Electronic supplementary Information

N-(5-Substituted Thiazol-2-yl)-2-aryl-3-(tetrahydro-2H-pyran-4-yl) Propanamides as Glucokinase Activators

Zhiqing Liu,[†,#] Qingzhang Zhu,[‡,#] Fuying Li,[†,§] Lina Zhang[‡], Ying Leng,[‡,*] Ao Zhang[†,*]

[†]*Synthetic Organic & Medicinal Chemistry Laboratory (SOMCL), Shanghai Institute of Materia Medica (SIMM), Chinese Academy of Sciences,* [‡] *State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica (SIMM), Chinese Academy of Sciences, Shanghai 201203, China.*

Contents

1. General Methods.

1.1 Chemistry. ^{1}H NMR spectral data were recorded in $CDCl_3$ on Varian Mercury 300 NMR spectrometer and ^{13}C NMR data were recorded in $CDCl_3$ on Varian Mercury 400 NMR spectrometer. Low-resolution mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded at an ionizing voltage of 70 eV on a Finnigan/MAT95 spectrometer. Elemental analyses were performed on a CE 1106 elemental analyzer. Optical rotations were determined with a JASCO DCP-1000 digital polarimeter and were the average of 3 measurements. Column chromatography was carried out on silica gel (200–300 mesh). All reactions were monitored using thin-layer chromatography (TLC) on silica gel plates. Yields were of purified compounds and were not optimized.

1.2 Biological assay.

1.2.1 Preparation of recombinant glucokinase protein: cDNA of human glucokinase (MGC: 1742, purchased from Ori-Gene Technologies, USA) was subcloned into the pET28a (+) expression vector, and expressed in Escherichia coli strain BL21 (DE3). The NH_2 terminal end of $(His)_6$-tag glucokinase fusion protein was purified by Ni-NTA metal chelate affinity chromatography and stored at -80 ^{o}C in 50 mM Tris-HCl pH7.4, 1 mM dithiothreitol (DTT), 50 mM NaCl and 10% glycerol.

1.2.2 Glucokinase enzymatic assay: The GK activity was assessed spectrometrically by a coupled reaction with glucose-6-phosphate dehydrogenase (G6PDH).[25,26] Briefly, GK catalyzes glucose phosphorylation to generate glucose-6-P, which was oxidized by the G6PDH with the concomitant reduction of NADPH. The product NADPH was then

monitored by the increase rate of absorbance at 340 nm in a plate reader (Spectra-Max 190; Molecular Devices, USA). All compounds were prepared in DMSO. The assay was performed in 96-well plates in a final volume of 100 µL containing 50 mM HEPES pH 7.4, 5 mM glucose, 25 mM KCl, 2 mM $MgCl_2$, 1 mM DTT, 1 mM ATP, 1 mM NADP, 2.5 U/mL G6PDH, 0.5 µg $(His)_6$-glucokinase and test compounds. The velocities of the enzyme reaction were expressed as mOD/min, and the fold activation of the enzyme was achieved by comparing with control (GK activation with only DMSO was considered as 100%). For EC_{50} determination, six different concentrations of compounds were tested in the assay, and the fold changes in activity versus controls were fitted to sigmoidal curve using a fourparameter logistic model in GraphPad Prism 4.

2. Preparative Procedure and Spectral Data

2.1 Preparation of C-5 aminoacid substituted aminothiazoles 5A-C.

To a solution of 2-(*tert*-butoxycarbonylamino)thiazole-5-carboxylic acid (**4**, 0.6 mmol) in CH_2Cl_2 (8 mL) pre-cooled in ice-bath was added dropwise a catalytic amount of DMF and a solution of $(COCl)_2$ (62 µL, 0.72 mmol) in CH_2CH_2 (2 mL). The mixture was warmed to rt, stirred for 2h and then re-cooled to 0^oC before addition of corresponding amino acid methyl ester hydrochloride (0.72 mmol) and Et_3N (1.8 mmol). The stirring was continued for 10h at rt and the solvent was evaporated. The residue was treated with EtOAc, washed successively with 1M HCl, water, saturated $NaHCO_3$ and brine, and then dried over Na_2SO_4. After filtration and evaporation, corresponding amides **5A-C** were obtained as yellow solid and used directly for next step.

Methyl 3-(2-(*tert*-butoxycarbonylamino)thiazole-5-carboxamido)propanoate (5A): light yellow solid, 58.6%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (s, 1H), 6.55 (t, *J* = 2.4 Hz, 1H), 3.70 (s, 3H), 3.68 (q, *J* = 6.0 Hz, 2H), 2.63 (t, *J* = 6.0 Hz, 2H), 1.59 (s, 9H).

(*S*)-Methyl 2-(2-(*tert*-butoxycarbonylamino)thiazole-5-carboxamido)-3-methyl butanoate (5B): white solid (*quant.*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.38 (br s, 1H), 7.88 (s, 1H), 6.27 (d, *J* = 8.4 Hz, 1H), 4.70 (m, 1H), 3.75 (s, 3H), 2.22 (m, 1H), 1.58 (s, 9H), 0.95 (m, 6H).

(*S*)-Methyl 2-(2-(*tert*-butoxycarbonylamino)thiazole-5-carboxamido)-4-methyl pentanoate (5C): light yellow solid, yield 95.7%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (s, 1H), 6.26 (d, *J* = 7.8 Hz, 1H), 4.77 (m, 1H), 3.74 (s, 3H), 1.68 (m, 2H), 1.62 (d, *J* = 9.3 Hz, 1H), 1.57 (s, 9H), 0.94 (m, 6H).

2.2 Preparation of C-5 aminoacid substituted aminothiazoles 6A-C.

To a solution of amides **5A-C** prepared above in CH_2Cl_2 (10 mL) pre-cooled in ice-bath was added dropwise a solution of TFA (2 mL) and the mixture was stirred at rt overnight. The reaction mixture was evaporated to dryness. The residue was treated with EtOAc, washed consecutively with saturated $NaHCO_3$, water and brine, and dried over Na_2SO_4. After filtration and evaporation, corresponding aminothiazoles **6A-C** were obtained as light yellow solid and used directly for next step.

Methyl 3-(2-aminothiazole-5-carboxamido)propanoate (6A): light yellow solid (70.0%); ^{1}H NMR ($CDCl_3$+CD_3OD, 300 MHz) δ 7.54 (s, 1H), 3.71 (s, 3H), 3.59 (t, *J* = 8.4 Hz, 2H), 2.64 (t, *J* = 8.4 Hz, 2H).

(*S*)-Methyl 2-(2-aminothiazole-5-carboxamido)-3-methylbutanoate (6B): light yellow solid (60.4%); ^{1}H NMR ($CDCl_3$+CD_3OD, 300 MHz) δ 7.81 (s, 1H), 7.08 (d, J = 8.1 Hz, 1H),

4.58 (m, 1H), 3.76 (s, 3H), 2.20 (m, 1H), 0.98 (m, 6H).

(*S*)-Methyl 2-(2-aminothiazole-5-carboxamido)-4-methylpentanoate (6C): light yellow solid (70.6%); ^{1}H NMR ($CDCl_3$+CD_3OD, 300 MHz) δ 7.57 (s, 1H), 4.70 (m, 1H), 3.75 (s, 3H), 1.68 (m, 3H), 0.97 (m, 6H).

2.3 General Procedure for the synthesis of 7a, 7c, 7e by condensation of acid 3 with an appropriate aminothiazole. To a solution of arylpropanoic acid **3** (85 mg, 0.25 mmol) and an appropriate aminothiazole (0.25 mmol) in CH_2Cl_2 (5 mL) cooled in ice-bath was added TBTU (0.5 mmol) and Et_3N or DIPEA (1.25 mmol). The reaction mixture was stirred at rt overnight, evaporated to dryness, and then treated with EtOAc (10 mL) and 0.1 M HCl (5 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined extracts were washed consecutively with *sat.* $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. After filtration and evaporation, the residue was purified by chromatography ($CHCl_3$: MeOH = 50:1 to 30:1) to give corresponding amides as white or yellow solid.

Hydrolysis of compounds 7a, 7c and 7e. To a solution of an aminoacid ester **7a**, **7c** or **7e** (0.06 mmol) in THF/H_2O (4 mL, 3:1) was added LiOH·H_2O (13 mg, 0.314 mmol) and the resulting mixture was stirred at rt for 18h. The solvent was evaporated and the residue was treated with EtOAc (5 mL) and acidified with 2M HCl to pH = 1. The aqueous layer was extracted with EtOAc and the combined extracts were washed with brine and dried over anhydrous Na_2SO_4. After filtration and evaporation, the crude product was purified by column chromatography ($CHCl_3$: MeOH : AcOH = 10:1:0.1) to give acids **7b**, **7d** and **7f** as white solid.

Methyl 3-(2-(2-(4-(Cyclopropylsulfonyl)phenyl)-3-(tetrahydro-2*H*-pyran-4-yl)propan

amido)thiazole-5-carboxamido)propanoate (7a): white foam, yield 50.0%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.2 (br s, 1H), 7.86 (s, 1H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.1 Hz, 2H), 6.92 (t, *J* = 5.7 Hz, 1H), 4.04 (t, *J* = 7.2 Hz, 1H), 3.87 (d, *J* = 10.5 Hz, 2H), 3.67 (m, 5H), 3.25 (t, *J* = 11.4 Hz, 2H), 2.62 (t, *J* = 6.0 Hz, 2H), 2.47 (m, 1H), 2.20 (m, 1H), 1.78 (m, 1H), 1.59 (d, *J* = 12.0 Hz, 2H), 1.34 (m, 5H), 1.01 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.3, 170.4, 161.0, 160.2, 144.0, 140.1, 139.6, 128.8, 128.4, 127.6, 67.6, 52.0, 49.3, 40.4, 35.2, 33.5, 32.8, 32.5, 6.1; EI-MS *m*/*z* 549 (M^+); HRMS cacld. for ($C_{25}H_{31}N_3O_7S_2Na$): 572.1501; found: 572.1491.

3-(2-(2-(4-(Cyclopropylsulfonyl)phenyl)-3-(tetrahydro-2*H*-pyran-4-yl)-propan-amido)thiazole-5-carboxamido)propanoic acid (7b): white foam (*quant.*); ^{1}H NMR ($CDCl_3$+CD_3OD, 300 MHz) δ 7.77 (s, 1H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 7.8 Hz, 2H), 3.9 (t, *J* = 7.2 Hz, 1H), 3.80 (d, *J* = 10.8 Hz, 2H), 3.50 (t, *J* = 6.0 Hz, 2H), 3.20 (t, *J* = 12.0 Hz, 2H), 2.49 (t, *J* = 5.4 Hz, 2H), 2.39 (m, 1H), 2.08 (m, 1H), 1.71 (m, 1H), 1.53 (d, *J* = 12.0 Hz, 2H), 1.23 (m, 5H), 0.94 (m, 2H); ^{13}C NMR ($CDCl_3$+CD_3OD, 100 MHz) δ 175.1, 170.9, 161.6, 160.8, 144.4, 139,3, 139.2, 128.7, 127.8, 127.2, 67.4, 48.7, 40.1, 35.2, 33.7, 32.5, 32.4, 32.3, 32.2, 5.8, 5.7; MALDI-MS *m*/*z* 536 (M^+). Anal. calcd. for ($C_{24}H_{29}N_3O_7S_2 \cdot 0.5H_2O$): C 52.93, N 7.72, H 5.55; Found: C 52.75, N 7.49, H 5.49.

(2*S*)-Methyl 2-(2-(2-(4-(cyclopropylsulfonyl)phenyl)-3-(tetrahydro-2*H*-pyran-4-yl)-propanamido)thiazole-5-carboxamido)-3-methylbutanoate (7c): white foam (60.5%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.0 (br s, 1H), 7.94 (d, *J* = 2.7 Hz, 1H), 7.85 (dd, *J* = 8.1, 2.7 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.0 (s, 1H, br), 4.04 (m, 1H), 3.89 (d, *J* = 11.1 Hz, 2H), 3.75 (s, 3H), 3.27 (t, *J* = 11.7 Hz, 2H), 2.48 (m, 1H), 2.22 (m, 2H), 1.80 (m, 1H), 1.60 (d, *J* = 11.7 Hz,

2H), 1.36 (m, 5H), 0.98 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.0, 170.8, 170.7, 161.3, 160.6, 144.2, 144.1, 140.2, 140.0, 128.8, 128.33, 128.29, 126.9, 67.6, 57.6, 52.4, 49.2, 49.1, 40.5, 40.3, 32.8, 32.6, 31.4, 19.0, 18.0, 6.0; EI-MS *m*/*z* 577 (M^+). Anal. calcd. for ($C_{27}H_{35}N_3O_7S_2 \cdot 0.3H_2O$): C 55.61, N 7.21, H 6.15; Found: C 55.41, N 7.06, H 6.18.

(2*S*)-2-(2-(2-(4-(Cyclopropylsulfonyl)phenyl)-3-(tetrahydro-2*H*-pyran-4-yl)propan amido)thiazole-5-carboxamido)-3-methylbutanoic acid (7d): white foam (91.7%); ^{1}H NMR (300 MHz, $CDCl_3$+CD_3OD) δ 7.87 (s, 1H), 7.76 (d, *J* = 8.1Hz, 2H), 7.52 (d, *J* = 8.1 Hz, 2H), 4.49 (s, 1H), 3.90 (t, *J* = 7.8 Hz, 1H), 3.84 (d, *J* = 10.8 Hz, 2H), 3.23 (t, *J* = 10.8 Hz, 2H), 2.39 (m, 1H), 2.11 (m, 2H), 1.73 (m, 1H), 1.55 (d, *J* = 12.3 Hz, 2H), 1.25 (m, 5H), 0.97 (d, *J* = 7.5 Hz, 2H), 0.90 (t, *J* = 6.0 Hz, 6H); MALDI-MS *m*/*z* 563.9 (M^+). HRMS cacld. for ($C_{26}H_{34}N_3O_7S_2$): 564.1838; found: 564.1852.

(2*S*)-Methyl 2-(2-(2-(4-(cyclopropylsulfonyl)phenyl)-3-(tetrahydro-2*H*-pyran- 4-yl) propanamido)thiazole-5-carboxamido)-4-methylpentanoate (7e): white foam (67.6%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.0 (brs, 1H), 7.88 (d, *J* = 4.2 Hz, 1H), 7.83 (dd, *J* = 8.4, 3.6 Hz, 2H), 7.53 (dd, *J* = 8.4, 3.6 Hz, 2H), 7.12 (s, 1H, br), 4.83 (m, 1H), 4.02 (m, 1H), 3.88 (d, *J* = 10.8 Hz, 2H), 3.71 (s, 3H), 3.26 (m, 2H), 2.48 (m, 1H), 2.20 (m, 1H), 1.78 (m, 1H), 1.63 (m, 5H), 1.31 (m, 5H), 1.00 (m, 2H), 0.92 (d, *J* = 5.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.24, 174.16, 161.3, 161.2, 160.7, 144.3, 144.2, 140.1, 139.9, 128.8, 128.2, 126.9, 67.6, 52.5, 51.2, 49.1, 49.0, 41.2, 40.4, 40.2, 32.8, 32.6, 25.0, 22.8, 21.8, 6.0; EI-MS *m*/*z* 591 (M^+). Anal. calcd. for ($C_{28}H_{37}N_3O_7S_2 \cdot 0.5H_2O$): C 55.98, N 6.99, H 6.38; Found: C 55.85, N 6.97, H 6.27.

(2*S*)-2-(2-(2-(4-(Cyclopropylsulfonyl)phenyl)-3-(tetrahydro-2*H*-pyran-4-yl)-

propanamido)thiazole-5-carboxamido)-4-methylpentanoic acid (**7f)**: white foam (95.1%); ^{1}H NMR (300 MHz, $CDCl_3$+CD_3OD) δ 7.87 (s, 1H), 7.76 (d, *J* = 8.1 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 4.53 (m, 1H), 3.90 (t, *J* = 7.8 Hz, 1H), 3.83 (d, *J* = 10.8 Hz, 2H), 3.24 (t, *J* = 13.2 Hz, 2H), 2.39 (m, 1H), 2.10 (m, 1H), 1.73 (m, 1H), 1.57 (m, 5H), 1.24 (m, 5H), 0.97 (d, *J* = 7.5 Hz, 2H), 0.88 (d, *J* = 2.7 Hz, 6H); MALDI-MS *m*/*z* 578 (MH^+). HRMS cacld. for ($C_{27}H_{35}N_3NaO_7S_2$): 600.1814; found: 600.1821.

2.4 General procedure for preparation of thiazole-triazoles 9a-c.

To a solution of *tert*-butyl 5-ethynylthiazol-2-ylcarbamate (0.31 mmol) and an appropriate azidoalkylester compound (0.62 mmol) in THF (5 mL) was added CuI (0.156 mmol), sodium L-ascorbate (0.31 mmol) and DIPEA (6.25 mmol). The mixture was stirred at rt for 1h. After the solvent was evaporated, the residue was purified by chromatography ($CHCl_3$: MeOH = 20:1) to give corresponding aminothiazole- triazoles **9a-c** as yellow oil.

Ethyl 4-(4-(2-(tert-butoxycarbonylamino)thiazol-5-yl)-1H-1,2,3-triazol-1-yl)butanoate (**9a)**: white solid (81.2%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.75 (br s, 1H), 7.73 (s, 1H), 7.60 (s, 1H), 4.47 (t, *J* = 6.6 Hz, 2H), 4.14 (q, *J* = 6.9 Hz, 2H), 2.38 (t, *J* = 6.0 Hz, 2H), 2.26 (m, 2H), 1.60 (s, 9H), 1.26 (t, *J* = 7.5 Hz, 3H).

Ethyl 3-(4-(2-(tert-butoxycarbonylamino)thiazol-5-yl)-1H-1,2,3-triazol-1-yl)propanoate (9b): white solid (91.0%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (s, 2H), 4.67 (t, *J* = 6.3 Hz), 4.15 (q, *J* = 7.2 Hz, 2H), 2.97 (t, *J* = 6.3 Hz, 2H), 1.59 (s, 9H), 1.23 (t, *J* = 7.2 Hz, 3H).

Ethyl 2-(4-(2-(tert-butoxycarbonylamino)thiazol-5-yl)-1H-1,2,3-triazol-1-yl)acetate (9c): white solid (91.0%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (s, 2H), 5.19 (s, 2H), 4.28 (q, *J* = 7.2 Hz, 2H), 1.60 (s, 9H), 1.31 (t, *J* = 7.2 Hz, 3H).

2.5 Preparation of triazoles 10a, **10b**, **10d.** These compounds were prepared by using a general condensation procedure similar to that for preparation of compounds **7a-f**. Compounds **10c** was prepared by hydrolysis of **10b** using a procedure similar to that for synthesis of **7b**.

Ethyl 4-(4-(2-(2-(4-(cyclopropylsulfonyl)phenyl)-3-(tetrahydro-2*H*-pyran-4-yl)propan amido) thiazol-5-yl)-1*H*-1,2,3-triazol-1-yl)butanoate (**10a)**: yellow solid (31.1%, purified by preparative TLC with EtOAc/1%MeOH/0.5%HOAc as the eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.46 (br s, 1H), 7.82 (m, 2H), 7.72 (m, 2H), 7.53 (m, 2H), 4.49 (t, *J* = 6.9 Hz, 2H), 4.13 (q, *J* = 7.5 Hz, 2H), 3.98 (t, *J* = 7.8 Hz, 1H), 3.88 (d, *J* = 9.0 Hz, 2H), 3.26 (t, *J* = 11.4 Hz, 2H), 2.45 (m, 1H), 2.38 (t, *J* = 6.6 Hz, 3H), 2.26 (m, 3H), 1.80 (m, 1H), 1.60 (m, 2H), 1.27 (m, 8H), 1.01 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 170.4, 158.2, 144.4, 139.8, 139.5, 133.4, 128.7, 128.1, 122.4, 120.0, 67.6, 60.8, 49.4, 49.2, 40.6, 32.7, 32.6, 30.6, 25.4, 14.1, 6.0; EI-MS *m*/*z* 601 (M^+). Anal. calcd. for ($C_{28}H_{35}N_5O_6S_2$·0.3HOAc): C 55.43, N 11.30, H 5.89; Found: C 55.79, N 10.93, H 6.16.

Ethyl 3-(4-(2-(2-(4-(cyclopropylsulfonyl)phenyl)-3-(tetrahydro-2*H*-pyran-4-yl)propan amido)thiazol-5-yl)-1*H*-1,2,3-triazol-1-yl)propanoate (10b): yellow solid (68.5%, purified by preparative TLC with EtOAc/5%MeOH/0.1%AcOH as the eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.46 (br s, 1H), 7.82 (d, *J* = 7.8 Hz, 2H), 7.81 (s, 1H), 7.74 (s , 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 4.70 (t, *J* = 6.3 Hz, 2H), 4.15 (q, *J* = 7.5 Hz, 2H), 3.96 (t, *J* = 7.5 Hz, 1H), 3.87 (d, *J* =4.8 Hz, 2H), 3.26 (t, *J* = 11.7 Hz, 2H), 2.99 (t, *J* = 6.3 Hz, 2H), 2.46 (m, 1H), 2.22 (m, 1H), 1.81 (m, 1H), 1.69 (d, *J* = 11.7 Hz, 2H), 1.34 (m, 8H), 1.01 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.4, 158.2, 144.3, 139.9, 139.3, 133.4, 128.7, 128.2, 122.4, 121.0, 67.6,

61.3, 49.2, 45.8, 40.6, 34.5, 32.8, 32.6, 14.0, 6.0; EI-MS *m*/*z* 587 (M^+). Anal. calcd. for ($C_{27}H_{33}N_5O_6S_2$·0.1HOAc): C 55.02, N 11.80, H 5.67; Found: C 55.32, N 11.40, H 5.78.

3-(4-(2-(2-(4-(Cyclopropylsulfonyl)phenyl)-3-(tetrahydro-2*H*-pyran-4-yl)propan amido)thiazol-5-yl)-1*H*-1,2,3-triazol-1-yl)propanoic acid (10c): white solid (93.5%); ^{1}H NMR (300 MHz, $CDCl_3$+CD_3OD) δ 7.76 (s, 1H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.49 (s, 1H), 7.44 (d, *J* = 8.1 Hz, 2H), 4.48 (t, *J* = 6.0 Hz, 2H), 3.82 (t, *J* = 7.5 Hz, 1H), 3.73 (d, *J* = 9.3 Hz, 2H), 3.14 (t, *J* = 9.6 Hz, 2H), 2.78 (t, *J* = 6.0 Hz, 2H), 2.31 (m, 1H), 2.01 (m, 1H), 1.62 (m, 1H), 1.47 (d, *J* = 12.0 Hz, 2H), 1.17 (m, 5H), 0.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD) δ 170.6, 157.6, 144.7, 139.2, 133.9, 128.6, 127.6, 121.4, 120.9, 67.3, 47.6, 45.7, 40.1, 34.0, 32.4, 32.2, 5.4; ESI-MS *m/z* 560 (MH^+). Anal. calcd. for ($C_{25}H_{29}N_5O_6S_2$·$2H_2O$): C 50.41, N 11.76, H 5.58; Found: C 50.74, N 11.45, H 5.27.

Ethyl 2-(4-(2-(2-(4-(cyclopropylsulfonyl)phenyl)-3-(tetrahydro-2H-pyran-4-yl) propanamido)thiazol-5-yl)-1H-1,2,3-triazol-1-yl)acetate (**10d)**: yellow solid (47.7%, purified by preparative TLC with EtOAc/5%MeOH/0.1%AcOH as the eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.47 (brs, 1H), 7.84 (s, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.73 (s , 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 5.24 (s, 2H), 4.28 (q, *J* = 6.9 Hz, 2H), 3.97 (t, *J* = 7.2 Hz, 1H), 3.88 (d, *J* = 11.1 Hz, 2H), 3.26 (t, *J* = 11.7 Hz, 2H), 2.46 (m, 1H), 2.22 (m, 1H), 1.81 (m, 1H), 1.60 (t, *J* = 12.0 Hz, 2H), 1.36 (m, 8H), 1.01 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 166.1, 157.9, 144.5, 139.9, 139.6, 134.0, 128.8, 128.0, 121.6, 121.2, 67.6, 62.5, 50.9, 40.4, 32.71, 32.67, 32.5, 13.9, 5.92, 5.88; EI-MS *m*/*z* 573 (M^+). Anal. calcd. for ($C_{26}H_{31}N_5O_6S_2$·0.4HOAc): C 53.85, N 11.72, H 5.50; Found: C 54.21, N 11.50, H 5.59.

2.6 General procedure for preparation of thiazole-triazoles 11a-g.

2-(4-(2-(*tert*-Butoxycarbonylamino)thiazol-5-yl)-1*H*-1,2,3-triazol-1-yl)acetic acid (obtained from hydrolysis of ester **9c** in 79.2% yield) was converted to amides **11a-g** following a similar procedure as that for preparation of compounds **7a-f**.

***tert*-Butyl 5-(1-(2-(methylamino)-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl)thiazol-2-yl carbamate (11a)**: white solid (*quant.*); ^{1}H NMR (300 MHz, $CDCl_3$+CD_3OD) δ 8.00 (s, 1H), 7.64 (s, 1H), 5.08 (s, 2H), 2.82 (d, *J* = 2.1 Hz, 3H), 1.58 (s, 9H).

***tert*-Butyl 5-(1-(2-(ethylamino)-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl)thiazol-2-yl carbamate (11b)**: white solid (*quant.*); ^{1}H NMR (300 MHz, $CDCl_3$+CD_3OD) δ 7.86 (s, 1H), 7.52 (s, 1H), 4.93 (s, 2H), 3.17 (m, 2H), 1.45 (s, 9H), 1.03 (t, *J* = 7.2 Hz, 3H).

***tert*-Butyl 5-(1-(2-(cyclopropylamino)-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl)thiazol-2-yl carbamate (11c)**: white solid (*quant.*); ^{1}H NMR (300 MHz, $CDCl_3$+CD_3OD) δ 7.99 (s, 1H), 7.64 (s, 1H), 5.02 (s, 2H), 2.72 (m, 1H), 1.58 (s, 9H), 0.78 (m, 2H), 0.55 (m, 2H).

***tert*-Butyl 5-(1-(2-(dimethylamino)-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl)thiazol-2-yl carbamate (11d)**: white solid (*quant.*); ^{1}H NMR (300 MHz, $CDCl_3$+CD_3OD) δ 7.96 (s, 1H), 7.30 (s, 1H), 5.30 (s, 2H), 3.17 (s, 3H), 3.04 (s, 3H), 1.58 (s, 9H).

***tert*-Butyl 5-(1-(2-(diethylamino)-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl)thiazol-2-yl carbamate (11e):** white solid (89.5%); ^{1}H NMR (300 MHz, $CDCl_3$+CD_3OD) δ 7.82 (s, 1H), 7.53 (s, 1H), 5.17 (s, 2H), 3.32 (m, 4H), 1.46 (s, 9H), 1.17 (t, *J* = 7.2 Hz, 3H), 1.03 (t, *J* = 7.2 Hz, 3H).

***tert*-Butyl 5-(1-(2-morpholino-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl)thiazol-2-yl-carbamate (11f):** white solid (93.3%); ^{1}H NMR (300 MHz, $CDCl_3$+CD_3OD) δ 7.94 (s, 1H), 7.64 (s, 1H), 5.35 (s, 2H), 3.74 (m, 4H), 3.64 (m, 4H), 1.58 (s, 9H).

***tert*-Butyl 5-(1-(2-(4-methylpiperazin-1-yl)-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl) thiazol-2-ylcarbamate (11g)**: white solid (95.0%); ^{1}H NMR (300 MHz, $CDCl_3$+CD_3OD) δ 7.86 (s, 1H), 7.66 (s, 1H), 5.29 (s, 2H), 3.67 (t, *J* = 4.8 Hz, 2H), 3.61 (t, *J* = 4.8 Hz, 2H), 2.47 (m, 4H), 2.34 (s, 3H), 1.58 (s, 9H).

2.7 Preparation of compounds 12a-g. These compounds were prepared by using a similar condensation procedure as that for preparation of compounds **7a-f**.

2-(4-(Cyclopropylsulfonyl)phenyl)-*N*-(5-(1-(2-(methylamino)-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl)thiazol-2-yl)-3-(tetrahydro-2*H*-pyran-4-yl)propanamide (**12a)**: yellow solid (39.0%); ^{1}H NMR (300 MHz, $CDCl_3$+CD_3OD) δ 8.03 (s, 1H), 7.86 (d, *J* = 8.7 Hz, 2H), 7.72 (s, NH), 7.69 (s, 1H), 7.64 (d, *J* = 8.1 Hz, 2H), 5.10 (s, 2H), 4.03 (t, *J* = 7.5 Hz, 1H), 3.92 (dd, *J* = 11.4, 3.0 Hz, 2H), 3.33 (t, *J* = 11.7 Hz, 2H), 2.81 (d, *J* = 3.6 Hz, 3H), 2.51 (m, 1H), 2.20 (m, 1H), 1.83 (m, 1H), 1.66 (d, *J* = 11.4 Hz, 2H), 1.37 (m, 5H), 1.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD) δ 170.6, 165.8, 165.7, 157.8, 144.6, 139.8, 139.3, 134.1, 128.7(2), 127.8(2), 121.7, 121.4, 67.5(2), 52.4, 48.5, 40.2, 32.6, 32.3, 26.1, 5.8; ESI-MS *m*/*z* 581 (M^++Na). Anal. calcd. for ($C_{25}H_{30}N_6O_5S_2 \cdot 1.2H_2O$): C 51.74, N 14.48, H 5.63; Found: C 51.80, N 14.13, H 5.34.

2-(4-(Cyclopropylsulfonyl)phenyl)-*N*-(5-(1-(2-(ethylamino)-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl)thiazol-2-yl)-3-(tetrahydro-2*H*-pyran-4-yl)propanamide (**12b)**: white solid (51.2%, purified by preparative TLC with EtOAc/5%MeOH/0.1%AcOH as the eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.51 (s, 1H), 7.55 (d, *J* = 8.1 Hz, 2H), 6.84 (t, *J* = 5.4 Hz, 1H, NH), 5.12 (s, 2H), 4.02 (t, *J* = 7.5 Hz, 1H), 3.87 (d, *J* = 11.4 Hz, 2H), 3.28 (m, 4H), 2.48 (m, 1H), 2.16 (m, 1H), 1.80 (m, 1H), 1.60 (t, *J* = 10.8 Hz,

2H), 1.35 (m, 5H), 1.19 (t, *J* = 6.3 Hz, 2H), 1.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD) δ 170.6, 165.0, 164.9, 157.8, 144.6, 139.8, 139.4, 134.0, 128.7 (2), 127.8 (2), 121.7, 121.4, 67.5 (2), 52.4, 48.5, 40.2, 34.6, 34.5, 32.6, 32.3, 14.0, 5.8; ESI-MS *m*/*z* 595 (M^++Na). Anal. calcd. for ($C_{26}H_{32}N_6O_5S_2$·0.3AcOH): C 54.08, N 14.23, H 5.66; Found: C 54.33, N 13.94, H 5.82.

***N*-(5-(1-(2-(Cyclopropylamino)-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl)thiazol-2-yl)-2-(4-(cyclopropylsulfonyl)phenyl)-3-(tetrahydro-2*H*-pyran-4-yl)propanamide** (**12c)**: yellow solid (48.1%, purified by preparative TLC with EtOAc/5%MeOH/0.1%AcOH as the eluent); ^{1}H NMR (300 MHz, $CDCl_3$+CD_3OD) δ 8.03 (s, 1H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.67 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 5.07 (s, 2H), 4.03 (t, *J* = 7.5 Hz, 1H), 3.91 (d, *J* = 11.1 Hz, 2H), 3.31 (t, *J* = 11.4 Hz, 2H), 2.72 (m, 1H), 2.50 (m, 1H), 2.20 (m, 1H), 1.83 (m, 1H), 1.64 (t, *J* = 11.7 Hz, 2H), 1.36 (m, 5H), 1.05 (m, 2H), 0.74 (m, 2H), 0.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD) δ 170.6, 166.4, 157.7, 144.6, 139.6, 139.2, 134.0, 128.7(2), 127.7(2), 121.7, 121.4, 67.4(2), 52.1, 48.5, 40.2, 32.5, 32.3, 22.4, 17.7, 5.7; ESI-MS *m*/*z* 607 (M^++Na). Anal. calcd. for ($C_{27}H_{32}N_6O_5S_2$·0.6AcOH): C 54.56, N 13.54, H 5.59; Found: C 54.20, N 13.69, H 5.59.

2-(4-(Cyclopropylsulfonyl)phenyl)-*N*-(5-(1-(2-(dimethylamino)-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl)thiazol-2-yl)-3-(tetrahydro-2*H*-pyran-4-yl)propanamide (**12d)**: Off-white solid (46.2%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.78 (d, *J* = 7.8 Hz, 2H), 7.58 (s, 1H), 7.51 (d, *J* = 8.1 Hz, 2H), 5.34 (s, 2H), 3.97 (t, *J* = 7.5 Hz, 1H), 3.83 (d, *J* = 11.1 Hz, 2H), 3.22 (t, *J* = 11.1 Hz, 2H), 3.10 (s, 3H), 2.96 (s, 3H), 2.45 (m, 1H), 2.24 (m, 1H), 1.77 (m, 1H), 1.56 (t, *J* = 10.2 Hz, 2H), 1.28 (m, 5H), 0.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD)

δ 170.5, 164.8, 157.5, 144.6, 139.4, 139.2, 133.8, 128.6(2), 127.6(2), 121.9, 121.4, 67.3(2), 50.7, 48.4, 40.1, 36.2, 35.6, 32.4, 32.2, 5.6; ESI-MS *m*/*z* 595 (M^++Na). Anal. calcd. for ($C_{26}H_{32}N_6O_5S_2$): C 54.53, N 14.67, H 5.63; Found: C 54.57, N 14.38, H 5.65.

2-(4-(Cyclopropylsulfonyl)phenyl)-*N*-(5-(1-(2-(diethylamino)-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl)thiazol-2-yl)-3-(tetrahydro-2*H*-pyran-4-yl)propanamide (12e): yellow solid (62.9%); ^{1}H NMR (300 MHz, $CDCl_3$+CD_3OD) δ 8.01 (s, 1H), 7.87 (d, *J* = 8.7 Hz, 2H), 7.70 (s, 1H), 7.50 (d, *J* = 8.7 Hz, 2H), 5.36 (s, 2H), 4.06 (t, *J* = 7.5 Hz, 1H), 3.93 (d, *J* = 10.8 Hz, 2H), 3.46 (m, 4H), 3.34 (t, *J* = 12.0 Hz, 2H), 2.53 (m, 1H), 2.23 (m, 1H), 1.84 (m, 1H), 1.68 (t, *J* = 12.3 Hz, 2H), 1.34 (m, 8H), 1.16 (t, *J* = 7.5 Hz, 3H), 1.08 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD) δ 170.5, 163.9, 157.5, 144.6, 139.4, 139.1, 133.9, 128.6 (2), 127.6 (2), 121.9, 121.4, 67.3 (2), 50.6, 48.3, 41.5, 40.8, 40.1, 32.4, 32.2, 13.7, 12.3, 5.6; ESI-MS *m*/*z* 623.2 (M^++Na). HRMS: *m/z* [M^++Na] calcd for $C_{28}H_{36}N_6NaO_5S_2$: 623.2086, found: 623.2096.

2-(4-(Cyclopropylsulfonyl)phenyl)-*N*-(5-(1-(2-(4-methylpiperazin-1-yl)-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl)thiazol-2-yl)-3-(tetrahydro-2*H*-pyran-4-yl)propanamide (12f): light yellow solid (52.0%, purified by preparative TLC with EtOAc/5%MeOH/0.1%AcOH as the eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.61 (s, 1H), 7.52 (d, *J* = 8.4 Hz, 2H), 5.33 (s, 2H), 3.97 (t, *J* = 7.5 Hz, 1H), 3.85 (d, *J* = 10.5 Hz, 2H), 3.63 (t, *J* = 4.5 Hz, 2H), 3.57 (t, *J* = 4.5 Hz, 2H), 3.24 (t, *J* = 10.8 Hz, 2H), 2.40 (m, 5H), 2.29 (s, 3H), 2.17 (m, 1H), 1.78 (m, 1H), 1.57 (t, *J* = 10.5 Hz, 2H), 1.32 (m, 5H), 0.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD) δ 170.6, 163.3, 157.8, 144.6, 139.7, 139.4, 133.9, 128.7(2), 127.9(2), 121.8, 121.6, 67.5(2), 54.4, 54.0, 50.7, 48.5, 45.5, 44.7, 41.8, 40.3, 32.6, 32.4, 5.81, 5.76; ESI-MS *m*/*z* 626 (M^+). Anal. calcd. for ($C_{29}H_{37}N_7O_5S_2$·AcOH): C 54.13, N 14.25, H

6.01; Found: C 54.10, N 14.49, H 6.02.

2-(4-(Cyclopropylsulfonyl)phenyl)-*N*-(5-(1-(2-morpholino-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl)thiazol-2-yl)-3-(tetrahydro-2*H*-pyran-4-yl)propanamide (12g): Off-white solid (42.3%, purified by preparative TLC with EtOAc/5%MeOH/0.1%AcOH as the eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.62 (s, 1H), 7.52 (d, *J* = 8.7 Hz, 2H), 5.34 (s, 2H), 3.96 (t, *J* = 7.5 Hz, 1H), 3.86 (d, *J* = 11.1 Hz, 2H), 3.69 (m, 4H), 3.59 (m, 4H), 3.25 (t, *J* = 10.8 Hz, 2H), 2.46 (m, 1H), 2.16 (m, 1H), 1.78 (m, 1H), 1.58 (t, *J* = 9.6 Hz, 2H), 1.31 (m, 5H), 1.01 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD) δ 170.5, 163.6, 157.7, 144.6, 139.6, 139.3, 133.9, 128.7(2), 127.8(2), 121.8, 121.5, 67.4(2), 66.2, 66.0, 50.6, 48.5, 45.3, 42.3, 40.2, 32.5, 32.3, 5.7. ESI-MS *m*/*z* 615 (MH^+). Anal. calcd. for ($C_{28}H_{34}N_6O_6S_2\cdot 0.8H_2O$): C 53.45, N 13.36, H 5.70; Found: C 53.83, N 12.92, H 5.70.

2.8 5-(1-(2-(Benzyloxy)ethyl)-1*H*-1,2,3-triazol-4-yl)thiazol-2-amine (13): This compound was prepared as yellow solid from thiazole **8** following a similar procedure as that for preparation of compounds **9a-c** in 68.3% yield. ^{1}H NMR (300 MHz, $CDCl_3$+CD_3OD) δ 7.71 (s, 1H), 7.22 (m, 6H), 4.48 (m, 4H), 3.79 (m, 2H).

2.9 *N*-(5-(1-(2-(Benzyloxy)ethyl)-1*H*-1,2,3-triazol-4-yl)thiazol-2-yl)-2-(4-(cyclo-propyl sulfonyl)phenyl)-3-(tetrahydro-2*H*-pyran-4-yl)propanamide (14): This compound was prepared by using a similar condensation procedure as that for preparation of compounds **7a-f**. white solid (57.5%); ^{1}H NMR (300 MHz, $CDCl_3$+CD_3OD) δ 11.65 (br s, 1H), 7.81 (m, 4H), 7.57 (d, *J* = 7.8 Hz, 2H), 7.29 (m, 5H), 4.62 (t, *J* = 6.3 Hz, 2H), 4.53 (s, 2H), 4.31 (t, *J* = 6.6 Hz, 1H), 4.06 (t, *J* = 6.6 Hz, 1H), 3.88 (d, *J* = 4.8 Hz, 2H), 3.26 (t, *J* = 11.7 Hz, 2H), 2.47 (m, 1H), 2.23 (m, 1H), 1.80 (m, 1H), 1.61 (m, 2H), 1.37 (m, 5H), 1.03 (m, 2H); ^{13}C NMR (100

MHz, $CDCl_3$) δ 170.3, 158.0, 144.2, 139.9, 139.1, 137.8, 133.2, 128.7, 128.5, 128.2, 127.9, 127.8, 122.6, 120.3, 73.1, 67.6, 65.9, 49.3, 47.6, 40.6, 32.8, 32.7, 30.3, 6.0. ESI-MS *m/z* 622 (M^+).

2.10 2-(4-(Cyclopropylsulfonyl)phenyl)-*N*-(5-(1-(2-hydroxyethyl)-1*H*-1,2,3-triazol-4-yl) thiazol-2-yl)-3-(tetrahydro-2*H*-pyran-4-yl)propanamide (15): To a solution of benzylether **14** (48 mg, 0.077 mmol) in CH_2Cl_2 (5 mL) was added *N*, *N*-dimethylaniline (0.187 g, 0.2 mL, 1.5 mmol) and $AlCl_3$ (0.2 g, 1.5 mmol). The mixture was stirred at rt for 5 h. The reaction was quenched by addition of 1N HCl (2 mL) and the aqueous layer was extracted with EtOAc (3 ×5 mL). The combined extracts were successively washed with saturated $NaHCO_3$, brine, and then dried over anhydrous Na_2SO_4. The solvent was removed and the crude product was purified by chromatography ($CHCl_3$: MeOH = 50:1 to 20:1) to give the title compound **15** as white solid (21 mg, 51.2%). ^{1}H NMR (300 MHz, $CDCl_3$+CD_3OD) δ 7.84 (s, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.61 (s, 1H), 7.55 (d, *J* = 8.7 Hz, 2H), 4.45 (t, *J* = 5.1 Hz, 2H), 3.94 (m, 3H), 3.85 (dd, *J* = 12.0, 3.0 Hz, 2H), 3.25 (t, *J* = 12.0 Hz, 2H), 2.42 (m, 1H), 2.14 (m, 1H), 1.77 (m, 1H), 1.58 (t, *J* = 12.6 Hz, 2H), 1.30 (m, 5H), 0.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD) δ 170.6, 157.8, 144.6, 139.5, 139.3, 133.7, 128.8(2), 128.0(2), 121.8, 121.2, 67.6(2), 60.5, 52.8, 48.7, 40.3, 32.7, 32.4, 5.92; ESI-MS *m*/*z* 554 (M^++Na). Anal. calcd. for ($C_{24}H_{29}N_5O_5S_2 \cdot 0.3H_2O$): C 53.67, N 13.04, H 5.56; Found: C 53.87, N 12.65, H 5.68.