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Click-based synthesis of triazolobithiazole ΔF508-CFTR correctors for cystic fibrosis

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ABSTRACT

Copper catalyzed azide-alkyne cycloaddition (CuAAC) chemistry is reported for the construction of previously unknown 5-(1*H*-1,2,3-triazol-1-yl)-4,5′-bithiazoles from 2-bromo-1-(thiazol-5-yl)ethanones. These novel triazolobithiazoles are shown to have cystic fibrosis (CF) corrector activity and, compared to the benchmark bithiazole CF corrector corr-**4a**, improved log*P* values (4.5 vs 5.96).

1. Introduction

Cystic fibrosis (CF) is a genetic disease affecting ~1 in 2500 Caucasians[1] which, in its most common form, is caused by the deletion of phenylalanine at position 508 in the CF transmembrane conductance regulator protein (ΔF508-CFTR).[2,3] Our CF small molecule discovery program identified bithiazoles that partially rescue ΔF508-CFTR cellular misprocessing (CF 'correctors'; Fig. 1). In exploring this structural class, positions 'a', 'b', and 'c' on the bithiazole scaffold were extensively modified.[4] The work reported here follows from earlier studies targeting pyrazolothiazoles where we had shown that this compound class, which uniquely allows access to analogs exploring position 'd' (not addressable with bithiazoles), was found to afford improved water solubility vis-à-vis bithazoles–albeit with lower CF corrector activity.[5]

This reduction in CF corrector activity in going from bithiazoles to pyrazolothiazoles caused us to consider exploring position 'e' on the bithiazole scaffold, hypothesizing that placing a triazole moiety at C5 might give improved aqueous solubility while maintaining or perhaps improving corrector activity. Herein, we report the development of chemistry for the construction of novel 5-(1*H*-1,2,3-triazol-1-yl)-4,5′-bithiazoles, along with CF corrector activity and log*P* data. Retrosynthetic analysis suggested that triazole formation might be accomplished by copper catalyzed azide-alkyne cycloadditon (CuAAC) through a 2-bromo-1-(thiazol-5-yl)ethanone intermediate (Fig. 1) and that a second bromination, now alpha to both the carbonyl and triazole moieties, might allow for α-bromoketone→thiazole formation.

2. Results and discussion

2.1. Chemistry

The requisite starting thiazoles (**1a**,**b**: R^1 = *t*-Bu and Ph, respectively) were prepared as detailed in Scheme 1. Thiourea was condensed with 3-chloro-2,4-pentadione to afford 1-(2-amino-4-methylthiazol-5-yl)ethanone in nearly quantitative yield.[6] The amino group in this 2-aminothiazole was then coupled with either pivalic (→**1a**; 85%) or benzoic (→**1b**; 79%) acid in CDI-mediated reactions to give the targeted amidothiazoles. After some experimentation, bromination alpha to the ketone carbonyl in **1** was effectively accomplished with pyridinium tribromide and 33 wt.% hydrobromic acid in acetic acid. Bromides **2a** and **2b** were thus obtained on ~1 g scale in 75% and 63% overall yield, respectively, from 3-chloro-2,4-pentadione.

α-Bromoketone **2** was next stirred in DMF with sodium azide at room temperature to obtain, in situ, the corresponding azido compound. On completion of the displacement, as monitored by TLC (1:1 EtOAc:hexanes), the appropriate alkyne, copper catalyst, sodium ascorbate, and water (250 μL per mL of DMF) were added to the reaction flask and the contents were stirred for an additional 6 h. Workup, consisting of dilution with water and extraction with EtOAc, followed by flash column chromatographic purification,

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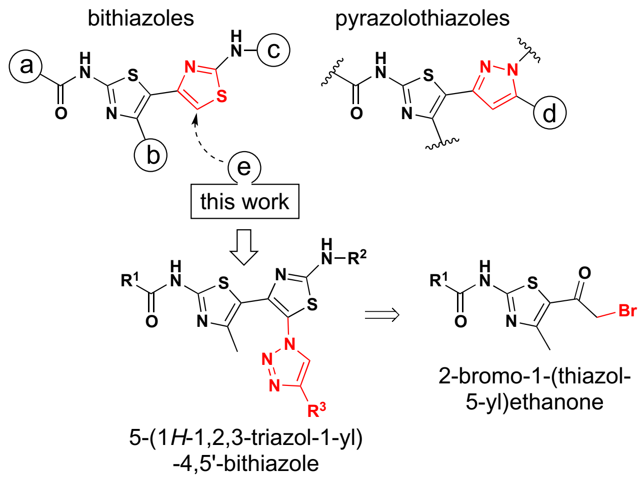
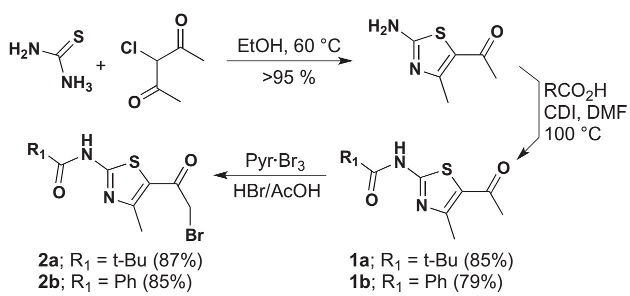
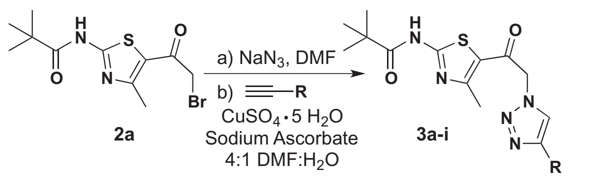


Figure 1. Bithiazole, pyrazolothiazole, and triazolobithiazole CF correctors.



Scheme 1. Synthesis of 2-bromo-1-(thiazol-5-yl)ethanones **2a**,**b**.

Table 1
One-pot synthesis of 1-(thiazol-5-yl)-2-(1*H*-1,2,3-triazol-1-yl)ethanones **3a–i**



Entry	Compound	R	Yield (%)
1	**3a**	–Ph	85
2	**3b**	$-CH_2OH$	76
3	**3c**	$-CH_2OCH_3$	73
4	**3d**	$-CH_2N(CH_3)_2$	56
5	**3e**	$-(CH_2)_3CN$	68
6	**3f**	$-CH_2N(CH_2CH_2)O$[a]	74
7	**3g**	$-COOCH_3$	52
8	**3h**	–4-Cl-Ph	95
9	**3i**	$-CH_2CH_2OH$	70

[a] Morpholine.

delivered the targeted 1-(thiazol-5-yl)-2-(1*H*-1,2,3-triazol-1-yl)ethanone (**3**). Using this methodology, a small collection of analogs was synthesized in moderate to good yield from α-bromoketone **2a** (Table 1).

Surprisingly, it was discovered that employing α-bromoketone **2b** as the starting material generally failed to give triazolo-thiazole products under the one-pot conditions outlined in Table 1; there was extensive product decomposition under the required prolonged reaction times. As a result, reactions employing **2b** were modified—two-pot reaction with isolated azide and the use of copper(I) iodide as catalyst (see Table 2)—which allowed for shorter reaction times; with these modifications, three of the alkynes delineated in Table 1 led to product (see Table 2).

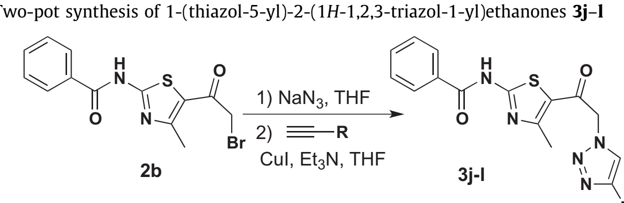
This unexpected click reaction problem with 2-bromo-1-(thiazolo-5-yl)ethanone **2b** led us to investigate the cause of these poor yielding cycloadditions. Thinking the amide proton may be the problem (either its increased acidity or the fact that it is less sterically encumbered than in **2a**), we decided to synthesize the N-methylated version of **2b** (e.g., **6**; Scheme 2). Heating a DMF solution of 1-(4-methyl-2-(methylamino)thiazol-5-yl)ethanone[5] 4 with benzoyl chloride delivered the acylated product 5, which was subsequently brominated in an analogous procedure to that used to prepare 2b. Bromide 6 was then subjected to a $CuSO_4$/sodium ascorbate click reaction with propargyl alcohol and provided the targeted cycloadduct **7** in fair yield [45%; in contrast, the non-methyl analog of **6** (e.g., **2b**) gave no cycloadduct with propargyl alcohol (result not shown)]. While other modifications such as the use of a Cu(I) ligand to stabilize the copper(I)-oxidation state might benefit these reactions,[7] the results with close analogs 2a and 6 suggest that the benzamide moiety is the root cause of the failed cycloadditions with **2b**.

With triazolothiazole **3** in hand, we addressed the two key questions central of the strategy alluded to in Figure 1: (i) would bromination of **3** result in the formation of a stable and useable 2-bromo-1-(thiazol-5-yl)-2-(1*H*-1,2,3-triazol-1-yl)ethanone and (ii) would the 2-bromo-2-(1*H*-1,2,3-triazol-1-yl)ethanone substructure in this bis-heterocycle react with *N*-substituted thioureas to give 5-(1*H*-1,2,3-triazol-1-yl)-4,5′-bithiazoles? Given that a pivalamide moiety at C2′ proved to be slightly more efficacious in corrector activity than the corresponding benzamide analog,[4,5] we addressed both questions using 1-(thiazol-5-yl)-2-(1H-1,2,3-triazol-1-yl)ethanone **3a**. After some experimentation, we found that bromination of **3a** proceeded most effectively by treatment with elemental bromine in dioxane at 60 °C.[8] Workup, consisting of quenching with 10% $NaHSO_3$ and EtOAc extraction, delivered 2-bromo-1-(thiazol-5-yl)-2-(1H-1,2,3-triazol-1-yl)ethanone **8a** in 45% yield (Scheme 3). While the yield for **3a**→**8a** was modest, product isolation was straightforward and **8a** was stable to manipulation. The Knorr condensation[9] of **8a** with various thioureas was also straight- forward, yielding 5-(1*H*-1,2,3-triazol-1-yl)-4,5′-bithiazoles **9–14** obtained in 56–92% yield. Saponification of the ester moiety in **14** (aq. KOH, THF) delivered acid analog **15**.

2.2. ΔF508-CFTR corrector activity

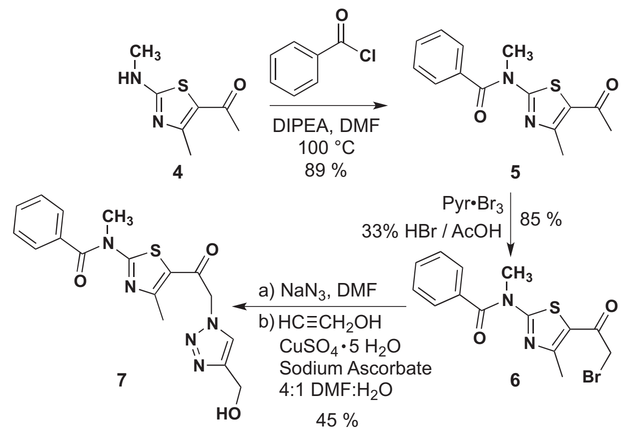
The ΔF508-CFTR corrector activities of triazolobithiazoles **9–15**[10] were evaluated by measurement of I^- influx in epithelial cells expressing ΔF508-CFTR and a fluorescent halide sensor as previously described.[11] The resulting v_{max} and EC_{50} data are tabulated in Scheme 3. While none of the triazolobithiazoles had

Table 2
Two-pot synthesis of 1-(thiazol-5-yl)-2-(1*H*-1,2,3-triazol-1-yl)ethanones **3j–l**

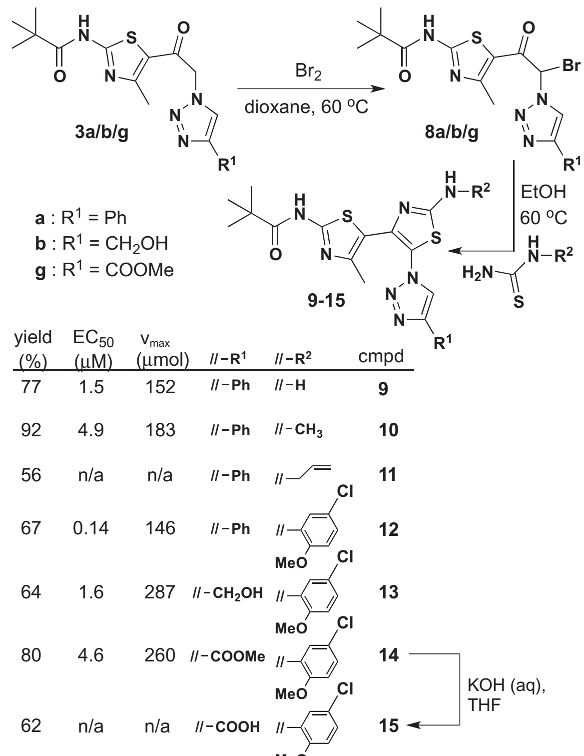


Entry	Compound	R	Yield (%)
1	**3j**	–Ph	69
2	**3k**	$-CH_2OCH_3$	75
3	**3l**	$-CH_2N(CH_2CH_2)O$[a]	55

[a] Morpholine.



Scheme 2. Synthesis of *N*-methyl 1-(thiazol-5-yl)-2-(1*H*-1,2,3-triazol-1-yl)ethanone **7**.



Scheme 3. Synthesis and corrector data for 5-(1*H*-1,2,3-triazol-1-yl)-4,5′-bithiazoles **9–15**.

ΔF508-CFTR corrector activity as good as benchmark bithiazole corr-**4a**, the results with analogs **13** and **14** are encouraging (Fig. 2).

2.3. Measured log *P* values

Encouraged by these results, we measured log *P* values (a measure of a compound's hydrophilicity/hydrophobicity)[12] of triazolobithiazoles **13–15**. The reference for this study is the 5.96 log *P* of corr-**4a**, which Lipinski's rules flag as a limitation.[13] We determined the capacity factor from HPLC retention times to give correlated log *P* values. As shown in Fig. 3, the log *P* values for compounds **13–15** were in the range 4.8–5.5.

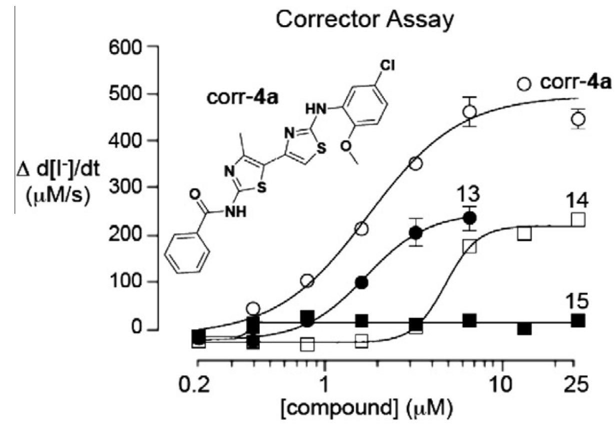


Figure 2. Dose-response showing I^- influx in ΔF508-CFTR cells treated for 24 h with triazolobithiazoles **13–15** or corr-**4a** and stimulated by a cAMP agonist (forskolin) and potentiator (genistein) (S.E., *n* = 4).

3. Conclusions

In summary, we have developed a practical synthesis of triazolobithiazoles, a previously unknown heterocyclic system. Several of the novel compounds reported here had ΔF508-CFTR corrector activity and improved log *P* compared to benchmark corrector corr-**4a**. These results will allow more extensive examination of triazolobithiazoles as potential development candidates for CF therapy.

4. Experimental section

4.1. Chemistry

4.1.1. General experimental procedures

All solvents and reagents were purchased from commercial suppliers and used without further purification. For reactions run in sealed microwave vials, oven-dried 5–10 mL or 10–20 mL vials containing a Teflon-coated stirrer bar and sealed with a Teflon-lined septum were used. Analytical thin layer chromatography was carried out on pre-coated plates (Silica gel 60 F254, 250 μm thickness) and visualized with UV light. Flash chromatography was performed with 60 Å, 35–70 μm silica gel. Concentration refers to rotary evaporation under reduced pressure. ^1H NMR spectra were recorded on spectrometers operating at 300, 400 or 600 MHz at ambient temperature with DMSO-d_6, MeOH-d_4, CD_3CN, acetone-d_6 or $CDCl_3$ as solvents. ^{13}C NMR spectra were recorded on spectrometers operating at 75, 100 or 150 MHz at ambient temper-

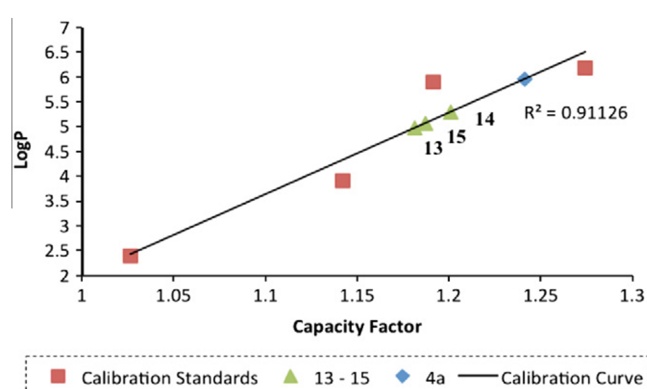


Figure 3. Log *P* measurement of triazolobithiazoles **13–15**.

ature. Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet; br, broad), integration, coupling constant (Hz). Chemical shifts are reported in parts per million relative to DMSO-d_6 (^{1}H, δ 2.50; ^{13}C, δ 39.52), $CDCl_3$ (^{1}H, δ 7.26; ^{13}C, δ 77.16), or TMS (^{1}H, δ 0.00; ^{13}C, δ 0.00). Infrared spectra were recorded on an ATI-FTIR spectrometer. The specifications of the LC/MS are as follows: electrospray (+) ionization, mass range 150–1500 Da, 20 V cone voltage, and C18 column (2.1 × 50 × 3.5 μm). Log*P* measurements were made as previously described.[5]

4.1.2. *N*-(5-Acetyl-4-methylthiazol-2-yl)pivalamide (1a), *N*-(5-acetyl-4-methylthiazol-2-yl)benzamide (1b), *N*-(5-(2-bromoacetyl)-4-methylthiazol-2-yl)pivalamide (2a), and *N*-(5-(2-bromoacetyl)-4-methyl thiazol-2-yl)benzamide (2b)

These compounds were prepared according to published methods and spectral data are in accord with established values.[3]

4.1.3. General procedure for copper catalyzed azide alkyne cycloaddition

A mixture of α-bromoketone (0.30 mmol) and sodium azide (22 mg, 0.34 mmol) were stirred in DMF (2 mL) at room temperature for 1 h. Alkyne (0.36 mmol) was added to the reaction followed by water (1 mL), $CuSO_4$ (4 mg, 0.016 mmol), and sodium L-ascorbate pentahydrate (6 mg, 0.032 mmol). The solution was stirred for 6 h then diluted with water (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organics were washed with water (45 mL) and brine (45 mL), dried over sodium sulfate, filtered, and concentrated. The resulting crude material was purified by flash chromatography.

4.1.4. *N*-(4-Methyl-5-(2-(4-phenyl-1H-1,2,3-triazol-1-yl)acetyl) thiaz-ol-2-yl)pivalamide (3a)

White solid (102 mg, 90%); mp 208–210 °C; IR (neat) ν_{max} 3151, 3115, 2964, 2875, 1666, 1524, 1372, 1319, 1284, 1150, 1115, 968 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.13 (s, 1H), 7.94 (s, 1H), 7.86 (d, *J* = 7, 1H), 7.43 (t, *J* = 7, 2H), 7.34 (t, *J* = 7, 2H), 5.63 (s, 2H), 2.68 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 183.5, 177.0, 160.2, 159.0, 148.4, 130.8, 129.1, 128.5, 126.2, 121.8, 121.5, 57.4, 39.7, 27.4, 18.9; HRMS (ESI): Calcd for $[C_{19}H_{21}N_5O_2S+H]^+$ 384.1494. Found 384.1486.

4.1.5. *N*-(5-(2-(4-(Hydroxymethyl)-1H-1,2,3-triazol-1-yl)acetyl)-4-methylthiazol-2-yl)pivalamide (3b)

White solid (77 mg, 76%); mp 185–186 °C; IR (neat) ν_{max} 3324, 3235, 3138, 2977, 2933, 1688, 1670, 1493, 1324, 1137, 1039, 968 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (s, 1H), 5.57 (s, 2H), 4.76 (s, 1H), 2.57 (s, 2H), 2.07 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 183.6, 178.2, 162.1, 157.6, 148.3, 124.2, 120.8, 57.4, 56.4, 39.8, 27.0, 18.1; HRMS (ESI): Calcd for $[C_{14}H_{19}N_5O_3S+H]^+$ 338.1287. Found 338.1286.

4.1.6. *N*-(5-(2-(4-(Methoxymethyl)-1H-1,2,3-triazol-1-yl)acetyl)-4-methylthiazol-2-yl)pivalamide (3c)

White solid (76 mg, 73%); mp 154–156 °C; IR (neat) ν_{max} 22977, 2933, 1679, 1537, 1493, 1368, 1315, 1226, 1146, 977 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 5.57 (s, 2H), 4.61 (s, 2H), 3.40 (s, 3H), 2.62 (s, 3H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.42, 177.20, 160.37, 158.84, 145.50, 124.65, 121.17, 66.08, 58.46, 57.27, 39.60, 27.21, 18.76; HRMS (ESI): Calcd for $[C_{15}H_{21}N_5O_3S+H]^+$ 352.1443. Found 352.1437.

4.1.7. *N*-(5-(2-(4-((Dimethylamino)methyl)-1H-1,2,3-triazol-1-yl)-acetyl)-4-methylthiazol-2-yl)pivalamide (3d)

Beige solid(61 mg,56%); mp 70–71 °C (decomp); IR (neat) ν_{max} 3138, 2960, 1679, 1528, 1368, 1310, 1230, 1141, 1035, 972 cm^{-1}; ^{1}H NMR (600 MHz, CD_3CN) δ 8.06 (s, 1H), 5.76 (s, 2H), 5.09 (s, 1H), 4.02 (s, 2H), 2.62 (s, 3H), 2.51 (s, 6H), 1.32 (s, 9H); ^{13}C NMR (150 MHz, CD_3CN) δ 185.0, 177.9, 161.3, 157.6, 140.4, 127.3, 122.2, 57.7, 52.8, 52.3, 42.7, 39.4, 26.3, 18.2; HRMS (ESI): Calcd for $[C_{16}H_{24}N_6O_2S+H]^+$365.1759. Found 365.1753.

4.1.8. *N*-(5-(2-(4-(3-Cyanopropyl)-1H-1,2,3-triazol-1-yl)acetyl)-4-methylthiazol-2-yl)pivalamide (3e)

White solid (76 mg, 68%); mp 72–73 °C (decomp); IR (neat) ν_{max} 2969, 2853, 1679, 1537, 1493, 1368, 1315, 1226, 1137, 1039, 977 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (s, 1H), 5.55 (s, 2H), 2.89 (t, *J* = 7, 2H), 2.60 (s, 3H), 2.42 (t, *J* = 7, 2H), 2.07 (p, *J* = 7, 2H), 1.32 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.7, 177.3, 160.5, 158.9, 146.0, 123.6, 121.1, 119.7, 57.3, 39.6, 27.2, 25.1, 24.4, 18.8, 16.7; HRMS (ESI): Calcd for $[C_{17}H_{22}N_6O_2S+H]^+$ 375.1603. Found 375.1596.

4.1.9. *N*-(4-Methyl-5-(2-(4-(morpholinomethyl)-1H-1,2,3-triazol-1-yl)acetyl)thiazol-2-yl)pivalamide (3f)

White solid (91 mg, 75%); mp 183–184 °C; IR (neat) ν_{max} 2964, 2929, 1675, 1533, 1497, 1426, 1372, 1319, 1146, 1110 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.62 (s, 1H), 5.56 (s, 2H), 3.67 (s, 6H), 2.59 (s, 3H), 2.49 (s, 4H), 1.31 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 183.5, 177.2, 160.3, 158.9, 144.6, 124.9, 121.2, 67.1, 57.3, 53.8, 53.5, 39.6, 27.2, 18.8; HRMS (ESI): Calcd for $[C_{18}H_{26}N_6O_3S+H]^+$ 407.1865. Found 407.1861.

4.1.10. Methyl 1-(2-(4-methyl-2-pivalamidothiazol-5-yl)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylate (3g)

White solid (57 mg, 52%); mp 211–213 °C; IR (neat) ν_{max} 3278, 3130, 2981, 1726, 1646, 1544, 1373, 1316, 1224, 1156, 996; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.40 (s, 1H), 8.27 (s, 1H), 5.64 (s, 2H), 3.96 (s, 3H), 2.66 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 182.12, 176.86, 160.99, 160.25, 159.01, 140.20, 129.55, 120.73, 57.05, 52.24, 39.39, 27.01, 18.54; HRMS (ESI) Calcd for $[C_{15}H_{19}N_5O_4S+H]^+$ 366.1236. Found 366.1233.

4.1.11. *N*-(5-(2-(4-(4-Chlorophenyl)-1H-1,2,3-triazol-1-yl)acetyl)-4-methylthiazol-2-yl)pivalamide (3h)

White solid (124 mg, 95%); mp 255–256 °C; IR (neat) ν_{max} 3120, 2969, 2933, 1679, 1661, 1528, 1457, 1368, 1315, 1235, 1137, 968; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.39 (s, 1H), 8.55 (s, 1H), 7.90 (d, *J* = 8.5, 2H), 7.51 (d, *J* = 8.5, 2H), 6.01 (s, 2H), 2.67 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 185.74, 178.31, 162.24, 157.19, 145.79, 132.95, 130.28, 129.65, 127.51, 124.06, 122.68, 57.98, 39.71, 27.02, 19.12; HRMS (ESI): Calcd for $[C_{19}H_{20}ClN_5O_2S+H]^+$ 418.1104. Found 418.1096.

4.1.12. *N*-(5-(2-(4-(3-Hydroxypropyl)-1H-1,2,3-triazol-1-yl)acetyl)-4-methylthiazol-2-yl)pivalamide (3i)

White solid (76 mg, 70%); mp 193–196 °C; IR (neat) ν_{max} 3144, 2930, 2872, 1685, 1529, 1489, 1374, 1315, 1140, 1043, 975 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.34 (s, 1H), 7.76 (s, 1H), 5.83 (s, 2H), 3.44 (t, *J* = 6.4, 2H), 2.66 (t, *J* = 7.6, 2H), 2.63 (s, 2H), 1.78–1.70 (m, 2H), 1.24 (s, 9H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 185.8, 178.0, 161.8, 156.6, 147.0, 123.9, 122.5, 60.5, 57.4, 39.5, 32.8, 26.8, 22.1, 18.8; HRMS (ESI): Calcd for $[C_{16}H_{23}N_5O_3S+H]^+$ 366.1592. Found 366.1603.

4.1.13. *N*-(4-Methyl-5-(2-(4-phenyl-1H-1,2,3-triazol-1-yl)acetyl)thiaz-ol-2-yl)benzamide (3j)

α-Bromoketone **2b** (50 mg, 0.147 mmol) was stirred at room temperature in DMF (4 mL) with sodium azide (10 mg, 0.161 mmol) for 2 h. The reaction was then diluted with water (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organics were washed with brine (30 mL), dried over sodium sulfate, and filtered. The reaction was concentrated, dissolved in dry THF (2 mL) in a flask covered with tin foil, and triethylamine (77 μL, 0.558 mmol), copper(I) iodide (70 mg, 0.372 mmol), and phenylacetylene (16 mg, 0.161 mmol) were added. The reaction was stirred 12 h at room temperature and quenched by the addition of aq. NH_4OH. The mixture was extracted with EtOAc (3 × 10 mL) and the combined organics were washed with brine, dried over sodium sulfate, filtered and concentrated. The crude material was purified by recrystallization in EtOAc/hexanes to yield **3j** as a white solid (38 mg, 69%); mp 222–224 °C; IR (neat) ν_{max} 2910, 1682, 1533, 1481, 1192, 1030, 965 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 1H), 8.14 (d, *J* = 7.3, 2H), 7.89 (d, *J* = 7.2, 2H), 7.69 (t, *J* = 7.4, 1H), 7.58 (t, *J* = 7.6, 2H), 7.48 (t, *J* = 7.7, 2H), 7.36 (t, *J* = 7.4, 1H), 6.06 (s, 2H), 2.73 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 185.1, 184.9, 161.4, 146.0, 133.0, 131.2, 130.5, 128.7, 128.5, 128.2, 127.7, 125.0, 122.8, 122.1, 57.1, 26.1.; HRMS Calcd for $[C_{21}H_{17}N_5O_2S+H]^+$ 404.1181. Found 404.1171.

4.1.14. *N*-(5-(2-(4-(Methoxymethyl)-1H-1,2,3-triazol-1-yl)acetyl)-4-methylthiazol-2-yl)benzamide (3k)

White solid (42 mg, 75%); mp 225–226 °C; IR (neat) ν_{max} 3158, 2924, 1670, 1536, 1488, 1322, 1283, 1098, 965 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.97–7.95 (m, 2H), 7.72 (s, 1H), 7.70–7.68 (m, 1H), 7.59–7.55(m, 2H), 5.63 (s, 2H), 4.65 (s, 2H), 3.44 (s, 3H), 2.66 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 183.1, 164.9, 160.4, 133.7, 130.9, 129.2, 127.6, 124.4, 121.1, 65.9, 58.3, 57.1, 50.9, 30.4, 18.5; HRMS (ESI): Calcd for $[C_{17}H_{17}N_5O_3S+H]$ +372.1130. Found 372.1131.

4.1.15. *N*-(4-Methyl-5-(2-(4-(morpholinomethyl)-1H-1,2,3-triazol-1-yl)acetyl)thiazol-2-yl)benzamide (3l)

White solid (690 mg, 55%); mp 232–233 °C; IR (neat) ν_{max} 2943, 2355, 2140, 2049, 1908, 1671, 1488, 1219, 1057, 965 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 8.18 (s, 1H), 8.00 (s, 1H), 7.72 (s, 1H), 7.62 (s, 1H), 5.95 (s, 1H), 3.66 (d, *J* = 28.1, 3H), 3.25 (s, 2H), 2.75 (s, 1H), 2.55 (s, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 185.2, 166.0, 161.4, 156.2, 142.7, 132.9, 131.5, 128.6, 128.3, 125.4, 122.1, 66.0, 57.0, 52.7, 18.2; HRMS (ESI): Calcd for $[C_{20}H_{22}N_6O_3S+H]^+$ 427.1552. Found 427.1543.

4.1.16. 1-(4-Methyl-2-(methylamino)thiazol-5-yl)ethanone (4)

Prepared following a published method; spectral data in accordance with established values.[5]

4.1.17. *N*-(5-Acetyl-4-methylthiazol-2-yl)-N-methylbenzamide (5)

1-(4-Methyl-2-(methylamino)thiazol-5-yl)ethanone (1.27 g, 7.47 mmol) and N,N-diisopropylethylamine (1.55 mL, 8.96 mmol) were added to a flask charged with DMF (40 mL). The reaction flask was then heated to 100 °C and benzoyl chloride (1.29 mL, 11.2 mmol) was added. The reaction was stirred at 100 °C for 12 h and monitored by thin-layer chromatography. Upon completion, the reaction was poured into ice-cold water and a precipitate formed. The precipitate was collected by filtration and the beige solid (**5**) was used without further purification (1.82 g, 89%); mp 128–130 °C; IR (neat) ν_{max} 2917, 1664, 1516, 1477, 1415, 1360, 1306, 1251, 1103, 1010, 946 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.58–7.52 (m, 3H), 7.52–7.47 (m, 2H), 3.66 (s, 3H), 2.69 (s, 3H), 2.53 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 191.2, 170.7, 160.3, 154.9, 133.8, 131.2, 128.7, 127.6, 126.0, 38.2, 30.6, 18.4; HRMS (ESI) Calcd for $[C_{14}H_{14}N_2O_2S+H]^+$ 275.0840. Found 275.0855.

4.1.18. *N*-(5-(2-Bromoacetyl)-4-methylthiazol-2-yl)-N-methylbenzamide (6)

N-(5-Acetyl-4-methylthiazol-2-yl)-*N*-methyl-benzamide (**5**; 100 mg, 0.36 mmol) and pyridinium tribromide (127 mg, 0.400 mmol) were added to a round bottom flask under a nitrogen atmosphere. The flask was charged with 1.5 mL of 33% HBr in acetic acid, then stirred at room temperature overnight. The reaction was quenched by the addition of water (2 mL) and a precipitate formed, which was collected by filtration. The filtrate was extracted with ethyl acetate (3 × 10 mL) and the precipitate was added to the combined organic extracts. These combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude material was purified by flash chromatography (2:1 EtOAc:hexanes) to afford **6** as an amorphous beige solid (108 mg, 85%); IR (neat) 2927, 1656, 1477, 1446, 1415, 1368, 1306, 1189, 1096, 1018 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.58–7.43 (m, 5H), 4.25 (s, 2H), 3.65 (s, 3H), 2.69 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 184.6, 170.8, 161.1, 157.8, 133.5, 131.4, 128.7, 127.6, 122.4, 38.4, 34.1, 18.6; HRMS Calcd for $[C_{14}H_{13}BrN_2O_2S+H]^+$ 352.9951 found 352.9927.

4.1.19. *N*-(5-(2-(4-(Hydroxymethyl)-1H-1,2,3-triazol-1-yl)acetyl)-4-methylthiazol-2-yl)-N-methylbenzamide (7)

N-(5-(2-Bromo-acetyl)-4-methylthiazol-2-yl)-N-methylbenzamide (**6**; 93.5 mg, 0.260 mmol) was dissolved in DMF (1.4 mL) and sodium azide (21.0 mg, 0.316 mmol) was added and stirred at room temperature for 30 min. The reaction was diluted with water (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organics were washed with brine (30 mL), dried over sodium sulfate, filtered, and concentrated. This crude azide was reconstituted in a 4:1 DMF:H_2O solution (1.5 mL) and copper(II) sulfate, sodium ascorbate, and propargyl alcohol were added. The reaction was stirred at room temperature for 2 h and monitored by thin layer chromatography. When complete, the reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3 × 15 mL); the combined organics were washed with brine, dried over sodium sulfate, filtered, and concentrated. The resulting crude material was purified by flash chromatography (EtOAc) to yield **7** as a beige solid (44 mg, 45%); mp 161–163 °C; IR (neat) ν_{max} 3321, 1684, 1655, 1475, 1410, 1299, 1016, 3064 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 7.92 (s, 1H), 7.68 (d, *J*= 6, 2H), 7.59 (t, *J* = 7.5, 1H), 7.54 (t, *J* = 7.5, 2H), 5.94 (s, 2H), 5.21 (t, *J* = 5.6, 1H), 4.56 (d, *J* = 5.6, 2H), 3.57 (s, 3H), 2.69 (s, 3H); ^{13}C NMR (150 MHz DMSO-d_6) δ 186.3, 171.0, 161.8, 155.7, 148.3, 134.1, 131.6, 129.0, 128.1, 124.8, 123.9, 57.6, 55.5, 38.6, 19.1; HRMS (ESI) Calcd for $[C_{17}H_{17}N_5O_3S+H]^+$ 372.1122 found 372.1097.

4.1.20. *N*-(5-(2-Bromo-2-(4-phenyl-1H-1,2,3-triazol-1-yl) acetyl)-4-methylthiazol-2-yl)pivalamide (8a)

N-(4-Methyl-5-(2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)acetyl)thi-azol-2-yl)pivalamide (**3a**; 50 mg, 0.14 mmol) was dissolved in dioxane (0.65 mL), the reaction flask was wrapped with tin foil, and the solution was heated to 60 °C. Elemental bromine (72 μL, 0.14 mmol) was added and the reaction was stirred for 5 h. The reaction was quenched by the addition of $NaHSO_3$ (2 mL) and the resulting mixture was extracted with EtOAc (3 × 4 mL). The combined organics were washed with water and brine, dried over sodium sulfate, filtered, and concentrated. The crude material was purified by flash chromatography (2:1 EtOAc:hexanes) to afford **8a** as a yellow amorphous solid (27 mg, 45%); IR (neat) ν_{max} 2910, 2850, 1634, 1524, 1369, 1200, 1145, 1039, 970 $cm^{-1}$$^1H$ NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1H), 8.49 (s, 1H), 7.91–7.85 (m, 2H), 7.56 (s, 1H), 7.43 (t, *J* = 7.6, 2H), 7.35 (t, *J* = 7.3, 1H), 3.69 (s, 2H), 2.70 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.6, 176.9, 162.0, 161.0, 149.2, 130.1, 129.1, 128.8, 126.1, 121.5, 119.2, 55.6, 39.6, 27.4, 19.1; HRMS (ESI) Calcd for $[C_{19}H_{20}BrN_5O_2S+H]^+$ 462.0591. Found 462.0589.

4.1.21. *N*-(5-(2-Bromo-2-(4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)-acetyl)-4-methylthiazol-2-yl)pivalamide (8b)

Yellow solid (16 mg, 35%); mp 120–121 °C; IR (neat) ν_{max} 3170, 2964, 2930, 1686, 1527, 1367, 1321, 1139, 1036 cm^{-1}; ^1H NMR

(600 MHz, DMSO-d_6) δ 11.46 (s, 1H), 8.76 (s, 1H), 8.33 (s, 1H), 5.18 (d, J = 5.8, 3H), 3.07 (s, 3H), 1.82 (s, 9H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 180.1, 178.0, 162.5, 161.5, 150.4, 124.1, 119.4, 57.9, 56.3, 39.9, 26.8, 18.8; HRMS (ESI) Calcd for $[C_{14}H_{18}BrN_5O_3S+H]^+$ 416.0392 found 416.0388.

4.1.22. Methyl 1-(1-bromo-2-(4-methyl-2-pivalamidothiazol-5-yl)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylate (8g)

Yellow solid (71 mg, 60%); mp 52–53 °C (decomp); IR (neat) ν_{max} 3284, 2964, 1737, 1666, 1524, 1479, 1372, 1212, 1141, 1035, 972 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.42 (br s, 1H), 8.81 (s, 1H), 7.51 (s, 1H), 3.99 (s, 3H), 2.70 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.9, 177.2, 162.4, 161.5, 160.8, 141.0, 130.1, 118.7, 54.5, 52.6, 39.6, 27.2, 19.1; HRMS (ESI) Calcd for $[C_{15}H_{18}BrN_5O_4S+H]^+$ 444.0341 found 444.0340.

4.1.23. *N*-(2-Amino-4′-methyl-5-(4-phenyl-1H-1,2,3-triazol-1-yl)-4,5′-bithiazol-2′-yl)pivalamide (9)

N-(2-Amino-4′-methyl-5-(4-phenyl-1H-1,2,3-triazol-1-yl)-4,5′-bithiazol-2′-yl)pivalamide (20 mg, 0.043 mmol) and thiourea (3 mg, 0.047 mmol) were dissolved in ethanol (0.210 mL) and the mixture was stirred at 60 °C for 3 h. The reaction was then concentrated and the crude material dissolved in EtOAc (3 mL). The organics were washed with water (4 mL) and brine (4 mL), dried over sodium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography (3:1 EtOAc:hexanes) to afford **9** (14 mg, 77%); mp 196–200 °C; IR (neat) ν_{max} 2964, 2920, 1684, 1630, 1515, 1479, 1372, 1310, 1132, 970 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (d, J = 8.0, 2H), 7.56 (s, 1H), 7.48 (t, J = 8.0, 2H), 7.43 (t, J = 8.0, 2H), 2.81 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.8, 171.0, 163.6, 157.2, 154.6, 129.1, 128.9, 126.7, 126.4, 125.3, 123.6, 39.4, 29.7, 27.1, 18.9; HRMS (ESI): Calcd for $[C_{20}H_{21}N_7OS_2+H]^+$ 440.1327. Found 440.1318.

4.1.24. *N*-(4′-Methyl-2-(methylamino)-5-(4-phenyl-1H-1,2,3-triazol-1-yl)-4,5′-bithiazol-2′-yl)pivalamide (10)

Brown solid (18 mg, 92%); mp 136–137 °C; IR (neat) ν_{max} 3231, 2964, 2929, 1675, 1533, 1400, 1301, 1221, 1150, 1026 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74–7.66 (m, 3H), 7.35 (t, J = 7.5, 2H), 7.28 (d, J = 7.4, 1H), 6.68 (s, 1H), 2.91 (d, J = 4.7, 3H), 1.88 (s, 3H), 1.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 158.4, 148.0, 146.2, 137.0, 129.8, 129.3, 129.1, 128.8, 126.1, 125.5, 121.9, 117.2, 39.4, 32.0, 27.4, 15.8; HRMS (ESI): Calcd for $[C_{21}H_{23}N_7OS_2+H]^+$ 454.1483. Found 454.1473.

4.1.25. *N*-(2-(Allylamino)-4′-methyl-5-(4-phenyl-1H-1,2,3-triazol-1-yl)-4,5′-bithiazol-2′-yl)pivalamide (11)

White solid (11 mg, 56%); mp 204–206 °C; IR (neat) ν_{max} 2969, 2924, 2720, 1679, 1617, 1519, 1484, 1368, 1324, 1146, 977 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 7.78 (d, J = 7.4, 2H), 7.73 (s, 1H), 7.41 (t, J = 7.4 3H), 7.33 (t, J = 7.4, 1H), 6.20 (s, 1H), 5.88 (ddd, J = 5.5, 10.2, 17.1, 1H), 5.32 (d, J = 17.1, 1H), 5.22 (d, J = 10.2, 1H), 3.92 (t, J = 5.5, 3H), 1.96 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 166.2, 157.9, 148.0, 146.5, 136.6, 132.9, 130.0, 129.1, 128.7, 126.2, 121.7, 118.1, 117.5, 116.7, 48.0, 39.3, 27.4, 15.9; HRMS (ESI) Calcd for $[C_{23}H_{25}N_7OS_2+H]^+$ 480.1632. Found 480.1630.

4.1.26. *N*-(2-(5-Chloro-2-methoxyphenylamino)-4′-methyl-5-(4-phenyl-1H-1,2,3-triazol-1-yl)-4,5′-bithiazol-2′-yl)pivalamide (12)

White solid (16 mg, 67%); mp 150–154 °C; IR (neat) ν_{max} 2964, 1675, 1604, 1533, 1479, 1284, 1257, 1035 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.17 (d, J = 2.5, 1H), 7.82–7.77 (m, 3H), 7.41 (t, J = 7.6, 2H), 7.34 (t, J = 7.6, 1H), 6.98 (dd, J = 2.5, 8.6, 1H), 6.81 (d, J = 8.6, 1H), 3.90 (s, 3H), 2.11 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.1, 159.9, 158.1, 148.3, 147.2, 146.3, 136.8, 130.0, 129.9, 129.1, 128.8, 126.5, 126.3, 122.6, 121.7, 118.0, 117.5, 117.0, 111.2, 56.3, 39.3, 27.4, 16.2; HRMS (ESI): Calcd for $[C_{27}H_{26}ClN_7O_2S_2+H]^+$ 580.1356. Found 580.1351.

4.1.27. *N*-(2-(5-Chloro-2-methoxyphenylamino)-5-(4-(hydroxylmethyl)-1H-1,2,3-triazol-1-yl)-4′-methyl-4,5′-bithiazol-2′-yl)pivalamide (13)

Yellow solid (15 mg, 64%); mp 172–173 °C; IR (neat) ν_{max} 2977, 1679, 1599, 1528, 1484, 1412, 1297, 1252, 1172, 1030 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 10.37 (s, 1H), 9.44 (s, 1H), 8.69 (d, J = 2.3, 1H), 7.93 (d, J = 6.2, 1H), 7.02–6.88 (m, 2H), 4.67 (s, 2H), 3.83 (s, 3H), 2.85 (s, 1H), 2.06 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, acetone-d_6) δ 176.5, 160.1, 158.1, 149.2, 146.9, 137.4, 131.0, 125.4, 125.1, 121.7, 117.9, 116.6, 111.7, 111.0, 109.0, 78.5, 55.9, 39.1, 26.5, 15.9; HRMS (ESI): Calcd for $[C_{22}H_{24}ClN_7O_3S_2+H]^+$ 534.1149. Found 534.1139.

4.1.28. Methyl 1-(2-(5-chloro-2-methoxyphenylamino)-4′-methyl-2′-pivalamido-4,5′-bithiazol-5-yl)-1H-1,2,3-triazole-4-carboxylate (14)

White solid (19 mg, 80%); mp 198–200 °C; IR (neat) ν_{max} 3169, 2955, 1737, 1693, 1675, 1541, 1497, 1435, 1372, 1292, 1221, 1043 cm^{-1}; ^{1}H NMR (600 MHz, acetone-d_6) δ 10.43 (s, 1H), 9.59 (s, 1H), 8.77 (s, 1H), 8.75 (d, J = 2.4, 1H), 7.03 (dt, J = 5.5, 8.7, 2H), 3.91 (s, 3H), 3.87 (s, 3H), 2.90 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (150 MHz, acetone-d_6) δ 176.5, 160.8, 160.5, 158.1, 147.4, 147.0, 139.9, 139.2, 131.9, 130.8, 125.4, 122.0, 118.0, 116.0, 115.9, 111.8, 55.9, 51.6, 39.1, 26.5, 16.2. HRMS (ESI): Calcd for $[C_{23}H_{24}ClN_7O_4S_2+H]^+$ 562.1098. Found 562.1092.

4.1.29. 1-(2-(5-Chloro-2-methoxyphenylamino)-4′-methyl-2′-pival-amido-4,5′-bithiazol-5-yl)-1H-1,2,3-triazole-4-carboxylic acid (15)

Beige solid (14 mg, 62%); mp 206–208 °C; IR (neat) ν_{max} 3169, 2955, 1737, 1693, 1675, 1541, 1497, 1435, 1372, 1292, 1221, 1043 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.57–13.19 (m, 1H), 11.92 (s, 1H), 10.32 (s, 1H), 9.07 (d, J = 0.9, 1H), 8.66 (s, 1H), 7.13–7.02 (m, 2H), 3.90 (s, 3H), 2.29 (s, 3H), 1.20 (s, 9H); ^{13}C NMR (100 MHz, acetone-d_6) δ 187.2, 161.4, 161.2, 158.8, 148.1, 140.7, 140.0, 132.6, 131.6, 126.1, 122.7, 118.8, 116.8, 116.4, 112.6, 56.6, 52.4, 39.8, 27.2, 17.0. HRMS (ESI): Calcd for $[C_{22}H_{22}ClN_7O_4S_2+H]^+$ 548.0941. Found 548.0933.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2012.06.046.

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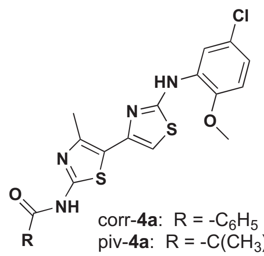

corr-**4a**: R = -C_6H_5
piv-**4a**: R = -$C(CH_3)_3$

(a) In our previously reported SAR study of 148 methylbithiazole analogues focused on the peripheral amide and aniline substructures (e.g., circled regions ‘a’ and ‘c’, respectively, of the bithiazole depicted in Fig. 1, we established that piv-**4a** (see right) is a more effective corrector than corr-**4a**.[10b] This, coupled with the click chemistry problems associated with the benzamide series, suggested to us that proceeding with only the pivalamide series (e.g., triazolobithiazoles 9–15) was appropriate; (b) Yoo, C. L.; Yu, G. J.; Yang, B.; Robins, L. I.; Verkman, A. S.; Kurth, M. J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2610.
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