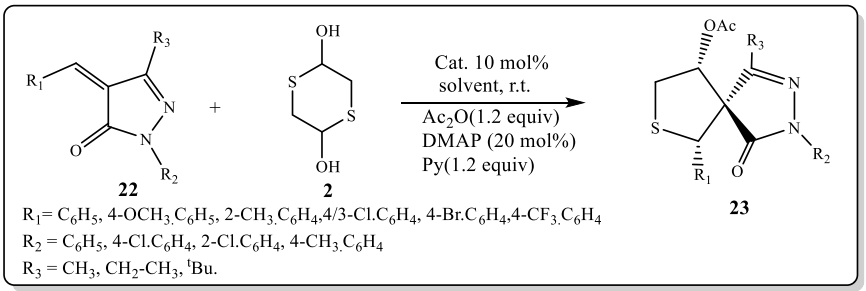


Scheme 9.12 Plausible mechanism for synthesis of spiro[indene-2,3′-thiophen]-1(3*H*)-one**21**

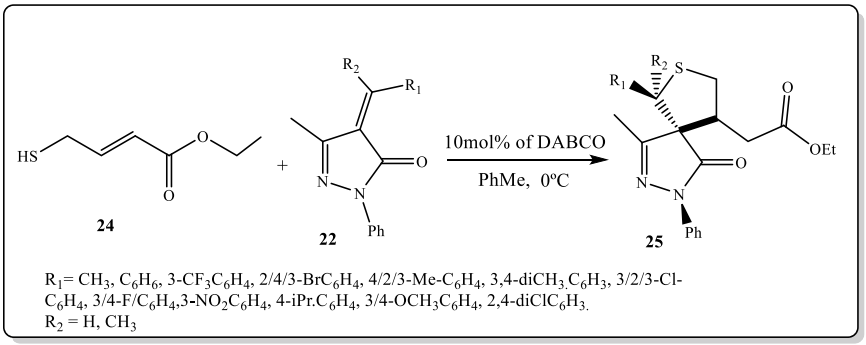
or the hydroxyl group of the tetrahydrothiophene ring in the main diastereomer **21** promoted stereoselective annulation of the Michael adducts **A** (Scheme 9.12).

Kaya et al. [30] developed a *N*,*N*-diisopropylethylamine (DMAP) catalyzed reaction of arylidenepyrazolones **22** with 1,4-dithiane-2,5-diol **2** to provide spiro[pyrazolone-4,3′-tetrahydrothiophene] derivatives **23** via diastereoselective sulfa-Michael/aldol domino reaction in 42–98% yield under mild reaction conditions (Scheme 9.13).

Later on, Cui et al. [31] have reported a new strategy for diastereoselective formation of spiro[tetrahydrothiophene-3,3′-pyrazol] derivatives **25** via DABCO catalyzed and anhydrous toluene-mediated Michael cyclization reaction of *trans*-ethyl 4-mercapto-2-butenoate **24** and differently substituted 4-benzylidene-5-methyl-2-phenylpyrazolones **22** at 0ºC. They have synthesized more than twenty compounds with 90–98% yield, and formed derivatives showed moderate to excellent diastereoselectivities. For the optimization of perfect reaction conditions, variety of solvents and different catalysts with loading amounts were examined, but the best yields and diastereoselective results were obtained using 10% DABCO as catalyst, toluene as solvents and 0° C temperature in 12 h reaction time (Scheme 9.14).



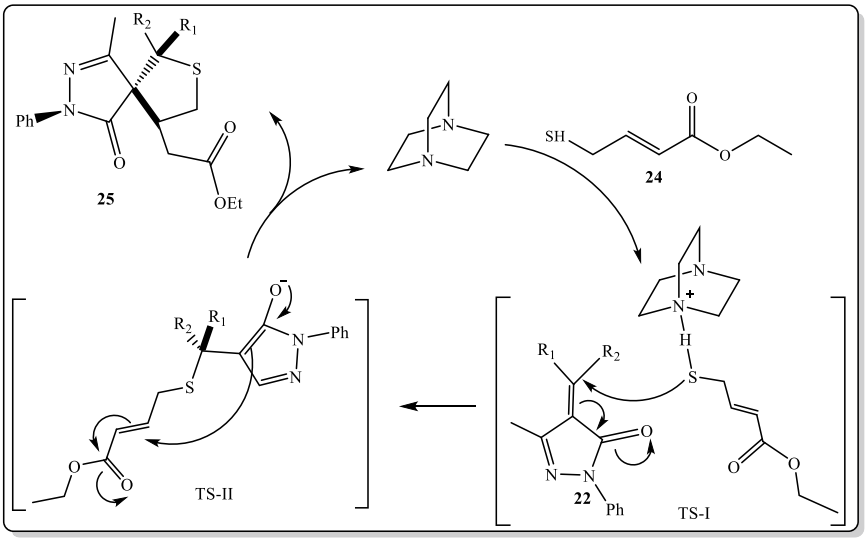
Scheme 9.13 Synthesis of spiro[pyrazolone-4,3′-tetrahydrothiophene] derivatives **23**



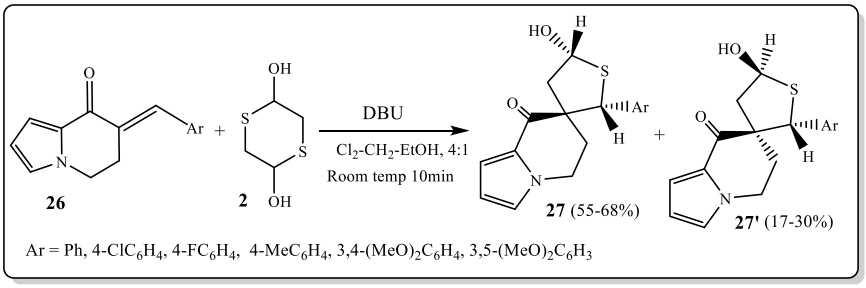
Scheme 9.14 Synthesis of spiro[tetrahydro thiophene-3,3′-pyrazol] derivatives **25**

Pathway for this cascade Michael/Michael cyclization reaction first involves the activation of trans-ethyl 4-mercapto-2-butenoate **24** by means of the tertiary amine of DABCO to generate intermediate TS I, which then go through the intermolecular sulfa-Michael addition to grant the intermediate TS II. Consequent TS II undergoes intramolecular Michael addition reaction by excellent diastereoselective fashion to provide spiro[tetrahydrothiophene-3,3′-pyrazol] derivatives. The catalyst DABCO was regenerated for further catalysis (Scheme 9.15).

Huang et al. [32] reported new and affordable synthesis of novel spiro skeleton 2′-aryl-4′-hydroxy-4′,5,5′,6-tetrahydro-2′*H*,8*H*-spiro[indolizine-7,3′-thiophen]-8-ones as mixture of two diastereomers **27** and **27′** via sulfa-Michael/aldol cascade reaction of (*E*)-7-arylidene-6,7-dihydroindolizin-8(5*H*)-ones **26** and 1,4-dithiane-2,5-diol **2** in low to moderate yields. A series of fourteen spiro[indolizine-thiophen] derivatives are produced as products when differently substituted reactants were stirred in one pot at room temperature for 10 min using DBU as catalyst and CH_2Cl_2–EtOH, 4:1 (5 ml) as solvent. The stereochemical arrangement of the products was established by single crystal X-ray diffraction analysis, and all the rest structures of products were characterized thoroughly by NMR, IR, HRMS, spectroscopic analysis (Scheme 9.16).



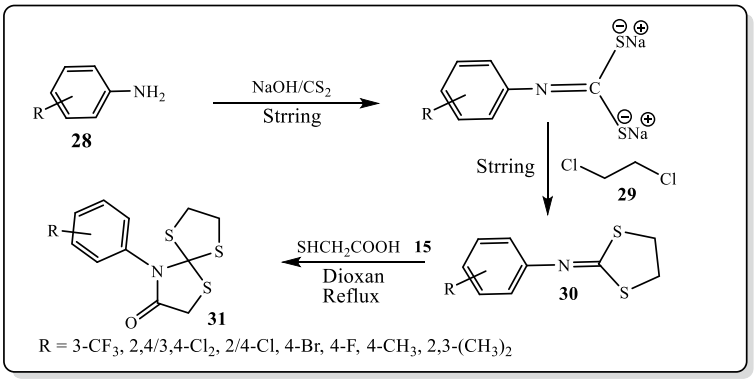
Scheme 9.15 Plausible pathway for cascade Michael/Michael cyclization reaction **25**



Scheme 9.16 Synthesis of spiro[indolizine-7,3′-thiophen]-8-ones **27** and **27′**

9.2.2 Construction of Dithiolane Ring Annulated Spiro Compounds

One of the fundamental objectives in both organic and pharmaceutical chemistry is design, synthesis, and manufacture of compounds with therapeutic potential in humans. The heterocyclic scaffolds gain special attention because they fit into a class of composite with demonstrated value in medicinal chemistry. Five-member heterocyclic ring dithiolane is a versatile biodynamic moiety found in biologically active compounds obtained from mangrove plants [33]. Despite this, dithiolanes have anti-HIV [34], neuroprotective [35], antiviral [36], PPAR-gamma agonist activities [37], and cannabinoid receptor [38] properties.



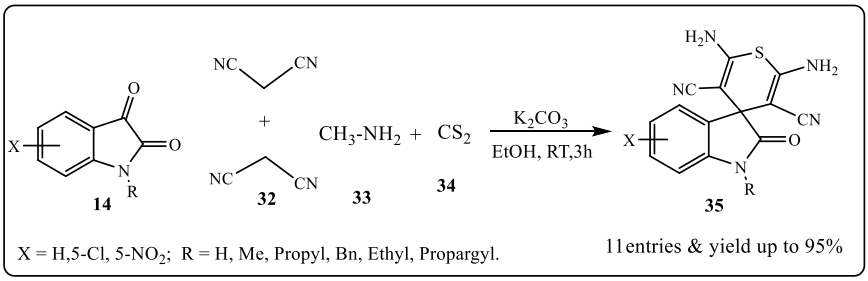
Scheme 9.17 Synthesis of spiro-[1,3-dithiolan-2,2′-thiazolidin]-4-ones

The amalgamation of heterocyclic rings via a spiro carbon atom frequently consequences in compounds with attractive biological activities, and Pandey et al. [39] reported the synthesis of a series of 3-substituted-spiro-[1,3-dithiolan-2,2′-thiazolidin]-4-ones **31** by the reaction between [1,3]dithiolan-2-ylidene-(substituted-phenyl)amine **29** and mercaptoacetic acid **15**. The compound [1,3]dithiolan-2-ylidene-(substituted-phenyl)amine **30** was synthesized by the reaction of substituted anilines **28**, sodium hydroxide, and carbon disulfide followed by the reaction of 1, 2-dichloroethane **29**. These substances were tested for antibacterial and antitubercular activity. Some of them inhibited bacterial and fungal growth significantly. Only a few of them had a moderate antitubercular profile. Docking studies were performed on several new compounds, and the results demonstrated that these compounds have a high binding energy and affinity for the active pocket, implying that they could be effective inhibitors of selective proteins (Scheme 9.17).

9.3 Construction of Six-Member Sulfur-Containing Rings

9.3.1 Construction of Thiopyran Ring Annulated Spiro Compounds

Thiopyran scaffolds have received extensive research among the sulfur-containing heterocyclic molecules, and investigations have proven their remarkable features, such as antibacterial [39] antihyperplasia [40], and antipsychotic [41] properties. Furthermore, one of the most notable aspects of these motifs is their use in cancer treatment [42, 43]. Therefore, chemists are looking new derivatives of thiopyran-containing heterocycles using innovative strategies to their synthesis. One another heterocyclic moiety oxindole is also well-known key organic scaffolds due to their



Scheme 9.18 Synthesis of substituted spiro[indoline-3,4′-thiopyran]-3,5-dicarbonitriles **35**

excellent benefits in medicinal organic chemistry [44]. The literature reveals some reports on synthesis of spiro scaffolds by combining these two oxindole and thiopyran heterocyclic moieties in one molecular frame to found application as scaffolds for drug discovery.

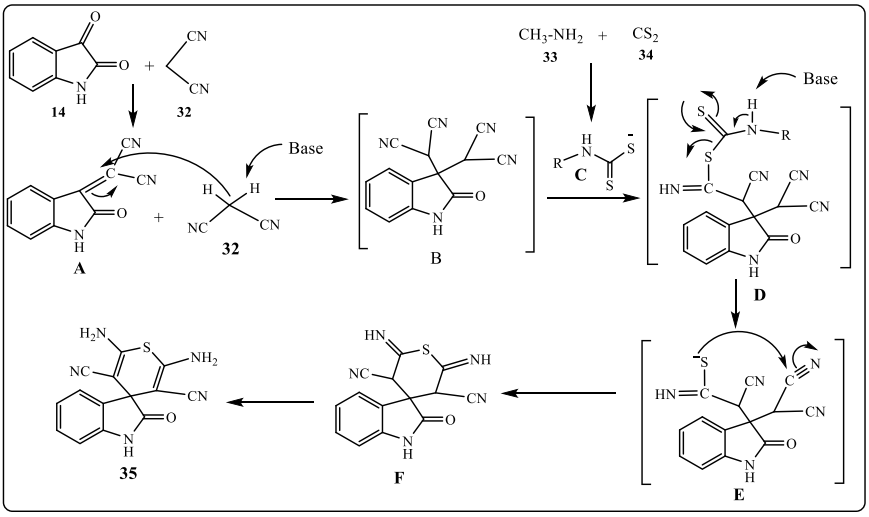
In this direction, Moghaddam et al. [45] discovered the synthesis of 2,6-diamino-1-alkyl-2oxospiro[indoline-3,4′-thiopyran]-3,5-dicarbonitrile **35** via one-pot, five-component reaction of substituted isatins **14**, malononitrile **32**, methyl amines **33**, and carbon disulfide **34**, using K_2CO_3 as mild base and ethanol as solvent at room temperature in high yields by stirring all substrates at room temperature for 3 h. The general scope of this reaction was investigated with various substitutions at nitrogen atom and aromatic ring of isatin derivatives (Scheme 9.18).

The concern mechanism for synthesis of these scaffolds **35** involves formation of Knoevenagel adduct by reaction of isatin**14** and malononitrile **32,** and its further reaction with base-generated carbanion of malononitrile **32** gives cyanosubstituted alkenyl oxindoles intermediate **B**. Simultaneously, another intermediate carbamodithioic acid **C** was generated by the reaction of methyl amine **33** with carbon disulfide **34**.

After that, the Michael addition of carbamodithioic acid **A** to intermediate **B** produces intermediate **D** which subsequently via hydrogen transfer and disconnection of C-S bond leads to formation of intermediate **E,** and this intermediate **F** through intramolecular cyclization and after that imine–enamine tautomerization provides the final spiro products **35**(Scheme 9.19).

Recently, Moghaddam et al. [46] synthesized a novel efficient MOF-based catalytic system NH_2·MIL-101(Fe)/ED and reported its catalytically efficiency to catalyze the synthesis of oxospiro-indolinethiopyrans **35** via four-component reaction of cyanoalkenyl oxindoles intermediate **B**, primary amines, carbon disulfide, and malononitrile in ethanol. The present heterogeneous catalytic system showed the superior activity toward the synthesis of **35**.

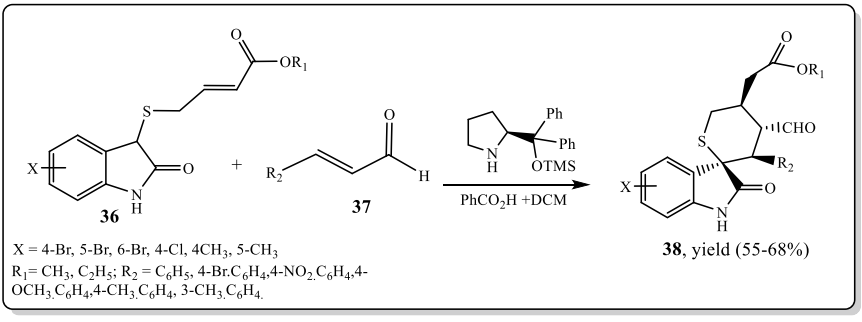
Asymmetric organocatalytic reactions are a popular research field in modern organic chemistry due to their unique ability to build complex chiral frameworks. Sulfur-containing functionalities have numerous uses in drug design due to their distinctive drug-like characteristics. As a result, the remarkably stereoselective



Scheme 9.19 Plausible mechanism for synthesis of spiro[indoline-3,4′-thiopyran]-3,5-dicarbonitriles**35**

creation of chiral sulfur-containing scaffolds has drawn the attention of many researchers. Organocatalytic asymmetric synthesis for assembling the chiral spirotetrahydrothiophene oxindoles via sulfa-Michael/aldol and sulfa-Michael/Michael cascade reactions has been well developed by Chunquan Sheng research group.

In 2016, Wang et al. [47] first time reported the asymmetric method for synthesis of chiral spirocyclic oxindole-tetrahydrothiopyran scaffold **38** by the reaction of 3-substituted indolin-2-one **36** and α, β-unsaturated aldehydes (enals) **37** using diphenylprolinyl silyl ether as organocatalyst and $PhCO_2H$ as the additive in DCM solvent (Scheme 9.20).



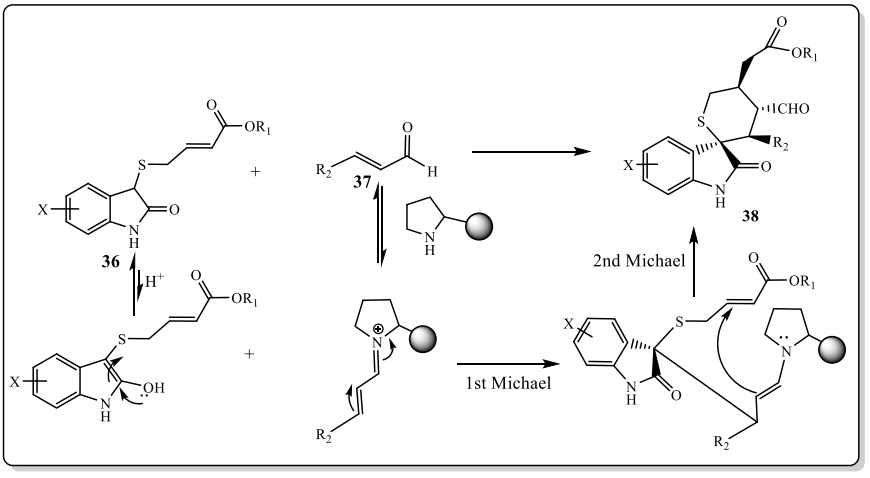
Scheme 9.20 Synthesis of chiral spirocyclic oxindole-tetrahydrothiopyran **38**

Enals **37** having electron-withdrawing and donating groups are smoothly participated to afford the target products with reasonable yield (55−68%) with stereoselectivities (dr > 30:1, ee ≥ 99%). Along with phenyl-substituted enals, heterocyclic-substituted α,β-unsaturated aldehydes such as furanyl provide the moderate yield (57%) of desired product with excellent enantioselectivity (ee > 99%). However, aliphatic enals **37**, such as pent-2-enal and 4-methylpent-2-enal, are failed to react with 3-substituted indolin-2-one. Likewise, the substituents either electron-withdrawing or electron-donating groups present on aromatic ring of 3-substituted indolin-2-one react smoothly to afford the desired products with high yields (57–74%) and stereoselectivities (dr > 30:1, ee > 99%).

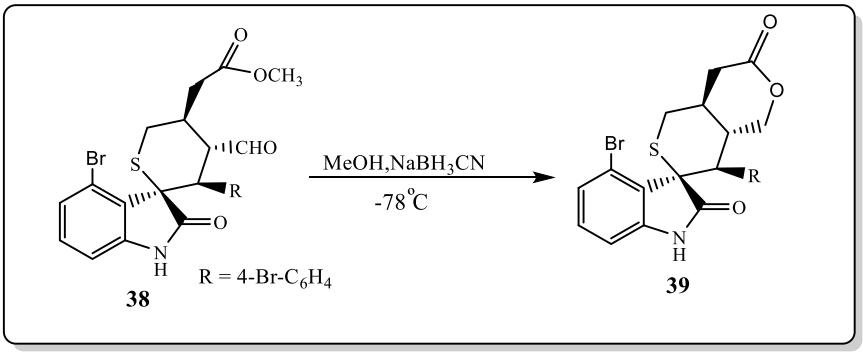
In this reaction, 3-substituted indolin-2-one **36** carrying the nucleophilic oxindole-C3 acts as the Michael donor and α,β-unsaturated ester as the Michael acceptor, and concern reaction mechanism involves the Michael –Michael cascade reaction (Scheme 9.21).

Further, to increasing the molecular complexity and diversity of synthesized spirocyclic oxindole-tetrahydrothiopyran **38** converted to spiro[indoline-3,7′-thiopyrano[4,3-c]pyran]-2,3′(4′H)-dione **39** via a one-step reduction-condensation reaction in good yield (72%) and outstanding enantioselectivity (ee > 99%) (Scheme 9.22).

The absolute configuration of the products was determined by X-ray crystallography analysis of product **39** as 3R,4a′S,8′S,8a′S. The synthesized spiro-oxindole-thiopyrans were assayed for in vitro antitumor activity against three types of human cancer cell lines with p53 in its wild type (A549 lung carcinoma cell, HCT116 colon cancer cell, and MDA-MB-231 breast cancer cell) by the standard MTT method. The results showed that bromo-substituted spiro compound showed the best antitumor activity.



Scheme 9.21 Plausible mechanism for synthesis of spirocyclic oxindole-tetrahydrothiopyran **38**



Scheme 9.22 One-step synthesis of spirocyclic oxindole-tetrahydrothiopyran **39**

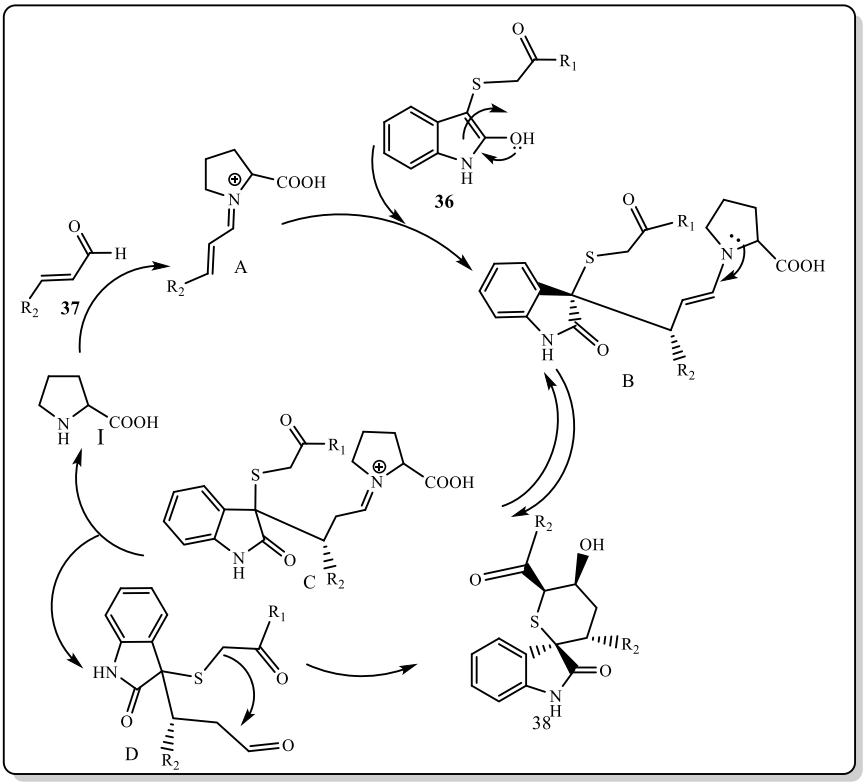
Later on, due to potential applications of spiro-oxindole-thiopyrans as antitumor drug agent, Wang et al. [48] expanded this work and explored the innovative synthetic methods to accumulate new spiro-tetrahydrothiopyran oxindole scaffolds **38** by a new Michael–aldol cascade reaction of diverse functional groups containing 3-substituted indolin-2-ones **36** and α,β-unsaturated aldehyde **37** to study their bioactivity and structure–activity relationship (SAR) which was found to be potent p53-MDM2 inhibitors with good antitumor activity.

To found the excellent yields of spiro-tetrahydrothiopyran oxindoles with better diastereoselectivity and enantioselectivity, authors studied this reaction using various organocatalysts including secondary amine, primary amine, and tertiary amine organocatalysts and chosen the racemic proline (I) as catalyst. Using the racemic proline (I), variety of substrates **36** reacted well with structurally diverse α,β-unsaturated aldehydes **37** to give the spiro-oxindole-thiopyrans **38** in good yield (51–78%) and excellent diastereoselectivities (dr > 20: 1). The plausible reaction mechanism for synthesis of desired product via Michael–aldol cascade reaction is depicted in Scheme 9.23.

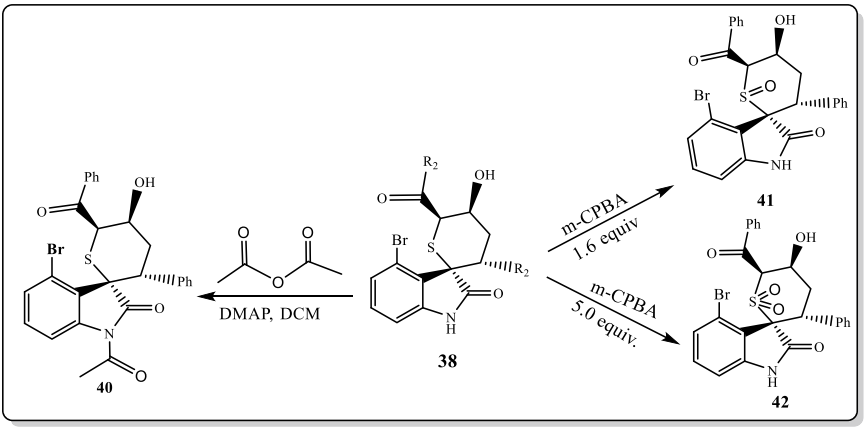
The relative arrangement of Michael–aldol cascade products **38** was obtained and determined by X-ray crystallography analysis, and it is also showed the presence of two intermolecular hydrogen bonds between the two enantiomers.

To further explore this study, one of the compounds, acylated **40**, was oxidized into sulfoxide **41**(yield 90%, > 20: 1 dr) and sulfone **42** in good yield (95%) using appropriate regents and catalyst as shown in Scheme 9.24.

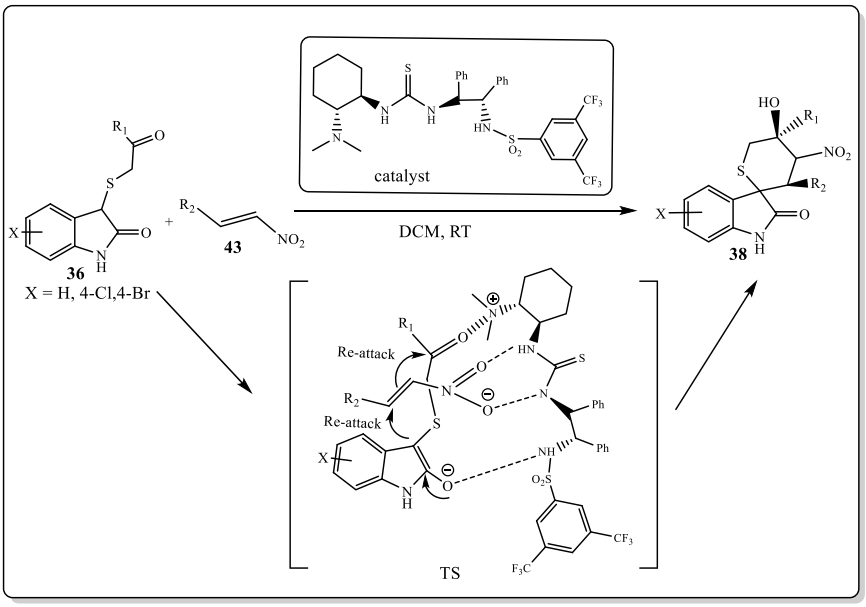
Further, to check the stability of hydroxyl group present on thiopyran ring, the common dehydration and chlorination reactions were accomplished and no reaction was observed which indicate the stability of hydroxyl group, which further confirms the hydrogen bonding. These compounds were assayed for in vitro antitumor activity against A549, numerous derivatives exhibited improved antitumor activity than nutlin-3, and some compounds exhibited good in vitro MDM2 inhibitory activity.



Scheme 9.23 Plausible pathway for the synthesis of spiro-tetrahydrothiopyran oxindoles **38**



Scheme 9.24 Acylation and oxidation of spiro-oxindole-thiopyrans **38**



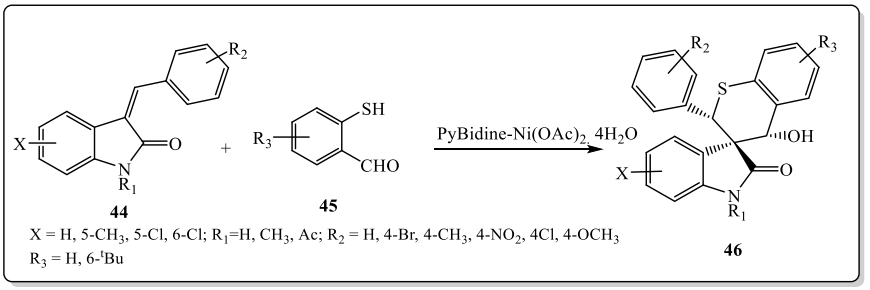
Scheme 9.25 Michael–Henry cascade synthesis of spirotetrahydrothiophene oxindole **38**

Owing to the synthetic challenge and therapeutic values of spiro-oxindole-thiopyrans, another study of Wang et al. [49] established the synthesis of spirotetrahydrothiophene oxindole scaffold **38** through organocatalytic asymmetric Michael–Henry cascade process using 3-substituted indolin-2-one **36** and nitroalkenes **43** to afford substituted spiro-tetrahydrothiopyran oxindoles having four successive stereogenic centers using DCM as solvent in reasonable to good yield (54 ~ 79%), with tremendous diastereo- and enantioselectivities (up to 93% ee) (Scheme 9.25).

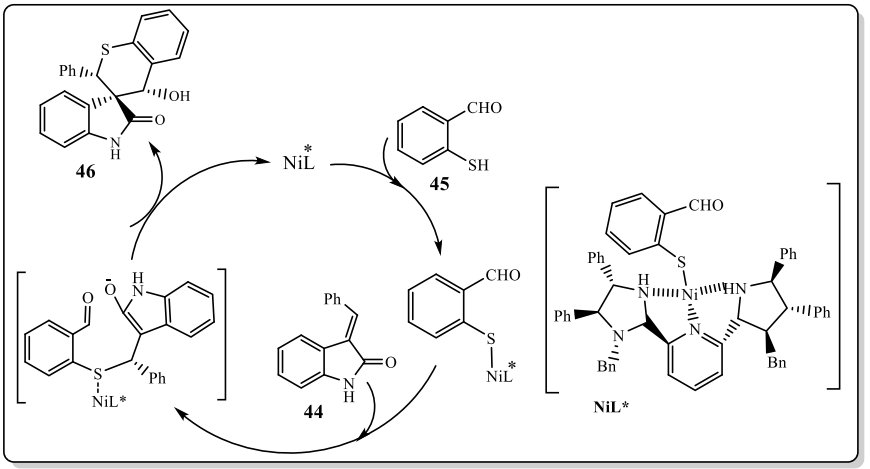
According to plausible mechanism, nitroalkenes are interact with the thiourea group of catalyst via multiple H-bonds which improved the electrophilic character of the β-carbon atom of nitroalkenes **43**. Then, intermolecular Michael reaction of nucleophilic oxindole-C3 at β-carbon atom of nitroalkenes occurs through Re-face attack. Subsequently, the carbanion (adjacent to the nitro group) produced from the Michael addition attacks the Re-face of the carbonyl group of substrate **36** to afford the Henry products **38.**

Arai et al. [50] synthesized highly diastereoselective and divergent synthesis of thiochromanyl-spirooxindole **46** via asymmetric Michael/aldol reaction of methyleneindolinones **44** with thiosalicylaldehydes **45** using PyBidine–Ni$(OAc)_2$ as catalyst in good yields with enantioselectivities (Scheme 9.26).

The planned catalytic cycle for the PyBidine–Ni$(OAc)_2$-catalyzed asymmetric reaction of methyleneindolinone and thiosalicylaldehyde is presented in Scheme 9.27.



Scheme 9.26 Synthesis of thiochromanyl-spirooxindole **46**

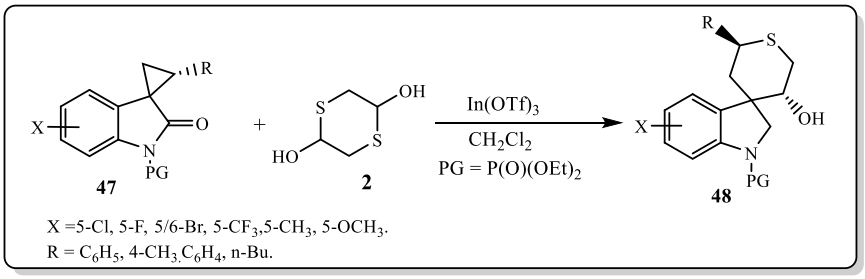


Scheme 9.27 Mechanism for synthesis of thiochromanyl-spirooxindole **46**

In continuous search of the new catalytic methods for synthesizing sulfur ring containing spirooxindoles, Hao et al. [51] demonstrated a facile synthesis of spiro[indoline-3,4′-thiopyran]-2-ones **48** via [3 + 3] annulation of spirocyclopropyl oxindoles **47** and 1,4-dithiane-2,5-diol **2** in the presence of Lewis catalyst $In(OTf)_3$.

The nature and position of substituents present on spirocyclopropyl oxindole **47** had negligible effect on the reactivity, and desired product obtained 75%–87% yield. However, a significant electronic effect of the substituents on the reaction's diastereoselectivity was detected (Scheme 9.28).

Zelisko et al. [52] reported the synthesis of spiro-substituted thiopyrano[2,3-d]thiazoles **52** using trans-aconitic acid **49** and the appropriate aromatic amines **28** and 5-arylidene-4-thioxo-2-thiazolidinone **50** to furnish rel-(5′R,6′R,7′R)-5′-carboxy-7′-aryl-1-aryl-3′,7′-dihydro-2H,2′H,5Hspiro[pyrrolidin-3,6′-thiopyrano[2,3-d]thiazol]-2,2′,5-triones **52.**

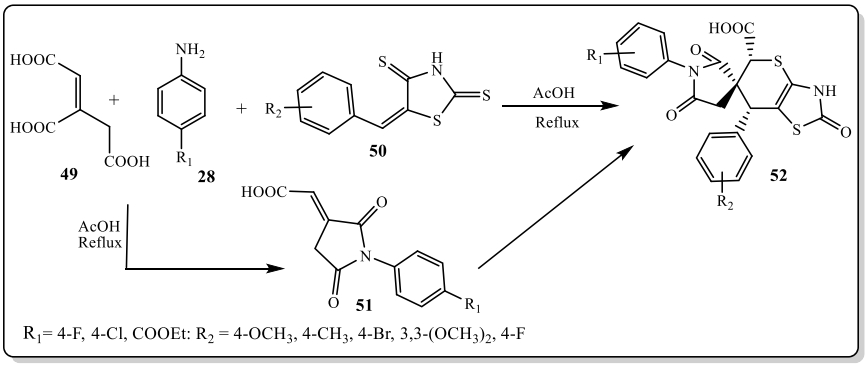


Scheme 9.28 Synthesis of diastereoselective spirocyclopropyl oxindole **48**

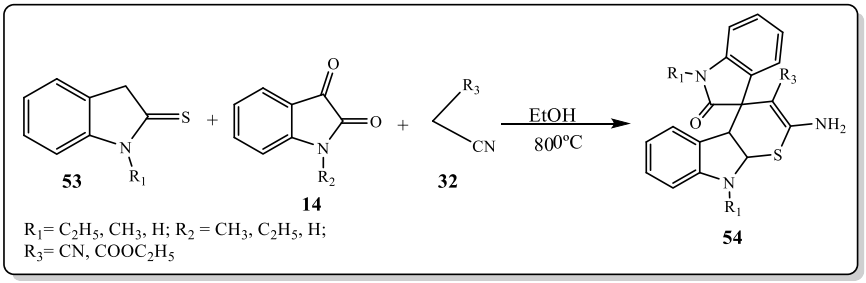
The proposed mechanism for synthesis of substituted spiro[pyrrolidin-3,6′-thiopyrano[2,3-d]thiazol]-2,2′,5-triones **52** first involves the reaction of trans-aconitic acid **49** with appropriate aromatic amine **28** to form the corresponding (2,5-dioxo-1-arylpyrrolidin-3-ylidene)-acetic acid **51** which then react with 5-arylidene-4-thioxo-2-thiazolidinone **50** to furnish final product via hetero-Diels–Alder reaction highly selective path (Scheme 9.29).

Majumdar et al. [53] evolved a straightforward and efficient method for the diversity-oriented synthesis of spiro[indoline-3,4′-thiopyrano[2,3-b]indole] derivatives via multicomponent reaction of indoline-2-thione **53**, isatin **14,** and ethyl cyanoacetate or malononitrile **32** under catalyst-free conditions in shorter reaction time with excellent yields under environmentally benign ethanol as solvent (Scheme 9.30).

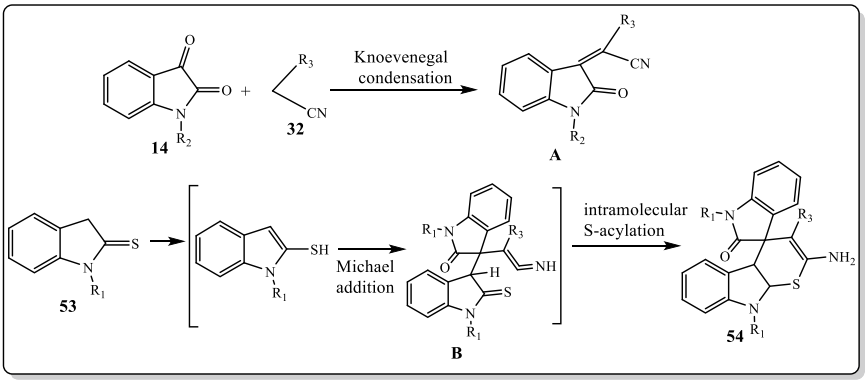
The probable mechanism for this catalyst-free reaction involves the first Knoevenagel condensation between isatin **14** and ethyl cyanoacetate/malononitrile **32** to form the cyanoolefin intermediate A. Then, Michael addition of **A** to the enol form of indole-2-thione **53** gives another intermediate **B** which undergoes an intramolecular



Scheme 9.29 Synthesis of spiro-substituted thiopyrano[2,3-d]thiazoles **52**



Scheme 9.30 Synthesis of spiro[indoline-3,4′-thiopyrano[2,3-b]indole] derivatives **54**

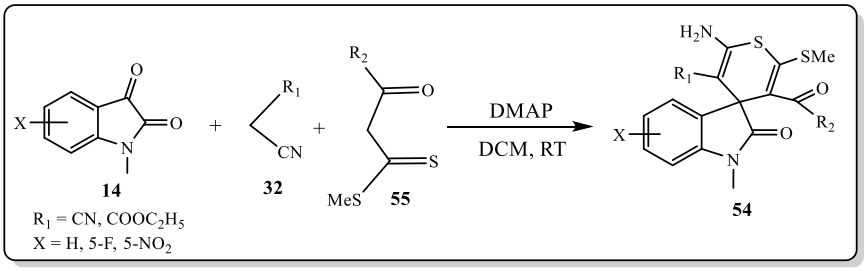


Scheme 9.31 Plausible mechanism for synthesis of spiro[indoline-3,4′-thiopyrano[2,3-b]indole] derivatives **54**

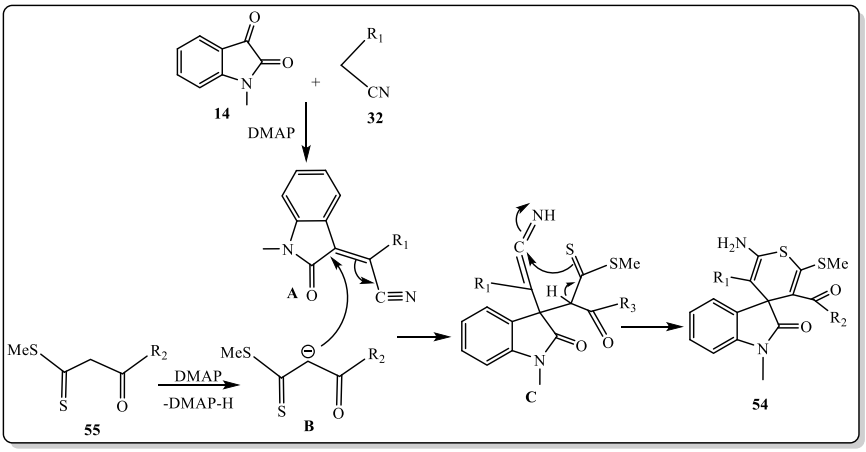
S-acylation to produce the spiro[indoline-3,4′-thiopyrano[2,3-b]indole] derivatives **54** (Scheme 9.31).

After that, Kurva et al. [54] synthesized the spiro[indoline-3,4′-thiopyran]-2-ones **54** via multicomponent reaction of *N*-methyl isatin **14**, malononitrile/ethyl cyanoacetate **32,** and β-oxodithioester **55** in high yields using base catalyst *N,N′*-dimethylaminopyridine (DMAP) in high yield (Scheme 9.32).

The proposed mechanism in this multicomponent reaction involves the DMAP-catalyzed Knoevenagel reaction between isatin**14** and malononitrile **32** for producing adduct **A.** Next, the carbanion generated from β-oxodithioester undergoes Michael addition with **A** for generating another intermediate **B** which subsequent undergoes base-assisted intramolecular cyclization **C** to give spiro[indoline-3,4′-thiopyran]-2-ones **54** (Scheme 9.33).



Scheme 9.32 Multicomponent synthesis of spiro[indoline-3,4′-thiopyran]-2-ones **54**

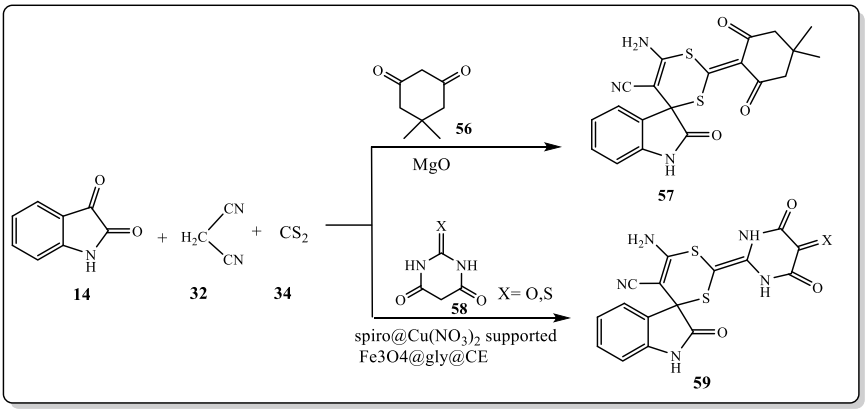


Scheme 9.33 Synthesis of spiro[indoline-3,4′-thiopyran]-2-ones **54**

9.3.2 Construction of Dithiine Ring Annulated Spiro Compounds

Sulfur-containing six-membered heterocyclic ring with two sulfur atoms at positions of 1 and 3 is extensively studied in organic synthesis. The derivative 2-vinyl-4H-1,3-dithiine has antithrombotic activity and present in garlic [55]. 1,3-dithiine heterocyclic compounds known as antimicrobial and antifungal agents [56] and some of compounds containing dithiane have been reported containing l,3-dithiin for glycinamide ribonucleotide formyltransferase [57], histone deacetylase, and DNA topoisomerase II-targeted inhibitors [58].

Due to the biological importance of 1,3-dithiine, Moghaddam et al. [59] investigated a reaction of indoline-2,3-diones **14**, malononitrile**32**, carbon disulfide **34,** and dimedone **56** under acidic and base conditions and reported the synthesis



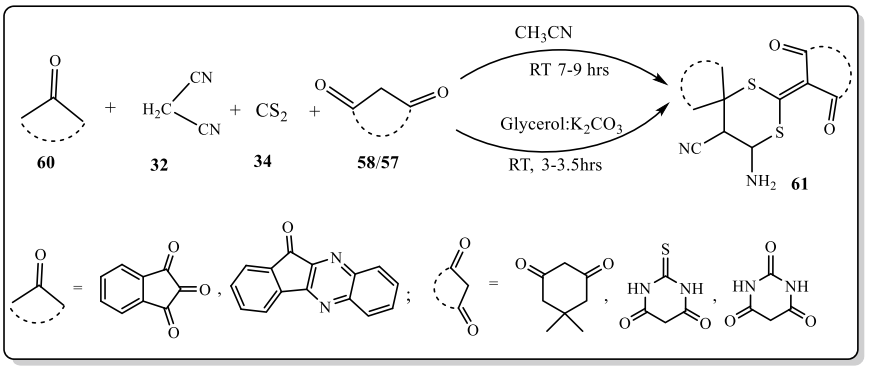
Scheme 9.34 Synthesis of spiro[indoline-3,4′-[1,3]dithiine]-5′-carbonitriles**57** and **59**

of 6′-amino-2′-(4,4-dimethyl-2,6-dioxocyclohexylidene)-2-oxospiro[indoline-3,4′-[1,3]dithiine]-5′-carbonitrile derivatives **57** acidic conditions, using MgO nanoparticles as a solid heterogeneous catalyst with better yields in less reaction time (Scheme 9.34).

Later on, Moghaddam et al. [60] reported the synthesis of new 6′-amino-2′-(tetrahydropyrimidin-5(2*H*)-ylidene)-2-oxospiro[indoline-3,4′-[1,3]dithiine]-5′-carbonitrile derivatives **59** from the three-component reaction of isatin **14**, malononitrile **32**, barbituric acid **58**, carbon disulfide **34** in the presence of spiro[indoline-3,4′-[1,3]dithiine]@$Cu(NO_3)_2$ supported on Fe_3O_4@gly@CE magnetic nanoparticle as competent and recyclable catalyst higher yields and less reaction time. The catalyst spiro[indoline-3,4′-[1,3]dithiine]@$Cu(NO_3)_2$ supported on Fe_3O_4@gly@CE is found in nanoscale range and has consistent morphology with no any agglomeration in its arrangement.

The antibacterial, antifungal activities and antioxidant activity against the DPPH free of all synthesized compounds shown in Scheme **34** were investigated. The results demonstrated excellent biological effects and a substantial link between their structure and biological features. (Scheme 9.34).

In continuous of this work, Moghaddam et al. [61] reported seven new derivatives of spiro-1,3-dithiines via the multicomponent reaction of compounds possessing active methylene groups (*e.g.*, dimedone, barbituric acid, and thiobarbituric acid) **56/57**, carbon disulfide **34**, malononitrile **32,** and polyring compounds containing a carbonyl group **60** (1*H*-indene-1,2,3-trione, 11*H*-indeno[1,2-b]quinoxalin-11-one and 7,8-dimethyl-11*H*-indeno[1,2-b]quinoxalin-11-one) to synthesize corresponding spiro[indeno[1,3]dithiine]-5′-carbonitriles **61** by incorporating various heterocyclic moieties. The given compounds were synthesized at ambient temperature with yields ranging from 70 to 90%. After that, Moghaddam et al. [62] improved the method and synthesized the polycyclic compounds containing [1,3]dithiine

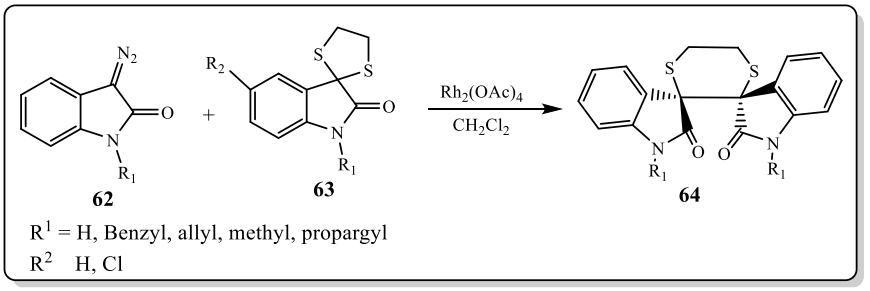


Scheme 9.35 Synthesis of polycyclic compounds containing [1, 3]dithiines **61**

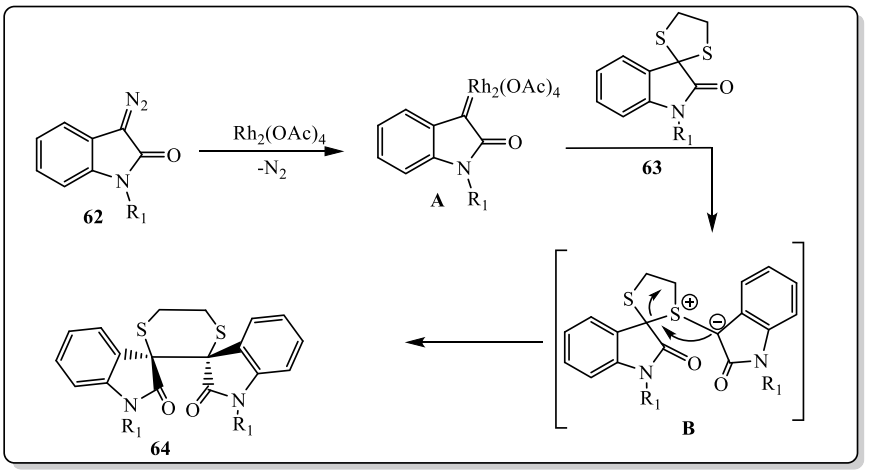
derivatives using glycerol:potassium carbonate used as a eutectic deep solventDES (Scheme 9.35).

Muthusamy et al. [63] demonstrated the diastereoselective synthesis of dispiro[1,4-dithiane/dithiepane]bisoxindoles **64** using rhodium(II) acetate dimer as a catalyst from the reaction of 3-diazo-2-oxindoles **62** and spiro-1,3-dithiolaneoxindole or -1,3-dithianeoxindoles **63** under gentle conditions in an extremely manner (Scheme 9.36).

Mechanistically, initially transient rhodium(II) carbenoid **A** was formed by reaction of cyclic diazomides **62** and rhodium(II) acetate which then react with compound dispiro[1,4-dithiane/dithiepane]bisoxindoles **63** to form sulfonium ylide intermediate **B**. Further, it undergoes Stevens's rearrangement to give the product **64** with high diastereoselectivity generating a new carbon–carbon bond with the expansion of the sulfur-containing ring (Scheme 9.37).



Scheme 9.36 Synthesis of dispiro[1,4-dithiane/dithiepane]bisoxindoles **64**



Scheme 9.37 Plausible mechanism for synthesis of dispiro[1,4-dithiane]bisoxindoles **64**

9.4 Conclusion

This chapter summarizes the synthesis, applications, and mechanistic paths for synthesis of five- and six-member sulfur-containing spiroheterocyclic compounds such as thiophene, thiolane, thiopyran, and dithiine. Role of intramolecular hydrogen bonding, formation of transition states, use of doped nanocatalyst, and chiral organocatalyst for synthesis of spiroheterocycles using different solvents are the key features of this chapter. The enantio- and diastereoselectivities as well as pharmacological properties of products are also discussed.

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Chapter 10
Synthesis and Biological Evaluation of Some Polycyclic Aromatic Hydrocarbons

Chetna Kumari, Nishu Dhanda, Nirmala Kumari Jangid, and Sudesh Kumar

10.1 Benzothiophene

10.1.1 Introduction

Because of their unique pharmacological and biological characteristics, heteroaromatic chemicals play crucial roles in identifying and advancing novel therapeutic candidates [1]. For many years, these substances have been utilized as anti-fungal, anti-oxidant, anti-bacterial, anti-inflammatory, anti-cancer, and anti-parasitic medications [2–5]. Benzothiophene has traditionally been produced using intramolecular cyclization and Claisen rearrangement processes. For instance, the intramolecular cyclization process of O-alkinylthioanisoles allowed for the regioselective synthesis of benzothiophene [6]. A recently described approach uses a Lewis acid catalyst to synthesize benzothiophene and dibenzothiophene from thiophenes and 2, 5-dimethoxy-THF [7].

Well-known candidates for heteroaromatic chemicals are benzothiophene and thiophenes, which are utilized in medications such as sertaconazole (**1**), raloxifene (**2**), and zileuton (**3**) (Fig. 10.1) [8–10]. Breast cancer patients are treated with raloxifene. Furthermore, compared to tamoxifen, a well-known anti-cancer medication with comparable biological characteristics, raloxifene has fewer side effects [11].

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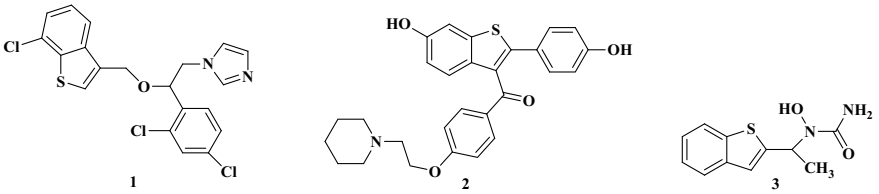


Fig. 10.1 Structure of sertaconazole **1**, raloxifene **2**, and zileuton **3**

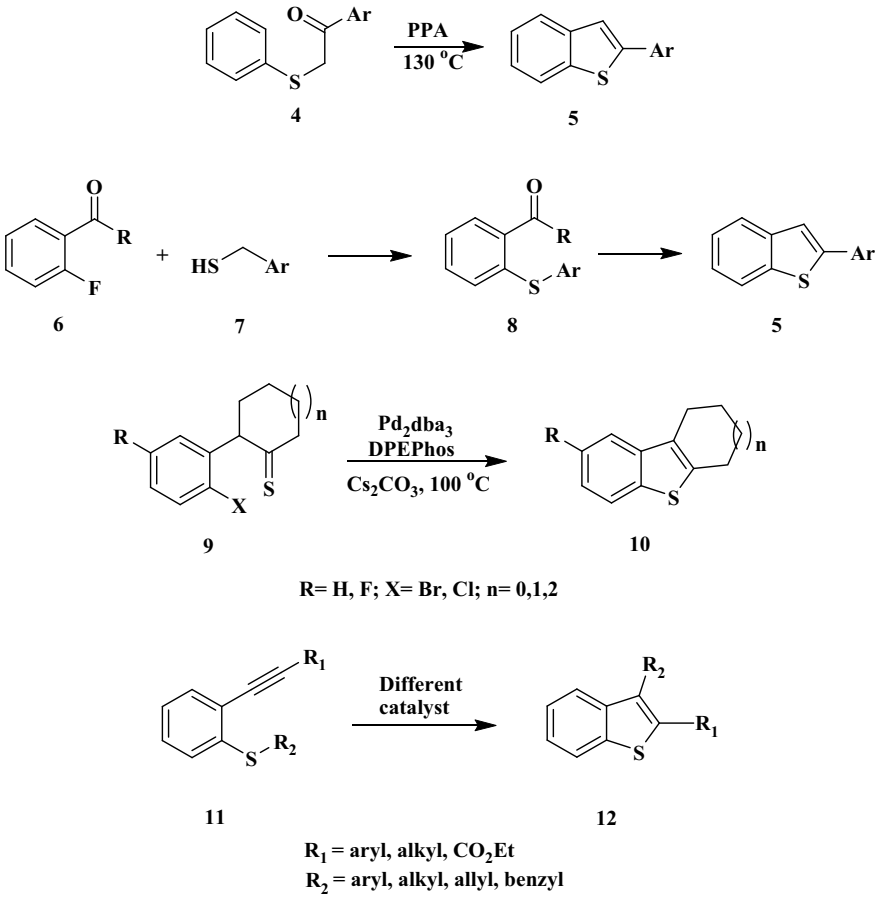
10.2 Synthesis

Several synthetic methods have been used and described to synthesize benzothiophene [12, 13]. Conventionally, 2-aryl benzothiophene (**5**) is produced using the widely recognized and applied domino cyclization/rearrangement reaction of a β-keto sulfide (**4**) catalyzed by acid [14]. An alternative approach makes use of the Knoevenagel condensation of an S-benzyl ortho-acylthiophenol (**8**), which is produced in situ from an ortho-fluoroketone (**6**) and a benzyl thiol (**7**) [12, 13]. A palladium-catalyzed method using an intramolecular C–S coupling reaction of an aryl halide with a thioketone was described [14, 15]. Originally designed to produce benzofurans from thioketone oxygen analogs (**9**), the authors discovered that the same circumstances could also be used for sulfur compounds, yielding moderate-to-good yields of fused benzothiophene (**10**). Recently, many theoretically distinct methods have been devised to break various bonds inside the benzothiophene ring (Scheme 10.1) [16–21].

10.2.1 Biological Activity

10.2.1.1 Benzothiophene: Anti-microbial Agents

Efforts have been made extensively over the last 10 years to create benzothiophene-based compounds that exhibit outstanding therapeutic efficacy and are active on many clinically approved therapeutic targets. Substitution at the heterocyclic thiophene ring rather than the aromatic component seemed more critical for the anti-microbial property of benzothiophene derivatives. In their study, Petsom et al. synthesized benzothiophene derivatives containing quinazoline-4-one. They then examined the anti-bacterial properties of these derivatives against two types of bacteria: Gram-positive ones, such as *Bacillus subtilis* (*BS*) and *Staphylococcus aureus* (*SA*), and Gram-negative ones, such as *Escherichia coli* (*EA*) and *Pseudomonas aeruginosa* (*PA*). Using a filter paper disc approach, the anti-fungal activity was evaluated against four distinct fungi: *Aspergillus niger* (*AN*), *Candida pinnacle* (*CP*), *Candida albicans* (*CA*), and *Rhizopus oryzae* (*RO*). The outcomes were compared with those of the standard medications, ampicillin and streptomycin. The effectiveness of compounds (**13**)

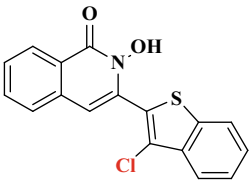


Scheme 10.1 General approaches for preparing benzo[b] thiophene derivatives

and (**14**) against *B. subtilis* and *E. coli* was demonstrated (Fig. 10.2) [22]. According to SAR research, benzothiophene's third-position chloro substituent boosts its anti-bacterial properties, and the attachment of fluoro and nitro groups in the phenyl groups linked to the quinazoline ring also enables anti-fungal properties [22].

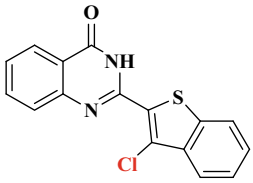
Anti-microbial Activity of Benzothiophene Derivatives: Structural Requirements

The benzothiophene nucleus has been discovered to have strong anti-microbial activity when substituted at all positions with various substituents; however, the first position is unsubstituted because it contains core sulfur. Benzothiophene's heterocyclic cores, such as oxadiazole, pyrazole, and thiazole, as well as groups like $–CH_2OH$ and $–CO_2CH_3$, boost the anti-microbial activity of the compound. The second position of the compound can be substituted with quinazoline and phenyl



13

IZ *(BS)* = 16mm
IZ *(EC)* = 12mm



14

IZ *(BS)* = 15 mm
IZ *(EC)* = 16 mm

Fig. 10.2 Anti-microbial properties of benzothiophene

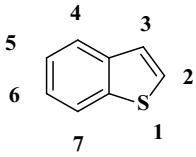


Fig. 10.3 Benzothiophene scaffold's structural requirements as anti-microbial agents

rings, including methoxy, methyl, and fluorine, or unsubstituted. In the same way, the substitutions for the pyrimidine, hydroxy group, and chloro group in the third position showed positive activity. Benzothiophene's fourth position can be replaced or left unsubstituted; substituents with hydroxyl and halogen groups have strong anti-bacterial properties. The benzo group connected to the first position of the benzimidazole core has also demonstrated anti-bacterial solid activity. The fifth or sixth position of the nucleus may be substituted with halogens or unsubstituted. For benzothiophene to show anti-bacterial action, it must contain nitro, halogens, and hydroxyl groups at positions 3, 4, and 6. It must also have fewer substituted benzothiophene at position 7 (Fig. 10.3).

10.2.1.2 Anti-cancer Agents

A tumor is a solid mass of cells that develops when one or more cells lose their ability to control their growth. This condition is known as cancer. Although there is genetic variation in the illness, malignant cells will always undergo metabolic modification [23]. It is one of the most significant risks to human existence and has received extraordinary attention globally. The creation of successful anti-cancer therapies, which incorporate the use of radiation therapy, chemotherapy, and surgery, has been the subject of extensive research [24]. Scientists have concentrated on numerous facets of cancer biology to create novel, effective medications with these properties. When developing anti-cancer drugs, medicinal chemists paid close attention to benzothiophene derivatives. Two anti-cancer medications, arzoxifene (**15**) and raloxifene (**16**), are the product of modifications made to the benzothiophene nucleus (Fig. 10.4) [25]. Compared to raloxifene, arzoxifene is much more potent in preventing mammary cancer in rats that have been caused by the carcinogen nitroso

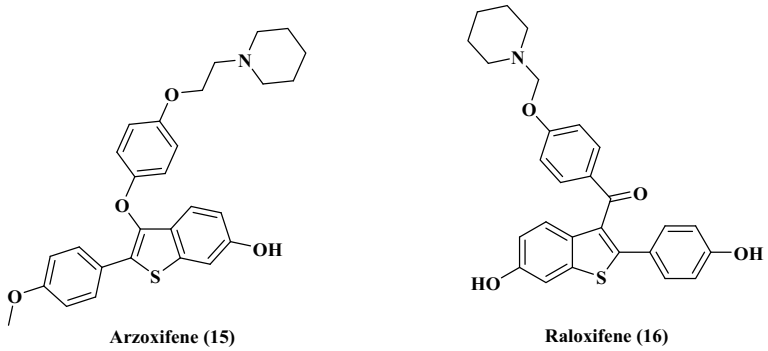


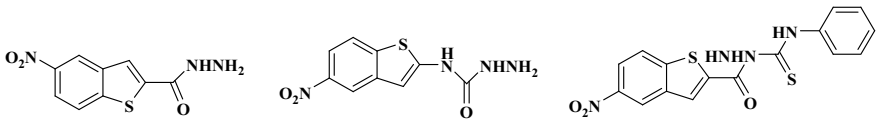
Fig. 10.4 Benzothiophene-based anti-cancer drugs

methyl ureave [25]. In postmenopausal women who have osteoporosis and high risk of breast cancer, raloxifene is used to treat osteoporosis and lower the risk of invasive breast cancer [26]. Perhaps more significantly, ongoing efforts have been focused on creating novel benzothiophene-based anti-cancer drugs targeting various enzymes and receptors.

10.2.1.3 Anti-inflammatory and Analgesic Agents

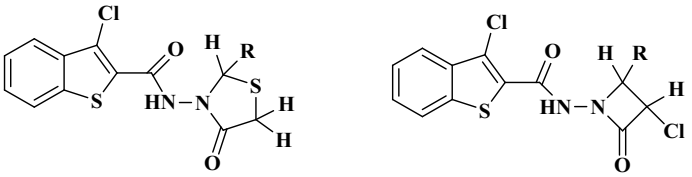
Many diseases have inflammation as their primary cause. An essential part of the immune system's reaction of the human body to pathogens, wounds, or trauma is inflammation. While inflammation is not the direct cause of many conditions, it frequently exacerbates pain and suffering [27]. According to recent research, inflammation plays a crucial role in infection and cancer but also in autoimmune diseases like multiple sclerosis, retinitis, psoriasis type I diabetes, atherosclerosis, rheumatoid arthritis, and Crohn's disease [28, 29]. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) in the treatment of several inflammatory disorders has proven to be highly beneficial.

After reviewing the above discussion, we summed up the following strategy for boosting the compounds' analgesic and anti-inflammatory properties: adding phenylthiosemicarbazide, semicarbazide, carbohydrazide, and pyrazole with p-anisyl and p-chlorophenyl substitutions at the third and fifth positions. The benzothiophene molecule exhibits good activity at the 3-position, where methyl and bromo replacements are introduced, leaving the remaining positions unsubstituted (Fig. 10.3). The anti-inflammatory and anti-nociceptive effects of compounds (**17–19**) were more potent than those of piroxicam (30% at 1 h, 25 mg/kg) at doses of 25 or 50 mg/kg. The action of semicarbazide (**18**), carbohydrazide (**17**), and phenylthiosemicarbazide (**19**) systems is more effective than that of carbohydrazide derivatives, according to SAR research (Fig. 10.5) [30].



(17) (18) (19)

Fig. 10.5 Benzothiophene-based anti-inflammatory and analgesic drugs



(20) (21)

R = 3-Cl-C_6H_4; R = 3-Br-C_6H_4; R = 4-OCH_3-C_6H_4; 3,4,-$(OCH)_3$-C_6H_3; 3-OCH_3-4-OH-C_6H_3; 3-OC_6H_5-C_6H_4; 4-N,N $(CH_3)_2$-C_6H_3

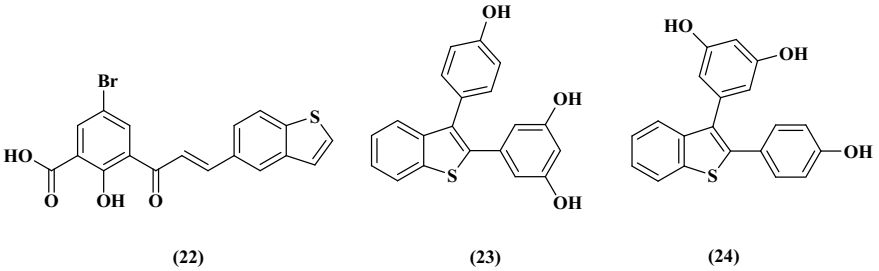
Fig. 10.6 Benzothiophene as anti-tubercular drugs

10.2.1.4 Anti-tubercular Agents

One of the fatal infectious diseases that has added to humanity's problems is tuberculosis (TB), a lung infection. Most tuberculosis cases are caused by *Mycobacterium tuberculosis* (*Mtb*), a pathogenic bacterial species of *Mycobacterium* [31]. Presently, 8.9–9.9 million new and recurring cases of tuberculosis are reported annually, and one-third of the world's population is afflicted with *Mtb* [26]. The current course of treatment involves a multi-drug regimen that must be followed for at least six months, but there is no assurance that the infection will be eradicated. Therefore, it is imperative to create novel anti-tubercular medications with quick action against mycobacteria in the intracellular environment that are less toxic and successfully kill MDR strains [32]. Using thiazolidinones (**20**) and azetidinones (**21**), which have a benzothiophene nucleus, Narute et al. conducted a quantitative structure–activity relationship (QSAR) analysis (Fig. 10.6) [33]. They concluded that the molecules bulky substitution and high nucleophilicity nature are conducive to their anti-tubercular action [33].

10.2.1.5 Anti-HIV Agents

Human immunodeficiency virus (HIV) infection causes the deadly disease known as acquired immune deficiency syndrome (AIDS). HIV infection impairs the body's defenses, making people more vulnerable to other diseases [34]. Over 30 million



(22) (23) (24)

Fig. 10.7 Benzothiophene as anti-HIV drugs

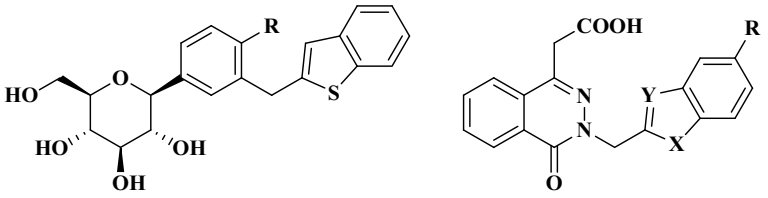
people are thought to be infected with HIV globally, and treatment of the virus continues to pose a significant challenge. Therefore, it is still crucial to find and develop newer anti-HIV drug candidates to address the issues surrounding this illness. Bioisosteric substitution of the phenyl ring with heteroaromatic and polycyclic rings is revealed by SAR study: enhanced action when thiophene or benzothiophene (**22**) was substituted for phenyl. Compounds (**23**) and (**24**) exhibit enhanced cytotoxicity potency (Fig. 10.7) [31, 35]. Combined with decitabine, a mutagenic nucleoside possessing anti-HIV-1 properties, these compounds limit HIV-1 replication.

10.2.1.6 Anti-diabetic Agents

The most prevalent chronic illness in the modern world, diabetes mellitus (DM), is characterized by high blood glucose levels brought on by either an absolute or relative inefficiency of circulating levels of insulin [36]. DM is a serious health concern. Diabetes may eventually result in retinopathy, neuropathy, and nephropathy due to microvascular damage in essential tissues. There is still a great demand for better anti-diabetes medications even though there are currently around a dozen kinds of anti-diabetes medicines on the market [37]. Ipragliflozin, ASP1941, (**25**), a benzothiophene derivative, is being researched to treat type-2 diabetes [38]. This section discusses compounds of benzothiophene, which show some anti-diabetic properties. Within the benzothiophene series, compound (**26**) exhibited good efficacy without any substitution, but compound (**27**) with fluorine substitution suppressed sorbitol accumulation in vivo (Fig. 10.8) [38, 39].

10.2.2 Conclusion

The synthesis of a wide range of multi-substituted benzothiophene, which is challenging by conventional methods, was made possible by the broad scope of benzothiophene synthesis and the adaptable C2-functionalizations. In summary, these molecules exhibit significant potential as effective active agents in medical chemistry.



(25 a, b)

a) = R = H
b) = R = F

(26-27)

X = S, Y= N, R = CF_3

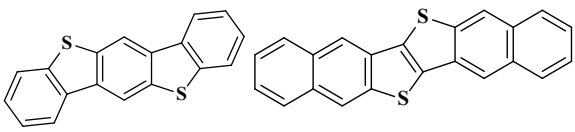
Fig. 10.8 Benzothiophene as anti-diabetic agents

10.3 Dibenzothiophene

10.3.1 Introduction

Stenhouse first synthesized dibenzothiophene in 1870 by heating diphenyl sulfide in the presence of iron nails. This compound was mistakenly identified as an isomer of diphenyl sulfide [40, 41]. Gilman et al. reported the synthesis of dibenzothiophene in 1938, employing $AlCl_3$ as a catalyst and biphenyl and sulfur as raw ingredients [42]. Dibenzothiophene is a flexible aromatic tricyclic molecule with a sulfur base. Organic and medicinal chemistry is the fundamental building block of beneficial organic compounds, including pharmaceutical medications and biologically active chemicals. Materials chemistry is a significant component of functional materials like organic semiconductors [43]. Dibenzothiophene is flexible heterocyclic sulfur-containing molecules typically essential to a wide range of significant organic substances, such as medicines, liquid crystals, photoactive chemicals, dyes, and conducting polymers (Fig. 10.9) [44–46]. Naphtho [2,3-b]-naphtho [2′,3′:4,5] thieno[2,3-d] thiophene (DNTT) and benzo [1,2-b:5,4-b′] bis [1] benzothiophene (BBBT) are two examples of sulfur-containing conjugated benzoheterocyclic compounds that show promise as materials for thin-film transistors.

Fig. 10.9 Benzo-fused thiophenes as organic electronics



BBBT

(28)

DNTT

(29)

10.3.2 Synthesis

Owing to the thiophene motif's vital role in a wide range of organic molecules across several sectors, several facile and effective synthesis techniques for dibenzothiophene have been developed recently. These techniques for creating dibenzothiophene and its derivatives include cyclizing C–S and C bonds to create a sulfur heterocycle with five members.

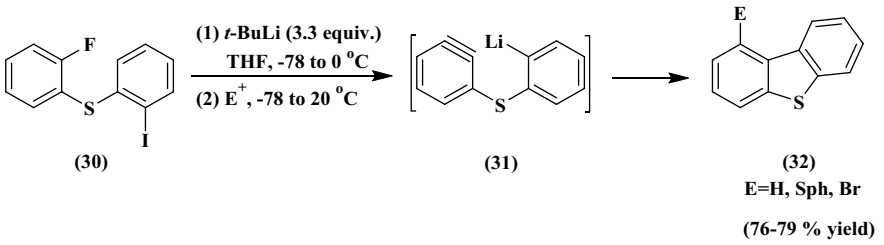
10.3.2.1 Transition Metal-Free C–S Bond Formation for Dibenzothiophene

10.3.3 C-X Cleavage for Dibenzothiophene Synthesis

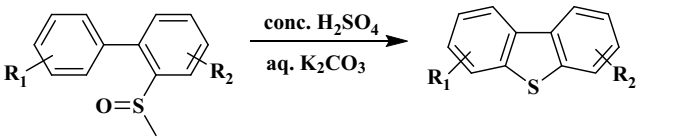
In 2006, Fanana's group discovered that C-X cleavage for dibenzothiophene synthesis produced functionalized dibenzothiophene derivatives by treating 2-fluorophenyl 2-iodophenyl thioether with 3.3 equiv. of *t*-BuLi. These derivatives then reacted with specific electrophiles (Scheme 10.2). An anionic cyclization on an aryl lithium intermediate tethered to benzyne is the process's mechanism [47].

10.3.3.1 C-H Functionalization for Dibenzothiophene

The Patel group disclosed a practical and effective process for generating unsymmetrical dibenzothiophene derivatives in 2012 (Scheme 10.3) [48]. Intramolecular cyclization of biaryl sulfoxides with sulfuric acid under low-temperature conditions yields dibenzothiophene with a very short reaction time. It is interesting to note that any position of dibenzothiophene can be reached by using this procedure. For instance, this method makes it simple to manufacture 1-substituted dibenzothiophene, which is hard to acquire by direct substitution reaction on dibenzothiophene.



Scheme 10.2 Dibenzothiophene-tethered aryllithiums via anionic cyclization



(33)

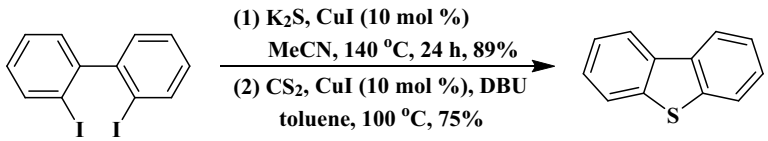
(34)

$R_1 = H; R_2 = H$ (94 %)

$R_1 = F; R_2 = H$ (92 %)

$R_1 = NO_2; R_2 = H$ (49 %)

Scheme 10.3 Biaryl methyl sulfoxides are intramolecularly cyclized for dibenzothiophene through acid-mediated processes



(35) (36)

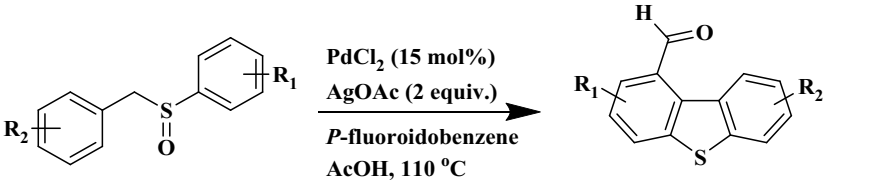
Scheme 10.4 Ullmann process with Cu catalyst for dibenzothiophene synthesis

10.3.3.2 Transition Metal-Catalyzed C–S Bond Formation for Dibenzothiophene

The Ullmann reaction of 2,2′-iodo substituted biphenyl with K_2S producing dibenzothiophene at 140 °C was reported by the Xi group in 2010. They developed a different one-pot process in 2013 for the very efficient preparation of dibenzothiophene [49]. This technique works well for building cyclic sulfur-containing molecular structures when 2,2′-iodine-substituted biphenyls are used as the substrate, and easily accessible, low-cost CS_2 is used as the sulfur source (Scheme 10.4) [49].

10.3.3.3 Transition Metal-Catalyzed C–C Bond Formation for Dibenzothiophene

Palladium-catalyzed double C–H bond activation of simple benzyl phenyl sulfoxides to produce dibenzothiophene (Scheme 10.5) [50]. Four hydrogen atoms are abstracted, and the products are created in a cascade reaction that is highly selective due to the reaction's well-regulated order. By using the palladium catalyst at a 15% molar ratio, this technique produced a range of dibenzothiophene derivatives in medium-to-good yields that were resistant to an extensive range of substrates. As a result, this approach has a significant innovative impact on organic synthesis [50].



(37)

(38)

R_1 = Me; R_2 = H (67-74 %)
R_1 = F; R_2 = H (53 %)
R_1 = Cl; R_2 = (51 %)
R_1 = H; R_2 = Cl (69 %)
R_1 = H; R_2 = Ph (46 %)

Scheme 10.5 Double C–H activation for dibenzothiophene, catalyzed by palladium and directed by sulfoxides

10.3.4 Conclusion

Numerous techniques have been established for the synthesis of dibenzothiophene and its derivatives by the production of C–S bonds, which bases, acids, or other non-metallic species can accelerate. Unfortunately, most of these techniques suffer from multi-step processes and pre-functionalization of synthesis precursors, making them neither environmentally friendly nor atom-economic. Transition metal-catalyzed coupling reactions have been a potent technique for synthesizing dibenzothiophene during the last ten years. For instance, it has been extensively documented that dibenzothiophene with a wide variety of functional groups at various positions can be synthesized by intramolecular C–H/S–H and C–H/C–S coupling processes, which are catalyzed by palladium and other transition metals.

10.4 Thienothiophene

10.4.1 Introduction

Conversely, thienothiophenes (TTs), which are composed of two annulated thiophene rings, ultimately form the planar system, and their incorporation into a molecular structure has the potential to significantly enhance or modify the essential characteristics of organic materials that are π-conjugated. Four main TT isomers differ from one another in the mutual orientation of the two cycles (Fig. 10.10) [51]. In comparison, thieno[3,4-b] thiophene (**41**) and the extremely unstable thieno[3,4-c] thiophene (**42**) are the least stable derivatives, whereas thieno[3,2-b] thiophene (**39**) and thieno[2,3-b] thiophene (**40**) are the most durable. The primary barrier to the

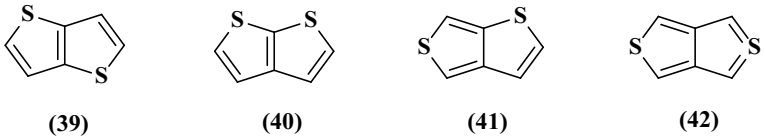
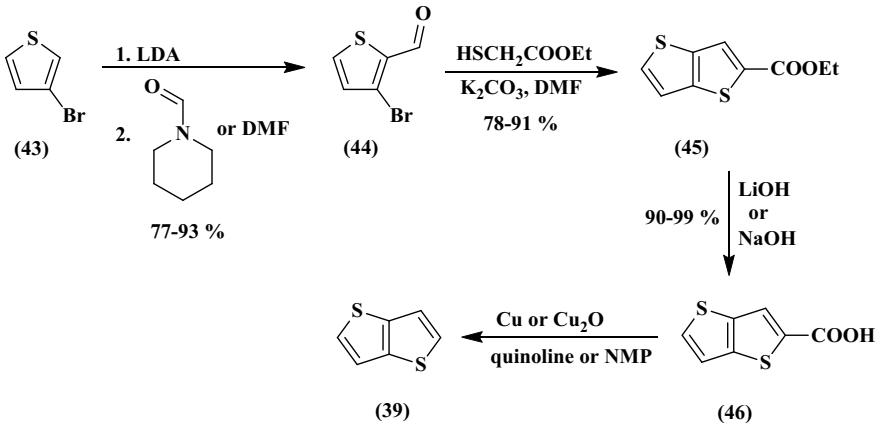


Fig. 10.10 Structure of four possible TT isomers (**39–42**)

simple manufacture of thienothiophene is the instability of the unsubstituted isomers (**41**) and (**42**). Furthermore, the obtained total yield, the number of reaction steps, and the availability of the employed starting materials are the primary determinants of a successful synthetic approach toward TTs (**39**) and (**40**). The procedure should follow stable intermediates and be simple to implement [52, 53].

10.4.2 Synthesis

A four-step reaction is used in the first synthetic technique, which is shown in Scheme 10.6 [54–58]. 3-bromothiophene (**43**) was selectively lithiated at position 2 using LDA. The generated lithium species was trapped by the reaction with N-formylpiperidine or N, N-dimethylformamide (DMF). This resulted in aldehyde (**44**) [54–56]. It then underwent cyclization with potassium carbonate acting as a base and ethyl thioglycolate. The C=C and C–S bonds in (45) were formed in this stage. Ester (**45**) was hydrolyzed to carboxylic acid (**46**) using lithium or sodium hydroxide. The final decarboxylation process used Cu/quinoline or CuO/N-methyl-2-pyrrolidone (NMP) [54]. This particular reaction sequence has a yield of approximately 50% overall.

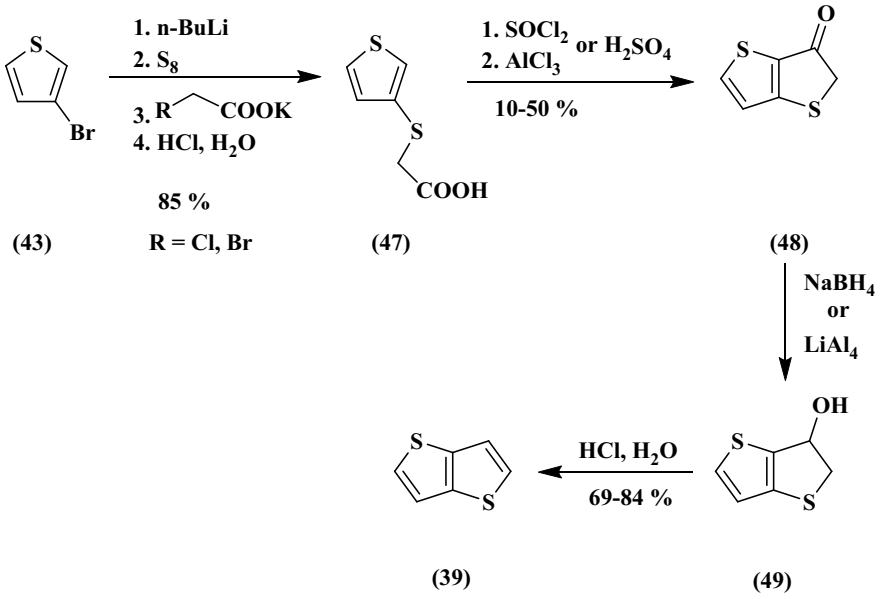


Scheme 10.6 Four-step method

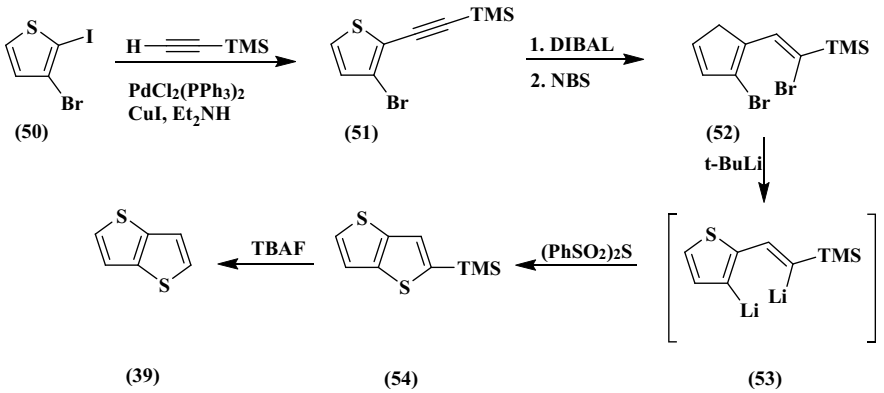
Three primary reaction steps are involved in this approach, which likewise begins with 3-bromothiophene (**43**) (Scheme 10.7) [59, 60]. The lithiation of (**43**) and the subsequent reaction with elementary sulfur produced an in vivo thiolate intermediate. This intermediate further substituted a halogen atom in either potassium chloroacetate or bromoacetate to yield carboxylic acid (**47**). There are two methods for carrying out the cyclization that follows. The first is an acid-catalyzed (H_2SO_4) cyclization; the corresponding acyl chloride was initially synthesized by Leriche et al. and then subjected to the intramolecular Friedel–Crafts acylation [60]. $NaBH_4$ or $LiAlH_4$ converted the ketone (**48**) produced to the intermediate alcohol (**49**) [59, 60]. By the following acid workup, alcohol (**49**) has (**39**). This series of reactions yields (**39**) out of the total 36% yield.

Trimethylsilyl (TMS) acetylene and 3-bromo-2-iodothiophene (**50**) are selectively cross-coupled in the final six synthesis routes leading to TT (**39**) (Scheme 10.8) [61]. Di(iso-butyl) aluminum hydride (DIBAL) reduction and NBS bromination were applied to the TMS-terminated alkyne (**51**). Following its lithiation to (**53**), the resultant dibromo derivative (**52**) underwent a reaction with bis(phenylsulfonyl)sulfide. (**39**) resulted from the last TMS-group elimination using tetrabutylammonium fluoride (TBAF). The literature does not provide the yields of the specific chemical steps.

This procedure, which works with acetal (Scheme 10.9), uses acetal (**56**). In sodium ethanolate or potassium carbonate, the bromine atom in 1,1-dimethoxyethylbromide was substituted by the beginning 2-sulphanylthiophene (**55**)



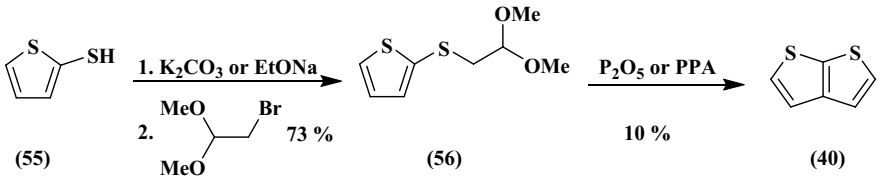
Scheme 10.7 Synthesis of (**39**)



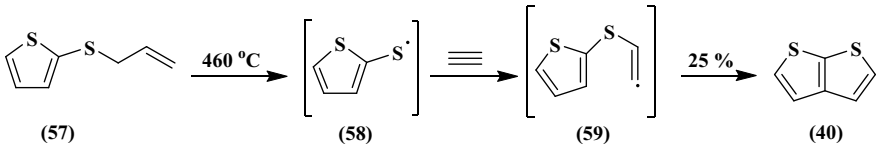
Scheme 10.8 Sonogashira cross-coupling in the production of (**39**)

as an S-nucleophile. Using polyphosphoric acid (PPA) or phosphorous oxide, the generated acetal (**56**) was cyclized to (**40**) [62, 63]. This chemical sequence has a 7% total yield.

Scheme 10.10 depicts the one-step gas phase production beginning from allyl(thiophene-2-yl) sulfide (**57**) [64]. The radical (**58**) was produced by the thermal cleavage of the sulfide (**57**), and it then interacted with acetylene. The last stage involved the formation of the (thiophene-2-yl) vinyl sulfide radical (**59**), which at 460 °C cyclized to produce thieno[2,3-b] thiophene (**40**) as a primary product with a 25% yield.



Scheme 10.9 Cyclization of acetal (**56**)



Scheme 10.10 Allyl(thiophene-2-yl) sulfide's gas phase reaction to TT (**40**)

10.4.3 Biological Activity

Prominent biological activities of thieno[2,3-b] thiophenes include anti-microbial, analgesic, anti-inflammatory, and anti-proliferative properties; they also oppose α_1-adrenoceptors and prevent cartilage degradation in articular diseases [65–71]. Nonetheless, because of the numerous uses for pyrazoles in the agrochemical and pharmaceutical industries and their analgesic, anti-pyretic, herbicidal, and anti-inflammatory qualities, the preparation of pyrazoles continues to be of significant interest [72, 73]. Because of their strong biological activity, pyridazine compounds are frequently used as anti-bacterial, anti-tuberculosis, anti-cancer, and anti-hypertensive drugs [74–81].

10.4.4 Conclusion

With a variety of therapeutic potentials, including anti-convulsant, anti-malarial, anti-bacterial, anti-mycobacterial, anti-depressant, anti-viral, anti-hypertensive, anti-cancer, anti-inflammatory, and anti-oxidant properties, thiophene and its derivatives constitute a significant class of chemicals in the medical profession.

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Chapter 11
Synthesis and Biological Evaluation of Some Thietane Derivatives

Surendra Kumar Bagaria, Nidhi Jangir, Shikha Agarwal, and Dinesh Kumar Jangid

11.1 General Introduction of Thietanes and Its Derivatives

One sulfur and three carbon atoms make up the four-membered ring of saturated chemical thietane. Researchers are more interested in other S and O heterocycles than thietane because of ring strain. Because bond eclipse effects produce ring puckering and an increase in bond angle strain in thietane (80.3 kJ $mol^{-}1$), the ring strain of the former is almost identical to that of the three-membered ring thiirane. However, it has been demonstrated that oxidized thietane molecules possess a number of known properties, such as anti-coccidial, insecticidal, depressive, and anti-cancer effects [1]. To better understand what will be described subsequently, the common nomenclature of numerous S-containing four-membered rings is shown in (Fig. 11.1).

The anal gland secretions of the ferret [2] and stoat [3] include a few simple alkyl and dialkyl thietanes. Several biological and pharmaceutical compounds contain thietane, including D-ring-modified thia derivatives 1 and 2 of the anti-cancer drug taxoids and docetaxels, [4] thiathromboxane A2 3, [5] sweetener 4, [6] pesticide 5, [7] thiaanalogue thietanose nucleosides 6 and 8, [8] and spiroannulated glyco-thietane nucleoside 7 [9] of the anti-viral (anti-HIV and HSV) drug oxetanocin A (Fig. 11.2). Thietanes are also beneficial and intermediates in organic synthesis, as well as flexible building blocks for the synthesis of sulfur-containing acyclic and heterocyclic molecules [10, 11].

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K. L. Ameta (ed.), *S-Heterocycles*, https://doi.org/10.1007/978-981-97-4308-7_11

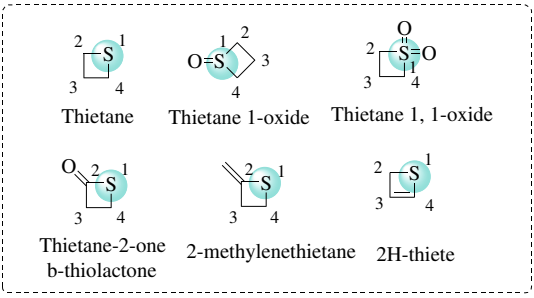


Fig. 11.1 Considerations regarding nomenclature

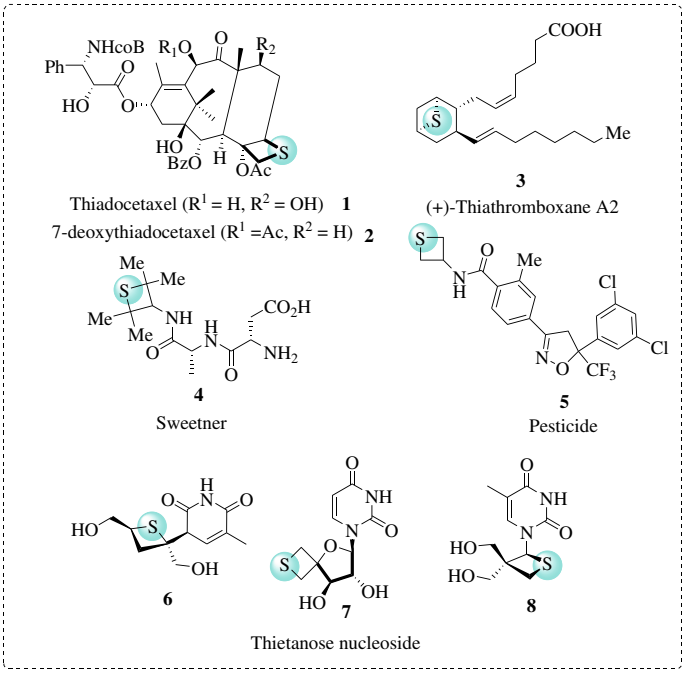


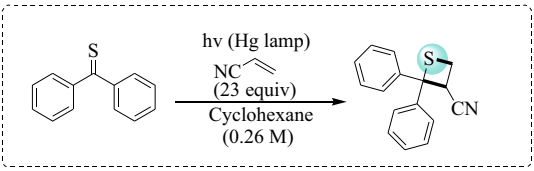
Fig. 11.2 Compounds with thietanes that are biologically active

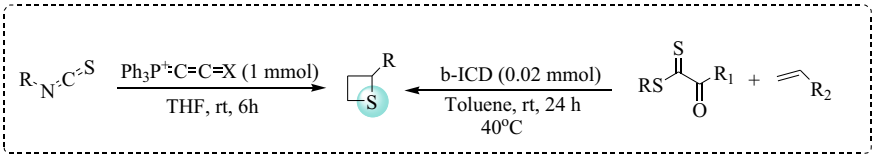
11.2 Synthetic Routes for Thietanes and Its Derivatives

In 2020 Kassir et al. reported cycloaddition reactions by using thioketones, such as thia-Paterno–Buchi (Scheme 11.1) to prepare thietanes from acryloyl derivatives and thiobenzophenones in cyclohexane [12].

A route for synthesizing thietane derivatives was reported by Yang et al. through a nucleophilic reaction between active phosphacumulenes and substituted isothiocyanate compounds in the presence of THF for six hours at room temperature.

Scheme 11.1 Preparation of thietanes dependent on concentration and light



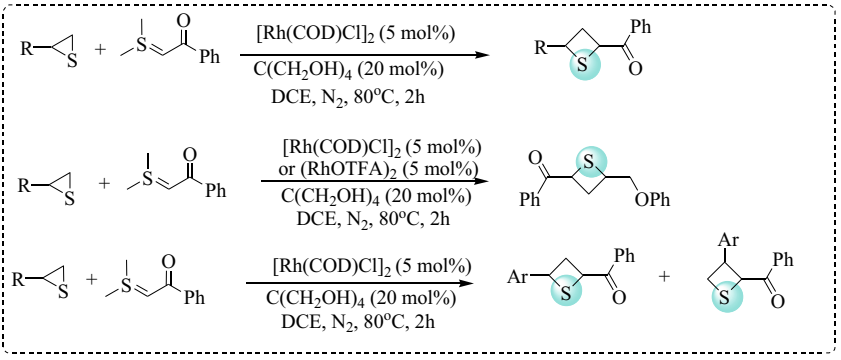


Scheme 11.2 Nucleophilic reaction for the preparation of thietanes

Using toluene as a solvent and dithioesters and allenoates catalyzed by β-ICD (beta-Isocupreidine) at − 40 °C for 24 h is another technique (Scheme 11.2) [13].

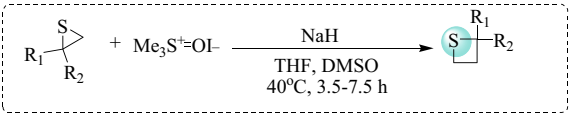
The electron-deficient sulfur ylides were unable to generate the corresponding functionalized thietanes via ring expansion with thiiranes due to their low nucleophilicity. Nonetheless, the electron-deficient sulfur ylides endured an electrophilic ring expansion of thiiranes to yield thietanes beneath the catalytic presence of rhodium. In moderate-to-good yields, 2-acyl-4-alkylthietanes were produced via the reaction of sulfur acyl ylides with 2-alkylthiiranes reported by Dong et al. Nevertheless, at 1:4 to 1:10 ratios, they interacted with 2-arylthiiranes to produce mixes of 2-acyl-4-arylthietanes and 2-acyl-3-arylthietanes (Scheme 11.3) [14].

The nucleophilic ring expansion of thiiranes can be used to synthesize thietanes. One carbon-containing nucleophile with an appropriate leaving group might be used to carry out the nucleophilic ring expansion of thiiranes. During the ring expansion process, the nucleophiles first open the rings of thiiranes. The resulting thiolates



Scheme 11.3 Functionalized thietanes are synthesized from thiiranes via electrophilic ring expansion

Scheme 11.4 Thietanes prepared via nucleophilic ring expansion from thiiranes



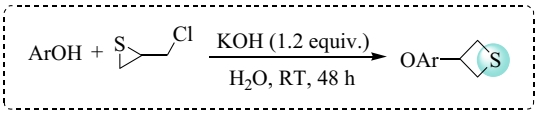
then act as nucleophiles for additional intramolecular displacement, which produces thietanes. One type of nucleophile is dimethyloxosulfonium methylide. The reactions of trimethylsulfoxonium iodide and various thiiranes at 40 °C in the presence of NaH in a combination of THF and DMSO produced the corresponding thietanes (Scheme 11.4) [15].

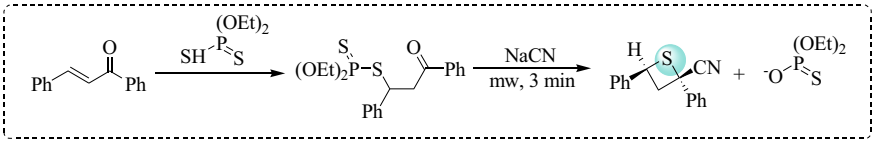
Under basic conditions, using various nitrophenols as nucleophiles in the ring expansion process of chloromethylthiirane led to the formation of the corresponding 3-(nitrophenoxy)thietanes described by Butkevich et al. in low-to-moderate yields (Scheme 11.5) [16].

2,4-diarylthietanes have also been synthesized from chalcones reported by Yadav et al. by using a microwave-assisted process. Chalcone reacts with O,O-diethyl hydrogen phosphorodithioate to form the Michael adduct, which is then cyclized by the cyanide anion to generate 84% of the compound thietane (Scheme 11.6) [17].

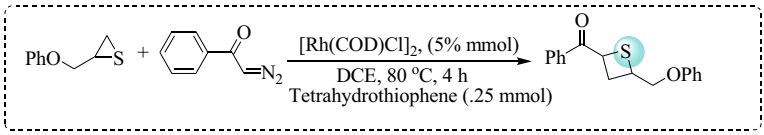
In the presence of sulfide additives, the reaction between thiirane and diazoacetophenone was examined by Dong et al. Although no acceptable product was found in the absence of sulfide additions, the needed product was obtained in a trace amount in the presence of dimethyl sulfide and in 10% yield in the presence of tetrahydrothiophene. According to the results, sulfide can encourage ring expansion (Scheme 11.7) [14].

Scheme 11.5 3-(nitrophenyloxy)thietane synthesized from chloromethylthiirane and nitrophenols



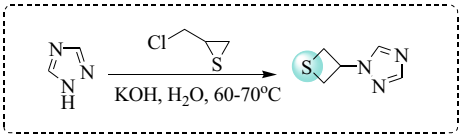


Scheme 11.6 2,4-diarylthietanes synthesized from chalcones

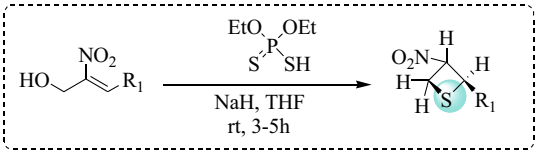


Scheme 11.7 Diazoacetophenone and 2-phenoxymethylthiirane interaction

Scheme 11.8 Synthesis of asymmetric 1-(thietan-3-yl)-1,2,4-triazole (II)



Scheme 11.9 One-pot diastereoselective synthesis of 3-nitrothietanes



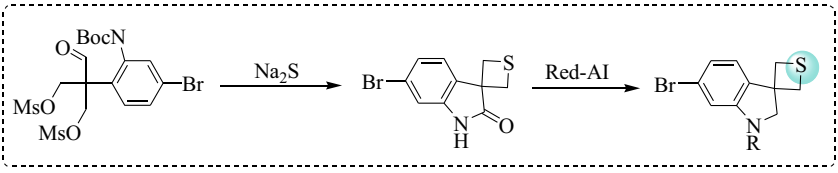
By reacting triazole with 2-chloromethylthiirane in H_2O with KOH presence, asymmetric 1-(thietan-3-yl)-1,2,4-triazole (II) synthesis was described by Khaliullin et al. (Scheme 11.8) [18].

A simple one-pot diastereoselective process was reported by Rai et al. in 2012 using NaH as a catalyst in THF solvent. Particularly for artificial sweeteners like alitame, the pharmacophore of polysubstituted thietanes is important [19]. The following synthetic protocol involved the simultaneous generation of a nucleophile, thia-Michael addition, and intramolecular cyclization to obtain the resulting 2,3-disubstituted thietanes, using Baylis–Hillman alcohols and O,O-diethyl hydrogen phosphorodithioates as starting substrates (Scheme 11.9).

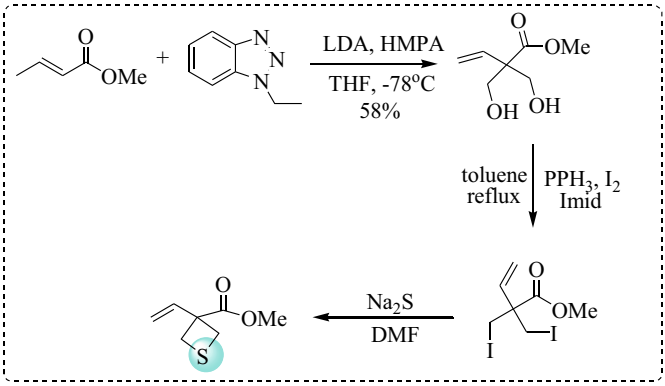
Thietane are typically synthesized by double hydroxymethylating oxindoles reported by Gonzalez et al., then activating and displacing them with sodium sulfide. The amide bond was then reduced with Red-Al to produce benzofused spirocycles (Scheme 11.10) [20].

By double-aldol condensation of methyl crotonate with 1-hydroxymethylbenzotriazole, Lu et al. reported producing a 58% yield of methyl 2,2-dihydroxymethylbut-3-enoate. Methyl-1-vinylthietane-1-carboxylate was obtained in two processes with a 51% yield following iodination and double displacement with sodium sulfide. Compound served as an intermediary in the whole synthesis of thioalkaloids from sesquiterpenes (Scheme 11.11) [21].

The synthesis of sulfur-containing glycomimetics of furanoses and pyranoses, as well as thietane-based square sugurs (thietanoses), has been facilitated by the widespread use of the cyclic thioetherification approach in recent decades [22]. In



Scheme 11.10 Sporadic thietane addition to oxindole cores

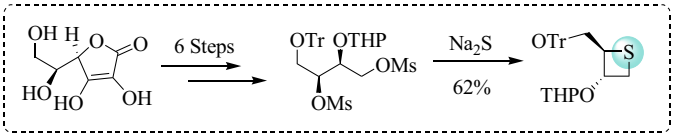


Scheme 11.11 Preparation of methyl 3-vinylthietane-3-carboxylate

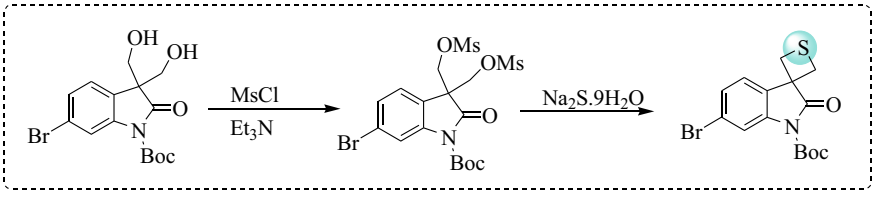
1996, vitamin C was used to create the first thietanose. First, vitamin C was converted into 1,3-dimesylate of 2,4-di-O-protected 1,2,3,4-butane-tetraol by six steps. After that, refluxing ethanol was treated with Na_2S, which resulted in a 62% yield of protected thietanose (Scheme 11.12).

6-bromo-3,3-bis(hydroxymethyl)indolin-2-one was first reacted with mesyl chloride and then treated with sodium sulfide to form 6-bromospiro[indoline-3,3′-thietan]-2-one, which was then transformed into the target inhibitor candidate in the development of novel class I phosphoinositide 3-kinase (PI3k) inhibitors reported by Gonzalez et al. (Scheme 11.13) [20].

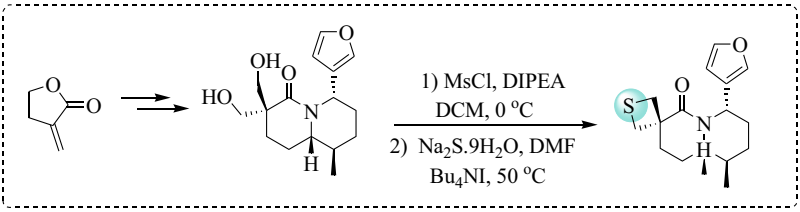
Herein, the original starting material, methylene-γ-butyrolactone, was changed into bis(hydroxymethyl)quinolizidinone reported by Lacharity et al. Following mesylation and the twofold displacement process with sodium sulfide, spirothietane-quinolizidine was obtained as a crucial intermediate. It was also used in the complete



Scheme 11.12 Optically active thietane synthesized from vitamin C



Scheme 11.13 Synthesis of the potential PI3K inhibitor containing thietane



Scheme 11.14 Nuphar sesquiterpene thioalkaloids: synthesis of spirothietanes as the fundamental intermediate

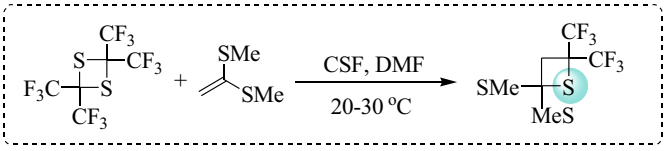
synthesis of four distinct Nuphar sesquiterpene thioalkaloids' natural products (Scheme 11.14) [23].

By reacting 2,2,4,4-tetrafluoro-1,3-dithietane with 1,1-dimethylthioethene, Petrov et al. synthesize 2,2-dimethylthio-4,4-di(trifluoromethyl)thietane with 80% yield (Scheme 11.15) [24].

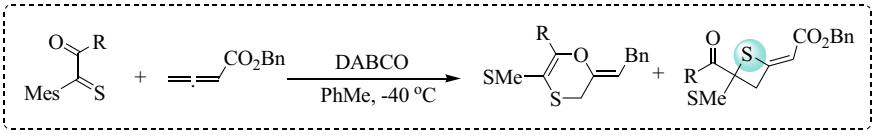
Formal [2 + 2] cycloaddition reaction reported by Yang et al. for the synthesis of thietan-2-ylideneacetates catalyzed by amines. Under tunable formal [4 + 2] and [2 + 2] cycloadditions catalyzed by DABCO, benzyl allenoate and methyl 2-oxoalkanedithioates formed 5-(methylthio)-2-phenylethylidene-2,3-dihydro-1,4-oxathiines and benzylthietane-2-ylideneacetates as byproducts (Scheme 11.16) [13].

N-(thietane-3-yl)isatin derivatives were produced in modest yields reported by Butkevich et al. via the interaction of isatins and chloromethylthiirane (Scheme 11.17) [16].

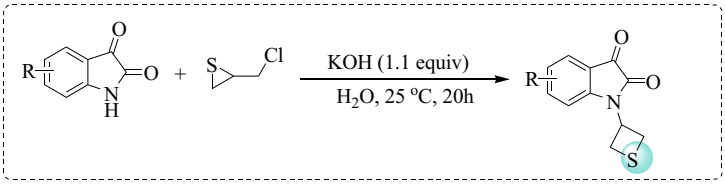
Herein, a process described for the preparation of thietanes that involved a reaction between cyclic carbonate esters of 1,3-diols and potassium thiocyanate, a sulfur donor (Scheme 11.18) [25].



Scheme 11.15 2,2-dimethylthio-4,4-di(trifluromethyl)thietane synthesized from 1,1-dimethylthioethene and 2,2,4,4-tetrakis(trifluromethyl)-1,3-dithietane

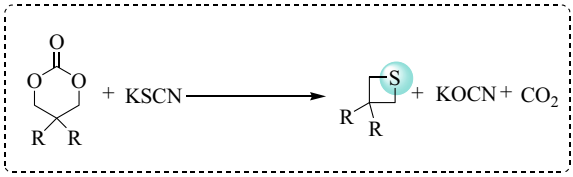


Scheme 11.16 Benzyl allenoate and dithioesters undergo a formal [2 + 2] cycloaddition catalyzed by DABCO to yield thietane-2-ylideneacetates



Scheme 11.17 N-(thietane-3-yl)isatins are synthesized by combining isatins and chloromethylthiirane

Scheme 11.18 Preparation of thietane

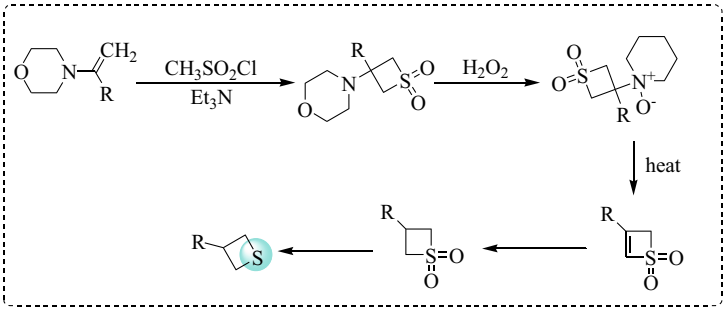


By cycloaddition of enamine to sulfene, functionalized 3-substituted thietanes have been produced. Numerous stages, including deamination and reduction, are required for this reaction (Scheme 11.19) [25].

Thietane was produced by treating 1,3-dihalopropane with sodium sulfide (Scheme 11.20) [25].

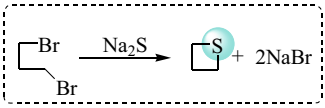
The reaction between allyl chloride and thiourea has also been used to produce thietane. During the procedure, thiourea transfers its sulfur to 1,3-dihalopropane, producing thietane (Scheme 11.21) [25].

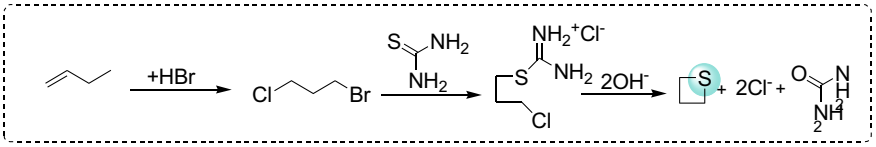
Sulfur dichloride interacted with δ-diketones to generate good yields of thietanes reported by Navjeet et al. (Scheme 11.22) [26].



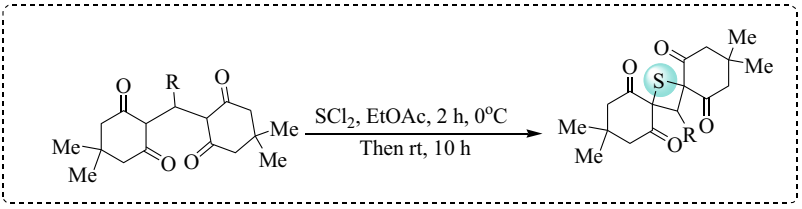
Scheme 11.19 Synthesis of functionalized 3-substituted thietanes derivatives via cycloaddition

Scheme 11.20 Reaction between 1,3-dihalopropane and sodium sulfide to form thietane derivatives





Scheme 11.21 Reaction between allyl chloride and thiourea to produce thietane



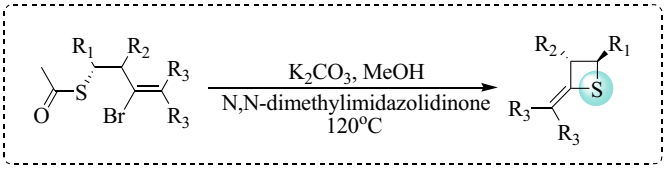
Scheme 11.22 Reaction between sulfur dichloride and δ-diketones to form thietanes

According to Navjeet et al., bromoalkenes with an acetylthio functionality underwent an intramolecular vinylic substitution process to provide 2-alkylidenethietane derivatives (Scheme 11.23) [26].

The γ-halo thiols, also known as 1,3-dihaloalkanes, provided thietanes reported by Navjeet et al. An example that serves as illustration is the cyclization of γ-halo thiols or their acetyl derivatives with bases (Scheme 11.24) [26].

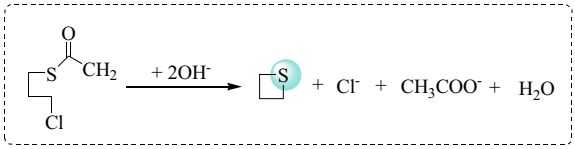
Thietanols were produced through the cyclization of (Z)-α-silyl vinyl sulfides with the aid of fluoride reported by Navjeet et al. (Scheme 11.25) [26].

In their study, Navjeet et al. described a procedure for synthesizing thietane derivatives from 1,3-diols. These dibenzoxazol-2-yl disulfide and tributylphosphine reactions produced 2-hydroxy alkyl thio benzoxazoles, which were then combined with potassium hydride to form thietanes (Scheme 11.26) [26].

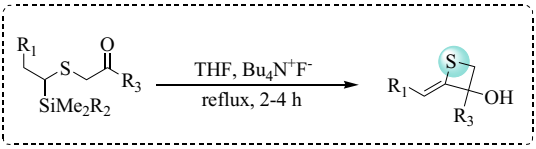


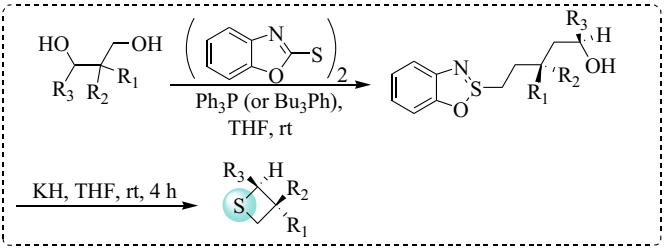
Scheme 11.23 Intramolecular vinylic substitution reaction for the preparation of thietanes

Scheme 11.24 Synthesis of thietane derivatives from γ-halo thiols



Scheme 11.25 Synthesis of thietane derivatives via the cyclization of (Z)-α-silyl vinyl sulfides





Scheme 11.26 Preparation of thietane derivatives

11.3 Biological Potency of Thietanes and Its Derivatives

At present, there is a great need for the creation of new and effective medicinal compounds because every person in the population is suffering from some kind of disease or the other. To overcome these diseases, researchers are constantly striving to design new drugs by exploring existing key compounds or identifying novel bioactive targets. In the current context, heterocyclic compounds are recognized to be crucial in the search for drugs with biological potency [27]. Sulfur-containing heterocycles are one of the most prominent classes of heterocyclic compounds in the field of chemistry [28]. Many sulfur-containing scaffolds are present in a variety of natural and pharmaceutical products, serving as physiologically active molecules in a spectrum of pathological conditions [29]. Recently, four-membered heterocycles (FMHs) have come to be recognized as important scaffolds in the drug-discovery process [30] because thietane is a valuable intermediary in the synthesis of organic compounds and an essential structural motif of some biological substances. However, the number of four-membered heterocycles [31] is very small compared to five- and six-membered heterocycles, but current research has demonstrated the significance of the thietane ring, which has resulted in the creation of multiple bioactive molecules [32]. The structures of some medicinally active compounds containing thietane fragments are shown in Fig. 11.3.

11.3.1 Anti-depressant and Anti-hypotensive Activity

Khaliullin et al. [33] reported the anti-depressant properties of purine derivatives containing a thietane fragment in 2018. The anti-depressant activity

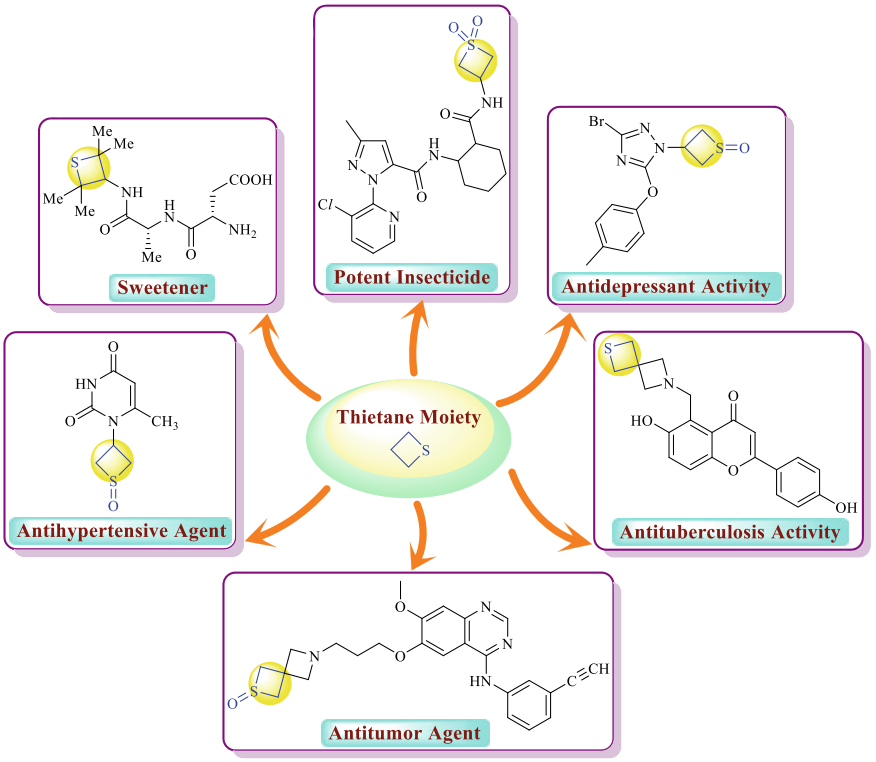


Fig. 11.3 Biologically active compounds with the thietane motif

was conducted using forced swimming tests (FSTs) and tail-suspension tests (TSTs). 3-methyl-7-(1,1-dioxothietan-3-yl)-8-cyclohexylamino-1-ethyl-1H-purine-2,6 (3H,7H)-dione (1) (Fig. 11.4) demonstrates strong anti-depressant action at a dose of 1.6 mg/kg without any sedative or psychostimulating effects.

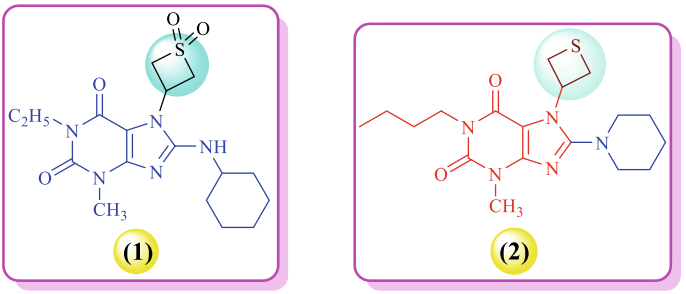


Fig. 11.4 Structure of thietane-based compounds found to have anti-depressant activity

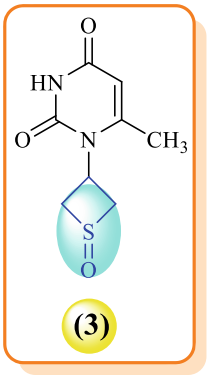


Fig. 11.5 Structure of a thietane-based compound (**3**) found to have anti-hypotensive activity

In 2020, Shabalina et al. [34] synthesized xanthine derivatives (**2**) (Fig. 11.4) containing a thietane ring as anti-depressant agents. The synthetic substances were examined in TST and FST to assess anti-depressant primary biological action. In both assessments, the total time of immobilization (TTI) was assessed.

Thietanepyrimidine-2,4-(1H,3H)-dione derivatives were described as anti-hypotensive drugs by Kataev et al. [35] in 2014. Many substances were synthesized and tested for their ability to lower blood pressure in comparison to the common medications amlodipine, lisinopril, and nebivolol. The most promising molecule was identified as 6-methyl-1-(1-oxothietan-3-yl)pyrimidine-2,4-(1H,3H)-dione (**3**) (Fig. 11.5), which exhibited noteworthy hypotensive efficacy at a dosage of 14.2 mg/kg. Systolic artery pressure (SAP) was reduced by 15% over a 90-min period by compound (**3**) containing thietane-1-oxide scaffold. Based on SAR research, oxidation of the thietane ring to either thietane 1-oxide or thietane 1,1-dioxide boosts the pharmacologic response of medications in contrast to unoxidized thietane ring.

11.3.2 Anti-cancer Activity

The deadly illness known as cancer is to blame for the rising death rate in the world. It results in the aberrant forms of the body's own cells reproducing and multiplying uncontrollably. The anti-cancer properties of a number of thietane-based compounds have been documented. It has also been discovered that compounds containing thietane 1,1-dioxide group are active as inhibitors of indoleamine-2,3-dioxygenase-1 (IDO1) and Zeste homolog 2 (EZH2), possibly having anti-cancer properties. Analogue (**4**) (Fig. 11.6) containing thietane 1,1-dioxide demonstrated good in vitro stability in inhibiting the Karpas-422 cancer cell line during the optimization of EZH2 inhibitors [36, 37]. Several hydroxyamidine-based small compounds, including (**5**) (Fig. 11.6), were investigated by Steeneck et al. [38] in order to find IDO1 inhibitors with a lower potential for glucuronidation. In the UGT1A9 glucuronidation experiment, the thietane 1,1-dioxide derivative (**5**) demonstrated good IDO1 inhibition

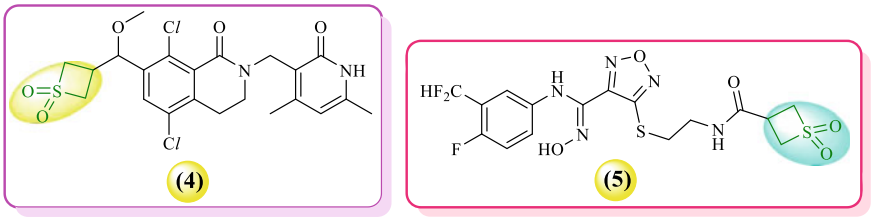


Fig. 11.6 Structure of a thietane motif containing compounds (**4, 5**) having anti-cancer properties

along with high stability; nevertheless, additional research was stopped because of the comparatively poor mouse liver microsomal stability. In their evaluation of structurally related compounds, Liu et al. [39] discovered that thietane 1-oxide and 1,1-oxide had good effectiveness as IDO1 inhibitors.

11.3.3 Anti-viral Activity

It has been discovered that compounds containing thietane inhibit 4-diphosphocytidyl-2-C-methyl-erythritol kinase (IspE) with anti-bacterial action, inhibit the mycobacterium tuberculosis H37Rv, and stop the respiratory syncytial virus (RSV) from fusing. It was shown that spirocyclic thietane, (**6**) (Fig. 11.7), a product of a preclinical RSV inhibitor, [40] exhibited minimal cytotoxicity in Hep-2 cells [41] along with some anti-viral action against RSV.

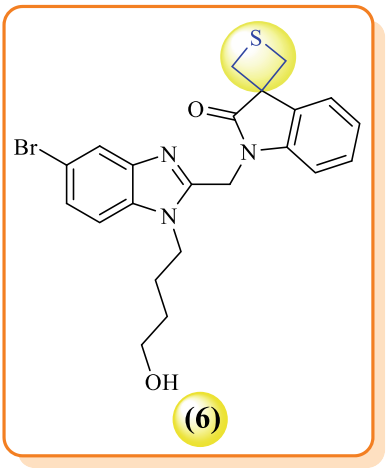


Fig. 11.7 Structure of a thietane-based compound (**6**) found to have anti-viral activity

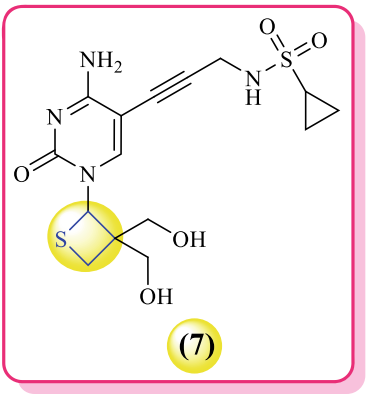


Fig. 11.8 Structure of a molecule (7) which contains thietane motif show anti-bacterial and anti-infection activity

11.3.4 Anti-bacterial and Anti-infection Activity

It was discovered that thietane derivative (**7**) (Fig. 11.8), which was discovered through investigation of the ribose sub-pocket of E. coli IspE, had intermediate water solubility along with good IspE inhibitory activity [42].

11.3.5 Anti-tuberculosis Activity

Agarwal et al. [43] produced a spirocyclic thietane, (**8**) (Fig. 11.9), using known M. tuberculosis Polyketide Synthase 13 inhibitors [44], and reported that it was effective against M. tuberculosis H37Rv, with a minimum inhibitory concentration (MIC) of 15.34 ug/mL.

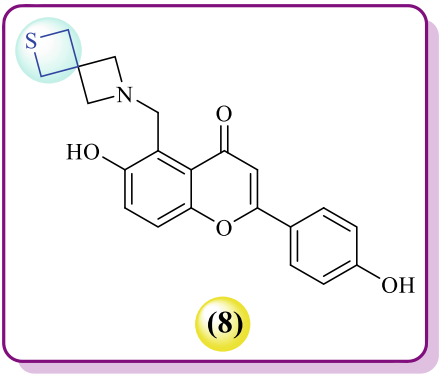


Fig. 11.9 Structure of a thietane-based compound (**8**) having anti-tuberculosis activity

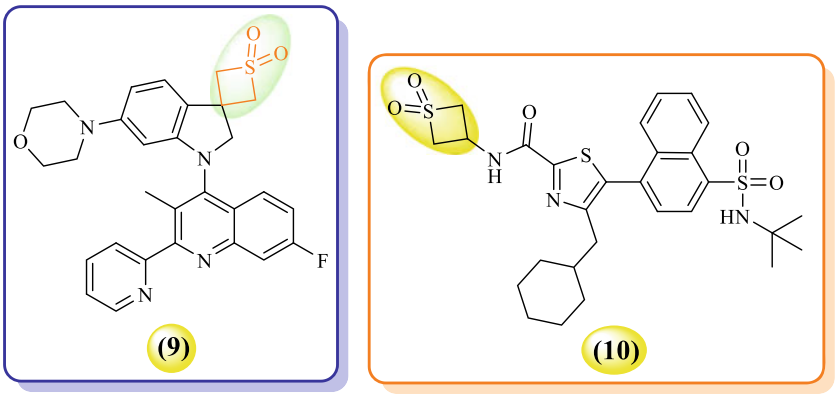


Fig. 11.10 Structure of a thietane ring containing compounds (**9 and 10**) having anti-inflammation activity

11.3.6 Anti-inflammation Activity

Furthermore, as phosphoinositide 3-kinase (PI3K) inhibitors and inverse agonists of the retinoic acid receptor-related orphan nuclear receptor (ROR), several compounds containing thietane groups have been found to have anti-inflammatory properties. Gonzalez-Lopez de Turiso et al. [45] examined several PI3K inhibitors based on the indoline ring and quinoline core in an effort to identify and evaluate dual PI3Kβ/δ inhibitors. Moderate suppression of both β and δ was seen in the derivative (**9**) (Fig. 11.10), a spirocyclic thietane 1,1-dioxide. The study of numerous selective thiazole-based inverse agonists of RORγ led to the investigation of other substitutions around the thiazole, such as thietane 1,1-dioxide bearing (**10**) (Fig. 11.10), which demonstrated great potency and selectivity for RORγ over RORβ [46, 47].

11.3.7 Anti-diabetic Activity

As potential anti-diabetic medications, compounds containing the thietane moiety have also been synthesized, which function as sodium glucose transporter (SGLT) inhibitors and as agonists of the G-protein coupled receptor (GPR40) [48]. Medium and long-chain free fatty acid receptors (FFAs) can activate the GPR40 receptor; however, because of certain drug toxicities resulting from the metabolism of the carboxylic acid moieties, Huang et al. [49] used tetrazole as a carboxylic acid isostere to find non-carboxylate inhibitors, which decreased the cytotoxicity of GPR40 agonists. Thietane 1,1-dioxide (**11**), as shown in Fig. 11.11, was found during this investigation and demonstrated to possess good potency and in vitro microsomal stability in both rats and humans. Research was done by Robinson et al. [50] and Mascitti et al. [51] on the use of spirocyclic rings in SGLT2 inhibitors. There

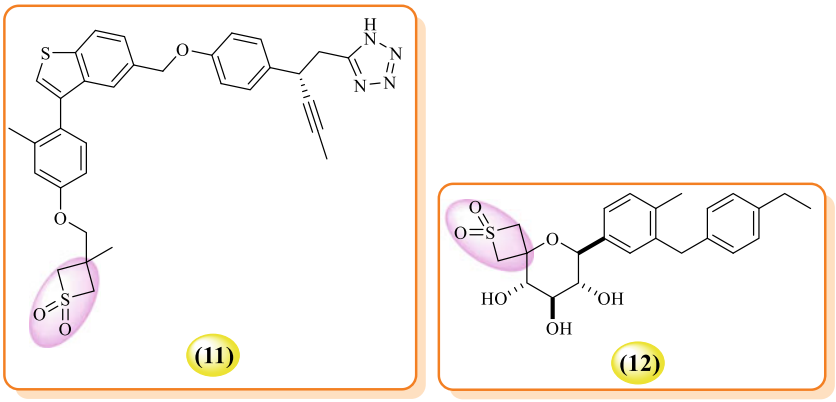


Fig. 11.11 Structure of a thietane motif containing compounds (**11 and 12**) having anti-diabetic activity

were found several thietane-containing compounds, (**12**) (Fig. 11.11) which shows selectivity for SGLT2 over SGLT1.

11.3.8 Anti-platelet and Anti-coagulant Activity

Thietane moieties are found to show anti-platelet and anti-coagulant activities against thrombi. A series of thietane-containing 2-(5-bromo-2,4-dihydro-3-oxo-1,2,4-triazolyl-4)acetic acid derivatives were synthesized by Gurevich et al. [52] Using separated blood samples, the anti-platelet and anti-coagulant activity of the produced compounds was evaluated in vitro. Compounds (**13**) and (**14**) (Fig. 11.12) exhibited the highest anti-platelet activity in the ADP-induced aggregation test, which was similar to acetylsalicylic acid. In the collagen-induced aggregation test, these compounds generally showed no hazardous hazards and outperformed the reference medications.

Klen et al. [53] synthesized and demonstrated new biologically active 1-thietanyl-1,2,4-triazole derivatives with anti-platelet activity. An analysis of the effects in the series of 1-(thietanyl-3)- and 1-(1,1-dioxothietanyl-3)-1,2,4-triazoles showed that the degree of S atom oxidation in the thietanyl ring has a substantial impact on the aggregant activity. The compounds (**15**) and (**16**) (Fig. 11.12), which have the dioxothietanyl ring, showed anti-aggregant properties. The rheological activity was mostly unaffected by the type of cation.

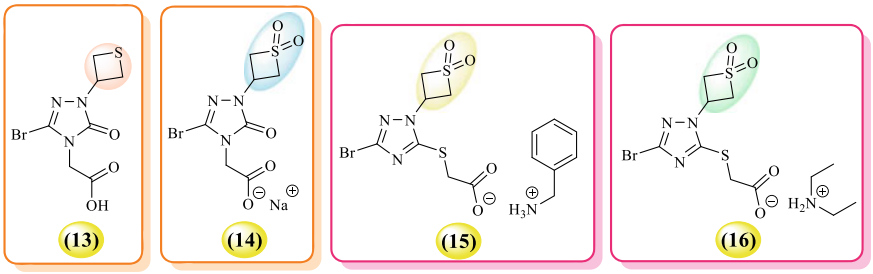


Fig. 11.12 Structure of a thietane ring containing compounds (**13–16**) having anti-platelet and anti-coagulant properties

11.4 Conclusion

Scientists are quite concerned about the innovative development of thietane and its derivatives since this molecule, which is privileged and pharmacologically active, is so important to medical science. In this chapter, many well-known and somewhat new methods for creating thietane rings are covered. Even though thietanes' preparation has been well examined, creating thietanes with various functionalizations is still a difficult task in organic chemistry that requires extra care. This chapter also covers the biological significance of the molecules possessing the synthesized thietane motif.

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Chapter 12
Synthesis and Biological Evaluation of Fused Thiazolotriazole and Imidazothiadiazole Scaffolds

Nishu Dhanda, Chetna Kumari, and Sudesh Kumar

12.1 Introduction

The fundamental structure of many clinically utilized drugs contains heterocyclic moieties, highlighting the significance of heterocycles in the formation of new pharmacologically active molecules [1]. Many S-containing scaffolds are found in a variety of medicines and natural products which act as biologically active molecules in multitude pathophysiological circumstances [2]. Because of sulfur strong volatility and reactivity, several chemicals containing sulfur also play a part in flavoring foods including meat, vegetables, and roasted goods including peanuts, cocoa, and coffee. Heterocycles containing sulfur showed a numerous range of pharmacological effects, comprising antiviral, antibacterial, anticancer, anti-tubercular, and anti-inflammatory. Thiazole, thiazepine, isothiazole, thiopyran, thiophene, and thiazolidine, which consist of five, six, and seven-membered rings, represent some of the sulfur-containing heterocycles that have been extensively studied in the branch of drug development [3].

The thiazole scaffold is present in Ravuconazole [4], Carumonam [5], Cefotaxime [6, 7], Cefdinir [8], and these all are FDA-approved drugs (Fig. 12.1).

Over the past 15 years, heterocyclic compounds have been increasingly prominent in the branch of organic synthesis and medicinal chemistry. Particularly, S-containing [5,5]-fused ring systems with a bridgehead nitrogen (Fig. 12.2) have gained recognition. These structural frameworks, serving as bioisosteres of imidazopyridazines, indolizines, and their analogs, are linked to a broad array of biological

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K. L. Ameta (ed.), *S-Heterocycles*, https://doi.org/10.1007/978-981-97-4308-7_12

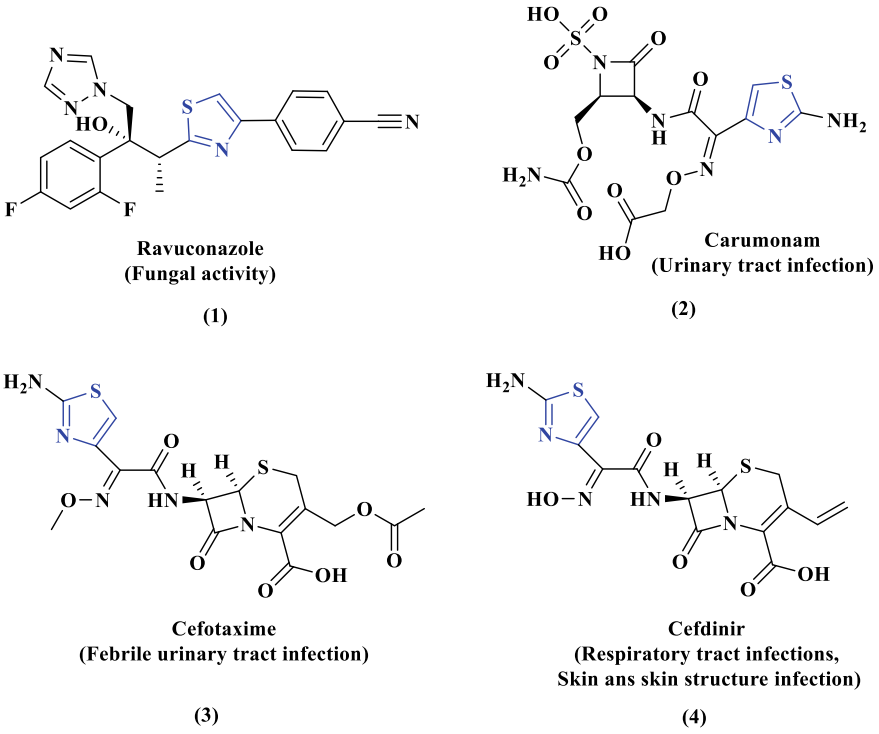


Fig. 12.1 Thiazole containing drugs

effects. Their utility in medicinal chemistry has increased as a result of these characteristics, particularly in light of molecular diversity and the continual search for new chemical space [9]. This chapter presents the one-pot synthesis and biological profile of thiazolotriazoles, imidazothiadiazole, and some miscellaneous reaction.

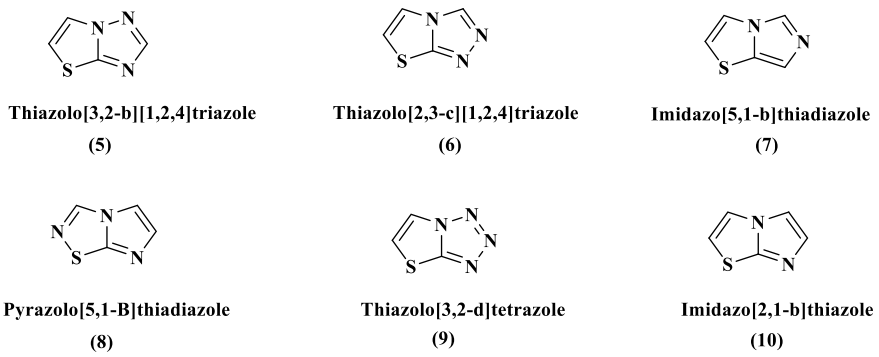


Fig. 12.2 [5,5]-fused ring systems with a bridgehead nitrogen

12.2 Thiazolotriazoles

12.2.1 Introduction

The thiazolotriazoles are those substances that have two fused triazole and thiazole rings in their structure and can occur in two main isomeric forms: thiazolo[3,2-b][1,2,4]triazoles and thiazolo[2,3-c][1,2,4]triazoles. The synthesis of thiazolo-1,2,4-triazoles has drawn a lot of focus recently because of the extensive range of biological activities they exhibit analgesic [10], antimicrobial [11], antipyretic [12], anti-inflammatory [13], anticancer, and vasodilatory [14].

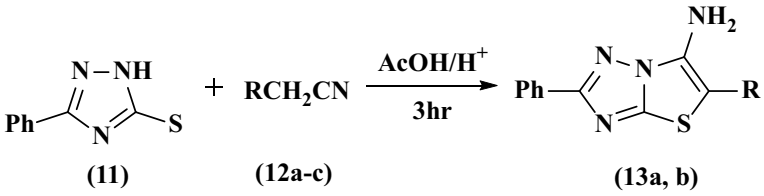
The acidified acetic acid environment ($AcOH/H^+$), employed in the synthesis of a range of multifunctional compounds, offers several advantages. These include reduced reaction duration, the possibility of one-pot reactions, and the direct utilization of cost-effective and safe cyano compounds containing active methylene groups, all without the formation of highly toxic, irritating, or hazardous halocyano derivatives [15].

12.2.2 Synthesis of Thiazolotriazoles

On heating of phenyltriazole **(11)** treating with CN compounds containing $-CH_2$ group like ethyl cyanoacetate, malononitrile and cyanoacetamide **(12a-c)** under standard reflux conditions through acidified acetic acid method furnished the phenyl-thiazolotriazoles **(13a,b)** in moderate yield (Scheme 12.1).

The synthesis of 6-amino-2-phenylthiazolotriazole-5-carboxamide **(13b)** by treating phenyltriazole **(11)** with bromocyanoacetamide **(14)** using KOH at room temperature (Scheme 12.2).

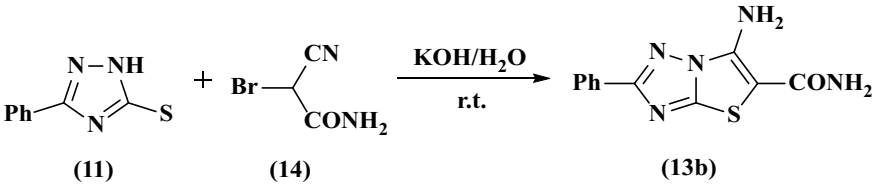
Generation of dimeric disulfide **(15)** with 81% yield on refluxing phenyltriazole **(11)** in the presence of acidified acetic acid formed dimeric disulfide **(15)** by nucleophilic attack on imine form. The formed compound **(16)**, followed by the intramolecular cyclization reaction, yielded the cyclized imino structures **(17)** via



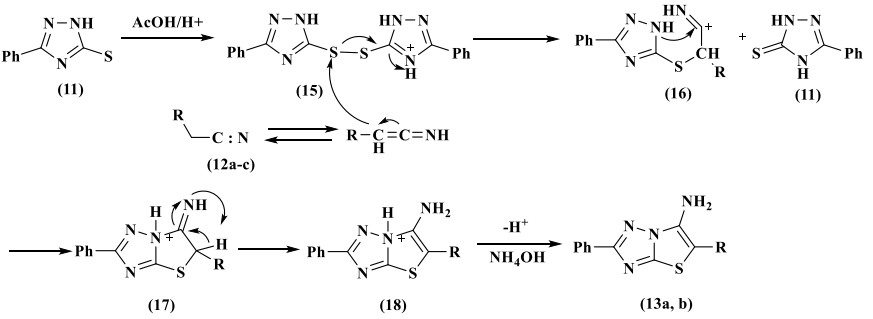
(11) **(12a-c)** **(13a, b)**

R = a; COOEt, b; $CONH_2$, c; CN

Scheme 12.1 Synthesis of phenyl-thiazolotriazoles



Scheme 12.2 Synthesis of phenyltriazole with bromocyanoacetamide



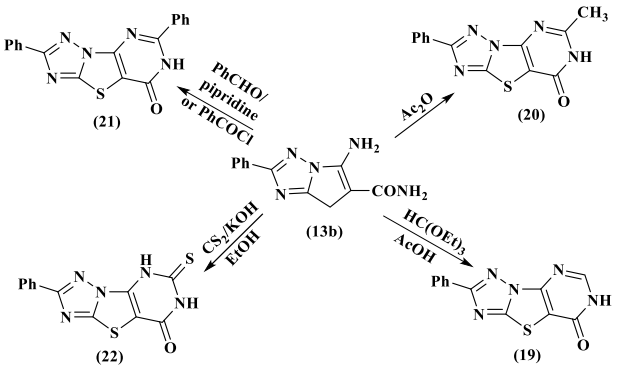
Scheme 12.3 Synthesis of phenyl-thiazolotriazoles

the protonation of **(17)** through H^+ furnished cyclized carbonium ion **(18)** followed by deportation generates the phenyl-thiazolotriazoles **(13a,b)** (Scheme 12.3) [16, 17].

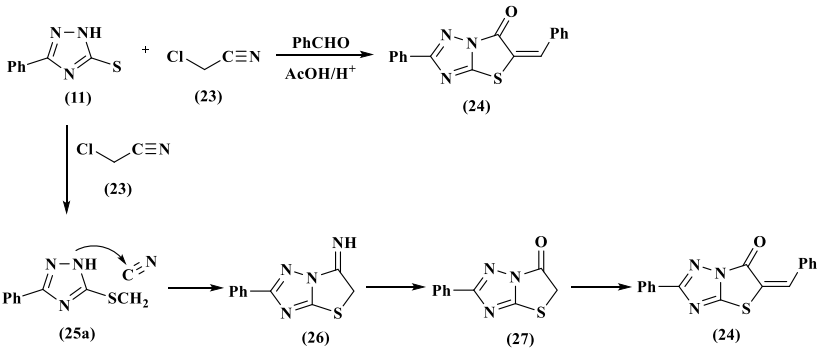
Formation of 2-phenyltriazolothiazolopyrimidin-8-one **(19)**, 6-methyl-2-phenyltriazolothiazolopyrimidin-8-one **(20)**, 2,6-diphenyltriazolothiazolopyrimid in-8-one **(21),** and 2-phenyl-6-thioxotriazolothiazolopyrimidin-8-one **(22)** and the reaction of 5-amino-2-phenylthiazolotriazole-6-carboxamide **(13b)** with acetic anhydride, triethyl orthoformate, benzaldehyde using piperidine (or C_7H_5ClO) and CS_2 in alcoholic KOH furnished the desired product with moderate yield (Scheme 12.4) [15].

5-benzylidene-2-phenylthiazolotriazol-6-one **(24)** has been synthesized by treating phenyltriazole **(11)** with $ClCH_2CN$ **(23)** and C_6H_5CHO using AcOH. The mechanism of **(24)** comprises the S-alkylation of phenyltriazole **(11)** and intramolecular cyclization. It occurs by the nucleophilic attack of NH on the CN group, leading to in the cyclized imine derivative **(26)**. The ketone is then hydrolyzed, and finally, the desired product **(27)** is obtained by condensation with benzaldehyde (Scheme 12.5) [15].

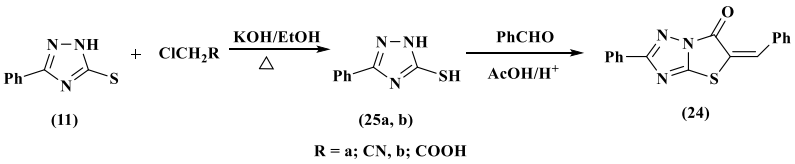
On refluxing 2-[(5-phenyltriazolo-3-yl)thio]acetonitrile/acetic acid **(25a,b)**, which is synthesized by treating phenyltriazole **(11)** with chloroacetic acid or chloroacetonitrile in alcoholic KOH, and benzaldehyde under the same reaction conditions yielded 5-benzylidene-2-phenylthiazolotriazol-6-one **(24)** (Scheme 12.6).



Scheme 12.4 Synthesis of triazolothiazolopyrimidine derivatives



Scheme 12.5 Synthesis of phenyltriazole with chloroacetonitrile



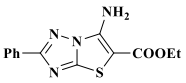
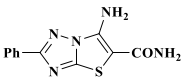
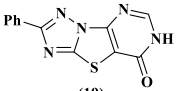
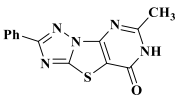
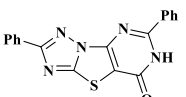
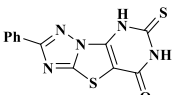
Scheme 12.6 Synthesis of 5-benzylidene-2-phenylthiazolotriazol-6-one

12.2.3 Biological Activity

Generating novel heterocyclic compounds with potential biological value was one of the goals of the current effort. The anti-fungal and anti-bacterial activity of a few of the recently synthesized compounds was illustrated. *Pseudomonas aeruginosa*, *Bacillus cereus*, *Escherichia coli*, *Staphylococcus aureus*, and *Serratia marcescens* were the microorganisms employed in the antibacterial research. *Scopulariopsis brevicaulis*,

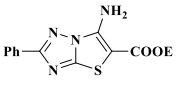
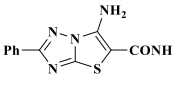
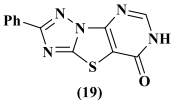
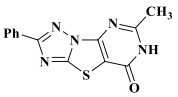
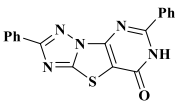
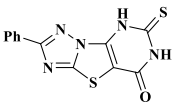
Geotrichum candidum, *Aspergillus flavus*, *Candida albicans*, *Fusarium oxysporum*, and *Trichophyton rubrum* were utilized as antifungal agents. Minimal Inhibitory Concentration (MIC) testing using the serial dilution approach was performed on both microbiological investigations [18]. The chemical whose MIC must be determined was diluted serially and concentrations were added to standard drops of the culture generated for the experiment. The resulting mixtures were then incubated for 16–18 h at 37 °C (Tables 12.1 and 12.2) [15].

Table 12.1 Antibacterial activity of certain selected chemicals [15]

Sample	*S. marcescens*	*P. aeruginosa*	*E. coli*	*S. aureus*	*B. cereus*
 (13a)	10(20)	–	12(20)	–	–
 (13b)	10(20)	–	15(20)	–	12(10)
 (19)	10(20)	–	–	–	–
 (20)	10(20)	–	12(20)	–	–
 (21)	10(20)	–	12(20)	–	–
 (22)	10(20)	–	12(20)	13(20)	12(2.5)
DMSO	10(20)	–	–	–	–
CHL[a]	12(1.25)	14(5.0)	12(0.3)	10(1.25)	34(0.3)

[a] CHL = Chloramphenicol as standard
MICs shown in brackets and inhibition zone measured in millimeters

Table 12.2 Antifungal activity of certain selected chemicals [15]

Sample	*G. candidum*	*C. albicans*	*A. flavus*	*T. rubrum*	*F. oxysporum*
 (13a)	11(20)	–	–	10(20)	–
 (13b)	11(20)	–	–	–	–
 (19)	–	–	–	–	–
 (20)	12(20)	–	–	–	–
 (21)	11(20)	–	–	–	–
 (22)	12(20)	–	–	–	–
DMSO	–	–	–	–	–
CHL[a]	24(0.3)	25(0.3)	24(2.5)	36(1.25)	20(10)

[a] CHL = Chloramphenicol as standard
MICs shown in brackets and inhibition zone measured in millimeters

12.3 Imidazothiadiazole

12.3.1 Introduction

Imidazothiadiazole is formed by two fused moieties imidazole and thiadiazole. Two possible forms of this compound are imidazo[1,3,4]thiadiazole **(28)** and imidazo[1,2,4] thiadiazole **(29)** and important scaffold for bioactive compounds (Fig. 12.3) [19].

Imidazo[2,1-b][1,3,4]thiadiazole **Imidazo[1,2-d][1,2,4]thiadiazole**

Fig. 12.3 Isomeric form of imidazothiadiazole

Subsequently, in these two isomeric forms, imidazo[1,3,4]thiadiazole **(28)** and its derivatives are broadly reported, and another isomer is rarely studied [20–22]. Imidazo[2,1-b][1,3,4]thiadiazole derivatives include multifarious biological activities including tubulin inhibitor [23], anti-microbial [24], antibacterial [25], anti-inflammatory [26], anti-fungal [27], anti-convulsant [28], anti-tumor [29], anti-cancer [30], and anti-tubercular [31]. The 1,3,4-thiadiazole molecule has a broad range of medical uses, with anti-inflammatory [32], anticancer [33], antibacterial [34], antiviral [35], and antioxidant [36]. Numerous imidazo[2,1-b]thiadiazole derivatives have been generated and show biological activities such as the phenylimidazo[2,1-b][1,3,4]thiadiazole derivatives **(30)** (antifungal agents) [37], diaryl substituted Hybrids **(31)** (anti-tubercular agents) [38], carbamic acid analogues **(32)** (anti-inflammatory or analgesic agents) [39], bromo-benzene substituted derivative **(33)** (anti-cancer agent) [40], ethylimidazo[1,3,4]thiadiazol-2-yl)-3-(imidazolidin-2-yl)acrylate **(34)** (anti-leishmanial agents) [41], and methylimidazo[1,3,4]thiadiazol-6-yl)phenoxy)propyl **(35)** (anesthetic agent) [42] (Fig. 12.4).

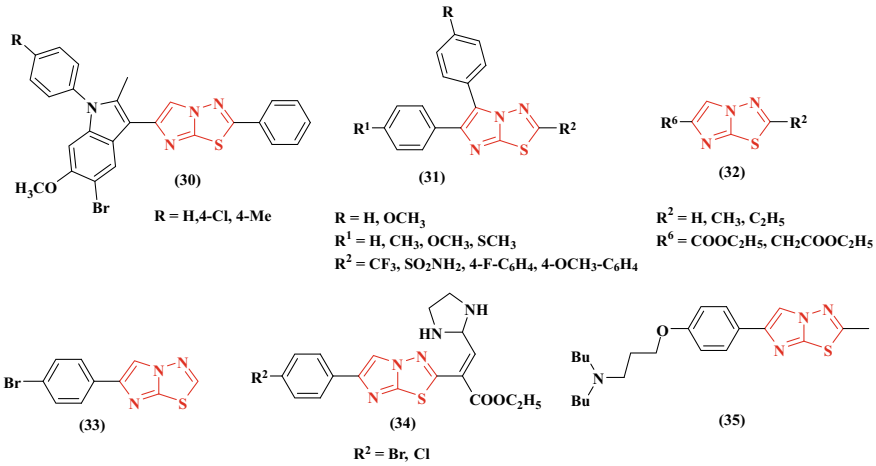


Fig. 12.4 Biologically active imidazo[2,1-b][1,3,4]thiadiazole derivatives

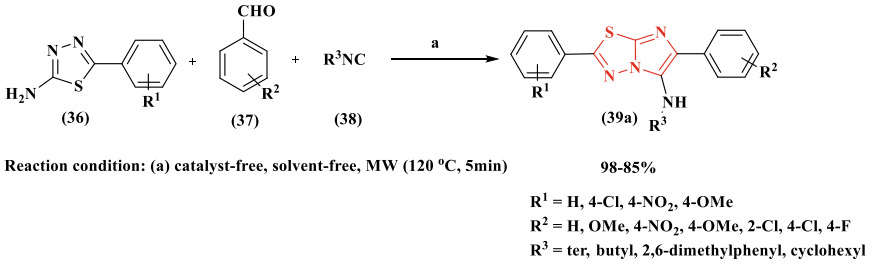
Several imidazo[2,1-b][1,3,4]thiadiazoles have been synthesized and examined for a wide spectrum of biological importance. These compounds differ in the substitutions at the 2, 5, and 6 positions of the scaffold [28].

12.3.2 Synthesis of Imidazothiadiazole

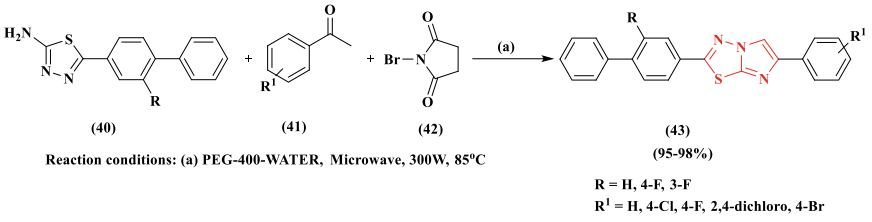
Wadhwa et al. demonstrated a one-pot reaction of imidazole[1,3,4]thiadiazole **(39a)** through Groebke–Blackburn–Bienayme reaction via the reaction between amines **(36)**, aromatic aldehydes **(37),** and isonitriles **(38)** under microwave irradiation at 120 °C furnished arylimidazothiadiazole in good yield (Scheme 12.7) [43].

A greener and effective approach for the reaction of biphenylimidazo[2,1-b][1,3,4]thiadiazole derivatives **(43)** was developed by Wagere et al. via three-component reaction of aminothiadiazole derivatives **(40)**, acetophenones **(41)**, and NBS **(42)** under microwave reaction condition in PEG-400 using water in high yield (Scheme 12.8) [44].

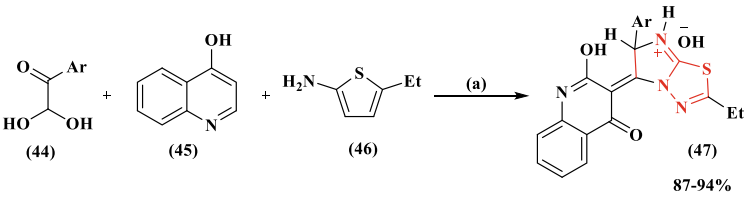
Khalafy et al. demonstrated a green and catalytic approach for the reaction of **(47)** via one-pot MCRs. The reaction of compound **(44)**, Quinolin-4-ol **(45)**, and 5-ethylthiophen-2-amine **(46)** under refluxed condition using Et_3N/NH_2SO_3H in water is to be furnished good yield of the desired product (Scheme 12.9) [45].



Scheme 12.7 One-pot synthesis of imidazo[1,3,4]thiadiazole derivatives



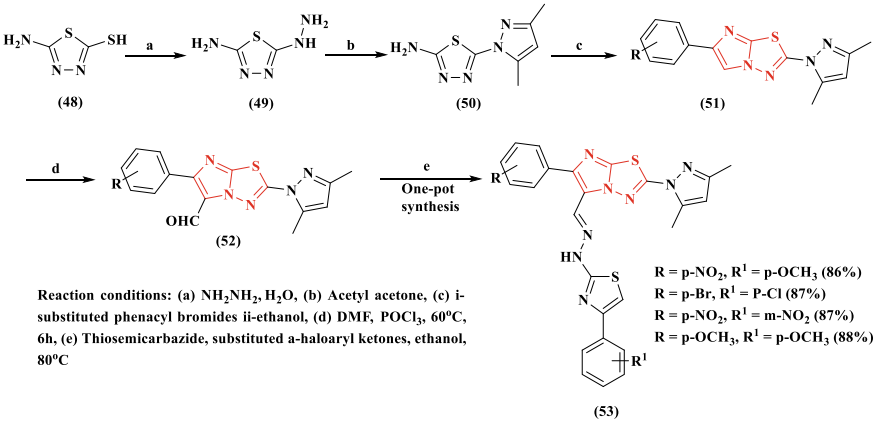
Scheme 12.8 Synthesis of biphenylimidazo[2,1-b][1,3,4]thiadiazole



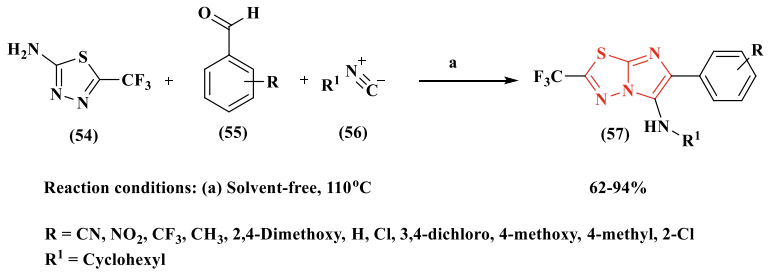
Scheme 12.9 Multi-component reaction of imidazo[1,3,4]thiadiazol-7-ium hydroxides

Syed et al. demonstrated that a one-pot efficient synthetic strategy was synthesized between **(52)**, thiosemicarbazide, and substituted α-halo ketones through ethanol at 80 °C to furnished imidazo[1,3,4]thiadiazole derivatives **(53)** in high yield including anti-tubercular and anti-fungal activities (Scheme 12.10) [46].

Sarchahi et al. demonstrated one-pot reaction for the generation of CF_3- comprising imidazo[2,1-b][1,3,4]thiadiazole derivative **(57)**, and the chemical methodology involves component **(54)**, aromatic aldehydes **(55)**, and third component **(56)** under standard conditions at 110 °C to be furnished the product **(57)** with good yield (Scheme 12.11) [47].



Scheme 12.10 Synthesis of imidazo [2,1-b][1,3,4]thiadiazole derivatives



Scheme 12.11 Derivatives containing $-CF_3$ functionalization

12.3.3 Biological Activity of Imidazo[2,1-b][1,3,4]Thiadiazole

In recent years, a broad amount of physiologically active imidazo[2,1-b][1,3,4]thiadiazole derivatives has been synthesized. Anti-inflammatory, anti-tubercular, anti-bacterial, anti-fungal, anti-leishmanial, anti-viral, and anti-cancer activities are among the most often noted. It has been discovered that the numerous substituents affect the biological data of the parent heterocycle. These derivatives have various substitutes at positions 2, 5, and 6 of the ring system. Among the tri-substituted imidazothiadiazole derivatives that exhibited strong anti-tubercular properties are **(59)** (MIC value = 3.125 mg/mL) [48], **(60)**, **(62)** (0.24–0.29 μ g/mL) [49] **(61)** (3.125 μg/mL) [50], and **(78)**(1.6–6.25 μg/mL) [46]. Anti-fungal activities were synthesized for compounds **(74)**, **(75)**, **(76)** [51], **(78)** [46], and **(79)** [52], with MIC values in the range of 5–100 μg/mL. Anti-bacterial activities were illustrated by derivatives **(72)** [53], **(73)** [54], **(74)**, **(75)**, **(76)** [51], and **(78)** [55], Compounds **(65)** (IC50 = 8 μM), **(66)** (IC50 = 0.11–2.98 μM) [56], **(67)** [57], **(68)** (IC50 = 489 nM) [58], **(69)** [59], and **(70)** [60]. Table 12.3 displays potential anti-cancer activities. 2,6-disubstituted imidazo[1,3,4]thiadiazole compounds have also shown anti-viral, anti-leishmanial, and anti-inflammatory properties [61].

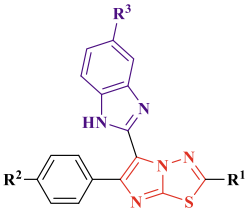
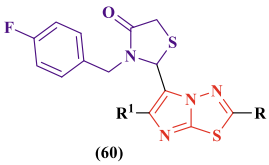
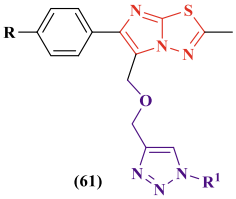
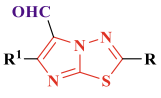
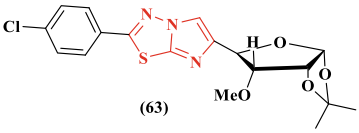
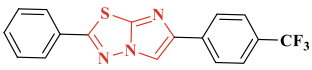
12.4 Miscellaneous Reaction

12.4.1 Pyrrolo[2,1-b]thiazole

12.4.1.1 Introduction

The hydrocarbon skeleton of pyrrolothiazoles is identical to that of imidazothiazoles, with the exception that nitrogen has been isosterically substituted at seventh position of the heterocyclic ring. The development of approach for synthesizing this heterocyclic scaffold is a crucial undertaking since pyrrolothiazoles and their derivatives also demonstrate anti-psychotic, anti-inflammatory, anti-convulsant, anti-cancer, and

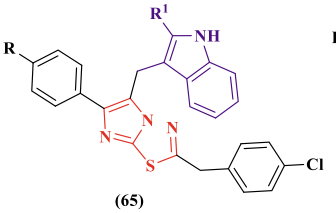
Table 12.3 Biological properties of imidazo[2,1-b][1,3,4]thiadiazole derivatives [19]

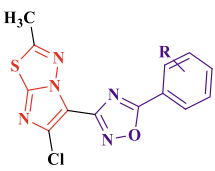
Imidazo[2,1-b][1,3,4]thiadiazole derivatives and its biological properties
 (58)
Anti-tubercular
 (59)  (60)  (61)  (62)
Anti-viral
 (63)
Anti-inflammatory
 (64)

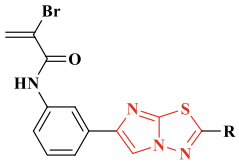
(continued)

Table 12.3 (continued)

Anti-cancer


(65)


(66)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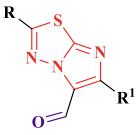
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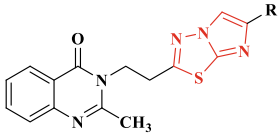
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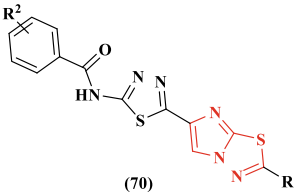
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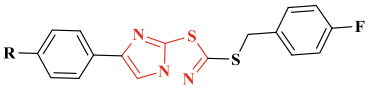
Anti-leishmanial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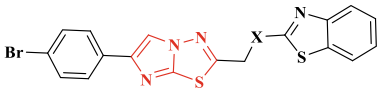
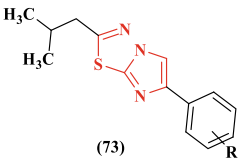

(72)

Anti-bacterial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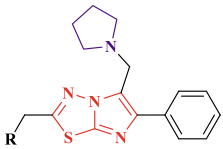
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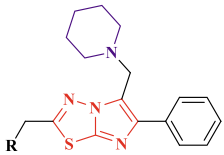
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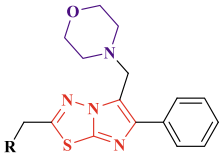
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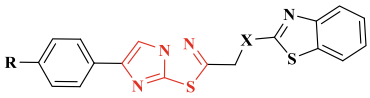
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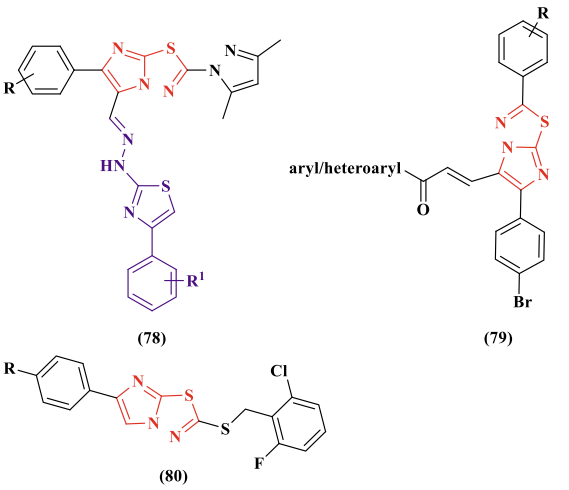
(continued)

Table 12.3 (continued)

Anti-fungal


other activity [62, 63]. Pyrrolo[2,1-b]thiazoles were mostly made by generating the bicyclic system from an existing pyrrole or thiazole ring by the use of alkylation and dipolar cycloaddition processes; however, they could also be made from acyclic synthons [64].

12.4.1.2 Synthesis of Pyrrolo[2,1-b]thiazoles

The simplest component of the [5,5]-fused N and S ring systems is the pyrrolothiazole **(81)** (Fig. 12.5) [64]. The fact that there are so many alternative synthetic pathways for their production may be due to their simplicity.

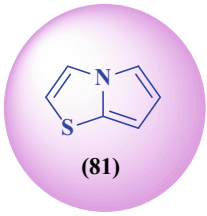
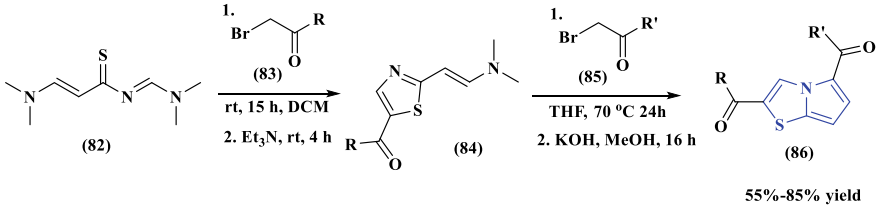
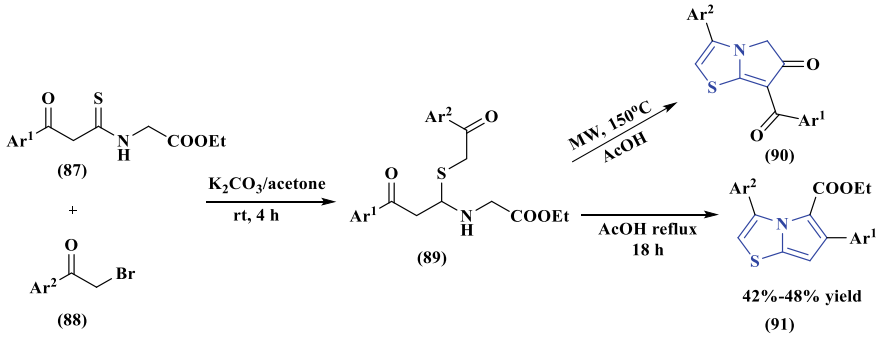


Fig. 12.5 Structure of pyrrolo[2,1-b]thiazoles



Scheme 12.12 Synthesis of pyrrolothiazoles derivatives



Scheme 12.13 Synthesis of pyrrolo[2,1-b] thiazol-6-ones and pyrrolo[2,1-b]thiazoles

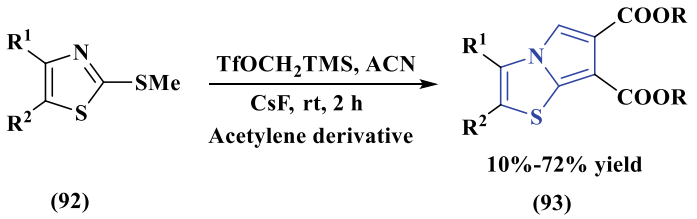
From α-Bromoketones and Thiazole Precursors

The initial reactant for this scaffold is compound **(82)**. As α-bromoketone's first molecule operates, a thiazole ring appears. A second reaction produces the required bicyclic structure **(86)** with substitutions in positions 2 and 5 [65]. The reaction of pyrrolo [2,1-b]thiazoles associated to a carbohydrate moiety in position 2 or 5 of the intended product was carried out by the authors through microwave heating and plausible yields (Scheme 12.12) [66].

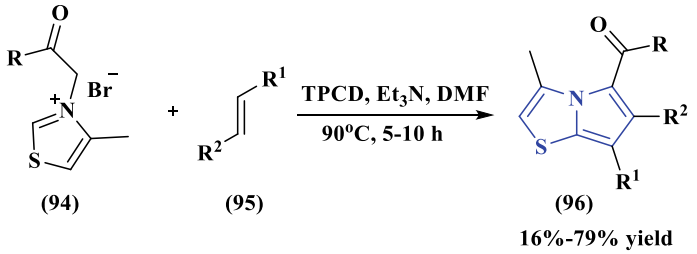
Reaction of α-aroyl ketene-N,S-acetals **(87)** with compound **(88)** through K_2CO_3/acetone at room temperature for 4 h leads to generation of an intermediate **(89)** followed by sequential cyclization under microwave condition at 150 °C furnished the pyrrolo[2,1-b] thiazol-6-ones **(90)**. After that same intermediate refluxed using AcOH formed the pyrrolo[2,1-b]thiazoles**(91)** with moderate yield (Scheme 12.13) [67].

From Thiazoles

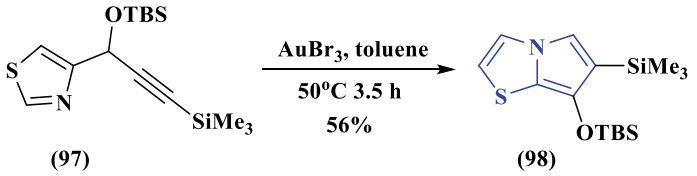
Berry et al. reported that alkylation of 2-methylthio-1,3-thiazole **(92)** they undergo cycloaddition reactions after quaternization with $TMSCH_2OTf$ and synthesis with



Scheme 12.14 Synthesis of pyrrolo [2,1-b]thiazoles derivatives



Scheme 12.15 Synthesis of pyrrolo [2,1-b]thiazole derivatives



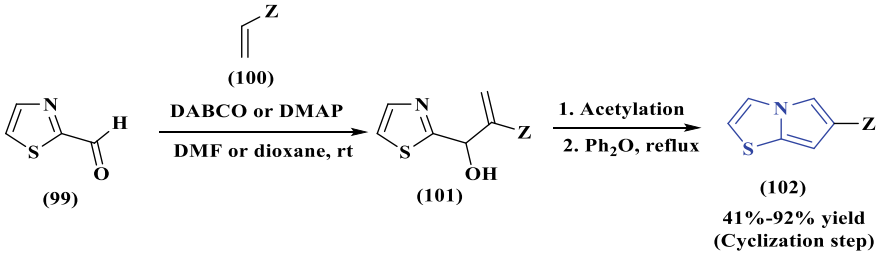
Scheme 12.16 Synthesis of pyrrolo[2,1-b]thiazole derivatives

alkynes at room temperature for 2 h furnished the desired product **(93)** with moderate yield (Scheme 12.14) [68].

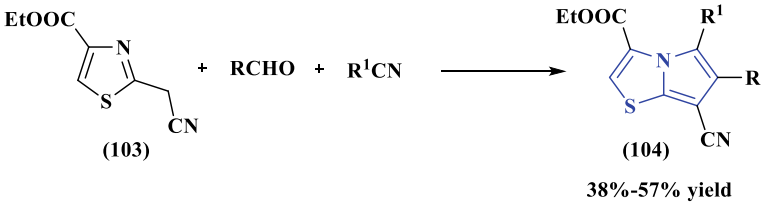
Shen et al. demonstrated the one-pot reaction of pyrrolo [2,1-b]thiazole derivatives. Subsequently, the treatment of ylide species **(94)** with electron-deficient alkene through TPCD, Et_3N, and DMF at 90 °C for 5–10 h afforded the desired product **(96)** with moderate yield exhibits anti-proliferative activity for Hep-G2 cancer cells (Scheme 12.15) [69].

The migration of Si, Sn, and Ge facilitated by gold for the reaction of fused pyrrole heterocycles was reported by Gevorgyan et al. [70] Compound **(98)** with moderate yield was obtained by a reaction with a single thiazole ring (Scheme 12.16). Through a transition metal-catalyzed cycloisomerization methodology, the same group has synthesized numerous additional 5,7-substituted pyrrolo[2,1-b]thiazole rings [71, 72].

The synthesis of pyrrolo[2,1-b] thiazoles derivatives has been synthesized for treatingthiazole-2-carboxaldehyde **(99)** with alkene through DABCO or DMAP,

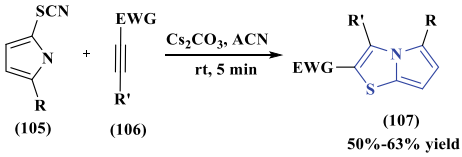


Scheme 12.17 Synthesis of pyrrolothiazoles' derivatives



Scheme 12.18 Synthesis of pyrrolo[2,1-b]thiazoles derivatives

Scheme 12.19 Synthesis of pyrrolo[2,1-b]thiazoles derivatives with electron withdrawing group



DMF at room temperature formed methyl thiazolyl adduct. Therefore, the resulting intermediate reaction with Ph_2O under standard reflux condition undergoes the desired compound fused bicyclic product **(102)** with good yield (Scheme 12.17) [73].

Bienayme and coworkers reported multicomponent reaction (MCR) of aldehyde and 2-cyanomethylthiazole **(103)** using DBU in n-butanol at room temperature. The [4 + 1] adduct was formed to an isocyanide at 100 °C to yield the desired product **(104)** with moderate yield (Scheme 12.18) [74].

From Pyrrole Derivatives

Werz et al. investigated that the reaction of pyrrole containing nitrogen **(105)** with the alkyne using Michael acceptor undergoes the loss of cyano group followed by cyclization under reaction condition to furnish appropriate fused ring system **(107)** with moderate yield (Scheme 12.19) [75].

12.4.2 Imidazotriazoles

Numerous studies have reported the pharmacological activities of [1,2,4]-triazoles. Here are a few examples: alprazolam [76], rilmazafon, trazodon benatradin, estazolam, trapidil, etoperidone, letrozole, nefazodone, anastrozole, vorozole, fluconazole, terconazole, itraconazole, and ribavirin which illustrate anti-depressant, hypotensive, transquillizer, anti-fungal, anti-viral, and so on [77–79]. The synthesis of imidazotriazoles has been prompted by the diverse range of biological activity, with the goal of exploring their potential therapeutic applications. Imidazole [80] or 1,2,4-triazole derivatives [81] are the starting materials used in traditional methods for the synthesis of imidazotriazoles.

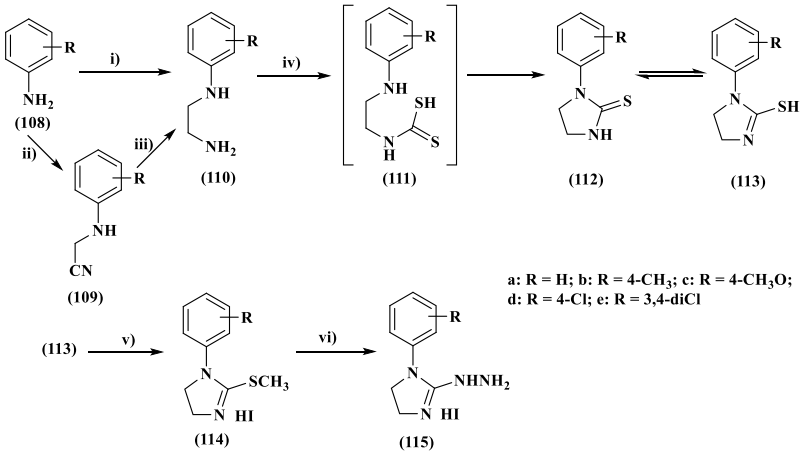
12.4.2.1 Synthesis and Biological Activity of Imidazotriazoles

These bridgehead nitrogen heterocyclic systems were demonstrated by Sztanke et al. fusing the [1,2,4]triazole and 4,5-dihydroimidazole nuclei [82]. Commercially accessible anilines were first transformed into equivalent N-arylethylenediamines. Subsequent condensation of these compounds in a xylene medium with carbon disulfide resulted in the synthesis of dithiocarbaminic acid derivatives. These compounds underwent cyclization in a boiling solvent to yield 1-arylimidazolidine-2-thiones **(112)**, along with the simultaneous release of H_2S gas. Methyl iodide alkylation of these compounds produced 75–85% yields of 1-aryl-2-methylthioimidazolines **(114)**. Therefore, refluxing these desired compounds with hydrazine hydrate, the excellent yields of 1-aryl-2-hydrazinoimidazolines were generated (Scheme 12.20).

Reaction of compound **(115)** with $HC(OEt)_3$ or derivatives of phenoxyacetic acid **(117)** under standard reflux condition for 6 h furnished the desired product 3-unsubstituted **(116)** or phenoxymethyl **(118–126)** 7-aryl-6,7-dihydroimidazo[1,2,4]triazoles.

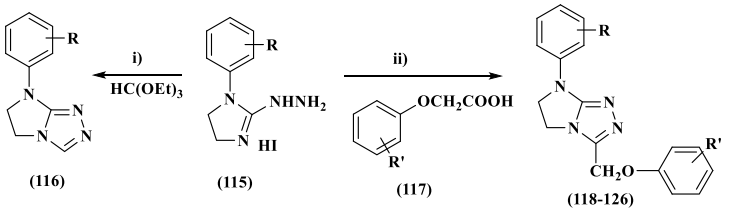
Subsequently, on boiling 2-hydrazineyl-1-(p-tolyl)-4,5-dihydro-1H-imidazole **(127)** with carbon sulfide in aqueous NaOH at room temperature for 30 min under standard reflux condition generates the 7-aryl-6,7-dihydroimidazo[1,2,4]triazol-3-thiol **(128).** Therefore, compound **(128)** treated with methyl iodide under optimized reaction condition afforded the desired product compound **(129)** with good yield. Compared to ampicillin, compound **(129)** demonstrated stronger antibacterial activity with the MIC value of 31.7 mM against Staphylococcus aureus ATCC 25,923 (Scheme 12.21).

Compounds **(120)** and **(125)** were verified against various human tumor cell lines, including LS180, SiHa, and T47D, showing anti-proliferative and apoptotic properties. Against the LS180 cell line, compound **(125)** was found to be the most active, with growth inhibition values of **(129)** and 54% for each tested concentration. On normal cell lines, particularly human skin fibroblasts, they demonstrated reduced cytotoxicity. These findings indicate that compound **(125)** should be investigated as a possible cancer-fighting substance. Compound **(120)** demonstrated effectiveness

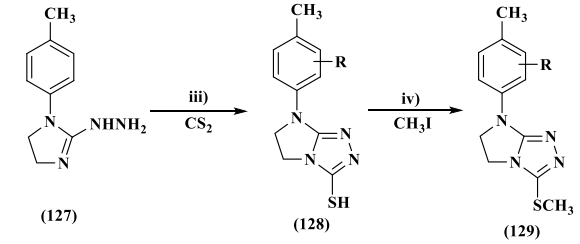


Reaction Conditions: i) aziridine, $AlCl_3$, dry toluene; ii) HCHO, $Na_2S_2O_5$, NaCN, water, reflux; iii) H_2, Ni/Ra, methanol/NH_3, 100 ^{0}C; iv) CS, xylene, rt, 20 min, reflux, 7 h; v) CH_3I/MeOH, rt, 48 h, reflux, 6 h; vi) hydrazine hydrate-MeOH, reflux, 24 h

Scheme 12.20 Synthesis of imidazotriazoles' derivatives

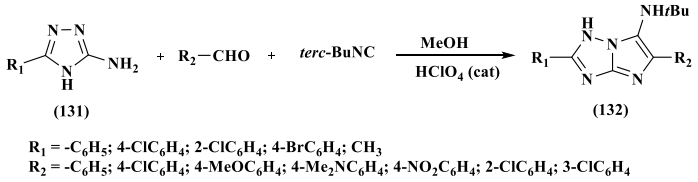


	R	R'
(118)	H	H
(119)	4-OCH_3	4-Cl
(120)	H	2-CH_3; 4-Cl
(121)	4-CH_3	4-Cl
(122)	4-CH_3	2-CH_3; 4-Cl
(123)	4-Cl	4-Cl
(124)	4-Cl	2-CH_3; 4-Cl
(125)	4-Cl	2,4-diCl
(126)	3,4-diCl	2,4-diCl



Reaction conditions: i) DMF, reflux, 6 h; ii) DMF, reflux, 6 h, NaOH 6%; iii) MeOH, NaOH-water, rt, 30 min, reflux, 14 h; iv) abs EtOH, rt, 24 h, reflux, 5 h, Na_2CO_3.

Scheme 12.21 Synthesis of imidazotriazoles derivatives



Scheme 12.22 Multi-component synthetic strategy to obtain imidazotriazoles

in breaking DNA strands in cancer cell lines, indicating that it might hold promise for the generation of new agents capable of breaking DNA strands.

Yan Huang et al. demonstrated the multi-component reactions' methodology for the generation of imidazo[1,2-b]-1,2,4-triazoles. Reaction of 1,2,4-triazoles derivatives **(131)** with aldehydes, and tert-butyl isocyanide using MeOH and HClO4 to obtain the product **(132)** with moderate yield (Scheme 12.22) [83].

12.5 Conclusion

These small, versatile organic scaffolds, known as sulfur- and nitrogen-containing [5,5]-fused ring structures, have found extensive use in medicinal chemistry and physiologically active compounds. Strategies for synthesizing these compounds have developed significantly over the past 15 years, with considering that some of these compounds' chemistry and preparation are not usually novel. This chapter discussed the S-containing [5,5]-fused ring system and a bridgehead nitrogen with numerous applications in medicinal chemistry. Protocol for thiazolotriazoles and imidazo[1,3,4]thiadiazole ring synthesis that utilizes one-pot multicomponent reactions under ideal reaction conditions has been proven to be active and beneficial. Various physiologically active scaffolds were generated by functionalization of the imidazo[1,3,4]thiadiazole ring system on positions 2, 5, and 6. Some miscellaneous reactions are also demonstrated and exhibit diverse medicinal application. However, as the number of applications has increased, imidazothiadiazole has recently attracted the interest of researchers. Imidazotriazoles and imidazothiadiazole derivatives have demonstrated efficacy in treating a broad spectrum of diseases. These compounds remain fascinating platforms for molecular variety, and this chapter certainly contributes to the further development of distinctive synthetic and chemical strategies.

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