Articles

FK506-Binding Protein Ligands: Structure-Based Design, Synthesis, and Neurotrophic/Neuroprotective Properties of Substituted 5,5-Dimethyl-2-(4-thiazolidine)carboxylates

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Structure-based design and discovery of novel neuroimmunophilin FK506-binding protein (FKBP) ligands were pursued in the present study. The binding mode of the known FKBP ligand **1** (3-(3-pyridyl)-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate) in complex with FKBP12 was investigated using LUDI simulation and upon which a novel scaffold structure predicted to possess improved binding affinity was designed. A virtual combinatorial library composed of diverse combinations of two substituted groups was constructed using Project Library, followed by an automated screening of the library against the ligand binding site on FKBP52 using DOCK. Forty-three candidate compounds that displayed favorable binding with the receptor were identified and synthesized. The neurotrophic activity of the candidate compounds was evaluated on chick dorsal root ganglion cultures in vitro. As a result, 15 compounds exhibited positive effects on ganglion neurite outgrowth in the presence of 0.15 ng/mL NGF, among which 7 compounds at testing concentrations of 1 pM and 100 pM showed greater efficacy than **1** at 100 pM. Compound **18** (3-(3-pyridyl)-1-propyl (2*S*)-5,5-dimethyl-1-(3,3-dimethyl-1,2-dioxobutyl)-2-(4-thiazolidine)carboxylate) afforded the most potent effect in promoting the processes of neurite outgrowth and which was in a concentration-dependent manner from 1 pM to 100 pM. Half-maximal effect occurred at about 10 pM. Moreover, **18** at a dosage of 10 mg/kg was found to be significantly neuroprotective in a mouse peripheral sympathetic nerve injury model induced by 8 mg/kg 6-hydroxydopamine. This study further suggests the clinical potential of novel FKBP ligands as a new therapeutic approach in the treatment of neurodegenerative disorders, such as Parkinson's disease.

Introduction

Immunophilins, including cyclophilins,[1] FK506-binding proteins (FKBPs),[2] and parvulins,[3] are a family of phylogenically conserved binding proteins, possessing peptidyl prolyl cis−trans isomerase activity that is essential for protein folding.[4,5] Immunophilins were originally discovered and studied in the immune system. It is well established that the immunosuppressive effects of cyclosporin A (CsA) and FK506, which have been widely used clinically in inhibiting immune responses in organ transplantation, result from binding to their cognate immunophilin receptors, cyclophilin A for CsA and FKBP12 (the 12-kDa FKBP) for FK506.[6] The immunosuppressant−immunophilin binary complex in turn binds to and inactivates the Ca^{2+}/calmodulin-dependent serine/threonine protein phosphatase calcineurin,[7,8] leading to blockage of the translocation of the nuclear factor of activated T-cells into the nucleus and ensuing inhibition of interleukin-2 gene transcription which is necessary for T-cell activation.[9]

Beyond the immune system, immunophilins are found enriched in neurons as well. Snyder and his colleagues first discovered that the FKBP12 level in the rat brain is 10−50-fold higher than its expression in the immune system,[10] suggesting that FKBP12 and other immunophilins may also play a pivotal role in regulating neural functions in the nervous system. Subsequently, spurred by the first report of the neuroregenerative effect of FK506 as demonstrated by its enhancement of neurite outgrowth in cultures of rat PC12 pheochromocytoma cells and sensory ganglia[11] and a following study published later in the same year that demonstrated the neuroprotective effect of FK506 in an animal model of focal cerebral ischaemia,[12] the functional role of immunophilins in the nervous system are extensively investigated in the past decade. Solid evidence from both in vitro cultures and in vivo animal studies raise the possibility of applying immunophilins, in particular FKBPs, as novel therapeutic targets for the development of effective intervention therapies against neurological disorders, particularly neurodegenerative diseases (see reviews[13−18]). Nevertheless, immunosuppressive ligands targeting immunophilins have been clinically linked with a number of adverse effects when administered chronically.[19−21] A strategy that could circumvent many of the problematic aspects of these immunosuppressants is the development of an mimic molecule designed to activate the neurotrophic and neuroprotective mechanisms associated with immunophilins in the nervous system while avoiding the interference in the immune system, so-called nonimmunosuppressive neuroimmunophilin ligand (NIL).[22−24]

FK506 is a natural macrolide product composed of two domain structures, the "FKBP-binding domain" binds to FKBPs and the "effector domain" binds to calcineurin (see Figure 1).[25]

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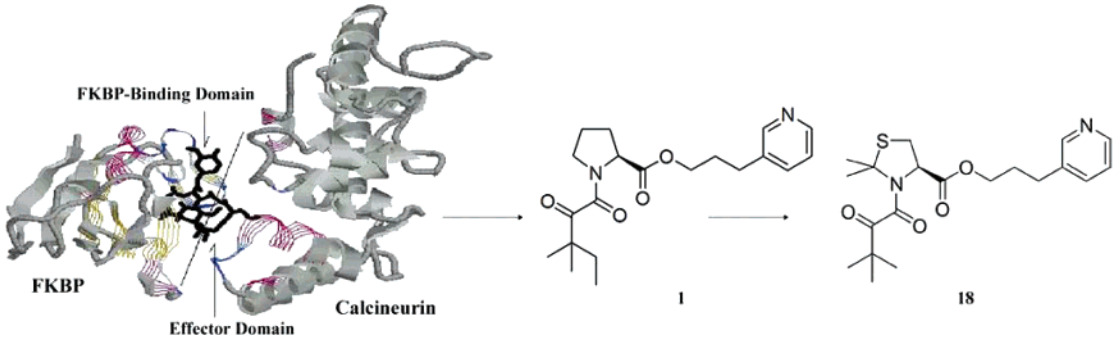


Figure 1. FK506 is composed of two domain structures, the "FKBP-binding domain" which binds to FKBP and the "effector domain" which binds to calcineurin. Small molecule **1** is a mimic structure of the "FKBP-binding domain" of FK506. Structural analogue **18** exhibited enhanced binding affinity to FKBP protein and greater therapeutic potential than **1**.

It is suggested that the neural functions of FK506 are conferred only by its "FKBP-binding domain" and independent of calcineurin inhibition associated with the "effector domain".[26] In light of this profound notion, a number of novel analogues of FK506 with NIL potential have been developed from different research groups. One typical example is the emergence of a small molecule, **1** (3-(3-pyridyl)-1-propyl (2*S*)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate), a mimic structure of the "FKBP-binding domain" of FK506 and devoid of the calcineurin binding domain as present in FK506 (see Figure 1).[27] Multiple studies have demonstrated that **1** is a highly potent neurotrophic and neuroprotective molecule in various in vitro and in vivo model systems but has no effect in the immune system,[27−33] further suggesting that the inhibition of immune responses and promotion of neural functions associated with an immunophilin ligand can be separated. Unfortunately, some of the positive data on **1** were questioned by Harper et al. who failed to reproduce the corresponding activities.[34] **1** was also shown to be ineffective in some other neural systems.[35−37] One possible explanation for the decreased activity of **1** in the nervous system in comparison with FK506 may originate from its much weaker binding affinity to FKBP protein, although the costructure of **1** in complex with FKBP12, determined by heteronuclear NMR spectroscopy, showed that **1** exhibits a binding mode analogous to that observed for FK506.[38]

Several isoforms of FKBP with disparate molecular size exist in the nervous system. Using a FKBP12-knockout mice model and a mouse monoclonal antibody that does not interact with FKBP12, Gold et al. first discovered that the high-molecular weight FKBP52 (also known as FKBP59 or hsp56), rather than FKBP12, mediated the neurotrophic action of FK506.[39,40] In agreement with this finding, Guo et al. found that FK506 afforded a similar protective effect against MPP+ toxicity in cultured dopaminergic neurons derived from FKBP12-knockout mice.[41] Further, FK506 and **1** were demonstrated to exhibit equipotent neuroprotection in both SH-SY5Y and U251 human cells, although FKBP12 mRNA expression was only detected in SH-SY5Y cells.[42] Upon ligand binding to FKBP52, a chaperone component of mature steroid receptor complex, a subsequent "gain-of-function" takes place following the disruption of the chaperone complex, involving the dissociation of p23 from hsp90 and the ensuing extracellular signal-regulated kinase (ERK1/2) activation.[43]

In view of the mechanistic significance of FKBP52 in mediating neuroimmunophilin ligands-inducible promotion of neuroregeneration and neuronal survival, in the present study, by means of computer-aided structure-based approach, we sought to design and discover novel ligands targeting FKBP52 that are expected to hold better therapeutic promise than **1**. As a result, a series of substituted 5,5-dimethyl-2-(4-thiazolidine)-carboxylate derivatives were synthesized and evaluated for their neurotrophic and neuroprotective efficacy in vitro and in vivo, respectively.

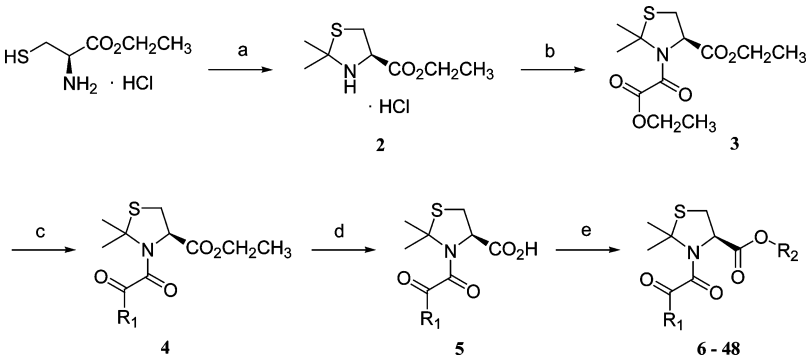
Results

Scaffold Design. To determine the molecular basis accounting for the week binding of **1** to FKBP and rationally design novel ligands with enhanced binding affinity, we initiated this study with a computer-aided analysis on the 3D bound structure of **1** in complex with FKBP12. LUDI, an automated fragment-based suggestive program for the de novo design of protein ligands developed by Bolm,[44] was applied. The basic idea of LUDI is to construct novel protein ligands by linking with a suitable spacer the molecular fragments which are positioned into the active site of a protein in such a way that hydrogen bonds can be formed with the protein and hydrophobic pockets are filled with hydrophobic groups.[45] In particular, LUDI can be used to provide rational suggestions for the modification of a known ligand by improving the favorable contacts with the protein.[45]

Computation was performed on a SGI O2 R10000 workstation equipped with the IRIX operating system (Silicon Graphic Inc.). The 3D complex structure of **1** with FKBP12 (PDB ID: 1F40)[38] was imported into the graphic modeling program InsightII 98.0 (Accelrys Inc.). By running LUDI calculation following the structural fixation and energy minimization, the bound structure of **1** as a template scaffold in the context of FKBP12 was examined in a link mode. Computational results indicated that there is an unoccupied space between the pyrrolidine ring of **1** and the vicinal protein surface but that can be saturated by the introduction of two methyl groups on the 5-position of the ring structure, which may improve the ligand binding to the protein through enhanced hydrophobic interactions. In addition, we observed that the replacement of the carbon atom on the 4-position of the pyrrolidine ring of **1** with an oxygen or sulfur atom leads to the formation of a potential polar interaction with the nearby residue Tyr-26 mediated by a middle water molecule. Based on these findings and consideration of structural stability, a novel scaffold structure presented in Scheme 1 was designed which retains all the favorable structural requirements for binding in FK506 and **1** but is expected to have increased FKBP binding affinity compared to **1**.

Library Construction. Since both substituted groups R_1 and R_2 in the scaffold structure (see Scheme 1) would make pivotal contributions to ligand binding to the protein, a virtual compound library containing diverse R_1 and R_2 combinations was constructed using Project Library 2.0 (MDL Information Systems Inc.), a multifunctional combinatorial library construc-

Scheme 1[a]



[a] Reagents and conditions: (a) $(CH_3)_2CO$, reflux, 1 h; (b) $C_2H_5OCOCOCl$, $(C_2H_5)_3N$, $(C_2H_5)_2O$, 0 °C, 1.5 h; (c) R_1MgCl or R_1MgBr, THF, −78 °C, 5 h; (d) 1 N LiOH, MeOH, 0 °C, 30 min; room temperature, overnight; 1 N HCl; (e) R_2OH, DCC, DMAP, camphorsulfonic acid, CH_2Cl_2, room temperature, overnight.

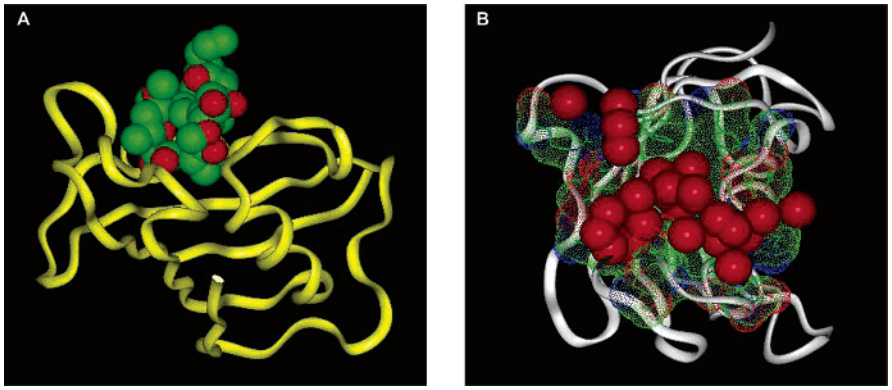


Figure 2. A: Costructure of hFKBP12 bound with FK506. B: Site points on FKBP52-I represented with red spheres. The molecular surface which was used to produce spheres was calculated by the program MS, available from Quantum Chemistry Program Exchanger.

tion program[46] as described below. The constructed library was then screened to identify the potential candidate compounds that display favorable binding to the protein active site.

According to the proposed synthetic route for the preparation of target compounds (see Scheme 1), R_1 and R_2 can be attached to the root structural moiety by the Grignard reaction and esterification, respectively. Therefore, the first step in the library construction was to select the appropriate Grignard reagents (R_1MgCl or R_1MgBr) and alcohols (R_2OH) from an Available Chemical Directory (MDL Information Systems, Inc.). By using the building-blocks clipper, the structural lists of selected reagents were processed into building blocks that were then used as Rgroup members by clipping the structures and adding attachment points. Then, the combinatorial library was built based on the root structure and Rgroup member lists, which was further expanded by enumeration, a process of automatic generation of fully specified structures. Finally, the constructed library was exported as a SDF file, which was then converted to a SYBYL MOL2 file that can be read by DOCK. As a result, a collection of 57120 virtual compounds constructed by 51 Grignard fragments and 2100 alcoholic fragments, containing the information about atom types and charges, was built for the next stage of computer screening.

Computer Screening. DOCK 4.0 (University of California at San Francisco; http://www.cmpharm.ucsf.edu/kuntz/), an automated molecular docking and database screening program developed by Kuntz et al.,[47,48] was used. The core of the DOCK searching and scoring algorithm is to superimpose the ligand atoms onto predefined site-points that map out the negative image of the protein binding site and evaluate the complementarity between the two.[49] On the basis of the potential role of FKBP52 in mediating the neurotrophic and neuroprotective effects of NILs,[39,40,50] we chose FKBP52 as the docking target.

Since the first N-terminal domain in FKBP52 (FKBP52-I) displays high sequence and structure similarity to FKBP12 (52% of sequence identity), especially among the residues defining the active site,[51] the high-resolution X-ray structure of human FKBP12 complexed with FK506 (PDB ID: 2FKE)[52] was used as a template for the determination of the binding site on FKBP52-I. By superimposing the NMR solution structure of FKBP52-I (PDB ID: 1ROT)[53] with the costructure of FKBP12 complexed with FK506 based on alpha carbon atoms, the corresponding binding site of FK506 on the surface of FKBP52-I was designated as the docking site and represented as a cluster of 33 site-points (as shown in Figure 2), which were generated by the sphere generation accessory program, SPHGEN, integrated into the DOCK program suite. The identified binding site was then gridded by the program GRID, which saves information about the steric and electrostatic environment at each point on a grid.

The fitness of molecules onto the FKBP52-I surface binding site was ranked in turn by three independent scoring functions integrated into DOCK. In detail, the entire collection of the constructed virtual library containing 57120 compounds was first screened by a contact score function, which provides a simple assessment of shape complementarity between the ligand and the protein. As a result, 10000 top-scoring compounds with the best orientation were saved. Then, the orientation of each of the 10000 compounds was searched and evaluated again based on an energy score function, a measurement of the extent of van der Waals and electrostatic interaction between the ligand

and the protein. The resulting 1000 top-scoring compounds were further tailored by a chemical score function to enhance recognition of chemical complementarity. Finally, following a modified procedure of Li et al.,[54] the top 500 compounds yielded from the chemical search were visually screened three times in the context of FKBP52-I using the InsightII 98.0 software package. After taking the molecular weight distribution, drug-like property, cost and availability of reagents, and synthetic accessibility into account, a subset of 43 candidate compounds were chosen to be synthesized.

It should be pointed out that some compounds in the library have one or more chiral centers. For these compounds, only one chiral center was examined during the docking process. In addition, for those flexible compounds having multiple possible conformations, a systematic search was performed with the available computational power. A minimization procedure allowing on-the-fly adjustment of a compound's orientation and conformation was also performed, aiming at improving the intermolecular interactions.

Chemistry. Candidate compounds can be prepared in several ways. A relatively simple and easy route was described in Scheme 1. Ethyl 5,5-dimethyl (2*S*)-2-(4-thiazolidine)carboxylate (**2**) was prepared following an established procedure,[55] through the simple treatment of commercially available optically active L-cysteine ethyl ester hydrochloride and acetone under refluxing condition. **2** was acylated by ethyl oxalyl chloride in the presence of triethylamine to afford ethyl 5,5-dimethyl (2*S*)-1-(1,2-dioxo-2-ethoxyethyl)-2-(4-thiazolidine)carboxylate. The ethoxy group attached to the dicarbonyl moiety in **3** was then nucleophilically substituted by alkylating group under treatment with Grignard reagent, at the reaction temperature −78 °C to reduce the occurrence of side substitution on the monocarbonyl ester moiety. The resulting product (**4**) underwent saponification by 1 N lithium hydroxide in methanol and then acidified by 1 N hyhydrochloric acid to yield the corresponding substituted (2*S*)-2-(4-thiazolidine)carboxylic acid (**5**), which was further reacted with various alcohols following a routine procedure to give the target compounds (**6**−**48**).

Biological Results. The neurotrophic activity of the target compounds was assessed in vitro in chick dorsal root ganglion (DRG) cultures following a previously described procedure of Lyons et al.[11] Due to the poor water solubility, the compounds were first dissolved in analytically pure DMSO at 1 mM and then diluted in DMEM to the final concentrations for the bioassays, in which the concentrations of DMSO were less than 10^{-7} M and had no detectable effects on the DRGs. The vehicle-treated control cultures received the same amount of DMSO as present in the highest concentrations of test compounds.

To determine an appropriate concentration for evaluation, a preliminary screening on several random compounds, at a wide concentration range from picomolar order to nanomolar order, was conducted. As a result, two concentrations of 1 pM and 100 pM, at which most test compounds displayed positive effects on neurite outgrowth in DRGs, were used for the subsequent biological screening. In addition, to quickly highlight those lead candidate compounds with improved therapeutic potential compared to **1** for further detailed analyses, two separate experimental runs on all target compounds at both concentrations were conducted. A third run was performed if the data yielded from the first two experiments exhibited big variance. The average results, as shown in Figure 3, revealed that about one-third out of a total of 43 test compounds promoted neurite outgrowth in DRGs in the presence of nerve growth factor (NGF) at a concentration of 0.15 ng/mL, which was used

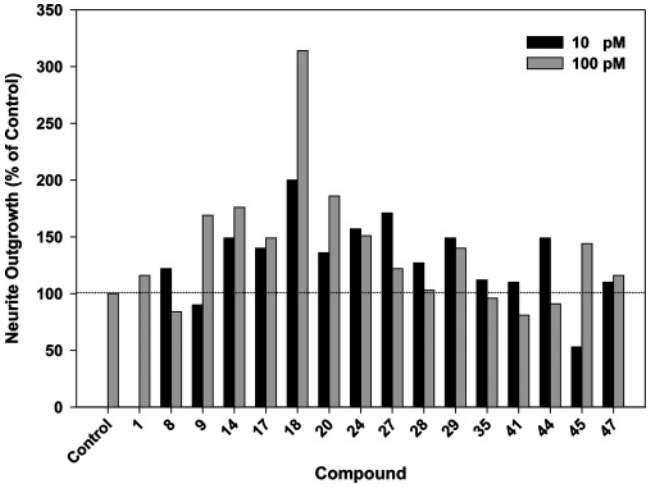


Figure 3. Effects of positive compounds on neurite outgrowth in DRG cultures. DRGs were treated with test compounds at 1 pM or 100 pM in the presence of 0.15 ng/mL NGF, and outgrowth was observed at 48 h. The control group was treated with the same amount of NGF. At either one or both concentrations, 15 test compounds potentiated neurite outgrowth in DRGs compared to the NGF only treated control group. Of them, compounds **14**, **17**, **18**, **20**, **24**, **27**, and **29** exhibited greater effects at both 1 pM and 100 pM than **1** at 100 pM. Data shown were the average results from two separate experiments. A total of 15−18 ganglion cultures for each group were included in each experimental run.

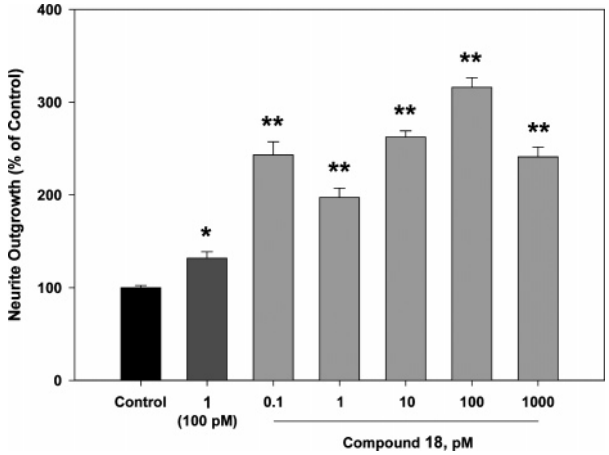


Figure 4. Compound **18** increased the neurite outgrowth in DRG cultures in a concentration-dependent manner. DRGs were treated with NGF (0.15 ng/mL) alone (control group) or in the presence of compound **18** (0.1, 1, 10, 100, or 1000 pM), and outgrowth was observed at 48 h. At all test concentrations, compound **18** significantly increased neurite outgrowth in DRGs compared to NGF alone-treated control cultures. Between 1 pM and 100 pM, **18** exerted a concentration-dependent increase of neurite processes with the maximal response at 100 pM. The activity decreased at a higher concentration (1000 pM). **1** at 100 pM only induced a slight potentiation on neurite outgrowth that was elicited by the same amount of NGF. Data are represented as mean ± SEM, n ≥ 3. * $P < 0.05$ and ** $P < 0.01$ compared to NGF alone-treated control cultures.

to induce small neurite processes in DRGs. Compounds **14**, **17**, **18**, **20**, **24**, **27**, and **29** exhibited greater efficacy at both 1 pM and 100 pM than **1** at 100 pM.

As demonstrated in Figure 3, compound **18** showed the most potent effect on the outgrowth of chicken sensory ganglia. An extensive investigation of the neurotrophic efficacy and concentration response profile of compound **18** was then performed (see Figures 4 and 5). As a result, compound **18** elicited a significant augmentation on the ganglion processes, even at a low concentration of 0.1 pM. Between 1 pM and 100 pM, **18**

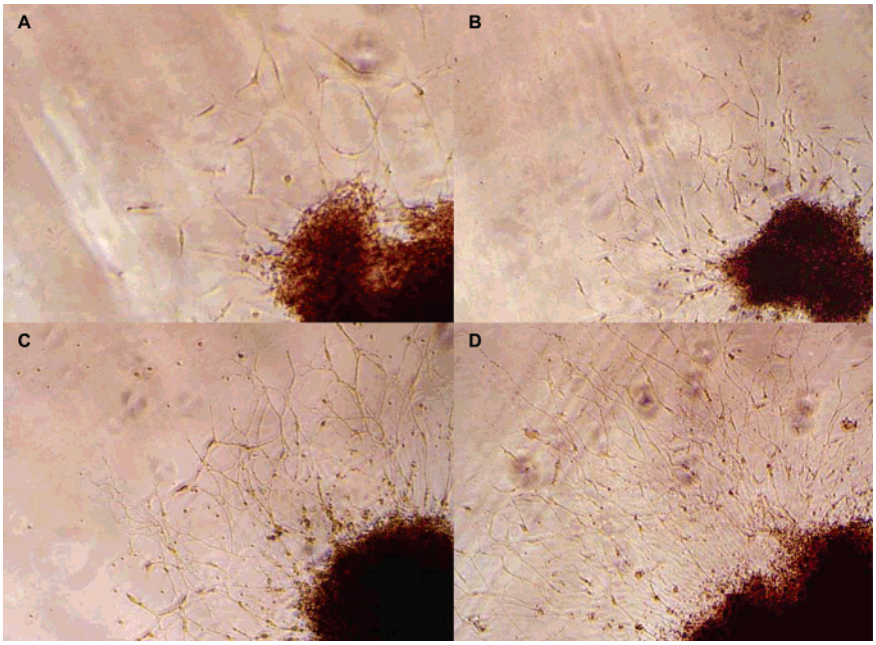


Figure 5. Representative micrographs of chick DRGs grown with NGF (0.15 ng/mL) alone or in the presence of compound **18** (1, 10, or 100 pM). (A) NGF at 0.15 ng/mL alone only elicited small neurite processes; (B) Compound **18** at 1 pM increased neurite processes that was elicited by NGF; (C) Compound **18** at 10 pM exerted greater potentiation on neurite processes than that observed at 1 pM; (D) Compound **18** at 100 pM showed the maximal effects on the number and length of neurite processes compared to NGF alone-treated cultures.

demonstrated a markedly concentration-dependent increase of gonglion processes with a maximal response at 100 pM. The half-maximal effect occurred at about 10 pM, and the activity decreased at a higher concentration (1 nM). **1** at 100 pM alone exerted a slight potentiation of neurite outgrowth induced by 0.15 ng/mL NGF. In the absence of exogenously added NGF, however, **18** and related compounds in the present study failed to promote neurite outgrowth in DRGs.

Encouraged by its promising in vitro neurotrophic activity, compound **18** was further evaluated for its neuroprotective activity in vivo. A standard mouse peripheral sympathetic nerve injury model induced by 6-hydroxydopamine (6-OHDA)[56] was employed and FK506 was used as a positive control. The neuroprotective effect of compound **18** was indirectly assessed by the measurement of norepinephrine (NE) content in mouse submandibular glands following the intraperitoneal injection of 6-OHDA. Results from these analyses demonstrated that the degree of injury of peripheral sympathetic nerves in mice was relevant to the dose of 6-OHDA administered. An intraperitoneal injection of 8 mg/kg 6-OHDA in mice induced a significant decrease of NE content in submandibular glands, $P < 0.01$ compared to the vehicle/vehicle-treated control groups.

Data shown in Table 1 demonstrated that pretreatment of mice with compound **18** at 10 mg/kg s.c. 4 h prior to 6-OHDA treatment and the subsequent daily treatment for 4 days following the lesion elicited a pronounced increase in the NE content in mouse submandibular glands compared to 6-OHDA/vehicle-treated control groups ($P < 0.01$), indicating a significant protection of peripheral sympathetic nerves against injury induced by 6-OHDA. This effect was comparable to that induced by 2 mg/kg FK506.

Table 1. Effects of FK506 and Compound **18** on Norepinephrine (NE) Content in Mouse Submandibular Glands Following Peripheral Sympathetic Nerve Injury Induced by Intraperitoneal Injection of 6-Hydroxydopamine (6-OHDA)[a]

treatment	NE content (μg/g wet weight)
vehicle/vehicle	2.38 ± 0.11
6-OHDA/vehicle	$1.77 \pm 0.21^{\#\#}$
6-OHDA/FK506, 2 mg/kg	$2.33 \pm 0.28^{**}$
6-OHDA/**18**, 10 mg/kg	$2.31 \pm 0.34^{**}$

[a] Mice were treated with FK506 (2 mg/kg, s.c.) or compound **18** (10 mg/kg, s.c.) 4 h prior to intraperitoneal injection of 6-OHDA (8 mg/kg) and daily for the subsequent 4 days following the 6-OHDA treatment. Animals were sacrificed 2 weeks after the last treatment. The NE content in mouse submandibular glands was measured by HPLC-ECD. Data are represented as mean ± SEM, $n \geq 3$. $^{\#\#}$ $P < 0.01$ compared to vehicle/vehicle-treated animals and ** $P < 0.01$ compared to 6-OHDA/vehicle-treated animals.

Discussion

Along with rapid advances in the fields of structural biology and computational graphics, computer-aided structure-based drug design has increasingly become an important strategy in the development of new pharmaceuticals. Starting with the investigation of the bound structure of the known neuroimmunophilin ligand **1** in complex with FKBP12 in a computer graphical environment, by sequentially applying a number of computation-based design programs, in the present study, we efficiently designed a novel scaffold structure that was predicted to possess improved binding affinity to FKBP, and then identified 43 potential candidates from a large compound collection. Fifteen compounds exhibited positive neurotrophic effects on neurite outgrowth in DRGs, 7 of which demonstrated greater efficacy at 1 pM and 100 pM than **1** at 100 pM, indicating the effectiveness of the state-of-the-art computational chemistry and modeling-guided drug design approaches in the development of potential therapies for human diseases. Computer-aided design and screening provide an efficient and automated strategy to highlight a small group of candidate hits from a large number of compounds for actual biological investigation.

Although much remains to be determined with respect to the underlying downstream pathways following the binding to FKBP52 that lead to promotion of neuroregeneration and the neuronal defense system afforded by FK506 and related neuroimmunophilin ligands in the nervous system, the current

state of knowledge is sufficient to demonstrate the clinical potential of these compounds as a novel therapeutic approach for the treatment of neurodegenerative disorders. As illustrated in the present study, compound **18** exhibited significant neurotrophic effects within a wide range of concentrations on sensory ganglia by increasing their sensitivity to NGF. NGF, at a concentration of 0.15 ng/mL, only induced some small neurite processes, which were markedly increased by compound **18** even at a low concentration of 0.1 pM. The observation that compound **18** at 0.1 pM was more effective than it was at 1 pM may imply that distinct molecular mechanisms may be involved in mediating the promotive effects of this compound on neurite outgrowth at different concentrations. Furthermore, compound **18** at a dosage of 10 mg/kg was demonstrated to be significantly neuroprotective against mice peripheral sympathetic nerve injury induced by 8 mg/kg of 6-OHDA, which was comparable to that elicited by 2 mg/kg of FK506. Taken together, results from both in vitro and in vivo studies indicate that compound **18** and its structural analogues hold the promise for further development as potential therapeutics for the treatment of a variety of neurological disorders, including Parkinson's disease. However, it should be noted that the neuroprotective efficacy of compound **18** was found to be relevant to the severity of the nerve injury caused by the injection of different doses of 6-OHDA. When the injection dose of 6-OHDA increased to 10 mg/kg which induced greater damage to the peripheral sympathetic nerves in mice, the sustained effect on NE content afforded by compound **18** was not statistically significant compared to 6-OHDA alone-treated mice, suggesting that this compound may be more effective in treating mild nerve injury. In the instance of severe injury, treatment with this compound alone is probably not sufficient to reverse the nerve damage induced, for example, by a higher dose of 6-OHDA.

Compound **18** and its analogues, including **1**, failed to elicit neurite outgrowth in DRGs in the absence of exogenously added NGF, suggesting that the neuroimmunophilin ligands-inducible neurotrophic activity is dependent upon NGF. In accordance with this observation, FK506 was found to require the addition of exogenous NGF as well to promote the neuronal outgrowth in PC12 cells.[11] Gold proposed that the underlying mechanism mediating the neurotrophic action of neuroimmunophlin ligands could form a convergence with the known neurotrophic factor (NTF, e.g. NGF) signal transduction pathway, leading to potentiated activity over NGF alone, and which may be mediated by the interaction between hsp90 and MAP kinase/ERK2.[40] Tanaka et al. demonstrated that both FK506 and **1** increased expression of neurotrophic factors, such as the glial cell line-derived neurotrophic factor and the striatal brain-derived neurotrophic factor, in the substantia nigra of a mouse brain, further suggesting that NILs-induced neurotrophic action may be at least partially dependent on NTFs activation.[57] In contrast to the neurotrophic analyses, we found that the neuroprotective activity of compound **18** against peripheral sympathetic nerve injury induced by 6-OHDA in mice did not require the presence of NGF. These observations suggest that the neurotrophic and neuroprotective effects afforded by this compound and other related NILs may be mediated by different signaling pathways. Several studies have demonstrated that NILs-induced neuroprotection is associated with their glutathione-activating effect and anti-apoptotic effect.[58−60] The rapid induction of heat shock protein response is proposed to be another component in the molecular mechanisms that underlie NILs-induced neuroprotection.[16,61,62] These results suggest that it should be treated differently when applying these compounds in treating different neurodegenerative conditions.

A preliminary analysis of the structure−activity relationship (SAR) of the test compounds revealed that R_1 and R_2 in the scaffold structure could be substituted by a variety of structurally diverse groups, but with a distinct impact on the biological activity afforded by these compounds. Overall, for R_1, aryl substituted C2−C3 alkyl or alkenyl, i.e., 3-(3-pyridyl)-1-phenyl, 3-phenyl-1-propyl, 3-phenyl-2-(*E*)-1-propyl, 2-(2-thienyl)-1-ethyl and 2-(2-chlorophenyl)-1-ethyl, or long chain alkyl or alkenyl, i.e., 10-decen-1-yl, were favorable to the biological activity, as exemplified by compounds **14**, **17**, **18**, **20**, **24**, **27**, and **29**, which were found to be highly neurotrophic to neurite outgrowth in DRGs cultures. In contrast, compounds containing short alkyl groups for R_1, such as pentyl or alkyl substituted with a cycloalkyl such as 3-cyclohexyl-1-propyl, were less effective. For R_2, either straight or branched lipophilic alkyl groups with appropriate length, including *tert*-butyl, 2-methyl-2-butyl, or *n*-hexyl, were found to be associated with increased biological activity. However, long chain alkyl such as *n*-octyl was proven to be harmful to the activity of the corresponding compounds. Although a detailed study of the SAR of these compounds will be needed, these analyses provided some insights into the further development of more potent FKBP ligands for the treatment of neurodegenerative diseases.

Conclusion

The present study demonstrated the effectiveness of the computer-aided molecular design and virtual screening approaches in our discovery of novel FKBP ligands that hold the promise of a novel therapeutic strategy for the treatment of neurodegenerative disorders, such as Parkinson's disease. In comparison with a number of neurotrophic proteins, compounds designed in this study are readily synthesized and devoid of the problems associated with large proteins, such as poor bioavailability and transportation that currently hamper their clinical application. Moreover, unlike many neurotrophic proteins, such as NGF, which elicit sprouting of normal sensory neurons,[63] compounds presented herein are anticipated to have little likelihood to induce aberrant sprouting of neuronal processes. These analyses suggest that these compounds are encouraging potential prospects for further investigation.

Experimental Section

Chemistry. General Methods. Melting points were determined in open capillary tubes on a RY-1 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker ARX 400 spectrometer or US Varian Unity Inova 600 spectrometer using tetramethylsilane (TMS) as an internal standard. The splitting pattern abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet, dd = doublet doublet, dt = doublet triplet, ddd = doublet doublet doublet, ddt = doublet doublet triplet. FAB mass spectra (FAB-MS) and EI high-resolution mass spectra (EI-HRMS) were recorded on a VG Zabspect mass spectrometer. Elemental analyses (C, H, N) were performed on a FISONS-1108 auto analyzer. Column chromatography was performed on silica gel H and analyzed by thin-layer chromatography using precoated silica gel GF_{254} plates.

Ethyl (2*S*)-5,5-Dimethyl-2-(4-thiazolidine)carboxylate Hydrochloride (2). A suspension of l-cysteine ethyl ester hydrochloride (10 g, 53.9 mmol) in dry acetone (150 mL) was refluxed for 1 h, during which the solid was gradually dissolved. After cooling to room temperature, the precipitate was collected by filtration, washed with cold acetone, and dried to afford compound **2** (9.75 g, 80.2%) as a white crystalline solid: mp 148−150 °C.

Ethyl (2*S*)-5,5-Dimethyl-1-(1,2-dioxo-2-ethoxyethyl)-2-(4-thiazolidine)carboxylate (3). A stirred suspension of ethyl (2*S*)-5,5-dimethyl-2-(4-thiazolidine)carboxylate hydrochloride **2** (1.95 g, 8.64 mmol) in dry ethyl ether (30 mL) was cooled to 0 °C, to which a solution of ethyl oxalyl chloride (1.77 g, 12.9 mmol) in dry ethyl ether (10 mL) together with a solution of triethylamine (1.83 g, 18.1 mmol) in dry ethyl ether (20 mL) were added dropwise separately at a rate to maintain the temperature of the reaction mixture below 5 °C. After addition the resulting mixture was stirred at 0 °C for further 1.5 h and then filtered to remove solids. The organic layer was collected, washed with water, dried over anhydrous $MgSO_4$, and concentrated in vacuo to afford compound **3** (2.1 g, 84.1%) as a pale yellow oil, which did not require further purification.

Ethyl (2*S*)-5,5-Dimethyl-1-(2-cyclohexyl-1,2-dioxoethyl)-2-(4-thiazolidine)carboxylate (4a). A solution of ethyl (2*S*)-5,5-dimethyl-1-(1,2-dioxo-2-ethoxyethyl)-2-(4-thiazolidine)carboxylate **3** (2.5 g, 8.65 mmol) in dry THF (75 mL) was cooled to −80 °C, to which a 2.0 M solution of cyclohexylmagnesium chloride (5.75 mL, 11.5 mmol) in ethyl ether was added at a rate to maintain the temperature of the reaction mixture not exceeding −70 °C. The resulting mixture was stirred at about −80 to −70 °C for additional 5 h and then poured into saturated solution of ammonium chloride in water (100 mL). After extraction with ethyl acetate, the organic layer was collected, washed with water, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude material was purified by column chromatography on silica gel using ethyl acetate−petroleum ether (1:10) as eluent to afford compound **4a** (2.2 g, 77.8%) as a pale yellow oil.

(2*S*)-5,5-Dimethyl-1-(2-cyclohexyl-1,2-dioxoethyl)-2-(4-thiazolidine)carboxylic Acid (5a). A mixture of ethyl (2*S*)-5,5-dimethyl-1-(2-cyclohexyl-1,2-dioxoethyl)-2-(4-thiazolidine)carboxylate **4a** (5.6 g, 17.1 mmol), 1 N LiOH (31 mL), and methanol (100 mL) was stirred at 0 °C for 30 min and then at room-temperature overnight. The reaction mixture was acidified to pH 1 with 1 N HCl, diluted with water, and extracted with ethyl acetate. The organic extracts were collected, washed with saturated brine solution, dried over anhydrous $MgSO_4$, and concentrated in vacuo to afford compound **5a** (4.5 g, 87.9%) as a white powder solid, which did not require further purification.

3-(3-Pyridyl)-1-propyl (2*S*)-5,5-Dimethyl-1-(2-cyclohexyl-1,2-dioxoethyl)-2-(4-thiazolidine)carboxylate (6). A mixture of (2*S*)-5,5-dimethyl-1-(2-cyclohexy-1,2-dioxolethyl)-2-(4-thiazolidine)-carboxylic acid **5a** (400 mg, 1.34 mmol), 3-(3-pyridyl)-1-propanol (275 mg, 2.01 mmol), dicyclohexylcarbodiimide (331 mg, 1.61 mmol), camphorsulfonic acid (94 mg, 0.41 mmol), and 4-(dimethylamino)pyridine (50 mg, 0.41 mmol) in methylene chloride (20 mL) was stirred overnight under an nitrogen atmosphere and then filtered to remove solids. The filtrate was washed with water, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude material was purified by column chromatography on silica gel using ethyl acetate−petroleum ether (3:1) as eluent to afford compound **6** (419 mg, 74.8%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12−1.39 (m, 6H), 1.67−2.02 (m, 6H), 1.88 (s, 3H), 1.96 (s, 3H), 2.72 (t, 2H, J = 7.8 Hz), 3.19 (m, 1H), 3.23 (dd, 1H, J = 2.0, 12.3 Hz), 3.32 (dd, 1H, J = 5.7, 12.3 Hz), 4.19 (m, 2H), 5.33 (dd, 1H, J = 2.0, 5.7 Hz), 7.27 (m, 1H), 7.56 (d, 1H, J = 7.9 Hz), 8.48 (s, 2H). FAB-MS $[M + H]^+$ = 419.2 *m*/*e*. EI-HRMS: calcd for $C_{22}H_{31}N_2O_4S$ $[M + H]^+$, 419.2004; found, 419.1971. Anal. ($C_{22}H_{30}N_2O_4S$): C, H, N.

3-Phenyl-1-propyl (2*S*)-5,5-Dimethyl-1-(2-cyclohexyl-1,2-dioxoethyl)-2-(4-thiazolidine)carboxylate (7). This compound was prepared from (2*S*)-5,5-dimethyl-1-(2-cyclohexyl-1,2-dioxoethyl)-2-(4-thiazolidine)carboxylic acid **5a** (400 mg, 1.34 mmol) and 3-phenyl-1-propanol (274 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (398 mg, 71.2%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10−1.37 (m, 6H), 1.63−1.97 (m, 6H), 1.88 (s, 3H), 1.95 (s, 3H), 2.69 (t, 2H, J = 7.4 Hz), 3.19 (m, 1H), 3.24 (dd, 1H, J = 1.5, 12.4 Hz), 3.33 (dd, 1H, J = 5.8, 12.4 Hz), 4.19 (m, 2H), 5.02 (dd, 1H, J = 1.5, 5.8 Hz), 7.20 (m, 3H), 7.31 (m, 2H). FAB-MS $[M + H]^+$ = 418.1 *m*/*e*. EI-HRMS: calcd for $C_{23}H_{31}NO_4S$ $[M]^+$, 417.1974; found, 417.1967. Anal. ($C_{23}H_{31}NO_4S$): C, H, N.

3-Phenoxy-1-propyl (2*S*)-5,5-Dimethyl-1-(2-cyclohexyl-1,2-dioxoethyl)-2-(4-thiazolidine)carboxylate (8). This compound was prepared from (2*S*)-5,5-dimethyl-1-(2-cyclohexyl-1,2-dioxoethyl)-2-(4-thiazolidine)carboxylic acid **5a** (400 mg, 1.34 mmol) and 3-phenoxy-1-propanol (305 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (440 mg, 75.8%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11−1.38 (m, 6H), 1.64−1.95 (m, 4H), 1.86 (s, 3H), 1.93 (m, 3H), 2.14 (m, 2H), 3.16 (m, 1H), 3.29 (m, 2H), 4.04 (m, 2H), 4.38 (m, 2H), 5.34 (dd, 1H, J = 3.0, 4.9 Hz), 6.88 (m, 2H), 6.95 (m, 1H), 7.28 (m, 2H). FAB-MS $[M + H]^+$ = 434.1 *m*/*e*. EI- HRMS: calcd for $C_{23}H_{32}NO_5S$ $[M + H]^+$, 434.2001; found, 434.1995. Anal. ($C_{23}H_{31}NO_5S$): C, H, N.

2-[*N*-Ethyl-*N*-(3-methylphenyl)]amino-1-ethyl (2*S*)-5,5-Dimethyl-1-(2-cyclohexyl-1,2-dioxoethyl)-2-(4-thiazolidine)carboxylate (9). This compound was prepared from (2*S*)-5,5-dimethyl-1-(2-cyclohexyl-1,2-dioxoethyl)-2-(4-thiazolidine)carboxylic acid **5a** (400 mg, 1.34 mmol) and 2-[*N*-ethyl-*N*-(3-methylphenyl)]amino-1-ethanol (360 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (454 mg, 73.7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14−1.35 (m, 9H), 1.66−1.94 (m, 4H), 1.86 (s, 3H), 1.94 (s, 3H), 2.31 (s, 3H), 3.20 (m, 3H), 3.37 (m, 2H), 3.54 (m, 2H), 4.30 (m, 2H), 5.36 (m, 1H), 6.53 (m, 3H), 7.10 (m, 1H). FAB-MS $[M + H]^+$ = 461.2 *m*/*e*. EI-HRMS: calcd for $C_{25}H_{36}N_2O_4S$ $[M]^+$, 460.2396; found, 460.2396. Anal. ($C_{25}H_{36}N_2O_4S$): C, H, N.

9-Decen-1-yl (2*S*)-5,5-Dimethyl-1-(2-cyclohexyl-1,2-dioxoethyl)-2-(4-thiazolidine)carboxylate (10). This compound was prepared from (2*S*)-5,5-dimethyl-1-(2-cyclohexyl-1,2-dioxoethyl)-2-(4-thiazolidine)carboxylic acid **5a** (400 mg, 1.34 mmol) and 9-decen-1-ol (314 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (370 mg, 63.1%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08−2.12 (m, 25H), 1.83 (s, 3H), 1.87 (s, 3H), 3.16 (m, 2H), 4.16 (m, 2H), 4.93 (m, 1H), 4.99 (m, 1H), 5.37 (t, 1H, J = 3.8 Hz), 5.80 (m, 1H). FAB-MS $[M + H]^+$ = 438.2 *m*/*e*. EI-HRMS: calcd for $C_{24}H_{39}NO_4S$ $[M]^+$, 437.2600; found, 437.2537. Anal. ($C_{24}H_{39}NO_4S$): C, H, N.

Ethyl (2*S*)-5,5-Dimethyl-1-(2-cyclopenyl-1,2-dioxoethyl)-2-(4-thiazolidine)carboxylate (4b). This intermediate compound was prepared from ethyl (2*S*)-5,5-dimethyl-1-(1,2-dioxo-2-ethoxyethyl)-2-(4-thiazolidine)carboxylate **3** (1.0 g, 3.46 mmol) and a 2.0 M solution of cyclopentylmagnesium chloride (2.3 mL, 4.6 mmol) in ethyl ether in the same procedure as described in the preparation of the intermediate compound **4a** (850 mg, 78.5%).

(2*S*)-5,5-Dimethyl-1-(2-cyclohexyl-1,2-dioxoethyl)-2-(4-thiazolidine)carboxylic Acid (5b). This intermediate compound was prepared from ethyl (2*S*)-5,5-dimethyl-1-(2-cyclopentyl-1,2-dioxoethyl)-2-(4-thiazolidine)carboxylate **4b** (850 mg, 2.72 mmol) in the same procedure as described in the preparation of the intermediate compound **5a** (687 mg, 88.6%).

3-(3-Pyridyl)-1-propyl (2*S*)-5,5-Dimethyl-1-(2-cyclopentyl-1,2-dioxoethyl)-2-(4-thiazolidine)carboxylate (11). This compound was prepared from (2*S*)-5,5-dimethyl-1-(2-cyclopentyl-1,2-dioxoethyl)-2-(4-thiazolidine)carboxylic acid **5b** (382 mg, 1.34 mmol) and 3-(3-pyridyl)-1-propanol (275 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (379 mg, 70.1%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60−1.77 (m, 8H), 1.88 (s, 3H), 1.96 (s, 3H), 1.99 (m, 2H), 2.72 (t, 2H, J = 8.0 Hz), 3.28 (dd, 1H, J = 2.2, 12.3 Hz), 3.33 (dd, 1H, J = 5.7, 12.3 Hz), 3.60 (m, 1H), 4.20 (m, 2H), 5.39 (dd, 1H, J = 2.2, 5.7 Hz), 7.28 (m, 1H), 7.56 (d, 1H, J = 7.8 Hz), 8.48 (s, 2H). FAB-MS $[M + H]^+$ = 405.3 *m*/*e*. EI-HRMS: calcd for $C_{21}H_{29}N_2O_4S$ $[M + H]^+$, 405.1848; found, 405.1840. Anal. ($C_{21}H_{28}N_2O_4S$): C, H, N.

Ethyl (2*S*)-5,5-Dimethyl-1-(3,3-dimethyl-1,2-dioxopentyl)-2-(4-thiazolidine)carboxylate (4c). This intermediate compound was prepared from ethyl (2*S*)-5,5-dimethyl-1-(1,2-dioxo-2-ethoxyethyl)-2-(4-thiazolidine)carboxylate **3** (2.5 g, 8.65 mmol) and a 1.0 M solution of 1,1-dimethylproplylmagnesium chloride (11.5 mL, 11.5 mmol) in ethyl ether in the same procedure as described in the preparation of the intermediate compound **4a** (1.99 g, 73.1%).

(2*S*)-5,5-Dimethyl-1-(3,3-dimethyl-1,2-dioxopentyl)-2-(4-thiazolidine)carboxylic Acid (5c). This intermediate compound was prepared from ethyl (2*S*)-5,5-dimethyl-1-(3,3-dimethyl-1,2-dioxopentyl)-2-(4-thiazolidine)carboxylate **4c** (1.99 g, 6.32 mmol) in the same procedure as described in the preparation of the intermediate compound **5a** (1.53 g, 84.1%).

3-(3-Pyridyl)-1-propyl (2*S*)-5,5-Dimethyl-1-(3,3-dimethyl-1,2-dioxopentyl)-2-(4-thiazolidine)carboxylate (12). This compound was prepared from (2*S*)-5,5-dimethyl-1-(3,3-dimethyl-1,2-dioxopentyl)-2-(4-thiazolidine)carboxylic acid **5c** (385 mg, 1.34 mmol) and 3-(3-pyridyl)-1-propanol (275 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (425 mg, 78.2%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.83 (t, 3H, J = 7.2 Hz), 1.19 (s, 3H), 1.27 (s, 3H), 1.73 (q, 2H, J = 7.2 Hz), 1.90 (s, 3H), 1.99 (s, 3H), 2.01 (m, 2H), 2.72 (t, 2H, J = 7.8 Hz), 3.24 (d, 1H, J = 12.0 Hz), 3.32 (dd, 1H, J = 6.0, 12.0 Hz), 4.23 (m, 2H), 4.93 (d, 1H, J = 6.0 Hz), 7.23 (m, 1H), 7.52 (d, 1H, J = 7.2 Hz), 8.47 (s, 2H). FAB-MS $[M + H]^+$ = 407.0 *m*/*e*. EI-HRMS: calcd for $C_{21}H_{31}N_2O_4S$ $[M + H]^+$, 407.2004; found, 407.1957. Anal. ($C_{21}H_{30}N_2O_4S$): C, H, N.

3-Phenyl-1-propyl (2*S*)-5,5-Dimethyl-1-(3,3-dimethyl-1,2-dioxopentyl)-2-(4-thiazolidine)carboxylate (13). This compound was prepared from (2*S*)-5,5-dimethyl-1-(3,3-dimethyl-1,2-dioxopentyl)-2-(4-thiazolidine)carboxylic acid **5c** (385 mg, 1.34 mmol) and 3-phenyl-1-propanol (274 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (387 mg, 71.4%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, 3H, J = 7.5 Hz), 1.18 (s, 3H), 1.27 (s, 3H), 1.72 (m, 2H), 1.90 (s, 3H), 1.98 (s, 3H), 2.02 (m, 2H), 2.70 (t, 2H, J = 7.6 Hz), 3.23 (dd, 1H, J = 1.2, 12.2 Hz), 3.31 (dd, 1H, J = 6.0, 12.2 Hz), 4.20 (m, 2H), 4.96 (dd, 1H, J = 1.2, 6.0 Hz), 7.17−7.31 (m, 5H). FAB-MS $[M + H]^+$ = 406.0 *m*/*e*. EI-HRMS: calcd for $C_{22}H_{31}NO_4S$ $[M^+]$, 405.1974; found, 405.1992. Anal. ($C_{22}H_{31}NO_4S$): C, H, N.

3-Phenyl-1-prop-2-(*E*)-enyl (2*S*)-5,5-Dimethyl-1-(3,3-dimethyl-1,2-dioxopentyl)-2-(4-thiazolidine)carboxylate (14). This compound was prepared from (2*S*)-5,5-dimethyl-1-(3,3-dimethyl-1,2-dioxopentyl)-2-(4-thiazolidine)carboxylic acid **5c** (385 mg, 1.34 mmol) and 3-phenyl-1-prop-2-(*E*)-enol (269 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (325 mg, 60.2%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (t, 3H, J = 7.5 Hz), 1.17 (s, 3H), 1.28 (s, 3H), 1.71 (m, 2H), 1.90 (s, 3H), 1.97 (s, 3H), 3.33 (m, 2H), 4.82 (m, 2H), 5.07 (dd, 1H, J = 2.7, 4.6 Hz), 6.25 (dt, 1H, J = 6.5, 15.9 Hz), 6.68 (d, 1H, J = 15.9 Hz), 7.26−7.40 (m, 5H). FAB-MS $[M + H]^+$ = 404.3 *m*/*e*. EI-HRMS: calcd for $C_{22}H_{29}NO_4S$ $[M^+]$, 403.1817; found, 403.1862. Anal. ($C_{22}H_{29}NO_4S$): C, H, N.

3-Phenoxy-1-propyl (2*S*)-5,5-Dimethyl-1-(3,3-dimethyl-1,2-dioxopentyl)-2-(4-thiazolidine)carboxylate (15). This compound was prepared from (2*S*)-5,5-dimethyl-1-(3,3-dimethyl-1,2-dioxopentyl)-2-(4-thiazolidine)carboxylic acid **5c** (385 mg, 1.34 mmol) and 3-phenoxy-1-propanol (305 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (423 mg, 74.9%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (t, 3H, J = 7.5 Hz), 1.17 (s, 3H), 1.26 (s, 3H), 1.71 (m, 2H), 1.88 (s, 3H), 1.95 (s, 3H), 2.15 (m, 2H), 3.24 (dd, 1H, J = 1.4, 12.2 Hz), 3.30 (dd, 1H, J = 5.8, 12.2 Hz), 4.05 (t, 2H, J = 6.1 Hz), 4.40 (m, 2H), 4.93 (dd, 1H, J = 1.4, 5.8 Hz), 6.90 (d, 2H, J = 7.7 Hz), 6.95 (t, 1H, J = 7.4 Hz), 7.30 (m, 2H). FAB-MS $[M + H]^+$ = 422.1 *m*/*e*. EI-HRMS: calcd for $C_{22}H_{31}NO_5S$ $[M^+]$, 421.1923; found, 421.1925. Anal. ($C_{22}H_{31}NO_5S$): C, H, N.

2-[*N*-Ethyl-*N*-(3-methylphenyl)]amino-1-ethyl (2*S*)-5,5-Dimethyl-1-(3,3-dimethyl-1,2-dioxopentyl)-2-(4-thiazolidine)carboxylate (16). This compound was prepared from (2*S*)-5,5-dimethyl-1-(3,3-dimethyl-1,2-dioxopentyl)-2-(4-thiazolidine)carboxylic acid **5c** (385 mg, 1.34 mmol) and 2-[*N*-ethyl-*N*-(3-methylphenyl)]-amino-1-ethanol (360 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (403 mg, 67.2%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (t, 3H, J = 7.5 Hz), 1.13 (t, 3H, J = 7.0 Hz), 1.18 (s, 3H), 1.28 (s,3H), 1.73 (m, 2H), 1.88 (s,3H), 1.96 (s, 3H), 2.31 (s, 3H), 3.16−3.18 (d, 1H, J = 12.2 Hz), 3.27 (dd, 1H, J = 5.9, 12.2 Hz), 3.38 (q, 2H, J = 7.0 Hz), 3.56 (t, 2H, J = 6.3 Hz), 4.31 (m, 2H), 4.98 (d, 1H, J = 5.9 Hz), 6.54 (m, 3H), 7.11 (m,1H). FAB-MS $[M + H]^+$ = 449.2 *m*/*e*. EI-HRMS: calcd for $C_{24}H_{36}N_2O_4S$ $[M^+]$, 448.2396; found, 448.2398. Anal. ($C_{24}H_{36}N_2O_4S$): C, H, N.

2-(2-Thienyl)-1-ethyl (2*S*)-5,5-Dimethyl-1-(3,3-dimethyl-1,2-dioxopentyl)-2-(4-thiazolidine)carboxylate (17). This compound was prepared from (2*S*)-5,5-dimethyl-1-(3,3-dimethyl-1,2-dioxopentyl)-2-(4-thiazolidine)carboxylic acid **5c** (385 mg, 1.34 mmol) and 2-(2-thienyl)-1-ethanol (257 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (373 mg, 70.1%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (t, 3H, J = 7.5 Hz), 1.17 (s, 3H), 1.27 (s,3H), 1.72 (m, 2H), 1.88 (s,3H), 1.94 (s,3H), 3.20 (m, 3H), 3.29 (dd, 1H, J = 5.9, 12.2 Hz), 4.39 (m, 2H), 4.97 (dd, 1H, J = 1.2, 5.9 Hz), 6.86 (d, 1H, J = 3.3 Hz), 6.94 (dd, 1H, J = 3.4, 5.1 Hz), 7.17 (dd, 1H, J = 1.1, 5.1 Hz). FAB-MS $[M + H]^+$ = 398.0 *m*/*e*. EI-HRMS: calcd for $C_{19}H_{27}NO_4S_2$ $[M^+]$, 397.1382; found, 397.1423. Anal. ($C_{19}H_{27}NO_4S_2$): C, H, N.

Ethyl (2*S*)-5,5-Dimethyl-1-(3,3-dimethyl-1,2-dioxobutyl)-2-(4-thiazolidine)carboxylate (4d). This intermediate compound was prepared from ethyl (2*S*)-5,5-dimethyl-1-(1,2-dioxo-2-ethoxyethyl)-2-(4-thiazolidine)carboxylate **3** (2.5 g, 8.65 mmol) and a 2.0 M solution of *tert*-butylmagnesium chloride (5.75 mL, 11.5 mmol) in ethyl ether in the same procedure as described in the preparation of the intermediate compound **4a** (1.94 g, 74.7%).

(2*S*)-5,5-Dimethyl-1-(3,3-dimethyl-1,2-dioxobutyl)-2-(4-thiazolidine)carboxylic Acid (5d). This intermediate compound was prepared from ethyl (2*S*)-5,5-dimethyl-1-(3,3-dimethyl-1,2-dioxobutyl)-2-(4-thiazolidine)carboxylate **4d** (1.94 g, 6.45 mmol) in the same procedure as described in the preparation of the intermediate compound **5a** (1.46 g, 83.1%).

3-(3-Pyridyl)-1-propyl (2*S*)-5,5-Dimethyl-1-(3,3-dimethyl-1,2-dioxobutyl)-2-(4-thiazolidine)carboxylate (18). This compound was prepared from (2*S*)-5,5-dimethyl-1-(3,3-dimethyl-1,2-dioxobutyl)-2-(4-thiazolidine)carboxylic acid **5d** (366 mg, 1.34 mmol) and 3-(3-pyridyl)-1-propanol (275 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (373 mg, 71.0%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (s, 9H), 1.91 (s, 3H), 1.98 (s, 3H), 2.01 (m, 2H), 2.72 (t, 2H, J = 7.5 Hz), 3.26 (dd, 1H, J = 1.5, 12.2 Hz), 3.33 (dd, 1H, J = 5.8, 12.2 Hz), 4.21 (m, 2H), 5.00 (dd, 1H, J = 1.5, 5.8 Hz), 7.25 (m, 1H), 7.54 (m, 1H), 8.47 (m, 2H). FAB-MS $[M + H]^+$ = 393.4 *m*/*e*. EI-HRMS: calcd for $C_{20}H_{29}N_2O_4S$ $[M + H]^+$, 393.1848; found, 393.1819. Anal. ($C_{20}H_{28}N_2O_4S$): C, H, N.

3-(6-Methyl-2-pyridyl)-1-propyl (2*S*)-5,5-Dimethyl-1-(3,3-dimethyl-1,2-dioxobutyl)-2-(4-thiazolidine)carboxylate (19). This compound was prepared from (2*S*)-5,5-dimethyl-1-(3,3-dimethyl-1,2-dioxobutyl)-2-(4-thiazolidine)carboxylic acid **5d** (366 mg, 1.34 mmol) and 3-(6-methyl-2-pyridyl)-1-propanol (304 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (360 mg, 66.2%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (s, 9H), 1.89 (s, 3H), 1.97 (s, 3H), 2.11 (m, 2H), 2.53 (s, 3H), 2.83 (t, 2H, J = 7.9 Hz), 3.27 (dd, 1H, J = 1.9, 12.3 Hz), 3.32 (dd, 1H, J = 5.5, 12.3 Hz), 4.21 (m, 2H), 5.03 (dd, 1H, J = 1.9, 5.5 Hz), 6.98 (m, 2H), 7.50 (t, 1H, J = 7.7 Hz). FAB-MS $[M + H]^+$ = 407.2 *m*/*e*. EI-HRMS: calcd for $C_{21}H_{30}N_2O_4S$ $[M]^+$, 406.1926; found, 406.1915. Anal. ($C_{21}H_{30}N_2O_4S$): C, H, N.

3-Phenyl-1-propyl (2*S*)-5,5-Dimethyl-1-(3,3-dimethyl-1,2-dioxobutyl)-2-(4-thiazolidine)carboxylate (20). This compound was prepared from (2*S*)-5,5-dimethyl-1-(3,3-dimethyl-1,2-dioxobutyl)-2-(4-thiazolidine)carboxylic acid **5d** (366 mg, 1.34 mmol) and 3-phenyl-1-propanol (274 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (368 mg, 70.3%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (s, 9H), 1.90 (s, 3H), 1.97 (s, 3H), 2.00 (m, 2H), 2.69 (t, 2H, J = 7.4 Hz), 3.24 (dd, 1H, J = 1.4, 12.3 Hz), 3.31 (dd, 1H, J = 5.8, 12.3 Hz), 4.19 (m, 2H), 5.02 (dd, 1H, J = 1.4, 5.8 Hz), 7.19 (m, 3H), 7.29 (m, 2H). FAB-MS $[M + H]^+$ = 392.4 *m*/*e*. EI-HRMS: calcd for $C_{21}H_{30}NO_4S$ $[M + H]^+$, 392.1896; found, 392.1864. Anal. ($C_{21}H_{29}NO_4S$): C, H, N.

1-Phenoxy-2-propyl (2*S*)-5,5-Dimethyl-1-(3,3-dimethyl-1,2-dioxobutyl)-2-(4-thiazolidine)carboxylate (21). This compound was prepared from (2*S*)-5,5-dimethyl-1-(3,3-dimethyl-1,2-dioxo-

butyl)-2-(4-thiazolidine)carboxylic acid **5d** (366 mg, 1.34 mmol) and 1-phenoxy-2-propanol (305 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (402 mg, 73.7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (d, 3H, J = 2.3 Hz), 1.28 (s, 9H), 1.88 (s, 3H), 1.94 (s, 3H), 3.29 (m, 2H), 4.30 (m, 2H), 5.01 (m, 1H), 5.31 (m, 1H), 6.93 (m, 3H), 7.28 (m, 2H). FAB-MS $[M + H]^+ = 408.3$ *m*/*e*. EI-HRMS: calcd for $C_{21}H_{29}NO_5S$ $[M]^+$, 407.1766; found, 407.1789. Anal. ($C_{21}H_{29}NO_5S$): C, H, N.

3-Cyclohexyl-1-propyl (2*S*)-5,5-Dimethyl-1-(3,3-dimethyl-1,2-dioxobutyl)-2-(4-thiazolidine)carboxylate (22). This compound was prepared from (2*S*)-5,5-dimethyl-1-(3,3-dimethyl-1,2-dioxobutyl)-2-(4-thiazolidine)carboxylic acid **5d** (366 mg, 1.34 mmol) and 3-cyclohexyl-1-propanol (285 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (370 mg, 69.5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (m, 2H), 1.11−1.26 (m, 6H), 1.28 (s, 9H), 1.62−1.70 (m, 7H), 1.89 (s, 3H), 1.95 (s, 3H), 3.28 (dd, 1H, J = 2.1, 12.2 Hz), 3.32 (dd, 1H, J = 5.4, 12.2 Hz), 4.14 (m, 2H), 5.04 (dd, 1H, J = 2.1, 5.4 Hz). FAB-MS $[M + H]^+ = 398.3$ *m*/*e*. EI-HRMS: calcd for $C_{21}H_{36}NO_4S$ $[M + H]^+$, 398.2365; found, 398.2342. Anal. ($C_{21}H_{35}NO_4S$): C, H, N.

3-(*N*,*N*-Dibenzylamino)-1-propyl (2*S*)-5,5-Dimethyl-1-(3,3-dimethyl-1,2-dioxobutyl)-2-(4-thiazolidine)carboxylate (23). This compound was prepared from (2*S*)-5,5-dimethyl-1-(3,3-dimethyl-1,2-dioxobutyl)-2-(4-thiazolidine)carboxylic acid **5d** (366 mg, 1.34 mmol) and 3-(*N*,*N*-dibenzylamino)-1-propanol (513 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (387 mg, 56.7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 9H), 1.82 (m, 2H), 1.86 (s, 3H), 1.90 (s, 3H), 2.49 (t, 2H, J = 6.7 Hz), 2.93 (d, 1H, J = 12.3 Hz), 3.14 (dd, 1H, J = 6.0, 12.3 Hz), 3.54 (s, 4H), 4.19 (m, 2H), 4.92 (d, 1H, J = 6.0 Hz), 7.22−7.35 (m, 10H). FAB-MS $[M + H]^+ = 511.3$ *m*/*e*. EI-HRMS: calcd for $C_{29}H_{38}N_2O_4S$ $[M]^+$, 510.2552; found, 510.2543. Anal. ($C_{29}H_{38}N_2O_4S$): C, H, N.

9-Decen-1-yl (2*S*)-5,5-Dimethyl-1-(3,3-dimethyl-1,2-dioxobutyl)-2-(4-thiazolidine)carboxylate (24). This compound was prepared from (2*S*)-5,5-dimethyl-1-(3,3-dimethyl-1,2-dioxobutyl)-2-(4-thiazolidine)carboxylic acid **5d** (366 mg, 1.34 mmol) and 9-decen-1-ol (314 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (323 mg, 58.6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (s, 9H), 1.28−1.37 (m, 10H), 1.64 (m, 2H), 1.89 (s, 3H), 1.96 (s, 3H), 2.04 (m, 2H), 3.28 (dd, 1H, J = 2.1, 12.2 Hz), 3.32 (dd, 1H, J = 5.4, 12.2 Hz), 4.15 (m, 2H), 4.93 (dd, 1H, J = 2.0, 12.2 Hz), 4.99 (dd, 1H, J = 2.0, 15.5 Hz), 5.04 (dd, 1H, J = 2.1, 5.4 Hz), 5.79 (ddt, 1H, J = 6.7, 12.2, 15.5 Hz). FAB-MS $[M + H]^+ = 412.4$ *m*/*e*. EI-HRMS: calcd for $C_{22}H_{38}NO_4S$ $[M + H]^+$, 412.2522; found, 412.2522. Anal. ($C_{22}H_{37}NO_4S$): C, H, N.

(2*R*)-1-Methoxy-2-propyl (2*S*)-5,5-Dimethyl-1-(3,3-dimethyl-1,2-dioxobutyl)-2-(4-thiazolidine)carboxylate (25). This compound was prepared from (2*S*)-5,5-dimethyl-1-(3,3-dimethyl-1,2-dioxobutyl)-2-(4-thiazolidine)carboxylic acid **5d** (366 mg, 1.34 mmol) and (2*R*)-1-methoxy-2-propanol (181 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (332 mg, 71.8%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (m, 12H), 1.89 (s, 3H), 1.96 (s, 3H), 3.30 (m, 2H), 3.34 (s, 3H), 3.43 (m, 2H), 5.02 (dd, 1H, J = 2.5, 4.9 Hz), 5.13 (m, 1H). FAB-MS $[M + H]^+ = 346.1$ *m*/*e*. EI-HRMS: calcd for $C_{16}H_{28}NO_5S$ $[M + H]^+$, 346.1688; found, 346.1654. Anal. ($C_{16}H_{27}NO_5S$): C, H, N.

Ethyl (2*S*)-5,5-Dimethyl-1-(1,2-dioxooctyl)-2-(4-thiazolidine)-carboxylate (4e). This intermediate compound was prepared from ethyl (2*S*)-5,5-dimethyl-1-(1,2-dioxo-2-ethoxyethyl)-2-(4-thiazolidine)carboxylate **3** (2.5 g, 8.65 mmol) and a 2.0 M solution of hexylmagnesium chloride (5.75 mL, 11.5 mmol) in THF in the same procedure as described in the preparation of the intermediate compound **4a** (2.01 g, 70.7%).

(2*S*)-5,5-Dimethyl-1-(1,2-dioxooctyl)-2-(4-thiazolidine)carboxylic Acid (5e). This intermediate compound was prepared from ethyl (2*S*)-5,5-dimethyl-1-(1,2-dioxooctyl)-2-(4-thiazolidine)carboxylate **4e** (2.01 g, 6.11 mmol) in the same procedure as described in the preparation of the intermediate compound **5a** (1.49 g, 81.0%).

3-(3-Pyridyl)-1-propyl (2*S*)-5,5-Dimethyl-1-(1,2-dioxooctyl)-2-(4-thiazolidine)carboxylate (26). This compound was prepared from (2*S*)-5,5-dimethyl-1-(1,2-dioxooctyl)-2-(4-thiazolidine)carboxylic acid **5e** (403 mg, 1.34 mmol) and 3-(3-pyridyl)-1-propanol (275 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (423 mg, 75.1%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (m, 3H), 1.28 (m, 6H), 1.54 (m, 2H), 1.87 (s, 3H), 1.97 (s, 3H), 2.00 (m, 2H), 2.71 (t, 2H, J = 7.1 Hz), 2.73 (m, 1H), 2.99 (m, 1H), 3.31 (m, 2H), 4.19 (m, 2H), 5.42 (dd, 1H, J = 2.8, 5.2 Hz), 7.26 (m, 1H), 7.54 (m, 1H), 8.48 (m, 2H). FAB-MS $[M + H]^+ = 421.3$ *m*/*e*. EI-HRMS: calcd for $C_{22}H_{32}N_2O_4S$ $[M]^+$, 420.2083; found, 420.2024. Anal. ($C_{22}H_{32}N_2O_4S$): C, H, N.

3-Phenyl-1-propyl (2*S*)-5,5-Dimethyl-1-(1,2-dioxooctyl)-2-(4-thiazolidine)carboxylate (27). This compound was prepared from (2*S*)-5,5-dimethyl-1-(1,2-dioxooctyl)-2-(4-thiazolidine)carboxylic acid **5e** (403 mg, 1.34 mmol) and 3-phenyl-1-propanol (274 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (399 mg, 71.0%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (m, 3H), 1.27 (m, 6H), 1.54 (m, 2H), 1.86 (s, 3H), 1.93 (s, 3H), 1.98 (m, 2H), 2.69 (t, 2H, J = 7.4 Hz), 2.70 (m, 1H), 2.99 (m, 1H), 3.30 (m, 2H), 4.17 (m, 2H), 5.43 (dd, 1H, J = 3.3, 4.5 Hz), 7.19 (m, 3H), 7.29 (m, 2H). FAB-MS $[M + H]^+ = 420.1$ *m*/*e*. EI-HRMS: calcd for $C_{23}H_{33}NO_4S$ $[M]^+$, 419.2130; found, 419.2145. Anal. ($C_{23}H_{33}NO_4S$): C, H, N.

3-Phenyl-1-prop-2-(*E*)-enyl (2*S*)-5,5-Dimethyl-1-(1,2-dioxooctyl)-2-(4-thiazolidine)carboxylate (28). This compound was prepared from (2*S*)-5,5-dimethyl-1-(1,2-dioxooctyl)-2-(4-thiazolidine)carboxylic acid **5e** (403 mg, 1.34 mmol) and 3-phenyl-1-prop-2-(*E*)-enol (269 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (330 mg, 59.1%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (m, 3H), 1.27 (m, 6H), 1.53 (m, 2H), 1.86 (s, 3H), 1.93 (s, 3H), 2.72 (m, 1H), 3.02 (m, 1H), 3.33 (dd, 1H, J = 5.8, 12.2 Hz), 3.38 (dd, 1H, J = 2.2, 12.2 Hz), 4.80 (m, 2H), 5.50 (dd, 1H, J = 2.2, 5.8 Hz), 6.23 (dt, 1H, J = 6.4, 15.9 Hz), 6.66 (d, 1H, J = 15.9 Hz), 7.33 (m, 5H). FAB-MS $[M + H]^+ = 418.1$ *m*/*e*. EI-HRMS: calcd for $C_{23}H_{32}NO_4S$ $[M + H]^+$, 418.2052; found, 418.2047. Anal. ($C_{23}H_{31}NO_4S$): C, H, N.

2-(2-Chlorophenyl)-1-ethyl (2*S*)-5,5-Dimethyl-1-(1,2-dioxooctyl)-2-(4-thiazolidine)carboxylate (29). This compound was prepared from (2*S*)-5,5-dimethyl-1-(1,2-dioxooctyl)-2-(4-thiazolidine)carboxylic acid **5e** (403 mg, 1.34 mmol) and 2-(2-chlorophenyl)-1-ethanol (314 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (398 mg, 67.6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (m, 3H), 1.29 (m, 6H), 1.53 (m, 2H), 1.84 (s, 3H), 1.89 (s, 3H), 2.66 (m, 1H), 2.98 (m, 1H), 3.09 (t, 2H, J = 6.8 Hz), 3.26 (m, 2H), 4.40 (t, 2H, J = 6.8 Hz), 5.40 (dd, 1H, J = 3.2, 4.9 Hz), 7.21 (m, 3H), 7.37 (m, 1H). FAB-MS $[M + H]^+ = 440.0$ *m*/*e*. EI-HRMS: calcd for $C_{22}H_{30}ClNO_4S$ $[M]^+$, 439.1584; found, 439.1554. Anal. ($C_{22}H_{30}ClNO_4S$): C, H, N.

Ethyl (2*S*)-5,5-Dimethyl-1-(1,2-dioxodecyl)-2-(4-thiazolidine)-carboxylate (4f). This intermediate compound was prepared from ethyl (2*S*)-5,5-dimethyl-1-(1,2-dioxo-2-ethoxyethyl)-2-(4-thiazolidine)carboxylate **3** (2.5 g, 8.65 mmol) and a 2.0 M solution of octylmagnesium chloride (5.75 mL, 11.5 mmol) in THF in the same procedure as described in the preparation of the intermediate compound **4a** (2.16 g, 69.8%).

(2*S*)-5,5-Dimethyl-1-(1,2-dioxoodecyl)-2-(4-thiazolidine)carboxylic Acid (5f). This intermediate compound was prepared from ethyl (2*S*)-5,5-dimethyl-1-(1,2-dioxodecyl)-2-(4-thiazolidine)carboxylate **4f** (2.16 g, 6.05 mmol) in the same procedure as described in the preparation of the intermediate compound **5a** (1.53 g, 76.9%).

3-(3-Pyridyl)-1-propyl (2*S*)-5,5-Dimethyl-1-(1,2-dioxodecyl)-2-(4-thiazolidine)carboxylate (30). This compound was prepared from (2*S*)-5,5-dimethyl-1-(1,2-dioxodecyl)-2-(4-thiazolidine)carboxylic acid **5f** (441 mg, 1.34 mmol) and 3-(3-pyridyl)-1-propanol (275 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (467 mg, 77.8%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.87 (t, 3H, J = 7.2 Hz), 1.29 (m, 10H), 1.55 (m, 2H), 1.87 (s, 3H), 1.94 (s, 3H), 2.01 (m, 2H), 2.70 (t, 2H, J = 7.8 Hz), 2.74 (m, 1H), 3.01 (m, 1H), 3.32 (m, 2H), 4.20 (m, 2H), 5.43 (dd,

1H, J = 2.4, 5.4 Hz), 7.25 (m, 1H), 7.53 (d, 1H, J = 7.8 Hz), 8.48 (s, 2H). FAB-MS $[M + H]^+$ =449.2 *m/e*. EI-HRMS: calcd for $C_{24}H_{36}N_2O_4S$ $[M]^+$, 448.2396; found, 448.2405. Anal. ($C_{24}H_{36}N_2O_4S$): C, H, N.

2-(2-Chlorophenyl)-1-ethyl (2*S*)-5,5-Dimethyl-1-(1,2-dioxodecyl)-2-(4-thiazolidine)carboxylate (31). This compound was prepared from (2*S*)-5,5-dimethyl-1-(1,2-dioxodecyl)-2-(4-thiazolidine)carboxylic acid **5f** (441 mg, 1.34 mmol) and 2-(2-chlorophenyl)-1-ethanol (314 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (422 mg, 67.5%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.87 (t, 3H, J = 7.2 Hz), 1.27 (m, 10H), 1.53 (m, 2H), 1.84 (s, 3H), 1.89 (s, 3H), 2.67 (m, 1H), 2.98 (m, 1H), 3.09 (t, 2H, J = 6.6 Hz), 3.28 (m, 2H), 4.39 (t, 2H, J = 6.6 Hz), 5.40 (dd, 1H, J = 3.6, 6.0 Hz), 7.20 (m, 3H), 7.36 (m, 1H). FAB-MS $[M + H]^+$ = 468.3 *m/e*. EI-HRMS: calcd for $C_{24}H_{35}ClNO_4S$ $[M + H]^+$, 468.1975; found, 468.1982. Anal. ($C_{24}H_{34}ClNO_4S$): C, H, N.

(2*R*)-1-Methoxy-2-propyl (2*S*)-5,5-Dimethyl-1-(1,2-dioxodecyl)-2-(4-thiazolidine)carboxylate (32). This compound was prepared from (2*S*)-5,5-dimethyl-1-(1,2-dioxodecyl)-2-(4-thiazolidine)carboxylic acid **5f** (441 mg, 1.34 mmol) and (2*R*)-1-methoxy-2-propanol (181 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (300 mg, 55.8%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.87 (t, 3H, J = 7.2 Hz), 1.23 (m, 13H), 1.55 (m, 2H), 1.86 (s, 3H), 1.92 (s, 3H), 2.70 (m,1H), 3.03 (m, 1H), 3.29 (m, 2H), 3.35 (s, 3H), 3.41 (m, 2H), 5.10 (m, 1H), 5.43 (m, 1H). FAB-MS $[M + H]^+$ = 402.1 *m/e*. EI-HRMS: calcd for $C_{20}H_{36}NO_5S$ $[M + H]^+$, 402.2314; found, 402.2316. Anal. ($C_{20}H_{35}NO_5S$): C, H, N.

2-Pentyl (2*S*)-5,5-Dimethyl-1-(1,2-dioxodecyl)-2-(4-thiazolidine)carboxylate (33). This compound was prepared from (2*S*)-5,5-dimethyl-1-(1,2-dioxodecyl)-2-(4-thiazolidine)carboxylic acid **5f** (441 mg, 1.34 mmol) and 2-pentanol (177 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (321 mg, 60.1%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.87 (t, 3H, J = 7.2 Hz), 0.91 (m, 3H), 1.21 (t, 3H, J = 7.8 Hz), 1.26−1.38 (m, 12H), 1.44−1.61 (m, 4H), 1.86 (s, 3H), 1.92 (s, 3H), 2.71 (m, 1H), 3.03 (m, 1H), 3.31 (m, 2H), 4.95 (m, 1H), 5.41 (m, 1H). FAB-MS $[M + H]^+$ = 400.1 *m/e*. EI-HRMS: calcd for $C_{21}H_{38}NO_4S$ $[M + H]^+$, 400.2522; found, 400.2504. Anal. ($C_{21}H_{37}NO_4S$): C, H, N.

Ethyl (2*S*)-5,5-Dimethyl-1-(1,2-dioxo-2-phenyl)ethyl-2-(4-thiazolidine)carboxylate (4g). This intermediate compound was prepared from ethyl (2*S*)-5,5-dimethyl-1-(1,2-dioxo-2-ethoxyethyl)-2-(4-thiazolidine)carboxylate **3** (2.5 g, 8.65 mmol) and a 2.0 M solution of phenylmagnesium chloride (5.75 mL, 11.5 mmol) in THF in the same procedure as described in the preparation of the intermediate compound **4a** (2.1 g, 75.6%).

(2*S*)-5,5-Dimethyl-1-(1,2-dioxo-2-phenyl)ethyl-2-(4-thiazolidine)carboxylic Acid (5g). This intermediate compound was prepared from ethyl (2*S*)-5,5-dimethyl-1-(1,2-dioxo-2-phenyl)ethyl-2-(4-thiazolidine)carboxylate **4g** (2.1 g, 6.54 mmol) in the same procedure as described in the preparation of the intermediate compound **5a** (1.49 g, 77.8%).

3-(3-Pyridyl)-1-propyl (2*S*)-5,5-Dimethyl-1-(1,2-dioxo-2-phenyl)-ethyl-2-(4-thiazolidine)carboxylate (34). This compound was prepared from (2*S*)-5,5-dimethyl-1-(1,2-dioxo-2-phenyl)ethyl-2-(4-thiazolidine)carboxylic acid **5g** (393 mg, 1.34 mmol) and 3-(3-pyridyl)-1-propanol (275 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (441 mg, 79.9%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80 (m, 2H), 1.99 (s, 3H), 2.09 (s, 3H), 2.57 (m, 2H), 3.31 (dd, 1H, J = 1.5, 12.2 Hz), 3.39 (dd, 1H, J = 5.8, 12.2 Hz), 3.98 (dt, 1H, J = 6.4, 10.9 Hz), 4.07 (dt, 1H, J = 6.4, 10.9 Hz), 5.20 (dd, 1H, J = 1.5, 5.8 Hz), 7.22 (m, 1H), 7.42−7.60 (m, 5H), 8.01 (m, 1H); 8.45 (m, 2H). FAB-MS $[M + H]^+$ = 413.3 *m/e*. EI-HRMS: calcd for $C_{22}H_{24}N_2O_4S$ $[M]^+$, 412.1457; found, 412.1450. Anal. ($C_{22}H_{24}N_2O_4S$): C, H, N.

3-Phenyl-1-propyl (2*S*)-5,5-Dimethyl-1-(1,2-dioxo-2-phenyl)-ethyl-2-(4-thiazolidine)carboxylate (35). This compound was prepared from (2*S*)-5,5-dimethyl-1-(1,2-dioxo-2-phenyl)ethyl-2-(4-thiazolidine)carboxylic acid **5g** (393 mg, 1.34 mmol) and 3-phenyl-1-propanol (274 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (411 mg, 74.7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80 (m, 2H), 1.99 (s, 3H), 2.09 (s, 3H), 2.56 (m, 2H), 3.30 (dd, 1H, J = 1.4, 12.1 Hz), 3.38 (dd, 1H, J = 5.8, 12.1 Hz), 3.93 (dt, 1H, J = 6.5, 10.9 Hz), 4.05 (dt, 1H, J = 6.5, 10.9 Hz), 5.20 (dd, 1H, J = 1.4, 5.8 Hz), 7.09−8.03 (m, 10H). FAB-MS $[M + H]^+$ = 412.4 *m/e*. EI-HRMS: calcd for $C_{23}H_{25}NO_4S$ $[M]^+$, 411.1504; found, 411.1492. Anal. ($C_{23}H_{25}NO_4S$): C, H, N.

3-Phenyl-1-prop-2-(*E*)-enyl (2*S*)-5,5-Dimethyl-1-(1,2-dioxo-2-phenyl)ethyl-2-(4-thiazolidine)carboxylate (36). This compound was prepared from (2*S*)-5,5-dimethyl-1-(1,2-dioxo-2-phenyl)ethyl-2-(4-thiazolidine)carboxylic acid **5g** (393 mg, 1.34 mmol) and 3-phenyl-1-prop-2-(*E*)-enol (269 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (335 mg, 61.1%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98 (s, 3H), 2.09 (s, 3H), 3.39 (d, 2H, J = 3.9 Hz), 4.54 (ddd, 1H, J = 1.2, 6.6, 12.7 Hz), 4.64 (m, 1H), 5.28 (t, 1H, J = 3.9 Hz), 5.99 (dt, 1H, J = 6.6, 15.9 Hz), 6.49 (d, 1H, J = 15.9 Hz), 7.26−8.03 (m, 10H). FAB-MS $[M + H]^+$ = 410.4 *m/e*. EI-HRMS: calcd for $C_{23}H_{23}NO_4S$ $[M]^+$, 409.1348; found, 409.1372. Anal. ($C_{23}H_{23}NO_4S$): C, H, N.

3-Cyclohexyl-1-propyl (2*S*)-5,5-Dimethyl-1-(1,2-dioxo-2-pheny)-ethyl-2-(4-thiazolidine)carboxylate (37). This compound was prepared from (2*S*)-5,5-dimethyl-1-(1,2-dioxo-2-phenyl)ethyl-2-(4-thiazolidine)carboxylic acid **5g** (393 mg, 1.34 mmol) and 3-cyclohexyl-1-propanol (285 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (397 mg, 71.0%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79−1.82 (m, 15H), 1.98 (s, 3H), 2.08 (s, 3H), 3.34 (dd, 1H, J = 1.9, 12.2 Hz), 3.38 (dd, 1H, J = 5.4, 12.2 Hz), 3.85 (dt, 1H, J = 6.9, 10.6 Hz), 3.98 (dt, 1H, J = 6.9, 10.6 Hz), 5.22 (dd, 1H, J = 1.9, 5.4 Hz), 7.42−8.08 (m, 5H). FAB-MS $[M + H]^+$ = 418.4 *m/e*. EI-HRMS: calcd for $C_{23}H_{32}NO_4S$ $[M + H]^+$, 418.2052; found, 418.2047. Anal. ($C_{23}H_{31}NO_4S$): C, H, N.

9-Decen-1-yl (2*S*)-5,5-Dimethyl-1-(1,2-dioxo-2-phenyl)ethyl-2-(4-thiazolidine)carboxylate (38). This compound was prepared from (2*S*)-5,5-dimethyl-1-(1,2-dioxo-2-phenyl)ethyl-2-(4-thiazolidine)carboxylic acid **5g** (393 mg, 1.34 mmol) and 9-decen-1-ol (314 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (336 mg, 58.2%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20−1.44 (m, 12H), 1.98 (s, 3H), 2.03 (m, 2H), 2.07 (s, 3H), 3.33 (dd, 1H, J = 1.9, 12.1 Hz), 3.38 (dd, 1H, J = 5.4, 12.1 Hz), 3.87 (dt, 1H, J = 6.8, 10.7 Hz), 3.99 (dt, 1H, J = 6.8, 10.7 Hz), 4.97 (m, 2H), 5.22 (dd, 1H, J = 1.9, 5.4 Hz), 5.79 (m, 1H), 7.47 (m, 2H), 7.61 (m, 1H), 8.02 (m, 2H). FAB-MS $[M + H]^+$ = 432.4 *m/e*. EI-HRMS: calcd for $C_{24}H_{33}NO_4S$ $[M]^+$, 431.2130; found, 431.2130. Anal. ($C_{24}H_{33}NO_4S$): C, H, N.

Ethyl (2*S*)-5,5-Dimethyl-1-[2-(4-chlorophenyl)-1,2-dioxoethyl]-2-(4-thiazolidine)carboxylate (4h). This intermediate compound was prepared from ethyl (2*S*)-5,5-dimethyl-1-(1,2-dioxo-2-ethoxyethyl)-2-(4-thiazolidine)carboxylate **3** (1.0 g, 3.46 mmol) and a 1.0 M solution of 4-chlorophenylmagnesium bromide (4.6 mL, 4.6 mmol) in ethyl ether in the same procedure as described in the preparation of the intermediate compound **4a** (829 mg, 67.3%).

(2*S*)-5,5-Dimethyl-1-[2-(4-chlorophenyl)-1,2-dioxoethyl]-2-(4-thiazolidine)carboxylic Acid (5h). This intermediate compound was prepared from ethyl (2*S*)-5,5-dimethyl-1-[2-(4-chlorophenyl)-1,2-dioxoethyl]-2-(4-thiazolidine)carboxylate **4h** (829 mg, 2.33 mmol) in the same procedure as described in the preparation of the intermediate compound **5a** (682 g, 89.2%).

3-(3-Pyridyl)-1-propyl (2*S*)-5,5-Dimethyl-1-[2-(4-chlorophenyl)-1,2-dioxoethyl]-2-(4-thiazolidine)carboxylate (39). This compound was prepared from (2*S*)-5,5-dimethyl-1-[2-(4-chlorophenyl)-1,2-dioxoethyl]-2-(4-thiazolidine)carboxylic acid **5h** (438 mg, 1.34 mmol) and 3-(3-pyridyl)-1-propanol (275 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (456 mg, 76.3%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.83 (m, 2H), 1.97 (s, 3H), 2.07 (s, 3H), 2.58 (m, 2H), 3.36 (m, 2H), 4.07 (m, 2H), 5.26 (m, 1H), 7.23 (m, 1H), 7.49 (m, 3H), 7.99 (m, 2H,), 8.45 (m, 2H). FAB-MS $[M + H]^+$ = 447.2 *m/e*. EI-HRMS: calcd for $C_{22}H_{23}ClN_2O_4S$ $[M]^+$, 446.1067; found, 446.1069. Anal. ($C_{22}H_{23}ClN_2O_4S$): C, H, N.

Ethyl (2*S*)-5,5-Dimethyl-1-[1,2-dioxo-2-(2,4,6-trimethylphenyl)]-ethyl-2-(4-thiazolidine)carboxylate (4i). This intermediate compound was prepared from ethyl (2*S*)-5,5-dimethyl-1-(1,2-dioxo-2-ethoxyethyl)-2-(4-thiazolidine)carboxylate **3** (2.5 g, 8.65 mmol) and a 1.0 M solution of 2,4,6-trimethylphenylmagnesium bromide (11.5 mL, 11.5 mmol) in THF in the same procedure as described in the preparation of the intermediate compound **4a** (2.23 g, 71.0%).

(2*S*)-5,5-Dimethyl-1-[1,2-dioxo-2-(2,4,6-trimethylphenyl)]ethyl-2-(4-thiazolidine)carboxylic Acid (5i). This intermediate compound was prepared from ethyl (2*S*)-5,5-dimethyl-1-[1,2-dioxo-2-(2,4,6-trimethylphenyl)]ethyl-2-(4-thiazolidine)carboxylate **4i** (2.23 g, 6.14 mmol) in the same procedure as described in the preparation of the intermediate compound **5a** (1.67 mg, 81.2%).

3-(3-Pyridyl)-1-propyl (2*S*)-5,5-Dimethyl-1-[1,2-dioxo-2-(2,4,6-trimethylphenyl)]ethyl-2-(4-thiazolidine)carboxylate (40). This compound was prepared from (2*S*)-5,5-dimethyl-1-[1,2-dioxo-2-(2,4,6-trimethylphenyl)]ethyl-2-(4-thiazolidine)carboxylic acid **5i** (449 mg, 1.34 mmol) and 3-(3-pyridyl)-1-propanol (275 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (386 mg, 63.5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.92 (s, 3H), 2.03 (s, 3H), 2.04 (m, 2H), 2.25 (s, 6H), 2.28 (s, 3H), 2.75 (t, 2H, J = 7.7 Hz), 3.31 (dd, 1H, J = 1.2, 12.3 Hz), 3.39 (dd, 1H, J = 6.0, 12.3 Hz), 4.28 (m, 2H), 5.36 (dd, 1H, J = 1.2, 6.0 Hz), 6.85 (s, 2H), 7.22 (m, 1H), 7.55 (m, 1H), 8.48 (m, 2H). FAB-MS $[M + H]^+$ = 455.1 *m*/*e*. EI-HRMS: calcd for $C_{25}H_{30}N_2O_4S$ $[M]^+$, 454.1926; found, 454.1909. Anal. ($C_{25}H_{30}N_2O_4S$): C, H, N.

3-Phenyl-1-propyl (2*S*)-5,5-Dimethyl-1-[1,2-dioxo-2-(2,4,6-trimethylphenyl)]ethyl-2-(4-thiazolidine)carboxylate (41). This compound was prepared from (2*S*)-5,5-dimethyl-1-[1,2-dioxo-2-(2,4,6-trimethylphenyl)]ethyl-2-(4-thiazolidine)carboxylic acid **5i** (449 mg, 1.34 mmol) and 3-phenyl-1-propanol (274 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (416 mg, 68.6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.92 (s, 3H), 2.02 (m, 2H), 2.03 (s, 3H), 2.25 (s, 6H), 2.28 (s, 3H), 2.73 (t, 2H, J = 7.5 Hz), 3.30 (dd, 1H, J = 1.2, 12.2 Hz), 3.37 (dd, 1H, J = 6.1, 12.2 Hz), 4.25 (m, 2H), 5.37 (dd, 1H, J = 1.2, 6.1 Hz), 6.85 (s, 2H), 7.20 (m, 3H), 7.28 (m, 2H). FAB-MS $[M + H]^+$ = 454.2 *m*/*e*. EI-HRMS: calcd for $C_{26}H_{32}NO_4S$ $[M + H]^+$, 454.2052; found, 454.2038. Anal. ($C_{26}H_{31}NO_4S$): C, H, N.

3-Cyclohexyl-1-propyl (2*S*)-5,5-Dimethyl-1-[1,2-dioxo-2-(2,4,6-trimethylphenyl)]ethyl-2-(4-thiazolidine)carboxylate (42). This compound was prepared from (2*S*)-5,5-dimethyl-1-[1,2-dioxo-2-(2,4,6-trimethylphenyl)]ethyl-2-(4-thiazolidine)carboxylic acid **5i** (449 mg, 1.34 mmol) and 3-cyclohexyl-1-propanol (285 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (361 mg, 58.7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (m, 2H), 1.11−1.28 (m, 6H), 1.60−1.70 (m, 7H), 1.91 (s, 3H), 2.01 (s, 3H), 2.25 (s, 6H), 2.28 (s, 3H), 3.32 (dd, 1H, J = 1.7, 12.2 Hz), 3.37 (dd, 1H, J = 5.6, 12.2 Hz), 4.20 (m, 2H), 5.38 (dd, 1H, J = 1.7, 5.6 Hz), 6.85 (s, 2H). FAB-MS $[M + H]^+$ = 460.2 *m*/*e*. EI-HRMS: calcd for $C_{26}H_{38}NO_4S$ $[M + H]^+$, 460.2522; found, 460.2495. Anal. ($C_{26}H_{37}NO_4S$): C, H, N.

3-Phenoxy-1-propyl (2*S*)-5,5-Dimethyl-1-[1,2-dioxo-2-(2,4,6-trimethylphenyl)]ethyl-2-(4-thiazolidine)carboxylate (43). This compound was prepared from (2*S*)-5,5-dimethyl-1-[1,2-dioxo-2-(2,4,6-trimethylphenyl)]ethyl-2-(4-thiazolidine)carboxylic acid **5i** (449 mg, 1.34 mmol) and 3-phenoxy-1-propanol (305 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (378 mg, 60.1%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90 (s, 3H), 1.99 (s, 3H), 2.19 (m, 2H), 2.23 (s, 6H), 2.28 (s, 3H), 3.30 (dd, 1H, J = 1.3, 12.3 Hz), 3.36 (dd, 1H, J = 5.8, 12.3 Hz), 4.08 (m, 2H), 4.45 (m, 2H), 5.35 (dd, 1H, J = 1.3, 5.8 Hz), 6.84 (s, 2H), 6.94 (m, 3H), 7.26 (m, 2H). FAB-MS $[M + H]^+$ = 470.1 *m*/*e*. EI-HRMS: calcd for $C_{26}H_{32}NO_5S$ $[M + H]^+$, 470.2001; found, 470.2077. Anal. ($C_{26}H_{31}NO_5S$): C, H, N.

2-Aminobenzyl (2*S*)-5,5-Dimethyl-1-[1,2-dioxo-2-(2,4,6-trimethylphenyl)]ethyl-2-(4-thiazolidine)carboxylate (44). This compound was prepared from (2*S*)-5,5-dimethyl-1-[1,2-dioxo-2-(2,4,6-trimethylphenyl)]ethyl-2-(4-thiazolidine)carboxylic acid **5i** (449 mg, 1.34 mmol) and 2-aminobenzyl alcohol (247 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (281 mg, 47.6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89 (s, 3H), 1.96 (s, 3H), 2.22 (s, 6H), 2.28 (s, 3H), 3.31 (dd, 1H, J = 1.5, 12.4 Hz), 3.36 (dd, 1H, J = 5.8, 12.4 Hz), 3.48−5.05 (br, 2H), 5.23 (m, 2H), 5.29 (dd, 1H, J = 1.5, 5.8 Hz), 6.74 (m, 2H), 6.84 (s, 2H), 7.17 (m, 2H). FAB-MS $[M + H]^+$ = 441.1 *m*/*e*. EI-HRMS: calcd for $C_{24}H_{28}N_2O_4S$ $[M]^+$, 440.1770; found, 440.1751. Anal. ($C_{24}H_{28}N_2O_4S$): C, H, N.

2-(*N*-Benzyl-*N*-methyl)amino-1-ethyl (2*S*)-5,5-Dimethyl-1-[1,2-dioxo-2-(2,4,6-trimethylphenyl)]ethyl-2-(4-thiazolidine)carboxylate (45). This compound was prepared from (2*S*)-5,5-dimethyl-1-[1,2-dioxo-2-(2,4,6-trimethylphenyl)]ethyl-2-(4-thiazolidine)carboxylic acid **5i** (449 mg, 1.34 mmol) and 2-(*N*-benzyl-*N*-methyl)amino-1-ethanol (332 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (353 mg, 54.7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91 (s, 3H), 2.01 (s, 3H), 2.24 (s, 6H), 2.28 (s, 6H), 2.77 (m, 2H), 3.30 (dd, 1H, J = 1.5, 12.3 Hz), 3.36 (dd, 1H, J = 5.8, 12.3 Hz), 3.58 (m, 2H), 4.37 (m, 2H), 5.38 (dd, 1H, J = 1.5, 5.8 Hz), 6.84 (s, 2H); 7.25 (m, 1H), 7.30 (m, 4H). FAB-MS $[M + H]^+$ = 483.2 *m*/*e*. EI-HRMS: calcd for $C_{27}H_{35}N_2O_4S$ $[M + H]^+$, 483.2318; found, 483.2370. Anal. ($C_{27}H_{34}N_2O_4S$): C, H, N.

1-Phenoxy-2-propyl (2*S*)-5,5-Dimethyl-1-[1,2-dioxo-2-(2,4,6-trimethylphenyl)]ethyl-2-(4-thiazolidine)carboxylate (46). This compound was prepared from (2*S*)-5,5-dimethyl-1-[1,2-dioxo-2-(2,4,6-trimethylphenyl)]ethyl-2-(4-thiazolidine)carboxylic acid **5i** (449 mg, 1.34 mmol) and 1-phenoxy-2-propanol (305 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (424 mg, 67.4%). ^{1}H NMR (400 MHz, $CDCl_3$) δ1.32 (m, 3H), 1.90 (s, 3H), 2.04 (s, 3H), 2.25 (s, 6H), 2.28 (s, 3H), 3.28 (dd, 1H, J = 3.5, 12.7 Hz), 3.42 (dd, 1H, J = 6.8, 12.7 Hz), 3.67 (m, 2H), 4.16 (m, 1H), 5.45 (dd, 1H, J = 3.5, 6.8 Hz), 6.89 (m, 5H), 7.26 (m, 2H). FAB-MS $[M + H]^+$ = 470.1 *m*/*e*. EI-HRMS: calcd for $C_{26}H_{31}NO_5S$ $[M]^+$, 469.1923; found, 469.1923. Anal. ($C_{26}H_{31}NO_5S$): C, H, N.

9-Decen-1-yl (2*S*)-5,5-Dimethyl-1-[1,2-dioxo-2-(2,4,6-trimethylphenyl)]ethyl-2-(4-thiazolidine)carboxylate (47). This compound was prepared from (2*S*)-5,5-dimethyl-1-[1,2-dioxo-2-(2,4,6-trimethylphenyl)]ethyl-2-(4-thiazolidine)carboxylic acid **5i** (449 mg, 1.34 mmol) and 9-decen-1-ol (314 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (321 mg, 50.6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28−1.38 (m, 10H), 1.67 (m, 2H), 1.91 (s, 3H), 2.01 (s, 3H), 2.02 (m, 2H), 2.25 (s, 6H), 2.28 (s, 3H), 3.32 (dd, 1H, J = 1.6, 12.3 Hz), 3.37 (dd, 1H, J = 5.7, 12.3 Hz), 4.22 (m, 2H), 4.93 (dd, 1H, J = 1.8, 10.2 Hz), 4.99 (dd, 1H, J = 1.8, 17.1 Hz), 5.38 (dd, 1H, J = 1.6, 5.7 Hz), 5.80 (ddt, 1H, J = 6.7, 10.2, 17.1 Hz), 6.85 (s, 2H). FAB-MS $[M + H]^+$ = 474.2 *m*/*e*. EI-HRMS: calcd for $C_{27}H_{40}NO_4S$ $[M + H]^+$, 474.2678; found, 474.2708. Anal. ($C_{27}H_{39}NO_4S$): C, H, N.

Ethyl (2*S*)-5,5-Dimethyl-1-(1,2-dioxo-4-methyl-4-phenyl)pentyl-2-(4-thiazolidine)carboxylate (4j). This intermediate compound was prepared from ethyl (2*S*)-5,5-dimethyl-1-(1,2-dioxo-2-ethoxyethyl)-2-(4-thiazolidine)carboxylate **3** (1.5 g, 5.19 mmol) and a 0.5 M solution of 2-methyl-2-phenylproplymagnesium chloride (13.8 mL, 6.9 mmol) in ethyl ether in the same procedure as described in the preparation of the intermediate compound **4a** (1.27 g, 64.7%).

(2*S*)-5,5-Dimethyl-1-(1,2-dioxo-4-methyl-4-phenyl)pentyl-2-(4-thiazolidine)carboxylic Acid (5j). This intermediate compound was prepared from ethyl (2*S*)-5,5-dimethyl-1-(1,2-dioxo-4-methyl-4-phenyl)pentyl-2-(4-thiazolidine)carboxylate **4j** (1.27 g, 3.34 mmol) in the same procedure as described in the preparation of the intermediate compound **5a** (894 mg, 76.7%).

3-(3-Pyridyl)-1-propyl (2*S*)-5,5-Dimethyl-1-(1,2-dioxo-4-methyl-4-phenyl)pentyl-2-(4-thiazolidine)carboxylate (48). This compound was prepared from (2*S*)-5,5-dimethyl-1-(1,2-dioxo-4-methyl-4-phenyl)ethyl-2-(4-thiazolidine)carboxylic acid **5j** (468 mg, 1.34 mmol) and 3-(3-pyridyl)-1-propanol (275 mg, 2.01 mmol) in the same procedure as described in the preparation of compound **6** (409 mg, 65.2%). ^{1}H NMR (600 MHz, $CDCl_3$) δ1.41 (s, 3H), 1.44 (s, 3H), 1.71 (s, 3H), 1.88 (s, 3H), 1.96 (m, 2H), 2.67 (t, 2H, J = 7.8 Hz), 2.74 (d, 1H, J = 16.2 Hz), 2.97 (dd, 1H, J = 6.0, 12.0 Hz), 3.07 (d, 1H, J = 12.0 Hz), 3.82 (d, 1H, J = 16.2 Hz), 4.15 (m,

2H), 4.59 (d, 1H, $J = 6.0$ Hz), 7.18−7.36 (m, 7H), 8.47 (m, 2H). FAB-MS $[M + H]^+ = 469.1$ *m/e*. EI-HRMS: calcd for $C_{26}H_{33}N_2O_4S$ $[M + H]^+$, 469.2161; found, 469.2187. Anal. ($C_{26}H_{32}N_2O_4S$): C, H, N.

Chick Dorsal Root Ganglion Cultures. Dorsal root ganglia (DRGs) were dissected from chick embryos of 8 d gestation and inoculated in rat rail collagen-coated culture flasks. Following a 1 h of attachment at 37 °C in a humidified 5% CO_2 atmosphere, the DRGs were treated with the test compounds plus 0.15 ng/mL of NGF in Dulbecco's modified Eagle's medium (DMEM). The control groups received the same amount of NGF only. The DRGs were further incubated in a 37 °C, 5% CO_2 incubator for 48 h prior to evaluation. The ganglia were observed under phase contrast with an Olympus CK2 inverted microscope and were scored based on the number and length of the neurite processes. Five to six DRGs were cultured per flask. The average scoring of 15−18 ganglia was taken as the determination of effect for each treatment. Statistically significant differences between groups were determined by a one-way analysis of variance followed by a Student-Newman-Keuls post hoc analysis.

Mouse Peripheral Sympathetic Nerve Injury Induced by Intraperitoneal Injection of 6-Hydroxydopamine. Eighteen 22 g adult female Kunming mice were grouped ($n = 10$ per group). Peripheral sympathetic nerves were lesioned by i.p. injection of 8 mg/kg 6-hydroxydopamine (6-OHDA). Mice received s.c. injection of the test compounds 4 h prior to 6-OHDA treatment and daily for 4 subsequent days following 6-OHDA lesion. The control groups received the same amount of vehicle. The animals were sacrificed 2 weeks after the last treatment, and the wet submandibuar glands in both sides were removed quickly and weighed. After homogenization together with internal standard compound 3,4-dihydroxybenzylamine hydrobromide and centrifugalization for 30 min, the norepinepherine content in 20 μL of supernatant fluid was measured by HPLC-ECD. Statistically significant differences between groups were determined by a one-way analysis of variance followed by a Student-Newman-Keuls post hoc analysis.

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Supporting Information Available: Elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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