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FULL PAPER

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# Copper-catalyzed one-pot coupling reactions of aldehydes (ketones), tosylhydrazide and 2-amino(benzo)thiazoles: An efficient strategy for the synthesis of *N*-alkylated (benzo) thiazoles

**Zengyang Xie**[1] | **Ruijiao Chen**[1] | **Mingfang Ma**[1] | **Lingdong Kong**[1] | **Jun Liu**[1] | **Cunde Wang**[2]

[1]Laboratory of New Antitumor Drug Molecular Design & Synthesis, College of Basic Medicine, Jining Medical University, Jining 272067, China

[2]School of Chemistry and Chemical Engineering, Yangzhou University, Yangzhou 225002, China

**Correspondence**
Zengyang Xie, Laboratory of New Antitumor Drug Molecular Design & Synthesis, College of Basic Medicine, Jining Medical University, Jining 272067, China.
Email: xiezyjnmc@126.com Cunde Wang, School of Chemistry and Chemical Engineering, Yangzhou University, Yangzhou 225002, China.
Email: wangcd@yzu.edu.cn

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An efficient and practical C–N bond formation methodology for the synthesis of *N*-alkylated (benzo)thiazoles was developed, via the copper-catalyzed one-pot two-step reactions of 2-amino(benzo)thiazoles and aldehydes (ketones) with tosylhydrazide. This cross-coupling reaction proceeded smoothly and tolerated a broad range of functional groups (46 examples). A variety of functionalized *N*-alkylated (benzo)thiazoles were obtained in moderate to high yields. Notably, gram-scale synthesis of fanetizole (anti-inflammatory drug) was also realized through this protocol.

**KEYWORDS**
C–N bonds, copper-catalyzed, *N*-(alkylamino)azoles, tosylhydrazones

## 1 | INTRODUCTION

The formation of C–N bonds has attracted considerable attention since the resulting products occur in various compounds of enormous practical importance, ranging from agrochemicals and pharmaceuticals to functional materials.[1] Among these C–N bond forming reactions, the *N*-alkylation of primary amines to higher amines is especially important and interesting because *N*-alkylated amines are usually used as key intermediates for the preparation of other valuable compounds like additives, dyes, polymers and bioactive compounds.[2]

One such class of *N*-alkylated amines are 2-*N*-(alkylamino)azoles which exhibit various physiological

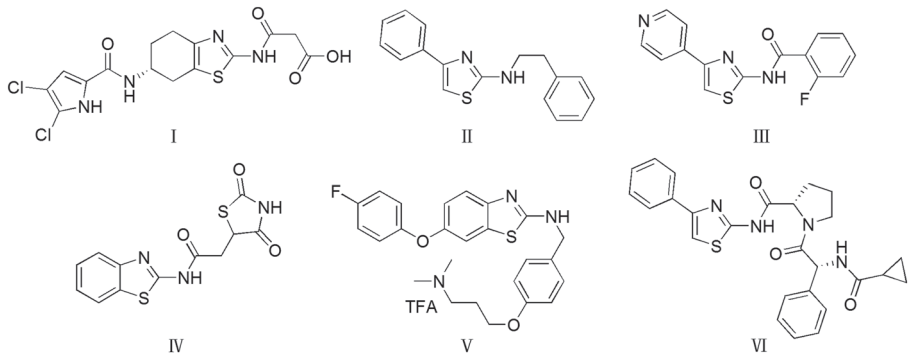
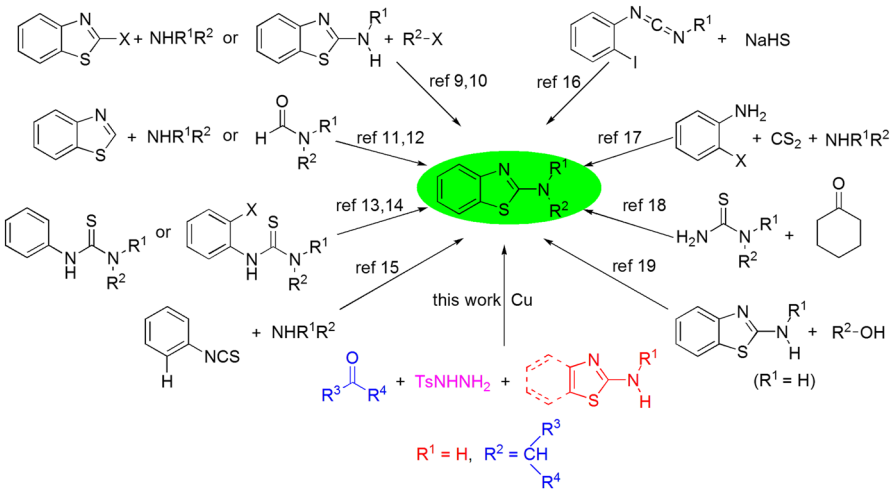



**FIGURE 1** Examples of bioactive 2-*N*-(alkylamino)azoles




**SCHEME 1** Various synthesis strategies for 2-*N*-(alkylamino) benzothiazoles

and pharmacological activities. For example, 4,5,6,7-tetrahydrobenzo[1,2-*d*]thiazole derivative **I** can be used as a DNA gyrase inhibitor,[3] fanetizole (**II**) is an anti-inflammatory drug,[4] compound **III** exhibits good Rho kinase inhibition potency with $K_i$ = 1.1 μM,[5] the 2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide analogue **IV** is found to show significant antioxidant activity,[6] while another 2-*N*-(alkylamino)benzothiazole analogue **V** has been reported to function as blocker of *N*-type calcium channel,[7] and compound **VI** is a potent HCV NS5A inhibitor ($EC_{50}$ = 4.6 nM) and is undergoing preclinical trials for the treatment of HCV infection[8] (Figure 1).

Considering the importance of 2-*N*-(alkylamino) azoles, a number of methods have been developed for their synthesis (Scheme 1). The successful protocols for the synthesis of 2-*N*-(alkylamino)azoles involve aminations of halobenzothiazoles with alkylamines[9] or cross-coupling reactions between aminazoles and aryl halides,[10] the direct oxidative couplings of azoles with amines[11] or formamides,[12] intramolecular cyclization of *N*-arylthioureas[13] or *ortho*-halophenylthioureas,[14] condensation of isothiocyanates with amines,[15] Cu-catalyzed condensation of sodium hydrosulfide with carbodiimide,[16] Cu-catalyzed/mediated three-component condensation reactions,[17] aerobic oxidative cyclization/dehydrogenation of thioureas and cyclohexanones[18] and metal-catalyzed *N*-alkylation of aminazoles with alcohols.[19] Although the above procedures are generally practical and versatile, some of them still have various limitations such as the use of noble metals and additives, a longer reaction time, a limited substrate scope and the generation of many unwanted wastes. Therefore, it would be of great importance to develop a novel protocol based on an inexpensive metal catalyst for the synthesis of 2-*N*-(alkylamino)azoles.

Tosylhydrazones which are easily obtained through the condensation of tosylhydrazides with carbonyl compounds, are valuable intermediates and have been successfully used in organic synthesis for over 60 years.[20] The pioneering studies were of two well-known name reactions called Shapiro reaction and Bamford-Stevens reaction, both of which showed great applications in the preparation of alkenes. In recent years, the use of tosylhydrazones as important building blocks to achieve complex compounds has attracted more attention. Tremendous efforts were made by Barluenga *et al.*,[21] Wang and co-workers[22] and others, who contributed valuable work on employing tosylhydrazones as versatile coupling partners to form various chemical bonds, including C–

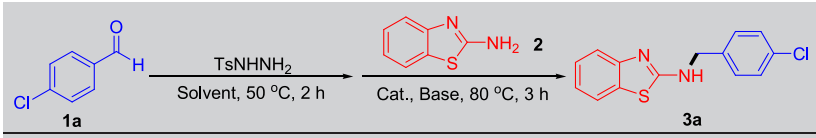
C,[23] C–S,[24] C–N,[25] C–O,[26] C–P,[27] C–B,[28] C–Sn,[29] C–Si[30] and N–N[31] bonds. Despite many significant achievements, developing more efficient C–N bond formation methodologies utilizing tosylhydrazones is still required because this may offer new chances for the synthesis of bioactive compounds.

Given the importance of 2-*N*-(alkylamino)azoles and unique reaction characteristics of tosylhydrazones, as well as our continuing studies of the formation of chemical bonds,[32] we made further exploration of the *N*-alkylation of primary amines. Herein, we report a more efficient strategy for the synthesis of *N*-alkylated (benzo) thiazoles through Cu-catalyzed one-pot two-step reactions of carbonyl compounds (aldehydes and ketones), tosylhydrazide and 2-amino(benzo)thiazoles. More interestingly, the anti-inflammatory drug fanetizole can also be synthesized successfully using our catalysis system.

## 2 | RESULTS AND DISCUSSION

At the outset of this study, the cross-coupling reaction of 2-aminobenzothiazole (**2**) and tosylhydrazone

**TABLE 1** Optimization of reaction conditions for synthesis of **3a**[a]




| Entry | Catalyst (mol%) | Base (equiv.) | Solvent | Yield (%)[b] |
|---|---|---|---|---|
| 1 | — | *t*-BuOLi (2.0) | 1,4-Dioxane | Trace |
| 2 | $Cu(OAc)_2$ (15) | *t*-BuOLi (2.0) | 1,4-Dioxane | 51 |
| 3 | $CuSO_4{\cdot}5H_2O$ (15) | *t*-BuOLi (2.0) | 1,4-Dioxane | 22 |
| 4 | $Cu(acac)_2$ (15) | *t*-BuOLi (2.0) | 1,4-Dioxane | 60 |
| 5 | $Cu(NO_3)_2{\cdot}3H_2O$ (15) | *t*-BuOLi (2.0) | 1,4-Dioxane | 35 |
| 6 | CuCl (15) | *t*-BuOLi (2.0) | 1,4-Dioxane | 47 |
| 7 | CuI (15) | *t*-BuOLi (2.0) | 1,4-Dioxane | 68 |
| 8 | CuO (15) | *t*-BuOLi (2.0) | 1,4-Dioxane | 19 |
| 9 | CuI (15) | NaOH (2.0) | 1,4-Dioxane | 15 |
| 10 | CuI (15) | $Cs_2CO_3$ (2.0) | 1,4-Dioxane | Trace |
| 11 | CuI (15) | $K_2CO_3{\cdot}0.5\ H_2O$ (2.0) | 1,4-Dioxane | Trace |
| 12 | CuI (15) | $Na_2CO_3$ (2.0) | 1,4-Dioxane | 33 |
| 13 | CuI (15) | KOH (2.0) | 1,4-Dioxane | Trace |
| 14 | CuI (15) | *t*-BuONa (2.0) | 1,4-Dioxane | 0 |
| 15 | CuI (15) | *t*-BuOK (2.0) | 1,4-Dioxane | 0 |
| 16 | CuI (15) | — | 1,4-Dioxane | 0 |
| 17 | CuI (15) | *t*-BuOLi (1.0) | 1,4-Dioxane | 30 |
| 18 | CuI (15) | *t*-BuOLi (3.0) | 1,4-Dioxane | 66 |
| 19 | CuI (10) | *t*-BuOLi (2.0) | 1,4-Dioxane | 57 |
| 20 | CuI (5) | *t*-BuOLi (2.0) | 1,4-Dioxane | 40 |
| 21 | CuI (20) | *t*-BuOLi (2.0) | 1,4-Dioxane | 69 |
| 22[c] | CuI (15) | *t*-BuOLi (2.0) | 1,4-Dioxane | 34 |
| 23[d] | CuI (15) | *t*-BuOLi (2.0) | 1,4-Dioxane | 82 |
| 24[e] | CuI (15) | *t*-BuOLi (2.0) | 1,4-Dioxane | 78 |
| 25[d] | CuI (15) | *t*-BuOLi (2.0) | Toluene | 75 |
| 26[d] | CuI (15) | *t*-BuOLi (2.0) | DMSO | 0 |
| 27[d] | CuI (15) | *t*-BuOLi (2.0) | DMF | Trace |

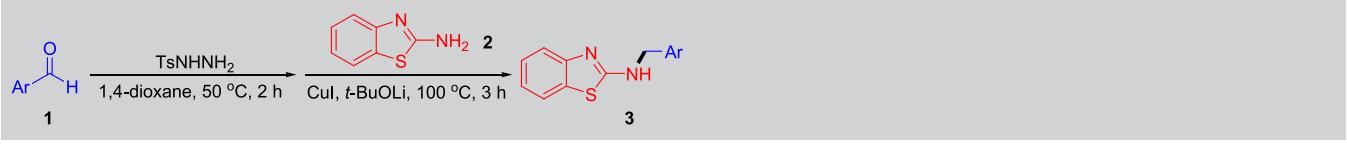
[a]Reaction conditions: **1a** (0.6 mmol), tosylhydrazide (0.6 mmol), solvent (4 ml) at 50°C for 2 h; then **2** (0.4 mmol), catalyst, base under heating at 80°C for 3 h.
[b]Isolated yields. [c]Reaction carried out at 60°C. [d]100°C. [e]120°C.

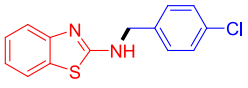
generated *in situ* from 4-chlorobenzaldehyde (**1a**) with tosylhydrazide was selected as a model to explore the reaction conditions. The reaction was performed through a one-pot strategy in two steps. Tosylhydrazone was easily prepared at 50°C for 2 h in 1,4-dioxane, followed by addition of **2**, catalyst and base into the resulting mixture without isolation of the intermediate, and the resulting solution was then heated at 80°C for another 3 h. It was found that only a trace amount of the desired product **3a** was detected under catalyst-free conditions (Table 1, entry 1). Seven types of simple copper salts were examined, and we found that all of them were favorable for this cross-coupling reaction; the best result was obtained when CuI was used as catalyst (Table 1, entry 7). Subsequently, with the catalyst CuI, the effects of various bases on the reaction were tested, with *t*-BuOLi affording the best yield, while other bases like NaOH, $Cs_2CO_3$, $K_2CO_3{\cdot}0.5H_2O$, $Na_2CO_3$, KOH, *t*-BuONa and *t*-BuOK resulted in lower yields (Table 1, entries 7 and 9–15). It should be noted that no target compound **3a** was detected in the absence of base which demonstrated that a base is indispensable to this transformation (Table 1, entry 16). Further studies on the base loading indicated that 2 equiv. of *t*-BuOLi was optimal.

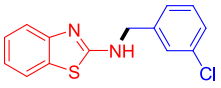
In addition, the effects of catalyst loading, reaction temperature and solvents were also investigated. When the CuI catalyst loading was reduced from 15 to 10 and then 5 mol%, the yield of **3a** was lowered from 68 to 57 and 40%, respectively (Table 1, entries 7, 19, 20). But no further improvement of yield was observed when the CuI loading was raised to 20 mol% (Table 1, entry 21). Furthermore, decreasing the reaction temperature to 60°C led to reduced yields of **3a** (Table 1, entry 22). To our delight, the yield was increased to 82% when the reaction was carried out at 100°C, while the yield did not increase when the reaction temperature reached 120°C (Table 1, entries 23 and 24). Finally, through the examination of various solvents, the use of 1,4-dioxane as a solvent was found to be the most appropriate choice compared with toluene, dimethylsulfoxide (DMSO) and dimethylformamide (DMF).

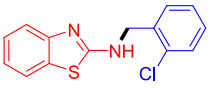
With the optimized reaction conditions in hand, we then examined the substrate scope of this transformation. Firstly, the *N*-alkylation of **2** with various aldehydes was evaluated. As evident from Table 2, benzaldehydes bearing electron-donating substituents on the aromatic ring gave better yields of the products than those having electron-withdrawing substituents (Table 2, 3**g–i** versus **3a–f**). This cross-coupling reaction was not sensitive to

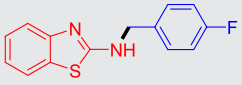
**TABLE 2** Substrate scope for the various aldehydes

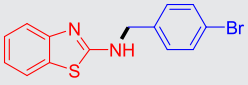


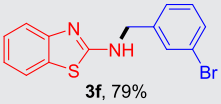


**3a**, 82%

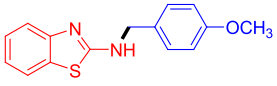

**3b**, 85%

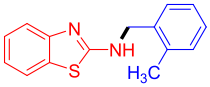

**3c**, 81%

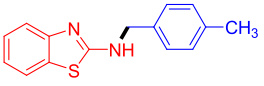

**3d**, 70%

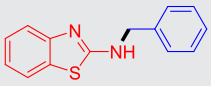

**3e**, 76%

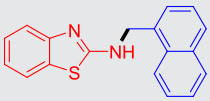

**3f**, 79%

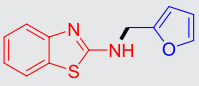

**3g**, 90%

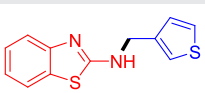

**3h**, 86%

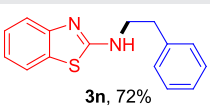

**3i**, 88%

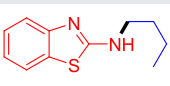

**3j**, 80%


**3k**, 89%


**3l**, 69%

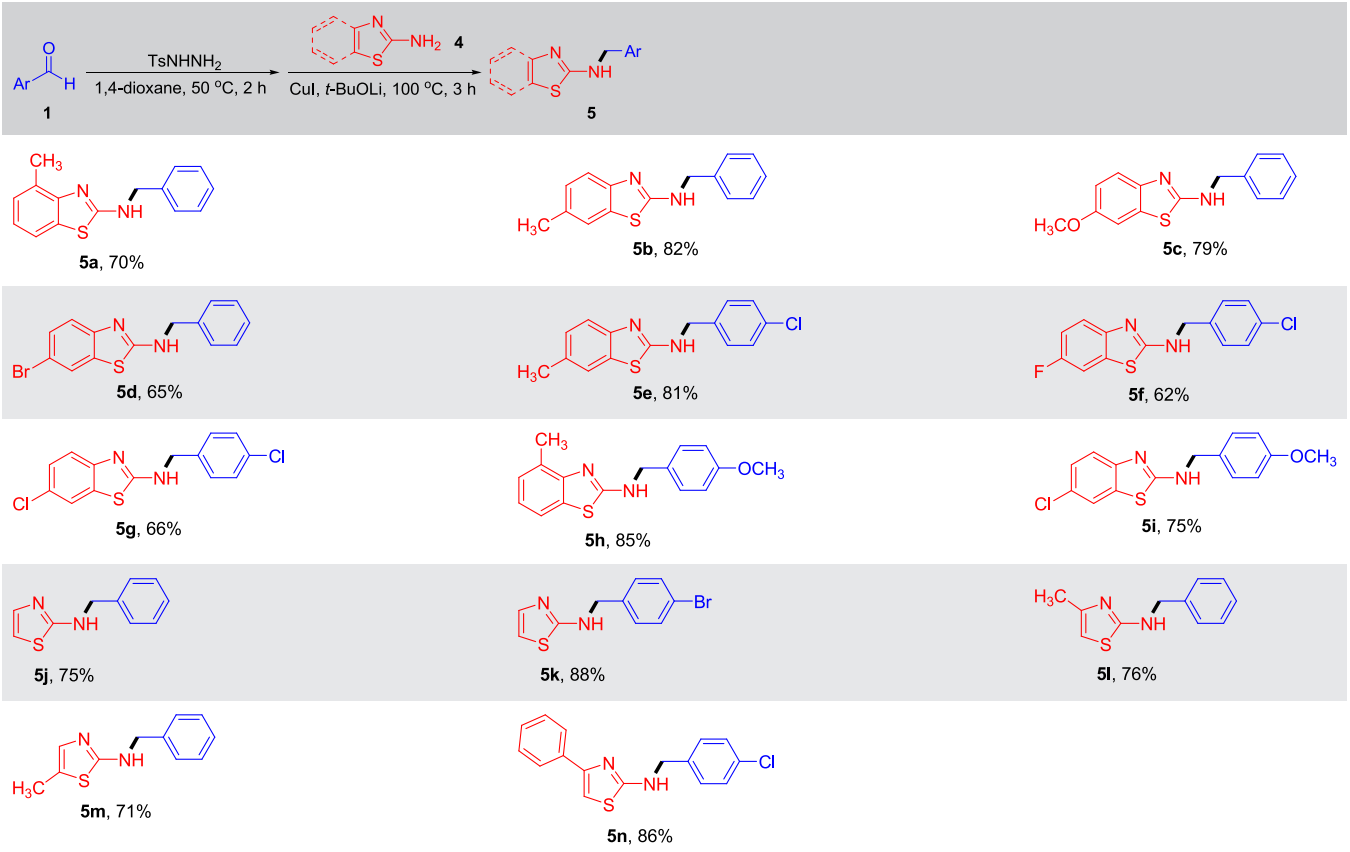

**3m**, 74%


**3n**, 72%


**3o**, 53%

The reaction was performed with **1** (0.6 mmol) and tosylhydrazide (0.6 mmol) in 1,4-dioxane (4 ml) at 50°C for 2 h. Then **2** (0.4 mmol), CuI (15 mol%) and *t*-BuOLi (2.0 equiv.) were added. The resulting solution was stirred at 100°C for another 3 h. Yields refer to isolated yields.

**TABLE 3** Substrate scope for various 2-amino(benzo)thiazoles and different aldehydes




The reaction was performed with **1** (0.6 mmol) and tosylhydrazide (0.6 mmol) in 1,4-dioxane (4 ml) at 50°C for 2 h. Then **4** (0.4 mmol), CuI (15 mol%) and *t*-BuOLi (2.0 equiv.) were added. The resulting solution was stirred at 100°C for another 3 h. Yields refer to isolated yields.

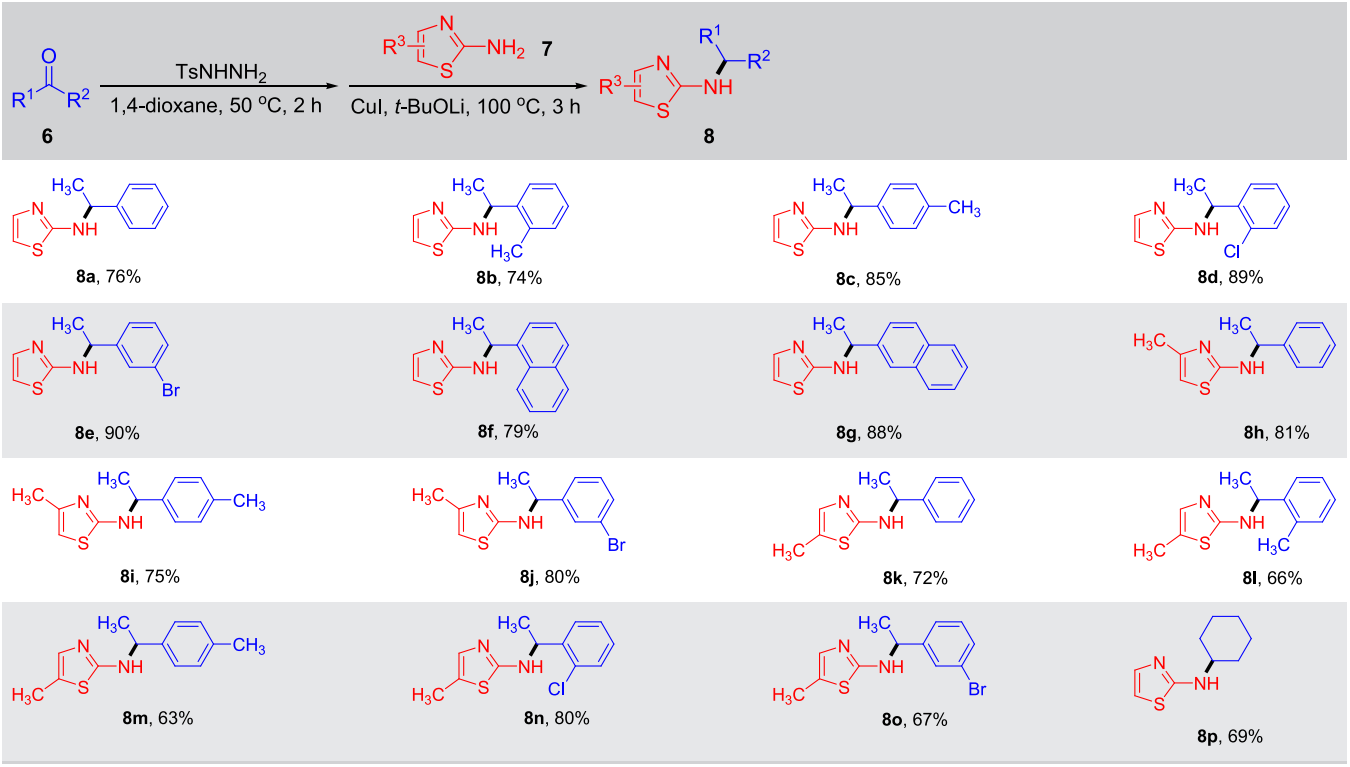
the steric effects of substituents in aldehydes and gave good yields. Unsubstituted benzaldehyde and 1-naphthaldehyde were suitable coupling partners which delivered the corresponding products with 80 and 89% yields, respectively (Table 2, 3**j** and 3**k**). Most interestingly, the reactions could mildly occur with heteroatom-containing aldehydes, where the corresponding products **3l** and **3m** could be achieved in satisfactory yields. Finally, aliphatic aldehydes (phenylacetaldehyde and butyraldehyde) can also be coupled to **2** under our experimental conditions to afford products **3n** and **3o**.

Next, the *N*-alkylation of various 2-amino(benzo)thiazoles with several different aldehydes was then examined, and the results are summarized in Table 3. It was found that the reaction could be influenced by the substituent group on substrates, as 2-aminobenzothiazoles with 6-$CH_3$ group (Table 3, **5e**) gave higher yields than the 6-F and 6-Cl counterparts (Table 3, **5f** and **5g**). Among the four kinds of 2-aminobenzothiazoles, 2-amino-6-bromobenzothiazole provided the corresponding product with the lowest yield when coupled with benzaldehyde (Table 3, **5d**). Moreover, the scope of non-benzo-fused 2-aminothiazoles with aldehydes were also screened, and the corresponding *N*-alkylated thiazoles were obtained in good yields (Table 3, **5j**–**n**).

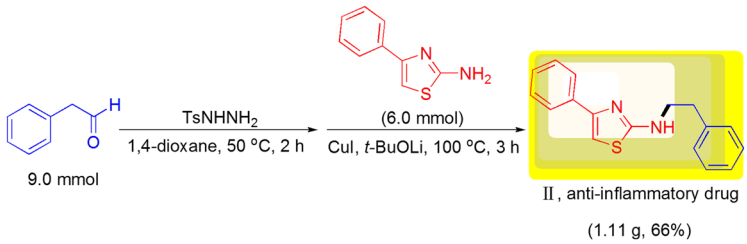
Compared with aldehyde-derived *N*-tosylhydrazones, the *N*-tosylhydrazones derived from ketones are less effective in the cross-coupling reaction, probably as a result of the steric hindrance of ketones.[33] To expand the utility of this protocol, the *N*-alkylation of non-benzo-fused 2-aminothiazoles with various ketones was also studied (Table 4). Once again, all the reactions proceeded well and provided the target products in good yields. It is noteworthy that the reaction yield was somewhat affected by the position of substituents in ketones (**8b** versus **8c**; **8f** versus **8g**; **8l** versus **8m**). We also found the reactivity of 4-methylthiazol-2-amine was much better which gave slightly higher yield than 5-methylthiazol-2-amine (**8h** versus **8k**; **8i** versus **8m**; **8j** versus **8o**). To our delight, aliphatic ketone showed good reactivity under the reaction conditions, and ideal yield was obtained when cyclohexanone was used as the substrate (Table 4, **8p**).

Next, to demonstrate the synthetic value of this cross-coupling, further experiment concerning a gram-scale synthesis of fanetizole was carried out with 4-phenylthiazol-2-

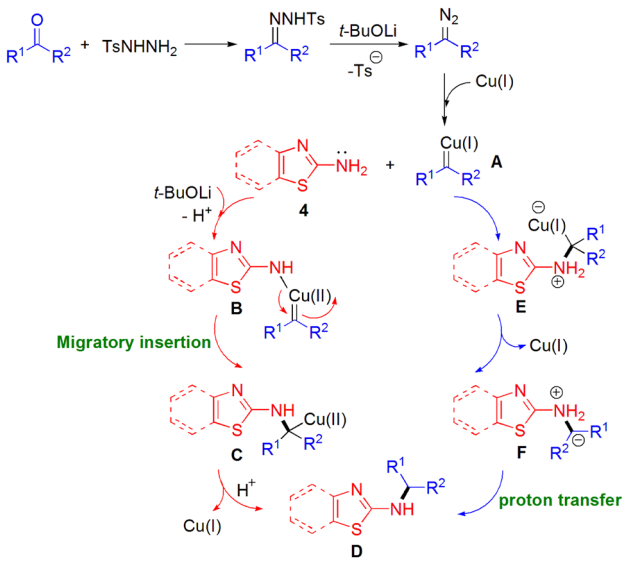
**TABLE 4** Substrate scope for various 2-aminothiazoles and different ketones




The reaction was performed with **6** (0.6 mmol) and tosylhydrazide (0.6 mmol) in 1,4-dioxane (4 ml) at 50°C for 2 h. Then **7** (0.4 mmol), CuI (15 mol%) and *t*-BuOLi (2.0 equiv.) were added. The resulting solution was stirred at 100°C for another 3 h. Yields refer to isolated yields.




**SCHEME 2** A gram-scale synthesis of anti-inflammatory drug **II**




**SCHEME 3** Possible reaction pathways for one-pot synthesis of *N*-alkylated (benzo)thiazoles

amine and phenylacetaldehyde (Scheme 2). Gratifyingly, the reaction proceeded smoothly under the optimized conditions and 1.11 g of the desired anti-inflammatory drug **II** was obtained in moderate yield.

Based on the above experimental results and related reports,[22d, 23u] two possible reaction pathways for the synthesis of *N*-alkylated (benzo)thiazoles were proposed, as shown in Scheme 3. At the beginning, tosylhydrazones are easily formed by coupling carbonyl compounds with tosylhydrazide, which undergo thermal decomposition to generate diazo compounds in the presence of *t*-BuOLi. Then, the reaction of diazo compounds and copper salt leads to the formation of copper–carbene species **A**.[25b] In one possible pathway (left side, red line), the coordination reaction of deprotonated 2-amino(benzo)thiazoles with copper atom on species **A** might proceed to produce the intermediate **B**, followed by migratory insertion to generate the intermediate **C**, which can finally be converted to the product **D** with release of the Cu(I) catalyst.

Another possibility is that nucleophilic attack of 2-amino(benzo)thiazoles on **A** leads to the generation of intermediates **E** and **F**, the latter undergoing a proton transfer process to give the final product (right side, blue line).

## 3 | CONCLUSIONS

In summary, we have developed a practical and efficient Cu-catalyzed coupling reaction of 2-amino(benzo)thiazoles and aldehydes (ketones) with tosylhydrazide to construct C–N bonds. This reaction proceeded in a one-pot two-step process and afforded various *N*-alkylated (benzo)thiazoles with moderate to good yields. A wide range of substrates, the use of readily available reagents and gram-scale synthesis application were salient features of the presented protocol. Further research concerning biological evaluations of these synthesized compounds is ongoing in our laboratory.

## 4 | EXPERIMENTAL

### 4.1 | General information

$^{1}$H NMR and $^{13}$C NMR spectra were recorded with a Bruker Avance III HD 400 MHz spectrometer in DMSO-$d_6$ solution (Supporting information). High-resolution electrospray ionization mass spectra (HR-ESI-MS) were recorded using a Thermo Scientific LTQ Orbitrap XL equipped with an ESI probe operating in positive-ion mode with direct infusion. TLC analyses were performed on commercial glass plates bearing a 0.25 mm layer of Merck silica gel 60$F_{254}$. Silica gel (200–300 mesh) was used for column chromatocstrphy. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Solvents were freshly distilled prior to use. Chemical shifts for $^{1}$H NMR are expressed in parts per million (ppm) relative to tetramethylsilane (0.0 ppm). Chemical shifts for $^{13}$C NMR are expressed in ppm relative to DMSO-$d_6$ (39.52 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets), coupling constant (Hz) and intecstrtion. All reactions were carried out under air unless noted.

### 4.2 | General procedure for synthesis of *N*-alkylated (benzo)thiazoles

A mixture of aldehyde (ketone) (0.6 mmol) and tosylhydrazide (0.6 mmol) in 1,4-dioxane (4 ml) was stirred at 50°C for 2 h. Then, 2-amino(benzo)thiazole (0.4 mmol), CuI (15 mol%) and *t*-BuOLi (2.0 equiv.) were added. The resulting solution was then stirred vigorously at 100°C for another 3 h in a sealed vessel. After completion of the reaction (monitored by TLC), the contents were cooled to room temperature and diluted with dichloromethane (20 ml). The mixture was washed with brine (3 × 10 ml), dried over anhydrous $Na_2SO_4$, filtered and concentrated to give the crude product. The residue was then subjected to flash chromatocstrphy on silica gel (petroleum ether–ethyl acetate mixtures) to afford the target *N*-alkylated (benzo)thiazoles.

#### 4.2.1 | *N*-(4-Chlorobenzyl)benzo[*d*]thiazol-2-amine (3a)[19c]

Yield: 90.1 mg (82%). $^{1}$H NMR (400 MHz, $d_6$-DMSO) δ 8.54 (t, $J$ = 5.7 Hz, 1H), 7.68 (d, $J$ = 7.8 Hz, 1H), 7.45–7.33 (m, 5H), 7.22 (t, $J$ = 7.7 Hz, 1H), 7.03 (t, $J$ = 7.5 Hz, 1H), 4.59 (d, $J$ = 5.8 Hz, 2H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 166.6, 152.8, 138.6, 132.0, 130.9, 129.7, 128.8, 126.1, 121.6, 121.5, 118.6, 46.9.

#### 4.2.2 | *N*-(3-Chlorobenzyl)benzo[*d*]thiazol-2-amine (3b)[19e]

Yield: 93.4 mg (85%). $^{1}$H NMR (400 MHz, $d_6$-DMSO) δ 8.56 (t, $J$ = 5.6 Hz, 1H), 7.68 (d, $J$ = 7.8 Hz, 1H), 7.46–7.30 (m, 5H), 7.22 (t, $J$ = 7.6 Hz, 1H), 7.03 (t, $J$ = 7.5 Hz, 1H), 4.62 (d, $J$ = 5.7 Hz, 2H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 166.6, 152.7, 142.2, 133.5, 130.9, 130.8, 127.5, 127.4, 126.5, 126.1, 121.6, 121.5, 118.7, 46.9.

#### 4.2.3 | *N*-(2-Chlorobenzyl)benzo[*d*]thiazol-2-amine (3c)[19e]

Yield: 89 mg (81%). $^{1}$H NMR (400 MHz, $d_6$-DMSO) δ 8.54 (t, $J$ = 5.6 Hz, 1H), 7.69 (d, $J$ = 7.8 Hz, 1H), 7.48 (t, $J$ = 8.0 Hz, 2H), 7.39 (d, $J$ = 8.0 Hz, 1H), 7.35–7.31 (m, 2H), 7.22 (t, $J$ = 7.6 Hz, 1H), 7.03 (t, $J$ = 7.5 Hz, 1H), 4.67 (d, $J$ = 5.6 Hz, 2H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 166.4, 152.7, 136.4, 132.8, 130.9, 129.8, 129.5, 129.4, 127.8, 126.0, 121.6, 121.5, 118.7, 45.4.

#### 4.2.4 | *N*-(4-Fluorobenzyl)benzo[*d*]thiazol-2-amine (3d)[19c]

Yield: 72.3 mg (70%). $^{1}$H NMR (400 MHz, $d_6$-DMSO) δ 8.51 (t, $J$ = 5.6 Hz, 1H), 7.67 (d, $J$ = 7.8 Hz, 1H), 7.46–7.36 (m, 3H), 7.25–7.15 (m, 3H), 7.02 (t, $J$ = 7.5 Hz, 1H), 4.58 (d, $J$ = 5.7 Hz, 2H). $^{13}$C NMR (100 MHz, $d_6$-DMSO)

δ 166.6, 161.8 (d, $J_{CF}$ = 242.4 Hz), 152.9, 135.6 (d, $J_{CF}$ = 3.0 Hz), 130.9, 129.9 (d, $J_{CF}$ = 8.2 Hz), 126.0, 121.5, 121.4, 118.6, 115.6 (d, $J_{CF}$ = 21.3 Hz), 46.9.

### 4.2.5 | *N*-(4-Bromobenzyl)benzo[*d*]thiazol-2-amine (3e)[19c]

Yield: 97 mg (76%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 8.55 (t, *J* = 5.6 Hz, 1H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.46–7.33 (m, 5H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 4.59 (d, *J* = 5.8 Hz, 2H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 166.6, 152.8, 142.4, 131.1, 130.3, 126.9, 126.1, 122.2, 121.6, 121.5, 118.7, 46.9.

### 4.2.6 | *N*-(3-Bromobenzyl)benzo[*d*]thiazol-2-amine (3f)[19e]

Yield: 100.9 mg (79%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 8.55 (t, *J* = 5.4 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 7.7 Hz, 2H), 7.39–7.29 (m, 3H), 7.27–7.18 (m, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 4.57 (d, *J* = 5.5 Hz, 2H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 166.5, 152.7, 142.4, 131.1, 130.9, 130.4, 130.3, 126.9, 126.1, 122.2, 121.6, 121.5, 118.7, 46.9.

### 4.2.7 | *N*-(4-Methoxybenzyl)benzo[*d*]thiazol-2-amine (3g)[19c]

Yield: 97.3 mg (90%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 8.43 (s, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 8.5 Hz, 2H), 7.21 (t, *J* = 7.7 Hz, 1H), 7.01 (t, *J* = 7.9 Hz, 1H), 6.91 (d, *J* = 8.5 Hz, 2H), 4.51 (d, *J* = 5.5 Hz, 2H), 3.72 (s, 3H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 166.6, 158.9, 152.9, 131.2, 130.9, 129.3, 127.0, 126.0, 121.4, 118.5, 114.2, 55.5, 47.2.

### 4.2.8 | *N*-(2-Methylbenzyl)benzo[*d*]thiazol-2-amine (3h)[13a]

Yield: 87.5 mg (86%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 8.38 (s, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.36 (dd, *J* = 26.7, 7.2 Hz, 2H), 7.24–7.17 (m, 4H), 7.02 (t, *J* = 7.5 Hz, 1H), 4.58 (d, *J* = 4.6 Hz, 2H), 2.34 (s, 3H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 166.5, 152.9, 136.9, 136.4, 130.9, 130.5, 128.3, 127.7, 126.3, 126.0, 121.4, 118.5, 45.9, 19.1.

### 4.2.9 | *N*-(4-Methylbenzyl)benzo[*d*]thiazol-2-amine (3i)[19c]

Yield: 89.5 mg (88%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 8.46 (t, *J* = 5.5 Hz, 1H), 7.66 (d, *J* = 7.9 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.29–7.08 (m, 5H), 7.01 (t, *J* = 7.5 Hz, 1H), 4.54 (d, *J* = 5.6 Hz, 2H), 2.28 (s, 3H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 166.7, 152.9, 136.6, 136.3, 130.9, 129.4, 127.9, 127.0, 126.0, 121.4, 118.5, 47.4, 21.2.

### 4.2.10 | *N*-Benzylbenzo[*d*]thiazol-2-amine (3j)[19c]

Yield: 76.9 mg (80%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 8.53 (t, *J* = 5.4 Hz, 1H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.39–7.33 (m, 5H), 7.29–7.19 (m, 2H), 7.02 (t, *J* = 7.5 Hz, 1H), 4.60 (d, *J* = 5.7 Hz, 2H).$^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 166.6, 152.8, 138.6, 132.0, 130.9, 129.7, 128.8, 126.0, 121.5, 121.4, 118.6, 46.9.

### 4.2.11 | *N*-(Naphthalen-1-ylmethyl)benzo[*d*]thiazol-2-amine (3k)[19c]

Yield: 103.4 mg (89%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 8.59 (t, *J* = 4.5 Hz, 1H), 8.15 (d, *J* = 8.0 Hz, 1H), 7.98 (d, *J* = 7.7 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.63–7.54 (m, 3H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.44 (d, *J* = 7.9 Hz, 1H), 7.24 (t, *J* = 7.6 Hz, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 5.09 (d, *J* = 4.9 Hz, 2H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 166.5, 152.9, 134.5, 133.8, 131.5, 130.9, 129.0, 128.3, 126.9, 126.4, 126.1, 126.0, 125.9, 124.0, 121.5, 121.4, 118.6, 45.9.

### 4.2.12 | *N*-(Furan-2-ylmethyl)benzo[*d*]thiazol-2-amine (3l)[34]

Yield: 63.6 mg (69%). $^1$H NMR (400 MHz, v$d_6$-DMSO) δ 8.44 (t, *J* = 5.0 Hz, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.62 (d, *J* = 6.8 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.39 (d, *J* = 19.0 Hz, 2H), 4.58 (d, *J* = 5.3 Hz, 2H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 166.3, 152.7, 152.2, 142.9, 130.1, 126.0, 121.6, 121.5, 118.7, 111.0, 108.0, 54.9.

### 4.2.13 | *N*-(Thiophen-3-ylmethyl)benzo[*d*]thiazol-2-amine (3m)

Yield: 72.9 mg (74%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 8.43 (t, *J* = 4.9 Hz, 1H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.51–7.39 (m, 3H), 7.22 (t, *J* = 7.7 Hz, 1H), 7.14 (d, *J* = 4.8 Hz, 1H), 7.06–7.00 (m,, 1H), 4.58 (d, *J* = 5.3 Hz, 2H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 166.5, 152.9, 140.1, 130.9, 127.5, 126.9, 126.5, 126.0, 121.4, 121.3, 118.6, 43.2. HRMS (ESI) calcd for $C_{12}H_{10}N_2S_2$ [$MH^+$]: 247.0358; found: 247.0361.

#### 4.2.14 | *N*-Phenethylbenzo[*d*]thiazol-2-amine (3n)[19k]

Yield: 73.3 mg (72%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 8.09 (t, $J$ = 5.2 Hz, 1H), 7.65 (d, $J$ = 7.9 Hz, 1H), 7.39 (d, $J$ = 7.9 Hz, 1H), 7.33–7.25 (m, 4H), 7.23–7.19 (m, 2H), 7.01 (t, $J$ = 7.5 Hz, 1H), 3.62–3.57 (m, 2H), 2.92 (t, $J$ = 7.3 Hz, 2H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 166.4, 153.2, 139.8, 130.8, 129.2, 128.8, 126.6, 126.0, 121.4, 121.3, 118.5, 45.8, 35.1.

#### 4.2.15 | *N*-Butylbenzo[*d*]thiazol-2-amine (3o)[19k]

Yield: 43.7 mg (53%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 7.97 (t, $J$ = 5.1 Hz, 1H), 7.66 (d, $J$ = 8.3 Hz, 1H), 7.36 (d, $J$ = 7.8 Hz, 1H), 7.22–7.17 (m, 1H), 7.01–6.97 (m, 1H), 3.37–3.33 (m, 2H), 1.60–1.53 (m, 2H), 1.40–1.32 (m, 2H), 0.91 (t, $J$ = 7.4 Hz, 3H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 166.6, 153.2, 130.0, 125.9, 121.3, 121.2, 118.4, 44.1, 31.3, 20.1, 14.1.

#### 4.2.16 | *N*-Benzyl-4-methylbenzo[*d*]thiazol-2-amine (5a)[19f]

Yield: 71.2 mg (70%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 8.51 (s, 1H), 7.48 (d, $J$ = 7.7 Hz, 1H), 7.45–7.31 (m, 4H), 7.27 (t, $J$ = 7.0 Hz, 1H), 7.05 (d, $J$ = 7.2 Hz, 1H), 6.92 (t, $J$ = 7.5 Hz, 1H), 4.59 (d, $J$ = 5.4 Hz, 2H), 2.45 (s, 3H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 166.1, 151.9, 139.5, 130.3, 128.8, 128.1, 127.7, 127.5, 126.7, 121.3, 118.9, 47.9, 18.6.

#### 4.2.17 | *N*-Benzyl-6-methylbenzo[*d*]thiazol-2-amine (5b)[19c]

Yield: 83.4 mg (82%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 8.40 (t, $J$ = 5.8 Hz, 1H), 7.47 (s, 1H), 7.39–7.33 (m, 4H), 7.28–7.23 (m, 2H), 7.03 (d, $J$ = 8.1, 1H), 4.58 (d, $J$ = 5.8 Hz, 2H), 2.32 (s, 3H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 166.0, 150.8, 139.5, 130.9, 130.6, 128.8, 127.9, 127.5, 127.1, 121.4, 118.3, 47.7, 21.2.

#### 4.2.18 | *N*-Benzyl-6-methoxybenzo[*d*]thiazol-2-amine (5c)[19c]

Yield: 85.4 mg (79%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 8.29 (t, $J$ = 5.4 Hz, 1H), 7.39–7.23 (m, 7H), 6.82 (d, $J$ = 8.7 Hz, 1H), 4.56 (d, $J$ = 5.5 Hz, 2H), 3.73 (s, 3H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 165.1, 154.8, 146.9, 139.5, 131.9, 128.8, 127.8, 127.5, 118.9, 113.4, 106.0, 55.9, 47.6.

#### 4.2.19 | *N*-Benzyl-6-bromobenzo[*d*]thiazol-2-amine (5d)[15b]

Yield: 83 mg (65%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 8.64 (t, $J$ = 5.1 Hz, 1H), 7.92 (s, 1H), 7.39–7.29 (m, 7H), 4.59 (d, $J$ = 5.4 Hz, 2H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 167.3, 152.1, 139.1, 133.1, 131.4, 128.9, 127.9, 127.6, 123.9, 119.9, 112.8, 47.7.

#### 4.2.20 | *N*-(4-Chlorobenzyl)-6-methylbenzo[*d*]thiazol-2-amine (5e)[19f]

Yield: 93.6 mg (81%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 8.43 (t, $J$ = 5.8 Hz, 1H), 7.48 (s, 1H), 7.41–7.33 (m, 4H), 7.26 (d, $J$ = 8.1 Hz, 1H), 7.03 (d, $J$ = 8.1, 1H), 4.56 (d, $J$ = 5.9 Hz, 2H), 2.31 (s, 3H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 165.9, 150.7, 138.7, 132.0, 130.9, 130.7, 129.7, 128.8, 127.1, 121.4, 118.3, 46.9, 21.2.

#### 4.2.21 | *N*-(4-Chlorobenzyl)-6-fluorobenzo[*d*]thiazol-2-amine (5f)

Yield: 72.6 mg (62%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 8.53 (t, $J$ = 5.8 Hz, 1H), 7.62 (d, $J$ = 8.8, 1H), 7.41–7.33 (m, 5H), 7.08–7.03 (m, 1H), 4.58 (d, $J$ = 5.8 Hz, 2H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 166.5, 157.7 (d, $J_{CF}$ = 236.7 Hz), 149.5, 138.5, 132.1, 131.9 (d, $J_{CF}$ = 11.2 Hz), 129.7, 128.8, 119.1 (d, $J_{CF}$ = 8.8 Hz), 113.4 (d, $J_{CF}$ = 23.6 Hz), 108.4 (d, $J_{CF}$ = 27.2 Hz), 46.9. HRMS (ESI) calcd for $C_{14}H_{10}ClFN_2S$ [$MH^+$]: 293.0310; found: 293.0316.

#### 4.2.22 | *N*-(4-Chlorobenzyl)-6-chlorobenzo[*d*]thiazol-2-amine (5g)[19f]

Yield: 81.6 mg (66%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 8.66 (t, $J$ = 5.8 Hz, 1H), 7.82 (d, $J$ = 2.2 Hz, 1H), 7.40–7.33 (m, 5H), 7.25–7.22 (m, 1H), 4.59 (d, $J$ = 5.8 Hz, 2H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 167.2, 151.8, 138.3, 132.6, 132.1, 129.7, 128.8, 126.2, 125.3, 121.2, 119.5.46.9.

#### 4.2.23 | *N*-(4-Methoxybenzyl)-4-methylbenzo[*d*]thiazol-2-amine (5h)[19f]

Yield: 96.7 mg (85%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 8.43 (t, $J$ = 5.7 Hz, 1H), 7.48 (d, $J$ = 7.7 Hz, 1H), 7.34

(d, $J$ = 8.6 Hz, 2H), 7.05 (d, $J$ = 7.3 Hz, 1H), 6.95–6.88 (m, 3H), 4.49 (d, $J$ = 5.8 Hz, 2H), 3.73 (s, 3H), 2.45 (s, 3H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 165.9, 158.9, 151.8, 131.3, 130.3, 129.5, 127.7, 126.7, 121.2, 118.8, 114.2, 55.5, 47.4, 18.6.

### 4.2.24 | *N*-(4-Methoxybenzyl)-6-chlorobenzo[*d*]thiazol-2-amine (5i)[19f]

Yield: 91.4 mg (75%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 8.54 (t, $J$ = 5.6 Hz, 1H), 7.80 (d, $J$ = 6.0 Hz, 1H), 7.37–7.21 (m, 4H), 6.91 (d, $J$ = 8.6 Hz, 2H), 4.50 (d, $J$ = 5.6 Hz, 2H), 3.72 (s, 3H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 167.2, 158.9, 151.9, 132.6, 130.9, 129.3, 126.1, 125.1, 121.1, 119.4, 114.3, 55.4, 47.2.

### 4.2.25 | *N*-Benzylthiazol-2-amine (5j)[35]

Yield: 57 mg (75%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 8.05 (t, $J$ = 5.4 Hz, 1H), 7.33–7.30 (m, 4H), 7.26–7.23 (m, 1H), 7.00 (d, $J$ = 3.2 Hz, 1H), 6.61 (d, $J$ = 3.4 Hz, 1H), 4.43 (d, $J$ = 5.8 Hz, 2H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 169.5, 139.8, 139.2, 128.7, 127.8, 127.3, 106.8, 48.2.

### 4.2.26 | *N*-(4-Bromobenzyl)thiazol-2-amine (5k)

Yield: 94.7 mg (88%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 8.08 (t, $J$ = 5.8 Hz, 1H), 7.52 (d, $J$ = 8.4 Hz, 2H), 7.29 (d, $J$ = 8.4 Hz, 2H), 6.99 (d, $J$ = 3.6 Hz, 1H), 6.62 (d, $J$ = 3.6 Hz, 1H), 4.40 (d, $J$ = 5.9 Hz, 2H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 169.3, 139.4, 139.1, 131.6, 130.0, 120.3, 107.0, 47.4. HRMS (ESI) calcd for $C_{10}H_9BrN_2S$ [$MH^+$]: 268.9743; found: 268.9748.

### 4.2.27 | *N*-Benzyl-4-methylthiazol-2-amine (5l)

Yield: 62.1 mg (76%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 7.93 (t, $J$ = 5.8 Hz, 1H), 7.33 (d, $J$ = 4.4 Hz, 4H), 7.27–7.22 (m, 1H), 6.15 (s, 1H), 4.40 (d, $J$ = 5.9 Hz, 2H), 2.08 (s, 3H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 168.8, 148.2, 139.8, 128.7, 127.8, 127.3, 100.6, 48.1, 17.8. HRMS (ESI) calcd for $C_{11}H_{12}N_2S$ [$MH^+$]: 205.0794; found: 205.0797.

### 4.2.28 | *N*-Benzyl-5-methylthiazol-2-amine (5m)

Yield: 58 mg (71%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 7.82 (t, $J$ = 5.2 Hz, 1H), 7.32 (d, $J$ = 4.4 Hz, 4H), 7.26–7.21 (m, 1H), 6.65 (s, 1H), 4.38 (d, $J$ = 5.6 Hz, 2H), 2.18 (s, 3H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 168.0, 140.0, 135.9, 128.7, 127.8, 127.3, 119.9, 47.8, 12.1. HRMS (ESI) calcd for $C_{11}H_{12}N_2S$ [$MH^+$]: 205.0794; found: 205.0796.

### 4.2.29 | *N*-(4-Chlorobenzyl)-4-phenylthiazol-2-amine (5n)

Yield: 103.5 mg (86%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 8.20 (t, $J$ = 5.9 Hz, 1H), 7.81 (d, $J$ = 7.2 Hz, 2H), 7.44–7.34 (m, 6H), 7.25 (t, $J$ = 7.2 Hz, 1H), 7.07 (s, 1H), 4.50 (d, $J$ = 5.9 Hz, 2H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 168.6, 150.4, 138.9, 135.3, 131.9, 129.9, 128.9, 128.7, 127.8, 126.1, 101.8, 47.5. HRMS (ESI) calcd for $C_{16}H_{13}ClN_2S$ [$MH^+$]: 301.0561; found: 301.0568.

### 4.2.30 | *N*-(1-Phenylethyl)thiazol-2-amine (8a)

Yield: 62.1 mg (76%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 8.08 (d, $J$ = 7.4 Hz, 1H), 7.37–7.29 (m, 4H), 7.21 (t, $J$ = 7.2 Hz, 1H), 6.95 (s, 1H), 6.56 (s, 1H), 4.78–4.71 (m, 1H), 1.42 (d, $J$ = 6.9 Hz, 3H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 168.6, 145.4, 139.2, 128.7, 127.2, 126.5, 106.6, 54.4, 23.9. HRMS (ESI) calcd for $C_{11}H_{12}N_2S$ [$MH^+$]: 205.0794; found: 205.0797.

### 4.2.31 | *N*-(1-*o*-Tolylethyl)thiazol-2-amine (8b)

Yield: 64.6 mg (74%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 8.08 (d, $J$ = 7.4 Hz, 1H), 7.36 (d, $J$ = 7.6 Hz, 1H), 7.17–7.07 (m, 3H), 6.94 (d, $J$ = 3.6 Hz, 1H), 6.53 (d, $J$ = 3.6 Hz, 1H), 4.97–4.90 (m, 1H), 2.36 (s, 3H), 1.38 (d, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 168.6, 143.5, 139.2, 135.1, 130.5, 126.9, 126.6, 125.1, 106.5, 50.7, 22.5, 19.1. HRMS (ESI) calcd for $C_{12}H_{14}N_2S$ [$MH^+$]: 219.0950; found: 219.0953.

### 4.2.32 | *N*-(1-*p*-Tolylethyl)thiazol-2-amine (8c)

Yield: 74.2 mg (85%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 8.01 (d, $J$ = 7.5 Hz, 1H), 7.23 (d, $J$ = 8.0 Hz, 2H), 7.10 (d, $J$ = 8.0 Hz, 2H), 6.94 (d, $J$ = 3.6 Hz, 1H), 6.54 (d, $J$ = 3.6 Hz, 1H), 4.72–4.65 (m, 1H), 2.25 (s, 3H), 1.40 (d, $J$ = 6.9 Hz, 3H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 168.8, 142.3, 139.1, 136.2, 129.2, 126.4, 106.5, 54.2, 23.9, 21.1. HRMS (ESI) calcd for $C_{12}H_{14}N_2S$ [$MH^+$]: 219.0950; found: 219.0951.

#### 4.2.33 | *N*-(1-(2-Chlorophenyl)ethyl) thiazol-2-amine (8d)

Yield: 85 mg (89%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 8.23 (d, $J$ = 7.3 Hz, 1H), 7.47 (dd, $J$ = 7.7, 1.7 Hz, 1H), 7.40 (dd, $J$ = 7.9, 1.3 Hz, 1H), 7.33–7.29 (m, 1H), 7.26–7.22 (m, 1H), 6.94 (d, $J$ = 3.6 Hz, 1H), 6.58 (d, $J$ = 3.6 Hz, 1H), 5.13–5.06 (m, 1H), 1.40 (d, $J$ = 6.9 Hz, 3H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 168.3, 142.7, 139.3, 132.2, 129.7, 128.9, 128.0, 127.0, 107.0, 51.5, 22.2. HRMS (ESI) calcd for $C_{11}H_{11}ClN_2S$ [$MH^+$]: 239.0404; found: 239.0410.

#### 4.2.34 | *N*-(1-(3-Bromophenyl)ethyl) thiazol-2-amine (8e)

Yield: 101.9 mg (90%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 8.10 (d, $J$ = 4.8 Hz, 1H), 7.55 (s, 1H), 7.39 (dd, $J$ = 16.4, 7.8 Hz, 2H), 7.28 (t, $J$ = 7.8 Hz, 1H), 6.98 (s, 1H), 6.60 (s, 1H), 4.81–4.71 (m, 1H), 1.41 (d, $J$ = 6.9 Hz, 3H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 168.6, 148.5, 139.2, 130.9, 130.0, 129.2, 125.7, 122.2, 107.1, 53.9, 23.8. HRMS (ESI) calcd for $C_{11}H_{11}BrN_2S$ [$MH^+$]: 282.9899; found: 282.9903.

#### 4.2.35 | *N*-(1-(Naphthalen-1-yl)ethyl) thiazol-2-amine (8f)

Yield: 80.4 mg (79%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 8.25 (d, $J$ = 7.2 Hz, 1H), 8.19 (d, $J$ = 8.3 Hz, 1H), 7.94 (d, $J$ = 7.7 Hz, 1H), 7.81 (d, $J$ = 8.1 Hz, 1H), 7.60–7.45 (m, 4H), 6.92 (d, $J$ = 3.6 Hz, 1H), 6.54 (d, $J$ = 3.6 Hz, 1H), 5.64–5.58 (m, 1H), 1.56 (d, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 168.5, 141.0, 139.1, 133.9, 131.0, 129.2, 127.7, 126.6, 126.0, 123.5, 122.6, 122.5, 106.6, 50.6, 22.9. HRMS (ESI) calcd for $C_{15}H_{14}N_2S$ [$MH^+$]: 255.0950; found: 255.0957.

#### 4.2.36 | *N*-(1-(Naphthalen-2-yl)ethyl) thiazol-2-amine (8g)

Yield: 89.5 mg (88%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 8.18 (d, $J$ = 7.4 Hz, 1H), 7.88–7.84 (m, 4H), 7.56–7.45 (m, 3H), 6.94 (d, $J$ = 3.6 Hz, 1H), 6.55 (d, $J$ = 3.6 Hz, 1H), 4.95–4.88 (m, 1H), 1.52 (d, $J$ = 6.9 Hz, 3H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 168.6, 142.9, 139.2, 133.3, 132.6, 128.4, 128.1, 127.9, 126.6, 126.1, 125.2, 124.8, 106.7, 54.6, 23.8. HRMS (ESI) calcd for $C_{15}H_{14}N_2S$ [$MH^+$]: 255.0950; found: 255.0956.

#### 4.2.37 | 4-Methyl-*N*-(1-phenylethyl) thiazol-2-amine (8h)

Yield: 70.7 mg (81%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 7.96 (d, $J$ = 7.7 Hz, 1H), 7.37–7.29 (m, 4H), 7.23–7.19 (m, 1H), 6.10 (s, 1H), 4.75–4.68 (m, 1H), 2.04 (s, 3H), 1.41 (d, $J$ = 6.9 Hz, 3H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 168.0, 148.1, 145.3, 128.7, 127.2, 126.5, 100.5, 54.3, 23.9, 17.8. HRMS (ESI) calcd for $C_{12}H_{14}N_2S$ [$MH^+$]: 219.0950; found: 219.0953.

#### 4.2.38 | 4-Methyl-*N*-(1-*p*-tolylethyl)thiazol-2-amine (8i)

Yield: 69.7 mg (75%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 7.91 (d, $J$ = 7.5 Hz, 1H), 7.23 (d, $J$ = 8.0 Hz, 2H), 7.11 (d, $J$ = 8.0 Hz, 2H), 6.09 (s, 1H), 4.69–4.62 (m, 1H), 2.26 (s, 3H), 2.03 (s, 3H), 1.39 (d, $J$ = 6.9 Hz, 3H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 168.1, 148.0, 142.2, 136.2, 129.3, 126.4, 100.5, 54.1, 23.9, 21.1, 17.7. HRMS (ESI) calcd for $C_{13}H_{16}N_2S$ [$MH^+$]: 233.1107; found: 233.1111.

#### 4.2.39 | *N*-(1-(3-Bromophenyl)ethyl)-4-methylthiazol-2-amine (8j)

Yield: 95.1 mg (80%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 8.00 (d, $J$ = 7.8 Hz, 1H), 7.56 (s, 1H), 7.42–7.36 (m, 2H), 7.28 (t, $J$ = 7.8 Hz, 1H), 6.13 (s, 1H), 4.77–4.70 (m, 1H), 2.04 (s, 3H), 1.40 (d, $J$ = 6.9 Hz, 3H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 167.8, 148.3, 148.1, 130.9, 130.1, 129.2, 125.8, 122.2, 100.9, 53.8, 23.9, 17.7. HRMS (ESI) calcd for $C_{12}H_{13}BrN_2S$ [$MH^+$]: 297.0056; found: 297.0061.

#### 4.2.40 | 5-Methyl-*N*-(1-phenylethyl) thiazol-2-amine (8k)

Yield: 62.9 mg (72%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 7.82 (s, 1H), 7.35–7.28 (m, 4H), 7.20 (t, $J$ = 7.0 Hz, 1H), 6.65 (s, 1H), 4.69 (d, $J$ = 5.6 Hz, 1H), 2.15 (s, 3H), 1.40 (d, $J$ = 6.7 Hz, 3H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 167.9, 145.5, 136.0, 128.7, 127.1, 126.5, 119.5, 54.0, 24.0, 12.1. HRMS (ESI) calcd for $C_{12}H_{14}N_2S$ [$MH^+$]: 219.0950; found: 219.0956.

#### 4.2.41 | 5-Methyl-*N*-(1-*o*-tolylethyl)thiazol-2-amine (8l)

Yield: 61.3 mg (66%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 7.83 (d, $J$ = 6.7 Hz, 1H), 7.35 (d, $J$ = 7.5 Hz, 1H), 7.16–7.06 (m, 3H), 6.59 (s, 1H), 4.91–4.84 (m, 1H), 2.34 (s, 3H), 2.14 (s, 3H), 1.35 (d, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 169.6, 143.6, 135.1, 130.5, 128.7, 126.9, 126.6, 125.1, 121.2, 50.4, 22.5, 19.1, 12.0. HRMS (ESI) calcd for $C_{13}H_{16}N_2S$ [$MH^+$]: 233.1107; found: 233.1111.

### 4.2.42 | 5-Methyl-*N*-(1-*p*-tolylethyl)thiazol-2-amine (8m)

Yield: 58.5 mg (63%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 7.76 (d, $J$ = 6.9 Hz, 1H), 7.22 (d, $J$ = 8.0 Hz, 2H), 7.10 (d, $J$ = 8.0 Hz, 2H), 6.59 (s, 1H), 4.67–4.60 (m, 1H), 2.25 (s, 3H), 2.14 (s, 3H), 1.37 (d, $J$ = 6.9 Hz, 3H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 167.3, 142.5, 136.1, 135.9, 129.2, 126.4, 119.7, 53.9, 24.0, 21.1, 12.0. HRMS (ESI) calcd for $C_{13}H_{16}N_2S$ [$MH^+$]: 233.1107; found: 233.1111.

### 4.2.43 | *N*-(1-(2-Chlorophenyl)ethyl)-5-methylthiazol-2-amine (8n)

Yield: 80.9 mg (80%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 7.99 (d, $J$ = 7.1 Hz, 1H), 7.46 (dd, $J$ = 7.7, 1.5 Hz, 1H), 7.39 (dd, $J$ = 7.8, 1.2 Hz, 1H), 7.31 (td, $J$ = 7.5, 1.1 Hz, 1H), 7.23 (td, $J$ = 7.6, 1.7 Hz, 1H), 6.59 (s, 1H), 5.07–5.00 (m, 1H), 2.15 (s, 3H), 1.38 (d, $J$ = 6.9 Hz, 3H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 166.8, 142.8, 136.2, 132.2, 129.7, 128.8, 127.9, 127.0, 120.3, 51.1, 22.2, 12.0. HRMS (ESI) calcd for $C_{12}H_{13}ClN_2S$ [$MH^+$]: 253.0561; found: 253.0564.

### 4.2.44 | *N*-(1-(3-Bromophenyl)ethyl)-5-methylthiazol-2-amine (8o)

Yield: 79.7 mg (67%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 7.86 (d, $J$ = 7.3 Hz, 1H), 7.53 (s, 1H), 7.40 (d, $J$ = 7.8 Hz, 1H), 7.34 (d, $J$ = 7.8 Hz, 1H), 7.27 (t, $J$ = 7.7 Hz, 1H), 6.60 (s, 1H), 4.75–4.68 (m, 1H), 2.16 (s, 3H), 1.38 (d, $J$ = 6.9 Hz, 3H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 167.0, 148.7, 136.0, 131.0, 129.9, 129.1, 125.7, 122.1, 120.2, 53.5, 23.9, 12.0. HRMS (ESI) calcd for $C_{12}H_{13}BrN_2S$ [$MH^+$]: 297.0056; found: 297.0061.

### 4.2.45 | *N*-Cyclohexylthiazol-2-amine (8p)[36]

Yield: 50.3 mg (69%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 7.42 (d, $J$ = 7.3 Hz, 1H), 6.96 (d, $J$ = 3.6 Hz, 1H), 6.54 (d, $J$ = 3.6 Hz, 1H), 3.45–3.39 (m, 1H), 1.92 (d, $J$ = 11.4 Hz, 2H), 1.72–1.65 (m, 2H), 1.58–1.54 (m, 1H), 1.31–1.15 (m, 5H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 168.6, 139.2, 105.9, 53.7, 32.8, 25.8, 24.9.

### 4.2.46 | *N*-Phenethyl-4-phenylthiazol-2-amine (II)

Yield: 1.11 g (66%). $^1$H NMR (400 MHz, $d_6$-DMSO) δ 7.84 (d, $J$ = 7.4 Hz, 2H), 7.76 (t, $J$ = 5.4 Hz, 1H), 7.40–7.20 (m, 8H), 7.05 (s, 1H), 3.54–3.46 (m, 2H), 2.92 (t, $J$ = 7.4 Hz, 2H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 168.6, 150.5, 139.9, 135.4, 129.2, 128.9, 128.8, 127.7, 126.6, 126.1, 101.3, 46.6, 35.2. HRMS (ESI) calcd for $C_{17}H_{16}N_2S$ [$MH^+$]: 281.1107; found: 281.1112.

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## ORCID

*Zengyang Xie* https://orcid.org/0000-0002-4152-1561

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## SUPPORTING INFORMATION

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