Antiinflammatory 4,5-Diarylpyrroles: Synthesis and QSAR

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A series of 2-substituted- and 2,3-disubstituted-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrroles was synthesized and found to be active in the rat adjuvant arthritis model of inflammation. The most active compounds were the 2-halo derivatives in the order of chloro > bromo > iodo. The same pattern of activity was observed for the 2,3-dihalopyrroles. Quantitative structure–activity relationship studies suggested that the activity could be correlated with the molar refractivity and the inductive field effect of the 2-substituent and the lipophilicity of the 3-substituent.

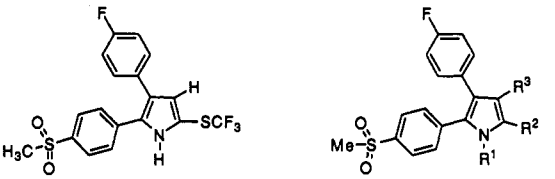
Introduction

Extensive research efforts in our laboratories have been committed to finding novel compounds for the treatment of inflammatory diseases such as arthritis. Like other laboratories, we have concentrated our efforts on the diaryl heterocycles,[1] with particular attention being given to the diarylpyrroles. Furthermore, we were interested in 2-substituted-4,5-diarylpyrroles that were as potent as indomethacin in the established adjuvant-induced arthritis rat model (AA), showed high renal and gastrointestinal safety in laboratory subjects, and had a drug elimination half-life in laboratory animals long enough to indicate a "once-a-day-dosing" regiment in man (see Porter[2]). One such compound was synthesized and reported by Cherkofsky as 2-[(trifluoromethyl)thio]-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole (**I**).[3]

During our investigations of alternative large-scale synthetic routes to **I**, which was originally synthesized using the highly toxic (trifluoromethyl)sulfenyl chloride[3] (Scheme 1), we discovered that some of our intended precursors (**II**) had potent oral antiinflammatory activity in AA. These discoveries prompted an analoging program to maximize the activity of this new series and gain a better understanding of the structure–activity relationship (SAR) for this type of compound.

Chemistry

Our first attempt to prepare the thiocyanate (-SCN) pyrrole **2** involved reacting **1**[3] with cupric thiocyanate ($Cu(SCN)_2$) to give the desired product in good to moderate yields. Subsequent preparations and yields were erratic, and the source of the problem was traced to the quality of the commercial $Cu(SCN)_2$. Only the "black"-colored reagent produced consistent results, whereas the "gray"-colored reagent (mostly CuSCN) produced little or no desired product. We next tried a procedure described by Brewster and Schroeder[4] that involved the reaction of **1** with NH_4SCN and bromine in AcOH. The yields were improved, but purification required chromatography, and the procedure required the use of the very volatile reagent bromine. Because of the erratic results with $Cu(SCN)_2$, we decided to prepare the reagent and react it with **1** *in situ* according to eq 1:



I II

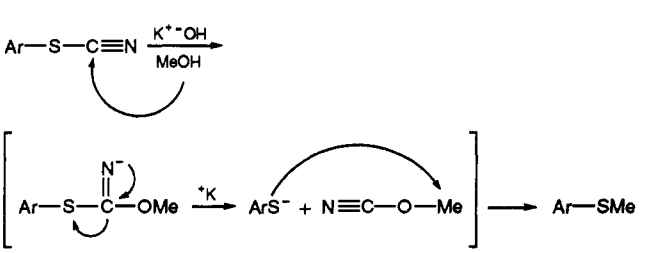
Figure 1. Structure of **I** and positions for Analoging (**II**).

$$2\ NH_4SCN + \text{anhydrous } CuSO_4 \xrightarrow{THF} [Cu(SCN)_2] \xrightarrow[THF]{1} Ar\text{–}SCN \quad (1)$$

95–100%

The only requirements for this procedure (method A, Scheme 1) were that the cupric sulfate had to be anhydrous and the solvent had to be dry. The 2-thiocyano *N*-methyl derivative **4b** was synthesized by converting **1** to its corresponding *N*-methyl derivative **4a** with NaH and MeI followed by reaction with thiocyanogen $(SCN)_2$. The method was also applicable for the preparation of **2** from **1**. However, the method was not used routinely because of the formation of a yellow very insoluble material thought to be a polymer of thiocyanogen.

During an attempt to purify crude **2** by recrystallization from a MeOH solution, we noticed that the alcohol solution became highly colored and the TLC of the solution showed the disappearance of **2** with the formation of another component. Mass spectral analysis showed the formation of a component with *m/e* 361. The material was isolated by chromatographic techniques and identified as the thioether **3**. A search of the literature produced a citation by Olsen and Snyder[5] explaining these results as shown in eq 2:



(2)

An authentic sample of **3** was synthesized by reacting **2** with MeOH and KOH (Scheme 2). The thioether **3** was

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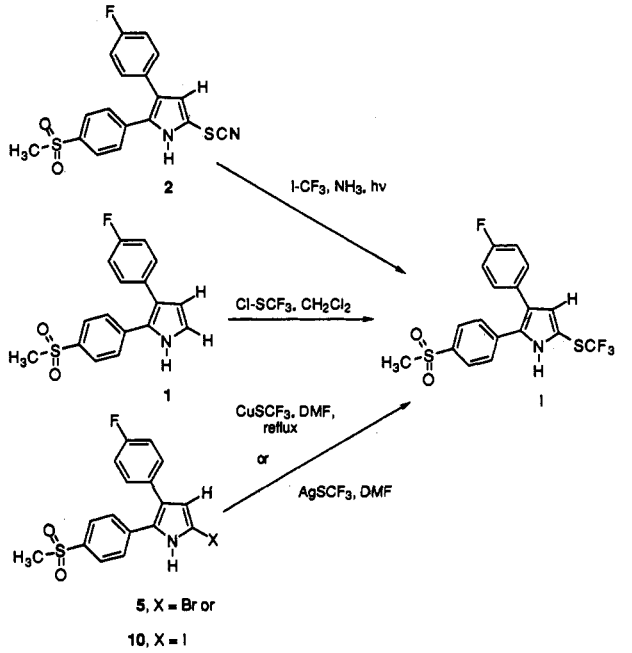
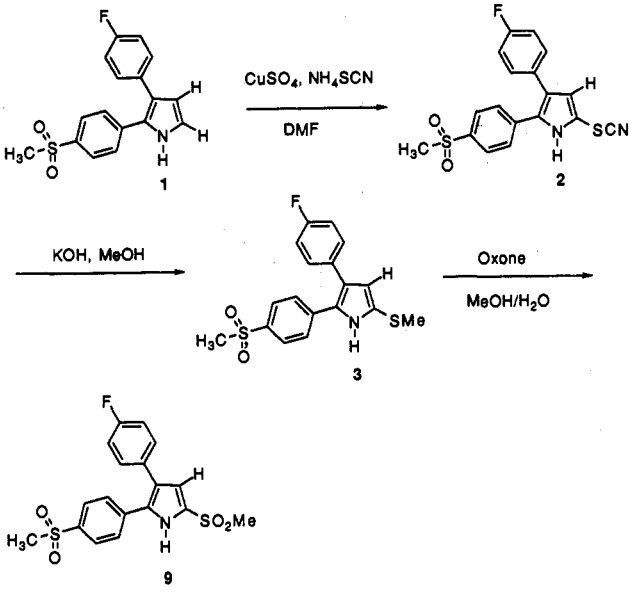
Scheme 1



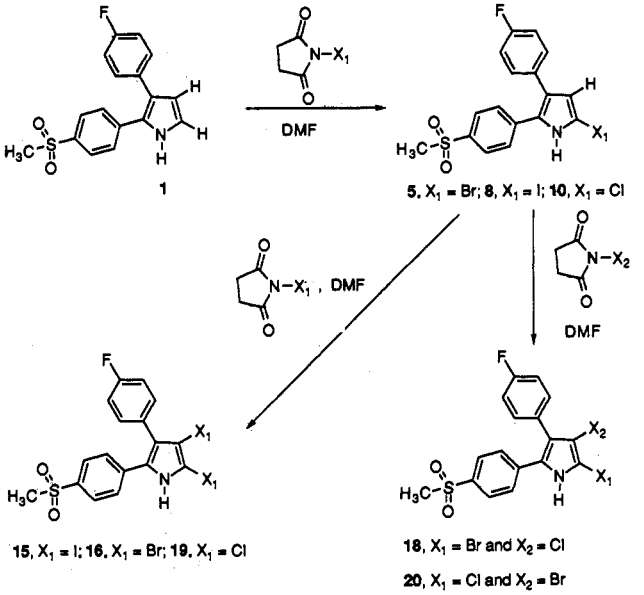
Scheme 2



oxidized to the corresponding sulfone **9** using Oxone (Scheme 2). The sulfonic acid, as the pyridine salt **6**, was prepared by reacting **1** with sulfur trioxide–pyridine complex.

The monohalogenation of the pyrroles was accomplished using the method described by Aiello et al.[6] and Gilow and Burton[7] (method D, Scheme 3) using *N*-halosuccinimide. Unlike those of Aiello et al.,[6] the pyrroles in our investigation had two possible sites (2′-C and 3′-C) for halogenation. Using the NMR of **1**, it was determined that the proton at 2′ had a resonance of δ 7.01 and the proton at 3′ had a resonance at δ 6.28. Using these markers, it was determined that all the monohalo substitutions on the pyrroles were at the 2-position. These results were in accord with those reported by Gilow and Burton.[7] The monohalogenated pyrroles **5**, **8**, and **10** were prepared by reacting **1** with 1 equiv of *N*-bromosuccinimide (NBS), *N*-iodosuccinimide (NIS), and *N*-chlorosuccinimide (NCS), respectively (method D). Other pyrroles (**11**, **14b**, **17b**, **21b**, and **22**) were monohalogenated using method D.

Scheme 3



Alternatively, **11** was synthesized by reacting the anion of **5** with MeI. *N*-Acetylpyrrole **21a** was initially prepared, in moderate yield, by reacting **1** with acetyl chloride. However, the approach described by Reddy et al.[8] using *N*-acetylimidazole[9] was more satisfactory. Compound **21a** was brominated with NBS to give **21b**. Pyrrole derivative **16** was "deprotected" with trifluoroacetic acid to give **5** in quantitative yield. Of the three halosuccinimides, the tendency to dihalogenate using 1 equiv of the reagent was in the order: NIS > NBS > NCS. It was also observed that the less pure the reagent, the greater the tendency to dihalogenate. As a consequence, all were purified before use.[10]

The 2,3-dibromo- (**16** and **23**), 2,3-dichloro- (**19** and **24**), and 2,3-diiodopyrrole (**15**) derivatives were prepared by reacting **1** with 2 equiv of the *N*-halosuccinimide. Compound **15** was also prepared by reacting **1** with I_2/AgF.[11] Mixed dihalogenated pyrrole derivative **18** (2-Br, 3-Cl) was synthesized by monobromination of **1** with NBS to get **5** which was chlorinated in the 3-position with NCS. Similarly, **1** was reacted with NCS to get **10** which was reacted with NBS to get **20** (2-Cl, 3-Br). No attempt was made to obtain "mixed" iodopyrroles.

Our first attempt to prepare the nitrile **12** involved reacting **5** with CuCN at room temperature. The approach was unsuccessful. When the same approach was attempted in refluxing DMF, the desired nitrile was obtained in low yield after column chromatography. Also identified from this reaction was **1** which resulted from the reduction of **5**. Via the general procedure described by Floyd et al.,[12] the desired nitrile **12** was prepared in high yield by reacting **1** with chlorosulfonyl isocyanate and DMF. The 2-nitropyrrole derivative **13** was synthesized by reacting **1** with acetyl nitrate.[12-16]

A small series of N-substituted pyrroles (N-R^1) was synthesized to determine if the acidic proton on nitrogen (R^1 = H) was necessary for potent antiinflammatory activity. This type of compound was represented by the *N*-methyl derivatives (R^1 = Me) **4b**, **11**, **23**, and **24**. The ethyl valerate **22** is an extension of this group of compounds. Should the N-H not be necessary, then the N-protected series (**14b**, R^1 = ^{t}Boc; **17b**, R^1 = Ts; and **21b**, R^1 = Ac) would be used to synthesize other derivatives.

These protective groups were removed under a number of reaction conditions.[17]

The first attempt to prepare the 2-fluoropyrrole involved refluxing **5** with $Hg(II)F_2$ in acetonitrile. The reaction mixture was very complicated as evidenced by TLC. Mass spectral analysis of the mixture showed *m/e* 472, 474, and 476, suggesting a dibrominated pyrrole; *m/e* 393 and 395 for **5**, and *m/e* 333 for a monofluorinated species. Because the mixture was so complicated, other methods were attempted. Attempts to react **5** or **10** with AgF were also not successful. An attempt to convert the nitropyrrole **13** to the corresponding amine by catalytic hydrogenation followed by photochemical Schiemann reaction to afford the fluoropyrrole was also unsuccessful.[18] Finally, we tried reacting **1** with xenon difluoride (XeF_2). A small amount of material was isolated and assumed to be pure, based on elemental analysis and low-resolution MS results. However, high-resolution MS showed molecular ions corresponding to a monofluorinated species and a difluorinated compound.[19] These results demonstrated that the material was not as pure as previous analytical data had indicated and that the desired monofluorinated compound was contaminated with the difluorinated product. No attempt was made to quantitate the composition. The material was submitted as the "mixture" of 2-fluoro- and 2,3-difluoro-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole (**25**) for AA evaluation. As of this writing, no acceptable method has been developed for the synthesis of the 2-fluoropyrrole derivative.

Biology

The primary assay for antiinflammatory activity of the compounds in this study was the rat-established adjuvant arthritis edema assay.[20,21] Arrigoni-Martelli[22] and the references therein have reported that the rat AA assay constitutes a delayed hypersensitivity response and may best represent autoimmune diseases (also see Shen[23]). Only the AA data were used for the SAR studies. The AA data were originally reported in units of mg/kg and were converted to μM/kg for quantitative structure–activity relationship (QSAR) studies. A small series of compounds was subjected to pharmacokinetic (PK) evaluation, and the results are shown in Table 4. The toxicity profile on a subset of compounds is shown in Table 5.

Computer Methods and Statistics

Statistical data were obtained using CA-Cricket Graph III v1.0 and StatWorks v1.2 by Computer Associates International, Inc., Islandia, NY, and StatView II v1.03 by Abacus Concepts, Inc., Berkeley, CA. Computer-generated ClogP and CMR were obtained using MedChem Software v3.0, Pomona College, Claremont, CA, or calculated as described by Hansch and Leo.[24]

QSAR studies used the following parameters: computer-calculated log P (ClogP) and molar refractivity (CMR) for the molecule and substituent parameters π, MR, $\mathcal{F}$, $\mathcal{R}$, σ_m, and σ_p as reported.[24-28] Statistical methods were in accord with Havilcek and Crain[29] and Dowdy and Wearden.[30] The following statistical measures were used; *n*, the number of samples in the regression; r^2, coefficient of determination; *r*, correlation coefficient; *s*, standard error of the regression; F-ratio; and the probability of finding a greater F-ratio. In the regression equations, the number in parentheses is the standard error of the estimate for the coefficient.

Results and Discussion

The data in Tables 1 and 2 show that for the 2-thio-1*H*-pyrroles, the AA activity was found to be as follows: **3** (SMe) > **2** (SCN) > **6** (SO_3H Pyr) ≫ **9** (SO_2Me). Attempts to determine the structural contribution to activity for this subset of compounds were limited because of the small sample, the lack of enough substituents parameters for **6**, and the "cross-correlation" of the parameters ($\mathcal{F}$, $\mathcal{R}$, σ_m, and σ_p) for **3**, **2**, and **9**.

In every case compared, the N-Me compound was less active than the corresponding N-H compound: **2** vs **4**, **5** vs **11**, **16** vs **23**, and **19** vs **24**. The same observations were made where R^1 was other than H or Me: **5**, R^1 = H, vs **14b**, R^1 = ^{t}Boc; **5** vs **17b**, R^1 = Ts; **5** vs **21b**, R^1 = Ac; and **10**, R^1 = H, vs **22**, R^1 = $(CH_2)_4CO_2Et$. These observations lead to the conclusion that the N-H is preferred for good antiinflammatory activity. However, since some of the compounds where R^1 was other than hydrogen also showed good activity, it was concluded that all the activity of this series did not reside in the nature (pK_a, hydrogen-bond-donating) of the N-H moiety.

Initial QSAR studies were conducted on a series of pyrroles where R^1 = H, R^2 = substituent under investigation, and R^3 = H. Initially, eq 3a was identified which correlated AA activity with the molar refractivity (MR) and σ_m of R^2. Not being sure as to which σ value to use (σ_m or σ_p) and lack of enough σ_o reported values in the literature, we substituted σ_p into eq 3a to give eq 3b. Clearly, eq 3a described a better relationship than eq 3b. Substituting CMR for MR in eq 3a resulted in a correlation that was not significantly different from the original equation. One approach around the σ_m vs σ_p problem was to use the Swain–Lupton field inductive effect ($\mathcal{F}$) and resonance effect ($\mathcal{R}$) parameters.[25,26,31] However, it is suggested that the use of $\mathcal{F}$ and $\mathcal{R}$ required that both parameters be used in the same regression,[31] which causes a problem for small data sets.[32] When $\mathcal{F}$ and $\mathcal{R}$ were substituted in eq 3a for σ_m, eq 4 resulted.

$$-\log(AA) = -0.167(\pm 0.026)R^2MR - 2.993(\pm 0.487)R^2\sigma_m + 2.058(\pm 0.418) \quad (3a)$$

$$n = 10 \quad r^2 = 0.894 \quad r = 0.945 \quad s = 0.228 \quad F = 29.496$$

$$-\log(AA) = -0.138(\pm 0.039)R^2MR - 1.434(\pm 0.433)R^2\sigma_p + 1.039(\pm 0.504) \quad (3b)$$

$$n = 9 \quad r^2 = 0.765 \quad r = 0.874 \quad s = 0.360 \quad F = 9.751$$

$$-\log(AA) = -0.191(\pm 0.024)R^2MR - 4.415(\pm 0.774)R^2\mathcal{F} + 0.211(\pm 0.456)R^2\mathcal{R} + 2.938(\pm 0.529) \quad (4)$$

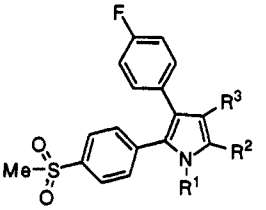
$$n = 9 \quad r^2 = 0.946 \quad r = 0.973 \quad s = 0.188 \quad F = 29.391$$

$$-\log(AA) = -0.187(\pm 0.021)R^2MR - 4.165(\pm 0.515)R^2\mathcal{F} + 2.789(\pm 0.390) \quad (5)$$

$$n = 9 \quad r^2 = 0.944 \quad r = 0.972 \quad s = 0.176 \quad F = 50.616$$

The magnitude of the coefficients for $\mathcal{F}$ and $\mathcal{R}$, in eq 4,

Table 1. Structural Features, Physical Data, and Adjuvant Arthritis (AA) ED_{50}'s for Compounds 1–24 and Mixture 25



cmpd	R^1	R^2	R^3	mp (°C)	% yield	formula[a]	method	AA ED_{50} (mg/kg)[b,c]
1	H	H	H	261–262		$C_{17}H_{14}FNO_2S$		>100.0
2	H	SCN	H	203–204	94	$C_{18}H_{13}FN_2O_2S_2$	A, B, C	3.90
3	H	SMe	H	171–173	80	$C_{18}H_{16}FNO_2S_2$		1.80
4b	Me	SCN	H	176–178	93	$C_{19}H_{15}FNO_2S_2$		>27.0
5	H	Br	H	169–170	100	$C_{17}H_{13}BrFNO_2S$	D	1.05
6	H	SO_3H Pyr	H	137–139	64	$C_{17}H_{14}NO_5S_2C_5H_5N$		12.7
7	H	$COCF_3$	H	282–283	96	$C_{18}H_{13}F_4NO_3S$		19.4
8	H	I	H	229–231	50	$C_{17}H_{13}IFNO_2S$	D	22.0
9	H	SO_2Me	H	224 dec	100	$C_{18}H_{15}FNO_4S_2$		36.6
10	H	Cl	H	206–208	95	$C_{17}H_{13}ClFNO_2S$	D	0.50
11	Me	Br	H	196–197	96	$C_{18}H_{15}BrFNO_2S$	D	1.70
12	H	CN	H	223 dec	96	$C_{18}H_{13}FN_2O_2S$		1.30
13	H	NO_2	H	241–243	28	$C_{17}H_{13}FN_2O_4S$		9.00
14b	tBoc	Br	H	262–263	98	$C_{22}H_{21}BrFNO_4S$	D	31.00
15	H	I	I	226 dec	100	$C_{17}H_{12}I_2FNO_2S$	D	41.3
16	H	Br	Br	247 dec	100	$C_{17}H_{12}Br_2NO_2S$		1.94
17b	SO_2Tol	Br	H	207–208	68	$C_{24}H_{19}BrFNO_4S_2$	D	>9.0
18	H	Br	Cl	231 dec	98	$C_{17}H_{12}BrClFNO_2S$		4.28
19	H	Cl	Cl	200 dec	94	$C_{17}H_{12}Cl_2FNO_2S$	D	1.50
20	H	Cl	Br	208 dec	97	$C_{17}H_{12}BrClFNO_2S$		3.40
21b	Ac	Br	H	121–125	25	$C_{19}H_{15}BrFNO_3S$	D	36.19
22	$(CH_2)_4CO_2Et$	Cl	H	74–78	51	$C_{24}H_{25}ClFNO_4S$	D	>100.0
23	Me	Br	Br	188–191	100	$C_{18}H_{14}Br_2FNO_2S$		4.16
24	Me	Cl	Cl	200–201	100	$C_{18}H_{14}Cl_2FNO_2S$		5.00
25	H	F	H and F					0.31
		std compds[d]						
		Ind					0.3	
		Pbz					10.0	
		Ibp					100.0	
		Asp					305.0	

[a] All compounds were analyzed for C, H, N, and S, and analytical results were within ±0.4% of the theoretical values. [b] Original data obtained in units of mg/kg and later converted to μM/kg for regression analysis (Table 2). [c] Standard error (SE) < ±20%. [d] Ind = indomethacin; Pbz = phenylbutazone; Ibp = ibuprofen; Asp = aspirin.

and the standard error for the $\mathcal{R}$ coefficient indicated that resonance was a minor contributor to activity for this series of compounds. Consequently, only $\mathcal{F}$ and MR were finally employed as illustrated in eq 5, and the found vs predicted activity is shown in Table 2. The result from this study demonstrated that molar refractivity and field inductive effects together were excellent predictors of AA activity in the rat for the 2-substituted-pyrroles. Equations 3a and 5 also predicted that the hypothetical 2-fluoro-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole would be the most active compound in AA for this type of compound.

In an attempt to determine the contribution to activity caused by substitution at the 3-position, a stepwise regression analysis was conducted on a series of 2-substituted-(R^2)-3-substituted-(R^3)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrroles using the following parameters: R^2MR, $R^2\mathcal{F}$, $R^3\pi$, R^3MR, $R^3\mathcal{F}$, $R^3\pi$, $R^3\sigma_m$, and $R^3\sigma_p$. The study resulted in eq 6.

$$-\log(AA) = -0.163(\pm0.023)R^2MR - 3.781(\pm0.699)R^2\mathcal{F} - 0.390(\pm0.167)R^3\pi + 2.359(\pm0.465) \quad (6)$$

$n = 14$ $r^2 = 0.858$ $r = 0.926$ $s = 0.250$ $F = 20.065$

Though eq 6 was statistically less significant than eq 5, it did introduce a third parameter (π) to the relationship. The only "outlier" observed using eq 6 was compound 16 (eq 6 ED_{50}, μM/kg: predicted 12.4 vs found 4.1). When 16 was removed from the regression, eq 7 resulted which

$$-\log(AA) = -0.163(\pm0.018)R^2MR - 3.861(\pm0.546)R^2\mathcal{F} - 0.528(\pm0.140)R^3\pi + 12.391(\pm0.363) \quad (7)$$

$n = 13$ $r^2 = 0.918$ $r = 0.958$ $s = 0.195$ $F = 33.896$

was a better predictor of activity than eq 6. The difference between the predicted and observed ED_{50}'s for 16 was not initially explainable. We are aware that some of the derived regression equations (eqs 4, 6, and 7) violate the "Topliss–Costello rule" which suggests or implies that "five data points are required per parameter in order to minimize the risk of chance correlation".[32,33]

The mixture of 2-fluoro- and 2,3-difluoro-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole was found to have an AA ED_{50} = 0.31 mg/kg. This result, along with the predicted values from eqs 5 and 7, further emphasizes the need to find an acceptable method for synthesizing the 2-fluoropyrrole derivative.

Some of the compounds in Table 1 were not used to generate eqs 3–7. Four (1, 4, 17b, and 22) had AA values reported as greater than (>); all except three were

Table 2. Calculated AA ED_{50}'s for the 4-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]pyrroles in Table 1[a] Using Eqs 5, 7a, and 8d

									AA ED_{50} (μM/kg)			
cmpd	R^1	R^2	R^3	$R^1\pi$	R^1MR	R^2MR	$R^2\mathcal{F}$	$R^3\pi$	found	calcd, eq 5	calcd, eq 7	calcd, eq 8b
1	H	H	H	0.00	1.03	1.03	0.00	0.00	>100.0	(<0.05)	(<0.05)	(<0.05)
2	H	SCN	H	0.00	1.03	13.40	0.36	0.00	10.47	16.6	15.2	13.7
3	H	SMe	H	0.00	1.03	13.82	0.20	0.00	4.89	4.3	4.3	4.3
4	Me	SCN	H	0.56	5.65	13.40	0.36	0.00	>27.0			(14.2)
5	H	Br	H	0.00	1.03	8.88	0.44	0.00	2.66	5.1	5.7	5.6
6	H	SO_3H	H	0.00	1.03	nv	nv	nv	26.76	nc		nc
7	H	$COCF_3$	H	0.00	1.03	11.17		0.00	47.16	43.2	38.9	nc
8	H	I	H	0.00	1.03	13.94	0.40	0.00	49.86	30.8	26.5	22.8
9	H	SO_2Me	H	0.00	1.03	13.49	0.54	0.00	93.02	96.8	77.6	60.7
10	H	Cl	H	0.00	1.03	6.03	0.41	0.00	1.43	1.1	1.5	1.7
11	Me	Br	H	0.56	5.65	8.88	0.44	0.00	1.70			5.8
12	H	CN	H	0.00	1.03	6.33	0.51	0.00	3.82	3.3	4.1	4.2
13	H	NO_2	H	0.00	1.03	7.36	0.67	0.00	24.97	24.0	24.8	21.5
14b	^tBoc	Br	H	1.62	26.77	8.88	0.44	0.00	32.0			61.0
15	H	I	I	0.00	1.03	13.94	0.40	1.12	72.82		103.5	93.0
16	H	Br	Br	0.00	1.03	8.88	0.44	0.86	4.10			(16.5)
17b	SO_2Tol	Br	H	nv	37.82	8.88	0.44	0.00	>9.0			nc
18	H	Br	Cl	0.00	1.03	8.88	0.44	0.71	9.98		13.5	13.7
19	H	Cl	Cl	0.00	1.03	6.03	0.41	0.71	3.90		3.5	4.1
20	H	Cl	Br	0.00	1.03	6.03	0.41	0.86	7.93		4.2	4.9
21b	Ac	Br	H	nv	11.18	8.88	0.44	0.00	82.95			81.2
22	$(CH_2)_4CO_2Et$	Cl	H	nv	35.09	6.03	0.41	0.00	>100.0			nc
23	Me	Br	Br	0.56	5.65	8.88	0.44	0.86	4.16			17.2
24	Me	Cl	Cl	0.56	5.65	6.03	0.41	0.71	5.00			4.2
2-F*	H	F	H	0.00	1.03	0.92	0.43	0.00		(0.15)	(0.26)	(0.34)
2,3-F**	H	F	F	0.00	1.03	0.92	0.43	0.14			0.31	(0.41)

[a] Two hypothetical compounds are included. * = hypothetical compound 2-fluoro-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole. ** = hypothetical compound 2,3-difluoro-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole. Parentheses = observed activity, where it existed, was not used to generate the regression equations which predicted these values.

N-substituted ($R^1 \neq H$); and two were proposed components of the mixture **25**: **III**, $R^1 = R^2 = H$ and $R^2 = F$, and **IV**, $R^1 = H$ and $R^2 = R^3 = F$. The predictive limits for the N-substituted species were expected and understandable since the N-R^1 contribution was not a part of the regression analyses. Via the information obtained from eqs 3–7, regression analyses were performed on the compounds in Table 1 with consideration of R^1, R^2, and R^3 and where appropriate parameter data were available. The substituent parameters π and MR for R^1 were used in conjunction with MR and $\mathcal{F}$ for R^2 and π for R^3. The results are shown in eq 8a,b.

$$-\log(AA) = 0.598(\pm0.238)R^1\pi - 0.080(\pm0.017)R^1MR - 0.149(\pm0.026)R^2MR - 3.408(\pm0.850)R^2\mathcal{F} - 0.433(\pm0.178)R^3\pi + 2.134(\pm0.543) \quad (8a)$$

$$n = 18 \quad r^2 = 0.817 \quad r = 0.904 \quad s = 0.290 \quad F = 10.746$$

When **16**, the outlier described above, was removed from the data set and a stepwise regression was performed, eq 8b resulted which was the best predictor of AA activity for the majority of the compounds in Table 1.

$$-\log(AA) = 0.632(\pm0.207)R^1\pi - 0.080(\pm0.015)R^1MR - 0.148(\pm0.022)R^2MR - 3.514(\pm0.739)R^2\mathcal{F} - 0.545(\pm0.162)R^3\pi + 2.193(\pm0.471) \quad (8b)$$

$$n = 17 \quad r^2 = 0.869 \quad r = 0.932 \quad s = 0.251 \quad F = 14.579$$

It was disturbing to find that none of the equations in Table 2 correctly predicted the activity of **1** ($R^1 = R^2 = R^3$) ($ED_{50} > 100\ \mu M$). The equations suggest that smaller MR and $\mathcal{F}$ values would result in better activity (−log AA), and since hydrogen's $MR_H = 1.03$ and $\mathcal{F}_H = 0.00$, its activity would be expected to approach the activity of **III** ($R^1 = R^2 = H$ and $R^2 = F$) where fluorine's $MR_F = 0.92$ and $\mathcal{F}_F = 0.43$. Presently, there is no explanation for these observations.[34] Equation 8b also failed to predict the observed AA activity of **11**, **16**, **20**, and **23**. Three were predicted to be less active than observed; **11** and **23** were N-Me derivatives, and **16** was the outlier in the original regression. Compound **20** was predicted to be more active than observed. The exact reason(s) for these poor fits is unknown, but it is possible that these compounds exhibit different pharmacokinetics.

Table 3. Correlation Matrix for Eq 8b

	−log AA	$R^1\pi$	R^1MR	R^2MR	$R^2\mathcal{F}$	$R^3\pi$
−log AA	1.000	−0.075	−0.388	−0.495	−0.254	−0.029
$R^1\pi$		1.000	0.740	−0.131	0.004	0.024
R^1MR			1.000	−0.119	0.022	−0.167
R^2MR				1.000	−0.351	−0.163
$R^2\mathcal{F}$					1.000	−0.126
$R^3\pi$						1.000

A serious limitation to a QSAR study using *in vivo* data is the assumption that all the compounds have the same or similar oral pharmacokinetics, a factor dependent upon GI absorption, drug metabolism, distribution, and total clearance. To assess the magnitude of this limitation, we conducted pharmacokinetic analysis on a small selected group of compounds as shown in Table 4. The most striking observation about the data in Table 4 was the inability to detect **2** in the blood of the rats, particularly when its degree of AA activity was considered. It is possible, considering the chemical reactivity of **2** as discussed above, that the active species is not the thiocyanate but some metabolite. Attempts to identify and isolate the metabolite(s) have not been successful.

In the absence of an active transport system across the intestinal mucosa, one would assume that molecular size or dispersion, as represented by CMR or MR, and lipophilicity, as represented by log P or π, would be major

Table 4. Pharmacokinetic Studies in the Rat for Selected Antiinflammatory 4,5-Diarylpyrroles[a]

cmpd	R^1	R^2	R^3	AA ED_{50} (μM/kg) po	dose (μM/kg)	$t_{1/2}$ (h)	V_d (L/kg)	F	C_{max} (μmol/L)
2	H	SCN	H		iv, 13.4	ndd	ndd	ndd	ndd
				10.47	po, 13.4	ndd	ndd	ndd	ndd
5	H	Br	H		iv, 6.3	10.2	3.5	1.06	2.0
				2.66	po, 12.7	9.9			3.0
10	H	Cl	H		iv, 7.1	6.1	9.0	1.00	1.4
				1.43	po, 14.3	5.8			2.3
11	Me	Br	H		iv, 12.2	13.7	10.0	0.64	2.9
					iv, 12.2	13.7	10.0	0.64	2.9
				4.16	po, 12.2	4.3			1.5
12	H	CN	H		iv, 14.7	13.7	5.7	1.34	4.1
				3.82	po, 14.7	17.3			2.9
16	H	Br	Br		iv, 10.6	29.3	4.3	0.85	2.8
				4.10	po, 10.6	47.5			1.5

[a] $t_{1/2}$ = elimination half-life; V_d = volume of distribution; F = observed bioavailability; C_{max} = maximum blood level reached after an oral dose of 5.0 mg/kg; ndd = no drug detected.

Table 5. Drug Safety Assessment for Selected 4,5-Diarylpyrroles[a]

assay	2	3	5	10	11	12	16
est AA paw, po, ED_{50} (μM/kg)	10.47	4.98	2.55	1.43	3.43	3.82	4.1
nonest AA paw, po, day 18 ED_{50} (μM/kg)	18.8	69.2	22.7	nd	nd	nd	nd
car paw, po, ED_{30} (μM/kg)	268.5	>276		nd	nd	nd	nd
GI lesion TD_{50} (μM/kg)	>335.0	>414.0	95.9	100.1	>416.0	>381.0	>211.0
GI TD_{50}/AA ED_{50}	>32.0	>83.0	36.0	70.0	>100.0	>100.0	>113.0
12-day tox (μM/kg) no-effect dose	>418.0	>99.0	>46.0	nd	nd	nd	nd
maximum tolerated dose	>418.0	>199.0		nd	nd	nd	nd
12-day no effect/AA ED_{50}	>40.0	>30.0	>43.0	nd	nd	nd	nd
Ames test	neg	neg	neg	neg	nd	nd	nd

[a] nd = not determined.

determinants in drug absorption from the GI tract.[35] Interestingly, these two parameters appeared in eq 7b. These observations might imply that the regression eq 7b had addressed the PK limitations and the field inductive effect may be important for the drug receptor or enzyme active-site interaction. To test this idea, a small set of compounds (**2**, **10**, **11**, **12**, and **16** in Table 4) was subjected to PK studies. All the compounds were dosed orally at 5.0 mg/kg, and all except **5** and **10** were doses at 5 mg/kg iv. Compounds **5** and **10** were dosed iv at 2.5 mg/kg. Dosing data were converted to μM/kg as expressed in Table 4. Except for **2**, the data in Table 4 would suggest that all the compounds had good bioavailability (F range of 65–134%), and for an oral dose of 5.0 mg/kg, elimination half-life ($t_{1/2}$) ranged from 5.8 to 47.5 h and maximum blood level (C_{max}) ranged from 1.5 to 3.0 μM/L.

Previously, we had designated **16** as being an outlier to the predictive ability of eqs 7 and 8b. Prior to PK studies, we reexamined the AA data and retested **16** for AA activity in an attempt to explain its nonconformity to the regression equations. These "rechecks" showed no errors that would explain the deviation. The answer may lie in the very long half-life ($t_{1/2}$ = 47.5 h) of this drug. This means that **16** (R^1 = H, R^2 = R^3 = Br) has a $t_{1/2}$ 4.8 times that of **5** (R^1 = R^3 = H, R^2 = Br) and 11 times that of **11** (R^1 = Me, R^2 = Br, R^3 = H). The observed elimination half-life may suggest that the effective blood level may be much higher over the course of the AA measurement than for other members of the series due to accumulation of the compound since its half-life is about twice the dosing interval. Thus, **16** may be more active than would have been predicted.

None of the halopyrrole derivatives showed any activity against representative enzymes of the arachidonic acid cascade such as rat basophilic leukemia 5-lipoxygenase (RBL-5LO)[36–40] (IC_{50} > 25 μM), bovine seminal vesicle prostaglandin synthetase (BSV-PGS),[41] (IC_{50} > 250 μM), and porcine pancreatic phospholipase-A_2 (PAN-PLA_2)[39,40,42,43] (IC_{50} > 250 μM); additionally, none was active in the rat carrageenan paw edema assay[39,40,44] (ED_{30} > 20.0 mg/kg) or the mouse phenylquinone writhing assay for analgesia (PQW)[45,46] (ED_{50} > 108 mg/kg). However, compound **2** was an extremely potent inhibitor of RBL-5LO (IC_{50} = 0.08 μM), a good to moderate inhibitor of BSV-PGS (IC_{50} = 6.2 μM), and inactive as an inhibitor of PAN-PLA_2 (IC_{50} > 25 μM) but a good inhibitor of rat polymorphonuclear leukocyte PLA_2 (PMN-PLA_2)[39,40,47] with an IC_{50} = 1.1 μM. Compound **2** was the only member of this series that was active in the "preventative" nonestablished adjuvant arthritis model[23,48] with an oral paw 18-day ED_{50} = 7.0 mg/kg and the mouse oral contact sensitivity model[49] with an ED_{35} = 8.0 mg/kg. It is possible that **2** may be active by a totally different mechanism from that of the other members of the series. Compound **3** was a good to moderate inhibitor of the above mentioned enzymes; it was moderately active in the nonestablished AA model with an ED_{50} = 25.0 mg/kg and the only member to show any activity in PQW with an ED_{50} = 46.3 mg/kg.

Recently, a distinct prostaglandin endoperoxide synthase was found whose expression was induced by mitogens and inflammatory mediators and repressed by glucocorticoids.[50–52] There is about 60% amino acid homology between prostaglandin endoperoxide synthase 1 and 2. Both enzymes carry out the same cyclooxygenase and peroxidase activities,[53] but the difference in amino acid sequence allows the potential for selective inhibition.[54] The possibility exists that these diarylpyrroles may be acting as selective prostaglandin endoperoxide synthase inhibitors.

Conclusion

Series of 2-substituted- and 2,3-disubstituted-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrroles were synthesized and assessed for their ability to inhibit the paw edema as produced in the adjuvant arthritis rat model.

QSAR studies, using regression analysis, suggest that the observed activity could be predicted by the field inductive effects and the molar refractivity associated with the 2-substituent. When the 2,3-disubstituted compounds were added to the analyses, the lipophilicity of the 3-substituent became important in predicting the AA activity. These studies also suggested that the hypothetical 2-fluoropyrrole derivative should be very active in this model of chronic arthritis. This finding has further emphasized the need to develop an effective large-scale synthesis of the fluoro derivative. The results from this study have generated an additional set of questions: On the basis of the presented biological profile, what is the mechanism of action of these compounds? On the basis of its chemical reactivity, its biological profile, and the PK results, what is the antiinflammatory species associated with compound **2**? These questions have identified areas for additional investigations in organic synthesis, pharmacology, and drug metabolism of this series of potential antiinflammatory drugs.

Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus, are uncorrected, and are listed in °C. The NMR spectra were recorded with an IBM/Bruker WPS 200 spectrometer, IR spectra were recorded with a Perkin-Elmer 1600 FTIR spectrophotometer, and mass spectra were obtained using the Hewlett-Packard HP5988A GC-MS system. Thin-layer chromatography (TLC) was performed on silica gel plates.

Chemical Syntheses. 2-[4-(Methylsulfonyl)phenyl]-3-(4-fluorophenyl)-1*H*-pyrrole (1). The compound was prepared as described by Cherkofsky:[3] mp 261–262; ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 3.22 (s, 3H, CH_3), 6.28 (t, 1H, N-C=CH), 7.01 (t, 1H, N-CH=C), 7.26–7.31 (m, 4H, 4-FPh), 7.51 (d, J = 8.4 Hz, 2H), 7.82 (d, J = 8.4 Hz, 2H, 4-SO_2Ph); ^{13}C NMR (100 MHz, DMSO-d_6) δ 43.429 (s), 111.110 (s), 115.245 (d), 115.457 (d), 120.388 (s), 122.489 (s), 125.486 (s), 126.995 (d), 127.048 (s), 130.075 (s), 130.159 (s), 132.981 (s), 133.159 (s), 137.744 (s), 137.919 (s), 159.607 (s), 162.027 (s); ^{19}F NMR (282.2 MHz, DMSO-d_6 TMS) δ −116.542; IR (nujol) 3340 (NH) cm^{-1}; MS (CH_4-CI) m/e 315. Anal. Calcd for $C_{17}H_{14}FNO_2S$, MW 315.36: C, 64.75; H, 4.47; N, 4.44; S, 9.97. Found: C, 64.70; H, 4.52; N, 4.40; S, 10.17.

***S*-[4-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrol-2-yl] Thiocyanic Acid Ester (2). Method A.** A suspension of 1 (31.54 g, 0.1 mol) and NH_4SCN (33.5 g, 0.44 mol) in 500 mL of dry dimethoxyethane (DME) was stirred at room temperature for 30 min and treated with anhydrous $CuSO_4$ (35.1 g, 0.22 mol). The mixture was stirred under dry nitrogen, in the dark, at room temperature for 24 h, filtered, and concentrated *in vacuo*. The residue was triturated with 300 mL of 5% $NaHCO_3$, and the resulting solid was collected by filtration, washed with water, and dried *in vacuo* to give the desired product in 94% (35.1 g) yield: mp 203–204; ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 3.18 (s, 3H, CH_3), 6.88 (d, J = 2.2 Hz, 1H, N-C=CH), 7.0–7.58 (m, 4H, Ar), 7.60 and 8.17 (2d, 4H, Ar), 12.67 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 43.316 (s), 106.529 (s), 111.217 (s), 115.457 (s), 115.670 (s), 120.767, 124.166 (s), 127.246, 128.194, 130.219, 130.303, 131.046 (s), 131.076 (s), 131.774 (s), 136.151 (s), 139.398 (s), 159.979 (s), 162.406 (s); ^{19}F NMR (282.2 MHz, DMSO-d_6) δ −115.386; IR (nujol) 3350 (NH), 2170 (CN) cm^{-1}; MS (CH_4-Cl) m/e 372. Anal. Calcd for $C_{18}H_{13}FN_2O_2S_2$, MW 372.43: C, 58.05; H, 3.52; N, 7.52; S, 17.22. Found: C, 58.33; H, 3.60; N, 7.53; S, 17.48.

Method B. A suspension of 1 (15.8 g, 50 mmol) in 250 mL of DME was reacted with $Cu(SCN)_2$ and stirred at room temperature for 72 h. The mixture was filtered, and the filtrate was evaporated at 70 °C until the appearance of the first solid. The flask was left standing at room temperature for 24 h, and the resulting solid was collected by filtration and identified as starting pyrrole 1. The filtrate was concentrated *in vacuo*, and the residue was triturated with CCl_4. The resulting solid was collected by filtration and dried *in vacuo* at 100 °C to give 2 in 27% (5.0 g) yield: mp 192 dec; IR (nujol) 3320 (NH), 2180 (CN) cm^{-1}.

Method C.[4] A mixture of 1 (15.8 g, 50 mmol) and NH_4SCN (8.0 g, 105 mmol) in 50 mL of AcOH was cooled in an ice bath and treated with bromine (8.0 g, 50 mmol) in 25 mL of AcOH. The mixture was stirred in the ice bath for 30 min and at room temperature for 16 h. The mixture was poured into 1 L of cold water, and the resulting precipitate was collected by filtration. The crude product was chromatographed on silica gel (toluene–EtOAc, 3:2), and the desired product was obtained in 71% (13.2 g) yield: mp 202 dec.

3-(4-Fluorophenyl)-2-[4-(methylsulfonyl)phenyl]-5-(methylthio)-1*H*-pyrrole (3). A solution of 2 (10.0 g, 26.85 mmol) in 100 mL of MeOH was treated with KOH (1.5 g, 27 mmol) and stirred at room temperature for 3 h under nitrogen. The mixture was concentrated *in vacuo*. The impure product was column chromatographed on silica gel (toluene–EtOAc, 3:2), and appropriate fractions were combined and concentrated to a solid. The solid was triturated with CCl_4, collected by filtration, and dried *in vacuo* to give the desired product in 80% (7.8 g) yield: mp 171–173; ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 2.43 (s, 3H, SCH_3), 3.18 (s, 3H, SO_2CH_3), 6.25 (d, 1H, N-C=CH), 6.7–7.87 (2m 8H, Ar), 11.73 (s, 1H, NH); IR (nujol) 3290 (NH) cm^{-1}; MS (CH_2-CI) m/e 361. Anal. Calcd for $C_{18}H_{16}FNO_2S_2$, MW 361.45: C, 59.81; H, 4.46; N, 3.88; S, 17.74. Found: C, 59.80; H, 4.29; N, 3.86; S, 17.60.

***S*-[4-(4-Fluorophenyl)-1-methyl-5-[4-(methylsulfonyl)-phenyl]-1*H*-pyrrole] Thiocyanic Acid Ester (4b).** A suspension of NaH (2.7 g, 112.5 mmol) in 200 mL of dry DMF was cooled in an ice bath and treated in small portions over 30 min with 1 (31.5 g, 99.9 mmol). The mixture was stirred in the ice bath for 30 min and at room temperature for 1 h and treated with MeI (15.6 g, 110 mmol). The mixture was stirred at room temperature for 16 h, and the resulting crystals were collected by filtration, washed with water, and dried to give 3-(4-fluorophenyl)-1-methyl-2-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole (**4a**) in 100% (32.9 g) yield: mp 225–226; IR (nujol) no N-H.

A solution of thiocyanogen $(SCN)_2$ was produced in CCl_4 by reacting $Pb(SCN)_2$ (22.1 g, 68.5 mmol) and bromine (9.9 g, 62.2 mmol) and treated with **4a** (20.5 g, 62.2 mmol) at room temperature for 72 h. The mixture was concentrated *in vacuo*, and the residue was triturated with petroleum ether, collected by filtration, and dried to give the desired product in 93% (22.4 g) yield: mp 176–178; ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 3.23 (s, 3H, CH_3), 3.67 (s, 3H, CH_3), 6.7–7.3 (m, 5H, N-C=CH, 4-FPh), 7.4 and 8.1 (2d, 4H, 4-SO_2Ph); IR (nujol) 2160 (CN) cm^{-1}; MS (CH_4-CI) m/e 386. Anal. Calcd for $C_{19}H_{15}FNO_2S_2$, MW 386.46: C, 59.05; H, 3.91; N, 7.25; S, 16.69. Found: C, 58.69; H, 3.80; N, 7.33; S, 16.85.

2-Bromo-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole (5). Method D. A solution of 1 (31.5 g, 0.1 mol) in 200 mL of DMF was cooled in an ice bath and treated with a solution of N-bromosuccinimide (NBS) (18.0 g, 0.1 mol) in 100 mL of DMF. The mixture was stirred in the ice bath until no starting pyrrole was detected by TLC (toluene–EtOAc, 3:2). The mixture was in the ice bath until no starting pyrrole was detected by TLC (toluene–EtOAc, 3:2). The mixture was diluted with 1 L of cold water. The resulting solid was collected by filtration, washed with 5% $NaHCO_3$ and water, and air-dried to give the product in 100% (41.5 g) yield as the monohydrate. An analytical sample was recrystallized from 2-propanol to give the desired compound as an anhydrous tan crystal: mp 169–170; ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 3.23 (s, 3H, CH_3) 6.36 (d, J = 2.2 Hz, 1H, C=CH), 7.08–7.35 (m, 4H, 4-FPh), 7.50 (d, J = 8.4 Hz, 2H), 7.84 (d, J = 8.4 Hz, 2H, 4-SO_2Ph), 12.15 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 43.430, 101.249, 112.719, 115.571, 115.190, 123.870, 127.132, 127.253, 127.268, 127.359, 127.397, 130.159, 130.234, 131.645, 131.676, 136.705, 138.283, 159.865, 162.285; ^{19}F NMR (282.2 MHz, DMSO-d_6) δ −115.661; IR (nujol) 3300 (NH) cm^{-1}; MS (CH_4-CI) m/e 393 (395). Anal. Calcd for $C_{17}H_{13}BrFNO_2S$, MW 394.27: C, 51.87; H, 3.32; N, 3.55; S, 8.13. Found: C, 51.83; H, 3.42; N, 3.68; S, 8.27.

Alternatively, **14b** was dissolved in CH_2Cl_2 and treated with 20% TFA to give **5** in 96% yield: mp 168–170; IR (nujol) 3300 (NH) cm^{-1}; MS (CH_4-CI) m/e 393, 395.

Compound **5** was also prepared by reacting **21b** (2.18 g, 5.0 mmol) with KOH (0.56 g, 10 mmol) in 25 mL of EtOH and 5 mL of water for 16 h at room temperature. The mixture was

concentrated *in vacuo*, and the residue was triturated with water. The resulting solid was collected by filtration, washed with water, dried, and recrystallized from EtOH–hexane to give the desired product in 96% (1.90 g) yield: mp 168–170; IR (nujol) 3290 (NH) cm^{-1}, no carbonyl; MS (CH_4-Cl) *m/e* 393, 395. In a similar manner, **17b** was treated with KOH in EtOH to give **5** in 97% yield: mp 168–170.

4-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole-2-sulfonic Acid, Pyridine Salt (6). A mixture of **1** (10.4 g, 33.0 mmol) and sulfur dioxide–pyridine (5.3 g, 33.0 mmol) in 150 mL of dry THF was refluxed for 16 h, cooled to room temperature, and left standing for 24 h. The resulting suspension was filtered, and the solid and filtrate were inspected by TLC (toluene–EtOAc, 3:2). The filtrate contained mostly starting pyrrole, and the solid contained only product. The solid was triturated with 50 mL of THF, collected by filtration, washed with Et_2O, and dried *in vacuo* to give the desired product in 64% (10.0 g) yield: mp 137–139; ^1H NMR (300 MHz, DMSO-d_6 TMS) δ 3.30 (s, 3H, CH_3), 6.5 (m, 1H, N-CH=C), 6.97–9.42 (m, 12H, Ar); IR (nujol) 3450 (NH) cm^{-1}; MS (CH_4-CI) *m/e* 395. Anal. Calcd for $C_{17}H_{14}NO_5S_2\ C_5H_5N$, MW 474.52: C, 55.68; H, 4.04; N, 5.90; S, 13.51. Found: C, 55.97; H, 4.10; N, 6.29; S, 13.78.

1-[4-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrol-2-yl]-2,2,2-trifluoroethanone (7). A solution of **1** (10.0 g, 31.7 mmol) in 100 mL of dichloroethane was treated dropwise with trifluoroacetic anhydride (6.7 g, 31.7 mmol) and refluxed for 3 h. The purple mixture was concentrated *in vacuo*, and the residue was triturated with 200 mL of Et_2O. The resulting solid was collected by filtration, washed with Et_2O, and dried to give the desired product in 96% (12.5 g) yield: mp 282–283; ^1H NMR (300 MHz, DMSO-d_6 TMS) δ 3.20 (s, 3H, CH_3), 6.8–7.5 (m, 5H, N-C=CH, 4-FPh), 7.50 and 8.10 (2d, 4H, 4-SO_2Ph), 13.10 (s, 1H, NH); *IR* (nujol) 3240 (NH), 1670 (C=O) cm^{-1}; MS (CH_4-CI) *m/e* 411. Anal. Calcd for $C_{19}H_{13}F_4NO_3S$, MW, 411.37; C, 55.47; H, 3.18; N, 3.41; S, 7.80; S, 7.80. Found: C, 55.41; H, 4.01; N, 3.47; S, 8.10.

2-Iodo-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole (8). By substituting *N*-iodosuccinimide (NIS) in Method D, the desired product was prepared in 50% yield: mp 229–231; ^1H NMR (300 MHz, DMSO-d_6 TMS) δ 3.12 (s, 3H, CH_3), 6.40 (s, 1H, C=CH), 7.2 (m, 4H, 4-FPh), 7.40 and 7.83 2d, 4H, 4-SO_2Ph), 12.3 (s, 1H, NH); IR (nujol) 3290 (NH) cm^{-1}; MS (CH_4-CI) *m/e* 441. Anal. Calcd for $C_{17}H_{13}IFNO_2S$, MW 441.26; C, 46.27; H, 2.97; N, 3.18; S, 7.27. Found: C, 46.10, H, 2.85; N, 3.20; S, 7.17.

3-(4-Fluorophenyl)-5-(methylsulfonyl)-2-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole (9). A suspension of **3** (7.0 g, 19.37 mmol) in 150 mL of MeOH–H_2O (1:1) was treated with Oxone (9.7 g) and stirred at room temperature until no starting material remained as evidenced by TLC ($CHCl_3$–MeOH, 9:1). The mixture was concentrated *in vacuo*, and the residue was triturated with 100 mL of water. The resulting pink solid was collected by filtration, washed with water and Et_2O, and dried *in vacuo* to give the desired product in 100% (7.6 g) yield: mp 224 dec; ^1H NMR (300 MHz, DMSO-d_6 TMS) δ 3.24 (s, 3H, CH_3), 3.30 (s, 3H, CH_3), 6.97 (d, 1H, N-C=CH), 7.0–7.45 (m, 4H, 4-FPh), 7.45 and 8.10 (2d, 4H, 4-SO_2Ph), 12.63 (s, 1H, NH); IR (nujol) 3320 (NH), 1320 cm^{-1}; MS (CH_4-CI) *m/e* 393. Anal. Calcd for $C_{18}H_{16}FNO_4S_2$, MW 393.45; C, 54.94; H, 5.00; N, 3.56; S, 16.30. Found: C, 54.88; H, 5.06; N, 3.63; S, 16.24.

2-Chloro-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole (10). By substituting *N*-chlorosuccinimide (NCS) in method A, the compound was synthesized in 95% yield: mp 206–208; ^1H NMR (300 MHz, DMSO-d_6 TMS) δ 3.23 (s, 3H, CH_3), 6.30 (s, 1H, C=CH), 7.07–7.37 (m, 4H, FPh), 7.52 and 7.85 (2d, 4H, SO_2Ph), 12.20 (s, 1H, NH); IR (nujol) 3280 (NH) cm^{-1}; MS (CH_4-CI) *m/e* 349. Anal. Calcd for $C_{17}H_{13}ClFNO_2S$, MW 349.81; C, 58.37; H, 3.75; N, 4.00; S, 9.17. Found: C, 58.54; H, 3.79; N, 4.20; S, 8.97.

5-Bromo-3-(4-fluorophenyl)-1-methyl-2-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole (11). A solution of **5** (6.7 g, 17 mmol) in 50 mL of DMSO was treated with NaH (0.41 g, 17 mmol) and stirred for 30 min. The mixture was reacted with 1.1 equiv of MeI in 25 mL of DMSO, stirred at room temperature for 16 h, and poured into 500 mL of water. The resulting precipitate was collected by filtration, washed with water, and air-dried to give the desired product in 96% (6.7 g) yield: mp 196–197 dec; ^1H NMR (300 MHz, DMSO-d_6 TMS) δ 3.10 (s, 3H, NCH_3), 3.50 (s, 3H, SO_2CH_3), 6.40 (s, 1H, N-C=CH), 6.8–7.2 (m, 4-FPh), 7.43 and 7.92 (2d, 4H, 4-SO_2Ph); MS (CH_4-CI) *m/e* 407 (409). Anal. Calcd for $C_{18}H_{15}BrFNO_2S$, MW 408.30: C, 52.95; H, 3.70; N, 3.34; S, 7.85. Found: C, 52.73; H, 3.71; N, 3.55; S, 7.76.

Alternatively, **1** was reacted with NaH and MeI to give **4a** (yield 97%, mp 226–227) which was reached with NBS as in method D to give the 1-methyl-2-bromopyrrole derivative **11** in an overall yield of 93%: mp 196–197.

4-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole-2-carbonitrile (12). A suspension of **1** (15.8 g, 50 mmol) in 100 mL of dry THF was cooled to −78 °C and treated dropwise with chlorosulfonyl isocyanate (10.6 g, 75 mmol). The mixture was stirred vigorously at −78 °C for 90 min and treated with dry DMF (10 mL). The mixture was allowed to reach room temperature and then poured onto 500 g of ice while vigorously stirring. The ice was allowed to melt, and the aqueous mixture was extracted with 3 × 200 mL of EtOAc. The extract was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* until the first appearance of solid. The "solution" was diluted with 200 mL of hexane and left standing for 16 h. The resulting solid was collected by filtration, washed with hexane, and dried to give the desired nitrile in 96% (16.3 g) yield: mp 223 dec; ^1H NMR (300 MHz, DMSO-d_6 TMS) δ 3.27 (s, 3H, CH_3), 7.1–7.4 (m, 5H, N-C=CH, 4-FPh), 7.56 and 7.93 (2d, 4H, 4-SO_2Ph), 11.20 (s, 1H, NH); IR (nujol) 3280 (NH), 2220 (CN) cm^{-1}; MS (CH_3-CI) *m/e* 340. Anal. Calcd for $C_{18}H_{13}FN_2O_2S$, MW 340.37; C, 63.51; H, 3.85; N, 8.23; S, 9.42. Found: C, 63.30; H, 3.66; N, 8.47; S, 9.25.

Alternatively, **5** (25 mmol) in 50 mL of DMF was treated with CuCN (25 mmol), refluxed for 5 h, and concentrated to a tar. The tar was dissolved in 100 mL of THF, filtered, concentrated, and column chromatographed on silica gel (toluene–EtOAc, 3:2). Appropriate fractions were combined and concentrated to a purple solid which was dissolved in 75 mL of THF, treated with activated carbon, and filtered to give a red filtrate. The filtrate was concentrated *in vacuo* and triturated with Et_2O. The resulting solid was collected by filtration, washed with Et_2O, and dried to give the desired nitrile in 21% (3.56 g) yield: mp 222–224; IR (nujol) 3280 (NH), 2230 (CN) cm^{-1}; MS *m/e* 340.

3-(4-Fluorophenyl)-2-[4-(methylsulfonyl)phenyl]-5-nitro-1*H*-pyrrole (13). Acetyl nitrile was prepared as described by Bordwell et al.[13-16] by adding 70% HNO_3 (4.5 g, 50 mmol) to acetic anhydride (35 mL, 371 mmol) and stirring at room temperature for 10 min. The acetyl nitrate ($CH_3C(=O)ONO_2$) (a potentially explosive reagent) solution was transferred to a dropping funnel and slowly added to a suspension of **1** (15.8 g, 50 mmol) in 100 mL of AcOH while stirring in an ice bath. The mixture was stirred in the ice bath for 1 h and concentrated *in vacuo* to a green solid (13.6 g) which appeared by TLC (toluene–EtOAc, 3:2) to decompose. The solid was triturated with Et_2O, collected by filtration, and dried *in vacuo* to give the desired product in 28% (5.1 g) yield: mp 241–243; ^1H NMR (300 MHz, DMSO-d_6 TMS) δ 3.27 (s, 3H, CH_3), 7.07–7.37 (m, 4H, 4-FPh), 7.40 (s, 1H, N-C=CH), 7.63 and 7.93 (2d, 4H, 4-SO_2Ph), 12.1 (s, 1H, NH); IR (nujol) 3310 (NH) cm^{-1}; MS (CH_4-CI) *m/e* 360. Anal. Calcd for $C_{17}H_{13}FN_2O_4S$, MW 360.36: C, 56.66; H, 3.64; N, 7.78; S, 8.90. Found: C, 56.78; H, 3.80; N, 7.49; S, 8.66.

1,1-Dimethylethyl 5-Bromo-3-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole-1-carboxylic Acid Ester (14b). A suspension of **1** (31.56 g, 0.1 mol) and (dimethylamino)pyridine (0.12 g) in 300 mL of dry acetonitrile was treated with di-*tert*-butyl dicarbonate (24.0 g, 0.11 mol) and stirred at room temperature for 24 h. The mixture was poured into 1 L of water while vigorously stirring. The resulting solid was collected by filtration, washed with water, and dried *in vacuo* to give 1,1-dimethylethyl 3-(4-fluorophenyl)-2-[4-(methylsulfonyl)-phenyl]-1*H*-pyrrole-1-carboxylic acid ester (**14a**) in 98% (40.6 g) yield: mp 262–263; ^1H NMR (300 MHz, DMSO-d_6 TMS) δ 1.26 (s, 9H, ^tBu), 3.22 (s, 3H, SCH_3), 6.54 (d, 1H, N-C=CH), 7.1 (m, 4H, 4-FPh), 7.50 (m, 3H), 7.92 (d, 2H, N-CH=C, 4-SO_2Ph); IR (nujol) 1760 (C=O) cm^{-1}; MS (CH_4-CI) *m/e* 415. Anal. Calcd for $C_{22}H_{22}FNO_4S$, MW 415.48; C, 63.59; H, 5.34; N, 3.37; S, 7.72. Found: C, 63.58; H, 5.40; N, 3.34; S, 7.69.

Compound **14a** was reacted with NBS as in method D to give the desired product in 68% yield after recrystallization from hexane-Et_2O: mp 121 dec; ^1H NMR (300 MHz, DMSO-d_6 TMS) δ 1.23 (s, 9H, ^tBu), 3.23 (s, 3H, CH_3), 6.77 (s, 1H, N-C=CH), 7.1 (m, 4H, 4-FPh), 7.50 and 7.95 (2d, 4H, 4-SO_2Ph); IR (nujol) 1760 (C=O) cm^{-1}; MS (CH_4-CI) *m/e* 494. Anal. Calcd for $C_{22}H_{21}BrFNO_4S$, MW 494.39: C, 53.44; H, 4.28; N, 2.83; S, 6.49. Found: C, 53.61; H, 4.01; N, 2.83; S, 6.22.

2,3-Diiodo-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole (15). By substituting **8** and NIS in method D, the desired product was obtained in 100% yield. Alternatively, 2-[4-(methylsulfonyl)phenyl]-3-(4-fluorophenyl)-1*H*-pyrrole[3] was treated with 2.1 equiv of NIS under the conditions in method A to produce the diiodo derivative in 100% yield: mp 226 dec; ^1H NMR (300 MHz, DMSO-d_6 TMS) δ 3.20 (s, 3H, CH_3), 7.2 (m, 4H, 4-FPh), 7.37 and 7.80 (2d, 4H, 4-SO_2Ph), 12.38 (s, 1H, NH); IR (nujol) 3300 (NH) cm^{-1}; MS (CH_4-CI) *m/e* 567. Anal. Calcd for $C_{17}H_{12}I_2FNO_2S$, MW 567.17: C, 36.00; H, 2.13; N, 2.47; S, 5.65. Found: C, 36.07; H, 2.28; N, 2.38; S, 5.80.

2,3-Dibromo-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole (16). A solution of **5** (3.9 g, 0.01 mol) in 50 mL of DMF was treated with NBS (1.8 g, 0.01 mol) and stirred at room temperature until no starting material was evidenced by TLC (toluene–EtOAc, 3:2). The mixture was poured into 500 mL of cold water. The resulting solid was collected by filtration, washed with water and 5% $NaHCO_3$, and dried to give the desired product in 100% (4.70 g) yield: mp 247 dec; ^1H NMR (300 MHz, DMSO-d_6 TMS) δ 3.20 (s, 3H, CH_3), 7.25 (m, 4H, 4-FPh). 7.42 and 7.83 (2d, 4H, 4-SO_2Ph); IR (nujol) 3340 (NH) cm^{-1}; MS (CH_4-CI) *m/e* 471 (473, 475). Anal. Calcd for $C_{17}H_{12}Br_2NO_2S$, MW 473.18: C, 43.15; H, 2.56; N, 2.96; S, 6.78. Found: C, 43.05; H, 2.61; N, 2.95; S, 6.79.

5-Bromo-3-(4-fluorophenyl)-1-[4-(methylphenyl)sulfonyl]-2-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole (17b). A solution of **1** (31.5, 0.1 mol) in 200 mL of dry DMF was cooled in an ice bath, treated with NaH (2.4 g, 0.1 mol), and stirred for 1 h. The mixture was treated with *p*-toluenesulfonyl chloride (19.0 g, 0.1 mol) and stirred at room temperature for 3 h. The mixture was poured into 1 L of cold water, and the resulting precipitate was collected by filtration, washed with water and Et_2O, and dried to give 3-(4-fluorophenyl)-1-[4-(methylphenyl)sulfonyl]-1-[4-methylsulfonyl)phenyl]-1*H*-pyrrole (**17a**) in 100% (46.9 g) yield: mp 228–229. By substituting **17a** in method D, the desired product was obtained in 68% yield after recrystallization for $CHCl_3$: mp 207–208; ^1H NMR (300 MHz, DMSO-d_6 TMS) δ 2.43 (s, 3H, $ArCH_3$), 3.30 (s, 3H, SO_2CH_3), 6.90 (s, 1H, N-C=CH), 7.0–8.0 (m, 8H, Ar); MS (CH_4-CI) *m/e* 547, 549. Anal. Calcd for $C_{24}H_{19}BrFNO_4S_2$, MW 548.25: C, 52.57; H, 3.49; N, 2.56; S, 11.70. Found: C, 52.50; H, 3.46; N, 2.41; S, 11.49.

2-Bromo-3-chloro-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole (18). A solution of **5** (19.7 g, 50 mmol) in 100 mL of DMF was treated with NCS (6.7 g, 50 mmol), stirred for 4 h at room temperature, and poured into 1 L of cold water. The resulting precipitate was collected by filtration, washed with water, and dried to give the desired product in 98% (21.0 g) yield: mp 231.5 dec; ^1H NMR (300 MHz, DMSO-d_6 TMS) δ 3.20 (s, 3H, CH_3), 7.25 (m, 4H, 4-FPh), 7.43 and 7.83 (2d, 4H, 4-SO_2Ph), 12.7 (s, 1H, NH); IR (nujol) 3340 (NH) cm^{-1}; MS (CH_4-CI) *m/e* 428. Anal. Calcd for $C_{17}H_{12}BrClFNO_2S$, MW 428.72: C, 47.63; H, 2.82; N, 3.27; S, 7.46. Found: C, 47.60; H, 2.77; N, 3.50; S, 7.63.

2,3-Dichloro-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole (19). By substituting 2-chloro and NCS in method B, the desired dichloro derivative was obtained in 94% yield: mp 200 dec; ^1H NMR (300 MHz, DMSO-d_6 TMS) δ 3.20 (s, 3H, CH_3), 7.1–7.3 (m, 4H, 4-FPh), 7.43 and 7.83 (2d, 4H, 4-SO_2Ph); IR (nujol) 3280 (NH) cm^{-1}; MS (CH_4-CI) *m/e* 383 (385). Anal. Calcd for $C_{17}H_{12}Cl_2FNO_2S$, MW 384.26: C, 53.14; H, 3.15; N, 3.65; S, 8.34. Found: C, 53.44; H, 3.12; N, 3.65; S, 8.30.

2-Chloro-3-bromo-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole (20). By substituting **10** and NBS in the synthesis of **18**, the desired product was obtained in 97% yield: mp 208 dec; ^1H NMR (300 MHz, DMSO-d_6 TMS) δ 3.20 (s, 3H, CH_3), 7.27 (m, 4H, 4-FPh), 7.42 and 7.83 (2d, 4H, 4-SO_2Ph), 12.75 (s, 1H, NH); IR (nujol) 3280 (NH) cm^{-1}; MS (CH_4-CI) *m/e* 428. Anal. Calcd for $C_{17}H_{12}BrClFNO_2S$, MW 428.72: C, 47.62; H, 2.82; N, 3.27; S, 7.48. Found: C, 47.41; H, 2.82; N, 3.32; S, 7.17.

1-[5-Bromo-3-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]-1*H*-pyrrol-1-yl]ethanone (21b). A solution of **1** (15.8 g, 0.05 mol) in 150 mL of dry DMF was treated with *N*-acetylimidazole (mp 89–95 °C) (6.06 g, 0.055 mol) and stirred for 1 h at room temperature. The mixture was diluted with 50 mL of Ac_2O, refluxed for 16 h, and concentrated *in vacuo*. The residue was column chromatographed on neutral alumina using toluene–EtOAc (3:2), and the appropriate fractions were combined and concentrated to give the intermediate *N*-acetylpyrrole **21a**. By treating **21a** with NBS as in method D, the desired product was obtained in 25% yield after chromatography on neutral alumina (toluene-EtOAc, 3:2): mp 121–125; ^1H NMR (300 MHz, DMSO-d_6 TMS) δ 2.40 (s, 3H, $COCH_3$), 3.27 (s, 3H, SO_2CH_3), 6.78 (s, 1H, N-C=CH), 7.0–7.2 (m, 4H, 4-FPH), 7.50 and 7.93 (2d, 4H, 4-SO_2-Ph); IR (nujol) 1740 (C=O) cm^{-1}; MS (CH_4-CI) *m/e* 435, 437. Anal. Calcd for $C_{19}H_{15}BrFNO_3S$, MW 436.21: C, 49.26; H, 3.26; N, 3.02; S, 6.92. Found: C, 48.89; H, 3.30; N, 3.33; S, 6.81.

5-Chloro-3-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole-1-pentanoic Acid Ethyl Ester (22). A solution of **1** (15.8 g, 50 mmol) in 100 mL of DMSO was cooled in an ice bath and treated in small portions with NaH (1.2 g, 50 mmol). The mixture was stirred in the ice bath for 30 min and treated with ethyl 5-bromovalerate (10.5 g, 50 mmol). The mixture was stirred in the ice bath for 1 h and for 16 h at room temperature. The mixture was poured into 1 L of water and extracted with 2 × 200 mL of EtOAc. The extract was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was column chromatographed on silica gel using toluene–EtOAc (3:2) as solvent. Appropriate fractions were combined, concentrated *in vacuo*, and triturated with petroleum ether to give the desired product in 78% (17.3 g) yield after collection by filtration and drying *in vacuo*: mp 73–75. Anal. Calcd for $C_{24}H_{26}FNO_4S$, MW 443.53: C, 65.01; H, 5.98; N, 3.08; S, 6.73. Found: C, 64.99; H, 5.91; N, 3.16; S, 6.23.

The above alkylated pyrrole was reacted with NCS as in method D to give the desired product in 51% yield: mp 74–78; ^1H NMR (300 MHz, DMSO-d_6 TMS) δ 1.13 (t, 3H, CH_3), 1 (33 and 1, 2m, 47H, CH_2CH_2), 2.13 (t, 2H, NCH_2), 3.30 (s, 3H, SO_2CH_3), 3.87 (t, 2H, CH_2CO), 4.00 (q, 2H, OCH_2), 6.50 (s, 1H, N-C=CH), 7.1 (m, 4H, 4-FPh), 7.55 and 7.98 (2d, 4H, 4-SO_2Ph); IR (nujol) 1720 cm^{-1}; MS (CH_4-CI) *m/e* 477, 479. Anal. Calcd for $C_{24}H_{25}ClFNO_4S$, MW 477.98: C, 60.31; H, 5.27; N, 2.93; S, 6.71. Found: C, 60.03; H, 5.30; N, 2.92; S, 6.68.

2,3-Dibromo-4-(4-fluorophenyl)-1-methyl-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole (23). A mixture of **4a** (5.0 g, 15.18 mmol) and NBS (5.4 g, 30.37 mmol) in 100 mL of CH_2Cl_2 was stirred at room temperature until TLC (toluene-EtOAc, 3:2) indicated no starting pyrrole remained (~30 min). The mixture was transferred to a separatory funnel containing 200 mL of 5% $NaHCO_3$. The organic layer was washed with water and brine, dried over $MgSO_4$, and filtered. The filtrate was treated with petroleum either to the cloud point and set aside for 1 h. The resulting crystals were collected by filtration, washed with petroleum ether, and dried to give the desired product in 100% (7.40 g) yield: mp 188–191; ^1H NMR (300 MHz, DMSO-d_6 TMS) δ 3.27 (s, 3H, CH_3), 3.57 (s, 3H, CH_3), 7.13 (d, 4H, 4-FPh), 7.50 and 7.93 (2d, 4H, 4-SO_2Ph); MS (CH_4-CI) *m/e* 485, 487, 489. Anal. Calcd for $C_{18}H_{14}Br_2FNO_2S$, MW 487.20: C, 44.37; H, 2.90; N, 2.88; S, 6.58. Found: C, 44.31; H, 2.92; N, 2.76; S, 6.50.

2,3-Dichloro-4-(4-fluorophenyl)-1-methyl-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole (24). By substituting **4a** in the synthesis of **23** and using 2.1 equiv of NCS, the desired product was obtained in 100% yield: mp 200–201; ^1H NMR (300 MHz, DMSO-d_6 TMS) δ 3.25 (s, 3H, CH_3), 3.52 (s, 3H, CH_3), 7.15 (m, 4H, 4-FPh), 7.50 and 7.93 (2d, 4H, 4-SO_2Ph); MS (CH_4-CI) *m/e* 397, 401. Anal. Calcd for $C_{18}H_{14}Cl_2FNO_2S$, MW 298.28: C, 54.28; H, 3.54; N, 3.52; S, 8.05. Found: C, 54.53; H, 3.49; N, 3.58; S, 8.11.

Attempted Synthesis of 2-Fluoro-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole (25). A solution of XeF_2 (2.10 g, 12.4 mmol) in 100 mL of dry THF was cooled to −78 °C and treated with a solution of **1** (7.7 g, 24.4 mmol) in 50 mL of dry THF. The reaction mixture was stirred at −78 °C for

15 min and allowed to stir for an additional 5 h at 0 °C. The mixture was filtered under dry nitrogen, and the filtrate was concentrated *in vacuo*. The residue was triturated with a mixture of toluene–EtOAc (4:1) and filtered, and the filtrate was concentrated *in vacuo* and subjected to chromatography on silica gel using EtOAc–hexanes (1:1) as mobile phase. Appropriate fractions were combined and concentrated *in vacuo* to give the desired product in 6.3% (0.26 g) yield, baed on XeF_2: mp 177–180; MS (CH_4-CI) *m/e* calcd for $C_{17}H_{13}NO_2F_2S$, 333.0635; found, 333.0625; calcd for $C_{17}H_{12}NO_2F_3S$, 351.0541; found, 351.0496. Anal. Calcd for $C_{17}H_{13}NO_2F_2S$, MW 333.36: C, 61.25; H, 3.93; N, 4.20; S, 9.62. Found: C, 61.22; H, 3.99; N, 4.23; S, 9.74. On the basis of high-resolution MS, the compound was considered to be contaminated by the 2,3-difluoro species.

Biological Methods. Established Adjuvant-Induced Arthritis in Rats.[20] Male Charles River rats (130–150 g) were injected subcutaneously in the plantar area of the right paw with 0.1 mL of adjuvant (Difco heat-killed, lyophilized *Mycobacterium butyricum* suspended in mineral oil, 5.0 mg/mL). Twenty nonarthritic controls were injected with mineral oil. The animals were held for 2 weeks to allow development of arthritis. Paw volumes (uninjected left hind paw) were measured, and the adjuvant-injected rats were culled and distributed to treatment groups of 10 of equal disease severity. Nonarthritic controls were distributed to two groups of 10. The rats were given oral doses of compound, PVA-Acacia (polyvinyl alcohol 1%, gum acacia, U.S.P. 5%), or 0.25% methocel (10 mL/kg) by gavage on that day and on the 6 following days. One day after the last dose, the paw volumes (uninjected left hind paw) were measured using a Ugo Basile volume differential meter Model 7101. Inhibiting effects were calculated by the following formula:

$$\%\ \mathrm{InH} = \{[\text{arthritic control mean paw volume (mL)}] - [\text{treatment group mean paw volume (mL)}]\}/\{[\text{arthritic control mean paw volume (mL)}] - [\text{nonarthritic control mean paw volume (mL)}]\} \times 100$$

Dose response regression lines of the percent inhibition were plotted, and the effective dose for 50% inhibition from control paw volume (ED_{50}, mg/kg) was determined. The standard error (SE) for this assay had been found to be $<\pm 20\%$.

Pharmacokinetic Studies. Male Sprague–Dawley rats (300–400 g) were dosed orally and intravenously with liquid formulations of **2**, **5**, **10**, **11**, **12**, and **16**. Plasma samples were collected from groups of three rats each at each time point, including the last 96-h postdose. Plasma (1 mL) was spiked with 20 μg of an internal standard and extracted with 10 mL of diethyl ether: cyclopentane: isopropyl alcohol (99.5:99.5:1). After being shaken for 30 min and centrifuged at 3000 rpm for 5 min, the organic layer was removed, transferred to a clean tube, and dried to completion under dry nitrogen. The residue was reconstituted in 200 μL of acetonitrile:water (65:35) for analysis.

A 50-mL aliquot of the solution was injected onto an HPLC system composed of a Perkin-Elmer Series 4 pump, a Perkin-Elmer Model ISS-100 autosampler, and a Zorbax 4.6- × 250-mm ODS column. Analyses were conducted isocratically. The mobile phase ranged from 30% to 60% acetonitrile in water and flowed at 1.5 mL/min. Absorbance was measured at 310 nm using a Perkin-Elmer LC-95 UV–vis detector. Data were collected by Hewlett-Packard 3390 A integrator.

12-Day Oral Tolerance in Long Evans Rats. Drugs were dosed at 0.0 (control), 10 ×, 20 ×, and 40 × AA ED_{50} (mg/kg/day) to 10 male Long Evans hooded rats (BLU:[LE]BS) once a day for 12 consecutive days. The drugs were formulated in 0.25% aqueous methyl cellulose (1500 CPS), and the particle size was 91% < 10 μm and 9% = 11–25 μm. Evaluations were made of mortality, signs of pharmacologic or toxic effect, body weight, organ weights, and gross necropsy findings. Results were expressed as the "maximum no-effect dose" and the "maximum tolerated dose".

Gastrointestinal Toxicity (GI Lesion) Assay. The gastrointestinal safety of a drug was evaluated relative to indomethacin and piroxicam. Male Sprague–Dawley rats weighing approximately 165 g were given single po doses of drug or vehicle. Eighteen to twentyfour hours after dosing, animals were anesthetized with 1.0% sodium pentobarbital ip in 0.9% saline. Each rat was injected iv with 1.0 mL of pontamine sky blue 6BX dye (15%, 0.9% saline) and euthanized. The small intestine and stomach were removed, opened, rinsed with tap water, and examined for the presence of mucosal lesions using a binocular dissecting microscope (10×) in coded, randomized order. Leakage of the protein-bound blue dye from damaged blood vessels aided visualization of mucosal changes. The occurrence of one lesion, regardless of its severity (erosion or hemorrhage), was considered a positive result. The median dose for production of gastrointestinal lesion (TD_{50}) was calculated by the moving-average method described by Thompson.[55]

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