Selective Cyclooxygenase-2 Inhibitors: Heteroaryl Modified 1,2-Diarylimidazoles Are Potent, Orally Active Antiinflammatory Agents

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A series of heteroaryl modified 1,2-diarylimidazoles has been synthesized and found to be potent and highly selective (1000−9000-fold) inhibitors of the human COX-2. 3-Pyridyl derived COX-2 selective inhibitor (**25**) exhibited excellent activity in acute (carrageenan induced paw edema, ED_{50} = 5.4 mg/kg) and chronic (adjuvant induced arthritis, ED_{50} = 0.25 mg/kg) models of inflammation. The relatively long half-life of **25** in rat and dog prompted investigation of the pyridyl and other heteroaromatic systems containing potential metabolic functionalities. A number of substituted pyridyl and thiazole containing compounds (e.g., **44**, **46**, **54**, **76**, and **78**) demonstrated excellent oral activity in every efficacy model evaluated. Several orally active diarylimidazoles exhibited desirable pharmacokinetics profiles and showed no GI toxicity in the rat up to 100 mg/kg in both acute and chronic models. The paper describes facile and practical syntheses of the targeted diarylimidazoles. The structure−activity relationships and antiinflammatory properties of a series of diarylimidazoles are discussed.

Introduction

Nonsteroidal antiinflammatory drugs (NSAIDs) such as aspirin have been in existence for about a century and have been used as first line therapy for relieving inflammation and pain associated with a number of arthritic conditions.[1] Chronic usage of these drugs has been associated with the propensity for side effects such as gastrointestinal irritation[2] and suppression of renal function[3] in part of the population. Without a handle on the mechanism(s), common strategies that attempted to modulate the adverse effect profile of NSAIDs have varied from developing prodrugs[4] to modifications of the marketed formulations.[5] In conjunction with broad screening of the congeners of the marketed or lead compounds in models of gastric damage, these approaches have helped identify compounds (e.g., DuP 697, meloxicam)[6,7] with lower incidence of gastric lesions. The empirical nature of this approach has, however, been less successful in stimulating researchers in the field. Alternately, co-therapy of an NSAID with a cytoprotective agent such as misoprostol has proven beneficial in minimizing gastrointestinal damage induced by selected antiinflammatory drugs.

In 1971, it was discovered that aspirin and other NSAIDs exhibit their antiinflammatory effect by inhibition of the cyclooxygenase (COX) enzyme and blockage of the synthesis of proinflammatory prostaglandins.[8] This theory, however, did not discriminate the therapeutic from the toxic effects of these drugs. In the late 1980s, a major breakthrough in antiinflammatory research occurred when it was reported[9] that cytokine interleukin-1 (IL-1) stimulated the synthesis of the COX enzyme in cultured human dermal fibroblasts. Subsequent publications reinforced that cyclooxygenase activity was also increased substantially by bacterial lipopolysaccharide (LPS) in human monocytes[10] in vitro and in murine peritoneal macrophages[11] in vivo. This increase was associated with de novo synthesis of a new COX protein. It was observed that the glucocorticoid dexamethasone blocked LPS induced prostaglandin release by inhibiting the induction of COX expression while having no effect on basal prostaglandin production.[10,11] Needleman and coauthors postulated the existence of an inducible, second isoform of COX enzyme and hypothesized on its potential benefits.[11] A year later, molecular cloning experiments identified a distinct isoform known as cyclooxygenase-2 (COX-2).[12]

The discovery of inducible enzyme (COX-2) and the accumulating evidence that it may be possible to separate its role from constitutive enzyme (COX-1) spurred the search for a "super NSAID" with improved 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 mediated) production of PG's in the gastrointestinal tract. The enormity of the COX-2 discovery is reflected in the unprecedented speed at which research laboratories have sought to validate its clinical implications. Recently, celecoxib[13] and refecoxib[14] became the first cyclooxygenase-2 selective inhibitors to enter the market.

Earlier we reported[15] our results on the syntheses and antiinflammatory activity of a series of 1,2-diarylimidazoles. These compounds (**1**) exhibited excellent potency (IC_{50} = 10−100 nM) and selectivity (COX-1/COX-2 = 10^3−10^4) for the human cyclooxygenase-2 enzyme. Many of these compounds also displayed impressive in vivo pharmacology in models of inflammation. During these studies, it was observed that

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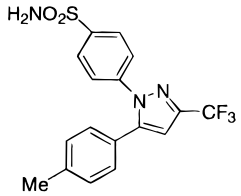
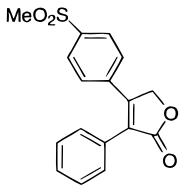
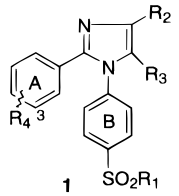


Celecoxib



Rofecoxib

arylsulfonamides (**1**, $R_1 = NH_2$) generally displayed a superior in vivo profile compared to the corresponding aryl sulfones (**1**, R_1 = Me). It was hypothesized that the lower logP of arylsulfonamide vs the aryl sulfone (ΔlogP $\sim$ 0.5) contributed to its improved absorption and bioavailability. In our continuing efforts to seek agents with better oral activity, we explored the replacement of the aromatic ring A in the lead template **1** by other aromatic heterocycles. It was postulated that heteroaromatic analogues with improved water solubility would also influence the observed plasma levels and bioavailability in animal models. This paper describes the syntheses, cyclooxygenase inhibitory activity, and the antiinflammatory properties of a series of heteroaryl modified 1,2-diarylimidazoles.



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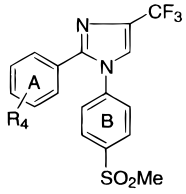
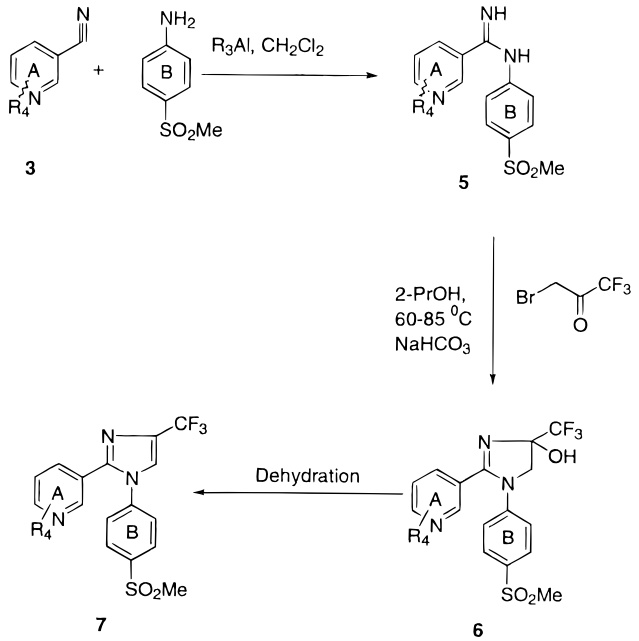


2

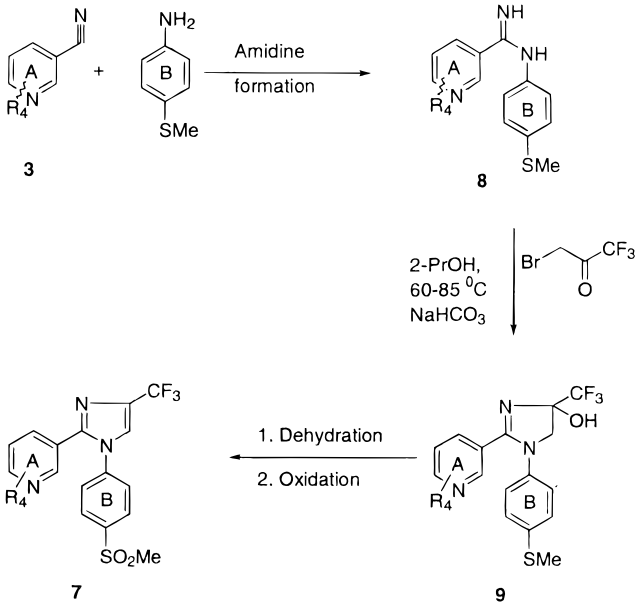
Chemistry

The 1,2-diarylimidazoles reported in this paper were synthesized using Schemes 1−9. A number of analogues containing a 4-(methylsulfonyl)phenyl group directly attached to the imidazole nitrogen were synthesized adopting the general methodology (Scheme 1) reported by us earlier.[15] However, in certain instances, the step involving amidine (**5**) formation gave inconsistent results during scale-up. Low solubility of some amidines in organic solvents and the presence of aluminum salts occasionally led to emulsion formation during the reaction work up. This made the isolation of pure amidines tedious. To improve organic solubility and to facilitate amidine formation, the process was modified and 4-(methylmercapto)aniline was used as the starting amine (Scheme 2). This variation generally led to incremental improvement in yield, but the problems associated with work up of relatively less soluble amidines continued to give erratic results on scale-up of the reaction. After limited success with alternate Lewis acids and solvents, base catalyzed amidine formation was studied on 3-cyanopyridine and 4-(methylmercapto) aniline. The results reported in Scheme 3 clearly indicate that the base and the reaction conditions significantly influence the outcome of the reaction. The reactions using lithium derived bases (examples **7** and **8**) generally did not give as good yields as obtained from bases containing sodium counterion (e.g., **1**−**4**, **9**). Sodium methoxide proved to be less efficient (examples **5** and **6**) possibly because of its stronger nucleophilicity and potential generation of less reactive imidate on reaction with 3-cyanopyridine.

Scheme 1



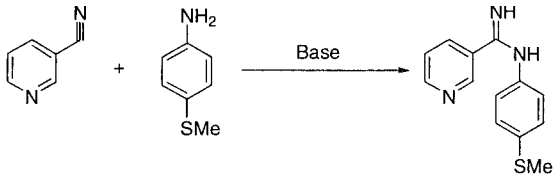
Scheme 2



Best results were obtained when the amidine formation was carried out in tetrahydrofuran with sodium bis-(trimethylsilyl)amide as base. After completion, the product (**8**, Scheme 2) was precipitated from the reaction mixture by pouring over ice−water and collected by filtration. The improved nucleophilicity of amidine **8** (vs **5**, Scheme 1) also influenced the alkylation/cyclization step. The reaction time for the synthesis of **9** (Scheme 2) was significantly shorter (3−6 h) in comparison to 18−36 h needed for the synthesis of **6** (Scheme 1). Use of these modifications simplified the preparation and scale-up of many target compounds. The isomeric compound (**34**), wherein the pyridyl moiety is switched to the imidazole *N*-1 position, was synthesized as in Scheme 1 using 3-aminopyridine and 4-methylsulfonylbenzonitriles as starting materials.

Synthesis of Aryl Nitriles. A number of aryl nitriles used in the Schemes 1, 2, and 6 were purchased

Scheme 3

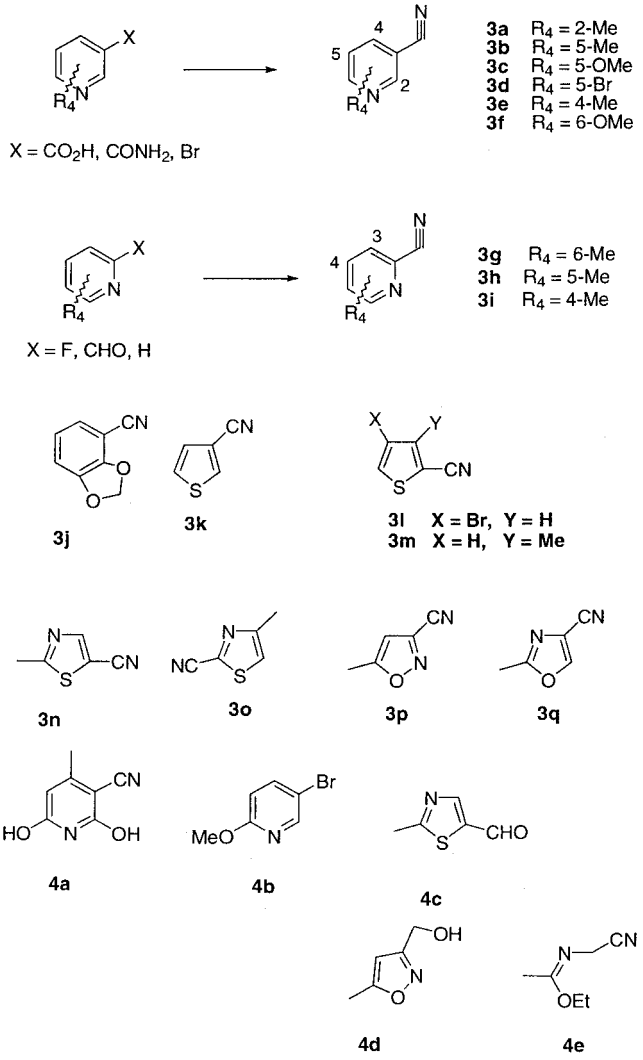


Experiment	Catalyst, Solvent	Reaction Conditions	Yield (%)
1	NaH (washed), DMSO	0-25 °C; 4 h	91
2	NaH (dispersion), DMSO	0-25 °C; 4 h	85
3	NaH (washed), THF	Reflux, 16 h	92
4	NaH (dispersion), DME	Reflux, 4 h	80
5	NaOMe in 25% MeOH, DMSO	25 °C; 16 h	50
6	NaOMe in 25% MeOH, THF	25 °C; 16 h	<10
7	BuLi, THF	-65-25 °C; 16 h	42
8	LDA, THF	-78-25 °C; 16 h	69
9	NaN(SiMe$_3$), THF	25 °C; 3-4 h	96

commercially or synthesized using the reported procedures. Some of the aryl nitriles were prepared from commercially available intermediates by displacement reactions or by functional group transformations (Scheme 4). For example, a number of 3-cyanopyridyl intermediates (**3a**−**3d**) were made from substituted nicotinic acid by conversion to the corresponding nicotinamides followed by dehydration using trifluoroacetic anhydride/triethylamine (see Experimental Section). 3-Cyano-4-methyl pyridine (**3e**) was prepared[17] from 2,6-dihydroxypyridine compound **4a** by conversion to its 2,6-dichloro derivative using $POCl_3$ followed by hydrogenolysis (NaOAc, $PdCl_2$). The intermediate **3f** containing a 6-methoxy substituent was synthesized by cyanation (DMF, CuCN, 120 °C) of the corresponding 3-bromopyridine compound **4b**.[18] Syntheses of 2-cyanopyridine compounds (**3g**−**3i**) were accomplished readily from commercially available intermediates. For example, the cyano substituent in intermediates **3g** and **3h** was incorporated by conversion of the corresponding 2-formyl (via oxime) and 2-fluoro (NaCN, DMSO) derivatives, respectively. 4-Picoline *N*-oxide was reacted with trimethylsilyl cyanide to give **3i** in a single pot process.[19]

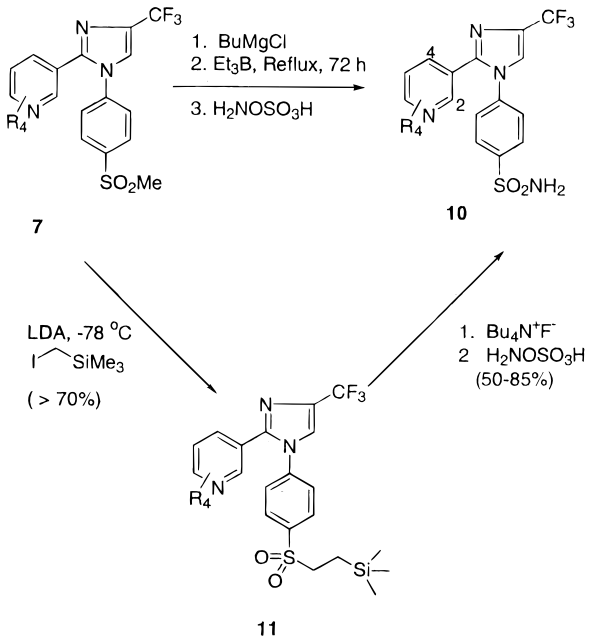
Several heteroaromatic nitriles (**3j**−**3p**) derived from thiophene, thiazoles, and isoxazole were synthesized by transformation of the corresponding formyl derivatives using the standard literature procedures (see Experimental Section). The aldehydes required for the synthesis of **3j**−**3m** were obtained commercially, while those needed for **3n**−**3p** were synthesized in the following manner. The intermediate 5-thiazolecarboxaldehyde (**4c**) was obtained by condensation of bromomalonaldehyde with thioacetamide in the presence of Hunig's base. Metalation[20] of 4-methylthiazole followed by quenching with dimethylformamide proceeded in a regioselective manner to give 4-methylthiazole-2-carboxaldehyde in 72% yield. The commercially available isoxazole intermediate (**4d**) was oxidized (oxalyl chloride, DMSO; 59%) to give the corresponding isoxazole-3-carboxaldehyde. The oxazole derivative **3q** was synthesized using the methodology reported[21] for similar compounds. The reaction of ethylacetimidate hydrochloride with aminoacetonitrile hydrochloride gave the imidate **4e** which was elaborated to the desired oxazole **3q** by treatment with ethyl formate and potassium *tert*-butoxide.

Scheme 4

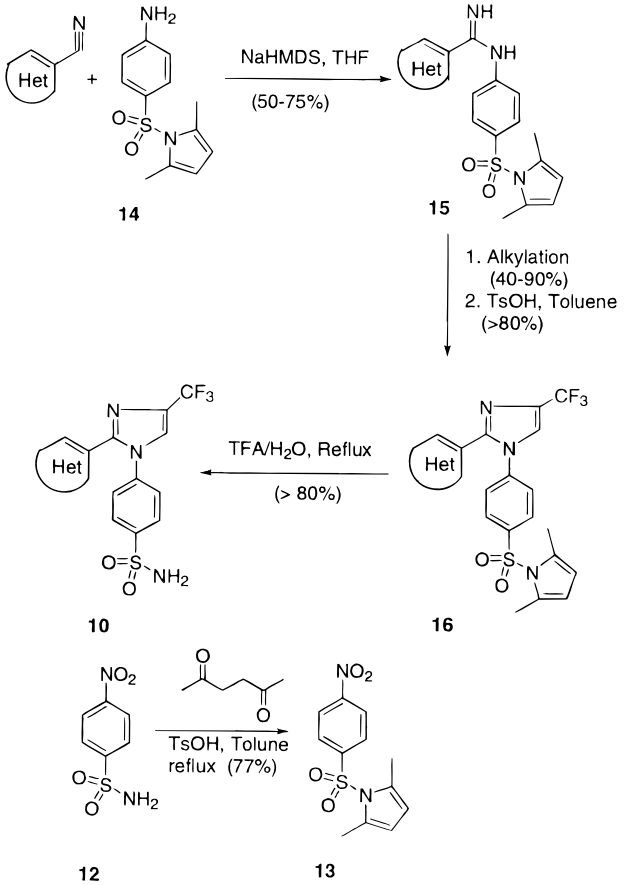


Synthesis of Aryl Sulfonamides. Diarylimidazoles containing the sulfonamide group were prepared utilizing the methodologies outlined in Schemes 5 and 6. A one-pot conversion of aryl methyl sulfone to aryl sulfonamide developed by Huang et al.[22] was utilized to synthesize a number of 1,2-diarylimidazoles.[15] This direct process (**7**−**10**, Scheme 5), however, gave low reaction yields (<10%) with pyridyl derived diarylimidazoles. Because of the longer reaction times (>72 h) and difficulties encountered in monitoring the progress of the reaction, a modified two-step process based on the methodology reported by Harring[23] was explored (Scheme 5). Regioselective generation of the carbanion (LDA, −78 °C) on aryl methyl sulfone **7**, followed by quenching with (iodomethyl)trimethylsilane, gave the trimethylsilylethyl sulfone intermediate (**11**) generally in high yields (>70%). Desilylation ($Bu_4N^+F^-$, THF, reflux, 1 h) to the sulfinic acid salts followed by treatment with hydroxylamine-*O*-sulfonic acid gave the desired arylsulfonamide (**10**) in good yield (50−85%).

Scheme 5

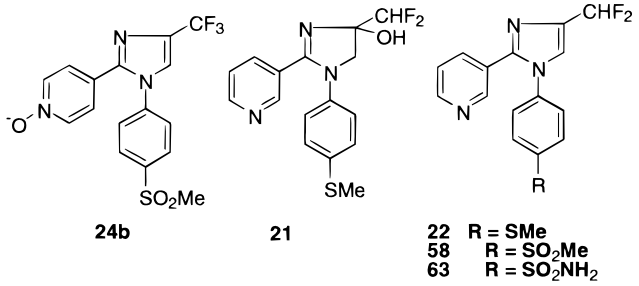


Scheme 6



Alternately, the desired arylsulfonamides (**10**) were prepared following the reaction sequence outlined in Scheme 6. The methodology is built on the successful features of Schemes 1−3. The aniline **14** using 2,5-dimethylpyrrole as the masked amino protecting group[24] was synthesized readily in two steps by starting with 4-nitrobenzenesulfonamide (**12**). Condensation of **12** with acetonylacetone (toluene, TsOH, reflux, 77%) followed by reduction (Raney-nickel, MeOH, H_2) of the resulting intermediate **13** gave the desired aniline **14** in a combined yield of >70%. Base catalyzed (NaHMDS, THF) amidine formation, alkylation, cyclization, and dehydration steps proceeded efficiently to give the intermediates in customary high yields. The sulfonamide (**10**) was generated in very high yield (>80%) from the intermediate **16**, by refluxing with aqueous trifluoroacetic acid.

Synthesis of Substituted Imidazoles. 1,2-Diarylimidazoles with different substituents (Me, CHF_2, CN, CO_2R, CH_2OH) at position-4 of the imidazole were prepared by reacting the useful amidine intermediate **8** with appropriate electrophiles, followed by elaboration of the sequence as discussed above in Schemes 1 and 2. For example, reaction of **8** with ethyl bromopyruvate under standard conditions (*i*-PrOH, $NaHCO_3$, reflux, 34%) gave the intermediate **20**, which was oxidized (oxone, 41%, Scheme 9) to the target **61**. The analogue **62** with a hydroxymethyl group at C-4 was obtained by reduction (DIBAL, 56%) of the corresponding ester compound **61** (Scheme 9). Similarly, the reaction of amidine **8** with 1-chloro-3,3-difluoroacetone[25] gave the cyclic intermediate **21**, which was dehydrated (Ac_2O, DMAP, reflux) to **22** and oxidized to the desired compound **58**.

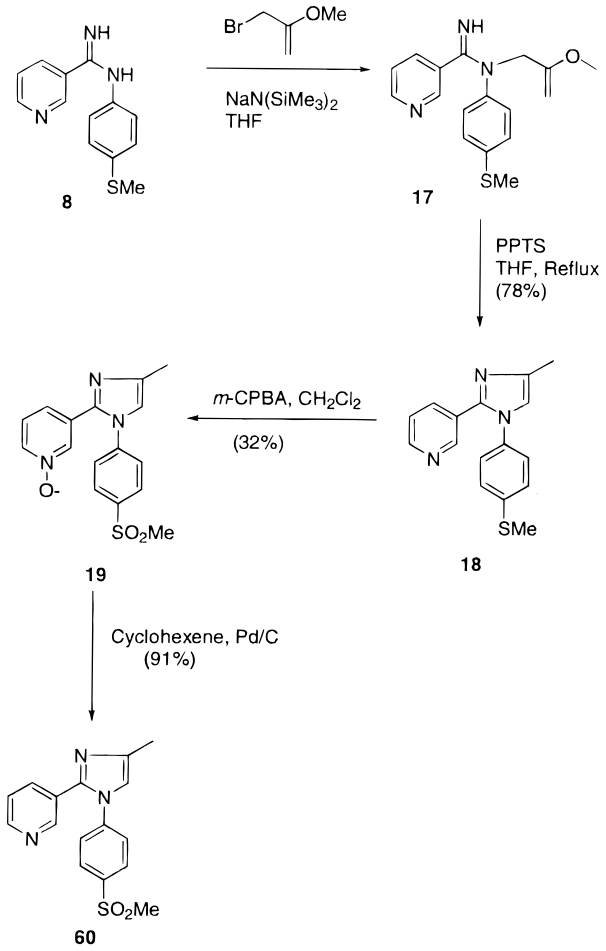


24b **21** **22** R = SMe; **58** R = SO_2Me; **63** R = SO_2NH_2

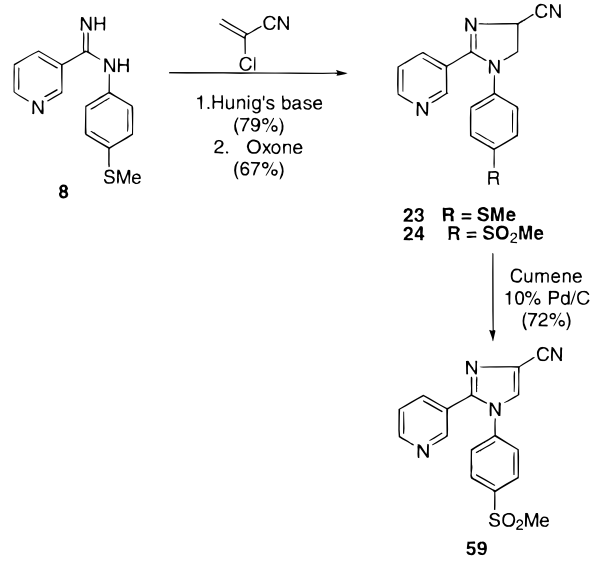
The compound containing a 4-methyl substituent in the imidazole ring was prepared as shown in Scheme 7. Direct alkylation/cyclization of the amidine **8** with 2-chloroacetone (2-PrOH, $NaHCO_3$, reflux, 24 h) was very sluggish and gave low yield (<20%) of the intermediate **18**. After several unsatisfactory attempts at modifying conditions, 1-bromo-2-methoxy-propene was found to be an effective reagent. The reaction of **8** with 1-bromo-2-methoxy-2-propene in THF using sodium bis-(trimethylsilyl)amide as a base gave the *N*-alkylated product **17** in a regioselective fashion. Treatment of **17** with pyridinium *p*-toluenesulfonate (aqueous THF, reflux, 78%) gave **18**, identical to the product obtained from the 2-chloroacetone reaction. Unlike our experiences with other analogues with different substitutions at C-4 of the imidazole ring (e.g., CF_3, CHF_2, CN), attempted oxidation of SMe group in **18** with oxone gave significant amounts of pyridine *N*-oxide (**19**). A two-step process involving oxidation (*m*-CPBA) of **18** to **19** followed by deoxygenation (cyclohexene, Pd/C) was utilized to prepare the target compound **60**.

The compound **59** with a cyano substituent at position-4 of the imidazole was synthesized as shown in Scheme 8. The reaction of amidine **8** with 2-chloroacrylonitrile using Hunig's base gave the imidazoline **23** in 79% yield. Sulfur oxidation (oxone, 67%) followed by aromatization (cumene, 10% Pd/C, reflux, 72%) of the

Scheme 7



Scheme 8

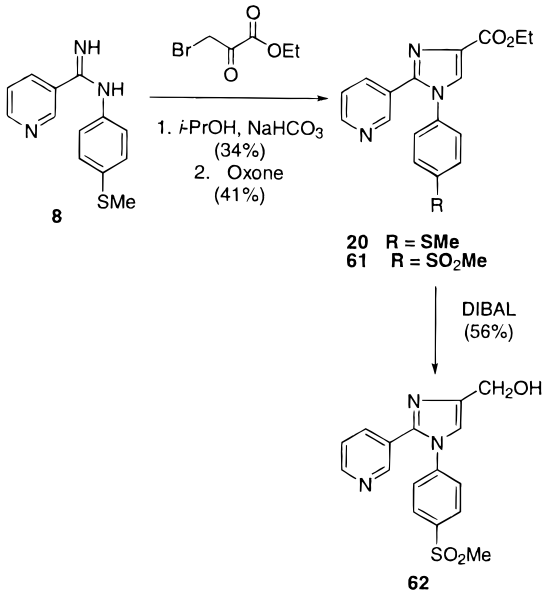


resulting dihydro intermediate **24** gave the desired compound **59**.

Results and Discussion

Our SAR studies[15] on 1,2-diarylimidazoles (**1**) demonstrated that the attachment of a methyl sulfone (or sulfonamide) bearing aryl ring B to the imidazole nucleus at *N*-1 gave superior COX-2 inhibitors compared

Scheme 9



to "the reversed analogues" wherein the aryl ring B was attached at the C-2 position of the imidazole. In complementary work done on 1,2-diarylpyrroles, we established[16] that COX-2 inhibitory activity was sensitive to the manipulation of the aryl sulfone ring. Specifically, addition of substituents to the aryl ring or modification of the SO_2R group yielded less potent inhibitors of the COX-2 enzyme. Similarly, our studies demonstrated that the presence of a trifluoromethyl group at C-4 position ($R_2 = CF_3$) of the imidazole ring contributes to excellent in vitro and in vivo properties observed with this class of compounds.[15] Utilizing these results, we selected the framework **2** to initiate heterocyclic exploration of the aryl ring A.

On the basis of our experience[15] with the modifications of aryl ring A in structure **1**, we had concluded that while there was flexibility and tolerance of a variety of substituents in the aryl ring, the C-3 position seemed to offer the optimum combination of potency and selectivity for human COX-2 enzyme. Thus, the 3-pyridyl analogue (**25**) was chosen as the first target for biological evaluation.

The compound **25** inhibited human cyclooxygenase-2 enzyme with an IC_{50} of 1.85 μM and selectivity (IC_{50} COX-1/IC_{50} COX-2) of >5000. In the human whole blood assay, the compound exhibited much superior potency, inhibiting LPS induced PGE_2 production with an IC_{50} of 0.2 μM. Similarly, the compound inhibited ionophore A-23187 induced TXB_2 production with an IC_{50} of 42 μM, indicating good selectivity for COX-2 enzyme. The compound **25** was also very potent orally in the rat air-pouch model and inhibited PGE_2 production with an ED_{50} of 0.2 mpk.

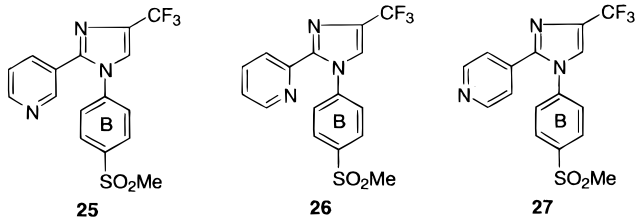


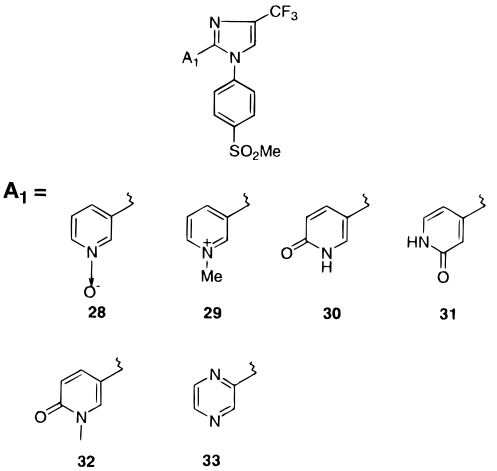
Table 1. Isomeric Pyridines

compd	COX-2 (IC_{50}, μM)[a]	COX-1 (IC_{50}, μM)[a]	HWB, PGE_2 (IC_{50}, μM)	HWB, TXB_2 (IC_{50}, μM)	air-pouch (% inhib., 2 mg/kg)
25	1.69 ± 0.39	>10000	0.20 ± 0.14	41.6 ± 0	100
26	1.5 ± 0.87	>1000	0.24	>10	100
27	>100	>100			

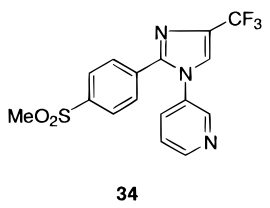
[a] Each result is the mean ± SD ($n \geq 2$).

The promising activity of **25** in human whole blood and air-pouch model prompted us to examine the isomeric pyridyl compounds **26** and **27.** As apparent by the data reported in Table 1, 4-pyridyl analogue **27** is a significantly less potent inhibitor of COX-2 (IC_{50} = >100 μM). 2-Pyridyl compound **26** seems very similar to the 3-pyridyl compound **25** in its in vitro profile. Both compounds showed 100% inhibition in the air-pouch model at a screening dosage of 2 mg/kg. However, further investigation of their behavior in in vivo models of inflammation demonstrated 3-pyridyl isomer **25** to be a superior compound. For example, in the carrageenan induced paw edema rat model, compound **26** showed 37% inhibition of edema at 30 mg/kg. The 3-pyridyl compound **25** performed significantly better controlling edema with an ED_{50} of 5.4 mg/kg. None of the compounds reported in Table 1 showed appreciable inhibition of LPS induced TNF production by human peripheral blood monocytes at 10 μM, further confirming the mechanism of action of these antiinflammatory agents.

To probe the important structural features responsible for enzyme activity, 3-pyridyl compound **25** was derivatized and the resulting products evaluated against COX-2 enzyme. Pyridine *N*-oxide analogue **28** was a less potent inhibitor of COX-2 enzyme (IC_{50} = >100 μM), and *N*-methylpyridinium analogue **29** was weakly active (IC_{50} = 69 μM). Of the pyridone compounds examined, isomeric pyridones **30** and **31** showed poor activity for COX-2 (IC_{50} = >100 μM). The *N*-methylpyridone **32** showed some activity (IC_{50}, COX-2 = 7 μM) and was moderately potent in the air-pouch model (45% inhibition of PGE_2 at 2 mg/kg). Interestingly, although 2- or 3-pyridyl derived compounds (**25** and **26**) are good inhibitors of the COX-2 enzyme, the pyrazine compound **33** was a relatively weak inhibitor (IC_{50}, = >100 μM).



Consistent with our observations in the 1,2-diarylimidazoles series,[15] the analogue **34** in which the pyridyl moiety is switched to the *N*-1 position was significantly less potent (IC_{50}, COX-2 = >100 μM).



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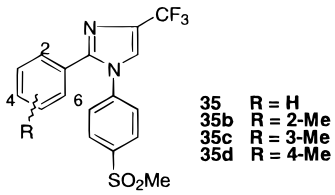


35 R = H
35b R = 2-Me
35c R = 3-Me
35d R = 4-Me

Compound **25** was evaluated in the acute (carrageenan induced paw edema) and the chronic (adjuvant induced arthritis) models of inflammation in the rat. The details of these assays are reported in the Experimental Section. The results, shown in Table 2, compare its profile with non-pyridyl compound **35**.[15] Diarylimidazoles **25** and **35** showed excellent selectivity for COX-2 enzyme, and both of them showed potency comparable with celecoxib in the chronic model of inflammation. However, in the acute model (carrageenan induced edema and hyperalgesia), compound **25** appears to be 4−7 times more potent than **35**. On oral exposure in rat at 10 mg/kg, compound **25** gave excellent blood levels (C_{max} of 10.5 μg/mL at 4.25 h). The observed plasma levels and potential tissue distribution can at least offer partial explanation to the superior effectiveness of **25** in acute models. The lower logP value of **25** compared to **35** (2.0 vs 2.8) may have contributed to its improved absorption and the observed plasma levels.

The results elaborated in Table 1 clearly show **25** as a very potent antiinflammatory and analgesic agent. To evaluate the GI safety, compound **25** was given orally (100 mg/kg/day) to rats in an adjuvant induced arthritis assay. No lesions or undesirable gastrointestinal toxicity were seen with this compound after chronic dosage for 10 days. The compound seems remarkably stable to metabolism and has a half-life of about 12 h in rat and approximately 88 h in dog. The longer half-life in dog stimulated us to probe compounds with built-in metabolic functionalities.

Modification of the Pyridyl Substituents. Based on our experience with 1,2-diarylimidazoles,[15] it was apparent that a variety of substituents (such as halogens, Me, OMe, SMe, CH_2OMe, NO_2, CF_3, NR_2) could be added to ring A to secure potent COX-2 inhibitors. Examination of these data indicated that introduction of a methyl or a OMe group might lead to a useful combination of potency, selectivity, and desirable pharmacokinetic properties. A number of substituted 3-pyridyl and 2-pyridyl derived compounds were synthesized and evaluated (Tables 3 and 4) for inhibitory activity vs the cyclooxygenase enzymes.

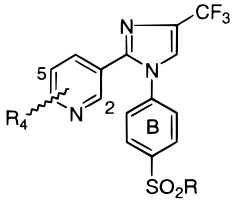
The arylsulfonamide compound **43** was a very potent (IC_{50} = 0.4 μM) and selective (COX-1/COX-2 = >2500) inhibitor of recombinant human COX-2 enzyme. The compound also caused complete blockage of PG production in the air-pouch assay at the screening dose of 2 mg/kg. However, because of the observed long half-life of **25** in dog and the lack of potential metabolic sites, no additional testing was done on this compound. The data reported in Table 3 suggest that a methyl substituent at the 2-, 5-, or 6-position in the pyridyl ring is well tolerated. The sulfonamide analogues (**44**−**46**) seem to be 3−5 times more potent than the corresponding

Table 2. In Vivo Pharmacology of 1,2-Diarylimidazoles

compd	COX-2 (IC_{50}, μM)[a]	COX-1 (IC_{50}, μM)[a]	selectivity COX-1/COX-2	edema (ED_{50}, mg/kg)	adj. arthr. (ED_{50}, mg/kg)	hyperalgesia (ED_{50}, mg/kg)
25	1.69 ± 0.39	>10000	>5000	5.4 ± 2.9	0.25 ± 0.14	8.2 ± 6.9
35[15]	0.13 ± 0	755 ± 231	5992	20.8 ± 0	0.15	56 ± 0

[a] Each result is the mean ± SD ($n \geq 2$).

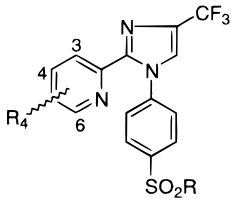
Table 3. Pyridyl Modifications



compd	R_4	R	COX-2 (IC_{50}, μM)[a]	COX-1 (IC_{50}, μM)[a]	air-pouch (% inhib., 2 mg/kg)
25	H	Me	1.69 ± 0.39	>10000	100
36	2-Me	Me	9.6 ± 7.7	>100	81
37	6-Me	Me	1.8 ± 0.1	>1000	93
38	5-Me	Me	1.8 ± 1.6	>1000	75
39	4-Me	Me	54	>100	
40	6-OMe	Me	1.2 ± 0.3	49	100
41	5-OMe	Me	37.6	>100	
42	5-Br	Me	0.95 ± 0.21	>1000	90
43	H	NH_2	0.44 ± 0.18	>1000	100
44	2-Me	NH_2	2.8 ± 0.64	>1000	100
45	6-Me	NH_2	0.29 ± 0.07	89	100
46	5-Me	NH_2	0.51 ± 0.02	>1000	96
47	4-Me	NH_2	51	>100	
48	5-OMe	NH_2	>100	>100	
49	5-Br	NH_2	0.34 ± 0.11	>1000	26

[a] Each result is the mean ± SD ($n \geq 2$).

Table 4. Pyridyl Modifications

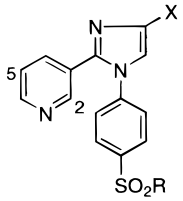


compd	R_4	R	COX-2 (IC_{50}, μM)[a]	COX-1 (IC_{50}, μM)[a]	air-pouch (% inhib., 2 mg/kg)
25	H	Me	1.69 ± 0.39	>10000	100
50	6-Me	Me	2.9 ± 2.6	>1000	92
51	5-Me	Me	1.3 ± 0.68	>1000	97
52	4-Me	Me	0.53 ± 0.13	>1000	84
53	3-Me	Me	5.8 ± 0.47	>1000	100
54	6-Me	NH_2	0.42 ± 0.13	>1000	100
55	5-Me	NH_2	0.73 ± 0.32	302	100
56	4-Me	NH_2	0.44 ± 0.19	84 ± 1.4	75
57	3-Me	NH_2	1.54 ± 0.15	338	100

[a] Each result is the mean ± SD ($n \geq 2$).

sulfones (**36**−**38**) in their inhibition of COX-2 enzyme. The sulfonamide analogues (**44**−**46**) performed very well in the air-pouch model, showing excellent inhibition (>95%) of PG production at 2 mg/kg. The analogues **39** and **47** containing a 4-methyl substituent were significantly less potent against COX-2 enzyme. 5-Methoxy analogues (**41** and **48**) were weak inhibitors of the human COX-2 enzyme. The results reflect a noteworthy deviation from our experiences with non-heteroaryl imidazoles[15] wherein a methoxy at the 3- or 5- position gave very potent COX-2 inhibitors. The compounds (**42** and **49**) containing a 5-bromo substituent were very potent and selective COX-2 inhibitors.

Table 5. Imidazole Substitutions



compd	R	X	COX-2 (IC_{50}, μM)[a]	COX-1 (IC_{50}, μM)[a]	air-pouch (% inhib., 2 mg/kg)
25	Me	CF_3	1.69 ± 0.39	>10000	100
58	Me	CHF_2	20.7 ± 17.4	>100	
59	Me	CN	24.4 ± 24.8	>100	
60	Me	Me	79	>100	
61	Me	CO_2Et	>100	>100	
62	Me	CH_2OH	934	>1000	
63	NH_2	CHF_2	1.83 ± 0.69	>100	19

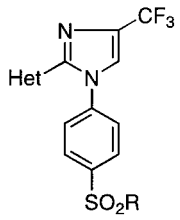
[a] Each result is the mean ± SD ($n \geq 2$).

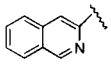
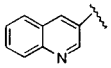
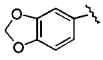
As an extension of the encouraging in vitro and in vivo results observed with methyl substituted 3-pyridyl compounds, isomeric methyl substituted 2-pyridyl analogues (Table 4) were also evaluated. Several analogues show good inhibitory potency against the COX-2 enzyme. None of the aryl sulfones (**50**−**53**) showed significant activity against COX-1 up to concentration of 1000 μM, indicating excellent selectivity for COX-2 enzyme. The affinity of sulfonamides **54**−**57** for COX-1 varies with the position of the methyl group in the aryl ring. Interestingly, 3-methyl analogues (**53** and **57**) were significantly more potent than similarly substituted analogues (**39** and **47**) in the 3-pyridyl series. All of these compounds also showed excellent inhibition (75−100%) of prostaglandin production in the air-pouch model.

Modification of the Imidazole Substituents. To study SAR and to potentially lower the half-life of lead compound **25**, the trifluoromethyl group in the imidazole ring was substituted by a number of metabolizable groups. These substituents had demonstrated good to excellent potency vs COX-2 enzyme in a previously reported[15] 1,2-diarylimidazole series. As shown in Table 5, most of the analogues tested were significantly less active than the lead compound **25**. A difluoromethyl analogue **63** was as potent as **25** in the human recombinant COX-2 enzyme assay but was only weakly active in the air-pouch model. The results reaffirm that CF_3 is very critical component of the pharmacophore in this series.

Heteroaryl Modifications. The research done on pyridyl and pyrazine derived analogues (vide supra) strongly suggests that the position of heteroatom in the ring and the orientation of the substituents greatly influence the potency versus COX-2 enzyme. The excellent properties demonstrated by some of these compounds swayed us to probe other heteroaromatic sys-

Table 6. Heteroaryl Modifications



compd	Het	R	COX-2 (IC_{50}, μM)[a]	COX-1 (IC_{50}, μM)[a]	air pouch (% inhib., 2 mg/kg)
25		Me	1.69 ± 0.39	>10000	100
64		Me	1.2 ± 0.67	32	
65		Me	1.7 ± 0.11	>1000	60
66		Me	0.63 ± 0.24	82	90
67		Me	1.1 ± 0.19	>100	0
68		Me	0.28 ± 0.15	1.1	78
69		Me	0.47 ± 0.43	>100	11
70		Me	51	>100	
71		Me	0.47	>100	24
72		NH_2	0.07 ± 0.005	55	95
73		Me	0.026 ± 0.01	>1000	75
74		Me	1.1	>1000	11
75		Me	0.94 ± 0.08	>1000	73
76		NH_2	0.52 ± 0.13	>1000	100
77		NH_2	0.43 ± 0.62	>1000	75
78		NH_2	0.11 ± 0.05	>1000	100
79		Me	4.15	>100	0
80		NH_2	0.41 ± 0.04	>1000	92

[a] Each result is the mean ± SD ($n \geq 2$).

tems. A number of compounds derived from five-member and bicyclic heterocyclic ring systems were synthesized and evaluated (Table 6). Many of these compounds carry a methyl substituent to facilitate metabolism. The isomeric quinoline compounds (**64**−**66**), which mimic 2-pyridyl (**26**) or 3-pyridyl (**25**) analogues, showed similar affinity for COX-2 enzyme, but the selectivity ratio (COX-1/COX-2) varied between 30 and >500. Of these compounds, **66** showed excellent blockage of prostaglandin production (90%) at 2 mg/kg in the air-pouch model. *N*-Methyl indole analogue **67** showed potency against COX-2, which was comparable with **25** and **26**. Compound **67**, however, performed poorly in the air-pouch assay. Benzodioxole derived compounds (**68** and **69**) were very potent inhibitors of COX-2 enzyme (IC_{50} = 0.28 and 0.47 μM, respectively). Compound **68** did not show good selectivity (COX-1/COX-2 = 4), and **69** showed poor inhibition of PG production in the air-pouch model. Among thiophene analogues, 2-thiophene derived compounds (**71**, **72**) were >100 times more

Table 7. In Vivo Pharmacology of Selected 1,2-Diarylimidazoles

compd	COX-2 (IC_{50}, μM)[a]	COX-1 (IC_{50}, μM)[a]	selectivity COX-1/COX-2	adj. arthr. (ED_{50}, mg/kg)[b]	edema (ED_{50}, mg/kg)[c]	hyperalgesia (ED_{50}, mg/kg)
25	1.69 ± 0.39	>10000	>5000	0.25 ± 0.14	5.4 ± 2.9	8.2 ± 6.9
37	1.8 ± 0.1	>1000	>550	0.20	41	33% (30)
44	2.8 ± 0.64	>1000	>350	1.00 ± 0.08	6.9	18
46	0.51 ± 0.02	>1000	>2000	0.67	7.5	32
51	1.3 ± 0.68	>1000	>600	1.00		20% (30)
53	5.8 ± 0.47	>1000	>150	0.30	35% (30)	
54	0.42 ± 0.13	>1000	>2000	0.64	8.2	20.3
76	0.52 ± 0.13	>1000	>2000	0.57	13.4	14.0
78	0.11 ± 0.05	>1000	>9000	0.33	13.4	18.5
35b	0.79 ± 0.17	789 ± 299	721	0.14	18	43
35c	0.08 ± 0.03	78 ± 19.8	1500	0.36 ± 0.16	23	46
35d	0.18 ± 0.8	25.9 ± 0.8	162		35.8	99
indomethacin	0.9	0.1	0.1	0.1	60% (20)	
naproxen				0.94		66% (10)

[a] Each result is the mean ± SD ($n \geq 2$). [b] ED_{50} values were determined using a minimum of four dose points, 8−10 animals/group. [c] ED_{50} values were determined using a minimum of four dose points and using 5 animals/group.

potent (vs COX-2 enzyme) than the corresponding 3-thiophene analogue (**70**). Compound **72** also caused 95% inhibition of prostaglandin production in the air-pouch model. Of the heterocycles evaluated, thiazole derived compounds demonstrated an excellent profile overall. For example, compound **76** was a potent (IC_{50}, COX-2 = 0.5 μM), selective (COX-1/COX-2 = >2000) inhibitor and also blocked PG production completely at a screening dosage of 2 mg/kg in the air-pouch model. Compound **78** was an even more potent (IC_{50} = 0.11 μM) and selective inhibitor. It also showed complete inhibition of prostaglandin production in the air-pouch model. For reasons not apparent, oxazole (**79**) did not show encouraging potency against the COX-2 enzyme. Isoxazole derived compound **80** was a potent, selective inhibitor of COX-2 and gave excellent inhibition (>90%) in the air-pouch model at 2 mg/kg.

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 (Table 7). Most of the compounds examined in adjuvant induced arthritis model showed excellent potency (ED_{50} = 0.2−1 mg/kg) in controlling inflammation. The behavior of these compounds in acute models of edema and hyperalgesia showed more variability with the structures. As is evident from the data in Table 7, several pyridyl compounds (e.g., **25**, **44**, **46**, **54**) showed excellent in vivo potency in every efficacy model evaluated. Consistent with results given in Table 2, selected methyl substituted pyridyl compounds (e.g., **44**, **46**, and **54**) were superior to the corresponding non-pyridyl analogues (**35b**, **35c**, and **35d**)[15] in edema and particularly in hyperalgesia models. Thiazole containing compounds **76** and **78** also showed excellent selectivity (for human COX-2) and superb potency in all the models of inflammation and pain.

Pharmacokinetics Studies in Rat. Several compounds with excellent pharmacological properties were examined in the rat to assess their pharmacokinetics (Table 8). Compound **25**, with a half-life of 11.6 h in rat, showed a longer life in dog (88 h). On the other hand, compounds such as (**44**, **46**, and **76**) demonstrated an excellent pharmacology profile and a very favorable terminal phase elimination half-life (3−5 h) in rat (Figure 1). On oral exposure in rat, heteroaromatic compounds (e.g., **25**, **44**, **46**, **76**) generally exhibited higher plasma levels (C_{max}) than observed with **35d**. These compounds (**25**, **44**, **76**) demonstrated excellent bioavailability (>90%) in rat on oral dosing at 20 mg/kg.

Table 8. Pharmacokinetics of Selected 1,2-Diarylimidazoles in Rat

compd	dose (mg/kg)	route of administration	elimination half-life[a] (h)
25	10	iv	11.6
44	10	iv	4.85 ± 1.26
46	10	iv	4.96 ± 0.75
76	2	iv	3.4
35d	2	iv	7.1

[a] Each result is the mean ± SD, 3−4 animals/group.

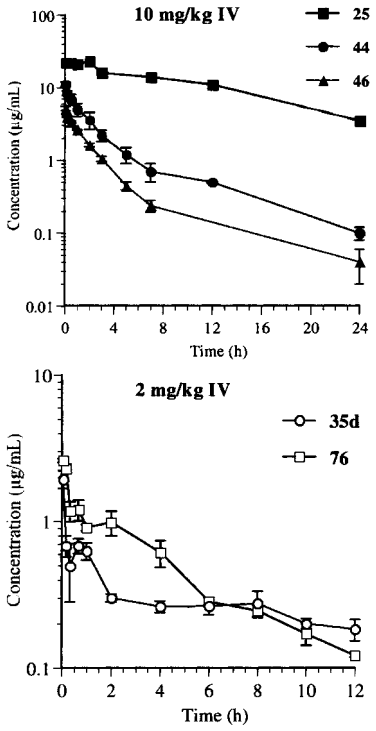


Figure 1. Pharmacokinetics of selected diarylimidazoles in rat.

Gastrointestinal Toxicity Studies. To test the COX-2 hypothesis and to establish their safety profile, the selected compounds from Table 7 were evaluated in acute gastric and intestinal toxicity studies (Table

Table 9. Gastric and Intestinal Toxicity Studies

compd	dose mg/kg (ig)	gastric[a] fasted rat	intestinal[a] fed rat
vehicle[b]		0/6	0/6
25	100	0/6	0/6
44	100	0/6	0/6
46	100	0/6	0/6
54	100	0/6	0/6
76	100	0/6	0/6
indomethacin	16	6/6	6/6

[a] Number of animals with damage/number of animals treated. [b] A total of 0.5% aqueous methylcellulose.

9). No gastric lesions were observed in the fasted rat after 5 h when the listed compounds (**25**, **44**, **46**, **54**, and **76**) were administered intragastrically at 100 mg/kg. Similarly no intestinal bleeding was detected in fed rats after 72 h when these compounds were administered intragastrically at 100 mg/kg. In contrast, indomethacin caused gastric and intestinal lesions in all the animals examined at 16 mg/kg. The compounds **25** and **76** were also evaluated in the chronic model (adjuvant induced arthritis) in rat at 100 mg/kg orally. Neither compound showed any gastrointestinal damage after dosing for 10 days, endorsing the safe profile of these compounds.

Conclusion

The series of 1,2-diarylimidazoles described in this paper are potent and highly selective inhibitors of human cyclooxygenase-2 enzyme. The enzymatic and in vivo data (air-pouch model) on isomeric pyridyl analogues indicates that 2- and 3- pyridyl compounds (**25** and **26**) are significantly more potent than 4-pyridyl analogue **27**. Pyridyl compound **25** also shows excellent antiinflammatory and analgesic properties in every efficacy model. The studies aimed at modulating the extended half-life of **25** resulted in a number of methylated pyridine analogues (e.g., **44**, **46**, **54**) that demonstrate an excellent overall profile in all in vitro and in vivo models (Table 7). Selected pyridyl compounds (e.g., **25**, **44**, **46**, and **54**) were superior to the corresponding non-pyridyl analogues (**35**, **35b**, **35c**, and **35d**) in edema and particularly in the hyperalgesia model (Tables 2, 7). Detailed investigation of the analogues derived from other heteroaromatic systems shows that their potency, selectivity, and in vivo profile are greatly influenced by the substitution pattern. Thiazole derived compounds (e.g., **76** and **78**) are very potent ($IC_{50} = 0.5$ and 0.1 μM, respectively) and selective (IC_{50} COX-1/COX-2 = >2000−9000) inhibitors of the human cyclooxygenase-2 enzyme. These compounds also exhibit superb potency in the adjuvant induced arthritis model ($ED_{50} \sim 0.6$ mg/kg) as well as in the carrageenan induced model of inflammation and hyperalgesia ($ED_{50} = 13-18$ mg/kg, Table 7). In imidazole substitutions, the CF_3 group at C-4 position (Table 5) gives the optimum potency and antiinflammatory properties. Excellent in vivo properties exhibited by a number of compounds (e.g, **44**, **46**, **54**, **76**, **78**) and the absence of GI toxicity in the selected compounds up to 100 mg/kg in rat demonstrates that heteroaryl modified 1,2-dairylimidazoles represent a series of potent 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.[26] The experimental details of the carrageenan induced paw edema and hyperalgesia models in the rat have also been published.[29] The rat adjuvant induced arthritis model was carried out using the procedures described earlier.[28] The gastric and intestinal toxicity studies in the rat and the mouse were conducted using the literature methods.[27,29]

Chemistry (General). NMR spectra were recorded in $CDCl_3$, DMSO-d_6, or MeOH-d_4 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, $\delta = 0.00$ ppm) and expressed in ppm. Infrared spectra were recorded on a Perkin-Elmer model 681 or a Perkin-Elmer model 685 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.

Trimethylaluminum, triethylaluminum, acetonylacetone, triethylborane, 3-bromo-1,1,1-trifluoroacetone, iodomethyltrimethylsilane, sodium bis(trimethylsilyl)amide, 2-chloroacrylonitrile, oxone, ethyl bromopyruvate, 1-bromo-2-methoxypropene, *m*-chloroperbenzoic acid, 4-(methylsulfonyl)aniline, 4-(methylmercapto)aniline, 4-nitro benzenesulfonamide, 5-bromonicotinic acid, methyl 5-hydroxynicotinate, 2-methyl-nicotinic acid, 2-fluoro-5-methyl pyridine, 4-picoline *N*-oxide, 5-methyl isoxazole-3-methanol, 4-methylthiazole-2-carboxaldehyde, 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 Containing a Methyl Sulfone Substituent. All diarylimidazoles containing a methyl sulfone group were prepared following the general Schemes 1−3. The synthesis of 3-[1-{4-(methylsulfonyl) phenyl-4-trifluoromethyl-1*H*-imidazol-2-yl]pyridine (**25**) is described below as an example for methods A and B.

3-[1-{4-(Methylsulfonyl)phenyl}-4-trifluoromethyl-1*H*-imidazol-2-yl]pyridine (25, Method A). Step 1: Preparation of *N*-[4-(Methylthio)phenyl]-3-pyridinecarboxamidamide (Base Catalyzed). To a solution of sodium bis(trimethylsilyl) amide in THF (380 mL, 1 M solution, 0.38 mol) was added dropwise at room temperature a solution of 4-(methylmercapto)aniline (50.0 g, 0.36 mol) in 50 mL of dry THF. After the mixture was stirred for 20 min, a solution of 3-cyanopyridine (39.4 g, 0.38 mol) in 20 mL of dry THF was added. The reaction mixture was stirred for 4 h then poured into 2 L of ice−water. The precipitate was collected by filtration, washed with a solution of ether and hexane (3/7, 300 mL), and air-dried to give 83.7 g of product as a light yellow solid (96% yield): mp (DSC) 157−159 °C; MIR 3275, 3072, 2918, 1661, 1604, 1561, 1482, 1376; ^{1}H NMR (CD_3OD) 8.88 (d, $J = 2$ Hz, 1H), 8.65 (dd, $J = 5$, 2 Hz, 1H), 8.24 (dd, $J = 8$, 2 Hz, 1H), 7.52 (dd, $J = 8$, 5 Hz, 1H), 7.32 (d, $J = 8$ Hz, 2H), 6.97 (d, $J = 8$ Hz, 2H), 2.47 (s, 3H); MS (CI) 244 (MH^+). Anal. ($C_{13}H_{13}N_3S$) C, H, N.

Step 1: Preparation of *N*-[4-(Methylthio)phenyl]-3-pyridinecarboximidamide (Acid Catalyzed). To a suspension of 4-(methylmercapto)aniline (50 g, 0.36 mol) in 1,2-dichloroethane (2 L) at 0 °C was added triethylaluminum (284 mL, 1.9 M solution in toluene, 0.47 mol) over 1 h. The reaction mixture was warmed to room temperature and stirred for 2 h. A solution of 3-cyanopyridine (56.1 g, 0.47 mol) in 1,2-dichloroethane (300 mL) was added over 10 min, and the reaction mixture heated to 70−80 °C. After 18 h, the reaction mixture was cooled to room temperature and poured over a slurry of silica gel (110 g) in chloroform/methanol (4/1, 1 L). After being stirred for 1 h, the mixture was filtered and the residue washed with a mixture of methylene chloride/methanol (4/1, 2 L). The combined filtrates were concentrated in vacuo, and the resulting brownish yellow solid was stirred with a solution of ethyl acetate/ether (4/1, 600 mL). The intermediate was filtered and washed with additional ethyl acetate/ether (4/1). The yellowish solid (53.0 g, 61%), identical to the product obtained above, was used in the next reaction without further purification.

Step 2: Preparation of 4,5-Dihydro-1-[4-(methylthio)-phenyl]-2-(3-pyridinyl)-4-(trifluoromethyl)-1*H*-imidazol-4-ol. To a mixture of *N*-[4-(methylthio)phenyl]-3-pyridinecarboximidamide (65.0 g, 0.27 mol) and sodium bicarbonate (33.6 g, 0.40 mol) in 2-propanol (2.3 L) was added 3-bromo-1,1,1-trifluoroacetone (81.6 g, 0.43 mol). The reaction mixture was heated at 50 °C for 1.5 h and at 75−80 °C for 3 h. The reaction mixture was cooled to room temperature and filtered. Part of the solvent (1.5 L) was removed under reduced pressure, and the mixture cooled to room temperature. The precipitated solid was filtered and washed with 2-propanol (200 mL) and acetonitrile (100 mL) to give 4,5-dihydro-1-[4-(methylthio)-phenyl]-2-(3-pyridinyl)-4-(trifluoromethyl)-1*H*-imidazol-4-ol as a pale yellow solid (60.1 g, 64%): mp (DSC) 192 °C; IR (KBr) 3412, 3034, 2826, 1601, 1581, 1550, 1495, 1400; ^{1}H NMR (DMSO-d_6) 8.60−8.66 (complex band, 2H), 7.84 (dd, J = 8, 2 Hz, 1H), 7.43 (dd, J = 8, 5 Hz, 1H), 7.32 (s, 1H), 7.17 (d, J = 8 Hz, 2H), 6.96 (d, J = 8 Hz, 2H), 4.36 (d, J = 11 Hz, 1H), 3.87 (d, J = 11 Hz, 1H), 2.43 (s, 3H); MS (EI) 353 (M^+). Anal. ($C_{16}H_{14}N_3SOF_3$) C, H, N, S.

Step 3: Preparation of 3-[1-{4-(Methylthio)phenyl}-4-trifluoromethyl-1*H*-imidazol-2-yl]pyridine. A mixture of 4,5-dihydro-1-[4-(methylthio)phenyl]-2-(3-pyridinyl)-4-(trifluoromethyl)-1*H*-imidazol-4-ol (103.3 g, 8.7 mmol) and *p*-toluenesulfonic acid monohydrate (15.5 g) in toluene (2.2 L) was heated to reflux for 4 h. The reaction mixture was cooled and the solvent removed under reduced pressure. The crude residue was redissolved in methylene chloride (900 mL) and treated with aqueous ammonium hydroxide (10%, 1.2 L). The mixture was stirred for 1 h and the organic layer separated. 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) as eluent to give 3-[1-{4-(methylthio)phenyl}-4-trifluoromethyl-1*H*-imidazol-2-yl]pyridine (92.1 g, 94%) as a brown solid: mp (DSC) 93 °C; IR (KBr) 3850, 3152, 3080, 2932, 1633, 1574, 1500, 1452; ^{1}H NMR ($CDCl_3$) 8.52−8.61 (complex band, 2H), 7.82 (dd, J = 8, 2 Hz, 1H), 7.48 (s, 1H), 7.26 (d, J = 8 Hz, 2H), 7.22−7.30 (complex band, 1H), 7.17 (d, J = 8 Hz, 2H), 2.52 (s, 3H); MS (CI) 336 (MH^+). Anal. ($C_{16}H_{12}N_3SF_3 \cdot 0.1H_2O$) C, H, N, S.

Step 4: Preparation of 3-[1-{4-(Methylsulfonyl)phenyl}-4-trifluoromethyl-1*H*-imidazol-2-yl]pyridine (25). A solution of oxone (379 g, 0.62 mol) in water (1.8 L) was added to the product of step 3 (103.2 g, 0.31 mol) in methanol (950 mL). The reaction is slightly exothermic, and the temperature of the reaction was prevented from rising by a surrounding water bath. After being stirred at room temperature for 1 h, the mixture was treated with dilute ammonium hydroxide (10%, 1 L). The contents were stirred for an hour and the precipitated solid filtered and washed with water. The crude mixture was chromatographed (silica gel, ethyl acetate/acetone 98/2) to give pure **1** (90.3 g, 79%) as a white solid: mp (DSC) 193 °C; IR (KBr) 3850, 3155, 3005, 1934, 1578, 1456, 1024; ^{1}H NMR ($CDCl_3$) 8.61 (dd, J = 5, 2 Hz, 1H), 8.53 (d, J = 2 Hz, 1H), 8.06 (d, J = 8 Hz, 2H), 7.82 (dd, J = 8, 2 Hz, 1H), 7.58 (s, 1H), 7.47 (d, J = 8 Hz, 2H), 7.31 (dd, J = 8, 5 Hz, 1H), 3.12 (s, 3H); MS (DCI) 368 (MH^+). Anal. ($C_{16}H_{12}N_3SO_2F_3$) C, H, N, S.

3-[1-{4-(Methylsulfonyl)phenyl}-4-trifluoromethyl-1*H*-imidazol-2-yl]pyridine (25, Method B). Step 1: Preparation of *N*-[4-(Methylsulfonyl)phenyl]-3-pyridinecarboxamidamide. To a suspension of 4-(methylsulfonyl)aniline hydrochloride (6 g, 28.8 mmol) in toluene (150 mL) at 0 °C was added trimethylaluminum (21.6 mL, 2 M solution in toluene, 43.2 mmol) over 15 min. The reaction mixture was warmed to room temperature and stirred for 2.5 h. A solution of 3-cyanopyridine (6.0 g, 57.6 mmol) in toluene (150 mL) was added over 10 min and the reaction mixture heated to 90−95 °C. After 24 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 ethyl acetate (1000 mL). The intermediate was filtered and washed with additional ethyl acetate. The pale yellowish solid (4.5 g, 34%) was used in the next reaction without further purification: mp (DSC) 265 °C; IR (KBr) 3898, 2991, 2916, 1618, 1593, 1564, 1506, 1491; ^{1}H NMR (DMSO-d_6) 9.10 (d, J = 2 Hz, 1H), 8.90 (dd, J = 5, 2 Hz, 1H), 8.37 (dd, J = 8, 5 Hz, 1H), 8.07 (d, J = 8 Hz, 2H), 7.66−7.76 (complex band, 3H), 3.27 (s, 3H); MS (DCI) 276 (MH^+). Anal. ($C_{13}H_{13}N_3SO_2 \cdot HCl \cdot 0.5H_2O$) C, H, N.

Step 2: Preparation of 4,5-Dihydro-1-[4-(methylsulfonyl)phenyl]-2-(3-pyridinyl)-4-(trifluoromethyl)-1*H*-imidazol-4-ol. To a mixture of amidine of step 1 (4.4 g, 16 mmol) and sodium bicarbonate (2.7 g, 32 mmol) in 2-propanol (400 mL) was added 3-bromo-1,1,1-trifluoroacetone (2.5 mL, 24 mmol). The reaction mixture was heated at 70−75 °C for 36 h, cooled to room temperature, and filtered. The residue was washed with methylene chloride, and the combined organic fractions were dried over sodium sulfate, filtered, and concentrated. The crude mixture (16.2 g) was chromatographed (silica gel, ethyl acetate/acetone (98:2) to give 4,5-dihydro-1-[4-(methylsulfonyl)phenyl]-2-(3-pyridinyl)-4-(trifluoromethyl)-1*H*-imidazol-4-ol (3.7 g, 60%) as a white solid: IR (KBr) 3854, 3752, 3676, 1585, 1498, 1466, 1419; ^{1}H NMR ($CDCl_3$) 9.12 (d, J = 2 Hz, 1H), 8.72 (dd, J = 5, 2 Hz, 1H), 7.82 (d, J = 8 Hz, 2H), 7.76 (dt, J = 8, 2 Hz, 1H), 7.34 (dd, J = 8, 5 Hz, 1H), 7.02 (d, J = 8 Hz, 2H), 4.40 (d, J = 11 Hz, 1H), 4.13 (d, J = 11 Hz, 1H), 3.04 (s, 3H); MS (EI) 385 (M^+). Anal. ($C_{16}H_{14}N_3SO_3F_3 \cdot 0.75H_2O$) C, H, N.

Step 3: Preparation of 3-[1-{4-(Methylsulfonyl)phenyl}-4-trifluoromethyl-1*H*-imidazol-2-yl]pyridine (25). A mixture of the product of step 2 (4.3 g, 11.2 mmol) and *p*-toluenesulfonic acid monohydrate (0.9 g, 4.73 mmol) in toluene (300 mL) was heated to reflux for 48 h. The reaction mixture was cooled and the solvent removed under reduced pressure. The crude residue was purified by chromatography on silica gel using ethyl acetate/acetone (98/2) to give pure **25** (2.3 g, 56%) as a white solid, identical in properties to the product described in step 4, method A.

All diarylimidazoles (**25**−**27**, **33**−**42**, **50**−**53**, **64**−**71**, **73**−**75**, and **79**) containing a methylsulfonyl group and a CF_3 group at position-4 of the imidazole ring were prepared by utilizing one of the methods described above. The experimental procedures given for method A generally gave superior yields and were preferred. The amidine formation was carried preferentially using the base-catalyzed process detailed in step 1, method A. Diarylimidazoles (**58**−**62**) containing different substituents at C-4 of imidazole ring were prepared by modifications of these conditions (vide infra).

General Procedure for the Preparation of 1,2-Diarylimidazoles Containing a Sulfonamide Substituent. All 1,2-diarylimidazoles with a sulfonamide group in the aryl rings were prepared following the general Schemes 5 and 6. The syntheses of **43**, **76,** and **46** are used as examples to describe the procedures (methods A, B, and C, respectively).

4-[2-(3-Pyridinyl)-4-(trifluoromethyl)-1*H*-imidazol-1-yl]benzenesulfonamide (43, Method A). Step 1: Prepara-

tion of 3-[4-(Trifluoromethyl)-1-[4-{(2-trimethyl silyl)-ethyl}sulfonyl]phenyl]-1*H*-imidazol-2-yl]pyridine. To diisopropylamine (2.48 mL, 18 mmol) in 20 mL of dry THF at 0 °C was added BuLi (8.6 mL, 1.90 M solution in hexane, 16 mmol). The solution was stirred for 5 min and then cooled to −78 °C with dry ice/2-propanol bath. A solution of **25** (5.0 g, 14 mmol) in 30 mL of dry THF was added over 10 min and the reaction mixture stirred for 1 h. (Iodomethyl)trimethylsilane (4.37 g, 20 mmol) was added dropwise and the mixture stirred overnight while allowing to warm to room temperature. The reaction was quenched with 200 mL of 1 N HCl and the aqueous phase extracted with ethyl acetate (3 × 60 mL). The combined organic fractions were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by chromatography on silica gel (ethyl acetate/hexane, 65:35) to give 4.36 g of 3-[4-(trifluoromethyl)-1-[4-{(2-trimethylsilyl)ethyl}sulfonyl]phenyl]-1*H*-imidazol-2-yl]pyridine as a white solid (71%): mp (DSC) 177−178 °C; ^{1}H NMR ($CDCl_3$) 8.57 (dd, J = 5, 2 Hz, 1H), 8.53 (dd, J = 2, 1 Hz, 1H), 7.96 (d, J = 8.5 Hz, 2H), 7.73 (m, 1H), 7.54 (m, 1H), 7.42 (d, J = 8.5 Hz, 2H), 7.25 (dd, J = 8, 5 Hz, 1H), 3.00 (m, 2H), 0.92 (m, 2H). Anal. ($C_{21}H_{24}F_3N_3O_2SSi$) C, H, N.

Step 2: Preparation of 4-[2-(3-Pyridinyl)-4-(trifluoromethyl)-1*H*-imidazol-1-yl]benzenesulfonamide (43). To a solution of the product of step 1 (4.28 g, 9.4 mmol) in 25 mL of dry THF was added tetrabutylammonium fluoride (28.3 mL, 1 M solution in THF, 28 mmol). The mixture was refluxed for 1 h and cooled to room temperature. A solution of sodium acetate (3.66 g, 47 mmol) in 10 mL of water and hydroxylamine-*O*-sulfonic acid (5.56 g, 47 mmol) were added sequentially, and the mixture was stirred for 1 h. The reaction mixture was quenched by adding water (50 mL) and extracted with ethyl acetate. The organic fractions were washed sequentially with saturated $NaHCO_3$ solution, water, and brine. After drying ($MgSO_4$) and filtration, the mixture was concentrated and the residue purified by chromatography on silica gel (ethyl acetate/acetone, 95:5) to give 2.77 g of **43** as a colorless solid (80%): mp 219−221 °C; IR (KBr) 3319, 3177, 3092, 3013, 1599, 1579, 1516, 1498; ^{1}H NMR (CD_3OD) 8.53 (br s, 2H), 8.07 (m, 1H), 7.97 (d, J = 8.5 Hz, 2H), 7.81 (ddd, J = 8, 2, 1.6 Hz, 1H), 7.53 (d, J = 8.5 Hz, 2H), 7.40 (dd, J = 8, 5 Hz, 1H); MS (DCI) 369 (MH^+). Anal. ($C_{15}H_{11}F_3N_4O_2S$) C, H, N, S.

4-[2-(2-Methylthiazol-4-yl)-4-(trifluoromethyl)-1*H*-imidazol-1-yl]benzenesulfonamide (76, Method B). The process shown in Scheme 6 utilizes **14** for amidine formation. A two-step preparation of **14** is shown following the synthesis of the target compound **76**.

Step 1: Preparation of *N*-[4-{(2,5-Dimethyl-1*H*-pyrrol-1-yl)sulfonyl} phenyl]-2-methyl-4-thiazolecarboximidamimide. To sodium bis(trimethylsilyl)amide (80 mL, 1 M solution in THF, 80 mmol) was added dropwise at room temperature a solution of **14** (20 g, 80 mmol) in 200 mL of dry THF. After the darkened reaction mixture was stirred for 10 min, a solution of 2-methylthiazole-4-carbonitrile (10.6 g, 84.8 mmol) in 50 mL of dry THF was added. The reaction mixture was stirred for 16 h and poured into 500 mL of ice−water and stirred for 10 min. The brownish solid precipitated and was filtered, washed with hexane, and dried to give *N*-[4-{(2,5-dimethyl-1*H*-pyrrol-1-yl)sulfonyl}phenyl]-2-methyl-4-thiazolecarboximidamimide (25.6 g, 85%). The product obtained was used in the next step without additional purification: mp (DSC) 197 °C; MIR 3491, 3374, 3082, 2923, 1654, 1581, 1484, 1357; ^{1}H NMR (DMSO-d_6) 8.07 (s, 1H), 7.63 (d, J = 8 Hz, 2H), 7.04 (d, J = 8 Hz, 2H), 6.72 (br s, 1H), 5.93 (s, 2H), 2.68 (s, 3H), 2.36 (s, 6H); MS (CI) 375 (MH^+). Anal. ($C_{17}H_{18}N_4S_2O_2$) C, H, N, S.

Step 2: Preparation of 1-[[4-{4,5-Dihydro-4-hydroxy-2-(2-methyl-4-thiazolyl)-4-(trifluoromethyl)-1*H*-imidazol-1-yl}phenyl]sulfonyl]-2,5-dimethyl-1*H*-pyrrole. To a suspension of the amidine obtained in step 1 (0.5 g, 1.3 mmol) and sodium bicarbonate (110 mg, 1.3 mmol) in 2-propanol (3 mL) was added 3-bromo-1,1,1-trifluoroacetone (200 mL, 1.9 mmol). The reaction mixture was heated at 80 °C for 16 h, cooled to room temperature, filtered, and concentrated. The crude mixture was chromatographed (silica gel, ethyl acetate/toluene 1:1) to give 1-[[4-{4,5-dihydro-4-hydroxy-2-(2-methyl-4-thiazolyl)-4-(trifluoromethyl)-1*H*-imidazol-1-yl}phenyl]sulfonyl-2,5-dimethyl-1*H*-pyrrole (0.32 g, 49%) as a brownish solid: mp (DSC) 221 °C; MIR 3123, 1593, 1581, 1517, 1499, 1363; ^{1}H NMR (DMSO-d_6) 8.14 (s, 1H), 7.58 (d, J = 8 Hz, 2H), 7.43 (br s, 1H), 6.97 (d, J = 8 Hz, 2H), 5.93 (s, 2H), 4.47 (d, J = 12 Hz, 1H), 3.94 (d, J = 12 Hz, 1H), 2.49 (s, 3H), 2.30 (s, 6H); MS (CI) 485 (MH^+). Anal. ($C_{20}H_{19}N_4S_2O_3F_3$) C, H, N, S.

Step 3: Preparation of 2,5-Dimethyl-1-[[4-{2-(2-methyl-4-thiazolyl)-4-(trifluoromethyl)-1*H*-imidazol-1-yl}phenyl]-sulfonyl]-1*H*-pyrrole. A mixture of the product from step 2 (6.1 g, 12.6 mmol) and *p*-toluenesulfonic acid monohydrate (0.91 g) in toluene (50 mL) was refluxed with a Dean−Stark trap for 19 h. The reaction mixture was cooled and the solvent removed under reduced pressure. The crude residue was dissolved in methylene chloride and washed with saturated sodium bicarbonate solution, dried over sodium sulfate, and filtered. The combined organic fractions were concentrated and the crude mixture purified by chromatography on silica gel (ethyl acetate/toluene, 3/7) to give 2,5-dimethyl-1-[[4-{2-(2-methyl-4-thiazolyl)-4-(trifluoromethyl)-1*H*-imidazol-1-yl}phenyl]-sulfonyl]-1*H*-pyrrole as a brownish solid (4.9 g, 83%): mp (DSC) 205 °C; MIR 3157, 3120, 2958, 2927, 1597, 1576, 1500, 1360; ^{1}H NMR ($CDCl_3$) 7.72 (d, J = 8 Hz, 2H), 7.67 (s, 1H), 7.43 (s, 1H), 7.40 (d, J = 8 Hz, 2H), 5.90 (s, 2H), 2.47 (s, 3H), 2.42 (s, 6H); MS (CI) 467 (MH^+). Anal. ($C_{20}H_{17}N_4S_2O_2F_3$) C, H, N, S.

Step 4: Preparation of 4-[2-(2-Methylthiazol-4-yl)-4-(trifluoromethyl)-1*H*-imidazol-1-yl]benzenesulfonamide (76). A mixture of the product from step 3 (5.6 g, 12 mmol) in trifluoroacetic acid (90 mL) and water (30 mL) was refluxed for 3 h. Trifluoroacetic acid was removed by distillation and the residue neutralized with saturated aqueous potassium carbonate. The product was extracted with methylene chloride (3 × 500 mL) and later with ether/acetone 8/2 (3 × 200 mL). The combined organic fractions were combined, dried over $MgSO_4$, and filtered. The filtrate was concentrated and the resulting crude residue purified by chromatography (silica gel, ethyl acetate/toluene, 6/4) to give **76** as a white solid (3.6 g, 77%): mp (DSC) 252 °C; IR (KBr) 3314, 1582, 1501, 1454, 1404, 1364; ^{1}H NMR ($CDCl_3$) 8.02 (d, J = 8 Hz, 2H), 7.58 (s, 1H), 7.46 (d, J = 8 Hz, 2H), 7.43 (s, 1H), 2.54 (s, 3H); MS (APCI) 389 (MH^+). Anal. ($C_{14}H_{11}N_4S_2O_2F_3$) C, H, N, S.

The synthesis of intermediate 1-[(4-aminophenyl)sulfonyl]-2,5-dimethyl-1*H*-pyrrole (**14**) used in the preparation above (step 1) is shown below.

Step 1: Preparation of 2,5-Dimethyl-1-[(4-nitrophenyl)sulfonyl]-1*H*-pyrrole (13). A mixture of 4-nitrobenzenesulfonamide (30.3 g, 0.15 mol), acetonylacetone (34.2 g, 0.30 mol), and *p*-toluenesulfonic acid (3.0 g) in 200 mL of toluene was refluxed under nitrogen using a Dean−Stark trap for 18 h. The reaction was cooled and then filtered through a silica gel column (700 g) followed by elution with ethyl acetate/hexane (3/7). The combined organic fractions containing the desired product were concentrated to give crude product as a brown solid. The crude solid was dissolved in hot ethyl acetate and boiled with activated charcoal. After filtration and concentration, the crude obtained was recrystallized from ethyl acetate/hexane to afford **13** as a light yellow solid (32.5 g, 77%): mp (DSC) 101−103 °C; ^{1}H NMR ($CDCl_3$) 8.34 (d, J = 8.5 Hz, 2H), 7.80 (d, J = 8.5 Hz, 2H), 5.92 (s, 2H), 2.38 (s, 6H). Anal. ($C_{12}H_{12}N_2O_4S$) C, H, N, S.

Step 2: Preparation of 1-[(4-Aminophenyl)sulfonyl]-2,5-dimethyl-1*H*-pyrrole (14). A mixture of **13** (7.3 g, 26 mmol) and Raney-nickel (0.7 g) in 70 mL of methanol was hydrogenated using a Parr apparatus at 50 psi. After 3 h, the catalyst was filtered and the filtrate concentrated to give **14** as a pale yellow solid (6.4 g, 98%): mp (DSC) 114 °C; MIR 3487, 3388, 1630, 1594, 1504, 1351, 1166; ^{1}H NMR ($CDCl_3$) 7.48 (d, J = 8.5 Hz, 2H), 6.63 (d, J = 8.5 Hz, 2H), 5.81 (s, 2H), 4.17 (br s, 2H), 2.40 (s, 6H); MS (APCI) 251 (MH^+). Anal. ($C_{12}H_{14}N_2O_2S$) C, H, N, S.

Method C, Synthesis of 4-[2-(3-Methylnicotinyl)-4-(trifluoromethyl)-1*H*-imidazol-1-yl}benzenesulfonamide (46). To a clear solution of **38** (0.75 g, 1.9 mmol) in tetrahydrofuran (25 mL) at 0 °C was added *n*-BuMgCl (24.8 mL, 2 M solution in THF, 49.6 mmol) slowly. After the mixture was stirred for an additional 15 min, the ice bath was removed and the solution stirred at room temperature for 2 h. The reaction mixture was re-cooled to 0 °C and triethylborane (9.5 mL, 1 M solution in THF, 9.5 mmol) was added. After being stirred for 2 h, the reaction was refluxed for 72 h. The reaction mixture was cooled to room temperature and treated with aqueous sodium acetate (2.3 g in 10 mL water). After the mixture was stirred for 5 min, solid hydroxylamine-*O*-sulfonic acid (2.3 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 magnesium sulfate, filtered, and concentrated. The crude solid was purified by chromatography (silica gel, toluene/2-propanol, 95/5) to give **46** (0.07 g, 8%) as a white solid: mp 242−243 °C; IR (KBr) 3320, 3177, 3092, 3013, 1599, 1580, 1516, 1499, 1441, 1406, 1361, 1346, 1288, 1255, 1219, 1167, 1122, 1028; ^{1}H NMR (CD_3OD) 8.48 (s, 1H), 8.33 (s, 1H), 8.16 (t, J = 1.2 Hz, 1H), 8.07 (d, J = 8.8 Hz, 2H), 7.82 (m, 1H), 7.62 (d, J = 8.8 Hz, 2H), 2.48 (s, 3H); MS (CI) 383 (MH^+). Anal. ($C_{16}H_{13}F_3N_4O_2S$) C, H, N, S.

All diarylimidazoles (**43**−**49**, **54**−**57**, **63**, **72**, **76**−**78**, **80**) containing a sulfonamide group in the aryl ring were prepared using one of the methods shown above. Methods A and B generally gave superior yields and were preferred.

Syntheses of Aryl Nitriles (3a−3q). The aryl nitriles used in the Schemes 1, 2, and 6 were either purchased commercially or prepared (Scheme 4) as follows:

3-Cyano-2-methylpyridine (3a) was prepared from 2-methylnicotinic acid as described below.

Step 1: Preparation of 2-Methylnicotinamide. To a stirred mixture of 2-methylnicotinic acid (15.0 g, 0.11 mol) and 1,1′-carbonyldiimidazole (36.0 g, 0.22 mol) was slowly added 300 mL of methylene chloride, and the mixture was stirred at room temperature overnight. Excess of ammonia gas was passed through the reaction using a dry ice condenser for about half an hour. After the reaction mixture was stirred at room temperature for an additional hour, the solvent was removed under vacuum. The residue obtained was dissolved in 500 mL of acetonitrile. The solution was concentrated to about half the volume and cooled. The precipitated white solid was filtered and recrystallized from ethanol/ether to give pure 2-methylnicotinamide as a colorless crystal (11.5 g, 76%): mp 160−163 °C; ^{1}H NMR (DMSO-d_6) 8.48 (dd, J = 5, 2 Hz, 2H), 7.90 (br s, 1H), 7.74 (dd, J = 8, 2 Hz, 1H), 7.55 (br s, 1H), 7.26 (dd, J = 8, 5 Hz, 2H), 2.54 (s, 3H). Anal. ($C_7H_8N_2O$) C, H, N.

Step 2: Preparation of 3-Cyano-2-methylpyridine (3a). To a suspension of 2-methylnicotinamide (11.1 g, 0.08 mol) in triethylamine (24.8 g, 0.24 mol) and 400 mL of methylene chloride was added trifluoroacetic anhydride (21.0 g, 0.10 mol) rapidly at 0 °C. The reaction was completed within minutes. The reaction was quenched by adding water and extracted with methylene chloride. The combined organic layers were washed with water and brine and dried over magnesium sulfate. After filtration, the filtrate was concentrated and the residue purified by chromatography on silica gel (ethyl acetate/hexane, 1:1) to give 3-cyano-2-methylpyridine (**3a**) as a pale yellow solid (7.2 g, 75%): mp 56−58 °C; ^{1}H NMR ($CDCl_3$) 8.72 (dd, J = 5, 2 Hz, 1H), 7.94 (dd, J = 8, 2 Hz, 1H), 7.29 (dd, J = 8, 5 Hz, 1H), 2.28 (s, 3H).

3-Cyano-5-methylpyridine (3b) was prepared from 5-methylnicotinamide[30] using the procedure described for preparation of **3a** (step 2).

3-Cyano-5-methoxypyridine (3c) was prepared from methyl 5-hydroxy nicotinic acid using the procedure described below.

Step 1: Preparation of 5-Methoxynicotinic Acid. To a suspension of sodium methoxide (4.21 g, 0.078 mol) in 125 mL of DMF was added dropwise at room temperature a solution of methyl 5-hydroxynicotinate (11.34 g, 0.074 mol) in DMF (25 mL). After the mixture was stirred for 30 min, iodomethane (11.07 g, 0.078 mol) was added and the reaction mixture stirred overnight. The solvent was removed under vacuum and the residue partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated to give 4.1 g of product as a pale yellow solid (33% yield). A mixture of the above product (4.0 g, 0.024 mol) and sodium hydroxide (3.8 g, 0.096 mol) in 200 mL of ethanol was refluxed for 3 h. After removal of the solvent, the residue was dissolved in 40 mL of water and acidified with 2 N HCl. The precipitate was filtered to give 3.65 g of 5-methoxynicotinic acid as a white solid (quantitative): mp 235−237 °C; ^{1}H NMR (CD_3OD) 8.62 (d, J = 1.5 Hz, 1H), 8.38 (d, J = 3.0 Hz, 1H), 7.33 (dd, J = 3, 1.5 Hz, 1H), 3.94 (s, 3H). Anal. ($C_7H_7NO_3 \cdot 0.1H_2O$) C, H, N.

Step 2: Preparation of 3-Cyano-5-methoxypyridine (3c). A suspension of methyl 5-methoxynicotinic acid (3.6 g, 0.024 mol) in 50 mL of thionyl chloride was refluxed overnight. After removal of the excess thionyl chloride, the residue was suspended in 40 mL of dichloroethane. Ammonia gas was bubbled into the reaction mixture at −30 °C for 15 min and the mixture warmed to room temperature. The solvent was removed under vacuum and the residue treated with hot ethanol. After filtration, the filtrate was concentrated to give 3.0 g of 5-methoxynicotinamide as a yellow solid. To a mixture of the crude amide (3.0 g, 0.02 mol) and triethylamine (6.61 g, 0.06 mol) in 125 mL of dichloromethane was added trifluoroacetic anhydride (5.38 g, 0.026 mol) rapidly at 0 °C. After the mixture was stirred for 30 min, the reaction was quenched by adding 200 mL of water. The aqueous phase was extracted with more dichloromethane. The combined organic layers were washed with brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated to give 2.5 g of product as a brown solid (93% yield): mp 98−100 °C; ^{1}H NMR ($CDCl_3$) 8.52 (d, J = 2 Hz, 1H), 8.49 (d, J = 3.0 Hz, 1H), 7.42 (dd, J = 3, 2 Hz, 1H), 3.92 (s, 3H).

The intermediate **3d** was prepared from 5-bromonicotininc acid using procedures described for **3a**. Similarly the intermediate **3e** was prepared following the reported methodology.[17]

3-Cyano-6-methoxypyridine (3f). To a solution of 6-methoxy-3-bromopyridine[18] (11 g, 58.5 mmol) in DMF (250 mL) was added CuCN (7.8 g, 87.8 mmol), and the mixture was heated to 120 °C for 24 h. The reaction mixture was cooled and filtered. The crude residue was washed with methylene chloride, and combined organic fractions were washed successively with water and brine. After drying over sodium sulfate, the organic fractions were filtered and concentrated. The crude greenish solid (12.7 g) was purified by chromatography (silica gel, hexane/ethyl acetate, 9/1) to give the recovered starting 6-methoxy-3-bromo pyridine (2.5 g, 23%) and the desired **3f** (1.85 g, 24%): mp (DSC) 97 °C; IR (KBr) 3429, 3080, 3011, 2569, 2229, 1996, 1603, 1562, 1495, 1448; ^{1}H NMR ($CDCl_3$) 8.50 (d, J = 2 Hz, 1H), 7.77 (dd, J = 8, 2 Hz, 1H), 6.82 (d, J = 5 Hz, 1H), 4.02 (s, 3H); MS (EI) 134 (M^+). Anal. ($C_7H_6N_2O$) C, H, N.

3-Cyano-6-methylpyridine (3g) was prepared in two steps by starting with 6-methyl-2-pyridinecarboxaldehyde and using the following procedure.

Step 1: Preparation of 6-Methyl-2-pyridinecarboxaldehyde, Oxime. To a mixture of hydroxylamine hydrochloride (2.89 g, 41.5 mmol) and pyridine (3.4 mL, 41.5 mmol) was added 6-methyl-2-pyridinecarboxaldehyde (5.0 g, 41.5 mmol) in installments over 5 min. The reaction mixture was stirred at room temperature for 20 min. Toluene (100 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. The residue obtained was suspended in water and extracted with ether. The combined ether fractions were dried over sodium sulfate, filtered, and concentrated. The crude mixture (4.45 g) was chromatographed (silica gel, hexane/ethyl acetate 8/2) to give 6-methyl-2-pyridine carboxaldehyde, oxime (3.9 g, 69%) as a white solid: IR (KBr) 3429, 3273, 2990, 2712, 1907, 1682, 1590, 1577; ^{1}H NMR (CD_3OD) 8.07 (s, 1H), 7.62−7.74 (complex band, 2H), 7.24 (dd, J = 8, 2

Hz, 1H), 2.52 (s, 3H); MS (EI) 136 (M^+). Anal. ($C_7H_6N_2O \cdot 0.2H_2O$) C, H, N.

Step 2: Preparation of 3-Cyano-6-methylpyridine (3g). The oxime (3.5 g, 25.7 mmol) obtained in step 1 was refluxed in acetic anhydride (20 mL) for 48 h. The solvent was removed under reduced pressure, and the resulting dark residue was treated with cold aqueous potassium carbonate. After extraction with methylene chloride (2 × 100 mL), the combined organic fractions were dried (sodium sulfate), filtered, and concentrated. The resulting dark brown solid (2.8 g) was chromatographed (silica gel, hexane/ethyl acetate 75/25) to give **3g** (2.3 g, 76%) as a white solid: mp (DSC) 74 °C; IR (KBr) 3439, 3063, 2359, 2233, 1990, 1589, 1460, 1446, 1379; ^{1}H NMR ($CDCl_3$) 7.74 (t, J = 8 Hz, 1H), 7.52 (dd, J = 8, 2 Hz, 1H), 7.38 (dd, J = 8, 2 Hz, 1H), 2.62 (s, 3H); MS (EI) 118 (M^+). Anal. ($C_7H_6N_2 \cdot 0.15H_2O$) C, H, N.

2-Cyano-5-methylpyridine (3h). 2-Fluoro-5-methylpyridine (39 g, 0.35 mol) and sodium cyanide (17.23 g, 0.35 mol) were added to 141 mL of DMSO and heated to 150 °C for 3 days. An additional 3 g (61.2 mmol) of sodium cyanide was added, and heating was continued for 5 h. The reaction was cooled and poured into 525 mL of ice water. The solution was filtered through a coarse fritted funnel. A dark brown solid was collected and air-dried. The solid was dissolved in methylene chloride, dried over $MgSO_4$, filtered, and concentrated to give 17 g (41%) of **3h** which was used in the next step without further purification: ^{1}H NMR ($CDCl_3$) 8.54 (s, 1H), 7.58−7.64 (complex band, 2H), 2.43 (s, 3H). Anal. ($C_7H_6N_2 \cdot 0.1H_2O$) C, H, N.

2-Cyano-4-methylpyridine (3i). 4-Picoline *N*-oxide (13.6 g; 0.124 mole) was suspended in 82 mL of THF under an inert atmosphere. To this solution were added cyanotrimethylsilane (20.1 mL, 0.15 mol) and DBU (4.32 g, 0.028 mol) in succession. The reaction mixture was stirred at 25 °C for 12 h and then refluxed for 4−5 h. After cooling to room temperature, the solvent was removed under reduced pressure. The resulting dark solid was dissolved in methylene chloride and applied to a bed of florisil in a 600 mL coarse-fritted funnel eluting with methylene chloride. The desired organic fractions were combined and concentrated to give **3i** (6.4 g, 44%): MIR 3049, 3026, 2979, 2926, 2234, 1599, 1470, 1444, 1297; ^{1}H NMR ($CDCl_3$) 8.56 (d, J = 5 Hz, 1H), 7.52 (s, 1H), 7.3 3 (d, J = 4 Hz, 1H), 2.44 (s, 3H). Anal. ($C_7H_6N_2$) C, H, N.

The compounds **3j**−**3m** were synthesized using the procedure described for **3g**. The aldehyde intermediates needed for their synthesis were purchased commercially.

2-Methyl-5-cyanothiazole (3n). Step 1: Preparation of 2-Methyl-5-thiazolecarboxaldehyde (4c). To a solution of thioacetamide (9.6 g, 63.6 mmol) in tetrahydrofuran (100 mL) were added *N*,*N*-diisopropylethylamine (11 mL, 63.6 mmol) and bromomalonaldehyde.[31] After the reaction mixture was stirred at room temperature for 36 h, the solvent was removed. The residue was dissolved in methylene chloride and washed with aqueous sodium bicarbonate and water. The combined organic fractions were dried ($MgSO_4$), filtered, and concentrated to give a dark brown liquid (10.9 g). Chromatography (silica gel, ethyl acetate/acetone 98/2) of the crude mixture gave pure **4c** (2.3 g, 28%): ^{1}H NMR ($CDCl_3$) 9.92 (s, 1H), 8.82 (s, 1H), 2.74 (s, 3H). Anal. ($C_5H_5NOS \cdot 0.75H_2O$) C, H, N.

Step 2: Preparation of 2-Methyl-5-cyanothiazole (3n). The compound was prepared from **4c** by following the procedure described for **3g**: ^{1}H NMR ($CDCl_3$) 8.08 (s, 1H), 2.72 (s, 3H). Anal. ($C_5H_4N_2S \cdot 0.25H_2O$) C, H, N.

4-Methylthiazole-2-carbonitrile (3o). Step 1: Preparation of 4-Methyl-2- thiazolecarboxaldehyde. To an oven-dried, three-neck flask equipped with a nitrogen inlet and an addition funnel were added butyllithium (42 mL, 2.5 M solution in THF, 100.5 mmol) and 100 mL of anhydrous ether. A solution of 4-methylthiazole (10 g, 100 mmol) in 25 mL of anhydrous ether was added over a 30 min period. At no time during the addition was the temperature allowed to rise above −68 °C. After the mixture was stirred at −78 °C for 1.5 h, a solution of *N*,*N*-dimethylformamide (10.6 g, 150 mmol) in 24 mL of ether was added all at once. The reaction solution was warmed slowly to 16 °C over a 12 h period and quenched carefully with ice and 72 mL of 4 N hydrochloric acid. The reaction mixture was transferred to a separatory funnel and diluted with an additional 100 mL of ether. The ether layer was washed with an additional 2 × 50 mL of 4 N hydrochloric acid. The pH of the aqueous layer was adjusted to 7.5 with solid sodium bicarbonate and extracted with 2 × 150 mL of ether. The organic extracts were dried ($MgSO_4$), filtered, and concentrated at room temperature to give 4-methyl-2-thiazolecarboxaldehyde as a yellow oil (9.1 g, 72%): MIR 3101, 2960, 2928, 1684, 1596, 1500, 1439, 1300, 1259, 1239, 1154; ^{1}H NMR ($CDCl_3$) 9.96 (s, 1H), 7.34 (s, 1H), 2.58 (s, 3H); MS (EI) 127 (M^+).

Step 2: Preparation of 4-Methyl-2-thiazolecarboxaldehyde, Oxime. To a solution of 4-methyl-2-thiazolecarboxaldehyde (14.2 g, 110 mmol) in 8.89 mL of pyridine (8.70 g, 110 mmol) was added hydroxylamine hydrochloride (7.64 g, 110 mmol). After being stirred at room temperature for 12 h, the reaction mixture was diluted with 200 mL of methylene chloride and extracted with 2 × 50 mL of water. The organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide an orange solid, which was washed with methylene chloride to remove the pyridinium hydrochloride. The crude, obtained (7.2 g, 46%) as mixture of *syn*- and *anti*-oximes, was used in the next reaction without further purification: mp 125 °C; MIR 2989, 1442, 1231, 1018; ^{1}H NMR (DMSO-d_6) 12.35 (br s, 1H), 11.96 (br s, 1H), 8.26 (s, 1H), 7.93 (s, 1H), 7.53 (s, 1H), 7.28 (s, 1H), 2.42 (s, 3H), 2.38 (s, 3H); MS (DCI) 143 (MH^+). Anal. ($C_5H_6N_2OS$) C, H, N.

Step 3: Preparation of 4-Methyl-2-thiazolecarbonitrile (3o). The oxime (6.37 g, 51 mmol) obtained in step 2 was dissolved in 25 mL of dioxane and 18 mL of anhydrous pyridine. The solution was cooled to 0 °C, and 7.9 mL of trifluoroacetic anhydride (11.7 g, 56 mmol) was added dropwise so that the reaction temperature did not rise above 7 °C. The reaction mixture was warmed to room temperature and stirred for 12 h. The reaction was diluted with 200 mL of methylene chloride and washed with 8 × 35 mL of water. The organic extracts were washed with brine (35 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide an oil. The crude mixture was chromatographed (silica gel, ethyl acetate/hexane 1/3) to provide **3o** as a yellow solid (4.56 g, 72%): mp (DSC) 196 °C; MIR 3123, 2929, 2227, 1700, 1501, 1491, 1406, 1169, 1115; ^{1}H NMR ($CDCl_3$) 7.26 (s, 1H), 2.55 (s, 3H); MS (EI) 124 (M^+).

5-Methyl-3-isoxazolecarbonitrile (3p). Step 1: Preparation of 5-Methyl-3- isoxazolecarboxaldehyde. To a three-neck flask equipped with nitrogen inlet, addition funnel, and temperature probe were added oxalyl chloride (102 mL, 2.0 M solution in methylene chloride, 204 mmol) and 305 mL of methylene chloride. After cooling to −78 °C, a solution of DMSO (34.9 g, 447 mmol) in 88 mL of methylene chloride was added slowly so that the temperature did not rise above −68 °C. After 10 min, a solution of 5-methylisoxazole-3-methanol (21 g, 186 mmol) in 168 mL of methylene chloride was added and the reaction stirred at −78 °C. The reaction was stirred for 15 min, and triethylamine (130 mL, 931 mmol) was added all at once. The reaction was warmed to room temperature, poured into 400 mL of water, and extracted with 400 mL of methylene chloride. The organic extracts were dried ($MgSO_4$), filtered, and concentrated to provide 5-methyl-3-isoxazolecarboxaldehyde as a brown oil (13.5 g, 59%). The compound was stored at −78 °C and was used in the next step without additional purification: ^{1}H NMR ($CDCl_3$) 10.12 (s, 1H), 6.41 (s, 1H), 2.54 (s, 3H).

Step 2: Preparation of 5-Methyl-3-isoxazolecarbonitrile (3p). 5-Methylisoxazole-3-carboxaldehyde was converted to **3p** using procedures described in steps 2 and 3 of compound **3o**: MIR 3142, 2258, 1591, 1434, 1407, 1245, 1005, 931, 803; ^{1}H NMR ($CDCl_3$) 6.35 (s, 1H), 2.51 (s, 3H); MS (EI) 108 (M^+).

2-Methyl-4-oxazolecarbonitrile (3q). Step 1: Preparation of Ethyl *N*-(Cyanomethyl)ethanimidate (4e). To a suspension of ethyl acetimidate hydrochloride (24.6 g, 20 mmol) in ether (50 mL) was added anhydrous potassium

carbonate (27.6 g, 20 mmol). After stirring for 5 min, a solution of aminoacetonitrile hydrochloride (18. 5 g, 20 mmol) in water (40 mL) was added and the mixture stirred for additional 90 min. The reaction was diluted with water (100 mL) and extracted with ether (2 × 300 mL). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated to give a crude liquid (14.8 g). Distillation of the crude mixture under reduced pressure (<65 °C) gave **4e** (10.2 g, 40%) as a colorless liquid which solidifies on standing in the refrigerator: MIR (KBr) 3995, 3970, 3945, 3380, 2395, 1650, 1601, 1512, 1409, 1373, 1283; ^{1}H NMR ($CDCl_3$) 4.16 (s, 2H), 4.10 (q, J = 7 Hz, 2H), 1.97 (s, 3H), 1.26 (t, J = 7 Hz, 3H).

Step 2: Preparation of 2-Methyl-4-oxazolecarbonitrile (3q). To a solution of **4e** (13 g, 0.1 mol) in THF (150 mL) at −10 °C were added potassium *tert*-butoxide (3.38 g, 0.1 mol) and ethyl formate (8.5 mL, 0.1 mol) successively. After being stirred at −10 °C for 3 h, the reaction mixture was left in the refrigerator overnight and then diluted with ether. The precipitated brown solid was filtered and dried under vacuum. The vacuum-dried solid was added to boiling acetic acid (60 mL) and refluxed for 2 min. The reaction mixture was cooled to room temperature, diluted with water, and adjusted to pH 7 by adding 1 N sodium hydroxide. The reaction mixture was extracted with ether (2 × 2 L). The combined organic fractions were dried ($MgSO_4$), filtered, and concentrated. The crude brownish solid was chromatographed (silica gel, hexane/ethyl acetate 1/1, detection $KMnO_4$ spray) to give **3q** (2.3 g, 21%) as a colorless liquid: MIR 3158, 3095, 2243, 1665, 1589, 1306; ^{1}H NMR ($CDCl_3$) 8.08 (s, 1H), 2.54 (s, 3H). Anal. ($C_5H_4N_2O$) C, H, N.

Pyridine Modifications. Number of pyridinium and pyridone containing analogues (**28**−**32**) were prepared by modification of compounds **25** and **27**.

3-[1-{4-(Methylsulfonyl)phenyl}-4-trifluoromethyl-1*H*-imidazol-2-yl]pyridine 1-oxide (28). To a solution of **25** (120 mg, 0.33 mmol) in methylene chloride (10 mL) was added *m*-chloroperoxybenzoic acid (120 mg, 0.39 mmol). After being stirred for 16 h, the reaction mixture was diluted with methylene chloride (100 mL) and washed with saturated aqueous sodium bicarbonate (60 mL). The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated. Chromatography of the crude mixture using methylene chloride/ethanol 92/8 gave **28** (102 mg, 82%) as a pale yellow solid: mp (DSC) 258 °C; IR (KBr) 3437, 3117, 2992, 2912, 1657, 1639, 1601, 1572; ^{1}H NMR ($CDCl_3$) 8.12−8.20 (complex band, 2H), 8.08 (d, J = 8 Hz, 2H), 7.58 (s, 1H), 7.48 (d, J = 8 Hz, 2H), 7.22−7.35 (complex band, 2H), 3.17 (s, 3H); MS (CI) 384 (MH^+). Anal. ($C_{16}H_{12}N_3SO_3F_3 \cdot 0.75H_2O$) C, H, N, S.

1-Methyl-3-[1-{4-(methylsulfonyl)phenyl}-4-trifluoromethyl-1*H*-imidazol-2-yl]pyridinium Iodide (29). A solution of **1** (200 mg, 0.54 mmol) in methylene chloride (10 mL) and iodomethane (0.35 mL, 5.4 mmol) was refluxed for 18 h. The precipitated white solid was filtered, washed with methylene chloride, and dried under vacuum to give **29** (250 mg, 91%): mp (DSC) 243 °C; IR (KBr) 3431, 3032, 2909, 1639, 1574, 1531, 1500; ^{1}H NMR (CD_3OD) 9.29 (d, J = 2 Hz, 1H), 8.93 (dd, J = 5, 2 Hz, 1H), 8.27 (s, 1H), 8.19 (dd, J = 8, 2 Hz, 1H), 8.14 (d, J = 8 Hz, 2H), 7.99 (dd, J = 8, 5 Hz, 1H), 7.77 (d, J = 8 Hz, 2H), 4.46 (s, 3H), 3.22 (s, 3H). Anal. ($C_{17}H_{15}N_3SO_2F_3I$) C, H, N, I.

5-[1-{4-(Methylsulfonyl)phenyl}-4-trifluoromethyl-1*H*-imidazol-2-yl]-2(1*H*)-pyridone (30). A solution of **40** (140 mg, 0.35 mmol) in methanol (10 mL) and hydrogen chloride in dioxane (7 mL, 6 N solution) was stirred at room temperature for 80 h. The reaction mixture was concentrated to remove the solvents. After neutralization with ammonium hydroxide, the product was extracted with methylene chloride. The organic fractions were dried (Na_2SO_4), filtered, and concentrated to give 72 mg of the crude product. Chromatography of the crude mixture (silica gel, methylene chloride/methanol/ ammonium hydroxide 98/2/0.2) gave **30** (42 mg, 31%) as a white solid: mp (DSC) 268 °C; IR (KBr) 3433, 3111, 1626, 1579, 1549, 1500, 1469, 1410; ^{1}H NMR ($CDCl_3$) 8.12 (d, J = 8 Hz, 2H), 7.52 (d, J = 8 Hz, 2H), 7.51 (s, 1H), 7.46 (d, J = 2 Hz, 1H), 7.33 (dd, J = 8, 2 Hz, 1H), 6.48 (d, J = 8 Hz, 1H), 3.16 (s, 3H); MS (DCI) 384 (MH^+). Anal. ($C_{16}H_{12}N_3SO_3F_3 \cdot 0.25H_2O$) C, H, N.

4-[1-{4-(Methylsulfonyl)phenyl}-4-trifluoromethyl-1*H*-imidazol-2-yl]-2(1*H*)-pyridone (31). Step 1: Preparation of 4-[1-{4-(Methylsulfonyl)phenyl}-4-trifluoromethyl-1*H*-imidazol-2-yl]pyridine 1-Oxide (24b). This intermediate (**24b**) was prepared by oxidation of **27** using the procedure described for the preparation of **28**: mp (DSC) 279 °C; IR (KBr) 3431, 3069, 1601, 1574, 1518, 1500, 1466, 1441; ^{1}H NMR ($CDCl_3$) 8.16 (d, J = 8 Hz, 2H), 8.08 (d, J = 8 Hz, 2H), 7.54 (s, 1H), 7.51 (d, J = 8 Hz, 2H), 7.26 (d, J = 8 Hz, 2H), 3.16 (s, 3H); MS (CI) 384 (MH^+). Anal. ($C_{16}H_{12}N_3SO_3F_3$) C, H, N, S.

Step 2: Preparation of 4-[1-{4-(Methylsulfonyl)phenyl}-4-trifluoromethyl-1*H*-imidazol-2-yl]-2(1*H*)-pyridone (31). A solution of **24b** in acetic anhydride was refluxed for 72 h. The reaction mixture was cooled and the precipitated product filtered. Chromatography of the crude mixture (silica gel, methylene chloride/methanol/ammonium hydroxide 95/5/0.5) gave the desired product **31** (250 mg, 51%) as a white solid: mp (DSC) 293 °C; IR (KBr) 3424, 3111, 3028, 2934, 1657, 1628, 1576, 1558, 1541, 1462; ^{1}H NMR (CD_3OD) 8.12 (d, J = 8 Hz, 2H), 8.07 (s, 1H), 7.73 (d, J = 8 Hz, 2H), 7.44 (d, J = 7 Hz, 1H), 6.48 (dd, J = 7, 2 Hz, 1H), 6.38 (d, J = 2 Hz, 1H), 3.18 (s, 3H); MS (APCI) 384 (MH^+). Anal. ($C_{16}H_{12}N_3SO_3F_3$) C, H, N.

1-Methyl-5-[1-{4-(methylsulfonyl)phenyl}-4-(trifluoromethyl)-1*H*-imidazol-2-yl]-2(1*H*)-pyridone (32). A solution of **40** (140 mg, 0.35 mmol) in methylene chloride (10 mL) and iodomethane (0.22 mL, 3.5 mmol) was stirred at 40−45 °C. The reaction progressed very slowly, and additional quantities of iodomethane and methylene chloride were added intermittently to the reaction mixture. After 7 days, the reaction mixture was concentrated to remove the solvents, and the crude mixture was purified on a silica gel column using ethyl acetate/acetone 9/2 to give **32** (71 mg, 50%): mp (DSC) 199 °C; IR (KBr) 3441, 3101, 2922, 2359, 2222, 1667, 1619, 1578, 1535; ^{1}H NMR ($CDCl_3$) 8.13 (d, J = 8 Hz, 2H), 7.87 (d, J = 2 Hz, 1H), 7.55 (d, J = 8 Hz, 2H), 7.48 (s, 1H), 6.87 (dd, J = 8, 2 Hz, 1H), 6.48 (d, J = 8 Hz, 1H), 3.57 (s, 3H), 3.14 (s, 3H); MS (DCI) 398 (MH^+). Anal. ($C_{17}H_{14}N_3SO_3F_3 \cdot 0.25H_2O$) C, H, N.

Preparation of 1,2-Diarylimidazoles with Different Substituents in Imidazole Ring. 1,2-Diarylimidazoles (**58**−**62**) with different substituents at position-4 of the imidazole ring were prepared as shown below. The compound **63** was prepared from **58** by using the conditions described for the synthesis of compound **43** (method A).

3-[4-(Difluoromethyl)-1-[4-(methylsulfonyl)phenyl]-1*H*-imidazol-2-yl] pyridine (58). Step 1: Preparation of 1-Chloro-3,3-difluoroacetone. To a solution of difluoroacetic acid (2.0 mL, 31 mmol) in THF (100 mL) was added triethylamine (4.1 mL, 31 mmol). After cooling the reaction solution in an ice bath under nitrogen, isobutyl chloroformate (4.1 mL, 31 mmol) was added in a dropwise fashion, and the resulting mixture was stirred while allowing to warm to room temperature. The mixed anhydride was freed of Et_3N−HCl by filtration and cooled in an ice bath. To this solution was added a solution of 2.8 g of diazomethane in ether, and the solution was allowed to warm to room temperature. After the mixture was stirred for 1 h, a solution of hydrogen chloride in dioxane (16.8 mL, 4 N solution) was added, and the mixture was stirred overnight. The solution was filtered and used in the next step without further processing.

Step 2: Preparation of 3-[4-(Difluoromethyl)-1-[4-(methylsulfonyl)phenyl]-1*H*-imidazol-2-yl]pyridine (58). To a solution of 1-chloro-3,3-difluoroacetone as prepared above were added 2-propanol (75 mL), **8** (1.88 g, 7.75 mmol), and sodium bicarbonate (12.6 g, 150 mmol). The mixture was subjected to distillation through a Vigreaux column to a head temperature of 65 °C, and then a reflux condenser was fitted. The mixture was refluxed for 6 h, cooled, and concentrated. The residue was partitioned between dichloromethane and water, and the aqueous layer was re-extracted with dichloromethane. The

combined organic fractions were dried (Na_2SO_4), filtered, and concentrated. Chromatography of the residue over silica gel using 10% methanol in ethyl acetate as eluent gave 920 mg of 4-(difluoromethyl)-4,5-dihydro-1-[4-(methylsulfonyl) phenyl]-2-(3-pyridinyl)-1*H*-imidazol-4-ol (**21**) contaminated with some starting amidine.

The crude product as obtained above was mixed with 25 mL of acetic anhydride and 50 mg of 4-(dimethylamino)pyridine. The mixture was refluxed for 2 h, cooled, and concentrated. The residue was partitioned between dichloromethane and water and the aqueous layer re-extracted with dichloromethane. The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated. Chromatography using 80% ethyl acetate in hexane gave 307 mg of **22** contaminated with about 10% of 4-(methylmercapto) acetanilide: ^{1}H NMR (CD_2Cl_2) 8.63 (dd, J = 4, 2 Hz, 1H), 8.58 (dd, J = 6, 2 Hz, 1H), 7.82 (dt, J = 9, 2 Hz, 1H), 7.44 (t, J = 4, 2 Hz, 1H), 7.29 (d, J = 9 Hz, 2H), 7.26 (d, J = 9 Hz, 1H), 7.17 (d, J = 9 Hz, 2H), 6.80 (t, J = 58 Hz, 1H), 2.54 (s, 3H).

A solution of **22** (307 mg) as obtained above in methanol (10 mL) and water (3 mL) was cooled in an ice bath, and oxone (1.31 g, 2.13 mmol) was added. The resulting mixture was stirred rapidly for 1 h. The mixture was diluted with water, neutralized with aqueous ammonium hydroxide, and extracted with ethyl acetate. The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated. Chromatography using a gradient of 0−5% MeOH−EtOAc gave **58** (250 mg, 74%) as a pure white crystalline solid: ^{1}H NMR ($CDCl_3$) 8.64 (dd, J = 6, 2 Hz, 1H), 8.57 (d, J = 2 Hz, 1H), 8.08 (d, J = 9 Hz, 2H), 7.84 (dt, J = 9, 2 Hz, 1H), 7.53 (t, J = 2 Hz, 1H), 7.48 (d, J = 9 Hz, 2H), 7.34 (dd, J = 9, 5 Hz, 1H), 6.83 (t, J = 50 Hz, 1H), 3.17 (s, 3H). Anal. ($C_{16}H_{13}F_2N_3O_2S$) C, H, N.

1-[4-(Methylsulfonyl)phenyl]-2-(3-pyridinyl)-1*H*-imidazole-4-carbonitrile (59). Step 1: Preparation of 4,5-Dihydro-1-[4-(methylthio)phenyl]-2-(3-pyridinyl)-1*H*-imidazole-4-carbonitrile (23). To a suspension of **8** (1.00 g, 4.1 mmol) in THF (20 mL) were added 2-chloroacrylonitrile (540 mg, 6.2 mmol) and diisopropylethylamine (796 mg, 6.2 mmol) successively. The reaction mixture was slowly heated to reflux. After refluxing for 6 h, an additional 540 mg of 2-chloroacrylonitrile was added. After refluxing overnight, the solvent was removed and the crude mixture chromatographed (silica gel, ethyl acetate) to give **23** (951 mg, 79%): ^{1}H NMR ($CDCl_3$) 8.73 (d, J = 2 Hz, 1H), 8.67 (dd, J = 5, 2 Hz, 1H), 7.85 (dt, J = 8, 2 Hz, 1H), 7.26 (dd, J = 9, 5 Hz, 1H), 7.15 (d, J = 9 Hz, 2H), 6.85 (d, J = 9 Hz, 2H), 5.10 (dd, J = 11, 7 Hz, 2H), 4.34 (dd, J = 11, 11 Hz, 1H), 4.28 (dd, J = 11, 7 Hz, 1H), 2.46 (s, 3H).

Step 2: Preparation of 4,5-Dihydro-1-[4-(methylsulfonyl)phenyl]-2-(3-pyridinyl)-1*H*-imidazole-4-carbonitrile (24). A solution of **23** (950 mg, 2.65 mmol) in methanol (25 mL) and water (10 mL) was cooled in an ice bath, and oxone (3.6 g, 5.8 mmol) was added. The resulting mixture was stirred for 2 h. The mixture was diluted with water, neutralized with aqueous ammonium hydroxide, and extracted with ethyl acetate. The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated. Chromatography on silica gel using 10% methanol in ethyl acetate gave **24** (532 mg, 67%) as a pure white crystalline solid: ^{1}H NMR ($CDCl_3$) 8.75 (m, 2H), 7.89 (dt, J = 8, 2 Hz, 1H), 7.82 (d, J = 9 Hz, 2H), 7.38 (dd, J = 9, 5 Hz, 1H), 6.95 (d, J = 9 Hz, 2H), 5.13 (dd, J = 11, 7 Hz, 1H), 4.51 (dd, J = 11, 11 Hz, 1H), 4.42 (dd, J = 11, 7 Hz, 1H), 3.07 (s, 3H). Anal. ($C_{16}H_{14}N_4O_2S$) C, H, N.

Step 3: Preparation of 1-[4-(Methylsulfonyl)phenyl]-2-(3-pyridinyl)-1*H*-imidazole-4-carbonitrile (59). To a mixture of **24** (512 mg, 1.6 mmol) in cumene (30 mL) was added 100 mg of 10% Pd/C. The reaction mixture was refluxed under a drying tube for 2 h. After cooling, the mixture was diluted with dichloromethane and methanol and filtered through a Celite bed. The organic fractions were concentrated and chromatographed on silica gel using a gradient of 0−10% MeOH−EtOAc as eluent to give **59** (275 mg, 72% based on conversion) in addition to the recovered **24** (114 mg): mp (DSC) 194 °C; MIR 2925, 2236, 1596, 1574, 1496, 1432, 1311; ^{1}H NMR ($CDCl_3$−CD_3OD) 8.53 (dd, J = 5, 2 Hz, 1H), 8.43 (d, J = 2 Hz, 1H), 8.00 (d, J = 9 Hz, 2H), 7.86 (s, 1H), 7.69 (dt, J = 9, 2 Hz, 1H), 7.44 (d, J = 9 Hz, 2H), 7.28 (dd, J = 9, 5 Hz, 1H), 3.08 (s, 3H). Anal. ($C_{16}H_{12}N_4O_2S\cdot0.25H_2O$) C, H, N.

3-[4-Methyl-1-{4-(methylsulfonyl)phenyl}-1*H*-imidazol-2-yl]pyridine (60). Step 1: Preparation of *N*-(2-Methoxy-2-propenyl)-*N*-[4-(methylthio)phenyl]-3-pyridinecarboximidamide (17). To a solution of **8** (5.0 g, 20.6 mmol) in dry THF (175 mL) was added sodium bis(trimethylsilyl)amide (22.6 mL, 1.0 M solution in THF, 22.6 mmol) over 10 min. After the mixture was stirred for an additional 15 min, 1-bromo-2-methoxy-2-propene[32] (10.6 mL, 10.3 mmol) was added and the mixture stirred overnight at room temperature. The reaction mixture was poured into ice−water and extracted with dichloromethane. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated and the residue chromatographed (silica gel, hexane/ethyl acetate 2/8) to give **17** (1.55 g, 24%; 40% based on **8** consumed) as a pale orange liquid, and recovered **8** (2.01 g, 40%): ^{1}H NMR (CD_2Cl_2) 8.50 (m, 2H), 7.51 (d, J = 6 Hz, 1H), 7.21 (dd, J = 6, 2 Hz, 1H), 7.01 (d, J = 8 Hz, 2H), 6.54 (d, J = 8 Hz, 2H), 4.25 (s, 2H), 4.18 (d, J = 9 Hz, 1H), 4.06 (d, J = 9 Hz, 1H), 3.62 (s, 3H), 2.37 (s, 3H).

Step 2: Preparation of 3-[4-Methyl-1-{4-(methylthio)-phenyl}-1*H*-imidazol-2-yl]pyridine (18). To a solution of **17** (1.55 g, 4.95 mmol) in THF (90 mL) was added a solution of pyridinium *p*-toluenesulfonate (582 mg, 2.32 mmol) in water (10 mL). After being stirred overnight at room temperature, the mixture was refluxed for 4 h. The reaction mixture was cooled and the solvent removed under reduced pressure. Chromatography of the resulting residue over silica gel using a gradient of 5−10% methanol in ethyl acetate gave **18** (1.09 g, 78%) as a white solid: mp (DSC) 123 °C; MIR 1497, 1431, 1389, 1096, 957, 806, 704; ^{1}H NMR (CD_2Cl_2) 8.55 (d, J = 2 Hz, 1H), 8.40 (dd, J = 5, 2 Hz, 1H), 7.64 (dt, J = 8, 2 Hz, 1H), 7.32 (d, J = 8 Hz, 2H), 7.13 (dd, J = 9, 5 Hz, 1H), 7.12 (d, J = 8 Hz, 2H), 6.96 (s, 1H), 2.52 (s, 3H), 2.08 (s, 3H). Anal. ($C_{16}H_{15}N_3S\cdot0.125H_2O$) C, H, N.

Step 3: Preparation of 3-[4-Methyl-1-{4-(methylsulfonyl)phenyl}-1*H*-imidazol-2yl]pyridine (60). A solution of **18** (567 mg, 1.80 mmol) in dichloromethane (14 mL) was cooled (0−5 °C, ice-bath) and *m*-chloroperoxybenzoic acid (1.33 g, 80−85% purity) added. After the mixture was stirred for 30 min, additional *m*-chloroperoxybenzoic acid (1.33 g) and dichloromethane (5 mL) were added. After being stirred for 1 h, the mixture was diluted with dichloromethane, and a white solid was isolated by filtration. The filtrate was washed with aqueous $NaHCO_3$ and the aqueous layer extracted with dichloromethane. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. Chromatography of the residue using a gradient of 0−50% MeOH−EtOAc gave **19** (213 mg) as a white solid.

A solution of **19** (213 mg) in absolute ethanol (20 mL) and cyclohexene (3 mL) was treated with 50 mg of 10% Pd/C. The reaction mixture was refluxed for 1 h, diluted with dichloromethane, and filtered through Celite. The combined organic fractions were concentrated to give **60** (184 mg, 29% from **18**) as a white solid: ^{1}H NMR (CD_2Cl_2) 8.58 (d, J = 5 Hz, 1H), 8.52 (dd, J = 5, 2 Hz, 1H), 7.94 (d, J = 8 Hz, 2H), 7.69 (m, 1H), 7.42 (d, J = 8 Hz, 2H), 7.24 (m, 1H), 7.01 (s, 1H), 3.12 (s, 3H), 2.32 (s, 3H). Anal. ($C_{16}H_{15}N_3SO_2\cdot H_2O$) C, H, N.

Ethyl-1-[4-(methylsulfonyl)phenyl]-2-(3-pyridinyl)-1*H*-imidazole-4-carboxylate (61). Step 1: Preparation of Ethyl-1-[4-(methylthio)phenyl]-2-(3-pyridinyl)-1*H*-imidazole-4-carboxylate (20). A mixture of **8** (5.00 g, 20.6 mmol), ethyl bromopyruvate (8.93 g, 90% purity, 41.2 mmol), and sodium bicarbonate (3.46 g) in 2-propanol (200 mL) was stirred at reflux for 18 h. After cooling to room temperature, the mixture was concentrated and the residue suspended in dichloromethane and washed with water and brine. The aqueous layer was extracted with dichloromethane again. The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated. Chromatography of the residue using ethyl acetate as eluent gave a brownish product **20** (2.39 g, 34%). An analytical sample was crystallized from ethyl acetate to

give **20** as a pale tan crystalline solid: mp (DSC) 150−151 °C; IR (KBr) 1700, 1543, 1499, 1325, 1258, 1223; ^{1}H NMR (CD_2Cl_2) 8.61 (d, J = 2 Hz, 1H), 8.53 (dd, J = 5, 2 Hz, 1H), 7.81 (s, 1H), 7.75 (dt, J = 8, 2 Hz, 1H), 7.28 (d, J = 8 Hz, 2H), 7.22 (dd, J = 9, 5 Hz, 1H), 7.16 (d, J = 8 Hz, 2H), 4.36 (q, J = 6 Hz, 2H), 2.50 (s, 3H), 1.37 (t, J = 6 Hz, 3H). Anal. ($C_{18}H_{17}N_3O_2S$) C, H, N.

Step 2: Preparation of Ethyl-1-[4-(methylsulfonyl)-phenyl]-2-(3-pyridinyl)-1*H*-imidazole-4-carboxylate (61). The compound was prepared by following the experimental procedure described for **59**, step 2: mp (DSC) 165 °C; IR ($CHCl_3$) 1727, 1555, 1323, 1156; ^{1}H NMR (CD_2Cl_2) 8.62 (dd, J = 5, 2 Hz, 1H), 8.52 (d, J = 2 Hz, 1H) 8.07 (d, J = 9 Hz, 2H), 7.92 (s, 1H), 7.88 (dd, J = 8, 2 Hz, 1H), 7.45 (d, J = 9 Hz, 2H), 7.33 (dd, J = 9, 5 Hz, 1H), 4.36 (q, J = 6 Hz, 2H), 3.09 (s, 3H), 1.38 (t, J = 6 Hz, 3H). Anal. ($C_{18}H_{17}N_3O_4S\cdot0.25H_2O$) C, H, N.

1-[4-(Methylsulfonyl)phenyl]-2-(3-pyridinyl)-1*H*-imidazole-4-methanol (62). To a cold solution (−70 °C, dry ice-2-propanol bath) of **61** (1.05 g, 2.8 mmol) in dichloromethane (35 mL) was added diisobutylaluminum hydride (7.1 mL, 1 M solution in toluene, 7.1 mmol) dropwise. The mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched by adding methanol, and the resulting pasty mixture was diluted with dichloromethane and 10% aqueous acetic acid. The layers were separated, and the aqueous layer was extracted with additional dichloromethane. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. Chromatography of the crude mixture using 25% methanol in ethyl acetate as eluent gave **62** (520 mg, 56%) as shining pale yellow plates: mp 210−211 °C; MIR 2954, 2919, 2850, 1305, 1288, 1149; ^{1}H NMR (AcOH-d_4) 8.69 (d, J = 5 Hz, 1H), 8.61 (d, J = 2 Hz, 1H), 8.10 (d, J = 9 Hz, 2H), 8.05 (dt, J = 8, 2 Hz, 1H), 7.62 (d, J = 9 Hz, 2H), 7.60 (dd, J = 8, 5 Hz, 1H), 7.55 (s, 1H), 4.81 (s, 2H), 3.17 (s, 3H). Anal. ($C_{16}H_{15}N_3O_3S\cdot0.375H_2O$) C, H, N.

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Supporting Information Available: Complete physical and spectral data for compounds **26**, **27**, **33**−**42**, **44, 46**−**57**, **63**−**75**, and **77**−**80** and the intermediates **3b** and **3d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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