Syntheses and reactions of methyl [3-(4-phenyl-thiazol-2-yl)-thioureido] alkanoates and related compounds

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Dedicated to Prof. Ibrahim A. I. Aly for his efforts in Organic Chemistry at Suez Canal University

Abstract

Thiazole thioureas **4a-d** and **6** bearing an amino acid ester residue were prepared by a *one-pot* sequential reaction of methyl thiocarbamate **2** with amino acid methyl ester hydrochlorides. Some chemoselective reactions of **4a,b** with alkyl halides were studied.

Keywords: Non-nucleoside RT inhibitors, PETT, thiazole thioureas, amino acids, isothioureas, thiazolidin-4-one, intermolecular hydrogen bond, intramolecular hydrogen bond interactions

Introduction

Acquired immune compromised deficiency syndrome (AIDS) is caused by HIV (a retrovirus) affecting 33 million people worldwide, mostly affecting women and children in Sub-Sahara Africa.[1] Three million people around the world die of AIDS each year and, so far, more than 25 million people have died of the disease.

Lately, multiple antiretroviral agents have been produced to block replication of the HIV-1 virus by blocking HIV reverse transcriptase[2] or by blocking HIV protease.[3] Among the most important anti-retroviral agents recently introduced are the non-nucleoside reverse transcriptase inhibitors (NNRTI), such as nevirapine[4] and delavirdine[5] able to reduce RT inhibition to subnanomolar concentrations.

Several heterocyclic thioureas have been reported as a new class of potent NNRTIs such phenethylthiazolyl-thiourea (PETT) derivatives.[6-9] Uckun *et al.*[10] described the synthesis of a series of thiazole thioureas with alkyl, aryl, heteroaryl substituents as newly identified NNRTI of HIV, including mutant strains of HIV, and effective in the treatment of multi-drug resistant HIV infection.

We have recently reported a new and efficient synthesis of novel quinazoline thioureas bearing an amino acid ester residue based on domino reaction of *N*-(2-cyanophenyl)benzimidoyl isothioyanate with amino acid methyl ester hydrochlorides.[11]

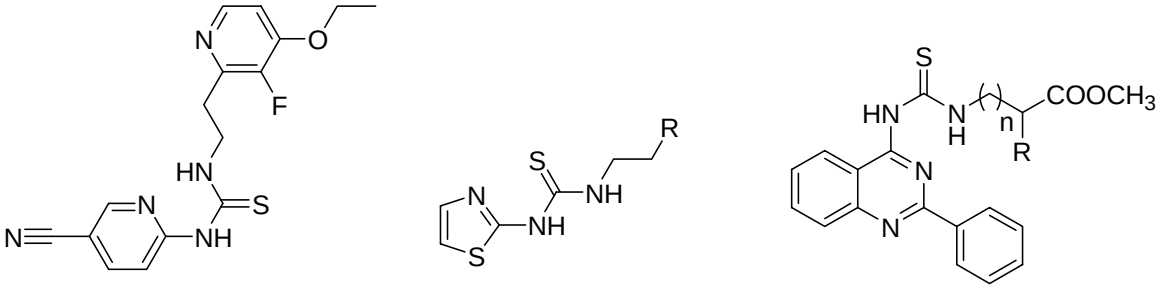


Figure 1

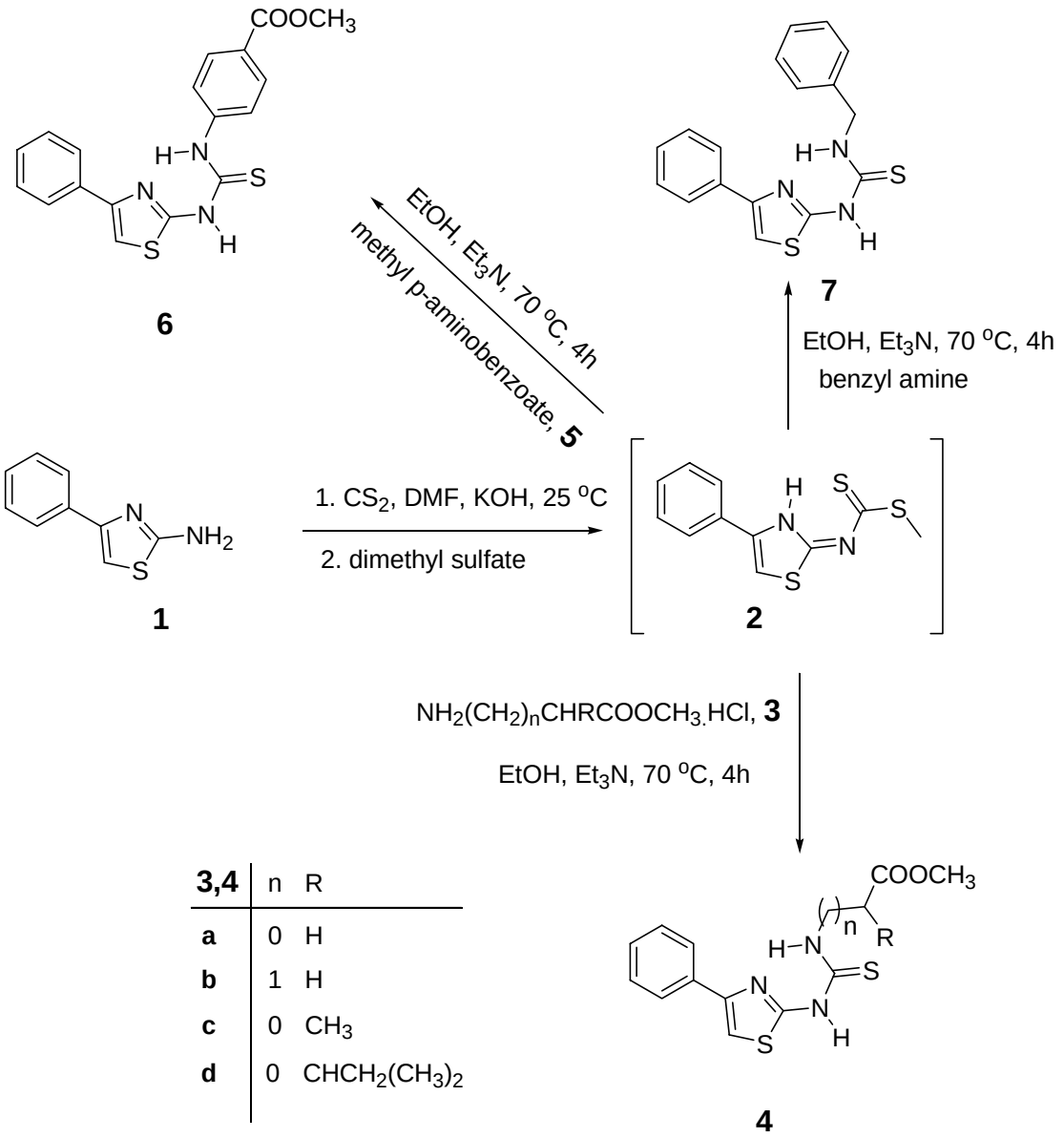
Results and Discussion

The synthesis of biologically active amino acid coupled derivatives was considered to be of a major interest.[11-14] In this paper, we described the development of a new series of thiazole thioureas bearing amino acid esters which can be used as potent NNRTIs.

The required thiazole thioureas **4a-d** and **6** were easily prepared starting from 4-phenyl-thiazol-2-ylamine (**1**) through methyl thiocarbamate **2** as a key intermediate in *one-pot* sequential reaction strategy (Scheme 1). First step; 4-phenyl-thiazol-2-ylamine (**1**) reacts with equimolar amount of carbon disulfide in basic media (KOH) using DMSO as solvent at 80 ºC for 2h. The reaction mixture was then cooled to 0 ºC and dimethyl sulfate was added simultaneously. The *in situ* generated methyl thiocarbamate **2** was extracted and used without further purification.

Compound **2** is an interesting reactive intermediate for the synthesis of a variety of heterocyclic compounds.[15] This reactivity is due to leaving group ability of SMe group when reacting with nucleophiles. Thus, equimolar amount of amino acid ester hydrochloride **3** adds to *in situ* generated methyl thiocarbamate **2** in the presence of triethylamine in ethyl alcohol to afford methyl [3-(4-phenyl-thiazol-2-yl)-thioureido] alkanoate **4.** Similarly, methyl *p*-aminobenzoate **5** adds to **2** to afford thiourea **6.**

The syntheses of **4a-d** and **6** reported herein have the advantage of *one-pot* synthesis in addition to operational simplicity and availability giving a series of very interesting compounds.



3,4	n	R
a	0	H
b	1	H
c	0	CH_3
d	0	$CHCH_2(CH_3)_2$

Scheme 1

The structure assignments of amino acid esters **4a-d** and **6** are based on spectral and physicochemical analysis. All isolated products exhibited a rather interesting conformation as indicated from all ^{1}H NMR spectra, figure 2. Thus, the ^{1}H NMR spectrum of **4b** showed three signals; a quartet, a triplet and a singlet at δ 4.12, 2.83 and 3.69 ppm consequent to two CH_2 groups of the β-alanine residue and OCH_3 group, respectively.

In addition the ^{1}H NMR spectrum of **4b** gave two exchangeable singlets at δ 11.29 and 10.57 ppm corresponding to two NH groups. This implies that N3–H group participate in a strong intramolecular hydrogen bond interaction with the thiazole nitrogen of the type N3–H···N=C.[10,11,16] The other N1–H group is involved in an intermolecular hydrogen bond with

either the thiocarbonyl of the thiourea of the type N1–H···S=C,[17-20] or the carbonyl of the amino acid residue of the type N1–H···O=C.[21-23]

The intermolecular hydrogen bond could be distinguished by comparison of the ^{1}H NMR spectra with similar compound lacking the ester function group. 1-Benzyl-3-(4-phenyl-thiazol-2-yl)-thiourea **7** was similarly prepared by the reaction of benzyl amine with *insitu* generated methyl thiocarbamate **2**, scheme 1**.** The ^{1}H NMR spectrum of **7** shows chemical shift at 11.49 ppm due to NH group participating in an intramolecular hydrogen bond; while gave chemical shift at 6.38 ppm due to N1H group.

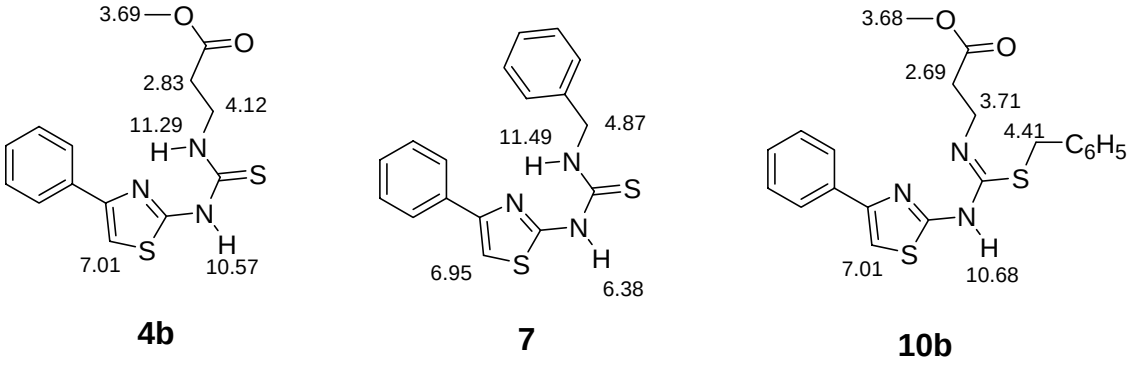


Figure 2. Selected ^{1}H NMR data of compounds **4b**, **7** and **10b**.

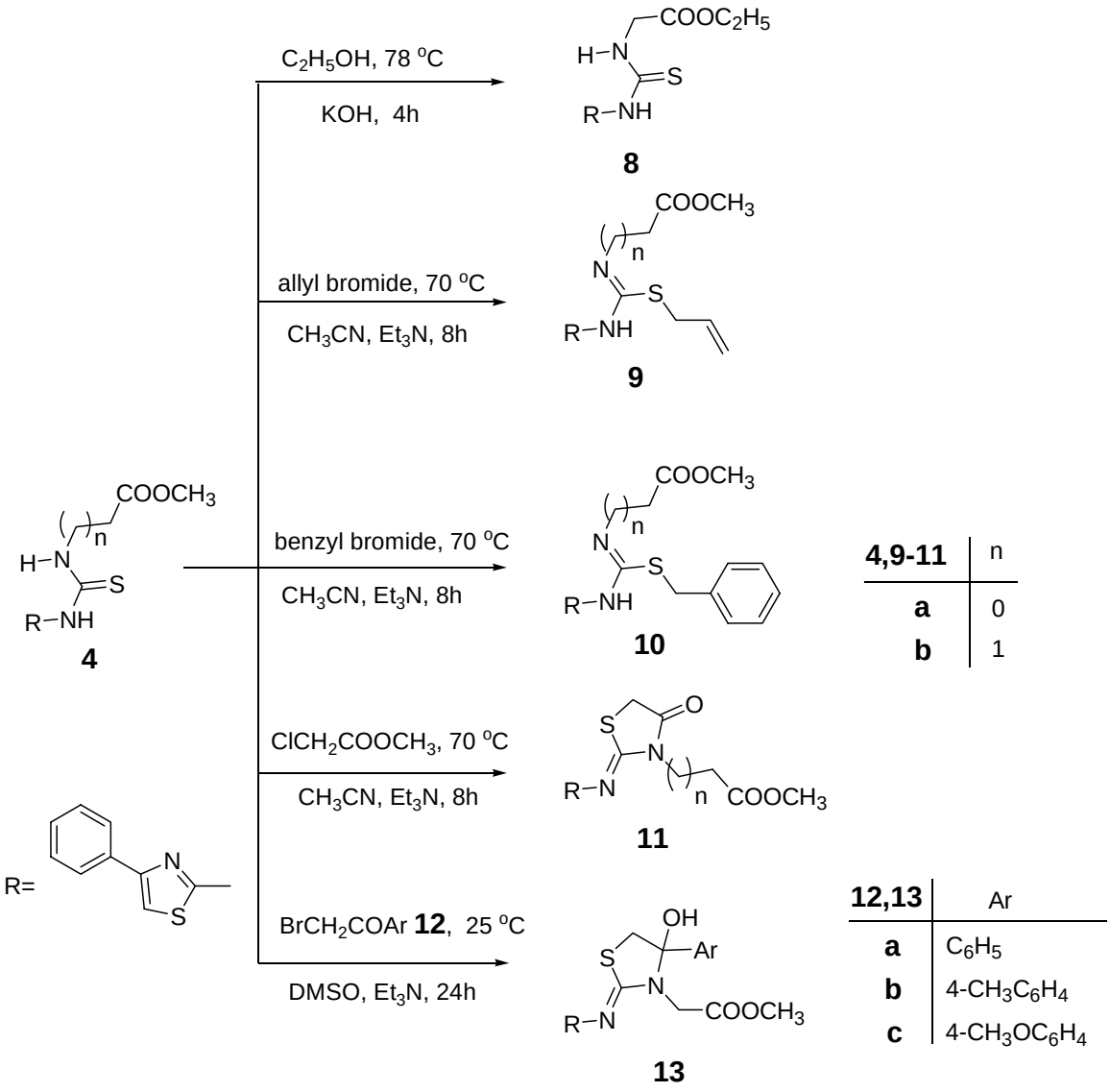
The reaction of glycine derivatives **4a** with absolute ethanol in the presence of potassium hydroxide furnished the trans-esterification product **8** (Scheme 2). The reaction of methyl [3-(4-phenyl-thiazol-2-yl)-thioureido] alkanoates **4a,b (**Gly and β-Ala) with electrophiles might give more evidence for structure elucidation beside chemical and biological importance. Thus, the reaction of **4a,b** with allyl bromide and benzyl bromide in the presence of Et_3N gave a single tautomeric chemoselective *S*-alkylated derivatives **9a,b** and **10a,b**[24-26] induced by hydrogen bond interactions. Earlier we reported the chemoselective *S*-alkylation reaction in similar compounds afforded only a single compound preserving the intramolecular hydrogen bond.[11]

The ^{1}H NMR spectrum clearly deduced the alkylation site and the position of double bond. The ^{1}H NMR spectrum of **10b** has shown a broad singlet at δ 10.68 attributed to N1H group partipating in an intermolecular hydrogen bond of the type N1–H···O=C,[21-23] figure 2. Also, the ^{1}H NMR spectrum of **10b** gave three signals at δ 4.41, 3.71 and 2.69 ppm consequent to SCH_2[24] and two CH_2 groups of the β-alanine residue, respectively.

Thiazolidin-4-one derivatives are known to exhibit diverse bioactivities such as antiHIV.[27] Hence, it seems of interest to attach thiazolidin-4-one bearing amino acid ester residue to amino thiazole moieties in single molecular framework to enhance the biological activity.

The reaction of methyl [3-(4-phenyl-thiazol-2-yl)-thioureido] alkanoates **4a,b (**Gly and β-Ala) with methyl chloroacetate resulted in the formation of thiazolidines **11a,b**. The ^{1}H NMR spectrum of **11a** shows three singlets at δ 4.64, 3.93 and 3.78 ppm typically associated with an NCH_2, SCH_2CO and OCH_3, respectively. This structure was in good agreement with our

previous results with methyl [4-oxo-2-(2-phenylquinazolin-4-ylimino)thiazolidin-3-yl]acetate preparation, figure 3.[11]



Scheme 2

Similarly, the reaction of glycine derivative **4a** with phenacyl bromides **12** afforded 4-hydroxythiazolidines **13a-c.** The ^{1}H NMR spectra of 4-hydroxythiazolidines **13a-c** gave completely different pattern compared to thiazolidine **11a,b.** The ^{1}H NMR spectrum of **13b** shows two doublets centered at δ 4.40 and δ 3.63 ppm (J_{AB} = 17.2 Hz) corresponding to an AB system of the prochiral hydrogen atoms of the NCH_2 group. In addition, apparent two doublets are displayed at δ 3.57 and 3.48 ppm (J_{AB} = 11.8 Hz) resulting from A and B parts of the AB quartets of SCH_2 groups.[11]

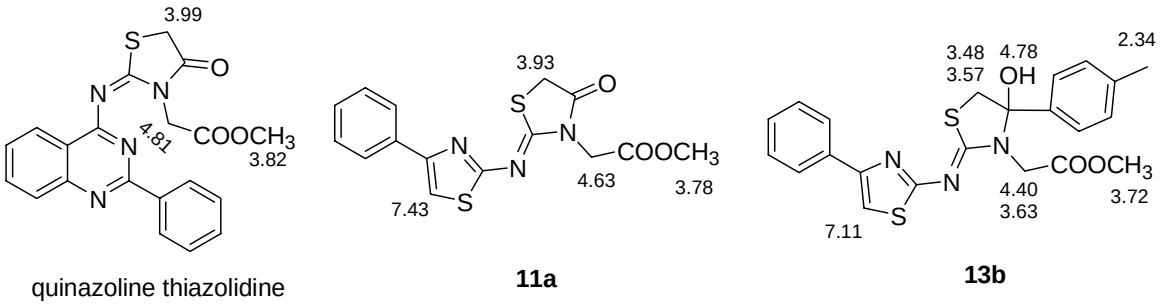


Figure 3. Selected ^{1}H NMR data of compounds **11a**, **13b** and quinazoline thiazolidine.[11]

Experimental Section

General Procedures. Solvent were purified and dried in the usual way. The boiling range of the petroleum ether used was 40-60 ^{o}C. Thin layer chromatography (TLC): silica gel 60 F_{254} plastic plates (E. Merck, layer thickness 0.2 mm) detected by UV absorption.
Elemental analyses were performed on a *Flash EA-1112* instrument at the Microanalytical laboratory, Faculty of Science, Suez Canal University, Ismailia, Egypt. Melting points were determined on a Buchi 510 melting-point apparatus and the values are uncorrected. NMR spectra measured with Bruker (200 MHz) and TMS (0.00 ppm) was used as internal standard. The starting compounds **1** was prepared according to described methods.[28]

General procedure for preparation of 4, 6 and 7
To a vigorously stirred solution of 4-phenyl-thiazol-2-ylamine (**1**) (0.9 g, 5.0 mmol) in dimethylsulfoxide (10 ml) at room temperature, carbon disulfide (0.4 ml, 6.5 mmol) and potassium hydroxide (0.31 g, 5.5 mmol) solution in 2 mL H_2O were added dropwise simultaneously over 30 min, the mixture was then allowed to stir for 30 min in water bath at 80 ºC. The reaction mixture was cooled in an ice bath to 0 ºC and dimethyl sulfate (0.5 mL, 5.0 mmol) was added dropwise for 15 min under cooling. Stirring was continued for 3 h, the reaction mixture was poured into ice-water and then it was extracted with chloroform. The solvent was removed by distillation under reduced pressure. Thus, the obtained crude methyl thiocarbamate **2** dissolved in ethanol 30 mL cooled to 10 ºC and was treated with nucleophiles [amino acid methyl ester hydrochloride **3** (5.0 mmol) and triethyl amine (0.7 mL, 5.0 mmol); methyl *p*-aminobenzoate **5** (0.75 g, 5.0 mmol) or benzyl amine (0.55 mL, 5.0 mmol)]. Stirring was continued for 3 h at 70 ºC. The reaction mixture was concentrated and the solid obtained was filtered, washed with water, dried and recrystallized from ethanol.
Methyl [3-(4-phenyl-thiazol-2-yl)-thioureido] acetate (4a). From $GlyOCH_3$·HCl **3a** (0.65 g). Colorless crystals (1.05 g, 67 %); mp 212-213 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 11.51 (1H, bs, D_2O exchangeable, NH), 9.77 (1H, bs, D_2O exchangeable, NH), 7.92 (2H, d, *J*= 8.0 Hz, ArH), 7.48–7.32 (3H, m, ArH), 7.03 (1H, s, CH-thiazole), 4.57 (2H, d, *J*= 4.2 Hz, $NHCH_2$), 3.86 (3H,

s, OCH_3). Anal. Calcd. For $C_{13}H_{13}N_3O_2S_2$ (307.4): C, 50.79; H, 4.26; N, 13.67; Found: C, 50.63; H, 4.19; N, 13.61.

Methyl 3-[3-(4-phenyl-thiazol-2-yl)-thioureido] propanoate (4b). From β-AlaOCH_3·HCl **3b** (0.7 g). Colorless crystals (1.35 g, 85 %); mp 202-203 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 11.29 (1H, bs, D_2O exchangeable, NH), 10.57 (1H, bs, D_2O exchangeable, NH), 7.86 (2H, d, *J* = 8.0 Hz, ArH), 7.48–7.33 (3H, m, ArH), 7.01 (1H, s, CH-thiazole), 4.12 (2H, q, *J*= 5.8 Hz, $NHCH_2$), 3.69 (3H, s, OCH_3), 2.83 (2H, t, *J*= 5.8 Hz, CH_2). Anal. Calcd. For $C_{14}H_{15}N_3O_2S_2$ (321.4): C, 52.32; H, 4.70; N, 13.07; Found: C, 52.29; H, 4.64; N, 12.89.

Methyl 2-[3-(4-phenyl-thiazol-2-yl)-thioureido] propanoate (4c). From L-AlaOCH_3·HCl **3c** (0.7 g). Colorless crystals (0.85 g, 53 %); mp 170-171 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 11.68 (1H, bs, D_2O exchangeable, NH), 10.71 (1H, bs, D_2O exchangeable, NH), 7.88 (2H, d, *J*= 8.0 Hz, ArH), 7.47–7.30 (3H, m, ArH), 7.02 (1H, s, CH-thiazole), 5.22–5.08 (1H, m, CH), 3.84 (3H, s, OCH_3), 1.67 (3H, d, *J*= 7.0 Hz, CH_3). Anal. Calcd. For $C_{14}H_{15}N_3O_2S_2$ (321.4): C, 52.32; H, 4.70; N, 13.07; Found: C, 52.24; H, 4.68; N, 12.93.

Methyl 4-methyl-2-[3-(4-phenyl-thiazol-2-yl)-thioureido]-pentanoate (4d). From L-LeuOCH_3·HCl **3d** (0.9 g). Colorless crystals (1.05 g, 57 %); mp 152-153 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 11.57 (1H, bs, D_2O exchangeable, NH), 10.93 (1H, bs, D_2O exchangeable, NH), 7.78 (2H, d, *J*= 8.0 Hz, ArH), 7.45–7.29 (3H, m, ArH), 7.01 (1H, s, CH-thiazole), 5.12 (1H, q, *J*= 7.2 Hz, CH), 3.81 (3H, s, OCH_3), 1.98–1.88 (3H, m, CH_2,CH), 1.03 (3H, d, *J* = 5.8 Hz, CH_3), 0.99 (3H, d, *J* = 5.8 Hz, CH_3). Anal. Calcd. For $C_{17}H_{21}N_3O_2S_2$ (363.5): C, 56.17; H, 5.82; N, 11.56; Found: C, 56.01; H, 5.66; N, 11.43.

Methyl 4-[3-(4-phenyl-thiazol-2-yl)-thioureido] benzoate (6).[29] From methyl 4-aminobenzoate **5** (0.75 g). Colorless crystals (1.4 g, 77 %); mp 201-202 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 13.25 (1H, bs, D_2O exchangeable, NH), 10.10 (1H, bs, D_2O exchangeable, NH), 8.15 (2H, d, *J*= 8.4 Hz, ArH), 7.90 (2H, d, *J*= 8.6 Hz, ArH), 7.76 (2H, d, *J*= 8.0 Hz, ArH), 7.47–7.33 (3H, m, ArH), 7.07 (1H, s, CH-thiazole), 3.94 (3H, s, OCH_3). Anal. Calcd. For $C_{18}H_{15}N_3O_2S_2$ (369.5): C, 58.52; H, 4.09; N, 11.37; Found: C, 58.48; H, 4.03; N, 11.31.

1-Benzyl-3-(4-phenyl-thiazol-2-yl)-thiourea (7).[29] From benzyl amine (0.55 mL). Colorless crystals (1.1 g, 68 %); mp 164-165 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 11.49 (1H, bs, D_2O exchangeable, NH), 7.53–7.38 (5H, m, ArH), 7.31– 7.22 (5H, m, ArH), 6.95 (1H, s, CH-thiazole), 6.38 (1H, bs, D_2O exchangeable, NH), 4.87 (2H, d, *J*= 5.0 Hz, $NHCH_2$). Anal. Calcd. For $C_{17}H_{15}N_3S_2$ (325.5): C, 62.74; H, 4.65; N, 12.91; Found: C, 62.68; H, 4.63; N, 12.88.

Derivatization reactions of 4a,b

Ethyl [3-(4-phenyl-thiazol-2-yl)-thioureido] acetate (**8**)**.** To a stirred solution of **4a** (1.55 g, 5.0 mmol) in absolute ethanol was added KOH (0.28 g, 5.0 mmol). The reaction mixture was refluxed for 4 h, and then evaporated under reduced pressure. The residue was collected and crystallized from ethanol to give white crystals.

Colorless crystals (1.3 g, 82 %); mp 198-199 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 11.48 (1H, bs, D_2O exchangeable, NH), 9.85 (1H, bs, D_2O exchangeable, NH), 7.87 (2H, d, *J*= 8.0 Hz, ArH),

7.48–7.32 (3H, m, ArH), 7.02 (1H, s, CH-thiazole), 4.61 (2H, d, *J*= 4.6 Hz, $NHCH_2$), 4.41 (2H, q, *J*= 7.2 Hz, OCH_2), 1.38 (3H, t, *J*= 7.0 Hz, CH_3). Anal. Calcd. For $C_{14}H_{15}N_3O_2S_2$ (321.4): C, 52.32; H, 4.70; N, 13.07; Found: C, 52.25; H, 4.66; N, 13.01.

Reactions with alkyl halides. To a stirred mixture of **4a,b** (5.0 mmol) in absolute ethanol (20 mL) and triethyl amine (0.7 mL, 5.0 mmol) was added the appropriate alkyl halide [benzyl bromide, allyl bromide and ethyl chloroacetate] (5.0 mmol). The reaction mixture was heated at 90 °C for 4 h, then evaporated under reduced pressure. The residue was recrystallized from ethanol.

Methyl [2-allyl-3-(4-phenyl-thiazol-2-yl)-isothioureido]-acetate (**9a**)**.** From Gly derivative **4a** (1.55 g) and allyl bromide (0.45 mL). Colorless crystals (0.85 g, 48 %); mp °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 11.02 (1H, bs, D_2O exchangeable, NH), 7.93 (2H, d, *J*= 8.0 Hz, ArH), 7.45–7.28 (3H, m, ArH), 7.03 (1H, s, CH-thiazole), 6.18-5.83 (1H, m, $CH=CH_2$), 5.31 (1H, d, *J*= 17.0 Hz, $CH=CH_2$), 5.15 (1H, d, *J*= 9.8 Hz, $CH=CH_2$), 4.22 (2H, d, *J*= 4.6 Hz, $NHCH_2$), 3.85–3.78 (5H, m, SCH_2, OCH_3). Anal. Calcd. For $C_{16}H_{17}N_3O_2S_2$ (347.5): C, 55.31; H, 4.93; N, 12.09; Found: C, 55.26; H, 4.84; N, 12.01.

Methyl 3-[2-allyl-3-(4-phenyl-thiazol-2-yl)-isothioureido]-propanoate (**9b**)**.** From β-Ala derivative **4b** (1.6 g) and allyl bromide (0.45 mL). Colorless crystals (1.1 g, 60 %); mp 75-76 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.68 (1H, bs, D_2O exchangeable, NH), 7.83 (2H, d, *J*= 7.0 Hz, ArH), 7.45–7.27 (3H, m, ArH), 7.00 (1H, s, CH-thiazole), 6.06-5.86 (1H, m, $CH=CH_2$), 5.31 (1H, d, *J*= 16.8 Hz, $CH=CH_2$,), 5.15 (1H, d, *J*= 10.8 Hz, $CH=CH_2$), 3.82 (2H, d, *J*= 7.0 Hz, SCH_2), 3.77–3.70 (5H, m, NCH_2, OCH_3), 2.72 (2H, t, *J* = 6.0 Hz, CH_2). Anal. Calcd. For $C_{17}H_{19}N_3O_2S_2$ (361.5): C, 56.48; H, 5.30; N, 11.62; Found: C, 56.35; H, 5.28; N, 11.46.

Methyl [2-benzyl-3-(4-phenyl-thiazol-2-yl)-isothioureido]-acetate (**10a**)**.** From Gly derivative **4a** (1.55 g) and benzyl bromide (0.6 mL). Colorless crystals (1.55 g, 78 %); mp 102-103 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 11.04 (1H, bs, D_2O exchangeable, NH), 7.97–7.88 (2H, m, ArH), 7.46–7.27 (8H, m, ArH), 7.05 (1H, s, CH-thiazole), 4.42 (2H, s, SCH_2), 4.19 (2H, d, *J*= 5.0 Hz, NCH_2), 3.85 (3H, s, OCH_3). Anal. Calcd. For $C_{20}H_{19}N_3O_2S_2$ (397.5): C, 60.43; H, 4.82; N, 10.57; Found: C, 60.38; H, 4.74; N, 10.43;

Methyl 3-[2-benzyl-3-(4-phenyl-thiazol-2-yl)-isothioureido]-propanoate (**10b**)**.** From β-Ala derivative **4b** (1.6 g) and benzyl bromide (0.6 mL). Colorless crystals (1.75 g, 85 %); mp 88-89 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.68 (1H, bs, D_2O exchangeable, NH), 7.84 (2H, d, *J*= 7.0 Hz, ArH), 7.46–7.27 (8H, m, ArH), 7.01 (1H, s, CH-thiazole), 4.41 (2H, s, SCH_2), 3.74–3.65 (5H, m, NCH_2, OCH_3), 2.68 (2H, t, *J*= 6.4 Hz, CH_2). Anal. Calcd. For $C_{21}H_{21}N_3O_2S_2$ (411.5): C, 61.29; H, 5.14; N, 10.21; Found: C, 61.15; H, 5.07; N, 10.13.

Methyl [4-Oxo-2-(4-phenyl-thiazol-2-ylimino)-thiazolidin-3-yl]-acetate (**11a**)**.** From Gly derivative **4a** (1.55 g) and ethyl chloroacetate (0.55 mL). Colorless crystals (1.05 g, 61 %); mp 182-183 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.92–7.86 (2H, m, ArH), 7.46–7.29 (4H, m, 3ArH, CH-thiazole), 4.64 (2H, s, NCH_2), 3.93 (2H, s, SCH_2), 3.78 (3H, s, OCH_3). Anal. Calcd. For $C_{15}H_{13}N_3O_3S_2$ (347.4): C, 51.86; H, 3.77; N, 12.10; Found: C, 51.81; H, 3.64; N, 12.96.

Methyl 3-[4-Oxo-2-(4-phenyl-thiazol-2-ylimino)-thiazolidin-3-yl]-propanoate (11b). From β-Ala derivative **4b** (1.6 g) and ethyl chloroacetate (0.55 mL). Colorless crystals (1.55 g, 87 %); mp 165-166 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.90 (2H, d, *J* = 7.8 Hz, ArH), 7.46–7.32 (4H, m, 3ArH, CH-thiazole), 4.19 (2H, t, *J*= 7.4 Hz, NCH_2), 3.8 (2H, s, SCH_2), 3.69 (3H, s, OCH_3), 2.74 (2H, t, *J*= 7.4 Hz, CH_2). Anal. Calcd. For $C_{16}H_{15}N_3O_3S_2$ (361.4): C, 53.17; H, 4.18; N, 11.63; Found: C, 53.03; H, 4.16; N, 11.54.

Reactions with phenacyl bromides

To a stirred mixture of **4a** (1.55 g, 5.0 mmol) in DMSO (10 mL) and triethyl amine (0.7 mL, 5.0 mmol) was added the appropriate phenacyl bromide **12** (5.0 mmol). The reaction mixture was left at room temperature over night, poured over water. The resultant solid was filtered off and recrystallized from ethanol.

Methyl [4-hydroxy-4-phenyl-2-(4-phenyl-thiazol-2-ylimino)-thiazolidin-3-yl]-acetate (**13a**)**.** From Gly derivative **4a** (1.55 g) and phenacyl bromide **12a** (1.0 g). Yellowish orange crystals (1.3 g, 62 %); mp 45-47 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.92 (2H, d, *J*= 7.0 Hz, ArH), 7.61 (2H, d, *J*= 7.8 Hz, ArH), 7.47–7.28 (6H, m, ArH), 7.11 (1H, s, CH-thiazole), 4.85 (1H, bs, D_2O exchangeable, OH), 4.46 (1H, d, *J*= 17.2 Hz, NCH_A), 3.77–3.66 (4H, m, OCH_3, NCH_B), 3.60 (1H, d, *J*= 11.8 Hz, SCH_A), 3.52 (1H, d, *J*= 11.8 Hz, SCH_B). Anal. Calcd. For $C_{21}H_{19}N_3O_3S_2$ (425.5): C, 59.27; H, 4.50; N, 9.87; Found: C, 59.12; H, 4.34; N, 9.67.

Methyl [4-Hydroxy-2-(4-phenyl-thiazol-2-ylimino)-4-*p*-tolyl-thiazolidin-3-yl]-acetate (**13b**)**.** From Gly derivative **4a** (1.55 g) and 4-methyl phenacyl bromide **12b** (1.05 g). Brownish crystals (0.95 g, 43 %); mp 40-41 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.90 (2H, d, *J*= 7.2 Hz, ArH), 7.48–7.17 (7H, m, ArH), 7.09 (1H, s, CH-thiazole), 4.78 (1H, bs, D_2O exchangeable, OH), 4.40 (1H, d, *J*= 17.2 Hz, NCH_A), 3.70 (3H, s, OCH_3), 3.63 (1H, d, *J*= 17.2 Hz, NCH_B), 3.57 (1H, d, *J*= 11.8 Hz, SCH_A), 3.48 (1H, d, *J*= 11.8 Hz, SCH_B), 2.34 (3H, s, CH_3). Anal. Calcd. For $C_{22}H_{21}N_3O_3S_2$ (439.6): C, 60.11; H, 4.82; N, 9.56; Found: C, 60.04; H, 4.76; N, 9.51.

Methyl [4-hydroxy-4-(4-methoxy-phenyl)-2-(4-phenyl-thiazol-2-ylimino)-thiazolidin-3-yl]-acetate (**13c**)**.** From Gly derivative **4a** (1.55 g) and 4-methoxy phenacyl bromide **12c** (1.15 g). Colorless crystals (1.3 g, 57 %); mp 50-51 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.92 (2H, d, *J*= 7.2 Hz, ArH), 7.52 (2H, d, *J*= 8.6 Hz, ArH), 7.43–7.27 (3H, m, ArH), 7.11 (1H, s, CH-thiazole), 6.92 (2H, d, *J*= 8.6 Hz, ArH), 4.80 (1H, bs, D_2O exchangeable, OH), 4.44 (1H, d, *J*= 17.0 Hz, NCH_A), 3.81 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.63 (1H, d, *J*= 17.0 Hz, NCH_B), 3.58 (1H, d, *J*= 12.0 Hz, SCH_A), 3.49 (1H, d, *J*= 12.0 Hz, SCH_B), 2.34 (3H, s, CH_3). Anal. Calcd. For $C_{22}H_{21}N_3O_4S_2$ (455.6): C, 58.00; H, 4.65; N, 9.22; Found: C, 57.89; H, 4.54; N, 9.13.

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