

THIAZOLE CORES AS ORGANIC FLUOROPHORE UNITS: SYNTHESIS AND FLUORESCENCE

DOI: <http://dx.medra.org/10.17374/targets.2020.23.116>Nataliya P. Belskaya^{*a,b}, Irena Kostova^c, Zhijin Fan^d^aUral Federal University, Mira str. 19, 620002 Ekaterinburg, Russia^bInstitute of Organic Synthesis, Ural Branch of Academy of Science, 620219 Ekaterinburg, Russia^cDepartment of Chemistry, Faculty of Pharmacy, Medical University, Dunav str. 2, 1000 Sofia, Bulgaria^dState Key Laboratory of Elemento-Organic Chemistry, College of Chemistry, Nankai University, 300071 Tianjin, PR China, Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Nankai University, 300071 Tianjin, P. R. China
(e-mail: n.p.belskaya@urfu.ru)

Abstract. Methods for the synthesis of thiazoles, which display photophysical properties, are presented and analyzed. The scope and limitations of well-known pathways used to construct this heterocyclic core, and the introduction of functional groups, substituents, and linear linkers to tune the fluorescence, are described. Relationships between structure and photophysical properties, and applications as photoswitches and in ion recognition, are also discussed.

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1. Introduction

Thiazole structures exhibit interesting properties that have attracted research attention owing to their abundance and potential as building blocks in the development of lead molecules, new drug candidates and biologically active compounds.¹⁻⁵ In the last decade, thiazoles have been applied as fluorescent dyes.⁶ The thiazole heterocyclic core is key to several natural products, such as luciferin, a compound responsible for bioluminescence in the firefly (Lampyridae) (Figure 1).⁷

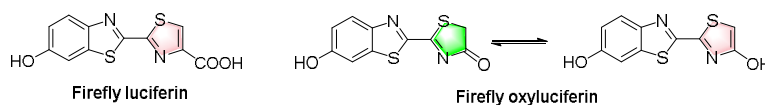


Figure 1. Structure of firefly luciferin and oxyluciferin.

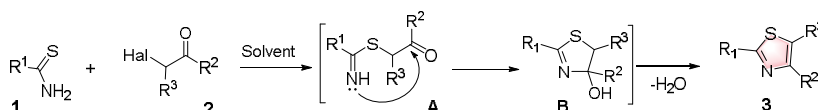
Owing to the expansion of materials science in the last decade, the design of novel thiazole derivatives for applications in this field has received increasing research interest. In this chapter, we report current progress in the development of fluorophores containing thiazole cores, their properties, and their main applications, covering the period 2009-2019.

2. Synthesis of fluorescent thiazoles

These new thiazoles with substituents necessary to afford meaningful fluorescence can be obtained using different pathways. One pathway involves preparing the heterocyclic core from starting reagents in which all additional groups are already present. Another pathway decorates the prepared thiazole with various functionalities according to the demands of the subsequent application. We have limited this survey to thiazoles that have exhibited photophysical properties. Fluorophore design with unique characteristics is guided by several definite rules and recommendations and usually requires introducing specific substituents, functionalities, chains, cyclic and heterocyclic fragments, multiple bonds, and tailored constructions that provide molecules with the necessary electronic density. However, in addition to the nature and strength of the electronic properties of substituents, their location in the molecule is also important. Furthermore, the design of new fluorophores must account for molecule structure symmetry, which significantly affects the substance's optical properties.

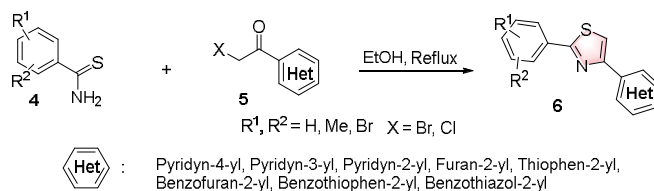
2.1. Main approaches to thiazole core construction

The most general and widely used method for constructing thiazole cycles is based on the condensation reaction of thiocarbonyl compounds with α -halogenocarbonyl derivatives (Hantzsch synthesis)¹ at room temperature or by heating in solvent (EtOH, DMF, acetone, acetic acid, toluene) in the presence of a catalytic amount of base (TEA, NaOAc, DIEA) or without any additive. This synthesis does not usually require severe conditions or expensive catalysts or reagents. Furthermore, various compounds can be obtained, with the electronic structures controlled and tuned by varying the electronic nature and spatial parameters of the substituents. Employing this synthetic method (Scheme 1), various 2,4-disubstituted and 2,4,5-trisubstituted thiazoles have been synthesized in good yields.⁸⁻²⁷



Scheme 1. Classical Hantzsch thiazole synthesis.

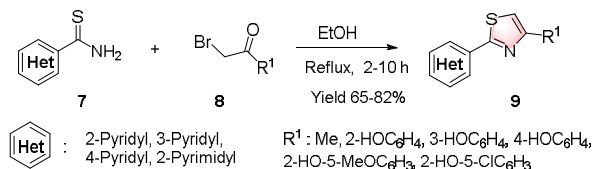
This reaction has a large scope, with aromatic α -halogenocarbonyl compounds and many different heterocyclic derivatives often used as electrophilic reagents.^{10,13,14,16,17,19,25-27} For example, a library of 4-heteroarylthiazoles **6** has been synthesized with good yields, as shown in Scheme 2.



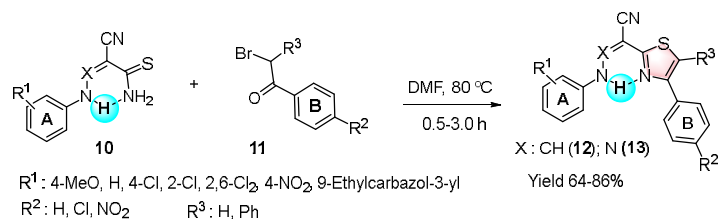
Scheme 2. Synthesis of 4-heteroarylthiazoles **6**.

Furthermore, various heterocyclic thioamides **7** can be used in this reaction (Scheme 3).^{12,15-20,22,26,27}

New thiazole derivatives **12** and **13** (Scheme 4) with conjugated system including flexible groups containing enamine (NH-CH=C-) or aza-enamine (NH-N=C-) chains on the C2 ring atom were synthesized by heating in DMF.²¹⁻²⁴

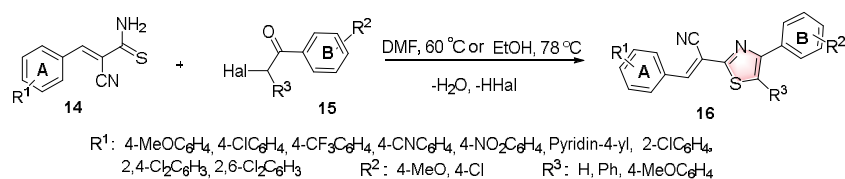


Scheme 3. Synthesis of 2-heteroarylthiazoles **9**.



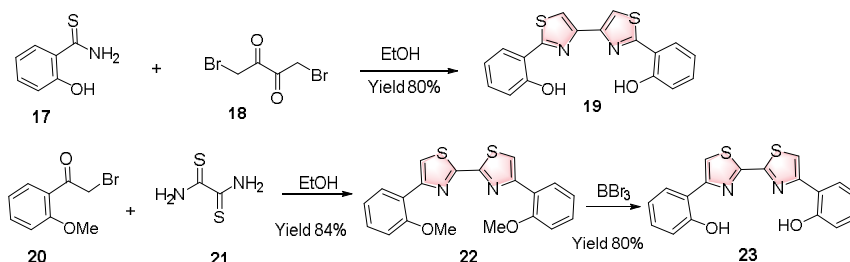
Scheme 4. Synthesis of enamine and aza-enamine thiazoles **12** and **13**.

3-Aryl-2-(thiazol-2-yl)acrylonitriles **16** were also synthesized using the Hantzsch thiazole synthesis, in which thioacetamides **14** were condensed with the corresponding α -halocarbonyl compounds **15** in DMF or ethanol (Scheme 5).²⁵



Scheme 5. Synthesis of thiazoles **16**.

4,4'-Bis-thiazole **19** and its isomeric form 2,2'-bisthiazole **23** were synthesized in good yields by the Hantzsch reaction of 2-hydroxythiobenzamide **17** with 1,4-dibromo-2,3-butanedione **18** and dithioamide **21** with 2-bromo-2-methoxyacetophenone **20**, respectively, in refluxing ethanol (Scheme 6).²⁸

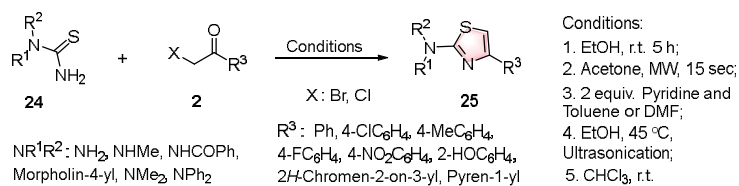


Scheme 6. Synthesis of bisthiazoles **19** and **23**.

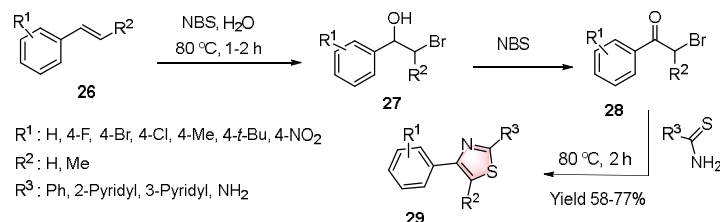
Thiourea has also been explored as a nucleophilic partner with haloketones to give 2-aminothiazole.²⁹⁻³⁶ 2-Amino-4-aryl thiazole derivatives **25** have been synthesized in a solution of α -bromoarylethanones **2** and thiourea **24** using different conditions (Scheme 7).³⁰⁻³³

Several studies have reported multicomponent one-pot implementations of the Hantzsch reaction. Styrenes **26** reacted with *N*-bromosuccinimide (NBS) and carbothioamide to afford the corresponding 2,4-disubstituted and 2,4,5-trisubstituted thiazoles **29** (Scheme 8).³⁷ The reaction mechanism involved the formation of bromohydrin **27** followed by NBS-mediated oxidation and *in-situ* formation of phenacyl

bromide **28**, which then underwent condensation with a carthioamide to form thiazoles **29** with good and high yields (Scheme 8).³⁷

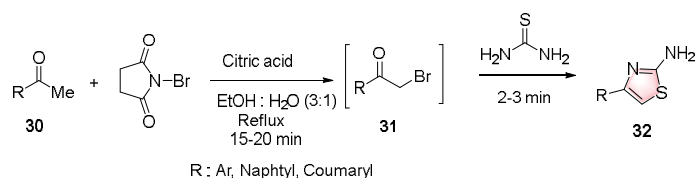


Scheme 7. Synthesis of 2-aminothiazoles **25**.



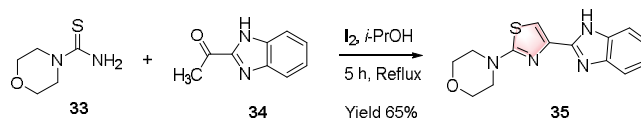
Scheme 8. NBS-assisted one-pot synthesis of substituted thiazoles from styrenes in water.

In a one-pot procedure using available arylalkyl ketones **30**, NBS, and thiourea, citric acid was employed as catalyst for the synthesis of 2-amino-4-arylthiazoles **32** via α -bromination with subsequent C–S and C–N bond formations (Scheme 9).³⁸



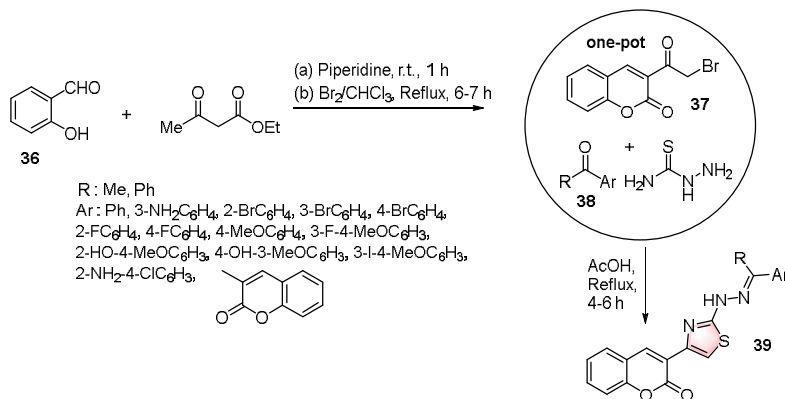
Scheme 9. One-pot synthesis of 2-amino-4-arylsubstituted thiazoles.

A multistep synthesis was developed to obtain novel push-pull dye **35**, which contains a benzimidazole fluorophore and thiazole unit. Dye **35** was polar and showed poor solubility (Scheme 10).³⁹⁻⁴³



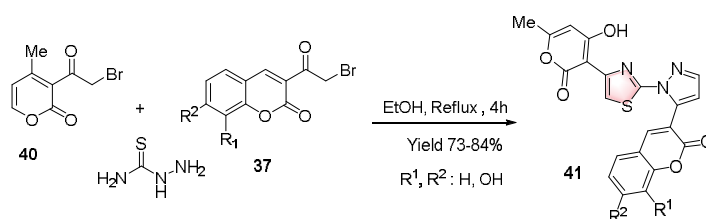
Scheme 10. Synthesis of (benzimidazol-2-yl)thiazole **35**.

Coumarin and pyran-2-one derivatives form an important class of oxygen-containing heterocyclic compounds with interesting photophysical, photochemical, and fluorescent properties. Therefore, many heterocyclic systems incorporating these oxygen-containing and thiazole cycles, have been synthesized.⁴⁴⁻⁴⁶ A multicomponent reaction strategy was used to synthesize the desired series of coumarinyl thiazoles **39**.⁴⁶ First, 3-(2-bromoacetyl)-2*H*-chromen-2-one **37** was readily synthesized by the base-catalyzed condensation of salicylaldehyde with ethyl acetoacetate, followed by bromination (Scheme 11).⁴⁶ Intermediate **37** was then treated with differently substituted acetophenones **38** and thiosemicarbazide in one-pot in the presence of glacial acetic acid as catalyst to obtain compounds **39** in 63-78% yields.



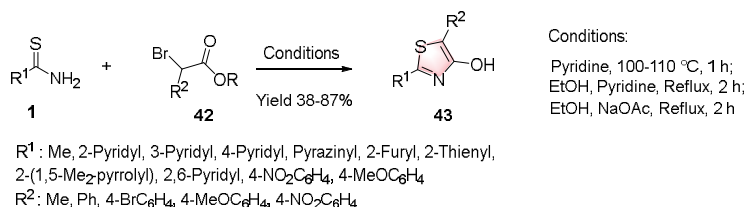
Scheme 11. Synthetic route toward coumarinyl thiazole analogues **39** via a one-pot reaction.

Systems containing both thiazole and pyrazole cycles were synthesized by using thiosemicarbazide as the thiocarbonyl nucleophilic center.^{44,49} A novel series of pyran- and coumarin-substituted thiazolyl-pyrazole-chromen-2-one derivatives **41** were efficiently synthesized through a convenient one-pot multicomponent transformation using the Hantzsch thiazole and Knorr pyrazole syntheses (Scheme 12).⁴⁴



Scheme 12. Synthesis of multiheterocycle thiazolyl derivatives **41**.

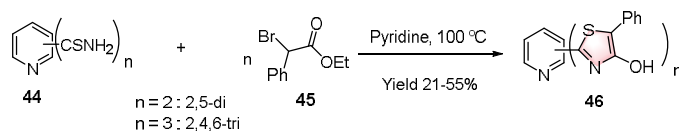
4-Hydroxythiazole derivatives have long been known,¹ but have only been intensively studied as fluorophores in the last ten years owing to their photophysical properties. In 2009, Beckert et al. found that 4-alkoxythiazole or 4-hydroxythiazole⁶ moieties afford interesting fluorescence.⁵⁰⁻⁵² Their synthesis involved the reaction of an appropriate thioamide **1** with α -halogenoesters **42** (Scheme 13). Notably, the effectiveness of the synthesis strongly depended on the availability/reactivity of the initial materials. This reaction can be realized at elevated temperatures without solvent or in small amounts of solvents. The nature of the substituent at the 2-position of hydroxythiazoles **43** can vary widely. Therefore, electron-poor pyridine and pyrazine were successfully used, as well as electron-rich furan, thiophene, and pyrrole.⁵⁰



Scheme 13. Synthesis of 4-hydroxythiazoles **43**.

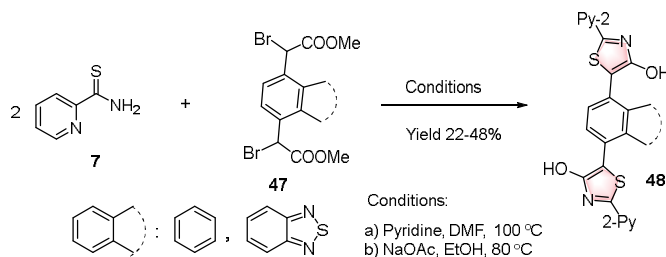
This route was also suitable for the synthesis of new bis- and tris(4-hydroxythiazoles) **46** with pyridine cores (Scheme 14).⁵¹ Therefore, **46a** ($n=2$) was prepared from the corresponding dithioamide **44a** ($n=2$) and

2 equiv. of ethyl bromoacetate **45** ($n=2$). Tris(thiazole) **46b** ($n=3$) was also prepared in good yield from pyridine-2,4,6-tricarbothioamide **44b** ($n=3$) in the same manner.



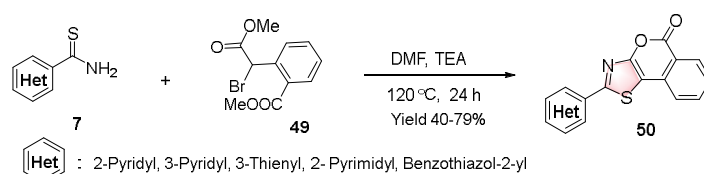
Scheme 14. Synthesis of bis- and tris(4-hydroxythiazoles) **46**.

Another pathway afforded 5,5'-bithiazole **48** from the condensation reaction of two molecules of thioamide **7** with bis(bromoacetate) **47** (Scheme 15).⁵²



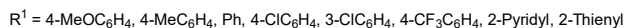
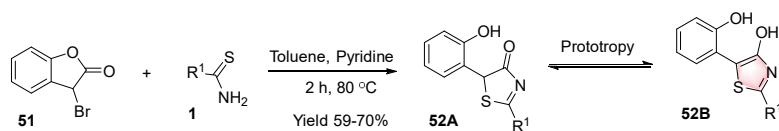
Scheme 15. Synthetic pathway to 5,5'-bi(hydroxythiazoles) **48**.

Fused tricyclic lactones **50** based on 4-hydroxy-1,3-thiazoles were synthesized by the reaction of dimethyl α -bromohomophthalate **49** with various heterocyclic thioamides **7** followed by an intramolecular esterification (Scheme 16).⁵³



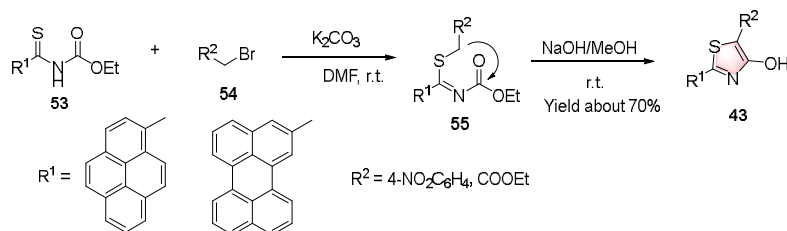
Scheme 16. Synthesis of 5*H*-isochromeno[4,3-*d*]thiazol-5-ones **50**.

4-Hydroxy-5-(2-hydroxyphenyl)-2-aryl-1,3-thiazoles **52** were prepared using a modified Hantzsch thiazole synthesis using brominated lactone **51**.⁵⁴ This modification involved base-catalyzed ring transformation of unstable intermediate [(2-oxo-2,3-dihydro-1*H*-indol-3-yl)sulfanyl]-(aryl)methaniminium bromide. Two bases, namely, aqueous ammonia and pyridine in toluene, were successfully applied to this transformation (Scheme 17).⁵⁴



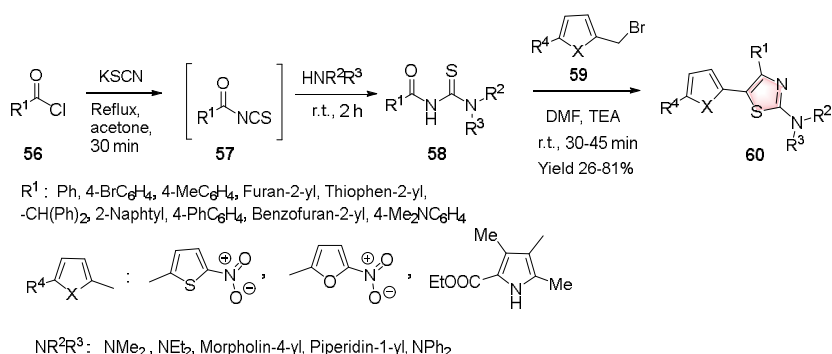
Scheme 17. Synthetic route to 4-hydroxy-5-(2-hydroxyphenyl)-2-aryl-1,3-thiazoles **52**.

2,5-Diaryl-4-hydroxythiazole **43** was obtained by reacting ethyl ethanethioylcarbamates **53** with nitrobenzylbromide or ethyl 2-bromoacetate **54** via cyclization of thioimidate **55** in sodium methoxide (Scheme 18).^{55,56}



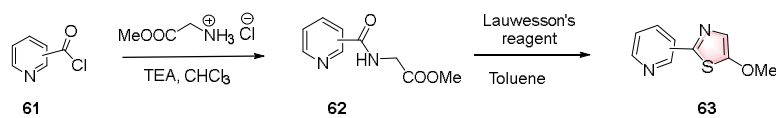
Scheme 18. Synthesis of compounds **43**.

A new approach to thiazole ring construction was proposed by the Radhakrishnan group.⁵⁷⁻⁵⁹ A series of 2,4,5-trisubstituted thiazoles **60** was obtained using a one-pot procedure (Scheme 19). This involved tandem nucleophilic alkylation reactions of 1-(acyl/aryl)-3,3-(disubstituted)thioureas **58** with a heteroarene bearing an activated methylene group followed by intramolecular Knoevenagel condensation-cyclization. The main advantages of this reaction are the short reaction time, good to excellent product yields, and the broad scope of reactants that afford access to different multiheterocyclic cores.⁵⁹



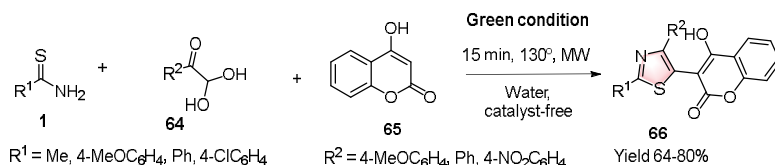
Scheme 19. One-pot synthesis of thiazole core through [4+1]-ring synthesis.

The preparation of 5-methoxy-2-(2-pyridyl)thiazole **63** was achieved by treating pyridyl chloride **61** with glycine methyl ester hydrochloride in the presence of triethylamine in chloroform. Further refluxing amide **62** with Lawesson's reagent led to the formation of compound **63** through a ring-closing process (Scheme 20).⁶⁰



Scheme 20. Synthesis of 5-methoxy-2-pyridylthiazoles **63**.

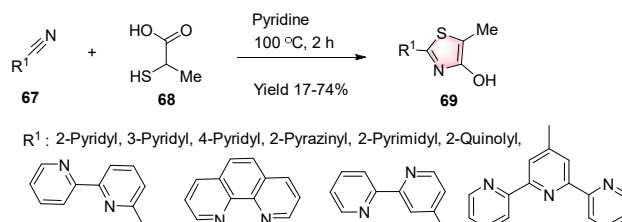
A clean, efficient, and catalyst-free multicomponent domino reaction of arylglyoxals **64**, cyclic 1,3-dicarbonyls **65**, and thioamides **1** under microwave conditions afforded trisubstituted thiazoles **66** (Scheme 21).⁶¹ As water was the best solvent, this reaction conforms with the principles of green chemistry. The screening of different organic solvents, such as toluene, THF, acetonitrile, and DMF, in the same model reaction afforded lower yields compared with the reaction in water.



Scheme 21. Synthesis of trisubstituted thiazoles **66** using a three-component reaction.

2.1.1. Erlenmeyer method for thiazole ring construction

The Erlenmeyer method is a less common approach used for the synthesis of luciferin and its derivatives.^{6,50,51,62,63} In this synthetic route, a ring-closing reaction occurs between an aromatic nitrile and α -mercaptoacid under mild conditions. As α -mercaptoacetic acid derivatives are not accessible as the corresponding α -bromo derivatives, the Hantzsch route is favored over the Erlenmeyer method. Aromatic nitriles were found to generally react slower than their heteroaromatic counterparts and give lower yields. Thiazoles **69** are yellow-colored compounds with sparing solubility in common organic solvents, but good solubility in DMF, DMSO, and DMA (Scheme 22).⁶

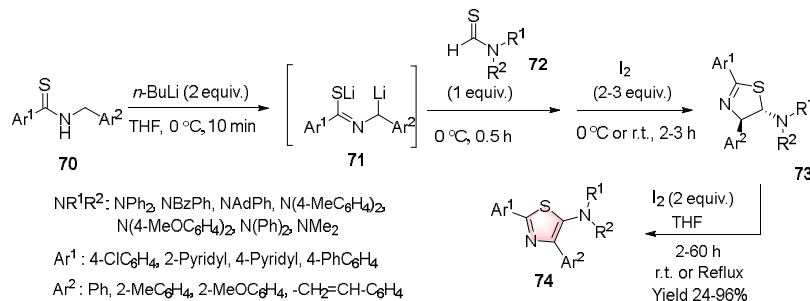


Scheme 22. Typical coupling reaction of heteroaryl nitriles **67** with α -mercaptoacid **68**.

As cyanogens are difficult to obtain and handle, a different approach based on dithiooxamide (rubeanic acid) has been proposed.⁵¹

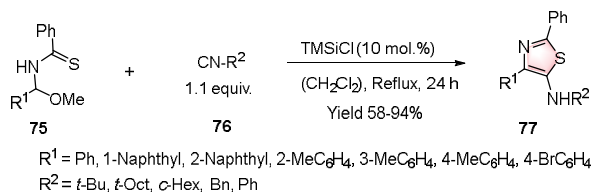
2.1.2. Different methods for thiazole ring construction

In the past century, many protocols have been developed for the synthesis of 5-aminothiazoles.⁶⁴⁻⁶⁶ 5-Aminothiazolines **74** were prepared by reacting secondary thioamides **70** with thioformamides **72** via generation of thioamide dianion **71**, followed by iodine addition. This reaction allows various substituents to be introduced at the 2-, 4-, and 5-positions (Scheme 23).⁶⁶



Scheme 23. Synthesis of 5-aminothiazoles **74**.

The [4+1]-cycloaddition of isocyanides to *N*-acylimine derivatives catalyzed by organosilane compounds has been used to afford various aminothiazoles **77** (Scheme 24).⁶⁵



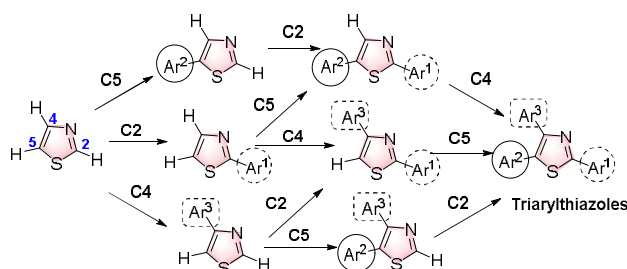
Scheme 24. Reaction of isocyanides with *N*-thioacyl *N,O*-acetals.

2.2. Modification of the thiazole core

Most thiazoles have been synthesized using the classical Hantzsch thiazole synthesis. Therefore, these structures might include aromatic or heteroaromatic rings, hydroxy and amino groups, and azo, hydrazono, enamino, and acrylonitrile fragments. However, the set of known starting halocarbonyl compounds and thioamides cannot provide the variety of substituents, nor the locations in the molecule, required by the designed fluorophore structures. In contrast, 1,3-thiazoles possess three carbon atoms to which a wide variety of substituents can be attached. They are also easy to conjugate or combine with other substituent groups to form multiple derivatives. Many different methods for thiazole ring modifications are currently known.

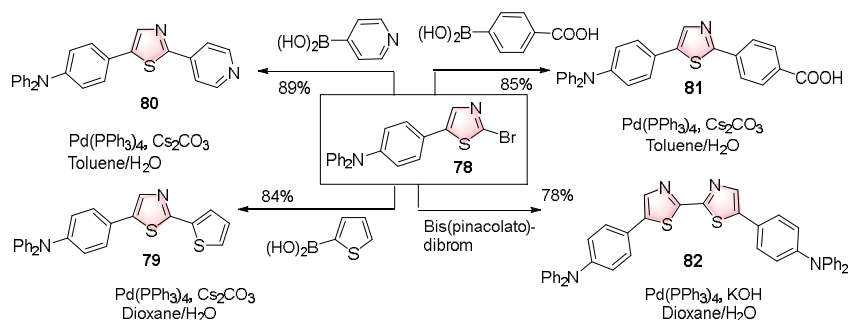
2.2.1. Aryl/heteroarylation of the thiazole ring

As aryl or hetaryl cyclic fragments are important in dyes, we will first discuss pathways reported for attaching aromatic cycles to thiazoles. Palladium-catalyzed cross coupling reactions, which have been extensively developed in recent decades, are the preferred method.⁶⁷⁻⁷⁸ Versatile protocols that can provide all possible arylthiazole substitution patterns (2-aryl, 4-aryl, 5-aryl, 2,4-diaryl, 2,5-diaryl, 4,5-diaryl, and 2,4,5-triaryl) from thiazole itself have been developed and applied to the synthesis of 150 arylthiazoles. However, as is usual for cross-coupling reactions, additional steps are required to prefunctionalize the parent thiazole with a halogen or a metal group at the position where new aryl groups are to be installed. In contrast to cross-coupling methods, aryl groups can be installed onto the thiazole core directly by C–H arylation (step economy). The three C–H bonds on thiazole (C2, C4, C5) are chemically nonequivalent, meaning that bond selectivity (regioselectivity) can be used in aryl-installing reactions. If a substituent is already present on the thiazole molecule, this can determine the direction of the next attack and reactivity of the carbon atoms (Scheme 25).⁷⁰



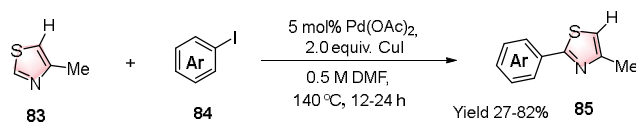
Scheme 25. Programmed synthesis of all thiazole substitution patterns.

Conventional C–C coupling reactions, such as Suzuki-Miyaura, Stille, and homocoupling reactions, and C–H activation have been used to prepare unexpectedly functionalized thiazole compounds **79-82** through one-pot Suzuki-Miyaura couplings followed by C–H activation reactions *via* 2-Br-substituted thiazole intermediate **78** using asymmetrical catalysis (Scheme 26).⁷⁴ Various *N*-donor-containing compounds had effective π -conjugated systems, allowing different triphenylamino, pyridine, thiophene, and benzoic acid tails to be synthesized using these method.



Scheme 26. Synthetic route to thiazole-containing triphenylamino compounds **79-82**.

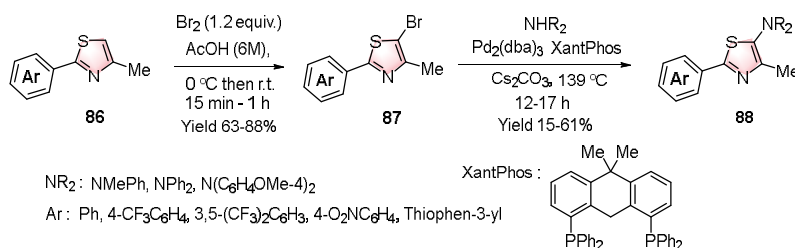
The application of aryl iodides allowed the direct C–H arylation of 4-methylthiazole **83** selectively at the 2-position of the thiazole ring, affording 2-aryl-4-methylthiazoles **85** in moderate to good yields (Scheme 27).⁷¹



Ar: 4- $\text{CF}_3\text{C}_6\text{H}_4$, 3,5-(CF_3) $_2\text{C}_6\text{H}_3$, 4- $\text{NO}_2\text{C}_6\text{H}_4$, Thiophen-2-yl

Scheme 27. Direct C–H arylation of 4-methylthiazole **83**.

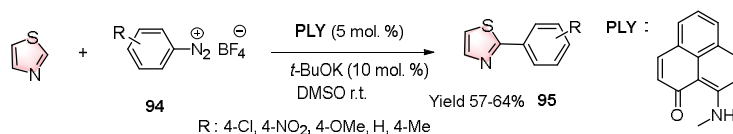
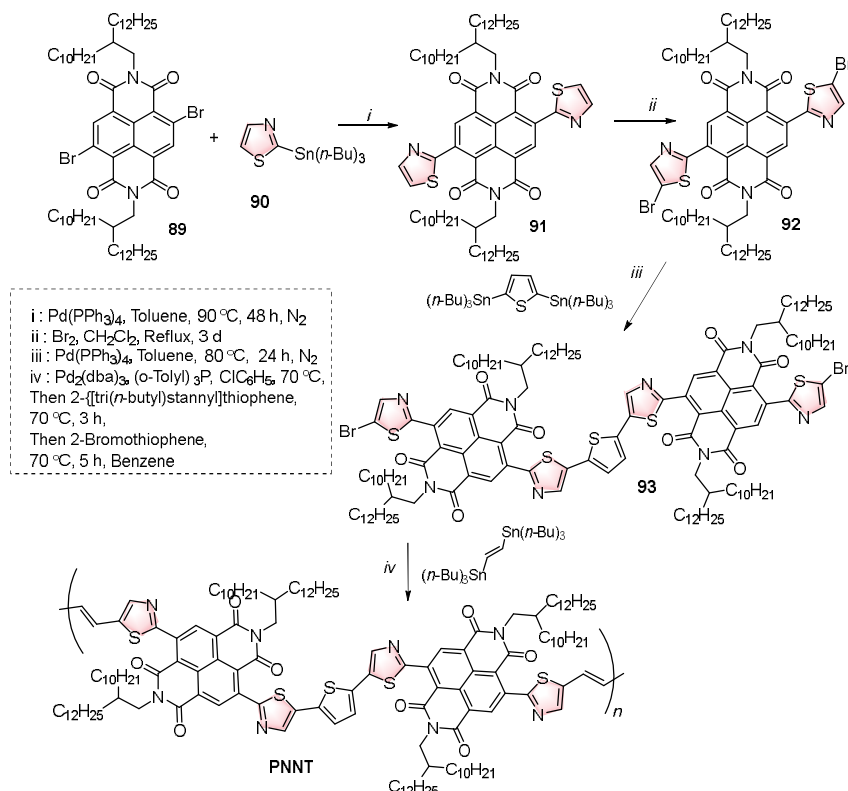
Buchwald-Hartwig amination conditions were well-suited to attaching an R_2N -substituent to the thiazole cycle. For example, the C-5 amination of thiazoles **87** with N -arylamines was successfully achieved using 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (XantPhos) as ligand in combination with $\text{Pd}_2(\text{dba})_3$ as catalyst (Scheme 28).⁷¹



Scheme 28. Buchwald-Hartwig amination to give thiazoles **88**.

The synthesis of polymer acceptor **PNNT** is outlined in Scheme 29. This multistep procedure involved several Stille coupling reactions, brominations, and a final Stille coupling polymerization step of monomer **93** with (*E*)-1,2-bis(tri-*n*-butylstannyl)ethene in anhydrous chlorobenzene at 70 °C (Scheme 29).⁷³ Polymer **PNNT** was found to have good electron mobility and an electron affinity similar to those of fullerenes. Selective activation of the thiazole ring for the cross-coupling reactions was achieved using *n*-BuLi.^{67,69,70,75,77}

The traditional metal-free direct arylation of heteroarenes is extremely rare. A notable effort reported the direct C–H arylation of heteroarenes under metal-free conditions at room temperature using an aryldiazonium salt as the coupling partner, catalyst, and *t*-BuOK (Scheme 30).⁷⁸



2.2.2. Alkylation of hydroxythiazoles

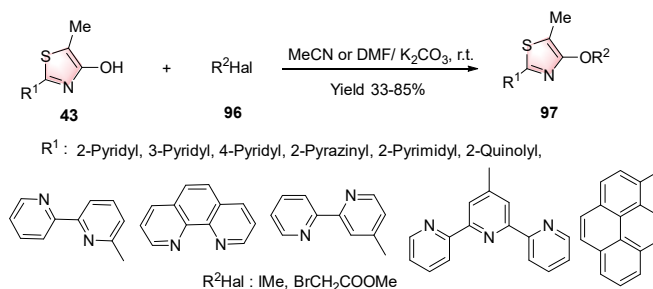
Alkylation is commonly used to modify hydroxythiazoles. This modification leads to drastic changes in the optical properties of hydroxythiazoles and increases their solubility in organic solvents.^{6,50-52,55,63,79-83} The hydroxyl group is alkylated by alkyl iodides or alkyl bromides *via* a Williamson-type etherification, as shown in Scheme 31.⁶

This reaction is convenient for introducing various functionalities.⁸⁴⁻⁸⁶ Azide-targeted reporter molecule **99** was synthesized for bio-orthogonal transformation into a fluorescent 1,2,3-triazole ring (Scheme 32).⁸⁶

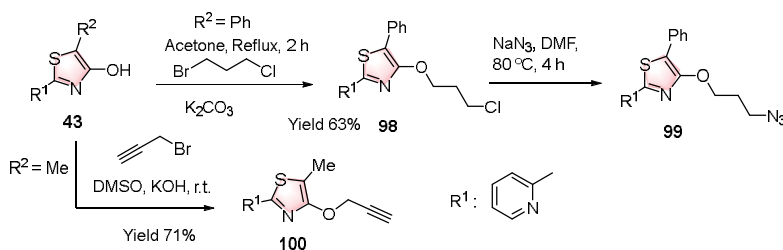
Star-shaped molecular structures can be prepared from 4-hydroxythiazoles by alkylation.⁸⁶ Thiazole **102** was synthesized by substituting 1,3,5-tris(bromomethyl)benzene with deprotonated 5-phenyl-(2-pyridin-2-yl)-1,3-thiazol-4-ol derivatives (Scheme 33). This compound with flexible peripheral alkyl chains showed facile self-assembly into a columnar superstructure, and exhibited strong fluorescence and liquid crystallinity.

Polymers containing 4-hydroxy-1,3-thiazoles units as non-classical fluorescence emitters, similar to the luciferin dye from glowworms, have been designed.^{83-85,87} Monomers were obtained by alkylation

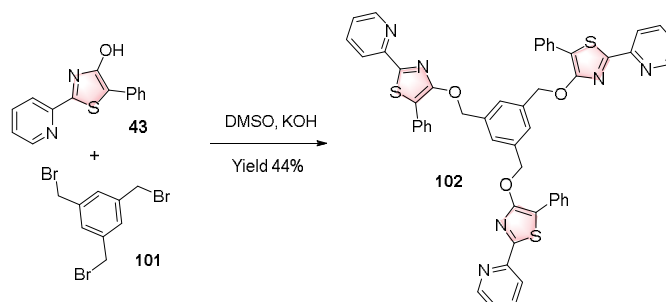
followed by attaching polymerizable methyl methacrylate units to the chromophore. Subsequent polymerization led to blue-emitting 1,3-thiazole polymer **105**. Standard conditions for the reversible addition–fragmentation chain transfer (RAFT) technique were applied (Scheme 34), using 2-cyano-2-propyl-benzodithioate as the chain transfer agent and azobisisobutyronitrile (AIBN) as the initiator. RAFT polymerization was selected as an efficient method for the polymerization of dye-functionalized methacrylates.⁸⁵



Scheme 31. Williamson-type etherification of 4-hydroxythiazoles.



Scheme 32. Functional thiazoles derived from alkylation.



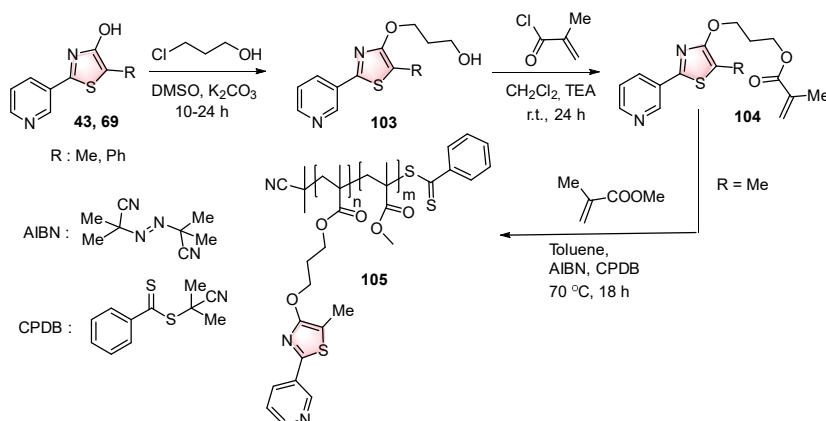
Scheme 33. Synthesis of 1,3,5-tristhiazole **102**.

Alkylation can also be a useful method for hydroxy group protection. Therefore, hydroxy-naphthoic acids were protected through alkylation, followed by multistep transformation into thiazoles.^{28,88} Subsequent deprotection of the methoxy group with boron tribromide gave **107** (Scheme 35).

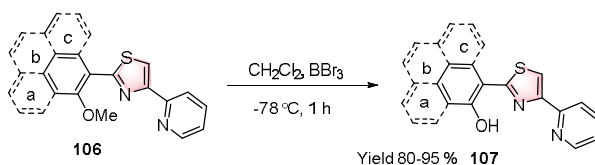
2.2.3. Introduction of substituents containing C=C, C=N, and N=N bonds

Thiazole can be easily converted to aldehydes by treating with a mixture of POCl₃ and DMF (Vilsmeier-Haack formylation), which can subsequently be readily transformed into various new derivatives through condensation with C and N nucleophiles.^{34,39,43,46,89-93} As shown in Scheme 36, thiazole **108** was subjected to a Vilsmeier-Haack formylation reaction to obtain aldehyde derivative **109**, which as then

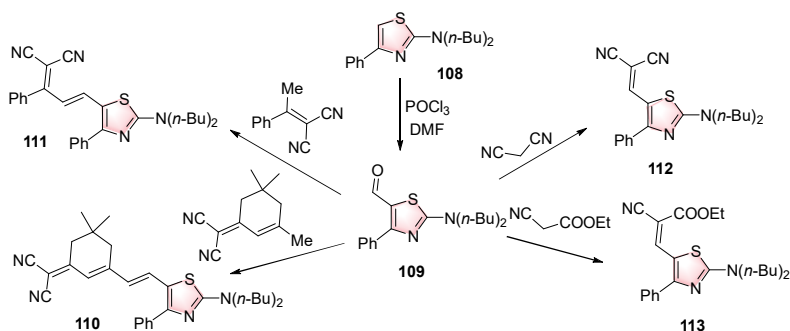
combined with different active methylene compounds in absolute ethanol in the presence of a catalytic amount of piperidine to give final desired dyes **110-113**.⁹²



Scheme 34. Synthesis of thiazole-containing polymer **105**.



Scheme 35. Synthesis naphthol-thiazole-based chemosensors **107**.

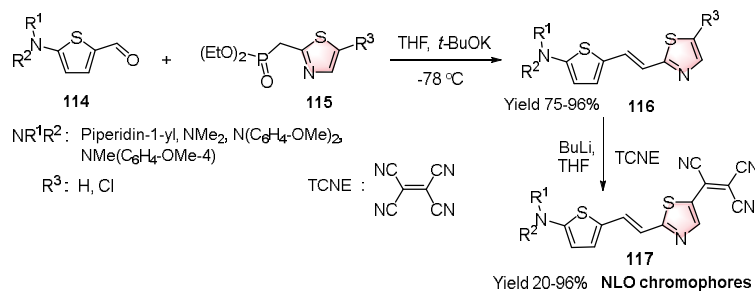


Scheme 36. Knoevenagel condensation of thiazole carbaldehyde **109**.

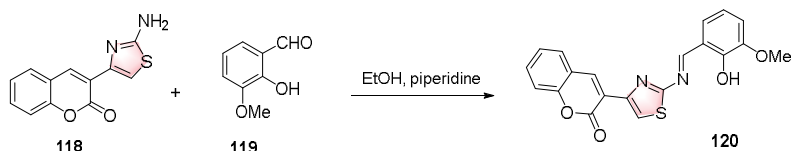
Coupling reactions between aldehydes and Horner-Wadsworth-Emmons (HWE) reagent (Scheme 37) have afforded **NLO** chromophore precursors **116** in exclusively the (*E*)-alkene configuration with high yields.⁹¹

Multifunctional Schiff base-derived chemosensor **120** was synthesized by the condensation of thiazolyamine derivative **118** with 2-hydroxy-3-methoxybenzaldehyde **119** in a basic ethanol solution with an excellent yield of 85%, as shown in Scheme 38.⁹³

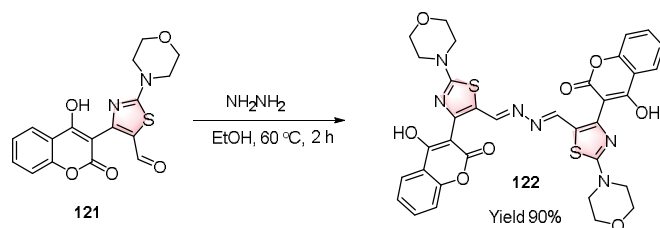
Symmetrical dye **122**, containing coumarin and thiazole units linked by an azomethine bridge, were obtained in good yield by heating thiazole carbaldehyde **121** with hydrazine (Scheme 39).⁹⁴



Scheme 37. Synthesis of NLO chromophores **117**.

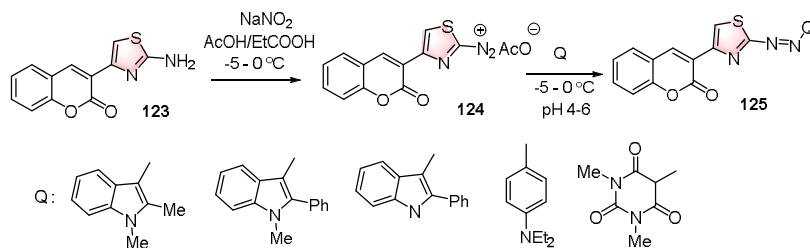


Scheme 38. Synthetic route to chemosensor **120**.



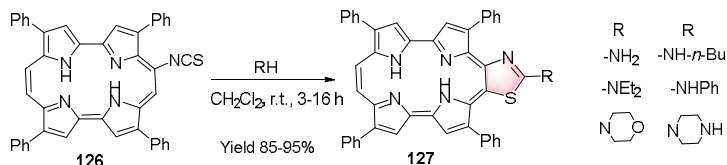
Scheme 39. Synthesis of bis(4-hydroxy-2H-chromen-2-one) **122**.

The synthesis of novel coumarin thiazole hybrids **125** was achieved by diazotization of 2-aminothiazole **123** followed by azo-coupling of the resulting diazonium salts **124** with various CH-acids (Q) (Scheme 40).⁹²



Scheme 40. Synthesis and structure of azo dyes **125**.

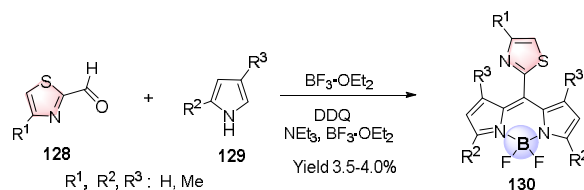
Combining two fragments in one molecule to obtain interesting photophysical properties or unusual electronic structures is of great interest. Therefore, a series of new thiazoles bearing fluorescent compounds, including coumarin residues (Schemes 11, 12, 21, 38, and 40),^{30,44-48,61,92-94} pyrenes (Schemes 18 and 31),^{33,55,56} porphyrins,^{13,14} have been synthesized. For example, thiazolo[4,5-*c*]porphycenes **127** were synthesized by reacting porphycene isothiocyanates **126** with primary and secondary amines (Scheme 41).⁹⁵



Scheme 41. Reaction of porphycene isothiocyanates **126** with primary and secondary amines.

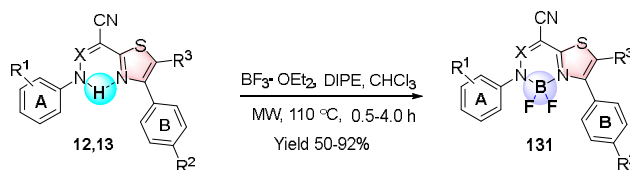
2.3. Complexation of thiazole derivatives

Complexation is an important chemical modification that can lead to significant changes in optical properties.^{24,31,48,68,82,83,96-98} Organoboron complexes are among the most important types of fluorescent dyes today. Boron dipyrromethene (BODIPY) dyes are the best fluorophores among organoboron complexes owing to their high quantum yield, sharp spectra, and high photostability. However, BODIPY dyes often show very small Stokes shifts and aggregation-caused quenching (ACQ). Compounds **130** were synthesized by the Lewis acid-catalyzed condensation reaction of thiazole aldehyde **128** with pyrrole derivatives (2-methylpyrrole or 2,4-dimethylpyrrole) **129** followed by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), reaction with TEA, and $\text{BF}_3 \cdot \text{OEt}_2$ addition (Scheme 42).^{99,100}



Scheme 42. Synthesis of BODIPY derivatives **130**.

The thiazole nitrogen atom can undergo complexation with boron atoms directly. Therefore, two new classes of efficient fluorophores, namely, 1,3,2-diazaborinine- and 1,2,4,3-triazaborinine-annulated thiazoles **131**, were successfully prepared using an improved synthetic strategy involving microwave irradiation (Scheme 43).²⁴



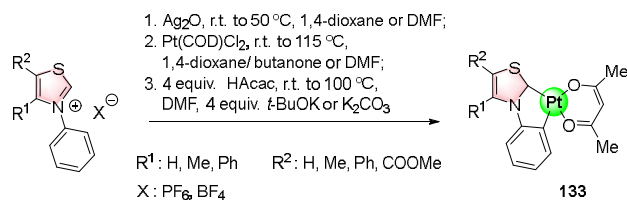
Scheme 43. Synthesis of BF_2 -thiazole complexes **131**.

BF_2 -complexes **131** showed a pronounced aggregation-induced emission enhancement effect (AIEE) owing to restricted intramolecular rotation, as well as *J*-type aggregation of the thiazole molecules, which explains the red-shift and lack of solid-state emissive properties for the parent thiazole.

Metal complexes of sulfur-containing heterocycles are also of great interest currently owing to their phosphorescent properties.¹⁰¹ Using transition metal complexes, the efficiency of organic ligands and optical characteristics can be enhanced. In particular, platinum(II) compounds have been described as highly efficient emitting molecules with potential application in OLEDs. *N*-Aryl-1,3-thiazol-2-ylidene C[∧]C cyclometalated platinum(II) complexes **133** were synthesized and showed a strong blue-green phosphorescence emission at 497-522 nm (Scheme 44).¹⁰¹

The most commonly described structures containing N[∧]N- and C[∧]N-coordinated 2-aryl-1,3-thiazoles and transition metals are iridium, platinum, or rhenium^{83,102-108} complexes, which show

interesting phosphorescent properties. The electronic structures and photophysical properties of a series of homoleptic Ir(III) complexes with triphenylamine-based thiazole ligands have been reported (Figure 2).¹⁰²



Scheme 44. Synthesis of Pt(II)-thiazole complexes.

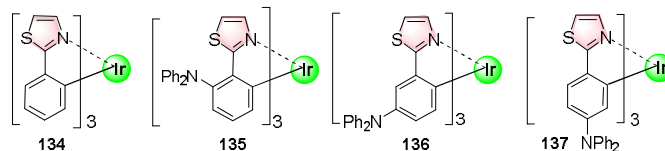


Figure 2. Ir(III)-thiazole complexes.

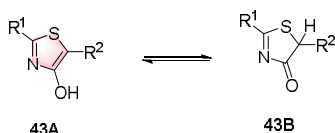
3. Photophysical properties

The importance of thiazoles is increasing owing to their excellent photophysical properties and extreme sensitivity to the introduction of substituents. Thiazole rings contain an *sp*²-hybridized nitrogen atom and *sp*³-hybridized sulfur atom that can act as donors.^{6,59} Various substituents, with electron-donating or electron-withdrawing natures, can crown the heterocyclic ring to change or tune the electronic character of the molecule. Furthermore, these substituents might be bulky groups or aromatic/heteroaromatic rings, which will strongly effect the conformation of the entire molecule. The spatial construction of substituents attached to the core structures can be localized in one plane or adopt twisted three-dimensional structures. These electronic and spatial features give rise to their unique fluorescent properties.⁵⁹ Thiazoles attached with aryl or heteroaryl groups (arylthiazoles) are attractive structural motifs that are frequently used in functional organic materials.

The most common fluorescent thiazoles are 4-hydroxy-thiazoles, 2- and 5-amino-thiazoles, and thiazoles containing lateral flexible conjugated bond systems. Therefore, in this section, these main fluorescence groups and relationships between their luminescence and structural features will be discussed.

3.1. 4-Hydroxythiazoles as chromophores and fluorophores

4-Hydroxy-1,3-thiazoles can exist in two tautomeric forms, namely, the aromatic enol form (A) and the keto form (B) (Scheme 45). NMR investigations showed that introducing at least one aromatic substituent in the 2- or 5-position gives rise to the enol form. Calculations (DFT-B3LYP 6-311G+(2d,)) for **43** in CHCl₃ and DMSO showed that 4-hydroxythiazole tautomer **43A** was preferred over thiazole-4(5*H*) tautomer **43B**.^{6,109}



Scheme 45. Equilibrium between enol and keto forms of 4-hydroxythiazoles **43**.

The presence of ionizing substituents, such as OH groups, in a fluorophore structure significantly affects its physicochemical and photophysical properties. 4-Hydroxythiazole solutions usually show blue fluorescence (440-480 nm) and a broad range of quantum yields of up to 87%.¹⁰⁹ The emission wavelengths are apparently affected by substituents R¹ and R² (Figure 3). The combination of an electron-deficient

heterocycle (pyrazine) at thiazole C2 and an electron-rich aromatic ring with a MeO group at thiazole C4 has been shown to be essential for absorption and emission. However, derivatives with strong electron-acceptor NO₂ groups in the C2-pyridine show weak fluorescence, as opposed to thiazoles with NMe₂ groups (strong electron donor).¹⁰⁹ Generally, pyridyl-substituted 4-hydroxythiazoles have more bathochromic absorptions and emissions than phenyl-substituted derivatives.

Compd	R ¹	R ²	λ_{abs} , nm	λ_{em} , nm
43a	2-Py	Ph	381	450
43b	3-Py	Ph	384	474
43c	3-Py	Me	451	442
43d	3-Py	4-NO ₂ C ₆ H ₄	410	430
43e	Pyrazine	4-MeOC ₆ H ₄	411	520
43f	2-(4-NO ₂)Py	Me	346	441
43g	2-(4-NMe ₂)Py	Me	347	475

Figure 3. Spectral data for 4-hydroxy-thiazole-based fluorophores **43** measured in DMSO.

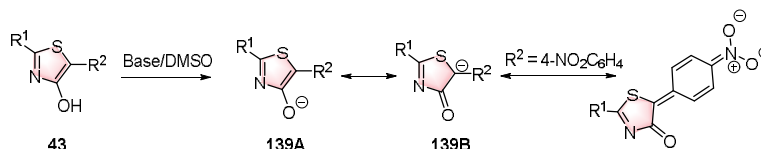
However, 4-hydroxy-5-nitrophenyl-2-(pyren-1-yl)thiazole **138** (Figure 4) with a thiazole C5-substituent of the opposite electronic nature (R²=4-NO₂C₆H₄) emitted light at about 608 nm with higher quantum yields (QY=0.19) in CHCl₃ and a very large Stokes shifts (186 nm) due to the intramolecular charge transfer character of HOMO-LUMO excitation, as confirmed by TD-DFT calculations.⁵⁵

λ_{abs} , nm	λ_{em} , nm	SS, cm ⁻¹	QY
424	608	7191	0.19

Figure 4. Spectral data for 4-hydroxy-5-nitrophenyl-2-(pyren-1-yl)thiazole **138**.

A common property among most hydroxythiazole and aminothiazole derivatives is dual fluorescence, which arises from intramolecular hydrogen bond formation.^{6,50,92,109,110} Intramolecular hydrogen bonding in the excited state can affect processes that occur after photon absorption, such as internal conversion, intersystem crossing, intramolecular charge transfer (ICT), and excited state internal proton transfer (ESIPT).

Ionization in some 4-hydroxythiazoles can also cause white fluorescence to appear in DMSO solution. This phenomenon is due to the coexistence of protonated and deprotonated species under the basic effect of DMSO. White fluorescence is a remarkable property for such simple systems, making these compounds of great interest for applications such as OLEDs (Scheme 46).¹⁰⁹



Scheme 46. Deprotonation of thiazole **43** and extended charge delocalization in 4-nitrophenylthiazole derivatives.

ESIPT is known to increase with enhanced acidity and/or basicity of the donor and acceptor groups after photoexcitation.^{6,8,10,28,109,110} Molecules that undergo ESIPT have a more thermodynamically favored enol form in the ground state (S₀), which is stabilized by the intramolecular hydrogen bond. After photoexcitation, the acidity of the donor group (OH) and basicity of the acceptor group (NH₂) must increase simultaneously due to charge density redistribution in chromophore **140** (Figure 5).¹⁰⁹ This process allows

the proton migrate from the acid to the basic center, generating phototautomer **141**, which displays a large bathochromic shift (98-119 nm) and unusually large Stokes shift (9000-9500 cm^{-1}).

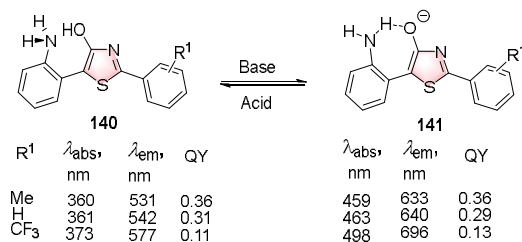


Figure 5. Experimental absorption and fluorescence maxima, and fluorescence quantum yields of 4-hydroxythiazoles **140** and their ionized form **141** in DMSO.

Conversion of the 4-hydroxythiazole OH group into an ester increases the solubility in organic solvents and leads to a high quantum yield and large Stokes shift. Notably, emission spectra for these compounds often show two maxima.^{6,50-52,63,79-83,86,111,112} The *O*-substituted compounds also exhibit fluorescence in the solid state, usually with bathochromic shifts compared with those in solution. For example, the solid state emission of pyrenylthiazoles **97** (Scheme 31) is located in the yellow-orange region of the visible spectrum. The quantum yields are slightly lower than those measured in solution (about 20%), at about 11-16%.^{55,56} The red-shift and lack of solid-state emissive properties for the parent hydroxythiazole are attributed to restricted intramolecular rotation and *J*-type aggregation of the thiazole molecules.⁸⁰

2-Pyrenylthiazoles **97** with alkylated and acylated 4-hydroxy groups emit in diluted chloroform solution in the region 608-622 nm with a quantum yield in the range of 0.2-0.3. Again, the outstanding features of the thiazole emission were large Stokes shifts (up to 180-210 nm/6800-8500 cm^{-1}) and strong solvatochromism. Similar large Stokes shifts were observed for 2-pyridine-2-yl-1,3-thiazoles and 2-pyrimidine-2-yl-1,3-thiazoles, which might be attributed to the significant geometry changes in the excited S_1 state resulting from intramolecular charge transfer that accompanied the HOMO to LUMO excitation.^{55,56}

Excellent results were obtained while investigating the optic properties of thiazoles **142** and **143** (Figure 6).⁸² These compounds exhibited different colors in THF solution (**142**, yellow-green; **143**, orange). This simple switching of methoxy- and nitro-substituents in the structure of thiazoles **142** and **143** resulted in considerable differences in absorption and emission. The long wavelength band was redshifted by 21 nm in UV/Vis spectra and by 47 nm in fluorescence spectra, while the Stokes shift increased from 120 to 146 nm.

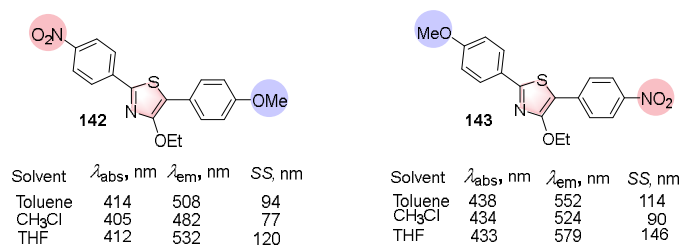


Figure 6. Solvatochromism of dyes **142** and **143**.

However, surprisingly, the nitro group induced bright fluorescence, in contrast to the phenomenon usually observed in organic chromophores and fluorophores. Solid-state fluorescence was a unique characteristic of these compounds.⁸²

3.2. Photophysical properties of 2- and 5-aminothiazoles

Aminothiazoles are the next largest class of extensively investigated thiazole compounds owing to their interesting optical properties.^{32-35,57-59,66,71} For example, 5-aminothiazoles **88** show strong absorption

from 338 to 430 nm and emission from 455 to 726 nm depending on the substituents at the 2-, 4-, and 5-positions.⁷¹ Generally, electron-rich groups at the 5-position and electron-withdrawing groups at the 2-position lead to redshift absorption and emission. Substituents at the 4-position have almost no influence on these spectra (Figure 7).

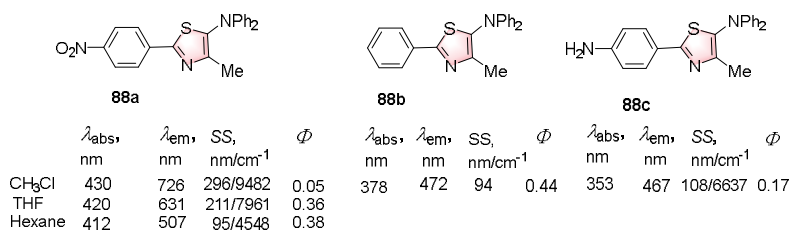


Figure 7. Photophysical properties of 2-aryl-5-*N,N*-diphenyl-4-methyl-thiazol-5-amines **88**.

The longest wavelengths for *N,N*-diphenylaminothiazoles **144** were in the range of 366-394 nm.⁶⁶ Replacing an aromatic substituent at the 2-position with a 2- or 4-pyridyl group shifted the wavelengths from 366-384 to 394 nm. Notably, replacing the one of *N*-aryl group with an *N*-benzyl or *N*-adamantyl substituent led to a hypsochromic effect up to 34 nm. The absorption spectra were not affected by the solvent polarity, while solvatochromism was observed. Finally, 5-aminothiazoles **144** showed a large Stokes shift of up to 137 nm (8709 cm⁻¹). The fluorescence results shown in Figure 8 clearly exhibit that electron-donating and electron-withdrawing groups on the aromatic groups at C2 and on the amino moiety at the 5-position can be introduced to change the fluorescence wavelength maxima position (Figure 8).

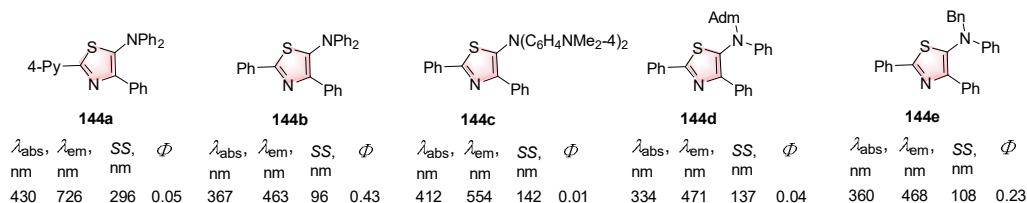


Figure 8. Photophysical properties of 2-aryl/hetaryl-5-amino-4-phenyl-thiazol-5-amines **144** in CHCl₃.

A systematic study of a large fluorophore library with thiazole/thiophene/furan cores showed large Stokes shifts, positive solvatochromism, acidochromism, and color tunability in different solvents.⁵⁷⁻⁵⁹ As a result of this study, the C5 position was identified as crucial in determining the color tunability. In toluene, absorption varied between 412 and 560 nm, while emission was in the range of 511-671 nm. The thiazole C4 position and thiophene C2-NO₂ formed the second charge transfer channel using donor and acceptor fragments. The molecules possessed large Stokes shifts, solvatochromism, and acidochromism.⁵⁹ Therefore, C2, C4, and C5 atoms on the thiazole ring and C5 on the linked heterocycle were important for fluorescence tunability (Figure 9).

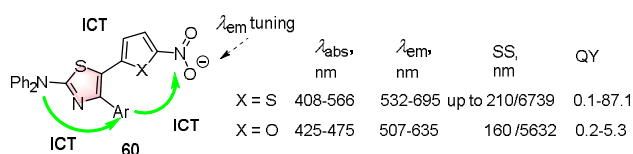


Figure 9. 1,3-Thiazole-based color-tunable multiheterocyclic organic fluorophores.

3.3. Thiazoles with flexible conjugated systems

The photophysical properties of organic compounds are dependent on their electronic and spatial structures. The length and type of linear chain combined with aromatic/heteroaromatic cycles, and other substituents or chromophore/fluorophores groups, are major factors affecting the photophysical properties. Among these groups, the most abundant are hydrazone, enamine, ethylene, imine- and azine fragments.

Various π - π linkers have been used to extend the conjugated system (double and triple bonds, heterocycles, azo- and azine group) at the thiazole C5 and C2 atom.^{24,25,39-41,89-93} Recently, new thiazole derivatives **12**, **13** (Figure 10), and **16** (Scheme 5) with flexible linear conjugated systems involving enamine **12**, aza-enamine **13** and acrylonitrile **16** side chains at the C2 ring atom were synthesized, with the type of spacer group linking the thiazole with the peripheral aromatic ring found to be very important.^{24,25}

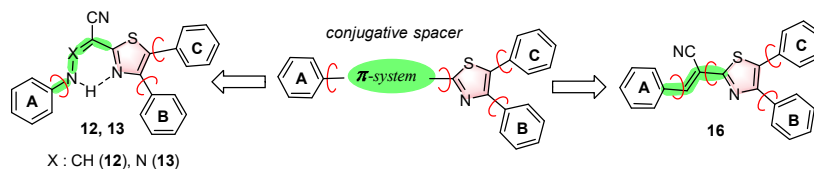


Figure 10. Structures of thiazoles with enamine **12**, aza-enamine **13**, and acrylonitrile **16** side chains at the C2 ring atom.

Thiazoles **16** have exhibited further outstanding photophysical properties. For example, fluorophores **16** showed stronger emission intensities ($\Phi_F=0.2-26.3\%$) than the corresponding thiazoles **12** ($\Phi_F=0.5-2.14\%$) and **13** ($\Phi_F=0.05-0.1\%$). Interesting results were obtained by comparing compounds **16** with the corresponding thiazoles without the acrylonitrile chain. Large differences in the absorption and emission maxima were observed, such as a bathochromic shift in the absorption, larger Stokes shifts, different behaviors in solvents, high sensitivity to microenvironment, and large Stokes shift (up to 179 nm) with increasing solvent polarity. It should be noted that a high Stokes shift is very useful for small organic fluorophores, especially for imaging applications.¹¹³

4. Photoswitches based on 1,3-thiazole derivatives

Photochromic compounds capable of reversibly transforming between two stable isomeric forms under irradiation with light of a certain wavelength are receiving considerable interest owing to their potential technical applications, including in the design of materials for molecular electronics, optical data storage systems, molecular logic devices and switches, photopharmacology, biological data visualization, and chemo- and biosensors.¹¹³ Among various photochromic molecules, diarylethenes are regarded as the best candidates for application owing to their good photochromic properties with high thermal stability, high fatigue resistance, and fast response time.¹¹⁴ The mechanism of diarylethene photochromism is usually explained by the photoinduced 6π -electrons pericyclic interconversion between the central hexatriene in the open form and cyclohexadiene in the closed form (Figure 11). The hexatriene moiety, as a part of two aromatic rings, arises from dearomatization of the aryl ring substituents at the central double bond and photocoloration.

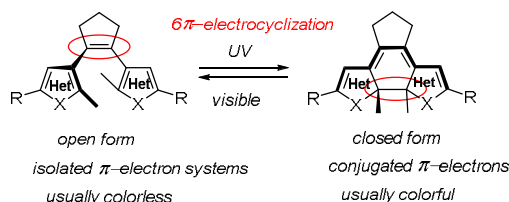


Figure 11. Reversible electrocyclic transformation of diarylethenes.

Various diarylethenes have been obtained with different numbers and locations of the thiazole ring in their system.^{67,69,72,75,115} For example, a central thiazole unit improved the chemical stability against oxidation, as well as the photocyclization reactivity, owing to reduced steric hindrance in compounds **145** (Figure 12).¹¹⁵

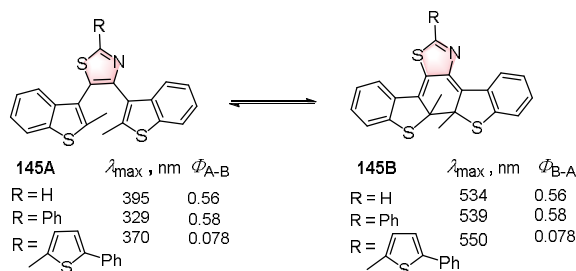


Figure 12. Photochromic terarylenes with a central thiazole ring.

Introducing and expanding the π -conjugated system at the 2-position of the thiazole ring led to a redshift of the absorption peaks for both open- and closed-ring isomers of terarylenes. The optical absorption band was shifted to a longer wavelength by introducing the π -conjugation unit.

Photochromic bis(thiazol-4-yl)maleimides **147** show an enhanced binding affinity toward complementary melamine receptors **146** in their ring-closed switching state, and might be used to create light-responsive supramolecular assemblies.¹¹⁸ Thiazoles are the best candidates for termini fragments owing to their high thermal and photochemical stabilities (Figure 13).

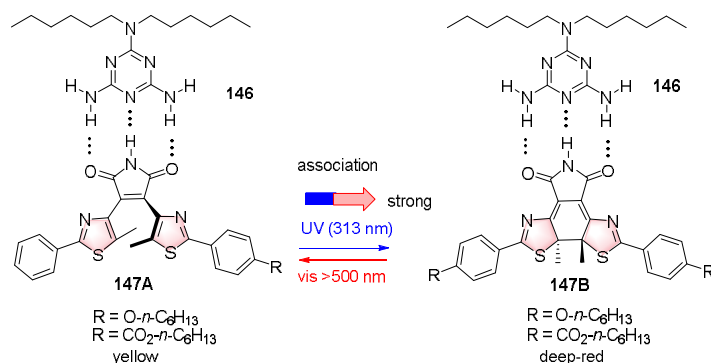


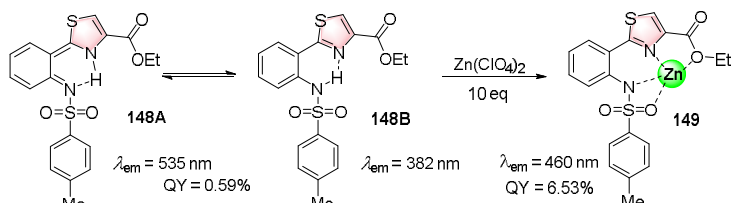
Figure 13. Photoswitchable triple hydrogen-bonding motif: Reversible photochemical ring-closure (opening) leads to enhanced (diminished) binding of the central diarylethene moiety in **147A/147B** to a complementary melamine receptor.

5. Cation sensors

Molecular fluorescent chemosensors for cation and anion recognition have attracted much attention owing to their important and diverse ecological, biological, and clinical applications.¹¹³ The absorption and emission spectra of various thiazoles were measured in the presence of transition metal ions and other ions, such as Fe^{3+} , Cr^{3+} , Al^{3+} , Fe^{2+} , Cd^{2+} , Co^{2+} , Ni^{2+} , Ca^{2+} , Cu^{2+} , Zn^{2+} , Hg^{2+} , Pb^{2+} , Ag^+ , Na^+ , and K^+ .^{10,15,28,42,117-119} A new ratiometric chemosensor has been developed for Zn^{2+} , Fe^{3+} , Cr^{3+} , Cu^{2+} , and Al^{3+} ions using strong coordination. It should be noted that different effects might result from the coordination with metal ions, such as changes in intensity or long wavelength shifts. Therefore, paramagnetic transition metal ions Fe^{2+} , Fe^{3+} , and Cu^{2+} coordinated to thiazole sensors, but partially or completely quenched the fluorescence emission due to the very fast and efficient nonradiative decay of the excited states, which resulted from electron or energy transfer between the open shell *d*-orbitals of the metal ions and thiazole. Meanwhile, Zn^{2+}

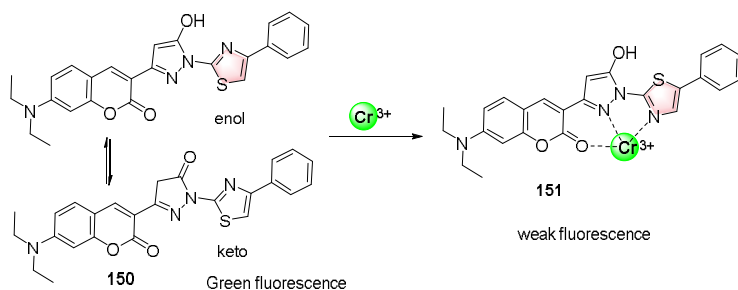
has closed-shell d -orbitals, which prevents energy or electron transfer processes taking place. Coordination with Zn^{2+} removes protons and disrupts ESIPT, causing emissions with a normal Stokes shift.^{10,118}

2-Aryl-substituted thiazoles bearing substituents with labile hydrogen atoms (hydroxy- or amino-(2'-tosylamidophenyl)thiazole **1** exhibited the detection of different metal ions in organic solvents or water-organic solvent/ethanol mixtures.^{9,10,118} Sensor **148** exhibited a remarkably large shift of 75 nm in the emission upon complexation with Zn^{2+} . The fluorescence mechanism of thiazoles can be attributed to (i) the inhibition of excited-state intramolecular proton transfer (ESIPT) and (ii) chelation-induced enhanced fluorescence by binding with Zn^{2+} (Scheme 47).¹¹⁸



Scheme 47. Plausible complexation mechanism between sensor **149** and Zn^{2+} .

Coumarin-based pyrazolone chemosensor **150** has the ability to detect Cr^{3+} ions *via* colorimetric and fluorescent modes.¹¹⁹ Cr^{3+} ion complexation with a compound gives a quick color response from fluorescent green to colorless and shows remarkable quenching of fluorescence at 506 nm in DMSO. Furthermore, confocal imaging of A-549 cells showed that thiazole **150** could be applied to detect Cr^{3+} in living cells (Scheme 48).



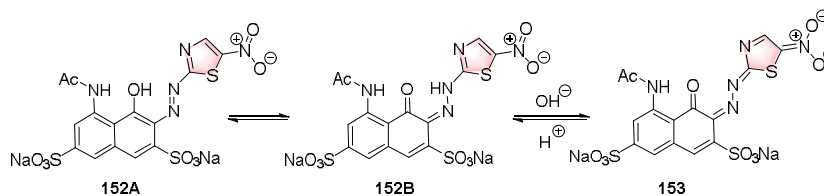
Scheme 48. Sensing mechanism for Cr^{3+} ions.

6. pH-Sensitive thiazole fluorescence

Protonation or deprotonation has a marked electronic effect, but can also induce a structural change if the formation or breaking of an intramolecular hydrogen bond is involved. In certain cases, such protonation/deprotonation events can be coupled with additional excited state processes, such as proton transfer, which could significantly affect the photophysical characteristics.

4-Hydroxy-1,3-thiazoles have been shown to exhibit pH-sensitive fluorescence.^{6,15,51,60,79,110,120} Upon deprotonating the hydroxyl-group with strong bases, such as KOH or NaH, a drastic change in color occurs combined with a bathochromic shift of fluorescence, leading to a red solution.⁶

Therefore, thiazole **152** offered a new pH indicator with high sensitivity and a significant color change from red to blue that is visible to the naked eye in a narrow pH range (3.2-4.0) with a high molar absorption coefficient.¹²⁰ The mechanism of the indicator was based on azo-hydrazone tautomerism (Scheme 49) and the nitro group absorbing electrons. The pH indicator has the potential to be used in the visualization of gastric fluid acid pH changes to treat gastric ulcers.



Scheme 49. Mechanism of pH sensing for thiazole **152**.

7. Conclusions

In summary, the thiazole core is a unique platform for the construction of new fluorophores with outstanding optical properties. The electronic nature of this heterocycle creates opportunities for obtaining fluorophores with excellent photophysical characteristics that make them extremely sensitive to the microenvironment. This heterocycle can be constructed using simple methods from a broad range of available starting compounds. Traditional and new procedures allow the introduction of various functional groups, substituents, aromatic/heterocyclic fragments, and linear chains, and the preparation of macrocyclic compounds and polymeric materials. Therefore, thiazole derivatives have shown multifunctional properties and exhibited fluorescence in both dilute solutions of different organic solvents and the solid state, with good to high quantum yields and large Stokes shifts, which increases their potential for use as a good fluorophores in biological, medical, and technical applications.

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