# 1,2-Diarylpyrroles as Potent and Selective Inhibitors of Cyclooxygenase-2

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Series of 1,2-diarylpyrroles has been synthesized and found to contain very potent and selective inhibitors of the human cyclooxygenase-2 (COX-2) enzyme. The paper describes short and practical syntheses of the target molecules utilizing the Paal−Knorr reaction. Electrophilic substitution on **1** proceeds in a regioselective fashion, and the method was used to generate a number of tetrasubstituted pyrroles. Detailed SAR on the series has been studied by modifications of the aryl rings and the substituents in the pyrrole ring. Diarylpyrrole **1** is a very potent (COX-2, $IC_{50}$ = 60 nm) and selective (COX-1/COX-2 = >1700) inhibitor whereas the isomeric **2** is completely inactive against COX-2. Modifications of the substituents on the fluorophenyl ring in **1** yields very potent inhibitors of COX-2 ($IC_{50}$ = 40−80 nm) with excellent selectivity (1200 to >2500) *vs* COX-1. Analog **20** containing a sulfonamide group is an excellent inhibitor of COX-2 with an $IC_{50}$ of 14 nm. Tetrasubstituted pyrroles containing groups such as $COCF_3$, $SO_2CF_3$, or $CH_2OAr$ at position 3 in the pyrrole ring give excellent inhibitors (COX-2, $IC_{50}$ = 30−120 nm). *In vivo* testing in the carrageenan-induced paw edema model in the rat establishes that the 1,2-diarylpyrroles are orally active antiinflammatory agents. Compound **3** is the most potent inhibitor of edema with an $ED_{50}$ of 4.7 mpk.

## Introduction

Nonsteroidal antiinflammatory drugs (NSAIDs) are widely used for treatment of the symptoms of acute and chronic inflammatory disorders such as osteoarthritis and rheumatoid arthritis. These agents reduce the pain and swelling of joints by blocking the production of prostaglandins (PG's)[1] from arachidonic acid. The chronic usage of these agents has been associated with adverse effects including gastrointenstinal ulceration and suppression of renal function.[2] The undesirable effects associated with NSAIDs are also believed to be due to the inhibition of prostaglandin production in the affected organs. It has recently been shown that the cyclooxygenase enzyme exists in two isoforms—a constitutive form cyclooxygenase-1 (COX-1) and an inducible form cyclooxygenase-2 (COX-2).[3−5] The COX-1 enzyme is responsible for maintaining homeostasis (gastric and renal integrity) whereas COX-2 induces inflammatory conditions[6−8] in response to the inflammatory and mitogenic stimuli, suggesting that COX-1 and COX-2 serve different physiological and pathological functions.

The hypothesis that selective COX-2 inhibitors could offer therapeutic advantages over the current NSAIDs has generated a lot of interest in the field, and a number of research laboratories are aggressively pursuing this objective. In this regard diaryl heterocycles are emerging as attractive templates for the synthesis of potent and selective inhibitors of cyclooxygenase-2 enzyme. Several interesting compounds (e.g., DuP 697,[9] SC-58635,[10] and SC-57666[11]) (Chart 1) and other variants of the central ring system have been reported.[12,13] This paper describes the synthesis and structure−activity relationship studies of substituted 1,2-diarylpyrroles.

Bimetopyrol is one of the earlier known 4,5-diarylpyrroles[13a] showing a spectrum of antiinflammatory and analgesic properties similar to typical NSAIDs. In rats, chronic administration of bimetopyrol at >25 mpk caused gastrointenstinal ulceration in some animals, suggesting that the compound is probably a nonselective COX inhibitor. More recently, Wilkerson et al. have reported[13b−d] substituted 4,5-diarylpyrroles (e.g., **I** and **II**) as antiinflammatory agents. These compounds are believed to be competitive, time dependent inhibitors[12e] of COX-2. Although only moderately potent and selective against the COX-2 enzyme,[13c] these compounds seem to offer better gastrointestinal safety[13d] in laboratory animals.

As part of our search for a potent and selective inhibitor of COX-2, compound **III** was identified as a lead through a broad screening program. The compound was a weak inhibitor of human COX-2 ($IC_{50}$ = 4.6 $\mu$M) and COX-1 ($IC_{50}$ = 25 $\mu$M) enzymes. In the whole cell assays, the compound was active against COX-2 ($IC_{50}$ = 2.4 $\mu$M in IL-1-stimulated dermal fibroblasts) although not selective, COX-1 ($IC_{50}$ = 1.0 $\mu$M in retinoic acid stimulated HL-60 cells). Similarly, in the human whole blood assays, compound **III** inhibited both LPS-induced $PGE_2$ production ($IC_{50}$ = 1.5 $\mu$M) and the ionophore A23187-induced $TXB_2$ production ($IC_{50}$ = 0.3 $\mu$M). The substitution pattern and the biological profile of **III** seemed different than the other diaryl heterocycles reported in the literature, and this prompted us to explore the series in depth. In the first attempt, the effect of a non-carboxylic acid functionality (e.g., Me) on the potency of the COX enzymes was studied. The compounds (**V**) containing ($R_1$ = OMe or F) were inactive against the human COX-2 and COX-1 enzymes. Attempted replacement of the COMe group in structure **V** with other isosteres such as $CO_2Me$, $CO_2$-

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**Chart 1**

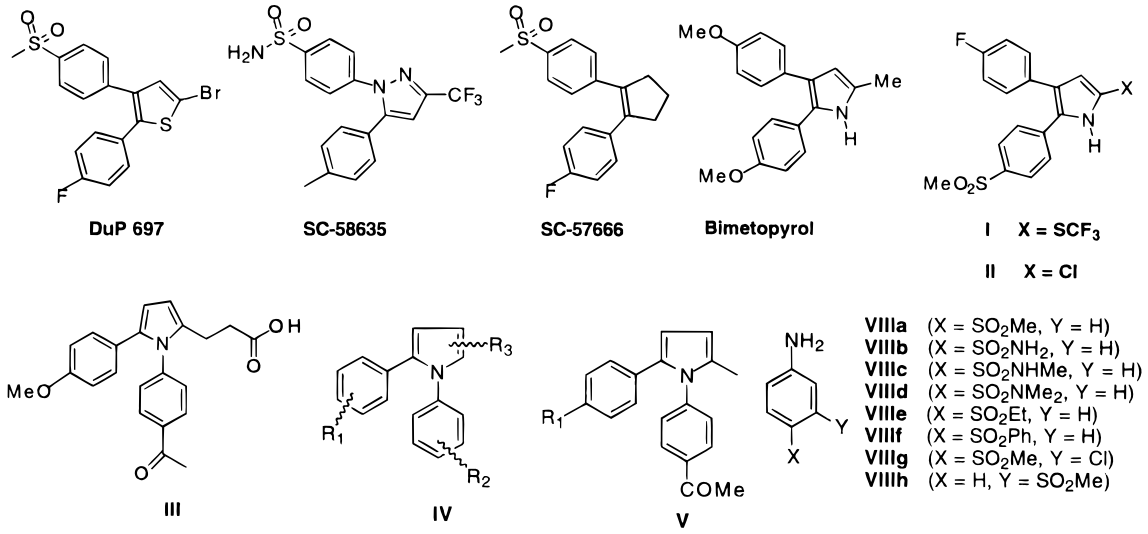
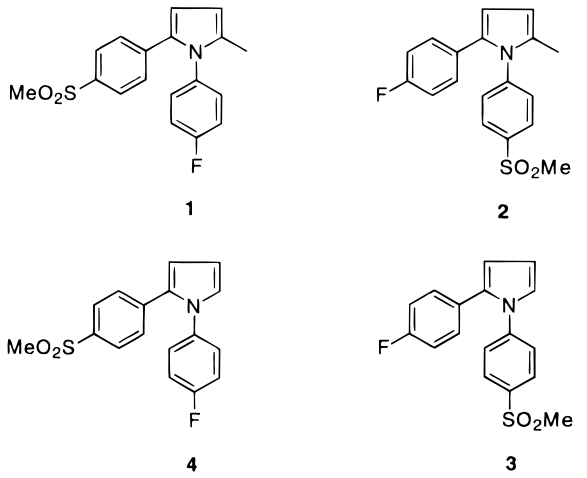



**Table 1.** 1,2-Diarylpyrroles as Cyclooxygenase Inhibitors **8** **37**

| compd | $IC_{50}$, $\mu$M COX-2 | $IC_{50}$, $\mu$M COX-1 | COX-1/COX-2 |
|---|---|---|---|
| **1** | 0.06 | >100 | >1700 |
| **2** | >100 | >100 | |
| **3** | 0.51 | >100 | >200 |
| **4** | 10.2 | >100 | |

$NEt_2$, SOMe, or $SO_2Me$ (**2**) gave inactive compounds against human COX-2.




Interestingly, on reversing the substitution of aryl groups in **2**, the resulting compound (**1**) showed excellent potency ($IC_{50}$, COX-2 = 60 nm) and selectivity ($IC_{50}$, COX-1 = >100 $\mu$M). Similarly, the desmethyl compound **3** inhibited COX-2 with an $IC_{50}$ = 0.5 $\mu$m while showing no inhibition of COX-1 at 100 $\mu$M. The isomer **4** obtained by reversing the aryl substitution pattern in **3** was much less potent. The activity of these isomeric pyrroles (**1**−**4**) against the human COX enzymes is summarized in Table 1. These results suggest that the presence of a substituent at C-5 in the pyrrole ring, next to the aryl ring bearing a $SO_2Me$ group, might have deleterious effect on its activity against COX-2 enzyme.[14] Although this observation would seem to contradict the biological activity observed with **III**, it is speculated that **III** containing the propionic acid chain might be binding to the COX enzymes differently[15] than the diarylpyrroles exemplified in this paper.

On the basis of the encouraging results reported in Table 1, different portions of the molecules **1** and **3** were modified to define and optimize the structural features essential for achieving the potency and selectivity against the human COX-2 and COX-1 enzymes.

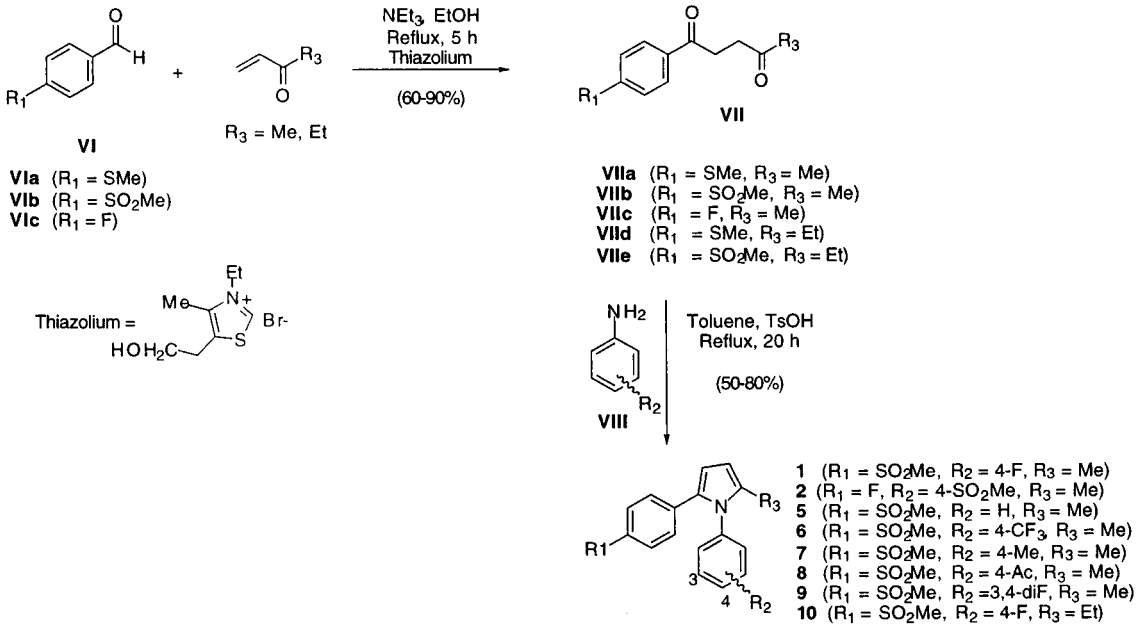
## Chemistry

Depending upon the substitution pattern, the 1,2-diarylpyrroles reported in this paper were synthesized using the Schemes 1−8. Our general synthetic strategy entailed the preparation of suitable 1,4-diketones followed by heating with appropriate amines in the Paal−Knorr condensation, cyclization to yield the targets. The analogs (**IV**) having an alkyl group ($R_3$ = Me or Et) at position 5 in the pyrrole ring were synthesized following the Schemes 1 and 2. The Stetter reaction[16] of substituted benzaldehydes with $\alpha,\beta$-unsaturated ketones using the thiazolium salt catalyst proved very versatile and high yielding ($NEt_3$, EtOH, reflux, 60−90%). One exception was the synthesis of methylsulfonyl bearing compound **VIIb**, which gave variable yields and was prepared preferentially by Oxone oxidation (MeOH/$H_2O$, room temperature, 2 h; >90%) of intermediate **VIIa**. The condensation of **VII** with aryl amines (Scheme 1) or aliphatic amines (Scheme 2) proceeded smoothly to give good yields (50−80%) of the desired pyrroles.

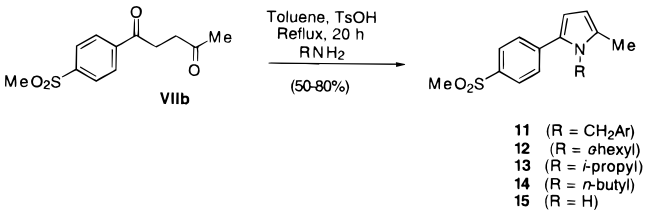
The syntheses of 1,2-diarylpyrroles without any substitution at position 5 in the pyrrole ring (e.g., **3** and **4**) were achieved utilizing the Schemes 3 and 4. In Scheme 3, the 2-(hydroxypropyl)-1,3-dioxane (**IX**) prepared[17] from dihydrofuran and 2,2-dimethyl-1,3-propanediol was oxidized to the aldehyde (**X**) using Swern oxidation. Addition of (4-fluorophenyl)magnesium bromide to **X** (−70 to 20 °C, 18 h; 87%), followed by oxidation of the resulting intermediate **XI** with PCC (20 °C, 3 h; 85%), gave the useful 1,4-keto acetal (**XII**). The intermediate **XII** was converted to the target pyrrole (**21**) by condensing with **VIIIc** in the presence of *p*-toluenesulfonic acid. The synthesis of reversed analog **4** was accomplished by conversion of **XII** to **XIII** by direct displacement ($NaSO_2Me$, DMF, 120−130 °C, 72 h; 79%) followed by the Paal−Knorr condensation with 4-fluoroaniline.

Alternately, these compounds could be prepared in a shorter route (Scheme 4) by reacting the Grignard reagent from commercially available 2-(2-bromoethyl)-1,3-dioxolane with 4-fluorobenzaldehyde (−70 °C, 2 h;

**Scheme 1**




**Scheme 2**




83%). Oxidation of the resulting alcohol (**XIV**) to the keto acetal (**XV**) followed by condensation and aromatization with substituted anilines under conditions described in Scheme 3 gave the desired pyrroles.

1,2-Diarylpyrroles containing a propionic acid side chain (**24** and **26**) were synthesized as shown in Scheme 5. The aldol condensation of furaldehyde with 4-fluoroacetophenone (NaOMe, MeOH, room temperature, 20 h) gave the unsaturated ketone **XVI** in 95% yield. The treatment of **XVI** with ethanol−aqueous hydrochloric acid (4/1) at 80−85 °C caused the furan ring opening, giving **XVII** and **XVIII** in yields of 33% and 26%, respectively. When subjected to reaction conditions individually, both **XVII** and **XVIII** yielded the thermodynamic ratio of the mixture (approximately 6/4) as judged by TLC. Compound **XVII** was reacted with **VIIIa** (TsOH, toluene, reflux; 76%) to give the pyrrole (**23**). The base hydrolysis of the ethyl ester (EtOH, aq. NaOH; 69%) yielded the targeted pyrrole (**24**) containing a propionic acid chain. To accomplish the synthesis of isomeric pyrrole **26**, compound **XVII** was converted to **XIX** by displacement reaction ($NaSO_2Me$, DMF, 135−140 °C, 30 h; 26%) and reacted with 4-fluoroaniline (TsOH, toluene, reflux; 75%). The base-catalyzed hydrolysis of the resulting ester (**25**) yielded the intended pyrrole (**26**) in 90% yield.

1,2-Diarylpyrrole (**27**) with a $CF_3$ group at position 5 was synthesized, in a one-step conversion from **4**, following the methodology reported by Baciocchi et al.[18] The reaction of **4** with trifluoromethyl iodide in the presence of $FeSO_4$ and $H_2O_2$ gave the desired **27** in an isolated yield of 43% (Scheme 6). The regiochemistry of the $CF_3$ group in the pyrrole ring was established using the NOE difference experiments.[19]

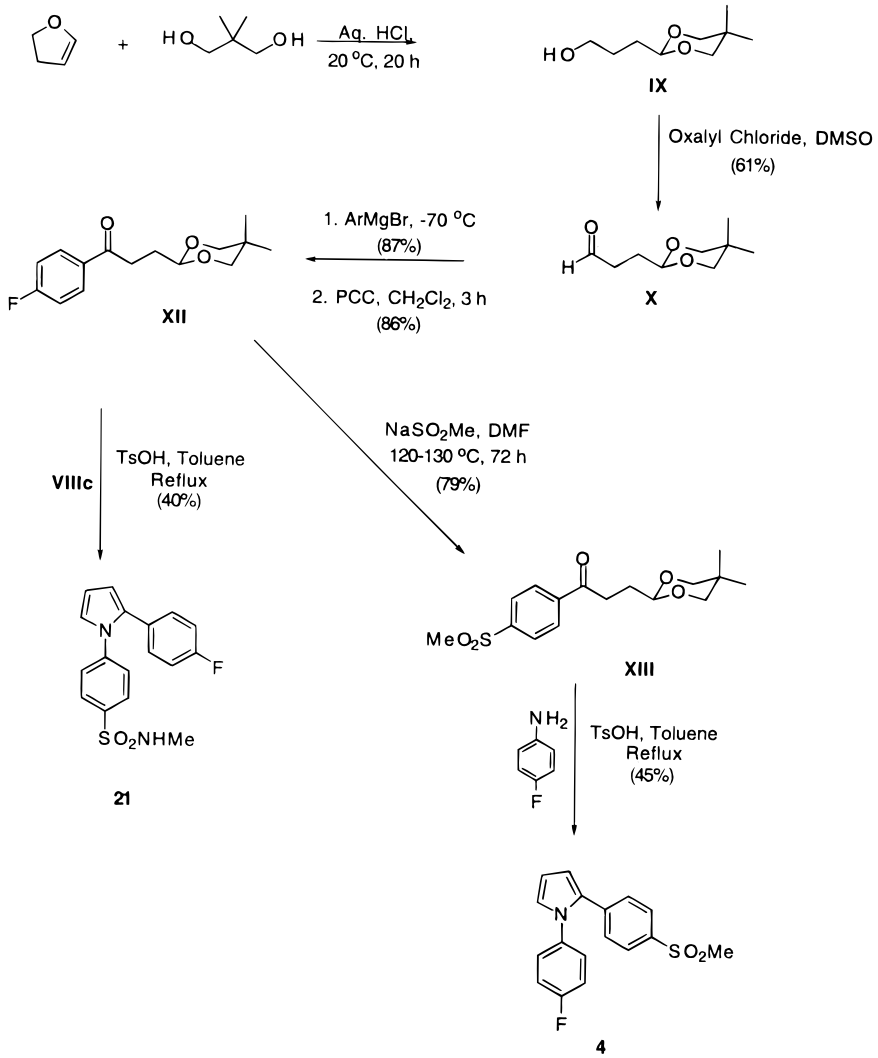
A number of tetrasubstituted pyrroles were synthesized (Scheme 7) by direct electrophilic substitution[20] on the pyrrole **1**. These reactions proceeded with very high regioselectivity, possibly because of the steric influence of the aryl ring bearing the methyl sulfone group. The regiochemistry of substitution was established by the NOE studies on the products. The yields on the reactions varied with electrophile chosen and the conditions employed (Table 2). No attempts were made to optimize the yields. The reaction of **1** with TFA−TFAA (50 °C, 3 h) gave **28** in 77% yield, whereas Friedel−Crafts acylations with acetyl chloride ($AlCl_3$, room temperature, 18 h), benzoyl chloride ($AlCl_3$, room temperature, 18 h), and triflic anhydride ($AlCl_3$, 44 °C, 48 h) gave **29**, **30**, and **31** in poorer yields (30%, 8%, and 10%, respectively) because of the lower conversions under the conditions used. The cyano derivative (**33**) was prepared in 77% yield by reaction with chlorosulfonyl isocyanate. Vilsmeier Haack ($POCl_3$, DMF) and Mannich (HCHO, $HNMe_2$) reactions gave **32** and **36** in yields of 71 and 23%, respectively. Similarly, reaction of **1** with AcOH and HCHO gave the acetoxymethylene derivative **37** in 22% yield. Direct halogenation of **1** with NBS and NCS gave the bromo (**34**) and the chloro (**35**) analogs in 88% and 10% yield, respectively.

The other substituents at position 3 in 1,2,3,5-tetrasubstituted pyrroles were obtained (Scheme 8) by manipulation of the functional groups. For example sodium borohydride reduction of **32** gave **38** in quantitative conversion. Compound **38** was reacted with substituted phenols under Mitsunobu reaction conditions ($PPh_3$, DEAD) to give the (aryloxy)methylene derivatives **39** and **40** (Scheme 8). The trifluoroacetyl group in **28** was subjected to similar transformations to yield **41** and **43**. The trifluoroethyl compound **42** was prepared from **41** using hydrogenation conditions (5% Pt on carbon, 60 psi, TFA, 48 h; 43%).

## Results and Discussion

All test compounds were evaluated for inhibitory activity against the consitutive (COX-1) and the inducible form (COX-2) of the human recombinant enzymes. Each $IC_{50}$ value is an average of at least two indepen-

**Scheme 3**



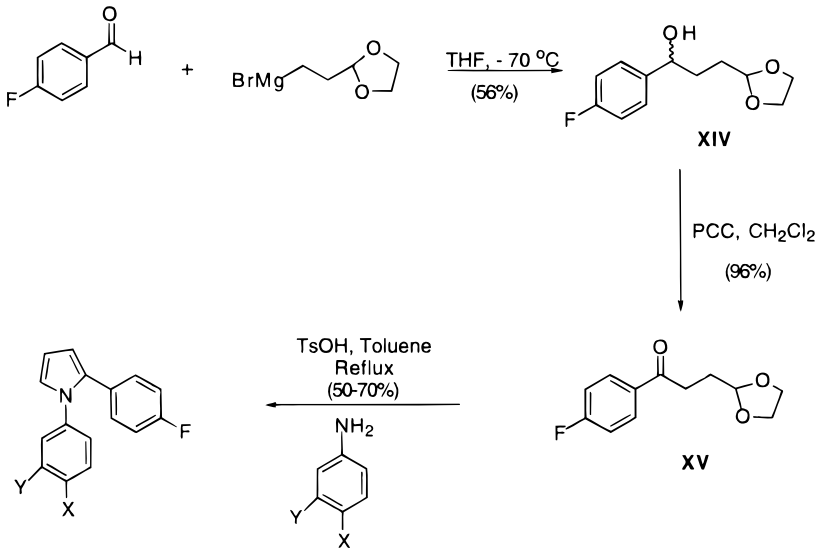

dent determinations. Some compounds were also tested in the cell and the human whole blood assay (see the Experimental Section). Potent and COX-2 selective compounds were studied further in the carrageenan-induced paw edema model in the rat.

**Aryl Ring Variations.** To evaluate the importance of 1,2-diaryl ring arrangement in **1**, the *N*-aryl ring was replaced by H or benzyl substituents (**15** and **11** in Table 3). Neither compound showed inhibition of the COX enzymes up to >100 $\mu$M. The cylcohexyl analog (**12**) was the most encouraging of these variations but was about 8 times less potent than the aryl analog (**1**). The branched alkyl or *n*-alkyl derivatives (e.g., **13** and **14**) were inactive, suggesting that the 1,2-diaryl arrangement was important for the optimum potency and selectivity in this series of compounds.

**Aryl Substituents.** Having established that aryl groups were important for optimum potency against the COX-2 enzyme, we concentrated our efforts on understanding the influence of aryl substituents on the activity (Table 4). Replacement of the fluoro substituent in **1** with H (**5**), Me (**7**), or $CF_3$ (**6**) resulted in very potent ($IC_{50}$ = 40−80 nm) and selective (COX-1/COX-2 = >1200) inhibitors of COX-2. The compound **8**, containing a substituent with increased size and polarity (COMe), was considerably less active. Similarly, the introduction of a smaller substituent such as F at position 3 (**9**) resulted in 3−4-fold loss of potency compared to **1**. The biological data in Table 3 indicates that this aryl ring might be somewhat forgiving and that the desirable biological properties might be accomplished by attenuating the substituents in this region.

**Aryl Sulfone Ring Modifications.** In order to understand the significance of $SO_2Me$ group in binding to the COX enzymes, both the sulfone ($SO_2R$) and the ring substituents in **3** were modified. The results from this study are summarized in Table 5. Increasing the size of methyl in $SO_2Me$ to ethyl (**17**) or phenyl (**18**) resulted in total loss of activity. Interestingly, adding a Cl group ortho to the $SO_2Me$ (**19**) yielded a completely inactive compound. The isosteric sulfonamide derivative (**20**) was a very potent compound with an $IC_{50}$ = 14 nm against the COX-2 enzyme and with selectivity (COX-1/COX-2) of 750. In consonance with the results on sulfone, increasing the size of sulfonamide group (**21**, **22**) destroyed the enzyme inhibitory activity completely. In addition, the regioisomeric derivative **16** obtained on moving the $SO_2Me$ in **3** from position 4 to position 3 showed no inhibition against either of the COX enzymes. The results clearly suggest that the $SO_2Me$ (or $SO_2NH_2$) group is an important part of the pharmacophore and the potency against the COX-2 enzyme is greatly affected by the small variations in the surroundings.

**Scheme 4**



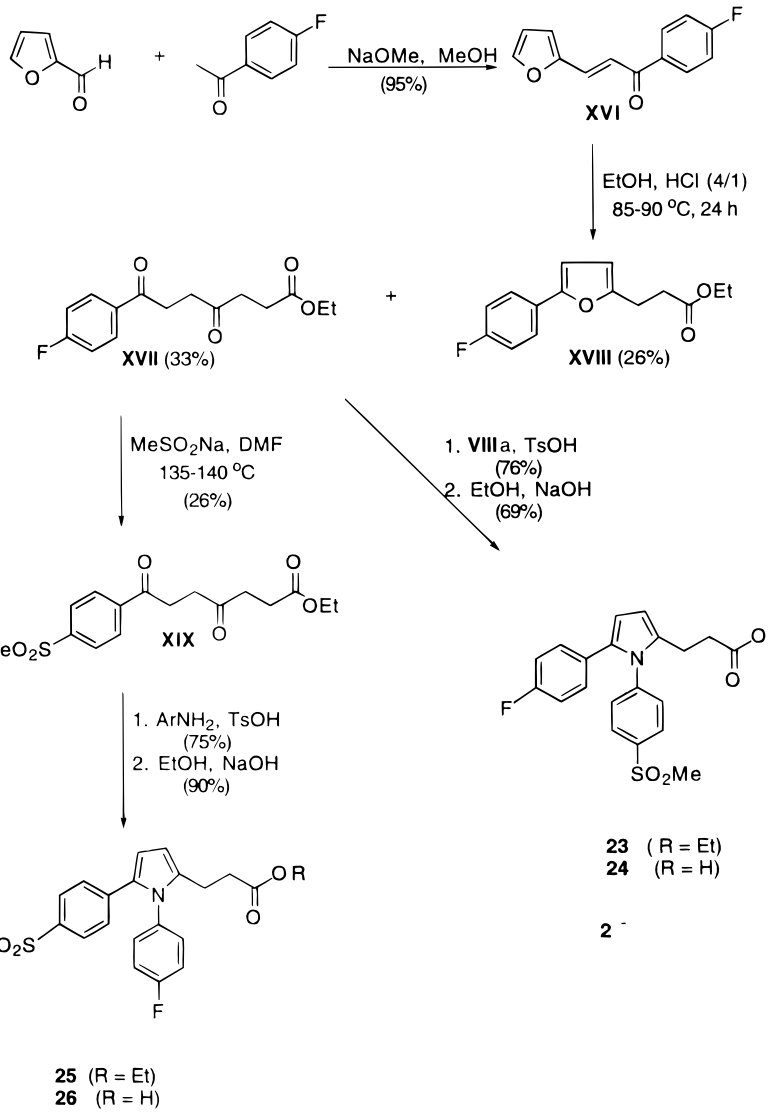

**3** (X = $SO_2Me$, Y = H)
**16** (X = H, Y = $SO_2Me$)
**17** (X = $SO_2Et$, Y = H)
**18** (X = $SO_2Ph$, Y = H)
**19** (X = $SO_2Me$, Y = Cl)
**20** (X = $SO_2NH_2$, Y = H)
**22** (X = $SO_2NMe_2$, Y = H)

**Pyrrole Substituents.** Having established earlier (Table 1) that the compound with a Me group at position 5 of pyrrole (**1**) was better than the noranalog (**4**), we explored the effect of other substituents at this position (Table 6). Increasing the size of the methyl group to $CF_3$ (**27**) or ethyl (**10**) resulted in substantial loss of activity against the COX-2 enzyme. The methyl group appears to yield the optimum potency at this position, and the small variations in the substituents seem to affect the binding to the COX enzyme adversely. To correlate with the initial lead (**III**), a propionic acid chain was introduced at position 5, but the resulting compound (**26**) was inactive against COX-2 up to 100 $\mu$M. The isomeric pyrrole (**24**, Scheme 5) was a weak inhibitor of COX-2 enzyme with an $IC_{50}$ of 7.5 $\mu$M. Similar to **III**, compound **24** also inhibited the LPS-induced $PGE_2$ production in the human whole blood assay with an $IC_{50}$ of 4.4 $\mu$M. Unlike **III**, the analog **24** was more selective ($IC_{50}$ for $TXB_2$ production = >50 $\mu$M). The isomeric pyrrole (**26**), on the other hand, failed to inhibit either $PGE_2$ or $TXB_2$ production up to a concentration of 50 $\mu$M. The results, on the compounds (**III**, **24**) bearing the propionic acid chain, suggest that these might be binding to the active sites on the COX enzymes differently than **26** or other diarylpyrroles listed in Table 6.

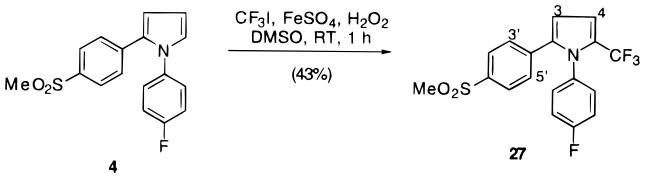
**Tetrasubstituted Pyrroles.** To explore the influence of substituents in the pyrrole ring and to stabilize the ring against potential oxidative metabolism, the pyrrole ring was modified by introducing substituents at position 3. The COX-2 potent and easily accessible **1** was used as the template for the study. The pyrrole ring in **1** was substituted at position 3 with groups such as halogens, acyl, nitrile, alkyl, alkoxyalkyl, aryloxyalkyl, alkyl sulfones, and the like (Table 7). Trifluoroacetyl derivative (**28**) inhibited COX-2 enzyme with an $IC_{50}$ of 120 nm whereas the other acyl modifications such as acetyl (**29**) and benzoyl (**30**) were about 8−12 times less potent. Trifluoromethyl sulfone analog (**31**) was very potent (COX-2, $IC_{50}$ = 60 nm) and selective (COX-1, $IC_{50}$ = >100 $\mu$M). The cyano (**33**) and the formyl (**32**) derivatives were less potent than the acyl or the sulfone analogs. Substitution with bromo or chloro (**34**, **35**) gave very potent compounds (COX-2, $IC_{50}$ = 20 and 50 nm, respectively) although the selectivity was much less than desirable. The trifluoroethyl compound (**42**) was very potent (COX-2, $IC_{50}$ = 140 nm) and selective while its hydroxylated derivative (**41**) was about 10 times less potent. The acetoxymethyl compound (**37**) was more potent than the hydroxymethyl (**38**) or dimethylamino (**36**) analogs. (Aryloxy)methyl compounds (**39** and **40**) were excellent inhibitors of the COX-2 enzyme ($IC_{50}$ = 30 and 80 nm, respectively) while showing no activity against the COX-1 up to 100 $\mu$m. Branching the methylene in **40** by addition of a $CF_3$ group (**43**) abolishes the activity completely. In general, the position 3 of pyrrole seems much more permissive and tolerant to a number of substituents and functional groups. The study proved very fruitful in generating a number of very potent and selective compounds.

**Rat Carrageenan-Induced Edema.** To assess their antiinflammatory activity, the selected 1,2-diarylpyrroles were evaluated in the carrageenan induced paw edema model in the rat (Table 8). Each test compound was dosed orally 2 h prior to the induction of inflammation by carrageenan injection, and the inhibition was measured 3 h after induction. All the compounds were screened at 10 or 20 mpk, and the maximum response observed was 66%. Compound **3** was the most potent of those listed in Table 8, controlling the edema with an $ED_{50}$ of 4.7 mpk. The sulfonamide **20** was also active but seemed to show variable response at different dosages (e.g., 33% and 34% at 3 and 30 mpk, respectively). The bromo (**34**) and the trifluoromethylsulfone (**31**) derivatives were active with $ED_{50}$s of approximately 10 and 20 mpk, respectively. (Aryloxy)methylene compound **14** showed very poor inhibition, probably because of its relatively larger molecular weight and poor cell penetration.

**Scheme 5**




**Scheme 6**




**Scheme 7**

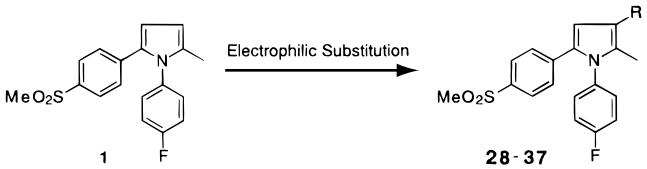



**Table 2.** Electrophilic Substitution in the Pyrrole Ring

| compd | electrophile | R | yield, % |
|---|---|---|---|
| **28** | TFA, TFAA | $COCF_3$ | 77 |
| **29** | AcCl, $AlCl_3$ | $COCH_3$ | 30 |
| **30** | PhCOCl, $AlCl_3$ | COPh | 8 |
| **31** | $Tf_2O$, $AlCl_3$ | $SO_2CF_3$ | 10 |
| **32** | DMF, $POCl_3$ | CHO | 71 |
| **33** | $ClSO_2NCO$ | CN | 77 |
| **34** | NBS | Br | 88 |
| **35** | NCS | Cl | 10 |
| **36** | HCHO, $HNMe_2$ | $CH_2NMe_2$ | 23 |
| **37** | HCHO, AcOH | $CH_2OAc$ | 22 |

## Conclusion

The series of 1,2-diarylpyrroles described in this paper are very potent ($IC_{50}$ = 15−100 nm) and selective (COX-1/COX-2 >1000) inhibitors of human COX-2 enzyme. The enzymatic potency and selectivity observed with these compounds is significantly superior to that reported on 4,5-diarylpyrroles.[13b−d] Detailed SAR studies on different portions of the molecule suggest that the potency and selectivity against the COX-2 enzyme is greatly influenced by the substitution pattern. Replacement of fluoroaryl ring with benzyl, cyclohexyl, or alkyl groups yields inactive or significantly less active compounds. The fluoro group in **1** may be substituted by H (**5**), $CF_3$ (**6**), or Me (**7**) groups to give compounds with excellent potency and selectivity. The aryl sulfone ring seems very sensitive, and small variation on the ring or the $SO_2R$ group destroys the activity completely. A 1,2-diarylpyrrole containing the sulfonamide (**20**) is the most potent compound reported in this paper ($IC_{50}$ = 14 nm). In the pyrrole substitutions, the methyl group at position 5 gives the optimum activity and selectivity. Removal of the methyl or replacement with larger alkyls ($CF_3$, Et, or $CH_2CH_2CO_2H$) yields significantly less active compounds. A number of tetrasubstituted pyrroles with groups such as $COCF_3$, $SO_2CF_3$, or $CH_2OAr$

**Scheme 8**

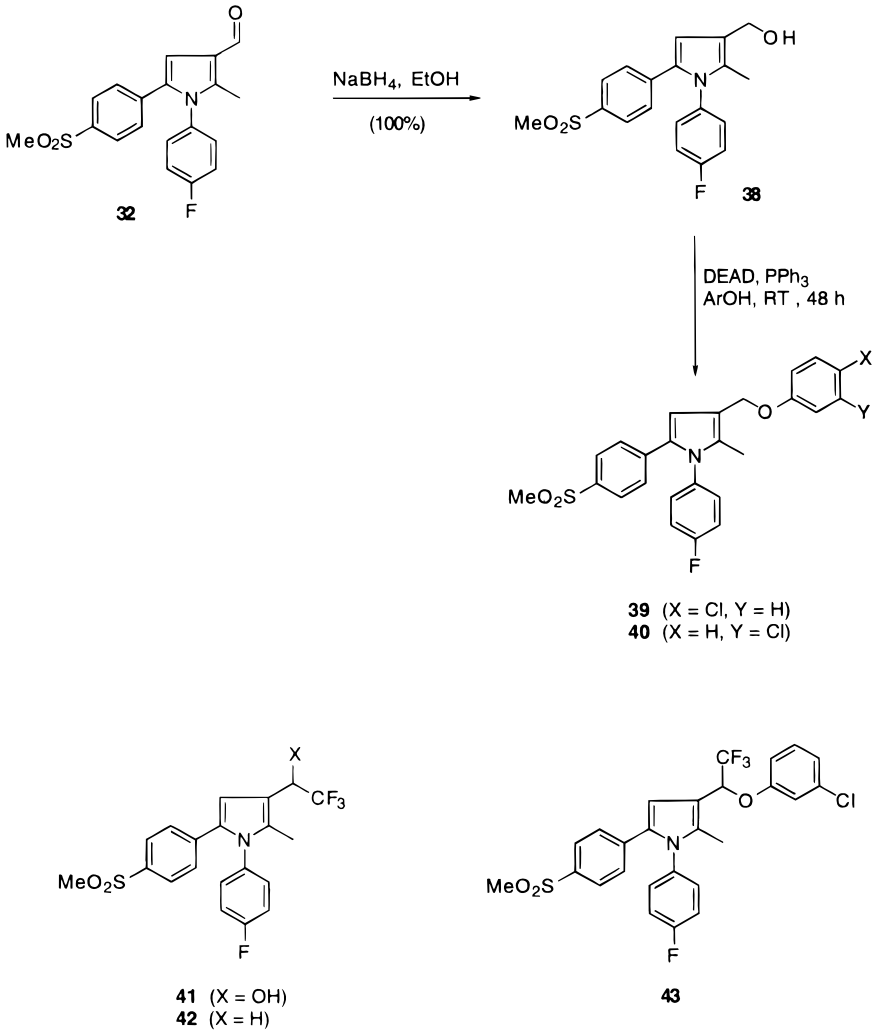
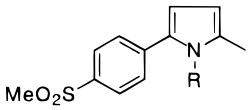
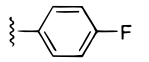
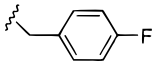
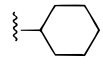


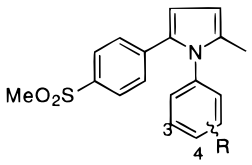

**Table 3.** Modification of the Aryl Ring



| Compound | R | COX-2 ($IC_{50}$, μM) | COX-1 ($IC_{50}$, μM) |
|---|---|---|---|
| **1** |  | 0.06 | >100 |
| **11** |  | >100 | >100 |
| **12** |  | 0.52 | >100 |
| **13** |  | >100 | >100 |
| **14** |  | >100 | >100 |
| **15** | H | >100 | >100 |

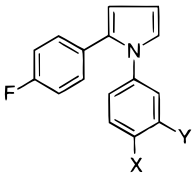
at position 3 show excellent potency ($IC_{50}$ = 30−120 nm). The oral activity observed with **3** ($ED_{50}$ = 4.7 mpk) and other diarylpyrroles in the carrageenan-induced paw edema model of inflammation in the rat indicates the potential utility of this series as antinflammatory agents. The SAR information reported in this paper should facilitate the development of other diaryl heterocycles derived COX-2 selective inhibitors. The paper also describes practical methods for the syntheses of 1,2-diarylpyrroles.

**Table 4.** Modification of the Aryl Substitutents



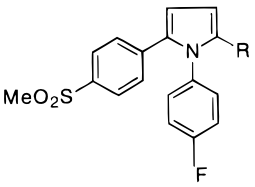
| compd | R | $IC_{50}$, $\mu$M COX-2 | $IC_{50}$, $\mu$M COX-1 | COX-1/COX-2 |
|---|---|---|---|---|
| **1** | 4-F | 0.06 | >100 | >1700 |
| **5** | H | 0.06 | >100 | >1700 |
| **6** | 4-$CF_3$ | 0.08 | >100 | >1250 |
| **7** | 4-$CH_3$ | 0.04 | >100 | >2500 |
| **8** | 4-$COCH_3$ | 2.87 | >100 | >30 |
| **9** | 3,4-diF | 0.25 | >100 | >400 |

**Table 5.** Modification of the Aryl Sulfone Ring



| compd | X | Y | $IC_{50}$, $\mu$M COX-2 | $IC_{50}$, $\mu$M COX-1 |
|---|---|---|---|---|
| **3** | $SO_2Me$ | H | 0.51 | >100 |
| **16** | H | $SO_2Me$ | >100 | >100 |
| **17** | $SO_2Et$ | H | >100 | >100 |
| **18** | $SO_2Ph$ | H | >100 | >100 |
| **19** | $SO_2Me$ | Cl | >100 | >100 |
| **20** | $SO_2NH_2$ | H | 0.014 | 10.5 |
| **21** | $SO_2NHMe$ | H | >100 | >100 |
| **22** | $SO_2NMe_2$ | H | >100 | >100 |

**Table 6.** 5-Substituted 1,2-Diarylpyrroles



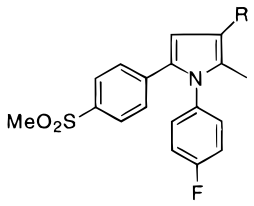
| ompd | R | $IC_{50}$, $\mu$M COX-2 | $IC_{50}$, $\mu$M COX-1 |
|---|---|---|---|
| **1** | Me | 0.06 | >100 |
| **4** | H | 10.2 | >100 |
| **10** | Et | >100 | >100 |
| **26** | $CH_2CH_2CO_2H$ | >100 | >100 |
| **27** | $CF_3$ | >100 | >100 |

## Experimental Section

**Biological Methods.** Expression and purification of human COX-1 and COX-2 enzymes and *in vitro* COX-1 and COX-2 enzyme assays have been described previously.[21] The inhibition of LPS-induced $PGE_2$ production and A23187-induced $TXB_2$ production in the human whole blood was studied utilizing the literature protocols.[22] The production of prostaglandins by human dermal fibroblasts and HL-60 cells after stimulation with IL-1 and retinoic acid was used as a cell-based assay for COX-2 and COX-1 activity, respectively.[24] The details of the carrageenan-induced paw edema model in the rats have been described previously.[11d,e,23]

**Chemistry: General.** NMR spectra were recorded in $CDCl_3$, DMSO-$d_6$, or MeOH-$d_4$ (Merck Isotopes) solution in 5 mm o.d. tubes (Wilmad-535) at 20 °C and were collected on either a General-Electric QE-300, a Varian VXR-400, or a Varian VXR-500 spectrometer at 300, 400, or 500 MHz for $^1H$ (75, 100, or 125 MHz for $^{13}C$). Nuclear Overhauser effect (NOE) difference spectra and two-dimensional NMR spectra were determined on the VXR-400. The chemical shifts ($\delta$) are relative to tetramethylsilane (TMS, $\delta$ = 0.00 ppm) and expressed in ppm. Infrared spectra were recorded on a Perkin-Elmer Model 681 grating spectrophotometer in $CHCl_3$ solution or using KBr pellets; frequencies are expressed in $cm^{-1}$. MIR were recorded on a Bio-Rad FTS-45 spectrophotometer. Melting points were determined on a Thomas-Hoover capillary melting point apparatus. DSC measurements were performed on a Dupont Model 912 Dual DSC system and run under nitrogen. Mass spectra were obtained on either a Finnigan-MAT Model 4500 or a Finnigan-MAT 8430 system. Microanalyses (C, H, N, S) were performed by the Microanalytical Group of the Physical Methodology Department, G. D. Searle & Co.

**Table 7.** Tetrasubstituted Pyrroles



| ompd | R | $IC_{50}$, $\mu$M COX-2 | $IC_{50}$, $\mu$M COX-1 |
|---|---|---|---|
| **1** | H | 0.06 | >100 |
| **28** | $COCF_3$ | 0.12 | >10 |
| **29** | $COCH_3$ | 1.61 | >100 |
| **30** | COPh | 1.02 | >30 |
| **31** | $SO_2CF_3$ | 0.06 | >100 |
| **32** | CHO | 3.23 | >100 |
| **33** | CN | 0.75 | >100 |
| **34** | Br | 0.02 | 0.8 |
| **35** | Cl | 0.05 | 4.5 |
| **36** | $CH_2NMe_2$ | 100 | >100 |
| **37** | $CH_2OAc$ | 0.47 | >100 |
| **38** | $CH_2OH$ | 3.88 | >100 |
| **39** | $CH_2OPh$(*p*-Cl) | 0.03 | >100 |
| **40** | $CH_2OPh$(*m*-Cl) | 0.08 | >100 |
| **41** | $CH(OH)CF_3$ | 1.44 | >100 |
| **42** | $CH_2CF_3$ | 0.14 | >100 |
| **43** | $CH(CF_3)OPh$(*m*-Cl) | >100 | >100 |

**Table 8.** Inhibition of Carrageenan-Induced Edema in Rats

| compd | rat paw edema % inhibn (10 mpk) | compd | rat paw edema % inhibn (10 mpk) |
|---|---|---|---|
| **1** | 25 | **14** | 1 |
| **3** | 42 | **20** | 30 |
| **5** | 21 | **29** | 13 |
| **6** | 31 | **31** | 30[a] |
| **7** | 25 | **34** | 34 |
| **9** | 17 | **41** | 15[a] |

[a] Dosed at 20 mpk.

4-(Methylsulfonyl)aniline, 3-(methylsulfonyl)aniline, sulfanilamide, 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide and other starting materials and reagents, unless otherwise specified, were all commercial products. Solvents used were reagent grade or were dried using conventional procedures. The reactions were routinely carried out under an inert atmosphere unless otherwise indicated. Analytical chromatography was performed on EM Reagents 0.25 mm silica gel 60-F plates. Preparative chromatographic separations were carried out on Merck silica gel 60 (230−400 mesh).

**General Procedure for the Preparation of 1,4-Diketones VIIa−e.** These compounds were prepared utilizing Stetter reaction (Scheme 1). The intermediates **VIIb** and **VIIe** were synthesized by oxidation of **VIIa** and **VIId**, respectively. The preparations of **VIIa** and **VIIb** are described below as examples.

**1-[4-(Methylthio)phenyl]pentane-1,4-dione (VIIa).** To a solution of 4-(methylthio)benzaldehyde (12 mL, 0.09 mol) in ethanol (30 mL), triethylamine (19.5 mL, 0.14 mol), methyl vinyl ketone (5.8 mL, 0.07 mol), and 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (3.53 g, 0.014 mol) were added. The mixture was heated at 75−80 °C for 20 h and cooled. The

solvent was removed under reduced pressure and the residue treated with 2 N HCl (300 mL). After extraction with methylene chloride, the organic layer was washed with aqueous sodium bicarbonate and water. The organic fractions were dried over $MgSO_4$, filtered, and concentrated to give a crude orange liquid (16.2 g). After chromatography on silica gel (hexane/ethyl acetate, 7/3), the desired compound **VIIa** was isolated as a pale yellow solid (12.3 g, 71%): mp (DSC) 75 °C; IR (KBr) 3410, 3030, 1711, 1680, 1591, 1556, 1491, 1427; $^1$H NMR ($CDCl_3$) 7.87 (d, $J$ = 8.0 Hz, 2H), 7.26 (d, $J$ = 8.0 Hz, 2H), 3.23 (t, $J$ = 7 Hz, 2H), 2.87 (t, $J$ = 7 Hz, 2H), 2.52 (s, 3H), 2.25 (s, 3H); MS (EI) 222 ($M^+$). Anal. ($C_{12}H_{14}SO_2$) C, H.

**1-[4-(Methylsulfonyl)phenyl]pentane-1,4-dione (VIIb).** To a solution of **VIIa** (7.8 g, 35 mmol) in methanol (150 mL) was added over 5 min Oxone (37.7 g, 61.4 mmol) dissolved in water (150 mL). After stirring at 25 °C for 2 h, the reaction mixture was diluted with water (400 mL) and extracted with methylene chloride (3 × 400 mL). The organic layer was washed with brine (200 mL), water (200 mL), and dried ($MgSO_4$). After filtration and concentration, the crude material was chromatographed (silica gel; hexane/ethyl acetate, 3/1) to give **VIIb** (8.0 g, 91%) as a white crystalline compound: mp (DSC) 138 °C; IR (KBr) 3435, 3098, 3003, 1944, 1713, 1686, 1593, 1572, 1406; $^1$H NMR ($CDCl_3$) 8.16 (d, $J$ = 8.0 Hz, 2H), 8.06 (d, $J$ = 8.0 Hz, 2H), 3.28 (t, $J$ = 7 Hz, 2H), 3.08 (s, 3H), 2.96 (t, $J$ = 7 Hz, 2H), 2.26 (s, 3H); MS (DCI, $NH_3$-PCI) 255 ($MH^+$). Anal. ($C_{12}H_{14}SO_4$) C, H.

**1-(4-Fluorophenyl)pentane-1,4-dione (VIIc):** mp (DSC) 53 °C; IR (KBr) 3910, 3416, 3107, 2912, 2602, 1979, 1917, 1676, 1641, 1595, 1508, 1408; $^1$H NMR ($CDCl_3$) 8.00 (complex dd, $J$ = 9, 5, 2H), 7.12 (complex t, $J$ = 9 Hz, 2H), 3.23 (t, $J$ = 6 Hz, 2H), 2.88 (t, $J$ = 6 Hz, 2H), 2.24 (s, 3H); MS (DCI, $NH_3$-PCI) 195 ($MH^+$). Anal. ($C_{11}H_{11}O_2F \cdot 0.1H_2O$) C, H.

**1-[4-(Methylthio)phenyl]hexane-1,4-dione (VIId):** mp 60−61 °C; MIR 2971, 2931, 1709, 1668, 1653, 1586, 1401, 1346; $^1$H NMR ($CDCl_3$) 7.93 (d, $J$ = 8 Hz, 2H), 7.23 (d, $J$ = 8 Hz, 2H), 3.25 (t, $J$ = 7 Hz, 2H), 2.82 (t, $J$ = 7 Hz, 2H), 2.52 (q, $J$ = 7 Hz, 2H), 2.46 (s, 3H), 1.10 (t, $J$ = 7 Hz, 2H); HRMS calcd for $M^+$ 236.0871, found 236.0868. Anal. ($C_{13}H_{16}SO_2$) C, H.

**1-[4-(Methylsulfonyl)phenyl]hexane-1,4-dione (VIIe):** mp 125−127 °C; MIR 3005, 2968, 2924, 2904, 1709, 1683, 1408, 1394, 1370, 1278; $^1$H NMR ($CDCl_3$) 8.15 (d, $J$ = 8 Hz, 2H), 8.06 (d, $J$ = 8 Hz, 2H), 3.26 (t, $J$ = 7 Hz, 2H), 3.10 (s, 3H), 2.90 (t, $J$ = 7 Hz, 2H), 2.48 (q, $J$ = 7 Hz, 2H), 1.12 (t, $J$ = 7 Hz, 2H); HRMS calcd for $M^+$ 269.0837, found 269.0838. Anal. ($C_{13}H_{16}SO_4$) C, H.

**4-Amino-*N*-methylbenzenesulfonamide (VIIIc).** To a suspension of of 4- nitrobenzenesulfonyl chloride (5 g, 22.56 mmol) in ether (250 mL) was added methylamine (5 mL, 40% aqueous solution, 56.4 mmol), and the mixture stirred at room temperature. After 16 h, the reaction mixture was concentrated to remove the solvent and the residue resuspended in methylene chloride. After the mixture was washed with 2 N HCl and brine, the organic fractions were dried ($MgSO_4$), filtered, and concentrated to give 4-nitro-*N*-methylbenzenesulfonamide (4.8 g, 98%): mp (DSC) 109 °C; IR (KBr) 3302, 3113, 2868, 1936, 1606, 1531, 1477, 1415, 1352, 1331, 1307; $^1$H NMR ($CDCl_3$) 8.40 (d, $J$ = 8 Hz, 2H), 8.07 (d, $J$ = 8 Hz, 2H), 4.84 (broad q, $J$ = 5 Hz, 1H), 2.73 (d, $J$ = 5 Hz, 3H). Anal. ($C_7H_8N_2SO_4$) C, H, N.

A solution of 4-nitro-*N*-methylbenzenesulfonamide (4.8 g, 22.2 mmol) in methanol (100 mL) was taken in a Parr bottle, and Raney nickel in methanol (∼2 g) was added. The reaction mixture was flushed with nitrogen and hydrogen several times and then maintained under hydrogen at delivery pressure of 5 psi. After being stirred at 25 °C for approximately 20 h, the reaction was vented and purged with nitrogen. The contents of the reaction were filtered and concentrated to give **VIIIc** as a white solid (4.1 g, 100%): mp (DSC) 105 °C; IR (KBr) 3464, 3373, 3244, 2980, 2932, 1900, 1628, 1597, 1502, 1468, 1439, 1408; $^1$H NMR ($CDCl_3$) 7.62 (d, $J$ = 8 Hz, 2H), 6.68 (d, $J$ = 8 Hz, 2H), 4.22 (broad q, $J$ = 5 Hz, 1H), 2.62 (d, $J$ = 5 Hz, 3H); MS (EI) 186 ($M^+$). Anal. ($C_7H_{10}N_2SO_2 \cdot 0.25H_2O$) C, H, N.

**4-Amino-*N,N*-dimethylbenzenesulfonamide (VIIId)** was synthesized from 4-nitrobenzenesulfonyl chloride and dimethylamine using the preparation described for **VIIIc**: mp (DSC) 173 °C, IR (KBr) 3466, 3370, 3250, 3229, 3040, 2974, 2874, 1917, 1788, 1637, 1597, 1570, 1504, 1471, 1456, 1334; $^1$H NMR ($CDCl_3$) 7.56 (d, $J$ = 8 Hz, 2H), 6.72 (d, $J$ = 8 Hz, 2H), 2.64 (s, 3H); MS (EI) 200 ($M^+$). Anal. ($C_8H_{12}N_2SO_2$) C, H, N, S.

**4-(Ethylsulfonyl)aniline (VIIIe).** To a solution of 1-fluoro-4-nitrobenzene (2 mL, 19.05 mmol) in DMF (50 mL) was added sodium thioethoxide (2.4 g, 28.58 mmol), and the mixture was heated at 90 °C. After 18 h, the solvent was partially removed under reduced pressure, and the residue was redissolved in methylene chloride and washed with water and brine. The organic fractions were dried ($MgSO_4$), filtered, and concentrated. The crude (3.04 g) obtained as an orange liquid was chromatographed (silica gel, hexane/ethyl acetate, 8/2) to give 1-(ethylthio)-4-nitrobenzene (1.91 g, 55%) as a yellowish solid: mp (DSC) 45 °C; IR (KBr) 3426, 3094, 3065, 2978, 2926, 1913, 1722, 1658, 1591, 1577, 1510, 1477, 1454, 1402, 1381; $^1$H NMR ($CDCl_3$) 8.13 (d, $J$ = 8 Hz, 2H), 7.32 (d, $J$ = 8 Hz, 2H), 3.05 (q, $J$ = 7.5 Hz, 2H), 1.39 (t, $J$ = 8 Hz, 3H). Anal. ($C_8H_9NSO_2$) C, H, N, S.

To a solution of 1-(ethylthio)-4-nitrobenzene (0.9 g, 4.92 mmol) in methylene chloride (100 mL) was added 3-chloroperoxybenzoic acid (3.9 g, 50−60%, 11.3 mmol) over 15 min. After 3 h, the reaction mixture was concentrated, and the residue was redissolved in ethyl acetate and washed with 4% NaOH, water, and brine. The organic fractions were dried ($MgSO_4$), filtered, and concentrated to give 1-(ethylsulfonyl)-4-nitrobenzene (1.01 g, 95%) as a light orange solid: mp (DSC) 139 °C; IR (KBr) 3433, 3113, 3067, 2883, 1940, 1689, 1608, 1533, 1475, 1452, 1414, 1400, 1381; $^1$H NMR ($CDCl_3$) 8.43 (d, $J$ = 8 Hz, 2H), 8.14 (d, $J$ = 8 Hz, 2H), 3.18 (q, $J$ = 7.5 Hz, 2H), 1.32 (t, $J$ = 8 Hz, 3H); MS (DCI, $NH_3$-PCI) 216 ($MH^+$). Anal. ($C_8H_9NSO_4$) C, H, N, S.

A solution of 1-(ethylsulfonyl)-4-nitrobenzene (1.0 g, 4.65 mmol) in methanol (20 mL) was taken in a Parr bottle, and Raney nickel in methanol (∼1 g) was added. The reaction mixture was flushed with nitrogen and hydrogen several times and then maintained under hydrogen at a delivery pressure of 5 psi. After being stirred at 25 °C for approximately 6 h, the reaction mixture was vented and purged with nitrogen. The contents of the reaction were filtered and concentrated to give **VIIIe** as a white solid (0.81 g, 93%): mp (DSC) 91 °C; IR (KBr) 3449, 3362, 3250, 3071, 2986, 1919, 1786, 1637, 1597, 1572, 1506, 1454, 1441, 1406; $^1$H NMR ($CDCl_3$) 7.62 (d, $J$ = 8 Hz, 2H), 6.68 (d, $J$ = 8 Hz, 2H), 3.03 (q, $J$ = 7.5 Hz, 2H), 1.23 (t, $J$ = 8 Hz, 3H); MS (EI) 185 ($M^+$). Anal. ($C_8H_{11}NSO_2$) C, H, N.

**4-(Phenylsulfonyl)aniline (VIIIf).** To a solution of 1-fluoro-4-nitrobenzene (4 g, 28.34 mmol) in dimethylformamide (100 mL) was added sodium benzenesulfinate (11.63 g, 70.87 mmol). The reaction mixture was heated at 85−90 °C for 32 h. After cooling, the solvent was removed under reduced pressure and the reaction mixture diluted with water. The product was extracted with methylene chloride and washed with brine. After drying ($MgSO_4$), filtration, and concentration, the crude brownish solid (9.2 g) was chromatographed (silica gel, hexane/ethyl acetate, 7/3) to give 1-nitro-4-(phenylsulonyl)benzene (2.9 g, 39%) as a white solid: mp (DSC) 144 °C; IR (KBr) 3426, 3103, 3069, 2876, 2365, 1936, 1801, 1686, 1606, 1583, 1531, 1479, 1452, 1400, 1356; $^1$H NMR ($CDCl_3$) 8.35 (d, $J$ = 8 Hz, 2H), 8.14 (d, $J$ = 8 Hz, 2H), 7.98 (d, $J$ = 8 Hz, 2H), 7.52−7.68 (complex band, 3H); MS (EI) 263 ($M^+$). Anal. ($C_{12}H_9NSO_4$) C, H, N.

A solution of 1-nitro-4-(phenylsulfonyl)benzene (2.9 g, 11 mmol) in methanol (58 mL) was taken in a Parr bottle, and Raney nickel in methanol (∼1.5 g) was added. The reaction mixture was flushed with nitrogen and hydrogen several times and then maintained under hydrogen at a delivery pressure of 5 psi. After being stirred at 25 °C for approximately 2 h, the reaction mixture was vented and purged with nitrogen. The contents of the reaction were filtered and concentrated to give **VIIIf** as a white solid (2.46 g, 96%): mp (DSC) 177 °C; IR (KBr) 3424, 3350, 3244, 3059, 2681, 1911, 1772, 1635, 1591, 1504, 1477, 1444, 1392; $^1$H NMR ($CDCl_3$) 7.91 (d, $J$ = 8 Hz, 2H), 7.70 (d, $J$ = 8 Hz, 2H), 7.42−7.53 (complex band, 3H), 6.63 (d, $J$ = 8 Hz, 2H), 4.16 (broad s, 2H); MS (EI) 233 ($M^+$). Anal. ($C_{12}H_{11}NSO_2$) C, H, N.

**3-Chloro-4-(methylsulfonyl)aniline (VIIIg)** was synthesized from 3-chloro-4-fluoronitrobenzene and sodium thiomethoxide using the three-step preparation described for **VIIIe**: mp (DSC) 174 °C; IR (KBr) 3476, 3372, 3248, 3100, 2926, 2646, 2386, 1936, 1792, 1633, 1593, 1550, 1485, 1429, 1421, 1402; $^1$H NMR ($CDCl_3$) 7.86 (d, $J$ = 8 Hz, 1H), 6.73 (d, $J$ = 2 Hz, 1H), 6.58 (dd, $J$ = 8, 2 Hz, 1H), 4.38 (broad s, 2H), 3.20 (s, 3H). Anal. ($C_7H_8NClSO_2$) C, H, N.

**5,5-Dimethyl-1,3-dioxane-2-propionaldehyde (X).** To a cold solution of oxalyl chloride (5.5 mL, 63.2 mmol) in methylene chloride (25 mL) at −78 °C was injected over 5 min DMSO (10.2 mL, 0.14 mol). After 15 min of stirring, a solution of **IX** (10 g, 57.5 mmol) in methylene chloride (100 mL) was added over 10 min. The reaction solution was stirred for 1 h, and triethylamine (40 mL, 0.2 mol) was added. After 1 h of stirring at −70 °C, the reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched with water and the mixture extracted with methylene chloride. The organic fractions were washed with aqueous sodium bicarbonate and brine. After drying ($Na_2SO_4$), filtration, and concentration, the crude mixture was chromatographed (silica gel, hexane/ethyl acetate, 7/3) to give **X** (6.1 g, 61%) as a colorless liquid: IR ($CHCl_3$) 3522, 2959, 2907, 2855, 2725, 2401, 1724, 1471, 1396, 1365, 1311; $^1$H NMR ($CDCl_3$) 9.78 (t, $J$ = 2 Hz, 1H), 4.52 (t, $J$ = 5 Hz, 1H), 3.59 (d, $J$ = 11 Hz, 2H), 3.42 (d, $J$ = 11 Hz, 2H), 2.58 (td, $J$ = 7, 2 Hz, 2H), 1.99 (td, $J$ = 7, 5 Hz, 2H), 1.17 (s, 3H), 0.72 (s, 3H); MS (DCI, $NH_3$-PCI) 173 ($MH^+$). Anal. ($C_9H_{16}O_3 \cdot 0.2H_2O$) C, H.

**α-(4-Fluorophenyl)-5,5-dimethyl-1,3-dioxane-2-propanol (XI).** To a cold solution of **X** (2 g, 11.62 mmol) in THF (50 mL) at −70 °C was added over 5 min (4-fluorophenyl)-magnesium bromide (8.7 mL, 2M solution in ether, 17.44 mmol). After 2 h of stirring at −70 °C, the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with water and extracted with ethyl acetate. The organic fractions were combined and washed successively with water and brine. After drying ($MgSO_4$), filtration, and concentration, the crude compound (3.5 g) was chromatographed to give **XI** (2.73 g, 87%) as a white solid: mp (DSC) 84 °C; IR (KBr) 3449, 2963, 2862, 1604, 1508, 1471, 1396, 1365; $^1$H NMR ($CDCl_3$) 7.32 (complex dd, $J$ = 9, 5 Hz, 2H), 7.02 (complex t, $J$ = 9 Hz, 2H), 4.70 (td, $J$ = 7, 3 Hz, 1H), 4.48 (t, $J$ = 5 Hz, 1H), 3.62 (d, $J$ = 11 Hz, 2H), 3.43 (d, $J$ = 11 Hz, 2H), 2.84 (d, $J$ = 3 Hz, 1H), 1.83−1.93 (complex band, 2H), 1.66−1.81 (complex band, 2H), 1.19 (s, 3H), 0.73 (s, 3H); MS (DCI) 268 ($M^+$). Anal. ($C_{15}H_{21}FO_3$) C, H.

**1-(4-Fluorophenyl)-3-(5,5-dimethyl-1,3-dioxan-2-yl)propanone (XII).** To a solution of **XI** (2.6 g, 10.7 mmol) in methylene chloride (100 mL) was added pyridinium chlorochromate (3.5 g, 16.05 mmol). After being stirred at room temperature for 3 h, the reaction mixture was diluted with ether and filtered through a short silica gel column. The column was eluted with ether, and the fractions containing the desired product (**XII**) were combined and concentrated (2.2 g, 85%): mp (DSC) 65 °C; IR (KBr) 3443, 2957, 2909, 1682, 1589, 1508, 1469, 1439, 1414, 1396, 1369, 1315; $^1$H NMR ($CDCl_3$) 8.01 (complex dd, $J$ = 9, 5 Hz, 2H), 7.12 (complex t, $J$ = 9 Hz, 2H), 4.57 (t, $J$ = 5 Hz, 1H), 3.60 (d, $J$ = 11 Hz, 2H), 3.44 (d, $J$ = 11 Hz, 2H), 3.12 (t, $J$ = 7 Hz, 2H), 2.08 (td, $J$ = 7, 5 Hz, 2H), 1.19 (s, 3H), 0.72 (s, 3H); MS (DCI, $NH_3$-PCI) 267 ($MH^+$). Anal. ($C_{15}H_{19}FO_3$) C, H.

**1-[4-(Methylsulfonyl)phenyl]-3-(5,5-dimethyl-1,3-dioxan-2-yl)propanone (XIII).** To a solution of **XII** (1.68 g, 6.3 mmol) in dimethylformamide (75 mL) was added methanesulfinic acid sodium (2.9 g, 28.4 mmol). The reaction mixture was heated at 120−130 °C for 72 h. After cooling, the solvent was removed under reduced pressure and the reaction mixture diluted with water. The product was extracted with methylene chloride and washed with brine. After drying ($MgSO_4$), filtration, and concentration, the crude solid (2.78 g) was chromatographed (silica gel, hexane/ethyl acetate, 6/4) to give **XIII** (1.62 g, 79%) as a white solid: mp (DSC) 104 °C; IR (KBr) 3431, 3013, 2953, 2868, 1686, 1655, 1649, 1572, 1508, 1473, 1437, 1398, 1363; $^1$H NMR ($CDCl_3$) 8.15 (complex d, $J$ = 8 Hz, 2H), 8.06 (complex d, $J$ = 8 Hz, 2H), 4.58 (t, $J$ = 5 Hz, 1H), 3.60 (d, $J$ = 11 Hz, 2H), 3.44 (d, $J$ = 11 Hz, 2H), 3.17 (t, $J$ = 7 Hz, 1H), 3.07 (s, 3H), 2.12 (td, $J$ = 7, 5 Hz, 2H), 1.18 (s, 3H), 0.72 (s, 3H); MS (DCI, $NH_3$-PCI) 327 ($MH^+$). Anal. ($C_{16}H_{22}SO_5$) C, H, S.

**α-(4-Fluorophenyl)-1,3-dioxolane-2-propanol (XIV).** A solution of 2-(2-bromoethyl)-1,3-dioxolane (1.76 mL, 15 mmol) in THF (10 mL) was added over 10 min to a suspension of magnesium turnings (410 mg, 16.5 mmol) in THF (10 mL). After 20 min of stirring, the reaction mixture was cooled to −70 °C and a solution of 4-fluorobenzaldehyde (1.07 mL, 10 mmol) in THF (10 mL) was added slowly. The reaction mixture was stirred at −70 °C for 2 h and the reaction quenched with aqueous ammonium chloride. The reaction solution was allowed to warm to room temperature and extracted with ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude obtained as a white liquid (2.54 g) was chromatographed (silica gel; hexane/ethyl acetate, 7/3) to give **XIV** as a colorless oil (1.88 g, 83%): IR ($CHCl_3$) 3416, 2883, 1606, 1510, 1140; $^1$H NMR ($CDCl_3$) 7.32 (complex dd, $J$ = 9, 5 Hz, 2H), 7.03 (complex t, $J$ = 8 Hz, 2H), 4.90 (t, $J$ = 5 Hz, 1H), 4.72 (td, $J$ = 5, 4 Hz, 1H), 3.97 (m, 2H), 3.87 (m, 2H), 2.68 (d, $J$ = 4 Hz, 1H), 1.68−1.96 (complex band, 4H); MS (EI) 226 ($M^+$). Anal. ($C_{12}H_{15}FO_3 \cdot 0.2H_2O$) C, H.

**3-(1,3-Dioxolan-2-yl)-1-(4-fluorophenyl)propan-1-one (XV).** To a solution of **XIV** (1.75 g, 7.74 mmol) in methylene chloride (100 mL) was added pyridinium chlorochromate (2.5 g, 11.6 mmol). After 3 h of stirring at room temperature, the reaction mixture was diluted with ether and filtered through a short silica gel column. The column was eluted with ether, and the fractions containing the desired product (1.69 g, 96%) were combined and concentrated as a white solid: mp (DSC) 69 °C; IR (KBr) 3431, 2897, 1684, 1597, 1509, 1439, 1412, 1365; $^1$H NMR ($CDCl_3$) 8.01 (complex dd, $J$ = 9, 5 Hz, 2H), 7.12 (complex t, $J$ = 9 Hz, 2H), 5.01 (t, $J$ = 4 Hz, 1H), 3.97 (m, 2H), 3.87 (m, 2H), 3.08 (t, $J$ = 7 Hz, 1H), 2.13 (td, $J$ = 7, 4 Hz, 2H); MS (DCI, $NH_3$-PCI) 225 ($MH^+$). Anal. ($C_{12}H_{13}FO_3$) C, H.

**1-(4-Fluorophenyl)-3-(2-furanyl)-2-propen-1-one (XVI).** To a solution of 2-furaldehyde (4.15 mL, 50 mmol) and 4-fluoroacetophenone (6.16 mL, 50 mmol) in methanol (200 mL) was added sodium methoxide (2.85 g, 50 mmol) over 10 min. After 18 h of stirring at room temperature, the reaction mixture was concentrated to remove the solvent, resuspended in ethyl acetate (600 mL), and diluted with water. The organic layer was separated, washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude solid (10.27 g) was chromatographed (silica gel, hexane/ethyl acetate, 7/3) to give **XVI** (8.9 g, 95%) as a white solid: mp (DSC) 72 °C; IR (KBr) 3433, 3107, 1662, 1604, 1589, 1554, 1506, 1475, 1410, 1390; $^1$H NMR ($CDCl_3$) 8.06 (complex dd, $J$ = 9, 5 Hz, 2H), 7.60 (d, $J$ = 15 Hz, 1H), 7.53 (d, $J$ = 2 Hz, 1H), 7.43 (d, $J$ = 15 Hz, 1H), 7.16 (complex t, $J$ = 9 Hz, 2H), 6.72 (d, $J$ = 3 Hz, 1H), 6.52 (complex dd, $J$ = 3, 2 Hz, 1H); MS (DCI, $NH_3$-PCI) 217 ($MH^+$). Anal. ($C_{13}H_{10}FO$) C, H.

**Ethyl 4-fluoro-γ,ζ-dioxobenzeneheptanoate (XVII).** A solution of **XVI** (4.35 g, 23.14 mmol) in ethanol (100 mL) and concentrated HCl (25 mL) was heated at 80−85 °C for 24 h. The solvent was removed under reduced pressure and redissolved in methylene chloride (800 mL). The organic layer was separated and concentrated to give blackish solid (5.55 g). The chromatography on silica gel using hexane/ethyl acetate (7/3) gave **XVIII** (1.7 g, 28%) and **XVII** (2.12 g, 33%) in order of elution.

**XVII:** mp (DSC) 73 °C; IR (KBr) 3441, 3074, 2986, 2957, 2907, 1728, 1703, 1672, 1595, 1506, 1479, 1414; $^1$H NMR ($CDCl_3$) 8.06 (m, 2H), 7.12 (t, $J$ = 8 Hz, 2H), 4.13 (q, $J$ = 7.5 Hz, 2H), 3.27 (t, $J$ = 7 Hz, 2H), 2.94 (t, $J$ = 7 Hz, 2H), 2.88 (t, $J$ = 7 Hz, 2H) 2.62 (t, $J$ = 7 Hz, 2H), 1.25 (t, $J$ = 7.5 Hz, 3H); MS (DCI, $NH_3$-PCI) 281 ($MH^+$). Anal. ($C_{15}H_{17}FO_4$) C, H.

**XVIII:** mp (DSC) 43 °C; IR (KBr) 3433, 2990, 2930, 1898, 1724, 1686, 1653, 1635, 1603, 1591, 1556, 1500, 1479, 1439, 1417; $^1$H NMR ($CDCl_3$) 7.57 (complex dd, $J$ = 9, 5 Hz, 2H), 7.04 (complex t, $J$ = 9 Hz, 2H), 6.46 (d, $J$ = 3 Hz, 1H), 6.10 (d, $J$ = 3 Hz, 1H), 4.15 (q, $J$ = 7 Hz, 2H), 3.04 (t, $J$ = 8 Hz, 2H) 2.68 (t, $J$ = 8 Hz, 2H), 1.25 (t, $J$ = 7 Hz, 3H); MS (DCI, $NH_3$-PCI) 263 ($MH^+$). Anal. ($C_{15}H_{15}FO_3$) C, H.

**Ethyl 4-(methylsulfonyl)-γ,ζ-dioxobenzeneheptanoate (XIX).** To a solution of **XVII** (870 mg, 3.1 mmol) in dimethylformamide (25 mL) was added methanesulfinic acid sodium

(1.27 g, 12.4 mmol). The reaction mixture was heated at 130−135 °C for 30 h. After cooling, the solvent was removed under reduced pressure and the reaction mixture diluted with water. The product was extracted with ethyl acetate and washed with brine. After drying ($MgSO_4$), filtration, and concentration, the crude dark brown solid (840 mg) was chromatographed (silica gel, hexane/ethyl acetate, 1/1) to give **XIX** (270 mg, 26%) as a white solid: mp (DSC) 97 °C; IR (KBr) 3435, 3024, 3009, 2980, 2924, 1730, 1707, 1682, 1653, 1635, 1595, 1572, 1471, 1435, 1404; $^1$H NMR ($CDCl_3$) 8.15 (d, $J$ = 8 Hz, 2H), 8.06 (d, $J$ = 8 Hz, 2H), 4.12 (q, $J$ = 7.5 Hz, 2H), 3.32 (t, $J$ = 7 Hz, 2H), 3.1 (s, 3H), 2.96 (t, $J$ = 7 Hz, 2H), 2.86 (t, $J$ = 7 Hz, 2H) 2.62 (t, $J$ = 7 Hz, 2H), 1.25 (t, $J$ = 7.5 Hz, 3H); MS (DCI, $NH_3$-PCI) 341 ($MH^+$). Anal. ($C_{16}H_{20}SO_6$) C, H, S.

**General Procedure for the Preparation of Diarylpyrroles.** These compounds were synthesized as in Schemes 1−5 by condensing 1,4-diketones with the appropriate amines. The procedure for the synthesis of **1** is described below as an example.

**1-(4-Fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)-phenyl]-1*H*-pyrrole (1).** A mixture of **VIIb** (580 mg, 2.28 mmol), 4-fluoroaniline (0.24 mL, 2.5 mmol), and *p*-toluenesulfonic acid (30 mg) in toluene (50 mL) was refluxed for 20 h using Dean−Stark apparatus. The reaction mixture was cooled, filtered, and concentrated. The crude mixture (820 mg) was chromatographed (silica gel, hexane/ethyl acetate, 7/3) to give pure **1** (595 mg, 79%) as a white solid: mp (DSC) 157 °C; IR (KBr) 3429, 3074, 2999, 1896, 1772, 1734, 1701, 1684, 1653, 1593, 1558, 1510, 1469, 1419; $^1$H NMR ($CDCl_3$) 7.68 (d, $J$ = 8 Hz, 2H), 7.16 (d, $J$ = 8 Hz, 2H), 7.06−7.15 (complex band, 4H), 6.5 (d, $J$ = 3 Hz, 1H), 6.13 (d, $J$ = 3 Hz, 1H), 3.00 (s, 3H), 2.13 (s, 3H); MS (EI) 329 ($M^+$). Anal. ($C_{18}H_{16}NSO_2F$) C, H, N, S.

**2-(4-Fluorophenyl)-5-methyl-1-[4-(methylsulfonyl)-phenyl]-1*H*-pyrrole (2):** mp (DSC) 206 °C; IR (KBr) 3427, 3098, 3049, 1593, 1564, 1523, 1496, 1439, 1412, 1385; $^1$H NMR ($CDCl_3$) 7.92 (complex d, $J$ = 8 Hz, 2H), 7.32 (complex d, $J$ = 8 Hz, 2H), 6.97 (complex dd, $J$ = 9, 5 Hz, 2H), 6.87 (complex t, $J$ = 9 Hz, 2H), 6.32 (d, $J$ = 3 Hz, 1H), 6.13 (d, $J$ = 3 Hz, 1H), 3.10 (s, 3H), 2.18 (s, 3H); MS (EI) 329 ($M^+$). Anal. ($C_{18}H_{16}NSO_2F$) C, H, N, S.

**2-(4-Fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole (3):** mp (DSC) 201 °C; MIR 3134, 1592, 1550, 1504, 1463, 1423, 1412, 1307; $^1$H NMR ($CDCl_3$) 7.89 (complex d, $J$ = 8 Hz, 2H), 7.32 (complex d, $J$ = 8 Hz, 2H), 7.08 (complex dd, $J$ = 9, 5 Hz, 2H), 6.97 (dd, $J$ = 3, 2 Hz, 1H), 6.96 (complex t, $J$ = 9 Hz, 2H), 6.44 (dd, $J$ = 3, 2 Hz, 1H), 6.42 (t, $J$ = 3 Hz, 1H), 3.08 (s, 3H); MS (EI) 315 ($M^+$). Anal. ($C_{17}H_{14}NSFO_2\cdot 0.2H_2O$) C, H, N, S.

**1-(4-Fluorophenyl)-2-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole (4):** mp (DSC) 163 °C; IR (KBr) 3436, 3119, 3074, 1635, 1593, 1541, 1510, 1450, 1423, 1394, 1346; $^1$H NMR ($CDCl_3$) 7.76 (d, $J$ = 8 Hz, 2H), 7.27 (d, $J$ = 8 Hz, 2H), 7.16 (complex dd, $J$ = 9, 5 Hz, 2H), 7.08 (complex t, $J$ = 9 Hz, 2H), 6.95 (dd, $J$ = 2.5, 1.5 Hz, 1H), 6.58 (dd, $J$ = 3, 1.5 Hz, 1H), 6.40 (dd, $J$ = 3, 2.5 Hz, 1H), 3.05 (s, 3H); MS (EI) 315 ($M^+$). Anal. ($C_{17}H_{14}NSFO_2$) C, H, N, S.

**2-Methyl-5-[4-(methylsulfonyl)phenyl]-1-phenyl-1*H*-pyrrole (5):** mp (DSC) 148 °C; IR (KBr) 3431, 3063, 3015, 2997, 2918, 2231, 1593, 1550, 1508, 1498, 1468, 1419, 1386, 1350; $^1$H NMR ($CDCl_3$) 7.65 (complex d, $J$ = 8 Hz, 2H), 7.35−7.44 (complex band, 3H), 7.02−7.13 (complex band, 4H), 6.51 (d, $J$ = 3 Hz, 1H), 6.13 (d, $J$ = 3 Hz, 1H), 2.98 (s, 3H), 2.15 (s, 3H); MS (EI) 311 ($M^+$). Anal. ($C_{18}H_{17}NSO_2$) C, H, N, S.

**2-Methyl-5-[4-(methylsulfonyl)phenyl]-1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrole (6):** mp (DSC) 130 °C; IR (KBr) 3433, 3080, 3007, 2924, 1614, 1593, 1558, 1471, 1415, 1388, 1325, 1309; $^1$H NMR ($CDCl_3$) 7.48 (m, 4H), 7.32 (d, $J$ = 8 Hz, 2H), 7.15 (d, $J$ = 8 Hz, 2H), 6.52 (d, $J$ = 3 Hz, 1H), 6.17 (d, $J$ = 3 Hz, 1H), 3.0 (s, 3H), 2.17 (s, 3H); MS (EI) 378 ($M^+$). Anal. ($C_{19}H_{16}NSO_2F_3$) C, H, N, S.

**2-Methyl-1-(4-methylphenyl)-5-[4-(methylsulfonyl)-phenyl]-1*H*-pyrrole (7):** mp (DSC) 144 °C; IR (KBr) 3429, 3007, 2926, 1720, 1709, 1687, 1657, 1593, 1550, 1512, 1469, 1439, 1388; $^1$H NMR ($CDCl_3$) 7.65 (d, $J$ = 8 Hz, 2H), 7.16 (m, 4H), 7.06 (d, $J$ = 8 Hz, 2H), 6.5 (d, $J$ = 3 Hz, 1H), 6.10 (d, $J$ = 3 Hz, 1H), 3.0 (s, 3H), 2.40 (s, 3H), 2.13 (s, 3H); MS (EI) 325 ($M^+$). Anal. ($C_{19}H_{19}NSO_2$) C, H, N, S.

**1-[4-[2-Methyl-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrol-1-yl]phenyl]ethanone (8):** mp (DSC) 182 °C; MIR 3106, 2922, 1685, 1602, 1592, 1510, 1416, 1351; $^1$H NMR ($CDCl_3$) 8.02 (d, $J$ = 8 Hz, 2H), 7.48 (d, $J$ = 8 Hz, 2H), 7.25 (d, $J$ = 8 Hz, 2H), 7.17 (d, $J$ = 8 Hz, 2H), 6.52 (d, $J$ = 3 Hz, 1H), 6.17 (d, $J$ = 3 Hz, 1H), 3.0 (s, 3H), 2.64 (s, 3H), 2.17 (s, 3H); MS (EI) 353 ($M^+$). Anal. ($C_{20}H_{19}NSO_3\cdot 1.0\ H_2O$) C, H, N, S.

**1-(3,4-Difluorophenyl)-2-Methyl-5-[4-(methylsulfonyl)-phenyl]-1*H*-pyrrole (9):** mp (DSC) 151 °C; IR (KBr) 3427, 3084, 3011, 2916, 2282, 1612, 1591, 1552, 1520, 1469, 1439, 1414, 1305; $^1$H NMR ($CDCl_3$) 7.72 (complex d, $J$ = 8 Hz, 2H), 7.22 (q, $J$ = 9 Hz, 1H), 7.20 (complex d, $J$ = 8 Hz, 2H), 7.02 (ddd, $J$ = 10, 7, 2 Hz, 2H), 6.94 (ddt, $J$ = 8, 4, 2 Hz, 1H), 6.48 (d, $J$ = 3 Hz, 1H), 6.12 (d, $J$ = 3 Hz, 1H), 3.01 (s, 3H), 2.13 (s, 3H); MS (EI) 347 ($M^+$). Anal. ($C_{18}H_{15}NSO_2F_2$) C, H, N.

**2-Ethyl-1-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole (10):** mp 119−120 °C; IR (KBr) 2968, 1590, 1509, 1424, 1315, 1301; $^1$H NMR ($CDCl_3$) 7.70 (d, $J$ = 8 Hz, 2H), 7.06−7.32 (complex band, 6H), 6.54 (d, $J$ = 3 Hz, 1H), 6.15 (d, $J$ = 3 Hz, 1H), 3.0 (s, 3H), 2.45 (q, $J$ = 7.5 Hz, 2H), 1.15 (t, $J$ = 7.5 Hz, 3H); HRMS calcd for $M^+$ 343.1042, found 343.1047. Anal. ($C_{19}H_{18}NSO_2F\cdot 0.35H_2O$) C, H, N.

**1-[(4-Fluorophenyl)methyl]-2-methyl-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole (11):** mp (DSC) 143 °C; IR (KBr) 3074, 3015, 2916, 1658, 1593, 1554, 1510, 1471, 1441, 1415, 1381; $^1$H NMR ($CDCl_3$) 7.82 (d, $J$ = 8 Hz, 2H), 7.43 (d, $J$ = 8 Hz, 2H), 7.00 (t, $J$ = 8 Hz, 2H), 6.86 (m, 2H), 6.37 (d, $J$ = 3 Hz, 1H), 6.08 (d, $J$ = 3 Hz, 1H), 5.12 (s, 2H), 3.03 (s, 3H), 2.17 (s, 3H); MS (EI) 343 ($M^+$). Anal. ($C_{19}H_{18}NSFO_2$) C, H, N, S.

**1-Cyclohexyl-2-methyl-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole (12):** mp (DSC) 141 °C; IR (KBr) 3435, 3015, 2932, 2855, 1593, 1508, 1469, 1448, 1410, 1379; $^1$H NMR ($CDCl_3$) 7.93 (complex d, $J$ = 8 Hz, 2H), 7.47 (complex d, $J$ = 8 Hz, 2H), 6.12 (d, $J$ = 3 Hz, 1H), 5.97 (d, $J$ = 3 Hz, 1H), 4.03 (tt, $J$ = 12, 3 Hz, 1H), 3.11 (s, 3H), 2.46 (s, 3H), 1.80−2.04 (complex band, 6H), 1.68 (broad d, $J$ = 10 Hz, 1H), 1.09−1.35 (complex band, 3H); MS (DCI, $NH_3$-PCI) 318 ($MH^+$). Anal. ($C_{18}H_{23}NSO_2$) C, H, N, S.

**1-(1-Methylethyl)-2-methyl-5-[4-(methylsulfonyl)-phenyl]-1*H*-pyrrole (13):** mp (DSC) 112 °C; IR (KBr) 1689, 1596, 1315, 1151, 957; $^1$H NMR ($CDCl_3$) 7.95 (d, $J$ = 8 Hz, 2H), 7.48 (d, $J$ = 8 Hz, 2H), 6.12 (d, $J$ = 3 Hz, 1H), 5.97 (d, $J$ = 3 Hz, 1H), 4.52 (h, $J$ = 7 Hz, 1H), 3.1 (s, 3H), 2.46 (s, 3H), 1.47 (d, $J$ = 7.5 Hz, 6H); MS (EI) 277 ($M^+$). Anal. ($C_{15}H_{19}NSO_2\cdot 0.25H_2O$) C, H, N.

**1-Butyl-2-methyl-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole (14):** mp (DSC) 79 °C; IR (KBr) 3420, 3020, 2932, 2874, 1595, 1510, 1471, 1417, 1375; $^1$H NMR ($CDCl_3$) 7.90 (d, $J$ = 8 Hz, 2H), 7.52 (d, $J$ = 8 Hz, 2H), 6.20 (d, $J$ = 3 Hz, 1H), 5.97 (d, $J$ = 3 Hz, 1H), 3.88 (t, $J$ = 7.5 Hz, 2H), 3.1 (s, 3H), 2.32 (s, 3H), 1.5 (m, 2H), 1.2 (m, 2H), 0.82 (t, $J$ = 7.5 Hz, 3H); MS (EI) 291 ($M^+$). Anal. ($C_{16}H_{21}NSO_2$) C, H, N, S.

**2-Methyl-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole (15):** mp (DSC) 160 °C; IR (KBr) 3397, 2926, 1601, 1585, 1512, 1469, 1431, 1300; $^1$H NMR ($CDCl_3$) 8.50 (broad s, 1H), 7.83 (complex d, $J$ = 8 Hz, 2H), 7.55 (complex d, $J$ = 8 Hz, 2H), 6.57 (t, $J$ = 3 Hz, 1H), 6.00 (t, $J$ = 3 Hz, 1H), 3.06 (s, 3H), 2.36 (s, 3H); MS (EI) 235 ($M^+$). Anal. ($C_{12}H_{13}NSO_2$) C, H, N, S.

**2-(4-Fluorophenyl)-1-[3-(phenylsulfonyl)phenyl]-1*H*-pyrrole (16):** mp (DSC) 164 °C; IR (KBr) 3439, 3065, 2910, 2361, 2338, 1772, 1734, 1716, 1653, 1597, 1558, 1504, 1483, 1464; $^1$H NMR ($CDCl_3$) 7.82 (dd, $J$ = 8, 2 Hz, 1H), 7.67 (d, $J$ = 2 Hz, 1H), 7.53 (t, $J$ = 8 Hz, 1H), 7.42 (dd, $J$ = 8, 2 Hz, 1H), 7.06 (m, 2H), 6.84−6.96 (complex band, 3H), 6.42 (m, 2H), 2.92 (s, 3H); MS (EI) 315 ($M^+$). Anal. ($C_{17}H_{14}NSFO_2\cdot 0.25H_2O$) C, H, N, S.

**2-(4-Fluorophenyl)-1-[4-(ethylsulfonyl)phenyl]-1*H*-pyrrole (17):** mp (DSC) 168 °C; IR (KBr) 3435, 3130, 3067, 2970, 2926, 1902, 1734, 1716, 1684, 1653, 1593, 1552, 1505, 1464, 1423, 1410, 1334; $^1$H NMR ($CDCl_3$) 7.85 (d, $J$ = 8 Hz, 2H), 7.70 (d, $J$ = 8 Hz, 1H), 7.07 (m, 2H), 6.96 (m, 3H), 6.42 (m, 2H), 3.13 (q, $J$ = 7.5 Hz, 1H), 1.27 (t, $J$ = 7.5 Hz, 3H); MS (EI) 329 ($M^+$). Anal. ($C_{18}H_{16}NSFO_2$) C, H, N, S.

**2-(4-Fluorophenyl)-1-[4-(phenylsulfonyl)phenyl]-1*H*-pyrrole (18):** mp (DSC) 204 °C; IR (KBr) 3439, 3134, 3098, 1900, 1591, 1550, 1506, 1496, 1462, 1421, 1412, 1332; $^1$H NMR ($CDCl_3$) 7.96 (d, $J$ = 8 Hz, 2H), 7.88 (d, $J$ = 8 Hz, 2H), 7.50−

7.62 (complex band, 3H), 7.22 (d, $J$ = 8 Hz, 2H), 7.06 (m, 2H), 6.88−6.97 (complex band, 3H), 6.38 (m, 2H); MS (EI) 377 ($M^+$). Anal. ($C_{22}H_{16}NSFO_2 \cdot 0.5H_2O$) C, H, N.

**1-[3-Chloro-4-(methylsulfonyl)phenyl]-2-(4-fluorophenyl)-1*H*-pyrrole (19):** mp (DSC) 142 °C; IR (KBr) 3431, 2914, 1635, 1591, 1547, 1506, 1479, 1419, 1392, 1313; $^1$H NMR ($CDCl_3$) 8.05 (d, $J$ = 8 Hz, 1H), 7.38 (d, $J$ = 2 Hz, 1H), 7.13 (m, 2H), 6.92−7.06 (complex band, 3H), 6.42 (m, 2H), 3.27 (s, 3H); MS (EI) 349 ($M^+$). Anal. ($C_{17}H_{13}NSFClO_2$) C, H, N, S.

**4-[2-(4-Fluorophenyl)-1*H*-pyrrol-1-yl]benzenesulfonamide (20):** mp (DSC) 206 °C; IR (KBr) 3352, 3265, 3132, 3098, 1900, 1792, 1740, 1670, 1595, 1552, 1502, 1460, 1423, 1334; $^1$H NMR ($CDCl_3$) 7.88 (complex d, $J$ = 8 Hz, 2H), 7.27 (complex d, $J$ = 8 Hz, 2H), 7.10 (complex dd, $J$ = 9, 5 Hz, 2H), 6.97 (m, 1H), 6.95 (complex t, $J$ = 9 Hz, 2H), 6.43 (dd, $J$ = 3, 2 Hz, 1H), 6.41 (t, $J$ = 3 Hz, 1H), 4.87 (broad s, 2H); MS (EI) 316 ($M^+$). Anal. ($C_{16}H_{13}N_2SFO_2$) C, H, N, S.

**4-[2-(4-Fluorophenyl)-1*H*-pyrrol-1-yl]-*N*-methylbenzenesulfonamide (21):** mp (DSC) 174 °C; IR (KBr) 3439, 3265, 3130, 1736, 1595, 1550, 1504, 1462, 1421, 1325; $^1$H NMR ($CDCl_3$) 7.80 (complex d, $J$ = 8 Hz, 2H), 7.27 (complex d, $J$ = 8 Hz, 2H), 7.10 (complex dd, $J$ = 9, 5 Hz, 2H), 6.96 (m, 1H), 6.94 (complex t, $J$ = 9 Hz, 2H), 6.37−6.44 (complex band, 2H), 4.43 (q, $J$ = 5 Hz, 1H), 2.70 (d, $J$ = 5 Hz, 3H). Anal. ($C_{17}H_{15}N_2SFO_2 \cdot 0.25H_2O$) C, H, N.

**4-[2-(4-Fluorophenyl)-1*H*-pyrrol-1-yl]-*N*,*N*-dimethylbenzenesulfonamide (22):** mp (DSC) 157 °C; IR (KBr) 3439, 3138, 1925, 1593, 1550, 1504, 1462, 1412, 1338; $^1$H NMR ($CDCl_3$) 7.82 (d, $J$ = 8 Hz, 2H), 7.27 (d, $J$ = 8 Hz, 2H), 7.07 (m, 2H), 6.86−7.94 (complex band, 3H), 6.40 (m, 2H), 2.72 (s, 6H); MS (EI) 344 ($M^+$). Anal. ($C_{18}H_{17}N_2SFO_2$) C, H, N, S.

**Ethyl 5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole-2-propanoate (23):** mp (DSC) 127 °C; IR (KBr) 3406, 2920, 1716, 1684, 1653, 1635, 1599, 1577, 1558, 1506, 1471, 1425, 1305; $^1$H NMR ($CDCl_3$) 7.92 (d, $J$ = 8 Hz, 2H), 7.35 (d, $J$ = 8 Hz, 2H), 6.97 (m, 2H), 6.85 (t, $J$ = 8 Hz, 2H), 6.32 (d, $J$ = 2 Hz, 1H), 6.13 (d, $J$ = 2 Hz, 1H), 4.13 (q, $J$ = 7.5 Hz, 2H), 3.1 (s, 3H), 2.78 (t, $J$ = 7.5 Hz, 2H), 2.54 (t, $J$ = 7.5 Hz, 2H), 1.25 (t, $J$ = 7.5 Hz, 3H); MS (EI) 415 ($M^+$). Anal. ($C_{22}H_{22}NSFO_4$) C, H, N, S.

**5-(4-Fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole-2-propanoic Acid (24).** A suspension of **23** (300 mg, 0.72 mmol) in ethanol (10 mL) and 2 N NaOH (4.5 mL) was stirred for 4 h. The clear solution obtained was concentrated to remove ethanol, diluted with 1 N NaOH (200 mL), and extracted with ether (200 mL). The aqueous layer was separated, acidified with concentrated HCl, and extracted with methylene chloride (2 × 350). The organic fractions were concentrated and crystallized using methylene chloride to give **24** (198 mg, 69%) as a white solid: mp (DSC) 192 °C; IR (KBr) 3429, 3063, 2926, 1711, 1653, 1635, 1593, 1550, 1522, 1496, 1485, 1421, 1313; $^1$H NMR ($CDCl_3$) 7.95 (d, $J$ = 8 Hz, 2H), 7.35 (d, $J$ = 8 Hz, 2H), 6.97 (m, 2H), 6.86 (t, $J$ = 8 Hz, 2H), 6.32 (d, $J$ = 2 Hz, 1H), 6.13 (d, $J$ = 2 Hz, 1H), 3.1 (s, 3H), 2.82 (t, $J$ = 7.5 Hz, 2H), 2.62 (t, $J$ = 7.5 Hz, 2H); MS (EI) 387 ($M^+$). Anal. ($C_{20}H_{18}NSFO_4 \cdot 1.0H_2O$) C, H, N, S.

**Ethyl 1-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole-2-propanoate (25):** mp (DSC) 134 °C; IR (KBr) 3057, 2982, 2902, 1903, 1714, 1653, 1595, 1550, 1508, 1471, 1446, 1425, 1392; $^1$H NMR ($CDCl_3$) 7.68 (d, $J$ = 8 Hz, 2H), 7.06−7.23 (complex band, 6H), 6.50 (d, $J$ = 2 Hz, 1H), 6.13 (d, $J$ = 2 Hz, 1H), 4.10 (q, $J$ = 7.5 Hz, 2H), 3.0 (s, 3H), 2.76 (t, $J$ = 7.5 Hz, 2H), 2.53 (t, $J$ = 7.5 Hz, 2H), 1.24 (t, $J$ = 7.5 Hz, 3H); MS (EI) 415 ($M^+$). Anal. ($C_{22}H_{22}NSFO_4$) C, H, N, S.

**1-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole-2-propanoic acid (26)** was synthesized from **25** using the procedure described for **24:** mp (DSC) 163 °C; IR (KBr) 3078, 2926, 2365, 2334, 1711, 1653, 1593, 1510, 1469, 1427, 1307; $^1$H NMR ($CDCl_3$) 7.68 (d, $J$ = 8 Hz, 2H), 7.06−7.18 (complex band, 6H), 6.50 (d, $J$ = 2 Hz, 1H), 6.13 (d, $J$ = 2 Hz, 1H), 3.0 (s, 3H), 2.76 (t, $J$ = 7.5 Hz, 2H), 2.56 (t, $J$ = 7.5 Hz, 2H); MS (EI) 387 ($M^+$). Anal. ($C_{20}H_{18}NSFO_4 \cdot 0.2H_2O$) C, H, N.

**1-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-(trifluoromethyl)-1*H*-pyrrole (27).** To a solution of **4** (550 mg, 1.75 mmol) in DMSO (10 mL) was added $FeSO_4 \cdot 7H_20$ (291 mg, 1.05 mmol). Excess of trifluoromethyl iodide gas was bubbled through the reaction solution for 2 min. Hydrogen peroxide (1.2 mL, 30% solution by wt, 10.5 mmol) was added and the mixture stirred at room temperature for 1 h. The reaction mixture was diluted with brine and extracted with ether. The organic fractions were dried ($MgSO_4$), filtered, and concentrated. The crude mixture (1 g) was chromatographed (silica gel, hexane/ethyl acetate, 7/3) to give pure **27** (292 mg, 43%) as a white solid: mp (DSC) 150 °C; IR (KBr) 3080, 3013, 2918, 1902, 1595, 1570, 1549, 1510, 1468, 1437, 1394; $^1$H NMR ($CDCl_3$) 7.76 (complex d, $J$ = 8 Hz, 2H), 7.26 (complex d, $J$ = 8 Hz, 2H), 7.24 (complex dd, $J$ = 9, 4.8 Hz, 2H), 7.09 (complex dd, $J$ = 9, 8 Hz, 2H), 6.80 (d, $J$ = 4 Hz, 1H), 6.52 (d, $J$ = 4 Hz, 1H), 3.02 (s, 3H); MS (EI) 383 ($M^+$). Anal. ($C_{18}H_{13}NSF_4O_2 \cdot 0.5H_2O$) C, H, N.

**2,2,2-Trifluoro-1-[1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl) phenyl]-1*H*-pyrrol-3-yl]ethanone (28).** To a solution of **1** (800 mg, 2.43 mmol) in trifluoroacetic acid (7 mL) was added trifluoroacetic anhydride (0.7 mL, 4.86 mmol), and the mixture was heated at 50 °C. After 3 h, the reaction mixture was poured over ice and neutralized with dilute ammonium hydroxide to pH ∼9. After extraction with ethyl acetate, the organic layer was washed successively with water and brine. The organic fractions were dried ($MgSO_4$), filtered, and concentrated, and the pale yellow crude solid (1.02 g) was chromatographed (silica gel, hexane/ethyl acetate, 7/3) to give **28** (800 mg, 77%) as a white solid: mp (DSC) 196 °C; IR (KBr) 3076, 3026, 2939, 2393, 1687, 1597, 1570, 1550, 1510, 1481, 1427, 1379, 1309; $^1$H NMR ($CDCl_3$) 7.76 (complex d, $J$ = 8 Hz, 2H), 7.26 (complex d, $J$ = 8 Hz, 2H), 7.14−7.22 (complex band, 4H), 6.95 (q, $J$ = 2 Hz, 1H), 3.04 (s, 3H), 2.50 (s, 3H); MS (EI) 425 ($M^+$). Anal. ($C_{20}H_{15}NSF_4O_3 \cdot 0.5H_2O$) C, H, N.

**1-[1-(4-Fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)-phenyl]-1*H*-pyrrol-3-yl]ethanone (29).** Acetyl chloride (120 $\mu$L, 1.67 mmol) was added slowly to a stirred slurry of aluminum chloride (223 mg, 1.67 mmol) in methylene chloride (15 mL) at −5 °C. After 30 min, a solution of **1** (500 mg, 1.52 mmol) in methylene chloride (20 mL) was added. The reaction mixture was allowed to warm to room temperature and stirred for 18 h. The reaction mixture was poured over ice−water and extracted with methylene chloride. The organic fraction was washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude yellowish solid (570 mg) was chromatographed (silica gel, hexane/ethyl acetate, 6/4) to give **29** (170 mg, 30%) as a white solid: mp (DSC) 211 °C; IR (KBr) 3072, 3013, 2924, 2205, 1905, 1709, 1649, 1595, 1568, 1552, 1510, 1477, 1425, 1390; $^1$H NMR ($CDCl_3$) 7.74 (d, $J$ = 8 Hz, 2H), 7.24 (d, $J$ = 8 Hz, 2H), 7.14 (d, $J$ = 8 Hz, 4H), 6.88 (s, 1H), 3.04 (s, 3H), 2.51 (s, 3H), 2.42 (s, 3H); MS (EI) 371 ($M^+$). Anal. ($C_{20}H_{18}NSFO_3 \cdot 0.25H_2O$) C, H, N.

**[1-(4-Fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)-phenyl]-1*H*-pyrrol-3-yl]phenylmethanone (30).** Benzoyl chloride (180 $\mu$L, 1.52 mmol) was added slowly to a stirred slurry of aluminum chloride (223 mg, 1.67 mmol) in methylene chloride (15 mL) at −10 °C. After 30 min, a solution of **1** (500 mg, 1.52 mmol) in methylene chloride (10 mL) was added. The reaction mixture was allowed to warm to room temperature and stirred for 20 h. The reaction mixture was poured over ice−water and extracted with methylene chloride. The organic fractions were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude yellowish solid (570 mg) was chromatographed (silica gel, hexane/ethyl acetate, 6/4) to give **30** (54 mg, 8%) as a white solid: IR (KBr) 3061, 2924, 2363, 1917, 1772, 1734, 1717, 1699, 1684, 1635, 1597, 1577, 1568; $^1$H NMR ($CDCl_3$) 7.90 (d, $J$ = 8 Hz, 2H), 7.73 (d, $J$ = 8 Hz, 2H), 7.57 (t, $J$ = 8 Hz, 1H), 7.50 (t, $J$ = 8 Hz, 2H), 7.14−7.27 (complex band, 6H), 6.76 (s, 1H), 3.02 (s, 3H), 2.45 (s, 3H); MS (EI) 433 ($M^+$). Anal. ($C_{25}H_{20}NSFO_3 \cdot 0.5H_2O$) C, H, N.

**1-(4-Fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)-phenyl]-3-[(trifluoromethyl)sulfonyl]-1*H*-pyrrole (31).** To a solution of **1** (10 g, 30.8 mmol) in methylene chloride (400 mL) at 0 °C were added aluminum chloride (4.6 g, 33.9 mmol) and trifluoromethanesulfonic anhydride (8 mL, 46.2 mmol). After 30 min, the reaction mixture was allowed to warm to room temperature and refluxed for 72 h. The reddish orange reaction mixture was cooled, poured over ice−water, and extracted with methylene chloride. The organic fractions were

washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude orange solid (16 g) was chromatographed (silica gel, hexane/ethyl acetate 7/3) to give **31** (1.35 g, 10%) as a white solid: mp 162−164 °C; $^1$H NMR ($CDCl_3$) 7.78 (d, $J$ = 8 Hz, 2H), 7.22 (d, $J$ = 8 Hz, 2H), 7.19 (m, 4H), 6.92 (s, 1H), 3.04 (s, 3H), 2.40 (s, 3H). Anal. ($C_{19}H_{15}NS_2F_4O_4$) C, H, N.

**1-(4-Fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)-phenyl]-1*H*-pyrrole-3-carboxaldehyde (32).** To a solution of **1** (1.55 g, 4.71 mmol) in dimethylformamide (3.65 mL, 47 mmol) and toluene (20 mL) was added over 10 min phosphorous oxychloride (3.5 mL, 37.7 mmol). After being stirred for 20 min, the reaction mixture was immersed in an oil bath at ∼70 °C and heated for 5 h. The reaction mixture was cooled, poured into aqueous sodium acetate solution, and extracted with ethyl acetate. The organic fractions were washed with 10% aqueous potassium carbonate and water. After drying ($Na_2SO_4$), filtration, and concentration, the crude yellowish liquid (2.06 g) was chromatographed (silica gel, hexane/ethyl acetate, 6/4) to give **32** (1.2 g, 71%): mp (DSC) 155 °C; IR (KBr) 3071, 3022, 2926, 2739, 1938, 1730, 1672, 1599, 1556, 1510, 1433, 1402, 1388; $^1$H NMR ($CDCl_3$) 9.98 (s, 1H), 7.76 (d, $J$ = 8 Hz, 2H), 7.22 (d, $J$ = 8 Hz, 2H), 7.14 (d, $J$ = 7 Hz, 4H), 6.92 (s, 1H), 3.02 (s, 3H), 2.42 (s, 3H); MS (EI) 357 ($M^+$). Anal. ($C_{19}H_{16}NSFO_3$) C, H, N.

**1-(4-Fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)-phenyl]-1*H*-pyrrole-3-carbonitrile (33).** To a cold solution of **1** (750 mg, 2.28 mmol) in dimethylformamide (8 mL)−acetonitrile (8 mL) at −78 °C was added chlorosulfonyl isocyanate (200 $\mu$L, 2.28 mmol). The reaction mixture was allowed to warm to 20 °C over 4 h, quenched by adding excess water, and extracted with ethyl acetate. The organic fractions were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude colorless liquid (0.77 g) was chromatographed (silica gel, hexane/ethyl acetate, 6/4) to give the target compound (620 mg, 77%) as a white solid: mp (DSC) 205 °C; IR (KBr) 3076, 2930, 2220, 1720, 1709, 1687, 1657, 1601, 1560, 1512, 1479, 1425, 1394; $^1$H NMR ($CDCl_3$) 7.74 (d, $J$ = 8 Hz, 2H), 7.20 (d, $J$ = 8 Hz, 2H), 7.14 (d, $J$ = 7 Hz, 4H), 6.68 (s, 1H), 3.04 (s, 3H), 2.30 (s, 3H); MS (EI) 354 ($M^+$). Anal. ($C_{19}H_{15}N_2SFO_2$) C, H, N.

**3-Bromo-1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole (34).** To a solution of **1** (3.3 g, 10 mmol) in THF (80 mL) at −70 °C was added over 10 min *N*-bromosuccinimide (1.78 g, 10 mmol). The reaction mixture was allowed to warm to 20 °C over 3 h and stirred for 18 h. After dilution with aqueous sodium bicarbonate, the reaction mixture was extracted with ethyl acetate. The organic fractions were washed with water, dried ($MgSO_4$), filtered, and concentrated. The crude yellowish liquid (4.52 g) was chromatographed (silica gel, hexane/ethyl acetate, 7/3) to give **34** (3.6 g, 88%): mp (DSC) 157 °C; IR (KBr) 3115, 3078, 2920, 1639, 1595, 1510, 1414, 1381; $^1$H NMR ($CDCl_3$) 7.70 (d, $J$ = 8 Hz, 2H), 7.16 (d, $J$ = 8 Hz, 2H), 7.12 (d, $J$ = 7 Hz, 4H), 6.53 (s, 1H), 3.04 (s, 3H), 2.10 (s, 3H); MS (EI) 407/409 ($M^+$). Anal. ($C_{18}H_{15}NSBrFO_2$) C, H, N, Br.

**3-Chloro-1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole (35).** To a solution of **1** (1 g, 3.03 mmol) in THF (100 mL) at −70 °C was added over 10 min *N*-chlorosuccinimide (488 mg, 3.65 mmol). The reaction mixture was allowed to warm to 20 °C over 3 h and stirred for 18 h. More *N*-chlorosuccinimide (450 mg, 3.37 mmol) was added, and the mixture was stirred for 6 h. After dilution with aqueous potassium carbonate, the reaction mixture was extracted with ethyl acetate. The organic fractions were washed with water, dried ($MgSO_4$), filtered, and concentrated. The crude dark orange solid (1.3 g) was chromatographed (silica gel, hexane/ethyl acetate, 1/1) to give **35** (107 mg, 10%): mp (DSC) 172 °C; $^1$H NMR ($CDCl_3$) 7.70 (d, $J$ = 8 Hz, 2H), 7.17 (d, $J$ = 8 Hz, 2H), 7.12 (d, $J$ = 7 Hz, 4H), 6.48 (s, 1H), 3.02 (s, 3H), 2.10 (s, 3H); MS (EI) 363 ($M^+$). Anal. ($C_{18}H_{15}NSClFO_2$) C, H, N.

**1-(4-Fluorophenyl)-*N*,*N*,2-trimethyl-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole-3-methanamine (36).** To a solution of formaldehyde (0.21 mL, 40% solution in water, 2.87 mmol) in acetic acid (2 mL) was added cautiously dimethylamine (325 $\mu$L, 40% solution in water, 2.87 mmol). The reaction mixture was allowed to cool to room temperature and was added to a solution of **1** (500 mg, 2.87 mmol) in AcOH (5 mL). After being heated at 50 −55 °C for 60 min, the reaction mixture was cooled and poured over ice. The solution was made alkaline with 2 N NaOH and extracted with methylene chloride. The organic fractions was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated to give the crude product (550 mg) as a yellowish liquid. Chromatography (silica gel, methylene chloride/methanol/ammonium hydroxide, 90/10/1) gave **36** (259 mg, 23%) as a white solid: mp (DSC) 142 °C; IR (KBr) 3059, 3030, 2964, 2937, 2853, 2814, 1919, 1597, 1562, 1510, 1460, 1429, 1414, 1379; $^1$H NMR ($CDCl_3$) 7.67 (d, $J$ = 8 Hz, 2H), 7.16 (d, $J$ = 8 Hz, 2H), 7.06−7.16 (complex band, 4H), 6.53 (s, 1H), 3.34 (s, 2H), 3.0 (s, 3H), 2.30 (s, 6H), 2.08 (s, 3H); MS (DCI, $NH_3$-PCI) 387 ($MH^+$). Anal. ($C_{21}H_{23}N_2SFO_2$) C, H, N.

**1-(4-Fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)-phenyl]-1*H*-pyrrol-3-yl]methyl Acetate (37).** To a solution of **1** (500 mg, 2.87 mmol) in AcOH (5 mL), was added formaldehyde (0.22 mL, 40% solution in water, 2.87 mmol). After being heated at 50−55 °C for 90 min, the reaction mixture was cooled and poured over ice. The solution was made alkaline with 2 N NaOH and extracted with methylene chloride. The organic fractions were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated to give the crude product (780 mg) as a yellowish liquid. Chromatography (silica gel, hexane/ethyl acetate, 6/4) gave **37** (250 mg, 22%) as a white solid: mp (DSC) 151 °C; IR (KBr) 3072, 2922, 1730, 1597, 1510, 1435, 1406, 1373; $^1$H NMR ($CDCl_3$) 7.68 (d, $J$ = 8 Hz, 2H), 7.16 (d, $J$ = 8 Hz, 2H), 7.04−7.16 (complex band, 4H), 6.58 (s, 1H), 5.07 (s, 2H), 3.0 (s, 3H), 2.13 (s, 3H), 2.08 (s, 3H); MS (EI) 401 ($M^+$). Anal. ($C_{21}H_{20}NSFO_4$) C, H, N.

**1-(4-Fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)-phenyl]-1*H*-pyrrole-3-methanol (38).** To a solution of **32** (1.4 g, 3.9 mmol) in EtOH (30 mL) was added sodium borohydride (297 mg, 7.84 mmol). After 3 h of refluxing, the reaction mixture was cooled to room temperature and quenched with drops of acetic acid. The solvent was removed under reduced pressure and the residue redissolved in methylene chloride. After the mixture was washed with 1 N HCl and brine, the organic fractions were filtered, concentrated, and chromatographed (silica gel, hexane/ethyl acetate, 1/1) to give **38** (1.4 g, 100%) as a white solid: mp (DSC) 148 °C; IR (KBr) 3069, 2993, 2916, 1890, 1593, 1558, 1510, 1471, 1435, 1375; $^1$H NMR ($CDCl_3$) 7.68 (d, $J$ = 8 Hz, 2H), 7.15 (d, $J$ = 8 Hz, 2H), 7.04−7.16 (complex band, 4H), 6.58 (s, 1H), 4.62 (s, 2H), 3.0 (s, 3H), 2.12 (s, 3H); MS (EI) 359 ($M^+$). Anal. ($C_{19}H_{18}NSFO_3 \cdot 0.4H_2O$) C, H, N, S.

**3-[(4-Chlorophenoxy)methyl]-1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole (39).** To a solution of **38** (300 mg, 0.83 mmol), 4-chlorophenol (107 mg, 0.83 mmol), and triphenylphosphine (219 mg, 0.83 mmol) in THF (20 mL) was added diethyl azodicarboxylate (132 $\mu$L, 0.83 mmol). The mixture was stirred at room temperature for 48 h. The solvent was removed under reduced pressure, and the crude (830 mg) was chromatographed (silica gel, hexane/ethyl acetate, 1/1) to give **39** (29 mg, 7%): mp (DSC) 145 °C; IR (KBr) 3071, 2922, 2872, 1716, 1653, 1595, 1579, 1510, 1490, 1435, 1410; $^1$H NMR ($CDCl_3$) 7.70 (d, $J$ = 8 Hz, 2H), 7.27 (d, $J$ = 8 Hz, 2H), 7.16 (d, $J$ = 8 Hz, 2H), 7.04−7.16 (complex band, 4H), 6.96 (d, $J$ = 8 Hz, 2H), 6.52 (s, 1H), 4.93 (s, 2H), 3.02 (s, 3H), 2.13 (s, 3H); MS (EI) 469 ($M^+$). Anal. ($C_{25}H_{21}NSClFO_3 \cdot 0.25H_2O$) C, H, N.

**3-[(3-Chlorophenoxy)methyl]-1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole (40).** To a solution of **38** (300 mg, 0.83 mmol), 3-chlorophenol (88 $\mu$L, 0.83 mmol), and triphenylphosphine (219 mg, 0.83 mmol) in THF (20 mL) was added diethyl azodicarboxylate (132 $\mu$L, 0.83 mmol). The mixture was stirred at room temperature for 48 h. The solvent was removed under reduced pressure, and the crude liquid (820 mg) was chromatographed (silica gel, hexane/ethyl acetate, 7/3) to give **40** (75 mg, 19%): mp (DSC) 139 °C; IR (KBr) 2922, 1716, 1684, 1653, 1593, 1558, 1539, 1510, 1477, 1435, 1361; $^1$H NMR ($CDCl_3$) 7.68 (complex d, $J$ = 8 Hz, 2H), 7.23 (t, $J$ = 8 Hz, 1H), 7.19 (complex d, $J$ = 8 Hz, 2H), 7.17 (complex dd, $J$ = 9, 5 Hz, 2H), 7.12 (complex t, $J$ = 9 Hz, 2H), 7.04 (t, $J$ = 2 Hz, 1H), 6.96 (ddd, $J$ = 8, 2, 1 Hz, 1H), 6.92

(ddd, $J$ = 8, 2, 1 Hz, 1H), 6.63 (s, 1H), 4.95 (s, 2H), 3.02 (s, 3H), 2.13 (s, 3H); MS (EI) 469 ($M^+$). Anal. ($C_{25}H_{21}NSClFO_3$) C, H, N.

**1-(4-Fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)-phenyl]-α-(trifluoromethyl)-1*H*-pyrrole-3-methanol (41).** To a solution of **28** (310 mg, 0.73 mmol) in ethanol (10 mL) and acetic acid (10 mL) in a Parr hydrogenation flask was added 4% Pd on C (51 mg). The system was sealed, purged with nitrogen (5 times) and hydrogen (5 times), and then pressurized to 5 psi of hydrogen. After the reaction was run on a shaker for 24 h, the system was vented, purged with nitrogen, and filtered. The filtrate was concentrated, and the crude (325 mg) was chromatographed (silica gel, hexane/ethyl acetate, 6/4) to give **41** (270 mg, 87%): mp (DSC) 213 °C; IR (KBr) 2918, 1720, 1691, 1657, 1597, 1547, 1510, 1439, 1302; $^1$H NMR ($CDCl_3$) 7.70 (d, $J$ = 8 Hz, 2H), 7.18 (d, $J$ = 8 Hz, 2H), 7.04−7.16 (complex band, 4H), 6.65 (s, 1H), 5.05 (m, 1H), 3.02 (s, 3H), 2.51 (d, $J$ = 6 Hz, 1H), 2.13 (s, 3H); MS (EI) 427 ($M^+$). Anal. ($C_{20}H_{17}NSF_4O_3$) C, H, N.

**1-(4-Fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)-phenyl]-3-(2,2,2-trifluoroethyl)-1*H*-pyrrole (42).** To a solution of **41** (325 mg, 0.76 mmol) in trifluoroacetic acid (5 mL) and acetic acid (10 mL) in a Parr hydrogenation flask was added 5% Pt on C (325 mg). The system was sealed, purged with nitrogen (5 times) and hydrogen (5 times), and then pressurized to 60 psi of hydrogen. After the reaction was run on a shaker for 48 h, the system was vented, purged with nitrogen, and filtered. The filtrate was concentrated, and the residue was redissolved in methylene chloride and washed with aqueous potassium carbonate and brine. After drying ($MgSO_4$), filtration, and concentration, the crude (320 mg) was chromatographed (silica gel, hexane/ethyl acetate, 7/3) to give **42** (135 mg, 43%): mp (DSC) 151 °C; IR (KBr) 3427, 1597, 1510, 1354, 1257; $^1$H NMR ($CDCl_3$) 7.70 (d, $J$ = 8 Hz, 2H), 7.18 (d, $J$ = 8 Hz, 2H), 7.04−7.14 (complex band, 4H), 6.50 (s, 1H), 3.28 (q, $J$ = 10.5 Hz, 2H), 3.02 (s, 3H), 2.08 (s, 3H); MS (EI) 411 ($M^+$). Anal. ($C_{20}H_{17}NSF_4O_2 \cdot 0.25H_2O$) C, H, N.

**3-[1-(3-Chlorophenoxy)-2,2,2-trifluoroethyl]-1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole (43).** To a solution of **41** (340 mg, 0.8 mmol), 3-chlorophenol (85 μL, 0.8 mmol), and triphenylphosphine (209 mg, 0.8 mmol) in THF (20 mL) was added diethyl azodicarboxylate (125 μL, 0.8 mmol). The mixture was stirred at room temperature for 48 h. The solvent was removed under reduced pressure, and the crude liquid (920 mg) was chromatographed (silica gel, hexane/ethyl acetate, 6/4) to give **43** (40 mg, 9%): IR (KBr) 2922, 1593, 1510, 1475, 1431, 1309; $^1$H NMR ($CDCl_3$) 7.70 (complex d, $J$ = 8 Hz, 2H), 7.21 (t, $J$ = 8 Hz, 1H), 7.08−7.20 (complex band, 6H), 7.00 (dd, $J$ = 8, 2 Hz, 1H), 6.97 (t, $J$ = 2 Hz, 1H), 6.86 (dd, $J$ = 8, 2 Hz, 1H), 6.64 (s, 1H), 5.42 (q, $J$ = 6 Hz, 1H), 3.02 (s, 3H), 2.16 (s, 3H); MS (EI) 537 ($M^+$). Anal. ($C_{26}H_{20}NSClF_4O_3$) C, H, N.

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## References

(1) (a) Vane, J. R. Inhibition of Prostaglandin Synthesis as a Mechanism of Action for Aspirin-Like Drugs. *Nature (New Biol.)* **1971**, *231*, 232−235. (b) Smith, J. B.; Willis, A. L. Aspirin Selectivity Inhibits Prostaglandin Production in Human Platelets. *Nature (New Biol.)* **1971**, *231*, 235−237.

(2) (a) Allison, M. C.; Howatson, A. G.; Torrence, C. J.; Lee, F. D.; Russel, R. I. Gastrointestinal Damage Associated wiith the Use of Nonsteroidal Antiinflammatory Drugs. *N. Engl. J. Med.* **1992**, *327*, 749−754. (b) Sontag, S. J. Prostaglandins in Peptic Ulcer Disease. An Overview of Current Status and Future Directions. *Drugs* **1986**, *32*, 445−457. (c) Patrono, C.; Dunn, M. J. The Clinical Significance of Inhibition of Renal Prostaglandin Synthesis. *Kidney Int.* **1987**, *32*, 1−12.

(3) Hla, T.; Neilson, K. Human Cyclooxygenase-2 cDNA. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 7384−7388.

(4) Xie, W.; Chipman, J. G.; Robertson, D. L.; Erikson, R. L.; Simmons, D. L. Expression of a Mitogen-Response Gene Encoding Prostaglandin Synthase is Regulated by mRNA Splicing. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 2692−2696.

(5) Kujubu, D. A.; Fletcher, B. S.; Varnum, B. C.; Lim, R. W.; Herschman, H. R. TIS10, a Phorbol Ester Tumor Promoter-Inducible mRNA From Swiss 3T3 Cells, Encodes a Novel Prostaglandin Synthase/Cyclooxygenase Homologue. *J. Biol. Chem.* **1991**, *266*, 12866−12872.

(6) (a) Masferrer, J. L.; Zweifel, B. S.; Manning, P. T.; Hauser, S. D.; Leahey, K. M.; Smith, W. G.; Isakson, P. C.; Seibert, K. Selective Inhibition of Inducible Cyclooxygenase-2 *In Vivo* is Antiinflammatory and Nonulcerogenic. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 3228−3232. (b) Seibert, K.; Masferrer, J. L. Role of Inducuble Cyclooxygenase (COX-2) in Inflammation. *Receptor* **1994**, *4*, 17−23.

(7) (a) Meade, E. A.; Smith, W. L.; DeWitt, D. L. Differential Inhibition of Prostaglandin Endoperoxide Synthase (Cyclooxygenase) Isozymes by Aspirin and Other Nonsteroidal Antiinflammatory Drugs. *J. Biol. Chem.* **1993**, *268*, 6610−6614. (b) Mitchell, J. A.; Akarasereemont, P.; Thiemerman, C.; Flower, R. J.; Vane, J. R. Selectivity of Nonsteroidal Antiinflammatory Drugs as Inhibitors of Constitutive and Inducible Cyclooxygenase. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 11693−11697. (c) Vane, J. R.; Mitchell, J. A.; Appleton, I.; Tomlinson, A.; Bishop-Bailey, D.; Croxtail, J.; Willoughby, D. A. Inducible Isoforms of Cyclooxygenase and Nitric-Oxide Synthase in Inflammation. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 2046−2050.

(8) Harada, Y.; Hatanaka, K.; Saito, M.; Majima, M.; Ogina, M.; Kawamura, M.; Ohno, T.; Yang, Q.; Katori, M.; Yamamoto, S. Detection of Inducible Prostaglandin H Synthase-2 in cells in the Exudate of Rat Carrageenan Induced Pleurisy. *Biomed. Res.* **1994**, *15*, 127−130.

(9) Gans, K. R.; Galbraith, W.; Roman, R. J.; Haber, S. B.; Kerr, J. S.; Schmidt, W. K.; Smith, C.; Hewews, W. E.; Ackerman, N. R. Antiinflammatory and Safety Profile of DuP 697, A Novel Orally Effective Prostaglandin Synthesis Inhibitor. *J. Pharmacol. Exp. Ther.* **1990**, *254*, 180−187.

(10) Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. Synthesis and Biological Evaluation of 1,5-Diarylpyrazole Class of Cyclooxygenase-2 Inhibitors: Identification of SC-58635 (Celecoxib). Submitted to *Chem.*

(11) (a) Reitz, D. B.; Li, J J.; Norton, M. B.; Reinhard, E. J.; Collins, J. T.; Anderson, G. D.; Gregory, S.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Isakson, P. C. Selective Cyclooxygenase Inhibitors: Novel 1,2-Diarylcyclopentenes are Potent and Orally Active COX-2 Inhibitors. *J. Med. Chem.* **1994**, *37*, 3878−3881. (b) Reitz, D. B.; Huang, H.-C.; Li, J. J.; Garland, D. J.; Manning, R. E.; Anderson, G. D.; Gregory, S.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Isakson, P. C. Selective Cyclooxygenase Inhibitors: Novel 4-Spiro 1,2-Diarylcyclopentenes are Potent and Orally Active COX-2 Inhibitors. *Biorg. Med. Chem. Lett.* **1995**, *5*, 867−872. (c) Reitz, D. B.; Li, J. J.; Norton, M. B.; Reinhard, E. J.; Huang, H.-C.; Penick, M. A.; Collins, J. T.; Garland, D. J.; Seibert, K.; Koboldt, C. M.; Gregory, S.; Veenhuizen, A.; Zhang, Y.; Isakson, P. C. Novel 1,2-Diarylcyclopentenes are Selective, Potent and Orally Active Cyclooxygenase Inhibitors. *Med. Chem. Res.* **1995**, *5*, 351−363. (d) Huang, H.-C.; Li, J. J.; Garland, D. J.; Chamberlain, T. S.; Reinhard, E. J.; Manning, R. E.; Seibert, K.; Koboldt, C. M.; Gregory, S. A.; Anderson, G. D.; Veenhuizen, A. W.; Zhang, Y.; Perkins, W. E.; Burton, E. G.; Cogburn, J. N.; Isakson, P. C.; Reitz, D. B. 1,2-Diarylspiro[2,4]heptenes as Orally Active, Highly Selective Cyclooxygenase-2 Inhibitors: Synthesis and Structure-Activity relationships. *J. Med. Chem.* **1996**, *39*, 253−266. (e) Li, J. J.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Collins, J. T.; Garland, D. J.; Gregory, S. A.; Huang, H.-C.; Isakson, P. C.; Koboldt, C. M.; Logusch, E. W.; Norton, M. B.; Perkins, W. E.; Reinhard, E. J.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y.; Reitz, D. B. 1,2-Diarylcyclopentenes as Selective Cyclooxygenase-2 Inhibitors and Orally Active Anti-inflammatory Agents. J. *Med. Chem.* **1995**, *38*, 4570−4578.

(12) (a) Gauthier, J. Y.; Leblanc, Y.; Black, W. C.; Chan, C. C.; Cromlish, W. A.; Gordon, R.; Kennedey, B. P.; Lau, C. K.; Leger, S.; Wang, Z.; Ethier, D.; Guay, J.; Mancini, J.; Riendeau, D.; Tagari, P.; Vickers, P.; Wong, E.; Xu, L.; Prasit, P. Synthesis and Biological Evaluation of 2,3-Diarylthiophenes as Selective COX-2 Inhibitors. Part II: Replacing The Heterocycle. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 87−92. (b) Huang, H.-C.; Chamberlain, T. S. Diaryl Indenes and Benzofurans: Novel Classes of Potent and Selective Cyclooxygenase-2 Inhibitors. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2377−2380. (c) Bertenshaw, S. R.; Talley, J. J.; Rogier, D. J.; Graneto, M. J.; Rogers, R. S.; Kramer, S. W.; Penning, T. D.; Koboldt, C. M.; Veenhuizen, A. W.; Zhang, Y.; Perkins, W. E. 3,4-Diarylthiophenes are Selective COX-2 Inhibitors. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2919−2922. (d) Leblanc, Y.; Gauthier, J. Y.; Ethier, D.; Guay, J.; Mancini, J.; Reindeau, D.; Tagari, P.; Vickers, P.; Wong, E.; Prasit, P. Synthesis and

Biological Evaluation of 2,3-Diarylthiophenes as Selective COX-2 and COX-1 Inhibitors. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2123−2128. (e) Copeland, R. A.; Williaks, J. M.; Rider, N. L.; Van Dyk, D. E.; Giannaras, J.; Nurnberg, S.; Covington, M.; Pinto, D.; Magolda, R. L.; Trzaskos, J. M. Selective Time Dependent Inhibition of Cyclooxygenase-2. *Med. Chem. Res.* **1995**, *5*, 384−393. (f) Pinto, D. J.; Pitts, W. J.; Copeland, R. A.; Covington, M. B.; Trzaskos, J.; Magolda, R. Selective Inhibition of Cyclooxygenase-2: Diaryl Heterocycles vs Classical NSAIDS. *Med. Chem. Res.* **1995**, *5*, 394−398.

(13) (a) Tanaka, K.; Yoshida, I. N.; Tomita, K.; Masuda, H. Diaryl Pyrroles: A New Series of Anti-inflammatory Agents. *Experientia* **1972**, *28*, 937−938. (b) Wilkerson, W. W.; Copeland, R. A.; Covington, M.; Trzaskos, J. M. Antiinflammatory 4,5-Diarylpyrroles. 2. Activity as a Function of Cyclooxygenase-2 Inhibition. *J. Med. Chem.* **1995**, *38*, 3895−3901. (c) Wilkerson, W. W.; Copeland, R. A.; Covington, M.; Grubb, M. F.; Hewes, W. E.; Kerr, J. S.; Trzaskos, J. M. Cyclooxygenase-2 Inhibitory 2-Substituted 4,5-Diarylpyrroles. *Med. Chem. Res.* **1995**, *5*, 399−408. (d) Wilkerson, W. W.; Galbraith, W.; Gans-Brangs, K.; Grubb, M.; Hewes, W. E.; Jaffee, B.; Kenney, J. P.; Kerr, J.; Wong, N. Antiinflammatory 4,5-Diarylpyrroles: Synthesis and QSAR. *J. Med. Chem.* **1994**, *37*, 988−998.

(14) These results are consistent with the first observation made by Len Lee in 1,5-diarylpyrazole series, unpublished results.

(15) Garavito, R. M.; Picot, D.; Loll, P. J. The X-Ray Structures of Cyclooxygenase-1 And Inhibitors. *Med. Chem. Res.* **1995**, *5*, 375−383.

(16) For a review on Stetter reaction, see: Stetter, H. Catalyzed Addition of Aldehydes to Activated Double Bonds—A New Synthetic Approach. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 639−712.

(17) Stowell, J. C.; Polito, M. A. A Facile Procedure for Producing $\gamma$-Halo Butyraldehyde Acetals. *J. Org. Chem.* **1992**, *57*, 2195−2196.

(18) Baciocchi, E.; Muraglia, E. Synthesis of Perfluoroalkylpyrroles by Homolytic Substitution with Perfluoroalkyl Radicals. *Tetrahedron Lett.* **1993**, *34*, 3799−3800.

(19) Irradiation of the pyrrole proton signal at $\delta$ 6.80 gave a positive NOE (12.4% signal enhancement) for the adjacent pyrrole proton at $\delta$ 6.52, suggesting that $CF_3$ group is at either the C-3 or C-5 position of the pyrrole nucleus. Further irradiation of the pyrrole proton signal at $\delta$ 6.52 gave 12.2% enhancements of the adjacent pyrrole proton at $\delta$ 6.80 and 8.8% signal enhancements of the protons at C-3′ and C-5′ on the aryl sulfone ring (see structure **27**), suugesting that the position C-3 on pyrrole ring must be unoccupied.

(20) For chemistry on electrophilic substitutions in pyrroles, see: (a) Bray, B. L.; Mathies, P. H.; Naef, R.; Solas, D. R.; Tidwell, T. T.; Artis, D. R.; Muchowski, J. M. *N*-(Triisopropylsilyl)pyrrole. A Progenator "Par Excellence" of 3-Substituted Pyrroles. *J. Org. Chem.* **1990**, *55*, 6317−6328. (b) Cerreto, F.; Villa, A.; Retico, A.; Scalzo, M. Studies on Anti-Candida Agents With a Pyrrole Moiety. Synthesis and Microbiological Activity of Some 3-Aminomethyl-1,5-Diaryl-2-Methyl-Pyrrole Derivatives. *Eur. J. Med. Chem.* **1992**, *27*, 701−708. (c) Gilow, H. M.; Burton, D. E. Bromination and Chlorination of Pyrrole and Some Reactive 1-Substituted Pyrroles. *J. Org. Chem.* **1981**, *46*, 2221−2225. (d) Chang, M. N.; Biftu, T.; Boulton, D. A.; Finke, P. E.; Hammond, M. l.; Pessolano, A. A.; Zambias, R. A.; Bailey, P.; Goldenberg, M.; Rackham, A. Syntheses and Analgesic/Antiinflammatory Activities of Novel 2-(5-Aroyl-Pyrrolo)Alkanoic Acids. *Eur. J. Med. Chem.* **1986**, *21*, 363−369.

(21) Gierse, J. K.; Hauser, S. D.; Creely, D. P.; Koboldt, C.; Rangwala, S. H.; Isakson, P. C.; Seibert, K. Expression and Selective Inhibition of the Constitutive and Inducible Forms of Human Cyclooxygenase. *Biochem. J.* **1995**, *305*, 479−484.

(22) (a) Patrignani, P.; Panara, M. R.; Greco, A.; Fusco, O.; Natoli, C.; Iacobelli, S.; Cipollone, F.; Ganci, A.; Creminon, C.; Maclouf, J.; Patrono, C. Biochemical and Pharmacological Characterization of the Cyclooxygenase Activity of Human Blood Prostaglandin Endoperoxide Synthases. *J. Pharmacol. Exp. Ther.* **1994**, *271*, 1705−1712. (b) Brideau, C.; Kargman, S.; Liu, S.; Dallob, A. L.; Ehrich, E. W.; Rodger, I. W.; Chan, C.-C. A Human Whole Blood Assay for Clinical Evaluation of Biochemical Efficay of Cyclooxygenase Inhibitors. *Inflamm. Res.* **1996**, *45*, 68−74.

(23) (a) Seibert, K.; Zhang, Y.; Leahy, K.; Hauser, S.; Masferrer, J.; Perkins, W.; Lee, L.; Isakson, P. Pharmacological and Biochemical Demonstration of the Role of Cyclooxygenase-2 in Inflammation and Pain. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 12013−12017. (b) Winter, C. A.; Risley, E. A.; Nuss, G. W. Carrageenan Induced Edema in Hind Paw of the Rat as an Assay for Antiinflammatory Drugs. *Proc. Soc. Exp. Biol. Med.* **1962**, *111*, 544−547.

(24) (a) Raz, A.; Wyche, A.; Siegel, N.; Needleman, P. Regulation of Fibroblast Cyclooxygenase Synthesis by Interleukin-1. *J. Biol. Chem.* **1988**, *263*, 3022−3028. (b) Seibert, K.; Masferrer, J. L.; Honda, A.; Raz, A.; Needleman, P. The Biochemical and Pharmacological Manipulation of Cellular Cyclooxygenase Activity. *Adv. Prostaglandin, Thromboxane, Leukotriene Res.* **1990**, *21*, 45−51.

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