Pergamon

Bioorganic & Medicinal Chemistry, Vol. 5, No. 4, pp 779–786, 1997

PII: S0968-0896(97)00025-4
0968-0896/97 $17.00 + 0.00

N-(5-Substituted) Thiophene-2-alkylsulfonamides as Potent Inhibitors of 5-Lipoxygenase

Scott A. Beers,* Elizabeth A. Malloy, Wei Wu, Michael Wachter, Justin Ansell, Monica Singer, Michele Steber, Arminda Barbone, Thomas Kirchner, David Ritchie and Dennis Argentieri

The R. W. Johnson Pharmaceutical Research Institute, 1000 Route 202, Raritan NJ 08869, U.S.A.

Abstract—Compound **4k** *N*-[5-(4-fluoro)phenoxythien-2-yl]methanesulfonamide is representative of a new class of potent inhibitors of 5-lipoxygenase (5-LO). These versatile compounds exhibit dose-dependent inhibition of 5-LO with IC_{50}s ranging from 20–100 nM in the rat basophilic leukemia (RBL-1) cell homogenate assay and submicromolar IC_{50}s in both the RBL-1 and human peripheral blood leukocyte (PBL) whole cell assays. Compound **4k** also showed significant anti-inflammatory activity in the adjuvant arthritic rat at an oral dose of 3 mg/kg. © 1997 Elsevier Science Ltd.

Introduction

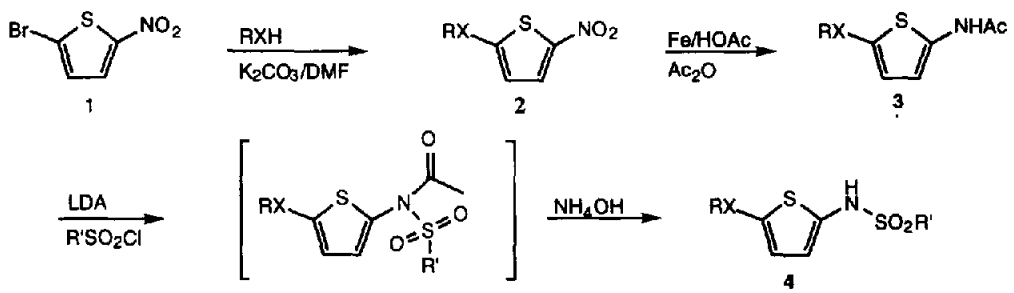
The 5-LO enzyme has been the focus of much research since its discovery.[1,2] Its catalysis of the first step in the leukotriene biosynthetic pathway makes it an attractive target for the treatment of a variety of inflammatory disorders involving excessive leukotriene production (e.g., asthma).[3–5] Although numerous compounds having either *N*-hydroxyureas or hydroxamic acids have shown impressive potency both in vitro and in vivo, these same moieties are often rapidly and extensively metabolized in vivo resulting in unacceptably short half-lives.[6–8] We wish to report the in vitro potency of a new class of 5-LO inhibitors as well as the in vivo potency of one member, compound **4k**, in the adjuvant arthritic rat.

Chemistry

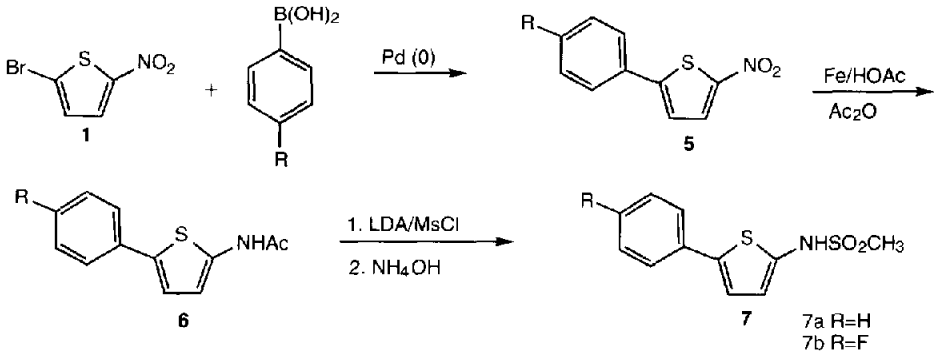
Scheme 1 shows the synthesis of target compounds **4**. The commercially available **1** is reacted with either a phenol or a mercaptan in DMF to give the nitro ether (or thioether) intermediate **2**. Since free amines at the 2-position of thiophenes are not stable without strong electron withdrawing groups at either the 3-/5-positions, we needed a suitable protecting group that would also act as an amine synthon and that could be easily removed once sulfonylation had been achieved. These conditions were all satisfied by reductive acylation of the nitro group of **2** in acetic acid–acetic anhydride to give the amide **3**. The amide was effectively deprotonated in THF at −78 °C using LDA. Addition of the desired alkyl or phenylsulfonyl chloride gave the sulfonylated amide intermediate, which was not isolated but rather worked up using methanolic ammonia in a 'one pot' procedure to give target sulfonamides **4**.

Scheme 2 shows the use of Suzuki coupling of **1** with the desired phenyl boronic acid to give biaryl nitro intermediates **5**. Reductive acylation with subsequent sulfonylation as described above gave targets **7**.

Scheme 3 shows the synthesis of compounds **15** and **18**. The commercially available **11** is reacted with phenylmagnesium bromide at −78 °C in THF to give carbinol **12**. The carbinol was then oxidized to the ketone **13**. Reductive acylation in the manner described above gave **14**. Treatment of **14** with *t*-butoxide followed by mesyl chloride and methanolic ammonia gave **15**. Carbinol **12** could also be reduced using triethylsilane and



Scheme 1.



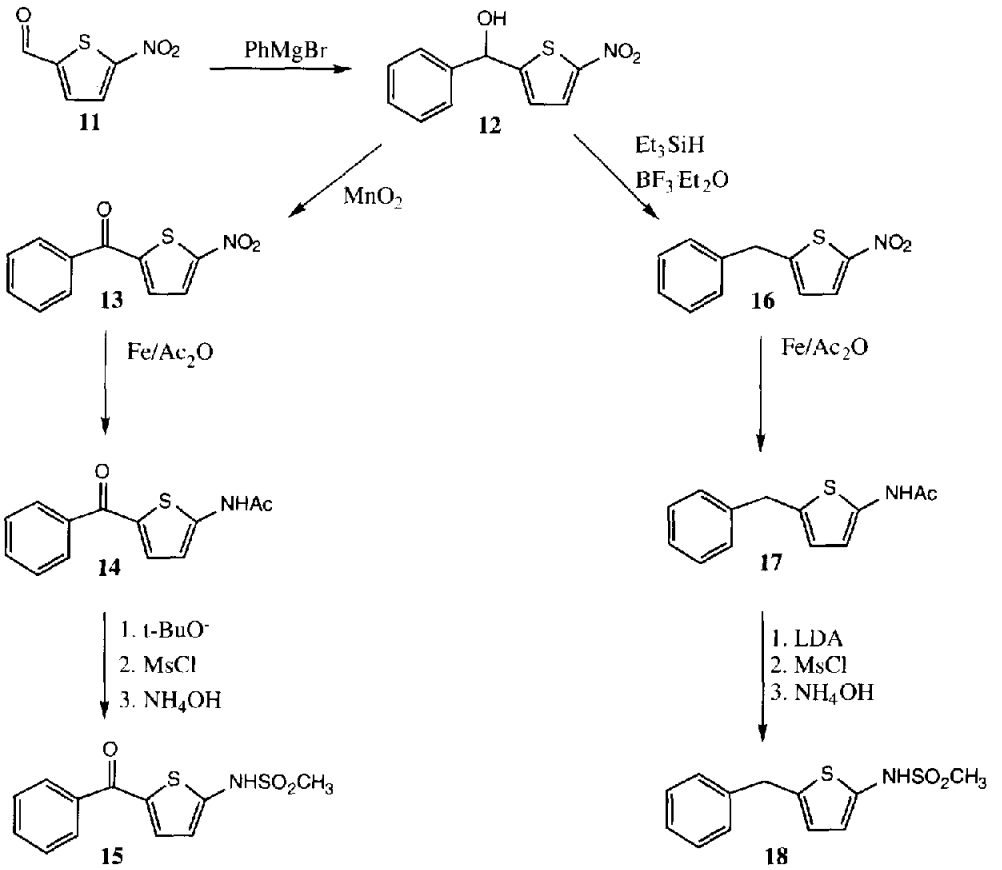
Scheme 2.

borontrifluoride etherate to give the methylene derivative **16**. Reductive acylation and mesylation gave **18**.

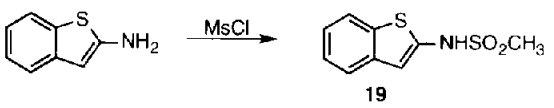
Scheme 4 shows the mesylation of 2-aminobenzo[b]-thiophene[9] to give **19**.

Results and Discussion

Table 1 lists all of the compounds and their respective IC_{50}s against both RBL-1 homogenate and whole cell. Some of the more potent compounds were also tested in the human PBL cellular assay as well. Several interesting observations can be made. The basic pharmacophore is *N*-thiophene-2-methanesulfonamide **4a**, which has an IC_{50} of 11 μM. Its phenyl analogue, *N*-phenylmethanesulfonamide (Acros) shows no detectable inhibition of 5-LO at this concentration indicating the unique importance of the thiophene ring system. Compound **4p** having sulfur as the connecting atom between thiophene and phenyl rings seems just slightly less potent than compound **4b**, which has oxygen connecting the rings. In addition while the S-cyclohexyl analogue **4bb** seems equally potent to **4b** in the cell-free assay it is significantly less potent than either **4b** or **4p** in the whole cell. The S-pentyl analogue **4dd** is not only more potent than **4bb** but is as potent in the whole cell as **4p** thereby obviating the need for an aromatic ring at this position of the molecule. While compound **18** is equally potent to **4b**, its carbonyl derivative **14** is virtually inactive against 5-LO. Although Biaryl compound **7a**, which has no connecting atom between rings,



Scheme 3.



19

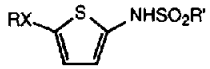
Scheme 4.

retained good potency relative to **4b**, its 4-fluoro analogue **7b** was less potent in the whole cell assay than either **7a** or 4-fluoro analogue **4k**. None of the acetamide precursors **3**, **6**, **14** or **17** showed any inhibition of the 5-LO enzyme in the cell homogenate assay at concentrations as high as 10 μM. The sulfonamide moiety is definitely necessary for the observed potency although modification of the methyl group of the sulfonamide led to retention of potency in compounds **4m**, **4s**, and **4t**. Only compound **4aa** showed significant drop-off in potency. Finally, the potency of this series of compounds is maintained over a wide variety of phenyl ring substitution patterns. Only compounds **4i** and **4z** showed significant losses in potency.

Conclusion

We have discovered a new and very versatile pharmacophore leading to a wide variety of compounds with submicromolar potency against 5-LO in both RBL-1 and human PBL whole cell assays. Many of the compounds show potency in vitro equal to or greater than that of Zileuton. These compounds are quite specific for 5-LO over 12, or 15-LO as is shown in Table

Table 1.



4, 7, 15, 18, 19

Compd	X	R	R'	RBL-1 cell free IC_{50} (mM)	RBL-1 whole cell IC_{50} (mM)	Human PBL IC_{50} (mM)
4a	H		Methyl	11.3	nt	
4b	O	Phenyl	Methyl	0.07	0.47	
4c	O	4-Cl-phenyl	Methyl	0.06	0.66	0.13
4d	O	2,4-Di-Cl-phenyl	Methyl	0.06	0.36	0.1
4e	O	2-CH_3-4-F-phenyl	Methyl	0.09	1.09	
4f	O	3-F-phenyl	Methyl	0.16	0.49	0.12
4g	O	2,4-Di-F-phenyl	Methyl	0.15	0.8	0.23
4h	O	4-SCH_3-phenyl	Methyl	0.1	0.66	
4i	O	4-SO_2CH_3-phenyl	Methyl	1.8	38.5	
4j	O	3-CH_3-phenyl	Methyl	0.12	0.31	0.35
4k	O	4-F-phenyl	Methyl	0.13	0.46	1.02
4l	O	3-CH_3-4-F-phenyl	Methyl	0.02	0.31	0.11
4m	O	Phenyl	n-butyl	0.36	1.12	
4n	O	1-naphthyl	Methyl	0.07	0.8	2.09
4o	O	3-Cl-4-F-phenyl	Methyl	0.03	0.89	
4p	S	Phenyl	Methyl	0.19	0.7	
4q	O	4-OCH_3-phenyl	Methyl	0.02	0.27	
4r	O	3-Cl-phenyl	Methyl	0.06	0.58	
4s	O	Phenyl	Phenyl	0.1	1.04	0.38
4t	O	Phenyl	Isopropyl	0.05	1.04	
4u	O	2,3-Di-CH_3-phenyl	Methyl	0.06	0.66	
4v	O	3-CF_3-phenyl	Methyl	0.05	0.78	0.25
4w	O	Tetrahydro-1-naphthyl	Methyl	0.05	0.5	
4x	O	2-naphthyl	Methyl	0.06	0.77	
4y	O	3-CH_3-4-F-phenyl	Methyl	0.02	0.31	
4z	O	3-isopropyl-phenyl	Methyl	0.61	4.7	
4aa	O	Phenyl	*n*-octyl	0.3	2.9	
4bb	S	Cyclohexyl	Methyl	0.07	2.59	
4cc	O	2-Br-4-F-phenyl	Methyl	0.06	1.4	
4dd	S	n-pentyl	Methyl	0.04	0.63	
4ee	O	3,5-Di-CF_3-phenyl	Methyl	0.31	6.5	
4ff	O	2-Cl-5-CF_3-phenyl	Methyl	0.14	1.8	
7a	Bond	Phenyl	Methyl	0.11	0.79	
7b	Bond	4-F-phenyl	Methyl	0.15	2.1	
15	CO	Phenyl	Methyl	>10	19.3	
18	CH_2	Phenyl	Methyl	0.11	0.38	
19		Fused phenyl	Methyl	>10	nt	
Zileuton				0.44	1.4	0.47

Table 2.

Compd	12-LO IC_{50} (μM)	15-LO % inh at 10 μM
4b	3	48
4j	1.5	35
4k	3	32
7a	4	23
NDGA	77%[a]	66[a]

[a]Tested at 1 μM.

2. Compound **4k** demonstrated efficacy in the adjuvant rat assay at concentrations as low as 3–30 mg/Kg. We are presently examining the anti-inflammatory activity of these compounds in the dog and will report on their in vivo efficacy in the near future.

Experimental

Melting points were determined on a Meltemp melting-point apparatus and are uncorrected. Mass spectra were recorded on a HP 5989A spectrometer using particle-beam ionization. Ammonia was used as the chemical ionization gas. Proton NMR spectra were recorded on a Bruker WP100SY spectrometer using tetramethylsilane as the internal standard. Elemental analyses were performed by Quantitative Technologies Inc. Whitehouse, NJ.

5-LO inhibitory assay (RBL-1 cell homogenate)

Rat basophilic leukemia cells (RBL-1; 5×10^7 viable cells/mL) were disrupted by homogenation on ice (four 20 s bursts) with a Brinkman polytron. Complete cell breakage was verified microscopically. The homogenate was then centrifuged at 9220 *g* for 48 min at 4 °C. The pellet was discarded and the supernatant was saved as the source of enzyme. The supernatant was preincubated for 5 min at 37 °C in the presence of 2 mM of $CaCl_2$ and compound or vehicle (1% dimethyl sulfoxide). The conversion of AA into products by 5-LO was initiated by adding 10 μL (50 μCi) of 1-^{14}C-AA to each tube and incubated at 37 °C for 20 min. The reaction was stopped by adjusting the pH of each sample to 3–3.5 with 2 M formic acid. Samples were extracted with three volumes of chloroform to isolate the products of 5-LO formed during the reaction. Fractions were dried under nitrogen, then resuspended in 40 μL of chloroform and spotted on silica gel HL plates. The plates were developed in A-9 solvent. The dried plates were analyzed using a Bioscan Imaging TLC scanner to determine the percentage of radiolabeled AA converted to 5-HETE in each sample.

5-LO inhibitory assay (RBL-1 whole cells)

RBL-1 cells were maintained in culture in minimal essential medium (Bio*Whittaker, Walkersville, MD), containing 12.5% fetal calf serum, 10 mg/mL streptomycin, 10 IU/mL penicillin G, 50 mg/mL gentamycin and 2 mM l-glutamine (Bio*Whittaker, Walkersville, MD). Cells were collected by centrifugation, washed once with HBSS, and resuspended at a concentration of 10^5 cells/mL. Cells were incubated in the presence of vehicle or drug then centrifuged at 800 *g* for 10 min at 4 °C. The supernatant was removed by aspiration and the cells were resuspended in 0.5 mL of Hank's balanced salt solution. The reaction was started by the addition of 20 μg/mL of calcium ionophore A 23187 (mixed calcium and magnesium salts, Calbiochem, La Jolla, CA) and allowed to proceed for 15 min, then stopped by plunging the tubes into a slush ice bath. The conversion of AA to 5-LO products was initiated by the addition of 10 μL (50 μCi) of 1-^{14}C-AA. Products were isolated by acidification and extraction, followed by thin-layer chromatography analysis described above. Radioactive areas corresponding to 5-HETE were quantitated by the Bioscan 2000 Imaging system.

Human peripheral blood leukocyte 5-LO inhibitory assay

Whole blood was drawn by venipuncture from healthy volunteers into EDTA Vacutainers (Becton Dickinson, San Jose, CA). Peripheral blood leukocytes were isolated with Leukoprep separation media (Becton Dickinson) according to the manufacturer's procedure and resuspended in Dulbecco's Modification of Eagle's medium (GIBCO, Grand Island, NY) at a density of 2×10^6 cells/mL. Cells were added to 96-well flat-bottom plates in a volume of 180 μL/well. Vehicle or test compound was added to the appropriate wells and incubated for 15 min prior to the addition of 10 μL of 0.5 mM calcium ionophore A23187 (Calbiochem, La Jolla, CA). The plates were incubated for 15 min at 37 °C and the reaction was stopped by chilling the plates to 4 °C for 5 min. A 100 μL sample of the supernatant was removed and the level of LTB_4 was quantified by RIA (Perseptive Diagnostics Inc., Cambridge, MA).

12-Lipoxygenase inhibition assay

Porcine leukocyte 12-LO (BIOMOL) is added to Hanks buffer in the presence of drug in test tubes. The mixture is preincubated at 37 °C for 10 min in a water bath. ^{14}C Arachidonic acid is added and the reaction is stopped after 30 min by the addition of 2 M formic acid. The mixture is then extracted with chloroform and the organic phase evaporated to dryness under a stream of nitrogen. The residue is then spotted and developed by means of silica gel TLC. Quantification of the 12-HETE is accomplished by measuring the radioactive emissions from the TLC plates using a Bioscan plate scanner. The inhibition of 12-HETE product formation is measured by comparing the 12-HETE formed in the control samples with the 12-HETE formed in the samples containing drug.

15-Lipoxygenase inhibition assay

Rabbit reticulocyte 15-LO (BIOMOL) is added to Hanks buffer in the presence of drug in test tubes. The mixture is preincubated with drug for 10 min at 37 °C. ^{14}C Arachidonic acid is then added and the reaction is allowed to proceed for 20 min before being stopped by the addition of 2 M formic acid. The reaction mixture is then extracted with chloroform and the organic phase is evaporated under a stream of nitrogen. The residue is spotted and developed on a silica gel TLC plate. Quantification of 15-HETE formation is accomplished by measuring the radioactivity with a Bioscan plate scanner. The inhibition of 15-LO is calculated by comparing the 15-HETE formed in the control tubes with the 15-HETE formed in the drug tubes. The nordihydroguaiaretic acid (NDGA) used to standardize this and the 12-LO assay was purchased from Aldrich Chemical Co.

Adjuvant-induced arthritis in rats

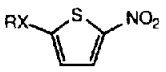
The initial volume displacement of the hind paws of male Sprague-Dawley rats (Charles River, Kingston, NY), weighing 250–300 g, were recorded on day 0 using a mercury plethysmograph (Buxco Electronics, Sharon, CT). The rats were then immunized by injecting 0.1 mL of *Mycobacterium butyricum* (Difco, Detroit, MI) suspension (7.5 mg/mL) in light paraffin oil (Sigma Chemical Corp., St Louis, MO) into the right subplantar footpad. A form of polyarthritis was initiated in the injected foot over 10 days as evidenced by an increase in paw volume recorded on day 10. A chronic immune response was elicited in the contralateral paw from days 10–14. The rats were administered vehicle or test compounds orally once each day on days 10–14. Compound effects were assessed on day 14, 4 h postcompound administration. The increase in hindpaw volumes was compared to day 10 values on both the injected and the contralateral paws. Percent inhibition was calculated by comparing the mean increase in paw volume in the treated group to that of the control group. Inhibition of swelling in the injected footpad is indicative of acute anti-inflammatory activity, while inhibition of swelling in the contralateral footpad is indicative of effects on the chronic immune response.

Table 3. The effects of compound **4k** in the adjuvant rat contralateral paw injected paw

mg/kg PO	% inh	SEM	mg/kg PO	% inh	SEM
3	32.6	9.48	3	54.9	10.06
30	46.05	0.695	30	88.6	9.32

Synthesis of nitro ethers/thioethers (2). Compound **1** (Lancaster) was solvated in dimethylformamide. To this was added one molar equivalent of the corresponding

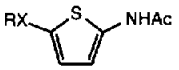
Table 4.



2

Compd	X	R	Yield (%)	mp (°C)	MS (MH^+)
2a	O	Phenyl	73	91.5-92.5	222
2b	O	4-Cl-phenyl	44	Oil	256
2c	O	2,4-Di-Cl-phenyl	78	67-69	291
2d	O	2-CH_3-4-F-phenyl	71	64-66	254
2e	O	3-F-phenyl	95	52-53	240
2f	O	2,4-Di-F-phenyl	86	61.3-66	258
2g	O	4-SCH_3-phenyl	100	Oil	268
2h	O	3-CH_3-phenyl	73	43-50	236
2i	O	4-F-phenyl	79	69-70	240
2j	O	3-CH_3-4-F-phenyl	69	61-64	254
2k	O	1-naphthyl	26	98-104	272
2l	O	3-Cl-4-F-phenyl	79	83-84	274
2m	S	Phenyl	62	34-38	238
2n	O	4-OCH_3-phenyl	83	75.5-79.5	252
2o	O	3-Cl-phenyl	73	Oil	256
2p	O	2,3-Di-CH_3-phenyl	67	68-70	250
2q	O	3-CF_3-phenyl	77	59-60	290
2r	O	Tetrahydro-1-naphthyl	28	Oil	276
2s	O	2-naphthyl	67	99-101	272
2t	O	2-CH_3-4-F-phenyl	71	64-66	254
2u	O	3-isopropylphenyl	72	Oil	264
2v	S	Cyclohexyl	70	Oil	244
2w	O	2-Br-4-F-phenyl	100	Oil	318
2x	S	n-pentyl	80	Oil	232
2y	O	3,5-CF_3-phenyl	76	79-82	358
2z	O	2-Cl-5-CF_3-phenyl	63	Oil	324

Table 5.



3, 6,14,17

Compd	X	R	Yield (%)	mp (°C)	MS (MH^+)
3a	H		40	160–161	142
3b	O	Phenyl	73	94–95	234
3c	O	4-Cl-phenyl	60	140–141	268
3d	O	2,4-Di-Cl-phenyl	60	129–130	302
3e	O	2-CH_3-4-F-phenyl	56	117.8–118.2	266
3f	O	3-F-phenyl	43	137–138	252
3g	O	2,4-Di-F-phenyl	66	150–151.5	270
3h	O	4-SCH_3-phenyl	45	150–151	280
3i	O	3-CH_3-phenyl	74	109–112	248
3j	O	4-F-phenyl	45	130.4–132.9	252
3k	O	3-CH_3-4-F-phenyl	36	155.4–158	266
3l	O	1-naphthyl	71	134–139	284
3m	O	3-Cl-4-F-phenyl	25	149–149.6	286
3n	S	Phenyl	76	141–142	250
3o	O	4-OCH_3-phenyl	35	147.4–148	264
3p	O	3-Cl-phenyl	49	110.5–112	268
3q	O	2,3-Di-CH_3-phenyl	91	131–131.7	262
3r	O	3-CF_3-phenyl	86	110–111	302
3s	O	Tetrahydro-1-naphthyl	49	138–145	288
3t	O	2-naphthoxy	44	159–160	284
3u	O	2-CH_3-4-F-phenyl	56	117.8–118.2	266
3v	O	3-isopropyl-phenyl	42	70–73	276
3w	S	Cyclohexyl	59	177–180	256
3x	O	2-Br-4-F-phenyl	37	150–152	330
3y	S	n-pentyl	31	91–92	244
3z	O	3,5-Di-CF_3-phenyl	59	164–165	370
3aa	O	2-Cl-5-CF_3-phenyl	35	175–177	336
6a	Bond	Phenyl	82	178–180	218
6b	Bond	4-F-phenyl	85	141–141.5	236
14	C=O	Phenyl	90	219–220	246
17	CH_2	Phenyl	47	141–142	232

phenol or mercaptan and two formula mass equivalents of potassium carbonate. The reaction was heated (in the case of the phenols) to 70 °C for 5 h or stirred at room temperature for 16 h (mercaptans). The reaction mix was then poured into ice-water. The crude products were obtained by either filtration or extraction with ethyl acetate. The products obtained were generally used without further purification although they could be recrystallized from methanol–water or column chromatographed on a silica gel column eluted with ethyl acetate:hexane, 1:1 if necessary. The physical data for these compounds is listed in Table 3.

Synthesis of acetamides (3, 6, 14 and 17). The nitrated precursor was solvated in a 1:1 mixture of acetic acid:acetic anhydride. To this was added iron powder (5 molar equiv). The reaction was stirred at 100 °C for 5 h before being poured into ice. The products were obtained by either filtration or neutralization with sodium bicarbonate followed by extraction with ethyl acetate. The compounds were used without further purification. Physical data for these compounds is listed in Table 4.

Synthesis of 2-nitro-5-phenylthiophene (5a). Compound **1** (4.00 g, 0.0192 mol) was solvated in toluene (100 mL). To this was added phenyl boric acid (2.60 g, 0.0213 mol), potassium carbonate (5.30 g, 0.0384 mol), tetrakis(triphenylphosphine)palladium(0) (0.66 g) and water (20 mL). This was stirred at reflux for 16 h after which time water was added and the layers separated. The organic layer was evaporated to a crude solid, which was purified on a silica gel column eluted with ethyl acetate:hexane (1:1) to give 3.22 g (82%) of **5a**; mp 121–123 °C; MS 206 (MH^+).

Synthesis of 2-nitro-5-(4-fluoro)phenylthiophene (5b). Compound **1** (3.50 g, 16.8 mmol) was solvated in toluene (100 mL). To this was added 4-fluorophenylboric acid (2.52 g, 0.0180 mol), potassium carbonate (4.56 g, 0.033 mol), tetrakis(triphenylphosphine)palladium(0) (0.58 g) and water (25 mL). This was stirred at reflux for 16 h after which time it was worked up and purified as described above giving 2.99 g (80%); mp 129–130 °C; MS 224 (MH^+).

Synthesis of sulfonylated compounds (4, 7 and 18). The acetamide precursors were solvated in THF and cooled

Table 6.

Compd	Yield (%)	Mp (°C)	MH^+	Formula	Anal.
4a	60	66-68	178	$C_5H_7NO_2S_2$	C,H,N
4b	49	78-80	270	$C_{11}H_{11}NO_3S_2$	C,H,N
4c	45	98-100	304	$C_{11}H_{10}ClNO_3S_2$	C,H,N
4d	52	83.5-84.5	338	$C_{11}H_9Cl_2NO_3S_2$	C,H,N
4e	64	85-86.5	302	$C_{12}H_{12}FNO_3S_2$	C,H,N
4f	49	76-77	288	$C_{11}H_{10}FNO_3S_2$	C,H,N
4g	71	75-76	306	$C_{11}H_9F_2NO_3S_2$	C,H,N
4h	67	141-143	316	$C_{12}H_{13}NO_3S_3$	C,H,N
4i	34	140-141	348	$C_{12}H_{13}NO5S_3$	C,H,N
4j	55	88-90	284	$C_{12}H_{13}NO_2S_2$	C,H,N
4k	52	90-91	288	$C_{11}H_{10}FNO_3S_2$	C,H,N
4l	60	103-106	302	$C_{12}H_{12}FNO_3S_2$	C,H,N
4m	64	Gum	312	$C_{14}H_{17}NO_3S_2$	C,H,N
4n	38	102-105	320	$C_{15}H_{13}NO_3S_2$	C,H,N
4o	52	Gum	339[a]	$C_{11}H_9ClFNO_3S_2$	C,H,N
4p	63	115-118	286	$C_{11}H_{11}NO_2S_3$	C,H,N
4q	41	75.5-76	300	$C_{12}H_{13}NO4S_2$	C,H,N
4r	66	84-86.5	304	$C_{11}H_{10}ClNO_3S_2$	C,H,N
4s	8.6	96-100	332	$C_{16}H_{13}NO_3S_2$	C,H,N
4t	7.3	185-190	298	$C_{14}H_{15}NO_3S_2$	C,H,N
4u	47	140-141.5	298	$C_{13}H_{15}NO_3S_2$	C,H,N
4v	60	59-60	338	$C_{12}H_{10}F_3NO_3S_2$	C,H,N
4w	55	112-116	324	$C_{15}H_{17}NO_3S_2$	C,H,N
4x	52	122-123	320	$C_{15}H_{13}NO_3S_2$	C,H,N
4y	42	100-101	302	$C_{12}H_{12}FNO_3S_2$	C,H,N
4z	13	Gum	312	$C_{14}H_{17}NO_3S_2$	C,H,N
4aa	64	35-40	368	$C_{18}H_{25}NO_3S_2$	C,H,N
4bb	67	63-64	292	$C_{11}H_{17}NO_2S_3$	C,H,N
4cc	62	100-102	367	$C_{11}H_9BrFNO_3S_2$	C,H,N
4dd	22	Oil	280	$C_{10}H_{17}NO_3S_3$	C,H,N
4ee	71	114-116	406	$C_{12}H_9F_5NO_3S_2$	C,H,N
4ff	52	Gum	372	$C_{12}H_9ClF_3NO_3S_2$	C,H,N
7a	47	180-181	254	$C_{11}H_{11}NO_2S_2$	C,H,N
7b	23	185.5-187	272	$C_{11}H_{10}FNO_2S_2$	C,H,N
18	55	91-92	268	$C_{12}H_{13}NO_3S_2$	C,H,N

[a] $[M+NH_4]^+$.

to −78 °C. Lithium diisopropylamide (1.0 molar equiv from a 1.5 M solution in cyclohexane) was then added. After 15 min, 1.0 molar equiv of the appropriate alkylsulfonyl chloride was added and the reaction was allowed to stir to ambient temperature for 1 h. The mix was evaporated in vacuo to an oil that was solvated in methanol. Ammonium hydroxide (5–10 equiv) was added and this was stirred for 30 min. The reaction mixture was again evaporated in vacuo and partitioned between methylene chloride and 1 N HCl. The organic layer was then washed with water, dried, and evaporated. If necessary the products could be purified on a silica gel column eluted with ethyl acetate:hexane (1:2). Physical data for these compounds is listed in Table 4.

Synthesis of the 2-nitro-5-methylphenyl carbinol intermediate (12). To a solution of **11** (3.76 g, 23.9 mmol) in dry THF cooled to −78 °C was added phenylmagnesium bromide (24.0 mL of 1 M soln). This was stirred to room temperature for 1 h before being quenched with aqueous ammonium chloride. The product was extracted with ether. The organic layer was dried over magnesium sulfate and evaporated in vacuo to a crude oil, which was purified on a silica gel column eluted with ethyl acetate:hexane (1:5) giving 2.53 g (45%) as a red oil. ^1H NMR ($CDCl_3$) δ 5.96 (s,1H,C*H*OH); MS 236 (MH^+).

Synthesis of 2-nitro-5-benzoylthiophene (13). Compound **12** (2.08 g, 8.84 mmol) was solvated in chloroform (50 mL). To this was added manganese dioxide (activated, 3.84 g). This was heated to reflux for 2 h. The reaction mixture was then filtered and washed with 100 mL additional chloroform. The filtrate was evaporated in vacuo to give **13** as an orange solid (1.89 g, 92%); mp 118–118.5 °C; MS 234 (MH^+).

Synthesis of *N*-(5-benzoylthien)-2-ylmethanesulfonamide (15). Compound **14** (1.57 g, 6.40 mmol) was solvated in acetonitrile. Potassium *tert*-butoxide (0.83 g, 7.40 mmol) was added and the mix was stirred for 30 min before the addition of methanesulfonyl chloride (0.60 mL, 7.7 mmol). The reaction mixture was then stirred for 1 h after which time it was concentrated in vacuo and resolvated in methanol:ammonium hydroxide (5:1). After 30 min the mix was then re-evaporated in vacuo and partitioned between 1 N HCl and methylene chloride. The organic layer was dried over

magnesium sulfate and evaporated in vacuo to a crude solid, which was recrystallized from methanol–water to give 650 mg (36%); mp 159.5–160.5 °C; ^{1}H NMR (DMSO-d_6) δ 3.17 (s, 3H); MS 282 (MH^+). Anal. calcd for $C_{12}H_{11}NO_3S_2$: C, 51.23; H, 3.94; N, 4.98. Found: C, 51.36; H, 3.97; N, 4.91.

Synthesis of 2-nitro-5-benzylthiophene (16). Compound **12** (1.37 g, 5.80 mmol) was solvated in methylene chloride (10 mL). To this was added triethylsilane (2.88 mL, 18.0 mmol). The mixture was then cooled to 0 °C before addition of boron trifluoride etherate (2.21 mL, 18.0 mmol). The mixture was stirred at room temperature for 14 h before addition of saturated sodium bicarbonate solution (50 mL). The product was extracted with ether. The organic phase was washed with water, dried over magnesium sulfate, and evaporated in vacuo to a brown oil (1.10 g, 87%). ^{1}H NMR ($CDCl_3$) δ 4.16 (s, 2H); MS 220 (MH^+).

Synthesis of *N*-(benzo[b]thiophene)-2-methanesulfonamide (19). The precursor 2-aminobenzo[b]thiophene[9] (1.50 g, 10.0 mmol) was dissolved in pyridine. Methanesulfonyl chloride (0.77 mL, 10 mmol) was added. This was stirred for 3 h after which time the reaction mixture was concentrated in vacuo. 1 N HCl was added and the product was extracted with ethyl acetate. Purification on a silica gel column eluted with ethyl acetate:hexane (1:4) afforded 1.32 g (58%) of **19**; mp 133–136 °C; ^{1}H NMR ($CDCl_3$) δ 7.70 (t, 2H), 7.32 (m, 2H), 7.13 (s, 1H), 3.11 (s, 3H); MS 228 (MH^+). Anal. calcd for $C_9H_9NO_2S_2$: C, 47.56; H, 3.99; N, 6.16. Found: C, 47.90; H, 4.06; N, 6.05.

References

1. Samuelsson, B. *Science* **1983**, *220*, 568.
2. Brooks, D. W.; Summers, J. B. *J. Med. Chem.* **1996**, *39*, 2629.
3. Drazen, J. M.; Austen, F. K. *Am. Rev. Respir. Dis.* **1987**, 985.
4. Henderson, W. R. *Ann. Allergy* **1994**, *72*, 272.
5. Israel, E. *Ann. Allergy* **1994**, *72*, 279.
6. Summers, J. B.; Gunn, B. P.; Mazdiyasni, H.; Goetze, A. M.; Young, G. W. *J. Med. Chem.* **1987**, *30*, 2121.
7. Summers, J. B.; Gunn, B. P.; Martin, J. G.; Mazdiyasni, H.; Stewart, A. O.; Young, P. R.; Goetze, A. M.; Bouska, J. B.; Dyer, R. D.; Brooks, D. W.; Carter, G. W. *J. Med. Chem.* **1988**, *31*, 3.
8. Summers, J. B.; Gunn, B. P.; Martin, J. G.; Martin, M. B.; Mazdiyasni, H.; Stewart, A. O.; Young, P. R.; Bouska, J. B.; Goetze, A. M.; Dyer, R. D.; Brooks, D. W.; Carter, G. W. *J. Med. Chem.* **1988**, *31*, 1960.
9. Stacey, G. W.; Villescusa, F. W.; Wollner, T. E. *J. Org. Chem.* **1965**, *30*, 4074.

(*Received in U.S.A.* 15 *August* 1996; *accepted* 23 *January* 1996)