# Design and Synthesis of the First Generation of Dithiolane Thiazolidinedione- and Phenylacetic Acid-Based PPAR$\gamma$ Agonists

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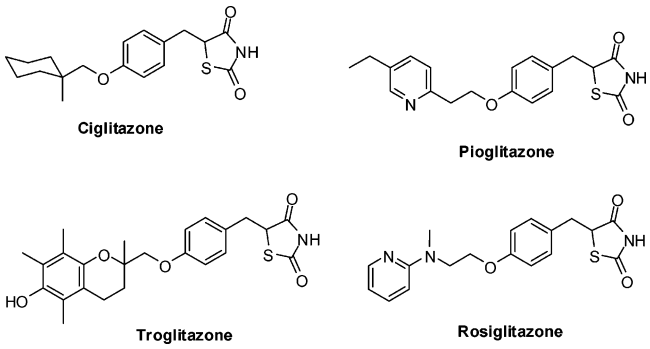
A series of novel derivatives of potent antioxidant vitamin, α-lipoic acid, and related analogues were designed, synthesized, and evaluated for their PPAR$\gamma$ agonist activities. Compounds **9a** and the water soluble analogue **11e** were found to be potent PPAR$\gamma$ agonists. Compound **9a** appeared to have a significant role in improving insulin sensitivity and reducing triglyceride levels in fa/fa rats as well as inhibited proliferation of a variety of normal and neoplastic cultured human cell types. These novel compounds may prove efficacious not only in the treatment of Type 2 diabetes, but also atherosclerosis, prevention of vascular restenosis, and inflammatory skin diseases.

## Introduction

Type 2 diabetes, a disease which has attained epidemic proportions in the United States and other regions of the world, is a condition in which target tissues develop resistance to the metabolic effects of insulin, impairment of glucose and lipid metabolism, and long term microvascular and macrovascular complications, resulting in potentially fatal cardiovascular events and renal failure. The thiazolidinediones (TZDs, also known as "glitazones") are insulin-sensitizing pharmacological agents that reduce insulin resistance and preserve islet $\beta$-cell function in Type 2 diabetes. These effects are largely mediated through the ability of these compounds to activate peroxisome proliferator-activated receptor-$\gamma$ (PPAR$\gamma$), a nuclear transcription factor that controls genetic programs involved in glucose and lipid homeostasis, energy metabolism, adipocyte differentiation, and maturation. Thus, PPAR$\gamma$ is the principal molecular target in the development of insulin-sensitizing antidiabetic agents.[1] Several classes of compounds are known to activate PPAR$\gamma$, which includes a putative natural ligand composed of a long chain fatty acid, cyclopentenone prostaglandins, thiazolidinediones, phenylacetic acids, and tyrosine-based compounds.[1]

Troglitazone, the first member of the class to be approved for clinical use, was removed from the market because of its association with rare, idiosyncratic life-threatening hepatitis.[2] Two later approved TZDs, pioglitazone and rosiglitazone (Chart 1), appear not to have this problem. Several TZDs and non-TZD PPAR$\gamma$ agonists are under intensive clinical development for the treatment of Type 2 diabetes and other components of the metabolic (insulin resistance) syndrome, including hypertriglyceridemia, hypertension and increased cardiovascular risk. Notwithstanding the hepatitis seen with troglitazone, the TZDs have proven to be generally safe compounds. In addition, several phenyl acetic and propionic acid derivatives have also been reported to activate PPAR$\gamma$ both in vitro and in vivo.[3−8] However, in animal and human studies, both TZD and non-TZD full PPAR$\gamma$ agonists have been shown to cause significant fluid retention, leading to an increase in intravascular volume by approximately 15%.[9] This is especially problematic in the target population for which these drugs are used. According to the recently published NCEP-ATP III Guidelines,[10] diabetes is designated a coronary heart disease (CHD) risk equivalent. Therefore, TZDs further predispose diabetics to significant risk of volume overload, systemic edema, and exacerbation of congestive heart failure. Thus, there is a substantial need for development of both TZD and non-TZD insulin-sensitizing PPAR$\gamma$ agonists that lack the adverse effect of fluid retention.

**Chart 1.** Structures of Representative Thiazolidinedione PPAR$\gamma$ Agonists




α-Lipoic acid (1,2-dithiolane-3-pentanoic acid), a potent antioxidant and free radical scavenger, is widely used for the treatment of aging skin and has also been reported to have beneficial effects on glucose metabolism[11] and blood pressure.[12] In eukaryotic dehydrogenases, it is covalently bound to a lysine residue. Exogenously supplied lipoic acid is taken up readily by a variety of cells and tissues where it is reduced rapidly to dihydrolipoic acid. Additionally it has been reported to have antiinflammatory and cytoprotective effects.[13]

Herein we report the design, synthesis, and biological evaluation of a unique class of hybrid lipoic-TZD derivatives,

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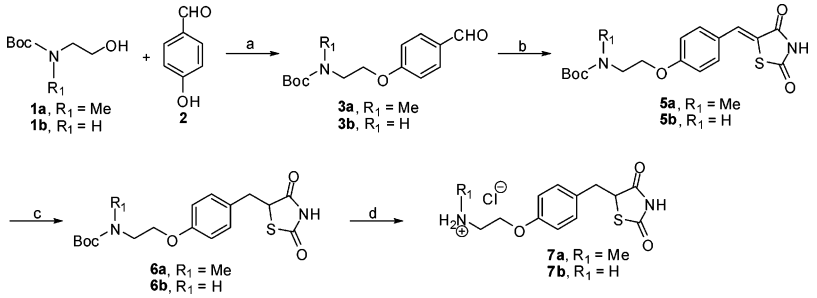
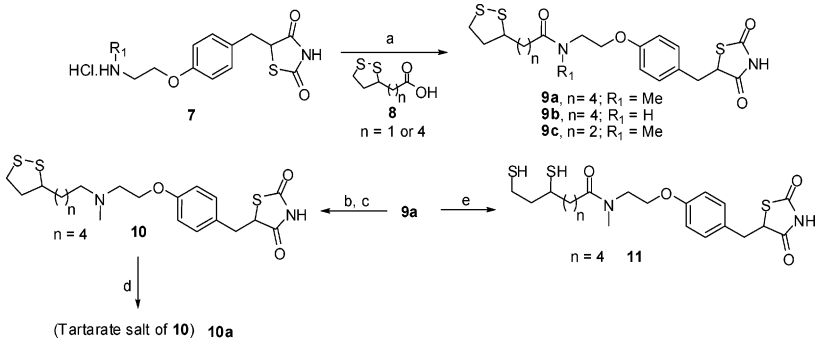
**Scheme 1**[a]




[a] Reagents and conditions: (a) $Ph_3P$, DIAD, THF, 0 °C to room temperature, 3 h, **3a** (58%), **3b** (61%); (b) 1,3-thiazolidine-2,4-dione **4**, benzoic acid, piperidine, reflux, 6 h, **5a** (89%), **5b** (93%); (c) Mg, methanol, 0 °C to room temperature, 4 h, **6a** (78%), **6b** (80%); (d) 4 M HCl in dioxane, 0 °C, 30 min **5a** (98%), **5b** (98%).

**Scheme 2**[a]




[a] Reagents and conditions: (a) i-PrOCOCl, $Et_3N$, DCM, 3 h, **9a** (72%), **9b** (64%), **9c** (56%); (b) alane−dimethylamine complex, THF, 0 °C, 15 min; (c) $I_2$, $NaHCO_3$, EtOAc (47% two steps); (d) DL-tartaric acid, THF, rt, 12 h, 92%; (e) $NaBH_4$, THF−$H_2O$, 0 °C, 1 h, 86%.

some of which were shown to induce transactivation of human PPARγ in the low nanomolar range, and describe aspects of their structure−activity relationship (SAR) with respect to their ability to transactivate PPARγ.[14−18] Results of molecular modeling studies explaining the SAR are also presented.

## Chemistry

The thiazolidinediones **7a** and **7b** were prepared according to a reported procedure[19] by coupling 4-hydroxybenzaldehyde **2** with Boc-protected alcohol **1** under Mitsunobu conditions to give aldehyde **3** (Scheme 1). Condensation of **3** with 2,4-thiazolidinedione in the presence of piperidine[20] gave the benzylidene **5**, which was reduced to the saturated 2,4-thiazolidinedione **6** using Mg/MeOH.[21] Removal of the Boc protecting group was accomplished employing anhydrous HCl in dioxane[22] to furnish the amine hydrochloride **7**. Condensing the amine **7** with acid **8** via the mixed anhydride gave amide **9a** or **9b** in which R = Me or H, respectively (Scheme 2). Treatment of **9a** with alane-*N*,*N*-dimethylethylamine [$C_2H_5N$-$(CH_3)_2$.$AlH_3$] complex[23] led to reduction of the amide carbonyl as well as the dithiolane ring. Reoxidation[24] of the dithiol to the disulfide (dithiolane ring) could be achieved using iodine and sodium bicarbonate to give the amine **10**. Reduction of the dithiolane ring S−S bond alone was readily achieved using sodium borohydride[25] in THF:$H_2O$ (10:1) furnishing the dithiane **11**.

To improve the pharmacokinetic profile of compound **9a** (vide infra), prodrugs were synthesized as described in Scheme 3. Starting with the dithiol **11**, treatment with succinic anhydride led to a mixture of bis acids **11b** along with the primary thioether mono-acid **11c**. The remaining free thiol moiety of **11c** could be differently reacted then to furnish mixed esters-acids such as **11d**. Alternatively, the hydrophilic diacetate **11a** was readily furnished upon exposure of **11** to acetic anhydride.

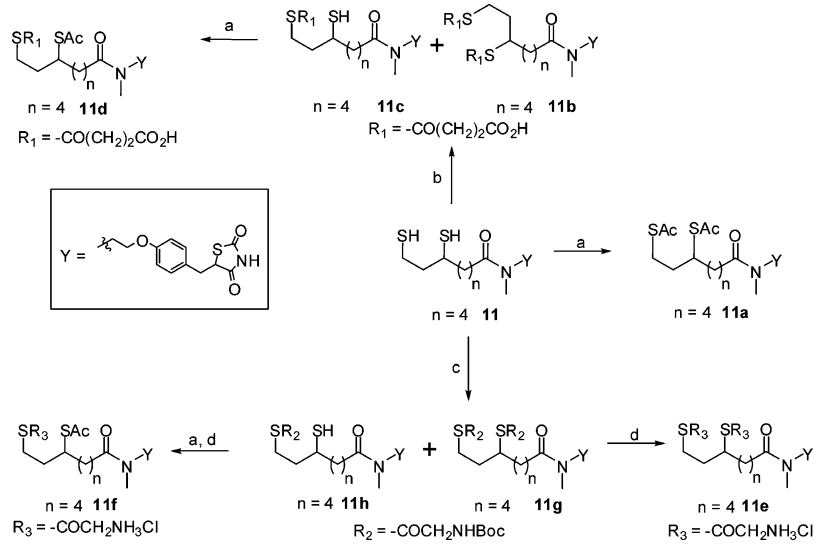
Finally, mono and bis-Boc-glycinates **11h** and **11g** were prepared from **11** by coupling with Boc-glycine. Deprotection and HCl salt formation occurred upon exposure of **11g** to anhydrous HCl to give **11e**. The mono glycinate (**11h**) was acylated and then deprotected-salted to give **11f**.

To study the effect of the spacer between the amide nitrogen and the phenoxy acid group,[26] derivatives with two and three methylene spacers, **18a** and **18b**, respectively, were synthesized as described in Scheme 5. These isosteres of TZD were prepared by coupling phenol **13** with alcohol **14** using diisopropyl azodicarboxylate (DIAD) and triphenylphosphine. Removal of the BOC group was accomplished using HCl in dioxane to afford the dialkylammonium chloride **16**. Coupling of this amine with lipoic acid using a mixed anhydride method in methylene chloride provided the ester-amide **17**.

Hydrolysis of the ester group of **17** employing sodium hydroxide furnished the acid **18** (Scheme 5). To study the effect of the spacer between the amide nitrogen and the phenoxy acetic acid group, derivatives with two (**18a**)- and three (**18b**)-methylene spacers were synthesized (Scheme 5) in routine fashion as in the prior scheme.

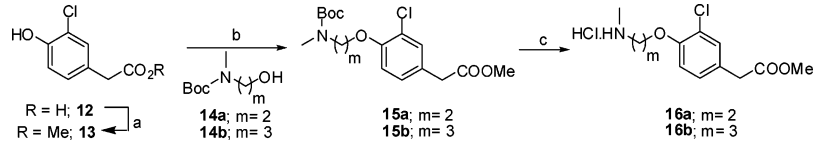
Of related interest, the effect of removal of the ethoxy spacer between the amide and the benzene ring could be studied by synthesis of compound **24** in which the amide nitrogen atom was directly attached to the phenyl ring. To achieve this goal, the aniline derivative **21**[27] was prepared from 4-hydroxybenzaldehyde **2** as described in Scheme 6. The 4-hydroxybenzaldehyde **2** was alkylated with the chloroacetamide **19** to give aryl ether **20**. Treatment of the amide **20** with KOH in toluene led to the 4-*N*-methylaminobenzaldehyde **21** (Mechanism provided as Scheme A in Supporting Information). The aldehyde **21** was then condensed with 2,4-thiazolidinedione **4** to give **22**, and reduction of the double bond using Mg metal in methanol at room temperature led to the saturated thiazolidinedione **23**.

**Scheme 3**[a]



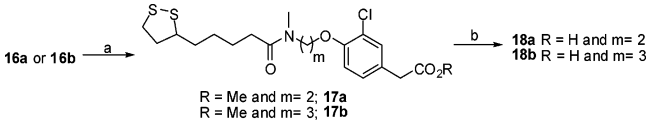
[a] Reagents and conditions: (a) $Ac_2O$ (2 equiv), pyridine, rt, 2 h, **11a** (88%), **11d** (76%); (b) succinic anhydride (1.2 equiv), pyridine, rt, 8 h, **11c** (51%) and **11b** (13%); (c) $BocNHCH_2CO_2H$, DCM, EDAC, HOBt, rt, 12 h, **11g** (72%), **11h** (21%); (d) 4 N HCl in dioxane, 0 °C, 30 min **11e** (76%), **11f** (45%, two steps).

**Scheme 4**[a]



[a] Reagents and conditions: (a) MeOH, $H_2SO_4$, reflux, 6 h, 95%; (b) $Ph_3P$, DIAD, THF, 0 °C to room temperature, 3 h, **15a** (69%), **15b** (63%); (c) 4 M HCl in dioxane, 0 °C, 30 min, **16a** (93%), **16b** (87%).

**Scheme 5**[a]



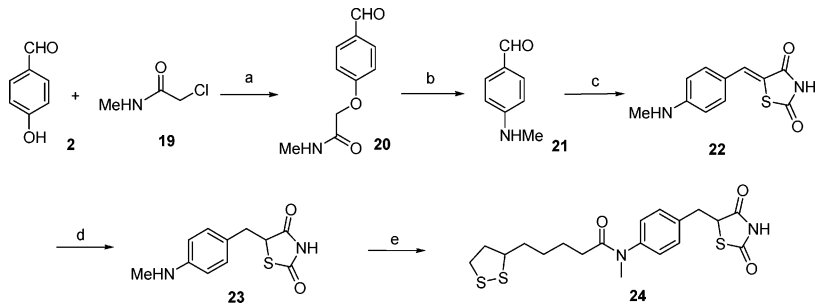
[a] Reagents and conditions: (a) r*ac*-lipoic acid, i-PrOCOCl, $Et_3N$, DCM, 3 h, **17a** (79%), **17b** (69%); (b) NaOH, MeOH, $H_2O$, rt, 3 h, **18a** (97%), **18b** (93%).

Coupling of the amine **23** with lipoic acid using hydroxy benzotriazole (HOBT) and *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDAC) furnished the target amide **24**.

## Results and Discussion

The PPAR$\gamma$ ligand binding domain (LBD) is a Y-shaped cavity extending from the C-terminal helix to the $\beta$-sheet lying between helices H3 and H6. This latter region is mostly hydrophobic and is buried mainly in the bottom half of the ligand binding domain (Figure 1).[28] In the cocrystal structure of rosiglitazone with PPAR$\gamma$ LBD (PDB id: 2PRG),[28] the TZD headgroup of rosiglitazone appears to be oriented toward the left-most part of this Y-shaped cavity and forms several primary and secondary hydrogen bonds with critical residues of the AF-2 helix of PPAR$\gamma$ including His323, His449, and Tyr473 (Figure 2). It has been clearly illustrated that the presence of these hydrogen bonds are crucial for agonist activity of PPAR$\gamma$ ligands.[28] It is believed that in response to these hydrogen bonding interactions, the AF2 helix closes onto the ligand-binding site and establishes a transcriptionally active form of the receptor which further recruits a coactivator protein to effectively stimulate gene transcription. Rosiglitazone appears to occupy roughly 40% of the ligand binding domain, while the rest of the space, largely in the downward hydrophobic arm of the Y-shaped pocket of the PPAR$\gamma$ receptor, remains unoccupied (Figure 1).[28] The large size and volume (~1300

**Scheme 6**[a]



[a] Reagents and conditions: (a) $K_2CO_3$; (b) KOH, toluene; (c) 1,3-thiazolidine-2,4-dione **4**, benzoic acid, piperidine, reflux, 6 h, 89%; (d) Mg, methanol, 0 °C to room temperature, 12 h, 73%; e) *rac*-lipoic acid, TEA, DCM, EDAC, HOBt, rt, 12 h, 78%.

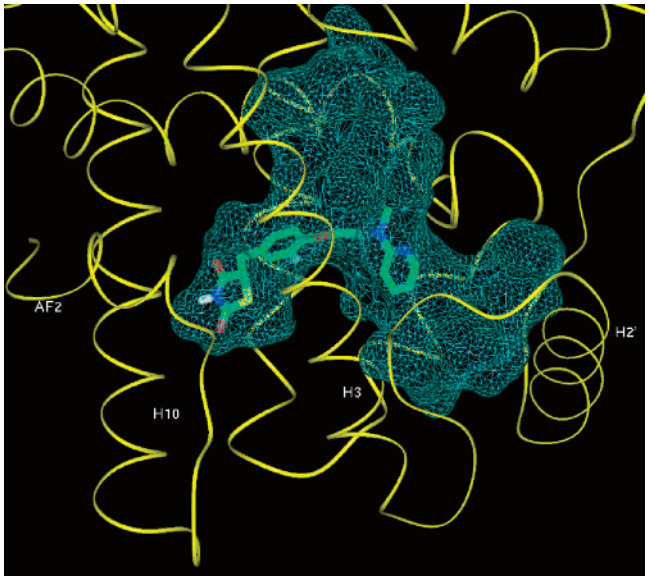



**Figure 1.** The ligand binding domain of the PPARγ receptor with cocrystallized rosiglitazone (colored by atom type). The receptor protein is shown as simplified ribbons (yellow), and the binding pocket is outlined as cyan-colored mesh. The binding pocket (mesh) was calculated using the Binding Site Analysis module in InsightII (2000).[19]

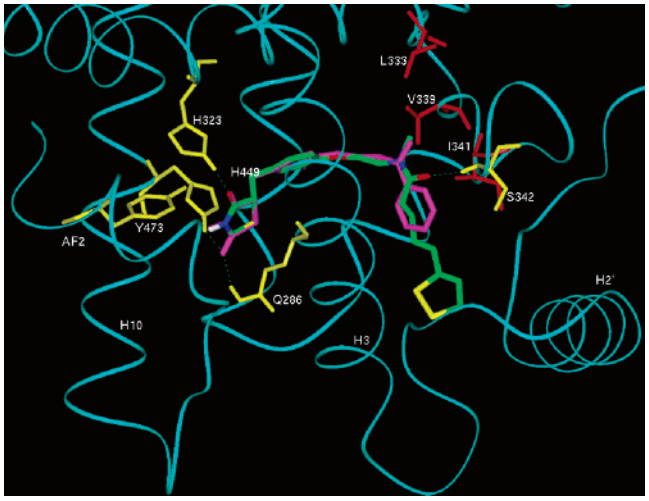
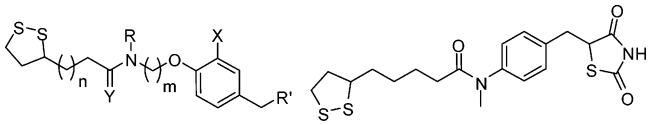



**Figure 2.** The proposed binding mode of **9a** (green) superimposed on the cocrystal structure of rosiglitazone (magenta) in the PPARγ LBD. The protein backbone is represented as a ribbon (cyan). Important residues of the AF-2 helix are shown in yellow. Important hydrogen bonds are illustrated as green dotted lines. Hydrophobic residues surrounding the *N*-methyl group of **9a** are shown in red.

Å$^3$) of the LBD explains its affinity to ligands of diverse sizes ranging from endogenous substrates such as fatty acid derivatives to synthetic ligands such as fibrates and thiazolidinedione (TZD) derivatives.[28] Recently, several 5-substituted 2-benzoylaminobenzoic acid (2-BABAs) PPARγ modulators have been reported to exert their effect without direct interaction with residues of the AF-2 helix. In fact, the X-ray crystal structures of these compounds with PPARγ have revealed a unique binding mode involving hydrogen bonding interactions with Ser342,[29,30] an amino acid residue occupying a different arm of the Y-shaped LBD.

On the basis of its hydrophobic nature and the ability to activate the PPAR receptors,[31] α-lipoic acid was chosen as a fragment for coupling with a common TZD pharmacophore to exploit the downward hydrophobic portion of the Y-pocket. The additional hydrophobic interaction is expected to improve the binding affinity of the ligands toward the receptor. Additionally, the presence of the lipoic acid moiety might attribute additional antiinflammatory and cytoprotective effects and may be related to its ability to reduce oxidative stress. On the basis of these considerations, several TZD and phenyl acetic acid derivatives were synthesized and tested for their ability to transactivate the PPARγ receptor. The results of the transactivation assay are presented in Table 1.

**Table 1.** Transactivation of PPARγ by Novel TZD and Phenyl Acetic Acid Derivatives




9-10; 17-18 24

| compound | R[1] | X | Y | *m* | *n* | R | $EC_{50}$ (μM) |
|---|---|---|---|---|---|---|---|
| **9a** | TZD | H | O | 2 | 3 | Me | 0.015 |
| **9b** | TZD | H | O | 2 | 3 | H | 10 |
| **9c** | TZD | H | O | 2 | 1 | Me | i.a[a] |
| **10** | TZD | H | H2 | 2 | 3 | Me | 28.00 |
| HCl salt of **10** | TZD | H | H2 | 2 | 3 | Me | 11.05 |
| **10a** | TZD | H | H2 | 2 | 3 | Me | 11.05 |
| **17a** | $CO_2Me$ | Cl | O | 2 | 3 | Me | i.a |
| **17b** | $CO_2Me$ | Cl | O | 3 | 3 | Me | 18.49 |
| **18a** | $CO_2H$ | Cl | O | 2 | 3 | Me | i.a |
| **18b** | $CO_2H$ | Cl | O | 3 | 3 | Me | 12.30 |
| **24** | – | – | – | – | – | – | i.a |
| rosiglitazone | – | – | – | – | – | – | 0.076 |
| pioglitazone | – | – | – | – | – | – | 0.55 |

[a] i.a: inactive up to 30 μM.

When compared to rosiglitazone and pioglitazone, the two most widely prescribed drugs for the treatment of Type 2 diabetes, compound **9a** was 5 and 37 times more potent, respectively, in the transactivation assay. Surprisingly, the replacement of a methyl group on the amide nitrogen by hydrogen (**9b**) resulted in 1000-fold loss in activity (10 μM). Reduction of the amide functionality in **9a** to the amine **10** reduced the activity to the micromolar range as well. Reducing the chain length between the amide carbonyl and [1,2]-dithiolane ring from four methylenes as in **9a** to two methylenes as in **9c** abolished activity. Modification of the 2,4-thiazolidinedione by replacement with an isosteric acid/ester group and introduction of chlorine on the aromatic ring gave compounds **17a** and **18a** with loss of activity. Interestingly, introduction of an additional methylene group between the nitrogen and oxygen gave compounds **17b** and **18b** with activity in the range of 12−18 μM. Finally, *N*-acylanilide **24** was not detectably active.

To understand the reasons for this observed SAR, the compounds were docked in the cocrystal structure with rosiglitazone removed, using the PPARγ ligand binding domain (PDB id: 2PRG).[28] In general, docking studies for most of the compounds of this series revealed a binding mode very similar to that of rosiglitazone as shown in Figure 2. In the TZD headgroup, the phenyl ring as well as the two methylene linkers in most of the molecules adopted a similar conformation to that of rosiglitazone in the crystal structure. Compounds exhibiting transactivation of PPARγ were found to retain important hydrogen bonds with the AF-2 helix residues that are crucial for the activity of PPARγ agonists.[28] The *N*-methyl group, also present in rosiglitazone, was found to have favorable hydrophobic interactions with residues Ile341, Val339, and Leu333 (Figure 2). The carbonyl group next to the *N*-methyl also appeared to form a potentially important hydrogen bond with the backbone amide of Ser342 (vide supra). The hydrophobic dithiolane moiety was found to fit in the downward arm of the

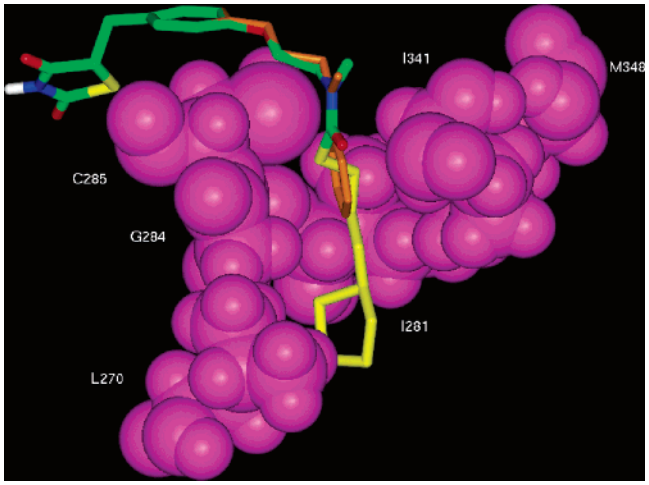



**Figure 3.** The proposed binding mode of **9a**, based on docking studies, reveal major hydrophobic interactions with the PPAR$\gamma$ LBD. For comparison, **9a** is superimposed on the receptor bound conformation of rosiglitazone (orange). Hydrophobic residues Leu270, Ile281, Gly284, Cys285, Ile341, and Met348 located in the downward arm of Y pocket interacting with **9a** are illustrated using CPK space filling models (magenta).

Y pocket and was involved in hydrophobic interactions with surrounding residues such as Cys285, Gly284, Ile281, Leu270, Met348, and Ile341. These hydrophobic interactions appear to improve the binding free energy of the ligand receptor complex. Such interactions have been proposed to contribute toward PPAR$\gamma$ binding affinity for a series of propionic acid derivatives.[32] However, it should be mentioned here that the most active compound of this series was as potent as rosiglitazone while compound **9a** in the present series is 5 times more potent than rosiglitazone.

Compound **9a** appears to meet all these requirements and is the most potent compound of the series. All the crucial hydrogen bonds with the AF-2 helix residues were found to be conserved (Figure 2). Additionally, hydrophobic interactions of the appended dithiolane moiety (Figure 3) and the presence of a Ser342 hydrogen bond (Figure 2) appear to be significant contributors toward its high potency. Compound **9b**, which lacks the *N*-methyl group, appears to lose some of the important hydrophobic interactions with surrounding residues such as I341, V339, and L333. The *N*-methyl group in rosiglitazone as well as **9a** was found to be similarly pointing upward, and its presence seemed essential for retaining the activity of the amide series. Similar behavior has also been observed for certain oxime analogues containing a 5-benzyl-2,4-thiazolidinedione moiety,[33,34] where removal of the *N*-methyl group from the compound was found to retard binding to the PPAR$\gamma$ receptor compared to the bioactive methyl analogue. Therefore, it might be hypothesized that the lower activity of **9b** could be due to the loss of hydrophobic interactions of the *N*-methyl group with complementary residues in the portion of the receptor. An additional explanation could include the probable metabolic differences between [N(H)C═O vs N($CH_3$)C═O], the former amide being more readily cleaved by peptidases and thereby deactivated (**7** has low potency).

Removing the linker between the nitrogen and the phenyl ring in **9a** furnished compound **24**, which is three atoms shorter than the prototype compounds of the series. In the binding mode proposed by the docking studies, the TZD ring of **24** was not able to interact with the residues of the AF-2 helix as clearly seen in Figure 4. This leads to loss of the critical hydrogen bonds paramount for the PPAR$\gamma$ receptor activity of the TZD


**Figure 4.** The proposed binding mode of **24** (magenta) in the PPAR$\gamma$ LBD superimposed on that of **9a** (yellow). Only important residues (colored by atom type) of the protein are shown. Hydrogen bonds are denoted as green dotted lines.

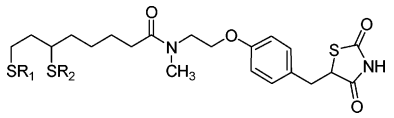
containing analogues. The increased distance between amide carbonyl and backbone hydrogen of Ser342 also results in loss of a hydrogen bond with this residue. These factors taken together would appear to explain the inability of **24** to induce transactivation of PPAR$\gamma$.

Modification of the 2,4-thiazolidinedione by replacement with isosteric acid/ester group and introduction of chlorine on the aromatic ring gave compounds **18a** and **18b**. On the basis of docking studies, the terminal carboxylate group in **18a** did not appear to form hydrogen bonds with all of the critical residues of the AF-2 helix. Lack of a putatively crucial tripartite hydrogen bonded group interaction might be one of the plausible reasons for the loss of activity of this compound. Interestingly, introduction of one additional methylene group between the side chain N and O produced the corresponding analogue **18b** having value of 12.30 $\mu$M activity. Docking of this compound revealed that the terminal carboxylate group was pushed forward toward the critical residues of the AF-2 helix, allowing **18b** to retain the important hydrogen bonds responsible for activation of the PPAR$\gamma$ receptor.

To summarize the SAR, the optimum spacer between N and O were found to be two methylenes for TZD derivatives and three methylenes in the case of phenyl acetic acid derivatives. We also found that a tetramethylene moiety was the optimal spacer between the amide carbonyl and the 1,2-dithiolane moiety. In the present series, compounds having a TZD as a headgroup were more potent than the corresponding carboxylate derivatives. The *N*-methylamide moiety seems to be important but not absolutely essential for potent agonist activity. On the basis of docking comparisons with this PPAR-$\gamma$ activity, it appears for this class that an L-shaped bend is enforced by the amide group. Optimal lengths for the arms of this "L" appear to be approximately 10 Å. More detailed SARs at this position are in progress.

The prodrug approach is commonly used to improve physicochemical, biopharmaceutical, and drug delivery properties of therapeutic agents. Ideally, an inactive pro-moiety is covalently attached to the parent molecule, and the resulting prodrug is converted to the parent drug in the body before it exhibits its pharmacological effect.[35,36] Compound **9a** has very low solubility in water (39 $\mu$g/mL). To overcome this problem, the S−S bond was reduced to the dithiol derivative **11** which showed considerable activity. Derivatization to give mono and dithio-amides gave more soluble derivatives (**11a**−**f**) that in many cases could be safely assumed to be more soluble and therefore more bioavailable candidates than the aqueously

**Table 2.** Transactivation of PPARγ by TZD-lipoate Derivatives



| compd | $R_1$ | $R_2$ | $EC_{50}$, μM | max. fold activation at 10 μM |
|---|---|---|---|---|
| **11** | H | H | 0.075 | 129.0 |
| **11a** | $COCH_3$ | $COCH_3$ | 0.039 | 149.9 |
| **11b** | $CO(CH_2)_2CO_2Na$ | $CO(CH_2)_2CO_2Na$ | 0.080 | 60.0 |
| **11c** | $CO(CH_2)_2CO_2Na$ | H | 0.02 | 177.2 |
| **11d** | $CO(CH_2)_2CO_2Na$ | $COCH_3$ | 0.15 | 168.4 |
| **11e** | $COCH_2NH_3Cl$ | $COCH_2NH_3Cl$ | 0.06 | 71.0 |
| **11f** | $COCH_2NH_3Cl$ | $COCH_3$ | 0.195 | 138.1 |

**Table 3.** Inhibition of PHA/PMA-Induced Interleukin-2 Secretion in Human T Lymphocytes by Rosiglitazone and Compounds **9a**, **11**, and **11e**

| T lymphocytes + PHA/PMA | IL-2 released | percent inhibition (pg/mL supernatant) |
|---|---|---|
| control (no drug) | 456 + 28 | - - |
| 10 μM rosiglitazone | 112 + 7 | 75 |
| 10 μM compound **9a** | 37 + 7 | 92 |
| 10 μM compound **11** | 91 + 6 | 80 |
| 10 μM compound **11e** | 37 + 6 | 92 |

(biologically) intractable dithiolane **9**. Because **11** could be oxidized chemically to **9**, it was assumed that **11** would revert to **9** by oxidation in vivo. The acyl derivatives of **11** should also serve after enzymatic hydrolysis, as precursors to **11** and hence **9**. The prodrugs of **11** had comparable activity in the nanomolar range but were more easily dissolved for bioassay. Careful pharmacodynamic studies to obtain exact bioavailability figures seemed premature at this point of the research but may be worthy of more detailed exploration at a later time.

Since compound **9a** was considered the primary drug from its prodrugs and because it had potent PPARγ activity, it was selected as a representative member for further biological activities.

**Effect on Inflammatory Interleukin Production.** TZDs have been shown to inhibit the activation of human peripheral blood lymphocytes and their production of inflammatory interleukins, such as interleukin (IL)-1β, IL-2, IL-6, interferon-γ (INFγ), and tumor necrosis factor-α (TNF-α).[37,38] The effects of compounds **9a**, etc. (**9a**, **11**, **11e**) compared to rosiglitazone on T lymphocte activation are shown in Table 3. The assay measured as the ability of the compounds to inhibit IL-2 production by mitogen-stimulated peripheral blood mononuclear cells, enriched in T lymphocytes.[31] At a concentration of 10 μM, compounds **9a**, **11e**, and **11** were more effective inhibitors of T lymphocyte IL-2 production than rosiglitazone. PPARγ activation has been shown to inhibit IL-2 production in T lymphocytes.[39]

**Effect on Adipocyte Differentiation and Adipogenesis.** Differentiation of preadipocytes into adipocytes is part of a metabolic response to nutritional and hormonal signaling and requires a cascade of changes in gene expression. Studies have suggested the importance of PPARγ in mediating such changes during terminal adipocyte differentiation. It is known that adipocyte differentiation depends on PPARγ [40−42] and forced expression of PPARγ and/or administering potent PPARγ agonists promotes adipose conversion of fibroblasts and myoblasts.[43,44] Compounds **9a** and **11e** and rosiglitazone similarly promoted the differentiation of murine 3T3-L1 preadipocyte fibroblasts ($IC_{50}$ ~ 0.6 μM) in culture by inducing terminal differentiation and lipid accumulation shown by staining the lipid-laden maturing adipocytes with Oil Red O (Figure 5).

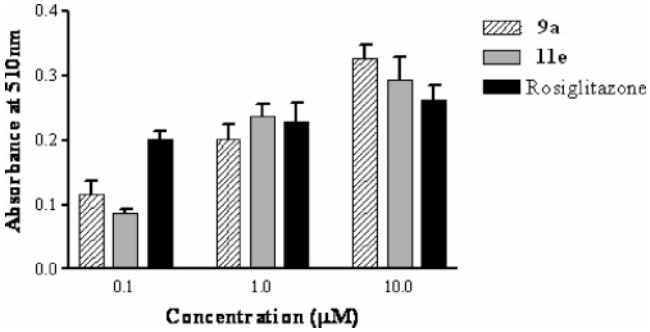



**Figure 5.** Induction of adipogenesis by rosiglitazone and compounds **9a** and **11e**.

**Table 4.** Antiproliferative Effects of Rosiglitazone, **9a**, and **11e**

| | $IC_{50}$ (μM) | | |
|---|---|---|---|
| human cell type | rosiglitazone | **9a** | **11e** |
| keratinocytes (primary culture) | 8 | 0.6 | 1 |
| HT-29 colon cancer cells | 45 | 10 | 8 |
| MCF-7 breast cancer cells | >50 | 15 | 25 |

**Effect on Growth of Human Keratinocytes.** Inflammatory, proliferative skin diseases such as psoriasis are associated with inappropriate hyperproliferation of keratinocytes and production of inflammatory cytokines, particularly IL-2, by T lymphocytes which invade the epidermis and contribute to the pathophysiology of the disease.[45] Table 4 shows the inhibitory effects of compounds **9a** and **11e** on proliferating human keratinocytes in culture. Both compounds **9a** and **11e** were approximately an order of magnitude more effective than rosiglitazone at inhibiting keratinocyte proliferation.[46] PPARγ activation has been shown to inhibit IL-2 production in T lymphocytes.[39]

**Effect on MCF-7 Breast Cancer Cells.** It has been suggested that the PPARγ transcriptional pathway could induce terminal differentiation of malignant breast epithelial cells and offers a nontoxic therapy for human breast cancer.[47] It has also been observed that treatment of MCF-7 breast cancer cell line with troglitazone, a thiazolidinedione, for 4 days reversibly inhibited cancer cell growth. This is mediated by inhibition of cellular proliferation by blocking certain critical events for G1/S phase progression. Compounds **9a** and **11e** were more effective than rosiglitazone at inhibiting the proliferation of MCF-7 human breast cancer cells (Table 4).

**Effect on H29 Colon Cancer Cells.** Rosiglitazone has been shown to induce differentiation in HT-29 cells, resulting in the inhibition of G1/S mitotic growth transition, resulting in inhibition of cell proliferation. [48] Our newly synthesized compounds **9a** and **11e** similarly inhibited the proliferation of HT-29 human colon cancer cells but were more potent than rosiglitazone in this regard. The $IC_{50}$ values are shown in Table 4. The $IC_{50}$ values shown in Table 4 are unlikely to be physiologically relevant, although other members of this class may be designed to improve the inhibitory potency in certain cancer cell lines.

**Toxicity Studies.** At all concentrations of rosiglitazone and synthetic compounds used in these studies, there was no evidence of cytotoxicity.

**Insulin-Sensitizing and Antidyslipidemic Effects in the Insulin-Resistant Zucker Fatty (fa/fa) Rat.** The first potent PPARγ agonist prototype synthesized, compound **9a**, was tested to determine its antidiabetic and triglyceride-lowering activities. The insulin resistant, genetically obese fa/fa Zucker rat is a

**Table 5.** Insulin Sensitizing and Triglyceride Lowering Effects of **9a** in Zucker Rats[a]

| | insulin (ng/mL) | glucose (mg/dL) | triglycerides (mg/dL) |
|---|---|---|---|
| control ($n = 8$) | 6.3 + 1.6 | 182 + 8 | 320 + 39 |
| **9a** ($n = 8$) | 1.4 + 0.2* | 180 + 19** | 54 + 4* |

[a] *$p < 0.025$; **N.S.

widely used animal model of Type 2 diabetes for the development of insulin-sensitizing and antidiabetic pharmaceutical agents, including the thiazolidinediones. The test group of insulin resistant, Zucker rats were given a dose of 100 mg/kg body weight of compound **9a**, or vehicle only (see Methods). The results are shown in Table 5. Although there was no effect on blood glucose over the period of time studied (4 weeks), compound **9a** produced a marked (78%) reduction in serum insulin levels. The body weight within both groups were similar. Food intake was not measured.

The genetically obese Zucker (fa/fa) fatty rat has been widely used as an animal model of type 2 diabetes in the development of antidiabetic drugs, particularly thiazolidinediones, for the identification and development of potential antidiabetic pharmaceutical agents.[49] However, this (fa/fa) rat, has been shown to have a missense point mutation (A→C) which results in an amino acid substitution at position 269 (Gln→Pro) in the extracellular ligand binding domain of the leptin receptor.[50] This mutation, which leads to severe insulin resistance and the development of type 2 diabetes, is exceedingly rare in humans and is not the determinant for common place type 2 diabetes seen in humans. Of interest is the fact that, unlike other thiazolidinediones which have demonstrable glucose-lowering effects, these lipoic acid derivatives, represented by compound **9a**, may be less effective in the Zucker genetic model and should therefore be tested in a dietary (high-fat, high-carbohydrate fed) model of insulin resistance, which more closely reflects obesity-related, insulin-resistant diabetes seen in humans. It should be noted that different PPAR$\gamma$ ligands can have variable effects in different in vivo animal models.[51,52]

Of considerable interest was the 83% reduction in triglycerides by compound **9a**. In comparison, rosiglitazone reduced triglycerides by approximately 40% in Zucker rats.[53] The ability for compound **9a** to activate PPAR$\alpha$ in the mouse construct was tested and determined to be 40 $\mu$M, which is similar to the well-known antidyslipidemic fibrates, known PPAR$\alpha$ agonists. This could account for the triglyceride-lowering effect shown in Table 5. These data indicate that **9a** and likely other related compounds in this class would be efficacious in improving insulin sensitivity and reducing triglycerides in insulin resistant, Type 2 diabetic patients and patients with primary (familial) or secondary hypertriglyceridemia (Table 5).

## Conclusion

In conclusion, we have discovered potent antidiabetic activity in a series of [1,2]-dithiolane pentamide thiazolidinediones. Comparisons of SAR with the docked structures revealed that the members of this subclass of PPAR$\gamma$ agonists have an enforced L-shape with an approximate 90° bend that fits into the Y-shaped or perhaps more aptly T-shaped LBD of the PPAR$\gamma$ agonist crystal structure. Each span of the "L" is optimally 9−12 Å with one acidic end and another lipophilic end. Compound **9a** is one of the most potent of such compounds and additionally has an effect on the growth of normal keratinocytes and neoplastic cells. Therefore, these novel compounds may prove efficacious not only in the treatment of type-2 diabetes, but also in atherosclerosis, prevention of vascular restenosis, inflammatory bowel disease, inflammatory skin diseases such as psoriasis and atopic dermatitis, neurodegenerative diseases such as multiple sclerosis and Alzheimer's disease, and neoplasms.[54]

## Experimental Section

**General Methods.** All reactions were carried out under an argon atmosphere with dry, appropriately distilled solvents stored over dried 4 Å molecular sieves (at least 24 h) using anhydrous techniques and conditions, unless otherwise stated.[1] To monitor reaction progress and chromatography fractions, thin-layer chromatography (TLC) was performed on precoated silica gel G or GP Uniplates from Analtech. The plates were visualized with a 254-nm UV light, iodine chamber, or charring with dilute sulfuric acid. Flash chromatography was carried out on silica gel 60 [Scientific Adsorbents Incorporated (SAI), particle size 32−63 $\mu$m, pore size 60 Å]. IUPAC names were generated using ACD/Name software, version 9.04 (ACD/Labs 9.00 release). Melting points were determined on an OptiMelt V.1.061 (Stanford Research Sysems, 2005) apparatus and are uncorrected. $^1$H NMR and $^{13}$C NMR spectra were recorded on Bruker 300, 400, and 500 MHz NMR machines. The chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane, and *J*-values are in Hz. IR spectra were recorded using a Thermo-Nicolet IR 300 FT/IR spectrometer on a germanium crystal plate as neat solids or liquids. The high-resolution mass spectra (HRMS) were recorded on a Micromass Q-Tof Micro mass spectrometer with lock spray source.

**Procedure for the Preparation of Ether 3a or 3b.** To a solution of *N*-methyl-*N*-Boc alcohol (2.86 mmol), phenol (3.42 mmol) and triphenylphosphine (1.12 g, 4.3 mmol) in dry THF (20 mL) was added diisopropyl azodicarboxylate (0.85 mL, 0.87 g, 4.3 mmol) dropwise at 0 °C, and the mixture was allowed to stir for 3 h at room temperature. THF was removed under reduced pressure, and the resulting residue was dissolved in EtOAc (50 mL), washed with 1 N NaOH (10 mL), water (10 mL), and brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated. The crude product was purified by column chromatography with ethyl acetate and hexanes to yield the coupled product.

***tert*-Butyl [2-(4-formylphenoxy)ethyl]methylcarbamate (3a):** White crystalline solid, 58%; mp:63.5−65.6 °C; $^1$H NMR ($CDCl_3$, 500 MHz): 1.47 (s, 9H), 2.99 (s, 3H), 3.64 (s, 2H), 4.20 (bs, 2H), 7.01 (d, $J = 8.5$ Hz, 2H), 7.84 (d, $J = 8.5$ Hz, 2H), 9.89 (s, 1H); $^{13}$C NMR ($CDCl_3$, 125 MHz): 28.8, 35.8, 36.5, 48.4, 66.7, 67.2, 80.0, 114.7, 130.0, 131.9, 155.6, 163.5, 190.4; HRMS calcd for $C_{15}H_{22}NO_4$ $[M + H]^+$ 280.1549, found 280.1544.

***tert*-Butyl [2-(4-formylphenoxy)ethyl]carbamate (3b):** White crystalline solid, 61%; mp: 87.9−89.8 °C;; $^1$H NMR ($CDCl_3$, 500 MHz): 1.46 (s, 9H), 3.58 (d, $J = 4.5$ Hz, 2H), 4.12 (t, $J = 5$ Hz, 2H), 5.10 (bs, 1H), 7.01 (d, $J = 8.5$ Hz, 2H), 7.84 (d, $J = 9$ Hz, 2H), 9.89 (s, 1H); $^{13}$C NMR ($CDCl_3$, 125 MHz): 28.7, 40.2, 67.7, 79.8, 114.7, 130.1, 131.9, 155.7, 163.3, 190.4; HRMS calcd for $C_{14}H_{20}NO_4$ $[M + H]^+$ 266.1392, found 266.1385.

**Procedure for the Preparation of 5.** A mixture of benzaldehyde (**3**, 10 mmol), thiazolidine-2,4-dione (1.17 g, 10 mmol), benzoic acid (0.160 g, 1.3 mmol), and piperidine (0.128 g, 150$\mu$L, 1.5 mmol) in toluene (25 mL) was refluxed for 6 h with continuous removal of water using a Dean−Stark apparatus. The reaction mixture was cooled to room temperature, and the resulting solid was collected by filtration, washed with water, and dried to afford **5**.

***tert*-Butyl (2-{4-[(*Z*)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)-methyl]phenoxy}ethyl)methylcarbamate (5a):** Bright yellow solid, 89%; mp: 157.2−160 °C; $^1$H NMR ($CD_3OD$, 500 MHz): 1.46 (s, 9H), 2.98 (s, 3H), 3.67 (bs, 2H), 4.26 (bs, 2H), 7.14 (d, $J = 8.5$ Hz, 2H), 7.59 (d, $J = 8.5$ Hz, 2H), 7.73 (s, 1H); $^{13}$C NMR ($CD_3OD$, 125 MHz): 28.0, 34.6, 44.3, 48.0, 66.4, 78.9, 115.2, 122.5, 126.2, 131.0, 131.9, 160.2, 167.9, 168.3; HRMS calcd for $C_{18}H_{23}N_2O_5S$ $[M + H]^+$ 379.1328, found 379.1325.

***tert*-Butyl (2-{4-[(*Z*)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)-methyl]phenoxy}ethyl)carbamate (5b)**: Yellow solid, 93%; mp: 165.2−166.5 °C; $^1$H NMR (DMSO-$d_6$, 500 MHz): 1.40 (s, 9H), 3.32 (t, $J$ = 5.5 Hz, 2H), 4.05 (t, $J$ = 5.5 Hz 2H), 7.05 (t, $J$ = 1.5 Hz, 1H), 7.11 (d, $J$ = 8.5 Hz, 2H), 7.56 (d, $J$ = 8.5 Hz, 2H), 7.76 (s, 1H); $^{13}$C NMR (DMSO-$d_6$, 125 MHz): 29.0, 40.0, 67.3, 78.4, 115.8, 121.0, 126.0, 132.0, 132.4, 160.4, 167.9, 168.3; HRMS calcd for $C_{17}H_{21}N_2O_5S$ $[M + H]^+$ 365.1171, found 365.1154.

**Procedure for the Preparation of 6.** A solution of thiazolidine-2,4-dione (**5**, 2 mmol) and magnesium turnings (1.0 g, 40 mmol) in dry MeOH (25 mL) was stirred at room temperature for 4 h. The reaction mixture was acidified with 6 N HCl to pH 6.5 and extracted with dichloromethane (2 × 15 mL). The combined organic layers were washed with water (10 mL) and brine (5 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed over silica gel using ethyl acetate and hexanes (4:6) to afford **6** as a colorless solid.

***tert*-Butyl (2-{4-[(2,4-dioxo-1,3-thiazolidin-5-yl)methyl]phenoxy}ethyl)methylcarbamate (6a)**: White solid, 78%; mp: 148.5−149.4 °C; $^1$H NMR ($CDCl_3$, 500 MHz): 1.47 (s, 9H), 2.98 (s, 3H), 3.09 (dd, $J$ = 9.5, 14.0 Hz, 1H), 3.47 (dd, $J$ = 3.5, 14.0 Hz, 1H), 3.60 (bs, 2H), 4.08 (bs, 2H), 4.49 (dd, $J$ = 3.5, 9.5 Hz, 1H), 6.85 (d, $J$ = 8.5 Hz, 2H), 7.15 (d, $J$ = 8.5 Hz, 2H), 9.30 (bs, 1H); $^{13}$C NMR ($CDCl_3$, 125 MHz): 28.8, 35.6, 38.1, 48.4, 54.0, 66.9, 80.2, 114.7, 115.2, 130.2, 156.4, 157.5, 170.6, 174.3; HRMS calcd for $C_{18}H_{25}N_2O_5S$ $[M + H]^+$ 381.1484, found 381.1492.

***tert*-Butyl (2-{4-[(2,4-dioxo-1,3-thiazolidin-5-yl)methyl]phenoxy}ethyl)carbamate (6b)**: White solid, 80%; mp: 121.2−122.7 °C; $^1$H NMR ($CDCl_3$, 500 MHz): 1.48 (s, 9H), 3.12 (dd, $J$ = 9.5, 14.0 Hz, 1H), 3.47 (dd, $J$ = 3.5, 14.0 Hz, 1H), 3.55 (bd, $J$ = 4 Hz,2H), 4.03 (t, $J$ = 5 Hz, 2H), 4.51 (dd, $J$ = 3.5, 9.5 Hz, 1H), 5.06 (bs, 1H), 6.87 (d, $J$ = 8.0 Hz, 2H), 7.17 (d, $J$ = 8.0 Hz, 2H), 8.96 (bs, 1H); $^{13}$C NMR ($CDCl_3$, 125 MHz): 28.7, 38.1, 40.4, 53.9, 67.4, 79.8, 114.7, 128.0, 130.3, 156.2, 157.8, 170.3, 174.1; HRMS calcd for $C_{17}H_{22}N_2O_5S$ $[M + Na]^+$ 389.1147, found 389.1141.

**Procedure for the Preparation of 7.** A solution of 4 N HCl in dioxane (10 mL) was added at once to a suspension of carbamates (**6**, 10 mmol) in anhydrous ether (25 mL) under a $N_2$ atmosphere at 0 °C, and the resulting mixture was allowed to stir for 30 min. The solvents were removed under vacuum to yield **7** as white amorphous solid.

**5-{4-[2-(Methylamino)ethoxy]benzyl}-1,3-thiazolidine-2,4-dione hydrochloride (7a)**: White solid, 98%; mp: 220.5−221.3 °C; $^1$H NMR ($CD_3OD$, 500 MHz): 2.81 (s, 3H), 3.17 (dd, $J$ = 9.0, 14.0 Hz, 1H), 3.38 (dd, $J$ = 4.0, 14.0 Hz, 1H), 3.46 (bs, 2H), 4.27 (bs, 2H), 4.73 (dd, $J$ = 4.0, 9.0 Hz, 1H), 6.98 (d, $J$ = 8.0 Hz, 2H), 7.24 (d, $J$ = 8.0 Hz, 2H); $^{13}$C NMR ($CD_3OD$, 125 MHz): 32.7, 37.1, 48.4, 53.5, 63.1, 114.3, 119.1, 129.5, 130.4, 157.0, 175.2; HRMS calcd for $C_{13}H_{16}N_2O_3S$ $[M + Na]^+$ 303.0779, found 303.0773.

**5-[4-(2-Aminoethoxy)benzyl]-1,3-thiazolidine-2,4-dione hydrochloride (7b)**: White solid, mp: 214.0−214.7 °C; 98%; $^1$H NMR ($CD_3OD$, 500 MHz): 3.16 (dd, $J$ = 9.0, 14.0 Hz, 1H), 3.38 (bs, 2H), 3.41 (dd, $J$ = 4.0, 14.0 Hz, 1H), 4.23 (bs, 2H), 4.73 (dd, $J$ = 4.0, 9.5 Hz, 1H), 6.98 (d, $J$ = 8.0 Hz, 2H), 7.23 (d, $J$ = 8.0 Hz, 2H); $^{13}$C NMR ($CD_3OD$, 125 MHz): 37.1, 39.2, 53.5, 64.0, 114.3, 129.4, 130.3, 157.1, 175.5; HRMS calcd for $C_{12}H_{15}N_2O_3S$ $[M + H]^+$ 267.0803, found 267.0795.

**General Procedure for the Preparation of Amides (9a−c).** To a 100 mL round-bottomed flask was added amine/amine hydrochloride (2.6 mmol) in anhydrous dichloromethane (30 mL). To this suspension triethylamine (0.37 mL, 2.7 mmol) was added at 0 °C, and the mixture was stirred at this temperature for an additional 10 min. Racemic lipoic/bisnorlipoic acid (2.7 mmol) was dissolved in anhydrous dichloromethane (20 mL) in a separate round-bottomed flask and was cooled to 0 °C. To this was added triethylamine (0.37 mL, 2.7 mmol) followed by the dropwise addition of isopropyl chloroformate (2.7 mL, 2.7 mmol, 1 M in toluene) over 10 min. The mixture was stirred for an additional 10 min at this temperature, and the resulting mixed anhydride was then transferred via cannula to the flask containing the free amine. The combined mixture was stirred at 0 °C for 1 h. Upon completion, water was added, and the aqueous layer was extracted with dichloromethane (2 × 50 mL). The combined organic layers were washed with 10% sodium bicarbonate (20 mL) and brine (20 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under vacuum, and the residue was chromatographed over silica gel (MeOH:$CHCl_3$, 1:99).

*N*-(2-{4-[(2,4-Dioxo-1,3-thiazolidin-5-yl)methyl]phenoxy}ethyl)-5-(1,2-dithiolan-3-yl)-*N*-methylpentanamide (9a): Viscous liquid, yield 72%; $^1$H NMR ($CDCl_3$, 300 MHz): 1.45 (m, 2H), 1.65 (m, 4H), 1.89 (m, 2H), 2.3 (t, $J$ = 7.4 Hz, 1H), 2.44 (m, 2H), 3.1 (m, 3H), 3.42 (dd, $J$ = 5 Hz, 18 Hz, 1H), 3.56 (m, 1H), 3.47 (t, $J$ = 6.7 Hz, 2H), 4.1 (t, $J$ = 6.7 Hz, 2H), 4.49 (dd, $J$ = 5, 12.3 Hz, 1H), 6.82 (d, $J$ = 8 Hz, 2H), 6.83 (d, $J$ = 8.6 Hz), 7.15 (d, $J$ = 8 Hz, 2H), 8.19 (bs, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz): 24.3, 24.7, 28.7, 28.8, 32.4, 32.9, 33.9, 34.6, 37.5, 37.6, 38.3, 39.9, 47.7, 48.9, 53.3, 65, 66.3, 114.5, 128.1, 130.2, 130.4, 157.5, 157.9, 170.7, 173.3, 174.5. HRMS calcd for $C_{21}H_{29}N_2O_4S_3$ $[M + H]^+$ 469.1284, found 469.1263; IR ($cm^{-1}$): 3030, 2926, 1752, 1696, 1609, 1512, 1303, 1244, 1154, 1052. HPLC (Method 1): 100% pure (1.65 min) at 241 nm; HPLC (Method 2): 99% pure (1.56 min) at 229.1 nm.

***N*-(2-{4-[(2,4-Dioxa-1,3-thiazolidine-5-yl)methyl]phenoxy}-ethyl)-5-(1,2-dithiolan-3-yl)pentanamide (9b):** Viscous liquid, 64%; $^1$H NMR ($CDCl_3$, 300 MHz): 1.5−1.45 (m, 2H), 1.75−1.5 (m, 6H), 1.8 (m, 2H), 2.2 (t, $J$ = 7.4 Hz, 1H), 2.3 (m, 2H), 3.2−3.0 (m, 3H), 3.4 (dd, $J$ = 4, 16 Hz, 1H), 3.5 (m, 1H), 3.6 (dd, 2H), 4.02 (t, $J$ = 5 Hz, 2H), 4.5 (dd, $J$ = 4, 9.3 Hz, 1H), 5.9 (bs, 1H), 6.83 (d, $J$ = 8.4 Hz), 7.14 (d, $J$ = 8.4 Hz, 2H), 8.3 (bs, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz): 25.7, 29.2, 30.3, 34.9, 36.7, 38, 38.8, 39.3, 40.6, 54, 56.7, 67.2, 115.1, 128.0, 130.9, 157.0, 170.0, 173.0, 174.0; HRMS calcd for $C_{20}H_{27}N_2O_4S_3$ $[M + H]^+$ 455.1127, found 455.1096; IR ($cm^{-1}$): 3021, 2926, 1752, 1698, 1609, 1516, 1303, 1234, 1159, 1052. HPLC (Method 1): 96% pure (1.89 min) at 241 nm; HPLC (Method 2): 94% pure (1.76 min) at 229.1 nm.

***N*-(2-{4-[(2,4-Dioxo-1,3-thiazolidin-5-yl)methyl]phenoxy}-ethyl)-3-(1,2-dithiolan-3-yl)-*N*-methylpropanamide (9c):** Viscous liquid, 56%; $^1$H NMR ($CDCl_3$): 2.0 (m, 1H), 2.65−2.80 (m, 3H), 3.0 (dd, $J$ = 4, 16 Hz, 1H), 3.1(m, 3H), 3.6 (m, 2H), 3.75 (t, 2H), 4.12 (t, $J$ = 5 Hz, 2H), 4.48 (dd, $J$ = 4, 9 Hz, 1H), 6.83 (d, $J$ = 8.6 Hz, 2H), 7.14 (d, $J$ = 8.4 Hz, 2H), 8.6 (bs, 1H); $^{13}$C NMR ($CDCl_3$): 34.4, 37.9, 38.1, 39.7, 40.0, 40.3, 48.5, 50.8, 51.2, 54.0, 65.4, 66.8, 115, 128.6, 130.8, 130.9, 157.9, 158.3, 171.5, 171.7, 171.9, 175.2; HRMS calcd for $C_{18}H_{23}N_2O_4S_3$ $[M + H]^+$ 427.0814, found 427.0807; IR ($cm^{-1}$): 3025, 2924, 2850, 1749, 1695, 1634, 1611, 1510, 1405, 1302, 1243, 1154. HPLC (Method 1): 95% pure (1.53 min) at 241 nm; HPLC (Method 2): 99% pure (1.43 min) at 229.1 nm.

**5-[(4-{2-[5-(1,2-Dithiolan-3-yl)pentylmethylamino]ethoxy}-phenyl)methyl]-1,3-thiazolidine-2,4-dione (10).** To a solution of amide **9a** (4.68 g, 10 mmol) in dry tetrahydrofuran (100 mL) at 0 °C was added alane−*N*,*N*-dimethylethylamine complex (40 mL, 20 mmol) dropwise over 30 min. After stirring for an additional 90 min at the same temperature, water (20 mL) was added, and the mixture was stirred at 0 °C for an additional 10 min. The precipitated aluminum hydroxide was filtered and washed with ethyl acetate. The filtrate was concentrated under vacuum, and the residue was diluted with water (50 mL) and extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated to a clear oil. The residue was dissolved in ethyl acetate (40 mL) and cooled to 0 °C. To this solution, chilled aqueous sodium bicarbonate solution (10% w/v, 100 mL) was added followed by a solution of iodine (2.54 g, 10 mmol) in ethyl acetate (50 mL) dropwise until a brown color persisted. After 15 min the reaction mixture was quenched with aqueous sodium thiosulfate solution (10% w/v 15 mL). The organic layer was separated and washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was chromatographed over silica gel (MeOH:$CHCl_3$, 2:98) to yield amine **10** (2.13 g, 47%) along with recovered starting material **9a** (0.87 g): $^1$H NMR ($CDCl_3$, 300 MHz): 1.34 (m, 2H)., 1.45 (m, 2H), 1.5 (m, 2H), 1.6 (m, 2H), 1.89 (dddd, $J$ = 6.7, 7.2, 18 Hz, 1H), 2.4 (s, 3H), 2.44

(dddd, $J$ = 6.7, 7.2 18 Hz, 1H), 2.58 (dd, $J$ = 9, 18 Hz, 1H), 2.90 (t, $J$ = 5.3 Hz, 2H), 3.2−3.0 (m, 3H), 3.40 (dd, $J$ = 3.6, 18 Hz, 1H), 3.5 (m, 1H), 4.06 (t, $J$ = 5.4 Hz, 2H), 4.34 (dd, $J$ = 3.7, 9 Hz, 1H), 6.77 (d, $J$ = 8.5 Hz, 2H), 7.2 (d, $J$ = 8.5 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 75 MHz): 25.4, 27.4, 29.4, 35.1, 38.4, 38.8, 40.6, 41.7, 55.0, 55.5, 56.9, 57.4, 65.0, 114.9, 129.7, 130.8, 157.7, 175.5, 180.0; HRMS calcd for $C_{21}H_{30}N_2O_3S_3$ $[M + H]^+$ 455.1491, found 455.1507; IR ($cm^{-1}$): 2925, 2851, 1749, 1697, 1607, 1586, 1462, 1301, 1243. HPLC (Method 1): 95% pure (1.67 min) at 241 nm; HPLC (Method 2): 99% pure (1.62 min) at 229.1 nm.

**Tartrate Salt of 5-[(4-{2-[5-(1,2-Dithiolan-3-ylpentyl)methylamino]ethoxy}phenyl) methyl]-1,3-thiazolidine-2,4-dione (10).** To a stirred solution of amine **10** (1.30 g, 2.86 mmol) in dry tetrahydrofuran (50 mL) at 0 °C was added a solution of DL-tartaric acid (0.40 g, 2.7 mmol) in THF (40 mL). After the addition was complete, the mixture was stirred at the same temperature for 12 h. The solvent was removed under vacuum, and the residue was washed with chloroform to remove unreacted amine. The product was recrystallized with ether−pentane (1:1 v/v) to yield the tartrate salt as a white crystalline powder (1.60 g, 92%): $^1$H NMR (DMSO-$d_6$, 300 MHz): 1.14−1.20 (m, 4H), 1.40−1.70 (m, 4H), 2.38 (m, 1H), 2.57 (s, 3H), 2.80 (m, 2H), 2.90−3.10 (m, 3H), 3.16 (t, 2H), 3.30 (dd, $J$ = 4, 16 Hz, 1H), 3.50 (m, 1H), 4.13 (s, 2H), 4.19 (t, 2H), 4.82 (dd, $J$ = 4.2, 9 Hz, 1H), 6.88 (d, $J$ = 8.4 Hz, 2H), 7.15 (d, $J$ = 8.4 Hz, 2H); $^{13}$C NMR (DMSO-$d_6$, 75 MHz): 25.1, 26.0, 29.2, 35.0, 37.2, 38.9, 40.7, 41.6, 54.0, 55.0, 56.7, 57.0, 64.3, 72.9, 115.2, 130.0, 131.2, 157.7, 172.8, 174.8, 174.9, 177.0.

***N*-(2-{4-[(2,4-Dioxo-1,3-thiazolidin-5-yl)methyl]phenoxy}ethyl)-6,8-dimercapto-*N*-methyloctanamide (11).** To a solution of **9a** (1.0 g, 2.13 mmol) in tetrahydrofuran (20 mL) at 0 °C was added a solution of sodium borohydride (0.16 g, 4 mmol in 2 mL of water). The mixture was allowed to stir at the same temperature for an additional 1 h. After completion of the reaction, aqueous 1 N HCl (5 mL) was added, and the solvent was removed under vacuum. The residue was diluted with water (20 mL) and extracted with chloroform (2 × 25 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was chromatographed over silica gel (1% methanol in chloroform) to yield dithiol **11** as a viscous liquid (0.87 g, 86%): $^1$H NMR ($CDCl_3$, 300 MHz): 1.30−1.36 (m, 2H), 1.40−1.70 (m, 6H), 1.80 (m, 1H), 2.33 (t, $J$ = 9.7 Hz, 1H), 2.60 (m, 2H), 2.80 (m, 1H), 3.12 (dd, $J$ = 9, 16 Hz, 1H), 3.14 (s, 3H), 3.42 (dd, $J$ = 4, 16 Hz, 1H), 3.73 (t, $J$ = 5.6 Hz, 2H), 4.09 (t, $J$ = 5.6 Hz, 2H), 4.39 (dd, $J$ = 4, 9 Hz, 1H), 6.76 (d, $J$ = 8 Hz, 2H), 7.08 (d, $J$ = 8 Hz, 2H), 10.4 (bs, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz): 22.7, 24.9, 25.3, 27.0, 27.2,33.2, 33.7, 34.5, 38.0, 38.1, 39.1, 40.6, 43.1, 48.4, 49.5, 56.8, 65.6, 66.9, 115.0, 128.8, 129.2, 130.7, 130.8, 157.9, 158.2, 171.6, 171.7, 174.1, 175.5, 175.6; HRMS calcd for $C_{21}H_{31}N_2O_4S_3$[M + H]$^+$ 471.1440, found 471.1482; IR ($cm^{-1}$): 3032, 2926, 1752, 1698, 1609, 1513, 1303, 1244, 1154, 1055.

***S,S′*-{8-[(2-{4-[(2,4-Dioxo-1,3-thiazolidin-5-yl)methyl]phenoxy}ethyl)(methyl)amino]-8-oxooctane-1,3-diyl} Diethanethioate (11a).** To a 25 mL two-neck round-bottomed flask was added **11** (0.47 g, 1.0 mmol) in pyridine (5 mL). To this solution acetic anhydride (0.336 g, 310$\mu$L, 3.3 mmol) was added. Stirring was continued for an additional 2 h at ambient temperature. Upon completion, aqueous HCl (10%v/v, 15 mL) was added, and the product was extracted with chloroform (2 × 25 mL). The combined organic layers were washed with water and brine and dried over anhydrous $MgSO_4$. Following concentration under vacuum, the crude diacetate was further purified by column chromatography over silica gel (60% ethyl acetate:hexanes) to yield **11a** as a viscous liquid (0.49 g, 88%): $^1$H NMR ($CDCl_3$, 300 MHz): 1.20−1.50 (m, 2H), 1.50−1.70 (m, 4H), 1.70−1.90 (m, 2H), 2.30 (t, $J$ = 6 Hz, 2H), 2.31 (m, 6H), 2.70−3.02 (m, 2H), 3.12 (dd, $J$ = 9.3, 16 Hz, 1H), 3.13 (s, 3H), 3.40 (dd, $J$ = 4, 16 Hz, 1H), 3.60 (m, 1H), 3.72 (t, $J$ = 5.2 Hz, 2H), 4.09 (t, $J$ = 5.2 Hz, 2H), 4.70 (dd, $J$ = 4, 9.3 Hz, 1H), 6.70 (d, $J$ = 8.3 Hz, 2H), 6.80 (d, $J$ = 8.3 Hz, 2H), 7.12 (d, $J$ = 8.3 Hz, 2H), 7.14 (d, $J$ = 8.3 Hz, 2H), 8.90 (bs, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz): 25.0, 25.2, 26.9, 27.3, 31.2, 32.6, 33.7, 34.2, 35.0, 35.1, 37.9, 38.1, 44.0, 48.3, 49.2, 54.0, 54.1, 66.7, 115.0, 128.5, 129.0, 130.7, 130.9, 157.0, 158.4, 171.2, 173.8, 174.0, 175.0, 196.1, 196.2; HRMS calcd for $C_{25}H_{36}N_2O_6S_3$ $[M + H]^+$ 555.1652, found 555.1746; IR (film, $cm^{-1}$): 3032, 2936, 1752, 1742, 1698, 1609, 1513, 1309, 1244, 1154, 1052. HPLC (Method 1): 95% pure (2.14 min) at 233.2 nm; HPLC (Method 2): 93% pure (2.89 min) at 229.1 nm.

**Preparation of 11b and 11c.** To a stirred solution of dithiol **11** (0.100 g 0.2 mmol) in pyridine (2 mL) was added succinic anhydride (0.024 g, 0.24 mmol) at room temperature, and the resulting mixture was stirred for an additional 8 h. After the completion of the reaction, aqueous HCl (10%v/v, 10 mL) was added, and the product was extracted with chloroform (2 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and concentrated to give the crude monosuccinate which was further purified by column chromatography over silica gel (1% methanol:chloroform) to yield monosuccinate **11c** (0.062 g, 51%) along with disuccinate **11b** (0.018 g, 13%).

**4,4′-[{8-[(2-{4-[(2,4-Dioxo-1,3-thiazolidin-5-yl)methyl]phenoxy}ethyl)(methyl)amino]-8-oxooctane-1,3-diyl}bis(thio)]bis(4-oxobutanoic acid) (11b):** Viscous liquid; $^1$H NMR ($CDCl_3$, 300 MHz): 1.43 (m, 4H), 1.83 (m, 4H), 1.79 (m, 1H), 2.35 (t, $J$ = 7.4 Hz, 2H), 2.64 (t, $J$ = 6.3 Hz, 4H), 2.80 (m, 1H), 2.78 (t, $J$ = 6.3 Hz, 4H), 3.10 (m, 1H), 3.16 (s, 3H), 3.33 (dd, $J$ = 3.8, 18 Hz, 1H), 3.72 (t, $J$ = 6 Hz, 2H), 4.08 (t, $J$ = 6 Hz, 2H), 4.52 (dd, $J$ = 3.8, 9 Hz, 1H), 6.80 (d, $J$ = 8.1 Hz), 6.79 (d, $J$ = 8.1 Hz, 2H), 7.13 (d, $J$ = 8.1 Hz, 2H), 7.15 (d, $J$ = 8.1 Hz, 2H), 8.30 (bs, 1H), 9.79 (bs, 2H);$^{13}$C NMR ($CDCl_3$, 75 MHz): 24 1, 26.5, 29.1, 30, 33.3(2C), 33.9, 37.4, 38.3(2C), 48.0, 53.5, 66.4, 114.6, 128.0, 130.3, 157.8, 171.0, 174.1, 174.8, 197.9; HRMS calcd for $C_{29}H_{39}N_2O_{10}S_3$ $[M + H]^+$ 671.1689, found 671.1654.

**4-({8-[(2-{4-[(2,4-Dioxo-1,3-thiazolidin-5-yl)methyl]phenoxy}ethyl)(methyl)amino]-3-mercapto-8-oxooctyl}thio)-4-oxobutanoic acid (11c):** Viscous liquid; $^1$H NMR ($CDCl_3$, 300 MHz): 1.46 (m, 4H), 1.63 (m, 4H), 1.75 (m, 1H), 2.33 (t, $J$ = 7.4 Hz, 2H), 2.67 (t, $J$ = 6.3 Hz, 2H), 2.80 (m, 1H), 2.83 (t, $J$ = 6.3 Hz, 2H), 3.10 (m, 1H), 3.13 (s, 3H), 3.35 (dd, $J$ = 3.8, 18 Hz, 1H), 3.72 (t, $J$ = 6 Hz, 2H), 4.08 (t, $J$ = 6 Hz, 2H), 4.50 (dd, $J$ = 3.8, 9 Hz, 1H), 6.80 (d, $J$ = 8.1 Hz), 6.81 (d, $J$ = 8.1 Hz, 2H), 7.11 (d, $J$ = 8.1 Hz, 2H), 7.13 (d, $J$ = 8.1 Hz, 2H), 8.30 (bs, 1H), 9.79 (bs, 1H);$^{13}$C NMR ($CDCl_3$, 75 MHz): 24 1, 26.5, 29.1, 30.0, 33.3, 33.9, 37.4, 38.3, 48.0, 53.5, 66.4, 114.6, 128.0, 130.3, 157.8, 171.0, 174.1, 174.8, 197.9; HRMS calcd for $C_{25}H_{35}N_2O_7S_3$ $[M + H]^+$ 571.1601, found 571.1654.

**4-({3-(Acetylthio)-8-[(2-{4-[(2,4-dioxo-1,3-thiazolidin-5-yl)-methyl]phenoxy}ethyl)(methyl)amino]-8-oxooctyl}thio)-4-oxobutanoic Acid (11d).** Compound **11d** was made from **11c** by following the acylation procedure mentioned in **11a** preparation: Viscous liquid, 76%; $^1$H NMR ($CDCl_3$): 1.30 (m, 2H), 1.59 (m, 4H), 1.75 (m, 2H), 2.29 (s, 3H), 2.32 (t, $J$ = 7.4 Hz, 2H), 2.68 (m, 2H), 2.80 (m, 2H), 3.10 (dd, $J$ = 9, 18 Hz, 1H), 3.13 (s, 3H), 3.35 (dd, $J$ = 3.8, 18 Hz, 1H), 3.54 (m, 1H), 3.71 (t, $J$ = 6 Hz, 2H), 4.08 (t, $J$ = 6 Hz, 2H), 4.50 (dd, $J$ = 3.8, 9 Hz, 1H), 6.82 (d, $J$ = 8.4 Hz, 2H), 7.11 (d, $J$ = 8.3 Hz, 2H); $^{13}$C NMR ($CDCl_3$): 24 8, 25.3, 26.7, 26.8, 29.4, 30.0, 31.2, 33.2, 33.7, 34.5, 34.8, 38.0, 38.1, 38.8, 43.7, 48.5, 49.6, 54.0, 54.1, 65.6, 66.9, 115.0, 128.6, 129.0, 130.7, 130.9, 150.0, 158.3, 171.6, 171.7, 174.5, 174.6, 175.5, 175.7, 196.3, 198.3; HRMS calcd for $C_{27}H_{37}N_2O_8S_3$ $[M + H]^+$ 613.1634, found 613.1649.

**Preparation of 11g and 11h.** To a suspension of *N-tert*-butyloxycarbonyl glycine (0.32 g, 1.8 mmol) in dry $CH_2Cl_2$ (15 mL) was added triethylamine (0.370 g, 0.47 mL, 3.4 mmol), and the mixture was stirred for 30 min at room temperature. HOBT (0.24 g, 1.8 mmol) and compound **11** (0.4 g, 0.85 mmol) were then added, and the resulting mixture was stirred for 10 min at room temperature. EDAC (0.36 g, 1.8 mmol) was added, and the mixture was stirred overnight at room temperature under a nitrogen atmosphere. The white precipitate was removed by filtration, and the filtrate was diluted with dichloromethane (30 mL), washed with aqueous HCl (5%v/v, 10 mL), 5% $NaHCO_3$ (10 mL), and brine, and dried over anhydrous $MgSO_4$. The organic layer was filtered

and concentrated under reduced pressure. The crude material was purified by flash chromatography on a silica gel column using chloroform:methanol (99:1) to yield diglycinate **11g** (0.48 g, 72%) and monoglycinate **11h** (0.113 g, 21%).

***S,S′*-{8-[(2-{4-[(2,4-Dioxo-1,3-thiazolidin-5-yl)methyl]phenoxy}ethyl)(methyl)amino]-8-oxooctane-1,3-diyl} bis{[(*tert*-butoxycarbonyl)amino]ethanethioate} (11g):** Viscous liquid;$^1$H NMR ($CDCl_3$, 300 MHz, mixture of rotamers): 1.43 (bs, 20H), 1.58 (m, 4H), 1.82 (m, 2H), 2.28 (t, $J$ = 7.3 Hz, 2.4H), 2.93 (t, $J$ = 7.3 Hz, 0.6H), 2.97 (m, 4H), 2.98 (s, 0.5H), 3.10 (s, 2.5H), 3.40 (bd, $J$ = 4 Hz, 1H), 3.51 (m, 1H), 3.71 (t, $J$ = 5.3 Hz, 2H), 4.03 (m, 6H), 4.46 (m, 1H), 5.31 (m, 2H), 6.80 (dd, $J$ = 8.3 Hz, 2H), 7.12 (dd, $J$ = 8.3 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 75 MHz, mixture of rotamers): 24.9, 25.3, 26.3, 26.8, 28.2, 28.7, 33.1, 33.6, 34.4, 35.0, 37.9, 38.2, 43.5, 48.4, 49.5, 50.7, 50.9, 54.1, 66.9, 77.7, 80.7, 115.0-(2C), 128.8, 130.7, 156.1, 158.0, 158.3, 171.6, 173.8, 174.0, 175.5, 198.5, 198.8; HRMS calcd for $C_{35}H_{53}N_4O_{10}S_3$ [M + H]$^+$ 785.1846, found 585.1614 [M-(2Boc)+H]$^+$; IR (film, cm$^{-1}$): 3032, 2934, 1757, 1745, 1698, 1609, 1513, 1309, 1244, 1154, 1052.

***S*-{8-[(2-{4-[(2,4-Dioxo-1,3-thiazolidin-5-yl)methyl]phenoxy}ethyl)(methyl)amino]-3-mercapto-8-oxooctyl} [(*tert*-butoxycarbonyl)amino]ethanethioate (11h):** Viscous liquid; $^1$H NMR ($CDCl_3$, 400 MHz): 1.47 (s, 9H), 1.53 (m, 2H), 1.64 (m, 4H), 1.92 (m, 2H), 2.34 (m, 2H), 2.81 (m, 1H), 3.01 (s, 0.5H), 3.10 (m, 4H), 3.13 (s, 2.5H), 3.42 (m, 1H), 3.74 (m, 2H), 4.05 (bd, $J$ = 5.2 Hz 1H), 4.10 (m, 4H), 4.49 (dd, $J$ = 4.0, 9.2 Hz 1H), 5.31 (bs, 1H), 6.82 (dd, $J$ = 8.3 Hz, 2H), 7.15 (dd, $J$ = 8.3 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 75 MHz, mixture of rotamers): 22.3, 24.5, 26.3, 28.3, 33.3, 37.9, 38.5, 38.7, 39.9, 48.0, 53.6, 66.6, 114.7(2C), 128.1, 130.4, 158.0, 158.3, 171.6, 173.8, 174.0, 175.5, 198.5, 198.8; HRMS calcd for $C_{28}H_{42}N_3O_7S_3$ [M + H]$^+$ 628.1582, found 528.1578 [M-Boc+H]$^+$.

**2,2′-[{8-[(2-{4-[(2,4-Dioxo-1,3-thiazolidin-5-yl)methyl]phenoxy}ethyl)(methyl)amino]-8-oxooctane-1,3-diyl}bis(thio)]bis(2-oxoethanaminium) Dichloride (11e).** A solution of 4 N HCl in dioxane (2 mL) was added at once to a suspension of **11g** (0.1 g, 0.13 mmol) in anhydrous ether (10 mL) under a $N_2$ atmosphere at 0 °C, and the resulting mixture was allowed to stir for 30 min. The solvents were removed under vacuum to yield **11e** as a pale yellow amorphous hygroscopic solid (0.064 g, 76%): $^1$H NMR ($CD_3OD$, 300 MHz, mixture of rotamers): 1.17 (m, 2H), 1.64 (m, 4H), 1.93 (m, 2H), 2.38 (t, $J$ = 7.1 Hz, 1.2H), 2.47 (t, $J$ = 7.1 Hz, 0.8H), 2.97 (s, 0.5H), 3.07 (m, 4H), 3.14 (s, 2.5H), 3.32 (bd, 2H), 3.75 (m, 4H), 4.10 (s, 4H), 4.16 (m, 2H), 4.71 (m, 1H), 6.87 (d, $J$ = 8.3 Hz, 2H), 7.18 (dd, $J$ = 8.1 Hz, 2H); $^{13}$C NMR ($CD_3OD$, 75 MHz, mixture of rotamers): 24.7, 25.0, 26.4, 26.6, 32.7, 33.1, 33.3, 34.4, 34.6, 36.9, 37.3, 44.3, 47.4, 49.4, 53.8, 65.6, 66.0, 114.7(2C), 129.1, 129.4, 130.8, 130.9, 158.2, 158.4, 172.5, 174.8, 175.1, 176.4, 193.1, 193.2; HRMS calcd for $C_{25}H_{37}N_4O_6S_3$ [M + H]$^+$ 585.1893, found 585.1902; IR (film, cm$^{-1}$): 3033, 2928, 1765, 1748, 1690, 1609, 1523, 1329, 1254, 1174, 1072. HPLC (Method 1): 94% pure (13.28 min) at 254 nm; HPLC (Method 2): 92% pure (13.48 min) at 254 nm.

**2-({3-(Acetylthio)-8-[(2-{4-[(2,4-dioxo-1,3-thiazolidin-5-yl)-methyl]phenoxy}ethyl)(methyl)amino]-8-oxooctyl}thio)-2-oxoethanaminium Chloride (11f).** To a 25 mL two-neck round-bottomed flask was added **11h** (0.05 g, 0.080 mmol) in pyridine (1 mL). To this solution was added acetic anhydride (0.112 g, 100 $\mu$L, 1 mmol). Stirring was continued for an additional 2 h at ambient temperature. Upon completion, cold 1 N HCl (15 mL) was added, and the product was extracted with chloroform (2 × 10 mL). The combined organic layers were washed with water and brine and dried over anhydrous $MgSO_4$. Following concentration under vacuum, the crude acetate was further purified by column chromatography over silica gel (70% ethyl acetate:hexanes) to yield monoacetate (0.035 g, 66%) which was further subjected to Boc deprotection.

A solution of 4 N HCl in dioxane (2 mL) was added at once to a suspension of monoacetate (0.03 g, 0.045 mmol) in anhydrous ether (10 mL) under a $N_2$ atmosphere at 0 °C, and the resulting mixture was allowed to stir for 30 min. The solvents were removed under vacuum to yield **11f** as a pale yellow amorphous hygroscopic solid (0.018 g, 68%): $^1$H NMR ($CDCl_3$, 500 MHz): 1.47 (m, 2H), 1.64 (m, 4H), 1.89 (m, 2H), 2.02 (s, 3H), 2.33 (s, 3H), 2.40 (dd, $J$ = 7.5, 15.0 Hz, 1H), 2.49 (dd, $J$ = 8, 16 Hz, 1H), 3.10 (m, 2H), 3.17(s, 2H), 3.38 (dt, $J$ = 4 Hz, 1H), 3.58 (m, 1H), 3.76 (m, 1H), 3.80 (t, $J$ = 4.5 Hz, 1H), 4.14 (t, $J$ = 5 Hz, 1H), 4.18 (t, $J$ = 5 Hz, 1H), 4.70 (m, 1H), 6.88 (d, $J$ = 8.4 Hz, 2H),7.20 (d, $J$ = 8.3 Hz, 2H);$^{13}$C NMR ($CDCl_3$, 100 MHz, mixture of rotamers): 22.7, 24.9, 25.0, 27.1, 27.3, 33.1, 33.2, 33.6, 33.7, 34.5, 35.1, 38.0, 38.2, 38.9, 39.2, 39.8, 40.6, 43.1, 48.4, 49.6, 54.1, 54.2, 56.8, 65.7, 66.9, 78.0, 115.1 (2C), 128.8, 129.3, 130.7, 130.9, 158.0, 158.3, 174.3, 175.5, 193.0, 193.2; HRMS calcd for $C_{25}H_{36}N_3O_6S_3$ [M + H]$^+$ 569.1688, found 569.1702.

Compounds **15a** and **15b** were prepared from **13** and **14** based on the general procedure mentioned above for the preparation of **3**.

**Methyl (4-{2-[(*tert*-butoxycarbonyl)(methyl)amino]ethoxy}-3-chlorophenyl)acetate (15a):** 69%, viscous liquid; $^1$H NMR ($CDCl_3$, 500 MHz): 1.46 (s, 9H), 3.05 (s, 3H), 3.54 (s, 2H), 3.64 (bs, 2H), 3.69 (s, 3H), 4.13 (m, 2H), 6.86 (d, $J$ = 8.0 Hz, 1H), 7.11 (dd, $J$ = 1.5, 8.5 Hz, 1H), 7.30 (s, 1H); $^{13}$C NMR ($CDCl_3$, 125 MHz): 28.7 (3C), 40.1, 48.5, 52.3, 67.9, 68.3, 79.7, 112.9, 122.6, 122.8, 127.0, 127.3, 128.5, 130.9, 131.0, 153.2, 155.2, 155.6, 171.4. HRMS calcd for $C_{17}H_{24}ClNO_5Na$ [M + Na]$^+$ 380.1241, found 380.1258.

**Methyl (4-{3-[(*tert*-butoxycarbonyl)(methyl)amino]propoxy}-3-chlorophenyl)acetate (15b):** 63%, viscous liquid; $^1$HNMR ($CDCl_3$, 400 MHz, mixture of rotamers): 1.41 (s, 9H), 2.03 (bs, 2H), 2.87 (s, 3H), 3.42 (t, $J$ = 6.4 Hz, 2H), 3.52 (s, 2H), 3.68 (s, 3H), 4.01 (bs, 2H), 6.86 (d, $J$ = 8.0 Hz, 1H), 7.09 (d, $J$ = 8.0 Hz, 1H), 7.28 (s, 1H); $^{13}$CNMR ($CDCl_3$, 100 MHz): 27.7, 28.4(3C), 34.6, 39.9, 45.9, 52.0, 68.0, 79.3, 113.2, 122.9, 127.1, 128.5, 131.0, 153.5, 155.8, 171.7; HRMS calcd for $C_{18}H_{26}ClNO_5Na$ [M + Na]$^+$ 394.1251, found 394.1258.

The compounds **16a** and **16b** were prepared from **15a** and **15b** following the procedure for the preparation of **7** as mentioned above.

**2-[2-Chloro-4-(2-methoxy-2-oxoethyl)phenoxy]-*N*-methylethanaminium chloride (16a):** 93%, viscous liquid; $^1$HNMR ($CDCl_3$, 500 MHz): 2.50 (s, 3H), 2.58 (bs, NH), 2.99 (bs, 2H), 3.51 (s, 2H), 3.66 (s, 3H), 4.10 (t, $J$ = 5.0 Hz, 2H), 6.86 (d, $J$ = 8.5 Hz, 1H), 7.08 (dd, $J$ = 1.5, 8.5 Hz, 1H), 7.26 (d, $J$ = 1.5 Hz, 1H); $^{13}$CNMR ($CDCl_3$, 125 MHz): 36.4, 40.1, 50.6, 52.3, 68.6, 113.7, 122.9, 127.3, 128.5, 130.9, 153.2, 171.4; HRMS calcd for $C_{12}H_{17}ClNO_3$ [M + H]$^+$ 258.0897, found 258.0896.

**3-[2-Chloro-4-(2-methoxy-2-oxoethyl)phenoxy]-*N*-methylpropan-1-aminium chloride (16b):** 87%, viscous liquid; $^1$HNMR ($CDCl_3$, 400 MHz): 2.15 (bs, 2H), 2.46 (s, 3H), 2.52 (bs, NH), 2.92 (bs, 2H), 3.52 (s, 2H), 3.68 (s, 3H), 4.13 (t, $J$ = 5.0 Hz, 2H), 6.84 (d, $J$ = 8.5 Hz, 1H), 7.08 (d, $J$ = 8.5 Hz, 1H),7.28 (s, 1H); $^{13}$CNMR ($CDCl_3$, 100 MHz): 27.4, 36.2, 38.4, 50.4, 52.7, 68.3, 113.9, 123.1, 127.7, 128.7, 131.3, 153.2, 171.6; HRMS calcd for $C_{13}H_{19}ClNO_3$ [M + H]$^+$ 272.1053, found 272.1044.

The compounds **17a** and **17b** were prepared from **16a** and **16b** by following the procedure for the preparation of amides **9a**−**c** as mentioned above.

**Methyl [3-chloro-4-(2-{[5-(1,2-dithiolan-3-yl)pentanoyl](methyl)amino}ethoxy)phenyl]acetate (17a):** 79%, viscous liquid; $^1$H NMR ($CDCl_3$, 500 MHz, mixture of rotamers): 1.47 (m, 2H), 1.68 (m, 4H), 1.89 (m, 1H), 2.33 (t, $J$ = 7.5 Hz, 1.5H), 2.44 (m, 1H), 2.52 (t, $J$ = 7.5 Hz, 0.5H), 3.02 (s, 0.7H), 3.09 (m, 1H), 3.14 (m, 1H), 3.22 (s, 2.3H), 3.53 (s, 2H), 3.57 (m, 1H), 3.68 (s, 3H), 3.78 (m, 2H), 4.11 (t, $J$ = 5.0 Hz, 0.5H), 4.16 (t, $J$ = 5.0 Hz, 1.5H), 6.84 (d, $J$ = 8.5 Hz, 1H), 7.11 (m, 1H), 7.26 (s, 1H); $^{13}$CNMR ($CDCl_3$, 125 MHz): 25.0, 25.3, 29.3, 29.5, 33.1, 33.5, 34.2, 35.1, 35.13, 38.3, 38.8, 40.2, 40.5, 48.2, 49.3, 52.4, 56.6, 56.7, 66.8, 68.1, 112.8, 113.1, 122.4, 122.8, 127.1, 127.8, 128.5, 128.6, 130.9, 131.2, 152.8, 153.1, 171.3, 171.4, 172.8, 172.9. HRMS calcd for $C_{20}H_{29}ClNO_4S_2$ [M + H]$^+$ 446.1227, found 446.1238. HPLC (Method 1): 100% pure (2.04 min) at 219.2 nm; HPLC (Method 2): 98% pure (1.80 min) at 233.4 nm.

**Methyl [3-chloro-4-(3-{[5-(1,2-dithiolan-3-yl)pentanoyl](methyl)amino}propoxy)phenyl]acetate (17b):** 69%, viscous liquid; $^1$H NMR ($CDCl_3$, 500 MHz): 1.40 (m, 2H), 1.65 (m, 4H), 1.90 (m, 1H), 1.98 (t, $J$ = 6.3 Hz, 2H), 2.30 (t, 1H), 2.36 (t, 1H), 2.45 (m, 1H), 2.90 (s, 1H), 3.03 (s, 1H), 3.15 (m, 1H), 3.59 (t, $J$ = 6.7 Hz, 2H), 3.69 (s, 3H), 4.01 (m, 2H), 6.80 (t, $J$ = 8.Hz, 1H), 7.11 (dt, $J$ = 2, 8 Hz, 1H), 7.29 (dd, $J$ = 2, 8.8 Hz, 1H); $^{13}$C NMR ($CDCl_3$, 125 MHz): 25 0, 25.5, 27.5, 28.3, 29.3, 29.4, 32.8, 33.5, 33.6, 35.0, 35.1, 36.3, 38.8, 38.9, 40.1, 40.2, 40.5, 40.6, 45.6, 46.5, 52.4, 52.5, 56.8, 65.4, 67.2, 113.3, 113.6, 122.9, 127.4, 127.8, 129.0, 129.1, 131.3, 131.4, 153.3, 153.7, 172.0, 172.1, 173.2, 173.3; HRMS calcd for $C_{21}H_{31}ClNO_4S_2$ $[M + H]^+$ 460.1305, found 460.1316. HPLC (Method 1): 100% pure (2.11 min) at 229.2 nm; HPLC (Method 2): 99.2% pure (1.84 min) at 229.1 nm.

**General Procedure for the Preparation of Acids 18a and 18b.** To a solution of ester **17** (0.5 mmol) in methanol (10 mL) was added 1 N NaOH (1.5 mL, 1.5 mmol) solution in water, and the mixture was stirred at room temperature for 3 h. The methanol was removed under vacuum, and the residue was acidified to pH 5 with 1 N HCl. The product was extracted with chloroform (2 × 25 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated to provide the crude acid which was further purified over silica gel (ethyl acetate:hexanes 4:6).

**[3-Chloro-4-(2-{[5-(1,2-dithiolan-3-yl)pentanoyl](methyl)amino}ethoxy)phenyl]acetic acid (18a):** 97%; viscous liquid;$^1$H NMR ($CDCl_3$, 500 MHz, mixture of rotamers): 1.46 (m, 2H), 1.65 (m, 4H), 1.87 (m, 1H), 2.34 (t, $J$ = 7.5 Hz, 1.5H), 2.41 (m, 1H), 2.52 (t, $J$ = 7.5 Hz, 0.5H), 3.03 (s, 0.7H), 3.09 (m, 1H), 3.14 (m, 1H), 3.24 (s, 2.3H), 3.55 (s, 2H), 3.56 (m, 1H), 3.79 (t, 2H), 4.10 (t, $J$ = 5.0 Hz, 0.5H), 4.15 (t, $J$ = 5.0 Hz, 1.5H), 6.84 (m, 1H), 7.12 (m, 1H), 7.30 (m, 1H), 9.93 (bs, 1H); $^{13}$C NMR ($CDCl_3$, 125 MHz): 25.0, 25.3, 29.3, 29.4, 33.2, 33.6, 34.5, 35.0, 35.04, 38.5, 38.8, 40.2, 40.5, 48.4, 49.5, 56.6, 56.7, 66.7, 68.0, 112.8, 113.1, 122.3, 122.8, 127.0, 127.6, 128.66, 128.7, 131.0, 131.2, 152.8, 153.1, 173.6, 173.8, 175.5, 175.7. HRMS calcd for $C_{19}H_{27}ClNO_4S_2$ $[M + H]^+$ 432.1070, found 432.1057.

**[3-Chloro-4-(3-{[5-(1,2-dithiolan-3-yl)pentanoyl](methyl)amino}propoxy)phenyl]acetic acid (18b):** 93%, viscous liquid; $^1$H NMR ($CDCl_3$, 500 MHz, mixture of rotamers): 1.38 (m, 2H), 1.67 (m, 4H), 1.89 (m, 1H), 1.94 (t, $J$ = 6.3 Hz, 2H), 2.32 (t, 1H), 2.37 (t, 1H), 2.45 (m, 1H), 2.89 (s, 1H), 3.01 (s, 1H), 3.17 (m, 1H), 3.63 (t, $J$ = 6.7 Hz, 2H), 4.05 (m, 2H), 6.81 (t, $J$ = 8.Hz, 1H), 7.13 (dt, $J$ = 2, 8 Hz, 1H), 7.32 (dd, $J$ = 2, 8.8 Hz, 1H); $^{13}$C NMR ($CDCl_3$, 125 MHz): 25 0, 25.5, 27.5, 28.3, 29.3, 29.4, 32.8, 33.5, 33.6, 35.0, 35.1, 36.3, 38.8, 38.9, 40.1, 40.2, 40.5, 40.6, 45.6, 46.5, 52.4, 52.5, 56.8, 65.4, 67.2, 113.3, 113.6, 122.9, 127.4, 127.8, 129, 129.1, 131.3, 131.4, 153.3, 153.7, 172.0, 172.1, 173.2, 173.3; HRMS calcd for $C_{20}H_{29}ClNO_4S_2$ $[M + H]^+$ 446.1227, found 446.1217

**(5*Z*)-5-[4-(Methylamino)benzylidene]-1,3-thiazolidine-2,4-dione (22).** A mixture of 4-aminomethyl benzaldehyde **21** (0.250 g, 1.85 mmol), thiazolidine-2,4-dione (0.2 g, 1.7 mmol), benzoic acid (0.01 g), and piperidine (0.2 mL) in 15 mL of toluene was refluxed for 6 h with continuous removal of water using a Dean−Stark apparatus. The reaction mixture was cooled to room temperature, and the resulting crystalline compound was filtered, washed with water, and dried to afford **22** as orange-yellow solid: 0.39 g, 89%, viscous liquid; $^1$H NMR ($CDCl_3$, 400 MHz, mixture of rotamers): 2.75 (d, 3H, $J$ = 3.2 Hz), 6.65 (d, 2H, $J$ = 8.4 Hz), 7.36 (d, 2H, $J$ = 8.8 Hz), 7.63 (s, 1H), 12.2 (bs, 1H); $^{13}$C NMR ($CDCl_3$, 100 MHz): 29.7, 112.3, 118.6, 120.9, 131.6, 132.5, 152.0, 170.6, 171.6; HRMS calcd for $C_{11}H_{10}N_2O_2S$ $[M + H]^+$ 234.0463, found 234.0457

**5-[4-(Methylamino)benzyl]-1,3-thiazolidine-2,4-dione (23).** A solution of thiazolidine-2,4-dione **22** (0.2 g, 0.85 mmol) and magnesium turnings (0.2 g, 8.3 mmol) in dry MeOH (10 mL) was stirred at room temperature for 12 h. The reaction mixture was neutralized with 1 N HCl and extracted with dichloromethane (2 × 15 mL). The combined organic layers were washed with water (10 mL) and brine (5 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed over silica gel using ethyl acetate and hexanes (4:6) to afford **23** as a yellow viscous liquid: 0.15 g, 73%; $^1$H NMR (DMSO-$d_6$, 400 MHz, mixture of rotamers): 2.76 (s, 3H), 3.01 (dd, 1H, $J$ = 9.0, 14.0 Hz), 3.33 (dd, 1H, $J$ = 4.4, 14.0 Hz), 4.64 (dd, 1H, $J$ = 4.4, 9.0 Hz), 6.59 (d, 2H, $J$ = 8.4 Hz), 7.03 (d, 2H, $J$ = 8.4 Hz); $^{13}$C NMR (DMSO-$d_6$, 100 MHz): 29.5, 37.2, 53.9, 112.3, 124.4, 129.7, 149.2, 172.3, 176.2; HRMS calcd for $C_{11}H_{12}N_2O_2S$ $[M + H]^+$ 236.0619, found 236.0623.

***N*-{4-[(2,4-Dioxo-1,3-thiazolidin-5-yl)methyl]phenyl}-5-(1,2-dithiolan-3-yl)-*N*-methylpentanamide (24).** To a suspension of racemic lipoic acid (0.093 g, 0.45 mmol) in dry $CH_2Cl_2$ (15 mL) was added triethylamine (0.135 g, 170 $\mu$L, 1.2 mmol), and the mixture was stirred for 30 min at room temperature. HOBT (0.060 g, 0.45 mmol) and **23** (0.070 g, 0.3 mmol) were added, and the resulting mixture was stirred for 10 min at room temperature. EDAC (0.087 g, 0.45 mmol) was added, and the mixture was stirred overnight at room temperature under a nitrogen atmosphere. The white precipitate was removed by filtration, and the filtrate was diluted with dichloromethane (20 mL), washed with 5% HCl (10 mL), 5% $NaHCO_3$ (10 mL), and brine (10 mL), and dried over anhydrous $MgSO_4$. The filtrate was concentrated under vacuum, and the residue was chromatographed over silica gel (ethyl acetate: hexanes, 3:7) to yield **24** (0.098 g, 78%): $^1$H NMR ($CDCl_3$, 300 MHz): 1.32 (m, 2H), 1.58(m, 4H), 2.03 (dddd, $J$ = 6.2,7.2, 18.6 Hz, 1H), 2.04 (t, 2H), 2.41 (dddd, $J$ = 6.2, 7.2, 18.7 Hz,1H), 3.07−3.22 (m, 3H), 3.25 (s, 3H), 3.49 (m, 1H), 3.53 (dd, $J$ = 4, 14 Hz, 1H), 4.54 (dd, $J$ = 4, 9 Hz, 1H), 7.15 (d, $J$ = 8.15 Hz), 7.29 (d, $J$ = 8.15 Hz, 2H), 8.7 (bs, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz): 25.5, 29.2, 34.2, 34.9, 37.2, 38.5, 38.8, 40.6, 53.3, 56.8, 128.0, 131.1, 136.1, 143.8, 170.6, 173.5, 174.6; HRMS calcd for $C_{19}H_{25}N_2O_3S_3$ $[M + H]^+$ 425.1022, found 425.1007; IR (cm$^{-1}$): 2925, 2852, 1753, 1699, 1624, 1601, 1511, 1461, 1390. HPLC (Method 1): 100% pure (1.56 min) at 229.2 nm; HPLC (Method 2): 97.6% pure (4.31 min) at 237.3 nm.

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**Supporting Information Available:** HRMS and HPLC data for the target compounds, biological methods, and computational methods are available free of charge via Internet at http://pubs.acs.org.

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