1,2-Benzothiazine 1,1-Dioxide P_2-P_3 Peptide Mimetic Aldehyde Calpain I Inhibitors

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A series of peptide mimetic aldehyde inhibitors of calpain I was prepared in which the P_2 and P_3 amino acids were replaced by substituted 3,4-dihydro-1,2-benzothiazine-3-carboxylate 1,1-dioxides. The effect of 2, 6, and 7-benzothiazine substituents and the P_1 amino acid was examined. Potency of these inhibitors, **15c**−**p**, against human recombinant calpain I is particularly dependent upon the 2-substituent, with methyl and ethyl generally more potent than hydrogen, isopropyl, isobutyl, or benzyl. The more potent diastereomer of **15m** possesses the (*S*) absolute configuration at the 3-position of the 3,4-dihydro-1,2-benzothiazine. Potency of the best inhibitors in this series ($IC_{50} = 5-7$ nM) compares favorably with that of conventional *N*-benzyloxycarbonyl dipeptide aldehyde inhibitors bearing L-Leu or L-Val residues at P_2. The achiral unsaturated 1,2-benzothiazine analogues **26a**−**d** are also potent calpain I inhibitors, while 3,4-dihydro-2,1-benzoxathiin (**15a,b**), 1,2,4-benzothiadiazine (**32a,b**), and tetrahydroisoquinolinone (**36a,b**) analogues are less potent.

Introduction

Calpains, nonlysosomal calcium-activated cysteine proteases present in most mammalian cells including neurons, have been implicated in neurodegeneration following cerebral ischemia, traumatic brain injury, spinal cord trauma, Alzheimer's disease, Parkinson's disease, multiple sclerosis, motor neuron damage, and muscular dystrophy.[1]

Two major calpains with identical catalytic domains but distinct calcium-binding domains are present in the cytoplasm of neurons. Calpain I is activated by low micromolar concentrations of calcium ion, while calpain II requires low millimolar concentrations of calcium ion. Calpains are inactive under normal physiological conditions where calcium ion concentrations are less than 200 nM. However, calpains become activated when trauma, ischemia, or excitotoxicity increases intracellular calcium ion concentrations in neurons. In response to ischemia or trauma, neurons release excitatory amino acids such as glutamate, which overstimulate NMDA receptors, causing an increase in intracellular calcium ion concentrations. Once activated by calcium, calpain degrades neuronal structural proteins including spectrin, tubulin, and neurofilament polypeptides contributing to neuronal death. Calpain I is thought to be more destructive in neurodegeneration than calpain II since it is activated by lower concentrations of calcium ion.

Calpain I inhibitors appear to prevent some of the damage caused by overactivated calpain under pathophysiological conditions and are therefore being investigated as possible treatments for neurodegeneration resulting from cerebral ischemia, traumatic brain injury, or spinal cord trauma.[1]

Endogenous peptide substrates of calpain generally contain L-Leu or L-Val residues at the P_2 site. Similarly, synthetic peptide-based calpain inhibitors frequently contain L-Leu or L-Val at P_2. Thus, various di- and tripeptide aldehydes[2−4] and α-ketoamides[5] containing L-Leu or L-Val at P_2 are potent reversible calpain inhibitors. The aldehyde or ketone functional group of these inhibitors reversibly forms a covalent bond with the thiol of the active site cysteine, thereby inactivating calpain. Likewise, certain di- and tripeptide diazomethyl ketones, halomethyl ketones, and acyloxymethyl ketones containing L-Leu or L-Val at P_2 are potent irreversible calpain inhibitors.[1,3] The lesser potency of peptide-based inhibitors containing other amino acids at P_2 initially lead to the hypothesis that the presence of L-Leu or L-Val was an absolute requirement for potent binding to calpain I.

The potential metabolic instability of the peptidic portion of these di- and tripeptide-based calpain inhibitors to degradation by intracellular and extracellular proteinases may limit their in vivo activity. This liability could potentially be circumvented by introduction of peptide mimetic addresses, an approach that has been investigated in this laboratory and elsewhere.[6,7] In the past few years, several $\psi[COCH_2]$ and $\psi[CH_2CH_2]$ P_2 pseudopeptide addresses[8,9] as well as P_2 proline and piperidine carboxylic acid analogues[10,11] have been described. The potency of some of these derivatives demonstrated that P_2 L-Leu or L-Val is not required for binding to calpain I. One particularly interesting potent class of calpain I inhibitors discovered in this laboratory consists of *N*-alkanesulfonyl dipeptide aldehydes and α-ketoamides containing D-amino acid residues at P_2.[12] For example, P_2 D-*O*-benzylserine derivative **1** is equipotent with the highly effective dipeptide aldehyde calpain I inhibitor *Z*-Val-Phe-H ($IC_{50} = 11$ nM).[4] Incorporation of various other D-amino acid residues including D-phenylglycine, D-phenylalanine, and D-homophenylalanine at P_2 provided similar potency with D-*O*-

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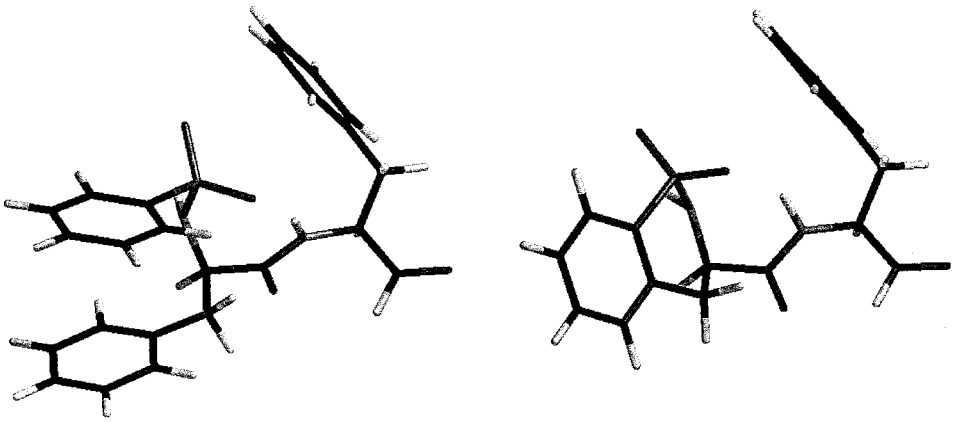
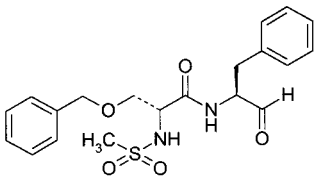
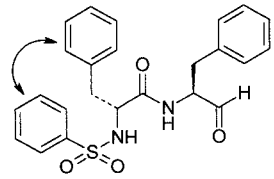


Figure 1. Models of $PhSO_2$-D-Phe-Phe-H (**2**, left) and its 3,4-dihydro-1,2-benzothiazine 1,1-dioxide P_2-P_3 analogue (**3**, right).

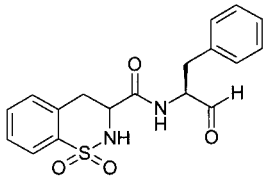
benzylserine. The methanesulfonyl group of **1** could be replaced by ethanesulfonyl or benzenesulfonyl. For example, the benzenesulfonyl P_2 D-phenylalanine derivative **2** is also a potent calpain I inhibitor.[13]



1 (IC_{50} = 11 nM)



2 (IC_{50} = 20 nM)



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We hypothesized that in the bioactive conformation of benzenesulfonyl P_2 D-phenylalanine analogue **2**, the benzene rings of the benzenesulfonyl group, and the P_2 D-phenylalanine are attracted by hydrophobic or $\pi-\pi$ interactions as shown in Figure 1. This suggested that we might construct a constrained peptide mimetic by conceptually superimposing the benzene ring of the P_2 D-phenylalanine group with the benzene ring of the benzenesulfonyl capping group to give a 3,4-dihydro-1,2-benzothiazine 1,1-dioxide P_2-P_3 mimic, as depicted in **3** and in Figure 1. Research on somatostatin provided some precedent for this approach: Two benzene rings of phenylalanine residues in a somatostatin analogue, which were hypothesized to stabilize peptide conformation via hydrophobic attraction, were successfully replaced by a disulfide bond.[14] As shown in Figure 1, the benzene ring of the benzothiazine in **3** occupies a position intermediate between the positions of the P_2 D-phenylalanine and the benzenesulfonyl benzene rings of **2**. However, this was not expected to decrease affinity for calpain I since the P_2 D-phenylalanine and benzenesulfonyl benzene rings of **2** are not absolutely required. More importantly, the positions of the remaining atoms in **2** and **3** are similar or identical.

The synthesis of a series of substituted 3,4-dihydro-1,2-benzothiazine 1,1-dioxides (**15**) and activity as calpain I inhibitors are described below. The synthesis and activity of unsaturated 1,2-benzothiazine 1,1-dioxides (**26**) and isosteric 1,2,4-benzothiadiazines (**32**) are also described. The activity of these compounds is compared to that of tetrahydroisoquinolinones (**36**),[15,16] carbonyl analogues of the 3,4-dihydro-1,2-benzothiazine 1,1-dioxides.

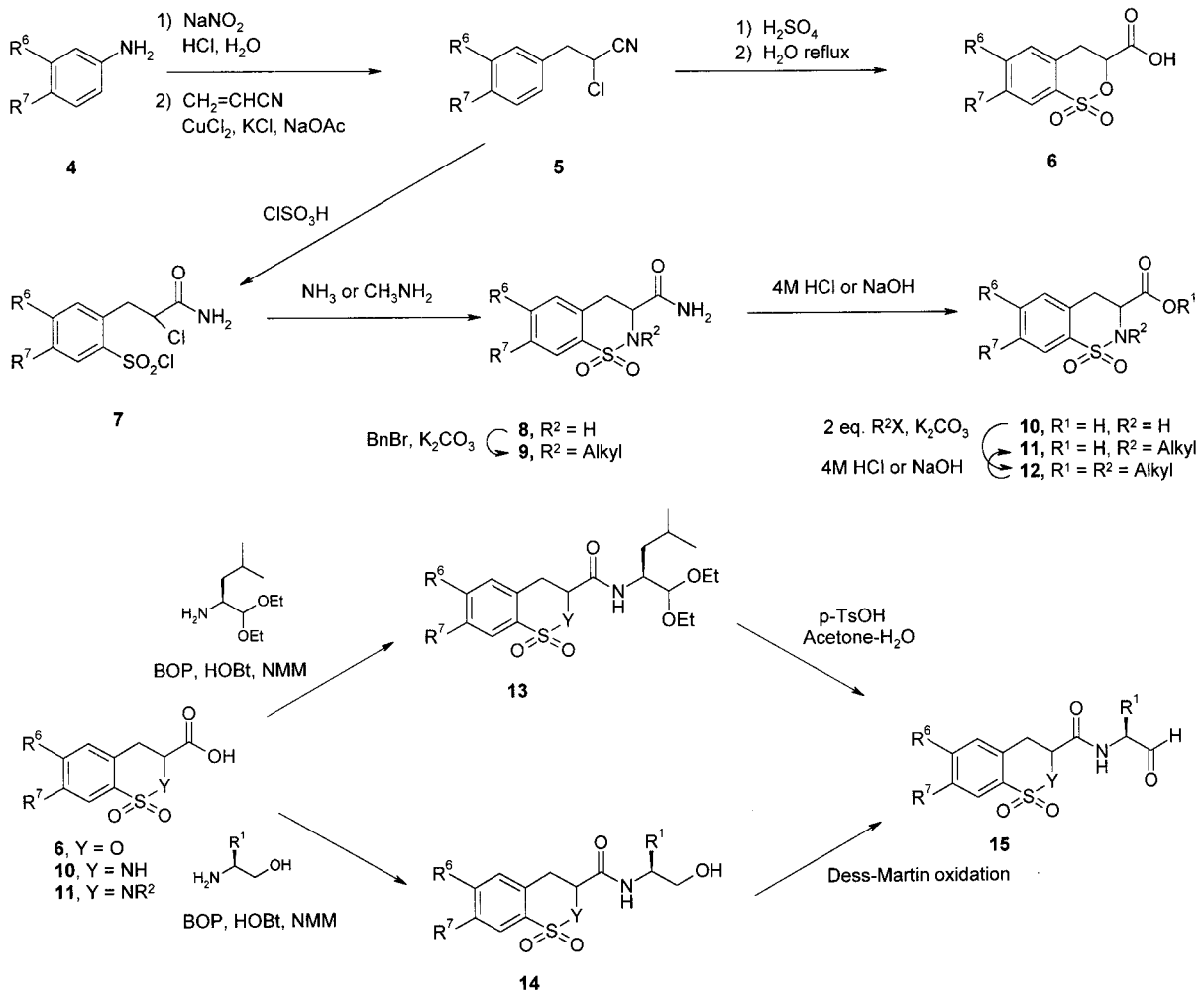
Chemistry

Racemic 3,4-dihydro-1,2-benzothiazine-2-carboxylate 1,1-dioxides were synthesized as shown in Scheme 1. Thus, aniline **4** was diazotized and treated with acrylonitrile and $CuCl_2$ in a Meerwein arylation reaction[17] to afford chloronitrile **5**. Sulfonation of **5** with concentrated sulfuric acid produced 3,4-dihydro-2,1-benzoxathiin-3-carboxylic acid **6**, while sulfonation of **5** with chlorosulfonic acid produced sulfonyl chloride **7**, which cyclized to 3,4-dihydro-1,2-benzothiazine-2-carboxylate 1,1-dioxides **8** or **9** (where R^2 is CH_3) upon reaction with ammonia or methylamine, respectively.[18] Alternatively, **8** was N-alkylated with benzyl bromide to yield **9** (where R^2 is benzyl). Hydrolysis of amide **9** with refluxing 6 M sodium hydroxide, with 4 M hydrochloric acid, or with 6 M sulfuric acid afforded 3,4-dihydro-1,2-benzothiazine-2-carboxylic acid **11**. 3,4-Dihydro-1,2-benzothiazine-2-carboxamide **8** was hydrolyzed to 3,4-dihydro-1,2-benzothiazine-2-carboxylic acid **10** with refluxing aqueous sodium hydroxide or hydrochloric acid. Treatment of **10** with ethyl iodide, isopropyl iodide, or isobutyl bromide produced N-alkylated alkyl ester **12**, the hydrolysis of which afforded 3,4-dihydro-1,2-benzothiazine-2-carboxylic acid **11**.

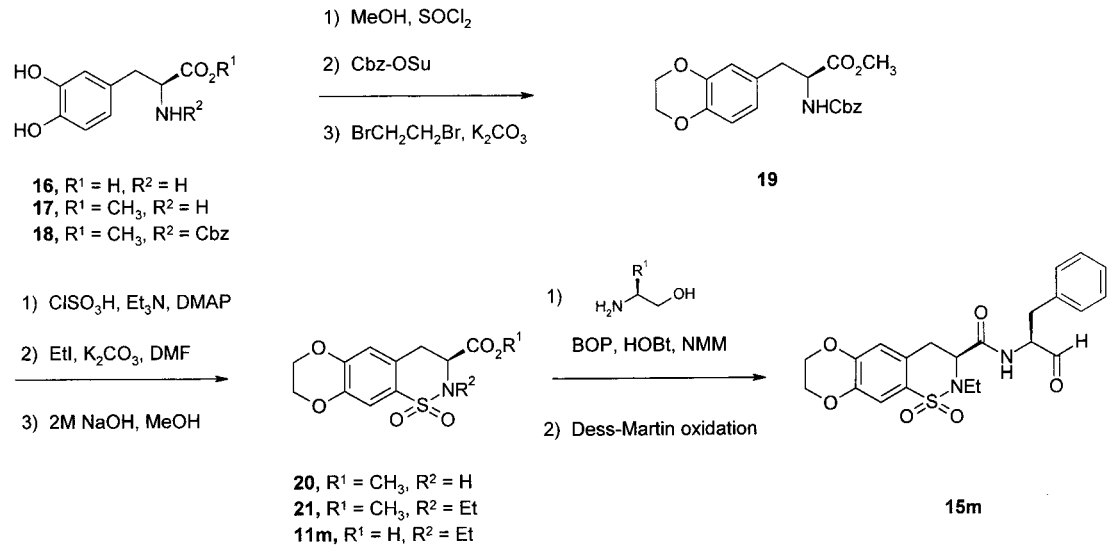
The routes depicted in Scheme 1 were utilized to prepare benzothiazines containing 6,7-dimethoxy, 6,7-ethylenedioxy, 6,7-dichloro, 6-chloro, and 6-fluoro substituents. 6-(Morpholin-4-yl)benzothiazine derivative **9k** was prepared from 6-fluorobenzothiazine **9g** by protracted treatment with excess morpholine in pyridine at 80−85 °C.[19] 6-Chlorobenzothiazine **11i** was dehalogenated to benzothiazine **11f** by hydrogenation over Raney nickel catalyst.

3,4-Dihydro-1,2-benzothiazine-2-carboxylic acids **10** and **11** as well as 3,4-dihydro-2,1-benzoxathiin-3-carboxylic acid **6** were coupled with L-leucinal diethyl acetal or L-phenylalaninol in the presence of benzotriazol-1-

Scheme 1



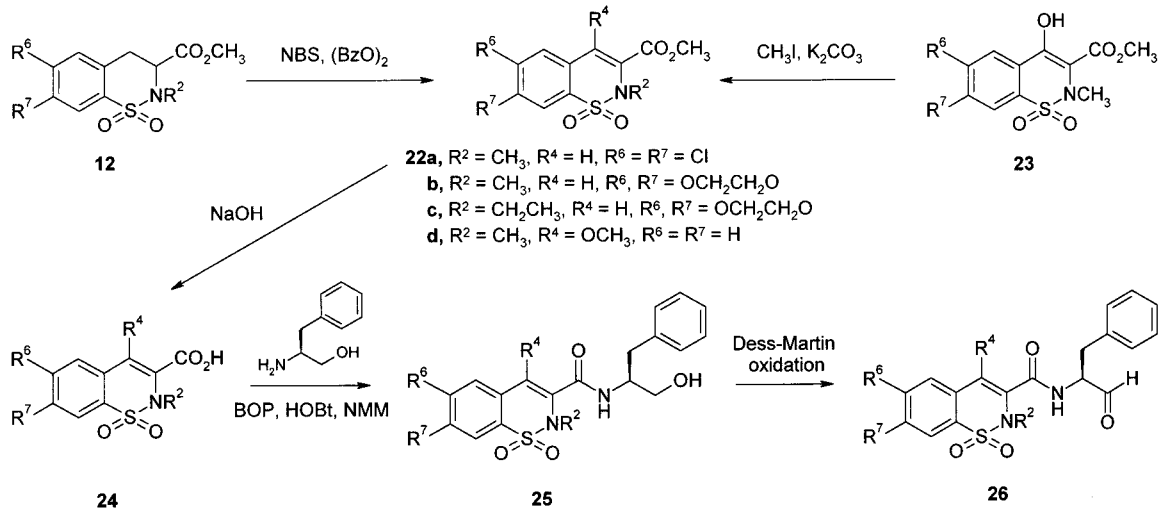
Scheme 2



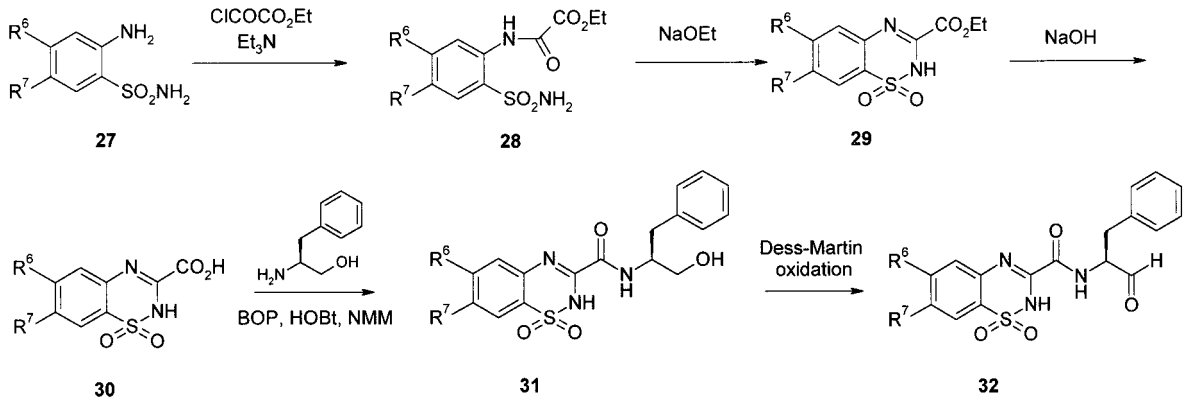
yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent) and HOBT to afford **13** and **14**, respectively. The C_3 diastereomeric diethyl acetals (**13**) or alcohols (**14**) were separated by chromatography whenever practical. Mild hydrolysis of these diethyl acetals **13** or Dess−Martin oxidation[12,20] of alcohols **14** provided the target aldehydes **15**.

A more efficient synthesis of ethylenedioxybenzothiazine **11m** was accomplished as depicted in Scheme 2. Thus, Fischer esterification of L-dihydroxyphenylalanine (L-DOPA, **16**) afforded **17.** Protection of the amino group gave benzyl carbamate **18**, which was treated with dibromoethane and potassium carbonate to produce ethylenedioxyphenylalanine derivative **19**. When **19** was

Scheme 3



Scheme 4



treated with chlorosulfonic acid at 0 °C, the benzyl carbamate was cleaved, and cyclization occurred to afford 3,4-dihydro-1,2-benzothiazine-2-carboxylate **20**. N-Alkylation with ethyl iodide followed by ester hydrolysis afforded (3*S*)-**11m** as depicted in Scheme 2 in 68% enantiomeric purity. The enantiomers of **11m** could be separated by chromatography on a Chiralpak AD reverse-phase chiral column. Alternatively, the two C_3 diastereomers of **14m** formed by condensation of **11m** with L-phenylalaninol could be separated by chromatography on silica gel prior to oxidation to aldehyde **15m**.

Unsaturated 1,2-benzothiazine analogues (**26**) were synthesized as shown in Scheme 3. 3,4-Dihydro-1,2-benzothiazine-2-carboxylates **12** were oxidized to 1,2-benzothiazine-2-carboxylates **22a**−**c** (R^4 = H) with *N*-bromosuccinimide. The 4-methoxy-1,2-benzothiazine-2-carboxylate **22d** (R^4 = MeO) was prepared by O-alkylation of **23**[21] with iodomethane.[22] The methyl ester in **22** was hydrolyzed to give **24**, which was condensed with L-phenylalaninol to produce alcohol **25**, oxidation of which gave aldehyde **26**.

1,2,4-Benzothiadiazine inhibitors (**32**) were synthesized according to Scheme 4. 2-Aminobenzenesulfonamide **27**[23] was condensed with ethyl oxalyl chloride to produce **28** and cyclized with sodium ethoxide to give 1,2,4-benzothiadiazine-3-carboxylate **29**.[24] Hydrolysis of the ethyl ester provided **30**, which was condensed with L-phenylalaninol to give **31** and subsequently oxidized to aldehyde **32**.

Isoquinolinone analogues (**36**) in which the sulfonyl of the benzothiazine was replaced by a carbonyl were synthesized as shown in Scheme 5. Racemic 1-oxoisoquinoline-3-carboxylate **33**[15,16] was N-methylated to **34** and then coupled with L-phenylalaninol to give **35**. The C_3 diastereomers were chromatographically separated and oxidized to aldehydes **36.**

Results and Discussion

The peptide mimetic aldehyde target compounds were evaluated as inhibitors of recombinant human calpain I as previously described in an assay utilizing Suc-Leu-Tyr-4-methoxy-2-naphthylamine as a fluorogenic substrate.[8,25] Inhibition of calpain II was not examined because it requires higher concentrations of calcium ion for activation and is therefore less likely to contribute to neurodegeneration. As shown in Table 1, 6,7-dimethoxy-3,4-dihydro-2,1-benzoxathiin-3-carboxyate derivatives (Y = O) **15a** and **15b**, bearing Ile and Phe substituents at P_1 are moderately potent inhibitors of calpain I (IC_{50} = 130 and 51 nM, respectively, as mixtures of C_3 diastereomers). The potency of **15a** and **15b** was very encouraging as compared to that of *Z*-Val-Phe-H (IC_{50} = 11 nM), CH_3SO_2-D-Ser(*O*Bn)-Phe-H (**1**, IC_{50} = 11 nM), or $PhSO_2$-D-Ser(*O*Bn)-Phe-H (**2**, IC_{50} = 20 nM) in light of previous studies that had revealed that the P_2 NH is required for potency. For example,

Scheme 5

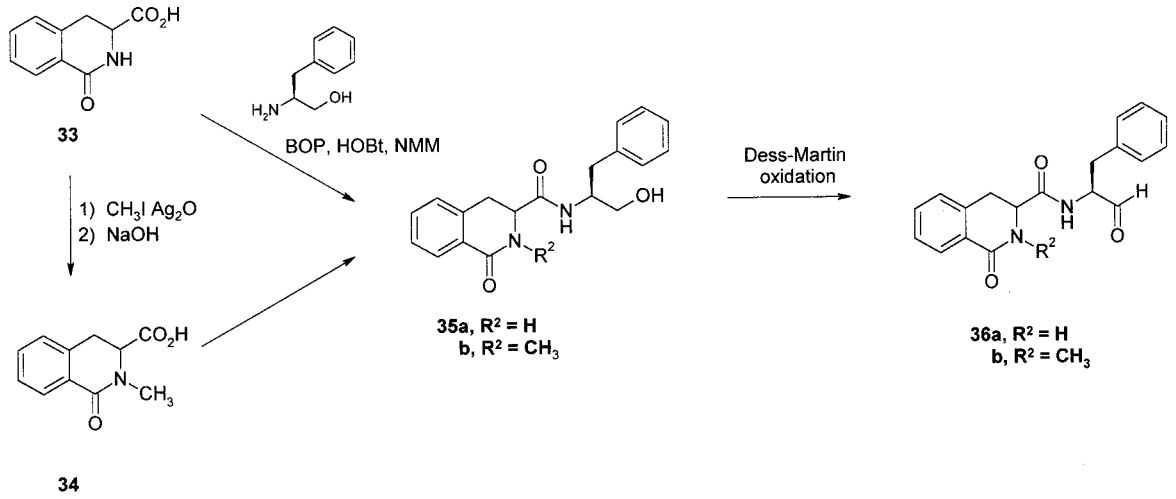
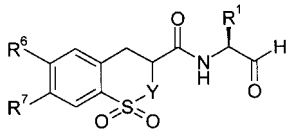


Table 1. Calpain I Inhibitory Activity of 3,4-Dihydro-1,2-benzothiazine-3-carboxylate Peptide Mimetic Aldehydes



					Calpain I IC_{50} (nM)		MOLT-4 cell IC_{50} (μM)
compd	R^6	R^7	R^1	Y	isomer 1	isomer 2	isomer 1
15a	OCH_3	OCH_3	i-Bu	O	130[a]		
15b	OCH_3	OCH_3	Bn	O	51[a]		2.2[a]
15c	OCH_3	OCH_3	Bn	NH	~700	~800	
15d	OCH_3	OCH_3	Bn	NCH_3	38	200	1.9
15e	OCH_3	OCH_3	Bn	NBn	150	~1000	
15f	H	H	Bn	NCH_3	28	110	1.7
15g	F	H	Bn	NCH_3	28[a]		2.4[a]
15h	Cl	Cl	Bn	NCH_3	7	21	1.3
15i	Cl	H	Bn	NiBu	~200	~200	
15j	Cl	H	Bn	NCH_3	5	15	2.2
15k	morpholin-4-yl	H	Bn	NCH_3	30	~500	4.1
15l	OCH_2CH_2O		Bn	NCH_3	24[a]		2.0[a]
15m	OCH_2CH_2O		Bn	NEt	7[b]	33	0.5
15n	OCH_2CH_2O		Bn	NiPr	30[a]		2.6[a]
15o	OCH_2CH_2O		i-Bu	NEt	37	~300	>3
15p	OCH_2CH_2O		$(CH_2)_4NHSO_2Ph$	NCH_3	36	107	1.8

[a] Mixture of (3*R*)- and (3*S*)-3,4-dihydrobenzothiazine-3-carboxylate diastereomers. [b] Isomer 1 of **15m** is the (3*S*)-3,4-dihydrobenzothiazine-3-carboxylate diastereomer.

P_2 N-methylation decreases the potency of P_2-D- and -L-dipeptide aldehydes by a factor of 46 and >1000, respectively[2,12] In contrast, the potency of benzoxathiin inhibitors **15a** and **15b** demonstrated that a hydrogen bond donor was not essential for good inhibition of calpain by this class of inhibitors. Precedence for potent peptide mimetics lacking a P_2 NH may be found in ψ-[$COCH_2$] and ψ[CH_2CH_2] P_2 pseudopeptide addresses as well as P_2 proline and piperidine carboxylic acid analogues.[8,10,11]

Next, we prepared 3,4-dihydro-1,2-benzothiazine-2-carboxylate **15c** containing the NH group, anticipated to confer beneficial hydrogen bonding. Disappointingly, in contrast to **15a** and **15b**, the two diastereomers of **15c** inhibit calpain I only weakly (IC_{50} = 700 and 800 nM). (Isomer 1 and isomer 2 in Table 1 refer to the more and less potent C_3 3,4-dihydro-1,2-benzothiazine diastereomers, respectively.) NMR spectroscopy revealed that the benzothiazine nitrogen reacts with the aldehyde in **15c** to form a six-membered cyclic hemiaminal; therefore, the aldehyde group is predominantly unavailable to react with the active site cysteine. Certain dipeptide aldehydes have previously been shown to form cyclic hemiaminals with the P_2 nitrogen.[26] Hemiaminal formation in the case of **15c** may be particularly favorable due to the constraining effect of the benzothiazine ring.

To prevent cyclic hemiaminal formation, we alkylated the benzothiazine nitrogen. Gratifyingly, one diastereomer of *N*-methyl benzothiazine **15d** was 20 times more potent than the N-unsubstituted analogue (**15c**). This welcome result, consistent with the potency of **15a,b** (above) again indicates that, in contrast to dipeptide aldehydes, the P_2 NH is not required for potency.[2,12] The more potent C_3 diastereomer of **15d** is five times more potent than the less potent diastereomer. Similarly, the P_2-L diastereomer of methanesulfonyl dipeptide aldehyde CH_3SO_2-L-Ser(*O*Bn)-Phe-H is five times less potent than CH_3SO_2-D-Ser(*O*Bn)-Phe-H (**1**).[12] The *N*-benzyl

analogue (**15e**) was less potent than the *N*-methyl benzothiazine analogue (**15d**).

The effect of the 6- and 7-benzothiazine substituents was investigated in a series of *N*-methyl benzothiazines (**15f**−**h** and **15j**−**l**). The 6-chloro- and 6,7-dichlorobenzothiazines are slightly more potent than 6,7-ethylenedioxy- or 6-fluorobenzothiazine, which are more potent than 6-(morpholin-4-yl) or 6,7-unsubstituted benzothiazines, which are in turn slightly more potent than 6,7-dimethoxybenzothiazine (**15d**).

The effect of N-substitution was examined in the 6,7-ethylenedioxybenzothiazine series. The *N*-ethyl analogue (**15m**) is more potent than the *N*-methyl (**15l**) or *N*-isopropyl (**15n**) analogues. Likewise, in the 6-chloro series, *N*-isobutyl benzothiazine (**15i**) is less potent than *N*-methyl benzothiazine (**15j**).

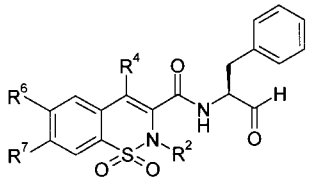
Finally, the P_1 amino acid substituent was evaluated. L-Phe at P_1 (**15l** and **15m**) provided greater potency than L-Ile (**15o**) or L-($PhSO_2$)Lys (**15p**) residues at P_1. In contrast, in the P_2-D series of dipeptide aldehydes, a P_1-L-($PhSO_2$)Lys residue increases potency four times relative to L-Phe.[12]

N-Ethyl-6,7-ethylenedioxybenzothiazine derivative **15m** was selected as a candidate for further biological investigation. A more efficient alternative synthesis of enantiomerically enriched benzothiazine-2-carboxylate **11m** commencing with L-DOPA (**16**) was achieved as shown in Scheme 2. In addition to providing requisite quantities of **15m**, this synthesis allowed the absolute configuration of the two diastereomers of **15m** to be determined. The more potent isomer of **15m** (isomer 1) has the (3*S*)-configuration, derived from L-DOPA (**16**), at the benzothiazine (as illustrated in Scheme 2). This result was unanticipated since, in contrast, CH_3SO_2-D-Ser(*O*Bn)-Phe-H from which the current series was designed is five times more potent than its diastereomer, CH_3SO_2-L-Ser(*O*Bn)-Phe-H.[12] Evidently, benzothiazine **15m** fits into the active site of calpain I in a slightly different orientation than the alkanesulfonyl-P_2-D-dipeptides such as **2**. Furthermore, since isopropyl or isobutyl groups are not required for potency of the P_2 benzothiazine inhibitors (**15**), the orientation of these inhibitors in the active site is apparently quite different from that of L,L-dipeptide aldehyde inhibitors that require Val or Leu at P_2.

The observation that both 3,4-dihydrobenzothiazine C_3 diastereomers of **15c**−**p** possess inhibitory activity suggested that an intermediate configuration between (3*R*) and (3*S*) might also bind strongly to calpain I. Indeed, as shown in Table 2, the potency of **26a** (IC_{50} = 15 nM) containing an achiral unsaturated benzothiazine mimetic is midway between that of the two diastereomers of 3,4-dihydrobenzothiazine **15h** (IC_{50} = 7, 21 nM). Furthermore, benzothiazines **26b** and **26c** are more potent than analogous 3,4-dihydrobenzothiazines **15l** and **15o**, respectively. Finally, calpain I tolerates the 4-methoxy benzothiazine substituent in **26d** (IC_{50} = 37 nM), which appears to have little effect on potency as compared to **15f** (IC_{50} = 28, 110 nM).

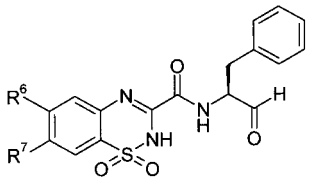
1,2,4-Benzothiadiazine aza analogues **32a,b** are also reasonably potent calpain I inhibitors (see Table 3). Interestingly, in contrast to **15c,** benzothiadiazines **32a,b** do not readily form cyclic hemiaminals despite the lack of *N*-alkyl substituents. This may be due to stabilization of the benzothiadiazine ring by tautomerization of the double bond.[27]

Table 2. Calpain I Inhibitory Activity of 1,2-Benzothiazine-3-carboxylate Peptide Mimetic Aldehydes



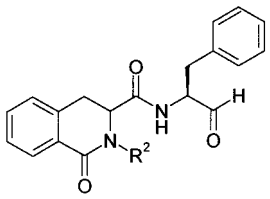
compd	R^4	R^6	R^7	R^2	calpain I IC_{50} (nM)	MOLT-4 cell IC_{50} (μM)
26a	H	Cl	Cl	CH_3	15	2.9
26b	H	OCH_2CH_2O		CH_3	6	0.9
26c	H	OCH_2CH_2O		CH_2CH_3	8	2.1
26d	OCH_3	H	H	CH_3	37	3.2

Table 3. Calpain I Inhibitory Activity of 1,2,4-Benzothiazine-3-carboxylate Peptide Mimetic Aldehydes



compd	R^6	R^7	Calpain I IC_{50} (nM)
32a	H	H	83
32b	OCH_2CH_2O		28

Table 4. Calpain I Inhibitory Activity of 1-Oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate Peptide Mimetic Aldehydes



		Calpain I IC_{50} (nM)	
compd	R^2	isomer 1	isomer 2
36a	H	∼5000[a]	
36b	CH_3	85	∼1000

[a] Mixture of (3*R*)- and (3*S*)-3,4-tetrahydroisoquinoline diastereomers.

Tetrahydroisoquinolinones **36a,b**, carbonyl analogues of **15c**−**p**, are benzoyl dipeptide aldehydes in which the benzoyl capping group has been conceptually superimposed with the benzyl P_2 side chain (see Table 4). Isoquinolinone **36a** exists as the cyclic hemiaminal and therefore inhibits calpain I only very weakly. The *N*-methyl analogue (**36b**), which cannot cyclize, is a moderately potent calpain inhibitor although several times less potent than the corresponding benzothiazine analogue **15f**. Related peptide mimetic analogues of thyrotropin-releasing hormone in which 1-oxotetrahydroisoquinoline-3-carboxylate replaces an N-terminal pyroglutamate residue display good biological potency.[15] Use of 1,2-benzothiazine-2-carboxylate or 3,4-dihydro-2,1-benzoxathiin-3-carboxylate as peptide mimetics is

novel. However, it is interesting that aryl and heteroaryl amides derived from the 1,2-benzothiazine-2-carboxylate pharmacophore **23**, exemplified by piroxicam, are potent cyclogenase inhibitors with excellent in vivo antiinflammatory actvity.[21,22] In addition, 3,4-dihydro-1,2-benzothiazine-2-carboxylates **7** and 3,4-dihydro-2,1-benzoxathiin-3-carboxylates **6** display tranquilizing and anticonvulsive effects in vivo.[18]

Many calpain inhibitors are relatively nonselective, inhibiting the cysteine protease cathepsin B and calpain I with similar potencies.[8] For example, the IC_{50} values of **1**, **2**, and *Z*-Val-Phe-H against cathepsin B are 38, 5, and 82 nM, respectively. While cathepsin B inhibition may not present a toxicity issue for a drug utilized in acute therapy, cathepsin B will compete with calpain for the inhibitor, decreasing its availability. In contrast to many inhibitors examined, **15m** displays good selectivity, inhibiting cathepsin B only 44% at 1 μM. Thus, **15m** is over 150 times selective toward calpain I. Evidently, the constrained geometry of **15m** prevents this inhibitor from binding strongly to the active site of cathepsin B.

Potencies of the most promising benzothiazine inhibitors (IC_{50} < 60 nM) were evaluated in a whole-cell assay. Calpain I in intact MOLT-4 cells (human T-cell leukemia cell line) was activated by treatment with calcium ion and the ionophore ionomycin to elevate intracellular calcium ion concentration. The activated calpain I cleaved spectrin into its characteristic breakdown products, which were resolved by SDS−PAGE and analyzed by immunoblot with a specific polyclonal antibody.[8] Intracellular potency of inhibitors was evaluated after a 10-min pretreatment. In the benzothiazine series, MOLT-4 cell potencies show some correlation with potencies against isolated calpain I (Tables 1 and 2). However, potency in the MOLT-4 cell assay must indicate other attributes such as good cell permeability and good aqueous solubility in addition to good potency against isolated calpain I. In the MOLT-4 cell assay, **15m** (isomer 1) is a particularly potent calpain I inhibitor and ranks as one of the most potent reversible inhibitors yet examined in this assay. The IC_{50} of **15m** in MOLT-4 cells is 500 nM, equipotent with **1**, and slightly more potent than *Z*-Val-Phe-H (800 nM). The solubility of **15m** in pH 7.4 physiological buffered saline is 0.2 mg/mL, equal to that of *Z*-Val-Phe-H. The solubility of the morpholino derivative (**15k**) is 0.3 mg/mL.

Conclusions

The peptide substrates of calpain and many calpain inhibitors typically contain L-Leu or L-Val residues at the P_2 site. Compounds **1** and **2**, discovered in this laboratory, are representatives of a class of peptide aldehyde inhibitors that contain alkanesulfonyl or benzenesulfonyl aromatic D-amino acid P_2 residues rather than the typical L-Leu or L-Val. By conceptually superimposing the benzene rings of the P_2 D-phenylalanine and the benzenesulfonyl group in **2**, we envisioned a class of 1,2-benzothiazine 1,1-dioxide peptide mimetics.

Indeed, a series of peptide mimetic aldehydes (**15d**−**p**) containing this P_2−P_3 benzothiazine replacement inhibited calpain I with a potency similar to that of the most potent L,L-dipeptide aldehydes. Alkylation of the benzothiazine nitrogen increases potency as compared to **15c** by preventing intramolecular cyclization between the benzothiazine nitrogen and the aldehyde group to form a hemiaminal.

One 3,4-dihydrobenzothiazine C_3 diastereomer, when separable from the other, was about 3−20 times more potent an inhibitor of calpain I. The absolute configuration of the more potent diasteromer of **15m** was determined by synthesis from L-DOPA to be (3*S*), which was derived from an L-amino acid. Peptide mimetic aldehydes derived from achiral unsaturated benzothiazine (**26**) inhibit calpain I with potencies intermediate between the two diastereomers of their 3,4-dihydrobenzothiazine analogues (**15**).

In summary, we have discovered a novel class of P_2−P_3 benzothiazine peptide mimetics that potently and selectively inhibit calpain I. These compounds inhibit calpain I with a potency similar to that of *Z*-Val-Phe-H or the alkanesulfonyl P_2-D-dipeptide aldehydes such as **1** from which they were designed. In intact MOLT-4 cells, the most potent inhibitor of the series (**15m**) ranks among the best reversible inhibitors evaluated in this laboratory. Significantly, probably because of its rigid structure, **15m** is a selective inhibitor of calpain I versus cathepsin B. In the future, the benzothiazine peptide mimetic may find utility as a constrained amino acid replacement in other enzyme inhibitors and receptor ligands.

Experimental Section

Melting points were recorded on a Mel-Temp apparatus and are uncorrected. ^{1}H NMR spectra were recoorded on a General Electric QE Plus 300 MHz spectrometer with tetramethylsilane as an internal standard. Electrospray low-resolution mass spectra were recorded on a Fisons VG platform II spectrometer. FAB high-resolution mass spectra were obtained by M-Scan, Inc. (West Chester, PA) on a VG analytical ZAB 2SE mass spectrometer. Elemental analyses were performed by QTI (Whitehouse, NJ). Molecular modeling was performed with SYBYL molecular mechanics force fields and Titan software (Schrödinger, Inc., Portland, OR).

General Procedure A: Condensation of Anilines with Acrylonitrile. 2-Chloro-3-(3,4-dimethoxyphenyl)propanenitrile (5a) (R^6 = R^7 = OCH_3). A modification of the procedure of Pöpel et al. was used.[18] To a vigorously stirred solution of 4-aminoveratrole (17.8 g, 116 mmol) in water (150 mL) and 12 N HCl (29 mL, 349 mmol) chilled in an ice−water bath was added dropwise a solution of sodium nitrite (9.2 g, 133 mmol) in water (15 mL) over 10−15 min. The mixture was stirred for an additional 15 min at the same temperature. This solution was added dropwise over 20 min to a vigorously stirred solution of acrylonitrile (18.6 g, 23 mL, 349 mmol), $CuCl_2 \cdot 2H_2O$ (3 g, 17.4 mmol), KCl (10 g, 134 mmol), and NaOAc (13.1 g, 160 mmol) in water (150 mL) and acetone (350 mL) chilled in an ice−water bath. The resulting mixture was allowed to stir while slowly warming to 20 °C over 24−48 h or until evolution of nitrogen gas had ceased. The acetone was removed on a rotary evaporator, and the residue was extracted with ethyl acetate (2 × 250 mL). The combined organic phase was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The dark residue was purified by flash chromatography (silica gel, dichloromethane) to give 6.0 g (23%) of the title compound as a pale yellow mobile oil. NMR ($CDCl_3$, δ): 3.25 (2H, d, J = 7 Hz), 3.88 (3H, s), 3.89 (3H, s), 4.53 (1H, t, J = 7 Hz), 6.79 (1H, s), 6.85 (2H, s). Anal. ($C_{11}H_{12}NO_2Cl$) C, H, N, Cl.

2-Chloro-3-(3-fluorophenyl)propanenitrile (5g) (R^6 = F; R^7 = H). From 3-fluoroaniline (25 g, 0.23 mol), the crude title compound (42 g) was obtained which was purified by flash chromatography on silica gel (10% CH_2Cl_2:hexanes) followed by further purification by distillation on a Kugelrohr apparatus

(125 °C, 0.3 mmHg) to give 22 g (53%). NMR ($CDCl_3$, δ): 3.30 (m, 2H), 4.56 (t, J = 7 Hz, 1H), 7.04 (m, 3H), 7.35 (m, 1H).

2-Chloro-3-(3,4-dichlorophenyl)propanenitrile (5h) ($R^6 = R^7 = Cl$). From 3,4-dichloroaniline (35 g, 0.22 mol), the crude title compound (41 g) was obtained which was purified by triple distillation on a Kugelrohr apparatus (160 °C, 0.5 mmHg) followed by treatment with decolorizing carbon in refluxing methanol to give 17.3 g (34%) of a yellow-orange mobile oil after filtration and concentration to constant weight. NMR ($CDCl_3$, δ): 3.26 (m, 2H), 4.56 (t, J = 7 Hz, 1H), 7.13 (m, 1H), 7.40 (m, 2H).

2-Chloro-3-(3-chlorophenyl)propanenitrile (5i) (R^6 = Cl; R^7 = H). From 3-chloroaniline (25 g, 196 mmol), the crude product (19.6 g) was obtained which was further purified by distillation on a Kugelrohr apparatus (140 °C, 0.2 mmHg) to afford 17.1 g (44%) of the title compound as a yellow mobile oil. NMR ($CDCl_3$, δ): 3.28 (2H, m), 4.57 (1H, t, J = 7 Hz), 7.20 (1H, m), 7.28−7.33 (3H, m).

2-Chloro-3-(3,4-ethylenedioxyphenyl)propanenitrile (5l) ($R^6 + R^7 = OCH_2CH_2O$). From 1,4-benzodioxan-6-amine (25 g, 165 mmol), the title compound (9.8 g, 26%) was obtained as a yellow solid. NMR ($CDCl_3$, δ): 3.2 (2H, d, J = 7 Hz), 4.25 (4H, s), 4.50 (1H, t, J = 7 Hz), 6.73−6.86 (3H, m).

3,4-Dihydro-6,7-dimethoxy-2,1-benzoxathiin-3-carboxylic acid (6a) ($R^6 = R^7 = OCH_3$). To a flask containing 1.0 g (4.4 mmol) of **5a** was added 1 mL of 98% H_2SO_4 while stirring. The viscous dark mixture was stirred overnight at 20 °C, diluted with water (5 mL), and held at reflux for 4 h. The mixture was cooled to 20 °C, water (25 mL) was added, and the stirring was continued for an additional 15 min. The resulting precipitate was filtered, washed to neutrality with water, and then allowed to air-dry. The dark crude product was purified by recrystallization from 1,4-dioxane (activated carbon) to give 290 mg (22%) of the title compound as a tan solid: mp 273−275 °C (dec). NMR ($CDCl_3$-DMSO-d_6, δ): 3.16−3.29 (2H, m), 3.81 (6H, s), 5.34 (1H, dd, J = 4 Hz, 12 Hz), 6.63 (1H, s), 7.11 (1H, s). MS m/z: 311 $(M + Na)^+$. Anal. ($C_{11}H_{12}O_7S \cdot 0.2H_2O$) C, H, N, S.

General Procedure B: Aromatic Chlorosulfonylation. 2-Chloro-3-(2-chlorosulfonyl-4,5-dimethoxyphenyl)propanamide (7a) ($R^6 = R^7 = OCH_3$). To a solution of **5a** (4.07 g, 18.0 mmol) in anhydrous chloroform (50 mL) chilled in an ice−water bath was added chlorosulfonic acid (4.2 g, 2.4 mL, 36.0 mmol) dropwise over 10−15 min. The mixture was stirred at this temperature for 5 h and poured into a separatory funnel containing chloroform (50 mL) and water (50 mL). The organic phase was washed further with water and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The brown sticky residue (2.8 g) was slurried with benzene (5 mL) for 15 min, decanted, and dried in vacuo to constant weight to give 2.5 g (41%) of the title compound as a red-brown solid. The intermediate was used without further purification. MS m/z: 342 $(M + H)^+$, Cl_2 isotope pattern.

2-Chloro-3-(2-chlorosulfonyl-4,5-dichlorophenyl)propanamide (7h) ($R^6 = R^7 = Cl$). 5h was heated to 150 °C for 1.5 h (2.5 g, 10.7 mmol) in neat chlorosulfonic acid (∼10 mL). Dropwise addition of the dark reaction mixture (cooled to 20 °C) to a vigorously stirred slurry of ice−water (∼100 g), vacuum filtration of the precipitate, washing with cold water, and drying to constant weight in vacuo gave the product (3.3 g, 89% yield) as a yellow solid. Anal. ($C_9H_7NO_3SCl_4 \cdot 0.3H_2O$) C, H; N, calcd 3.93; found 3.38.

2-Chloro-3-(2-chlorosulfonyl-5-chlorophenyl)propanamide (7i) (R^6 = Cl; R^7 = H). To a dry flask equipped with a magnetic stirrer, rubber septum, and drying tube was added **5i** (5.0 g, 25.0 mmol). Chlorosulfonic acid (17 mL) was added while stirring over 5−10 min at 20 °C. An appreciable exotherm was observed along with gas evolution (HCl) that persisted for 10−15 min following completion of the addition. After being stirred for an additional 1 h, the mixture was heated to 100 °C for 1 h, cooled to 20 °C, and added dropwise while vigorously stirring to an ice−water slurry (∼500 g). The resulting precipitate was collected by vacuum filtration, washed with water several times, and dried in vacuo to constant weight to afford 8.9 g of crude title compound as a pale yellow solid. NMR analysis suggested the presence of the desired product as well as an unidentified regioisomer. NMR (DMSO-d_6, δ): 3.37 (1H, ABq), 3.60 (1H, ABq), (J = 7 Hz, 14 Hz), 4.59 & 4.80 (1H, 2t, J = 7 Hz), 7.18−7.26 (2H, m), 7.65−7.80 (1H, m). The product was used without further purification.

2-Chloro-3-(2-chlorosulfonyl-4,5-ethylenedioxyphenyl)propanamide (7l) ($R^6 + R^7 = OCH_2CH_2O$). From **5l** (3.0 g, 13.4 mmol), the title compound (2.4 g, 51%) was obtained as a tan solid, which was used without further purification.

General Procedure C: Reaction of Sulfonyl Chloride with Ammonia. 3,4-Dihydro-6,7-dimethoxy-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxide (8c) ($R_6 = R_7 = OCH_3$). To a flask containing a solution of NH_3 in 1,4-dioxane (0.5M, 30 mL) was added **7a** (1.0 g, 2.9 mmol). The mixture was refluxed for 2 h, cooled to room temperature, and concentrated in vacuo. The residue was slurried in water, and the solid was collected by vacuum filtration, washed to neutrality with water, and dried in vacuo to constant weight to give 0.31 g (37%) of the title compound as an off-white solid. MS m/z: 287 $(M + H)^+$, 309 $(M + Na)^+$.

3,4-Dihydro-6,7-ethylenedioxy-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxide (8l) ($R^6 + R^7 = OCH_2CH_2O$). From **7l** (2.4 g, 7.1 mmol) and concentrated NH_4OH (50 mL) of the title compound (0.87 g, 44%) was obtained following flash chromatography on silica gel (25% ethyl acetate/hexanes to ethyl acetate). MS m/z: 283 $(M - H)^-$.

General Procedure D: Reaction of Sulfonyl Chloride with Primary Amines. 3,4-Dihydro-6,7-dimethoxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxide (9d) ($R^6 = R^7 = OCH_3$; Y = NCH_3). A mixture of **7a** (1.1 g, 3.2 mmol) in 40% aqueous methylamine (10 mL) was stirred while refluxing. Water (1−2 mL) was added after 30 and 45 min to facilitate stirring. After a total reflux period of 1.5 h, the mixture was cooled in an ice−water bath, and the solid was collected by vacuum filtration and washed to neutrality with water before being dried to constant weight in vacuo. The title compound (0.57 g, 59%) was obtained as an off-white solid; mp 215−222 °C. NMR (DMSO-d_6, δ): 2.58 (3H, s), 2.97−3.28 (2H, m), 4.51 (3H, s), 4,52 (3H, s), 4.53 (1H, dd, J = 5 Hz, 12 Hz), 7.02 (1H, s), 7.12 (1H, s), 7.44 (1H, br; absent in D_2O), 7.64 (1H, br; absent in D_2O). MS m/z: 301 $(M + H)^+$, 323 $(M + Na)^+$. Anal. ($C_{12}H_{16}N_2O_7S$) C, H, N, S.

General Procedure E: Alkylation of Sulfonamide. 3,4-Dihydro-6,7-dimethoxy-2-benzyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxide (9e) ($R^6 = R^7 = OCH_3$; Y = NBn). A mixture of **8c** (250 mg, 0.87 mmol) and anhydrous potassium carbonate (300 mg, 2.2 mmol) in DMF (3 mL) was treated with benzyl bromide (0.11 mL, 0.96 mmol). The mixture was stirred while being warmed to 95−100 °C. After 5 h, an additional 0.05 mL of benzyl bromide was added, and the mixture was stirred overnight at 95−100 °C. The mixture was cooled to 20 °C, the solvent was evaporated in vacuo, and the residue was partitioned between ethyl acetate and 5% aqueous citric acid solution. The organic phase was washed further with saturated aqueous sodium bicarbonate solution, brine, dried over anhydrous magnesium sulfate, filtered, and concentrated to afford 310 mg (94%) of the title compound as a pale yellow solid that was used without further purification. MS m/z: 377 $(M + H)^+$, 399 $(M + Na)^+$.

3,4-Dihydro-6-fluoro-2-methyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxide (9g) (R^6 = F; R^7 = H; Y = NCH_3). From **7g** (14.1 g, 52.6 mmol) and methylamine, the title compound (7.2 g, 53%) was obtained following flash chromatography on silica gel (30−80% ethyl acetate/hexanes). NMR ($CDCl_3$, δ): 2.59 (s, 3H), 3.08−3.21 (m, 2H), 4.49−4.55 (m, 1H), 7.27−7.40 (m, 2H), 7.47 (br, 1H, CONH), 7.68 (br, 1H, CONH), 7.77−7.81 (m, 1H). MS m/z: 259 $(M + H)^+$. Anal. ($C_{10}H_{11}N_2O_3FS \cdot 0.05C_6H_{14}$) C, H, N, S, F.

3,4-Dihydro-6,7-dichloro-2-methyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxide (9h) ($R^6 = R^7$ = Cl; Y = NCH_3). From **7h** (3.0 g, 8.5 mmol) and methylamine, the title compound (0.94 g, 36%) was obtained following flash chroma-

tography on silica gel (25% ethyl acetate/hexanes). MS *m/z*: 307, 309, 311 $(M + H)^+$, Cl_2 isotope pattern.

3,4-Dihydro-6-chloro-2-methyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxide (9j) (R^6 = Cl; R^7 = H; Y = NCH_3). From **7i** (8.0 g, 25.3 mmol) and methylamine, the title compound (3.4 g, 49%) was obtained following flash chromatography on silica gel (25% ethyl acetate/hexanes to ethyl acetate). NMR (DMSO-d_6, δ): 2.60 (3H, s), 3.11−3.19 (2H, m), 4.48 (1H, dd, J = 6 Hz), 7.47−7.74 (5H, m; 3Ar + $2NH_2$). MS *m/z*: 275, 277, Cl isotope pattern.

3,4-Dihydro-6-(4-morpholino)-2-methyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxide (9k) (R^6 = 4-morpholino; R^7 = H; Y = NCH_3). A solution of **9g** (2.0 g, 7.75 mmol) in pyridine (30 mL) was treated with morpholine (6.75 g, 77.5 mmol) and warmed to 80−85 °C while being stirred. After 10 days, the mixture was concentrated in vacuo, and the residue was partitioned between ethyl acetate and water. The organic phase was washed twice more with water and then brine, dried over anhydrous magnesium sulfate, filtered, and concentrated to give 2.6 g of the crude product, which was further purified by recrystallization (ethyl acetate/hexanes) to afford 1.7 g (71%) of the title compound as an off-white solid. NMR (DMSO-d_6, δ): 2.70 (s, 3H), 3.18−3.33 (m, 6H), 3.82−3.85 (m, 4H), 4.12−4.18 (m, 1H), 6.75 (s, 1H), 6.84 (dd, J = 2 Hz, 8 Hz, 1H), 7.65 (d, J = 8 Hz, 1H); MS *m/z*: 326 $(M + H)^+$.

3,4-Dihydro-6,7-ethylenedioxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxide (9l) (R^6 + R^7 = OCH_2CH_2O; Y = NCH_3). From **7l** (1.0 g, 2.9 mmol) and methylamine, the title compound (0.77 g, 88%) was obtained as an off-white solid. NMR (DMSO-d_6, δ): 2.56 (3H, s), 2.95−3.04 (2H, m), 4.25, 4.26 (4H, 2s), 4.40−4.46 (1H, ABq, J = 6 Hz), 6.95 (1H, s), 7.12 (1H, s), 7.43 (1H, br; absent in D_2O), 7.63 (1H, br; absent in D_2O).

General Procedure F: Amide Hydrolysis. 3,4-Dihydro-6,7-dimethoxy-2*H*-1,2-benzothiazine-3-carboxylic Acid 1,1-Dioxide (10c) (R^6 = R^7 = OCH_3). A slurry of **8c** (300 mg, 1.05 mmol) in 6 N NaOH (7 mL) was heated to reflux. After about 10 min, the mixture became homogeneous. Reflux was continued for an additional 30−40 min, at which time TLC analysis revealed complete consumption of starting material. The mixture was cooled to room temperature, a small amount of water was added to dissolve precipitated solids, and the pH was adjusted to ∼3 with 6 N HCl. The resulting precipitate was collected by vacuum filtration, washed to neutrality with water, and dried to constant weight in vacuo to give 250 mg (84%) of the title compound as a white solid. NMR (DMSO-d_6, δ): 2.97−3.18 (2H, m), 3.76 (6H, 2s), 4.33 (1H, m; dd in D_2O), 7.10 (1H, s), 7.57 (1H, s), 7.58 (1H, d, J = 11 Hz; absent in D_2O). MS *m/z*: 286 $(M - H)^-$. Anal. ($C_{11}H_{13}NO_6S$) C, H, N, S.

3,4-Dihydro-6,7-ethylenedioxy-2*H*-1,2-benzothiazine-3-carboxylic Acid 1,1-Dioxide (10l) (R^6 + R^7 = OCH_2CH_2O). Treatment of **8l** (250 mg, 0.88 mmol) with NaOH afforded the title compound (228 mg, 91%) as a tan solid. NMR (DMSO-d_6, δ): 2.86−3.08 (2H, m), 4.25−4.33 (5H, m + s), 6.90 (1H, s), 7.08 (1H, s), 7.60 (1H, d, J = 11 Hz; NH, absent in D_2O). MS *m/z*: 284 $(M - H)^-$.

3,4-Dihydro-6,7-dimethoxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylic Acid 1,1-Dioxide (11d) (R^6 = R^7 = OCH_3; Y = NCH_3). Treatment of **9d** (500 mg, 1.7 mmol) with NaOH afforded the title compound (480 mg, 96%) as a buff white solid; mp 196−200 °C. MS *m/z*: 300 $(M - H)^-$.

3,4-Dihydro-6,7-dimethoxy-2-benzyl-2*H*-1,2-benzothiazine-3-carboxylic Acid 1,1-Dioxide (11e) (R^6 = R^7 = OCH_3; Y = NBn). Treatment of **9e** (290 mg, 0.77 mmol) with NaOH afforded the title compound (183 mg, 63%) as a white solid. NMR (DMSO-d_6, δ): 3.13−3.27 (2H, m), 3.78 (6H, s), 4.19 (2H, ABq, J = 16 Hz), 4.54−4.59 (1H, dd, J = 6 Hz), 7.04 (1H, s), 7.14 (1H, s), 7.18−7.33 (5H, m), 13.2 (1H, br; absent in D_2O). MS *m/z*: 378 $(M + H)^+$, 400 $(M + Na)^+$.

3,4-Dihydro-2-methyl-2*H*-1,2-benzothiazine-3-carboxylic Acid 1,1-Dioxide (11f) (R^6 = H; R^7 = H; Y = NCH_3). A solution of **11i** (550 mg, 2.0 mmol) in ethanol (25 mL) was shaken on a Parr apparatus with Raney nickel (∼1 g, 50% aqueous, pH 9) under 50 psi hydrogen at room temperature for 18 h. The mixture was filtered through a bed of Celite filter aid, and the filtrate was concentrated on a rotary evaporator. The residue was dissolved in water (10 mL), acidified to pH 3, and extracted with ethyl acetate. The organic phase was washed with brine, dried over magnesium sulfate, filtered, and concentrated to give 378 mg (79%) of the title compound as a white solid. NMR ($CDCl_3$, δ): 2.63 (s, 3H), 3.01−3.35 (m, 2H), 4.70−4.76 (m, 1H), 7.42−7.71 (m, 4H). MS *m/z*: 240 $(M - H)^-$. Anal. ($C_{10}H_{11}NO_4S$) C, H, N, S.

3,4-Dihydro-6-fluoro-2-methyl-2*H*-1,2-benzothiazine-3-carboxylic Acid 1,1-Dioxide (11g) (R^6 = F; R^7 = H; Y = NCH_3). Amide **9g** (1.0 g, 3.87 mmol) was refluxed in 4 N aqueous HCl in 1,4-dioxane to give the title compound (0.43 g, 43%) following recrystallization (ether/hexanes). MS *m/z*: 258 $(M - H)^-$. Anal. ($C_{10}H_{10}FNO_4S$) C, H, N, S, F.

3,4-Dihydro-6,7-dichloro-2-methyl-2*H*-1,2-benzothiazine-3-carboxylic Acid 1,1-Dioxide (11h) (R^6 = R^7 = Cl; Y = NCH_3). 9h (200 mg, 0.65 mmol) was refluxed in 4 N aqueous HCl in 1,4-dioxane to give the title compound (200 mg, 100%) following lyophilization of the reaction mixture. NMR (DMSO-d_6, δ): 2.64 (s, 3H), 3.13−3.37 (m, 2H), 4.72−4.77 (m, 1H), 7.87 (s, 1H), 7.98 (s, 1H). MS *m/z*: 308, 310, 312 $(M + H)^+$, Cl_2 isotope pattern.

3,4-Dihydro-6-chloro-2-isobutyl-2*H*-1,2-benzothiazine-3-carboxylic Acid 1,1-Dioxide (11i) (R^6 = Cl; R^7 = H; Y = N−i-Bu). A solution of **12i** (175 mg, 0.47 mmol) in 1,4-dioxane (7 mL) was treated with 4 N HCl (10 mL) and refluxed for 1.5 h. Upon cooling to 20 °C, a white precipitate formed. The 1,4-dioxane was removed on the rotary evaporator; the solid was collected by vacuum filtration, washed with water, and dried to constant weight to give 148 mg (100%) of the title compound. MS *m/z*: 316, 318 $(M - H)^-$, Cl isotope pattern.

3,4-Dihydro-6-chloro-2-methyl-2*H*-1,2-benzothiazine-3-carboxylic Acid 1,1-Dioxide (11j) (R^6 = Cl; R^7 = H; Y = NCH_3). A slurry of **9j** (500 mg, 1.8 mmol) in 6 M sulfuric acid (15 mL) was heated to reflux and stirred for 1.5 h. The mixture was cooled to 20 °C and extracted with ethyl acetate (50 mL), and the organic phase was washed twice with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated to afford 430 mg (86%) of the title compound. MS *m/z*: 274, 276 $(M + H)^+$, Cl isotope pattern.

3,4-Dihydro-6,7-ethylenedioxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylic Acid 1,1-Dioxide (11l) (R^6 + R^7 = OCH_2CH_2O; Y = NCH_3). Treatment of **9l** (600 mg, 2.0 mmol) with NaOH afforded the title compound (550 mg, 92%) as a pale yellow solid. NMR (DMSO-d_6, δ): 2.59 (3H, s), 3.01−3.24 (2H, m), 4.25, 4.26 (4H, 2s), 4.64−4.70 (1H, ABq, J = 6 Hz), 6.95 (1H, s), 7.11 (1H, s), 13.40 (1H, br; absent in D_2O). MS *m/z*: 298 $(M - H)^-$.

3,4-Dihydro-6,7-ethylenedioxy-2-ethyl-2*H*-1,2-benzothiazine-3-carboxylic Acid 1,1-Dioxide (11m) (R^6 + R^7 = OCH_2CH_2O; Y = NEt). Method A: A mixture of **12m** (200 mg, 0.59 mmol) in ethanol (1.5 mL) and 4 N NaOH (3 mL) was stirred at room temperature for 2 h. A small amount of solid separated from the initially homogeneous solution, and the mixture was warmed to ∼50 °C to re-establish homogeneity. This process was repeated over the next 4 h, whereupon the mixture was acidified to pH 2 (4N HCl), and the resulting oily precipitate was extracted into ethyl acetate. The organic phase was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated to afford 153 mg (83%) of the title compound as a white solid, which was used without further purification. NMR ($CDCl_3$, δ): 0.99 (3H, t, J = 7 Hz), 2.96−3.09 (4H, m), 4.25 (4H, br), 4.47 (1H, t, J = 8 Hz), 6.97 (1H, s), 7.10 (1H, s). MS *m/z*: 312 $(M - H)^-$.

Method B: To a mixture of 272 mg (0.83 mmol) of **21** in 1.0 mL of MeOH and 3 mL of H_2O was added 1.25 mL (3.0 equiv) of 2 N NaOH at 0 °C while being stirred. After 5 min, the ice bath was removed, and the mixture was stirred at 20 °C for 2 h. The mixture was diluted with 5 mL of H_2O, and the solvent was evaporated. The aqueous solution was then extracted with ether. The aqueous layer was acidified to pH ∼3 with HCl and extracted with CH_2Cl_2. The combined extracts were dried and evaporated to afford 250 mg (96%) of

a white solid. NMR ($CDCl_3$, δ): 1.09 (t, 3H, J = 7.1 Hz), 3.01 (m, 1H) 3.26 (m, 3H), 4.14 (dd, 1H, J = 7 Hz), 4.28 (s, 4H), 6.82 (s, 1H), 7.34 (s, 1H). MS *m/z*: 314 $(M + H)^+$. The enantiomers of **11m** were separated by chromatography at 30 °C on a 4.6 × 25 cm Chiralpak AD reverse-phase chiral column (Chiral Technologies, Exton, PA) eluted with MeCN-TFA (99.8:0.2) at 1.0 mL/min. Two enantiomers were detected by absorption at 254 nM: 4.0 min (32%) and 4.5 min (68%). Optical rotation detection revealed that the 4.0 peak is levorotatory and that the 4.5 peak is dextrorotatory. Condensation of **11m** with L-phenylalanol gave a 2:1 mixture of diastereomers **14m** in which the R_f 0.3 isomer predominated (NMR, see below). Anal. ($C_{13}H_{15}NO_6S$) C, H, N.

3,4-Dihydro-6,7-ethylenedioxy-2-isopropyl-2*H*-1,2-benzothiazine-3-carboxylic Acid 1,1-Dioxide (11n) ($R^6 + R^7 = OCH_2CH_2O$; Y = N-i-Pr). A solution of **12n** (165 mg, 0.45 mmol) in ethanol (3 mL) was treated with 6 N NaOH, refluxed for 5 h and allowed to cool to 20 °C while being stirred overnight. The mixture was acidified to pH 3 with HCl and extracted with ethyl acetate. The organic phase was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated to give 126 mg (86%) of the title compound as a white solid. NMR ($CDCl_3$, δ): 0.58 (d, J = 7 Hz, 3H), 1.17 (d, J = 7 Hz, 3H), 3.29 (m, 2H), 4.05 (m, 1H), 4.30 (s+m, 5H), 6.84 (s, 1H), 7.35 (s, 1H). MS *m/z*: 326 $(M - H)^-$. Anal. ($C_{14}H_{17}NO_6S \cdot 0.2H_2O$) C, H, N, S.

Isobutyl 3,4-Dihydro-6-chloro-2-isobutyl-2*H*-1,2-benzothiazine-3-carboxylate 1,1-Dioxide (12i) (R^6 = Cl; R^7 = H; Y = N−i-Bu; R = i-Bu). A mixture of **10i** (540 mg, 2.06 mmol), potassium carbonate (1.4 g, 10.3 mmol), and isobutyl bromide (0.71 g, 0.56 mL, 5.16 mmol) in DMF (10 mL) was stirred at 70 °C. After 18 h, the solvent was evaporated in vacuo, and the residue was partitioned between ethyl acetate and water. The organic phase was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (30% ether/hexanes) to give 270 mg (35%) of the title compound as a white solid. NMR ($CDCl_3$, δ): 0.82 (d, J = 7 Hz, 6H), 0.96 (s, J = 7H, 6H), 2.71 (m, 2H), 2.90 (m, 2H), 3.16 (m, 2H), 3.48 (m, 2H), 4.38 (m, 1H), 7.37 (m, 2H), 7.73 (t, J = 8 Hz, 1H). MS *m/z*: 373, 375 $(M + H)^+$, Cl isotope pattern.

Ethyl 2-Ethyl-3,4-dihydro-6,7-ethylenedioxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-Dioxide (12m) ($R^6 + R^7 = OCH_2CH_2O$; R = Et; Y = NEt). A stirred mixture of **10m** (220 mg, 0.42 mmol) and anhydrous potassium carbonate (293 mg, 2.12 mmol) in DMF was treated with ethyl iodide (0.07 mL, 0.87 mmol) and warmed to 65 °C. After 3 h, an additional aliquot of ethyl iodide (0.07 mL) was added and stirring was continued for another 3 h. The mixture was filtered, the DMF was stripped in vacuo, and the residue was partitioned between ethyl acetate and water. The organic phase was washed with saturated aqueous sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue was further purified by flash chromatography on silica gel (dichloromethane) to afford 200 mg (76%) of the title compound. NMR ($CDCl_3$, δ): 1.16 (3H, t, J = 7 Hz), 1.32 (3H, t, J = 7 Hz), 3.08−3.29 (4H, m), 4.24−4.31 (6H, m), 4.45 (1H, dd, J = 6 Hz), 6.76 (1H, s), 7.32 (1H, s). MS *m/z*: 342 $(M + H)^+$, 364 $(M + Na)^+$.

Isopropyl 3,4-Dihydro-6,7-ethylenedioxy-2-isopropyl-2*H*-1,2-benzothiazine-3-carboxylate 1,1-Dioxide (12n) ($R^6 + R^7 = OCH_2CH_2O$; Y = N-i-Pr; R = i-Pr). From **10m** (200 mg, 0.70 mmol), the title compound (167 mg, 65%) was obtained as a white solid following preparative TLC on silica gel (CH_2Cl_2). NMR ($CDCl_3$, δ): 0.66 (d, J = 7 Hz, 3H), 1.15 (d, J = 7 Hz, 3H), 1.28 (d, J = 6 Hz, 6H), 3.11−3.39 (m, 2H), 3.93−3.99 (m, 1H), 4.18−4.27 (s+m, 5H), 5.07−5.11 (m, 1H), 6.77 (s, 1H), 7.30 (s, 1H). MS *m/z*: 370 $(M + H)^+$.

General Procedure G: Amide Formation. *N*-(3,4-Dihydro-6,7-dimethoxy-2,1-benzoxathiin-3-carbonyl)-L-leucinal 1,1-Dioxide Diethyl Acetal (13a) ($R^6 = R^7 = OCH_3$; R^1 = i-Bu; Y = O). A solution of **6a** (180 mg, 0.63 mmol), HOBt (93 mg, 0.69 mmol), and *N*-methylmorpholine (NMM) (202 mg, 2.0 mmol) in DMF (2 mL) was cooled in an ice−water bath and treated with BOP reagent (304 mg, 0.69 mmol). After being stirred an additional 15 min, the mixture was treated with a solution of L-leucinal diethyl acetal (130 mg, 0.69 mmol) in DMF (1 mL). The resulting mixture was stirred overnight while slowly warming to 20 °C. The DMF was removed under reduced pressure, and the residue was partitioned between ethyl acetate and 5% aqueous citric acid. The organic phase was washed with saturated aqueous sodium bicarbonate, water, and brine; dried over anhydrous magnesium sulfate; filtered; and concentrated. The residue was further purified by flash chromatography on silica gel (25−50% ethyl acetate/hexanes) to afford 126 mg (44%) of the title compound as an amorphous solid product. MS *m/z*: 482 $(M + Na)^+$. Anal. ($C_{21}H_{33}NO_8S$) C, H, N.

***N*-(3,4-Dihydro-6,7-ethylenedioxy-2-ethyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-leucinal 1,1-Dioxide Diethyl Acetal (13o) ($R^6 + R^7 = OCH_2CH_2O$; R^1 = i-Bu; Y = NEt).** From **11m** (350 mg, 1.12 mmol) and L-leucinal diethyl acetal (275 mg, 1.45 mmol), the crude title compound (574 mg) was obtained. Separation of diastereomers was achieved by flash chromatography on silica gel (50% ethyl acetate/hexanes). Isomer a: 162 mg (30%). MS *m/z*: 507 $(M + Na)^+$. Isomer b: 160 mg (29%). MS *m/z*: 507 $(M + Na)^+$.

***N*-(3,4-Dihydro-6,7-dimethoxy-2,1-benzoxathiin-3-carbonyl)-L-phenylalaninol 1,1-Dioxide (14b) ($R^6 = R^7$ = OCH3; R^1 = Bn; Y = O).** From **6a** (61 mg, 0.21 mmol) and L-phenylalaninol (42 mg, 0.28 mmol), the title compound (64 mg, 72%) was obtained as a mixture of diastereomers. MS *m/z:* 422 $(M + H)^+$, 444 $(M + H)^+$.

***N*-(3,4-Dihydro-6,7-dimethoxy-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninol 1,1-Dioxide (14c) ($R^6 = R^7 = OCH_3$; R^1 = Bn; Y = NH).** From **10c** (100 mg, 0.35 mmol), the crude title compound (176 mg) was obtained as a mixture of diastereomers that were separated by flash chromatography on silica gel (EtOAc:hexanes, 1:1 to 3:1). Isomer a: 40 mg (27%). MS *m/z:* 421 $(M + H)^+$. Isomer b: 54 mg (37%). MS *m/z:* 421 $(M + H)^+$. Anal. ($C_{20}H_{24}N_2O_6S \cdot 0.5H_2O$) C, H, N, S.

***N*-(3,4-Dihydro-6,7-dimethoxy-2-methyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninol 1,1-Dioxide (14d) ($R^6 = R^7 = OCH_3$; R^1 = Bn; Y = NCH_3).** From **11d** (250 mg, 0.83 mmol), the crude title compound (343 mg) was obtained as a mixture of diastereomers that were separated by flash chromatography on silica gel (EtOAc:hexanes, 1:3 to 1:1). Isomer a: 123 mg (34%). MS *m/z*: 435 $(M + H)^+$. Isomer b: 118 mg (33%). MS *m/z*: 435 $(M + H)^+$.

***N*-(2-Benzyl-3,4-dihydro-6,7-dimethoxy-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninol 1,1-Dioxide (14e) ($R^6 = R^7 = OCH_3$; R^1 = Bn; Y = NBn).** From **11e** (155 mg, 0.41 mmol), the crude title compound (220 mg) was obtained as a mixture of diastereomers, partial separation being achieved by flash chromatography on silica gel (ether to 10% ethyl acetate/ether). Isomer a: 27 mg (13%). MS *m/z*: 511 $(M + H)^+$, 533 $(M + Na)^+$. Isomer b: 30 mg (14%). MS *m/z*: 511 $(M + H)^+$, 533 $(M + Na)^+$. Intermediate fractions gave an additional 105 mg (50%) of the diastereomeric mixture.

***N*-(3,4-Dihydro-2-methyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninol 1,1-Dioxide (14f) (R^6 = H; R^7 = H; R^1 = Bn; Y = NCH_3).** From **11f** (200 mg, 0.83), the crude title compound was obtained as a mixture of diastereomers that were separated by preparative thin-layer chromatography on silica gel using ethyl acetate as eluent. Isomer a (R_f 0.6): 120 mg (39%). NMR ($CDCl_3$, δ): 0.95 (3H, t). MS *m/z*: 375 $(M + H)^+$. Isomer b (R_f 0.7): 81 mg (26%). NMR ($CDCl_3$, δ): 0.77 (3H, t). MS *m/z*: 375 $(M + H)^+$.

***N*-(3,4-Dihydro-2-methyl-6-fluoro-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninol 1,1-Dioxide (14g) (R^6 = F; R^7 = H; R^1 = Bn; Y = NCH_3).** From **11g** (200 mg, 0.83), the crude title compound was obtained as a mixture of diastereomers. Attempted separation of these isomers by preparative TLC on silica gel (10% methanol/CH_2Cl_2) gave only one characterizable isomer of R_f 0.7; 78 mg (26%). MS *m/z*: 393 $(M + H)^+$.

***N*-(3,4-Dihydro-6,7-dichloro-2-methyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninol 1,1-Dioxide (14h) ($R^6 = R^7 = Cl$; $R^1 = Bn$; $Y = NCH_3$).** From **11h** (200 mg, 0.65 mmol), the crude title compound was obtained as a mixture of diastereomers that were separated by flash chromatography on silica gel using ethyl acetate as eluent. Isomer a: 60 mg (21%). MS *m/z*: 465, 467, 469 $(M + H)^+$, Cl_2 isotope pattern. Isomer b: 100 mg (35%). MS *m/z*: 465, 467, 469 $(M + H)^+$, Cl_2 isotope pattern.

***N*-(3,4-Dihydro-6-chloro-2-isobutyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninol 1,1-Dioxide (14i) (R^6 = Cl; $R^7 = H$; $R^1 = Bn$; $Y = N$-i-Bu).** From **11i** (146 mg, 0.46 mmol), the crude title compound was obtained as a mixture of diastereomers that were separated by preparative TLC on silica gel using 50% ethyl acetate/hexanes as eluent. Isomer a (R_f = 0.5): 76 mg (37%). MS *m/z*: 450, 452 $(M + H)^+$, Cl_2 isotope pattern. Isomer b (R_f 0.6): 81 mg (39%). MS *m/z*: 450, 452 $(M + H)^+$, Cl_2 isotope pattern.

***N*-(6-Chloro-3,4-dihydro-2-methyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninol 1,1-Dioxide (14j) (R^6 = Cl; $R^7 = H$; $R^1 = Bn$; $Y = NCH_3$).** From **11j** (420 mg, 1.52 mmol), the crude product (690 mg) was obtained as a mixture of diastereomers. Separation was achieved by flash chromatography on silica gel (30% ethyl acetate/hexanes to 50% ethyl acetate/hexanes) to give two isomers of the title compound. Isomer a: 78 mg (13%). MS *m/z*: 409, 411 $(M + H)^+$, 431, 433 $(M + Na)^+$. Isomer b: 71 mg (11%). MS *m/z*: 409, 411 $(M + H)^+$, 431, 433 $(M + Na)^+$.

***N*-(3,4-Dihydro-6,7-ethylenedioxy-2-methyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninol 1,1-Dioxide (14l) ($R^6 + R^7 = OCH_2CH_2O$; $R_1 = Bn$; $Y = NCH_3$).** From **11l** (404 mg, 1.35 mmol), the title compound (475 mg, 81%) was obtained as a mixture of diastereomers following purification on silica gel (30% ethyl acetate/hexanes). This product was used in the subsequent step without further purification. MS *m/z*: 433 $(M + H)^+$, 455 $(M + Na)^+$.

***N*-(3,4-Dihydro-6,7-ethylenedioxy-2-ethyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninol 1,1-Dioxide (14m) ($R^6 + R^7 = OCH_2CH_2O$; $R_1 = Bn$; $Y = NEt$).** From **11m** (134 mg, 0.43 mmol), the crude product (203 mg) was obtained as a mixture of diastereomers. Separation by flash chromatography on silica gel (50% ethyl acetate/hexanes) gave two isomers of the title compound. Isomer a (R_f 0.3): 75 mg (39%). MS *m/z*: 447 $(M + H)^+$, 469 $(M + Na)^+$. Isomer b (R_f 0.4): 82 mg (43%). MS *m/z*: 447 $(M + H)^+$, 469 $(M + Na)^+$.

***N*-(3,4-Dihydro-6,7-ethylenedioxy-2-isopropyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninol 1,1-Dioxide (14n) ($R^6 + R^7 = OCH_2CH_2O$; $R^1 = Bn$; $Y = N$-i-Pr).** From **11n** (120 mg, 0.37), the crude title compound (183 mg) was obtained. Attempted separation of diastereomers on silica gel (either flash chromatography or preparative TLC using 3% $MeOH/CH_2Cl_2$) was unsuccessful, giving 85 mg of the diastereomeric mixture. MS *m/z*: 461 $(M + H)^+$.

***N*$_\alpha$-(3,4-Dihydro-6,7-ethylenedioxy-2-methyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-*N*$_\epsilon$-(benzenesulfonyl)lysinol 1,1-Dioxide (14p) ($R^6 + R^7 = OCH_2CH_2O$; $R^1 = (CH_2)_4NHSO_2Ph$; $Y = NEt$).** From **11l** (70 mg, 0.23 mmol) and L-*N*$_\epsilon$-(benzenesulfonyl)lysinol trifluoroacetic acid salt (117 mg, 0.30 mmol), the crude product (144 mg) was obtained as a mixture of diastereomers. Separation was effected by preparative TLC on silica gel (5% $MeOH/CH_2Cl_2$). Isomer a: 31 mg (25%). MS *m/z:* 554 $(M + H)^+$. Isomer b: 31 mg (25%). MS *m/z:* 554 $(M + H)^+$.

***N*-(3,4-Dihydro-6-(4-morpholino)-2-methyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninol 1,1-Dioxide (14k) (R^6 = Morpholino; $R^1 = Bn$; $Y = NCH_3$).** From **11k** (200 mg, 0.61 mmol), the crude product (357 mg) was obtained as a mixture of diastereomers that were separated by flash chromatography on silica gel (75% ethyl acetate/hexanes). Isomer a: 116 mg (41%). MS *m/z*: 460 $(M + H)^+$; Isomer b: 113 mg (40%). MS *m/z*: 460 $(M + H)^+$.

General Procedure H: Acetal Hydrolysis. *N*-(3,4-Dihydro-6,7-dimethoxy-2,1-benzoxathiin-3-carbonyl)-L-leucinal 1,1-Dioxide (15a) ($R^6 = R^7 = OCH_3$; R^1 = i-Bu; $Y = O$). A solution of **13a** (16 mg, 0.035 mmol) in a mixture of acetone (0.5 mL) and water (0.75 mL) was treated with *p*-TsOH·H_2O (7 mg, 0.037 mmol). After being stirred overnight at 20 °C, the mixture was brought to reflux for 1 h, cooled to 20 °C, and extracted into ethyl acetate. The organic phase was washed with saturated aqueous sodium bicarbonate, water, and brine; dried ($MgSO_4$); filtered; and concentrated to afford 10 mg (77%) of **15a** as a mixture of diastereomers. When an oil was obtained, it was triturated with ether or hexanes in order to provide a solid. NMR ($CDCl_3$, δ): 1.00 (6H, m), 1.6−1.8 (3H, m), 3.2−3.5 (4H, m), 3.92 (6H, s), 4.61 (1H, m), 5.44 (1H, dd), 6.72 (1H, s), 7.24 (1H, m), 9.56 (0.5H, s), 9.58 (0.5H, s). MS *m/z*: 386 $(M + H)^+$, 408 $(M + Na)^+$. Anal. ($C_{17}H_{23}NO_7S·0.4H_2O$) C, H, N.

General Procedure I: Dess−Martin Oxidation. *N*-(3,4-Dihydro-6,7-dimethoxy-2,1-benzoxathiin-3-carbonyl)-L-phenylalaninal 1,1-Dioxide (15b) ($R^6 = R^7 = OCH_3$; R^1 = Bn; $Y = O$). A solution of **14b** (30 mg, 0.071 mmol) in dichloromethane (10 mL) chilled in an ice−water bath was treated with 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one (Dess−Martin periodinane, 60 mg, 0.14 mmol). After 1 h, TLC analysis indicated complete consumption of starting material. The mixture was stirred for 5 min with 10% aqueous sodium thiosulfate solution and poured into a separatory funnel. The organic phase was washed once more with 10% sodium thiosulfate followed by saturated aqueous sodium bicarbonate (2×), water, and brine; dried ($MgSO_4$); filtered; and concentrated to afford 30 mg (99%) of the title compound as an off-white amorphous solid. When an oil was obtained, it was triturated with ether or hexanes in order to provide a solid. (Chromatography on silica was avoided because of its tendency to epimerize peptide aldehydes.) NMR ($CDCl_3$, δ): 3.1−3.5 (4H, m), 3.92 (6H, s), 4.79 (1H, m), 5.40 (1H, dd), 6.70 (1H, s), 7.25 (6H, m), 9.61 (0.5H, s), 9.65 (0.5H, s). MS *m/z*: 420 $(M + H)^+$. Anal. ($C_{20}H_{21}NO_7S·1.3H_2O$) C, H, N.

***N*-(3,4-Dihydro-6,7-dimethoxy-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninal 1,1-Dioxide (15c) ($R^6 = R^7 = OCH_3$; $R^1 = Bn$; $Y = NH$), Isomer 1.** From **14c** (35 mg, 0.083 mmol), the title compound (32 mg, 91%) was obtained as a pale yellow solid. NMR ($CDCl_3$, δ): 2.8−3.4 (4H, m), 3.5 (6H, br. s), 4.04 (1Hm), 4.95 (1H, dd), 6.85 (1H, s), 7.25 (6H, m). MS *m/z*: 417 $(M - H)^-$.

***N*-(3,4-Dihydro-6,7-dimethoxy-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninal 1,1-Dioxide (15c) ($R^6 = R^7 = OCH_3$; $R^1 = Bn$; $Y = NH$), Isomer 2.** From **14c** (20 mg, 0.048 mmol), the title compound (18 mg, 90%) was obtained as a pale yellow solid. NMR ($CDCl_3$, δ): 2.8−3.4 (4H, m), 3.89 (6H, s), 4.04 (1Hm), 4.91 (1H, dd), 6.63 (1H, s), 7.25 (6H, m). MS *m/z*: 417 $(M - H)^-$.

***N*-(3,4-Dihydro-6,7-dimethoxy-2-methyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninal 1,1-Dioxide (15d) ($R_6 = R_7 = OCH_3$; $R_1 = Bn$; $Y = NCH_3$), Isomer 1.** From **14d** (50 mg, 0.12 mmol), the title compound (47 mg, 94%) was obtained as a white solid. NMR ($CDCl_3$, δ): 2.49 (3H, s), 3.20 (4H, m), 3.91 (6H, s), 4.25 (1H, t), 4.77 (1H, dd), 6.75 (1H, s), 7.25 (6H, m), 9.67 (1H, s). MS *m/z*: 433 $(M + H)^+$, 455 $(M + Na)^+$. FAB−HRMS (*m/z*): $(M + H)^+$ calcd for $C_{21}H_{25}N_2O_6S$, 443.1433; found, 433.1409.

***N*-(3,4-Dihydro-6,7-dimethoxy-2-methyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninal 1,1-Dioxide (15d) ($R^6 = R^7 = OCH_3$; $R^1 = Bn$; $Y = NCH_3$), Isomer 2.** From **14d** (50 mg, 0.12 mmol), the title compound (48 mg, 96%) was obtained as a white solid. NMR ($CDCl_3$, δ): 2.62 (3H, s), 3.20 (4H, m), 3.91 (6H, s), 4.35 (1H, dd), 4.79 (1H, dd), 6.75 (1H, s), 7.25 (6H, m), 9.65 (1H, s). MS *m/z*: 433 $(M + H)^+$, 455 $(M + Na)^+$. Anal. ($C_{21}H_{24}N_2O_6S·1.0H_2O$) C, H, N.

***N*-(2-Benzyl-3,4-dihydro-6,7-dimethoxy-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninal 1,1-Dioxide (15e) ($R^6 = R^7 = OCH_3$; $R^1 = Bn$; $Y = NBn$), Isomer 1.** From **14e** (28 mg, 0.06 mmol), the title compound (20 mg, 71%) was obtained. NMR ($CDCl_3$, δ): 3.00 (1H, dd), 3.09 1H, dd), 3.95 (3H, s), 3.97 (3H, s), 4.30−4.70 (4H, m), 6.8−7.4 (12H, m), 8.98 (1H, s). MS *m/z*: 509 $(M + H)^+$, 531 $(M + Na)^+$. FAB−HRMS (*m/z*): $(M + H)^+$ calcd for $C_{27}H_{29}N_2O_6S$, 509.1746; found, 509.1750.

***N*-(2-Benzyl-3,4-dihydro-6,7-dimethoxy-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninal 1,1-Dioxide (15e) ($R^6 = R^7 = OCH_3$; R^1 = Bn; Y = NBn), Isomer 2.** From **14e** (25 mg, 0.05 mmol), the title compound (23 mg, 82%) was obtained. NMR ($CDCl_3$, δ): 2.88 (1H, dd), 3.02 1H, dd), 3.25 (2H, m), 3.95 (3H, s), 3.97 (3H, s), 4.35 (4H, m), 6.8−7.4 (12H, m), 9.39 (1H, s). MS *m*/*z*: 509 $(M + H)^+$, 531 $(M + Na)^+$. FAB−HRMS (*m*/*z*): $(M + H)^+$ calcd for $C_{27}H_{29}N_2O_6S$, 509.1746; found, 509.1744.

***N*-(3,4-Dihydro-2-methyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninal 1,1-Dioxide (15f) (R^6 = H; R^7 = H; R^1 = Bn; Y = NCH_3), Isomer 1.** From **14f** (107 mg, 0.29 mmol), the title compound (84 mg, 79%) was obtained. NMR (DMSO-d_6, δ): 2.35 (3H, s), 2.8−3.4 (4H, m), 4.55 (2H, m), 7.3−7.8 (8H, m), 8.70 (1H, d), 9.58 (1H, s). MS *m*/*z*: 373 $(M + H)^+$. Anal. ($C_{19}H_{20}N_2O_4S \cdot 1.1H_2O$) C, H, N.

***N*-(3,4-Dihydro-2-methyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninal 1,1-Dioxide (15f) (R^6 = H; R^7 = H; R^1 = Bn; Y = NCH_3), Isomer 2.** From **14f** (76 mg, 0.20 mmol), the title compound (64 mg, 84%) was obtained. NMR (DMSO-d_6, δ): 2.60 (3H, s), 2.9−3.3 (4H, m), 4.49 (1H, m), 4.59 (1H, dd), 7.3−7.8 (8H, m), 8.73 (1H, d), 9.58 (1H, s). MS *m*/*z*: 373 $(M + H)^+$. Anal. ($C_{19}H_{20}N_2O_4S \cdot 1.0H_2O$) C, H, N.

***N*-(3,4-Dihydro-2-methyl-6-fluoro-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninal 1,1-Dioxide (15g) (R^6 = F; R^7 = H; R^1 = Bn; Y = NCH_3).** From **14g** (41 mg, 0.10 mmol), the title compound (33 mg, 83%) was obtained as a white solid. (DMSO-d_6, δ): 2.4−3.4 (7H, m), 4.55 (2H, m), 7.2−7.8 (7H, m), 8.75 (1H, d), 9.58 (1H, s). MS *m*/*z*: 391 $(M + H)^+$. FAB−HRMS (*m*/*z*) $(M + H)^+$ calcd for $C_{19}H_{19}N_2O_4SF$, 391.1128; found, 391.1140.

***N*-(3,4-Dihydro-6,7-dichloro-2-methyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninal 1,1-Dioxide (15h) (R^6 = R^7 = Cl; R^1 = Bn; Y = NCH_3), Isomer 1.** From **14h** (50 mg, 0.11 mmol), the title compound (45 mg, 90%) was obtained. NMR ($CDCl_3$, δ): 2.55 (3H, S), 3.0−3.4 (4H, m), 4.11 (1H, m), 4.78 (1H, m), 7.1−7.4 (5H, m), 7.46 (1H, s), 7.89 (1H, s), 9.68 (1H, s). MS *m*/*z:* 441, 443, 445 $(M + H)^+$, Cl_2 isotope pattern. Anal. ($C_{19}H_{20}N_2O_4SCl_2 \cdot 0.8H_2O$) C, H, N.

***N*-(3,4-Dihydro-6,7-dichloro-2-methyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninal 1,1-Dioxide (15h) (R^6 = R^7 = Cl; R^1 = Bn; Y = NCH_3), Isomer 2.** From **14h** (32 mg, 0.07 mmol), the title compound (27 mg, 84%) was obtained. NMR ($CDCl_3$, δ): 2.63 (3H, s), 3.0−3.4 (4H, m), 4.18 (1H, dd), 4.76 (1H, dd), 7.1−7.4 (5H, m), 7.46 (1H, s), 7.89 (1H, s), 9.66 (1H, s). MS *m*/*z*: 441, 443, 445 $(M + H)^+$, Cl_2 isotope pattern. Anal. ($C_{19}H_{20}N_2O_4SCl_2 \cdot 0.8H_2O$) C, H, N.

***N*-(3,4-Dihydro-6-chloro-2-isobutyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninal 1,1-Dioxide (15i) (R^6 = Cl; R^7 = H; R^1 = Bn; Y = N-i-Bu), Isomer 1.** From **14i** (41 mg, 0.09 mmol), the title compound (36 mg, 88%) was obtained. NMR ($CDCl_3$, δ): 0.72 (3H, d), 0.80 (3H, d), 2.29 (2H, m), 3.0−3.4 (4H, m), 3.77 (1H, t), 4.77 (1H, m), 7.1−7.4 (7H, m), 7.73 (1H, d), 9.64 (1H, s). MS *m*/*z*: 449, 451 $(M + H)^+$, Cl isotope pattern. Anal. ($C_{22}H_{25}N_2O_4SCl \cdot 0.5H_2O$) C, H, N.

***N*-(3,4-Dihydro-6-chloro-2-isobutyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninal 1,1-Dioxide (15i) (R^6 = Cl; R^7 = H; R^1 = Bn; Y = N-i-Bu), Isomer 2.** From **14i** (41 mg, 0.09 mmol), the title compound (37 mg, 90%) was obtained. NMR ($CDCl_3$, δ): 0.65 (6H, m), 2.29 (2H, m), 2.9−3.4 (4H, m), 3.79 (1H, t), 4.65 (1H, dd), 7.1−7.4 (7H, m), 7.73 (1H, d), 9.63 (1H, s). MS *m*/*z*: 449, 451 $(M + H)^+$, Cl isotope pattern. Anal. ($C_{22}H_{25}N_2O_4SCl \cdot 0.85CH_2Cl_2$) C, H; N, calcd 5.32; found 4.83.

***N*-(6-Chloro-3,4-dihydro-2-methyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninal 1,1-Dioxide (15j) (R^6 = Cl; R^7 = H; R^1 = Bn; Y = NCH_3), Isomer 1.** From **14j** (25 mg, 0.06 mmol), the title compound (19 mg, 76%) was obtained as an off-white solid. NMR ($CDCl_3$, δ): 2.61 (3H, s), 2.9−3.5 (4H, m), 4.10 (1H, dd), 4.18 (1H, m), 4.75 (1H, dd), 7.2−7.5 (7H, m), 7.75 (1H, d), 9.65 (1H, s). MS *m*/*z*: 405, 407 $(M + H)^+$. Anal. ($C_{19}H_{19}N_2O_4SCl \cdot 0.8H_2O$) C, H, N.

***N*-(6-Chloro-3,4-dihydro-2-methyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninal 1,1-Dioxide (15j) (R^6 = Cl; R^7 = H; R^1 = Bn; Y = NCH_3), Isomer 2.** From **14j** (25 mg, 0.06 mmol), the title compound (21 mg, 84%) was obtained as an off-white solid. NMR ($CDCl_3$, δ): 2.61 (3H, s), 2.9−3.5 (4H, m), 4.10 (1H, dd), 4.18 (1H, m), 4.75 (1H, dd), 7.2−7.5 (7H, m), 7.75 (1H, d), 9.65 (1H, s). MS *m*/*z*: 405, 407 $(M + H)^+$. Anal. ($C_{19}H_{19}N_2O_4SCl \cdot 0.8H_2O \cdot 0.25CH_2Cl_2$) C, H, N.

***N*-(3,4-Dihydro-6-(4-morpholino)-2-methyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninal 1,1-Dioxide (15k) (R^6 = Morpholino; R^1 = Bn; Y = NCH_3), Isomer 1.** From **14k** (102 mg, 0.22 mmol), the title compound (91 mg, 89%) was obtained. NMR ($CDCl_3$, δ): 2.52 (3H, s), 3.0−3.3 (8H, m), 3.86 (4H, m), 4.05 (1H, t), 4.73 (1H, m), 6.75, (1H, s), 6.86 (1H, d), 7.25 (5H, m), 7.67 (1H, d), 9.66 (1H, s). MS *m*/*z*: 458 $(M + H)^+$. Anal. ($C_{23}H_{27}N_3O_5S \cdot 0.25CH_2Cl_2$) C, H; N, calcd 8.78; found 8.16.

***N*-(3,4-Dihydro-6-(4-morpholino)-2-methyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninal 1,1-Dioxide (15k) (R^6 = Morpholino; R^1 = Bn; Y = NCH_3), Isomer 2.** From **14k** (63 mg, 0.14 mmol), the title compound (56 mg, 89%) was obtained. NMR ($CDCl_3$, δ): 2.58 (3H, s), 3.0−3.3 (8H, m), 3.84 (4H, m), 4.12 (1H, dd), 4.71 (1H, dd), 6.72, (1H, s), 6.83 (1H, d), 7.25 (5H, m), 7.66 (1H, d), 9.63 (1H, s). MS *m*/*z*: 458 $(M + H)^+$. Anal. ($C_{23}H_{27}N_3O_5S \cdot 0.35CH_2Cl_2$) C, H; N, calcd 8.62; found 7.86.

***N*-(3,4-Dihydro-6,7-ethylenedioxy-2-methyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninal 1,1-Dioxide (15l) ($R^6 + R^7 = OCH_2CH_2O$; R^1 = Bn; Y = NCH_3).** From **13l** (100 mg, 0.23 mmol), the title compound (67 mg, 67%) was obtained as a buff-white solid. NMR (DMSO-d_6, δ): 2.35 (1.5H, s), 2.55 (1.5H, s), 2.8−3.4 (4H, m), 4.31 (4H, br. s), 4.50 (2H, m), 6.97 (1H, s), 7.15 (1H, s), 7.25 (5H, m), 8.69 (1H, dd), 9.57 (1H, s). MS *m*/*z*: 431 $(M + H)^+$, 453 $(M + Na)^+$. Anal. ($C_{21}H_{22}N_2O_6S \cdot 0.75H_2O$) C, H, N.

***N*-(3,4-Dihydro-6,7-ethylenedioxy-2-ethyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninal 1,1-Dioxide (15m) ($R^6 + R^7 = OCH_2CH_2O$; R^1 = Bn; Y = NEt), Isomer 1.** From **14m** (30 mg, 0.07 mmol, R_f 0.3 isomer), the title compound (25 mg, 83%) was obtained as a white amorphous solid. NMR ($CDCl_3$, δ): 0.92 (3H, t), 2.86 (2H, dt), 3.0−3.3 (4H, m), 3.74 (1H, dd), 4.28 (4H, s), 4.73 (1H, dd), 6.80 (1H, s), 7.24 (6H, m), 9.64 (1H, s). MS *m*/*z*: 445 $(M + H)^+$, 467 $(M + Na)^+$. Anal. ($C_{22}H_{24}N_2O_6S$) C, H, N.

***N*-(3,4-Dihydro-6,7-ethylenedioxy-2-ethyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninal 1,1-Dioxide (15m) ($R^6 + R^7 = OCH_2CH_2O$; R^1 = Bn; Y = NEt), Isomer 2.** From **14m** (30 mg, 0.07 mmol, R_f 0.4 isomer), the title compound (27 mg, 90%) was obtained as a white amorphous solid. NMR ($CDCl_3$, δ): 0.78 (3H, t), 2.82 (2H, dt), 3.0−3.3 (4H, m), 3.80 (1H, dd), 4.27 (4H, s), 4.62 (1H, dd), 6.81 (1H, s), 7.25 (6H, m), 9.61 (1H, s). MS *m*/*z*: 445 $(M + H)^+$, 467 $(M + Na)^+$. Anal. ($C_{22}H_{24}N_2O_6S \cdot 0.2CH_2Cl_2$) C, H, N.

***N*-(3,4-Dihydro-6,7-ethylenedioxy-2-isopropyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninal 1,1-Dioxide (15n) ($R^6 + R^7 = OCH_2CH_2O$; R^1 = Bn; Y = N-i-Pr).** From **14n** (78 mg, 0.17 mmol), the title compound (63 mg, 81%) was obtained as a white solid. NMR (DMSO-d_6, δ): 0.42 (3H, m), 0.85 (1.5H, d), 0.92 (1.5H, d), 2.8−3.3 (3H, m), 3.95 (1H, m), 4.25 (4H, br. s), 4.46 (1H, m), 7.0−7.3 (7H, m), 8.22 (1H, d), 9.46 (0.5H, s), 9.48 (0.5H, s). MS *m*/*z*: 459 $(M + H)^+$. Anal. ($C_{23}H_{26}N_2O_6S \cdot 1.0H_2O$) C, H, N.

***N*-(3,4-Dihydro-6,7-ethylenedioxy-2-ethyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-leucinal 1,1-Dioxide (15o) ($R^6 + R^7 = OCH_2CH_2O$; R^1 = i-Bu; Y = NEt), Isomer 1.** From **13o** (155 mg, 0.32 mmol), the title compound (118 mg, 89%) was obtained as a white solid. NMR ($CDCl_3$, δ): 0.95 (t, J = 7 Hz, 6H), 1.07 (t, J = 7 Hz, 3H), 1.20 (m, 1H), 1.73 (m, 2H), 2.99 (m, 1H), 3.16−3.45 (m, 3H), 3.83 (m, 1H), 4.29 (br, 4H), 4.57 (m, 1H), 6.83 (s, 1H), 7.25 (br, 1H), 7.34 (s, 1H), 9.57 (s, 1H). MS *m*/*z*: 411 $(M + H)^+$. FAB−HRMS (*m*/*z*): $(M + H)^+$ calcd for $C_{19}H_{26}N_2O_6S$, 411.1590; found, 411.1595.

***N*-(3,4-Dihydro-6,7-ethylenedioxy-2-ethyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-leucinal 1,1-Dioxide (15o) ($R^6 + R^7 = OCH_2CH_2O$; R^1 = i-Bu; Y = NEt), Isomer 2.** From **13o** (158 mg, 0.32 mmol), the title compound (119 mg, 89%) was obtained as a white solid. NMR ($CDCl_3$, δ): 0.96 (t, J = 7 Hz,

6H), 1.07 (t, J = 7 Hz, 3H), 1.22 (m, 1H), 1.74 (m, 2H), 2.95 (m, 1H), 3.25−3.35 (m, 3H), 3.95 (m, 1H), 4.29 (br, 4H), 4.46 (m, 1H), 6.83 (s, 1H), 7.25 (br, 1H), 7.34 (s, 1H), 9.55 (s, 1H). MS m/z: 411 $(M + H)^+$.

N_α-(3,4-Dihydro-6,7-ethylenedioxy-2-methyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-N_ϵ-(benzenesulfonyl)lysinal 1,1-Dioxide (15p) ($R^6 + R^7 = OCH_2CH_2O$; $R^1 = (CH_2)_4NHSO_2Ph$; Y = NEt), Isomer 1. From **14p** (30 mg, 0.05 mmol), the title compound (27 mg, 90%) was obtained as a white solid. NMR ($CDCl_3$, δ): 1.56 (6H, m), 2.76 (3H, s), 2.94 (2H, m), 3.1−3.4 (2H, m), 3.90 (1H, dd), 4.29 (4H, br. s), 4.53 (1H, m), 4.70 (1H, m), 6.86 (1H, s), 7.3−7.6 (5H, m), 7.82 (1H, d), 9.56 (1H, s). MS m/z: 552 $(M + H)^+$. Anal. ($C_{24}H_{29}N_3O_8S_2 \cdot 1.5H_2O$) C, H, N.

N_α-(3,4-Dihydro-6,7-ethylenedioxy-2-methyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-N_ϵ-(benzenesulfonyl)lysinal 1,1-Dioxide (15p) ($R^6 + R^7 = OCH_2CH_2O$; $R^1 = (CH_2)_4NHSO_2Ph$; Y = NEt), Isomer 2. From **14p** (30 mg, 0.05 mmol), the title compound (28 mg, 93%) was obtained as a white solid. NMR ($CDCl_3$, δ): 1.56 (6H, m), 2.76 (3H, s), 2.96 (2H, m), 3.19 (2H, m), 3.90 (1H, dd), 4.29 (4H, br. s), 4.3−4.6 (2H, m), 6.83 (1H, s), 7.3−7.6 (5H, m), 7.85 (1H, d), 9.56 (1H, s). MS m/z: 552 $(M + H)^+$. Anal. ($C_{24}H_{29}N_3O_8S_2 \cdot 0.65CH_2Cl_2$) C, H; N: calcd 6.92; found 6.19.

3-(3,4-Dihydroxyphenyl)-L-alanine Methyl Ester Hydrochloride (17). Thionyl chloride (6.57 mL, 90 mmol) was added dropwise to a solution of L-DOPA (**16**) (1.97 g, 10 mmol) in MeOH (100 mL) at 0 °C. After 18 h at 20 °C, the solvent was evaporated, and the oily product was treated with toluene (3 × 15 mL) and evaporated. The yield of white solid was 3.26 g (100%). NMR (DMSO-d_6, δ): 2.90 (m, 2H), 3.38 (bs, 2H), 3.61 (s, 3H), 4.08 (m, 1H), 6.40 (d, 1H, J = 7 Hz), 6.59 (s, 1H), 6.65-(d, 2H, J = 7 Hz). 8.59 (bs, 1H), 8.90 (d, 1H, J = 10 Hz). MS m/z: 212 $(M + H)^+$.

***N*-(Benzyloxycarbonyl)-3-(3,4-dihydroxyphenyl)-L-alanine Methyl Ester (18).** A suspension of **17** (4.94 g, 20 mmol) and *N*-methylmorpholine (4.4 mL, 2.0 equiv) in 8 mL of THF and 1 mL of water was stirred at 20 °C as benzyloxycarbonyloxysuccinimide (4.98 g, 20 mmol) in 8 mL of 1,4-dioxane was added dropwise. The reaction mixture was stirred overnight. The solvent was evaporated, and the residue was diluted with ethyl acetate (100 mL). The ethyl acetate solution was washed with water (20 mL), 5% $NaHCO_3$ (20 mL), 3% citric acid (20 mL), and brine (20 mL) and dried over $MgSO_4$. Filtration and concentration afforded 5.36 g (78%) of a white solid. NMR ($CDCl_3$, δ): 2.99 (m, 2H), 3.65 (s, 3H), 4.59 (m, 1H), 5.04 (s, 2H), 5.39 (m, 1H), 6.38 (bs, 2H), 6.42 (d, 1H, J = 7 Hz), 6.60 (s, 1H), 6.67 (d, 1H, J = 7 Hz), 7.30 (m, 5H). MS m/z: 346 $(M + H)^+$.

***N*-(Benzyloxycarbonyl)-3-(3,4-ethylenedioxyphenyl)-L-alanine Methyl Ester (19).** A suspension of **18** (13.40 g, 38.8 mmol) and K_2CO_3 (53.66 g, 388 mmol) in acetone (200 mL) was refluxed under N_2 for 30 min. Dibromoethane (13.37 mL, 77.6 mmol) was added in one portion. The suspension was refluxed for 40 h, the solid was filtered, and the filtrate was evaporated. The residue after evaporation was diluted with 150 mL of water and extracted with CH_2Cl_2 (3 × 70 mL). The CH_2Cl_2 extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was washed with small amount of ether to give 12.26 g (85%) of white solid. NMR ($CDCl_3$, δ): 3.01 (d, 2H, J = 5.2 Hz), 3.73 (s, 3H), 4.22 (s, 4H), 6.52 (d, 1H, J = 7 Hz), 6.60 (s, 1H), 6.75 (d, 1H, J = 7 Hz), 7.34 (m, 5H). MS m/z: 372 $(M + H)^+$. Anal. ($C_{20}H_{21}NO_6 \cdot 0.2H_2O$) C, H, N.

Methyl 3,4-Dihydro-6,7-ethylenedioxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-Dioxide (20). A solution of **19** (14.82 g, 40 mmol) in dry $CHCl_3$ (150 mL) was mechanically stirred at 0 °C as chlorosulfonic acid (13.32 mL, 5.0 equiv) in $CHCl_3$ (100 mL) was added dropwise over ∼1 h. The solution turned yellow, and then a thick oily suspension appeared. After addition, the reaction mixture was stirred at 20 °C for 3 h. The mixture was cooled to ∼5 °C, and a solution of Et_3N (43 mL, 10 eq) and DMAP (733 mg, 0.3 eq) in $CHCl_3$ (50 mL) was added. After ∼14 h at 20 °C and 3 h reflux, the mixture was poured into ice−water (500 mL) and separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with water, 3% HCl, 5% $NaHCO_3$, and brine and dried. The crude product was dissolved in CH_2Cl_2 and filtered through a short silica column (EtOAc hexanes, 80:20) to remove remaining Et_3N−HCl. Evaporation of the solvent afforded 3.0 g (25%) of a white solid. NMR ($CDCl_3$, δ): 3.20 (ABq, 2H, J = 5.1 Hz, 16 Hz), 3.82 (s, 3H), 4.33 (s, 4H), 4.60 (m, 1H), 4.99 (d, 1H, J = 8 Hz), 6.77 (s, 1H), 7.39 (s, 1H). MS m/z: 300 $(M + H)^+$. Anal. ($C_{12}H_{13}NO_6S$) C, H; N calcd 4.68; found 5.10.

Methyl 3,4-Dihydro-6,7-ethylenedioxy-2-ethyl-2*H*-1,2-benzothiazine-3-carboxylate 1,1-Dioxide (21). A solution of **20** (317 mg, 1.06 mmol) and K_2CO_3 (513 mg, 3.5 eq) in 2.0 mL of DMF was stirred under N_2 as EtI (0.339 mL, 4.0 equiv) was added. After 14 h at 20 °C, the mixture was diluted with CH_2Cl_2 (20 mL). The solid was filtered and washed with CH_2Cl_2. The filtrates were washed with water, 3% citric acid, 5% of $NaHCO_3$, and brine and dried. Evaporation of the solvent afforded 313 mg (90% yield) of a pure white solid. NMR ($CDCl_3$, δ): 1.09 (t, 3H, J = 7.1 Hz), 3.01−3.4 (m, 6H), 3.79 (s, 3H), 4.25 (s, 4H), 4.15 (1H, dd, J = 6 Hz, 11 Hz), 6.74 (s, 1H), 7.28 (s, 1H). MS m/z: 328 $(M + H)^+$. Anal. ($C_{14}H_{17}NO_6S$) C, H, N.

Methyl 6,7-Dichloro-2-methyl-2*H*-1,2-benzothiazine-3-carboxylate 1,1-Dioxide (22a) (R^4 = H; R^6 = R^7 = Cl; Y = NCH_3; R = CH_3). To a solution **12h** (256 mg, 0.79 mmol) in CCl_4−CH_2Cl_2 (25 mL−5 mL) was added NBS (155 mg, 0.87 mmol) and dibenzoylperoxide (38 mg, 0.16 mmol). The mixture was refluxed in the dark for 1 h, at which time TLC analysis showed complete consumption of starting material. After being cooled to 20 °C, dichloromethane was added, and the mixture was washed with 10% sodium thiosulfate, water, and brine; dried over anhydrous magnesium sulfate; filtered; and concentrated to give 250 mg of the title compound, subsequently used without further purification. NMR ($CDCl_3$, δ): 3.18 (s, 3H), 3.87 (s, 3H), 7.43 (s, 1H), 7.59 (s, 1H), 7.87 (s, 1H).

Methyl 6,7-Ethylenedioxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylate 1,1-Dioxide (22b) ($R^6 + R^7 = OCH_2CH_2O$; R^4 = H; Y = NMe; R = CH_3). Treatment of **12l** (R = CH_3; 150 mg, 0.48 mmol) with NBS as above provided the title compound (100 mg, 66%) after flash chromatography on silica gel (30% ethyl acetate/hexanes). MS m/z: 312 $(M + H)^+$.

Methyl 2-Methyl-4-methoxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-Dioxide (22d) (R = Me; R^4 = OMe; R^6 = R^7 = H; Y = NMe). This compound was prepared according to Zinnes et al.[22] Thus, a solution of methyl 2-methyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide[21] (**23**, 500 mg, 1.86 mmol) in acetone (10 mL) was treated with anhydrous potassium carbonate (2.6 g, 18.6 mmol) and iodomethane (1.32 g, 9.29 mmol) and refluxed for 40 h. The mixture was filtered and concentrated, and the residue was partitioned between ethyl acetate and water. The organic phase was washed with saturated aqueous sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated to afford 285 mg (54%) of the title compound as a yellow viscous oil, used subsequently without further purification. NMR ($CDCl_3$, δ): 3.03 (s, 3H), 3.83 (s, 3H), 3.91 (s, 3H), 7.67−7.72 (m, 2H), 7.81−7.88 (m, 2H). MS m/z: 284 $(M + H)^+$.

6,7-Dichloro-2-methyl-2*H*-1,2-benzothiazine-3-carboxylic Acid 1,1-Dioxide (24a) (R^4 = H; R^6 = R^7 = Cl; Y = NCH_3). To a solution of **22a** (250 mg, 0.77 mmol) in MeOH (10 mL) and DMF (3 mL) was added 5 N NaOH (25 mL). The mixture was warmed to ∼50 °C while being stirred for 20 min, at which time TLC analysis showed complete consumption of starting material. The mixture was cooled to 20 °C, the MeOH was stripped on the rotary evaporator, and the residue was diluted with water (25 mL) and clarified by filtration. Addition of dilite HCl to pH 2 gave a precipitate that was collected by vacuum filtration, washed with water, and dried overnight to afford 128 mg (54% overall from 9a) of the title compound. MS m/z: 306, 308, 310 $(M - H)^-$, Cl_2 isotope pattern.

2-Methyl-4-methoxy-2*H*-1,2-benzothiazine-3-carboxylic Acid 1,1-Dioxide (24d) (R^4 = OMe; R^6 = R^7 = H; Y =

NMe). A solution of **22d** (159 mg, 0.56 mmol) in methanol (3 mL) was treated with 5 N NaOH (2 mL) and stirred at room temperature for 20 min, at which time TLC analysis showed complete consumption of starting material. The methanol was removed on the rotary evaporator, and the aqueous residue was adjusted to pH 3 with 4 N HCl. The precipitate so formed was collected by vacuum filtration, washed with water, and allowed to air-dry to constant weight to give 94 mg (62%) of the title compound as a white solid. MS *m*/*z*: 292 $(M + Na)^+$. Anal. ($C_{11}H_{11}NO_5S$) C, H, N, S.

***N*-(6,7-Dichloro-2-methyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninol 1,1-Dioxide (25a) (R^4 = H; R^6 = R^7 = Cl; R^1 = Bn; Y = NCH_3).** From **24a** (100 mg, 0.32 mmol), the title compound (137 mg) was obtained following flash chromatography on silica gel (50% ethyl acetate/hexanes). MS *m*/*z*: 441, 443, 445 $(M + H)^+$, Cl_2 isotope pattern.

***N*-(6,7-Ethylenedioxy-2-methyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninol 1,1-Dioxide (25b) (R^4 = H; $R^6 + R^7 = OCH_2CH_2O$; R^1 = Bn; Y = NCH_3).** From **24b** (80 mg, 0.27 mmol), the title compound (96 mg, 83%) was obtained following flash chromatography on silica gel (50% ethyl acetate/hexanes). MS *m*/*z*: 431 $(M + H)^+$.

***N*-(6,7-Ethylenedioxy-2-ethyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninol 1,1-Dioxide (25c) (R^4 = H; $R^6 + R^7 = OCH_2CH_2O$; R^1 = Bn; Y = NEt).** From **24c** (100 mg, 0.32 mmol), the title compound (136 mg, 95%) was obtained following flash chromatography on silica gel (50% ethyl acetate/hexanes). MS *m*/*z*: 445 $(M + H)^+$.

***N*-(2-Methyl-4-methoxy-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninol 1,1-Dioxide (25d) (R^4 = OMe; R^6 = R^7 = H; R^1 = Bn; Y = NMe).** From **24d** (22 mg, 0.08 mmol), the title compound (32 mg, 99%) was obtained. MS *m*/*z*: 403 $(M + H)^+$.

***N*-(6,7-Dichloro-2-methyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninal 1,1-Dioxide (26a) (R^4 = H; R^6 = R^7 = Cl; R^1 = Bn; Y = NCH_3).** From **25a** (50 mg, 0.11 mmol), the title compound (942 mg, 84%) was obtained as an off-white solid. NMR ($CDCl_3$, δ): 2.76 (3H, s), 3.3 (2H, m), 4.88 (1H, dd), 4.78 (1H, m), 7.00 (1H, d), 7.2−7.4 (5H, m), 7.63 (1H, s), 7.97 (1H, s), 9.71 (1H, s). MS *m*/*z*: 437, 439, 441 $(M - H)^-$; Cl_2 isotope pattern. Anal. ($C_{19}H_{16}N_2O_4SCl_2 \cdot 1.1C_6H_{14}$) C, H, N.

***N*-(6,7-Ethylenedioxy-2-methyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninal 1,1-Dioxide (26b) (R^4 = H; $R^6 + R^7 = OCH_2CH_2O$; R^1 = Bn; Y = NCH_3).** From **25b** (52 mg, 0.12 mmol), the title compound (41 mg, 79%) was obtained as a white solid. NMR ($CDCl_3$, δ): 2.66 (3H, s), 3.2−3.5 (4H, m), 4.32 (1H, dd), 4.82 (1H, m), 6.99 (1H, s), 7.03 (1H, d), 7.2−7.4 (5H, m), 7.39 (1H, s), 9.69 (1H, s). MS *m*/*z*: 429 $(M + H)^+$. FAB−HRMS (*m*/*z*): $(M + H)^+$ calcd for $C_{21}H_{20}N_2O_6S$, 429.1120; found, 429.1123.

***N*-(6,7-Ethylenedioxy-2-ethyl-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninal 1,1-Dioxide (26c) (R^4 = H; $R^6 + R^7 = OCH_2CH_2O$; R^1 = Bn; Y = NEt).** From **25c** (135 mg, 0.30 mmol), the title compound (109 mg, 81%) was obtained as a pale yellow solid. NMR ($CDCl_3$, δ): 0.67 (3H, t), 3.23 (2H, dq), 4.32 (1H, dd), 4.82 (1H, m), 6.96 (1H, d), 6.99 (1H, s), 7.2−7.4 (5H, m), 7.44 (1H, s), 9.69 (1H, s). MS *m*/*z*: 441 $(M - H)^-$. Anal. ($C_{22}H_{22}N_2O_6S \cdot 1.5CH_2Cl_2$) C, H, N.

***N*-(2-Methyl-4-methoxy-2*H*-1,2-benzothiazine-3-carbonyl)-L-phenylalaninal 1,1-Dioxide (26d) (R^4 = OMe; R^6 = R^7 = H; R^1 = Bn; Y = NMe).** From **25d** (32 mg, 0.08 mmol), the title compound (25 mg, 76%) was obtained. NMR ($CDCl_3$, δ): 2.97 (3H, s), 3.27 (2H, dq), 3.54 (3H, s), 4.93 (1H, dd), 7.2−7.4 (5H, m), 7.69 (2H, m), 7.85 (1H, d), 8.13 (1H, d), 9.73 (1H, s). MS *m*/*z*: 401 $(M + H)^+$. FAB−HRMS (*m*/*z*): $(M + H)^+$ calcd for $C_{20}H_{20}N_2O_5S$, 401.1171; found, 401.1167.

4,5-Ethylenedioxy-2-sulfanilamide Hydrochloride (27b) ($R^6 + R^7 = OCH_2CH_2O$). A mixture of 2*H*-1,2,4-benzothiadiazine-3(4*H*)-one 1,1-dioxide[23] (1.0 g, 3.0 mmol) in concentrated hydrochloric acid (40 mL) was stirred and refluxed for 18 h. The mixture was clarified by filtration and concentrated in vacuo. The residue was triturated with ether to give 1.0 g (96%) of the title compound as a tan solid. MS *m*/*z*: 231 $(M + H - HCl)^+$.

Ethyl 2-(Oxalylamino)benzenesulfonamide (28a) (R^6 = R^7 = H). To a solution of *o*-sulfanilamide (10.5 g, 61 mmol) in THF chilled in an ice−water bath was added triethylamine (8.9 mL, 64 mmol) followed by slow dropwise addition of ethyl oxalyl chloride (7.2 mL, 64 mmol) over 5−10 min. The mixture was allowed to slowly warm to 20 °C over 5 h. The precipitate was removed by filtration, and the concentrated filtrate was recrystallized (ethyl acetate) to give 9.0 g (54%) of the title compound. MS *m*/*z*: 273 $(M + H)^+$. Anal. ($C_{10}H_{12}N_2O_5S$) C, H, N, S.

Ethyl 2*H*-1,2,4-Benzothiadiazine-3-carboxylate 1,1-Dioxide (29a) (R^6 = R^7 = H). To a flask containing anhydrous ethanol (25 mL) was added NaH (60% suspension in mineral oil; 155 mg, 4.0 mmol). The mixture was stirred for 15 min, and **28a** (1.0 g, 3.7 mmol) was added in one portion. The mixture was stirred for 2 h, at which time TLC analysis showed complete consumption of starting material. Water (50 mL) was added, the pH was adjusted to 3−4 (4 N HCl), and the ethanol was removed on the rotary evaporator. The precipitate was collected by vacuum filtration, washed with water, and dried to constant weight to afford 0.66 g (71%) of the title compound. MS *m*/*z*: 273 $(M + H)^+$.

***N*-(2*H*-1,2,4-Benzothiadiazine-3-carbonyl)-L-phenylalaninal 1,1-Dioxide (32a) (R^6 = R^7 = H; R^1 = Bn; Y = NH).** This compound was prepared by hydrolysis of **29a** to **30a** followed by condensation with phenylalaninol and Dess−Martin oxidation of **31a** (43 mg, 0.12 mol) to give the title compound (14 mg, 33%). NMR ($CDCl_3$, δ): 3.20 (2H, m), 4.78 (1H, dd), 7.1−7.4 (6H, m), 7.49 (1H, t), 7.63 (1H, t), 7.96 1H, d), 8.09 (1H, d, D_2O exchange), 9.63 (1H, s), 9.87 (1H, s, D_2O exchange). MS *m*/*z*: 358 $(M + H)^+$. FAB−HRMS (*m*/*z*): $(M + H)^+$ calcd for $C_{17}H_{16}N_3O_2S$, 358.0862; found, 358.0853.

***N*-(2*H*-6,7-Ethylenedioxy-1,2,4-benzothiadiazine-3-carbonyl)-L-phenylalaninal 1,1-Dioxide (32b) ($R^6 + R^7 = OCH_2CH_2O$; R^1 = Bn; Y = NH).** This compound was prepared by hydrolysis of **29b** to **30b** followed by condensation with phenylalaninol and Dess−Martin oxidation. From **31b** (23 mg, 0.06 mol), the title compound (22 mg, 96%) was obtained. NMR ($CDCl_3$, δ): 3.19 (2H, m), 4.31 (4H, br. s), 4.78 (1H, m), 6.75 (1H, s), 7.2−7.4 (5H, m), 7.43 (1H, s), 8.17 (1H, br. d), 9.62 (1H, s), 9.72 (1H, br. s). MS *m*/*z*: 416 $(M + H)^+$. FAB−HRMS (*m*/*z*): $(M + H)^+$ calcd for $C_{19}H_{18}N_3O_6S$, 416.0916; found, 416.0902.

1-Oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (33) (R^6 = R^7 = H). A slurry of *N*-benzoyl-2-carboxyphenylalanine[15,16] (6.4 g, 20.4 mmol) in 6 N HCl (250 mL) was stirred while being refluxed for 18 h. The resulting homogeneous solution was cooled to 20 °C, giving a precipitate that was collected by vacuum filtration, washed with water, and dried to afford 3.05 (78%) of the title compound. NMR ($CDCl_3$−CD_3OD, δ): 3.01−3.31 (m, 2H), 4.29 (m, 1H), 7.18−7.41 (m, 3H), 7.94 (t, J = 8 Hz, 1H). MS *m*/*z*: 190 $(M - H)^-$.

2-Methyl-1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (34) (R^6 = R^7 = H). A solution of **33** (1.5 g, 7.8 mmol) in DMF (70 mL) was treated with iodomethane (9.7 mL, 157 mmol) and silver(I) oxide (5.5 g, 23.5 mmol) and stirred in the dark for 7 days. The mixture was filtered through Celite, the DMF was removed in vacuo, and the residue was partitioned between ethyl acetate and water. The organic phase was washed with 10% aqueous sodium thiosulfate, water, and brine; dried over anhydrous magnesium sulfate; filtered; and concentrated to give 0.96 g (56%) of methyl 2-methyl-1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate following flash chromatography on silica gel (30% ethyl acetate/hexanes). NMR ($CDCl_3$, δ): 3.17 (s, 3H), 3.23−3.50 (m, 2H), 3.61 (s, 3H), 4.21 (m, 1H), 7.12 (d, J = 7 Hz, 1H), 7.32−7.38 (m, 2H), 8.06 (d, J = 7 Hz, 1H). Hydrolysis of methyl 2-methyl-1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (0.95 g, 4.3 mmol) with NaOH gave the title compound (0.66 g, 74%). MS *m*/*z*: 204 $(M - H)^-$.

***N*-(1-Oxo-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-phenylalaninol (35a) (R^6 = R^7 = H; Y = NH).** From **33** (200 mg, 1.05 mmol), the crude product (353 mg) was purified by preparative TLC on silica gel (10% MeOH/CH_2Cl_2). This

purified 55:45 mixture of diastereomers (135 mg) was not readily separated by further chromatography. MS *m*/*z*: 325 $(M + H)^+$.

***N*-(1-Oxo-2-methyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-phenylalaninol (35b) ($R^6 = R^7 = H$; Y = NCH_3).** From **34** (250 mg, 1.22 mmol), the crude product (486 mg) was obtained as a mixture of diastereomers that was separated by preparative TLC on silica gel (5% MeOH/CH_2Cl_2). Isomer a: 114 mg (28%). MS *m*/*z*: 339 $(M + H)^+$. Isomer b: 107 mg (26%). MS *m*/*z*: 339 $(M + H)^+$.

***N*-(1-Oxo-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-phenylalaninal (36a) ($R^6 = R^7 = H$; Y = NH).** From **35a** (55:45 mixture of diastereomers, 28 mg, 0.09 mol), the title compound (13 mg, 46%) was obtained. NMR ($CDCl_3$, δ): 2.7−3.5 (4H, m), 3.1−3.5 (2H, m), 4.2−4.6 (2H, m), 6.8−7.6 (8H, m), 7.92 (1H, d). MS *m*/*z*: 323 $(M + H)^+$. FAB−HRMS (*m*/*z*): $(M + H)^+$ calcd for $C_{19}H_{19}N_2O_3$, 323.1396; found, 323.1380.

***N*-(1-Oxo-2-methyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-phenylalaninal (36b) ($R^6 = R^7 = H$; Y = NCH_3), Isomer 1.** From **35b** (39 mg, 0.12 mol), the title compound (30 mg, 77%) was obtained. NMR ($CDCl_3$, δ): 2.90 (2H, d), 3.16 (3H, s), 3.3−3.5 (2H, m), 4.12 (1H, d), 4.60 (1H, dd), 6.32 (1H, d), 6.67 (2H, m), 7.13 (4H, m), 7.36 (1H, t), 7.44 (1H, t), 8.03 (1H, d), 9.50 (1H, s). MS *m*/*z*: 337 $(M + H)^+$. Anal. ($C_{20}H_{20}N_2O_3 \cdot 1.5H_2O$) C, H, N.

***N*-(1-Oxo-2-methyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-phenylalaninal (36b) ($R^6 = R^7 = H$; Y = NCH_3), Isomer 2.** From **35b** (43 mg, 0.13 mol), the title compound (22 mg, 51%) was obtained. NMR ($CDCl_3$, δ): 2.90 (2H, m), 3.02 (3H, s), 3.1−3.5 (2H, m), 4.08 (1H, d), 4.43 (1H, dd), 6.30 (1H, d), 6.95 (2H, m), 7.1−7.5 (7H, m), 7.95 (1H, d), 9.27 (1H, s). MS *m*/*z*: 337 $(M + H)^+$. Anal. ($C_{20}H_{20}N_2O_3 \cdot 1.25H_2O$) C, H, N.

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Supporting Information Available: Elemental analyses and high-resolution mass spectra for selected intermediates and targets. This material is available free of charge via the Internet at http://pubs.acs.org.

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