One-Pot, Four-Component Synthesis of Novel Imidazo[2,1-*b*]thiazol-5-amine Derivatives

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Abstract: Novel imidazo[2,1-*b*]thiazol-5-amine derivatives were synthesized by a one-pot, four-component reaction of 2-bromoacetophenone derivatives, aromatic aldehydes, thiourea, and isocyanides in the presence of ammonium chloride (NH_4Cl) in toluene under reflux conditions. Moderate to good yields resulted and the reaction showed tolerance toward a range of aromatic aldehydes with electron-donating and electron-withdrawing substituents on either *para* or *ortho* positions.

Key words: heterocyclic compounds, multicomponent reactions, isocyanides, thiourea, ammonium chloride

Among nitrogen- and sulfur-containing heteroaromatic compounds, imidazole and imidazo[2,1-*b*]thiazole derivatives are crucial core structures used to create drugs and materials. They exhibit significant biological activities including antitumor,[1–3] antibacterial,[4,5] antifungal,[6] and antihelmintic properties.[7] They have also been studied as potent enzyme inhibitors and cellular activity against IGF-IR, EGFR, and ErbB2 has been noted.[8] A series of imidazo[2,1-*b*]thiazole acetohydrazones was synthesized by Andreani et al. and their diuretic activity was screened; these studies showed that a potent diuretic activity was confirmed for the 2-methyl derivative bearing a phenyl ring at the 6-position.[9]

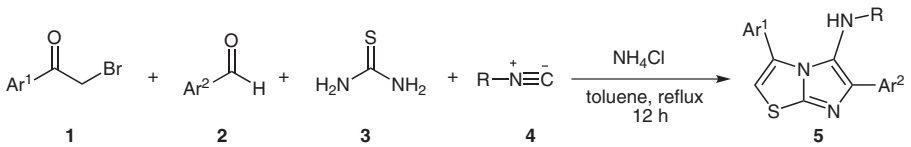
Multicomponent reactions (MCRs) offer convenient, safe, short, selective, high yielding, and often environmentally benign procedures, based on readily available starting materials.[10] In addition, the synthetic efficiency and rational design, particularly in heterocyclic chemistry, has been enhanced by the use of multicomponent reaction strategies.[11,12] Multicomponent reactions based on isocyanide[13,14] are also increasingly being employed and they have been particularly important tools in pharmaceutical chemistry.[15]

As a part of our studies on the development of novel synthetic procedures in heterocyclic chemistry[16–18] and on the preparation of bioactive molecules,[19–21] we disclose herein a novel protocol for the synthesis of imidazo[2,1-*b*]thiazol-5-amine derivatives based on MCRs; this new method can underpin other useful approaches to drug design especially in heterocyclic medicinal chemistry (Scheme 1).

Bienaymé and Bouzid introduced a three-component reaction of heteroaromatic amidines, aldehydes, and isocyanide to synthesize fused 3-aminoimidazoles.[22a] Since then, the synthesis of various heterocycles[22b] with important biological activities[22c] has been reported based on such a three-component reaction.

In this work, we have focused on the four-component reaction of 2-bromoacetophenones **1**, aromatic aldehydes **2**, thiourea **3**, and isocyanides **4** (Scheme 1), in which 4-arylthiazol-2-amine derivatives **6** are produced in situ by the reaction of **1** and **3**, followed by reaction of intermediate **6** with compounds **2** and **4** to give the title compounds **5** (Scheme 2).

The synthesis of imidazo[2,1-*b*]thiazol-5-amine derivatives (Scheme 1) was initially investigated by examining the reaction of 2,4′-bromoacetophenone (1 mmol), 2-nitrobenzaldehyde (1 mmol), thiourea (1 mmol), and cyclohexyl isocyanide (1.2 mmol). To optimize the reaction conditions, the mentioned model reaction was carried out in various solvents and under solvent-free conditions. The



Scheme 1 Synthesis of imidazo[2,1-*b*]thiazol-5-amine derivatives **5**

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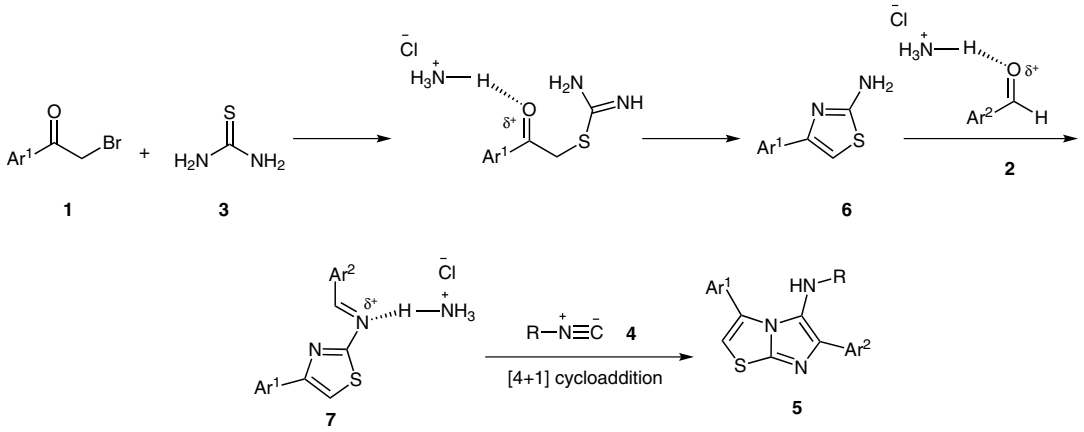


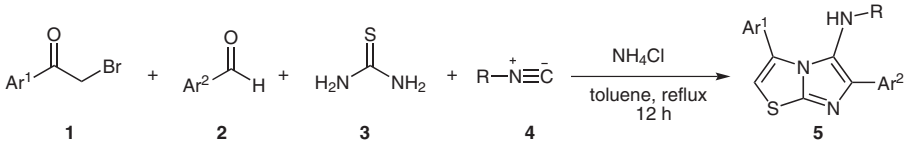
Scheme 2 Plausible mechanism for the synthesis of imidazo[2,1-*b*]thiazol-5-amine derivatives **5**

results showed that the yield of the reaction in toluene was higher than those obtained in other organic solvents, in water, and under solvent-free conditions. It should be noted that the corresponding product **5a** (Table 1, entry 1) was obtained upon heating to reflux and no reaction was observed at room temperature. Although toluene was found to be the best solvent, the yield of the reaction was still only 10%. Since the usefulness of ammonium chloride has been demonstrated in a number of isocyanide-based MCRs[23–25] and also in other chemical reactions,[26,27] the model reaction was then conducted in the presence of NH_4Cl (1 mmol) in toluene under reflux conditions; under these conditions the corresponding product was obtained in good yield (75%).

The structure of 3-(4-bromophenyl)-*N*-cyclohexyl-6-(2-nitrophenyl)imidazo[2,1-*b*]thiazol-5-amine (**5a**) was confirmed by mass spectroscopy fragmentation pattern analysis, and on the basis of its ^1H and ^{13}C NMR spectra. The MS peak (*m*/*z* 496/498) associated with the molecular ion was observed and was in accordance with calculated mass for $C_{23}H_{21}BrN_4O_2S$.

The MS shows a peak (*m*/*z* 413/415) that is related to elimination of the cyclohexyl ring. A fairly strong peak was also observed (*m*/*z* 371/373) resulting from loss of CN and NH_2 from the latter ion. The observation of two peaks with similar intensity in the mentioned fragments indicates the presence of the bromine atom. Elimination of Br· gave the expected peak (*m*/*z* 292).

Table 1 Synthesis of Imidazo[2,1-*b*]thiazol-5-amine Derivatives **5**



Entry	Ar^1	Ar^2	R	Product	Yield (%)[a]
1	4-BrC_6H_4	2-$O_2NC_6H_4$	cyclohexyl	**5a**	75
2	Ph	4-$O_2NC_6H_4$	cyclohexyl	**5b**	85
3	Ph	2-FC_6H_4	cyclohexyl	**5c**	78
4	Ph	4-$MeOC_6H_4$	cyclohexyl	**5d**	70
5	Ph	2-BrC_6H_4	cyclohexyl	**5e**	80
6	4-BrC_6H_4	4-ClC_6H_4	cyclohexyl	**5f**	60
7	Ph	2-$O_2NC_6H_4$	1,1,3,3-tetramethylbutyl	**5g**	75
8	4-BrC_6H_4	4-$O_2NC_6H_4$	1,1,3,3-tetramethylbutyl	**5h**	90
9	4-$MeOC_6H_4$	Ph	1,1,3,3-tetramethylbutyl	**5i**	80
10	4-BrC_6H_4	4-ClC_6H_4	1,1,3,3-tetramethylbutyl	**5j**	65

[a] Isolated yield.

^{1}H NMR spectrum of **5a** consisted of multiplet signals for the cyclohexyl rings (δ = 0.51–1.32 ppm, 10 H), N-CH resonance (δ = 1.92–1.95 ppm, 1 H), and a singlet signal for the cyclohexyl NH group (δ = 2.34 ppm, 1 H). The proton associated with the thiazole ring gave a singlet at δ = 6.65 ppm and signals related to eight aromatic protons were observed around 7.42–7.85 ppm. The ^{13}C spectrum showed 18 distinct resonances, as expected.

As indicated in Table 1, the variability of the four-component reaction with respect to the isocyanides and 2-bromoacetophenone derivatives was examined under the optimized conditions. To explore the limitations of this reaction, we extended it to various *para*- and *ortho*-substituted benzaldehydes. As can be seen in Table 1, the yield of products seems to be affected by the nature of substituents and their positions on the benzaldehyde. The yields increased when electron-withdrawing *para*-substituents were present, and evidently steric effects operate in the case of *ortho*-substituted benzaldehydes for which lower yields were observed.

Additionally, the reactivity of more hindered isocyanide (1,1,3,3-tetramethylbutyl isocyanide) was investigated in the four-component reaction. In this case, we found that the reactions proceeded quite well and no significant difference was observed.

It should be noted that in the absence of ammonium chloride the corresponding products were obtained in poor yields and, in some cases, no reaction occurred. It is worth mentioning that in the presence of NH_4Cl (1 mmol), the reactions proceed either with electron-withdrawing or electron-donating *para*- and *ortho*-substituted benzaldehydes and desired products were obtained in reasonable yields.

A plausible mechanism for the formation of the imidazo[2,1-*b*]thiazol-5-amine derivatives **5** is shown in Scheme 2. It can be assumed that the initial step is the formation of 4-arylthiazol-2-amines **6** from the reaction of 2-bromoacetophenone derivatives **1** and thiourea **3**. As reported previously, heteroaromatic amidines react efficiently with isocyanide and aldehydes.[22] Therefore, aromatic aldehyde **2** reacts with **6**, producing *N*-benzilidene-4-arylthiazol-2-amine derivatives **7**. Finally [4+1] cycloaddition of isocyanide **4** with **7** gives the products **5a**–**k**. To support the proposed mechanism, compound **6** was isolated from the reaction mixture and its structure was confirmed by comparison with authentic samples.[28] Upon treatment of this compound with aromatic aldehydes **2** and isocyanides **4** the products obtained were analyzed and their physicochemical data were found to be in good agreement with those obtained from the one-pot, four-component reactions.

To verify the structure of prepared compounds, we prepared an authentic sample of *N*-cyclohexyl-3-methyl-6-phenylimidazo[2,1-*b*]thiazole-5-amine (**11**; Scheme 3), as a known compound reported by Adib et al.[29] We therefore synthesized **11** by using our procedure (Scheme 3) and, for this purpose, chloroacetone **8** was used instead of 2-bromoacetophenone derivatives and its reaction with benzaldehyde **9**, thiourea **3**, and cyclohexyl isocyanide **10** was conducted under the optimal conditions; the corresponding product was obtained and the structure of **11** was confirmed.

In summary, we have developed a novel, efficient, one-pot, four-component synthesis of imidazo[2,1-*b*]thiazol-5-amine derivatives through the reaction of 2-bromoacetophenone derivatives, aromatic aldehydes, thiourea, and isocyanides in the presence of ammonium chloride. No undesirable side reactions were observed and products were obtained in moderate to good yields.

Melting points were measured with a Kofler hot stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker FT-500, using TMS as an internal standard. IR spectra were obtained with a Shimadzu 470 spectrophotometer (KBr disks). MS were recorded with an Agilent Technology (HP) mass spectrometer operating at an ionization potential of 70 eV. Elemental analysis was performed with an Elementar Analysensystem GmbH VarioEL CHNS mode.

Synthesis of Imidazo[2,1-*b*]thiazol-5-amine Derivatives; General Procedure

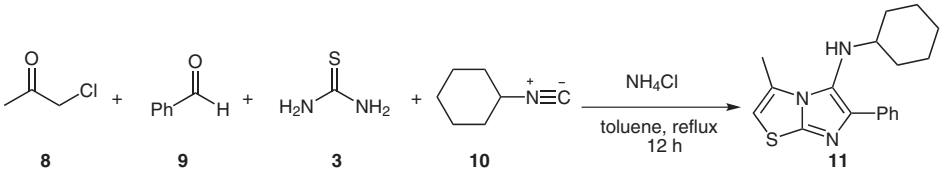
A mixture of 2-bromoacetophenone derivative **1** (1 mmol), appropriate aromatic aldehyde **2** (1 mmol), thiourea **3** (1 mmol), isocyanide derivative **4** (1.2 mmol), ammonium chloride (1 mmol), and toluene (5 mL) was heated at reflux for 12 h. Upon completion of the reaction (monitored by TLC), the mixture was cooled to r.t., the solvent was removed under reduced pressure, and the residue was purified by column chromatography (petroleum ether–EtOAc, 3:1).

3-(4-Bromophenyl)-*N*-cyclohexyl-6-(2-nitrophenyl)imidazo[2,1-*b*]thiazol-5-amine (5a)

Yield: 0.37 g (75%); orange powder; mp 199–200 °C.

IR (KBr): 3351, 2927, 2851, 1611, 1569, 1444, 1361 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.51–1.32 (m, 10 H, 5 × CH_2, cyclohexyl), 1.92–1.95 (m, 1 H, NCH), 2.34 (s, 1 H, NH), 6.65 (s, 1 H, CH, thiazole), 7.42–7.47 (m, 3 H, H-4, H-2′, H-6′), 7.60–7.65 (m, 3 H, H-5, H-3′, H-5′), 7.80 (d, *J* = 7.6 Hz, 1 H, H-6), 7.84 (d, *J* = 8.0 Hz, 1 H, H-3).



Scheme 3 Synthesis of *N*-cyclohexyl-3-methyl-6-phenylimidazo[2,1-*b*]thiazol-5-amine (**11**)

^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.1, 25.4, 32.3, 57.2, 110.3, 123.9, 124.2, 127.9, 128.4, 128.6, 129.1, 130.8, 131.6, 132.1, 132.2, 134.9, 146.2, 149.1.

MS: *m*/*z* (%) = 498 (35) $[M + 2]^+$, 496 (35) $[M]^+$, 415 (10), 371 (35), 292 (20), 119 (100), 83 (35), 55 (94).

Anal. Calcd for $C_{23}H_{21}BrN_4O_2S$: C, 55.54; H, 4.26; N, 11.26. Found: C, 55.74; H, 4.40; N, 11.15.

_N_-Cyclohexyl-6-(4-nitrophenyl)-3-phenylimidazo[2,1-*b*]thiazol-5-amine (5b)
Yield: 0.35 g (85%); powder yellow; mp 188–190 °C.

IR (KBr): 3321, 2924, 2847, 1596, 1556, 1491, 1369 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.67–1.34 (m, 10 H, 5 × CH_2, cyclohexyl), 1.94–1.99 (m, 1 H, NCH), 3.90 (d, *J* = 3.7 Hz, 1 H, NH), 7.18 (s, 1 H, CH, thiazole), 7.53–7.54 (m, 3 H, H-3′, H-4′, H-5′), 7.72–7.74 (m, 2 H, H-2′, H-6′), 8.21 (d, *J* = 9.0 Hz, 2 H, H-2, H-6), 8.41 (d, *J* = 9.0 Hz, 2 H, H-3, H-5).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 23.6, 25.2, 31.7, 56.3, 110.4, 123.8, 127.9, 128.0, 128.2, 129.2, 129.3, 129.4, 129.5, 131.4, 131.7, 133.2, 134.5, 145.1, 149.0.

MS: *m*/*z* (%) = 418 (48) $[M]^+$, 336 (27), 308 (98), 290 (11), 189 (11), 262 (50), 159 (17), 133 (16), 102 (100), 55 (34).

Anal. Calcd for $C_{23}H_{22}N_4O_2S$: C, 66.01; H, 5.30; N, 13.39. Found: C, 66.25; H, 5.17; N, 13.09.

_N_-Cyclohexyl-6-(2-fluorophenyl)-3-phenylimidazo[2,1-*b*]thiazol-5-amine (5c)
Yield: 0.30 g (78%); yellow powder; mp 131–132 °C.

IR (KBr): 3400, 2925, 2851, 1556, 1496 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.46–1.34 (m, 10 H, 5 × CH_2, cyclohexyl), 1.86–1.90 (m, 1 H, NCH), 3.09 (br s, 1 H, NH), 6.60 (s, 1 H, CH, thiazole), 7.13 (ddd, *J* = 9.0, 8.1, 1.0 Hz, 1 H, H-3), 7.23 (dt, *J* = 7.5, 1.0 Hz, 1 H, H-5), 7.28–7.30 (m, 1 H, H-4), 7.46–7.48 (m, 3 H, H-3′, H-4′, H-5′), 7.65–7.67 (m, 2 H, H-2′, H-6′), 7.79 (dt, *J* = 7.5, 1.7 Hz, 1 H, H-6).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 23.8, 25.1, 31.9, 56.2, 110.0, 115.5, 115.7, 122.4, 122.5, 124.2, 125.5, 127.8, 128.4, 129.0, 129.3, 129.5, 130.0, 131.4, 132.2, 133.3, 144.7, 158.9 (d, J_{C-F} = 243.0 Hz).

MS: *m*/*z* (%) = 391 (72) $[M]^+$, 308 (98), 281 (100), 176 (37), 159 (20), 149 (26), 134 (40), 123 (28), 102 (80), 89 (27), 55 (45), 43 (45).

Anal. Calcd for $C_{23}H_{22}FN_3S$: C, 70.56; H, 5.66; N, 10.73. Found: C, 70.75; H, 5.77; N, 10.61.

_N_-Cyclohexyl-6-(4-methoxyphenyl)-3-phenylimidazo[2,1-*b*]thiazol-5-amine (5d)
Yield: 0.28 g (70%); yellow powder; mp 168–170 °C.

IR (KBr): 3280, 2929, 2852, 1650, 1586 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.85–1.85 (m, 10 H, 5 × CH_2, cyclohexyl), 2.01–2.06 (m, 1 H, NCH), 3.85 (s, 1 H, NH), 3.90 (s, 3 H, OCH_3), 6.97 (d, *J* = 8.8 Hz, 2 H, H-3, H-5), 7.19 (s, 1 H, CH, thiazole), 7.34–7.43 (m, 3 H, H-3′, H-4′, H-5′), 7.88 (d, *J* = 7.5 Hz, 2 H, H-2′, H-6′), 8.02 (d, *J* = 8.8 Hz, 2 H, H-2, H-6).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 24.2, 25.0, 31.9, 47.6, 55.6, 113.8, 114.4, 126.5, 127.5, 128.6, 130.7, 132.4, 133.0, 150.5, 162.9, 163.7, 165.4, 168.1.

MS: *m*/*z* (%) = 403 (1) $[M]^+$, 279 (6), 149 (70), 135 (46), 113 (12), 97 (20), 83 (65), 57 (100), 43 (66).

Anal. Calcd for $C_{24}H_{25}N_3OS$: C, 71.43; H, 6.24; N, 10.41. Found: C, 71.80; H, 6.33; N, 10.66.

6-(2-Bromophenyl)-_N_-cyclohexyl-3-phenylimidazo[2,1-*b*]thiazol-5-amine (5e)
Yield: 0.36 g (80%); yellow powder; mp 194–195 °C.

IR (KBr): 3280, 2929, 2852, 1650, 1586 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.43–1.29 (m, 10 H, 5 × CH_2, cyclohexyl), 1.93–1.96 (m, 1 H, NCH), 2.85 (d, *J* = 8.1 Hz, 1 H, NH), 6.61 (s, 1 H, CH, thiazole), 7.21 (dt, *J* = 7.7, 1.6 Hz, 1 H, H-4), 7.36 (dt, *J* = 7.7, 1.0 Hz, 1 H, H-5), 7.46–7.47 (m, 3 H, H-3′, H-4′, H-5′), 7.55 (dd, *J* = 7.7, 1.6 Hz, 1 H, H-6), 7.37–7.67 (m, 3 H, H-3, H-2′, H-6′).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 23.5, 25.1, 31.7, 55.9, 109.8, 123.3, 127.1, 127.9, 129.0, 129.3, 129.5, 132.4, 132.8, 133.2, 135.6, 137.2, 143.8, 146.5.

MS: *m*/*z* (%) = 453 (30) $[M + 2]^+$, 451 (30) $[M]^+$, 391 (40), 370 (37), 341 (50), 308 (59), 281 (65), 263 (31), 225 (40), 189 (18), 167 (22), 149 (70), 111 (38), 91 (100), 57 (78).

Anal. Calcd for $C_{23}H_{22}BrN_3S$: C, 61.06; H, 4.90; N, 9.29. Found: C, 61.22; H, 4.93; N, 9.33.

3-(4-Bromophenyl)-6-(4-chlorophenyl)-_N_-cyclohexylimidazo[2,1-*b*]thiazol-5-amine (5f)
Yield: 0.29 g (60%); yellow powder; mp 166–168 °C.

IR (KBr): 3386, 2925, 2850, 1597, 1489 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.66–1.47 (m, 10 H, 5 × CH_2, cyclohexyl), 2.06–2.09 (m, 1 H, NCH), 2.56 (d, *J* = 4.1 Hz, 1 H, NH), 6.61 (s, 1 H, CH, thiazole), 7.35 (d, *J* = 8.5 Hz, 2 H, H-3, H-5), 7.46 (d, *J* = 8.2 Hz, 2 H, H-2′, H-6′), 7.66 (d, *J* = 8.2 Hz, 2 H, H-3′, H-5′), 7.99 (d, *J* = 8.5 Hz, 2 H, H-2, H-6).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 24.0, 25.3, 32.1, 56.8, 110.7, 122.6, 127.8, 128.0, 128.2, 128.7, 130.6, 131.0, 131.4, 132.2, 133.6, 137.0, 145.4.

MS: *m*/*z* (%) = 489 (5) $[M + 4]^+$, 487 (20) $[M + 2]^+$, 485 (15) $[M]^+$, 404 (50), 377 (55), 296 (11), 180 (32), 159 (100), 101 (17), 83 (22), 69 (27), 55 (47).

Anal. Calcd for $C_{23}H_{21}BrClN_3S$: C, 56.74; H, 4.35; N, 8.63. Found: C, 56.59; H, 4.21; N, 8.84.

_N_-(2,4,4-Trimethylpentane-2-yl)-6-(2-nitrophenyl)-3-phenylimidazo[2,1-*b*]thiazol-5-amine (5g)
Yield: 0.34 g (75%); yellow powder; mp 169–170 °C.

IR (KBr): 3279, 2920, 2847, 1615, 1577, 1535, 1479, 1354 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.49 [s, 6 H, $C(CH_3)_2$], 0.70 [s, 9 H, $C(CH_3)_3$], 0.72 (s, 2 H, CH_2), 2.47 (s, 1 H, NH), 6.63 (s, 1 H, CH, thiazole), 7.43 (dt, *J* = 7.5, 1.0 Hz, 1 H, H-4), 7.50–7.54 (m, 5 H, H-2′, H-3′, H-4′, H-5′, H-6′), 7.61 (dt, *J* = 7.5, 1.4 Hz, 1 H, H-5), 7.85 (dd, *J* = 7.5, 1.0 Hz, 1 H, H-6), 7.86 (dd, *J* = 7.5, 1.4 Hz, 1 H, H-3).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 27.5, 30.5, 31.2, 54.9, 58.6, 110.6, 123.7, 128.1, 128.2, 129.0, 129.3, 129.7, 131.8, 131.9, 133.8, 136.4, 145.5, 149.0.

MS: *m*/*z* (%) = 448 (2) $[M]^+$, 279 (15), 176 (13), 167 (55), 149 (100), 134 (30), 113 (17), 104 (26), 83 (35), 71 (53), 57 (96).

Anal. Calcd for $C_{25}H_{28}N_4O_2S$: C, 66.94; H, 6.29; N, 12.49. Found: C, 66.80; H, 5.96; N, 12.22.

3-(4-Bromophenyl)-_N_-(2,4,4-trimethylpentane-2-yl)-6-(4-nitrophenyl)imidazo[2,1-*b*]thiazol-5-amine (5h)
Yield: 0.47 g (90%); yellow powder; mp 185–186 °C.

IR (KBr): 3280, 2925, 2847, 1615, 1577, 1535, 1479, 1360 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.61 [s, 6 H, $C(CH_3)_2$], 0.84 [s, 9 H, $C(CH_3)_3$], 0.86 (s, 2 H, CH_2), 2.69 (s, 1 H, NH), 6.72 (s, 1 H, CH, thiazole), 7.45 (d, *J* = 8.3 Hz, 2 H, H-2′, H-6′), 7.71 (d, *J* = 8.3 Hz, 2 H, H-3′, H-5′), 8.20 (d, *J* = 9.0 Hz, 2 H, H-2, H-6), 8.26 (d, *J* = 9.0 Hz, 2 H, H-3, H-5).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.4, 31.3, 31.6, 55.9, 61.1, 111.2, 123.5, 123.9, 127.9, 128.4, 129.0, 130.6, 132.1, 132.7, 138.2, 141.8, 146.2, 147.3.

MS: *m*/*z* (%) = 528 (5) $[M + 2]^+$, 526 (5) $[M]^+$, 416 (98), 397 (15), 340 (12), 180 (13), 159 (37), 57 (100).

Anal. Calcd for $C_{25}H_{27}BrN_4O_2S$: C, 56.93; H, 5.16; N, 10.62. Found: C, 57.15; H, 5.10; N, 10.80.

3-(4-Methoxyphenyl)-*N*-(2,4,4-trimethylpentane-2-yl)-6-phenylimidazo[2,1-*b*]thiazol-5-amine (5i)
Yield: 0.35 g (80%); yellow powder; mp 129–131 °C.

IR (KBr): 3245, 2925, 2865, 1660, 1575 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.47 [s, 6 H, $C(CH_3)_2$], 0.71 [s, 9 H, $C(CH_3)_3$], 0.80 (s, 2 H, CH_2), 3.49 (s, 1 H, NH), 3.77 (s, 3 H, OCH_3), 7.11 (s, 1 H, CH, thiazole), 6.92 (d, *J* = 8.8 Hz, 2 H, H-3′, H-5′), 7.49–7.54 (m, 3 H, H-3, H-4, H-5), 7.68 (d, *J* = 6.5 Hz, 2 H, H-2, H-6), 7.86 (d, *J* = 8.8 Hz, 2 H, H-2′, H-6′).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 27.8, 30.7, 31.4, 55.0, 58.8, 101.4, 109.7, 113.1, 125.5, 126.3, 127.1, 128.1, 128.4, 128.7, 128.8, 129.4, 130.1, 134.0, 140.3, 145.1, 157.9.

Anal. Calcd for $C_{26}H_{31}N_3OS$: C, 72.02; H, 7.21; N, 9.69. Found: C, 72.23; H, 7.15; N, 9.55.

3-(4-Bromophenyl)-6-(4-chlorophenyl)-*N*-(2,4,4-trimethylpentane-2-yl)imidazo[2,1-*b*]thiazol-5-amine (5j)
Yield: 0.19 g (0.60%); pale-yellow solid; mp 182–183 °C.

IR (KBr): 3420, 2948, 2859, 1542, 1489 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.58 [s, 6 H, $C(CH_3)_2$], 0.83 [s, 9 H, $C(CH_3)_3$], 0.85 (s, 2 H, CH_2), 2.69 (s, 1 H, NH), 6.63 (s, 1 H, CH, thiazole), 7.37 (d, *J* = 8.6 Hz, 2 H, H-3, H-5), 7.45 (d, *J* = 8.4 Hz, 2 H, H-2′, H-6′), 7.67 (d, *J* = 8.4 Hz, 2 H, H-3′, H-5′), 7.85 (d, *J* = 8.6 Hz, 2 H, H-2, H-6).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 27.8, 30.6, 31.3, 55.1, 59.0, 111.1, 122.1, 127.2, 127.8, 129.0, 129.3, 130.8, 131.0, 131.7, 132.8, 134.3, 139.5, 145.5.

MS: *m*/*z* (%) = 517 (1.2) $[M + 2]^+$, 515 (1) $[M]^+$, 405 (60), 377 (25), 279 (12), 239 (10), 167 (17), 149 (100), 91 (15), 57 (48).

Anal. Calcd for $C_{25}H_{27}BrClN_3S$: C, 58.09; H, 5.26; N, 8.13. Found: C, 58.28; H, 5.33; N, 8.30.

Synthesis of *N*-Cyclohexyl-3-methyl-6-phenylimidazo[2,1-*b*]thiazol-5-amine (11)
A mixture of chloroacetone **8** (1 mmol), benzaldehyde **9** (1 mmol), thiourea **3** (1 mmol), cyclohexylisocyanide **10** (1.2 mmol), ammonium chloride (1 mmol), and toluene (5 mL) was heated at reflux for 12 h. After completion of the reaction, the mixture was cooled to r.t., the solvent was removed under reduced pressure and the residue was purified by column chromatography (petroleum ether–EtOAc, 7:1).

***N*-Cyclohexyl-3-methyl-6-phenylimidazo[2,1-*b*]thiazol-5-amine**
Yield: 0.15 g (50%); pale-yellow powder; mp 136–138 °C.

IR (KBr): 3417, 3032, 2929, 2852, 1698, 1552, 1447 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.00–1.89 (m, 10 H, 5 × CH_2, cyclohexyl), 2.40 (s, 1 H, NH), 2.46 (s, 3 H, CH_3), 3.73–3.75 (m, 1 H, NCH), 5.60 (s, 1 H, CH, thiazole), 7.33–7.37 (m, 3 H, H-3, H-4, H-5), 7.49 (d, *J* = 6.7 Hz, 2 H, H-2, H-6).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.5, 23.6, 23.8, 25.8, 33.6, 34.0, 56.8, 99.4, 125.8, 128.1, 128.5, 128.9, 129.1, 132.3, 136.6, 152.0.

MS: *m*/*z* (%) = 311 (3) $[M]^+$, 218 (22), 201 (77), 140 (21), 105 (100), 77 (42), 55 (11).

Anal. Calcd for $C_{18}H_{21}N_3S$: C, 69.42; H, 6.80; N, 13.49. Found: C, 69.13; H, 7.15; N, 13.25.

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