1,2-Diarylimidazoles as Potent, Cyclooxygenase-2 Selective, and Orally Active Antiinflammatory Agents

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Received January 13, 1997[⊗]

Series of 1,2-diarylimidazoles has been synthesized and found to contain highly potent and selective inhibitors of the human COX-2 enzyme. The paper describes a short synthesis of the target 1,2-diarylimidazoles starting with aryl nitriles. Different portions of the diarylimidazole (**I**) were modified to establish SAR. Systematic variations of the substituents in the aryl ring B have yielded very potent (IC_{50} = 10−100 nm) and selective (1000−12500) inhibitors of the COX-2 enzyme. The study on the influence of substituents in the imidazole ring established that a CF_3 group at position 4 gives the optimum oral activity. A number of the diarylimidazoles showed excellent inhibition in the adjuvant induced arthritis model (e.g., ED_{50} = 0.02 mpk for **22** and **34**). The diarylimidazoles are also potent inhibitors of carrageenan-induced edema (ED_{50} = 9−30 mpk) and hyperalgesia (ED_{50} = 11−40 mpk). Several orally active diarylimidazoles show no GI toxicity in the rat and mouse up to 200 mpk.

Introduction

Nonsteroidal antiinflammatory drugs (NSAIDs) are widely utilized agents for the treatment of inflammation, pain, and fever.[1] Some of these drugs have been in existence for over a century, but only in 1971 was it established that they act by blocking the production of prostaglandins (PG's) *via* the cyclooxygenase pathway.[2] The chronic usage of these drugs has, however, been linked to the induction of gastrointestinal mucosal lesions, perforations, and bleeding in part of the population.[3] Decreased renal function has been observed in some patients.[4] These limitations of NSAIDs have been associated with the inhibition of PG's in the stomach and kidney. The efforts to improve the adverse effect profile of the current NSAIDs have focused on developing prodrugs[5] or modifications of the marketed formulations.[6] These approaches have been only partially successful.

Alternately, the steroidal antiinflammatory drugs (glucocorticoids) offer more potent and efficacious agents, but their serious side effect profile has limited their potential in chronic inflammatory diseases such as rheumatoid arthritis.[7] The discovery of a cytokine inducible enzyme (COX-2)[8−10] and the emerging evidence that it may be possible to separate its role from the constitutive enzyme (COX-1) has stimulated the quest for a newer agent with better therapeutic potential. A potent and selective COX-2 inhibitor should block the PG's production in inflammatory cells while not interfering with the homeostatic (COX-1) production of PG's in the gastrointestinal tract.[11−14] A diarylpyrazole-based selective COX-2 inhibitor (SC-58635)[15] is undergoing clinical trials for the treatment of inflammatory disorders. In addition, meloxicam, approved in some European countries, is reported to be a selective COX-2 inhibitor.[16] Variants of the central ring system[17−20] of SC-58635 have been pursued aggressively. Recently, we reported our results on a series of 1,2-diarylpyrroles.[21] This paper describes the syntheses, structure−activity relationships, and antiinflammatory activity of 1,2-diarylimidazoles.

Table 1. 1,2-Diarylimidazoles as Cyclooxygenase Inhibitors

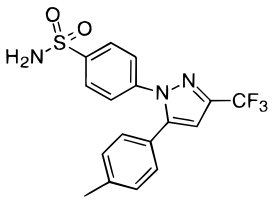
compd	IC_{50}, μM COX-2	IC_{50}, μM COX-1	air pouch (% inhib, 2 mpk)
5	0.24	>100	53
6	0.11	23	98
7	>100	>100	
8	5.85	>100	

Flumizole (**1**) is one of the early known 4,5-diarylimidazoles showing antiinflammatory and analgesic activities similar to indomethacin. The compound was in clinic but was reported to show complex pharmacokinetics in humans.[22] Tiflamizole (**2**) is about 8 times as potent as indomethacin in the rat adjuvant induced arthritis assay. In clinical trials, the compound exhibited dose-limiting incidence of GI ulceration probably because of the nonselective inhibition of the cyclooxygenase enzymes.[23] Gauthier et al.[24] have recently reported that 4,5-diarylimidazole (**3**) is inactive against both COX-1 and COX-2 up to >30 μM. Encouraged by the excellent potency and selectivity observed with 1,2-diarylpyrroles (**4**)[21] and the antinflammatory activity reported for **1** and **2**, we decided to synthesize and explore the 1,2-diarylimidazoles (**I**) for their potential as antiinflammatory agents.

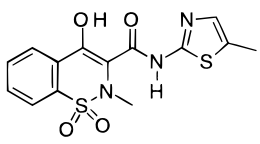
In studying the effect of pyrrole substituents on the activity against cyclooxygenase enzymes, it was observed[21] that R_4 in **4** was more tolerant of substituent variations than R_3 and that the modifications of substituents at R_4 gave very potent and selective inhibitors of the COX-2 enzyme. To expand on this study and to evaluate the potential of 1,2-diarylimidazoles, we synthesized **5**−**8** as the first variants of **I** (R_4 = Me, CF_3). The activity of these diarylimidazoles against human COX enzymes is summarized in Table 1. The results show that the analogs (**5** and **6**) containing a 4-(methylsulfonyl)phenyl group directly attached to the imida-

[⊗] Abstract published in *Advance ACS Abstracts,* April 15, 1997.

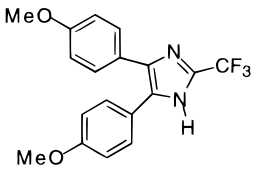
S0022-2623(97)00022-8 CCC: $14.00



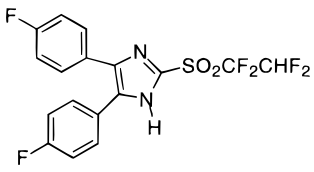
SC-58635



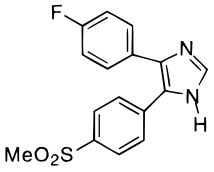
Meloxicam



Flumizole (1)

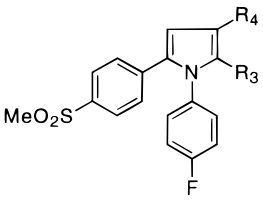


Tiflamizole (2)



3

zole nitrogen are significantly more potent than the isomeric compounds (**7** and **8**) wherein the aryl groups have been "reversed". The analog **6**, bearing a trifluoromethyl group at position 4 of the imidazole ring, was about 2 times more potent than the methyl analog (**5**) against the human COX-2 enzyme. Compound **6** was also superior to **5** in the carrageenan-induced air-pouch model in the rat, showing 98% inhibition of the prostaglandin production at a screening dosage of 2 mpk. On the basis of these encouraging results, a series of 1,2-diarylimidazoles was synthesized to study and define the essential structural features for achieving the optimum potency and selectivity *vs* the COX-2 enzyme.



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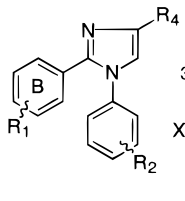
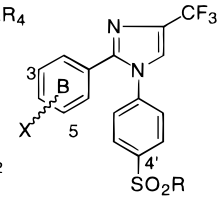
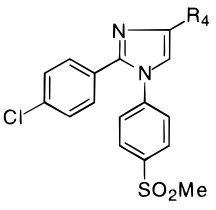


I

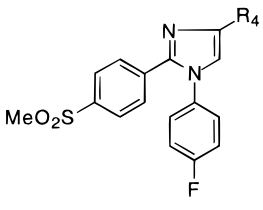


III



5 (R_4 = Me)

6 (R_4 = CF_3)



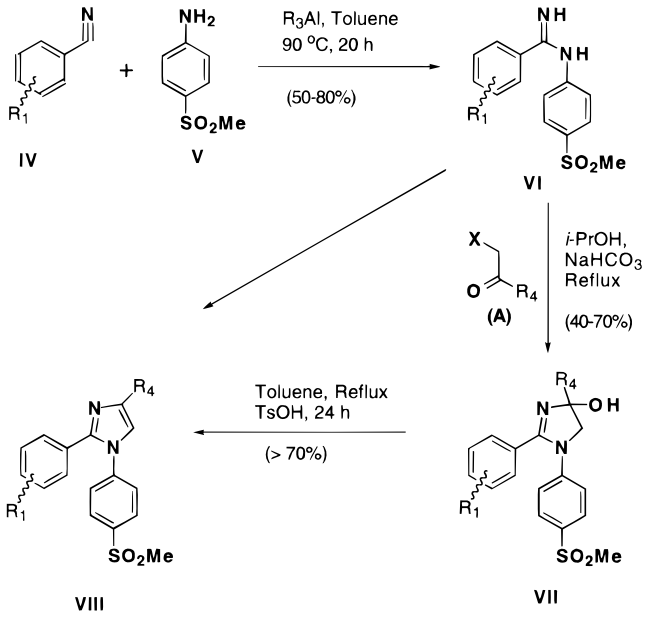
7 (R_4 = Me)

8 (R_4 = CF_3)

Chemistry

The 1,2-diarylimidazoles reported in this paper were synthesized using Schemes 1−6. Our general strategy

Scheme 1

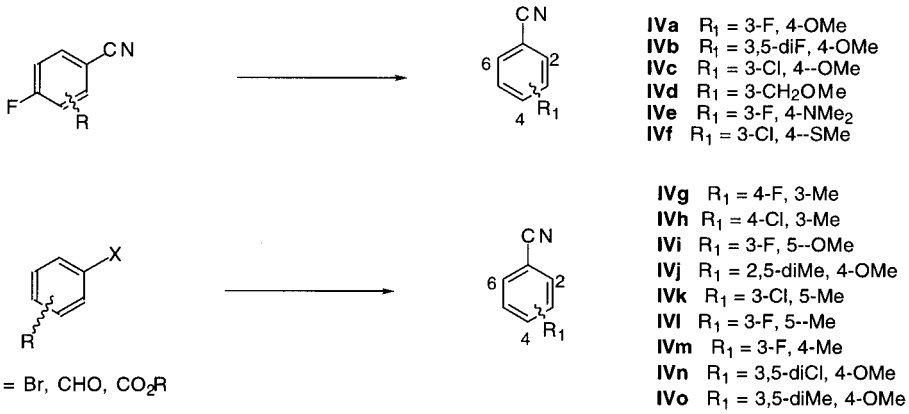


R_4 = Me, CF_3, Ar, CO_2R, CH_2OAr

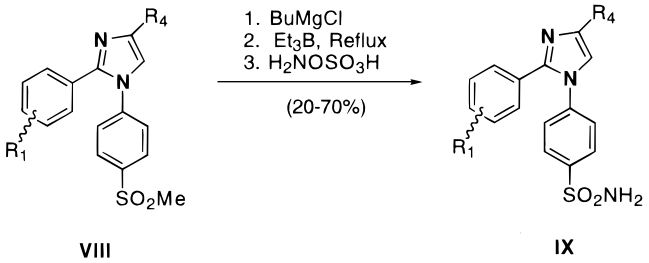
for the synthesis of compounds containing a 4-(methylsulfonyl)phenyl group directly attached to the imidazole nitrogen is outlined in Scheme 1. The key step in this sequence involves the reaction of the versatile amidine intermediate (**VI**) with 2-halomethyl ketone derivatives (**A**) to give the imidazoline (**VII**). This reaction was carried out preferentially by refluxing a solution of **VI** in 2-propanol utilizing mild base such as $NaHCO_3$. This alkylation/cyclization reaction works with a number of 2-halomethyl ketones **A** (e.g., R_4 = CF_3, Ar, CO_2R, CH_2OAr). When R_4 is a CF_3 group, the reaction proceeds in very high regioselectivity and no traces of the isomeric product (e.g., **84**) are isolated. In some instances (e.g., when R_4 = Ph), the intermediate **VII** was not isolated and the reaction proceeds directly to the targeted imidazole **VIII**. In other cases, the carbinol intermediate **VII** was dehydrated using acid catalyst (TsOH, toluene, reflux) to give the desired diarylimidazoles (**VIII**) in excellent yield. The amidine intermediate (**VI**) was prepared from the aryl nitriles (**IV**) and the 4-(methylsulfonyl)aniline (**V**), utilizing the modified Weinreb methodology developed by Garigipati.[25] The isomeric compounds (**7**, **8**; Table 1) were synthesized following the Scheme 1 and using 4-fluoroaniline as the starting amine (see the Experimental Section).

A number of aryl nitriles (**IV**) used in the Scheme 1 were purchased commercially. Some of these (**IVa**−**q**) were prepared from commercially available intermediates by displacement reactions or by functional group transformations (Scheme 2). For example, compounds **IVa** and **IVb** were prepared from 3,4-difluorobenzonitrile and 3,4,5-trifluorobenzonitrile, respectively, by displacement reaction (NaOMe, MeOH, RT, 24 h) in approximately 50% yield each. In an analogous manner, the nitrile (**IVd**) was prepared in 40% yield from 3-cyanobenzyl bromide by reaction with NaOMe. The other nitriles were prepared by the transformation of the aldehyde, the aldoxime, or the carboxylic acid group using the known literature procedures (see the Experimental Section). In some instances, the commercially available aryl bromides or carboxylic esters were con-

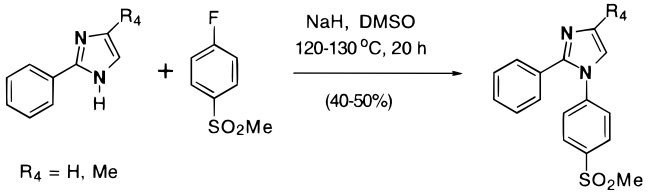
Scheme 2



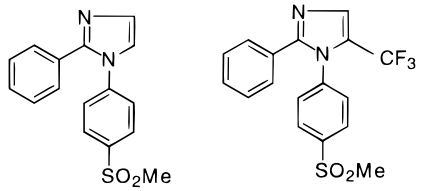
Scheme 3



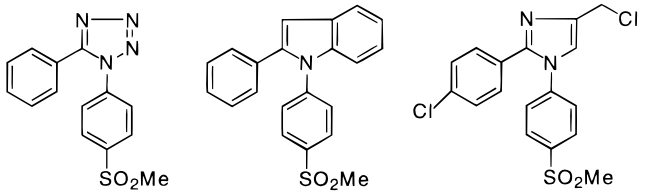
Scheme 4



83 R_4 = H
83A R_4 = Me



83 **84**



85 **86** **93**

verted to the aryl aldehydes and then transformed to the target aryl nitriles (e.g., **IVg**, **IVh**, and **IVm**, **IVn**, respectively).

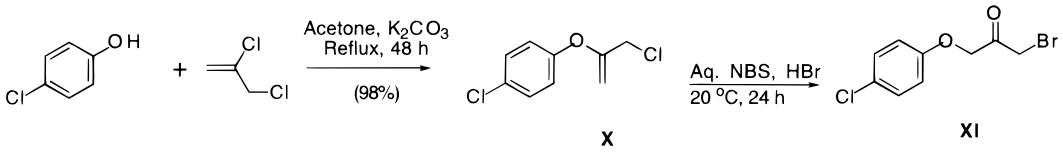
The diarylimidazoles containing the sulfonamide group were prepared (Scheme 3) from the corresponding methyl sulfone derivatives utilizing the one-pot procedure described by Huang et al.[26] The yields for the reaction varied with the substituents (R_1) in the aryl ring and were typically from 20 to 70%.

The 1,2-diarylimidazoles analogs containing a H or Me group at position 4 of the imidazole ring (**VIII**, R_4 = H, Me) were synthesized in a one-step process (Scheme 4) from commercially available 2-phenylimidazole or 4-methyl-2-phenylimidazole. Thus, the reaction of 4-fluorophenyl methyl sulfone with 2-phenylimidazole (NaH, DMSO, 120−130 °C, 120 h) gave **83** in 54% yield. Similarly, reaction of 4-fluorophenyl methyl sulfone with 4-methyl-2-phenylimidazole gave **83A** in 40−50% yield. The direct synthesis of analogs (**VIII**, R_4 = H, Me) was superior to the methodology discussed in Scheme 1. For example, the reaction of the chloroacetone (15 mol excess) with amidine **VI** (Scheme 1) was very sluggish (reflux, >72 h) and gave variable yield (12−27%) of the desired compound **5**. The methodology reported in Scheme 4 was also successfully applied to the synthesis of **85** and **86**.

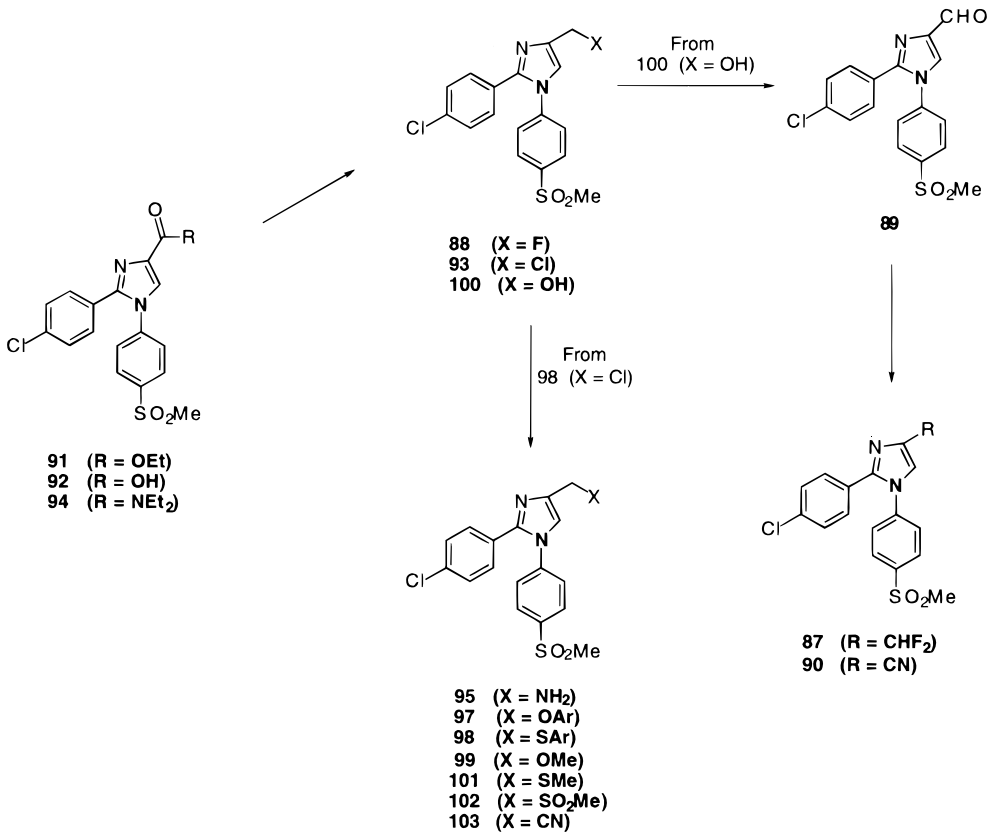
The synthesis of 1,2-diarylimidazoles containing an (aryloxy)methyl substituent at position 4 (**VIII**, R_4 = CH_2OAr) was accomplished utilizing the sequence outlined in Scheme 5. The necessary α-bromomethyl ketone intermediate (**XI**) was prepared (Scheme 5) from the vinyl halide (**X**) and aqueous *N*-bromosuccinimide (NBS) utilizing the reported methodology.[31] The intermediate **XI** is unstable and was used crude in the next step without extensive purification. The intermediate (**X**) was prepared in 98% yield by the alkylation of 4-chlorophenol with 2,3-dichloropropene (acetone, K_2CO_3, reflux, 48 h).

Compound **91** with a carboethoxy group at position 4 in the imidazole ring was utilized to synthesize additional analogs containing a hydroxymethyl (**100**), an aldehyde (**89**), a cyano (**90**), a fluoromethyl (**88**), a difluoromethyl (**87**), a carboxylic acid (**92**), a diethylcarboxamide (**94**), an arylthioalkyl (**98**), a methoxymethyl (**99**), a methylthiomethyl (**101**), and a cyanomethyl (**103**) group in direct or sequential reaction manipulations (Scheme 6). The reduction of **91** (DIBAL, −70 °C) gave the hydroxymethyl derivative (**100**). Compound **100** was oxidized (Swern conditions, 49%) to the aldehyde (**89**) or converted to the chloromethyl derivative **93** ($SOCl_2$, reflux, 1 h, 67%). The useful chloromethyl intermediate **93** was converted to a variety of targets (e.g., **95**, **97**−**99**, **101**−**103**) by nucleophilic displacement reactions (see the Experimental Section). Monofluoromethyl (**88**) and difluoromethyl (**87**) derivatives were

Scheme 5



Scheme 6



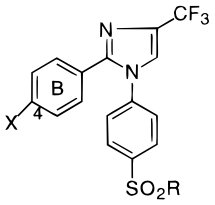
synthesized from the hydroxymethyl (**100**) and the aldehyde (**89**) analogs using (diethylamido)sulfur trifluoride (DAST) as the fluorinating agent in 42 and 24% yield, respectively. The carboethoxy compound (**91**) was also hydrolyzed (MeOH, 1N NaOH, reflux, 57%) to the carboxylic acid (**92**) and converted (DMF, oxalyl chloride, $HNEt_2$, 85%) to the amide (**94**) analogs. The compound containing a cyano group (**90**) was synthesized from the carboxaldehyde derivative (**89**) in a direct one-pot procedure[35] (H_2NOSO_3H, pyridine, EtOH, reflux, 85%).

Results and Discussion

All the test compounds were screened against human COX-1 and COX-2 enzymes to evaluate their potency and selectivity.[27] Each IC_{50} value is an average of at least two independent determinations. The compounds with suitable potency and selectivity were tested in the carrageenan-induced air pouch model to estimate the inhibition of prostaglandin production at screening dosage of 2 mpk. The compounds with >80% PG inhibition in this assay were evaluated in the carrageenan-induced models of paw edema and hyperalgesia in the rat. The candidates with good oral activity in these acute models were tested in the adjuvant induced arthritis model of chronic inflammation in the rat. The promising compounds exhibiting the most favorable *in vivo* pharmacological properties were then evaluated in models of gastrointestinal toxicity.

Aryl Ring Variations. Having established earlier (Table 1) that the 1,2-diarylimidazole analogs (**5** and **6**) containing a 4-(methylsulfonyl)phenyl group at N-1 were more potent than the reversed analogs (**7**, **8**), we initiated efforts to evaluate the influence of aryl ring substituents to the enzymatic activity. The extensive SAR work done by these laboratories on the modifications of SO_2R group and the aryl ring bearing this group in 1,2-diarylpyrroles[21] and 1,2-diarylcyclopentenes[18e] reveals that this ring system is very sensitive to small variations. The presence of a SO_2Me or a SO_2NH_2 group at the *para* position of the phenyl ring gives the optimum potency against the COX-2 enzyme. In addition, we had established that, in the 1,2-diarylpyrrole series,[21] the replacement of the second aryl ring by aliphatic or cycloalkyl groups yields significantly less potent compounds. Utilizing these observations, we started with the framework **III** and explored the effect of substituents, in the aryl ring (B), on the potency and selectivity against the COX enzymes (Table 2). The aryl ring B was substituted at position 4 with number of groups such as halogens, methyl, methoxy, methylamino, thiomethyl, methyl sulfoxide, methyl sulfone, and the like. The results from Table 2 show a number of potent analogs with very similar activity against the COX-2 enzyme ($IC_{50} = 0.10-0.16\ \mu M$), but their affinity for COX-1 enzymes varies significantly, giving selectivity (COX-1/COX-2) of 13−6025. The compound (**10**)

Table 2. Modifications of the Aryl Substituents



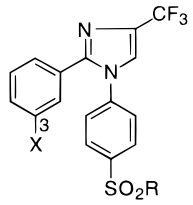
compd	X	R	IC$_{50}$, μM COX-2	IC$_{50}$, μM COX-1	selectivity COX-1/ COX-2	air pouch (% inhib, 2 mpk)
6	Cl	Me	0.11	23	210	98
9	F	Me	0.10	36	360	82
10	H	Me	0.12	723	6025	98
11	Me	Me	0.16	26	160	88
12	OMe	Me	0.57	3.0	5	
13	NHMe	Me	1.47	53.5	36	
14	NMe_2	Me	0.70	5.0	7	
15	SMe	Me	0.16	2.1	13	79
16	SOMe	Me	>100	>100		
17	SO_2Me	Me	5.7	>100	17	
18	Cl	NH_2	0.01	1.6	160	98
19	F	NH_2	0.01	1.9	190	98
20	H	NH_2	0.04	19.3	482	100
21	Me	NH_2	0.04	4.6	115	63

with no substituent at position 4 gave the best selectivity (6025). Compound **9**, containing a 4-fluoro substituent, inhibited COX-2 with an IC$_{50}$ of 100 nm and selectivity of 360. The analogs having a methoxy (**12**), a thiomethyl (**15**), or a dimethylamino (**14**) group at position 4 gave much lower selectivity (5−13) for the COX-2 enzyme. The sulfonamides (**18**−**21**) of the active sulfone derivatives were also evaluated. Generally, these compounds showed enhanced potency against the COX-2 enzyme (IC$_{50}$ = 10−40 nm). The unsubstituted compound (**20**) also showed a decrease in the selectivity ratio for the COX-2 enzyme compared to the sulfone derivative **10**. The various potent and selective COX-2 inhibitors (e.g., **6**, **10**, **18**−**20**) were also orally active, showing excellent inhibition of PGE_2 production (>90%) in the rat air-pouch model at the screening dosage of 2 mpk.

Inferring from the results in Table 2, we left position 4 in the aryl ring B (**III**) unoccupied and explored the effect of moving the substituents to position 3. The results of the study are listed in Table 3. The potency of the 3-substituted analogs (**22**−**28**) *vs* the COX-2 enzyme is very similar to or marginally better than the corresponding 4-substituted analogs (*cf*. Table 2). The affinity of these analogs for the COX-1 enzyme is significantly reduced, resulting in remarkable improvement in the selectivity ratio in some instances. For example, the 3-chloro (**22**) and the 3-fluoro (**23**) analogs show selectivities of 6000 and >8300 compared to the selectivities of 210 and 360, repectively, for the corresponding 4-substituted analogs **6** and **9**. The compounds containing 3-methoxy, 3-thiomethyl, and 3-amino derivatives also showed improvement in the selectivity ratio. The latter compounds, however, did not perform as well in the rat air-pouch model. The sulfonamides of selected compounds (**34**−**37**) gave excellent inhibitors of COX-2 enzyme (IC$_{50}$ = 7−30 nM). Most of the potent and selective COX-2 inhibitors also showed excellent inhibition in the carrageenan-induced PG production in the rat air-pouch model on oral administration.

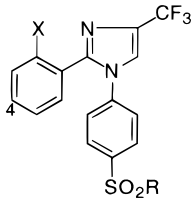
The study on B-ring substitution in **III** was also expanded to the monosubstituents at position 2 (Table

Table 3. Modifications of the Aryl Substituents



compd	X	R	IC$_{50}$, μM COX-2	IC$_{50}$, μM COX-1	selectivity COX-1/ COX-2	air pouch (% inhib, 2 mpk)
22	Cl	Me	0.06	360	6000	89
23	F	Me	0.12	>1000	>8300	88
24	Br	Me	0.08	>100	>1250	84
25	Me	Me	0.06	90	1500	77
26	CF_3	Me	0.21	>100	>480	42
27	OMe	Me	0.35	>100	>300	45
28	SMe	Me	0.35	>100	>300	0
29	CH_2OMe	Me	68.1	>100		
30	NMe_2	Me	3.2	42.2	13	
31	NHMe	Me	0.92	>100	>100	25
32	NH_2	Me	5.89	>100		
33	NO_2	Me	0.58	>100	>175	80
34	Cl	NH_2	0.008	6.2	775	99
35	F	NH_2	0.03	67.7	2250	98
36	Br	NH_2	0.007	4.5	640	
37	Me	NH_2	0.03	3.2	106	95

Table 4. Modifications of the Aryl Substituents

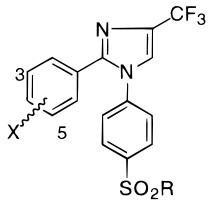


compd	X	R	IC$_{50}$, μM COX-2	IC$_{50}$, μM COX-1	selectivity COX-1/ COX-2	air pouch (% inhib, 2 mpk)
38	Cl	Me	0.9	>100	>100	
39	F	Me	0.4	>100	>250	97
40	Me	Me	0.8	577	720	95
41	OMe	Me	100	>100		
42	F	NH_2	0.1	22.3	223	100
43	Me	NH_2	0.2	8.2	41	96

4). In general, these compounds were not as potent as the corresponding positional isomers listed in Tables 2 and 3. The sulfone derivatives (e.g., **39**, **40**) showed good selectivity for the COX-2 enzyme. The 2-methoxy derivative (**41**) was totally inactive against the COX enzymes up to 100 μM, suggesting that a bulkier group at position 2 might distort the active orientation of the aryl rings. All the potent COX-2 inhibitors showed impressive inhibition of PG production (>95%) in the air-pouch model at the screening dosage of 2 mpk.

The results from the monosubstitutions in the aryl ring B in **III** indicate that the substituents at position 3 and position 4 give more potent COX-2 inhibitors than those at position 2. To expand on these observations, a number of disubstituted analogs with substituents at positions 3 and 4 or 3 and 5 (Table 5) were synthesized and examined in the COX enzyme assays. Of the 3,4-disubstituted analogs tested, 4-methoxy-3-halo derivatives gave optimum *in vitro* and *in vivo* activity. For example, the 4-methoxy-3-chloro analog (**45**) showed good potency (IC$_{50}$ for COX-2 = 130 nM) and selectivity (2280) as well as >90% PGE_2 inhibition in the primary *in vivo* assay. The analog (**54**), wherein the substituents

Table 5. Modifications of the Aryl Substituents



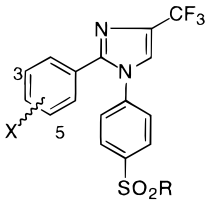
compd	X	R	IC50, μM COX-2	IC50, μM COX-1	selectivity COX-1/COX-2	air pouch (% inhib, 2 mpk)
44	4-OMe-3-F	Me	0.15	49	327	98
45	4-OMe-3-Cl	Me	0.13	296	2280	92
46	4-SMe-3-Cl	Me	0.04	>100	>2500	0
47	4-NMe_2-3-Cl	Me	0.32	1.56	5	87
48	4-NMe_2-3-F	Me	0.33	17.1	52	
49	4-NHMe-3-Cl	Me	0.66	>100	>150	69
50	4-Me-3-Cl	Me	0.03	12	400	10
51	4-Me-3-F	Me	0.11	>100	>900	47
52	3-Me-4-F	Me	0.17	24.1	142	90
53	3-Me-4-Cl	Me	0.09	7.84	87	64
54	3-OMe-4-Cl	Me	0.25	>100	>400	0
55	3-NMe_2-4-Cl	Me	1.04	>100	>100	69
56	3,4-OCH_2O−	Me	0.17	1.1	71	78
57	3,4-diF	Me	0.12	>100	>830	87
58	3,4-diMe	Me	0.33	30	91	15
59	3-Me-5-Cl	Me	0.08	>1000	>12500	63
60	3-Me-5-F	Me	0.11	>100	>900	87
61	3-OMe-5-F	Me	0.96	>100	>100	63
62	3-CF_3-5-F	Me	>100	67		
63	3,5-diCl	Me	0.17	>100	>600	5
64	2-Me-5-F	Me	>100	>100		
65	2-Me-6-Cl	Me	>100	>100		
66	4-OMe-3-F	NH_2	0.03	3.8	127	89
67	4-OMe-3-Cl	NH_2	0.02	5.8	290	100
68	4-OMe-3-Br	NH_2	0.03	2.74	91	
69	4-SMe-3-Cl	NH_2	0.01	3.54	35	
70	4-Me-3-Cl	NH_2	0.003	0.57	190	85
71	3-OMe-4-Cl	NH_2	0.02	8.6	430	100
72	3,4-diF	NH_2	0.03	29.8	993	83
73	3-Me-5-Cl	NH_2	0.04	>100	2500	61
74	3-Me-5-F	NH_2	0.03	82	2730	80
75	3-OMe-5-F	NH_2	0.46	>100	>220	

at positions 3 and 4 were transposed (*cf.* **45**) had good *in vitro* potency but surprisingly no activity in the air pouch model. Similarly, the 4-(methylthio)-3-chloro analog (**46**) showed poor *in vivo* activity despite its excellent *in vitro* profile. Since 3-substituted compounds (Table 3) had exhibited excellent selectivity for the COX-2 enzyme, a number of 3,5-disubstituted compounds were also synthesized to examine their potential. The analog **59** with a 3-methyl-5-chloro substituent inhibited the COX-2 enzyme with an IC_{50} of 80 nM and selectivity of >12500. Compound **59**, however, exhibited only moderate *in vivo* potency (63% inhibition at 2 mpk) in the air-pouch model. The replacement of the methyl in **60** by a trifluoromethyl group (**62**) aborted completely its activity against the COX-2 enzyme. In a similar vein, although the 2-methyl compound (**40**, Table 4) or monohalogenated compounds (**23** and **38** in Tables 3 and 4, respectively) are potent inhibitor of COX-2, the analogs with combination of two substituents (**64** and **65**) were inactive in the *in vitro* assays. The sulfonamide of the 4-methoxy-3-chloro analog (**67**) was a very potent (IC_{50} = 20 nM) COX-2 inhibitor and showed complete inhibition of prostaglandin production in the air pouch model at the screening dosage. Compound **71** obtained by transposition of 3,4-substituents in **67** also showed very similar potency in the enzymatic and air pouch assays. The sulfonamide (**71**) was exceptionally superior to the corresponding sulfone analog (**54**) in the air-pouch assay. This is the only example in this paper revealing such a dramatic shift between a sulfonamide *vs* a sulfone analog in *in vivo* activity. The reasons for this extreme difference are not very apparent, but on the basis of results reported in this paper, the sulfonamides generally show enhancement in *in vivo* potency, usually with loss of some enzyme selectivity. The lower log *P* value of the sulfonamide analogs (e.g., 2.8 for **18**) *vs* the sulfone analogs (e.g., 3.3 for **6**) might be contributing to their improved absorption and quicker onset of action.

As an extension of the encouraging results on the *in vitro* and *in vivo* biology observed with 4-methoxy-3-halo analogs (**44**, **45**, and **67**), several trisubstituted analogs (Table 6) were synthesized and evaluated. Many of these compounds gave potent and selective COX-2 inhibitors, but the 4-methoxy-3,5-difluoro analogs (**76** and **82**) were the best performers in the air-pouch assay. The 4-methoxy-2,5-dimethyl derivative (**80**) was a less potent COX-2 inhibitor than the 4-methoxy-3,5-dimethyl analog (**79**).

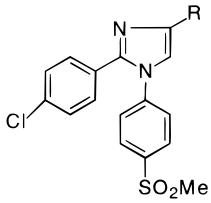
Imidazole Ring Modifications. In order to understand the effect of the substituents in the imidazole ring on the enzymatic activity, the analog (**83**) lacking the 4-CF_3 group and the positional isomer (**84**) with a CF_3 group moved to position 5 were synthesized (see the Experimental Section). Both these analogs were inactive against the COX-1 and COX-2 enzymes up to a

Table 6. Modifications of the Aryl Substituent



compd	X	R	IC50, μM COX-2	IC50, μM COX-1	selectivity COX-1/COX-2	air pouch (% inhib, 2 mpk)
76	4-OMe-3,5-diF	Me	0.17	>100	>588	89
77	4-OMe-3,5-diCl	Me	0.14	>100	>714	25
78	4-OMe-3,5-diBr	Me	0.09	>100	>1111	0
79	4-OMe-3,5-diMe	Me	0.72	91	126	29
80	4-OMe-2,5-diMe	Me	12.2	>100		
81	4-NMe_2-3,5-diCl	Me	0.14	>100	>714	25
82	4-OMe-3,5-diF	NH_2	0.03	35	1167	100

Table 7. Modifications of the Imidazole Substituents



compd	R	IC50, μM COX-2	IC50, μM COX-1	air pouch (% inhib, 2 mpk)
5	Me	0.24	>100	53
6	CF_3	0.11	23	98
83[a]	H	>100	>100	
87	CHF_2	0.61	>100	41
88	CH_2F	0.41	>100	36
89	CHO	1.6	>100	
90	CN	0.23	>100	69
91	CO_2Et	5.7	>100	
92	CO_2H	>100	>100	
94	CO_2NEt_2	>100	>100	
95	CH_2NH_2	>100	>100	
96	Ph	0.24	>100	6
97	CH_2OPh(4-Cl)	0.03	>100	15
98	CH_2SPh(4-Cl)	0.05	>100	0
99	CH_2OMe	3.72	>100	
100	CH_2OH	8.35	>100	
101	CH_2SMe	0.32	>100	10
102	CH_2SO_2Me	>100	>100	
103	CH_2CN	1.54	>100	

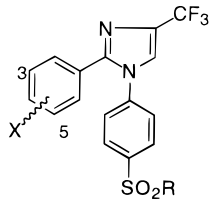
[a] Lacks the Cl in Ph ring.

concentration of 100 μM. Similarly, the replacement of the central imidazole ring with a tetrazole (**85**) or an indole (**86**) ring gave compounds with no activity *vs* the COX enzymes suggesting that the central imidazole ring with a 4-CF_3 substituent forms an important part of the pharmacophore.

On the basis of these results, SAR studies on the imidazole nucleus in **III** were restricted to exploration of the effect of the substituents at position 4 (Table 7). Position 4 was substituted with a variety of groups so as to affect the electronic, steric, log *P*, pK_a, and other physical properties of the molecule. As also indicated in Table 1, the 4-CF_3 analog (**6**) is a superior, orally active agent compared to the 4-Me analog (**5**). The difluoromethyl (**87**) and monofluoromethyl (**88**) analogs were less active in both the *in vitro* and the *in vivo* models. The cyano compound (**90**) inhibited the COX-2 enzyme with an IC_{50} of 230 nM and showed about 70% inhibition of the prostaglandin production in the air pouch assay. Derivatives containing functional groups such as the carboxaldehyde (**89**), the carboxylic ester (**91**), the carboxylic acid (**92**), and the amide (**94**) were much less potent against the COX-2 enzyme. The compound with a 4-(aryloxy)methyl (e.g., **97**) and the (arylthio)methyl (e.g., **98**) substituents gave excellent potency (IC_{50} = 30 and 50 nM respectively) and selectivity (>2000) for the COX-2 enzyme. Unfortunately, neither of these compounds demonstrated appreciable *in vivo* activity. The compounds containing substituents such as methoxymethyl (**99**), hydroxymethyl (**100**), and (methylsulfonyl)methylene (**102**) groups were significantly inferior to the trifluoromethyl analogs. The results suggest that although it is possible to obtain very potent and selective COX-2 inhibitors by modifications of the substituents at position 4, the CF_3 group offers the best overall *in vitro* and *in vivo* profile of the compounds investigated.

***In Vivo* Pharmacological Studies.** The potent and selective COX-2 inhibitors emerging from the SAR studies were evaluated in the acute (carrageenan-induced rat paw edema) and the chronic (adjuvant-induced arthritis in the rat) models of inflammation. The potent antiinflammatory agents were also tested in the hyperalgesia model in the rat. The details of all these assays are reported in the Experimental Section. As can be seen from Table 8, most of the diarylimidazoles tested were excellent inhibitors of the adjuvant-induced arthritis (AA) and some were more potent than indomethacin, naproxen, piroxicam, and other marketed NSAIDs. The 4-chloro compound (**6**) was an excellent inhibitor in the chronic adjuvant-induced arthritis assay with an ED_{50} of 0.03 mpk. The same compound was not very effective against carrageenan-induced edema, showing only 9% inhibitin at 30 mpk. In comparison, its sulfonamide derivative (**18**) was very potent in the AA assay and showed remarkable improvement over **6** against the carrageenan-induced inflammation (ED_{50} = 8.7 mpk). Compound **18** was also very potent in the hyperalgesia model (ED_{50} = 11 mpk). The log *P* of sulfonamide **18** is 2.8 compared to 3.3 for the sulfone analog (**6**), and this might provide better absorption and quicker onset of action. The nonchlorinated compounds (**10** and **20**) were very potent and demonstrated similar inhibitions (ED_{50} ~0.15 mpk) in the chronic model of inflammation. The sulfonamide compound (**20**) was again superior to the sulfone compound (**10**) in the acute models of inflammation and hyperalgesia. The com-

Table 8. *In Vivo* Pharmacology of Selected 1,2-Diarylimidazoles



			IC_{50}, μM		ED_{50}, mpk		
compd	X	R	COX-2	COX-1	edema	AA	hyperalgesia
6	4-Cl	Me	0.11	23	9% (30)	0.03	
18	4-Cl	NH_2	0.01	1.6	8.7	0.03	11
10	H	Me	0.12	723	20.8	0.15	56
20	H	NH_2	0.04	19.3	9.8	0.17	32
11	4-Me	Me	0.16	26	35.8		99
25	3-Me	Me	0.06	90	23.0	0.36	46
22	3-Cl	Me	0.06	360	25.8	0.02	40
34	3-Cl	NH_2	0.008	6.2		0.02	22
23	3-F	Me	0.12	>1000		0.06	
40	2-Me	Me	0.8	577	17.8	0.14	43
44	4-OMe-3-F	Me	0.15	49	29.4	0.07	53
66	4-OMe-3-F	NH_2	0.03	3.8	19.0	0.07	36
45	4-OMe-3-Cl	Me	0.13	296	35% (50)	0.49	29% (50)
67	4-OMe-3-Cl	NH_2	0.02	5.80	11.3	0.03	35
50	4-Me-3-Cl	NH_2	0.003	0.57	20.9	0.18	55
76	4-OMe-3,5-diF	Me	0.17	>100	26% (30)	1.0	
	indomethacin		0.9	0.1	60% (20)	0.1	
	naproxen					0.94	
	piroxicam					0.15	
	DuP 697					0.25	
	diclofenac					0.05	

Table 9. Gastric and Intestinal Toxicity Studies

compound	dose, mpk (ig)	gastric[a] mouse	gastric[a] rat	intestinal[a] rat
18	20	1/10	0/6	0/6
18	200	2/10	0/10	3/6
20	20	0/10	0/6	0/6
20	200	0/10	0/6	0/6
25	20	0/10		
25	200	0/10		
44	20	0/10		
44	20	0/10		
34	200		0/4	
40	200		0/4	
67	200		0/4	
indomethacin	ED_{50} = 1 mpk			

[a] Number of animals with damage/number of animals treated.

pound with a methyl substituent at position 4 (**11**) was not very potent in the hyperalgesia model (ED_{50} = 99 mpk). The 3-Me analog (**25**), a very potent and selective COX-2 inhibitor, was very effective (ED_{50} = 0.06 mpk) in the adjuvant arthritis model. Similar to 4-chloro compounds, the 3-chloro analogs (**22** and **34**) were excellent performers in the AA assay showing ED_{50}'s of 0.02 mpk. Both of these compounds were also potent in the hyperalgesia assay. Among the disubstituted derivatives, the 4-methoxy-3-chloro analog (**67**) showed excellent inhibition in the arthritis model (ED_{50} = 0.03 mpk) and in the edema model (ED_{50} = 11 mpk). Trisubstituted 4-methoxy-3,5-difluoro derivative (**76**) did not prove as effective in the *in vivo* models as in the *in vitro* assays.

Gastrointestinal Toxicity Studies. To test the hypothesis on the selective COX-2 inhibitors and to establish their safety profile, the selected compounds were evaluated in the acute gastric and intestinal toxicity studies (Table 9). No gastric lesions were observed in the mouse or rat after 5 h when **20** was administered intragastrically at 20 or 200 mpk. Similarly no intestinal bleeding was detected in the rats after 72 h when **20** was administered intragastrically at 20 or 200 mpk. On the other hand, compound **18** with a selectivity ratio of 160 for COX-2 enzyme showed intestinal bleeding in three of six rats at 200 mpk. Compound **18** showed no gastric lesions in rats up to 200 mpk and was also safe in the rat intestinal toxicity model at 20 mpk. All the other selected COX-2 inhibitors showed no gastric lesions in the mouse or rat at 200 mpk. In contrast, indomethacin caused gastric lesions in the mouse with an ED_{50} of 1 mpk.

Conclusion

The series of 1,2-diarylimidazoles described in this paper are very potent (IC_{50} = 10−100 nm) and selective (COX-1/COX-2 = 10^3−10^4) inhibitors of human COX-2 enzyme. The enzymatic and *in vivo* data on the isomeric diarylimidazoles suggests that the compounds **5** and **6** containing a (methylsulfonyl)phenyl group attached at N-1 are more potent than **7** and **8**, wherein this group is switched to the C-2 position. Detailed SAR studies on the different portions of the molecule indicate that their potency, selectivity, and *in vivo* profile are greatly influenced by the substitution pattern. In the aryl ring substitutions, the 4-substituted compounds yield very potent inhibitors (IC_{50} = 10−120 nm, Table 2) of COX-2 enzyme with very good oral activity. The 3-monosubstituted analogs, however, give the optimum combination of potency (IC_{50} = 8−120 nm, Table 3), selectivity (800−8300), and oral antiinflammatory activity. In the disubstituted compounds, 4-methoxy-3-halo analogs (e.g., **44**, **66**, and **67**) give orally active, potent inhibitors of the COX-2 enzyme. In general, the compounds containing a sulfonamide (*vs* a sulfone) group show superior *in vivo* activity as well as enhanced potency against the COX-2 enzyme. The sulfonamides, however,

display reduced selectivity for the COX-2 enzyme. In the imidazole substitutions, the CF_3 group at C-4 generally gives the optimum potency and antiinflammatory activity. Replacement of the CF_3 group on the imidazole ring by other substituents (e.g., (aryloxy)-methyl, CHF_2, CH_2F, CN, Table 7) gives potent *in vitro* but less active *in vivo* analogs. Similarly, replacement of the central imidazole ring in **6** with a tetrazole (**85**) or an indole (**86**) ring yields inactive compounds. The excellent potency observed with a number of diarylimidazoles in the adjuvant-induced arthritis model (e.g., ED_{50} = 0.02 mpk with **22** and **34**, Table 8) indicates their potential as useful antiinflammatory agents. A number of these compounds also exhibited promising activity in the carrageenan-induced acute models of inflammation (ED_{50} = 9−30 mpk) and hyperalgesia (ED_{50} = 11−40 mpk). The absence of GI toxicity in the selected compounds up to 200 mpk in the rat and mouse demonstrates that 1,2-diarylimidazoles represent a promising series of antiinflammatory agents with an improved side effect profile.

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.[27] The experimental details of the carrageenan-induced paw edema and hyperalgesia models in the rat have also been published.[18d,e,28] The rat adjuvant-induced arthritis model was carried out using the procedures described earlier.[18d,e,29] The gastric and intestinal toxicity studies in the rat and the mouse were conducted using the literature methods.[30]

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 ^{1}H (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 (δ) are relative to tetramethylsilane (TMS, δ = 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 at Searle.

4-(Methylsulfonyl)aniline, 4-fluorophenyl methyl sulfone, trimethylaluminum, 3-bromo-1,1,1-trifluoroacetone, 2,3-dichloropropene, 2-phenylimidazole, 5-phenyl-1*H*-tetrazole, 2-phenylindole, 3,5-dimethyl-*p*-anisic acid, 3-fluoro-4-methylbenzoic acid, 3,5-dichloro-4-methoxybenzonitrile, 2,5-dimethyl-*p*-anisaldehyde, 4-bromo-2-chlorotoluene, 3,4-difluorobenzonitrile, 3-chloro-4-fluorobenzonitrile, 3-amino-4--chlorobenzonitrile, 3-chloro-5-methylbenzaldehyde, 3-fluoro-5-methylbenzaldehyde, 4-chlorophenol, 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 1,2-Diarylimidazoles (Scheme 1). All aryl sulfone compounds discussed in Tables 1−6 were prepared following the general Scheme 1. The synthesis of 1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-(trifluoromethyl)-1*H*-imidazole (**10**) is described below as an example.

Preparation of 1-[4-(Methylsulfonyl)phenyl]-2-phenyl-4-(trifluoromethyl)-1*H*-imidazole (10). Step 1: Preparation of *N*-[4-(Methylsulfonyl)phenyl]benzenecarboximidamide. To a suspension of 4-(methylsulfonyl)aniline (12 g, 70 mmol) in toluene (400 mL) at 0 °C was added over 15 min trimethylaluminum (52.5 mL, 2 M solution in toluene, 0.1 mol). The reaction mixture was warmed to room temperature and stirred for 3.5 h. A solution of benzonitrile (14.5 g, 0.14 mol) in toluene (300 mL) was added over 10 min and the reaction mixture heated to 70−75 °C. After 17 h, the reaction mixture was cooled to room temperature and poured over a slurry of silica gel in chloroform/methanol (2/1). After filtration, the residue was washed with a mixture of methylene chloride/methanol (2/1). The combined filtrates were concentrated *in vacuo*, and the resulting yellowish solid was stirred with a mixture of hexane/ether (2/1, 1000 mL). The intermediate was filtered and washed with additional hexane/ether (2/1). The yellowish solid *N*-[4-(methylsulfonyl)phenyl]benzenecarboximidamide (16.7 g, 87%) was used in the next reaction without further purification: mp (DSC) 163 °C; MIR 3461, 3361, 1645, 1622, 1572, 1484, 1380, 1299; ^{1}H NMR (DMSO-d_6) 7.92 (m, 2H), 7.81 (d, J = 8 Hz, 2H), 7.40−7.52 (complex band, 3H), 7.04 (d, J = 8 Hz, 2H), 6.68 (br s, 2H), 3.15 (s, 3H); MS (ESI) 275 (MH^+). Anal. ($C_{14}H_{14}N_2SO_2 \cdot 0.25H_2O$) C, H, N, S.

Step 2: Preparation of 4-Hydroxy-1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-(trifluoromethyl)-4,5-dihydro-1*H*-imidazole. To a mixture of *N*-[4-(methylsulfonyl)phenyl]-benzenecarboximidamide (16.5 g, 60.1 mmol) and sodium bicarbonate (10.1 g, 0.12 mol) in 2-propanol (900 mL) was added 3-bromo-1,1,1-trifluoroacetone (8.7 mL, 84 mmol). After the reaction mixture was heated at 75−80 °C for 20 h, the solvent was removed. The residue was redissolved in methylene chloride and washed with water. The organic fractions were combined, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude mixture was purified by chromatography (silica gel, hexane/ethyl acetate, 45/55) to give 4-hydroxy-1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-(trifluoromethyl)-4,5-dihydro-1*H*-imidazole (13.6 g, 59%) as a white solid: mp (DSC) 230 °C; IR (KBr) 3422, 3080, 2937, 2741, 1909, 1608, 1587, 1566, 1498, 1462; ^{1}H NMR (DMSO-d_6) 7.73 (d, J = 8 Hz, 2H), 7.40−7.60 (complex band, 5H), 7.38 (s, 1H), 7.03 (d, J = 8 Hz, 2H), 4.48 (d, J = 11 Hz, 1H), 3.97 (d, J = 11 Hz, 1H), 3.15 (s, 3H); MS (EI) 384 (M^+). Anal. ($C_{17}H_{15}N_2F_3SO_3$) C, H, N, S.

Step 3: Preparation of 1-[4-(Methylsulfonyl)phenyl]-2-phenyl-4-(trifluoromethyl)-1*H*-imidazole (10). A mixture of 4-hydroxy-1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-(trifluoromethyl)-4,5-dihydro-1*H*-imidazole (3.34 g, 8.7 mmol) and *p*-toluenesulfonic acid monohydrate (0.34 g) in toluene (500 mL) was heated to reflux for 72 h. The reaction mixture was cooled and the solvent removed under reduced pressure. The crude residue was redissolved in methylene chloride and washed with water, aqueous sodium bicarbonate, and brine. After drying (Na_2SO_4), filtration, and concentration *in vacuo*, the crude mixture (5.2 g) was purified by chromatography on silica gel using hexane/ethyl acetate (55/45) to give pure **10** (3 g, 93%) as a white solid: mp (DSC) 194 °C; MIR 3124, 2997, 2915, 1579, 1531, 1502, 1475, 1446, 1409, 1366; ^{1}H NMR ($CDCl_3$) 8.02 (d, J = 8 Hz, 2H), 7.53 (s, 1H), 7.43 (d, J = 8 Hz, 2H), 7.30−7.42 (complex band, 5H), 3.10 (s, 3H); MS (EI) 366 (M^+). Anal. ($C_{17}H_{13}N_2F_3SO_2$) C, H, N, S.

Compounds **5**−**9**, **11**−**17**, **22**−**33**, **38**−**41**, **44**−**65**, **76**−**81**, **91**, **96**, and **97** were also prepared in an analogous manner starting with **V** and the appropriate aryl nitriles (**IV**). In step 1, methylene chloride or 1,2-dichloroethane was used successfully as alternate solvent, where solubility of reactants in toluene was a problem. Similarly, the trimethylaluminum may be substituted by triethylaluminum in this step. When aryl nitriles or α-halo ketones were not commercially available, they were prepared by the procedures described below.

Preparation of 1,2-Diarylimidazoles by Functional Group Transformations (Scheme 6). Compound **91**, prepared as above, was utilized to synthesize the following compounds:

2-(4-Chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1*H*-imidazole-4-methanol (100). To a solution of **91** (1.15 g, 2.84 mmol) in dichloromethane (25 mL) at −70 °C was added dropwise diisobutylaluminum hydride (9.9 mL, 1 M solution in toluene, 9.9 mmol). The mixture was stirred while warming to room temperature, and then quenched by addition of methanol. The resulting gelatinous mass was dissolved in dilute aqueous hydrochloric acid, the pH adjusted to 4 with sodium hydroxide, and the mixture extracted with dichloromethane. The organic extracts were dried (Na_2SO_4), filtered, and evaporated. Trituration of the residue with ethyl acetate gave 151 mg (15%) of **100** as a solid: mp 205−208 °C; MIR 3400, 3214, 3156, 3099, 3062, 3008, 2951, 2921, 2853, 1675, 1596, 1569, 1498, 1461, 1421, 1408, 1351, 1313; ^{1}H NMR (CD_3COOD) 8.09 (d, J = 7 Hz, 2H), 7.61 (d, J = 7 Hz, 2H), 7.42 (s, 4H), 4.82 (s, 2H), 3.18 (s, 3H). Anal. ($C_{19}H_{17}N_2ClSO_4$) C, H, N.

2-(4-Chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1*H*-imidazole-4-carboxaldehyde (89). To a 1:1 solution of dimethyl sulfoxide and dichloromethane (8 mL) at −70 °C was added dropwise oxalyl chloride (320 μL, 3.69 mmol). After 10 min of stirring, a solution of **100** (670 mg, 1.85 mmol) in a 1:1 solution of dimethyl sulfoxide and dichloromethane (25 mL) was added. The stirring was continued while the reaction mixture was warmed to 0 °C. After the mixture was stirred at 0 °C for 15 min, triethylamine (1.87 g, 18.5 mmol) was added and the mixture stirred overnight at room temperature. The reaction mixture was partitioned between dichloromethane and water, and the organic layer was washed with water and brine. After being dried over sodium sulfate, the organic fractions were filtered, and concentrated. The chromatography of the residue over silica gel using a gradient of 50−75% ethyl acetate−hexane gave **89** (330 mg, 49%) as an off-white solid: mp (DSC) 203 °C; MIR 1687, 1595, 1535, 1498, 1473, 1414, 1309, 1289; ^{1}H NMR ($CDCl_3$) 10.00 (s, 1H), 8.09 (d, J = 7 Hz, 2H), 7.97 (s, 1H), 7.49 (d, J = 7 Hz, 2H), 7.38 (s, 4H), 3.18 (s, 3H). Anal. ($C_{17}H_{13}N_2ClSO_3$) C, H, N.

2-(4-Chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1*H*-imidazole-4-carbonitrile (90). A solution of **89** (82 mg, 0.23 mmol) and hydroxylamine *O*-sulfonic acid (51 mg, 0.45 mmol) in 10 mL of absolute ethanol and 1 mL of pyridine was refluxed overnight. After cooling, the mixture was evaporated and the residue taken up in dichloromethane. The solution was washed with aqueous sodium bicarbonate, dried over sodium sulfate, filtered, and concentrated. The chromatography of the residue over silica gel using 50−50 ethyl acetate-hexane as eluent gave **90** (71 mg, 86%), as a pure white crystalline solid: mp (DSC) 205 °C; MIR 3130, 2241, 1467, 1417, 1092, 846; ^{1}H NMR ($CDCl_3$) 8.07 (d, J = 7 Hz, 2H), 7.71 (s, 1H), 7.44 (d, J = 7 Hz, 2H), 7.33 (d, J = 5 Hz, 2H), 7.28 (d, J = 5 Hz, 2H), 3.13 (s, 3H). Anal. ($C_{17}H_{12}N_3ClSO_2 \cdot 0.25H_2O$) C, H, N.

2-(4-Chlorophenyl)-4-(fluoromethyl)-1-[4-(methylsulfonyl)phenyl]-1*H*-imidazole (88). To a suspension of **100** (250 mg, 0.69 mmol) in 5 mL of dichloromethane was added dropwise a solution of (diethylamido)sulfur trifluoride (166 mg, 1.03 mmol) in 1 mL of dichloromethane. As the addition proceeded, the mixture became homogeneous. After 2 h of stirring, the reaction was quenched by adding water. The layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over sodium sulfate, filtered, and evaporated. The chromatography of the residue over silica gel using 60% ethyl acetate−hexane as eluent gave **88** (106 mg, 42%) as a pale yellow solid: mp (DSC) 167 °C; MIR 1498, 1417, 1309, 1301, 1288, 1091, 955; ^{1}H NMR ($CDCl_3$) 8.02 (d, J = 7 Hz, 2H), 7.40 (d, J = 7 Hz, 2H), 7.30 (m, 4H), 7.24 (s, 1H), 5.42 (d, J = 37 Hz, 2H), 3.13 (s, 3H). Anal. ($C_{17}H_{14}N_2ClFSO_2 \cdot 0.25H_2O$) C, H, N.

2-(4-Chlorophenyl)-4-(difluoromethyl)-1-[4-(methylsulfonyl)phenyl]-1*H*-imidazole (87). To a suspension of **89** (150 mg, 0.42 mmol) in 5 mL of dichloromethane was added dropwise a solution of (diethylamido)sulfur trifluoride (201 mg, 1.25 mmol) in 1 mL of dichloromethane. After being stirred at room temperature for 30 min, the mixture was partitioned between dichloromethane and water. The aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over sodium sulfate, filtered, and evaporated. The chromatography of the residue over silica gel using 50% ethyl acetate−hexane as eluent followed by crystallization from ethyl acetate−hexane gave **87** (21 mg, 24%) as very small pale beige plates: mp 179−190 °C; ^{1}H NMR (CD_2Cl_2) 7.99 (d, J = 7 Hz, 2H), 7.42 (m, 3H), 7.28 (s, 4H), 6.74 (t, J = 57 Hz, 1H), 3.07 (s, 3H). Anal. ($C_{17}H_{13}N_2ClF_2SO_2$) C, H, N.

2-(4-Chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1*H*-imidazole-4-carboxylic Acid (92). A suspension of **91** (929 mg, 2.29 mmol) in 16 mL of methanol and 16 mL of 1 N aqueous sodium hydroxide was stirred at reflux for 1 h. After cooling, the mixture was concentrated, water was added, and the resulting mixture was acidified with acetic acid. The mixture was extracted with dichloromethane. The combined organic extracts were dried over sodium sulfate, filtered, and evaporated. Acetic acid was removed by azeotropic distillation with toluene to give **92** (520 mg, 57%) as a white crystalline solid: mp (DSC) 121 °C; MIR 3141, 3098, 3073, 3021, 2926, 1724, 1695, 1313, 1212, 1150; ^{1}H NMR (CD_3COOD) 8.25 (s, 1H), 8.13 (d, J = 7 Hz, 2H), 7.66 (d, J = 7 Hz, 2H), 7.46 (d, J = 5 Hz, 2H), 7.42 (d, J = 5 Hz, 2H), 3.24 (s, 3H). Anal. ($C_{17}H_{13}N_2ClSO_4 \cdot 1.0H_2O$) C, H, N.

2-(4-Chlorophenyl)-*N*,*N*-diethyl-1-[4-(methylsulfonyl)-phenyl]-1*H*-imidazole-4-carboxamide (94). To a solution of dimethylformamide (44 μL, 0.57 mmol) and acetonitrile (1.5 mL) at 0 °C was slowly added oxalyl chloride (36 μL, 0.42 mmol). After 10 min, **92** (150 mg, 0.40 mmol) was added as a solid and the reaction stirred for 10 min. Additional amounts of dimethylformamide (139 μL, 1.79 mmol) and oxalyl chloride (104 μL, 1.19 mmol) were added successively. After 10 min, pyridine (193 μL, 2.39 mmol) and diethylamine (247 μL, 2.39 mmol) were added, and the mixture was stirred for 1 h. The reaction mixture was partitioned between ethyl acetate and water, and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered, and evaporated. Chromatography of the residue over silica gel using ethyl acetate as eluent gave **94** (147 mg, 85%) as a pure white solid: mp (DSC) 225 °C; MIR 3109, 1604, 1536, 1467, 1411, 1311, 1288, 1273, 1267, 1092, 833, 780; ^{1}H NMR ($CDCl_3$) 8.03 (d, J = 7 Hz, 2H), 7.78 (s, 1H), 7.43 (d, J = 7 Hz, 2H), 7.29 (s, 4H), 4.04 (m, 2H), 3.56 (m, 2H), 3.12 (s, 3H), 1.30 (s, 6H). Anal. ($C_{21}H_{22}N_3ClSO_3 \cdot 0.25H_2O$) C, H, N.

2-(4-Chlorophenyl)-4-(chloromethyl)-1-[4-(methylsulfonyl)phenyl]-1*H*-imidazole (93). A suspension of **100** (1.82 g, 4.96 mmol) in 10 mL of chloroform was treated with thionyl chloride (1.18 g, 9.92 mmol), and the resulting mixture was refluxed for 1 h. An additional amount of thionyl chloride (1.18 g) was added, and the mixture was refluxed for 1 h. After cooling, the mixture was concentrated and the residue chromatographed over silica gel using 50% ethyl acetate−hexane as eluent to give **93** (1.26 g, 67%) as a very pale yellow crystalline solid: mp 166−169 °C; ^{1}H NMR ($CDCl_3$) 8.01 (d, J = 7 Hz, 2H), 7.40 (d, J = 7 Hz, 2H), 7.30 (s, 4H), 7.24 (s, 1H), 4.68 (s, 2H), 3.12 (s, 3H).

2-(4-Chlorophenyl)-4-[[(chlorophenyl)thio]methyl]-1-[4-(methylsulfonyl)phenyl]-1*H*-imidazole (98). A mixture of **93** (150 mg, 0.394 mmol), 4-thiocresol (98 mg, 0.79 mmol), and potassium carbonate (136 mg, 0.98 mmol) was stirred at room temperature. After 20 h, the mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate, and the combined organic extracts were dried (Na_2SO_4), filtered, and evaporated. Chromatography of the residue over silica gel using 50−50 ethyl acetate−hexane as eluent gave **98** (124 mg, 61%) as a glassy solid: mp (DSC) 51 °C; MIR 1595, 1494, 1415, 1406, 1313, 1151, 1091; ^{1}H NMR ($CDCl_3$) 7.97 (d, J = 7 Hz, 2H), 7.35 (d, J = 7 Hz, 2H), 7.31 (d, J = 7 Hz, 2H), 7.28 (s, 4H), 7.11 (d, J = 7 Hz, 2H), 7.01 (s, 1H), 4.18 (s, 2H), 3.10 (s, 3H), 2.32 (s, 3H). Anal. ($C_{24}H_{21}N_2ClS_2O_2$) C, H, N.

2-(4-Chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-[(methylthio) methyl]-1*H*-imidazole (101). A solution of **93** (150 mg, 0.39 mmol) and sodium thiomethoxide (55 mg, 0.79 mmol) in dimethylformamide (5 mL) was stirred at room temperature for 3 days. The mixture was partitioned between ethyl acetate and water, and the organic layer was dried (Na_2SO_4), filtered, and evaporated. Chromatography of the residue over silica gel using a gradient of 50−60% ethyl acetate in hexane as

eluent gave **101** (64 mg, 40%) as a pale yellow oil: MIR 2915, 1594, 1499, 1463, 1417, 1405, 1390, 1312, 1288; ^{1}H NMR ($CDCl_3$) 7.98 (d, J = 7 Hz, 2H), 7.39 (d, J = 7 Hz, 2H), 7.28 (m, 4H), 7.12 (s, 1H), 3.76 (s, 2H), 3.11 (s, 3H), 2.22 (s, 3H). Anal. ($C_{18}H_{17}N_2ClS_2O_2 \cdot 0.5H_2O$) C, H, N.

2-(4-Chlorophenyl)-4-(methoxymethyl)-1-[4-(methylsulfonyl)phenyl]-1*H*-imidazole (99). Sodium metal (46 mg, 2 mmol) was carefully added to 2 mL of methanol and the reaction stirred to get a clear solution. A solution of **93** (167 mg, 0.44 mmol) in methanol was added and the mixture stirred at room temperature overnight. The mixture was then partitioned between ethyl acetate and water, and the organic extracts were dried (Na_2SO_4), filtered, and evaporated. Chromatography of the residue over silica gel using ethyl acetate as eluent gave **99** (120 mg, 72%) as a white crystalline solid: mp 171−172 °C; MIR 2924, 1595, 1498, 1465, 1417, 1407, 1311, 1288, 1149; ^{1}H NMR (CD_2Cl_2) 7.95 (d, J = 7 Hz, 2H), 7.41 (d, J = 7 Hz, 2H), 7.31 (d, J = 5 Hz, 2H), 7.28 (d, J = 5 Hz, 2H), 7.19 (s, 1H), 4.44 (s, 2H), 3.56 (s, 3H), 3.21 (s, 3H). Anal. ($C_{18}H_{17}N_2ClSO_3$) C, H, N.

2-(4-Chlorophenyl)-4-[(methylsulfonyl)phenyl]-1-[4-(methyl sulfonyl)phenyl]-1*H*-imidazole (102). A mixture of **93** (240 mg, 0.66 mmol) and methanesulfinic acid sodium salt (134 mg, 1.31 mmol) of in 4 mL of DMF was stirred at 80 °C for 1 h. After cooling, the mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate, and the combined organic extracts were dried (Na_2SO_4), filtered, and evaporated. Chromatography of the residue over silica gel using ethyl acetate as eluent gave **102** (158 mg, 57%) as a pure white solid: mp (DSC) 136 °C; MIR 3021, 1595, 1499, 1418, 1407, 1302; ^{1}H NMR ($CDCl_3$) 8.01 (d, J = 7 Hz, 2H), 7.43 (d, J = 7 Hz, 2H), 7.37 (s, 1H), 7.31 (d, J = 7 Hz, 2H), 7.26 (d, J = 7 Hz, 2H), 4.35 (s, 2H), 3.12 (s, 3H), 3.06 (s, 3H). Anal. ($C_{18}H_{17}N_2ClS_2O_4$) C, H, N.

2-(4-Chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1*H*-imidazole-4-acetonitrile (103). A mixture of **93** (250 mg, 0.66 mmol) and potassium cyanide (86 mg) in 4 mL of dry DMF was stirred overnight at 80 °C. An additional 86 mg of KCN was added, and the stirring continued for 8 h. After cooling, the mixture was partitioned between dichloromethane and water. The aqueous layer was extracted with dichloromethane, and the combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and evaporated. Chromatography of the residue over silica gel using 60% ethyl acetate−toluene as eluent followed by trituration of the product with ethyl acetate gave **103** (65 mg, 27%) as a white crystalline solid: mp (DSC) 197 °C; MIR 2252, 1596, 1500, 1466, 1417, 1408, 1313, 1289, 1152, 1092, 756; ^{1}H NMR ($CDCl_3$) 8.02 (d, J = 7 Hz, 2H), 7.41 (d, J = 7 Hz, 2H), 7.28 (m, 4H), 7.26 (s, 1H), 3.82 (s, 2H), 3.13 (s, 3H). Anal. ($C_{18}H_{14}N_3ClSO_2$) C, H, N.

2-(4-Chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1*H*-imidazole-4-methanamine (95). Step 1. A solution of **93** (500 mg, 1.31 mmol) and sodium azide (256 mg, 3.94 mmol) in 5 mL of dry DMF was stirred overnight at room temperature. The mixture was partitioned between ethyl acetate and water. The aqueous layer was further extracted with ethyl acetate, and the combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and evaporated. Chromatography of the residue over silica gel using 50−50 ethyl acetate−hexane as eluent gave the azide (340 mg, 67%) as a pure white crystalline solid: mp (DSC) 186 °C; MIR 2097, 1595, 1499, 1465, 1418, 1407, 1312, 1288, 1151, 1092; ^{1}H NMR ($CDCl_3$) 8.02 (d, J = 7 Hz, 2H), 7.42 (d, J = 7 Hz, 2H), 7.30 (s, 4H), 7.19 (s, 1H), 4.44 (s, 2H), 3.12 (s, 3H). Anal. ($C_{17}H_{14}N_5ClSO_2$) C, H, N.

Step 2. A solution of the azide obtained above (178 mg, 0.46 mmol) and triphenylphosphine (144 mg, 0.55 mmol) in THF (5 mL) and water (0.5 mL) was stirred overnight at room temperature. The mixture was concentrated and then partitioned between ethyl acetate and 3 N aqueous HCl. The aqueous layer was besified to pH 10 with NH_4OH and extracted with dichloromethane. After drying (Na_2SO_4), the organic extracts were filtered and evaporated. Trituration of the residue with ethyl acetate gave **95** as a pure white crystalline solid (116 mg, 70%): mp (DSC) 162 °C; MIR 2925, 1595, 1499, 1464, 1418, 1407, 1391, 1311, 1289, 1151, 1091, 957, 835; ^{1}H NMR (CD_2Cl_2) 7.95 (d, J = 7 Hz, 2H), 7.40 (d, J = 7 Hz, 2H), 7.29 (m, 4H), 7.09 (s, 1H), 3.86 (s, 2H), 3.08 (s, 3H), 1.73 (br s, 2H). Anal. ($C_{17}H_{16}N_3ClSO_2 \cdot 0.5H_2O$) C, H, N.

General Procedure for the Preparation of 1,2-Diarylimidazoles Containing a Sulfonamide Substituent (Scheme 3). All 1,2-diarylimidazoles with a sulfonamide group in the aryl rings were prepared following the general Scheme 3. The synthesis of compound **20** is described below to illustrate the procedure.

4-[2-Phenyl-4-(trifluoromethyl)-1*H*-imidazol-1-yl]benzenesulfonamide (20). To a clear solution of **10** (4.5 g, 12.4 mmol) in tetrahydrofuran (100 mL) at 0 °C was added *n*-BuMgCl (24.8 mL, 2M solution in THF, 49.6 mmol) over 15 min. After an additional 20 min of stirring, the ice bath was removed and the solution stirred for 2.5 h. The reaction mixture was recooled to 0 °C, and triethylborane (62 mL, 1 M solution in THF, 62 mmol) was added. After being stirred for 1.5 h, the reaction mixture was heated to reflux for 72 h. The reaction mixture was cooled to room temperature and treated with aqueous sodium acetate (13.6 g in 40 mL water). After 10 min of stirring, solid hydroxylamine *O*-sulfonic acid (13.6 g) was added in small portions over 10 min. The reaction mixture was stirred for 20 h and extracted with ether. The ethereal layer was dried over sodium sulfate, filtered, and concentrated. The crude solid was purified by chromatography (silica gel, toluene/ethyl acetate, 75/25) to give pure **20** (3.22 g, 71%): mp (DSC) 238 °C; IR (KBr) 3327, 3175, 3132, 3032, 2679, 1701, 1587, 1520, 1500, 1471, 1448, 1412 ; ^{1}H NMR (CD_3-OD) 8.00 (s, 1H), 7.98 (d, J = 8 Hz, 2H), 7.48 (d, J = 8 Hz, 2H), 7.30−7.42 (complex band, 5H); MS (EI) 367 (M^+). Anal. ($C_{16}H_{12}N_3F_3SO_2$) C, H, N, S.

Compounds **18**, **19**, **21**, **34**−**37**, **42**, **43**, **66**−**75**, and **82** were also prepared using this method.

Syntheses of Aryl Nitriles IV. The aryl nitriles used in the Schemes 1 were either purchased commercially or prepared (Scheme 2) as follows.

3-Fluoro-4-methoxybenzonitrile (IVa). To a solution of 3,4-difluorobenzonitrile (9.5 g, 68.3 mmol) in methanol (400 mL) was added slowly at 0−5 °C sodium methoxide (7.4 g, 0.14 mol). After being stirred at room temperature for 20 h, the reaction mixture was concentrated, suspended in methylene chloride, and washed with water. The organic layer was dried over sodium sulfate, filtered, and concentrated. The crude solid (9.2 g) was purified by chromatography (silica gel, hexane−ethyl acetate, 7/3) to give **IVa** (5.6 g, 54%): mp (DSC) 102 °C; IR (KBr) 3449. 3103, 3065, 2853, 2228, 1616, 1579, 1554, 1518, 1475, 1421, 1317; ^{1}H NMR ($CDCl_3$) 7.43 (dd, J = 9,2 Hz, 1H), 7.37 ((dd, J = 8,2 Hz, 1H), 7.00 (t, J = 9 Hz, 1H), 3.96 (s, 3H); MS (EI) 151 (M^+). Anal. (C_8H_6NFO) C, H, N.

The substituted 4-methoxybenzonitriles (**IVb**−**d**) were prepared from the corresponding fluoro derivatives by the displacement reaction conditions exemplified above.

3-Fluoro-4-(dimethylamino)benzonitrile (IVe). To a solution of 3,4-difluorobenzonitrile (15.4 g, 0.11 mol) in 200 mL of dry THF was added a solution of dimethylamine (15.7 g, 0.53 mol) in 50 mL of THF at 0 °C. The reaction mixture was stirred overnight at room temperature. The solvent was removed and the residue partitioned between methylene chloride and water. The organic layer was washed with water and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated to give 17.8 g (99%) of **IVe** as a low melting solid: mp 36−39 °C; ^{1}H NMR ($CDCl_3$) 7.31 (dd, J = 8, 2 Hz, 1H), 7.23 (dd, J = 11, 2 Hz, 1H), 6.77 (t, J = 8 Hz, 1H), 3.01 (s, 6H). Anal. ($C_9H_9N_2F$) C, H, N.

3-Chloro-4-(methylthio)benzonitrile (IVf). To a solution of 3-chloro-4-fluorobenzonitrile (10.0 g, 64 mmol) in 200 mL of DMF was added NaSMe (5.4 g, 77 mmol), and the reaction mixture stirred at 80 °C overnight. The cooled mixture was treated with water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo* to give 10.86 g (90%) of **IVf** as a white solid: ^{1}H NMR ($CDCl_3$) 7.60 (d, J = 2 Hz, 1H), 7.53 (dd, J = 8, 2 Hz, 1H), 7.18 (d, J = 8 Hz, 1H), 2.52 (s, 3H).

4-Fluoro-3-methylbenzonitrile (IVg). Step 1: Preparation of 3-methyl-4-fluorobenzaldehyde. To a cold solution (−70 °C) of 5-bromo-2-fluorotoluene (6 mL, 47.2 mmol) in THF (100 mL) was added slowly *n*-BuLi (39 mL, 1.6 M solution in

hexanes, 61.3 mmol). The reaction mixture was warmed to −10 °C over 3 h and the recooled to −70 °C. Dimethylformamide (7.2 mL, 94.2 mmol) was added to the reaction slowly and the mixture warmed to −40 °C over 2 h. After the reaction was quenched with aqueous ammonium chloride solution, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried (Na_2SO_4), filtered, and concentrated. The crude yellowish liquid (6.2 g) was chromatographed (silica gel, hexane−ethyl acetate, 9/1) to give 3-methyl-4-fluorobenzaldehyde (4.9, 75%) as a colorless liquid: IR (KBr) 3110, 3072, 2928, 1715, 1693, 1588, 1493, 1451, 1426, 1390; ^{1}H NMR ($CDCl_3$) 9.95 (s, 1H), 7.70−7.80 (complex band, 2H), 7.15 (t, J = 8 Hz, 1H), 2.37 (s, 3H); MS (EI) 137 (M^+). Anal. (C_8H_7FO) C, H, N.

Step 2: Preparation of 4-Fluoro-3-methylbenzonitrile (IVg). The aldehyde from the above step was converted to the nitrile following a literature procedure.[32] To a solution of the aldehyde obtained above (6.7 g, 48.6 mmol) in nitroethane (4 mL, 55.8 mmol) was added pyridinium hydrochloride (6.6 g, 55.8 mmol), and the mixture was refluxed for 24 h. The reaction mixture was cooled to room temperature and diluted with methylene chloride. The organic layer was washed with 0.25 N HCl, dried ($MgSO_4$), filtered, and concentrated. The crude solid (5.52 g) was chromatographed (silica gel, ethyl acetate−toluene, 7/3) to give **IVg** (2.2 g, 33%): mp (DSC) 60 °C; ^{1}H NMR ($CDCl_3$) 7.42−7.56 (complex band, 2H), 7.15 (t, J = 8 Hz, 1H), 2.30 (s, 3H); MS (EI) 135 (M^+). Anal. ($C_8H_6NF\cdot 1.0H_2O$) C, H, N.

4-Chloro-3-methylbenzonitrile (IVh). To a mixture of hydroxylamine hydrochloride (5.53 g, 0.08 mol) and pyridine (12.3 mL, 0.15 mol) was added rapidly 5-bromo-2-chlorobenzaldehyde (11.70 g, 76 mmol). The reaction mixture was stirred at room temperature for 15 min. Toluene (250 mL) was then added and the solution refluxed for 4 h using a Dean−Stark water trap. The reaction mixture was cooled, filtered, and concentrated to give 10.0 g of **IVh** as pale yellow solid (87%): ^{1}H NMR ($CDCl_3$) 7.55 (s, 1H), 7.46 (m, 2H), 2.44 (s, 3H).

The intermediate 5-bromo-2-chlorobenzaldehyde was synthesized from 5-bromo-2-chlorotoluene using the procedure (step 1) described for **IVg**.

3-Fluoro-5-methoxybenzonitrile (IVi) was prepared from 3-bromo-5-fluoroanisole using the two-step procedure described for **IVh** above. The intermediate 3-bromo-5-fluoroanisole was synthesized from 1-bromo-3,5-difluorobenzene by displacement reaction (NaOMe, DMF, 20 °C, 24 h, 30%) exemplified described for **IVa**.

Compounds **IVj**, **IVk**, and **IVl** were synthesized from 2,5-dimethyl-*p*-anisaldehyde, 3-chloro-5-methylbenzaldehyde, and from 3-fluoro-5-methylbenzaldehyde, respectively, using the procedure described for **IVh**. The intermediates 3-chloro-5-methylbenzaldehyde and 3-fluoro-5-methylbenzaldehyde were prepared by selective oxidation of 5-chloro(fluoro)-*m*-xylene following the literature procedure.[33]

3-Fluoro-4-methylbenzonitrile (IVm). This nitrile was prepared from 3-fluoro-4-methylbenzoic acid as follows.

Step 1. To a solution of 3-fluoro-4-methylbenzoic acid (5.0 g, 0.032 mol) in 20 mL of dry THF at 0 °C was added in a dropwise fashion borane−tetrahydrofuran complex (49 mL, 1 M solution in THF, 49 mmol). The reaction mixture was warmed and stirred at room temperature for 3.5 h. Water was added carefully to react with excess of reagent, and the aqueous phase was extracted with methylene chloride. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated under vacuum to give 4.2 g of the benzyl alcohol as a clear oil (94%). This was oxidized to the corresponding aldehyde as follows.

Step 2. To a solution of oxalyl chloride (13.3 g, 105 mmol) in methylene chloride (250 mL) was added slowly at −70 °C a solution of dimethyl sulfoxide (16.4 g, 0.21 mol) in methylene chloride (50 mL). A solution of the above alcohol (13.3 g, 95 mmol) in methylene chloride (40 mL) was added in a dropwise fashion. After 1.5 h of stirring, triethylamine (66.2 mL, 0.48 mol) was added and the mixture allowed to warm to room temperature over 3 h. Water (500 mL) was added and the organic layer separated. The aqueous phase was extracted with more methylene chloride, and the combined organic layers were washed with water and brine and dried over $MgSO_4$. After filtration, the solvent was removed to give 11.41 g (86%) of the benzaldehyde as a yellow oil.

The crude aldehyde was converted to the desired nitrile **IVm** using the procedure described for **IVh**: ^{1}H NMR ($CDCl_3$) 7.32 (m, 3H), 2.36 (s, 3H).

3,5-Dichloro-4-methoxybenzonitrile (IVn). To a solution of methyl 3,5-dichloro-4-methoxybenzoate (18.8 g, 74 mmol) in 350 mL of dry THF was added dropwise at room temperature LAH (147 mL of 1.0 M THF solution, 147 mmol). The reaction mixture was refluxed for 2 h. After cooling, the solution was quenched with 15 mL of ethyl acetate, followed by sequential treatment with 5.4 mL of water, 5.4 mL of 15% NaOH, and 16.2 mL of water. The mixture was stirred for 0.5 h and filtered. The filtrate was concentrated to give the alcohol which was used without further purification (73%). The benzyl alcohol was converted to the aldehyde (93%) using Swern oxidation as described in the synthesis of **IVm**. The desired nitrile (**IVn**) was synthesized from the resulting 3,5-dichloro-4-methoxybenzaldehyde using the procedure described for **IVh**: ^{1}H NMR ($CDCl_3$) 7.62 (s, 2H), 3.97 (s, 3H).

3,5-Dimethyl-4-methoxybenzonitrile (IVo) was synthesized in 65% yield from 3,5-dimethyl-*p*-anisic acid utilizing the reported one-step procedure.[34]

4-Chloro-3-methoxybenzonitrile (IVp). To a solution of 5-bromo-2-chloroanisole (10 g, 45.1 mmol) in DMF (100 mL) was added CuCN (8 g, 90.2 mmol), and the mixture was heated to 110 °C for 24 h. The reaction mixture was cooled, filtered, and poured over ice. The crude mixture was extracted with ethyl acetate and washed successively with water and brine. After being dried over sodium sulfate, the organic fractions were filtered and concentrated. The crude solid (10 g) was purified by chromatography (silica gel, hexane−ethyl acetate, 9/1) to give **IVp** (4.35 g, 55%): mp (DSC) 77 °C; MIR 2230, 1586, 1568, 1481, 1456, 1402, 1284; ^{1}H NMR ($CDCl_3$) 7.47 (d, J = 8 Hz, 1H), 7.22 ((dd, J = 8, 2 Hz, 1H), 7.15 (t, J = 2 Hz, 1H), 3.94 (s, 3H); MS (EI) 167 (M^+). Anal. ($C_8H_6NClO\cdot 0.1H_2O$) C, H, N.

4-Chloro-3-(dimethylamino)benzonitrile (IVq). To a stirred mixture was 3-amino-4-chlorobenzonitrile (5.0 g, 36 mmol) and paraformaldehyde (10.8 g, 0.36 mol) in 200 mL of acetic acid was added cautiously sodium cyanoborohydride (11.3 g, 0.18 mol). The mixture was stirred at room temperature for 18 h and poured into 200 mL of cold 25% NaOH solution. The aqueous phase was extracted with methylene chloride. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated under vacuum to give 5.74 g of **IVq** as a brown oil (88%): ^{1}H NMR ($CDCl_3$) 7.43 (d, J = 8 Hz, 1H), 7.27 (d, J = 2 Hz, 1H), 7.20 (dd, J = 8, 2 Hz, 1H), 2.85 (s, 6H). Anal. ($C_9H_9N_2Cl$) C, H, N.

1-Bromo-3-(4-chlorophenoxy)propan-2-one (XI). The intermediate **XI** (Scheme 5) was prepared using a two-step process.

Step 1: 1-Chloro-4-(2-chloro-1-methyleneethoxy)benzene (X). To a solution of 4-chlorophenol (6.1 g, 47.4 mmol) in acetone (200 mL) were added potassium carbonate (13.1 g, 94.7 mmol) and 2,3-dichloropropene (6.6 mL, 71 mmol). After 48 h of reflux, the reaction mixture was cooled to room temperature and filtered. The residue was washed with more acetone, and the combined organic fractions were concentrated. The crude pale brown liquid (11.5 g) was chromatographed (silica gel, hexane−ethyl acetate, 85/15) to give **X** (8.9 g, 98%): IR (KBr) 3041, 2924, 2866, 1640, 1593, 1582, 1487, 1453, 1371; ^{1}H NMR ($CDCl_3$) 7.25 (d, J = 8 Hz, 2H), 6.88 (d, J = 8 Hz, 2H), 5.53 (d, J = 2 Hz, 1H), 5.44 (d, J = 2 Hz, 1H), 4.56 (s, 2H); MS (EI) 202, 204 (M^+, M + 2). Anal. (C_8H_7FO) C, H, N.

Step 2: 1-Bromo-3-(4-chlorophenoxy)propan-2-one (XI). To a turbid solution of the above intermediate (3.0 g, 15.7 mmol) in acetonitrile (80 mL) and water (20 mL) was added in one portion recrystallized NBS (4.84 g, 31.4 mmol). The catalytic amount of 48% HBr (40 mL) was added to the reaction and the mixture stirred at room temperature for 24 h. The reaction was diluted with ether (200 mL) and treated with 5% w/v solution of sodium thiosulfate (20 mL). The organic layer was separated and washed with saturated sodium bicarbonate and brine. The organic fractions were dried over sodium sulfate, filtered, and concentrated. The

purification of the crude liquid (4.8 g) through a short silica gel column (hexane−ethyl acetate, 8/2) gave **XI** (1.4 g), which was used in the next reaction without additional purification: ^{1}H NMR ($CDCl_3$) 7.26 (d, J = 8 Hz, 2H), 6.83 (d, J = 8 Hz, 2H), 4.78 (s, 2H), 4.38 (s, 2H).

1-[4-(Methylsulfonyl)phenyl]-2-phenyl-1*H*-imidazole (83). To a solution of 2-phenylimidazole (1 g, 6.9 mmol) in DMSO (10 mL) was added sodium hydride (280 mg, 60% dispersion in mineral oil, 7 mmol). After 20 min of stirring at room temperature, a solution of 4-fluorophenyl methyl sulfone (1.2 g, 6. 9 mmol) was added. The reaction mixture was heated at 120−130 °C for 120 h, cooled to room temperature, and poured over ice. The residue was filtered and the crude yellowish solid (1.52 g) chromatographed (silica gel, hexane−ethyl acetate, 1/1) to give pure **83** (1.15 g, 54%) as a white solid: mp (DSC) 137 °C; IR (KBr) 3431, 2897, 1596, 1496, 1414, 1304; ^{1}H NMR ($CDCl_3$) 7.96 (d, J = 8 Hz, 2H), 7.40 (d, J = 8 Hz, 2H), 7.25−7.40 (complex band, 5H), 3.08 (s, 3H); MS (APCI) 299 (M^+). Anal. ($C_{16}H_{14}N_2SO_2$) C, H, N, S.

Similarly, the tetrazole and indole derivatives (**85** and **86**) were prepared from the commercially available 5-phenyl-1*H*-tetrazole and 2-phenylindole, respectively, by using the procedure described for **83**.

1-[4-(Methylsulfonyl)phenyl]-2-phenyl-5-(trifluoromethyl)-1*H*-imidazole (84). To a solution of **83** (400 mg, 1.34 mmol) in DMSO (10 mL) was added $FeSO_4 \cdot 7H_2O$ (224 mg, 0.84 mmol). Excess of trifluoromethyl iodide gas was bubbled through the reaction solution for 2 min. Hydrogen peroxide (0.82 mL, 30% solution by wt, 8.04 mmol) was added, and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was diluted with brine and extracted with ether. The organic fractions were dried (Na_2SO_4), filtered, and concentrated. The crude mixture was chromatographed (silica gel, ethyl acetate−toluene, 6/4) to give the recovered starting material (290 mg) and the pure **84** (48 mg) as a white solid: mp 166−168 °C; MIR 3096, 1594, 1562, 1498, 1467, 1448, 1415, 1358, 1312; ^{1}H NMR ($CDCl_3$) 8.05 (d, J = 8 Hz, 2H), 7.68 (s, 1H), 7.52 (d, J = 8 Hz, 2H), 7.22−7.38 (complex band, 5H), 3.12 (s, 3H); MS (APCI) 367 (MH^+). Anal. ($C_{17}H_{13}N_2SF_3O_2 \cdot 0.25H_2O$) C, H, N, S.

Supporting Information Available: Complete physical and spectral data for compounds **5**−**9**, **11**−**19**, **21**−**82**, **85**, **86**, **91**, **96**, and **97** and the intermediates **IVb**−**d**,**i**−**l**,**o** (18 pages). Ordering information is given on any current masthead page.

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JM9700225