

Synthesis of some new 5-arylidene-2,4-thiazolidinedione esters

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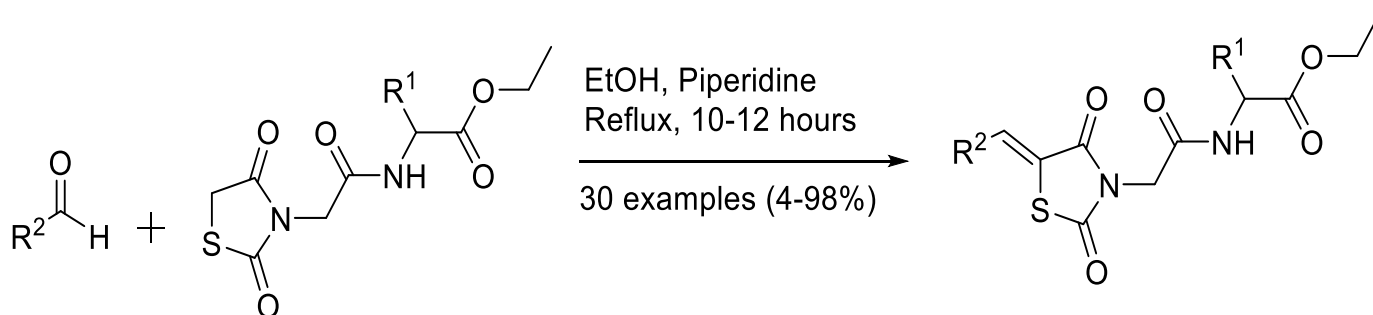
Received 10-14-2020

Accepted 01-23-2021

Published on line 01-31-2021

Abstract

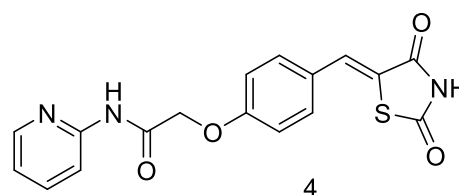
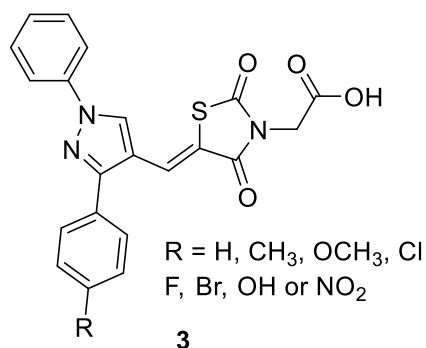
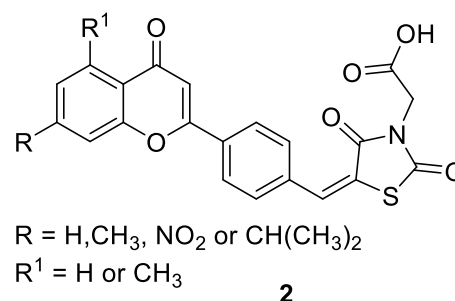
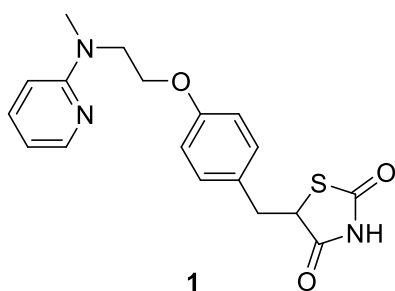
Compounds containing the 1,3-thiazolidine-2,4-dione scaffold are gaining increasing scientific interest as potential interventional agents for a variety of disease states. A four-step synthesis of ethyl-(2-(5-arylidene-2,4-dioxothiazolidin-3-yl)acetyl)glycinates, alaninates, butanoates, valinates and norvalinates is described. The synthesis began by converting 1,3-thiazolidine-2,4-dione into its potassium salt, which was treated with ethyl (2-chloroacetamido)glycinates, alaninates, butanoates, valinates and norvalinates, respectively, to obtain the penultimate products. These products were then subjected to a Knoevenagel condensation reaction with different aldehydes to obtain the desired products in low to excellent yields.



Keywords: Thiazolidinedione, alaninate, glycinate, butanoate, valinate, norvalinate

Introduction

1,3-Thiazolidine-2,4-dione (TZD)-containing compounds have been reported to show many different pharmacological activities.¹ A few of these compounds are indicated in Figure 1. Glitazones, like rosiglitazone (**1**), are currently marketed for the treatment of type 2 diabetes.² Thiazolidinedione, linked to chromones via benzylidene moiety (**2**), have been reported to act as aldose reductase inhibitors.³ Aneja and co-workers have reported that a series compounds of 5-((3-(aryl)-1-phenyl-1H-pyrazol-4-yl) methylene)-3-phenyl thiazolidine-2,4-diones (**3**) have antibacterial and antiviral activity.⁴ A new series of 5-benzylidene-2,4-thiazolidinedione derivatives (**4**) have been reported by Patil *et al.* to have anticancer activity.⁵ Rekha *et al.* synthesized 5-substituted-arylidine-2,4-thiazolidinediones derivatives (**5**), and reported them to have anti-inflammatory activities.⁶ Sharma *et al.* have synthesized a series of 2,4 thiazolidinediones (**6**), following a structure-based virtual screening, in order to explore structure-activity relationships for inhibition of the *P. falciparum* cysteine protease falcipain-2 (FP-2) and whole-cell antiparasitic activity.⁷ Most compounds were reported to display low micromolar antiplasmodial activities against the *P. falciparum* drug-resistant W2 strain.⁸ Alagawadi and Alegaon⁹ reported the synthesis and *in vitro* antifungal activity of 5-substituted-2,4-thiazolidinedione derivatives (**7**). Their compounds were found to be active against tested fungal strains at 1–64 µg/mL concentrations. Kumar *et al.* have reported a series of 5-((E)-4-((E)-(substituted aryl/alkyl)methyl) benzylidene)thiazolidine-2,4-dione derivatives (**8**) which were tested for their antioxidant properties by determining their effects on superoxide anion formation and the 2,2-diphenyl-1-picrylhydrazyl (DPPH) stable free radical.¹⁰



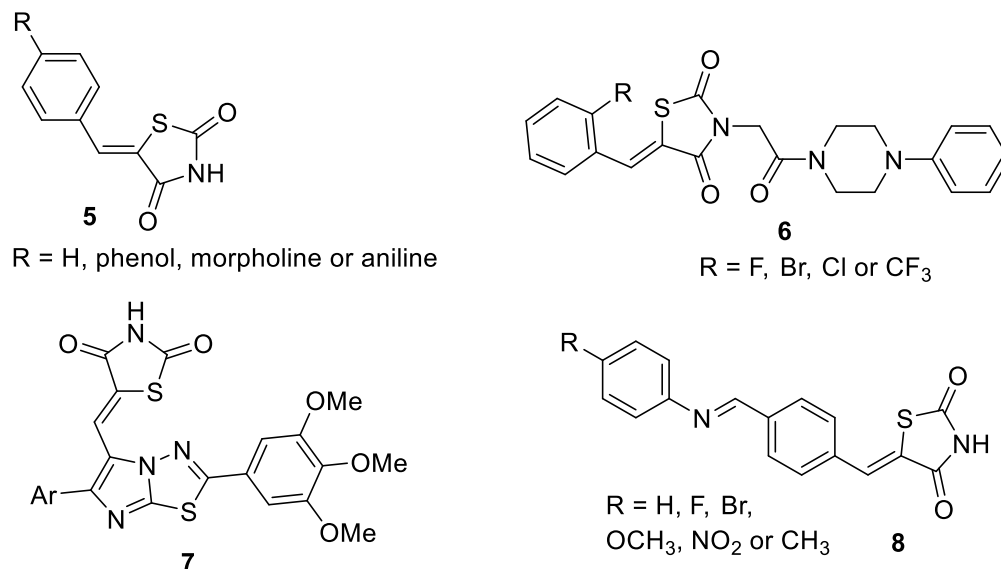


Figure 1. Compounds containing the thiazolidinedione moiety.

In view of the number of compounds containing the thiazolidinedione moiety possessing different biological activities shown above, we sought to synthesize novel 5-arylidene-2,4-thiazolidinedione esters. The syntheses of these compounds, using Knoevenagel condensation reaction as a key step, was designed schematically to consist of the arylidene (aryl) chain, TZD scaffold, two-carbon linker as well as an amino acid chain (Figure 2), which is similar to that described by Kumar *et al.*¹¹

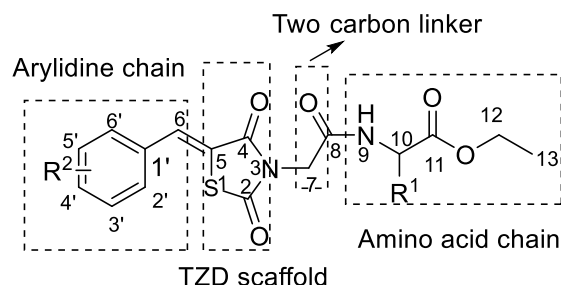
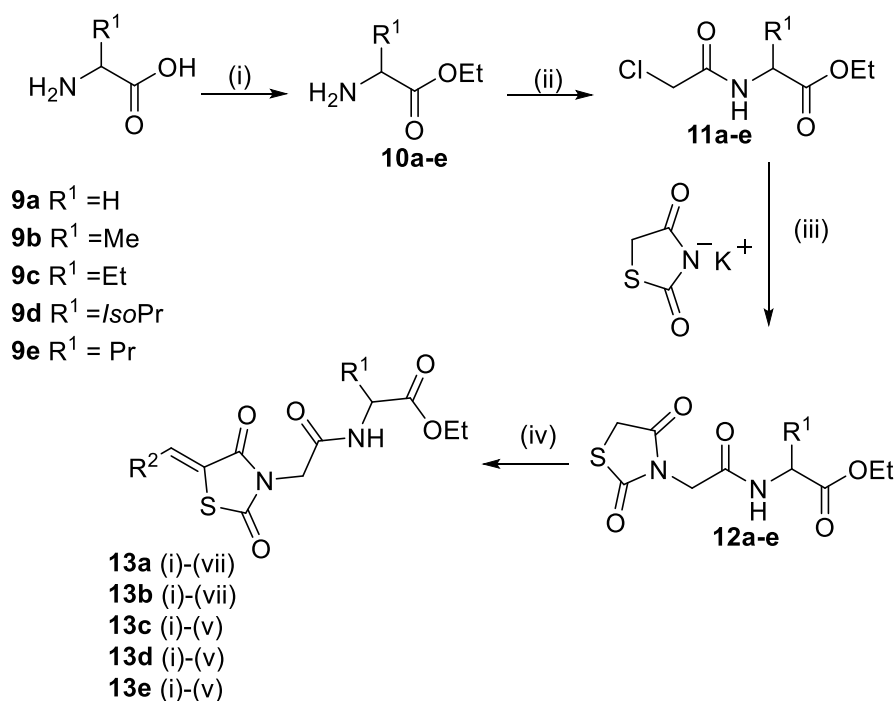


Figure 2. Schematic representation of ethyl-(2-(5-Arylidene-2,4-dioxothiazolidin-3-yl)acetyl)esters derivatives.

Results and Discussion

The synthesis of 5-arylidene-2,4-thiazolidinedione esters started with protection of the five different amino acids **9** as esters **10** by using thionyl chloride in the presence of ethanol at lower temperatures (0-5 °C) (Scheme 1). Compounds **10** were then each treated with bromoacetyl chloride to obtain the ethyl (2-chloroacetamido) esters **11**. Treatment of compounds **11** with a potassium salt of thiazolidinedione¹² gave compounds **12** in excellent yields (i.e., **12a**, 89%; **12b**, 92%; **12c**, 88%; **12d**, 89%; and **12e**, 79%). Finally, compounds **12** were subjected to Knoevenagel-reaction conditions using various aldehydes to provide the desired products **13** in low-to-excellent yields, as shown in Table 1 below. As the protected amino acid chain was extended from glycine to alanine, valine or norvaline (Scheme 1), a chiral centre was created at position

H-10 of the desired molecule (Figure 2). Thus, ^1H NMR spectra containing these amino acids moieties showed the multiplicity of the N-H signal H-9 as a doublet, and not a triplet that was shown by glycine-moiety-containing compounds. After a Knoevenagel condensation reaction step, ^1H NMR spectra of compounds **13a-e** were characterised by the absence of aldehydic proton peaks at ~ 9 ppm, confirming the consumption of the aldehydes. In addition, the spectra were characterised by the appearance of an aryl proton peak as a singlet at ~ 7.9 ppm. ^{13}C NMR spectra of compounds **13a-e** were characterised by lack of an aldehydic carbon peak at ~ 190 ppm with the appearance of a new aryl carbon signal at ~ 134 ppm, confirming that the condensation reaction was successful. After the introduction of a fluorine atom at the *para* position of the phenyl ring, interestingly, the ^1H NMR spectra of compounds **13avii**, **13bvii**, **13dv**, and **13eiv** showed a coupling between the fluorine and the neighbouring proton signal H-3', H-5' at 7.81 ppm, and H-2', H-6' at 7.48 ppm appearing as a doublet of doublets instead of the expected doublet. This observation was further supported by ^{13}C NMR spectra which revealed coupling between the fluorine and the carbon signals C-2', C-6' as well as C-3', C-5' which showed two extra signals appearing as doublets instead of the expected singlet. This was further confirmed by ^{19}F NMR spectra of compounds **13avii**, **13bvii**, **13dv**, and **13eiv**, which showed coupling between protons H-3', H-5', H-2' and H-6' and appeared as a multiplet instead of a singlet.



Scheme 1. Reagents and conditions: (i) SOCl_2 , ethanol, 0-5 °C; (ii) K_2CO_3 , bromoacetyl chloride, DCM, -10 °C to rt; (iii) THF, reflux; (iv) aldehydes, piperidine, ethanol, reflux.

Table 1. % yields of products **13**

Entry	R ¹	R ²	Yield (%)
13ai	H	Ph	50
13aai		4-OMePh	54
13aiii		4-NO ₂ Ph	98
13aiv		4-OMe, 3-OHPh	97
13av		piperonayl	54
13avi		4-MePh	46
13avii		4-FPh	12
13bi	Me	Ph	50
13bii		4-OMePh	98
13biii		4-NO ₂ Ph	90
13biv		4-OMe, 3-OHPh	61
13bv		piperonayl	53
13bvi		4-MePh	31
13bvii		4-FPh	11
13bviii		Furanyl	34
13ci	Et	Ph	10
13cii		4-OMePh	37
13ciii		4-MePh	8
13civ		4-OHPh	6
13cv		Furanyl	11
13di	Iso-Pr	Ph	24
13dii		4-OMePh	38
13diii		4-OMe, 3-OHPh	12
13div		4-OHPh	4
13dv		4-FPh	11
13ei	Pr	4-OMePh	17
13eii		4-MePh	12
13eiii		4-OHPh	26
13eiv		4-FPh	21
13ev		Furanyl	65

Conclusions

Five series of glycines **13a**, alanines **13b**, butanoates **13c**, valines **13d**, and norvalines **13e** derivatives were successfully synthesised in average yields of 52%, 54%, 14%, 14% and 28%, respectively, in four reaction steps. Modified known methods were followed in synthesizing these compounds.

Experimental Section

General. All reagents used were analytical grade reagents from Sigma-Aldrich and Fluka. Thin-layer chromatography (TLC) was carried out using Macherey-Nagel Alugram Sil G/UV₂₅₄ plates, pre-coated with 0.25 mm silica gel 60. Detection was done under ultraviolet light at 254 nm. ¹H NMR (400 MHz), ¹³C NMR (100 MHz) and ¹⁹F NMR (376.5 MHz) spectra were recorded on a Bruker 400 MHz spectrometer using DMSO-*d*₆ or CDCl₃ as solvents and TMS at 0.00 ppm as an internal standard. Values for the chemical shifts are expressed in parts per million (ppm). The following abbreviations are used: br.s for broad singlet, s for singlet, d for doublets, dd for doublet of doublets, q for quartet, quint for quintet and m for multiplet and (*J*) for coupling constants measured in hertz (Hz). All the melting points were determined on a Buchi melting point B-540 apparatus using capillary tubes. Infrared spectra were run on a Bruker platinum 22 vector Fourier Transform spectrometer (FTIR). Mass spectra (High Resolution) were recorded on a Waters GCT using a column called the Restek Rxi Wintegra Guard (15 m, 0.25 mm ID, 0.25 µm film thickness) mass spectrometer. The samples were dissolved in acetonitrile and injected at a volume of 1 µl at a mode of 10:1 and temperature of 280 °C. The source temperature was 100 °C and the de-solvation temperature was set at 300 °C. Helium gas was used as the carrier gas. The software used to control the hyphenated system and to do all data manipulation was MassLynx 4.1 (SCN 704).

General procedure for synthesis of ethyl (2-chloroacetamido) esters (11a-e)

Amino esters (**10**), which were obtained from corresponding acids (**9**) were cooled to -10 °C before being treated with a solution of bromoacetyl chloride (1 mmol) and potassium carbonate (3 mmol) in a mixture of dichloromethane and water (1:1). The resulting solution was allowed to warm up to room temperature before being stirred for 16 hours at the same temperature. After this reaction time, the mixture was extracted with dichloromethane, and the organic extracts were subsequently washed with brine before being dried over MgSO₄ and filtered before being concentrated on a rotary evaporator. The products obtained were used without further purification.

Ethyl (2-chloroacetyl)glycinate (11a).¹³ Compound was obtained as a white solid (4.90 g, 96%); m.p = 75-76 °C. Spectroscopic data were similar to the one described by Kumar *et al.*

Ethyl (2-chloroacetyl)alaninate (11b).¹⁴ Compound was obtained as a colourless oil (7.60 g, 98%). Spectroscopic data were similar to those described by Aladzheva *et al.*

Ethyl 2-(2-chloroacetamido)butanoate (11c). A reaction of **10c**¹⁵ (2.04 g, 15.2 mmol) and bromoacetyl chloride (1.27 ml, 15.2 mmol) gave compound **11c** as a brown oil (2.74 g, 88%); IR (KBr cm⁻¹): 3233, 2968, 1727, 1250; ¹H NMR (400 MHz, CDCl₃) δ_H (ppm) 7.17 (d, 1H, *J* 6.8, Hz, NH), 4.45 (quint, 1H, *J* 4.0 Hz, CHNH), 4.12 (q, 2H, *J* 4.0 Hz, OCH₂CH₃), 3.84 (s, 2H, CH₂Cl), 1.81-1.91 (1H, m, CHCH₃), 1.22 (t, 3H, *J* 6.0 Hz, CH₃CH₂O), 0.87 (3H, t, *J* 7.2 Hz, CH₃CH₂O); ¹³C NMR (100 MHz, CDCl₃) δ_C (ppm) 171.7 (C=O) 165.9 (C=O), 61.5 (OCH₂CH₃), 42.4 (CH₂Cl), 28.7 (CHNH), 25.3 (CH₂CH₃), 14.1 (CH₃CH₂O). 9.3 (CH₃CH₂).

Ethyl (2-chloroacetyl)valinate (11d).¹⁶ Compound **11d** was obtained as a colourless oil (6.74 g, 89%). Spectroscopic data were similar to those described by Khadidja *et al.*

Ethyl (2-chloroacetyl)norvalinate (11e). A reaction of **10e**¹⁵ (5.03 g, 34.4 mmol) and bromoacetyl chloride (2.89 ml, 34.4 mmol) gave compound **10e** as a colourless oil (5.74 g, 79%); IR (KBr cm⁻¹): 3272, 2962, 1733, 1290; ¹H NMR (400 MHz, CDCl₃) δ_H (ppm) 8.68 (d, 1H, *J* 3.6, Hz, NH), 5.75 (s, 2H, CH₂Cl) 4.22 (quint, 1H, *J* 4.8 Hz, CHNH), 4.13 (q, 2H, *J* 4.0 Hz, OCH₂CH₃), 3.93-3.89 (m, 2H, CH₂CH), 1.70-1.64 (1H, m, CH₂CH₃), 1.22 (t, 3H, *J* 2.0 Hz, CH₃CH₂O); 0.88 (t, 3H, *J* 7.2 Hz, CH₃CH₂); ¹³C NMR (100 MHz, CDCl₃) δ_C (ppm) 172.1 (C=O) 166.7 (C=O), 62.1 (OCH₂CH₃), 52.5 (CHNH), 33.4 (CH₂CH₃), 29.3 (CH₂Cl), 18.9 (CH₃CH), 14.5 (CH₃CH₂O), 13.9 (CH₃CH₂).

General procedure for synthesis of ethyl 2-(2,4-dioxothiazolidin-3-yl) acetyl esters (12a-e)

A mixture of potassium salt of 1,3-thiazolidine-2,4-dione (1 mmol) and ethyl (2-chloroacetamido) derivatives (**11a-e**) (1 mmol) in tetrahydrofuran (THF) was refluxed for 12 hours. After cooling to room temperature, the mixture was filtered through cotton wool and the filtrate concentrated on a rotary evaporator to provide the ethyl 2-(2,4-dioxothiazolidin-3-yl) acetyl derivatives (**12a-e**) which were used without further purification.

Ethyl (2-(2,4-dioxothiazolidin-3-yl)acetyl)glycinate (12a). A reaction of the potassium salt of 1,3-thiazolidine-2,4-dione (4.50 g, 38.3 mmol) and **11a** (6.90 g, 38.3 mmol) gave compound **12a** as a white solid (8.50 g, 89%); m.p = 110-112 °C; IR (KBr cm^{-1}): 3294, 3108 1738, 1652; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ_{H} (ppm) 8.67 (t, 1H, J 5.6 Hz, NH), 4.27 (s, 2H, CH_2N), 4.17 (s, 2H, CH_2S), 4.11 (q, 2H, J 7.2 Hz, OCH_2CH_3), 3.86 (d, 2H, J 5.6 Hz, CH_2NH), 1.19 (t, 3H, J 7.2 Hz, $\text{CH}_3\text{CH}_2\text{O}$); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ_{C} (ppm) 172.4 (C=O), 172.0 (C=O), 169.9 (C=O), 166.2 (C=O), 61.0 (OCH_2CH_3), 43.4 (CH_2N), 41.5 (CH_2NH), 34.5 (CH_2S), 14.5 ($\text{CH}_3\text{CH}_2\text{O}$).

Ethyl (2-(2,4-dioxothiazolidin-3-yl)acetyl)alaninate (12b). A reaction of the potassium salt of 1,3-thiazolidine-2,4-dione (3.55 g, 30.3 mmol) and **11b** (5.87 g, 30.3 mmol) gave compound **12b** as a white solid (9.70 g, 92%); m.p = 100-101 °C; IR (KBr cm^{-1}): 3288, 3078, 1735, 1687; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ_{H} (ppm) 6.62 (d, 1H, J 6.4 Hz, NH), 4.48 (quint, 1H, J 7.2 Hz, CHNH), 4.25 (s, 2H, CH_2N), 4.13 (q, 2H, J 7.2 Hz, OCH_2CH_3), 3.99 (s, 2H, CH_2S), 1.33 (d, 3H, J 7.2 Hz, CH_3CH), 1.21 (t, 3H, J 7.2, $\text{CH}_3\text{CH}_2\text{O}$); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ_{C} (ppm) 172.7 (C=O), 171.4 (C=O), 171.1 (C=O), 164.3 (C=O), 61.7 (OCH_2CH_3), 48.5 (CHNH), 43.5 (CH_2N), 33.9 (CH_2S), 18.3 (CH_3CH), 14.1 ($\text{CH}_3\text{CH}_2\text{O}$).

Ethyl 2-(2-(2,4-dioxothiazolidin-3-yl)acetamido)butanoate (12c). A reaction of the potassium salt of 1,3-thiazolidine-2,4-dione (4.50 g, 21.7 mmol) and **11c** (2.54 g, 21.7 mmol) gave compound **12c** as a white solid (5.43 g, 79%); m.p = 109-110 °C; IR (KBr cm^{-1}): 3279, 3077, 1738, 1682, ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ_{H} (ppm) 6.55 (d, 1H, J 6.4 Hz, NH), 4.35 (quint, 1H, J 7.2 Hz, CHNH), 4.24 (s, 2H, CH_2NH), 4.23 (q, 2H, J 4.0 Hz, OCH_2CH_3), 4.06 (s, 2H, CH_2S), 1.94-1.86 (m, 1H, CH_aCH_3), 1.79-1.68 (m, 1H, CH_bCH_3), 1.30 (t, 3H, J 8.0 Hz, CH_3CH_2), 0.91 (t, 3H, J 7.6 Hz, $\text{CH}_3\text{CH}_2\text{O}$); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ_{C} (ppm) 172.1 (C=O), 171.5 (C=O), 171.0 (C=O), 165.9 (C=O), 60.9 (OCH_2CH_3), 58.0 (CHNH), 43.3 (CH_2N), 34.4 (CH_2S), 30.6 (CH_2CH_3), 19.3 (CH_3CH), 18.5 (CH_3CH_2), 14.5 ($\text{CH}_3\text{CH}_2\text{O}$).

Ethyl (2-(2,4-dioxothiazolidin-3-yl)acetyl)valinate (12d). A reaction of the potassium salt of 1,3-thiazolidine-2,4-dione (3.79 g, 32.3 mmol) and **11d** (7.16 g, 32.3 mmol) gave compound **12d** as a white solid (7.91 g, 81%); m.p = 118-120 °C; IR (KBr cm^{-1}): 3262, 3080, 1736, 1685; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ_{H} (ppm) 8.57 (d, 1H, J 7.6 Hz, NH), 4.28 (s, 2H, CH_2N), 4.16 (quint, 1H, J 8.4 Hz, CHNH), 4.12 (q, 2H, J 4.0 Hz, OCH_2CH_3), 4.09 (s, 2H, CH_2S), 2.04-2.03 (m, 2H, $\text{CH}(\text{CH}_3)_2$), 1.19 (t, 3H, J 6.4 Hz, $\text{CH}_3\text{CH}_2\text{O}$), 0.87 (s, 6H, $(\text{CH}_3)_2\text{CH}$); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ_{C} (ppm) 172.3 (C=O), 171.9 (C=O), 171.6 (C=O), 165.9 (C=O), 61.0 (OCH_2CH_3), 58.0 (CHNH), 43.3 (CH_2N), 34.3 (CH_2S), 30.6 ($\text{CH}(\text{CH}_3)_2$), 19.6 (CH_3CH), 18.5 (CH_3CH), 14.6 ($\text{CH}_3\text{CH}_2\text{O}$).

Ethyl (2-(2,4-dioxothiazolidin-3-yl)acetyl)norvalinate (12e). A reaction of the potassium salt of 1,3-thiazolidine-2,4-dione (3.97 g, 33.8 mmol) and **11e** (7.50 g, 33.8 mmol) gave compound **12e** as a white solid (8.08 g, 81%); m.p = 119-120 °C; IR (KBr cm^{-1}): 3282, 3076, 1737, 1685; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ_{H} (ppm) 8.62 (d, 1H, J 6.4 Hz, NH), 4.27 (s, 2H, CH_2N), 4.22 (quint, 1H, J 8.0 Hz, CHNH), 4.17 (s, 2H, CH_2S), 4.08 (q, 2H, J 5.6 Hz, OCH_2CH_3), 1.65-1.59 (m, 2H, CH_2CH), 1.31-1.19 (m, 2H, CH_2CH_3), 1.18 (t, 3H, J 6.4 Hz, $\text{CH}_3\text{CH}_2\text{O}$), 0.87 (t, 3H, J 6.4 Hz, CH_3CH_2); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ_{C} (ppm) 172.3 (C=O), 172.2 (C=O), 172.0 (C=O), 165.8 (C=O), 61.0 (OCH_2CH_3), 52.4 (CHNH), 43.3 (CH_2N), 34.4 (CH_2S), 33.5 (CH_2CH), 18.9 (CH_2CH_3), 14.5 ($\text{CH}_3\text{CH}_2\text{O}$), 13.9 (CH_3CH_2).

General procedure for the synthesis of ethyl (2-(5-arylidene-2,4-dioxothiazolidin-3-yl)acetyl)ester derivatives (13a-e). To a suspension of compounds **12** (1 mmol) in ethanol was added appropriate aldehydes

(1 mmol) followed by catalytic amount of piperidine (10%). The resultant mixture was refluxed for 12 hours. After being allowed to cool down to room temperature, the mixture was poured into ice water and the resultant precipitate collected by filtration. The solids obtained were further purified by washing with methanol to afford the desired compounds (**13a-e**).

Ethyl (2-(5-benzylidene-2,4-dioxothiazolidin-3-yl)acetyl)glycinate (13ai). A reaction of benzaldehyde (0.40 ml, 3.84 mmol) and **12a** (1.03 g, 3.84 mmol) gave compound **13ai** as a brown solid (0.71 g, 52%); m.p = 185-187 °C; IR (KBr cm⁻¹): 3210, 3076, 1745, 1737, 1724, 1684, 1186; ¹H NMR (400 MHz, DMSO-*d*₆) δ_H (ppm) 8.78 (t, 1H, *J* = 5.6 Hz, NH), 7.97 (s, 1H, Aryl-H), 7.66 (d, 2H, *J* 6.8 Hz, 2 × Ar-H), 7.56-7.53 (m, 3H, 3 × Ar-H), 4.35 (s, 2H, CH₂N), 4.09 (q, 2H, *J* 6.8 Hz, OCH₂CH₃), 3.89 (d, 2H, *J* 4.8 Hz, CH₂NH), 1.20 (t, 3H, *J* 6.8 Hz, CH₃CH₂O); ¹³C NMR (100 MHz, DMSO-*d*₆) δ_C (ppm) 169.9 (C=O), 167.5 (C=O), 166.6 (C=O), 165.7 (C=O), 133.8 (Aryl-CH), 133.3 (Ar-CH), 131.2 (Ar-C), 130.6 (2 × Ar-CH), 129.9 (2 × Ar-CH), 121.6 (Ar-C), 61.0 (OCH₂CH₃), 43.7 (CH₂N), 41.3 (CH₂NH), 14.49 (CH₃CH₂O); HRMS (ESI-TOF) *m/z*; calculated for C₁₆H₁₆N₂O₅S-H: 347.0780, found M⁺-H: 347.0783.

Ethyl (2-(5-(4-methoxybenzylidene)-2,4-dioxothiazolidin-3-yl)acetyl)glycinate (13aii).¹¹ A reaction of *p*-anisaldehyde (0.47 ml, 3.84 mmol) and **12a** (1.05 g, 3.84 mmol) gave compound **13aii** as a white solid (0.72 g, 50%); m.p = 208-211 °C; Spectroscopic data were found to be similar to those reported by Kumar *et al*.

Ethyl (2-(5-(4-nitrobenzylidene)-2,4-dioxothiazolidin-3-yl)acetyl)glycinate (13aiii). A reaction of 4-nitrobenzaldehyde (0.58 g, 3.84 mmol) and **12a** (1.04 g, 3.84 mmol) gave compound **13aiii** as a white solid (1.57 g, 98%); m.p = 204 -208 °C; IR (KBr cm⁻¹): 3291, 3084, 1744, 1695, 1661, 1612, 1154; ¹H NMR (400 MHz, DMSO-*d*₆) δ_H (ppm) 8.80 (s, 1H, NH), 8.36 (d, 2H, *J* 8.4 Hz, 2 × Ar-H), 8.10 (s, 1H, Aryl-H), 7.93 (d, 2H, *J* 8.4, 2 × Ar-H), 4.37 (s, 2H, CH₂N), 4.10 (q, 2H, *J* 7.2 Hz, OCH₂CH₃), 3.90 (d, 2H, *J* 5.2 Hz, CH₂NH), 1.20 (t, 3H, *J* 7.2 Hz, CH₃CH₂O); ¹³C NMR (100 MHz, DMSO-*d*₆) δ_C (ppm) 169.9 (C=O), 167.0 (C=O), 166.0 (C=O), 165.4 (C=O), 148.2 (Ar-CNO₂), 139.6 (Ar-C), 131.6 (2 × Ar-CH), 131.3 (Aryl-CH), 125.9 (Ar-C), 124.8 (2 × Ar-CH), 61.0 (OCH₂CH₃), 43.9 (CH₂N), 41.3 (CH₂NH), 14.5 (CH₃CH₂O); HRMS (ESI-TOF) *m/z*; calculated for C₁₆H₁₅N₃O₇S+H: 394.0631, found M⁺+H: 394.0634.

Ethyl (2-(5-(4-hydroxy-3-methoxybenzylidene)-2,4-dioxothiazolidin-3-yl)acetyl)glycinate (13aiv).

A reaction of vanillin (0.58 g, 3.84 mmol) and **12a** (1.02 g, 3.84 mmol) gave compound **13aiv** as a yellow solid (1.47 g, 97%); m.p = 233-234 °C; IR (KBr cm⁻¹): 3378, 3294, 2987, 1742, 1727, 1677, 1657, 1168; ¹H NMR (400 MHz, DMSO-*d*₆) δ_H (ppm) 8.78 (s, 1H, NH), 7.86 (s, 1H, Aryl-H), 7.20 (s, 1H, Ar-H), 7.12 (d, 1H, *J* 8.0 Hz, Ar-H), 6.92 (d, 1H, *J* 8.1 Hz, Ar-H), 4.33 (s, 2H, CH₂N), 4.09 (q, 2H, *J* 6.8 Hz, CH₂OCH₃), 3.88 (d, 2H, *J* 5.2 Hz, CH₂N), 3.82 (s, 3H, OCH₃), 1.19 (t, 3H, *J* 7.2 Hz, CH₃CH₂O); ¹³C NMR (100 MHz, DMSO-*d*₆) δ_C (ppm) 169.9 (C=O), 167.7 (C=O), 166.3 (C=O), 165.8 (C=O), 151.1 (Ar-COCH₃), 148.7 (Ar-COH), 134.7 (Aryl-CH), 125.0 (Ar-CH), 124.2 (Ar-C), 116.9 (Ar-CH), 116.6 (Ar-C), 114.7 (Ar-CH), 61.0 (OCH₂CH₃), 56.1 (OCH₃), 43.5 (CH₂N), 41.3 (CH₂NH), 14.5 (CH₃CH₂O); HRMS (ESI-TOF) *m/z*; calculated for C₁₇H₁₈N₂O₇S: 394.0835, found M⁺: 394.0838.

Ethyl (2-(5-(benzo[d][1,3]dioxol-5-ylmethylene)-2,4-dioxothiazolidin-3-yl)acetyl) glycinate (13av). A reaction of piperonal (0.58 g, 3.84 mmol) and **12a** (1.01 g, 3.84 mmol) gave compound **13av** as a yellow solid (0.81 g, 54%), m.p = 211-212 °C; IR (KBr cm⁻¹): 3287, 3094, 1730, 1682, 1658, 1623, 1155; ¹H NMR (400 MHz, DMSO-*d*₆) δ_H (ppm) 8.82 (t, 1H, *J* 5.7 Hz, NH), 7.94 (s, 1H, Aryl-H), 7.28-7.25 (m, 2H, 2 × Ar-H), 7.17 (d, 1H, *J* 8.0 Hz, Ar-H), 6.20 (s, 1H, OCH₂O), 4.39 (s, 2H, CH₂N), 4.15 (q, 2H, *J* 7.1 Hz, OCH₂CH₃), 3.93 (d, 2H, *J* 5.8 Hz, CH₂NH), 1.25 (t, 3H, *J* 7.1 Hz, CH₃CH₂O); ¹³C NMR (100 MHz, DMSO-*d*₆) δ_C (ppm) 169.9 (C=O), 167.5 (C=O), 166.2 (C=O), 165.7 (C=O), 150.1 (Ar-C), 148.3 (Ar-C), 133.9 (Aryl-CH), 127.5 (Ar-C), 126.6 (Ar-CH), 119.0 (Ar-C), 109.8 (Ar-CH), 109.7 (Ar-CH), 102.6 (OCH₂O), 61.0 (OCH₂CH₃), 43.6 (CH₂N), 41.3 (CH₂NH), 14.5 (CH₃CH₂O); HRMS (ESI-TOF) *m/z*; calculated for C₁₇H₁₆N₂O₇S: 392.0678, found M⁺: 392.0681.

Ethyl (2-(5-(4-methylbenzylidene)-2,4-dioxothiazolidin-3-yl)acetyl)glycinate (13avi). A reaction of *p*-tolualdehyde (0.30 ml, 2.28 mmol) and **12a** (0.82 g, 2.28 mmol) gave compound **13avi** as a white solid (0.38 g, 46%); m.p = 220–221 °C; IR (KBr cm⁻¹): 3279, 3045, 1740, 1663, 1658, 1612, 1150; ¹H NMR (400 MHz, DMSO-*d*₆) δ_H (ppm) 8.77 (t, 1H, *J* 5.6 Hz, NH), 7.93 (s, 1H, Aryl-H), 7.54 (d, 2H, *J* 8.0 Hz, 2 × Ar-H), 7.37 (d, 2H, *J* 8.0 Hz, 2 × Ar-H), 4.34 (s, 2H, CH₂N), 4.09 (q, 2H, *J* 7.2 Hz, OCH₂CH₃), 3.89 (d, 2H, *J* 6.0 Hz, CH₂NH), 2.37 (s, 3H, CH₃), 1.19 (t, 3H, *J* 7.2 Hz, CH₃CH₂O); ¹³C NMR (100 MHz, DMSO-*d*₆) δ_C (ppm) 169.9 (C=O), 167.5 (C=O), 166.7 (C=O), 165.7 (C=O), 141.6 (Ar-CCH₃), 133.9 (Aryl-CH), 130.7 (2 × ArCH), 130.6 (Ar-C), 130.5 (2 × Ar-CH), 120.3 (Ar-C), 61.0 (OCH₂CH₃), 43.7 (CH₂N), 41.3 (CH₂NH), 21.6 (ArCH₃), 14.6 (CH₃CH₂O); HRMS (ESI-TOF) *m/z*; calculated for C₁₇H₁₈N₂O₅S+H: 363.0936 found M⁺+H: 363.0939.

Ethyl (2-(5-(4-fluorobenzylidene)-2,4-dioxothiazolidin-3-yl)acetyl)glycinate (13avii). A reaction of 4-fluorobenzaldehyde (0.31 ml, 2.88 mmol) and **12a** (0.75 g, 2.88 mmol) gave compound **13avii** as a yellow solid (0.12 g, 12%); m.p = 169–170 °C; IR (KBr cm⁻¹): 3299, 2922, 1740, 1683, 1658, 1612, 1180; ¹H NMR (400 MHz, DMSO-*d*₆) δ_H (ppm) 8.83 (t, 1H, *J* 6.0 Hz, NH), 8.05 (s, 1H, Aryl-H), 7.81 (dd, 2H, ⁴*J*_{FF} 8.8 Hz, *J*_{HH} 5.6 Hz, 2 × Ar-H), 7.48 (dd, 2H, ³*J*_{FF} 17.6 Hz, *J*_{HH} 8.8 Hz, 2 × Ar-H), 4.40 (s, 2H, CH₂N), 4.21 (q, 2H, *J* 6.0 Hz, CH₂OCH₃), 3.95 (d, 2H, *J* 5.6 Hz, CH₂NH), 1.27 (t, 3H, *J* 8.4 Hz, CH₃CH₂O); ¹⁹F NMR (376.5 MHz, DMSO-*d*₆) δ_F (ppm) -107.92–(-109.06) (m, 1F, Ar-F) ¹³C NMR (100 MHz, DMSO-*d*₆) δ_C (ppm) 169.9 (C=O), 167.4 (C=O), 166.1 (C=O), 165.6 (C=O), 163.5 (d, ¹*J* 250.0 Hz, Ar-CF), 133.2 (d, ³*J* 9.0 Hz, 2 × Ar-CH), 132.8 (Aryl-CH), 130.0 (d, ⁴*J* 3.0 Hz, Ar-C), 121.3 (Ar-C), 117.1 (d, ²*J* 22.0 Hz, 2 × Ar-CH), 61.1 (OCH₂CH₃), 43.7 (CH₂N), 41.3 (CH₂NH), 14.5 (CH₃CH₂O); HRMS (ESI-TOF) *m/z*; calculated for C₁₆H₁₅FN₂O₅S+H: 367.0686 found M⁺+H: 367.0689.

Ethyl (2-(5-benzylidene-2,4-dioxothiazolidin-3-yl)acetyl)alaninate (13bi). A reaction of benzaldehyde (0.40 ml, 3.65 mmol) and **12b** (1.05 g, 3.65 mmol) gave compound **13bi** as a white solid (0.64 g, 50%); m.p = 167–168 °C; IR (KBr cm⁻¹): 3287, 3087, 1734, 1687, 1660, 1608, 1149; ¹H NMR (400 MHz, DMSO-*d*₆) δ_H (ppm) 8.79 (d, 1H, *J* 6.8 Hz, NH), 7.96 (s, 1H, Aryl-H), 7.65 (d, 2H, *J* 7.2 Hz, 2 × Ar-H), 7.58–7.5 (m, 3H, 3 × Ar-H), 4.29 (s, 2H, CH₂N), 4.26 (quint, 2H, *J* 7.2 Hz, CHNH), 4.08 (q, 2H, *J* 6.2 Hz, OCH₂CH₃), 1.30 (d, 3H, *J* 7.2 Hz, CH₃CH) 1.18 (t, 3H, *J* 7.2 Hz, CH₃CH₂O); ¹³C NMR (100 MHz, DMSO-*d*₆) δ_C (ppm) 172.7 (C=O), 167.5 (C=O), 165.7 (C=O), 165.5 (C=O), 133.9 (Aryl-CH), 133.3 (Ar-C), 131.3 (Ar-CH), 130.6 (2 × Ar-CH), 129.9 (2 × Ar-CH), 121.5 (Ar-C), 61.1 (OCH₂CH₃), 48.4 (CH₂NH), 43.6 (CH₂N), 17.4 (CH₃CH), 14.4 (CH₃CH₂O); HRMS (ESI-TOF) *m/z*; calculated for C₁₇H₁₈N₂O₅S: 362.0936, found M⁺: 362.0939.

Ethyl (2-(5-(4-methoxybenzylidene)-2,4-dioxothiazolidin-3-yl)acetyl)alaninate (13bii). A reaction of *p*-anisaldehyde (0.45 ml, 3.65 mmol) and **12b** (1.02 g, 3.65 mmol) gave compound **13bii** as a brown solid (1.34 g, 98%); m.p = 208–209 °C; IR (KBr cm⁻¹): 3296, 3085, 1733, 1681, 1659, 1183; ¹H NMR (400 MHz, DMSO-*d*₆) δ_H (ppm) 8.77 (d, 1H, *J* 6.6 Hz, NH), 7.92 (s, 1H, Aryl-H), 7.62 (d, 2H, *J* 8.3 Hz, 2 × Ar-H), 7.12 (d, 2H, *J* 8.3 Hz, 2 × Ar-H), 4.32 (s, 2H, CH₂N), 4.25 (quint, 1H, *J* 6.8 Hz, CHNH), 4.08 (q, 2H, *J* 7.8 Hz, OCH₂CH₃), 3.84 (s, 3H, OCH₃), 1.30 (d, 3H, *J* 7.0 Hz, CH₃CH) 1.19 (t, 3H, *J* 6.9 Hz, CH₃CH₂O); ¹³C NMR (100 MHz, DMSO-*d*₆) δ_C (ppm) 172.6 (C=O), 167.5 (C=O), 165.8 (C=O), 165.5 (C=O), 161.7 (Ar-COCH₃), 133.8 (Aryl-CH), 132.8 (2 × Ar-CH), 125.8 (Ar-C), 118.2 (Ar-C), 115.5 (2 × Ar-CH), 61.0 (OCH₂CH₃), 56.0 (OCH₃), 48.4 (CHNH), 43.5 (CH₂N), 17.5 (CH₃CH), 14.5 (CH₃CH₂O); HRMS (ESI-TOF) *m/z*; calculated for C₁₈H₂₀N₂O₆S: 392.4260, found M⁺: 392.4262.

Ethyl (2-(5-(4-nitrobenzylidene)-2,4-dioxothiazolidin-3-yl)acetyl)alaninate (13biii). A reaction of 4-nitrobenzaldehyde (0.55 g, 3.65 mmol) and **12b** (1.02 g, 3.65 mmol) in ethanol (20 ml) gave compound **13biii** as a brown solid (1.31 g, 90%); m.p = 223–224 °C; IR (KBr cm⁻¹): 3325, 3035, 1760, 1737, 1687, 1671, 1159; ¹H NMR (400 MHz, DMSO-*d*₆) δ_H (ppm) 8.88 (d, 1H, *J* 6.9 Hz, NH), 8.43 (d, 2H, *J* 8.8 Hz, Ar-H), 8.16 (s, 1H, Aryl-H), 7.99 (d, 2H, *J* 8.4 Hz, 2 × Ar-H), 4.42 (s, 2H, CH₂N), 4.34 (quint, 1H, *J* 7.2 Hz, CHNH), 4.16 (q, 2H, *J* 6.0 Hz, OCH₂CH₃), 1.38 (d, 3H, *J* 7.3 Hz, CH₃CH), 1.29 (t, 3H, *J* 7.1 Hz, CH₃CH₂O); ¹³C NMR (100 MHz, DMSO-*d*₆) δ_C (ppm) 172.6 (C=O), 167.0 (C=O), 165.4 (C=O), 165.3 (C=O), 148.1 (Ar-CNO₂), 139.6 (Ar-C), 131.56 (2 × Ar-CH),

131.3 (Aryl-CH), 126.4 (Ar-C), 125.8 (2 × Ar-CH), 61.1 (OCH₂CH₃), 48.4 (CH₂NH), 43.8 (CH₂N), 17.5 (CH₃CH), 14.44 (CH₃CH₂O); HRMS (ESI-TOF) *m/z*; calculated for C₁₇H₁₇N₃O₇S: 407.0787, found M⁺: 407.0786.

Ethyl (2-(5-(4-hydroxy-3-methoxybenzylidene)-2,4-dioxothiazolidin-3-yl)acetyl)alaninate (13biv). A reaction of vanillin (0.55 g, 3.65 mmol) and **12b** (1.03 g, 3.65 mmol) gave compound **13biv** as a yellow solid (0.88 g, 61%); m.p = 183-184 °C; IR (KBr cm⁻¹): 3294, 2954, 1737, 1720, 1682, 1654, 1168; ¹H NMR (400 MHz, DMSO-*d*₆) δ_H (ppm) 8.76 (d, 1H, *J* 6.9 Hz, NH), 7.87 (s, 1H, Aryl-H), 7.22 (d, 1H, *J* 1.6 Hz Ar-CH), 7.12 (dd, 1H, *J*₁ 8.4 Hz, *J*₂ 1.6 Hz Ar-CH), 6.94 (d, 1H, *J* 8.0 Hz, Ar-CH), 4.25 (s, 2H, CH₂N), 4.24 (quint, 1H, *J* 7.2 Hz, CHNH), 4.07 (q, 2H, *J* 6.0 Hz, OCH₂CH₃), 3.83 (s, 3H, OCH₃), 1.30 (d, 3H, *J* 7.6 Hz, CH₃CH) 1.18 (t, 3H, *J* 7.2 Hz, CH₃CH₂O); ¹³C NMR (100 MHz, DMSO-*d*₆) δ_C (ppm) 172.7 (C=O), 167.6 (C=O), 165.8 (C=O), 165.6 (C=O), 150.3 (Ar-COCH₃), 148.5 (Ar-COH), 134.6 (Aryl-CH), 124.8 (Ar-C), 124.7 (Ar-CH), 117.1 (Ar-C), 116.7 (Ar-CH), 114.7 (Ar-CH), 61.2 (OCH₂CH₃), 56.1 (OCH₃), 48.4 (CHN), 43.5 (CH₂N), 17.5 (CH₃CH), 14.4 (CH₃CH₂O); HRMS (ESI-TOF) *m/z*; calculated for C₁₈H₂₀N₂O₇S: 408.0991, found M⁺: 408.0993.

Ethyl (2-(5-(benzo[d][1,3]dioxol-5-ylmethylene)-2,4-dioxothiazolidin-3-yl)acetyl)alaninate (13bv). A reaction of piperonal (0.55 g, 3.65 mmol) and **12b** (1.01 g, 3.65 mmol) gave compound **13bv** as a yellow solid (0.79 g, 53%), m.p = 174-175 °C, ¹H NMR (400 MHz, DMSO-*d*₆) δ_H (ppm) 8.77 (d, 1H, *J* 7.0 Hz, NH), 7.88 (s, 1H, Aryl-CH), 7.23-7.19 (m, 2H, 2 × Ar-H), 7.11 (d, 1H, *J* 8.0 Hz, Ar-H), 6.15 (s, 2H, OCH₂O), 4.31 (s, 2H, CH₂N), 4.25 (quint, 1H, *J* 7.2, CHNH), 4.08 (q, 2H, *J* 6.4 Hz, OCH₂CH₃), 1.29 (d, 3H, *J* 7.2, CH₃CH) 1.18 (t, 3H, *J* 6.8 Hz, CH₃CH₂O), ¹³C NMR (100 MHz, DMSO-*d*₆) δ_C (ppm) 172.6 (C=O), 167.4 (C=O), 165.7 (C=O), 165.5 (C=O), 150.1 (Ar-C), 148.7 (Ar-C), 133.9 (Aryl-H), 127.5 (Ar-C), 126.7 (Ar-CH), 118.9 (Ar-C), 109.8 (Ar-CH), 109.7 (Ar-CH), 102.6 (OCH₂O), 61.0 (OCH₂CH₃), 48.4 (CHNH), 43.5 (CH₂N), 17.4 (CH₃CH), 14.4 (CH₃CH₂O), IR (KBr cm⁻¹): 3315, 2998, 1736, 1680, 1654, 1610 (C=O stretch), 1156, HRMS (ESI-TOF) *m/z*; calculated for C₁₈H₁₈N₂O₇S: 406.0835, found M⁺: 406.0832.

Ethyl (2-(5-(4-methylbenzylidene)-2,4-dioxothiazolidin-3-yl)acetyl)alaninate (13bvi). A reaction of *p*-tolualdehyde (0.32 ml, 2.75 mmol) and **12b** (0.82 g, 2.75 mmol) gave compound **13bvi** as a white solid (0.32 g, 31%); m.p = 213-214 °C; IR (KBr cm⁻¹): 3282, 2922, 1735, 1682, 1659, 1614, 1148; ¹H NMR (400 MHz, DMSO-*d*₆) δ_H (ppm) 8.77 (d, 1H, *J* 7.2 Hz, NH), 7.93 (s, 1H, Aryl-H), 7.54 (d, 2H, *J* 8.0 Hz, 2 × Ar-H), 7.37 (d, 2H, *J* 8.0 Hz, 2 × Ar-H), 4.28 (s, 2H, CH₂N), 4.25 (quint, 1H, *J* 7.2 Hz, CHNH), 4.09 (q, 2H, *J* 7.4 Hz, OCH₂CH₃), 2.51 (s, 3H, CH₃), 1.30 (d, 3H, *J* 7.2 Hz, CH₃CH) 1.14 (t, 3H, *J* 6.8 Hz, CH₃CH₂O); ¹³C NMR (100 MHz, DMSO-*d*₆) δ_C (ppm) 172.6 (C=O), 167.5 (C=O), 165.7 (C=O), 165.5 (C=O), 141.6 (Ar-CCH₃), 133.9 (Aryl-CH), 130.7 (2 × Ar-CH), 130.9 (Ar-C), 130.50 (2 × Ar-CH), 120.3 (Ar-C), 61.0 (OCH₂CH₃), 48.4 (CHNH), 43.6 (CH₂N), 21.6 (Ar-CH₃) 17.5 (CH₃CH), 14.4 (CH₃CH₂O); HRMS (ESI-TOF) *m/z*; calculated for C₁₈H₂₀N₂O₅S+H: 376.1093, found M⁺+H: 377.1096.

Ethyl (2-(5-(4-fluorobenzylidene)-2,4-dioxothiazolidin-3-yl)acetyl)alaninate (13bvii). A reaction of 4-fluorobenzaldehyde (0.30 ml, 2.75 mmol) and **12b** (0.821 g, 2.75 mmol) gave compound **13bvii** as a yellow solid (0.11 g, 11%); m.p = 203-204 °C; IR (KBr cm⁻¹): 3285, 2984, 1733, 1685, 1657, 1638 1183; ¹H NMR (400 MHz, DMSO-*d*₆) δ_H (ppm) 8.77 (d, 1H, *J* 6.8 Hz, NH), 7.99 (s, 1H, Aryl-H), 7.73 (dd, 2H, ⁴*J*_{FH} 8.8 Hz, *J*_{HH} 5.6 Hz, 2 × Ar-H), 7.41 (dd, 2H, ³*J*_{FH} 17.6 Hz, *J*_{HH} 8.8 Hz, 2 × Ar-H), 4.13 (s, 2H, CH₂N), 4.12 (quint, 1H, *J* 3.2 Hz, CHNH), 4.06 (q, 2H, *J* 2.8 Hz, OCH₂CH₃), 1.42 (d, 3H, *J* 7.2 Hz, CH₃CH) 1.23 (t, 3H, *J* 4.8 Hz, CH₃CH₂O); ¹⁹F NMR (376.5 MHz, DMSO-*d*₆) δ_F (ppm) -108.30-(-108.36) (m, 1F, Ar-F); ¹³C NMR (100 MHz, DMSO-*d*₆) δ_C (ppm) 172.6 (C=O), 167.3 (C=O), 165.6 (C=O), 165.4 (C=O), 163.5 (d, ¹*J* 255.0 Hz, Ar-C), 133.1 (d, ³*J* 9.0 Hz, 2 × Ar-CH), 132.8 (Aryl-CH), 130.0 (d, ⁴*J* 3.0 Hz, Ar-C), 121.3 (Ar-C), 117.1 (d, ²*J* 9.0 Hz, 2 × Ar-CH), 61.0 (OCH₂CH₃), 48.4 (CHNH), 43.6 (CH₂N), 17.5 (CH₃CH), 14.4 (CH₃CH₂O); HRMS (ESI-TOF) *m/z*; calculated for C₁₇H₁₇FN₂O₅S+H: 381.0842, found M⁺+H: 381.0845.

Ethyl (2-(5-(furan-2-ylmethylene)-2,4-dioxothiazolidin-3-yl)acetyl)alaninate (13bviii). A reaction of furfural (0.46 ml, 4.82 mmol) and **12b** (1.02 g, 4.82 mmol) in ethanol (20 ml) gave compound **13bviii** as a white solid

(0.18 g, 34%); m.p = 172-173 °C; IR (KBr cm^{-1}): 3296, 3085, 1733, 1681, 1659, 1183; ^1H NMR (400 MHz, DMSO- d_6) δ_{H} (ppm) 8.75 (d, 1H, J 6.8 Hz, NH), 8.11 (d, 1H, J 1.6 Hz, Ar-CH), 7.80 (s, 1H, Aryl-H), 7.17 (d, 1H, J 3.6 Hz, Ar-CH), 6.78 (dd, 1H, J_1 3.6 Hz, J_2 1.6 Hz, Ar-CH), 4.22 (s, 2H, CH_2N), 4.11 (quint, 1H, J 2.4 Hz, CHNH), 4.06 (q, 2H, J 4.4 Hz, OCH_2CH_3), 1.29 (d, 3H, J 7.2 Hz, CH_3CH) 1.18 (t, 3H, J 7.2 Hz, $\text{CH}_3\text{CH}_2\text{O}$); ^{13}C NMR (100 MHz, DMSO- d_6) δ_{C} (ppm) 172.6 (C=O), 168.2 (C=O), 165.5 (C=O), 165.4 (C=O), 149.6 (C), 148.4 (CH), 120.3 (Aryl-CH), 120.0 (C-H) 118.1 (C), 114.1 (CH), 61.0 (OCH_2CH_3), 48.4 (CHNH), 43.46 (CH_2N), 17.46 (CH_3CH), 14.44 ($\text{CH}_3\text{CH}_2\text{O}$); HRMS (ESI-TOF) m/z ; calculated for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_6\text{S}+\text{H}$: 353.0729, found M^++H : 353.0731.

Ethyl 2-(2-(5-benzylidene-2,4-dioxothiazolidin-3-yl)acetamido)butanoate (13ci). A reaction of benzaldehyde (0.32 ml, 3.12 mmol) and **12c** (0.90 g, 3.12 mmol) gave compound **13ci** as a white solid (0.16 g, 10%); m.p = 175-176 °C; IR (KBr cm^{-1}): 3304, 2923, 1735, 1687, 1661, 1607, 1149; ^1H NMR (400 MHz, DMSO- d_6) δ_{H} (ppm) 8.71 (d, 1H, J 7.6 Hz, NH), 7.97 (s, 1H, Aryl-H), 7.65 (d, 2H, J 7.2 Hz, 2 \times Ar-H), 7.61-7.50 (m, 3H, 3 \times Ar-H), 4.35 (s, 2H, CH_2N), 4.20 (quint, 1H, J 3.6 Hz, CHNH), 4.09 (q, 2H, J 3.6 Hz, OCH_2CH_3), 1.76-1.71 (m, 1H, CH_aCH_3) 1.68-1.62 (m, 1H, CH_bCH_3), 1.23 (t, 3H, J 7.2 Hz, $\text{CH}_3\text{CH}_2\text{O}$), 0.90 (t, 3H, J 7.2 Hz, CH_3CH_2); ^{13}C NMR (100 MHz, DMSO- d_6) δ_{C} (ppm) 172.1 (C=O), 167.5 (C=O), 165.7 (C=O), 165.1 (C=O), 133.8 (Aryl-CH), 133.3 (Ar-C), 131.2 (Ar-CH), 130.6 (2 \times Ar-CH), 129.9 (2 \times Ar-CH), 121.6 (Ar-C), 62.0 (OCH_2CH_3), 54.0 (CHNH), 43.6 (CH_2N), 24.9 (CH_2CH_3), 14.5 ($\text{CH}_3\text{CH}_2\text{O}$), 10.6 (CH_3CH_2); HRMS (ESI-TOF) m/z ; calculated for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_5\text{S}+\text{H}$: 377.1093, found M^++H : 377.1096.

Ethyl 2-(2-(5-(4-methoxybenzylidene)2,4-dioxothiazolidin-3-yl)acetamido)butanoate (13cii). A reaction of *p* anisaldehyde (0.26 ml, 2.08 mmol) and **12c** (0.60 g, 2.08 mmol) gave compound **13cii** as a white solid (0.31 g, 37%); m.p = 207-208 °C; ^1H NMR (400 MHz, DMSO- d_6) δ_{H} (ppm) 8.70 (d, 1H, J 7.6 Hz, NH), 7.93 (s, 1H, Aryl-H), 7.62 (d, 2H, J 8.8 Hz, 2 \times Ar-H), 7.13 (d, 2H, J 8.8 Hz, 2 \times Ar-H), 4.15 (s, 2H, CH_2N), 4.12 (quint, 1H, J 2.8 Hz, CHNH), 4.07 (q, 2H, J 3.6 Hz, OCH_2CH_3), 3.84 (s, 3H, OCH_3), 1.78-1.73 (m, 1H, CH_aCH_3) 1.70-1.61 (m, 1H, CH_bCH_3), 1.19 (t, 3H, J 7.2 Hz, $\text{CH}_3\text{CH}_2\text{O}$), 0.90 (t, 3H, J 7.2 Hz, CH_3CH_2); ^{13}C NMR (100 MHz, DMSO- d_6) δ_{C} (ppm) 172.0 (C=O), 167.5 (C=O), 165.8 (2 \times C=O), 161.7 (Ar-COCH₃), 133.9 (Aryl-CH), 133.8 (2 \times Ar-CH), 125.8 (Ar-C), 118.2 (Ar-C), 115.5 (2 \times Ar-CH), 61.0 (OCH_2CH_3), 56.0 (OCH_3), 54.0 (CHNH), 43.6 (CH_2N), 24.9 (CH_2CH_3), 14.5 ($\text{CH}_3\text{CH}_2\text{O}$), 10.6 (CH_3CH_2); IR (KBr cm^{-1}): 3297, 2978, 1734, 1685, 1665, 1602, 1183; HRMS (ESI-TOF) m/z ; calculated for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_6\text{S}+\text{H}$: 407.1199, found M^++H : 407.1272.

Ethyl 2-(2-(5-(4-methylbenzylidene)2,4-dioxothiazolidin-3-yl)acetamido)butanoate (13ciii). A reaction of *p* tolualdehyde (0.40 ml, 3.47 mmol) and **12c** (0.80 g, 3.47 mmol) gave compound **13ciii** as a white solid (0.11 g, 8%); m.p = 206-207 °C; IR (KBr cm^{-1}): 3284, 2987, 1749, 1685, 1667, 1606, 1149; ^1H NMR (400 MHz, DMSO- d_6) δ_{H} (ppm) 8.71 (d, 1H, J 7.6 Hz, NH), 7.93 (s, 1H, Aryl-H), 7.55 (d, 2H, J 8.0 Hz, 2 \times Ar-H), 7.13 (d, 2H, J 8.0 Hz, 2 \times Ar-H), 4.16 (s, 2H, CH_2N), 4.14 (quint, 1H, J 3.6 Hz, CHNH), 4.08 (q, 2H, J 3.6 Hz, OCH_2CH_3), 2.37 (s, 3H, Ar-CH₃), 1.77-1.71 (m, 1H, CH_aCH_3) 1.68-1.62 (m, 1H, CH_bCH_3), 1.19 (t, 3H, J 7.2 Hz, $\text{CH}_3\text{CH}_2\text{O}$), 0.90 (t, 3H, J 7.2 Hz, CH_3CH_2); ^{13}C NMR (100 MHz, DMSO- d_6) δ_{C} (ppm) 172.0 (C=O), 167.5 (C=O), 165.8 (2 \times C=O), 141.6 (Ar-CCH₃), 133.9 (Aryl-CH), 133.7 (2 \times Ar-CH), 130.6 (Ar-C), 130.5 (2 \times Ar-CH), 120.3 (Ar-C), 61.0 (OCH_2CH_3), 54.0 (CHNH), 43.6 (CH_2N), 24.9 (CH_2CH_3), 21.4 (Ar-CH₃), 14.5 ($\text{CH}_3\text{CH}_2\text{O}$), 10.6 (CH_3CH_2); HRMS (ESI-TOF) m/z ; calculated for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_5\text{S}+\text{H}$: 391.1249, found M^++H : 391.1251.

Ethyl 2-(2-(5-(4-hydroxybenzylidene)2,4-dioxothiazolidin-3-yl)acetamido)butanoate (13civ). A reaction of 4-hydroxybenzaldehyde (0.42 g, 2.77 mmol) and **12c** (0.80 g, 2.77 mmol) gave compound **13civ** as a white solid (0.06 g, 6%); m.p = 185-186 °C; IR (KBr cm^{-1}): 3287, 3087, 1734, 1687, 1660, 1608, 1149; ^1H NMR (400 MHz, DMSO- d_6) δ_{H} (ppm) 10.43 (s, 1H, OH), 8.70 (d, 1H, J 7.6 Hz, NH), 7.86 (s, 1H, Aryl-H), 7.51 (d, 2H, J 8.8 Hz, 2 \times Ar-H), 6.93 (d, 2H, J = 8.8 Hz, 2 \times Ar-H), 4.33 (s, 2H, CH_2N), 4.17 (quint, 1H, J 2.8 Hz, CHNH), 4.09 (q, 2H, J 7.2 Hz, OCH_2CH_3), 1.77-1.71 (m, 1H, CH_aCH_3), 1.67-1.60 (m, 1H, CH_bCH_3), 1.19 (t, 3H, J 7.2 Hz, $\text{CH}_3\text{CH}_2\text{O}$), 0.90 (t, 3H, J 7.2 Hz, CH_3CH_2); ^{13}C NMR (100 MHz, DMSO- d_6) δ_{C} (ppm) 172.0 (C=O), 167.7 (C=O), 165.9 (C=O), 165.8

(C=O), 160.7 (Ar-COH), 134.3 (Aryl-CH), 133.1 (2 × Ar-CH), 124.3 (Ar-C), 116.9 (2 × Ar-CH), 116.8 (Ar-C), 61.0 (OCH₂CH₃), 54.0 (CHNH), 43.5 (CH₂N), 24.9 (CH₂CH₃), 14.5 (CH₃CH₂O), 10.6 (CH₃CH₂); HRMS (ESI-TOF) *m/z*; calculated for C₁₈H₂₀N₂O₆S+H: 392.1042, found M⁺+H: 393.1045.

Ethyl 2-(2-(5-(furan-2-ylmethylene)-2,4-dioxothiazolidin-3-yl)acetamido)butanoate (13cv) A reaction of furfural (0.20 ml, 2.43 mmol) and **12c** (0.70 g, 2.43 mmol) gave compound **13cv** as a white solid (0.11 g, 11%); m.p = 184-185 °C; IR (KBr cm⁻¹): 3292, 2971, 1735, 1686, 1660, 1615, 1144; ¹H NMR (400 MHz, DMSO-*d*₆) δ_H (ppm) 8.69 (d, 1H, *J* 8.4 Hz, NH), 8.10 (d, 1H, *J* 1.2 Hz, CH), 7.80 (s, 1H, Aryl-H), 7.17 (d, 1H, *J* 3.6 Hz, CH), 6.77 (dd, 1H, *J* 3.6 Hz, and *J* 1.6 Hz, CH), 4.14 (s, 2H, CH₂N), 4.11 (quint, 1H, *J* 3.6 Hz, CHNH), 4.07 (q, 2H, *J* 3.6 Hz, OCH₂CH₃), 1.77-1.72 (m, 1H, CH_aCH₃), 1.71-1.60 (m, 1H, CH_bCH₃), 1.18 (t, 3H, *J* 7.0 Hz, CH₃CH₂O), 0.90 (t, 3H, *J* 7.6 Hz, CH₃CH₂); ¹³C NMR (100 MHz, DMSO-*d*₆) δ_C (ppm) 172.0 (C=O), 168.2 (C=O), 165.8 (C=O), 165.5 (C=O), 149.6 (C), 148.4 (CH), 120.2 (Aryl-CH), 119.9 (CH), 118.9 (C), 114.1 (CH), 61.0 (OCH₂CH₃), 54.0 (OCH₃), 43.5 (CH₂N), 24.9 (CH₂CH₃), 14.5 (CH₃CH₂O), 10.6 (CH₃CH₂); HRMS (ESI-TOF) *m/z*; calculated for C₁₆H₁₈N₂O₆S+H: 367.0886, found M⁺+H: 367.0889.

Ethyl (2-(5-benzylidene-2,4-dioxothiazolidin-3-yl)acetyl)valinate (13di). A reaction of benzaldehyde (0.22 ml, 2.08 mmol) and **12d** (0.70 g, 2.08 mmol) gave compound **13di** as a yellow solid (0.26 g, 24%); m.p = 167-168 °C; IR (KBr cm⁻¹): 3294, 2963, 1734, 1688, 1663, 1608, 1147; ¹H NMR (400 MHz, DMSO-*d*₆) δ_H (ppm) 8.67 (d, 1H, *J* 8.4 Hz, NH), 7.97 (s, 1H, Aryl-H), 7.65 (d, 2H, *J* 7.2 Hz, 2 × Ar-H), 7.58-7.52 (m, 3H, 3 × Ar-H), 4.39 (s, 2H, CH₂N), 4.18 (quint, 1H, *J* 6.0 Hz, CHNH), 4.12 (q, 2H, *J* 2.4 Hz, OCH₂CH₃), 2.06 (septet, 1H, *J* 4.0 Hz, CHCH₃), 1.20 (t, 3H, *J* 4.8 Hz, CH₃CH₂O), 0.90 (t, 6H, *J* 6.4 Hz, (CH₃)₂CH); ¹³C NMR (100 MHz, DMSO-*d*₆) δ_C (ppm) 171.6 (C=O), 167.5 (C=O), 165.9 (C=O), 165.7 (C=O), 133.9 (Aryl-CH), 130.6 (Ar-C), 129.9 (2 × Ar-CH), 128.6, (Ar-C), 128.5 (2 × Ar-CH), 121.5 (Ar-C), 61.4 (OCH₂CH₃), 54.1 (CHNH), 43.6 (CH₂N), 30.6 (CHCH₃), 19.3 (CH₃CH), 18.5 (CH₃CH), 14.3 (CH₃CH₂O); HRMS (ESI-TOF) *m/z*; calculated for C₁₉H₂₂N₂O₅S+H: 391.1249, found M⁺+H: 391.1251.

Ethyl (2-(5-(4-methoxybenzylidene)-2,4-dioxothiazolidin-3-yl)acetyl)valinate (13dii). A reaction of *p* anisaldehyde (0.40 ml, 3.30 mmol) and **12d** (0.70 g, 3.30 mmol) gave compound **13dii** as a yellow solid (0.51 g, 38%); m.p = 182-183 °C; IR (KBr cm⁻¹): 3240, 2939, 1740, 1735, 1663, 1601, 1172; ¹H NMR (400 MHz, DMSO-*d*₆) δ_H (ppm) 8.66 (d, 1H, *J* 8.0 Hz, NH), 7.92 (s, 1H, Aryl-H), 7.61 (d, 2H, *J* 8.0 Hz, 2 × Ar-H), 7.12 (d, 2H, *J* 8.0 Hz, 2 × Ar-H), 4.18 (s, 2H, CH₂N), 4.15 (quint, 1H, *J* 3.6 Hz, CHNH), 4.10 (q, 2H, *J* 3.6 Hz, OCH₂CH₃), 3.89 (s, 3H, OCH₃), 2.05 (septet, 1H, *J* 6.8 Hz, CH(CH₃)₂), 1.20 (t, 3H, *J* 7.2 Hz, CH₃CH₂O), 0.90 (t, 6H, *J* 6.4 Hz, (CH₃)₂CH); ¹³C NMR (100 MHz, DMSO-*d*₆) δ_C (ppm) 171.6 (C=O), 167.5 (C=O), 165.9 (C=O), 165.8 (C=O), 161.7 (Ar-COCH₃), 133.8 (Aryl-CH), 132.8 (2 × Ar-CH), 125.8, (Ar-C), 118.2 (Ar-C), 115.5 (2 × Ar-CH), 61.0 (OCH₂CH₃), 58.0 (CHNH), 56.0 (OCH₃), 43.5 (CH₂N), 30.6 (CH(CH₃)₂), 19.3 (CH₃CH), 18.5 (CH₃CH), 14.4 (CH₃CH₂O); HRMS (ESI-TOF) *m/z*; calculated for C₂₀H₂₄N₂O₆S+H: 421.1355, found M⁺+H: 421.1352.

Ethyl (2-(5-(4-hydroxy-3-methoxybenzylidene)-2,4-dioxothiazolidin-3-yl)acetyl)valinate (13diii). A reaction of vanillin (0.37 g, 2.40 mmol) and **12d** (0.70 g, 2.40 mmol) gave compound **13diii** as a yellow solid (0.12 g, 12%); m.p = 187-188 °C; IR (KBr cm⁻¹): 3243, 2966, 1733, 1672, 1653, 1601, 1170; ¹H NMR (400 MHz, DMSO-*d*₆) δ_H (ppm) 10.10 (s, 1H, OH), 8.70 (d, 1H, *J* 8.4 Hz, NH), 7.93 (s, 1H, Aryl-H), 7.26 (d, 1H, *J* 1.6 Hz, Ar-H), 7.18 (dd, 2H, *J*₁ 8.4 Hz, *J* 1.6 Hz, Ar-H), 7.01 (d, 1H, *J* 8.4 Hz, Ar-H), 4.22 (s, 2H, CH₂N), 4.20 (quint, 1H, *J* 3.6 Hz, CHNH), 4.15 (q, 2H, *J* 3.6 Hz, OCH₂CH₃), 3.89 (s, 1H, OCH₃), 2.12 (septet, 1H, *J* 6.8 Hz, CH(CH₃)₂), 1.20 (t, 3H, *J* 6.0 Hz, CH₃CH₂O), 0.95 (t, 6H, *J* 6.4 Hz, (CH₃)₂CH); ¹³C NMR (100 MHz, DMSO-*d*₆) δ_C (ppm) 171.6 (C=O), 167.6 (C=O), 165.9 (C=O), 165.8 (C=O), 150.3 (Ar-COCH₃), 148.5 (Ar-COH), 134.6 (Aryl-CH), 124.8 (Ar-C), 124.7 (Ar-CH), 117.1 (Ar-C), 116.7 (Ar-CH), 114.9 (Ar-CH), 61.0 (OCH₂CH₃), 58.0 (CHNH), 56.1 (OCH₃), 43.5 (CH₂N), 30.6 (CH(CH₃)₂), 19.3 (CH₃CH), 18.5 (CH₃CH), 14.35 (CH₃CH₂O); HRMS (ESI-TOF) *m/z*; calculated for C₂₀H₂₄N₂O₇S+H: 437.1304, found M⁺+H: 437.1307.

Ethyl (2-(5-(4-hydroxybenzylidene)-2,4-dioxothiazolidin-3-yl)acetyl)valinate (13div). A reaction of 4-hydroxybenzaldehyde (0.40 ml, 2.40 mmol) and **12d** (0.70 g, 2.40 mmol) gave compound **13div** as a yellow solid (0.034 g, 4%); m.p = 178-179 °C; IR (KBr cm^{-1}): 3299, 2968, 1739, 1730, 1682, 1660, 1172; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ_{H} (ppm) 10.43 (s, 1H, OH), 8.65 (d, 1H, J 8.4 Hz, NH), 7.86 (s, 1H, Aryl-H), 7.53 (d, 2H, J 8.8 Hz, 2 \times Ar-H), 6.93 (d, 2H, J 8.4 Hz, 2 \times Ar-H), 4.19 (s, 2H, CH_2N), 4.16 (quint, 1H, J 3.6 Hz, CHNH), 4.08 (q, 2H, J 3.6 Hz, OCH_2CH_3), 2.06 (septet, 1H, J 6.4 Hz, $\text{CH}(\text{CH}_3)_2$), 1.21 (t, 3H, J 7.2 Hz, $\text{CH}_3\text{CH}_2\text{O}$), 0.90 (t, 6H, J 6.4 Hz, $(\text{CH}_3)_2\text{CH}$); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ_{C} (ppm) 171.6 (C=O), 167.6 (C=O), 166.0 (C=O), 165.9 (C=O), 160.7 (Ar-COH), 134.3 (Aryl-CH), 133.1 (2 \times Ar-CH), 124.2 (Ar-C), 116.9 (2 \times Ar-CH), 61.0 (OCH_2CH_3), 58.0 (CHNH), 43.5 (CH_2N), 30.6 ($\text{CH}(\text{CH}_3)_2$), 19.3 (CH_3CH), 18.5 (CH_3CH), 14.4 ($\text{CH}_3\text{CH}_2\text{O}$); HRMS (ESI-TOF) m/z ; calculated for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_6\text{S}+\text{H}$: 407.1199, found M^++H : 407.1202.

Ethyl (2-(5-(4-Fluorobenzylidene)-2,4-dioxothiazolidin-3-yl)acetyl)valinate (13dv). A reaction of 4-fluorobenzaldehyde (0.25 ml, 2.32 mmol) and **12d** (0.70 g, 2.32 mmol) in ethanol (20 ml) gave compound **13dv** as a yellow solid (0.11 g, 11%); m.p = 216-217 °C; IR (KBr cm^{-1}): 3283, 2961, 1736, 1686, 1662, 1614, 1149; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ_{H} (ppm) 8.65 (d, 1H, J 8.4 Hz, NH), 7.99 (s, 1H, Aryl-H), 7.74 (dd, 2H, $^4J_{\text{FH}}$ 8.4 Hz, J_{HH} 5.6 Hz, 2 \times Ar-H), 7.42 (dd, 2H, $^3J_{\text{FH}}$ 17.6 Hz, J_{HH} 8.8 Hz, 2 \times Ar-H), 4.17 (s, 2H, CH_2N), 4.15 (quint, 1H, J 3.6 Hz, CHNH), 4.10 (q, 2H, J 3.6 Hz, OCH_2CH_3), 2.05 (septet, 1H, J 6.8 Hz, $\text{CH}(\text{CH}_3)_2$), 1.20 (t, 3H, J 7.2 Hz, $\text{CH}_3\text{CH}_2\text{O}$), 0.90 (t, 6H, J 6.4 Hz, CH_3CH); ^{19}F NMR (376.5 MHz, $\text{DMSO}-d_6$) δ_{F} (ppm) -108.02-(-108.36) (m, 1F, Ar-F); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ_{C} (ppm) 171.6 (C=O), 167.3 (C=O), 165.8 (C=O), 165.6 (C=O), 163.5 (d, 1J 250.0 Hz, Ar-CF), 133.2 (d, 3J 9.0 Hz, 2 \times Ar-CH), 132.8 (Aryl-CH), 130.0 (d, 4J 3.0 Hz, Ar-C), 121.2 (Ar-C), 117.1 (d, 2J 22.0 Hz, 2 \times Ar-CH), 61.0 (OCH_2CH_3), 58.1 (CHNH), 43.6 (CH_2N), 30.6 ($\text{CH}(\text{CH}_3)_2$), 19.3 (CH_3CH), 18.5 (CH_3CH), 14.5 ($\text{CH}_3\text{CH}_2\text{O}$); HRMS (ESI-TOF) m/z ; calculated for $\text{C}_{19}\text{H}_{21}\text{FN}_2\text{O}_5\text{S}+\text{H}$: 409.1155, found M^++H : 409.1158.

Ethyl (2-(5-(4-methoxybenzylidene)-2,4-dioxothiazolidin-3-yl)acetyl)norvalinate (13ei). A reaction of *p*-anisaldehyde (0.40 ml, 3.30 mmol) and **12e** (0.70 g, 3.30 mmol) gave compound **13ei** as a white solid (0.22 g, 17%); m.p = 204-205 °C; IR (KBr cm^{-1}): 3303, 2960, 1734, 1687, 1663, 1593, 1183; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ_{H} (ppm) 8.72 (d, 1H, J 7.6 Hz, NH), 7.91 (s, 1H, Aryl-H), 7.61 (d, 2H, J 8.8 Hz, 2 \times Ar-H), 7.12 (d, 2H, J 8.8 Hz, 2 \times Ar-H), 4.32 (s, 2H, CH_2N), 4.21 (quint, 1H, J 5.2 Hz, CHNH), 4.09 (q, 2H, J 3.6 Hz, OCH_2CH_3), 3.83 (s, 3H, OCH_3), 1.66-1.60 (m, 2H, CH_2CH_3), 1.34-1.28 (m, 2H, CH_2CH), 1.18 (t, 3H, J 6.8 Hz, $\text{CH}_3\text{CH}_2\text{O}$), 0.89 (t, 3H, J 7.8 Hz, CH_3CH_2); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ_{C} (ppm) 172.3 (C=O), 167.6 (C=O), 165.8 (2 \times C=O), 161.7 (Ar-COCH₃), 133.9 (Aryl-CH), 132.8 (2 \times Ar-CH), 125.8 (Ar-C), 118.2 (Ar-C), 115.5 (2 \times Ar-CH), 61.0 (OCH_2CH_3), 55.9 (OCH_3), 52.4 (CHNH), 43.5 (CH_2N), 33.5 (CH_2CH), 18.9 (CH_2CH_3), 14.5 ($\text{CH}_3\text{CH}_2\text{O}$), 13.9 (CH_3CH_2); HRMS (ESI-TOF) m/z ; calculated for $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_6\text{S}+\text{H}$: 421.1355, found M^++H : 421.1358.

Ethyl (2-(5-(4-methylbenzylidene)-2,4-dioxothiazolidin-3-yl)acetyl)norvalinate (13eii). A reaction of *p*-tolualdehyde (0.29 ml, 2.32 mmol) and **12e** (0.70 g, 2.32 mmol) gave compound **13eii** as a white solid (0.12 g, 13%); m.p = 196-197 °C; IR (KBr cm^{-1}): 3241, 2960, 1734, 1689, 1661, 1599, 1149; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ_{H} (ppm) 8.72 (d, 1H, J 7.6 Hz, NH), 7.91 (s, 1H, Aryl-H), 7.54 (d, 2H, J 8.0 Hz, 2 \times Ar-H), 7.37 (d, 2H, J 8.0 Hz, 2 \times Ar-H), 4.32 (s, 2H, CH_2N), 4.21 (quint, 1H, J 5.2 Hz, CHNH), 4.09 (q, 2H, J 3.6 Hz, OCH_2CH_3), 2.37 (s, 3H, Ar-CH₃), 1.69-1.57 (m, 2H, CH_2CH_3), 1.37-1.34 (m, 2H, CH_2CH), 1.18 (t, 3H, J 6.8 Hz, $\text{CH}_3\text{CH}_2\text{O}$), 0.89 (t, 3H, J 7.8 Hz, CH_3CH_2); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ_{C} (ppm) 172.3 (C=O), 167.6 (C=O), 165.8 (2 \times C=O), 141.7 (Ar-CCH₃), 133.9 (Aryl-CH), 130.7 (2 \times Ar-CH), 130.3 (2 \times Ar-CH), 120.3 (Ar-C), 61.0 (OCH_2CH_3), 52.4 (CHNH), 43.5 (CH_2N), 33.5 (CH_2CH), 21.6 (Ar-CH₃), 18.9 (CH_2CH_3), 14.5 ($\text{CH}_3\text{CH}_2\text{O}$), 13.9 (CH_3CH_2); HRMS (ESI-TOF) m/z ; calculated for $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_5\text{S}+\text{H}$: 405.1406, found M^++H : 405.1409.

Ethyl (2-(5-(4-hydroxybenzylidene)-2,4-dioxothiazolidin-3-yl)acetyl)norvalinate (13eiii). A reaction of 4-hydroxybenzaldehyde (0.30 g, 2.42 mmol) and **12e** (0.70 g, 2.42 mmol) gave compound **13eiii** as a yellow solid (0.24 g, 26%); m.p = 125-126 °C; IR (KBr cm^{-1}): 3308, 2989, 1730, 1668, 1631, 1601, 1153; ^1H NMR (400 MHz,

DMSO-*d*₆) δ_{H} (ppm) 10.36 (s, 1H, OH), 8.66 (d, 1H, *J* 7.6 Hz, NH), 7.86 (s, 1H, Aryl-H), 7.51 (d, 2H, *J* 8.4 Hz, 2 × Ar-H), 6.93 (d, 2H, *J* 8.8 Hz, 2 × Ar-H), 4.25 (s, 2H, CH₂N), 4.22 (quint, 1H, *J* 5.2 Hz, CHNH), 4.10 (q, 2H, *J* 3.6 Hz, OCH₂CH₃), 1.69–1.59 (m, 2H, CH₂CH₃), 1.36–1.30 (m, 2H, CH₂CH), 1.18 (t, 3H, *J* 6.8 Hz, CH₃CH₂O), 0.88 (t, 3H, *J* 7.2 Hz, CH₃CH₂); ¹³C NMR (100 MHz, DMSO-*d*₆) δ_{C} (ppm) 172.2 (C=O), 167.6 (C=O), 165.9 (C=O), 165.8 (C=O), 160.7 (Ar-COH), 134.3 (Aryl-CH), 133.1 (2 × Ar-CH), 124.3 (Ar-C), 117.0 (Ar-C), 116.9 (2 × Ar-CH), 61.0 (OCH₂CH₃), 52.4 (CHNH), 43.6 (CH₂N), 33.6 (CH₂CH), 18.9 (CH₂CH₃), 14.5 (CH₃CH₂O), 13.9 (CH₃CH₂); HRMS (ESI-TOF) *m/z*; calculated for C₁₉H₂₂N₂O₆S+H: 407.1199, found M⁺+H: 407.1202.

Ethyl (2-(5-(4-fluorobenzylidene)-2,4-dioxothiazolidin-3-yl)acetyl)norvalinate (13eiv). A reaction of 4-fluorobenzaldehyde (0.16 ml, 1.32 mmol) and **12e** (0.40 g, 1.32 mmol) gave compound **13eiv** as a yellow solid (0.11 g, 21%); m.p = 240–241 °C; IR (KBr cm^{−1}): 3285, 2964, 1735, 1686, 1657, 1609, 1147; ¹H NMR (400 MHz, DMSO-*d*₆) δ_{H} (ppm) 8.72 (d, 1H, *J* 7.6 Hz, NH), 7.99 (s, 1H, Aryl-H), 7.74 (dd, 2H, ⁴*J*_{FH} 8.8 Hz, *J*_{HH} 5.6 Hz, 2 × Ar-H), 7.42 (dd, 2H, ³*J*_{FH} 17.2 Hz, *J*_{HH} 8.4 Hz, 2 × Ar-H), 4.23 (s, 2H, CH₂N), 4.13 (quint, 1H, *J* 3.6 Hz, CHNH), 4.09 (q, 2H, *J* 5.2 Hz, OCH₂CH₃), 1.69–1.59 (m, 2H, CH₂CH₃), 1.36–1.30 (m, 2H, CH₂CH), 1.88 (t, 3H, *J* 7.2 Hz, CH₃CH₂O), 0.88 (t, 3H, *J* 7.2 Hz, CH₃CH₂); ¹⁹F NMR (376.5 MHz, DMSO-*d*₆) δ_{F} (ppm) −108.28–(−108.36) (m, 1F, Ar-F); ¹³C NMR (100 MHz, DMSO-*d*₆) δ_{C} (ppm) 172.2 (C=O), 167.3 (C=O), 165.7 (C=O), 165.6 (C=O), 163.6 (d, ¹*J* 250.0 Hz, Ar-CF), 133.1 (d, ³*J* 9.0 Hz, 2 × Ar-CH), 132.8 (Aryl-CH), 130.0 (d, ⁴*J* 3.0 Hz, Ar-C), 121.2 (Ar-C), 117.1 (d, ²*J* 22.0 Hz, 2 × Ar-CH), 61.0 (OCH₂CH₃), 52.4 (CHNH), 43.6 (CH₂N), 33.9 (CH₂CH), 18.9 (CH₂CH₃), 14.5 (CH₃CH₂O), 13.9 (CH₃CH₂); HRMS (ESI-TOF) *m/z*; calculated for C₁₉H₂₁FN₂O₅S+H: 409.1155, found M⁺+H: 409.1158.

Ethyl (2-(5-(furan-2-ylmethylene)-2,4-dioxothiazolidin-3-yl)acetyl)norvalinate (13ev). A reaction of furfural (0.20 ml, 2.42 mmol) and **12e** (0.70 g, 2.42 mmol) gave compound **13ev** as a brown solid (0.61 g, 65%); m.p = 181–182 °C; IR (KBr cm^{−1}): 3285, 2959, 1735, 1684, 1662, 1615, 1147; ¹H NMR (400 MHz, DMSO-*d*₆) δ_{H} (ppm) 8.65 (dd, 1H, *J*₁ 21.2 Hz, *J*₂ 7.6 Hz, Ar-H), 8.10 (s, 1H, NH), 7.79 (s, 1H, Aryl-H), 7.17 (d, 1H, *J* 3.6 Hz, Ar-H), 6.78 (t, 1H, *J* 1.6 Hz, Ar-H), 4.36 (s, 2H, CH₂N), 4.23 (quint, 1H, *J* 5.6 Hz, CHNH), 4.11 (q, 2H, *J* 3.6 Hz, OCH₂CH₃), 1.56–1.48 (m, 2H, CH₂CH₃), 1.36–1.32 (m, 2H, CH₂CH), 1.20 (t, 3H, *J* 6.8 Hz, CH₃CH₂O), 0.88 (t, 3H, *J* 7.2 Hz, CH₃CH₂); ¹³C NMR (100 MHz, DMSO-*d*₆) δ_{C} (ppm) 172.2 (C=O), 168.1 (C=O), 165.9 (C=O), 165.7 (C=O), 149.6 (Ar-C), 148.4 (Ar-CH), 120.2 (Aryl-CH), 119.9 (Ar-CH), 118.2 (Ar-C), 114.1 (Ar-CH), 60.9 (OCH₂CH₃), 58.1 (CHNH), 43.5 (CH₂N), 33.6 (CH₂CH), 18.9 (CH₂CH₃), 14.5 (CH₃CH₂O), 13.9 (CH₃CH₂); HRMS (ESI-TOF) *m/z*; calculated for C₁₇H₂₀N₂O₆S+H: 381.1042, found M⁺+H: 381.1045.

Acknowledgements

The authors would like to thank the National Research Foundation (NRF) of South Africa and the Sasol Inzalo Foundation for the scholarships offered to Mr NR Tshiluka and the THUTHUKA research funds for sponsoring this research.

Supplementary Material

Supplementary data (¹H NMR, ¹³C NMR, ¹⁹F NMR and IR spectra of all the products) associated with this paper can be found in the online version.

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