Supporting Information

Phenotypic Optimization of Urea-Thiophene Carboxamides to Yield Potent, Well Tolerated and Orally Active Protective Agents Against Aminoglycoside-Induced Hearing Loss

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Figure S1: Reproducibility of Zebrafish Lateral Line Hair Cells Viability Assay; **Table S1**: Pharmacokinetic and Toxicological Properties of **90; Figure S2 & S3, Figures S2, S3** and **Table S2**: Compound **90** Crystal Structure Determination **Tables S4 & S5**: Non-interference in Antimicrobial Activity of Aminoglycoside Antibiotics; Full **Experimental Procedures** and Characterization of Compounds **1-99** (PDF)

SMILES strings for reported compounds (CSV)

Assessment of Compound Efficacy in Zebrafish Lateral Line Hair Cells:

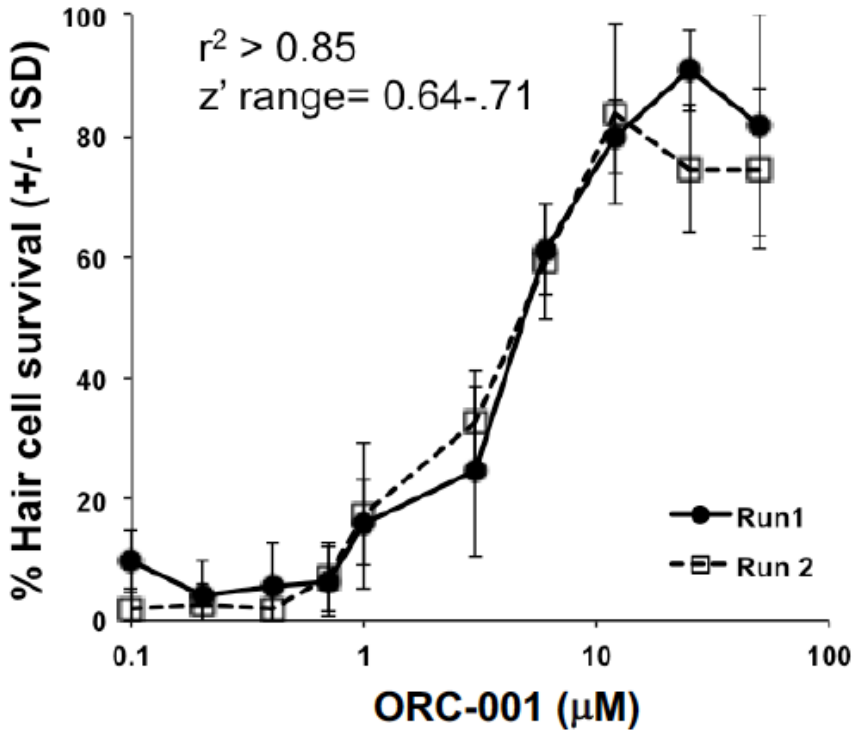


Figure S1. Reproducibility of Zebrafish Lateral Line Hair Cell Protection Assay. Zebrafish larvae were incubated with **1** (ORC-001) and neomycin (200 μM) as described. Hair cell survival was determined as described. Results of two separate runs on two different dates are shown.

Table S1: Pharmacokinetic and toxicological properties of ORC-13661

Physical Characteristics	**Results**
Molecular Weight	390.89 (427.3 as HCl salt)
Kinetic solubility of the free base in PBS (pH 7.4)	86 µM
Thermodynamic solubility - HCl salt (0.5% Methylcellulose/Saline)	>3mg/mL but <10mg/mL
cLogP	3.69
TPSA	87.46
ADMET tests	
HepG2 IC_{50} (cytotoxicity)	>300 µM
MDR1-MDCK/PGP x 10^{-6} cm/s	A-B 1.24, B-A 46.9, A-B (w/CSA) 5.2, B-A (w/CSA) 3.65
CYP Inhibition IC_{50} (µM)	2C9(60), 2C19(58), 2D6(>100), 3A4(46)
Microsomal Intrinsic Clearance (Rat, Dog, Monkey, Human)	16, 9, 9, 4 (µL/min/mg protein)
Microsomal half-life (Rat, Dog, Monkey, Human)	89, 152, 147, 328 (minutes)
Hepatocyte Scale Up unbound clearance (Rat, Dog, Monkey, Human)	32, 63, 18, 6.7 (mL/min/kg)
Hepatocyte Half-life (Rat, Dog, Monkey, Human)	205, 150, 267, 525 (minutes)
Protein Binding (Rat, Dog, Monkey, Human)	86%, 90%, 82%, 89%
in vitro metabolic profile (Rat, Dog, Monkey, Human)	Minimal metabolism for man and NHP, modest for dog and rat – no unique metabolites in human
PAMPA	4.1 (x10^{-6} cm/s)
Safety/Toxicology Tests	
hERG IC_{50}	5.64 µM
Rat Efficacious Dose (5 mg/kg) C_{max}	0.24 µM
hERG IC_{20}(est)/ Rat Efficacious Dose unbound C_{max} = safety ratio	1.8 µM / 0.024 = 75
Ames mutagenicity	Not mutagenic
7 day dose finding toxicology - rat	NOAEL > 100mg/kg/day, MTD > 300mg/kg/day
7 day dose finding toxicology – dog	NOAEL > 30mg/kg/day, MTD > 100mg/kg/day
Secondary Pharmacology	
CEREP – screening (55 assays) 10 µM conc.	D1, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{5A}, µ(mop), NTS_1, Na^+ channel showed % inhibition > 50%
- Na_V 1.5 50% max inhibition	30 µM
- 5-HT_{2A} agonist, 5-HT_{2A} Antagonist, 5-HT_{2B} agonist, 5-HT_{2B} antagonist, $OPRM_1$ agonist	Negative activation

Structure Determination of ORC-13661 HCl.

Structure solved by Brandon Mercado, Ph.D., Yale University Chemical and Biophysical Instrumentation Center.

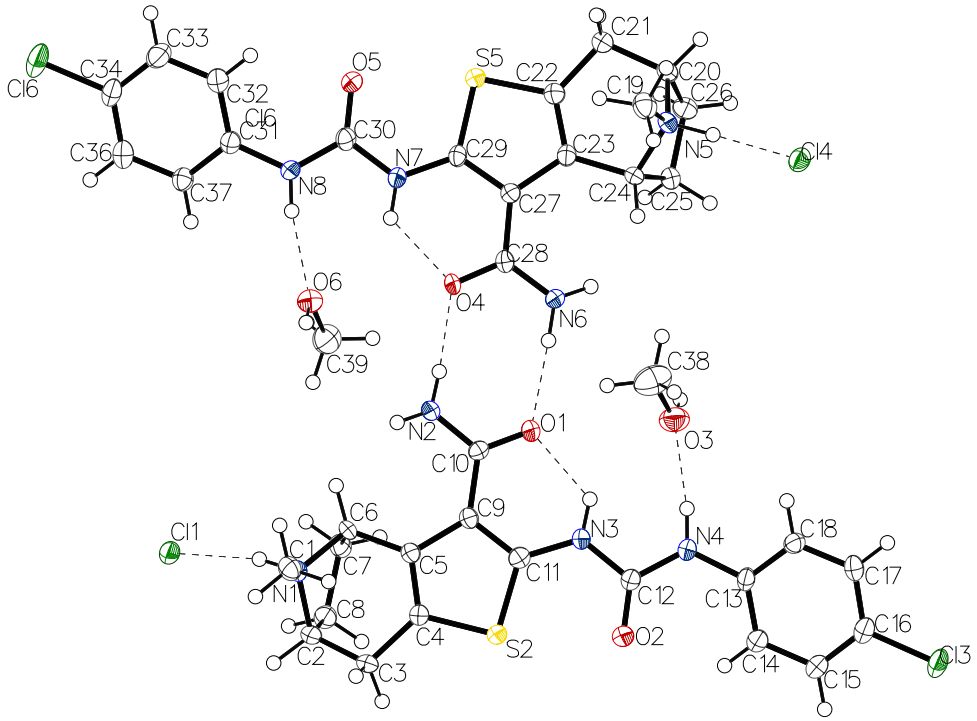


Figure S2.

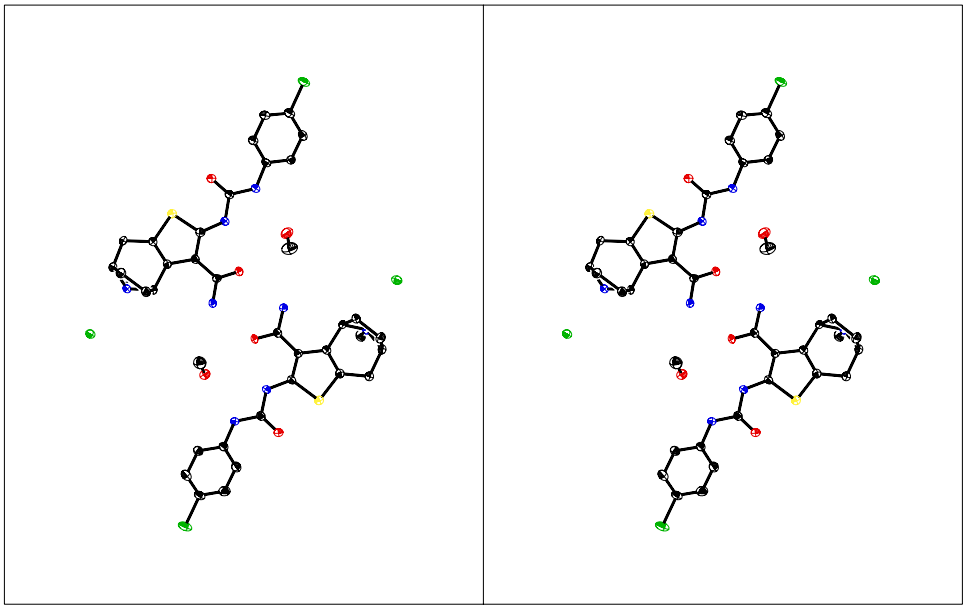


Figure S3. A Stereo view of **ORC-13661 HCl**

Table S2. Crystal data and structure refinement for **90** (ORC-13661.)

Identification code	ORC-13661	
Empirical formula	$C_{19}H_{24}Cl_2N_4O_3S$	
Formula weight	459.38	
Temperature	93(2) K	
Wavelength	1.54187 Å	
Crystal system	Monoclinic	
Space group	*I* 2	
Unit cell dimensions	a = 17.551(12) Å	α = 90°
	b = 12.5203(4) Å	β = 111.33(5)°
	c = 21.614(14) Å	γ = 90°
Volume	4424(4) $Å^3$	
Z	8	
Density (calculated)	1.379 mg/m^3	
Absorption coefficient	3.757 mm^{-1}	
F(000)	1920	
Crystal size	0.150 x 0.150 x 0.080 mm^3	
Θ range for data collection	2.794 to 68.159°.	
Index ranges	$-21 \le h \le 21$, $-15 \le k \le 15$, $-26 \le l \le 26$	
Reflections collected	74485	
Independent reflections	8030 [R(int) = 0.0510]	
Completeness to θ = 67.687°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.753 and 0.631	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	8030 / 1 / 562	
Goodness-of-fit on F^2	1.075	
Final R indices [I>2σ(I)]	R1 = 0.0296, wR2 = 0.0697	
R indices (all data)	R1 = 0.0336, wR2 = 0.0725	
Absolute structure parameter	0.020(5)	
Largest diff. peak and hole	0.193 and -0.251 $e.Å^{-3}$	

Supporting Information 5: Non-interference in Antimicrobial Activity of Aminoglycoside Antibiotics (AGAs) *in vitro*[1, 2]

Fractional Inhibitory Concentration (FIC) test of each of the three compounds against four strains of *P. aeruginosa* at Micromyx in Kalamazoo Michigan and the H37Rv strain of *M. tuberculosis* at Dr. Eric Nuermberger's laboratory at Johns Hopkins Medical Center, Baltimore Maryland.

Differing concentrations of the compounds were tested along with serial dilutions of the AGs to determine the Mean Inhibitory Concentration (MIC) of the AGA against each bacterial strain to evaluate synergy, interference or indifference. Table S5-1 displays the summary results of one compound (**90**, ORC-13661) in a FIC test against five strains of *P. aeruginosa* using four different AGAs. For each AG, and each test compound, the FIC index (FICI) was calculated:

FICI = FIC-AG/MIC-AG+ FIC-test/MIC-test

Results were similar for each of the three compounds and all showed an "indifference" of the MIC to the presence of our compounds. Table S5-2 shows results of the MICs tests with mycobacterium TB and Amikacin.

Table S4. Fractional Inhibitory Concentration of **90** (ORC-13661) for four AGs against five strains of P. aeruginosa. (The FICI between 0.6 and 2.0 show indifference, i.e. no synergy, no interference)

ORC-13661		**Mean FICI**				
Aminoglycoside	Mean FICI Range	***P. aeruginosa* 103 ATCC 27853**	***P. aeruginosa* 6160**	***P. aeruginosa* 6322 (AG resistant)**	***P. aeruginosa* 6325**	***P. aeruginosa* 6471**
Tobramycin	0.70-1.28	1.14	0.70	NA	1.28	0.86
Amikacin	0.71-1.14	1.07	0.71	NA	1.14	1.14
Kanamycin	0.93-2.00	NA	0.93	NA	1.43	2.00
Neomycin	0.93-1.43	1.28	1.00	0.93	1.43	1.43

Table S5. Mean Inhibitory Concentration test: Mtb H37Rv at 1 or 10 uM in complete 7H9 broth medium.

	Nothing	ORC-4471		ORC-4572		ORC-13661	
		1 µM	10 µM	1 µM	10 µM	1 µM	10 µM
Nothing	+++/+++	+++/+++	++/++	+++/+++	++/+++	+++/+++	+++/+++
Amikacin - 0.5 µg/ml	+-/0						
Amikacin - 1.0 µg/ml	0/0	0/0	0/0	0/0	0/0	0/0	0/0

* All samples were prepared in 7H9 media w/10% OADC – no Tween and run in duplicate.
(+/ -) questionable clumps**; (0)** no visible growth; **(+ , ++, +++)** visible growth

Experimental Section:

ADMET characterization

Compounds **1** and **90** were characterized by Pharmaron Inc. using established protocols. Half-life was calculated from serial measurements of drug concentration by LC/MS. The area under the serum concentration-time curve (AUC) was calculated by noncompartmental analysis using WinNonlin Version 4.0 (Pharsight, Mountain View, CA.).

hERG inhibition[3, 4]

Compounds were evaluated for hERG inhibition by Ricerca Inc. using HEK-293 cells expressing human hERG (K_v11.1). Compound effects on the peak tail current using voltage-clamped cells using PatchExpress 7000A instrument. Compounds were incubated with cells until a steady state level current was reached. After the final compound concentration was tested, the test compound was washed out and a positive control (10 μM cisapride) was tested. IC_{50} values were determined based of current responses analyzed using nonlinear regression to fit data to a one-site dose-response model using MathIQ software (AIM).

In vitro toxicity[5, 6]

Toxicity of compounds was evaluated using HepG2 cells grown in culture. Cells were treated with test compounds over a range of concentrations for 72 hours. 24 hours after drug removal, cell viability was determined using CellTiterGlo (Promega Corp.).

General Chemistry Procedures.

All reactions were performed under a dry atmosphere of nitrogen unless otherwise specified. Indicated reaction temperatures refer to the reaction bath, while room temperature (rt) is noted as 25 ºC. Commercial grade reagents and anhydrous solvents were used as received from vendors and no attempts were made to purify or dry these components further. Removal of solvents under reduced pressure was accomplished with a Buchi rotary evaporator at approximately 28 mm Hg pressure using a Teflon-linked KNF vacuum pump. Thin layer chromatography was performed using either 1" x 3" AnalTech No. 02521 or Merck 60 F254 silica gel plates with fluorescent indicator using appropriate solvent mixtures. Visualization of TLC plates was made by observation with either short wave UV light (254 nm lamp), 10% phosphomolybdic acid in ethanol or in iodine vapors. Medium pressure Flash column chromatography was carried out using either a Teledyne Isco CombiFlash Companion Unit with RediSep Rf silica gel columns or a Biotage Isolera with SiliCycle HP cartridges. Proton NMR spectra were obtained either on 300 MHz Bruker Nuclear Magnetic Resonance Spectrometer or 500 MHz Bruker Nuclear Magnetic Resonance Spectrometer and chemical shifts (δ) are reported in parts per million (ppm) and coupling constant (*J*) values are given in Hz, with the following spectral pattern designations: s, singlet; d, doublet; t, triplet, q, quartet; dd, doublet of doublets; m, multiplet; br, broad singlet; sym, symmetrical. Tetramethylsilane (TMS) was used as an internal reference. Melting points are uncorrected and were obtained using a MEL-TEMP Electrothermal melting point apparatus. Mass spectroscopic analyses were performed either using positive mode electron spray ionization (ESI) on a Varian ProStar LC-MS with a 1200L quadrupole mass spectrometer

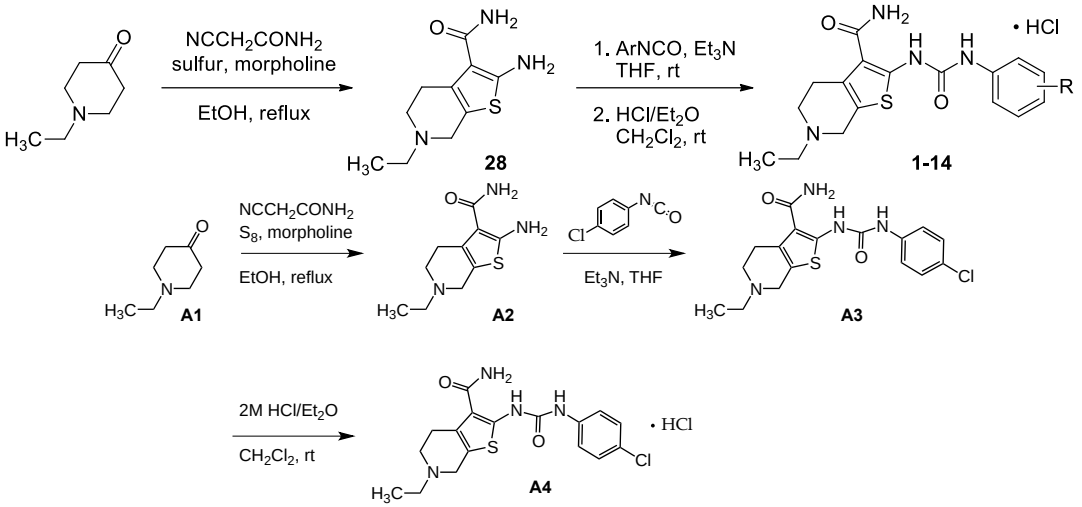
or using positive mode atmospheric pressure chemical ionization (APCI) on a Shimadzu LC-MS system. High performance liquid chromatography (HPLC) purity analysis was conducted using a Varian Pro Star HPLC system with a binary solvent system A and B using a gradient elution [A, H_2O with 0.1% trifluoroacetic acid (TFA); B, CH_3CN with 0.1% TFA] and flow rate = 1 mL/min, with UV detection at 254 nm. All final compounds were purified to ≥95% purity and these purity levels were measured by a Varian Pro Star HPLC system. Three different Varian Pro Star HPLC methods were used to establish compound purity. HPLC Method A: Phenomenex Luna C18(2) column (4.6 × 250 mm); mobile phase, A = H_2O with 0.1% TFA and B = CH_3CN with 0.1% TFA; gradient 10–95% B (0.0–10 min; hold for 6 min); UV detection at 254 nm. HPLC Method B: SunFire C18 column (4.6 × 250 mm); mobile phase, A = H_2O with 0.1% TFA and B = CH_3CN with 0.1% TFA; gradient: 10–100% B (0.0–20 min; hold for 5 min); UV detection at 254 nm. HPLC Method C: SunFire C18 column (4.6 × 250 mm); mobile phase, A = H_2O with 0.1% TFA and B = CH_3CN with 0.1% TFA; gradient: 0–100% B (0.0–15 min; hold for 5 min)); UV detection at 254 nm.

Experimental Methods

Compounds **9**, **12-13**, **15**, **27**, **34-39** and **46-48** were purchased from commercial vendors. Identity and purity were confirmed ≥95% by HPLC-MS.

Synthesis of compounds.

Scheme 1



Preparation of 2-[3-(4-Chloro-3-methylphenyl)ureido]-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (A4, 1, ORC-001).

Step One. 2-Amino-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide (A2, 28 in Table 3). A stirred mixture of N-ethyl-4-pyrrolidinone (**A1**, 22.7 g, 178 mmol), 2-cyanoacetamide (16.5 g, 197 mmol), sulphur (6.87 g, 215 mmol) and morpholine (31.5 g, 362 mmol) in ethanol (350 mL) was heated to reflux under nitrogen for 5 h. After this time, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was mixed with saturated aqueous sodium bicarbonate (200 mL), water (200 mL). The aqueous mixture was extracted with methylene chloride (5 × 200 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was triturated with cold methanol (30 mL) and filtered. The filter cake was washed with cold methanol (2 × 10 mL) and then dried under reduced pressure to provide compound **A2** (**28** in Table 3)as a yellow solid (21.7 g, 54%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.98 (s, 2H), 6.52 (bs, 2H), 3.29 (s, 2H), 2.66 (d, J = 4.8 Hz, 2H), 2.60 (d, J = 4.8 Hz, 2H), 2.46 (q, J = 7.2 Hz, 2H), 1.04 (t, J = 7.2 Hz, 3H); LRMS *m/z* 226 $[M+H]^+$.

Step Two. 2-[3-(4-Chlorophenyl)ureido]-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide (A3). To the stirred solution of compound **A2** (450 mg, 2.00 mmol) in anhydrous tetrahydrofuran (10 mL) at room temperature under nitrogen was

added a solution of 4-chlorophenyl isocyanate (400 mg, 2.40 mmol) in anhydrous methylene chloride (6 mL) dropwise over 3 min. Then the reaction mixture was stirred overnight at room temperature. The reaction mixture was filtered. The filter cake was washed with methylene chloride (5 mL) and then dried under reduced pressure to provide the product **A3** as a white solid (301 mg, 38%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.94 (s, 1H), 10.12 (s, 1H), 7.52–7.45 (m, 4H), 7.34 (d, *J* = 9.0 Hz, 2H), 3.45 (s, 2H), 2.77 (d, *J* = 4.8 Hz, 2H), 2.65 (d, *J* = 4.8 Hz, 2H), 2.55–2.45 (m, 2H), 1.07 (t, *J* = 6.6 Hz, 3H).

Step Three. 2-[3-(4-Chlorophenyl)ureido]-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (A4, ORC-001, 1 in Table 1). To the stirred mixture of compound **A3 (**157 mg, 0.400 mmol) in methylene chloride (50 mL) at room temperature was added hydrochloric acid (2 M in diethyl ether, 0.300 mL, 0.600 mmol). After addition, the mixture was concentrated under reduced pressure. The resulting solid was triturated with methylene chloride and filtered to afford compound **A4** (**1** in Table 1) as yellow solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.94 (s, 1H), 10.84 (bs, 1H), 10.22 (s, 1H), 7.75–6.90 (m, 6H), 4.49 (d, *J* = 14.5 Hz, 1H), 4.22–4.16 (m, 1H), 3.65–3.62 (m, 1H), 3.38–3.05 (m, 5H), 1.32 (t, *J* = 7.2 Hz, 3H); LRMS *m/z* 379 $[M+H]^+$.

Compounds Prepared by Scheme 1

2-[3-(4-Bromophenyl)ureido]-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (2 in Table 1**).** ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.96 (s, 1H), 10.44 (bs, 1H), 10.28 (s, 1H), 7.46 (s, 4H), 4.62-4.44 (m, 1H), 4.28–4.12 (m, 1H), 3.73–3.59 (m, 1H), 3.31–3.16 (m, 3H), 3.15–3.00 (m, 2H), 1.30 (t, *J*=7.0 Hz, 3H); LRMS *m/z* 423 $[M+H]^+$.

6-Ethyl-2-{[(4-iodophenyl)carbamoyl]amino}-4*H*,5*H*,6*H*,7*H*-thieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (3 in Table 1**).** ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.95 (s, 1H), 10.16 (s, 1H), 7.60 (d, *J*=8.8 Hz, 2H), 7.32 (d, *J*=8.8Hz, 2H), 3.61-3.39 (m, 2H), 2.88–2.63 (m, 4H), 2.61–2.45 (m, 2H), 1.08 (t, *J*=7.1Hz, 3H); LRMS *m/z* 471 $[M+H]^+$.

2-{[(2,4-Dichlorophenyl)carbamoyl]amino}-6-ethyl-4*H*,5*H*,6*H*,7*H*-thieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (4 in Table 1**).** ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.95 (s, 1H), 10.16 (s, 1H), 7.58 (m, 2H), 7.42 (s, 1H), 7.67-7.31 (m, 4H), 3.61-3.39 (m, 2H), 2.88–2.63 (m, 4H), 2.61–2.45 (m, 2H), 1.08 (t, *J*=7.1 Hz, 2H); LRMS *m/z* 413 $[M+H]^+$.

6-Ethyl-2-{[(naphthalen-2-yl)carbamoyl]amino}-4*H*,5*H*,6*H*,7*H*-thieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (6 in Table 1**).** ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.00 (s, 1H), 10.26 (s, 1H), 8.78-8.18 (s, 1H), 7.87-7.74 (m, 3H), 7.67-7.31 (m, 4H), 3.31-3.41 (m, 2H), 2.83–2.72 (m, 7H), 2.70–2.60 (m, 2H), 2.58–2.48 (m, 2H), 1.08 (t, *J*=7.1 Hz, 2H); LRMS *m/z* 395 $[M+H]^+$.

2-[({[1,1'-Biphenyl]-4-yl}carbamoyl)amino]-6-ethyl-4*H*,5*H*,6*H*,7*H*-thieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (7 in Table 1**).** ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.63-7.53 (m, 6H), 7.41 (t, *J*= 7.3 Hz, 2H), 7.29 (t, *J*= 7.3 Hz, 1H), 3.63 (bs, 2H),

2.67 (q, *J*= 7.2 Hz, 2H), 1.21 (t, *J*= 7.2 Hz, 3H); LRMS *m/z* 421 $[M+H]^+$.

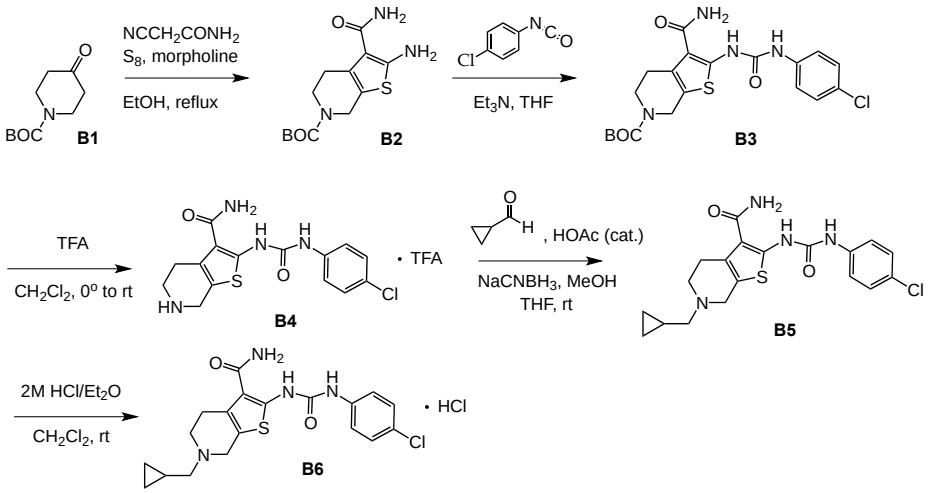
6-Ethyl-2-[3-(4-(trifluoromethyl)phenyl)ureido]-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (8 in Table 1**).** ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.04 (s, 1H), 10.85 (bs, 1H), 10.60 (s, 1H), 8.15–6.90 (m, 6H), 4.60–4.46 (m, 1H), 4.26–4.15 (m, 1H), 3.67–3.60 (m, 1H), 3.49–3.00 (m, 5H), 1.32 (t, *J* = 7.2 Hz, 3H); MS *m/z* 413 $[M+H]^+$.

2-{[(Phenyl)carbamoyl]amino}-6-ethyl-4*H*,5*H*,6*H*,7*H*-thieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (14 in Table 1**).** ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.95 (s, 1H), 10.16 (s, 1H), 7.58 (m, 2H), 7.42 (s, 1H), 7.67-7.31 (m, 4H), 3.61-3.39 (m, 2H), 2.88–2.63 (m, 4H), 2.61–2.45 (m, 2H), 1.08 (t, *J*=7.1 Hz, 2H); LRMS *m/z* 345 $[M+H]^+$.

2-[3-({4-Chlorophenyl)carbamothioyl}-amino]-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (A4, 26 in Table 3**).** ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.9 (s, 1H), 10.85 (bs, 1H), 10.22 (s, 1H), 7.75–6.90 (m, 6H), 4.50 (d, *J* = 14.5 Hz, 1H), 4.22–4.18 (m, 1H), 3.65–3.62 (m, 1H), 3.38–3.05 (m, 5H), 1.32 (t, *J* = 7.2 Hz, 3H); LRMS *m/z* 395 $[M+H]^+$.

6-Ethyl-2-[(phenylcarbamoyl)amino]-4*H*,5*H*,7*H*-thieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (32 in Table 3**).** ^{1}H NMR (300 MHz, MeOH-d_4) δ 8.01-7.93 (m, 2H), 7.68-7.61 (m, 3H), 3.72 (bs, 2H), 2.94 (dd, *J*= 14.2, 4.8 Hz, 4H), 2.72 (q, *J*= 7.2, 2H), 1.23 (t, *J*= 7.2 Hz, 3H); LRMS *m/z* 330 $[M+H]^+$.

Scheme 2



Preparation of 2-[3-(4-Chlorophenyl)ureido]-6-(cyclopropylmethyl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (B6, 53 in Table 6).

Step One. *tert*-Butyl 2-Amino-3-carbamoyl-4,5-dihydrothieno[2,3-*c*]pyridine-6(7*H*)-carboxylate (B2). A suspension of cyanoacetamide (4.65 g, 55.3 mmol), *tert*-butyl 4-oxopiperidine-1-carboxylate (**B1**, 10.0 g, 50.3 mmol), sulfur (1.92 g, 59.9 mmol), and

morpholine (8.71 mL, 100 mmol) in ethanol (50 mL) was heated to reflux for 4 h and then cooled to room temperature. The reaction mixture was concentrated under reduced pressure. The resulting residue was triturated with a 1:1 mixture of methylene chloride and ethyl acetate to afford compound **B2** as a light orange solid (14.2 g, 95%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.98 (bs, 2H), 6.60 (bs, 2H), 4.27 (bs, 2H), 3.55–3.48 (m, 2H), 2.71–2.67 (m, 2H), 1.42 (s, 9H); LRMS *m/z* 298 $[M+H]^+$.

Step Two. *tert*-Butyl 3-Carbamoyl-2-[3-(4-chlorophenyl)ureido]-4,5-dihydrothieno[2,3-*c*]pyridine-6(7*H*)-carboxylate (B3, 59 in Table 6). A solution of 4-chlorophenyl isocyanate (11.1 g, 72.3 mmol), compound **B2** (19.5 g, 65.6 mmol), and triethylamine (12.0 mL, 86.1 mmol) in anhydrous tetrahydrofuran (150 mL) was stirred at room temperature for 16 h. After this time, the reaction mixture was concentrated under reduced pressure. The resulting residue was triturated with a mixture of 1:1 methylene chloride and ethyl acetate to afford compound **B3** (**59** in Table 6) as an off-white solid (25.3 g, 86%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.85 (s, 1H), 10.20 (s, 1H), 7.52–7.45 (m, 3H), 7.34 (d, J = 9.0 Hz, 2H), 6.94 (bs, 1H), 4.43 (s, 2H), 3.57–3.53 (m, 2H), 2.79–2.75 (m, 2H), 1.43 (s, 9H); LRMS *m/z* 473 $[M+Na]^+$.

Step Three. 2-[3-(4-Chlorophenyl)ureido]-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide Trifluoroacetate (B4, 40 in Table 5). To a solution of compound **B3** (**59**, 16.0 g, 35.5 mmol) in methylene chloride (100 mL) was added trifluoroacetic acid (30.0 mL, 392 mmol) dropwise over 5 min at 0 °C. After the addition complete, the reaction mixture was warmed to room temperature and stirred for 4 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was triturated with ethyl acetate (75 mL) to afford compound **B4** (**40** in Table 5) as an off-white solid (16.5 g, quantitative yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.97 (s, 1H), 10.24 (s, 1H), 9.17 (bs, 2H), 7.60–7.12 (m, 6H), 4.25 (s, 2H), 3.37–3.34 (m, 2H), 3.01–2.98 (m, 2H); LRMS *m/z* 351 $[M+H]^+$.

Step Four. 2-[3-(4-Chlorophenyl)ureido]-6-(cyclopropylmethyl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide (B5). To a slurry of compound **B4** (300 mg, 0.645 mmol) in methanol (4 mL) and tetrahydrofuran (2 mL) two drops of glacial acetic acid and cyclopropanecarbaldehyde (94.0 mg, 1.34 mmol) were added. After stirring at room temperature for 5 min, sodium cyanoborohydride (122 mg, 1.94 mmol) was added and the reaction mixture was stirred for an additional 3 h. After this time, the reaction was quenched with water (25 mL) and saturated aqueous sodium bicarbonate (50 mL). The resulting mixture was extracted with ethyl acetate (100 mL). The extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was triturated with methylene chloride to afford compound **B5** as a white solid (245 mg, 94%): ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.95 (s, 1H), 10.16 (s, 1H), 7.54–7.40 (m, 3H), 7.33 (d, J = 9.0 Hz, 2H), 6.83 (bs, 1H), 3.54 (s, 2H), 2.84–2.78 (m, 2H), 2.78–2.69 (m, 2H), 2.36 (s, 2H), 0.95–0.87 (m, 1H), 0.53–0.45 (m, 2H), 0.17–0.09 (m, 2H); LRMS *m/z* 405 $[M+H]^+$.

Step Five. 2-[3-(4-Chlorophenyl)ureido]-6-(cyclopropylmethyl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (B6, 53 in Table 6). To a solution of compound **A5** (121 mg, 0.299 mmol) in tetrahydrofuran (5 mL) was added hydrochloric acid (2 M in diethyl ether, 0.200 mL, 0.400 mmol). After stirring at room temperature for 15 min, the reaction mixture was concentrated under reduced pressure and the resulting residue was triturated with methylene chloride to afford compound **B6** (**53** in Table 6) as a yellow solid (94 mg, 71%): ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.97 (s, 1H), 10.28 (bs, 1H), 10.26 (s, 1H), 7.55–7.48 (m, 3H), 7.35 (d, J = 9.0 Hz, 2H), 7.14 (bs, 1H), 4.61–4.57 (m, 1H), 4.31–4.28 (m, 1H), 3.72–3.70 (m, 1H), 3.39–3.36 (m, 1H), 3.22–3.19 (m, 1H), 3.11–3.08 (m, 3H), 1.19–1.11 (m, 1H), 0.70–0.63 (m, 2H), 0.45–0.39 (m, 2H); LRMS *m/z* 405 $[M+H]^+$.

Compounds Prepared by Scheme 2

2-[3-(4-Chlorophenyl)ureido]-5-ethyl-5,6-dihydro-4*H*-thieno[2,3-*c*]pyrrole-3-carboxamide Hydrochloride (42 in Table 5). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.99 (s, 1H), 11.27 (s, 1H), 10.39 (s, 1H), 7.70–6.80 (m, 6H), 4.88–4.38 (m, 4H), 3.40–3.38 (m, 2H), 1.31 (t, J = 7.1 Hz, 3H); LRMS *m/z* 365 $[M+H]^+$.

2-[3-(4-Chlorophenyl)ureido]-6-n-propyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (49 in Table 6). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.94 (s, 1H), 10.84 (bs, 1H), 10.22 (s, 1H), 7.75–6.90 (m, 6H), 4.49 (d, J = 14.5 Hz, 1H), 4.22–4.16 (m, 1H), 3.65–3.62 (m, 1H), 3.38–3.05 (m, 7H), 1.32 (t, J = 7.2 Hz, 3H); LRMS *m/z* 393 $[M+H]^+$.

2-[3-(4-Chlorophenyl)ureido]-6-isobutyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (50 in Table 6). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.95 (s, 1H), 10.27 (s, 1H), 9.98 (bs, 1H), 7.90–6.80 (m, 6H), 4.55–3.63 (m, 3H), 3.20–3.00 (m, 4H), 2.63–2.15 (m, 2H), 1.00 (bs, 6H); LRMS *m/z* 407 $[M+H]^+$.

2-[3-(4-Chlorophenyl)ureido]-6-neopentyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (51 in Table 6). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.92 (s, 1H), 10.27 (s, 1H), 9.85 (bs, 1H), 7.80–6.90 (m, 6H), 4.56–4.29 (m, 2H), 3.57–3.42 (m, 2H), 3.24–2.97 (m, 4H), 1.10 (s, 9H); LRMS *m/z* 421 $[M+H]^+$.

2-[3-(4-Chlorophenyl)ureido]-6-isopropyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (52 in Table 6). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.03 (s, 1H), 10.28 (s, 1H), 10.25 (bs, 1H), 7.55–7.02 (m, 6H), 4.43–4.39 (m, 1H), 4.36–4.28 (m, 1H), 3.71–3.61 (m, 2H), 3.30–3.04 (m, 3H), 1.36–1.32 (m, 6H); LRMS *m/z* 393 $[M+H]^+$.

2-[3-(4-Chlorophenyl)ureido]-6-(cyclobutylmethyl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (54 in Table 6). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.95 (s, 1H), 10.34 (bs, 1H), 10.26 (s, 1H), 7.77–6.94 (m, 6H), 4.47–4.38 (m, 1H), 4.23–4.11 (m, 1H), 3.65–3.54 (m, 1H), 3.31–3.21 (m, 3H), 3.13–3.04 (m, 2H), 2.87–2.78 (m, 1H), 2.19–2.07 (m, 2H), 1.95–1.78 (m, 4H); LRMS *m/z* 419 $[M+H]^+$.

2-[3-(4-Chlorophenyl)ureido]-6-(cyclopentylmethyl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (55 in Table 6). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.95 (s, 1H), 10.27 (s, 1H), 10.14 (bs, 1H), 7.73–6.98 (m, 6H), 4.57–4.53 (m, 1H), 4.30–4.22 (m, 1H), 3.70–3.61 (m, 1H), 3.33–3.07 (m, 5H), 2.38–2.27 (m, 1H), 1.91–1.83 (m, 2H), 1.68–1.52 (m, 4H), 1.32–1.20 (m, 2H); LRMS *m/z* 433 $[M+H]^+$.

2-[3-(4-Chlorophenyl)ureido]-6-(cyclohexylmethyl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (56 in Table 6). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.94 (s, 1H), 10.27 (s, 1H), 10.15 (bs, 1H), 7.70–7.00 (m, 6H), 4.58–4.53 (m, 1H), 4.25–4.22 (m, 1H), 3.66–3.59 (m, 1H), 3.43–3.31 (m, 1H), 3.12–3.00 (m, 4H), 1.90–1.60 (m, 6H), 1.33–1.11 (m, 3H), 1.02–0.92 (m, 2H); LRMS *m/z* 447 $[M+H]^+$.

2-[3-(4-Chlorophenyl)ureido]-6-(3-methoxypropyl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (57 in Table 6). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.95 (s, 1H), 10.30 (bs, 1H), 10.26 (s, 1H), 7.70–7.00 (m, 6H), 4.57–4.53 (m, 1H), 4.26–4.22 (m, 1H), 3.71–3.62(m, 1H), 3.48–3.40 (m, 2H), 3.28–3.20 (m, 6H), 3.13–3.06 (m, 2H), 2.04–1.96 (m, 2H); LRMS *m/z* 423 $[M+H]^+$.

2-[3-(4-Chlorophenyl)ureido]-6-(tetrahydro-2*H*-pyran-4-yl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (58 in Table 6). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.00 (s, 1H), 10.41 (bs, 1H), 10.27 (s, 1H), 7.72–7.30 (m, 5H), 7.11 (bs, 1H), 4.51–4.47 (m, 1H), 4.39–4.33 (m, 1H), 4.04–3.96 (m, 2H), 3.81–3.75 (m, 1H), 3.59–3.51 (m, 1H), 3.40–3.35 (m, 2H), 3.32–3.28 (m, 1H), 3.17–3.09 (m, 2H), 2.12–2.09 (m, 1H), 2.07–1.98 (m, 1H), 1.83–1.72 (m, 2H); LRMS *m/z* 435 $[M+H]^+$.

***tert*-Butyl 4-{3-Carbamoyl-2-[3-(4-chlorophenyl)ureido]-4,5-dihydrothieno[2,3-*c*]pyridin-6(7*H*)-yl}acetate (60 in Table 6).** ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.96 (s, 1H), 10.18 (s, 1H), 7.63–6.81 (m, 6H), 3.52–3.41 (m, 2H), 2.85–2.72 (m, 2H), 2.71–2.63 (m, 2H), 2.50–2.41 (m, 2H), 2.29–2.19 (m, 2H), 1.37 (s, 9H); LRMS *m/z* 465 $[M+H]^+$.

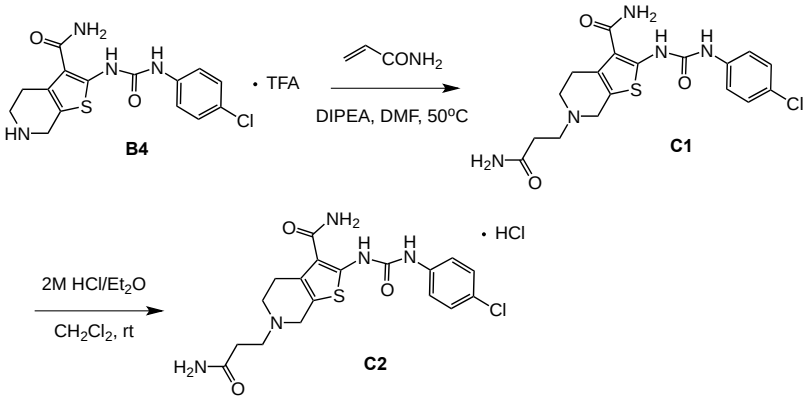
***tert*-Butyl 4-{3-Carbamoyl-2-[3-(4-chlorophenyl)ureido]-4,5-dihydrothieno[2,3-*c*]pyridin-6(7*H*)-yl}butanoate (62 in Table 6).** ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.96 (s, 1H), 10.18 (s, 1H), 7.63–6.70 (m, 6H), 3.52–3.41 (m, 2H), 2.85–2.72 (m, 2H), 2.71–2.61 (m, 2H), 2.50–2.40 (m, 2H), 2.29–2.19 (m, 2H), 1.81–1.67 (m, 2H), 1.39 (s, 9H); LRMS *m/z* 493 $[M+H]^+$.

***tert*-Butyl 5-{3-Carbamoyl-2-[3-(4-chlorophenyl)ureido]-4,5-dihydrothieno[2,3-*c*]pyridin-6(7*H*)-yl}pentanoate (63 in Table 6).** ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.94 (s, 1H), 10.17 (s, 1H), 7.61–7.29 (m, 5H), 6.84 (bs, 1H), 3.50–3.40 (m, 2H), 2.82–2.74 (m, 2H), 2.68–2.59 (m, 2H), 2.47–2.40 (m, 2H), 2.25–2.19 (m, 2H), 1.57–1.48 (m, 4H), 1.40 (s, 9H); LRMS *m/z* 507 $[M+H]^+$.

***tert*-Butyl 6-{3-Carbamoyl-2-[3-(4-chlorophenyl)ureido]-4,5-dihydrothieno[2,3-*c*]pyridin-6(7*H*)-yl}hexanoate (64 in Table 6).** ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.95 (s, 1H), 10.19 (s, 1H), 7.70–7.30 (m, 5H), 6.89 (bs, 1H), 3.68–3.40 (m, 3H), 2.93–2.70

(m, 3H), 2.52–2.48 (m, 2H), 2.23–2.17 (m, 2H), 1.66–1.49 (m, 4H), 1.40 (s, 9H), 1.35–1.28 (m, 2H); LRMS *m/z* 521 $[M+H]^+$.

Scheme 3



Preparation of 6-(3-Amino-3-oxopropyl)-2-[3-(4-chlorophenyl)ureido]-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (C2).

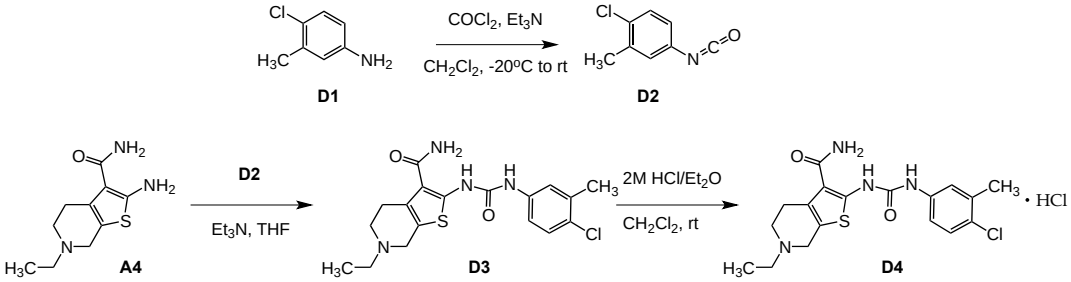
Step One. 6-(3-Amino-3-oxopropyl)-2-[3-(4-chlorophenyl)ureido]-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide (C1). A solution of compound **B4** (200 mg, 0.431 mmol), acrylamide (156 mg, 2.19 mmol), and diisopropylethylamine (0.400 mL, 2.25 mmol) in *N*,*N*-dimethylformamide (2.5 mL) was heated at 50 °C for 8 h. After this time, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluting with 0% to 10% methanol/methylene chloride to afford compound **C1** as a yellow solid (180 mg, 99%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.95 (s, 1H), 10.19 (s, 1H), 7.59–7.29 (m, 6H), 6.90–6.73 (m, 2H), 3.48 (s, 2H), 2.83–2.65 (m, 6H), 2.33–2.25 (m, 2H); LRMS *m/z* 422 $[M+H]^+$.

Step Two. 6-(3-Amino-3-oxopropyl)-2-[3-(4-chlorophenyl)ureido]-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (C2). To a solution of compound **C1** (90.0 mg, 0.210 mmol) in tetrahydrofuran (2.5 mL) and methanol (2.5 mL) was added hydrochloric acid (2 M in diethyl ether, 0.140 mL, 0.280 mmol). After stirring at room temperature for 30 min, the reaction mixture was concentrated under reduced pressure and the resulting residue was triturated with methylene chloride to afford compound **C2** as a yellow solid (95 mg, 99%): ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.94 (s, 1H), 10.55 (bs, 1H), 10.27 (s, 1H), 7.62 (bs, 1H), 7.55–7.30 (m, 5H), 7.19–7.02 (m, 2H), 4.52–4.48 (m, 1H), 4.28–4.25 (m, 1H), 3.68–3.60 (m, 1H), 3.49–3.42 (m, 3H), 3.13–3.08 (m, 2H), 2.74–2.67 (m, 2H); LRMS *m/z* 422 $[M+H]^+$.

Compounds Prepared by Scheme 3

***tert*-Butyl 3-{3-Carbamoyl-2-[3-(4-chlorophenyl)ureido]-4,5-dihydrothieno[2,3-*c*]pyridin-6(7*H*)-yl}propanoate Hydrochloride (61 in Table 6).** ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.96 (s, 1H), 10.16 (s, 1H), 7.62–7.28 (m, 5H), 6.83 (bs, 1H), 3.49 (s, 2H), 2.80–2.63 (m, 6H), 2.47–2.41 (m, 2H), 1.40 (s, 9H); LRMS *m/z* 479 $[M+H]^+$.

Scheme 4



Preparation of 2-[3-(4-Chloro-3-methylphenyl)ureido]-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (D4).

Step One. 1-Chloro-4-isocyanato-2-methylbenzene (D2). To the stirred mixture of 4-chloro-3-methylaniline (**D1**, 1.01 g, 7.13 mmol) and triethylamine (866 mg, 8.56 mmol) in methylene chloride (20 mL) at –20 °C under nitrogen was added phosgene solution (0.15 weight/weight in toluene, 6.15 g, 9.13 mmol) dropwise over 5 min. After addition, the reaction mixture was warmed up to room temperature over 2 h, and then stirred at room temperature for another 2 h. After this time, the reaction mixture was cooled to 0 °C, and slowly quenched with saturated aqueous sodium bicarbonate (30 mL). The mixture was extracted with ethyl acetate (100 mL). The organic extract was washed with 2 M hydrochloric acid (50 mL), brine (30 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The resulting residue was triturated with methylene chloride (40 mL) and filtered. The filtrate was concentrated under reduced pressure to provide compound **D2** as a light brown liquid (1.08 g, 90%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 8.4 Hz, 1H), 6.97 (d, J = 2.4 Hz, 1H), 6.88–6.84 (m, 1H), 2.34 (s, 3H).

Step Two. 2-[3-(4-Chloro-3-methylphenyl)ureido]-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide (D3). To the stirred solution of compound **A4** (450 mg, 2.00 mmol) in anhydrous tetrahydrofuran (10 mL) at room temperature under nitrogen was added a solution of compound **D2** (402 mg, 2.40 mmol) in anhydrous methylene chloride (6 mL) dropwise over 3 min. Then the reaction mixture was stirred overnight at room temperature. The reaction mixture was filtered. The filter cake was washed with methylene chloride (5 mL) and then dried under reduced pressure to provide compound **D3** as a white solid (301 mg, 38%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.94 (s, 1H), 10.12 (s, 1H), 7.48–6.75 (m, 5H), 3.45 (s, 2H), 2.77 (d, J = 4.8 Hz, 2H), 2.65 (d, J = 4.8 Hz, 2H), 2.55–2.45 (m, 2H), 2.30 (s, 3H), 1.07 (t, J = 6.6 Hz, 3H).

Step Four. 2-[3-(4-Chloro-3-methylphenyl)ureido]-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (D4). To the stirred mixture of compound **D3** (157 mg, 0.400 mmol) in methylene chloride (50 mL) at room temperature was added hydrochloric acid (2 M in diethyl ether, 0.300 mL, 0.600 mmol). After addition, the mixture was concentrated under reduced pressure. The resulting solid was triturated with methylene chloride and filtered to afford compound **D4** as yellow solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.94 (s, 1H), 10.84 (bs, 1H), 10.22 (s, 1H), 7.75–6.90 (m, 5H), 4.49 (d, J = 14.5 Hz, 1H), 4.22–4.16 (m, 1H), 3.65–3.62 (m, 1H), 3.38–3.05 (m, 5H), 2.30 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H); LRMS *m/z* 393 $[M+H]^+$.

Compounds Prepared by Scheme 4

2-[3-(2,3-Dichlorophenyl)ureido]-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (5 in Table 1). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.88 (s, 1H), 10.59 (bs, 1H), 9.84 (s, 1H), 7.88 (dd, J = 7.8 and 1.8 Hz, 1H), 7.75–7.15 (m, 4H), 4.54–4.48 (m, 1H), 4.24–4.15 (m, 1H), 3.68–3.62 (m, 1H), 3.34–3.13 (m, 3H), 3.06 (bs, 2H), 1.31 (t, J = 7.2 Hz, 3H); LRMS *m/z* 413 $[M+H]^+$.

2-[3-(3-Cyanophenyl)ureido]-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (10 in Table 1). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.06 (s, 1H), 10.78 (bs, 1H), 10.56 (s, 1H), 7.99 (s, 1H), 7.88–6.85 (m, 5H), 4.55–4.46 (m, 1H), 4.25–4.15 (m, 1H), 3.68–3.62 (m, 1H), 3.32–3.00 (m, 5H), 1.32 (t, J = 7.2 Hz, 3H); LRMS *m/z* 370 $[M+H]^+$.

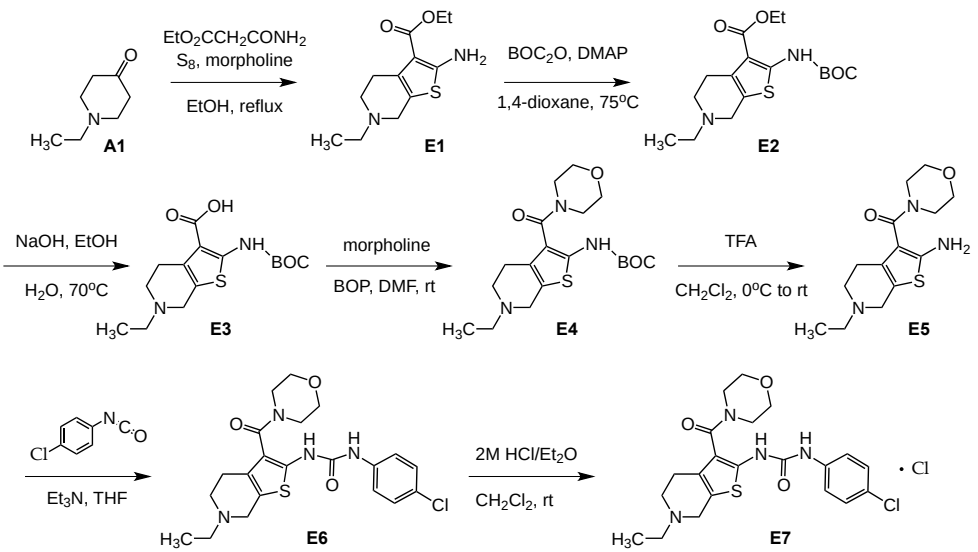
2-[3-(4-Chlorobenzyl)ureido]-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (11 in Table 1). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.68 (s, 1H), 10.62 (bs, 1H), 8.29 (t, J = 5.4 Hz, 1H), 7.69–6.90 (m, 6H), 4.49–4.42 (m, 1H), 4.28 (d, J = 5.4 Hz, 2H), 4.17–4.10 (m, 1H), 3.68–3.60 (m, 1H), 3.31–3.00 (m, 5H), 1.30 (t, J = 7.1 Hz, 3H); LRMS *m/z* 393 $[M+H]^+$.

1-(4-Chlorophenyl)-3-(3-cyano-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-2-yl)urea Hydrochloride (19 in Table 2). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.19 (s, 1H), 9.32 (s, 1H), 7.48 (d, J = 9.0 Hz, 2H), 7.36 (d, J = 9.0 Hz, 2H), 3.49–3.43 (m, 2H), 2.77–2.69 (m, 2H), 2.59–2.53 (m, 4H), 1.07 (t, J = 7.0 Hz, 3H); LRMS *m/z* 361 $[M+H]^+$.

2-[3-(4-Chlorophenyl)ureido]-4-methyl-5-(morpholinomethyl)thiophene-3-carboxamide Hydrochloride (45 in Table 5). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.65 (s, 1H), 10.43 (bs, 1H), 10.25 (s, 1H), 7.64 (bs, 1H), 7.50 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 8.7 Hz, 2H), 7.34 (bs, 1H), 4.46 (s, 2H), 4.00–3.94 (m, 2H), 3.73 (t, J = 11.7 Hz, 2H), 3.36–3.22 (m, 2H), 3.16–3.05 (m, 2H), 2.36 (s, 3H); LRMS *m/z* 407 $[M-H]^-$.

2-[3-(4-Chlorophenyl)ureido]-5,5,7,7-tetramethyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (87 in Table 8). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.80 (s, 1H), 10.27 (s, 1H), 9.38 (bs, 2H), 7.80–6.90 (m, 6H), 2.92 (s, 2H), 1.73 (s, 6H), 1.44 (s, 6H); LRMS *m/z* 407 $[M+H]^+$.

Scheme 5



Preparation of 1-(4-Chlorophenyl)-3-[6-ethyl-3-(morpholine-4-carbonyl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-2-yl]urea Hydrochloride (E7, 20 in Table 2).

Step One. Ethyl 2-Amino-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxylate (E1). A solution of ethyl 2-cyanoacetate (4.87 g, 43.1 mmol), 1-ethylpiperidin-4-one (**A1**, 5.00 g, 39.3 mmol), sulfur (1.50 g, 46.8 mmol), and morpholine (6.80 mL, 78.1 mmol) in ethanol (30 mL) was heated to reflux for 6 h and then the reaction mixture was cooled to room temperature, concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluting with methylene chloride to methanol to methylene chloride (1:19). Further purification by flash column chromatography on silica gel was required eluting from methylene chloride to ethyl acetate to afford compound **E1** as a light orange solid (9.77 g, 98%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95 (bs, 2H), 4.26 (q, *J* = 7.2 Hz, 2H), 3.42–3.41 (m, 2H), 2.88–2.80 (m, 2H), 2.77–2.69 (m, 2H), 2.57 (q, *J* = 7.2 Hz, 2H), 1.33 (t, *J* = 7.2 Hz, 3H), 1.16 (t, *J* = 7.2 Hz, 3H).

Step Two. Ethyl 2-(*tert*-Butoxycarbonylamino)-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxylate (E2). A solution of compound **E1 (**2.00 g, 7.86 mmol), di-*tert*-butyl dicarbonate (3.50 g, 16.0 mmol), and 4-dimethylaminopyridine (97.0 mg, 0.790 mmol) in anhydrous 1,4-dioxane (25 mL) was stirred at 75 °C for 3 h. After this time, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting residue was dissolved in chloroform (200 mL) and washed with water (200 mL). The aqueous layer was back extracted with chloroform (3 × 100 mL). The combined organics were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford compound **E2** as an orange viscous oil (3.43 g, >100%) that was used in the next step without further purification.

Step Three. 2-(*tert*-Butoxycarbonylamino)-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxylic Acid (E3). To the solution of compound **E2** (3.43 g, crude) in

ethanol (25 mL) and water (12 mL) was added sodium hydroxide (1.28 g, 32.0 mmol). The reaction mixture was heated to 70 °C for 1 h. After this time, the reaction mixture was cooled to room temperature and diluted with water (25mL) and ethyl acetate (75 mL). The layers were separated. The aqueous layer was neutralized with 0.5 M citric acid to pH 7. The aqueous layer was then chilled to 0 °C for 16 h. After this time, the resulting solids were collected by suction filtration to afford compound **E3** as a light orange solid (1.60 g, 62% over two steps): ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.11 (bs, 1H), 3.70–3.60 (m, 2H), 2.88–2.76 (m, 4H), 2.66 (q, *J* = 7.0 Hz, 2H), 1.48 (s, 9H), 1.11 (t, *J* = 7.0 Hz, 3H); LRMS *m/z* 325 $[M-H]^-$.

Step Four. *tert*-Butyl 6-ethyl-3-(morpholine-4-carbonyl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-2-ylcarbamate (E4). To the solution of compound **H3** (250 mg, 0.766 mmol), diisopropylethylamine (0.300 mL, 1.69 mmol), and morpholine (100 mg, 1.15 mmol) in *N*,*N*-dimethylformamide (3 mL) was added (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) (678 mg, 1.53 mmol). After stirring at room temperature for 16 h, the reaction mixture was diluted with ethyl acetate (50 mL) and water (75 mL). The layers were separated and the aqueous layer was back extracted with methylene chloride (75 mL) and ethyl acetate (100 mL). The combined organics were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluting with methylene chloride to ethyl acetate to afford compound **E4** as a yellow solid (285 mg, 94%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (bs, 1H), 3.78–3.45 (m, 10H), 2.86–2.78 (m, 2H), 2.74–2.69 (m, 2H), 2.67–2.62 (m, 2H), 1.50 (s, 9H), 1.19 (t, *J* = 7.0 Hz, 3H); LRMS *m/z* 396 $[M+H]^+$.

Step Five. (2-Amino-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-3-yl)(morpholino)methanone (E5). To the solution of compound **E4** (285 mg, 0.721 mmol) in anhydrous methylene chloride (5 mL) was added trifluoroacetic acid (3 mL) at 0 °C. The reaction mixture was gradually warmed to room temperature over 2 h and stirred at room temperature for another 14 h. After this time, the reaction mixture was concentrated under reduced pressure. The resulting residue was dissolved in methylene chloride (50 mL), washed with saturated aqueous sodium bicarbonate (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford compound **H5** as a glassy brown solid (145 mg, 68%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.38 (bs, 2H), 3.71–3.63 (m, 4H), 3.65–3.53 (m, 4H), 3.45 (s, 2H), 2.73–2.69 (m, 2H), 2.62–2.56 (m, 4H), 1.16 (t, *J* = 7.0 Hz, 3H); LRMS *m/z* 296 $[M+H]^+$.

Step Six. 1-(4-Chlorophenyl)-3-[6-ethyl-3-(morpholine-4-carbonyl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-2-yl]urea (E6). A solution of compound **E5** (125 mg, 0.423 mmol) and 4-chlorophenyl isocyanate (84.0 mg, 0.547 mmol) in anhydrous tetrahydrofuran (3.5 mL) was stirred at room temperature for 16 h. After this time, the reaction mixture was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluting with methylene chloride to methanol/methylene chloride (1:19) to afford compound **E6** as a glassy brown solid (150 mg, 79%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (bs, 1H), 7.83 (bs, 1H), 7.21–7.16 (m,

4H), 3.80–3.52 (m, 10H), 2.75–2.53 (m, 6H), 1.18 (t, *J* = 7.0 Hz, 3H); LRMS *m/z* 449 $[M+H]^+$.

Step Seven. 1-(4-Chlorophenyl)-3-[6-ethyl-3-(morpholine-4-carbonyl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-2-yl]urea Hydrochloride (E7, 20 in Table 2). To the solution of compound **H6** (150 mg, 0.334 mmol) in anhydrous methylene chloride (3.5 mL) was added hydrochloric acid (2 M in diethyl ether, 0.220 mL, 0.440 mmol). After stirring at room temperature for 20 min, the reaction mixture was diluted with ethyl acetate (20 mL), sonicated, and the solids collected by suction filtration to afford compound **E7** (**20** in Table 2) as a yellow solid (136 mg, 84%): ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.21 (bs, 1H), 10.03 (bs, 1H), 9.61 (bs, 1H), 7.49 (d, *J* = 9.0 Hz, 2H), 7.35 (d, *J* = 9.0 Hz, 2H), 4.58–4.51 (m, 1H), 4.26–4.17 (m, 1H), 3.81–3.70 (m, 3H), 3.62–3.47 (m, 6H), 3.32–3.20 (m, 3H), 2.91–2.83 (m, 1H), 2.78–2.69 (m, 1H), 1.30 (t, *J* = 7.0 Hz, 3H); LRMS *m/z* 449 $[M+H]^+$.

Compounds Prepared by Scheme 5

2-[3-(4-Chlorophenyl)ureido]-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxylic Acid Trifluoroacetate (16 in Table 2). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.78 (s, 1H), 10.47 (s, 1H), 9.91(bs, 1H), 7.44 (dd, *J*=42.9, 8.7Hz, 4H), 4.65-4.07 (m, 1H), 3.80-3.38 (m, 3H), 3.18–2.83 (m, 3H), 1.28 (t, *J*=7.2Hz, 3H); LRMS *m/z* 380 $[M+H]^+$.

Methyl 2-[3-(4-Chlorophenyl)ureido]-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxylate Hydrochloride (17 in Table 2). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.57 (s, 1H), 10.36 (s, 1H), 7.43 (dd, *J*=46.9, 8.7Hz, 4H), 3.82 (s, 3H), 3.51–3.37 (m, 2H), 2.85-2.41 (m, 6H), 1.06 (t, *J*=7.0Hz, 3H); LRMS *m/z* 394 $[M+H]^+$.

N-Methyl 2-[3-(4-Chlorophenyl)ureido]-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (18 in Table 2). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.7 (s, 1H), 10.1 (s, 1H), 7.43 (dd, *J*=48.0, 9.0Hz, 4H), 4.26-3.96 (m, 2H), 3.17 (d, *J*=1.5Hz, 3H), 3.03-2.68 (m, 6H), 1.15 (t, *J*=7.0Hz, 3H); LRMS *m/z* 393 $[M+H]^+$.

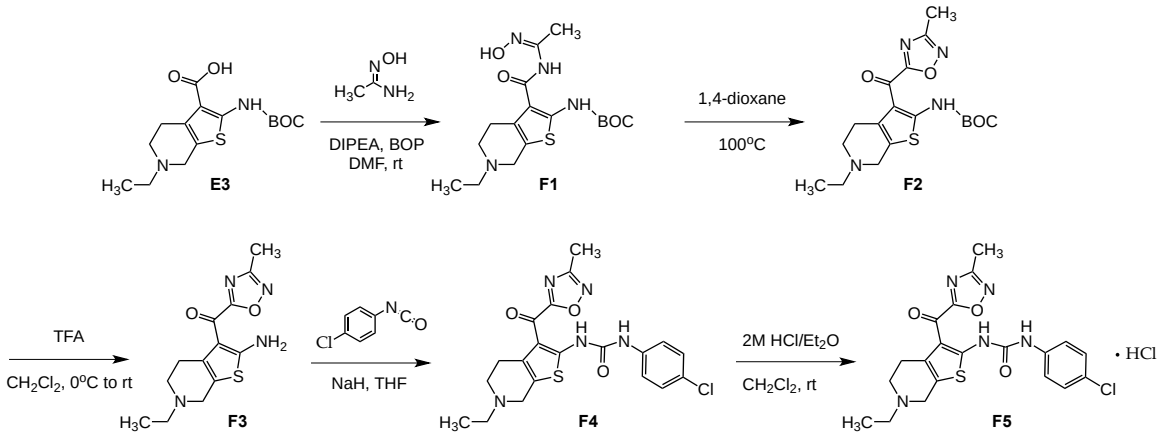
2-[3-(4-Chlorophenyl)ureido]-6-ethyl-*N*-(oxetan-3-yl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (23 in Table 2). ^{1}H NMR (300 MHz, CD_3OD) δ 7.53–7.30 (m, 4H), 4.46–3.60 (m, 7H), 2.93–2.62 (m, 6H), 1.21 (t, *J* = 7.2 Hz, 3H); LRMS *m/z* 435 $[M+H]^+$.

2-[3-(4-Chlorophenyl)ureido]-6-ethyl-*N*-(2-hydroxyethyl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (24 in Table 2). ^{1}H NMR (300 MHz, CD_3OD) δ 7.49–7.28 (m, 4H), 4.65–4.25 (m, 2H), 3.90–3.38 (m, 8H), 3.25–3.15 (m, 2H), 1.44 (t, *J* = 7.4 Hz, 3H); LRMS *m/z* 423 $[M+H]^+$.

2-[3-(4-Chlorophenyl)ureido]-6-ethyl-*N*-(2-morpholinoethyl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide Dihydrochloride (25 in Table 2). ^{1}H

NMR (300 MHz, DMSO-d_6) δ 11.23 (bs, 1H), 10.96 (bs, 1H), 10.67 (s, 1H), 10.48 (s, 1H), 8.06 (t, J = 5.1 Hz, 1H), 7.54–7.33 (m, 4H), 4.53–3.83 (m, 6H), 3.75–3.50 (m, 10H), 3.40–3.10 (m, 4H), 1.33 (t, J = 7.2 Hz, 3H); LRMS *m/z* 492 $[M+H]^+$.

Scheme 6



Preparation of 1-(4-Chlorophenyl)-3-[6-ethyl-3-(3-methyl-1,2,4-oxadiazol-5-yl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-2-yl]urea Hydrochloride (F5, 21 in Table 2).

Step One. *tert*-Butyl 6-Ethyl-3-[1-(hydroxyimino)ethylcarbamoyl]-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-2-ylcarbamate (F1). To a solution of compound **E3** (300 mg, 0.919 mmol), diisopropylethylamine (0.320 mL, 1.80 mmol), and *N*'-hydroxyacetimidamide (102 mg, 1.38 mmol) in *N*,*N*-dimethylformamide (3.5 mL) was added (benzotriazol-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate (BOP reagent) (813 mg, 1.84 mmol). After stirring at room temperature for 16 h, the reaction mixture was diluted with ethyl acetate (50 mL) and water (75 mL). The layers were separated and the aqueous layer was back extracted with methylene chloride (75 mL) and ethyl acetate (100 mL). The combined organics were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluting with methylene chloride to ethyl acetate and then to methanol/methylene chloride (1:19) to afford compound **F1** as a yellow solid (340 mg, 97%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.33 (bs, 1H), 4.77 (bs, 2H), 3.55 (s, 2H), 2.95–2.92 (m, 2H), 2.81–2.76 (m, 2H), 2.62 (q, J = 7.0 Hz, 2H), 2.04 (s, 3H), 1.51 (s, 9H), 1.19 (t, J = 7.0 Hz, 3H); LRMS *m/z* 383 $[M+H]^+$.

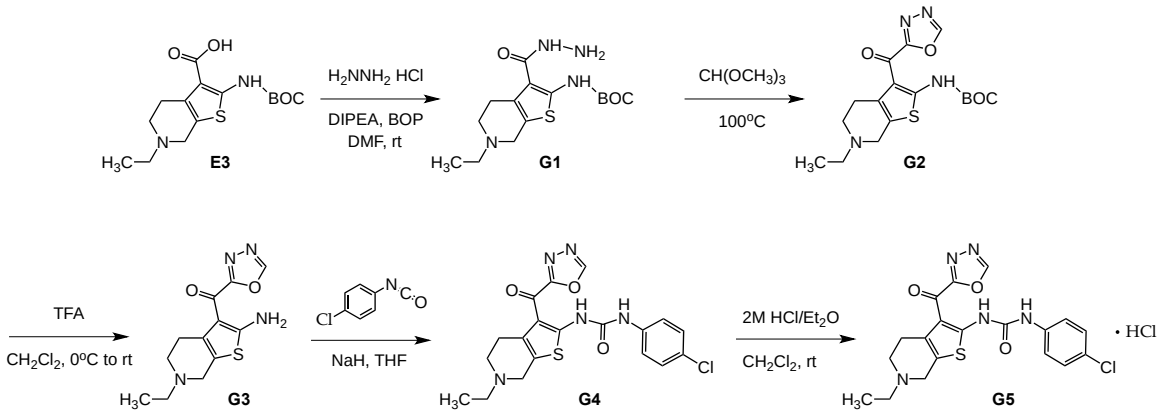
Step Two. *tert*-Butyl 6-Ethyl-3-(3-methyl-1,2,4-oxadiazol-5-yl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-2-ylcarbamate (F2). A solution of compound **F1** (340 mg, 0.889 mmol) in anhydrous 1,4-dioxane (5 mL) was heated to reflux for 14 h. After this time, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluting with methylene chloride to methanol/methylene chloride (1:19) to afford compound **F2** as a yellow solid (118 mg, 36%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.40 (bs, 1H), 3.59 (s, 2H), 3.04–3.01 (m, 2H), 2.84–2.81 (m, 2H), 2.64 (q, J = 7.0 Hz, 2H), 2.46 (s, 3H), 1.57 (s, 9H), 1.19 (t, J = 7.0 Hz, 3H); LRMS *m/z* 365 $[M+H]^+$.

Step Three. 6-Ethyl-3-(3-methyl-1,2,4-oxadiazol-5-yl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-2-amine (F3). To a solution of compound **F2** (87.0 mg, 0.240 mmol) in anhydrous methylene chloride (3 mL) was added trifluoroacetic acid (3 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 24 h. After this time, the reaction mixture was concentrated under reduced pressure. The resulting residue was dissolved in methylene chloride (50 mL), washed with saturated aqueous sodium bicarbonate (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluting with methylene chloride to methanol/methylene chloride (1:19) to afford compound **F3** as a yellow solid (38 mg, 60%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.17 (bs, 2H), 3.48 (s, 2H), 2.99–2.96 (m, 2H), 2.82–2.79 (m, 2H), 2.62 (q, *J* = 7.0 Hz, 2H), 2.39 (s, 3H), 1.18 (t, *J* = 7.0 Hz, 3H); LRMS *m/z* 265 $[M+H]^+$.

Step Four. 1-(4-Chlorophenyl)-3-[6-ethyl-3-(3-methyl-1,2,4-oxadiazol-5-yl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-2-yl]urea (F4). To a solution of compound **F3** (38.0 mg, 0.140 mmol) in anhydrous tetrahydrofuran (2 mL) was added sodium hydride (60% dispersed in oil, 10.0 mg, 0.250 mmol) in one portion under nitrogen. After stirring at room temperature for 5 min, 4-chlorophenyl isocyanate (22.0 mg, 0.140 mmol) was added. The reaction mixture was stirred at room temperature for 10 min. After this time, the reaction was quenched with slow addition of methanol (5 mL) and the resulting mixture was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluting with methylene chloride to methanol/methylene chloride (1:19) to afford compound **F4** as an off-white solid (25 mg, 43%): ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.44 (bs, 1H), 10.35 (bs, 1H), 7.47 (d, *J* = 9.0 Hz, 2H), 7.32 (d, *J* = 9.0 Hz, 2H), 3.52–3.49 (m, 2H), 2.88–2.84 (m, 2H), 2.75–2.68 (m, 2H), 2.59–2.52 (m, 2H), 2.47 (s, 3H), 1.09 (t, *J* = 7.0 Hz, 3H); LRMS *m/z* 418 $[M+H]^+$.

Step Five. 1-(4-Chlorophenyl)-3-[6-ethyl-3-(3-methyl-1,2,4-oxadiazol-5-yl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl]urea Hydrochloride (F5, 21 in Table 2). To a solution of compound **F4** (25 mg, 0.060 mmol) in anhydrous methylene chloride (5 mL) was added hydrochloric acid (2 M in diethyl ether, 0.10 mL, 0.20 mmol). After stirring at room temperature for 15 min, the reaction mixture was concentrated under reduced pressure and the resulting residue was triturated with methylene chloride to afford compound **F5** (**21** in Table 2) as a white solid (22 mg, 81%): ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.62 (bs, 1H), 10.53 (bs, 1H), 10.40 (bs, 1H), 7.57 (d, *J* = 9.0 Hz, 2H), 7.41 (d, *J* = 9.0 Hz, 2H), 4.62–4.51 (m, 1H), 4.30–4.19 (m, 1H), 3.81–3.70 (m, 1H), 3.31–3.13 (m, 5H), 2.50 (s, 3H), 1.32 (t, *J* = 7.0 Hz, 3H); LRMS *m/z* 418 $[M+H]^+$.

Scheme 7



Preparation of 1-(4-Chlorophenyl)-3-[6-ethyl-3-(1,3,4-oxadiazol-2-yl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-2-yl]urea Hydrochloride (G5, 22 in Table 2).

Step One. *tert*-Butyl 6-Ethyl-3-(hydrazinecarbonyl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-2-ylcarbamate (G1). To a solution of compound **E3** (500 mg, 1.53 mmol), diisopropylethylamine (1.34 mL, 7.53 mmol), and hydrazine hydrochloride (210 mg, 3.07 mmol) in *N*,*N*-dimethylformamide (4 mL) was added (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) (1.37 g, 3.10 mmol). After stirring at room temperature for 16 h, the reaction mixture was diluted with ethyl acetate (50 mL) and water (75 mL). The layers were separated and the aqueous layer was back extracted with methylene chloride (75 mL) and ethyl acetate (100 mL). The combined organics were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluting with methylene chloride to methanol/methylene chloride (1:9) to afford compound **G1** as a yellow solid (418 mg, 80%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.75 (bs, 1H), 6.93 (bs, 1H), 4.02 (bs, 2H), 3.56 (s, 2H), 2.82–2.78 (m, 4H), 2.62 (q, *J* = 7.2 Hz, 2H), 1.52 (s, 9H), 1.18 (t, *J* = 7.2 Hz, 3H); LRMS *m/z* 341 $[M+H]^+$.

Step Two. *tert*-Butyl 6-Ethyl-3-(1,3,4-oxadiazol-2-yl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-2-ylcarbamate (G2). A mixture of compound **G1** (640 mg, 1.88 mmol) and trimethyl orthoformate (15.0 mL, 137 mmol) were heated to 120 °C for 30 h. After this time, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluting with methylene chloride to methanol/methylene chloride (1:19) to afford compound **G2** as a yellow solid (414 mg, 63%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.23 (bs, 1H), 8.36 (s, 1H), 3.49 (s, 2H), 2.99–2.92 (m, 2H), 2.87–2.78 (m, 2H), 2.64 (q, *J* = 7.2 Hz, 2H), 1.55 (s, 9H), 1.20 (t, *J* = 7.2 Hz, 3H); LRMS *m/z* 251 $[M+H]^+$.

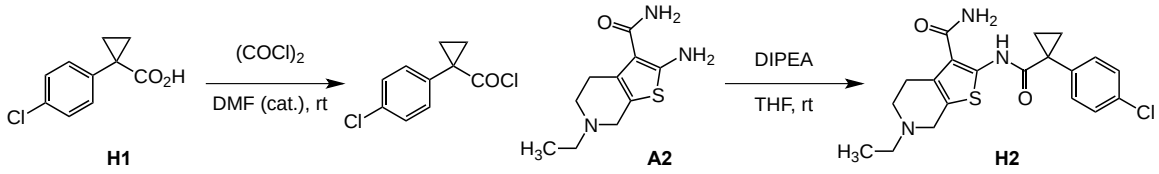
Step Three. 6-Ethyl-3-(1,3,4-oxadiazol-2-yl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-2-amine (G3). To a solution of compound **G2** (410 mg, 1.17 mmol) in anhydrous methylene chloride (3 mL) was added trifluoroacetic acid (3 mL) at 0 °C. After stirring

at 0 °C for 3 h, the reaction mixture was concentrated under reduced pressure. The resulting residue was dissolved in methylene chloride (75 mL), washed with saturated aqueous sodium bicarbonate (75 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluting with methylene chloride to methanol/methylene chloride (1:9) to afford compound **G3** as a yellow solid (138 mg, 47%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (s, 1H), 6.06 (bs, 2H), 3.49 (s, 2H), 2.93–2.88 (m, 2H), 2.81–2.77 (m, 2H), 2.61 (q, *J* = 7.0 Hz, 2H), 1.18 (t, *J* = 7.0 Hz, 3H); LRMS *m/z* 251 $[M+H]^+$.

Step Four. 1-(4-Chlorophenyl)-3-[6-ethyl-3-(1,3,4-oxadiazol-2-yl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-2-yl]urea (G4). To a solution of compound **J3** (133 mg, 0.531 mmol) in anhydrous tetrahydrofuran (3 mL) was added sodium hydride (60% dispersed in oil, 22.0 mg, 0.550 mmol) in one portion at 0 °C under nitrogen. After stirring at 0 °C for 5 min, 4-chlorophenyl isocyanate (90.0 mg, 0.590 mmol) was added. The reaction mixture was warmed to room temperature and stirred at room temperature for 45 min. After this time, the reaction was quenched with slow addition of methanol (5 mL) and the resulting mixture was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluting with methylene chloride to methanol/methylene chloride (1:9) to afford compound **G4** as a yellow solid (175 mg, 82%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.62 (bs, 1H), 8.38 (s, 1H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 7.17 (bs, 1H), 3.60 (s, 2H), 2.97–2.95 (m, 2H), 2.83–2.81 (m, 2H), 2.65 (q, *J* = 7.5 Hz, 2H), 1.19 (t, *J* = 7.5 Hz, 3H); LRMS *m/z* 404 $[M+H]^+$.

Step Five. 1-(4-Chlorophenyl)-3-[6-ethyl-3-(1,3,4-oxadiazol-2-yl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-2-yl]urea Hydrochloride (G5, 22 in Table 2). To a solution of compound **G4** (175 mg, 0.433 mmol) in anhydrous methylene chloride (3 mL) and anhydrous tetrahydrofuran (3 mL) was added hydrochloric acid (2 M in diethyl ether, 0.300 mL, 0.600 mmol). After stirring at room temperature for 15 min, the reaction mixture was concentrated under reduced pressure and the resulting residue was triturated with methylene chloride to afford compound **G5** (**22** in Table 2) as a yellow solid (133 mg, 70%): ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.63 (s, 1H), 10.46 (bs, 1H), 10.42 (s, 1H), 9.37 (s, 1H), 7.55 (d, *J* = 9.0 Hz, 2H), 7.39 (d, *J* = 8.5 Hz, 2H), 4.63–4.56 (m, 1H), 4.29–4.21 (m, 1H), 3.81–3.72 (m, 1H), 3.42–3.36 (m, 1H), 3.26–3.12 (m, 4H), 1.32 (t, *J* = 7.0 Hz, 3H); LRMS *m/z* 404 $[M+H]^+$.

Scheme 8



H1 **A2** **H2**

Preparation of 2-[1-(4-Chlorophenyl)cyclopropanecarboxamido]-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (H2, 33 in Table 3).

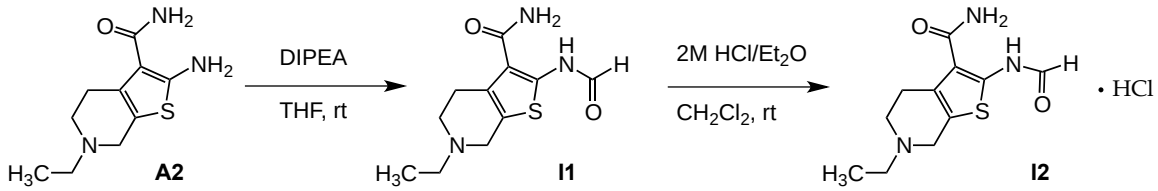
Step One. 2-[1-(4-Chlorophenyl)cyclopropanecarboxamido]-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide (H2, 33 in Table 3). To a solution of 1-(4-chlorophenyl)cyclopropanecarboxylic acid (**H1**, 131 mg, 0.666 mmol) in anhydrous methylene chloride (3 mL) was added oxalyl chloride (0.100 mL, 1.17 mmol) followed by 2 drops of *N*,*N*-dimethylformamide at room temperature under nitrogen. After stirring at room temperature for 1 h, the reaction mixture was concentrated under reduced pressure. The resulting residue was dissolved in anhydrous tetrahydrofuran (3 mL). To the resulting solution was added diisopropylethylamine (0.200 mL, 1.12 mmol) followed by a suspension of compound **A2** (150 mg, 0.666 mmol) in anhydrous tetrahydrofuran (3 mL). After stirring at room temperature for 3 h, the reaction mixture was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography on silica gel eluting with methylene chloride to methanol/methylene chloride (1:19). Further purification by trituration with acetonitrile gave compound **H2** (**33** in Table 3) as a light yellow solid (87 mg, 32%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.79 (bs, 1H), 7.47–7.42 (s, 4H), 5.56 (bs, 2H), 3.57 (s, 2H), 2.82–2.77 (m, 4H), 2.62 (q, *J* = 7.0 Hz, 2H), 1.78–1.74 (m, 2H), 1.20–1.12 (m, 5H); LRMS *m/z* 404 $[M+H]^+$.

Compounds prepared by Scheme 8

[2S]-N-{3-carbamoyl-6-ethyl-4H,5H,6H,7H-thieno[2,3-c]pyridine-2-yl}pyrrolidine-2-carboxamide (30 in Table 3). LRMS *m/z* 323 $[M+H]^+$.

N'1-{3-carbamoyl-6-ethyl-4H,5H,6H,7H-thieno[2,3-c]pyridine-2-yl}-N1-(4-chlorophenyl)cyclopropane-1,1-dicraboxamide (31 in Table 3). LRMS *m/z* 447 $[M+H]^+$.

Scheme 9



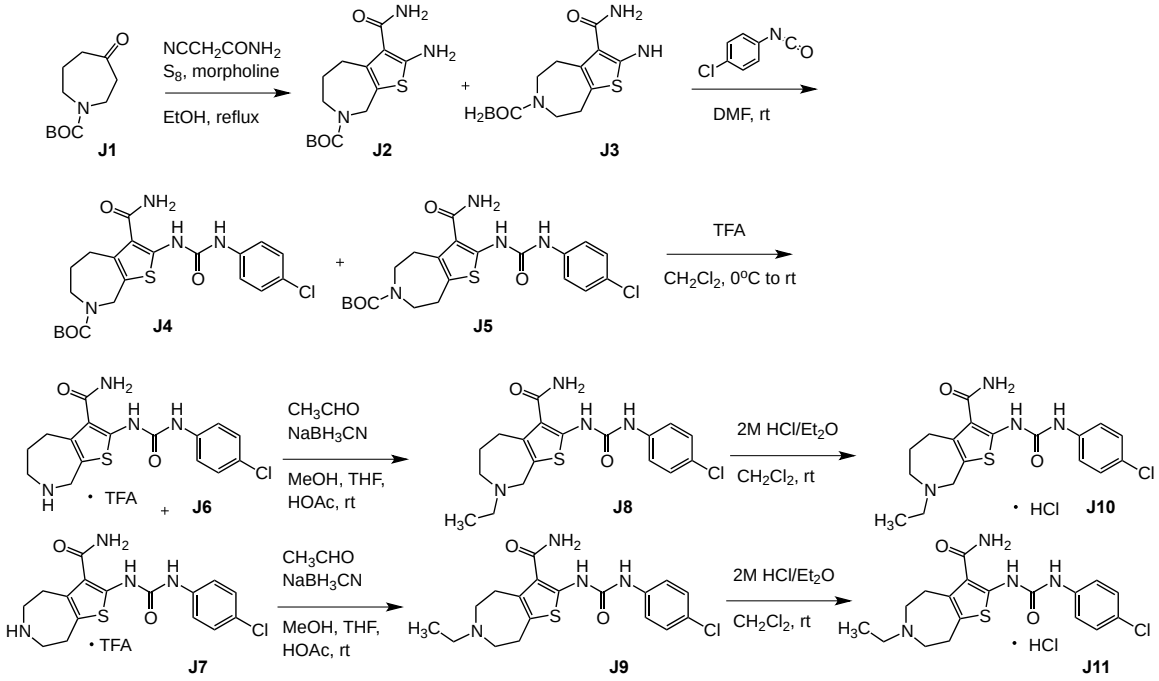
Preparation of 6-Ethyl-2-formamido-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (I2, 29 in Table 3).

Step One. 6-Ethyl-2-formamido-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide (I1). The mixture of compound **A2** (225 mg, 1.00 mmol) in formic acid (5 mL) and water (1 mL) was stirred overnight at room temperature. After that time, the reaction mixture was concentrated under reduced pressure. The residue was mixed with saturated aqueous sodium bicarbonate (50 mL) and extracted with methylene chloride (3 × 150 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluting with methanol/methylene chloride (15:85) to afford compound **I1** as an off-white solid (208 mg, 82%): ^{1}H NMR (300 MHz,

DMSO-d_6) δ 11.44 (s, 1H), 8.40 (s, 1H), 7.52 (bs, 1H), 7.03 (bs, 1H), 3.48 (s, 2H), 2.76 (d, J = 4.8 Hz, 2H), 2.65 (d, J = 4.8 Hz, 2H), 2.54–2.47 (m, 2H), 1.07 (t, J = 7.0 Hz, 3H); LRMS m/z 254 $[M+H]^+$.

Step Two. 6-Ethyl-2-formamido-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxamide Hydrochloride (I2, 29 in Table 3). To the mixture of compound **I1** (152 mg, 0.600 mmol) in water (6 mL) and methanol (2 mL) at room temperature was added 1 M hydrochloric acid (1.00 mL, 1.00 mmol). After addition, the mixture was sonicated to form clear solution and then lyophilized to afford compound **I2** (**29** in Table 3) as a white solid (165 mg, 95%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.49 (s, 1H), 10.94 (bs, 1H), 8.44 (s, 1H), 7.61 (bs, 1H), 7.37 (bs, 1H), 4.55-4.49 (m, 1H), 4.25-4.17 (m, 1H), 3.29–3.07 (m, 6H), 1.31 (t, J = 7.2 Hz, 3H); LRMS m/z 254 $[M+H]^+$.

Scheme 10



Preparation of 2-[3-(4-Chlorophenyl)ureido)-7-ethyl-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*c*]azepine-3-carboxamide Hydrochloride (J10, 43 in Table 5).

Step One. *tert*-Butyl 2-Amino-3-carbamoyl-5,6-dihydro-4*H*-thieno[2,3-*c*]azepine-7(8*H*)-carboxylate (S2) and *tert*-Butyl 2-Amino-3-carbamoyl-7,8-dihydro-4*H*-thieno[2,3-*d*]azepine-6(5*H*)-carboxylate (J2 and J3). The mixture of compound **J1** (1.00 g, 4.69 mmol), 2-cyanoacetamide (394 mg, 4.69 mmol), sulphur (150 mg, 4.69 mmol), and morpholine (410 mg, 4.71 mmol) in ethanol (10 mL) was heated to reflux for 4 h under nitrogen. After cooled to room temperature, the reaction mixture was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluting with 4% methanol/methylene chloride to provide an

inseparable mixture of isomers **J2** and compound **J3** as a yellow solid (564 mg, 39%): LRMS *m/z* 312 $[M+H]^+$.

Step Two. *tert*-Butyl 3-Carbamoyl-2-[3-(4-chlorophenyl)ureido]-5,6-dihydro-4*H*-thieno[2,3-*c*]azepine-7(8*H*)-carboxylate (S4) and *tert*-Butyl 3-Carbamoyl-2-[3-(4-chlorophenyl)ureido]-7,8-dihydro-4*H*-thieno[2,3-*d*]azepine-6(5*H*)-carboxylate (J4 and J5). To the stirred mixture of compound **J2** and **J3** (300 mg, 0.963 mmol) in *N*,*N*-dimethylformamide (2 mL) at room temperature under nitrogen was added 4-chlorophenyl isocyanate (148 mg, 0.964 mmol). After addition, the reaction mixture was stirred for 21 h. After this time, the reaction mixture was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluting with 50% ethyl acetate/methylene chloride to provide an inseparable mixture of isomers **J4** and **J5** as a white solid (375 mg, 84%): LRMS *m/z* 487 $[M+Na]^+$.

Step Three. 2-[3-(4-Chlorophenyl)ureido]-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*c*]azepine-3-carboxamide Trifluoroacetae (S6) and 2-[3-(4-Chlorophenyl)ureido]-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*d*]azepine-3-carboxamide Trifluoroacetae (J6 and J7). To the mixture of compound **J4** and **J5** (374 mg, 0.804 mmol) in methylene chloride (4 mL) was added trifluoroacetic acid (2 mL). After addition, the reaction mixture was stirred for 1 h and then concentrated under reduced pressure. The resulting residue was purified by reverse phase semi-preparative HPLC, eluting with 0.05% TFA in acetonitrile/water (gradient from 10% to 100%, Phenomenex Luna column) to afford compound **J6** as a white solid (188 mg, 49%) and compound **J7** as a white solid (106 mg, 28%). Compound **J6**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.06 (s, 1H), 10.05 (s, 1H), 8.77 (s, 2H), 7.70–7.30 (m, 6H), 4.32 (s, 2H), 3.37 (bs, 2H), 2.96–2.94 (m, 2H), 1.87 (bs, 2H); LRMS *m/z* 365 $[M+H]^+$. Compound **J7**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.02 (s, 1H), 9.94 (s, 1H), 8.85 (s, 2H), 7.70–7.30 (m, 6H), 3.22 (bs, 4H), 3.08–2.98 (m, 4H); LRMS *m/z* 365 $[M+H]^+$.

Step Four. 2-[3-(4-Chlorophenyl)ureido]-7-ethyl-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*c*]azepine-3-carboxamide (J8). To the stirred mixture of compound **J6** (185 mg, 0.386 mmol), acetaldehyde (5 M solution in tetrahydrofuran, 0.160 mL, 0.800 mmol), and acetic acid (2 drops) in anhydrous methanol (6 mL) and anhydrous tetrahydrofuran (3 mL) at room temperature under nitrogen was added sodium cyanoborohydride (73.0 mg, 1.16 mmol). After addition, the reaction mixture was stirred for 17 h. After this time, the reaction mixture was diluted with methylene chloride (100 mL), washed with saturated aqueous sodium bicarbonate (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluting with 20% to 60% methanol/methylene chloride to provide compound **J8** as a light yellow solid (92 mg, 61%): LRMS *m/z* 393 $[M+H]^+$.

Step Five. 2-[3-(4-Chlorophenyl)ureido]-7-ethyl-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*c*]azepine-3-carboxamide Hydrochloride (J10, 43 in Table 5). To the stirred mixture of compound **J8** (41.0 mg, 0.104 mmol) in methanol (3 mL) and methylene chloride (3 mL) at room temperature was added hydrochloric acid (2 M in diethyl ether, 0.100 mL, 0.200 mmol). After addition, the reaction mixture was stirred for 5 min and concentrated

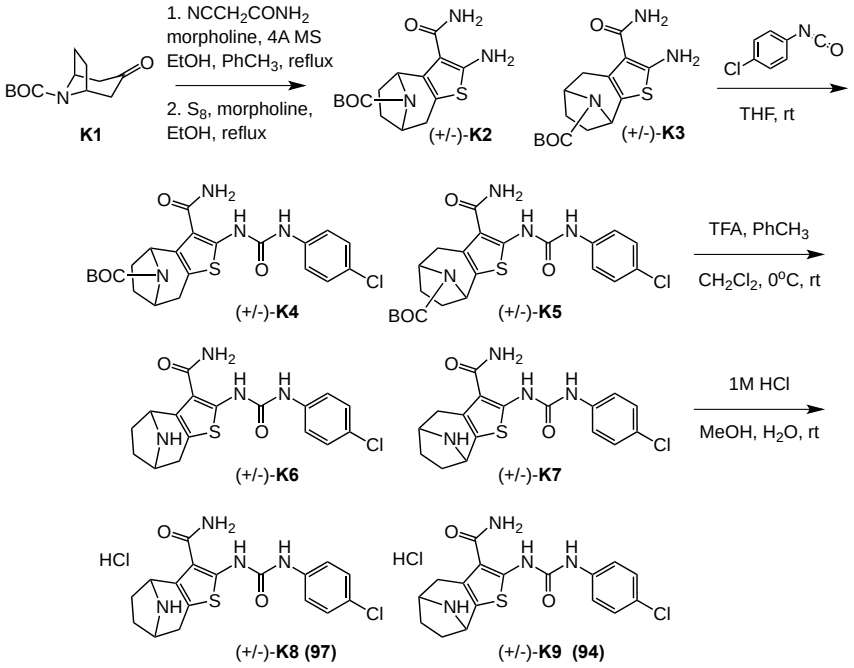
under reduced pressure. The resulting residue was dissolved in acetonitrile (1 mL) and water (1 mL) and lyophilized to provide compound **J10** (**43** in Table 5) as an off-white solid (45 mg, 100%): ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.12 (s, 1H), 10.11 (s, 1H), 10.04 (bs, 1H), 7.70–7.30 (m, 6H), 4.56–4.40 (m, 2H), 3.59–3.36 (m, 2H), 3.09–2.94 (m, 4H), 2.01–1.84 (m, 2H), 1.25 (t, J = 7.2 Hz, 3H); LRMS *m/z* 393 $[M+H]^+$.

Compounds Prepared by Scheme 10

2-[3-(4-Chlorophenyl)ureido]-5-ethyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine-3-carboxamide Hydrochloride (41 in Table 5). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.58 (s, 1H), 10.18 (s, 1H), 9.85 (bs, 1H), 7.65–7.15 (m, 6H), 4.52–3.68 (m, 3H), 3.29–3.00 (m, 5H), 1.30 (t, J = 7.2 Hz, 3H); LRMS *m/z* 379 $[M+H]^+$.

2-[3-(4-Chlorophenyl)ureido]-6-ethyl-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*d*]azepine-3-carboxamide Hydrochloride (J11, 44 in Table 5). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.27 (bs, 1H), 10.05 (s, 1H), 10.02 (s, 1H), 7.70–7.25 (m, 6H), 3.60–3.56 (m, 2H), 3.25–3.06 (m, 8H), 1.27 (t, J = 7.2 Hz, 3H); LRMS *m/z* 393 $[M+H]^+$.

Scheme 11



Preparation of (+/-)-2-[3-(4-Chlorophenyl)ureido]-5,6,7,8-tetrahydro-4*H*-5,8-epiminocyclohepta[*b*]thiophene-3-carboxamide Hydrochloride [(+/-)-K8 (97) and (+/-)-K9 (94) in Figure 2].

Step One. (+/-)-*tert*-Butyl 2-Amino-3-carbamoyl-5,6,7,8-tetrahydro-4*H*-5,8-epiminocyclohepta[*b*]thiophene-9-carboxylate [(+/-)-X2 and (+/-)-X3, mixture of regioisomers]. The stirred mixture of *tert*-butyl 3-oxo-8-azabicyclo[3.2.1]octane-8-

carboxylate (**K1**, 2.48 g, 11.0 mmol), 2-cyanoacetamide (1.02 g, 12.1 mmol), morpholine (1.92 g, 22.0 mmol), and 4Å molecular sieves (4.00 g) in ethanol (100 mL) and toluene (60 mL) was heated to reflux under nitrogen overnight. After this time, the reaction mixture was cooled to room temperature and filtered. The filter cake was washed with ethanol (30 mL) and filtered. The filtrate was concentrated. The resulting residue was purified by a silica gel plug eluting with methanol/methylene chloride (1:9) to provide a partially purified product which was used in the subsequent step without further purification (1.10 g): LRMS *m/z* 192 $[M+H\text{-Boc}]^+$. The stirred mixture of the product described above (1.10 g), sulfur (145 mg, 4.52 mmol), and morpholine (656 mg, 7.53 mmol) in ethanol (40 mL) was heated to reflux overnight under nitrogen. After this time, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting residue was mixed with saturated aqueous sodium bicarbonate (30 mL). The resulting aqueous mixture was extracted with methylene chloride (3 × 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluting with ethyl acetate/hexanes (8:2) to provide an inseparable regioisomers (+/-)-**K2** and (+/-)-**K3** as a yellow solid (391 mg, 11%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.02 (bs, 0.25 H), 6.70–6.40 (m, 3.75 H), 5.05 (d, J = 5.4 Hz, 0.86H), 4.62 (d, J = 5.4 Hz, 0.14H), 4.32 (bs, 1H), 3.08–2.94 (m, 1H), 2.30–1.81 (m, 4H), 1.61–1.50 (m, 1H), 1.36 and 1.30 (2 s, 9H); LRMS *m/z* 325 $[M+H]^+$.

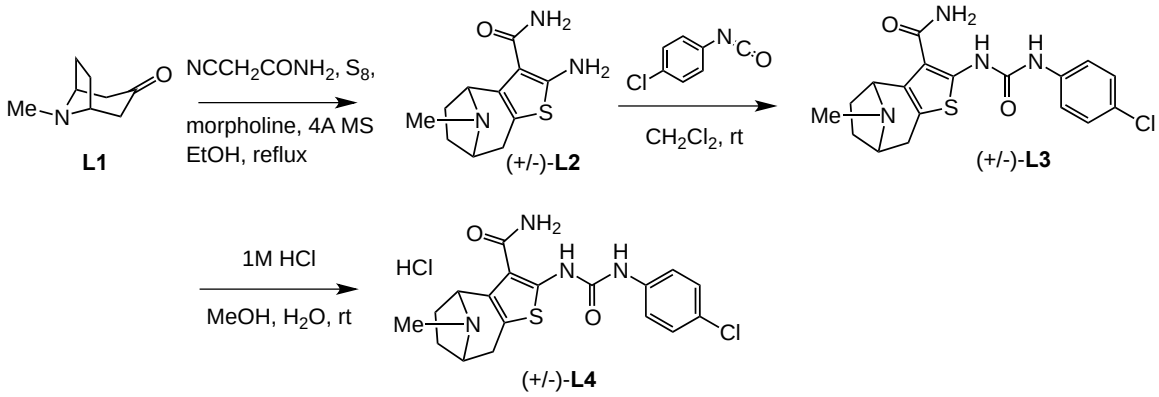
Step Two. (+/-)-*tert*-Butyl 3-Carbamoyl-2-[3-(4-chlorophenyl)ureido]-5,6,7,8-tetrahydro-4*H*-5,8-epiminocyclohepta[*b*]thiophene-9-carboxylate [(+/-)-K4, (regioisomer A) and (+/-)-K5 (regioisomer B)]. To the stirred mixture of regioisomers (+/-)-**K2** and (+/-)-**K3** (387 mg, 1.20 mmol) in methylene chloride (8 mL) at room temperature under nitrogen was added 4-chlorophenyl isocyanate (221 mg, 1.44 mmol). After addition, the reaction mixture was stirred overnight and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluting with ethyl acetate/hexanes (9:1) to provide regioisomer A (+/-)-**K4** as a pale yellow solid (396 mg, 69%) and regioisomer B (+/-)-**K5** as a yellow solid (112 mg, 20%). Regioisomer A [(+/-)-**K4**]: ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.59–10.51 (m, 1H), 10.06 (s, 1H), 7.51–6.80 (m, 6H), 5.03 (d, J = 5.1 Hz, 1H), 4.38 (bs, 1H), 3.19–3.10 (m, 1H), 2.29–1.90 (m, 4H), 1.65–1.60 (m, 1H), 1.36 and 1.28 (2 bs, 9H); LRMS *m/z* 475 $[M-H]^-$. Regioisomer B [(+/-)-**K5**]: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.09–11.01 (m, 1H), 10.20 (s, 1H), 7.62–6.70 (m, 6H), 4.82 (d, J = 5.1 Hz, 1H), 4.38 (bs, 1H), 2.15–1.52 (m, 6H), 1.23 (bs, 9H); LRMS *m/z* 475 $[M+H]^+$.

Step Three. (+/-)-2-[3-(4-Chlorophenyl)ureido]-5,6,7,8-tetrahydro-4*H*-5,8-epiminocyclohepta[*b*]thiophene-3-carboxamide [(+/-)-K6 and (+/-)-K7, mixture of regioisomers). To the stirred mixture of regioisomers (+/-)-**K4** and (+/-)-**K5** (3.5:1) (500 mg, 1.05 mmol) in methylene chloride (20 mL) and toluene (3 mL) at room temperature under nitrogen was added trifluoroacetic acid (4.60 g, 40.3 mmol). After addition, the reaction mixture was stirred for 4 h and concentrated under reduced pressure. The resulting residue was mixed with saturated aqueous sodium bicarbonate (30 mL). The resulting aqueous mixture was extracted with 5% methanol/methylene chloride (4 × 60 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered,

and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluting with ammonium hydroxide/methanol/methylene chloride (1:14:85) to provide an inseparable regioisomers (+/-)-**K6** and (+/-)-**K7** (3.5:1) as a white solid (321 mg, 81%): LRMS *m/z* 377 $[M+H]^+$.

Step Four. (+/-)-2-[3-(4-Chlorophenyl)ureido]-5,6,7,8-tetrahydro-4*H*-5,8-epiminocyclohepta[*b*]thiophene-3-carboxamide Hydrochloride [(+/-)-K8 (97) and (+/-)-K9 (94), mixture of regioisomers in Figure 2]. To the stirred mixture of regioisomers (+/-)-**K6** and (+/-)-**K7** (3.5:1) (37 mg, 0.10 mmol) in methanol at room temperature was added 1 M hydrochloric acid (2.0 mL, 2.0 mmol). The mixture was sonicated for 20 min, diluted with water, and lyophilized to provide a mixture of regioisomers (+/-)-**K8** (**97** in Figure 2) and (+/-)-**K9** (**94** in Figure 2) as a 3.5:1 mixture of isomers as a white solid (39 mg, 96%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.05 (s, 0.18H), 10.29 and 10.28 (2 s, 1H), 10.13 (s, 0.82H), 9.52 (bs, 1H), 9.23 and 9.21 (2 s, 0.18H), 9.01 and 8.98 (2 s, 0.82H), 7.55–7.20 (m, 6H), 5.00–4.95 (m, 1H), 4.31 (bs, 1H), 3.26–3.16 (m, 1H), 2.98–2.72 (m, 1H), 2.28–2.05 (m, 3H), 1.84–1.76 (m, 1H); LRMS *m/z* 377 $[M+H]^+$.

Scheme 12



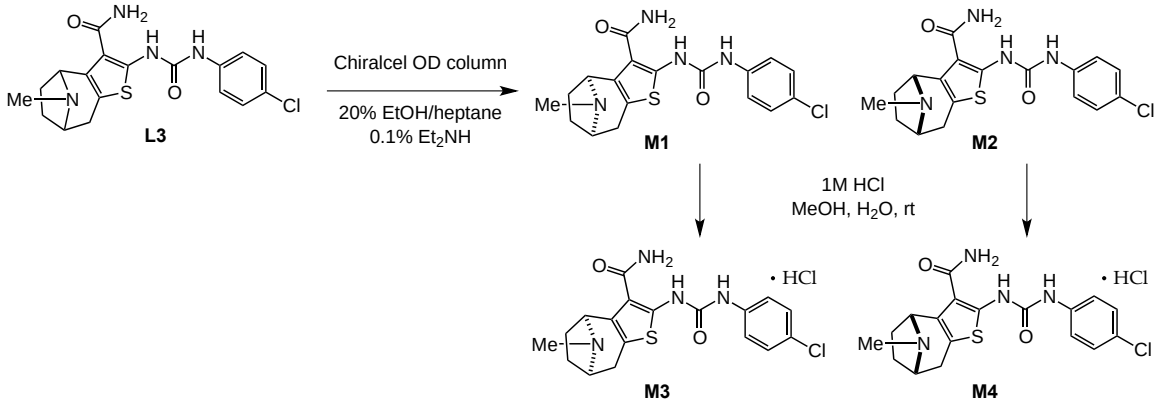
Preparation of (+/-)-2-[3-(4-Chlorophenyl)ureido)-9-methyl-5,6,7,8-tetrahydro-4*H*-5,8-epiminocyclohepta[*b*]thiophene-3-carboxamide Hydrochloride [(+/-)-L4, 88 in Figure 2].

Step One. (+/-)-2-Amino-9-methyl-5,6,7,8-tetrahydro-4*H*-5,8-epiminocyclohepta[*b*]-thiophene-3-carboxamide [(+/-)-L2]. The stirred mixture of tropinone (**L1**, 3.00 g, 21.6 mmol), 2-cyanoacetamide (1.99 g, 23.7 mmol), sulphur (830 mg, 25.9 mmol), and morpholine (3.75 g, 43.0 mmol) in ethanol (80 mL) was heated to reflux under nitrogen for 4 h. After this time, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting residue was diluted with saturated aqueous sodium bicarbonate (60 mL) and extracted with methylene chloride (3 × 150 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluting with methanol/methylene chloride (1:9) to provide compound (+/-)-**L2** as a brown solid (396 mg, 8%): LRMS *m/z* 238 $[M+H]^+$.

Step Two. (+/-)-2-[3-(4-Chlorophenyl)ureido]-9-methyl-5,6,7,8-tetrahydro-4*H*-5,8-epiminocyclohepta[*b*]thiophene-3-carboxamide [(+/-)-L3]. To the stirred mixture of compound (+/-)-**L2** (375 mg, 1.58 mmol) in methylene chloride (10 mL) at room temperature under nitrogen was added a solution of 4-chlorophenyl isocyanate (255 mg, 1.66 mmol) in methylene chloride (10 mL). The reaction mixture was stirred overnight and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluting with methanol/methylene chloride (15:85) to provide compound (+/-)-**L3** as an off-white solid (369 mg, 60%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.70 (bs, 1H), 10.05 (bs, 1H), 7.90–6.50 (m, 6H), 4.11 (bs, 1H), 2.99 (d, J = 14.1 Hz, 1H), 2.35–1.95 (m, 7H), 1.79 (bs, 1H), 1.48 (bs, 1H); LRMS *m/z* 391 $[M+H]^+$.

Step Three. (+/-)-2-[3-(4-Chlorophenyl)ureido]-9-methyl-5,6,7,8-tetrahydro-4*H*-5,8-epiminocyclohepta[*b*]thiophene-3-carboxamide Hydrochloride [(+/-)-L4, 88 in Figure 2]. To the mixture of compound (+/-)-**L3** (78 mg, 0.20 mmol) in methanol (3 mL) at 0 °C was added 1 M hydrochloric acid (0.30 mL, 0.30 mmol). After addition, the mixture was stirred for 5 min, diluted with water (6 mL), and lyophilized to provide compound (+/-)-**L4** (**88** in Figure 2) as a white solid (81 mg, 95%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.31 (bs, 0.38H), 10.34 and 10.32 (2 s, 1H), 10.22–10.18 (m, 1.62H), 7.60–7.33 (m, 6H), 4.94–4.82 (m, 1H), 4.19–4.09 (m, 1H), 3.38–3.16 (m, 1H), 2.86–2.68 (m, 4H), 2.49–2.08 (m, 3H), 1.89–1.79 (m, 1H); LRMS *m/z* 391 $[M+H]^+$.

Scheme 13



Preparation of (-) and (+)-2-[3-(4-Chlorophenyl)ureido]-9-methyl-5,6,7,8-tetrahydro-4*H*-5,8-epiminocyclohepta[*b*]thiophene-3-carboxamide Hydrochloride [(-)-M3, (-)-89 in Table 8 and (+)-M4, (+)-90, ORC-13661 in Table 8].

Step One. Chiral separation of (-)-2-[3-(4-Chlorophenyl)ureido]-9-methyl-5,6,7,8-tetrahydro-4*H*-5,8-epiminocyclohepta[*b*]thiophene-3-carboxamide [(-)-M3] and (+)-2-[3-(4-Chlorophenyl)ureido]-9-methyl-5,6,7,8-tetrahydro-4*H*-5,8-epiminocyclohepta[*b*]thiophene-3-carboxamide [(+)-M4]. Compound (+/-)-**L3** (720 mg) was separated by chiral preparative HPLC (20 µm CHIRALCEL OD, 5 cm × 50 cm, 100 mL/min flow rate, 120 mg/injection) eluting with 0.1% diethylamine in 20%

ethanol/heptane to provide (-)-**M1** as a white solid (268 mg, 37%), followed by (+)-**M2** (250 mg, 35%) as a white solid. Compound (-)-**M1**: LRMS *m/z* 391 $[M+H]^+$. Compound (+)-**M2**: LRMS *m/z* 391 $[M+H]^+$.

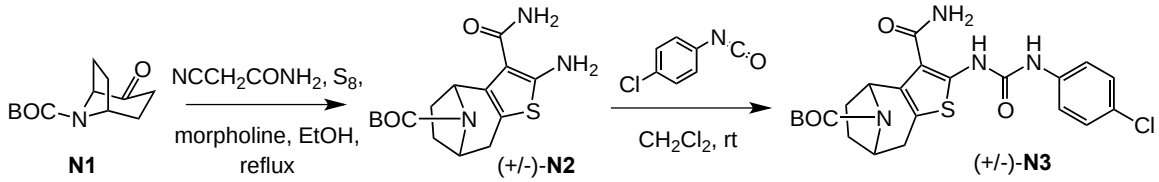
Step Two. (-)-2-[3-(4-Chlorophenyl)ureido]-9-methyl-5,6,7,8-tetrahydro-4*H*-5,8-epiminocyclohepta[*b*]thiophene-3-carboxamide Hydrochloride [(-)-M3, (-)-89 in Table 8] and (+)-2-[3-(4-Chlorophenyl)ureido]-9-methyl-5,6,7,8-tetrahydro-4*H*-5,8-epiminocyclohepta[*b*]thiophene-3-carboxamide Hydrochloride [(+)-M4, 90 in Table 8]. To the stirred mixture of compound (-)-**M1** (240 mg, 0.610 mmol) in methanol (30 mL) at room temperature was added 1 M hydrochloric acid (1.25 mL, 1.25 mmol) dropwise. After addition, the mixture was stirred for 10 min. After this time, the mixture was diluted with water (10 mL) and lyophilized to provide compound (-)-**M3 89** in Table 8] as a white solid (255 mg, 97%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.24 (bs, 0.40 H), 10.34 and 10.32 (2 s, 1H), 10.19–10.16 (m, 1.60H), 7.51–7.48 (m, 4H), 7.35 (d, J = 9.0 Hz, 2H), 4.95–4.82 (m, 1H), 4.19–4.08 (m, 1H), 3.43–3.17 (m, 1H), 2.88–2.68 (m, 4H), 2.45–2.09 (m, 3H), 1.89–1.80 (m, 1H); LRMS *m/z* 391 $[M+H]^+$; $[\alpha]_D$= -5.5º (c = 0.2, MeOH). **90**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.20 (bs, 0.34H), 10.34 and 10.31 (2 s, 1H), 10.18 (s, 1H), 10.16 (bs, 0.66H), 7.54–7.33 (m, 6H), 4.94–4.90 (m, 1H), 4.20–4.06 (m, 1H), 3.42–3.16 (m, 1H), 2.88–2.65 (m, 4H), 2.49–2.28 (m, 2H), 2.21–2.09 (m, 1H), 1.89–1.80 (m, 1H); LRMS *m/z* 391 $[M+H]^+$; $[\alpha]_D$= +3.5º (c = 0.2, MeOH).
Free base (**M1** and **M2**) optical rotations. **88**: -19.5º (c = 0.2, MeOH), T=25 ºC. **89**: +18.5º (c = 0.2, MeOH), T=25 ºC.

Compounds Prepared by Scheme 13

(+)-[1*R*,8*S*]-4-{[(4-Chlorophenyl)carbamoyl]amino}-11-methyl-3-thia-11-azatricyclo[6.2.1.0^{2,6}]undeca-2(6),4-diene-5-carboxamide Hydrochloride [(+)-92 in Table 8]. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.19 (bs, 0.34H), 10.35 and 10.30 (2 s, 1H), 10.18 (s, 1H), 10.17 (bs, 0.66H), 7.50–7.33 (m, 6H), 4.95–4.91 (m, 1H), 4.20–4.06 (m, 1H), 3.42–3.16 (m, 1H), 2.88–2.65 (m, 4H), 2.49–2.28 (m, 2H), 2.21–2.09 (m, 1H), 1.89–1.80 (m, 1H); HRMS (ESI) *m/z* calculated for $C_{18}H_{19}ClN_4O_2S$ $[M+H]^+$ 391.09899, found 391.09907; $[\alpha]_D$= +38º (c = 0.1g/100mL, MeOH), T = 22.2 ºC.

(-)-[1*S*,8*R*]-4-{[(4-Chlorophenyl)carbamoyl]amino}-11-methyl-3-thia-11-azatricyclo[6.2.1.0^{2,6}]undeca-2(6),4-diene-5-carboxamide Hydrochloride [(-)-93 in Table 8]. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.22 (bs, 0.40 H), 10.34 and 10.32 (2 s, 1H), 10.19–10.16 (m, 1.60H), 7.50–7.49 (m, 4H), 7.35 (d, J = 9.0 Hz, 2H), 4.95–4.82 (m, 1H), 4.19–4.09 (m, 1H), 3.43–3.17 (m, 1H), 2.88–2.71 (m, 4H), 2.45–2.09 (m, 3H), 1.88–1.81 (m, 1H); HRMS (ESI) *m/z* calculated for $C_{18}H_{19}ClN_4O_2S$ $[M+H]^+$ 391.09899, found 391.09944; $[\alpha]_D$ = -51.2º (c = 0.102g/100mL, MeOH), T = 28.1 ºC.

Scheme 14

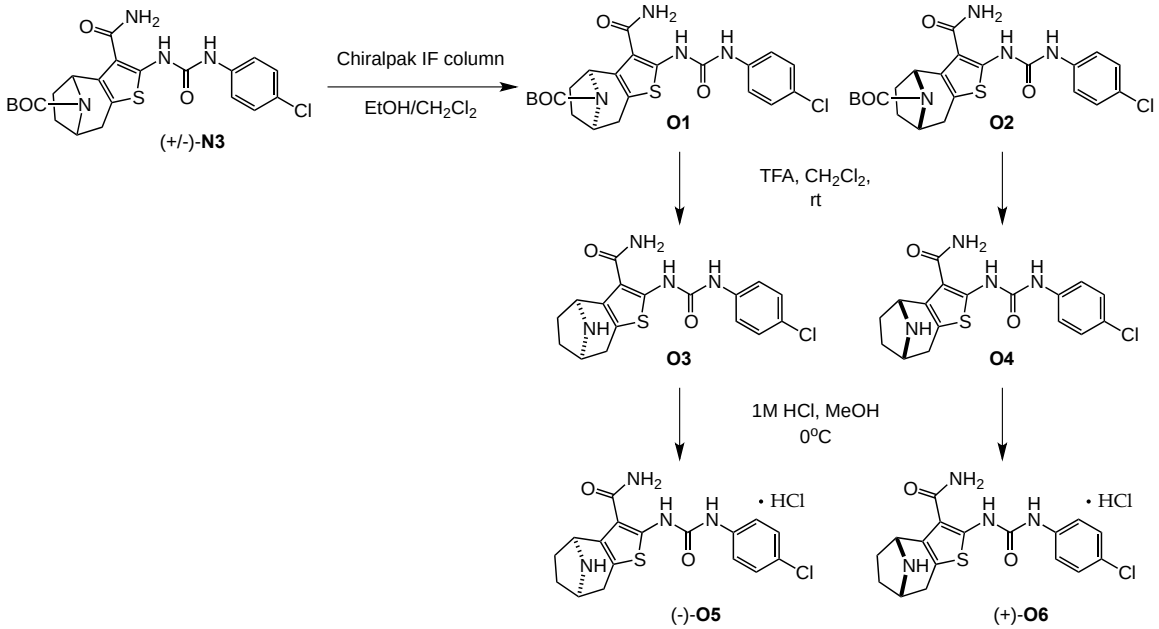


Preparation of (+/-)-2-[3-(4-Chlorophenyl)ureido]-5,6,7,8-tetrahydro-4*H*-5,8-epiminocyclohepta[*b*]thiophene-3-carboxamide (N3, 97 in Figure 2).

Step 1. (+/-)-**tert-Butyl 4-Amino-3-carbamoyl-5-thia-11-azatricyclo[6.2.1.0^{2,6}]undeca-2[6],3-diene-11-carboxylate (N2).** Into a 500-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of (+/-)-tert-butyl-2-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (**N1**) (9.0g, 40 mmol, 1.00 equiv) in ethanol (300 mL), 2-cyanoacetamide (3.7g, 44 mmol, 1.10 equiv), S_8 (1.41 g, 1.10 equiv), morpholine (10.4 g, 3.00 equiv). The resulting solution was stirred for 48 h at 50^{o}C in an oil bath. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with ethyl acetate/petroleum ether (1:10 ~ 1:1). This yielded 9.5 g (73%) of (+/-)-tert-butyl-4-amino-3-carbamoyl-5-thia-11-azatricyclo[6.2.1.0^{2,6}]undeca-2[6],3-diene-11-carboxylate (**N2**) as a yellow solid: LRMS *m/z* 324 $[M+H]^+$.

Step 2. (+/-)-**tert-Butyl 3-Carbamoyl-4-([(4-chlorophenyl]carbamoyl]amino)-5-thia-11-azatricyclo[6.2.1.0^{2,6}]undeca-2[6],4-diene-carboxylate (N3, 97 in Figure 2).** Into a 500mL 3-necked round-bottom flask, was placed a solution of (+/-)-tert-butyl-4-amino-3-carbamoyl-5-thia-11-azatricyclo[6.2.1.0^{2,6}]undeca-2[6],3-diene-11-carboxylate **N2** (9.5g, 29 mmol, 1.00 equiv), 1-chloro-4-isocyanatobenzene (4.95g, 32 mmol, 1.10 equiv) in dichloromethane (200 mL). The resulting solution was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with ethyl acetate/petroleum ether (1:10 ~ 1:1). This resulted in 11.5 g (82 %) of (+/-)-tert-butyl-3-carbamoyl-4-([(4-chlorophenyl]carbamoyl]amino)-5-thia-11-azatricyclo[6.2.1.0^{2,6}]undeca-2[6],4-diene-carboxylate (**N3**, **97** in Figure 2) as a yellow solid: ^{1}H NMR (300 MHz, CD_3OD) δ 7.48-7.42(m, 2H), 7.31-7.27(m, 2H), 5.20-5.18(br, 1H), 4.59-4.52(br, 1H), 2.53-2.49(m, 1H), 2.39- 2.04(m, 4H), 1.81-1.72(br, 1H), 1.46-1.38(m, 9H); LRMS *m/z* 477 $[M+H]^+$.

Scheme 15



Preparation of (-)-[1*S*,8*R*]-4-([(4-Chlorophenyl]carbamoyl]amino)-5-thia-11-azatricyclo[6.2.1.0^{2,6}]undeca-2[6],4-diene-carboxamide Hydrochloride [(-)-O5, (-)-98 in Table 8] and (+)-[1*R*,8*S*]-4-([(4-chlorophenyl]carbamoyl]amino)-5-thia-11-azatricyclo[6.2.1.0^{2,6}]undeca-2[6],4-diene-carboxamide Hydrochloride [(+)-O6, (+)-99 in Table 8].

Step 1. (-)-tert-Butyl 3-Carbamoyl-4-([(4-chlorophenyl]carbamoyl]amino)-5-thia-11-azatricyclo[6.2.1.0^{2,6}]undeca-2[6],4-diene-carboxylate [(-)-O1] and (+)-tert-Butyl 3-Carbamoyl-4-([(4-chlorophenyl]carbamoyl]amino)-5-thia-11-azatricyclo[6.2.1.0^{2,6}]undeca-2[6],4-diene-carboxylate [(+)-O2]. 11.6g of (+/-)-tert-butyl-3-carbamoyl-4-([(4-chlorophenyl]carbamoyl]amino)-5-thia=11-azatricyclo[6.2.1.0^{2,6}]undeca-2[6],4-diene-carboxylate (**N3**) was separated by Supercritical Fluid Chromatography (SFC) using a ChiralPak IF column with Mobile Phase A: CO_2:50, Mobile Phase B: MeOH:CH_2Cl_2 = 1:1:50, to yield (-)-tert-butyl-3-carbamoyl-4-([(4-chlorophenyl]carbamoyl]amino)-5-thia-11-azatricyclo[6.2.1.0^{2,6}]undeca-2[6],4-diene-carboxylate [(-)-**O1**] and (+)-tert-butyl-3-carbamoyl-4-([(4-chlorophenyl]carbamoyl]amino)-5-thia-11-azatricyclo[6.2.1.0^{2,6}]undeca-2[6],4-diene-carboxylate [(+)-**O2**].

Step 2. (-)-[1*S*,8*R*]-4-([(4-Chlorophenyl]carbamoyl]amino)-5-thia-11-azatricyclo[6.2.1.0^{2,6}]undeca-2[6],4-diene-carboxamide [(-)-O3]. Into a 250-mL 3-necked round-bottom flask, was placed a solution of (-)-tert-butyl-3-carbamoyl-4-([(4-chlorophenyl]carbamoyl]amino)-5-thia-11-azatricyclo[6.2.1.0^{2,6}]undeca-2[6],4-diene-carboxylate [(-)-**O1**, 5.0g, 11 mmol, 1.00 equiv] in dichloromethane (100 mL), trifluoroacetic acid (20 mL). The resulting solution was stirred for 30 min at room temperature. The resulting mixture was concentrated under vacuum. The residue was

diluted with 100 mL of EtOAc, washed with 2x100 mL of sodium bicarbonate/H_2O and 2x100 mL of brine. The organic phase was dried over anhydrous sodium sulfate. The solids were filtered out. This resulted in 3.5g (89%) of (-)-**O3** as a yellow solid: LRMS *m/z* 377 $[M+H]^+$.

Step 3. (-)-[1*S*,8*R*]-4-([(4-Chlorophenyl]carbamoyl]amino)-5-thia-11-azatricyclo[6.2.1.0^{2,6}]undeca-2[6],4-diene-carboxamide Hydrochloride [(-)-O5, 98 in Table 8]. Into a 250-mL 3-necked round-bottom flask, was placed a solution of **(-)-[**1*S*,8*R*]-4-([(4-chlorophenyl]carbamoyl]amino)-5-thia-11-azatricyclo[6.2.1.0^{2,6}]undeca-2[6],4-diene-carboxamide [(-)-**O3**, 3.5g, 9.3 mmol, 1.00 equiv] in methanol (100 mL) and 1 M HCl (18.6 mL). The resulting solution was stirred for 30 min at 0ºC in an ice/salt bath. The resulting mixture was concentrated under vacuum. This resulted in 3.2520 g (85%) of **(-)-[**1S,8R]-4-([(4-chlorophenyl]carbamoyl]amino)-5-thia-11-azatricyclo[6.2.1.0^{2,6}]undeca-2[6],4-diene-carboxamide hydrochloride [(-)-**O5**, **98** in Table 8] as a pink solid: ^{1}H NMR (300 MHz, DMSO) δ 10.27 (s, 1H), 10.10 (s, 1H), 9.46 (br, 1H), 8.99 (d, *J* = 9.3 Hz, 1H), 7.51-7.17(m, 6H), 5.0(s, 1H), 4.32(s, 1H), 3.31-3.24(m, 1H), 2.80(d, *J* = 16.8 Hz, 1H), 2.27 - 2.09(m, 3H), 1.82-1.69(br, 1H); HRMS (ESI) *m/z* calculated for $C_{17}H_{17}ClN_4O_2S$ $[M+H]^+$ 377.08334, found 377.08347; $[\alpha]_D$ (free base) +3.66º (c = 0.25, MeOH).

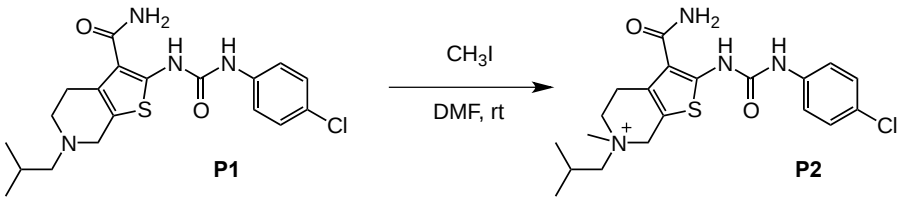
Compounds Prepared by Scheme 15

(+)-2-[3-(4-Chlorophenyl)ureido]-5,6,7,8-tetrahydro-4*H*-5,8-epiminocyclohepta[*b*]thiophene-3-carboxamide Hydrochloride [95 in Table 8]. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.04 (m, 1H), 10.31 (s, 1H), 9.83 (bs, 1H), 9.28 (bs, 1H), 7.75–6.90 (m, 6H), 4.94 (bs 1H), 4.30 (bs, 1H), 3.30–3.12 (m, 1H), 2.99–2.89 (m, 1H), 2.29–2.02 (m, 3H), 1.90–1.79 (m, 1H); LRMS *m/z* 377 $[M+H]^+$; $[\alpha]_D$ +42.5º (c = 0.2, MeOH), T = 25 ºC.

(-)-2-[3-(4-Chlorophenyl)ureido]-5,6,7,8-tetrahydro-4*H*-5,8-epiminocyclohepta[*b*]thiophene-3-carboxamide Hydrochloride [96 in Table 8]. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.05 (s, 1H), 10.31 (s, 1H), 9.80 (bs, 1H), 9.26 (bs, 1H), 7.80–6.79 (m, 6H), 4.94 (bs, 1H), 4.30 (bs, 1H), 3.31 (d, *J* = 15.3 Hz, 1H), 2.96 (d, *J* = 16.5 Hz, 1H), 2.29–2.03 (m, 3H), 1.95–1.85 (m, 1H); HRMS (ESI) *m/z* calculated for $C_{17}H_{17}ClN_4O_2S$ $[M+H]^+$ 377.08334, found 377.08349; $[\alpha]_D$ -39.5º (c = 0.2, MeOH), T = 25 ºC.

(+)-[1*R*,8*S*]-4-([(4-chlorophenyl]carbamoyl]amino)-5-thia-11-azatricyclo[6.2.1.0^{2,6}]undeca-2[6],4-diene-carboxamide Hydrochloride O6 [99 in Table 8]. ^{1}H NMR (300 MHz, DMSO): δ 10.27 (s, 1H), 10.13 (s, 1H), 9.64 (br, 1H), 9.01 (d, *J* = 9.0 Hz, 1H), 7.57-7.21(m, 6H), 5.0(s, 1H), 4.31(s, 1H), 3.31-3.24(m, 1H), 2.80(d, *J* = 17.1 Hz, 1H), 2.27 - 2.08(m, 3H), 1.82-1.77(br, 1H); HRMS (ESI) *m/z* calculated for $C_{17}H_{17}ClN_4O_2S$ $[M+H]^+$ 377.08334, found 377.08357; $[\alpha]_D$ (free base) -3.44º (c = 0.25, MeOH).

Scheme 16



Preparation of 3-Carbamoyl-2-[3-(4-chlorophenyl)ureido]-6-isobutyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-6-ium Iodide (P2) (71 in Table 7).

Step One. 3-Carbamoyl-2-[3-(4-chlorophenyl)ureido]-6-isobutyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-6-ium Iodide (P2, 71 in Table 7). A solution of compound **P1** (30 mg, 0.074 mmol) and iodomethane (14 mg, 0.096 mmol) in *N*,*N*-dimethylformamide (1.5 mL) was stirred at room temperature for 18 h. After this time, the reaction mixture was concentrated under reduced pressure. The resulting residue was triturated with methylene chloride to afford compound **P2** (**71** in Table 1) as a light yellow solid (27 mg, 68%): ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.81 (s, 1H), 10.26 (s, 1H), 7.80–6.90 (m, 6H), 4.59 (s, 2H), 3.70–3.63 (m, 2H), 3.41–3.31 (m, 2H), 3.19–3.12 (m, 2H), 3.10 (s, 3H), 2.36–2.34 (m, 1H), 1.08 (d, J = 6.8 Hz, 3H), 1.05 (d, J = 6.8 Hz, 3H); LRMS *m/z* 421 $[M]^+$.

Compounds Prepared by Scheme 16

3-Carbamoyl-2-[3-(4-chlorophenyl)ureido]-6-ethyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-6-ium Iodide (68 in Table 7). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.80 (s, 1H), 10.26 (s, 1H), 7.72–7.29 (m, 5H), 7.14 (bs, 1H), 4.59–4.52 (m, 2H), 3.71–3.58 (m, 2H), 3.51–3.42 (m, 2H), 3.20–3.10 (m, 2H), 3.05 (s, 3H), 1.34 (t, J = 7.0 Hz, 3H); LRMS *m/z* 393 $[M]^+$.

3-Carbamoyl-2-[3-(4-chlorophenyl)ureido]-6,6-diethyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-6-ium Iodide (69 in Table 7). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.79 (s, 1H), 10.26 (s, 1H), 7.80–7.00 (m, 6H), 4.56 (s, 2H), 3.65–3.35 (m, 6H), 3.13–3.10 (m, 2H), 1.28 (t, J = 7.5 Hz, 6H); LRMS *m/z* 407 $[M]^+$.

3-Carbamoyl-2-[3-(4-chlorophenyl)ureido]-6-methyl-6-neopentyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-6-ium Iodide (72 in Table 7). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.81 (s, 1H), 10.26 (s, 1H), 7.80–6.90 (m, 6H), 4.68–4.63 (m, 2H), 3.71–3.67 (m, 2H), 3.18–3.09 (m, 7H), 1.18 (s, 9H); LRMS *m/z* 435 $[M]^+$.

3-Carbamoyl-2-[3-(4-chlorophenyl)ureido]-6-(cyclopropylmethyl)-6-methyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-6-ium Iodide (73 in Table 7). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.80 (s, 1H), 10.26 (s, 1H), 7.80–7.00 (m, 6H), 4.62 (ABq, J = 15.0 Hz,

2H), 3.75–3.41 (m, 3H), 3.28–3.12 (m, 6H), 1.26–1.23 (m, 1H), 0.75 (bs, 2H), 0.41 (bs, 2H); LRMS *m/z* 419 $[M+H]^+$.

3-Carbamoyl-2-[3-(4-chlorophenyl)ureido]-6-(cyclobutylmethyl)-6-methyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-6-ium Iodide (74 in Table 7). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.80 (s, 1H), 10.26 (s, 1H), 7.80–7.00 (m, 6H), 4.51 (s, 2H), 3.65–3.45 (m, 4H), 3.14 (bs, 2H), 3.03 (s, 3H), 2.98–2.90 (m, 1H), 2.20–1.70 (m, 6H); LRMS *m/z* 433 $[M+H]^+$.

3-Carbamoyl-2-[3-(4-chlorophenyl)ureido]-6-(cyclopentylmethyl)-6-methyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-6-ium Iodide (75 in Table 7). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.81 (s, 1H), 10.26 (s, 1H), 7.80–7.00 (m, 6H), 4.58 (s, 2H), 3.70–3.46 (m, 4H), 3.17–3.14 (m, 2H), 3.10 (s, 3H), 2.42–2.39 (m, 1H), 1.99–1.20 (m, 8H); LRMS *m/z* 447 $[M+H]^+$.

3-Carbamoyl-2-[3-(4-chlorophenyl)ureido]-6-(cyclohexylmethyl)-6-methyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-6-ium Iodide (76 in Table 7). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.81 (s, 1H), 10.26 (s, 1H), 7.80–7.00 (m, 6H), 4.58 (s, 2H), 3.75–3.60 (m, 2H), 3.28–3.12 (m, 4H), 3.09 (s, 3H), 2.10–1.55 (m, 6H), 1.40–1.00 (m, 5H); LRMS *m/z* 461 $[M+H]^+$.

6-(4-*tert*-Butoxy-4-oxobutyl)-3-carbamoyl-2-[3-(4-chlorophenyl)ureido]-6-methyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-6-ium Trifluoroacetate (78 in Table 7). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.83 (s, 1H), 10.27 (s, 1H), 7.80–6.90 (m, 6H), 4.59 (s, 2H), 3.68–3.37 (m, 4H), 3.16–3.14 (m, 2H), 3.11 (s, 3H), 2.35–1.97 (m, 4H), 1.41 (s, 9H); LRMS *m/z* 507 $[M+H]^+$.

6-(5-*tert*-Butoxy-5-oxopentyl)-3-carbamoyl-2-[3-(4-chlorophenyl)ureido]-6-methyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-6-ium Iodide (79 in Table 7). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.80 (s, 1H), 10.26 (s, 1H), 7.80–6.90 (m, 6H), 4.56 (s, 2H), 3.70–3.36 (m, 4H), 3.15 (bs, 2H), 3.08 (s, 3H), 2.30–2.27 (m, 2H), 1.80–1.50 (m, 4H), 1.41 (s, 9H); LRMS *m/z* 521 $[M+H]^+$.

6-(6-*tert*-Butoxy-6-oxohexyl)-3-carbamoyl-2-[3-(4-chlorophenyl)ureido]-6-methyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-6-ium Iodide (80 in Table 7). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.81 (s, 1H), 10.26 (s, 1H), 7.80–7.00 (m, 6H), 4.60–4.50 (m, 2H), 3.68–3.35 (m, 4H), 3.15 (bs, 2H), 3.08 (s, 3H), 2.25–2.22 (m, 2H), 1.78–1.53 (m, 4H), 1.40 (s, 9H), 1.32–1.27 (m, 2H); LRMS *m/z* 535 $[M+H]^+$.

3-Carbamoyl-2-[3-(4-chlorophenyl)ureido]-6-(3-methoxypropyl)-6-methyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-6-ium Iodide (81 in Table 7). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.81 (s, 1H), 10.26 (s, 1H), 7.70–7.00 (m, 6H), 4.65–4.59 (m, 2H), 3.69–3.41 (m, 6H), 3.26 (s, 3H), 3.16–3.14 (m, 2H), 3.09 (s, 3H), 2.09–2.02 (m, 2H); LRMS *m/z* 437 $[M+H]^+$.

3'-Carbamoyl-2'-[3-(4-chlorophenyl)ureido]-5',7'-dihydro-4'*H*-spiro[pyrrolidine-1,6'-thieno[2,3-*c*]pyridin]-1-ium Bromide (82 in Table 7). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.81 (s, 1H), 10.26 (s, 1H), 7.71–6.99 (m, 6H), 4.60 (s, 2H), 3.74–3.69 (m, 2H), 3.63–3.50 (m, 4H), 3.22–3.16 (m, 2H), 2.18–2.10 (m, 4H); LRMS *m/z* 405 $[M+H]^+$.

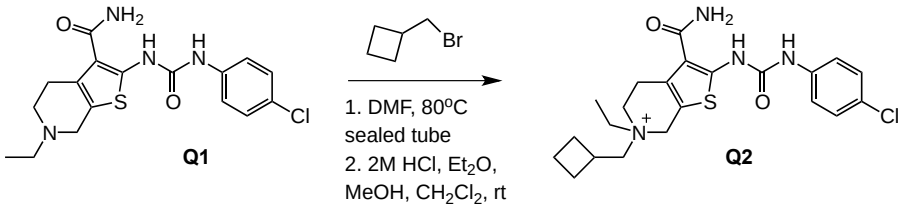
3'-Carbamoyl-2'-[3-(4-chlorophenyl)ureido]-5',7'-dihydro-4'*H*-spiro[morpholine-4,6'-thieno[2,3-*c*]pyridin]-4-ium Iodide (83 in Table 7). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.80 (s, 1H), 10.27 (s, 1H), 7.80–6.90 (m, 6H), 4.80 (s, 2H), 4.15–3.85 (m, 6H), 3.58–3.50 (m, 4H), 3.18 (bs, 2H); LRMS *m/z* 421 $[M+H]^+$.

3-Carbamoyl-2-[3-(4-chlorophenyl)ureido]-5-ethyl-5-methyl-5,6-dihydro-4*H*-thieno[2,3-*c*]pyrrol-5-ium Iodide (84 in Table 7). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.14 (s, 1H), 10.37 (s, 1H), 7.70–6.90 (m, 6H), 5.00–4.97 (m, 1H), 4.88–4.82 (m, 2H), 4.73–4.68 (m, 1H), 3.72–3.66 (m, 2H), 3.25 (s, 3H), 1.31 (t, *J* = 7.0 Hz, 3H); LRMS *m/z* 379 $[M+H]^+$.

1-{3-Carbamoyl-2-[3-(4-chlorophenyl)ureido]-4,5,6,7-tetrahydrobenzo[*b*]thiophen-6-yl}-1-methylazetidin-1-ium Iodide (85 in Table 7). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.94 (s, 1H), 10.20 (s, 1H), 7.80–6.70 (m, 6H), 4.67–3.89 (m, 5H), 3.12–2.70 (m, 8H), 2.35–1.65 (m, 3H); LRMS *m/z* 419 $[M+H]^+$.

3-Carbamoyl-2-[3-(4-chlorophenyl)ureido]-*N*,*N*,*N*-trimethyl-4,5,6,7-tetrahydrobenzo[*b*]thiophen-6-aminium Iodide (86 in Table 7). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.94 (s, 1H), 10.20 (s, 1H), 7.80–6.70 (m, 6H), 3.76 (bs, 1H), 3.29–2.80 (m, 13H), 2.27 (bs, 1H), 1.77–1.74 (m, 1H); LRMS *m/z* 407 $[M+H]^+$.

Scheme 17



Preparation of 3-Carbamoyl-2-[3-(4-chlorophenyl)ureido]-6-(cyclobutylmethyl)-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-6-ium Chloride (Q2, 77 in Table 7).

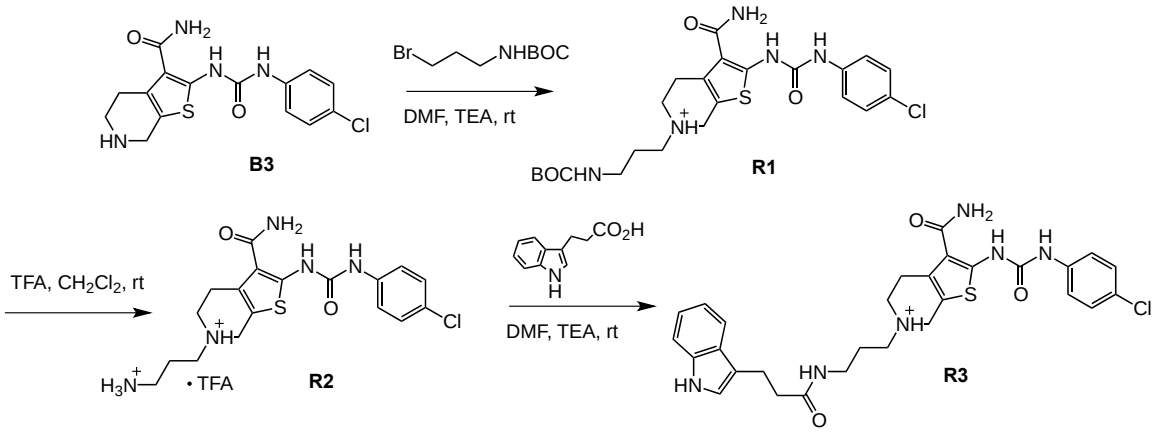
Step One. 3-Carbamoyl-2-[3-(4-chlorophenyl)ureido]-6-(cyclobutylmethyl)-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-6-ium Chloride (Q2, 77 in Table 7). A solution of compound **CC1** (400 mg, 1.06 mmol) and (bromomethyl)cyclobutane (1.59 g, 10.7 mmol) in *N*,*N*-dimethylformamide (5 mL) was heated to 80 °C in a sealed tube for 22 h. After this time, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluting with methanol to 5% ammonium hydroxide/methanol followed by reverse phase semi-preparative HPLC eluting with 0.05% TFA in acetonitrile/water (gradient from 10% to 100%, Phenomenex Luna

column). The product was dissolved in a mixture of methanol (2 mL), methylene chloride (5 mL), and hydrochloride (2 M in diethyl ether, 1 mL). The resulting solution was concentrated under reduced pressure to afford compound **Q2** (**77** in Table 7) as an off-white solid (55 mg, 11%): ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.79 (s, 1H), 10.29 (s, 1H), 7.70–6.90 (m, 6H), 4.55–4.45 (m, 2H), 3.61–3.58 (m, 2H), 3.41–3.35 (m, 4H), 3.20–3.05 (m, 2H), 2.90–2.80 (m, 1H), 2.20–1.70 (m, 6H), 1.28 (t, J = 7.1 Hz, 3H); LRMS *m/z* 447 $[M+H]^+$.

Compounds Prepared by Scheme 17

3-Carbamoyl-2-[3-(4-chlorophenyl)ureido]-6-isopropyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridin-6-ium Iodide (70 in Table 7). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.80 (s, 1H), 10.26 (s, 1H), 7.80–7.00 (m, 6H), 4.66–4.47 (m, 2H), 3.85–3.54 (m, 3H), 3.14 (bs, 2H), 2.92 (s, 3H), 1.41–1.36 (m, 6H); LRMS *m/z* 407 $[M+H]^+$.

Scheme 18



Preparation of 2-{[(4-Chlorophenyl)carbamoyl]amino}-6-{3-[3-(1*H*-indol-3-yl)propanamido]propyl}-4*H*,5*H*,6*H*,7*H*-thieno[2,3-*c*]pyridine-3-carboxamide (R3, 67 in Table 6).

Step 1. 6-(3-Aminopropyl)-2-{[(4-chlorophenyl)carbamoyl]amino}-4*H*,5*H*,6*H*,7*H*-thieno[2,3-*c*]pyridine-3-carboxamide (R1). A stirred suspension of tert-butyl-N-[3-(2-{[(4-benzoylphenyl)carbamoyl]amino}-3-carbamoyl-4H,5H,6H,7H-thieno[2,3-c]pyridin-6-yl)propyl]carbamate (**R1**) (70 mg, 0.14 mmol) in 4 mL of methylene chloride at room temperature was treated with 2 mL of TFA. The resulting solution was stirred at room temperature for 40 min whereupon it was concentrated in a rotary evaporator. The product was taken up in MeOH and the solution concentrated in *vacuo* (x2) to afford (**R2**) as a light tan solid in quantitative yield: LRMS *m/z* 408 $[M+H]^+$.

2-{[(4-Chlorophenyl)carbamoyl]amino}-6-{3-[3-(1*H*-indol-3-yl)-propanamido]propyl}-4*H*,5*H*,6*H*,7*H*-thieno[2,3-*c*]pyridine-3-carboxamide (R3, 67 in Table 6). To a stirred solution of 6-(3-aminopropyl)-2-{[(4-chlorophenyl)carbamoyl]amino}-4H,5H,6H,7H-thieno[2,3-c]pyridine-3-carboxamide

(**R2**) (0.14 mmol) in anhydrous THF (1.5) were added triethylamine (93 μL, 0.66 mmol), 3-indolepropionic acid (31 mg, 0.16 mmol), EDC•HCl (31 mg, 0.16 mmol), HOBt (25 mg, 0.16 mmol) and the resultant mixture was stirred at room temperature for 8 h. Upon completion, the solvent was removed *in vacuo* and the oil was taken up in methylene chloride. The organics were washed with water (x2) and dried (anhydrous Na_2SO_4) and evaporated to afford the crude product **67** which was purified by flash chromatography Isolera system (SiO_2 gel as stationary phase, 12 g HP column, dry loading) using methylene chloride–methylene chloride/MeOH (0%- 12% MeOH in methylene chloride) to afford **67** (Table 6) as a brown solid (31 mg, 37% yield): ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.55 (d, *J*= 15.5 Hz, 1H), 7.50- 7.43 (m, 2H), 7.34–7.24 (m, 3H), 7.12–6.95 (m, 3H), 3.38 (bs, 2H), 3.17 (t, *J*= 6.7 Hz, 2H), 3.06 (t, *J*= 7.2 Hz, 2H), 2.82–2.74 (m, 2H), 2.68–2.61 (m, 2H), 2.55 (t, *J*= 7.2 Hz, 2H), 2.36-2.27 (m, 2H), 1.67–1.54 (m, 2H); LRMS *m/z* 579 $[M+H]^+$.

Compounds Prepared by Scheme 18

2-{[(4-Chlorophenyl)carbamoyl]amino}-6-{3-[3-(pyridin-3-yl)propanamido]propyl}-4*H*,5*H*,6*H*,7*H*-thieno[2,3-*c*]pyridine-3-carboxamide (65 in Table 6). ^{1}H NMR (300 MHz, MeOH-d_4) δ 8.13–8.04 (m, 1H), 7.88–7.81 (m, 1H), 7.75–7.68 (m, 1H), 7.57–7.22(m, 4H), 3.52 (bs, 2H), 3.42–3.33 (m, 2H), 3.18 (t, *J*=6.6 Hz, 2H), 2.87–2.72 (m, 4H), 2.65-2.56 (m, 2H), 2.48-2.40 (m, 2H), 1.73-1.59 (m, 2H); LRMS *m/z* 541 $[M+H]^+$.

2-{[(4-Chlorophenyl)carbamoyl]amino}-6-{3-[3-(naphthalen-1-yl)propanamido]propyl}-4*H*,5*H*,6*H*,7*H*-thieno[2,3-*c*]pyridine-3-carboxamide (66 in Table 6). ^{1}H NMR (300 MHz, MeOH-d_4) δ 8.13–8.04 (m, 1H), 7.88–7.81 (m, 1H), 7.75–7.68 (m, 1H), 7.57–7.22(m, 8H), 3.52 (bs, 2H), 3.42–3.33 (m, 2H), 3.18 (t, *J*=6.6 Hz, 2H), 2.87–2.72 (m, 4H), 2.65-2.56 (m, 2H), 2.48-2.40 (m, 2H), 1.73-1.59 (m, 2H); LRMS *m/z* 590 $[M+H]^+$.

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