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

Sumit Kumar,<sup>†,a</sup> Aditi Arora,<sup>†,a</sup> Shivani Sapra,<sup>a</sup> Rajesh Kumar,<sup>b</sup> Brajendra K. Singh<sup>†,a</sup> and Sunil K. Singh<sup>†,c</sup>

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, thiagazole, 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

<sup>a</sup>Bioorganic Laboratory, Department of Chemistry, University of Delhi, Delhi-110007, India. E-mail: singhbk@chemistry.du.ac.in

<sup>b</sup>Department of Chemistry, R. D. S College, B. R. A. Bihar University, Muzaffarpur, 842002, India

<sup>c</sup>Department of Chemistry, Kirori Mal College, University of Delhi, Delhi-110007, India. E-mail: chem.sunil@kmc.du.ac.in

<sup>†</sup> Authors have equal contribution.



Sumit Kumar

Sumit Kumar obtained his Master's Degree in Organic Chemistry from Department of Chemistry, University of Delhi in 2020 and Honours Degree from Kirori mal College, University of Delhi in 2018. He is a third year PhD student under the supervision of Prof. Brajendra K. Singh, Department of Chemistry, University of Delhi. His research interests include design and synthesis of sugar-modified heterocyclic motifs of therapeutic importance.

He visited Medgar Evers College, City University of New York (CUNY) in the Chemistry and Environmental Science Department as a Research Scholar. He has published several research articles in various reputed journals such as *European Journal of Polymer Chemistry*, *New Journal of Chemistry*, *Beilstein Journal of Organic Chemistry*, and others.



Aditi Arora

Aditi Arora obtained her Honours Degree from Miranda House, University of Delhi in 2018. She completed her Master's in Organic Chemistry from Department of Chemistry, University of Delhi in 2020. She was a Gold Medalist during her Master's. At present, she is pursuing PhD from Department of Chemistry, University of Delhi. Her research interests include design and synthesis of carbohydrate and coumarin modified molecules. She has published several research articles in various reputed journals.



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.<sup>2</sup> 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



Shivani Sapra

*Shivani Sapra did her Master's in Chemistry from Chaudhary Charan Singh University, Meerut in 2018. Earlier, she did her graduation from Shyam Lal College, University of Delhi in 2016. After that she worked as a Project fellow in Sri Venkateswara College, University of Delhi. At present, she is working under Prof. BK Singh, Department of Chemistry. Her research interest lies in the field of modification of sugar molecules.*

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.<sup>3</sup> Importantly, thiazolines are synthesized through the conventional post-translational modification of cysteine residues.<sup>4</sup>

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.<sup>5</sup> To date, researchers have identified over 30 distinct thiazoline structures present in food and natural sources,<sup>6</sup> with notable examples



Brajendra K. Singh

*Professor Brajendra K. Singh currently holds the position of Professor in the Department of Chemistry, University of Delhi, Delhi, India. He visited the Department of Chemistry, University of Leuven, Leuven, Belgium as International Scholar for the period November 2005–April 2007 and then as post-doctoral fellow till November 2009. His key interest areas are the study and investigation of bio-catalysis and*

*metal-catalysis, C–H activation, specifically in the design, synthesis and evaluation of bioactive compounds and LED mediated synthesis. He has published more than 85 research articles in internationally reputed journals. He has delivered around 30 Invited Lectures in various National and International Conferences at different Universities and Institutes. He has served and serving in different capacities in administration of Delhi university.*



Rajesh Kumar

*Dr Rajesh Kumar received his Master of Science degree in Chemistry from University of Delhi in 2010. He joined the same Department for a PhD and completed his PhD in 2017 and during his PhD, Dr Kumar visited University of Southern Denmark as a Research Assistant from December 2014 to August 2015. After completion of PhD, he joined as Assistant Professor in Chemistry at B. R. A. Bihar University, India. He*

*has published more than 30 research papers in reputed national and international journals such as Journal of Organic Chemistry, Theranostics, European Polymer Journal etc. His research interest lies in Metal complexes, Biotransformations, Catalysis, Green Chemistry, Nucleoside and Heterocyclic Chemistry.*



Sunil K. Singh

*Dr Sunil K Singh, received his PhD in 2010 from the Department of Chemistry, University of Delhi, India in the area of synthesis of modified nucleosides and biocatalytic organic transformations. After completing his PhD, he joined Kirori Mal College a constituent College of the University of Delhi as an Assistant Professor in 2011. Recently, he is promoted to Associate Professor in the same Department. He has published more than 31 articles in the Journal of international repute.*



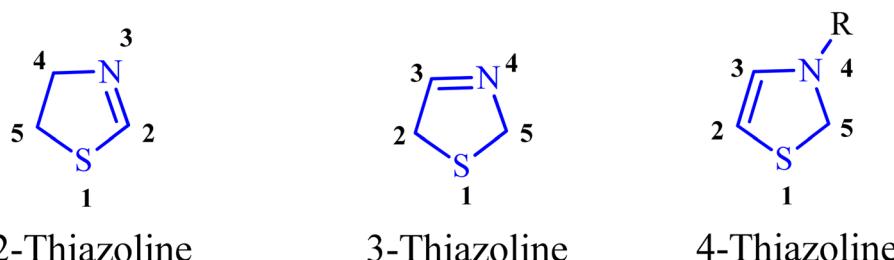


Fig. 1 General structure and numbering of the thiazoline heterocycle.

found in cooked meat<sup>7</sup> and specific exotic fruits such as litchis (Fig. 2).<sup>8</sup>

Thiazoline heterocycles can be found in a multitude of bioactive natural compounds of peptide origin (Fig. 3).<sup>9</sup> 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).<sup>10</sup> These compounds were initially isolated from the marine cyanobacterium *Lyngbya majuscule* by Harvey ex Gomont and subsequently identified by Moore, Paul, and other researchers.<sup>11</sup> 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.<sup>12</sup> Although, most chemical processes use serine residues, however, cysteine residues are used in the biosynthetic pathway of thiazolines.<sup>13</sup> In processed foods, the

Maillard reaction occurs, leading to the generation of these molecules through interactions involving dicarbonyl compounds, aldehydes, ammonia, and hydrogen sulfide.<sup>14</sup> The pharmacological attributes of thiazoline have also been investigated. Some thiazoline compounds exhibit noteworthy properties such as anti-HIV<sup>15</sup> and anti-cancer<sup>16</sup> activities, and they are also capable of inhibiting cell division (Fig. 4).<sup>17</sup>

In 1909, Richard Willstätter successfully synthesized the first thiazolines by dialkylating thioamides.<sup>18</sup> 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.<sup>19</sup>

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

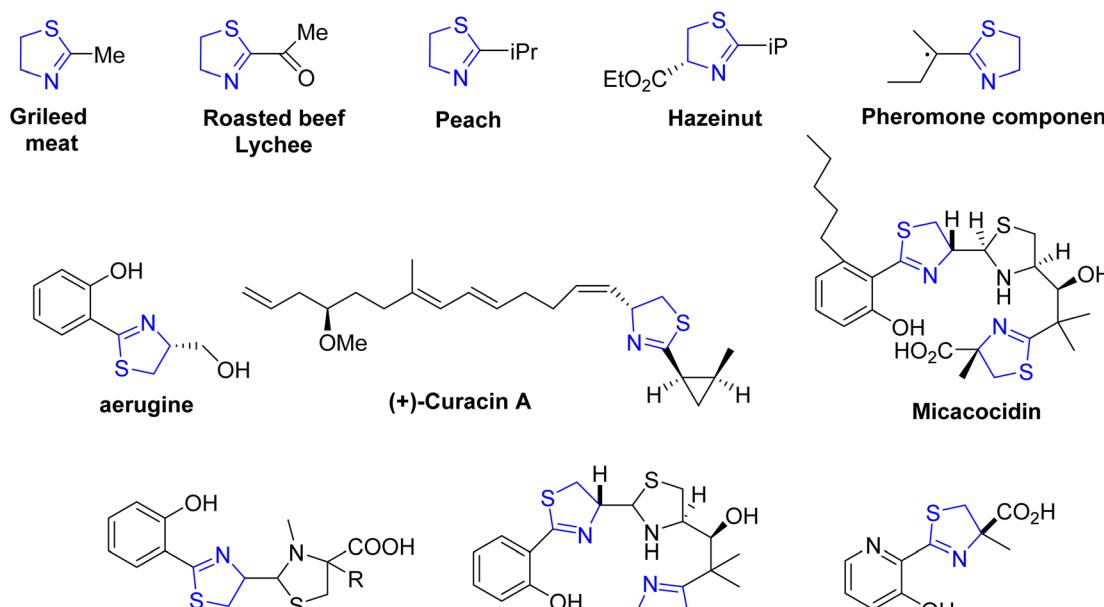


Fig. 2 Derivatives of thiazolines sourced from natural origins.



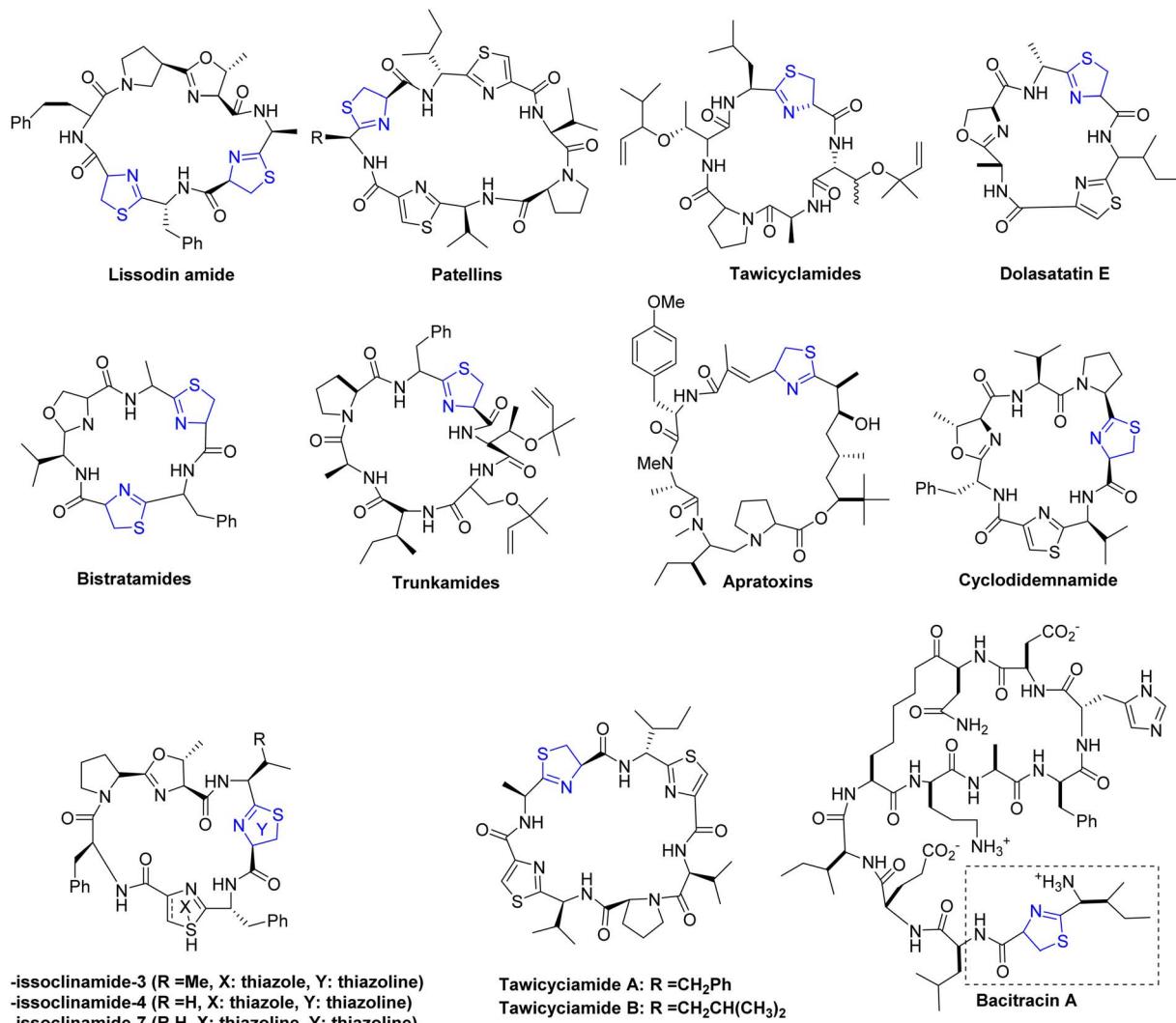


Fig. 3 Cyclopeptide alkaloids containing thiazoline as structural segments.

rings within their molecular structures.<sup>23,24</sup> They also serve as ligands in coupling reactions catalyzed by transition metals.<sup>25</sup> 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.<sup>26</sup> 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.<sup>27,28</sup>

## 2. Recent advances in the synthesis

Jeon *et al.*<sup>29</sup> 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).

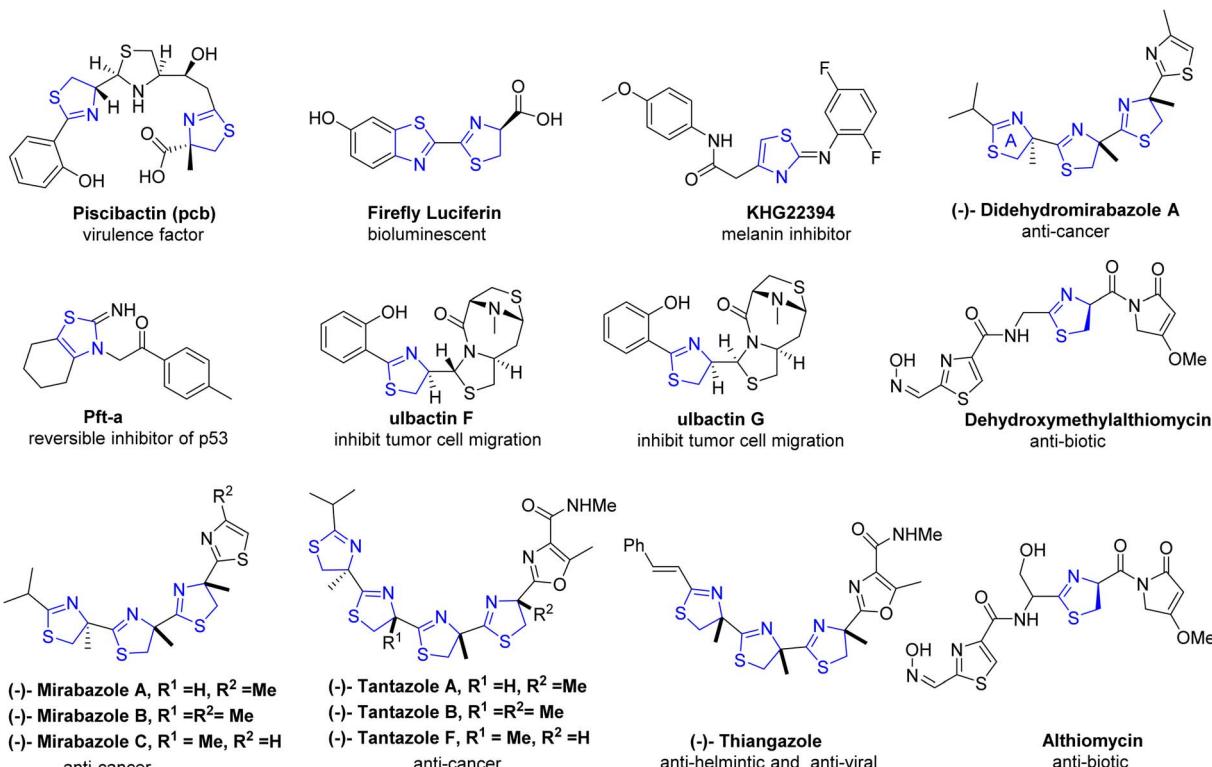
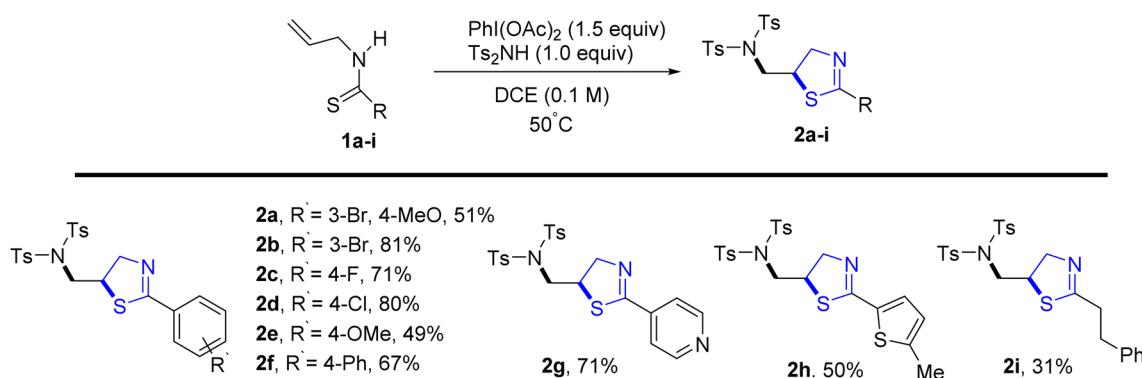


Fig. 4 Nature derived biological active scaffolds in relevance of thiazoline.



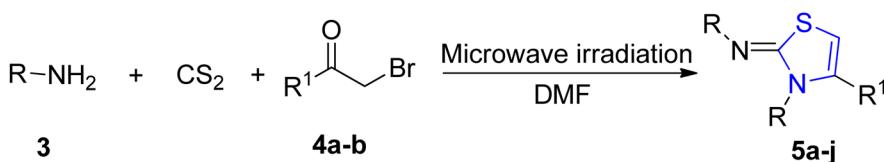
Scheme 1 Synthesis of thiazolines 2a–2i.

Multicomponent reactions (MCRs) are gaining growing appeal due to their enhanced efficiency, reduced waste generation, atom economy, and straightforward procedures.<sup>30</sup> With the use of microwave technology, Appalanaidu *et al.*<sup>31</sup> developed a novel one-pot technique to obtain the thiazoline analogues following a 3-CR between carbon disulfide, 1<sup>o</sup>-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  $\text{CS}_2$  to produce the HBr salt of the corresponding thiazoline derivatives. Subsequently, these obtained salts were neutralized using a saturated solution of  $\text{Na}_2\text{CO}_3$ , yielding the final thiazoline analogs 5a–5j (Scheme 2).

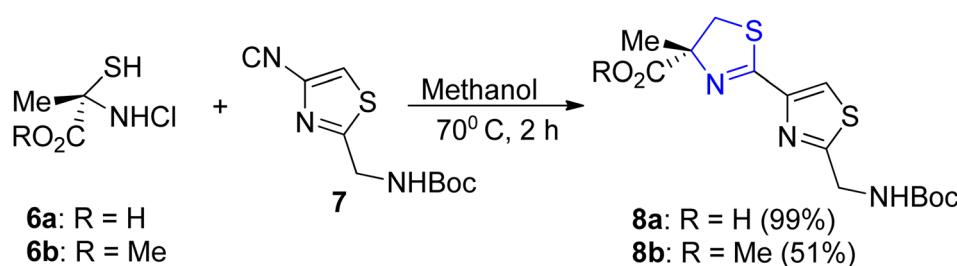
Four different research laboratories have used Pattenden's method<sup>32</sup> for thiazoline synthesis to achieve the synthesis of largazole, which is isolated from fungi.<sup>33–36</sup> Thiazoline-thiazole



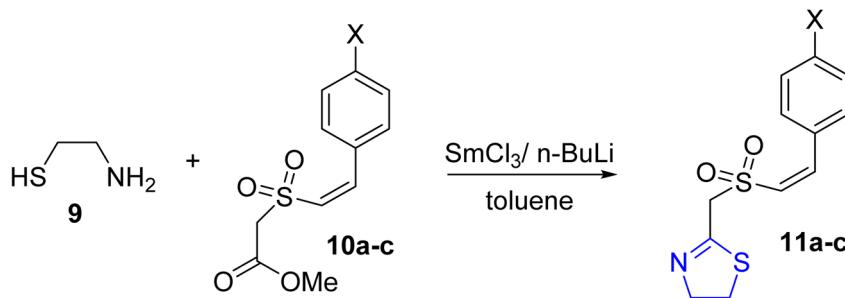


Entry	R	$\text{R}^1$	Product	Entry	R	$\text{R}^1$	Product
1			 5a, 91%	6			 5f, 88%
2			 5b, 94%	7			 5g, 91%
3			 5c, 88%	8			 5h, 92%
4			 5d, 90%	9			 5i, 90%
5			 5e, 86%	10			 5j, 91%

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  $\alpha$ -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<sub>3</sub>N, lower yield of the thiazole ester **8b** was observed (Scheme 3).

Padmavathi *et al.*<sup>37</sup> synthesized thiazolines **11a–c** through the condensation of Z-styryl sulfonylacetate **10a–c** with aminothiol **9**, catalyzed by SmCl<sub>3</sub> in the presence of *n*-butyllithium (Scheme 4). The SmCl<sub>3</sub>-activated carbonyl carbon served as the site of nucleophilic attack by the thiol during the reaction.

Alom *et al.*<sup>38</sup> 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  $\alpha,\alpha$ -difluoroalkylamines gives high yields under favorable conditions (Scheme 6). In accordance with this scheme, Fukuhara *et al.*<sup>39</sup> 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.

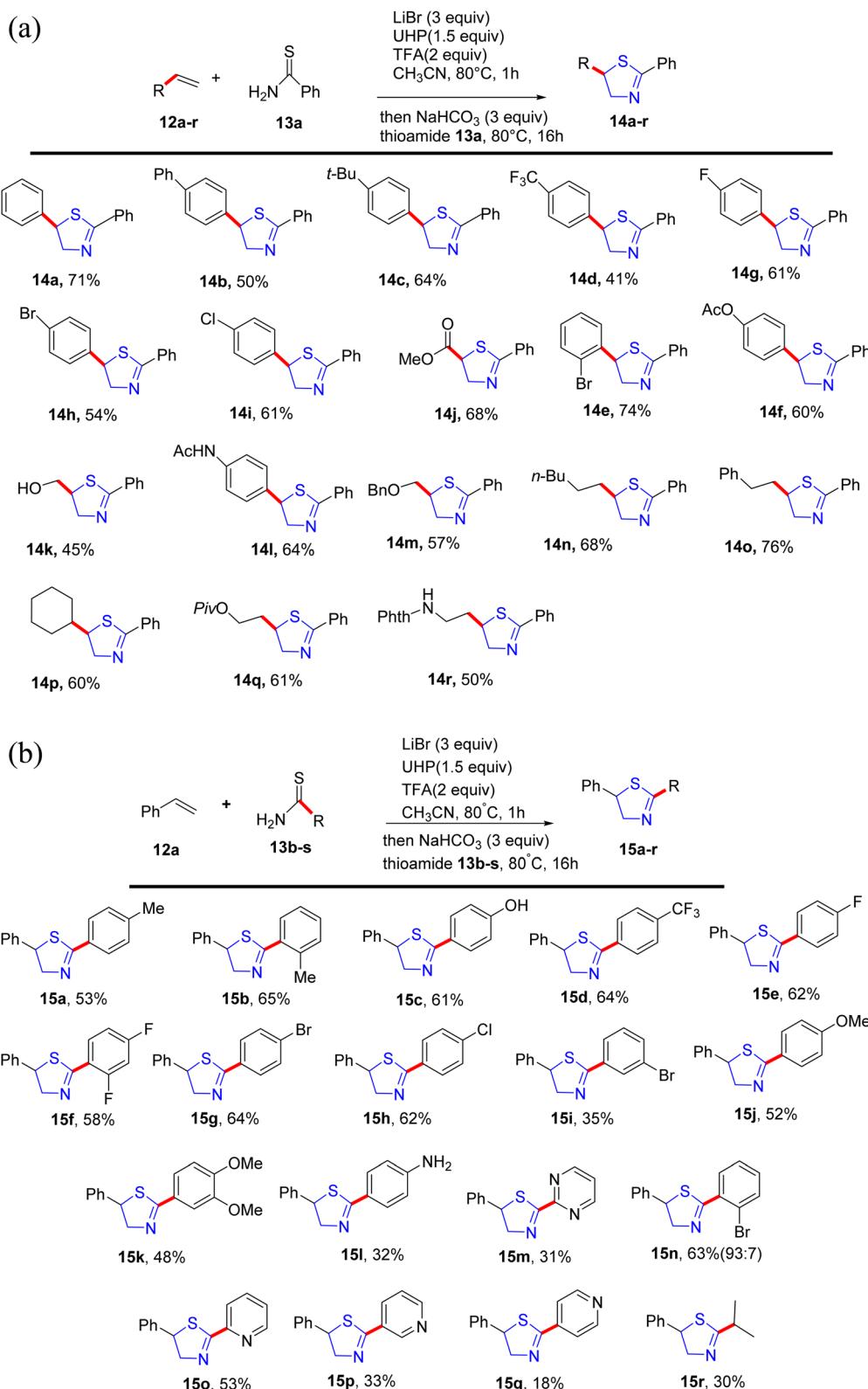
Alsharif *et al.*<sup>40</sup> designed and developed an approach with a primary focus on synthesizing novel thiazolines. However, the current methodologies present challenges in the convenient synthesis of thiazoline derivatives **21a–l** and **23a–p**, as depicted in Scheme 7a and b. The investigation 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.<sup>41</sup> HFIP also facilitates a wide spectrum of reactions.<sup>42</sup>

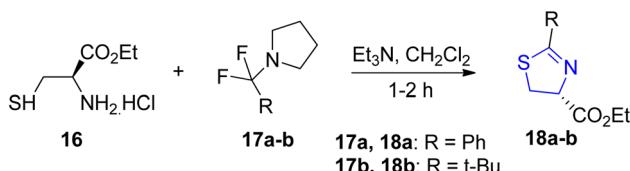
Kamila *et al.*<sup>43</sup> recently unveiled an efficient approach for the synthesis of arylated thiazolines, utilizing aminothiol **24** and aryl ketonitriles **25a–k** as substrates, all achieved without the presence of any solvents (Scheme 8). The incorporation of microwave radiation facilitated 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.*<sup>44</sup> 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-exomethylene group was observed to be less than 6%.

Viñuelas-Zahínos *et al.*<sup>45</sup> 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)<sub>2</sub>](NO<sub>3</sub>)<sub>2</sub>·H<sub>2</sub>O, [NiCl(ATHTd)(H<sub>2</sub>O)]Cl, [ZnCl<sub>2</sub>(ATHTd)<sub>2</sub>], and



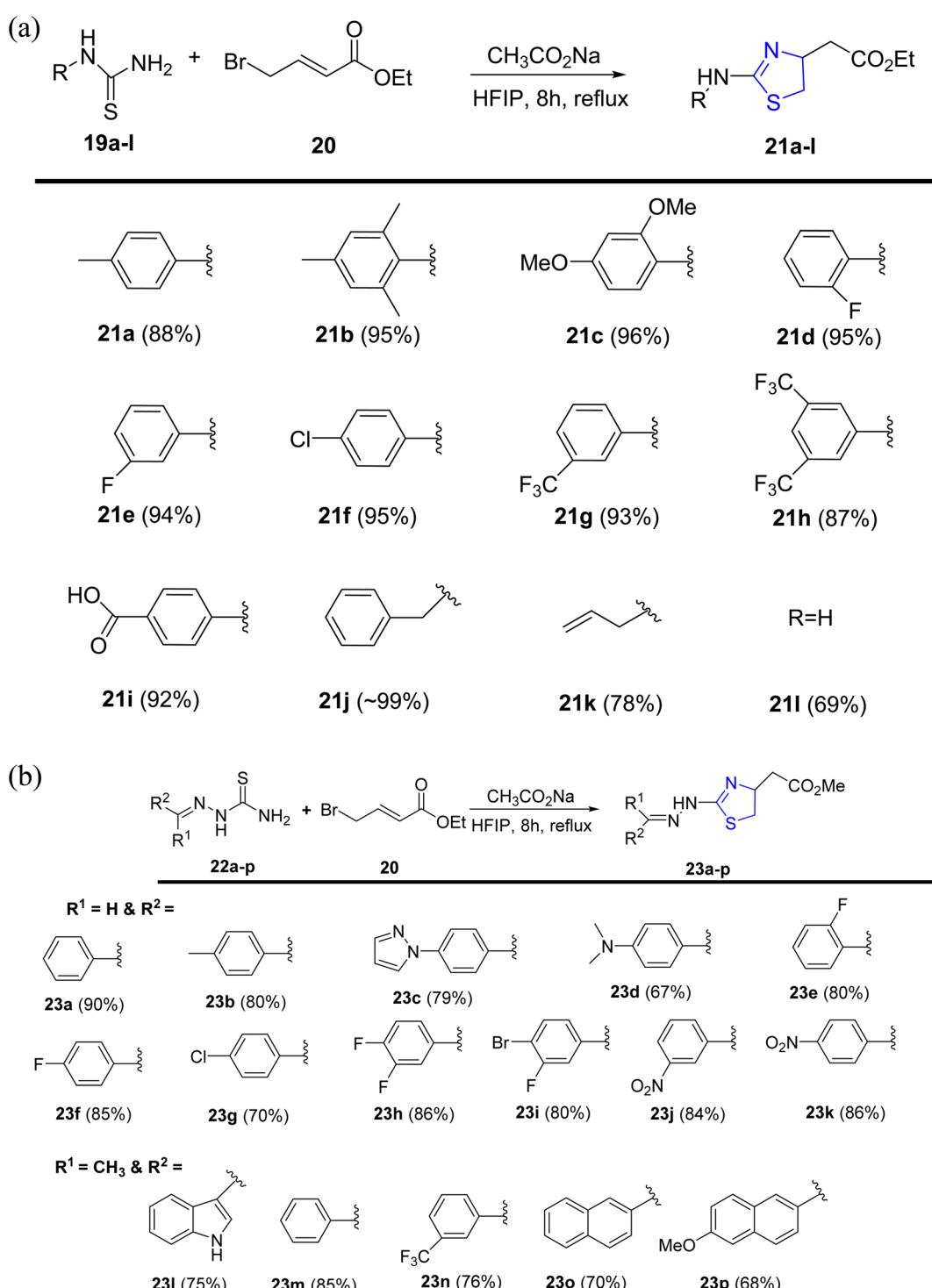
Scheme 5 (a) Substrate scope for alkene. (b) Substrate scope for thioamide.



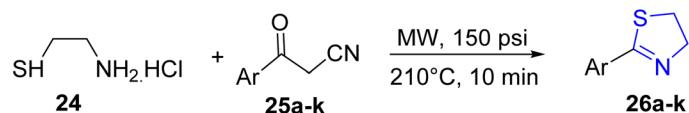
**Scheme 6** Synthesis of thiazolines 18a–b.

[CuCl<sub>2</sub>(ATHTd)]. These complexes were also subjected to solid-state characterization using spectroscopic techniques and X-ray diffraction, along with elemental analysis.

Attanasi *et al.*<sup>46</sup> 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

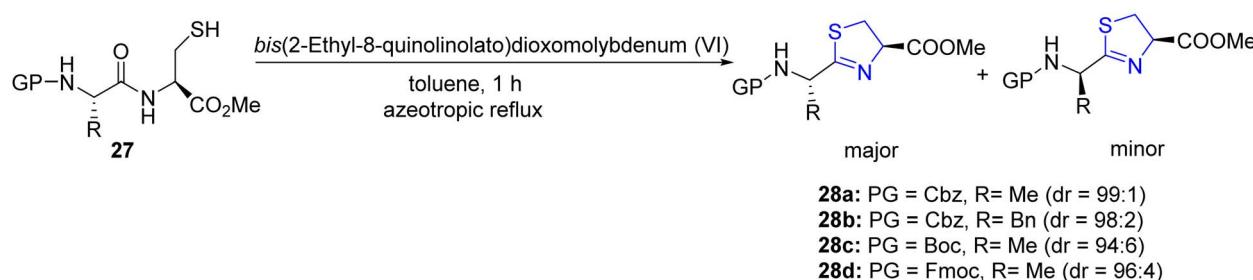


**Scheme 7** (a) Synthesis of thiazoline derivatives **21a–l**. (b) Synthesis of thiazoline derivatives **23a–p**.

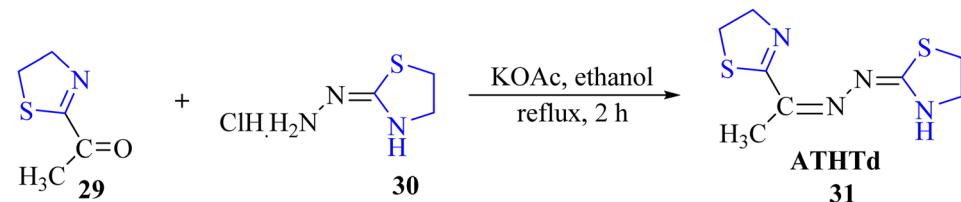


Compound (a-k)	25/26	Compound (a-k)	25/26
a	Ar = Ph	g	Ar = 2,4-(MeO) <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>
b	Ar = 4-Me-C <sub>6</sub> H <sub>4</sub>	h	Ar = 2,4-(Cl)2-C <sub>6</sub> H <sub>3</sub>
c	Ar = 4-MeO-C <sub>6</sub> H <sub>4</sub>	i	Ar = 3,4,5-(MeO) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>
d	Ar = 4-Cl-C <sub>6</sub> H <sub>4</sub>	j	Ar = 4-CN-C <sub>6</sub> H <sub>4</sub>
e	Ar = 4-F-C <sub>6</sub> H <sub>4</sub>	k	Ar = 4-Br-C <sub>6</sub> H <sub>4</sub>
f	Ar = Naphth-1-yl		

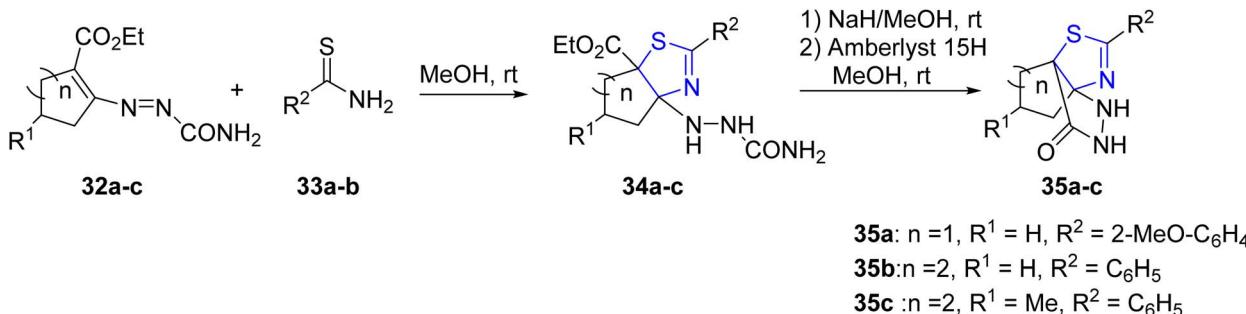
Scheme 8 Synthesis of thiazoline derivatives 26a–k.



Scheme 9 Synthesis of thiazolines 28a–d.



Scheme 10 Synthesis of ATHTd 31.



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

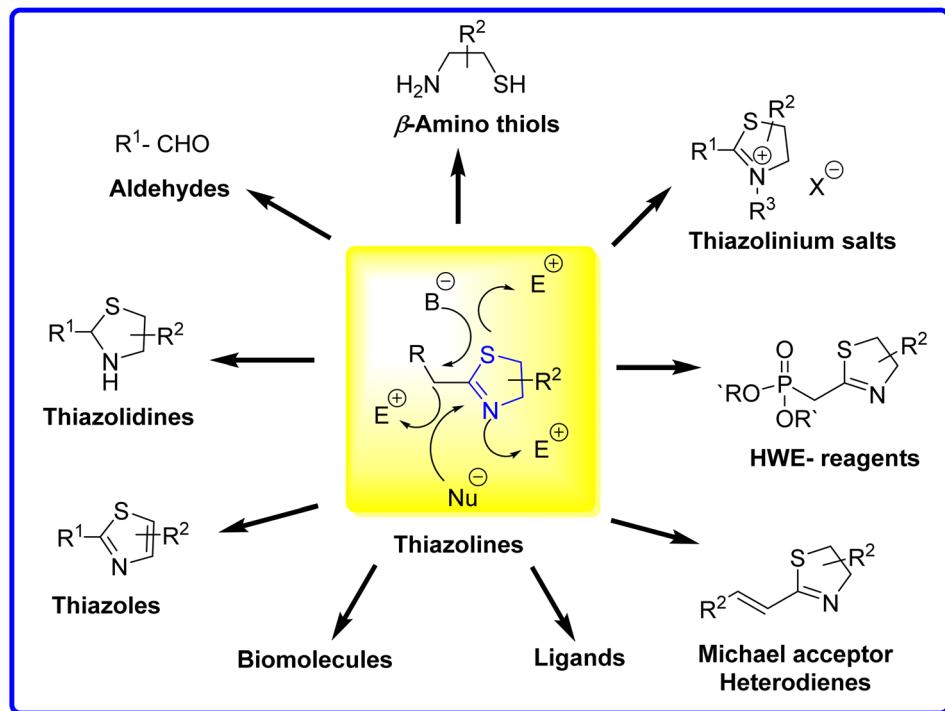
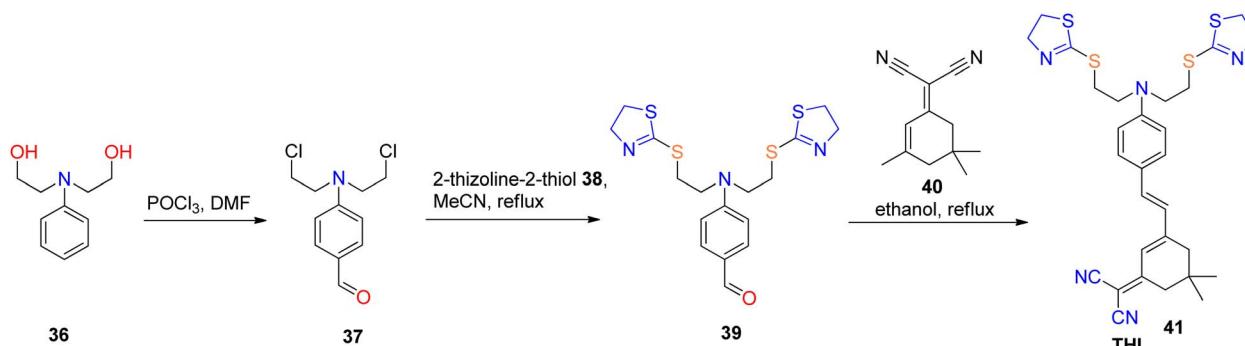


Fig. 5 Reactivity and applications of thiazolines.



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

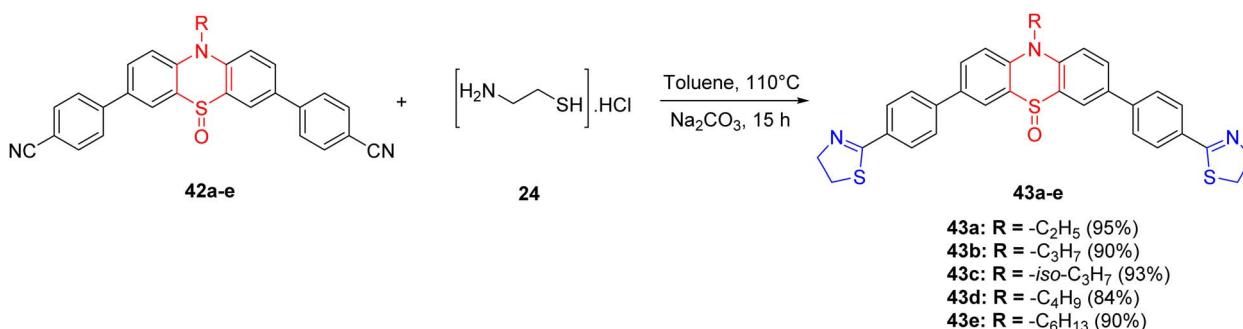
complexes **35a–c**, as depicted in Scheme 11 to synthesize a variety of cycloalkyl-thiazolines **34a–c**, which were further transformed into fused cycloalkyl-thiazolinepyrazole complexes **35a–c** (Scheme 11).

### 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,<sup>47,48</sup> β-amino thiols,<sup>49,50</sup> thiazoles,<sup>51,52</sup> and

thiazolinium salts<sup>53</sup> (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,<sup>54</sup> and vinyl thiazolines, which function as Michael acceptors or heterodienes.<sup>55</sup> 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.<sup>19</sup>

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<sup>56,57</sup> and chiral ligands utilized in asymmetric catalysis.<sup>58,59</sup> The discussion here encompasses the role of thiazolines in fluorescence, catalysis, pharmacology, and other diverse fields.

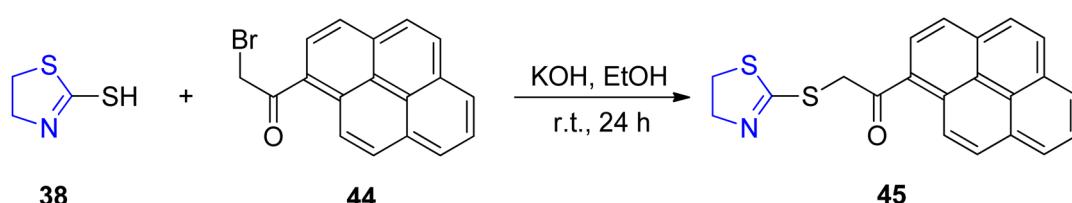
### 3.1. Fluorescence property

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.<sup>60,61</sup> Diverse sensor modalities have been employed for the detection of metal ions, encompassing quantum dots (QDs), nanomaterials, organic molecules, and biopolymers.<sup>62,63</sup> 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.<sup>64,65</sup>

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.*<sup>66</sup> engineered a fluorescent sensor designated as THI 41, characterized

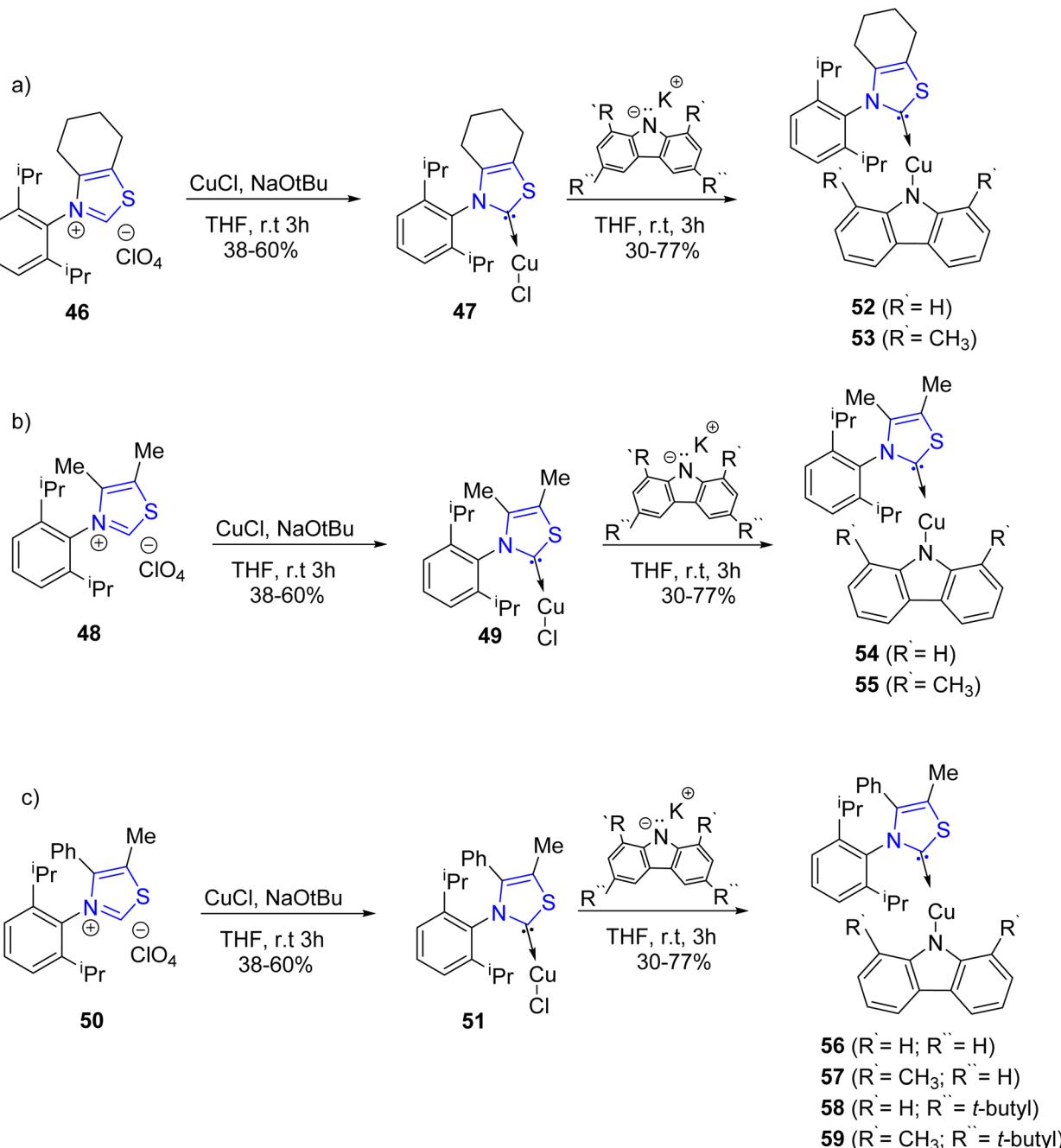
by the inclusion of a  $\text{Hg}^{2+}$ -sensitive thiazoline moiety, an electron-deficient dicyanovinyl functionality, and an electron-rich diethylamino group. The strong affinity between  $\text{S}^{2-}$  ions and  $\text{Hg}^{2+}$  ions was observed to induce a reversal in the binding interaction between probe 41 and  $\text{Hg}^{2+}$  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  $\text{Hg}^{2+}$  ions. The synthesis of 4-(bis(2-chloroethyl)amino)benzaldehyde 37 followed a previously established procedure.<sup>67</sup> 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  $\text{Hg}^{2+}$ . Furthermore, employing a confocal laser scanning microscope, it was conclusively demonstrated that THI 41 can serve as a proficient fluorescent probe for visualizing  $\text{Hg}^{2+}$  ions within living HeLa cells, without any observable adverse effects on cervical cancer and epithelial cells.<sup>51</sup>

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.<sup>68,69</sup> Chaudhary *et al.*<sup>70</sup>



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



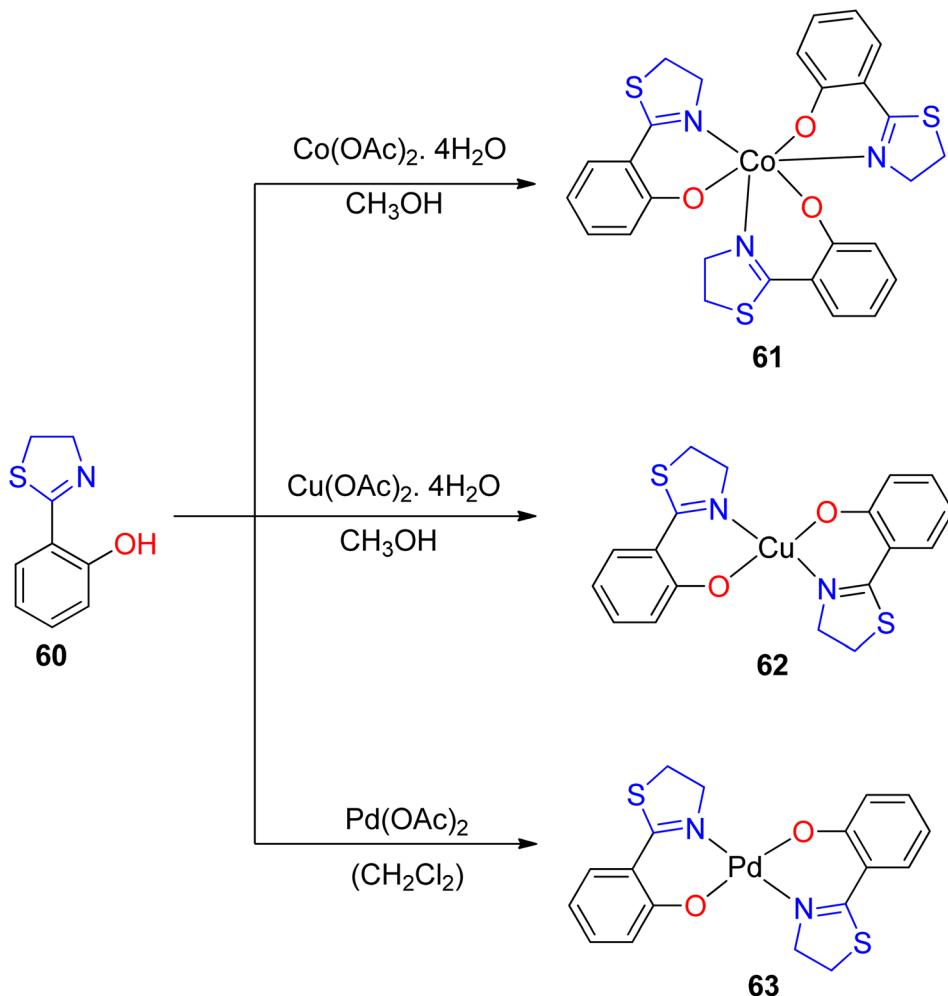


Scheme 15 (a–c) Synthesis of CMA emitters 52–59.

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.

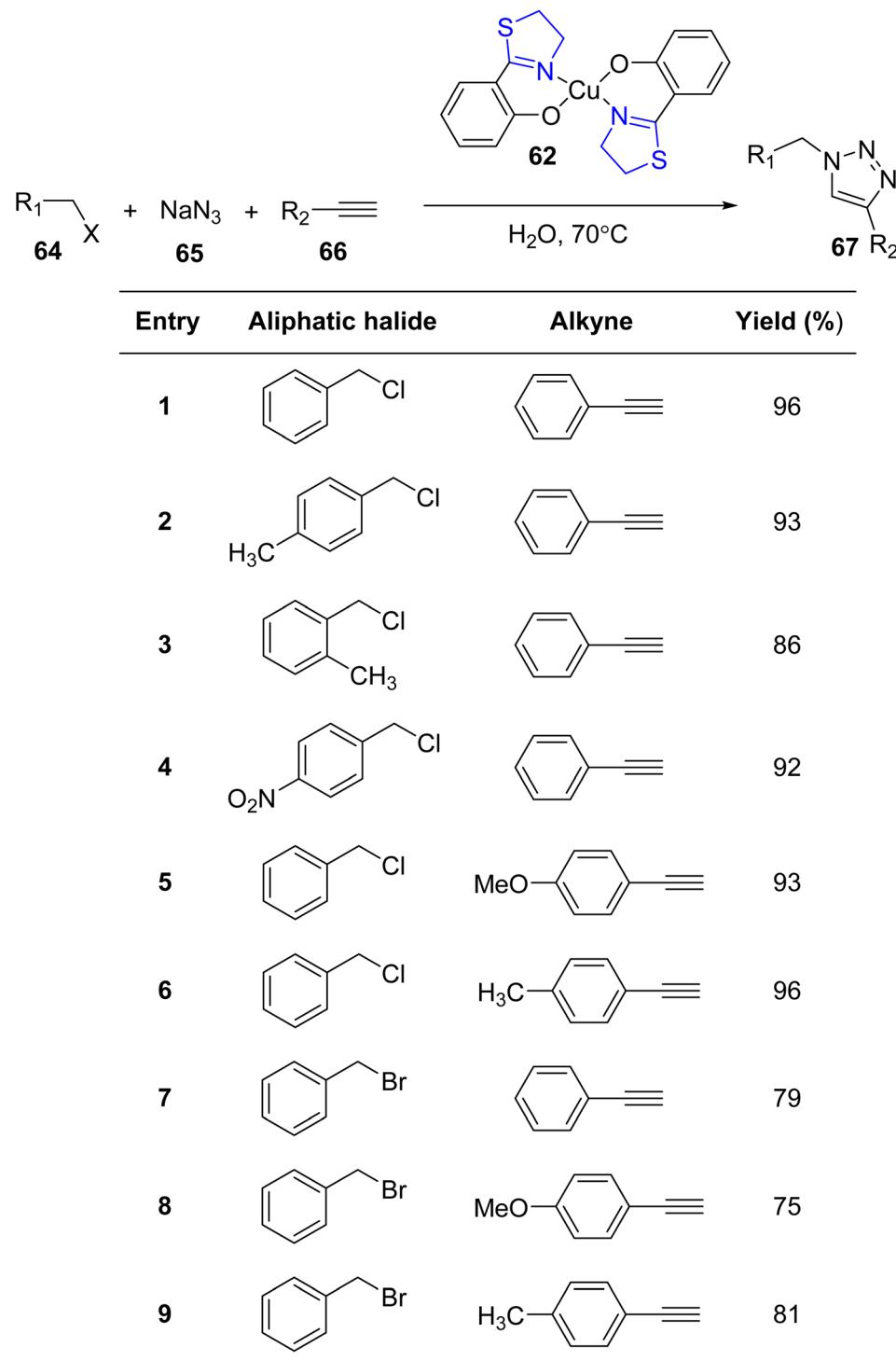
Compound **43c** exhibited a remarkable minimum detection limit of 0.98 parts per million (ppm) for TFA, while compound **43a** demonstrated a noteworthy minimum detection limit of 13.1 parts per billion (ppb) for HCl. Further elucidation of the energy gap between the highest occupied molecular orbital (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.<sup>55</sup>

Copper ions in the form of  $\text{Cu}^{2+}$  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  $\text{Cu}^{2+}$  ions, a plethora of fluorescent chemosensors are available; however, only a limited subset of these sensors are categorized as “turn-on” sensors, primarily because  $\text{Cu}^{2+}$ , being paramagnetic, exerts a quenching effect on

fluorescence.<sup>71</sup> Preferred among these are the “turn-on” fluorescence sensors, as they exhibit a reduced susceptibility to false positive signals and offer enhanced multiplexing capabilities.<sup>72</sup> Utilizing a one-pot synthetic approach, Wang *et al.*<sup>73</sup> 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  $\text{Cu}^{2+}$ . 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  $\text{Cu}^{2+}$ . This complexation was corroborated by spectroscopic analysis, density functional theory (DFT) measurements, and Fourier-transform infrared (FTIR) data. In the presence of  $\text{Hg}^{2+}$ , 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

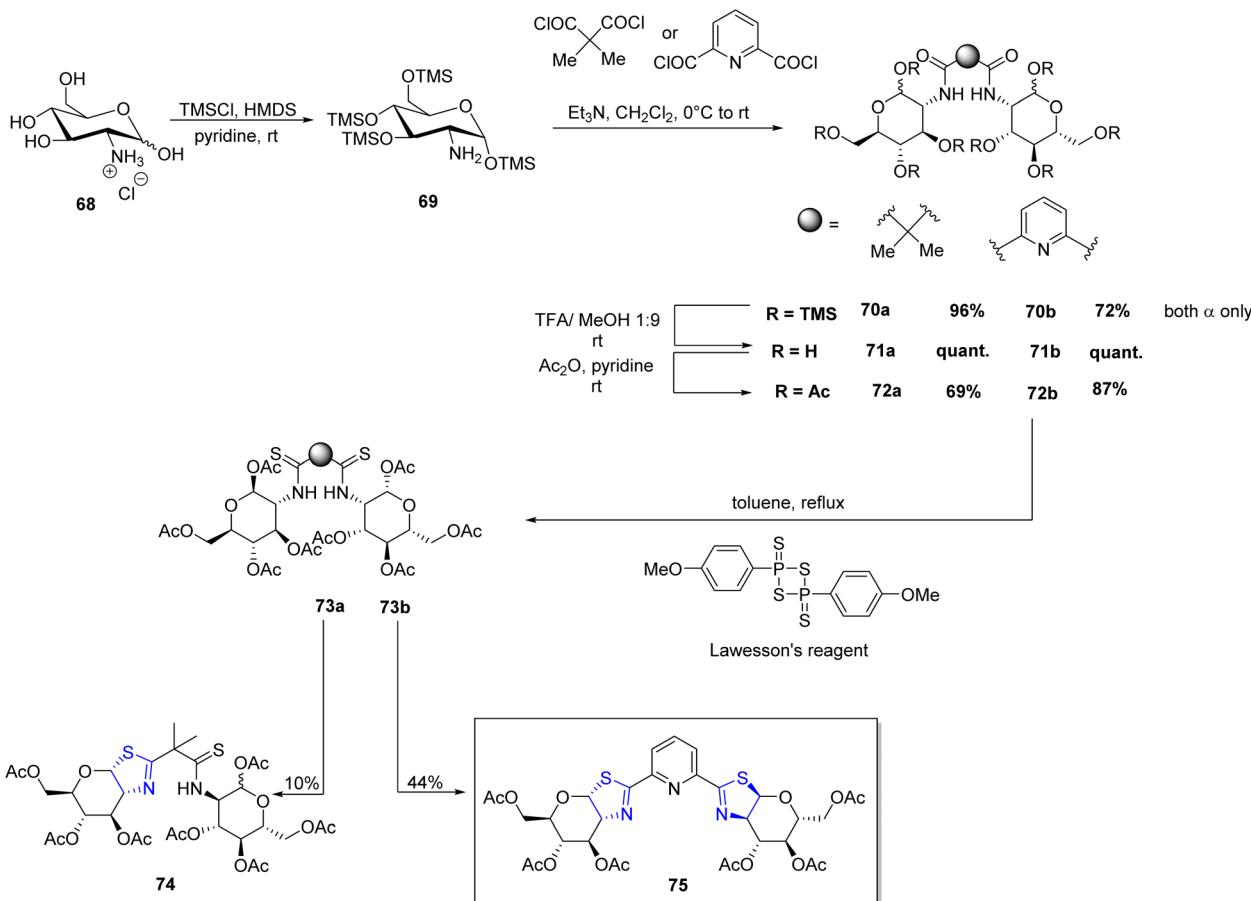
sensitive and selective “turn-on” fluorescence response for the detection of  $\text{Cu}^{2+}$ . Employing statistical deviations and linear regression analyses, the **45**- $\text{Cu}^{2+}$  complex was evaluated for its detection limit and association constant. The results indicated the functionality of sensor **45** for  $\text{Cu}^{2+}$  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.





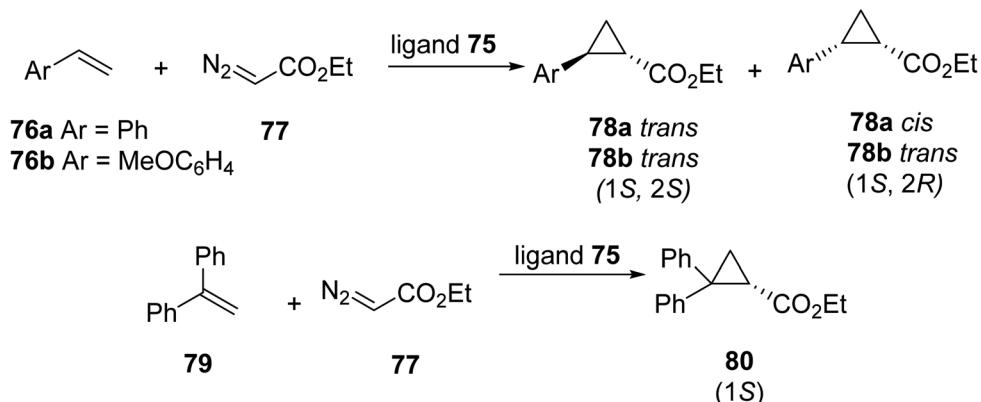
Scheme 18 Synthesis of a ligand 75.

stems from their notable advantages, including high decay rates and emission efficiency. Ruduss *et al.*<sup>74</sup> 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.<sup>75</sup> 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<sup>-2</sup>). 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.<sup>76,77</sup> 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.<sup>78,79</sup> 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,<sup>80</sup> 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.<sup>81</sup> 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)	$[\text{RuCl}_2(\text{p-cymene})]_2$	$\text{CH}_2\text{Cl}_2, 0^\circ\text{C}$	44	55:45	Racemic	
2	Styrene (76a)	$\text{Cu}(\text{OTf}) \bullet 0.5\text{Ph} \bullet \text{H}$	$\text{CH}_2\text{Cl}_2, 0^\circ\text{C}$	65	58:42	28	18
3	Styrene (76a)	$\text{Cu}(\text{OTf}) \bullet 0.5\text{Ph} \bullet \text{H}$	$\text{CH}_2\text{Cl}_2, -20^\circ\text{C}$	nr	-	-	-
4	Styrene (76a)	$\text{Cu}(\text{OTf}) \bullet 0.5\text{Ph} \bullet \text{H}$	$\text{CH}_2\text{Cl}_2, 35^\circ\text{C}$	70	63:37	22	20
5	Styrene (76a)	$\text{Cu}(\text{OTf}) \bullet 0.5\text{Ph} \bullet \text{H}$	Toluene, $0^\circ\text{C}$	64	54:46	22	24
6	Styrene (76a)	$\text{Cu}(\text{OTf}) \bullet 0.5\text{Ph} \bullet \text{H}$	$\text{Et}_2\text{O}, 0^\circ\text{C}$	44	61:39	18	16
7	4-methoxy styrene (76b)	$\text{Cu}(\text{OTf}) \bullet 0.5\text{Ph} \bullet \text{H}$	$\text{CH}_2\text{Cl}_2, 0^\circ\text{C}$	19	70:30	24	10
8	1,1-Diphenyl ethylene (79)	$[\text{RuCl}_2(\text{p-cymene})]_2$	$\text{CH}_2\text{Cl}_2, 0^\circ\text{C}$	5	-	Racemic	
9	1,1-Diphenyl ethylene (79)	$\text{Cu}(\text{OTf}) \bullet 0.5\text{Ph} \bullet \text{H}$	$\text{CH}_2\text{Cl}_2, 0^\circ\text{C}$	6	-	Racemic	

Scheme 19 Asymmetric cyclopropanation processes.

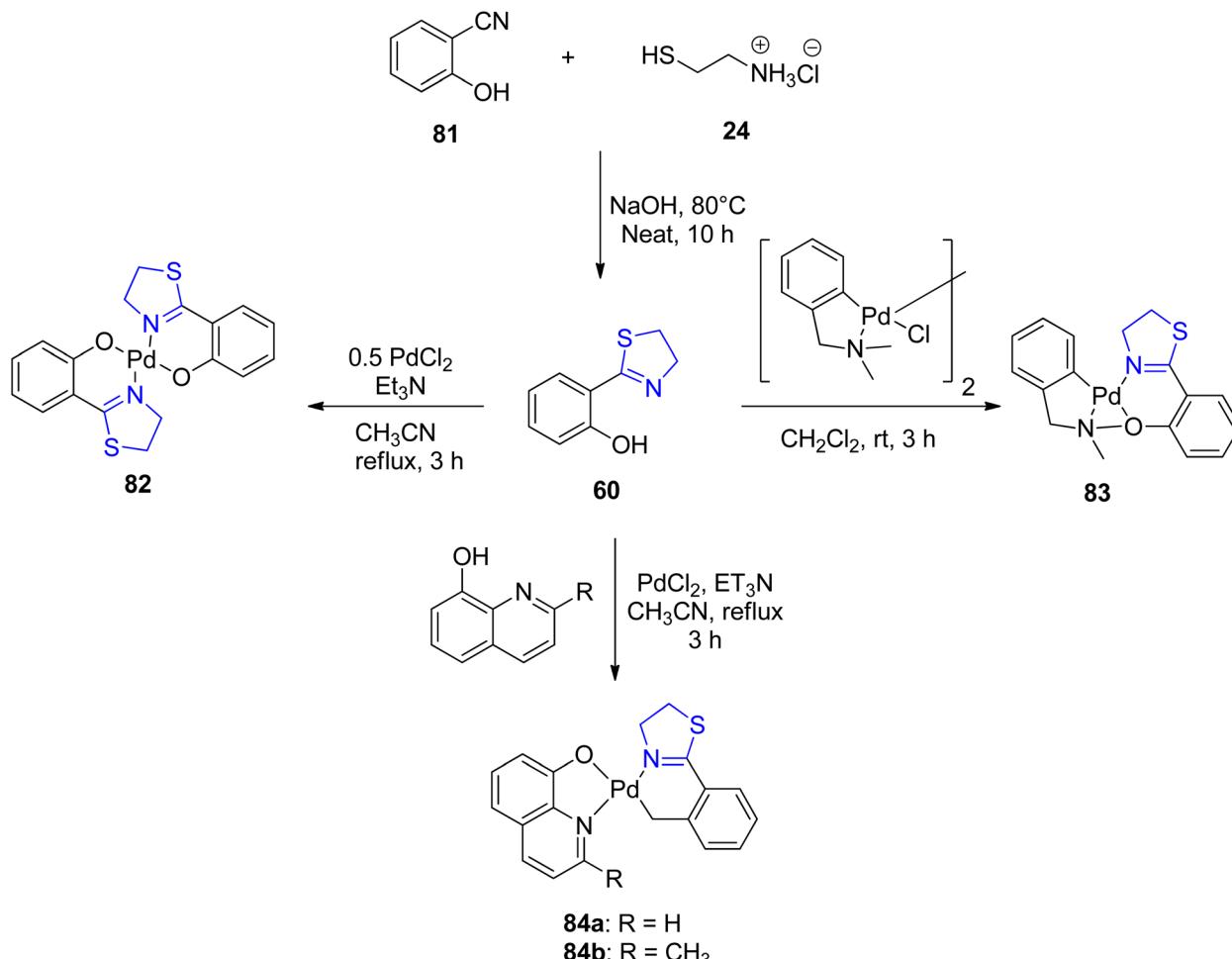
catalyzed reactions in synthetic organic chemistry. Recent focus has been directed toward bis(thiazolines) following their synthesis, including various pyridyl bis(thiazolines) and methylene-bridged bis(thiazolines), as established by Masson and Gulea. This renewed attention underscores the emerging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

Amini *et al.*<sup>84</sup> 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).<sup>69</sup> 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.*<sup>85</sup> gave the first synthetic methodology for pyridyl 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.

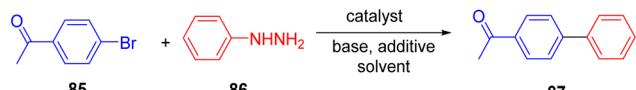
processes (Scheme 19). Per-OTMS group was used to protect the amino sugar **68** in order to obtain the desired acetyl-protected bis(amide). The resultant derivative **69** was firstly protected with the OTMS group followed by its reaction with dipicolinic acid chloride to yield **70b**. Compound **70b** on subsequent desilylation and acetylation gave the bis(amide) **72b**. Under the conditions as outlined in the literature,<sup>86</sup> 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.*<sup>87</sup> 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<sup>2</sup>–Csp<sup>2</sup> 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<sup>-1</sup> (Scheme 21).

McKeon *et al.*<sup>88</sup> reported the convergent preparation of thiazoline & oxazoline containing six non-*C*<sub>2</sub>-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*- $\beta$ -nitrostyrene **92** & indole **91**, the ligands **90a–f** gave enantioselectivity as high as 76% (Scheme 23).

McKeon *et al.*<sup>89</sup> 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



Entry	Catalyst	Base	Additive	Solvent	T [°C]	Time (h)
1	82	K <sub>2</sub> CO <sub>3</sub>	-	DMF	60	3
2	82	K <sub>2</sub> CO <sub>3</sub>	-	DMA	60	3
3	82	K <sub>2</sub> CO <sub>3</sub>	-	NMP	60	3
4	82	K <sub>2</sub> CO <sub>3</sub>	-	CH <sub>3</sub> CN	60	3
5	82	K <sub>2</sub> CO <sub>3</sub>	-	Toluene	60	3
6	82	K <sub>2</sub> CO <sub>3</sub>	-	Isopropanol	60	3
7	82	K <sub>2</sub> CO <sub>3</sub>	-	Ethanol	60	3
8	82	K <sub>2</sub> CO <sub>3</sub>	-	THF	60	3
9	82	Na <sub>2</sub> CO <sub>3</sub>	-	DMF	60	3
10	82	Cs <sub>2</sub> CO <sub>3</sub>	-	DMF	60	3
11	82	NaOAc	-	DMF	60	3
12	82	TEA	-	DMF	60	3
13	82	NaOH	-	DMF	60	3
14	82	K <sub>2</sub> CO <sub>3</sub>	-	DMF	60	3
15	82	K <sub>2</sub> CO <sub>3</sub>	-	DMF	120	3
16	82	K <sub>2</sub> CO <sub>3</sub>	-	DMF	120	2
17	82	K <sub>2</sub> CO <sub>3</sub>	CuI (0.5)	DMF	120	2
18	82	K <sub>2</sub> CO <sub>3</sub>	KI (0.5)	DMF	120	2
19	82	K <sub>2</sub> CO <sub>3</sub>	Nal (0.5)	DMF	120	2
20	82	K <sub>2</sub> CO <sub>3</sub>	Nal (0.2)	DMF	120	2
21	83	K <sub>2</sub> CO <sub>3</sub>	Nal (0.1)	DMF	120	2
22	84a	K <sub>2</sub> CO <sub>3</sub>	Nal (0.2)	DMF	120	2
23	84b	K <sub>2</sub> CO <sub>3</sub>	Nal (0.2)	DMF	120	2
24	83	K <sub>2</sub> CO <sub>3</sub>	Nal (0.2)	DMF	120	2
25	83	K <sub>2</sub> CO <sub>3</sub>	Nal (0.2)	DMF	120	2
26	-	K <sub>2</sub> CO <sub>3</sub>	Nal (0.2)	DMF	120	2
27	83	-	Nal (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<sub>1</sub> = *t*-Bu, R<sub>2</sub> = Bn) in the allylation reaction of benzaldehyde [85% (*R*)] was elucidated through the proposal of a transition state.

Liu *et al.*<sup>90</sup> 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*- $\beta$ -nitrostyrene 92, as shown in Scheme 28a and b. The reason behind the observed enantioselectivity was attributed to the NH– $\pi$  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.

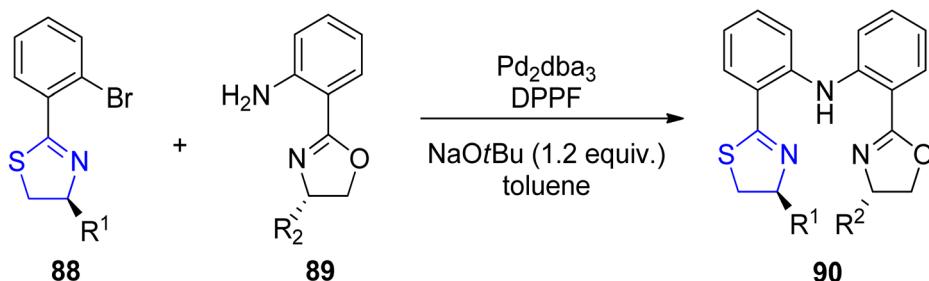
Abrunhosa-Thomas *et al.*<sup>91</sup> reported a series of thiazoline ligands substituted with a sulfinyl or sulfanyl moiety. The ligands were assessed for their catalytic properties in an allylic substitution reaction catalysed by palladium. Using *t*-BuLi, deprotonation was performed at the  $\alpha$ -position followed by addition of diphenyl disulfide. Thus, the enantiopure 2-isopropyl-thiazolines 102a–c<sup>92</sup> 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  $\alpha$ -sulfinyl-thiazolines (*R*, *Rs*)-104a as well as (*R*, *Ss*)-104b as a diastereomeric mixture (Scheme 29a).<sup>93</sup>  $\alpha$ , $\beta$ -unsaturated thiazolines 105 when treated with thiol, gave  $\beta$ -sulfanyl-thiazolines 106 (Scheme 29b). Starting with commercially available (*S*)-methioninol 108 and phenyldithioic methyl ester 107,<sup>94</sup> compound 110 was synthesized in 2 steps; thioacetylation 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

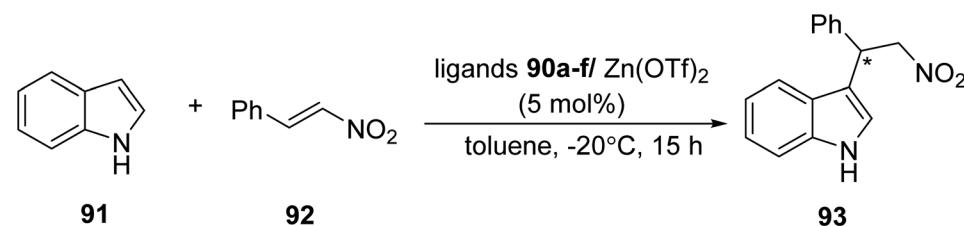
**3.3.1. Anti-cancer.** According to the World Health Organization (WHO) survey, it is projected that the number of cancer patients will increase by 26 million by the year 2030. This escalation in cancer cases is expected to establish cancer as a prominent global cause of mortality, resulting in an estimated 17 million annual fatalities.<sup>95,96</sup> 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.<sup>97</sup> 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.<sup>98,99</sup> 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).<sup>100</sup>



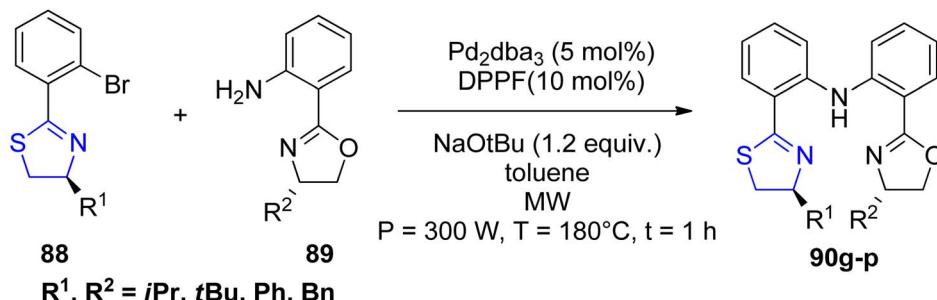


Entry	Ligands	R <sup>1</sup>	R <sup>2</sup>	Thermal (% yield)	Microwave (% yield)
1	<b>90a</b>	iPr	iPr	26	64
2	<b>90b</b>	tBu	tBu	28	83
3	<b>90c</b>	Ph	Ph	6	25
4	<b>90d</b>	Bn	Bn	19	64
5	<b>90e</b>	tBu	Bn	27	72
6	<b>90f</b>	Bn	tBu	17	61

Scheme 22 Synthetic scheme for non-*C*<sub>2</sub>-symmetric ligands **90a**–**f**.

Entry	Ligand	R <sub>1</sub>	R <sub>2</sub>	Thermal (% yield)	Microwave (% yield)
1	<b>90a</b>	iPr	iPr	26	64
2	<b>90b</b>	tBu	tBu	28	83
3	<b>90c</b>	Ph	Ph	6	25
4	<b>90d</b>	Bn	Bn	19	64
5	<b>90e</b>	tBu	Bn	27	72
6	<b>90f</b>	Bn	tBu	17	61

Scheme 23 Zinc catalyzed Friedel–Crafts alkylation reaction.



Entry	Ligand	$\text{R}^1$	$\text{R}^2$	Yield (%)
1	<b>90g</b>	<i>i</i> Pr	<i>t</i> Bu	70
2	<b>90h</b>	<i>i</i> Pr	Ph	70
3	<b>90i</b>	<i>i</i> Pr	Bn	59
4	<b>90j</b>	<i>t</i> Bu	<i>i</i> Pr	68
5	<b>90k</b>	<i>t</i> Bu	Ph	79
6	<b>90l</b>	Ph	<i>i</i> Pr	31
7	<b>90m</b>	Ph	<i>t</i> Bu	41
8	<b>90n</b>	Ph	Bn	29
9	<b>90o</b>	Bn	<i>i</i> Pr	48
10	<b>90p</b>	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.<sup>101–104</sup> Ability to induce apoptosis and impede cell division<sup>105</sup> have been identified as anticancer action mechanisms.

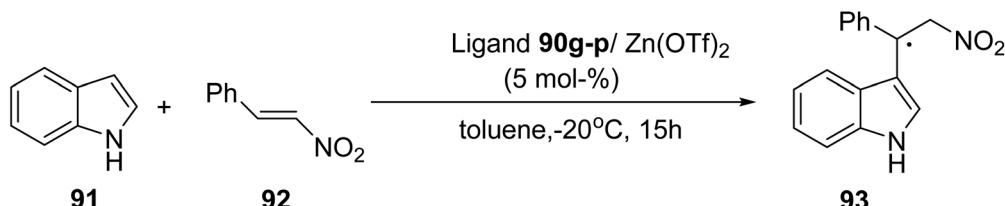
The structurally distinct diastereomers, ulbactin F **118** as well as ulbactin G **119**, with a tricyclic ring structure including nitrogen and sulfur, were identified by Igarashi *et al.*<sup>106</sup> from sponge-derived *Brevibacillus* sp. With the use of X-ray crystallography and NMR measurements,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

Wang *et al.*<sup>107</sup> 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  $\text{IC}_{50}$  values of  $22.58 \mu\text{g mL}^{-1}$  for A-549 and  $19.41 \mu\text{g mL}^{-1}$  for Bcap-37, respectively.

El-Helw *et al.*<sup>108</sup> 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  $\text{Et}_3\text{N}$  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.*<sup>109</sup> 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 <sup>1</sup>	R <sup>2</sup>	Yield [%]	ee [%]
1	90g	iPr	tBu	100	19(R)
2	90h	iPr	Ph	100	56(R)
3	90i	iPr	Bn	100	69(R)
4	90j	tBu	iPr	100	8(S)
5	90k	tBu	Ph	99	67(R)
6	90l	Ph	iPr	100	rac
7	90m	Ph	tBu	100	59(R)
8	90n	Ph	Bn	99	32(R)
9	90o	Bn	iPr	100	21(R)
10	90p	Bn	Ph	94	64(R)

Scheme 25 Zinc catalyzed Friedel–Crafts alkylation reaction.

this intermediate.<sup>110</sup> 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.<sup>111</sup> The final acetohydrazides **134a–k** were synthesized by reacting carbothioamide **133** with phenacyl bromide (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<sup>112</sup> was utilized in the process of total synthesis of the new anticancer

natural product cyclic depsipeptide largazole, which was discovered in 2008.<sup>113</sup> 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.*<sup>114</sup> 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.<sup>115</sup> 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,<sup>33,115</sup> Guerra-Bubb *et al.*<sup>116</sup> 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).<sup>117</sup> Acrolein **145** was used to formulate the heptenoic acid fragment **148** (Scheme



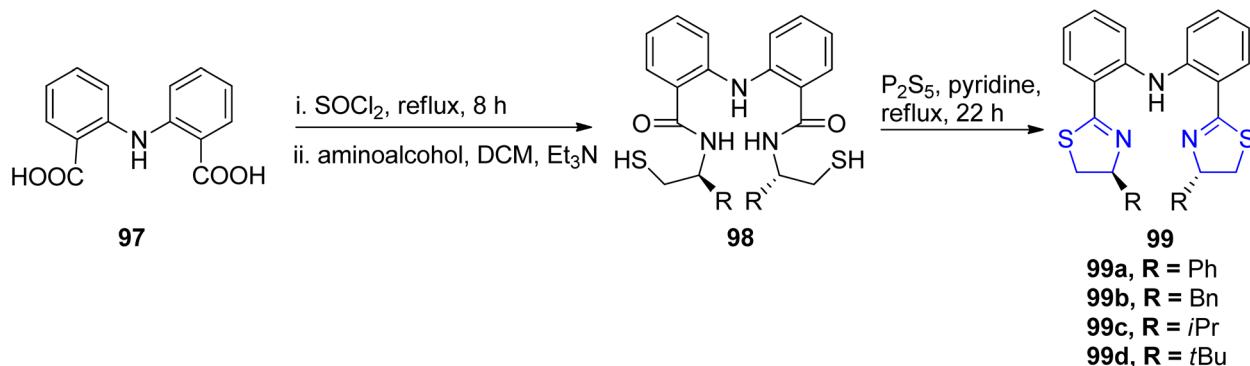
1.  $\text{CrCl}_3$  (0.1equiv.),  $\text{Mn}$ (3 equiv.)  
ligand **90a-p** (0.12 equiv.)  
DIPEA (0.3equiv.)  
 $\text{Me}_3\text{SiCl}$ , THF/ACN(7:1)  
16h, r.t.  
2. 1M HCl, THF

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

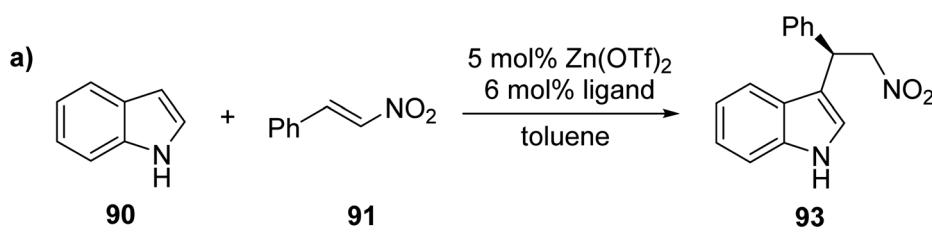
Scheme 26 NHK allylation reaction with benzaldehyde **94**.

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).<sup>118</sup> The required substrate **150** was obtained in two phases of deprotection, coupling with PyBOP and Hunigs base with a yield of 91%. T3P

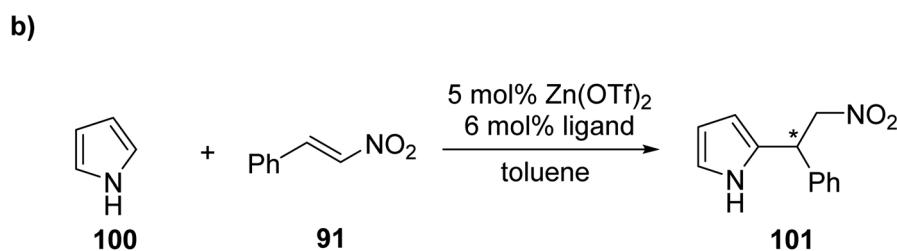
and Hunigs base were used to produce the required macrocycle **151** in 30% yield after conversion of compound **150** to amino acid in a one-pot reaction. Using TFA and *i*Pr<sub>3</sub>SiH<sub>8</sub> in degassed dichloromethane, the macrocycle **151** was deprotected to give disulfide **152** instead of the anticipated thiol (Scheme 37b).



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



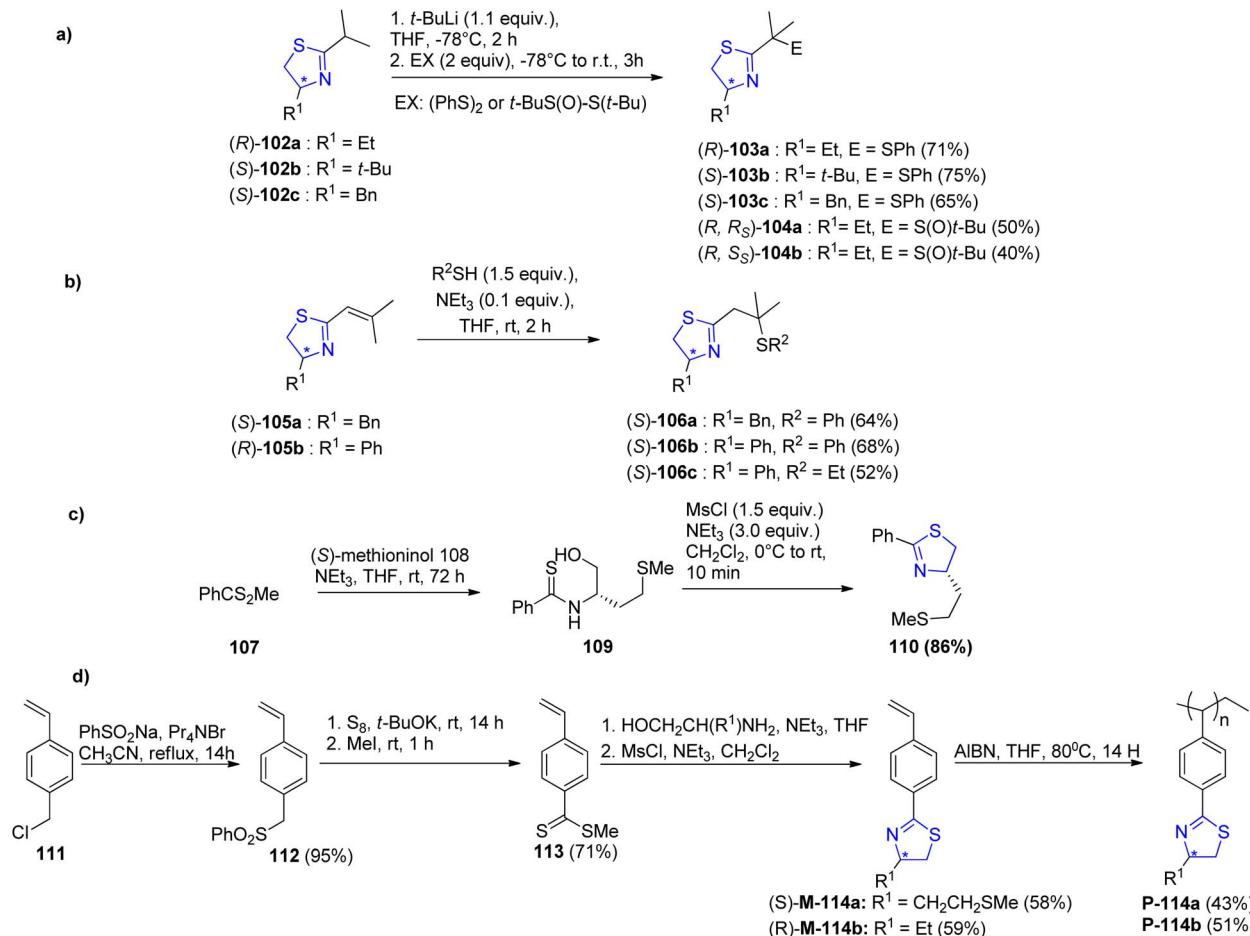
Entry	Ligand	T [°C]	Yield [%]	ee [%]
1	<b>99a</b>	10	99	78
2	<b>99b</b>	10	99	59
3	<b>99c</b>	10	93	11
4	<b>99d</b>	10	87	2



Entry	Ligand	T [°C]	Yield [%]	ee [%]
1	<b>99a</b>	20	73	45
2	<b>99b</b>	20	71	73
3	<b>99c</b>	20	76	27
4	<b>99d</b>	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  $\text{Et}_3\text{SiH}$  rather than  $i\text{Pr}_3\text{SiH}$  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.<sup>119</sup> 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  $\text{IC}_{50}$  value of 6.2  $\mu\text{M}$ , which is probably because the free thiol gets degraded in the cellular environment. Similar to largazole, the prodrugs 152 and 154 showed  $\text{IC}_{50}$  values of 0.91 & 0.12  $\mu\text{M}$ , respectively.

Taher *et al.*<sup>120</sup> 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.

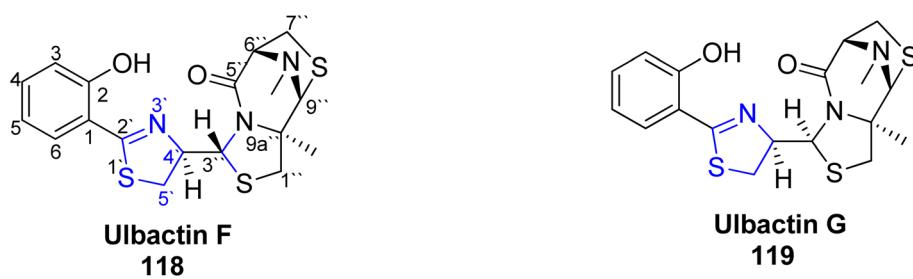
One of the most commonly used chemotherapy drugs in the treatment of various malignancies is cisplatin,<sup>121</sup> but it is associated with a high level of toxicity and adverse effects.<sup>122</sup> New chemotherapeutic drugs must therefore be developed in order to obtain less harmful and efficient drugs for cancer treatment. A Pd(II) complex, PdPyTT 162 was synthesized and described by Espino *et al.*<sup>123</sup> using the ligand PyTT 161 (Scheme 39). The ligand was prepared according to the reported methodology,<sup>124</sup> with a few minor adjustments as per published literature.<sup>125</sup> 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.*<sup>126</sup> 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)	Enantiomeric Excess (ee) (%)	Product Configuration
1	( <i>R</i> )- <b>103a</b>	>95 (24h)	37	( <i>R</i> )
2	( <i>S</i> )- <b>103b</b>	>95(24 h)	43	( <i>S</i> )
3	( <i>S</i> )- <b>103c</b>	>95(48h)	40	( <i>S</i> )
4	( <i>R,R<sub>S</sub></i> )- <b>104a</b>	30 (168h)	47	( <i>R</i> )
5	( <i>R,S<sub>S</sub></i> )- <b>104b</b>	30 (168h)	47	( <i>R</i> )
6	( <i>S</i> )- <b>106a</b>	50 (120 h)	49	( <i>S</i> )
7	( <i>S</i> )- <b>106b</b>	60 (120h)	73	( <i>S</i> )
8	( <i>S</i> )- <b>106c</b>	80(120h)	42	( <i>S</i> )
9	( <i>S</i> )- <b>110</b>	>95(24h)	66	( <i>R</i> )

Scheme 30 Asymmetrically induced allylic substitution reaction catalysed by palladium.

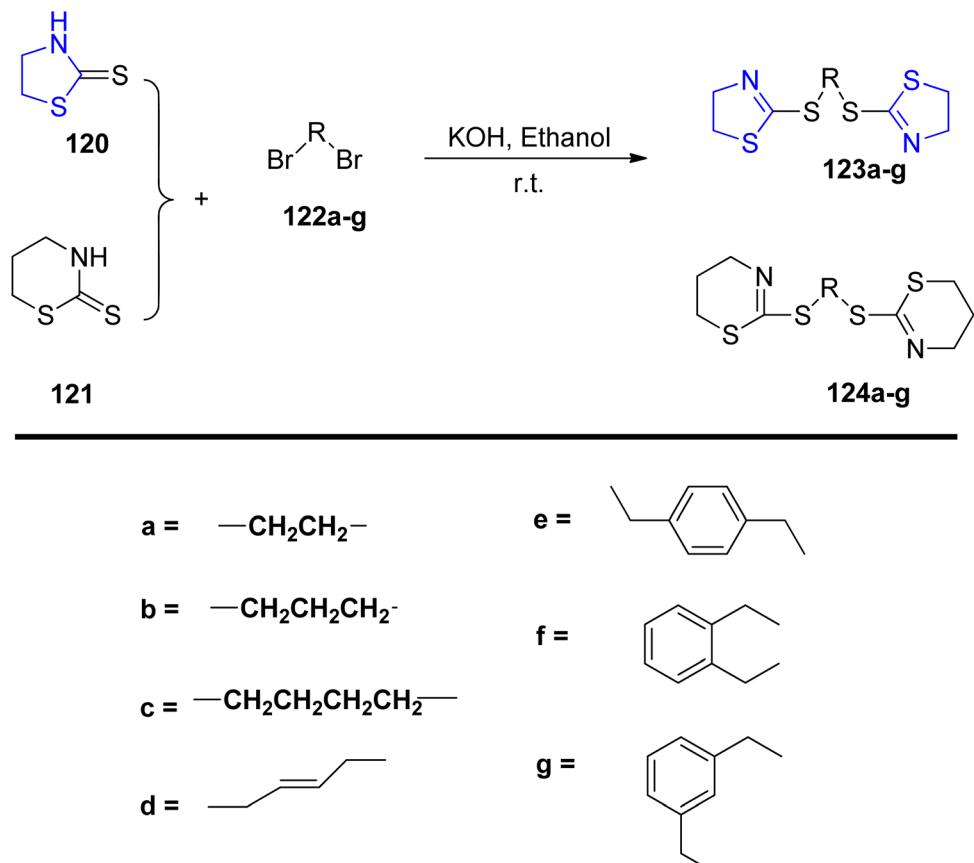
Scheme 31 Structures of ulbactin F **118** and ulbactin G **119**.

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<sup>2+</sup> and Zn<sup>2+</sup> 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.

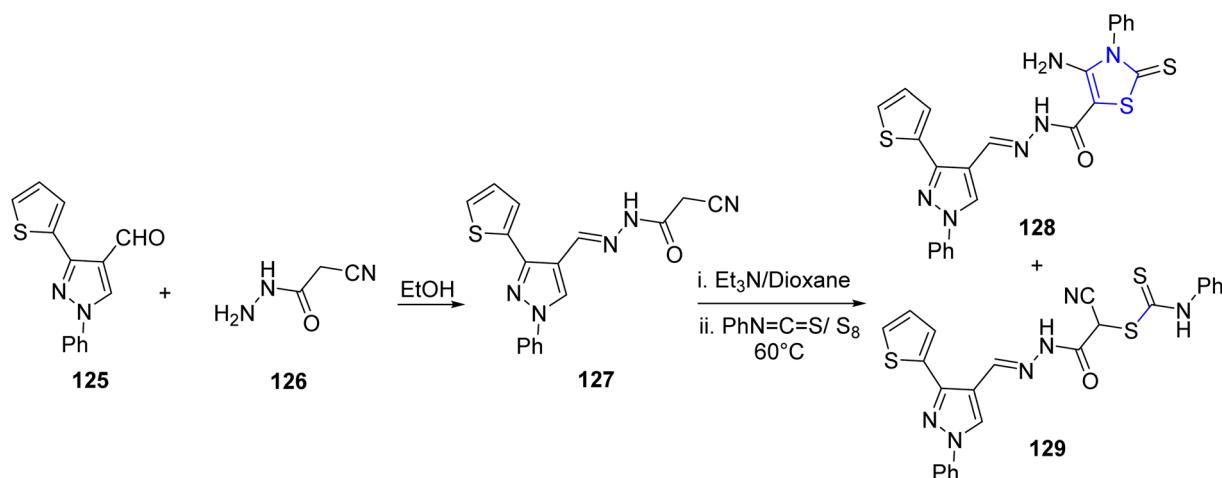
Altintop *et al.*<sup>127</sup> synthesized acetohydrazide compounds **179–218**, which were subsequently evaluated for their

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-[(arylthio)acetohydrazides were then synthesized by treating ester derivatives **167a–e** with hydrazine hydrate **168a–e**. These hydrazides **168a–e** were further transformed into 1-(arylothioacetyl)-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.

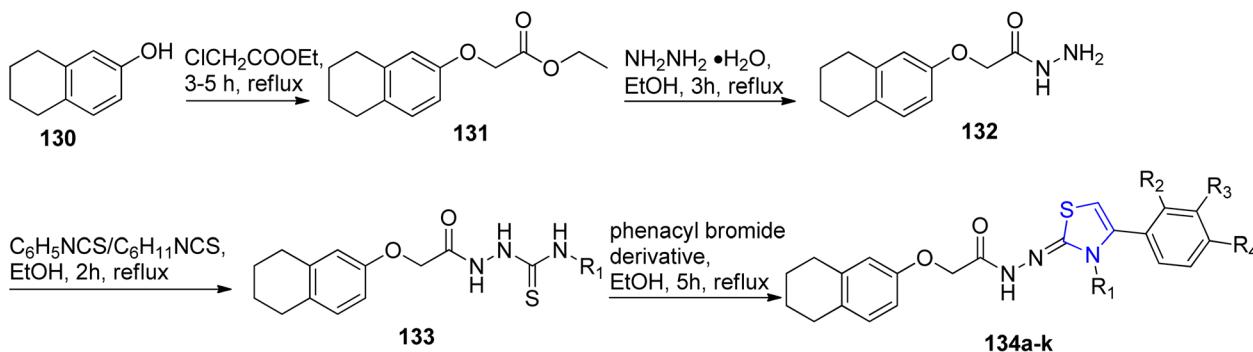


Scheme 33 Synthesis of thiazoline derivative 128.

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  $8.3 \pm 2.6 \mu\text{g mL}^{-1}$ , surpassing cisplatin ( $IC_{50}$  range:  $13.7 \pm 1.2 \mu\text{g mL}^{-1}$ ). Compound **195** also demonstrated DNA synthesis inhibition on C6 cells and exhibited lower

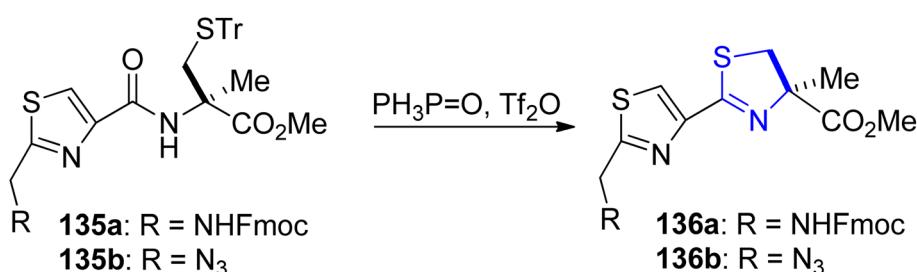
toxicity to NIH/3T3 cells with an  $IC_{50}$  value in the range of  $416.7 \pm 28.9 \mu\text{g mL}^{-1}$ .

Mabkhout *et al.*<sup>128</sup> 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 <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>
134a	Cyclohexyl	H	H	H
134b	Cyclohexyl	H	H	OCH <sub>3</sub>
134c	Phenyl	H	H	H
134d	Phenyl	H	H	CH <sub>3</sub>
134e	Phenyl	H	H	OCH <sub>3</sub>
134f	Phenyl	H	H	Br
134g	Phenyl	H	H	Cl
134h	Phenyl	H	H	F
134i	Phenyl	H	NO <sub>2</sub>	H
134j	Phenyl	H	H	NO <sub>2</sub>
134k	Phenyl	Cl	Cl	H

Scheme 34 Synthesis of the compounds 134a–k.

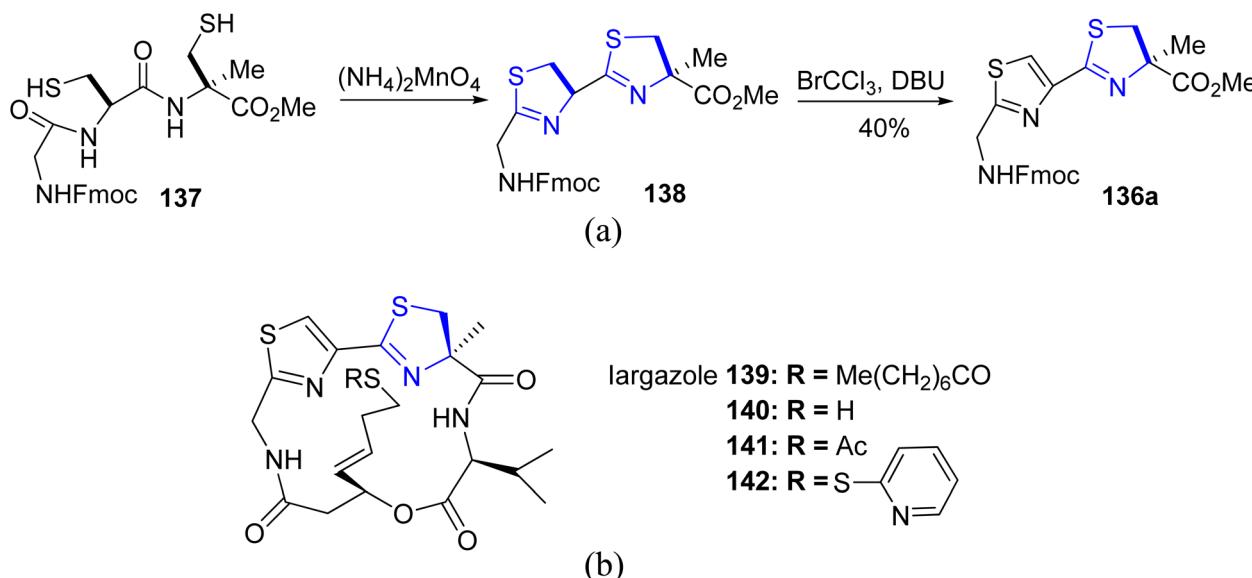


Scheme 35 Synthesis of thiazoline esters 136a–b.

when refluxed with the suitable aniline derivatives (Scheme 42). Next, the reaction of the thiazoline-2-thione derivative 221a with 2-oxo-N'-phenylpropane hydrazoneyl 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.*<sup>129</sup> Initially, the intermediate 227 was prepared by treatment of *p*-toluidine 226 in ethanolic media with phenacyl bromide 177.<sup>130</sup> 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  $\text{Et}_3\text{N}$  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.

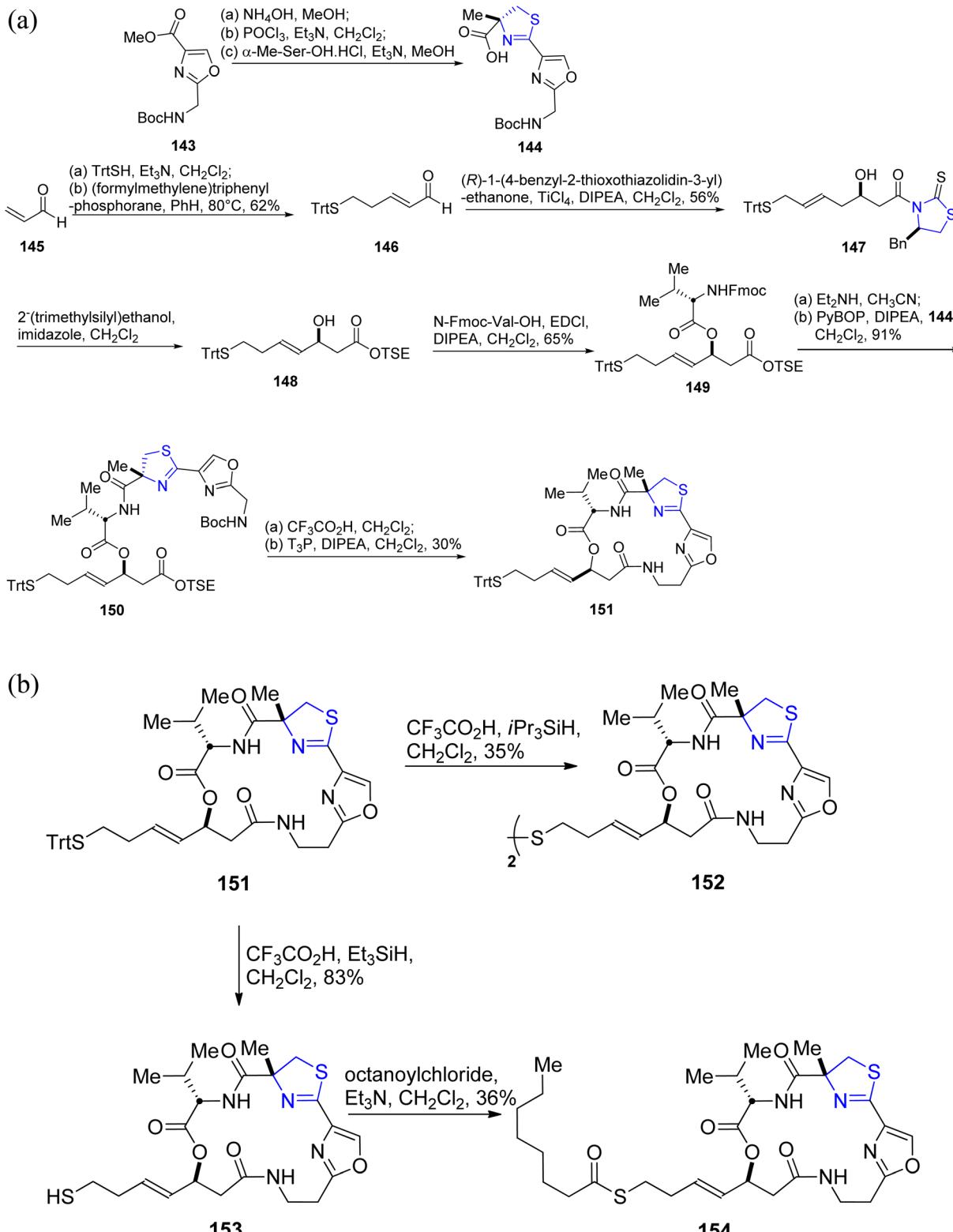
**3.3.2. Anti-microbial.** As per the reports from the CDC (Centers for Disease Control and Prevention), over two million individuals acquire drug-resistant bacterial infections annually, leading to the mortality of more than 23 000 people.<sup>131</sup> Due to the capacity of microorganisms to develop resistance to treatments, bacterial and fungal infections have emerged as significant contributors to global morbidity and mortality.<sup>132</sup> 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.<sup>133,134</sup> 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.<sup>135–137</sup>

Asiri *et al.*<sup>138</sup> 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 anti-fungal 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  $\text{IC}_{50}$  values of  $79 \mu\text{g mL}^{-1}$  and  $49 \mu\text{g mL}^{-1}$ , respectively.

Bondock *et al.*<sup>139</sup> 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  $\alpha$ -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.

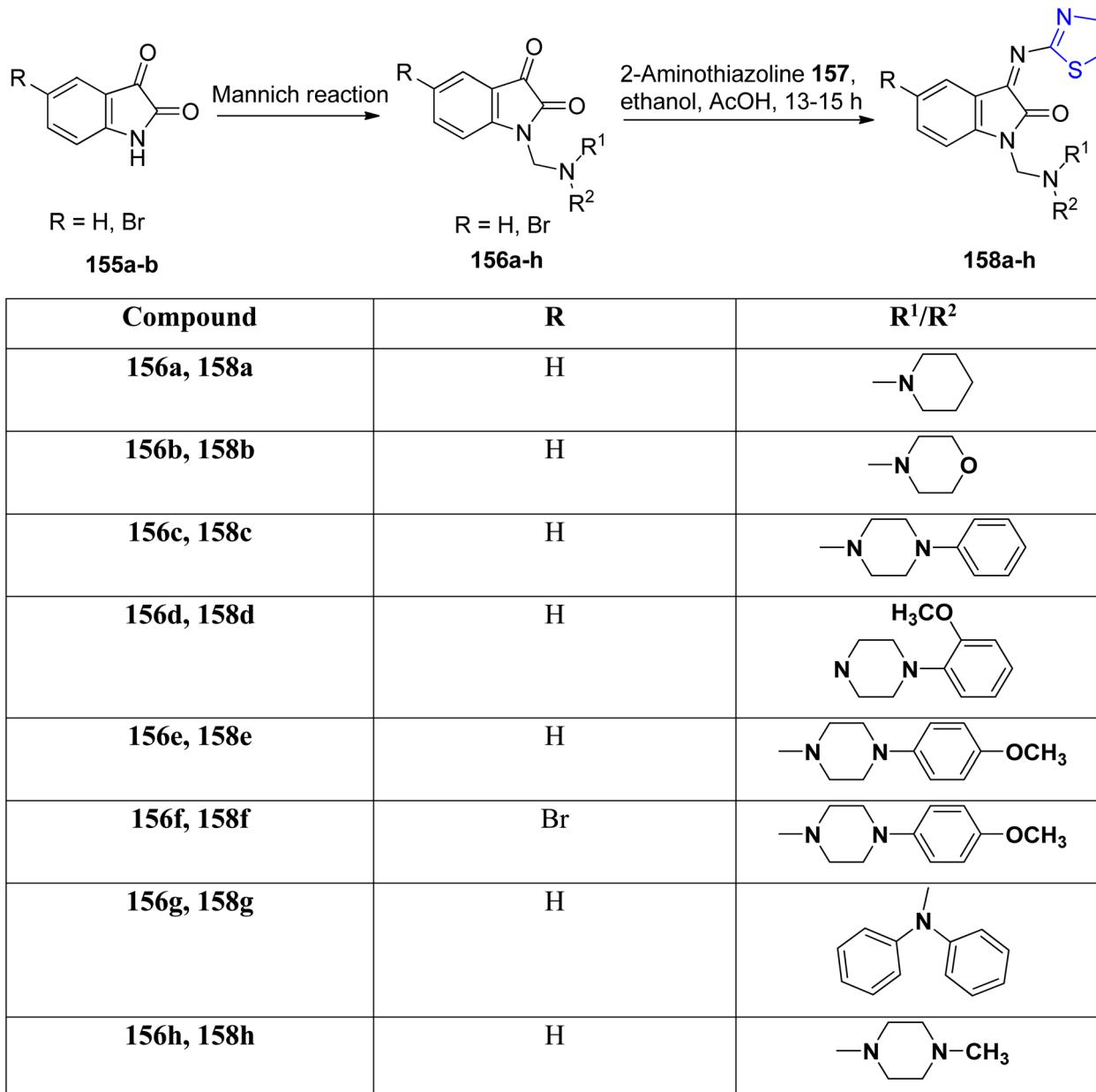




Scheme 37 (a) Synthetic scheme for largazole analogue 151. (b) Synthesis of largazole analogues 152–154.

Viñuelas-Zahínos *et al.*<sup>140</sup> 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

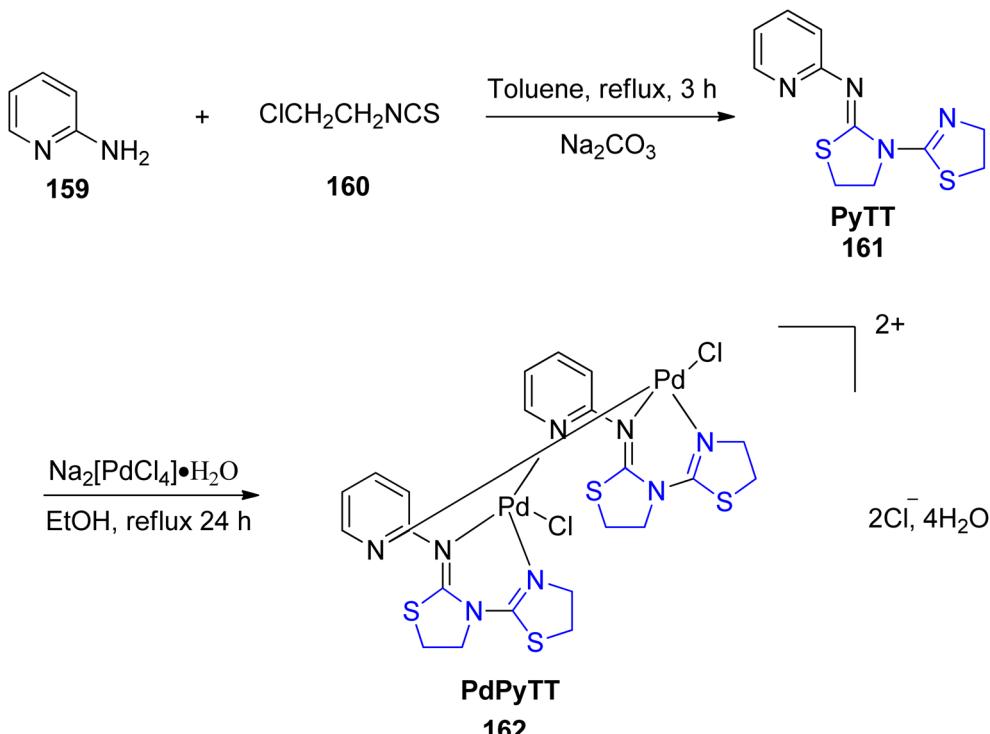


Scheme 38 Synthesis of novel isatin-thiazoline 158a-h.

by Doornbos and Peer.<sup>141</sup> 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<sup>-1</sup>, 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.*<sup>142</sup> 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,



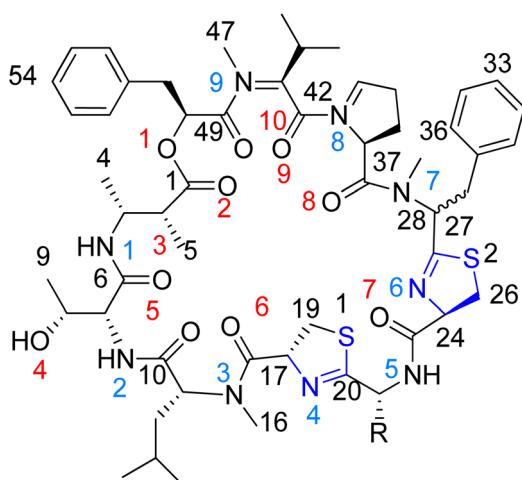
Scheme 39 Synthesis of thiazoline-based palladium(II) complex 162.

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:  $25 \mu\text{g mL}^{-1}$ ) showed highest antibacterial activity against *E. coli*. These results are almost equivalent to approved drug ciprofloxacin.

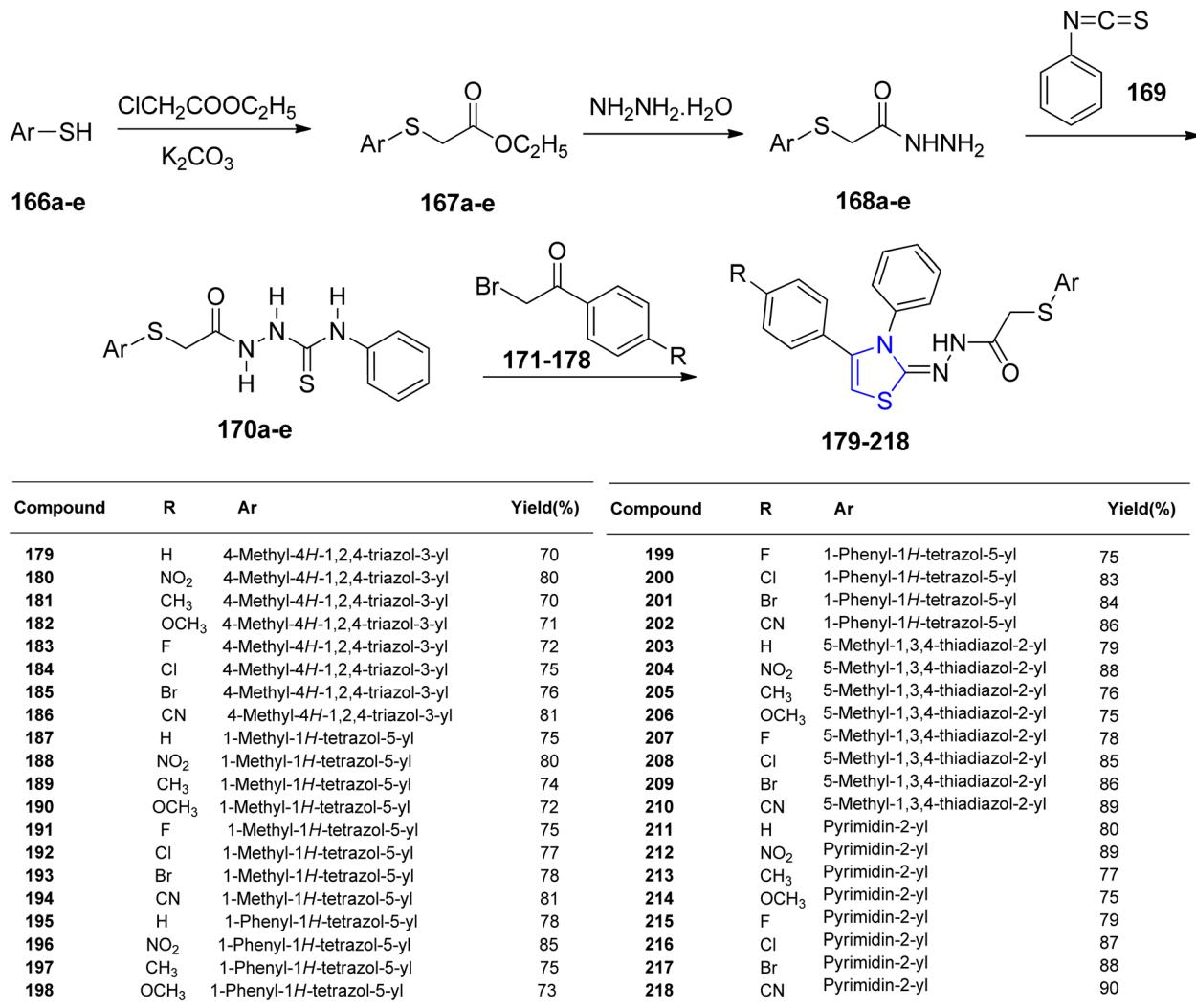
Furthermore, compounds 252a and 252d displayed anti-fungal properties when tested against clinical isolates of *Candida* that had developed resistance to itraconazole and fluconazole.

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.*<sup>143</sup> 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.<sup>144</sup>

Ke *et al.*<sup>145</sup> 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.<sup>146,147</sup> 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<sub>50</sub> values of  $0.61 \mu\text{mol L}^{-1}$ ,  $0.95 \mu\text{mol L}^{-1}$ , and  $2.31 \mu\text{mol L}^{-1}$ , respectively; while compounds 260b, 260e, 261c, and 261g with EC<sub>50</sub> values of  $1.83 \mu\text{mol L}^{-1}$ ,  $6.79 \mu\text{mol L}^{-1}$ ,  $7.09 \mu\text{mol L}^{-1}$  and  $2.49 \mu\text{mol L}^{-1}$ , respectively, exhibited enhanced antiviral



Scheme 40 Grassypeptolides 163–165, the cyclic depsipeptides.



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.

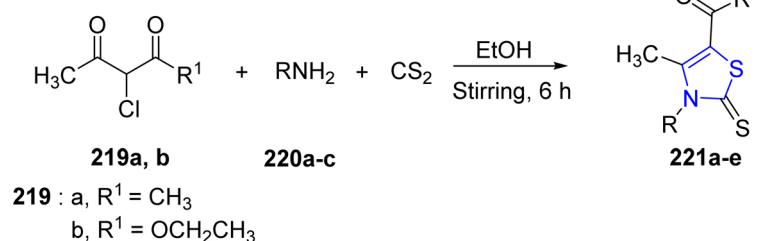
Meleddu *et al.*<sup>148</sup> detailed the synthesis and development of a series of indol-2-one analogues, which were subsequently investigated for their impact on HIV-1 reverse transcriptase (RT). Initially, thiosemicarbazones 266a–b were synthesized by refluxing an ethanolic solution containing substituted isatins 265a–b and compound 264. Subsequently, through treatment of compound 266a–b with variously substituted bromo- or chloroacetophenones 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<sub>50</sub> values for 268a–m were in the range 15–29  $\mu$ M, whereas 10–27  $\mu$ M for compounds 269a–l.

Hussein *et al.*<sup>149</sup> 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

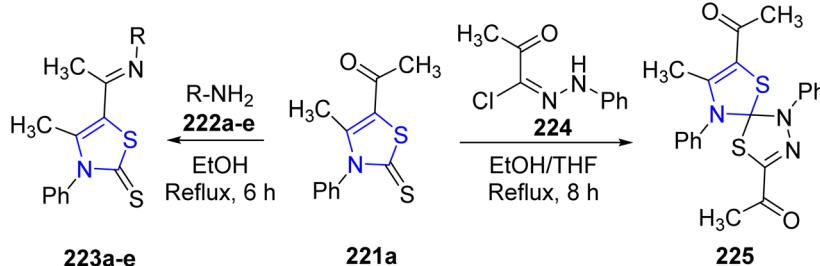
ethanolic solutions of thiosemicarbazones 274a–e with phenacyl bromides 275a–e, as depicted in Scheme 51. Characterization of the prepared compounds was conducted through spectroscopic measurements and elemental analysis. A total of 28 novel compounds were evaluated for their potential antibacterial 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<sup>-1</sup>.

**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.<sup>150</sup>



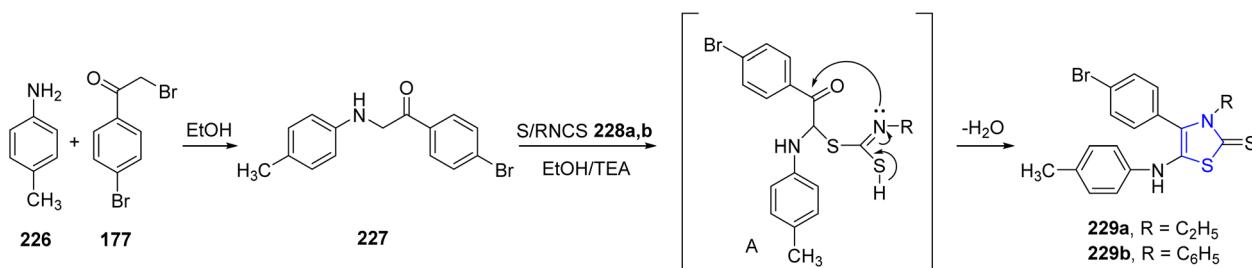


221	R	$R^1$	Yield (%)
a	Ph	$CH_3$	92
b	Ph	$OCH_2CH_3$	85
c	H	$CH_3$	85
d	H	$OCH_2CH_3$	75
e	PhNH	$OCH_2CH_3$	85



223	R	Yield (%)
a	$NH_2$	55
b	Ph	50
c	NH-Ph	60
d	$-\text{C}_6\text{H}_4-\text{N}_3-$	50
e	$-\text{C}_6\text{H}_4-\text{NH}-\text{C}_6\text{H}_4-$	45

Scheme 42 Synthesis of new thiazoline derivatives.



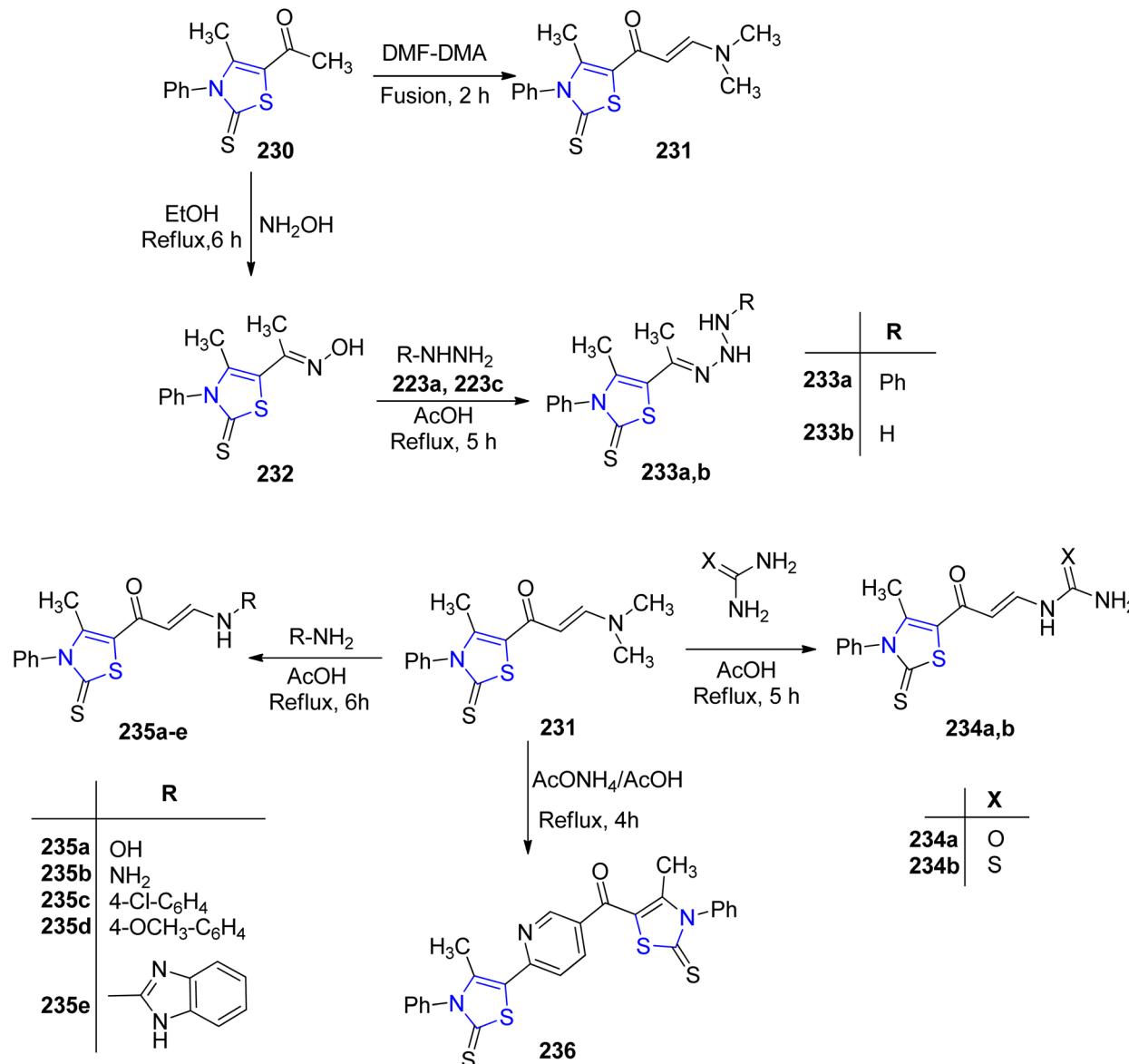
Scheme 43 Synthesis of thiazoline-based derivatives 229a-b.

Approximately 25% of individuals aged 65 and older experience diabetes-related complications, and this percentage is steadily increasing.<sup>151</sup> The vast majority of DM patients come from the underdeveloped or developing parts of the world.<sup>152,153</sup> 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.<sup>154</sup>

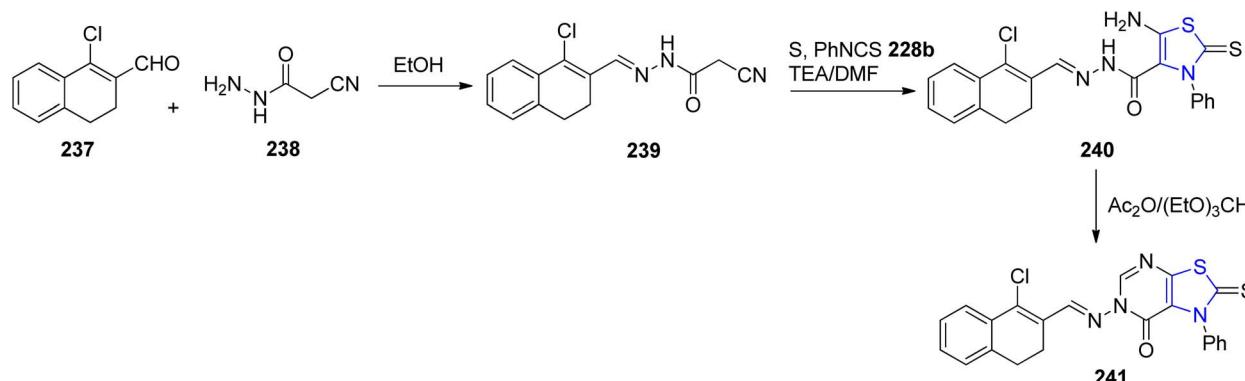
The two incretin hormones, GLP-1 and GIP, are deactivated by the enzyme dipeptidyl peptidase IV (DPP-4). Therefore, DPP-4 inhibitors play a vital role by slowing down the activity of GIP and GLP-1 hormones, thereby maintaining glucose homeostasis. The therapeutic potential of the DPP-4 enzyme makes it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

Ali *et al.*<sup>156</sup> 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 benzoxazin-4-ones **284a-c** with substituted thiazoles **285a/b** gave benzoxazin-4-ones **286a-f**.<sup>157</sup> In

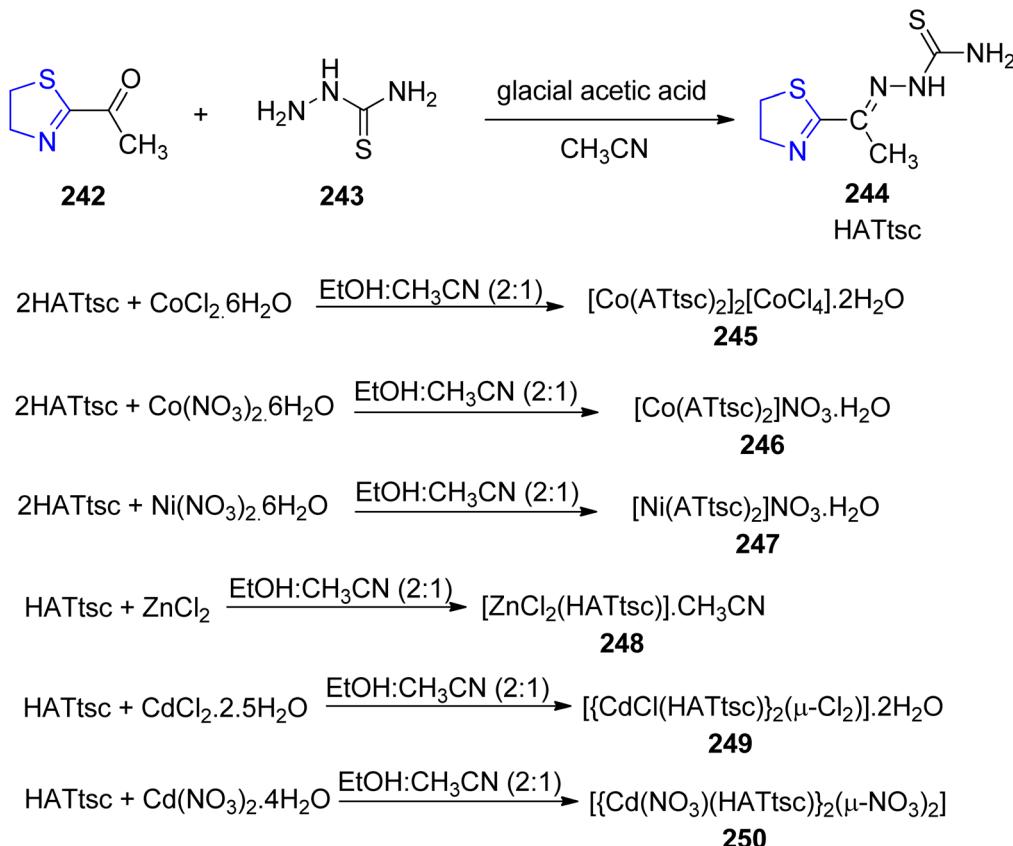




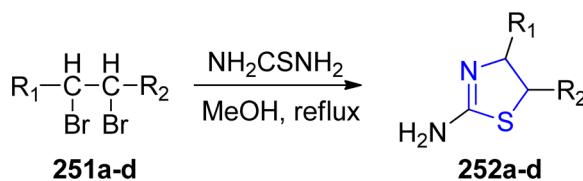
Scheme 44 Synthesis of novel thiazoline-2-thione derivatives.



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.

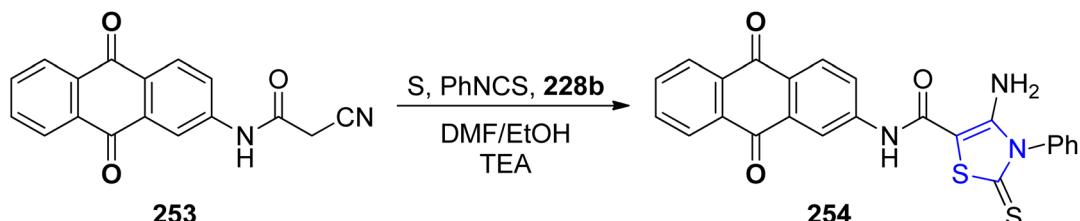


Compounds	R <sub>1</sub>	R <sub>2</sub>
<b>251a, 252a</b>	H	(CH <sub>2</sub> ) <sub>8</sub> COOCH <sub>3</sub>
<b>251b, 252b</b>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>7</sub>	(CH <sub>2</sub> ) <sub>7</sub> COOCH <sub>3</sub>
<b>251a, 252b</b>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub> CHOHCH <sub>2</sub>	(CH <sub>2</sub> ) <sub>7</sub> COOCH <sub>3</sub>
<b>251a, 252b</b>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>4</sub>	(CH <sub>2</sub> ) <sub>2</sub> CHOH(CH <sub>2</sub> ) <sub>7</sub> COOCH <sub>3</sub>

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 quinazolin-4-ones **287a-f** thus obtained were condensed with aldehydes **288a-d** to yield a sequence of Schiff bases **289a-x** (Scheme 52).<sup>158</sup> 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<sub>50</sub> of 1.12 nM) were the most encouraging.



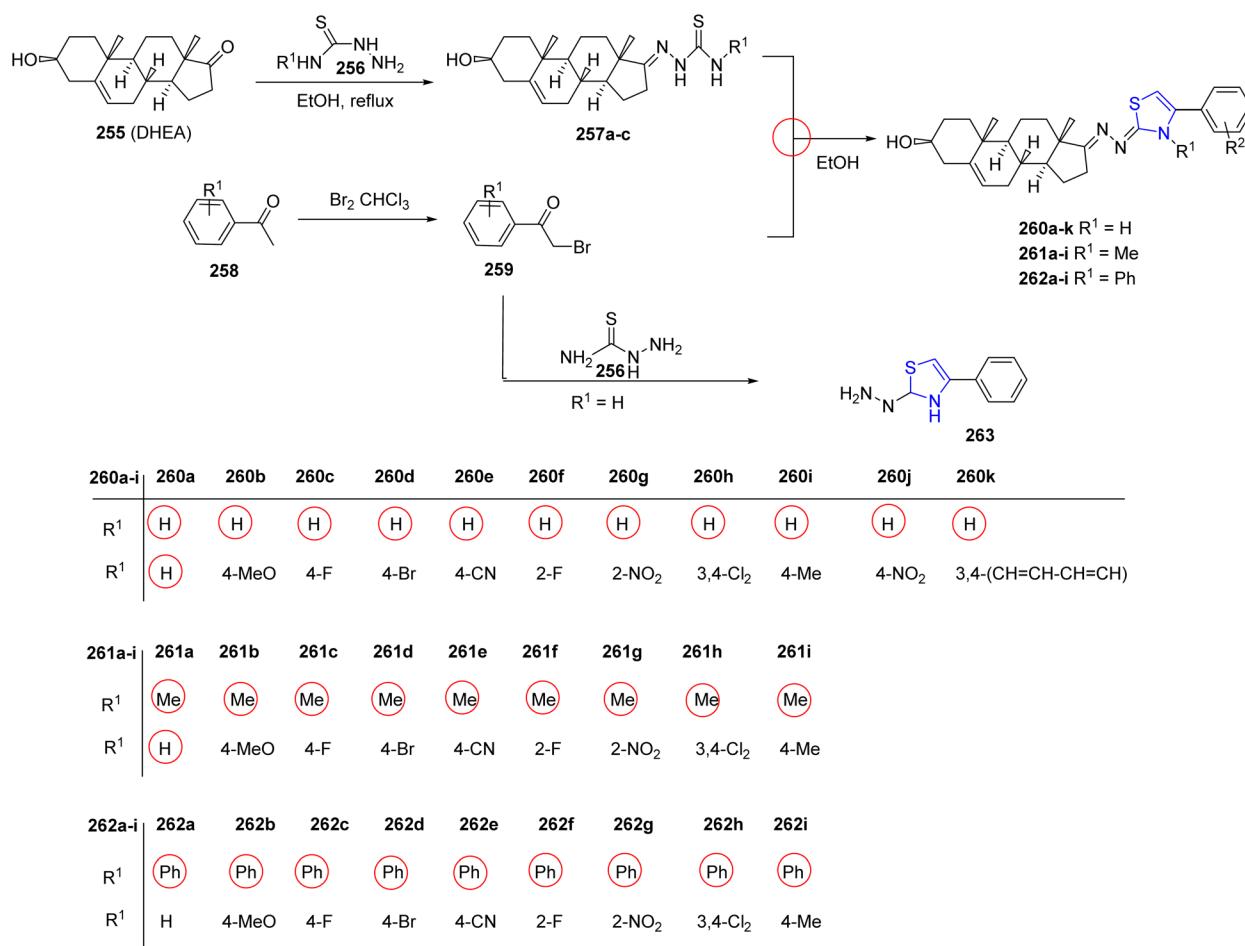
**Scheme 48** Synthesis of thiazoline derivative 254

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

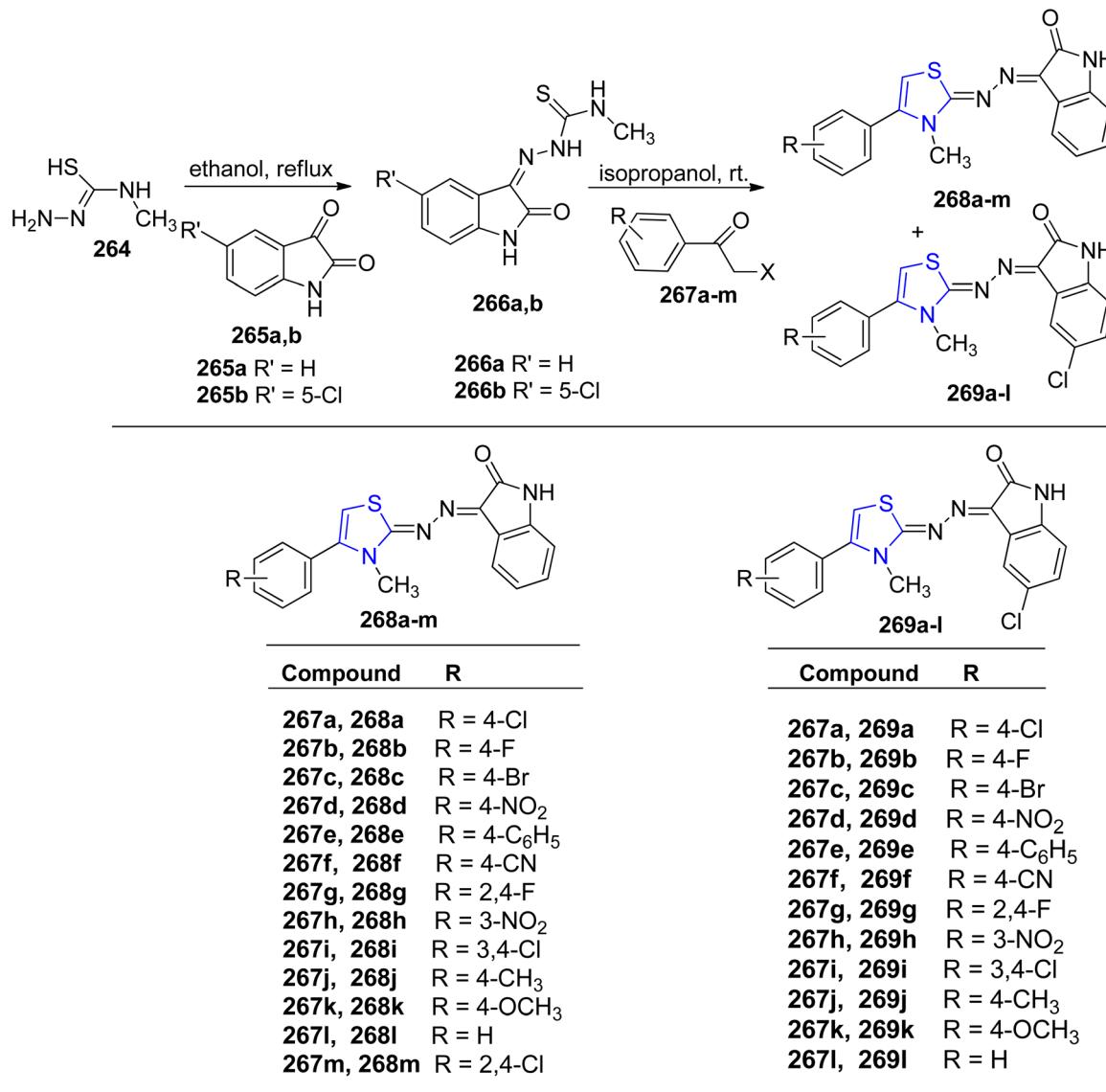
Utilizing small heterocyclic compounds to inhibit aldose reductase (ALR2) is a viable approach for developing innovative anti-diabetic medications. To identify a lead as a potential novel anti-diabetic drug, Shehzad *et al.*<sup>159</sup> synthesized thiazoline analogues 294a–k, 295a–f, 296a–l and 297a–j. 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 ( $IC_{50} = 1.39 \pm 2.21 \mu\text{M}$ ) and 297e ( $IC_{50} = 1.52 \pm 0.78 \mu\text{M}$ ) were

identified to be the most efficient ones in comparison to the reference drug, sorbinil ( $IC_{50} = 3.14 \pm 0.02 \mu M$ ). Compound **296b** demonstrated good selectivity for the intended ALR2 with just 23.4% inhibition for ALR1.

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



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



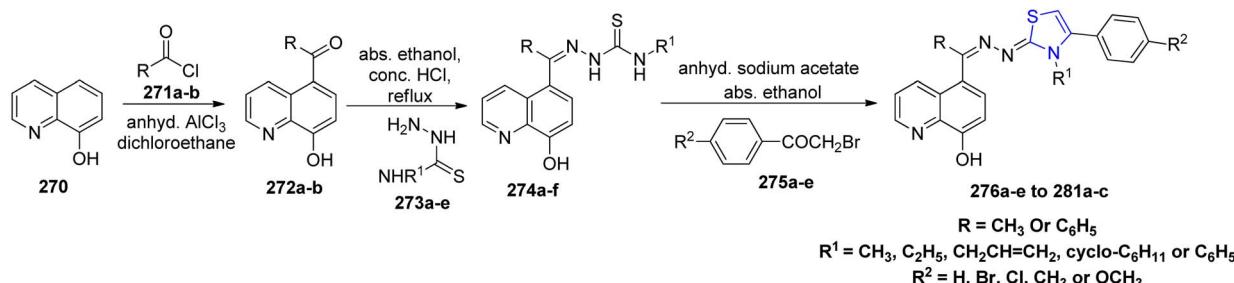
Scheme 50 Synthesis of isatin thiazoline hybrids 268a-m and 269a-l.

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 ( $K_i = 0.13 \mu\text{M}$ ) in sub-micromolar quantities. The  $K_i$  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  $\alpha$ -MSH.<sup>161</sup> A novel thiazoline analogue, KHG22394 302 was synthesized by Kim *et al.*<sup>162</sup> 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

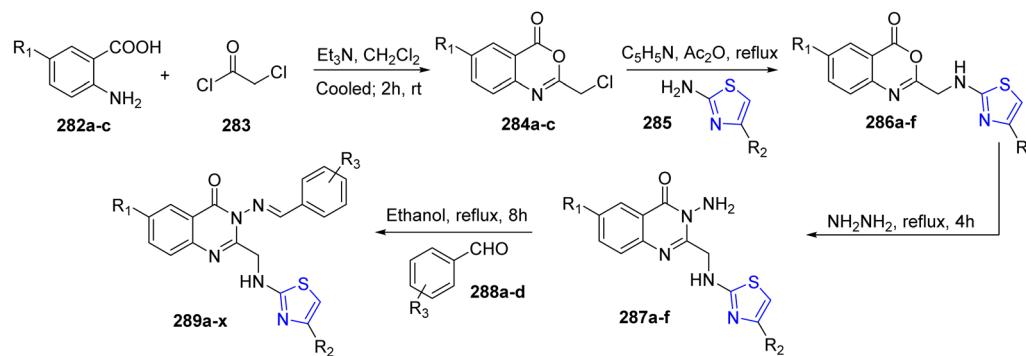
factor linked to microphthalmia, which in turn decreases melanin formation (Mitf). In B16 melanoma cells, KHG22394 upregulates the ERK pathway while downregulating the protein levels of Mitf and tyrosinase. Despite not directly inhibiting tyrosinase activity, KHG22394's hypopigmentary impact is due to the downregulation of Mitf and tyrosinase as a result.

Hosamani *et al.*<sup>163</sup> 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 ( $\text{MIC} = 0.09 \mu\text{g mL}^{-1}$ ) 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 <sup>1</sup>	R <sup>2</sup>	Yield(%)	Compound no.	R	R <sup>1</sup>	R <sup>2</sup>	Yield(%)
276a	CH <sub>3</sub>	CH <sub>3</sub>	H	89	278e	CH <sub>3</sub>	CH <sub>2</sub> CH=CH <sub>2</sub>	OCH <sub>3</sub>	63
276b	CH <sub>3</sub>	CH <sub>3</sub>	Br	81	279a	CH <sub>3</sub>	cyclo-C <sub>6</sub> H <sub>11</sub>	H	73
276c	CH <sub>3</sub>	CH <sub>3</sub>	Cl	72	279b	CH <sub>3</sub>	cyclo-C <sub>6</sub> H <sub>11</sub>	Br	76
276d	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	84	279c	CH <sub>3</sub>	cyclo-C <sub>6</sub> H <sub>11</sub>	Cl	66
276e	CH <sub>3</sub>	CH <sub>3</sub>	OCH <sub>3</sub>	78	279d	CH <sub>3</sub>	cyclo-C <sub>6</sub> H <sub>11</sub>	CH <sub>3</sub>	83
277a	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	H	74	279e	CH <sub>3</sub>	cyclo-C <sub>6</sub> H <sub>11</sub>	OCH <sub>3</sub>	86
277b	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	Br	88	270a	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	H	64
277c	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	Cl	81	280b	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	Br	53
277d	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	70	280c	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	Cl	70
277e	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	OCH <sub>3</sub>	64	280d	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	89
278a	CH <sub>3</sub>	CH <sub>2</sub> CH=CH <sub>2</sub>	H	70	280e	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	OCH <sub>3</sub>	75
278b	CH <sub>3</sub>	CH <sub>2</sub> CH=CH <sub>2</sub>	Br	80	281a	C <sub>6</sub> H <sub>5</sub>	cyclo-C <sub>6</sub> H <sub>11</sub>	H	66
278c	CH <sub>3</sub>	CH <sub>2</sub> CH=CH <sub>2</sub>	Cl	67	281b	C <sub>6</sub> H <sub>5</sub>	cyclo-C <sub>6</sub> H <sub>11</sub>	Br	73
278d	CH <sub>3</sub>	CH <sub>2</sub> CH=CH <sub>2</sub>	CH <sub>3</sub>	62	281c	C <sub>6</sub> H <sub>5</sub>	cyclo-C <sub>6</sub> H <sub>11</sub>	Cl	78

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



Compound	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Compound	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>
289a	H	H	H	289m	I	CH <sub>3</sub>	H
289b	H	H	2-CN	289bn	I	CH <sub>3</sub>	2-CN
289c	H	H	3-NO <sub>2</sub>	289o	I	CH <sub>3</sub>	3-NO <sub>2</sub>
289d	H	H	4-OH	289p	I	CH <sub>3</sub>	4-OH
289e	H	CH <sub>3</sub>	H	289q	CH <sub>3</sub>	H	H
289f	H	CH <sub>3</sub>	2-CN	289r	CH <sub>3</sub>	H	2-CN
289g	H	CH <sub>3</sub>	3-NO <sub>2</sub>	289s	CH <sub>3</sub>	H	3-NO <sub>2</sub>
289h	H	CH <sub>3</sub>	4-OH	289t	CH <sub>3</sub>	H	4-OH
289i	I	H	H	289u	CH <sub>3</sub>	CH <sub>3</sub>	H
289j	I	H	2-CN	289v	CH <sub>3</sub>	CH <sub>3</sub>	2-CN
289k	I	H	3-NO <sub>2</sub>	289w	CH <sub>3</sub>	CH <sub>3</sub>	3-NO <sub>2</sub>
289l	I	H	4-OH	289x	CH <sub>3</sub>	CH <sub>3</sub>	4-OH

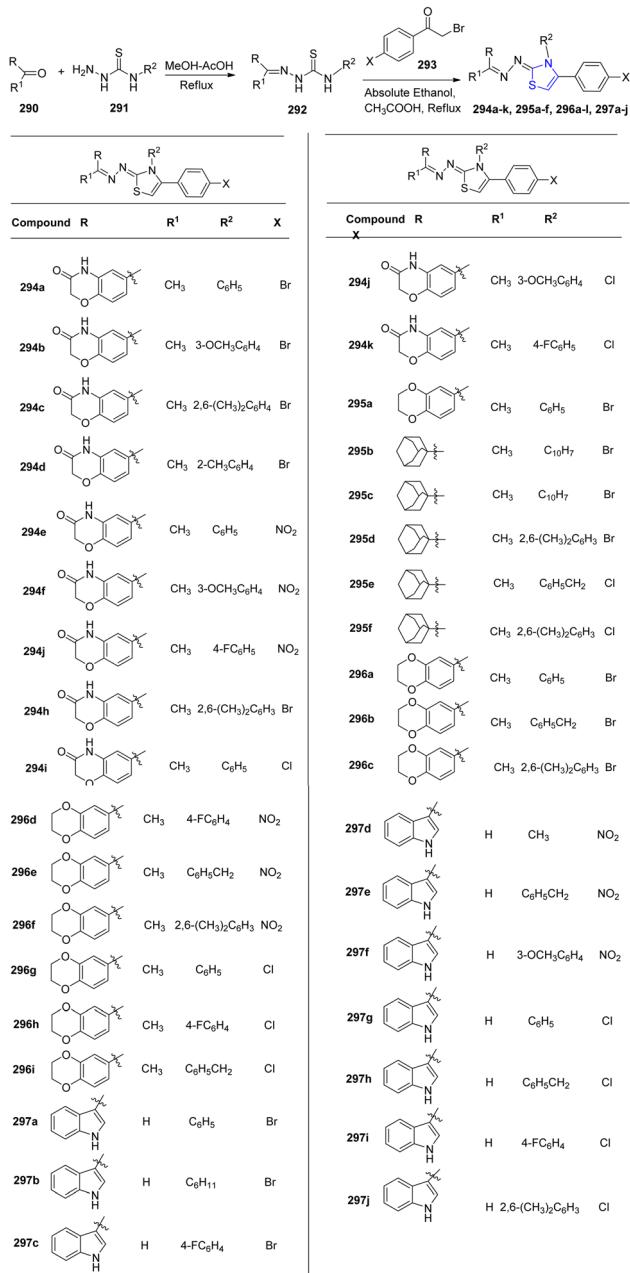
Scheme 52 Synthetic scheme for quinoline linked thiazoline derivatives.

## 4. Miscellaneous

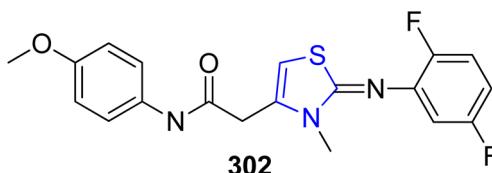
Nonlinear optical (NLO) materials are cost-effective and easily tunable in terms of absorption wavelength, making them

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,





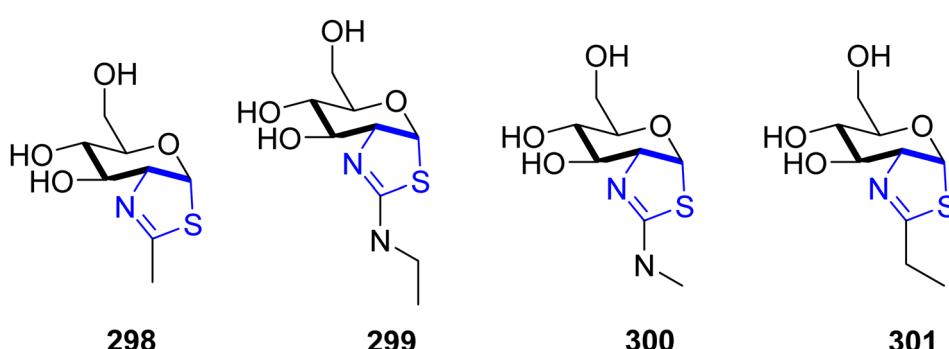
Scheme 53 Synthesis of thiazoline derivatives 294a-k, 295a-f, 296a-l and 297a-j.



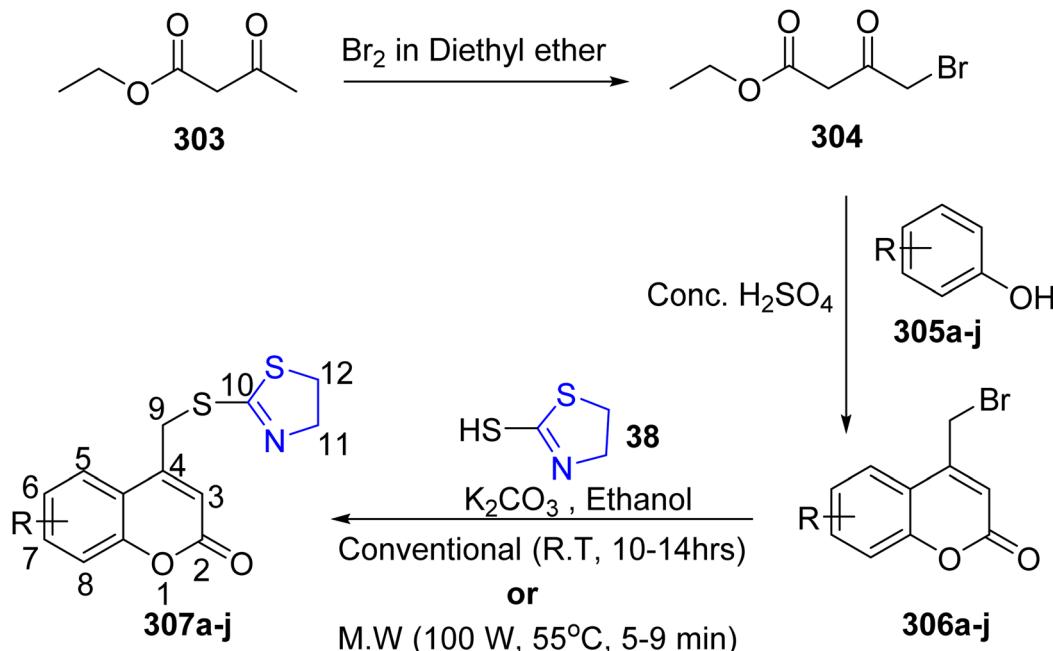
Scheme 55 Structure of KHG22394.

solid physics, dynamic image processing, nuclear science, and biophysics.<sup>164,165</sup> Thiazoline derivatives are fascinating molecules because of their potential usage in nonlinear optics (NLO). Haroon *et al.*<sup>166</sup> described four new thiazoline derivatives with the chemical formulae C<sub>27</sub>H<sub>24</sub>ClN<sub>3</sub>O<sub>2</sub>S, C<sub>27</sub>H<sub>23</sub>ClN<sub>4</sub>O<sub>2</sub>S, C<sub>26</sub>H<sub>21</sub>N<sub>5</sub>O<sub>2</sub>S, and C<sub>28</sub>H<sub>30</sub>ClN<sub>3</sub>S. 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  $\beta$ -hydroxy thioamide functionality. The synthetic pathways employed for the



Scheme 54 Structures of NGT and its derivatives.



Product	R	Yield(%)		Time(min)	
		<sup>a</sup> C	<sup>b</sup> M	C	M
<b>307a</b>	6- $\text{CH}_3$	63	88	600	5
<b>307b</b>	6-Cl	71	83	630	7
<b>307c</b>	6- $\text{OCH}_3$	75	91	670	6
<b>307d</b>	5,6-Benzo	64	82	810	8
<b>307e</b>	7- $\text{CH}_3$	66	86	640	6
<b>307f</b>	7-Cl	68	84	650	7
<b>307g</b>	7- $\text{OCH}_3$	69	87	720	6
<b>307h</b>	5,7-di $\text{CH}_3$	61	81	840	9
<b>307i</b>	6-Br	64	88	730	8
<b>307j</b>	7-Br	62	87	720	8

<sup>a</sup>C— Conventional:

<sup>b</sup>M— Microwave.

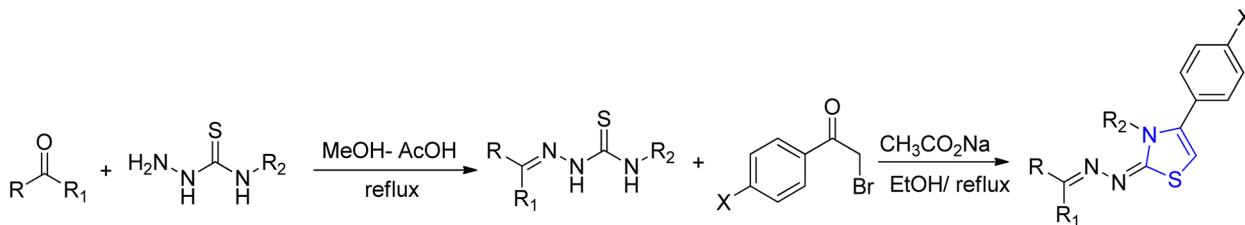
Scheme 56 Synthesis of coumarin-thiazoline hybrids **307a-j**.

production of cyclopeptide YM-216391 **317** and thiopeptide-based antibiotics such as GE2270C1, GE2270T, and GE2270A exemplify the utility of this approach.<sup>167,168</sup> When  $\beta$ -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  $\text{MnO}_2$ . YM-216391 dose-dependently inhibited the growth of human cervical cancer HeLa S3 cells with an  $\text{IC}_{50}$  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.*<sup>169</sup> synthesized one such fragment of the natural product, largazole, in five steps. The synthesis began by transforming Fmoc-Gly-NH<sub>2</sub> **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





308a-d

309a/b

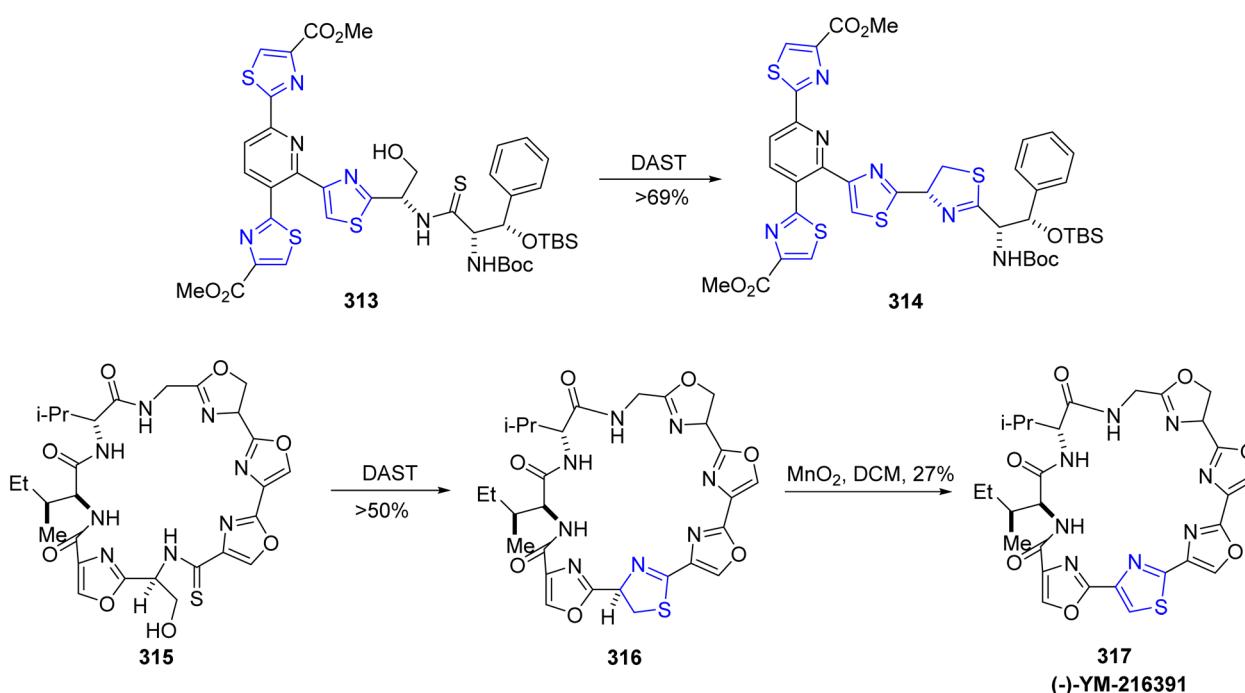
310

311a/b

312a-d

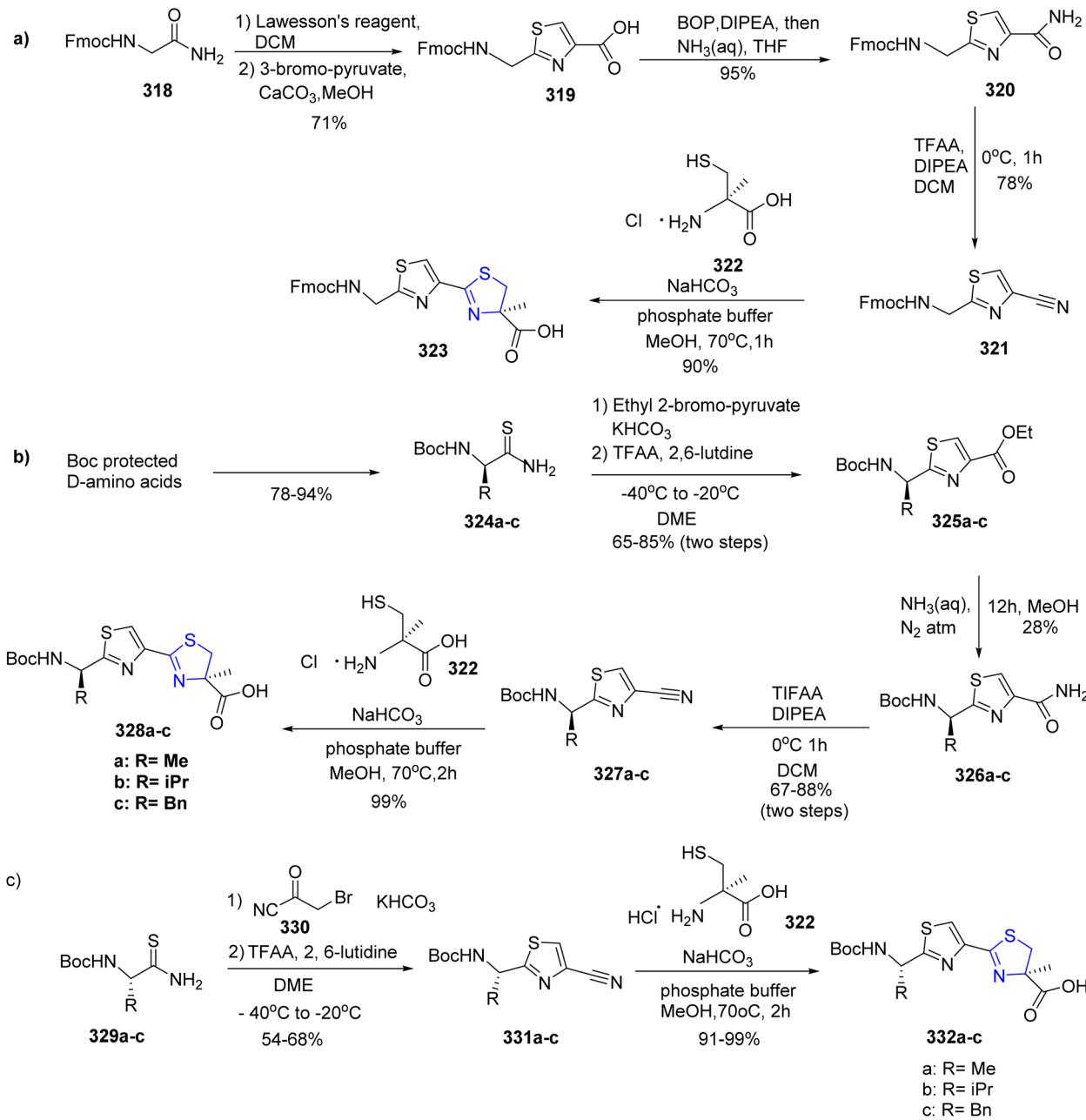
Compound	R	R <sub>1</sub>	R <sub>2</sub>	X
312a		H	2,6-(CH <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	NO <sub>2</sub>
312b		CH <sub>3</sub>	2,6-(CH <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	Cl
312c		CH <sub>3</sub>	2-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	Cl
312d		CH <sub>3</sub>	2,6-(CH <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	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.<sup>170</sup> 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.<sup>171</sup> 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.<sup>172</sup> The direct condensation reaction between the

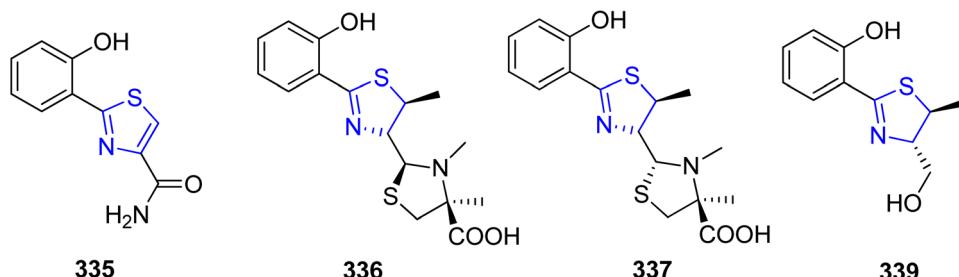
unprotected thioamide 324c and bromopyruvate resulted in a partially racemized product, thus making this approach crucial. The thus obtained ethyl esters 325a-c then underwent ammonolysis on treatment with aqueous ammonia to give compounds 326a-c. This was followed by dehydration to yield the compounds 327a-c.<sup>173</sup> 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





333a  $R^1 = H$        $R^2 = H$   
 333b  $R^1 = H$        $R^2 = 4\text{-Bromobenzoyl}$   
 338  $R^1 = CH_3$        $R^2 = H$

334  $R^1 = H$        $R^2 = CONH_2$   
 340  $R^1 = CH_3$        $R^2 = CH_2OH$   
 341  $R^1 = CH_3$        $R^2 = CHO$   
 342  $R^1 = CH_3$        $R^2 = CONH_2$



Scheme 60 Neuroactive thiazoline metabolites.

carbonitriles 331a–c.<sup>174</sup> 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.<sup>175</sup> Actinomycetes and other bacteria have a specialized environment provided by the Philippine cone snail *Conus pulicarius*. Lin *et al.*<sup>176</sup> 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-HT<sub>2B</sub> 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	RT	Reverse transcriptase
MCRs	Multicomponent Reactions	LD <sub>50</sub>	Lethal dose
DFBP	<i>N</i> -( $\alpha$ , $\alpha$ -Difluorobenzyl)pyrrolidine	DM	Diabetes mellitus
DFMPP	<i>N</i> -(1,1-Difluoro-2,2-dimethylpropyl)-pyrrolidine	CVD	Cardiovascular disease
NMR	Nuclear Magnetic Resonance	GLP-1	Glucagon-like peptide 1
DNA	Deoxyribonucleic acid	Mitf	Microphthalmia-associated transcription factor
ATHTd	<i>N</i> -(2-Acetyl-2-thiazoline)- <i>N</i> '-(2-thiazolidin-2-one)azine	DPP-4	Dipeptidyl peptidase IV
HFIP	Hexafluoroisopropanol	GIP	Glucose-dependent insulinotropic polypeptide
QDs	Quantum Dots	nM	Nano-mole
ICT	Intramolecular Charge Transfer	ALR	Aldose reductase
TFA	Trifluoroacetic acid	$\beta$ -	$\beta$ -Acetylglucosaminidases
HCl	Hydrochloric acid	GlcNAcases	
TEA	Triethylamine	NGT	NAG-thiazoline
RNA	Ribonucleic acid	$\alpha$ -MSH	$\alpha$ -Melanocyte-stimulating hormone
Ppb	Parts per billion	ERK	Extracellular signal-regulated kinase
Ppm	Parts per million	MIC	Minimum inhibitory concentration
DFT	Density Functional Theory	NLO	Nonlinear optical
HOMO	Highest Occupied Molecular Orbital	EIMS	Electron ionization mass spectral
Mcf-7	Human breast cancer cell line	TFAA	Trifluoroacetic anhydride
LOD	Limit of detection	Fmoc	Fluorenylmethoxycarbonyl
OLED	Organic light-emitting diode	Boc	<i>tert</i> -Butyloxycarbonyl
Dipp	<i>N</i> , <i>N</i> -Diisopropylphenyl		
Cbz	Carbazole		
A549	Human lung carcinoma cell line		
LUMO	Lowest Occupied Molecular Orbital		
WOLED	White organic light-emitting diode		
McCbz	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 <sub>50</sub>	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		
$\mu$ g	Microgram		
$\mu$ M	Micromole		
mM	Millimole		
HATtsc	2-Acetyl-2-thiazoline thiosemicarbazone		
CVB3	Coxsackie type B3		
EV71	Enterovirus 71		
kg	Kilogram		

## Conflicts of interest

There are no conflicts to declare.

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