Synthesis, Characterization, and DGAT1 Inhibition of New 5-Piperazinethiazole and 5-Piperidinethiazole Analogs

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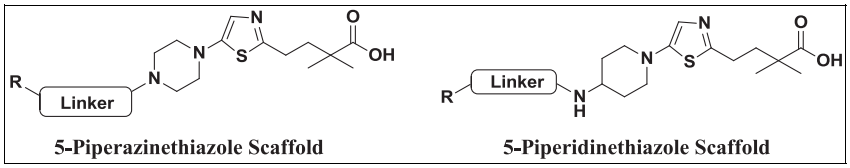

In this study, a novel series of 5-piperazinethiazole 2,2-dimethylbutanoic acid and 5-piperidinethiazole 2,2-dimethylbutanoic acid derivatives have been synthesized. Structures of the newly synthesized compounds have been elucidated using ^{1}H-NMR, ^{13}C-NMR, high-resolution mass spectroscopy, and high-performance liquid chromatographic analysis. The synthesized derivatives have been evaluated *in vitro* for their ability to inhibit the enzyme diacylglycerol acyltransferase 1 responsible for triglyceride biosynthesis.

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INTRODUCTION

Diacylglycerol acyltransferase 1 (DGAT1) is an enzyme involved in the final committed step of triglyceride biosynthesis [1]. Inhibitors of DGAT1 can find potential application as anti-obesity agents [2] and in conditions that require reduction in triglycerides. Several DGAT1 inhibitors have been reported (Fig. 1). A recent publication [3] highlights a series of carboxylic acid derivatives, exemplified by compound **1**, as DGAT1 inhibitors. Of late, we have reported [4] a substituted 5-phenyl thiazole scaffold, exemplified by compound **2**, for its DGAT1 inhibition. We further identified that combining a carboxylic acid such as 2,2-dimethylbutanoic acid along with 5-phenylthiazole, as shown in compound **3**, also exhibited promising DGAT1 inhibition and resulted in a 5-phenylthiazole 2,2-dimethylbutanoic acid scaffold [5]. In our efforts to identify novel heterocyclic scaffolds for DGAT1 inhibition, we envisaged replacing the phenyl ring of our 5-phenylthiazole 2,2-dimethylbutanoic acid scaffold with non-aromatic saturated heterocycles such as piperazine and piperidine (Fig. 2). This modification resulted in 5-piperazinethiazole 2,2-dimethylbutanoic acid (**4**) and 5-piperidinethiazole 2,2-dimethylbutanoic acid (**5**) scaffolds. Diversifications at both these scaffolds were undertaken by attaching substituted phenyl or cyclohexyl groups to the 5-piperazinethiazole or 5-piperidinethiazole cores through a variety of linkers. The synthesis, characterization, and *in vitro* DGAT1 activity of these novel 5-piperazinethiazole and 5-piperidinethiazole derivatives is discussed.

RESULTS AND DISCUSSION

A common intermediate, CBZ-glycine (**7**), required for the synthesis of the desired 5-piperazinethiazole and 5-piperidinethiazole scaffolds, was synthesized by incorporating a benzyl carbamate protection (CBZ) on the amine functionality of glycine (**6**) using benzyl chloroformate (Scheme 1) as reported in literature [6]. Another important intermediate, 5-methoxy-4,4-dimethyl-5-oxopentanoic acid (**10**), was also synthesized (Scheme 2) using literature mentioned procedure [7] starting from 2,2-dimethyl glutaric anhydride (**8**).

The synthesis of 5-piperazinethiazole 2,2-dimethylbutanoic acid derivatives (**19–27**) was initiated (Scheme 3) by the BOC (*tert*-Butyloxy carbamate) protection of 1-benzylpiperazine (**11**) with BOC anhydride [8] to 1-BOC-4-benzylpiperazine (**12**). Compound **12** was subjected to debenzylation using 10% Pd/C and ammonium formate [9] to yield the corresponding *tert*-butyl piperazine-1-carboxylate (**13**). Compound **13** was then coupled along with compound **7** using HATU [10] to afford the amide, *tert*-butyl 4-(2-(((benzyloxy)carbonyl)amino)acetyl)piperazine-1-carboxylate (**14**). Deprotection of the CBZ [11] group on **14** by hydrogenation in the presence of 10% Pd/C afforded the free amine, *tert*-butyl 4-(2-aminoacetyl)piperazine-1-carboxylate (**15**). Compound **15** was further coupled with compound **10** in the presence of HATU as the coupling reagent to give *tert*-butyl 4-(2-(5-methoxy-4,4-dimethyl-5-oxopentanamido)acetyl)piperazine-1-carboxylate (**16**). Cyclization of **16** using Lawesson's reagent [12] resulted in the formation of BOC protected 5-piperazinethiazole

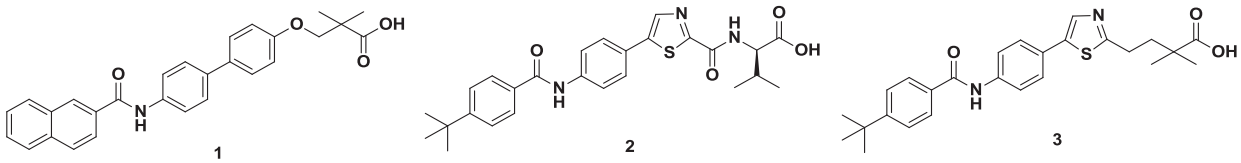


Figure 1. Structures of some diacylglycerol acyltransferase 1 inhibitors.

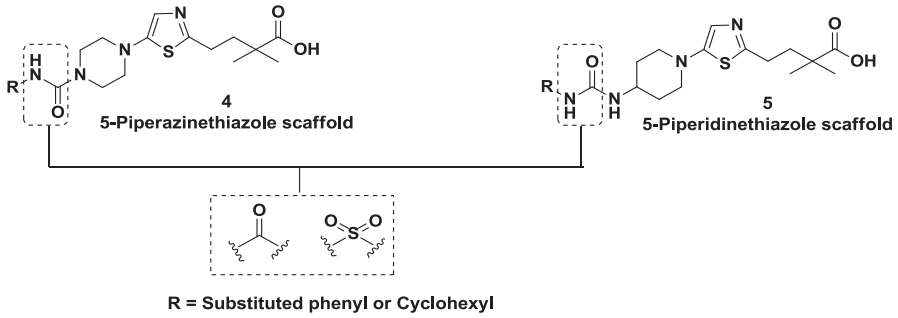
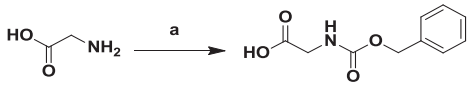


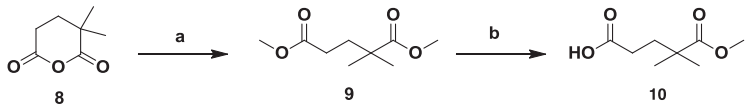
Figure 2. 5-Piperazinethiazole and 5-piperidinethiazole scaffolds.

Scheme 1. Synthesis of CBZ-glycine (7)



Reaction Conditions: a. Benzyl chloroformate, 2.0N NaOH solution, 0 °C.

Scheme 2. Synthesis of 5-methoxy-4,4-dimethyl-5-oxopentanoic acid (**10**).

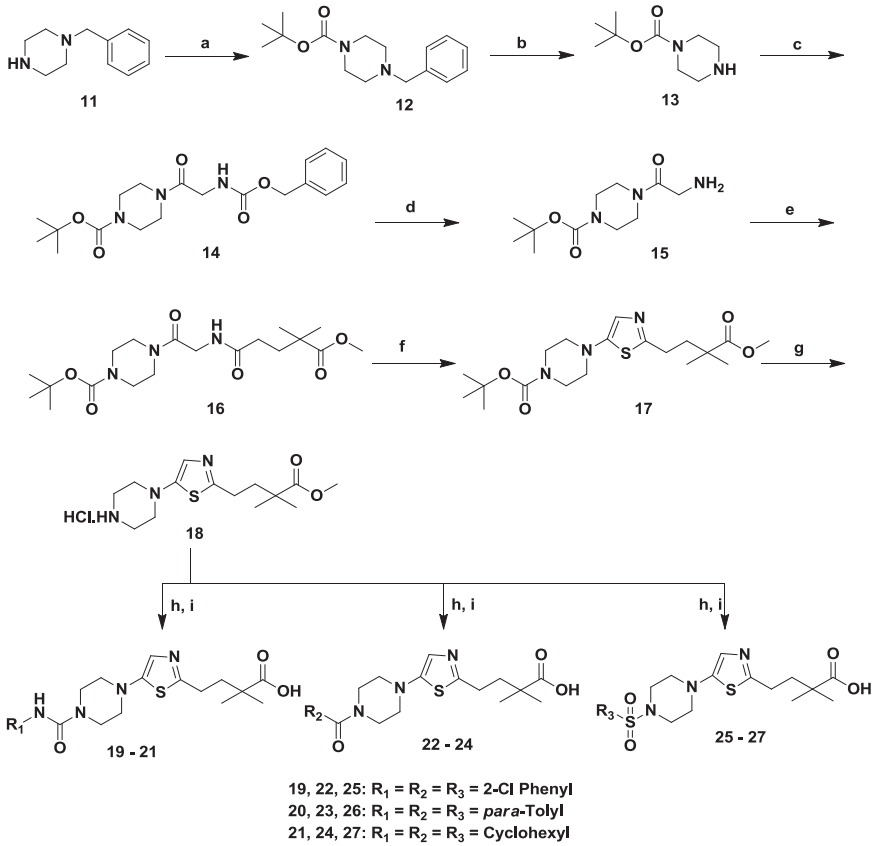


Reaction Conditions: a. Sulfuric acid, MeOH, 55 °C; **b.** Potassium carbonate, MeOH/THF/Water, rt.

2,2-dimethylbutanoate methyl ester (**17**). Deprotection of BOC [13] protecting functionality in **17** under acidic conditions resulted in the key intermediate, methyl 2,2-dimethyl-4-(5-(piperazin-1-yl)thiazol-2-yl)butanoate hydrochloride (**18**), which was subsequently used for further diversification. The use of two different amine protecting groups, BOC and CBZ, in this synthetic route provides for orthogonal protection of the two amine functionalities allowing for successful implementation of this synthetic strategy. However, reversing this protecting strategy by incorporating CBZ protection on the benzyl piperazine and BOC protection on the glycine proved ineffective as the eventual deprotection of the CBZ group to yield compound **18** was unsuccessful.

Diversification of compound **18** at the piperazine –NH was subsequently undertaken to yield the desired 5-piperazinethiazole derivatives. Treatment of **18** with various isocyanates in the presence of triethylamine followed by alkaline hydrolysis using lithium hydroxide afforded the corresponding urea compounds (**19–21**). Similarly coupling with acid chlorides yielded the corresponding amide analogs (**22–24**) and using sulfonyl chlorides in place of isocyanates yielded the corresponding sulfonamide derivatives (**25–27**). Replacing 1-benzylpiperazine (**11**) with 1-benzylpiperidin-4-amine (**28**) and following a similar sequence as in the case of 5-piperazinethiazole scaffold yielded the key amino piperidine intermediate methyl 4-(5-(4-aminopiperidin-1-yl)thiazol-2-yl)-2,2-dimethylbutanoate hydrochloride (**35**). Urea (**36–40**), amide (**41**), and sulfonamide (**42** and **43**) derivatives were synthesized from compound **35** following treatment with corresponding isocyanates, acid chloride, and sulfonyl chlorides respectively (Scheme 4).

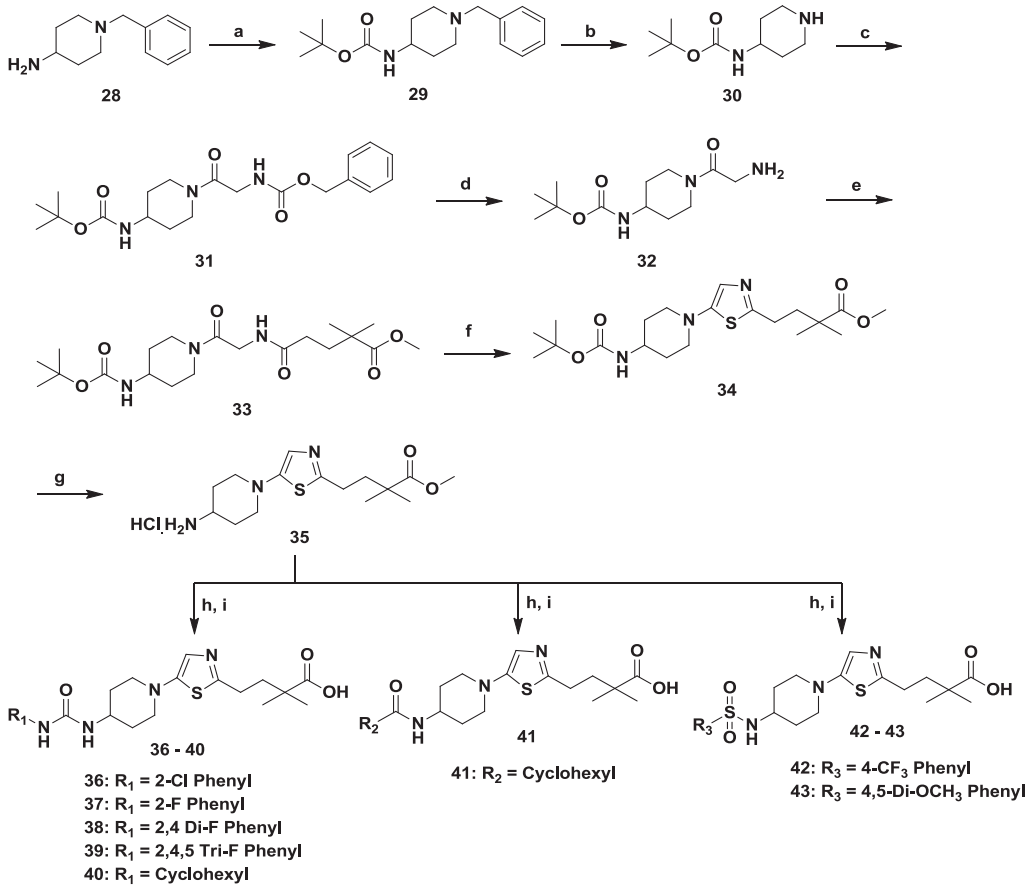
Scheme 3. Synthesis of 5-piperazinethiazole 2,2-dimethylbutanoic acid derivatives (**19–27**).



Reaction Conditions: a. BOC anhydride, $NaHCO_3$, 1,4-Dioxane/Water, 0 °C; **b.** 10% Pd.C, $HCOONH_4$, MeOH, reflux; **c.** Compound **7**, HATU, TEA, DMF, rt; **d.** 10% Pd.C/H_2, MeOH/THF, rt; **e.** Compound **10**, HATU, TEA, DMF, rt; **f.** Lawesson's reagent, 1,4-Dioxane, reflux; **g.** 5N HCl in isopropanol, rt; **h.** For compounds **16 - 18**, R_1NCO, TEA, CH_2Cl_2, rt; For compounds **19 - 21**, R_2COCl, TEA, CH_2Cl_2, rt; For compounds **22 - 24**, R_3SO_2Cl, TEA, CH_2Cl_2, rt; **i.** LiOH/H_2O, THF/MeOH, rt.

The structures of these newly synthesized 5-piperazine thiazole and 5-piperidine thiazole analogs were confirmed using ^{1}H-NMR, ^{13}C-NMR, and high-resolution mass spectroscopic (HRMS) analysis. In addition, high-performance liquid chromatographic (HPLC) purities of these final compounds (**19–27** and **36–43**) were also determined. The ^{1}H-NMR of 5-piperazinethiazole analogs (**19–27**) recorded in DMSO-d_6 exhibits a singlet representing the thiazole –CH proton around 6.8 ppm. All piperazine $–CH_2$ protons appear between 2.9–3.1 and 3.2–3.6 as multiplets. The two $–CH_3$ protons of dimethyl butanoic acid side chain appear as a sharp singlet around 1.1 ppm. The $–CH_2$ protons present on a carbon adjacent to the thiazole ring appear between 2.7 and 2.8 ppm whereas the methylene protons adjacent to dimethyl carbon appear between 1.7 and 1.8 ppm as multiplets. Aromatic protons of the phenyl substituents appear between 7.0 and 8.3 ppm. Protons of the cyclohexyl substituent appear as multiplets between 1.1 and 1.8 ppm. In case of 5-piperidine thiazole analogs (**36–43**), the ^{1}H-NMR signal due to thiazole –CH appears around 6.7 ppm as a singlet. The 4-position –CH proton of the piperidine ring appears as a multiplet between 3.6 and 3.7 ppm. All other piperidine $–CH_2$ protons are scattered as multiplets between 1.3–3.3 ppm. The acid head protons of the dimethyl butanoic acid side chain appear as multiplets around 1.7–1.8 ppm and 2.7–2.8 ppm. The –NH of the 4-amino piperidine appears around 6.7 ppm as a doublet. Aromatic protons of the phenyl substituent appear between 6.6 and 8.0 ppm. Protons of the cyclohexyl substituent appear as multiplets between 1.1 and 1.8 ppm. These signals appear to be consistent with the structures of the final compounds (**19–27** and **36–43**).

Scheme 4. Synthesis of 5-piperidinethiazole 2,2-dimethylbutanoic acid derivatives (**36–43**).



Reaction Conditions:

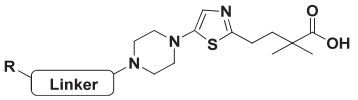
a. BOC anhydride, $NaHCO_3$, 1,4-Dioxane/Water, 0 °C; **b.** 10% Pd.C, $HCOONH_4$, MeOH, reflux; **c.** HATU, TEA, DMF, rt; **d.** 10% Pd.C/H_2, MeOH/THF, rt; **e.** 5-methoxy-4,4-dimethyl-5-oxopentanoic acid, HATU, TEA, DMF, rt; **f.** Lawesson's reagent, 1,4-Dioxane, reflux; **g.** 5N HCl in isopropanol, rt; **h.** For compounds **33 - 37**, R_1NCO, TEA, CH_2Cl_2, rt; For compound **38**, R_2COCl, TEA, CH_2Cl_2, rt; For compounds **39 and 40**, R_3SO_2Cl, TEA, CH_2Cl_2, rt; **i.** $LiOH/H_2O$, THF/MeOH, rt.

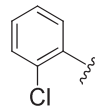
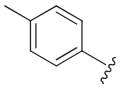
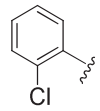
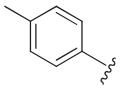
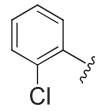
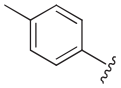
In the ^{13}C-NMR of 5-piperazine thiazole analogs (**19–27**) recorded in DMSO-d_6, the carboxylic acid carbon appears consistently around 178.8 ppm. The prominent signals corresponding to the carbons of thiazole ring in all compounds were observed nearly at 122.4, 154.1, and 158.5 ppm. In case of urea derivatives, carbonyl carbon appears around 155.4 ppm, whereas amide carbonyl appears around 169.6 ppm. The piperazine –CH_2 carbons appear around 52.3 ppm. The carbon on the 2,2 dimethyl carboxylic acid side chain that is attached directly to the thiazole ring appears around 29.4 ppm and the one next to it appears around 41.6 ppm. The quartenary carbon adjacent to the carboxylic acid and the dimethyl carbons on it appear around 43.6 and 25.3 ppm, respectively. In case of the ^{13}C-NMR of 5-piperidine thiazole analogs (**36–43**) the –CH_2 carbons next to the ring nitrogen appear around 51.1 ppm , the –CH_2 carbons next to these appear around 31.4 ppm, and the piperidine –CH also appears around 51.1 ppm . The carbon assignments are a further proof of evidence towards these compound structures. The HRMS were also found to be in agreement with molecular formulae of the synthesized compounds. The HRMS spectra of all final compounds with an error range of less than ± 5.0 ppm along with their HPLC chromatograms provide substantial proof of purity for these compounds. Thus all synthesized compounds exhibited spectral data consistent with their structures.

Diacylglycerol acyltransferase 1 inhibition. The synthesized heterocyclic analogs were studied *in vitro* for their DGAT1 inhibition using (Tables 1 and 2) an enzymatic assay that measured a triolein output from diolein and radiolabeled oleoyl-CoA [14]. These DGAT1 assays were performed using 2.5 μg of the protein from a post nuclear supernatant preincubated with 100 μL of the assay buffer [100 mM Tris-HCl (pH 7.5), 250 mM sucrose, and 1.25 mg/mL fatty acid

Table 1

Diacylglycerol acyltransferase 1 inhibition of 5-piperazinethiazole analogs.

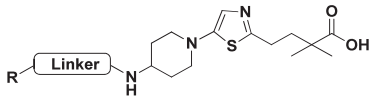


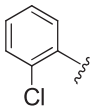
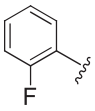
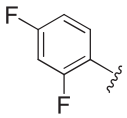
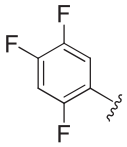
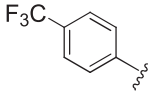
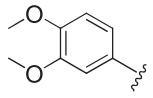
Compound no.	Linker	R	DGAT 1% inhibition [1 μM]
19			31
20			22
21			30
22			33
23			34
24			42
25			34
26			49
27			30
2 (Standard)	—	—	84

DGAT1, diacylglycerol acyltransferase 1.

Table 2

Diacylglycerol acyltransferase 1 inhibition of 5-piperidinethiazole analogs.



Compound no.	Linker	R	DGAT 1% inhibition [1 μM]
36			NA
37			NA
38			15
39			07
40			NA
41			20
42			16
43			NA
2 (Standard)	—	—	84

DGAT1, diacylglycerol acyltransferase 1; NA, not active.

free BSA] containing a known concentration of the inhibitor and supplemented using 2047.5 μM of 1,2-dioleoylglycerol. The DGAT1 reaction was initiated following an addition of 16.8 nci of [^{14}C]-oleoyl CoA. The reaction was terminated after 10 min of incubation at 37°C using 300 μL alkaline ethanol stop solution mix [12.5% of 100% non-denatured ethanol, 10% deionized water, 2.5% NaOH, and 75% stop solution (78.4% isopropanol, 19.6% n-heptane, and 2% deionized water)]. The ^{14}C triglyceride formed in this reaction was extracted using

600 μL of heptane. A total of 250 μL of this extracted heptane was added to scintillation fluid and subjected to radioactivity measurement. The screening of DGAT1 inhibitors was carried out at 1.0 μM concentration.

Compound **2** (DGAT1 inhibition = 84% [1 μM]) [4] that has been developed in-house was used as a standard during the assay. Compounds possessing the 5-piperazinethiazole 2,2-dimethylbutanoic acid scaffold (Table 1, **19–27**) exhibited moderate DGAT1 inhibition ranging from 22–49%. Compounds **19–21** possessing the urea linker exhibited DGAT1 inhibition ranging from 22% to 32%, compounds **22–24** possessing the amide linker ranged between 30% and 35% while compounds **25–27** possessing the sulfonamide linker ranged between 30% and 49%. On the other hand, compounds possessing the 5-piperidinethiazole 2,2-dimethylbutanoic acid scaffold (Table 2, **36–43**) exhibited low DGAT1 inhibition at 1 μM concentration. While the urea analogs (**36–40**) in this scaffold ranged in between 0–16%, the amide analog **41** exhibited **20**% DGAT1 inhibition, and the sulfonamide analogs **42** and **43** exhibited 16% and 0% DGAT1 inhibition, respectively. The 5-piperazinethiazole 2,2-dimethylbutanoic acid scaffold thus appears better than the 5-piperidinethiazole 2,2-dimethylbutanoic acid scaffold.

CONCLUSIONS

In summary, we have described the synthesis of two novel scaffolds, 5-piperidinethiazole 2,2-dimethylbutanoic acid and 5-piperazinethiazole 2,2-dimethylbutanoic acid. The synthesized compounds were characterized using ^{1}H-NMR, ^{13}C-NMR, HRMS, and HPLC analysis. The synthesized derivatives were evaluated for their DGAT1 enzymatic assay wherein the 5-piperazinethiazole 2,2-dimethylbutanoic acid derivatives exhibited moderate DGAT1 inhibition and the 5-piperidinethiazole 2,2-dimethylbutanoic acid analogs exhibited low DGAT1 inhibition.

EXPERIMENTAL

Unless mentioned otherwise, all reactions were performed under atmosphere. Unless otherwise specified all reagents were obtained from Aldrich and solvents were obtained from Thomas Baker and used without further purification. ^{1}H-NMR (either 300 or 500 MHz) and ^{13}C-NMR (either 75 or 125 MHz) spectra were recorded on a Bruker spectrometer using either $CDCl_3$ or DMSO-d_6 as the solvent. Chemical shifts, δ, are reported in ppm relative to the solvent peak. Multiplicities are indicated by s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Coupling constants, J, are reported in Hertz. Mass spectral (MS) data were obtained on a Bruker Daltonics spectrometer using an electrospray ionization-quadrupole-time of flight analyzer. All melting points have been determined on a manually operated Veego (VMP-1) melting point apparatus and are reported uncorrected. HPLC purities have been determined using a Waters Alliances 2695 system implementing either method A or method B.

High-performance liquid chromatography solvents.
A: Acetonitrile
B: 0.01 M NH_4OAc + 0.5% TEA, pH 5.0 with AcOH

High-performance liquid chromatography columns.
Column 1: Poroshell 120 C18, (50 × 4.6 mm I.D.),2.7 μm operated at 1 mL/min, detection at 239 nm
Column 2: Ascentis TM Express (50 × 4.6 mm I.D.), 2.7 μm operated at 1 mL/min, detection at 288 nm

High-performance liquid chromatography methods.
Method A: Elution with 20–80% linear gradient of A in 6 min followed by 20–80% linear gradient of B in 1 min that is continued using a isocratic elution with 80% B for 3 min using Column 1.
Method B: Elution with 20–80% linear gradient of A in 6 min followed by 20–80% linear gradient of B in 1 min that is continued using an isocratic elution with 80% B for 3 min using Column 2.

2-(((Benzyloxy)carbonyl)amino)acetic acid (7). A mixture of compound **6** (10 g, 133 mmol, 1.0 equiv) and 2.0 N aqueous sodium hydroxide solution (253 mL, 506 mmol, 3.9 equiv) were cooled in an ice bath to 0°C. Under vigorous stirring benzyl chloroformate (19 mL, 133 mmol, 1.0 equiv) and 2.0 N aqueous sodium hydroxide solution (280 mL, 560 mmol, 4.2 equiv) were added simultaneously over a period of 2 min. The resulting mixture was stirred for 20 min at RT and extracted with diethyl ether (4 × 150 mL). The aqueous layer was separated and acidified using concentrated HCl to a pH of 2.0. The resulting emulsion was extracted with ethyl acetate (3 × 200 mL). The organic phases were combined, washed with brine, dried over sodium sulfate, and concentrated under reduced pressure to afford the title compound as light brown needles (11 g, 40%); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 12.56 (bs, 1H, –COOH), 7.56 (t, J = 6.0 Hz ,1H, amide–NH), 7.33–7.32 (m, 5H, PhH), 5.02 (s, 2H, $-OCH_2$), 3.66 (d, J = 6.0 Hz , 2H, $-C(O)CH_2$); mp: 118–120°C; MS (ESI−): m/z 210.1 $[M+H]^+$

Dimethyl 2,2-dimethylpentanedioate (9). To a solution of 3,3-dimethyldihydro-2H-pyran-2,6-(3H)-dione (30 g, 211 mmol, 1.0 equiv) in MeOH (300 mL) was added catalytic amount of H_2SO_4 (0.2 mL, 4.2 mmol, 0.02 equiv) under nitrogen and heated to 55°C for 24 h. The reaction mass was cooled and solvent was removed under reduced pressure to obtain pale brown oil. The oil was purified by silica gel column chromatography using 2:8 EtOAc:petroleum ether to obtain title compound as an oil (33 g, 83%); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.68 (s, 6H, $-OCH_3$), 2.32–2.27 (m, 2H, $-C(O)-CH_2$), 1.92–1.86 (m, 2H, $-CH_2-C-$), 1.20 (s, 6H, $-C(CH_3)_2$); MS (ESI+): m/z 189.1 $[M+H]^+$.

5-Methoxy-4,4-dimethyl-5-oxopentanoic acid (10). To a solution of dimethyl 2,2-dimethylpentanedioate (30 g, 159 mmol, 1.0 equiv) in MeOH (300 mL) and THF (198 mL) was added K_2CO_3 (44.1 g, 319 mmol, 2.0 equiv) followed by Water (198 mL) and stirred at RT for 24 h. The organic solvent was removed at reduced pressure to obtain residue which was poured onto water and extracted with ethyl acetate (2 × 100 mL). The aqueous layer was acidified with 3.0 N HCl and extracted with ethyl acetate (3 × 250 mL). Then combined organic layer was washed with brine solution, dried over sodium sulfate, and evaporated to obtain the title compound as an oil (22 g, 79%); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 12.10 (bs, 1H, –COOH), 3.59 (s, 3H, $-OCH_3$), 2.16–2.10 (m, 2H, $-C(O)CH_2$), 1.75–1.70

(m, 2H, $-CH_2-C-$), 1.10 (s, 6H, $-C(CH_3)_2$); MS (ESI−): *m/z* 173 $[M-H]^-$.

tert-Butyl 4-benzylpiperazine-1-carboxylate (12). To a cooled solution of BOC anhydride (43.5 mL, 187 mmol, 1.1 equiv) and sodium bicarbonate (22.6 g, 213 mmol, 1.2 equiv) in 1,4-dioxane (300 mL) and water (300 mL) was added compound **11** (30 g, 170 mmol, 1.0 equiv) over 10 min. The resulting suspension was stirred at 5–10°C for 1 h, allowed to warm to RT, and then stirred for 24 h. The reaction mixture was diluted with water and extracted with chloroform (3 × 800 mL). The organic layer was dried over sodium sulfate and evaporated to obtain an off-white solid. The solid was crystallized in EtOAc/petroleum ether to yield the desired compound as a white solid (46.5 g, 99%); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.32–7.28 (m, 5H, PhH), 3.50 (s, 2H, $-CH_2-$Ph), 3.43–3.40 (m, 4H, 2 × piperazine–CH_2), 2.39–2.36 (m, 4H, 2 × piperazine–CH_2), 1.44 (s, 9H, $-C(CH_3)_3$); mp: 70–72°C; MS (ESI+): *m/z* 277.2 $[M+H]^+$.

tert-Butyl piperazine-1-carboxylate (13). To a solution of compound 1**2** (46 g, 166 mmol, 1.0 equiv) in MeOH (460 mL) was added 10% palladium on carbon (4.6 g, 10% w/w) and ammonium formate (31.5 g, 499 mmol, 3.0 equiv) and refluxed at 65°C for 2 h. The reaction mixture was filtered through celite and the filtrate was concentrated under reduced pressure to obtain a pale brown solid. To this water was added and the resulting mixture was extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate, and the solvent was removed under reduced pressure to obtain an off-white solid. The solid was crystallized in chloroform/petroleum ether to obtain the title compound as a white solid (26 g, 84%); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.39–3.36 (m, 4H, 2 × piperazine–CH_2), 2.81–2.77 (m, 4H, 2 × piperazine–CH_2), 1.73–1.72 (m, 1H, piperazine–NH), 1.45 (s, 9H, $-C(CH_3)_3$); mp: 44–46°C; MS (ESI+): *m/z* 187.1 $[M+H]^+$.

tert-Butyl 4-(2-(((benzyloxy)carbonyl)amino)acetyl)piperazine-1-carboxylate (14). To a solution of compound **7** (15.7 g, 75 mmol, 1.0 equiv) in DMF (280 mL) were added HATU (34.3 g, 90 mmol, 1.2 equiv), compound 1**3** (14 g, 75 mmol, 1.0 equiv), and TEA (20.9 mL, 150 mmol, 2.0 equiv). The reaction mixture was stirred at RT for 4 h followed by the removal of organic solvent to obtain a pale brown residue. This was then purified by silica gel column chromatography using 1:9 CH_3OH:$CHCl_3$ to obtain a pale green solid. The solid was crystallized in chloroform/petroleum ether to obtain the title compound as a white solid (27 g, 95%); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.34–7.27 (m, 5H, Ar–H), 5.01 (s, 2H, $-OCH_2$), 3.86 (d, J = 6.0 Hz , 2H, $-C(O)-CH_2$), 3.38 (m, 4H, 2 × piperazine–CH_2), 3.26 (m, 4H, 2 × piperazine–CH_2), 1.38 (s, 9H, $-C(CH_3)_3$); mp: 80–82°C; MS (ESI+): *m/z* 400.2 $[M+Na]^+$.

tert-Butyl 4-(2-aminoacetyl)piperazine-1-carboxylate (15). To a solution of compound **14** (27 g, 71.5 mmol, 1.0 equiv) in MeOH (270 mL) and THF (270 mL) was added 10% palladim on carbon (2.7 g, 25.4 mmol, 10% w/w). The mixture was hydrogenated in a Parr shaker at 60–65 psi of H_2 pressure for 2 h. The reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure to obtain an off-white solid. The obtained solid was crystallized in chloroform/petroleum ether to yield the title compound as a white solid (16.7 g, 96%); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.60–3.59 (m, 2H, piperazine–CH_2), 3.46 (s, 2H, $-C(O)-CH_2$), 3.43–3.42 (m, 4H, 2 × piperazine–CH_2), 3.35–3.34 (m, 2H, piperazine–CH_2), 1.46 (s, 9H, $-C(CH_3)_3$); mp: 96–98°C; MS (ESI+): *m/z* 244.2 $[M+H]^+$.

tert-Butyl 4-(2-(5-methoxy-4,4-dimethyl-5-oxopentanamido) acetyl)piperazine-1-carboxylate (16). To a solution of compound **10** (6.6 g, 41.1 mmol, 1.0 equiv) in DMF (200 mL) were added HATU (18.7 g, 49.3 mmol, 1.2 equiv), compound **15** (10 g, 41.1 mmol, 1.0 equiv), and TEA (11.5 mL, 82 mmol, 2.0 equiv). The reaction mixture was stirred at RT for 4 h following which it was concentrated under vacuum to obtain a pale brown residue. This was further purified by silica gel column chromatography using 1:9 MeOH:$CHCl_3$ to get a pale green solid. The solid was crystallized in chloroform/petroleum ether to obtain the title compound as a white solid (15.1 g, 92%); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.93 (t, 1H, J = 5.4 Hz, amide–NH), 4.05–3.90 (d, J = 5.4 Hz, 2H, $-C(O)-CH_2-N-$), 3.57 (s, 3H, $-OCH_3$), 3.38 (m, 4H, 2 × piperazine–CH_2), 3.23 (m, 4H, 2 × piperazine–CH_2), 2.08–2.03 (m, 2H, $-C(O)CH_2$), 1.71–1.66 (m, 2H, $-CH_2-C-$), 1.46 (s, 9H, $-C(CH_3)_3$), 1.18 (s, 6H, $-C(CH_3)_2$); mp: 106–108°C; MS (ESI+): *m/z* 400 $[M+H]^+$.

tert-Butyl 4-(2-(4-methoxy-3,3-dimethyl-4-oxobutyl)thiazol-5-yl)piperazine-1-carboxylate (17). To a solution of compound **16** (13 g, 32.5 mmol, 1.0 equiv) in 1,4-dioxane (130 mL) was added Lawesson's Reagent (13.2 g, 32.5 mmol, 1.0 equiv) and heated to reflux for 1.5 h. The reaction mixture was subsequently cooled, diluted with water, and neutralized using a saturated solution of sodium carbonate. The product was separated from the aqueous mixture using EtOAc. The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a dark brown residue. The residue was subjected to column chromatography using 3:7 EtOAc:$CHCl_3$ to get a dark yellow colored solid that was crystallized in chloroform/petroleum ether to yield the desired product as an off-white solid (3.6 g, 28%); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 6.82 (s, 1H, thiazole–H), 3.58 (s, 3H, $-OCH_3$), 3.43–3.40 (m, 4H, 2 × piperazine–CH_2), 2.96–2.93 (m, 4H, 2 × piperazine–CH_2), 2.72–2.66 (m, 2H, thiazole–CH_2), 1.87–1.81 (m, 2H, $-CH_2-C$), 1.39 (s, 9H, $-C(CH_3)_3$), 1.14 (s, 6H, $-C(CH_3)_2$); mp: 72–74°C; MS (ESI+): *m/z* 398.2 $[M+H]^+$.

Methyl 2,2-dimethyl-4-(5-(piperazin-1-yl)thiazol-2-yl)butanoate hydrochloride (18). To compound **17** (3.5 g, 8.80 mmol, 1.0 equiv) was added 5.0 N HCl in isopropanol (25.2 mL, 176 mmol, 20.0 equiv) the mixture was stirred overnight at RT. Subsequently, the solvent was removed under reduced pressure to obtain a solid which was stirred in diethyl ether, filtered, and dried to obtain the desired product as an off-white solid (2.7 g, 91%); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 9.33 (bs, 2H, $-NH_2$), 6.98 (s, 1H, thiazole–H), 3.58 (s, 3H, $-OCH_3$), 3.25 (m, 4H, 2 × piperazine–CH_2), 3.19 (m, 4H, 2 × piperazine–CH_2), 2.79–2.73 (m, 2H, thiazole–CH_2), 1.89–1.83 (m, 2H, $-CH_2-C-$), 1.14 (s, 6H, $-C(CH_3)_2$); mp: >250°C; MS (ESI+): *m/z* 298.2 $[M+H]^+$.

tert-Butyl (1-benzylpiperidin-4-yl)carbamate (29). To a cooled solution of BOC anhydride (40.3 mL, 173 mmol, 1.1 equiv) and sodium bicarbonate (20.9 g, 197 mmol, 1.2 equiv) in 1,4-dioxane (300 mL) and water (300 mL) was added compound **28** (32.2 mL, 158 mmol, 1.0 equiv) over 10 min. The resulting suspension was stirred at 5–10°C for 1 h, and the reaction mixture was allowed to warm up to RT stirred for an additional 24 h. The reaction mixture was diluted with water and extracted with chloroform (3 × 800 mL). The organic layer was dried over sodium sulfate and evaporated to obtain an off-white solid. The solid was crystallized in EtOAc/petroleum ether to yield the desired compound as a white solid (41.5 g, 91%); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.31–7.21 (m, 5H, PhH), 6.75 (d, J = 7.8 Hz, 1H, $-C(O)-NH-$), 3.39 (s, 2H, $-CH_2-$Ph), 3.18

(m, 1H, piperidine–CH), 2.72–2.68 (m, 2H, piperidine–CH_2), 1.93–1.86 (m, 2H, piperidine–CH_2), 1.65–1.61 (m, 2H, piperidine–CH_2), 1.34 (s, 9H, –$C(CH_3)_3$), 1.32–1.28 (m, 2H, piperidine–CH_2); mp: 123–125°C; MS (ESI+): *m/z* 291.2 $[M+H]^+$.

tert-Butyl piperidin-4-ylcarbamate (30). To a solution of **29** (41 g, 141 mmol, 1.0 equiv) in MeOH (820 mL) was added 10% palladium on carbon (4.1 g, 10% w/w), and the reaction mixture was hydrogenated in a Parr shaker at 60–65 psi H_2 pressure for 5 h. The reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure to obtain an off-white solid, which was crystallized in $CHCl_3$/petroleum ether to obtain the title compound as a white solid (24 g, 85%); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 6.73 (d, J = 7.5 Hz, 1H, C(O)–NH–), 3.21 (m, 1H, piperidine–CH), 2.86–2.82 (m, 2H, piperidine–CH_2), 2.40–2.32 (m, 2H, piperidine–CH_2), 1.83 (bs, 1H, piperidine–NH), 1.61–1.57 (m, 2H, piperidine–CH_2), 1.35 (s, 9H, –$C(CH_3)_3$), 1.23–1.09 (m, 2H, piperidine–CH_2); mp: 161–163°C; MS (ESI+): *m/z* 201.1$[M+H]^+$.

[1-(2-Benzyloxycarbonylamino-acetyl)-piperidin-4-yl]-carbamic acid terthyphen;butyl ester (31). To a solution of compound **7** (20.9 g, 100 mmol, 1.0 equiv) in DMF (380 mL) were added HATU (45.6 g, 120 mmol, 1.2 equiv), compound **30** (20 g, 100 mmol, 1.0 equiv), and TEA (27.8 mL, 200 mmol, 2.0 equiv). The mixture was stirred at RT for 4 h following which the organic solvent was removed to obtain a pale brown residue. This was purified by silica gel column chromatography using 1:9 CH_3OH:$CHCl_3$ to get a light green colored solid. The solid was crystallized in chloroform/petroleum ether to obtain the title compound as a white solid (26 g, 66%); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.33 (bs, 5H, PhH), 7.23 (t, J = 5.7 Hz, 1H, –C(O)–NH–piperidine), 6.88 (d, J = 7.5 Hz, 1H, –C–NH–C(O)–), 5.01 (s, 2H, –OCH_2), 4.17–4.13 (m, 1H, piperidine–CH), 3.81 (t, J = 5.1 Hz, 2H, –C(O)–CH_2), 3.73–3.68 (m, 1H, piperidine–CH), 3.43 (bs, 1H, piperidine–CH), 3.05–2.95 (m, 1H, piperidine–CH), 2.73–2.63 (m, 1H, piperidine–CH), 1.70 (bs, 2H, piperidine–CH_2), 1.36 (s, 9H, –$C(CH_3)_3$), 1.27–1.11 (m, 2H, piperidine–CH_2); mp: 156–158°C; MS (ESI+): *m/z* 392.2 $[M+H]^+$.

tert-Butyl (1-(2-aminoacetyl)piperidin-4-yl)carbamate (32). To a solution of compound **31** (27.5 g, 70.2 mmol, 1.0 equiv) in MeOH (275 mL) and THF (275 mL) was added 10% palladium on carbon (2.7 g, 10% w/w). The reaction mixture was hydrogenated in a Parr shaker at 60–65 psi H_2 pressure for 2 h. The reaction mixture was filtered through celite and the filtrate concentrated under reduced pressure to obtain an off-white solid. This solid was crystallized in $CHCl_3$/petroleum ether to afford the title compound as a white solid (17.1 g, 95%); NMR (300 MHz, DMSO-d_6): δ 6.86 (d, J = 7.5 Hz, 1H, –C(O)–NH), 4.23–4.18 (m, 1H, piperidine–CH), 3.67–3.62 (m, 1H, piperidine–CH), 3.43 (m, 2H, –NH_2), 3.27 (m, 3H, –C(O)–CH_2 and piperidine–CH), 2.98–2.90 (m, 1H, piperidine–CH), 2.71–2.63 (m, 1H, piperidine–CH), 1.68 (bs, 2H, piperidine–CH_2), 1.36 (s, 9H, –$C(CH_3)_3$), 1.28–1.09 (m, 2H, piperidine–CH_2); mp: 86–88°C; MS (ESI+): *m/z* 258 $[M+H]^+$.

Methyl 5-((2-(4-((tert-butoxycarbonyl)amino)piperidin-1-yl)-2-oxoethyl)amino)-2,2-dimethyl-5-oxopentanoate (33). To a solution of compound **10** (5.4 g, 31.1 mmol, 1.0 equiv) in DMF (160 mL) were added HATU (14.2 g, 37.3 mmol, 1.2 equiv), compound **34** (8 g, 31.1 mmol, 1.0 equiv) and TEA (8.7 mL, 62.2 mmol, 2.0 equiv). The mixture was stirred at RT for 4 h following which the solvent was removed under vacuum to obtain a pale brown residue. This was purified by silica gel column chromatography using 1:9 CH_3OH:$CHCl_3$ to obtain a light green solid. The solid was crystallized in chloroform/petroleum ether to obtain the title compound as a white solid (10.8 g, 84%); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.91 (t, J = 5.4 Hz, 1H, –C–NH–C(O)–), 6.89 (d, J = 7.5 Hz, 1H, –C(O)–NH–piperidine), 4.17–4.13 (m, 1H, piperidine–CH), 3.89–3.84 (m, 2H, –C(O)–CH_2–N–), 3.57 (s, 3H, –OCH_3), 3.43 (bs, 1H, piperidine–CH), 3.04–2.96 (m, 1H, piperidine–CH), 2.66 (m, 2H, –C(O)–CH_2), 2.10–2.02 (m, 2H, piperidine–CH_2), 1.71–1.65 (m, 4H, –CH_2–C– and piperidine–CH_2), 1.36 (s, 9H, –$C(CH_3)_3$), 1.31–1.16 (m, 2H, piperidine–CH_2), 1.08 (s, 6H, –$C(CH_3)_2$); mp: 81–83°C; MS (ESI+): *m/z* 414.2 $[M+H]^+$.

Methyl 4-(5-(4-((tert-butoxycarbonyl)amino)piperidin-1-yl) thiazol-2-yl)-2,2-dimethylbutanoate (34). To a solution of compound **33** (10.6 g, 25.6 mmol, 1.0 equiv) in 1,4-dioxane (106 mL) was added Lawesson's reagent (10.4 g, 25.6 mmol, 1.0 equiv) and heated to reflux for 1 h. The reaction mixture was subsequently cooled, added to water, and neutralized with a saturated solution of sodium carbonate. The product was separated from the aqueous mixture using EtOAc. The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure to get a dark brown residue. The residue was subjected to column chromatography using 3:7 EtOAc:$CHCl_3$ to get a dark yellow colored solid that was crystallized in $CHCl_3$/petroleum ether to yield the desired product as an off-white solid (3.2 g, 30%); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 6.88 (d, J = 7.8 Hz, 1H, –C(O)–NH–piperidine), 6.73 (s, 1H, thiazole–H), 3.58 (s, 3H, –OCH_3), 3.26 (bs, 1H, piperidine–CH), 2.80–2.70 (m, 2H, piperidine–CH_2), 2.69–2.64 (m, 2H, thiazole–CH_2), 1.86–1.80 (m, 2H, –CH_2–C–), 1.78–1.73 (m, 2H, piperidine–CH_2), 1.52–1.45 (m, 4H, 2 × piperidine–CH_2), 1.36 (s, 9H, –$C(CH_3)_3$), 1.13 (s, 6H, –$C(CH_3)_2$); mp: 103–105°C; MS (ESI+): *m/z* 412.2 $[M+H]^+$.

Methyl 4-(5-(4-aminopiperidin-1-yl)thiazol-2-yl)-2,2-dimethyl-butanoate hydrochloride (35). To compound **34** (3.1 g, 7.53 mmol, 1.0 equiv) was added 5.0 N HCl in isopropanol (21.5 mL, 151 mmol, 20.0 equiv) and the mixture was stirred for 16 h at RT. Solvent was removed under reduced pressure to obtain an off-white solid, which was stirred in diethyl ether, filtered, and dried to obtain the title compound as an off-white solid (2 g, 76%); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 8.17 (bs, 2H, –NH_2), 6.89 (s, 1H, thiazole–H), 3.58 (s, 3H, –OCH_3), 3.46–3.33 (m, 2H, piperidine–CH_2), 3.16 (bs, 1H, piperidine–CH), 2.87–2.80 (m, 2H, piperidine–CH_2), 2.77–2.72 (m, 2H, thiazole–CH_2), 1.95–1.91 (m, 2H, piperidine–CH_2), 1.87–1.81 (m, 2H, –CH_2–C–), 1.71–1.59 (m, 2H, piperidine–CH_2), 1.14 (s, 6H, $C(CH_3)_2$); mp: >250°C ; MS (ESI+): *m/z* 312.2 $[M+H]^+$.

General procedure I. ***Synthesis of 5-piperazinethiazole analogs (19–21) and 5-piperidinethiazole analogs (36–40) possessing the urea linker.*** To a suspension of compound **18** (0.3 mmol, 1.0 equiv) in DCM (2 mL) was added TEA (0.7 mmol, 2.5 equiv) followed by the appropriately substituted isocyanate (0.3 mmol, 1.1 equiv) and the mixture was stirred for 24 h at RT. The reaction mixture was then concentrated and purified using flash column chromatography (1:1 EtOAc-petroleum ether) to afford the desired methyl ester. Replacing compound **18** with compound **35** resulted in synthesis of the corresponding 5-piperidinethiazole analogs (**36–40**).

General procedure II. ***Synthesis of 5-piperazinethiazole analogs (22–24) and 5-piperidinethiazole analog (41) possessing the amide linker.*** To a suspension of compound **18** (0.3 mmol, 1.0 equiv) in DCM (2 mL) was added TEA (0.7 mmol, 2.5 equiv) followed by the appropriately substituted

acid chloride (0.3 mmol, 1.1 equiv), and the mixture was stirred for 24 h at RT. The reaction mixture was then concentrated and purified using flash column chromatography (4:6 EtOAc: petroleum ether) to afford the desired methyl ester. Replacing compound **18** with compound **35** resulted in synthesis of the corresponding 5-piperidinethiazole analog (**41**).

General procedure III. ***Synthesis of 5-piperazinethiazole analogs (25–27) and 5-piperidinethiazole analogs (42 and 43) possessing the sulfonamide linker.*** To a suspension of compound **18** (0.3 mmol, 1.0 equiv) in DCM (2 mL) was added TEA (0.7 mmol, 2.5 equiv) followed by the appropriately substituted sulfonyl chloride (0.3 mmol, 1.1 equiv), and the mixture was stirred for 24 h at RT. The reaction mixture was then concentrated and purified using flash column chromatography (4:6 EtOAc-petroleum ether) to afford the desired methyl ester. Replacing compound **18** with compound **35** resulted in synthesis of the corresponding 5-piperidinethiazole analog (**42** and **43**).

General procedure IV. ***Deprotection of esters.*** To a solution of the methyl ester (1 equiv), synthesized either using general procedure I, II, or III in THF and MeOH was added 1.0 M solution of LiOH in water (4 equiv) and stirred for 20 h at RT. The solvent was removed, the obtained residue was diluted with water and acidified to pH 2 using 2.0 M HCl. The solid thus obtained was filtered and dried to yield the desired acid.

4-(5-(4-((2-Chlorophenyl)carbamoyl)piperazin-1-yl)thiazol-2-yl)-2,2-dimethylbutanoic acid (19). The methyl ester was synthesized by general procedure I using 2-chlorophenyl isocyanate (50.6 mg, 0.3 mmol, 1.1 equiv) as the substituted isocyanate and subsequently deprotected by following general procedure IV to afford the title compound (51 mg, 38%) as an off-white solid; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 12.16 (bs, 1H, –COOH), 8.34 (s, 1H, Ar–NH–C(O)–), 7.45 (t, J = 7.8 Hz, 2H, 2 × Ar–H), 7.27 (t, J = 7.8 Hz, 1H, Ar–H), 7.13 (t, J = 7.8 Hz, 1H, Ar–H), 6.86 (s, 1H, thiazole–H), 3.57 (m, 4H, 2 × piperazine–CH_2), 3.04 (m, 4H, 2 × piperazine–CH_2), 2.76–2.70 (m, 2H, thiazole–CH_2), 1.85–1.79 (m, 2H, –CH_2–C–), 1.12 (s, 6H, –C(CH_3)$_2$); ^{13}C-NMR (125 MHz, DMSO-d_6): δ 178.83, 158.41, 155.44, 154.14, 136.97, 129.74, 128.94, 127.69 (2C), 126.27, 122.36, 52.32 (4C), 43.74, 41.61, 29.41, 25.30 (2C); mp: 172–174°C; HRMS (ESI−) calcd for C20H25ClN4O3S [M–H]$^-$ 435.1263, found 435.1268 (error 1.15 ppm); HPLC: retention time 3.35 min, purity 98.83% (Method A).

2,2-Dimethyl-4-(5-(4-(p-tolylcarbamoyl)piperazin-1-yl)thiazol-2-yl)butanoic acid (20). The methyl ester was synthesized by general procedure I using 1-isocyanato-4-methylbenzene (43.9 mg, 0.3 mmol, 1.1 equiv) as the substituted isocyanate and subsequently deprotected by following general procedure IV to afford the title compound (72 mg, 59%) as an off-white solid; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 12.23 (bs, 1H, –COOH), 8.52 (s, 1H, A–NH), 7.31 (d, J = 8.4 Hz, 2H, 2 × Ar–H), 7.01 (d, J = 8.4 Hz, 2H, 2 × Ar–H), 6.85 (s, 1H, thiazole–H), 3.55 (m, 4H, 2 × piperazine–CH_2), 3.02 (m, 4H, 2 × piperazine–CH_2), 2.76–2.70 (m, 2H, thiazole–CH_2), 2.21 (s, 3H, tolyl–CH_3), 1.85–1.79 (m, 2H, –CH_2–C–), 1.12 (s, 6H, –C(CH_3)$_2$); ^{13}C-NMR (125 MHz, DMSO-d_6): δ 178.86, 158.38, 155.47, 154.16, 138.21, 131.11, 129.18 (2C), 122.32, 120.28 (2C), 52.38 (4C), 43.57, 41.61, 29.41, 25.31 (2C), 20.81; mp: 186–188°C; HRMS (ESI+) calcd for C21H28N4O3S [M + H]$^+$ 417.1955, found 417.1948 (error 1.68 ppm); HPLC: retention time 3.38 min, purity 96.83% (Method A).

4-(5-(4-(Cyclohexylcarbamoyl)piperazin-1-yl)thiazol-2-yl)-2,2-dimethylbutanoic acid (21). The methyl ester was synthesized by general procedure I using cyclohexyl isocyanate (41.2 mg, 0.3 mmol, 1.1 equiv) as the isocyanate and subsequently deprotected by following general procedure IV to afford the title compound (76 mg, 62%) as an off-white solid; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 12.23 (bs, 1H, –COOH), 6.82 (s, 1H, thiazole–H), 6.28 (d, J = 7.5 Hz, 1H, cyclohexyl–NH), 3.37 (m, 4H, 2 × piperazine–CH_2), 2.94 (m, 4H, 2 × piperazine–CH_2), 2.74–2.69 (m, 2H, thiazole–CH_2), 1.84–1.78 (m, 2H, –CH_2–C–), 1.74–1.64 (m, 4H, 2 × cyclohexyl–CH_2), 1.56–1.53 (m, 1H, cyclohexyl–CH), 1.21–1.15 (m, 6H, 3 × cyclohexyl–CH_2), 1.11 (s, 6H, –C(CH_3)$_2$); ^{13}C-NMR (125 MHz, DMSO-d_6): δ 178.83, 158.23, 157.13, 154.27, 122.15, 52.31 (4C), 49.65, 43.32, 41.60, 33.56 (2C), 29.39, 25.83, 25.54 (2C), 25.29 (2C); mp: 178–180°C; HRMS (ESI−) calcd for C20H32N4O3S [M–H]$^-$ 407.2122, found 407.2123 (error 0.24 ppm); HPLC: retention time 3.16 min, purity 98.48% (Method A).

4-(5-(4-(2-Chlorobenzoyl)piperazin-1-yl)thiazol-2-yl)-2,2-dimethylbutanoic acid (22). The methyl ester was synthesized by general procedure II using 2-chlorobenzoyl chloride (57.7 mg, 0.3 mmol, 1.1 equiv) as the substituted acid chloride and subsequently deprotected by following general procedure IV to afford the title compound (19 mg, 15%) as an off-white solid; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 12.21 (bs, 1H, –COOH), 7.56–7.50 (m, 1H, Ar–H), 7.48–7.44 (m, 1H, Ar–H), 7.42–7.39 (m, 2H, 2 × Ar–H), 6.83 (s, 1H, thiazole–H), 3.77 (t, J = 5.1 Hz, 2H, piperazine–CH_2), 3.24 (t, J = 5.1 Hz, 2H, piperazine–CH_2), 3.12–3.08 (q, J = 5.1 Hz, 2H, piperazine–CH_2), 2.97 (t, J = 5.1 Hz, 2H, piperazine–CH_2), 2.75–2.69 (m, 2H, thiazole–CH_2), 1.83–1.78 (m, 2H, –CH_2–C–), 1.11 (s, 6H, –C(CH_3)$_2$); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 178.79, 166.00, 158.79, 153.76, 135.87, 131.11, 129.91, 129.58, 128.47 , 128.12 , 122.72 , 52.36 (4C), 45.92, 41.59, 29.39, 25.28 (2C); mp: 172–174°C; HRMS (ESI+) calcd for C20H24ClN3O3S [M + H]$^+$ 422.1300, found 422.1270 (error 7.10 ppm); HPLC: retention time 3.19 min, purity 96.73% (Method A).

2,2-Dimethyl-4-(5-(4-(4-methylbenzoyl)piperazin-1-yl)thiazol-2-yl)butanoic acid (23). The methyl ester was synthesized by general procedure II using 4-methylbenzoyl chloride (50.9 mg, 0.3 mmol, 1.1 equiv) as the substituted acid chloride and subsequently deprotected by following general procedure IV to afford the title compound (19 mg, 16%) as an off-white solid; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 12.26 (bs, 1H, –COOH), 7.30 (d, J = 8.1 Hz, 2H, 2 × Ar–H), 7.23 (d, J = 8.1 Hz, 2H, 2 × Ar–H), 6.83 (s, 1H, thiazole–H), 3.55 (m, 4H, 2 × piperazine–CH_2), 3.03 (m, 4H, 2 × piperazine–CH_2), 2.74–2.69 (m, 2H, thiazole–CH_2), 2.32 (s, 3H, tolyl–CH_3), 1.83–1.78 (m, 2H, –CH_2–C–), 1.11 (s, 6H, –C(CH_3)$_2$); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 178.80, 169.69, 158.61, 153.91, 139.83, 133.10, 129.38 (2C), 127.58 (2C), 122.53, 52.41 (4C), 41.59 (2C), 29.39, 25.28 (2C), 21.37; mp: 150–152°C; HRMS (ESI−) calcd for C21H27N3O3S [M–H]$^-$ 400.1700, found 400.1719 (error 4.75 ppm); HPLC: retention time 3.30 min, purity 96.42% (Method A).

4-(5-(4-(Cyclohexanecarbonyl)piperazin-1-yl)thiazol-2-yl)-2,2-dimethylbutanoic acid (24). The methyl ester was synthesized by general procedure II using cyclohexanecarbonyl chloride (48.2 mg, 0.3 mmol, 1.1 equiv) as the substituted acid chloride and subsequently deprotected by following general procedure IV to afford the title compound (73 mg, 62%) as an off-white solid; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 12.18 (bs, 1H, –COOH), 6.83 (s, 1H, thiazole–H), 3.57 (m, 4H, 2 × piperazine–CH_2), 2.96 (m, 4H, 2 × piperazine–CH_2), 2.75–2.69 (m, 2H, thiazole–CH_2), 2.58 (m, 1H, cyclohexyl–CH), 1.84–1.78 (m, 2H, –CH_2–C–), 1.68–1.61 (m, 4H, 2 × cyclohexyl–CH_2), 1.32–1.22

(m, 6H, 3 × cyclohexyl–CH_2), 1.11 (s, 6H, –$C(CH_3)_2$); ^{13}C-NMR (125 MHz, DMSO-d_6): δ 178.83, 173.98, 158.55, 153.98, 122.42, 52.96 (2C), 52.47 (2C), 44.51, 41.60, 40.69, 29.58 (2C), 29.41, 26.03, 25.60 (2C), 25.30 (2C); mp: 152–154°C; HRMS (ESI+) calcd for C20H31N3O3S $[M+H]^+$ 394.2159, found 394.2150 (error 2.28 ppm); HPLC: retention time 3.43 min, purity 97.55% (Method A).

4-(5-(4-((2-Chlorophenyl)sulfonyl)piperazin-1-yl)thiazol-2-yl)-2,2-dimethylbutanoic acid (25). The methyl ester was synthesized by general procedure III using 2-chlorobenzenesulfonyl chloride (69.5 mg, 0.329 mmol, 1.1 equiv) as the substituted sulfonyl chloride and subsequently deprotected by following general procedure IV to afford the title compound (71 mg, 52%) as an off-white solid; ^{1}H-NMR (500 MHz, DMSO-d_6): δ 12.22 (bs, 1H, –COOH), 8.01 (d, J = 7.5 Hz, 1H, Ar–H), 7.74–7.69 (m, 2H, 2 × Ar–H), 7.59 (t, J = 7.5 Hz, 1H, Ar–H), 6.84 (s, 1H, thiazole–H), 3.31 (m, 4H, 2 × piperazine–CH_2), 3.08 (m, 4H, 2 × piperazine–CH_2), 2.74–2.71 (m, 2H, thiazole–CH_2), 1.83–1.80 (m, 2H, –CH_2–C–), 1.12 (s, 6H, –$C(CH_3)_2$); ^{13}C-NMR (125 MHz, DMSO-d_6): δ 178.80, 159.02, 153.53, 135.56, 135.24, 132.88, 132.14, 131.43, 128.42, 122.97, 52.22 (4C), 45.17, 41.59, 29.39, 25.28 (2C); mp: 165–167°C; HRMS (ESI+) calcd for C19H24ClN3O4S2 $[M+H]^+$ 458.0970, found 458.0973 (error 0.65 ppm); HPLC: retention time 3.95 min, purity 99.03% (Method B).

2,2-Dimethyl-4-(5-(4-tosylpiperazin-1-yl)thiazol-2-yl)butanoic acid (26). The methyl ester was synthesized by general procedure III using 4-methylbenzene-1-sulfonyl chloride (62.8 mg, 0.3 mmol, 1.1 equiv) as the substituted sulfonyl chloride and subsequently deprotected by following general procedure IV to afford the title compound (69 mg, 52%) as an off-white solid; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 12.22 (bs, 1H, –COOH), 7.62 (d, J = 8.4 Hz, 2H, 2 × Ar–H), 7.45 (d, J = 8.4 Hz, 2H, 2 × Ar–H), 6.78 (s, 1H, thiazole–H), 3.06 (m, 4H, 2 × piperazine–CH_2), 2.97 (m, 4H, 2 × piperazine–CH_2), 2.72–2.66 (m, 2H, thiazole–CH_2), 2.39 (s, 3H, tolyl–CH_3), 1.80–1.75 (m, 2H, –CH_2–C–), 1.09 (s, 6H, –$C(CH_3)_2$); ^{13}C-NMR (125 MHz, DMSO-d_6): δ 178.79, 158.96, 153.38, 144.40, 132.22, 130.42 (2C), 128.10 (2C), 122.88, 51.68 (4C), 45.62, 41.58, 29.37, 25.27 (2C), 21.50; mp: 201–203°C; HRMS (ESI−) calcd for C20H27N3O4S2 $[M-H]^-$ 436.1370, found 436.1378 (error 1.83 ppm); HPLC: retention time 4.03 min, purity 97.39% (Method A).

4-(5-(4-(Cyclohexylsulfonyl)piperazin-1-yl)thiazol-2-yl)-2,2-dimethylbutanoic acid (27). The methyl ester was synthesized by general procedure III using cyclohexanesulfonyl chloride (60.2 mg, 0.3 mmol, 1.1 equiv) as the substituted sulfonyl chloride and subsequently deprotected by following general procedure IV to afford the title compound (45 mg, 35%) as an off-white solid; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 12.22 (bs, 1H, –COOH), 6.83 (s, 1H, thiazole–H), 3.40 (m, 1H, cyclohexyl–CH), 3.03 (m, 4H, 2 × piperazine–CH_2), 2.75–2.68 (m, 2H, thiazole–CH_2), 1.99–1.96 (m, 2H, cyclohexyl–CH_2), 1.84–1.73 (m, 4H, –CH_2–C– and cyclohexyl–CH_2), 1.61–1.23 (m, 6H, 3 × cyclohexyl–CH_2), 1.11 (s, 6H, –$C(CH_3)_2$); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 178.81, 158.73, 153.79, 122.63, 59.94, 52.73 (4C), 45.26, 41.59, 29.38, 28.46, 26.60 (2C), 25.29 (2C), 24.92 (2C); mp: 190–192°C; HRMS (ESI−) calcd for C19H31N3O4S2 $[M-H]^-$ 428.1683, found 428.1664 (error 4.44 ppm); HPLC: retention time 3.88 min, purity 97.09% (Method A).

4-(5-(4-(3-(2-Chlorophenyl)ureido)piperidin-1-yl)thiazol-2-yl)-2,2-dimethylbutanoic acid (36). The methyl ester was synthesized by general procedure I using 2-chlorophenyl isocyanate (66.4 mg, 0.4 mmol, 1.1 equiv) as the substituted isocyanate and subsequently deprotected by following general procedure IV to afford the title compound (103 mg, 58%) as an off-white solid; ^{1}H-NMR (500 MHz, DMSO-d_6): δ 12.28 (bs, 1H, –COOH), 8.17 (d, J = 8.5 Hz, 1H, Ar–H), 7.97 (s, 1H, Ar–NH–C(O)–), 7.39 (d, J = 7.5 Hz, 1H, Ar–H), 7.23 (t, J = 7.5 Hz, 1H, Ar–H), 7.14 (d, J = 7.2 Hz, 1H, –C(O)–NH–piperidine), 6.94 (t, J = 7.5 Hz, 1H, Ar–H), 6.80 (s, 1H, thiazole–H), 3.66 (bs, 1H, piperidine–CH), 3.31–3.28 (m, 2H, piperidine–CH_2), 2.91 (t, J = 10.0 Hz, 2H, piperidine–CH_2), 2.75–2.71 (m, 2H, thiazole–CH_2), 1.92 (d, J = 10.0 Hz, 2H, piperidine–CH_2), 1.85–1.81 (m, 2H, –CH_2–C–), 1.56–1.50 (q, J = 10.0 Hz, 2H, piperidine–CH_2), 1.13 (s, 6H, –$C(CH_3)_2$); ^{13}C-NMR (125 MHz, DMSO-d_6): δ 178.83, 157.65, 154.44, 137.14, 129.52, 127.91 (2C), 122.79, 121.56, 121.37, 120.92, 51.21 (2C), 45.70, 41.61, 31.44 (2C), 29.32, 25.30 (3C); mp: 187–189°C; HRMS (ESI+) calcd for C21H27ClN4O3S $[M+H]^+$ 451.1565, found 451.1555 (error 2.22 ppm); HPLC: retention time 3.60 min, purity 99.88% (Method A).

4-(5-(4-(3-(2-Fluorophenyl)ureido)piperidin-1-yl)thiazol-2-yl)-2,2-dimethylbutanoic acid (37). The methyl ester was synthesized by general procedure I using 2-fluorophenyl isocyanate (59.2 mg, 0.4 mmol, 1.1 equiv) as the substituted isocyanate and subsequently deprotected by following general procedure IV to afford the title compound (128 mg, 75%) as an off-white solid; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 12.22 (bs, 1H, –COOH), 8.19 (bs, 1H, Ar–NH–C(O)–), 8.11 (t, J = 8.1 Hz, 1H, Ar–H), 7.18–7.11 (dd, J = 8.4 Hz, 1H, Ar–H), 7.05 (t, J = 7.8 Hz, 1H, Ar–H), 6.92–6.88 (m, 1H, Ar–H), 6.78 (s, 1H, thiazole–H), 6.74 (d, J = 7.8 Hz, 1H, –C(O)–NH–piperidine), 3.63 (bs, 1H, piperidine–CH), 3.28–3.24 (m, 2H, piperidine–CH_2), 2.89 (t, J = 9.9 Hz, 2H, piperidine–CH_2), 2.74–2.68 (m, 2H, thiazole–CH_2), 1.91–1.78 (m, 4H, piperidine–CH_2 and –CH_2–C–), 1.55–1.48 (q, J = 9.9 Hz, 2H, piperidine–CH_2), 1.11 (s, 6H, –$C(CH_3)_2$); ^{13}C-NMR (125 MHz, DMSO-d_6): δ 178.84, 157.63, 154.58, 154.45, 152.93, 151.01, 128.74, 124.83, 121.73, 120.39, 115.21, 51.19 (2C), 45.56, 41.61, 31.47 (2C), 29.36 (2C), 25.30 (2C); mp: 194–196°C; HRMS (ESI+) calcd for C21H27FN4O3S $[M+H]^+$ 435.1861, found 435.1855 (error 1.38 ppm); HPLC: retention time 3.25 min, purity 99.48% (Method A).

4-(5-(4-(3-(2,4-Difluorophenyl)ureido)piperidin-1-yl)thiazol-2-yl)-2,2-dimethylbutanoic acid (38). The methyl ester was synthesized by general procedure I using 2,4-difluoro-1-isocyanatobenzene (67.0 mg, 0.4 mmol, 1.1 equiv) as the substituted isocyanate and subsequently deprotected by following general procedure IV to afford the title compound (116 mg, 65%) as an off-white solid; ^{1}H-NMR (500 MHz, DMSO-d_6): δ 12.25 (bs, 1H, –COOH), 8.18 (s, 1H, Ar–NH–C(O)–), 8.08–8.05 (m, 1H, Ar–H), 7.26–7.22 (m, 1H, Ar–H), 6.98 (t, J = 8.5 Hz, 1H, Ar–H), 6.79 (s, 1H, thiazole–H), 6.69 (d, J = 8.5 Hz, 1H, –C(O)–NH–piperidine), 3.64 (bs, 1H, piperidine–CH), 3.29–3.26 (m, 2H, piperidine–CH_2), 2.90 (t, J = 10.0 Hz, 2H, piperidine–CH_2), 2.74–2.71 (m, 2H, thiazole–CH_2), 1.92–1.89 (m, 2H, piperidine–CH_2), 1.84–1.81 (m, 2H, –CH_2–C–), 1.56–1.49 (q, J = 10.0 Hz, 2H, piperidine–CH_2), 1.13 (s, 6H, –$C(CH_3)_2$); ^{13}C-NMR (125 MHz, DMSO-d_6): δ 178.84, 157.63, 154.66, 154.43, 125.32, 121.57 (2C), 121.50, 111.36, 111.29, 104.00, 51.21 (2C), 45.63, 41.60, 31.47 (2C), 29.35, 25. 29 (3C); mp: 185–187°C; HRMS (ESI−) calcd for C21H26F2N4O3S $[M-H]^-$ 451.1621, found 451.1602 (error 4.21 ppm); HPLC: retention time 3.32 min, purity 99.67% (Method A).

2,2-Dimethyl-4-(5-(4-(3-(2,4,5-trifluorophenyl)ureido)piperidin-1-yl)thiazol-2-yl)butanoic acid (39). The methyl ester was synthesized by general procedure I using 1,2,4-trifluoro-5-

isocyanatobenzene (74.8 mg, 0.432 mmol, 1.1 equiv) as the substituted isocyanate and subsequently deprotected by following general procedure IV to afford the title compound (132 mg, 71%) as an off-white solid; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 12.22 (bs, 1H, –COOH), 8.38 (bs, 1H, Ar–NH–C(O)–), 8.21–8.11 (m, 1H, Ar–H), 7.59–7.49 (m, 1H, Ar–H), 6.78–6.75 (m, 2H, Ar–H, –C(O)–NH–piperidine), 3.61 (bs, 1H, piperidine–CH), 3.27–3.23 (m, 2H, piperidine–CH_2), 2.89 (t, J = 9.9 Hz, 2H, piperidine–CH_2), 2.73–2.68 (m, 2H, thiazole–CH_2), 1.90–1.78 (m, 4H, piperidine–CH_2, –CH_2–C–), 1.55–1.45 (m, 2H, piperidine–CH_2), 1.11 (s, 6H, –$C(CH_3)_2$); ^{13}C-NMR (125 MHz, DMSO-d_6): δ 178.82, 157.70, 154.37, 147.70, 145.87, 144.07, 142.02, 125.77, 121.65, 108.00, 105.74, 51.14 (2C), 45.64, 41.60, 31.36 (2C), 29.33, 25.29 (3C); mp: 192–194°C; HRMS (ESI+) calcd for C21H25F3N4O3S $[M+H]^+$ 471.1672, found 471.1665 (error 1.48 ppm); HPLC: retention time 3.80 min, purity 99.52% (Method A).

4-(5-(4-(3-Cyclohexylureido)piperidine-1-yl)thiazol-2-yl)-2,2-dimethylbutanoic acid (40). The methyl ester was synthesized by general procedure I using cyclohexyl isocyanate (54.1 mg, 0.4 mmol, 1.1 equiv) as the substituted isocyanate and subsequently deprotected by following general procedure IV to afford the title compound (102 mg, 69%) as an off-white solid; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 12.24 (bs, 1H, –COOH), 6.76 (s, 1H, thiazole–H), 5.76 (d, J = 7.8 Hz, 1H, Ar–NH–C(O)–), 5.64 (d, J = 7.8 Hz, 1H, –C(O)–NH–piperidine), 3.52 (bs, 1H, piperidine–CH), 3.28–3.24 (m, 2H, piperidine–CH_2), 2.84 (t, J = 9.9 Hz, 2H, piperidine–CH_2), 2.74–2.68 (m, 2H, thiazole–CH_2), 1.85–1.79 (m, 4H, piperidine–CH_2 and –CH_2–C–), 1.74 (m, 2H, cyclohexyl–CH_2), 1.61 (m, 2H, piperidine–CH_2), 1.48–1.33 (m, 4H, 2 × cyclohexyl–CH_2), 1.23 (m, 3H, cyclohexyl–CH and cyclohexyl –CH_2), 1.13 (s, 6H, –$C(CH_3)_2$), 1.07–1.04 (m, 2H, cyclohexyl–CH_2); ^{13}C-NMR (125 MHz, DMSO-d_6): δ 178.83, 173.98, 158.55, 153.98, 122.42, 52.96 (2C), 52.47 (2C), 44.51, 41.60, 29.58 (3C), 29.41, 26.03, 25.60 (3C), 25.33 (2C); mp: 176–178°C; HRMS (ESI+) calcd for C21H34N4O3S $[M+H]^+$ 423.2424, found 423.2413 (error 2.60 ppm); HPLC: retention time 3.17 min, purity 99.63% (Method A).

4-(5-(4-(Cyclohexanecarboxamido)piperidin-1-yl)thiazol-2-yl)-2,2-dimethylbutanoic acid (41). The methyl ester was synthesized by general procedure II using cyclohexanecarbonyl chloride (63.3 mg, 0.4 mmol, 1.1 equiv) as the substituted acid chloride and subsequently deprotected by following general procedure IV to afford the title compound (19 mg, 12%) as an off-white solid; ^{1}H-NMR (500 MHz, DMSO-d_6): δ 12.25 (bs, 1H, –COOH), 7.66 (d, J = 8.0 Hz, 1H, –C(O)–NH–piperidine), 6.76 (s, 1H, thiazole–H), 3.65 (bs, 1H, piperidine–CH), 3.30 (m, 1H, cyclohexyl–CH), 2.82 (t, J = 11.5 Hz, 2H, piperidine–CH_2), 2.73–2.70 (m, 2H, thiazole–CH_2), 2.06 (t, J = 11.5 Hz, 1H, piperidine–CH), 1.83–1.80 (m, 2H, –CH_2–C–), 1.76–1.74 (m, 2H, piperidine–CH_2), 1.70–1.59 (m, 5H, cyclohexyl–CH and 2 × Cyclohexyl–CH_2), 1.52–1.46 (q, J = 10.5 Hz, 2H, piperidine–CH_2), 1.34–1.27 (q, J = 11.5 Hz, 2H, cyclohexyl–CH_2), 1.23–1.16 (m, 3H, 2 × cyclohexyl–CH_2 and cyclohexyl–CH), 1.13 (s, 6H, –$C(CH_3)_2$); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 178.83, 175.01, 157.42, 154.38, 121.52, 51.56 (3C), 45.12, 44.42, 41.59, 30.95 (2C), 29.68 (2C), 29.32, 25.91, 25.74 (2C), 25.29 (2C); mp: 190–192°C; HRMS (ESI+) calcd for C21H33N3O3S $[M+H]^+$ 408.2315, found 408.2308 (error 1.71 ppm); HPLC: retention time 3.09 min, purity 96.85% (Method A).

2,2-Dimethyl-4-(5-(4-(4-(trifluoromethyl)phenylsulfonamido)piperidin-1-yl)thiazol-2-yl)butanoic acid (42). The methyl ester was synthesized by general procedure III using 4-(trifluoromethyl)benzene-1-sulfonyl chloride (105.7 mg, 0.4 mmol, 1.1 equiv) as the substituted sulfonyl chloride and subsequently deprotected by following general procedure IV to afford the title compound (82 mg, 40%) as an off-white solid; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 12.22 (bs, 1H, –COOH), 8.09 (d, J = 7.2 Hz, 1H, –$S(O)_2$–NH–), 8.03 (d, J = 8.4 Hz, 2H, 2 × Ar–H), 7.97 (d, J = 8.4 Hz, 2H, 2 × Ar–H), 6.69 (s, 1H, thiazole–H), 3.23–3.19 (m, 3H, piperidine–CH and piperidine–CH_2), 2.77–2.65 (m, 4H, piperidine–CH_2 and thiazole–CH_2), 1.80–1.75 (m, 2H, –CH_2–C–), 1.62–1.59 (m, 2H, piperidine–CH_2), 1.53–1.41 (m, 2H, piperidine–CH_2), 1.09 (s, 6H, –$C(CH_3)_2$); ^{13}C-NMR (125 MHz, DMSO-d_6): δ 178.81, 157.65, 154.07, 146.45, 127.70 (3C), 127.01 (2C), 121.79 (2C), 51.16 (2C), 50.07, 41.58, 31.75 (2C), 29.32, 25.27 (3C); mp: 216–218°C; HRMS (ESI−) calcd for C21H26F3N3O4S2 $[M-H]^-$ 504.1244, found 504.1241 (error 0.59 ppm); HPLC: retention time 4.15 min, purity 99.60% (Method A).

4-(5-(4-(3,4-Dimethoxyphenylsulfonamido)piperidin-1-yl)thiazol-2-yl)-2,2-dimethylbutanoic acid (43). The methyl ester was synthesized by general procedure III using 3,4-dimethoxybenzene-1-sulfonyl chloride (102.2 mg, 0.4 mmol, 1.1 equiv) as the substituted sulfonyl chloride and subsequently deprotected by following general procedure IV to afford the title compound (62 mg, 31%) as an off-white solid; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 12.22 (bs, 1H, –COOH), 7.62 (d, J = 6.9 Hz, 1H, –$S(O)_2$–NH–), 7.40–7.33 (m, 2H, 2 × Ar–H), 7.11 (d, J = 8.1 Hz, 1H, Ar–H), 6.70 (s, 1H, thiazole–H), 3.81 (s, 6H, 2 × –OCH_3), 3.23–3.19 (m, 2H, piperidine–CH_2), 3.07 (bs, 1H, piperidine–CH), 2.71–2.69 (m, 4H, piperidine–CH_2, thiazole–CH_2), 1.82–1.75 (m, 2H, –CH_2–C–), 1.58 (m, 2H, piperidine–CH_2), 1.47 (m, 2H, piperidine–CH_2), 1.10 (s, 6H, –$C(CH_3)_2$); ^{13}C-NMR (125 MHz, DMSO-d_6): δ 178.82, 157.57, 154.16, 152.19, 149.10, 133.93, 121.70, 120.37, 111.56, 109.66, 56.24 (2C), 51.17 (2C), 49.84, 41.59, 31.66 (2C), 29.32, 25.28 (3C); mp: 184–186°C; HRMS (ESI−) calcd for C22H31N3O6S2 $[M-H]^-$ 496.1582, found 496.1583 (error −0.20 ppm); HPLC: retention time 3.08 min, purity 98.18% (Method A).

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