5-Substituted 3-thiophenesulfonamides as carbonic anhydrase inhibitors

K Chow, R Lai, JM Holmes, M Wijono, LA Wheeler, ME Garst

Department of Chemical Sciences and Biological Sciences, Allergan Inc, 2525 Dupont Drive, Irvine, CA 92715, USA

(Received 21 July 1995; accepted 31 October 1995)

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.

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 main-



tained 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 14ad are obtained from the acids 10k and 10l (scheme 4). Compound 15, an intermediate to compounds 17–20, is desilvlated 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: $R_1 = n - C_4H_9$; 9c: $R_1 = n - C_6H_{13}$; 9d: $R_1 = 4 - C_6H_4OCH_3$; 9e: $R_1 = 4 - C_6H_4 - n - C_6H_9$; 9f: $R_1 = 2 - C_5H_4N$; 9g: $R_1 = 2 - C_6H_4F$; 9h: $R_1 = 3, 5 - C_6H_3F_2$; 9i: $R_1 = 3 - C_6H_4CF_3$; 9j: $R_1 = 3 - C_6H_4F$; 9k: $R_1 = 4 - C_6H_4CH_2OH$; 9l: $R_1 = 3 - C_6H_4CH_2OH$; 9m: $R_1 = 4 - C_6H_4OH$; 9n: $R_1 = 3 - C_6H_4OH$.



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



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

177





Scheme 6.

philic attack by cysteine [12]. None of the compounds were found to be reactive (table II).

Placement of the sulfonamide functionality at the 3position 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.

Scheme 5.

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 IC₅₀ 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 nucleoTable I. CA inhibition.

H ₂ NO ₂ S							
		ζR					
		s [x					
Compoun	d X	R I	C ₅₀ (nM) CA (II)				
1	Acetazolan	nide	6				
3	Ethoxzolan	nide	0.5				
6a	MK 927	7	4				
9a	OH	C_6H_5	74				
9b	OH	$n - \dot{C}_4 H_9$	32				
9c	OH	$n-C_5H_{11}$	31				
9d	ОН	4-C ₆ H ₄ OCH ₃	16				
9f	OH	$2-C_5H_4N$	240				
9k	OH	4-C ₆ H ₄ CH ₂ OH	41				
9m	OH	4-C ₆ H ₄ OH	26				
9n	OH	3-C ₆ H ₄ OH	37				
17	OH	4-C ₆ H₄CHO	18				
18	OH	$4-C_6H_4CH_2OC(O)CH$	H ₃ 21				
10a	0	C_6H_5	13				
10b	0	$n-C_4H_9$	27				
10c	0	$n-C_5H_{11}$	14				
10d	0	$4-C_6H_4OCH_3$	26				
10e	0	$4 - C_6 H_4 C_4 H_9$	8.7				
101	0	$2-C_5H_4N$	19				
10g	0	$2-C_6H_4F$	18				
10N 10:	0	$3, 5 - C_6 H_3 F_2$	15				
101	0	$3 - C_6 \Pi_4 C \Gamma_3$	8.3				
10j 10k	0	3-С ₆ п ₄ г 4 С Ц СО Ц	12				
10k	0	4-C H CHO	J.4 13				
101	Õ	3-C-H-CO-H	13				
101	ŏ	3-C.H.CHO	73				
10m	Õ	4-C₄LOH	17				
10n	Õ	3-C ₄ H ₄ OH	6.7				
11a	0	4-C ₆ H ₄ OC(O)CH ₃	12				
11b	0	4-C ₆ H ₄ OC(O)C ₂ H ₅	9				
11c	0	3-C ₆ H ₄ OC(O)CH ₃	3.6				
11d	0	3-C ₆ H ₄ OC(O)C ₆ H ₅	5.3				
12	0	4-OH-3-CH ₂ NMe ₂ C ₆	H₄ 30				
13	0	3,5-CH2NMe ₂ 4-OHC	₆ H₄ 155				
14a	0	$4-C_6H_4CO_2C_2H_5$	6				
14b	0	$4-C_6H_4CO_2tC_4H_9$	3				
14c	0	$4-C_6H_4CO_2CH_2CH_2NN$	Me_2 25				
14d	0	$3-C_6H_4CO_2tC_4H_9$	25				
19	0	$4-C_6H_4CH_2OC(O)CH$	\mathbf{H}_3 6				
20	0	$4-C_6H_4CH_2OH$	17				
218	OCH ₃	$4-C_6H_4CH_2OH$	13				
410 22		$3-C_6H_4CF_3$	18				
44 23o		L_6 L_6 H_5	90				
23a 73h	NOU	4-U6H4UCH3 C6U	51 52				
23c	NOU	соп ₅ "С Ц	55 22				
26	H	<i>п-</i> С ₄ П9 n-С-Н	22				
		<i>n</i> -C ₅ II ₁₁	<u> </u>				

Table II. Cystelle reactivity.								
H ₂ NO ₂ S K								
Compound	X	R	Cysteine reaction (min ⁻¹)					
1	Acetazolamide		0.000 035					
3	Ethoxzolamide		0.0014					
6 a	MK 927		< 0.000 05					
10a	0	C_6H_5	< 0.000 05					
10c	Ο	$n-C_5H_{11}$	< 0.000 05					

Table II Cysteine reactivity

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 (electronwithdrawing 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}^{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

¹H NMR (299.943 MHz) and ¹³C NMR spectra (75.492 MHz) were obtained in CDCl₃ 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 $\pm 0.4\%$ 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 etha-nol and heated at ca 200 °C for a few minutes. All reactions involving moisture-sensitive reagents were carried out in ovenor 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 (MgSO₄), concentrated and purified by flash chromatography using hexane to give 0.98 g (55%) **8a**: ¹H NMR (CDCl₃) 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: ¹H NMR (CDCl₃) 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: ¹H NMR (CDCl₃) 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: ¹H NMR (CDCl₃) 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: ¹H NMR (CDCl₃) 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: ¹H NMR (CDCl₃) 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.

H₂NO₂S

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	<i>n</i> -C ₅ H ₁₁	31	76
9d	OH	4-C6H4OCH3	16	51
10a	0	C6H5	13	81
10c	0	$n-C_5H_{11}$	14	71
10d	0	4-C ₆ H₄OCH ₃	26	53
10e	0	4-C ₆ H₄C₄H9	8.7	53
10j	0	3-C ₆ H₄F	12	75
10k	0	$4-C_6H_4CO_2H$	3.4	63
101	0	3-C ₆ H ₄ CO ₂ H	11	30
10n	0	3-C ₆ H₄OH	6.7	53
11a	0	$4-C_6H_4OC(O)CH_3$	12	39
11b	0	$4-C_6H_4OC(O)C_2H_5$	9	41
11c	0	3-C ₆ H ₄ OC(O)CH ₃	3.6	64
11d	0	3-C ₆ H ₄ OC(O)C6H ₅	5.3	64
1 4 a	0	$4-C_6H_4CO_2C_2H_5$	6	40
14b	0	4-C ₆ H ₄ CO ₂ - <i>t</i> -C ₄ H9	3	25
19	0	$4-C_6H_4CH_2OC(0)CH$	H ₃ 6	45

¹H NMR (CDCl₃) 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: ¹H NMR (CDCl₃) 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: ¹H NMR (CDCl₃) 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: ¹H NMR (CDCl₃) 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-butyldimethylsiloxymethylphenyl)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-butyldimethylsiloxymethylphenyl)methyl]thiophene 81. Protecting group used was tetrahydropyranyl. The compound was purified by flash chromatography using 15:1 hexane/ethyl acetate to give 8.4 g (81%) 81 as a light yellow oil (mixture of diastereomers).

4-Bromo-2-[1-trimethylsiloxy-1-(4-tert-butyldimethylsiloxyphenyl)methyl]thiophene 8m. The compound was purified by flash chromatography using hexane to give 6.8 g (73%) 8m as a colorless oil: ¹H NMR (CDCl₃) 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-trimethylsiloxy1-(3-tert-butyldimethylsiloxyphenyl)methyl]thiophene 8n. The compound was purified by flash chromatography using hexane to give 8.45 g (71%) 8n as a colorless oil: ¹H NMR (CDCl₃) 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 preparartion 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 (MgSO₄), 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 (MgSO₄), 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: ¹H 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); ¹³C 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: ¹H 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); ¹³C NMR (acetone- d_6) δ 152.58, 141.13, 128.67, 121.22, 69.84, 38.59, 27.46, 22.14, 13.67; Anal (C₉H₁₅NO₃S₂) 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: ¹H 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); ¹³C 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 C₁₁H₁₉NO₃S₂ 277.0806, found 277.0826; anal (C₁₁H₁₉NO₃S₂) 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: ¹H 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); ¹³C 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 C₁₂H₁₃NO₄S₂ 299.028601, found 299.0290; anal (C₁₂H₁₃NO₄S₂) 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: ¹H 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), 7.82 (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); ¹³C 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 C₁₀H₁₀N₂O₃S₂ 270.0132, found 270.0111.

5-[1-Hydroxy-1-(2-fluorophenyl)methyl]-3-thiophenesulfonamide 9g. The compound was not isolated. The crudeproduct 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:.¹H 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 C₁₂H₁₃NO₄S₂ 299.028601, found 299.0267; anal (C₁₂H₁₃NO₄S₂) C, H, N.

5-[1-(hydroxy)-1-(3-hydroxymethylphenyl)methyl]-3-thiophenesulfonamide 91. The compound was not isolated. The crude product was taken on directly to 101 and 101' 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: ¹H 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); ¹³C NMR (acetone- d_6) δ 158.24, 154.63, 144.58, 136.09, 128.86, 128.22, 122.42, 116.16, 72.03; LRMS *mle* 285 (M⁺); HRMS exact mass calc for C₁₁H₁₁NO₄S₂ 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: ¹H NMR (acetone- d_6) 8 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); ¹³C NMR (acetone- d_6) 8 158.75, 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 C₁₁H₁₁NO₄S₄ 285.01295, found 285.0112; anal (C₁₁H₁₁NO₄S₄) C, H, N.

General procedure for the preparartion 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 (MgSO₄), filtered, and concentrated. The compound was recrystallized from chloroform/ethyl acetate/hexane to give 40 mg (65%) **10a** as white crystals: ¹H 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); ¹³C 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 C₁₁H₉NO₃S₂ 267.00238, found 266.9989; anal (C₁₁H₉NO₃S₂) 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: ¹H 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); ¹³C 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-(1-0xoheptyl)-3-thiophenesulfonamide 10c. The compound was purified by recrystallization from chloroform/hexane to give 31 mg (61%) 10c as white crystals: ¹H 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); ¹³C 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 C₁₁H₁₈NO₃S₂ (MH⁺) 276.0728, found 276.0715; anal (C₁₁H₁₈NO₃S₂) 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: ¹H 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); ¹³C 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 C₁₂H₁₁NO₄S₂ 297.012951, found 297.0128; anal (C₁₂H₁₁NO₄S₂) C, H, N.

5-[1-0xo-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: ¹H 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); ¹³C 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 C₁₅H₁₇NO₃S₂ 323.06499, found 323.0660; anal (C₁₅H₁₇NO₃S₂) C, H, N.

5-[1-Oxo-1-(2-pyridyl)methyl]-3-thiophenesulfonamide **10**f. The compound was purified by recrystallization from methanol/ water to give 0.14 g (58%) **10f** as white crystals: ¹H 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); ¹³C 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 C₁₀H₈N₂O₃S₂ 267.9976, found 267.9946; anal (C₁₀H₈N₂O₃S₂) 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: ¹H 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); ¹³C 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 C₁₁H₈FNO₃S₂ 284.992965, found 284.9925; anal (C₁₁H₈FNO₃S₂) 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: ¹H 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); ¹³C 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); ¹³C 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 C₁₂H₈F₃NO₃S₂ 334.9898, found 334.9874; anal (C₁₂H₈F₃NO₃S₂) 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); ¹³C 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 C₁₁H₈FNO₃S₂ 284.992965, found 284.9939; anal (C₁₁H₈FNO₃S₂) 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); ¹³C 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 C₁₂H₉NO₅S₂ 310.99222, found 310.9915; anal (C₁₂H₉NO₅S₂) C, H, N.

5-[1-Oxo-1-(4-formylphenyl)methyl]-3-thiophenesulfonamide 10k'. Oxidation was accomplished with manganese dioxide (MnO₂). 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); ¹³C 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 C₁₂H₉NO₄S₂ 294.9973, found 294.9970.

5-[1-Oxo-1-(3-carboxyphenyl)methyl]-3-thiophenesulfonamide **101.** The compound was purified by recrystallization from THF/hexane to give 0.32 g (45%) **101** 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); ¹³C 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 C₁₂H₉NO₅S₂ 310.9922, found 310.9928; anal (C₁₂H₉NO₅S₂) C, H, N.

5-[1-Oxo-1-(3-formylphenyl)methyl]-3-thiophenesulfonamide 101'. Oxidation was accomplished with MnO₂. The compound was purified by flash chromatography using 2:1 ethyl acetate/hexane to give 0.10 g (67%) 101' 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); ¹³C 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 + NH₄)⁺; HRMS exact mass calc for C₁₂H₉NO₄S₂ 294.997301, found 294.9971; anal (C₁₂H₉NO₄S₂) 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); ¹³C 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 C₁₁H₉NO₄S₂ 282.9973, found 282.9958; anal (C₁₁H₉NO₄S₂) 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); ¹³C 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 C₁₁H₉NO₄S₂ 282.9973, found 282.9969; anal (C₁₁H₉NO₄S₂) 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 Ac₂O (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 (MgSO₄), 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); ¹³C 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 C₁₃H₁₁NO₅S₂ 325.00787, found 325.0045; anal (C₁₃H₁₁NO₅S₂) 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 (MgSO₄), 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); ¹³C 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 C₁₄H₁₃NO₅S₂ 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 (MgSO₄), concentrated and purified by flash chromatography using 1:1 ethyl acetate/hexane to give 0.10 g (83%) **11c** as a colorless oil: ¹H 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); ¹³C 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 *mie* 325 (M⁺); HRMS exact mass calc for C₁₃H₁₁NO₅S₂ 325.00787, found 325.0057; anal (C₁₃H₁₁NO₅S₂) 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 (MgSO₄), concentrated and purified by flash chromatography using 1:1 ethyl acetate/hexane to give 0.12 g (88%) **11d** as a pale yellow oil: ¹H 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); ¹³C 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 (C₁₈H₁₃NO₅S₂) 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: ¹H 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); ¹³C 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: ¹H 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); ¹³C 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 *mle* 340 (M⁺); HRMS exact mass calc for C₁₄H₁₆N₂O₄S₂ 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: ¹H 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); ¹³C NMR (acetone- d_6) δ 188.0, 166.4, 146.7, 145.8,

183

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 CH₂Cl₂ (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: ¹H 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); ¹³C 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**: ¹H 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); ¹³C 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 C₁₆H₁₉N₂O₅S₂ 383.0735, found 383.0737.

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

Compound **101** (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: ¹H 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); ¹³C 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 C₁₆H₁₇NO₅S₂ 367.0548, found 310.9928 (M-C₄H₈); anal (C₁₆H₁₇NO₅S₂) 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-[1tetrahydropyranyloxy-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 (MgSO₄) and concentrated. Purification by flash chromatography using 60% ethyl acetate/hexane gave 0.74 g (100%) **16** as an offwhite foam (mixture of diastereomers): ¹H 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 CH₂Cl₂ 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 NaHCO₃ followed with water (3 ×) and brine. The solution was dried over MgSO₄ and the solvent removed under vacuum to afford 47 mg (93%) **17** as a clear colorless oil: ¹H 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), 7.93 (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); ¹³C 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 C₁₂H₁₁NO₄S₂ 297.012951, found 297.0128.

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

Pyridine (0.23 mL, 2.9 mmol) and Ac₂O (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 Ac₂O were added. After 9 h the reaction was quenched with water and extracted with ethyl acetate. The combined organic portions were dried (MgSO₄) 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 (MgSO₄), concentrated and purified by flash chromatography using 1:1 ethyl acetate/hexane to give 0.37 g (77%) **18** as a colorless oil: ¹H 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 (MgSO₄), filtered and concentrated. Recrystallization from ethyl acetate/hexane gave 0.17 g (86%) **19** as white crystals: ¹H 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); ¹³C 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 (C₁₄H₁₃NO₅S₂) 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 reac-

tion 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 (MgSO₄) and concentrated to give 0.15 g (95%) **20**: ¹H 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); ¹³C 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 C₁₂H₁₁NO₄S₂ 297.012951, found 297.0153; anal (C₁₂H₁₁NO₄S₂) 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 (MgSO₄) and concentrated. Purification by flash chromatography using 60% ethyl acetate/hexane gave 0.12 g (24%) **21a** as a pale yellow solid: 1H 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); ¹³C 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 guenched with water and extracted with ethyl acetate. The combined organic phases were dried (MgSO₄) 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 (MgSO₄), concentrated and purified by flash chromatography using 30% ethyl acetate/hexane to give 0.16 g (76%) 21b as a white solid: ¹H 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); ¹³C 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 + NH₄)⁺; HRMS exact mass calc for $C_{13}H_{12}F_3NO_3S_2$ 351.02107, found 351.0207; anal $(C_{13}H_{12}F_{3}NO_{3}S_{2})C,H,N.$

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 (MgSO₄), 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%: ¹H 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); ¹³C 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 C₁₃H₁₃NO₄S₂ 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 (MgSO₄) and concentrated. Recrystallization from chloroform/ethyl acetate gave 0.070 g (66%) **23a** as a white solid (mixture of *E* and *Z* isomers): ¹H 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). ¹³C 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 C₁₂H₁₂N₂O₄S₂ 312.023850, found 312.0247; anal (C₁₂H₁₂N₂O₄S₂) 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 (MgSO₄) and concentrated. Recrystallization from ethyl acetate/hexane gave 0.033 g (62%) **23b** as a white solid (mixture of *E* and *Z* isomers): ¹H 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); ¹³C 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 C₁₁H₁₀N₂O₃S₂ 282.01329, found 282.0101; anal (C₁₁H₁₀N₂O₃S₂) 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 (MgSO₄) 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): ¹H 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); ¹³C 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 C₉H₁₄N₂O₃S₂ 262.044586, found 262.0415; anal (C₉H₁₄N₂O₃S₂) 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 H₂ 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: ¹H NMR (CDCl₃) 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 CH₂Cl₂ (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 NH₄OH (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 (MgSO₄), 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: ¹H 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); ¹³C NMR (acetone-d₆) 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 C₁₀H₁₇NO₂S₂ 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/min² stream of CO₂ gas. A stock solution of the buffer consisted of 30.0 mL of 1 M Na₂CO₃ and 20.6 mL of 1 M NaHCO₃ 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 IC₅₀ 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].

References

- 1 Maren TH (1967) Physiol Rev 47, 595-781
- 2 Maren TH (1987) Drug Dev Res 10, 255-276
- 3 Epstein DL, Grant WM (1977) Arch Ophthalmol 95, 1378-1382

- 4 Lichter PR, Newman LP, Wheeler NC, Beal OV (1978) Am J Ophthalmol 85, 495-502
- 5 Maren TH, Jankowska L, Sanyal G, Edelhauser HF (1983) Exp Eye Res 36, 457-479
- 6 Stein A, Pinke R, Krupin T et al (1983) Am J Ophthalmol 95, 222-228
- 7 Hennekes R, Pfeiffer N, Lippa E, Garus H, Grehn F, Jaeger A (1988) Invet Ophthalmol Vis Sci 29 (suppl), 82
- 8 Dean TR, Chen HH, May JA (1994) US Pat 5 308 863
- 9 Baldwin JJ, Ponticello GS, Anderson PS et al (1989) J Med Chem 32, 2510-2513
- 10 Holmes JM, Lee GCM, Wijono M, Weinkam R, Wheeler LA, Garst ME (1994) J Med Chem 37, 1646–1651
- 11 Maren TH (1960) J Pharmacol Exp Ther 130, 26--29
- 12 Conroy CW, Schwam H, Maren TH (1984) Drug Met Disp 512, 614-618
- 13 Sugrue MF, Gautheron P, Mallorga P et al (1990) Br J Pharmacol 99, 59-64
- 14 Maren TH (1974) Invest Ophthalmol Vis Sci 13, 479

186