Articles

Design, Synthesis, and Evaluation of Benzothiadiazepine Hydroxamates as Selective Tumor Necrosis Factor-α Converting Enzyme Inhibitors

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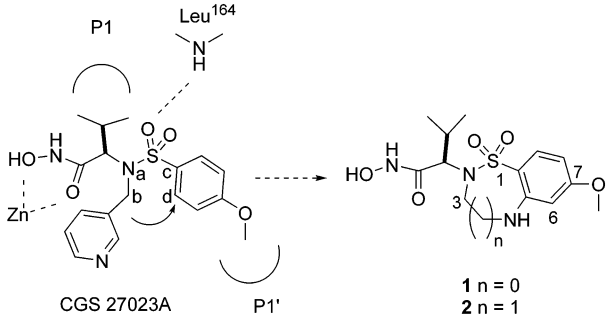
Elevated levels of tumor necrosis factor-α (TNF-α) have been associated with several inflammatory diseases, and therefore, strategies for its suppression have become important targets in drug discovery. Our efforts to suppress TNF-α have centered on the inhibition of TNF-α converting enzyme (TACE) through the use of hydroxamate inhibitors. Starting from broad-spectrum matrix metalloproteinase (MMP) inhibitors, we have designed and synthesized novel benzothiadiazepines as potent and selective TACE inhibitors. The benzothiadiazepines were synthesized with variation in P1 and P1′ in order to effect potency and selectivity. The inhibitors were evaluated versus porcine TACE (pTACE), and the initial selectivity was assessed with counterscreens of MMP-1, -2, and -9. Several potent and selective inhibitors were discovered with compound **41** being the most active against pTACE (K_i = 5 nM) while still maintaining good selectivity versus the MMP's (at least 75-fold). Most compounds were assessed in the human peripheral blood mononuclear cell assay (PBMC) and the human whole blood assay (WBA) to determine their ability to suppress TNF-α. Compound **32** was the most potent compound in the PBMC assay (IC_{50} = 0.35 μM), while compound **62** was the most active in the WBA (IC_{50} = 1.4 μM).

Introduction

Tumor necrosis factor-α (TNF-α) is a cytokine normally produced by mononuclear cells in response to immunostimuli to protect against infection, tissue destruction, and tumors.[1] However, when overproduced, it is proinflammatory in nature and initiates a cascade of other agents including IL-1 and IL-6. The overproduction of TNF-α has been linked to several diseases including rheumatoid arthritis (RA),[2] Crohn's disease,[3] and psoriasis.[4] TNF-α is initially produced as a membrane-bound 26 kDa propeptide on the cell surface. TNF-α converting enzyme (TACE)[5,6] is the metalloproteinase that processes pro-TNF-α to its soluble 17 kDa form, thus resulting in its release from the cell surface. TACE (ADAM-17) is a member of the adamalysin/reprolysin subfamily contained within the metzincin superfamily, which also includes the matrix metalloproteinases (MMPs).[7,8] In fact, initially it was shown that a subset of MMP inhibitors was capable of inhibiting the release of TNF-α from cells through their interaction with TACE.[9−11] In the intervening time, TACE has been purified and cloned[12,13] as well as crystallized with a bound inhibitor.[14] As the major sheddase identified in the release of soluble TNF-α, there has been a great deal of interest in the design of TACE inhibitors[15] in order to suppress the amount of circulating TNF-α.[16] The beneficial effect of TNF-α suppression was demonstrated clinically via two protein-based drugs in RA and Crohn's disease.[17−20] A bioavailable small molecule that could achieve this level of effectiveness is highly desirable. As a result, we undertook the structure-based design of novel TACE inhibitors via MMP inhibitor leads.

Scheme 1. Benzothiadiazepine Design



Design

An early, non-peptidic lead compound to emerge from the MMP field was the Novartis compound CGS 27023A.[21] Scheme 1 shows the general binding features of CGS 27023A functioning as an MMP inhibitor that we utilized in our design.[21] The tetrahedral sulfone not

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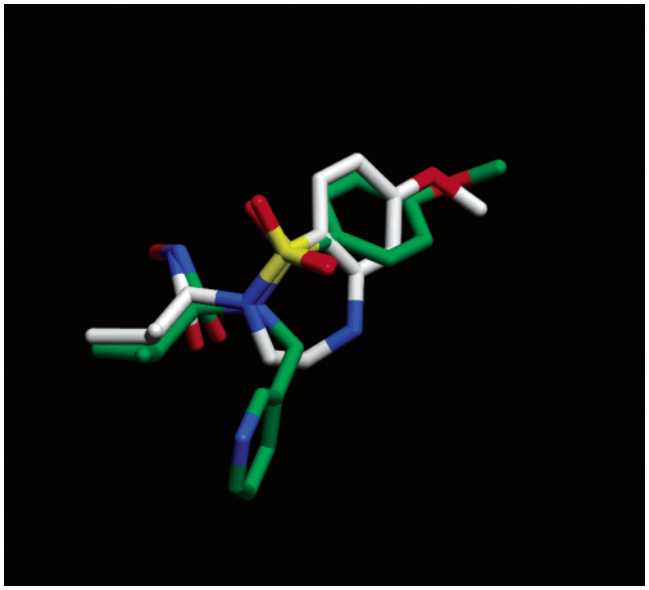


Figure 1. Overlay of benzothiadiazepine **2** (white) and CGS 27023A (green).

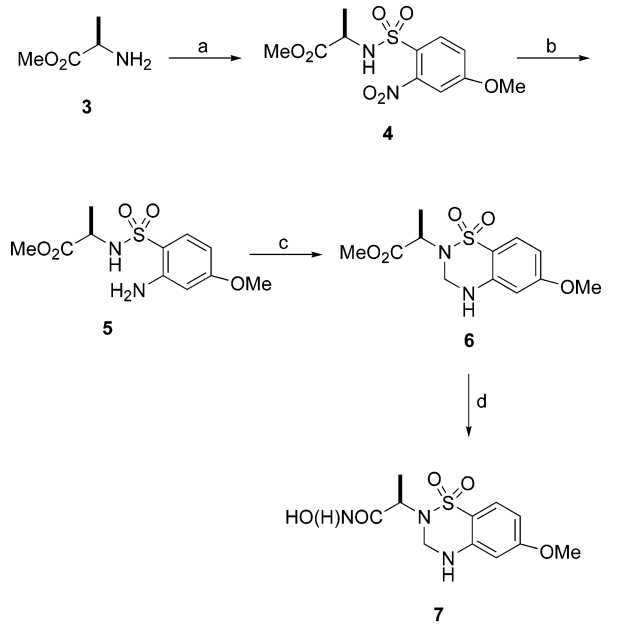
only directs the *p*-methoxyphenyl group into the S1′ pocket but also acts as a hydrogen bond acceptor from Leu-164 of the protein backbone. In turn, the pyridyl group is oriented toward the solvent-exposed area of the active site and therefore has minimal contact with the protein. In addition, the sulfonamide orients bond a−b and bond c−d synplanar to one another, thus placing b and d in proximity. We felt this was an excellent place to constrain the system and proposed to connect b to d while removing the pyridyl ring, since it appeared solvent exposed. In addition, from docking experiments it appeared that insertion of a hydrogen bond donor would be beneficial for interaction with the backbone amide carbonyl of residue Pro-221. This hydrogen bond could best be realized with the installation of an N−H at the ring juncture. The above requirements are best fulfilled by a six-membered benzothiadiazine **1** or seven-membered benzothiadiazepine **2** as shown in Scheme 1. In fact, benzothiadiazepine **2** could adopt a conformation similar to that of CGS 27023A as shown by an overlay in Figure 1.

Synthesis

As shown in Scheme 2, the benzothiadiazine **7** was synthesized from the methyl ester of D-alanine **3**. Commercially available 4-methoxy-2-nitrobenzenesulfonyl chloride was coupled with **3** to give sulfonamide **4**, which was subsequently reduced. The resulting aniline **5** was stirred in methanol with formaldehyde and then cyclized with *p*-toluenesulfonic acid to give the six-membered ring **6**. Direct conversion of the methyl ester to the target hydroxamate **7** was accomplished with a hydroxylamine solution.

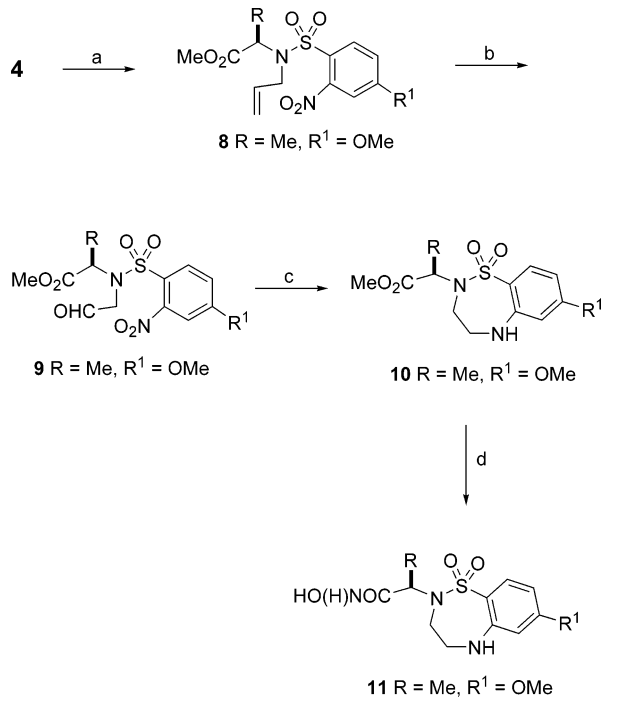
As illustrated with compound **11** (Scheme 3), the first benzothiadiazepines were synthesized from the sulfonamide **4**. Alkylation of the sulfonamide with allyl bromide gave **8**, which was oxidized to aldehyde **9**. Treatment of **9** with zinc/acetic acid at reflux effected reduction of the nitro group with a concomitant intramolecular reductive alkylation to generate benzothiadiazepine **10**. Again, the methyl ester was converted

Scheme 2[a]



[a] Reagents: (a) 4-methoxy-2-nitrobenzenesulfonyl chloride, iPr_2NEt, CH_2Cl_2, 0 °C; (b) H_2, 10% Pd/C, MeOH; (c) (i) 37% HCHO, MeOH, (ii) *p*-TsOH, DMF; (d) NH_2OH, KOH, MeOH.

Scheme 3[a]

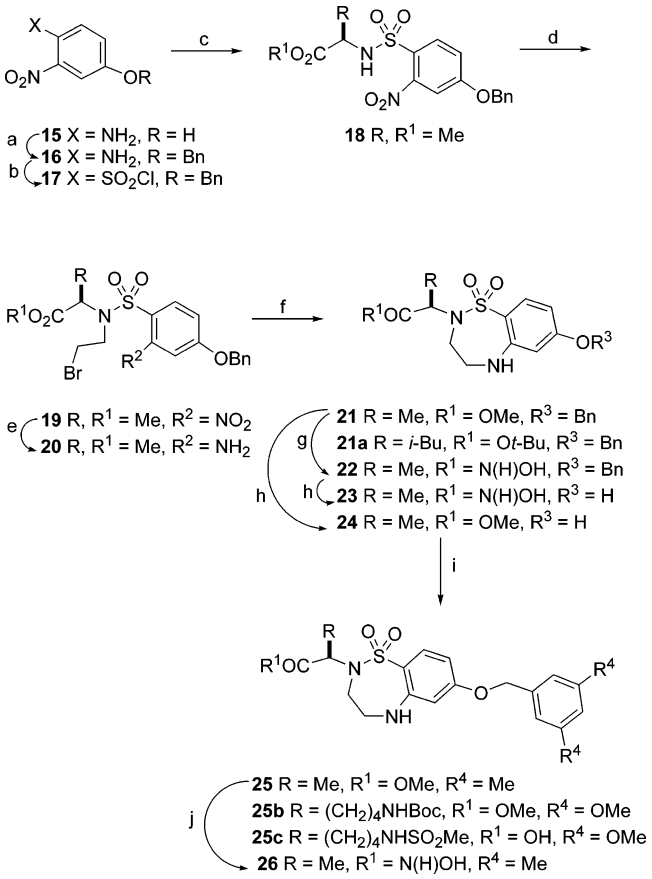


[a] Reagents: (a) 60% NaH, allyl bromide, DMF; (b) (i) O_3, CH_2Cl_2, MeOH, (ii) Me_2S; (c) Zn, HOAc, Δ; (d) H_2NOH, KOH, MeOH.

to the target hydroxamate **11** with a hydroxylamine solution. Compound **2** and compounds **11**−**14** were made in this manner according to Scheme 3.

Synthesis of second-generation benzothiadiazepines required a suitably protected C-7 hydroxyl group. As illustrated with compound **26** in Scheme 4, the synthesis was initiated with a chemoselective alkylation of 4-amino-3-nitrophenol **15** to give the benzyl-protected **16**. Diazotization of **16** allowed for its conversion to the sulfonyl chloride **17**. On a large scale, *we found that the use of commercially available sulfurous acid solutions was*

Scheme 4[a]

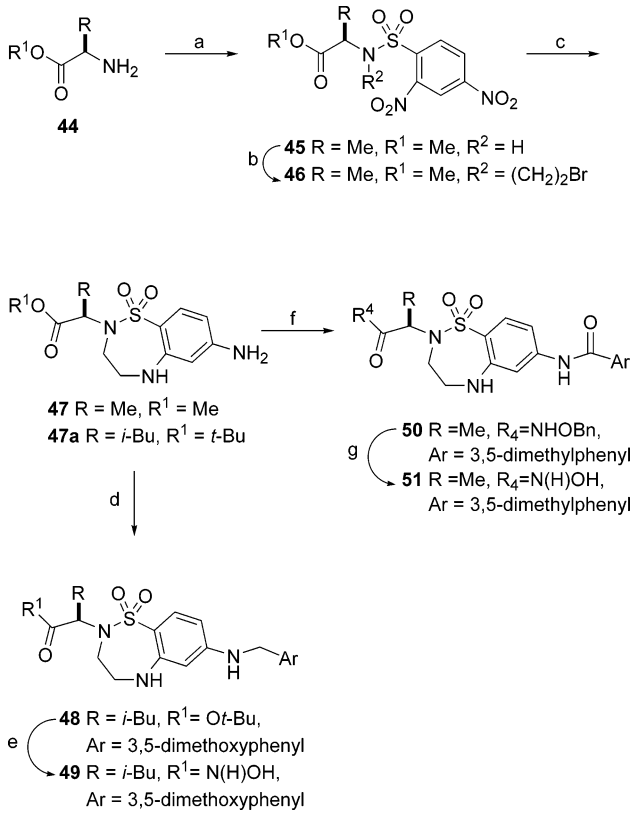


[a] Reagents: (a) 1 M KOtBu, BnBr, DMF, 0 °C; (b) (i) $NaNO_2$, TFA, HCl, 0 °C, (ii) H_2SO_3, $CuCl_2$, CuCl, AcOH; (c) D-Ala-OMe·HCl, iPr_2NEt, CH_2Cl_2, 0 °C; (d) $BrCH_2CH_2OH$, DEAD, PPh_3, THF; (e) Fe, AcOH, 60 °C; (f) NMM, DMF, 80 °C; (g) H_2NOH, KOH, MeOH; (h) H_2, 5% $Pd/BaSO_4$, MeOH; (i) 1 M KOtBu, 3,5-dimethylbenzyl bromide, DMF, 0 °C; (j) H_2NOH, KOH, MeOH (method A) or (i) TFA, CH_2Cl_2; (ii) BOP reagent, H_2NOH·HCl, NMM, DMF (method B).

more convenient than the use of gaseous sulfur dioxide for this transformation. Condensation of **17** with a wide variety of amino acid esters produced sulfonamide **18**. The sulfonamide was substituted under Mitsunobu conditions[22] to give bromide **19**. Reduction of the nitro gave aniline **20**, which was cyclized to benzothiadiazepine **21** by heating with 4-methylmorpholine. Treatment of **21** with a hydroxylamine solution gave the hydroxamate **22**, which was debenzylated to **23**. The benzyl group of **21** was also removed to give the versatile phenol **24**. In many cases, phenol **24** was alkylated with substituted benzyl bromides to give **25**. This was processed to the hydroxamate via two methods depending on the ester present in **25**. For methyl esters, the aforementioned direct transformation with hydroxylamine was used to afford **26** (method A; compounds **27**−**30** were made via this method). If a *tert*-butyl ester was present, it was converted to the carboxylate and then directly coupled with BOP reagent and hydroxylamine to give the target hydroxamate (method B; compounds **31**−**40** were made via this method).

As shown in Scheme 5, an amino group was incorporated at C-7 with the use of commercially available 2,4-dinitrophenylsulfonyl chloride. Hence, sulfonamide **45** was used in the Mitsunobu reaction to give bromide **46**. Reduction of **46** followed by cyclization in warm DMF

Scheme 5[a]



[a] Reagents: (a) NMM, 2,4-dinitrobenzenesulfonyl chloride, dioxane; (b) $BrCH_2CH_2OH$, DEAD, PPh_3, THF; (c) (i) Fe, AcOH, 60 °C, (ii) NMM, DMF, 80 °C; (d) 3,5-dimethoxybenzaldehyde, $NaBH_4$, EtOH; (e) (i) TFA, CH_2Cl_2, (ii) H_2NOBn, BOP, NMM, DMF, (iii) H_2, 5% $Pd/BaSO_4$, MeOH; (f) (i) LiOH, THF/H_2O, (ii) H_2NOBn, BOP, NMM, DMF, (iii) 3,5-dimethylbenzoic acid, BOP reagent, NMM, DMF; (g) H_2, 5% $Pd/BaSO_4$, MeOH.

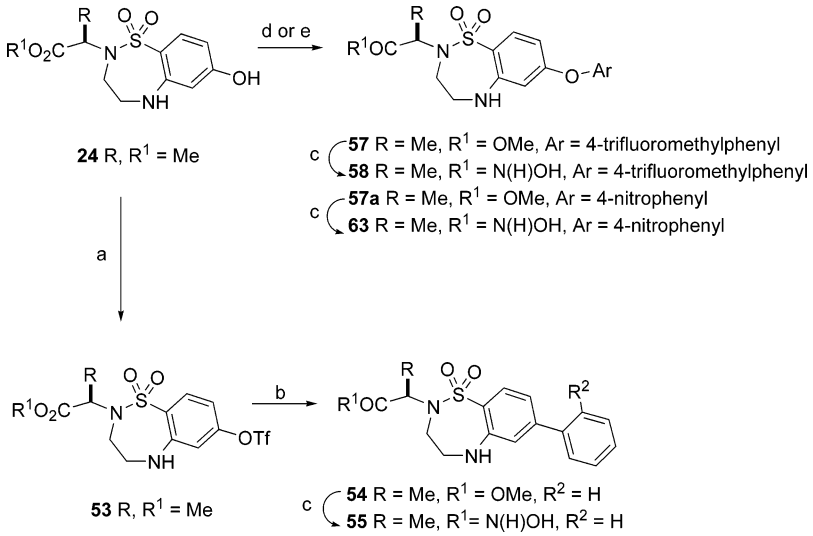
gave the versatile benzothiadiazepine **47** (**47a** was obtained in an analogous manner starting with D-Leu-OtBu and 2,4-dinitrophenylsulfonyl chloride). Reductive amination of **47a** with 3,5-dimethoxybenzaldehyde gave **48**. The ester was converted to the *O*-benzyl-protected hydroxamate before hydrogenation afforded the target hydroxamate **49**. Conversion of **47** to the *O*-benzyl hydroxamate followed by an acylation with 3,5-dimethylbenzoic acid gave **50**. Hydrogenation of this material gave hydroxamate **51**.

As illustrated with compound **55** (Scheme 6), phenol **24** was also converted to aryl triflate **53** and utilized for palladium couplings. Again, standard derivatization of ester **54** gave hydroxamate **55**. Compound **56** was also made by this method. As shown with compound **58**, phenol **24** was directly coupled to 4-(trifluoromethyl)-benzeneboronic acid[23,24] to give phenyl ether **57**, which was in turn processed to hydroxamate **58**. Compounds **59**−**62** were made in analogous fashion. Ether production was also accomplished by an S_NAr reaction of **24** with 1-fluoro-4-nitrobenzene and cesium carbonate to yield **57a**. Normal processing via method A gave the hydroxamate **63**.

Results and Discussion

The newly synthesized hydroxamates were evaluated against porcine TACE (pTACE) to assess their inhibitory potency.[25] Porcine TACE was selected as a result of its availability and its high homology to human

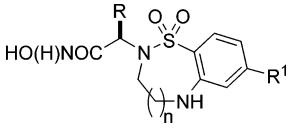
Scheme 6[a]



[a] Reagent: (a) Tf_2O, iPr_2NEt, CH_2Cl_2, −78 °C; (b) $Pd(OAc)_2$, $C_6H_5B(OH)_2$, PPh_3, toluene, 110 °C; (c) H_2NOH, KOH, MeOH; (d) $Cu(OAc)_2$, Et_3N, 4-trifluoromethylbenzeneboronic acid, 4 Å molecular sieves, CH_2Cl_2; (e) 1-fluoro-4-nitrobenzene, Cs_2CO_3, DMF.

TACE. All compounds were then screened for initial selectivity against MMP-1, -2, and -9.[25] Broad-spectrum MMP inhibitors have displayed musculoskeletal pain and inflammation as a side effect in clinical trials;[26,27] hence, it was our desire to achieve at least 100-fold selectivity for pTACE over MMP-1, -2, and -9. As shown in Table 1, we were gratified to observe good pTACE affinity for benzothiadiazepine **11**, thereby validating our design (Scheme 1). The six-membered benzothiadiazine **7** was about 10-fold less active versus pTACE than the seven-membered **11**. This was also reflected in their MMP values, and therefore, we concentrated on the seven-membered template. With this information in hand, we examined the effect of substitution at P1 and P1′ of the benzothiadiazepine. Without substitution at P1 and P1′, the benzothiadiazepine was inactive as shown with compound **12**. However, most of the activity was restored with a P1 methyl substitution as in **13**, which was about 2-fold less active than **11** in pTACE. In contrast, methoxy substitution alone at P1′ (see compound **14**) was inactive. Early optimization of P1 indicated that an isopropyl group was beneficial, since **2** was about 4-fold more active than **11**.

Table 1. In Vitro Evaluation: Early Inhibitors

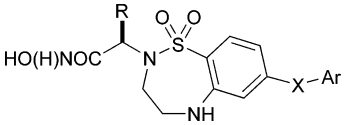


				K_i [a] (nM)			
compd	*n*	R	R^1	pTACE	MMP-1	MMP-2	MMP-9
7	0	Me	OMe	3100	>4949	312	1050
11	1	Me	OMe	274	1060	8	104
12	1	H	H	>1000	>4949	1915	>2128
13	1	Me	H	484	>4949	75	567
14	1	H	OMe	>1000	>4949	1497	>2128
2	1	iPr	OMe	71	732	52	751

[a] K_i values are an average from three determinations. Standard deviations are less than 15% in all cases.

With these early compounds, we were able to validate our design; however, to attain more affinity for pTACE, we needed to go deeper into S1′. In addition, we surmised that as the main recognition pocket for the MMPs, S1′ would be an excellent location to achieve selectivity for pTACE over the MMPs. With a methyl in P1, we began to probe S1′ with benzyl groups alkylated on the C-7 phenol. The phenol itself, **23**, did have affinity for pTACE (K_i = 391 nM); however, it was virtually devoid of selectivity versus the MMPs with only a 2-fold margin over MMP-1 relative to pTACE. The benzyl ether **22** did not improve the pTACE activity; however, selectivity against MMP-1 was increased to at least 7-fold. The selectivity of the benzyl substituent over MMP-1 is probably attributed to the short S1′ pocket of MMP-1[28−30] relative to the S1′ pocket of TACE. Selectivity versus MMP-2 and -9 remained unaffected as a result of their long S1′ pockets, and therefore, other factors were considered. In this lower section of S1′, homology modeling of TACE predicted pronounced curvature[31] whereas the MMPs are essentially linear. Taking advantage of this, it has been our experience[32] that an appropriately placed 3,5-disubstituted aromatic will maintain a good fit in TACE while clashing into the wall of the MMP S1′pocket. We initially installed the 3,5-dimethyl substituent in **26** and observed about a 3-fold increase in pTACE affinity (K_i = 229 nM) relative to the parent benzyl **22**. *In accord with the model,*[31] *the 3,5-dimethyl substitution of* ***26*** *also dramatically improved the selectivity over the MMPs with an MMP-9 selectivity of at least 9-fold*. The 3,5-dichloro substitution of **27** gave a profile similar to that of **26**, whereas the 3,5-dimethoxy **28** provided increases not only in pTACE activity (K_i = 27 nM) but also in MMP selectivity, since **28** was selective over MMP-2 by 18-fold relative to pTACE. As we progressed to the larger 3,5-diethoxy substitution, **29**, the pTACE activity (K_i = 81 nM) decreased 3-fold relative to **28**, indicating that the 3,5-diethoxy substitution was approaching a size incompatible with the size of the S1′ of pTACE. The picolyl ether **30** was also investigated but was found to have diminished (2-fold) pTACE affinity relative to **26**. To optimize the template further, we turned our attention to the isobutyl substituent in P1.

Table 2. In Vitro Evaluation of Benzothiadiazepine Inhibitors



				K_i [a] (nM)				IC_{50} [b] (μM) or % inhibition @ 10 μM	
compd	R	X	Ar	pTACE	MMP-1	MMP-2	MMP-9	PBMC	WBA
23	Me	OH		391	980	<2.8	100	NT	21%
22	Me	OCH_2	phenyl	705	>4949	<2.8	3.6	NT	30%
26	Me	OCH_2	3,5-dimethylphenyl	229	>4949	136	>2128	NT	2%
27	Me	OCH_2	3,5-dichlorophenyl	153	>4949	49	1209	0.94	12%
28	Me	OCH_2	3,5-dimethoxyphenyl	27	>4949	491	>2128	0.77	28 μM
29	Me	OCH_2	3,5-diethoxyphenyl	81	>4949	690	>2128	4.5	26%
30	Me	OCH_2	2,6-dimethyl-4-pyridinyl	544	>4949	75	1839	2.9	37%
31	iBu	OH		89	479	11	80	9.5	20%
32	iBu	OCH_2	phenyl	177	548	<2.8	<2.1	0.35	39%
33	iBu	OCH_2	3,5-dimethoxyphenyl	17	>4949	154	>2128	5.4	16%
34	iPr	OCH_2	3,5-dimethoxyphenyl	10	>4949	647	981	4.0	11%
35	iPr	OCH_2	3,5-diethoxyphenyl	51	>4949	3001	>2128	8.2	17%
36	iPr	OCH_2	4,5-dimethyl-2-thiazolyl	290	>4949	361	>2128	24.5	0%
37	$(CH_2)_2CO_2Me$	OCH_2	3,5-dimethoxyphenyl	177	>4949	1595	>2128	7.2	0%
38	$(CH_2)_2CO_2Me$	OCH_2	3,5-diethoxyphenyl	242	>4949	960	>2128	6.2	0%
39	$(CH_2)_3CO_2Me$	OCH_2	3,5-dimethoxyphenyl	10	>4949	332	>2128	0.9	31%
40	$(CH_2)_3CO_2Me$	OCH_2	3,5-diethoxyphenyl	13	>4949	1376	>2128	1.1	24 μM
41	$(CH_2)_4NHSO_2Me$	OCH_2	3,5-dimethoxyphenyl	5	>4949	391	>2128	1.9	38 μM
42	$(CH_2)_4NHBoc$	OCH_2	3,5-dimethoxyphenyl	77	>4949	32	118	NT	3%
43	$(CH_2)_4NH_2$	OCH_2	3,5-dimethoxyphenyl	31	>4949	231	>2128	NT	3%
49	iBu	$NHCH_2$	3,5-dimethoxyphenyl	56	>4949	75	347	NT	19%
51	Me	NHC(O)	3,5-dimethylphenyl	>1000	>4949	94	993	NT	NT
55	Me		phenyl	>1000	272	<2.8	8	NT	NT
56	Me		2-(trifluoromethyl)phenyl	>1000	>4949	2518	>2128	NT	NT
58	Me	O	4-(trifluoromethyl)phenyl	758	>4949	<2.8	7	0.84	44%
59	Me	O	4-methoxyphenyl	621	>4949	<2.8	<2.1	NT	NT
60	Me	O	phenyl	734	>4949	23	3	NT	NT
61	Me	O	4-biphenyl	>1000	2019	<2.8	<2.1	NT	NT
62	Me	O	3-nitrophenyl	129	>4949	85	96	0.47	1.4 μM
63	Me	O	4-nitrophenyl	11	>4949	8	19	1.2	15 μM

[a] K_i values are from three determinations. Standard deviations are less than 15% in all cases. [b] IC_{50} values are an average from three donors.

When the rigidity of the template and the lipophilicity in P1 were increased, the parent isobutyl **31** had a 4-fold increase in affinity for pTACE over the P1 methyl compound **23**. The same effect was observed for the benzyl compound **32** compared to the P1 methyl compound **22**. To restore the MMP selectivity, the 3,5-dimethoxy substitution was installed, and **33** was almost 2-fold more active versus pTACE than the P1 methyl analogue **28**. Continuing to probe P1, we installed the isopropyl group along with the 3,5-dimethoxybenzyl to afford **34**, which was about 2-fold better than **28** and **33** versus pTACE. Perhaps even more important was the effect the P1 isopropyl had on the MMP-2 selectivity, since **34** had a selectivity of 60-fold for pTACE over MMP-2. Trying to capitalize on this, we again increased the size of the 3,5-substitution to diethoxy; however, **35** lost pTACE affinity while retaining excellent MMP selectivity. We also found heterocycles that were accommodated in S1′, since the thiazole **36** had good activity for pTACE and selectivity against MMP-1, -2, and -9.

In an effort to gain more affinity, we extended P1 by utilizing glutamate and homoglutamate methyl esters at that position. The glutamate ester was paired with the 3,5-dimethoxy (**37**) and 3,5-diethoxy (**38**) but proved to be unattractive with only moderate pTACE affinity. However, the homoglutamate ester of both the 3,5-dimethoxy (**39**) and 3,5-diethoxy (**40**) surprisingly displayed 18-fold more affinity for pTACE than its corresponding glutamate. In keeping with the trend above, the 3,5-diethoxy **40** had excellent selectivity over the MMPs tested (100-fold over MMP-2).

Continuing in the P1 position, several lysine derivatives were also incorporated. The best compound in the lysine series was the methyl sulfonamide **41**, which had excellent pTACE affinity (K_i = 5 nM) and excellent MMP selectivity (70-fold over MMP-2). Lipophilic groups such as the *N*-Boc of **42** had a detrimental effect on MMP selectivity. However, this was reversed by conversion to the parent amine **43**.

At this point, we assessed different substitution patterns at C-7 to probe S1′. The 3,5-dimethoxybenzyl substituent was incorporated into an amine (compound **49**); however, it displayed diminished pTACE affinity (3-fold) when compared to the corresponding 3,5-dimethoxybenzyl ether **33**. In addition, amine **49** lacked substantial selectivity over MMP-2 and -9 and only displayed selectivity over MMP-1. Switching to the amide **51** resulted in an altered projection into S1′ and a compound inactive in pTACE.

Other substitution patterns were probed as we investigated the direct attachment of the distal ring, which gave the biaryl **55**. These data suggest that the curvature of the pTACE S1′ cannot accommodate the biaryl of **55**; however, **55** was accommodated by the somewhat linear MMP S1′. The added *o*-trifluoromethyl

of **56** had poor affinity in pTACE and MMP-1, -2, and -9. In this case, the 2-substitution probably disrupts the binding in the MMP S1′ much like the 3,5-disubstitution discussed earlier.

To install some curvature back into P1′, the phenyl ethers were examined. Substitution of the distal ring with small groups in the para position was allowable because the trifluoromethyl (**58**), methoxy (**59**), and unsubstituted cases (**60**) all showed fair pTACE affinity while lacking MMP-2 and -9 selectivity. Large groups (P1′ biphenyl **61**) unable to negotiate the putative curvature of the TACE S1′ were inactive while still showing excellent MMP-2 and -9 activity. Moderate pTACE activity was observered for mono substitution at the meta position because the 3-nitro group of **62** was tolerated. However, the best substitution was the 4-nitro, as shown by **63** (pTACE $K_i = 11$ nM).

Cellular Assays

As shown in Table 2, the best compounds were assessed in two cellular assays, the human peripheral blood mononuclear cell assay (PBMC)[33] and the human whole blood assay (WBA),[25] for their ability to suppress the formation of TNF-α brought about by lipopolysaccharide (LPS) stimulation. Success in the PBMC assay relies on the ability of the inhibitor to penetrate into the cells, thus enabling it to inhibit TACE and thereby to suppress the release of intracellular, soluble TNF-α.[34,35] In the WBA, compounds must also have the ability to penetrate cells; however, this is complicated by several other factors, the foremost being protein binding. The majority of the benzothiadiazepines had poor activity in the WBA. Nevertheless, several compounds displayed reasonable PBMC activity, indicating some ability to penetrate cells. In fact, two phenyl ethers (**58** and **62**) and a benzyl ether (**32**) had PBMC values only slightly displaced from their pTACE values, indicating good cell penetration. However, for the most part, the 3,5-disubstituted benzyl ethers had PBMC values displaced by at least 20-fold from their pTACE values. An exception to this was **27**, which had its PBMC value displaced by only 6-fold from the pTACE value. Yet, even this case did not translate well into the WBA because **27** exhibited poor inhibition (12% inhibition at 10 μM in WBA). Protein binding presumably has an effect on the WBA value of **27**, since the free fraction is only 0.6% in human whole blood. Contrast this with the most potent benzothiadiazepine in the WBA compound **62** ($IC_{50} = 1.4$ μM), which has an 8-fold higher free fraction (5% free) in protein binding.

Conclusion

Utilizing structure-based design principles, we have converted a sulfonamide MMP lead structure into a novel benzothiadiazepine inhibitor. From key structural differences between the MMPs and TACE, we modified substitution patterns within P1′ to obtain selectivity and affinity exclusively for TACE. The majority of these inhibitors have displayed poor translation into cellular assays, and we have suggested a combination of variables to be optimized. However, with their affinity for TACE and selectivity over the MMPs, the benzothiadiazepines should aid in the design and development of future metalloproteinase inhibitors.

Experimental Section

All reactions were performed under nitrogen with continuous magnetic stirring unless otherwise stated. Anhydrous solvents from commercial sources were used for all reactions. All other reagents and solvents were reagent grade and used as received from commercial sources. Flash chromatography was performed with E. Merck Kieselgel 60 silica gel (230−400 mesh). As indicated, final compounds were purified via reversed-phase high-performance liquid chromatography (HPLC) on a Dynamax C18 column using gradiant elution (solvent A, water; solvent B, acetonitrile). All ^{1}H NMR were obtained on a Varian Inova spectrometer (operating at 300 MHz), and the signals are reported in ppm relative to TMS. All mass spectra were recorded on a Finnigan Navigator mass spectrometer using electrospray ionization (ESMS) in the positive (pos) or negative (neg) mode as indicated. Elemental analysis was performed by Quantitative Technologies Inc, Bound Brook, NJ.

Hydroxamic acids were prepared via two methods.

Method A (from a Methyl Ester). A 1.76 M NH_2OH stock solution was prepared by dissolving hydroxylamine hydrochloride (2.34 g) in hot MeOH (12 mL). After the mixture was stirred for 5 min, a solution of KOH (2.81 g) in MeOH (7 mL) was added dropwise. The resulting solution was cooled to room temperature and filtered. The filtrate (approximately a 1.76 M NH_2OH stock solution) was stored under nitrogen and used in the next step. The methyl ester (1.17 mmol) was dissolved in MeOH (5 mL) prior to the addition of the 1.76 M NH_2OH stock solution (2.66 mL, 4.68 mmol). After the mixture was stirred for 2 h, 1 N HCl was added to adjust the pH to ∼5. The solution was concentrated, and the residue was partitioned between EtOAc and water. The organic layer was dried and concentrated. Reverse-phase HPLC (water/acetonitrile) or flash chromatography of the resulting residue gave the desired hydroxamate.

Method B (from a *tert*-Butyl Ester). The *tert*-butyl ester (0.58 mmol) was dissolved in CH_2Cl_2 (3 mL), and the mixture was cooled to 0 °C prior to the addition of TFA (15 mL). The reaction mixture was warmed to room temperature and was stirred for 2 h (monitored by TLC for disappearance of *tert*-butyl ester). The solution was concentrated and dried to give the crude carboxylate, which was used directly in the next step. The crude carboxylate was dissolved in DMF prior to the addition of *N*-methylmorpholine (0.26 mL, 2.4 mmol). The mixture was cooled to 0 °C, and BOP reagent (294 mg, 0.66 mmol) was added. After the mixture was stirred for 20 min at 0 °C, $HONH_2$·HCl (82 mg, 1.2 mmol) was added. The reaction mixture was warmed to room temperature and was stirred overnight. The solvent was removed, and the resulting residue was partitioned between EtOAc and saturated NH_4Cl solution. The EtOAc was dried and concentrated. Flash chromatography or reverse-phase HPLC (water/acetonitrile) of the resulting residue gave the desired hydroxamate.

***N*-(4-Methoxy-2-nitrobenzenesulfonyl)-D-Alanine Methyl Ester (4).** D-Alanine methyl ester hydrochloride **3** (3.9 g, 28.1 mmol) was dissolved in CH_2Cl_2 prior to the addition of diisopropylethylamine (12.2 mL, 70.2 mmol). After the mixture was cooled to 0 °C, 4-methoxy-2-nitrobenzenesulfonyl chloride (8.5 g, 33.7 mmol) was added dropwise. The reaction mixture was warmed to room temperature and was stirred overnight. The reaction mixture was washed with 1 N HCl, saturated $NaHCO_3$, and brine. The CH_2Cl_2 was dried, filtered, and concentrated. Flash chromatography (35% ethyl acetate/hexane) of the resulting residue gave the sulfonamide **4** (6.4 g, 20.1 mmol, 71%) as a white foam. ^{1}H NMR ($CDCl_3$): δ 1.47 (d, 3H), 3.56 (s, 3H), 3.85 (s, 3H), 4.2 (m, 1H), 6.01 (br d, 1H), 7.14 (dd, 1H), 7.4 (d, 1H), 7.98 (d, 1H). ESMS (neg), *m*/*z*: 317.1 (M − H).

***N*-(4-Methoxy-2-aminobenzenesulfonyl)-D-Alanine Methyl Ester (5).** The sulfonamide **4** (3.8 g, 11.9 mmol) was dissolved in a mixture of MeOH (10 mL) and THF (3 mL) prior to the addition of 10% Degussa Pd/C (380 mg). The solution was placed on a Parr at 50 psi for 18 h. The solution was filtered and concentrated. This gave the crude aniline **5** (3.4

g, 11.8 mmol, 99%) as a white foam of sufficient purity for the next step. ^{1}H NMR ($CDCl_3$): δ 1.36 (d, 3H), 3.55 (s, 3H), 3.79 (s, 3H), 3.93 (m, 1H), 4.94 (br s, 2H), 5.42 (br d, 1H), 6.2 (d, 1H), 6.34 (dd, 1H), 7.58 (d, 1H). ESMS (pos), *m*/*z*: 289.2 (M + H).

2(*R*)-(6-Methoxy-1,1-dioxo-3,4-dihydro-1*H*-1λ^6-benzo-[1,2,4]thiadiazin-2-yl)propionic Acid Methyl Ester (6). The aniline **5** (400 mg, 1.4 mmol) was dissolved in MeOH (4 mL) prior to the addition of 37% formaldehyde (1.8 mL). After being stirred overnight, the solution was concentrated and then was filtered through silica gel to give a clear oil (360 mg). A portion of this material (100 mg) was dissolved in DMF (2 mL) prior to the addition of *p*-TsOH (10 mg). The solution was stirred overnight before being concentrated. Flash chromatography (30−70% ethyl acetate/hexane) of the resulting residue gave the thiadiazine **6** (7 mg, 0.02 mmol) as a white foam. ^{1}H NMR ($CDCl_3$): δ 1.46 (d, 3H), 3.54 (s, 3H), 3.77 (s, 3H), 4.4 (br s, 1H), 4.58 (m, 2H), 5.06 (m, 2H), 6.11 (d, 1H), 6.43 (dd, 1H), 7.57 (d, 1H). ESMS (pos), *m*/*z*: 323.0 (M + Na).

***N*-Hydroxy-2(*R*)-(6-methoxy-1,1-dioxo-3,4-dihydro-1*H*-1λ^6-benzo[1,2,4]thiadiazin-2-yl)propionamide (7).** The thiadiazine **6** (60 mg, 0.2 mmol) was incorporated into method A, and HPLC gave the hydroxamate **7** (15 mg, 0.05 mmol, 25%) as a white powder. ^{1}H NMR (DMSO): δ 1.17 (br d, 3H), 3.69 (s, 3H), 4.04 (m, 1H), 4.89 (br d, 1H), 5.12 (dd, 1H), 6.19 (br s, 1H), 6.28 (dd, 1H), 7.13 (br s, 1H), 7.35 (d, 1H), 8.91 (br s, 1H), 10.74 (s, 1H). ESMS (neg), *m*/*z*: 299.8 (M − H). HRMS calcd for ($C_{11}H_{15}N_3O_5S$ + H) 302.081 068, found 302.081 282.

***N*-(4-Methoxy-2-nitrobenzenesulfonyl)-*N*-(allyl)-D-Alanine Methyl Ester (8).** The sulfonamide **4** (4.54 g, 14.26 mmol) was dissolved in DMF prior to the addition of allyl bromide (2.47 mL, 28.5 mmol) followed by portionwise addition of 60% NaH (0.86 g, 21.4 mmol). After 20 min, pH 7 phosphate buffer (200 mL) was added, and the mixture was extracted with EtOAc. The EtOAc was washed with pH 7 buffer, water, and brine before being dried and concentrated. The resulting residue was purified by flash chromatography (30−40% ethyl acetate/hexane) to give **8** (2.85 g, 56%) as a yellow liquid. ^{1}H NMR ($CDCl_3$): δ 1.49 (d, 3H), 3.66 (s, 3H), 3.84−3.93 (m, 1H), 3.92 (s, 3H), 4.04−4.12 (m, 1H), 4.79 (q, 1H), 5.06−5.22 (m, 2H), 5.75−5.90 (m, 1H), 7.08−7.13 (m, 2H), 7.98 (d, 1H). ESMS (pos), *m*/*z*: 381.0 (M + Na).

Methyl 2(*R*)-[7-Methoxy-2,3,4,5-tetrahydrobenzo[1,2,5-*f*]thiadiazepine-1,1-dioxide]propanoate (10). Ozone was bubbled into a solution of **8** (2.70 g, 7.53 mmol) in CH_2Cl_2/MeOH (1:1, 100 mL) at −78 °C until the reaction mixture turned green. The reaction mixture was purged with N_2 until it was bright-yellow. Methyl sulfide (3.2 mL) was added, and the reaction mixture was stirred at ambient temperature overnight. The mixture was concentrated to yield the aldehyde **9** as yellow oil, which was used immediately. The aldehyde **9** was dissolved in HOAc (100 mL), and the mixture was cooled with a water bath (15−20 °C) prior to the addition of Zn powder (13 g) portionwise. The mixture was heated at reflux for 3 h. After cooling to room temperature, the reaction mixture was diluted with chloroform (50 mL). The mixture was filtered, and the filter cake was washed with EtOH/$CHCl_3$ (1:1, 200 mL). The filtrate was concentrated and purified by flash chromatograph (40−60% ethyl acetate/hexane) to afford the benzothiadiazepine **10** (0.42 g, 18% for two steps) as a light-yellow solid. ^{1}H NMR ($CDCl_3$): δ 1.38 (d, 3H), 3.50−3.62 (m, 7H), 3.78 (s, 3H), 4.73 (q, 1H), 6.21 (d, 1H), 6.43 (dd, 1H), 7.68 (d, 1H). MS (CI, NH_3), *m*/*z*: 315 (M + H).

***N*-Hydroxy-2(*R*)-[7-methoxy-2,3,4,5-tetrahydrobenzo-[1,2,5-*f*]thiadiazepine-1,1-dioxide]propanamide (11).** The methyl ester **10** (0.37 g, 1.17 mmol) was incorporated into method A, and preparative TLC purification (7.5% MeOH/$CHCl_3$) gave the hydroxamate **11** (90 mg, 24%). ^{1}H NMR (CD_3OD): δ 1.33 (d, 3H), 3.34−3.42 (m, 1H), 3.59 (t, 2H), 3.67−3.75 (m, 1H), 3.78 (s, 3H), 4.43 (q, 1H), 6.40−6.44 (m, 2H), 7.56 (d, 1H). ESMS (neg), *m*/*z*: 314.1 (M − H). HRMS calcd for ($C_{12}H_{18}N_3O_5S$ + H) 316.0967, found 316.0954. Anal. ($C_{12}H_{17}N_3O_5S\cdot0.7H_2O$) C, H, N, S.

Compounds **2** and **12**−**14** were synthesized in a fashion analogous to that of compound **11**.

***N*-Hydroxy-2-[2,3,4,5-tetrahydrobenzo[1,2,5-*f*]thiadiazepine-1,1-dioxide]ethanamide (12).** ^{1}H NMR (CD_3OD): δ 3.35−3.39 (m, 2H), 3.57−3.61 (m, 2H), 3.72 (s, 2H), 6.92−6.99 (m, 2H), 7.35 (m, 1H), 7.71 (dd, 1H). MS (CI, NH_3), *m*/*z*: 272 (M + H). HRMS calcd for ($C_{10}H_{14}N_3O_4S$ + H) 272.0705, found 272.0711. Anal. ($C_{10}H_{14}N_3O_4S$) C, H, N, S.

***N*-Hydroxy-2(*R*)-[2,3,4,5-tetrahydrobenzo[1,2,5-*f*]-thiadiazepine-1,1-dioxide]propanamide (13).** ^{1}H NMR (CD_3OD): δ 1.33 (d, 3H), 3.36−3.45 (m, 1H), 3.60 (t, 2H), 3.68−3.77 (m, 1H), 4.47 (q, 1H), 6.81−6.90 (m, 2H), 7.27 (m, 1H), 7.65 (dd, 1H). ESMS (neg), *m*/*z*: 283.9 (M − H). HRMS calcd for ($C_{11}H_{16}N_3O_4S$ + H) 286.0862, found 286.0863. Anal. ($C_{11}H_{16}N_3O_4S_1\cdot0.1H_2O$) C, H, N, S.

***N*-Hydroxy-2-[7-methoxy-2,3,4,5-tetrahydrobenzo[1,2,5-*f*]thiadiazepine-1,1-dioxide]ethanamide (14).** ^{1}H NMR (CD_3OD): δ 3.28−3.35 (m, 2H), 3.54−3.58 (m, 2H), 3.68 (s, 2H), 3.80 (s, 3H), 6.50−6.55 (m, 2H), 7.62 (d, 1H). ESMS (neg) 300.0 (M − H). HRMS calcd for ($C_{11}H_{15}N_3O_5S$ + H) 302.0811, found 302.0807. Anal. ($C_{11}H_{15}N_3O_5S_1\cdot0.1H_2O$) C, H, N, S.

***N*-Hydroxy-2(*R*)-[7-(methoxy)-2,3,4,5-tetrahydrobenzo-[1,2,5-*f*]thiadiazepine-1,1-dioxide]-4-methylpentanamide (2).** ^{1}H NMR (CD_3OD): δ 0.88 (d, 3H), 0.98 (d, 3H), 2.13−2.24 (m, 1H), 3.26−3.38 (m, 1H), 3.51−3.61 (m, 2H), 3.76 (s, 3H), 3.76−3.85 (m, 2H), 6.38−6.41 (m, 2H), 7.58 (d, 1H). ESMS (neg), *m*/*z*: 342.0 (M − H). HRMS calcd for ($C_{14}H_{22}N_3O_5S$ + H) 344.1280, found 344.1277. Anal. ($C_{14}H_{22}N_3O_5S$) C, H, N, S.

4-Benzyloxy-2-nitroaniline (16). 4-Amino-3-nitrophenol **15** (25 g, 162.2 mmol) was dissolved in DMF and cooled to 0 °C. 1 M potassium *tert*-butoxide (162.2 mL) was added dropwise over 20 min. After the mixture was stirred for 30 min at 0 °C, benzyl bromide (19.8 mL, 162.2 mmol) in DMF was added dropwise. After 30 min at 0 °C, the reaction was quenched with NH_4Cl solution. 4-Benzyloxy-2-nitroaniline **16** (32 g, 131 mmol, 81%) was isolated by filtration. ^{1}H NMR ($CDCl_3$): δ 5.03 (s, 2H), 5.9 (br s, 2H), 6.76 (d, 1H), 7.14 (dd, 1H), 7.4 (m, 5H), 7.65 (d, 1H). MS (CI, NH_3), *m*/*z*: 245 (M + H).

4-Benzyloxy-2-nitrobenzenesulfonyl Chloride (17). 4-Benzyloxy-2-nitroaniline **16** (1.5 g, 6.1 mmol) was dissolved in TFA (20 mL) and concentrated HCl (2 mL). After the mixture was cooled to 0 °C, $NaNO_2$ (529.6 mg, 7.7 mmol) in H_2O was added dropwise over 30 min. Once the addition was complete, the reaction mixture was stirred an additional 5 min. The resulting solution was poured into AcOH (20 mL), H_2SO_3 (20 mL), and $CuCl_2$ (412.8 mg, 3.1 mmol) containing a catalytic amount of CuCl (ca. 25 mg) at 0 °C. After 35 min at room temperature, the solid material was filtered off and was washed with water. This provided 4-benzyloxy-2-nitrobenzenesulfonyl chloride **17** (1.5 g, 4.6 mmol, 75%). ^{1}H NMR ($CDCl_3$): δ 5.23 (s, 2H), 2.6 (m, 1H), 7.39 (d, 1H), 7.42 (m, 5H), 8.14 (d, 1H). ESMS (neg), *m*/*z*: 307.8 (M − Cl + OH − H).

***N*-(4-Benzyloxy-2-nitrobenzenesulfonyl)-D-alanine Methyl Ester (18).** D-Alanine methyl ester hydrochloride (5.7 g, 40.8 mmol) was dissolved in CH_2Cl_2 and diisopropylethylamine (14.8 mL, 85.1 mmol). At 0 °C, 4-benzyloxy-2-nitrobenzenesulfonyl chloride **17** (11.1 g, 34.0 mmol) was added dropwise in CH_2Cl_2. After being stirred overnight, the solution was washed with 1 N HCl. The CH_2Cl_2 was dried, filtered, and concentrated. Flash chromatography (10−40% ethyl acetate/hexane) of the resulting residue gave the sulfonamide **18** (10.6 g, 26.9 mmol, 66%). ^{1}H NMR ($CDCl_3$): δ 1.48 (d, 3H), 3.51 (s, 3H), 4.19 (m, 1H), 5.18 (s, 2H), 6.01 (br d, 1H), 7.19 (dd, 1H), 7.41 (m, 5H), 7.49 (d, 1H), 7.97 (d, 1H). ESMS (pos), *m*/*z*: 416.9 (M + Na).

***N*-(4-Benzyloxy-2-nitrobenzenesulfonyl)-*N*-(bromoethylene)-D-alanine Methyl Ester (19).** The sulfonamide **18** (10.6 g, 26.9 mmol) was dissolved in THF prior to the addition of triphenylphosphine (14.1 g, 53.8 mmol) and 2-bromoethanol (3.8 mL, 53.8 mmol). At room temperature, diethyl azodicarboxylate (8.5 mL, 53.8 mmol) was added dropwise and the reaction mixture was stirred overnight. The THF was removed, and flash chromatography (10−40% ethyl acetate/hexane) of

the resulting residue gave the alkylated sulfonamide **19** (11.5 g, 22.9 mmol, 85%). ^{1}H NMR ($CDCl_3$): δ 1.54 (d, 3H), 3.38−3.58 (m, 3H), 3.61 (s, 3H), 3.62−3.78 (m, 1H), 4.2 (m, 1H), 4.75 (q, 1H), 5.16 (s, 2H), 7.16 (d, 1H), 7.2 (dd, 1H), 7.41 (m, 5H), 7.97 (d, 1H). ESMS (pos), *m/z*: 522.8 (M + Na).

***N*-(4-Benzyloxy-2-aminobenzenesulfonyl)-*N*-(bromoethylene)-D-alanine Methyl Ester (20).** The sulfonamide **19** (11.5 g, 22.9 mmol) was dissolved in glacial AcOH and H_2O prior to the addition of Fe dust (12.8 g). This solution was heated at 60 °C for 1 h. After the mixture was cooled to room temperature, the Fe was filtered off and the AcOH was removed. The resulting residue was dissolved in EtOAc and washed with saturated $NaHCO_3$ solution. The EtOAc was dried, filtered, and concentrated to give the crude aniline **20** (8.9 g, 8.9 mmol, 39%), which was directly used in the next procedure. ^{1}H NMR ($CDCl_3$): δ 1.43 (d, 3H), 3.38−3.5 (m, 2H), 3.54 (s, 3H), 3.57−3.77 (m, 2H), 4.2 (m, 1H), 4.62 (q, 1H), 5.01 (br s, 2H), 5.06 (s, 2H), 6.23 (d, 1H), 6.4 (dd, 1H), 7.39 (m, 5H), 7.54 (d, 1H). ESMS (neg), *m/z*: 470.8 (M − H).

Methyl 2(*R*)-[7-Benzyloxy-2,3,4,5-tetrahydrobenzo[1,2,5-*f*]thiadiazepine-1,1-dioxide]propanoate (21). The crude aniline **20** (7.1 g, 15.1 mmol) was dissolved in DMF, and *N*-methylmorpholine (5.1 mL, 47.1 mmol) was added. This mixture was heated at 80 °C for 5 h. After it was cooled, the DMF was removed and EtOAc was added. The EtOAc was washed with brine, dried, and concentrated. Flash chromatography (10−50% ethyl acetate/hexane) of the resulting residue gave the cyclized product **21** (4.4 g, 11.3 mmol, 75%). ^{1}H NMR ($CDCl_3$): δ 1.38 (d, 3H), 3.42−3.6 (m, 2H), 3.53 (s, 3H), 3.62 (m, 2H), 4.31 (m, 1H), 4.73 (q, 1H), 5.05 (s, 2H), 6.26 (d, 1H), 6.51 (dd, 1H), 7.38 (m, 5H), 7.69 (d, 1H). ESMS (pos), *m/z*: 413.0 (M + Na). Anal. ($C_{19}H_{22}N_2O_5S$) C, H, N, S.

***N*-Hydroxy-2(*R*)-[7-benzyloxy-2,3,4,5-tetrahydrobenzo-[1,2,5-*f*]thiadiazepine-1,1-dioxide]propanamide (22).** Compound **21** (0.64 mmol) was incorporated into method A and recrystallized from benzene to give the hydroxamate **22** (160 mg, 0.41 mmol, 64%) as a white powder. ^{1}H NMR (DMSO): δ 1.14 (t, 3H), 3.2 (m, 2H), 3.35−3.7 (m, 2H), 4.22 (q, 1H), 5.03 (s, 2H), 6.41 (m, 2H), 6.54 (br s, 1H), 7.28−7.44 (m, 6H), 8.85 (br s, 1H), 10.59 (br s, 1H). ESMS (pos), *m/z*: 413.0 (M + Na). HRMS calcd for ($C_{19}H_{22}N_2O_5S$ + H) 391.132 769, found 391.131 503. Anal. ($C_{19}H_{22}N_2O_5S$) C, H, N.

***N*-Hydroxy-2(*R*)-[7-hydroxy-2,3,4,5-tetrahydrobenzo-[1,2,5-*f*]thiadiazepine-1,1-dioxide]propanamide (23).** The hydroxamate **22** (100 mg, 0.25 mmol) was dissolved in MeOH (10 mL) prior to the addition of 5% Pd/$BaSO_4$ (150 mg). The solution was placed on a Parr apparatus at 35 psi. After 2.5 h, the solution was filtered and was concentrated to give the hydroxamate **23** (59.9 mg, 0.2 mmol, 80%) as a white powder. ^{1}H NMR (DMSO): δ 1.12 (t, 3H), 3.16 (m, 1H), 3.3−3.6 (m, 3H), 4.19 (q, 1H), 6.16 (d, 1H), 6.21 (s, 1H), 6.4 (br s, 1H), 7.3 (d, 1H), 8.85 (br s, 1H), 9.87 (s, 1H), 10.61 (s, 1H). ESMS (neg), *m/z*: 299.7 (M − H). HRMS calcd for ($C_{11}H_{15}N_3O_5S$ + H) 302.081 068, found 302.080 845. Anal. ($C_{11}H_{15}N_3O_5S\cdot0.25C_6H_6$) C, H, N.

Methyl 2(*R*)-[7-Hydroxy-2,3,4,5-tetrahydrobenzo[1,2,5-*f*]thiadiazepine-1,1-dioxide]propanoate (24). The benzothiadiazepine **21** (2.4 g, 6.1 mmol) was dissolved in MeOH, and 10% Pd/C (240 mg) was added. This mixture was hydrogenated at 50 psi on a Parr for 4 h. The Pd/C was removed, and the MeOH was concentrated to give the phenol **24** (2.0 g, 5.6 mmol, 92%). ^{1}H NMR ($CDCl_3$): δ 1.38 (d, 3H), 3.43−3.52 (m, 2H), 3.58 (s, 3H), 3.61 (m, 2H), 4.34 (m, 1H), 4.73 (q, 1H), 6.16 (d, 1H), 6.33 (dd, 1H), 7.64 (d, 1H). ESMS (neg), *m/z*: 299.7 (M − H).

Methyl 2(*R*)-[7-(3,5-Dimethylbenzyloxy)-2,3,4,5-tetrahydrobenzo[1,2,5-*f*]thiadiazepine-1,1-dioxide]propanoate (25). The phenol **24** (100 mg, 0.33 mmol) was dissolved in DMF and cooled to 0 °C. At 0 °C, 1 M KOtBu (0.36 mL, 0.36 mmol) in tBuOH was added dropwise. After 20 min, 3,5-dimethylbenzyl bromide (66.3 mg, 0.33 mmol) was added and the reaction mixture was warmed to room temperature. After 15 h, the reaction was quenched with saturated NH_4Cl solution and EtOAc was added. The EtOAc was washed with brine, dried, and concentrated. Flash chromatography (20−60% ethyl acetate/hexane) of the resulting residue afforded the alkylated phenol **25** (85 mg, 0.20 mmol, 61%). ^{1}H NMR ($CDCl_3$): δ 1.38 (d, 3H), 2.32 (s, 6H), 3.44−4.56 (m, 2H), 3.54 (s, 3H), 3.62 (m, 2H), 4.3 (m, 1H), 4.73 (q, 1H), 4.97 (s, 2H), 6.25 (d, 1H), 6.51 (dd, 1H), 6.98 (m, 3H), 7.69 (d, 1H). ESMS (pos), *m/z*: 418.9 (M + H).

***N*-Hydroxy-2(*R*)-[7-(3,5-dimethylbenzyloxy)-2,3,4,5-tetrahydrobenzo[1,2,5-*f*]thiadiazepine-1,1-dioxide]propanamide (26).** The ester **25** was incorporated into method A, and the resulting residue was recrystallized from benzene to give the hydroxamate **26** (30 mg, 0.07 mmol) as a white powder. ^{1}H NMR (300 MHz, DMSO): δ 1.13 (t, 3H), 2.24 (s, 6H), 3.2 (m, 1H), 3.4−3.65 (m, 3H), 4.22 (q, 1H), 4.93 (s, 2H), 6.4 (m, 2H), 6.54 (br s, 1H), 6.93 (s, 1H), 6.98 (s, 2H), 7.41 (d, 1H), 8.85 (s, 1H), 10.62 (s, 1H). ESMS (neg), *m/z*: 417.8 (M − H). HRMS calcd for ($C_{20}H_{25}N_3O_5S$ + H) 420.159 318, found 420.158 900. Anal. ($C_{20}H_{25}N_3O_5S$) C, H, N.

Compounds **27**−**43** were synthesized in fashion analogous to that of compound **26**.

***N*-Hydroxy-2(*R*)-[7-(3,5-dichlorobenzyloxy)-2,3,4,5-tetrahydrobenzo[1,2,5-*f*]thiadiazepine-1,1-dioxide]propanamide (27).** ^{1}H NMR (DMSO): δ 1.14 (t, 3H), 3.17−3.3 (m, 2H), 3.35−3.7 (m, 2H), 4.22 (q, 1H), 5.05 (s, 2H), 6.4 (m, 2H), 6.58 (br s, 1H), 7.46 (m, 3H), 7.57 (m, 1H), 8.86 (br s, 1H), 10.64 (br s, 1H). ESMS (neg), *m/z*: 457.6 (M − H). HRMS calcd for ($C_{18}H_{19}N_3O_5SCl_2$ + H) 460.050 073, found 460.051 100. Anal. ($C_{18}H_{19}N_3O_5SCl$) C, H, N.

***N*-Hydroxy-2(*R*)-[7-(3,5-dimethoxybenzyloxy)-2,3,4,5-tetrahydrobenzo[1,2,5-*f*]thiadiazepine-1,1-dioxide]propanamide (28).** ^{1}H NMR (DMSO): δ 1.14 (d, 3H), 3.24 (m, 1H), 3.35−3.7 (m, 3H), 4.23 (q, 1H), 4.97 (s, 2H), 6.4 (m, 3H), 6.55 (m, 3H), 7.41 (d, 1H), 8.85 (s, 1H), 10.63 (s, 1H). ESMS (neg), *m/z*: 449.7 (M − H). HRMS calcd for ($C_{20}H_{25}N_3O_7S$ + H) 452.149 147, found 452.148 200. Anal. ($C_{20}H_{25}N_3O_7S\cdot0.25C_6H_6$) C, H, N.

***N*-Hydroxy-2(*R*)-[7-(3,5-diethoxybenzyloxy)-2,3,4,5-tetrahydrobenzo[1,2,5-*f*]thiadiazepine-1,1-dioxide]propanamide (29).** ^{1}H NMR (DMSO): δ 1.12 (d, 3H), 1.27 (t, 6H), 3.2 (m, 1H), 3.4−3.65 (m, 3H), 3.96 (q, 4H), 4.21 (q, 1H), 4.94 (s, 2H), 6.38 (m, 3H), 6.5 (m, 3H), 7.4 (d, 1H), 8.85 (d, 1H), 10.62 (br s, 1H). ESMS (pos), *m/z*: 479.9 (M + H). HRMS calcd for ($C_{22}H_{29}N_3O_7S$ + H) 480.180 448, found 480.178 600. Anal. ($C_{22}H_{29}N_3O_7S\cdot0.2C_6H_6$) C, H, N.

***N*-Hydroxy-2(*R*)-[7-(2,6-methylpyridyl-4-methyleneoxy)-2,3,4,5-tetrahydrobenzo[1,2,5-*f*]thiadiazepine-1,1-dioxide]-propanamide (30).** ^{1}H NMR (DMSO): δ 1.13 (d, 3H), 2.47 (s, 6H), 3.2−3.6 (m, 4H), 4.21 (q, 2H), 5.01 (s, 2H), 6.41 (m, 2H), 6.56 (s, 1H), 7.02 (s, 2H), 7.42 (d, 1H), 8.86 (s, 1H), 10.63 (s, 1H). ESMS (pos), *m/z*: 421.3 (M + H). HRMS calcd for ($C_{19}H_{24}N_4O_5S$ + H) 421.154 567, found 421.155 300.

***N*-Hydroxy-2(*R*)-[7-benzyloxy-2,3,4,5-tetrahydrobenzo-[1,2,5-*f*]thiadiazepine-1,1-dioxide]-4-methylpentanamide (32).** The ester **21a** (produced in analogy to **21** but starting from d-Leu-OtBu and **17**) (268 mg, 0.56 mmol) was incorporated into method B, and reverse-phase HPLC gave the hydroxamate **32** (90 mg, 0.2 mmol) as a white powder. ^{1}H NMR (DMSO): δ 0.75 (t, 6H), 1.3−1.5 (m, 3H), 3.3 (m, 1H), 3.48 (m, 3H), 4.2 (t, 1H), 5.05 (s, 2H), 6.36−6.5 (m, 3H), 7.3−7.44 (m, 6H), 10.73 (s, 1H). ESMS (neg), *m/z*: 431.9 (M − H). HRMS calcd for ($C_{21}H_{27}N_3O_5S$ + H) 434.174 968, found 434.174 735.

***N*-Hydroxy-2(*R*)-[7-hydroxy-2,3,4,5-tetrahydrobenzo-[1,2,5-*f*]thiadiazepine-1,1-dioxide]-4-methylpentamide (31).** The hydroxamate **32** (40 mg, 0.1 mmol) was dissolved in MeOH (5 mL) prior to the addition of 5% Pd/$BaSO_4$ (120 mg). The solution was placed on a Parr apparatus at 55 psi. After 2 h, the solution was filtered and was concentrated. Reverse-phase HPLC of the resulting residue gave hydroxamate **31** (25.2 mg, 0.07 mmol) as a white powder. ^{1}H NMR (DMSO): δ 0.74 (t, 6H), 1.3−1.5 (m, 3H), 3.25 (m, 1H), 3.37−3.5 (m, 3H), 4.19 (t, 1H), 6.15 (dd, 1H), 6.22 (d, 1H), 7.32 (d, 1H), 10.72 (br s, 1H). ESMS (neg), *m/z*: 341.8 (M − H). HRMS calcd for ($C_{14}H_{21}N_3O_5S$ + H) 344.128 018, found 344.125 763.

***N*-Hydroxy-2(*R*)-[7-(3,5-dimethoxybenzyloxy)-2,3,4,5-tetrahydrobenzo[1,2,5-*f*]thiadiazepine-1,1-dioxide]-4-methylpentanamide (33).** ^{1}H NMR (DMSO): δ 0.73 (t, 6H), 1.3−1.5 (m, 3H), 3.1 (m, 1H), 3.5 (m, 3H), 3.7 (s, 6H), 4.2 (t, 1H), 4.97 (s, 2H), 6.37−6.54 (m, 6H), 7.42 (d, 1H), 8.84 (s, 1H), 10.73 (s, 1H). ESMS (neg), *m*/*z*: 491.7 (M − H). HRMS calcd for ($C_{23}H_{31}N_3O_7S$ + H) 494.196 098, found 494.196 400.

***N*-Hydroxy-2(*R*)-[7-(3,5-dimethoxybenzyloxy)-2,3,4,5-tetrahydrobenzo[1,2,5-*f*]thiadiazepine-1,1-dioxide]-3-methylbutanamide (34).** ^{1}H NMR (DMSO): δ 0.76 (dd, 6H), 2.0 (m, 1H), 3.24 (m, 1H), 3.4 (m, 3H), 3.68 (m, 1H), 3.7 (s, 6H), 4.95 (s, 2H), 6.38 (m, 4H), 6.42 (d, 2H), 7.42 (d, 1H), 8.8 (s, 1H), 10.6 (s, 1H). ESMS (neg), *m*/*z*: 478.0 (M − H). HRMS calcd for ($C_{22}H_{29}N_3O_7S$ + H) 480.180 448, found 480.183 058.

***N*-Hydroxy-2(*R*)-[7-(3,5-diethoxybenzyloxy)-2,3,4,5-tetrahydrobenzo[1,2,5-*f*]thiadiazepine-1,1-dioxide]-3-methylbutanamide (35).** ^{1}H NMR (DMSO): δ 0.68 (dd, 6H), 1.18 (t, 6H), 1.9 (m, 1H), 3.17 (m, 1H), 3.3 (m, 2H), 3.6 (m, 2H), 3.87 (q, 4H), 4.85 (s, 2H), 6.29 (m, 4H), 6.41 (d, 2H), 7.33 (d, 1H), 8.71 (s, 1H), 10.5 (br s, 1H). ESMS (neg), *m*/*z*: 505.8 (M − H). HRMS calcd for ($C_{24}H_{33}N_3O_7S$ + H) 508.211 748, found 508.213 100.

***N*-Hydroxy-2(*R*)-[7-(4,5-dimethylthiazolyl-2-methyleneoxy)-2,3,4,5-tetrahydrobenzo[1,2,5-*f*]thiadiazepine-1,1-dioxide]-3-methylbutanamide (36).** ^{1}H NMR (DMSO): δ 0.76 (dd, 6H), 2.03 (m, 1H), 2.22 (s, 3H), 2.29 (s, 3H), 3.25 (m, 1H), 3.4 (m, 2H), 3.71 (m, 2H), 5.23 (s, 2H), 6.42 (m, 3H), 7.44 (d, 1H), 8.8 (s, 1H), 10.59 (s, 1H). ESMS (neg), *m*/*z*: 452.9 (M − H). HRMS calcd for ($C_{19}H_{26}N_4O_5S_2$ + H) 455.142 289, found 455.142 300.

***N*-Hydroxy-2(*R*)-[7-(3,5-dimethoxybenzyloxy)-2,3,4,5-tetrahydrobenzo[1,2,5-*f*]thiadiazepine-1,1-dioxide]-4-methoxycarbonylbutanamide (37).** ^{1}H NMR (DMSO): δ 1.75−1.9 (m, 2H), 2.1−2.25 (m, 2H), 3.29−3.45 (m, 4H), 3.49 (s, 3H), 3.7 (s, 6H), 4.96 (s, 2H), 6.42 (m, 4H), 6.54 (d, 2H), 7.42 (d, 1H), 8.88 (s, 1H), 10.66 (br s, 1H). ESMS (neg), *m*/*z*: 521.9 (M − H). HRMS calcd for ($C_{23}H_{29}N_3O_9S$ + H) 524.170 277, found 524.169 500.

***N*-Hydroxy-2(*R*)-[7-(3,5-diethoxybenzyloxy)-2,3,4,5-tetrahydrobenzo[1,2,5-*f*]thiadiazepine-1,1-dioxide]-4-methoxycarbonylbutanamide (38).** ^{1}H NMR (DMSO): δ 1.26 (t, 6H), 1.75−1.9 (m, 2H), 2.1−2.25 (m, 2H), 3.28−3.49 (m, 4H), 3.49 (s, 3H), 3.96 (q, 4H), 4.15 (t, 1H), 4.94 (s, 2H), 6.36−6.5 (m, 6H), 7.42 (d, 1H), 8.87 (br s, 1H), 10.65 (br s, 1H). ESMS (neg), *m*/*z*: 549.8 (M − H). HRMS calcd for ($C_{25}H_{33}N_3O_9S$ + H) 552.201 577, found 552.199 500.

***N*-Hydroxy-2(*R*)-[7-(3,5-dimethoxybenzyloxy)-2,3,4,5-tetrahydrobenzo[1,2,5-*f*]thiadiazepine-1,1-dioxide]-4-methoxycarbonylpentanamide (39).** ^{1}H NMR (DMSO): δ 1.25−1.45 (m, 2H), 1.5−1.68 (m, 2H), 2.21 (t, 2H), 3.26−3.6 (m, 4H), 3.49 (s, 3H), 3.7 (s, 6H), 4.11 (t, 1H), 4.95 (s, 2H), 6.38−6.42 (m, 3H), 6.53 (d, 2H), 7.41 (d, 1H), 10.65 (br s, 1H). ESMS (pos), *m*/*z*: 538.2 (M + H). HRMS calcd for ($C_{24}H_{31}N_3O_9S$ + H) 538.185 927, found 538.185 700. Anal. ($C_{24}H_{31}N_3O_9S$·0.4TFA) C, H, N.

***N*-Hydroxy-2(*R*)-[7-(3,5-diethoxybenzyloxy)-2,3,4,5-tetrahydrobenzo[1,2,5-*f*]thiadiazepine-1,1-dioxide]-4 methoxycarbonylpentanamide (40).** ^{1}H NMR (DMSO): δ 1.26 (t, 6H), 1.3−1.45 (m, 2H), 1.45−1.68 (m, 2H), 2.21 (t, 2H), 3.25−3.5 (m, 4H), 3.49 (s, 3H), 3.95 (q, 4H), 4.11 (t, 1H), 4.94 (s, 2H), 6.36−6.42 (m, 3H), 6.49 (d, 2H), 7.41 (d, 1H), 10.67 (br s, 1H). ESMS (pos), *m*/*z*: 566.2 (M + H). HRMS calcd for ($C_{26}H_{35}N_3O_9S$ + H) 566.217 227, found 566.217 500. Anal. ($C_{26}H_{35}N_3O_9S$·H_2O) C, H, N.

***N*-Hydroxy-2(*R*)-[7-(3,5-dimethoxybenzyloxy)-2,3,4,5-tetrahydrobenzo[1,2,5-*f*]thiadiazepine 1,1-dioxide]-6-*N*-(methanesulfonyl)hexylamide (41).** Trifluoroacetic acid (1 mL) was added to compound **25b** (produced in analogy to **25** but starting from D-Lys(Boc)-OMe and **17**) (72 mg, 0.12 mmol) in methylene chloride (1 mL) at room temperature. After 20 min, the solvent was removed. This was azeotroped with chloroform three times, and the resulting residue was taken forward without additional purification. ^{1}H NMR ($CDCl_3$): δ 7.59 (d, 1H), 7.58 (br s, 2H), 6.51 (m, 3H), 6.39 (m, 2H), 6.29 (br s, 3H), 4.96 (s, 2H), 4.46 (t, 1H), 3.76 (s, 6H), 3.69 (m, 1H), 3.58−3.24 (m, 3H), 3.38 (s, 3H), 2.93 (m, 2H), 1.82−1.57 (m, 4H), 1.37 (m, 2H). ESMS (pos), *m*/*z*: 508 (M + H).

Methanesulfonyl chloride (8 mg, 0.067 mmol) was added to the previous compound (27 mg, 0.045 mmol) in THF/H_2O (4 mL, 3:1) in the presence of lithium hydroxide (9.4 mg, 0.22 mmol) at room temperature. The reaction mixture was stirred overnight, and then the solvent was removed. The residue was dissolved in water (10 mL) and extracted with ethyl acetate (3×). The organic layer was washed with brine, dried, and filtered. The solvent was removed to provide the product **25c** as a brittle foam (22 mg, 86%). ^{1}H NMR ($CDCl_3$): δ 7.63 (d, 1H), 6.53 (d, 2H), 6.50 (d, 1H), 6.41 (t, 1H), 6.38 (s, 1H), 4.97 (s, 2H), 4.62 (m, 2H), 3.78 (s, 6H), 3.80−3.57 (m, 4H), 3.45 (m, 2H), 3.00 (m, 1H), 2.90 (s, 3H), 1.94 (m, 1H), 1.76 (m, 1H), 1.57−1.24 (m, 4H). ESMS (neg), *m*/*z*: 570 (M − H).

Compound **25c** was converted to hydroxamic acid analogue **41** by method B. ^{1}H NMR (DMSO): δ 10.69 (s, 1H), 7.41 (d, 1H), 6.86 (br t, 1H), 6.54 (s, 1H), 6.53 (s, 1H), 6.41 (m, 3H), 4.95 (s, 2H), 4.11 (t, 1H), 3.70 (s, 6H), 3.56−3.29 (m, 4H), 2.80 (s, 3H), 2.77 (m, 2H), 1.64−1.03 (m, 6H). ESMS (neg), *m*/*z*: 570 (M − H). HRMS calcd for ($C_{24}H_{34}N_4O_9S_2$ + H) 587.1845, found 587.1426.

***N*-Hydroxy-2(*R*)-[7-(3,5-dimethoxybenzyloxy)-2,3,4,5-tetrahydrobenzo[1,2,5-*f*]thiadiazepine-1,1-dioxide]-6-*N*-[(1,1-dimethylethoxy)carbonyl]hexylamide (42).** ^{1}H NMR (DMSO): δ 10.66 (s, 1H), 7.41 (d, 1H), 6.69 (br t, 1H), 6.54 (s, 1H), 6.53 (s, 1H), 6.41 (m, 3H), 4.95 (s, 2H), 4.09 (t, 1H), 3.70 (s, 6H), 3.68−3.30 (m, 4H), 2.75 (m, 2H), 1.65−0.98 (m, 6H), 1.32 (s, 9H). ESMS (neg), *m*/*z*: 607 (M − H). HRMS calcd for ($C_{28}H_{40}N_4O_9S$ + H) 609.2594, found 609.2579.

***N*-Hydroxy-2(*R*)-[7-(3,5-dimethoxybenzyloxy)-2,3,4,5-tetrahydrobenzo[1,2,5-*f*]thiadiazepine-1,1-dioxide]-6-aminohexylamidetrifluoroacetic Acid Salt (43).** Trifluoroacetic acid (1 mL) was added to compound **42** (20 mg, 0.033 mmol) in methylene chloride (1 mL) at room temperature. After 20 min, the solvent was removed. The resulting residue was azeotroped with chloroform three times. The final residue was taken up in water (2 mL) and lyophilized to afford compound **43** as a white powder (17 mg, 83%). ^{1}H NMR (DMSO): δ 10.70 (s, 1H), 8.88 (s, 1H), 7.57 (br s, 3H), 7.43 (d, 1H), 6.54 (s, 1H), 6.53 (s, 1H), 6,43 (m, 3H), 4.96 (s, 2H), 4.12 (t, 1H), 3.70 (s, 6H), 3.52−3.26 (m, 4H), 2.65 (m, 2H), 2.47 (m, 1H), 1,65−1.04 (m, 6H). ESMS (pos), *m*/*z*: 509 (M + H). HRMS calcd for ($C_{23}H_{32}N_4O_7S$ + H) 509.2070, found 509.2066. Anal. ($C_{25}H_{33}F_3N_4O_9S$·2TFA) C, H, N.

Methyl *N*-[(2,4-Dinitrophenyl)sulfonyl]-D-alaninate (45). D-Alanine methyl ester hydrochloride salt (10 g, 71.6 mmol) was dissolved in CH_2Cl_2 (100 mL) and washed with 10% sodium carbonate (2 × 40 mL). After the mixture was dried over $MgSO_4$, the solvent was removed to provide the free base amino acid. *N*-Methylmorpholine (14.5 g, 143 mmol) was added to d-Ala-OMe in dioxane (75 mL) followed by dropwise addition of 2,4-dinitrobenzenesulfonyl chloride (19.1 g, 71.6 mmol) in dioxane (50 mL). This mixture was stirred for 24 h at room temperature and then was evaporated. The crude product was dissolved in ethyl acetate (100 mL) and was washed with water, 10% citric acid, saturated $NaHCO_3$ (2×), and brine. After the mixture was dried over $MgSO_4$, the solvent was removed and the crude product was purified by recrystallization (ethyl acetate/hexane) to afford **45** (5.81 g, 24%) as a light-yellow crystalline solid. ^{1}H NMR ($CDCl_3$): δ 8.75 (d, 1H), 8.29 (dd, 1H), 8.29 (d, 1H), 6.14 (d, 1H), 4.32 (m, 1H), 3.59 (s, 1H), 1.53 (d, 3H). ESMS (neg), *m*/*z*: 332 (M − H). HRMS calcd for ($C_{10}H_{11}N_3O_8S$ + H) 334.0345, found 334.0349. Anal. ($C_{10}H_{11}N_3O_8S$) C, H, N.

Methyl *N*-(2-Bromoethyl)-*N*-[(2,4-dinitrophenyl)sulfonyl]-D-alaninate (46). Diethyl azadicarboxylate (16.3 g, 93.6 mmol) was added dropwise at room temperature to **45** (20.8 g, 62.4 mmol), triphenylphosphine (25.2 g, 93.6 mmol), and 2-bromoethanol (11.7 g, 93.6 mmol) in THF (225 mL). After the mixture was stirred for 24 h, the solvent was removed and the residue was purified by flash chromatography (20−50% ethyl acetate/hexane) to provide **46** (25.9 g, 94%) as a viscous

oil. ^{1}H NMR ($CDCl_3$): δ 8.53 (dd, 1H), 8.43 (d, 1 H), 8.30 (d, 1H), 4.81 (q, 1H), 3.82 (m, 1H), 3.68 (m, 1H), 3.65 (s, 3H), 3.43 (m, 2H), 1.60 (d, 3H). ESMS (pos), *m*/*z*: 440 (M − H).

Methyl (2*R*)-2-(7-Amino-1,1-dioxido-4,5-dihydro-1,2,5-benzothiadiazepin-2(3*H*)-yl)propanoate (47). Iron dust (7.65 g, 137 mmol) was added in one portion to **46** (6.03 g, 13.7 mmol) in acetic acid/water (85 mL, 16:1). This solution was heated at 60 °C for 1.5 h. The reaction mixture was diluted with ethyl acetate (500 mL), and the solids were filtered. With stirring, saturated $NaHCO_3$ (200 mL) was added to the ethyl acetate solution followed by addition of solid $NaHCO_3$ until no gas evolution was noted. The aqueous solution was extracted with ethyl acetate. The ethyl acetate layer was washed with water, saturated $NaHCO_3$, and brine. After it was dried over $MgSO_4$, the crude product was concentrated [ESMS (pos), *m*/*z*: 404 (M + Na)]. The resulting residue was dissolved in DMF (250 mL) prior to the addition of *N*-methylmorpholine (1.71 g, 16.9 mmol). This solution was heated at 80 °C for 5.5 h. The solvent was removed, and the residue was dissolved in ethyl acetate. The ethyl acetate was washed with water, saturated $NaHCO_3$, and brine. After drying over $MgSO_4$ the crude product was concentrated. The resulting residue was purified by flash chromatography (30−70% ethyl acetate/hexane) to provide **47** (1.76 g, 43%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 7.13 (d, 1H), 6.08 (br t, 1H), 5.94 (dd, 1H), 5.90 (d, 1H), 5.54 (s, 2H), 4.41 (q, 1H), 3.51 (s, 3H), 3.45−3.17 (m, 4H), 1.19 (d, 3H). ESMS (neg), *m*/*z*: 524 (M − H). HRMS calcd for ($C_{12}H_{17}N_3O_4S$ + H) 300.1018, found 300.1028. Anal. ($C_{12}H_{17}N_3O_4S$) C, H, N.

***N*-(2-{(1*R*)-2-[(Benzyloxy)amino]-1-methyl-2-oxoethyl}-1,1-dioxido-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepin-7-yl)-3,5-dimethylbenzamide (50).** Lithium hydroxide monohydrate (0.74 g, 17.6 mmol) in water (10 mL) was added to **47** (1.76 g, 5.88 mmol) in tetrahydrofuran (25 mL) at room temperature. After 1 h, the solvent was removed. The residue was dissolved in water (30 mL) and was washed with ether (2×). The ether layer was discarded, and the aqueous layer was acidified with 1 N HCl. The aqueous layer was then extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to provide the carboxylate intermediate as a brittle foam. ^{1}H NMR (CD_3OD): δ 7.33 (d, 1H), 6.11 (dd, 1H), 6.05 (d, 1H), 4.54 (q, 1H), 3.59 (m, 2H), 3.45 (m, 1H), 3.23 (m, 1H), 1.31 (d, 3H). ESMS (neg), *m*/*z*: 284 (M − H). HRMS calcd for ($C_{11}H_{15}N_3O_4S$ +H) 286.0862, found 286.0847.

Diisopropylethylamine (3.51 g, 27.2 mmol) was added dropwise at 0 °C to the compound from the previous reaction (1.55 g, 5.43 mmol), BOP reagent (2.64 g, 5.98 mmol), and benzylhydroxylamine hydrochloride (1.30 g, 8.15 mmol) in DMF (25 mL). The ice bath was removed after 0.5 h, and the reaction mixture was stirred overnight at room temperature. The solvent was removed. The residue was dissolved in ethyl acetate (100 mL) and was washed with water, saturated $NaHCO_3$, and brine. After drying over $MgSO_4$, the crude product was purified by flash chromatography (1−10% MeOH/CH_2Cl_2) to provide the protected hydroxamic acid intermediate (1.94 g, 91%) as a white solid. ^{1}H NMR (CD_3OD): δ 7.36 (d, 1H), 7.32 (m, 5H), 6.16 (dd, 1H), 6.05 (d, 1H), 4.73 (d, 1H), 4.63 (d, 1H), 4.36 (q, 1H), 3.47 (m, 3H), 3.34 (m, 1H), 1.29 (d, 3H). ESMS (pos), *m*/*z*: 391 (M + H). HRMS calcd for ($C_{18}H_{22}N_4O_4S$ + H) 391.1440, found 391.1440. Anal. ($C_{18}H_{22}N_4O_4S$) C, H, N.

Diisopropylethylamine (170 mg, 1.32 mmol) was added dropwise at 0 °C to the compound from the previous reaction (103 mg, 0.26 mmol), BOP reagent (140 mg, 0.32 mmol), and 3,5-dimethylbenzoic acid (48 mg, 0.32 mmol) in DMF (2 mL). The ice bath was removed after 0.5 h, and the reaction mixture was stirred overnight at room temperature. The solvent was removed, and the residue was dissolved in ethyl acetate. The ethyl acetate was washed with water, 10% citric acid, saturated $NaHCO_3$, and brine. After drying over $MgSO_4$, the crude product was purified by flash chromatography (1−10% MeOH/CH_2Cl_2) to provide **50** (79 mg, 58%). ^{1}H NMR (CD_3OD): δ 7.60 (d, 1H), 7.47 (m, 2H), 7.30 (m, 5H), 7.20 (m, 1H), 7.07 (m, 2H), 4.73 (d, 1H), 4.61 (d, 1H), 4.40 (q, 1H), 3.52 (m, 4H), 2.34 (s, 6H), 1.31 (d, 3H). ESMS (pos), *m*/*z*: 545 (M + Na). HRMS calcd for ($C_{27}H_{30}N_4O_5S$ + H) 523.2015, found 523.2013.

***N*-Hydroxy-2(*R*)-[7-(*N*-3,5-dimethylbenzoylamino)-2,3,4,5-tetrahydrobenzo[1,2,5-*f*]thiadiazepine-1,1-dioxide]-propylamide (51).** A sample of 5% palladium on barium sulfate (unreduced, 50 mg) was added to **50** (79 mg, 0.15 mmol) in methanol (10 mL). A balloon filled with hydrogen was attached via a three-way stopcock, and the atmosphere above the reaction mixture was removed and replaced with hydrogen three times. After 0.45 h, the catalyst was filtered off and the filtrate was concentrated. The crude product was dissolved in THF (1 mL) and was crystallized by slow addition of ether (30 mL). The hydroscopic solid was filtered and dried under vacuum to provide compound **51** (33 mg, 50%). ^{1}H NMR (DMSO): δ 10.65 (s, 1H), 10.21 (s, 1H), 8.87 (s, 1H), 7.49 (m, 4H), 7.19 (s, 1H), 7.03 (dd, 1H), 6.64 (br s, 1H), 4.24 (q, 1H), 3.62−3.18 (m, 4H), 2.32 (s, 6H), 1.15 (d, 3H). ESMS (pos), *m*/*z*: 455 (M + Na). HRMS calcd for ($C_{20}H_{24}N_4O_5S$ + H) 433.1546, found 433.1548.

***tert*-Butyl (2*R*)-2-[7-[(3,5-Dimethoxybenzyl)oxy]-1,1-dioxido-4,5-dihydro-1,2,5-benzothiadiazepin-2(3*H*)-yl]-4-methylpentanoate (48).** Ethanol (300 μL) was added to compound **47a** (produced in analogy to **47** but starting from D-Leu-OtBu and 2,4-dinitrobenzenesulfonyl chloride) (117 mg, 0.31 mmol) and 3,5-dimethoxybenzaldehyde (51 mg, 0.31 mmol). After the mixture was stirred for 5 h at room temperature, sodium borohydride (12 mg, 0.31 mmol) was added in one portion and the viscous reaction mixture was stirred overnight at room temperature. The reaction was quenched with saturated ammonium chloride (3 mL) prior to the addition of water (10 mL). The aqueous solution was extracted with ethyl acetate. The organic layer was washed with water, saturated $NaHCO_3$, and brine. After the mixture was dried over $MgSO_4$, the solvent was evaporated and the crude product was purified by flash chromatography (20−70% ethyl acetate/hexane) to provide **48** (104 mg, 64%). ^{1}H NMR ($CDCl_3$): δ 7.54 (d, 1H), 6.45 (s, 2H), 6.35 (m, 1H), 6.12 (dd, 1H), 5.82 (d, 1H), 4.56 (m, 1H), 4.24 (s, 2H), 3.76 (s, 6H), 3.55 (m, 1H), 3.51 (m, 3H), 3.36 (m, 1H), 1.59 (m, 3H), 1.23 (s, 9H), 0.90 (d, 6H). ESMS (neg), *m*/*z*: 532 (M − H). HRMS calcd for ($C_{27}H_{39}N_3O_6S$ + Na) 556.2457, found 556.2471.

***N*-Hydroxy-2(*R*)-[7-(*N*-(3,5-dimethoxymethyleneamino)-2,3,4,5-tetrahydrobenzo[1,2,5-*f*]thiadiazepine-1,1-dioxide]-4-methylpentamide (49).** Compound **48** (91 mg, 0.17 mmol) was dissolved in trifluoroacetic acid (3 mL). After 1.5 h, the trifluoroacetic acid was removed. The crude product was azeotroped with chloroform (5 mL) three times. Drying overnight under vacuum provided the acid intermediate as a brittle foam that was carried forward without further purification. ^{1}H NMR ($CDCl_3$): δ 7.68 (br s), 7.56 (d, 1H), 6.55 (s, 1H), 6.52−6.35 (m, 4H), 4.67 (m, 1H), 4.22 (s, 2H), 3.81 (s, 3H), 3.80−3.55 (m, 4H), 1.65 (m, 3H), 0.93 (d, 6H). ESMS (neg), *m*/*z*: 476 (M − H). HRMS calcd for ($C_{23}H_{31}N_3O_6S$ + H) 478.2012, found 478.2014. Diisopropylethylamine (110 mg, 0.85 mmol) was added dropwise at 0 °C to the compound from the previous reaction (0.17 mmol), BOP reagent (83 mg, 0.19 mmol), and benzylhydroxylamine hydrochloride (54 mg, 0.34 mmol) in DMF (2 mL). The ice bath was removed after 0.5 h, and the reaction mixture was stirred overnight at room temperature. The solvent was removed, and the residue was dissolved in ethyl acetate. The ethyl acetate was washed with water, saturated $NaHCO_3$, and brine. After the mixture was dried over $MgSO_4$, the crude product was purified by flash chromatography (1−10% MeOH/CH_2Cl_2) to provide the protected hydroxamic acid intermediate (74 mg, 75%). ^{1}H NMR (CD_3OD): δ 10.05 (s, 1H), 7.47 (d, 1H), 7.31 (m, 5H), 6.47 (d, 2H), 6.39 (t, 1H), 6.18 (dd, 1H), 5.61 (d, 1H), 4.80 (d, 1H), 4.69 (d, 1H), 4.62 (dd, 1H), 4.49 (br t, 1H), 4.25 (d, 2H), 3.77 (s, 6H), 3.68−3.50 (m, 2H), 3.25 (m, 1H), 3.10 (m, 2H), 1.90 (m, 1H), 1.67 (m, 2H), 0.98 (d, 3H), 0.93 (d, 3H). ESMS (pos), *m*/*z*: 583 (M + H). HRMS calcd for ($C_{30}H_{38}N_4O_6S$ + H) 583.2590, found 583.2584.

A sample of 5% palladium on barium sulfate (unreduced, 50 mg) was added to the compound from the previous reaction (74 mg, 0.13 mmol) in methanol (5 mL). A balloon filled with hydrogen was attached via a three-way stopcock, and the atmosphere above the reaction mixture was removed and replaced with hydrogen three times. After 0.45 h, the catalyst was filtered off and the filtrate was concentrated. The crude product was dissolved in THF (1 mL) and was crystallized by slow addition of ether (30 mL). The hydroscopic solid was filtered and dried under vacuum to provide analogue **49** (17 mg, 27%). ^{1}H NMR (CD_3OD): δ 7.37 (d, 1H), 6.48 (d, 2H), 6.31 (t, 1H), 6.14 (dd, 1H), 5.99 (d, 1H), 4.39 (m, 1H), 4.24 (s, 2H), 3.71 (s, 6H), 3.53−3.25 (m, 4H), 1.58 (m, 3H), 0.86 (m, 6H). ESMS (pos), *m*/*z*: 493 (M + H). HRMS calcd for ($C_{23}H_{32}N_4O_6S$ + H) 493.2121, found 493.2134. Anal. ($C_{23}H_{32}N_4O_6S\cdot1.2H_2O$) C, H, N.

Methyl (2*R*)-2-[1,1-Dioxido-7-{[(trifluoromethyl)sulfonyl]oxy}-4,5-dihydro-1,2,5-benzothiadiazepin-2(3*H*)-yl]propanoate (53). Trifluoromethanesulfonic anhydride (48 mg, 0.17 mmol) was added to **24** (51 mg, 0.17 mmol) and DIEA (66 mg, 0.51 mmol) in methylene chloride (5 mL) at −78 °C under nitrogen. The reaction mixture was stirred for 2.5 h, and the reaction was quenched at −78 °C by the addition of saturated ammonium chloride. After warming to room temperature, the solution was extracted with methylene chloride. The organic layer was washed with brine and then was dried over $MgSO_4$. After filtration, the solvent was removed and the residue was purified by flash chromatography (10−50% ethyl acetate/hexane) to afford **53** (47 mg, 64%). ^{1}H NMR ($CDCl_3$): δ 7.83 (d, 1H), 6.74 (dd, 1H), 6.64 (d, 1H), 4.73 (m, 2H), 3.85 (m, 1H), 3.71 (m, 1H), 3.62−3.48 (m, 2H), 3.54 (s, 3H), 1.42 (d, 3H). ESMS (pos), *m*/*z*: 433 (M + H).

Methyl (2*R*)-2-(1,1-Dioxido-7-phenyl-4,5-dihydro-1,2,5-benzothiadiazepin-2(3*H*)-yl)propanoate (54). Palladium acetate (5 mg, 0.022 mmol) was added to **53** (47 mg, 0.11 mmol), phenylboronic acid (27 mg, 0.22 mmol), triphenylphosphine (28 mg, 0.11 mmol), and potassium carbonate (60 mg, 0.43 mmol) in degassed toluene (10 mL) under nitrogen. The reaction mixture was heated to reflux for 45 min. After the mixture was cooled, water (10 mL) was added and the mixture was extracted with ethyl acetate. The organic layer was washed with water, 10% citric acid, saturated $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$ and was filtered. The solvent was removed, and the residue was purified by flash chromatography (20−60% ethyl acetate/hexane) to afford **54** (25 mg, 64%). ^{1}H NMR ($CDCl_3$): δ 8.25 (dd, 1H), 7.82 (d, 1H), 7.63−7.35 (m, 4H), 7.10 (dd, 1H), 6.91 (d, 1H), 4.77 (q, 1H), 4.50 (bs, 1H), 3.68−3.43 (m, 4H), 3.56 (s, 3H), 1.41 (d, 3H, 7.4). ESMS (pos), *m*/*z*: 361 (M + H).

***N*-Hydroxy-2(*R*)-[7-phenyl-2,3,4,5-tetrahydrobenzo[1,2,5-*f*]thiadiazepine-1,1-dioxide]propylamide (55).** Compound **54** was converted to hydroxamic acid analogue **55** via method A. ^{1}H NMR (DMSO): δ 10.66 (s, 1H), 7.58−7.34 (m, 6H), 7.13 (d, 1H),7.02 (dd, 1H), 4.27 (q, 1H), 3.70−3.35 (m, 4H), 1.17 (d, 3H). ESMS (pos), *m*/*z*: 362 (M + H). HRMS calcd for ($C_{17}H_{19}N_3O_4S$ + H) 362.1174, found 362.1180.

***N*-Hydroxy-2(*R*)-[7-(2-trifluromethylphenyl)-2,3,4,5-tetrahydrobenzo[1,2,5-*f*]thiadiazepine-1,1-dioxide]propylamide (56).** Compound **56** was synthesized in a fashion analogous to that of compound **55**. ^{1}H NMR (DMSO): δ 10.67 (s, 1H), 7.79 (d, 1H), 7.70−7.59 (m, 2H), 7.52 (d, 1H), 7.36 (d, 1H), 6.77 (s, 1H), 6.64 (d, 1H), 4.28 (q, 1H), 3.78−3.35 (m, 4H), 1.16 (d, 3H). ESMS (pos), *m*/*z*: 430 (M + H). HRMS calcd for ($C_{18}H_{18}F_3N_4O_4S$ + H) 430.1048, found 430.1063. Anal. ($C_{18}H_{18}F_3N_3O_4S\cdot0.7TFA$) C, H, N.

Methyl 2(*R*)-[7-(4-(Trifluoromethyl)phenoxy)-2,3,4,5-tetrahydrobenzo[1,2,5-*f*]thiadiazepine-1,1-dioxide]propanoate (57). The phenol **24** (150 mg, 0.5 mmol) was dissolved in CH_2Cl_2 (6 mL) prior to the addition of $Cu(OAc)_2$ (100 mg, 0.55 mmol), 4-(trifluoromethyl)benzeneboronic acid (190 mg, 1.0 mmol), powdered 4 Å molecular sieves (353 mg), and triethylamine (0.35 mL, 2.5 mmol). After being stirred for 18 h in the open air, the solution was filtered and was washed with 1 N HCl and 1 N NaOH. The organic layer was dried and concentrated. Flash chromatography (20−60% ethyl acetate/hexane) of the resulting residue gave the ester **57** (125 mg, 0.28 mmol, 56%) as a white foam. ^{1}H NMR ($CDCl_3$): δ 1.41 (d, 3H), 3.45−3.6 (m, 2H), 3.61 (s, 3H), 3.62−3.71 (m, 2H), 4.51 (m, 1H), 4.75 (q, 1H), 6.34 (d, 1H), 6.49 (m, 1H), 7.1 (d, 2H), 7.62 (d, 2H), 7.74 (d, 1H). ESMS (pos), *m*/*z*: 445.1 (M + H).

***N*-Hydroxy-2(*R*)-[7-(4-trifluoromethylphenoxy)-2,3,4,5-tetrahydrobenzo[1,2,5-*f*]thiadiazepine-1,1-dioxide]propanamide (58).** The ester **57** (110 mg, 0.25 mmol) was incorporated into method A, and flash chromatography (1−10% MeOH/CH_2Cl_2) gave the hydroxamate **58** (32 mg, 0.07 mmol, 28%) as a white powder. ^{1}H NMR (DMSO): δ 1.15 (d, 3H), 3.25 (m, 1H), 3.43−3.7 (m, 3H), 4.24 (q, 1H), 6.43 (m, 2H), 6.72 (m, 1H), 7.23 (d, 2H), 7.53 (d, 1H), 7.75 (d, 2H), 8.87 (s, 1H), 10.64 (s, 1H). ESMS (neg), *m*/*z*: 444.1 (M − H). HRMS calcd for ($C_{18}H_{18}F_3N_3O_5S$ + H) 446.099 753, found 446.099 100. Anal. ($C_{18}H_{18}F_3N_3O_5S$) C, H, N.

Compounds **59**−**62** were synthesized in a fashion analogous to that of compound **58**.

***N*-Hydroxy-2(*R*)-[7-(4-methoxyphenoxy)-2,3,4,5-tetrahydrobenzo[1,2,5-*f*]thiadiazepine-1,1-dioxide]propanamide (59).** ^{1}H NMR (DMSO): δ 1.13 (d, 3H), 3.2 (m, 1H), 3.35−3.65 (m, 3H), 3.72 (s, 3H), 4.22 (q, 1H), 6.27 (m, 2H), 6.6 (m, 1H), 6.95 (d, 2H), 7.02 (d, 2H), 7.44 (d, 2H), 8.86 (s, 1H), 10.63 (s, 1H). ESMS (neg), *m*/*z*: 406.1 (M − H).

***N*-Hydroxy-2(*R*)-[7-phenoxy-2,3,4,5-tetrahydrobenzo-[1,2,5-*f*]thiadiazepine-1,1-dioxide]propanamide (60).** ^{1}H NMR (DMSO): δ 1.14 (d, 1H), 3.2 (m, 1H), 3.38−3.7 (m, 3H), 4.22 (q, 1H), 6.31 (m, 2H), 6.65 (m, 1H), 7.05 (d, 2H), 7.18 (t, 1H), 7.42 (m, 3H), 8.86 (d, 1H), 10.62 (s, 1H). ESMS (neg), *m*/*z*: 376.1 (M − H). HRMS calcd for ($C_{17}H_{19}N_3O_5S$ + H) 378.112 368, found 378.113 500.

***N*-Hydroxy-2(*R*)-[7-(4-phenylphenoxy)-2,3,4,5-tetrahydrobenzo[1,2,5-*f*]thiadiazepine-1,1-dioxide]propanamide (61).** ^{1}H NMR (DMSO): δ 1.15 (d, 3H), 3.22 (m, 1H), 3.4−3.7 (m, 3H), 4.25 (q, 1H), 6.39 (m, 2H), 6.68 (m, 1H), 7.15 (d, 2H), 7.35 (t, 1H), 7.4−7.54 (m, 3H), 7.63 (d, 2H), 7.71 (d, 2H), 8.86 (s, 1H), 10.64 (s, 1H). ESMS (neg), *m*/*z*: 452.1 (M − H). HRMS calcd for ($C_{23}H_{23}N_3O_5S$ + H) 454.143 668, found 454.144 000.

***N*-Hydroxy-2(*R*)-[7-(3-nitrophenoxy)-2,3,4,5-tetrahydrobenzo[1,2,5-*f*]thiadiazepine-1,1-dioxide]propanamide (62).** ^{1}H NMR (DMSO): δ 1.16 (d, 3H), 3.2 (m, 1H), 3.38−3.74 (m, 3H), 4.24 (q, 1H), 6.37−6.48 (m, 2H), 6.71 (m, 1H), 7.54 (m, 2H), 7.69 (t, 1H), 7.83 (t, 1H), 8.04 (dd, 1H), 8.87 (s, 1H), 10.64 (s, 1H). ESMS (neg), *m*/*z*: 421.1 (M − H). HRMS calcd for ($C_{17}H_{18}N_4O_7S$ + H) 423.097 446, found 423.095 600.

Methyl 2(*R*)-[7-(4-Nitrophenoxy)-2,3,4,5-tetrahydrobenzo[1,2,5-*f*]thiadiazepine-1,1-dioxide]propanoate (57a). The phenol **24** (200 mg, 0.67 mmol) was dissolved in DMF (5 mL) prior to the addition of 1-fluoro-4-nitrobenzene (0.08 mL, 0.74 mmol) and Cs_2CO_3 (391 mg, 1.2 mmol). After 2.5 h, the solution was quenched with aqueous NH_4Cl and extracted with EtOAc. The organic layer was dried, filtered, and concentrated. Flash chromatography (20−60% ethyl acetate/hexane) of the resulting residue gave **57a** (170 mg, 0.4 mmol, 60%). ^{1}H NMR (DMSO): δ 1.43 (d, 3H), 4.6−4.6 (m, 2H), 3.62 (s, 3H), 3.72 (m, 2H), 4.46 (m, 1H), 4.77 (q, 1H), 6.4 (d, 1H), 6.54 (dd, 1H), 7.08 (d, 2H), 7.8 (d, 1H), 8.24 (d, 2H). ESMS (neg), *m*/*z*: 420.1 (M − 1).

***N*-Hydroxy-2(*R*)-[7-(4-nitrophenoxy)-2,3,4,5-tetrahydrobenzo[1,2,5-*f*]thiadiazepine-1,1-dioxide]propanamide (63).** Ester **57a** (165 mg, 0.39 mmol) was incorporated into method A, and flash chromatography (1−10% MeOH/CH_2Cl_2) gave the hydroxamate **63** (120 mg, 0.28 mmol, 72%) as a white solid. ^{1}H NMR (DMSO): δ 1.17 (d, 3H), 3.3 (m, 1H), 3.4−3.7 (m, 3H), 4.25 (q, 1H), 6.47 (dd, 1H), 6.54 (d, 1H), 6.78 (m, 1H), 7.22 (d, 2H), 7.55 (d, 1H), 8.24 (d, 2H), 8.87 (s, 1H), 10.64 (s, 1H). ESMS (pos), *m*/*z*: 423.1 (M + H). HRMS calcd for ($C_{17}H_{18}N_4O_7S$ + H) 423.097 446, found 423.098 600.

Protein Binding in Human Serum. The protein binding was determined by equilibrium dialysis using the Dianorm system (Munchen, Germany). This device consists of Teflon cells and Diachema cellulose based dialysis membrane with a

molecular weight cutoff of 10 kDa. The membranes were soaked in doubly deionized water for 15 min and then in 0.1 M potassium phosphate buffer (pH 7.4) for another 15 min to remove glycerol. Stock solutions of compounds (in acetonitrile) were added to serum samples to yield final concentrations of 10 μM. An amount of 1 mL of serum was dialyzed against 1 mL of 0.1 M potassium phosphate buffer (pH 7.4) at 8 rpm for 2 h at 37 °C in a temperature-controlled water bath. After dialysis, the cells were drained using PTFE draining tubes into preweighed polypropylene tubes of 1 mL of complementary matrix. The mixed matrix minimizes potential nonspecific adsorption of the compound. The mixed matrix samples were extracted using acetonitrile protein precipitation. The supernatant was dried under nitrogen and reconstituted in 25/75/0.1 acetonitrile/water/formic acid (v/v/v). LC−MS−MS analysis was performed on a Micromass Quattro Ultima (Manchester, M23 9LZ, U.K.) triple quadrupole mass spectrometer. The liquid chromatography system consisted of a Shimadzu (Columbia, MD) LC-10Ad*vp* LC pump and a Leap Technologies (Carrboro, NC) HTC PAL autosampler. A gradient elution was performed using a YMC ODS-AQ S-5 2.0 mm × 50 mm column (Milford, MA) at a flow rate of 350 μL/min. Multiple reaction monitoring (MRM) in the positive mode was used for sample analysis.

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