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5-Substituted 3-thiophenesulfonamides as carbonic anhydrase inhibitors

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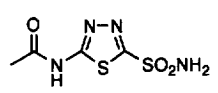
Summary — A series of 5-substituted 3-thiophenesulfonamides was prepared from 4-bromo-2-thiophene carboxaldehyde. Several of these compounds inhibited carbonic anhydrase II in vitro at concentrations of less than 10 nM. In the ex vivo assay, these compounds have inhibitory values in the 25–81% range. Additionally, none of these compounds exhibit sensitization potential as determined by in vitro measurement of cysteine reactivity.

carbonic anhydrase inhibitor / thiophene sulfonamide

Introduction

Systemic carbonic anhydrase inhibitors (CAIs) have been successfully used in the control of elevated intraocular pressure (IOP) associated with glaucoma for over 30 years. When administered orally, agents such as acetazolamide **1**, methazolamide **2**, ethoxzolamide **3** and dichlorophenamide **4** lower IOP by inhibiting carbonic anhydrase in secretory cells of the ciliary body resulting in the reduction of aqueous humor formation [1, 2]. However the dosage required for a therapeutic effect also causes a multitude of deleterious side-effects such as depression, fatigue, anorexia, gastrointestinal disturbance and parathesias [3, 4]. A topically effective CAI administered directly to the eye might obviate these undesirable systemic side-effects. The route of administration would localize the action of the drug to the eye offering target tissue specificity. Early attempts at topically administering systemically active CAIs were largely unsuccessful due to these agents poor ability to penetrate the cornea. Feasibility for a topically active CAI was only recently demonstrated with trifluoromethylacetazolamide **5** [5, 6]. Shortly thereafter, topical efficacy in glaucomatous patients was achieved with the Merck compound, MK 927 **6a** [7]. The successful use of a topical CAI for controlling intraocular pressure was recently acknowledged with the approval of the Merck compound Dorzolamide (Trusopt) **6b**.



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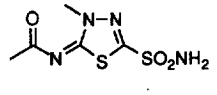

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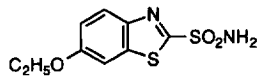

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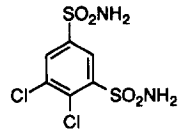

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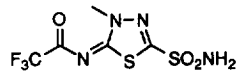

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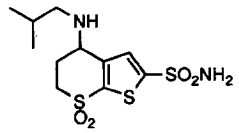
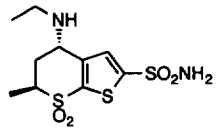


6a



6b

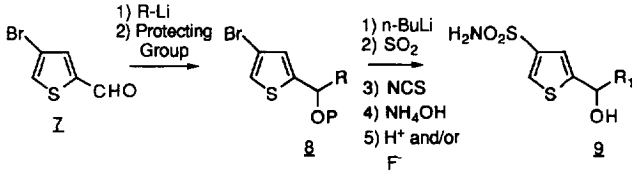
With our ongoing interest in glaucoma therapy, topical CAIs represented a logical target for our research efforts. Earlier work from our laboratory has shown that modifications which greatly simplified the structure of the Merck compound, MK 927, still maintained potent carbonic anhydrase inhibitory activity. In this article we extend the study by exploring the effect of regiochemistry of the sulfonamide group on carbonic anhydrase inhibition. All previous work has

described heterocyclic CAIs with the sulfonamide at the 2-position of the five-membered ring [8, 9]. In this paper we describe the synthesis and carbonic anhydrase inhibitory activity of novel 5-substituted 3-thiophenesulfonamides.

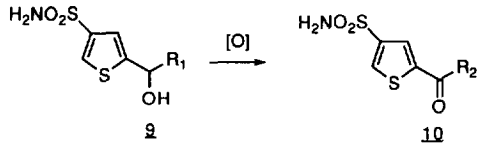
Chemistry

4-Bromo-2-thiophene carboxaldehyde **7** is the starting reagent for the compound in this series. In the first step, a 1,2-addition is made to the aldehyde functionality with an appropriate lithio reagent followed by protection of the resulting alcohol as the trimethylsilyl ether or tetrahydropyranyl ether **8**. Sulfamoylation at the 3-position is then accomplished by the following sequence of reactions: metal halogen exchange with n-butyllithium, reaction with sulfur dioxide, oxidation to the sulfonyl chloride with N-chlorosuccinamide and then amination with concentrated ammonium hydroxide to give the sulfonamide. Subsequent deprotection with acid and/or fluoride ion gives **9** (scheme 1).

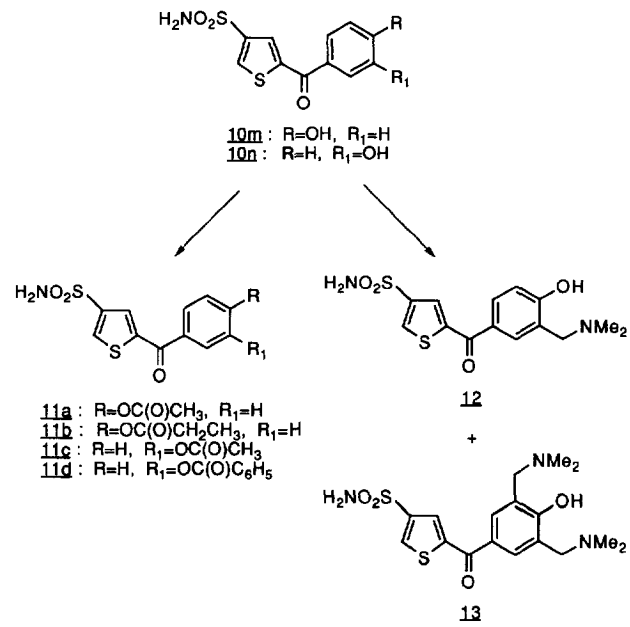
The corresponding keto compounds **10** are obtained by Jones' or manganese dioxide oxidation of **9** (scheme 2). Further functionalizations are performed on compounds **10k–n**. Acylation of **10m** and **10n** give the esters **11a–d** and aminomethylation of **10m** affords **12** and **13** (scheme 3). The reverse esters **14a–d** are obtained from the acids **10k** and **10l** (scheme 4). Compound **15**, an intermediate to compounds **17–20**, is desilylated with tetra-*n*-butylammonium fluoride (TBAF) to give **16**. Oxidation with tetrapropylammonium perruthenate (TPAP) and removal of the tetrahydropyranyl (THP) group with *para*-toluenesulfonic acid (TsOH) affords **17**. Alternatively, compound **16** can be carried on to compound **18** by acylation with acetic anhydride followed by removal of the THP group. Oxidation of **18** with Jones' reagent gives **19** and subsequent hydrolysis affords **20** (scheme 5). Compounds **9** and **10** are also used as intermediates



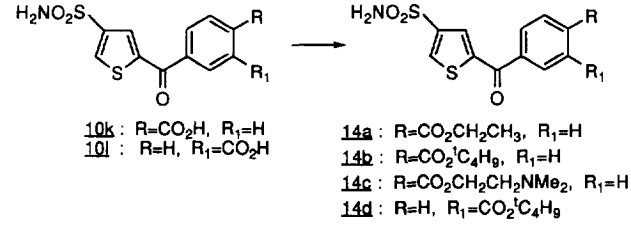
Scheme 1. **9a**: $R_1 = C_6H_5$; **9b**: $R_1 = n\text{-}C_4H_9$; **9c**: $R_1 = n\text{-}C_6H_{13}$; **9d**: $R_1 = 4\text{-}C_6H_4OCH_3$; **9e**: $R_1 = 4\text{-}C_6H_4\text{-}n\text{-}C_6H_9$; **9f**: $R_1 = 2\text{-}C_5H_4N$; **9g**: $R_1 = 2\text{-}C_6H_4F$; **9h**: $R_1 = 3,5\text{-}C_6H_3F_2$; **9i**: $R_1 = 3\text{-}C_6H_4CF_3$; **9j**: $R_1 = 3\text{-}C_6H_4F$; **9k**: $R_1 = 4\text{-}C_6H_4CH_2OH$; **9l**: $R_1 = 3\text{-}C_6H_4CH_2OH$; **9m**: $R_1 = 4\text{-}C_6H_4OH$; **9n**: $R_1 = 3\text{-}C_6H_4OH$.



Scheme 2. **10a**: $R_2 = C_6H_5$; **10b**: $R_2 = n\text{-}C_4H_9$; **10c**: $R_2 = n\text{-}C_6H_{13}$; **10d**: $R_2 = 4\text{-}C_6H_4OCH_3$; **10e**: $R_2 = 4\text{-}C_6H_4\text{-}n\text{-}C_6H_9$; **10f**: $R_2 = 2\text{-}C_5H_4N$; **10g**: $R_2 = 2\text{-}C_6H_4F$; **10h**: $R_2 = 3,5\text{-}C_6H_3F_2$; **10i**: $R_2 = 3\text{-}C_6H_4CF_3$; **10j**: $R_2 = 3\text{-}C_6H_4F$; **10k**: $R_2 = 4\text{-}C_6H_4CH_2OH$; **10l**: $R_2 = 3\text{-}C_6H_4CH_2OH$; **10m**: $R_2 = 4\text{-}C_6H_4OH$; **10n**: $R_2 = 3\text{-}C_6H_4OH$.

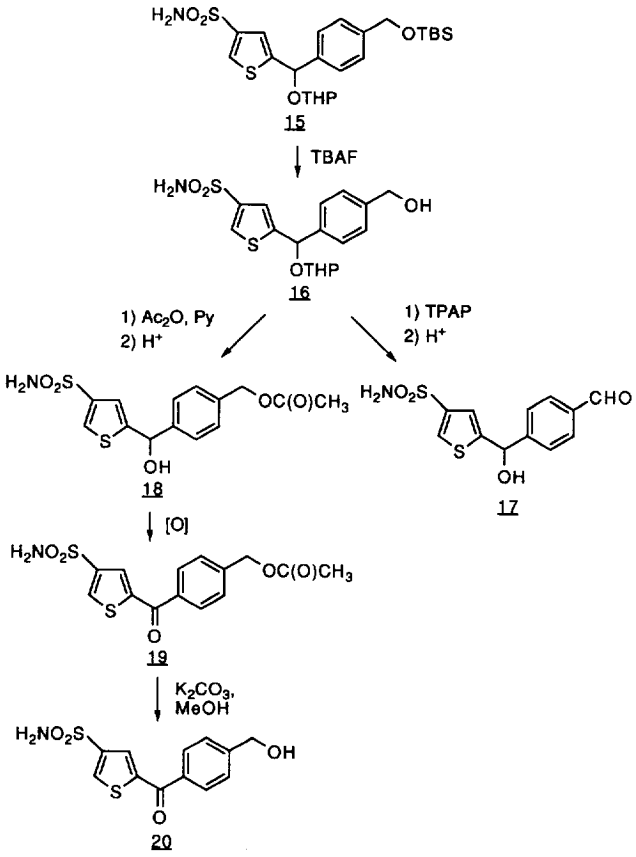


Scheme 3.

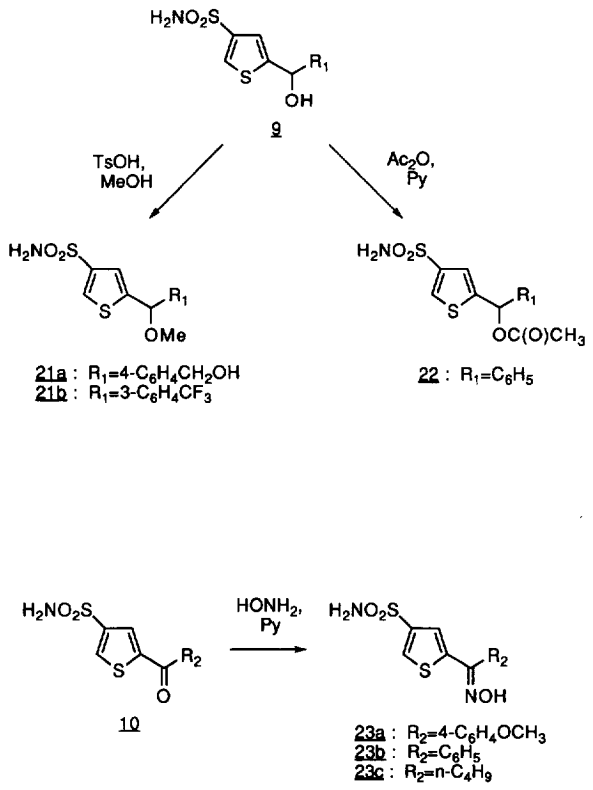


Scheme 4.

for appending other functional groups at the 5 position of the thiophene ring. Treatment of **9** or **10** with TsOH/methanol, acetic anhydride (Ac_2O)/pyridine or hydroxylamine/pyridine afford compounds **21**, **22** and



Scheme 5.



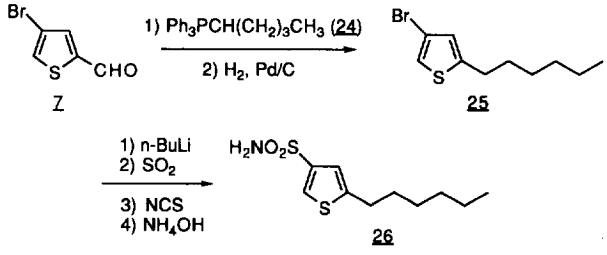
Scheme 6.

23, respectively (scheme 6). The 5-alkyl substituted compound **26** is prepared by a Wittig reaction of **7** with **24** followed by hydrogenation of the resulting olefin and subsequent sulfamoylation (scheme 7).

Discussion

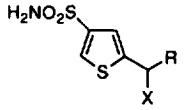
Our laboratory had previously reported that singly substituted 2-thiophenesulfonamides were potent inhibitors of human carbonic anhydrase II [10]. As a continuation of this effort, we sought to determine the effect of regiochemistry of the sulfonamide functionality on carbonic anhydrase inhibition. Specifically, a series of 5-substituted 3-thiophenesulfonamides were prepared and evaluated for inhibitory activity against human carbonic anhydrase II [11]. The IC_{50} values of the compounds prepared are listed in table I. In addition, since some arenesulfonamides have been found to cause ocular sensitization, representative compounds were tested for their susceptibility to nucleophilic attack by cysteine [12]. None of the compounds were found to be reactive (table II).

Placement of the sulfonamide functionality at the 3-position of the thiophene ring does not effect the potency of the compounds in inhibiting carbonic anhydrase. In fact several of the agents exhibit IC_{50} values below 10 nM. The structure–activity relationship (SAR) in the 3-thiophenesulfonamide series is very similar to that observed in the 2-thiophenesulfonamide series. The most active compounds are those



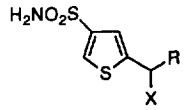
Scheme 7.

Table I. CA inhibition.



Compound	*X*	*R*	*IC_{50} (nM) CA (II)*
1	Acetazolamide		6
3	Ethoxzolamide		0.5
6a	MK 927		4
9a	OH	C_6H_5	74
9b	OH	n-C_4H_9	32
9c	OH	n-C_5H_{11}	31
9d	OH	4-$C_6H_4OCH_3$	16
9f	OH	2-C_5H_4N	240
9k	OH	4-$C_6H_4CH_2OH$	41
9m	OH	4-C_6H_4OH	26
9n	OH	3-C_6H_4OH	37
17	OH	4-C_6H_4CHO	18
18	OH	4-$C_6H_4CH_2OC(O)CH_3$	21
10a	O	C_6H_5	13
10b	O	n-C_4H_9	27
10c	O	n-C_5H_{11}	14
10d	O	4-$C_6H_4OCH_3$	26
10e	O	4-$C_6H_4C_4H_9$	8.7
10f	O	2-C_5H_4N	19
10g	O	2-C_6H_4F	18
10h	O	3,5-$C_6H_3F_2$	15
10i	O	3-$C_6H_4CF_3$	8.3
10j	O	3-C_6H_4F	12
10k	O	4-$C_6H_4CO_2H$	3.4
10k'	O	4-C_6H_4CHO	13
10l	O	3-$C_6H_4CO_2H$	11
10l'	O	3-C_6H_4CHO	7.3
10m	O	4-C_6H_4OH	17
10n	O	3-C_6H_4OH	6.7
11a	O	4-$C_6H_4OC(O)CH_3$	12
11b	O	4-$C_6H_4OC(O)C_2H_5$	9
11c	O	3-$C_6H_4OC(O)CH_3$	3.6
11d	O	3-$C_6H_4OC(O)C_6H_5$	5.3
12	O	4-OH-3-$CH_2NMe_2C_6H_4$	30
13	O	3,5-CH2$NMe_2$4-OHC_6H_4	155
14a	O	4-$C_6H_4CO_2C_2H_5$	6
14b	O	4-$C_6H_4CO_2tC_4H_9$	3
14c	O	4-$C_6H_4CO_2CH_2CH_2NMe_2$	25
14d	O	3-$C_6H_4CO_2tC_4H_9$	25
19	O	4-$C_6H_4CH_2OC(O)CH_3$	6
20	O	4-$C_6H_4CH_2OH$	17
21a	OCH_3	4-$C_6H_4CH_2OH$	13
21b	OCH_3	3-$C_6H_4CF_3$	18
22	$OC(O)CH_3$	C_6H_5	90
23a	NOH	4-$C_6H_4OCH_3$	31
23b	NOH	$C6H_5$	53
23c	NOH	n-C_4H_9	22
26	H	n-C_5H_{11}	21

Table II. Cysteine reactivity.



Compound	*X*	*R*	*Cysteine reaction (min^{-1})*
1	Acetazolamide		0.000 035
3	Ethoxzolamide		0.0014
6a	MK 927		< 0.000 05
10a	O	C_6H_5	< 0.000 05
10c	O	n-C_5H_{11}	< 0.000 05

with the ketone and oxime groups at the 5-position of the thiophene ring. An electron-rich functionality (hydroxyl, methoxy, alkyl or acetoxy moieties) at the 5-position of the thiophene ring decreases the potency of the compounds in inhibiting carbonic anhydrase.

Interactions away from the active site were also explored. The phenyl ring of 5-benzoyl-3-thiophene sulfonamide was functionalized with a variety of substituents at different positions. In this region of the enzyme pocket, electronic effects (electron-withdrawing or electron-donating capabilities), hydrogen bond donators or acceptors do not greatly alter the IC_{50} value of the compound. Rather, steric effects are the dominant factor effecting activity. Bulky or multiple substituents on the phenyl ring dramatically weaken carbonic anhydrase inhibition. Substitution at the *meta* position appears to be more sensitive to steric influences than at the *para* position.

Compounds exhibiting low IC_{50} values were further evaluated for their ability to inhibit carbonic anhydrase in the albino rabbit eye after topical administration (ex vivo assay) [13]. (Instead of using the pH stat assay to determine the carbonic anhydrase activity in the iris-ciliary body homogenate, the modified version of the changing pH principle of Philpot and Philpot described in reference [6] was used.) The compounds were evaluated at a concentration of 2% and demonstrated carbonic anhydrase inhibition from 25–81% (table III).

Conclusion

We have shown that the regiochemistry of the sulfonamide group does not effect the carbonic anhydrase inhibitory activity of thiophene sulfonamides. 5-Substituted 3-thiophenesulfonamides are potent inhibitors of carbonic anhydrase with IC_{50} values in the nanomolar range. However, the ex vivo inhibitory

values of these compounds when administered at a concentration of 2% indicate they have poor ocular penetration and would not be suitable for use as topical agents. In order to decrease intraocular pressure, the carbonic anhydrase enzyme must essentially be totally inhibited [1, 14]. Therefore, a viable topical CAI must have an ex vivo inhibitory value in the high 90 percentile.

Experimental protocols

Chemistry

^{1}H NMR (299.943 MHz) and ^{13}C NMR spectra (75.492 MHz) were obtained in $CDCl_3$ or acetone-d_6 unless otherwise stated, and chemical shifts are reported in d units (parts per million) downfield from tetramethylsilane. Elemental analyses are within ±0.4% of the calculated values and were performed at Robertson Microlit Laboratories. Analytical thin layer chromatography (TLC) was performed on precoated 0.25 mm silica gel 60PF-254, and the spots were visualized with UV or by spraying with a solution of 5% phosphomolybdic acid in ethanol and heated at ca 200 °C for a few minutes. All reactions involving moisture-sensitive reagents were carried out in oven- or flame-dried apparatus under argon (Ar). THF was freshly distilled from calcium hydride or barium oxide and stored over 4 Å molecular sieves under N_2. *n*-Butyllithium (a 1.6 M solution in hexanes, *s*-butyllithium (a 1.3 M solution in cyclohexane), butylmagnesium chloride (a 2.0 M solution in tetrahydrofuran) and hexylmagnesium bromide (a 2.0 M solution in diethyl ether) were purchased from Aldrich and used as received. Unless otherwise stated, all commercial reagents were used as received. All chromatography was completed on silica gel unless indicated otherwise.

*General procedure for the preparation of **8a–8n**. 4-Bromo-2-[1-trimethylsiloxy-1-phenylmethyl]thiophene **8a***
Phenyllithium (2.6 mL, 5.2 mmol, 2 M in cyclohexane-ether) was added dropwise to a –78 °C solution of 4-bromo-2-thiophenecarboxaldehyde **7** (1.0 g, 5.2 mmol) in dry THF (26 mL). After 2 h, another 0.5 mL of phenyllithium was added to the mixture and stirring continued for 30 min. Trimethylsilyl chloride (0.73 mL, 5.7 mmol) was added, the cooling bath was removed and the mixture stirred for another 30 min. The reaction was quenched with water, the layers were separated and the aqueous portion extracted with ethyl ether. The combined organic phases were dried ($MgSO_4$), concentrated and purified by flash chromatography using hexane to give 0.98 g (55%) **8a**: ^{1}H NMR ($CDCl_3$) δ 7.29–7.40 (m, 5H), 7.11 (s, 1H), 6.68 (s, 1H), 5.90 (s, 1H), 0.13 (s, 9H).

*4-Bromo-2-[1-(trimethylsiloxy)pentyl]thiophene **8b***. The compound was purified by flash chromatography using hexane to give 2.24 g (67%) **8b** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.09 (s, 1H), 6.78 (s, 1H), 4.83 (dd, *J* = 5, 7 Hz, 1H), 1.70–1.72 (m, 2H), 1.27–1.35 (m, 4 H), 0.89 (t, *J* = 7 Hz, 3 H), 0.10 (s, 3H).

*4-Bromo-2-[1-(trimethylsiloxy)heptyl]thiophene **8c***. The compound was purified by flash chromatography using hexane to give 1.2 g (67%) **8c** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.09 (d, *J* = 1 Hz, 1H), 6.78 (s, 1H), 4.82 (dd, *J* = 5, 7 Hz, 1H), 1.60–1.80 (m, 2H), 1.20–1.40 (m, 8H), 0.88 (t, *J* = 6 Hz, 3H), 0.10 (s, 9H).

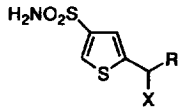
*4-Bromo-2-[1-trimethylsiloxy-1-(4-methoxyphenyl)methyl]-thiophene **8d***. The compound was purified by flash chromatography using 30:1 hexane/ethyl acetate to give 2.48 g (85%) **8d** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.27 (d, *J* = 10 Hz, 2H), 7.17 (s, 1H), 6.85 (d, *J* = 10 Hz, 2H), 6.63 (s, 1H), 5.93 (s, 1H), 3.80 (s, 3H), 0.10 (s, 3H).

*4-Bromo-2-[1-trimethylsiloxy-1-(4-butylphenyl)methyl]thiophene **8e***. The compound was purified by flash chromatography using hexane to give 4.25 g (51%) **8e** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.28 (d, *J* = 8 Hz, 2H), 7.15 (d, *J* = 8 Hz, 2H), 7.10 (s, 1H), 6.68 (s, 1H), 5.87 (s, 1H), 2.60 (t, *J* = 10 Hz, 2H), 1.57 (sextet, *J* = 10 Hz, 2H), 1.37 (sextet, *J* = 10 Hz, 2H), 0.93 (t, *J* = 10 Hz, 3H), 0.12 (s, 9H).

*4-Bromo-2-[1-triethylsiloxy-1-(2-pyridyl)methyl]thiophene **8f***. Protecting group used was triethylsilyl. The compound was purified by flash chromatography using 20:1 hexane/ethyl acetate to give 4.1 g (68%) **8f** as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 8.52 (d, *J* = 5 Hz, 1H), 7.71 (dt, *J* = 2, 8 Hz, 1H), 7.59 (d, *J* = 8 Hz, 1H), 7.17–7.21 (m, 1H), 7.09 (s, 1H), 6.85 (s, 1H), 6.04 (s, 1H), 0.91 (t, *J* = 8 Hz, 9H), 0.62 (q, *J* = 8 Hz, 6H).

*4-Bromo-2-[1-trimethylsiloxy-1-(2-fluorophenyl)methyl]thiophene **8g***. The compound was purified by flash chromatography using hexane to give 4.9 g (48%) **8g** as a colorless oil:

Table III. Ex vivo data.



Compound	*X*	*R*	*IC_{50} (nM) CA (II)*	*Ex vivo % inhibition*
1		Acetazolamide	6	67
3		Ethoxzolamide	0.5	100
6a		MK 927	4	99
9c	OH	n-C_5H_{11}	31	76
9d	OH	4-C6H4OCH3	16	51
10a	O	$C6H_5$	13	81
10c	O	n-C_5H_{11}	14	71
10d	O	4-$C_6H_4OCH_3$	26	53
10e	O	4-$C_6H_4C_4H9$	8.7	53
10j	O	3-C_6H_4F	12	75
10k	O	4-$C_6H_4CO_2H$	3.4	63
10l	O	3-$C_6H_4CO_2H$	11	30
10n	O	3-C_6H_4OH	6.7	53
11a	O	4-$C_6H_4OC(O)CH_3$	12	39
11b	O	4-$C_6H_4OC(O)C_2H_5$	9	41
11c	O	3-$C_6H_4OC(O)CH_3$	3.6	64
11d	O	3-$C_6H_4OC(O)C6H_5$	5.3	64
14a	O	4-$C_6H_4CO_2C_2H_5$	6	40
14b	O	4-$C_6H_4CO_2$-t-C_4H9	3	25
19	O	4-$C_6H_4CH_2OC(O)CH_3$	6	45

^{1}H NMR ($CDCl_3$) δ 7.54 (m, 1H), 7.25 (m, 1H), 6.99–7.17 (m, 3H), 6.72 (s, 1H), 6.26 (s, 1H), 0.12 (s, 9H).

4-Bromo-2-[1-trimethylsiloxy-1-(3,5-difluorophenyl)methyl]-thiophene ***8h***. The compound was purified by flash chromatography using hexane to give 2.55 g (43%) **8h** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.13 (d, J = 1 Hz, 1H), 6.91 (m, 2H), 6.72 (m, 2H), 5.84 (s, 1H), 0.13 (s, 9H).

4-Bromo-2-[1-trimethylsiloxy-1-(3-trifluoromethylphenyl)-methyl]thiophene ***8i***. The compound was purified by flash chromatography using hexane to give 6.76 g (75%) **8i** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.66 (s, 1H), 7.44–7.58 (m, 3H), 7.14 (s, 1H), 6.70 (s, 1H), 5.94 (s, 1H), 0.13 (s, 9H).

4-Bromo-2-[1-trimethylsiloxy-1-(3-fluorophenyl)methyl]thiophene ***8j***. The compound was purified by flash chromatography using hexane to give 4.82 g (23%) **8j** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.28–7.35 (m, 1H), 7.11–7.16 (m, 3H), 6.95–7.02 (m, 1H), 6.70 (s, 1H), 5.89 (s, 1H), 0.12 (s, 9H).

4-Bromo-2-[1-tetrahydropyranyloxy-1-(4-tert-butyldimethylsil-oxymethylphenyl)methyl]thiophene ***8k***. Protecting group used was tetrahydropyranyl. The compound was purified by flash chromatography using 15:1 hexane/ethyl acetate to give 9.3 g (85%) **8k** as a light yellow oil (mixture of diastereomers).

4-Bromo-2-[1-tetrahydropyranyloxy-1-(3-tert-butyldimethylsil-oxymethylphenyl)methyl]thiophene ***8l***. Protecting group used was tetrahydropyranyl. The compound was purified by flash chromatography using 15:1 hexane/ethyl acetate to give 8.4 g (81%) **8l** as a light yellow oil (mixture of diastereomers).

4-Bromo-2-[1-trimethylsiloxy-1-(4-tert-butyldimethylsiloxy-phenyl)methyl]thiophene ***8m***. The compound was purified by flash chromatography using hexane to give 6.8 g (73%) **8m** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.22 (d, J = 9 Hz, 2H), 7.10 (s, 1H), 6.81 (d, J = 9 Hz, 2H), 6.65 (s, 1H), 5.84 (s, 1H), 0.99 (s, 9H), 0.21 (s. 6H), 0.10 (s, 9H).

4-Bromo-2-[1-trimethylsiloxyl-(3-tert-butyldimethylsiloxy-phenyl)methyl]thiophene ***8n***. The compound was purified by flash chromatography using hexane to give 8.45 g (71%) **8n** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.20 (t, J = 6 Hz, 1H), 6.95 (d, J = 6 Hz, 1H), 6.90 (m, 1H), 6.77–6.80 (m, 1H), 6.66 (s, 1H), 5.82 (s, 1H), 0.95 (s. 9H), 0.20 (s, 6H), 0.12 (s, 9H).

General procedure for the prepararion of ***9a–n*** *from* ***8a–n***. *5-[1-Hydroxy-1-phenylmethyl]-3-thiophenesulfonamide* ***9a***

n-BuLi (1.4 mL, 2.3 mmol) was added dropwise to a –100 °C solution of **8a** (0.78 g, 2.3 mmol) in dry THF (46 mL). After 30 min, SO_2 was bubbled over the surface of the solution for 10 min. Ethyl ether (10 mL) was added and the solution warmed to ambient temperature and stirred for 1 h. The solvent was removed in vacuo, the residue taken up in CH_2Cl_2 (46 mL), and *n*-chlorosuccinimide (NCS) (0.34 g, 2.5 mmol) was added. After stirring at ambient temperature for 1 h, the solution was filtered and concentrated. The residue was dissolved in acetone (30 mL), and NH_4OH (10 mL) was added. After 15 min the solution was diluted with water and then extracted with ethyl acetate. The organic phase was washed with water (twice) followed by brine. The organic phase was dried ($MgSO_4$), filtered, and concentrated. The residue was dissolved in THF (25 mL) and tetra-*n*-butylammonium fluoride (TBAF) (2.3 mL, 2.3 mmol) was added. After 20 min reaction was diluted with water and extracted with ethyl acetate. The organic phase was washed with water (twice) followed by brine. The organic phase was dried ($MgSO_4$), filtered, and concentrated. The compound was purified by flash chromatography using 3:2 hexane/ethyl acetate. Recrystallization from chloroform/ethyl acetate/hexane gave 0.21 g (34%) **9a** as a white solid: ^{1}H NMR (acetone-d_6) δ 7.90 (s, 1H), 7.30–7.50 (m, 5H), 7.10 (s, 1H), 6.55 (bs, 2H), 6.05 (d, J = 4 Hz, 1H), 5.46 (d, J = 4 Hz, 1H); ^{13}C NMR (acetone-d_6) δ 154.19, 145.29, 144.91, 129.58, 128.89, 128.45, 127.51, 122.76, 72.35; LRMS *m/e* 269 (M^+).

5-(1-Hydroxypentyl)-3-thiophenesulfonamide ***9b***. The compound was purified by flash chromatography using 40% ethyl acetate/hexane to give 0.98 g (59%) **9b** as a yellow oil: ^{1}H NMR (acetone-d_6) δ 7.82 (s, 1H), 7.20 (s, 1H), 5.35 (bs, 2H), 4.80 (t, J = 5 Hz, 1H), 1.70–2.88 (m, 2H), 1.24–1.48 (m, 4H), 0.88 (t, J = 5 Hz, 3H); ^{13}C NMR (acetone-d_6) δ 152.58, 141.13, 128.67, 121.22, 69.84, 38.59, 27.46, 22.14, 13.67; Anal ($C_9H_{15}NO_3S_2$) C, H, N.

5-[1-Hydroxyheptyl]-3-thiophenesulfonamide ***9c***. The compound was purified by flash chromatography using 40% ethyl acetate/hexane to give 0.21 g (23%) **9c** as a white solid: ^{1}H NMR (acetone-d_6) δ 7.88 (s, 1H), 7.24 (s, 1H), 5.06 (bs, 2H), 4.88–4.89 (m, 1H), 2.43–2.45 (m, 1H), 1.79–1.81 (m, 2H), 1.25–1.31 (m, 8H), 0.86–0.88 (m, 3H); ^{13}C NMR (acetone-d_6) δ 152.74, 141.26, 128.86, 121.07, 70.06, 39.07, 31.47, 28.76, 25.27, 22.34, 13.78; LRMS *m/e* 278 (MH^+); HRMS exact mass calcd for $C_{11}H_{19}NO_3S_2$ 277.0806, found 277.0826; anal ($C_{11}H_{19}NO_3S_2$) C, H, N.

5-[1-Hydroxy-1-(4-methoxyphenyl)methyl]-3-thiophenesulfonamide ***9d***. The compound was purified by flash chromatography using 60% ethyl acetate/hexane to give 0.63 g (52%) **9d** as a yellow oil: ^{1}H NMR (acetone-d_6) δ 7.88 (d, J = 2 Hz, 1H), 7.38 (d, J = 9 Hz, 2H), 7.07 (m, 1H), 6.92 (d, J = 9 Hz, 2H), 6.54 (bs, 2H), 5. 99 (d, J = 4 Hz, 1H), 5.34 (d, J = 4 Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (acetone-d_6) δ 160.70, 154.53, 144.80, 137.29, 128.79, 128.27, 122.55, 114.80, 71.97, 55.58; LRMS *m/e* 299 (M^+); HRMS exact mass calc for $C_{12}H_{13}NO_4S_2$ 299.028601, found 299.0290; anal ($C_{12}H_{13}NO_4S_2$) C, N, H.

5-[1-Hydroxy-1-(4-butylphenyl)methyl]-3-thiophenesulfonamide ***9e***. The compound was not isolated. The crude product was taken on directly to **10e** without purification.

5-[1-Hydroxy-1-(2-pyridyl)methyl]-3-thiophenesulfonamide ***9f***. The compound was purified by flash chromatography using 3:1 ethyl acetate/hexane to give 0.50 g (44%) **9f** as a white foam: ^{1}H NMR (acetone-d_6) δ 8.55 (d, J = 6 Hz, 1H), 7.89 (d, J = 1 Hz, 1H), 7.84 (t, J = 8Hz, 1H), 7.63 (d, J = 8 Hz, 1H), 7.32 (ddd, J = 1, 5, 8 Hz, 1H), 7.27 (d, J = 1 Hz, 1H), 6.56 (br, s, 2H), 6.05 (s, 1H), 5.75 (bs, 1H); ^{13}C NMR (acetone-d_6) δ 162.97, 152.33, 149.85, 144.89, 138.35, 128.66, 124.03, 122.99, 121.34, 72.83; LRMS *m/e* 270 (M^+); HRMS exact mass calc for $C_{10}H_{10}N_2O_3S_2$ 270.0132, found 270.0111.

5-[1-Hydroxy-1-(2-fluorophenyl)methyl]-3-thiophenesulfonamide ***9g***. The compound was not isolated. The crude product was taken on directly to **10g** without purification.

5-[1-Hydroxy-1-(3,5-difluorophenyl)methyl]-3-thiophenesulfonamide ***9h***. The compound was not isolated. The crude product was taken on directly to **10h** without purification.

5-[1-Hydroxy-1-(3-trifluoromethylphenyl)methyl]-3-thiophenesulfonamide ***9i***. The compound was not isolated. The crude product was taken on directly to **10i** without purification.

5-[1-Hydroxy-1-(3-fluorophenyl)methyl]-3-thiophenesulfonamide ***9j***. The compound was not isolated. The crude product was taken on directly to **10j** without purification.

5-[1-Hydroxy-1-(4-hydroxymethylphenyl)methyl]-3-thiophenesulfonamide ***9k***. The compound was purified by flash chromatography using 60% ethyl acetate/hexane to give 0.03 g (31%) **9k** as a colorless oil:.^{1}H NMR (acetone-d_6) δ 7.89 (d, J = 1 Hz, 1H), 7.43 (d, J = 8 Hz, 2H), 7.35 (d, J = 8 Hz, 2H), 7.09 (d, J = 1 Hz, 1H), 6.55 (bs, 2 H), 6.04 (d, J = 4 Hz, 1H), 5.44 (d, J = 4.0 Hz, 1H), 4.62 (d, J = 5 Hz, 2H), 4.23 (t, J = 5 Hz, 1H); 13C NMR (acetone-d_6) δ 153.28, 143.86, 142.84, 142.37, 127.43, 126.85, 126.39, 121.71, 71.27, 63.56; LRMS *m/e* 299 (M^+); HRMS exact mass calc for $C_{12}H_{13}NO_4S_2$ 299.028601, found 299.0267; anal ($C_{12}H_{13}NO_4S_2$) C, H, N.

5-[1-(hydroxy)-1-(3-hydroxymethylphenyl)methyl]-3-thiophenesulfonamide ***9l***. The compound was not isolated. The crude product was taken on directly to **10l** and **10l'** without purification.

5-[1-(Hydroxy)-1-(4-hydroxyphenyl)methyl]-3-thiophenesulfonamide ***9m***. Purification using 50% ethyl acetate/hexane gave 0.26 g (83%) **9m** as a white foam: ^{1}H NMR (acetone-d_6) δ 8.40 (bs, 1H), 7.89 (d, J = 2 Hz, 1H), 7.18 (t, J = 8 Hz, 1H), 7.11 (d, J = 2 Hz, 1H), 6.92–6.97 (m, 2H), 6.75–6.78 (m, 1H), 6.56 (bs, 2H), 5.97 (s, 1H), 5.40 (bs, 1H); ^{13}C NMR (acetone-d_6) δ 158.24, 154.63, 144.58, 136.09, 128.86, 128.22, 122.42, 116.16, 72.03; LRMS *m/e* 285 (M^+); HRMS exact mass calc for $C_{11}H_{11}NO_4S_2$ 285.012951, found 285.0124.

5-[1-Hydroxy-1-(3-hydroxyphenyl)methyl]-3-thiophenesulfonamide ***9n***. The compound was purified by flash chromatography using 3:2 ethyl acetate/hexane to give 0.8 g (88%) **9n** as a light yellow foam: ^{1}H NMR (acetone-d_6) δ 8.40 (bs, 1H), 7.89 (d, J = 2 Hz, 1H), 7.18 (t, J = 8 Hz, 1H), 7.11 (d, J = 2 Hz, 1H), 6.92–6.97 (m, 2H), 6.75–6.78 (m, 1H), 6.56 (bs, 2H), 5.97 (s, 1H), 5.40 (bs, 1H); ^{13}C NMR (acetone-d_6) δ 158.75, 154.03, 146.77, 144.71, 130.60, 128.37, 122.62, 118.58, 115.77, 114.26, 72.19; LRMS *m/e* 285 (M^+); HRMS exact mass calc for $C_{11}H_{11}NO_4S_4$ 285.01295, found 285.0112; anal ($C_{11}H_{11}NO_4S_4$) C, H, N.

General procedure for the prepararion of ***10a–n*** *from* ***9a–n***. *5-[1-Oxo-1-phenylmethyl)-3-thiophenesulfonamide* ***10a***
Jones' reagent (0.095 mL, 0.25 mmol) was added to a solution of **9a** (63 mg, 0.23 mmol) in acetone (5 mL). After 10 min, a few drops of isopropyl alcohol were added, and the solution diluted with water. The solution was extracted with ethyl acetate. The organic phase was washed with water (twice) followed by brine. The organic phase was dried ($MgSO_4$), filtered, and concentrated. The compound was recrystallized from chloroform/ethyl acetate/hexane to give 40 mg (65%) **10a** as white crystals: ^{1}H NMR (acetone-d_6) δ 8.48 (s, 1H), 7.90–7.95 (m, 3H), 7.60–7.75 (m, 3H), 6.80 (bs, 2H); ^{13}C NMR (acetone-d_6) δ 187.71, 146.16, 145.82, 138.08, 136.09, 133.65, 132.43, 129.79, 129.57; LRMS *m/e* 267 (M^+); HRMS exact mass calc for $C_{11}H_9NO_3S_2$ 267.00238, found 266.9989; anal ($C_{11}H_9NO_3S_2$) C, H, N.

5-(1-Oxopentyl)-3-thiophenesulfonamide ***10b***. The compound was purified by recrystallization from chloroform to give 38 mg (81%) **10b** as white crystals: ^{1}H NMR (acetone-d_6) δ 8.22 (s,1H), 7.96 (s, 1H), 5.10 (bs, 2H), 2.90 (t, J = 8 Hz, 2H), 1.73 (p, J = 8 Hz, 2H), 1.4 (sextet, J = 8 Hz, 2H), 0.95 (t, J = 7 Hz, 3H); ^{13}C NMR (acetone-d_6) δ 193.17, 146.89, 142.88, 135.74, 128.63, 38.75, 26.20, 22.14, 13.58; LRMS *m/e* 246 ($M-H)^-$; HRMS exact mass calc for $C_9H_{13}NO_3S_2$ 247.0336, found 247.0331; anal ($C_9H_{13}NO_3S_2$) C, H, N.

5-(1-Oxoheptyl)-3-thiophenesulfonamide ***10c***. The compound was purified by recrystallization from chloroform/hexane to give 31 mg (61%) **10c** as white crystals: ^{1}H NMR (acetone-d_6) δ 8.21 (s, 1H), 7.94 (s, 1H), 5.01 (bs, 2H), 2.89 (t, J = 7 Hz, 2H), 1.73 (p, J = 7 Hz, 2H), 1.30–1.34 (m, 6 H), 0.88 (t, J = 8 Hz, 3H); ^{13}C NMR (acetone-d_6) δ 193.23, 146.87, 142.86, 135.74, 128.64, 39.04, 31.35, 28.69, 24.08, 22.27, 13.77; LRMS *m/e* 276 (MH^+); HRMS exact mass calc for $C_{11}H_{18}NO_3S_2$ (MH^+) 276.0728, found 276.0715; anal ($C_{11}H_{18}NO_3S_2$) C, H, N.

5-[1-Oxo-1-(4-methoxyphenyl)methyl]-3-thiophenesulfonamide ***10d***. The compound was purified by recrystallization from chloroform/ethyl acetate/hexane to give 0.13 g (65%) **10d** as white crystals: ^{1}H NMR (acetone-d_6) δ 9.45 (bs, 1H), 8.43 (d, J = 1 Hz, 1H), 7.95 (d, J = 1Hz, 1 H), 7.89 (d, J = 9 Hz, 2H), 7.04 (d, J = 9 Hz, 2H), 6.81 (bs, 2H); ^{13}C NMR (acetone-d_6) δ 186.65, 165.11, 146.60, 146.28, 135.82, 132.71, 131.94, 130.68, 115.17, 55.11; LRMS *m/e* 297 (M^+); HRMS exact mass calc for $C_{12}H_{11}NO_4S_2$ 297.012951, found 297.0128; anal ($C_{12}H_{11}NO_4S_2$) C, H, N.

5-[1-Oxo-1-(4-butylphenyl)methyl]-3-thiophenesulfonamide ***10e***. The compound was purified by recrystallization from ethyl acetate/hexane to give 1.12 g (71%) **10e** as white crystals: ^{1}H NMR (acetone-d_6) δ 8.45 (d, J = 1 Hz, 1H), 7.93 (d, J = 1 Hz, 1H), 7.85 (d, J = 8 Hz, 2H), 7.45 (d, J = 8 Hz, 2H), 6.78 (bs, 2H), 2.74 (t, J = 8 Hz, 2H), 1.60–1.68 (m, 2H), 1.38 (h, J = 8 Hz, 2H), 0.93 (t, J = 7 Hz, 3H); ^{13}C NMR (acetone-d_6) δ 187.87, 149.90, 146.47, 146.41, 136.28, 135.88, 132.48, 130.45, 129.96, 36.13, 34.10, 22.91, 14.04; LRMS *m/e* 323 (M^+); HRMS exact mass calc for $C_{15}H_{17}NO_3S_2$ 323.06499, found 323.0660; anal ($C_{15}H_{17}NO_3S_2$) C, H, N.

5-[1-Oxo-1-(2-pyridyl)methyl]-3-thiophenesulfonamide ***10f***. The compound was purified by recrystallization from methanol/water to give 0.14 g (58%) **10f** as white crystals: ^{1}H NMR (acetone-d_6) δ 8.83 (d, J = 4 Hz, 1H), 8.61 (d, J = 2 Hz, 1H), 8.44 (d, J = 2 Hz, 1H), 8.21 (d, J = 8 Hz, 1H), 8.11 (dt, J = 2,8 Hz, 1H), 7.75 (ddd, J = 2, 5, 8 Hz, 1H), 6.80 (brs, 2H); ^{13}C NMR (acetone-d_6) δ 182.60, 153.19, 148.92, 145.07, 141.12, 138.21, 137.74, 133.73, 128.13, 123.82; LRMS *m/e* 268 (M^+); HRMS exact mass calc for $C_{10}H_8N_2O_3S_2$ 267.9976, found 267.9946; anal ($C_{10}H_8N_2O_3S_2$) C, H, N.

5-[1-Oxo-1-(2-fluorophenyl)methyl]-3-thiophenesulfonamide ***10g***. The compound was purified by recrystallization from hexane/ethyl acetate to give 0.29 g (66%) **10g** as pale yellow crystals: ^{1}H NMR (acetone-d_6) δ 8.50 (d, J = 1 Hz, 1H), 7.79 (t, J = 1 Hz, 1H), 7.68–7.73 (m, 2 H), 7.34–7.44 (m, 2H), 6.80 (bs, 2H); ^{13}C NMR (acetone-d_6) δ 184.92, 162.02, 158.70, 146.41, 146.08, 137.09, 134.66, 134.55, 133.14, 133.10, 130.99, 127.07, 125.59, 125.54, 117.42, 117.14; LRMS *m/e* 284 ($M-H)^-$; HRMS exact mass calc for $C_{11}H_8FNO_3S_2$ 284.992965, found 284.9925; anal ($C_{11}H_8FNO_3S_2$) C, H, N.

5-[1-Oxo-1-(3,5-difluorophenyl)methyl]-3-thiophenesulfonamide ***10h***. The compound was purified by recrystallization from hexane/ethyl acetate to give 96 mg (57%) **10h** as a white solid: ^{1}H NMR (acetone-d_6) δ 8.51 (s, 1H), 7.99 (s, 1H), 7.52 (m, 2H), 8.40 (m, 1H), 6.79 (brs, 2H); ^{13}C NMR (acetone-d_6) δ 185.33, 165.35, 165.19, 162.04, 161.88, 146.22, 144.61,

141.10, 140.99, 140.88, 137.09, 133.10, 113.11, 112.99, 112.87, 112.76, 108.97, 108.64, 108.29; LRMS *m/e* 303 (M^+); HRMS exact mass calc for $C_{11}H_7F_2NO_3S_2$ 302.9835, found 302.9855; anal ($C_{11}H_7F_2NO_3S_2$) C, H, N.

5-[1-Oxo-1-(3-trifluoromethylphenyl)methyl]-3-thiophenesulfonamide ***10i***. The compound was purified by recrystallization from hexane/ethyl acetate to give 1.73 g (66%) **10i** as a white solid: ^1H NMR (acetone-d_6) δ 8.52 (d, J = 1 Hz, 1H), 8.22 (d, J = 8 Hz, 1H), 8.17 (s, 1H), 8.06 (d, J = 8 Hz, 1H), 7.95 (d, J = 1 Hz, 1H), 7.88 (d, J = 8 Hz, 1H), 6.78 (bs, 2H); ^{13}C NMR (acetone-d_6) δ 187.22, 146.73, 145.49, 139.29, 137.27, 133.91, 133.33, 132.02, 131.58, 131.13, 130.37, 130.32, 130.28, 126.93, 126.68, 126.63, 126.57, 123.31; LRMS *m/e* 336 (MH^+); HRMS exact mass calc for $C_{12}H_8F_3NO_3S_2$ 334.9898, found 334.9874; anal ($C_{12}H_8F_3NO_3S_2$) C, H, N.

5-[1-Oxo-1-(3-fluorophenyl)methyl]-3-thiophenesulfonamide ***10j***. The compound was purified by recrystallization from hexane/ethyl acetate to give 1.22 g (59%) **10j** as a white solid: ^1H NMR (acetone-d_6) δ 8.49 (s,1H), 7.95 (s, 1H), 7.60–7.77 (m, 3H), 7.46–7.52 (m, 1H), 6.79 (bs); ^{13}C NMR (acetone-d_6) δ 187.52, 187.49, 165.43, 162.15, 154.23, 147.05, 140.35, 140.26, 135.64, 132.14, 132.03, 131.64, 126.39, 126.36, 121.02, 120.74, 116.92, 116.62; LRMS *m/e* 285 (M^+); HRMS exact mass calc for $C_{11}H_8FNO_3S_2$ 284.992965, found 284.9939; anal ($C_{11}H_8FNO_3S_2$) C, H, N.

5-[1-Oxo-1-(4-carboxyphenyl)methyl]-3-thiophenesulfonamide ***10k***. The compound was purified by flash chromatography using 20% methanol/chloroform with a small amount of acetic acid to give 0.19 g (89%) **10k** as a white solid: ^1H NMR (acetone-d_6) δ 8.51 (d, J = 1 Hz, 1H), 8.23 (d, J = 8 Hz, 2H), 8.01 (d, J = 8 Hz, 2H), 7.94 (d, J = 1 Hz, 1H), 6.79 (bs, 2H); ^{13}C NMR (acetone-d_6) δ 188.03, 167.24, 146.70, 145.87, 142.00, 137.15, 135.28, 133.39, 131.07, 130.22; LRMS *m/e* 311 (M^+); HRMS exact mass calc for $C_{12}H_9NO_5S_2$ 310.99222, found 310.9915; anal ($C_{12}H_9NO_5S_2$) C, H, N.

5-[1-Oxo-1-(4-formylphenyl)methyl]-3-thiophenesulfonamide ***10k'***. Oxidation was accomplished with manganese dioxide (MnO_2). The compound was purified by flash chromatography using 50% ethyl acetate/hexane to give 16 mg (54%) **10k'** as a light yellow solid: ^1H NMR (acetone-d_6) δ 10.21 (s, 1H), 8.52 (d, J = 1 Hz, 1H), 8.12 (q, J = 10 Hz, 4H), 7.94 (d, J = 1 Hz, 1H), 6.79 (bs, 2H); ^{13}C NMR (acetone-d_6) δ 193.26, 187.99, 146.78, 145.79, 42.99, 140.48, 137.31, 133.49, 130.81, 130.76; LRMS *m/e* 295 (M^+); HRMS exact mass calc for $C_{12}H_9NO_4S_2$ 294.9973, found 294.9970.

5-[1-Oxo-1-(3-carboxyphenyl)methyl]-3-thiophenesulfonamide ***10l***. The compound was purified by recrystallization from THF/hexane to give 0.32 g (45%) **10l** as a white solid: ^1H NMR (acetone-d_6) δ 8.51 (d, J = 1 Hz, 1H), 8.50 (s, 1H), 8.34 (dt, J = 1, 8 Hz, 1H), 8.16 (dt, J = 1, 8 Hz, 1H), 7.96 (d, J = 1 Hz, 1H), 7.77 (t, J = 8 Hz, 1H), 6.81 (bs, 2H); ^{13}C NMR (acetone-d_6) δ 187.69, 167.25, 146.61, 145.83, 138.71, 137.03, 134.72, 134.29, 133.07, 132.58, 131.04, 130.40; LRMS *m/e* 311 (M^+); HRMS exact mass calc for $C_{12}H_9NO_5S_2$ 310.9922, found 310.9928; anal ($C_{12}H_9NO_5S_2$) C, H, N.

5-[1-Oxo-1-(3-formylphenyl)methyl]-3-thiophenesulfonamide ***10l'***. Oxidation was accomplished with MnO_2. The compound was purified by flash chromatography using 2:1 ethyl acetate/hexane to give 0.10 g (67%) **10l'** as a off-white solid: ^1H NMR (acetone-d_6) δ 10.18 (s, 1H), 8.52 (d, J = 1 Hz, 1H), 8.14 (s, 1H), 8.23 (dt, J = 1, 8 Hz, 2H), 7.97 (d, J = 1 Hz, 1H), 7.85 (t, J = 8 Hz, 1H), 6.80 (bs, 2H); ^{13}C NMR (acetone-d_6) δ 192.98, 187.55, 146.63, 145.68, 139.13, 138.18, 137.11, 135.47, 134.05, 133.15, 131.04, 130.92; LRMS *m/e* 313 ($M + NH_4$)$^+$; HRMS exact mass calc for $C_{12}H_9NO_4S_2$ 294.997301, found 294.9971; anal ($C_{12}H_9NO_4S_2$) C, H, N.

5-[1-Oxo-1-(4-hydroxyphenyl)methyl]-3-thiophenesulfonamide ***10m***. The compound was purified by flash chromatography using 50% ethyl acetate/hexane to give 78 mg (78%) **10m** as a colorless oil: ^1H NMR (acetone-d_6) δ 9.45 (bs, 1H), 8.43 (d, J = 1 Hz, 1H), 7.95 (d, J = 1 Hz, 1H), 7.89 (d, J = 9 Hz, 2H), 7.04 (d, J = 9 Hz, 2H), 6.81 (bs, 2H); ^{13}C NMR (acetone-d_6) δ 186.52, 163.32, 146.67, 145.98, 135.64, 132.98, 131.68, 129.63, 116.55; LRMS *m/e* 283 (M^+); HRMS exact mass calc for $C_{11}H_9NO_4S_2$ 282.9973, found 282.9958; anal ($C_{11}H_9NO_4S_2$) C, H, N.

5-[1-Oxo-1-(3-hydroxyphenyl)methyl]-3-thiophenesulfonamide ***10n***. The compound was purified by flash chromatography using 50% ethyl acetate/hexane to give 0.35 g (59%) **10n** as a yellow solid: ^1H NMR (acetone-d_6) δ 8.46 (d, J = 1 Hz, 1H), 7.93 (d, J = 1 Hz, 1H), 7.32–7.46 (m, 3H), 7.15–7.19 (m, 1H), 6.86 (bs, 2H); ^{13}C NMR (acetone-d_6) δ 188.07, 158.89, 146.39, 146.30, 139.66, 136.53, 132.72, 131.16, 121.46, 121.15, 116.54; LRMS *m/e* 283 (M^+); HRMS exact mass calc for $C_{11}H_9NO_4S_2$ 282.9973, found 282.9969; anal ($C_{11}H_9NO_4S_2$) C, H, N.

5-[1-Oxo-1-(4-acetoxyphenyl)methyl]-3-thiophenesulfonamide ***11a***.

A mixture of **10m** (58 mg, 0.20 mmol), pyridine (81 mL, 1.0 mmol) and Ac_2O (94 mL, 1.0 mmol) in THF (4 mL) was stirred at ambient temperature for 1 h. The mixture was diluted with ethyl acetate, and then washed twice with water and once with brine. The organic phase was dried ($MgSO_4$), concentrated and purified by flash chromatography using 50% ethyl acetate/hexane to give 51 mg (75%) **11a** as tan crystals: ^1H NMR (acetone-d_6) δ 8.47 (d, J = 1 Hz, 1H), 7.98 (d, J = 9 Hz, 2H), 7.96 (d, J = 1 Hz, 1H), 7.37 (d, J = 9 Hz, 2H), 6.78 (bs, 2H), 2.32 (s, 3H); ^{13}C NMR (acetone-d_6) δ 187.28, 169.87, 155.96, 146.54, 146.17, 136.64, 135.69, 132.84, 131.85, 123.48, 20.97; LRMS *m/e* 325 (M^+); HRMS exact mass calc for $C_{13}H_{11}NO_5S_2$ 325.00787, found 325.0045; anal ($C_{13}H_{11}NO_5S_2$) C, H, N.

5-[1-Oxo-1-(4-propionoxyphenyl)methyl]-3-thiophenesulfonamide ***11b***.

A mixture of **10m** (0.10 g, 0.35 mmol), propionic acid (26 mL, 0.35 mmol), pyridine (85 mL, 1.05 mmol) and 1-(3-dimethylaminopropyl)-3-ethyl carbodiine (EDCI) (70 mg, 0.37 mmol) in THF (3.5 mL) was stirred at ambient temperature for 20 h. The mixture was diluted with ethyl acetate and washed with water (3 ×), then brine. The organic phase was dried ($MgSO_4$), concentrated and purified by flash chromatography using 1:1 ethyl acetate/hexane to give 77 mg (65%) **11b** as a colorless oil: ^1H NMR (acetone-d_6) δ 8.47 (s, 1H), 7.99 (d, J = 9 Hz, 2H), 7.95 (s, 1H), 6.79 (bs, 2H), 2.67 (q, J = 7 Hz, 2H), 1.21 (t, J = 7 Hz, 3H); ^{13}C NMR (acetone-d_6) δ 187.21, 173.34, 155.96, 146.38, 146.09, 136.59, 135.50, 132.74, 131.79, 123.37, 27.90, 9.02; LRMS *m/e* 339 (M^+); HRMS exact mass calc for $C_{14}H_{13}NO_5S_2$ 339.0235, found 339.0233.

5-[1-Oxo-1-(3-acetoxyphenyl)methyl]-3-thiophenesulfonamide ***11c***.

Pyridine (62 mL, 0.78 mmol) and Ac_2O (74 mL, 0.78 mmol) were added to a solution of **10n** (0.10 g, 0.37 mmol) in THF

(7.4 mL). After 18 h, the mixture was diluted with ethyl acetate and washed with water (3 ×), followed by brine. The organic phase was dried ($MgSO_4$), concentrated and purified by flash chromatography using 1:1 ethyl acetate/hexane to give 0.10 g (83%) **11c** as a colorless oil: ^{1}H NMR (acetone-d_6) δ 8.22 (d, J = 1 Hz, 1H), 7.69 (d, J = 1 Hz, 1H), 7.53 (dd, J = 1, 8 Hz, 1H), 7.37 (t, J = 8 Hz, 1H), 7.39 (s, 1H), 7.18–7.22 (m, 1H), 6.50 (bs, 2H), 2.04 (s, 3H); ^{13}C NMR (acetone-d_6) δ 187.36, 170.09, 152.46, 146.54, 145.82, 139.52, 136.89, 133.03, 131.06, 127.58, 127.46, 123.47, 20.87; LRMS *m/e* 325 (M^+); HRMS exact mass calc for $C_{13}H_{11}NO_5S_2$ 325.00787, found 325.0057; anal ($C_{13}H_{11}NO_5S_2$) C, H, N.

*5-[1-Oxo-1-(3-benzoyloxyphenyl)methyl]-3-thiophenesulfonamide **11d**.*

A mixture of **10n** (0.10 g, 0.35 mmol), benzoic acid (0.043 g, 0.35 mmol), pyridine (85 mL, 1.1 mmol) and EDCI (0.070 g, 0.37 mmol) in THF (3.5 mL) was stirred at ambient temperature for 20 h. Another 0.035 g of EDCI, 0.021 g of benzoic acid and 40 mL of pyridine were added and the mixture stirred for 4 h. The mixture was diluted with ethyl acetate and washed with water (3 ×), then brine. The organic phase was dried ($MgSO_4$), concentrated and purified by flash chromatography using 1:1 ethyl acetate/hexane to give 0.12 g (88%) **11d** as a pale yellow oil: ^{1}H NMR (acetone-d_6) δ 8.50 (d, J = 1 Hz, 1H), 8.21 (d, J = 7 Hz, 2H), 8.00 (d, J = 1 Hz, 1H), 7.59–7.88 (m, 7H), 6.78 (bs, 2H); ^{13}C NMR (acetone-d_6) δ 187.37, 165.87, 152.63, 146.62, 145.85, 139.70, 136.94, 135.16, 133.12, 131.21, 130.51, 130.03, 127.70, 123.62; anal ($C_{18}H_{13}NO_5S_2$) C, H, N.

*5-[1-Oxo-1-(3-(N,N-dimethylmethylamino)-4-hydroxyphenyl)-methyl]-3-thiophenesulfonamide **12** and 5-[1-oxo-1-(3,5-(bis-N,N-dimethylmethylamino)-4-hydroxyphenyl)methyl]-3-thiophenesulfonamide **13***

Formaldehyde (0.21 mL, 2.6 mmol, 37%) and dimethylamine (0.89 mL, 7.9 mmol, 40%) were added to a solution of **10m** (0.25 g, 0.88 mmol) in EtOH (3 mL). The reaction was heated at reflux for 15 h, then concentrated and subjected to flash chromatography using 5:1 chloroform/methanol to give 0.049 g (16%) **12** as a yellow solid: ^{1}H NMR (acetone-d_6) δ 8.39 (d, J = 1 Hz, 1H), 7.92 (d, J = 1 Hz, 1H), 7.81 (dd, J = 2,9 Hz, 1H), 7.67 (d, J = 2 Hz, 1H), 6.85 (d, J = 9 Hz, 1H), 3.82 (s, 2H), 2.38 (s, 6H); ^{13}C NMR (acetone-d_6) δ 187.44, 168.05, 147.07, 146.09, 135.62, 133.66, 131.90. 126.35, 124.04, 60,51, 44.40; LRMS *m/e* 398 (MH^+).

Further elution with 2:1 methanol/ chloroform containing 5% triethylamine gave 0.18 g (51%) **13** as a yellow solid: ^{1}H NMR (acetone-d_6) δ 8.39 (d, J = 1 Hz, 1H), 7.93 (d, J = 1 Hz, 1H), 7.75 (s, 2H), 3.66 (s, 4H), 2.32 (s, 12H); ^{13}C NMR (acetone-d_6) δ 186.36, 165.03, 146.76, 146.20, 135.47, 132.12, 131.56, 131.51, 128.89, 123.76, 116.81, 62.74, 44.42; LRMS *m/e* 340 (M^+); HRMS exact mass calc for $C_{14}H_{16}N_2O_4S_2$ 340.05515, found 340.0570.

*5-[1-Oxo-1-(4-carboethoxyphenyl)methyl]-3-thiophenesulfonamide **14a***

Compound **10k** (0.10 g, 0.32 mmol) was added to a solution of *o*-ethylisourea (0.19 g, 1.1 mmol) in THF (1.6 mL). The solution was heated at 50 °C for 72 h, and then cooled, filtered through a plug of celite and concentrated. Purification by flash chromatography using 35% ethyl acetate/hexane gave 0.084 g (74%) **14a** as a white solid: ^{1}H NMR (acetone-d_6) δ 8.5 (d, J = 1 Hz, 1H), 8.2 (d, J = 8 Hz, 2H), 8.1 (d, J = 8 Hz, 2H), 7.92 (d, J = 1 Hz, 2H), 6.8 (brs, 2H), 4.4 (q, J = 7 Hz, 2H), 1.39 (t, J = 7 Hz, 3H); ^{13}C NMR (acetone-d_6) δ 188.0, 166.4, 146.7, 145.8, 142.0, 137.2, 135.2, 133.4, 130.8, 130.2, 62.1, 14.5; LRMS *m/e* 338 ($M-H)^-$; HRMS exact mass calc for $C_{14}H_{13}NO_5S_2$ 339.0235, found 339.0216; anal ($C_{14}H_{13}NO_5S_2$) C, H, N.

*5-[1-Oxo-1-(4-carbo-t-butoxyphenyl)methyl]-3-thiophenesulfonamide **14b***

Compound 10k (0.11 g, 0.35 mmol) was added to a solution of *o-t*-butylisourea (0.11 g, 0.53 mmol) in CH_2Cl_2 (1.75 mL). The solution was heated at 50 °C for 2 h. An additional 2 equiv of *o-t*-butylisourea was added and the reaction heated at 50 °C for another 2 h. The reaction was diluted with THF and absorbed onto silica. Purification by flash chromatography using 30% ethyl acetate/hexane gave 0.087 g (68%) **14b** as a white solid: ^{1}H NMR (acetone-d_6) δ 8.50 (d, J = 1 Hz, 1H), 8.16 (d, J = 9 Hz, 2H), 8.00 (d, J = 9 Hz, 2H), 7.93 (d, J = 1 Hz, 1H), 6.79 (brs, 2 H), 1.61 (s, 9H); ^{13}C NMR (acetone-d_6) δ 188.01, 165.60, 146.66, 145.90, 141.67, 137.08, 136.68, 133.40, 130.65, 130.10, 82.40, 28.17; LRMS *m/e* 368 (M^+).

*5-[1-Oxo-1-(4-carbo-(2-dimethylamino)ethoxyphenyl)methyl]-3-thiophenesulfonamide **14c***

Compound **10k** (0.25 g, 0.80 mmol) was added to a solution of *o*-(2-dimethylamino) ethoxyisourea (0.60 g, 2.8 mmol) in THF (4 mL). The solution was heated at 50 °C for 12 h. An additional 0.60 g of *o*-(2-dimethylamino)ethoxyisourea was added and the reaction heated at 50 °C for another 12 h. The reaction was filtered and concentrated. Purification by flash chromatography using 5% methanol/chloroform gave 0.069 g (22%) **14c**: ^{1}H NMR (acetone-d_6) δ 8.47 (d, J = 1 Hz, 1H), 8.29 (d, J = 9 Hz, 2H), 8.00 (d, J = 9 Hz, 2H), 7.89 (d ,J = 1 Hz, 1H), 4.73 (t, J = 5 Hz, 2H), 3.65 (t, J = 5 Hz, 2H), 3.03 (s, 6H); ^{13}C NMR (acetone-d_6) δ 188.70, 166.82, 146.62, 145.96, 142.67, 137.73, 134.41, 133.75, 131.57, 130.52, 60.60, 57.43, 44.07; LRMS *m/e* 383 (MH^+); HRMS exact mass calc for $C_{16}H_{19}N_2O_5S_2$ 383.0735, found 383.0737.

*5-[1-Oxo-1-(3-carbo-t-butoxyphenyl)methyl]-3-thiophenesulfonamide **14d***

Compound **10l** (0.10 g, 0.32 mmol) was added to a solution of *o-t*-butylisourea (0.13 g, 0.64 mmol) in THF (1.75 mL). The solution was heated at 50 °C for 2 h. An additional 0.26 g of *o-t*-butylisourea was added and the reaction heated at 50 °C for another 2 h. The reaction was cooled, filtered through a plug of celite and concentrated. Purification by flash chromatography using 30% EtOAc/hexane gave 0.080 g (68%) **14d** as a white solid: ^{1}H NMR (acetone-d_6) δ 8.5 (d, J = 1 Hz, 1H), 8.34 (m, 1H), 8.25 (m, 1H), 8.12 (m, 1H), 7.94 (d, J = 1 Hz, 1H), 7.74 (m, 1H), 6.8 (brs, 2H), 1.6 (s, 9H); ^{13}C NMR (acetone-d_6) δ 187.1, 165.1, 146.3, 145.4, 138.2, 136.6, 134.0, 133.6, 133.5, 132.7, 130.4, 129.9, 82.2, 28.2; LRMS *m/e* 368 (M^+); HRMS exact mass calc for $C_{16}H_{17}NO_5S_2$ 367.0548, found 310.9928 ($M-C_4H_8$); anal ($C_{16}H_{17}NO_5S_2$) C, H, N.

*5-[1-Tetrahydropyranyloxy-1-(4-hydroxymethylphenyl)methyl]-3-thiophenesulfonamide **16***

TBAF (2.1 mL, 2.1 mmol) was added to a solution of 5-[1-tetrahydropyranyloxy-1-(4-*tert*-butyldimethylsiloxymethylphenyl)methyl]-3-thiophenesulfonamide (0.96 g, 1.9 mmol) in THF (20 mL). After 30 min, the reaction was quenched with water and ethyl acetate was added. The organic phase was washed twice with water, once with brine, then dried ($MgSO_4$) and concentrated. Purification by flash chromatography using 60% ethyl acetate/hexane gave 0.74 g (100%) **16** as an off-white foam (mixture of diastereomers): ^{1}H NMR (acetone-d_6) δ 7.97 (s), 7.95 (s), 7.32–7.48 (s), 6.97 (s), 6.60 (bs), 6.55 (bs), 6.05 (s), 5.98 (s), 4.82–4.85 (m), 4.58–4.68 (m), 4.17–4.28 (m), 3.90–3.97 (m), 3.68–3.75 (m), 3.40–3.56 (m), 1.44–1.98 (m).

5-[1-Hydroxy-1-(4-formylphenyl)methyl]-3-thiophenesulfonamide ***17***

A mixture of **16** (120 mg, 0.32 mmol), 4 Å molecular sieves, and 4-methylmorpholine *N*-oxide (NMO) (56 mg, 0.48 mmol) in CH_2Cl_2 was stirred for 15 min before TPAP (5.6 mg, 0.16 mmol) was added. After 4 h, the mixture was filtered through a plug of silica, eluting with ethyl acetate. The filtrate was concentrated and the residue purified by flash chromatography using 50% ethyl acetate/hexane to give 42 mg (34%) of a colorless oil.

The above product (63 mg, 0.17 mmol) and a catalytic amount of TsOH were added to 5 mL of methanol. After 4 h at ambient temperature, the solution was diluted with ethyl acetate and washed with saturated $NaHCO_3$ followed with water (3 ×) and brine. The solution was dried over $MgSO_4$ and the solvent removed under vacuum to afford 47 mg (93%) **17** as a clear colorless oil: ^{1}H NMR (acetone-d_6) δ 10.04 (s, 1H), 7.94 (d, J = 8 Hz, 2H), 7.93 (s, 1H), 7.73 (d, J = 8 Hz, 2H), 7.18 (s, 1H), 6.58 (bs, 2H), 6.20 (d, J = 4 Hz, 1H) 5.77 (d, J = 4 Hz, 1H); ^{13}C NMR (acetone-d_6) δ 193.18, 152.98, 151.60, 145.00, 137.49, 130.86, 128.86, 128.06, 123.12, 71.78; LRMS *m/e* 297 (M^+); HRMS exact mass calc for $C_{12}H_{11}NO_4S_2$ 297.012951, found 297.0128.

5-[1-Hydroxy-1-(4-acetoxymethylphenyl)methyl]-3-thiophenesulfonamide ***18***

Pyridine (0.23 mL, 2.9 mmol) and Ac_2O (0.32 mL, 2.9 mmol) were added to a solution of **16** (0.74 g, 1.9 mmol) in CH_2Cl_2 (19 mL). After 15 h, an additional 0.23 mL of pyridine and 0.32 mL of Ac_2O were added. After 9 h the reaction was quenched with water and extracted with ethyl acetate. The combined organic portions were dried ($MgSO_4$) and concentrated. The crude product was dissolved in 19 mL of methanol and a catalytic amount of TsOH was added. After 3.5 h, the mixture was washed twice with water, and then once with brine. The organic portion was dried ($MgSO_4$), concentrated and purified by flash chromatography using 1:1 ethyl acetate/hexane to give 0.37 g (77%) **18** as a colorless oil: ^{1}H NMR (acetone-d_6) δ 7.90 (s, 1H), 7.48 (d, J = 8 Hz, 2H), 7.37 (d, J = 8 Hz, 2H), 7.12 (s, 1H), 6.55 (bs, 2H), 6.08 (s, 1H), 5.50 (bs, 1H), 5.10 (s, 2H), 2.08 (s, 3H); ^{13}C NMR (acetone-d_6) δ 171.33, 153.91, 145.10, 144.88, 137.37, 129.35, 128.45, 127.58, 122.70, 72.04, 66.24, 20.70; LRMS *m/e* 359 (M + NH_4)$^+$; HRMS exact calc for $C_{14}H_{15}NO_5S_2$ 339.023516, found 339.0209.

5-[1-Oxo-1-(4-acetoxymethylphenyl)methyl]-3-thiophenesulfonamide ***19***

Compound **18** (0.20 g, 0.60 mmol) was added to 6 mL of acetone. To the solution was added Jones' reagent (0.22 mL, 0.60 mmol). The solution was stirred at ambient temperature for 15 min and then a few drops of isopropyl alcohol was added. The solution was diluted with water and extracted with ethyl acetate. The organic phase was washed with water (twice) followed by brine. The organic phase was dried ($MgSO_4$), filtered and concentrated. Recrystallization from ethyl acetate/hexane gave 0.17 g (86%) **19** as white crystals: ^{1}H NMR (acetone-d_6) δ 8.47 (d, J = 1 Hz, 1H), 7.93 (s, 1H), 7.92 (d, J = 8 Hz, 2H), 7.62 (d, J = 8 Hz, 2H), 6.80 (bs, 2H), 5.22 (s, 2H), 2.10 (s, 3H); ^{13}C NMR (acetone-d_6) δ 187.96, 171.32, 146.55, 146.24, 143.13, 137.88, 136.65, 132.93, 130.44, 129.11, 65.81, 20.69; LRMS *m/e* 340 (MH^+); anal ($C_{14}H_{13}NO_5S_2$) C, H, N.

5-[1-Oxo-1-(4-hydroxymethylphenyl)methyl]-3-thiophenesulfonamide ***20***

K_2CO_3 (0.19 g, 1.4 mmol) was added to a solution of **19** (0.18 g, 0.53 mmol) in MeOH (4.7 mL). After 2.5 h, the reaction was quenched with 1 N HCl and diluted with ethyl acetate. The organic phase was washed with water (twice), followed by brine and then dried ($MgSO_4$) and concentrated to give 0.15 g (95%) **20**: ^{1}H NMR (acetone-d_6) δ 8.46 (d, J = 1 Hz, 1H), 7.93 (d, J = 1 Hz, 1H), 7.89 (d, J = 8 Hz, 2H), 7.59 (d, J = 8 Hz, 2H), 6.79 (bs, 2H), 4.77 (d, J = 5 Hz, 2H), 4.51 (t, J = 5 Hz, 1H); ^{13}C NMR (acetone-d_6) δ 187.99, 149.33, 146.45, 146.40, 136.83, 136.34, 132.65, 130.25, 127.60, 64.12; LRMS *m/e* 297 (M^+); HRMS exact mass calc for $C_{12}H_{11}NO_4S_2$ 297.012951, found 297.0153; anal ($C_{12}H_{11}NO_4S_2$) C, H, N.

5-[1-Methoxy-1-(4-hydroxymethylphenyl)methyl]-3-thiophenesulfonamide ***21a***

TsOH (3 mg) was added to a solution of **9k** (0.62 g, 1.6 mmol) in methanol. After 4 h, the reaction was incomplete. Another 3 mg of TsOH was added and stirring continued for another 1 h. Another 3 mg of TsOH was added and the solution heated at 50 °C for 1 h. The solvent was removed in vacuo and the residue dissolved in water and neutralized with saturated sodium bicarbonate. The water was extracted with ethyl acetate and the combined organic phases were dried ($MgSO_4$) and concentrated. Purification by flash chromatography using 60% ethyl acetate/hexane gave 0.12 g (24%) **21a** as a pale yellow solid: ^{1}H NMR (acetone-d_6) δ 3.35 (s, 3H), 4.24 (t, J = 6 Hz, 1H), 4.64 (d, J = 6 Hz, 2H), 5.56 (s, 1H) 6.56 (brs, 2H), 7.08 (d, J = 1 Hz, 1H), 7.39 (s, 4H), 7.94 (d, J = 1Hz, 1H); ^{13}C NMR (acetone-d_6) δ 57.0, 64.4, 81.0, 123.6, 127.8, 127.9, 129.0, 140.6, 143.7, 144.7, 150.9; LRMS *m/e* 313 (M^+).

5-[1-Methoxy-1-(3-trifluoromethylphenyl)methyl]-3-thiophenesulfonamide ***21b***

Sodium borohydride (0.027 g, 0.72 mmol) was added to a 0 °C solution of **10i** (0.2 g, 0.60 mmol) in methanol (25 mL). After 20 min, the reaction was quenched with water and extracted with ethyl acetate. The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was dissolved in methanol (10 mL) and TsOH (0.11 g, 0.60 mmol) was added to the solution. The solution was heated to reflux for 24 h, then cooled and concentrated. The residue was dissolved in ethyl acetate and water was added. The solution was neutralized with a saturated sodium bicarbonate solution and the layers were separated. The aqueous portion was extracted with ethyl acetate. The combined organic phases were dried ($MgSO_4$), concentrated and purified by flash chromatography using 30% ethyl acetate/hexane to give 0.16 g (76%) **21b** as a white solid: ^{1}H NMR (acetone-d_6) δ 7.99 (d, J = 2 Hz, 1H), 7.66–7.80 (m, 4H), 7.23–7.24 (m, 1H), 6.59 (bs, 2H), 5.76 (s, 1H), 3.41 (s, 3H); ^{13}C NMR (acetone-d_6) δ 149.68, 145.16, 143.91131.85, 131.73, 131.30, 130.90, 129.66, 127.35, 126.14, 126.09, 126.03, 124.47, 124.42, 124.36, 124.32, 123.74, 80.71, 57.40; LRMS *m/e* 369 (M + NH_4)$^+$; HRMS exact mass calc for $C_{13}H_{12}F_3NO_3S_2$ 351.02107, found 351.0207; anal ($C_{13}H_{12}F_3NO_3S_2$) C, H, N.

5-[1-Acetoxy-1-phenylmethyl]-3-thiophenesulfonamide ***22***

To a solution of **9a** (160 mg, 0.59 mmol) in THF (5 mL) was added acetic anhydride (0.12 mL, 1.3 mmol), pyridine (0.11 mL, 1.3 mmol) and a catalytic amount of 4-dimethylaminopyridine. The mixture was stirred at ambient temperature for 1 h, then another 2.2 equiv of acetic anhydride (0.12 mL, 1.3 mmol) and pyridine (0.11 mL, 1.3 mmol) were added. After another 1 h, the mixture was diluted with ethyl acetate and washed twice with water. The combined extracts were dried ($MgSO_4$), concentrated, and purified by flash chromatography using 65% ethyl acetate/hexane to give 18 mg (9.8%) **22** and 24 mg of polyacylated product. The polyacylated product was dissolved

in ethyl ether and saturated sodium bicarbonate solution was added. After stirring at ambient temperature for 16 h, the material was processed as above to give another 2.3 mg of **22**. The total yield of **22** was 11%: ^{1}H NMR (acetone-d_6) δ 7.91 (s, 1H), 7.37–7.41 (m, 5H), 7.21 (s, 1H), 6.99 (s, 1H), 5.11 (bs), 2.16 (s, 3H); ^{13}C NMR (acetone-d_6) δ 169.89, 147.05, 141,32, 138.32, 129.99, 128.95, 126.89, 123.97, 72.29, 21.16; LRMS *m/e* 311 (M^+); HRMS exact mass calc for $C_{13}H_{13}NO_4S_2$ 311.02860, found 311.0278.

5-[1-Hydroxyimino-1-(4-methoxyphenyl)methyl])-3-thiophenesulfonamide ***23a***

A solution of **10d** (0.10 g, 0.34 mmol) and hydroxylamine hydrochloride (0.23 g, 3.4 mmol) in pyridine (5.0 mL) was placed in a sealed tube and heated to 50 °C. After 24 h, the mixture was cooled, diluted with ethyl acetate and washed three times with water, then once with brine. The combined extracts were dried ($MgSO_4$) and concentrated. Recrystallization from chloroform/ethyl acetate gave 0.070 g (66%) **23a** as a white solid (mixture of *E* and *Z* isomers): ^{1}H NMR (acetone-d_6) δ 11.54 (s), 10.58 (s), 8.22 (s), 7.96 (s), 7.40–7.48 (m), 7.00–7.08 (m), 6.60–6.68 (m), 3.86 (s). ^{13}C NMR (acetone-d_6) δ 161.87, 161.70, 150.73, 145.38, 145.09, 144.22, 135.80, 132.93, 132.07, 132.00, 131.96, 131.69, 131.63, 130.10, 129.77, 129.62, 126.32, 124.94, 114.90, 114.77, 60.61, 55.76; LRMS *m/e* 312 (M^+); HRMS exact mass calc for $C_{12}H_{12}N_2O_4S_2$ 312.023850, found 312.0247; anal ($C_{12}H_{12}N_2O_4S_2$) C, H, N.

5-[1-Hydroxyimino-1-phenylmethyl]-3-thiophenesulfonamide ***23b***

A solution of **10a** (0.052 g, 0.19 mmol) and hydroxylamine hydrochloride (0.14 g, 1.9 mmol) in pyridine (5.0 mL) was placed in a sealed tube and heated to 50 °C. After 24 h, the mixture was cooled, diluted with ethyl acetate and washed three times with water, then once with brine. The combined extracts were dried ($MgSO_4$) and concentrated. Recrystallization from ethyl acetate/hexane gave 0.033 g (62%) **23b** as a white solid (mixture of *E* and *Z* isomers): ^{1}H NMR (acetone-d_6) δ 11.69 (bs), 10.65 (bs), 8.25 (s), 7.98)s), 7.37–7.59 (m), 7.02 (s), 6.58–6.64 (m); ^{13}C NMR (acetone-d_6) δ 151.05, 144.19, 137.32, 135.40, 133.06, 130.79, 130.29, 130.20, 130.07, 129.93, 129.70, 129.56, 129.48, 126.34; LRMS *m/e* 283 (MH^+); HRMS exact mass calc for $C_{11}H_{10}N_2O_3S_2$ 282.01329, found 282.0101; anal ($C_{11}H_{10}N_2O_3S_2$) C, H, N.

5-(1-Hydroxyiminopentyl)-3-thiophenesulfonamide ***23c***

A solution of **10b** (0.10 g, 0.40 mmol) and hydroxylamine hydrochloride (0.28 g, 4.0 mmol) in pyridine (5.0 mL, 2.2 mmol) was placed in a sealed tube and heated to 50 °C. After 15 h, the mixture was cooled, diluted with ethyl acetate and washed three times with water, then once with brine. The combined extracts were dried ($MgSO_4$) and concentrated. TLC showed the reaction to be incomplete. The mixture was redissolved in pyridine (5 mL) and hydroxylamine hydrochloride (0.28 g, 4.0 mmol) was added. The reaction vessel was sealed and heated at 60 °C for 20 h. The mixture was processed as described above, and then the residue was flash chromatographed using 30% ethyl acetate/hexane to give 0.078 g (74%) **23c** as a white solid (mixture of *E* and *Z* isomers): ^{1}H NMR (acetone-d_6) δ 11.12 (s), 10.50 (s), 8.16 (s), 7.92 (s), 7.78 (s), 7.55 (s), 6.64 (bs, 2 H), 2.68–2.80 (m, 2H), 1.56–1.67 (m, 2H), 1.36–1.45 (m, 2H), 0.89–0.95 (m,3H); ^{13}C NMR (acetone-d_6) δ 154.66, 149.38, 145.45, 144.32, 144.18, 134.94, 132.60, 129.84, 127.10, 124.12, 33.42, 26.23, 23.40, 22.93, 14.03, 13.98; LRMS *m/e* 262 (M^+); HRMS exact mass calc for $C_9H_{14}N_2O_3S_2$ 262.044586, found 262.0415; anal ($C_9H_{14}N_2O_3S_2$) C, H, N.

2-Hexyl-4-bromothiophene ***25***

Potassium *t*-butoxide (1.9 g, 16 mmol) was added to a solution of pentyltriphenylphosphonium bromide (0.50 g, 16 mmol) in THF (105 mL). After 1 h, a solution of 4-bromo-2-thiophenecarboxaldehyde **7** (2.0 g, 10.5 mmol) in THF (20 mL) was added to the mixture and stirring was continued for another hour. The reaction was quenched with water and the organic layer was separated and washed twice with water, and then once with brine. The organic phase was dried ($MgSO_4$), concentrated and purified by flash chromatography using hexane to give 2.2 g (85.5%) of a colorless oil. Wilkenson's catalyst (0.22 g) was added to a solution of the above product in methanol. The mixture was stirred under an atmosphere of H_2 for 16 h. The solvent was evaporated and the residue flash chromatographed using hexane to give 2.2 g (98.9%) **25** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.01 (s, 1H), 6.71 (s, 1H), 2.77 (t, *J* = 7 Hz, 2H), 1.65 (m, 2H), 1.28–1.35 (m, 6H), 0.89 (t, *J* = 7 Hz, 3H).

5-Hexyl-3-thiophenesulfonamide ***26***

n-BuLi (4.9 mL, 7.8 mmol) was added dropwise to a –100 °C solution of **25** (1.9 g, 7.8 mmol) in dry THF (78 mL). After 30 min, SO_2 was bubbled over the surface of the solution for 10 min. Ethyl ether (20 mL) was added and the solution warmed to ambient temperature and stirred for 2.5 h. The solvent was removed in vacuo, the residue taken up in CH_2Cl_2 (78 mL), and NCS (1.2 g, 8.6 mmol) was added. After stirring at ambient temperature for 2 h, the solution was filtered and concentrated. The residue was dissolved in acetone (50 mL), and NH_4OH (10 mL) was added. After 10 min the solution was diluted with water and then extracted with ethyl acetate. The organic phase was washed with water (twice) followed by brine. The organic phase was dried ($MgSO_4$), filtered, and concentrated. The compound was purified by flash chromatography using 3:1 hexane/ethyl acetate to give 1.24 g (64%) **26** as a pale yellow solid: ^{1}H NMR (acetone-d_6) δ 7.76 (d, *J* = 1 Hz, 1H), 7.07 (d, *J* = 1 Hz, 1H), 5.21 (bs, 2H), 2.76 (q, *J* = 8 Hz, 2H), 1.65 (p, *J* = 8 Hz, 2H), 1.28–1.38 (m, 6 H), 0.87 (t, *J* = 7 Hz, 3H); ^{13}C NMR (acetone-d_6) δ 149.39, 141.13, 127.47, 121.61, 31.23, 31.06, 29.80, 28.45, 22.25, 13.76; LRMS *m/e* 247 (M^+); HRMS exact mass calc for $C_{10}H_{17}NO_2S_2$ 247.07007, found 247.0684; anal ($C_{10}H_{17}NO_2S_2$) C, H, N.

Pharmacology

In vitro inhibition of human carbonic anhydrase II

Inhibition of human carbonic anhydrase II (Sigma C6156) was assessed by using a modified version of the changing pH principle of Philpot and Philpot [10] The IC_{50} was determined from the enzyme activity. The enzyme activity is the time required to neutralize a buffered solution of enzyme and, where desired, inhibitor, by a 100 mL/min^2 stream of CO_2 gas. A stock solution of the buffer consisted of 30.0 mL of 1 M Na_2CO_3 and 20.6 mL of 1 M $NaHCO_3$ made up to a volume of 100 mL. All reagents were kept below 5 °C. To a reaction vessel in which CO2 flow was carefully stabilized was added 0.4 mL of phenol red, followed by the enzyme (dilution and volume will vary), and where desired, a 0.01–100 mg/L solution of inhibitor. The volume was immediately made up to 0.7 mL with water. Buffer (0.1 mL) was added rapidly and timing begun with a stop watch. The run ended when the indicator turned from red to yellow. The IC_{50} was obtained from a plot of time (s) versus inhibitor concentration (nM).

Ex vivo studies
Rabbit iris and ciliary body was obtained and prepared as described in reference [12]. Instead of using the pH stat assay to determine the carbonic anhydrase activity in the iris-ciliary body homogenate, the changing pH principle of Philpot and Philpot described in reference [10] was used.

Reaction of sulfonamides with cysteine
The protocol used in this assay is described in reference [11].

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