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Design and synthesis of 3-(2-cinnamamidoethylsulfonyl) thiazolidine-4- carboxylate derivatives as novel angiotensin converting enzyme (ACE) inhibitors

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ABSTRACT

*A series of 3-(2-cinnamamidoethylsulfonyl)thiazolidine-4-carboxylate derivatives were designed, synthesized, and evaluated for their angiotensin converting enzyme (ACE) inhibitory activity. Their structures were verified by ^{1}H NMR, ^{13}C NMR, IR, and MS. All these compounds exhibited inhibitory activity against ACE with IC_{50} value of 3-9 mM, and **10g** showed the most potent activity.*

Key words: Angiotensin Converting Enzyme; Hypertension; Inhibitors; Synthesis; 3-(2-Cinnamamidoethylsulfonyl) thiazolidine-4-carboxylate

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INTRODUCTION

Hypertension is a common and often progressive disease that has attracted more and more attentions in developing high-efficiency antihypertensive agents because of its high frequency and concomitant risks associated with cardiovascular diseases [1-5]. In the view of physiopathology, hypertension involves changes in at least one of the hemodynamic variables (cardiac output, arterial stiffness or peripheral resistance) that determine measurable blood pressure [6]. Each of these variables is a potential therapeutic target. Therefore, modern treatment strategies may focus on normalizing vascular structure and function. It has been well-established that the Renin-Angiotensin System (RAS) is an important regulator of cardiovascular function and plays a pivotal role in the pathophysiological treatment of various cardiovascular diseases [7].

Angiotensin Converting Enzyme (ACE) is a membrane-bound metalloprotease that catalyses the conversion of angiotensin I to angiotensin II, which is the most active known as a octapeptide of the RAS and acts on regulation of blood pressure and blood volume, as well as body fluid balance [8]. Thus, ACE has been recognized as one of the major targets in the cure of hypertension and other cardiovascular diseases. Actually, several ACE inhibitors, in clinical and basic research, have been used as effective drugs to inhibit the ACE in the management of cardiovascular diseases. For example, captopril, enalapril, fosinopril, and ramepril are currently available in the market for the treatment of hypertension [9,10]. However, all these drugs also produce side effects (like dry cough, hyperkalemia, rashes, loss of taste, first dose hypotensin and acute renal failure) [11]. Therefore, this is still needed to search and develop novel ACE inhibitors with higher-effective together with lower side effects.

Recently, α,β-unsaturated esters, amides [12] and ketones [13] as the candidates of ACE inhibitory are developed by researchers. It is well known that α,β-unsaturated compounds are good Michael acceptors. They could react with nucleophile at the active site of enzyme to afford Michael type addition products, leading to the enzyme inactivation [14-16]. Moreover, when the amide group of peptides replaced by sulfonamide group will lead to analogues possessing improved *in vivo* stability and altered conformation [17,18]. Sulfonamides also have a variety of

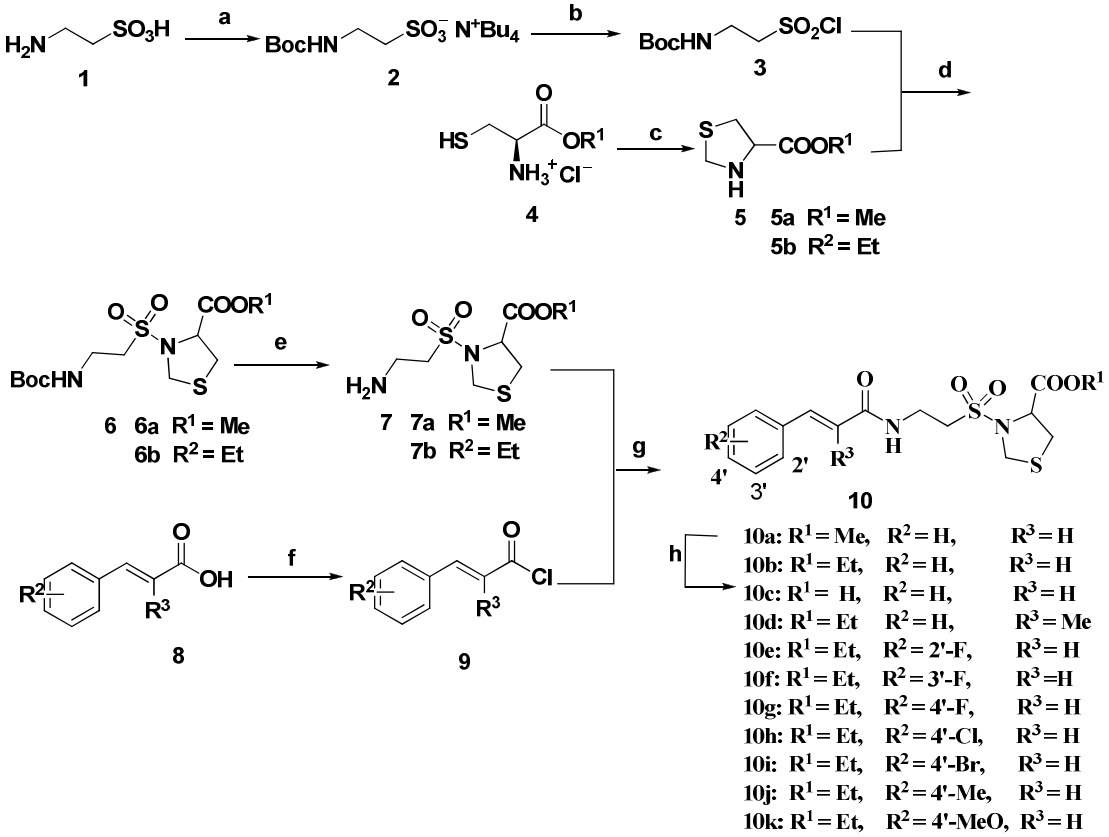
biological activities such as antibacterial, insulin releasing, anti-inflammatory, and so on [19-21]. As we know, compounds including heterocyclic ring is of interest because of their ability to confer a wide range of biological and pharmacological properties [22]. Some thiazolidine and its derivatives not only present effective anti-HIV [23] or anti-cancer [24,25] and cell division inhibition activities [26], but also in low toxicity.

Based on this design strategy, we herein describe the design, synthesis and evaluation of 3-(2-cinnamamido ethylsulfonyl)-thiazolidine-4-carboxylate derivatives as novel ACE inhibitors.

EXPERIMENTAL SECTION

Chemistry

The synthetic pathways for the target compounds **10** are outlined in Scheme 1. The quaternary ammonium salt **2** was prepared through one-pot process of taurine, di-tert-butyl dicarbonate (Boc_2O) and tetrabutylammonium hydroxide in high yields [27], followed by treatment with triphosgene to give the sulfonyl chloride **3** [28]. Condensation of compound **3** and **5**, which generated from L-cystein ester hydrochloride and paraformaldehyde [29], afforded compound **6**. Then deprotection of **6** with trifluoroacetic acid to give the primary amine **7**. Finally, the reaction of **7** with a series of cinnamoylchloride derivatives **9**, which come from the corresponding cinnamic acids **8** afforded the desired target products **10**. All compounds synthesized were characterized by ^{1}H NMR, ^{13}C NMR, IR, and MS.



Scheme 1 Synthesis of compounds 10a-10k. Reagents and conditions: (a) Boc_2O, Bu_4NOH; (b) $(COCl_2)_3$, cat. DMF, CH_2Cl_2; (c) $(HCHO)_n$, K_2CO_3, CH_2Cl_2; (d) NMM, THF; (e) TFA, CH_2Cl_2; (f) $SOCl_2$, PhH; (g) NMM, THF; (h) 2N NaOH, MeOH

Reagents and general procedures

Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. Melting points were determined on a digital melting point apparatus and are uncorrected. ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) spectra were recorded on a Bruker-DMX 400 spectrometer in $CDCl_3$ or DMSO-d_6 at 25 °C. Chemical shifts (δ) are expressed in part per million (ppm) relative to internal tetramethylsilane, coupling constants (*J*) are in Hertz, and signals are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet;m, multiplet; br s, broad singlet. Electron impact mass (EI-MS) spectra were recorded on a Thermo TRACE DSQ EI-mass spectrometer. Element analyses were carried out on an element vario EL series element analyzer.

Tert-Butyl 2-(tetrabutylammonium sulfonyl)ethylcarbamate (2)

A mixture of taurine **1** (2.94 g, 24 mmol), $(Boc)_2O$ (6.62 g, 30 mmol), 25% tetrabutylammonium hydroxide (24.37 g,

24 mmol) in 80 mL THF/H_2O (v/v, 3:1) was stirred at room temperature overnight. Then 40 mL water was added and the mixture was extracted with CH_2Cl_2 (3 × 60 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified through recrystallization (ether-ethyl acetate) to give desired product **2** (89% yield) as a white needle solid. M.p.: 85.4-86.3 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.02 (12H, t, *J* = 9.6 Hz), 1.41 (1H, s), 1.44-1.51 (7H, m), 1.61-1.71 (8H, m), 1.32 (1H, s), 2.89-2.93 (2H, m), 3.26-3.32 (8H, m), 3.53-3.58 (2H, m), 6.15 (1H, s).

***Tert*-Butyl 2-(chlorosulfonyl)ethylcarbamate (3)**

To a solution of quaternary ammonium salt **2** (1.00 g, 2.15 mmol) in dry CH_2Cl_2 (7.5 mL) under N_2 was added dry DMF (0.2 mL) followed by the addition of triphosgene (0.32 g, 1.07 mmol). The resulting solution was stirred at room temperature for 1 h. After evaporation, the residue was purified through flash column chromatograph (silica gel, PE-EtOAc, 3:1) to give desired product (0.87 g, 64 % yield) as a clear oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.58 (9H, s), 3.91 (2H, t, *J* = 6.8 Hz), 4.27 (2H, t, *J* = 6.4 Hz), 9.17 (1H, s).

Thiazolidine-4-carboxylate (5) [30]

To a solution of **4** (0.09 mol) in dry CH_2Cl_2 (90 mL) was added anhydrous K_2CO_3 (37.26 g, 0.27 mol) and paraformaldehyde (4.05 g, 0.27 mol) under N_2. After stirring for 24 h at room temperature, the crude mixture was filtered and washed with water (100 mL). The filtrate was extracted with CH_2Cl_2 (3 × 60 mL) and dried with anhydrous Na_2SO_4. The crude product was purified by flash column chromatography on silica gel (PE/EtOAc, 3:1) to give desired product as an oil. Yield: 65%, GC-MS *m*/*z*: 147 (R_1 = CH_3); Yield: 66%, GC-MS *m*/*z*: 161 (R_2 = CH_2CH_3).

3-(2-(*tert*-Butoxyamide)ethylsulfonyl)thiazolidine-4-Carboxyl*ate* (6)

To a stirred solution of compound **5a** or **5b** (9.38 mmol) in dry THF (14 mL) was added anhydrous 4-methylmorpholine (NMM) (2.7 mL, 24.8 mmol). And then a solution of compound **3** (1.94 g, 7.95 mmol) in dry THF (110 mL) was added dropwise at 0 °C. After reaction at 0 °C for 1 h and 15 h at room temperature, the mixture was filtered and the resulting solution was evaporated under vacuum. The residue was dissolved in EtOAc and the solution was washed successively with 1 M $KHSO_4$, saturated NaCl, 5% aqueous $NaHCO_3$, and saturated NaCl. The organic layer was concentrated and the residue was purified through flash column chromatography on silica gel (PE/EtOAc, 5:1) to give the pure product **6** as oil.

Methyl 3-(2-(*tert*-butoxyamide)ethylsulfonyl)thiazolidine-4-Carboxylate (6a): Yield: 50%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.56 (9H, s), 3.33 (1H, s), 3.34 (1H, s), 3.48-3.36 (2H, m), 3.80 (2H, s), 3.81 (1H, s), 4.13 (2H, q, *J* = 6.4 Hz), 4.41 (1H, d, *J* = 8.8 Hz), 4.78 (1H, d, *J* = 8.8 Hz), 5.02 (1H, t, *J* = 5.2 Hz), 9.15 (s, 1H).

Ethyl 3-(2-(*tert*-butoxyamide)ethylsulfonyl)thiazolidine-4-Carboxylate (6b): Yield: 64%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.31 (3H, t, *J* = 7.2 Hz), 1.56 (9H, s), 3.33 (2H, d, *J* = 5.2 Hz), 3.36-3.48 (2H, m), 4.06-4.19 (2H, m), 4.25 (2H, q, *J* = 7.2 Hz), 4.41 (1H, d, *J* = 8.8 Hz), 4.78 (1H, d, *J* = 8.8 Hz), 5.00 (1H, t, *J* = 5.2 Hz), 9.15 (s, 1H).

3-(2-Aminoethylsulfonyl)thiazolidine-4-carboxylate (7)

Trifluoroacetic acid (3 mL) was added dropwise to a solution of compound **6** (0.89 mmol) in CH_2Cl_2 (3 mL) at 0 °C under N_2. The mixture was stirred at room temperature for 1 h. After concentration under reduced pressure, the residue was dissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$. The organic phase was dried with anhydrous Na_2SO_4 and then purified through flash column chromatography on silica gel (PE/EtOAc, 1:5) to give pure product **7** as colorless oil.

Methyl 3-(2-aminoethylsulfonyl)thiazolidine-4-carboxylate (**7a)**: Yield: 59%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.28-3.37 (3H, m). 3.38-3.48 (1H, m), 3.68-3.78 (1H, m), 3.82 (1H, s), 3.85-4.03 (1H, m), 4.31 (1H, d, *J* = 8.8 Hz), 4.72 (1H, d, *J* = 8.8 Hz), 4.77 (1H, br s), 5.06 (1H, d, *J* = 5.4 Hz), 8.20 (1H, s).

Ethyl 3-(2-aminoethylsulfonyl)thiazolidine-4-carboxylate (**7b)**: Yield: 81%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.32 (3H, t, *J* = 7.2 Hz), 3.28-3.36 (3H, m), 3.38-3.47 (1H, m), 3.65-3.78 (1H, m), 3.88-4.00 (1H, m), 4.26 (2H, q, *J* = 7.2 Hz), 4.31 (1H, d, *J* = 8.8 Hz), 4.74 (1H, d, *J* = 9.2 Hz), 5.05 (1H, dd, *J* = 5.6, 4.8 Hz), 6.95 (1H, s), 8.21 (1H, s).

Cinnamoyl Chloride and its derivatives (9)

To a 100 mL round-bottomed flask was added **8** (13 mmol), dry benzene (40 mL), and thionyl chloride (3.5 mL, 29 mmol). The mixture was stirred under reflux for 5 h, then cooled and evaporated. The crude product was used directly for the next step without further purified.

General procedures for the synthesis of 3-(2-cinnamamidoethylsulfonyl)-thiazolidine- 4-carboxylate and its derivatives (10a-b, 10d-k)

The compound **7** (1.6 mmol) and anhydrous NMM（0.38 mL, 3.5 mmol）were dissolved in dry THF (3.7 mL), then compounds **9** (1.7 mmol) in THF (3.8 mL) was added dropwise at 0 °C with stirring. After reaction for 1 h at 0 °C and 15 h at room temperature, the mixture was filtered and evaporated. The residue was then dissolved in EtOAc and washed with 1 M $KHSO_4$, saturated NaCl, 5% $NaHCO_3$, and saturated NaCl, respectively. The organic phase was dried with anhydrous Na_2SO_4 and evaporated under vaccum. The crude product was purified through flash column chromatography on silica gel (PE/EtOAc, 3:1) to give target products **10a-b, 10d-k**.

(*E*)-methyl 3-(2-cinnamamidoethylsulfonyl)thiazolidine-4-carboxylate (10a): Yield: 65%; white solid; m.p.: 97.2-98.1 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ：3.34 (2H, d, *J* = 5.2 Hz), 3.80 (3H, s), 4.25-4.40 (2H, m), 4.42 (1H, d, *J* = 8.8 Hz), 4.80 (1H, d, *J* = 8.8 Hz), 5.04 (1H, t, *J* = 5.2 Hz), 5.50 (2H, td, *J* = 6.8, 2.4 Hz), 6.98 (1H, d, *J* = 15.6 Hz), 7.38-7.48 (3H, m), 7.55-7.63 (2H, m), 7.87 (1H, d, *J* = 15.6 Hz), 9.35 (s, 1H); ^{13}C NMR($CDCl_3$, 100 MHz) δ: 34.7 (s), 49.9 (s), 50.7 (s), 53.1 (s), 63.6 (s), 115.3 (s), 128.5 (s), 129.1 (s), 131.2 (s), 133.8 (s), 148.1 (s), 162.1 (s), 167.2 (s), 170.2 (s); IR (KBr) cm^{-1}: 1742, 1659, 1334, 1144, 978, 772; EI-MS *m/z*: 266 [M-$SCH_2CHCOOCH_2CH_3$]$^+$, 146, 131, 103.

(*E*)-ethyl 3-(2-cinnamamidoethylsulfonyl)thiazolidine-4-carboxylate (10b): Yield: 47%; white solid; m.p.: 93.2-94.3 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.30 (3H, t, *J* = 7.2 Hz), 3.34 (2H, d, *J* = 4.8 Hz), 3.44-3.57 (2H, m), 4.25 (2H, q, *J* = 7.2 Hz), 4.28-4.40 (2H, m), 4.42 (1H, d, *J* = 8.8 Hz), 4.80 (1H, d, *J* = 8.8 Hz), 5.01 (1H, t, *J* = 5.2 Hz), 6.99 (1H, d, *J* = 15.6 Hz), 7.38-7.48 (3H, m), 7.55-7.63 (2H, m), 7.86 (1H, d, *J* = 15.6 Hz), 9.35(s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.1 (s), 34.8 (s), 49.9 (s), 50.7 (s), 62.3 (s), 63.6 (s), 115.4 (s), 128.5 (s), 129.1 (s), 131.2 (s), 133.9 (s), 148.1 (s), 162.2 (s), 167.2 (s),169.7 (s); IR (KBr) cm^{-1}: 1746, 1651, 1342, 1136, 978, 768; EI-MS *m/z* : 266 [M-$SCH_2CHCOOCH_2CH_2CH_3$]$^+$, 160, 131, 103.

(*E*)-3-(2-cinnamamidoethylsulfonyl) thiazolidine-4-carboxylic acid (10c)

To a mixture of compound **10a** (0.13 mmol) in MeOH (0.4 mL) was added 2N NaOH (0.2 mL). The mixture was stirred at room temperature for 0.5 h. After that the solution was acidified to pH 1-2, and the solution was extracted by CH_2Cl_2. the organic phase was dried with anhydrous Na_2SO_4 and concentrated. The product was purified further by filtering through a short pad of silica gel (EtOAc/EtOH, 2:1) to get target product **10c**. Yield: 75%; white solid; m.p. 191.4-191.9 °C; ^{1}HNMR ($CDCl_3$ + DMSO-d_6, 400 MHz) δ: 3.17-3.28 (1H, m), 3.33-3.50 (3H, m), 3.65-3.68 (1H, m), 3.83-4.00 (1H, m), 4.33 (1H, d, *J* = 8.8 Hz), 4.71 (1H, d, *J* = 8.8 Hz), 4.88 (1H, d, *J* = 7.2 Hz), 6.68 (1H, d, *J* = 15.6 Hz), 7.28-7.39 (3H, m), 7.50 (1H, s), 7.51 (1H, s),7.56 (1H, d, *J* = 15.6 Hz), 9.08 (1H, br s); ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 100 MHz) δ: 34.3 (s), 35.2 (s), 49.4 (s), 52.2 (s), 64.7 (s), 121.2(s), 127.6 (s), 128.7 (s), 129.4 (s), 134.7 (s), 140.1 (s), 166.1 (s), 174.3 (s); IR (KBr) cm^{-1}: 3394, 1655, 1334, 1140, 764; ESI-MS *m/z*: 369 [M-H]$^-$.

(*E*)-ethyl 3-(2-(2-methyl-3-phenylacrylamido)ethylsulfonyl)thiazolidine-4-carboxylate (10d): Yield: 24%; yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ:3.35 (1H, s), 3.46-3.59 (2H, m), 2.26 (3H, q, *J* = 7.2 Hz), 4.34-4.39 (1H, m),4.46 (1H, d, *J* = 8.6 Hz), 4.81 (1H, d, *J* = 8.6 Hz), 5.03 (1H, d, *J* = 5.2 Hz), 6.97 (1H, d, *J* = 1.5 Hz), 7.35-7.42 (m, 5H), 9.17(s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.1 (s), 15.9 (s), 34.5 (s), 34.8 (s), 49.9 (s), 50.4 (s), 62.3 (s), 63.7 (s), 128.6 (s), 128.9 (s), 129.5 (s), 130.8 (s), 134.5 (s), 138.3 (s), 163.6 (s), 169.7 (s), 173.9 (s); IR (KBr) cm^{-1}: 1734, 1651, 1433, 1144, 922, 752; EI-MS *m/z*: 280 [M-$SCH_2CHCOOCH_2CH_2CH_3$]$^+$, 160, 145, 117.

(*E*)-ethyl 3-(2-(3-(2-fluorophenyl)acrylamido)ethylsulfonyl)thiazolidine-4-carboxylate (10e): Yield: 17%; white solid; m.p.: 97.3-97.9 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.31 (3H, d, *J* = 7.2 Hz), 3.34 (1H, s), 3.35 (1H, s), 3.44-3.56 (m, 2H), 4.25 (2H, q, *J* = 7.2 Hz), 4.30-4.41 (m, 2H), 4.43 (1H, d, *J* = 8.8 Hz), 4.80 (1H, d, *J* = 8.8 Hz), 5.02 (1H, t, *J* = 5.2 Hz), 7.10-7.17 (2H, m,), 7.21 (1H, td, *J* = 7.6, 0.8 Hz), 7.40-7.45 (m, 1H), 7.57 (1H, td, *J* = 7.8, 1.6 Hz), 7.93 (1H, d, *J* = 15.6 Hz), 9.34 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.1 (s), 34.8 (s), 49.9 (s), 50.7 (s), 62.3 (s), 63.6 (s), 116.3 (s), 116.6 (s), 118.1 (s), 118.3 (s), 122.0 (s), 124.7 (s), 130.2 (s), 132.6 (s),132.7 (s), 140.9 (s), 160.4 (s), 162.0 (s), 163.0 (s), 167.1 (s), 169.6 (s); IR (KBr) cm^{-1}: 1746, 1663, 1489, 1204, 1037, 756,; EI-MS *m/z*: 284 [M-$SCH_2CHCOOCH_2CH_2CH_3$]$^+$, 160, 149, 121, 101.

(*E*)-ethyl 3-(2-(3-(3-fluorophenyl)acrylamido)ethylsulfonyl)thiazolidine-4-carboxylate (10f): Yield: 18%; white solid; m.p.: 80.5-81.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.29 (3H, t, *J* = 7.2 Hz), 3.32 (1H, s), 3.34 (1H, s), 3.44-3.55 (2H, m), 4.24 (2H, q, *J* = 7.2 Hz), 4.26-4.38 (2H, m), 4.41 (1H, d, *J* = 8.8 Hz), 4.78 (1H, d, *J* = 8.8 Hz), 5.00 (1H, t, *J* = 5.2 Hz), 7.10-7.17 (1H, m), 7.27-7.32 (1H, m), 7.34-7.42 (2H, m), 7.80 (1H, d, *J* = 15.6 Hz), 9.34 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.9 (s), 34.7 (s), 49.9 (s), 50.7 (s), 62.3 (s), 63.6 (s), 114.6 (d), 116.9 (s), 118.1 (d), 124.6 (d), 130.7 (d), 136.1 (d), 146.5 (s), 162.1 (s), 163.0 (d), 166.9 (s), 169.7 (s); IR (KBr) cm^{-1}: 1726, 1619, 1330, 1144, 724; EI-MS *m/z*: 284 [M-$SCH_2CHCOOCH_2CH_2CH_3$]$^+$, 160, 149, 121, 101.

(*E*)-ethyl 3-(2-(3-(4-fluorophenyl)acrylamido)ethylsulfonyl)thiazolidine-4-carboxylate (10g): Yield: 16%; white solid; m.p.: 114.5-115.7 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.31 (3H, t, *J* = 7.2 Hz), 3.34 (2H, d, *J* = 5.2 Hz), 3.43-3.59 (2H, m), 4.25 (2H, q, *J* = 7.2 Hz), 4.28-4.40 (2H, m), 4.42 (1H, d, *J* = 8.8 Hz), 4.80 (1H, d, *J* = 8.8 Hz), 5.01(1H, t, *J* = 5.2 Hz), 6.93 (1H, d, *J*= 15.6 Hz), 7.12 (2H, t, *J* = 8.8 Hz), 7.55-7.63 (2H, m), 7.83 (1H, d, *J* = 15.6 Hz), 9.35 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.3 (s), 34.6 (s), 50.0 (s), 50.6 (s), 62.3 (s), 64.0 (s), 115.2 (s), 116.2 (s), 116.5 (s), 130.2 (s), 130.5 (s), 130.6 (s), 146.7 (s), 162.1 (s), 163.1 (s), 165.7 (s), 167.1 (s), 169.7 (s); IR (KBr) cm^{-1}: 1738, 1623, 1592, 1342, 1144, 831, 617; EI-MS *m/z*: 284 [M-$SCH_2CHCOOCH_2CH_2CH_3$]$^+$, 160, 149, 121, 101.

(*E*)-ethyl 3-(2-(3-(4-chlorophenyl)acrylamido)ethylsulfonyl)thiazolidine-4-carboxylate (10h): Yield: 34%; white solid; m.p.: 108.2-109.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.30 (3H, d, *J* = 7.2 Hz), 3.33 (1H, s), 3.34 (1H, s), 3.44-3.56 (2H, m), 4.24 (2H, q, *J* = 7.2 Hz), 4.26-4.39 (2H, m), 4.42 (1H, d, *J* = 8.8 Hz), 4.79 (1H, d, *J* = 8.8 Hz), 5.01 (1H, t, *J* = 5.2 Hz), 6.98 (1H, d, *J* = 15.6 Hz), 7.53 (2H, dt, *J* = 7.6, 2.4 Hz), 7.80 (1H, d, *J* = 15.6 Hz), 9.33(1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.1 (s), 34.7 (s), 49.9 (s), 50.7 (s), 62.3 (s), 63.6 (s), 116.0 (s), 129.4 (s), 129.7(s), 132.4 (s), 137.2 (s), 146.5 (s), 162.1 (s), 167.0 (s), 169.7 (s); IR (KBr) cm^{-1}: 1746, 1489, 1239, 823, 669; EI-MS *m/z*: 300 [M-$SCH_2CHCOOCH_2CH_2CH_3$]$^+$, 165, 160, 137, 101.

(*E*)-ethyl 3-(2-(3-(4-bromophenyl)acrylamido)ethylsulfonyl)thiazolidine-4-carboxylate (10i): Yield: 45%; white solid; m.p.71.3-73.2 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.32 (3H, t, *J* = 7.2 Hz), 3.35 (2H, d, *J* = 4.8 Hz), 3.44-3.57 (2H, m), 4.26 (2H, q, *J* = 7.2 Hz), 4.30-4.39 (2H, m), 4.43 (1H, d, *J* = 8.8 Hz), 4.80 (1H, d, *J* = 8.8 Hz), 5.02 (1H, t, *J* = 5.2 Hz), 7.01 (1H, d, *J* = 15.2 Hz), 7.45-7.48 (2H, m), 7.56-7.59 (2H, m), 7.80 (1H, d, *J* = 15.6 Hz), 9.34 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.1 (s), 34.8 (s), 49.9 (s), 50.7(s), 62.3 (s), 63.6 (s), 116.2 (s), 125.6 (s), 129.9 (s), 132.4 (s), 132.8 (s), 146.5 (s), 162.1 (s), 167.0 (s), 169.7 (s); IR (KBr) cm^{-1}: 1742, 1667, 1485, 1243, 1148, 974, 815, 495; EI-MS *m/z*: 344 [M-$SCH_2CHCOOCH_2CH_2CH_3$]$^+$, 209, 160, 102.

(*E*)-ethyl 3-(2-(3-p-tolylacrylamido)ethylsulfonyl)thiazolidine-4-carboxylate (10j): Yield: 15%; white solid; m.p.: 81.8-82.7 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.31 (3H, t, *J* = 7.2 Hz), 2.40 (3H, s), 3.34 (2H, d, *J* = 5.2 Hz), 3.44-3.57 (2H, m), 4.25 (2H, q, *J* = 7.2 Hz), 4.28-4.40 (2H, m), 4.43 (1H, d, *J* = 8.8 Hz,), 4.80 (1H, d, *J* = 8.8 Hz), 5.02 (1H, t, *J* = 5.2 Hz), 6.93 (2H, d, *J* = 15.6 Hz), 7.23 (2H, d, *J* = 7.6 Hz), 7.49 (2H, d, *J* = 8.4 Hz), 7.85 (1H, d, *J* = 15.6 Hz), 9.35 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.1 (s), 21.6 (s), 34.8 (s), 49.9 (s), 50.7 (s), 62.3 (s), 63.6 (s), 114.1 (s), 128.6 (s), 129.8 (s), 131.2 (s), 142.0 (s), 148.2 (s), 162.2 (s), 167.3 (s), 169.7 (s); IR (KBr) cm^{-1}: 1741, 1657, 1515, 1431, 1328, 1208, 1142, 971, 722; EI-MS *m/z*: 280 [M-$SCH_2CHCOOCH_2CH_2CH_3$]$^+$, 160, 145, 115.

(*E*)-ethyl 3-(2-(3-(4-methoxyphenyl)acrylamido)ethylsulfonyl)thiazolidine-4-carboxylate (10k): Yield: 14%; white solid; m.p.: 132.8-133.5 °C. ^{1}H NMR($CDCl_3$, 400 MHz) δ: 1.30 (3H, t, *J* = 7.2 Hz), 3.34 (2H, d, *J* = 2.4 Hz), 3.44-3.55 (2H, m), 3.86 (3H, s), 4.25 (2H, q, *J* = 7.2 Hz), 4.28-4.40 (2H, m), 4.43 (1H, d, *J* = 8.8 Hz), 4.80 (1H, d, *J* = 8.8 Hz), 5.01 (1H, t, *J* = 5.2 Hz), 6.84 (1H, d, *J* = 15.2 Hz), 6.92-6.95 (2H, m), 7.52-7.57 (2H, m), 7.84 (1H, d, *J* = 15.2 Hz), 9.35 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.1 (s), 34.8 (s), 49.9 (s), 50.8 (s), 55.5 (s), 62.3 (s), 63.6 (s), 112.5 (s), 114.5 (s), 126.6 (s), 130.4 (s), 148.0 (s), 162.2 (s), 167.4 (s), 196.7 (s); IR (KBr) cm^{-1}: 1742, 1659, 1596, 1429, 1354, 1259, 1176, 823, 625; EI-MS *m/z*: 296 [M-$SCH_2CHCOOCH_2CH_2CH_3$]$^+$, 160, 133, 121.

Angiotensin Converting Enzyme (ACE) Inhibition Assay *in Vitro*

ACE inhibition experiment was carried out using HPLC [31]. The substrate, hippuryl-histidyl-leucine (HHL), and ACE from rabbit lung (EC 3.4.15.1) were obtained from Sigma-Aldrich (St. Louis, MO, U.S.A.). 100 μL of 5 mM HHL dissolved in 100 mM sodium borate buffer containing 300 mM sodium chloride (pH 8.3) and 80 μL of ACE inhibitory peptide solution were incubated at 37 °C for 10 min in 1.5 mL polyethylene micro centrifuge tubes placed in a water bath. Then 20 μL of ACE (0.1 U/mL) which dissolved in distilled water was added to the reaction mixture and again incubated at 37 °C for 30 min. The reaction was stopped with 250 μL of 1 M HCl. 80 μL of buffer solution was used as control solution. The hippuric acid liberated from HHL was quantized through HPLC using a C_{18} column (Waters, USA) with dimension of 4.6 mm × 150 mm and thermostated at 30 °C. The samples were filtered through a 0.22 μm polyvinylidene fluoride filter and 10 μL was injected. The column was eluted with 38% methanol in water (v/v) containing 0.1% trifluoroacetic acid at a flow rate of 0.5 mL/min and the detector was monitored at 228 nm. The IC_{50} value was defined as the concentration of inhibitor required to inhibit 50% of the ACE activity.

The inhibition ratio (I) was calculated as follows:

$$I\ \% = \frac{A - B}{A} \times 100\ \%$$

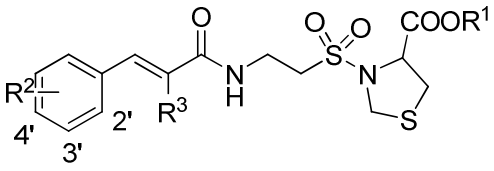
Where, A is the peak area of hippuric acid in control sample; B is the peak area of hippuric acid in the sample

containing ACE inhibitory peptide.

RESULTS AND DISCUSSION

ACE inhibitory activity *in vitro* The ACE inhibitory activity of compounds **10a-10k** *in vitro* was measured by the literature method [31] which used reversed phase high performance liquid chromatography (HPLC) quantitation of the hippuric acid (HA) formed after enzymatic cleavage of the substrate hippuryl-histidyl-leucine (HHL) and separation the unreacted substrate. The amount of released HA is directly proportional to the ACE activity. Captopril, a known ACE inhibitor drug, has been used as standard for comparison with the inhibitory activity of synthesized new analogues. The results are presented in Table **1**.

Table 1. Inhibitory activity against ACE of compounds 10a-10k



Compound	R^1	R^2	R^3	IC_{50}[a] (mM)
10a	Me	H	H	3.97
10b	Et	H	H	5.67
10c	H	H	H	8.67
10d	Et	H	Me	5.10
10e	Et	2'-F	H	4.86
10f	Et	3'-F	H	6.42
10g	Et	4'-F	H	3.81
10h	Et	4'-Cl	H	4.34
10i	Et	4'-Br	H	4.02
10j	Et	4'-Me	H	3.95
10k	Et	4'-MeO	H	5.49
Captopril[b]				38.9（nM）

[a] *The IC_{50} values represent the average of three independent experiments;*
[b] *Values in the literature is 18.1 nM [30].*

As shown in Table **1**, the 11 compounds demonstrated ACE inhibitory activities with IC_{50} values ranging from 3.0 to 9.0 mM, and compound **10g**, which was substituted with a ethyl in position R^1, a hydrogen in position R^2, and a 4-fluorine in position R^3, showed the most active inhibitory. The hydrogen-bonding between the carboxylate binding the thiazolidine and the enzyme maybe not important because of esterification it provided slight improvement in potency (**10a** and **10b** vs **10c**). Compared to **10b**, the compound **10d** (R^3 = Me) showed similar results (**10d** vs **10b**). The effects of the substituents position in phenyl ring were also studied, and the *para*-substituted exerted the most potency activity (**10g** vs **10e** and **10f**). It is noted that there is no obvious effect on activity when the phenyl ring with different electron-withdrawing groups such as F, Cl, Br (**10g**, **10h** and **10i**). However, when R^2 was substituted with methoxyl group instead of methyl, the decrease of activity was observed (**10j** vs **10k**).

ACE is a zinc-containing peptidyl dipeptide hydrolase, and many ACE inhibitors were designed based on the zinc-interacting groups. However, the zinc-coordinating groups were different. In the case of α,β-unsaturate amide, the zinc ion coordinates to the carbonyl of the ketone, whereby the carbonyl group becomes polarized and is subject to a nucleophilic attack. It was therefore thought that if the α,β-unsaturated amide moiety is incorporated into the basic structural frame of a simple substrate in such a way that it would bind the enzyme with its carbonyl group being coordinated to the zinc ion, then there may occur a Michael type addition reaction on the α,β-unsaturated amide by the catalytic carboxylate, leading to irreversible inhibition of the enzyme [16]. Our results demonstrated that series of different substituents, which containing electron-withdrawing groups or electron-donating groups, in phenyl ring derivatives have a slight effect on inhibitory activity on ACE probably due to the same mechanism. The results obtained here will be further study and considered as interesting future prospects.

CONCLUSION

In conclusion, a series of 3-(2-cinnamamidoethylsulfonyl)thiazolidine-4-carboxylate derivatives was designed and synthesized in an attempt to identify a new class of ACE inhibitors. Among these compounds, **10g** was one of the most active compounds against ACE *in vitro*. Structure-activity relationships (SARs) analysis required us to further optimize the structure mainly aim to the thiazolidine ring and the results will be reported shortly.

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