_N_-{3-[2-(4-Alkoxyphenoxy)thiazol-5-yl]-1-methylprop-2-ynyl}carboxy Derivatives as Acetyl-CoA Carboxylase Inhibitors–Improvement of Cardiovascular and Neurological Liabilities via Structural Modifications

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Supporting Information

- Protocols for hACC1 and hACC2 Assays.
- Experimental procedures for the synthesis of **5b**,**5d-f**, **5h-i, 9**, **9**-(*S*), **9**-(*R*) and **12**.
- Chiral HPLC chromatograms of **9**-(*S*) and **9**-(*R*).
- Table S1 – ^{1}H and ^{13}C NMR, and MS of the new compounds.
- Table S2 – Analytical data of the new compounds.
- Table S3 – Pharmacokinetic profiles of **1**-(±), **9**-(±), **9**-(*S*) and **9**-(*R*) in rats.

General Spectroscopic and Experimental Data. The NMR spectra were obtained on Bruker ARX-300 and Varian Inova-500 magnetic resonance spectrometer with internal standard as indicated for individual compounds. The chemical shifts are given in delta (δ) values and the coupling constants (J) in Hertz (Hz). Mass spectral analyses were accomplished using different techniques, including desorption chemical ionization (DCI), atmospheric pressure chemical ionization (APCI), and electrospray ionization (ESI), as specified for individual compounds. Elemental analysis was performed by Robertson Microlit Laboratories, Inc., Madison, New Jersey. All manipulations were performed under nitrogen atmosphere unless otherwise mentioned. All solvents and reagents were purified when necessary using standard procedures. Flash column chromatography was performed on silica gel 60 (Merck, 230-400 mesh) using the indicated solvent, or on Isco Companion system. Preparative HPLC was performed on an automated Gilson HPLC system. Mobile phase A: 0.1% TFA in H_2O. Mobile phase B: 0.1% TFA in CH_3CN.

hACC1 and hACC2 Assays. The ACC2 enzymatic assay has been developed using purified recombinant human ACC1 and ACC2 expressed in HEK293 and baculovirus/Sf9 system, respectively. In order to increase the expression and solubility of the protein, a chimeric version of ACC2 ("mito-minus"), in which the N-terminal transmembrane domain (1-275 amino acids of ACC2) was replaced with the corresponding ACC1 sequence (1-133 amino acids). The enzymatic assay measures ACC mediated incorporation of [^{14}C] CO_2 into [^{14}C]-Malonyl CoA. The assay was preformed in 40µL reaction in a 96-well plate format. The assay buffer contains 50 mM Hepes/NaOH, pH 7.5, 10 mM citrate, 20 mM $MgCl_2$, 2 mM DTT, and 0.075% BSA. First, 20µL of test compounds was dissolved in 1% DMSO in assay buffer was dispensed into 96-well. Then, 10µL of enzyme in assay buffer was dispensed. The reaction was initiated by adding the following substrate mixture in assay buffer: 0.5 mM ATP, 0.25 mM acetyl-CoA, and 4 mM $NaHCO_3$ (0.6 mCi). The reaction was carried out at room temperature for 35 minutes and terminated by adding 100µL of 1N HCl. The plate was air-dried in a fume hood at room temperature overnight. 30µL of distilled water was added followed by adding 150µL of SuperMix liquid scintillation fluid (PerkinElmer). The radioactivity was determined in PerkinElmer microbeta after vigorous shaking. The IC_{50} value was calculated from eight-point dose response curve of test compounds in duplicates.

Synthesis of N-(4-(2-(4-(cyclopropylmethoxy)phenoxy)thiazol-5-yl)but-3-yn-2-yl)acetamide (5d)

4-(5-Bromothiazol-2-yloxy)phenol. A solution of 2,5-dibromothiazole (5 g, 20.58 mmol) and hydroquinone (4.53 g, 41.16 mmol) in DMF (100mL) was treated with potassium carbonate (2.86g, 20.58 mmol) and the mixture was heated at 140°C for 2 h. The reaction was cooled to 25°C, poured into water (400 mL) and extracted with diethyl ether (3 x 250 mL). The combined organics was washed with water (3 x 150 mL) and brine (150 mL), dried over sodium sulfate and concentrated. The crude concentrate (6.4 g) was purified on a silica gel flash column eluting with a solvent gradient (10% to 25% ethyl acetate in hexanes) to provide 3.6 g (64%) of the product as a white solid. ^{1}H NMR (300 MHz, DMSO-D_6) δ ppm 9.70 (s, 1 H), 7.40 (s, 1 H), 7.10 - 7.23 (m, 2 H), 6.73 - 6.92 (m, 2 H); MS (ESI) *m/z* 273.6 $(M + H)^+$.

5-Bromo-2-(4-(cyclopropylmethoxy)phenoxy)thiazole. To a solution of 4-(5-bromothiazol-2-yloxy)phenol (2g, 7.35 mmol), cyclopropylmethanol (1.17 mL, 14.7 mmol), and resin-triphenylphosphine (3.7g, 3mmol/g) in THF (70 mL) was added diethyl azodicarboxylate (1.75 mL, 11mmol) dropwise at ambient temperature under nitrogen. The reaction mixture was stirred for 4 hours and concentrated *in vacuo*. The crude concentrate was purified by reverse-phase HPLC on an Atlantis C18 column (1.9 x 10 cm, 5 μm particle size) using a gradient of 5% to 95% acetonitrile : 0.1% aqueous TFA to provide 1.81g (79%) of the desired product. ^{1}H NMR (300 MHz, DMSO-D_6) δ ppm 7.42 (s, 1 H), 7.21 - 7.36 (m, 2 H), 6.96 - 7.06 (m, 2 H), 3.83 (d, *J* = 6.99 Hz, 2 H), 1.11 - 1.30 (m, 1 H), 0.51 - 0.66 (m, 2 H), 0.25 - 0.38 (m, 2 H); MS (ESI) *m/z* 327.1 $(M + H)^+$.

2-(4-(2-(4-(Cyclopropylmethoxy)phenoxy)thiazol-5-yl)but-3-yn-2-yl)isoindoline-1,3-dione. A solution of 5-bromo-2-(4-(cyclopropylmethoxy)phenoxy)thiazole (1.9 g, 5.86 mmol), 2-(1-Methyl-prop-2-ynyl)-isoindole-1,3-dione (1.64 g, 8.2 mmol), and Et_3N (4 mL, 629 mmol) in THF (40 mL) was degassed and treated with $Pd(PPh_3)_2Cl_2$ (70 mg, 0.1 mmol) and CuI (5 mg, 0.05 mmol). The reaction mixture was heated under nitrogen at 75°C for 2.5 h. The solvent was evaporated and the crude concentrate was purified on a silica gel flash column eluting with a solvent gradient of 65% to 95% ethyl acetate in hexanes to provide 2.3 g (88%) of the desired compound as a light yellow solid. MS (ESI) *m/z* 302.8 $(M + H)^+$.

4-(2-(4-(Cyclopropylmethoxy)phenoxy)thiazol-5-yl)but-3-yn-2-amine. To a solution of 2-(4-(2-(4-(cyclopropylmethoxy)phenoxy)thiazol-5-yl)but-3-yn-2-yl)isoindoline-1,3-dione (2.2g, 4.95 mmol) in EtOH (30 mL) was added hydrazine monohydrate (1.4 mL, 29.7 mmol). The reaction mixture was heated at 60°C for 45 min and filtered. The filtrate was concentrated and purified on a silica gel flash column eluting with methylene chloride/methanol/concentrated ammonium hydroxide (90/8/2) to provide 1.51g of the desired product (97%). ^{1}H NMR (300 MHz, DMSO-D_6) δ ppm 7.40 (s, 1 H), 7.24 - 7.36 (m, 2 H), 6.94 - 7.07 (m, 2 H), 3.83 (d, *J* = 6.99 Hz, 2 H), 3.71 - 3.81 (m, 1 H), 1.89 - 1.98 (m, 2 H), 1.25 (d, *J* = 6.62 Hz, 3 H), 1.11 - 1.23 (m, 1 H), 0.52 - 0.65 (m, 2 H), 0.27 - 0.37 (m, 2 H); MS (ESI) *m/z* 315.2$(M + H)^+$.

N-(4-(2-(4-(Cyclopropylmethoxy)phenoxy)thiazol-5-yl)but-3-yn-2-yl)acetamide (5d). To a solution of 4-(2-(4-(cyclopropylmethoxy)phenoxy)thiazol-5-yl)but-3-yn-2-amine (210 mg, 0.67 mmol) and triethylamine (280 uL, 2mmol) in methylene chloride (5mL) was added acetyl chloride (58uL, 0.8 mmol) at ambient temperature. The reaction was stirred for 10 min and concentrated. The concentrate was purified on a silica gel flash column eluting with a solvent gradient of 50% to 85% ethyl acetate in hexanes to provide 205 mg (86%) of **5d**.

N-(3-(2-(4-Isopropoxyphenoxy)thiazol-5-yl)-1-phenylprop-2-ynyl)acetamide (5b)

Under a nitrogen atmosphere 5-iodo-2-(4-ispropoxyphenoxy)thiazole (1.0 g. 2.77 mmol), *N*-(1-phenylprop-2-ynyl)acetamide (0.575 g, 3.32 mmol; Messina, F. *et al*, *J. Org. Chem.* **1999**, *64*, 3767-3769.), and triethylamine (1.93 mL, 13.85 mmol) were dissolved in THF (17 mL). The solution was then degassed and treated with dichlorobis(triphenylphosphine)palladium (II) (0.097 g, 0.139 mmol) followed by copper (I) iodide (0.016 g, 0.083 mmol). It was then heated at reflux for 1.75 hr, cooled

to room temperature, and filtered. The filtrate was concentrated *in vacuo*. Purification by flash chromatography eluting with 10% to 30% EtOAc / hexanes gave 0.469 g (42%) of **5b**.

Analytical LC-MS was performed on a Finnigan Navigator mass spectrometer and Agilent 1100 HPLC system running Xcalibur 1.2 and Open-Access 1.3 software. The mass spectrometer was operated under positive APCI ionization conditions. The HPLC system comprised an Agilent Quaternary pump, degasser, column compartment,autosampler and diode-array detector, with a Sedere Sedex 75 evaporative light-scattering detector. The column used was a Phenomenex Luna Combi-HTS C8(2) 5µm 100Å (2.1mm × 30mm). A gradient of 10-100% acetonitrile (A) and 0.1% trifluoroacetic acid in water (B) was used, at a flow rate of 1.5mL/min (0-0.1 min 10% A, 0.1-3.1 min 10-100% A, 3.1-3.9 min 100-10% A, 3.9-4.0 min 100-10% A). 94.6% pure.

The HPLC system was an Agilent Series 1100 comprised of Agilent Quaternary pump, degasser, column compartment,autosampler and diode-array detector. The column used was an Agilent Zorbac SB-C18 rapid resolution 4.6 x 150mm 3.5 micron. A gradient of 10-100% acetonitrile (A) and 0.1% trifluoroacetic acid in water (B) was used, at a flow rate of 1.5mL/min. 95.1% pure.

Methyl 4-(2-(4-(cyclopropylmethoxy)phenoxy)thiazol-5-yl)but-3-yn-2-ylcarbamate (5h).

To a solution of 4-(2-(4-(cyclopropylmethoxy)phenoxy)thiazol-5-yl)but-3-yn-2-amine (210 mg, 0.67 mmol) and triethylamine (280 uL, 2mmol) in methylene chloride (5 mL) was added methyl chloroformate (63 µL, 0.80 mmol) at ambient temperature. The reaction mixture was stirred for 10 min and concentrated. The concentrate was purified on a silica gel flash column eluting with a solvent gradient of 20% to 50% ethyl acetate in hexanes to provide 185 mg (74%) of **5h**.

1-(4-(2-(4-(Cyclopropylmethoxy)phenoxy)thiazol-5-yl)but-3-yn-2-yl)-3-methylurea (5i). To a solution of 4-(2-(4-(cyclopropylmethoxy)phenoxy)thiazol-5-yl)but-3-yn-2-amine (210 mg, 0.67 mmol) in methylene chloride (5 mL) was added methyl isocyanate (50 uL, 1.34 mmol) at ambient temperature. The reaction mixture was stirred for 4 h and concentrated. The concentrate was purified on a silica gel flash column eluting with a solvent gradient of 50% to 85% ethyl acetate in hexanes to provide 245 mg (98%) of **5i**.

Synthesis of N-(4-(2-(3-chloro-4-(cyclopropylmethylamino)phenoxy)thiazol-5-yl)but-3-yn-2-yl)acetamide (5e)

4-(5-Bromothiazol-2-yloxy)-2-chloroaniline. (2-Chloro-4-hydroxy-phenyl)-carbamic acid tert-butyl ester (1.5 g, 6.2 mmol), 2,5-dibromo-thiazole (1.5 g, 6.2 mmol) and K_2CO_3 (940 mg, 6.82 mmol) were combined in DMSO in a microwave tube. The tube was capped and the reaction was heated at 135 ^oC for 30 min in the microwave. The contents were then cooled, poured into a large excess of water and the organics were diluted with ethyl acetate. The aqueous layer was extracted (3x) and the combined organics were dried (Na_2SO_4), filtered and concentrated. The residue was purified by regular phase chromatography (Biotage Horizon) to give the desired compound (1.58 g, 5.2 mmol, 84%. The Boc protecting group comes off) as an oil. ^1H NMR (300 MHz, DMSO-D_6) δ ppm 7.40 (s, 1 H), 7.34 (d, *J* = 2.94 Hz, 1 H), 7.10 (d, *J* = 2.57 Hz, 1 H), 7.07 (d, *J* = 2.57

Hz, 1 H), 6.84 (d, *J* = 8.82 Hz, 2 H); MS (ESI APCI) *m/z*: 305.0 $(M + H)^+$.

N-(4-(2-(4-Amino-3-chlorophenoxy)thiazol-5-yl)but-3-yn-2-yl)acetamide. 4-(5-Bromothiazol-2-yloxy)-2-chloroaniline (1.58 g, 5.2 mmol), N-(1-methyl-prop-2-ynyl)-acetamide (562 mg, 5.1 mmol), CuI (30 mg, 0.16 mmol), Et_3N (1.65 mL) and THF (13.0 mL) were combined in a pressure tube and degassed for 2 min with N_2. $PdCl_2(PPh_3)_2$ (137 mg, 0.2 mmol) was added, the reaction was capped and then heated to 80 ^oC for 30 min. The reaction was cooled, poured into NH_4Cl (sat, aq) and diluted with EtOAc. The layers were separated, the aqueous layer extracted with EtOAc and the combined organics were dried (Na_2SO_4), filtered and concentrated. The residue was purified by regular phase chromatography (Biotage Horizon) to provide the desired product (1.13 g, 3.38 mmol) as a light brown oil. ^1H NMR (300 MHz, DMSO-D_6) δ ppm 8.41 (d, *J* = 7.72 Hz, 1 H), 7.47 (s, 1 H), 7.34 (d, *J* = 2.94 Hz, 1 H), 7.08 (dd, *J* = 8.82, 2.57 Hz, 1 H), 6.84 (d, *J* = 8.82 Hz, 1 H), 5.53 (s, 2 H), 4.73 - 4.87 (m, 1 H), 1.81 (s, 3 H), 1.32 (d, *J* = 6.99 Hz, 3 H); MS (ESI APCI) *m/z*: 336.1 $(M + H)^+$.

N-(4-(2-(3-Chloro-4-(cyclopropylmethylamino)phenoxy)thiazol-5-yl)but-3-yn-2-yl)acetamide (5e). N-(4-(2-(4-Amino-3-chlorophenoxy)thiazol-5-yl)but-3-yn-2-yl)acetamide (584 mg, 1.7 mmol) was combined with cyclopropanecarbaldehyde (127 µl, 1.7 mmol) in 8.5 ml of buffer solution (composed of 6 g NaOAc, 8.5 ml HOAc and 250 ml MeOH. This solution was prepared and stored for use as solvent for reductive amination reactions). To the reaction solution was added sodium cyanoborohydride (118 mg, 1.87 mmol) and the mixture was stirred at 70 ^oC for 2 h. The reaction was quenched with water and overwhelmed with EtOAc. The layers were separated, the aqueous portion was extracted with EtOAc and the combined organics were dried (Na_2SO_4), filtered and concentrated. The residue was purified by regular phase chromatography (Biotage Horizon) to provide **5e** (280 mg, 0.71 mmol, 42%) as a light brown oil.

HPLC method A:

System: Agilent 1100 HPLC system comprised of an Agilent Quaternary pump, degasser, column compartment, autosampler and diode-array detector, with a Sedere Sedex 75 evaporative light-scattering detector.

Column: Phenomenex Luna 5 micron C18 (250 x 4.60 mm)

Gradient: 50% water (0.1% TFA) to 90% acetonitrile in 15 min and hold for 5 min at a flow rate of 1.5 mL/min

Results: Retention time: 8.182 min, 97% pure.

HPLC method B:

System: Agilent 1100 HPLC system comprised of an Agilent Quaternary pump, degasser, column compartment, autosampler and diode-array detector, with a Sedere Sedex 75 evaporative light-scattering detector.

Column: Phenomenex Luna Combi- HTS C8(2) 5µm 100Å (2.1mm × 30mm).

Gradient: 10-100% acetonitrile (A) and 10mM ammonium acetate in water (B) was used, at a flow rate of 1.5mL/min.

Results: Retention time: 1.91 min, 100% pure.

N-(4-(2-(4-Isopropoxyphenoxy)thiazol-5-yl)but-3-yn-2-yl)propionamide (5f). To a solution of 4-(2-(4-isopropoxyphenoxy)thiazol-5-yl)but-3-yn-2-amine (302 mg, 1 mmol. see Supporting Information of reference 14) in methylene chloride (10 mL) at room temperature, was added TEA (1.2 mL) followed by propionyl chloride (185 mg, 2 mmol). After 10 minutes, methanol (1 mL) was added and the solvents were evaporated. The product was purified on a silica gel flash column eluting with a gradient of 10 to 30% ethyl acetate in hexane to provide 249 mg (70%) of **5f** as an off-white powder.

Synthesis of N-(1-(3-(2-(4-isopropoxyphenoxy)thiazol-5-yl)isoxazol-5-yl)ethyl)acetamide (9)

4-Isopropoxyphenol. To a solution of hydroquinone (55.7 g, 0.5 mol) and 2-iodopropane (57.5 g, 0.33 mol) in ethanol was added a solution of potassium hydroxide (78.5 g, 0.5 mol) in water (100 mL). The dark brown solution was refluxed for 16 h. Ethanol was evaporated, the aqueous phase was acidified with 2N HCl and extracted with ethyl acetate (3 x 200 mL). Combined organics was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated, triturated with methylene chloride and filtered. The filtrate was concentrated and purified on a silica gel flash column (eluting with 5~35% ethyl acetate in hexane) to give 23.0 g of product as a brown oil (46% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 6.69 - 6.83 (m, 4 H), 4.78 (s, 1 H), 4.33 - 4.49 (m, 1 H), 1.30 (d, *J* = 5.88 Hz, 6 H); MS (ESI): *m/z* 151 $(M - H)^-$.

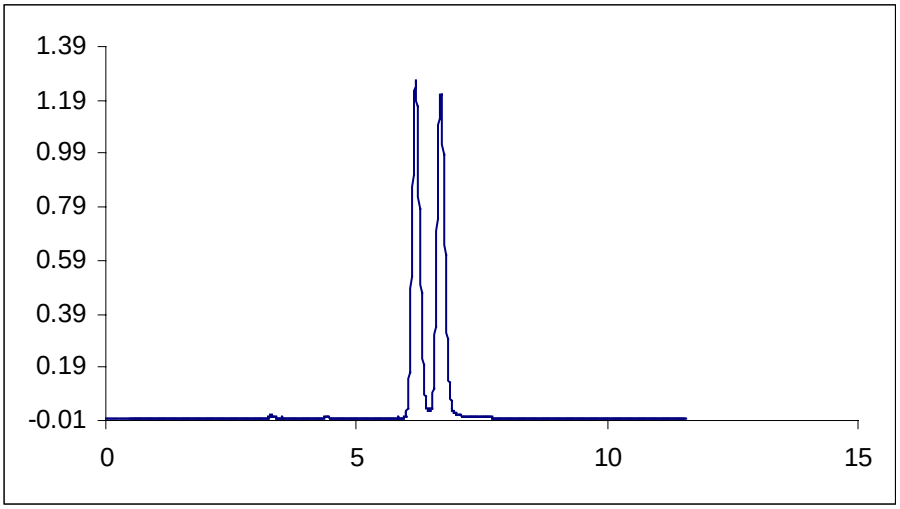
2-(4-Isopropoxyphenoxy)thiazole (3). A mixture of 4-isopropylphenol (15.5 g, 0.1 mol), 2-bromothiazole (18.2 g, 0.11 mol) and potassium carbonate (15.2 g, 0.11 mol) in DMSO was heated at 160 ^{o}C under nitrogen for 6 h. The reaction mixture was cooled and treated with water, and the aqueous phase was extracted with methylene chloride. The combined organics was washed with brine, dried and concentrated to give 27.5 g of dark brown oil, which was purified on a silica gel flash column (eluting with 5~35% ethyl acetate in hexane) to afford 21.5 g of **3** as a brown oil (91% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.22 (d, *J* = 4.04 Hz, 1 H), 7.13 - 7.21 (m, 2 H), 6.85 - 6.96 (m, 2 H), 6.76 (d, *J* = 3.68 Hz, 1 H), 4.42 - 4.61 (m, 1 H), 1.34 (d, *J* = 6.25 Hz, 6 H); MS (ESI): *m/z* 236 $(M + H)^+$.

(*R*)-(+)-N-(1-(3-(2-(4-Isopropoxyphenoxy)thiazol-5-yl)isoxazol-5-yl)ethyl)acetamide (9-(*R*)).

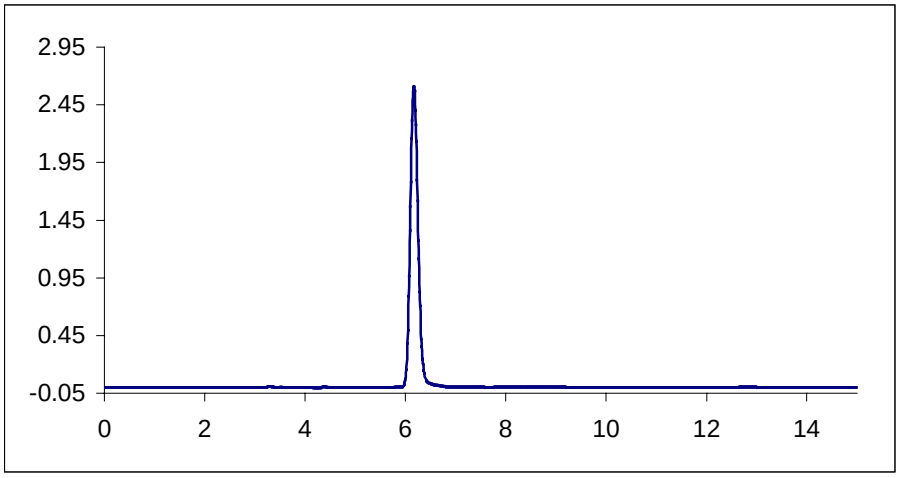
(*R*)-2-(But-3-yn-2-yl)isoindoline-1,3-dione (4-(*R*)) (R = Me). To a solution of (S)-(-)-propargyl-2-ol (1.36 g, 0.019 mol), phthalimide (2.9 g, 0.019 mol) and triphenylphosphine (7.6 g, 0.029 mol) in 50 mL of tetrahydrofuran was added a solution of DEAD in toluene (12.6 mL of 40% wt. solution, 0.029 mol) at 0 ^{o}C dropwise. The reaction mixture was stirred at room temperature for 3 h. Solvent was evaporated and the residue was dissolved in ether and stored in refrigerator overnight. The white solid was filtered. The filtrate was concentrated and purified on a silica gel flash column, eluting with 5~30% ethyl acetate in hexane, to give 3.17 g of **4**-(*R*) (83% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.82 - 7.92 (m, 2 H), 7.68 - 7.78 (m, 2 H), 5.15 - 5.29 (m, 1 H), 2.35 (d, *J* = 2.57 Hz, 1 H), 1.72 (d, *J* = 6.99 Hz, 3 H). MS (ESI), *m/z*: 200.0 $(M+H)^+$.

(9-(*R*)). **9-(*R*)** was synthesized by using the same procedure as described for **9** substituting **4** with **4-**(*R*)**.** $[\alpha]^{25}_{D}$ = +86.2 ^{o} (c = 0.5, $CHCl_3$). Chiral HPLC analysis (Column: Chiralcel OD-H 4.6 mmID x 250 mm, Mobile Phase: Hex/EtOH/MeOH = 80/10/10), ee = 100%.

Recemate **9**



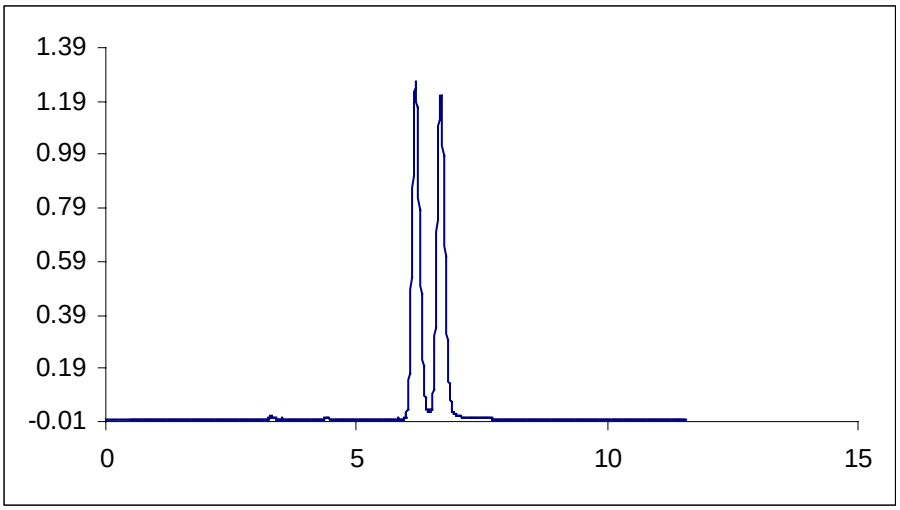
Compound **9**-(*R*) e.e. = 100%



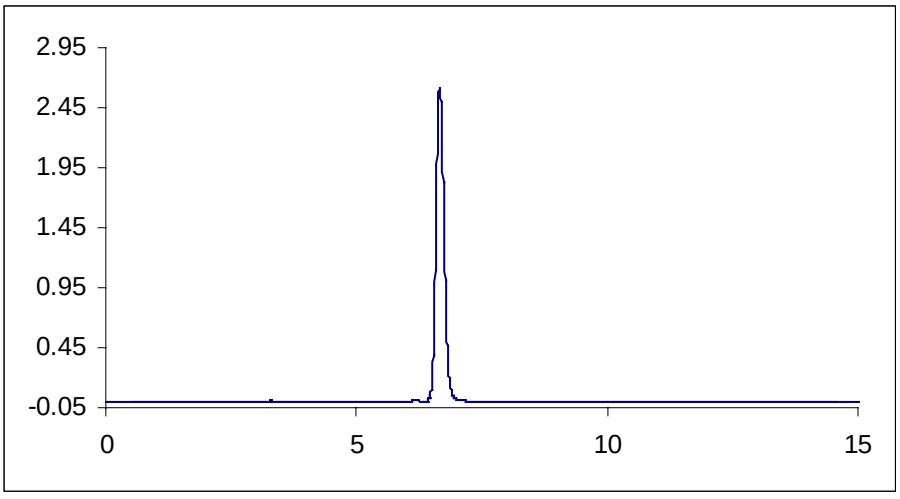
(*S*)-(-)-N-(1-(3-(2-(4-Isopropoxyphenoxy)thiazol-5-yl)isoxazol-5-yl)ethyl)acetamide (9-(*S*)). **9**-(*S*) was synthesized by using the same sequence as described for **9**-(*R*), substituting chiral starting material (*S*)-(-)-propargyl-2-ol with (*R*)-(+)-propargyl-2-ol. $[\alpha]^{25}_{D}$ = -86.8 ^{o} (c = 0.5, $CHCl_3$).

Chiral HPLC Analytical Conditions:
Column: chiralcel OD-H, 4.6 mmID x 25 cm
Mobile Phase: Hex/EtOH/MeOH = 80/10/10
Flow Rate: 0.8 mL/min
Detector: UV 280 nm
Column Temperature: 40 ^{o}C

Recemate **9**



Compound **9**-(*S*) e.e. = 99.0%
RT6.617 / RT 6.659 = 0.5/99.5



Synthesis of N-(1-(2'-(4-isopropoxyphenoxy)-2,5'-bithiazol-5-yl)ethyl)acetamide (12)

2-(4-Isopropoxyphenoxy)-5-(tributylstannyl)thiazole (7). To a solution of **3** (2.4 g, 0.01 mol) in dry THF was added *n*-BuLi (4.4 mL, 2.5 M in hexane) at –78 ^{o}C dropwise. After stirring for 1 h, tributyltin chloride (3.0 mL, 0.011 mol) was added slowly. The brown solution was then stirred for 3 h while warming up to room temperature. Water was added and the mixture was extracted with ethyl acetate. The combined organics was washed with saturated NH_4Cl and brine, dried over magnesium sulfate and concentrated. The crude material was purified on a silica gel flash column (eluting with 5~20% ethyl acetate in hexane) to give 4.85 g of **7** as clear oil (93% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.15 - 7.23 (m, 2 H), 7.12 (s, 1 H), 6.84 - 6.96 (m, 2 H), 4.43 - 4.60 (m, 1 H), 0.82 - 1.74 (m, 33 H); MS (ESI) *m/z*: 526.2 $(M + H)^{+}$.

2'-(4-Isopropoxyphenoxy)-2,5'-bithiazole (10). A mixture of 2-bromothiazole (1.1 g, 0.0067 mol), **7** (4.2 g, 0.008 mol) and tetrakis(triphenylphosphine)palladium (0.55 g, 0.00048 mol) was heated at 60 ^{o}C under nitrogen overnight. The reaction mixture was cooled, diluted with methylene chloride and filtered through a pad of celite. The filtrate was concentrated and purified on a silica gel flash column (eluting with 5-35% ethyl acetate in hexane) to give 2.4 g of **10** as a light yellow solid (94% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.72 (d, *J* = 3.31 Hz, 1 H), 7.64 (s, 1 H), 7.25 (d, *J* = 3.31 Hz, 1 H), 7.18 - 7.23 (m, 2 H), 6.88 - 6.97 (m, 2 H), 4.46 - 4.59 (m, 1 H), 1.35 (d, *J* = 6.25 Hz, 6 H); MS (ESI) *m/z*: 318.9 $(M + H)^{+}$.

1-(2'-(4-Isopropoxyphenoxy)-2,5'-bithiazol-5-yl)ethanol (11). To a solution of **10** (0.7 g, 0.0022 mol) in dry THF was added *n*-BuLi (1.0 mL, 2.5 M hexane solution, 0.0025 mol) dropwise at –78 ^{o}C. The yellow solution was stirred for 1 h before $_{\text{acetaldehyde}}$ (0.25 mL, 0.0044 mol) was added. After stirring at room temperature for an additional hour. The reaction was quenched with sat NH_4Cl solution and the mixture was $_{\text{extracted}}$ with ethyl acetate. Combined organics was washed with brine, dried over magnesium sulfate and concentrated. The residue was purified on a silica gel flash column (eluting with 20~40% ethyl acetate in hexane) to give 0.66 g of **11** as yellow oil (83% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.58 (s, 1 H), 7.53 (s, 1 H), 7.15 - 7.24 (m, 2 H), 6.87 - 6.96 (m, 2 H), 5.17 (dd, *J* = 6.07, 4.23 Hz, 1 H), 4.46 - 4.58 (m, 1 H), 1.62 (d, *J* = 6.25 Hz, 3 H), 1.58 (s, 1 H), 1.35 (d, *J* = 5.88 Hz, 6 H); MS (ESI) *m/z*: 362.9 $(M + H)^{+}$.

N-(1-(2'-(4-Isopropoxyphenoxy)-2,5'-bithiazol-5-yl)ethyl)acetamide (12). To a solution of **11** (2.75 g, 0.0075 mol) in 75 mL of 2:1 mixture of methylene chloride and acetonitrile was added excess trifluoroborane dietherate (7.5 mL). The reaction mixture was heated at reflux for 12 h. After cooling to rt, the mixture was filtered, the filtrate was concentrated and the crude was purified on a silica gel flash column (eluting with 50-100% ethyl acetate in hexane) to give 2.25 g of **12** as a light yellow solid (74% yield).

Table S1 ^{1}H and ^{13}C NMR and MS of the new compounds			
#	^{1}H NMR (300 MHz, δ, ppm)	^{13}C NMR (126 MHz, DMSO-D_6, δ, ppm)	MS
5b	($CDCl_3$) 7.49 (d, *J* = 6.62 Hz, 2 H), 7.29 - 7.43 (m, 4 H), 7.17 (d, *J* = 9.19 Hz, 2 H), 6.90 (d, *J* = 9.19 Hz, 2 H), 6.22 (d, *J* = 8.46 Hz, 1 H), 5.97 (d, *J* = 8.46 Hz, 1 H), 4.44 - 4.58 (m, 1 H), 2.04 (s, 3 H), 1.34 (d, *J* = 5.88 Hz, 6 H).		HRMS calcd for C23H22N2O3S $(M + H)^+$ 407.14239 found 407.14263.
5d	(DMSO-D_6) 8.41 (d, *J* = 7.72 Hz, 1 H), 7.48 (s, 1 H), 7.23 - 7.38 (m, 2 H), 6.93 - 7.07 (m, 2 H), 4.68 - 4.89 (m, 1 H), 3.83 (d, *J* = 6.99 Hz, 2 H), 1.81 (s, 3 H), 1.32 (d, *J* = 6.99 Hz, 3 H), 1.14 - 1.27 (m, 1 H), 0.50 - 0.67 (m, 2 H), 0.21 - 0.42 (m, 2 H).	173.10, 168.10, 156.85, 148.05, 142.32, 121.53, 115.61, 111.25, 96.72, 72.44, 70.61, 36.22, 22.33, 21.45, 10.02	MS (ESI) *m/z* 357.2 $(M + H)^+$.
5e	(DMSO-D_6) 8.41 (d, *J* = 8.09 Hz, 1 H), 7.47 (s, 1 H), 7.43 (d, *J* = 2.57 Hz, 1 H), 7.19 (dd, *J* = 9.01, 2.76 Hz, 1 H), 6.80 (d, *J* = 8.82 Hz, 1 H), 5.42 (t, *J* = 5.70 Hz, 1 H), 4.74 - 4.88 (m, 1 H), 3.04 (t, *J* = 6.07 Hz, 2 H), 1.76 - 1.86 (m, 3 H), 1.32 (d, *J* = 6.99 Hz, 3 H), 1.04 - 1.21 (m, 1 H), 0.41 - 0.54 (m, 2 H), 0.18 - 0.31 (m, 2 H).	176.3, 172.0, 146.5, 144.8, 143.0, 122.6, 121.2, 119.6, 113.4, 112.5, 96.4, 72.3, 59.0, 38.5, 22.4, 21.8, 11.4, 3.9;	HRMS (TOF) calc for C19H20ClN3O2S: 389.09648; found: 390.10398 $(M + H)^+$.
5f	($CDCl_3$) 7.29 (s, 1 H), 7.12 - 7.21 (m, 2 H), 6.85 - 6.96 (m, 2 H), 5.62 (d, *J* = 7.72 Hz, 1 H), 4.92 - 5.15 (m, 1 H), 4.52 (heptet, *J* = 5.88 Hz, 1 H), 2.21 (q, *J* = 7.48 Hz, 2 H), 1.45 (d, *J* = 6.62 Hz, 3 H), 1.34 (d, *J* = 5.88 Hz, 6 H), 1.16 (t, *J* = 7.54 Hz, 3 H).		MS (ESI), *m/z* : 359 $(M + H)^+$.
5h	(DMSO-D_6) 7.76 (d, J = 8.78Hz, 1 H), 7.48 (s, 1 H), 7.21 - 7.37 (m, 2 H), 6.94 - 7.08 (m, 2 H), 4.44 - 4.65 (m, 1 H), 3.83 (d, *J* = 6.99 Hz, 2 H), 3.54 (s, 3 H), 1.34 (d, *J* = 6.99 Hz, 3 H), 1.16 - 1.28 (m, 1 H), 0.52 - 0.64 (m, 2 H,) 0.25 - 0.38 (m, 2 H).	173.14, 156.86, 148.07, 142.32, 121.55, 115.62, 111.22, 96.69, 72.44, 70.82, 51.42, 40.00, 38.64, 21.41, 10.02;	MS (ESI) *m/z* 373.1 $(M + H)^+$.
5i	(DMSO-D_6) 7.45 (s, 1 H), 7.20 - 7.36 (m, 2 H), 6.91 - 7.09 (m, 2 H), 6.40 (d, *J* = 8.46 Hz, 1 H), 5.72 (q, *J* = 4.41 Hz, 1 H), 4.56 - 4.74 (m, 1 H), 3.83 (d, *J* = 6.99 Hz, 2 H), 2.54 (d, *J* = 4.78 Hz, 3 H), 1.31 (d, *J* = 6.99 Hz, 3 H), 1.14 - 1.26 (m, 1 H), 0.49 - 0.70 (m, 2 H), 0.22 - 0.42 (m, 2 H).	172.96, 157.48, 156.84, 148.07, 142.07, 121.53, 115.62, 111.47, 97.90, 72.44, 70.38, 40.00, 37.34, 26.27, 22.12, 10.02.	MS (ESI) *m/z* 372.2 $(M + H)^+$.
9	($CDCl_3$) 7.51 (s, 1 H), 7.15 - 7.25 (m, 2 H), 6.86 - 6.96 (m, 2 H), 6.36 (s, 1 H), 5.88 (d, *J* = 8.46 Hz, 1 H), 5.26 - 5.43 (m, 1 H), 4.45 - 4.61 (m, 1 H), 2.03 (s, 1 H), 1.56 (d, *J* = 7.35 Hz, 3 H), 1.35 (d, *J* = 5.88 Hz, 6 H).	174.89, 168.65, 155.78, 155.17, 147.96, 139.23, 121.77, 118.79, 116.74, 98.45, 69.74, 41.27, 22.41, 21.70, 18.81.	MS (ESI), *m/z* : 388.0 $(M + H)^+$.
9-(*S*)	($CDCl_3$) 7.48 - 7.56 (m, 1 H), 7.15 - 7.24 (m, 2 H), 6.86 - 6.98 (m, 2 H,), 6.36 (s, 1 H), 5.79 (d, *J* = 8.09 Hz, 1 H), 5.23 - 5.46 (m, 1 H,), 4.41 - 4.67 (heptet, *J* = 6.25 Hz, 1 H,), 2.03 (s, 3 H), 1.57 (d, *J* = 6.99 Hz, 3 H), 1.35 (d, *J* = 6.25 Hz, 6 H).	175.02, 174.94, 168.78, 155.84, 155.24, 148.00, 139.36, 121.90, 118.82, 116.78, 98.51, 69.77, 41.34, 22.48, 21.75, 18.87.	MS (ESI), *m/z* : 388.1 $(M+H)^+$.
9-(*R*)	(DMSO-D_6) 8.49 (d, *J* = 7.93 Hz, 1 H), 7.94 (s, 1 H), 7.31 - 7.37 (m, 2 H), 7.00 - 7.05 (m, 2 H), 6.88 (s, 1 H), 5.05 - 5.15 (m, 1 H), 4.58 - 4.68 (m, 1 H), 1.87 (s, 3 H), 1.43 (d, *J* = 7.32 Hz, 3 H), 1.29 (d, *J* = 6.10 Hz, 6 H).	174.94, 174.93, 168.70, 155.79, 155.19, 147.98, 139.25, 121.78, 118.81, 116.76, 98.45, 69.77, 41.29, 22.41, 21.71, 18.83;	MS (ESI), *m/z* : 388.1 $(M+H)^+$.

Table S2 Analytical data of the new compounds							
#	Formula	Calcd C (found)	Calcd H (found)	Calcd N (found)	Calcd S (found)	HRMS	Purities (%) from two HPLC methods
5b	$C_{23}H_{21}N_2O_3S$					HRMS calcd for $C_{23}H_{22}N_2O_3S$ $(M + H)^+$ 407.14239 found 407.14263.	95.1, 94.6
5d	$C_{19}H_{20}N_2O_3S$	64.02 (64.02)	5.66 (5.59)	7.86 (7.73)			
5e	$C_{19}H_{20}ClN_3O_2S.H_2O$	55.94 (56.11)	5.44 (4.86)	10.3 (9.85)		HRMS (TOF) calc for $C_{19}H_{20}ClN_3O_2S$: 389.09648; found: 390.10398 $(M + H)^+$.	97, 100
5f	$C_{19}H_{22}N_2O_3S$	63.66 (63.49)	6.19 (6.26)	7.82 (7.90)	8.95 (9.09)		
5h	$C_{19}H_{20}N_2O_4S$	61.27 (60.97)	5.41 (5.50)	7.52 (7.36)			
5i	$C_{19}H_{21}N_3O_3S$	61.44 (61.39)	5.70 (5.83)	11.31 (11.01)			
9	$C_{19}H_{21}N_3O_4S$	58.90 (58.84)	5.46 (5.27)	10.85 (10.82)	8.28 (8.30)		
9-(*S*)	$C_{19}H_{21}N_3O_4S$	58.90 (58.91)	5.46 (5.30)	10.85 (10.91)	8.28 (8.64)		
9-(*R*)	$C_{19}H_{21}N_3O_4S$	58.90 (59.00)	5.46 (5.27)	10.85 (10.92)	8.28 (8.42)		
12	$C_{19}H_{21}N_3O_3S_2$	56.55 (56.59)	5.25 (5.18)	10.41 (10.32)	15.89 (15.89)		

Table S3, Pharmacokinetic profile of **1**-(±), **9**-(±), **9**-(*S*) and **9**-(*R*) in rats (5 mg/kg, n = 3)[a]							
cpds	*F* (%)	*Vss* (L/kg)	Clp (L/hr•kg)	Oral $t_{1/2}$ (h)	Oral AUC (μg•hr/mL)	*C* max (μg/mL)	*T* max (h)
1-(±)	80	5.0	0.2	>12	18.9	0.90	2.0
9-(±)	61	1.4	0.2	4.4	13.5	1.20	4.3
9-(*S*)	102	1.6	0.3	3.2	19.4	1.86	5.3
9-(*R*)	98	1.5	0.2	4.5	23.5	2.05	4.3

[a]The vehicle used for pharmacokinetic study: 10% DMSO in PEG-400