Note

Sodium Hydroxide Catalysed N–Alkylation of (Hetero)Aromatic Primary Amines and N1, C5- Dialkylation of 4-Phenyl -2- aminothiazoles with Benzyl Alcohols

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Sodium Hydroxide Catalysed *N*-Alkylation of (Hetero) Aromatic Primary Amines and N_1, C_5 - Dialkylation of 4-phenyl -2-aminothiazoles with Benzyl Alcohols

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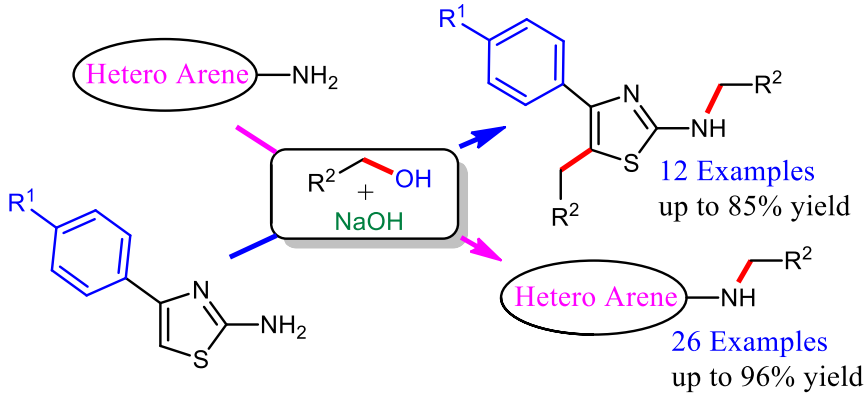


Abstract.

In the presence of catalytic amount of NaOH, the selective *N*-alkylation of various heteroaromatic primary amines is reported. With one equivalent of NaOH, N_1, C_5-dialkylation of 4-phenyl-2-aminothiazoles has been investigated. Reaction of *in-situ* generated aldehyde with amine yields the *N*-alkylated and N_1, C_5-dialkylated products through hydride ion transformation from alcohol.

The C–N bond forming reactions has attracted enormously over the last two decades and find its application in all areas of organic chemistry, ranging from the laboratory bench, to the synthesis of pharmaceutical fine chemicals and the production of bulk chemicals.[1-4] Among the C–N bond forming reactions the *N*-alkylation of primary amines is an important

due to tremendous utility of these amines in industries for the synthesis of dyes, additives, agrochemicals, functional materials and pharmacophores for the synthesis of bioactive molecules.[5-8] Arguably, the direct *N*-alkylation of amines with alcohols is most desirable, due to the ready and inexpensive availability of wide range of alcohols and theoretically produces only water as a by-product. In this regard many groups have achieved *N*-alkylation of amines with alcohols using transition metal/metal complexes as catalysts through borrowing hydrogen methodology.[9] Beside all these recent advancements, major drawbacks of these methods are requirement of transition metal catalysts to promote this transformation efficiently. Thus, transition metal separation from organic products is of particular importance for the synthesis of pharmaceutical fine chemicals because of their residual toxicity in the target compounds is a central issue to consider, hence the development of more improved synthetic routes without transition metal is desirable. Although transition metal-free *N*-alkylation of amines with alcohols were known but reactions demand harsh conditions such as high temperature (250-300 °C), high pressure, very long reaction time (10 days), strong basic conditions, and large excess of alcohols or amines, consequently low yields and poor selectivities were reported.[10-16] Very recently Qing Xu and co-workers reported the transition metal-free *N*-alkylation of sulphonamides and aromatic amines in presence of base (10-100 mol%) and external addition of catalytic amount of aldehyde.[17]

Recently, we have reported the transition metal-free imine synthesis through activation of alcohol by base in presence of amines.[18,19] In continuation of our efforts to explore C–N bond forming reactions,[20-24] we sought to investigate the direct *N*-alkylation of hetero aromatic primary amines with alcohols using NaOH as catalyst (20 mol%) under transition metal-free conditions.

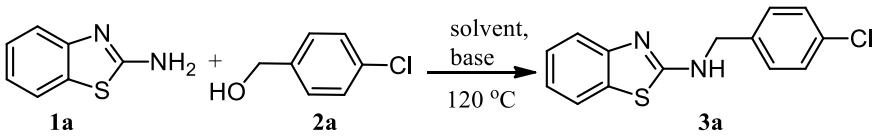
2-Aminobenzothiazoles and thiazoles are versatile synthetic intermediates and are widely used in the synthesis of various biologically active compounds.[25-30] Particularly, *N*-

alkylated thiazoles and benzothiazoles exhibit different pharmacological and physiological activities.[31,32] As a result, much attention has been paid for the synthesis of these compounds.[33-39] By considering the importance of 2-aminobenzothiazole derivatives, we investigated herewith the *N*-alkylation of 2-amino benzothiazoles and the method has been extended to other heteroaromatic amines including pyridine, pyrimidine and pyrazines with various alcohols. Under these conditions we found the N_1, C_5-dialkylation of 4-phenyl-2-aminothiazoles and there were no reports found for this type of transformation.

At the start of our studies, we investigated the *N*-alkylation of 2-aminobenzothiazole **1a** with 4-chloro benzyl alcohol **2a** as alkylating agent and results are illustrated in Table 1. In the presence of NaOH in toluene at room temperature no product **3a** was formed (Table 1, entry 1). When the reaction is performed at 100 ^{o}C, the *N*-alkylated product was observed with 80% GC-yield (Table 1, entry 2). Conversion reached to 100% (93% isolated), when the reaction temperature was increased to 120 ^{o}C (Table 1, entry 3). However, the reaction does not proceed efficiently in other solvent system (Table 1, entries 4-8). Alternately, screening of different bases (KOH, Na_2CO_3, K_2CO_3, KO^{t}Bu, and NaO^{t}Bu) was performed (Table 1, entries 9-13). After extensive screening of various bases and solvents, NaOH showed good activity and selectivity in toluene at 120 ^{o}C and the similar yield (93%) was observed even with 20 mol% of NaOH (Table 1, entry 14), reaction completely retarded in absence of NaOH (table 1 entry 15). To rule out the catalytic activity of trace impurities of transition metals in commercially available NaOH, two experiments were performed using pure Na metal and NaH (Table 1, entries 16 and 17). These species also provided similar yield and selectivity of the product for the present transformation. These facts supports that, the role of catalytic activity of trace metal impurities from the commercial NaOH is less probable. To examine the role of oxygen, the reaction was performed under nitrogen atmosphere, it was also provided 90% isolated yield of **3a** (Table 1, entry 18). Further, **2a** was subjected to

oxidation in absence of amine under open and nitrogen atmosphere, only 2% and 1% yield of aldehyde was observed respectively (Table 1, entries 19 and 20). Oxidation under nitrogen atmosphere may be due to the presence of trace amount of oxygen from the commercial cylinder. These reactions clearly indicate that, the *in-situ* generated catalytic aldehyde is responsible for the current transformation.

Table 1. Optimization of reaction conditions for **3a**[a]



1a **2a** **3a**

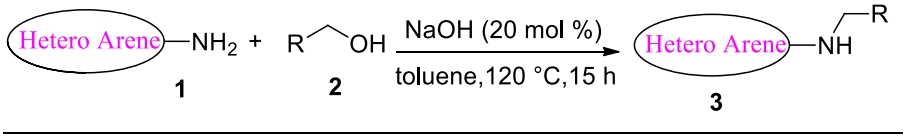
entry	base	solvent	yield (%)[b]
1[c]	NaOH	toluene	---
2[d]	NaOH	toluene	80
3	NaOH	toluene	100(93)
4	NaOH	DMF	---
5	NaOH	DMSO	---
6	NaOH	H_2O	---
7	NaOH	glycerol	---
8	NaOH	chloro benzene	70
9	KOH	toluene	85
10	Na_2CO_3	toluene	---
11	K_2CO_3	toluene	30
12	NaO^tBu	toluene	87
13	KO^tBu	toluene	95
14[e]	**NaOH**	**toluene**	**100(93)**
15	---	toluene	---
16	Na metal	toluene	100
17	NaH	toluene	100
18[f]	NaOH	toluene	100(90)
19[e,g]	NaOH	toluene	2
20[e,f,g]	NaOH	toluene	1

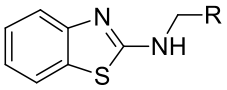
[a]Reaction conditions unless otherwise stated: **1a** (1.0 mmol), **2a** (1.2 mmol), base (1.0 mmol), solvent (1.0 mL), 120 °C, 15 h, under atmospheric air. [b]GC yields. [c]Room temperature. [d]100 °C. [e]NaOH 20 mol %. [f]Nitrogen atmosphere. [g]Without **1a** yield refers to corresponding aldehyde (See figs. **S2-S6** in supporting information for entries 19 and 20). Numbers in parenthesis are isolated yield.

The scope of the reaction was then investigated with 2-aminobenzothiazoles and benzyl alcohols as alkylating agents (Table 2). Under these optimized conditions, various substituted benzyl alcohols reacted with 2-aminobenzothiazole to yield the corresponding *N*-alkylated

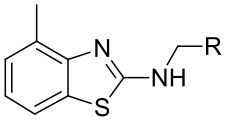
products in good yield. Benzyl alcohols having electron donating (methyl or methoxy) groups transformed into *N*-alkylated 2-aminobenzothiazoles in high yield (**3b-d**). Electronic effects associated with electron- withdrawing substituents (Cl, Br) on the phenyl ring (either o/m/p) does not affect the efficiency of the *N*-alkylation of 2-aminobenzothiazole (**3e-g**).

Table 2. *N*-Alkylation of various hetero amines with benzyl alcohols[a]

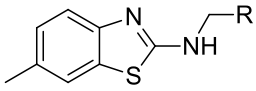




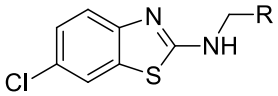
3b, R = 4-MeC_6H_4; 94%
3c, R = 4-$OMeC_6H_4$; 96%
3d, R = 3-$OMeC_6H_4$; 91%
3e, R = 2-ClC_6H_4; 80%
3f, R = 3-ClC_6H_4; 94%
3g, R = 4-BrC_6H_4; 94%
3h, R = Ph; 96%
3i, R = 3-pyridinyl; 93%



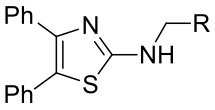
3j, R = 4-$OMeC_6H_4$; 91%
3k, R = Ph; 87%



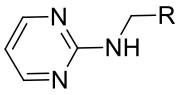
3l, R = Ph; 90%
3m, R = 4-ClC_6H_4; 83%



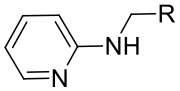
3n, R = 4-ClC_6H_4; 90%
3o, R = 4-$OMeC_6H_4$; 82%
3p, R = Ph; 89%



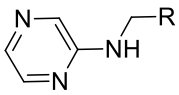
3q, R = Ph; 85%
3r, R = 4-ClC_6H_4; 80%



3s, R = Ph; 91%
3t, R = 4-MeC_6H_4; 90%
3u, R = 4-ClC_6H_4; 93%



3v, R = Ph; 90%
3w, R = 4-MeC_6H_4; 92%



3x, R = Ph; 92%
3y, R = 4-MeC_6H_4; 90%
3z, R = 4-ClC_6H_4; 91%

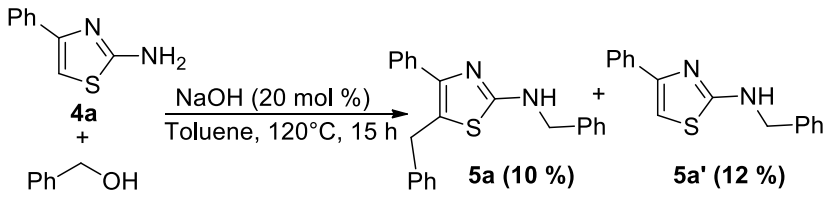
[a]Reaction conditions unless otherwise stated: amine (1 mmol), alcohol (1.2 mmol), NaOH (20 mol %), toluene (1 mL), 120° C, 15 h; isolated yield.

Unsubstituted benzylic alcohol and hetero benzylic alcohol (pyridin-3-ylmethanol) too provided the desired products in excellent yield (**3h**, **3i**). The *N*-alkylation of different substituted 2-aminobenzothiazoles was then studied. *N*-Alkylation of 2-aminobenzothiazoles bearing electron releasing (Me) and electron withdrawing (halogen) groups afforded the

corresponding *N*-alkylated products in 82-91% yield (**3j-p**). Remarkably 4, 5-diphenyl 2-aminothiazole was also given required products in good yields (**3q, 3r**). Notably the products (**3a-r**) were purified without column chromatography (See the typical procedure). Further we have extended the present transformation to other hetero aromatic amines such as 2-amino pyrimidine, 2-amino pyridine and amino pyrazine. These heterocyclic amines also afford good to excellent yields of *N*-alkylated products (**3s-3z**) irrespective of alcohols under the optimised conditions. No desired products were observed with other alcohols such as cyclohexanol, *n*-heptanol, 3-methylbut-2-en-1-ol and cinnamyl alcohol.

Having developed a synthetic method for *N*-alkylation of heteroamines, we finally explored the current concise transformation for dialkylation of **4a** (Scheme 1). The optimized conditions of table 2, were applied to **4a**, with benzyl alcohol as alkylating agent, a mixture

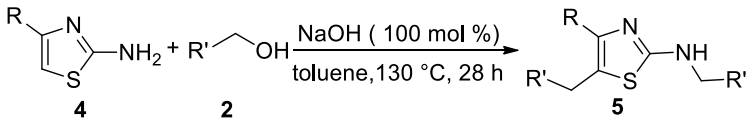
Scheme 1.

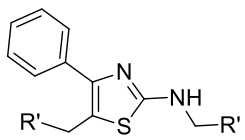


of di- and mono-alkylated products **5a** and **5a'** were obtained. Under these conditions, the formation of dialkylated product **5a** was quite interesting, and no such reports exist in literature. Hence we became interested to investigate the conditions for selective formation of a single dialkylated product **5a**. The identified conditions for this transformation were three equivalents of benzyl alcohol, one equivalent amine **4a** at 130 ^{o}C in toluene and 28 h of reaction time. These revised optimum conditions were applied to explore the synthesis of N_1, C_5-dialkyl-4-phenylthiazol-2-amines (**Table 3**). It was found that N_1, C_5-dialkylation of **4a** proceeded smoothly with benzylic alcohols having electron-releasing and withdrawing substituents (**2a-c**) to give corresponding products (**5a-c)** in good yields. Similarly, the

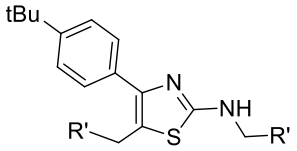
presence of electron-releasing/withdrawing groups on 4-phenylthiazol-2-amines afforded the corresponding dialkylated products (**5d-l**) in good yields with irrespective of benzylic alcohols. Under these conditions dialkylation of unsubstituted 2-aminothiazole was not observed as it undergoes charring. The formation of **5h** was further confirmed by single-crystal XRD (See Fig S1).

Table 3. N_1, C_5-Dialkylation of 4-phenyl 2-aminothiazoles with various alcohols[a]

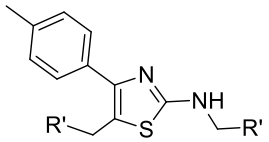




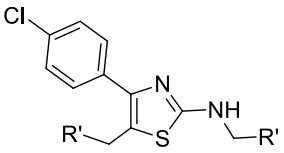
5a, R' = Ph; 81%
5b, R' = 4-$MeOC_6H_4$;78%
5c, R' = 4-ClC_6H_4; 82%



5d, R' = Ph; 83%
5e, R' = 4-MeC_6H_4 ; 80%
5f, R' = 4-$MeOC_6H_4$; 80%
5g, R' = 4-ClC_6H_4; 81%
5h, R' = 2-ClC_6H_4; 85%



5i, R' = Ph; 80%
5j, R' = 2-ClC_6H_4; 81%

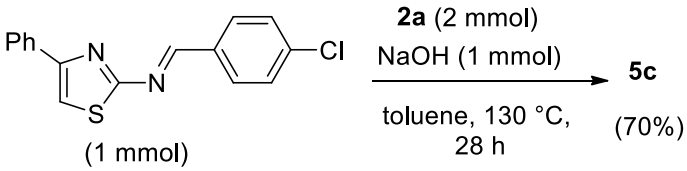


5k[b], R' = Ph; 80%
5l[b], R' = 2-ClC_6H_4; 82%

[a]Reaction conditions unless otherwise stated: amine **4** (1 mmol), alcohol **2** (3 mmol), NaOH (1.0 mmol), toluene (1 mL), 130 °C, 28 h; Isolated yield. [b]Reaction time 36 h.

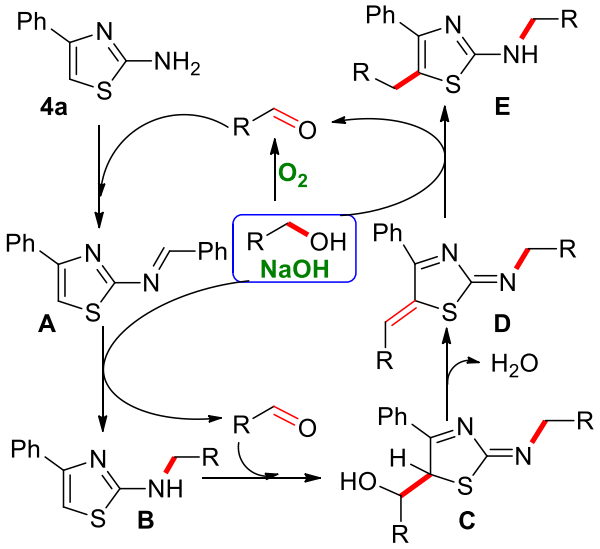
The formation of di alkylated product may be due to the electron rich nature of five membered thiazole compared to six membered pyridine, pyrimidine and pyrazine systems. The substitution of phenyl ring at C_4 may further increase the electron density on C_5 of **4a.** Further to confirm the current transformation we performed reaction starting from imine (Scheme 2), under the same reaction conditions, 70% of dialkylated product **5c** was isolated

Scheme 2. Mechanistic experiment



along with 68% of 4-chloro benzoic acid after work-up. Based on the above experimental evidence and previous reports,[17–19] we proposed a plausible mechanism (Scheme 3). Initially, alcohol was partly oxidised to aldehyde in presence of NaOH and air as an oxidant.[40,41] The reaction of aldehyde and amine **4a** generate imine intermediate **A**. In presence of base, dehydrogenation of alcohol with simultaneous hydrogenation of imine lead to aldehyde and *N*-alkylated product **B** respectively. Nucleophilic addition of **B** to aldehyde may form iminoalcohol **C**, and its dehydration gives another intermediate **D**. Through hydride ion transfer process, it provides the final product **E**.

Scheme 3. Possible mechanism for the N_1, C_5-dialkylation of 4-phenyl 2-aminothiazole.



In summary, we have developed a novel method for *N*-alkylation of hetero amines with benzylic alcohols as alkylating agents in presence of catalytic NaOH under mild conditions. Reaction of 4-phenylthiazol-2-amines with benzyl alcohols gave N_1, C_5-dibenzyl-4-phenylthiazol-2-amines in good yields with one equivalent of NaOH. Compared to previously known transition metal catalysts, NaOH is inexpensive, readily available, convenient to use

without any special precautions. The method is applicable for a wide range of benzylic alcohols as alkylating agents.

EXPERIMENTAL SECTION

General: All commercially available chemicals and reagents were used without any further purification unless otherwise indicated. ^{1}H and ^{13}C NMR spectra were recorded at 500/200, and 125/50 MHz, respectively. The spectra were recorded in DMSO as solvent. Multiplicity was indicated as follows: s (singlet); d (doublet); t (triplet); m (multiplet); dd (doublet of doublets), etc. Coupling constants (J) were given in Hz. Chemical shifts are reported in δ relative to TMS as an internal standard. The peaks around δ values of ^{1}H NMR (2.5), ^{13}C NMR (39.4) are correspond to deuterated DMSO and δ value (3.3) in ^{1}H NMR is of water. Progress of the reactions was monitored by thin layer chromatography (TLC). Silica gel 100-200 mesh size was used for column chromatography.

Typical procedure for synthesis of (3a): In a 25 mL round bottomed flask, 150 mg (1.0 mmol) of 2-amino benzothiazole (**1a),** 171 mg (1.2 mmol) of 4-chloro benzyl alcohol (**2a)**, 8 mg (0.2 mmol) of sodium hydroxide (NaOH) and 1.0 mL of toluene were placed. The reaction flask was heated at 120 °C for 15 h in an oil bath. After completion of the reaction, the flask allowed to attaining room temperature, and toluene was removed under reduced pressure. To the residue 20 mL of water was added, stirred for 5 min on magnetic stirrer at room temperature and the solid was collected through filtration and washed with 10% ethyl acetate in hexane (10 mL) solution to get white solid in 93% yield (255 mg; 0.93 mmol) of **3a**. [**Note:** The products (**3a-r**) obtained were pure (by NMR analysis) without separation by column chromatography, but by simple solvent wash. The products obtained from liquid and solid benzylic alcohols were washed with only hexane and ethylacetate/hexane (1:9)

respectively. Products **3s–z** were purified by column chromatography (the eluent for products **3s-3w** (9:1) and for the products **3x-3z** (7:3) ethylacetate/hexane).

Charecteristion data of all compounds:

N-(4-chlorobenzyl)benzo[d]thiazol-2-amine (3a)[33]:

Yield 93% (255 mg); ^{1}H NMR (500 MHz, DMSO): δ 4.58(d, *J* = 6 Hz, 2H), 7.03(t, *J* = 7.5 Hz, 1H),7.22 (t, *J* = 7.5 Hz, 1H), 7.38 – 7.40 (m, 5H), 7.66 (d, *J* = 7.5 Hz , 1H) 8.54 (t, *J* = 6 Hz, 1H); ^{13}C NMR (125 MHz, DMSO): 46.8, 118.5,121.3, 121.5, 126.0, 128.7, 129.6, 130.8, 131.9, 138.4, 152.7, 166.5.

N-(4-methylbenzyl)benzo[d]thiazol-2-amine (3b)[33] :

Yield 94% (239 mg); ^{1}H NMR (500 MHz, DMSO): δ 2.27 (s, 3H), 4.54 (d, *J* = 5 Hz, 2H), 7.02 (t, *J* = 7.5 Hz, 1H), 7.14 (d, *J* = 8, 2H), 7.22 (t, *J* = 8 Hz, 1H), 7.26 (d, *J* = 8 Hz, 2H), 7.38 (d, *J* = 8, 1H), 7.65 (d, *J* = 8 Hz, 1H), 8.47 (t, *J* = 5, 1H) ; ^{13}C NMR (125 MHz, DMSO): 23.0, 49.3, 120.4, 123.2, 127.8, 129.7, 131.2, 132.7, 138.1, 138.4, 154.8, 168.5.

N-(4-methoxybenzyl)benzo[d]thiazol-2-amine (3c)[33] :

Yield 96% (259 mg); ^{1}H NMR (500 MHz, DMSO): δ 3.72 (s, 3H), 4.51 (d, *J* = 5 Hz, 2H), 6.89 (d, *J* = 7 Hz, 2H), 7.01 (t, *J* = 7.5 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.30 (d, *J* = 7.5 Hz, 2H), 7.38 (d, *J* = 8 Hz, 1H), 7.65 (d, *J* = 8 Hz, 1H), 8.42(s, 1H) ; ^{13}C NMR (125 MHz, DMSO): 49.0, 57.3, 116.1, 120.3, 123.2, 127.8, 131.1, 132.7, 133.1, 154.8, 160.7, 168.4.

N-(3-methoxybenzyl)benzo[d]thiazol-2-amine (3d):

Yield 91% (246 mg); ^{1}H NMR (500 MHz, DMSO): δ 3.73 (s, 3H), 4.56 (d, *J* = 5.5 Hz, 2H), 6.82 (d, *J* = 8 Hz, 1H), 6.94 (d, *J* = 6.5 Hz, 2H), 7.02 (t, *J* = 7.5 1H), 7.20 – 7.27 (m, 2H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.66 (d, *J* = 7.5 Hz, 1H), 8.49 (t, *J* = 5.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO): 47.1, 54.9, 112.2, 112.9, 118.0, 119.4, 120.8, 125.4, 129.3, 130.3, 140.4, 152.34, 159.2, 166.1; IR(KBr): 672, 751, 796, 978, 1043, 1163, 1264, 1342, 1451, 1566, 1612, 2896, 3464; HRMS calcd for $C_{15}H_{15}N_2OS$: 271.0906, found: 271.0934.

N-(2-chlorobenzyl)benzo[d]thiazol-2-amine (3e)[33] :

Yield 80% (219 mg); ^{1}H NMR (500 MHz, DMSO): δ 4.67 (d, *J* = 5.5 Hz, 2H), 7.03 (t, *J* = 7.5 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.30 – 7.35 (m, 2H), 7.38 (d, *J* = 8.0 Hz , 1H), 7.47 (s, 2H), 7.67 (d, *J* = 7.5 Hz, 1H), 8.53 (s, 1H) ; ^{13}C NMR (125 MHz, DMSO): 47.3, 120.5, 123.3, 123.4, 127.8, 129.5, 131.2, 131.4, 131.5, 132.8, 134.6, 138.2, 154.6, 168.3.

N-(3-chlorobenzyl)benzo[d]thiazol-2-amine (3f):

Yield 94% (257 mg); ^{1}H NMR (500 MHz, DMSO): δ 4.60 (d, *J* = 6 Hz, 2H), 7.04 (t, *J* = 7.5 Hz, 1H), 7.23 (t, *J* = 7 Hz, 1H),7.33 (t, *J* = 8.5 Hz, 2H), 7.37 – 7.40 (m, 2H), 7.42 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 1H); 8.56 (t, *J* = 6Hz, 1H); ^{13}C NMR (125 MHz, DMSO): 46.9, 118.6, 121.4, 126.0, 126.4, 127.4, 127.5, 130.7, 130.8, 133.5, 142.1, 152.7, 166.6; IR(KBr): 677, 755, 865, 975, 1075, 1116, 1221, 1261, 1339, 1446, 1566, 1609, 2899, 2981, 3086, 3137, 3179, 3473. HRMS calcd for $C_{14}H_{12}ClN_2S$: 275.041, found: 275.0412.

N-(4-bromobenzyl)benzo[d]thiazol-2-amine (3g)[33] :

Yield 94% (300 mg); ^{1}H NMR (500 MHz, DMSO): δ 4.56 (d, *J* = 5.5 Hz, 2H), 7.02 (t, *J* = 7.5 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.33 (d, *J* = 8Hz, 2H), 7.37 (d, *J* = 8Hz , 1H), 7.53 (d, *J* = 8 Hz, 2H), 7.66 (d, *J* = 7.5 Hz, 1H), 8.53 (t, *J* = 5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO); 48.7, 120.5, 122.3, 123.3, 123.3, 127.8, 131.8, 132.7, 133.5, 140.8, 154.6, 168.4.

N-benzylbenzo[d]thiazol-2-amine (3h)[33]:

Yield 96% (230 mg); ^{1}H NMR (500 MHz, DMSO): δ 4.60 (d, *J* = 5.5 Hz, 2H), 7.02 (t, *J* = 7.5 Hz, 1H), 7.20 – 7.27 (m, 2H), 7.33 – 7.40 (m, 5H), 7.66 (d, *J* = 8Hz, 1H), 8.52 (t, *J* = 5 Hz, 1H) ;^{13}C NMR (125 MHz, DMSO): 47.4, 118.4, 121.3, 125.8, 127.3, 127.6, 128.6, 130.6, 139.2, 152.7, 166.5.

N-(pyridin-3-ylmethyl)benzo[d]thiazol-2-amine (3i):

Yield 93% (224 mg); ^{1}H NMR (500 MHz, DMSO): δ 4.62 (d, *J* = 5.5 Hz , 2H), 7.03 (t, *J* = 7.5 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.36-7.41 (m, 2H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.78 (d, *J* =

8 Hz, 1H), 8.47 (d, *J* = 4 Hz, 1H), 8.56 (t, *J* = 5.5 Hz, 1H), 8.61 (s, 1H); ^{13}C NMR (125 MHz, DMSO): 45.2, 118.7, 121.4, 121.6, 123.9, 126.0, 130.9, 134.9, 135.7, 148.7, 149.3, 152.7, 166.5; IR (KBr): 629, 705, 762, 1049, 1101, 1122, 1208, 1433, 1538, 2362, 2921, 3167, 3428. HRMS calcd for $C_{13}H_{12}N_3S$: 242.0753, found: 242.0774.

4-methyl-N-(4-methoxybenzyl)benzo[d]thiazol-2-amine (3j):

Yield 91% (258 mg); ^{1}H NMR (500 MHz, DMSO): δ 2.44 (s, 3H), 3.72 (s, 3H), 4.48 (d, *J* = 6 Hz, 2H), 6.89 – 6.92 (m, 3H), 7.03 (d, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.46(d, *J* = 8 Hz, 1H), 8.41(t, *J* = 5.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO): 18.8, 47.6, 55.7, 114.4, 119.0, 121.4, 126.9, 127.9, 129.7, 130.5, 131.5, 152.0, 159.1, 166.1; IR (KBr): 625, 702, 755, 810, 833, 869, 888, 925, 963, 1027, 1069, 1174, 1215, 1245, 1285, 1353, 1404, 1449, 1513, 1534, 1594, 1762, 1828, 2362, 2626, 2839, 2914, 3231, 3866. HRMS calcd for $C_{16}H_{17}N_2OS$: 285.1062 found: 285.1031.

N-benzyl-4-methylbenzo[d]thiazol-2-amine (3k):

Yield 87% (221 mg); ^{1}H NMR (500 MHz, DMSO): δ 2.43 (s, 3H), 4.57 (d, *J* = 5.5 Hz, 2H), 6.91 (t, *J* = 8 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 1H), 7.26 (t, *J* = 7 Hz, 1H), 7.34 (t, *J* = 8 Hz, 2H), 7.40 (d, *J* = 7 Hz, 2H), 7.46 (d, *J* = 7.5 Hz, 1H), 8.48 (t, *J* = 5.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO): 18.0, 47.3, 118.2, 120.7, 126.1, 126.9, 127.1, 127.5, 128.2, 129.7, 138.8, 151.2, 165.4; IR (KBr): 617, 689, 742, 771, 881, 1027, 1077, 1209, 1242, 1453, 1523, 1556, 1644, 1733, 2359, 2921, 3209, 3437, 3645, 3732, 3796, 3922. HRMS calcd for $C_{15}H_{15}N_2S$: 255.0956, found: 255.0948.

N-benzyl-6-methylbenzo[d]thiazol-2-amine (3l)[33]:

Yield 90% (228 mg); ^{1}H NMR (500 MHz, DMSO): δ 2.30 (s, 3H), 4.58 (d, *J* = 5.5 Hz, 2H), 7.01 (d, *J* = 8 Hz, 1H), 7.24 – 7.28 (m, 1H), 7.32 – 7.38 (m, 4H), 7.45 (s, 1H), 8.39 (t, *J* = 5.5Hz, 1H) ;^{13}C NMR (125 MHz, DMSO): 21.2, 47.6, 118.2, 121.3, 127.0, 127.4, 127.8, 128.8, 130.5, 130.9, 139.4, 150.7, 166.0.

N-(4-chlorobenzyl)-6-methylbenzo[d]thiazol-2-amine (3m):

Yield 83% (239 mg); ^{1}H NMR (500 MHz, DMSO): δ 2.31 (s, 3H), 4.56 (d, J = 5 Hz, 2H), 7.02 (d, J = 8 Hz, 1H), 7.26 (d, J = 8.5 Hz, 1H), 7.39 (s, 4H), 7.46 (s, 1H), 8.42 (t, J = 5 Hz, 1H) ;^{13}C NMR (125 MHz, DMSO): 21.2, 46.8, 118.3, 121.3, 127.0, 128.7, 129.6, 130.6, 130.9, 132.0, 138.6, 150.6, 165.9 ; IR (KBr): 677, 729, 814, 1014, 1086, 1262, 1348, 1464, 1616, 2364, 2854, 2912, 3452; MS m/z 289 $[M + H]^{+}$, 243, 242, 214, 186, 125, 128, 104. CHNS calcd for $C_{15}H_{13}ClN_2S$: C (62.38), H (4.54), N(9.70), S (11.1), found: C (62.41), H (4.52), N (9.72), S (11.07).

6-Chloro-N-(4-chlorobenzyl)benzo[d]thiazol-2-amine (3n):

Yield 90% (278 mg); ^{1}H NMR (500 MHz, DMSO): δ 4.58 (d, J = 6Hz, 2H), 7.23 (dd, J_1 = 6.5Hz, J_2 = 2Hz, 1H), 7.35 – 7.42 (m, 5H), 7.80 (d, J = 2Hz, 1H), 8.67 (t, J = 6Hz, 1H); ^{13}C NMR (125 MHz, DMSO): 46.9, 119.4, 121.1, 125.2, 126.1, 128.8, 129.6, 132.1, 132.5, 138.2, 151.7, 167.2; IR (KBr): 682, 726, 767, 815, 1090, 1257, 1345, 1445, 1570, 1613, 2360, 2903, 3085, 3452. HRMS calcd for $C_{14}H_{11}Cl_2N_2S$: 309.0021, found: 309.0016.

6-Chloro-N-(4-methoxybenzyl)benzo[d]thiazol-1-amine (3o):

Yield 82% (249 mg); ^{1}H NMR (200 MHz, DMSO): δ 3.72 (s, 3H), 4.49 (d, J = 4.6 Hz, 2H), 6.88 (d, J = 8.2 Hz, 2H), 7.19 – 7.38 (m, 4H), 7.77 (s, 1H), 8.55 (s, 1H); ^{13}C NMR (50 MHz, DMSO): 47.2, 55.4, 114.2, 119.3, 121.0, 125.1, 126.1, 129.3, 130.9, 132.5, 151.8, 158.9, 167.2; IR (KBr): 607, 767, 821, 1031, 1172, 1250, 1345, 1446, 1509, 1547, 1567, 1603, 2842, 2971, 3174, 3411. HRMS calcd for $C_{15}H_{14}ClN_2OS$: 305.0516, found: 305.0517.

N-benzyl-6-chlorobenzo[d]thiazol-2-amine (3p)[33]:

Yield 89% (244 mg); ^{1}H NMR (500 MHz, DMSO): δ 4.59 (d, J = 6 Hz, 2H), 7.22 – 7.28 (m, 2H), 7.33 – 7.38 (m, 5H), 7.79 (d, J = 2.5 Hz, 1H), 8.62 (t, J = 6Hz, 1H); ^{13}C NMR (125 MHz, DMSO): 47.7, 119.4, 121.1, 125.1, 126.1, 127.5, 127.8, 128.8, 132.5, 139.1, 151.8, 167.3.

N-benzyl-4,5-diphenylthiazol-2-amine (3q):

Yield 85% (290 mg); ^{1}H NMR (500 MHz, DMSO): δ 4.49 (d, *J* = 5.5 Hz, 2H), 7.19 (d, *J* = 7 Hz, 2H), 7.23 – 7.30 (m, 7H), 7.34 – 7.41 (m, 6H), 8.26 (t, *J* = 6 Hz, 1H); ^{13}C NMR (125 MHz, DMSO): 47.4, 118.7, 126.9, 127.0 127.2, 127.4, 127.9, 128.2, 128.4, 128.6, 128.8, 132.5, 135.3, 139.0, 144.8, 165.8. IR (KBr): 690, 760, 971, 1068, 1230, 1324, 1417, 1580, 1956, 2356, 2962, 3085, 3195, 3416; HRMS calcd for $C_{22}H_{19}N_2S$: 343.1269, found: 343.1266.

N-(4-chlorobenzyl)-4,5-diphenylthiazol-2-amine (3r):

Yield 80% (300 mg); ^{1}H NMR (500 MHz, DMSO): δ 4.48 (d, *J* = 6 Hz, 2H), 7.19 (d, *J* = 7 Hz, 2H) , 7.24 – 7.30 (m, 6H), 7.38 (d, *J* = 6.5 Hz, 2H), 7.4 (s, 4H), 8.28 (t, *J* = 6Hz, 1H); ^{13}C NMR (125 MHz, DMSO): 47.3, 119.7, 127.8, 128.0, 128.7, 128.9, 129.1, 129.4, 129.6, 130.0, 132.2, 133.2, 136.0, 138.9, 145.6, 166.4. IR (KBr): 694, 759, 1082, 1218, 1318, 1420, 1485, 1563, 1770, 1894, 1960, 2349, 2893, 2959, 3075, 3197, 3418; MS m/z 399 $[M + Na]^+$, 377 $[M + H]^+$, 375, 331, 302, 301, 261, 223, 217, 156, 140, 97, 81; CHNS calcd for $C_{22}H_{17}ClN_2S$: C (70.11), H (4.55), N (7.43), S (8.51), found: C (70.17), H (4.55), N(7.40), S (8.48).

N-benzylpyrimidin-2-amine (3s)[17]:

Yield 91% (168 mg); ^{1}H NMR (500 MHz, DMSO): δ 4.49 (d, *J* = 6 Hz, 2H), 6.56(t, *J* = 5 Hz, 1H) 7.18 – 7.21 (m, 1H), 7.27 – 7.29 (m, 4H), 7.70 (t, *J* = 5 Hz, 1H), 8.25 (d, *J* = 5Hz, 2H); ^{13}C NMR (125 MHz, DMSO): 44.5, 110.8, 127.1, 127.6, 128.7, 141.07, 158.6, 162.9.

N-(4-methylbenzyl)pyrimidin-2-amine (3t)[17]:

Yield 90% (179 mg); ^{1}H NMR (500 MHz, DMSO): δ 2.25(s, 3H), 4.43 (d, *J* = 6.5 Hz, 2H), 6.55(t, *J* = 4.5 Hz, 1H) 7.08(d, *J* = 7.5 Hz, 2H), 7.17(d, *J* = 8 Hz, 2H), 7.62 (t, *J* = 6.5 Hz, 1H), 8.24 (d, *J* = 5Hz, 2H); ^{13}C NMR (125 MHz, DMSO): 21.3, 44.2, 110.8, 127.6, 129.3, 136.1, 138.0, 158.6, 162.9.

N-(4-chlorobenzyl)pyrimidin-2-amine (3u)[17]:

Yield 93% (204 mg); ^{1}H NMR (500 MHz, DMSO): δ 4.45 (d, *J* = 6.5 Hz, 2H), 6.57(t, *J* = 5 Hz, 1H) 7.30 – 7.35 (m, 4H), 7.72 (t, *J* = 6.5 Hz, 1H), 8.25 (d, *J* = 5Hz, 2H); ^{13}C NMR (125 MHz, DMSO): 43.9, 111.0, 128.7, 129.5,131.6, 140.2, 158.6, 162.8.

N-benzylpyridin-2-amine (3v)[17]:

Yield 90% (165 mg); ^{1}H NMR (500 MHz, DMSO): δ 4.46 (d, *J* = 6 Hz, 2H), 6.46 (t, *J* = 6 Hz, 1H), 6.49 (d, *J* = 8.5 Hz, 1H) 7.01 (t, *J* = 5.5 Hz, 1H), 7.20 (t, *J* = 7 Hz, 1H), 7.27 – 7.36 (m, 5H), 7.94 (d, *J* = 5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO): 44.8, 108.8, 112.3, 127.1, 127.8, 128.8, 137.3, 141.3, 148.2, 159.3.

N-(4-methylbenzyl)pyridin-2-amine (3w)[17]:

Yield 92% (182 mg); ^{1}H NMR (500 MHz, DMSO): δ 2.25 (s, 3H), 4.40 (d, *J* = 6 Hz, 2H), 6.44 – 6.48 (m, 2H), 6.94 (s, 1H), 7.09 (d, *J* = 7 Hz, 2H), 7.19 (d, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.93 (d, *J* = 3.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO): 21.3, 44.5, 108.7, 112.3, 127.8, 129.4, 136.1, 137.2, 138.2, 148.2, 159.3.

N-benzylpyrazin-2-amine (3x):

Yield 92% (170 mg); ^{1}H NMR (500 MHz, DMSO): δ 4.47 (d, *J* = 6 Hz, 2H), 7.21 – 7.25 (m, 1H), 7.30 – 7.34 (m, 4H), 7.58 (t, *J* = 5.5 Hz, 1H), 7.65(d, *J* = 3 Hz, 1H), 7.91 (s, 1H), 7.97(s, 1H); ^{13}C NMR (125 MHz, DMSO): 44.2, 127.4, 127.9, 128.9, 131.9, 133.9, 140.4, 142.2, 155.5; IR (KBr): 696, 753, 822, 1001, 1056, 1324, 1426, 1567, 1771, 1897, 2356, 3039, 3088, 3231, 3425; HRMS calcd for $C_{11}H_{12}N_3$: 186.1031, found: 186.1010.

N-(4-methylbenzyl)pyrazin-2-amine (3y):

Yield 90% (179 mg); ^{1}H NMR (500 MHz, DMSO): δ 2.26 (s, 3H), 4.41 (d, *J* = 6 Hz, 2H), 7.11(d, *J* = 7.5, Hz, 2H), 7.20 (d, *J* = 8 Hz, 2H), 7.51 (d, *J* = 5 Hz, 1H), 7.64 (d, *J* = 2.5 Hz, 1H), 7.90 (s, 1H), 7.95 (s, 1H); ^{13}C NMR (125 MHz, DMSO): 21.3, 44.0, 127.9, 129.5, 131.85, 133.9, 136.4, 137.3, 142.1, 155.5; IR (KBr): 686, 807, 1002, 1050, 1103, 1144,

1198, 1329, 1429, 1571, 1910, 2358, 2996, 3094, 3231, 3427; HRMS calcd for $C_{12}H_{14}N_3$: 200.1188, found: 200.1176.

N-(4-chlorobenzyl)pyrazin-2-amine (3z):

Yield 91% (199 mg); ^{1}H NMR (500 MHz, DMSO): δ 4.46 (d, *J* = 6 Hz, 2H), 7.33 – 7.38 (m, 4H), 7.62 (t, *J* = 6Hz, 1H) 7.66 (d, *J* = 2.5 Hz, 1H), 7.90 (s, 1H), 7.97 (s, 1H); ^{13}C NMR (125 MHz, DMSO):43.5, 128.8, 129.7, 132.0, 133.9, 139.5, 142.1, 155.4; IR (KBr): 695, 799, 1002, 1090, 1193, 1319, 1428, 1577, 1900, 2354, 2930, 3243, 3424; HRMS calcd for $C_{12}H_{14}N_3$: 220.0642, found: 220.0672.

Synthesis of N,5-dibenzyl-4-phenylthiazol-2-amine (5a): In a 25 mL round bottomed flask, 176 mg (1.0 mmol) of 4-phenylthiazol-2-amine **4a,** 324 mg (3.0 mmol) of benzyl alcohol, 40 mg (1.0 mmol) of sodium hydroxide (NaOH) and 1.0 mL of toluene were placed. The reaction flask was heated at130 °C for 28 h in an oil bath. After completion of the reaction, the flask was allowed to attain room temperature, and 20 mL of water was added. The product was extracted with EtOAc (30 mL × 3). Removal of the organic solvent under reduced pressure, the residue left out was subjected to column chromatography on silica gel using dichloromethane/ethyl acetate (95:5) as eluent. After removal of the solvent, **5a** was obtained in 81% yield (288 mg; 0.81 mmol). ^{1}H NMR (500 MHz, DMSO): ppm 4.08 (s, 2H), 4.45 (d, *J* = 5.5 Hz, 2H), 7.19 – 7.26 (m, 4H), 7.28 – 7.34 (m, 5H), 7.37 – 7.40 (t, *J* = 7.5 Hz, 4H), 7.57 (d, *J* = 7.5 Hz, 2H), 8.00 (t, *J* = 5.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO): 32.6, 47.9, 119.3, 126.8, 127.4, 127.6, 127.9, 128.4, 128.7, 129.0, 135.8, 139.7, 140.9, 146.5, 166.0; IR (KBr):702, 845, 1025, 1165, 1232, 1331, 1423, 1449, 1490, 1569, 2949, 3024, 3183, 3450. HRMS calcd for $C_{23}H_{21}N_2S$: 357.1425, found: 357.1455.

N-benzyl-4-phenylthiazol-2-amine (5a'):

Yield 12% (32 mg); ^{1}H NMR (500 MHz, DMSO): δ 4.51 (d, *J* = 6 Hz, 2H), 7.04 (s, 1H) 7.25 (t, *J* = 7.5 Hz, 2H), 7.32 – 7.41 (m, 6H), 7.82 (d, *J* = 7.5 Hz, 2H), 8.18 (t, *J* = 5.5 Hz, 1H); ^{13}C

NMR (125 MHz, DMSO): 48.2, 101.6, 126.0, 127.4, 127.7, 128.0, 128.7, 128.9, 135.2, 139.7, 150.3, 168.8; IR (KBr): 698, 726, 974, 1023, 1065, 1106, 1334, 1424, 1482, 1585, 2892, 2929, 2977, 3025, 3057, 1101, 3212, 3429. HRMS calcd for $C_{16}H_{15}N_2S$: 267.0957, found: 267.0973.

N,5-bis(4-methoxybenzyl)-4-phenylthiazol-2-amine (5b):

Yield 78% (324 mg); ^{1}H NMR (500 MHz, DMSO): δ 3.70 (s, 3H), 3.71 (s, 3H), 4.00 (s, 2H), 4.35 (d, *J* = 6 Hz, 2H), 6.85 – 6.90 (m, 4H), 7.09 (d, *J* = 8.5 Hz, 2H), 7.28 – 7.31 (m, 3H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.57 (d, *J* = 7 Hz, 2H) 7.89 (t, *J* = 6Hz, 1H); ^{13}C NMR (125 MHz, DMSO): 31.8, 47.4, 55.4, 114.1, 114.3, 120.0, 127.6, 128.4, 128.7, 129.3, 129.5, 131.6, 132.8, 135.8, 146.1, 158.2, 158.7, 165.9; IR (KBr): 695, 804, 1030, 1164, 1245, 1294, 1427, 1510, 1590, 2898, 2939, 3098, 3204, 3425. HRMS calcd for $C_{25}H_{25}N_2O_2S$: 417.1637, found: 417.1653.

N,5-bis(4-chlorobenzyl)-4-phenylthiazol-2-amine (5c):

Yield 82% (348 mg); ^{1}H NMR (500 MHz, DMSO): δ 4.07 (s, 2H), 4.42 (d, *J* = 6 Hz, 2H), 7.20 (d, *J* = 8.5 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.35 – 7.41 (m, 8H), 7.51 (d, *J* = 7.5 Hz, 2H), 8.05 (t, *J* = 6Hz, 1H); ^{13}C NMR (125 MHz, DMSO): 31.4, 46.6, 118.3, 127.2, 127.9, 128.1, 128.4, 129.2, 129.8, 130.9, 130.9, 131.4, 135.1, 138.3, 139.3, 146.2, 165.4; IR (KBr): 700, 774, 808, 1012, 1088, 1238, 1326, 1408, 1487, 1571, 1738, 2924, 2956, 3081, 3188, 3436. HRMS calcd for $C_{23}H_{19}Cl_2N_2S$: 425.0646, found: 425.0657.

N,5-dibenzyl-4-(4-tert-butylphenyl)thiazol-2-amine (5d):

Yield 83% (342 mg); ^{1}H NMR (500 MHz, DMSO): δ 1.28 (s, 9H), 4.07 (s, 2H), 4.42 (d, *J* = 6 Hz, 2H), 7.19 – 7.25 (m, 4H), 7.29 – 7.40 (m, 8H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.96 (t, *J* = 6 Hz, 1H); ^{13}C NMR (125 MHz, DMSO): 31.5, 32.6, 34.7, 47.8, 118.7, 125.4, 126.8, 127.3, 127.9, 128.1, 128.4, 128.7, 129.0, 133.0, 139.8, 140.9, 146.4, 150.0, 165.9; IR (KBr): 711,

844, 973, 1023, 1111, 1163, 1329, 1422, 1451, 1494, 1593, 2363, 2898, 2959, 3105, 3220, 3426. HRMS calcd for $C_{27}H_{29}N_2S$: 413.2051, found: 413.2071.

4-(4-tert-Butylphenyl)-N,5-bis(4-methylbenzyl)thiazol-2-amine (5e):

Yield 80% (352 mg); ^{1}H NMR (500 MHz, DMSO): δ 1.28 (s, 9H), 2.26 (s, 6H), 4.00 (s, 2H), 4.35 (d, *J* = 5 Hz, 2H), 7.06 – 7.13 (m, 6H), 7.23 (d, *J* = 7.5 Hz, 2H), 7.38 (d, *J* = 8 Hz, 2H), 7.46 (d, *J* = 8 Hz, 2H), 7.86 (t, *J* = 5.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO): 20.7, 20.8, 31.2, 32.0, 34.4, 47.4, 118.7, 125.1, 127.6, 127.8, 128.0, 128.9, 129.2, 132.7, 135.5, 136.1, 136.4, 137.6, 146.0, 149.7, 165.5; IR (KBr): 678, 793, 842, 980, 1019, 1109, 1169, 1331, 1424, 1460, 1509, 1594, 1799, 1894, 2365, 2961, 3102, 3208, 3423. HRMS calcd for $C_{29}H_{33}N_2S$: 441.2364, found: 441.2379.

4-(4-tert-Butylphenyl)-N,5-bis(4-methoxybenzyl)thiazol-2-amine (5f):

Yield 80% (377 mg); ^{1}H NMR (500 MHz, DMSO): δ 1.28 (s, 9H), 3.71 (s, 3H), 3.72 (s, 3H), 3.99 (s, 2H), 4.33 (d, *J* = 5.5 Hz, 2H), 6.85 – 6.89 (m, 4H), 7.10 (d, *J* = 7.5 Hz, 2H), 7.28 (d, *J* = 7.5 Hz, 2H), 7.39 (d, *J* = 7 Hz, 2H), 7.49 (d, *J* = 7.5 Hz, 2H), 7.85 (t, *J* = 5.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO): 31.5, 31.8, 34.7, 47.4, 55.4, 114.1, 114.3, 119.4, 125.4, 128.1, 129.3, 129.4, 131.7, 132.9, 133.1, 146.1, 149.9, 158.2, 158.7, 165.8; IR (KBr): 678, 730, 808, 1031, 1106, 1168, 1248, 1427, 1459, 1510, 1593, 1876, 1919, 2361, 2959, 3212, 3423. HRMS calcd for $C_{29}H_{33}N_2O_2S$: 473.2262, found: 473.2288.

4-(4-tert-Butylphenyl)-N,5-bis(4-chlorobenzyl)thiazol-2-amine (5g):

Yield 81% (389 mg); ^{1}H NMR (500 MHz, DMSO): δ 1.27 (s, 9H), 4.06 (s, 2H), 4.41 (d, *J* = 6 Hz, 2H), 7.20 (d, *J* = 8.5 Hz, 2H), 7.35 – 7.40 (m, 8H), 7.44 (d, *J* = 8.5 Hz, 2H), 8.02 (t, *J* = 6 Hz, 1H); ^{13}C NMR (125 MHz, DMSO): 31.5, 31.9, 34.7, 47.1, 118.2, 125.5, 128.1, 128.6, 128.9, 129.8, 130.3, 131.4, 131.9, 132.8, 138.9, 139.9, 146.7, 150.1, 165.8; IR (KBr):687, 729, 811, 1013, 1090, 1267, 1328, 1360, 1406, 1458, 1489, 1575, 1896, 2362, 2962, 3087, 3197, 3424. HRMS calcd for $C_{27}H_{27}Cl_2N_2S$: 481.1272, found: 481.1278.

4-(4-tert-Butylphenyl)-N,5-bis(2-chlorobenzyl)thiazol-2-amine (5h):

Yield 85% (408 mg); ^{1}H NMR (500 MHz, DMSO): δ 1.27 (s, 9H), 4.15 (s, 2H), 4.52 (d, *J* = 5.5 Hz, 2H), 7.24-7.35 (m, 5H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.43 - 7.49 (m, 5H), 8.01 (t, *J* = 5.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO): 30.5, 31.2, 34.4, 45.1, 116.9, 125.2, 127.3, 127.7, 127.7, 128.7, 128.9, 129.3, 129.5, 129.5, 130.3, 132.5, 132.5, 132.9, 136.4, 137.9, 146.4, 149.9, 165.2; IR (KBr): 691, 750, 841, 1040, 1118, 1168, 1242, 1326, 1442, 1587, 2874, 2961, 3094, 3200, 3425. HRMS calcd for $C_{27}H_{27}Cl_2N_2S$: 481.1273, found: 481.1301.

N,5-dibenzyl-4-p-tolylthiazol-2-amine (5i):

Yield 80% (296 mg); ^{1}H NMR (500 MHz, DMSO): δ 2.30 (s, 3H), 4.05 (s, 2H), 4.42 (d, *J* = 5.5 Hz, 2H), 7.17 – 7.25 (m, 6H), 7.28 – 7.37 (m, 6H), 7.44 (d, *J* = 8 Hz, 2H), 7.96 (t, *J* = 6 Hz, 1H); ^{13}C NMR (125 MHz, DMSO): 20.9, 32.3, 47.6, 118.4, 126.5, 127.0, 127.6, 128.0, 128.1, 128.4, 128.7, 129, 13.76, 136.6, 139.4, 140.7, 146.2, 165.6; IR (KBr): 693, 723, 827, 975, 1163, 1239, 1329, 1425, 1447, 1495, 1592, 2897, 3205, 3433. HRMS calcd for $C_{24}H_{23}N_2S$: 371.1583, found: 371.1590.

N,5-bis(2-chlorobenzyl)-4-p-tolylthiazol-2-amine (5j):

Yield 81% (355 mg); ^{1}H NMR (500 MHz, DMSO): δ 2.30 (s, 3H), 4.14 (s, 2H), 4.51 (d, *J* = 5.5 Hz, 2H), 7.18 (d, *J* = 8 Hz, 2H), 7.24 – 7.35 (m, 5H), 7.39 (d, *J* = 8 Hz, 2H), 7.43 (d, *J* = 7.5 Hz, 2H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.99 (t, *J* = 6Hz, 1H); ^{13}C NMR (125 MHz, DMSO): 20.7, 30.3, 45.0, 116.7, 127.0, 127.4, 127.7, 128.4, 128.7, 128.8, 129.1, 129.3, 130.1, 132.3, 132.4, 132.7, 136.2, 136.4, 137.8, 146.3, 165.1; IR (KBr): 695, 744, 825, 1040, 1168, 1234, 1326, 1443, 1505, 1589, 2362, 2890, 2927, 2963, 3064, 3197, 3429. HRMS calcd for $C_{24}H_{21}Cl_2N_2S$: 439.0803, found: 439.0813.

N,5-dibenzyl-4-(4-chlorophenyl)thiazol-2-amine (5k):

Yield 80% (312 mg); ^{1}H NMR (500 MHz, DMSO): δ 4.07 (s, 2H), 4.42 (d, *J* = 6 Hz, 2H), 7.18 – 7.26 (m, 4H), 7.29 – 7.36 (m, 6H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.57 (d, *J* = 8.5 Hz, 2H),

8.01 (t, J = 6 Hz, 1H); ^{13}C NMR (125 MHz, DMSO): 32.6, 47.8, 120.1, 126.9, 127.4, 127.9, 128.5, 128.7, 129.0, 130.1, 132.1, 134.6, 139.6, 140.6, 145.0, 166.0; IR (KBr): 696, 754, 835, 973, 1012, 1087, 1164, 1426, 1448, 1483, 1591, 2360, 2898, 3207, 3423. HRMS calcd for $C_{23}H_{20}ClN_2S$: 391.1036, found: 391.1041.

N,5-bis(2-chlorobenzyl)-4-(4-chlorophenyl)thiazol-2-amine (5l):

Yield 82% (376 mg); ^{1}H NMR (500 MHz, DMSO): δ 4.16 (s, 2H), 4.53 (d, J = 6Hz, 2H), 7.26 – 7.34 (m, 5H), 7.43 – 7.49 (m, 5H), 7.55 (d, J = 8.5 Hz, 2H), 8.06 (t, J = 5.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO): 30.5, 45.2, 118.5, 127.3, 127.7, 128.5, 128.8, 128.9, 129.3, 129.5, 129.7, 130.4, 131.9, 132.5, 132.9, 134.2, 136.3, 137.7, 145.0, 165.45; IR (KBr): 693, 746, 832, 1040, 1089, 1164, 1234, 1328, 1443, 1587, 2891, 3197, 3419. HRMS calcd for $C_{23}H_{18}Cl_3N_2S$: 459.0256. found: 459.0258.

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Supporting Information Available. Copies of NMR spectra for all compounds and HRMS spectra for new compounds free of charge via the internet at http://pubs.acs.org. Crystallographic data for compound **5h** (CCDC- 916195) can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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