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2*H*-Thieno[3,2-*e*]- and [2,3-*e*]-1,2-thiazine-6-sulfonamide 1,1-Dioxides as Ocular Hypotensive Agents: Synthesis, Carbonic Anhydrase Inhibition and Evaluation in the Rabbit

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Abstract—Novel non-chiral 2*H*-thieno[3,2-*e*]- and [2,3-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxides were synthesized for evaluation as potential candidates for the treatment of glaucoma. All of the compounds prepared were potent high affinity inhibitors of human carbonic anhydrase II, $K_i < 0.5$ nM. Additionally, inhibition of recombinant human carbonic anhydrase IV was determined for selected compounds; these were shown to be moderate to potent inhibitors of this isozyme with IC_{50} values ranging from 4.25 to 73.6 nM. Of the compounds evaluated for their ability to lower intraocular pressure in naturally hypertensive Dutch-belted rabbits, **5a**, **17a3**, **17b1**, **17b2**, **17h2** and **17i1** showed significant efficacy (> 20% decrease) in this model following topical ocular administration.

Introduction

Elevated intraocular pressure (ocular hypertension) is believed to lead to damage and eventual death of nerve fibers within the optic nerve. The resulting progressive reduction of the field of vision ultimately leads to blindness. Current therapeutic intervention for glaucoma is primarily directed toward physiological mechanisms that lead to the reduction of intraocular pressure in an effort to prevent nerve fiber damage.[1] Carbonic anhydrase (CA) is intimately involved in the production of aqueous humor, and inhibitors of this enzyme are effective in lowering intraocular pressure by reducing the production of aqueous humor. Agents such as Diamox and Neptazane have been used systemically for the treatment of ocular hypertension for over 40 years.[2–4] Unfortunately, patient compliance for this therapy has generally been poor due to a variety of non-life threatening, but discomforting, systemic side effects resulting from the inhibition of extraocular enzyme.

Topical ocular administration of a carbonic anhydrase inhibitor has long been viewed as an attractive alternative to oral therapy because of the expectation that it would reduce the incidence and magnitude of side effects, and thereby improve patient compliance. This interest in the development of a topical ocular CA inhibitor has lead to the recent introduction of dorzolamide[5] (**A**), from the laboratories of Merck & Co., and brinzolamide[6] (**B**), from our own laboratories. These CA inhibitors are both topically effective for lowering intraocular pressure in glaucoma therapy. Both of these compounds display a pronounced stereoselectivity with regard to enzyme inhibition and subsequent in vivo efficacy. Dorzolamide, with two chiral centers (4*S*, 6*S*), is the one diastereomer that is therapeutically effective. Similarly, brinzolamide (4*R*) is the therapeutically effective enantiomer of this structure.

Because of the considerable disadvantages associated with the preparation of a single enantiomer, either by a stereoselective synthesis or resolution, it was of interest to identify non-chiral analogues of brinzolamide (**B**) that possessed the desired physicochemical profile and requisite biological activity. We had previously observed that 2-substituted 3,4-dihydro-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxides (such as **C**)

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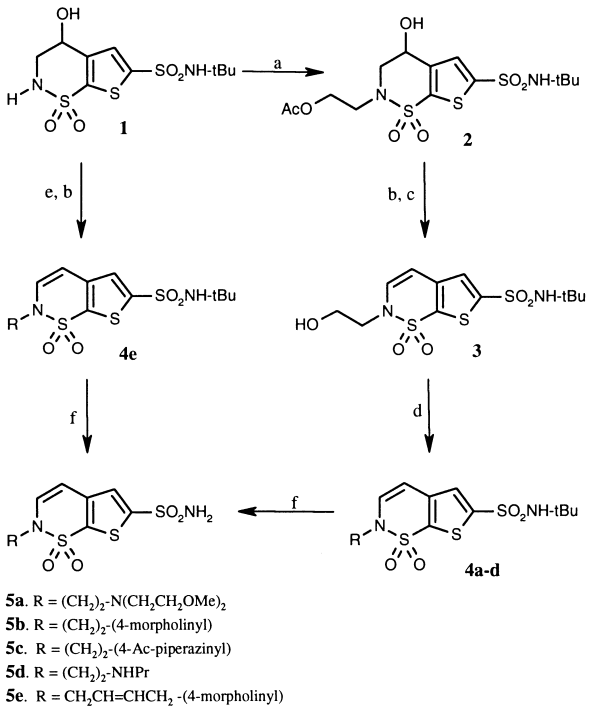
demonstrated potent inhibition of human CA-II ($K_i = 0.49 \pm 0.15$ nM, $IC_{50} = 2.51$ nM), indicating that a substituent at position four of this structure was not required to achieve the desired level of enzyme inhibition.[7] This observation suggested that appropriately substituted derivatives of the parent heterocyclic ring, devoid of any chiral centers, would provide an attractive series of molecules for evaluation as potential therapeutic agents (Fig. 1).

Though substitution at C4 proved to be quite beneficial in enhancing biological activity in the dihydrothienothiazine series of compounds, including brinzolamide, such substitution in the parent heterocycle did not appear desirable. The orientation of such a substituent would be anticipated to result in unfavorable interactions with the wall of the active site pocket. Substitution at ring positions two and three appeared more attractive, since such substituents would be oriented toward the top of the active site pocket and would provide an opportunity to form favorable binding interactions with residues on the surface of this portion of the enzyme. Therefore, the synthesis of a few examples of 2-aminoalkyl substituted analogues and an extended series of 2-substituted 3-(4-morpholinylmethyl)-2*H*-thieno[3,2-*e*]- and [2,3-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxides was pursued in order to evaluate these compounds as potential candidates for topical ocular glaucoma therapy.



Scheme 1. Reagents: (a) 2-Bromoethyl acetate, NaH/DMF; (b) i. Ms_2O and triethylamine or 2,6-lutidine/THF; ii. DBN/DMF; (c) NaOH/MeOH; (d) i. Ms_2O/THF; ii. alkylamine; (e) i. NaH, 1,4-dibromo-2-butene/DMF; ii. Morpholine; (f) TFA.

Chemistry

The sequence used for the preparation of 2-substituted 2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxides is shown in Scheme 1. Dehydration of **2**, prepared by alkylation of **1**[8] with 1-acetoxy-2-bromoethane, was accomplished by initial formation of the mesylate followed by elimination in the presence of DBU to give the thieno[3,2-*e*]-1,2-thiazine ring, and subsequent deprotection with aqueous base provided the intermediate alcohol, **3**. Conversion of **3** to the mesylate followed by treatment with the appropriate amine afforded compounds **4a**–**d**. Deprotection of the sulfonamide by treatment with trifluoroacetic acid provided **5a**–**d**. The preparation of **5e** followed a similar sequence, namely alkylation of **1** with 1,4-dibromo-2-butene followed by treatment with morpholine, and finally dehydration to give **4e**. Deprotection of **4e,** as before, gave **5e**.

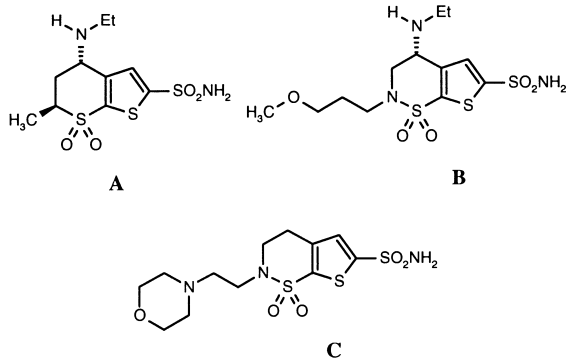
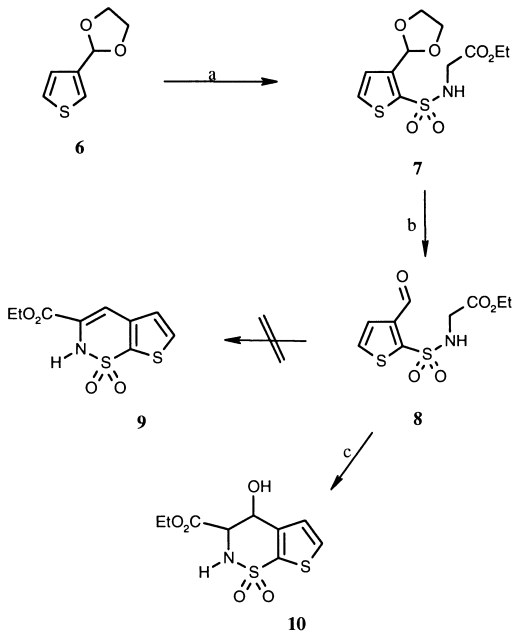


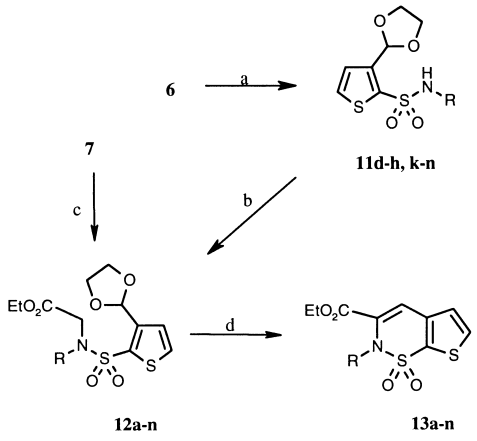
Figure 1.

The synthetic procedures used to prepare 2,3-disubstituted 2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxides are shown in Schemes 2–5. Compound **9** was initially envisioned as a desirable intermediate for the introduction of a variety of substituents on the nitrogen atom at position two. Lithiation of the ethylene glycol acetal of 3-thiophenecarboxaldehyde[9] (**6**) followed by reaction with sulfur dioxide and *N*-chlorosuccinimide provided the intermediate 2-sulfonyl chloride, which was reacted with glycine ethyl ester to give **7**. Acidic hydrolysis of **7** provided the aldehyde **8**, but all attempts to prepare **9** directly from **8** were unsuccessful. When **8** was treated with DBU, the cyclized product, **10**, was obtained in modest yield. Attempts to affect dehydration of **10** under a variety of conditions all resulted in the consumption of **10** while producing no identifiable products. Since **9** was unavailable as a strategic intermediate, it was necessary to introduce the desired nitrogen substituent prior to cyclization. This approach required the use of intermediate **12**, which could be prepared from either **7** or **11**, and which readily cyclized upon treatment with DBU to give the desired 2-substituted 3-carbethoxy intermediates **13** (Scheme 3). Incorporation of an aryl group at position two of **13** required the preparation of the appropriate intermediate **11**. Reduction of the ester group of **13** with DIBAL-H gave the primary alcohols, **14,** which were sulfamoylated (*n*-butyllithium, sulfur dioxide, hydroxylamine-*O*-sulfonic acid) to give sulfonamides **15** in good yield (Scheme 4).

Mesylation of the alcohol followed by reaction with the appropriate amine provided the desired compounds, **17**.

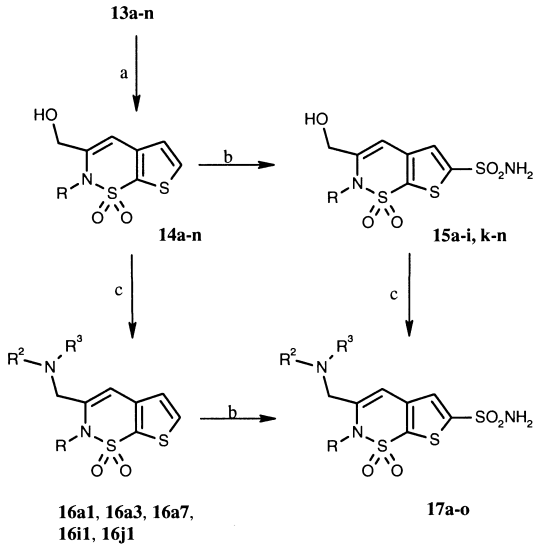


Scheme 2. Reagents: (a) i. *n*-BuLi/THF; ii. SO_2; iii. NCS/CH_2Cl_2; iv. glycine ethyl ester; (b) HCl/THF; (c) DBU, molecular seives/EtOAc.

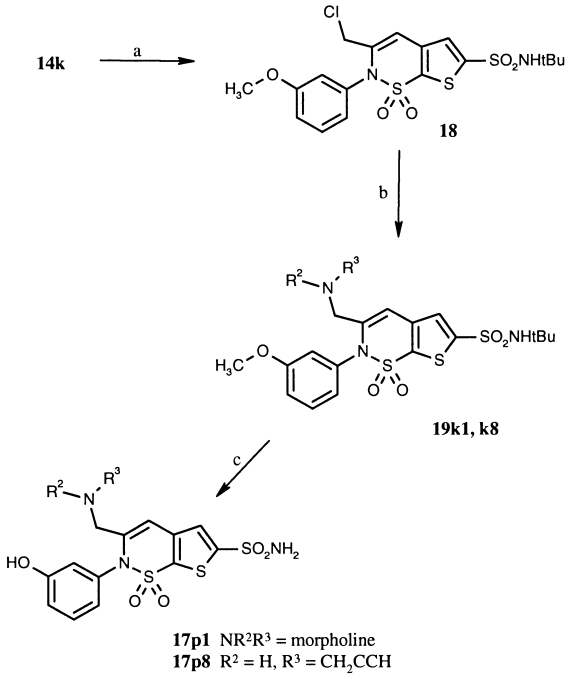


Scheme 3. Reagents: (a) i. *n*-BuLi/THF; ii. SO_2; iii. NCS/CH_2Cl_2; iv. primary or secondary amine; (b) i. Ethyl bromoacetate/DMF; ii. *t*-BuOK/DMF; (c) i. Alkyl halide/DMF; ii. *t*-BuOK/DMF; (d) i. *p*-TsOH/acetone; ii. DBN/EtOAc.

Alternately, by reversing the order of these last two steps, one could initially obtain the amine **16,** which gave **17** upon sulfamoylation. Of these two sequences, the former, proceeding through **15,** was the preferred route. A variation of this approach, involving the incorporation of a *t*-butyl protected sulfonamide group, was used for the preparation of the 2-(3-hydroxyphenyl) substituted compounds (Scheme 5). Reaction of **14k** by following a sequence utilizing *n*-butyllithium, sulfur dioxide, *N*-chlorosuccinimide, and *t*-butylamine readily provided the sulfonamide with concomitant chlorination of the alcohol to give **18**. Reaction of **18** with the desired amine gave **19k1** and **19k8**, and these, following treatment with boron tribromide, provided the desired phenolic compounds **17p1** and **17p8**, respectively (Table 1).



Scheme 4. Reagents: (a) DIBAL-H/THF; (b) i. *n*-BuLi/THF; ii. SO_2; iii. HOSA, NaOAc/H_2O; (c) i. Ms_2O/THF; ii. Alkyl amine/THF.



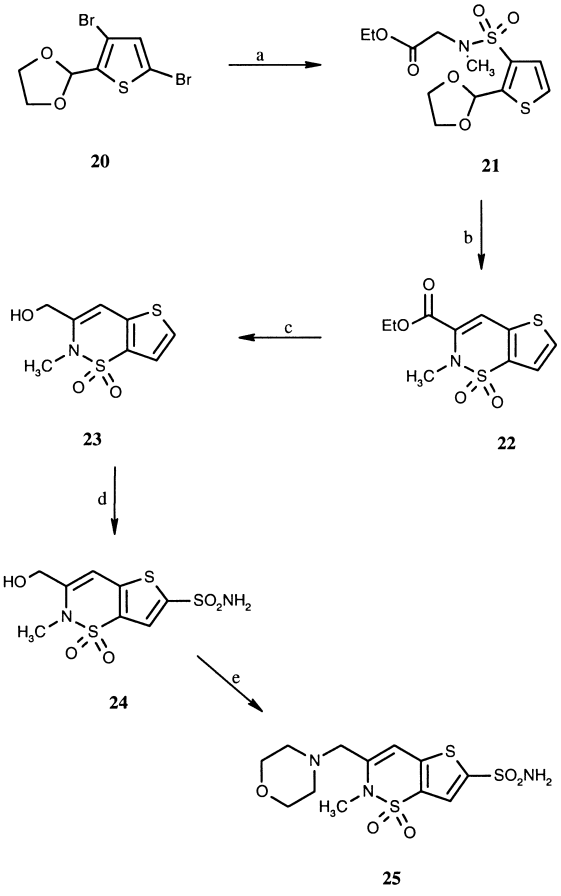
Scheme 5. Reagents: (a) i. *n*-BuLi/THF; ii. SO_2; iii. NCS/CH_2Cl_2; iv. *t*-$BuNH_2$; (b) i. *p*-TsCl/THF; ii. Amine/DMF; (c) Borontribromide/CH_2Cl_2.

The synthesis of a representative member of the isomeric thieno[2,3-*e*]-1,2-thiophene ring system was accomplished by a sequence similar to that used for the preparation of the thieno[3,2-*e*]-1,2-thiazine-6-sulfonamides (Scheme 6). The readily available ethylene glycol acetal of 3,5-dibromo-2-thiophenecarboxaldehyde[10] (**20**) served as starting material. Halogen to hydrogen exchange of the bromine atom at ring position five of compound **20** was accomplished by metallation with *n*-butyllithium followed by treatment with 1-propanol to give 3-bromo-2-thiophenecarboxaldehyde acetal. This compound was not isolated, but was sulfamoylated

directly to give **21** by using the procedure described for the preparation of **18**, though sarcosine ethyl ester was used as the amine. Cleavage of the acetal group of **21** with trifluoroacetic acid gave the aldehyde, which underwent facile cyclization upon treatment with DBN to give **22**. Compound **22** was converted to **25** through a series of steps similar to those described in Scheme 4.

Table 1. Substituent legend for compounds **11**–**17**

	R		NR^2R^3	
a	Me	**1**	4-morpholinyl	
b	Et	**2**	CH_2CH_2OMe	CH_2CH_2OMe
c	nPr	**3**	CH_2CH_2OMe	$CH_2CH_2CH_2OMe$
d	iPr	**4**	CH_2CH_2OH	CH_2CH_2OH
e	allyl	**5**	CH_2CH_2OH	H
f	CH_2cPr	**6**	CH_2CH_2OMe	Me
g	cHexyl	**7**	CH_2CH_2OMe	allyl
h	$(CH_2)_2OMe$	**8**	$CH_2C{\equiv}CH$	H
i	$(CH_2)_3OMe$	**9**	cPr	H
j	CH_2–C_6H_4–(4-OMe)	**10**	1-imidazoyl	
k	C_6H_4–(3-OMe)			
m	C_6H_3–(3,4-OMe)			
n	C_6H_4–4-(4-Morpholinyl)			
o	$(CH_2)_3OH$			
p	C_6H_4–(3-OH)			



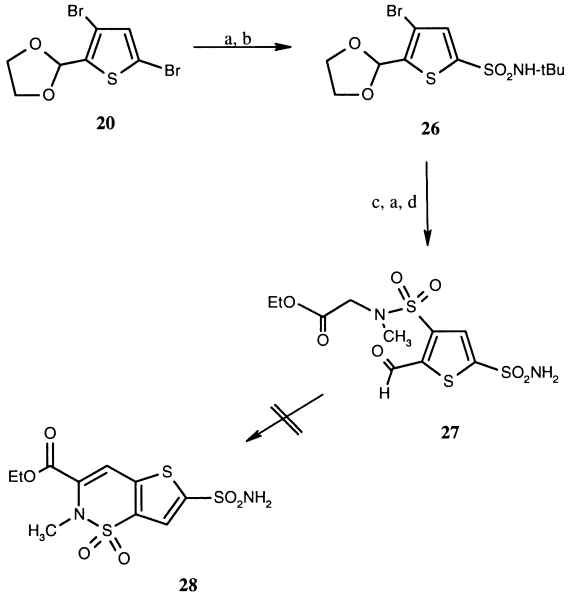
Scheme 6. Reagents: (a) i. *n*-BuLi, 1-propanol/Et_2O; ii. *n*-BuLi; iii. SO_2; iv. NCS/CH_2Cl_2; v. Sarcosine ethyl ester; (b) i. TFA/acetone; ii. DBN, molecular seives/EtOAc; (c) DIBAL-H/THF; (d) i. *n*-BuLi/THF; ii. SO_2; iii. HOSA, $NaOAc/H_2O$; (e) i. *p*-TsCl/THF; ii. Morpholine/THF.

It is informative to note that attempts to prepare the desirable synthetic intermediate **28** by cyclization of the thiophene-2,4-disulfonamide **27**, where the protected primary sulfonamide was introduced into the thiophene ring prior to ring closure, were unsuccessful (Scheme 7). Treatment of **20** with *n*-butyllithium followed by reaction with sulfur dioxide and then treatment with *N*-chlorosuccinimide resulted in exchange of the bromine at position five to give the intermediate sulfonyl chloride. This product was reacted with *t*-butylamine to give the protected sulfonamide **26**. The structure of **26** was confirmed by a subsequent halogen–proton exchange reaction; the coupling constants for the two thiophene protons in the product of this reaction were consistent for a 2,5-disubstituted thiophene. Treatment of **26** with a second metallation sequence (*n*-butyllithium/sulfur dioxide/*N*-chlorosuccinimide) resulted in exchange of the bromine at position three to give the sulfonyl chloride intermediate. Reaction of the sulfonyl chloride with sarcosine ethyl ester followed by hydrolysis of the acetal, which required prolonged treatment with trifluoroacetic acid and resulted in concomitant cleavage of the *t*-butyl group, provided **27**. All attempts to obtain the desired intermediate **28** by cyclization of **27** produced decomposition, most probably by way of a nucleophilic attack on the electron deficient thiophene ring.

Results and Discussion

Biological assays

The ability of the target compounds to inhibit human carbonic anhydrase II (hCA-II) was determined using a pH-stat assay similar to that previously described; this assay measures the ability of a compound to inhibit the carbonic anhydrase catalyzed hydration of carbon



Scheme 7. Reagents: (a) i. *n*-BuLi/THF; ii. SO_2; iii. NCS/CH_2Cl_2; (b) *t*-$BuNH_2$; (c) NaH/THF; (d) i. Sarcosine ethyl ester; ii. TFA.

dioxide (IC_{50}).[11,12] Inhibitor binding to hCA-II was determined using a fluorescence competition assay that monitors the decrease in fluorescence resulting from the displacement of dansylamide from the enzyme by an inhibitor (K_i).[12,13] The ability of compounds to lower intraocular pressure was evaluated by testing in a colony of naturally ocular hypertensive Dutch-belted rabbits.

As illustrated in Table 2, compounds **5**, **17** and **25** all showed high affinities for hCA-II and were all potent inhibitors of the enzyme, with inhibition constants in the low nanomolar range. This level of CA-II inhibition is well within the range required to achieve a decrease in intraocular pressure, provided, of course, that the physicochemical properties of a particular compound are satisfactory to permit access to the target tissue, the ciliary body. A series of specific, predictive criteria that a molecule must satisfy to demonstrate topical ocular efficacy in lowering intraocular pressure have been proposed.[14] These criteria were modified during the development of dorzolamide to include the requirement that the molecule possess an amphoteric character, e.g., that it has a weakly acidic primary sulfonamide and a weakly basic amine.[15] It has been suggested that this amphoteric property facilitates the sequestering of the compound in ocular tissues such as the stroma, which would provide a depot of the inhibitor from which to maintain the relatively high concentration of inhibitor required to achieve the level of enzyme inhibition necessary to reduce aqueous humor formation. Compounds **5a–c,e**, containing weakly basic alkylamines (pK_a 5.34–6.69) at ring position two (Table 2), were particularly potent inhibitors of hCA-II, while **5d**, which incorporates a significantly more basic amine (pK_a 8.27), was a weaker inhibitor with a lower affinity for the enzyme. The 4-morpholinyl-2-butenyl group introduced

Table 2. In vitro enzyme data and physicochemical data for compounds **5**, **17** and **25**

Compound	hCA-II		rhCA-IV	Solubility pH 5.0 (%)	*DC* pH 7.4	pK_a[c]
	IC_{50} (nM)[a]	K_i (nM)[b]	IC_{50} (nM)[a]			
5a	0.91	0.34 (0.03)	—	0.442	17.0	5.90; 8.45
5b	0.82	0.32 (0.08)	15.2 (0.80)	0.201	4.97	5.34; 8.27
5c	0.96	0.25 (0.02)	—	0.067	1.91	5.49; 8.43
5d	2.25	0.52 (0.05)	73.6	2.52	2.3	8.27[d]
5e	—	0.24 (0.06)	—	—	6.09	6.69; 8.56
17a1	1.66	0.26 (0.03)	16.9 (1.3)	0.03	12	5.01; 8.34
17a3	—	0.08 (0.01)	—	1.24	52.6	6.13; 8.53
17a6	1.17	0.15 (0.04)	—	0.634	18.2	6.45; 8.34
17a7	1.11	0.10 (0.01)	16.9 (1.4)	0.028	172	5.95; 8.37
17b1	1.11	0.21 (0.03)	—	0.323	19.3	5.20; 8.49
17b2	1.04	0.21 (0.02)	—	0.451	53.5	5.46; 8.40
17b4	0.96	0.33 (0.06)	—	4.41 +	2.55	6.28; 8.39
17c1	1.24	0.27 (0.02)	—	0.007	55.9	5.26; 8.36
17c2	1.48	0.15 (0.01)	—	0.007	177	5.52; 8.61
17c8	1.52	0.10 (0.01)	—	0.024	42.5	5.68; 8.47
17d1	1.46	0.33 (0.03)	—	0.0076	61	5.33[e]
17d8	1.60	0.47 (0.10)	—	0.113	29.7	5.64; 8.46
17e1	0.99	0.16 (0.06)	23.3 (0.9)	0.041	42.5	5.09; 8.44
17f1	1.41	0.30 (0.08)	—	0.081	57	5.87; 8.23
17g1	0.79	0.31 (0.01)	49.5	0.002	322	5.64; 8.24
17h1	5.58	0.22 (0.02)	39.9	0.218	3.85	5.93; 8.17
17h2	4.41	0.21 (0.01)	—	2.54	13.5	5.53; 8.47
17i1	2.63	0.25 (0.02)	23.6	0.768	14.8	5.24; 8.43
17i9	3.12	0.26 (0.05)	—	3.61	19.8	6.36; 8.46
17i10	2.23	0.12 (0.01)	—	0.156	6.32	6.08; 8.37
17j1	2.01	0.11 (0.04)	5.45 (0.25)	0.0027	222	5.33, 8.49
17k1	1.27	0.15 (0.01)	7.41 (0.60)	0.013	148	5.30; 8.27
17k5	1.16	0.11 (0.01)	—	0.27	10.1	6.61; 8.32
17m1	1.05	0.08 (0.01)	10.1 (0.99)	0.055	40.1	5.24; 8.43
17n1	1.50	0.12 (0.01)	8.65 (0.35)	0.034	68.8	5.45; 8.22
17o1	1.62	0.20 (0.03)	—	0.40	3.16	5.39; 8.46
17p1	1.15	0.15 (0.05)	4.25 (0.37)	0.014	57.1	5.22, 8.51
17p8	0.60 (0.11)	0.16 (0.01)	6.25 (1.66)	—	39.1	5.71; 8.23
25	2.52	0.21 (0.01)	—	0.026	8.7	8.38[f]
Brinzolamide	3.19 (0.30)	0.13 (0.01)	44.9	0.4	6.56	5.9; 8.3
Dorzolamide	3.74 (0.02)	0.51 (0.09)	32.0 (0.7)	—	15.2	—
Acetazolamide	8.88	—	17.5	—	—	—
Methazolamide	12.5	—	205	—	—	—
Methylbenzolamide	3.90	—	5.6	—	—	—

[a]Single determinations except duplicates as noted with standard deviation.
[b]Mean of at least two determinations with standard deviation.
[c]Amine and sulfonamide values, respectively.
[d]Value includes both the amine and the sulfonamide ionization, 2 equivalents.
[e]Unable to obtain satisfactory inflection for sulfonamide p*K*.
[f]Unable to obtain satisfactory inflection for amine p*K*.

into compound **5e** provided a very potent inhibitor of hCA-II; the inhibition was sufficiently beyond the limits of the current assay that a reliable inhibition constant could not be determined for this compound.

Incorporation of the weakly basic 4-morpholinylmethyl group into position C3 and a variety of alkyl and aryl substituents at N2 provided compounds **17a1**–**17p1**, all of which displayed a high affinity (K_i) as well as good inhibition for hCA-II (Table 2). Branching at the α-carbon of an N2 alkyl substituent was observed to be detrimental to enzyme affinity as demonstrated by the reduction in affinity of **17d1** compared to that of compounds **17a**–**c1**. Interestingly, **17g1**, with a cyclohexyl substituent, showed very good inhibition of hCA-II. The ethers **17h1** and **17i1** showed a modest decrease in inhibition in spite of a high affinity for the enzyme. Incorporation of an aromatic moiety such as 4-methoxyphenylmethyl (**17j1**) or 3-methoxyphenyl (**17k1**) into the molecule at ring position two provided a modest improvement in inhibitor affinity for the enzyme, relative to aliphatic substituents. The high affinity observed for **17n1** suggests that a region of considerable bulk tolerance exists beyond the phenyl group. A comparison of the in vitro enzyme data for **17a1** and **25** reveals that the orientation of the sulfur atom in the thiophene ring relative to the thiazine ring has no apparent effect on enzyme binding or inhibition.

Since recent observations[15–18] suggest a significant role for CA isozyme IV in the control of intraocular pressure, representative examples of structures **5** and **17** were tested for their ability to inhibit isozyme IV. Recombinant human CA-IV (rhCA-IV), which lacks the trans-membrane glycosylphosphatidylinositol anchor portion of the native enzyme, has been shown to be functionally equivalent to CA-IV isolated from human lung.[19,20] The compounds that were evaluated against rhCA-IV were also shown to be moderate to potent inhibitors of this isoform, with IC_{50} values from 73.6 nM to 4.25 nM. A comparison of the inhibition constants of **5b** and **5d** suggests that, as with hCA-II, the presence of a charged species, such as a protonated amine, within the substituent on N2 is detrimental to rhCA-IV binding. Additionally, compounds **17h1** and **17i1**, bearing methoxyalkyl groups at N2, show relatively low inhibition, again suggesting, as with hCA-II, the detrimental nature of polar functionality in this region of the molecule. Interestingly, **17g1**, with an N2 cyclohexyl substituent, also displays a relatively low level of inhibition of rhCA-IV, in contrast to the very good inhibition of hCA-II. Incorporation of a phenyl substituent at N2 provided the most potent inhibitors of rhCA-IV. A comparison of **17k1** and **17p1** suggests that a hydroxyl group on the phenyl ring provides a modest binding advantage over the methoxy group, while the presence of a second methoxy group in the *para* position (**17m1**) does not appear to be detrimental to inhibition. The activity of **17n1** suggests that, as observed for hCA-II, significant bulk can be tolerated at the *para* position of the phenyl group while maintaining good inhibition of rhCA-IV. Additionally, the high level of enzyme inhibition provided by **17j1** implies that the phenyl group for this compound might assume a more desirable orientation than when directly attached to the nitrogen atom.

As observed with other sulfonamide inhibitors of CA-II, compounds **5** and **17** displayed a higher value for the inhibition constant (IC_{50}) for rhCA-IV than for hCA-II (2.7- to 33-fold higher). With the exception of the compounds bearing polar substituents or a cyclohexyl moiety as noted above, the potencies of the compounds evaluated were more comparable to acetazolamide ($IC_{50} = 17.5$ nM) than methazolamide ($IC_{50} = 206$ nM). Further, the potency of several of the compounds was comparable to that of methylbenzolamide[21] ($IC_{50} = 5.6$ nM), a compound which has been reported to have a higher affinity for bovine CA-IV than benzolamide.[22] In general, compounds **17** showed a greater inhibition of rhCA-IV than that observed for the 3,4-dihydro-2*H*-thieno[3,2-*e*]-1,2-thiazines, such as brinzolamide.[23] An X-ray crystallographic analysis of the enzyme–inhibitor complexes formed upon co-crystallization of **17k1** and **17p1** with hCA-II and murine CA-IV is in progress and will be reported in due course.[24]

In view of our concern regarding the effect that basicity might have on the in vivo availability of these compounds, it was of interest to evaluate compounds that incorporate a variety of other weakly basic amines into the molecule at position C3. These compounds were modestly stronger bases (p*K* 5.51 to 6.64) than the compounds bearing the 4-morpholinylmethyl group (p*K* 5.01 to 5.33). This modest increase in basicity was not detrimental for inhibitor binding to the enzyme, since all of these compounds were also potent high affinity inhibitors of hCA-II (Table 2). For example, modification of **17a1** by the incorporation of *N*-(2-methoxyethyl)-*N*-(3-methoxypropyl)amine, *N*-(2-methoxyethyl)methylamine, or *N*-(2-methoxyethyl)-*N*-allylamine (**17a3, a6, a7**) resulted in an increase in enzyme affinity and inhibition, particularly for **17a3** with an approximately 3-fold increase in affinity as the p*K* increased from 5.01 to 6.13. The inhibition constant of **17a3** appeared to be beyond the limits of the assay since a reliable value could not be obtained. Replacement of the 4-morpholinylmethyl group of **17b1** with bis(2-methoxyethyl)amine resulted in no change in the enzyme affinity or inhibition and only a minimal increase in the basicity of **17b2**; however, the distribution coefficient increased 3-fold. Incorporation of diethanolamine as the base resulted in a modest decrease in enzyme affinity; however, the basicity of **17b4** increased by one p*K* unit and the distribution coefficient decreased 20-fold relative to **17b2**, providing an increase of more than 10-fold in solubility. Inclusion of the heteroaromatic amine imidazole into **17i10** provided a 2-fold increase in affinity relative to **17i1** with a modest increase in inhibition.

Representative compounds were evaluated for their ability to lower intraocular pressure (IOP) in naturally hypertensive Dutch-belted rabbits. The response of a compound in this model is considered to be a rather good predictor of the IOP response of the same compound in primate models of glaucoma and in man. A

test compound that decreases the baseline intraocular pressure by at least 4 mmHg or a decrease of greater than 15% is considered to provide a favorable response. However, compounds which decrease intraocular pressure by more than 20% are of primary interest for subsequent evaluation in primate models of glaucoma.

In the present study, the maximum decrease in IOP was observed within the first 2 h after dosing each of the compounds (Table 3). All of the compounds were administered as suspensions with the exception of **17b4** and **17h2**, which were sufficiently soluble to provide solutions. It was previously observed that brinzolamide effectively lowered IOP in the rabbit and the monkey when topically administered as a suspension.[25] The 2-substituted compounds **5a** and **5b** both showed a favorable reduction of pressure in this model, 21.6 and 18.2%, respectively. Within the series of 2,3-disubstituted compounds that were evaluated, four compounds (**17a6**, **17a7**, **17m1**, **25**) provided a reduction in pressure that was in the 15–20% range, while five compounds (**17a3**, **17b1**, **17b2**, **17h2**, **17i1**) lowered pressure greater than 20%. Further, two compounds, **17a3** and **17b2**, provided an IOP reduction comparable to that of brinzolamide and dorzolamide in this model of ocular hypertension. The remainder of the compounds that were evaluated provided no significant reduction of intraocular pressure at the test dose.

Table 3. Reduction of IOP in naturally hypertensive Dutch-Belted rabbits

Compound[a]	Δ^{max} mm Hg[b]	Max IOP dec (%)
5a	−7.0 (0.47)	21.6
5b	−5.2 (0.70)	18.2
17a1	−3.8 (1.19)*	11
17a3	−10.4 (0.89)	36.1
17a6	−4.1 (0.61)	15.8
17a7	−4.9 (0.58)	19
17b1	−5.6 (0.77)	22.8
17b2	−9.6 (0.86)	32.5
17b4	−2.1 (0.36)	9.1
17d8	−2.5 (0.48)	9.1
17e1	−2.6 (0.37)	10.7
17f1	−2.9 (0.87)**	11
17g1	−2.6 (0.75)**	9.8
17h2	−4.9 (0.95)	20.2
17i1	−5.6 (0.61)	21.2
17j1	−3.5 (0.52)	12.6
17k1	−3.0 (0.50)	11.7
17m1	−4.1 (1.04)**	15.7
17o1	−3.5 (0.69)	13.7
25	−7.0 (0.56)	19.7
Brinzolamide	−9.7 (1.05)	30.2
Dorzolamide[c]	−7.2 (0.92)	29.6

[a]pH 5.0, 1 mg total dose.
[b]Mean (SEM). Significance of difference from control group $P < 0.001$, except $*P < 0.05$ and $**P < 0.01$.
[c]pH 7.4.

The compounds that provided a 15–20% reduction in IOP displayed a broad range in lipophilicity, with DC values ranging from 5 for **5b** (18% reduction) to 172 for **17a7** (19% reduction). However, those compounds that lowered pressure greater than 20% fell within a much narrower lipophilicity range, with DC values between 13.5 and 53.5, suggesting that this lower range is preferred for this class of compounds. Though all of the compounds (except **17h2**) that lowered pressure greater than 20% were dosed as suspensions, it is of interest to note that there is an overlap in solubility for the members of these two groups of active compounds. The more active compounds generally had the greater intrinsic solubility (Table 2). A comparison of **17b2** and **17b4** illustrates that high solubility alone does not correlate with efficacy, and further suggests a lower limit for lipophilicity within this class of inhibitors. The basicity of the amine did not appear to have a significant impact on in vivo efficacy in Dutch-belted rabbits, since there was essentially no difference in the pK range between the compounds that produced a 15–20% reduction and those that resulted in a >20% reduction (5.24 to 6.45 and 5.20 to 6.13, respectively). Furthermore, the inactive compounds had a similar basicity range, 5.01 to 6.28 (Table 3).

Conclusions

A facile approach to the synthesis of non-chiral 2- and 2,3-substituted 2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxides has been provided. These compounds were shown to be potent high affinity inhibitors of hCA-II ($K_i < 0.5$ nM) and moderate to potent inhibitors of rhCA-IV (73.6 to 4.25 nM). Selected compounds within these series were shown to lower IOP in naturally hypertensive Dutch-belted rabbits, demonstrating that non-chiral derivatives of brinzolamide are efficacious in lowering IOP in the rabbit when topically administered as suspensions. Compounds **5a**, **17a3**, **17b1**, **17b2**, **17h2**, and **17i1** were identified as candidates for subsequent evaluation in primate models of glaucoma.

Experimental

Melting points were determined in open capillaries using a Thomas-Hoover Uni-Melt Apparatus and are uncorrected. Organic extracts were dried over $MgSO_4$ (unless otherwise noted) which was removed by filtration and washed with the appropriate dry solvent. Chromatography refers to low pressure column chromatography conducted on 230–400 mesh silica gel from E. Merck. Evaporations were performed under reduced pressure on a rotary evaporator at 40 °C unless otherwise indicated. ^{1}H NMR spectra were determined at 200 MHz with a Varian Model VXR-200 spectrometer and ^{13}C NMR were determined at 50.3 MHz with the Varian instrument. Spectra were recorded in $CDCl_3$ or Me_2SO-d_6, and chemical shifts are reported in parts per million (δ) relative to tetramethylsilane as internal standard. Elemental analyses were performed by Atlantic Microlabs, Norcross, Georgia and are within ±0.4% of the theoretical values.

2-[2-(Acetoxy)ethyl]-*N*-(1,1-dimethylethyl)-4-hydroxy-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide (2). Sodium hydride (60% dispersion in mineral oil,

0.42 g, 10.6 mmol) was added to a solution of *N*-(1,1-dimethylethyl)-4-hydroxy-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide (**1**)[8] (3.00 g, 8.82 mmol) in anhydrous DMF (50 mL) which was under a nitrogen atmosphere and at ambient temperature. After stirring for 20 min the mixture was cooled to 0 °C and 2-bromoethyl acetate (2.21 g, 13.2 mmol, 1.46 mL) was added; stirring continued at this temperature for 2 h followed by stirring for 18 h at ambient temperature. The reaction mixture was added to 5% aqueous $NaHCO_3$ (100 mL) and this mixture was extracted with EtOAc (2×200 mL). The combined extracts were dried and evaporated to an oil which was purified by chromatography (EtOAc/hexane, 1:1) to give a foam (3.36, 89%): ^{1}H NMR (DMSO-d_6) δ 8.17 (s, 1H), 7.59 (s, 1H), 6.15 (br s, 1H), 4.82 (t, J = 6 Hz, 1H), 4.21 (t, J = 6 Hz, 2H), 3.99 (dd, J = 6 and 14 Hz, 1H), 3.80 (dd, J = 6 and 14 Hz, 1H), 3.59 (t, J = 6 Hz, 2H), 2.02 (s, 3H), 1.02 (s, 9H).

2-(2-Hydroxyethyl)-*N*-(1,1-dimethylethyl)-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide (3). To a solution of **2** (3.36 g, 7.89 mmol) and 2,6-lutidine (3.00 mL, 25.7 mmol) in anhydrous THF (30 mL) under nitrogen was added methanesulfonic anhydride (2.06 g, 11.8 mmol). This mixture was stirred for 30 min at ambient temperature followed by evaporation to a residue. Anhydrous DMF (50 mL) and DBU (1 mL) were added to the residue and this mixture was heated at 165 °C (bath temperature) for 20 min and evaporated to dryness. Methanol (50 mL) and 2 N NaOH (20 mL) were added to the residue and this mixture was stirred for 2 h at ambient temperature. Methanol was evaporated and the aqueous mixture was extracted with EtOAc (2×100 mL). The combined extracts were dried and evaporated to give the desired product as an oil (2.78 g, 96%): ^{1}H NMR (DMSO-d_6) δ 8.21 (s, 1H), 7.71 (s, 1H), 7.09 (d, J = 7.8 Hz, 1H), 6.44 (d, 1H, J = 7.8 Hz), 5.00 (t, 1H), 3.79 (t, J = 5.4 Hz, 2H), 3.60 (q, J = 5.4 Hz, 2H), 1.19 (s, 9H).

***N*-(1,1-Dimethylethyl)-2-[4-(4-morpholinyl)-2-butenyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide (4e).** Sodium hydride (60% dispersion in mineral oil, 0.113 g, 2.82 mmol) was added to a solution of **1** (0.80 g, 2.35 mmol) in anhydrous DMF (50 mL) under nitrogen. After 20 min, the reaction mixture was cooled (ice bath), 1,4-dibromo-2-butene (0.754 g, 3.53 mmol) was added and the mixture stirred for 2 h. Morpholine (5 mL) was added and the reaction mixture was stirred at ambient temperature for 18 h. DMF was evaporated under reduced pressure and the residue was mixed with 5% aqueous $NaHCO_3$ (100 mL) and extracted with EtOAc (2×100 mL). The combined extracts were dried and evaporated to a residue which was purified by chromatography (EtOAc) to give the desired product as a viscous oil (0.65 g, 58%): ^{1}H NMR (DMSO-d_6) δ 8.18 (s, 1H), 7.61 (s, 1H), 6.13 (d, J = 7.6 Hz, 1H), 5.71 (m, 1H), 4.86 (m, 1H), 3.91 (t, J = 6.4 Hz, 2H), 3.79 (m, 2H), 3.57 (t, J = 4.5 Hz, 4H), 2.94 (m, 2H), 2.31 (m, 4H), 1.21 (s, 9H). To a solution of this oil (0.64 g, 1.34 mmol) in anhydrous THF (30 mL) under nitrogen was added methanesulfonic anhydride (0.349 g, 2.00 mmol) and 2,6-lutidine (0.431 g, 4.02 mmol). After 30 min, additional methanesulfonic anhydride (0.349 g, 2.00 mmol) and 2,6-lutidine (0.431 g, 4.02 mmol) were added and the reaction mixture was stirred for 30 min. Evaporation of the solvent provided a residue which was dissolved in anhydrous DMF (50 mL) and DBN (1 mL) was added. This mixture was heated at reflux temperature for 1 h, cooled, poured into 5% aqueous $NaHCO_3$ (100 mL) and extracted with EtOAc (2×100 mL). The combined extracts were dried and evaporated to a residue which was purified by chromatography (5% MeOH/CH_2Cl_2) to give a viscous oil (0.35 g, 57%): ^{1}H NMR (DMSO-d_6) δ 8.22 (s, 1H), 7.73 (s, 1H), 7.05 (d, J = 7.7 Hz, 1H), 6.53 (d, J = 7.7 Hz, 1H), 5.66 (m, 2H), 4.36 (m, 2H), 3.52 (m, 4H), 2.89 (m, 2H), 2.27 (m, 4H), 1.19 (s, 9H).

2-[2-[Bis(2-methoxyethyl)amino]ethyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride (5a). To a solution of **3** (1.02 g, 2.79 mmol) and triethylamine (0.84 g, 8.36 mmol) in anhydrous THF (50 mL) under nitrogen was added methanesulfonic anhydride (0.80 g, 4.18 mmol). This mixture was stirred at ambient temperature for 30 min followed by evaporation to a residue which was dissolved in EtOAc (80 mL) and washed with 5% aqueous $NaHCO_3$ (50 mL). The organic phase was dried and evaporated to give a solid (1.06 g) which was dissolved in anhydrous DMF (50 mL) and bis(2-methoxyethyl)amine (5 mL) was added. This mixture was heated at reflux temperature for 1 h, cooled and poured into 5% aqueous $NaHCO_3$ (100 mL). The solution was extracted with EtOAc (2×100 mL) and the combined extracts were dried and evaporated to give a crude oil which was purified by chromatography (gradient, 50% to 100% EtOAc/hexane) to give **4a** as a viscous oil (0.89 g, 66%): ^{1}H NMR (DMSO-d_6) δ 8.22 (s, 1H), 7.70 (s, 1H), 7.12 (d, J = 7.8 Hz, 1H), 6.47 (d, J = 7.8 Hz, 1H), 3.78 (t, J = 5.5 Hz, 2H), 3.25 (t, J = 6.0 Hz, 4H), 3.14 (s, 6H), 2.71 (t, J = 5.5 Hz, 2H), 2.58 (t, J = 6.0 Hz, 4H), 1.19 (s, 9H). A solution of this oil in trifluoroacetic acid (8 mL) was stirred at ambient temperature for 18 h. Evaporation gave a residue which was mixed with 5% aqueous $NaHCO_3$ (50 mL) and extracted with EtOAc (2×80 mL). The combined extracts were dried and evaporated to a residue which was purified by chromatography (gradient, 3 to 5% MeOH/CH_2Cl_2) to give an oil (0.74 g) which was converted to the HCl salt by treatment with 2 N HCl in EtOH (0.63 g, 79%): mp 60–65 °C; ^{1}H NMR (DMSO-d_6) δ 10.90 (br s, 1H), 8.16 (s, 2H), 7.71 (s, 1H), 7.17 (d, J = 7.7 Hz, 1H), 6.60 (d, J = 6.9 Hz, 1H), 4.28 (br s, 2H), 3.69 (br s, 4H), 3.5–3.7 (6 H), 3.25 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 149.8, 141.6, 134.0, 133.9, 127.5, 126.3, 66.2, 66.1, 66.0, 58.2, 52.7. Anal. ($C_{14}H_{23}N_3O_6S_3$·HCl) C, H, N.

2-[2-(4-Morpholinyl)ethyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride (5b). Treatment of **3** in a manner similar to that described for the preparation of **5a**, but using morpholine, gave, after chromatography (gradient, 70% to 100% EtOAc in hexane), the free base (mp 135–137 °C) which was converted to the HCl salt (67%): mp 234–236 °C; ^{1}H NMR (DMSO-d_6) δ 8.15 (s, 2H), 7.71 (s, 1H), 7.18 (d, J = 7.8 Hz, 2H), 6.62 (d, J = 7.8 Hz, 2H), 4.25 (br s, 2H), 3.94 (br s, 2H),

3.71 (br s, 2H), 3.30 (m, 4H), 3.13 (br s, 2H); ^{13}C NMR (DMSO-d_6) δ 149.9, 141.6, 133.8, 127.5, 126.4, 103.6, 63.2, 54.1, 51.3; MS (EI) m/z 380 (M^+). Anal. ($C_{12}H_{17}N_3O_5S_3$·HCl) C, H, N.

2-[2-[4-Acetyl-(1-piperazinyl)]ethyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide (5c). Treatment of **3** in a manner similar to that described for the preparation of **5a**, but using 1-acetylpiperazine, gave, after chromatography (gradient, EtOAc to 10% EtOH/EtOAc), a solid which was recrystallized from MeOH/CH_2Cl_2 to give **5c** (52%): mp 180–183 °C; ^{1}H NMR (DMSO-d_6) δ 8.08 (s, 2H), 7.67 (d, J = 1.4 Hz, 1H), 7.11 (d, J = 7.6 Hz, 1H), 6.53 (d, J = 7.6 Hz, 1H), 3.86 (t, J = 5.8 Hz, 2H), 3.31 (4H, m), 2.55 (2 H), 2.32 (m, 4H), 1.94 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 168.1, 148.9, 141.2, 134.3, 127.5, 126.5, 103.1, 56.8, 52.8, 52.2, 45.6, 45.1, 21.1; IR (KBr) 3095, 2954, 1613, 1448, 1349, 1319, 1161. Anal. ($C_{14}H_{20}N_4O_5S_3$) C, H, N.

2-[2-(Propylamino)ethyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride (5d). Treatment of **3** in a manner similar to that described for the preparation of **5a**, but using propylamine, provided **5d** (50%): mp 208–210 °C; ^{1}H NMR (DMSO-d_6) δ 9.21 (br s, 2H), 8.16 (br s, 2H), 7.71 (s, 1H), 7.19 (d, J = 7.7 Hz, 1H), 6.58 (d, J = 7.8 Hz, 1H), 4.16 (t, J = 7.0 Hz, 2H), 3.19 (br s, 2H), 2.85 (br s, 2H), 1.60 (t, J = 8.0 Hz, 2H);^{13}C NMR (DMSO-d_6) δ 149.8, 141.6, 134.00, 127.5, 126.3, 103.1, 48.3, 45.6, 42.7, 18.9, 10.9. Anal. ($C_{11}H_{17}N_3O_4S_3$·HCl) C, H, N.

2-[4-(4-Morpholinyl)-2-butenyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride (5e). A solution of **4e** (0.35 g, 0.82 mmol) in trifluoroacetic acid (5 mL) was stirred at ambient temperature for 3 days and evaporated to dryness. The residue was combined with 5% aqueous $NaHCO_3$ (50 mL) and this mixture was extracted with EtOAc (2×80 mL). The combined extracts were dried and evaporated to a residue which was purified by chromatography (6% MeOH/CH_2Cl_2) to give a viscous oil (0.21 g, 68%). To a solution of this oil in MeOH (5 mL) was added a 2 N solution of HCl in EtOH (2 mL); this mixture was evaporated to give the hydrochloride salt as an amorphous solid (0.152 g, 50%): mp 108–112 °C; ^{1}H NMR (DMSO-d_6) δ 10.3 (br s, 1H), 8.15 (br s, 2H), 7.71 (s, 1H), 7.13 (d, J = 7.7 Hz, 1H), 6.57 (d, J = 7.7 Hz, 1H), 6.15–5.75 (m, 2H), 4.80 (d, J = 5.5 Hz, 2H), 4.05–3.60 (m, 4H), 3.34 (br s, 4H), 2.99 (br t, 2H). Anal. ($C_{12}H_{19}N_3O_5S_3$·HCl·0.5 H_2O) C, H, N.

***N*-[[3-(1,3-Dioxolan-2-yl)-2-thienyl]sulfonyl]-glycine ethyl ester (7).** To a solution of 3-thiophenecarboxaldehyde ethylene glycol acetal (**6**)[9] (10.0 g, 64.0 mmol) in THF (100 mL) at −70 °C and under nitrogen was added *n*-butyllithium (28.2 mL of a 2.5 M solution in hexane) and the mixture was maintained at this temperature for 50 min. Sulfur dioxide gas was passed over the reaction mixture (10 min) and stirring continued for 1 h at ambient temperature. Evaporation provided a residue which was dissolved in CH_2Cl_2 (150 mL) and cooled on an ice/MeOH bath. Following the addition of *N*-chlorosuccinimide (11.11 g, 83.0 mmol), this mixture was stirred for 18 h, gradually warming to ambient temperature. The reaction mixture was filtered through a filter aide that was rinsed with CH_2Cl_2 (150 mL). To the cooled (0 °C) filtrate was added 5% aqueous $NaHCO_3$ (200 mL) followed by the addition of glycine ethyl ester hydrochloride in two portions (26.8 g, 192 mmol). The mixture was stirred at ambient temperature for 3 h and the aqueous layer was separated and extracted with CH_2Cl_2 (2×100 mL). The combined extracts were washed with water (120 mL), dried and evaporated to a residue which was purified by chromatography (40% EtOAc in hexane) to give an oil (16.5 g, 61%): ^{1}H NMR (DMSO-d_6) δ 8.48 (br s, 1H), 7.82 (d, J = 4.9 Hz, 1H), 7.20 (d, J = 5.2 Hz, 1H), 6.18 (s, 1H), 4.10–3.90 (m, 4H), 4.01 (q, J = 7.2 Hz, 2H), 3.77 (s, 2H), 1.12 (t, J = 7.1 Hz, 3H). Anal. ($C_{11}H_{15}NO_6S_2$) C, H, N.

***N*-[(3-Formyl-2-thienyl)sulfonyl]-glycine ethyl ester (8).** To a solution of **7** (31.0 g, 97.0 mmol) in THF (100 mL) was added 3 N HCl and this mixture was stirred for 6 h at room temperature. Brine (100 mL) was added and the mixture was extracted with EtOAc (3×100 mL). The combined extracts were washed with brine (20 mL), dried and evaporated to give a colorless glass (22.0 g, 82%): ^{1}H NMR (DMSO-d_6) δ 10.33 (s, 1H), 9.01 (br s, 1H), 7.90 (d, J = 5.2 Hz, 1H), 7.53 (d, J = 5.2 Hz, 1H), 3.91 (s, 2H), 3.90 (q, J = 7.2 Hz, 2H), 1.07 (t, J = 7.2 Hz, 3H).

Ethyl 3,4-dihydro-4-hydroxy-2*H*-thieno[3,2-*e*]-1,2-thiazine-3-carboxylate 1,1-dioxide (10). To a solution of **8** (4.50 g, 16.2 mmol) in EtOAc (150 mL) was added DBU (1 mL) and molecular sieves (5 g). The mixture was heated at reflux temperature for 1 h, cooled to room temperature, and 1 N HCl (100 mL) was added. The organic layer was separated, dried, and evaporated to give a residue (3.10 g) which solidified from EtOAc/hexane to give recovered starting material (1.45 g); evaporation of the filtrate gave **10** (1.78 g, 40%) as a viscous oil: ^{1}H NMR (DMSO-d_6) δ 7.91 (d, J = 4.8 Hz, 1H), 7. 86 (brs, 1H), 7.19 (d, J = 5.0 Hz, 1H), 5.79 (d, J = 8.2 Hz, 1H), 4.88 (dd, 1H), 4.72 (dd, 1H), 4.20 (q, J = 7.1 Hz, 2H), 1.24 (t, J = 7.1 Hz, 3H).

3-(1,3-Dioxolan-2-yl)-*N*-(1-methylethyl)-2-thiophenesulfonamide (11d). Prepared by using the procedure described for the preparation of **7**, but isopropylamine (26.1 g, 441 mmol) and triethylamine (10 mL) were added to the intermediate sulfonyl chloride prepared from **6** (23.0 g, 147 mmol). Purification by chromatography (30% EtOAc in hexane) gave a colorless oil (25.3 g, 62%): ^{1}H NMR (DMSO-d_6) δ 7.88 (br s, 1H), 7.81 (d, J = 5.2 Hz, 1H), 7.20 (d, J = 5.2 Hz, 1H), 6.21 (s, 1H), 4.01 (m, 5H), 0.99 (d, J = 2.6 Hz, 6H).

Compounds **11e**–**h** and **11k**–**n** were prepared from **7** and the appropriate amine using a procedure similar to that described for the synthesis of **11d**.

3-(1,3-Dioxolan-2-yl)-*N*-(2-propenyl)-2-thiophenesulfonamide (11e). Allylamine; purified by chromatography (gradient, 10 to 40% EtOAc in hexane) to give an oil (12%): ^{1}H NMR (DMSO-d_6) δ 8.12 (br s, 1H), 7.84 (d,

$J = 5.2$ Hz, 1H), 7.22 (d, $J = 5.2$ Hz, 1H), 6.21 (s, 1H), 5.8 (m, 1H), 5.1 (m, 2H), 4.15–3.95 (m, 4H), 3.52 (m, 2H).

***N*-Cyclopropylmethyl-3-(1,3-dioxolan-2-yl)-2-thiophenesulfonamide (11f).** Cyclopropylmethylamine; purified by chromatography (gradient, hexane to 50% EtOAc in hexane) to give an oil (63%): ^{1}H NMR (DMSO-d_6) δ 8.01 (br s, 1H), 7.82 (d, $J = 5.2$ Hz, 1H), 7.20 (d, $J = 5.2$ Hz, 1H), 6.21 (s, 1H), 4.09 (m, 4H), 2.74 (d, $J = 6.9$ Hz, 2H), 0.82 (m, 1H), 0.39 (m, 2H), 0.10 (m, 2H).

3-(1,3-Dioxolan-2-yl)-*N*-cyclohexyl-2-thiophenesulfonamide (11g). Cyclohexylamine; purified by chromatography (25% EtOAc in hexane) to give an oil (72%): ^{1}H NMR (DMSO-d_6) δ 7.92 (s, 1H), 7.81 (d, $J = 5.0$ Hz, 1H), 7.20 (d, $J = 5.0$ Hz, 1H), 6.22 (s, 1H), 4.15–3.90 (m, 4H), 3.05 (m, 1H), 1.62 (m, 5H), 1.14 (m, 5H).

3-(1,3-Dioxolan-2-yl)-*N*-(2-methoxyethyl)-2-thiophenesulfonamide (11h). 2-Methoxyethylamine; purified by chromatography (50% EtOAc in hexane) to give an oil (79%): ^{1}H NMR ($CDCl_3$) δ 7.45 (d, $J = 4.9$ Hz, 1H), 7.26 (d, $J = 4.9$ Hz, 1H), 6.29 (s, 1H), 4.06 (br s, 4H), 3.43 (m, 2H), 3.28 (s, 3H), 3.17 (m, 2H).

3-(1,3-Dioxolan-2-yl)-*N*-(3-methoxyphenyl)-2-thiophenesulfonamide (11k). *m*-Anisidine; purified by chromatography (30% EtOAc in hexane) to give a solid (62%): mp 112–114 °C; ^{1}H NMR (DMSO-d_6) δ 10.52 (s, 1H), 7.81 (d, $J = 5.0$ Hz, 1H), 7.19 (d, $J = 5.0$ Hz, 1H), 7.15 (m, 1H), 6.8–6.6 (m, 3H), 6.17 (s, 1H), 4.15–3.85 (m, 4H), 3.67 (s, 3H).

3-(1,3-Dioxolan-2-yl)-*N*-(3,4-dimethoxyphenyl)-2-thiophenesulfonamide (11m). 3,4-Dimethoxyaniline; purified by chromatography (EtOAc:hexane, 1:1) to give a dark syrup (58%): ^{1}H NMR (DMSO-d_6) δ 10.12 (s, 1H), 7.79 (d, $J = 5.2$ Hz, 1H), 7.17 (d, $J = 5.2$ Hz, 1H), 6.85 (d, $J = 8.6$ Hz, 1H), 6.67 (m, 2H), 6.10 (s, 1H), 4.1–3.8 (m, 4H), 3.68 (s, 3H), 3.63 (s, 3H); MS (CI) m/z 372 (M + 1).

3-(1,3-Dioxolan-2-yl)-*N*-[(4-(4-morpholinyl)phenyl]-2-thiophenesulfonamide (11n). 4-Morpholinophenyl; purified by recrystallization (57%, EtOAc/hexane): mp 171–174 °C; ^{1}H NMR (DMSO-d_6) δ 10.00 (s, 1H), 7.78 (d, $J = 5.2$ Hz, 1H), 7.16 (d, $J = 5.2$ Hz, 1H), 6.95 (d, $J = 9.1$ Hz, 2H), 6.82 (d, $J = 9.1$ Hz, 2H), 6.08 (s, 1H), 4.15–3.85 (m, 4H), 3.69 (t, $J = 5.0$ Hz, 4H), 3.02 (t, $J = 4.9$ Hz, 4H).

***N*-[[3-(1,3-Dioxolan-2-yl)thien-2-yl]sulfonyl]-*N*-methylglycine ethyl ester (12a).** Prepared by using the procedure described for the preparation of **7**, but a solution of sarcosine ethyl ester hydrochloride (15.0 g, 97.6 mmol) was mixed with the intermediate sulfonyl chloride (prepared from 37.3 mmol of **6**). Purification by chromatography (30% to 50% EtOAc/hexane) gave an oil (8.95 g, 72%): ^{1}H NMR (DMSO-d_6) δ 7.92 (d, $J = 5.2$ Hz, 1H), 7.26 (d, $J = 5.2$ Hz, 1H), 6.13 (s, 1H), 4.10–3.90 (m, 8H), 2.87 (s, 3H), 1.13 (t, $J = 7.1$ Hz, 3H); MS (CI) m/z 336 (M + 1).

***N*-[[3-(1,3-Dioxolan-2-yl)thien-2-yl]sulfonyl]-*N*-ethyl-glycine ethyl ester (12b).** A solution of **7** (7.5 g, 23.0 mmol) in anhydrous DMF (35 mL) was added to a cold (ice bath) suspension of 60% sodium hydride in mineral oil (1.02 g, 26.0 mmol) in DMF (25 mL) under nitrogen. After stirring this mixture for 30 min ethyl bromide (1.92 mL, 26.0 mmol) was added and after stirring for 2 h additional sodium hydride (0.51 g, 13.0 mmol) and ethyl bromide (1 mL) were added. The reaction mixture was stirred for 18 h at ambient temperature and evaporated to a residue which was suspended in 5% aqueous $NaHCO_3$ (150 mL). This mixture was extracted with EtOAc (3×50 mL) and the combined extracts were washed with brine (70 mL), dried, and evaporated to an amber oil (6.46 g, 80% crude yield) which was used in the next step without further purification (88% pure by NMR): ^{1}H NMR (DMSO-d_6) δ 7.90 (d, $J = 5.2$ Hz, 1H), 7.25 (d, $J = 5.2$ Hz, 1H), 6.15 (s, 1H), 4.15–3.90 (m, 8H), 3.20 (q, $J = 7.2$ Hz, 2H), 1.56 (t, $J = 7.2$ Hz, 3H), 1.05 (t, $J = 7.0$ Hz, 3H).

***N*-[[3-(1,3-Dioxolan-2-yl)thien-2-yl]sulfonyl]-*N*-propylglycine ethyl ester (12c).** From **7** and bromopropane/NaI (oil, 69%): ^{1}H NMR (DMSO-d_6) δ 7.90 (d, $J = 5.0$ Hz, H1), 7.23 (d, $J = 5.0$ Hz), 6.15 (s, 1H), 4.15–3.90 (m, 8H), 3.19 (t, $J = 7.5$ Hz, 2H), 1.48 (q, $J = 7.5$ Hz, 2H), 1.15 (t, $J = 7.5$ Hz, 3H), 0.79 (t, $J = 7.5$ Hz, 3H).

***N*-[[3-(1,3-Dioxolan-2-yl)thien-2-yl]sulfonyl]-*N*-(1-methylethyl)-glycine ethyl ester (12d).** To a solution of **11d** (25.0 g, 90.3 mmol) in anhydrous DMF (350 mL) at 0° was added a 1 M solution of potassium *t*-butoxide in *t*-butanol (99.3 mL, 99.3 mmol) followed by the addition of ethyl bromoacetate (12 mL, 18.1 g, 108.4 mmol); this mixture was stirred for 1 h and then allowed to stand at 5 °C for 18 h. The reaction mixture was diluted with 5% aqueous $NaHCO_3$ (600 mL) and extracted with ether (3×300 mL). The combined extracts were dried and evaporated to a syrup (36.25 g, 99%) which was used in the next reaction without further purification: ^{1}H NMR (DMSO-d_6) δ 7.89 (d, $J = 5.6$ Hz, 1H), 7.24 (d, $J = 5.5$ Hz, 1H), 6.14 (s, 1H), 4.2–3.9 (m, 8H), 1.19 (t, $J = 7.0$ Hz, 3H), 0.92 (d, $J = 5.0$ Hz, 6H).

***N*-[[3-(1,3-Dioxolan-2-yl)thien-2-yl]sulfonyl]-*N*-(2-propenyl)-glycine ethyl ester (12e).** Prepared from **11e** and ethyl bromoacetate as described for the preparation of **12d** (amber oil, 76%): ^{1}H NMR (DMSO-d_6) δ 7.93 (d, $J = 5.2$ Hz, 1H), 7.26 (d, $J = 5.2$ Hz, 1H), 6.16 (s, 1H), 5.65 (m, 1H), 5.3–5.1 (m, 2H), 4.1–3.9 (m, 11H), 1.14 (t, $J = 7.0$ Hz, 3H); MS (CI) m/z 362 (M + 1).

***N*-[[3-(1,3-Dioxolan-2-yl)thien-2-yl]sulfonyl]-*N*-methylcyclopropyl-glycine ethyl ester (12f).** Prepared from **11f** and ethyl bromoacetate as described for the preparation of **9d** (oil, 97%): ^{1}H NMR (DMSO-d_6) δ 7.91 (d, $J = 5.2$ Hz, 1H), 7.22 (d, $J = 5.2$ Hz, 1H), 6.14 (s, 1H), 4.18 (s, 2H), 4.1–3.9 (m, 6H), 3.13 (d, $J = 7.0$ Hz, 2H), 1.15 (t, $J = 7.12$ Hz, 3H), 0.85 (m, 1H), 0.42 (m, 2H), 0.13 (m, 2H); MS (CI) m/z 376 (M + 1).

***N*-Cyclohexyl-*N*-[(3-formyl-thien-2-yl)sulfonyl]-glycine methyl ester (12g).** Prepared from **11g** and methyl

bromoacetate as descibed for the preparation of **12d**, but isolated as the aldehyde following treatment with aqueous 2 N HCl for 4 h at ambient temperature and subsequent extraction with EtOAc (2×100 mL), drying, and evaporation to give an oil (94%): ^{1}H NMR (DMSO-d_6) δ 7.97 (d, J = 5.2 Hz, 1H), 7.56 (d, J = 5.2 Hz, 1H), 4.16 (s, 2H), 3.65 (m, 1H), 3.62 (s, 3H), 1.75–1.05 (m, 10H).

***N*-[[(3-Formyl-thien-2-yl)sulfonyl]-*N*-(2-methoxyethyl)-glycine methyl ester (12h).** Prepared from **11h** as described for the preparation of **12g**, but purified by chromatography (EtOAc/hexane, 2:1) to give a syrup (87%): ^{1}H NMR ($CDCl_3$) δ 10.35 (s, 1H), 7.60 (d, J = 5.2 Hz, 1H), 7.50 (d, J = 5.4 Hz, 1H), 4.30 (s, 2H), 3.63 (s, 3H), 3.55 (s, 4H), 3.26 (s, 3H).

***N*-[3-(1,3-Dioxolan-2-yl)thien-2-yl]sulfonyl]-*N*-(3-methoxypropyl)-glycine ethyl ester (12i).** From **7** and 1-bromo-3-methoxypropane/NaI (oil, 90%): ^{1}H NMR (DMSO-d_6) δ 7.91 (d, J = 5.0 Hz, 1H), 7.27 (d, J = 5.0 Hz, 1H), 6.13 (s, 1H), 4.10 (s), 4.05 (q, J = 7.2 Hz, 2H), 4.01 (m, 4H), 3.30 (m, 4H), 3.18 (s, 3H), 1.70 (m, 2H), 1.14 (t, J = 7.2 Hz, 3H); MS (CI) m/z 394 (M + 1).

***N*-[[3-(1,3-Dioxolan-2-yl)thien-2-yl]sulfonyl]-*N*-[(4-methoxyphenyl)methyl]-glycine ethyl ester (12j).** From **7** and 4-methoxybenzyl chloride with *t*-BuOK/*t*-BuOH (oil, 98%): ^{1}H NMR (DMSO-d_6) δ 7.92 (d, J = 5.2 Hz, 1H), 7.27 (d, J = 5.2 Hz, 1H), 7.11 (d, J = 6.7 Hz, 2H), 6.86 (d, J = 6.7 Hz, 2H), 6.19 (s, 1H), 4.38 (s, 2H), 4.09–3.86 (m, 6H), 3.90 (s, 2H), 3.71 (s, 3H), 1.06 (t, J = 7.1 Hz, 3H).

***N*-[[3-(1,3-Dioxolan-2-yl)thien-2-yl]sulfonyl]-*N*-(3-methoxyphenyl)-glycine ethyl ester (12k).** Prepared from **11k** as described for the preparation of **12d** (oil, 95%): ^{1}H NMR (DMSO-d_6) δ 7.90 (d, J = 5.4 Hz, 1H), 7.27 (d, J = 5.4 Hz, 1H), 7.25 (s, 1H), 6.89 (m, 2H), 6.74 (m, 1H), 5.86 (s, 1H), 4.51 (s, 2H), 4.09 (q, J = 7.2 Hz, 2H), 3.67 (s, 3H), 1.15 (t, J = 7.2 Hz, 3H).

***N*-[[3-(1,3-Dioxolan-2-yl)thien-2-yl]sulfonyl]-*N*-(3,4-dimethoxyphenyl)-glycine ethyl ester (12m).** Prepared from **11m** as described for the preparation of **12d** (oil, 99%): ^{1}H NMR ($CDCl_3$) δ 7.46 (d, J = 5.0 Hz, 1H), 7.25 (d, J = 5.0 Hz, 1H), 6.84 (m, 2H), 6.75 (d, J = 8.7 Hz, 1H), 6.02 (s, 1H), 4.46 (s, 2H), 4.25–3.95 (m, 6H), 3.86 (s, 3H), 3.77 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H).

***N*-[[3-(1,3-Dioxolan-2-yl)thien-2-yl]sulfonyl]-*N*-[4-(morpholin-4-yl)phenyl]-glycine methyl ester (12n).** Prepared from **11n** as described for the preparation of **12g** (oil, 99%): ^{1}H NMR (DMSO-d_6) δ 7.88 (d, J = 5.0 Hz, 1H), 7.27 (d, J = 5.0 Hz, 1H), 7.03 (d, J = 9.1 Hz, 2H), 6.88 (d, J = 9.1 Hz, 2H), 5.89 (s, 1H), 4.46 (s, 2H), 4.15–3.85 (m, 4H), 3.69 (m, 4H), 3.63 (s, 3H), 3.11 (m, 4H).

Ethyl 2-Methyl-2*H*-thieno[3,2-*e*]-1,2-thiazine-3-carboxylate 1,1-dioxide (13a). A solution of **12a** (8.80 g, 26.3 mmol) and *p*-toluenesulfonic acid (1.0 g) in acetone (250 mL) at ambient temperature was stirred for 18 h. Water (0.5 mL) was added and the mixture stirred for 4 h followed by the addition of 5% aqueous $NaHCO_3$ (50 mL). The mixture was extracted with EtOAc (2×200 mL) and the combined extracts were dried and evaporated to give the crude aldehyde which was dissolved in EtOAc (150 mL) and DBN (0.5 g) was added. After heating at reflux temperature for 2 h, the mixture was cooled to ambient temperature, washed with 5% aqueous $NaHCO_3$ (50 mL), dried, and evaporated to a residue which was purified by chromatography (gradient, 30% to 50% EtOAc in hexane) to give unreacted **12a** (1.39 g, 16%) and a gummy solid (5.05 g, 70%): ^{1}H NMR (DMSO-d_6) δ 8.06 ((d, J = 5.2 Hz, 1H), 7.73 (s, 1H), 7.48 (d, J = 5.2 Hz, 1H), 4.31 (q, J = 7.2 Hz, 2H), 3.15 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H); MS (CI) m/z 274 (M + 1).

Compounds **13b–n** were prepared using a procedure similar to that described for the synthesis of **13a**. See Table 4.

2-Methyl-2*H*-thieno[3,2-e]-1,2-thiazine-3-methanol 1,1-dioxide (14a). To a solution of **13a** (1.00 g, 3.66 mmol) in anhydrous THF (20 mL) at −70 °C was added DIBAL-H (1.0 M, 7.69 mL, 7.69 mmol). The mixture was warmed to ambient temperature and stirred for 2 h; additional DIBAL-H (20 mL, 20 mmol) was added and the reaction mixture was stirred for 18 h. Methanol (100 mL) was added and the mixture evaporated to a residue to which 2 N HCl (50 mL) was added followed by extraction with EtOAc (2×80 mL). The combined extracts were dried and evaporated to give a solid which was recrystallized (EtOAc/hexane) to give a colorless solid (0.80 g, 95%): mp 128–130 °C; ^{1}H NMR (DMSO-d_6) δ 7.95 (d, J = 5.0 Hz, 1H), 7.21 (d, J = 5.0 Hz, 1H), 6.51 (s, 1H), 5.57 (t, J = 4.8 Hz, 1H), 4.34 (d, J = 4.8 Hz, 2H), 3.32 (s, 3H).

Compounds **14b–n** were prepared using a procedure similar to that described for the synthesis of **14a**. See Table 5.

3-Hydroxymethyl-2-methyl-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide (15a). To a solution of **14a** (3.20 g, 13.8 mmol) in anhydrous THF (50 mL) under nitrogen at −70 °C was added *n*-butyllithium (12.7 mL of a 2.5 M solution, 31.9 mmol) over 5 min. The mixture was stirred for 10 min before a stream of sulfur dioxide was passed over the surface of the reaction mixture for 5 min. The reaction mixture was warmed to ambient temperature and then evaporated to a residue which was suspended in water (200 mL) and cooled (0 °C). Hydroxylamine-*O*-sulfonic acid (4.70 g, 41.6 mmol) and sodium acetate trihydrate (7.53 g, 55.4 mmol) were added and the mixture was stirred at ambient temperature for 18 h followed by neutralization with 5% aqueous $NaHCO_3$ (50 mL). This mixture was extracted with EtOAc (2×200 mL) and the combined extracts were dried and evaporated to a residue which was recrystallized (EtOAc/hexane) to give a solid (3.55 g, 83%): mp 144–146 °C; ^{1}H NMR (DMSO-d_6) δ 8.08 (s, 2H), 7.69 (s, 1H), 6.64 (s, 1H), 5.65 (t, J = 5.4 Hz, 1H), 4.37 (d, J = 5.4 Hz, 2H), 3.51 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 149.1, 145.4, 140.8, 127.6, 125.6, 101.9, 60.5, 29.5. Anal. ($C_8H_{10}N_2O_5S_3$) C, H, N.

Table 4. NMR data for compounds **13**

	^{1}H NMR (DMSO-d_6) δ	mp (°C)	Yield (%)
13b	8.07 (d, J = 5.1 Hz, 1H), 7.82 (s, 1H), 7.49 (d, J = 5.1 Hz, 1H), 4.33 (q, J = 7.2 Hz, 2H), 3.74 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.0 Hz, 3H), 0.95 (t, J = 7.0 Hz, 3H)	Oil	61
13c	7.91 (d, J = 5.2 Hz, 1H), 7.25 (d, J = 5.2 Hz, 1H), 6.15 (s, 1H), 4.03 (m, 2H), 1.48 (m, 2H), 1.15 (t, J = 7.0 Hz, 3H), 0.79 (t, J = 7.3 Hz, 3H)	Oil	52
13d	8.02 (d, J = 5.0 Hz, 1H), 7.79 (s, 1H), 7.48 (d, J = 5.0 Hz, 1H), 4.31 (q, J = 7.1 Hz, 2H), 4.01 (m, 1H), 1.32 (t, J = 7.1 Hz, 3H), 1.21 (d, J = 6.8 Hz, 6H)	97–99	50 (from **11d**)
13e	8.06 (d, J = 5.0 Hz, 1H), 7.81 (s, 1H), 7.48 (d, J = 5.0 Hz, 1H), 5.6–5.4 (m, 1H), 5.05 (d, J = 8.5 Hz, 2H), 4.34 (q, J = 7.1 Hz, 4H), 1.32 (t, J = 7.1 Hz, 3H)	Oil	60
13f	8.07 (d, J = 5.2 Hz, 1H), 7.86 (s, 1H), 7.50 (d, J = 5.2 Hz, 1H), 4.33 (q, J = 7.1 Hz, 2H), 3.67 (d, J = 6.9 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H), 0.63 (m, 1H), 0.18 (m, 2H), 0.05 (m, 2H)	Oil	63
13g	8.04 (d, J = 5.0 Hz, 1H), 7.82 (s, 1H), 7.45 (d, J = 5.1 Hz, 1H), 3.86 (s, 3H), 3.61 (m, 1H), 1.80–1.45 (m, 7H), 1.30–0.86 (m, 3H)	155–157	67 (from **11g**)
13h	7.62 (s, 1H), 7.57 (d, J = 5.1 Hz, 1H), 7.15 (d, J = 5.1 Hz, 1H), 4.13 (t, J = 4.9 Hz, 2H), 3.91 (s, 3H), 3.27 (t, J = 4.9 Hz, 2H), 2.97 (s, 3H) ($CDCl_3$)	61–64	94
13i	8.06 (d, J = 5.0 Hz, 1H), 7.77 (s, 1H), 7.48 (d, J = 5.0 Hz, 1H), 4.32 (q, J = 7.1 Hz, 2H), 3.83 (t, J = 7.0 Hz, 2H), 3.05 (s, 3H), 2.99 (t, J = 6.0 Hz, 2H), 1.59 (m, 2H), 1.31 (t, J = 7.0 Hz, 3H)	82–83	54 (from **11i**)
13j	7.98 (d, J = 5.8 Hz, 1H), 7.66 (d, J = 0.8 Hz, 1H), 7.29 (d, J = 5.8 Hz, 1H), 6.84 (d, J = 8.2 Hz, 2H), 6.67 (d, J = 8.8 Hz, 2H), 4.91 (s, 2H), 4.31 (q, J = 7.1 Hz, 2H), 3.63 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H)	Oil	55
13k	8.13 (d, J = 5.0 Hz, 1H), 7.96 (s, 1H), 7.60 (d, J = 5.0 Hz, 1H), 7.31 (t, J = 8.1 Hz, 1H), 6.99 (m, 1H), 6.62 (m, 2H), 4.09 (q, J = 5.1 Hz, 2H), 3.74 (s, 3H), 1.02 (t, J = 7.1 Hz, 3H)	107–109	46
13m	7.69 (s, 1H), 7.64 (d, J = 5.1 Hz, 1H), 7.27 (d, J = 5.1 Hz, 1H), 6.84 (d, J = 1.6 Hz, 1H), 6.75 (d, J = 8.7 Hz, 1H), 6.54 (dd, J = 8.7 and 1.6 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 1.09 (t, J = 7.1 Hz, 3H) ($CDCl_3$)	Foam	75
13n	8.11 (d, J = 5.1 Hz, 1H), 7.92 (s, 1H), 7.57 (d, J = 5.1 Hz, 1H), 6.88 (s, 4H), 3.71 (m, 4H), 3.66 (s, 3H), 3.12 (m, 4H)	220–222	54

Table 5. NMR data for compounds **14**

	^{1}H NMR (DMSO-d_6) δ	mp (°C)	Yield (%)
14b	7.94 (d, J = 5.0 Hz, 1H), 7.23 (d, J = 5.0 Hz, 1H), 6.64 (s, 1H), 5.60 (t, J = 5.4 Hz, 1H, exchange), 4.35 (d, J = 5.4 Hz, 2H), 3.84 (q, J = 7.1 Hz, 2H), 1.10 (t, J = 7.1 Hz, 3H)	Oil	94
14c	7.89 (d, J = 5.0 Hz, 1H), 7.23 (d, J = 5.0 Hz, 1H), 6.67 (s, 1H), 5.6 (br s, 1H), 4.35 (s, 2H), 3.76 (t, J = 7.3 Hz, 2H), 1.6–1.4 (m, 2H), 0.72 (t, J = 7.4 Hz, 3H)	65–67	99
14d	7.91 (d, J = 5.0 Hz, 1H), 7.22 (d, J = 5.0 Hz, 1H), 5.59 (t, J = 4.6 Hz, 1H), 6.74 (s, 1H), 4.32 (m, 3H), 1.29 (d, J = 6.9 Hz, 6H)	67–69	63
14e	7.96 (d, J = 5.0 Hz, 1H), 7.24 (d, J = 5.0 Hz, 1H), 6.65 (s, 1H), 5.9–5.7 (m, 1H), 5.62 (t, J = 5.6 Hz, 1H), 5.07 (d, J = 11 Hz, 1H), 4.92 (d, J = 18 Hz, 1H), 4.45 (m, 2H), 4.30 (d, J = 5.6 Hz, 2H); MS (CI) m/z 257 (M + 1).	51–53	93
14g	7.48 (d, J = 5.0 Hz, 1H), 6.98 (d, J = 5.0 Hz, 1H), 6.69 (s, 1H), 4.49 (d, J = 5.9 Hz, 2H), 3.89 (m, 1H), 2.12 (t, J = 5.9 Hz, 1H), 1.78 (m, 7H), 1.25 (m, 3H) ($CDCl_3$)	119–121	81
14h	7.52 (d, J = 5.1 Hz, 1H), 7.01 (d, J = 5.1 Hz, 1H), 6.47 (s, 1H), 4.43 (d, J = 6.8 Hz, 2H), 3.97 (t, J = 4.9 Hz, 2H), 3.69 (t, J = 4.9 Hz, 2H), 3.36 (s, 3H) ($CDCl_3$)	Oil	88
14i	7.92 (d, J = 5.0 Hz, 1H), 7.22 (d, J = 5.0 Hz, 1H), 6.63 (s, 1H), 5.56 (t, J = 4.7 Hz, 1H), 4.32 (d, J = 4.7 Hz, 2H), 3.83 (t, J = 7.4 Hz, 2H), 3.17 (t, J = 6.0 Hz, 2H), 3.13 (s, 3H), 1.68 (m, 2H)	Oil	99
14j	7.95 (d, J = 5.0 Hz, 1H), 7.21 (d, J = 5.0 Hz, 1H), 6.99 (d, J = 8.8 Hz, 2H), 6.80 (d, J = 8.8 Hz, 2H), 6.62 (s, 1H), 5.61 (t, J = 4.6 Hz, 1H), 4.96 (s, 2H)	Oil	99
14k	8.03 (d, J = 5.1 Hz, 1H), 7.37 (d, J = 5.1 Hz, 1H), 7.36 (d, J = 5.1 Hz, 1H), 7.07 (m, 1H), 6.85–6.75 (m, 3H), 5.48 (t, J = 4.6 Hz, 1H), 3.93 (J = 4.6 Hz, 2H), 3.77 (s, 3H)	141–143	73
14m	8.02 (d, J = 5.0 Hz, 1H), 7.35 (d, J = 5.0 Hz, 1H), 7.2 (m, 1H), 7.02 (m, 1H), 6.80 (m, 1H), 6.77 (s, 1H), 5.45 (t, J = 4.6 Hz, 1H), 3.94 (d, J = 4.6 Hz, 2H), 3.80 (s, 3H), 3.73 (s, 3H)	Foam	97
14n	8.01 (d, J = 5.0 Hz, 1H), 7.34 (d, J = 5.0 Hz, 1H), 7.06 (d, J = 9.1 Hz, 2H), 6.98 (d, J = 9.1 Hz, 2H), 6.76 (s, 1H), 5.46 (t, J = 4.6 Hz, 1H), 3.91 (d, J = 4.6 Hz, 2H), 3.73 (m, 4H), 3.17 (m, 4H)	Oil	95

Compounds **15b**–**i** and **15k**–**n** were prepared using a procedure similar to that described for the synthesis of **15a**. See Table 6.

2-Methyl-3-[(4-morpholinyl)methyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-dioxide (16a1). To a solution of **14a** (0.79 g, 3.42 mmol) and triethylamine (1.04 g, 10.3 mmol) in anhydrous THF (30 mL) at ambient temperature was added methanesulfonic anhydride (0.89 g, 5.13 mmol). After 30 min, morpholine (2 mL) was added and the mixture was stirred for an additional hour at ambient temperature and then heated at reflux temperature for 1 h; solvent was evaporated and 5% aqueous $NaHCO_3$ (80 mL) added. This mixture was extracted with EtOAc (2×200 mL) and the combined extracts were dried and evaporated to an oil which was purified by chromatography (30 to 50% EtOAc in hexane) to give a colorless solid (0.82 g, 84%): mp 104–106 °C; ^{1}H NMR (DMSO-d_6) δ 7.94 (d, J = 5.0 Hz, 1H), 7.18 (d, J = 5.0 Hz, 1H), 6.53 (s, 1H), 3.57 (t, J = 4.8 Hz, 4H), 3.39 (s, 3H), 3.38 (s, 2H), 2.40 (t, J = 4.6 Hz, 4H).

2-Methyl-3-[[*N*-(2-methoxyethyl)-*N*-(3-methoxypropyl)-amino]methyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-dioxide (16a3). Reaction of **14a** (2.97 g, 12.9 mmol) with 3-methoxypropylamine as described for the preparation

Table 6. NMR data for compounds **15**

	^{1}H NMR (DMSO-d_6) δ	mp (°C)	Yield (%)
15b	8.07 (s, 2H), 7.70 (s, 1H), 6.75 (s, 1H), 5.68 (t, J = 5.1 Hz, 1H), 4.37 (d, J = 5.1 Hz, 2H), 3.86 (q, J = 7.0 Hz, 2H), 1.09 (t, J = 7.0 Hz, 3H)	163–165	74
15c	8.07 (s, 2H), 7.70 (s, 1H), 6.77 (s, 1H), 5.66 (t, J = 5.2 Hz, 1H), 4.36 (d, J = 5.4 Hz, 2H), 3.78 (t, J = 7.4 Hz, 2H), 1.49 (q, J = 7.3 Hz, 2H), 0.72 (t, J = 7.4 Hz, 3H)	143–145	63
15d	8.05 (s, 2H), 7.70 (s, 1H), 6.84 (s, 1H), 5.65 (t, J = 4.6 Hz, 1H), 4.33 (m, 3H), 1.31 (d, J = 7.0 Hz, 3H)	Oil	98
15e	8.08 (s, 2H), 7.71 (s, 1H), 6.76 (s, 1H), 5.9–5.6 (m, 2H), 5.10 (d, J = 11 Hz, 1H), 4.92 (d, J = 18 Hz, 1H), 4.46 (d, J = 4.8 Hz, 2H), 4.30 (d, J = 4.8 Hz, 2H)	Glass	66
15f	8.07 (s, 2H), 7.71 (s, 1H), 6.79 (s, 1H), 5.67 (t, J = 4.8 Hz, 1H), 4.40 (d, J = 4.8 Hz, 2H), 3.71 (d, J = 7.1 Hz, 2H), 1.02 (m, 1H), 0.32 (m, 4H)	Oil	35 (from **14f**)
15g	8.05 (s, 2H), 7.69 (s, 1H), 6.86 (s, 1H), 5.65 (br s, 1H), 4.35 (s, 2H), 3.89 (m, 1H), 1.75 (m, 7H), 1.22 (m, 3H)	Glass	77
15h	8.06 (s, 2H), 7.69 (s, 1H), 6.74 (s, 1H), 5.65 (t, J = 4.5 Hz, 1H), 4.36 (d, J = 4.5 Hz, 2H), 3.96 (t, J = 5.3 Hz, 2H), 3.4–3.2 (m, 4H), 3.06 (s, 3H)	Oil	68
15i	8.07 (s, 2H), 7.70 (s, 1H), 6.76 (s, 1H), 5.64 (t, J = 4.6 Hz, 1H), 4.35 (d, J = 4.6 Hz, 2H), 3.86 (m, 2H), 3.19 (m, 2H), 3.14 (s, 3H), 1.69 (m, 2H)	Oil	86
15k	8.12 (s, 2H), 7.83 (s, 1H), 7.40 (t, J = 8.1 Hz, 1H), 7.09 (m, 1H), 6.95 (s, 1H), 6.79 (m, 2H), 5.56 (t, J = 4.5 Hz, 1H), 3.96 (d, J = 4.5 Hz, 2H), 3.77 (s, 3H)	180–182	72
15m	8.12 (s, 2H), 7.82 (s, 1H), 7.03 (d, J = 8.3 Hz, 1H), 6.90–6.75 (m, 3H), 5.55 (t, J = 4.5 Hz, 1H), 3.95 (d, J = 4.5 Hz, 2H), 3.80 (s, 3H), 3.74 (s, 3H)	Foam	77
15n	8.11 (s, 2H), 7.81 (s, 1H), 7.08 (d, J = 9.1 Hz, 2H), 6.88 (s, 1H), 5.53 (t, J = 4.6 Hz, 1H), 3.93 (br s, 2H), 3.73 (m, 4H), 3.18 (m, 4H)	Oil	31 (from **14n**)

of **16a1** provided the intermediate secondary aminoether as an oil (84%) which was reacted with 2-bromoethyl methyl ether (DMF/NaH; 100 °C, 18 h). Purification by chromatography (EtOAc to 10% MeOH in EtOAc) gave a syrup (0.70 g, 39%): ^{1}H NMR (DMSO-d_6) δ 7.96 (d, J = 5.0 Hz, 1H), 7.19 (d, J = 5.0 Hz, 1H), 6.53 (s, 1H), 3.58 (m, 4H), 3.40 (s, 3H), 3.32 (d, J = 4.7 Hz, 2H), 2.40 (m, 4H).

2-Methyl-3-[[*N*-(2-methoxyethyl)-*N*-(2-propenyl)amino]-methyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-dioxide (16a7). Reaction of **14a** (2.00 g, 8.66 mmol) with 2-methoxyethylamine as described for the preparation of **16a1** provided the intermediate secondary aminoether as an oil (78%) which was reacted with allyl bromide. Purification by chromatography (25% EtOAc in hexane) gave an oil (1.6 g, 74%): ^{1}H NMR (DMSO-d_6) δ 7.95 (d, J = 5.0 Hz, 1H), 7.19 (d, J = 5.0 Hz, 1H), 6.56 (s, 1H), 5.88 (m, 1H), 5.20 (m, 1H), 3.53 (s, 2H), 3.45 (t, J = 5.9 Hz, 2H), 3.37 (s, 3H), 3.22 (s, 3H), 3.15 (m, 2H), 2.65 (t, J = 5.9 Hz, 2H).

2-(3-Methoxypropyl)-3-[(4-morpholinyl)methyl]-2*H*-thieno-[3,2-*e*]-1,2-thiazine 1,1-dioxide (16i1). Prepared from **14i** in a manner similar to that described for **16a1** to give a syrup (94%): ^{1}H NMR (DMSO-d_6) 7.92 (d, J = 5.1 Hz, 1H), 7.19 (d, J = 5.1 Hz, 1H), 6.64 (s, 1H), 3.91 (t, J = 7.2 Hz, 2H), 3.56 (t, J = 4.8 Hz, 4H), 3.36 (s, 2H), 3.16 (m, 2H), 3.13 (s, 3H), 2.39 (t, J = 4.2 Hz, 4H), 1.72 (m, 2H).

2-[(4-Methoxyphenyl)methyl]-3-[(4-morpholinyl)methyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-dioxide (16j1). Prepared from **14j** in a manner similar to that described for **16a1** (88%): mp 112–114 °C; ^{1}H NMR (DMSO-d_6) δ 7.97 (d, J = 5.1 Hz, 1H), 7.20 (d, J = 5.1 Hz, 1H), 6.96 (d, J = 8.7 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 6.65 (s, 1H), 5.10 (s, 2H), 3.67 (s, 2H), 3.58 (t, J = 4.5 Hz, 4H), 3.21 (s, 2H), 2.38 (s, 4H).

2-Methyl-3-(4-morpholinylmethyl)-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride (17a1). To a mixture of **16a1** (0.30 g, 1.04 mmol) in anhydrous THF (30 mL) under nitrogen at −65 °C was added *n*-butyllithium (2.5 M, 0.625 mL, 1.56 mmol) over a 5 min period. The mixture was stirred at −50 °C for 10 min and at −70 °C for 1 h. Sulfur dioxide was passed over the reaction mixture for 5 min followed by warming the mixture to ambient temperature and evaporation to provide a residue. Cold water (50 mL) and 5% aqueous $NaHCO_3$ (50 mL) were added to the residue and this mixture was extracted with EtOAc (100 mL) to give 0.17 g (58%) of unreacted starting material. Hydroxylamine-*O*-sulfonic acid (0.294 g, 2.60 mmol) was added to the aqueous solution which was stirred at ambient temperature for 3 h. The reaction mixture was extracted with EtOAc (2×100 mL) and the combined extracts were dried and evaporated to give the free base (0.098 g, 26%). The combined crude product from two batches (0.383 g) was treated with 1.5 M HCl/MeOH (1 mL) and evaporated to give the HCl salt; recrystallization from a mixture of EtOH and water gave a yellow solid (0.172 g, 11%): mp 231–233 °C (dec); ^{1}H NMR (DMSO-d_6) δ 11.56 (br s, 1H), 8.16 (s, 2H), 7.82 (s, 1H), 7.16 (s, 1H), 4.35 (br s, 2H), 3.92 (m, 4H), 3.40 (m, 2H), 3.27 (s, 3H), 3.18 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 149.7, 138.8, 134.5, 128.1, 116.0, 62.9, 55.6, 50.6, 34.5. Anal. ($C_{12}H_{17}N_3O_5S_3$·HCl·0.5 H_2O) C, H, N.

3-[[*N*-(2-Methoxyethyl)-*N*-(3-methoxypropyl)amino]methyl]-2-methyl-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride (17a3). Prepared from **16a3** as described for **17a1** (42%, recrystallized from 2-propanol): mp 173–175 °C; ^{1}H NMR (DMSO-d_6) 8.19 (s, 2H), 7.82 (s, 1H), 7.24 (s, 1H), 4.41 (br s, 2H), 3.76 (m, 4H), 3.45–3.25 (m, 7H), 3.22 (s, 6H), 2.03 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 149.8, 138.8, 135.2, 128.1, 116.3, 69.1, 65.8, 58.3, 57.9, 51.0, 50.4, 34.5, 22.9. Anal. ($C_{15}H_{23}N_3O_6S_3$·HCl) C, H, N.

3-[*N*-(2-Methoxyethyl)-*N*-methylamino]methyl]-2-methyl-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide (17a6). To a solution of **15a** (0.80 g, 2.58 mmol) and methanesulfonic anhydride (0.67 g, 3.87 mmol) in anhydrous THF (30 mL) at 0 °C was added triethylamine (0.52 g, 5.16 mmol). After 30 min the reaction mixture was cooled (ice bath) and *N*-(2-methoxyethyl)methylamine (1 mL) was added. This mixture was allowed to warm to ambient temperature, stirred for 2 h and heated at reflux temperature for 10 min followed by evaporation to a residue which was combined with 2 N HCl (50 mL) and extracted with EtOAc (100 mL). The aqueous layer was separated, combined with 5% aqueous $NaHCO_3$ (150 mL) and extracted with EtOAc (2×100 mL). The combined extracts were dried and evaporated to an oil which was purified by chromatography (4% MeOH in CH_2Cl_2) to give a solid (0.635 g, 66%): mp 127–129 °C (dec); ^{1}H NMR (DMSO-d_6) δ 8.08 (s, 2H), 7.65 (s, 1H), 6.64 (s, 1H), 3.46 (m, 4H), 3.40 (s, 3H), 3.24 (s, 3H), 2.59 (t, J = 5.8 Hz, 3H), 2.21 (s, 3H). Anal. ($C_{12}H_{19}N_3O_5S_3$) C, H, N.

3-[[*N*-(2-Methoxyethyl)-*N*-(2-propenyl)amino]methyl]-2-methyl-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride (17a7). Prepared from **16a7** as described for **17a1** (58%, recrystallized from CH_2Cl_2/hexane): mp 107–109 °C; ^{1}H NMR (DMSO-d_6) δ 8.07 (br s, 2H), 7.65 (s, 1H), 6.67 (s, 1H), 5.98–5.75 (m, 1H), 5.20 (m, 2H), 3.55 (s, 2H), 3.45 (t, J = 5.9 Hz, 2H), 3.42 (s, 3H), 3.22 (s, 3H), 3.15 (m, 1H), 2.65 (t, J = 5.9 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 149.0, 143.0, 140.4, 134.9, 127.5, 126.6, 118.1, 105.5, 70.0, 57.9, 56.2, 56.1, 51.5, 30.3. Anal. ($C_{14}H_{21}N_3O_5S_3$) C, H, N.

2-Ethyl-3-[(4-morpholinyl)methyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride (17b1). Prepared from **15b** and morpholine as described for **17a6** but converted to the HCl salt (56%): mp 239–241 °C; ^{1}H NMR (DMSO-d_6) δ 8.17 (s, 2H), 7.86 (s, 1H), 7.29 (s, 1H), 4.40 (br s, 2H), 3.94 (m, 6H), 3.10 (m, 4H), 0.77 (t, J = 6.8 Hz, 3H); MS (CI) m/z 394 (M + 1). Anal. ($C_{13}H_{19}N_3O_5S_3$·HCl) C, H, N.

2-Ethyl-3-[[bis(2-methoxyethyl)amino]methyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride (17b2). Prepared from **15b** and bis(2-methoxyethyl)amine as described for **17a6** but converted to the HCl salt (43%): mp 185–186 °C; ^{1}H NMR (DMSO-d_6) δ 8.17 (s, 2H), 7.83 (s, 1H), 7.32 (s, 1H), 4.4 (br s, 2H), 3.9–3.6 (m, 6H), 3.4 (br s, 4H), 3.30 (s, 6H), 0.79 (t, J = 7.0 Hz, 3H). Anal. ($C_{15}H_{25}N_3O_6S_3$·HCl) C, H, N.

2-Ethyl-3-[[bis(2-hydroxyethyl)amino]methyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride (17b4). Prepared from **15b** and diethanolamine as described for **17a6** but converted to the HCl salt (66%): mp 211–214 °C; ^{1}H NMR (DMSO-d_6) δ 8.19 (s, 2H), 7.83 (s, 1H), 7.35 (s, 1H), 5.18 (br s, 2H), 4.47 (br s, 2H), 3.85 (m, 8H), 3.31 (br s, 4H), 0.75 (t, J = 6.9 Hz, 3H). Anal. ($C_{13}H_{21}N_3O_6S_3$·HCl) C, H, N.

3-[(4-Morpholinyl)methyl]-2-propyl-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride (17c1). Prepared from **15c** and morpholine as described for **17a6** but converted to the HCl salt (47%): mp 201–203 °C; ^{1}H NMR (DMSO-d_6) δ 8.15 (s, 2H), 7.85 (s, 1H), 7.22 (s, 1H), 4.35 (br s, 2H), 4.0–3.8 (m, 6H), 3.22 (br s, 4H), 1.22 (m, 2H), 0.59 (t, J = 7.3 Hz, 3H); MS (CI) m/z 408 (M + 1). Anal. ($C_{14}H_{21}N_3O_5S_3$·HCl) C, H, N.

3-[[Bis(2-methoxyethyl)amino]methyl]-2-propyl-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride (17c2). Prepared from **15c** and bis(2-methoxyethyl)amine as described for **17a6** but converted to the HCl salt (42%): mp 201–203 °C; ^{1}H NMR (DMSO-d_6) δ 10.7 (br s, 1H), 8.19 (s, 2H), 7.83 (s, 1H), 7.3 (br s, 1H), 4.41 (br s 2H), 4.0–3.6 (m, 8H), 3.38 (br s, 2H), 3.31 (s, 6H), 1.2 (m, 2H), 0.60 (t, J = 7.4 Hz, 3H). Anal. ($C_{16}H_{27}N_3O_6S_3$·HCl) C, H, N.

2-Propyl-3-[(2-propynylamino)methyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide (17c8). Prepared from **15c** and propargylamine as described for **17a6** (40%): mp 136–138 °C; ^{1}H NMR DMSO-d_6) δ 8.07 (s, 2H), 7.69 (s, 1H), 6.76 (s, 1H), 3.83 (t, J = 7.0 Hz, 2H), 3.67 (s, 2H), 3.32 (s, 2H), 3.15 (s, 1H), 2.7 (br s, 1H), 1.45 (q, J = 7.0 Hz, 2H), 0.69 (t, J = 7.5 Hz, 3H). Anal. ($C_{13}H_{17}N_3O_4S_3$) C, H, N.

2-(1-Methylethyl)-3-[(4-morpholinyl)methyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide (17d1). Prepared from **15d** and morpholine as described for **17a6** (32%): mp 196–198 °C; ^{1}H NMR (DMSO-d_6) δ 8.06 (s, 2H), 7.64 (s, 1H), 6.77 (s, 1H), 4.42 (m, 1H), 3.61 (t, J = 4.3 Hz, 4H), 3.45 (s, 2H), 2.42 (br s, 4H), 1.40 (d, J = 6.9 Hz, 6H); ^{13}C NMR (DMSO-d_6) δ 148.6, 142.2, 139.8, 130.0, 127.5, 108.8, 66.2, 60.4, 53.7, 52.4, 21.7. Anal. ($C_{14}H_{21}N_3O_5S_3$) C, H, N.

2-(1-Methylethyl)-3-[(2-propynylamino)methyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide (17d8). Prepared from **15d** and propargylamine as described for **17a6** (39%): mp 133–135 °C; ^{1}H NMR (DMSO-d_6) δ 8.06 (s, 2H), 7.68 (s, 1H), 6.82 (s, 1H), 4.38 (m, 1H), 3.69 (s, 2H), 3.33 (d, J = 2.5 Hz, 2H), 3.14 (t, J = 2.3 Hz, 1H), 1.32 (d, J = 6.9 Hz, 6 H); ^{13}C NMR (DMSO-d_6) δ 148.6, 143.6, 140.0, 130.6, 127.8, 109.5, 82.3, 74.2, 53.7, 49.7, 35.9, 21.7. Anal. ($C_{13}H_{17}N_3O_4S_3$) C, H, N.

3-[(4-Morpholinyl)methyl]-2-(2-propenyl)-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide (17e1). Prepared from **15e** and morpholine as described for **17a6** (64%): mp 136–138 °C; ^{1}H NMR (DMSO-d_6) δ 8.06 (s, 2H), 7.65 (s, 1H), 6.75 (s, 1H), 5.6–5.9 (m, 1H), 5.05 (d, J = 11 Hz, 1H), 4.80 (d, J = 18 Hz, 1H), 4.56 (d, J = 4.7 Hz, 2H), 3.57 (m, 4H), 3.27 (s, 2H), 2.36 (m, 4H); MS (CI) m/z 406 (M + 1). Anal. ($C_{14}H_{19}N_3O_5S_3$) C, H, N.

2-Cyclopropylmethyl-3-[(4-morpholinyl)methyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride (17f1). Prepared from **15f** and morpholine as described for **17a6** but converted to the HCl salt (30%): mp 120–130 °C; ^{1}H NMR (DMSO-d_6) δ 8.15 (s, 2H), 7.88 (s, 1H), 7.28 (s, 1H), 4.45 (s, 2H), 3.1–4.1 (br m, 4H), 0.6 (m, 1H), 0.15 (m, 4H). Anal. ($C_{15}H_{21}N_3O_5S_3$·HCl·0.4 2-propanol) C, H, N.

2-Cyclohexyl-3-[(4-morpholinyl)methyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide (17g1). Prepared from **15g** and morpholine as described for **17a6** (33%): mp 200–202 °C; ^{1}H NMR (DMSO-d_6) δ 8.05 (s, 2H), 7.62 (s, 1H), 6.74 (s, 1H), 3.98 (m, 1H), 3.58 (br s, 4H), 3.45 (s, 2H), 2.48 (s, 4H), 2.08–1.50 (m, 7H), 1.40–0.99 (m, 3H); ^{13}C NMR (DMSO-d_6) δ 148.6, 142.2, 139.9, 129.9, 127.5, 108.7, 66.3, 61.7, 60.5, 52.4, 31.6, 26.0, 24.8. Anal. ($C_{17}H_{25}N_3O_5S_3$) C, H, N.

2-(2-Methoxyethyl)-3-[(4-morpholinyl)methyl]-2*H*-thieno-[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide (17h1). Prepared from **15h** and morpholine as described for **17a6** (32%): mp 164–166 °C; ^{1}H NMR (DMSO-d_6) δ 8.05 (s, 2H), 7.63 (s, 1H), 6.7 (s, 1H), 4.03 (dd, 2H), 3.55 (m, 4H). Anal. ($C_{14}H_{21}N_3O_6S_3$) C, H, N.

2-(2-Methoxyethyl)-3-[[bis(2-methoxyethyl)amino]methyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride (17h2). Prepared from **15h** and bis(2-methoxyethyl)amine as described for **17a6** but converted to the HCl salt (31%): mp 180–182 °C; ^{1}H NMR (DMSO-d_6) δ 10.75 (br s, 1H), 8.18 (s, 2H), 7.81 (s, 1H), 7.28 (s, 1H), 4.41 (br s, 2H), 4.00 (m, 2H), 3.78 (m, 4H), 3.39 (m, 4H), 3.90 (s, 6H), 3.17 (m, 2H), 2.87 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 149.0, 138.3, 132.9, 127.8, 118.4, 69.3, 65.9, 58.2, 57.7, 54.2, 51.5, 47.7. Anal. ($C_{16}H_{27}N_3O_7S_3$·HCl) C, H, N.

2-(3-Methoxypropyl)-3-[(4-morpholinyl)methyl]-2*H*-thieno-[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride (17i1). Prepared from **16i1** as described for **17a6** (35%): mp 145–149 °C; ^{1}H NMR (DMSO-d_6) δ 8.19 (s, 2H), 7.85 (s, 1H), 7.28 (s, 1H), 4.38 (br s, 2H), 3.97 (4.1–3.6, 8H), 3.5–2.9 (m, 8H), 1.40 (br s, 2H); ^{13}C NMR (DMSO-d_6) δ 149.5, 149.5, 138.6, 128.1, 68.5, 63.1, 57.8, 50.6. Anal. ($C_{15}H_{23}N_3O_6S_3$·HCl) C, H, N.

3-[(Cyclopropylamino)methyl]-2-(3-methoxypropyl)-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride (17i9). Prepared from **15i** and cyclopropylamine as described for **17a6** but converted to the HCl salt (20%): mp 210–211 °C; ^{1}H NMR (DMSO-d_6) δ 9.85 (s, 2H), 8.19 (s, 2H), 7.79 (s, 1H), 7.24 (s, 1H), 4.19 (s, 2H), 3.90 (t, J = 5 Hz, 2H), 3.5 (m, 2H), 3.10 (s, 3H), 3.07 (t, J = 6 Hz, 2H), 2.65 (m, 1H), 1.49 (m, 2H), 1.04 (d, J = 6 Hz, 4H); ^{13}C NMR (DMSO-d_6) δ 146.4, 135.7, 131.6, 127.9, 124.8, 111.7, 65.4, 54.7, 44.1, 41.3, 25.6, 24.9; MS (CI) m/z 408 (M + 1). Anal. ($C_{14}H_{21}N_3O_5S_3$ · HCl·0.33 2-propanol) C, H, N.

3-[(1-Imidazolyl)methyl]-2-(3-methoxypropyl)-2*H*-thieno-[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide (17i10). Prepared from **15i** and imidazole as described for **17a6** (36%): mp 197–199 °C; ^{1}H NMR (DMSO-d_6) δ 8.11 (s, 2H), 7.74 (s, 1H), 7.72 (s, 1H), 7.16 (s, 1H), 6.96 (s, 1H), 6.81 (s, 1H), 5.21 (s, 2H), 3.80 (t, J = 6 Hz, 2H), 3.12 (s, 3H), 1.53 (m, 2H); MS (CI) m/z 419 (M + 1). Anal. ($C_{14}H_{18}N_4O_5S_3$) C, H, N.

2-[(4-Methoxyphenyl)methyl]-3-[(4-morpholinyl)methyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride (17j1). Prepared from **16j1** as described for **17a6** (20%): mp 212–214 °C; ^{1}H NMR (DMSO-d_6) δ 8.14 (s, 2H), 7.64 (s, 1H), 7.12 (br s), 7.00 (d, J = 8.6 Hz, 2H), 6.69 (d, J = 8.6 Hz, 2H), 5.04 (s, 2H), 4.43 (br s, 2H), 3.94 (br s, 4H), 3.69 (br s, 2H), 3.41 (br s, 2H), 3.21 (br s, 4H). Anal. ($C_{19}H_{23}N_3O_6S_3$·HCl) C, H, N.

2-(3-Methoxyphenyl)-3-[(4-morpholinyl)methyl]-2*H*-thieno-[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride (17k1). Prepared from **15k** and morpholine as described for **17a6** but converted to the HCl salt (29%): mp 170–174 °C; ^{1}H NMR (DMSO-d_6) δ 8.22 (s, 2H), 7.95 (s, 1H), 7.59 (s, 1H), 7.35 (t, J = 8.1 Hz, 1H), 7.06 (m, 1H), 6.96 (s, 1H), 6.67 (dd, J = 1.2 and 7.6 Hz, 1H), 3.91 (br s, 4H), 3.79 (s, 3H), 3.57 (br s, 2H), 3.20 (br s, 4H); ^{13}C NMR (DMSO-d_6) δ 159.8, 150.3, 139.0, 135.2, 130.3, 128.4, 119.4, 115.2, 114.6, 63.1, 62.4, 55.6, 50.7, 25.6, 10.4. Anal. ($C_{18}H_{21}N_3O_6S_3$·HCl·0.33 1-propanol) C, H, N.

2-(3-Methoxyphenyl)-3-[(2-hydroxyethylamino)methyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride (17k5). Prepared from **15k** and ethanolamine as described for **17a6** but converted to the HCl salt (26%): mp 137–140 °C; ^{1}H NMR (DMSO-d_6) δ 9.48 (s, 2H), 8.22 (s, 2H), 7.91 (s, 1H), 7.45 (s, 1H), 7.37 (t, J = 8.1 Hz, 1H), 7.07 (m, 1H), 6.92 (m, 1H), 6.72 (m, 1H), 5.30 (s, 1H), 3.79 (s, 3H) 3.74 (br s, 4H), 3.00 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 159.8, 150.2, 139.2, 135.2, 135.1, 130.5, 130.4, 128.2, 119.7, 115.3, 115.2, 114.5, 56.3, 55.5, 48.1, 47.1. Anal. ($C_{16}H_{19}N_3O_6S_3$·HCl·0.5 H_2O) C, H, N.

2-(3,4-Dimethoxyphenyl)-3-[(4-morpholinyl)methyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride (17m1). Prepared from **15m** and morpholine as described for **17a6** but converted to the HCl salt (46%): mp 219–221 °C; ^{1}H NMR (DMSO-d_6) δ 11.7 (br s, 2H), 8.21 (s, 2H), 7.94 (s, 1H), 7.5 (br s, 1H), 7.04 (d, J = 1.6 Hz, 1H) 6.96 (d, J = 8.7 Hz, 1H), 6.57 (dd, J = 8.7 and 1.6 Hz, 1H), 3.91 (br s, 6H), 3.77 (s, 6H), 3.17 (br s, 4H). Anal. ($C_{19}H_{23}N_3O_7S_3$·HCl) C, H, N.

2-[(4-Morpholinyl)phenyl]-3-[(4-morpholinyl)methyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride (17n1). Prepared from **15n** and morpholine as described for **17a6** but converted to the HCl salt (32%): mp 230–235 °C (dec); ^{1}H NMR (DMSO-d_6) δ 8.22 (s, 2H), 7.94 (s, 1H), 7.56 (s, 1H), 7.06 (dd, J = 9.1, 18.7 Hz, 2H), 6.96 (d, J = 9.1 Hz, 2H), 4.82 (br s, 2H), 3.92 (br s, 6H), 3.70 (br s, 4H), 3.16 (br s, 6H); ^{13}C NMR (DMSO-d_6) δ 151.3, 150.2, 139.0, 133.4, 130.8, 128.7, 128.4, 124.6,115.0, 65.9, 63.0, 55.6, 50.6, 47.0. Anal. ($C_{21}H_{26}N_4O_6S_3$·HCl·H_2O) C, H, N.

2-(3-Hydroxypropyl)-3-(4-morpholinylmethyl)-2*H*-thieno-[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide (17o1). A solution of **17j1** (1.00 g, 2.25 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C and bromodimethylborane (0.82 g, 6.75 mmol) was added. The reaction mixture was allowed to warm to ambient temperature and, after stirring for 3 h, was diluted with EtOAc (100 mL) and water (100 mL). The organic layer was separated, dried and evaporated to a residue which was purified by

chromatography (gradient, 50% EtOAc in hexane to EtOAc) to give a viscous syrup which crystallized (chlorobutane/hexane) to give a colorless solid (0.76 g, 79%): mp 135–138 °C; ^{1}H NMR (DMSO-d_6) δ 8.09 (s, 2H), 7.67 (s, 1H), 6.76 (s, 1H), 4.55 (t, J = 4.8 Hz, 1H), 3.97 (t, J = 7.2 Hz, 2H), 3.59 (br s, 4H), 3.41 (s, 2H), 3.30 (m, 2H), 2.42 (br s, 4H), 1.63 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 148.8, 140.8, 139.9, 128.0, 127.6, 107.9, 66.1, 59.7, 52.6, 42.5, 32.9; MS (CI) m/z 424 (M + 1). Anal. ($C_{14}H_{21}N_3O_6S_3$) C, H, N.

2-(3-Hydroxyphenyl)-3-(4-morpholinylmethyl)-2*H*-thieno-[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide (17p1). To a solution of **19k1** (0.86 g, 1.63 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added a 1 M solution of boron tribromide in CH_2Cl_2 over 3 min. The mixture was warmed to ambient temperature and allowed to stir for 2 h. The reaction mixture was poured into 5% aqueous $NaHCO_3$ (100 mL) and extracted with EtOAc (2×100 mL). The combined extracts were dried and evaporated to dryness. Chromatography on silica (5% MeOH/CH_2Cl_2) gave a solid, which was recrystallized (EtOAc/hexane) to give an off white solid (0.39 g, 52%): mp 220–222 °C; ^{1}H NMR (DMSO-d_6) δ 9.80 (s, 1H), 8.10 (s, 2H), 7.67 (s, 1H), 7.22 (t, J = 8.1 Hz, 1H), 6.92 (s, 1H), 6.84 (s, 1H), 6.64 (m, 2H), 3.52 (br s, 4H), 3.01 (s, 2H), 2.24 (br s, 4H); ^{13}C NMR (DMSO-d_6) δ 157.7, 149.4, 141.6, 140.3, 135.0, 129.7, 128.6, 128.0, 119.5, 116.4, 116.2, 108.1, 66.1, 59.2, 52.3. Anal. ($C_{17}H_{19}N_3O_6S_3$) C, H, N.

2-(3-Hydroxyphenyl)-3-[(2-propynylamino)methyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride (17p8). A solution of **19p8** (0.53 g, 1.2 mmol) was treated with boron tribromide as described for the preparation of **17p1**; column chromatography (30% hexane in EtOAc) gave an oil that was converted to the HCl salt; recrystallization (EtOH/CH_2Cl_2) gave a yellowish solid (0.27 g, 57%): mp 195–198 °C; ^{1}H NMR (DMSO-d_6) δ 10.05 (br s, 1H), 8.22 (s, 2H), 7.93 (s, 1H), 7.40 (s, 1H), 7.24 (t, J = 8.3 Hz, 1H), 6.89 (m, 1H), 6.64 (m, 2H), 3.86 (s, 2H), 3.77 (s, 2H), 3.68 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 158.1, 150.2, 139.1, 135.0, 134.8, 130.7, 130.2, 128.3, 118.3, 116.9, 115.5, 115.0, 79.9, 74.6, 46.1, 34.9. Anal. ($C_{16}H_{15}N_3O_5S_3$·HCl) C, H, N.

3-Chloromethyl-*N*-(1,1-dimethylethyl)-2-(3-methoxphenyl)-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide (18). To a solution of **14k** (4.81 g, 14.9 mmol) in anhydrous THF (80 mL) at −70 °C was added *n*-butyllithium (2.5 M, 14.9 mL, 37.2 mmol) and the mixture was stirred for 1 h followed by the introduction of sulfur dioxide gas over the surface of the reaction mixture for 5 min. The mixture was warmed to ambient temperature, evaporated to dryness and the residue was mixed with dichloromethane (250 mL); this suspension was cooled on an ice bath and *N*-chlorosuccinimide (6.96 g, 52.1 mmol) was added. After stirring for 2 h, *t*-butylamine (15 mL, 143 mmol) was added and stirring continued for 16 h followed by the addition of 5% aqueous $NaHCO_3$ (200 mL). This mixture was extracted with EtOAc (2×200 mL) and the combined extracts were dried and evaporated to an oil which was purified by chromatography (40% EtOAc in hexane) to give an oil (4.41 g, 62%): ^{1}H NMR (DMSO-d_6) δ 8.24 (s, 1H), 7.86 (s, 1H), 7.39 (t, J = 8.2 Hz, 1H), 7.2–7.0 (m, 2H), 6.9–6.7 (m, 2H), 4.32 (s, 2H), 3.74 (s, 3H), 1.20 (s, 9H); MS (CI) m/z 477 (M + 1).

***N*-(1,1-Dimethylethyl)-2-(3-methoxphenyl)-3-[(4-morpholinyl)methyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide (19k1).** To a solution of **18** (0.86 g, 1.88 mmol) in anhydrous THF (50 mL) at 0 °C was added *p*-toluenesulfonyl chloride (0.57 g, 3.0 mmol) and triethylamine (0.523 mL, 3.76 mol). After stirring for 1 h, morpholine (3 mL) and DMF (30 mL) were added and the mixture heated at reflux temperature for 2 h. Evaporation of the solvent provided a residue which was combined with 5% aqueous $NaHCO_3$ (100 mL) and the mixture was extracted with EtOAc (2×100 mL). The combined extracts were dried and evaporated to a syrup which was purified by chromatography (EtOAc in hexane, 1:1) to give a glassy solid (0.86 g, 91%): mp 75–80 °C; ^{1}H NMR (DMSO-d_6) δ 8.23 (s, 1H), 7.83 (s, 1H), 7.39 (t, J = 8.2 Hz, 1H), 7.09 (m, 1H), 6.93 (s, 1H), 6.81 (m, 2H), 3.76 (s, 3H), 3.52 (m, 4H), 3.30 (d, J = 4.7 Hz, 2H), 2.25 (m, 4H), 1.22 (s, 9H).

***N*-(1,1-Dimethylethyl)-2-(3-methoxyphenyl)-3-[(2-propynylamino)methyl-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide (19k8).** To a solution of **18** (1.0 g, 2.1 mmol) in anhydrous DMF (20 mL) was added propargylamine (1.77 g, 32.1 mmol); this mixture was stirred at ambient temperature for 30 min followed by heating at 80 °C for 2 h and evaporation to dryness. The residue was combined with 5% aqueous $NaHCO_3$ (100 mL) and extracted with EtOAc (2×100 mL). The combined extracts were dried and evaporated to an oil which was purified by chromatography (EtOAc/hexane, 1:1) to give a syrup (0.53 g, 51%): ^{1}H NMR (DMSO-d_6) δ 8.24 (s, 1H), 7.86 (s, 1H), 7.37 (t, J = 8.3 Hz, 1H), 7.08 (m, 1H), 6.95 (s, 1H), 6.78 (m, 2H), 3.76 (s, 3H), 3.28 (m, 5H), 3.02 (s, 1H), 1.22 (s, 9H).

3,5-Dibromo-2-(1,3-dioxolan-2-yl)-thiophene (20). A mixture consisting of 3,5-dibromo-2-thiophenecarboxaldehyde[10] (11.0 g, 40.7 mmol), *p*-toluenesulfonic acid (0.25 g) and ethylene glycol (5.06 g, 81.5 mmol) in toluene (150 mL) was heated at reflux temperature for 1.5 h; water was removed by a Dean-Stark trap. The reaction mixture was cooled and poured into 5% aqueous $NaHCO_3$ (100 mL). The organic layer was separated, dried and evaporated to a residue. Purification of this crude material by chromatography (6% EtOAc in hexane) gave an oil (10.33 g, 81%): ^{1}H NMR ($CDCl_3$) δ 6.93 (s, 1H), 6.05 (s, 1H), 4.13–4.00 (m, 4H).

***N*-[2-(1,3-Dioxolan-2-yl)-3-thienyl]sulfonyl]-*N*-methylglycine ethyl ester (21).** To a solution of **20** (10.0 g, 31.8 mmol) in anhydrous ether (150 mL) at −75 °C was added *n*-butyllithium (2.5 M in hexane, 13.4 mL, 33.4 mmol) while maintaining the temperature below −65 °C; a precipitate formed during the addition. After the addition was complete, 1-propanol (1.91 g, 31.8 mmol) was added to quench the 2-lithio species and provide a solution of 3-bromo-2-(1,3-dioxolan-2-yl)thiophene. To this solution was added a solution of *n*-butyllithium

(2.5 M in hexane, 13.4 mL, 33.4 mmol) followed by passing sulfur dioxide over the reaction mixture for about 10 min. This mixture was warmed to ambient temperature and evaporated to dryness. The residue was mixed with CH_2Cl_2 (150 mL), cooled to 0 °C, and *N*-chlorosuccinimide was added followed by stirring for 40 min. Saturated aqueous Na_2HCO_3 (100 mL) was added to the mixture followed by sarcosine ethyl ester HCl salt (7.34 g, 47.8 mmol) and stirring continued for 30 min. The organic layer was separated, dried, and evaporated to a residue which was purified by chromatography (30% EtOAc in hexane) to give a viscous oil (5.96 g, 53%): ^{1}H NMR (DMSO-d_6) δ 7.75 (d, J = 5.5 Hz, 1H), 7.32 (d, J = 5.4 Hz, 1H), 6.41 (s, 1H), 4.1–3.9 (m, 8H), 2.86 (s, 3H), 1.15 (t, J = 7.2 Hz, 3H).

Ethyl 2-methyl-2*H*-thieno[2,3-*e*]-1,2-thiazine-3-carboxylate 1,1-dioxide (22). A mixture of **21** (5.86 g, 16.5 mmol) and trifluoroacetic acid (8 mL) in acetone (50 mL) was heated at reflux temperature for 1 h, cooled, and poured into water (100 mL). Acetone was evaporated and the residue was combined with 5% aqueous $NaHCO_3$ (50 mL) and this mixture was extracted with EtOAc (2×150 mL). The combined extracts were dried and evaporated to give crude aldehyde which was dissolved in EtOAc (100 mL) followed by the addition of DBN (1 mL) and molecular sieves (5 g). This mixture was heated at reflux temperature for 15 min, cooled, and poured into 2 N HCl (50 mL). The organic layer was separated, dried, and evaporated to an oil which was purified by chromatography (30% EtOAc in hexane) to give an off-white solid (3.60 g, 79%): mp 87–89 °C: ^{1}H NMR (DMSO-d_6) δ 8.06 (d, J = 5.3 Hz, 1H), 7.91 (s, 1H), 7.53 (d, J = 5.4 Hz, 1H), 4.32 (q, J = 7.1 Hz, 2H), 3.11 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H).

2-Methyl-2*H*-thieno[2,3-*e*]-1,2-thiazine-3-methanol 1,1-dioxide (23). To a solution of **22** (3.16 g, 11.6 mmol) in anhydrous THF (30 mL) at 0 °C was added DIBAL-H (1.0 M, 29.0 mL, 29.0 mmol). This mixture was stirred for 30 min, warmed to ambient temperature, and stirred for an additional 30 min. The mixture was evaporated to a residue which was combined with EtOAc (100 mL) and poured into 2 N HCl (50 mL). The organic layer was separated, washed with brine, dried and evaporated to an oil which was purified by chromatography (EtOAc/hexane, 1/1) to give an oil which solidified upon standing (2.3 g, 88%): mp 78–80° C; ^{1}H NMR (DMSO-d_6) δ 7.64 (d, J = 5.4 Hz), 7.40 (d, J = 5.4 Hz), 6.61 (s, 1H), 5.61 (t, J = 4.8 Hz, 1H), 4.35 (d, J = 4.8 Hz, 2H), 3.34 (s, 3H).

3-Hydroxymethyl-2-methyl-2*H*-thieno[2,3-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide (24). A solution of **23** (1.00 g, 4,33 mmol) in anhydrous THF (30 mL) was treated as described for the preparation of **15a** to give, after purification by chromatography (50% to 80% EtOAc in hexane), a viscous oil (0.80 g, 60%): ^{1}H NMR (DMSO-d_6) δ 7.90 (s, 2H), 7.72 (s, 1H), 6.73 (s, 1H), 5.73 (t, J = 4.7 Hz, 1H), 4.39 (d, J = 4.7 Hz, 2H), 3.36 (s, 3H).

2-Methyl-3-(4-morpholinylmethyl)-2*H*-thieno[2,3-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide (25). To a solution of **24** (0.78 g, 2.52 mmol) and triethylamine (1.02 g, 10.1 mmol) in anhydrous THF (30 mL) at ambient temperature was added *p*-toluenesulfonyl chloride (0.961 g, 5.04 mmol). After stirring for 4.5 h, morpholine (2 mL) was added and the mixture stirred for 1 h followed by heating at reflux temperature for 10 min. The reaction mixture was evaporated to a residue which was combined with 5% aqueous $NaHCO_3$ (80 mL). This mixture was extracted with EtOAc (2×100 mL) and the combined extracts were dried and evaporated to an oil which was purified by chromatography (5% to 10% CH_3OH in CH_2Cl_2) to give an amorphous solid (0.41 g, 43%). Recrystallization from EtOAc/CH_2Cl_2 gave a yellowish solid: mp 192–194 °C; ^{1}H NMR (DMSO-d_6) δ 7.92 (s, 2H), 7.72 (s, 1H), 6.77 (s, 1H), 3.62 (m, 4H), 3.45 (s, 2H), 3.43 (s, 3H), 2.41 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 144.4, 144.3, 143.7, 142.5, 126.2, 122.2, 102.2, 66.1, 60.1, 52.6, 29.5. Anal. ($C_{12}H_{17}N_3O_5S_3$) C, H, N.

4-Bromo-5-(1,3-dioxolan-2-yl)-*N*-(1,1-dimethylethyl)-thiophene-2-sulfonamide (26). A solution of **20** (2.09 g, 6.66 mmol) in anhydrous THF (20 mL) was treated as described for the preparation of **18** to give, after purification by chromatography (30% EtOAc in hexane), an oil (1.83 g, 74%); ^{1}H NMR (DMSO-d_6) δ 7.97 (s, 1H), 7.56 (s, 1H), 6.04 (s, 1H), 4.01 (m, 4H), 1.17 (s, 9H).

***N*-[[5-(Aminosulfonyl)-2-formyl-thiophen-3-yl]sulfonyl]-*N*-methyl-glycine ethyl ester (27).** To a solution of **26** (5.63 g, 15.21 mmol) in anhydrous THF (60 mL) at room temperature was added NaH (60% dispersion in mineral oil, 0.669 g, 16.7 mmol) under nitrogen. After stirring for 1.5 h, the mixture was cooled to −70 °C and *n*-butyllithium (9.13 mL, 22.8 mmol) was added. An aliquot was removed after 15 min and quenched with water; NMR showed that lithiation was complete: ^{1}H NMR (DMSO-d_6) δ 7.76 (s, 1H), 7.44 (d, J = 5.1 Hz, 1H), 7.19 (d, J = 5.1 Hz, 1H), 6.07 (s, 1H), 3.96 (m, 4H), 1.13 (s, 9H). Sulfur dioxide was passed over the reaction mixture for 5 min followed by warming to room temperature and evaporation. The residue was suspended in CH_2Cl_2 (150 mL), cooled on an ice bath, and *N*-chlorosuccinimide (4.06 g, 30.4 mmol) was added. After stirring the mixture for 1 h at ambient temperature, sarcosine ethyl ester HCl salt (7.01 g, 45.6 mmol) and 5% $NaHCO_3$ (100 mL) were added and the mixture stirred for 3 h. The organic phase was separated, dried, and evaporated to a residue which was purified by chromatography (30% EtOAc in hexane) to give a gum (5.07 g, 65%); ^{1}H NMR (DMSO-d_6) δ 8.01 (s, 1H), 7.69 (s, 1H), 6.41 (s, 1H), 4.15 (t, J = 7.0 Hz, 2H), 4.06 (m, 6H), 2.90 (s, 3H), 1.19 (s, 9H), 1.15 (t, J = 7.0 Hz, 3H). A portion (1.00 g, 2.13 mmol) of this intermediate was dissolved in trifluoroacetic acid (5 mL) and stirred at room temperature for 18 h. Evaporation of the reaction mixture provided a residue which was suspended in 5% aqueous $NaHCO_3$ (150 mL) and extracted with EtOAc (2×100 mL). The combined extracts were dried and evaporated to a residue which was purified by chromatography (40% EtOAc in hexane) to give a viscous oil which solidified upon standing (0.35 g, 44%): mp 105–107 °C; ^{1}H NMR (DMSO-d_6) δ 10.29 (s, 1H), 8.18 (s, 2H), 7.84 (s, 1H), 4.25 (s, 2H), 4.06 (q, J = 7.2 Hz, 2H),

2.95 (s, 3H), 1.38 (t, $J=7.2$ Hz, 3H); HRMS (FAB) m/z for $C_{10}H_{14}N_2O_7S_3$: Calcd: 371.0036. Found: 371.0041.

Aqueous solubility determination. The compound of interest was added to 0.1 M phosphate buffer at pH 7.4 and the pH was adjusted as desired. Samples containing an excess of undissolved material were stirred at ambient temperature for a minimum of 18 h. Sample pH was adjusted as required and the mixture stirred an additional 15 min and filtered through a 0.45 micron nylon filter. The filtrate was analyzed by RP-HPLC against concentration standards for the compound of interest.

Distribution coefficients. Partitioning of compounds between *n*-octanol and aqueous buffer was determined at pH 5.0 and 7.4 using 0.1 M phosphate buffers. The initial concentration (C_1) of compound in buffer and the buffer concentration following extraction with *n*-octanol (C_2) were determined by RP-HPLC analysis against concentration standards for the specific compound. The distribution coefficient (DC) of a compound at a given pH was calculated using the equation $DC_{pH}=(C_1-C_2)/C_2$.

pK_a determination. Ionization constants were determined by potentiometric titration (Kyoto AT-310 Potentiometric Titrator) in water or a mixture of water and an organic solvent such as methanol, acetone, or acetonitrile. If a solvent mixture was used, the nominal pK_a values were plotted against the percentage of organic solvent to provide by extrapolation the pK_a of the compound in water.

Biological assays

In vitro inhibition of hCA-II. Inhibition of hCA-II activity was determined using a pH stat assay similar to that previously described[11,12] wherein enzyme activity is proportional to the volume of an NaOH solution required to maintain the pH of the reaction mixture at a predetermined value. A Radiometer VIT 90 Video titration system jacketed glass reaction vessel was maintained at 4 °C with a circulating water bath. The assay measured the rate of CO_2 hydration by determining the addition rate of a 0.15 N NaOH solution to the reaction vessel containing 0.02 M HEPES buffer (5 mL), pH 7.2, such that this value was maintained over a period of 4 min as CO_2 (approximately 13% CO_2 in helium) was bubbled into the buffer as a stream of premixed CO_2 (5 mL/min) and helium (35 mL/min). The rate of addition of NaOH to the buffer in the absence of hCA-II was defined as blank. The rate (slope) increase following the introduction of 10 L of hCA-II (Sigma Chemical Co.) to the buffer (0.35 E.U./mL) reflected the control level of hCA-II activity. Enzyme inhibition was determined by addition to the enzyme buffer mixture of various aliquots (5 to 100 μL) of a suitable concentration of inhibitor dissolved in a mixture of ethanol and water (1:1, volume) followed by stirring for 4 min prior to the introduction of substrate. IC_{50}, the inhibitor concentration resulting in 50% inhibition of the enzyme activity, was obtained from the plot of the net rate (slope) increase of NaOH addition against log inhibitor volume.

In vitro inhibition of rhCA-IV. Inhibition constants were determined using the same pH stat assay procedure described above, but using rhCA-IV (0.26 E.U./mL) prepared as described previously.[19,20]

In vitro binding of inhibitor to hCA-II. Inhibitor binding to hCA-II was determined using a fluorescence competition assay.[12,13] Displacement of dansylamide from hCA-II was determined at 37 °C in cuvettes (3 mL) containing 1×10^{-8} M enzyme (Sigma Chemical Co.), 5×10^{-5} M dansylamide, and 100 mM disodium hydrogen phosphate at pH 7.4. At time zero the test or control articles were added in a dose volume of 30 μL and the mixture was incubated at 37 °C for 3 min; the fluorescence intensity for each concentration was the average of triplicate determinations. Fluorescence measurements were made with a Perkin–Elmer LS-50B luminescence spectrometer using a thermostatically controlled cell maintained at 37 °C with excitation and emission wavelengths of 280 and 460 nm, respectively. Relative binding of the inhibitor was determined by measuring and comparing the average fluorescence intensities of the treated versus control reactions. Binding constants were estimated from a Dixon plot of the data (reciprocal of the average relative fluorescence intensity versus inhibitor concentration), for each concentration. Reported binding constants are generally the mean of at least duplicate determinations.

Acute intraocular pressure determination. Intraocular pressure was determined with an applanation pneumatonometer after light corneal anesthesia with 0.1% proparacaine. Following an IOP measurement, residual anesthetic was washed out of the eyes with saline. After two subsequent baseline IOP measurements were recorded, one eye of each of the seven to ten Dutch-belted rabbits in the test group was topically dosed with two 25 μL aliquots of compound (1 mg total dose) and the contralateral eye was dosed with vehicle. Subsequent IOP measurements were taken at 0.5, 1, 2, 3, and 4 h. Compounds were formulated as 2% suspensions, with the exception of **17b4** and **17h2**, which were 2% solutions, in acetate buffered mannitol vehicle containing 0.01% benzalkonium chloride, 0.01% disodium EDTA, 0.1% polysorbate 80, 0.8% hydroxypropylmethylcellulose, and adjusted to pH 5.0.

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