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Synthesis of novel amide and urea derivatives of thiazol-2-ethylamines and their activity against *Trypanosoma brucei rhodesiense*

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Abstract

2-(2-Benzamido)ethyl-4-phenylthiazole (**1**) was one of 1035 molecules (grouped into 115 distinct scaffolds) found to be inhibitory to *Trypanosoma brucei*, the pathogen causing human African trypanosomiasis, at concentrations below 3.6 μM and non-toxic to mammalian (Huh7) cells in a phenotypic high-throughput screen of a 700,000 compound library performed by the Genomics Institute of the Novartis Research Foundation (GNF). Compound **1** and 72 analogues were synthesized in this lab by one of two general pathways. These plus 10 commercially available analogues were tested against *T. brucei rhodesiense* STIB900 and L6 rat myoblast cells (for cytotoxicity) in vitro. Forty-four derivatives were more potent than **1**, including eight with IC_{50} values below 100 nM. The most potent and most selective for the parasite was the urea analogue 2-(2-piperidin-1-ylamido)ethyl-4-(3-fluorophenyl)thiazole (**70**, IC_{50} = 9 nM, SI > 18,000). None of 33 compounds tested were able to cure mice infected with the parasite; however, six compounds caused temporary reductions of parasitemia (≥97%) but with subsequent relapses. The lack of in vivo efficacy was at least partially due to their poor metabolic stability, as demonstrated by the short half-lives of 15 analogues against mouse and human liver microsomes.

Keywords

Thiazole; Amide; Urea; Antitrypanosomal; Metabolic stability

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1. Introduction

Human African trypanosomiasis (HAT) occurs in 36 nations of sub-Saharan Africa. In 2015 the World Health Organization (WHO) estimated 20,000 actual cases with 65 million people at risk. Transmitted by tsetse flies, the disease is due to a chronic infection of *Trypanosoma brucei gambiense* (in western and Central Africa, over 98% of reported cases) or an acute infection of *Trypanosoma brucei rhodesiense* (in southern and eastern Africa). The *T. b. gambiense* infection is characterized by a slow progression from early (hemolymphatic) stage—where many patients are asymptomatic—to late stage disease, after the parasites have entered the central nervous system (CNS). The *T. b. rhodesiense* infection is characterized by earlier onset of symptoms and a more rapid progression from early to late stage. In either case, late stage HAT is always fatal if untreated.[1],[2]

The need for new anti-HAT drugs continues to persist, as current drugs are few, antiquated, toxic, prone to resistance, and require parenteral administration. Treatments for *T. b. rhodesiense* infections are limited to suramin (a polysulfonated naphthylurea) for early stage and melarsoprol (an organoarsenical) for late stage disease. First line treatments for *T. b. gambiense* infections include pentamidine (an aromatic diamidine) for early stage and nifurtimox-eflornithine combination therapy (NECT) for late stage disease.[1-4]

This laboratory has prepared a large number of aromatic diamidines that were assayed against the trypanosome. Among the most promising were the 3,5-bis(amidinoaryl)isoxazoles[5,6] and the 3,3-bis(amidinoaryl)benzenes,[7,8] which are all analogues of 2,5-bis(4-amidinophenyl)furan (furamidine)[9,10] having different central rings. After the failure of pafuramidine[11,12] (an orally active prodrug of furamidine) in clinical trials against early stage HAT,[13] our attention has shifted to non-amidine treatments of the disease. Two promising non-amidine anti-HAT drug candidates, the nitrated imidazole derivative fexninidzole[14] and the benzoxaborole SCYX,[15] have entered clinical trials in recent years. A phenotypic high-throughput screen of a 700,000 compound library performed by the Genomics Institute of the Novartis Research Foundation (GNF) led to the identification of 1035 compounds that inhibited growth of *T. brucei* in vitro at concentrations below 3.6 μM and were non-toxic to mammalian cells (Huh7). The 1035 hits could be grouped into 115 distinct scaffolds. These scaffolds was further refined based in part on their relative ease of synthesis, a lack of chiral carbon atoms, and druglike features including low molecular weight and adherence to Lipinski's rules. Work toward optimization of one of these scaffolds in the lab of a collaborator has been reported.[16]

2. Chemistry

The lead compound, 2-(2-benzamido)ethyl-4-phenylthiazole (**1**, Table 1) was one of several other scaffolds from the GNF library selected for optimization in this laboratory or those of our collaborators. The syntheses of more than 70 analogues are described herein. Analogues **2–73** have modifications of either the 4-thiazolyl aromatic ring (R_2, **2-26**, Table 1), the carbonyl substituent (R_1) or the carbonyl group itself (**27–55**, Table 2), or at both R_1 and R_2 (**56–73**, Table 3). The commercially available 4-alkyl-2-arylthiazoles **74–83** (Table 4) are regioisomers of 10 synthesized compounds with reversed substitution patterns on the thiazole rings.

The synthesis of **1**, based upon that of its [^{14}C] isotopomer,[17] is depicted in Scheme 1. The benzoylation of 3-aminopropionitrile (**84**) gave the cyano-amide **85**,[18] which was converted to thioamide **86**[18] using sodium hydrosulfide and magnesium chloride in DMF.[19] A Hantzsch thiazole synthesis involving **86** and 2-bromoacetophenone[17] gave the lead compound **1**. Similar reactions of **86** with other 1-aryl-2-bromoethanones gave substituted phenyl (**2–21**) and heteroaromatic (**22–26**) analogues. Initially these reactions were performed in refluxing ethanol.[17] However, it was later found that these reactions proceed equally well at room temperature.

A variation of this pathway was employed for compounds **27–73** (Scheme 2). Treatment of **84** with di-*tert*-butyl dicarbonate in the presence of Montmorillonite K10[20] gave intermediate **87**,[21] which was converted to thioamide **88**[22] under the same conditions described above for **86**. The reaction of **88** with the appropriate 2-bromoacetophenone derivative in refluxing ethanol effected both thiazole ring closure and amine deprotection to give the 4-arylthiazol-2-ethylamine synthons **89a–f**, which conveniently precipitated from the reaction mixture as their hydrobromide salts. The reaction of **89a** with the appropriate acyl chloride and triethylamine in THF gave amides **27–43** and trisubstituted ureas **44**, **46–48** (Table 2). Analogous reactions involving anhydrides, isocyanates, chloroformates, or sulfonyl chlorides gave trisubstituted urea **45**, *N,N'*-disubstituted ureas **49–52**, carbamate **53**, and sulfonamides **54–55**, respectively (Table 2). The reaction of synthons **89b–f** with the appropriate acyl halides gave amides **57–66** and ureas **67–73** (Table 3).

3. Biological Results

3.1. Antiparasitic activities

3.1.1. In vitro potencies—Synthesized compounds **1–73** along with commercial compounds **74–83** were tested for activity against human pathogenic *T. b. rhodesiense* as well as toxicity to L6 rat myoblast cells[23] (Tables 1–4). The selectivity index (SI, the ratio of cytotoxic to antitrypanosomal IC_{50} values) was also determined for each compound. Standard drugs included pentamidine and melarsoprol (against the parasite) and podophyllotoxin (for cytotoxicity).

The effects of modification of the 4-thiazolyl substituent (R_2) are shown in Table 1. This subset of compounds includes substituted phenyl (**2–21**) and heteroaromatic (**22–26**) analogues. The cyano, trifluoromethyl, nitro, and methoxy derivatives (**2–8**) were all less potent than **1** (IC_{50} = 632 nM, SI = 162). Only members of the halogenated analogue subset (**9–21**) exhibited enhanced potencies, with the greatest enhancements found with the fluorinated derivatives. The 2-fluorophenyl derivative **9** (IC_{50} = 156 nM) was the most potent of the monosubstituted compounds, followed by the 4-fluoro (**11,** IC_{50} = 218 nM), 3-fluoro (**10,** IC_{50} = 233 nM), the 3-chloro (**12,** IC_{50} = 452 nM) and 3-bromo (**14**, IC_{50} = 553 nM) analogues. The 3-fluoro and 4-fluoro isomers **10** and **11** were similarly potent, but in all other cases the 3-substituted analogues **2**, **5**, **7**, **12**, and **14** were more potent than their 4-substituted isomers. The 2,4– and 3,4-difluoro derivatives **16** and **19** were similar in potency to 2-fluoro analogue **9**. The other difluoro isomers **17**, **18**, and **20**, as well as the trifluoro analogue **21** were all less potent than **1.** Replacement of the benzene ring with furan, thiophene or pyridine (compounds **22–26**) resulted in diminished potency in all instances. In summary, seven halogenated phenyl analogues were more potent than **1**, including fluorinated derivatives **9**, **16**, and **19** with IC_{50} values below 200 nM. The 3,4-difluoro analogue **19** (IC_{50} = 145 nM, SI = 211) was the most potent of this subset, while its 2,4-difluoro isomer **16** (IC_{50} = 162 nM, SI > 1593) was the third most potent and the most highly selective for the parasite. Modifications at this site resulted in less than fivefold enhancements of potency.

Enhancements of potency of up to 30–fold were observed upon modification of the ring attached to the carbonyl carbon (R_1, compounds **27–55**, Table 2). This subset includes amides **27–43**, ureas **44–52**, carbamate **53**, and sulfonamides **54–55**. Among the substituted benzamides **27–35**, the 3-nitro (**29,** IC_{50} = 150 nM) and 3-cyano (**27,** IC_{50} = 171 nM) derivatives were the most potent followed by 3-fluoro (**31**), 2-fluro (**30**) and 2-chloro (**33**) analogues having IC_{50} values between 350 and 500 nM. The 3-cyano (**27**), – fluoro (**31**), and –chloro (**34**) substituted analogues were more potent than their 4-substituted isomers. While the replacement of benzene with furan (**37**) or thiophene (**38** and **39**) resulted in enhanced potency relative to **1,** replacement with pyrrole (**36**) or pyridine (**40** and **41**) did not. The 3-thiophenyl amide **39** (IC_{50} = 190 nM) was the most potent in this group, followed by 2-thiophenyl (**38**) and furanyl (**37**) analogues with IC_{50} values between 250 and 500 nM. Enhanced potencies were also observed in cyclohexyl (**43**, IC_{50} = 164 nM, SI = 1250) and cyclopentyl (**42**, IC_{50} = 268 nM, SI = 648), in which the benzene ring is replaced with cycloalkanes. These two compounds were also the most highly selective for the parasite among compounds **27-43**, and the only ones with selectivity indices above 500.

The greatest enhancements in activities were observed in the trisubstituted ureas, in which the benzene ring is replaced with a cyclic amine. The most potent example was piperidinyl urea **46** (IC_{50} = 20.4 nM, SI = 11900), followed by azepanyl urea **48** (IC_{50} = 51.6 nM, SI = 4450), and pyrrolidinyl urea **44** (IC_{50} = 125 nM, SI = 1960). The aromatization of the pyrrolidine ring to pyrrole led to decreased potency (**44** vs **45**), as did the replacement of piperidine with morpholine (**46** vs **47**). By contrast, all of the *N,N'*-disubstituted ureas **49-52**, which are derived from primary amines, were less potent than the lead compound **1**, as was carbamate derivative **53**.

An amide or urea group proved to be essential to activity. Replacement of the carbonyl group with a sulfonyl (**54–55**) resulted in 80– to 120-fold decreases in potency when compared to **1**. Elimination of the benzoyl groups led to diminished activity but to a lesser extent compared to the sulfonamides. The primary amino synthetic intermediates **89a–c** exhibited IC_{50} values of 2.2, 16.3, and 15.9 μM, respectively (data not shown), being less potent than the corresponding benzamides **1**, **9** and **10**. The difference in potency between **89a** and **1** was less than 4-fold, but much greater disparities (over 100-fold and nearly 70-fold) existed in the other two pairs.

Incremental enhancements of potency were achieved by incorporating modifications at both ends of the molecule (**56–73**, Table 3). The potencies of amides **27**, **29**, **31**, and **38** were enhanced by almost 2-fold by fluorination of the 4-thiazolyphenyl ring (**56–58**, **59–61**, **62–63**, and **64–66**, respectively) in all instances but the 2-fluorophenyl analogue **56**, where diminished activity was observed. However, none of the amides **56–66** exhibited IC_{50} values below 100 nM or selectivity indices above 500. The effects of aromatic fluorination were more pronounced in the urea analogues. The potency of pyrrolidinyl urea **44** was enhanced more than twofold, accompanied by higher selectivity, in the cases of 2–and 3-fluorophenyl analogues **67** and **68** but not the 4-fluorophenyl isomer **69**. By contrast, enhanced potency relative to piperidinyl urea **46** was observed with both the 3- and 4-fluoro analogues **70** and **71**. Attempts at isolating the 2-fluorophenyl analogue in this series were unsuccessful. The potency of **46** was also enhanced in the cases of the 2,4- and 3,4-difluorophenyl derivatives **72** and **73**. The piperidine ureas **46** and **70–73**, in addition to being the five most potent compounds, were also the most highly selective for the parasite, with selectivity indices between 9,000 and 19,000. The 3-fluoro analogue **70** (IC_{50} = 9 nM, SI > 18,800), was the most potent and most highly selective overall, being 70 times more potent than **1**.

Commercially available compounds **74–83** are regioisomers of 10 synthesized analogues with reversed substitution patterns on the thiazole rings. The activities and selectivities of each pair of compounds are shown side by side (Table 4). Differences in potency were less than 2-fold in seven out of 10 cases. The greatest difference (3-fold) existed between **79** and **33**. The correlations of potency within each pair suggest that that activity is indifferent to a reversed substitution pattern on the thiazole ring. Subsequent to the time when these experiments was performed, the corresponding regioiosmer of **1** and a number of closely related analogues have been identified as hits against *T. b. brucei* in other high throughput screens.[24,2] A patent[25] published while this manuscript was in progress gave activities of a number of 2-arylthiazoles, 26 of which are regioisomers of the test compounds in this study. A similar table showing side-by-side comparisons of activities of a total of 29 pairs of regioisomers is available in the supplemental data file. While the data derived from different strains of the trypanosome are not directly comparable, the results are qualitatively similar. The SAR trends in the 4-arylthiazoles were mirrored by the 2-arylthiazoles with respect to modifications to both R_1 and R_2. For example, fluorination of the R_2 aromatic ring led to slightly enhanced activity, while replacement of the benzene ring with heterocycles led to diminished acitivity in both groups. Similar enhancements or decreases in activity were obtained by modification of the R_1 group, most notably by the replacement of this benzene ring with a piperidine, and activity was lost by replacement of the carbonyl group with a sulfonyl function.

Overall, antiparasitic IC_{50} values ranged from 9 nM to >300 μM, and 44 analogues were more potent than the lead compound. Potencies were below 100 nM for eight compounds, below 200 nM for another 18 analogues, and below 500 nM for another 15 derivatives. The ureas were clearly significantly more potent than the amides, as well as being more selective for the parasite. Urea **70** (IC_{50} = 9 nM, SI > 18,000) was the most potent and the most selective for the parasite. The other seven urea derivatives with potencies below 100 nM had selectivity indices between 3,000 and 12,000. By contrast, compound **57** was the most potent amide analogue (IC_{50} = 104 nM); however, its SI was only around 300.

3.1.2. In vivo efficacies—Thirty-three compounds (**1**, **9–12**, **16**, **27**, **29–31**, **33**, **37–39**, **42–44**, **46**, **47**, **56–69**) having IC_{50} values below 0.2 μg/mL were administered intraperitoneally (ip) to mice infected with *T. b. rhodesiense* STIB900 following a modification of an established protocol[8] in which groups of two mice were treated with three consecutive daily 40 mg/kg doses beginning 24 hours post infection. Despite their in vitro potencies, none of compounds cured any infected mice (data not shown). Seven compounds (amides **12**, **16**, **42**, **56**, **61**, and **65** and urea **44**) did cause reductions in parasitemia in both mice by at least 97% (compared to the untreated control group) as observed at either the 24 or 96 hour timepoint following the final dose, or by at least 90% in the case of urea **46**. However, subsequent relapses occurred in all cases.

3.2. Metabolic stability

To determine if metabolic instability contributed to the lack of in vivo efficacy, we examined the stability of 15 select compounds (**1**, **9**, **10**, **16**, **30**, **43**, **44**, **46**, **57**, **60**, **62**, **65**, **67**, **68**, and **70**, Table 5) in mouse liver microsomes (MLM) and human liver microsomes (HLM) with and without the NADPH cofactor. Fourteen of these analogues (all but **70**) had been tested against the parasite in vivo. As a whole, the compounds exhibited poor metabolic stability in MLM (containing NADPH) with half-lives ranging from 0.3 to 11 minutes. Moreover, eight of the compounds (**1**, **9**, **10**, **16**, **30**, **43**, **62** and **65**) underwent significant NADPH-independent metabolism (defined as with less than 85% substrate remaining) in MLM with 0.4% to 83% substrate remaining after a 60-minute incubation. The poor metabolic stability of these compounds in MLM likely contributed to their lack of efficacy in mice infected with *T. b. rhodesiense* STIB900. In contrast, these compounds exhibited improved metabolic stability in HLM (containing NADPH) with half-lives ranging from 4.9 to 50 min. Several compounds (**1**, **10**, **16**, **62**, and **65**) also underwent significant NADPH-independent metabolism in HLM with 24% to 80% substrate remaining after 60 minutes incubation. As a whole, the 10 amide analogues (**1**, **9**, **10**, **16**, **30**, **43**, **57**, **60**, **62**, and **65**) were more stable to both MLM and HLM than the five urea analogues (**44**, **46**, **67**, **68**, and **70**). Only three molecules (amides **16**, **57**, and **60** having fluorophenyl substituents on the thiazole ring and/or electron withdrawing benzoyl substituents) exhibited better metabolic stability in both MLM ($t_{1/2} > 5$ min) and HLM ($t_{1/2} > 25$ min). The piperidyl urea derivative **70**, which was the most potent against the parasite in vitro ($IC_{50} = 9$ nM), exhibited low metabolic stability in MLM ($t_{1/2} = 1.6$ min) and was the least stable to HLM ($t_{1/2} = 4.9$ min). This compound was synthesized after the completion of the efficacy studies of the other compounds. Based upon its poor metabolic stability and the fact that the in vivo efficacy of the pyrrolidyl urea was not enhanced an aromatic 3-fluoro substituent (**44** vs **68**), the in vivo evaluation of **70** was deemed to be unnecessary.

4. Discussion

These results were promising regarding the preparation of a set of analogues and their in vitro activities against the parasite. A relatively facile synthetic pathway was amenable to a large number of functional groups, giving rise to a structurally diverse set of analogues, many of which were more potent than the lead compound, including eight with IC_{50} values below 100 nM. The high potencies ($IC_{50} < 25$ nM) of the five piperidine urea derivatives **46** and **70–73**, were especially promising. However, none of the compounds tested in vivo were able to cure infected mice. At best, several analogues brought about significant reductions in parasitemia, only to be followed by relapses. The microsomal studies indicated that these compounds, as a whole, had poor metabolic stability in MLM and likely had limited exposure in mouse plasma after intraperitoneal administration. With future analogues, the extent of plasma exposure may be confirmed by pharmacokinetic studies. These results further underline the importance of considering both in vitro activity and metabolic stability in selecting candidates for in vivo efficacy studies, while at the same time they provide a rationale for continued work on this scaffold.

The analogues in this study had modifications primarily at either end of the molecule. In all of the synthesized derivatives **2–73**, the thiazol-2-ethylamine core of the lead compound was left intact. Only in the commercial compounds **74–83** was this portion of the molecule altered by reversal of the substituents on the thiazole ring, and none of these analogues were tested for metabolic stability. Whether the internal core of compounds **1–73**, particularly the ethylene bridge between the thiazole ring and the amide nitrogen, contributes to their poor metabolic stability remains largely unexplored. Work is currently underway, with particular emphasis on structural modifications of the internal portion of the molecule, to retain high potency while at the same time increasing metabolic stability, with the ultimate goal of obtaining in vivo efficacy against the trypanosome.

5. Experimental

5.1. Biological protocols

5.1.1. Antiparasitic activity—In vitro antitrypanosomal activities against *T. b. rhodesiense* (STIB900) and cytotoxicities against L6 rat myoblast cells were measured following established protocols.[23] In vivo experiments were performed as previously reported with modifications to reduce the stringency of the mouse model of infection for the new chemical scaffolds and with a smaller mouse group size.[8] Female NMRI mice were infected intraperitoneally (ip) with 10^4 STIB900 bloodstream trypanosome forms. Experimental groups of two mice were treated with the test compounds administered at 40 mg/kg ip on three consecutive days from day 1 to day 3 post infection (120 mg/kg ip total dose). A control group was infected but remained untreated. The tail blood of all mice was checked for parasitemia reduction (versus untreated control mice) at 24 and 96 hour timepoints after the final dose of the compounds. Mice were euthanized after 96 hours if the tail blood was not parasite free. The tail blood of aparasitemic mice was examined twice per week for 30 days post infection, and mice with detected parasitemia relapses were euthanized. The mice that remained aparasitemic until day 30 were considered as cured. All protocols and procedures were reviewed and approved by the local veterinary authroites of the Canton Base-Stadt, Switzerland.

5.1.2. Metabolic stability—Metabolic stability was evaluated using liver microsomes derived from mouse and human sources. Microsomal incubations were carried out according to a protocol described previously[26] with modifications. Briefly, substrate stock solutions were prepared in DMSO and DMSO content was kept at 0.5% (v/v) in final incubations.

Incubation mixtures (final volume 0.2 mL) consisted of substrate (3 μM), liver microsomes (0.5 mg/mL) from mouse (pool of 1000, CD-1 male mouse) or human (pool of 50, mixed gender) (XenoTech LLC, Lenexa, KS) in a phosphate buffer (100 mM, pH 7.4) containing 3.3 mM $MgCl_2$. After a 5-minute pre-equilibration period at 37 °C, reactions (in triplicate) were initiated by adding the NADPH cofactor (1 mM). For NADPH-independent reactions, the cofactor was replaced with water. Aliquots (10 μl) of the reaction mixtures were removed at 0, 15, 30, and 60 minutes and individually mixed with 200 μL of ice-cold acetonitrile containing internal standard. The mixtures were vortex-mixed, and precipitated protein was removed by centrifugation at 2,250 × g for 15 min. The supernatant fractions were dried using a 96-well microplate evaporator (Apricot Designs Inc., Covina, CA) under N_2 at 50 °C and reconstituted with 100 μL 50% methanol containing 0.1% trifluoroacetic acid before UPLC-MS/MS analysis. In vitro half-life ($t_{1/2}$) was obtained by analyzing the substrate concentration vs. incubation time curve using the one-phase exponential decay model (GraphPad Prism® 5.0, San Diego, CA).

5.2. Chemistry

Uncorrected melting points were measured on a Thomas–Hoover Capillary or a Thermo Scientific 9200 melting point apparatus. ^1H NMR spectra were recorded in DMSO-d_6 on a Varian Inova 400 MHz spectrometer. Anhydrous solvents were purchased from Aldrich Chemical Co., Milwaukee, WI, in Sure-seal® containers and were used without further purification. .Organic starting materials were purchased from Aldrich Chemical Co. or were prepared by established procedures as noted. Compounds **74-83** were purchased from ChemDiv, San Diego, CA.

Reaction mixtures were monitored by TLC on silica gel or by reverse phase HPLC. Combined organic layers of extraction mixtures were neutralized as necessary with acidic or basic washes, washed with saturated NaCl solution and dried over $MgSO_4$ before being evaporated under reduced pressure. Normal phase flash column chromatography was performed using Davisil grade 633, type 60A silica gel (200–425 mesh). Analytical HPLC chromatograms were recorded on an Agilent 1200 series chromatograph using a Zorbax Rx C8 column (4.6 × 75 mm, 3.5 μm) maintained at 40 °C and UV photodiode array detection at 230, 254, 265, 290, and 320 nm. Area % values are reported at the wavelengths where the strongest signals of the products were observed. Mobile phases consisted of mixtures of methanol (0–95%) in water containing formic acid (80 mM), ammonium formate (20 mM) and triethylamine (15 mM). Samples were eluted at appropriate gradients at a flow rate of 1.5 mL/min. Low resolution ESI mass spectra were recorded on an Agilent Technologies 1100 Series LC/MSD Trap mass spectrometer. In cases of hydrochloride salts, the *m/z* values reported are those of the free bases. Elemental analyses were measured by Atlantic Microlab, Norcross, GA, and unless stated otherwise, were within ± 0.4% of calculated values. The compounds frequently analyzed correctly for fractional moles of water and/or other solvents; in each case the ^1H NMR spectra was consistent with the analysis.

5.2.1. General procedure for preparation of benzamides 1-26—A mixture of 3-(benzamido)thiopropionamide **86** (0.9-1.5 mmol) and the appropriate 1-aryl-2-bromoethanone (1-1.6 equiv) in EtOH (10 mL) was stirred at reflux for 2-3 hours (for **1**, **4-8**,

and **10-15**) or overnight at room temperature (for all others). Reaction mixtures were extracted into EtOAc (3× from basified aqueous phases as needed) or were diluted with water to give precipitated product. Compound **1** was purified by column chromatography; all others were purified by direct recrystallization or precipitation.

5.2.1.1. 2-(2-Benzamido)ethyl-4-phenylthiazole (1): was prepared from **86** and 2-bromoacetophenone. After column chromatography (silica, hexanes/EtOAc 1:1), the product was recrystallized from EtOAc and hexane to give white crystals (272 mg, 59%): mp 112-113 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (t, J = 5.6 Hz, 1H), 7.98 (d, J = 0.7 Hz, 1H), 7.97 – 7.92 (m, 2H), 7.87 – 7.81 (m, 2H), 7.58 – 7.51 (m, 1H), 7.50 – 7.41 (m, 4H), 7.39 – 7.29 (m, 1H), 3.69 (q, J = 6.6 Hz, 2H), 3.40 – 3.25 (m, 2H); EIMS m/z 309.1 (M + 1)$^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{18}H_{16}N_2OS$: C, 70.10; H, 5.23; N, 9.08; S, 10.40. Found: C, 69.81; H, 5.13; N, 9.00; S, 10.25.

5.1.1.2. 2-(2-Benzamido)ethyl-4-(3-cyanophenyl)thiazole (2): was prepared from **86** and 2-bromo-3′-cyanoacetophenone.[27] The reaction mixture was diluted with water to give a white solid (369 mg, 91%): mp 148-149 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (t, *J* = 5.6 Hz, 1H), 8.38 (t, *J* = 1.8 Hz, 1H), 8.28 (ddd, *J* = 8.0, 1.8, 1.2 Hz, 1H), 8.21 (s, 1H), 7.85 – 7.81 (m, 2H), 7.80 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.57 – 7.48 (m, 1H), 7.51 – 7.41 (m, 2H), 3.69 (td, *J* = 6.8, 5.5 Hz, 2H), 3.32 (t, *J* = 6.8 Hz, 2H); EIMS *m/z* 334. 0 (M + 1)$^+$; HPLC 100 area% (265 nm). Anal. Calcd for $C_{19}H_{15}N_3OS$: C, 68.45; H, 4.53; N, 12.60. Found: C, 68.15; H, 4.35; N, 12.37.

5.2.1.3. 2-(2-Benzamido)ethyl-4-(4-cyanophenyl)thiazole (3): was prepared from **86** and 2-bromo-4′-cyanoacetophenone. After extraction, the crude product was recrystallized from EtOH and water to give a white powder (347 mg, 86%): mp 128-129 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (t, *J* = 5.6 Hz, 1H), 8.27 (s, 1H), 8.14 (d, *J* = 8.5 Hz, 2H), 7.91 (d, *J* = 9.0 Hz, 2H), 7.87 – 7.79 (m, 2H), 7.57 – 7.48 (m, 1H), 7.51 – 7.41 (m, 2H), 3.69 (q, *J* = 6.8, 5.5 Hz, 2H), 3.33 (t, *J* = 6.9 Hz, 2H); EIMS *m/z* 334. 0 (M + 1)$^+$; HPLC 100 area% (290 nm). Anal. Calcd for $C_{19}H_{15}N_3OS$: C, 68.45; H, 4.53; N, 12.60. Found: C, 68.16; H, 4.46; N, 12.30.

5.2.1.4. 2-(2-Benzamido)ethyl-4-(4-trifluoromethylphenyl)thiazole (4): was prepared from **86** and 2-bromo-4′-trifluoromethylacetophenone. After extraction, the product was recrystallized from EtOH to give a white solid (78 mg, 17%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (t, *J* = 5.7 Hz, 1H), 8.22 (s, 1H), 8.20 – 8.13 (m, 2H), 7.88 – 7.81 (m, 2H), 7.81 – 7.76 (m, 2H), 7.58 – 7.50 (m, 1H), 7.47 (ddt, *J* = 8.4, 6.5, 1.5 Hz, 2H), 3.69 (q, *J* = 6.9 Hz, 2H), 3.34 (t, *J* = 6.9 Hz, 2H); EIMS *m/z* 377.6 (M + 1)$^+$; HPLC 100 area% (265 nm). Anal. Calcd for $C_{19}H_{15}F_3N_2OS$: C, 60.63; H, 4.02; N, 7.44. Found: C, 60.51; H, 3.93; N, 7.42.

5.2.1.5. 2-(2-Benzamido)ethyl-4-(3-nitrophenyl)thiazole (5): was prepared from **86** and 2-bromo-3′-nitroacetophenone). The reaction mixture was diluted with water (10 mL) to give a white precipitate (347 mg, 80%): mp 161-162 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (t, *J* = 2.0 Hz, 1H), 8.70 (t, *J* = 5.6 Hz, 1H), 8.39 (ddd, *J* = 7.8, 1.8, 1.0 Hz, 1H), 8.31 (s, 1H), 8.19 (ddd, *J* = 8.2, 2.4, 1.0 Hz, 1H), 7.87 – 7.80 (m, 2H), 7.74 (t, *J* = 8.0 Hz, 1H), 7.57 – 7.49 (m, 1H), 7.49 – 7.41 (m, 2H), 3.70 (q, *J* = 6.8 Hz, 2H), 3.35 (t, *J* = 6.8 Hz, 2H); EIMS *m/z* 354.2 $(M + 1)^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{18}H_{15}N_3O_3S{\cdot}0.2H_2O$: C, 60.56; H, 4.35; N, 11.77. Found: C, 60.51; H, 4.18; N, 11.80.

5.2.1.6. 2-(2-Benzamido)ethyl-4-(4-nitrophenyl)thiazole (6)[28,29]: was prepared from **86** and 2-bromo-4′-nitroacetophenone . After. After extraction, the product was recrystallized from EtOH to give off-white crystals (318 mg, 75%): mp 156-157 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (t, *J* = 5.6 Hz, 1H), 8.35 (s, 1H), 8.33 – 8.26 (m, 2H), 8.25 – 8.18 (m, 2H), 7.88 – 7.80 (m, 2H), 7.56 – 7.50 (m, 1H), 7.49 – 7.42 (m, 2H), 3.70 (td, *J* = 6.8, 5.5 Hz, 2H), 3.34 (t, *J* = 6.9 Hz, 2H); EIMS *m/z* 354.1 $(M + 1)^+$; HPLC 100 area% (230 nm). Anal. Calcd for $C_{18}H_{15}N_3O_3S$: C, 61.18; H, 4.28; N, 11.89; S, 9.07. Found: C, 61.16; H, 4.27; N, 11.70; S, 9.13.

5.2.1.7. 2-(2-Benzamido)ethyl-4-(3-methoxyphenyl)thiazole (7): was prepared from and 2-bromo-3′-methoxyacetophenone. The extract was concentrated to a small volume and was triturated with hexanes to give a white precipitate (304 mg, 75%): mp 89-90°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (t, *J* = 5.5 Hz, 1H), 8.00 (s, 1H), 7.88 – 7.78 (m, 2H), 7.58 – 7.49 (m, 3H), 7.49 – 7.41 (m, 2H), 7.34 (dd, *J* = 8.3, 7.6 Hz, 1H), 6.91 (ddd, *J* = 8.2, 2.6, 1.0 Hz, 1H), 3.80 (s, 3H), 3.68 (td, *J* = 6.9, 5.5 Hz, 2H), 3.31 (t, *J* = 6.9 Hz, 2H); EIMS *m/z* 339.6$(M + 1)^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{19}H_{18}N_2OS{\cdot}0.1H_2O$: C, 67.07; H, 5.39; N, 8.23. Found: C, 66.91; H, 5.41; N, 8.28.

5.2.1.8. 2-(2-Benzamido)ethyl-4-(4-methoxyphenyl)thiazole (8): was prepared from **86** and 2-bromo-4′-methoxyacetophenone. The reaction mixture was diluted with water to give a white precipitate (311 mg, 75%): mp 135-136 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (t, *J* = 5.6 Hz, 1H), 7.92 – 7.86 (m, 2H), 7.86 – 7.81 (m, 2H), 7.80 (s, 1H), 7.56 – 7.50 (m, 1H), 7.50 – 7.42 (m, 2H), 7.03 – 6.94 (m, 2H), 3.79 (s, 3H), 3.67 (td, *J* = 6.9, 5.5 Hz, 2H), 3.29 (t, *J* = 7.0 Hz, 2H); EIMS *m/z* 339.1$(M + 1)^+$; HPLC 99.0 area% (265 nm). Anal. Calcd for $C_{19}H_{18}N_2OS{\cdot}0.3H_2O$: C, 66.37; H, 5.45; N, 8.15. Found: C, 66.18; H, 5.30; N, 8.07.

25.2.1.9. 2-(2-Benzamido)ethyl-4-(2-fluorophenyl)thiazole hydrochloride (9): was prepared from **86** and 2-bromo-2′-fluoroacetophenone.[30] An ethanolic solution of the evaporated extract was treated with saturated ethanolic HCl and diluted with ether to give a precipitate (324 mg, 74%); mp 120-126 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 (t, J = 5.6 Hz, 1H), 8.12 (td, J = 7.9, 2.0 Hz, 1H), 7.91 – 7.84 (m, 2H), 7.83 (d, J = 1.6 Hz, 1H), 7.57 – 7.50 (m, 1H), 7.49 – 7.43 (m, 2H), 7.43 – 7.36 (m, 1H), 7.35 – 7.24 (m, 2H), 3.69 (td, J = 6.9, 5.5 Hz, 2H), 3.33 (t, J = 6.9 Hz, 2H); EIMS m/z 327.1 $(M + 1)^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{18}H_{15}FN_2OS{\cdot}HCl$: C, 59.58; H, 4.44; N, 7.72; Cl, 9.77. Found: C, 59.82; H, 4.35; N, 7.89; Cl, 9.57.

5.2.1.10. 2-(2-Benzamido)ethyl-4-(3-fluorophenyl)thiazole (10): was prepared from **86** and 2-bromo-3′-fluoroacetophenone. Incremental dilution of the reaction mixture with water gave a white precipitate (223 mg, 57%): mp 88-89 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (t, *J* = 5.6 Hz, 1H), 8.10 (s, 1H), 7.88 – 7.82 (m, 2H), 7.82 – 7.78 (m, 1H), 7.75 (ddd, *J* = 10.6, 2.7, 1.5 Hz, 1H), 7.58 – 7.49 (m, 1H), 7.49 – 7.41 (m, 3H), 7.21 – 7.11 (m, 1H), 3.68 (q, *J* = 6.8 Hz, 2H), 3.31 (t, *J* = 6.9 Hz, 2H); EIMS *m/z* 327.4 $(M + 1)^+$; HPLC 100 area%

(254 nm). Anal. Calcd for $C_{18}H_{15}FN_2OS$: C, 66.24; H, 4.63; N, 8.58. Found: C, 65.95; H, 4.55; N, 8.56.

5.2.1.11. 2-(2-Benzamido)ethyl-4-(4-fluorophenyl)thiazole (11): was prepared from and 2-bromo-4′-fluoroacetophenone. The reaction mixture was diluted with water to give a white precipitate (323 mg, 82%): mp 145-146 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (t, J = 5.6 Hz, 1H), 8.04 – 7.96 (m, 2H), 7.96 (s, 1H), 7.88 – 7.80 (m, 2H), 7.58 – 7.48 (m, 1H), 7.47 (ddt, J = 8.3, 6.6, 1.4 Hz, 2H), 7.31 – 7.20 (m, 2H), 3.68 (td, J = 6.9, 5.6 Hz, 2H), 3.30 (t, J = 7.0 Hz, 2H); EIMS m/z 327.1 $(M + 1)^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{18}H_{15}FN_2OS \cdot 0.1H_2O$: C, 65.87; H, 4.67; N, 8.54. Found: C, 65.72; H, 4.62; N, 8.47.

5.2.1.12. 2-(2-Benzamido)ethyl-4-(3-chlorophenyl)thiazole (12): was prepared from and 2-bromo-3′-chloroacetophenone.. Addition of water to the reaction mixture gave a white precipitate (320 mg, 75%); mp 109 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (t, J = 5.6 Hz, 1H), 8.13 (s, 1H), 8.00 (t, J = 1.9 Hz, 1H), 7.92 (dt, J = 7.7, 1.4 Hz, 1H), 7.87 – 7.80 (m, 2H), 7.58 – 7.49 (m, 1H), 7.46 (dtd, J = 11.8, 7.1, 5.2 Hz, 3H), 7.39 (ddd, J = 8.0, 2.2, 1.1 Hz, 1H), 3.68 (td, J = 6.8, 5.5 Hz, 2H), 3.31 (t, J = 7.0 Hz, 2H); EIMS m/z 343.2 $(M + 1)^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{18}H_{15}ClN_2OS$: C, 63.06; H, 4.41; N, 8.17. Found: C, 63.04; H, 4.42; N, 8.23.

5.2.1.13. 2-(2-Benzamido)ethyl-4-(4-chlorophenyl)thiazole (13): was prepared from and 2-bromo-4′-chloroacetophenone. The extract was evaporated to a white solid (380 mg), which was recrystallized from EtOH to give off-white crystals (155 mg, 37%): mp 154-155 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (t, J = 5.6 Hz, 1H), 8.04 (s, 1H), 8.01 – 7.93 (m, 2H), 7.88 – 7.80 (m, 2H), 7.58 – 7.42 (m, 5H), 3.68 (td, J = 6.9, 5.5 Hz, 2H), 3.31 (t, J = 6.9 Hz, 2H); EIMS m/z 343.1 $(M + 1)^+$; HPLC 100 area% (230 nm). Anal. Calcd for $C_{18}H_{15}ClN_2OS$: C, 63.06; H, 4.41; N, 8.17. Found: C, 62.67; H, 4.26; N, 8.07.

5.2.1.14. 2-(2-Benzamido)ethyl-4-(3-bromophenyl)thiazole (14): was prepared from **86** and 2,3′-dibromoacetophenone The extract was concentrated to a small volume and triturated with hexanes to give a white solid (311 mg, 65%); mp 96-97 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (t, J = 5.6 Hz, 1H), 8.15 (t, J = 1.8 Hz, 1H), 8.13 (s, 1H), 7.96 (ddd, J = 7.8, 1.6, 1.0 Hz, 1H), 7.88 – 7.80 (m, 2H), 7.58 – 7.50 (m, 2H), 7.50 – 7.43 (m, 2H), 7.40 (t, J = 7.9 Hz, 1H), 3.68 (td, J = 6.9, 5.6 Hz, 2H), 3.31 (t, J = 6.9 Hz, 2H); EIMS m/z 387.0 $(M + 1)^+$, 389.0 $(M + 3)^+$; HPLC 100 area% (230 nm). Anal. Calcd for $C_{18}H_{15}BrN_2OS \cdot 0.1H_2O$: C, 55.56; H, 3.94; N, 7.20. Found: C, 55.42; H, 3.76; N, 7.29.

5.2.1.15. 2-(2-Benzamido)ethyl-4-(4-bromophenyl)thiazole (15): was prepared from **86** and 2,4′-dibromoacetophenone. The extract was evaporated to a white solid (440 mg), which was recrystallized from EtOH to give off-white crystals (207 mg, 44%): mp 158-159 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (t, J = 5.6 Hz, 1H), 8.05 (s, 1H), 7.95 – 7.86 (m, 2H), 7.88 – 7.80 (m, 2H), 7.69 – 7.58 (m, 2H), 7.57 – 7.48 (m, 1H), 7.51 – 7.41 (m, 2H), 3.67 (td, J = 6.9, 5.5 Hz, 2H), 3.31 (t, J = 6.9 Hz, 2H); EIMS m/z 387.2 $(M + 1)^+$, 389.1 $(M + 3)^+$; HPLC 100 area% (265 nm). Anal. Calcd for $C_{18}H_{15}BrN_2OS$: C, 55.82; H, 3.90; N, 7.23; S, 8.28. Found: C, 55.86; H, 3.31; N, 7.17; s, 8.14.

5.2.1.16. 2-(2-Benzamido)ethyl-4-(2,4-difluorophenyl)thiazole (16): was prepared from **86** (416 mg, 2.00 mmol) and 2-bromo-2′,4′-difluoroacetophenone (470 mg, 2.00 mmol). The evaporated extract was recrystallized from EtOH/H_2O (2:1, 75 mL) to give white crystals (340 mg, 49%): mp 124-125 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (t, *J* = 5.6 Hz, 1H), 8.15 (td, *J* = 8.9, 6.8 Hz, 1H), 7.88 – 7.80 (m, 3H), 7.58 – 7.50 (m, 1H), 7.50 – 7.43 (m, 2H), 7.38 (ddd, *J* = 11.8, 9.3, 2.6 Hz, 1H), 7.23 – 7.13 (m, 1H), 3.68 (td, *J* = 6.9, 5.5 Hz, 2H), 3.32 (t, *J* = 6.9 Hz, 2H); EIMS *m/z* 345.1 $(M + 1)^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{18}H_{14}F_2N_2OS·0.3H_2O$: C, 61.81; H, 4.21; N, 8.01. Found: C, 61.56; H, 4.21; N, 7.94.

5.2.1.17. 2-(2-Benzamido)ethyl-4-(2,5-difluorophenyl)thiazole (17): was prepared from **86** and 2-bromo-2′,5′-difluoroacetophenone[31] The reaction mixture was concentrated by heating, and water was added to give white crystals (274 mg, 91%): mp 123-124 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (t, *J* = 5.6 Hz, 1H), 7.95 (d, *J* = 2.6 Hz, 1H), 7.89 – 7.80 (m, 3H), 7.57 – 7.50 (m, 1H), 7.49 – 7.43 (m, 2H), 7.39 (ddd, *J* = 10.8, 9.1, 4.6 Hz, 1H), 7.24 (ddt, *J* = 9.0, 7.3, 3.5 Hz, 1H), 3.69 (q, *J* = 6.5 Hz, 2H), 3.32 (t, *J* = 6.8 Hz, 2H); EIMS *m/z* 345.4 $(M + 1)^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{18}H_{14}F_2N_2OS$: C, 62.78; H, 4.10; N, 8.13. Found: C, 62.60; H, 4.28; N, 8.04.

5.2.1.18. 2-(2-Benzamido)ethyl-4-(2,6-difluorophenyl)thiazole hydrochloride (18): was prepared from **86** and 2-bromo-2′,6′-difluoroacetophenone.[32] The evaporated extract was recrystallized twice from EtOH, saturated ethanolic HCl, and ether to give white crystals (305 mg, 73%): mp 158-167 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (t, *J* = 5.6 Hz, 1H), 7.89 – 7.80 (m, 3H), 7.58 – 7.42 (m, 4H), 7.28 – 7.16 (m, 2H), 3.66 (td, *J* = 7.0, 5.5 Hz, 2H), 3.32 (t, *J* = 7.0 Hz, 2H); EIMS *m/z* 345.4 $(M + 1)^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{18}H_{14}F_2N_2OS·HCl$: C, 56.77; H, 3.97; N, 7.36; Cl, 8.93. Found: C, 56.56; H, 4.04; N, 7.27; Cl, 9.17.

5.2.1.19. 2-(2-Benzamido)ethyl-4-(3,4-difluorophenyl)thiazole (19): was prepared from **86** and 2-bromo-3′,4′-difluoroacetophenone.[32] Concentration of the reaction mixture followed by incremental dilution with water gave white crystals (351 mg, 93%): mp 103-103 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (t, *J* = 5.5 Hz, 1H), 8.07 (s, 1H), 7.96 (ddd, *J* = 12.2, 7.9, 2.2 Hz, 1H), 7.87 – 7.81 (m, 2H), 7.81 – 7.76 (m, 1H), 7.57 – 7.41 (m, 4H), 3.67 (td, *J* = 6.8, 5.5 Hz, 2H), 3.30 (t, *J* = 6.9 Hz, 2H); EIMS *m/z* 345.1 $(M + 1)^+$; HPLC 98.2 area% (254 nm). Anal. Calcd for $C_{18}H_{14}F_2N_2OS$: C, 62.78; H, 4.10; N, 8.13. Found: C, 62.52; H, 3.99; N, 7.95.

5.2.1.20. 2-(2-Benzamido)ethyl-4-(3,5-difluorophenyl)thiazole (20): was prepared from **86** and 2-bromo-3′,5′-difluoroacetophenone.[33] The reaction mixture was concentrated by heating, and water was added to give white crystals (326 mg, 91%): mp 118-119 °C;^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (t, *J* = 5.6 Hz, 1H), 8.22 (s, 1H), 7.87 – 7.79 (m, 2H), 7.71 – 7.60 (m, 2H), 7.57 – 7.47 (m, 1H), 7.50 – 7.41 (m, 2H), 7.20 (tt, *J* = 9.3, 2.4 Hz, 1H), 3.68 (td, *J* = 6.8, 5.5 Hz, 2H), 3.31 (t, *J* = 6.8 Hz, 2H); EIMS *m/z* 345.0 $(M + 1)^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{18}H_{14}F_2N_2OS·0.1H_2O$: C, 62.45; H, 4.13; N, 8.09. Found: C, 62.42; H, 4.04; N, 8.03.

5.2.1.21. 2-(2-Benzamido)ethyl-4-(2,4,5-trifluorophenyl)thiazole (21): was prepared from **86** and 2-bromo-2′,4′,5′-trifluoroacetophenone. [34] The reaction mixture was heated and diluted with more EtOH to dissolve precipitated product and was then diluted with water to give white needles (337 mg, 87%); mp 139-140 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (t, J = 5.6 Hz, 1H), 8.04 (ddd, J = 11.7, 9.2, 7.0 Hz, 1H), 7.92 (d, J = 2.7 Hz, 1H), 7.87 – 7.75 (m, 2H), 7.70 (td, J = 10.9, 6.8 Hz, 1H), 7.53 (ddt, J = 8.1, 6.4, 1.4 Hz, 1H), 7.46 (ddt, J = 8.3, 6.5, 1.4 Hz, 2H), 3.68 (td, J = 6.8, 5.6 Hz, 2H), 3.32 (t, J = 6.8 Hz, 2H); EIMS m/z 363.1 $(M + 1)^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{18}H_{13}F_3N_2OS$: C, 59.66; H, 3.62; N, 7.73. Found: C, 59.48; H, 3.48; N, 7.70.

5.2.1.22. 2-(2-Benzamido)ethyl-4-(furan-2-yl)thiazole (22): was prepared from and 2-bromo-1-(furan-2-yl)ethanone.[35] The evaporated extract was recrystallized from hexanes containing the minimum volume of EtOAc to give white crystals (231 mg, 77%): mp 88-89 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (t, J = 5.6 Hz, 1H), 7.88 – 7.81 (m, 2H), 7.73 (dd, J = 1.7, 0.7 Hz, 1H), 7.67 (s, 1H), 7.58 – 7.50 (m, 1H), 7.50 – 7.40 (m, 2H), 6.78 (dd, J = 3.4, 0.8 Hz, 1H), 6.59 (dd, J = 3.4, 1.9 Hz, 1H), 3.65 (td, J = 6.9, 5.5 Hz, 2H), 3.28 (t, J = 6.9 Hz, 2H); EIMS m/z 299.1 $(M + 1)^+$; HPLC 100 area% (265 nm). Anal. Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39. Found: C, 64.39; H, 4.69; N, 9.38.

5.2.1.23. 2-(2-Benzamido)ethyl-4-(thiophen-2-yl)thiazole (23): was prepared from **86** and 2-bromo-1-(thiophen-2-yl)ethanone.[35] The evaporated extract was recrystallized from hexanes containing the minimum volume of EtOAc to give a white solid (251 mg, 78%): mp 116-117 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (t, J = 5.6 Hz, 1H), 7.86 – 7.82 (m, 2H), 7.81 (s, 1H), 7.58 – 7.50 (m, 3H), 7.50 – 7.42 (m, 2H), 7.11 (dd, J = 5.1, 3.6 Hz, 1H), 3.65 (td, J = 6.9, 5.6 Hz, 2H), 3.28 (t, J = 6.9 Hz, 2H); EIMS m/z 315.1 $(M + 1)^+$; HPLC 98.1 area% (290 nm). Anal. Calcd for $C_{16}H_{14}N_2OS_2$: C, 61.12; H, 4.49; N, 8.91. Found: C, 60.91; H, 4.47; N, 8.98.

5.2.1.24. 2-(2-Benzamido)ethyl-4-(pyridin-2-yl)thiazole (24): was prepared from **86** and 2-bromo-1-(pyridin-2-yl)ethanone hydromide.[36] A decolorized (Norit) ethanolic solution of the evaporated filtrated was treated with saturated ethanolic HCl (1 mL) and diluted with ether. This solution was evaporated to dryness. The residue was dissolved in a mixture of aqueous HCl and EtOH and then basified with 1 N NaOH to give a precipitate (226 mg, 61%): mp 129-132 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (t, J = 5.6 Hz, 1H), 8.64 – 8.57 (m, 1H), 8.16 (s, 1H), 8.06 (dd, J = 7.9, 1.1 Hz, 1H), 7.89 (tdd, J = 7.7, 4.4, 1.8 Hz, 1H), 7.86 – 7.80 (m, 2H), 7.57 – 7.49 (m, 1H), 7.49 – 7.39 (m, 2H), 7.35 (ddd, J = 7.5, 4.8, 1.3 Hz, 1H), 3.69 (q, J = 6.7 Hz, 2H), 3.33 (t, J = 6.9 Hz, 2H); EIMS m/z 309.7 $(M + 1)^+$; HPLC 99.3 area% (254 nm). Anal. Calcd for $C_{17}H_{15}N_3OS \cdot H_2O$: C, 62.36; H, 5.23; N, 12.83. Found: C, 62.15; H, 5.14; N, 12.68.

5.2.1.25. 2-(2-Benzamido)ethyl-4-(pyridin-3-yl)thiazole hydrochloride (25): was prepared from **86** and 2-bromo-1-(pyridin-3-yl)ethanone hydromide (prepared analogously to its 2-pyridyl analogue).[36] The evaporated extract was dissolved in EtOH, filtered, treated with saturated ethanolic HCl, and diluted with ether to give a solid (201 mg, 48%): mp 174-176 °C dec.; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.36 (d, J = 2.0 Hz, 1H), 8.91 (dt, J =

8.2, 1.7 Hz, 1H), 8.81 (dd, *J* = 5.5, 1.4 Hz, 1H), 8.76 (t, *J* = 5.6 Hz, 1H), 8.47 (s, 1H), 8.00 (dd, *J* = 8.1, 5.6 Hz, 1H), 7.88 – 7.80 (m, 2H), 7.57 – 7.49 (m, 1H), 7.49 – 7.41 (m, 2H), 3.71 (q, *J* = 6.6 Hz, 2H), 3.36 (t, *J* = 6.9 Hz, 2H); EIMS *m/z* 309.7 $(M + 1)^+$ of free base; HPLC 99.1 area% (254 nm). Anal. Calcd for $C_{17}H_{15}N_3OS \cdot 1.1HCl \cdot 0.25H_2O$: C, 57.68; H, 4.73; N, 11.87; Cl, 11.02. Found: C, 57.49; H, 4.72; N, 11.69; Cl, 11.25.

5.2.1.26 2-(2-Benzamido)ethyl-4-(pyridin-4-yl)thiazole hydrochloride (26): was prepared from **86** and 2-bromo-1-(pyridin-4-yl)ethanone hydromide (prepared analogously to its 2-pyridyl analogue).[36] The evaporated extract was dissolved in EtOH, treated with Norit, and filtered. The filtrate was treated with saturated ethanolic HCl, and diluted with ether to give a solid (346 mg, 81%): mp 215-218 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.90 (d, *J* = 5.8 Hz, 2H), 8.84 (s, 1H), 8.75 (t, *J* = 5.6 Hz, 1H), 8.45 (d, *J* = 6.7 Hz, 2H), 7.87 – 7.80 (m, 2H), 7.57 – 7.49 (m, 1H), 7.49 – 7.41 (m, 2H), 3.76 – 3.66 (m, 2H), 3.38 (t, *J* = 6.8 Hz, 2H); EIMS *m/z* 310.0 $(M + 1)^+$; HPLC 100 area% (230 nm). Anal. Calcd for $C_{17}H_{15}N_3OS \cdot HCl \cdot 0.6H_2O$: C, 57.25; H, 4.86; N, 11.78; Cl, 9.94. Found: C, 57.06; H, 4.77; N, 11.74; Cl, 10.22.

5.2.2. General procedure for preparation of amides 27-43—A suspension of 4-phenylthiazol-2-ethylamine hydrobromide (89a, 1-1.1 mmol, 1 equiv) and the appropriate acyl halide (minimum of 1.2 equiv) in THF (10 mL) was chilled to 0 °C. Triethylamine (minimum of 3 equiv) was added and the mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with water and extracted into EtOAc (3×), and the crude product obtained was recrystallized from an appropriate solvent, unless stated otherwise.

5.2.2.1. 2-[2-(3-Cyanobenzamido)]ethyl-4-phenylthiazole (27): was prepared from **89a** and 3-cyanobenzoyl chloride. The product was recrystallized from EtOAc and hexanes to give a solid (300 mg, 85%): mp 125 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (t, *J* = 5.6 Hz, 1H), 8.28 – 8.19 (m, 1H), 8.15 (dt, *J* = 8.0, 1.6 Hz, 1H), 8.01 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.98 (s, 1H), 7.96 – 7.91 (m, 2H), 7.70 (t, *J* = 7.8 Hz, 1H), 7.47 – 7.39 (m, 2H), 7.37 – 7.28 (m, 1H), 3.70 (td, *J* = 6.8, 5.5 Hz, 2H), 3.32 (t, *J* = 6.8 Hz, 2H); EIMS *m/z* 334.0 $(M + 1)^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{19}H_{15}N_3OS$: C, 68.45; H, 4.53; N, 12.60. Found: C, 68.18; H, 4.53; N, 12.48.

5.2.2.2. 2-[2-(4-Cyanobenzamido)]ethyl-4-phenylthiazole (28)[25]: was prepared from **89a** and 4-cyanobenzoyl chloride. The product was recrystallized from EtOH and water to give a solid (256 mg, 70%): mp 119 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.95 (t, *J* = 5.6 Hz, 1H), 8.05 – 7.88 (m, 7H), 7.48 – 7.39 (m, 2H), 7.38 – 7.29 (m, 1H), 3.70 (td, *J* = 6.9, 5.5 Hz, 2H), 3.32 (t, *J* = 63.9 Hz, 2H); EIMS *m/z* 334.2 $(M + 1)^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{19}H_{15}N_3OS \cdot 01H_2O$: C, 68.08; H, 4.57; N, 12.54. Found: C, 68.00; H, 4.40; N, 12.41.

5.2.2.3. 2-[2-(3-Nitrobenzamido)]ethyl-4-phenylthiazole (29): was prepared from **89a** and 3-nitrobenzoyl chloride. The product was recrystallized from EtOAc and hexanes to give a solid (271 mg, 73%): mp 111-112 °C;^{1}H NMR (400 MHz, DMSO-d_6) δ 9.08 (t, *J* = 5.6 Hz, 1H), 8.68 (t, *J* = 2.0 Hz, 1H), 8.39 (ddd, *J* = 8.2, 2.3, 1.1 Hz, 1H), 8.28 (ddd, *J* = 7.8, 1.8, 1.0

Hz, 1H), 7.98 (d, *J* = 0.8 Hz, 1H), 7.96 – 7.90 (m, 2H), 7.79 (t, *J* = 8.0 Hz, 1H), 7.42 (td, *J* = 7.1, 1.1 Hz, 2H), 7.37 – 7.28 (m, 1H), 3.73 (q, *J* = 6.9 Hz, 2H), 3.34 (t, *J* = 6.8 Hz, 2H); EIMS *m/z* 354.0 $(M + 1)^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{18}H_{15}N_3O_3S$: C, 61.18; H, 4.28; N, 11.89. Found: C, 61.31; H, 4.24; N, 11.99.

5.2.2.4. 2-[2-(2-Fluorobenzamido)]ethyl-4-phenylthiazole (30): was prepared from **89a** and 2-fluorobenzoyl chloride. The product was recrystallized from EtOAc and hexanes to give a solid (246 mg, 71%): mp 70 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 8.55 – 8.49 (m, 1H), 7.99 (s, 1H), 7.98 – 7.93 (m, 2H), 7.63 (td, *J* = 7.5, 1.8 Hz, 1H), 7.53 (dddd, *J* = 8.4, 7.2, 5.3, 1.9 Hz, 1H), 7.47 – 7.39 (m, 2H), 7.38 – 7.31 (m, 1H), 7.31 – 7.22 (m, 2H), 3.69 (td, *J* = 6.9, 5.5 Hz, 2H), 3.29 (t, *J* = 7.0 Hz, 2H); EIMS *m/z* 327.2 $(M + 1)^+$; HPLC 100 area % (254 nm). Anal. Calcd for $C_{18}H_{15}FN_2OS$: C, 66.24; H, 4.63; N, 8.58. Found: C, 66.11; H, 4.61; N, 8.46.

5.2.2.5. 2-[2-(3-Fluorobenzamido)]ethyl-4-phenylthiazole (31): was prepared from **89a** and 3-fluorobenzoyl chloride. The product was recrystallized from EtOAc and hexanes to give a solid (239 mg, 69%): mp 108-109 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 8.79 (t, *J* = 5.6 Hz, 1H), 7.97 (s, 1H), 7.97 – 7.90 (m, 2H), 7.70 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.63 (ddd, *J* = 10.1, 2.7, 1.5 Hz, 1H), 7.53 (td, *J* = 8.0, 5.8 Hz, 1H), 7.46 – 7.36 (m, 3H), 7.36 – 7.29 (m, 1H), 3.68 (td, *J* = 6.9, 5.6 Hz, 2H), 3.31 (t, *J* = 7.0 Hz, 2H);EIMS *m/z* 327.2 $(M + 1)^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{18}H_{15}FN_2OS$: C, 66.24; H, 4.63; N, 8.58. Found: C, 65.95; H, 4.63; N, 8.55.

5.2.2.6. 2-[2-(4-Fluorobenzamido)]ethyl-4-phenylthiazole (32): was prepared from **89a** and 4-fluorobenzoyl chloride. The product was recrystallized from EtOH and water to give a solid (292 mg, 85%): mp 114 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 8.72 (t, *J* = 5.6 Hz, 1H), 7.97 (s, 1H), 7.96 – 7.86 (m, 4H), 7.48 – 7.38 (m, 2H), 7.38 – 7.24 (m, 3H), 3.67 (td, *J* = 6.9, 5.5 Hz, 2H), 3.30 (t, *J* = 7.0 Hz, 2H); EIMS *m/z* 327.0 $(M + 1)^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{18}H_{15}FN_2OS$: C, 66.24; H, 4.63; N, 8.58. Found: C, 66.14; H, 4.54; N, 8.44.

5.2.2.7. 2-[2-(2-Chlorobenzamido)]ethyl-4-phenylthiazole (33): was prepared from **89a** and 2-chlorobenzoyl chloride. The mixture was evaporated, and the residue was dissolved, with heating, in a mixture of aqueous HCl and EtOH to give, after cooling, white needles (270 mg, 73%) as the free base: mp 119 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 8.64 (t, *J* = 5.6 Hz, 1H), 7.99 (s, 1H), 7.99 – 7.92 (m, 2H), 7.53 – 7.39 (m, 5H), 7.39 – 7.29 (m, 2H), 3.66 (q, *J* = 6.4 Hz, 2H), 3.34 – 3.25 (m, 2H); EIMS *m/z* 343.5 $(M + 1)^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{18}H_{15}ClN_2OS$: C, 63.06; H, 4.41; N, 8.17; Cl, 10.34. Found: C, 63.04; H, 4.38; N, 8.44 ; Cl, 10.08.

5.2.2.8. 2-[2-(3-Chlorobenzamido)]ethyl-4-phenylthiazole (34): was prepared from **89a** and 3-chlorobenzoyl chloride. The product was recrystallized from EtOAc and hexanes (205 mg, 57%): mp 84-85 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 8.82 (t, *J* = 5.6 Hz, 1H), 7.97 (s, 1H), 7.96 – 7.90 (m, 2H), 7.87 (t, *J* = 1.8 Hz, 1H), 7.80 (ddd, *J* = 7.7, 1.7, 1.1 Hz, 1H), 7.61 (ddd, *J* = 8.0, 2.2, 1.1 Hz, 1H), 7.51 (t, *J* = 7.9 Hz, 1H), 7.47 – 7.38 (m, 2H), 7.38 – 7.28 (m, 1H), 3.68 (td, *J* = 6.9, 5.5 Hz, 2H), 3.31 (t, *J* = 6.9 Hz, 2H); EIMS *m/z* 343.3 $(M + 1)^+$;

HPLC 100 area% (254 nm). Anal. Calcd for $C_{18}H_{15}ClN_2OS$: C, 63.06; H, 4.41; N, 8.17. Found: C, 62.96; H, 4.31; N, 8.14.

5.2.2.9. 2-[2-(4-Chlorobenzamido)]ethyl-4-phenylthiazole hydrochloride (35): was prepared from **89a** and 4-chlorobenzoyl chloride. The product was crystallized as the HCl salt from EtOH and saturated ethanolic HCl (1 mL) to give white needles (94.3 mg, 23%): mp 162-165 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.81 (t, *J* = 5.6 Hz, 1H), 7.97 (s, 1H), 7.96 – 7.91 (m, 2H), 7.89 – 7.83 (m, 2H), 7.58 – 7.51 (m, 2H), 7.47 – 7.38 (m, 2H), 7.38 – 7.29 (m, 1H), 3.68 (td, *J* = 6.9, 5.5 Hz, 2H), 3.30 (d, *J* = 7.0 Hz, 2H); EIMS *m/z* 343.0 $(M + 1)^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{18}H_{15}ClN_2OS·HCl$: C, 57.00; H, 4.25; N, 7.369; Cl, 18.69. Found: C, 57.23; H, 4.33; N, 7.46; Cl, 18.44.

5.2.2.10. 2-(2-Pyrrol-2-ylamido)ethyl-4-phenylthiazole (36): A suspension of pyrrole-2-carboxylic acid (335 mg, 3.02 mmol) in dichloromethane (10 mL) was treated with EDCI·HCl (302 mg, 1.58 mmol). After 1 hour the mixture was poured into water and extracted into ether to give the anhydride as a white solid (210 mg, 68%). This was dissolved in THF (10 mL) and transferred to a stirred mixture of **89a** (301 mg, 1.06 mmol) and triethylamine (175 μL, 1.26 mmol) in THF (10 mL). After 2.5 hours, more triethylamine (225 μL) was added, and the mixture was stirred overnight. Additional acid (112 mg, 1.01 mmol) and EDCI·HCl (191 mg, 1.00 mmol) were added and the mixture was stirred overnight. The reaction was extracted into ether (3×). The product was recrystallized from EtOAc/hexanes and then from EtOH/water to give precipitated product (180 mg, 57%): mp 113 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.43 (s, 1H), 8.19 (t, *J* = 5.7 Hz, 1H), 7.96 (s, 1H), 7.96 – 7.90 (m, 2H), 7.48 – 7.38 (m, 2H), 7.38 – 7.28 (m, 1H), 6.84 (td, *J* = 2.7, 1.4 Hz, 1H), 6.74 (ddd, *J* = 3.9, 2.5, 1.5 Hz, 1H), 6.07 (dt, *J* = 3.6, 2.4 Hz, 1H), 3.63 (q, *J* = 6.7 Hz, 2H), 3.27 (t, *J* = 7.0 Hz, 2H); EIMS *m/z* 298.0 $(M + 1)^+$; HPLC 99.0 area% (265 nm). Anal. Calcd for $C_{16}H_{15}lN_2OS$: C, 64.62; H, 5.08; N, 14.13. Found: C, 64.87; H, 5.05; N, 14.34.

5.2.2.11. 2-(2-Furan-2-ylamido)ethyl-4-phenylthiazole (37): was prepared from **89a** and 2-furanoyl chloride. The mixture reaction was extracted into ether. The product was recrystallized from ethanolic HCl and ether to give a white solid (262 mg, 72%): mp 130-140 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (t, *J* = 5.8 Hz, 1H), 7.97 (s, 1H), 7.96 – 7.90 (m, 2H), 7.83 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.48 – 7.38 (m, 2H), 7.38 – 7.29 (m, 1H), 7.10 (dd, *J* = 3.5, 0.8 Hz, 1H), 6.62 (dd, *J* = 3.5, 1.8 Hz, 1H), 3.64 (td, *J* = 7.0, 5.7 Hz, 2H), 3.28 (t, *J* = 7.0 Hz, 2H); EIMS *m/z* 299.4 $(M + 1)^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{16}H_{14}lNO_2S·0.6HCl$: C, 60.01; H, 4.60; N, 8.75; Cl, 6.64. Found: C, 60.12; H, 4.53; N, 8.68; Cl, 6.56.5.2.2.12. 2-(2-Thiophen-2-ylamido)ethyl-4-phenylthiazole (38) was prepared from **89a** and thiophene-2-carbonyl chloride. The product was recrystallized from ethanolic HCl and ether as a white solid (246 mg, 66%): mp 110-114 °C dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 (t, *J* = 5.6 Hz, 1H), 7.97 (s, 1H), 7.96 – 7.90 (m, 2H), 7.78 – 7.71 (m, 2H), 7.47 – 7.38 (m, 2H), 7.38 – 7.28 (m, 1H), 7.14 (dd, *J* = 5.0, 3.8 Hz, 1H), 3.65 (td, *J* = 7.0, 5.6 Hz, 2H), 3.29 (t, *J* = 7.0 Hz, 2H); EIMS *m/z* 315.2 $(M + 1)^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{16}H_{14}NO_2S·0.1HCl$: C, 60.42; H, 4.44; N, 8.81; Cl, 1.11. Found: C, 60.48; H, 4.53; N, 8.68; Cl, 1.17.

5.2.2.13. 2-(2-Thiophen-3-ylamido)ethyl-4-phenylthiazole (39): A mixture of thiophene-3-carboxylic acid (201 mg, 1.95 mmol) and thionyl chloride (1.0 mL, 13.7 mmol) in toluene (10 mL) was refluxed for 2 hours. The mixture was evaporated, and the acyl halide was dissolved in dichlormethane (10 ml), followed by the addition of **89a** (301 mg, 1.06 mmol) and triethylamine (0.5 mL, 3.6 mmol). The mixture was stirred overnight and worked up by dilution with water and extraction into dichloromethane. EtOAc/hexanes to give white crystals (208 mg, 63%): mp 98-118 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52 (t, *J* = 5.7 Hz, 1H), 8.11 (dd, *J* = 3.0, 1.3 Hz, 1H), 7.97 (s, 1H), 7.96 – 7.90 (m, 2H), 7.58 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.49 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.43 (dd, *J* = 8.4, 6.9 Hz, 2H), 7.38 – 7.28 (m, 1H), 3.64 (td, *J* = 7.0, 5.6 Hz, 2H), 3.29 (t, *J* = 7.0 Hz, 2H); EIMS *m/z* 315.1 (M + 1)$^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{16}H_{14}NO_2S$: C, 61.12 H, 4.49; N, 8.91. Found: C, 60.88; H, 4.73; N, 8.88.

5.2.2.14. 2-(2-Pyridin-3-ylamido)ethyl-4-phenylthiazole dihydrochloride (40): was prepared from **89a** and nicotinoyl chloride hydrochloride. The product was recrystallized from ethanolic HCl a white solid (309 g, 81%):mp 175-178 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.29 (t, *J* = 5.5 Hz, 1H), 9.20 (dd, *J* = 2.1, 0.8 Hz, 1H), 8.92 (dd, *J* = 5.4, 1.5 Hz, 1H), 8.65 (dt, *J* = 8.1, 1.8 Hz, 1H), 7.99 (s, 1H), 7.97 – 7.93 (m, 2H), 7.91 (dd, *J* = 8.0, 5.2 Hz, 1H), 7.48 – 7.38 (m, 2H), 7.38 – 7.29 (m, 1H), 3.74 (td, *J* = 6.9, 5.5 Hz, 2H), 3.35 (t, *J* = 6.9 Hz, 2H); EIMS *m/z* 310.0 (M + 1)$^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{17}H_{15}N_3OS{\cdot}2HCl{\cdot}0.25H_2O$: C, 52.79; H, 4.56; N, 10.86; Cl, 18.33. Found: C, 52.72; H, 4.73; N, 10.74; Cl, 18.06.

5.2.2.15. 2-(2-Pyridin-4-ylamido)ethyl-4-phenylthiazole (41): was prepared from **89a** and isonicotinoyl chloride hydrochloride. The reaction mixture was diluted with water to give a white solid (220 mg, 67%): mp 116 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.98 (t, *J* = 5.6 Hz, 1H), 8.76 – 8.69 (m, 2H), 7.97 (s, 1H), 7.96 – 7.90 (m, 2H), 7.77 – 7.70 (m, 2H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.38 – 7.28 (m, 1H), 3.70 (q, *J* = 6.8 Hz, 2H), 3.32 (t, *J* = 6.9 Hz, 2H); EIMS *m/z* 310.0 (M + 1)$^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{17}H_{15}N_3OS{\cdot}$. $1H_2O$: C, 65.61; H, 4.92; N, 13.50. Found: C, 65.62; H, 5.00; N, 13.28.

5.2.2.16. 2-(2-Cyclopentylamido)ethyl-4-phenylthiazole (42): was prepared from **89a** and cyclopentanecarbonyl chloride. The product was recrystallized from EtOAc/hexanes as ivory crystals (161 mg, 52%); mp 106-107 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (s, 1H), 7.96 – 7.89 (m, 3H), 7.47 – 7.41 (m, 2H), 7.38 – 7.29 (m, 1H), 3.45 (td, *J* = 6.8, 5.6 Hz, 2H), 3.16 (t, *J* = 6.9 Hz, 2H), 2.59 – 2.46 (m, 1H), 1.77 – 1.66 (m, 2H), 1.66 – 1.54 (m, 4H), 1.53 – 1.43 (m, 2H); EIMS *m/z* 301.1 (M + 1)$^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{17}H_{20}N_2OS$: C, 67.97; H, 6.71; N, 9.32. Found: C, 67.81; H, 6.70; N, 9.29.

5.2.2.17. 2-(2-Cyclohexylamido)ethyl-4-phenylthiazole (43): was prepared from **89a** and cyclohexanecarbonyl chloride. The product was recrystallized from EtOAc/hexanes as white crystals (249 mg, 78%); mp 112-114 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (s, 1H), 7.96 – 7.91 (m, 2H), 7.88 (t, *J* = 5.6 Hz, 1H), 7.48 – 7.38 (m, 2H), 7.38 – 7.28 (m, 1H), 3.43 (q, *J* = 6.7 Hz, 2H), 3.15 (t, *J* = 6.8 Hz, 2H), 2.07 (tt, *J* = 11.5, 3.2 Hz, 1H), 1.68 (dd, *J* = 10.0, 6.8 Hz, 4H), 1.60 (d, *J* = 9.3 Hz, 1H), 1.38 – 1.06 (m, 5H); EIMS *m/z* 315.2 (M + 1)$^+$;

HPLC 100 area% (254 nm). Anal. Calcd for $C_{18}H_{22}N_2OS$: C, 68.75; H, 7.05; N, 8.91. Found: C, 68.45; H, 7.08; N, 8.80.

5.2.3. General procedure for preparation of trisubstituted ureas 44-48

—A suspension of 4-phenylthiazol-2-ethylamine hydrobromide (**89a**, 1.05-1.1 mmol) and the appropriate carbamoyl chloride or anhydride (minimum of 1.2 equivalents) in THF (10 mL) was chilled to 0 °C. Triethylamine (minimum of 3 equivalents) was added, and the mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with water and extracted into EtOAc (3×), and the crude product obtained was recrystallized from an appropriate solvent, unless stated otherwise.

5.2.3.1. 2-(2-Pyrrolidin-1-ylamido)ethyl-4-phenylthiazole hydrochloride sesquihydrochloride (44): was prepared from **89a** and pyrrolidine-1-carbonyl chloride. The crude product was recrystallized from ethanolic HCl/ ether to give a solid (244 mg, 68%): mp 129-154 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (s, 1H), 7.97 – 7.90 (m, 2H), 7.48 – 7.39 (m, 2H), 7.38 – 7.29 (m, 1H), 3.42 (t, J = 7.2 Hz, 2H), 3.25 – 3.13 (m, 6H), 1.84 – 1.71 (m, 4H); EIMS m/z 302.0 $(M + 1)^+$; HPLC 98.1 area% (254 nm). Anal. Calcd for $C_{16}H_{19}N_3OS \cdot 1.5HCl \cdot 0.7H_2O$: C, 52.12; H, 5.99; N, 11.40; Cl, 14.42. Found: C, 51.79; H, 6.01; N, 11.29; Cl, 14.70.

5.2.3.2. 2-(2-Pyrrol-1-ylamido)ethyl-4-phenylthiazole (45): was prepared from **89a** and 1*H*-pyrrole-1-carboxylic anhydride[37], and the reaction mixture was worked up by extraction into ether. The product was recrystallized from EtOAc/hexanes (262 mg, 84%): mp 100-101 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (t, J = 5.6 Hz, 1H), 7.98 (s, 1H), 7.96 – 7.89 (m, 2H), 7.46 – 7.39 (m, 2H), 7.39 – 7.35 (m, 2H), 7.35 – 7.28 (m, 1H), 6.21 (t, J = 2.2 Hz, 2H), 3.65 (td, J = 6.9, 5.5 Hz, 2H), 3.31 (t, J = 6.9 Hz, 2H); EIMS m/z 298.0 $(M + 1)^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{16}H_{15}N_3OS$: C, 64.62; H, 5.08; N, 14.13. Found: C, 64.40; H, 5.04; N, 14.19.

5.2.3.3. 2-(2-Piperidin-1-ylamido)ethyl-4-phenylthiazole (46)[25]: was prepared from **89a** and piperidine-1-carbonyl chloride. The crude product was recrystallized from EtOAc/ hexanes to give a white solid (162 mg, 49%); mp 105-106 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (s, 1H), 7.96 – 7.90 (m, 2H), 7.48 – 7.38 (m, 2H), 7.38 – 7.28 (m, 1H), 6.64 (t, J = 5.4 Hz, 1H), 3.41 (td, J = 7.0, 5.4 Hz, 2H), 3.28 – 3.23 (m, 4H), 3.16 (t, J = 7.0 Hz, 2H), 1.51 (dt, J = 11.2, 5.6 Hz, 2H), 1.46 – 1.35 (m, 4H); EIMS m/z 316.2 $(M + 1)^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{17}H_{21}N_3OS \cdot 0.2H_2O$: C, 64.00; H, 6.76; N, 13.17. Found: C, 64.02; H, 6.69; N, 13.12.

5.2.3.4. 2-(2-Morpholin-4-ylamido)ethyl-4-phenylthiazole hydrochloride (47): was prepared from **89a** and morpholine-4-carbonyl chloride, and the reaction mixture diluted with water and extracted into ether (3×). The product was recrystallized from ethanolic HCl/ ether as a white solid (271 mg, 70%): mp 103-135 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (s, 1H), 7.95 (dd, J = 8.3, 1.3 Hz, 2H), 7.48 – 7.39 (m, 2H), 7.38 – 7.29 (m, 1H), 6.81 (s, 1H), 3.57 – 3.50 (m, 4H), 3.43 (t, J = 7.0 Hz, 2H), 3.26 (dd, J = 5.6, 4.1 Hz, 4H), 3.22 – 3.14 (m, 2H); EIMS m/z 318.2 $(M + 1)^+$; HPLC 100 area% (254 nm). Anal. Calcd for

$C_{16}H_{19}N_3O_2S \cdot 0.95HCl \cdot 0.6H_2O$: C, 52.96; H, 5.88; N, 11.58; Cl, 9.28. Found: C, 52.89; H, 5.64; N, 11.54; Cl, 9.01.

5.2.3.5. 2-(2-Azepan-1-ylamido)ethyl-4-phenylthiazole (48): was prepared from **89a** and azepane-1-carbonyl chloride (prepared from azepane by modification of the method of McGhee.[38] The product was recrystallized from EtOAc/hexanes as white needles (173 mg, 50%): mp 81-82 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 7.96 (d, $J = 0.6$ Hz, 1H), 7.96 – 7.90 (m, 2H), 7.48 – 7.38 (m, 2H), 7.37 – 7.28 (m, 1H), 6.39 (t, $J = 5.5$ Hz, 1H), 3.42 (td, $J = 6.8$, 5.4 Hz, 2H), 3.34 – 3.24 (m, 4H), 3.17 (t, $J = 6.9$ Hz, 2H), 1.57 (pt, $J = 4.7$, 2.8, 2.3 Hz, 4H), 1.44 (dt, $J = 7.3$, 2.7 Hz, 4H); EIMS *m/z* 330.1 $(M + 1)^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{18}H_{23}N_3OS$: C, 65.62; H, 7.04; N, 12.75. Found: C, 65.83; H, 7.16; N, 12.54.

5.2.4. General procedure for preparation of disubstituted ureas 49-52 and carbamate 53—The appropriate isocyanate or chloroformate (minimum of 1 equivalent) was added to a mixture of 4-phenylthiazol-2-ethylamine hydrobromide (**89a**, 1-1.05 mmol) and *N,N*-diisopropylethylamine (minimum of 2 equivalents) in dichloromethane (10 mL). After stirring overnight at room temperature, the reaction mixture was diluted with water and extracted into dichloromethane (3×). The product was recrystallized from an appropriate solvent.

5.2.4.1. 1-(*tert*-Butyl)-3-[2-(4-phenylthiazol-2-yl)ethyl]urea (49): was prepared from **89a** and tert-butylisocyanate using triethylamine in place of *N,N*-diisopropylethylamine. Recrystallization of the product from EtOAc/hexanes gave white needles (230 mg, 75): mp 162-163 C°; ^1H NMR (400 MHz, DMSO-d_6) δ 7.97 (d, $J = 0.9$ Hz, 1H), 7.97 – 7.91 (m, 2H), 7.48 – 7.38 (m, 2H), 7.33 (dddd, $J = 9.3$, 6.5, 2.0, 1.2 Hz, 1H), 5.80 (t, $J = 5.9$ Hz, 1H), 5.74 (s, 1H), 3.39 (q, $J = 6.5$ Hz, 2H), 3.11 (t, $J = 6.8$ Hz, 2H), 1.21 (d, $J = 0.6$ Hz, 9H); EIMS *m/z* 304.1 $(M + 1)^+$; HPLC 98.6 area% (265 nm). Anal. Calcd for $C_{16}H_{21}N_3OS$: C, 63.33 H, 6.98; N, 13.85. Found: C, 63.14; H, 7.09; N, 13.73.

5.2.4.2. 1-Benzyl-3-[2-(4-phenylthiazol-2-yl)ethyl]urea (50): was prepared from **89a** and benzyl isocyanate. The product was recrystallized from EtOH/water as white granules (294 mg, 87%): mp 131-134 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 7.98 (d, $J = 0.5$ Hz, 1H), 7.97 – 7.90 (m, 2H), 7.48 – 7.40 (m, 2H), 7.36 – 7.26 (m, 3H), 7.25 – 7.16 (m, 3H), 6.47 (t, $J = 6.0$ Hz, 1H), 6.12 (t, $J = 5.9$ Hz, 1H), 4.20 (d, $J = 6.0$ Hz, 2H), 3.47 (q, $J = 6.5$ Hz, 2H), 3.16 (t, $J = 6.8$ Hz, 2H); EIMS *m/z* 338.1 $(M + 1)^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{19}H_{19}N_3OS$: C, 67.63 H, 5.68; N, 12.45. Found: C, 67.85; H, 5.79; N, 12.54.

5.2.4.3. 1-Cyclohexyl-3-[2-(4-phenylthiazol-2-yl)ethyl]urea (51): was prepared from **89a** and cyclohexyl isocyanate. The product was recrystallized from EtOAc and then from EtOH/water to give a white powder (199 mg, 60%): mp 139-140 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 7.97 (d, $J = 0.6$ Hz, 1H), 7.97 – 7.92 (m, 2H), 7.48 – 7.39 (m, 2H), 7.38 – 7.29 (m, 1H), 5.91 – 5.82 (m, 2H), 3.43 (q, $J = 6.6$ Hz, 2H), 3.38 – 3.29 (m, 1H), 3.12 (t, $J = 6.8$ Hz, 2H), 1.73 (dd, $J = 12.6$, 3.8 Hz, 2H), 1.62 (dt, $J = 12.8$, 4.0 Hz, 2H), 1.55 – 1.46 (m, 1H), 1.31 – 1.18 (m, 2H), 1.17 – 0.98 (m, 3H); EIMS *m/z* 330.1 $(M + 1)^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{18}H_{23}N_3OS$: C, 65.62 H, 7.04; N, 12.75. Found: C, 65.47; H, 7.16; N, 12.70.

5.2.4.4. 1-Phenyl-3-[2-(4-phenylthiazol-2-yl)ethyl]urea (52): was prepared from **89a** and phenyl isocyanate. The product was recrystallized from EtOH/water as white needles (283 mg, 83%): mp 193-195 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (s, 1H), 7.99 (d, J = 0.8 Hz, 1H), 7.98 – 7.92 (m, 2H), 7.48 – 7.40 (m, 2H), 7.40 – 7.29 (m, 3H), 7.21 (ddd, J = 8.5, 7.4, 0.7 Hz, 2H), 6.88 (tq, J = 7.5, 1.1 Hz, 1H), 6.29 (t, J = 5.8 Hz, 1H), 3.55 (q, J = 6.5 Hz, 2H), 3.21 (t, J = 6.7 Hz, 2H; EIMS m/z 324.0 $(M + 1)^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{18}H_{17}N_3OS$: C, 66.85 H, 5.30; N, 12.99. Found: C, 66.97; H, 5.35; N, 13.10.

5.2.4.5. Phenyl [2-(4-phenylthiazol-2-yl)ethyl]carbamate (53): was prepared from **89a** and phenyl chloroformate using triethylamine in place of *N*,*N*-diisopropylethylamine. The product was recrystallized from EtOH/water to give white needles (261 mg, 80%); mp 101-104 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (s, 1H), 7.99 – 7.92 (m, 3H), 7.53 – 7.40 (m, 2H), 7.40 – 7.31 (m, 3H), 7.26 – 7.14 (m, 1H), 7.12 – 7.03 (m, 2H), 3.51 (q, J = 6.8 Hz, 2H), 3.25 (t, J = 6.9 Hz, 2H); EIMS m/z 325.1 $(M + 1)^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{18}H_{16}N_3O_2S$: C, 66.64 H, 4.97; N, 8.64. Found: C, 66.40 H, 5.17; N, 8.48.

5.2.5. General procedure for compounds 54-73—A suspension of one of the 4-arylthiazol-2-ethylamine hydrobromides **89a-f** (1 mmol) in THF (10 mL) was treated with triethylamine (minimum of 2.5 equivalents). The appropriate sulfonyl, acyl, or carbamoyl chloride was added (minimum of 1.1 equivalents), and the mixture was stirred overnight at room temperature before being diluted with water and extracted into EtOAc (3×. The products were recrystallized from EtOAc/hexane unless stated otherwise.

5.2.5.1. 2-(2-Benzenesulfonamido)ethyl-4-phenylthiazole hydrochloride (54): was prepared **89a** and benzenesulfonyl chloride. The product was converted to the HCl salt using ethanolic HCl followed by recrystallization from EtOH to give a solid (342 mg, 82%): mp 166 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (s, 1H), 7.94 – 7.88 (m, 3H), 7.84 – 7.79 (m, 2H), 7.67 – 7.62 (m, 1H), 7.62 – 7.56 (m, 2H), 7.48 – 7.38 (m, 2H), 7.38 – 7.28 (m, 1H), 3.25 – 3.10 (m, 4H); EIMS m/z 345.1 $(M + 1)^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{17}H_{16}N_2O_2S{\cdot}HCl$: C, 53.60 H, 4.50; N, 7.35; Cl, 9.31. Found: C, 53.59 H, 4.45; N, 7.23; Cl, 9.19.

5.2.5.2. 2-(2-p-Toluenesulfonamido)ethyl-4-phenylthiazole (55): was prepared from **89a** and tosyl chloride. The product was converted to the HCl salt using ethanolic HCl and ether to give a white solid (363 mg, 86%): mp 165-173 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (s, 1H), 7.94 – 7.87 (m, 2H), 7.84 – 7.76 (m, 1H), 7.71 – 7.64 (m, 2H), 7.47 – 7.40 (m, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.35 – 7.28 (m, 1H), 3.15 (q, J = 3.9, 3.0 Hz, 4H), 2.36 (s, 3H); EIMS m/z 359.0 $(M + 1)^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{18}H_{18}N_2O_2S{\cdot}HCl{\cdot}0.25H_2O$: C, 54.12 H, 4.92; N, 7.01; Cl, 8.88. Found: C, 54.28; H, 4.80; N, 7.06; Cl, 8.59.

5.2.5.3. 2-[2-(3-Cyanobenzamido)]ethyl-4-(2-fluorophenyl)thiazole (56): was prepared from **89b** and 3-cyanobenzoyl chloride as a white solid (283 mg, 78%): mp 115-116 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (t, J = 5.5 Hz, 1H), 8.24 (t, J = 1.7 Hz, 1H), 8.14 (dt, J = 7.9, 1.4 Hz, 1H), 8.10 (td, J = 7.9, 1.9 Hz, 1H), 8.01 (dt, J = 7.5, 1.2 Hz, 1H), 7.87 (dd, J = 2.6, 0.6 Hz, 1H), 7.70 (t, J = 7.8 Hz, 1H), 7.45 – 7.36 (m, 1H), 7.36 – 7.24 (m, 2H), 3.71 (q, *J* = 6.7 Hz, 2H), 3.33 (t, *J* = 6.8 Hz, 2H); EIMS *m/z* 352.1 $(M + 1)^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{19}H_{14}FN_3OS$: C, 64.94 H, 4.02; N, 11.96. Found: C, 64.64; H, 4.11; N, 11.81.

5.2.5.4. 2-[2-(3-Cyanobenzamido)]ethyl-4-(3-fluoropheny)lthiazole (57): was prepared from **89c** and 3-cyanobenzoyl chloride as white crystals (303 mg, 86%): mp 114-115 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 8.91 (t, *J* = 5.6 Hz, 1H), 8.24 (td, *J* = 1.7, 0.6 Hz, 1H), 8.14 (ddd, *J* = 7.9, 1.8, 1.2 Hz, 1H), 8.11 (s, 1H), 8.01 (ddd, *J* = 7.7, 1.7, 1.2 Hz, 1H), 7.79 (ddd, *J* = 7.8, 1.6, 0.9 Hz, 1H), 7.75 – 7.66 (m, 2H), 7.47 (td, *J* = 8.0, 6.1 Hz, 1H), 7.16 (dddd, *J* = 9.0, 8.2, 2.7, 0.9 Hz, 1H), 3.70 (td, *J* = 6.8, 5.5 Hz, 2H), 3.32 (t, *J* = 6.39 Hz, 2H); EIMS *m/z* 352.1 $(M + 1)^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{19}H_{14}FN_3OS$: C, 64.94 H, 4.02; N, 11.96. Found: C, 64.75; H, 4.19; N, 11.83.

5.2.5.5. 2-[2-(3-Cyanobenzamido)]ethyl-4-(4-fluorophenyl)thiazole (58): was prepared from **89d** and 3-cyanobenzoyl chloride as white crystals (68 mg, 19%): mp 126-128 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 8.90 (t, *J* = 5.6 Hz, 1H), 8.24 (t, *J* = 1.8 Hz, 1H), 8.14 (ddd, *J* = 7.9, 1.9, 1.2 Hz, 1H), 8.05 – 7.93 (m, 4H), 7.70 (t, *J* = 7.9 Hz, 1H), 7.33 – 7.18 (m, 2H), 3.70 (q, *J* = 6.8 Hz, 2H), 3.31 (t, *J* = 6.8 Hz, 2H); EIMS *m/z* 352.1 $(M + 1)^+$; HPLC 100 area % (254 nm). Anal. Calcd for $C_{19}H_{14}FN_3OS{\cdot}0.2H_2O$: C, 64.28 H, 4.09; N, 11.84. Found: C, 64.21; H, 4.11; N, 11.66.

5.2.5.6. 2-[2-(3-Nitrobenzamido)]ethyl-4-(2-fluorophenyl)thiazole (59): was prepared from **89b** and 3-nitrobenzoyl chloride as white crystals (276 mg, 74%): mp 114-115 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 9.09 (t, *J* = 5.6 Hz, 1H), 8.70 – 8.64 (m, 1H), 8.39 (ddd, *J* = 8.3, 2.4, 1.0 Hz, 1H), 8.28 (dt, *J* = 7.8, 1.4 Hz, 1H), 8.10 (td, *J* = 7.9, 1.9 Hz, 1H), 7.87 (d, *J* = 2.5 Hz, 1H), 7.79 (t, *J* = 8.0 Hz, 1H), 7.39 (dddd, *J* = 8.8, 7.2, 5.2, 1.8 Hz, 1H), 7.35 – 7.22 (m, 2H), 3.73 (td, *J* = 6.8, 5.5 Hz, 2H), 3.35 (t, *J* = 6.8 Hz, 2H); EIMS *m/z* 372.1 $(M + 1)^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{18}H_{14}FN_3O_3S$: C, 58.21 H, 3.80; N, 11.31. Found: C, 58.18; H, 3.85; N, 11.27.

5.2.5.7. 2-[2-(3-Nitrobenzamido)]ethyl-4-(3-fluorophenyl)thiazole (60): was prepared from **89c** and 3-nitrobenzoyl chloride as white crystals (301 mg, 81%): mp 106 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 9.08 (t, *J* = 5.6 Hz, 1H), 8.67 (t, *J* = 2.0 Hz, 1H), 8.39 (ddd, *J* = 8.2, 2.3, 1.1 Hz, 1H), 8.28 (ddd, *J* = 7.8, 1.7, 1.0 Hz, 1H), 8.11 (s, 1H), 7.83 – 7.73 (m, 2H), 7.72 (ddd, *J* = 10.7, 2.6, 1.5 Hz, 1H), 7.46 (td, *J* = 8.0, 6.1 Hz, 1H), 7.16 (dddd, *J* = 9.1, 8.3, 2.7, 1.0 Hz, 1H), 3.73 (q, *J* = 6.9, 2H), 3.34 (t, *J* = 6.9 Hz, 2H); EIMS *m/z* 372.1 $(M + 1)^+$; HPLC 98.6 area% (254 nm). Anal. Calcd for $C_{18}H_{14}FN_3O_3S{\cdot}0.25H_2O$: C, 57.51 H, 3.89; N, 11.18. Found: C, 57.32; H, 3.71; N, 11.05.

5.2.5.8. 2-[2-(3-Nitrobenzamido)]ethyl-4-(4-fluorophenyl)thiazole (61): was prepared from **89d** and 3-nitrobenzoyl chloride as white crystals (261 mg, 70%): mp 143-144 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 9.08 (t, *J* = 5.6 Hz, 1H), 8.67 (ddd, *J* = 2.3, 1.7, 0.5 Hz, 1H), 8.39 (ddd, *J* = 8.2, 2.3, 1.0 Hz, 1H), 8.28 (ddd, *J* = 7.8, 1.7, 1.1 Hz, 1H), 8.05 – 7.93 (m, 3H), 7.79 (dd, *J* = 8.3, 7.7 Hz, 1H), 7.32 – 7.17 (m, 2H), 3.72 (td, *J* = 6.9, 5.5 Hz, 2H), 3.33 (d, *J* = 6.8 Hz, 2H); EIMS *m/z* 372.1 $(M + 1)^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{18}H_{14}FN_3O_3S$: C, 58.21 H, 3.80; N, 11.31. Found: C, 58.35; H, 3.93; N, 11.17.

5.2.5.9. 2-[2-(3-Fluorobenzamido)]ethyl-4-(3-fluorophenyl)thiazole (62): was prepared from **89c** and 3-fluorobenzoyl chloride as white crystals (266 mg, 77%): mp 106-107 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (t, *J* = 5.6 Hz, 1H), 8.10 (s, 1H), 7.80 (ddd, *J* = 7.8, 1.6, 0.9 Hz, 1H), 7.74 (ddd, *J* = 10.7, 2.7, 1.5 Hz, 1H), 7.69 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.62 (ddd, *J* = 10.1, 2.7, 1.5 Hz, 1H), 7.50 (dtd, *J* = 22.2, 8.0, 6.0 Hz, 2H), 7.39 (tdd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 7.16 (dddd, *J* = 9.0, 8.2, 2.7, 0.9 Hz, 1H), 3.68 (td, *J* = 6.8, 5.5 Hz, 2H), 3.31 (t, *J* = 6.9 Hz, 2H); EIMS *m/z* 345.2 (M + 1)$^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{18}H_{14}F_2N_2OS$: C, 62.78 H, 4.10; N, 8.13. Found: C, 62.59; H, 4.16; N, 8.03.

5.2.5.10. 2-[2-(3-Fluorobenzamido)]ethyl-4-(4-fluorophenyl)thiazole (63): was prepared from **89d** and 3-fluorobenzoyl chloride as white crystals (266 mg, 77%): mp 122 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (t, *J* = 5.6 Hz, 1H), 7.99 (dd, *J* = 8.9, 5.6 Hz, 2H), 7.96 (s, 1H), 7.69 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.62 (ddd, *J* = 10.1, 2.7, 1.5 Hz, 1H), 7.53 (td, *J* = 8.0, 5.8 Hz, 1H), 7.39 (tdd, *J* = 8.4, 2.7, 1.0 Hz, 1H), 7.30 – 7.21 (m, 2H), 3.68 (td, *J* = 6.9, 5.6 Hz, 2H), 3.30 (t, *J* = 7.0 Hz, 2H); EIMS *m/z* 345.2 (M + 1)$^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{18}H_{14}F_2N_2OS$: C, 62.78 H, 4.10; N, 8.13. Found: C, 62.72; H, 4.17; N, 8.06.

5.2.5.11. 2-(2-Thiophen-2-ylamido)ethyl-4-(2-fluorophenyl)thiazole (64): was prepared from **89b** and thiophene-2-carbonyl chloride as white crystals (267 mg, 80%): mp 139-141 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (t, *J* = 5.7 Hz, 1H), 8.12 (td, *J* = 7.9, 1.9 Hz, 1H), 7.86 (d, *J* = 2.6 Hz, 1H), 7.75 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.73 (dd, *J* = 3.7, 1.2 Hz, 1H), 7.45 – 7.37 (m, 1H), 7.36 – 7.24 (m, 2H), 7.15 (dd, *J* = 5.0, 3.7 Hz, 1H), 3.66 (td, *J* = 6.9, 5.6 Hz, 2H), 3.31 (t, *J* = 6.9 Hz, 2H); EIMS *m/z* 333.1 (M + 1)$^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{16}H_{13}FN_2OS_2$: C, 57.81 H, 3.94; N, 8.43. Found: C, 57.72; H, 4.06; N, 8.37.

5.2.5.12. 2-(2-Thiophen-2-ylamido)ethyl-4-(3-fluorophenyl)thiazole (65): was prepared from **89c** and thiophene-2-carbonyl chloride as ivory needles (266 mg, 79%): mp 137-138 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (t, *J* = 5.7 Hz, 1H), 8.10 (d, *J* = 0.6 Hz, 1H), 7.84 – 7.77 (m, 1H), 7.77 – 7.69 (m, 3H), 7.47 (td, *J* = 8.0, 6.1 Hz, 1H), 7.17 (ddd, *J* = 8.1, 2.7, 0.8 Hz, 1H), 7.16 – 7.11 (m, 1H), 3.65 (q, *J* = 6.6 Hz, 2H), 3.30 (t, *J* = 6.9 Hz, 2H); EIMS *m/z* 333.2 (M + 1)$^+$; HPLC 98.9 area% (265 nm). Anal. Calcd for $C_{16}H_{13}FN_2OS_2$: C, 57.81 H, 3.94; N, 8.43. Found: C, 57.68; H, 3.97; N, 8.31.

5.2.5.13. 2-(2-Thiophen-2-ylamido)ethyl-4-(4-fluorophenyl)thiazole (66): was prepared from **89d** and thiophene-2-carbonyl chloride as a white solid (268 mg, 80%): mp 124-125 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (t, *J* = 5.7 Hz, 1H), 8.03 – 7.96 (m, 2H), 7.96 (s, 1H), 7.75 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.72 (dd, *J* = 3.8, 1.2 Hz, 1H), 7.31 – 7.18 (m, 2H), 7.14 (dd, *J* = 5.0, 3.7 Hz, 1H), 3.65 (td, *J* = 6.9, 5.6 Hz, 2H), 3.29 (t, *J* = 7.0 Hz, 2H); EIMS *m/z* 333.2 (M + 1)$^+$; HPLC 100 area% (265 nm). Anal. Calcd for $C_{16}H_{13}FN_2OS_2$: C, 57.81 H, 3.94; N, 8.43. Found: C, 57.61; H, 4.03; N, 8.39.

5.2.5.14. 2-(2-Pyrrolidin-1-ylamido)ethyl-4-(2-fluorophenyl)thiazole (67): was prepared from **89b** and pyrrolidine-1-carbonyl chloride as a white solid (111 mg, 34%): mp

102-103 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (td, *J* = 7.8, 1.7 Hz, 1H), 7.85 (d, *J* = 2.6 Hz, 1H), 7.45 – 7.36 (m, 1H), 7.35 – 7.26 (m, 2H), 6.32 (t, *J* = 5.6 Hz, 1H), 3.42 (td, *J* = 7.0, 5.5 Hz, 2H), 3.25 – 3.14 (m, 6H), 1.84 – 1.73 (m, 4H); EIMS *m/z* 320.1 (M + 1)$^+$; HPLC 99.1 area% (254 nm). Anal. Calcd for $C_{16}H_{18}FN_3OS.0.2H_2O$: C, 59.50; H, 5.74; N, 13.01. Found: C, 59.39; H, 5.71; N, 13.00.

5.2.5.15. 2-(2-Pyrrolidin-1-ylamido)ethyl-4-(3-fluorophenyl)thiazole (68): was prepared from **89c** and pyrrolidine-1-carbonyl chloride as white crystals (256 mg, 80%): mp 118-120 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (s, 1H), 7.80 (ddd, *J* = 7.8, 1.6, 0.9 Hz, 1H), 7.75 (ddd, *J* = 10.7, 2.7, 1.5 Hz, 1H), 7.48 (td, *J* = 8.0, 6.2 Hz, 1H), 7.17 (dddd, *J* = 9.0, 8.3, 2.7, 0.9 Hz, 1H), 6.31 (t, *J* = 5.6 Hz, 1H), 3.41 (td, *J* = 7.0, 5.6 Hz, 2H), 3.25 – 3.13 (m, 6H), 1.85 – 1.71 (m, 4H); EIMS *m/z* 320.3 (M + 1)$^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{16}H_{18}FN_3OS$: C, 60.17; H, 5.68; N, 13.16. Found: C, 60.02; H, 5.66; N, 13.11.

5.2.5.16. 2-(2-Pyrrolidin-1-ylamido)ethyl-4-(4-fluorophenyl)thiazole (69): was prepared from **89d** and pyrrolidine-1-carbonyl chloride as ivory crystals (246 mg, 77%): mp 128-129 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 – 7.96 (m, 2H), 7.95 (s, 1H), 7.32 – 7.21 (m, 2H), 6.31 (t, *J* = 5.6 Hz, 1H), 3.41 (td, *J* = 7.1, 5.5 Hz, 2H), 3.24 – 3.18 (m, 4H), 3.16 (t, *J* = 7.0 Hz, 2H), 1.85 – 1.73 (m, 4H); EIMS *m/z* 320.2 (M + 1)$^+$; HPLC 98.3 area% (254 nm). Anal. Calcd for $C_{16}H_{18}FN_3OS$: C, 60.17; H, 5.68; N, 13.16. Found: C, 60.12; H, 5.73; N, 13.15.

5.2.5.17. 2-(2-Piperidin-1-ylamido)ethyl-4-(3-fluorophenylt)hiazole (70): was prepared from **89c** and piperidine-1-carbonyl chloride as a white solid (278 mg, 83%): mp 102-103 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (s, 1H), 7.80 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.74 (ddd, *J* = 10.7, 2.7, 1.5 Hz, 1H), 7.48 (td, *J* = 8.0, 6.2 Hz, 1H), 7.21 – 7.11 (m, 1H), 6.63 (t, *J* = 5.4 Hz, 1H), 3.45 – 3.36 (m, 2H), 3.28 – 3.22 (m, 4H), 3.16 (t, *J* = 6.9 Hz, 2H), 1.57 – 1.46 (m, 2H), 1.45 – 1.34 (m, 4H); EIMS *m/z* 334.2 (M + 1)$^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{17}H_{20}FN_3OS$: C, 61.24; H, 6.05; N, 12.60. Found: C, 61.22; H, 6.11; N, 12.60.

5.2.5.18. 2-(2-Piperidin-1-ylamido)ethyl-4-(4-fluorophenyl)thiazole (71): was prepared from **89d** and piperidine-1-carbonyl chloride as a white powder (203 mg, 60%): mp 107-108 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 – 7.96 (m, 2H), 7.95 (d, *J* = 0.7 Hz, 1H), 7.31 – 7.22 (m, 2H), 6.63 (t, *J* = 5.5 Hz, 1H), 3.41 (td, *J* = 6.9, 5.3 Hz, 2H), 3.25 (dd, *J* = 6.5, 4.4 Hz, 4H), 3.16 (t, *J* = 7.0 Hz, 2H), 1.56 – 1.46 (m, 2H), 1.45 – 1.35 (m, 4H); EIMS *m/z* 334.1 (M + 1)$^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{17}H_{20}FN_3OS$: C, 61.24; H, 6.05; N, 12.60. Found: C, 61.15; H, 5.98; N, 12.39.

5.2.5.19. 2-(2-Piperidin-1-ylamido)ethyl-4-(2,4-difluorophenyl)thiazole (72): was prepared from **89e** and piperidine-1-carbonyl chloride as an off-white powder (232 mg, 65%): mp 104 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (td, *J* = 8.9, 6.8 Hz, 1H), 7.83 (d, *J* = 2.6 Hz, 1H), 7.38 (ddd, *J* = 11.8, 9.2, 2.6 Hz, 1H), 7.20 (td, *J* = 8.4, 2.5 Hz, 1H), 6.64 (t, *J* = 5.4 Hz, 1H), 3.41 (td, *J* = 6.9, 5.3 Hz, 2H), 3.25 (dd, *J* = 6.5, 4.4 Hz, 4H), 3.17 (t, *J* = 6.9 Hz, 2H), 1.57 – 1.46 (m, 2H), 1.45 – 1.34 (m, 4H); EIMS *m/z* 352.1 (M + 1)$^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{17}H_{19}F_2N_3OS{\cdot}0.2H_2O$: C, 57.51; H, 5.51; N, 11.84. Found: C, 57.47; H, 5.31; N, 11.70.

5.2.5.20. 2-(2-Piperidin-1-ylamido)ethyl-4-(3,4-difluorophenyl)thiazole (73): was prepared from **89f** and piperidine-1-carbonyl chloride as ivory crystals (287 mg, 81%): mp 100-103 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (s, 1H), 7.97 (ddd, J = 12.2, 7.8, 2.1 Hz, 1H), 7.86 – 7.76 (m, 1H), 7.50 (dt, J = 10.7, 8.6 Hz, 1H), 6.63 (t, J = 5.4 Hz, 1H), 3.40 (td, J = 6.8, 5.3 Hz, 2H), 3.29 – 3.21 (m, 4H), 3.16 (t, J = 6.9 Hz, 2H), 1.51 (q, J = 6.2 Hz, 2H), 1.45 – 1.34 (m, 4H); EIMS *m/z* 352.1 (M + 1)$^+$; HPLC 100 area% (254 nm). Anal. Calcd for $C_{17}H_{19}F_2N_3OS{\cdot}0.5H_2O$: C, 56.65; H, 5.59; N, 11.66. Found: C, 56.54; H, 5.59; N, 11.57.

5.2.6. N-(2-Cyanoethyl)benzamide (85)[18]—A solution of benzoyl chloride (11.98 g, 85.22 mmol) in THF (50 mL) was added dropwise to a solution of 3-aminopropionitrile (**84**, 5.98 g, 85.3 mmol) and triethylamine (15 mL, 107.6 mmol) in THF (50 mL) at −5 °C (ice-salt bath). The reaction mixture was stirred overnight at room temperature before being poured into water and extracted into EtOAC (3×). The dried, evaporated extract was recrystallized from hexanes and the minimum volume of EtOAC to give white crystals (12.36 g, 83%): mp 94 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 (t, J = 5.7 Hz, 1H), 7.90 – 7.82 (m, 2H), 7.60 – 7.50 (m, 1H), 7.53 – 7.44 (m, 2H), 3.50 (td, J = 6.5, 5.7 Hz, 2H), 2.78 (t, J = 6.5 Hz, 2H); HPLC 100 area% (230 nm). Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.86; H, 5.80; N, 16.22.

5.2.7. 3-(Benzamido)thiopropionamide (86)[18]—A mixture of sodium hydrosulfide hydrate (1.68 g, 22.54 mmol) and magnesium chloride (1.97 g, 20.69 mmol) in DMF (20 mL) was stirred for 20 minutes at room temperature before the addition of 15-crown-5 (0.2 mL, 1.01 mmol) and *N*-(2-cyanoethyl)benzamide (**85**, 1.75 mg, 10.05 mmol). The mixture was stirred overnight before being poured over ice to give a white precipitate. This material was recrystallized from toluene/EtOH to give white crystals (1.31 g, 63%): mp 171-172 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.44 (s, 1H), 9.25 (s, 1H), 8.53 (t, J = 5.7 Hz, 1H), 7.87 – 7.79 (m, 2H), 7.56 – 7.47 (m, 1H), 7.50 – 7.41 (m, 2H), 3.59 (dt, J = 7.7, 5.8 Hz, 2H), 2.75 (dd, J = 8.0, 6.6 Hz, 2H); HPLC 99.3 area % (254 nm). Anal. Calcd for $C_{10}H_{12}N_2OS$: C, 57.67; H, 5.81; N, 13.45. Found: C, 57.91; H, 5.74; N, 13.31.

5.2.8. 3-(Boc-amino)propionitrile (87)[21]—3-Aminopropionitrile (1.30 g, 18.53 mmol) was added dropwise to a stirred mixture of Montmorillonite K10 (199 mg) in molten di-*tert*-butyl dicarbonate (4.07 g, 18.7 mmol). After 1 hour, the mixture was diluted with EtOAC and filtered, The filtrate was evaporated to an oil, which was triturated with hexanes to give white crystals (2.63 g, 83%): mp 45 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.16 (t, J = 6.0 Hz, 1H), 3.15 (q, J = 6.3 Hz, 2H), 2.59 (t, J = 6.5 Hz, 2H), 1.39 (s, 9H). Anal. Calcd for $C_8H_{14}N_2O_2$: C, 56.45; H, 8.29; N, 16.46. Found: C, 56.51; H, 8.23; N, 16.25.

5.2.9. 3-(Boc-amino)thiopropionamide (88)[22]—The title compound was prepared analogously to compound **86** above from 3-(Boc-amino)propionitrile (**87**, 4.35 g. 25.56 mmol). The reaction mixture was poured over ice-water and extracted into dichloromethane. The extract was evaporated under reduced pressure followed by vacuum distillation (to remove residual DMF). The residue was recrystallized from EtOH/water to give white crystals (4.52 g, 87%): mp 111-112 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.39 (s, 1H), 9.17 (s, 1H), 6.79 (t, J = 5.4 Hz, 1H), 3.24 (ddd, J = 9.0, 7.5, 5.8 Hz, 2H), 2.63 – 2.52 (m, 2H), 1.37 (s, 9H). Anal. Calcd for $C_8H_{16}N_2OS$: C, 47.03; H, 7.89; N, 13.71. Found: C, 47.13; H, 7.90; N, 13.44.

5.2.10. General procedure for amine hydrobromides 89a-f—A solution of 3-(boc-amino)thiopropionamide (**88**) and the appropriate α-bromoacetophenone (1 equivalent) in EtOH (10- 20 mL) was refluxed until the reaction was complete by HPLC (3-5 hours). Upon cooling, product precipitated from solution. The mixture was diluted was ether and the product was filtered off.

5.2.10.1. 4-Phenylthiazol-2-ethylamine hydrobromide (89a): was prepared from **88** (2.05 g, 10.03 mmol) and 2-bromoacetophenone (2.00 g, 10.04 mmol) as a white solid (2.62 g, 92%): mp 187-188 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (s, 1H), 8.02 – 7.94 (m, 2H), 7.88 (s, 3H), 7.50 – 7.40 (m, 2H), 7.40 – 7.31 (m, 1H), 3.40 – 3.26 (m, 4H); HPLC 100 area % (254 nm). Anal. Calcd for $C_{11}H_{12}N_2S \cdot HBr$: C, 46.32; H, 4.59; N, 9.82; Br, 28.02. Found: C, 46.38; H, 4.63; N, 9.77; Br, 27.85.

5.2.10.2. 4-(2-Fluorophenyl)thiazol-2-ethylamine hydrobromide (89b): was prepared from **88** (1.33 g, 6.51 mmol) and 2-bromo-2′-fluoroacetophenone[30] (1.88 g, 8.66 mmol) as a white solid (1.88 g, 95%): mp 164-166 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (td, J = 7.8, 1.7 Hz, 1H), 7.94 (d, J = 2.6 Hz, 1H), 7.91 (s, 3H), 7.42 (tdd, J = 7.1, 5.3, 2.6 Hz, 1H), 7.37 – 7.27 (m, 2H), 3.42 – 3.34 (m, 2H), 3.34 – 3.26 (m, 2H); HPLC 100 area% (254 nm). Anal. Calcd for $C_{11}H_{11}FN_2S \cdot HBr$: C, 43.58; H, 3.99; N, 9.24; Br, 26.35. Found: C, 43.30; H, 4.02; N, 9.25; Br, 26.10.

5.2.10.3. 4-(3-Fluorophenyl)thiazol-2-ethylamine hydrobromide (89c): was prepared from **88** (1.06 g, 5.19 mmol) and 2-bromo-3′-fluoroacetophenone (1.14 g, 5.25 mmol) as a white solid (1.49 g, 100%): mp 178-179 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (s, 1H), 7.91 (s, 3H), 7.85 – 7.79 (m, 2H), 7.50 (td, J = 8.0, 6.1 Hz, 1H), 7.19 (dddd, J = 9.1, 8.3, 2.6, 1.0 Hz, 1H), 3.41 – 3.28 (m, 4H); HPLC 100 area% (254 nm). Anal. Calcd for $C_{11}H_{11}FN_2S \cdot HBr$: C, 43.58; H, 3.99; N, 9.24; Br, 26.35. Found: C, 43.32; H, 4.03; N, 908; Br, 26.26.

5.2.10.4. 4-(4-Fluorophenyl)thiazol-2-ethylamine hydrobromide (89d): was prepared from **88** (3.07 g, 15.03 mmol) and 2-bromo-4′-fluoroacetophenone (3.26 g, 15.02 mmol) as a white solid (4.16 g, 86%): mp 219 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (s, 1H), 8.07 – 7.97 (m, 2H), 7.91 (s, 3H), 7.36 – 7.21 (m, 2H), 3.40 – 3.24 (m, 4H); HPLC 100 area % (254 nm). Anal. Calcd for $C_{11}H_{11}FN_2S \cdot HBr$: C, 43.58; H, 3.99; N, 9.24; Br, 26.35. Found: C, 43.52; H, 4.00; N, 9.05; Br, 26.16.

5.2.10.5. 4-(2,4-Difluorophenyl)thiazol-2-ethylamine hydrobromide (89e): was prepared from **88** (331 mg, 1.62 mmol) and 2-bromo-2′,4′-fluoroacetophenone (380 mg, 1.62 mmol) as a white solid (468 mg, 90%): mp 197 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (td, J = 8.9, 6.8 Hz, 1H), 7.91 (d, J = 2.7 Hz, 1H), 7.90 (s, 3H); 7.40 (ddd, J = 11.8, 9.3, 2.6 Hz, 1H), 7.27 – 7.17 (m, 1H), 3.41 – 3.28 (m, 4H); HPLC 100 area% (254 nm). Anal. Calcd for $C_{11}H_{10}F_2N_2S{\cdot}HBr$: C, 41.13; H, 3.45; N, 8.72. Found: C, 40.88; H, 3.56; N, 8.59.

5.2.10.6. 4-(3,4-Difluorophenyl)thiazol-2-ethylamine hydrobromide (89f): was prepared from **88** (1.75 g, 8.57 mmol) and 2-bromo-3′,4′-fluoroacetophenone[323232] (1.98 g, 8.44 mmol) as a white solid (2.49 mg, 92%): mp 191-193 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (d, J = 0.8 Hz, 1H), 8.01 (dddd, J = 12.2, 7.9, 2.2, 0.8 Hz, 1H), 7.86 (s, 3H), 7.80 (dddd, J = 8.7, 4.3, 2.2, 1.3 Hz, 1H), 7.48 (ddd, J = 10.7, 9.0, 8.2 Hz, 1H), 3.36 – 3.21 (m, 4H); HPLC 100 area% (254 nm). Anal. Calcd for $C_{11}H_{10}F_2N_2S{\cdot}HBr$: C, 41.13; H, 3.45; N, 8.72. Found: C, 41.16 H, 3.46; N, 8.74.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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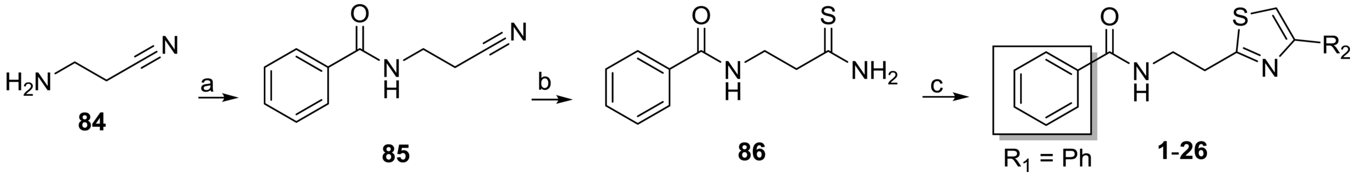
References

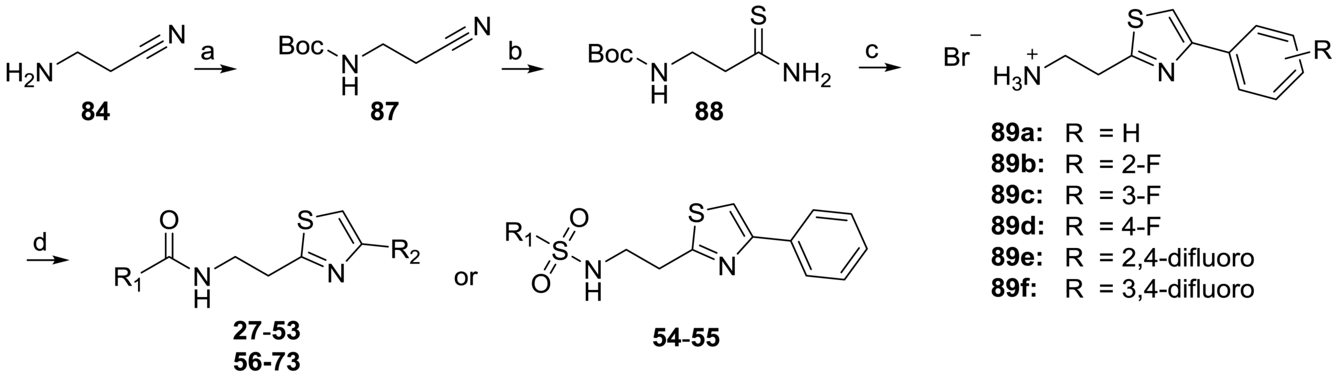
1. [5 January 2016] http://www.who.int/mediacentre/factsheets/fs259/en/.
2. Sykes ML, Baell JB, Kaiser M, Chatelain E, Moawad SR, Ganame D, Ioset J-R, Avery VM. PLoS Negl Trop Dis. 2012; 6:e1896. [PubMed: 23209849]
3. Astelbauer F, Walochnik J. Int. J. Antimicrob. Agents. 2011; 38:118. [PubMed: 21549569]
4. Burri C. Parasitology. 2010; 137:1987. [PubMed: 20961469]
5. Patrick DA, Bakunov SA, Bakunova SM, Kumar EVKS, Lombardy RJ, Jones SK, Bridges AS, Zhirnov O, Hall JE, Wenzler T, Brun R, Tidwell RR. J. Med. Chem. 2007; 50:2468. [PubMed: 17439202]
6. Patrick DA, Bakunov SA, Bakunova SM, Wenzler T, Brun R, Tidwell RR. Bioorg. Med. Chem. 2014; 22:559. [PubMed: 24268543]
7. Patrick DA, Ismail MA, Arafa RK, Wenzler T, Zhu X, Pandharkar T, Jones SK, Werbovetz KA, Brun R, Boykin DW, Tidwell RR. J. Med. Chem. 2013; 56:5473. [PubMed: 23795673]
8. Wenzler T, Yang S, Patrick DA, Braissant O, Ismail MA, Tidwell RR, Boykin DW, Wang MZ, Brun R. Antimicrob. Agents Chemother. 2014; 58:4452. [PubMed: 24867978]
9. Dann O, Fick H, Pietzner B, Walkenhorst E, Fernbach R, Zeh D. Justus Liebigs Ann. Chem. 1975:160.
10. Das BP, Boykin DW. J. Med. Chem. 1977; 20:531. [PubMed: 321783]
11. Anbazhagan M, Boykin DW. Heterocycl. Commun. 2003; 9:117.
12. Ansede JH, Anbazhagan M, Brun R, Easterbrook JD, Hall JE, Boykin DW. J. Med. Chem. 2004; 47:4335. [PubMed: 15294005]
13. Harrill AH, DeSmet KD, Wolf KK, Bridges AS, Eaddy JS, Kurtz CL, Hall JE, Paine MF, Tidwell RR, Watkins PB. Toxicol. Sci. 2012; 130:416. [PubMed: 22940726]
14. Torreele E, Trunz BB, Tweats D, Kaiser M, Brun R, Mazue G, Bray MA, Pecoul B. PLoS Neglected Trop. Dis. 2010; 4:e923.
15. Jacobs RT, Nare B, Wring SA, Orr MD, Chen D, Sligar JM, Jenks MX, Noe RA, Bowling TS, Mercer LT, Rewerts C, Gaukel E, Owens J, Parham R, Randolph R, Beaudet B, Bacchi CJ, Yarlett N, Plattner JJ, Freund Y, Ding C, Akama T, Zhang YK, Brun R, Kaiser M, Scandale I, Don R. PLoS Neglected Trop. Dis. 2011; 5:e1151.

16. Tatipaka HB, Gillespie JR, Chatterjee AK, Norcross NR, Hulverson MA, Ranade RM, Nagendar P, Creason SA, McQueen J, Duster NA, Nagle A, Supek F, Molteni V, Wenzler T, Brun R, Glynne R, Buckner FS, Gelb MH. J. Med. Chem. 2014; 57:828. [PubMed: 24354316]
17. Young RC, Ganellin CR, Griffiths R, Mitchell RC, Parsons ME, Saunders D, Sore NE. Eur. J. Med. Chem. 1993; 28:201.
18. Zee-Cheng K-Y, Cheng C-C. J. Heterocycl. Chem. 1970; 7:1439.
19. Manaka A, Sato M. Synth. Commun. 2005; 35:761.
20. Chankeshwara SV, Chakraborti AK. J. Mol. Catal. A: Chem. 2006; 253:198.
21. Houssin R, Bernier JL, Henichart JP. Synthesis. 1988:259.
22. Barker PL, Gendler PL, Rapoport H. J. Org. Chem. 1981; 46:2455.
23. Bakunova SM, Bakunov SA, Patrick DA, Kumar EVKS, Ohemeng KA, Bridges AS, Wenzler T, Barszcz T, Kilgore Jones S, Werbovetz KA, Brun R, Tidwell RR. J. Med. Chem. 2009; 52:2016. [PubMed: 19267462]
24. Peña I, Pilar Manzano M, Cantizani J, Kessler A, Alonso-Padilla J, Bardera AI, Alvarez E, Colmenarejo G, Cotillo I, Roquero I, de Dios-Anton F, Barroso V, Rodriguez A, Gray DW, Navarro M, Kumar V, Sherstnev A, Drewry DH, Brown JR, Fiandor JM, Martin J. J. Sci. Rep. 2015; 5:8771.
25. Baell, J.; Piggott, M.; Russell, S.; Toynton, A.; Rahmani, R.; Ferrins, L.; Nguyen, N. 2015. WO2015172196A1
26. Wang MZ, Zhu X, Srivastava A, Liu Q, Sweat JM, Pandharkar T, Stephens CE, Riccio E, Parman T, Munde M, Mandal S, Madhubala R, Tidwell RR, Wilson WD, Boykin DW, Hall JE, Kyle DE, Werbovetz KA. Antimicrob. Agents Chemother. 2010; 54:2507. [PubMed: 20368397]
27. Hogarth PM, Pietersz GA, Moloney GP. WO2004058747A1. 2004
28. Silberg A, Benko A, Panczel IA. Stud. Cercet. Chim. 1965; 13:655.
29. Silberg A, Benko A, Panczel IA. Rev. Roum. Chim. 1965; 10:617.
30. Nishida, H.; Arikawa, Y.; Hirase, K. 2009. WO2009041705A2
31. Eberle, M.; Bachmann, F.; Strebel, A.; Roy, S.; Saha, G.; Sadhukhan, SK.; Saxena, R.; Srivastava, S. 2005. WO2005061476A2
32. Ridge DN, Hanifin JW, Harten LA, Johnson BD, Menschik J, Nicolau G, Sloboda AE, Watts DE. J. Med. Chem. 1979; 22:1385. [PubMed: 533886]
33. Biagetti, M.; Contini, SA.; Genski, T.; Guery, S.; Leslie, CP.; Mazzali, A.; Pizzi, DA.; Sabbatini, FM.; Seri, C. 2009. WO2009095377A1
34. Borhani, DW.; Calderwood, DJ.; Frank, KE.; Davis, HM.; Josephsohn, NS.; Skinner, BS. 2008. WO2008063287A2
35. Kajigaeshi S, Kakinami T, Okamoto T, Fujisaki S. Bull. Chem. Soc. Jpn. 1987; 60:1159.
36. Hoover, DJ.; Witter, KG. 2008. WO2008004117A1
37. Boger DL, Patel M. J. Org. Chem. 1987; 52:2319.
38. McGhee WD, Pan Y, Talley JJ. Tetrahedron Lett. 1994; 35:839.



Scheme 1.

Synthesis of compounds **1-26**. Reagents and conditions: a) benzoyl chloride, Et_3N, THF, −5 °C to rt, overnight; b) NaHS·xH_2O, $MgCl_2$, 15-crown-5, DMF, rt; c) appropriate 1-aryl-2-bromoethanone, EtOH, reflux or rt. Structures **1-26** are defined in Table 1.

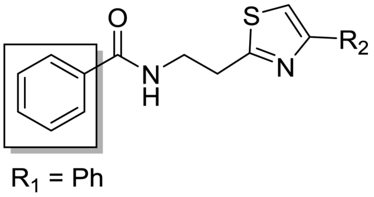


Scheme 2.

Synthesis of compounds **27-73**. Reagents and conditions: a) Boc$_2$O, Montmorillonite K-10; b) NaHS·xH$_2$O, MgCl$_2$, 15-crown-5-, DMF, rt; c) appropriate 1-aryl-2-bromoethanone, EtOH, reflux;; d) appropriate carbonyl or sulfonyl chloride, anhydride, or isocyanate, Et$_3$N (or DIEA), THF (or DCM). Structures **27-55** and **56–73** are defined in Tables 2 and 3, respectively.

Table 1

Structures, antitrypanosomal activities, and selectivities of thiazole derivatives **1-26**



Compd	R$_2$	*T. b. rhodesiense* [a]		Cytotox.[b]
		IC$_{50}$[c] (μM)	SI[d]	IC$_{50}$[c] (μM)
1	phenyl	0.632	162	103
2	3-cyanophenyl	1.90	69	131
3	4-cyanophenyl	42.7	1	44.1
4	4-(trifluoromethyl)phenyl	145	<1	24.6
5	3-nitrophenyl	2.72	47	127
6	4-nitrophenyl	29.3	>9	>255
7	3-methoxyphenyl	6.11	11	69.2
8	4-methoxyphenyl	18.3	5	99.7
9	2-fluorophenyl	0.156	624	97.2
10	3-fluorophenyl	0.233	239	55.8
11	4-fluorophenyl	0.218	1130	247
12	3-chlorophenyl	0.452	125	56.4
13	4-chlorophenyl	13.3	7	95.9
14	3-bromophenyl	0.553	94	51.9
15	4-bromophenyl	34.7	1	46.3
16	2,4-difluorophenyl	0.162	>1590	>257
17	2,5-difluorophenyl	1.63	40	65.3
18	2,6-difluorophenyl	1.22	133	162
19	3,4-difluorophenyl	0.145	211	30.6
20	3,5-difluorophenyl	1.62	36	58.1
21	2,4,5-trifluorophenyl	2.13	116	248
22	2-furanyl	2.53	53	134
23	2-thiophenyl	1.62	63	102
24	2-pyridyl	3.63	57	209
25	3-pyridyl	4.64	45	207
26	4-pyridyl	10.3	21	217
pentamidine		2.8	11400	31.8
melarsoprol		4.0	1280	5.12
podophyllotoxin				0.017

[a] *Trypanosoma brucei rhodesiense* (STIB900)[23]

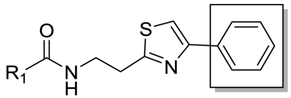
[b] Cytotoxicity to L6 rat myoblast cells[23]

[c] The IC_{50} values are the mean of two independent assays. Coefficients of variation were less than 50%.

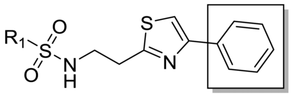
[d] Selectivity index for *T. b. rhodesiense* expressed as the ratio IC_{50} (L6 cells) / IC_{50} (*T. b. rhodesiense*). Values are rounded to the nearest integer or to the third significant figure.

Table 2

Structures, antitrypanosomal activities, and selectivities of thiazole derivatives **27-55**[a]



27-53 R_2 = Ph



54-55 R_2 = Ph

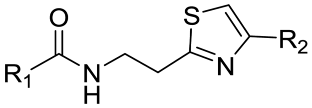
Compd	R_1	*T. b. rhodesiense*		Cytotox[b]
		IC_{50} (μM)	SI	IC_{50} (μM)
1	phenyl	0.632	162	69.0
27	3-cyanophenyl	0.171	404	58.0
28	4-cyanophenyl	40.6	1	42.4
29	3-nitrophenyl	0.150	283	79.0
30	2-fluorophenyl	0.460	172	77.8
31	3-fluorophenyl	0.383	203	35.4
32	4-fluorophenyl	1.42	25	93.0
33	2-chlorophenyl	0.483	193	47.8
34	3-chlorophenyl	1.50	32	>237
35	4-chlorophenyl	34.5	>7	42.5
36	2-pyrrolyl	2.01	21	87.7
37	2-furanyl	0.482	182	71.2
38	2-thiophenyl	0.255	280	49.1
39	3-thiophenyl	0.190	259	120
40	3-pyridyl	1.59	75	60.1
41	4-pyridyl	16.5	4	174
42	cyclopentyl	0.268	648	205
43	cyclohexyl	0.164	1250	244
44	*N*-pyrrolidinyl	0.125	1960	62.8
45	*N*-pyrrolyl	1.74	36	243
46	*N*-piperidinyl	0.0204	11900	>248
47	*N*-morpholinyl	0.510	>486	229
48	*N*-azepanyl	0.0516	4450	98.9
49	*tert*-butylamino	1.83	54	>267
50	benzylamino	90.1	>3	91.1
51	cyclohexylamino	10.1	9	>278
52	phenylamino	>309	nd[e]	183
53	phenoxy	61.8	3	89.4
54	phenyl	75.8	1	69.3
55	4-methylphenyl	52.9	1	69.0

[a] Experimental parameters and controls are shown at the bottom of Table 1.

[b] Not determinable.

Table 3

Structures, antitrypanosomal activities, and selectivities of thiazole derivatives **54-73**[a]

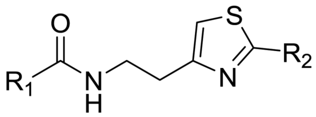


Compd	**R$_1$**	**R$_2$**	***T. b. rhodesiense*** [a]		**Cytotox.**[b]
			IC$_{50}$^{c} (nM)	**SI^d**	**IC$_{50}$^{c} (μM)**
56	3-cyanophenyl	2-fluorophenyl	0.393	473	186
57	3-cyanophenyl	3-fluorophenyl	0.104	302	31.3
58	3-cyanophenyl	4-fluorophenyl	0.130	303	39.2
59	3-nitrophenyl	2-fluorophenyl	0.133	252	33.5
60	3-nitrophenyl	3-fluorophenyl	0.129	176	22.7
61	3-nitrophenyl	4-fluorophenyl	0.147	120	17.7
62	3-fluorophenyl	3-fluorophenyl	0.325	142	46.2
63	3-fluorophenyl	4-fluorophenyl	0.340	124	42.1
64	2-thiophenyl	2-fluorophenyl	0.177	230	40.8
65	2-thiophenyl	3-fluorophenyl	0.149	326	48.6
66	2-thiophenyl	4-fluorophenyl	0.177	189	33.6
67	*N*-pyrrolidinyl	2-fluorophenyl	0.0495	4790	237
68	*N*-pyrrolidinyl	3-fluorophenyl	0.0517	3370	174
69	*N*-pyrrolidinyl	4-fluorophenyl	0.316	474	150
70	*N*-piperidinyl	3-fluorophenyl	0.0090	18800	169
71	*N*-piperidinyl	4-fluorophenyl	0.0120	10200	123
72	*N*-piperidinyl	2,4-difluorophenyl	0.0099	9960	98.2
73	*N*-piperidinyl	3,4- difluorophenyl	0.0097	11700	114

[a] Experimental parameters and controls are shown at the bottom of Table 1.

Table 4

Comparison of thiazole geometry to antitrypanosomal activity[a]



74-83

Compd	***T. b. rhodesiense*** IC$_{50}$ (μM)[b]	SI[b]	**Compd**	**R$_1$**	**R$_2$**	***T. b. rhodesiense*** IC$_{50}$ (μM)	**SI**	**Cytotox.** IC$_{50}$ (μM)
10	0.233	239	**74**	phenyl	3-fluorophenyl	0.201	325	65.3
11	0.218	1133	**75**	phenyl	4-fluorophenyl	0.165	261	43.2
13	13.3	7	**76**	phenyl	4-chlorophenyl	11.4	>23	>263
30	0.460	172	**77**	2-fluorophenyl	phenyl	0.536	130	69.6
31	0.383	203	**78**	3-fluorophenyl	phenyl	0.843	40	33.5
33	0.483	193	**79**	2-chlorophenyl	phenyl	1.52	61	92.8
34	1.50	32	**80**	3-chlorophenyl	phenyl	0.642	99	63.3
35	34.5	>7	**81**	4-chlorophenyl	phenyl	30.6	1	30.1
38	0.255	280	**82**	2-thiophenyl	phenyl	0.223	427	95.1
43	0.164	1254	**83**	cyclohexyl	phenyl	0.192	1050	202

[a] Experimental parameters and controls are shown at the bottom of Table 1.

[b] Data reproduced from Tables 1 and 2.

Table 5

Stability of select compounds to mouse and human liver microsomes

	T. b. rhodesiense [a]	**MLM**		**HLM**	
Compd	**IC$_{50}$ (μM)**	**Microsomal t$_{1/2}$ (min)**[b]	**Substrate remaining**[c]	**Microsomal t$_{1/2}$ (min)**[b]	**Substrate remaining**[c]
1	0.632	1.1	43%	28	80%
9	0.156	1.9	29%	34	96%
10	0.233	3.2	48%	22	75%
16	0.162	5.5	22%	50	67%
30	0.460	1.5	60%	36	93%
43	0.164	0.6	0.4%	8.0	104%
44	0.125	0.5	89%	13	88%
46	0.0204	1.7	102%	9.1	104%
57	0.104	7.6	97%	34	98%
60	0.129	11	106%	27	107%
62	0.325	4.7	62%	24	69%
65	0.149	1.6	83%	9.4	24%
67	0.0495	0.3	101%	11	100%
68	0.0517	1.8	105%	17	103%
70	0.0090	1.6	90%	4.9	102%

[a] *Trypanosoma brucei rhodesiense* (STIB900), data reproduced from Table 1

[b] Microsomal t$_{1/2}$ was determined in the presence of the NADPH cofactor.

[c] Substrate concentrations were determined in incubations without NADPH after 60 min and normalized to concentrations at time zero.