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5-Alkylated thiazolidinones as follicle-stimulating hormone (FSH) receptor agonists

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Abstract—We prepared analogs of potent thiazolidinone-based follicle-stimulating hormone (FSH) agonists **1**, that is, **3** that contained an additional 5-alkyl substituent. This extra substituent was added to reduce synthetic problems that arose during preparation of analogs of **1**. These compounds (**3**) were evaluated in a Chinese hamster ovary (CHO) cell line that expressed recombinant human FSH receptor (FSHR) and a luciferase reporter gene regulated by a cAMP response element (CRE). Selected compounds were also tested on a CHO-cell line that over expressed the FSHR for the ability to induce cAMP production. When the 5-alkyl substituent was a methyl group as in analog **16a**, similar FSH activity (i.e., EC_{50} = 51 nM, 100% efficacy relative to hFSH) to the analogous 5-hydrogen series compound (e.g., **2**) was observed; thus, proving that a small 5-alkyl substituent was well tolerated. New derivatives of **3**, in which the potentially hydrolytically labile secondary amide function of **1** (–CONH–) was modified to other moieties (e.g., $–CH_2NH–$, $–CH_2S–$, and $–CH_2O-CONH–$), were also prepared and evaluated. These congeners (namely **21**, **22**, and **24**) also displayed good potency in the CRE-luciferase assay.

1. Introduction

Follicle-stimulating hormone (FSH) is a 38 kDa glycoprotein that is synthesized and released, as with luteinizing hormone (LH), from the anterior pituitary gland under the control of gonadotropin-releasing hormone (GnRH). These hormones bind to their respective membrane receptors (FSHR, LHR), which are G protein-coupled receptors that stimulate adenylyl cyclase resulting in the activation of a cAMP signaling cascade. FSH and LH act directly on the ovary to promote the development of selected follicles by stimulating granulosa and theca cell proliferation and differentiation, leading to ovulation. Recombinant human FSH (hFSH) has been used clinically for fertility treatment in women; however, its expense and mode of administration (injection) have spurred the need to find small molecule agonists that could be taken orally. Conversely, orally active small molecule antagonists of FSH action could lead to a new class of non-steroidal contraceptive agents.[1]

Several series of small molecule modulators of the FSHR have been reported. (Bis)sulfonic acids[2] and monosulfonic acids[3] were shown to be functional antagonists that displaced FSH in receptor binding assays. However, these compounds suffered from poor cell permeability and absorption properties, precluding their ability to be used successfully in vivo.

Recently, a more 'drug-like' class of 6-amino-4-phenyltetrahydroquinoline derivatives[4] displayed excellent antagonist activity in several hFSH-based cellular assays, but unlike the sulfonic acid class, they were not able to compete with FSH in a receptor binding assay. The authors[4] offered a possible explanation for this profile in that these antagonists interacted with the seven transmembrane region of the G protein-coupled FSHR and, thereby, induced a conformational change that disrupted normal activation.

Keywords: Follicle-stimulating hormone; FSH; FSH receptor agonist; Thiazolidinone.
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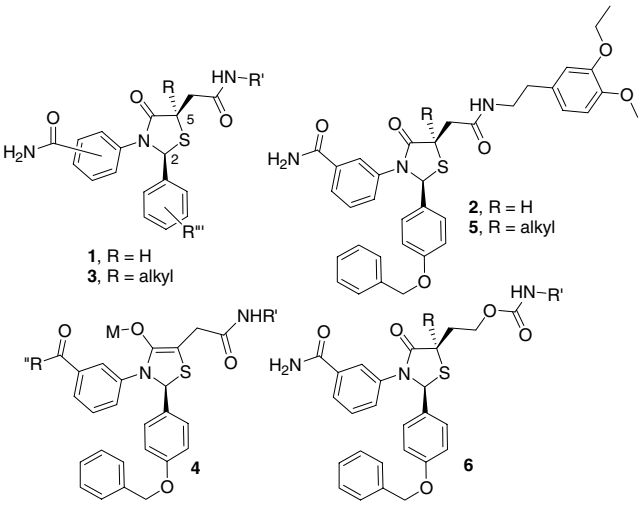
Several different series of small molecule FSHR agonists have also been reported recently through screening of large encoded combinatorial libraries. Gao[5] described an approach that led to the identification of several potential sub-series of biaryl urea-containing compounds. A subsequent report[6] described the optimization of one of the sublibraries of biaryl diketopiperazines. These compounds showed high potency in a human FSHR (hFSHR) luciferase reporter assay and, in addition, stimulated cAMP accumulation in hFSHR-transfected Chinese hamster ovary (CHO) cells. These reports did not disclose any binding data for the compounds.

Thiazolidinone-based compounds **1** were also identified as hFSHR agonists via screening of encoded combinatorial libraries.[7] One representative, 3-((2*S**, 5*R**)-2-(4-benzyloxy-phenyl)-5-{[2-(3-ethoxy-4-methoxy-phenyl)-ethylcarbamoyl]-methyl}-4-oxo-thiazolidin-3-yl)-benzamide **2**, was recently profiled.[8] It was a potent activator of human and rat FSHRs based on luciferase reporter gene screens and also caused hFSH-dependent cAMP accumulation, as well as estradiol secretion in rat granulosa cells. However, like the 6-amino-4-tetrahydroquinoline antagonists,[4] it too failed to compete with FSH in a standard radioligand receptor binding assay leading to the speculation that this compound and analogs were allosteric activators.[9] A γ-lactam analog of thiazolidinone congener **2** that possessed similar FSH agonist activity was recently described.[10]

The thiazolidinone series, however, suffered from synthetic liabilities since the undesired trans isomer of **1** predominated over the desired cis isomer regardless of the synthetic method attempted. In addition, cis/trans isomer separation by chromatography or crystallization leading to **1** was difficult, except on small scale by HPLC, and this was sometimes further complicated by epimerization at the 5-position of purified cis compounds.

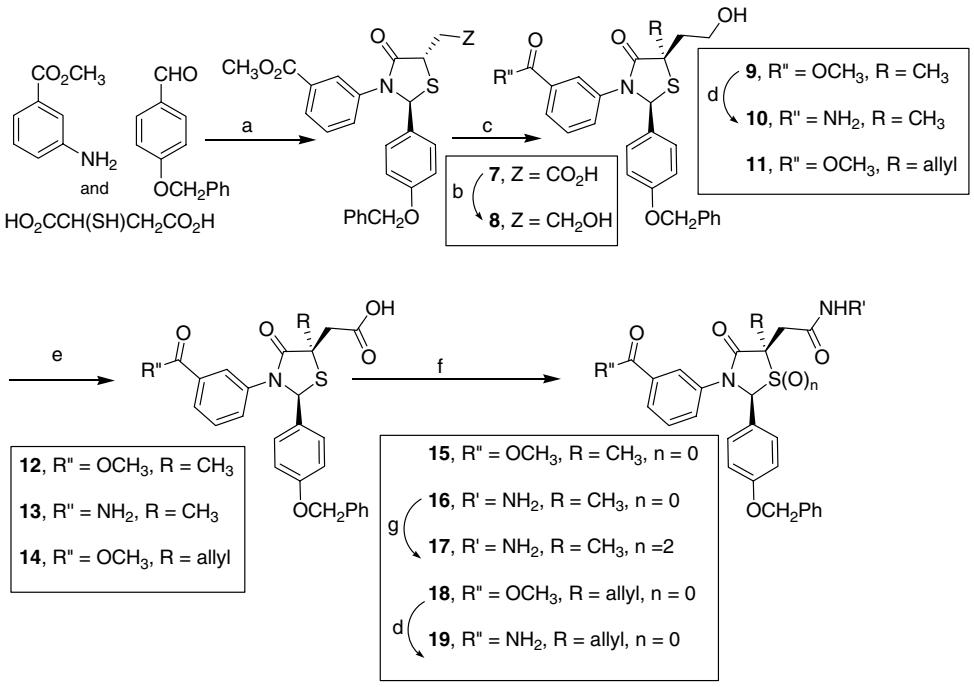
With this in mind, we sought the preparation of analogs of **1**, that is, **3** with an additional 5-alkyl substituent that would lock the two different pharmacophore side chains (at positions 2 and 5) into the syn orientation and impede epimerization at the 5-position. The desired syn configuration could be achieved via alkylation of the enolate of intermediate **4**. The 2-benzyloxyphenyl substituent of **4** should sterically drive alkylation predominantly to the opposite face of the thiazolidinone ring forcing a syn relationship between the pharmacophore units. Furthermore, straightforward synthetic manipulation of the side chains would produce the desired target compounds. Herein, we describe the preparation and FSH agonist activity of several 5-alkyl analogs of **2** (e.g., **5**).[11] In addition, new derivatives of **5** in which the secondary amide function (–CONH–) was modified to other moieties (e.g., $–CH_2NH–$, $–CH_2S–$), and a new sub-series of carbamate analogs **6** were prepared and evaluated.



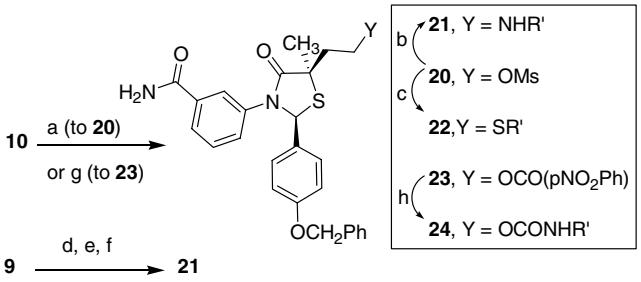
2. Chemical syntheses

As outlined in Scheme 1, condensation of methyl-3-aminobenzoate, 4-benzyloxybenzaldehyde, and mercaptosuccinic acid led to the desired 2,3,5-trisubstituted thiazolidinone **7** in 95% yield that was predominantly the trans isomer (>9:1). All attempts to alkylate **7** failed, thus, the 5-acetic acid group of **7** was converted to the benzotriazole ester using the BOP reagent and this ester was reduced with sodium borohydride to the 5-ethanol derivative **8**. Compound **8** was treated with slightly more than 2 equiv of lithium hexamethyldisilazide and lithium chloride at low temperature, and the resultant enolate was further reacted with methyl iodide to form **9** in 39% yield or allyl bromide to form **11** in 37% yield. An NOE correlation experiment confirmed a coupling through space between the 5-methyl group on thiazolidinone central ring and the 2-proton that was attached to this same ring, confirming these groups were cis to one another. A large amount of starting material **8** was also recovered from these reactions. Primary amide **10** was prepared in 66% yield upon reaction of ester **9** with ammonium hydroxide. Primary alcohols **9**–**11** were oxidized to the corresponding carboxylic acids **12**–**14** using Jones reagent (40–70% yields). These acids in turn were converted to amide target compounds **15**, **16** and **18**, respectively, using standard amidation methods (HATU, DIEA, 60–95% yields). The ester **18** was transformed in 84% yield to primary amide **19** with ammonium hydroxide. The sulfone **17** could be prepared upon reaction of **16** with *m*-CPBA (83% yield).

Referring to Scheme 2, primary alcohol **10** was converted to the mesylate **20** (56% yield) and then reacted with a primary amine to provide secondary amine target compounds **21** in 63% yield. Alternatively, amines **21** could be prepared via a three-step procedure involving oxidation of alcohol **9** with PCC to the corresponding aldehyde (62% yield), reductive amination of this aldehyde



Scheme 1. Reagents and conditions: (a) CH_3CN, molecular sieves 4 Å, 80 °C; (b) BOP, DIEA, THF for 6 h then reduced with 1.15 equiv $NaBH_4$; (c) LiCl, $LiNTMS_2$, RX, −78 °C to −40 °C; (d) NH_4OH, CH_3OH; (e) Jones oxidation, 0 °C; (f) $R'NH_2$, HATU, DIEA, DMF; (g) *m*-CPBA, NMP, 60 °C.



Scheme 2. Reagents and conditions: (a) MsCl, pyridine, 0 °C; (b) $R'NH_2$, benzene, reflux; (c) R′SH, NaH, DMF, 55 °C; (d) pyridinium chlorochromate, 0 °C; (e) $R'NH_2$, $NaBH(OAc)_3$, HOAc, CH_2Cl_2, rt; (f) NH_4OH, CH_3OH; (g) 4-nitrophenyl chloroformate, pyridine, CH_2Cl_2, 0 °C; (h) $R'NH_2$, CH_2Cl_2, 0 °C.

with the requisite primary amine, and then final conversion of the methyl ester group to the carboxamide (26% yield from the aldehyde). Thioether analogs **22** were prepared from mesylate **20** via displacement of the mesyl moiety with the appropriate thiol reagent (19–62% yields). The carbamate analogs **24** were obtained by reacting the *p*-nitrophenyl carbonate **23** with various primary amines (~80% yields). The carbonate **23** was derived from alcohol **10** via reaction with 4-nitrophenyl chloroformate (83% yield).

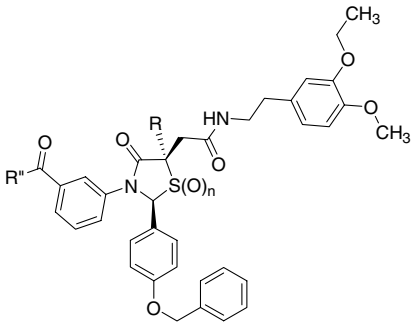
3. Results and discussion

The compounds in Tables 1 and 2 were tested in the agonist mode in a CHO cell line that expressed recombinant hFSHR and a luciferase reporter gene regulated by a cAMP response element (CRE).[9,12] None of the compounds were active when the luciferase assay was run in antagonist mode (data not shown). Selected compounds were also tested for the ability to induce cAMP production in a receptor-dependent manner using a CHO cell line that overexpressed the FSHR gene.[2,13] These selected compounds were tested subsequently in CHO cells that did not express the FSHR by measuring cAMP production. The compounds were inactive suggesting the lack of a FSHR-independent, nonspecific effect (data not shown). A few compounds were further evaluated in additional functional activity assays (Table 3), including compound-induced estradiol production in rat primary ovarian granulosa cells and progesterone secretion in a clonal mouse adrenal Y1 cell line that was engineered to stably express the hFSHR gene.[2,3] In all assays agonist efficacies are reported relative to hFSH. Like the thiazolidinone analogs (**1** and **2**) on which these compounds are based,[7–9] none of the compounds here were able to displace [^{125}I]hFSH from hFSHR in a standard receptor binding assay.

Referring to Table 1, we were gratified to find that the analog of direct comparison to **2**, namely **16a**, which differs only in the replacement of the 5-hydrogen of **2** with a 5-methyl moiety, was equally efficacious in luciferase reporter gene and cAMP assays, and nearly as potent (EC_{50} of 51 vs 13 nM). Similarly, compound **19** with a larger allyl moiety in the 5-position also displayed full agonist efficacy and was only 2-fold less potent than **16a**. Thus, small substituents in the 5-position of **1** leading to **3** were tolerated.

The primary amide moieties of **16a** or **19** ($R'' = NH_2$) were not essential for the molecule's FSH agonist activ-

Table 1.



Compound	R	R″	*n*	EC_{50} (nM) (% efficacy compared to FSH)	
				hFSHR-dependent CRE-LUC	hFSHR cAMP production
2	H	NH_2	0	14 ± 3 (*n* = 5, 100%)	167 ± 117 (*n* = 3, 76%)
15	CH_3	OCH_3	0	170 (*n* = 1, 73%)	800 (*n* = 1, 50%)
16a	CH_3	NH_2	0	51 ± 42 (*n* = 4, 100%)	100 (*n* = 1, 91%)
17	CH_3	NH_2	2	20 (*n* = 1, 73%)	900 (*n* = 1, 100%)
18	$CH_2CH{=}CH_2$	OCH_3	0	1750 (*n* = 1, 93%)	NT
19	$CH_2CH{=}CH_2$	NH_2	0	106 (*n* = 1, 100%)	NT

Data represent means ± SEM for replicate experiments (*n*) as indicated in parentheses.
NT, not tested.

ity. The corresponding methyl ester-containing compounds (R″ = OCH_3) **15** and **18** were also effective agonists in the luciferase reporter gene assay, although there was a 3- to10-fold drop in potency relative to the amide congeners. The thiazolidinone ring sulfur of **16a** could be oxidized to the sulfone moiety to afford **17**. Although this compound retained agonist efficacy and potency, it was highly unstable and rapidly degraded (over 24 h period at 37 °C) to a multitude of ring-opened products under a variety of mild conditions,[14] including simulated fluids SGF (simulated gastric fluid), SIF (simulated intestinal fluid), and SIBLM (simulated bile/lecithin mixture) as well as rat plasma.[15] Under identical conditions, compound **16a** was completely stable for the length of the test period (24 h).

Previous investigators found that substituted-phenethylamine amides of the 5-acetic acid moiety of **1** provided the best hFSH potency. The optimum appendage found among these substituted phenethylamine was the 3-ethoxy-4-methoxy-phenethylamine moiety that compound **2** contains.[7,9] We decided to extend this SAR (Table 2) and looked at a few substituted benzylamine adducts (**16b**–**16d**). However, since amides are often the site of hydrolytic and/or metabolic instability, we also wanted to replace the secondary amide group of **3** with other moieties, namely secondary amines (**21a** and **21b**), thioethers (**22a** and **22b**), and carbamates (**24a**–**24g**).

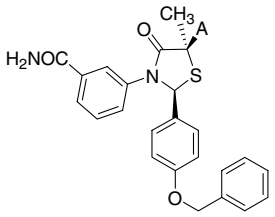
What is apparent immediately upon perusal of Table 2 is that an amide side chain emanating from the thiazolidinone 5-position was essential for FSH activity. The synthetic precursors to **16**, ethyl alcohol **10**, and acetic acid **11** were devoid of activity in the luciferase assay. In agreement with the previous investigations into the SAR of **1** that found substituted phenethylamines to be optimum for activity, substituted benzylamine adducts **16b**–**16d** were less potent by an order of magnitude over the phenethylamine congeners such as **2** or **16a**.

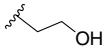
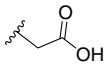
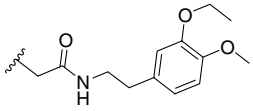
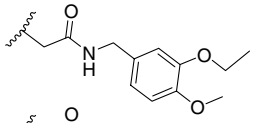
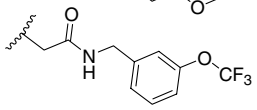
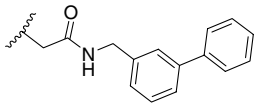
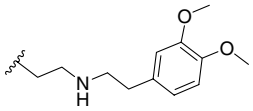
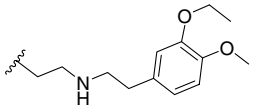
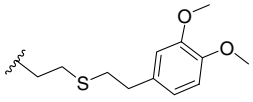
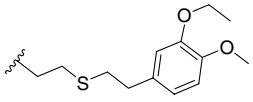
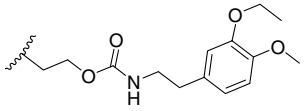
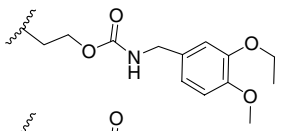
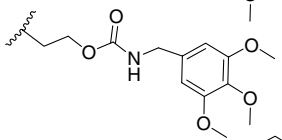
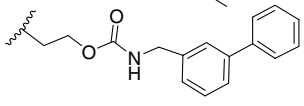
Conversion of the secondary amide of **16a** to a secondary amine led to analogs **21a** and **21b**. These compounds were also full agonists but approximately 3- to 7-fold weaker in both functional assays. The thio ethers **22a** and **22b** retained potency and efficacy relative to **16b** in the luciferase assay but **22a** was less active and efficacious in the cAMP assay (**22b** not tested).

We also took advantage of intermediate **10** to prepare a new sub-series of carbamate-containing compounds **24a**–**24f**. These carbamates differed structurally from the amide congeners in that they were longer in length by the addition of a $–CH_2O–$ linkage. Compound **24a** with the same 3-ethoxy-4-methoxy-phenethylamine appendage as **16a** was slightly less potent than **16a** in the luciferase assay. To assess whether a shorter chain length would result in greater activity, we prepared the corresponding benzylamine analog **24b**. In fact, luciferase potency did increase with the shorter chain length to an EC_{50} value (30 nM), on par with **16a**. This prompted the preparation of a library of approximately 50 carbamate analogs, the most potent of which are **24c**–**24g**. These compounds generally showed good potency and were full or nearly full agonists in the luciferase assay. However, this sub-series showed much weaker potency (EC_{50}s in low micromolar range) and/or partial agonism in the cAMP assay as compared to **16a**.

Several of the better analogs were further evaluated in additional hFSH-based functional assays as shown in Table 3. The standard **2** and close derivative **16a** were of approximately equal activity in the Y1 adrenal and granulosa cell assays. The two additional compounds that were tested in the Y1 assay, the secondary amine **21b** and carbamate **24d**, lost potency and were partial

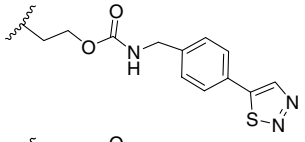
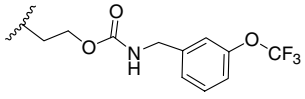
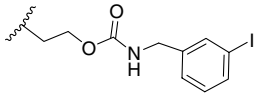
Table 2.



Compound	A	EC_{50} (nM) (% efficacy compared to FSH)	
		hFSHR-dependent CRE-LUC activity	cAMP production
10		>30,000 (n = 1)	NT
11		>30,000 (n = 1)	NT
16a		51 ± 42 (n = 4, 100%)	100 (n = 1, 91%)
16b		605 ± 20 (n = 2, 90%)	NT
16c		290 (n = 1, 100%)	NT
16d		780 (n = 1, 98%)	NT
21a		165 ± 35 (n = 2, 93%)	710 (n = 1, 65%)
21b		210 ± 40 (n = 2, 99%)	400 (n = 1, 96%)
22a		60 (n = 1, 87%)	820 (n = 1, 50%)
22b		40 (n = 1, 100%)	NT
24a		110 ± 30 (n = 2, 99%)	1800 (n = 1, 100%)
24b		30 (n = 1, 76%)	NT
24c		30 (n = 1, 82%)	NT
24d		44 ± 13 (n = 2, 97%)	1000 (n = 1, 42%)

(*continued on next page*)

Table 2 (*continued*)

Compound	A	EC_{50} (nM) (% efficacy compared to FSH)	
		hFSHR-dependent CRE-LUC activity	cAMP production
24e		205 ± 35 (*n* = 2, 91%)	1800 (*n* = 1, 24%)
24f		80 (*n* = 1, 100%)	2300 (*n* = 1, 63%)
24g		370 (*n* = 1, 100%)	NT

Data represent means ± SEM for replicate experiments (*n*) as indicated in parentheses.
NT = not tested.

Table 3.

Compound	EC_{50} (nM) (% efficacy compared to FSH)			
	hFSHR-dependent CRE-LUC activity	hFSHR cAMP production	Y1 adrenal (progesterone)	granulosa (aromatase)
2	14 ± 3 (*n* = 5, 100%)	167 ± 117 (*n* = 3, 76%)	530 ± 390 (*n* = 3, 93%)	70 ± 6 (*n* = 2, 77%)
16a	51 ± 42 (*n* = 4, 100%)	100 (*n* = 1, 91%)	<300 (*n* = 1, 99%)	107 ± 39 (*n* = 2, 94%)
21b	210 ± 40 (*n* = 2, 99%)	400 (*n* = 1, 96%)	1300 (*n* = 1, 47%)	NT
22b	40 (*n* = 1, 100%)	NT	NT	26 (*n* = 1, 78%)
24d	44 ± 13 (*n* = 2, 97%)	1000 (*n* = 1, 42%)	1310 (*n* = 1, 56%)	410 (*n* = 100%)
24f	80 (*n* = 1, 100%)	2300 (*n* = 1, 63%)	NT	120 ± 10 (*n* = 2, 62%)

Data represent means ± SEM for replicate experiments as indicated in parentheses.
NT = not tested.

agonists in the Y1 assay. Thioether **22b**, and carbamates **24d** and **24f** were tested in the granulosa cell assay and were generally in the same activity range as acetic acid amides **2** and **16a**.

To conclude, we demonstrated the straightforward preparation of 5-alkylated analogs (**3**) of potent thiazolidinone-based FSH agonist **1**. These compounds (**3** and **5**) were designed to reduce synthetic problems that arose in the preparation of analogs of **1**. FSH activity data for specific 5-methyl analogs (e.g., **16a**) were similar to corresponding 5-hydrogen-containing compounds (e.g., **2**). We also prepared derivatives of **3** that replaced the secondary amide functional group with other, potentially less hydrolytically unstable groups. In this fashion, secondary amine (**21**), thioethers (**22**), and carbamate (**24**) analogs were made and evaluated for FSH activity. All these analogs retained good FSH activity, although in certain circumstances either potency or efficacy was reduced.

4. Experimental

General methods: Appropriate safety practices were observed during all laboratory functions. General solvents and chemicals were purchased from VWR and used without further treatment. Anhydrous and deuterated solvents as well as fine chemicals were purchased from Aldrich Chemical Co. and used without further treatment. Microanalyses were performed by Robertson Microlit Labs (Madison, NJ). High-resolution mass spectra were taken on a Waters LC-TOFMS instrument. Accurate masses were measured to within 5 ppm of the calculated values. Proton (^{1}H) was taken on a Bruker DPX300 (300 MHz) instrument and delta values (δ) were measured in ppm using tetramethylsilane as an internal standard (δ = 0 ppm). High-performance liquid chromatography (HPLC) was performed with an Agilent 1100F series instrument with autosampler, thermoregulated column oven, and a diode array detector.

4.1. [(2*S**, 5*S**)-3-[3-(Methoxycarbonyl)phenyl]-2-[4-(benzyloxy)phenyl]-4-oxo-1,3-thiazolidin-5-yl]acetic acid (7)

At room temperature under N_2, methyl-3-aminobenzoate (18.12 g, 119.865 mmol), 4-benzyloxybenzaldehyde (25.44 g, 119.865 mmol), and mercaptosuccinic acid (27.00 g, 179.798 mmol) in acetonitrile (200 mL) were heated at reflux for 4 days. The resulting brown solution was concentrated in vacuo. The brown syrup was partitioned between 1:1 water: CH_2Cl_2 (800 mL). The $CH_2Cl_2$was dried over $MgSO_4$ and concentrated in vacuo to a brown syrup. SiO_2 gravitational chromatography elution with hexane/EtOAc (3:1, 2 L), (2:1, 2 L), (1:1, 4 L), (1:1.5, 2 L) afforded an orange powder

(48.57 g, 85% yield). ^{1}H NMR (DMSO-d_6) δ 2.93 (dd, J = 8.37, 8.38 Hz, 1H), 3.04 (dd, J = 17.26, 3.95 Hz, 1H), 3.83 (s, 3H), 4.51 (ddd, J = 5.42, 3.94, 1.48 Hz, 1H), 5.00 (s, 2H), 6.47 (d, J = 1.48 Hz, 1H), 6.90 (d, J = 8.87 Hz, 2H), 7.31 (d, J = 6.90 Hz, 1H), 7.34 (m, 6H), 7.43 (t, J = 7.88 Hz, 1H), 7.53 (dd, J = 7.89, 0.99 Hz, 1H), 7.73 (d, J = 7.89 Hz, 1H), 7.94 (t, J = 1.48 Hz, 1H), 12.66 (br s, 1H). Anal. HRMS Calcd for $C_{26}H_{23}NO_6S+H^+$, 478.13189; found (ESI, $[M+H]^+$), 478.133. HPLC purity 91.9% at 210–370 nm, 9.8 min; Xterra RP18, 3.5 μm, 150 × 4.6 mm column, 1.2 mL/min, 85/15–5/95 (ammon. form. buff. Ph = 3.5/ACN+MeOH) for 10 min, hold 4 min.

4.2. Methyl-3-[(2*S**,5*S**)-2-[4-(benzyloxy)phenyl]-5-(2-hydroxyethyl)-4-oxo-1,3-thiazolidin-3-yl]benzoate (8)

At room temperature under N_2, benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (5.0 g, 11.305 mmol) and diisopropylethylamine (2.33 mL, 13.360 mmol) were added to a solution of [(2*S**,5*S**)-3-[3-(methoxycarbonyl)phenyl]-2-[4-(benzyloxy)phenyl]-4-oxo-1,3-thiazolidin-5-yl]acetic acid. Compound **7** (4.90 g, 10.277 mmol) in THF (200 mL) and the reaction mixture was stirred for 6 h. The brown solution was cooled to 0 °C upon which $NaBH_4$ (450 mg, 11.819 mmol) was added. Gas evolution persisted for about 0.5 h, after which the slightly cloudy brown solution was stirred at room temperature for 60 h. The solution was concentrated in vacuo to a brown syrup and partitioned between 1:1 EtOAc: cold aqueous 2 N HCl (500 mL). The aqueous layer was further extracted with EtOAc (2× 100 mL). All organic layers were combined and extracted with ice-cold saturated aqueous $NaHCO_3$ (200 mL), water (150 mL), and brine (100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to a brown syrup. Biotage SiO_2 chromatography (40 M cartage), 3:1/hexane:EtOAc (1 L), 2:1/hexane:EtOAc (3 L), afforded the title compound as a light brown powder (2.81 g, 63% yield). ^{1}H NMR (DMSO-d_6) δ 1.17 (m, 1H), 2.22 (m, 1H), 3.53 (m, 1H), 3.64 (m, 1H), 3.83 (s, 3H), 4.32 (dd, J = 4.02, 0.72 Hz, 1H), 4.72 (t, J = 5.13 Hz, 1H), 5.01 (s, 2H), 6.55 (s, 1H), 6.88 (q, d, J = 8.79, 1.83 Hz, 2H), 7.30 (m, 7H), 7.43 (t, J = 8.05 Hz, 1H), 7.55 (dd, J = 6.95, 1.10 Hz, 1H), 7.12 (d, J = 8.06 Hz, 1H), 7.95 (t, J = 2.20 Hz, 1H). HRMS calcd for $C_{26}H_{25}NO_5S+H^+$, 464.15262; found (ESI, $[M+H]^+$), 464.1524. HPLC purity 74% at 210 nm; 72% at 230 nm; t_R = 25.9 min; Primesphere, 5 μm, C18-HC, 4.6 × 250 mm column, 1 mL/min, gradient: (A) water; (B) acetonitrile.

4.3. Methyl-3-[(2*S**,5*R**)-2-[4-(benzyloxy)phenyl]-5-(2-hydroxyethyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl]benzoate (9)

n-Butyl lithium (48.37 mL, 120.917 mmol, 2.0 M solution in hexane) was added to THF (100 mL) at 0 °C under N_2, by syringe. After 5 min, 1,1,1,3,3,3-hexamethyl disilazane (32.00 g, 115.66 mmol) was added to the pale yellow solution over 3 min producing gas evolution. The resulting colorless solution was stirred at 0 °C for 25 min. This solution of lithium 1,1,1,3,3,3,-hexamethyldisilazane in THF (182 mL solution) was added to a solution of methyl 3-[(2*S**,5*S**)-2-[4-(benzyloxy)phenyl]-5-(2-hydroxyethyl)-4-oxo-1,3-thiazolidin-3-yl]benzoate (**8**, 24.27 g, 52.573 mmol), lithium chloride (8.91 g, 210.290 mmol) in THF (350 mL) at −45 °C at a rate where the reaction temperature was kept at −45± 3 °C (about 4 min). The resulting dark brown mixture was stirred at −78 °C for 3.5 h. To the dark brown solution was added iodomethane (7.18 g, 262.863 mmol) at −78 °C and the reaction mixture was stirred at this temperature for 2.5 h. The resulting dark purple solution was warmed to −40 °C and then quenched with saturated aqueous NH_4Cl (500 mL). The resulting brown solution was partitioned with EtOAc (500 mL). The aqueous layer was further extracted with EtOAc (500 mL). All organic layers were combined, washed with brine (300 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to a dark brown syrup. Biotage Flash-75 (75-L cartridge) elution schedule: hexane:EtOAc/3:1 (16 L), 2:1 (12 L), 1:1 (16 L), 0:1 (8 L). Collection of the clean fractions afforded a yellow foam (9.71 g, 39% yield) of the title compound and recovered starting material (12.18 g). ^{1}H NMR (DMSO-d_6) δ 1.63 (s, 3H), 1.92 (m, 1H), 2.14 (m, 1H), 3.56 (m, 4H), 3.81 (s, 3H), 4.67 (t, J = 3.11 Hz, 1H), 4.99 (s, 2H), 6.61 (s, 1H), 6.83 (d, J = 8.68 Hz, 2H), 7.29 (m, 2H), 7.34 (m, 3H), 7.38 (m, 1H), 7.41 (d, J = 8.68 Hz, 1H), 7.53 (d, J = 8.68 Hz, 1H), 7.88 (s, 1H). An NOE correlation experiment confirmed a coupling through space between the 5-methyl group on thiazolidinone central ring and the 2-proton that was attached to this same ring, confirming these groups were cis to one another. HRMS calcd for $C_{27}H_{27}NO_5S+H^+$, 478.16827; found (ESI, $[M+H]^+$), 478.1665. HPLC purity 89% at 210 nm; 91.8% at 230 nm; t_R = 20.6 min; Capcell Pak, UG120, 4.6 × 150 mm column, 1 mL/min, gradient: (A) water; (B) acetonitrile.

4.4. 3-[(2*S**,5*R**)-2-[4-(Benzyloxy)phenyl]-5-(2-hydroxyethyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl]benzamide (10)

Ammonium hydroxide (20 mL, 30% aqueous solution) was added to a solution of methyl 3-[(2*S**,5*R**)-2-[4-(benzyloxy)phenyl]-5-(2-hydroxyethyl)-5- methyl-4-oxo-1,3-thiazolidin-3-yl]benzoate (**9**, 1.00 g, 2.094 mmol) in methyl alcohol (15 mL) at room temperature in a coated flask opened to the atmosphere. The resulting brown cloudy mixture was sealed with a Teflon™ screw cap and stirred for 4 days. The yellow solution was concentrated in vacuo to a brown syrup. Biotage SiO_2 chromatography (5% MeOH:CH_2Cl_2) afforded the title compound as a yellow foam (640 mg, 66% yield). ^{1}H NMR (DMSO-d_6) δ 1.62 (s, 3H), 2.00 (qd, J = 8.02, 2.82 Hz, 1H), 2.16 (q, J = 8.02 Hz, 1H), 3.62 (m, 1H), 3.71 (m, 1H), 4.66 (t, J = 5.31 Hz, 1H), 4.99 (s, 2H), 6.51 (s, 2H), 6.87 (d, J = 8.85 Hz, 2H), 7.30 (m, 7H), 7.40 (dq, J = 7.78, 0.05 Hz, 2H), 7.63 (dt, J = 7.78, 1.41 Hz, 1H), 7.80 (t, J = 1.77 Hz, 1H), 7.93 (br s, 2H). HRMS calcd for $C_{26}H_{26}N_2O_4S+H^+$, 463.16860; found (ESI, $[M+H]^+$), 463.1689. HPLC purity 98.2% at 210 nm; 99.1% at 230 nm; t_R = 16.8 min; Capcell Pak, UG120, 4.6 × 150 mm column, 1 mL/min, gradient: (A) water; (B) acetonitrile.

4.5. Methyl-3-[(2*S**,5*R**)-5-allyl-2-[4-(benzyloxy)phenyl]-5-(2-hydroxy ethyl)-4-oxo-1,3-thiazolidin-3-yl]benzoate (11)

Using the procedure for compound **9** except using allyl bromide as the alkylating agent afforded the title compound as a yellow powder (790 mg, 36% yield). ^{1}H NMR (DMSO-d_6) δ 1.94 (m, 1H), 2.10 (m, 1H), 3.56 (m, 4H), 2.58 (m, 2H), 3.64 (m, 2H), 3.92 (s, 3H), 4.66 (t, J = 3.11 Hz, 1H), 4.99 (s, 2H), 5.15 (dd, J = 10.70 Hz, 1H), 5.19 (dd, J = 10.70 Hz, 1H), 5.97 (m, 1H), 6.41 (s, 1H), 6.86 (d, J = 8.68 Hz, 2H), 7.29 (m, 2H), 7.34 (m, 2H), 7.38 (m, 1H), 7.51 (d, J = 8.68 Hz, 1H), 7.70 (d, J = 8.68 Hz, 1H), 7.83 (s, 1H). MS (ESI) m/z 504; HPLC purity 98.7% at 210 nm; 99.0% at 230 nm; t_R = 24.8 min; Inertsil, ODS3, 8 μm, 4.6 × 250 mm column, 1 mL/min, gradient: (A) water; (B) acetonitrile. Anal. Calcd for $C_{29}H_{29}NO_5S$: C, 69.16; H, 5.80; N, 2.78. Found: C, 69.13; H, 6.06; N, 2.74.

4.6. {(2*S**,5*R**)-2-[4-(Benzyloxy)phenyl]-3-[3-(methoxycarbonyl)phenyl]-5-methyl-4-oxo-1,3-thiazolidin-5-yl}acetic acid (12)

Methyl-3-[(2*S**,5*R**)-2-[4-(benzyloxy)phenyl]-5-(2-hydroxyethyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl]benzoate (**9**) (160 mg, 0.32 mmol) was oxidized with Jones reagent according to the procedure for **13** above. Chromatography of the crude product on silica gel and elution with 1% methanol in CH_2Cl_2 afforded 70 mg (44% yield) of the title compound as a foam; ^{1}H NMR ($CDCl_3$): δ 1.79 (s, 3H); 3.30, 3.00 (dd, J = 16 Hz, 2H), 3.82 (s, 3H), 6.20 (s, 1H) 4.83 (s, 2H), 7.9–6.7(m, 13H), 9.7 (br, 1H); MS (ES-positive): $[M+H]^+$ 492. HPLC purity 80.5% at 210 nm, 81.6% at 230 nm, t_R = 17.7 min; INERTSIL ODS-2, 4.6 × 150 mm column, 1 mL/min, 10 mM $NH_4H_2PO_4$ (pH 3)/ACN.

4.7. {(2*S**,5*R**)-3-[3-(Aminocarbonyl)phenyl]-2-[4-(benzyloxy)phenyl]-5-methyl-4-oxo-1,3-thiazolidin-5-yl}acetic acid (13)

3-[(2*S**,5*R**)-2-[4-(Benzyloxy)phenyl]-5-(2-hydroxyethyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl]benzamide (**10**, 200 mg, 0.43 mmol) was dissolved in acetone (25 mL) and cooled to −10 °C/N_2. To this solution 1.4 M Jones reagent (0.5 mL) was added over a period of 5 min. The orange colored mixture was stirred at −10 °C for 2 h. The mixture was treated consecutively with methanol (1 mL), saturated aqueous solution of sodium bicarbonate (2 mL) and acetic acid (1 mL) and then filtered. After evaporation, the residue was diluted with water (15 mL) and extracted four times with CH_2Cl_2 (40 mL/extraction). The CH_2Cl_2 solution was washed with water, dried with $MgSO_4$, and evaporated. Chromatography of the crude product on silica gel and elution with 4% methanol in CH_2Cl_2 afforded 100 mg (40% yield) of the title compound as a white solid; ^{1}H NMR (DMSO-d_6): δ ^{1}H NMR (DMSO-d_6) δ 2.93 (dd, J = 8.37, 8.38 Hz, 1H), 3.04 (dd, J = 17.26, 3.95 Hz, 1H), 4.51 (ddd, J = 5.42, 3.94, 1.48 Hz, 1H), 5.00 (s, 2H), 6.47 (d, J = 1.48 Hz, 1H), 6.90 (d, J = 8.87 Hz, 2H), 7.31 (d, J = 6.90 Hz, 1H), 7.34 (m, 6H), 7.43 (t, J = 7.88 Hz, 1H), 7.44 (m, 2H) 7.53 (dd, J = 7.89, 0.99 Hz, 1H), 7.73 (d, J = 7.89 Hz, 1H), 7.94 (t, J = 1.48 Hz, 1H), 12.66 (br s, 1H). HRMS calcd for $C_{26}H_{24}N_2O_5S+H^+$, 477.14787; found (ESI, $[M+H]^+$), 477.1483. HPLC purity 84.3% at 210 nm, t_R = 13.9 min 85.4% at 230 nm, t_R = 13.9 min; Inertsil ODS2, 5 μm, 4.6 × 150 mm column, 1.0 mL/min, gradient: (A) 10 mM $NH_4H_2PO_4$ (pH 3); (B) acetonitrile.

4.8. {(2*S**,5*R**)-5-Allyl-2-[4-(benzyloxy)phenyl]-3-[3-(methoxycarbonyl)phenyl]-4-oxo-1,3-thiazolidin-5-yl}acetic acid (14)

Using the Jones oxidation procedure to produce compound **13**, methyl 3-[(2*S**,5*R**)-5-allyl-2-[4-(benzyloxy)phenyl]-5-(2-hydroxy ethyl)-4-oxo-1,3-thiazolidin-3-yl]benzoate (**11**, 400 mg, 0.794 mmol) was converted to the title compound: yellow foam (275 mg, 67% yield). ^{1}H NMR (DMSO-d_6): 2.52–2.60 (q and s, J = 7 Hz, 5H), 2.61–2.67 (t, J = 7 Hz, 2H), 2.75–2.89 (dd, J = 15.07, 15.07 Hz, 2H), 3.69 (s, 3H), 4.95–4.97 (d, J = 12 Hz, 1H), 5.15 (s, 3H), 5.13–5.23 (ddd, J = 19.04, 10.30, 1.99 Hz, 1H), 5.94–6.01 (m, 1H), 6.29 (s, 1H), 6.780–6.83 (m, 3H), 7.27–7.38 (m, 5H), 7.39–7.45 (m, 4H), 7.60–7.61 (d, J = 2 Hz, 1H), 7.78 (s, 1H), 7.90–7.91 (br s, 1H), 8.09–8.05 (t, J = 6 Hz, 1H). MS (ESI) $[M+H]^+$ 518. HPLC purity 94.0% at 230 nm, t_R = 26.5 min; Inertsil ODS 3, 4.6 × 250 mm, 8 μm column, 1 mL/min, gradient: (A) 0.1% TFA in water; (B) acetonitrile.

4.9. Methyl-3-[(2*S**,5*R**)-2-[4-(benzyloxy)phenyl]-5-(2-{[2-(3-ethoxy-4-methoxy-phenyl)ethyl]amino}-2-oxoethyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl]benzoate (15)

{(2*S**,5*R**)-2-[4-(Benzyloxy)phenyl]-3-[3-(methoxycarbonyl)phenyl]-5-methyl-4-oxo-1,3-thiazolidin-5-yl}acetic acid (**12**, 240 mg, 0.49 mmol) was dissolved in DMF (15 mL) and treated at room temperature under N_2 with diisopropylethylamine (76 mg, 0.59 mmol) and 3-ethoxy-4-methoxyphenethylamine (114 mg, 0.59 mmol) in DMF (0.5 mL). To this solution *O*-(7-azabenzotriazole-1-yl)-*N*,*N*,*N*′,*N*′-tetra-methyl uronium hexafluorophosphate (233 mg, 0.59 mmol) was added. The resulting solution was stirred at rt/N_2 for 20 h. It was diluted with ethyl acetate (220 mL), washed with brine (3× 20 mL/extraction), dried with $MgSO_4$ and evaporated. Chromatography of the crude product on silica gel and elution with 1.5% methanol in CH_2Cl_2 afforded 250 mg (76% yield) of the title compound as a white solid; ^{1}H NMR ($CDCl_3$): δ 3.58, 3.50 (2m, 2H), 3.87, 3.84 (2s, 3H each), 4.04 (m, 2H), 4.95 (s, 2H), 6.17 (s, 1H), 7.9–6.6 (m, 16H); MS (ES-positive): $[M+H]^+$ 669. HPLC purity 82% at 210 nm, 85% at 230 nm, t_R = 17.5 min; Inertsil, 5 ODS2, 4.6 × 150 mm column, 1 mL/min, gradient: (A) water; (B) acetonitrile.

The following compounds were prepared using the procedure of compound **15**:

4.10. 3-[(2*S**,5*R**)-2-[4-(Benzyloxy)phenyl]-5-(2-{[2-(3-ethoxy-4- methoxyphenyl)-ethyl]amino}-2-oxoethyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl]benzamide (16a)

From **13** and 3-ethoxy-4-methoxyphenethylamine. Chromatography of the crude product on silica gel

and elution with 3% methanol in CH_2Cl_2 afforded 74 mg (60% yield) of the title compound as a white powder; ^{1}H NMR (DMSO-d_6): δ 1.57 (s, 3H), 2.63 (q, 2H), 2.81(s, 2H), 3.69 (s, 3H), 3.82 (m, 2H), 4.96 (s, 2H), 6.46 (s, 1H), 8.2–6.7 (m, 16H): HRMS calcd for $C_{37}H_{39}N_3O_6S+H^+$, 654.26323; found (ESI, $[M+H]^+$), 654.2607. HPLC purity 97.1% at 210 nm, 98.0% at 230 nm, t_R = 19.5 min; Capcell PAK C19 4.6 × 150 mm column, 1 mL/min, acetonitrile/water.

4.11. 3-((2*S**,5*R**)-2-[4-(Benzyloxy)phenyl]-5-{2-[(3-ethoxy-4-methoxybenzyl)amino]-2-oxoethyl}-5-methyl-4-oxo-1,3-thiazolidin-3-yl)benzamide (16b)

From **13** and 3-ethoxy-4-methoxybenzylamine. ^{1}H NMR (DMSO-d_6) δ 1.14 (t, J = 6.24 Hz, 3H), 1.62 (s, 3H), 2.94 (d, J = 4.50 Hz, 2H), 3.69 (s, 3H), 3.71 (q, J = 6.24 Hz, 2H), 4.23 (qd, J = 27.6, 5.44 Hz, 2H), 4.96 (s, J = 4.5 Hz, 2H), 6.48 (s, 1H), 6.78 (d,d and s, J = 8.55, 1.65, 5H), 7.24 (m, 10H), 7.59 (d, J = 8.55, 1H), 7.80 (s, 1H), 7.89 (s, 1H), 8.63 (t, J = 5.95 Hz, 1H). HRMS calcd for $C_{36}H_{37}N_3O_6S+H^+$, 640.24758; found (ESI, $[M+H]^+$), 640.2462. HPLC purity 92.7% at 210 nm, 93.1% at 230 nm; t_R = 18.7 min; Xterra MS C18, 5 μ, 4.6 × 150 mm column, 1.0 mL/min, gradient: (A) water; (B) ACN.

4.12. 3-[(2*S**,5*R**)-2-[4-(Benzyloxy)phenyl]-5-methyl-4-oxo-5-(2-oxo-2-{[3-(trifluoromethoxy)benzyl]amino}ethyl)-1,3-thiazolidin-3-yl]benzamide (16c)

From **13** and 3-trifluoromethoxybenzylamine. ^{1}H NMR (DMSO-d_6) δ 1.62 (s, 3H), 2.94 (s, 2H), 4.23 (qd, J = 27.6, 5.44 Hz, 2H), 4.96 (s, 2H), 6.48 (s, 1H), 6.79 (d, J = 8.55, 2H), 7.18 (d, J = 8.55, 1H), 7.28 (s, 1H), 7.21 (m, 12H), 7.59 (d, J = 8.55, 1H), 7.80 (s, 1H), 7.89 (s, 1H), 8.63 (t, J = 5.95 Hz, 1H). HRMS calcd for $C_{34}H_{30}F_3N_3O_5S+H^+$, 650.19310; found (ESI, $[M+H]^+$), 650.1922. HPLC purity 89.4% at 210 nm, 89.6% at 230 nm; t_R = 21.4 min; Xterra MS C18, 5 μm, 4.6 × 150 mm column, 1.0 mL/min, gradient: (A) water; (B) ACN.

4.13. 3-((2*S**,5*R**)-2-[4-(Benzyloxy)phenyl]-5-{2-[([1,1′-biphenyl]-3-ylmethyl)amino]-2-oxoethyl}-5-methyl-4-oxo-1,3-thiazolidin-3-yl)benzamide (16d)

From **13** and 3-phenylbenzylamine. ^{1}H NMR (DMSO-d_6) δ 1.62 (s, 3H), 2.94 (s, 2H), 3.69 (s, 3H), 4.23 (qd, J = 27.6, 5.44 Hz, 2H), 4.96 (s, J = 4.5 Hz, 2H), 6.48 (s, 1H), 6.78 (d,d and s, J = 8.55, 1.65 Hz, 2H), 7.24 (m, 16H), 7.59 (d, J = 8.55, 1H), 7.80 (s, 1H), 7.89 (s, 1H), 8.63 (t, J = 5.95 Hz, 1H). HRMS calcd for $C_{39}H_{35}N_3O_4S+H^+$, 642.24210; found (ESI, $[M+H]^+$), 642.2433. HPLC purity 81.7% at 210 nm, 81.9% at 230 nm; t_R = 21.9 min; Xterra MS C18, 5 μm, 4.6 × 150 mm column, 1.0 mL/min, gradient: (A) water; (B) ACN.

4.14. 3-[(2*S**,5*R**)-2-[4-(benzyloxy)phenyl]-5-(2-{[2- (3-ethoxy-4-methoxy-phenyl)ethyl]amino}-2-oxoethyl)-5-methyl-1,1-dioxido-4-oxo-1,3-thiazolidin-3-yl]benzamide (17)

3-[(2*S**,5*R**)-2-[4-(Benzyloxy)phenyl]-5-(2-{[2-(3-ethoxy-4-methoxyphenyl)-ethyl]amino-2-oxoethyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl]benzamide (**18**, 770 mg, 1.18 mmol) was dissolved in 1-methyl-2-pyrrolidinone (20 mL) and treated with 3-chloroperoxy-benzoic acid (2 g, 60%purity, 7 mmol). The resulting solution was stirred at 60 °C /N_2 for 2 days. All the solvent was removed at 60 °C under reduced pressure. The residue was dissolved in ethyl acetate (400 mL), washed with 10% aqueous sodium sulfite solution (45 mL), saturated aqueous sodium bicarbonate solution (45 mL), brine, and dried with $MgSO_4$. After evaporation of the solvent, the crude product was purified by chromatography on silica gel. Elution with 3% methanol in CH_2Cl_2 afforded 695 mg (83% yield) of the title compound as a white solid; ^{1}H NMR (DMSO-d_6): δ 1.29 (t, 3H), 1.67 (s, 3H), 2.64 (q, 2H), 2.97 (m, 2H), 3.30 (m, 2H), 3.71 (s, 3H), 3.97 (q, 2H), 5.02 (s, 2H), 6.80 (s, 1H), 8.24–6.71 (m, 16H); MS (ES-positive): $[M+H]^+$ 686. HRMS calcd for $C_{37}H_{39}N_3O_8S+H^+$, 686.25306; found (ESI, $[M+H]^+$), 686.2548. HPLC purity 86% at 210 nm; 87% at 230 nm; t_R = 22.7 min; Inertsil, ODS3, 8 μm, 4.6 × 250 mm column, 1 mL/min, gradient: (A) water; (B) acetonitrile.

4.15. Methyl-3-[(2*S**,5*R**)-5-allyl-2-[4-(benzyloxy)phenyl]-5-(2-{[2-(3-ethoxy-4-methoxyphenyl)ethyl]amino}-2-oxoethyl)-4-oxo-1,3-thiazolidin-3-yl]benzoate (18)

From **14** and 3-ethoxy-4-methoxyphenethylamine. Yellow powder (290 mg, 94% yield). ^{1}H NMR (DMSO-d_6): 1.24–1.27 (t, J = 7 Hz, 3H), 2.52–2.60 (q and s, J = 7 Hz, 5H), 2.61–2.67 (t, J = 7 Hz, 2H), 2.75–2.89 (dd, J = 15.07, 15.07 Hz, 2H), 3.16–3.21 (m, 1H), 3.38–3.43 (m, 1H), 3.69 (s, 2H), 3.86–3.93 (m, 1H), 4.95–4.97 (d, J = 12 Hz, 1H), 5.15 (s, 3H), 5.23–5.33 (ddd, J = 19.04, 10.30, 1.99 Hz, 1H), 5.94–6.01 (m, 1H), 6.29 (s, 1H), 6.68–6.6.72 (m, 2H), 6.780–6.83 (m, 3H), 7.27–7.38 (m, 5H), 7.39–7.45 (m, 5H), 7.60–7.61 (d, J = 2 Hz, 1H), 7.78 (s, 1H), 7.90–7.91 (br s, 1H), 8.09–8.05 (t, J = 6 Hz, 1H). MS (ESI) $[M+H]^+$ 695. HPLC purity 88% at 210 nm; 91% at 230 nm; t_R = 24.5 min; Inertsil, 5 ODS2, 4.6 × 150 mm column, 1 mL/min, gradient: (A) water; (B) acetonitrile.

4.16. 3-[(2*S**,5*R**)-5-Allyl-2-[4-(benzyloxy)phenyl]-5-(2-{[2-(3-ethoxy-4-methoxyphenyl)ethyl]amino}-2-oxoethyl)-4-oxo-1,3- thiazolidin-3-yl]benzamide (19)

Compound **18** (230 mg, 0.331 mmol) was stirred with ammonia in methanol to afford the title compound as a yellow syrup (190 mg, 84% yield). ^{1}H NMR (DMSO-d_6): 1.24–1.27 (t, J = 7 Hz, 3H), 2.52–2.60 (q and s, J = 7 Hz, 5H), 2.61–2.67 (t, J = 7 Hz, 2H), 2.75–2.89 (dd, J = 15.07, 15.07 Hz, 2H), 3.16–3.21 (m, 1H), 3.38–3.43 (m, 1H), 3.69 (s, 2H), 3.86–3.93 (m, 1H), 4.95–4.97 (br s, 2H), 5.13–5.23 (ddd, J = 19.04, 10.30, 1.99 Hz, 1H), 5.94–6.01 (m, 1H), 6.29 (s, 1H), 6.68–6.6.72 (m, 2H), 6.780–6.83 (m, 3H), 7.27–7.38 (m, 5H), 7.39–7.45 (m, 5H), 7.60–7.61 (d, J = 2 Hz, 1H), 7.78 (s, 1H), 7.90-7.91 (br s, 1H), 8.09–8.05 (t, J = 6 Hz, 1H). HRMS calcd for $C_{39}H_{41}N_3O_6S+H^+$, 680.27888; found (ESI, $[M+H]^+$), 680.2758. HPLC purity 98% at 210 nm; 98% at 230 nm; t_R = 20.9 min; Inertsil, 5 ODS2, 4.6 × 150 mm column, 1 mL/min, gradient: (A) water; (B) acetonitrile.

4.17. Methanesulfonic acid 2-[(2*S**,5*R**)-2-(4-benzyloxy-phenyl)-3-(3-carbamoyl-phenyl)-5-methyl-4-oxo-thiazolidin-5-yl]-ethyl ester (20)

Methanesulfonyl chloride (148 mg, 1.29 mmol) was added to a stirred solution of 3-[(2*S**,5*R**)-2-[4-(benzyloxy)phenyl]-5-(2-hydroxyethyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl]benzamide (**10**, 200 mg, 0.433 mmol) in pyridine (5 mL) at 0 °C under N_2. The resulting red solution was stirred at 0 °C for 2 h. The red solution was concentrated in vacuo to a red syrup. Biotage SiO_2 chromatography 3% MeOH:CH_2Cl_2 afforded a yellow powder (130 mg, 56% yield). ^{1}H NMR (DMSO-d_6) δ 1.66 (s, 3H), 2.29 (m, 1H), 2.45 (m, 1H), 2.50 (s, 3H), 4.44 (m, 2H), 5.00 (s, 2H), 6.58 (s, 1H), 6.86 (d, J = 8.65 Hz, 2H), 7.32 (m, 6H), 7.44 (m, 2H), 7.63 (d, J = 7.68 Hz, 1H), 7.82 (s, 1H), 7.89 (s, 1H), 8.57 (br s, 2H). MS (ESI) $[M+H]^+$ 541.

4.18. 3-[(2*S**,5*R**)-2-[4-(Benzyloxy)phenyl]-5-(2-{[2-(3,4-dimethoxy phenyl)ethyl]amino}ethyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl]benzamide (21a)

3,4-Dimethoxy phenethylamine (200 mg, 1.104 mmol) was added to a stirred solution of methanesulfonic acid 2-[(2*S**,5*R**)-2-(4-benzyloxy-phenyl)-3-(3-carbamoyl-phenyl)-5- methyl-4-oxo-thiazolidin-5-yl]-ethyl ester (**20**, 110 mg, 0.204 mmol) in DMF (10 mL) at room temperature under N_2. The resulting yellow solution was heated at 75 °C for 6 h and then concentrated in vacuo to a brown syrup. Gravitational SiO_2 chromatography 4% MeOH:CH_2Cl_2 afforded the title compound as a yellow powder (80 mg, 63% yield). ^{1}H NMR (DMSO-d_6) δ 0.24 (br s, 1H), 1.64 (s, 3H), 2.04 (m, 1H), 2.18 (m, 1H), 2.72 (m, 6H), 3.70 (s, 3H), 3.73 (s, 3H), 4.99 (s, 2H), 6.57 (s, 1H), 6.74 (dd, J = 8.11, 1.53 Hz, 1H), 6.84 (m, 4H), 7.28 (m, 9H), 7.63 (d, J = 7.56 Hz, 1H), 7.86 (s, 1H), 7.97 (br s, 2H). HRMS calcd for $C_{36}H_{39}N_3O_5S+H^+$, 626.26832; found (ESI, $[M+H]^+$), 626.2673. HPLC purity 88% at 210 nm; t_R = 15.9 min; Primesphere, C18-HC, 5 μm, 4.6 × 250 mm column, 1 mL/min, gradient: (A) 10 mM $NH_4H^2PO^4$ (pH 3.0); (B) acetonitrile.

4.19. 3-[(2*S**,5*R**)-2-[4-(Benzyloxy)phenyl]-5-(2-{[2-(3-ethoxy-4-methoxy phenyl)ethyl]amino}ethyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl]benzamide (21b)

Pyridinium chlorochromate (4.51 g, 20.941 mmol) was added to CH_2Cl_2 (100 mL) at 0 °C under N_2. To the orange mixture was added methyl 3-[(2*S**,5*R**)-2-[4-(benzyloxy)phenyl]-5-(2-hydroxyethyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl]benzoate (**9**, 1.00 g, 2.094) in CH_2Cl_2 (60 mL) dropwise over 30 min. The resulting dark brown mixture was stirred at 0 °C 2 h and then quenched with water (150 mL), diluted with CH_2Cl_2 (100 mL), and filtered through Celite. The organic layer was extracted with water (2× 150 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to a dark brown syrup. Biotage SiO_2 chromatography (40 s cartridge) 1:1/hexane:EtOAc afforded methyl 3-[(2*S**,5*R**)-2-[4-(benzyloxy)phenyl]-5- methyl-4-oxo-5-(2-oxoethyl)-1,3-thiazolidin-3-yl]benzoate as a yellow powder (617 mg, 62% yield). ^{1}H NMR (DMSO-d_6) δ 1.74 (s, 3H), 3.26 (s, 2H), 3.88 (s, 3H), 5.03 (s, 2H), 6.70 (s, 1H), 6.90 (d, J = 8.06, 2H), 7.35 (m, 7H), 7.46 (t, J = 8.06 Hz, 1H), 7.62 (d, J = 7.87 Hz, 1H), 7.76 (dd, J = 7.63, 0.78 Hz, 1H), 7.98 (s, 1H), 9.82 (s, 1H). MS (ESI) $[M+H]^+$ 476.

Sodium triacetoxyborohydride (67 mg, 0.315 mmol), 3-ethoxy-4-methoxy phenethylamine (45 mg, 0.231 mmol), and glacial acetic acid (12 μL) were added to a solution of this aldehyde (100 mg, 0.210 mmol) in dichloroethane (5 mL) at room temperature under N_2. The resulting yellow mixture was stirred at room temperature for 90 min and quenched with saturated aqueous $NaHCO_3$ (10 mL). More CH_2Cl_2 was added and the solution was washed with water and dried over $MgSO_4$. Concentration in vacuo afforded a brown syrup. Biotage SiO_2 (40 s) chromatography 3.5% MeOH:CH_2Cl_2 afforded methyl 3-[(2*S**,5*R**)-2-[4-(benzyloxy)phenyl]-5-(2-{[2-(3-ethoxy-4-methoxyphenyl)ethyl]amino}ethyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl]benzoate as a brown powder (68 mg, 58% yield). ^{1}H NMR (DMSO-d_6) δ 1.26 (t, J = 6.95 Hz, 3H), 1.61 (s, 3H), 1.90 (m, 1H), 2.11 (m, 1H), 2.63 (m, 6H), 3.35 (br s, 1H), 3.70 (s, 3H), 3.81 (s, 3H), 3.92 (q, J = 6.95 Hz, 2H), 4.98 (s, 2H), 6.59 (s, 1H), 6.69 (d, J = 8.09 Hz, 1H), 6.80 (m, 4H), 7.18 (m, 8H), 7.54 (d, J = 8.18 Hz, 1H), 7.69 (d, J = 7.69 Hz, 1H), 7.91 (s, 1H). MS (ESI) $[M+H]^+$ 655. This compound (250 mg, 0.382 mmol) was reacted with ammonia in methanol to afford the title compound as a yellow powder (110 mg, 45% yield). ^{1}H NMR (DMSO-d_6) δ 1.26 (t, J = 6.95 Hz, 3H), 1.61 (s, 3H), 1.90 (m, 1H), 2.11 (m, 1H), 2.63 (m, 6H), 3.35 (br s, 1H), 3.81 (s, 3H), 3.92 (q, J = 6.95 Hz, 2H), 4.98 (s, 2H), 6.59 (s, 1H), 6.69 (d, J = 8.09 Hz, 1H), 6.80 (m, 4H), 7.18 (m, 8H), 7.54 (d, J = 8.18 Hz, 1H), 7.69 (d, J = 7.69 Hz, 1H), 7.91 (s, 1H), 7.97 (br s, 2H). HRMS calcd for $C_{37}H_{41}N_3O_5S+H^+$, 640.28397; found (ESI, $[M+H]^+$), 640.2835. HPLC purity 94.1% at 210 nm, 94.1% at 230 nm, t_R = 13.25 min; Inertsil, 5 ODS2, 4.6 × 150 mm column, 1 mL/min, gradient: (A) 10 mM $NH_4H_2PO_4$ (pH 3.0); (B) acetonitrile.

4.20. 3-[(2*S**,5*R**)-2-[4-(Benzyloxy)phenyl]-5-(2-{[2- (3,4-dimethoxy phenyl)ethyl]thio}ethyl)-5-methyl-4-oxo-1,3-thiazolidin-3- yl]benzamide (22a)

Sodium hydride (20 mg, 0.509 mmol) was added to a solution of 3,4-dimethoxyphenethane thiol (97 mg, 0.489 mmol) in DMF (4 mL) at room temperature under N_2. After 30 min, this solution was added to a solution of methanesulfonic acid 2-[(2*S**,5*R**)-2-(4-benzyloxy-phenyl)-3-(3-carbamoyl-phenyl)-5- methyl-4-oxo-thiazolidin-5-yl]-ethyl ester (**20**, 110 mg, 0.205 mmol) in DMF (30 mL) and the reaction mixture was heated at 55 °C for 3 hrs. The resultant yellow solution was cooled to room temperature and quenched with 2 N HCl (50 mL). The reaction mixture was diluted with CH_2Cl_2 (40 mL), washed with water, dried over $MgSO_4$, filtered, and concentrated in vacuo. Biotage SiO_2 chromatography 2% MeOH:CH_2Cl_2 afforded the title compound as a yellow powder (410 mg, 19% yield). ^{1}H NMR (DMSO-d_6) δ 1.63 (s, 3H), 2.00 (m, 1H), 2.21 (m, 1H), 2.54 (m, 1H), 2.73 (m, 5H), 3.69 (s, 3H), 3.70 (s, 3H), 4.98 (s, 2H), 6.56 (s, 1H), 6.73 (dd, J = 8.18,

1.47 Hz, 1H), 6.83 (t, $J = 9.93$ Hz, 1H); MS (ESI) $[M+H]^+$ 643. HPLC purity 90.6% at 210 nm; 91.9% at 230 nm; $t_R = 17.6$ min; Inertsil, 5 ODS2, 4.6×150 mm column, 1 mL/min, gradient: (A) water; (B) acetonitrile. CHN $C_{36}H_{38}N_2O_5S \cdot 1/10H_2O$: Calcd C, 67.05; H, 5.97; N, 4.34. Found: C, 67.37; H, 6.24; N, 4.52.

4.21. 3-[(2*S**,5*R**)-2-[4-(Benzyloxy)phenyl]-5-(2-{[2-(3-ethoxy-4-methoxyphenyl)ethyl]thio}ethyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl]benzamide (22b)

Using the procedure of the above example (**22a**) and substituting 4-ethoxy-3-methoxyphenethane thiol for 3,4-dimethoxyphenylethane thiol afforded the title compound as a yellow powder (220 mg, 62% yield). ^{1}H NMR (DMSO-d_6) δ 1.27 (t, $J = 7.23$ Hz, 3H), 1.63 (s, 3H), 2.01 (td, $J = 13.88$, 4.36 Hz, 1H), 2.22 (td, $J = 13.88$, 4.36 Hz, 1H), 2.54 (td, $J = 13.88$, 4.36 Hz, 1H), 2.57 (td, $J = 13.88$, 4.36 Hz, 1H), 2.71 (m, 1H) 2.77 (s, 3H), 2.82 (td, $J = 13.88$, 4.36 Hz, 1H), 3.71 (s, 3H), 3.94 (q, $J = 7.23$ Hz, 2H), 4.98 (s, 2H), 6.55 (s, 1H), 6.72 (dd, $J = 9.92$, 1.98 Hz, 1H), 6.83 (2d, $J = 5.16$,1.19 Hz, 2H), 6.87 (d, $J = 5.16$ Hz, 2H), 7.29 (d, $J = 5.95$ Hz, 2H), 7.34 (d, $J = 7.94$ Hz, 2H), 7.40 (d, $J = 6.35$ Hz, 2H), 7.41 (br s, 2H), 7.43 (dd, $J = 7.92$, 1.19 Hz, 1H), 7.64 (d, $J = 7.92$ Hz, 1H), 7.83 (m, $J = 1.19$ Hz, 1H), 7.93 (br s, 1H); MS (ESI) $[M+H]^+$ 657. HPLC purity 86.8% at 210 nm, 86.5% at 230 nm, $t_R = 24.2$ min; Capcell PAK C18 4.6×150 mm column, 1 mL/min, water/acetonitrile. Anal. Calcd for $C_{37}H_{40}N_2O_5S_2$: C, 67.66; H, 6.14; N, 4.26. Found: C, 67.28; H, 6.32; N, 4.20.

4.22. 2-{(2*S**,5*R**)-3-[3-(Aminocarbonyl)phenyl]-2-[4-(benzyloxy)phenyl]-5-methyl-4-oxo-1,3-thiazolidin-5-yl}ethyl 4-nitrophenyl carbonate (23)

A solution of 3-[(2*S**,5*R**)-2-[4-(benzyloxy)phenyl]-5-(2-hydroxyethyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl]benzamide (**10**, 1.7 g, 3.8 mmol) in CH_2Cl_2 (50 mL)/pyridine (5 mL) was treated with 4-nitrophenyl chloroformate (1.1 g, 5.7 mmol) at 0 °C under N_2. After stirring at room temperature under N_2 for 1.5 h, it was diluted with water (100 mL) and extracted with CH_2Cl_2 (4× 50 mL). The combined CH_2Cl_2 solution was washed with water, dried with $MgSO_4$, and evaporated. Chromatography of the crude product on silica gel and elution with 2% methanol in CH_2Cl_2 afforded 1.9 g (83% yield) of the title compound as a white solid; ^{1}H NMR (DMSO-d_6): δ, 1.69 (s, 3H), 2.62, 2.20 (mm, 2H), 2.62, 2.20 (mm, 2H), 4.59 (m, 2H), 4.99 (s, 2H), 6.61 (s, 1H), 8.40–6.80 (m, 17H, aromatic); MS (ES-positive): $[M+H]^+$ 628; Anal. Calcd for $C_{33}H_{29}N_3O_8S$: C, 63.15; H, 4.66; N, 6.69. Found: C, 62.86; H, 4.55; N, 6.47.

4.23. 2-{(2*S**,5*R**)-3-[3-(Aminocarbonyl)phenyl]-2-[4- (benzyloxy)phenyl]-5-methyl-4-oxo-1,3-thiazolidin-5-yl}ethyl 2-(3-ethoxy-4-methoxyphenyl)ethylcarbamate (24a)

2-{(2*S**,5*R**)-3-[3-(Aminocarbonyl)phenyl]-2-[4-(benzyloxy)phenyl]-5-methyl-4-oxo-1,3-thiazolidin-5-yl}ethyl 4-nitrophenyl carbonate (**23**, 200 mg, 0.31 mmol) in CH_2Cl_2 (10 mL) was treated with 3-ethoxy-4-methoxyphenethyl-amine (200 mg, 1.03 mmol) in CH_2Cl_2 (2 mL) at −10 °C /N_2. After stirring at 0 °C under N_2 for 5 h, it was diluted with aqueous 1 N hydrochloric acid (50 mL) and extracted with CH_2Cl_2 (4×50 mL). The CH_2Cl_2 solution was washed with water, dried with $MgSO_4$, and evaporated. Chromatography of the crude product on silica gel and elution with 2% methanol in CH_2Cl_2 afforded 204 mg (90% yield) of the title compound as a white solid; ^{1}H NMR (DMSO-d_6): δ 1.29 (t, 3H), 1.64 (t, 3H), 2.20 (m, 2H), 2.62 (t, 2H), 3.18 (m, 2H) 3.69 (s, 3H), 3.96 (q, 2H), 4.20 (m, 2H), 4.98 (s, 2H), 6.55 (s, 1H), 8.0–6.6 (m, 16H); HRMS calcd for $C_{38}H_{41}N_3O_7S+H^+$, 684.27380; found (ESI, $[M+H]^+$), 684.2755. HPLC purity 92.6% at 210 nm; 93.4% at 230 nm; $t_R = 21.4$ min; Inertsil, 5 ODS2, 4.6×150 mm column, 1 mL/min, gradient: (A) water; (B) acetonitrile. Anal. Calcd for $C_{37}H_{39}N_3O_7S$: C, 66.74; H, 6.04; N, 6.14. Found: C, 66.75; H, 6.23; N, 6.07.

4.24. 2-{(2*S**,5*R**)-3-[3-(Aminocarbonyl)phenyl]-2-[4-(benzyloxy)phenyl]-5-methyl-4-oxo-1,3-thiazolidin-5-yl}ethyl 3,4,5-trimethoxybenzylcarbamate (24b)

Ethoxy-4-methoxybenzaldehyde (3.6 g, 20 mmol) and methyl hydroxylamine HCl salt (4.0 g, 48 mmol) were dissolved in dry pyridine (15 mL) and stirred for 5 h at room temperature under N_2. The resulting suspension was filtered and filtrate was evaporated at 40 °C under reduced pressure to give a light brown solid. The solid material was dissolved in methanol (25 mL), diluted with water (25 mL), and was cooled at 0 °C to induce crystallization. The white crystalline material was collected by filtration, rinsed with methanol, and dried in vacuum to give 2.75 g (66% yield) of 3-ethoxy-4-methoxybenzaldehyde methoxyoxime as a white powder; ^{1}H NMR (DMSO-d_6) δ 1.32 (t, 3H), 3.78 (s, 3H), 3.85 (s, 3H), 4.00 (q, 2H), 6.90–7.30 (m, 3H), 8.11(s, 1H); MS (ES-positive): $[M+H]^+$ 210. HPLC determined that this compound 99% purity.

This compound (2.51 g) was dissolved in THF (15 mL) and treated with 1 M diborane in THF (36 mL, 36 mmol) at rt/N_2. The solution was heated under reflux for 2 h, then cooled to 0 °C, and treated with water (10 mL) and 20% KOH aqueous solution (10 mL). The mixture was heated under reflux for 1.5 h and extracted with CH_2Cl_2. Evaporation of CH_2Cl_2extract and chromatography of crude product on silica gel afforded 2.1 g (62% yield) of 3-ethoxy-4-methoxybenzylamine as a light brown oil; ^{1}H NMR (DMSO-d_6) δ 1.31 (t, 3H), 3.71 (s, 3H), 3.97 (q, 2H), 4.28 (s, 2H), 6.70–7.00 (m, 3H).

Using the procedure of compound **24a** and substituting 3-ethoxy-4-methoxybenzylamine, the title compound was obtained as a white solid; ^{1}H NMR (DMSO-d_6) δ 1.26 (t, 3H), 1.64 (s, 3H), 2.25 (m, 2H), 3.69 (s, 3H), 3.90 (q, 2H), 4.12 (d, $J = 7.5$ Hz, 2H), 4.25 (m, 2H), 4.97 (s, 2H), 6.55 (s, 1H), 6.70–8.00 (m, 16H); MS (ES-positive): $[M+H]^+$ 670. HRMS calcd for $C_{37}H_{39}N_3O_7S+H^+$, 670.25815; found (ESI, $[M+H]^+$), 670.2587. HPLC purity 88.5% at 210 nm, 90.3% at 230 nm, $t_R = 20.3$ min; Xterra MS, C18, 5 μm, 4.6×150 mm column, 1 mL/min, gradient: (A) water; (B) acetonitrile.

4.25. 2-{(2*S**,5*R**)-3-[3-(Aminocarbonyl)phenyl]-2-[4-(benzyloxy)phenyl]-5-methyl-4-oxo-1,3-thiazolidin-5-yl}ethyl 3,4,5-trimethoxybenzylcarbamate (24c)

Using the procedure of compound **24a** and substituting 3,4,5-trimethoxybenzylamine in place of 3-ethoxy-4-methoxyphenethyl-amine, the title compound was obtained as a white solid: ^{1}H NMR (DMSO-d_6) δ 1.62 (s, 3H), 2.11 (m, 1H), 2.29 (m, 1H), 3.59 (s, 1H), 2.58 (m, 2H), 3.58 (s, 3H), 3.62 (s, 6H), 4.11 (d, J = 5.35 Hz, 1H), 4.21 (m, 1H), 4.99 (s, 2H), 6.84 (d, J = 6.11 Hz, 3H), 6.84 (d, J = 8.68 Hz, 2H), 7.29 (m, 2H), 7.34 (m, 5H), 7.38 (m, 1H), 7.58 (m, 1H), 7.70 (s, 1H), 7.83 (s, 1H). HRMS calcd for $C_{37}H_{39}N_3O_8S+H^+$, 686.25306; found (ESI, $[M+H]^+$), 686.2535. HPLC purity 89.4% at 210 nm, 91.0% at 230 nm; t_R = 19.6 min; Xterra MS C18 4.6 × 150 mm column, 1 mL/min, gradient: (A) water; (B) ACN.

4.26. 2-{(2*S**,5*R**)-3-[3-(aminocarbonyl)phenyl]-2-[4-(benzyloxy)phenyl]-5-methyl-4-oxo-1,3-thiazolidin-5-yl}ethyl [1,1′-biphenyl]-3-ylmethylcarbamate (24d)

Using the procedure of compound **24a** and substituting 3-phenyl-benzylamine in place of 3-ethoxy-4-methoxy-phenethyl-amine, the title compound was obtained as a white solid: ^{1}H NMR (DMSO-d_6) δ 1.67 (s, 3H), 2.13 (m, 2H), 4.18 (m, 4H), 4.99 (s, 2H), 6.56 (s, 1H), 6.82 (d, J = 8.85 Hz, 2H), 7.24 (m, 9H), 7.39 (m, 4H), 7.47 (t, J = 8.07 Hz, 2H), 7.52 (d, J = 6.27 Hz, 1H), 7.60 (m, 3H), 7.74 (t, J = 6.07 Hz, 1H), 7.81 (s, 1H), 7.91 (s, 1H). HRMS calcd for $C_{40}H_{37}N_3O_5S+H^+$, 672.25267; found (ESI, $[M+H]^+$), 672.251. HPLC purity 91.9% at 210 nm, 93.1% at 230 nm, t_R = 17.1 min; X Terra MS C18, 5 μm, 4.6 × 150 mm column, 1 mL/min, gradient: (A) water; (B) ACN.

4.27. 2-{(2*S**,5*R**)-3-[3-(Aminocarbonyl)phenyl]-2-[4-(benzyloxy)phenyl]-5-methyl-4-oxo-1,3-thiazolidin-5-yl}ethyl 4-(1,2,3-thiadiazol-5-yl)benzylcarbamate (24e)

Using the procedure of **24a** and substituting 4-(1,2,3-thiadiazol-5-yl)benzylamine, the title compound was obtained as a white solid; ^{1}H NMR (DMSO-d_6) δ 1.66 (s, 3H), 2.18 (m, 1H), 2.32 (m, 1H), 4.16 (m, 1H), 4.27 (d, J = 6.18 Hz, 2H), 4.28 (m, 1H), 4.96 (s, 2H), 6.57 (s, 1H), 6.82 (d, J = 8.56 Hz, 2H), 7.25 (m, 8H), 7.38 (m, 4H), 7.61 (d, J = 7.65 Hz, 1H), 7.78 (t, J = 6.18 Hz, 1H), 7.81 (s, 1H), 7.96 (s, 1H), 8.20 (d, J = 8.08 Hz, 2H), 9.59 (s, 1H). HRMS calcd for $C_{36}H_{33}N_5O_5S_2+H^+$, 680.19959; found (ESI, $[M+H]^+$), 680.201. HPLC purity 94.2% at 210 nm, 94.8% at 230 nm, t_R = 20.2 min; X Terra MS C18, 5 μm, 4.6 × 150 mm column, 1 mL/min, gradient: (A) water; (B) ACN.

4.28. 2-{(2*S**,5*R**)-3-[3-(Aminocarbonyl)phenyl]-2-[4-(benzyloxy)phenyl]-5-methyl-4-oxo-1,3-thiazolidin-5-yl}ethyl 3-(trifluoromethoxy)benzylcarbamate (24f)

Using the procedure of compound **24a** and substituting 3-trifluoromethoxybenzylamine, the title compound was obtained as a white solid; ^{1}H NMR (DMSO-d_6) δ 1.65 (s, 3H), 2.20 (m, 2H), 4.25 (m, 4H), 5.00 (s, 2H), 6.55 (s, 1H), 6.80–8.00 (m, 17H); HRMS calcd for $C_{35}H_{32}F_3N_3O_6S+H^+$, 680.20367; found (ESI, $[M+H]^+$), 680.204. HPLC purity 93.9% at 210 nm, 93.9% at 230 nm, t_R = 22.6 min; Xterra MS C18, 4.6 × 150 mm, 5 μm column, 1 mL/min, gradient: (A) water; (B) ACN. Anal. Calcd for $C_{35}H_{32}F_3N_3O_6S$: C, 61.85; H, 4.75; N, 6.18. Found: C, 61.75; H, 4.82; N, 6.09.

4.29. 2-{(2*S**,5*R**)-3-[3-(Aminocarbonyl)phenyl]-2-[4-(benzyloxy)phenyl]-5-methyl-4-oxo-1,3-thiazolidin-5-yl}ethyl 3-iodobenzylcarbamate (24g)

Using the procedure of compound **24a** and substituting 3-iodobenzylamine, the title compound was obtained as a white solid; ^{1}H NMR (DMSO-d_6) δ 1.65 (s, 3H), 2.25 (m, 2H), 4.17 (m, 4H), 4.98 (s, 2H), 6.55 (s, 1H), 6.70–8.15 (m, 17H); MS (ES-positive): $[M+H]^+$ 722. HPLC purity 90.4% at 210 nm, 91.3% at 230 nm; t_R = 22.3 min; Xterra MS C18, 4.6 × 150 mm column, 1 mL/min, gradient: (A) water; (B) ACN. Anal. Calcd for $C_{34}H_{32}IN_3O_5S$: C, 56.59; H, 4.47; N, 5.82. Found: C, 56.91; H, 4.60; N, 5.53.

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