

# **The Chemistry of 5-aminothiazole and its derivatives**

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## List of Abbreviations

Å	ångström unit
AIE	aggregation induced emission
Ar	Aryl
BODIHY	boron difluoride hydrazone
BODIPY	4,4-difluoro-4-bora-3a,4a-diazas-indacene
BOPHY	(bis(difluoroboron)-1,2-bis((1H-pyrrol-2-yl)methylene)hydrazine
Calcd.	Calculated
Conc.	Concentration
CT	charge transfer
δ	chemical shift
DFT	density functional theory
DMAP	4-dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide
ESI-MS	electrospray ionization mass spectrometry
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectra
ICT	intramolecular charge transfer
<i>J</i>	coupling constant (NMR)
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
Me	methyl
MS	mass spectroscopy
<i>n</i> -BuLi	normal butyllithium
NBS	<i>N</i> -bromosuccinimide
NIR	near infrared
Ph	phenyl
THF	tetrahydrofuran
Φ <sub>F</sub>	quantum yield

# **Chapter 1**

## **General introduction**

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## 1.1. Thiazoles: synthesis and properties

Thiazoles are five-membered heteroaromatics containing sulfur and nitrogen atoms in a cyclic ring system. One of the distinctive features of thiazoles is that they have a sulfur atom, which is a soft base, and a nitrogen atom, which is a hard base. This feature implies that thiazoles can coordinate to a range of soft and hard metals. The nitrogen atom in this compound can accept an electrophilic carbon atom to form ammonium salts, whose structure is seen in natural vitamin B1. Moreover, the calculated  $\pi$ -electron density of thiazoles suggested that C<sub>5</sub> is the most favorable site followed by C<sub>4</sub> for electrophilic substitutions, while C<sub>2</sub> is preferable site for nucleophilic substitutions (Figure 1).<sup>1</sup>

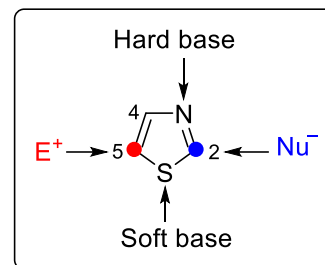


Figure 1. Thiazole structure.

The first synthesis of thiazole was introduced by Hantzsch in 1887 by reacting  $\alpha$ -halocarbonyl and thioamides. This reaction does not require a harsh condition or expensive catalysts. Employing this synthetic method, a variety of 2,4- and 2,4,5- substituted thiazoles can be isolated in good yields. Since then, numerous thiazole derivatives are massively synthesized. Nowadays, many thiazole-based compounds are in clinical use such as dasatinib as an anticancer,<sup>2</sup> and ritonavir as an anti-HIV agent (Figure 2).<sup>3</sup> Additionally, thiazoles have three carbon atoms at the 2-, 4-, and 5-positions, to which a wide variety of substituents can be principally introduced. Therefore, a wide range of thiazole derivatives have been tremendously developed.

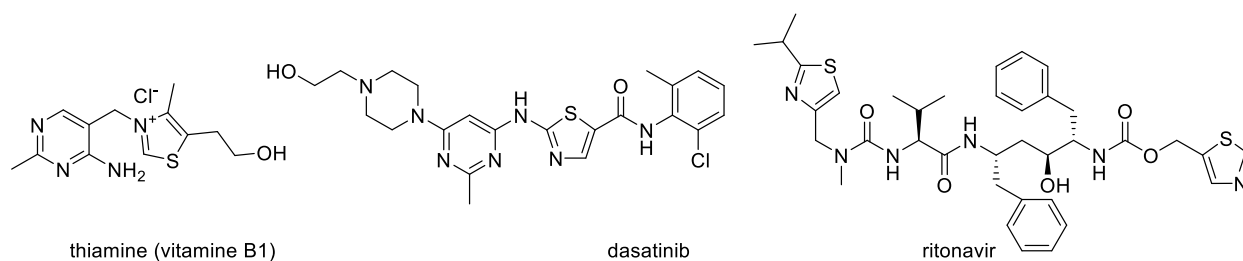
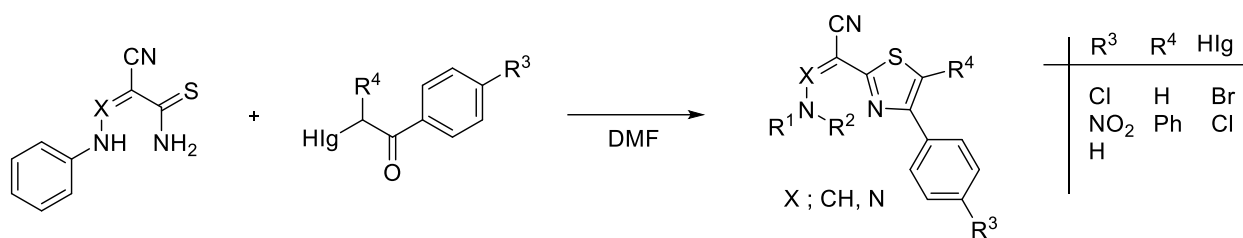


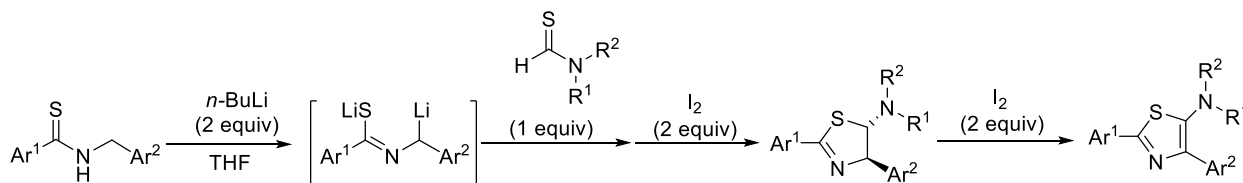
Figure 2. Selected examples of thiazole-based compounds.

Recently, Lugovik and co-workers<sup>4</sup> reported the reaction of arylaminothioacrylamides or azanamines with halocarbonyls to form di- and tri- substituted thiazole derivatives bearing aryl enamine side-chains. This developed Hantzsch process reaction allows us to introduce two aromatic cycles onto thiazole ring simultaneously (Scheme 1).



**Scheme 1.** Synthesis of enamine and aza-enamine thiazoles.

Another synthetic approach to thiazole frameworks is by [4+1]-cycloaddition of isocyanides and *N*-thioacyl *N,O*-acetals in the presence of organosilane compounds as catalysts. This reaction proceeded smoothly to produce an aminothiazole library.<sup>5</sup> Meanwhile, Murai and coworkers have previously synthesized the first example of 1,3-thiazole derivatives having a *N*-arylamino group at the 5-position of a thiazole ring. Those compounds were synthesized with facile synthetic routes following diversity-oriented synthesis from readily available starting materials (Scheme 2).<sup>6</sup> The detail of this procedure is shown in Chapter 2.



**Scheme 2.** Synthesis of 5-aminothiazoles.

A series of 5-H thiazoles can be synthesized in moderate to good yields following the Hantzsch synthesis reaction. This method allows us to insert various substituents onto the thiazole ring. Alternatively, a remarkable synthetic protocols for 5-H thiazoles is via palladium(II)-catalyzed C-C coupling and C-N condensation cascade by using  $\alpha$ -thio-cyanomethyl ketones and aryl boronic acids as starting materials.<sup>7</sup> Recently, Ni<sup>8</sup> and coworkers described a three-component strategy for thiazole formation from readily available acetophenones, benzylamines, and sulfur powder under metal-free conditions. These reports have elegantly described the synthesis of 5-H thiazoles with a wide range of tolerable substituent at the 2- and -4 position of thiazole ring. However, so far, access to 5-H thiazoles having a 2-pyridyl group at 4 positions of the thiazole ring is only via thioamide and thioformamide cyclocondensation.<sup>9</sup> In fact, these compounds can be potentially used as organic ligands to a various metal center.

## 1.2. The chemistry of 5-aminothiazoles

5-aminothiazoles have been used as the model for new types of fluorescent compounds having flexible and non-planar carbon skeletons. These compounds can be readily synthesized from the reaction of secondary thioamides and thioformamides.<sup>6</sup> Besides, they show a finely tuned absorption and emission properties that change by solely modulating their electronic properties<sup>10</sup> as well as upon the external stimuli such as the addition of acids.<sup>11</sup> As a recent example, thiazoles containing a diarylamino group at the 5-position of thiazole ring showed dual emission both in solid and in a solution state<sup>12</sup> and while other 5-aminothiazole derivatives showed mechanochromic properties.<sup>13</sup>

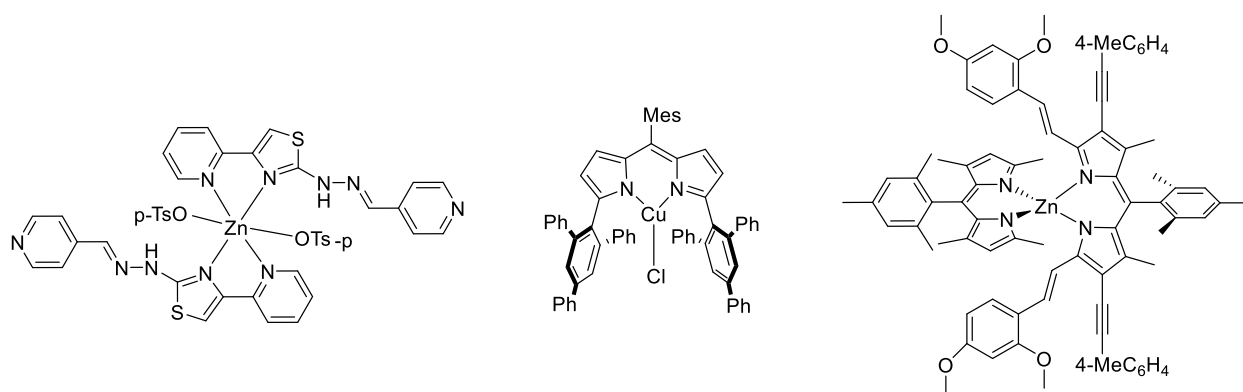
Furthermore, the tuning of the effective structure and reactivity of the fluorescent compounds are important objects concerning on the development of metal-catalysts in organic reactions. In this regards, fluorescent compounds bearing thiazole core are of interest because of their strong coordination ability to the metal center and their potential catalytic activity of the resulting metal complexes in various organic reactions.

## 1.3. First-row transition metal complexes

First-row transition metals are those in which the 3d orbital electron shell contains between one or nine electrons.<sup>14</sup> Several transition metals are usually found to bind to organic ligands as organic catalysts,<sup>15–17</sup> and few of them are found in fluorescent compounds.<sup>18–20</sup> In fact, the presence of a metal surface closest to the fluorescent molecule can manipulate the decay rate of the fluorophore and produce drastic spectral changes.<sup>21</sup> Moreover, interactions between metallic surface with fluorophores give a beneficial effect on photophysical properties such as an increased quantum yield, improved photostability and a reduced lifetime of fluorophores.<sup>22</sup>

Some of the first-row transition metals such as cobalt, copper, nickel and zinc are widely used as complexing agents for various purposes. For example, zinc metal complexes with thiazole pyridine-based ligands are biologically active as anti-microbial and anti-tumor agents. Scharf and co-workers<sup>18</sup> succeeded in the synthesis of copper (II) and zinc (II) coordinated to dipyrrene chelates to form luminescent materials with strong photophysical properties. Meanwhile, Sakamoto<sup>19</sup> reported a bright-red emission with large pseudo stokes shift for zinc complexes with two unidentical dipyrrene chelates (Figure 3). Most fluorescent materials containing first-row transition metal complexes are based on dipyrrene ligands. Therefore, the development of a new type of first-row transition metal coordinated to 1,5-bidentate nitrogen ligands are highly in demand.

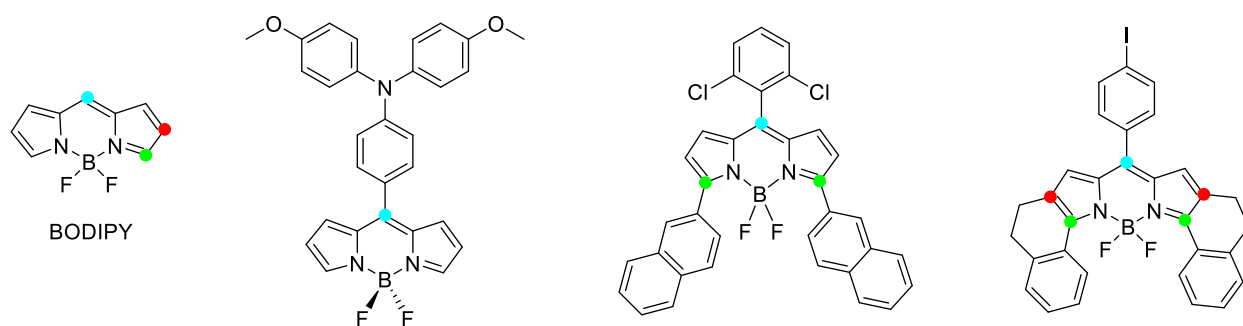




**Figure 3** Transition complexes coordinated to organic ligands.

## 1.4. Boron-organic based fluorophores

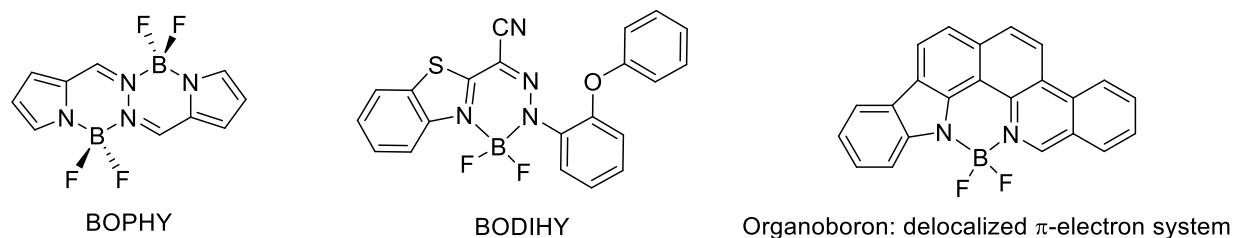
Complexation with a boron atom is common strategy to synthesize new organic fluorophores. A boron atom is a non-toxic alternative to transition metals. Boron atom coordinated to organic  $\pi$ -conjugated system increases its  $\pi$ -electron accepting ability.<sup>23</sup> Moreover, the presence of boron atom in the organic fluorophore can manipulate their electronic properties such as reducing the band gap, enhancing the electron affinity, and inducing strong intramolecular charge-transfer (ICT) processes.<sup>24</sup> The most common organic boron-based fluorophore is 4,4-difluoro-4-bora-3a,4a-diazas-indacene (BODIPY). This complex shows excellent optical properties, photochemically stable and high quantum yields. Due to the modifiable dipyrrene framework, the photophysical properties of BODIPY can be easily tuned by introducing various substituents at the meso position and two dipyrrene rings (Figure 4).<sup>25–28</sup> Consequently, several modified BODIPY have been massively reported.



**Figure 4.** 4,4-difluoro-4-bora-3a,4a-diazas-indacene (BODIPY) and its derivatives.

Apart from BODIPY, BODIPY-like fluorophores such as (bis(difluoroboron)-1,2-bis((1H-pyrrol-2-yl)methylene)hydrazine (BOPHY) also show excellent optical properties that enable them to be a good candidate as molecular sensors and photosensitizers for solar cells.<sup>29,30</sup> Meanwhile, boron difluoride hydrazone (BODIHY) show aggregation induced emission and reversible mechanochromism

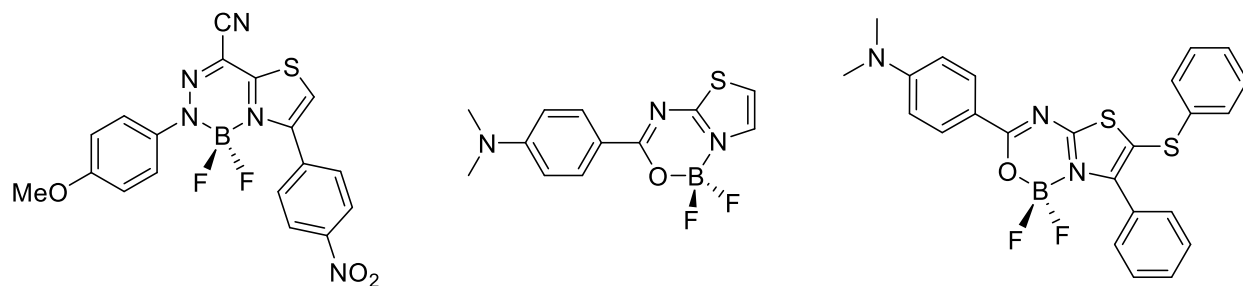
properties.<sup>31,32</sup> Similarly, some organoborons with delocalized  $\pi$ -electron systems which show large stoke shift and tunable optical properties have also been synthesized and utilized for bioimaging (Figure 5).<sup>33,34</sup>



**Figure 5.** BODIPY-like compounds: BOPHY, BODIHY, and organoboron with delocalized  $\pi$ -electron system.

## 1.5. Boron-thiazole based fluorophores

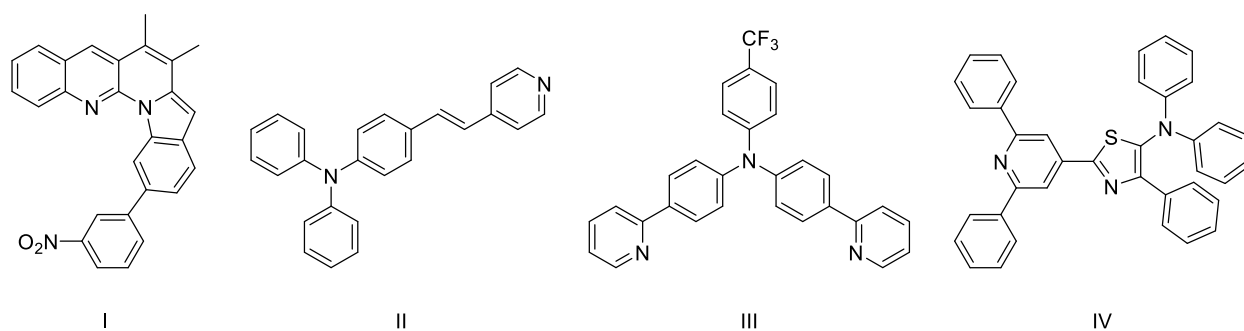
Boron-thiazole based complexes are emerging as a promising alternative for accessing new types of fluorophores. The nitrogen atom in the thiazole ring can accept various types of Lewis acid species including a boron atom. This nitrogen atom can undergo complexation with a boron atom to give new candidate fluorophores based on boron-thiazole complexes. The development of fluorophores which use boron as a main element is reported by Lugovik<sup>24</sup> and Potopnyk.<sup>35</sup> Those boron-thiazole complexes showed an aggregation induce emission (AIE) and solid-state emission properties. Moreover, their optical properties can be tuned by introducing a variety of substituents to the thiazole ring (Figure 6). Although boron complex fluorophores have been massively investigated, the formation of boron-thiazole based complexes are rarely reported.



**Figure 6.** Boron-thiazole based complexes.

Nitrogen-based heterocycles such as pyrazine,<sup>36,37</sup> benzimidazole,<sup>38</sup> and pyridyl<sup>39–41</sup> is an electron  $\pi$ -deficient unit which are commonly used to design organic fluorophore having push-pull systems. The nitrogen atom can be protonated by Lewis or Brønsted acid results in the turn on-off emission<sup>42</sup> and pronounced reversible halochromic properties.<sup>43</sup> Acid-base interaction between fluorophore and Lewis acids often results in unexpected photophysical properties such as white light emission.<sup>39,44</sup> Meanwhile,

the photophysical properties of 5-*N*-arylaminothiazoles showing white light emission from single fluorescent dye upon the treatment with Brønsted acids have been successfully characterized (Figure 7).<sup>11</sup>



**Figure 7.** Acid-responsive compounds. On/Off emission properties upon the addition of acid (I), white light emission upon the addition of acid (II-IV)

## 1.6 Overview of this thesis

This thesis describes the chemistry of 5-aminothiazoles and their derivatives. In Chapter 2, the synthesis, photophysical properties and coordination of 5-aminothiazole derivatives having pyridyl groups at 2 and/or 4 position of a thiazole ring are discussed. Direct complexation with first-row transition metal i.e., nickel atom resulted in nickel-thiazole complexes. Furthermore, their photophysical properties and catalytic activity in hydroamination reaction is described. Chapter 3 presents the preparation of 5-H thiazoles via reaction of *in situ* generated thioamide dianions and thioformamides. The effect of 4-pyridyl group substituent at the thiazole ring on the formation of 5-H thiazole and its plausible reaction pathway is described. Chapter 4 discloses the synthesis and photophysical properties of boron-thiazole complexes. A series of thiazole ligands were synthesized via Buchwald-Hartwig amination reaction. Complexation with  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  readily yielded in boron complexes of thiazole-bridged 1,5-bidentate nitrogen ligands. Treatment with Lewis and Brønsted acid shifted the absorption spectra to the longer absorption wavelength. Additionally, a series of first-row transition metal-thiazole based complexes were prepared. Lastly, experimental data, and theoretical calculation were summarized.

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## Chapter 2

### Synthesis, properties, and coordination of 5-aminothiazoles having pyridyl groups

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## 2.1. Introduction

Since Hantzsch's report on the synthesis of thiazoles, their various derivatives have been reported massively. In fact, 2,5- and 2,4,5- substituted thiazoles can be synthesized in good yields via this classical method. Nowadays, the chemistry of thiazoles has been extended to the development of thiazole-based fluorescent materials. These fluorescent compounds exhibit unique photophysical properties such as aggregation induced emission (AIE),<sup>1,2</sup> mechanochromism<sup>3</sup> and some of them are acid-responsive fluorescent compounds.<sup>4,5</sup>

5-N-arylaminothiazoles are a class of fluorescence compounds bearing flexible conformational geometry with non-planar carbon skeletons.<sup>6</sup> These compounds are synthesized by reacting secondary thioamide and thioformamides via thioamide dianions and thiazolines for the first time. This synthetic protocol allows us to access a wide range of unprecedented 5-aminothiazoles with various substituents at the 2- and 4-positions of a thiazole ring. Nevertheless, the synthesis and elucidation of properties of 5-arylaminothiazoles having a 2-pyridyl group at the 4-position is less investigated despite their high potential utility as new metal ligands. To fill that gap, I was interested in the effect of the substituents at the 2-position of a thiazole ring on their photophysical properties.

Thiazole is described as a ligand due to its ability to connect to several electron donor containing fragments of recognized coordination ability such as pyridyl. This modification has been used as a strategy to synthesize metal-thiazole based ligands. Intense studies onto thiazole-based ligands coordinated to the transition metal which exhibit exceptional luminescence properties have continuously grown for the last several years. The most commonly reported thiazole coordinated to transition metals showing luminescence properties are complex of ruthenium,<sup>7</sup> iridium,<sup>8</sup> and rhenium.<sup>9</sup> Recently, some thiazole-based compounds have been discovered to be able for the detection of zinc ions. The complexation of  $\text{Zn}^{2+}$  with the ligands gives a significant response to turn on emission properties<sup>10</sup> and changes the emission color.<sup>11</sup> Moreover, fluorescence sensing is considered for its fast detection time, high efficiency, and simplicity.

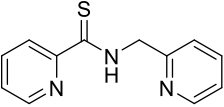
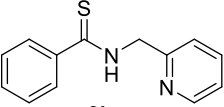
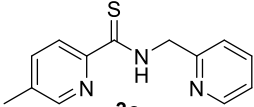
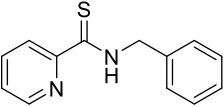


## 2.2. Results and discussion

### 2.2.1. Synthesis of secondary thioamides

The preparation of secondary thioamides started from the reaction of aromatic aldehydes **1** with elemental sulfur and benzylic amines **2**. The reaction was carried out in DMF at 80 °C for 3 h to give secondary thioamides **3**. A wide series of unprecedented secondary thioamides bearing pyridyl and/or phenyl groups were collected in moderate to high yields (Table 1).

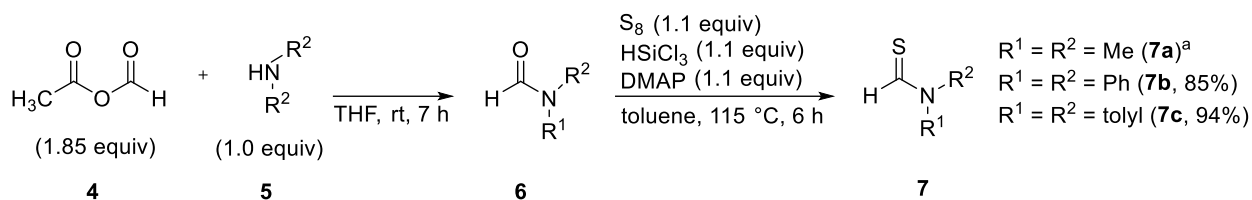
**Table 1.** Preparation of secondary thioamides<sup>a</sup>

$  \begin{array}{c} \text{O} \\ \parallel \\ \text{Ar}^1\text{C}-\text{H} \end{array} + \frac{1}{8} \text{S}_8 + \text{H}_2\text{N}-\text{CH}_2-\text{Ar}^2 \xrightarrow[\text{DMF, 80 } ^\circ\text{C, 3h}]{-\text{H}_2\text{O}} \begin{array}{c} \text{S} \\ \parallel \\ \text{Ar}^1\text{C}-\text{NH}-\text{CH}_2-\text{Ar}^2 \end{array}  $				
entry	1	2	product	yield(%) <sup>b</sup>
1	Ar <sup>1</sup> = 2-pyridyl <b>1a</b>	Ar <sup>2</sup> = 2-pyridyl <b>2a</b>	 <b>3a</b>	78
2	Ar <sup>1</sup> = Ph <b>1b</b>		 <b>3b</b>	64
4	Ar <sup>1</sup> = 3-methyl pyridyl <b>1c</b>		 <b>3c</b>	64
5	Ar <sup>1</sup> = 2-pyridyl <b>1d</b>	Ar <sup>2</sup> = Ph <b>2b</b>	 <b>3d</b>	86

<sup>a</sup> The reaction was carried out as follows, unless otherwise noted: To a solution of aromatic aldehydes **1** (1.0 equiv) was added elemental sulfur (1.1 equiv) in dimethylformamide (5 mL), and the mixture was stirred. To this was added benzylic amines (1.1 equiv) **2** (1.3 equiv), and the mixture was stirred.<sup>b</sup> Isolated yield.

### 2.2.4. Synthesis of thioformamides

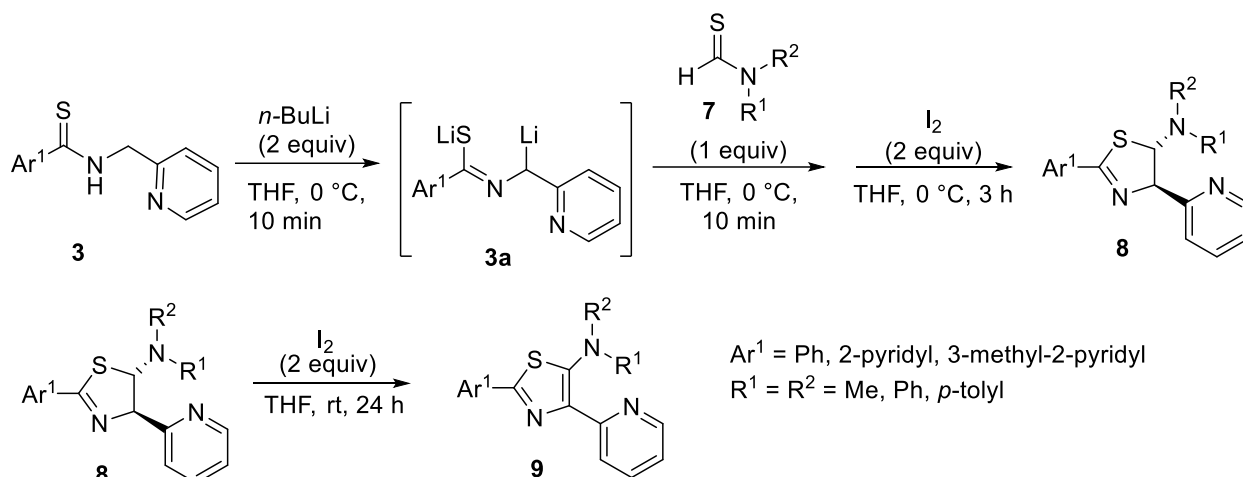
Thioformamides were prepared by amination reactions of formic acetic acid anhydride **4** with diarylamines **5** to give formamides **6** (Scheme 1). Further reaction of **6** with elemental sulfur and trichlorosilane in the presence of DMAP gave thioformamides **7**.



**Scheme 1.** Preparation of thioformamides, <sup>a</sup> Purchased from a chemical company.

### 2.2.3 Synthesis of 5-aminothiazolines and 5-aminothiazoles

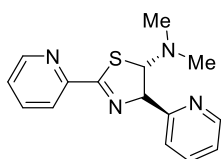
The synthesis of 5-aminothiazole derivatives was conducted by reacting secondary thioamides **3** with thioformamides **7** at low temperature to give thiazolines **8** (Scheme 2). Initially, thioamides **3** were treated with *n*-butyllithium at low temperature to generate thioamide dianions **3a**. Addition of thioformamides **7** followed by iodine to the reaction mixture afforded thiazolines **8** (Table 2). Further oxidation of thiazolines **8** with 2 equivalents of iodine gave the desired 5-aminothiazoles **9**.



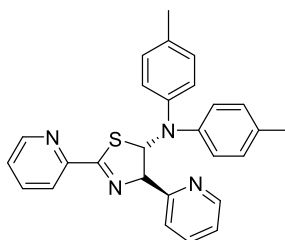
**Scheme 2.** Preparation of thiazolines and thiazoles.

**Table 2.** A series of isolated thiazolines<sup>a</sup>

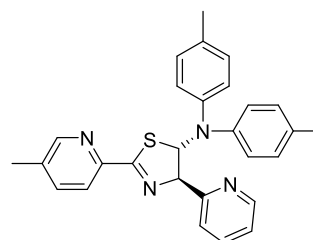
5-aminothiazolines



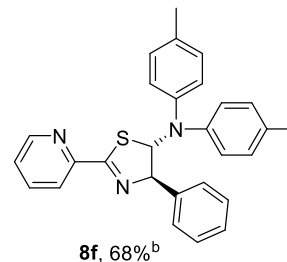
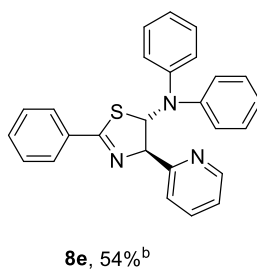
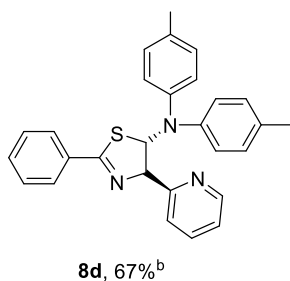
**8a**, not isolated<sup>c</sup>



**8b**, 46%<sup>b</sup>



**8c**, 95%<sup>b</sup>



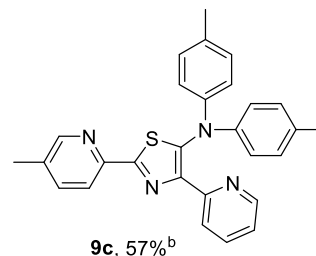
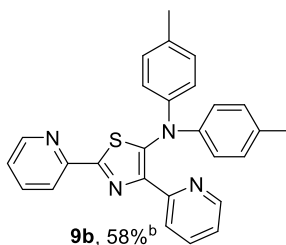
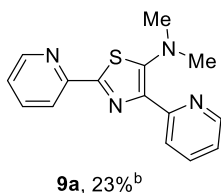
<sup>a</sup> The reaction was carried out as follows, unless otherwise noted: To a solution of thioamide **3** (1.0 equiv) in THF (3 mL) was slowly added *n*-BuLi (2.0 equiv), and the mixture was stirred. To this was added thioformamide **7** (1.0 equiv), and the mixture was stirred. To this was added iodine (2.0 equiv), and the mixture was stirred. <sup>b</sup> Isolated yield. <sup>c</sup> The reaction of directly converted to **9a** in 23% yield.

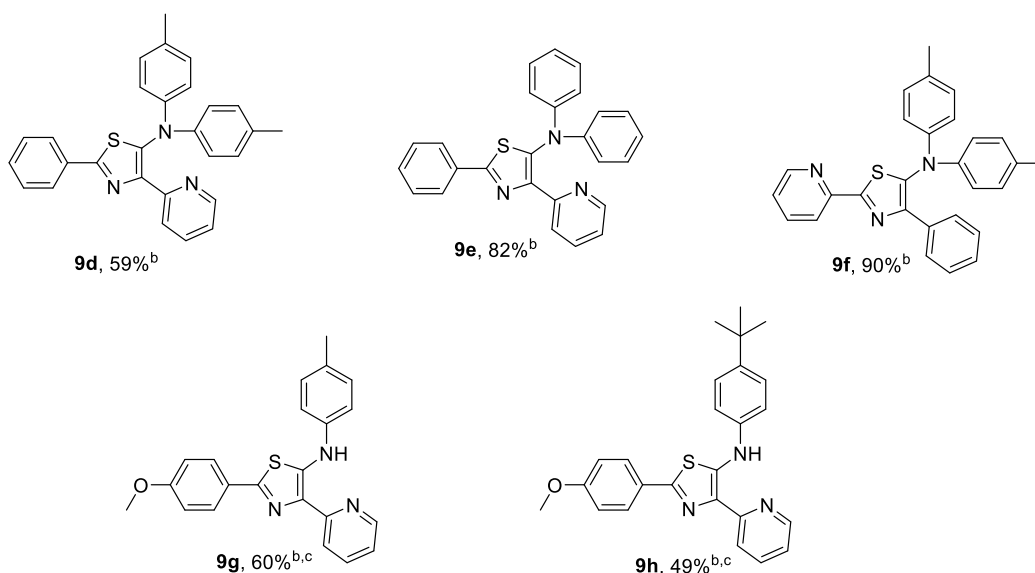
An identical reaction enabled me to provide a wide range of substituents attached at the 2-, 4- and 5-positions of the thiazole ring. As a result, the introduction of pyridyl groups at the 2- and 4-positions gave **9a** in 23% yield. Replacement of a methyl group with other functional groups at the 5-position of thiazole ring led to the increase of the product yields. Incorporation of a tolyl group significantly improved the product yield in 58% (**9b**). In addition, introducing a methyl group at para position of pyridyl moiety gave **9c** in 57%. Furthermore, incorporating pyridyl groups only to the 2- or 4- positions of thiazole ring afforded thiazole products **9d**, **9e**, and **9f** in 59%, 82% and 90% yields, respectively (Table 3).

In addition, I also synthesized different types of 5-aminothiazole derivatives **9g** and **9h**. These compounds were synthesized via bromination of 5-H **1'** thiazole to give **2'** followed by Buchwald-Hartwig amination reaction to give **9g** and **9a** in 60% and 25% yield, respectively (Scheme 3). The detail of synthesis procedures of 5-H thiazoles, bromination and the amination reaction are discussed later in the Chapter 3 and 4.

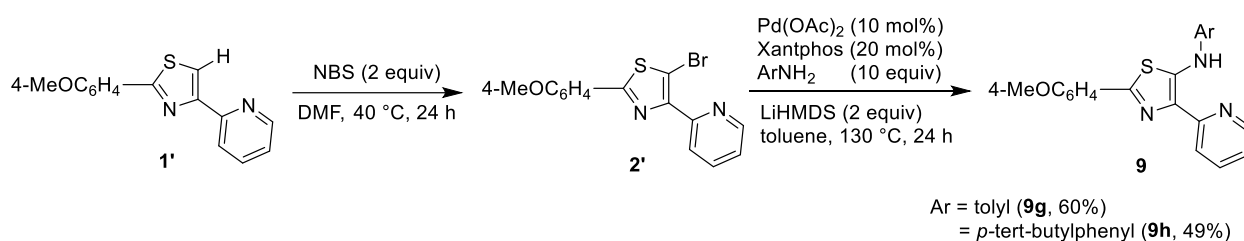
**Table 3.** A series of isolated 5-aminothiazole derivatives having pyridyl groups<sup>a</sup>

5-aminothiazoles





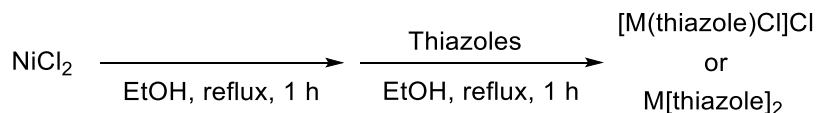
<sup>a</sup> The reaction was carried out as follows, unless otherwise noted: To a solution of thiazoline **8** (1.0 equiv) in THF (3 mL) was added iodine (2.0 equiv), and the mixture was stirred. <sup>b</sup> Isolated yield. <sup>c</sup> The reaction was carried out by reacting 5-bromothiazoles (1.0 equiv) and amines (10.0 equiv) in the presence of Pd(OAc)<sub>2</sub> (10 mmol%), Xantphos (20 mmol%), and LiHMDS (2.0 equiv) in toluene as a solvent at 130 °C for 24 h.



**Scheme 3.** Synthesis of thiazole **9g** and **9h**.

## 2.2.4. Synthesis of first-row transition metal complexes

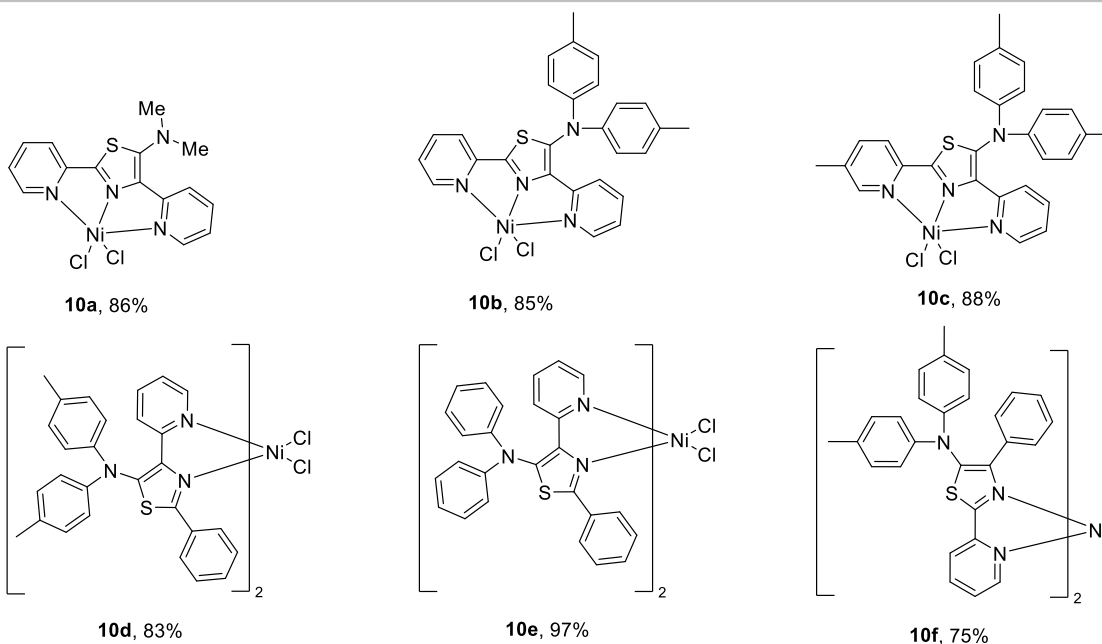
A series of thiazole-based ligand metal complexes were prepared following the procedure as depicted in Table 4.<sup>12</sup> The preparation of complexes was performed in two steps; (i) refluxing metal source, in ethanol under inert atmosphere, (ii) synthesis of the desired final product by reacting the corresponding ligand **9** with refluxed metal sources (Scheme 4).



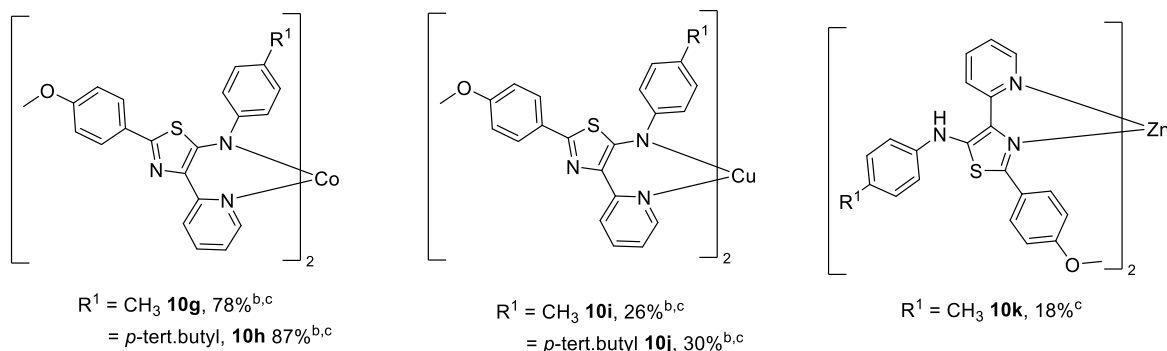
**Scheme 4.** Preparation of metal-thiazole complexes.

**Table 4.** Preparation of first-row transition metal-thiazole complexes complexes<sup>a</sup>.

**Nickel-thiazole complexes**



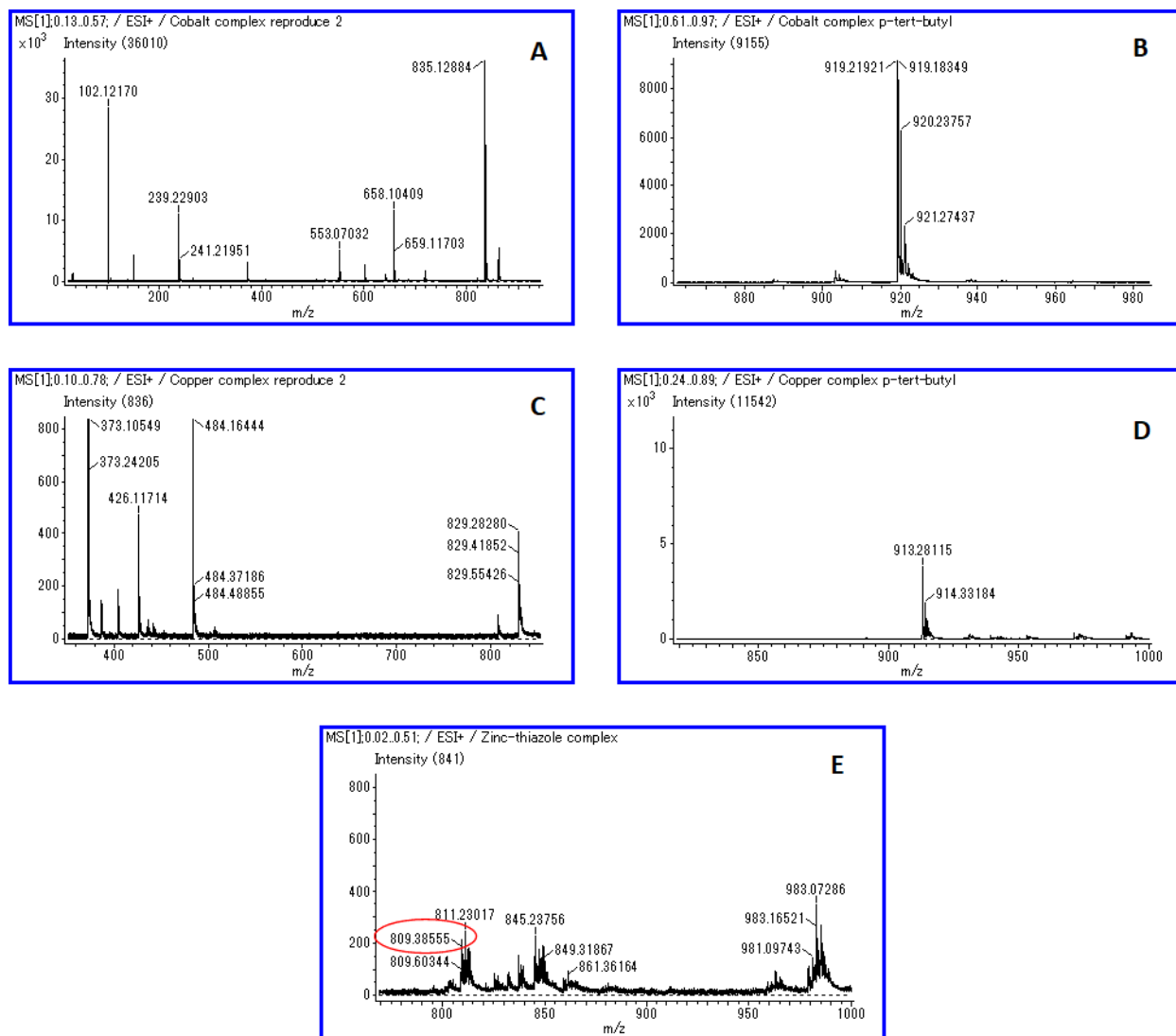
**Cobalt, copper and zinc-thiazole complexes**



<sup>a</sup> The reaction was carried out as follows, unless otherwise noted: Solution of  $\text{MX}_2 \cdot x \text{H}_2\text{O}$  (1.0 equiv) in ethanol (7 mL) was stirred at reflux. To this was added thiazole **10** (1.0 equiv) in THF or ethanol (5 mL), and the mixture was stirred at reflux for another 1 h. <sup>b</sup>  $\text{MX}_2$  (0.5 equiv),  $\text{NEt}_3$  (2.0 equiv), in dichloromethane as a solvent and at room temperature for 24 h. <sup>c</sup> Run in 0.2 mmol scale,  $\text{MX}_2$  (0.5 equiv). Percentages represent isolated yields.

As a result, all metal complexes were isolated from low to high yields. Most of them showed limited solubility in many organic solvents. To our delight, nickel complexes **10d**, and **10f** exhibited better solubility than the other complexes. Additionally, I also carried out the reaction which may lead to a series of other first-row transition metal-complexes (**10g-k**). The reaction was performed in dichloromethane as a solvent in the presence of triethylamine as a base at room temperature for 24 hours to give thiazole-complex adducts from low to good yields. Most of the isolated complexes suffered from poor solubilities. In contrast, copper-thiazole complexes adduct **10i** and **10j** showed good solubility in organic solvents.

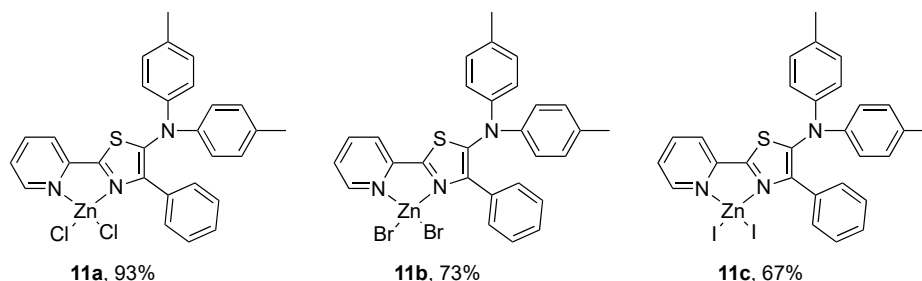
Moreover, the predicted formations of the complexes were supported by ESI mass data analyses (Figure 1). The results showed that Methanol might include the formation of cobalt complex **10g** and **10h**. While the formation of copper complexes **10i** and **10j** was found together with Na in a matrix. Furthermore, the mass number of zinc complexes **10k** was found to be in accordance with the prediction's formation. Although other impurities may still include in the isolated complex. However, at the present stage, the formation of those isolated complexes is still ambiguous.



**Figure 1.** ESI mass spectra for a series of metal-thiazole complexes; (A) **10g**, (B) **10h**, (C) **10i**, (D) **10j**, and (E) **10k**.

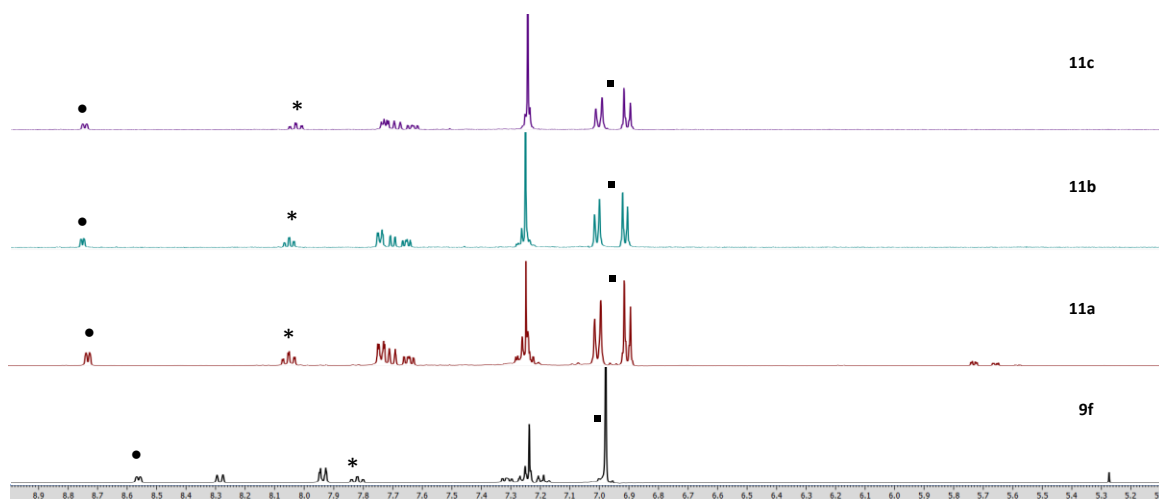
### 2.2.5. Synthesis of zinc thiazole complexes

Having succeeded with the synthesis of nickel, cobalt, copper, and zinc complexes, I then turned my attention to the synthesis of zinc thiazole complexes having different counter anions **11a-11c**. The synthesis of these complexes was simply mixing 0.15 mmol of the thiazole ligand **9f** with zinc halides at room temperature in THF as a solvent for 24 h. Following this procedure, a series of zinc complexes were successfully synthesized in moderate to high yield (Figure 2).



**Figure 2.** A series of zinc thiazole complexes.

Solutions of zinc complexes in deuterated chloroform were prepared for NMR analyses (Figure 3). With the addition of 1 equivalent zinc ion, the signal of proton of the thiazole ligand at 8.57 ppm and 7.83 ppm shifted to downfield at 8.75 ppm and 8.04 ppm, respectively. Furthermore, in the formation of zinc complexes, two new doublet peaks integrated for 8 protons assigned to phenyl rings in the tolyl groups appeared at 7.00 ppm and 6.90 ppm, respectively. However, the proton signal and chemical shift of the complexes are almost identical despite having different counter anions at the zinc center. These results indicate that the formation of a zinc thiazole complex is formed on the addition of zinc halides.

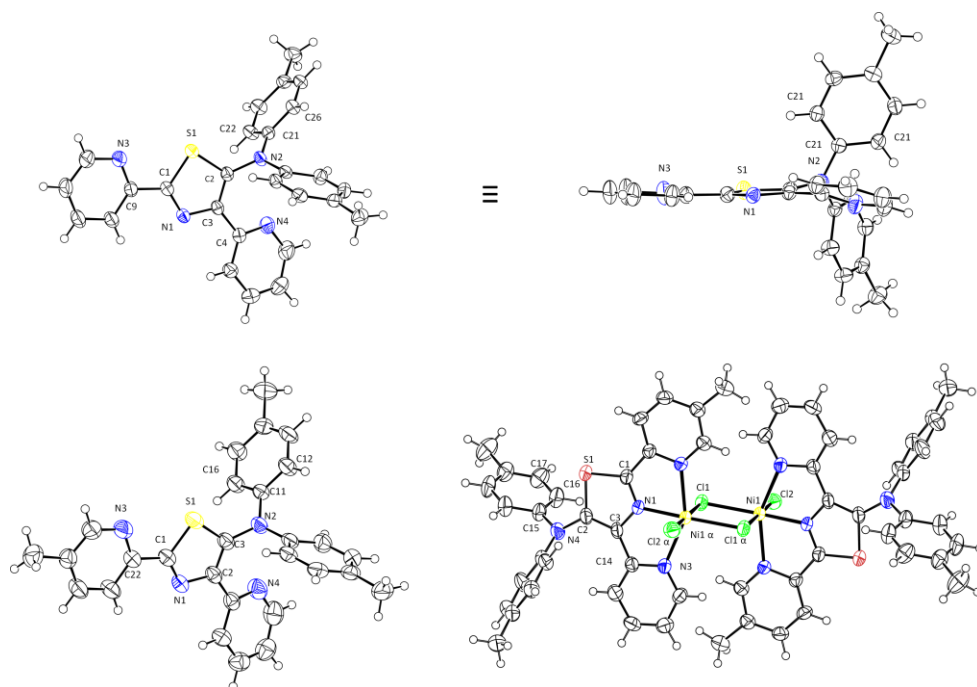


**Figure 3.** <sup>1</sup>H NMR spectra of thiazole ligand and its zinc thiazole complexes.

## 2.2.6. Molecular structure

High-quality single crystals of thiazoles **9b** and **9c** were grown by slow diffusion of dichloromethane in hexane and isolated in the triclinic space group  $P\bar{1}$  as a green crystal (Figure 4). X-ray crystallography analysis for 5-aminothiazole derivatives **9b** and **9c** confirmed the twisted conformation geometry of amino groups at the 5-position of a thiazole ring with torsion angles  $150.89^\circ$  (C2-N2-C21-C26) and  $147.84^\circ$  (C3-N2-C11-C12), respectively.

On the other hand, green crystal suitable for X-ray crystallography analysis of **10c** was cultivated from methanol in acetone at room temperature. The crystal structure showed the formation of dinuclear nickel complexes with trans configuration in a distorted octahedral geometry (Figure 4). Two bridging Cl atoms connect two central nickel atoms between two dimers with a distance of  $3.602 \text{ \AA}$  between Ni1 $\alpha$ -Ni1. The distance of bridging Ni1 $\alpha$ -Cl1 was  $2.600 \text{ \AA}$ , longer than that of Ni1 $\alpha$ -Cl1 with  $2.363 \text{ \AA}$ . The atoms Cl2 $\alpha$ -Ni1 $\alpha$ -Cl1 were almost linearly oriented with a bond angle of  $177.55(4)^\circ$ , while the atoms Cl2-Ni1-N2 was almost perpendicularly oriented with a bond angle of  $89.15^\circ$ . In addition, the angle of Cl2 $\alpha$ -Ni1 $\alpha$ -N1 was found to be  $92.52^\circ$ . Interestingly, the amino groups in complex **10c** (C2-N4-C15-C20) were more twisted compared to the free ligand **9c** with torsion angle of  $154.48^\circ$ . Moreover, the distance of Ni1 $\alpha$ -N1 (thiazole ring) and Ni1 $\alpha$ -N3 (pyridyl group) was found to be  $1.970$  and  $2.198 \text{ \AA}$ , respectively.



**Figure 4.** X-ray crystal structure of **9b** (upper left), side view of **9b** (upper right), **9c** (bottom left), and nickel-complex **10c** (bottom right).



**Table 5.** Crystal data and structure refinement for **9b**

Chemical formula	C <sub>27</sub> H <sub>22</sub> N <sub>4</sub> S
$M_r$	434.54
Crystal system, space group	Triclinic, $P\bar{1}$
Temperature (K)	293
$a, b, c$ (Å)	9.2820 (1), 11.5556 (2), 11.6974 (2)
$\alpha, \beta, \gamma$ (°)	64.5605 (19), 80.9699 (13), 88.7167 (15)
$V$ (Å <sup>3</sup> )	1117.53 (3)
$Z$	2
Radiation type	Mo $K\alpha$
$\mu$ (mm <sup>-1</sup> )	0.17
Crystal size (mm)	0.43 × 0.43 × 0.30
Absorption correction	Numerical
$T_{\min}, T_{\max}$	0.877, 0.925
No. of measured, independent and observed [ $I > 2\sigma(I)$ ] reflections	9850, 5010, 4591
$R_{\text{int}}$	0.016
$(\sin \theta/\lambda)_{\text{max}}$ (Å <sup>-1</sup> )	0.650
$R[F^2 > 2\sigma(F^2)], wR(F^2), S$	0.039, 0.120, 1.06
No. of reflections	5010
No. of parameters	291
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{\text{max}}, \Delta\rho_{\text{min}}$ (e Å <sup>-3</sup> )	0.28, -0.23

**Table 6.** Crystal data and structure refinement for **9c**

Chemical formula	C <sub>28</sub> H <sub>24</sub> N <sub>4</sub> S
$M_r$	448.57
Crystal system, space group	Triclinic, $P\bar{1}$
Temperature (K)	193
$a, b, c$ (Å)	9.407 (3), 11.689 (4), 12.393 (4)
$\alpha, \beta, \gamma$ (°)	115.971 (4), 102.307 (2), 91.501 (2)
$V$ (Å <sup>3</sup> )	1185.8 (7)
$Z$	2
Radiation type	Mo $K\alpha$
$\mu$ (mm <sup>-1</sup> )	0.16
Crystal size (mm)	0.43 × 0.37 × 0.34
Absorption correction	Numerical
$T_{\min}, T_{\max}$	0.872, 0.921
No. of measured, independent and observed [ $I > 2\sigma(I)$ ] reflections	10688, 5374, 3854
$R_{\text{int}}$	0.027
$(\sin \theta/\lambda)_{\text{max}}$ (Å <sup>-1</sup> )	0.650
$R[F^2 > 2\sigma(F^2)],$ $wR(F^2), S$	0.047, 0.135, 0.97
No. of reflections	5374
No. of parameters	301
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{\text{max}}, \Delta\rho_{\text{min}}$ (e Å <sup>-3</sup> )	0.25, -0.32

**Table 7.** Crystal data and structure refinement for **10c**

Chemical formula	C <sub>28</sub> H <sub>24</sub> Cl <sub>2</sub> N <sub>4</sub> NiS
$M_r$	578.18
Crystal system, space group	Monoclinic, $P2_1/n$
Temperature (K)	293
$a, b, c$ (Å)	15.9050 (11), 8.6642 (4), 20.5670 (9)
$\beta$ (°)	107.528 (6)
$V$ (Å <sup>3</sup> )	2702.6 (3)
$Z$	4
Radiation type	Mo $K\alpha$
$\mu$ (mm <sup>-1</sup> )	1.02
Crystal size (mm)	0.17 × 0.11 × 0.11
Absorption correction	Numerical
$T_{\min}, T_{\max}$	0.843, 0.918
No. of measured, independent and observed [ $I > 2\sigma(I)$ ] reflections	23061, 6205, 4449
$R_{\text{int}}$	0.102
$(\sin \theta/\lambda)_{\text{max}}$ (Å <sup>-1</sup> )	0.650
$R[F^2 > 2\sigma(F^2)],$ $wR(F^2), S$	0.065, 0.200, 1.06
No. of reflections	6205
No. of parameters	328
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{\text{max}}, \Delta\rho_{\text{min}}$ (e Å <sup>-3</sup> )	1.42, -0.84

### 2.2.7. Photophysical properties of 5-aminothiazole derivatives and their metal complexes

The absorption spectra of isolated 5-aminothiazole derivatives in chloroform are shown in Figure 5. The absorption maxima are ranging from 349 to 398 nm. That of thiazole **9a** was in the shortest absorption region, and it gradually shifted to the longer wavelengths by introducing a tolyl group at the amino site such as **9b**. Interestingly, the incorporation of a methyl group at the para position of a pyridyl group slightly shifted the absorption maxima to the shorter wavelength such as **9c**. Further blue-shift absorption was observed by replacing a tolyl group with a phenyl group at the 2-position of the thiazole ring of **9d**. In addition, on placing of a phenyl group at the 2-position and amino site of thiazole ring for **9e** shifted the absorption maxima to 374 nm. While the introduction of a phenyl group at the 4-position of thiazole ring for **9f** shifted the absorption maxima to 396 nm. Furthermore, the absorption maxima of **9g** and **9h** was observed at 371 and 372 nm, respectively.

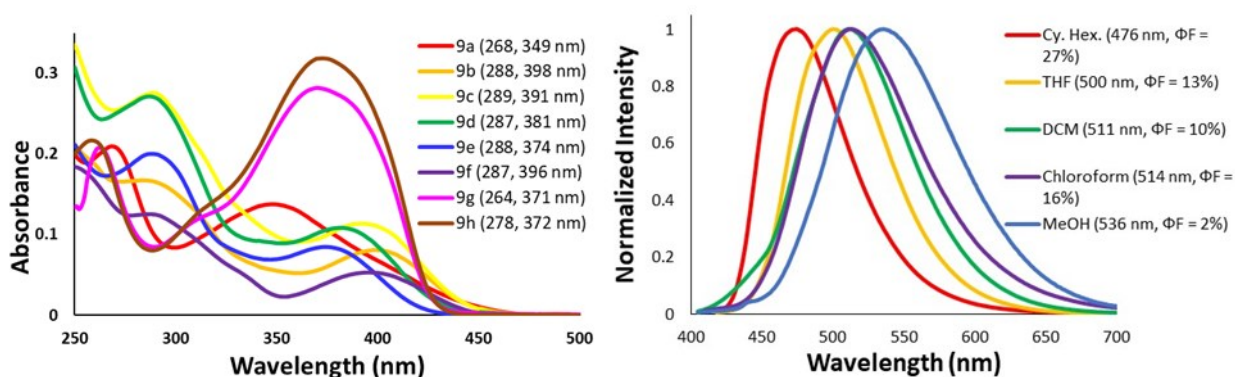
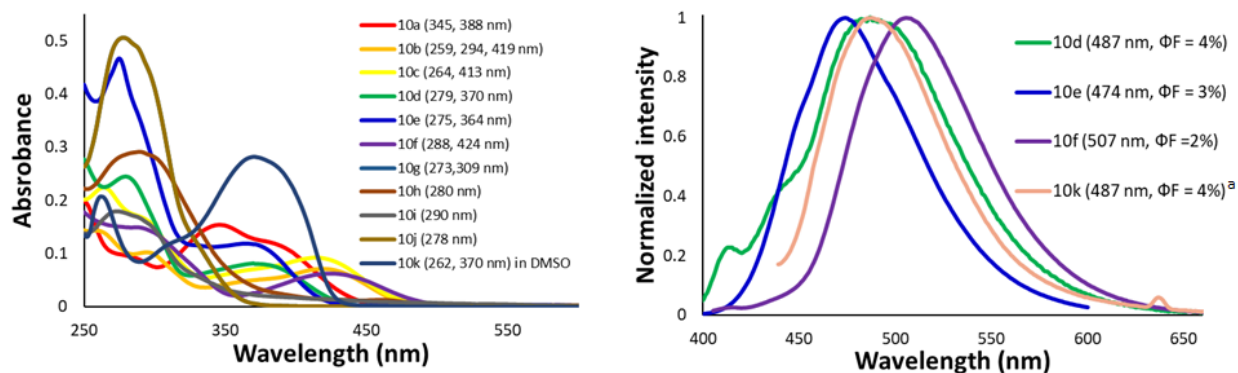


Figure 5. Absorption spectra for 5-aminothiazole derivatives in chloroform (left) and emission spectra of **9c** (right).

Furthermore, the emission color of the isolated 5-aminothiazoles were observed to vary in solution polarity and exhibit a tunable emission wavelength in the range of 432-563 nm. The emission maxima of **9c** showed great dependencies on solvent polarity, thus their peak emissions were greatly affected. Large red shifts in emission maxima (Figure 5) were observed from nonpolar (cyclohexane) to polar (MeOH) solvent and cover blue to green color. Interestingly, the emission color was also affected by the substituent attached at the thiazole ring.

The photophysical properties of thiazole complexes were also investigated. The absorption spectra in chloroform were recorded as shown in Figure 6. The longest absorption spectra were observed spanning from 278 to 424 nm. The absorption maxima of **10a** were observed at 388 nm and significantly red shifted for the thiazole complex having a tolyl group at amino site such as **10b**. The presence of methyl group at the para position of the pyridyl group slightly shifted the absorption maxima to the shorter

wavelength of **10c**. For **10d** the absorption maxima were blue shifted to 370 nm by introducing a phenyl substituent at the 2-position of thiazole ring. Meanwhile, replacing a tolyl group to a phenyl group at the 2-position of thiazole ring and amino site shifted the absorption maxima to 364 nm such as **10e**. Moreover, nickel-thiazole complex having a phenyl substituent at the 4-position instead of pyridyl and tolyl groups at the amino site **10f** was observed at 424 nm. Furthermore, the absorption of cobalt, copper, and zinc complexes **10g-k** adducts were observed spanning from 262 nm to 309 nm.



**Figure 6.** Absorption spectra of metal-thiazole complexes (left) and emission spectra for complex **10d**, **10e**, **10f** and **10k** in chloroform (right). <sup>a</sup> Emission in solid state.

In addition, the formation of nickel complex turned the emission properties off such as in **10a**, **10b** and **10c**. There was no emission observed neither in a solid state nor solution states. In contrast, the coordination formation had no effect to the emission of **10d**, **10e** and **10f**. Even though the emission properties shut down in the solid states, but it is still emissive in a solution to some extent under UV illumination. In the case of copper and copper complex adducts no emission was observed neither in a solid state nor solution states. Interestingly, zinc complex adducts **10k** showed bright green emission in a solid state (Figure 7). The details of the photophysical properties of the complexes are shown in Table 8.

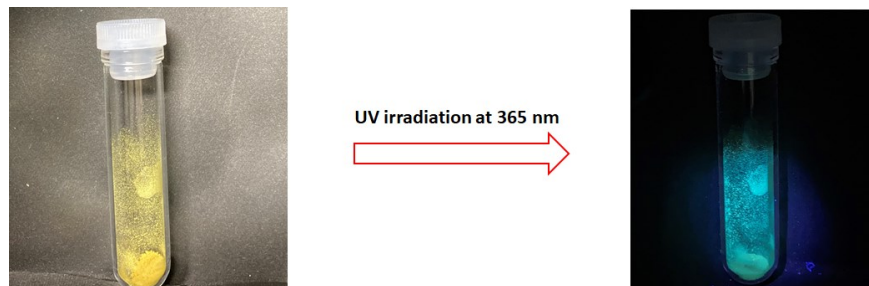
**Table 8.** UV-visible spectra of 5-aminothiazole derivatives and their complexes

Thiazole ( <b>9</b> ) / Complex ( <b>10</b> )	UV-Vis		
	$\lambda_{\text{abs}}$ (nm) <sup>a</sup>	$\lambda_{\text{em}}$	$\Phi_F$
<b>9a</b> / <b>10a</b> <sup>b</sup>	349 / 388	467 / non-emissive	0.04 / non-emissive
<b>9b</b> / <b>10b</b>	398 / 419	525 / non-emissive	0.13 / non-emissive
<b>9c</b> / <b>10c</b>	391 / 413	514 / non-emissive	0.16 / non-emissive
<b>9d</b> / <b>10d</b>	381 / 370	486 / 487	0.20 / 0.04
<b>9e</b> / <b>10e</b>	374 / 364	476 / 474	0.31 / 0.03
<b>9f</b> / <b>10f</b>	396 / 424	505 / 505	0.42 / 0.02
<b>9g</b> / <b>10g</b>	371 / 309	non-emissive	non-emissive
<b>9g</b> / <b>10h</b>	371 / 280	non-emissive	non-emissive

<b>9h / 10i</b>	372 (432) <sup>d</sup> / 290	non-emissive (weak emission) <sup>d</sup> / non-emissive	(weak emission) <sup>d</sup> / non-emissive
<b>9h / 10j</b>	372 (432) <sup>d</sup> / 278	non-emissive (weak emission) <sup>d</sup> / non-emissive	(weak emission) <sup>d</sup> / non-emissive
<b>9g / 10k<sup>c</sup></b>	371 / 372 (440) <sup>d</sup>	non-emissive / non-emissive (487) <sup>d</sup>	non-emissive / (0.04) <sup>d</sup>

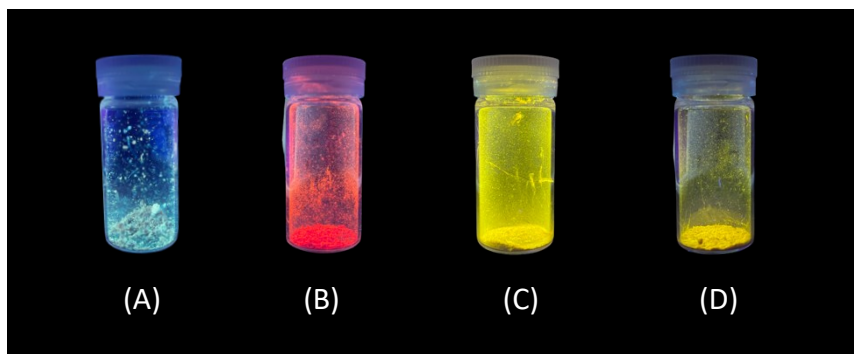
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<sup>a</sup> In CHCl<sub>3</sub>, [solute] = 1 x 10<sup>-5</sup> M,      <sup>b</sup> Measured in MeOH, [solute] = 1 x 10<sup>-5</sup> M      <sup>c</sup> Measured in DMSO      <sup>d</sup> Solid state



**Figure 7.** Complex **10k** in day light (left) and under UV-radiation (right).

The photophysical properties of a series of zinc-thiazole complexes were investigated in both solutions and solid states (Table 9). The absorption maxima of zinc complexes **11a-c** in THF were observed at 390 nm in all cases. Nevertheless, zinc thiazole having iodide as counter anion **11c** slightly blue shifted at 384 nm. Similarly, their emission maxima showed no significant change even I introduced different counter anions on the zinc center. In contrast, the absorption and emission maxima in solid state showed significant difference compared to its free ligands. The longest absorption maxima were spanning from 440 nm to 452 nm. While their emission maxima were varied depend on the counter anions on the zinc center. Zinc thiazole complex having chloride atoms attached at the zinc center showed significant red shifted at 611 nm compared to its free ligands at 475 nm. Furthermore, the introduction of bromide and iodide atoms to the zinc center shifted the emission maxima to a shorter emission wavelength at 550 nm and 548 nm, respectively. Moreover, the quantum yield of the complexes dropped significantly in the solid state. However, the difference in emission color under UV irradiation at 365 nm was still easily visible to the naked eye (Figure 8).



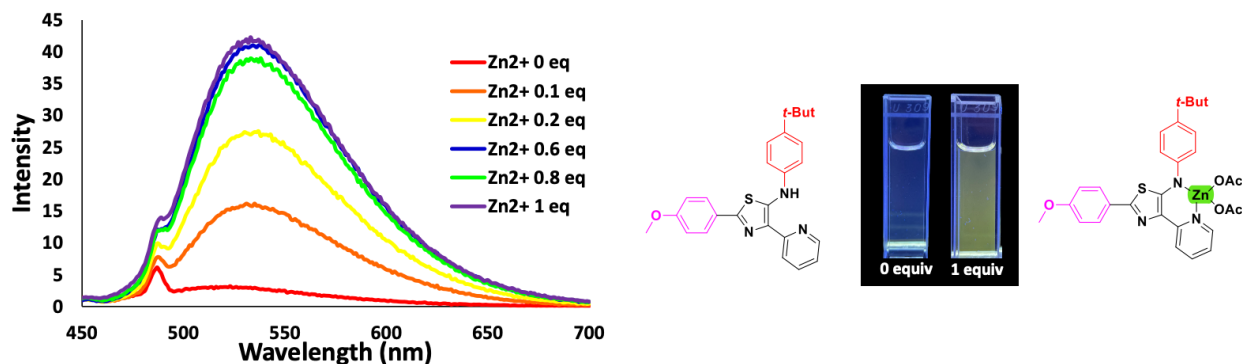
**Figure 8.** solid state emission of (A) thiazole ligand **9f**, (B) complex **11a**, (C) **11b**, and (D) **11c** under UV radiation at 365 nm.

**Table 9.** Spectroscopic data of thiazole ligand and zinc thiazole complexes in solutions and in a solid state.

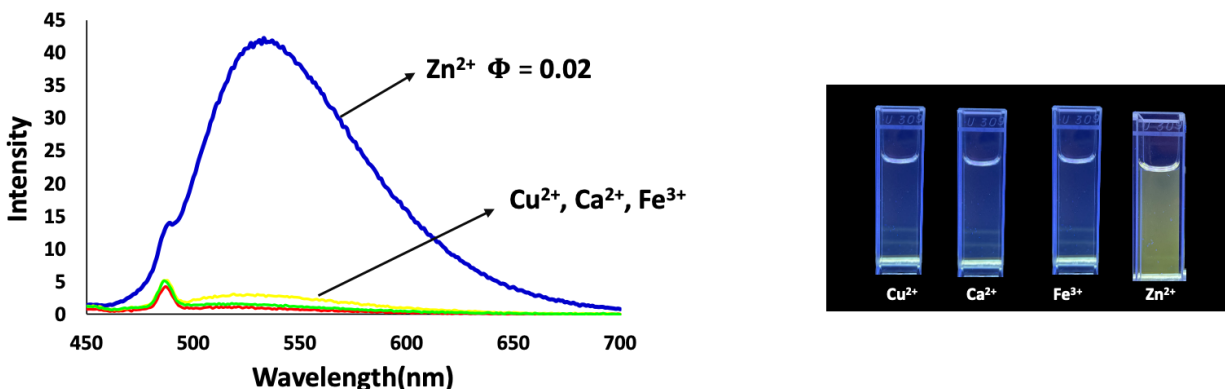
Thiazole	$\lambda_{\text{abs}}$ (nm)	$\log \varepsilon$	$\lambda_{\text{ex}}$ (nm)	$\lambda_{\text{em}}$ (nm) <sup>a</sup>	$\nu_{\text{ss}}$ [cm <sup>-1</sup> ] (nm)	$\Phi_{\text{F}}$
<b>ligand 9f</b>	280 390	3.92	385	495	[5504] (105)	0.46
<b>11a</b>	282 390	3.64	384	497	[5520] (107)	0.44
<b>11b</b>	284 390	4.10	384	495	[5504] (105)	0.75
<b>11c</b>	288 384	4.22	386	494	[5798] (110)	0.43
<b>ligand 9f<sup>b</sup></b>	451	-	370	475	[1120] (24)	0.52
<b>11a<sup>b</sup></b>	440	-	365	611	[6360] (171)	0.02
<b>11b<sup>b</sup></b>	440	-	380	550	[4545] (110)	0.05
<b>11c<sup>b</sup></b>	452	-	492	548	[3875] (123)	0.02
Measured in THF    C = 10 <sup>-5</sup> M <sup>a</sup> Excited in $\lambda_{\text{max}}$ <sup>b</sup> Solid state						

### 2.2.8. Sensing of Zn<sup>2+</sup> with 5-aminothiazoles

The investigation of 5-aminothiazole as fluorescence sensing was started by titrating various cations such as Cu<sup>2+</sup>, Ca<sup>2+</sup>, Fe<sup>3+</sup>, and Zn<sup>2+</sup> into a THF solution of ligand type dipyrromethene **9h**. The results showed that compound **9h** showed a high selectivity for Zn<sup>2+</sup>. With the addition of Zn<sup>2+</sup>, the emission intensity at 533 nm continued to increase with the appearance of a green emission with a low quantum yield ( $\Phi_{\text{F}}$ ) of 0.02 under UV irradiation at 365 nm (Figure 9).

**Figure 9.** Fluorescence titration of **9h** with different amounts of zinc ions in THF solution.

In contrast, the emission properties of **9h** towards cations other than  $\text{Zn}^{2+}$  did not show any change in emission intensity even after the addition of 1 equivalent of cations (**Figure 10**). These results imply that **9h** has excellent capabilities as a candidate for  $\text{Zn}^{2+}$  fluorescence sensing.



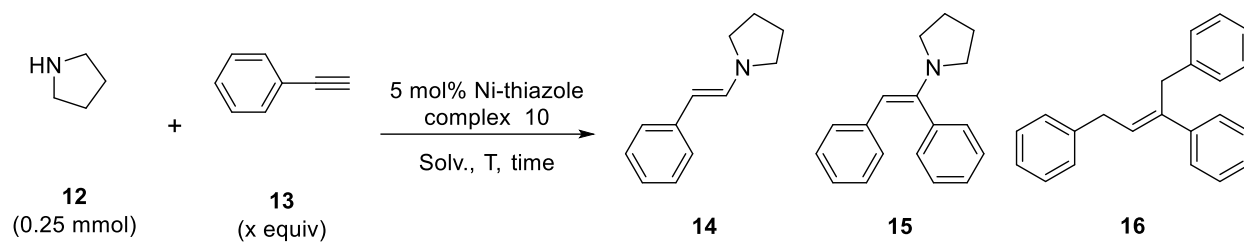
**Figure 10.** Fluorescence titration of **9h** with different cations in THF solution.

### 2.2.9. Catalytic activity of nickel-thiazole based complexes

As mentioned before, most of the nickel-thiazole complexes were poorly soluble in organic solvents and not recognized to further investigation except complexes **10d** and **10f**. To commence the evaluation of catalytic activity, I examined the hydroamination reaction of pyrrolidine **12** and ethynylbenzene **13** under various conditions (Table 10). The reaction between 0.25 mmol of **12** with 1 equivalent of **13** in the presence of the complex **10d** catalyst in tetrahydrofuran at 80 °C gave **15** as a product (entry 1). By increasing the number of equivalents of ethynylbenzene, product **16** was isolated in addition to product **15** (entry 2). Furthermore, the use of complex **10d** instead of **10e** in the reaction also gave **15** as a product (entry 3). I also screened the effect of solvent combination in the reaction, and this experiment revealed that the combination solvent between tetrahydrofuran and toluene with prolonging the reaction time gave no distinction in the final product (entry 4).



**Table 10.** Evaluation of catalytic activity of nickel-thiazole complexes in hydroamination reaction.



entry	catalyst	x (equiv)	solvent	T (°C)	time (h)	products <sup>a</sup>
1	<b>10d</b>	1	THF	80	3	<b>15</b>
2	<b>10d</b>	2	THF	80	3	<b>15,16</b>
3	<b>10e</b>	1	THF	80	3	<b>15</b>
4	<b>10e</b>	1	THF : Toluene (1:1)	115	4	<b>15</b>

<sup>a</sup> Based on GC-MS

## 2.3. Summary of Chapter 2

In summary, a series of 5 aminothiazole derivatives having pyridyl groups were successfully synthesized and systematically characterized. The absorption and emission properties of isolated 5-aminothiazoles were finely tuned by solely varying the substituents attached at the thiazoles ring and its amino site. The longest absorption spectra are spanning from 349 to 396 nm. The emission maxima for **9c** were ranging from 477 to 536 nm and were also affected by solvent polarity. The isolated 5-aminothiazoles adopts highly twisted conformation for the amino site to the thiazole ring. The properties of 5-aminothiazoles were suitable in the preparation of nickel-thiazole based complexes. The crystal structure of nickel-thiazole complex **10c** confirmed the formation of dinuclear metal complexes with atom chlorine acts as a bridge between two dimers. Additionally, the formation of cobalt, copper, and zinc complexes might be formed by simply reacting 5-aminothiazole derivatives with metal sources. However, the structure of the complexes has not been completely confirmed. In addition, thiazole compound **9h** exhibited selectivity toward zinc ions. This result implies that **9h** is applicable to fluorescence sensing for zinc ions. The catalytic activity of nickel-thiazole complex **10d** and **10f** was also screened in hydroamination reaction. However, no desired product was observed.

## 2.4. Experimental section

**General Remarks.** All reagents and solvents were purchased from commercial sources and were used without purifications.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were measured with TMS and  $\text{CDCl}_3$  as an internal standard, respectively. HRMS were recorded on a double-focusing mass spectrometer (EI). IR spectra were obtained by using I zinc complexes ATR and KBr pellets. UV-vis absorption, fluorescence and absolute quantum yields were obtained on the respective spectrometers. ESI-Mass spectra were obtained by using ESI-Mass spectrometer. Column chromatography was performed on silica gel 60N. The compounds **3a**<sup>13</sup>, **3b**<sup>14</sup>, **3d**<sup>6</sup>, **7a**<sup>15</sup>, **7b-c**<sup>6</sup>, **8e** and **9e**<sup>16</sup> were prepared according to literature procedures.

### General Procedure for the Preparation of Formamides.

To a solution of diarylamines (1 equiv) in THF was added acetic formic anhydrous (1.85 equiv) at room temperature, and the mixture was stirred for 7 h. The resulting mixture was then quenched with NaOH 1M and poured into  $\text{Et}_2\text{O}$ . The organic layer was dried over  $\text{MgSO}_4$  and concentrated in vacuo. The pure final product, white crystal, was collected after recrystallization.

### General Procedure for the Preparation of Thioformamides.

To a solution of formamides (1 equiv) in toluene (3 mL) was added elemental sulfur (1.1 equiv) and the mixture was stirred. To this was added DMAP (1.1 equiv), and the mixture was stirred. To this mixture was added  $\text{HSiCl}_3$  (1.1 equiv), and the mixture was stirred at  $115\text{ }^\circ\text{C}$  for 6 h. The resulting mixture was poured into saturated  $\text{NaHCO}_3$  and extracted with dichloromethane. The organic layer was dried over  $\text{MgSO}_4$  and concentrated in vacuo. The residue was purified by column chromatography ( $\text{SiO}_2$ ) to give the corresponding thioformamides.

### General Procedure for the Preparation of Thiazolines.

To a solution of thioamides (1 equiv) in THF was added slowly a 1.25 M solution of *n*-buthyllithium in *n*-hexane (2 equiv) at  $0\text{ }^\circ\text{C}$ , and the mixture was stirred for 10 minutes in this temperature. To this was added thioformamides (1 equiv) at  $0\text{ }^\circ\text{C}$ , and the mixture was stirred for 10 minutes at this temperature. To this was added iodine (2-3 equiv) at  $0\text{ }^\circ\text{C}$ , and the mixture was stirred for 2 h at  $0\text{ }^\circ\text{C}$ . The resulting mixture was poured into a saturated aqueous solution of  $\text{Na}_2\text{S}_2\text{O}_3$  and extracted with  $\text{Et}_2\text{O}$ . The organic layer was dried over  $\text{MgSO}_4$  and concentrated in vacuo. The residue was purified by column chromatography ( $\text{SiO}_2$ ) to give the corresponding thiazolines.

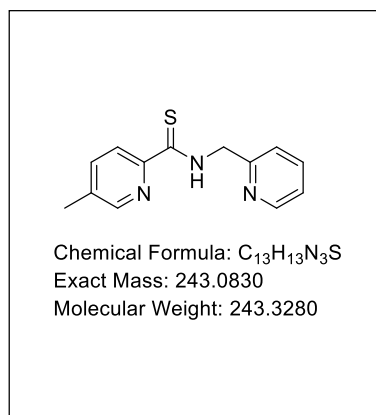
### General Procedure for the Preparation of Thiazoles.

To a solution of thiazolines (1 equiv) in THF was added iodine (2 equiv) at room temperature, and the mixture was stirred for 24 h. The resulting mixture was poured into a saturated aqueous solution of  $\text{Na}_2\text{S}_2\text{O}_3$  and extracted with  $\text{Et}_2\text{O}$ . The organic layer was dried over  $\text{MgSO}_4$  and concentrated in vacuo. The residue was purified by column chromatography ( $\text{SiO}_2$ ) to give the corresponding thiazoles.

### General Procedure for the Preparation of Nickel-Thiazole Complexes.

$\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$  (1 equiv) in 10 mL ethanol ( $\text{EtOH}$ ) was heated to reflux for 1 h. Thiazole solution (1 equiv) in 5 mL of THF or  $\text{EtOH}$  was added dropwise to the refluxing solution and further refluxed for another 1 h. The hot mixture was filtered over celite and concentrated in vacuo. The final product, solid participate, was collected by filtration, and followed several washes with ethanol.

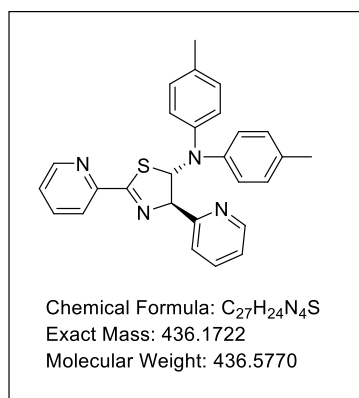
### 5-Methyl-N-(pyridin-2-ylmethyl)pyridine-2-carbothioamide (3c)



To a solution 5-methylpicolinaldehyde (0.363, 3.0 mmol) in DMF (4.0 mL) was added elemental sulfur (0.105 g, 3.3 mmol) at room temperature. To this was added 2-picolylamine (0.4 mL, 3.9 mmol) and stirred for 3 h at 80 °C. The mixture was cooled to room temperature. The combined organic phase as washed with brine and extracted with Et<sub>2</sub>O. The organic layer was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The crude material as purified by column chromatography (SiO<sub>2</sub>, hexane/EtOAc = 2:1) to give secondary

thioamide **3c** (0.15 g, 64%) as a yellow solid (mp 73-74°C): IR (KBr) 3262, 1594, 1571, 1519, 1435, 1321, 1280, 1213 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.39 (s, 3H), 5.17 (d, *J* = 4.1 Hz, 2H), 7.25-7.28 (m, 2H), 7.39 (d, *J* = 2.8 Hz, 1H), 7.60 (dd, 1H), 7.71 (m, 1H), 8.37 (d, *J* = 2.3 Hz, 1H), 8.58 (d, *J* = 8.2 Hz, 1H), 8.64 (d, *J* = 4.1 Hz, 1H) <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ 18.5, 50.5, 122.3, 122.7, 124.8, 126.1, 136.9, 137.2, 147.3, 149.3, 151.4, 155.0, 191.8; MS (EI) *m/z* 243(M<sup>+</sup>); HRMS (EI) calcd for C<sub>13</sub>H<sub>13</sub>N<sub>3</sub>S, 243.0830; found, 243.0836.

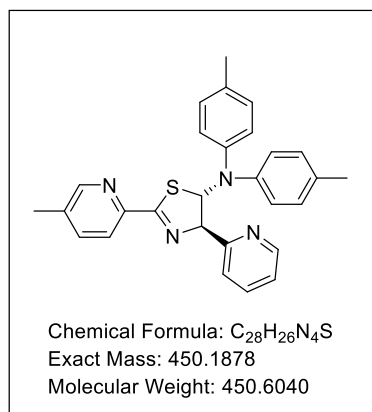
### 2,4-Di(pyridin-2-yl)-N,N-di-p-tolyl-4,5-dihydrothiazol-5-amine (8b)



To a solution of *N*-(pyridin-2-ylmethyl)pyridine-2-carbothioamide (0.344 g, 1.5 mmol) in THF (3 mL) was added slowly a 1.25 M *n*-butyllithium in hexane (2.2 mL, 3 mmol), and the mixture stirred for 10 min at 0 °C. To this mixture was added *N,N*-di-*p*-tolylmethanethioamide (0.361 g, 1.0 mmol) at 0 °C, and the mixture was stirred at this temperature for 15 min. Then, I<sub>2</sub> (0.759 g, 3 mmol) in 2 mL THF was added at 0 °C and continuously stirred at the same temperature for 3 h. The resulting mixture was poured into saturated aqueous solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and extracted with

CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was then dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO<sub>2</sub>, hexane : EtOAc = 5 : 1) to give 5-aminothiazoline **8b** (0.304 g, 46%) as a ochre yellow solid (mp: 70-72 °C); IR (KBr) 3049, 1585, 1567, 1505, 1464, 1434, 1422, 1294, 1002, 810, 781, 736 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.27 (s, 6H, Me) 6.12 (d, *J* = 4.3 Hz, 1H) 6.74 (d, *J* = 4.8 Hz, 1H) 6.97-6.99 (m, 4H) 7.04-7.05 (m, 4H) 7.21 (d, *J* = 7.7 Hz, 1H) 7.23-7.24 (m, 1H), 7.35-7.38 (m, 1H) 7.60-7.63 (m, 1H), 7.73 (t, 1H), 7.95 (d, *J* = 7.7 Hz, 1H), 8.64-8.68 (dd, 2H); <sup>13</sup>C NMR (500 MHz, CDCl<sub>3</sub>) δ 20.8, 78.7, 84.2, 121.5, 122.5, 123.6, 125.5, 129.4, 129.8, 133.0, 136.5, 136.7, 143.8, 149.3, 149.8, 151.6, 159.1, 171.8; MS (EI) *m/z* 436 (M<sup>+</sup>); HRMS (EI) calcd for C<sub>27</sub>H<sub>24</sub>N<sub>4</sub>S, 436.1722; found, 436.1690.

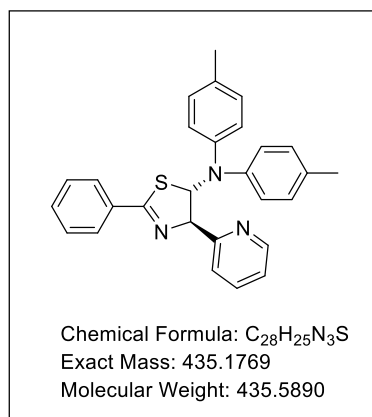
### 2-(5-Methylpyridin-2-yl)-4-(pyridin-2-yl)-N,N-di-p-tolyl-4,5-dihydrothiazol-5-amine (8c)



To a solution of 5-methyl-N-(pyridin-2-ylmethyl)pyridine-2-carbothioamide (0.088 g, 0.36 mmol) in THF (1 mL) was added slowly a 1.25 M *n*-butyllithium in hexane (0.5 mL, 0.72 mmol), and the mixture stirred for 10 min at 0 °C. To this mixture was added *N,N*-di-p-tolylmethanethioamide (0.086 g, 0.36 mmol) at 0 °C, and the mixture was stirred at this temperature for 15 min. Then, I<sub>2</sub> (0.182 g, 0.72 mmol) in 1 mL THF was added at 0 °C and continuously stirred at the same temperature for 3 h. The resulting mixture was poured into saturated

aqueous solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was then dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO<sub>2</sub>, hexane : EtOAc = 3 : 1) to give 5-aminothiazoline **8c** (0.154 g, 95%) as a ochre yellow solid (mp: 51-52 °C); IR (KBr) 3419 3082, 2916, 1609, 1588, 1517, 1470, 1319, 1001, 808, 504 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.25 (s, 6H), 2.37 (s, 3H), 6.09 (d, *J* = 4.1 Hz, 1H), 6.70 (d, *J* = 4.1 Hz, 1H), 6.91 (d, *J* = 5.5 Hz, 1H), 6.97-6.98 (m, 2H), 7.01-7.03 (m, 5H), 7.17-7.21 (m, 2H), 7.50 (d, *J* = 5.5 Hz, 1H), 7.57-7.61 (m, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 8.46-8.47 (m, 1H), 8.62 (d, *J* = 4.1 Hz, 1H); <sup>13</sup>C (400 MHz, CDCl<sub>3</sub>) δ 20.72, 117.9, 119.4, 199.9, 121.3, 122.9, 124.7, 129.8, 130.1, 134.7, 137.1, 137.3, 137.5, 141.1, 148.9, 149.2, 149.5, 149.9, 152.4; MS (EI) *m/z* 450 (M<sup>+</sup>); HRMS (EI) calcd for C<sub>28</sub>H<sub>26</sub>N<sub>4</sub>S, 450.1878; found, 450.1720.

### 2-Phenyl-4-(pyridin-2-yl)-N,N-di-p-tolyl-4,5-dihydrothiazol-5-amine (8d)

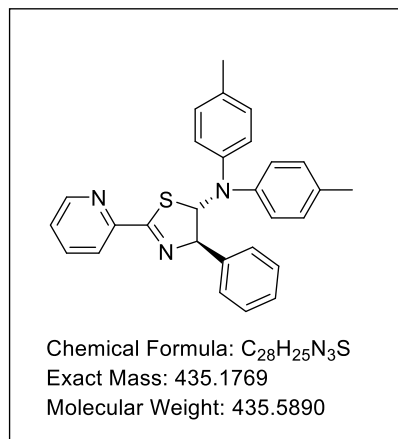


To a solution of N-(pyridin-2-ylmethyl)benzothioamide (0.230 g, 1.0 mmol) in THF (5 mL) was added slowly a 1.25 M *n*-butyllithium in hexane (1.4 mL, 2.0 mmol), and the mixture stirred for 10 min at 0 °C. To this mixture was added *N,N*-di-p-tolylmethanethioamide (0.240 g, 1 mmol) at 0 °C, and the mixture was stirred at this temperature for 15 min. Then, I<sub>2</sub> (0.5 g, 2.0 mmol) in 3 mL THF was added at 0 °C and continuously stirred at the same temperature for 3 h. The resulting mixture was poured into saturated aqueous solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and

extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was then dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO<sub>2</sub>, hexane : EtOAc = 5 : 1) to give 5-aminothiazoline **8d** (0.295 g, 67%) as a yellow solid (mp: 43-44 °C); IR (KBr) 3025, 2919, 1586, 1508, 1432, 1231, 1039, 949, 808, 765, 690, 570 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.26 (s, 6H), 6.10 (d, *J* = 3.2 Hz, 1H), 6.76 (d, *J* = 3.2 Hz, 1H), 6.95-6.98 (m, 4H), 7.03-7.05 (m, 4H), 7.17-7.22 (m, 2H), 3.75-3.79 (m, 2H), 7.43-

7.46 (m, 1H), 7.57-7.62 (td, 1H), 7.78-7.81 (m, 2H), 8.62-8.63 (m, 1H);  $^{13}\text{C}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  20.8, 79.7, 83.6, 117.9, 121.4, 122.7, 123.3, 128.4, 128.5, 129.9, 131.3, 133.2, 133.8, 136.7, 143.5, 149.6, 159.1; MS (EI)  $m/z$  435( $\text{M}^+$ ); HRMS (EI) calcd for  $\text{C}_{28}\text{H}_{25}\text{N}_4\text{S}$ , 435.1769; found, 435.1770.

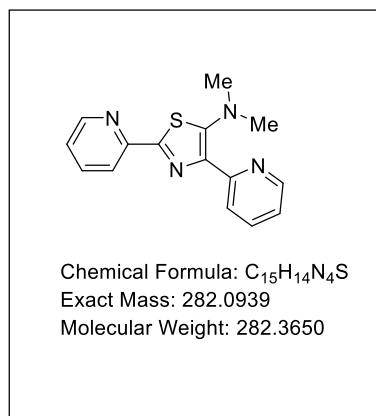
#### 4-Phenyl-2-(pyridin-2-yl)-N,N-di-p-tolyl-4,5-dihydrothiazol-5-amine (8f)



To a solution of N-benzylpyridine-2-carbothioamide (1.141 g, 5.0 mmol) in THF (5 mL) was added slowly a 1.25 M *n*-butyllithium in hexane (6 mL, 10.0 mmol), and the mixture stirred for 10 min at 0 °C. To this mixture was added *N,N*-di-*p*-tolylmethanethioamide (1.026 g, 5.0 mmol) at 0 °C, and the mixture was stirred at this temperature for 15 min. Then,  $\text{I}_2$  (2.53 g, 10.0 mmol) in 5 mL THF was added at 0 °C and continuously stirred at the same temperature for 3 h. The resulting mixture was poured into saturated aqueous solution of  $\text{Na}_2\text{S}_2\text{O}_3$  and extracted with  $\text{CH}_2\text{Cl}_2$ . The organic layer was then dried

over  $\text{MgSO}_4$  and concentrated *in vacuo*. The residue was purified by flash column chromatography ( $\text{SiO}_2$ , hexane : EtOAc = 10 : 1) to give 5-aminothiazoline **8f** (1.482 g, 68%) as a yellow solid (mp: 50-51 °C); IR (KBr) 3421, 2920, 1604, 1508, 1240, 1033, 964, 788, 730, 574  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.26 (s, 6H), 5.99 (d,  $J$  = 4.6 Hz, 1H), 6.29 (d,  $J$  = 4.6 Hz, 1H), 6.87 (d,  $J$  = 4.1 Hz, 1H), 6.95-6.97 (m, 3H), 7.05 (d,  $J$  = 8.2 Hz, 4H), 7.27-7.28 (m, 1H), 7.34 (d,  $J$  = 4.1 Hz, 4H), 3.37-3.39 (m, 1H), 7.72-7.76 (td, 1H), 8.08 (d,  $J$  = 7.8 Hz, 1H), 8.68 (d,  $J$  = 5.5 Hz, 1H);  $^{13}\text{C}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  20.28, 80.77, 123.22, 123.66, 124.58, 126.56, 128.13, 128.63, 128.98, 129.42, 130.05, 133.39, 136.76, 143.71, 146.17, 149.46, 151.07; MS (EI)  $m/z$  435( $\text{M}^+$ ); HRMS (EI) calcd for  $\text{C}_{28}\text{H}_{25}\text{N}_3\text{S}$ , 435.1769; found, 435.1799.

#### *N,N*-Dimethyl-2,4-di(pyridin-2-yl)thiazol-5-amine (9a)

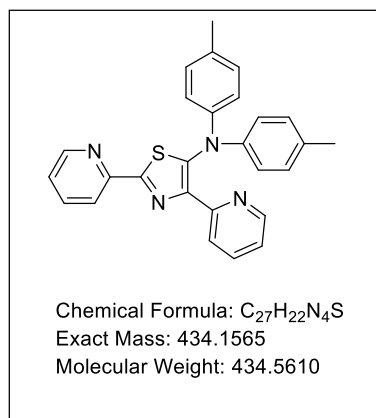


To a solution of *N*-(pyridin-2-ylmethyl)pyridine-2-carbothioamide (0.344 g, 1.5 mmol) in THF (3 mL) was added slowly a 1.25 M *n*-butyllithium in hexane (4.4 mL, 3 mmol), and the mixture stirred for 15 min at 0 °C. To this mixture was added *N,N*-dimethylmethanethioamide (0.257 mL, 3 mmol) at 0 °C, and the mixture was stirred at this temperature for 15 min. Then,  $\text{I}_2$  (1.5215 g, 3 mmol) in 2 mL THF was added at 0 °C and continuously stirred at the same temperature for 3 h. The resulting mixture was poured into saturated aqueous solution of

$\text{Na}_2\text{S}_2\text{O}_3$  and extracted with  $\text{CH}_2\text{Cl}_2$ . The organic layer was then dried over  $\text{MgSO}_4$  and concentrated *in*

*vacuo*. The residue was purified by flash column chromatography (SiO<sub>2</sub>, (EtOAc = 2 : 1) to give 5-aminothiazole **9a** (0.193 g, 23%) as a yellow solid (mp: 64-65 °C); IR (KBr) 3420, 2923, 1586, 1564, 1501, 1472, 1433, 1413, 1366, 1145, 1001, 783, 741 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.94 (s, 6H) 7.21-7.22 (d, 1H) 7.23 (t, 1H) 7.73-7.77 (td, 1H) 7.79-7.83 (td, 1H) 8.13-8.14 (d, 1H) 8.27-8.29 (d, 1H) 8.53-8.54 (d, 1H) 8.74-8.75 (d, 1H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ 46.41, 118.91, 121.13, 123.43, 123.51, 136.65, 136.79, 148.82, 149.21, 151.95, 154.11, 154.82, 157.13, 135.57; (EI) *m/z* 282 (M<sup>+</sup>); HRMS (EI) calcd for C<sub>15</sub>H<sub>14</sub>N<sub>4</sub>S, 282.0939; found, 282.0938.

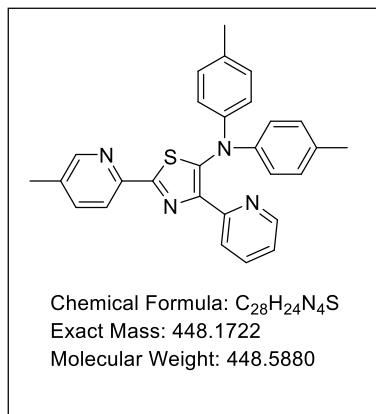
### 2,4-Di(pyridin-2-yl)-N,N-di-p-tolylthiazol-5-amine (9b)



To a solution of 2,4-di(pyridin-2-yl)-N,N-di-p-tolylthiazoline (0.305 g, 0.70 mmol) in THF (3 mL) was added Iodine (0.354 g, 1.4 mmol) at room temperature, and the mixture was stirred for 24 hours at this temperature. The resulting mixture was poured into aqueous saturated solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was then dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO<sub>2</sub>, hexane : EtOAc = 5 : 1) to give 5-aminothiazole **9b** (0.23 g, 76%) as a greenish yellow solid (mp:

171-172 °C); IR (KBr) 3053, 3021, 2917, 2856, 2359, 1882, 1784, 1505, 1292, 811 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.22 (s, 6H), 6.95-7.04 (m, 9H), 7.24-7.27 (m, 1H), 7.50 (td, 1H), 7.73-7.79 (m, 2H), 8.32-8.35 (m, 1H), 8.50-8.51 (m, 1H), 8.53-8.55 (m, 1H); <sup>13</sup>C NMR (500 MHz, CDCl<sub>3</sub>) δ 20.8, 119.7, 112.1, 112.2, 122.7, 124.4, 129.8, 133.0, 136.1, 136.9, 144.7, 146.3, 147.5, 149.32, 149.39, 151.5, 151.8, 162.8; MS (EI) *m/z* 434 (M<sup>+</sup>); HRMS (EI) calcd for C<sub>27</sub>H<sub>22</sub>N<sub>4</sub>S, 434.1565; found, 434.1549.

### 2-(5-Methylpyridin-2-yl)-4-(pyridin-2-yl)-N,N-di-p-tolylthiazol-5-amine (9c)

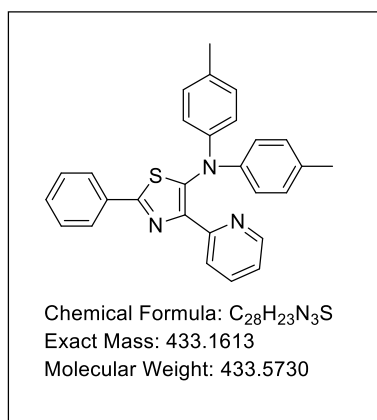


To a solution of 2-(5-methylpyridin-2-yl)-4-(pyridin-2-yl)-N,N-di-p-tolylthiazoline (0.154 g, 0.34 mmol) in THF (2 mL) was added Iodine (0.160 g, 0.68 mmol) at room temperature, and the mixture was stirred for 24 hours at this temperature. The resulting mixture was poured into aqueous saturated solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was then dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO<sub>2</sub>, hexane : EtOAc = 3 : 1) to give 5-aminothiazole **9c** (0.077 g, 59%) as a yellow solid

(mp: 116-117 °C); IR (KBr) 1686, 1605, 1383, 1314 1287, 1002, 810 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.23

(s, 6H) 2.36 (s, 3H) 6.95-6.95 (m, 1H) 6.98 (d, 6H) 7.01 (t, 1H) 7.04-7.07 (m, 1H) 7.51-7.53 (m, 1H) 7.57-7.59 (dd, 1H) 7.78 (d, 1H) 8.26-8.27 (m, 1H) 8.33 (d, 1H) 8.58 (s, 1H);  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  18.6, 20.8, 119.0, 119.2, 121.2, 122.1, 122.7, 129.7, 132.8, 134.4, 136.0, 137.3, 144.6, 149.1, 149.51, 149.6, 151.9, 161.8, 163.3; MS (EI)  $m/z$  434 ( $\text{M}^+$ ); HRMS (EI) calcd for  $\text{C}_{28}\text{H}_{24}\text{N}_4\text{S}$ , 448.1722; found, 448.1716

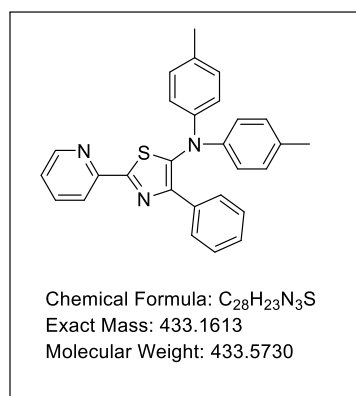
## 2-Phenyl-4-(pyridin-2-yl)-N,N-di-p-tolylthiazol-5-amine (9d)



To solution 2-phenyl-4-(pyridin-2-yl)-N,N-di-p-tolylthiazoline (0.291 g, 0.67 mmol) in THF (6mL) was added iodine (0.339 g, 1.34 mmol) and the mixture was stirred for 24 hours at room temperature. The resulting mixture was poured into aqueous saturated solution of  $\text{Na}_2\text{S}_2\text{O}_3$  and extracted with  $\text{CH}_2\text{Cl}_2$ . The organic layer was then dried over  $\text{MgSO}_4$  and concentrated *in vacuo*. The residue was purified by flash column chromatography ( $\text{SiO}_2$ , hexane : EtOAc = 10 : 1) to give 5-aminothiazole **9d** (0.171 g, 59%) as a yellow solid (mp: 135-136 °C); IR (KBr) 3420, 1507,

1475, 1426, 1314, 1290, 814, 761, 686  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.29 (s, 6H), 7.03-7.05 (m, 4H), 7.07-7.09 (m, 4H), 7.42-7.45 (m, 2H), 7.47-7.48 (m, 2H), 8.02-8.03 (d,  $J$  = 3.7 Hz, 2H), 8.22 (d,  $J$  = 6.4, 2H), 9.09-9.10 (d,  $J$  = 3.7 Hz, 1H);  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  20.8, 102.3, 118.1, 122.1, 122.4, 122.8, 126.6, 127.7, 128.8, 129.9, 130.2, 133.4, 144.4, 150.4, 156.3, 162.8; MS (EI)  $m/z$  433 ( $\text{M}^+$ ); HRMS (EI) calcd for  $\text{C}_{28}\text{H}_{23}\text{N}_3\text{S}$ , 433.1613; found, 433.1612.

## 4-Phenyl-2-(pyridin-2-yl)-N,N-di-p-tolylthiazol-5-amine (9f)



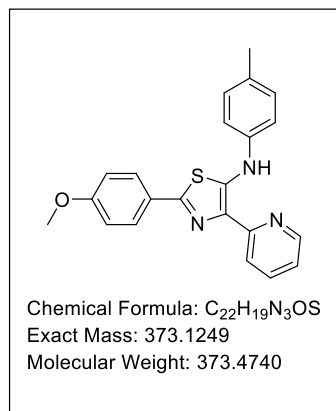
To solution 4-phenyl-2-(pyridin-2-yl)-N,N-di-p-tolyl-4,5-dihydrothiazoline (0.0244 g, 0.056 mmol) in THF (4mL) was added iodine (0.0283 g, 0.112 mmol), and the mixture was stirred for 24 hours at room temperature. The resulting mixture was poured into aqueous saturated solution of  $\text{Na}_2\text{S}_2\text{O}_3$  and extracted with  $\text{CH}_2\text{Cl}_2$ . The organic layer was then dried over  $\text{MgSO}_4$  and concentrated *in vacuo*. The residue was purified by flash column chromatography ( $\text{SiO}_2$ , hexane : EtOAc = 10 : 1) to give 5-aminothiazole **9f** (0.0219 g, 90%) as a greenish yellow solid (mp: 192-193

°C); IR (KBr) 3421, 2921, 1586, 1569, 1506, 1470, 1424, 12990, 1002, 811, 508  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.24 (s, 6H), 6.96-7.04 (m, 8H), 7.18-7.22 (tt, 1H), 7.24-7.25 (m, 1H), 7.26-7.28, (dd, 1H), 7.31-7.34 (td, 1H), 7.81-7.85 (td, 1H), 7.93-7.96 (dd, 2H), 8.28-8.30 (d, 1H) 8.56-8.57 (d, 1H);  $^{13}\text{C}$  NMR (400 MHz,



CDCl<sub>3</sub>)  $\delta$  20.7, 119.6, 121.75, 124.4, 127.4, 127.9, 128.2, 129.8, 132.7, 133.5, 137.5, 143.8, 144.54, 148.4, 148.8, 151.2; MS (EI)  $m/z$  433 ( $M^+$ ); HRMS (EI) calcd for C<sub>28</sub>H<sub>23</sub>N<sub>3</sub>S, 433.1613; found, 433.1621.

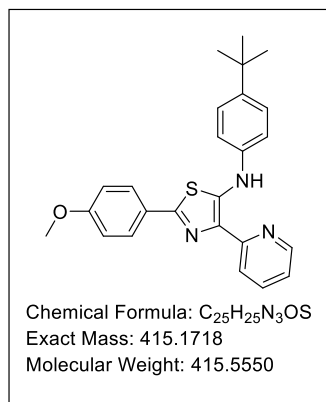
### 2-(5-Methoxypyridin-2-yl)-4-phenyl-N-(p-tolyl)thiazol-5-amine (9g)



Pd(OAc)<sub>2</sub> (0.067 g, 10 mol%), Xantphos (0.347 g, 20 mol%) and 5-Bromothiazole (1.042 g, 3 mmol) were weighted into Schlenk tube that was sealed with a septum and purged with argon (3 times). Toluene (12 mL) then injected, and the reaction was continued for 15 min at 130 °C. *p*-toluidine (3.214 g, 30 mmol) and LHMDS (6 mL, 6 mmol) were then injected via syringe and the reaction was allowed to stir 24 h at 130 °C. The reaction mixture was filtered through a bed of Celite and washed with CH<sub>2</sub>Cl<sub>2</sub>. The filtrate was concentrated in vacuo and purified via silica gel flash column

chromatography (SiO<sub>2</sub>, hexane : EtOAc = 30 : 1) and recrystallization (Hexane : dichloromethane) to give the corresponding thiazoles (0.66 g, 60%) as a yellow solid. (mp: 136 °C): IR (ATR) 2996, 1589, 1565, 1547, 1513, 1395, 1320, 1294, 1240, 1167, 1146, 1025, 971, 827, 782, 703, 493 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  2.33 (s, 3H), 3.84 (s, 3H) 6.93 (d,  $J$  = 8.53 Hz, 2H), 7.07-7.24 (m, 5H), 7.74 (t, 1H), 7.82-7.85 (m, 2H), 8.23 (s, 1H), 8.52 (d,  $J$  = 4.49 Hz, 1H), 11.5 (s, 1H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  20.8, 55.4, 114.3, 117.8, 119.7, 120.8, 127.0, 130.0, 136.8, 139.9, 146.8, 147.1, 160.3; MS (EI)  $m/z$  373 ( $M^+$ ); HRMS (EI) calcd for C<sub>22</sub>H<sub>19</sub>N<sub>3</sub>OS, 373.1249; found, 373.1245.

### N-(4-(tert-butyl)phenyl)-2-(5-methoxypyridin-2-yl)-4-phenylthiazol-5-amine (9h)

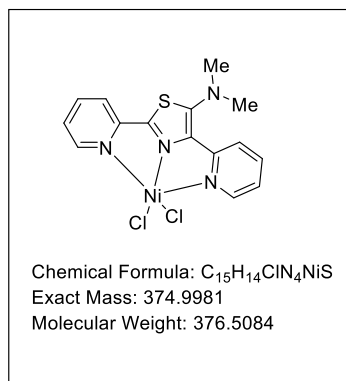


Pd(OAc)<sub>2</sub> (0.04 g, 10 mol%), Xantphos (0.23 g, 20 mol%) and 5-Bromothiazole (0.69 g, 2 mmol) were weighted into Schlenk tube that was sealed with a septum and purged with argon (3 times). Toluene (12 mL) then injected, and the reaction was continued for 15 min at 130 °C. *p*-tert. butylamine (3.1 mL g, 20 mmol) and LHMDS (4 mL, 4 mmol) were then injected via syringe and the reaction was allowed to stir 24 h at 130 °C. The reaction mixture was filtered through a bed of Celite and washed with CH<sub>2</sub>Cl<sub>2</sub>. The filtrate was concentrated in vacuo and purified via silica gel flash

column chromatography (SiO<sub>2</sub>, hexane : EtOAc = 30 : 1) (Hexane : dichloromethane) and GPC to give the corresponding thiazoles (0.41 g, 49%) as a pale yellow solid. (mp: 120 °C): IR (ATR) 2956, 1587, 1563, 1535, 1471, 1387, 1245, 1170, 1032, 825, 782, 705, 541, 513 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.35 (s, 9H), 3.83 (s, 3H) 6.93 (d,  $J$  = 8.98 Hz, 2H), 7.04-7.07 (m, 1H), 7.24-7.28 (m, 2H), 7.40 (d,  $J$  = 8.08 Hz, 2H), 7.72 (t, 1H),

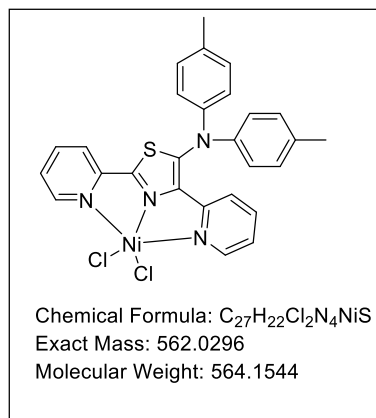
7.84 (d,  $J = 8.53$  Hz, 2H), 8.12-8.28 (m, 1H), 8.51 (d,  $J = 4.94$  Hz, 1H), 11.6 (s, 1H);  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  31.5, 34.0, 55.4, 111.9, 112.3, 114.3, 117.2, 117.3, 119.6, 120.7, 125.7, 126.3, 127.0, 130.3, 130.7, 136.6, 139.7, 145.0, 145.4, 147.1, 149.0, 155.8, 160.3; MS (EI)  $m/z$  415( $\text{M}^+$ ); HRMS (EI) calcd for  $\text{C}_{25}\text{H}_{25}\text{N}_3\text{OS}$ , 415.1718; found, 415.1705

#### Complex [Ni(9a)Cl] (10a)



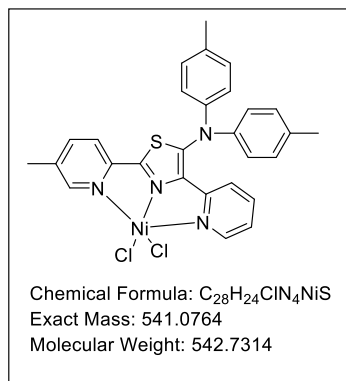
$\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$  (0.03 g, 0.1 mmol) was taken in ethanol (6 mL) and was heated to reflux. The *N,N*-dimethyl-2,4-di(pyridin-2-yl)thiazol-5-amine (0.03 g, 0.1 mmol) solution in EtOH (4 mL) was added dropwise the refluxing solution and was further refluxed for another 1 h. The final mixture was concentrated in vacuo. Green participate product was then washed by ethanol and diethyl ether. Yield: 0.0355 g (86 %) (mp: 264-265 °C); IR (KBr) 3274, 1597, 1545, 1507, 1463, 1374, 1078, 786  $\text{cm}^{-1}$ ; ESI-MS calcd. for  $\text{C}_{15}\text{H}_{14}\text{Cl}_2\text{N}_4\text{NiS}$ , 374.9981; found 375.80881.

#### Complex [Ni(9b)Cl<sub>2</sub>] (10b)



$\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$  (20 mg, 0.1 mmol) was taken in ethanol (6 mL) and was heated to reflux. The 2,4-di(pyridin-2-yl)-*N,N*-di-*p*-tolylthiazoline (0.0434 g, 0.1 mmol) solution in THF (2 mL) was added dropwise to the refluxing solution and was further refluxed for another 1 h. The final product, a green solid participate, was collected after the reaction mixture was concentrated in vacuo (85 %) (mp: 193-194 °C); IR (KBr) 3421, 2921, 2852, 1597, 1506, 1455, 1262, 811, 778, 676  $\text{cm}^{-1}$ ; ESI-MS calcd. for  $\text{C}_{27}\text{H}_{22}\text{Cl}_2\text{N}_4\text{NiS}$ , 562.0607; found 562.03006.

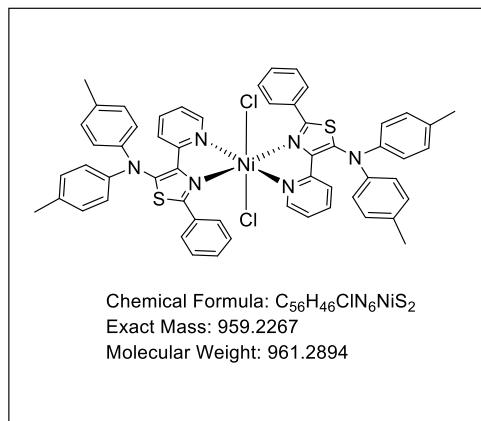
#### Complex [Ni(9c)Cl] (10c)



$\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$  (0.0128 g, 0.047 mmol) was taken in 5 mL ethanol (EtOH) and heated to reflux. The 2-(5-methylpyridin-2-yl)-4-(pyridin-2-yl)-*N,N*-di-*p*-tolylthiazol-5-amine (0.0210 g, 0.047 mmol) solution in 4 mL THF was added dropwise to the refluxing solution and was further refluxed for another 1 h. The final mixture was concentrated in vacuo. Yellowish green participate product was then washed by ethanol and diethyl ether. Yield:

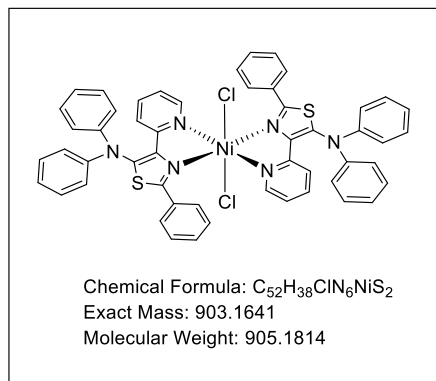
0.0240 g (88 %) (mp: 306-307 °C); IR (KBr) 3370, 1600, 1506, 1455, 1267, 813  $\text{cm}^{-1}$ ; ESI-MS calcd. for  $\text{C}_{28}\text{H}_{24}\text{Cl}_2\text{N}_4\text{NiS}$ , 541.0764; found 542.23659.

#### Complex [Ni(9d)<sub>2</sub>Cl] (10d)



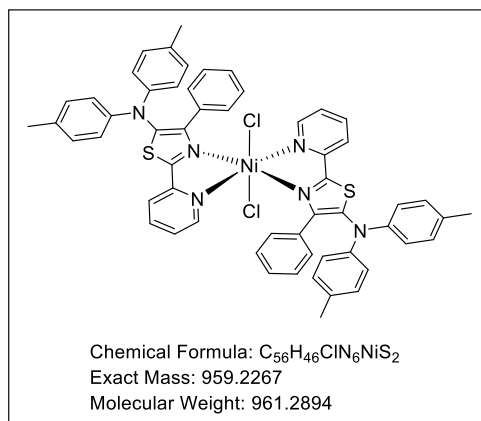
$\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$  (0.0240 g, 0.08 mmol) was taken in 5 mL ethanol (EtOH) and heated to reflux. The 2-phenyl-4-(pyridin-2-yl)-N,N-di-p-tolylthiazol-5-amine (0.0240 g, 0.08 mmol) solution in 4 mL THF was added dropwise to the refluxing solution and was further refluxed for another 1 h. The final mixture was concentrated in vacuo. Dark green particulate product was then washed by ethanol and diethyl ether. Yield: 0.0665 g (83 %) (mp: 292-293 °C); IR (KBr) 3383, 2921, 1707, 1603, 1473, 1361, 1238, 813, 682, 566  $\text{cm}^{-1}$ ; ESI-MS calcd. for  $\text{C}_{56}\text{H}_{46}\text{ClN}_6\text{NiS}_2$ , 959.2267; found 959.04252.

#### Complex [Ni(9bb)<sub>2</sub>Cl] (10e)



$\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$  (0.013 g, 0.05 mmol) was taken in ethanol (6 mL) and was heated to reflux. The 2-Phenyl-(2-pyridyl)-5-diphenylaminothiazole (0.02 g, 0.05 mmol) solution in THF (2 mL) was added dropwise to the refluxing solution and was further refluxed for another 1 h. The final mixture was filtered over celite and concentrated in vacuo. Green particulate product were collected. Yield: 0.0356 g (97%) (mp: 177-178°C); IR (KBr) 3384, 1602, 1489, 1360, 1237, 753, 694  $\text{cm}^{-1}$ ; ESI-MS calcd. for  $\text{C}_{52}\text{H}_{38}\text{Cl}_2\text{N}_6\text{NiS}_2$ , 903.1641; found 903.04247.

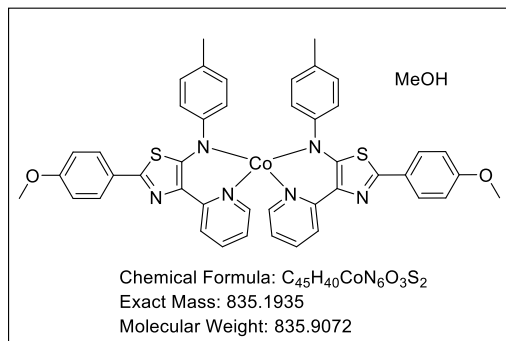
#### Complex [Ni(9f)<sub>2</sub>Cl] (10f)



$\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$  (0.0130 g, 0.05 mmol) was taken in 5 mL ethanol (EtOH) and heated to reflux. The 4-phenyl-2-(pyridin-2-yl)-N,N-di-p-tolylthiazol-5-amine (0.0210 g, 0.05 mmol) solution in 4 mL THF was added dropwise to the refluxing solution and was further refluxed for another 1 h. The final mixture was concentrated in vacuo. Green particulate product was then washed by ethanol and diethyl ether. Yield: 0.0487 g (97 %)

(mp: 292-293 °C); IR (KBr) 3370, 1600, 1506, 1455, 1267, 813  $\text{cm}^{-1}$ ; ESI-MS calcd. for  $\text{C}_{56}\text{H}_{46}\text{ClN}_6\text{NiS}_2$ , 959.2267; found 961.10500.

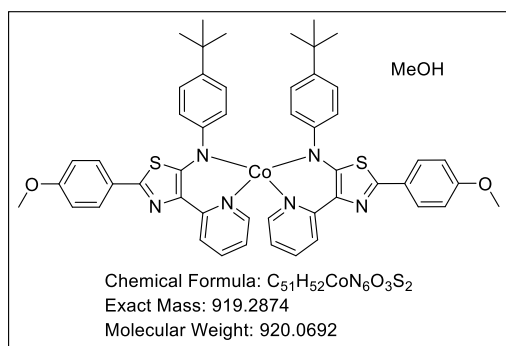
#### Complex [Co(9g)<sub>2</sub>]MeOH (10g)



To a 10 mL dichloromethane solution of thiazole ligand **9g** (0.112 g, 0.3 mmol) was added cobalt chloride (0.065 g, 0.15 mmol) in MeOH or THF. To the solution mixture was added triethylamine (0.085 mL, 0.6 mmol). The solution was stirred for 24 h at room temperature. The mixture then filtrated through bed of celite and purified by column chromatography ( $\text{SiO}_2$ , hexane : EtOAc = 5 : 1) to give

complex **10g** (0.188 g, 78%) as a green solid (mp: 141 °C); IR (ATR) 2986, 2361, 2342, 1704, 1593, 1565, 1507, 1457, 1238, 1422, 1156, 1091, 1043, 1091, 1043, 1019, 838, 620, 472  $\text{cm}^{-1}$ ; ESI-MS calcd. for  $\text{C}_{45}\text{H}_{40}\text{CoN}_6\text{O}_3\text{S}_2$ , 559.2267; found 835.14587.

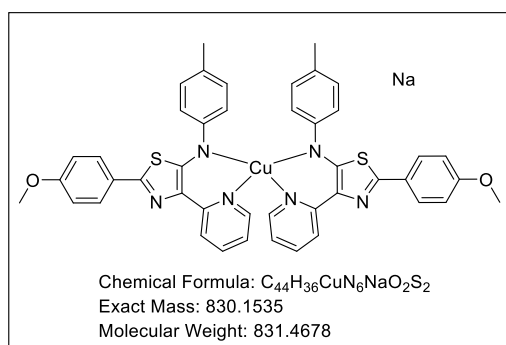
#### Complex [Co(9h)<sub>2</sub>] (10h)



To a 10 mL dichloromethane solution of thiazole ligand **9g** (0.10 g, 0.2 mmol) was added cobalt chloride (0.013 g, 0.10 mmol) in MeOH or THF. The solution was stirred for 24 h at room temperature. The mixture then filtrated through bed of celite and purified by column chromatography ( $\text{SiO}_2$ , hexane : EtOAc = 5 : 1) to give complex **10h** (0.1124 g, 63%) as a pale green solid (mp: 119 °C); IR (ATR) 2957, 1601, 1507,

1304, 1241, 1170, 1023, 946, 866, 835, 793, 700, 555  $\text{cm}^{-1}$ ; ESI-MS calcd. for  $\text{C}_{51}\text{H}_{52}\text{CoN}_6\text{O}_3\text{S}_2$ , 919.2874; found 919.21921.

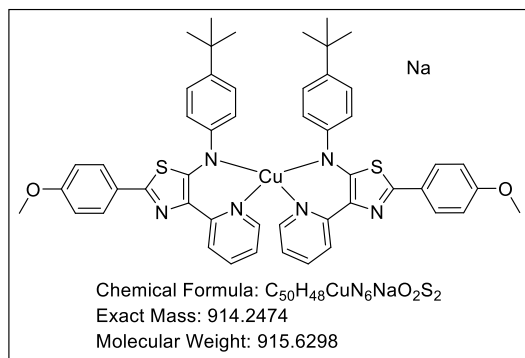
#### Complex [Cu(9g)<sub>2</sub>] (10i)



To a 10 mL dichloromethane solution of thiazole ligand **9g** (0.112 g, 0.3 mmol) was added copper chloride (0.020 g, 0.15 mmol) in MeOH or THF. To the solution mixture was added triethylamine (0.06 mL, 0.4 mmol). To the solution mixture was added triethylamine (0.085 mL, 0.6 mmol). The solution was stirred for 24 h at room temperature. The mixture then filtrated through bed of celite and purified by column

chromatography (SiO<sub>2</sub>, hexane : EtOAc = 5 : 1) to give complex **10i** (0.0643 g, 26%) as a pale yellow solid (mp: > 48 °C); IR (ATR) 2361, 1647, 1506, 1306, 1250, 1169, 1063, 1025, 870, 835, 797, 698, 614, 542, 492 cm<sup>-1</sup>; ESI-MS calcd. for C<sub>44</sub>H<sub>36</sub>CuN<sub>6</sub>NaO<sub>2</sub>S<sub>2</sub>, 830.1535; found 829.28280.

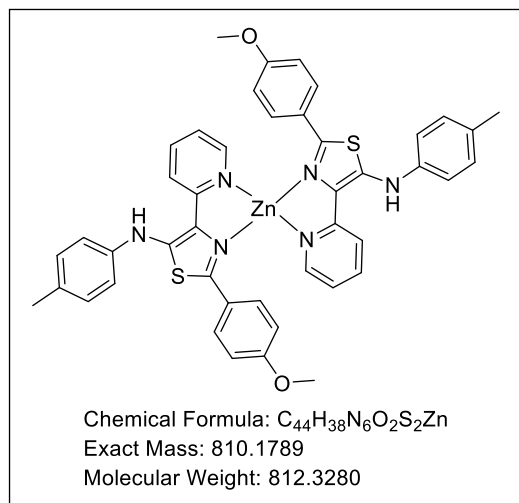
#### Complex [Cu(9h)<sub>2</sub>] (10j)



To a 10 mL dichloromethane solution of thiazole ligand **9h** (0.112 g, 0.3 mmol) was added cobalt chloride (0.065 g, 0.15 mmol) in MeOH or THF. To the solution mixture was added triethylamine (0.06 mL, 0.4 mmol). The solution was stirred for 24 h at room temperature. The mixture was then filtrated through bed of celite and purified by column chromatography (SiO<sub>2</sub>, hexane : EtOAc = 5 : 1) to give

complex **10j** (0.0643 g, 26%) as a pale yellow solid (mp: 48 °C); IR (ATR) 2958, 1599, 1507, 1463, 1434, 1305, 1251, 1170, 1129, 1065, 1026, 951, 873, 835, 796, 781, 748, 706, 614, 549, 518 cm<sup>-1</sup>; ESI-MS calcd. for C<sub>50</sub>H<sub>48</sub>CuN<sub>6</sub>NaO<sub>2</sub>S<sub>2</sub>, 914.2474; found 914.33184.

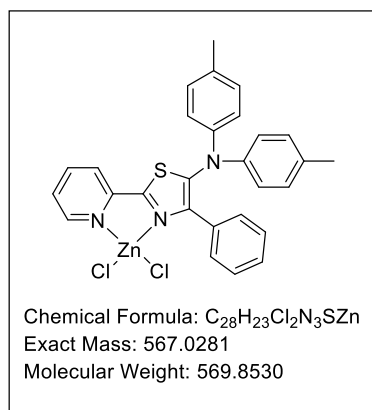
#### Complex [Cu(9g)<sub>2</sub>] (10k)



ZnCl<sub>2</sub> (0.020 g, 0.15 mmol) was taken in 8 mL ethanol (EtOH) and heated to reflux. The solution of thiazole ligand **9g** (0.112 g, 0.3 mmol) was added (0.112 g, 0.3 mmol) in 1 mL THF was added dropwise to the refluxing solution and was further refluxed for another 1 h. The formed yellow precipitate **10k** was filtrated and concentrated in vacuo. Yield: 0.0438 g (18 %) (mp: > 350 °C); IR (ATR) 3284, 1603, 1508, 1481, 1365, 1295, 1250, 1182, 1028, 813, 775, 749, 724, 657, 620, 557, 511, 483, 467, 410 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO) δ 2.26 (s, 3H), 3.78 (s, 3H), 7.01 (d, *J* = 8.93

MHz, 2H), 7.18-7.26 (m, 5H), 7.81 (d, *J* = 9.16 MHz, 2H), 7.88 (td, 1H), 8.10 (d, *J* = 7.79 MHz, 1H), 8.62 (d, *J* = 4.12 MHz, 1H), 11.5 (s, 1H); ESI-MS calcd. for C<sub>44</sub>H<sub>38</sub>N<sub>6</sub>O<sub>2</sub>S<sub>2</sub>Zn, 810.1789; found 809.38555

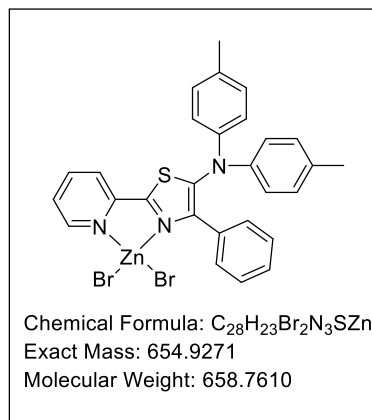
### Complex [Zn(9e)]Cl<sub>2</sub> (**11a**)



To a 5 mL THF solution of thiazole ligand **9e** (0.065 g, 0.15 mmol) was added zinc chloride (0.02 g, 0.15 mmol) in THF. The solution was stirred for 24 h at room temperature. The mixture then washed with hexane and diethyl Eter to give complex **11a** (0.079 g, 93%) as a red solid (mp: 230-233 °C); IR (ATR) 1600, 1505, 1474, 1454, 1357, 1259, 811, 780, 753, 698, 501 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 2.25 (s, 6H), 6.90 (d, *J* = 8.53 MHz, 4H), 7.00 (d, *J* = 8.08 MHz, 4H), 7.26-7.26 (m, 3H) 7.63-7.66 (m, 1H), 7.69-7.71 (m, 1H), 7.74 (dd, 2H), 8.04 (td, 1H), 8.74 (d, *J* = 4.94 MHz, 1H);

<sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ 20.9, 25.6, 68.2, 121.5, 122.8, 126.9, 128.5, 128.8, 129.6, 129.8, 130.2, 134.8, 141.1, 143.3, 145.3, 145.6, 147.1, 148.8, 154.7; ESI-MS calcd. for C<sub>28</sub>H<sub>23</sub>Cl<sub>2</sub>N<sub>3</sub>SZn, 567.0281; found 352.68813.

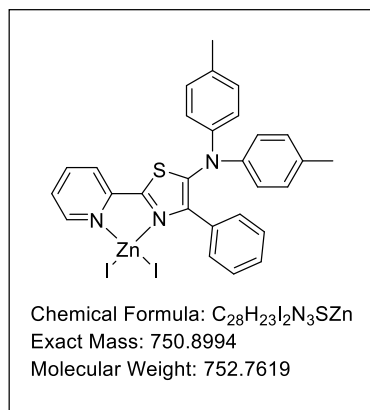
### Complex [Zn(9e)]Br<sub>2</sub> (**11b**)



To a 5 mL THF solution of thiazole ligand **9e** (0.065 g, 0.15 mmol) was added zinc bromide (0.034 g, 0.15 mmol) in THF. The solution was stirred for 24 h at room temperature. The mixture then washed with hexane and diethyl Eter to give complex **11b** (0.072 g, 73%) as a yellow solid (mp: > 250 °C); IR (ATR) 3027, 2969, 1738, 1602, 1539, 1506, 1476, 1455, 1364, 1228, 1216, 1011, 807, 776, 700, 556, 510, 408 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 2.25 (s, 6H), 6.90 (d, *J* = 8.53 MHz, 4H), 7.00 (d, *J* = 8.08 MHz, 4H), 7.26-7.26 (m, 3H) 7.63-7.66 (m, 1H), 7.69-7.71 (m, 1H), 7.74 (dd, 2H), 8.04 (td, 1H), 8.74 (d, *J* = 4.94 MHz, 1H); <sup>13</sup>C NMR

(400 MHz, CDCl<sub>3</sub>) δ 20.8, 121.5, 122.8, 126.9, 128.5, 128.8, 129.6, 129.8, 130.2, 134.8, 141.1, 143.3, 145.3, 145.6, 147.1, 148.8, 154.7; ESI-MS calcd. for C<sub>28</sub>H<sub>23</sub>Br<sub>2</sub>N<sub>3</sub>SZn, 654.9271; found 304.6669.

### Complex [Zn(9e)]I<sub>2</sub> (11c)



To a 5 mL THF solution of thiazole ligand **9e** (0.065 g, 0.15 mmol) was added zinc iodide (0.047 g, 0.15 mmol) in THF. The solution was stirred for 24 h at room temperature. The mixture then washed with hexane and diethyl Eter to give complex **11c** (0.076 g, 67%) as a yellow solid (mp: > 250 °C); IR (ATR) 3026, 2969, 1738, 1597, 1506, 1472, 1449, 1369, 1228, 1216, 1159, 1012, 810, 771, 700, 573, 513, 411 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 2.25 (s, 6H), 6.90 (d, *J* = 8.53 MHz, 4H), 7.00 (d, *J* = 8.08 MHz, 4H), 7.26-7.26 (m, 3H) 7.63-7.66 (m, 1H), 7.69-7.71 (m, 1H), 7.74 (dd, 2H), 8.04 (td, 1H), 8.74 (d, *J* = 4.94 MHz, 1H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ 20.8, 121.5, 122.8, 126.9, 128.5, 128.8, 129.6, 129.8, 130.2, 134.8, 141.1, 143.3, 145.3, 145.6, 147.1, 148.8, 154.7; ESI-MS calcd. for C<sub>28</sub>H<sub>23</sub>I<sub>2</sub>N<sub>3</sub>SZn, 750.8994; found 444.62836.

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## Chapter 3

### Synthesis of 5-H thiazoles via thioamide dianions with thioformamides: pyridylmethyl group on the nitrogen atom of thiazole promotes the formation of 5-H thiazoles

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### 3.1. Introduction

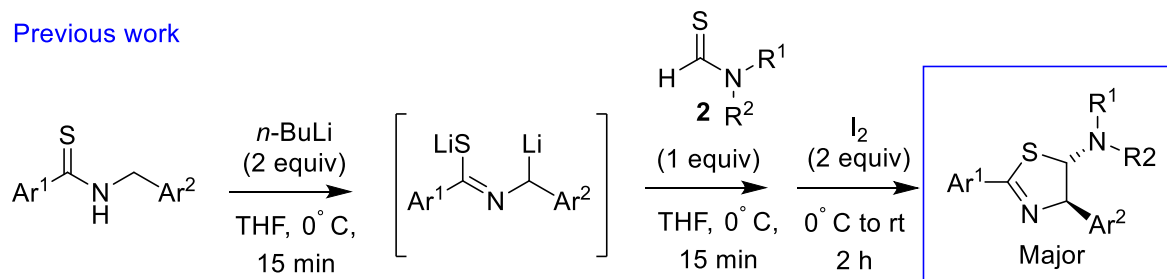
Most of the thiazole compounds are synthesized via the reaction reported by Hantzsch. However, the set of starting materials such as carbonyl and thioamides only provide limited variety of substituent onto thiazole ring. Therefore, it is difficult to introduce designed substituents to the specific position of a thiazole ring via this method, as required by fluorophore materials.

In fact, 1,3 thiazoles possess three carbon atoms to which potentially can be attached with various substituents. The introduction of designed substituents attached to the specific carbon atom led to the specific characteristic of thiazole derivatives.<sup>1-4</sup> In recent years, new methods for the thiazole synthesis have been reported. A guideline for the arylation of positions 4 and 5 of thiazole via Pd-catalyzed cross-coupling reactions such as Buchwald-Hartwig amination reaction, Suzuki-Miyaura and Stille cross-coupling have been reported. These methods provide a clean strategy to afford a thiazole ring with various substituents attached to the desired carbon atom on a thiazole ring.<sup>2,5-7</sup> Alternatively, Yu and coworker reported an efficient synthesis of 2,4 disubstituted thiazoles via dehydrogenation reaction of thiazolines by employing MnO<sub>2</sub> as dehydrogenating reagents.<sup>8</sup> This method successfully delivered a various types of thiazoline derivatives to thiazole compounds.

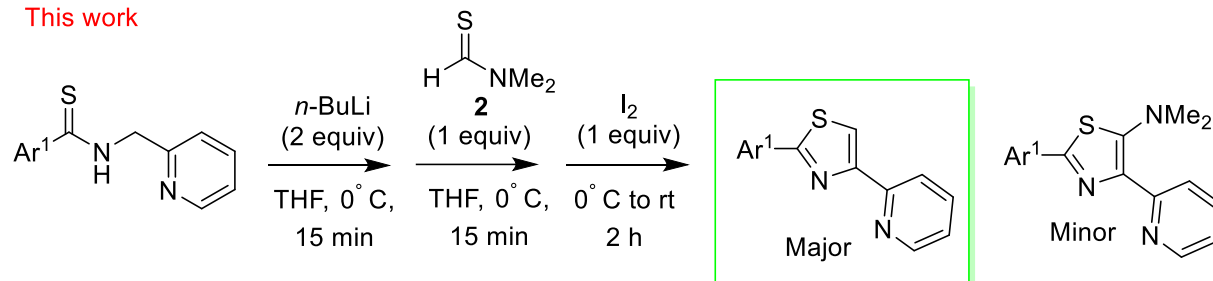
Similarly, the reaction of *in-situ* generated thioamide dianions with thioformamides afforded a library of thiazoline derivatives as a major product. An identical reaction also provides a series of thiazole derivatives after oxidation of thiazolines with 2 equivalents of iodine. This synthetic protocol allows us to access a wide range of unprecedented 5-aminothiazoles with various substituents at the 2- and 4-positions of a thiazole ring.<sup>9</sup>

Interestingly, in my experiment the reaction of thioamides with dimethylthioformamide gave 5-H thiazoles as a major product along with dimethylaminothiazoles. Therefore, in this chapter I shifted my attention to the investigation of the effect of substituents at the 2-position of a thiazole ring to the formation of 5-H thiazoles (Chart 1).

Previous work



This work

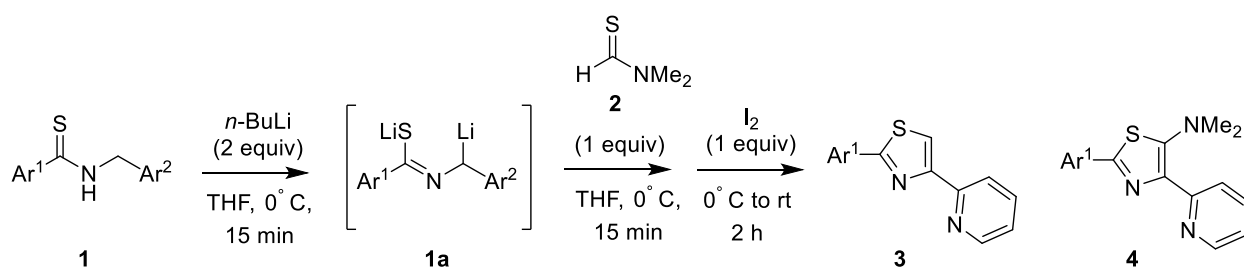


**Chart 1.** Synthetic procedures of thiazolines and 5-H thiazoles.

## 3.2. Results and discussion

### 3.2.1. Synthesis of 5-H thiazoles

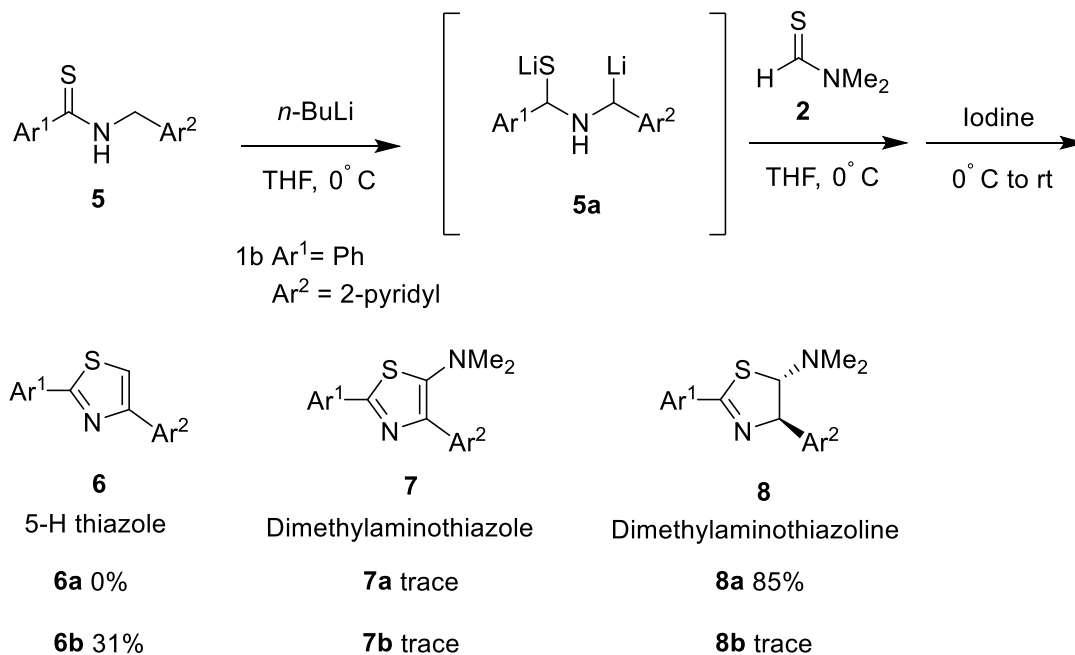
The synthesis of 5-H thiazoles were carried out by reacting thioamide having *N*-methylpyridylthioamides **1b** with *N,N*-dimethylthioformamide (**2**) to give 5-H thiazole **3b** as a major product. Initially, the treatment of secondary thioamides with butyllithium at low temperature turned the reaction mixture to deep purple, which was indicative of the formation of thioamides dianions. The addition of dimethylthioformamide to this generated thioamide dianions followed by oxidation reaction with iodine gave 5-H thiazoles along with the formation of 5-dimethylaminothiazoles as a minor product (Scheme 1). By following this procedure, a wide range of 5-H thiazole derivatives were isolated in moderate to high yields.



**Scheme 1.** Synthesis of 5-H thiazoles via reaction of secondary thioamides and thioformamides

### 3.2.2. The effect of the substituents at the 2-position of the thiazole ring

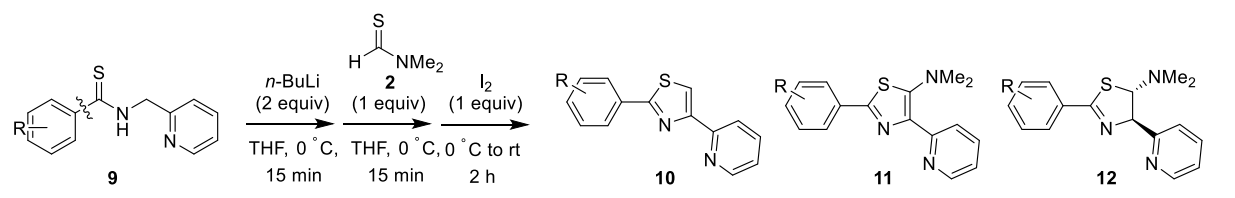

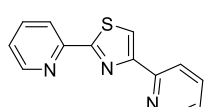
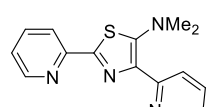
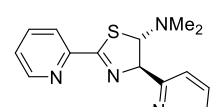

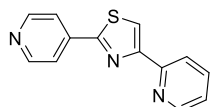
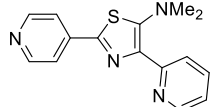
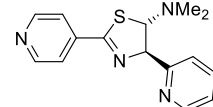
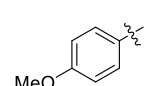
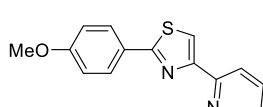
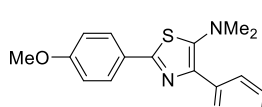
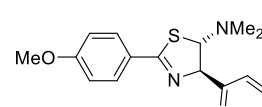
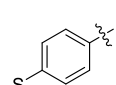
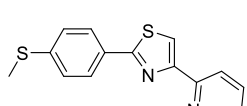
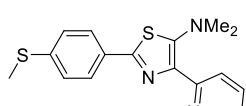
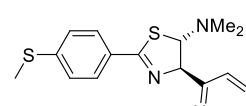
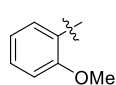
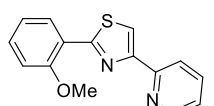
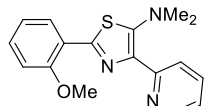
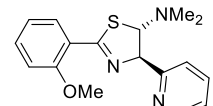
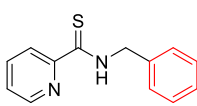
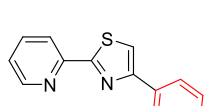
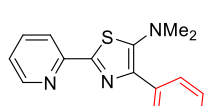
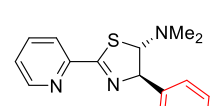
As described previously,<sup>9</sup> the reaction of *N*-methylphenyl thioamide **5** with *N,N*-dimethylthioformamide (**2**) gave *N,N*-dimethylaminothiazolines **6** as a major product along with a small amount of 5-aminothiazole **7** (Scheme 2). The formation of 5-H thiazole was not observed at all. In contrast, we found that the reaction of *N*-methylpyridyl thioamides **1** with *N,N*-dimethylthioformamide (**2**) accommodates the formation of 5-H thiazole **3** as a major product. Encouraged by this interesting result, I shifted my attention to evaluate the effect of the substituent at the 2-position of a thiazole ring on the formation of 5-H thiazoles.



**Scheme 2.** Reaction of *N*-methylphenyl thioamides with *N,N*-dimethylthioformamide

The reaction was then extended to secondary thioamides having electron-deficient substituents such as 2-pyridyl (**9a**) and 4-pyridyl (**9b**) groups. The reaction with *N,N*-dimethylthioformamide (**2**) resulted in the formation of 5-H thiazoles in up to 55% yields (Table 1). Moreover, thioamides with 4-methoxyphenyl (**9c**) and 4-methylthiophenyl (**9d**) groups gave comparable results (60% and 56% yields, respectively). These experimental results show that the substituents at the 2-position of a thiazole ring do not affect the reaction efficiency. Thioamide with a 2-methoxyphenyl group (**9e**) gave the desired 5-H thiazole **10e** in only 20% yield. On the other hand, the introduction of a phenyl substituent to the 4-position of a thiazole ring significantly reduced the yield to 3% (**10f**). In addition to 5-H thiazoles **10**, *N,N*-dimethylaminothiazoles **11a-f** were also obtained in moderate yields. These results confirm that the pyridyl moiety at the 4-position of a thiazole ring predominantly facilitates deamination reactions. However, no formation of thiazolines **12** was observed after reaction completion, except for thioamide having a phenyl substituent at the 4-position **9f**, which gave a trace amount of the corresponding thiazoline **12f**.

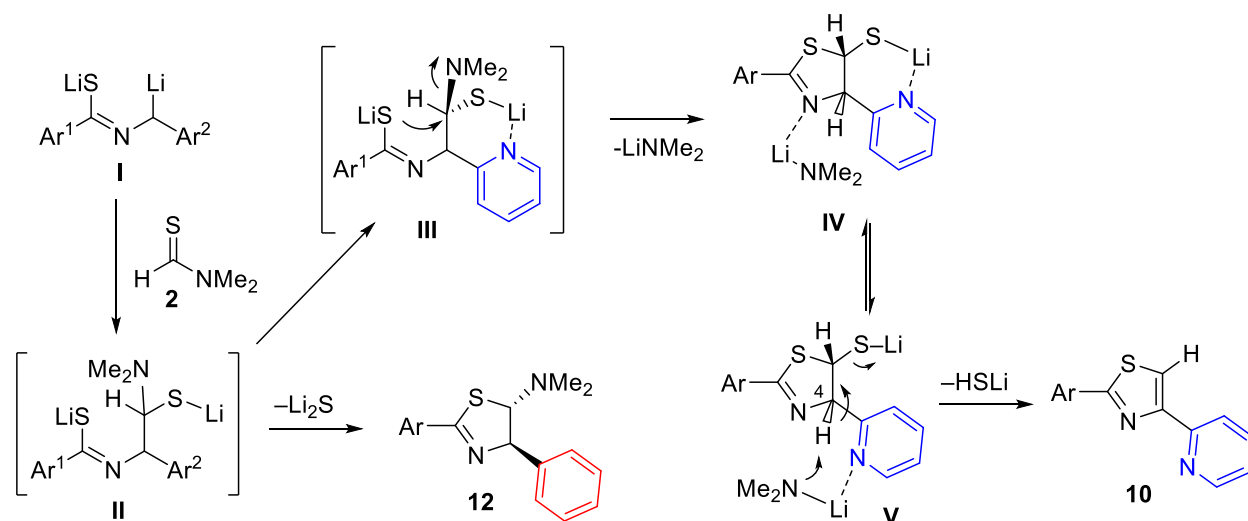
**Table 1.** Product distribution of the reaction between thioamides and *N,N*-dimethylthioformamide<sup>a</sup>

			
 <b>9a</b>	 <b>10a</b> 52% <sup>a</sup>	 <b>11a</b> 18% <sup>a</sup>	 <b>12a</b> 0% <sup>a</sup>
 <b>9b</b>	 <b>10b</b> 55%	 <b>11b</b> 18%	 <b>12b</b> 0%
 <b>9c</b>	 <b>10c</b> 41% 60% <sup>b</sup>	 <b>11c</b> 35% 24% <sup>b</sup>	 <b>12c</b> 0%
 <b>9d</b>	 <b>10d</b> 56%	 <b>11d</b> 28%	 <b>12d</b> 0%
 <b>9e</b>	 <b>10e</b> 20%	 <b>11e</b> 16%	 <b>12e</b> 0%
 <b>9f</b>	 <b>10f</b> 3%	 <b>11f</b> 27%	 <b>12f</b> trace

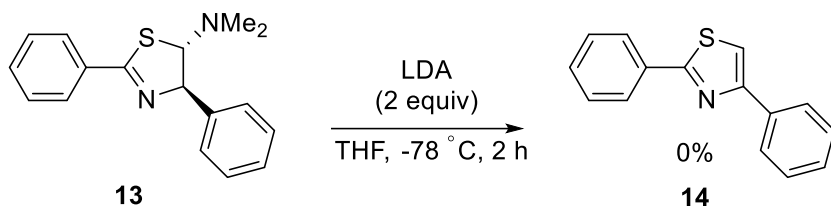
All reactions were carried out in 2.0 mmol scale unless otherwise noted; <sup>a</sup> Carried out in 3.0 mmol scale. <sup>b</sup> Carried out in 1.0 mmol scale

### 3.2.3. Plausible mechanism reaction

A plausible reaction pathway to 5-H thiazoles **10** is shown in Scheme 3. Deprotonation from secondary thioamides with *n*-BuLi may generate thioamide dianions **I**, which then react with thioformamide **2** to form **II** as an intermediate. In the reaction of the dianion derived from *N*-methylphenyl thioamide, a LiS group acts as a leaving group to give 5-aminothiazoline **12**. In contrast, a pyridyl group such as Ar<sup>2</sup> in **II** may coordinate to lithium to generate intermediate **III**, which may reduce the leaving ability of the LiS group, and thus a dimethylamino group in **III** may act as a leaving group to form **IV** and lithium dimethylamide (LiNMe<sub>2</sub>). Finally, LiNMe<sub>2</sub> acts as a base to deprotonate from the 4-position of the thiazoline ring to lead to the formation of **12**. As in intermediate **V**, coordination of the nitrogen atom of the pyridyl group to lithium may enhance the basicity of LiNMe<sub>2</sub>. In fact, attempted deprotonation from thiazoline **13** with LDA failed to give 5-H thiazole **14**, as shown in Scheme 4.



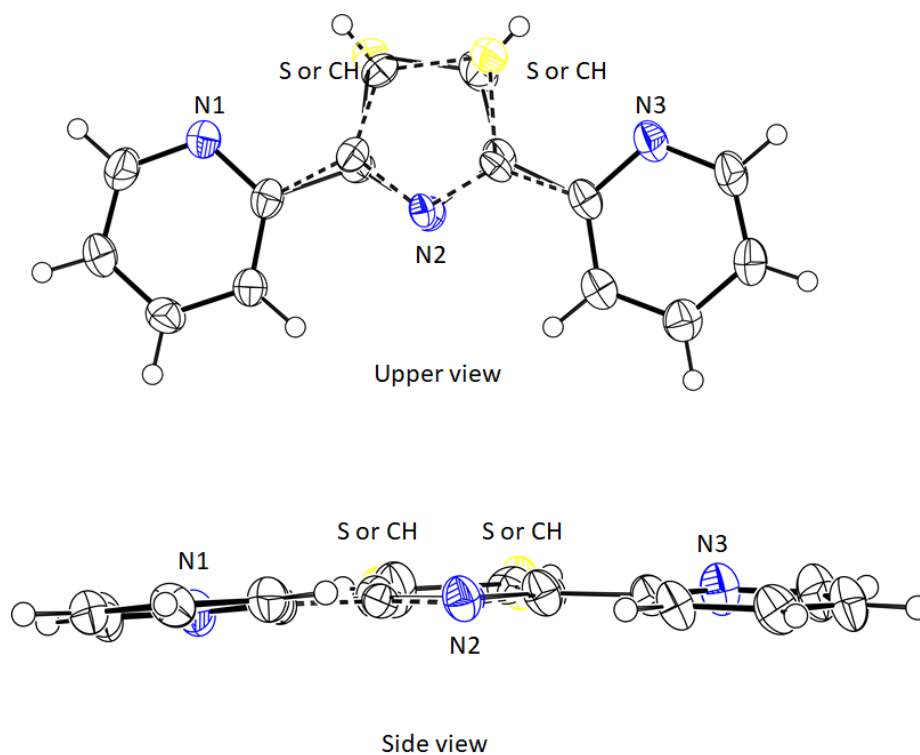
**Scheme 3.** Plausible reaction pathway for 5-H thiazoles **10**



**Scheme 4.** Reaction of thiazoline **13** with LDA

### 3.2.4. Molecular structure

The structure of **10a** was confirmed by X-ray crystallography (Figure 1). A single crystal suitable for X-ray crystallography of **10a** was obtained by the slow diffusion method. The crystal contains three independent molecules, and the sulfur atom and C-H group are disordered. Nevertheless, the molecular structure shows that two 2-pyridyl rings are in the same plane as the thiazole ring. Moreover, the nitrogen atom of the pyridyl group attached at the 2- and 4-positions is oriented close to the sulfur atom on the thiazole ring.



**Figure 1.** ORTEP drawing of **10a**; thermal ellipsoids are shown at 50% probability.



### 3.3. Summary of Chapter 3

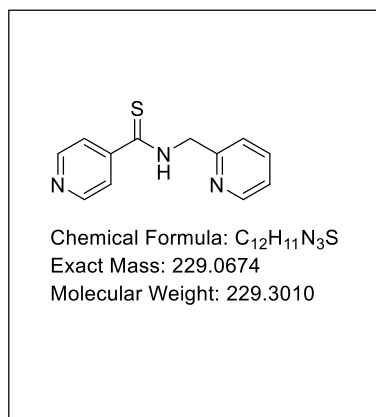
In summary, the synthesis of 5-H thiazoles via thioamide dianions, especially those with a pyridymethyl group on the nitrogen atom with *N,N*-dimethylthioformamide has been disclosed. The substituents attached at the 2-position of a thiazole ring do not significantly affect the formation of 5-H thiazoles. In contrast, the introduction of a phenyl group at the 4-position of the thiazole ring greatly decreases the formation of 5-H thiazoles.

### 3.4. Experimental section

**Characterization:** The IR spectra were obtained on a JASCO FT-IR 410 spectrophotometer.  $^1\text{H}$  NMR, and  $^{13}\text{C}$  NMR spectra were measured on JNM-ECS400 (392 MHz), JNM-AL400 (396 MHz), JNM ECX-400P (400 MHz), JNM ECA-500 (500 MHz) in a deuterated solvent. Chemical shifts of  $^1\text{H}$  and  $^{13}\text{C}$  are reported in  $\delta$  values referred to tetramethylsilane or  $\text{CDCl}_3$  as an internal standard, respectively. All spectra were acquired in the proton-decoupled mode. The mass spectra (MS) and high-resolution mass spectra (HRMS) were taken on a JMS-700 mass spectrometers. Melting points were determined by using a OptiMelt MPA100 melting point system. Preparative recycling gel permeation chromatography (GPC) was performed on Japan Analytical Industry LC9201R/U recycling preparative HPLC equipped with JAIGEL-1H and -2H columns (chloroform as an eluent).

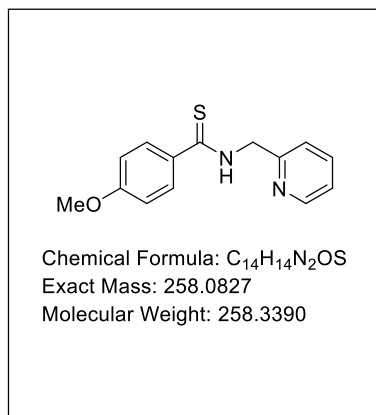
**Materials:** Hexane, ethyl acetate (EtOAc), and THF were purchased from Kanto Chemical Co., Ltd., and used without purification. Acetone, magnesium sulfate anhydrous ( $\text{MgSO}_4$ ), dichloromethane ( $\text{CH}_2\text{Cl}_2$ ) and used without further purification. Column chromatography was run on silica gel 60 N (Spherical, Neutral, 40-50  $\mu\text{m}$ ) of Kanto Chemical Co., Ltd. The secondary thiomides **1a**,<sup>9</sup> **1b**,<sup>10</sup> **9a**<sup>10</sup> and **9f**<sup>11</sup> were prepared by reported procedures.

#### *N*-(pyridin-2-ylmethyl)pyridine-4-carbothioamide (**9b**)



To a solution isonicotinaldehyde (1.89 mL, 20 mmol) in DMF (8.0 mL) was added elemental sulfur (0.704 g, 22 mmol) at room temperature. To this was added 2-picolyamine (2.62 mL, 26 mmol), and the mixture was stirred for 3 h at 80 °C. The mixture was cooled to room temperature. The combined organic phase was washed with brine and extracted with  $\text{Et}_2\text{O}$ . The organic layer was dried over  $\text{MgSO}_4$  and concentrated under reduce pressure. The crude material was purified by column chromatography ( $\text{SiO}_2$ , hexane/EtOAc = 5:1) to give the corresponding secondary thioamide **9b** (0.82 g, 18 %) as a yellow solid (mp 180-183 °C): IR (KBr) 3253, 1594, 1523, 1434, 1374, 1321, 1213, 1044, 997, 969, 747  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.30 (s, 2H), 7.21-7.28 (t, 3H), 7.41-7.44 (m, 1H), 7.62 (d,  $J$  = 8.0 Hz, 1H), 7.79-7.83 (td, 1H), 7.87-7.89 (t, 1H), 8.57-8.59 (m, 1H), 8.63-8.66 (m, 1H);  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  50.3, 122.5, 122.8, 124.8, 126.1, 137.2, 137.2, 147.4, 149.1, 151.4, 154.9, 191.1; MS (EI)  $m/z$  229( $\text{M}^+$ ); HRMS (EI) calcd for  $\text{C}_{12}\text{H}_{11}\text{N}_3\text{S}$ : 229.0674; found: 229.0666.

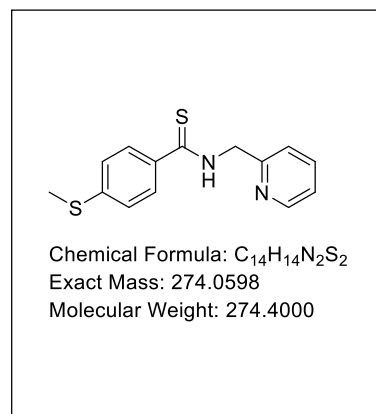
#### 4-methoxy-*N*-(pyridin-2-ylmethyl)benzothioamide (**9c**)



To a solution 4-methoxybenzaldehyde (1.20 mL, 10 mmol) in DMF ( 8.0 mL) was added elemental sulfur (0.35 g, 11 mmol) at room temperature. To this was added 2-picolylamine (1.31 mL, 13 mmol), and the mixture was stirred for 3 h at 80 °C. The mixture was cooled to room temperature. The combined organic phase was washed with brine and extracted with Et<sub>2</sub>O. The organic layer was dried over MgSO<sub>4</sub> and concentrated under reduce pressure. The crude material was purified by column chromatography (SiO<sub>2</sub>, hexane/EtOAc = 5:1) to give the

corresponding secondary thioamide **7c** (1.73 g, 67 %) as a yellow solid (mp 79-82 °C): IR (KBr) 3309, 1602, 1567, 1528, 1504, 1437, 1292, 1257, 1171, 1024, 948, 835, 763, cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.83 (s, 3H), 5.04 (d, *J* = 4.1 Hz, 2H), 6.88-6.94 (m, 2H), 7.23-7.26 (m, 1H), 7.33 (d, *J* = 7.7 Hz, 1H), 7.69-7.73 (td, 1H), 7.90-7.93 (m, 2H), 8.55 (d, *J* = 5.0 Hz, 1H), 9.38 (s, 1H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ 50.5, 55.5, 55.6, 113.7, 122.4, 122.8, 128.8, 133.6, 137.2, 148.7, 154.3, 162.3, 196.8; MS (EI) *m/z* 258(M<sup>+</sup>); HRMS (EI) calcd for C<sub>14</sub>H<sub>14</sub>N<sub>2</sub>OS: 258.0827; found: 258.0853.

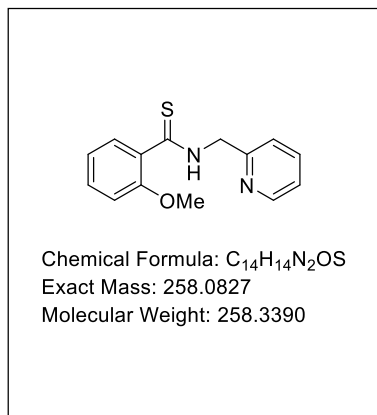
#### 4-(methylthio)-*N*-(pyridin-2-ylmethyl)benzothioamide (**9d**)



To a solution 4-(methylthio)benzaldehyde (2.60 mL, 20 mmol) in DMF ( 10.0 mL) was added elemental sulfur (0.704 g, 22 mmol) at room temperature. To this was added 2-picolylamine (2.62 mL, 26 mmol), and the mixture was stirred for 3 h at 80 °C. The mixture was cooled to room temperature. The combined organic phase was washed with brine and extracted with Et<sub>2</sub>O. The organic layer was dried over MgSO<sub>4</sub> and concentrated under reduce pressure. The crude material was purified by column chromatography (SiO<sub>2</sub>, hexane/EtOAc = 5:1) to give the

the corresponding secondary thioamide **7d** (3.93 g, 71 %) as a light yellow solid (mp 86-88 °C): IR (KBr) 3278, 1592, 1516, 1476, 1429, 1401, 1319, 1229, 1186, 1092, 949, 823, 752 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.50 (s, 3H), 5.10 (d, *J* = 4.1 Hz, 2H), 7.23-7.45 (m, 4H), 7.78-7.89 (m, 3H), 8.56-8.57 (m, 1H), 9.51 (s, 1H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ 15.2, 50.5, 122.4, 122.9, 125.4, 126.6, 127.4, 129.8, 129.9, 137.2, 143.3, 148.7, 154.1, 196.8; MS (EI) *m/z* 274(M<sup>+</sup>); HRMS (EI) calcd for C<sub>14</sub>H<sub>14</sub>N<sub>2</sub>S<sub>2</sub>: 274.0598; found: 274.0606.

## 2-methoxy-*N*-(pyridin-2-ylmethyl)benzothioamide (9e)

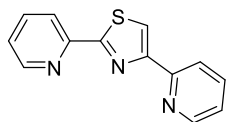


To a solution 2-methoxybenzaldehyde (2.40 mL, 20 mmol) in DMF ( 8.0 mL) was added elemental sulfur (0.704 g, 22 mmol) at room temperature. To this was added 2-picolyamine (2.62 mL, 26 mmol) and, the mixture was stirred for 3 h at 80 °C. The mixture was cooled to room temperature. The combined organic phase was washed with brine and extracted with Et<sub>2</sub>O. The organic layer was dried over MgSO<sub>4</sub> and concentrated under reduce pressure. The crude material was purified by column chromatography (SiO<sub>2</sub>, hexane/EtOAc = 10:1) to

give the corresponding secondary thioamide **9e** (1.04 g, 20 %) as a light yellow solid (mp 83-84 °C): IR (KBr) 2319, 1597, 1573, 1525, 1482, 1454, 1433, 1376, 1267, 1246, 1205, 1205, 1025, 749, 789, 448 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.00 (s, 3H), 5.18 (d, *J* = 4.0 Hz, 2H), 6.95 -7.15 (m, 3H), 7.38-7.43 (m, 1H), 7.50-7.68 (m, 1H), 7.76-7.89 (m, 1H), 8.48-8.51 (td, 1H), 8.57 (d, *J*= 4.5 Hz, 1H), 10.95 (s, 1H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ 51.7, 56.1, 111.5, 120.9, 122.0, 122.6, 126.8, 132.4, 134.8, 136.9, 148.9, 154.7, 155.8, 194.3; MS (EI) *m/z* 258(M<sup>+</sup>); HRMS (EI) calcd for C<sub>14</sub>H<sub>14</sub>N<sub>2</sub>OS: 258.0827; found: 258.0831.

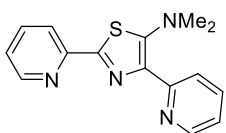
## 2,4-di(pyridin-2-yl)thiazole (10a)

To a solution of *N*-(pyridin-2-ylmethyl)pyridine-2-carbothioamide (0.68 g, 3.0 mmol) in THF (10 mL) was added slowly a 1.25 M *n*-butyllithium in hexane (4.6 mL, 6.0 mmol), and the mixture was stirred for 15 min at 0 °C. To this mixture was added *N,N*-dimethylthioformamide (0.25 mL, 3.0 mmol) at 0 °C, and the mixture was stirred at this temperature for 30 min. Then, I<sub>2</sub> (0.76 g, 3.0 mmol) in THF (5 mL) was added at 0 °C, and The mixture was continuously stirred at the room temperature for 3 h. The resulting mixture was poured into saturated aqueous solution of NH<sub>4</sub>Cl and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was then dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO<sub>2</sub>, hexane : EtOAc = 5 : 1) to give the corresponding thiazole **10a** and dimethylaminothiazole **11a**.



Chemical Formula: C<sub>13</sub>H<sub>9</sub>N<sub>3</sub>S  
Exact Mass: 239.0517  
Molecular Weight: 239.2960

**10a** (0.37 g, 52 %) as a orange solid (mp: 132-135 °C): IR (KBr) 3180, 3034, 2998, 1586, 1567, 1506, 1464, 1436, 1057, 1001, 781, 751, 736, 694, 672, 619 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.24-7.25 (m, 2H), 7.34-7.43 (m, 1H), 7.82-7.86 (td, 1H), 8.02 (s, 1H), 8.30-8.32 (d, *J* = 7.7 Hz, 1H), 8.41-8.43 (d, *J* = 7.9 Hz, 1H), 8.63-8.64 (d, *J* = 3.6 Hz, 1H), 8.70 (d, *J* = 3.2 Hz, 1H); <sup>13</sup>C NMR (500 MHz, CDCl<sub>3</sub>) δ 119.5, 119.8, 121.1, 122.9, 124.6, 137.0, 149.5, 151.3, 152.5, 156.5, 169.0 ; MS (EI) *m/z* 239(M<sup>+</sup>); HRMS (EI) calcd for C<sub>13</sub>H<sub>9</sub>N<sub>3</sub>S, 239.0517; found, 239.0505.

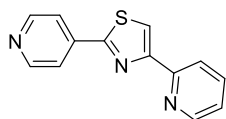


Chemical Formula: C<sub>15</sub>H<sub>14</sub>N<sub>4</sub>S  
Exact Mass: 282.0939  
Molecular Weight: 282.3650

**11a** (0.15, 18%) as brown oil: IR (KBr) 3420, 2923, 1586, 1564, 1501, 1472, 1433, 1413, 1366, 1145, 1001, 783, 741 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.94 (s, 6H) 7.21-7.22 (d, 1H) 7.23 (t, 1H) 7.73-7.77 (td, 1H) 7.79-7.83 (td, 1H) 8.13-8.14 (d, 1H) 8.27-8.29 (d, 1H) 8.53-8.54 (d, 1H) 8.74-8.75 (d, 1H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ 46.3, 118.7, 121.0, 123.3, 125.0, 125.9, 136.3, 136.7, 136.9, 149.0, 149.1, 151.9, 154.4, 157.2; (EI) *m/z* 282 (M<sup>+</sup>); HRMS (EI) calcd for C<sub>15</sub>H<sub>14</sub>N<sub>4</sub>S: 282.0939; found: 282.0938.

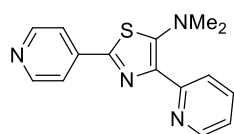
#### 4-(pyridin-2-yl)-2-(pyridin-4-yl)thiazole (**10b**)

To a solution of *N*-(pyridin-2-ylmethyl)pyridine-4-carbothioamide (0.44 g, 2.0 mmol) in THF (10 mL) was added slowly a 1.25 M *n*-butyllithium in hexane (2.6 mL, 4.0 mmol), and the mixture was stirred for 15 min at 0 °C. To this mixture was added *N,N*-dimethylthioformamide (0.166 mL, 2.0 mmol) at 0 °C, and the mixture was stirred at this temperature for 30 min. Then, I<sub>2</sub> (0.51 g, 2.0 mmol) in 5 mL THF was added at 0 °C and continuously stirred at the room temperature for 3 h. The resulting mixture was poured into saturated aqueous solution of NH<sub>4</sub>Cl and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was then dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO<sub>2</sub>, hexane : EtOAc = 5 : 1) to give the corresponding thiazole **10b** and dimethylaminothiazole **11b**.



Chemical Formula: C<sub>13</sub>H<sub>9</sub>N<sub>3</sub>S  
Exact Mass: 239.0517  
Molecular Weight: 239.2960

**10b** (0.25 g, 55 %) as a yellow brownish solid (mp 143-145 °C): IR (KBr) 3108, 2923, 1586, 1464, 1421, 1296, 1275, 1057, 1001, 782, 736, 693, 620 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.33-7.37 (m, 2H), 7.81-7.85 (td, 2H), 8.30-8.32 (m, 1H), 8.62-8.64 (m, 2H), 8.68-8.69 (d, *J* = 4.5 Hz, 2H); <sup>13</sup>C NMR (500 MHz, CDCl<sub>3</sub>) δ 119.9, 120.0, 121.3, 123.0, 124.7, 137.1, 137.5, 149.1, 149.6, 151.3, 152.3; MS (EI) *m/z* 239(M<sup>+</sup>); HRMS (EI) calcd for C<sub>13</sub>H<sub>9</sub>N<sub>3</sub>S: 239.0517; found: 239.0503.

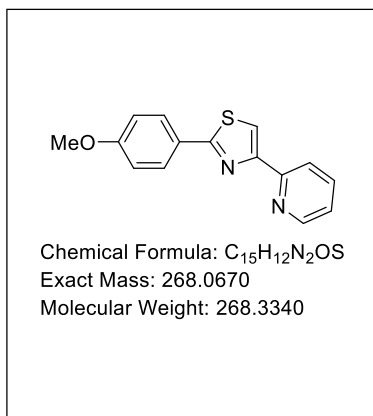


Chemical Formula: C<sub>15</sub>H<sub>14</sub>N<sub>4</sub>S  
Exact Mass: 282.0939  
Molecular Weight: 282.3650

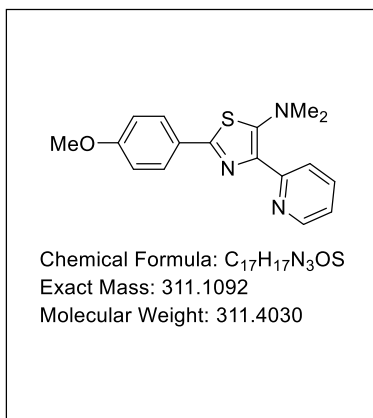
**11b** (0.09 g, 18 %) as a brown sticky oil: IR (KBr) 3048, 2944, 1585, 1563, 1502, 1470, 1432, 1413, 1360, 1000, 921, 784, 739 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.94 (s, 6H), 7.21-7.28 (m, 2H), 7.73-7.83 (dt, 2H), 8.12 (d, *J* = 7.6 Hz, 1H), 8.27 (d, *J* = 8.0 Hz, 1H), 8.53 (m, 1H), 8.77 (s, 1H); <sup>13</sup>C NMR (500 MHz, CDCl<sub>3</sub>) δ 46.4, 119.0, 121.0, 121.2, 123.4, 123.5, 136.8, 136.9, 148.6, 149.2, 151.9, 152.3; MS (EI) *m/z* 282(M<sup>+</sup>); HRMS (EI) calcd for C<sub>15</sub>H<sub>14</sub>N<sub>4</sub>S, 282.0939; found: 282.0954.

### 2-(4-methoxyphenyl)-4-(pyridin-2-yl)thiazole (**10c**)

To a solution of *N*-benzyl-4-methoxybenzothioamide (0.25 g, 1.0 mmol) in THF (8 mL) was added slowly a 1.25 M *n*-butyllithium in hexane (1.4 mL, 2.0 mmol), and the mixture was stirred for 15 min at 0 °C. To this mixture was added *N,N*-dimethylthioformamide (0.08 mL, 1.0 mmol) at 0 °C, and the mixture was stirred at this temperature for 30 min. Then, I<sub>2</sub> (0.25 g, 1.0 mmol) in 5 mL THF was added at 0 °C and continuously stirred at the room temperature for 3 h. The resulting mixture was poured into saturated aqueous solution of NH<sub>4</sub>Cl and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was then dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO<sub>2</sub>, hexane : EtOAc = 5 : 1) to give the corresponding thiazole **10c** and dimethylaminothiazole **11c**.



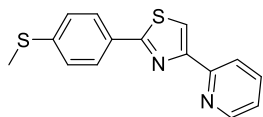
**10c** (0.15 g, 60 %) as a an ocher solid (mp 100-103 °C): IR (KBr) 3085, 3000, 2934, 1606, 1588, 1567, 1518, 1476, 1417, 1305, 1246, 1180, 1060, 1025, 834, 778, 714, 671 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.87 (s, 3H), 6.96-6.99 (m, 2H), 7.25-7.32 (m, 3H), 7.89-7.98 (m, 2H), 8.34 (s, 1H), 8.64-8.65 (d, *J* = 4.1 Hz, 1H); <sup>13</sup>C NMR (500 MHz, CDCl<sub>3</sub>) δ 55.5, 114.3, 116.2, 121.4, 122.8, 126.7, 128.1, 137.1, 149.4, 152.7, 155.8, 161.3, 168.0 ; MS (EI) *m/z* 268(M<sup>+</sup>); HRMS (EI) calcd for C<sub>15</sub>H<sub>12</sub>N<sub>2</sub>OS: 268.0670; found: 268.0663.



**11c** (0.11 g, 18 %) as a brown sticky oil: IR (KBr) 2952, 1607, 1585, 1566, 1536, 1480, 1415, 1304, 1251, 1172, 1132, 1031, 973, 917, 835, 789, 746, 712, 519 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.86 (s, 3H), 3.29 (d, *J* = 8.2 Hz, 3H), 3.84 (s, 3H), 6.93-6.95 (m, 1H), 7.24-7.32 (m, 3H), 7.92-7.94 (m, 2H), 8.29 (m, 1H), 8.98-9.20 (m, 1H); <sup>13</sup>C NMR (500 MHz, CDCl<sub>3</sub>) δ 46.8, 55.4, 113.9, 114.2, 114.4, 121.1, 123.5, 127.2, 127.4, 128.2, 134.2, 136.8, 148.8, 160.7; MS (EI) *m/z* 311(M<sup>+</sup>); HRMS (EI) calcd for C<sub>17</sub>H<sub>17</sub>N<sub>3</sub>OS: 311.1092; found: 311.1081.

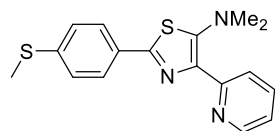
## 2-(4-(methylthio)phenyl)-4-(pyridin-2-yl)thiazole (**10d**)

To a solution of 4-(methylthio)-*N*-(pyridin-2-ylmethyl)benzothioamide (0.55 g, 2.0 mmol) in THF (10 mL) was added slowly a 1.25 M *n*-butyllithium in hexane 3.0 mL, 4.0 mmol), and the mixture was stirred for 15 min at 0 °C. To this mixture was added *N,N*-dimethylthioformamide (0.166 mL, 2.0 mmol) at 0 °C, and the mixture was stirred at this temperature for 30 min. Then, I<sub>2</sub> (0.51 g, 2.0 mmol) in 5 mL THF was added at 0 °C and continuously stirred at the room temperature for 3 h. The resulting mixture was poured into saturated aqueous solution of NH<sub>4</sub>Cl and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was then dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO<sub>2</sub>, hexane : EtOAc = 5 : 1) to give the corresponding thiazole **10d** and dimethylaminothiazole **11d**.



Chemical Formula: C<sub>15</sub>H<sub>12</sub>N<sub>2</sub>S<sub>2</sub>  
Exact Mass: 284.0442  
Molecular Weight: 284.3950

**10d** (0.32 g, 56 %) as an ocher solid (mp 98-100 °C): IR (KBr) 3082, 1590, 1424, 1397, 1239, 1092, 1064, 994, 810, 772, 737, 702 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.53 (s, 3H), 7.25-7.32 (m, 5H), 7.93-7.95 (m, 2H), 8.19-8.39 (m, 1H), 8.66-8.67 (d, *J* = 5.0 Hz, 1H); <sup>13</sup>C NMR (500 MHz, CDCl<sub>3</sub>) δ 15.4, 116.7, 121.4, 122.9, 126.2, 126.9, 130.3, 137.1, 141.5, 149.4, 152.6, 156.0, 167.7; MS (EI) *m/z* 284(M<sup>+</sup>); HRMS (EI) calcd for C<sub>15</sub>H<sub>12</sub>N<sub>2</sub>S, 284.0442: found: 284.0440.



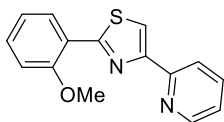
Chemical Formula: C<sub>17</sub>H<sub>17</sub>N<sub>3</sub>S<sub>2</sub>  
Exact Mass: 327.0864  
Molecular Weight: 327.4640

**11d** (0.18 g, 28 %) as a yellow solid; (Mp: 87-89 °C) IR (KBr) 2950, 1585, 1566, 1537, 1478, 1415, 1398, 1132, 1093, 971, 918, 817, 701 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.50 (s, 3H), 2.91 (s, 6H), 7.24-7.27 (m, 3H), 7.86-7.88 (m, 3H), 8.21 (d, *J* = 7.7 Hz, 1H), 8.86-8.87 (m, 1H); <sup>13</sup>C NMR (500 MHz, CDCl<sub>3</sub>) δ 15.5, 46.7, 121.1, 123.5, 126.1, 126.2, 131.0, 136.4, 137.5, 140.0, 149.0, 154.1, 154.6, 154.8; MS (EI) *m/z* 284(M<sup>+</sup>); HRMS (EI) calcd for C<sub>17</sub>H<sub>17</sub>N<sub>3</sub>S<sub>2</sub>: 327.0864; found: 327.0857.

## 2-(2-methoxyphenyl)-4-(pyridin-2-yl)thiazole (10e)

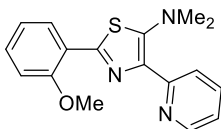
To a solution of *N*-benzyl-2-methoxybenzothioamide (0.51 g, 2.0 mmol) in THF (8 mL) was added slowly a 1.25 M *n*-butyllithium in hexane (3.8 mL, 4.0 mmol), and the mixture was stirred for 15 min at 0 °C. To this mixture was added *N,N*-dimethylthioformamide (0.17 mL, 2.0 mmol) at 0 °C, and the mixture was stirred at this temperature for 30 min. Then, I<sub>2</sub> (0.51 g, 2.0 mmol) in 5 mL THF was added at 0 °C and continuously stirred at the room temperature for 3 h. The resulting mixture was poured into saturated aqueous solution of NH<sub>4</sub>Cl and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was then dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO<sub>2</sub>, hexane : EtOAc = 5 : 1) to give the corresponding thiazole **10e** and dimethylaminothiazole **11e**.





Chemical Formula: C<sub>15</sub>H<sub>12</sub>N<sub>2</sub>OS  
Exact Mass: 268.0670  
Molecular Weight: 268.3340

**10e** (0.10 g, 20 %) as a yellow brownish solid (mp 105-106 °C): IR (KBr) 3126, 1586, 1569, 1497, 1465, 1418, 1332, 1289, 1267, 1251, 1180, 1161, 1117, 1059, 1019, 751, 714, 673, cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.04 (s, 3H), 6.82-7.13 (m, 3H), 7.38-7.43 (m, 2H), 7.81-7.85 (m, 1H), 8.34-8.36 (m, 1H), 8.53-8.56 (dd, 1H), 8.63-8.64 (d, *J* = 4.5 Hz, 1H); <sup>13</sup>C NMR (500 MHz, CDCl<sub>3</sub>) δ 55.6, 111.4, 118.1, 121.1, 121.3, 122.3, 122.6, 128.5, 130.7, 137.0, 149.4, 153.1, 154.1, 156.5, 162.3; MS (EI) *m/z* 268(M<sup>+</sup>); HRMS (EI) calcd for C<sub>15</sub>H<sub>12</sub>N<sub>2</sub>OS: 268.0670; found: 268.0676.

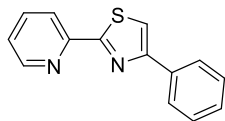


Chemical Formula: C<sub>17</sub>H<sub>17</sub>N<sub>3</sub>OS  
Exact Mass: 311.1092  
Molecular Weight: 311.4030

**11e** (0.10 g, 16 %) as a brown oil: IR (KBr) 3300, 2954, 1586, 1463, 1415, 1289, 1247, 1180, 1160, 1115, 1050, 1023, 921, 754 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 2.92 (s, 6H), 4.00 (s, 3H), 6.94-7.15 (m, 3H), 7.29-7.33 (td, 1H), 7.72-7.75 (td, 1H), 8.15-8.19 (m, 1H), 8.41-8.43 (dd, 1H), 8.54-8.73 (m, 1H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ 46.5, 55.7, 111.4, 120.8, 121.0, 123.0, 123.5, 127.7, 129.6, 132.0, 135.6, 136.2, 149.0, 154.8, 155.4, 155.8; MS (EI) *m/z* 311(M<sup>+</sup>); HRMS (EI) calcd for C<sub>17</sub>H<sub>17</sub>N<sub>3</sub>OS: 311.1092; found: 311.1088.

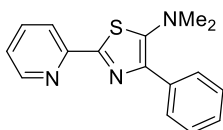
#### 4-phenyl-2-(pyridin-2-yl)thiazole (**10f**)

To a solution of *N*-benzylpyridine-2-carbothioamide (0.45 g, 2.0 mmol) in THF (8 mL) was added slowly a 1.25 M *n*-butyllithium in hexane (3.8 mL, 4.0 mmol), and the mixture was stirred for 15 min at 0 °C. To this mixture was added *N,N*-dimethylthioformamide (0.17 mL, 2.0 mmol) at 0 °C, and the mixture was stirred at this temperature for 30 min. Then, I<sub>2</sub> (0.51 g, 2.0 mmol) in 5 mL THF was added at 0 °C and continuously stirred at the room temperature for 3 h. The resulting mixture was poured into saturated aqueous solution of NH<sub>4</sub>Cl and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was then dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO<sub>2</sub>, hexane : EtOAc = 5 : 1) to give the corresponding thiazole **10f** along with dimethylthiazole **11f** and dimethylthiazoline **12f**.



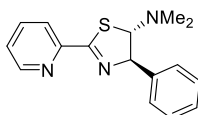
Chemical Formula:  $C_{14}H_{10}N_2S$   
Exact Mass: 238.0565  
Molecular Weight: 238.3080

**10f** (0.02 g, 3 %) as a pale brown solid (mp: 67-69 °C): IR (KBr) 3113, 1582, 1565, 1501, 1465, 1434, 1229, 1276, 1075, 1057, 998, 785, 743, 732, 693, 675, 616  $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.31-7.37 (m, 2H), 7.43-7.46 (t, 2H), 7.59 (s, 1H), 7.79-7.84 (td, 1H), 7.98-8.00 (m, 2H), 8.31-8.33 (d,  $J$  = 7.7 Hz, 1H), 8.61-8.62 (d,  $J$  = 4.5 Hz, 1H);  $^{13}C$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  115.3, 120.0, 124.6, 126.4, 128.3, 128.8, 134.5, 137.1, 149.4, 151.5, 156.7, 168.7; MS (EI)  $m/z$  238 ( $M^+$ ); HRMS (EI) calcd for  $C_{14}H_{10}N_2S$ : 238.0565; found: 238.0566.



Chemical Formula:  $C_{16}H_{15}N_3S$   
Exact Mass: 281.0987  
Molecular Weight: 281.3770

**11f** (0.15 g, 27 %) as a brown oil; IR (KBr) 2952, 1585, 1565, 1482, 1433, 1384, 1143, 1092, 1001, 916, 698, 619  $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  2.88 (s, 6H), 7.30-7.39 (m, 2H), 7.43-7.47 (m, 3H), 7.86-7.93 (m, 1H), 7.98-8.03 (m, 1H), 8.36-8.45 (m, 1H), 8.64-8.65 (m, 1H);  $^{13}C$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  46.2, 118.9, 123.6, 127.1, 127.7, 128.3, 135.2, 136.9, 140.9, 149.1, 152.0, 154.0, 156.9; MS (EI)  $m/z$  281 ( $M^+$ ); HRMS (EI) calcd for  $C_{16}H_{15}N_3S$ : 281.0987; found: 281.3770.



Chemical Formula:  $C_{16}H_{17}N_3S$   
Exact Mass: 283.1143  
Molecular Weight: 283.3930

**12f** trace as an orange oil; IR (KBr) 3290, 3059, 2951, 1280, 1176, 1149, 1045, 1025, 996, 958, 836, 789, 743, 698, 537  $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  2.20 (s, 6H), 5.15 (d,  $J$  = 2.0, 1H), 5.63 (d,  $J$  = 2.0 Hz, 1H), 7.18-7.22 (m, 4H), 7.30-7.37 (m, 2H), 7.71 (td, 1H), 8.12 (d,  $J$  = 8.3 Hz, 1H), 8.65 (dd, 1H);  $^{13}C$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  40.1, 84.9, 88.9, 121.9, 125.6, 126.2, 127.8, 128.7, 136.6, 139.6, 149.4, 151.3, 170.9 ; MS (EI)  $m/z$  283 ( $M^+$ ); HRMS (EI) calcd for  $C_{16}H_{17}N_3S$ : 283.1143; found: 283.1170.

**Crystal data and structure refinement 10a**

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Empirical formula	C <sub>13</sub> H <sub>9</sub> N <sub>3</sub> S	
Molecular weight	239.29	
Crystal system	monoclinic	
Space group	C2/c	
Temperature	123 (K)	
Unit cell dimension	a = 16.7618 (19) Å	α = 90
	b = 11.9433 (8) Å	β = 80.9699 (13)°
	c = 23.653 (3) Å	γ = 90
Volume	4499.5 (9) Å <sup>3</sup>	
Z	16	
Density (calculated)	1.413 Mg/m <sup>3</sup>	
Absorption coefficient	0.265 mm <sup>-1</sup>	
<i>F</i> (000)	1984	
Crystal size	0.20 × 0.14 × 0.11 mm <sup>3</sup>	
The range of data collection	1.812 to 27.499°	
Index ranges	-21 ≤ h ≤ 21, -15 ≤ k ≤ 12, -30 ≤ l ≤ 30	
Reflection collected	19766	
Independent reflection	5186 [R (int) = 0.113]	
Completeness to theta = 27.50°	99.9%	
Max. min. transmission	0.233 and 1.000	
Refinement method	Full-matrix least-squares on F <sup>2</sup>	
Data / restraints / parameters	5186 / 344 / 398	
Goodness-of-fit on <i>F</i> <sup>2</sup>	1.026	
Final R indices [ <i>I</i> > 2σ( <i>I</i> )]	R <sub>I</sub> = 0.0835, wR <sub>2</sub> = 0.1358	
R indices (all data)	R <sub>I</sub> = 1.358, wR <sub>2</sub> = 0.2748	
Largest diff. peak and hole	0.60 and -0.67 e Å <sup>-3</sup>	

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## Chapter 4

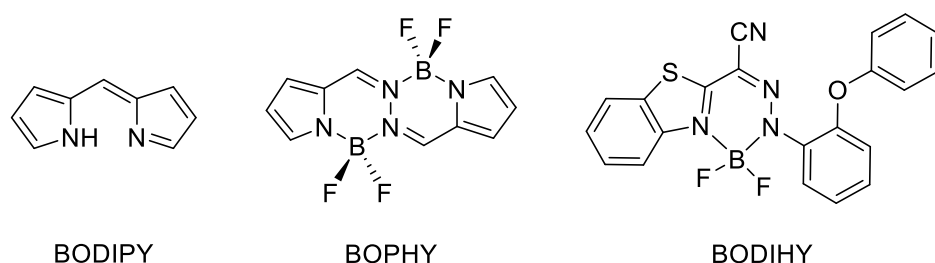
### Boron complexes of thiazole-bridged 1,5- bidentate nitrogen ligands: synthesis and acid-responsive photophysical properties

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## 4.1. Introduction

Fluorescent molecules containing a boron atom such as boron difluorides have received an increasing amount of interest. These dyes are highly popular because of their excellent optical characteristics, photochemical stability, and low cytotoxicity. Among those boron difluoride dyes, the most known is 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (**BODIPY**). These compounds typically show relatively narrow absorption and emission bands, high molar absorption coefficients, and excellent fluorescence quantum yields.<sup>1</sup> Recent studies have shown that the introduction of an aryl group and heteroatom substituents at the meso position of BODIPY induces a large Stokes shift,<sup>2</sup> and an interesting dual-state emission (DSE) with mechanochromism properties.<sup>3,4</sup> Furthermore, modification at the pyrrole ring of BODIPY shifts the emission maxima to the NIR region.<sup>5-7</sup> Apart from BODIPY, other four-coordinated boron complexes compounds such as bis(difluoroboron)-1,2-bis((1H-pyrrol-2yl)methylene)hydrazine (**BOPHY**) and boron-difluoride (BF<sub>2</sub>)-hydrazone complexes (**BODIHY**) have also exhibited high quantum yields, aggregation-induced emission enhancement (AIEE) and mechanochromism properties (Chart 1).<sup>8-10</sup>



**Chart 1.** Selected example of boron difluoride dyes.

Thiazole boron complexes also exhibit unique photophysical properties comparable to the above-mentioned boron complexes. For instance, boron-thiazole complexes containing an aryl-aza enamine structure show high solid state emission and aggregation induced emission enhancement (AIEE) properties.<sup>11</sup> *N,O*-chelated organoboron complexes have also been reported to show finely tuned photophysical properties with aggregation-induced emission properties.<sup>12,13</sup> However, the example of boron complexes coordinated by such as ligands are still limited. Therefore, the design and synthesis of 1,5-bidentate nitrogen ligands having a thiazole ring are of interest.

Meanwhile, acid-responsive changes in photophysical properties, i.e., halochromism, have received increasing attention. Halochromism<sup>14</sup> refers to the change in the photophysical properties of

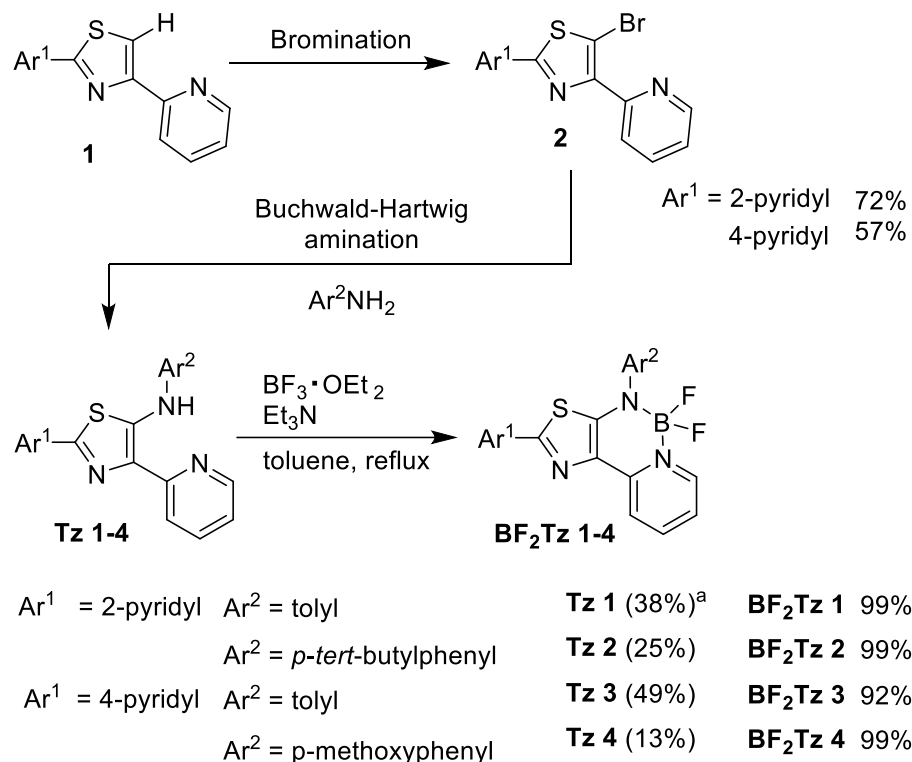
dyes in response to interaction with acid, base, and ion salts. Compounds having a  $\pi$ -conjugated system with strong built-in donor–acceptor interactions tend to exhibit a more pronounced halochromic effect due to an enhanced ability to redistribute charge density and promote charge transfer (CT) absorption.<sup>15</sup> Additionally, *N*-heteroaromatic compounds also exhibit halochromic properties which are marked by a prominent absorption changes under acidic conditions.<sup>16</sup> Likewise, interaction between a nitrogen atom in the acceptor unit of a donor–acceptor–donor (D–A–D) compound system and Lewis acid tris(pentafluorophenyl) borane,  $B(C_6F_5)_3$ , results in a dramatic red-shift of absorption spectra and enhancement of quantum yield.<sup>17</sup> In addition, the treatment of organic dyes bearing pyridyl fragments and *N*-alkylimino groups with a Brønsted acid also significantly affected the absorption spectrum.<sup>18</sup>

In this chapter I have designed and synthesized a series of thiazole-bridged 1,5-bidentate nitrogen ligands and their boron complexes. The photophysical properties of the boron complexes and the effect of acids on their absorption and emission spectra are disclosed.

## 4.2. Results and discussion

### 4.2.1. Synthesis of ligands and boron complexes

The thiazole-bridged 1,5-bidentate nitrogen ligands (**Tz**) were prepared in two-step reactions as depicted in Scheme 1. The initial step was the preparation of 5-bromothiazole **2** via the halogenation of 5-H thiazole **1** in dimethylformamide as a solvent. Subsequently, the Hartwig-Buchwald amination reaction was carried out with THF as a solvent at 80 °C for 24 h in the presence of **10** equivalents of amines and palladium catalyst to give the corresponding ligands **Tz**. As a result, the introduction of 2-pyridyl group at the 2-position of a thiazole ring and a tolyl group at the amino site delivered **Tz1** in 38% yield. Replacement of a tolyl group with a bulkier substituent, *p*-tert-butylphenyl, decreased the product yield to 25% for **Tz 2**. Furthermore, **Tz 3** which has a 4-pyridyl group attached to the 2-position of the thiazole ring and a tolyl group at the amino site was synthesized in 49% yield. In addition, introducing 4-methoxyphenyl group at the amino site gave **Tz 4** in 13%. Finally, ligands **Tz** reacted with boron trifluoride ( $\text{BF}_3 \cdot \text{OEt}_2$ ) in the presence of triethylamine as a base under reflux in toluene to give **BF<sub>2</sub>Tz** in high yields. The boron complexes involved Et<sub>2</sub>O even after the purification by column chromatography except for **BF<sub>2</sub>Tz 2**.

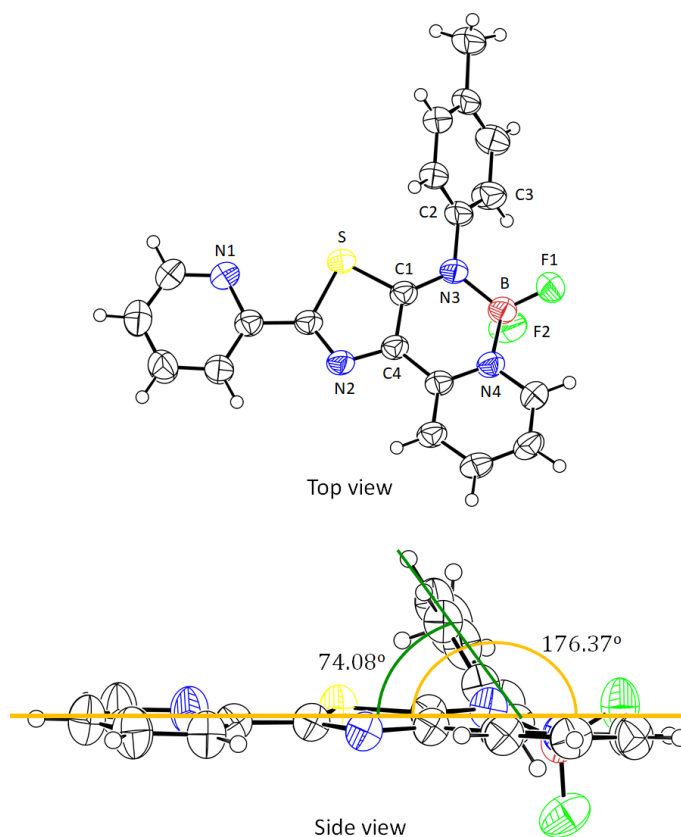


**Scheme 1.** Synthesis of thiazole-based ligands (**Tz**) and boron-thiazole complexes (**BF<sub>2</sub>Tz**). <sup>a</sup> Using toluene as a solvent,  $\text{Cs}_2\text{CO}_3$  as a base, 130 °C, 24 h.



#### 4.2.2. Molecular structure

The molecular structure of **BF<sub>2</sub>Tz 1** as confirmed by single crystal crystallography diffraction is shown in Figure 1. A suitable single crystal was obtained from slow evaporation in dilute toluene and hexane. The results confirmed that two nitrogen atoms and two fluorine atoms coordinated to a boron atom. The boron atom adopts a nearly tetrahedral geometry in which the bond angle of F1-B-F2 is 110.27° and that of N3-B-N4 is 108.05°. The thiazole ring and the substituents attached at the 2- and 5-positions are almost in the same plane, as can be seen in the dihedral angle of N2-C4-C5-N4 (176.37°). Furthermore, the amino group is deviated from a thiazole ring by about 74.08°. In the molecule, the nitrogen atom on the pyridyl ring (N1) is close, not to a nitrogen atom (N2), but rather to a sulphur atom, in the thiazole ring. The distance between N1 and S is 2.78 Å, which is within the sum of van der Waals radii of these elements (3.55 Å). This suggested that a significant interaction may be present between those two atoms. In addition, the dihedral angle between a thiazole ring and a tolyl group at the amino site is 128.9(2)°. The detail parameter of crystal **BF<sub>2</sub>Tz 1** is shown in Table 1.



**Figure 1.** X-ray crystallography of **BF<sub>2</sub>Tz 1**.

**Table1.** Crystal data and structure refinement for **BF<sub>2</sub>Tz 1**.

Chemical formula	C <sub>20</sub> H <sub>15</sub> BF <sub>2</sub> N <sub>4</sub> S
$M_r$	392.23
Crystal system, space group	Triclinic, $P\bar{1}$
Temperature (K)	293
$a, b, c$ (Å)	7.9896 (2), 9.2646 (3), 13.4601 (4)
$\alpha, \beta, \gamma$ (°)	105.166 (3), 96.037 (2), 108.811 (3)
$V$ (Å <sup>3</sup> )	890.46 (5)
$Z$	2
Radiation type	Mo $K\alpha$
$\mu$ (mm <sup>-1</sup> )	0.22
Crystal size (mm)	0.20 × 0.17 × 0.14
Diffractometer	Rigaku Mercury CCD (2x2 bin mode)
Absorption correction	Numerical
$T_{\min}, T_{\max}$	0.913, 0.942
No. of measured, independent and observed [ $I > 2\sigma(I)$ ] reflections	8310, 4063, 2984
$R_{\text{int}}$	0.016
$(\sin \theta/\lambda)_{\text{max}}$ (Å <sup>-1</sup> )	0.650
$R[F^2 > 2\sigma(F^2)], wR(F^2), S$	0.042, 0.115, 1.04
No. of reflections	4063
No. of parameters	254
H-atom treatment	H-atom parameters constrained
$\Delta_{\text{max}}, \Delta_{\text{min}}$ (e Å <sup>-3</sup> )	0.21, -0.18

### 4.2.3. Absorption and fluorescence spectra of ligands and boron complexes

The absorption maxima of **Tz** in toluene exhibited two absorption bands at around 371 nm and 404 nm. Similarly, the absorption band of **Tz** recorded in chloroform appeared at two regions: 367 nm and 411 nm (Figure 2, Table 2). Notably, no emission was observed for **Tz**.

**Table 2.** Absorption maxima of **Tz** recorded in toluene and chloroform.

Thiazole	Solvent	Toluene	CHCl <sub>3</sub>
<b>Tz 1</b>	$\lambda_{\text{abs}}$ (nm)	377	373
		398	404
	log $\epsilon$	4.37	4.28
		4.37	4.28
<b>Tz 2</b>	$\lambda_{\text{abs}}$ (nm)	372	370
		399 (s)	404
	log $\epsilon$	4.29	4.12
		4.26	4.12
<b>Tz 3</b>	$\lambda_{\text{abs}}$ (nm)	371	369
		404 (s)	403
	log $\epsilon$	4.36	4.18
		4.30	4.16
<b>Tz 4</b>	$\lambda_{\text{abs}}$ (nm)	374	367
		398	411
	log $\epsilon$	4.56	4.13
		4.56	4.12

[conc. = 10<sup>-5</sup> M]

Furthermore, the UV-Vis spectra of **BF<sub>2</sub>Tz** recorded in chloroform exhibited absorption maxima from 388 to 395 nm, while the emission maxima were observed from 504 to 516 nm (Figure 3). The absorption band of **BF<sub>2</sub>Tz 1**, which has a tolyl group on the nitrogen atom was observed at 388 nm and its emission band appeared at 513 nm. The introduction of a *p*-*tert*-butylphenyl group to the aromatic ring attached to the nitrogen atom, i.e., **BF<sub>2</sub>Tz 2** showed similar absorption and emission bands at 389 and 512 nm, respectively. Interestingly, **BF<sub>2</sub>Tz 2** and **BF<sub>2</sub>Tz 3** showed green emission in the solid state, albeit with a low quantum yield 0.08 and 0.11, respectively. To achieve a deep understanding of the effect of substituents on the photophysical behavior, we replaced the 2-pyridyl group at the 2-position of the thiazole ring with a 4-pyridyl group, which has greater electron-withdrawing character. The absorption band of **BF<sub>2</sub>Tz 3** was observed at 395 nm, and unexpectedly the emission maxima shifted to a shorter wavelength at 404 nm. The introduction of an electron-donating substituent, i.e., *p*-methoxyphenyl group,

to the aromatic ring attached to the nitrogen atom to a significant led the bathochromic shift for **BF<sub>2</sub>Tz 4**. Its absorption band was observed at 398 nm, while its emission maxima appeared at 516 nm. The isolated boron complexes showed very short fluorescent lifetimes both in solid and solution state (Table 3). All complexes show large Stokes shifts (up to 125 nm), which is greater than those of ordinary BODIPY and its analogues. However, a significant effect was not observed for the photophysical properties of **BF<sub>2</sub>Tz** even when we changed the substituents on ligands. Likewise, the absorption and emission spectra of **Tz** and **BF<sub>2</sub>Tz** were almost independent of the solvent polarities.

**Table 3.** Photophysical properties **BF<sub>2</sub>Tz** in chloroform. [conc. = 10<sup>-5</sup> M].

Thiazole	$\lambda_{\text{abs}}$ (nm)	log $\epsilon$	$\lambda_{\text{ex}}$ (nm)	$\lambda_{\text{em}}$ (nm) <sup>a</sup>	$\nu_{\text{ss}}$ [cm <sup>-1</sup> ] (nm)	$\Phi_{\text{F}}$ <sup>b</sup>	$\chi^2$ <sup>c,d</sup>	$\tau$ (ns) <sup>c,d</sup>
<b>Tz 1</b>	373 404	4.28 4.28	-	-	-	-	-	-
<b>BF<sub>2</sub>Tz 1</b>	388	4.17	381	513	[6280] (125)	0.28	1.08	1.23
<b>BF<sub>2</sub>Tz 2</b>	389	7.58	382	512	[6175] (123)	0.37	0.74	1.22
<b>BF<sub>2</sub>Tz 3</b>	395	3.87	389	504		0.36	0.92	1.01
<b>BF<sub>2</sub>Tz 4</b>	398 484 (s)	3.93 -	392	516	[5745] (118)	0.12	2.45	0.67
<b>BF<sub>2</sub>Tz 2<sup>e</sup></b>	463	-	481	520	[2367] (57)	0.08	0.82	0.70
<b>BF<sub>2</sub>Tz 3<sup>e</sup></b>	474	-	492	541	[2612] (67)	0.11	4.49	1.07

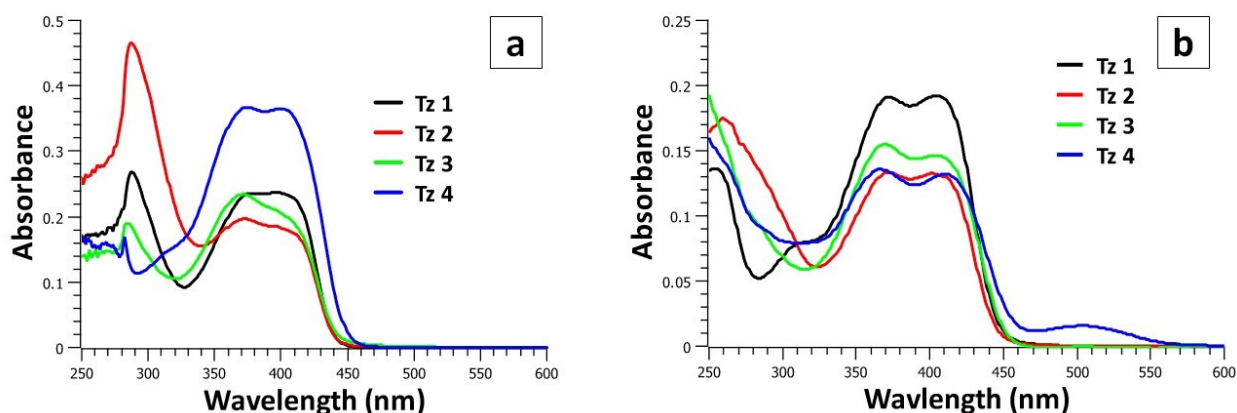
<sup>a</sup> Excited in  $\lambda_{\text{max}}$

<sup>b</sup> Absolute fluorescence of quantum yield

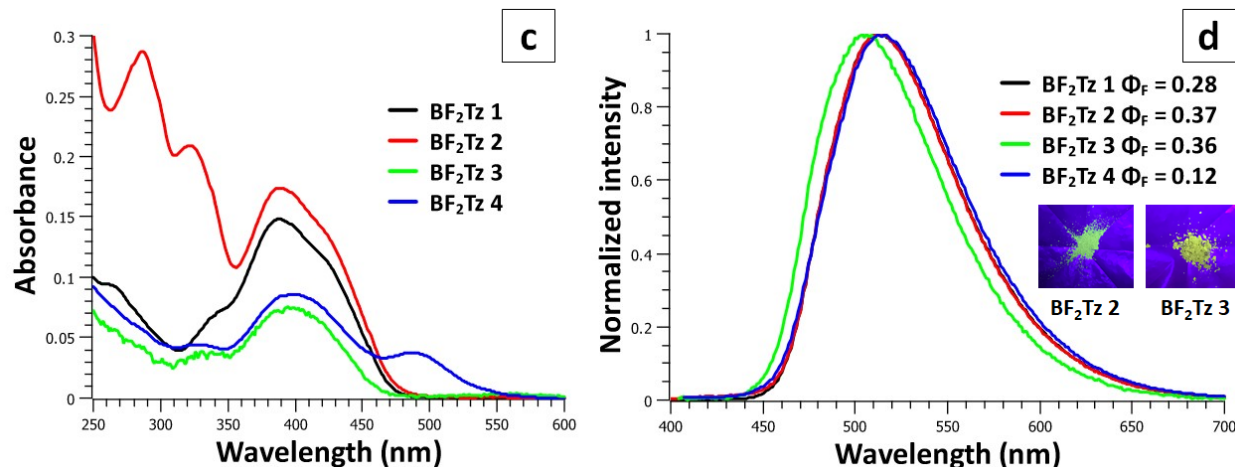
<sup>c</sup> Excited at 365 nm

<sup>d</sup> In dichloromethane

<sup>e</sup> Solid state



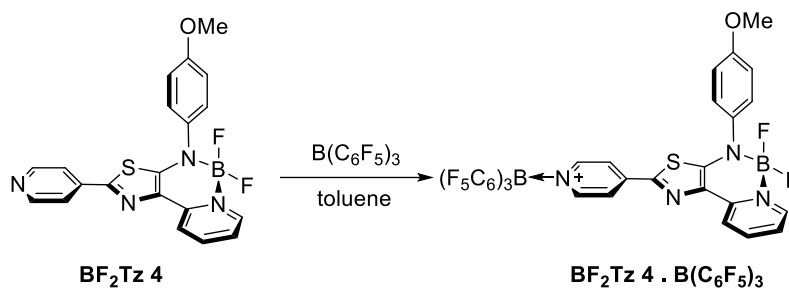
**Figure 2.** (a) Absorption spectra of **Tz** in toluene, (b) in chloroform [conc. = 10<sup>-5</sup> M]



**Figure 3.** (c) Absorption and (d) emission spectra of **BF<sub>2</sub>Tz** in chloroform [conc. = 10<sup>-5</sup> M]. Inset: solid state emission of **BF<sub>2</sub>Tz 2** and **BF<sub>2</sub>Tz 3**.

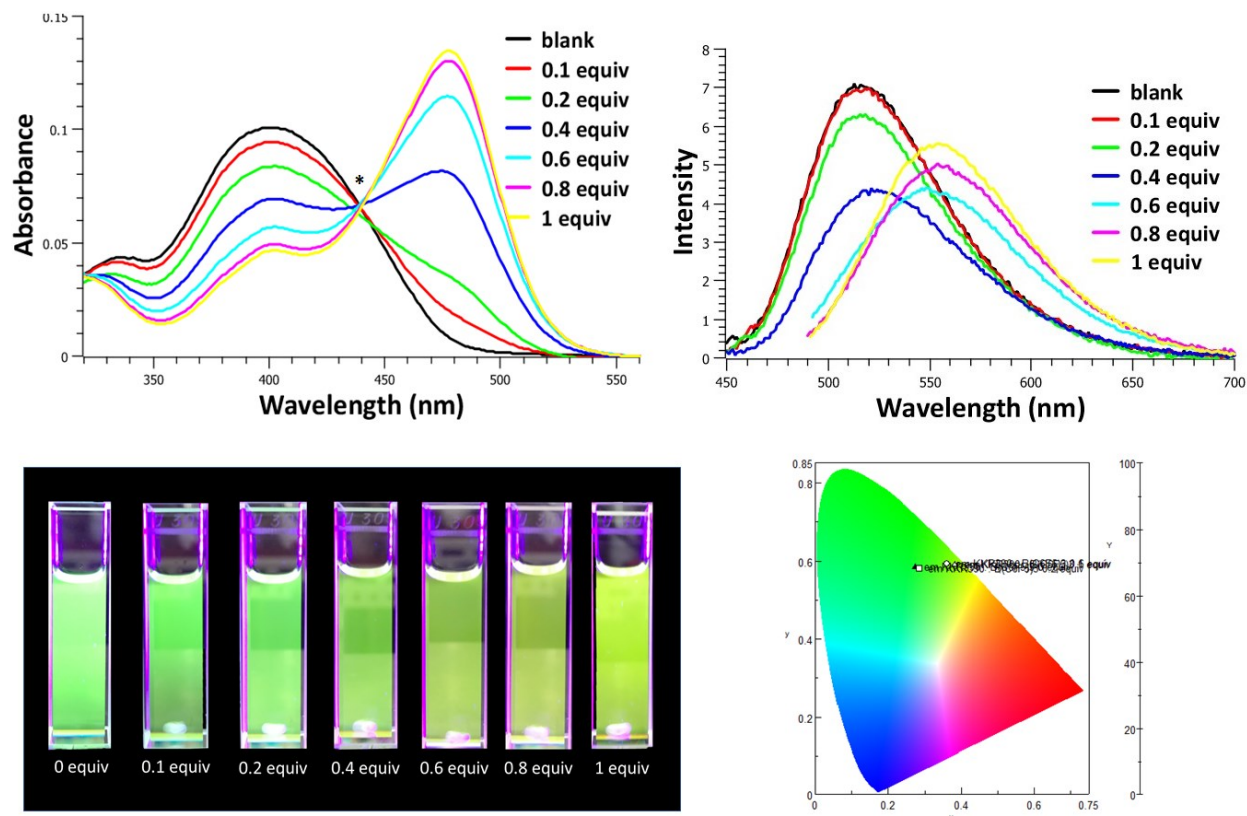
#### 4.2.4. Halochromic properties

The response of the photophysical properties of **BF<sub>2</sub>Tz** to Lewis and Brønsted acids is of interest since **BF<sub>2</sub>Tz**s possess a Lewis basic pyridyl group. First, we investigated the photophysical change in **BF<sub>2</sub>Tz 4** upon the addition of Lewis acid B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> in toluene solution, as shown in Scheme 2.



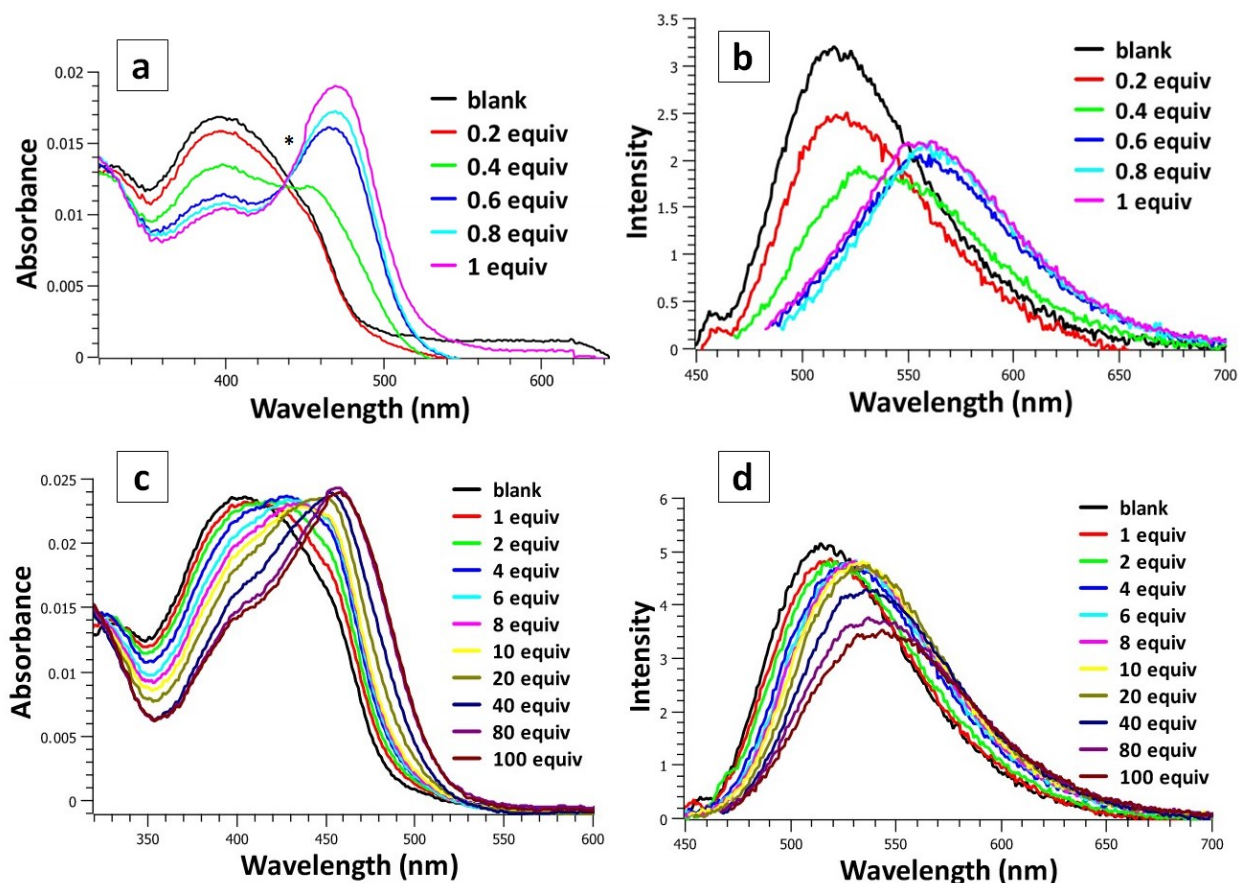
**Scheme 2.** Titration of **BF<sub>2</sub>Tz 4** with Lewis acid B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub>.

The intensity at 402 nm gradually decreased accompanied by the emergence of a new red-shifted absorption band at 474 nm. A clear isosbestic point was observed at 441 nm, which implied the formation of a 1:1 complex of B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> and **BF<sub>2</sub>Tz 4**. The fluorescence spectra showed a red-shifted emission band upon the addition of B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub>. In a blank solution, the emission band was observed at 516 nm. Upon the addition of the acid, the emission intensity gradually decreased and shifted to 553 nm after the addition of B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub>. Furthermore, the color of the solution changed from green to yellowish-green (Figure 4). Furthermore, the halochromic properties of **BF<sub>2</sub>Tz 3** upon addition of B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> have also been investigated. Notably, **BF<sub>2</sub>Tz** having a 2-pyridyl group (**BF<sub>2</sub>Tz 1** and **BF<sub>2</sub>Tz 2**) did not show halochromic properties. Therefore, the halochromism was specific to **BF<sub>2</sub>Tz 4**, and the pyridyl nitrogen atom in **BF<sub>2</sub>Tz 4** appears to coordinate to the boron atom.



**Figure 4.** Absorption (upper left) and emission spectra (upper right) of **BF<sub>2</sub>Tz 4** [conc. =  $10^{-5}$  M] upon the addition of  $B(C_6F_5)_3$  in toluene. The color of the solution changes upon the addition of acid under the irradiation of the light at 365 nm (bottom left) and CIE diagram (bottom right).

The treatment of complex **BF<sub>2</sub>Tz 4** with triflic acid (TfOH) as a Brønsted acid showed a similar behavior. The addition of TfOH led to a decrease in the absorption band at 398 nm, while a new red-shifted band appeared at 469 nm, probably due to the formation of protonated species. The isosbestic point at 437 nm may suggest that protonation takes place at only one nitrogen atom in **BF<sub>2</sub>Tz 4**. Regarding emission, the intensity at 515 nm gradually decreased upon the addition of TfOH. With continuous increases in the acid concentration, a pronounced red-shift band appeared at 562 nm (Figure 5 a, b). Other Brønsted acids such as trifluoroacetic acid (TFA), led to a gradual shift of the absorption band to a longer wavelength. Protonation of the nitrogen atom in a pyridyl ring was confirmed by the emergence of a new red-shifted band at 458 nm. The emission spectra showed a decrease in intensity accompanied by a red-shifted emission band (Figure 5 c, d). Moreover, while the emission was completely quenched in the case of TfOH, with the addition of TFA, the emission became weaker but did not fully disappear. The fluorescence-quenching phenomena of thiazole derivatives having a 4-pyridyl ring at the 2-position upon the addition of acid have also been reported.<sup>18</sup>



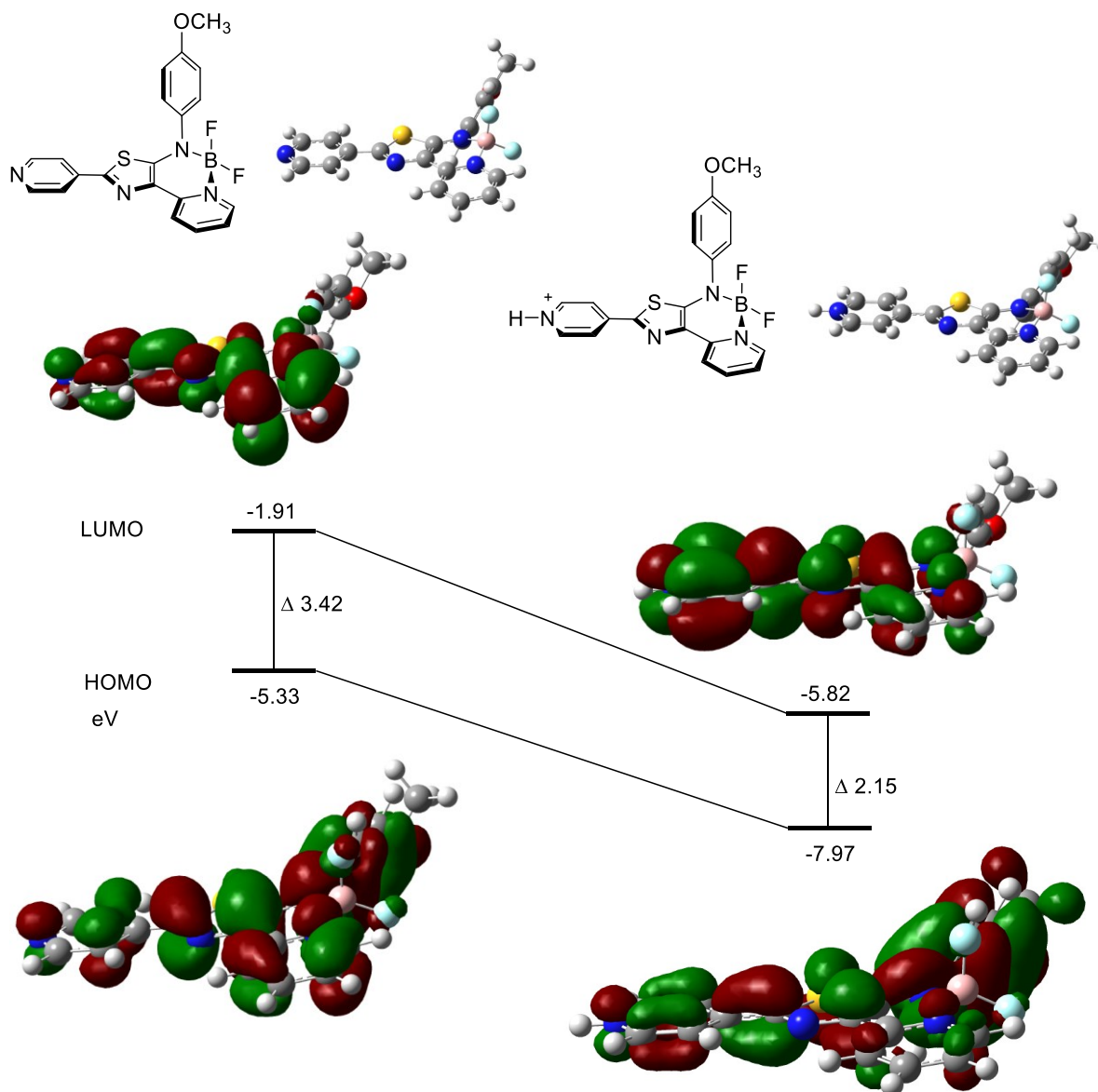
**Figure 5.** (a) Absorption and (b) emission spectra of **BF<sub>2</sub>Tz 4** upon the addition of TfOH, and (c) absorption and (d) emission spectra of **BF<sub>2</sub>Tz 4** upon the addition of TFA in chloroform. [conc. = 10<sup>-5</sup> M].

#### 4.2.5. Density functional theory calculations

To understand the photophysical properties of **BF<sub>2</sub>Tz 4** and its protonated form, DFT calculations were carried out at the B3LYP/6-31G (d, p) level.<sup>19</sup> The calculated HOMO and LUMO, and optimized structural geometries, are shown in Figure 6. The optimized molecular structures showed that two substituents attached to the thiazole ring in **BF<sub>2</sub>Tz 4** and its protonated species are located in nearly the same plane as the thiazole ring. In contrast, the methoxyphenyl group attached to the 5-position of the thiazole ring is highly deviated from the thiazole ring, which is consistent with the results of X-ray analyses. The HOMO of **BF<sub>2</sub>Tz 4** is delocalized over the 4- and 2-pyridyl rings, the thiazole ring and the phenyl ring on the nitrogen atom. The HOMO of protonated **BF<sub>2</sub>Tz 4** is also delocalized over almost all the substituent moieties. LUMOs of **BF<sub>2</sub>Tz 4** and its protonated species are localized over the 4- and 2-pyridyl rings and a thiazole ring, whereas the methoxyphenyl group on the nitrogen atom does not contribute to the LUMOs at all. These results are in accordance with the experimental results which showed that the replacement



of the substituents at the aromatic ring on the nitrogen atom does not significantly affect the absorption and emission spectra. The energy gap between HOMO and LUMO of **BF<sub>2</sub>Tz 4** is 3.42 eV. Although the protonation of **BF<sub>2</sub>Tz 4** decreases the energy levels of HOMO and LUMO, the energy level of LUMO drops further to result in a smaller energy gap (2.15 eV) between HOMO and LUMO. These computational results are in accordance with the experimental results that the protonation of **BF<sub>2</sub>Tz 4** shifted the absorption and emission to longer wavelengths.



**Figure 6.** Frontier orbitals of **BF<sub>2</sub>Tz 4** and its protonated species.



### 4.3. Summary of Chapter 4

In summary, I have demonstrated new types of thiazole-bridged 1,5-bidentate nitrogen ligands (**Tz**) and their boron complexes for the first time. The ligands were synthesized in low to good yields via bromination and Buchwald–Hartwig amination of 5-H thiazoles. A complexation reaction of **Tz** with boron trifluoride ( $\text{BF}_3 \cdot \text{OEt}_2$ ) gave **BF<sub>2</sub>Tz** in high yields. A new **BF<sub>2</sub>Tz** exhibited strong absorption and emission bands with a large Stokes shift up to 125 nm and solid state emission, i.e., **BF<sub>2</sub>Tz 2**. Furthermore, **BF<sub>2</sub>Tz** showed efficient acid-responsive properties (halochromism) with a significant absorption spectral shift of 79 nm upon the addition of the Lewis acid  $\text{B}(\text{C}_6\text{F}_5)_3$ . Spectral shifts of 71 nm and 54 nm were also observed upon the addition of TfOH and TFA as a Brønsted acid, respectively. In addition, the energy gap between HOMO – LUMO of **BF<sub>2</sub>Tz 4** decreased after protonation from 3.42 eV to 2.15 eV based on DFT calculations.

## 4.6. Experimental section

### Synthesis of 1,5-nitrogen bidentate thiazole ligands (Tz)

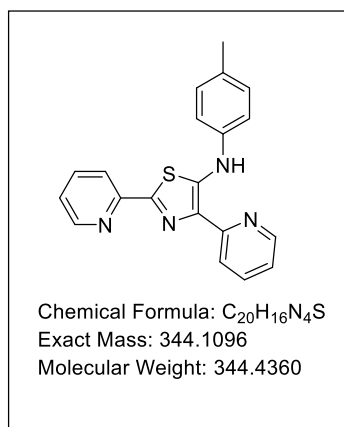
#### General procedure A.

$\text{Pd}(\text{OAc})_2$  (10 mol%) and Xantphos (20 mol%) were weighted into Schlenk tube that was sealed with a septum and purged with argon (3 times). Toluene (6 mL) was then injected, and the reaction was continued for 15 min at 130 °C. 5-Bromothiazole (1 equiv.) in 4 mL toluene was then injected via syringe followed by the addition of an amine (10 equiv.) and LiHMDS (2 equiv.). The reaction mixture was filtered through a bed of Celite and washed with  $\text{CH}_2\text{Cl}_2$ . The filtrate was concentrated in vacuo and purified via silica gel flash column chromatography ( $\text{SiO}_2$ , hexane : EtOAc) to give the corresponding thiazoles.

#### General procedure B.

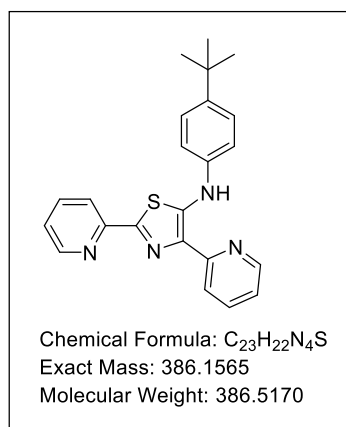
$\text{Pd}(\text{OAc})_2$  (10 mol%), Xantphos (20 mol%), and 5-bromothiazole (1 equiv.) were weighted into Schlenk tube that was sealed with a septum and purged with argon (3 times). THF (10 mL), amine (10 equiv.) and LiHMDS (2 equiv.) were then injected via syringe, and the reaction was continued for 24 h at 80 °C. After that, the reaction mixture was quenched with  $\text{NaHCO}_3$  and extracted with  $\text{CH}_2\text{Cl}_2$ . The filtrate was concentrated in vacuo and purified via silica gel flash column chromatography ( $\text{SiO}_2$ , hexane : EtOAc) to give the corresponding thiazoles.

#### 1,5-Bidentate nitrogen ligand Tz 1



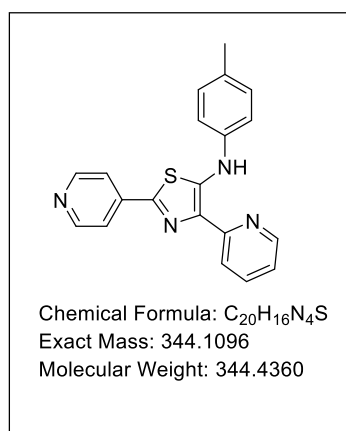
**General procedure A.** (1.5 mmol scale) ( $\text{SiO}_2$ , hexane : EtOAc = 30:1) to give the corresponding thiazole (0.06 g, 38% ) as a yellow solid (mp: 102-103 °C): IR (KBr) 3048, 1585, 1567, 1507, 1463, 1436, 1420, 1296, 1264, 1057, 1001, 784, 737, 620  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.33 (s, 3H), 7.07-7.11 (m, 1H), 7.15-7.21 (m, 3H), 7.27-7.29 (m, 2H), 7.69-7.77 (m, 2H), 8.17-8.25 (dd, 2H), 8.52-8.54 (m, 2H), 11.8 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  20.8, 117.8, 118.8, 119.8, 120.4, 122.9, 130.0, 131.3, 131.9, 136.6, 136.7, 139.2, 147.0, 148.6, 149.1, 149.2, 152.2, 155.8; MS (EI)  $m/z$  311( $\text{M}^+$ ): HRMS (EI) calculated for  $\text{C}_{20}\text{H}_{16}\text{N}_4\text{S}$ , 344.1096: found 344.1115.

### 1,5-Bidentate nitrogen ligand Tz 2



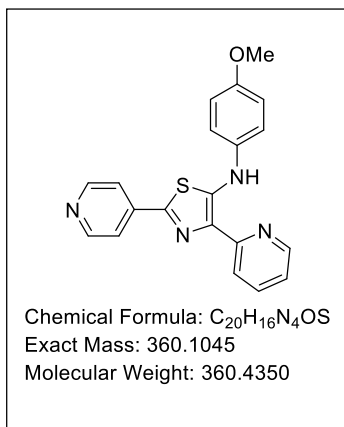
**General procedure B.** (0.8 mmol scale) ( $SiO_2$ , hexane : EtOAc = 10:1) to give the corresponding thiazole (0.08 g, 25% ) as a yellow solid (mp: 252-143 °C): IR (ATR) 2959, 1587, 1564, 1512, 1471, 1432, 1400, 1234, 1195, 1144, 832, 786, 777, 541  $cm^{-1}$ ;  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  1.33 (s, 9H), 7.09-7.11 (m, 1H), 7.19-7.22 (m, 1H), 7.32-7.35 (m, 2H), 7.37-7.39 (m, 2H), 7.72-7.78 (m, 2H), 8.18-8.19 (d,  $J$  = 8.02 Hz, 1H), 8.26-8.27 (d,  $J$  = 8.02 Hz, 1H), 8.53-8.54 (m, 2H), 11.87 (s, 1H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  31.5, 34.4, 117.6, 118.8, 119.8, 120.4, 122.9, 126.3, 128.2, 131.4, 132.1, 134.0, 136.8, 139.2, 145.4, 147.1, 148.7, 149.2, 152.2, 155.8; MS (EI)  $m/z$  386( $M^+$ ): HRMS (EI) calculated for  $C_{23}H_{22}N_4S$ , 386.1565: found 368.1551.

### 1,5-Bidentate nitrogen ligand Tz 3



**General procedure B.** (1.5 mmol scale) ( $SiO_2$ , hexane : EtOAc = 10:1) to give the corresponding thiazole (0.06 g, 49% ) as a yellow solid (mp: 203-208 °C): IR (ATR) 3305, 1700, 1638, 1585, 1536, 1513, 1460, 1392, 1352, 1317, 1104, 812, 780, 765, 720, 503  $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  2.35 (s, 3H), 7.11-7.14 (m, 1H), 7.19-7.21 (m, 2H), 7.24-7.26 (m, 4H), 7.72-7.74 (dd, 1H), 7.75-7.80 (td, 1H), 8.24-8.26 (d,  $J$  = 8.08 Hz, 1H), 8.54-8.55 (m, 1H), 8.61-8.62 (dd, 1H), 11.82 (s, 1H);  $^{13}C$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  20.9, 118.2, 119.27, 120.2, 120.8, 130.2, 131.5, 132.7, 136.8, 139.2, 141.1, 144.4, 147.1, 148.1, 150.3, 153.8; MS (EI)  $m/z$  344( $M^+$ ): HRMS (EI) calculated for  $C_{20}H_{16}N_4S$ , 344.1096: found 344.1111.

### 1,5-Bidentate nitrogen ligand Tz 4



**General procedure B.** (1.3 mmol scale) ( $SiO_2$ , hexane : EtOAc = 3:1). The obtained fraction was then subjected to GPC to give the corresponding thiazole (0.061 g, 13% ) as a yellow solid (mp: 162 °C): IR (ATR) 2827, 1566, 1553, 1504, 1480, 1461, 1403, 1240, 1038, 808, 780, 717, 544  $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  3.83 (s, 3H), 6.93-6.96 (d,  $J$  = 8.98 Hz, 2H), 7.10-7.13 (t, 1H), 7.28-7.30 (d,  $J$  = 8.53 Hz, 2H), 7.71-7.72 (d,  $J$  = 5.39 Hz, 2H), 7.75-7.79 (t, 1H), 8.21-8.23 (td, 1H), 8.52-8.53 (d,  $J$  = 4.94 Hz, 1H), 8.58-8.59 (d,  $J$  = 5.39 Hz, 2H), 11.6 (s, 1H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  55.7, 114.9, 119.2, 120.2, 120.6, 120.8, 131.2, 135.2, 136.8, 141.7, 143.8,

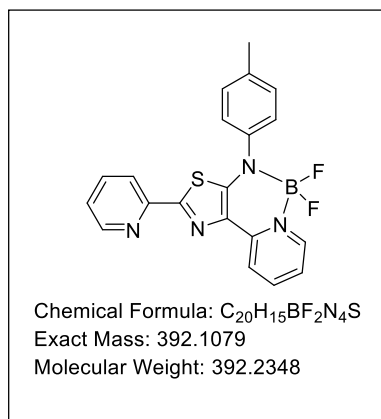
147.1, 149.5, 150.1, 155.4, 156.1; MS (EI)  $m/z$  360( $M^+$ ): HRMS (EI) calculated for  $C_{20}H_{16}N_4OS$ , 360.1045: found 360.1051.

### Synthesis of Boron complex thiazoles ( $BF_2Tz$ )

#### General procedure.

To a solution of 1,5-bidentate nitrogen ligands (**Tz**) in toluene (5 mL) was added dropwise  $Et_3N$  (2.5 equiv.), followed by  $BF_3 \cdot OEt_2$  (5 equiv.). The mixture was stirred under reflux for 2 h. The resulting mixture was quenched with water and extracted with  $CH_2Cl_2$ . The organic layer was then dried over  $MgSO_4$  and concentrated in vacuo. The residue was purified via silica gel flash column chromatography ( $SiO_2$ , hexane : EtOAc) and then subjected to GPC to give the corresponding boron complex thiazoles ( $BF_2Tz$ ).

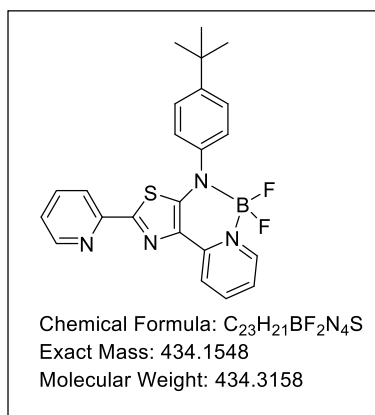
#### Boron complex thiazole $BF_2Tz$ 1 involving one equiv of $Et_2O$



(0.1 mmol scale) ( $SiO_2$ , hexane : EtOAc = 5:1) to give the corresponding boron-thiazole complex (0.070 g, 99% ) as a yellow solid (mp: 178-180 °C): IR (ATR) 3420, 1625, 1567, 1484, 1445, 1267, 1082, 1034, 777, 507  $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  1.37-1.40 (t, 6H,  $CH_3$  of  $Et_2O$ ), 2.37 (s, 3H), 3.13-3.19 (m, 4H,  $CH_2$  of  $Et_2O$ ), 7.22-7.28 (m, 4H), 7.40 (d,  $J$  = 8.2 Hz, 2H), 7.76-7.80 (t, 1H), 7.95-7.99 (t, 1H), 8.07 (d,  $J$  = 8.2 Hz, 1H), 8.30 (d,  $J$  = 8.2 Hz, 1H), 8.46 (d,  $J$  = 5.9 Hz, 1H), 8.51 (d,  $J$  = 4.5 Hz, 1H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  8.79, 21.2, 46.8, 119.0, 119.1, 119.9, 123.6,

125.4, 130.4, 136.9, 137.1, 139.9, 140.4, 147.0, 148.9, 163.1;  $^{19}F$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  -150.9, -133.4;  $^{11}B$  NMR (128 MHz,  $CDCl_3$ )  $\delta$  -1.84 – -1.22; MS (EI)  $m/z$  392( $M^+$ ): HRMS (EI) calculated for  $C_{20}H_{15}BF_2N_4S$ , 392.1079: found 392.1060.

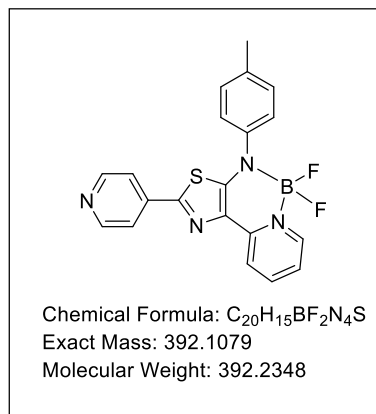
#### Boron complex thiazole $BF_2Tz$ 2



(0.1 mmol scale) ( $SiO_2$ , hexane : EtOAc = 10:1) to give the corresponding boron-thiazole complex (0.051 g, 99% ) as a red solid (mp: 252-253 °C): IR (KBr) 2965, 1625, 1567, 1494, 1447, 1260, 1084, 1033, 780  $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  1.34 (s, 9H), 7.24-7.27 (m, 4H), 7.43 (s, 2H), 7.76-7.80 (t, 1H), 7.95-7.99 (t, 1H), 8.08-8.10 (d,  $J$  = 7.63 Hz, 1H), 8.28-8.30 (d,  $J$  = 8.08 Hz, 1H), 8.46-8.51 (dd, 2H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ ) 31.4, 34.6, 118.9, 119.7, 123.6, 125.1, 125.6, 126.6, 136.7, 139.9, 140.3, 141.7143.8, 147.1, 149.2, 149.9, 151.5, 152.3,

160.9  $cm^{-1}$ ;  $^{19}F$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  -150.9, -133.3;  $^{11}B$  NMR (128 MHz,  $CDCl_3$ )  $\delta$  -1.36 – -0.79; MS (EI)  $m/z$  434( $M^+$ ): HRMS (EI) calculated for  $C_{23}H_{21}BF_2N_4S$ , 434.1548: found 434.1541.

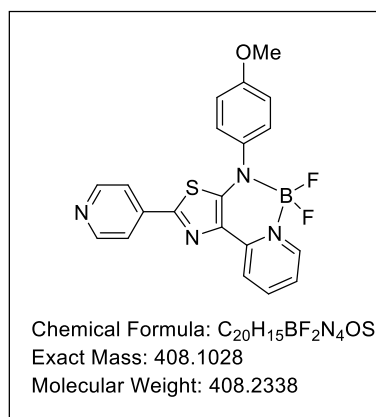
### Boron complex thiazole BF<sub>2</sub>Tz 3 involving one equiv of Et<sub>2</sub>O



(0.1 mmol scale) (SiO<sub>2</sub>, hexane : EtOAc = 5:1) to give the corresponding boron-thiazole complex (0.072 g, 92% ) as a ochre yellow solid (mp:120-121 °C): IR (ATR) 2920, 2851, 1705, 1622, 1564, 1486, 1551, 1258, 1085, 1017, 796, 700, 506 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.37-1.40 (t, CH<sub>3</sub> of Et<sub>2</sub>O), 2.41 (s, 3H), 3.13-3.19 (m, CH<sub>2</sub> of Et<sub>2</sub>O), 7.27-7.29 (d, *J* = 8.2 Hz, 2H), 7.36-7.40 (m, 3H), 7.77-7.85 (d, *J* = 5.59 Hz, 2H), 8.04-8.07 (m, 1H), 8.32-8.34 (d, *J* = 7.79 Hz, 1H), 8.52-8.53 (d, *J* = 5.95 Hz, 1H), 8.61-8.62 (m, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) 29.7, 118.9, 119.5, 119.7, 120.1,

125.3, 127.6, 128.3, 130.1, 130.5, 132.5, 134.3, 140.1, 140.7, 150.1, 161.5 cm<sup>-1</sup>; <sup>19</sup>F NMR (400 MHz, CDCl<sub>3</sub>) δ -150.9, -133.4; <sup>11</sup>B NMR (128 MHz, CDCl<sub>3</sub>) δ -1.65; MS (EI) *m/z* 392(M<sup>+</sup>): HRMS (EI) calculated for C<sub>20</sub>H<sub>15</sub>BF<sub>2</sub>N<sub>4</sub>S, 392.1079: found 392.1060.

### Boron complex thiazole BF<sub>2</sub>Tz 4



(0.1 mmol scale) purified by GPC (0.060 g, 99%) as a red solid (mp: 181-183 °C): IR (ATR) 2921, 2852, 1623, 1567, 1490, 1447, 1244, 1052, 1023, 772, 760, 632, 520 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.37-1.41 (t, 6H, CH<sub>3</sub> of Et<sub>2</sub>O), 3.12-3.19 (m, 4H, CH<sub>2</sub> of Et<sub>2</sub>O), 3.86 (s, 3H), 6.99-7.01 (d, *J* = 8.53 Hz, 2H), 7.40-7.42 (d, *J* = 8.53 Hz, 3H), 7.87-7.88 (d, *J* = 5.39 Hz, 2H), 8.07-8.10 (t, 1H), 8.33-8.35 (d, *J* = 8.53 Hz, 1H), 8.53-8.55 (d, *J* = 6.28 Hz, 1H), 8.60-8.63 (m, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 8.78, 46.6, 55.6, 115.1, 120.1, 120.3, 120.4, 120.6, 126.8, 137.1, 140.3, 141.2, 143.9.1,

144.9, 146.8, 146.9, 150.0, 158.9, 161.5; <sup>19</sup>F NMR (400 MHz, CDCl<sub>3</sub>) δ -150.9, -133.2; <sup>11</sup>B NMR (128 MHz, CDCl<sub>3</sub>) δ -1.43; MS (EI) *m/z* 408(M<sup>+</sup>): HRMS (EI) calculated for C<sub>20</sub>H<sub>15</sub>BF<sub>2</sub>N<sub>4</sub>OS, 408.1028: found 408.1015.

## 4.6. References

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## Chapter 5

## Summary of this thesis

In this thesis, I have described the synthesis and photophysical properties of 5-aminothiazoles having a pyridyl group and its derivatives. The structural modifications of 5-aminothiazoles led to the unique photophysical properties which were sensitive to the solvent polarities. Moreover, they showed potential features as organic ligands.

Chapter 2 described the synthesis and photophysical properties of 5-aminothiazoles having a pyridyl group. 5-Aminothiazoles were synthesized with facile diversity-oriented synthesis from readily available starting materials via reaction of thioamides dianion and thioformamides. An introduction of various substituents at the 2-position of thiazole ring (i.e., 2-pyridyl, 4-Methyl phenyl, and phenyl) and at the amino site (i.e., tolyl and phenyl) significantly influenced the absorption and emission spectra of the isolated compounds. The X-ray analysis confirmed that the substituent at the amino site were twisted from thiazole ring, while its nickel complex formation showed dinuclear metal complexes with atom chlorine acts as a bridge between two dimers. Moreover, the N-H thiazole compound showed extreme selectivity toward zinc ions make it applicable as an excellent candidate for zinc ion sensing.

Chapter 3 discussed the synthesis of 5-H thiazoles via *in-situ* generated thioamide dianions and thioformamide. The reported synthetic route gave 5-H thiazoles as a major product along with 5-dimethylaminothiazoles as a minor product, and a trace amount of thiazolines. The presence of pyridylmethyl group may play an important role for the formation of 5-H thiazole. The proposed reaction mechanism described that the pyridylmethyl group at the 4-position of thiazole ring may act as a coordination site for lithium atom to give 5-H thiazoles as the final product. In addition, the replacement of 2-pyridyl group with phenyl significantly decreased the formation of 5-H thiazoles.

In Chapter 4, the synthesis and photophysical properties of a series of boron complex of thiazole bridged 1,5-bidentate ligands were described. A series of 1,5 bidentate ligands were synthesized via bromination of 5-H thiazoles followed by Buchwald-Hartwig amination reaction. Subsequently, reaction with  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  gave boron complexes in high yield. These boron complexes showed strong absorption and emission properties. Moreover, they showed a large stoke shift up to 125 nm and solid state emission properties. Thiazole-boron complex having a 4-pyridyl group at the 2-position at the thiazole ring exhibited halochromic properties upon addition of Lewis and Brønsted acid which was indicated by a clear isosbestic point in its absorption spectra. DFT calculations showed the decreased of energy gap between HOMO-LUMO after protonation took place.



## List of Publications

### Original papers

1. "Synthesis of 5-H Thiazoles via Thioamide Dianions with Thioformamides: Pyridylmethyl Group on the Nitrogen Atom of Thiazole Promotes the Formation of 5-H Thiazoles"  
Puji Pamungkas, K. K.; Hattori, S.; Maruyama, T.; Ebihara, M.; Murai, T. *Heterocycles* **2021**, 103 (1), 258.
2. Boron complexes of thiazole-bridged 1,5-bidentate nitrogen ligands: synthesis and acid-responsive photophysical properties  
Puji Pamungkas, K. K.; Maruyama, T.; Murai, T. *Org. Biomol. Chem.* **2021**, 19 (31), 6804–6811.

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