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Cite this: *RSC Adv.*, 2024, **14**, 902

Recent advances in the synthesis and utility of thiazoline and its derivatives

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Received 22nd September 2023
Accepted 18th December 2023

DOI: 10.1039/d3ra06444a

rsc.li/rsc-advances

Thiazolines and their derivatives hold significant importance in the field of medicinal chemistry due to their promising potential as pharmaceutical agents. These molecular entities serve as critical scaffolds within numerous natural products, including curacin A, thiangazole, and mirabazole, and play a vital role in a wide array of physiological reactions. Their pharmacological versatility encompasses anti-HIV, neurological, anti-cancer, and antibiotic activities. Over the course of recent decades, researchers have extensively explored and developed analogs of these compounds, uncovering compelling therapeutic properties such as antioxidant, anti-tumor, anti-microbial, and anti-inflammatory effects. Consequently, thiazoline-based compounds have emerged as noteworthy targets for synthetic endeavors. In this review, we provide a comprehensive summary of recent advancements in the synthesis of thiazolines and thiazoline-based derivatives, along with an exploration of their diverse potential applications across various scientific domains.

1. Introduction

Heterocyclic compounds play a pivotal role in various domains such as pharmaceuticals, catalytic ligands, fine chemicals, and agrochemicals.[1] Among these compounds, thiazolines, sulfur-containing analogs, have received relatively less attention. Thiazolines constitute a specific class of organic compounds characterized by a five-membered ring structure composed of

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four carbon atoms and one sulfur atom, with the potential for a nitrogen atom substitution (Fig. 1). This heterocyclic ring system is a derivative of thiazole, a structurally similar compound featuring sulfur and nitrogen atoms within the five-membered ring. Thiazolines exhibit diverse applications and attract interest in both organic and medicinal chemistry (Fig. 2). Their broad biological relevance has resulted in their presence in a wide range of synthetic and natural products (Fig. 3), thereby enhancing their significance over time.[2] While encountering unsubstituted thiazolines in their pure form is rare, their derivatives are more prevalent, with specific derivatives showcasing bioactivity. A noteworthy aspect of thiazolines is their occurrence in various biologically active molecules, including specific antibiotics and natural products (Fig. 4). Thiazolines can also be identified in certain vitamins and coenzymes, underscoring their importance in biological processes.[3] Importantly, thiazolines are synthesized through the conventional post-translational modification of cysteine residues.[4]

Within the extensive class of thiazolines, a diverse range of heterocyclic compounds, certain volatile derivatives stand out for their significant role in flavor and food chemistry.[5] To date, researchers have identified over 30 distinct thiazoline structures present in food and natural sources,[6] with notable examples

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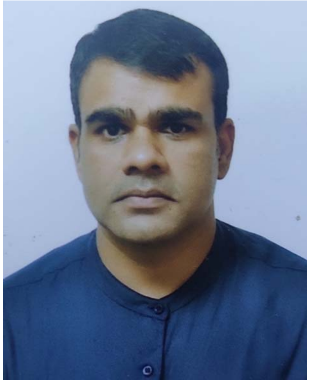

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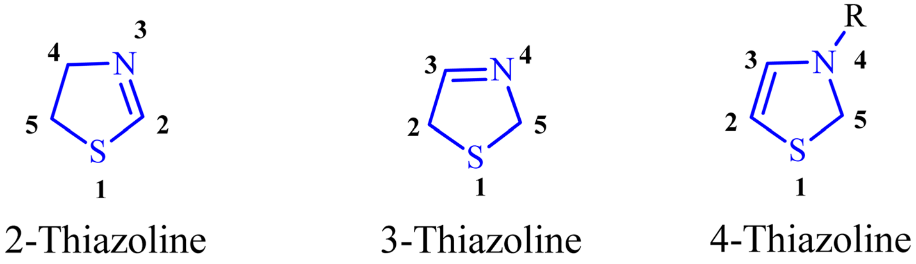


Fig. 1 General structure and numbering of the thiazoline heterocycle.

found in cooked meat[7] and specific exotic fruits such as litchis (Fig. 2).[8]

Thiazoline heterocycles can be found in a multitude of bioactive natural compounds of peptide origin (Fig. 3).[9] Thiazolines can be further functionalized to introduce various chemical groups, making them versatile building blocks for the synthesis of diverse organic molecules. The thiazoline ring constitutes a structural component in various compounds, with the apratoxins serving as prominent contemporary illustrations (Fig. 3).[10] These compounds were initially isolated from the marine cyanobacterium *Lyngbya majuscule* by Harvey ex Gomont and subsequently identified by Moore, Paul, and other researchers.[11] Thiazoline imparts conformational stability and facilitates binding to proteins, RNA, and DNA by serving as a recognition site. The amide group of the preceding residue undergoes nucleophilic attack by the cysteine thiol group, followed by a dehydration step, resulting in the formation of thiazolines from peptides.[12] Although, most chemical processes use serine residues, however, cysteine residues are used in the biosynthetic pathway of thiazolines.[13] In processed foods, the Maillard reaction occurs, leading to the generation of these molecules through interactions involving dicarbonyl compounds, aldehydes, ammonia, and hydrogen sulfide.[14] The pharmacological attributes of thiazoline have also been investigated. Some thiazoline compounds exhibit noteworthy properties such as anti-HIV[15] and anti-cancer[16] activities, and they are also capable of inhibiting cell division (Fig. 4).[17]

In 1909, Richard Willstatter successfully synthesized the first thiazolines by dialkylating thioamides.[18] Thiazoles substituted in the industrial setting act as precursors for the synthesis of the amino acid cysteine, wherein 2-aminothiazoline-4-carboxylic acid serves as an intermediate compound during the commercial manufacturing process of L-cysteine.[19]

Thiazolines play a pivotal role in the synthesis of pharmaceuticals and biologically active natural compounds, exemplified by micacocidin, which exhibits antibacterial properties (Fig. 3).[20,21] The role of firefly luciferin in the bioluminescent process of fireflies is extensively documented in scientific literature.[22] Numerous fascinating natural compounds, among them curacin A, largazole, and tantazole B, feature thiazoline

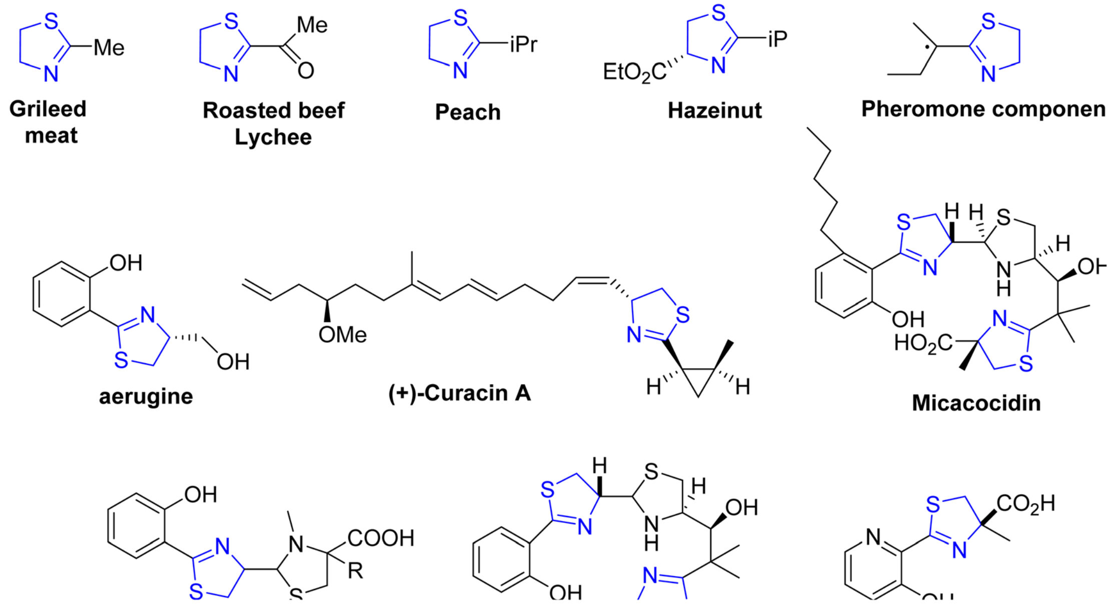


Fig. 2 Derivatives of thiazolines sourced from natural origins.

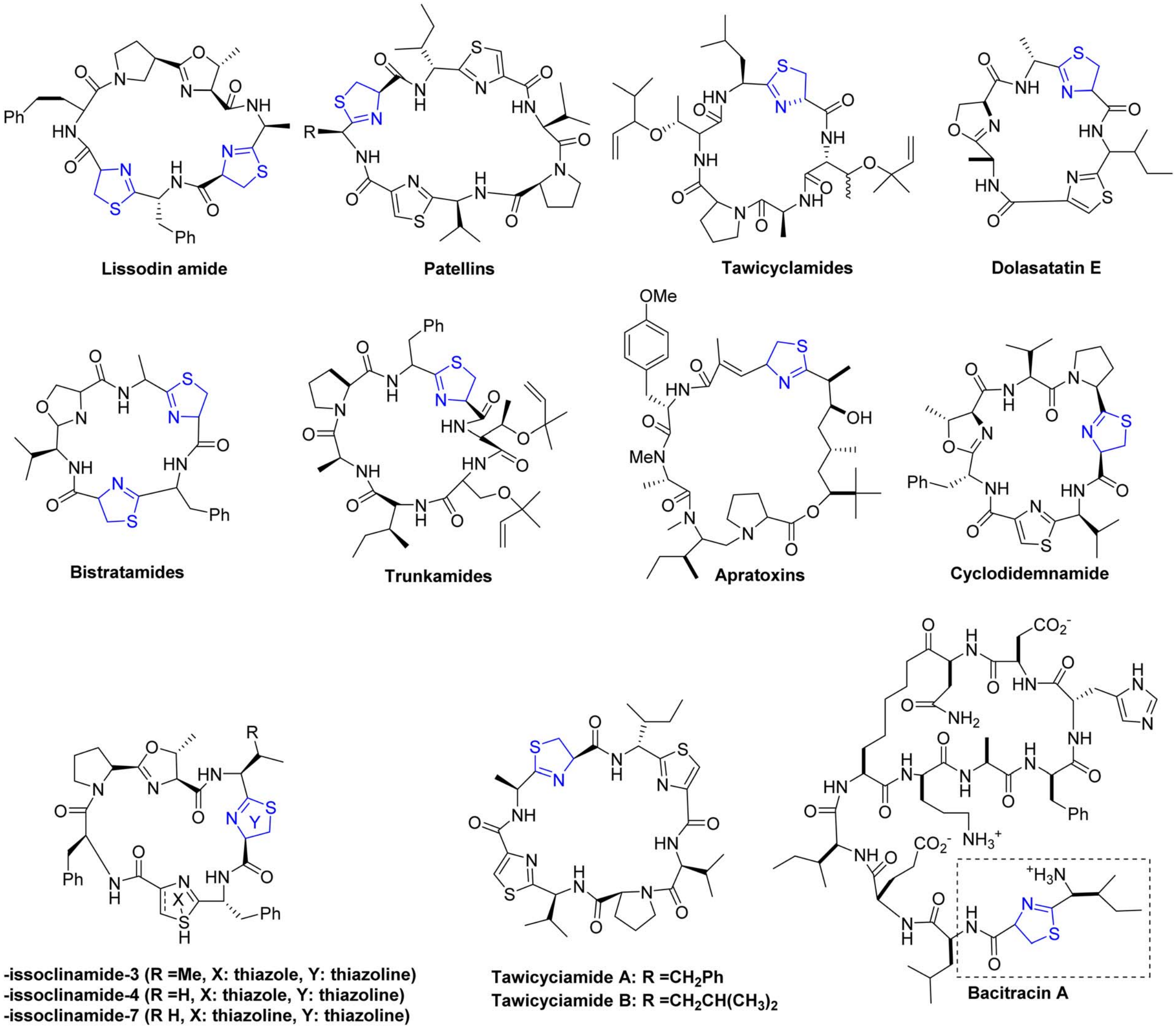


Fig. 3 Cyclopeptide alkaloids containing thiazoline as structural segments.

rings within their molecular structures.[23,24] They also serve as ligands in coupling reactions catalyzed by transition metals.[25] Due to the distinctive properties of sulfur, there has been a recent surge in research on the chemical attributes of thiazolines. Furthermore, thiazoline derivatives have garnered increased attention as valuable ligands in chemical synthesis and asymmetric catalysis.[26] Overall, thiazolines are intriguing compounds with important roles in both natural products and synthetic chemistry. Their unique structural features and diverse applications continue to make them a subject of interest for researchers in various fields. An updated exploration of this field is imperative, given the expanding applications of thiazolines over time. Therefore, our objective is to provide a comprehensive overview of thiazolines, encompassing their chemistry, synthetic methodologies, and applications that have contributed to their increased utilization within the pharmaceutical sector, as ligands in asymmetric catalysis, and in organic synthesis over the past fifteen years. We have exclusively focused on the reports that have not been addressed in prior literature.[27,28]

2. Recent advances in the synthesis

Jeon *et al.*[29] reported a metal-free oxidative di-functionalization of *N*-allylthioamides. In this methodology, thiazoline frameworks were synthesized under mild conditions by employing PIDA as the oxidant in conjunction with electron-deficient amines. Various benzothioamides and substrates with differing electron densities were used to produce thiazolines **2a–2f** in high yields. Additionally, this process was applicable to amides derived from both thiophene **2h** and pyridine **2g**, as well as an aliphatic amide **2i**, demonstrating compatibility under standard reaction conditions (Scheme 1).

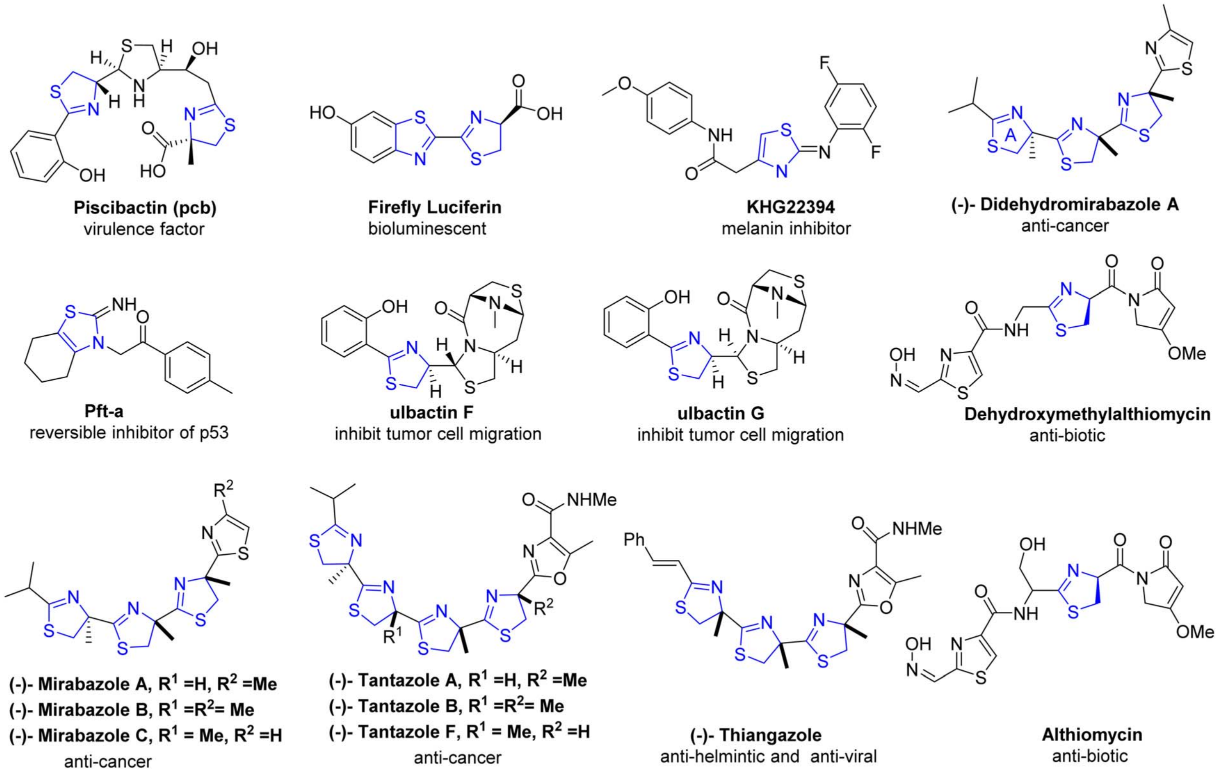
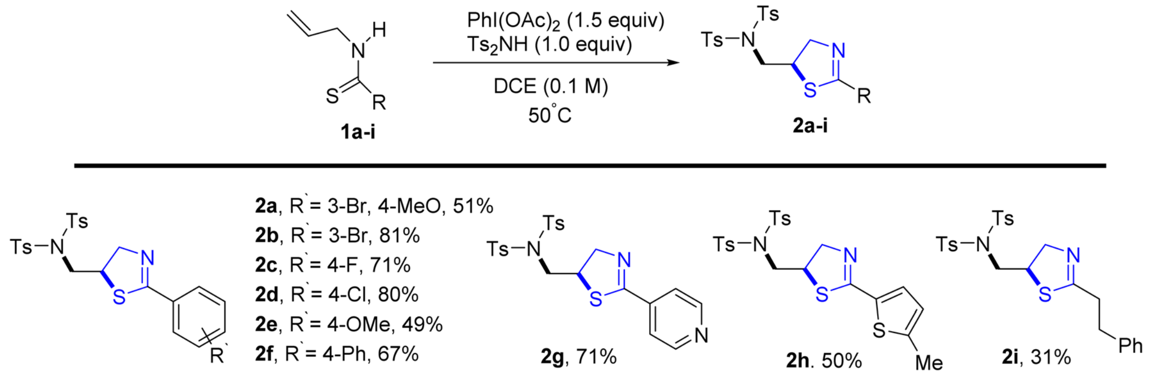


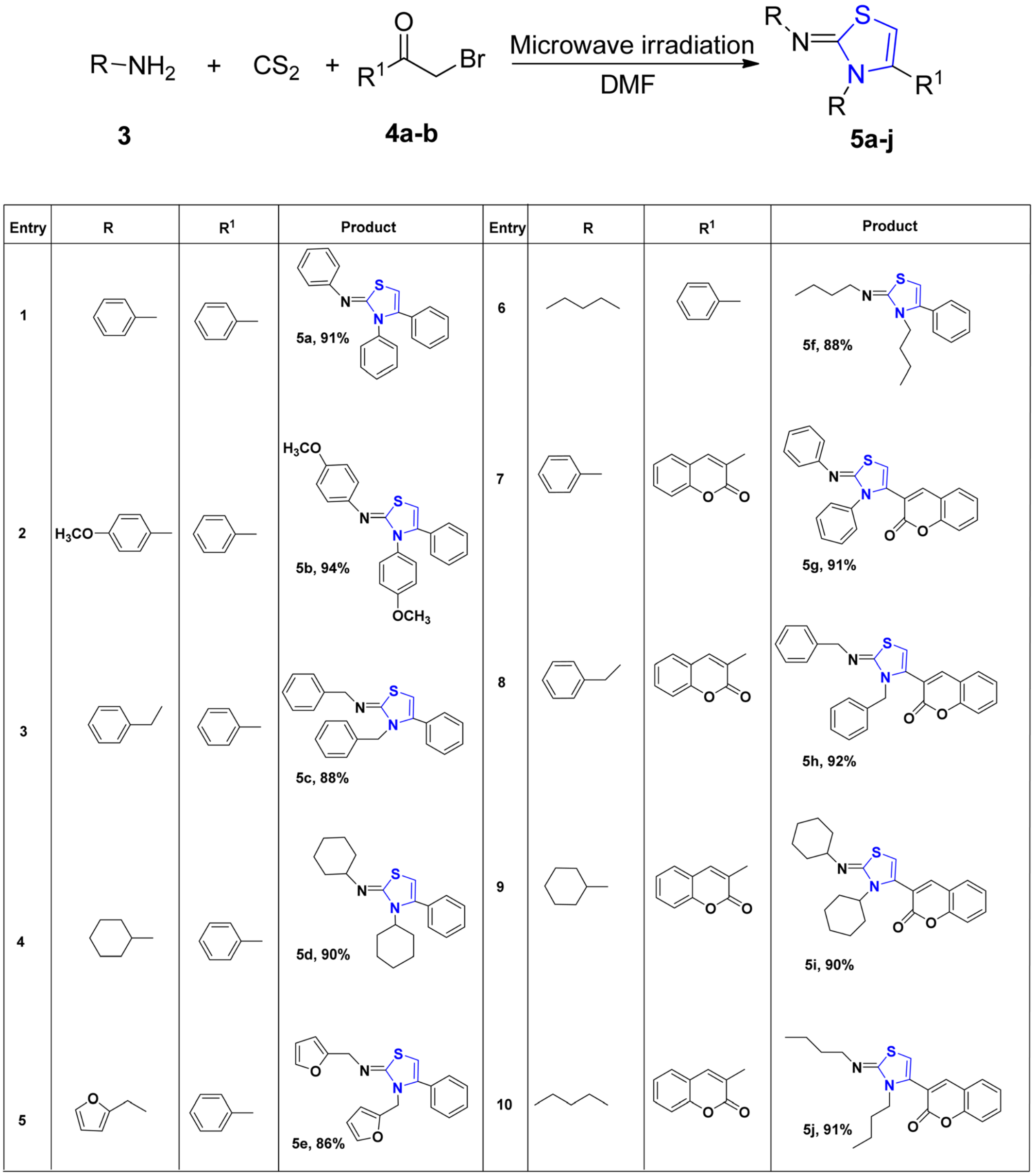
Fig. 4 Nature derived biological active scaffolds in relevance of thiazoline.



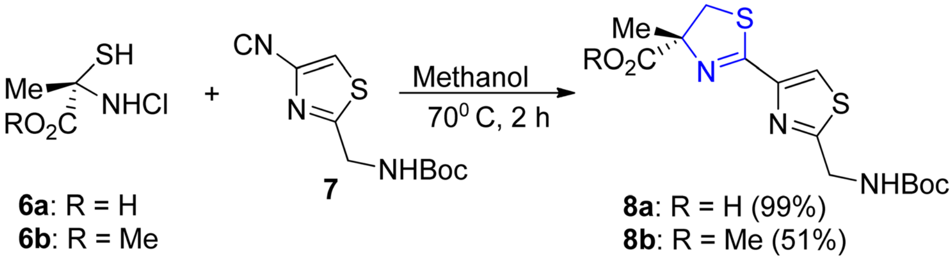
Scheme 1 Synthesis of thiazolines **2a–2i**.

Multicomponent reactions (MCRs) are gaining growing appeal due to their enhanced efficiency, reduced waste generation, atom economy, and straightforward procedures.[30] With the use of microwave technology, Appalanaidu *et al.*[31] developed a novel one-pot technique to obtain the thiazoline analogues following a 3-CR between carbon disulfide, 1°-amine **3** and differently substituted bromo acylketones **4**. This methodology enables the synthesis of desired compounds in a single step, yielding excellent yields, rendering it particularly valuable in the fields of synthetic and medicinal chemistry. Various primary amines, including aniline, butylamine, furan-2-ylmethanamine, benzylamine, cyclohexylamine, 2-bromo-1-phenylethanone, and substituted anilines, were subjected to treatment with CS_2 to produce the HBr salt of the corresponding thiazoline derivatives. Subsequently, these obtained salts were neutralized using a saturated solution of Na_2CO_3, yielding the final thiazoline analogs **5a–5j** (Scheme 2).

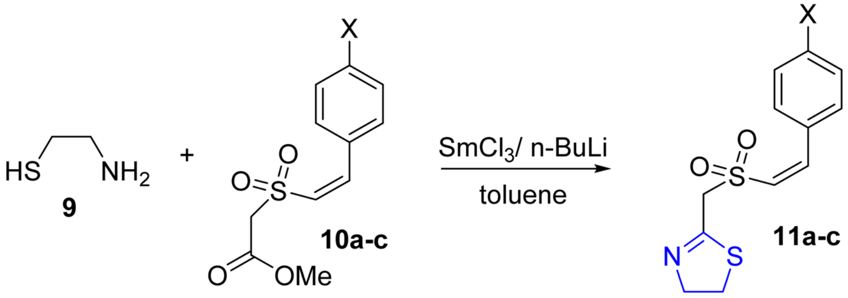
Four different research laboratories have used Pattenden's method[32] for thiazoline synthesis to achieve the synthesis of largazole, which is isolated from fungi.[33–36] Thiazoline–thiazole



Scheme 2 Synthesis of thiazoline derivatives 5a–5j.



Scheme 3 Synthesis of thiazoline thiazole molecule 8a–b.



Compound	10	11
a	H	H
b	Me	Me
c	Cl	Cl

Scheme 4 Synthesis of thiazolines **11a–c**.

acid **8a** can be obtained in a quantifiable yield through the cyclo-condensation of α-methylcysteine hydrochloride **6a** with nitrile **7** under optimized conditions. These conditions involve maintaining a temperature of 70 °C for 2 hours in a phosphate solution with a pH of 5.95 in methanol. However, when conducting the reaction using methyl ester **6b** in EtOH at 50 °C for 72 hours with the addition of Et_3N, lower yield of the thiazole ester **8b** was observed (Scheme 3).

Padmavathi *et al.*[37] synthesized thiazolines **11a–c** through the condensation of *Z*-styryl sulfonylacetate **10a–c** with aminothiol **9**, catalyzed by $SmCl_3$ in the presence of *n*-butyllithium (Scheme 4). The $SmCl_3$-activated carbonyl carbon served as the site of nucleophilic attack by the thiol during the reaction.

Alom *et al.*[38] have successfully outlined a practical synthetic approach for the important pharmaceutical motif, thiazoline **14** and **15**. This method utilizes a straightforward one-pot process involving intermolecular alkene **12** and thioamide **13** substrates that are readily available and straightforward to obtain. Notably, it exhibits compatibility with a diverse array of functional groups, as demonstrated in Scheme 5a and b.

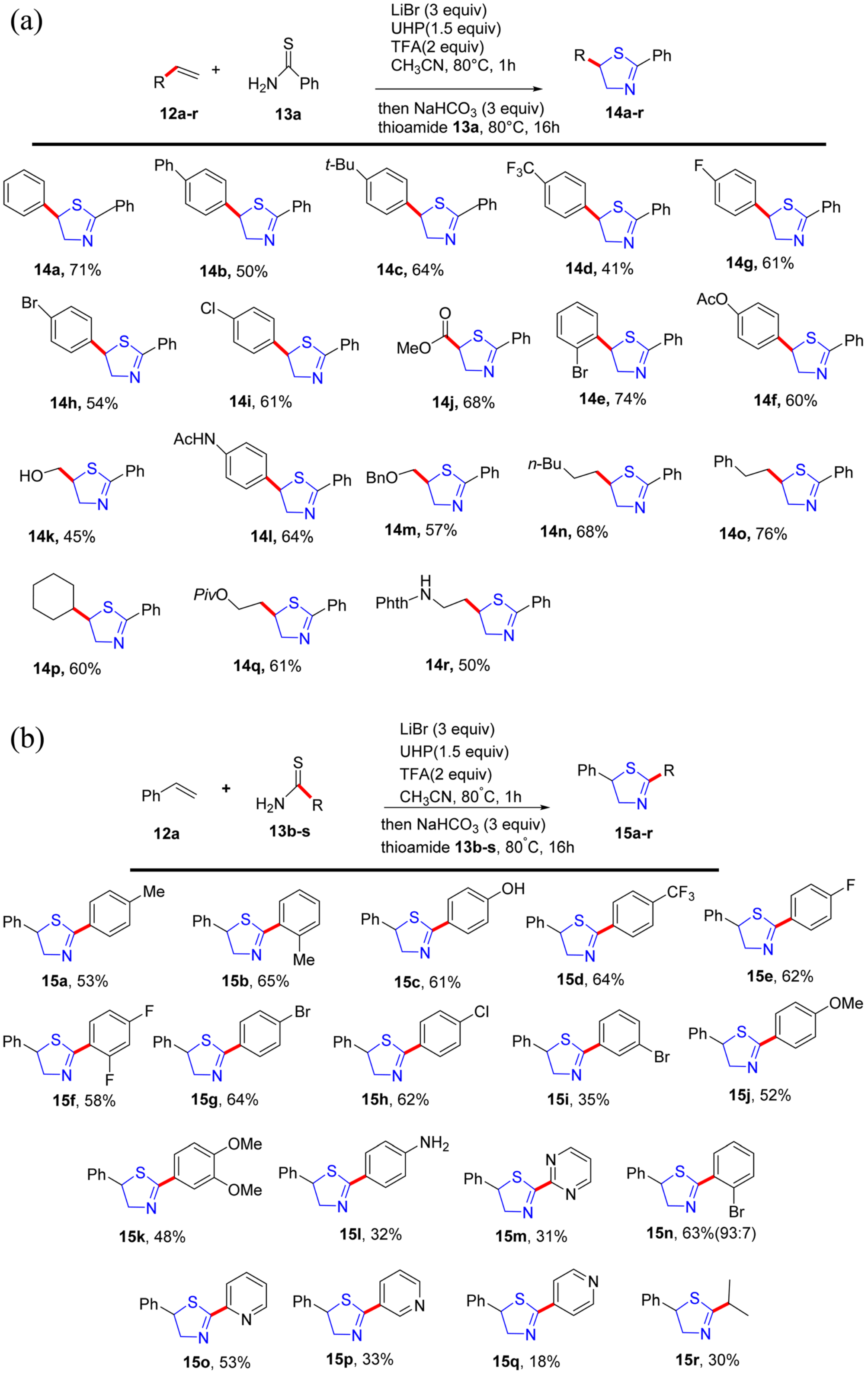
The transformation of amino thiols into thiazolines through the utilization of α,α-difluoroalkylamines gives high yields under favorable conditions (Scheme 6). In accordance with this scheme, Fukuhara *et al.*[39] synthesized phenyl thiazoline **18a** and *tert*-butyl thiazoline **18b** through the reaction of an ester **16** with **17a** (DFBP) and **17b** (DFMPP), respectively. To prevent racemization of the carbon containing the carboxylate group, triethylamine was introduced after the addition of difluoroalkylamine.

Alsharif *et al.*[40] designed and developed an approach with a primary focus on synthesizing novel thiazolines. However, the current methodologies present challenges in the convenient synthesis of thiazoline derivatives **21a–l** and **23a–p**, as depicted in Scheme 7a and b. The investigation relied on hexafluoroisopropanol, a solvent known for its strong hydrogen bonding and polar characteristics. Due to its recyclability and recoverability, coupled with the fact that most reactions do not necessitate extensive work-up and rigorous purification, HFIP stands out as an environmentally friendly solvent.[41] HFIP also facilitates a wide spectrum of reactions.[42]

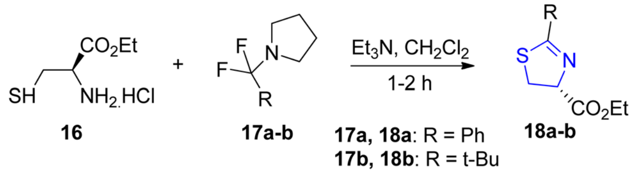
Kamila *et al.*[43] recently unveiled an efficient approach for the synthesis of arylated thiazolines, utilizing aminothiol **24** and aryl ketonitriles **25a–k** as substrates, all achieved without the presence of any solvents (Scheme 8). The incorporation of microwave radiation facilitated the condensation process. The authors outlined a methodology encompassing a thiol nucleophilic attack, water elimination, and the formation of an acrylonitrile derivative. Subsequently, the amino group participated in an intramolecular conjugate attack on the acrylonitrile derivative, resulting in the desired 2-aryl-thiazolines **26a–k**, with acetonitrile removal as the final step.

Sakakura *et al.*[44] reported the synthesis of thiazolines **28a–d** through a dehydrative cyclization process of *S*-unprotected cysteine dipeptide **27** catalysed by molybdenum(VI). Notably, under optimized conditions (Scheme 9), the epimerization of the C-2-exomethine group was observed to be less than 6%.

Viñuelas-Zahínos *et al.*[45] reported the synthesis of the thiazoline-based ligand ATHTd **31**. The synthetic procedure for **31** involved addition of an ethanolic solution of 2-acetyl-2-thiazoline **29** to the ethanolic solution of the hydrochloride salt of (2-thiazolin-2-yl) hydrazine **30**, along with potassium acetate. The reaction mixture was subsequently refluxed for 2 hours to yield compound **29** (Scheme 10). Characterization was conducted using various spectroscopic techniques, elemental analysis, and X-ray diffraction. Furthermore, ATHTd **31** was employed for complexation with Ni, Zn, and Cu metal ions, resulting in the corresponding complexes $[Ni(ATHTd)_2](NO_3)_2\cdot H_2O$, $[NiCl(ATHTd)(H_2O)_2]Cl$, $[ZnCl_2(ATHTd)_2]$, and



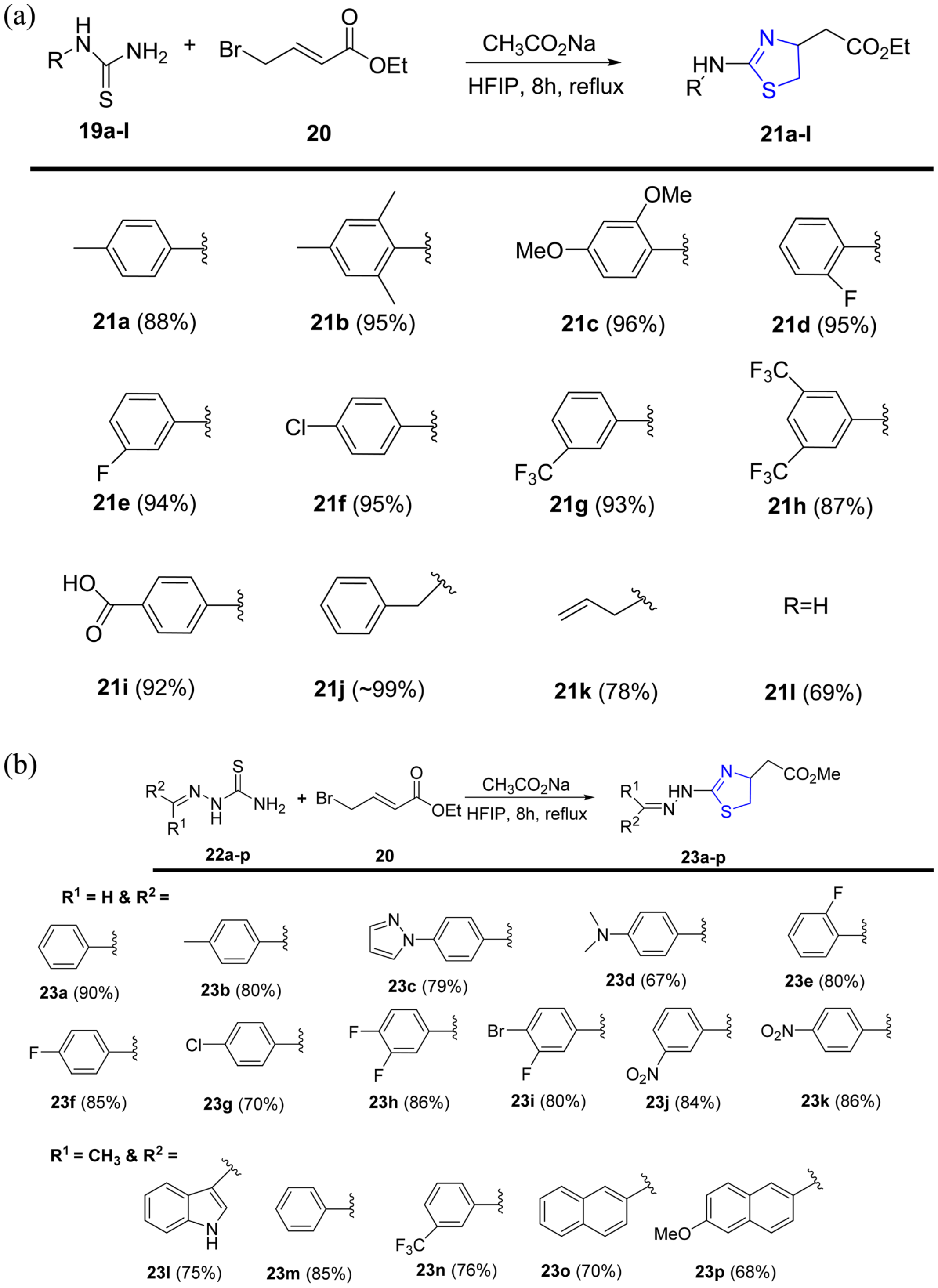
Scheme 5 (a) Substrate scope for alkene. (b) Substrate scope for thioamide.



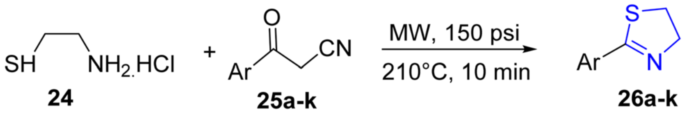
Scheme 6 Synthesis of thiazolines **18a–b**.

$[CuCl_2(ATHTd)]$. These complexes were also subjected to solid-state characterization using spectroscopic techniques and X-ray diffraction, along with elemental analysis.

Attanasi *et al.*[46] employed thioamides **33a–b** and cycloalkenyl-1-diazenes **32a–c** for the synthesis of diverse cycloalkyl-thiazolines **34a–c**. Subsequently, these compounds were further converted into fused cycloalkyl–thiazolinepyrazole

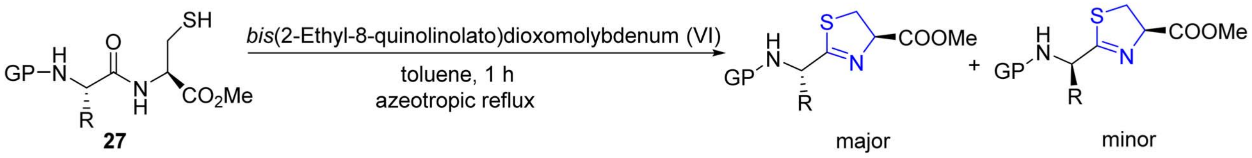


Scheme 7 (a) Synthesis of thiazoline derivatives **21a–l**. (b) Synthesis of thiazoline derivatives **23a–p**.



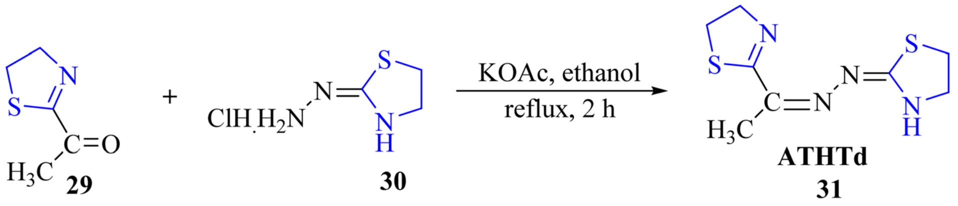
Compound (a-k)	25/26	Compound (a-k)	25/26
a	Ar= Ph	**g**	Ar = 2,4-$(MeO)_2$-C_6H_3
b	Ar = 4-Me-C_6H_4	**h**	Ar = 2,4-(Cl)2-C_6H_3
c	Ar = 4-MeO-C_6H_4	**i**	Ar = 3,4,5-$(MeO)_3$-C_6H_2
d	Ar = 4-Cl-C_6H_4	**j**	Ar = 4-CN-C_6H_4
e	Ar = 4-F-C_6H_4	**k**	Ar = 4-Br-C_6H_4
f	Ar = Naphth-1-yl		

Scheme 8 Synthesis of thiazoline derivatives **26a–k**.

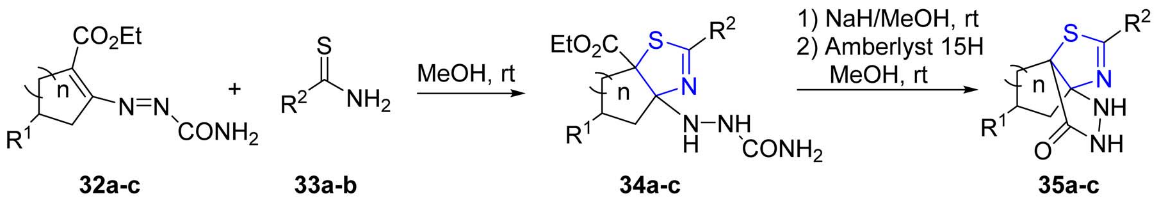


28a: PG = Cbz, R= Me (dr = 99:1)
28b: PG = Cbz, R= Bn (dr = 98:2)
28c: PG = Boc, R= Me (dr = 94:6)
28d: PG = Fmoc, R= Me (dr = 96:4)

Scheme 9 Synthesis of thiazolines **28a–d**.



Scheme 10 Synthesis of ATHTd **31**.



35a: n =1, R^1 = H, R^2 = 2-MeO-C_6H_4
35b:n =2, R^1 = H, R^2 = C_6H_5
35c :n =2, R^1 = Me, R^2 = C_6H_5

Scheme 11 Synthesis of cycloalkyl–thiazolines **34a–c** and fused cycloalkyl–thiazolinepyrazole complexes **35a–c**.

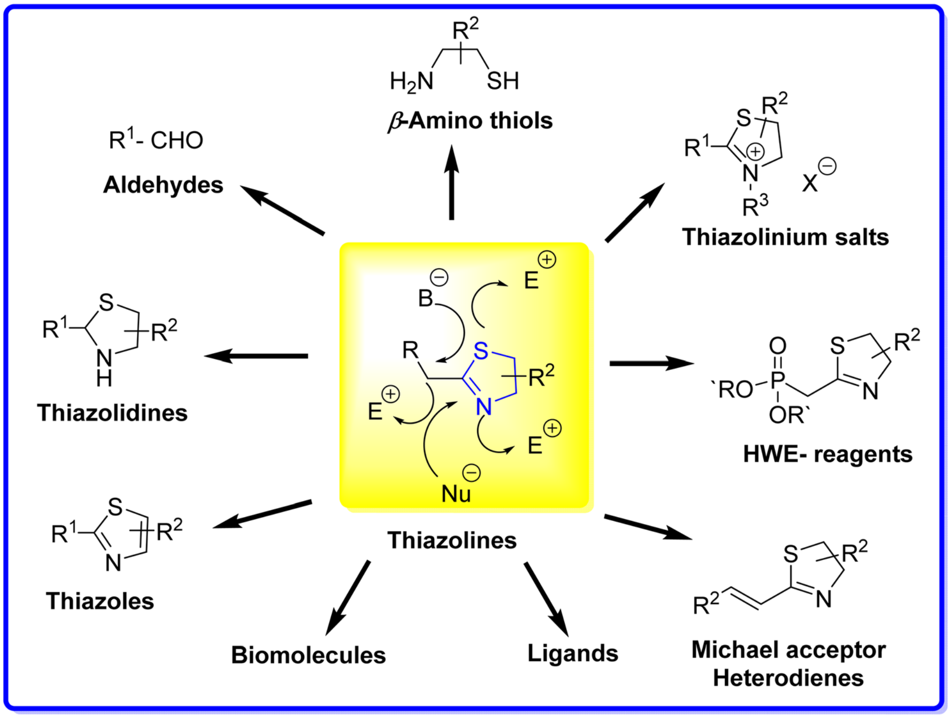
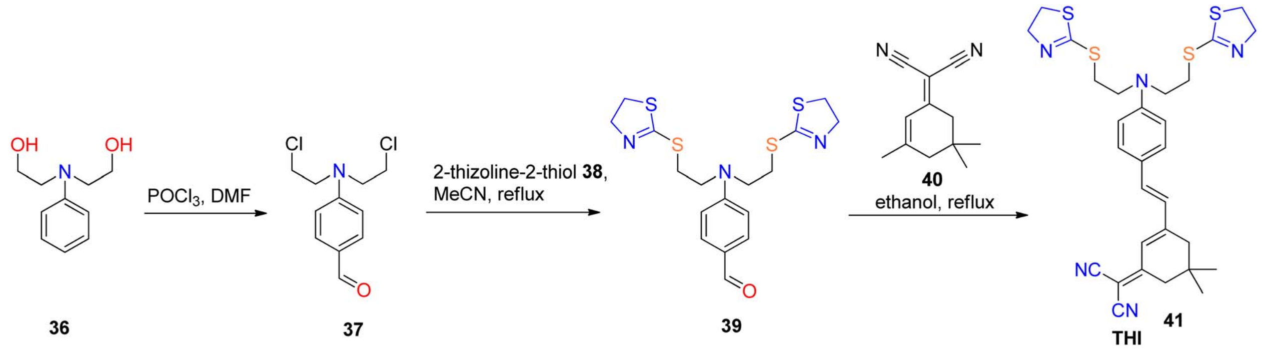


Fig. 5 Reactivity and applications of thiazolines.



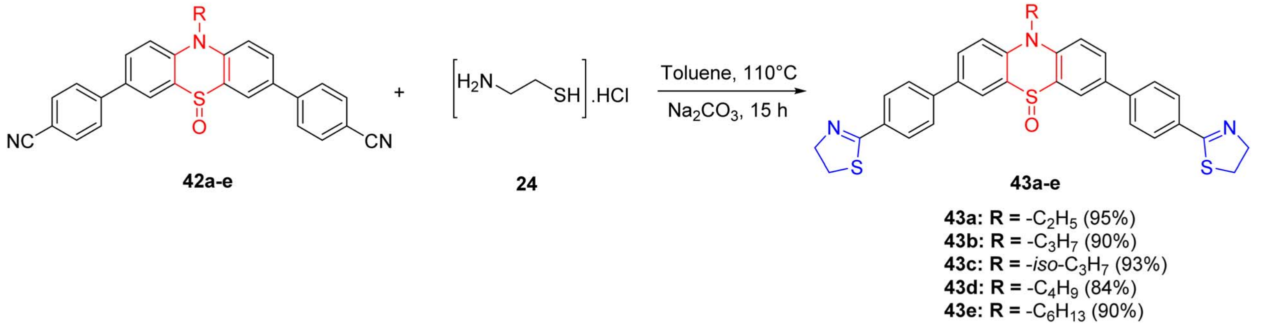
Scheme 12 Synthesis of new red-emitting fluorescent probe (THI) **41**.

complexes **35a–c**, as depicted in Scheme 11 to synthesize a variety of cycloalkyl–thiazolines **34a–c**, which were further transformed into fused cycloalkyl–thiazolinepyrazole complexes **35a–c** (Scheme 11).

3. Reactivity and application of thiazolines

Thiazolines exhibit reactivity due to the presence of two nucleophilic centres localized on the nitrogen and sulfur atoms, along with an electrophilic centre on the carbon atom of the C═N bond. This versatility makes thiazolines as valuable reagents in the synthesis of diverse compounds, including carbonyls,[47,48] β-amino thiols,[49,50] thiazoles,[51,52] and thiazolinium salts[53] (Fig. 5). When treated with a base, the resulting carbanion can engage with various electrophiles, giving rise to a range of functionalized thiazolines. Examples include thiazoline phosphonates, serving as valuable synthetic intermediates in applications such as Horner–Wadsworth–Emmons (HWE) reactions,[54] and vinyl thiazolines, which function as Michael acceptors or heterodienes.[55] In industrial applications, substituted thiazoles play a crucial role as precursors in the synthesis of the amino acid cysteine. Specifically, 2-aminothiazoline-4-carboxylic acid serves as an intermediate in the commercial manufacturing process of L-cysteine.[19]

Furthermore, thiazolines with a chiral centre find applications as chiral auxiliaries or building blocks, enabling the



Scheme 13 Synthesis of novel "push–pull" compounds **43a–e**.

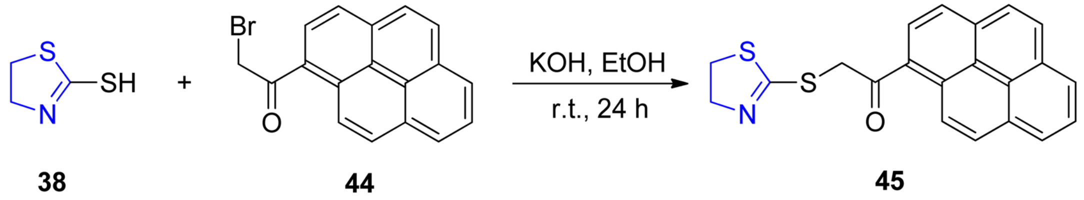
synthesis of more complex chiral structures. These structures include thiazoline-containing biomolecules[56,57] and chiral ligands utilized in asymmetric catalysis.[58,59] The discussion here encompasses the role of thiazolines in fluorescence, catalysis, pharmacology, and other diverse fields.

3.1. Fluorescence property

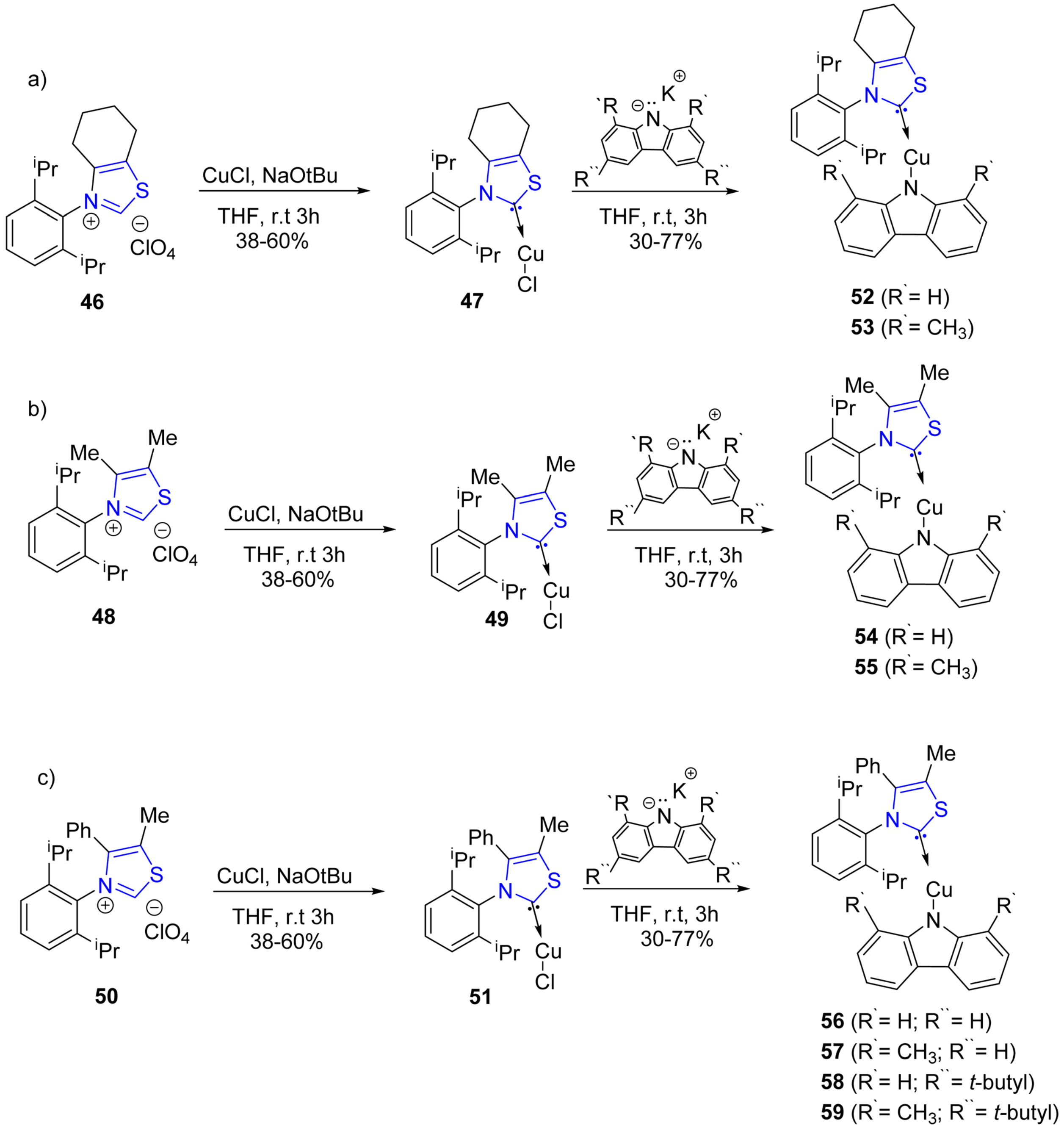
Fluorescence-based sensors exhibit several merits, including ease of manipulation and operation, swift response kinetics, exceptional sensitivity, straightforward instrumentation, cost-effectiveness, and the attainment of low detection limits. Consequently, these attributes render them a preferential choice when contrasted with alternative analytical methodologies.[60,61] Diverse sensor modalities have been employed for the detection of metal ions, encompassing quantum dots (QDs), nanomaterials, organic molecules, and biopolymers.[62,63] Nevertheless, there remains an imperative requirement for the development of highly sensitive and biocompatible near-infrared (NIR) sensors capable of discerning heavy metal ions within biological systems. Recent times have witnessed a notable surge in enthusiasm for fluorescent sensors, owing to their substantial potential in the realm of ion detection within biologically relevant media, characterized by their exceptional selectivity and sensitivity.[64,65]

Even when present at low concentrations, the harmful contaminant mercury (Hg) can exert significant deleterious effects on both the environment and human health. Consequently, there is an acute demand for methodologies that exhibit high sensitivity, efficacy, and precision in detecting mercuric ions within biological matrices. Erdemir *et al.*[66] engineered a fluorescent sensor designated as THI **41**, characterized by the inclusion of a Hg^{2+}-sensitive thiazoline moiety, an electron-deficient dicyanovinyl functionality, and an electron-rich diethylamino group. The strong affinity between S^{2-} ions and Hg^{2+} ions was observed to induce a reversal in the binding interaction between probe **41** and Hg^{2+} ions. Additionally, probe **41** manifested a positive solvatochromic effect attributable to intramolecular energy transfer, facilitated by the diethylamino functionality, toward the dicyanovinyl group. Moreover, it was found to be highly selective for Hg^{2+} ions. The synthesis of 4-(bis(2-chloroethyl)amino)benzaldehyde **37** followed a previously established procedure.[67] Subsequently, 2-thiazoline-2-thiol **38** was reacted with benzaldehyde **37** in acetonitrile, and the resulting mixture was refluxed for a duration of 72 hours to yield compound **39**. In the final step of the synthesis, compound **39** was subjected to reflux with compound **40** in a mixture of piperidine and ethanol for a duration of 12 hours, resulting in the formation of the fluorescent probe THI **41**, as depicted in Scheme 12. The determined detection limit for THI **41** was 7.22 mM, and it exhibited a satisfactory linear correlation with varying levels of Hg^{2+}. Furthermore, employing a confocal laser scanning microscope, it was conclusively demonstrated that THI **41** can serve as a proficient fluorescent probe for visualizing Hg^{2+} ions within living HeLa cells, without any observable adverse effects on cervical cancer and epithelial cells.[51]

Within the realm of chemistry, the detection of volatile acids represents an economically promising domain. This is primarily attributed to the pivotal role of pH estimation in ascertaining acidity levels, which holds significant importance across a spectrum of applications encompassing chemical reactions, biological processes, the pharmaceutical industry, and environmental monitoring.[68,69] Chaudhary *et al.*[70]



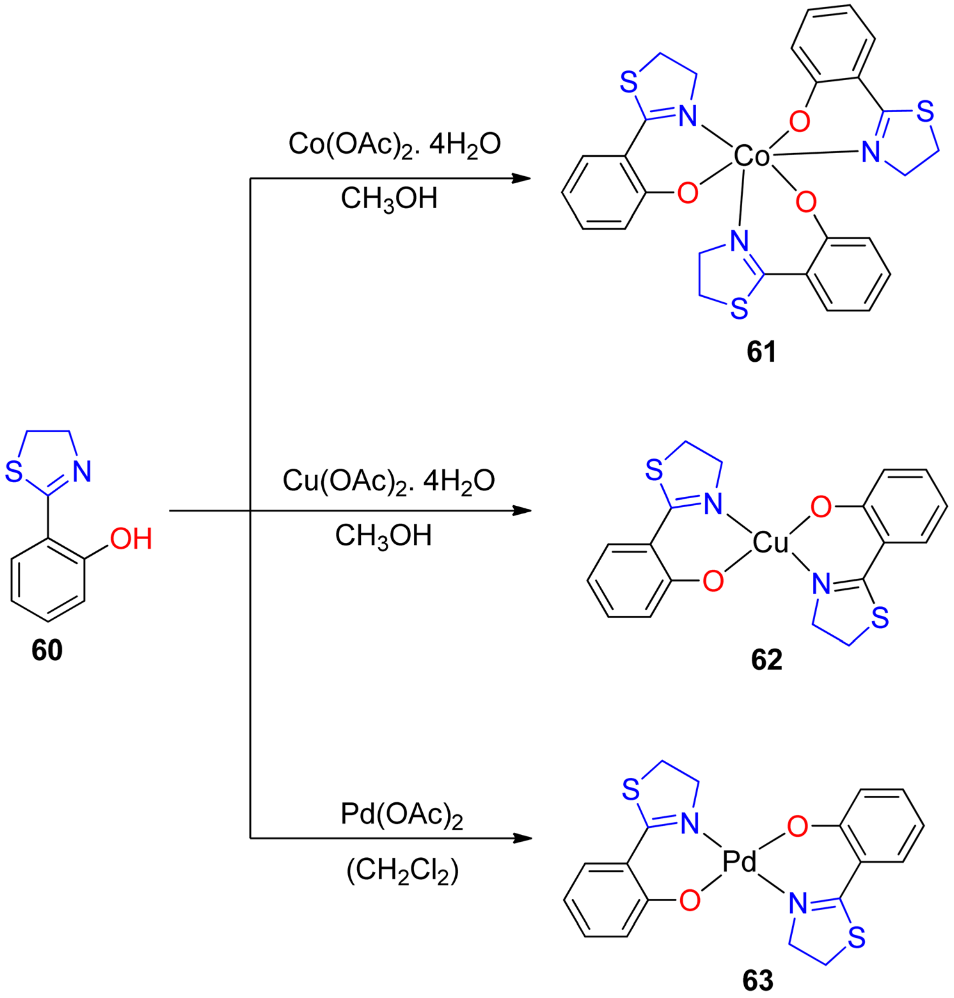
Scheme 14 Synthesis of a "turn-on" thiazoline–pyrene sensor **45**.



Scheme 15 (a–c) Synthesis of CMA emitters **52–59**.

successfully synthesized six novel compounds, denoted as **43a–e**, exhibiting acid-sensitive attributes with exceptional yields ranging from 84% to 95%. These compounds were designed with a thiazoline ring serving as the electron acceptor moiety and a phenothiazine ring acting as the electron-donor unit. The synthesis of thiazoline-based compounds **43a–e**, hinging on the phenothiazine-5-oxide ring, was accomplished utilizing a previously established methodology (Scheme 13).

The reaction involved refluxing the precursor molecules **42a–e** in the presence of cysteamine hydrochloride **24** and sodium carbonate in toluene under a nitrogen atmosphere at 110 °C for a duration of 15 hours. Notably, compounds **43a–e** exhibited robust fluorescence both in solution and in solid states. The incorporation of phenyl rings endowed these compounds with the ability to detect volatile acids, such as trifluoroacetic acid (TFA) and hydrochloric acid (HCl), owing to the presence of a thiazoline unit. In absorption and emission experiments, a distinctive red-shift was observed, attributed to the protonation of the thiazoline ring, induced by potent intramolecular charge transfer (ICT) interactions. The addition of triethylamine



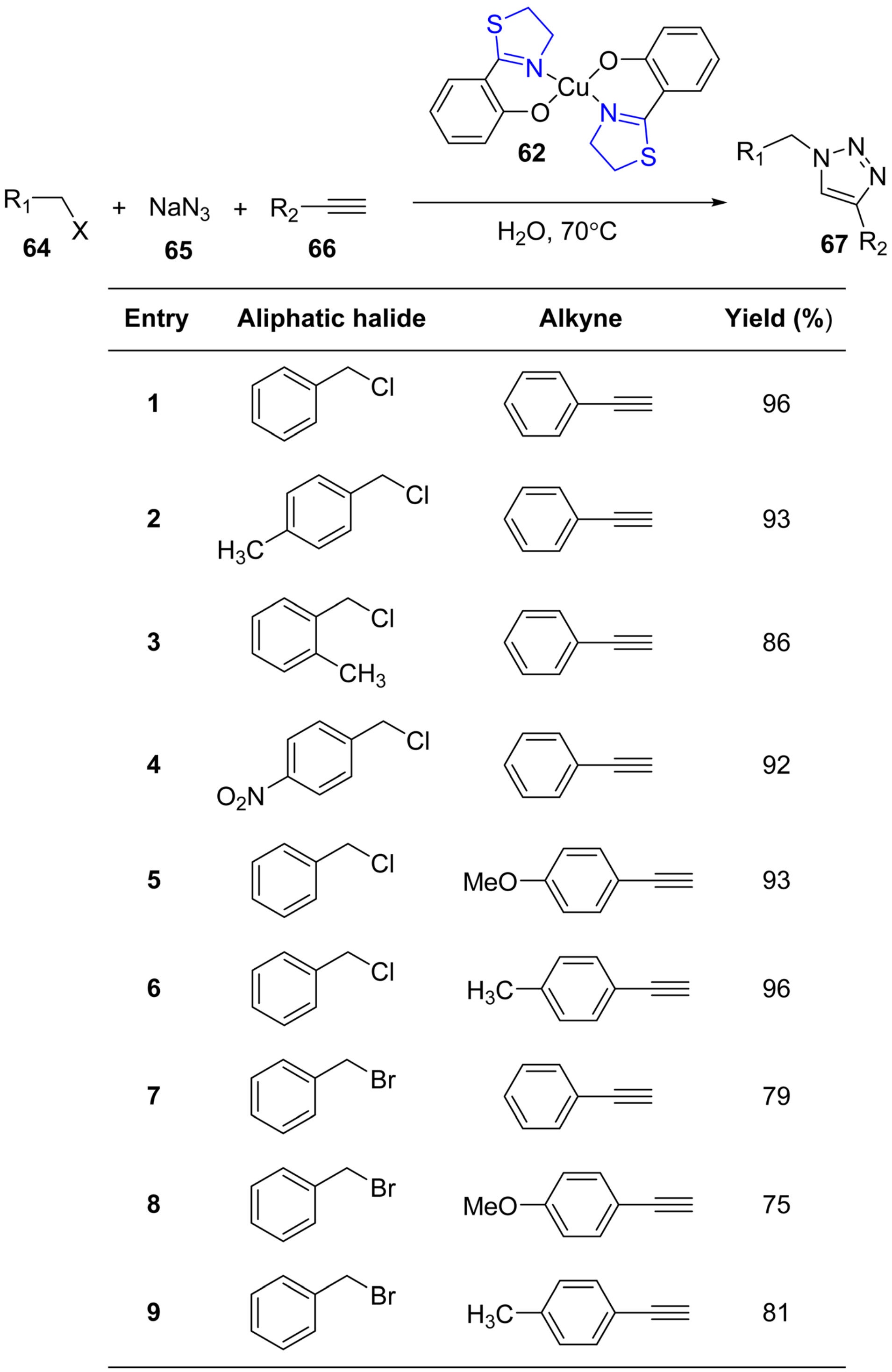
Scheme 16 Synthesis of complexes **61–63**.

(TEA) was found to reverse these spectral alterations. Upon exposure to acids, a distinct color change from colorless to yellow was observed, which could subsequently be reverted to colorless upon the addition of TEA.

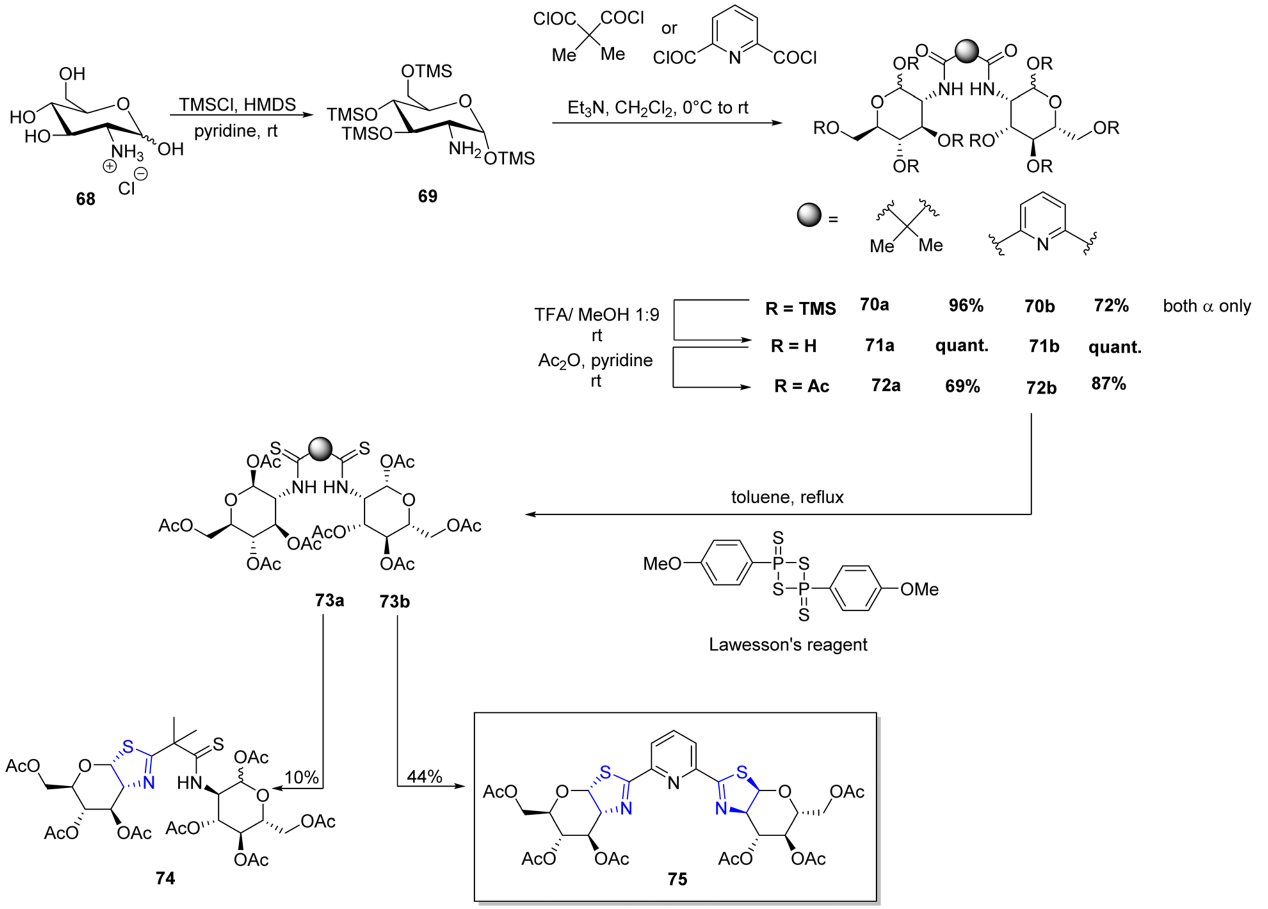
Compound **43c** exhibited a remarkable minimum detection limit of 0.98 parts per million (ppm) for TFA, while compound **43a** demonstrated a noteworthy minimum detection limit of 13.1 parts per billion (ppb) for HCl. Further elucidation of the energy gap between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of compounds **43a–e**, as well as their protonated analogues, was conducted through density functional theory (DFT) studies.[55]

Copper ions in the form of Cu^{2+} hold a dual significance in scientific contexts, as they function as both significant metal pollutants and essential micronutrients for all known life forms. In the case of Cu^{2+} ions, a plethora of fluorescent chemosensors are available; however, only a limited subset of these sensors are categorized as "turn-on" sensors, primarily because Cu^{2+}, being paramagnetic, exerts a quenching effect on fluorescence.[71] Preferred among these are the "turn-on" fluorescence sensors, as they exhibit a reduced susceptibility to false positive signals and offer enhanced multiplexing capabilities.[72] Utilizing a one-pot synthetic approach, Wang *et al.*[73] successfully synthesized a sensor denoted as **45**, which incorporated both thiazoline **38** and pyrene moieties **44**. This sensor was subsequently employed to enhance the fluorescence emission of pyrene monomers, thereby enabling the development of a highly sensitive and selective detector for Cu^{2+}. The synthetic route to produce sensor **45** is detailed in Scheme 14. Fluorescent titration experiments were conducted, and Job's plots were subsequently employed to ascertain a stoichiometry of 2 : 1 between sensor **45** and Cu^{2+}. This complexation was corroborated by spectroscopic analysis, density functional theory (DFT) measurements, and Fourier-transform infrared (FTIR) data. In the presence of Hg^{2+}, compound **45** exhibited an "on-off" fluorescence response at 460 nm, although qualitative detection was achieved. Notably, when exposed to a range of investigated metal ions, sensor **45** singularly demonstrated a remarkably sensitive and selective "turn-on" fluorescence response for the detection of Cu^{2+}. Employing statistical deviations and linear regression analyses, the **45**-Cu^{2+} complex was evaluated for its detection limit and association constant. The results indicated the functionality of sensor **45** for Cu^{2+} detection across a wide pH spectrum, spanning from 2.0 to 11.0.

The development of white organic light-emitting diodes (WOLEDs) for forthcoming lighting technologies has garnered substantial interest. Luminescent complexes featuring carbene–metal–amide bonding, incorporating metals like Cu, Au, and Ag, present a compelling alternative to costly metal-based OLEDs employing elements such as Ir and Pt. This preference



Scheme 17 [3 + 2]-Cycloaddition reaction between azide and alkyne substrates.

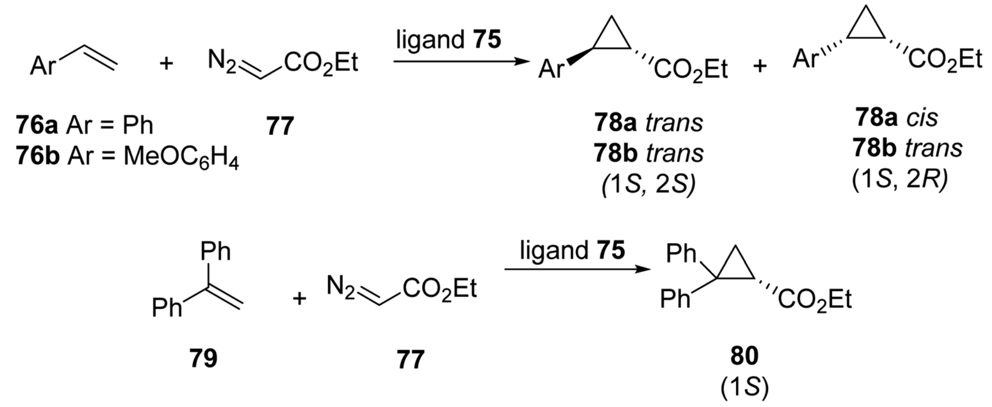


Scheme 18 Synthesis of a ligand 75.

stems from their notable advantages, including high decay rates and emission efficiency. Ruduss *et al.*[74] reported the synthesis of eight novel Cu(I) complexes, designated as **52–59**, featuring an uncharacterized carbene moiety derived from 1,3-thiazoline. These compounds underwent comprehensive evaluation to ascertain their photoluminescent properties and their prospective utility in organic light-emitting diodes (OLEDs). The synthesis of carbene precursors, specifically **46**, **48**, and **50**, was accomplished following established procedures available in the literature.[75] Subsequently, these precursors underwent *in situ* carbene generation to yield the corresponding Cu(I) complexes, specifically **47**, **49**, and **51**. These Cu(I) complexes were then subjected to reactions with various deprotonated carbazolides, including *t*BuCbz, Cbz, MetBuCbz, and MeCbz, to facilitate the synthesis of amide ligands, as depicted in Scheme 15a–c. The orchestration of both monomer and excimer components was carefully executed to achieve electroluminescence (EL) under optimized emitter structure and mass fraction conditions. This served as the foundational framework for the development of a white organic light-emitting diode (WOLED) characterized by an impressive quantum efficiency of 16.5%, accompanied by a single emission exhibiting a peak brightness exceeding 40 000 candelas per square meter (cdm^{-2}). Notably, the broad overlapping emission bands of the monomer and excimer components ensured a color rendering index (CRI) exceeding 80 for the resultant WOLED.

3.2. Catalytic property

The versatile chelating capabilities exhibited by multi-donor ligands containing sulfur (S), nitrogen (N), and oxygen (O) atoms in coordination with transition metal ions have garnered significant attention in numerous catalytic reactions.[76,77] A representative example of such ligands is Htzol, a naturally occurring compound found in (*S*) (−)-desferrithiocin. Investigations have revealed that substituting a thiazoline ring with an oxazoline ring induces a profound alteration in the reactivity of the respective ligand.[78,79] When contrasted with its oxazoline counterpart, the utility of thiazolines as ligands in coordination and organometallic chemistry is relatively limited. Since Helmchen began researching thiazoline-containing ligands in 1991,[80] their use in asymmetric catalysis has decreased. As reported by López-Cortés and collaborators, substituting the oxazoline backbone with a thiazoline counterpart results in an enhancement of the catalytic activity.[81] The development of innovative chiral ligands holds paramount significance in scientific research, given the pivotal role of asymmetric metal-



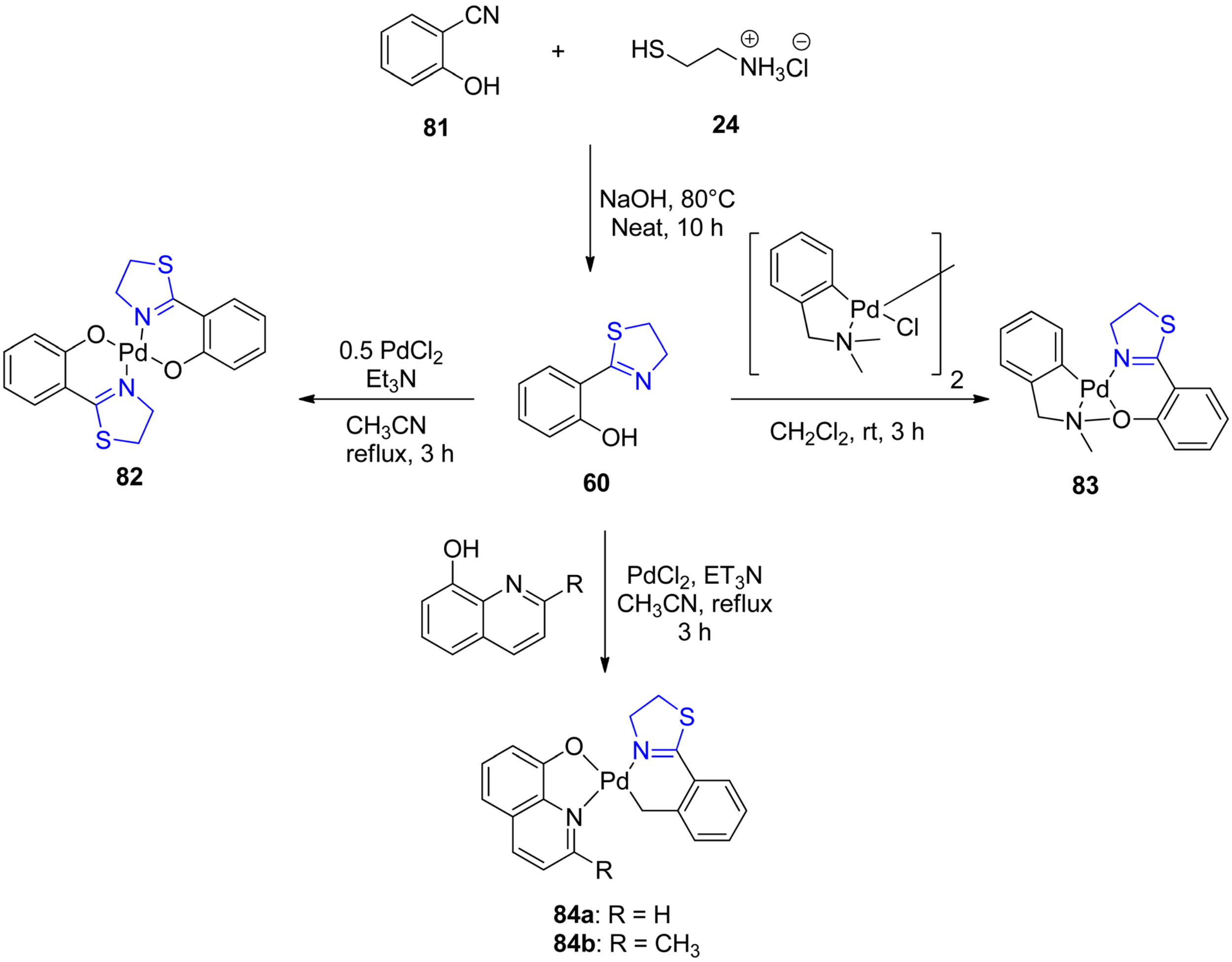
Entry	Alkene	Metal salt	Conditions	Yield (%)	trans:cis	ee trans (%)	ee cis (%)
1	Styrene (**76a**)	[RuCl$_2$(p-cymene)]$_2$	CH$_2$Cl$_2$, 0°C	44	55:45	Racemic	
2	Styrene (**76a**)	Cu(OTf)•0.5Ph•H	CH$_2$Cl$_2$, 0°C	65	58:42	28	18
3	Styrene (**76a**)	Cu(OTf)•0.5Ph•H	CH$_2$Cl$_2$, -20°C	nr	-	-	-
4	Styrene (**76a**)	Cu(OTf)•0.5Ph•H	CH$_2$Cl$_2$, 35°C	70	63:37	22	20
5	Styrene (**76a**)	Cu(OTf)•0.5Ph•H	Toluene, 0°C	64	54:46	22	24
6	Styrene (**76**a)	Cu(OTf)•0.5Ph•H	Et$_2$O, 0°C	44	61:39	18	16
7	4-methoxy styrene (**76b**)	Cu(OTf)•0.5Ph•H	CH$_2$Cl$_2$, 0°C	19	70:30	24	10
8	1,1-Diphenyl ethylene (**79**)	[RuCl$_2$(p-cymene)]$_2$	CH$_2$Cl$_2$, 0°C	5	-	Racemic	
9	1,1-Diphenyl ethylene (**79**)	Cu(OTf)•0.5Ph•H	CH$_2$Cl$_2$, 0°C	6	-	Racemic	

Scheme 19 Asymmetric cyclopropanation processes.

catalyzed reactions in synthetic organic chemistry. Recent focus has been directed toward bis(thiazolines) following their synthesis, including various pyridyl bis(thiazolines) and methylene-bridged bis(thiazolines), as established by Masson and Gulea. This renewed attention underscores the emerging importance of thiazoline-containing ligands in contemporary research endeavors.[82] The thiazolines, which are sulfur-analogs of oxazolines and amongst the vast range of chiral ligands, are a relatively new family of ligands.[83]

Amini *et al.*[84] provided an account of the catalytic competence of a thiazoline–Cu(II) complex in facilitating cycloaddition reactions without the need for additional redox cofactors. They synthesized three novel complexes, featuring Pd(II), Cu(II), and Co(III), employing Htzol (thiazoline-based compound) **60** as a ligand. Htzol ligand exhibited bidentate thiazoline coordination, serving as an O, N-donor. The standard synthetic approach for the complexes entailed the reaction of the thiazoline ligand with metal acetates in a methanolic solvent medium, as described in Scheme 16. Subsequently, complexes **61–63** were investigated for their catalytic efficacy in promoting the [3 + 2]-cycloaddition reaction between alkyl halide **64**, sodium azide **65** and alkyne substrates **66** (Scheme 17).[69] Optimization of reaction conditions, including catalyst loading, reaction temperature, and reaction duration, was performed to enhance the efficiency of the azide–alkyne cycloaddition reactions.

Irmak *et al.*[85] gave the first synthetic methodology for pyridiyl bis(thiazoline) ligand based on sugar (Scheme 18). Further, it was investigated for its use in asymmetric cyclopropanation



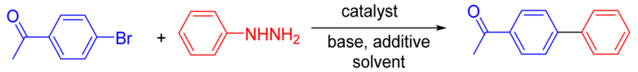
Scheme 20 Synthetic scheme for ligand **60** and its corresponding complexes **82**, **83** and **84a–b** with Pd.

processes (Scheme 19). Per-OTMS group was used to protect the amino sugar **68** in order to obtain the desired acetyl-protected bis(amide). The resultant derivative **69** was firstly protected with the OTMS group followed by its reaction with dipicolinic acid chloride to yield **70b**. Compound **70b** on subsequent desilylation and acetylation gave the bis(amide) **72b**. Under the conditions as outlined in the literature,[86] bis(amide) **72b** when refluxed with Lawesson's reagent produced the bis(thioamide) **73b**. Double cyclization could eventually be achieved by extending the reaction period. As a result, target compound **75** was achieved with a 44% total yield (Scheme 18). They conducted experiments using pyridyl bis(thiazoline) **75** as a ligand in metal-catalysed cyclopropanation reactions involving styrene **76** and ethyl diazoacetate **77** under varying conditions. Subsequently, they also explored the reaction with two other alkenes, namely 4-methoxy styrene compound **76b** and 1,1-diphenyl ethylene **79** (Scheme 19).

Sudharsan *et al.*[87] conducted an investigation into the formation of thiazoline–ligand complexes with Pd(II), yielding both homo- and heteroleptic complexes, as depicted in Scheme 20. The synthesized compounds were subsequently assessed for their catalytic capabilities. These compounds served as catalysts in reactions involving the generation of Csp^2–Csp^2 bonds. Characterization of Pd(II) complexes **82, 83**, and **84a–b**, as well as ligand **60**, was achieved through spectroscopic analysis, elucidating their crystal and molecular structures. Under optimized reaction conditions, Pd(II) complex **83** exhibited exceptional catalytic activity in the synthesis of biaryls **87** from phenylhydrazine **86** and aryl halides **85**, achieving a remarkable turnover frequency of 49.5 h^{-1} (Scheme 21).

Mckeon *et al.*[88] reported the convergent preparation of thiazoline & oxazoline containing six non-C_2-symmetric ligands **90a–f** by microwave irradiation. The amination reaction was catalysed by Pd(II) (Scheme 22). In a zinc catalysed Friedel–Crafts alkylation reaction involving *trans*-β-nitrostyrene **92** & indole **91**, the ligands **90a–f** gave enantioselectivity as high as 76% (Scheme 23).

Mckeon *et al.*[89] reported the synthesis of ten novel ligand analogues denoted as **90g–p** (Scheme 24), aiming to enhance enantioselectivity in the Friedel–Crafts reaction, as outlined in Scheme 25. Furthermore, these ligands were employed in the NHK allylation reaction with benzaldehyde **94**, catalyzed by chromium (Scheme 26). The X-ray analysis of the Fe(II) complex of the ligand revealed its tridentate ligating behavior. Based on



85 + 86 → 87

Entry	Catalyst	Base	Additive	Solvent	T [°C]	Time (h)
1	82	K_2CO_3	-	DMF	60	3
2	82	K_2CO_3	-	DMA	60	3
3	82	K_2CO_3	-	NMP	60	3
4	82	K_2CO_3	-	CH_3CN	60	3
5	82	K_2CO_3	-	Toluene	60	3
6	82	K_2CO_3	-	Isopropanol	60	3
7	82	K_2CO_3	-	Ethanol	60	3
8	82	K_2CO_3	-	THF	60	3
9	82	Na_2CO_3	-	DMF	60	3
10	82	Cs_2CO_3	-	DMF	60	3
11	82	NaOAc	-	DMF	60	3
12	82	TEA	-	DMF	60	3
13	82	NaOH	-	DMF	60	3
14	82	K_2CO_3	-	DMF	60	3
15	82	K_2CO_3	-	DMF	120	3
16	82	K_2CO_3	-	DMF	120	2
17	82	K_2CO_3	CuI (0.5)	DMF	120	2
18	82	K_2CO_3	KI (0.5)	DMF	120	2
19	82	K_2CO_3	NaI (0.5)	DMF	120	2
20	82	K_2CO_3	NaI (0.2)	DMF	120	2
21	83	K_2CO_3	NaI (0.1)	DMF	120	2
22	84a	K_2CO_3	NaI (0.2)	DMF	120	2
23	84b	K_2CO_3	NaI (0.2)	DMF	120	2
24	83	K_2CO_3	NaI (0.2)	DMF	120	2
25	83	K_2CO_3	NaI (0.2)	DMF	120	2
26	-	K_2CO_3	NaI (0.2)	DMF	120	2
27	83	-	NaI (0.2)	DMF	120	2

Scheme 21 Synthesis of bi-aryls **87** from phenylhydrazine **86** and aryl halides **85**.

this crystallographic evidence, the remarkable enantioselectivity observed with ligand **90e** ($R_1 = t$-Bu, R_2 = Bn) in the allylation reaction of benzaldehyde [85% (*R*)] was elucidated through the proposal of a transition state.

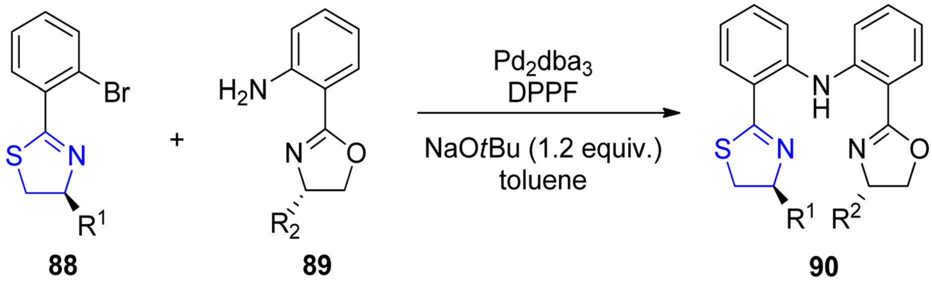
Liu *et al.*[90] reported the synthesis of four new ligand analogues **99a–d** as part of an effort to improve the enantioselectivity in the Friedel–Crafts reaction, as illustrated in Scheme 27. The primary focus of the research was to investigate the asymmetric Friedel–Crafts alkylation of indole derivatives **91** and pyrrole **100** with *trans*-β-nitrostyrene **92**, as shown in Scheme 28a and b. The reason behind the observed enantioselectivity was attributed to the NH–π interaction between the catalyst and the incoming aromatic system in the transition state. This interaction was confirmed by comparing the enantioselectivity and the absolute configuration of the products in reactions catalysed by the specially designed ligands.

Abrunhosa-Thomas *et al.*[91] reported a series of thiazoline ligands substituted with a sulfinyl or sulfanyl moiety. The ligands were assessed for their catalytic properties in an allylic substitution reaction catalysed by palladium. Using *t*-BuLi, deprotonation was performed at the α-position followed by addition of diphenyl disulfide. Thus, the enantiopure 2-isopropyl-thiazolines **102a–c**,[92] were transformed into their corresponding sulfanyl-thiazolines **103a–c** (Scheme 29a). Similar to this, thiazoline (*R*)-**102a** as well as the (*R*)/(*S*) *tert*-butyl thiosulfinate were used to obtain α-sulfinyl-thiazolines (*R*, *R*s)-**104a** as well as (*R*, *S*s)-**104b** as a diastereomeric mixture (Scheme 29a).[93] α,β-unsaturated thiazolines **105** when treated with thiol, gave β-sulfanyl-thiazolines **106** (Scheme 29b). Starting with commercially available (*S*)-methioninol **108** and phenyldithioic methyl ester **107**,[94] compound **110** was synthesized in 2 steps; thioacylation followed by intramolecular cyclization (Scheme 29c). Sulfanyl-thiazoline polymer **114a–b** was synthesized as the first immobilized version of the ligand from vinyl benzene **111** (Scheme 29d). When analyzed for their ability to asymmetrically induce the allylic substitution reaction catalysed by palladium, none of the newly synthesized ligands produced a significant excess of the desired enantiomer. Following 24 hours, the thiazoline polymer **P-114a** produced complete conversion (similar to the monomeric homologue **110**), but with reduced ee (36% as compared to 66% ee) (Scheme 30).

3.3. Pharmacological

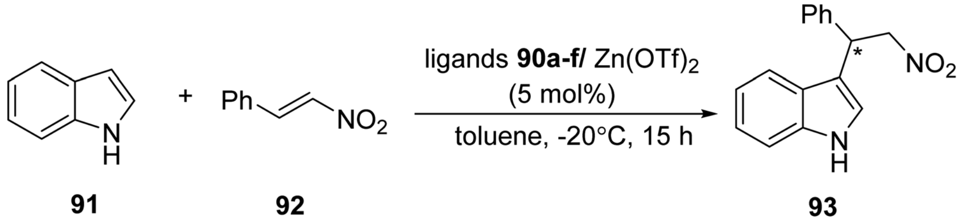
3.3.1. Anti-cancer. According to the World Health Organization (WHO) survey, it is projected that the number of cancer patients will increase by 26 million by the year 2030. This escalation in cancer cases is expected to establish cancer as a prominent global cause of mortality, resulting in an estimated 17 million annual fatalities.[95,96] In developing nations, the relative mortality rate due to cancer is notably elevated. While chemotherapy serves as a fundamental component of cancer treatment, its application is often limited due to the significant side effects it entails, along with a substantial medical challenge known as drug resistance to cancer chemotherapy medications.[97] At the molecular level, research is being done to determine the cause of resistance and enable synthesis of improved chemotherapeutics.

Numerous thiazoline derivatives exhibit anticancer properties, encompassing a range of molecular characteristics and biological diversity. Oligothiazoline compounds, sourced from nature, include marine compounds like tantazole B, mirabazole, and thiangazole, which demonstrate selective toxicity against murine solid tumors.[98,99] Oligomers based on the 2-thiazoline moiety are cytotoxic to the cell lines HCT-116 (colon cancer), HPAC (pancreatic cancer) and PC-3 (prostate cancer).[100]



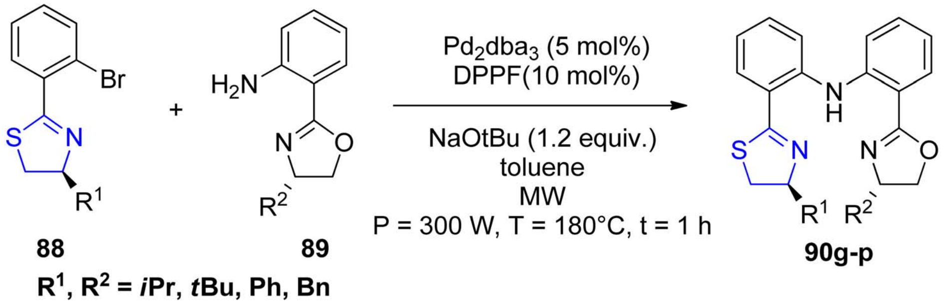
Entry	Ligands	R^1	R^2	Thermal (% yield)	Microwave (% yield)
1	**90a**	*i*Pr	*i*Pr	26	64
2	**90b**	*t*Bu	*t*Bu	28	83
3	**90c**	Ph	Ph	6	25
4	**90d**	Bn	Bn	19	64
5	**90e**	*t*Bu	Bn	27	72
6	**90f**	Bn	*t*Bu	17	61

Scheme 22 Synthetic scheme for non-C_2-symmetric ligands **90a–f**.



Entry	Ligand	R_1	R_2	Thermal (% yield)	Microwave (% yield)
1	**90a**	*i*Pr	*i*Pr	26	64
2	**90b**	*t*Bu	*t*Bu	28	83
3	**90c**	Ph	Ph	6	25
4	**90d**	Bn	Bn	19	64
5	**90e**	*t*Bu	Bn	27	72
6	**90f**	Bn	*t*Bu	17	61

Scheme 23 Zinc catalyzed Friedel–Crafts alkylation reaction.



Entry	Ligand	R^1	R^2	Yield (%)
1	**90g**	*i*Pr	*t*Bu	70
2	**90h**	*i*Pr	Ph	70
3	**90i**	*i*Pr	Bn	59
4	**90j**	*t*Bu	*i*Pr	68
5	**90k**	*t*Bu	Ph	79
6	**90l**	Ph	*i*Pr	31
7	**90m**	Ph	*t*Bu	41
8	**90n**	Ph	Bn	29
9	**90o**	Bn	*i*Pr	48
10	**90p**	Bn	Ph	62

Scheme 24 Synthesis of ligand class **90g–p**.

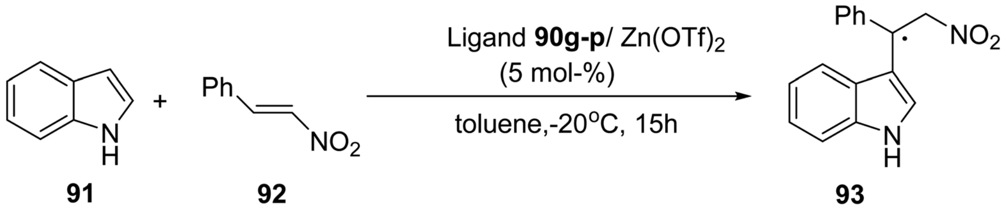
Additionally, artificial thiazoline derivatives with anti-proliferative action have been thoroughly researched and described in literature.[101–104] Ability to induce apoptosis and impede cell division[105] have been identified as anticancer action mechanisms.

The structurally distinct diastereomers, ulbactin F **118** as well as ulbactin G **119**, with a tricyclic ring structure including nitrogen and sulfur, were identified by Igarashi *et al.*[106] from sponge-derived *Brevibacillus* sp. With the use of X-ray crystallography and NMR measurements, compounds **118** and **119** were structurally characterized (Scheme 31). These substances in micromolar quantities prevent tumor cells from metastasizing. Compounds **118** ($IC_{50} = 6.4$ μM) and **119** ($IC_{50} = 6.1$ μM) display non-cytotoxic inhibition of the metastasis of the A431 cancer cells. Isomer **118** also prevents cell invasion of 26-L5 cells ($IC_{50} = 1.7$ μM) as well as the metastasis of the EC109 cancer cells ($IC_{50} = 2.1$ μM). Thus, it displays anti-metastatic properties.

Wang *et al.*[107] employed dibromides **122** in the synthesis of a series of novel multi-thioether derivatives of thiazoline **123**, as illustrated in Scheme 32. Structural characterization was conducted through spectroscopic analysis, elemental analysis, and infrared (IR) measurements. Furthermore, the synthesized compounds underwent evaluation for their anti-cancer efficacy. The biological assessment revealed that compound **123g** exhibited notably enhanced anti-tumor effects, with IC_{50} values of 22.58 μg mL^{-1} for A-549 and 19.41 μg mL^{-1} for Bcap-37, respectively.

El-Helw *et al.*[108] reported the synthesis of two newly identified active N-heterocycles: the thiazoline derivative **128** and 2-cyano acetohydrazide **127**. The N-condensation product, equivalent to **127**, was generated through refluxing an ethanolic solution containing carboxaldehyde **125** and hydrazide **126** for a duration of 2 hours, as described in Scheme 33. Subsequently, compound **127** was subjected to an initial treatment with Et_3N in dioxane as the solvent, followed by a reaction with phenyl isothiocyanate in the presence of elemental sulfur, yielding compounds **128** and **129** as the final products. The *in vitro* anticancer properties of the synthesized compounds were assessed in two distinct cancer cell lines, MCF7 and HepG2. Remarkably, compound **127** demonstrated the highest efficacy against both cell lines.

Turan-Zitouni *et al.*[109] established a hydrazine bridge between the thiazoline and the tetralin rings. Tetrahydro naphthol **130** on treatment with 2-chloro acetate gave intermediate **131**. Further, acetohydrazide **132** was synthesized from



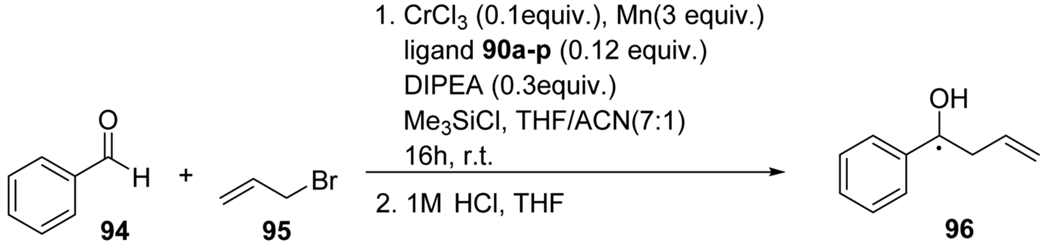
Entry	Ligand	R^1	R^2	Yield [%]	*ee* [%]
1	**90g**	*i*Pr	*t*Bu	100	19(*R*)
2	**90h**	*i*Pr	Ph	100	56(*R*)
3	**90i**	*i*Pr	Bn	100	69(*R*)
4	**90j**	*t*Bu	*i*Pr	100	8(*S*)
5	**90k**	*t*Bu	Ph	99	67(*R*)
6	**90l**	Ph	*i*Pr	100	rac
7	**90m**	Ph	*t*Bu	100	59(*R*)
8	**90n**	Ph	Bn	99	32(*R*)
9	**90o**	Bn	*i*Pr	100	21(*R*)
10	**90p**	Bn	Ph	94	64(*R*)

Scheme 25 Zinc catalyzed Friedel–Crafts alkylation reaction.

this intermediate.[110] The acetohydrazide **132** thus obtained was treated with ethanolic solution of cyclohexyl as well as phenyl isothiocyanate to give carbothioamide **133** according to the literature report.[111] The final acetohydrazides **134a–k** were synthesized by reacting carbothioamide **133** with phenacyl bromdie (Scheme 34). The anticancer potency of **134a–k** derivatives was assessed on the MCF-7, NIH/3T3 & the A549 cancer cell lines by following the MTT method, studying the inhibition of DNA synthesis as well as analysis of flow cytometry. Compound **134e** consisting of a 4-methoxyphenyl moiety displayed excellent anti-cancer efficacy against the MCF-7 cell line with enhanced apoptotic cell percentage as well as improved inhibition of DNA synthesis. Compounds **134f** (4-bromo), **134g** (4-chloro) and **134h** (4-fluorophenyl) exhibited significant apoptotic levels in A549 cancer cell line with concentrations lower than that of cisplatin. While testing the compound's anti-cholinesterase activity, it was revealed that compound **134h** inhibited acetylcholinesterase (AChE) by 49.92%.

Kelly's synthetic method for thiazoline preparation[112] was utilized in the process of total synthesis of the new anticancer natural product cyclic depsipeptide largazole, which was discovered in 2008.[113] A good yield of thiazoline esters **136a–b** were produced by treating amides **135a–b** with triphenylphosphine oxide and trifluoroanhydride (Scheme 35). In refluxing toluene, the double dehydrative cyclization of the tripeptide **137** resulted in the formation of (bis)thiazoline **138**, which was easily oxidized to **135a** (Scheme 36a). Using this methodology, Numajiri *et al.*[114] achieved the total synthesis of largazole **139** and its derivative **140–142** (Scheme 36b). The depsipeptide largazole **139**, obtained from cyanobacterium of Symploca genus, exhibits excellent anti-cancer efficacy.[115] Strong inhibitory effect against histone deacetylases was observed in biological testing of the synthetic largazole (HDAC) as well as the *S*-modified analogs.

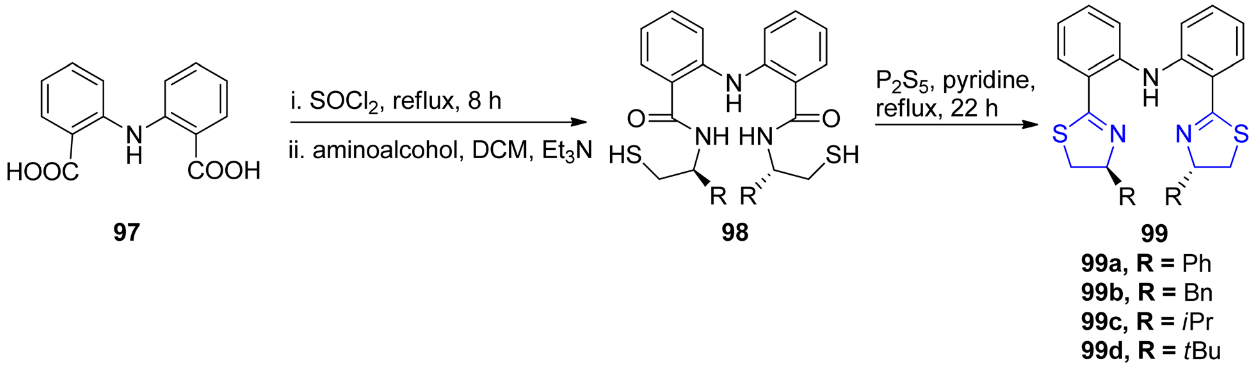
As a potential alternative for cancer therapeutics, largazole, which was first discovered by Luesch.[33,115] Guerra-Bubb *et al.*[116] reported the synthesis of an analogue of largazole **139**. Beginning with the well-known oxazole **143**, the thiazoline–oxazole fragment **144** was obtained (Scheme 37a).[117] Acrolein **145** was used to formulate the heptenoic acid fragment **148** (Scheme



Entry	Ligand	R^1	R^2	Conversion [%]	Yield [%]	*ee* [%]
1	**90g**	*i*Pr	*t*Bu	98	77	19(*R*)
2	**90h**	*i*Pr	Ph	100	78	35(*R*)
3	**90i**	*i*Pr	Bn	99	81	13(*R*)
4	**90j**	*t*Bu	*i*Pr	100	84	3(*S*)
5	**90k**	*t*Bu	Ph	100	88	11(*R*)
6	**90l**	Ph	*i*Pr	89	80	5(*S*)
7	**90m**	Ph	*t*Bu	100	90	12(*R*)
8	**90n**	Ph	Bn	100	87	11(*S*)
9	**90o**	Bn	*i*Pr	100	85	5(*S*)
10	**90p**	Bn	Ph	100	87	9(*S*)
11	**90a**	*i*Pr	*i*Pr	94	78	39(*S*)
12	**90b**	*t*Bu	*t*Bu	100	87	10(*R*)
13	**90c**	Ph	Ph	100	81	31(*S*)
14	**90d**	Bn	Bn	85	67	6(*S*)
15	**90e**	*t*Bu	Bn	100	84	85(*R*)
16	**90f**	Bn	*t*Bu	100	75	55(*R*)

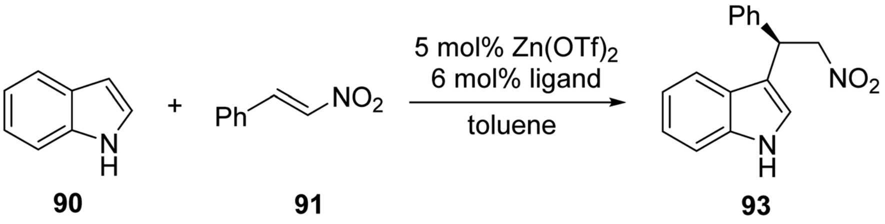
Scheme 26 NHK allylation reaction with benzaldehyde **94**.

37a). The first step in the macrocycle construction involved synthesis of peptide **149** by treatment of acid **148** with *N*-Fmoc-Val-OH in presence of EDCI (Scheme 37a).[118] The required substrate **150** was obtained in two phases of deprotection, coupling with PyBOP and Hunigs base with a yield of 91%. T3P and Hunigs base were used to produce the required macrocycle **151** in 30% yield after conversion of compound **150** to amino acid in a one-pot reaction. Using TFA and $i\mathrm{Pr_3SiH_8}$ in degassed dichloromethane, the macrocycle **151** was detritylated to give disulfide **152** instead of the anticipated thiol (Scheme 37b).



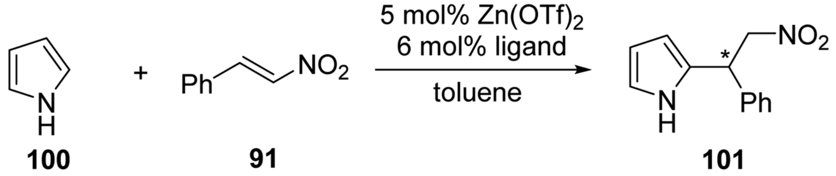
Scheme 27 Diphenylamine-tethered bis(thiazoline) ligands **99a–d**.

a)



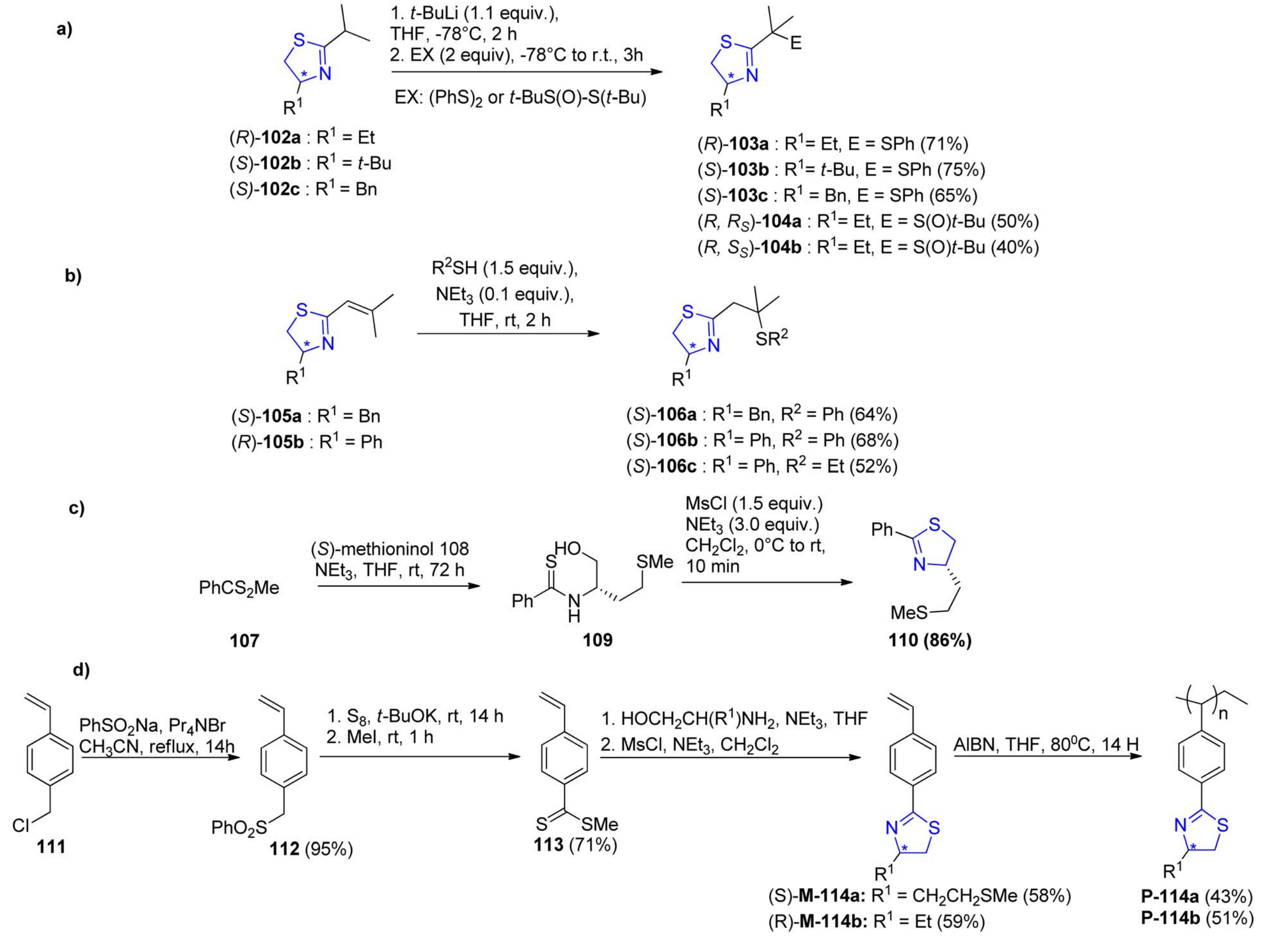
Entry	Ligand	*T* [°C]	Yield [%]	*ee* [%]
1	**99a**	10	99	78
2	**99b**	10	99	59
3	**99c**	10	93	11
4	**99d**	10	87	2

b)



Entry	Ligand	*T* [°C]	Yield [%]	*ee* [%]
1	**99a**	20	73	45
2	**99b**	20	71	73
3	**99c**	20	76	27
4	**99d**	20	40	01

Scheme 28 (a and b) Asymmetric Friedel–Crafts alkylation.



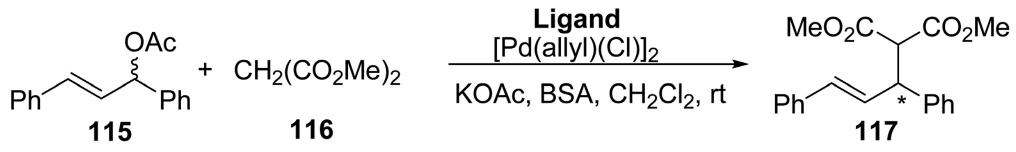
Scheme 29 (a–d) Synthetic scheme for chiral thiazoline ligands.

Interestingly, it was found that the required thiol **153** was prepared when the trityl residue of **151** was removed with Et_3SiH rather than iPr_3SiH in degassed dichloromethane. This thiol was then instantly acylated to produce the desired octanoyl-thioester **154**. Using a previously established optimized homogeneous assay carried out on a 384-well plate, compounds **152–154** were examined for their inhibitory efficacy against HDACs 1–9.[119] According to the findings of these studies, compound **153** was found to be more active and potent in comparison to the largazole. However, it is less potent than largazole thiol. **153** was substantially less active than in the biochemical model with an IC_{50} value of 6.2 μM, which is probably because the free thiol gets degraded in the cellular environment. Similar to largazole, the prodrugs **152** and **154** showed IC_{50} values of 0.91 & 0.12 μM, respectively.

Taher *et al.*[120] conducted a condensation reaction involving Mannich bases **156a–h** and thiazoline **157**, resulting in the synthesis of a series of novel isatin-thiazoline derivatives denoted as **158a–h**, as outlined in Scheme 38. These newly synthesized compounds underwent comprehensive characterization through spectroscopic analysis. Notably, all the prepared compounds exhibited efficacy against MCF-7.

One of the most commonly used chemotherapy drugs in the treatment of various malignancies is cisplatin,[121] but it is associated with a high level of toxicity and adverse effects.[122] New chemotherapeutic drugs must therefore be developed in order to obtain less harmful and efficient drugs for cancer treatment. A Pd(II) complex, PdPyTT **162** was synthesized and described by Espino *et al.*[123] using the ligand PyTT **161** (Scheme 39). The ligand was prepared according to the reported methodology,[124] with a few minor adjustments as per published literature.[125] Additionally, its cytotoxicity and pro-apoptotic potential were examined in the HL-60 cancer cell line. The Pd complex, PdPyTT **162** also reduced cell viability in a time- & dose-dependent manner, similar to cisplatin. In addition, the palladium compound boosted caspase-3 and caspase-9 activation and the percentage of cells exhibiting apoptotic morphology. Also, PdPyTT enhanced DNA oxidative damage and intracellular ROS generation, identical with that of cisplatin.

Kwan *et al.*[126] identified a series of cyclic depsipeptides, specifically compounds **163–165**, featuring bis-thiazoline moieties as constituents, within the *Lyngbya confervoides* extract, as depicted in Scheme 40. Compound **165** exhibited enhanced metal affinity, potentially contributing to its



Entry	Ligand	Conversion %(time)	Enantiometric Excess (ee) (%)	Product Configuration
1	(*R*)-**103a**	>95 (24h)	37	(*R*)
2	(*S*)-**103b**	>95(24 h)	43	(*S*)
3	(*S*)-**103c**	>95(48h)	40	(*S*)
4	(*R*,R_S)**104a**	30 (168h)	47	(*R*)
5	(*R*,S_S)-**104b**	30 (168h)	47	(*R*)
6	(*S*)-**106a**	50 (120 h)	49	(*S*)
7	(*S*)-**106b**	60 (120h)	73	(*S*)
8	(*S*)-**106c**	80(120h)	42	(*S*)
9	(*S*)-**110**	>95(24h)	66	(*R*)

Scheme 30 Asymmetrically induced allylic substitution reaction catalysed by palladium.

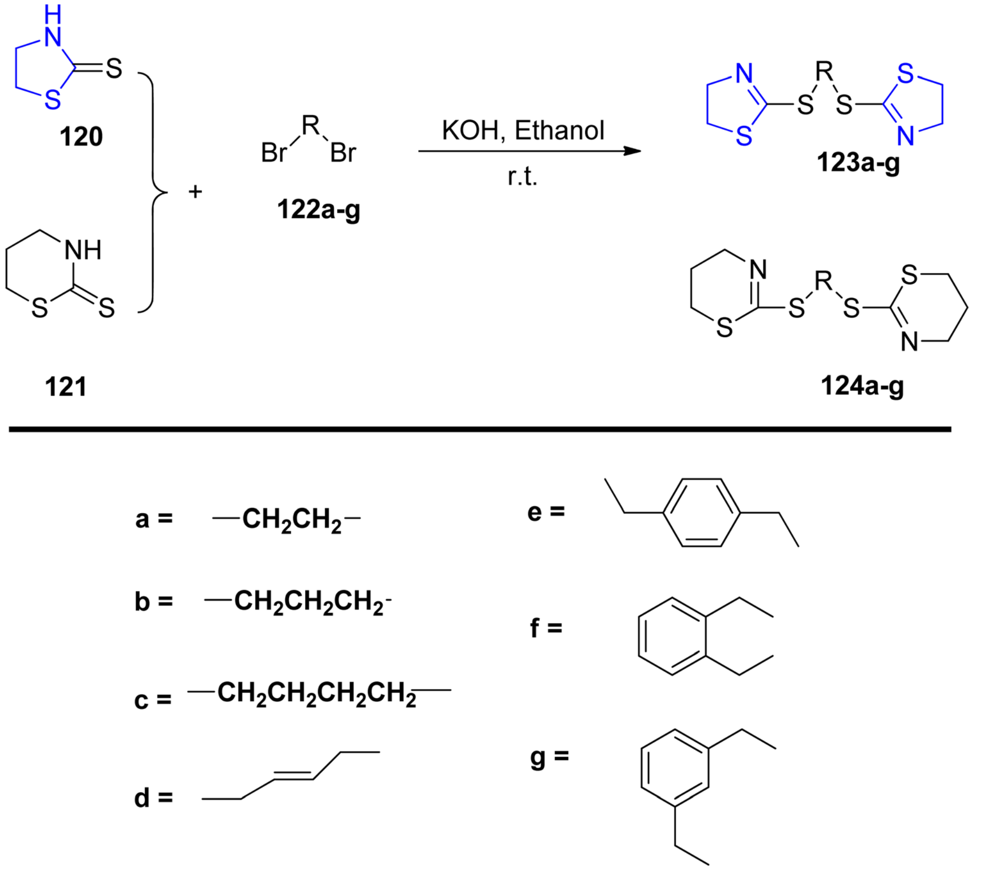
Ulbactin F
118

Ulbactin G
119

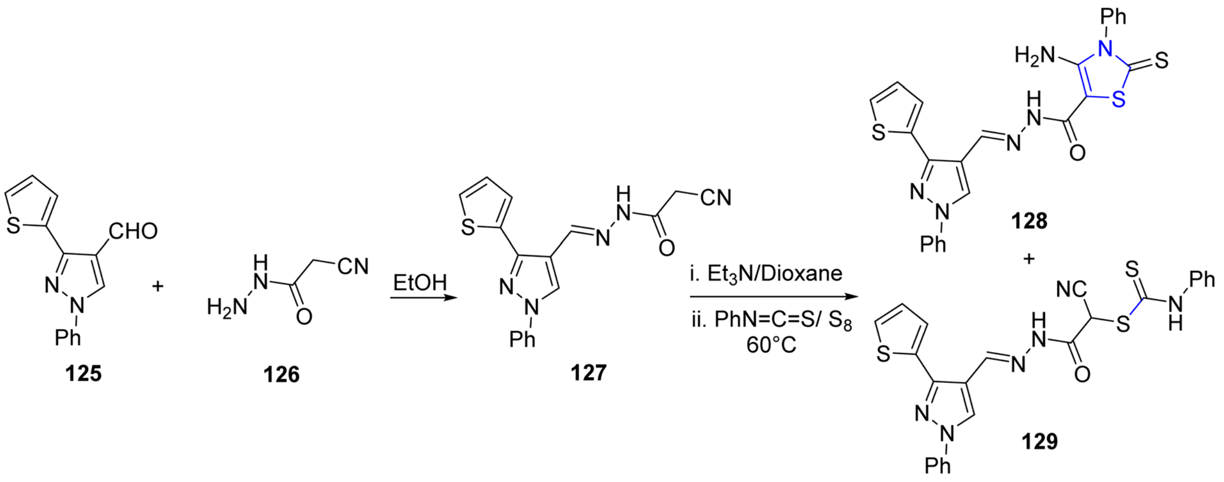
Scheme 31 Structures of ulbactin F **118** and ulbactin G **119**.

increased potency. Structure–activity relationships among these analogues were evident in their *in vitro* cytotoxic effects. While the activity experienced only a modest decrease (3–4 fold) upon replacing the ethyl group in compound **163** with a methyl group in compound **164**, a notable enhancement in potency (16–23 fold) was observed when the phenyl moiety flanking the thiazoline molecule was inverted. Both compounds **163** and **165** demonstrated binding to Cu^{2+} and Zn^{2+} metal ions, with the capacity to arrest the cell cycle at the G1 phase at lower doses and at the G2/M phases at higher concentrations.

Altıntop *et al.*[127] synthesized acetohydrazide compounds **179–218**, which were subsequently evaluated for their antibacterial properties and cytotoxic effects against NIH/3T3 cells. Thiol compounds **166a–e** were combined with potassium carbonate to obtain thioacetate derivatives **167a–e**. The 2-[(aryl)thio]acetohydrazides were then synthesized by treating ester derivatives **167a–e** with hydrazine hydrate **168a–e**. These hydrazides **168a–e** were further transformed into 1-(arylthioacetyl)-4-phenyl thiosemicarbazides **170a–e** by reacting them with phenyl isothiocyanate **169**. The final target compounds **179–218** were produced by ring-closure through treatment of thiosemicarbazides **170a–e** with various analogues of 2-bromoacetophenones **171–178** (Scheme 41). Among the compounds tested, compound **200** exhibited the highest



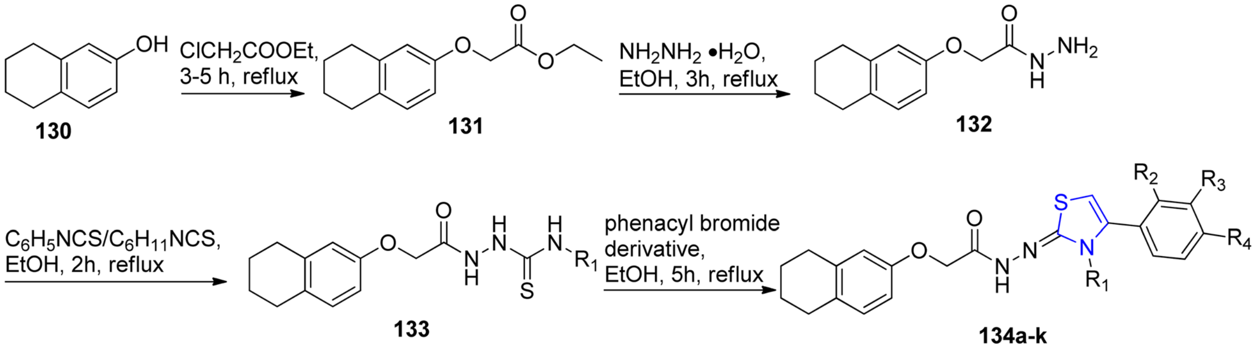
Scheme 32 Synthesis of thiazoline and thiazine multi-thioether.



Scheme 33 Synthesis of thiazoline derivative **128**.

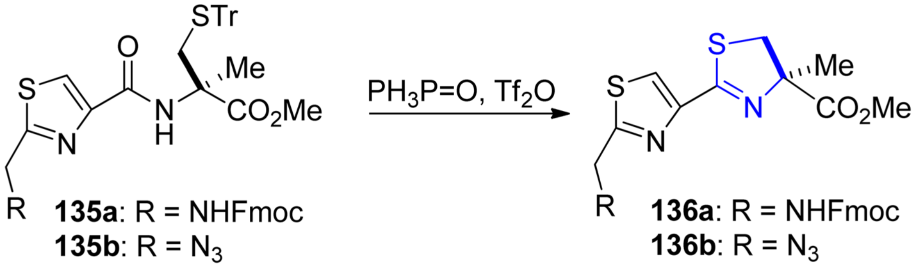
antibacterial activity against *Pseudomonas aeruginosa*, while compound **201** displayed the most potent antifungal activity against *Candida albicans*. In terms of cytotoxicity against C6 glioma cells, compound **195** emerged as the most effective with an IC_{50} value of 8.3 ± 2.6 μg mL^{-1}, surpassing cisplatin (IC_{50} range: 13.7 ± 1.2 μg mL^{-1}). Compound **195** also demonstrated DNA synthesis inhibition on C6 cells and exhibited lower toxicity to NIH/3T3 cells with an IC_{50} value in the range of 416.7 ± 28.9 μg mL^{-1}.

Mabkhot *et al.*[128] successfully synthesized a series of novel thiazoline compounds. The reaction sequence for the synthesis of thiazolines **221a–e** involved treatment of dione **219a/b** with 1° amines **220a–c** at room temperature in ethanolic media. Compound **221a** resulted in the formation of thiazolines **223a–e**



Compounds	R$_1$	R$_2$	R$_3$	R$_4$
134a	Cyclohexyl	H	H	H
134b	Cyclohexyl	H	H	OCH_3
134c	Phenyl	H	H	H
134d	Phenyl	H	H	CH_3
134e	Phenyl	H	H	OCH_3
134f	Phenyl	H	H	Br
134g	Phenyl	H	H	Cl
134h	Phenyl	H	H	F
134i	Phenyl	H	NO_2	H
134j	Phenyl	H	H	NO_2
134k	Phenyl	Cl	Cl	H

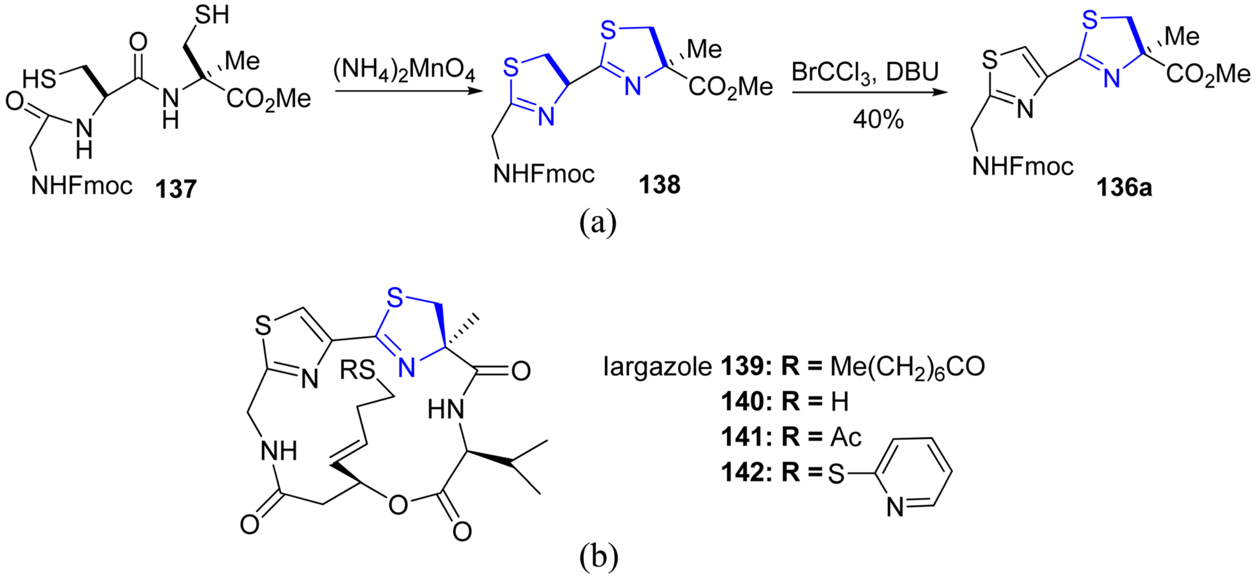
Scheme 34 Synthesis of the compounds **134a–k**.



Scheme 35 Synthesis of thiazoline esters **136a–b**.

when refluxed with the suitable aniline derivatives (Scheme 42). Next, the reaction of the thiazoline-2-thione derivative **221a** with 2-oxo-*N*′-phenylpropane hydrazonoyl chloride **224** produced the spiro-compound **225** (Scheme 42). The compounds were assessed for their anti-tumor properties against HepG2 as well as HCT-116 cancer cell lines. The outcomes showed that the thiazoline compounds, **223b** and **221c**, had a considerable effect on the two cell lines. The inhibitory activity of thiazolines **221c**, **223b**, and **223d** against *Salmonella* sp. was found to be promising as determined by anti-microbial screening. Additionally, the reference compound gentamycin and the thiazolines **221e** and **223b** were found to have equivalent inhibitory activity against *Escherichia coli.*

Recent research has shown that multitargeting kinase inhibitors is an efficient strategy for restricting cancer growth. Thiazoline-based derivatives **229a/b** were developed and



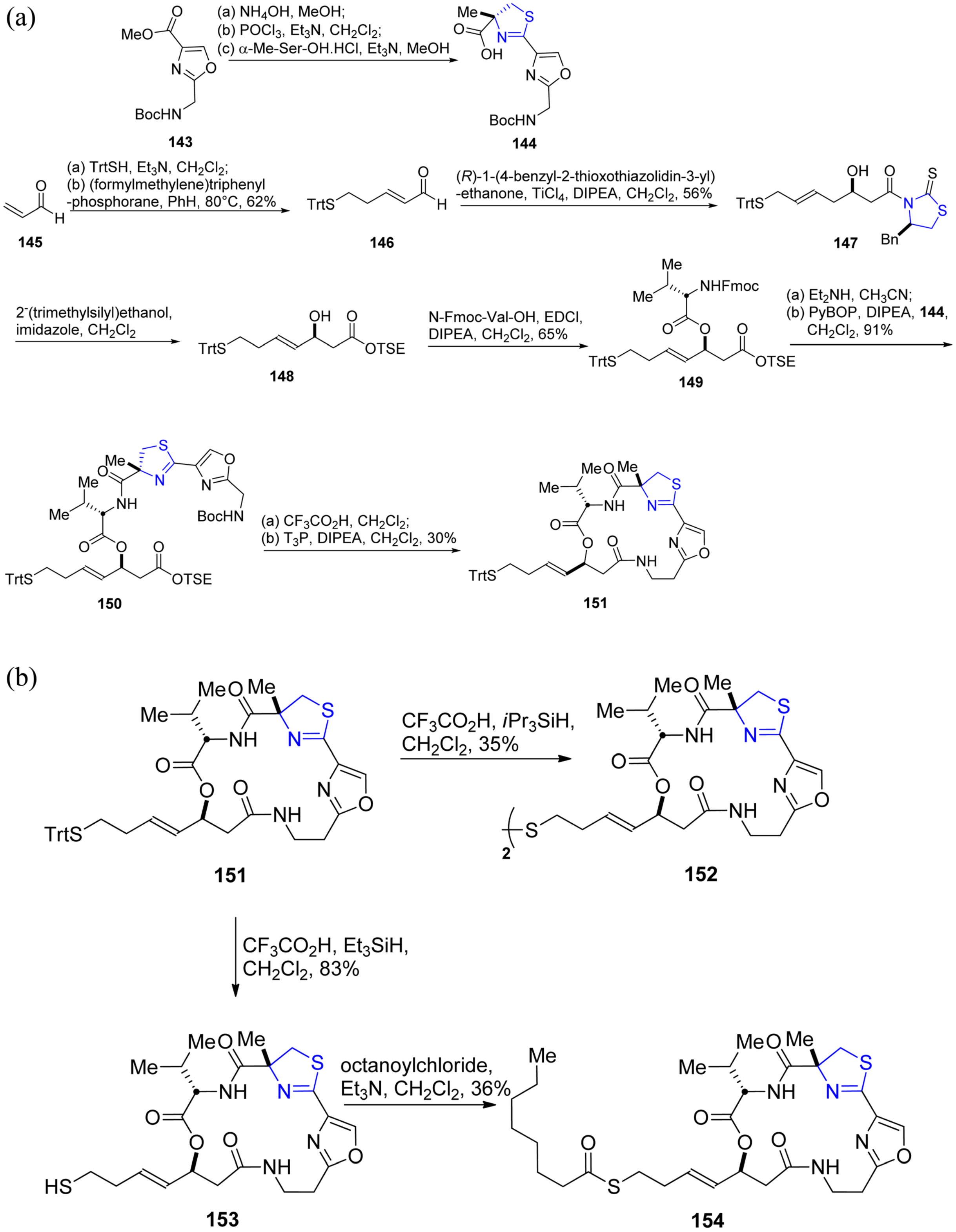
Scheme 36 (a) Synthesis of thiazoline esters **136a**. (b) Synthetic largazole **139** and its derivatives **140–142**.

synthesized by Alamshany *et al.*[129] Initially, the intermediate **227** was prepared by treatment of *p*-toluidine **226** in ethanolic media with phenacyl bromide **177**.[130] Further, the target thiazolines **229a/b** were synthesized by a condensation reaction between intermediate **227** and isothiocyanates **228a/b** in a refluxing ethanolic solution containing Et_3N as the catalyst (Scheme 43). Compound **227** was the only effective one against a broad range of bacteria (Gram-positive as well as Gram-negative) & fungi. Additionally, *in vitro* analysis was also carried out against HepG-2, HCT-116 & MCF-7 cancer cell lines.

3.3.2. Anti-microbial. As per the reports from the CDC (Centers for Disease Control and Prevention), over two million individuals acquire drug-resistant bacterial infections annually, leading to the mortality of more than 23 000 people.[131] Due to the capacity of microorganisms to develop resistance to treatments, bacterial and fungal infections have emerged as significant contributors to global morbidity and mortality.[132] Microbe's resilience in harsh environments pose challenges for finding effective treatments. The demand for potent antimicrobial drugs that can inhibit or eradicate pathogens without harming host cells has increased due to the sharp rise in life-threatening bacterial and fungal infections.[133,134] In light of the rapid emergence of drug resistance, the development of novel antimicrobial agents necessitates distinctive chemical characteristics compared to currently employed drugs. Heterocyclic compounds featuring nitrogen and sulfur represent well-established chemical moieties present in various natural products and essential medications. A paramount concern in contemporary medicine revolves around the proliferation of antimicrobial resistance, particularly in multi-drug resistant microorganisms. Thiazolines have gained prominence due to their significant synthetic and biological relevance, serving as vital scaffolds. Compounds incorporating the thiazoline moiety have been associated with diverse biological effects, including antimicrobial activity, underscoring their biomedical importance.[135–137]

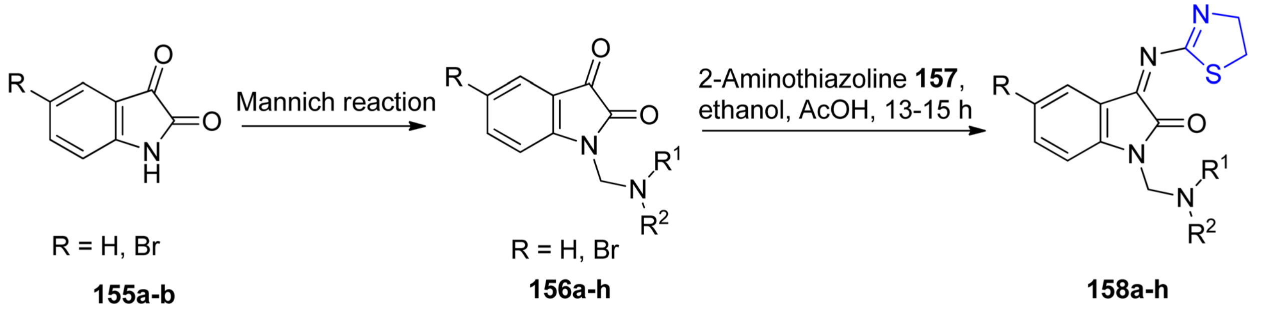
Asiri *et al.*[138] developed a synthetic methodology to obtain twelve 2-thione analogues of thiazoline (Scheme 44). The compounds thus synthesized were characterized by spectroscopic experiments, IR measurements, X-ray and elemental analysis. Additionally, the biological activities of the compounds were also investigated against various microorganisms and human cancer cell lines. The thiazoline derivatives **233a**, **233b**, **235a**, **235c** and **236** demonstrated significant antifungal properties when tested against *Aspergillus fumigatus*, in comparison to the conventional medicines. Additionally, all the thiazoline derivatives were found to be effective against *Candida albicans*, with the exception of compound **233b**. Moreover, the compounds also exhibited anti-bacterial activity against both Gram-positive as well as Gram-negative bacteria. On evaluation of the cytotoxic effects of compounds **232**, **235b** and **236** against HCT-116 as well as the HepG-2 cancer cell lines, compound **235b** was found to be the most efficient with IC_{50} values of 79 μg mL^{-1} and 49 μg mL^{-1}, respectively.

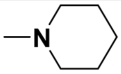
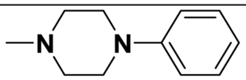
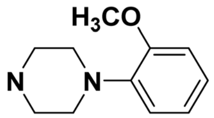
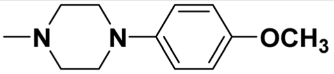
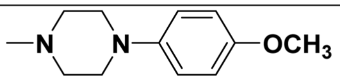
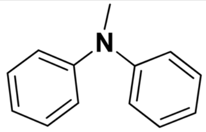
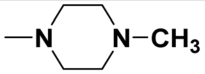
Bondock *et al.*[139] outlined a practical synthetic approach to generate novel thiazoline derivatives intended for antimicrobial evaluation. This synthetic methodology involved the reaction of cyanoacetic acid hydrazide **238** with α-halocarbonyl compound **237**, as depicted in Scheme 45. The interaction of the aldehyde functionality in compound **237** with cyanoacetohydrazide led to the formation of compound **239**. Subsequently, the key intermediate **240** was derived through reaction with phenyl isothiocyanate **228b**. The final cyclized pyrimidinone analogue **241**, was synthesized by treating intermediate **240** with a mixture of triethylorthoformate and acetic anhydride. The compounds were further assessed for their antimicrobial properties.



Scheme 37 (a) Synthetic scheme for largazole analogue **151**. (b) Synthesis of largazole analogues **152–154**.

Viñuelas-Zahínos *et al.*[140] reported the synthesis of Schiff base ligand **244** *via* condensation reaction of thiazoline **242** with thiosemicarbazide **243**. The ligand thus obtained was complexed with different metal ions (Co, Ni, Zn and Cd) to yield complexes **245**, **246**, **247**, **248**, **249** and **250** (Scheme 46). The precursor **242** was synthesized by using the procedure outlined

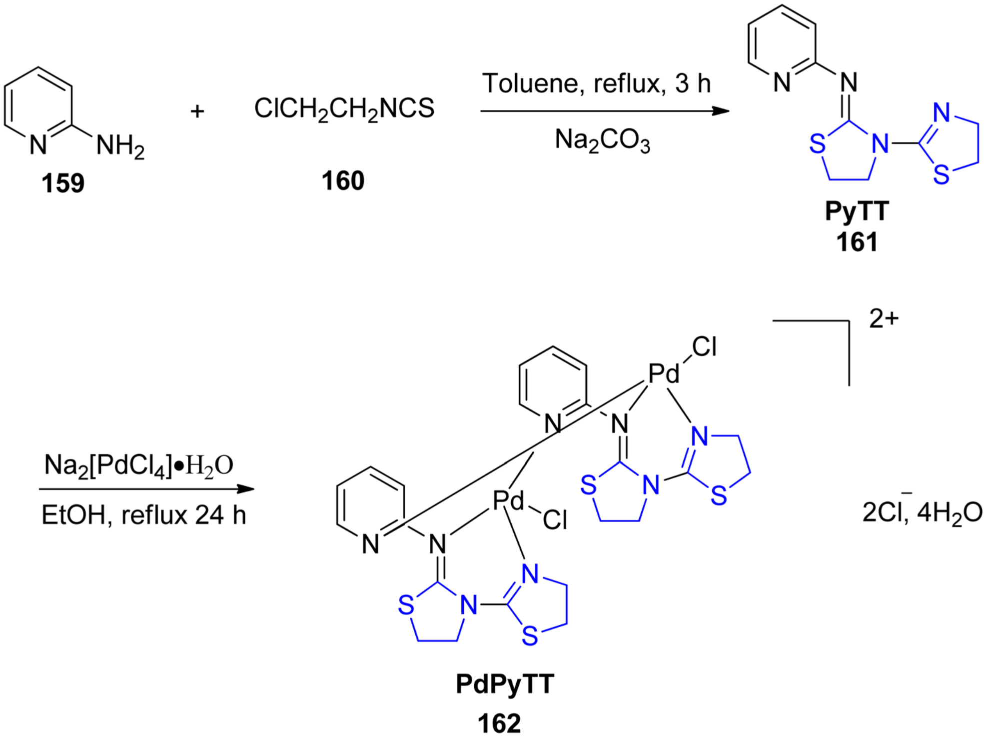


Compound	R	R^1/R^2
156a, 158a	H	
156b, 158b	H	
156c, 158c	H	
156d, 158d	H	
156e, 158e	H	
156f, 158f	Br	
156g, 158g	H	
156h, 158h	H	

Scheme 38 Synthesis of novel isatin–thiazoline **158a–h**.

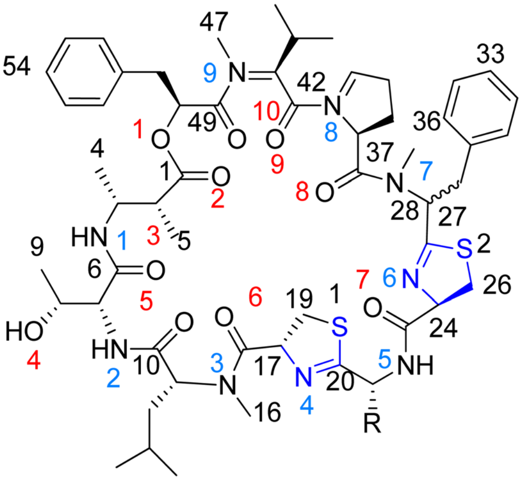
by Doornbos and Peer.[141] The anti-bacterial efficacy of the ligand **244** and the complexes **245–250** was also investigated against *B. subtilis*, *S. epidermidis*, *E. faecalis*, *E. coli* and *S. aureus*. Antimicrobial studies have demonstrated that cadmium complexes exhibit the most potent antimicrobial activity against various microorganisms. The MIC values for cadmium(II) complexes **249** and **250** against *E. faecalis*, *E. coli*, *S. epidermidis*, and *S. aureus* were found to be 50, 25, 12.5, and 25 mg mL^{-1}, respectively. In these instances, the antibacterial activity is enhanced compared to both the free HATtsc ligand and cadmium(II) salts. Concerning *B. subtilis*, the activity of complexes **249** and **250** matches that of the salts and surpasses that of HATtsc. However, it's important to note that these complexes exhibit no activity against *P. aeruginosa.* The observed low minimum inhibitory concentration (MIC) values for *B. subtilis* can be attributed to the interference of Cd(II) compounds with the process of cell separation.

Ahmad *et al.*[142] designed and synthesized a diverse library of thiazoline analogues, incorporating long-chain esters of fatty acids. These analogues were developed to inhibit CYP51 in *Candida albicans* and PDF in *Escherichia coli.* The corresponding thiazoline derivatives, denoted as **252a–d**, were obtained by subjecting the dibromo derivative to thiourea treatment, as depicted in Scheme 47. Comprehensive investigations into the antibacterial and antifungal activities of these compounds were conducted. Characterization involved spectroscopic analyses,



Scheme 39 Synthesis of thiazoline-based palladium(II) complex **162**.

infrared (IR) and mass analysis. Notably, these molecules exhibited remarkable antibacterial efficacy against the tested microbes, comparable to commonly used drugs like fluconazole and ciprofloxacin. Among all the synthesized compounds, compound **252a** (MIC: 25 μg mL^{-1}) showed highest antibacterial activity against *E. coli.* These results are almost equivalent to approved drug ciprofloxacin.



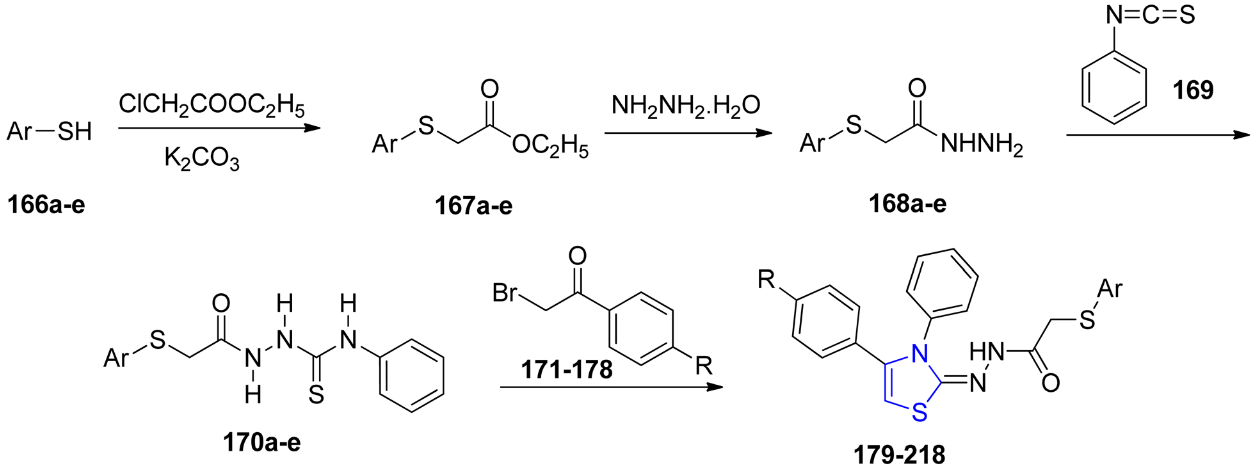
163: R = Et, 28*R*
164: R = Me, 28*R*
165: R = Et, 28*S*

Scheme 40 Grassypeptolides **163–165**, the cyclic depsipeptides.

Furthermore, compounds **252a** and **252d** displayed antifungal properties when tested against clinical isolates of *Candida* that had developed resistance to itraconazole and fluconazole.

A facile and practical methodology for developing novel heterocyclic compounds based on anthraquinone for testing their anti-bacterial properties was disclosed by Gouda *et al.*[143] The thiazoline analogue **254** was synthesized by reaction of compound **253** with PhNCS **228b** (Scheme 48). The precursor acetamide **253** was obtained by following the previously described scheme.[144]

Ke *et al.*[145] investigated steroidal analogues of thiazoline as potential antiviral agents, leveraging the diverse biological properties inherent in naturally derived heterocyclic molecules. The steroid-based thiazoline heterocycles were synthesized by following a simple condensation reaction (Scheme 49). The literature reported procedure was modified appropriately while preparing the intermediates **257a–c.**[146,147] The target thiazolines **260a–k**, **261a–i**, **262a–i** were obtained by treating the intermediates **257a–c** with the required amount of acetophenone **259.** Dihydrothiazole **263** was synthesized to explore the impact of introducing various fragments on its activity. The synthesized compounds were assessed for their potential antiviral effectiveness against CVB3 and EV71 viruses. Compounds **260b**, **260g**, and **260i** demonstrated efficiency against EV71 having EC_{50} values of 0.61 μmol L^{-1}, 0.95 μmol L^{-1}, and 2.31 μmol L^{-1}, respectively; while compounds **260b**, **260e**, **261c**, and **261g** with EC_{50} values of 1.83 μmol L^{-1}, 6.79 μmol L^{-1}, 7.09 μmol L^{-1} and 2.49 μmol L^{-1}, respectively, exhibited enhanced antiviral



Compound	R	Ar	Yield(%)
179	H	4-Methyl-4*H*-1,2,4-triazol-3-yl	70
180	NO$_2$	4-Methyl-4*H*-1,2,4-triazol-3-yl	80
181	CH$_3$	4-Methyl-4*H*-1,2,4-triazol-3-yl	70
182	OCH$_3$	4-Methyl-4*H*-1,2,4-triazol-3-yl	71
183	F	4-Methyl-4*H*-1,2,4-triazol-3-yl	72
184	Cl	4-Methyl-4*H*-1,2,4-triazol-3-yl	75
185	Br	4-Methyl-4*H*-1,2,4-triazol-3-yl	76
186	CN	4-Methyl-4*H*-1,2,4-triazol-3-yl	81
187	H	1-Methyl-1*H*-tetrazol-5-yl	75
188	NO$_2$	1-Methyl-1*H*-tetrazol-5-yl	80
189	CH$_3$	1-Methyl-1*H*-tetrazol-5-yl	74
190	OCH$_3$	1-Methyl-1*H*-tetrazol-5-yl	72
191	F	1-Methyl-1*H*-tetrazol-5-yl	75
192	Cl	1-Methyl-1*H*-tetrazol-5-yl	77
193	Br	1-Methyl-1*H*-tetrazol-5-yl	78
194	CN	1-Methyl-1*H*-tetrazol-5-yl	81
195	H	1-Phenyl-1*H*-tetrazol-5-yl	78
196	NO$_2$	1-Phenyl-1*H*-tetrazol-5-yl	85
197	CH$_3$	1-Phenyl-1*H*-tetrazol-5-yl	75
198	OCH$_3$	1-Phenyl-1*H*-tetrazol-5-yl	73
199	F	1-Phenyl-1*H*-tetrazol-5-yl	75
200	Cl	1-Phenyl-1*H*-tetrazol-5-yl	83
201	Br	1-Phenyl-1*H*-tetrazol-5-yl	84
202	CN	1-Phenyl-1*H*-tetrazol-5-yl	86
203	H	5-Methyl-1,3,4-thiadiazol-2-yl	79
204	NO$_2$	5-Methyl-1,3,4-thiadiazol-2-yl	88
205	CH$_3$	5-Methyl-1,3,4-thiadiazol-2-yl	76
206	OCH$_3$	5-Methyl-1,3,4-thiadiazol-2-yl	75
207	F	5-Methyl-1,3,4-thiadiazol-2-yl	78
208	Cl	5-Methyl-1,3,4-thiadiazol-2-yl	85
209	Br	5-Methyl-1,3,4-thiadiazol-2-yl	86
210	CN	5-Methyl-1,3,4-thiadiazol-2-yl	89
211	H	Pyrimidin-2-yl	80
212	NO$_2$	Pyrimidin-2-yl	89
213	CH$_3$	Pyrimidin-2-yl	77
214	OCH$_3$	Pyrimidin-2-yl	75
215	F	Pyrimidin-2-yl	79
216	Cl	Pyrimidin-2-yl	87
217	Br	Pyrimidin-2-yl	88
218	CN	Pyrimidin-2-yl	90

Scheme 41 Synthetic scheme for thiazoline analogues **179–218**.

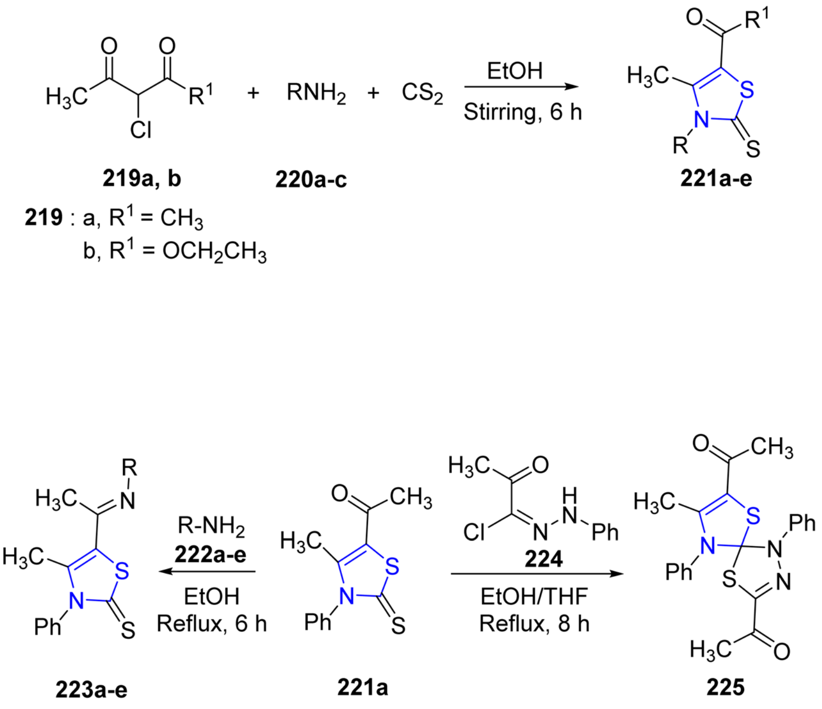
activity against CVB3 compared to control such as ribavirin or pirodavir, as determined through *in vitro* analysis.

Meleddu *et al.*[148] detailed the synthesis and development of a series of indol-2-one analogues, which were subsequently investigated for their impact on HIV-1 reverse transcriptase (RT). Initially, thiosemicarbazones **266a–b** were synthesized by refluxing an ethanolic solution containing substituted isatins **265a–b** and compound **264**. Subsequently, through treatment of compound **266a–b** with variously substituted bromo- or chloro-acetophenones **267a–m** in isopropanol, the resulting compounds **268a–m** and **269a–l** were obtained in high yields, as outlined in Scheme 50. These compounds demonstrated micromolar-level activity against ribonuclease H and DNA polymerase. IC$_{50}$ values for **268a–m** were in the range 15–29 μM, whereas 10–27 μM for compounds **269a–l**.

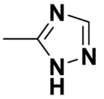
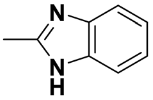
Hussein *et al.*[149] designed and synthesized a novel series of thiazoline quinoline derivatives through the cyclization of quinoline thiosemicarbazone. The preparation involved the synthesis of hydrazones **276a–e** and **281a–c** by treating ethanolic solutions of thiosemicarbazones **274a–e** with phenacyl bromides **275a–e**, as depicted in Scheme 51. Characterization of the prepared compounds was conducted through spectroscopic measurements and elemental analysis. A total of 28 novel compounds were evaluated for their potential antibacterial properties. In comparison to the reference drug gatifloxacin, most of the investigated compounds displayed moderate efficacy against various bacterial strains. Similar results were observed when assessing the compounds for their antifungal properties, using ketoconazole as the reference drug. Notably, these compounds demonstrated significant anti-inflammatory activity, with indomethacin serving as the reference. Furthermore, when the most potent compounds, **277b** and **280e**, were tested on mice, they were found to be non-toxic even at high doses of 400 mg kg^{-1}.

3.3.3. Anti-diabetic.

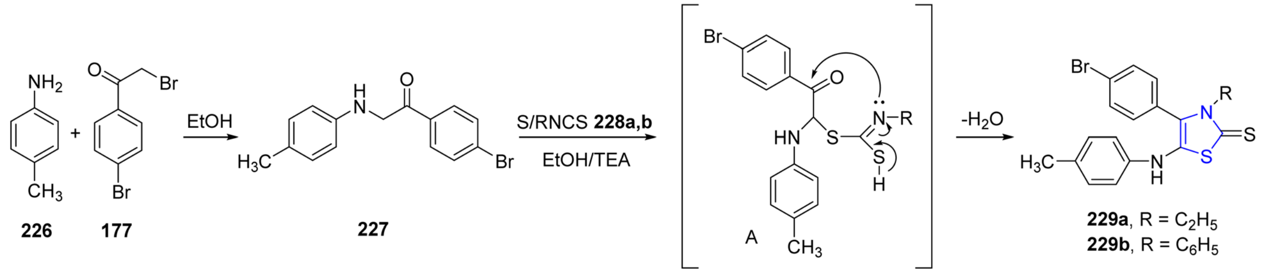
Diabetes mellitus, or diabetes, is a chronic condition disrupting food processing in the body. The global prevalence of diabetes mellitus (DM) has surpassed 400 million individuals, marking a concerning increase.[150]



221	R	R^1	Yield (%)
a	Ph	CH_3	92
b	Ph	OCH_2CH_3	85
c	H	CH_3	85
d	H	OCH_2CH_3	75
e	PhNH	OCH_2CH_3	85

223	R	Yield (%)
a	NH_2	55
b	Ph	50
c	NH-Ph	60
d		50
e		45

Scheme 42 Synthesis of new thiazoline derivatives.

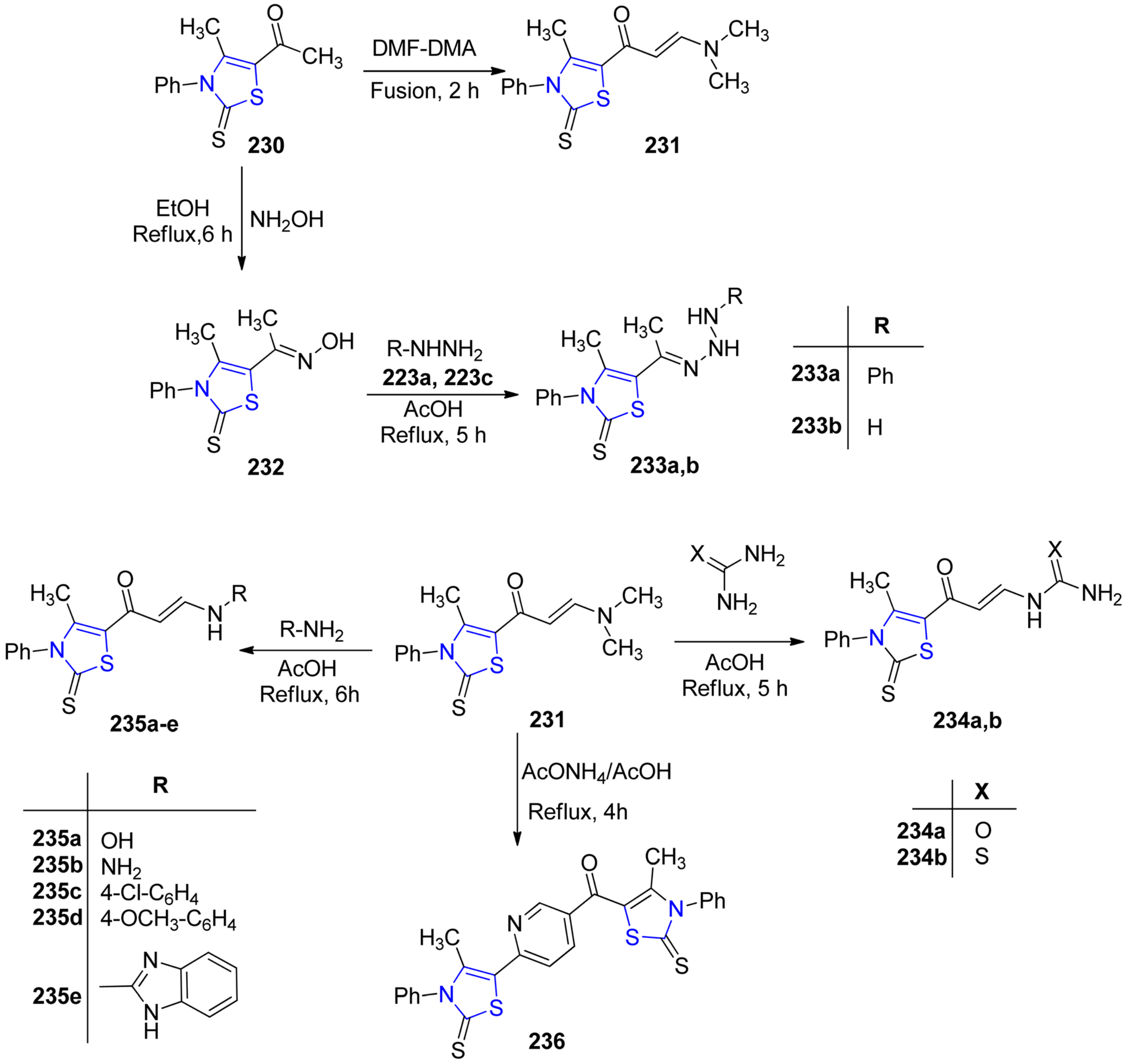


Scheme 43 Synthesis of thiazoline-based derivatives **229a–b**.

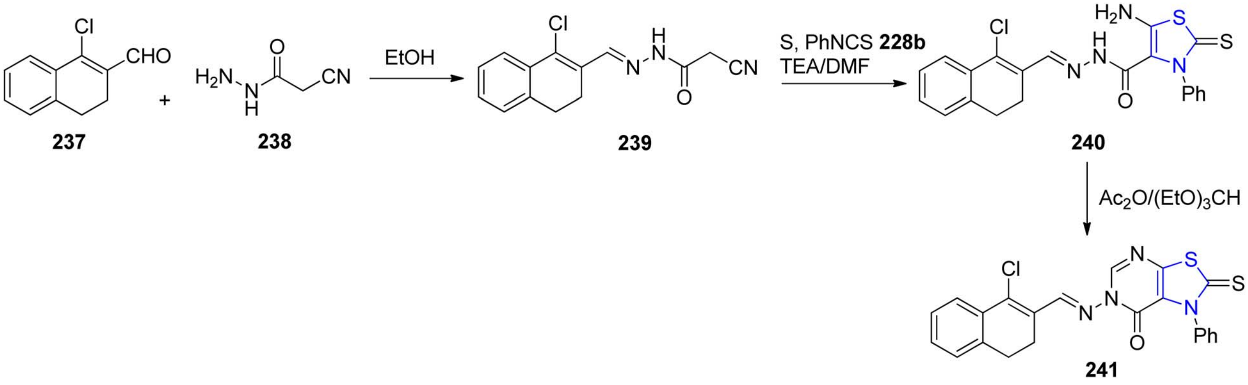
Approximately 25% of individuals aged 65 and older experience diabetes-related complications, and this percentage is steadily increasing.[151] The vast majority of DM patients come from the underdeveloped or developing parts of the world.[152,153] Current diabetic medications have limitations, including inconsistent responses among individuals, difficulty in achieving glucose control, and potential side effects. Managing diabetes often requires multiple self-care measures, including medication management. Additionally, individuals with diabetes often have concurrent chronic conditions such as cardiovascular disease (CVD), hypertension, high cholesterol, and depression, which may require additional drug treatments.[154]

The two incretin hormones, GLP-1 and GIP, are deactivated by the enzyme dipeptidyl peptidase IV (DPP-4). Therefore, DPP-4 inhibitors play a vital role by slowing down the activity of GIP and GLP-1 hormones, thereby maintaining glucose homeostasis. The therapeutic potential of the DPP-4 enzyme makes it a preferred target in pharmacology.[155]

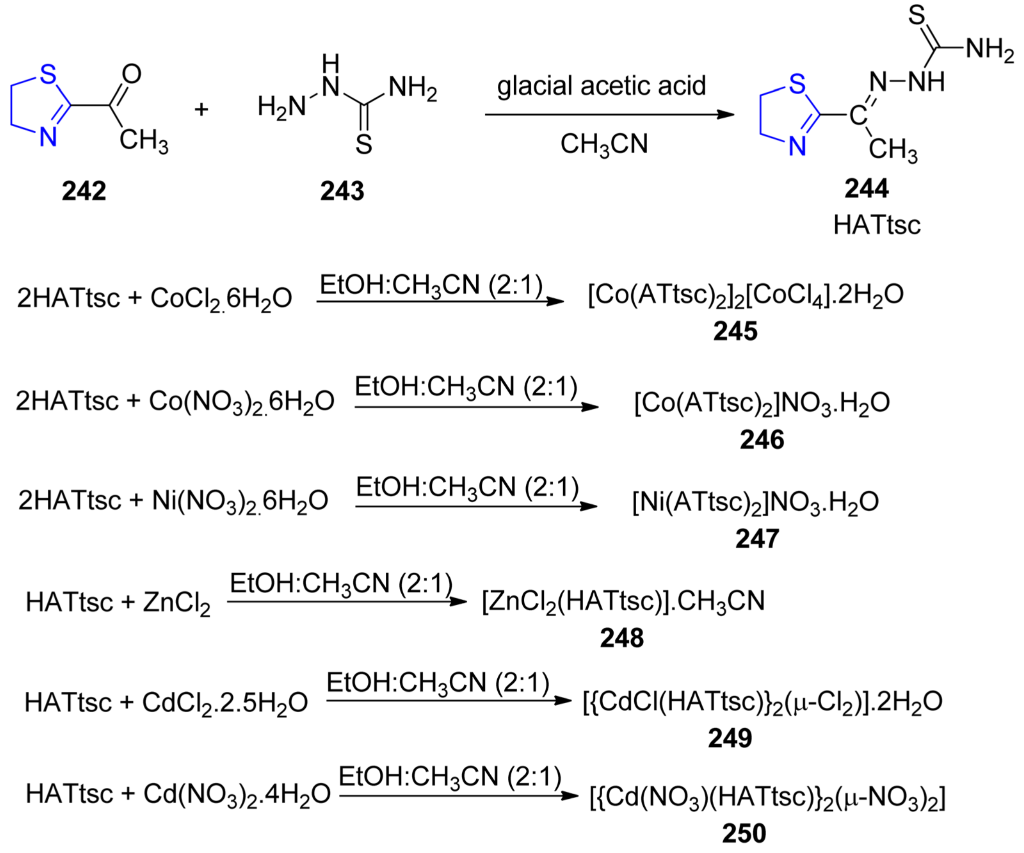
Ali *et al.*[156] synthesized a distinct class of thiazoline derivatives linked to quinazoline. Initially, three different derivatives of anthranilic acid **282a–c** were reacted with acetyl chloride **283** to give the cyclized benzoxazin-4-ones **284a–c.** Further, a condensation reaction of these benzoxain-4-ones **284a–c** with substituted thiazoles **285a/b** gave benzoxain-4-ones **286a–f.**[157] In



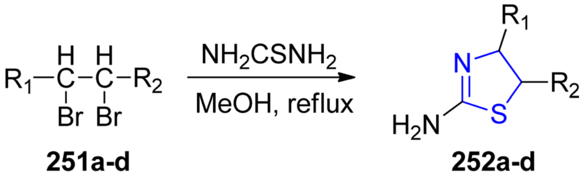
Scheme 44 Synthesis of novel thiazoline-2-thione derivatives.



Scheme 45 Synthesis of thiazoline **240** and thiazolo[5,4-*d*]pyrimidinone derivative **241**.



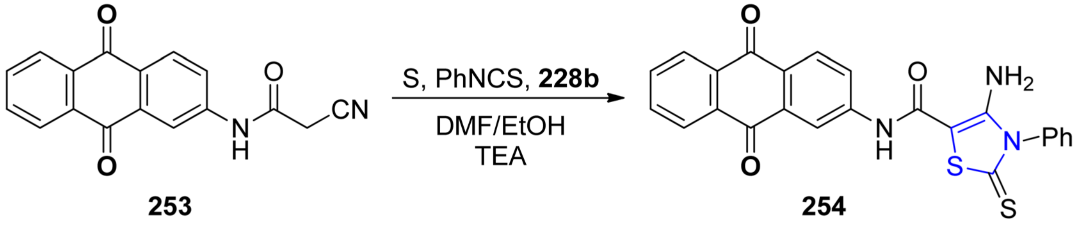
Scheme 46 Synthesis of novel ligand, HATtsc **244** and its complexes **245–250**.



Compounds	R_1	R_2
251a, 252a	H	$(CH_2)_8COOCH_3$
251b, 252b	$CH_3(CH_2)_7$	$(CH_2)_7COOCH_3$
251a, 252b	$CH_3(CH_2)_5CHOHCH_2$	$(CH_2)_7COOCH_3$
251a, 252b	$CH_3(CH_2)_4$	$(CH_2)_2CHOH(CH_2)_7COOCH_3$

Scheme 47 Synthesis of thiazoline derivative **252a–d**.

the final stage, quinazolin-4-ones **287a–f** were prepared by refluxing alcoholic solution of **286a–f** with hydrazine hydrate for 4 hours. Additionally, the quinazoli-4-ones **287a–f** thus obtained were condensed with aldehydes **288a–d** to yield a sequence of Schiff bases **289a–x** (Scheme 52).[158] The compounds thus obtained were also assessed for their inhibitory action against dipeptidyl peptidase IV (DPP-4) *invitro*. Utilizing linagliptin as a benchmark, compounds that displayed good to moderate activity were contrasted. The results for compound **289x** (IC_{50} of 1.12 nM) were the most encouraging.

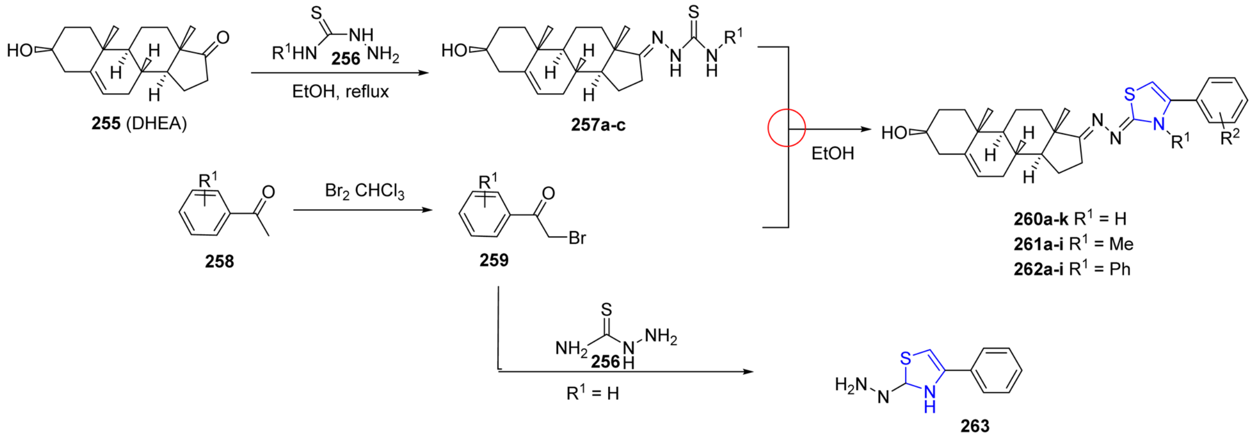


Scheme 48 Synthesis of thiazoline derivative **254**.

Compound **289x** possessed unique chemical features which provided DPP-4 with better inhibitory selectivity in comparison to DPP-8 or DPP-9.

Utilizing small heterocyclic compounds to inhibit aldose reductase (ALR2) is a viable approach for developing innovative anti-diabetic medications. To identify a lead as a potential novel anti-diabetic drug, Shehzad *et al.*[159] synthesized thiazoline analogues **294a–k, 295a–f, 296a–l** and **297a–j**. In order to obtain the thiazoline derivatives **294–297**, four different types of carbonyl group-bearing compounds were used, with yields ranging from 76 to 92% (Scheme 53). Compounds **296b** (IC_{50} = 1.39 ± 2.21 μM) and **297e** (IC_{50} = 1.52 ± 0.78 μM) were identified to be the most efficient ones in comparison to the reference drug, sorbinil (IC_{50} = 3.14 ± 0.02 μM). Compound **296b** demonstrated good selectivity for the intended ALR2 with just 23.4% inhibition for ALR1.

3.3.4. **Others.** The majority of β-acetylglucosaminidases (β-GlcNAcases) are susceptible to inhibition by NAG-thiazoline (NGT) and its analogues. However, exceptions include insect and bacterial chitinolytic β-GlcNAcases, like OfHex1 from the insect *Ostrinia furnacalis*, which plays a crucial role in the molting process. The NGT complex of essential GH20 chitinolytic β-GlcNAcase OfHex1 for insect molting was crystallized and its structure was published by Liu *et al.*[160] The structure analysis

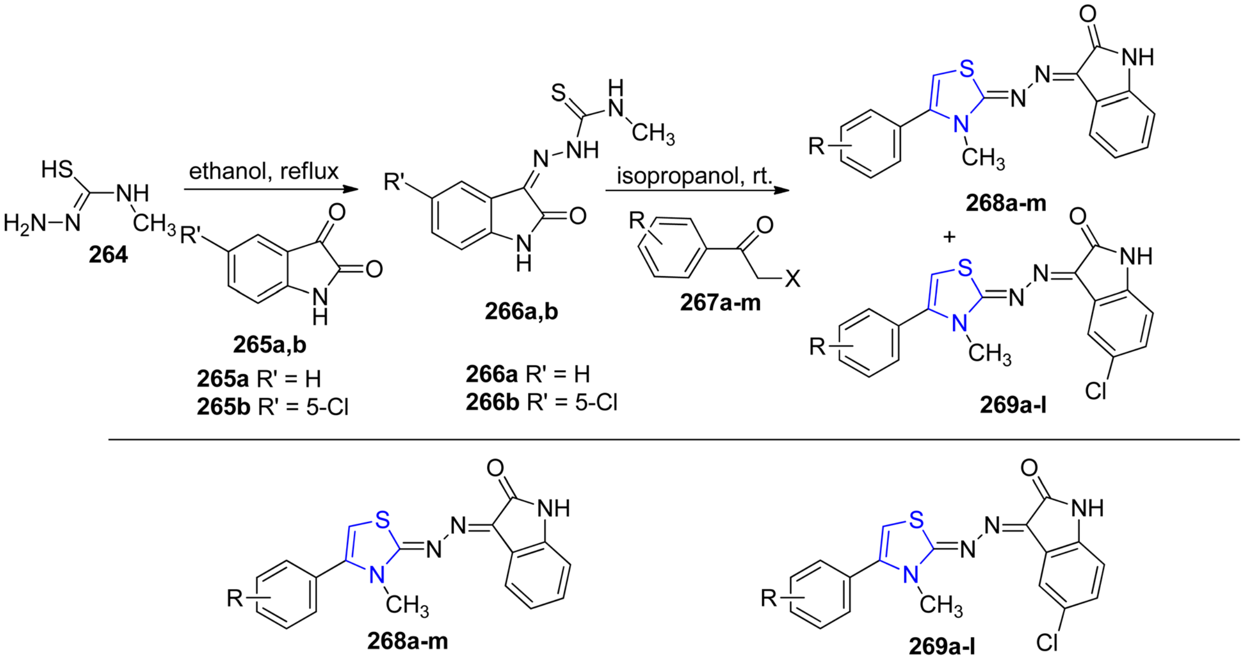


260a-i	260a	260b	260c	260d	260e	260f	260g	260h	260i	260j	260k
R^1	H	H	H	H	H	H	H	H	H	H	H
R^1	H	4-MeO	4-F	4-Br	4-CN	2-F	2-NO_2	3,4-Cl_2	4-Me	4-NO_2	3,4-(CH=CH-CH=CH)

261a-i	261a	261b	261c	261d	261e	261f	261g	261h	261i
R^1	Me	Me	Me	Me	Me	Me	Me	Me	Me
R^1	H	4-MeO	4-F	4-Br	4-CN	2-F	2-NO_2	3,4-Cl_2	4-Me

262a-i	262a	262b	262c	262d	262e	262f	262g	262h	262i
R^1	Ph	Ph	Ph	Ph	Ph	Ph	Ph	Ph	Ph
R^1	H	4-MeO	4-F	4-Br	4-CN	2-F	2-NO_2	3,4-Cl_2	4-Me

Scheme 49 Synthesis of a number of steroid derivatives with thiazoline heterocycles.



Compound	R
267a, 268a	R = 4-Cl
267b, 268b	R = 4-F
267c, 268c	R = 4-Br
267d, 268d	R = 4-NO_2
267e, 268e	R = 4-C_6H_5
267f, 268f	R = 4-CN
267g, 268g	R = 2,4-F
267h, 268h	R = 3-NO_2
267i, 268i	R = 3,4-Cl
267j, 268j	R = 4-CH_3
267k, 268k	R = 4-OCH_3
267l, 268l	R = H
267m, 268m	R = 2,4-Cl

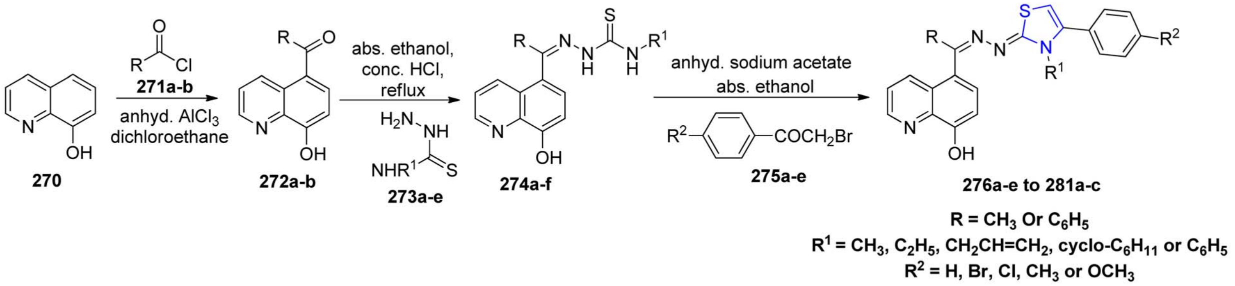
Compound	R
267a, 269a	R = 4-Cl
267b, 269b	R = 4-F
267c, 269c	R = 4-Br
267d, 269d	R = 4-NO_2
267e, 269e	R = 4-C_6H_5
267f, 269f	R = 4-CN
267g, 269g	R = 2,4-F
267h, 269h	R = 3-NO_2
267i, 269i	R = 3,4-Cl
267j, 269j	R = 4-CH_3
267k, 269k	R = 4-OCH_3
267l, 269l	R = H

Scheme 50 Synthesis of isatin thiazoline hybrids **268a–m** and **269a–l**.

of OfHEx1 revealed the presence of a sizable active pocket, which could explain the weak inhibitory effect of NGT. A derivative of NGT (NMAGT) was synthesized based on this crystal structure and found to inhibit OfHEx1 (Ki = 0.13 μM) in sub-micromolar quantities. The Ki value was less than 600 times than that of NGT (Scheme 54). Molecular dynamics simulation studies also confirmed the match of NMAGT with that of the active pocket.

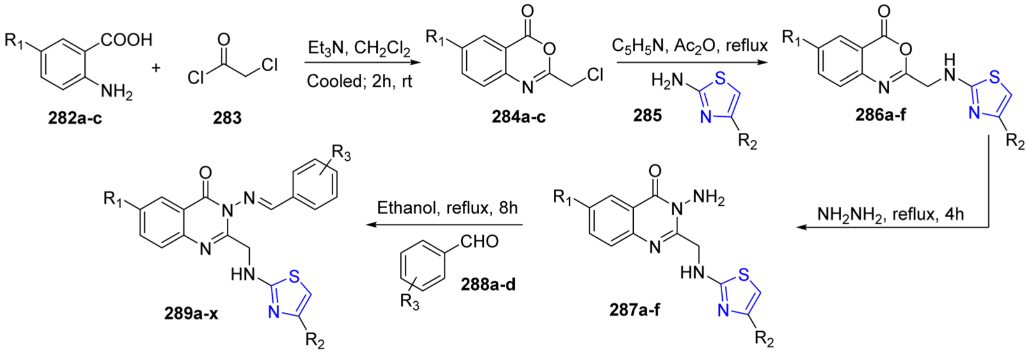
Human skin and hair contain the biological pigment melanin. Pigmentation development in animals depends on α-MSH.[161] A novel thiazoline analogue, KHG22394 **302** was synthesized by Kim *et al.*[162] as a skin whitener (Scheme 55). Although, KHG22394 does not inhibit the tyrosinase enzyme directly, but according to the research data it has been shown that it greatly reduces melanin synthesis in a dose-dependent way. ERK activity has been shown to inhibit the transcription factor linked to microphthalmia, which in turn decreases melanin formation (Mitf). In B16 melanoma cells, KHG22394 upregulates the ERK pathway while downregulating the protein levels of Mitf and tyrosinase. Despite not directly inhibiting tyrosinase activity, KHG22394's hypopigmentary impact is due to the downregulation of Mitf and tyrosinase as a result.

Hosamani *et al.*[163] employed microwave irradiation to establish an efficient methodology for synthesizing coumarin–thiazolines **307a–j**, as illustrated in Scheme 56. Characterization of these compounds **307a–j** was accomplished through spectroscopic and elemental analyses. Notably, compound **307b** exhibited remarkable efficacy (MIC = 0.09 μg mL^{-1}) with minimal toxicity to normal cells, as determined *via in vitro* anti-tubercular screening on Vero cells. Furthermore, compounds **307b** and **307i** demonstrated complete DNA cleavage, establishing them as the most effective *in vitro* agents against the MtbH37 strain.



Compound no.	R	R^1	R^2	Yield(%)
276a	CH_3	CH_3	H	89
276b	CH_3	CH_3	Br	81
276c	CH_3	CH_3	Cl	72
276d	CH_3	CH_3	CH_3	84
276e	CH_3	CH_3	OCH_3	78
277a	CH_3	C_2H_5	H	74
277b	CH_3	C_2H_5	Br	88
277c	CH_3	C_2H_5	Cl	81
277d	CH_3	C_2H_5	CH_3	70
277e	CH_3	C_2H_5	OCH_3	64
278a	CH_3	$CH_2CH{=}CH_2$	H	70
278b	CH_3	$CH_2CH{=}CH_2$	Br	80
278c	CH_3	$CH_2CH{=}CH_2$	Cl	67
278d	CH_3	$CH_2CH{=}CH_2$	CH_3	62
278e	CH_3	$CH_2CH{=}CH_2$	OCH_3	63
279a	CH_3	cyclo-C_6H_{11}	H	73
279b	CH_3	cyclo-C_6H_{11}	Br	76
279c	CH_3	cyclo-C_6H_{11}	Cl	66
279d	CH_3	cyclo-C_6H_{11}	CH_3	83
279e	CH_3	cyclo-C_6H_{11}	OCH_3	86
270a	CH_3	C_6H_5	H	64
280b	CH_3	C_6H_5	Br	53
280c	CH_3	C_6H_5	Cl	70
280d	CH_3	C_6H_5	CH_3	89
280e	CH_3	C_6H_5	OCH_3	75
281a	C_6H_5	cyclo-C_6H_{11}	H	66
281b	C_6H_5	cyclo-C_6H_{11}	Br	73
281c	C_6H_5	cyclo-C_6H_{11}	Cl	78

Scheme 51 Synthetic scheme for quinoline–thiazoline analogues **276a–e** to **281a–c**.

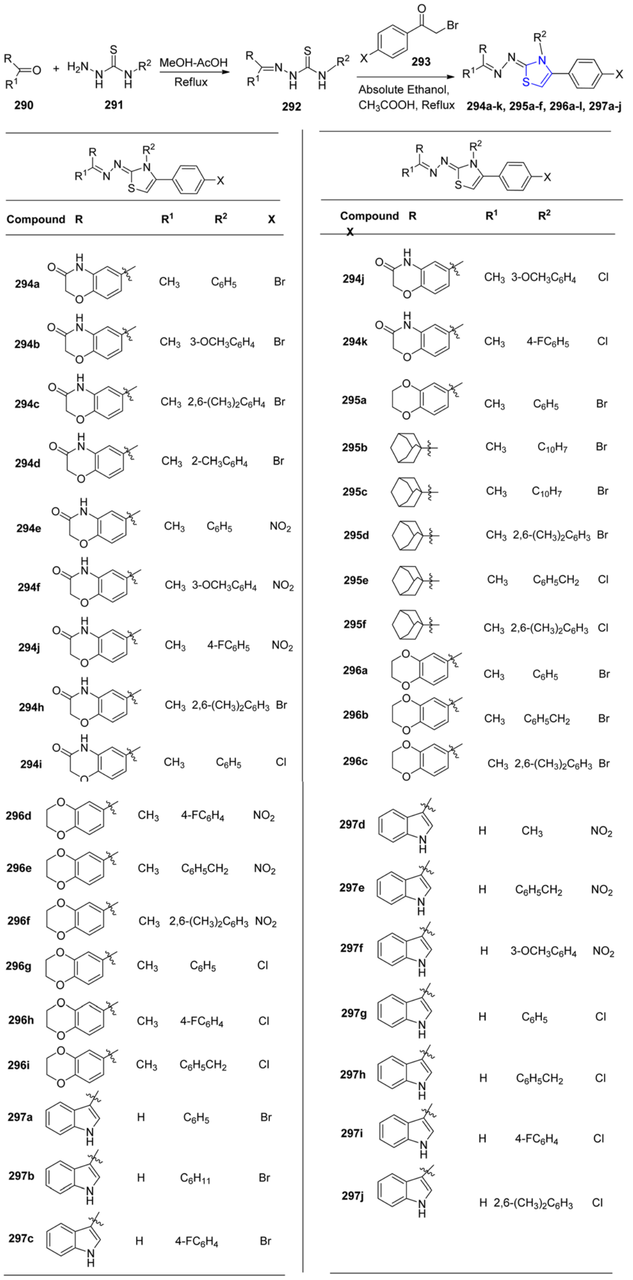


Compound	R_1	R_2	R_3
289a	H	H	H
289b	H	H	2-CN
289c	H	H	3-NO_2
289d	H	H	4-OH
289e	H	CH_3	H
289f	H	CH_3	2-CN
289g	H	CH_3	3-NO_2
289h	H	CH_3	4-OH
289i	I	H	H
289j	I	H	2-CN
289k	I	H	3-NO_2
289l	I	H	4-OH
289m	I	CH_3	H
289bn	I	CH_3	2-CN
289o	I	CH_3	3-NO_2
289p	I	CH_3	4-OH
289q	CH_3	H	H
289r	CH_3	H	2-CN
289s	CH_3	H	3-NO_2
289t	CH_3	H	4-OH
289u	CH_3	CH_3	H
289v	CH_3	CH_3	2-CN
289w	CH_3	CH_3	3-NO_2
289x	CH_3	CH_3	4-OH

Scheme 52 Synthetic scheme for quinoline linked thiazoline derivatives.

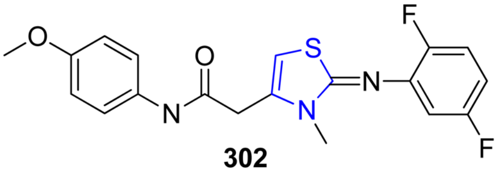
4. Miscellaneous

Nonlinear optical (NLO) materials are cost-effective and easily tunable in terms of absorption wavelength, making them versatile for applications in information technology, telecommunications, and healthcare sector. Researchers, both experimental and computational, are drawn to these NLO compounds for their diverse applications in optical computing, biophysics,



Compound	R^1	R^2	X
294a	CH_3	C_6H_5	Br
294b	CH_3	$3\text{-}OCH_3C_6H_4$	Br
294c	CH_3	$2,6\text{-}(CH_3)_2C_6H_4$	Br
294d	CH_3	$2\text{-}CH_3C_6H_4$	Br
294e	CH_3	C_6H_5	NO_2
294f	CH_3	$3\text{-}OCH_3C_6H_4$	NO_2
294j	CH_3	$4\text{-}FC_6H_5$	NO_2
294h	CH_3	$2,6\text{-}(CH_3)_2C_6H_3$	Br
294i	CH_3	C_6H_5	Cl
296d	CH_3	$4\text{-}FC_6H_4$	NO_2
296e	CH_3	$C_6H_5CH_2$	NO_2
296f	CH_3	$2,6\text{-}(CH_3)_2C_6H_3$	NO_2
296g	CH_3	C_6H_5	Cl
296h	CH_3	$4\text{-}FC_6H_4$	Cl
296i	CH_3	$C_6H_5CH_2$	Cl
297a	H	C_6H_5	Br
297b	H	C_6H_{11}	Br
297c	H	$4\text{-}FC_6H_4$	Br
294j	CH_3	$3\text{-}OCH_3C_6H_4$	Cl
294k	CH_3	$4\text{-}FC_6H_5$	Cl
295a	CH_3	C_6H_5	Br
295b	CH_3	$C_{10}H_7$	Br
295c	CH_3	$C_{10}H_7$	Br
295d	CH_3	$2,6\text{-}(CH_3)_2C_6H_3$	Br
295e	CH_3	$C_6H_5CH_2$	Cl
295f	CH_3	$2,6\text{-}(CH_3)_2C_6H_3$	Cl
296a	CH_3	C_6H_5	Br
296b	CH_3	$C_6H_5CH_2$	Br
296c	CH_3	$2,6\text{-}(CH_3)_2C_6H_3$	Br
297d	H	CH_3	NO_2
297e	H	$C_6H_5CH_2$	NO_2
297f	H	$3\text{-}OCH_3C_6H_4$	NO_2
297g	H	C_6H_5	Cl
297h	H	$C_6H_5CH_2$	Cl
297i	H	$4\text{-}FC_6H_4$	Cl
297j	H	$2,6\text{-}(CH_3)_2C_6H_3$	Cl

Scheme 53 Synthesis of thiazoline derivatives **294a–k**, **295a–f**, **296a–l** and **297a–j**.

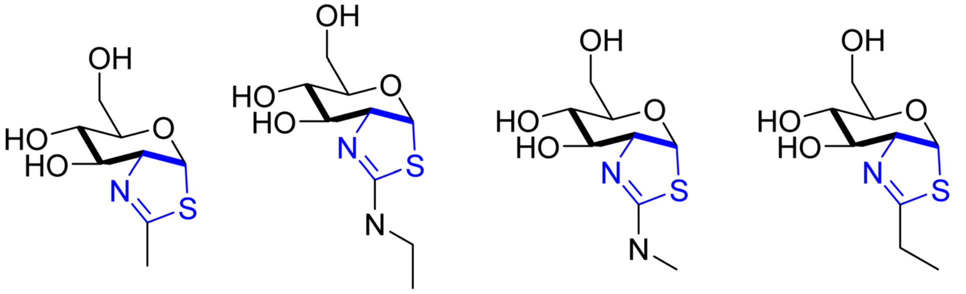


302

Scheme 55 Structure of KHG22394.

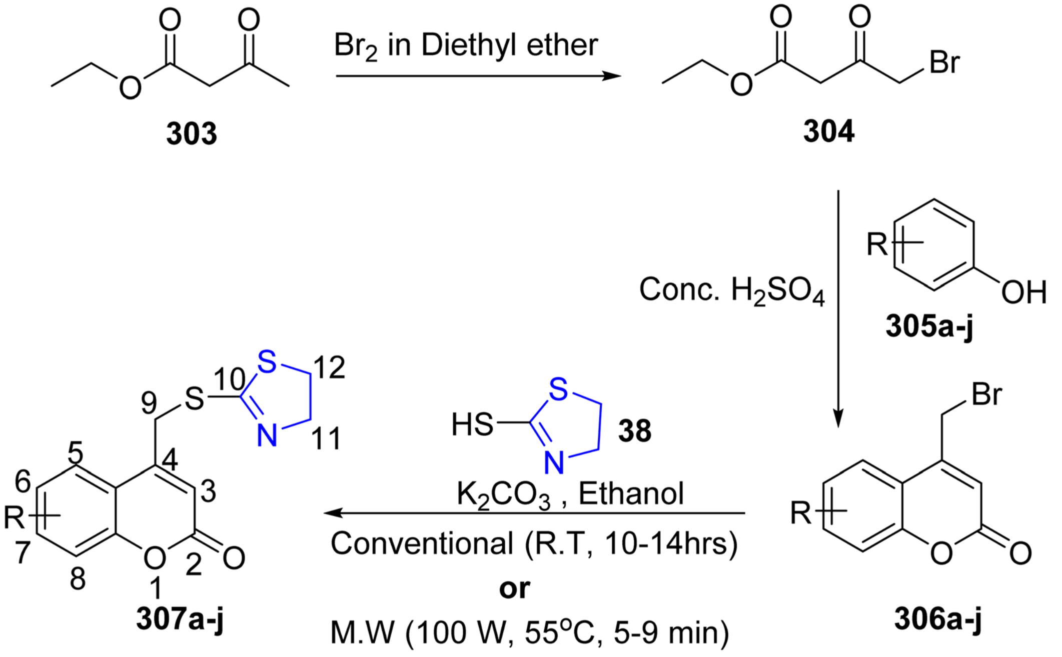
solid physics, dynamic image processing, nuclear science, and biophysics.[164,165] Thiazoline derivatives are fascinating molecules because of their potential usage in nonlinear optics (NLO). Haroon *et al.*[166] described four new thiazoline derivatives with the chemical formulae $C_{27}H_{24}ClN_3O_2S$, $C_{27}H_{23}ClN_4O_2S$, $C_{26}H_{21}N_5O_2S$, and $C_{28}H_{30}ClN_3S$. Characterization of the synthesized compounds was done by using spectroscopic experiments, elemental analysis and FTIR measurements. The two-step process used to obtain the new thiazoline derivatives **312a–d** with varied substitutions is detailed in Scheme 57. The first step of the synthetic procedure began by condensing varied carbonyl molecules **318a–d** with thiosemicarbazides **319** in methanolic solution to yield thiosemicarbazone intermediates **310.** These intermediates were then subjected to a cyclization reaction in ethanolic media with two different phenacyl bromides **311a/b** to yield the thiazoline analogues. The energy gap of the compounds was in the order: **312a–d** >**312c** > **312b** > **312d** > **312a.** The least HOMO–LUMO energy gap in **312a** makes it the sensitive and reactive molecule, while **312c** has the highest energy gap, and thus is the most stable of all the examined compounds. Using a variety of various functionals, including HF, B3LYP, LC-BLYP, CAM-B3LYP, M06 & M062X in coupling with 6-311+G(d,p) basis set, the NLO characteristics of the examined compounds **312a–d** were estimated. Furthermore, at 0.02389 and 0 nm, the signals $\gamma(-\omega,\omega,0,0)$ and $\gamma(-2\omega,\omega,\omega,0)$ indicating the electro-optic Kerr effect and second harmonic production, respectively, were also studied. The NLO results clearly showed that compounds **312a–d** have attractive NLO traits and are suitable NLO aspirants for next-generation optoelectronic devices.

The thiazoline moiety can also be synthesized through cyclodehydration of compounds containing the β-hydroxy thioamide functionality. The synthetic pathways employed for the



298 **299** **300** **301**

Scheme 54 Structures of NGT and its derivatives.



Product	R	Yield(%)		Time(min)	
		[a]C	[b]M	C	M
307a	6-CH_3	63	88	600	5
307b	6-Cl	71	83	630	7
307c	6-OCH_3	75	91	670	6
307d	5,6-Benzo	64	82	810	8
307e	7-CH_3	66	86	640	6
307f	7-Cl	68	84	650	7
307g	7-OCH_3	69	87	720	6
307h	5,7-diCH_3	61	81	840	9
307i	6-Br	64	88	730	8
307j	7-Br	62	87	720	8

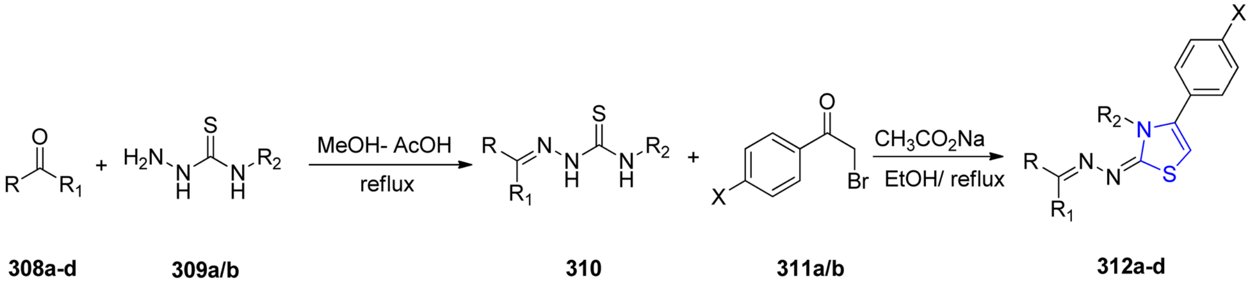
[a]C— **C**onventional: [b]M— **M**icrowave.

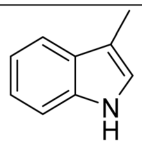
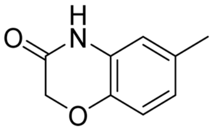
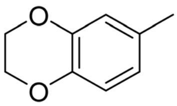
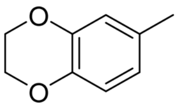
Scheme 56 Synthesis of coumarin–thiazoline hybrids **307a–j**.

production of cyclopeptide YM-216391 **317** and thiopeptide-based antibiotics such as GE2270C1, GE2270T, and GE2270A exemplify the utility of this approach.[167,168] When β-hydroxy thioamides **313** and **315** were exposed to DAST, they underwent intramolecular cyclization, leading to the formation of thiazolines **314** and **316** (Scheme 58). Compound **316** underwent oxidation to ultimately yield the cyclopeptide YM-216391 **317** in the presence of MnO_2. YM-216391 dose-dependently inhibited the growth of human cervical cancer HeLa S3 cells with an IC_{50} value of 14 nM. YM-216391 also showed potent cytotoxic activity against a human cancer cell line panel.

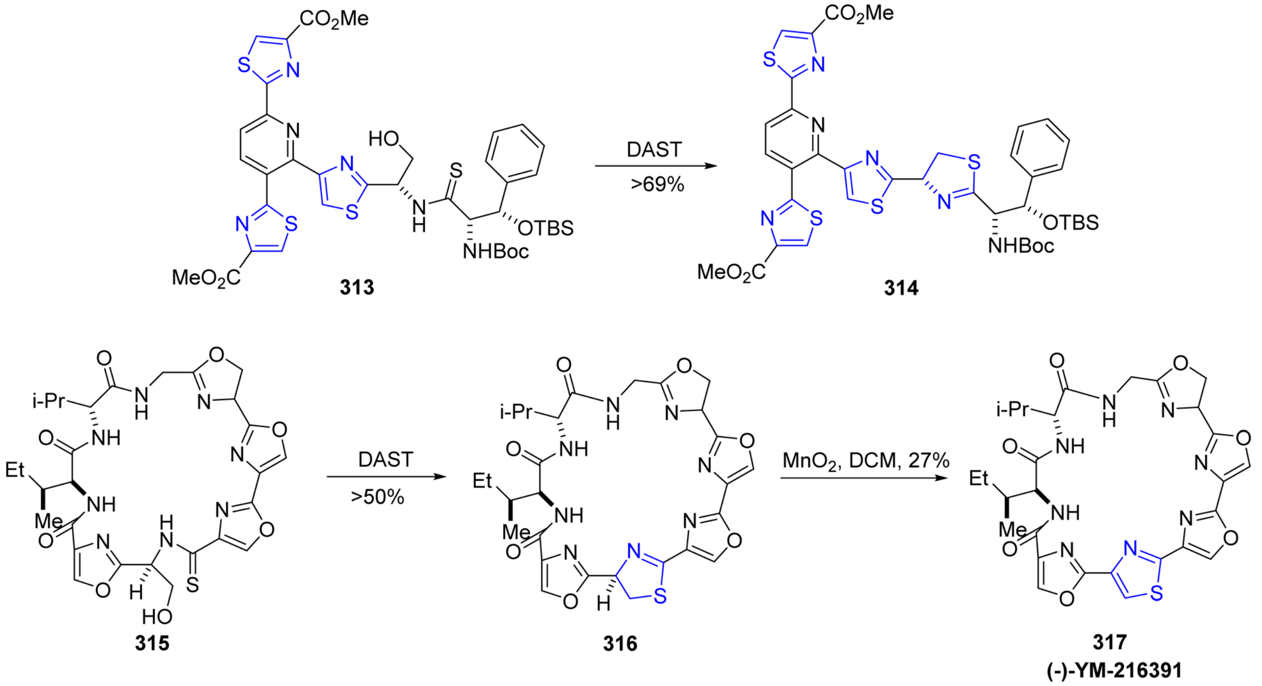
Scientific literature has documented the existence of over 3000 compounds containing thiazole-4-carbonitrile. These derivatives, including 4-carbonitrile and 4-carbimidate variations of thiazole, can be readily synthesized under mild conditions, yielding satisfactory yields, from thiazole–oxazoline and thiazole–thiazolines, respectively.

Diness *et al.*[169] synthesized one such fragment of the natural product, largazole, in five steps. The synthesis began by transforming Fmoc-Gly-NH_2 **318** with Lawesson's reagent to yield the Fmoc-protected product, which was further condensed with bromopyruvate to give thiazole acid **319** by following literature

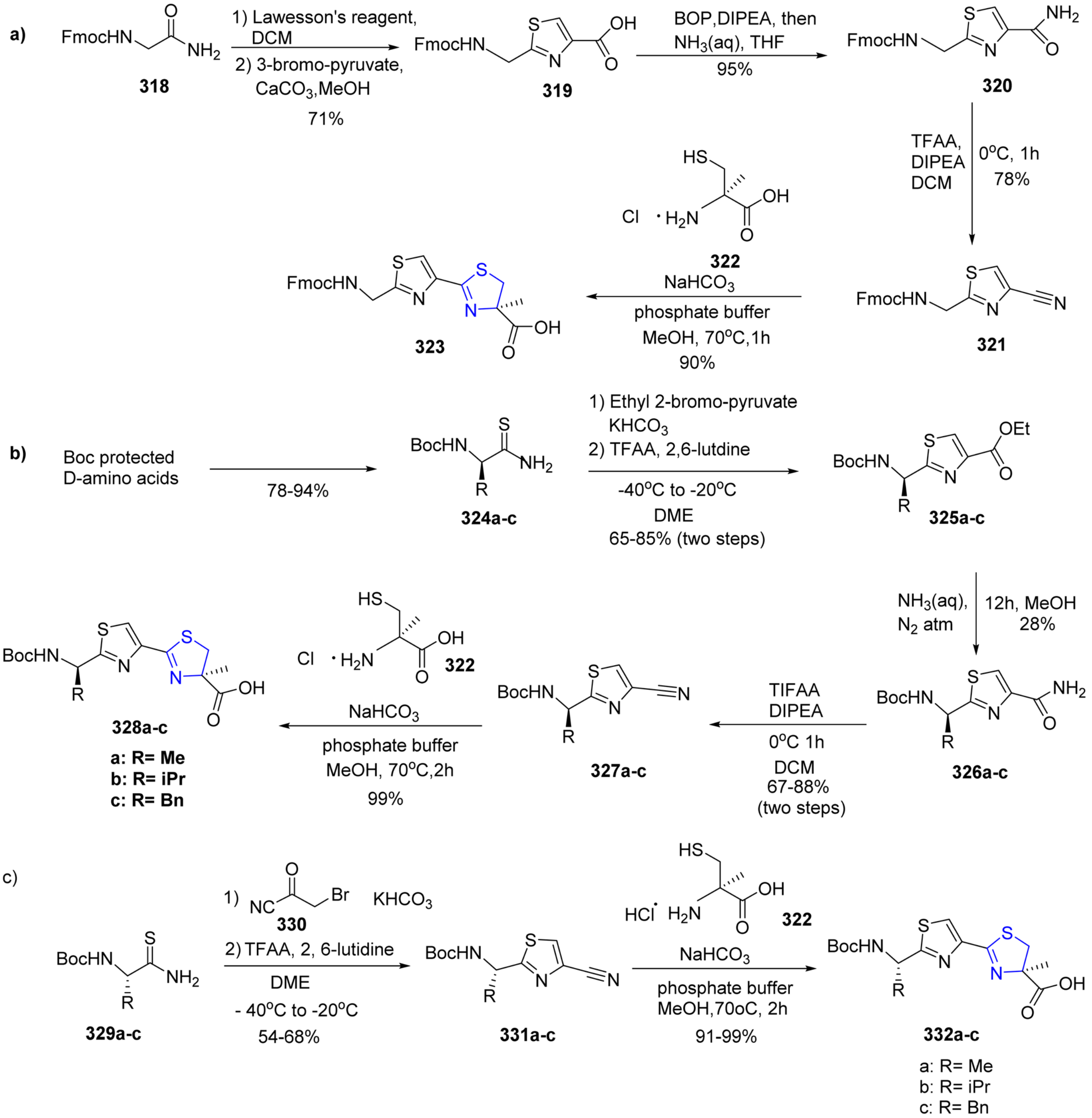


Compound	R	R₁	R₂	X
312a		H	2,6-(CH$_3$)$_2$C$_6$H$_3$	NO$_2$
312b		CH$_3$	2,6-(CH$_3$)$_2$C$_6$H$_3$	Cl
312c		CH$_3$	2-CH$_3$C$_6$H$_4$	Cl
312d		CH$_3$	2,6-(CH$_3$)$_2$C$_6$H$_3$	Cl

Scheme 57 Synthesis of thiazoline derivatives **312a–d**.

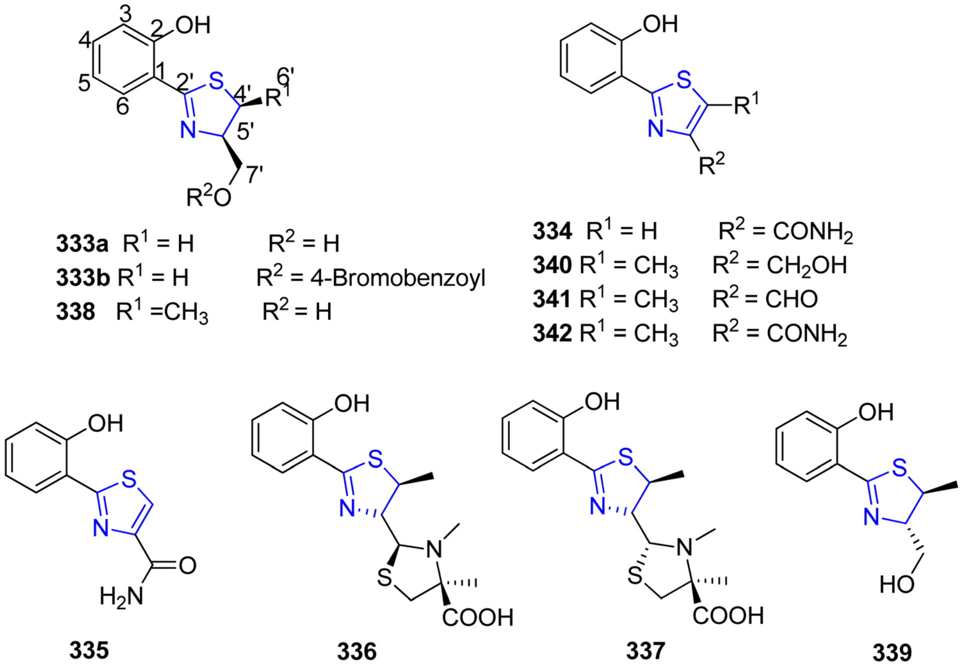


Scheme 58 Synthesis of thiazoline **314** and (−)-YM-216391 **317**.



Scheme 59 (a–c) Synthetic scheme for thiazoline fragment of the largazole derivatives.

procedure.[170] The resulting amide **320** was then transformed to the appropriate nitrile derivative **321** by dehydrating the amide with trifluoroacetic anhydride (TFAA). The Fmoc group was retained by rapid condensation with cysteine **322**.[171] The Fmoc-protected glycine amide **318** was transformed into the building block **323** with an overall yield of 47% (Scheme 59a). The other building blocks were protected by Boc-group since there was a chance that the Fmoc-protecting group might be lost during the final condensation. A modified Hantzsch process was utilized to condense the Boc-protected amino acids with 2-bromo-pyruvate ethyl ester to yield the corresponding thioamides **324a–c**.[172] The direct condensation reaction between the unprotected thioamide **324c** and bromopyruvate resulted in a partially racemized product, thus making this approach crucial. The thus obtained ethyl esters **325a–c** then underwent ammonolysis on treatment with aqueous ammonia to give compounds **326a–c**. This was followed by dehydration to yield the compounds **327a–c**.[173] In order to obtain the desired compounds **328a–c**, a condensation reaction was performed between cysteine **322** and carbonitriles **327a–c** with an overall yield of 43–72% (Scheme 59b). However, Scheme 59c describes a more effective method for creating a library of these building blocks. Fortunately, substituting the pyruvate derivative with nitrile **330** did result in good yields of the appropriate



Scheme 60 Neuroactive thiazoline metabolites.

carbonitriles **331a–c**.[174] A final condensation reaction with the cysteine derivative **322** resulted in the formation of the required thiazole-thiazoline building blocks **332a–c** (Scheme 59c).

Cone snails have been associated with various actinomycetes and other bacteria, some of which possess neurologically active properties upon extraction.[175] Actinomycetes and other bacteria have a specialized environment provided by the Philippine cone snail *Conus pulicarius*. Lin *et al.*[176] conducted research on *Streptomyces* sp. CP32, one of the active isolates from *C. pulicarius*. Five known analogues **333–337** and five novel analogues, **338–342** known as pulicatins A–E, were isolated using the assay-guided fractionation (Scheme 60). These molecules attach themselves to the human receptors, specifically the human 5-HT2B serotonin receptor. Additionally, **338** was discovered to be an important constituent of the *Streptomyces* sp. strain CT8, obtained from the hepatopancreas of the cone snail *C. tribblei*.

5. Future prospectus & conclusions

Thiazolines, also known as dihydrothiazoles, represent a class of 5-membered heterocyclic compounds characterized by the presence of both sulfur and nitrogen atoms within the ring structure. This isomeric heterocyclic family has garnered significant attention in the realm of chemistry due to its multifaceted role as efficient ligands in asymmetric catalysis and as crucial intermediates in synthetic organic chemistry. Thiazolines exhibit notable chelating capabilities with transition metal ions. Despite their relative novelty among chiral ligands compared to their oxygen counterparts (oxazolines), thiazolines exhibit distinct behavior in a variety of metal-catalysed reactions.

The versatility of these novel heterocyclic molecules has led to their wide-ranging applications, spanning organic synthesis, pharmaceuticals, agrochemistry, and catalysis. In recent years, a plethora of thiazoline analogues have been synthesized and explored for their intriguing therapeutic potential, encompassing anti-cancer properties, anti-oxidant effects, anti-inflammatory, anti-viral, and anti-microbial characteristics. Extensive research has also delved into their capacity to inhibit various enzymes, including urease, butyrylcholinesterase, and carboxylesterase.

Natural sources have yielded substances with key structural motifs known as thiazolines, exemplified by compounds such as thiangazole, luciferin, kalkitoxin, curacin A, and mirabazole B and C. Many of these compounds exhibit remarkable biological attributes, including neurological effects, anti-HIV activity, anti-cancer potential, and bioluminescence.

The burgeoning significance of thiazolines is indisputable, given their prevalence in chemical synthesis, pharmaceuticals, and natural products. However, it is noteworthy that the development of their synthetic strategies is still evolving, with advancements trailing behind their oxygen analogues. Over the past 15 years, the research landscape in this domain, encompassing the synthesis and applications of thiazoline derivatives, has expanded significantly. To fully harness the myriad unique properties of these compounds, the establishment of comprehensive structure–activity relationships is imperative.

In our assessment, thiazolines represent a captivating class of compounds within the catalysis field. It is crucial to acknowledge that their chemistry is still evolving, and their complete potential remains unrealized. It is plausible that further advancements will transpire as the distinctive attributes of the sulfur atom are more fully exploited.

6. Abbreviations

HIV	Human Immunodeficiency Virus
MCRs	Multicomponent Reactions
DFBP	*N*-(α,α-Difluorobenzyl)pyrrolidine
DFMPP	*N*-(1,1-Difluoro-2,2-dimethylpropyl)-pyrrolidine
NMR	Nuclear Magnetic Resonance
DNA	Deoxyribonucleic acid
ATHTd	*N*-(2-Acetyl-2-thiazoline)-*N*′-(2-thiazolidin-2-one) azine
HFIP	Hexafluoroisopropanol
QDs	Quantum Dots
ICT	Intramolecular Charge Transfer
TFA	Trifluoroacetic acid
HCl	Hydrochloric acid
TEA	Triethylamine
RNA	Ribonucleic acid
Ppb	Parts per billion
Ppm	Parts per million
DFT	Density Functional Theory
HOMO	Highest Occupied Molecular Orbital
Mcf-7	Human breast cancer cell line
LOD	Limit of detection
OLED	Organic light-emitting diode
Dipp	*N*-2,6-Diisopropylphenyl
Cbz	Carbazole
A549	Human lung carcinoma cell line
LUMO	Lowest Occupied Molecular Orbital
WOLED	White organic light-emitting diode
MeCbz	1,8-Dimethylcarbazole
HBr	Hydrobromic acid
EtOH	Ethanol
NIR	Near infra-red
EL	Electroluminescence
CRI	Colour Rendering Index
Htzol	2-(2′-Hydroxyphenyl)-2-thiazoline
NHK	Nozaki–Hiyama–Kishi
TMS	Tetramethylsilane
WHO	World Health Organization
HPAC	Human Pancreatic Cancer
PC-3	Classical prostate cancer cell line
HCT-116	Human colorectal carcinoma cell line
IC_{50}	Half-maximal Inhibitory Concentration
MS	Mass spectrometry
HepG2	Liver hepatocellular carcinoma cell line
NIH/3T3	Mouse embryoblast cell line
AChE	Acetylcholinesterase
HDAC	Histone deacetylase
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ROS	Reactive oxygen species
mL	Millilitre
µg	Microgram
µM	Micromole
mM	Millimole
HATtsc	2-Acetyl-2-thiazoline thiosemicarbazone
CVB3	Coxsackie type B3
EV71	Enterovirus 71
kg	Kilogram
RT	Reverse transcriptase
LD_{50}	Lethal dose
DM	Diabetes mellitus
CVD	Cardiovascular disease
GLP-1	Glucagon-like peptide 1
Mitf	Microphthalmia-associated transcription factor
DPP-4	Dipeptidyl peptidase IV
GIP	Glucose-dependent insulin tropic polypeptide
nM	Nano-mole
ALR	Aldose reductase
β-GlcNAcases	β-Acetylglucosaminidases
NGT	NAG-thiazoline
α-MSH	α-Melanocyte-stimulating hormone
ERK	Extracellular signal-regulated kinase
MIC	Minimum inhibitory concentration
NLO	Nonlinear optical
EIMS	Electron ionization mass spectral
TFAA	Trifluoroacetic anhydride
Fmoc	Fluorenylmethoxycarbonyl
Boc	*tert*-Butyloxycarbonyl

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We appreciate the University of Delhi's Institute of Imminence for providing financial support to research and development. Sumit Kumar (File No. 09/045(1798)/2020-EMR-I) and Aditi Arora (File No. 09/0045(11270)/2021-EMR-I) thank CSIR for awarding SRF & JRF Awards, respectively.

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