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

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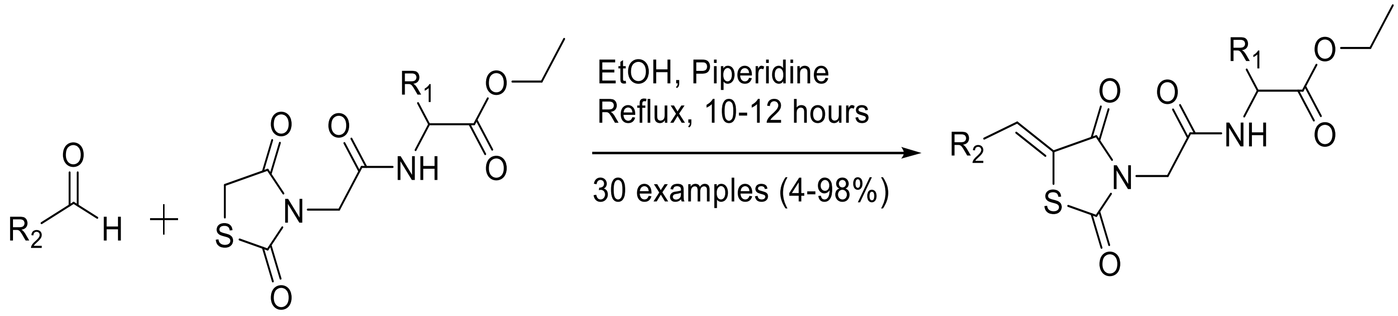
Abstract

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-arylidine-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

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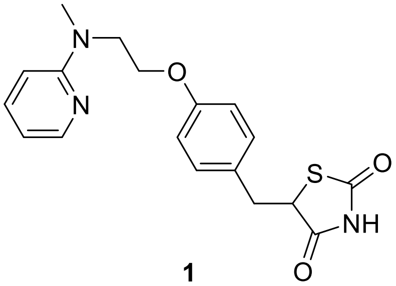
Introduction

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 Alegaon[9] 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]



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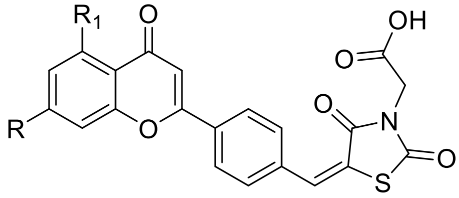
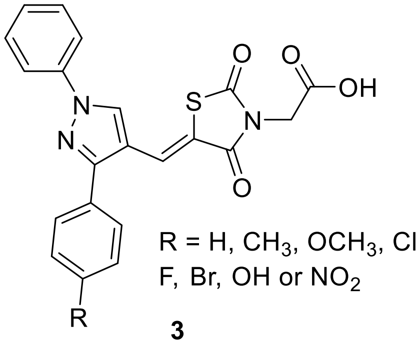


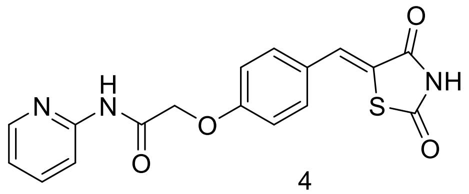
R = H,CH$_3$, NO$_2$ or CH(CH$_3$)$_2$
R1 = H or CH$_3$

2



R = H, CH$_3$, OCH$_3$, Cl
F, Br, OH or NO$_2$

3



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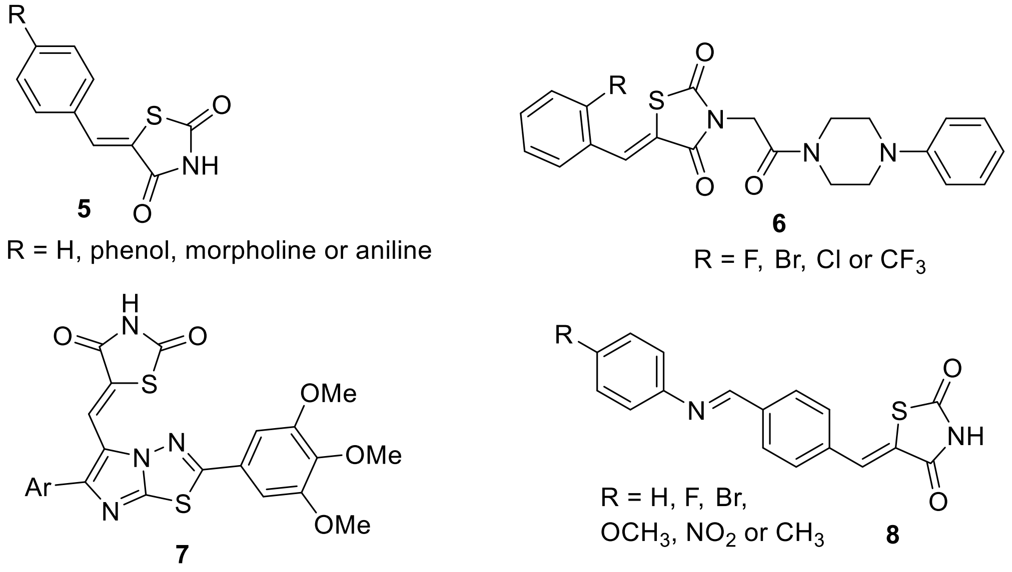


Figure 1: Compounds containing the thiazolidinedione moiety

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 e*t al.*[11]

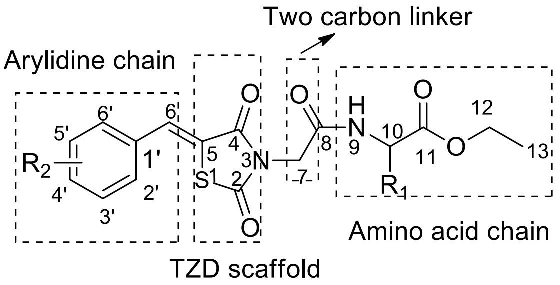
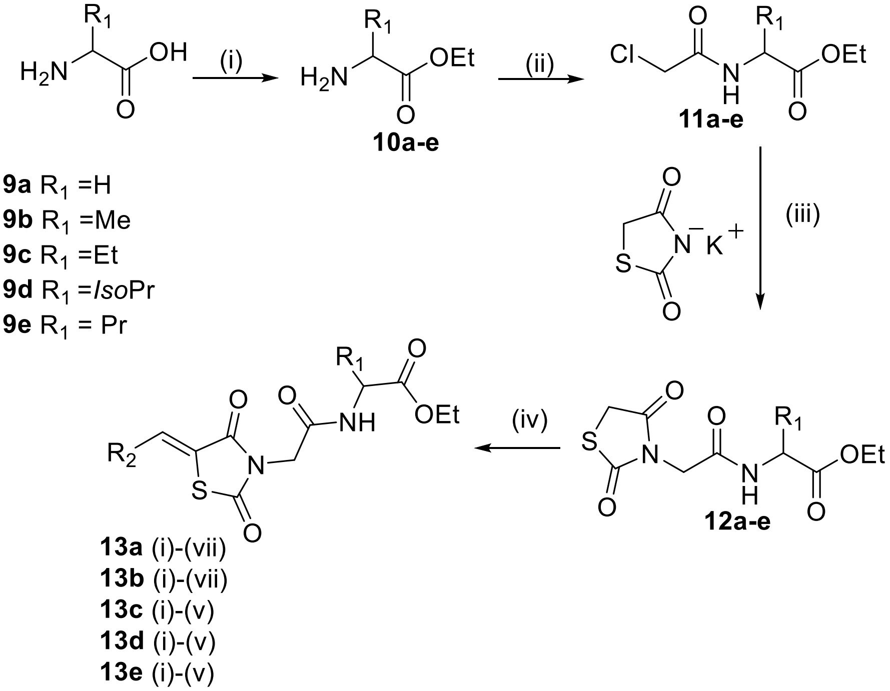


Figure 2: Schematic representation of ethyl-(2-(5-Arylidine-2,4-dioxothiazolidin-3-yl)acetyl)esters derivatives

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 thiazolidinedione[12] 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, ^{1}H 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, ^{1}H 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 ^{1}H 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
13aii		4-OMePh	54
13aiii		4-NO_2Ph	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_2Ph	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 glycinates **13a**, alaninates **13b**, butanoates **13c**, valinates **13d**, and norvalinates **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/UV_{254} plates, pre-coated with 0.25 mm silica gel 60. Detection was done under ultraviolet light at 254 nm. ^1H NMR (400 MHz), ^{13}C NMR (100 MHz) and ^{19}F NMR (376.5 MHz) spectra were recorded on a Bruker 400 MHz spectrometer using DMSO-d_6 or $CDCl_3$ 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 been 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 $MgSO_4$ 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, $CDCl_3$) δ_H (ppm) 7.17 (d, 1H, *J* 6.8, Hz, NH), 4.45 (quint, 1H , *J* 4.0 Hz, *CH*NH), 4.12 (q, 2H, *J* 4.0 Hz, OCH_2CH_3), 3.84 (s, 2H, CH_2Cl), 1.81-1.91 (1H, m, $CHCH_3$), 1.22 (t, 3H, *J* 6.0 Hz, CH_3CH_2O), 0.87 (3H, t, *J* 7.2 Hz, CH_3CH_2O); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm) 171.7 (C=O) 165.9 (C=O), 61.5 (OCH_2CH_3), 42.4 (CH_2Cl), 28.7 (*CH*NH), 25.3 (CH_2CH_3), 14.1 (CH_3CH_2O). 9.3 (CH_3CH_2).

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, $CDCl_3$) δ_H (ppm) 8.68 (d, 1H, *J* 3.6, Hz, NH), 5.75 (s, 2H, CH_2Cl) 4.22 (quint, 1H , *J* 4.8 Hz, *CH*NH), 4.13 (q, 2H, *J* 4.0 Hz, OCH_2CH_3), 3.93-3.89 (m, 2H, CH_2CH), 1.70-1.64 (1H, m, CH_2CH_3), 1.22 (t, 3H, *J* 2.0 Hz, CH_3CH_2O); 0.88 (t, 3H, *J* 7.2 Hz, CH_3CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm) 172.1 (C=O) 166.7 (C=O), 62.1 (OCH_2CH_3), 52.5 (*CH*NH), 33.4 (CH_2CH_3), 29.3 (CH_2Cl), 18.9 (CH_3CH), 14.5 (CH_3CH_2O), 13.9 (CH_3CH_2).

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; ^{1}H NMR (400 MHz, 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, CH_3CH$_2$O); ^{13}C NMR (100 MHz, 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 (CH_3CH$_2$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; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ_H (ppm) 6.62 (d, 1H, *J* 6.4 Hz, NH), 4.48 (quint, 1H, *J* 7.2 Hz, *CH*NH), 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, CH_3CH$_2$O); ^{13}C NMR (100 MHz, 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 (*CH*NH), 43.5 (CH_2N), 33.9 (CH_2S), 18.3 (CH_3CH), 14,1 (CH_3CH$_2$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 1**1c** (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, ^{1}H NMR (400 MHz, DMSO-d$_6$) δ_H (ppm) 6.55 (d, 1H, *J* 6.4 Hz, NH), 4.35 (quint, 1H, *J* 7.2 Hz, *CH*NH), 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, CH_3CH$_2$O); ^{13}C NMR (100 MHz, 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 (*CH*NH), 43.3 (CH_2N), 34.4 (CH_2S), 30.6 (CH_2CH$_3$), 19.3 (CH_3CH), 18.5 (CH_3CH$_2$), 14.5 (CH_3CH$_2$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; ^{1}H NMR (400 MHz, 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, *CH*NH), 4.12 (q, 2H, *J* 4.0 Hz, OCH_2CH$_3$), 4.09 (s, 2H, CH_2S), 2.04-2.03 (m, 2H, *CH*(CH$_3$)$_2$), 1.19 (t, 3H, *J* 6.4 Hz, CH_3CH$_2$O), 0.87 (s, 6H, $(CH_3)_2$CH); ^{13}C NMR (100 MHz, 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 (*CH*NH), 43.3 (CH_2N), 34.3 (CH_2S), 30.6 (*CH*(CH$_3$)$_2$), 19.6 (CH_3CH), 18.5 (CH_3CH), 14.6 (CH_3CH$_2$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; ^{1}H NMR (400 MHz, 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, *CH*NH), 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, CH_3CH$_2$O), 0.87 (t, 3H, *J* 6.4 Hz, CH_3CH$_2$); ^{13}C NMR (100 MHz, 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 (*CH*NH), 43.3 (CH_2N), 34.4 (CH_2S), 33.5 (CH_2CH), 18.9 (CH_2CH$_3$), 14.5 (CH_3CH$_2$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; ^{1}H 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, CH_2N), 4.09 (q, 2H, *J* 6.8 Hz, O$CH_2$$CH_3$), 3.89 (d, 2H, *J* 4.8 Hz, CH_2NH), 1.20 (t, 3H, *J* 6.8 Hz, $CH_3$$CH_2$O); ^{13}C NMR (100 MHz, DMSO-d_6), δ_C (ppm) 169.9 (C=O), 167.5 (C=O, 166.6 (C=O), 165.7 (C=O), 133.8 (Aryl-CH), 133.3 (Ar-CH), 131.2 (Ar-C), 130.6 (2 × Ar-CH), 129.9 (2 × Ar-CH), 121.6 (Ar-C), 61.0 (OCH_2CH3), 43.7 (CH_2N), 41.3 (CH_2NH), 14.49 ($CH_3$$CH_2$O); HRMS (ESI-TOF) m/z; calculated for $C_{16}H_{16}N_2O_5S$-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; ^{1}H 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, CH_2N), 4.10 (q, 2H, *J* 7.2 Hz, O$CH_2$$CH_3$), 3.90 (d, 2H, *J* 5.2 Hz, CH_2NH), 1.20 (t, 3H, *J* 7.2 Hz, $CH_3$$CH_2$O); ^{13}C NMR (100 MHz, DMSO-d_6), δ_C (ppm) 169.9 (C=O), 167.0 (C=O), 166.0 (C=O), 165.4 (C=O), 148.2 (Ar-CNO_2), 139.6 (Ar-C), 131.6 (2 × Ar-CH), 131.3 (Aryl-CH), 125.9 (Ar-C), 124.8 (2 × Ar-CH), 61.0 (O$CH_2$$CH_3$), 43.9 ($CH_2$N), 41.3 ($CH_2$NH), 14.5 ($CH_3$$CH_2$O); HRMS (ESI-TOF) m/z; calculated for $C_{16}H_{15}N_3O_7S$+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; ^{1}H 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, CH_2N), 4.09 (q, 2H, *J* 6.8 Hz,CH_2OCH_3), 3.88 (d, 2H, *J* 5.2 Hz, CH_2N), 3.82 (s, 3H, OCH_3), 1.19 (t, 3H, *J* 7.2 Hz, $CH_3$$CH_2$O); ^{13}C NMR (100 MHz, DMSO-d_6), δ_C (ppm) 169.9(C=O), 167.7 (C=O), 166.3 (C=O), 165.8 (C=O), 151.1 (Ar-COCH_3), 148.7 (Ar-COH), 134.7 (Aryl-CH), 125.0 (Ar-CH), 124.2 (Ar-C), 116.9 (Ar-CH), 116.6 (Ar-C), 114,7 (Ar-CH), 61.0 (O$CH_2$$CH_3$), 56.1 (O$CH_3$), 43.5 ($CH_2$N), 41.3 ($CH_2$NH), 14.5 ($CH_3$$CH_2$O); HRMS (ESI-TOF) m/z; calculated for $C_{17}H_{18}N_2O_7S$: 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; ^{1}H 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, OCH_2O), 4.39 (s, 2H, CH_2N), 4.15 (q, 2H, *J* 7.1 Hz, O$CH_2$$CH_3$), 3.93 (d, 2H, *J* 5.8 Hz, CH_2NH), 1.25 (t, 3H, *J* 7.1 Hz, $CH_3$$CH_2$O); ^{13}C 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 (O*CH*$_2$O), 61.0 (O*CH*$_2$CH$_3$), 43.6 (*CH*$_2$N), 41.3 (*CH*$_2$NH), 14.5 (*CH*$_3$CH$_2$O); HRMS (ESI-TOF) m/z; calculated for $C_{17}H_{16}N_2O_7S$: 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; ^{1}H 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, *CH*$_2$N), 4.09 (q, 2H, *J* 7.2 Hz, O*CH*$_2$CH$_3$), 3.89 (d, 2H, *J* 6.0 Hz*, CH*$_2$NH,), 2.37 (s, 3H, *CH*$_3$), 1.19 (t, 3H, *J* 7.2 Hz, *CH*$_3$CH$_2$O); ^{13}C 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-*C*CH$_3$), 133.9 (Aryl-CH), 130.7 (2 × ArCH), 130.6 (Ar-C), 130.5 (2 × Ar-CH), 120.3 (Ar-C), 61.0 (O*CH*$_2$CH$_3$), 43.7 (*CH*$_2$N), 41.3 (*CH*$_2$NH), 21.6 (ArCH$_3$), 14.6 (*CH*$_3$CH$_2$O); HRMS (ESI-TOF) *m/z*; calculated for $C_{17}H_{18}N_2O_5S$+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** (075 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; ^{1}H 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, $^4J_{FH}$ 8.8 Hz, J_{HH} 5.6 Hz, 2 × Ar-H), 7.48 (dd, 2H, $^3J_{FH}$ 17.6 Hz, J_{HH} 8.8 Hz, 2 × Ar-H), 4.40 (s, 2H, *CH*$_2$N), 4.21 (q, 2H, *J* 6.0 Hz, *CH*$_2$OCH$_3$), 3.95 (d, 2H, *J* 5.6 Hz, *CH*$_2$NH,), 1.27 (t, 3H, *J* 8.4 Hz, *CH*$_3$CH$_2$O); ^{19}F NMR (376.5 MHz, DMSO-d$_6$) δ$_F$ (ppm) -107.92-(-109.06) (m, 1F, Ar-F) ^{13}C 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, ^1J 250.0 Hz, Ar-*C*F), 133.2 (d, ^3J 9.0 Hz, 2 × Ar-CH), 132.8 (Aryl-CH), 130.0 (d, ^4J 3.0 Hz, Ar-C), 121.3 (Ar-C), 117.1 (d, ^2J 22.0 Hz, 2 × Ar-CH), 61.1 (O*CH*$_2$CH$_3$), 43.7 (*CH*$_2$N), 41.3 (*CH*$_2$NH), 14.5 (*CH*$_3$CH$_2$O); HRMS (ESI-TOF) *m/z*; calculated for $C_{16}H_{15}FN_2O_5S$+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; ^{1}H 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, *CH*$_2$N), 4.26 (quint, 2H, *J* 7.2 Hz, *CH*NH), 4.08 (q, 2H, *J* 6.2 Hz, O*CH*$_2$CH$_3$), 1.30 (d, 3H, *J* 7.2 Hz, *CH*$_3$CH) 1.18 (t, 3H, *J* 7.2 Hz, *CH*$_3$CH$_2$O); ^{13}C 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 (O*CH*$_2$CH$_3$), 48.4 (*CH*$_2$NH), 43.6 (*CH*$_2$N), 17.4 (*CH*$_3$CH), 14.4 (*CH*$_3$CH$_2$O); HRMS (ESI-TOF) m/z; calculated for $C_{17}H_{18}N_2O_5S$: 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; ^{1}H 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, *CH*$_2$N), 4.25 (quint, 1H, *J* 6.8 Hz, *CH*NH), 4.08 (q, 2H, *J* 7.8 Hz, O*CH*$_2$CH$_3$), 3.84 (s, 3H, O*CH*$_3$), 1.30 (d, 3H, *J* 7.0 Hz, *CH*$_3$CH) 1.19 (t, 3H, *J* 6.9 Hz, *CH*$_3$CH$_2$O); ^{13}C 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-*C*OCH$_3$), 133.8 (Aryl-CH), 132.8 (2 × Ar-CH), 125.8 (Ar-C), 118.2 (Ar-C), 115.5 (2 × Ar-CH), 61.0 (O*CH*$_2$CH$_3$), 56.0 (O*CH*$_3$), 48.4 (*CH*NH), 43.5 (*CH*$_2$N), 17.5 (*CH*$_3$CH), 14.5 (*CH*$_3$CH$_2$O); HRMS (ESI-TOF) m/z; calculated for $C_{18}H_{20}N_2O_6S$: 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; ^{1}H 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, *CH*$_2$N), 4.34 (quint, 1H, *J* 7.2 Hz, *CH*NH), 4.16 (q, 2H, *J* 6.0 Hz, OCH_2CH_3), 1.38 (d, 3H, *J* 7.3 Hz, CH_3CH), 1.29 (t, 3H, *J* 7.1 Hz, CH_3CH_2O); ^{13}C 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-CNO_2), 139.6 (Ar-C), 131.56 (2 × Ar-CH), 131.3 (Aryl-CH), 126.4 (Ar-C), 125.8 (2 × Ar-CH), 61.1 (OCH_2CH_3), 48.4 (CH_2NH), 43.8 (CH_2N), 17.5 (CH_3CH), 14.44 (CH_3CH_2O); HRMS (ESI-TOF) m/z; calculated for $C_{17}H_{17}N_3O_7S$: 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; ^{1}H 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, CH_2N), 4.24 (quint, 1H, *J* 7.2 Hz, *CH*NH), 4.07 (q, 2H, *J* 6.0 Hz, OCH_2CH_3), 3.83 (s, 3H, OCH_3), 1.30 (d, 3H, *J* 7.6 Hz, CH_3CH) 1.18 (t, 3H, *J* 7.2 Hz, CH_3CH_2O); ^{13}C 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-$COCH_3$), 148.5 (Ar-*C*OH), 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 (OCH_2CH_3), 56.1 (OCH_3), 48.4 (*CH*N), 43.5 (CH_2N), 17.5 (CH_3CH), 14.4 (CH_3CH_2O); HRMS (ESI-TOF) m/z; calculated for $C_{18}H_{20}N_2O_7S$: 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, ^{1}H 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, OCH_2O), 4.31 (s, 2H, CH_2N), 4.25 (quint, 1H, *J* 7.2, *CH*NH), 4.08 (q, 2H, *J* 6.4 Hz, OCH_2CH_3), 1.29 (d, 3H, *J* 7.2, CH_3CH) 1.18 (t, 3H, *J* 6.8 Hz, CH_3CH_2O), ^{13}C 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 (OCH_2O), 61.0 (OCH_2CH_3), 48.4 (*CH*NH), 43.5 (CH_2N), 17.4 (CH_3CH), 14.4 (CH_3CH_2O), IR (KBr cm^{-1}): 3315, 2998, 1736, 1680, 1654, 1610 (C=O stretch), 1156, HRMS (ESI-TOF) m/z; calculated for $C_{18}H_{18}N_2O_7S$: 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; ^{1}H 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, CH_2N), 4.25 (quint, 1H, *J* 7.2 Hz, *CH*NH), 4.09 (q, 2H, *J* 7.4 Hz, OCH_2CH_3), 2.51 (s, 3H, CH_3), 1.30 (d, 3H, *J* 7.2 Hz, CH_3CH) 1.14 (t, 3H, *J* 6.8 Hz, CH_3CH_2O); ^{13}C 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-CCH_3), 133.9 (Aryl-CH), 130.7 (2 × Ar-CH), 130.9 (Ar-C), 130.50 (2 × Ar-CH), 120.3 (Ar-C), 61.0 (OCH_2CH_3), 48.4 (*CH*NH), 43.6 (CH_2N), 21.6 (Ar-CH_3) 17.5 (CH_3CH), 14.4 (CH_3CH_2O); HRMS (ESI-TOF) m/z; calculated for $C_{18}H_{20}N_2O_5S$+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; ^{1}H 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, CH_2N), 4.12 (quint, 1H, *J* 3.2 Hz, *CH*NH), 4.06 (q, 2H, *J* 2.8 Hz, OCH_2CH_3), 1.42 (d, 3H, *J* 7.2 Hz, CH_3CH) 1.23 (t, 3H, *J* 4.8 Hz, CH_3CH_2O); ^{19}F NMR (376.5 MHz, DMSO-d_6) δ_F (ppm) -108.30-(-108.36) (m, 1F, Ar-F); ^{13}C 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 (OCH_2CH_3), 48.4 (*CH*NH), 43.6 (CH_2N), 17.5 (CH_3CH), 14.4 (CH_3CH_2O); HRMS (ESI-TOF) m/z; calculated for $C_{17}H_{17}FN_2O_5S$+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; ^{1}H 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$_2$*N), 4.11 (quint, 1H, *J* 2.4 Hz, *CH*NH), 4.06 (q, 2H, *J* 4.4 Hz, O*CH$_2$*CH$_3$), 1.29 (d, 3H, *J* 7.2 Hz, *CH$_3$*CH) 1.18 (t, 3H, *J* 7.2 Hz, *CH$_3$*CH$_2$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 (O*CH$_2$*CH$_3$), 48.4 (*CH*NH), 43.46 (*CH$_2$*N), 17.46 (*CH$_3$*CH), 14.44 (*CH$_3$*CH$_2$O); HRMS (ESI-TOF) m/z; calculated for $C_{15}H_{16}N_2O_6S$+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; ^{1}H 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 × Ar-H), 7.61-7.50 (m, 3H, 3 × Ar-H), 4.35 (s, 2H, *CH$_2$*N), 4.20 (quint, 1H, *J* 3.6 Hz, *CH*NH), 4.09 (q, 2H, *J* 3.6 Hz, O*CH$_2$*CH$_3$), 1.76-1.71 (m, 1H, *CH$_a$*CH$_3$) 1.68-1.62 (m, 1H, *CH$_b$*CH$_3$), 1.23 (t, 3H, *J* 7.2 Hz, *CH$_3$*CH$_2$O), 0.90 (t, 3H, *J* 7.2 Hz, *CH$_3$*CH$_2$); ^{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 × Ar-CH), 129.9 (2 × Ar-CH), 121.6 (Ar-C), 62.0 (O*CH$_2$*CH$_3$), 54.0 (*CH*NH), 43.6 (*CH$_2$*N), 24.9 (*CH$_2$*CH$_3$), 14.5 (*CH$_3$*CH$_2$O), 10.6 (*CH$_3$*CH$_2$); HRMS (ESI-TOF) m/z; calculated for $C_{18}H_{20}N_2O_5S$+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; ^{1}H 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 × Ar-H), 7.13 (d, 2H, *J* 8.8 Hz, 2 × Ar-H), 4.15 (s, 2H, *CH$_2$*N), 4.12 (quint, 1H, *J* 2.8 Hz, *CH*NH), 4.07 (q, 2H, *J* 3.6 Hz, O*CH$_2$*CH$_3$), 3.84 (s, 3H, O*CH$_3$*), 1.78-1.73 (m, 1H, *CH$_a$*CH$_3$) 1.70-1.61 (m, 1H, *CH$_b$*CH$_3$), 1.19 (t, 3H, *J* 7.2 Hz, *CH$_3$*CH$_2$O), 0.90 (t, 3H, *J* 7.2 Hz, *CH$_3$*CH$_2$); ^{13}C NMR (100 MHz, DMSO-d$_6$), δ$_C$ (ppm) 172.0 (C=O), 167.5 (C=O), 165.8 (2 × C=O), 161.7 (Ar-*C*OCH$_3$), 133.9 (Aryl-CH), 133.8 (2 × Ar-CH), 125.8 (Ar-C), 118.2 (Ar-C), 115.5 (2 × Ar-CH), 61.0 (O*CH$_2$*CH$_3$), 56,0 (O*CH$_3$*), 54.0 (*CH*NH), 43.6 (*CH$_2$*N), 24.9 (*CH$_2$*CH$_3$), 14.5 (*CH$_3$*CH$_2$O), 10.6 (*CH$_3$*CH$_2$); IR (KBr cm^{-1}): 3297, 2978, 1734, 1685, 1665, 1602, 1183; HRMS (ESI-TOF) m/z; calculated for $C_{19}H_{22}N_2O_6S$+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; ^{1}H 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 × Ar-H), 7.13 (d, 2H, *J* 8.0 Hz, 2 × Ar-H), 4.16 (s, 2H, *CH$_2$*N), 4.14 (quint, 1H, *J* 3.6 Hz, *CH*NH), 4.08 (q, 2H, *J* 3.6 Hz, O*CH$_2$*CH$_3$), 2.37 (s, 3H, Ar-*CH$_3$*), 1.77-1.71 (m, 1H, *CH$_a$*CH$_3$) 1.68-1.62 (m, 1H, *CH$_b$*CH$_3$), 1.19 (t, 3H, *J* 7.2 Hz, *CH$_3$*CH$_2$O), 0.90 (t, 3H, *J* 7.2 Hz, *CH$_3$*CH$_2$); ^{13}C NMR (100 MHz, DMSO-d$_6$), δ$_C$ (ppm) 172.0 (C=O), 167.5 (C=O), 165.8 (2 × C=O), 141.6 (Ar-*C*CH$_3$), 133.9 (Aryl-CH), 133.7 (2 × Ar-CH), 130.6 (Ar-C), 130.5 (2 × Ar-CH), 120.3 (Ar-C), 61.0 (O*CH$_2$*CH$_3$), 54.0 (*CH*NH), 43.6 (*CH$_2$*N), 24.9 (*CH$_2$*CH$_3$), 21.4 (Ar-*CH$_3$),* 14.5 (*CH$_3$*CH$_2$O), 10.6 (*CH$_3$*CH$_2$); HRMS (ESI-TOF) m/z; calculated for $C_{19}H_{22}N_2O_5S$+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-hydoxybenzaldehyde (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; ^{1}H 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 × Ar-H), 6.93 (d, 2H, *J* = 8.8 Hz, 2 × Ar-H), 4.33 (s, 2H, *CH$_2$*N), 4.17 (quint, 1H, *J* 2.8 Hz, *CH*NH), 4.09 (q, 2H, *J* 7.2

Hz, O*CH*$_2$CH$_3$), 1.77-1.71 (m, 1H, *CH$_a$*CH$_3$), 1.67-1.60 (m, 1H, *CH$_b$*CH$_3$), 1.19 (t, 3H, *J* 7.2 Hz, *CH$_3$*CH$_2$O), 0.90 (t, 3H, *J* 7.2 Hz, *CH$_3$*CH$_2$); ^{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-*C*OH), 134.3 (Aryl-CH), 133.1 (2 × Ar-CH), 124.3 (Ar-C), 116.9 (2 × Ar-CH), 116.8 (Ar-C), 61.0 (O*CH$_2$*CH$_3$), 54,0 (*C*HNH), 43.5 (*CH$_2$*N), 24.9 (*CH$_2$*CH$_3$), 14.5 (*CH$_3$*CH$_2$O), 10.6 (*CH$_3$*CH$_2$); HRMS (ESI-TOF) m/z; calculated for $C_{18}H_{20}N_2O_6S$+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 (0.11g g, 11%); m.p = 184-185 °C; IR (KBr cm^{-1}): 3292, 2971, 1735, 1686, 1660, 1615, 1144; ^{1}H 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, *CH$_2$*N), 4.11 (quint, 1H, *J* 3.6 Hz, *CH*NH), 4.07 (q, 2H, *J* 3.6 Hz, O*CH$_2$*CH$_3$), 1.77-1.72 (m, 1H, *CH$_a$*CH$_3$) 1.71-1.60 (m, 1H, *CH$_b$*CH$_3$), 1.18 (t, 3H, *J* 7.0 Hz, *CH$_3$*CH$_2$O), 0.90 (t, 3H, *J* 7.6 Hz, *CH$_3$*CH$_2$); ^{13}C 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 (O*CH$_2$*CH$_3$), 54,0 (O*CH$_3$*), 43.5 (*CH$_2$*N), 24.9 (*CH$_2$*CH3), 14.5 (*CH$_3$*CH$_2$O), 10.6 (*CH$_3$*CH$_2$); HRMS (ESI-TOF) m/z; calculated for $C_{16}H_{18}N_2O_6S$+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; ^{1}H 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, *CH$_2$*N), 4.18 (quint, 1H, *J* 6.0 Hz, *CH*NH), 4.12 (q, 2H, *J* 2.4 Hz, O*CH$_2$*CH$_3$), 2.06 (septet, 1H, *J* 4.0Hz, *CH*CH$_3$), 1.20 (t, 3H, *J* 4.8 Hz, *CH$_3$*CH$_2$O), 0.90 (t, 6H, *J* 6.4 Hz, (*CH$_3$)$_2$*CH); ^{13}C 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 (O*CH$_2$*CH$_3$), 54.1 (*CH*NH), 43.6 (*CH$_2$*N), 30.6 (*CH*CH$_3$), 19.3 (*CH$_3$*CH), 18.5 (*CH$_3$*CH), 14.3 (*CH$_3$*CH$_2$O); HRMS (ESI-TOF) m/z; calculated for $C_{19}H_{22}N_2O_5S$+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; ^{1}H 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, *CH$_2$*N), 4.15 (quint, 1H, *J* 3.6 Hz, *CH*NH), 4.10 (q, 2H, *J* 3.6 Hz, O*CH$_2$*CH$_3$), 3.89 (s, 3H, OCH$_3$) 2.05 (septet, 1H, *J* 6.8Hz, *CH*(CH$_3$)$_2$), 1.20 (t, 3H, *J* 7.2 Hz, *CH$_3$*CH$_2$O), 0.90 (t, 6H, *J* 6.4 Hz, (*CH$_3$)$_2$*CH); ^{13}C 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-*C*OCH$_3$), 133.8 (Aryl-CH), 132.8 (2 × Ar-CH), 125.8, (Ar-C), 118.2 (Ar-C), 115.5 (2 × Ar-CH), 61.0 (O*CH$_2$*CH$_3$), 58.0 (*CH*NH), 56.0 (O*CH$_3$*), 43.5 (*CH$_2$*N), 30.6 (*CH*(CH$_3$)$_2$), 19.3 (*CH$_3$*CH), 18.5 (*CH$_3$*CH), 14.4 (*CH$_3$*CH$_2$O); HRMS (ESI-TOF) m/z; calculated for $C_{20}H_{24}N_2O_6S$+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; ^{1}H 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, *CH$_2$*N), 4.20 (quint, 1H, *J* 3.6 Hz, *CH*NH), 4.15 (q, 2H, *J* 3.6 Hz, O*CH$_2$*CH$_3$), 3.89 (s, 1H, OCH$_3$), 2.12 (septet, 1H, *J* 6.8Hz, *CH*(CH$_3$)$_2$), 1.20 (t, 3H, *J* 6.0 Hz, *CH$_3$*CH$_2$O), 0.95 (t, 6H, *J* 6.4 Hz, (*CH$_3$)$_2$*CH); ^{13}C 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-*C*OCH$_3$), 148.5 (Ar-*C*OH), 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 (O*CH$_2$*CH$_3$), 58.0 (*CH*NH), 56.1 (O*CH$_3$*), 43.5 (*CH$_2$*N), 30.6 (*CH*(CH$_3$)$_2$),

19.3 (CH_3CH), 18.5 (CH_3CH), 14.35 (CH_3CH_2O); HRMS (ESI-TOF) m/z; calculated for $C_{20}H_{24}N_2O_7S$+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; ^{1}H NMR (400 MHz, 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 × Ar-H), 6.93 (d, 2H, *J* 8.4 Hz, 2 × Ar-H), 4.19 (s, 2H, CH_2N), 4.16 (quint, 1H, *J* 3.6 Hz, *CH*NH), 4.08 (q, 2H, *J* 3.6 Hz, OCH_2CH_3), 2.06 (septet, 1H, *J* 6.4 Hz, *CH*$(CH_3)_2$), 1.21 (t, 3H, *J* 7.2 Hz, CH_3CH_2O), 0.90 (t, 6H, *J* 6.4 Hz, $(CH_3)_2$CH); ^{13}C NMR (100 MHz, 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-*C*OH), 134.3 (Aryl-CH), 133.1 (2 × Ar-CH), 124.2 (Ar-C), 116.9 (2 × Ar-CH), 61.0 (OCH_2CH_3), 58.0 (*CH*NH), 43.5 (CH_2N), 30.6 (*CH*$(CH_3)_2$), 19.3 (CH_3CH), 18.5 (CH_3CH), 14.4 (CH_3CH_2O); HRMS (ESI-TOF) m/z; calculated for $C_{19}H_{22}N_2O_6S$+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; ^{1}H NMR (400 MHz, 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, $^{4}J_{FH}$ 8.4 Hz, J_{HH} 5.6 Hz, 2 × Ar-H), 7.42 (dd, 2H, $^{3}J_{FH}$ 17.6 Hz, J_{HH} 8.8 Hz, 2 × Ar-H), 4.17 (s, 2H, CH_2N), 4.15 (quint, 1H, *J* 3.6 Hz, *CH*NH), 4.10 (q, 2H, *J* 3.6 Hz, OCH_2CH_3), 2.05 (septet, 1H, *J* 6.8 Hz, *CH*$(CH_3)_2$), 1.20 (t, 3H, *J* 7.2 Hz, CH_3CH_2O), 0.90 (t, 6H, *J* 6.4 Hz, CH_3CH); ^{19}F NMR (376.5 MHz, DMSO-d_6) δ_F (ppm) -108.02-(-108.36) (m, 1F, Ar-F); ^{13}C NMR (100 MHz, 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, ^{1}J 250.0 Hz, Ar-*C*F), 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), 121.2 (Ar-C), 117.1 (d, ^{2}J 22.0 Hz, 2 × Ar-CH), 61.0 (OCH_2CH_3), 58.1 (*CH*NH), 43.6 (CH_2N), 30.6 (C*H*$(CH_3)_2$), 19.3 (CH_3CH), 18.5 (CH_3CH), 14.5 (CH_3CH_2O); HRMS (ESI-TOF) m/z; calculated for $C_{19}H_{21}FN_2O_5S$+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; ^{1}H NMR (400 MHz, 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 × Ar-H), 7.12 (d, 2H, *J* 8.8 Hz, 2 × Ar-H), 4.32 (s, 2H, CH_2N), 4.21 (quint, 1H, *J* 5.2 Hz, *CH*NH), 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, CH_3CH_2O), 0.89 (t, 3H, *J* 7.8 Hz, CH_3CH_2); ^{13}C NMR (100 MHz, DMSO-d_6), δ_C (ppm) 172.3 (C=O), 167.6 (C=O), 165.8 (2 × C=O), 161.7 (Ar-*C*OCH_3), 133.9 (Aryl-CH), 132.8 (2 × Ar-CH), 125.8 (Ar-C), 118.2 (Ar-C), 115.5 (2 × Ar-CH), 61.0 (OCH_2CH_3), 55.9 (OCH_3), 52.4 (*CH*NH), 43.5 (CH_2N), 33.5 (CH_2CH), 18.9 (CH_2CH_3), 14.5 (CH_3CH_2O), 13.9 (CH_3CH_2); HRMS (ESI-TOF) m/z; calculated for $C_{20}H_{24}N_2O_6S$+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; ^{1}H NMR (400 MHz, 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 × Ar-H), 7.37 (d, 2H, *J* 8.0 Hz, 2 × Ar-H), 4.32 (s, 2H, CH_2N), 4.21 (quint, 1H, *J* 5.2 Hz, *CH*NH), 4.09 (q, 2H, *J* 3.6 Hz, OCH_2CH_3), 2.37 (s, 3H, Ar-CH_3), 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, CH_3CH_2O), 0.89 (t, 3H, *J* 7.8 Hz, CH_3CH_2); ^{13}C NMR (100 MHz, DMSO-d_6), δ_C (ppm) 172.3 (C=O), 167.6 (C=O), 165.8 (2 × C=O), 141.7 (Ar-*C*CH_3), 133.9 (Aryl-CH), 130.7 (2 × Ar-CH), 130.3 (2 × Ar-CH), 120.3 (Ar-C), 61.0 (OCH_2CH_3), 52.4 (*CH*NH), 43.5 (CH_2N), 33.5 (CH_2CH), 21.6 (Ar-CH_3), 18.9 (CH_2CH_3), 14.5 (CH_3CH_2O), 13.9 (CH_3CH_2); HRMS (ESI-TOF) m/z; calculated for $C_{20}H_{24}N_2O_5S$+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; ^{1}H 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, CH_2N), 4.22 (quint, 1H, *J* 5.2 Hz, *CH*NH), 4.10 (q, 2H, *J* 3.6 Hz, OCH_2CH$_3$), 1.69-1.59 (m, 2H, CH_2CH$_3$), 1.36-1.30 (m, 2H, CH_2CH), 1.18 (t, 3H, *J* 6.8 Hz, CH_3CH$_2$O), 0.88 (t, 3H, *J* 7.2 Hz, CH_3CH$_2$); ^{13}C 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-*C*OH), 134.3 (Aryl-CH), 133.1 (2 × Ar-CH), 124.3 (Ar-C), 117.0 (Ar-C), 116.9 (2 × Ar-CH), 61.0 (OCH_2CH$_3$), 52.4 (*CH*NH), 43.6 (CH_2N), 33.6 (CH_2CH), 18.9 (CH_2CH$_3$), 14.5 (CH_3CH$_2$O), 13.9 (CH_3CH$_2$); HRMS (ESI-TOF) m/z; calculated for $C_{19}H_{22}N_2O_6S$+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; ^{1}H 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, $^4J_{FH}$ 8.8 Hz, J_{HH} 5.6 Hz, 2 × Ar-H), 7.42 (dd, 2H, $^3J_{FH}$ 17.2 Hz, J_{HH} 8.4 Hz, 2 × Ar-H), 4.23 (s, 2H, CH_2N), 4.13 (quint, 1H, *J* 3.6 Hz, *CH*NH), 4.09 (q, 2H, *J* 5.2 Hz, OCH_2CH$_3$), 1.69-1.59 (m, 2H, CH_2CH$_3$), 1.36-1.30 (m 2H, CH_2CH), 1.88 (t, 3H, *J* 7.2 Hz, CH_3CH$_2$O), 0.88 (t, 3H, *J* 7.2 Hz, CH_3CH$_2$); ^{19}F NMR (376.5 MHz, DMSO-d$_6$) δ_F (ppm) -108.28-(-108.36) (m, 1F, Ar-F); ^{13}C 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, ^1J 250.0 Hz, Ar-*C*F), 133.1 (d, ^3J 9.0 Hz, 2 × 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 × Ar-CH), 61.0 (OCH_2CH$_3$), 52.4 (*CH*NH), 43.6 (CH_2N), 33.9 (CH_2CH), 18.9 (CH_2CH$_3$), 14.5 (CH_3CH$_2$O), 13.9 (CH_3CH$_2$); HRMS (ESI-TOF) m/z; calculated for $C_{19}H_{21}FN_2O_5S$+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; ^{1}H 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, CH_2N), 4.23 (quint, 1H, *J* 5.6 Hz, *CH*NH), 4.11 (q, 2H, *J* 3.6 Hz, OCH_2CH$_3$), 1.56-1.48 (m, 2H, CH_2CH$_3$), 1.36-1.32 (m, 2H, CH_2CH), 1.20 (t, 3H, *J* 6.8 Hz, CH_3CH$_2$O), 0.88 (t, 3H, *J* 7.2 Hz, CH_3CH$_2$); ^{13}C 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 (OCH_2CH$_3$), 58.1 (*CH*NH), 43.5 (CH_2N), 33.6 (CH_2CH), 18.9 (CH_2CH$_3$), 14.5 (CH_3CH$_2$O), 13.9 (CH_3CH$_2$); HRMS (ESI-TOF) m/z; calculated for $C_{17}H_{20}N_2O_6S$+H: 381,1042, found M$^+$+H: 381.1045.

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Supplementary Material

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

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