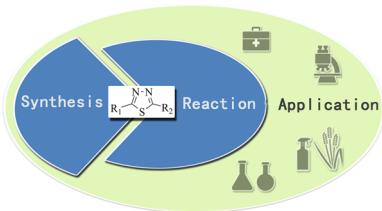


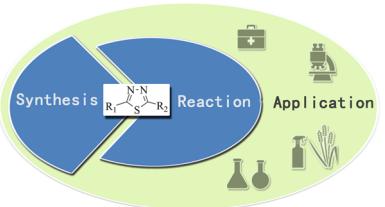
# **1,3,4-Thiadiazole: Synthesis, Reactions, and Applications in Medicinal, Agricultural, and Materials Chemistry**

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<b>1. INTRODUCTION</b>	
Over the past decades, the bulk of chemists' interests have been on heterocyclic compounds and their various derivatives as well as their applications in the pharmaceutical and chemical fields. Research concerning many kinds of heterocyclic compounds, such as pyrazole, <sup>1</sup> tetrahydroquinolines, <sup>2</sup> benzotriazole, <sup>3</sup> 1,2,3,4-tetrazine, <sup>4</sup> thiazole, <sup>5</sup> 2-thiazoline, <sup>6</sup> pyrimidine, and so on, <sup>7</sup> has been the subject of numerous recent reviews. Thiadiazole is a prevalent and important five-membered heterocyclic system containing two nitrogen atoms and a sulfur atom. There are several isomers of thiadiazole including 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, and 1,3,4-thiadiazole (Figure 1).	
A glance at standard reference works shows 1,3,4-thiadiazole has been investigated more than other isomers. The 1,3,4-thiadiazole ring is a very weak base due to the inductive effect of the sulfur atom and possesses relatively high aromaticity. <sup>8</sup> It is	
 1,2,3-Thiadiazole    1,2,4-Thiadiazole    1,2,5-Thiadiazole    1,3,4-Thiadiazole	
<b>Figure 1.</b> Isomers of thiadiazole.	

## 1. INTRODUCTION

Over the past decades, the bulk of chemists' interests have been on heterocyclic compounds and their various derivatives as well as their applications in the pharmaceutical and chemical fields. Research concerning many kinds of heterocyclic compounds, such as pyrazole,<sup>1</sup> tetrahydroquinolines,<sup>2</sup> benzotriazole,<sup>3</sup> 1,2,3,4-tetrazine,<sup>4</sup> thiazole,<sup>5</sup> 2-thiazoline,<sup>6</sup> pyrimidine, and so on,<sup>7</sup> has been the subject of numerous recent reviews. Thiadiazole is a prevalent and important five-membered heterocyclic system containing two nitrogen atoms and a sulfur atom. There are several isomers of thiadiazole including 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, and 1,3,4-thiadiazole (Figure 1).

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**Figure 1.** Isomers of thiadiazole.

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relatively stable in aqueous acid solutions but can undergo ring cleavage with aqueous base. In addition, the ring is also shown to be very electron deficient due to the electron-withdrawing effect of the nitrogen atoms and relatively inert toward electrophilic substitution but susceptible to nucleophilic attack, whereas when substitutions are introduced into the 2' or 5' position of this ring, it would be highly activated and readily react to yield diverse derivatives. Thus, possessing these properties, 1,3,4-thiadiazole derivatives are applied widely in pharmaceutical, agricultural, and materials chemistry. In particular, the 1,3,4-thiadiazoles display a broad spectrum of biological activities including antimicrobial,<sup>9</sup> antituberculosis,<sup>10</sup> antioxidant,<sup>11</sup> anti-inflammatory,<sup>9i,12</sup> anticonvulsants,<sup>13</sup> antidepressant and anxiolytic,<sup>14</sup> antihypertensive,<sup>15</sup> anticancer,<sup>11a,16</sup> and antifungal activity.<sup>17</sup> The most familiar thiadiazole-containing compound could be the acetazolamide, the very famous carbonic anhydrase inhibitor, being used in treatment of glaucoma,<sup>18</sup> high-altitude illness,<sup>19</sup> epileptic seizures,<sup>20</sup> idiopathic intracranial hypertension,<sup>21</sup> hemiplegic migraine,<sup>22</sup> cystinuria,<sup>23</sup> obstructive sleep apnea,<sup>24</sup> congenital myasthenic syndromes,<sup>25</sup> etc. 1,3,4-Thiadiazoles also exhibit high potential as pesticides in the fields of herbicides, fungicides, insecticides, bactericides, and even plant-growth regulators. Thiadiazole-derived agrochemicals are commercial, but some were banned. In addition, for 1,3,4-thiadiazole core's electron-deficient nature and good electron-accepting ability as well as thermal and chemical stability, thiadiazoles are widely applied in optics and electrochemistry. In addition, applications are much focused on their charge-transporting capacity, photoluminescence, photoconductivity, mesomorphism to obtain liquid crystals, anti-corrosive activity of metal, etc. Thus, we realize there is a necessity for a comprehensive review to summarize the enormous amount of scattered literature about 1,3,4-thiadiazoles into classifications to facilitate the following thiadiazole research.

In this review, we give an overview to the synthesis of the 1,3,4-thiadiazole ring and its derivatives both in solution and in the solid phase that has been reported in this decade as the first part. In addition, the reactivity and synthetic capacity of 1,3,4-thiadiazoles are summarized in the second part. It involves the reactivity of atoms on the 1,3,4-thiadiazole ring as well as some important substitutes on the 2' or 5' position carbon. This review also covers important properties and applications in medicinal, agrichemical, and materials chemistry in the third part. On the basis of the bioisosterism between  $-O-$  and  $-S-$ , 1,3,4-oxadiazole acts as the bioisostere of 1,3,4-thiadiazole.<sup>26</sup> They possess similar physical and chemical properties which produce broadly similar biological and materials properties. Thus, we will make a brief comparison between them in the fourth part. Cited references are restricted to journals, reviews, and books. Literature coverage extends up to the date of writing this review.

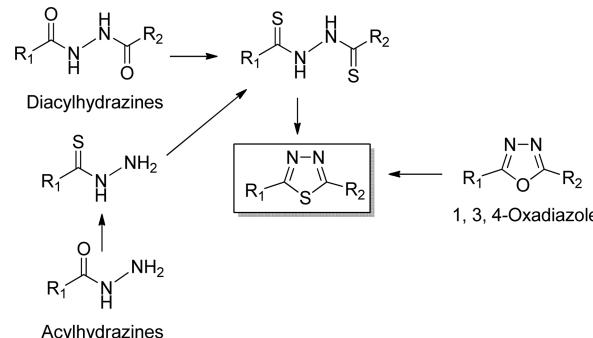
## 2. SYNTHESIS OF 1,3,4-THIADIAZOLE

Development of 1,3,4-thiadiazole chemistry is linked to the discovery of phenylhydrazines and hydrazine in the late 19th century. The numbering of the 1,3,4-thiadiazole ring system is illustrated (Figure 2). Commonly, 1,3,4-thiadiazoles can be available via general routes from cyclization of acylhydrazines including *N,N'*-diacylhydrazines and monoacylhydrazines or transformation from 1,3,4-oxadiazoles (Scheme 1). We can also synthesize 1,3,4-thiadiazoles from thiohydrazines including thiosemicarbazides, thiocarbazides, dithiocarbazates, thioacylhy-



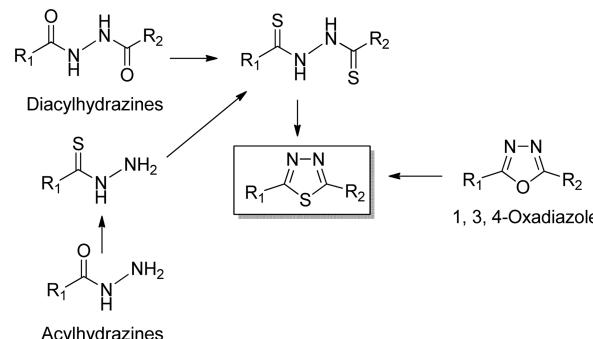
Figure 2. Numbering of the 1,3,4-thiadiazole ring system.

Scheme 1. General Preparation of 1,3,4-Thiadiazoles from Acylhydrazines or 1,3,4-Oxadiazoles



drazines, and bithioureas (Scheme 2). Herein, we summarized some recent strategies on the synthesis of 1,3,4-thiadiazole derivatives in the hopes that this classification can aid chemists in their preparation.

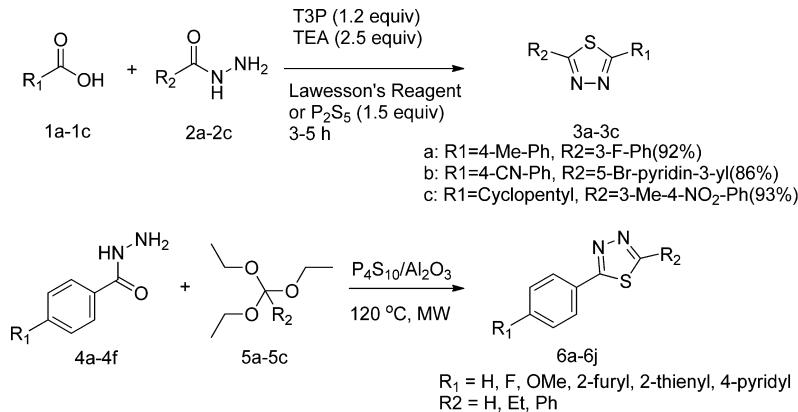
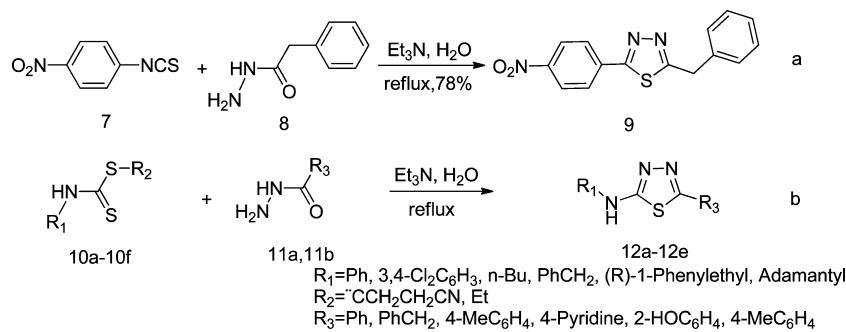
Scheme 2. General Preparation of 1,3,4-Thiadiazoles from Thiohydrazines



### 2.1. From Acylhydrazines

As summarized in Scheme 1, 1,3,4-thiadiazoles can be prepared via sulfuration of the corresponding 1,4-dicarbonyl or acyl precursors using phosphorus sulfide reagents such as  $P_2S_5$  and Lawesson's reagent.<sup>27</sup> However, the common methods reported always suffer from harsh conditions or stoichiometric formation of an intractable byproduct.

**2.1.1. From Acid Hydrazides.** In the past decades, several kinds of one-pot syntheses of 1,3,4-thiadiazoles have been reported, which can avoid the tedious work of multistep syntheses. Among these methods, some are still conducted under harsh conditions whereas others have been improved. Augustine et al. report a one-pot synthesis of 1,3,4-thiadiazoles directly from carboxylic acids using propylphosphonic anhydride (T3P) (Scheme 3a)<sup>28</sup> wherein it acts as both a coupling and a cyclodehydration reagent. In most cases, the reaction proceeded with high efficiency and broad functional group tolerance; however, the products were contaminated with a small percentage of byproduct 1,3,4-oxadiazole (3–5%) but could be easily purified by recrystallization or column chromatography.

**Scheme 3. Synthesis of 1,3,4-Thiadiazoles Directly from Carboxylic Acids and Acid Hydrazides****Scheme 4. Synthesis of 1,3,4-Thiadiazoles from Acid Hydrazide and the Sulfur Reagents**

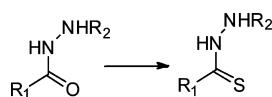
Polshettiwar et al. prepared 1,3,4-thiadiazoles from acid hydrazides under microwave irradiation in a single step (Scheme 3b).<sup>29</sup> Various aromatic and heterocyclic hydrazides (4a–4f) reacted efficiently with triethyl orthoformate, triethyl orthopropionate, and triethyl orthobenzoate (5a–5c) catalyzed by solid-supported NafionNR50 and thionating agent phosphorus pentasulfide in alumina ( $P_4S_{10}/Al_2O_3$ ) without any solvent, providing moderate to good yields of 1,3,4-thiadiazoles.

Reaction between acid hydrazide and the sulfur reagents  $CS_2$ ,<sup>30</sup> isothiocyanate, or dithiocarbamates to prepare thiadiazoles always consists of two or more steps,<sup>31</sup> the first of which is to synthesize relevant thiosemicarbazides or dithiocarbazides which then convert into thiadiazoles (see sections 2.2.1 and 2.2.3). One-pot synthesis of this kind of reaction is rare. Isothiocyanate 7 has been reported to directly react with acid hydrazide to get 2-substituted-1,3,4-thiadiazole in the presence of water and triethylamine (Scheme 4a).<sup>12d,31,32</sup> Under the same condition, they prepared a series of high-yield 5-substituted-2-amino-1,3,4-thiadiazoles using dithiocarbamates and acid hydrazides in water (Scheme 4b).

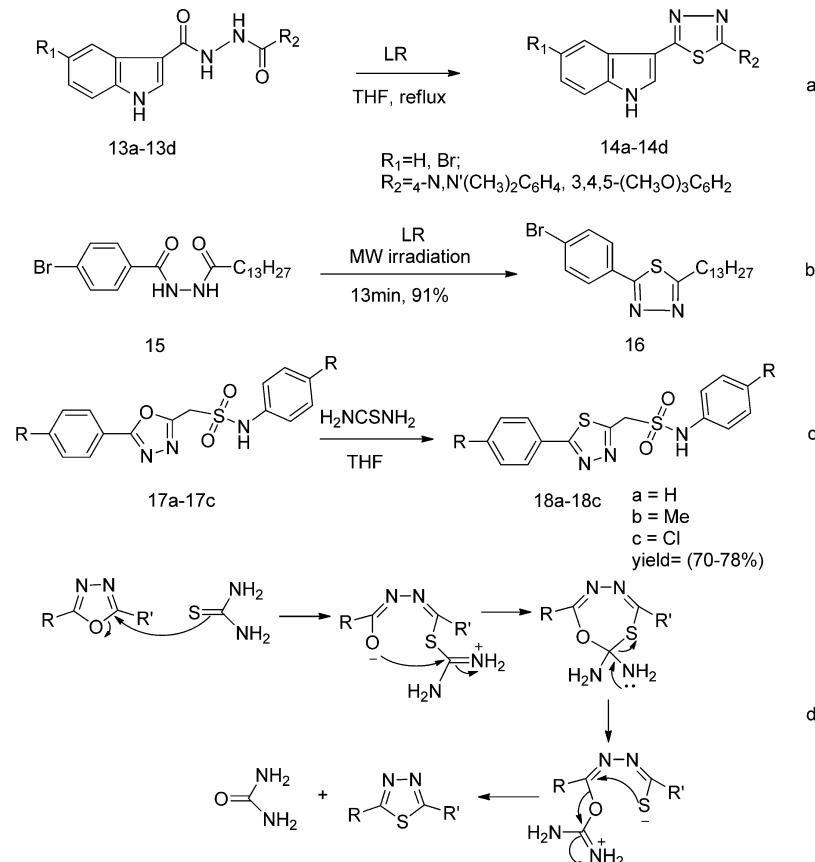
Acylhydrazines can be converted into thioacylhydrazides through thionation by Lawesson's reagent,<sup>33</sup>  $P_2S_5$ , and  $H_2S/HCl$  (Scheme 5),<sup>34</sup> followed by cyclization of the latter into thiadiazoles. We introduce this part in section 2.2.4. In addition, acylhydrazines can be acylated and transformed into diacylhy-

drazines then cyclodehydrated to form thiadiazole, which is discussed in the following section.<sup>27d,35</sup>

**2.1.2. From Diacylhydrazines.** Cyclization of *N,N'*-diacylhydrazines is a very common and convenient way to synthesize 1,3,4-thiadiazoles. This method has been well studied by many chemists employing phosphorus sulfides (i.e.,  $P_2S_5$ <sup>36</sup> and Lawesson's reagent) in solvents, such as DMF,  $CH_2Cl_2$ , THF, dioxane, and PhMe. Solventless synthesis by microwave radiation has also been reported frequently in recent publications. Thionation of diacylhydrazine 13a–13d with Lawesson's reagent LR followed by oxidative cyclization in different solvents (i.e., tetrahydrofuran, toluene, dioxane, and xylene) led to the indolyl-1,3,4-thiadiazoles 14a–14d (Scheme 6a) and afforded the highest yields in dry tetrahydrofuran.<sup>16g</sup> Routine methods for synthesizing the thiadiazoles in solvent are typically conducted with long reaction times at increased temperatures, low yields, lots of byproducts, anhydrous hydrocarbon solvent, and sulfurization reagent, causing the method to be environmentally unfriendly. By contrast, solvent-free reactions under microwave irradiation can probably overcome these drawbacks (Scheme 6b).<sup>37</sup> It can bring reduced pollution, low costs, and simplicity in processing and handling. Use of microwave irradiation as a nonconventional source of energy has proven to be very beneficial in this area. *N*-Acylation of 4-bromobenzohydrazide with myristoyl chloride afforded the unsymmetrical *N,N'*-diacylhydrazine 15, which was cyclized into the corresponding thiadiazole 16 with a yield of 91% in 13 min. However, the process shown in Scheme 6a has also been conducted with Lawesson's reagent under solvent-free conditions using microwave irradiation, yielding a mixture of byproducts along with desired thiadiazole 14. Thus, appropriate reaction conditions can probably participate to improve the

**Scheme 5. Synthesis of Thioacylhydrazides from Acylhydrazines**

Scheme 6. Synthesis of 1,3,4-Thiadiazoles from Diacylhydrazines



reactive efficiency, but specific reagents' reactivities should be involved.

## 2.2. From Thiohydrazines

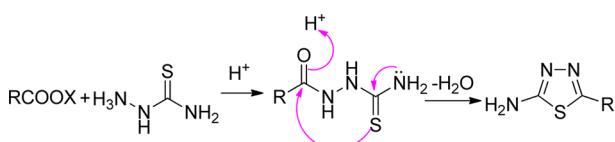
1,3,4-Thiadiazoles can also be prepared by cyclizing thiohydrazines or its equivalents. Each derivative of thiohydrazines can introduce special kinds of substituents to the thiadiazole ring, which allows for 1,3,4-thiadiazoles with a broad spectrum of reactivity and bioactivity. We herein classify thiohydrazines into thiosemicarbazides, thiocarbazides, dithiocarbazates, thioacylhydrazines, bithioureas, and other miscellanea. The strategies on the synthesis of 1,3,4-thiadiazole derivatives have been summarized below.

**2.2.1. From Thiosemicarbazides.** Many syntheses of 1,3,4-thiadiazoles proceed from thiosemicarbazides, substituted thiosemicarbazides, or thiosemicarbazones. Cyclization of thiosemicarbazides or substituted thiosemicarbazides efficiently lead to 2-amino-1,3,4-thiadiazoles, which have been widely studied as crucial intermediates when preparing 1,3,4-thiadiazole derivatives. In this reaction, acylation (Scheme 7) or Schiff base formation on the  $\alpha$ -amino group initiates cyclization of thiosemicarbazides and upon the action of a dehydrating agent such as EDCI, DCC, TMSCl, TsCl, PPh<sub>3</sub>,

SOCl<sub>2</sub>, PCl<sub>5</sub>, and diphenyl chlorophosphate to obtain thiadiazoles. Many common acylating agents such as carboxylic acid,<sup>16f,38</sup> acid halide,<sup>39</sup> and acid anhydride (Scheme 8a and 8b) have been used.<sup>10a,c,40</sup> Metal oxidants such as acidic aluminum oxide and ferric chloride and aldehydes employed to form Schiff base (Scheme 8c and 8d) were reported.<sup>10a,13,41</sup> Nucleophilic attack onto iso(thio)cyanates can also cause thiosemicarbazide to be (thio)acylated.<sup>42</sup> In addition, directly treating thiourea with acidamide to can produce thiosemicarbazides.<sup>12d</sup> An interaction between carboxylic acids and thiosemicarbazide in ionic liquids, which have been widely employed as potential substitutes of conventional solvents for a variety of chemical processes, has been used for preparation of both mono- and bicyclic 2-amino-1,3,4-thiadiazole derivatives (Scheme 8e).<sup>43</sup> Treatment of sulfinyl-bis((2,4-dihydroxyphenyl) methanethione) (STB) with appropriate thiosemicarbazides or hydrazides in methanol afforded *N*-substituted 5-amino-1,3,4-thiadiazole 28 or analogue 27 without the amine group (Scheme 8f).<sup>44</sup> In the reaction of STB with nucleophiles, first the linear product of thioacyl derivative is formed, which transforms into the thiol form. Elimination of H<sub>2</sub>S or H<sub>2</sub>O molecule finally gives the 1,3,4-thiadiazole ring. Thus, electrophilic substrate STB also acts as an endogenous cyclizing reagent. Additionally, nitriles 29 in a medium of PPA (phenylpropanolamine) are readily converted to iminoesters of PPA, which upon reaction with thiosemicarbazide are converted into amidazones 30, followed by loss of a molecule of ammonia to give compounds 31 (Scheme 8g).

1,3,4-Thiadiazolium mesoionic derivatives shared the formula (Figure 3) with the structure having well-separated regions of

Scheme 7. Mechanism of Cyclization of Thiosemicarbazides



Scheme 8. Synthesis of 1,3,4-Thiadiazoles from Thiosemicarbazides

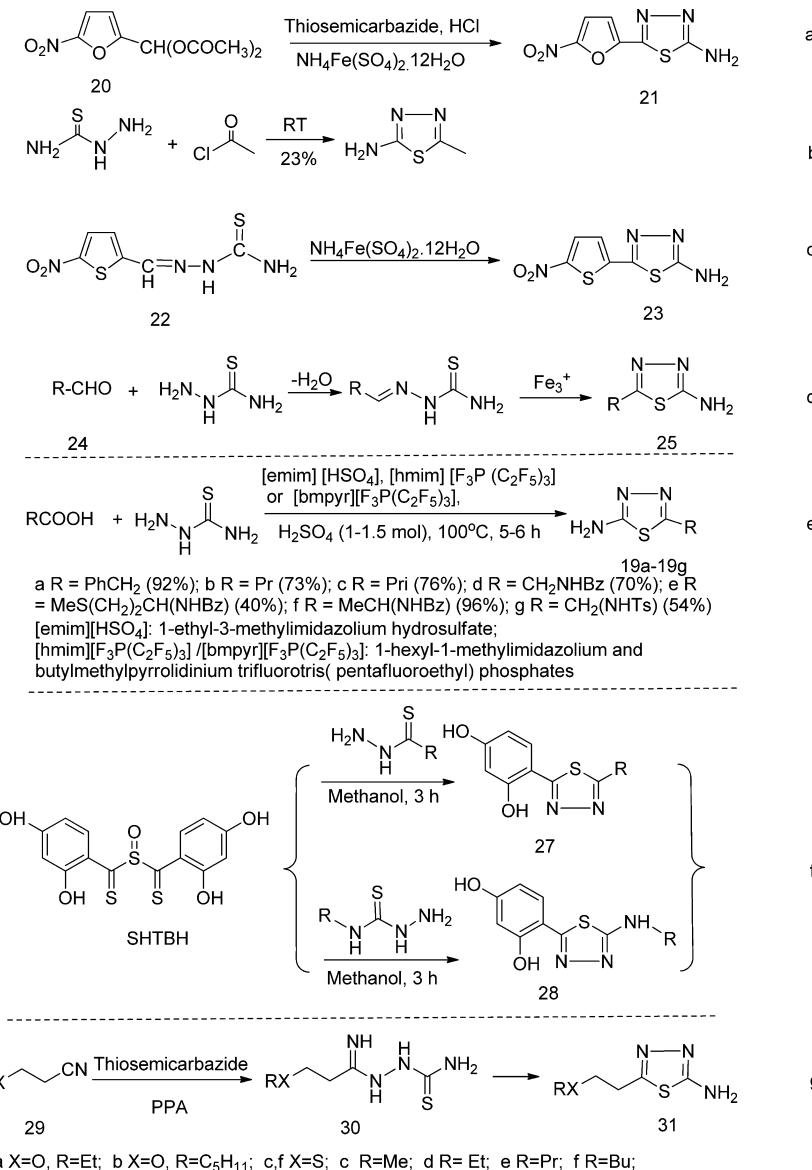


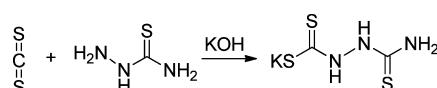
Figure 3. 1,3,4-Thiadiazolium mesoionic derivatives.

positive and negative charge supporting a neutral balance overall, with this character attracting much attention in photochemical studies. This structure associated with a polyheteroatomic system enables them to interact with biomolecules, and the overall neutral nature is conducive to membrane transport, which is significant in pharmaceutical chemistry. A series of 4-phenyl-5-styryl-1,3,4-thiadiazolium-2-phenylamines were well studied for their antiparasitic activities, and their synthesis is shown in Scheme 9.<sup>46</sup>

Thiosemicarbazides treated with CS<sub>2</sub> can also produce 1,3,4-thiadiazoles<sup>47</sup> but first forming dithiocarbazates (Scheme 9), which we will introduce in section 2.2.3.

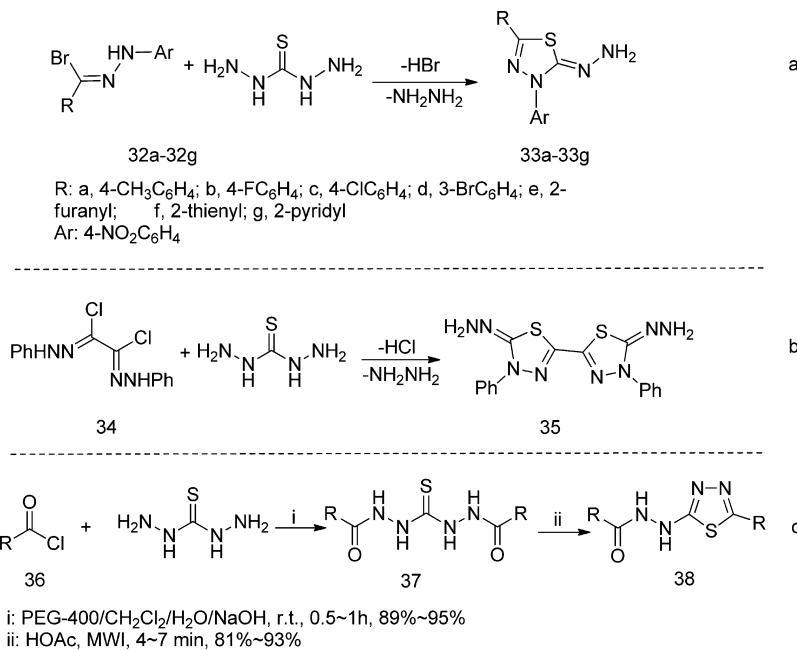
**2.2.2. From Thiocarbazides.** Thiocarbazide, also called carbonothioic dihydrazide, and its derivatives share a similar mechanism with thiosemicarbazide to synthesize thiadiazole. The only differences come from the introduced substituents

Scheme 9. Synthesis of 4-Phenyl-5-styryl-1,3,4-thiadiazolium-2-phenylamines



onto 1,3,4-thiadiazole, i.e., 2-amino (by thiosemicarbazide) and 2-acylhydazine (by thiocarbazide). Thiocarbazides have been used to prepare 1,3,4-thiadiazol-2-yl hydrazones or hydrazides. Treatment of carbonothioic dihydrazide with the appropriate hydrazoneoyl halide 32a–32g affords thiadiazoles 33a–33g (Scheme 10a).<sup>48</sup> By the same method in the same paper, the authors also prepared bis(1,3,4-thiadiazol-2-yl)hydrazones (Scheme 10b). Aside from hydrazoneoyl halide, Sayed's team also treated aldehydes with 2-(phenylmethylene)carbonothioic dihydrazide to get the corresponding hydrazones.<sup>48,49</sup> To avoid long-term environmental issues associated with conventional routines, Li et al. reported a new, an expedited, and an ecofriendly route for preparation of (un)substituted benzaldehyde (5-aryl-1,3,4-thiadiazol-2-yl) hydrazones using thiocarbo-

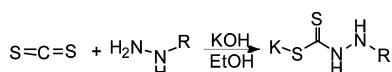
Scheme 10. Synthesis of 1,3,4-Thiadiazoles from Thiocarbazides



hydrazide as the starting material,<sup>50</sup> easily recoverable silica-supported dichlorophosphate as the dehydrant, and a microwave as the heat source. It demonstrated a high-yield method worthy of reference. In addition, a method for preparation of 1,3,4-thiadiazol-2-yl hydrazides by thiocarbazide under microwave radiation is demonstrated (Scheme 10c).

**2.2.3. From Dithiocarbazates.** As mentioned above, dithiocarbazates are synthesized by carbon disulfide as the sulfur source reagent reacting with hydrazine, hydrazides, hydrazone, thiosemicarbazide (mentioned in Scheme 9), or thioacylhydrazine usually under basic conditions (Scheme 11).

Scheme 11. Synthesis of Dithiocarbazates from Thioacylhydrazine

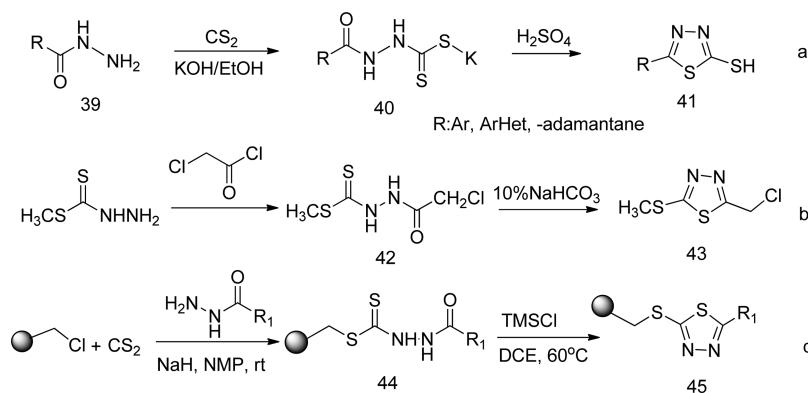


In the same step, dithiocarbazates were always acylated followed by cyclodehydration (concentrated sulfuric acid always being the dehydrant, occasionally CF<sub>3</sub>COOH) to generate 2-thiol/thione 1,3,4-thiadiazoles. Wei et al. and Kadi

et al. reported a general method to synthesize dithiocarbazate and 1,3,4-thiadiazole with acylhydrazide (Scheme 12a).<sup>9i,51</sup> Compounds 33a–33g and 35 can also be generated by dithiocarbazates with hydrazonoyl halide 32a–32g and 34 as reported by Sayed et al.<sup>48</sup> Another routine for preparing 1,3,4-thiadiazole is to primarily get dithiocarbazate acylated by chloroacetylchloride and then dehydrated (Scheme 12b).<sup>52</sup> Solid-phase syntheses of 1,3,4-thiadiazole derivatives via selective, reagent-based cyclization of acyldithiocarbazates have also been reported frequently. Gong et al. summarized several suitable methods for solid-phase synthesis of 1,3,4-thiadiazoles using CS<sub>2</sub> in the presence of sodium hydride at room temperature to prepare various acyldithiocarbazate resins 44 and then cyclodehydrate to generate the target compounds 45 (Scheme 12c).<sup>53</sup> Gong et al. used the Merrifield resin as a polymer support, investigated various reagents for cyclization reactions of the acyldithiocarbazates 44, including EDCI, DCC, TMSCl, TsCl, PPh<sub>3</sub>, SOCl<sub>2</sub>, PCl<sub>5</sub>, and diphenyl chlorophosphate, and found TMSCl and diphenyl chlorophosphate to be relatively ideal choices for the 1,3,4-thiadiazole 45.

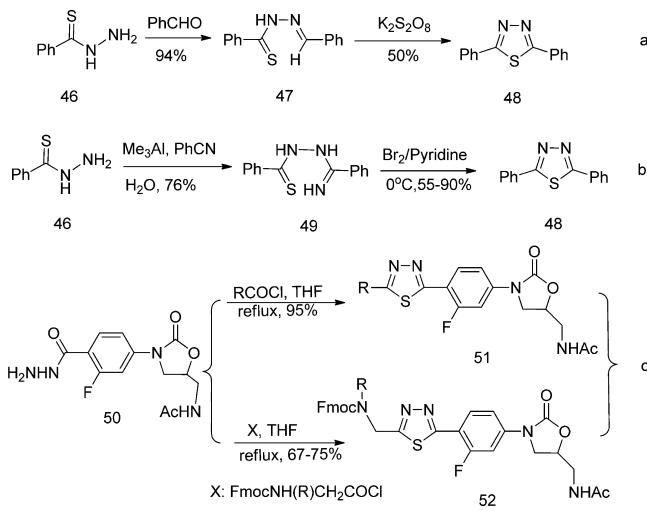
**2.2.4. From Thiohydrazides.** Thiohydrazide is very similar to thiosemicarbazide in chemical structure with the only

Scheme 12. Synthesis of 1,3,4-Thiadiazoles from Dithiocarbazates



difference being the former lack of the  $\alpha$ -amino group. As a result, thiohydrazide is also a regular in the synthesis “hodgepodge” of 1,3,4-thiadiazoles using similar methods with thiosemicarbazide. As reported, the process is to acylate thiohydrazides (with carboxylic acid, acid halide, acid anhydride) or form Schiff base (with aldehyde) and hydrazone (with nitrile) and then cyclodehydrate *in situ* to synthesize 1,3,4-thiadiazoles. Fararr et al. reported preparation of 2,5-dimethylphenyl-1,3,4-thiadiazole **48** by treating thiobenzhydrazide **46** with benzaldehyde to produce the thiohydrazide derivative **47** (Scheme 13a) and with benzonitrile producing N-

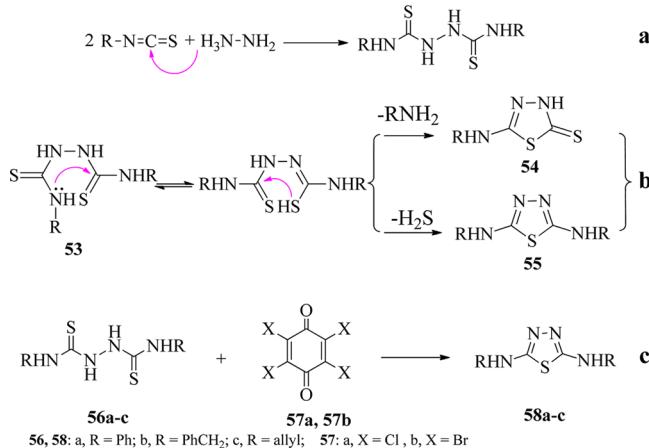
### Scheme 13. Synthesis of 1,3,4-Thiadiazoles from Thiohydrazides



thiobenzoylbenzamidrazone **49** (Scheme 13b) with  $K_2S_2O_8$  and  $I_2$ /pyridine as oxidants, respectively.<sup>54</sup> Formation of the thiadiazole ring can be rationalized by deprotonation of thiohydrazide and then intramolecular attack of the thiolate anion on the amidinyl or iminyl carbon atom and loss of ammonia or hydrogen after proton transfer. A neutral or acidic condition is probably favorable in Scheme 13a, whereas it has an adverse effect for formation of thiadiazoles in Scheme 13b. Reaction of thiobenzhydrazide **50** with acid chlorides in refluxing THF afforded a variety of 1,3,4-thiadiazolyl phenyl oxazolidinone analogues **51** in good yield. Addition of Fmoc-glycyl chloride or Fmoc-sarcosine acid chloride (prepared from Fmoc-sarcosine and thionyl chloride using a catalytic amount of DMF) in refluxing THF afforded the Fmoc-protected 2-aminomethyl-1,3,4-thiadiazole analogues **52** (Scheme 13c), and the Fmoc protecting group can be removed by treating with piperidine.<sup>55</sup> Preparation of coumarin-1,3,4-thiadiazole derivatives is also reported by condensation of coumarin-3-carbothiohydrazide with esters (ethyl orthoformate, trimethyl orthoacetate, and trimethyl orthobenzoate). Diethyl chlorophosphate can also be used to synthesize 1,3,4-thiadiazoles.<sup>56</sup>

**2.2.5. From Bithioureas.** Bithiourea with an  $\alpha$ -amino on each end can be prepared by reacting isothiocyanates with hydrazines (Scheme 14a) or thiosemicarbazides.<sup>57</sup> It then can be cyclodehydrated to afford a 2,5-amino-1,3,4-thiadiazole which is a very important intermediate to further prepare other 2,5-bis-substituent-1,3,4-thiadiazoles. Formation may be explained in terms of intramolecular nucleophilic attack by either the 2-thiol or the NH group and detachment of the RNH

### Scheme 14. Synthesis of 1,3,4-Thiadiazoles from Bithioureas



or HS moiety as depicted in Scheme 14b. When aniline or allylamine is eliminated, the product would be a 5-substituted amino-3*H*-[1,3,4]thiadiazole-2-thione **54**, whereas when  $H_2S$  is displaced, the product formed would be an *N,N*-disubstituted-[1,3,4]thiadiazole-2,5-diamine **55**.<sup>58</sup> Adding tetrahydrofuran (THF) solutions of **56a–56c** to 2:1 solutions of **57a** and **57b** in the same solvent produced quinoxaline derivatives with the 2,5-disubstituted amino-1,3,4-thiadiazoles **58a–58c** as minor products (yields of 12–15% in the case of **57a**, 21–26% in the case of **57b**) (Scheme 14c).<sup>59</sup> Ethenetetracarbonitrile (TCNE), considered a highly electron-deficient and strongly electrophilic reagent, was demonstrated to be very important in condensation of **56a–56c** to get the corresponding thiadiazoles and thiadiazole-2-thiones, in comparison to the routine of adding **56a–56c** to ethyl acetate or chlorobenzene without TCNE for 96 h, giving again compounds **56a–56c**, which did not follow the previous sequence of chemical reactions.<sup>60</sup>

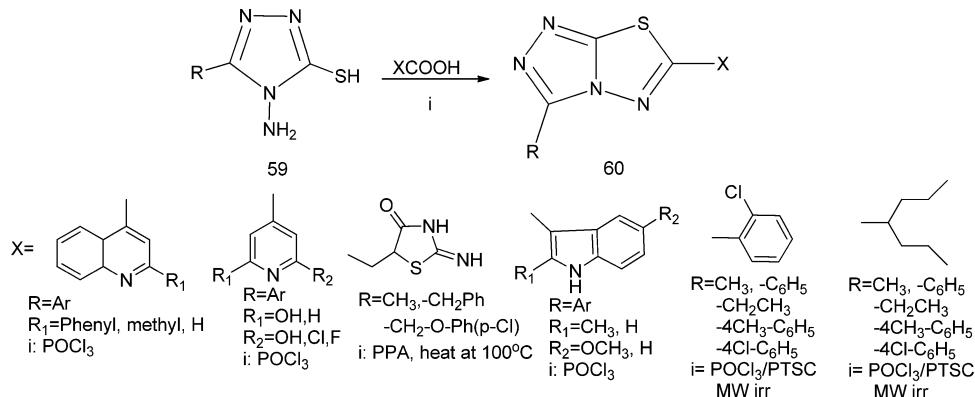
### 2.3. From 1,3,4-Oxadiazoles

Replacement of  $-O-$  by  $-S-$  in some heterocycles was reported viz. transformation of epoxides to episulfides by the action of thiocyanates or thiourea. However, there is little in the literature about the conversion of 1,3,4-oxadiazoles to 1,3,4-thiadiazoles.<sup>61</sup> Padmavathi et al. successively reported interconversion of 1,3,4-oxadiazoles with thiourea in THF to get 1,3,4-thiadiazoles, which was demonstrated to be a simple and pretty high-yielding method (Scheme 6c). It hypothesizes the probable mechanism involves initial attack at positions 2' or 5' of 1,3,4-oxadiazole by the S atom of thiourea assisted by the nitrogen lone electron pair on the amino followed by ring-opening reaction to yield the thiuronium salt. This thiuronium salt undergoes rearrangement to form mesomeric oxouronium salt via formation of an oxathiadiazepine derivative. Further ring closure of oxouronium salt will lead to formation of thiadiazole with elimination of a urea molecule (Scheme 6d).<sup>62</sup>

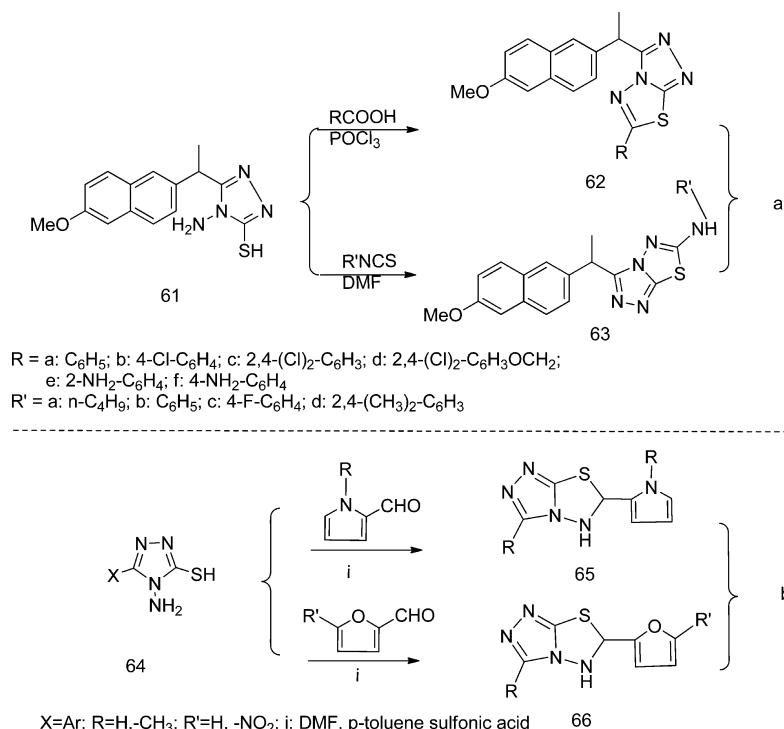
### 2.4. From 4-Amino-5-mercaptop-1,2,4-triazoles

1,2,4-Triazolo[3,4-*b*]-1,3,4-thiadiazole is a very important fused heterocyclic system associating two versatile nuclei thiadiazole and triazole. Herein, we involve this kind of compounds as 1,3,4-thiadiazole derivatives and briefly introduce the synthesis method from 4-amino-5-mercaptop-1,2,4-triazoles. The reactions are proceeded by treating 4-amino-5-mercaptop-1,2,4-triazoles regularly with acids (Schemes 15 and 16a),<sup>9f,16h,63</sup> isothiocya-

Scheme 15. Synthesis of 1,3,4-Thiadiazoles from 4-Amino-5-mercaptop-1,2,4-triazoles with Acids



Scheme 16. Synthesis of 1,3,4-Thiadiazoles from 4-Amino-5-mercaptop-1,2,4-triazoles with Isothiocyanates



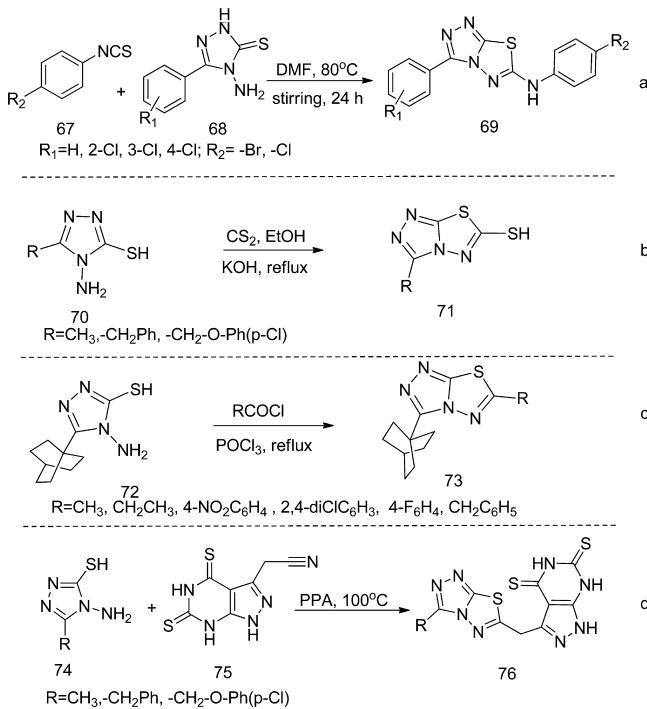
nates (Schemes 16a and 17a),<sup>63b,64</sup> aldehydes (Scheme 16b),<sup>63a</sup> CS<sub>2</sub> (Scheme 17b),<sup>16b,65</sup> nitriles (Scheme 17d), and acyl chlorides (Scheme 17c).<sup>16h,65</sup>

## 2.5. Miscellaneous

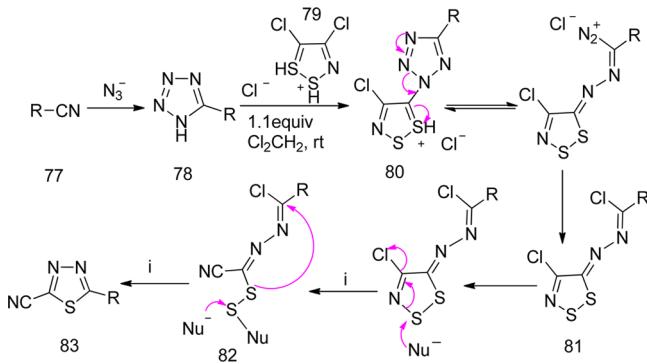
Several uncommon approaches have been reported for the synthesis of 1,3,4-thiadiazole derivatives. Le et al. reported the synthesis of 1,3,4-thiadiazoles and its oligomers from tetrazoles via hydrazoneoyl chlorides (Schemes 18 and 19a).<sup>66</sup> Tetrazole 78 starting from cyanide 77 reacts with Appel salt 79 via nitrile with elimination of HCl to afford 2,5-disubstituted tetrazole 80, which could equilibrate with the stabilized diazonium tautomer, which with chloride gives the dichloro compound 81. The dithiazole ring of compound 81 was presumably opened by nucleophilic attack on sulfur, generating a cyano group on the disulfide 82, which suffers further nucleophilic attack leading to cyclization and providing cyano-1,3,4-thiadiazole 83. Furthermore, compound 83 can be repeated to give a series of unsymmetrical thiadiazole oligomers (Scheme 19a). It is also well established that reactions of diazo compounds with

thiocarbonyl dipolarophiles lead to 2,5-dihydro-1,3,4-thiadiazoles.<sup>67</sup> Diazo 87 reacted with compound 88 in a 1,3-dipolar cycloaddition manner to yield thiadiazole 89. In this reaction, diazomethylphosphonates 87a and 87b are attractive reagents for 1,3-dipolar cycloadditions, which in the case of C=S dipolarophiles exceed the reactivity of the frequently used diazoacetates 87c. Synthetic applications of these intermediates are limited by the availability of their precursors, and only "thiofluorenone" 88d is sufficiently reactive toward 87a to give the appropriate 2,5-dihydro-1,3,4-thiadiazole derivative 89d (Scheme 19b). Radwan et al. also reported treatment of 3-cyanoacetyl indole 90 with phenylisothiocyanate and potassium hydroxide afforded the potassium salt intermediate 91, which was converted into the corresponding thioacetanilide derivative 92 upon treatment with 10% hydrochloric acid.<sup>68</sup> The thioacetanilide 92 reacted with hydrazoneoyl chlorides 93a–93f in refluxing ethanol and in the presence of triethylamine to afford 1,3,4-thiadiazole 95a–95f (69–77% yield) (Scheme 20).

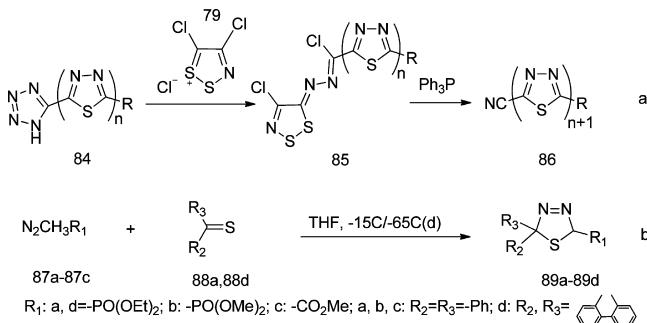
**Scheme 17. Synthesis of 1,3,4-Thiadiazoles from 4-Amino-5-mercaptop-1,2,4-triazoles with Isothiocyanates and  $\text{CS}_2$ , Nitriles, and Acyl Chlorides**



**Scheme 18. Mechanism of Synthesis of 1,3,4-Thiadiazoles from Tetrazoles via Hydrazonoyl Chlorides**



**Scheme 19. Synthesis of Thiadiazole Oligomers and 2,5-Dihydro-1,3,4-thiadiazole Derivative**



R<sub>1</sub>: a, d=PO(OEt)<sub>2</sub>; b: -PO(OMe)<sub>2</sub>; c: -CO<sub>2</sub>Me; a, b, c: R<sub>2</sub>=R<sub>3</sub>=Ph; d: R<sub>2</sub>, R<sub>3</sub>=

### 3. REACTIVITY AND SYNTHETIC APPLICATION OF 1,3,4-THIADIAZOLE

As with most azoles, thiadiazoles are very weak bases due to the inductive effects of the extra heteroatoms. Unsubstituted 1,3,4-thiadiazole ring (first achieved by Goerdeler and Ohm in 1956) with obvious aromaticity cannot easily be substituted nucleophilically, and electrophilic substitutions on carbon are practically unknown, apart from a few halogenations and mercurations,<sup>69</sup> while substituted thiadiazoles are susceptible to nucleophilic attack on a carbon atom with leaving groups generally displaced easily.<sup>70</sup> The ring nitrogen atoms suffer electrophilic attack depending on the tautomerizability of the substituents on the C-2 or C-5 position and 1,3,4-thiadiazolium salts or 1,3,4-thiadiazol-2(3H)-ones that can be prepared. Electrophilic attack on ring sulfur atoms is rarely found; as a result, the reactivity of 1,3,4-thiadiazoles arises from the nucleophilic center localized on the ring nitrogen atoms and from the electrophilic center on the carbon of the C=N bond. A supplementary reactivity can arise from conversions of substituents attached to C2/5. Thus, 1,3,4-thiadiazoles are versatile reagents for synthesis of various compounds (Scheme 21). Several kinds of 1,3,4-thiadiazole derivatives were named as in Figure 4. The tautomerism of 1,3,4-thiadiazole is primarily presented by thione–thiol or amino–imino transformation on the C-2 or C-5 position (Scheme 22).<sup>71</sup>

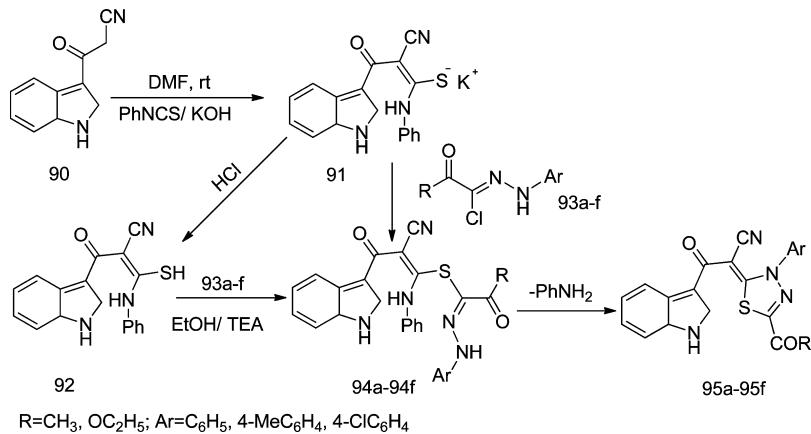
The thiadiazole heterocycle can be preserved or altered depending on the target to hit. Intramolecular rearrangement or an electrophilic substituent on N atoms can result in formation of 1,3,4-thiadiazoline and 1,3,4-thiadiazolidine, which will also be introduced. Protonation and alkylation or acylation on the ring nitrogen atom giving thiadiazolinium salts or 1,3,4-thiadiazol-2(3H)-ones can be classified in section 3.1. Section 3.2 includes the main reactions on the ring carbon atom with subclassification based on different common leaving groups. The heterocyclic substituent on the thiadiazole ring preparing imidazothiadiazole and other heterocyclic compounds will be discussed in section 3.3. Metal complex and macromolecular chemistry will be introduced in section 3.4. The last two sections focus on the ring-opening reaction and other miscellaneous reactions.

#### 3.1. Reactivity of the Ring Nitrogen Atom

The reactivity of the ring nitrogen atom arises from the electrophilic reactions depending on the tautomeric equilibrium of thione–thiol or amine–imine at position 2' or 5'. At the forms of thione or imine, deprotonation of ring N–H makes the ring N atom vulnerable to alkylation or acylation or transforming to 1,3,4-thiadiazolium salts. Reactions are conducted with electrophiles such as halides (alkyl halides,<sup>72</sup> benzyl halides,<sup>72c,73</sup> allylic halides,<sup>74</sup> hydroxalkyl halides, and heterocyclic halides),<sup>75</sup> trimethylsilylmethyl trifluoromethanesulfonate, formaldehyde, etc.<sup>76</sup>

Ohta et al. reported 2-trifluoroacetamide-5-*tert*-butyl-1,3,4-thiadiazole can be alkylated by cyclopropylmethyl bromide with a 91% yield (Scheme 23a).<sup>72b</sup> Methyl halides (always iodides and bromides) were frequently reported to produce 3-methyl-1,3,4-thiadiazoles in aprotic solvents such as DMF<sup>72a</sup> in the presence of K<sub>2</sub>CO<sub>3</sub>.<sup>77</sup> Apart from alkyl thiadiazoles, hydroxalkyl thiadiazoles 99a and 99b have also been reported to be obtained by treatment of bromoethanol solution with amino-thiadiazole 98a and 98b (Scheme 23b).<sup>75a</sup> Polvonov et al. reported alkylation of 5-anilino-(*p*-toluidino, morpholino)-1,3,4-thiadiazoline-2-thiones (100a–100c) with allyl bromide

Scheme 20. Synthesis of 1,3,4-Thiadiazoles from 3-Cyanoacetyl indole



Scheme 21. General Reactions of 1,3,4-Thiadiazoles

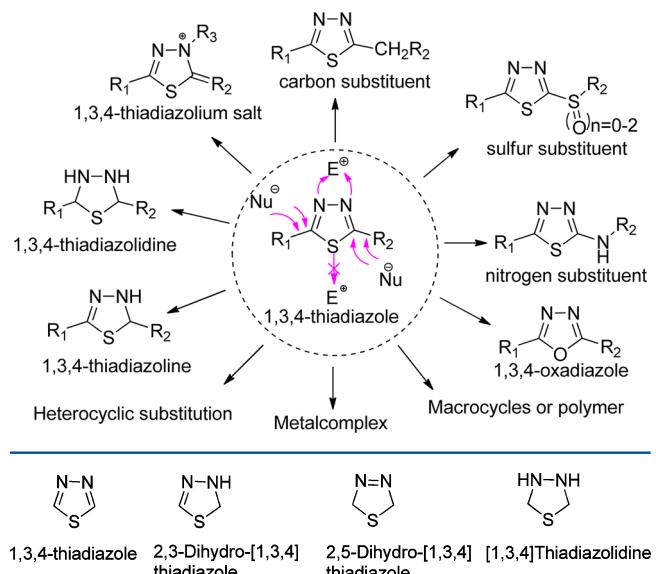
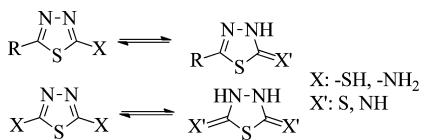


Figure 4. Several kinds of 1,3,4-thiadiazole derivatives.

Scheme 22. Tautomerism of 1,3,4-Thiadiazole

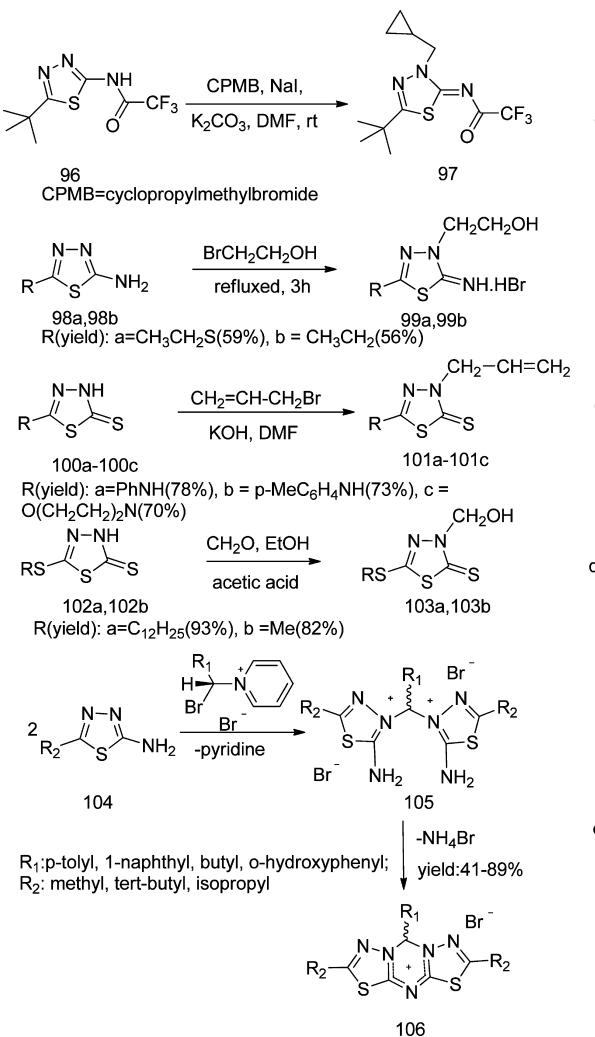


gave the *N*-allyl derivatives **101a–101c** (Scheme 23c) as the basic product.<sup>74</sup> In addition, formaldehyde also readily affords hydroxymethyl thiadiazole derivatives (Scheme 23d).<sup>76b,c</sup> Pyridinium halides electrophilically attack the thiadiazole ring nitrogen atoms in parallel with the increasing nitrogen-NPA charges and a decreasing activation barrier for alkylation of those nitrogen centers.<sup>78</sup> The novel fused tricyclic ring systems bis(1,3,4-thiadiazolo)-1,3,5-triazinium halides (SNS) have attracted extensive research and were prepared previously from reacting *N*-(1-haloalkyl)pyridinium halides with amino-thiadiazoles **104a–104c** (Scheme 23e).

### 3.2. Reactivity of the Ring Carbon Atom

In this part we will introduce the reactivity attached to the ring carbon atom including the introduction and interconversions of

Scheme 23. Reactivity of the Ring Nitrogen Atom of 1,3,4-Thiadiazole



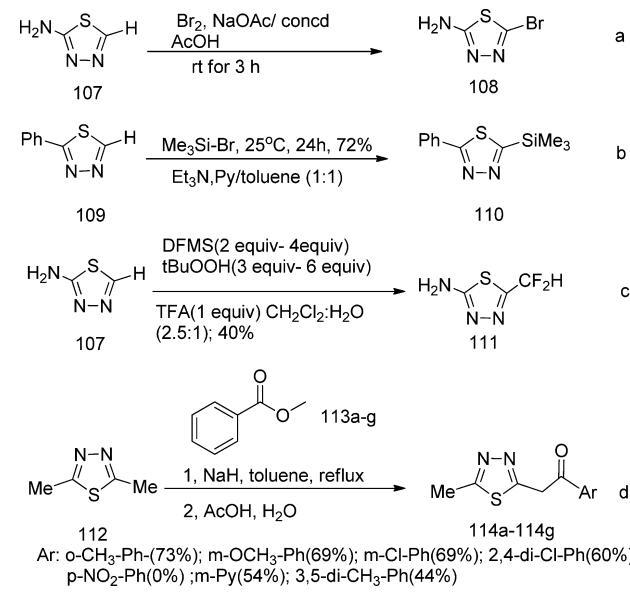
several important leaving substituents associated with the ring carbon atoms (i.e., halogens, carbon substituents, nitrogen substituents, oxygen substituents, and sulfur substituents). Electrophilic attack on unsubstituted thiadiazole is rarely reported, whereas when a substituent is introduced onto the 1,3,4-thiadiazole ring it can proceed. Nucleophilic attack on the ring carbon atom occurs readily due to the electron-deficient

nature of the ring. In addition, the leaving substituents on the ring carbon atoms are also highly activated to be substituted.

### 3.2.1. Reactivity of the Ring Carbon Atom and Carbon Link Substituents Attached to the Ring Carbon Atom

Electrophilic substitution on the ring carbon atom of 1,3,4-thiadiazoles is rare due to the low electron density of ring carbons, whereas it can be accomplished via rearrangement of intermediate  $\sigma$ -complex thiadiazolium salts as radical halogenations, providing chlorinated or brominated 2-halo-5-substituent thiadiazoles.<sup>80</sup> The electrophilic agents are generally polarized halogenating agents that provide the halonium ion with or without a catalyst. Lachance et al. reported 2-amide 1,3,4-thiadiazole **107** can undergo electrophilic substitution with molecular bromine (Scheme 24a).<sup>81</sup> Direct electrophilic

**Scheme 24. Reactivity of the Ring Carbon Atom and Carbon Link Substituents Attached to the Ring Carbon Atom**



silylation of 1,3,4-thiadiazole **109** with TMSBr (trimethylsilyl bromide) under basic conditions results in a novel synthesis of C-trimethylsilylthiadiazole **110** (Scheme 24b).<sup>82</sup> The difluoromethyl group ( $\text{CF}_2\text{H}$ ) is an intriguing structural motif that has great potential in the areas of pharmaceuticals, agrochemicals, and materials. Fujiwara et al. reported the invention of a new reagent ( $\text{Zn}(\text{SO}_2\text{CF}_2\text{H})_2$ , DFMS) for the innate trifluoromethylation of organic substrates including 1,3,4-thiadiazole **107** by nucleophilic attack to the C-2 atom via a radical process (Scheme 24c).<sup>83</sup> Likewise, Ji et al. also introduced a practical method for trifluoromethylation of 1,3,4-thiadiazole **107** under the condition of  $\text{NaSO}_2\text{CF}_3$  (3.0–6.0 equiv) and  $t\text{-BuOOH}$

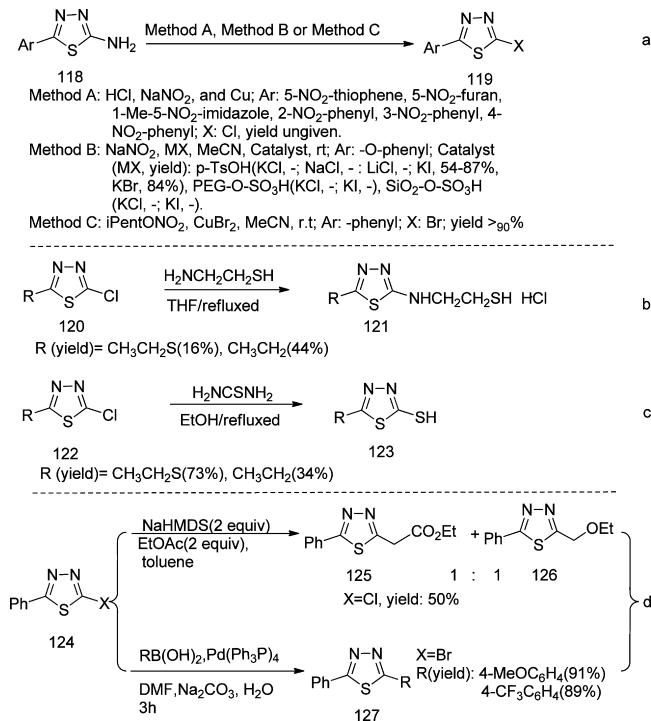
(5.0–10.0 equiv) in a solution of dichloromethane ( $\text{DCM}:\text{H}_2\text{O}$  (2.5:1) with a yield of 33%.<sup>84</sup>

Treating methylthiadiazole **112** with aromatic carboxylic acid esters **113a–113g** in the presence of sodium hydride got the methyl group substituted. In addition, reacting with acyl chloride **115** in the presence of triethylamine gives rise to formation of mixtures of diacylated thiadiazoles **116** and **117**; generally the latter is rearranged on heating in higher boiling solvents to give **116** (Schemes 24d and 25).<sup>85</sup>

### 3.2.2. Reactivity of Halogens Attached to the Ring Carbon Atom

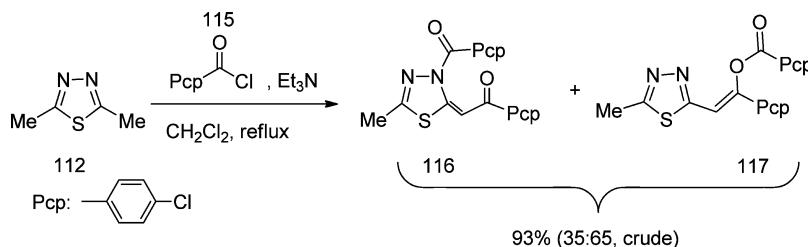
Most halo-substituted thiadiazoles are prepared through two general methods: direct substitution on the ring C-2 atom, which we introduced in section 3.2.1, and halo substitution of diazonium salt (Scheme 26a). The

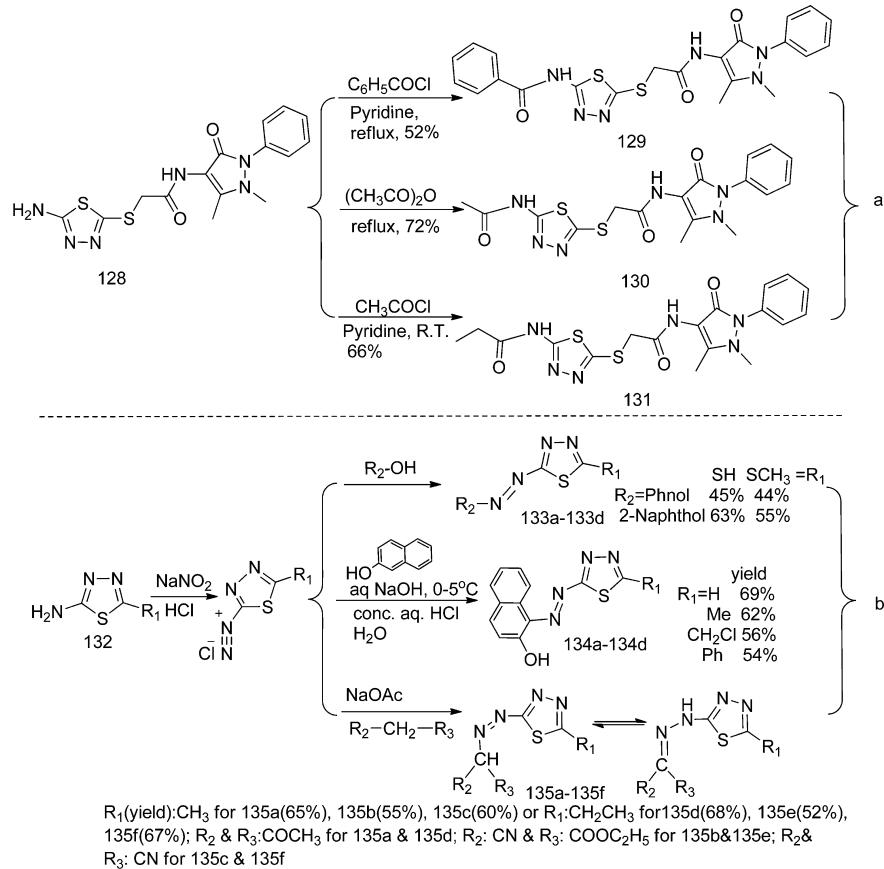
**Scheme 26. Reactivity of Halogens Attached to the Ring Carbon Atom**



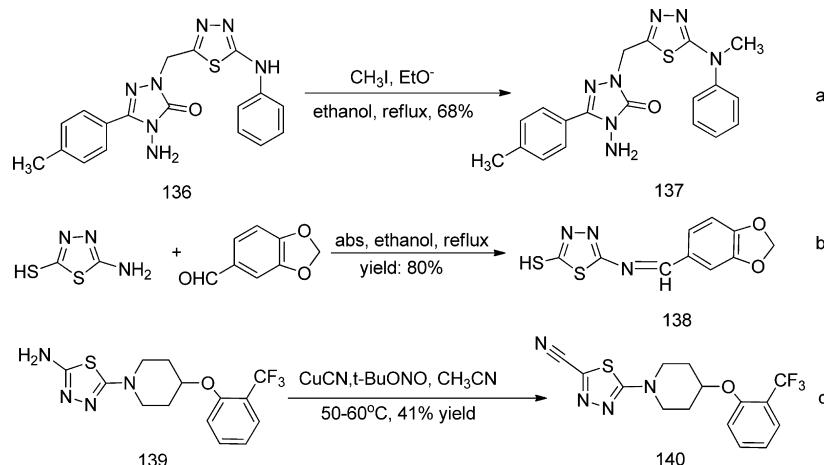
electronegativity of the halogen atom of halo-substituted thiadiazoles leads to an electropositive carbon atom which is readily attacked by nucleophiles displacing the halogen atom. Thus, halo-substituted thiadiazoles are highly reactive and react with a wide range of nucleophiles, and this kind of reaction is frequently reported. Most common nucleophiles are oxygenic (e.g., alcohol),<sup>86</sup> nitrogenic (e.g., amides,<sup>75a,87</sup> hydrazides,<sup>87b,88</sup> nitrogenous heterocyclic compounds; this part will be

**Scheme 25. Reaction of Methylthiadiazole**



Scheme 27. *N*-Acylation and Diazotization Coupling of 2(5)-Amino-1,3,4-thiadiazole

Scheme 28. Nucleophilic Reactions of 1,3,4-Thiadiazole

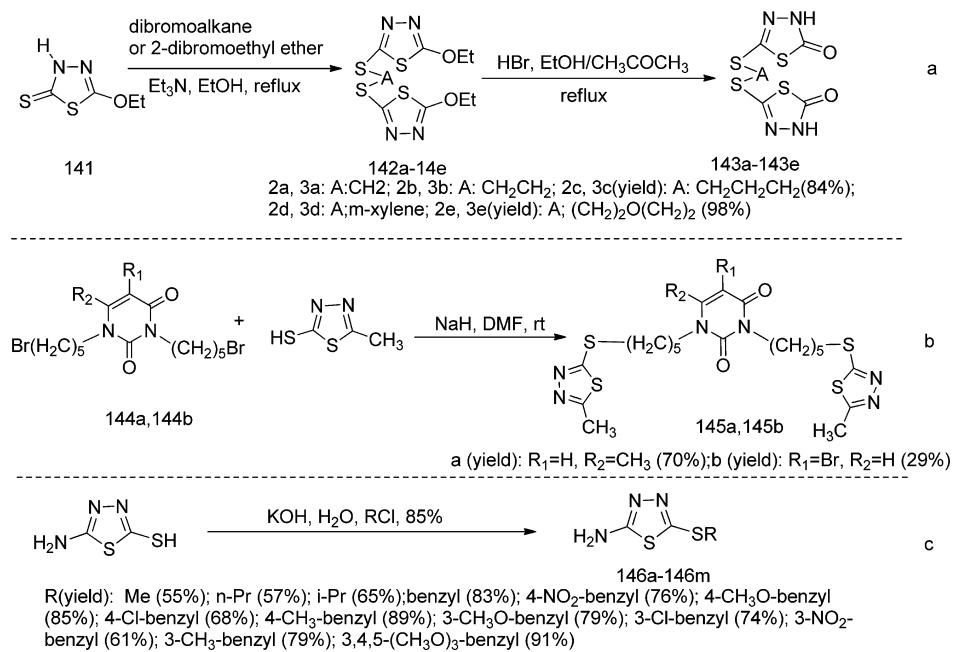


summarized and introduced in section 3.2.1), and sulfuric (e.g., thiourea,<sup>75a,87c,89</sup> mercapto compounds<sup>90</sup>) radicals and alkyl or aryl compounds.<sup>91</sup> Tahghighi et al. introduced alkynyl by the propargyl amine reacting with 2-chloro-1,3,4-thiadiazole;<sup>87a</sup> Wang et al. prepared 2-methylamino/ethylamino/hydroxylethylamino/hydrazinyl-5-aryloxymethyl-1,3,4-thiadiazoles from 2-halo-1,3,4-thiadiazoles;<sup>87b</sup> Prathap et al. obtained 2-hydrazinyl-5-(pyridin-3-yl)-1,3,4-thiadiazole by nucleophilic substitution of the 2-chloro of the thiadiazole.<sup>88</sup> All of the reactions occurred under mild conditions. Aminothiol thiadiazoles are hot spots in radioprotective research and can be generally prepared from halo thiadiazoles and cysteamine (Scheme

26b).<sup>75a,87c</sup> Halo thiadiazoles converting into mercapto thiadiazoles (Scheme 26c)<sup>75a,87c</sup> and alkyl or aryl thiadiazoles (Scheme 26d) are also reported frequently.<sup>91</sup>

**3.2.3. Reactivity of Nitrogen Link Substituents Attached to the Ring Carbon Atom.** Amino thiadiazoles are versatile, as the amino substituent activates the thiadiazole ring for further reactivity and the amino group itself is open for further transformations. Apart from nucleophilic substitution of amino on the ring carbon atom, amino thiadiazoles are available for many kinds of reactions owing to their aromaticity including (thio)acylation,<sup>14,17c,39,92</sup> diazotization and nitrogen coupling reaction,<sup>93</sup> oxidation,<sup>91</sup> alkylation,<sup>94</sup> or arylation and forming

Scheme 29. Replacement of 2(S)-Sulfur Substituents



Schiff's base reactions.<sup>95</sup> Herein, we share several interesting ones among them.

N-Acylation of the amino agent on 1,3,4-thiadiazole for amides is always conducted with some powerful acylation agents such as anhydrides and acyl chlorides (Scheme 27a).<sup>92e</sup> Acylation can be slowed down by the existence of electrophilic agents on the thiadiazole ring, in which case concentrated sulfuric acid is added as catalyst.<sup>39</sup> Likewise, introduction of sulfonyl to the 2-amino-1,3,4-thiadiazole makes its sulfonylation mainly by reaction with sulfonyl chlorides (almost the benzene sulfonyl chlorides) different from direct oxidation of 2(S)-mercapto-1,3,4-thiadiazoles, which will be summarized in section 3.2.4.<sup>92d</sup> The target compounds 1,3,4-thiadiazole sulfonamides are potent inhibitors of  $\alpha$ -carbonic anhydrases.<sup>96</sup>

2(S)-Amino-1,3,4-thiadiazole can also have a diazotization-coupling reaction which is performed with sodium nitrite and hydrochloric acid under common diazotization condition yielding thiadiazole diazonium salt and then reacting with electron-donating groups to ensure the coupling (Scheme 27b).<sup>93,95a,97</sup> Thiadiazole diazonium salt can easily be deaminated and substituted by hydroxide or chloride to afford the 2(S)-hydroxy or 2(S)-chloro derivative via treatment with sodium nitrite in cold aqueous hydrochloric acid solution followed by boiling for 10 min.<sup>91</sup>

The electron pair on the amino nitrogen atom makes nucleophilic substitution easily proceed. Compound **136** can be converted to its methylated derivative **137** by treatment with methyl iodide in the presence of sodium ethoxide (Scheme 28a).<sup>94b</sup> Nucleophilic addition between primary amine and carbonyl aldehyde/ketone to prepare Schiff base is also common for amino-substituted thiadiazoles. Condensation of thiadiazole with piperonal in refluxing ethanol was a step forward toward formation of compound **138** (Scheme 28b).<sup>95a</sup> Microwave irradiation was also used to shorten the reaction time and increase yields in contrast to the traditional method.<sup>95b</sup>

We summarized the method that 2-amino-1,3,4-thiadiazoles were substituted and converted into 2-halo-1,3,4-thiadiazoles in

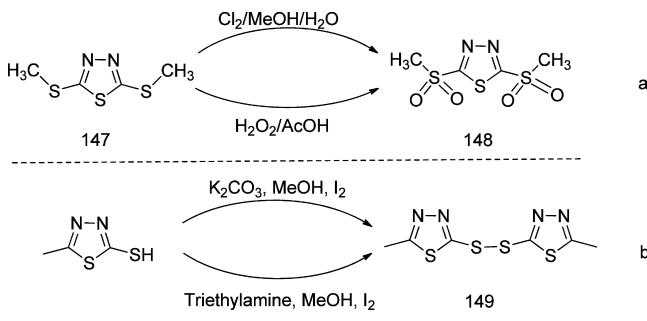
section 3.2.2. In addition, the amino can be substituted by other agents, such as nitrile (Scheme 28c).<sup>98</sup>

### 3.2.4. Reactivity of Sulfur/Oxygen Link Substituents Attached to the Ring Carbon Atom.

There are a few reports about studies on the reactivity of oxygen link substituents attached to the 1,3,4-thiadiazole ring carbon atom for this decade. Sulfur substituents are mainly mercapto, which can be directly introduced during thiadiazole cyclization, as summarized in section 2.2; however, owing to their important characteristic in pharmaceuticals and materials they have been attracting the interest of a huge number of researchers. 2(S)-Sulfur substituents can be readily replaced and oxidized into sulfoxides, sulfone, or disulfide.<sup>99,101c,e,100</sup> Reactions of halides with thiols to synthesize diverse thiadiazole sulfides are frequently reported (Scheme 26c).<sup>91,10a,14,101</sup> Cho et al. reported a common method of *S*-alkylation and *O*-dealkylation.<sup>102</sup> Reaction of **141** with the appropriate  $\alpha,\omega$ -dibromoalkane or 2-dibromoethyl ether in the presence of triethylamine in ethanol yielded *S*-alkylated dimers **142a–142e**. Then the ethoxy group of **142** was cleanly dealkylated with HBr to give compound **143**, and the IR spectrum result suggested **143** existed as a lactam (Scheme 29a). In this reaction of *S*-alkylation, metal salts (common potassium salts and sodium salts) are primarily produced as intermediates when S<sup>2-</sup> forms, followed by treatment with halides to produce the thioether derivatives. Alkaline reacting conditions are needed, and common alkaline reagents include potassium hydroxide, sodium hydride, sodium methoxide, etc. Dibromide **144** reacting with 2-mercaptop-5-methyl-1,3,4-thiadiazole produced bis-substituted compound **145** (Scheme 2b).<sup>101b</sup> Both **143** and **145** are intermediates of macrocyclic thiadiazole derivatives which will be summarized separately in section 3.4. Clerici et al. synthesized a series of thioether derivatives by suspending 2-amino-5-mercaptop-1,3,4-thiadiazole in KOH solution and then treating with the appropriate alkyl halide **146a–146m** (Scheme 29c). Another common reaction of 2(S)-mercaptop-1,3,4-thiadiazoles was oxidation of the mercapto group, which was always conducted by strong oxidants such as

gaseous chlorine, hydrogen peroxide, and iodine. Pernerstorfer et al. reported two possible ways for generation of sulfone **148** and found that **147** can be cleanly oxidized with  $H_2O_2$  in acetic acid and isolated by precipitation with water, which demonstrated this method was more convenient than the other (Scheme 30a). They used the solid phase to synthesize

**Scheme 30. Oxidation of the 2(S)-Mercapto-1,3,4-thiadiazoles**



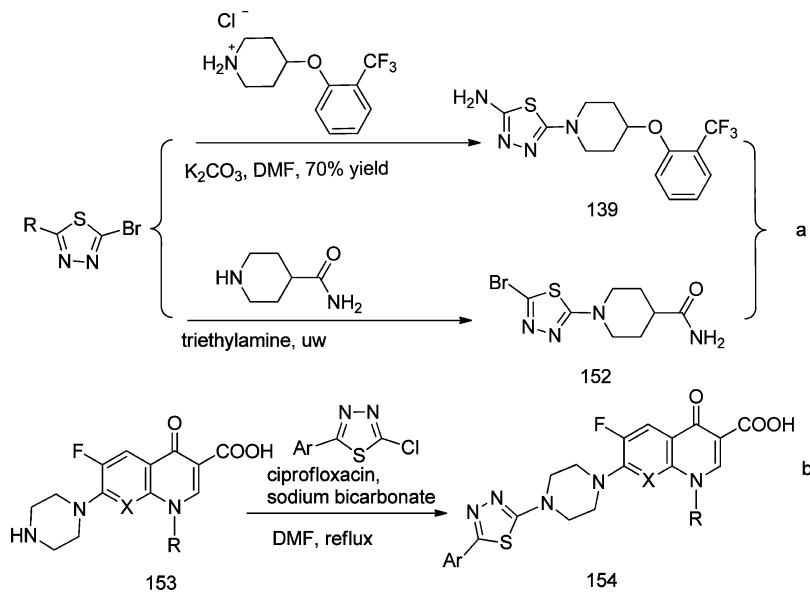
sulfone, and LC-MS analysis showed that formation of the sulfoxides occurred within a few minutes, whereas further oxidation yielding the sulfones took 4–5 h.<sup>100a</sup> Solid-phase synthesis emerged as a powerful tool for drug discovery, especially in pharmaceutical research to build random libraries, which can cover a broad chemical space to provide compounds for future screening. Tian et al. reported the disulfide compounds were obtained through oxidation of the corresponding mercaptan by iodine in basic solution and were very sensitive to oxygen and can easily be further oxidized to the corresponding sulfoxide (Scheme 30b).<sup>100b</sup> General synthesis of thiadiazole disulfides by oxidative coupling of 30%  $H_2O_2$  in ethanol/ $H_2O$  was also reported, and the reactions proceed smoothly with good yields (80–90%).<sup>100c</sup> As mercapto is a strong electron-withdrawing group, this causes the C-2 or C-5 atom to be more electron deficient, allowing nucleophilic attacks of 2(5)-mercapto-1,3,4-thiadiazole to frequently occur. Pernerstorfer et al. reported the double nucleophilic sub-

stitution of the compound in the solid phase.<sup>100a</sup> In addition, dissolving 2,5-dimercapto-1,3,4-thiadiazole in ethanol and reacting with hydrazine hydrate to produce 2,5-dihydrazino-1,3,4-thiadiazole was also reported.<sup>99</sup>

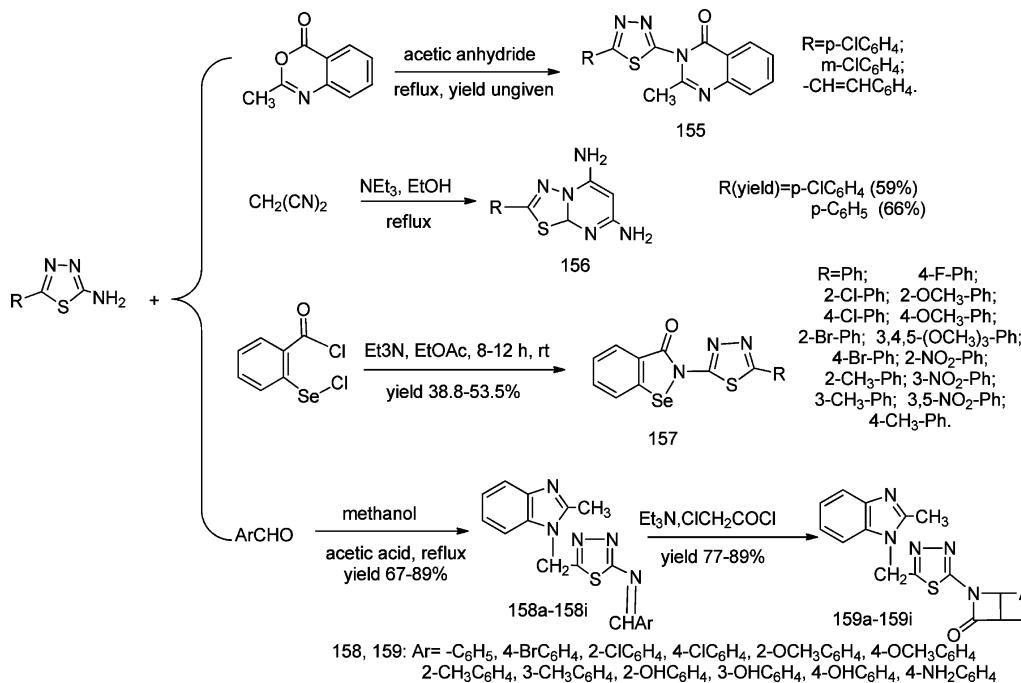
### 3.3. Synthesis of Heterocyclic Substituents 1,3,4-Thiadiazoles

Di/polyheterocyclic compounds derived from 1,3,4-thiadiazole have emerged over recent years.<sup>103</sup> Chemists have substituted different heterocyclic rings at position 2 or 3 to get potent drugs, pesticides, and antioxidants. The main reactive sites lie on the thiadiazole ring C-2 or the nitrogen atom on position 3, and common reactive groups on C-2 are halogen or amino. As it easily dissociates, 2-halogen substituents can be replaced by  $\alpha/\beta$  amine and are often treated with piperidine/piperazine or other nitrogen cycloalkane derivatives as one of the common substitutions of this part.<sup>98,104</sup> This reaction is always conducted under mild and basic conditions. 2-Amino is more active, which can nucleophilically attack on halides,<sup>105</sup> nitriles,<sup>106</sup> and carbonyl compounds or replace the ether bond of cyclic parts to obtain 1,3,4-thiadiazole-R heterocyclic compounds (R represents different kinds of heterocyclic agents), and sometimes the ring N3 was attacked simultaneously to yield thiadiazole-containing fused heterocycles.<sup>13,16b,107</sup> We herein summarize several common reactions. Oballa et al. and Xiao et al. separately reported that 2-bromide-1,3,4-thiadiazoles reacted with piperidines to prepare new stearoyl-CoA desaturase (SCD) inhibitor and spinal muscular atrophy (SMN) protein modulator (Scheme 31a).<sup>98,104a</sup> Similarly, Foroumadi et al. treated 2-Cl,5-Ar-1,3,4-thiadiazoles with some piperazinyl quinolones with pretty high yields (Scheme 31b).<sup>104j,108</sup> The 2-halogen-1,3,4-thiadiazole also reportedly coupled with the pyrrolidinol to give the thiadiazole-substituted pyrrolidinol under similar conditions.<sup>104e</sup> With regard to the nucleophilic attack of 2-amino-1,3,4-thiadiazoles, we herein summarized several common reactions (Scheme 32). On refluxing amine 1,3,4-thiadiazoles with 2-methylbenzoxazin-4(3H)-one one obtains 3-(1,3,4-thiadiazolyl)-2-methyl quinazolinones **155**,<sup>13</sup> reaction with malononitrile in absolute ethanol and in the presence of

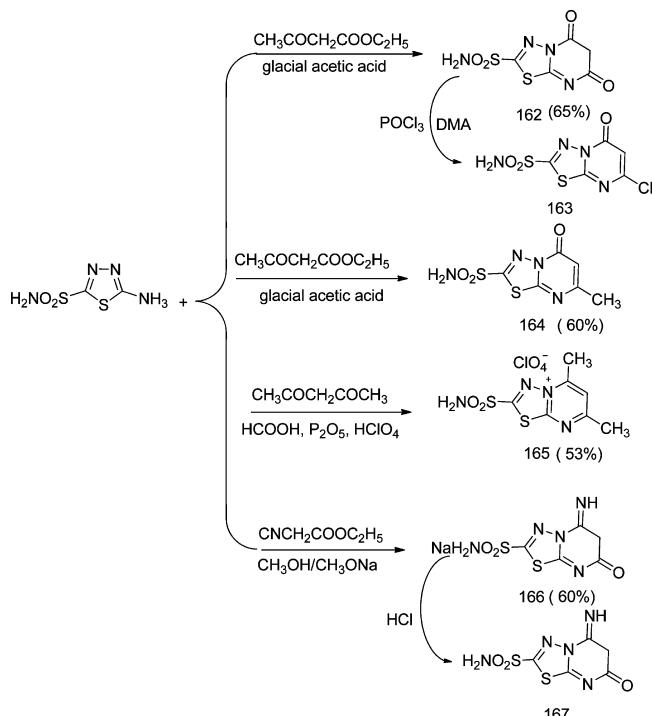
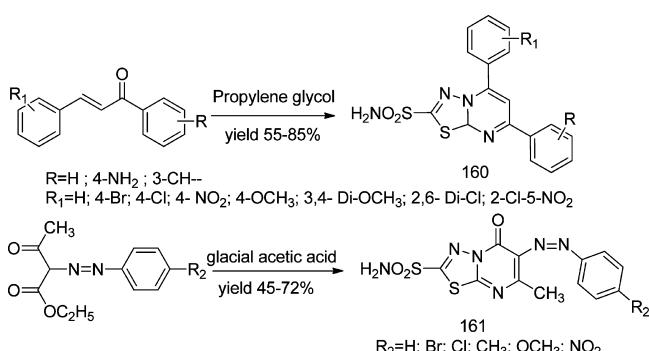
**Scheme 31. Reactions of 2-Br(Cl)-1,3,4-Thiadiazoles**



Scheme 32. Nucleophilic Attack of 2-Amino-1,3,4-thiadiazoles



triethylamine afforded 2-phenyl-8*H*-[1,3,4] thiadiazolo[3,2-*a*]pyrimidine-5,7-diamine **156**,<sup>106</sup> reaction with 2-chlorosele-nobenzoyl chloride yields 1,3,4-thiadiazole-containing benziselenazolone derivatives **157a–157o**,<sup>105</sup> and reaction with various selected aromatic aldehydes furnished Schiff bases **158a–158i** and then underwent cycloaddition to form the four-membered  $\beta$ -lactam ring.<sup>107a</sup> As for compound **156**, its formation resulted from both cyano groups of malononitrile reacting with both the C-2 amine and the N-3 atom. Apart from this, coreactions between the C-2 substituent and the N-3 atom to prepare fused heterocycles are not new. The most common reports were about obtaining the imidazo[2,1-*b*][1,3,4]-thiadiazoles. Khazi et al. published a comprehensive review introducing their chemistry;<sup>109</sup> consequently, we here choose not to give details. However, we bring other examples about the [1,3,4]thiadiazolo[3,2-*a*]pyrimidines (Schemes 33 and 34). A series of sulfonamide derivatives of [1,3,4]thiadiazolo[3,2-*a*]pyrimidine was synthesized by treating 2-amino-1,3,4-thiadiazole-5-sulfonamide with the appropriate chalcones to produce compound **160**, while phenyldiazenyl butyrate yielded compound **161**, dicarbonyl compounds produced

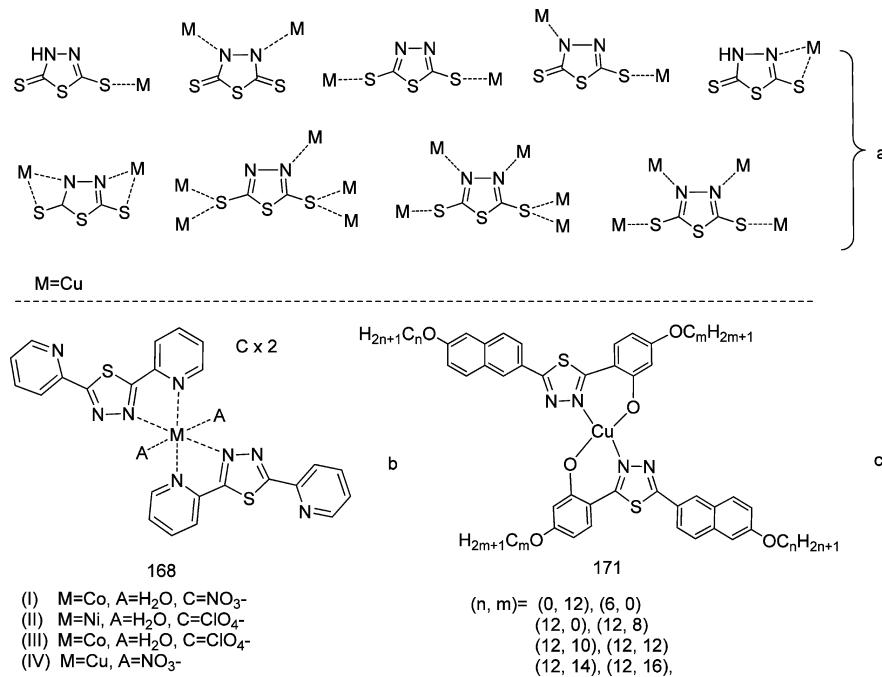
Scheme 34. Synthesis of [1,3,4]Thiadiazolo[3,2-*a*]pyrimidines from 2-Amino-1,3,4-thiadiazole-5-sulfonamideScheme 33. Synthesis of [1,3,4]Thiadiazolo[3,2-*a*]pyrimidines

compounds **162/163/164**, acetylacetone provided compound **165**, and ethyl cyanoacetate in a methanolic solution of sodium methoxide produced compound **166**.<sup>107b</sup>

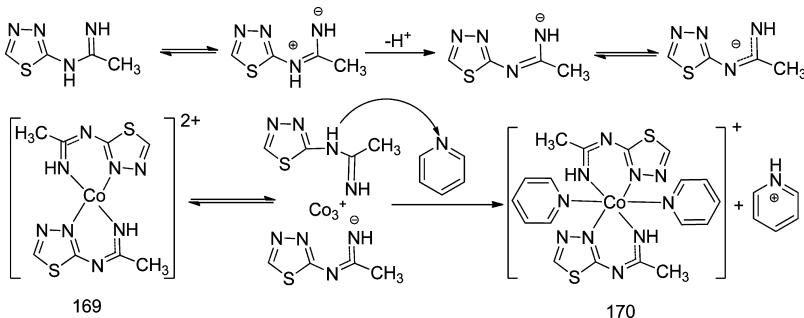
### 3.4. Synthesis of Metal Complex and Macromolecule

1,3,4-Thiadiazole derivatives are intriguing ligands in coordination chemistry since they can achieve versatile coordination modes using exocyclic or endocyclic nitrogen or sulfur donors.<sup>9g,36b,110</sup> In complexation reactions with metal ions,

Scheme 35. Metal Complex of 1,3,4-Thiadiazoles



Scheme 36. Mechanism of 1,3,4-Thiadiazoles Bridging Metal Centers



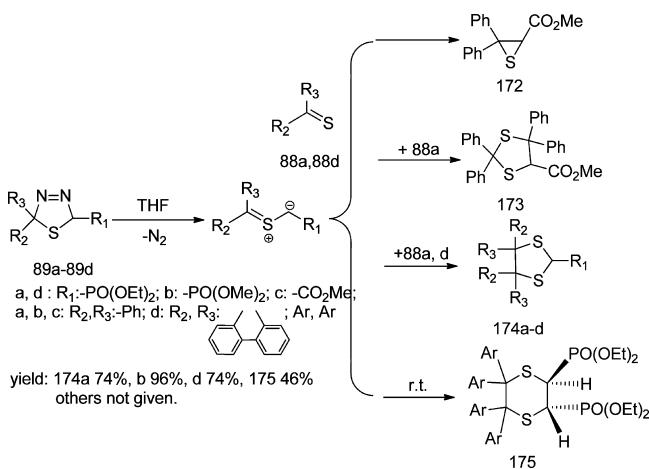
they usually show tautomerism, acid–base equilibrium, and redox behavior based on the conversions shown on Scheme 22. Due to the multiple donor sites, 1,3,4-thiadiazoles and its derivatives possessing (a) the nitrogen atoms,<sup>111</sup> (b) the thiocarbonyl sulfur atoms,<sup>112</sup> or (c) one nitrogen atom and one sulfur atom on either the same side or different sides of the molecule are well-known ligands for transition metal ions.<sup>113</sup> In addition, the  $\pi$  electron in the aromatic 1,3,4-thiadiazole ring may also potentially coordinate with metal ions.<sup>110f</sup> Over the years 1,3,4-thiadiazole metal complexes have been drawing increasing interest and extensively applied in pharmaceuticals, agrochemicals, and materials chemistry. As shown in Scheme 35a, Li et al. summarized the coordination modes of 2,5-dithiolate-1,3,4-thiadiazole (SSS) with three novel W(Mo)/Cu/S cluster-based layered polymers.<sup>114</sup> Bentiss et al. reported 2,5-bis(2-pyridyl)-1,3,4-thiadiazole, namely, bptd, was found to form the monomeric complexes,  $Co(bptd)_2(H_2O)_2(NO_3)_2$  (**I**),  $Ni(bptd)_2(H_2O)_2(ClO_4)_2$  (**II**),  $Co(bptd)_2(H_2O)_2(ClO_4)_2$  (**III**), and  $Cu(bptd)_2(NO_3)_2$  (**IV**) with Co(II), Ni(II), and Cu(II) in the presence of nitrate or perchlorate anions (see Scheme 35b).<sup>110a</sup> Herein is an example of the mechanism for formation of amidine ligand and its deprotonation to illustrate the mechanism of 1,3,4-thiadiazoles bridging metal centers (Scheme 36).<sup>110c</sup> Apart from the nitrogen or sulfur atom, the

oxygen atom on the ring substituent was also reported to serve as a donor site (Scheme 35c).<sup>36b</sup> 1,3,4-Thiadiazole as an electron-deficient unit containing two electron-withdrawing imine groups ( $C=N$ ) can be used as electron-accepting units for donor–acceptor (D–A)  $\pi$ -conjugated polymers. Model compounds ( $PhC\equiv C-Ar-C\equiv CPh$ ; Ar = 1,3,4-thiadiazole; Ph = dialkoxy-*p*-phenylene, *N*-alkyl-2,5-pyrrolylene as the electron-donating units) were synthesized as a new charge transfer structure of a typical poly(arylethyneylene) (PAE) system.<sup>115</sup> In addition,  $\pi$ -conjugated polymers with thiophenes as the D units and 1,3,4-thiadiazoles as the A units incorporated in a thiophene–thiadiazole–thiophene pattern are also synthesized for better electronic and optical properties.<sup>116</sup> The excellent properties and extensive applications of 1,3,4-thiadiazole polymers are summarized in section 4.

### 3.5. Miscellaneous

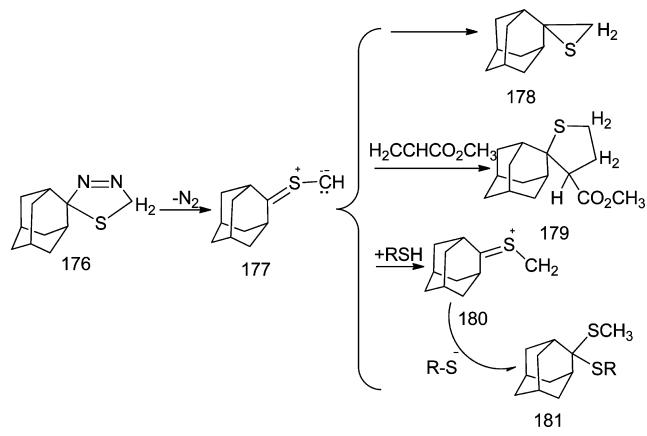
We introduced 1,3-dipolar cycloadditions realized by reacting diazo compounds with thiocarbonyl dipolarophiles leading to 2,5-dihydro-1,3,4-thiadiazoles **89a–89d** in Scheme 19b, while 1,3-dipolar cycloreversion with  $N_2$  elimination from compounds **89a–89d** can afford thiirane **172**, 1,3-dithiolanes **173/174**, and dithiane **175** (Scheme 37).<sup>67</sup> In addition, 2',5'-dihydrospiro[adamantane-2,2'-(1,3,4)-thiadiazole] **176** elimi-

**Scheme 37. 1,3-Dipolar Cycloreversion from Thiocarbonyl Dipolarophiles**



nating N<sub>2</sub> to furnish adamantanethione S-methylide was also reported as a 1,3-dipolar cycloreversion reaction (Scheme 38).<sup>117</sup> The S-methylide 177 could not be isolated. In the

**Scheme 38. 1,3-Dipolar Cycloreversion Reaction of 2',5'-Dihydrospiro[adamantane-2,2'-(1,3,4)-thiadiazole]**



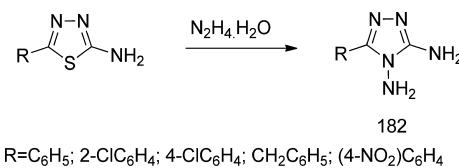
absence of intercepting reagents, it underwent electrocyclization, affording spirothiirane 178, cycloaddition with methyl acrylate giving rise to 179, and reaction with thiols affording dithioacetals 181 via thionium ion 180 as the CH<sub>2</sub> group, which is the basic center. Thermalysis of 1,3,4-thiadiazoles is conducted at a pretty high ambient temperature. Thermal decomposition or mass spectra products of thiadiazoles are presumably RNCS, HNCS, HCN, CS<sub>2</sub>, and sulfur isomers when an exocyclic S atom is present; the fragmentation can be rationalized by assuming cleavage of the heterocycle between the N–N and the C–S bonds.<sup>71a,b,118</sup>

Transformation between different heterocycles is intriguing and common. We summarized before about the conversion between 1,3,4-thiadiazole and 1,3,4-oxadiazole. In addition, 1,3,4-thiadiazole can also be converted to 1,2,4-triazoles easily (Scheme 39).<sup>119</sup>

#### 4. APPLICATION OF 1,3,4-TIADIAZOLE

Multiple properties of 1,3,4-thiadiazole derivatives have been well documented for decades, and their attachments with other heterocycles or metal ions often ameliorate the performances

**Scheme 39. Synthesis of 1,2,4-Triazoles from 1,3,4-Thiadiazole**



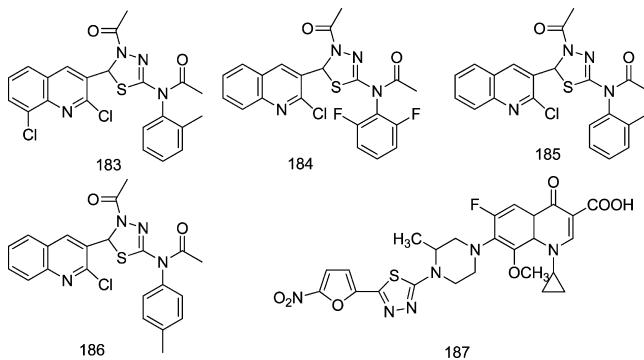
depending on the type of substituent and position of attachments. For its versatility, 1,3,4-thiadiazole is broadly applied in pharmaceutical, agromedicine, and materials chemistry; herein we introduce them separately.

#### 4.1. Applications in Pharmaceutical Chemistry

After the discovery of the carbonic anhydrases inhibitor acetazolamide AAZ, the synthesis and biological activities of many 1,3,4-thiadiazoles were reported. A large number of these derivatives have been reported to possess diverse pharmacological properties such as herbicidal, antiviral, antiparasitic, antitubercular, anticonvulsant, analgesic, and antisecretory activities. Moreover, much interest has also been focused on the antibiotic (including antibacterial and antifungal), anti-inflammatory, and anticancer activities displayed by compounds incorporating other heterocyclic systems. Owing to the different activities 1,3,4-thiadiazoles possess, we classify them as follows.

**4.1.1. Antibiotic Activity.** 1,3,4-Thiadiazoles are reported to exhibit a broad spectrum of antimicrobial activities.<sup>9h,122</sup> The thiadiazole ring commonly acted as a scaffold and attached different pharmacophore agents which also possess similar antimicrobial activities via its multiple reactivity sites summarized above. The familiar pharmacophore agents were quinoline, pyrazole, triazole, piperine, imidazoline, etc., which were reported to show various bioactivities (Scheme 40). Bhat

**Scheme 40. 1,3,4-Thiadiazole Derivatives Having Antibiotic Activity**



et al. synthesized 2,8-substituted quinolin-1,3,4-thiadiazoleyl acetamide derivatives and performed *in vitro* antimicrobial activity against *Staphylococcus aureus*, *Streptococcus pyogenes*, *Salmonella typhimurium*, and *Escherichia coli*.<sup>120</sup> Compounds 183 and 184 showed better inhibitory effects with MIC = 16 µg/mL (controlled to amoxicillin MIC = 32 µg/mL) for *S. aureus*, and 185 and 186 showed better results with MIC = 16 µg/mL (controlled to amoxicillin MIC = 32 µg/mL) for *S. pyogenes*. In addition, modifications of clinically used antimicrobial drugs by 1,3,4-thiadiazoles resulting in efficacy increase were also reported. Foroumadi's group contributed

much to this direction, who prepared several hybrids of 1,3,4-thiadiazoles and different quinolones including ciprofloxacin, norfloxacin, enoxacin, levofloxacin, and gatifloxacin with enhanced antibacterial activity against some Gram-positive organisms compared to the parent quinolones, and we introduced them as follow. Compounds **152a–152c** showed interesting activity against Gram-positive bacteria (MIC = 8–30 µg/mL); in particular, **152a** (ciprofloxacin derivative in nitroimidazolyl 1,3,4-thiadiazole series) exhibited excellent activity against *S. aureus* (62 times more potent than ciprofloxacin) and *Staphylococcus epidermidis* (31 times more potent than ciprofloxacin).<sup>108a</sup> In addition, benzylthio- and benzylsulfonyl-1,3,4-thiadiazolyl moieties attached to the N-4 hydrogen of the piperazinyl group of norfloxacin, ciprofloxacin, and enoxacin were comparable or more potent against tested Gram-positive bacteria than the respective parent drugs, and 5-(nitroaryl)-1,3,4-thiadiazole-levofloxacin hybrids showed similar results as well.<sup>108b,121</sup> Additionally, nitroaryl thiadiazole–gatifloxacin hybrid **187** exhibited more potent inhibitory activity against Gram-positive bacteria with respect to reference drug gatifloxacin.<sup>104h</sup>

Some anti-*Helicobacter pylori* agents were also synthesized, as several nitroimidazole/nitrothiophene 5-(nitroaryl)-1,3,4-thiadiazoles also reported by Foroumadi et al. showed more powerful antibacterial activity against *H. pylori* than the referenced metronidazole<sup>89</sup> and some acetazolamide AAZ derivatives also prepared against *H. pylori* with the mechanism of targeting the *hpCA* (a β-carbonic anhydrases found in the cytoplasm of *H. pylori*, essential for acid acclimation and survival of the pathogen).<sup>92d</sup> Other than the *hpCA*, another β-CA *Brucella suis* CA from *Brucella suis* was as well targeted for antibacterial activity and treated with some other acetazolamide–sulfonamide/sulfamate derivatives.<sup>122</sup> As CA is a very important agent for many diseases, we summarize it separately later.

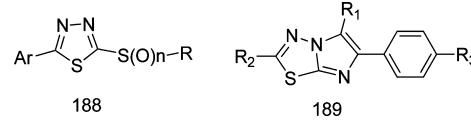
Derivatives of 1,2,4-triazole and 1,3,4-thiadiazole condensed the core, and 1,3,4-thiadiazole-oxazolidinone hybrids are constantly being reported with favorable antibacterial activities.<sup>9f,64,123</sup> The triazolo-1,3,4-thiadiazoles **60e** bearing ethyl, phenyl, and *p*-tolyl groups exhibited significant inhibitory activity, which might be possibly due to the presence of the electron-releasing ability to the condensed nucleus. In addition, **60f** with a substituent at the sixth and third positions was more potent, possibly due to the electron inductive effect. Compounds **69a–69h** had higher activity toward Gram-positive bacteria than currently used antibiotics (ampicillin and cefuroxime), and several can be comparable to vancomycin. Replacement of the morpholine C ring of linezolid with a 1,3,4-thiadiazolyl ring led to oxazolidinone analogues **51** and **52** having more potent antibacterial activity against both Gram-positive and Gram-negative organisms than its parent linezolid as reference.

Almost all of the reported 1,3,4-thiadiazole derivatives showed preferable antibacterial activities against Gram-positive bacteria than Gram-negative bacteria, and the probable reason may be their differences in the structure of the cell wall. Many lipopolysaccharides (LPS) in the additional outer membrane of Gram-negative bacteria confers a negative charge and repels hydrophobic compounds. This specific structure of the cell wall makes it so that very large or intensively hydrophobic molecules are not able to penetrate the interior of the bacterial cell,<sup>124</sup> while the cell wall of the Gram-positive bacteria, generally made of peptidoglycan, hardly prevent hydrophobic

substances from penetrating into the cell. Thus, based on the 1,3,4-thiadiazole scaffold, introduction of multiple substituents regarding the hydrophobicity, charge, or molecular mass to avoid the above problems can be a feasible direction.

Among this field, it is worth mentioning that some 1,3,4-thiadiazoles have promising antituberculosis activity as well (Scheme 41).

**Scheme 41.** 1,3,4-Thiadiazole Derivatives Having Antituberculosis Activity



Foroumadi et al. synthesized several series of 1,3,4-thiadiazoles **188** (*Ar* = 5-nitro-2-furyl, nitroimidazolyl, and 5-nitro-2-thienyl; *n* = 0–2) tested for their antituberculosis activities having MICs ranging from 0.39 to 6.25 µg/mL, but some showed lower activity owing largely to the number of oxygens and the kind of R substituent.<sup>10a,c,d,101a</sup> Different cyclic secondary amines or even corresponding alcohols, nitriles, and thiazolidinone substituents of *R*<sub>1</sub> can hardly improve the antituberculosis potency of imidazo[2,1-*b*][1,3,4]thiadiazoles **189**, while introduction of rhodanine-3-acetic acid to *R*<sub>1</sub> strengthened the activity, which may serve as promising lead scaffolds for further generation of new anti-TB agents.<sup>40</sup> Quinolone as a favorable antibacterial pharmacophore was hybridized with 1,3,4-thiadiazole, getting better anti-TB activities than when hybridized with other heteroaryl groups such as benzothiazole and tetrazole.<sup>10e,125</sup> In addition, Rollas et al. synthesized a series of 2-amino-1,3,4-thiadiazoles representing different levels of anti-TB abilities. They evaluated the structure–antituberculosis activity relationship and found low-activity molecules are poorly responsive to the activity prognostication, because they form a buffer zone consisting of compounds that can include both pharmacophores and antipharmacophores.<sup>118a,126</sup> Minakuchi et al. targeted the *M. tuberculosis* CAs and processed molecular cloning, biochemical characterization, and inhibition studies of one of these enzymes, i.e., mtCA 1. They found 1,3,4-thiadiazole sulfonamides to be poorly selective of hCA II (a human basic CA) to mtCA 1, but it represented the starting point for designing new antimycobacterial agents possessing a completely new mechanism of action.<sup>127</sup>

The antifungal activity of 1,3,4-thiadiazoles was reportedly less than its antibacterial activity. The results were hardly noticed.<sup>9c,i,128</sup>

#### 4.1.2. Anti-inflammatory and Analgesic Activity.

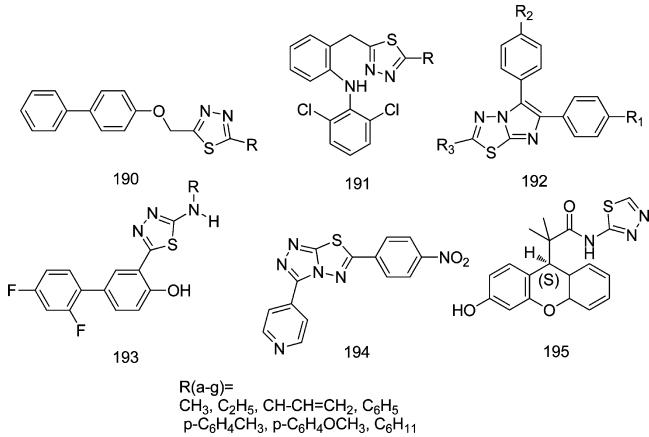
Inflammation is part of a complex nonspecific immune response of vascular tissue to harmful stimuli with several different kinds of intricate trigger mechanisms.<sup>129</sup> It is considered as a mechanism of immune response, plays a pivotal role in self-protection of organisms, and initiates the healing process. Yet, not all of the inflammatory response is good; some improper ones are even fatal. Thus, inflammation on one hand is viewed as a beneficial response to injury but on the other hand as an inherently pathological phenomenon. Common anti-inflammatory and analgesic drugs are steroids, nonsteroidal anti-inflammatory drugs (NSAIDs), immune-selective anti-inflammatory derivatives (imSAIDs), herbs, and

some diet foods. In this respect, application of 1,3,4-thiadiazole derivatives focus on the NSAIDs and steroids.

NSAIDs as a kind of classical therapy for inflammation and pain exert their effects through inhibition of cyclooxygenases (COXs), the key enzyme in prostaglandin (PG) biosynthesis from arachidonic acid (AA). There are two types of COX enzymes, namely, COX-1 and COX-2; COX-1 is generally regarded as a constitutive enzyme involved in the physiological production of PGs and provides maintenance functions such as cytoprotection in the stomach, whereas inducible COX-2 mediates inflammation. Commonly used NSAIDs are non-selective COXs inhibitor aspirin, ibuprofen, fenbufen, diclofenac sodium, indomethacin, etc., and COX-2 inhibitor celecoxib, etoricoxib, meloxicam, and some other similar derivatives.<sup>130</sup> Synthesis or modification to prepare optimized 1,3,4-thiadiazole anti-inflammatory compounds is continually reported. Most of them were derived from modifying current clinical drugs with 1,3,4-thiadiazoles for better output.

The modifications mainly focus on two aspects, the carboxylic acid moiety or nitrogen heterocyclic ring, in order to reduce ulcerogenic potential, which is a common side effect of NSAIDs, and retain anti-inflammatory activity (Scheme 42).

**Scheme 42. 1,3,4-Thiadiazole Derivatives Bearing Anti-Inflammatory and Analgesic Activity**



Kumar et al. substituted the carboxylic acid moiety of flurbiprofen by 1,3,4-thiadiazoles prepared compound **190** with comparable anti-inflammatory activity to reference drug flurbiprofen.<sup>42</sup> Amir et al. replaced the carboxylic acid group of diclofenac with 1,3,4-thiadiazoles synthesized compound **191**.<sup>131</sup> These compounds not only showed a significant reduction in ulcerogenic activity in comparison to the standard drug (diclofenac) but also have much better results than the series of 1,3,4-oxadiazole and 1,2,4-triazole derivatives. Likewise, compound **193a–193g** derived from diflunisal of carboxylic acid modification by 1,3,4-thiadiazoles showed anti-inflammatory activities as percent inhibitory effects of 41.4–57.2% against the carrageenan-induced paw edema, significantly more than their parent drug diflunisal with a 24.2% inhibition.<sup>132</sup>

Another analgesic and antipyretic–antipyrene possessing pyrazole nucleus was attached with 2,5-disubstituted-1,3,4-thiadiazole counterparts through various linkages to form compounds **128–131**, among which compounds **128** and **130** display distinctive anti-inflammatory and analgesic profiles with a fast onset of action comparable with diclofenac Na and

revealed a super gastrointestinal safety profile.<sup>92e</sup> Gadad et al. synthesized a novel class of imidazo[2,1-*b*]1,3,4-thiadiazoles **192** as COX-2 inhibitors similar to celecoxib. However, these compounds did not show competitively selective COX-2 inhibitory and *in vivo* anti-inflammatory activity to reference drug celecoxib.<sup>107c</sup> Another 1,3,4-thiadiazole condensed nucleus system 1,2,4-triazolo-[3,4-*b*]-1,3,4-thiadiazole was also studied. Compound **194** was evaluated for the anti-inflammatory, analgesic, ulcerogenic, and lipid peroxidation activities, all results were better than those of the standard drug ibuprofen.<sup>133</sup>

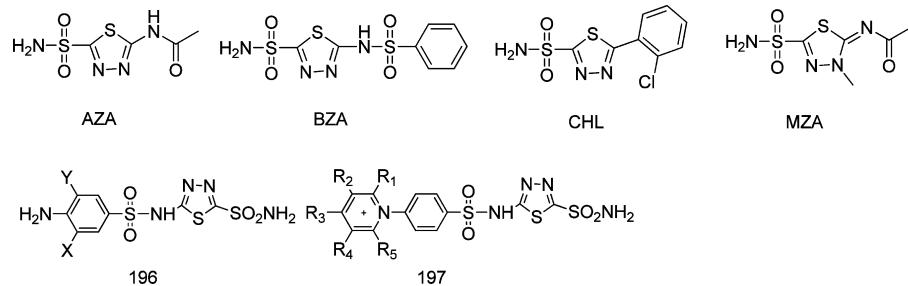
Still many other 1,3,4-thiadiazole derivatives were synthesized with different kinds of chemical groups (e.g., arylsulfonyl, isoxazolo[4,5-*d*]pyridazine, adamantane, benzoxazolinone, etc.) and tested for their anti-inflammatory and analgesic activities but not giving ideal results, so we did not summarize them herein.<sup>91,12b,d,134</sup>

Steroid anti-inflammatory drugs, in particular glucocorticoids, reduced inflammation mainly due to transcriptional repression (transrepression, TR), while on the other hand, the induced transcription of certain genes by the ligand-bound GR (glucocorticoid receptor), a process termed transactivation (TA), which led to many side effects, such as diabetes, obesity, and muscle atrophy. Thus, extensive researchers developed ligands termed “dissociated” glucocorticoid receptor agonists (DGRA) or “selective glucocorticoid receptor modulator/agonists (SGRM/SEGRA)” to obtain high selectivity of TR/TA.<sup>135</sup> Compound **195** and its derivatives synthesized by Weinstein et al. as potent and selective GR ligands perform reduced transactivation relative to steroidal agonists while retaining good transrepression activities.<sup>136</sup> Arg611/Gln570 residues provide a rich source of H-bond donors. Asn564 may engage in two H bonds to the amide NH and thiazole N. The 1,3,4-Thiadiazole amide moiety played an important role in forming a triad of H bonds with Asn564 and Gln642 of GR ligand-binding domain (LBD), which force Gln642 to undergo a shift in position and markedly reduced transactivation-mediated side effects.

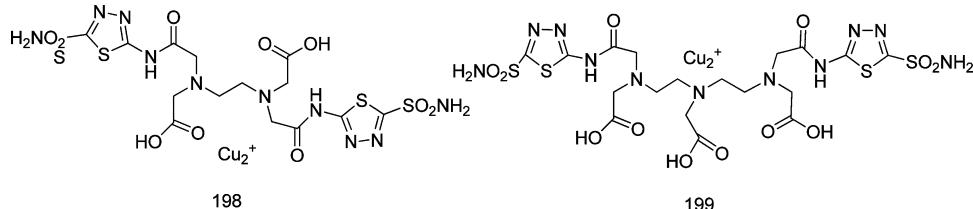
**4.1.3. Anticancer Activity.** Cancer is a multifactor-causing disease, known medically as a malignant neoplasm. Tumorigenesis emerges with many abnormal physiological phenomena, i.e., the most obvious unregulated cell growth and apoptosis, hypoxia, pH reduction (tumor acidity), tumor angiogenesis, cell adherence changes, and metastasis, etc.<sup>137</sup>

1,3,4-Thiadiazoles showed broad-spectrum anticancer activities against human cancers and targeted molecular involved in proliferation, survival, and metastasis including the following: carbonic anhydrase (CA), matrix metalloproteinases (MMPs), histone deacetylases (HDALs), B-cell lymphoma 2(Bcl-2), Bcl-XL, Bcl-2-associated X protein (Bax), Akt/PKB, tubulin, focal adhesion kinase (FAK), protein tyrosine kinases, etc. The 1,3,4-thiadiazole ring took effect on cancers mainly owing to the two nitrogen atoms' high electron-donating ability to build favorable H bonds or to chelate certain metal ions; sometimes only one nitrogen atom functioned. Furthermore, different kinds of substituents introduced to the C2/C5 of the 1,3,4-thiadiazole scaffold nucleus were also conducive to strengthen the desirable abilities, i.e., –NH<sub>2</sub>, –SO<sub>3</sub>H, etc., introducing methods which we summarized in section 3. Thus, based on the targets we classified the reported 1,3,4-thiadiazoles into compounds to regular hypoxia tolerance, tumor invasion, angiogenesis, and cell-cycle-related events to control or prevent cancers.

Scheme 43. Famous CAs Inhibitors



Scheme 44. Novel CAs Inhibitors with Copper–Polyamino–Polycarboxylate Tails



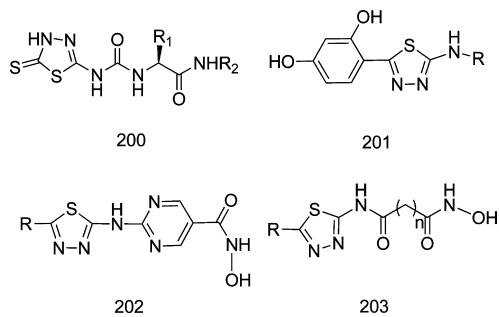
Carbonic anhydrases (CAs) are ubiquitous metalloenzymes, present throughout most living organisms, which catalyze the reversible interconversion of  $\text{CO}_2$  and  $\text{HCO}_3^-$ , thus play roles in respiration, pH, and homeostasis. Details of structure features, classifications, and diverse inhibitors of CAs were summarized in a recent *Chemical Reviews* article.<sup>96</sup> Carbonic anhydrase IX (CA IX) is a membrane-associated zinc-metal glycoprotein, composed of a short intracellular region, a single transmembrane helix, and an extracellular proteoglycan domain as well as a catalytic CA domain, i.e., zinc ion. CA IX always overexpressed in cancer cells resulting in hypoxia,<sup>138</sup> which makes it a promising target against multiple cancers. Famous CAs inhibitors acetazolamide (AZA), benzolamide (BZA), chlorolamide (CHL), and methazolamide (MZA), all of which are sulfonamide 1,3,4-thiadiazoles, show inhibitory activity against CA IX but without high selectivity of CA II (a basic CA) to CA IX in cancer treatment (Scheme 43).<sup>47b,138,139</sup> This predicament was repeated in recent published studies. Compounds 196 and 197 showed similar  $K_i$  (inhibition kinetic constant) of CA IX comparable to the traditional CAs inhibitors but with an even better  $K_i$  of CA II (nearly 10 times less: smaller  $K_i$ , better inhibitory activity), which resulted a poorer selectivity of CA II to CA IX.<sup>140</sup> The mechanism of sulfonamide 1,3,4-thiadiazoles inhibiting CAs accounted for  $\text{Zn}^{2+}$  coordination of the sulfamoyl moiety, the organic scaffold of 1,3,4-thiadiazole establishing van der Waals interactions, and the ring nitrogen atoms participating in a hydrogen-bond interaction.<sup>96</sup> The thiadiazole ring, differently from the thiophene and thiadiazoline scaffolds, can also participate in a hydrogen-bond interaction with the active site of CA, whereas compounds 198 and 199 displayed  $K_i$  (nM) of hCA II (198 13.4; 199 4.3), hCA IX (198 8.3; 199 4.8), and hCA XII (another cancer-associated CA, 198 2.8; 199 0.6) which approved favorable results. The reason the authors inferred probably is due to the fact that the copper–polyamino–polycarboxylate tails interact in a distinct manner with the active site cavities of these isoforms (Scheme 44).<sup>141</sup>

Focal adhesion kinase (FAK) is a focal adhesion-associated protein kinase involved in cellular adhesion and spreading processes.<sup>142</sup> The smaller FAK fragment termed “killer FAT” associates with death signaling, and overexpression of FAK

leads to inhibition of apoptosis and an increase in the prevalence of metastatic tumors.<sup>143</sup> Thus, Sun et al. synthesized a series of 1,3,4-thiadiazole derivatives containing 1,4-benzodioxan which showed comparable FAK inhibitory activity to reference drug staurosporine, and several compounds displayed competitive anticancer capacities against HEPG2, HELO, SW1116, and BGC823 cancer cell lines. The molecular docking modeling result with FAK demonstrated the nitrogen atom on the thiadiazole ring built a H bond with the amino hydrogen of GLY505 which was believed to contribute to the anticancer activity.<sup>144</sup>

Cancer cells grew rapidly and can hardly be satisfied by simple diffusion of nutrient substances and  $\text{O}_2$  from cell to cell when it is beyond a certain size, generally 1–2 mm<sup>3</sup>.<sup>145</sup> Then, tumors induce blood vessel growth (angiogenesis) by secreting various growth factors (e.g., VEGF) and regulate relevant factors conducive to blood vessel development.<sup>13,71</sup> Thus, effective control of cancer angiogenesis is approved be a reliable anticancer method, especially for malignant cancers, and angiogenesis-associated factors varied much, which provide us diverse targets (for a comprehensive introduction see Miller's article in *Chemical Reviews*).<sup>146a</sup> Matrix metalloproteinases (MMPs) are zinc-dependent enzymes, and special ones target the extracellular matrix (ECM) for degradation and then promote formation of new blood vessels (angiogenesis).<sup>146b</sup> In addition, MMPs were reported to regulate production of angiostatin, a potent angiogenesis inhibitor that inhibits tumor growth.<sup>147</sup> Thus, Rizzo et al. used computational modeling techniques (MM-GBSA and MM-PBSA analysis techniques to estimate binding affinities and selectivities) to stimulate a series of 5-substituted-1,3,4-thiadiazole-2-thiones 200 selectively inhibiting two specific MMPs, stromelysin-1 and gelatinase-A (Scheme 45). The result showed thiadiazoles selected stromelysin-1 over gelatinase-A. These compounds contain a novel zinc binding group where coordination occurs through the exocyclic sulfur of a thiadiazole group. In addition, the authors concluded selectivity that appeared to be dominated by (1) increased favorable van der Waals interactions, (2) increased favorable Coulombic interactions, and (3) decreased unfavorable total electrostatic energies for the ligands with

**Scheme 45. Matrix Metalloproteinases Inhibitors and Histone Deacetylases Inhibitors**



stromelysin-1.<sup>148</sup> These conclusions can be well predicated for developing MMPs inhibitors.

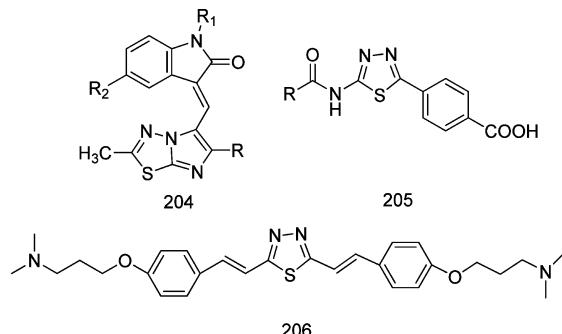
The cell cycle is a series of events taking place in the cell leading to its replication, which consists of four distinct phases: G<sub>1</sub> phase, S phase, G<sub>2</sub> phase, and M phase. The cell cycle is strictly controlled in normal cells but out of regulation in cancer cells. This process refers to so many different kinds of enzymes and factors that a huge amount of anticancer studies have targeted it.

In the field of 1,3,4-thiadiazole antiproliferative study, Matysiakin et al. performed much work.<sup>16a,118b,c,149</sup> They found the amine substituent at C5 is not necessary for the antiproliferative activity of 2-(2,4-dihydroxyphenyl)-1,3,4-thiadiazoles; however, the N-substituent amino thiadiazoles 201 showed stronger antiproliferation rates,<sup>118c</sup> and the analogues (R = halophenyl) were demonstrated to be the most interesting against the human cell lines (T47D (breast cancer), SW707 (rectal adenocarcinoma), A549 (non-small cell lung carcinoma), and HCV29T (bladder cancer)) in vitro, which were systems with the hydrophobic substituents of electron-withdrawing character. In addition, 2,4-dihydroxyphenyl was believed to play a significant role in the antiproliferative activity for its favorable hydrophobic–hydrophilic character and affecting the electronic properties of the whole compound.<sup>118b,149b,c,150</sup> They also found 2-(4-fluorophenoxyamino)-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole (FABT) treatment can decrease the non-small cell lung cancer A549 cell proliferation; this result may be due to inhibition of the ERK1/2 kinase pathway and cell-cycle arrest in G<sub>0</sub>/G<sub>1</sub> phase and suggested that FABT acted by inhibiting protein phosphorylation but without affecting gene expression.<sup>149d</sup> In addition, the anticancer effect of 2-(4-chlorophenoxyamino)-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole (4ClABT) was attributed to decreased DNA synthesis, prominent changes in tumor cell morphology, as well as reduced cell motility.<sup>151</sup>

Other researchers took a different route by focusing on histone deacetylases (HDACs), which have a role in regulation of gene expression, cell proliferation, cell migration, cell death, and angiogenesis.<sup>152</sup> Abnormal HDACs were reportedly associated with different cancers. Rajak et al. and Guan et al. synthesized compounds 202 and 203 based on three structure requirements of most HDAC inhibitors (a Zn<sup>2+</sup> binding group, a linker domain, and a surface recognition motif).<sup>16f,153</sup> The 1,3,4-thiadiazole nucleus of compounds 202 and 203 functions as the surface recognition motif. Derivatives with *p*-hydroxyphenyl/methoxyphenyl of compound 202 showed high potency in HDAC inhibition and antiproliferation against Ehrlich ascites carcinoma cells. Compound 203 (R = phenyl, n = 5) was molded to bind with HDAC-1, demonstrating that the

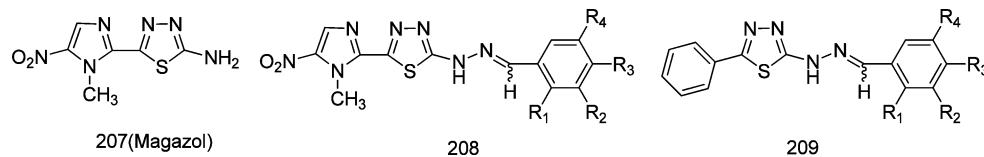
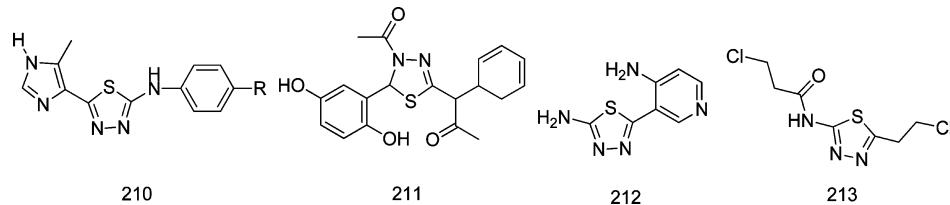
nitrogen of the thiadiazole ring built two H bonds with Phe 197 and had a similar binding mode to reference drug SAHA in the active site of HDAC-1, in which the former ( $IC_{50} = 0.089 \mu M$ ) displayed a better HDAC inhibitory effect than the latter ( $IC_{50} = 0.15 \mu M$ ). Again, Andreani et al. reported compound 204 had broad anticancer activities, and the analogue 204a (R = -CH<sub>3</sub>, H, -OCH<sub>3</sub>) was particularly active against colon carcinoma cell lines HT-29 (a pGI<sub>50</sub> of 6.16  $\mu M$  with a low toxicity) and blocked the cell-cycle progression with cell arrest in the G<sub>2</sub>/M phase (Scheme 46).<sup>154</sup> The ability of compound 204a was

**Scheme 46. Other Anticancer Analogues of 1,3,4-Thiadiazole**



evidenced by inhibition of ornithine decarboxylase ODC (catalyze the first and committed step in the synthesis of polyamines, which are important for stabilizing DNA structure and the DNA double strand-break repair pathway) and followed by a late induction of apoptosis with activation of caspase proteases.<sup>155</sup> Continually, protein kinase CK2 as a key suppressor of apoptosis was treated with aminothiadiazoles 205, resulting in inhibition values of  $IC_{50}$  ranging from 1.2 to 29.9  $\mu M$ , much higher than its aminothiazole analogue for the reason that the 3' N and 4' CH as well as the amino of thiazole can bind well with the CK2 ATP binding pocket while the 4 position of the thiadiazole ring placed a nitrogen which revealed a potential electrostatic repulsion to the backbone carbonyl oxygen of Glu114.<sup>156</sup> However, the oxadiazole analogues showed less inhibitory activities, implying a significant contribution from the sulfur atom.<sup>157</sup> In addition, compound 206<sup>158</sup> was reported to induce the early-phase apoptosis in A549 cells via the Bcl-XL down-regulation and that of the late phase through up-regulation of Bax expression as well as inhibition of Akt/PKB activation. In addition, Yang et al. synthesized a series of cinnamic acyl 1,3,4-thiadiazole amides showing antitubulin activities, and the thiadiazole ring formed  $\pi$ –cation interactions with the Lys D, 352 of the colchicine binding site of tubulin, suggesting 1,3,4-thiadiazoles can potentially block cell division.<sup>16e</sup>

As for other miscellaneous anticancer studies, 1,3,4-thiadiazole metal complex of platinum(II) containing DMSO and selenium showed anticancer properties.<sup>105,111b</sup> Imidazothiadiazoles modified based on levamisole (a well-known immunomodulator), triazolothiadiazoles structured similarly to flavones, indoylthiadiazoles being analogous to camalexin, and 1,3,4-thiadiazoles possessing  $\gamma$ -butenolide moiety showed a broad spectrum of anticancer potency.<sup>16g,s1,159</sup> Thiophenothiadiazoles possessed relatively high cytotoxicity against thymocytes and low cytotoxicity against blood lymphocytes and revealed a general stimulating effect on the B-cell response

**Scheme 47.** Anti-*T. cruzi* Analogues of 1,3,4-Thiadiazole**Scheme 48.** Anti-*T. gondii* Analogues of 1,3,4-Thiadiazole

which can be auspicious for tumor chemotherapeutic agents study.<sup>160</sup>

**4.1.4. Antiparasitic Activity.** Parasitic diseases such as leishmaniasis, malaria, and trypanosomiasis have a significant impact in developing countries, affecting hundreds of millions of people. Application using 1,3,4-thiadiazoles derivatives against parasite has a long history.

Chagas disease, caused by the protozoan parasite *Trypanosoma cruzi*, continues to rank among the most important public health problems in South America.<sup>161</sup> Recent research in this field focuses on decreasing the toxicity and mutagenicity of the parent drug, magazol, [1-methyl-2-(5-amino-1,3,4-thiadiazole)-5-nitroimidazole], which represents a promising alternative of nifurtimox and benznidazole used to treat acute cases but with many side effects (Scheme 47).<sup>162</sup> Magazol was found to have about 3–4 times higher anti-*T. cruzi* efficiency than nifurtimox and benznidazole for its suitable amphiphilic balance and influence key detoxification enzyme trypanothione reductase.<sup>163</sup> Cytotoxic and genotoxic studies revealed that magazol had high cytotoxicity even at 2 µg/mL, resulting in cell viability already less than 70% by both necrosis and apoptosis and drug-induced DNA damage with a possible induction of the repair mechanism.<sup>164</sup> For reducing existing side effects, Carvalho et al. introduced arylhydrazones to magazol getting trypanocidal 1,3,4-thiadiazole-2-arylhydrazone derivatives 208 and 209. All analogues of 209 were less active than 208, reinforcing the pharmacophoric contribution of the nitroimidazole group to the mechanism of action against *T. cruzi*. Among the series 208, the derivative 208a with 3,4-dihydroxyphenyl had an IC<sub>50</sub> = 5.3 µM, 2-fold more potent than the prototype magazol (IC<sub>50</sub> = 9.9 µM), and changed its redox behavior, which could eventually improve its therapeutic profile and safety.<sup>165</sup> 3D-QSAR results suggested that bulky substituents in positions 3 (R<sub>2</sub>) and 5 (R<sub>4</sub>) and electron-rich groups in position 4 (R<sub>3</sub>) enhanced the activity, which correlated well with the experimental IC<sub>50</sub> result of 208a. In addition, 208a satisfied Lipinski's rule of five and had good potential for in vivo absorption.<sup>166</sup> However, 208a showed a high potency in vitro, while no decrease of parasitemia or mortality was observed in vivo, suggesting little correlation between in vitro effect and in vivo treatment.<sup>167</sup> In addition, Chauvière et al. introduced several structural changes to magazol including substitutions on the two rings of the basic nucleus, replacement of the thiadiazole by an oxadiazole, replacement of the nitroimidazole part by a nitrofuran or a nitrothiophene, and substitutions on the exocyclic nitrogen

atom for evaluation of an improved import by the glucose or purine transporters, but activity tests indicated that megazol was more active than the derivatives.<sup>168</sup> Even though there have been several promising trials, we still have a long way to go.

Moving on to another common parasite, *Toxoplasma gondii* can also cause toxoplasmosis, which has a serious effect on immune-compromised patients and fetuses by crossing the placenta when the mother is infected with *T. gondii* during pregnancy. Toxoplasma's resistance to antitoxoplasmosis medication exists seriously especially for the neonates and pregnant women whose treatments are really exceptional.<sup>169</sup> In addition to studying magazol derivatives against *T. cruzi*, Carvalho et al. also synthesized some 2-amino-1,3,4-thiadiazoles 210 containing a 5-methyl-imidazoyl group structurally similar to megazol and evaluated their anti-*T. gondii* activities (Scheme 48). Results showed a significant decrease in the percentage of infected cells and in the mean number of tachyzoites per cell from concentrations of 0.1, 1, and 10 mM, when compared with hydroxyurea and sulfadiazine (standard drugs). In addition, 210a (R = H) was the most selective against intracellular parasites and showed low toxicity. The 1,3,4-thiadiazoles possessed comparable or better anti-*T. gondii* abilities to thiosemicarbazides and 4-thiazolidinones, which had been previously approved as having anti-*T. gondii* potency.<sup>170</sup>

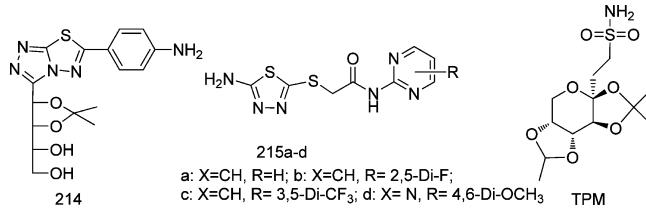
Leishmaniasis is one of the most neglected tropical diseases, with more than 12 million people worldwide currently infected and 350 million people in 88 countries considered at risk, annual incidence being 2 million.<sup>171</sup> The cases of *Leishmania*–HIV coinfection are even worse.<sup>172</sup> Leishmaniasis caused by *Leishmania*, a genus that is the same as *T. cruzi*, belongs to order Trypanosomatida. Leishmaniasis is divided into three types, as cutaneous leishmaniasis caused by *L. major*, *L. tropica*, *L. aethiopica*, and *L. mexicana*, mucocutaneous leishmaniasis by *L. brasiliensis*, and visceral leishmaniasis by *L. donovani* complex (*L. donovani*, *L. infantum* syn. *L. chagasi*).<sup>173</sup> Traditionally used drugs including sodium stibogluconate (pentostam), meglumine antimonate (glucantime), miltefosine, pentamidine, and amphotericin B are toxic and cause severe side effects such as pancreatitis and cardiac toxicity. Moreover, they are expensive and require long-term treatment.<sup>174</sup> Foroumadi et al. synthesized several anti-leishmaniasis series of 1,3,4-thiadiazoles with nitrofuran/nitrothiophene/nitroimidazole attached to the S position and 2-cycle amino (i.e., piperidine, morpholine, piperazine, para-substituted piperazine, and benzylaminotriazole).<sup>87a,104d,g,i,k,l,175</sup> The vast majority of new compounds had

better leishmanicidal activity than the reference drug at noncytotoxic concentrations. It has been observed that the nitroimidazole derivatives showed the best antileishmanial activity, the nitrofurans followed, and the nitrothiophene were least active. In addition, piperazine derivatives possessed high flexibility in leishmanicidal activity for the different types and positions of substitutions against both the promastigotes and the intracellular amastigotes form of *L. major*. They also reported that some of the nitroheteroaryl-1,3,4-thiadiazole derivatives with potent antileishmanial activity can selectively inhibit *L. major* topoisomerase catalytic activity through formation of DNA-cleavage complexes.<sup>176</sup> In addition, later studies showed 1,3,4-thiadiazole derivatives induced loss of plasma membrane integrity, DNA breakage, proteolysis of PARP (polyADP-ribose polymerase), and necrotic-like death in the parasites, as well as a significant reduction of acid phosphatase level, one of the most important factors contributing to the spread of the virulent parasites and infection in host cells.<sup>177</sup> Apart from *L. major*, *L. donovani* was also reported to be inhibited by compound 211 with an inhibitory potency comparable with the reference drug amphotericin B at concentrations as low as 50  $\mu\text{M}$ .<sup>178</sup>

In addition, the novel treatment is achieved by a combination of antifolates and pteridine reductase (PTR1) inhibitors. Even antifolates can lead to severely impairing DNA replication, and resulting in cell death, they are currently not employed in the therapy because of the pteridine reductase (PTR1) activity of the target organisms.<sup>179</sup> Virtual calculated ternary complex of LmPTR1-NADPH-2-amino-1,3,4-thiadiazole showed the ligand to be involved in multiple interactions. In addition, based on this model, the 5 position of 2-amino-1,3,4-thiadiazole had huge potency to accommodate different kinds of substituents; thus, diverse 1,3,4-thiadiazoles were synthesized based on 2-amino-1,3,4-thiadiazole and evaluated for inhibition of both *L. major* and *L. mexicana* promastigotes. Results displayed all 26 compounds were more active compared to the starting hit. When in combination with a famous antifolate (pyrimethamine; 5-(4-chlorophenyl)-6-ethylpyrimidine-2,4-diamine), compound 212 exhibited over 85% of parasite growth inhibition and almost no toxicity against the MRC5 cells, suggesting a better safety profile with respect to the other compounds and the hit antifolate itself. Compound 213 however showed activity when administrated in a single agent even much better than 212 in or off combination.<sup>38c</sup>

**4.1.5. Antiviral Activity.** Studies reported for the antiviral activity of 1,3,4-thiadiazoles were not satisfying. Researchers made various attempts but obtained moderate activity or even lower in most cases. 1,2,4-Triazolo[3,4-*b*]-1,3,4-thiadiazoles with 3,6-substituted by substituted phenyl, heterocyclic groups such as furan, thiophene, pyrazine, pyridine, pyrrole, coumarin, etc., adamantyl (compound 73), and acyclic C-nucleosides (compound 214) showed much lower in vitro anti-HIV-1 (IIIB) and HIV-2 (ROD) activity in MT-4 cells potency than the reference drug (Scheme 49).<sup>65,180</sup> Additionally, 2-arylthioacetamino-1,3,4-thiadiazoles were synthesized and evaluated as non-nucleoside HIV-1 reverse transcriptase inhibitors (NNRTIs) inhibiting the enzyme by an allosteric interaction with a site adjacent to the NRTI binding site (the non-nucleoside inhibitor binding site, namely, NNBS). Even though the nitrogen atom and the amino group of thiadiazole can make H bonds with the RT NNBS residues and the 5 position substituent can also contribute to the interaction with NNBS observed through docking simulation, the new 1,3,4-

**Scheme 49. Antiviral Analogues of 1,3,4-Thiadiazole**



thiadiazole compounds lacked outstanding performance in contrast to their benzoimidazole analogues and the reference drug zidovudine.<sup>181</sup>

**4.1.6. Anticonvulsants Activity.** Epilepsy is a common and diverse set of neurological disorders characterized by seizures. Anticonvulsants are more accurately called antiepileptic drugs (abbreviated AEDs).<sup>182</sup> The long-established AEDs were placed on an extended list of therapeutic agents against epilepsy, based on the functional mechanism, and can be classified into the following categories: those related to blockage of voltage-dependent sodium channels to inhibit release of excitatory neurotransmitters, enhanced GABAergic transmission, inhibition of T-type calcium channels or kainate/AMPA receptors, and combination of the above actions.<sup>183</sup> However, most of the anticonvulsants acted on more than one mechanism; we can hardly actually identify exact categories for a new drug. Thus, in recent years, researchers seldom discovered a new drug from new mechanism-driven design but through conventional screening or existing drug structure modification. 1,3,4-Thiadiazole derivative acetazolamide AZA, 2-acetylamido-1,3,4-thiadiazole-5 sulfonamide was first used as an AED in 1952.<sup>184</sup> As a sulfonamide analogue, AZA as well as methazolamide (MZA) targets carbonic anhydrase; we summarized this in section 4.1.4, which in the brain has an important role in the neurone–glia metabolic relationship. AZA and other CAIs acted on the seizure by the mechanism that CAs catalyze interconversion of CO<sub>2</sub> and HCO<sub>3</sub><sup>-</sup>, the latter of which combines with hydrogen exchange across the glial membrane for sodium and chloride as well as contributed the current through the  $\gamma$ -amino butyrate A (GABA<sub>A</sub>) receptors. CAs are also involved in the maintenance of Cl<sup>-</sup> and K<sup>+</sup> concentrations in glial cells. As CAs are ubiquitous in the human body, AZA and many sulfonamide drugs cannot be very selective for different CA, with some undesirable side effects coming up, even some being fatal.<sup>185</sup> Adamantyl introduced into AZA and MZA getting compound 216/217/218/219 was better CAIs and lipophilic potency level and slightly less effective than topiramate (TPM) (Scheme 50). The MZA analogues 217 possessed higher Clog P than AZA analogues 216, and adamantlylacetamides ( $n = 1$ ) were more lipophilic than adamantlylcarboxamides ( $n = 0$ ) and corresponding ureas 218 and 219, but both adamantlylcarboxamide derivatives 216a and 217a ( $n = 0$ ) exhibited the highest protection against induced convulsions (>90%), in contrast to other derivatives and reference drugs. hCA II abundant in the brain was much more sensitive to inhibition by these sulfonamides than the hCA I, which was favorable for anticonvulsant benefit.<sup>186</sup> Since lipophilicity guaranteeing the penetrability of the drug to the brain is an important factor influencing biological activity, some researchers are focusing on introducing lipophilic agents to improve the activity. Some 1,3,4-thiadiazole sulfonamides incorporating with valproyl moiety (compound 220) and some lipophilic agents (compound 216a and 221–224) as well

Scheme 50. Anticonvulsants Analogues of 1,3,4-Thiadiazole

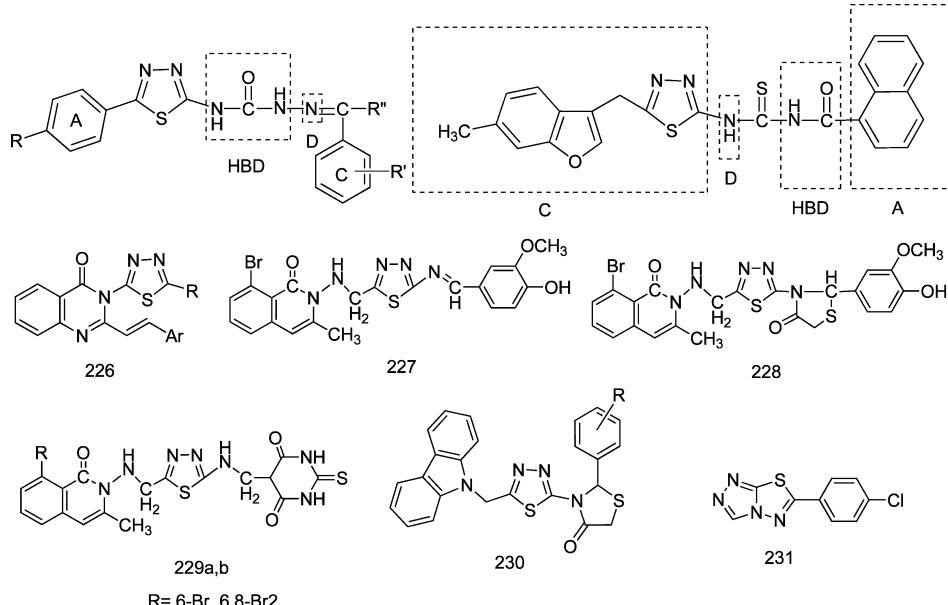
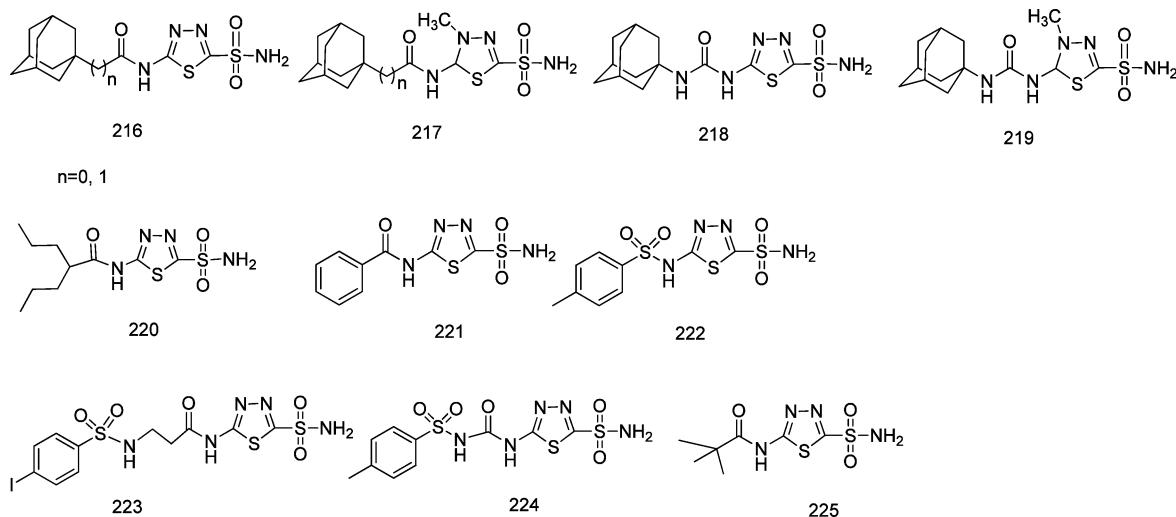


Figure 5. Four essential binding sites of the pharmacophore model.

as other different alkyl/arylcarboxamido/sulfonamido/ureido moieties in the 5 position were reported. Results revealed the correlation of the lipophilicity ( $\text{ClogP}$ ), in vitro CA inhibition, and in vivo anticonvulsant activity of these compounds was not really straightforward, which corresponded with former citations. The best anticonvulsants **216a** and **220** possessed good lipophilicity with  $\text{ClogP}$  of 1.82 and 1.52, respectively, whereas some less lipophilic compounds (such as **225**,  $\text{ClogP}$  of 0.10) showed in vivo activity similar to that of **216a** and **220**, yet many quite lipophilic compounds (for example, **223** and **224**) possessed rather diminished anticonvulsant activity.<sup>187</sup> Thus, other mechanisms may be involved in compounds anticonvulsant capacities, such as different selectivity of brain CAs and the ability of binding plasma proteins.

In addition to sulfonamide modification, researchers in this decade introduced many different agents to 1,3,4-thiadiazole for better and safer anticonvulsants, such as quinazoline, (thio)-semicarbazone, thiourea, (benzo)triazole, some clinical anti-convulsant pharmacophores, etc.<sup>183,188</sup> A proposed semi-

carbazones-based pharmacophore model consisted of the following four essential binding sites: (i) an aromatic hydrophobic binding site (A); (ii) a hydrogen-bonding domain (HBD); (iii) an electron-donor group (D), and (iv) another hydrophobic–hydrophobic site regulating the pharmacokinetic properties of the anticonvulsant (C) (see Figure 5). The 1,3,4-thiadiazoloquinazolinone also was reportedly applied to this model.<sup>190</sup> Some thiadiazole thiourea derivatives indicated therapeutic potential in petit mal seizures.<sup>191</sup> For the thiadiazoloquinazolinone **226**, substitution of 1,3,4-thiadiazoles at the third position and a styryl moiety at the second position of 4(3*H*)-quinazolinone led to the development of new chemical entities with potent sedative–hypnotic and CNS depressant activities as compared to anticonvulsant activity.<sup>13,192</sup> A mono- or dibromo group on the sixth or eighth position of the quinazolinone nucleus was found to increase the anticonvulsant activity. Compounds **227–229** exhibited the same or even better anticonvulsant degree than the reference

drug phenytoin sodium, sodium valproate and lamotrigine in the MES or PTZ test.<sup>193</sup> Introduction of naphthyl may increase the lipophilicity of 1,3,4-thiadiazole, but its derivatives have a wide anticonvulsant activity span from 0 to 90% against PTZ-induced convulsions in mice.<sup>194</sup> Carbazole, chemically and structurally similar to 5H-dibenzo[*b,f*]azepine, which was present in carbamazepine, and 1,2,3-triazole, involved in Rufinamide, were two potential antiepileptic agents incorporated with 1,3,4-thiadiazole showing favorable results. Compound 230 showed good anticonvulsant response in the MES test with protection of 60–90% at a dose of 40 mg/kg i.p., better than the corresponding oxadiazoles.<sup>195</sup> In addition, compound 231 inhibited clonic seizures, tonic seizures, and lethality induced by sc-PTZ at rates of 90%, 100%, and 100%, respectively, compared to carbamazepine (0%, 100%, and 100%) and possessed higher safety than the marketed drugs carbamazepine and valproate with an ED<sub>50</sub> value of 23.7 mg/kg and a PI (TD<sub>50</sub>/ED<sub>50</sub>) of 10.8,<sup>196</sup> whereas phenothiazine-, benzotriazole-, and benzofuran-based and even phenytoin-modified 1,3,4-thiadiazoles showed similarly competitive potency;<sup>197</sup> thus, the SAR of 1,3,4-thiadiazole derivatives to anticonvulsant activity needs further investigation.

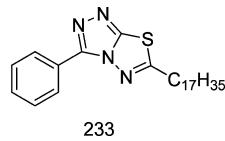
**4.1.7. Antidepressant Activity.** We stated that some 1,3,4-thiadiazoles possessed CNS depressant potency; it may be of benefit for anticonvulsant treatment, but for depression, another kind of psychiatric disorder related to the adverse effect of antiepileptic drugs, it should be mediated by antidepressant treatment.<sup>198</sup> Antidepressants are used for not only simple depressive disorders but also a wide range of psychiatric conditions, including social anxiety disorder, anxiety disorders, and dysthymia (mild chronic depression). Nine main classes and dozens of miscellaneous antidepressants are commercial and often augmented by nonantidepressant off-label drugs in antidepressant treatment.<sup>199</sup> A updated review summarized the antidepressant potential of nitrogen-containing heterocyclic moieties including 1,3,4-thiadiazole;<sup>200</sup> herein, we briefly introduce several antidepressive 1,3,4-thiadiazole derivatives from this decade. Compound 232 as a monoamine oxidase MAO inhibitor abolished the enzyme activity by a one-electron mechanism, chelating the Zn<sup>2+</sup> ions to interact with enzyme. In addition, its 1-(4-chlorophenyl)-3-(4-methoxy-phenyl)amino and 1-(4-chlorophenyl)-3-(4-dimethyl-aminophenyl)amino derivatives showed significant antidepressant activity, which decreased immobility time by 77.99% and 76.26% compared to the standard imipramine (82%).<sup>47a</sup> Fatty acid [1,2,4]triazolo-[3,4-*b*]1,3,4-thiadiazoles exhibited more significant antidepressant activity than oxadiazole and triazole substitution. Compound 233 (Scheme 51), possessing high lipophilicity

panied by a two times lower therapeutic dose range than essential to induce side effects such as sedation and amnesia.<sup>14</sup>

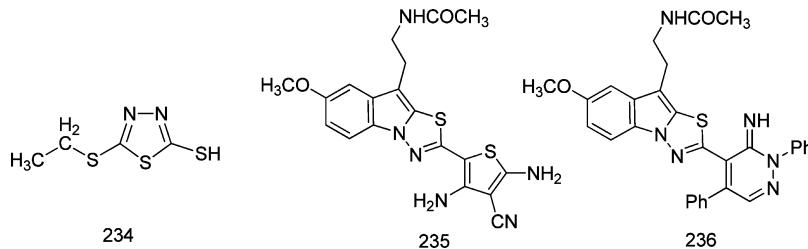
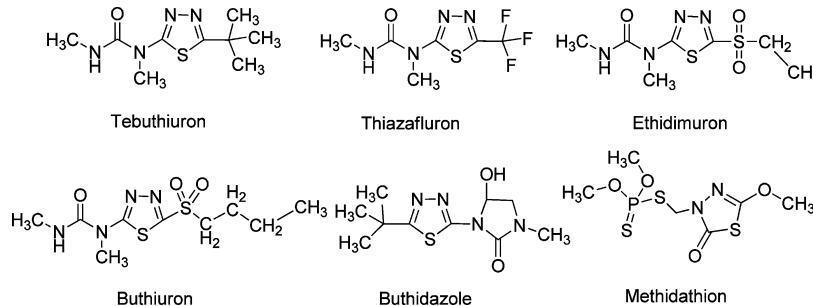
**4.1.8. Antioxidant Activity.** Antioxidants can remove free radical intermediates from the oxidation reactions and then terminate chain reactions which can cause damage or death to the cell. They are often reducing agents such as thiols, ascorbic acid, or polyphenols.<sup>202</sup> As with the chemical antioxidants, cells are protected against oxidative stress by an interacting network of antioxidant enzymes, such as superoxide dismutase (SODs), catalase, peroxiredoxins, and thioredoxin and glutathione systems.<sup>203</sup> Literature about 1,3,4-thiadiazoles' antioxidant activities is not rare. *N*-(2,4-Dimethylphenyl)-5-(4-nitrophenyl)-1,3,4-thiadiazol-2-amine showed higher superoxide anion-scavenging activity than the reference antioxidant propyl gallate. It may be attributed to the presence of a strong electron-withdrawing group (NO<sub>2</sub>) which could stabilize the formed negatively charged adduct created by superoxide.<sup>11b</sup> This result agreed with Chidananda's report.<sup>204</sup> Some (benzo)-imidazolthiadiazoles and triazolothiadiazoles showed potential antioxidant activities against various in vitro systems such as 2,2-diphenyl-1-picrylhydrazyl DPPH radical, superoxide radical, microsomal NADPH-dependent inhibition of lipid peroxidation LP levels, nitric oxide scavenging activity, or microsomal ethoxyresorufin O-deethylase EROD, but the results were not surprising.<sup>11a,205</sup> Thiol and aminothiol compounds derived from 1,3,4-thiadiazoles reported much more antioxidant property than the corresponding analogues derived from benzothiazoles to scavenge free radicals (DPPH<sup>•</sup>, ABTS<sup>•+</sup>, •OH) in vitro with thiols being better than aminothiols. Among these compounds, analogue 234 (Scheme 52) scavenged DPPH<sup>•</sup> and ABTS<sup>•+</sup> free radicals with an IC<sub>50</sub> values of 0.053 and 0.023 mM, respectively, and at 60 μM gave 83% protection against 2-deoxyribose degradation by •OH comparatively higher than that of the radioprotectors WR-2721 and WR-1065, while in vivo tests benzothiazoles showed a more efficient radioprotective effect. A hypothesis was raised that a direct link exists between the thiol function for catching the radical and the aromatic ring for trapping of this radical.<sup>75a,87c</sup> In addition, the literature reported that 1,3,4-thiadiazoles exhibited lower antioxidant property in both nitric oxide and DPPH methods than the oxadiazole units.<sup>61a,b</sup> Melatonin, the pineal gland indole, as a potent endogenous antioxidant, and its thiadiazoloindole derivatives 235 and 236 were able to reduce the mutagenicity effect of cyclophosphamide, which was possibly attributed to their antioxidant activity in male mice. In addition, its activity could not be affected by the presence of thiadiazole ring. However, the presence of a thiadiazole ring alone with an acetonitrile side chain fused to a melatonin moiety could not affect melatonin activity.<sup>206</sup>

**4.1.9. Miscellaneous.** Other pharmaceutical applications of 1,3,4-thiadiazoles are widely varied; herein we introduce them briefly. Carbonic anhydrase inhibitor AZA has been used as an antiglaucoma drug for a long time, but its skeleton 5-amino-1,3,4-thiadiazole-2-sulfonamide was still modified with different groups for better activities and avoiding the undesired side effects of existing drugs of the market.<sup>207</sup> Though sulfonamides incorporating with a 1,3,4-thiadiazole nucleus showed outstanding inhibitory activities on different isoforms of carbonic anhydrases, isozyme-specific inhibitors were hardly discovered,<sup>139,208</sup> which we also mentioned earlier in this review. In addition, thiadiazole derivatives targeted various enzymes, that is, aminopeptidase N inhibitors,<sup>38a</sup> tyrosinase inhibitors,<sup>209</sup>

Scheme 51. Antidepressant Analogues of 1,3,4-Thiadiazole



(ClogP = 10.37), exhibited reductions in immobility time in the forced swim test at a dose of 30 mg/kg compared to reference drug clomipramine, while a three times higher dopamine concentration might increase its antidepressant activity.<sup>201</sup> In addition, 2-amino-5-(3-methoxy-benzylsulfanyl)-1,3,4-thiadiazole had a mixed antidepressant-anxiolytic activity accom-

**Scheme 52.** Antioxidant Analogues of 1,3,4-Thiadiazole**Scheme 53.** Herbicidal Analogues of 1,3,4-Thiadiazole

phosphodiesterases PDE7 inhibitors,<sup>72a,210</sup> neutral endopeptidase inhibitors for treatment of female sexual arousal disorder,<sup>35,211</sup> c-jun N-terminal kinase inhibitors,<sup>101e</sup> fatty acid amide hydrolase (FAAHa) inhibitors,<sup>27d</sup> matrix metalloproteinase inhibitors,<sup>212</sup> inhibitors of both neuronal and inducible nitric oxide synthase,<sup>213</sup> as well as obesity-associated enzymes and receptors including cannabinoid-1 receptor antagonist,<sup>214</sup> mitochondrial CA V, and VB,<sup>215,216</sup> and liver-targeted stearoyl-CoA desaturase (SCD) inhibitors and C-aryl glucoside SGLT2 inhibitors for treatment of diabetes and dyslipidemia.<sup>98,217</sup> Thiadiazole fungicide was also reported to have an effect on thyroid and hepatic enzyme activity in juvenile female rats.<sup>218</sup> Thiadiazoles acted as antagonist of human adenosine A3 receptor and the orphan nuclear receptor estrogen-related receptor  $\alpha$ .<sup>219</sup> It also has an effect on aquaporin 4 (AQP4) and plays potent neuroprotective and antiarrhythmic roles.<sup>220</sup> Moreover, 2-mercapto-5-phenyl-amino-1,3,4-thiadiazole (MPATD) has been used as a chelating agent for determining small amount of cadmium, Cd, from biological samples.<sup>221</sup>

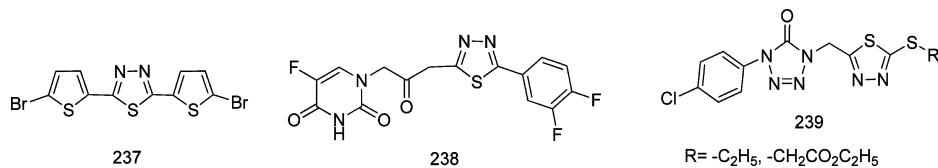
#### 4.2. Applications in Agromedicine Chemistry

**4.2.1. Applications as Pesticides.** Pesticides are a category of chemicals formulated to kill or repel a pest or halt its reproduction. Traditional pesticides can be classified into the following main substituent chemicals: herbicides, fungicides, insecticides, bactericides, virucides, and so on. The term pesticide also extends to plant-growth regulators.<sup>222</sup>

**4.2.1.1. Herbicidal Activity.** Herbicides used to kill unwanted plants are also grouped into different families as the urea class based on chemical structure. Urea herbicides are soil applied and used to pre- and postemergent totally control weeds and woody and herbaceous plants just before or during active plant growth.<sup>223</sup> It is absorbed by the roots and transported to the plants xylem and phloem,<sup>224</sup> where it inhibits photosynthesis specifically by inhibiting electron transport primarily at the reducing side of photosystem II.<sup>225</sup> Urea herbicides are generally of low acute toxicity,<sup>226</sup> but as urea herbicides are metabolized to aniline derivatives, which are potent oxidants of hemoglobin, methemoglobinemia (18–80%), toxicity has

been documented as well as hemolysis.<sup>227</sup> Tebuthiuron is a nonselective broad-spectrum herbicide of the urea class and highly effective in killing and keeping out vegetation, being used to keep paved roads, railways, sidewalks (pavements), and fence lines permanently devoid of vegetation, and is commonly used for reducing tree and shrub density in bush-encroached areas.<sup>228</sup> It is highly soluble in water and adsorbs only weakly to soil particles, and the half-life of tebuthiuron is 360 days with a high persistence in the plant and soil. It also was reported that the degradation time of tebuthiuron residues varied under different climate or soil conditions.<sup>229</sup> In addition to TBH, urea class herbicides involve a thiadiazole nucleus and also include thiazafluron,<sup>230</sup> etidimuron,<sup>231</sup> buthiuron, and the nonurea derivative buthidazole.<sup>232</sup> Ethidimuron ETD was also applied as a nonselective herbicide similar to TBH also with a long-term persistence in soil.<sup>231</sup> Its degradation by microorganisms was also very slow and gives essentially demethyl-ethidimuron (A-ETD). Many herbicidal agents are bearing the thiadiazole core, and the core did not have a direct effect on the activity. Thus, we can assume the thiadiazole core in the herbicidal agents plays a structural role in the herbicidal activity. This aspect of application has failed to attract researchers, because ETD, thiazafluron, and buthidazole (Scheme 53) were listed as obsolete and nonclassified compounds as pesticides in the WHO classification guidelines. In addition, little has been reported in the literature about them in this decade.<sup>233</sup>

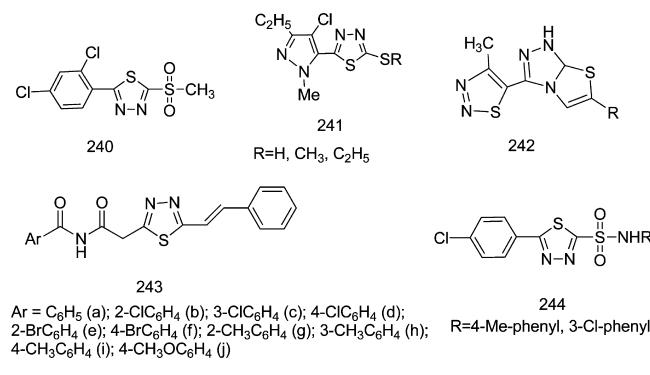
**4.2.1.2. Insecticidal Activity.** Beyond doubt, the most famous application in this aspect is methidathion, a non-systemic organophosphorous insecticide and acaricide with stomach and contact action acting on the enzyme acetylcholinesterase by irreversible inactivation, which is essential to nerve function in insects.<sup>234</sup> The compound is a highly toxic compound in EPA (Environmental Protection Agency) toxicity class I and used to control a variety of insects and mites in many crops, especially useful against scale insects. A regulation review had a comprehensive introduction of methidathion,<sup>235</sup> so we will not summarize it here. Some new insecticidal thiadiazole compounds were as reported to function on some other mechanisms. Thienyl 1,3,4-thiadiazoles can be photo-

**Scheme 54.** Insecticidal Analogues of 1,3,4-Thiadiazole

sensitized by ultraviolet light and showed phototoxicities against the larvae of southern armyworm (*Pseudaletia separata* Walker) only under irradiated conditions. Compound 237 exhibited the highest photolarvical activity with a mortality of about 70.7% (Scheme 54). The degree of mortality was increased with increasing accessibility period of the insects to photosensitizer-loaded leaves during exposure to light; they also showed photocleavage action to pBR322 DNA.<sup>236</sup> Some novel 1,3,4-thiadiazole-5-fluorouracil acetamides derivatives acting as RNA interference insecticides possessed a good combination of stomach toxicity as well as contact toxicity against *Tetranychus cinnabarinus* and *Aphis craccivora*. Compound 238 against *A. craccivora* was better than commercialized 1,3,4-thiadiazole insecticide thiacycloprid and comparable to another commercialized product, imidacloprid. Introduction of fluorines to the meta and para positions of the benzene ring was essential for high bioactivity.<sup>237</sup> Moreover, tetrazolinone derived from 1,3,4-thiadiazoles was also synthesized for discovering better pesticides. The results of a greenhouse in vivo test indicated that all target compounds did not display herbicidal activity; however, some of them exhibited good in vivo insecticidal activity at a concentration of 250 mg/L, among which compound 239a results in 82.5% mortality against *A. medicagini* and 239b with 80.0% against *T. cinnabarinus*.<sup>238</sup>

**4.2.1.3. Antifungal Activity.** We briefly introduced some of the aforementioned 1,3,4-thiadiazoles possessing antifungal activity; herein, we summarize some fungicides used in agriculture. Sulfide/sulfoxide/sulfonamide thiadiazoles were frequently reported for their moderate fungicide activities against *Gibberella zeae*, *Botrytis cinerea*, *Sclerotinia sclerotiorum*, *Fusarium oxysporum*, and *Cytospora mandshurica*. The compounds bearing a thiadiazole moiety did not show competitive activity compared to those derived from oxadiazole and different substituents to the thiadiazole nucleus whether heterocyclic or phenyl groups. Therein, compound 240 showed the highest potency with an inhibitory rate of 70.6% against *G. zeae*, 63.7% against *F. oxysporum*, and 63.5% against *C. mandshurica*, better than the reference drugs Hymexazol, Myclobutanil, and Thiophanatemethyl at a concentration of 50 µg/mL (Scheme 55).<sup>17a,b,d</sup> In addition, compound 241 showed more than 90% inhibition of rice sheath blight caused by *Rhizoctonia solani* even at 100 ppm, but for its corresponding oxadiazoles the activity was retained.<sup>239</sup> In addition, pyridazine-substituted 1,3,4-thiadiazoles was fungicidally active against wheat leaf rust, *Puccinia recondita*, and their activity was influenced by the nature of the substituents. The 3D-QSAR modes gave a good correlation between the variations on percent inhibition and the steric–electrostatic properties.<sup>240</sup> Other than these six fungi, triazolothiadiazoles 242 also showed broad-spectrum fungicidal capacities against other kinds, some therein with growth inhibition from 60% to 93%.<sup>241</sup>

**4.2.1.4. Virucidal Activity.** Tobacco mosaic virus was also reported to be inhibited by 1,3,4-thiadiazoles. Therein, compound 244 exhibited approximately 45% TMV inhibition, in a comparable range to that displayed by the commercial

**Scheme 55.** Antifungal Analogues of 1,3,4-Thiadiazole

ningnanmycin.<sup>242</sup> Analogues of 242 also showed better anti-TMV activity than standard drugs ribavirin and tiadinil at concentrations of 500 µg/mL at 100 and 50 µg/mL.<sup>241</sup>

**4.2.1.5. Plant-Growth-Regulating Activity.** Aroylurea 1,3,4-thiadiazoles 243 possessed plant-growth-regulating activities by displaying moderate to good cytokinin activities and auxin activities, among which 243i exhibited comparable auxin activity to indoleacetic acid IAA and 243d and 243h showed comparable cytokinin activity to kinetin KT.<sup>243</sup>

**4.2.2. Ecologic and Public Health Risks.** As many pesticides were persistent in soil in addition to long-history and large-scale applications as well as sometimes uncontrollable pesticide misuses, pesticide contamination spreads worldwide and cross-kingdom. Thiadiazoyl pesticides were also on the list. Risks imperiled soil, water, plants, animals, and humans, and it was a good example that humans pay for themselves. After application, the long-persistent chemicals most probably caused soil pollutant at first. Many countries and regions detected pesticides residues in soil.<sup>231,244</sup> The above residues contaminated the water through drift, runoff, seepage, leaching, drainage, evaporation and atmosphere transport, rainfall, and ground or surface water movement increased the contamination risk.<sup>245</sup> A 10-year study by the U.S. Geological Survey's (USGS's) National Water-Quality Assessment (NAWQA) Program provided a national-scale view of pesticide occurrence in streams and groundwater finding pesticides usually occurred as mixtures of multiple pesticide compounds frequently present in streams and to a lesser amount in groundwater, in many streams at concentrations that exceeded water-quality benchmarks for aquatic life or fish-eating wildlife. Tebuthiuron was listed in the most frequently detected pesticides.<sup>246</sup> News about pesticides detected in water has been continually reported worldwide.<sup>247</sup> Pesticides moving from soil to plants caused bioconcentration and residues in agricultural products.<sup>244a,247c,248</sup> Through the food chain, pesticides directly risked the health of human and animals.<sup>249</sup> Therefore, a comprehensive and effective supervision mechanism of pesticides production and application, strict residue monitoring and removing methods, and improved acknowledge of pesticides to users can be expected to decrease the risks.

### 4.3. Applications in Material Chemistry

1,3,4-Thiadiazole with its electron-deficient nature and good electron-accepting ability showed interesting optical, electronic, and chemical properties. It had been studied as an excellent candidate for organic bridging ligands to form new functional coordination polymers as aforementioned. The two heteroatoms, N and S, with free electron pairs could provide active coordination sites for metal ions or/and hydrogen-bond acceptors to expand polymeric frameworks. Moreover, introduction of amino/mercapto/hydroxyl substituents possessing tautomeric ability as well as some other common metal chelating ligands (such as phenyl, pyridyl,<sup>250</sup> thiophene, etc.) can extend thiadiazole's approach into structure coordination chemistry. With the presence of conjugated  $\pi$  systems and the electron transfer between heteroatoms (mainly N, S) and metal, again with thermotic stability, the polymeric metal–organic frameworks with a thiadiazole motif exhibited potential applications in catalysis, luminescence, magnetism, sorption, ion exchange, nonlinear optics, electricity, etc.<sup>115b,251</sup> Herein, we introduced them below.

**4.3.1. Optical Applications.** Three new monomers containing 2,5-diphenyl-1,3,4-thiadiazole containing vinyl have been synthesized, and their polymers which can emit strong blue or green fluorescence have good solubility in  $\text{CHCl}_3$  or DMF.<sup>252</sup> A coordination polymer of formula  $[\text{Cd}(\text{Haip})_2(\text{H}_2\text{O})_2]_2\text{H}_2\text{O}$  with a 2-amino-5-mercapto-1,3,4-thiadiazole as the ligand exhibited a two-dimensional framework which further assembled into a three-dimensional supramolecular network via interlayer  $\pi$ – $\pi$ -stacking interactions and strong hydrogen bonds, showing emitting blue photoluminescence in the solid state at room temperature.<sup>253</sup> Photoinduced intermolecular charge transfer, the key to photoluminescence, needed a molecular assembly containing electron-donor units and electron-accepting units as well as an intermolecular  $\pi$ -conjugated structure. The aromatic 1,3,4-thiadiazole ring allows good  $\pi$ -electron conjugation and was demonstrated as a good candidate for its electron-withdrawing property.<sup>115a,116a,254</sup> It was also hypothesized that the luminance emission of the metal–thiadiazole network might be attributable to the intraligand transitions modulated by metal coordination and/or ligand-to-metal charge transfer (LMCT).<sup>255</sup> Fluorescent chemosensors with their simplicity, high sensitivity, and fast response time have attracted enormous interest. With thiadiazoles as a fluorophore, the emitted fluorescence can be quenched or enhanced by a metal ion, suggesting that the metal–thiadiazole complexes can be used as metal-ion-selective sensors even via the naked eye detecting modes. In addition, these proposed methods can be tentatively utilized for determination of heavy metal ions in tap water, river water, and industrial wastewater samples.<sup>256</sup>  $\text{Cu}^{2+}$  complexes derived from unsymmetric 1,3,4-thiadiazoles exhibited mesogenic properties, and an excited-state intramolecular proton transfer (ESIPT) reaction in this type of *o*-hydroxy-1,3,4-thiadiazole was also observed accompanied by the two phototautomer forms, enol and keto, coexisting in the excited state.<sup>36b</sup> The photoinduced excited-state intramolecular proton transfer (ESIPT) process facilitated the transference of the H atom and formation of phototautomers with the most striking feature being their ultrafast nature and the highly Stokes-shifted fluorescence of the tautomer produced through the process.<sup>257</sup> In addition, the ESIPT also was the most probable mechanism involved in photostabilization of polystyrene (PS) films by 1,3,4-thiadiazoles through changing the energy of the absorbed

photon to the intermolecular proton transfer.<sup>258</sup> In addition, photoresponsive properties were also exhibited based on the ability of polymers' chromophores to undergo several reversible trans–cis–trans photoisomerizations. The cis–trans isomerization of azo-polyurethanes containing the *s*-triazolo[3,4-*b*]thiadiazole was investigated and demonstrated as a good candidate for optical laser writing.<sup>259</sup> Furthermore, thiadiazole core units formed nematic mesophases and possessed liquid crystalline properties. In the study of dye-sensitized solar cells, novel dendrimers with thiadiazole as the core units, chalcone as the surface group, and triazole as the branching were used as optical memory devices by photoisomerization, and the thiolate/disulfide system or nitrogenous parts of 1,3,4-thiadiazoles additionally acted as the redox-active electrolyte to connect the electrodes.<sup>100b,260</sup> Compound 245 as a potent Aquaporin 4 AQP4 inhibitor was developed as a positron emission tomography (PET) ligand for AQP4 imaging for diagnostic examination of some nervous diseases.<sup>261</sup>

**4.3.2. Electrochemical Applications.** With phenyl units and 1,3,4-thiadiazole rings linked through acetylene groups, a  $\pi$  system extending throughout the molecular structure called a poly(aryl-ethynylene) (PAE) system was obtained. Polymers involving this system showed rather low intramolecular reorganization energies and can be considered as candidates for n-type semiconductors.<sup>115b</sup> 1,3,4-Thiadiazole-dithiolate/disulfide usually showed protoprotic tautomerism, acid–base equilibrium, and redox behavior based on a mercapto–disulfido conversion in the assembly reactions with metal ions, which were reportedly used as multidentate linkers or capacitance measurements in semiconductors.<sup>114,262</sup> An amperometric sensor with attractive sensing behavior was prepared using solid carbon paste as substrate for poly(2-amino-5-mercapto-1,3,4-thiadiazole) (AMT, PAMT) film.<sup>263</sup> In addition, the PAMT film was also used for selective determination of L-cysteine and folic acid.<sup>264</sup> 2,5-Dimercapto-1,3,4-thiadiazole (DMcT) polymer PDMcT was also used to entrap a great deal of glucose oxidase GOx or tyrosinase and form PDMcT–enzyme composites and then coelectrodeposited with poly-(DMcT) on an Au electrode, which was demonstrated as sensitive glucose and phenolic biosensors.<sup>265</sup> In this decade, organosulfur-based compounds with multiple thiol groups or disulfide moieties have received attention as potential cathode electroactive materials for lithium/lithiumion rechargeable batteries due to their high capacities to release and capture lithium ions during charge/discharge cycles as well as the advantage of low cost. However, the sluggish kinetics of the redox reactions at room temperature, the lack of electronic conductivity, and the poor charge/discharge durability in liquid electrolyte systems made organosulfur materials application limited. DMcT was reported as one of the most promising organosulfur compounds as a cathode active material, and its redox reaction can be accelerated by the high electrocatalytic activity of the conducting polymers poly(3,4-ethylenedioxythiophene) (PEDOT),<sup>116d,251b,266</sup> polypyrrole (Ppy), and polyaniline (PA).<sup>266a,267,268</sup> Except for dye-sensitized solar cell, 1,3,4-thiadiazoles were also applied to form thin films of coordination complexes which had particular optical, electrical, magnetic, and catalytic properties.<sup>269</sup> In addition, two new perylene diimide derivatives achieved by functionalizing the basic perylene molecular core at imide nitrogen with 1,3,4-thiadiazole rings made possible the fabrication of n-type organic thin-film transistors able to work in air.<sup>270</sup>

**4.3.3. Additive Applications.** Organic compounds bearing heteroatoms with high electron density such as phosphorus, sulfur, nitrogen, or oxygen or those containing multiple bonds which can be adsorbed onto the metal surface through electron transfer from the adsorbed species to the vacant d orbital in the metal to form a coordinate type link are effective as corrosion inhibitors for protecting metals.<sup>110<sup>h</sup></sup> Among these organic compounds 1,3,4-thiadiazole containing two imino groups ( $\text{—C}=\text{N}$ ) and a S atom and its derivatives with amino, thio, hydroxyl, phenyl, alkyl,<sup>271</sup> and some heterocyclic substituents have displayed excellent inhibition ability in various media. The adsorption behavior of these thiadiazole derivatives on the metal surface could occur directly on the basis of donor behavior of the heteroatoms (e.g., N atom and S atom) bearing the lone pair of electrons and the extensively delocalized  $\pi$  electrons of the thiadiazole derivative molecules with the acceptor behavior of the vacant d orbitals of metal surface atoms<sup>272,273</sup> to form a protective film to copper,<sup>274</sup> silver,<sup>275</sup> mild steel,<sup>276</sup> bronze,<sup>277</sup> brass,<sup>110<sup>h</sup></sup> cobalt, and so on.<sup>278</sup> They acted as different types of inhibitors which potentially decrease the cathodic, anodic, or corrosion currents as well that are anodic-type inhibitors, cathodic inhibitors, and mixed-type inhibitors.<sup>279</sup> Absorption depends on many factors always being time dependent and pH-dependent, and the protection efficiency increases with properly increasing inhibitor concentration and ambient temperature; the structural and electronic effects of the inhibitors as well as the interaction mode with the metal surface and the molecular sizes are also reported in relation to the inhibiting efficiencies.<sup>273,280</sup>

In addition to anticorrosive ability for metal, 1,3,4-thiadiazole derivatives showing favorable load-carrying and extreme pressure capacity, antiwear, and friction-reducing properties are used as additives in lubricants (e.g., rapeseed oil (RSO), ester-based lubricants). It is rationalized that these properties are achieved by the S atom reacting with the metal surface and the N atom and other heteroatoms (e.g., P atom) absorbed onto the metal surface to produce a thin chemical protecting film. Moreover, chelation of lone pair electrons of the N atom with the iron surface is beneficial to minimize the corrosion of S.<sup>281</sup>

**4.3.4. Miscellaneous.** Thiadiazoles can be used as bridging ligands to construct new porous metal–organic frameworks (PMOFs) or porous coordination polymers (PCPs) with the property of magnetism. The nitrogen donors accompanying the aromatic nature and versatile frameworks of 1,3,4-thiadiazole ligands in metal–inorganic coordination polymers are hypothesized for invoking the magnetic behavior.<sup>282</sup> 2-Mercapto-5-methyl-1,3,4-thiadiazole forming the first- and second-generation Janus scorpionate ligands [HB(mtdaMe)<sup>3+</sup>] (mtdaMe = 2-mercaptop-5-methyl-1,3,4-thiadiazolyl) constructed complex with Fe<sup>2+</sup> showed diamagnetic and paramagnetic activity.<sup>111<sup>c</sup></sup> Two isomorphous 3D porous metamagnets,  $\{[\text{M}_6(\text{N}_3)_{12}\text{L}_6]\cdot(\text{H}_2\text{O})_{13}\}_{\infty}$  ( $\text{M} = \text{Ni}^{\text{II}}; \text{Co}^{\text{II}}$ ), have been constructed from 2-(1,3,4-thiadiazol-2-ylthio)acetic acid; both exhibited global metamagnetic behaviors resulting from strong intrachain ferromagnetic couplings and weak interchain antiferromagnetic interactions. Several novel rare earth iron coordination polymers bridged by (1,3,4-thiadiazole-2,5-diylidithio)diacetic acid were also reported followed the Curie–Weiss paramagnetic behavior in a certain temperature range.<sup>283</sup> Thiadiazoles also can be introduced to BINOL-based ligands which showed excellent catalytic effectiveness in the asymmetric addition of diethylzinc to aldehydes.<sup>284</sup> Thio

groups-substituted 1,3,4-thiadiazoles as a heavy-metal ion trapping agent forming the metal–S bond were anchored onto the silica gel surface, suggesting the potential for heavy cation removal from an ecosystem.<sup>285</sup>

## 5. BRIEF COMPARISON OF BIOISOSTERES 1,3,4-THIADIAZOLE AND 1,3,4-OXADIAZOLE

1,3,4-Oxadiazole shares a very similar scaffold chemical structure with 1,3,4-thiadiazole with the only difference being replacing the  $-\text{O}-$  with  $-\text{S}-$ . On the basis of the concept of isostere,  $-\text{O}-$  and  $-\text{S}-$  belong to the divalent-atom bioisosteres and similarly 1,3,4-oxadiazole shows isosterism to 1,3,4-thiadiazole.<sup>239,240</sup> 1,3,4-Oxadiazole exhibits similar physicochemical properties to 1,3,4-thiadiazole, extending to the biochemical similarity which is emphasized more in terms of bioisostere instead of structural mimetics and are applied widely in drug design.<sup>286</sup> Thus, 1,3,4-oxadiazoles possess almost all of the bioactivities and materials properties of their thiadiazole analogues.<sup>287</sup> In addition, many studies reported in the literature revealed compounds having a 1,3,4-thiadiazole ring showed better biological activities than the corresponding compounds having an oxadiazole ring.<sup>16<sup>f</sup>,195,288</sup> The design of bioisosteres frequently introduces structural changes that can be beneficial or deleterious depending on the context with size, shape, electronic distribution, polarizability, dipole, polarity, lipophilicity, and  $\text{pK}_a$  potentially contributing to improving potency, enhancing selectivity, altering physical properties, reducing or redirecting metabolism, eliminating or modifying toxicophores, and acquiring novel intellectual property.<sup>28</sup> Though belonging to the chalcogen, the different configuration of extranuclear electrons and bigger atomic radius make S less electronegative than O, getting a longer C–S bond and bigger C–C distance as well as a bigger van der Waals radius but a smaller C–S–C bond angle in comparison with those of O. A bigger log  $P$  indicates the S atom possesses higher lipophilicity than the O atom. However, the O atom exchanging to a S atom in the thiadiazoles studied does not cause a dramatic change in desolvation energy.<sup>289</sup> Substitution of the O atom by a S atom can influence the binding affinity of acceptors and ligand compounds, which is determined by electrostatic, hydrophilic, and hydrophobic interactions.<sup>290</sup> Its reported diminution in binding affinity on this exchange of O by S can be also reasonably ascribed to the decrease in hydrogen bonding.<sup>291</sup>

Comparison of the equilibrium geometry for 1,3,4-oxadiazole and 1,3,4-thiadiazole (Table 1) shows a similar tendency with bioisosteres of O and S.<sup>292</sup> The structural changes by substitution of O by S make the 1,3,4-thiadiazole ring more narrow and the lower half (the half containing a S atom) longer but the upper half (suppose divided based on the C–C line) wider as for the bigger  $\angle(\text{C}=\text{N}—\text{N})$ . These kinds of structure changes and the lower electronegativity of the S atom let it lower the negative charge densities on nitrogen atoms less than those of the oxadiazole ring. Hence, the negative charge on the nitrogen atoms of thiadiazoles is higher than in oxadiazoles, which leads to formation of more stable complexes with a metal and H bond as well as the higher reactivity with electron-withdrawing groups. The same holds true for the protonation ability of thiadiazoles being higher than that for oxadiazoles.<sup>289</sup> In addition, the S atom exhibits more effectively hybridizing s and p orbitals and being more polarizable, which are favorable for intermolecular interactions in thin film.<sup>251<sup>d</sup></sup> Therefore, 1,3,4-thiadiazole possesses a weaker solubilizing effect for oligothiophenes.<sup>293</sup> In addition, the literature revealed a unique

**Table 1. Equilibrium Geometry for 1,3,4-Oxadiazole and 1,3,4-Thiadiazole**

coordinate a (X = O, S)	MP2/6-31G**b	
	1,3,4-oxadiazole	1,3,4-thiadiazole
R(C—X)	1.361 Å	1.717 Å
R(C=N)	1.302 Å	1.317 Å
R(N—N)	1.402 Å	1.370 Å
R(C—H)	1.075 Å	1.077 Å
∠(C—X—C)	101.4°	86.5°
∠(X—C=N)	113.6°	114.9°
∠(C=N—N)	105.7°	111.9°
∠(X—C—H)	118.3°	122.5°
∠(N=C—H)	128.1°	122.6°
μ	3.17	3.43

<sup>a</sup>Bond lengths in Angstroms and angles in degrees.  $\mu$  is the dipole moment in Debye. <sup>b</sup>At the MP2 (Moller–Plesset) level of theory using the 6-31G\*\* basis set.

intramolecular C=O---S interaction for acylamino-1,3,4-thiadiazole, resulting in it being inactive for inhibition on STAT3 (signal transducer and activator of transcription 3) transcription and STAT3 dimerization.<sup>32a</sup> Better inhibition efficiency on the corrosion of mild steel is obtained by 2,5-bis(4-dimethylaminophenyl)-1,3,4-thiadiazole probably due to the possibility for this molecule to accept through the sulfur orbital a charge transfer from the metal surface.<sup>279b</sup> 1,3,4-Thiadiazole exhibits stronger aromaticity and thermotic stability, which also contribute to the differences of activities to its oxadiazole analogue.<sup>70</sup> In addition, small difference has an effect on the exchange of oxygen for sulfur enabling mass spectrometric fragmentation pathways of 2-(4'-methoxy)-phenyl-S-phenyl-1,3,4-thiadiazoles not observed for oxadiazoles, e.g., rearrangements leading to formation of [H<sub>3</sub>CO—C<sub>6</sub>H<sub>4</sub>—S]<sup>+</sup> and [C<sub>6</sub>H<sub>5</sub>—S]<sup>+</sup> ions.<sup>294</sup> The difference in properties between 1,3,4-thiadiazole and 1,3,4-oxadiazole can be widely used in the bioisosteric substitutions for searching more favorable results, but many properties are also decided by other functional groups attached to the thi(ox)adiazole ring which should be paid attention to.

## 6. CONCLUSION

As a triheterocycle, 1,3,4-thiadiazole is composed of two electron-deficient carbon atoms, two interconnected nitrogen atoms, and a sulfur atom with lone electron pairs. This kind of structure leads to an electron-deficient nature, obvious aromaticity, and pretty high thermotic stability. The ring itself can hardly react, but with a substitution on the C3' or CS' position, 1,3,4-thiadiazoles are highly activated and ready to react. The nitrogen atoms tend to nucleophilic attack, and the carbon atoms can suffer both nucleophilic substitutions and electrophilic attacks. In addition, the common leaving substituents attaching to carbon atoms are also possess very high reactivities which are a very important of the reactivity of 1,3,4-thiadiazoles. In particular, for the hydroxyl group, amino group, and thiol group on the C3' or CS' position, the equilibriums of hydroxyl–carbonyl, amino–imino, and thiol–thione introduce the tautomerism to 1,3,4-thiadiazoles accompanying the proton transfer and charge transfer process which can change the electron distribution and reactivity of a specific atom. This character is also widely applied in the synthesis of metal–organic complex and polymers. Nitrogen-containing and sulfur-containing groups possessing electron

lone pairs can function as the electron donors associated with the electron acceptors forming the charge transport which attract much interest in electrochemistry. Though 1,3,4-thiadiazoles exhibit versatile properties and special applications in pharmaceuticals, agrochemicals, and materials chemistry, many aspects also need further study. Literature reporting the different kinds of bioactivities of 1,3,4-thiadiazoles are various, but the studies are not systematic enough and the mechanisms of some main bioactivities, e.g., antibacterial, antifungal, and antiparasitic activities, are not clear. Activities of many analogues are not favorable, and *in vivo* experimental data are deficient even having excellent *in vitro* experimental results. Though microwave radiation conditions and methods of one-pot synthesis are introduced, the traditional reaction conditions are usually used which are mostly extreme conditions and not being environmentally friendly enough. For the following research, 1,3,4-thiadiazole can still be a very stable scaffold structure introducing different kinds of substituents to search for favorable results. The ring nitrogen atoms and ring sulfur atom as well as amino groups and mercapto groups attached to the ring carbon atoms will likely be the focus of future development and taking full advantage of their special properties.

With this wealth of synthetic chemical and application knowledge exhibited by compounds containing the 1,3,4-thiadiazole scaffold, we can expect many further developments of this template in drug discovery, novel materials exploration, agromedicine development, or even new applications in some other fields. In addition, the continuing interest of future research will certainly focus more on developing in the modifications based on the thiadiazole scaffold and pharmacophores to build low molecular weight medicine with high efficacy (both *in vitro* and *in vivo*) and low side effects on cancer, epilepsy, inflammation, bacterial infection, and so on. Moreover, 1,3,4-thiadiazoles demonstrate favorable performance in applications on materials. Therefore, continuing research on the conformation and highly ordered supermolecular structures of this simplest heterocycle in optics and electromagnetism will let us access a new research aspect of thiadiazole. Nevertheless, even for the fruitful thiadiazole derivatives we obtained further exploration on favorable chemosynthesis methods and conditions of 1,3,4-thiadiazoles is necessary and will certainly contribute to the chemistry of heterocyclic compounds in the development of new drugs and functional materials for practical applications.

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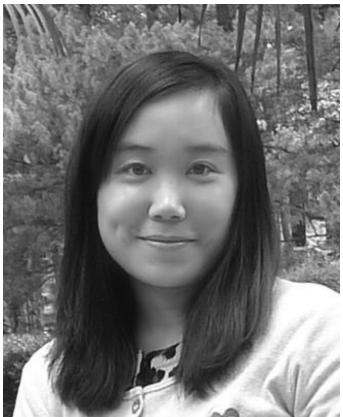
\*E-mail: zhuhl@nju.edu.cn.

### Author Contributions

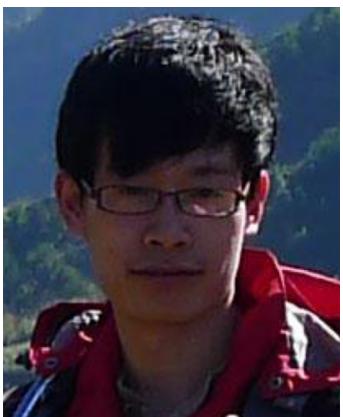
<sup>†</sup>Both C.-Y.L. and Y.H. contributed equally to the work.

### Notes

The authors declare no competing financial interest.

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