Synthesis and Structure−Activity Relationship of a New Series of COX-2 Selective Inhibitors: 1,5-Diarylimidazoles

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The synthesis and the pharmacological activity of a series of 1,5-diarylimidazoles developed as potent and selective cyclooxygenase-2 (COX-2) inhibitors are described. The new compounds were evaluated both in vitro (COX-1 and COX-2 inhibition in human whole blood) and in vivo (carrageenan-induced paw edema, air-pouch, and hyperalgesia tests). Modification of all the positions of two regioisomeric imidazole cores led to the identification of 4-[4-chloro-5-(3-fluoro-4-methoxyphenyl)imidazol-1-yl]benzenesulfonamide (UR-8880, **51f**) as the best candidate, which is now undergoing Phase I clinical trials.

Inhibition of cyclooxygenase (COX), one of the key enzymes in the arachidonic acid (AA) cascade[1] is the main mechanism by which nonsteroidal antiinflammatory drugs (NSAIDs) exert their antiinflammatory action. This enzyme bis-oxygenates AA to PGG_2, which is subsequently degraded to vasoactive and inflammatory mediators such as prostaglandins (PGs), prostacyclin (PGI_2), and thromboxane-A_2. The therapeutic use of NSAIDs, especially in chronic diseases, has revealed their association with well-known side effects at the gastrointestinal level (mucosal damage, bleeding)[2] and, less frequently, at the renal[3] level.

After the discovery a decade ago of two COX isoforms,[4] it was recognized[5] that selective inhibitors of the inducible form (COX-2, cytokine inducible, and expressed mainly in inflammatory cells) could provide antiinflammatory agents devoid of the undesirable effects associated with classical, nonselective NSAIDs. The inhibition of COX-1, the form constitutively present in many tissues such as stomach, kidney, and platelets, by nonselective NSAIDS may be responsible for the secondary effects associated with their use.

Although modifications of established nonselective agents, such as lengthening the carboxyl side chain of indomethacin[6] (**1**), have been strategies for the design of COX-2 selective inhibitors,[7] the main effort has been addressed to the diarylheterocycle class,[8] based on early known antiinflammatory drugs, such as flumizole. Two compounds in this class, celecoxib[9] (**2**) and rofecoxib[10] (**3**), were the first COX-2 selective inhibitors to reach the market for the oral treatment of acute pain, osteoarthritis, and rheumatoid arthritis, and two new diarylheterocyclic derivatives valdecoxib (**4**)[11a] and etoricoxib (**5**)[12] have recently been introduced (Figure 1). A water-soluble prodrug of valdecoxib, parecoxib,[11b] has also been recently marketed for the parenteral treatment of postoperative pain. In addition, some of them are undergoing clinical trials for the treatment of certain forms of cancer and Alzheimer's disease.

Overall, these selective COX-2 inhibitors have fulfilled the hope that they would exhibit a reduced risk in gastrointestinal events, although it is becoming increasingly apparent that they can cause nearly identical renal effects to those observed with nonselective NSAIDs. Cardiovascular concerns regarding the use of these agents have recently emerged. Direct long-term studies are needed before the relevance of this issue can be determined.[13]

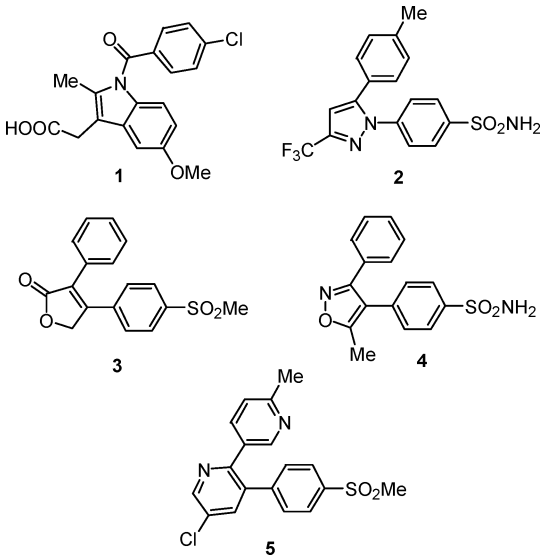

Figure 1.

To achieve good activity and selectivity, the diarylheterocycle COX-2 selective inhibitors require the presence of a 4-methylsulfonylphenyl group attached to an unsaturated (generally five-membered) ring in which an additional vicinal lipophilic moiety is present. The methylsulfonyl group can only be replaced by a SO_2NH_2 group, whereas the lipophilic pocket is usually occupied by an optionally substituted phenyl ring or a bulky alkoxy substituent. The nature of the central scaffold is crucial for the activity, although in many instances it does not establish well-defined electrostatic interactions with any of the amino acid residues, as shown either in the crystal structure of COX-2/inhibitor[14] complexes or in different calculations, by ourselves[15] and others.[16] Presumably, the highly lipophilic active site

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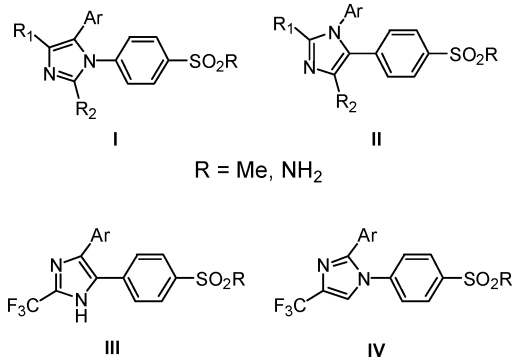
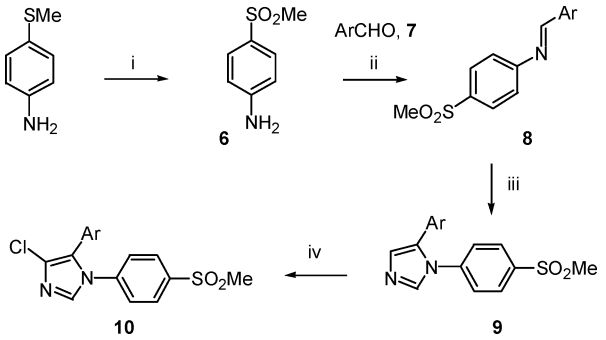


Figure 2.

Scheme 1[a]



[a] H_2O_2, Na_2WO_4, H_2O, 65 °C, 1.5 h; (ii) toluene, Dean−Stark, 110 °C, 24−48 h; (iii) TosMIC, K_2CO_3, DME, MeOH, reflux, 3 h; (iv) NCS, acetonitrile, 81 °C, 24 h.

requires a given (low) polarity of the central scaffold. Furthermore inclusion of water molecules and the rearrangement of some lateral chains inside the active site makes general predictions using molecular modeling very difficult.[15]

Regioisomeric imidazoles have been explored previously as replacements of the central heterocyclic core. The 4,5-diarylimidazoles **III**[17] showed diminished potency vs **2**, while the 1,2-diarylimidazoles **IV** were shown to be potent COX-2 selective inhibitors only when a trifluoromethyl group was present in the 4 position.[18] None of them, however, was pursued in further development.

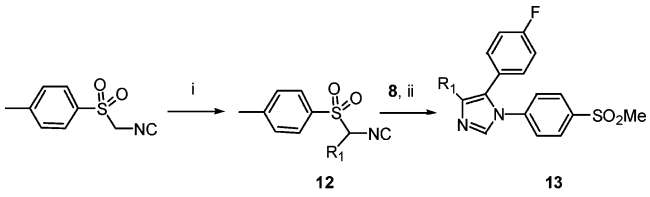
As a new approach to the diarylheterocycle class of COX-2 inhibitors, we report here the structure−activity relationships (SAR) of new 1,5-diarylimidazoles **I** and **II** (Figure 2), in which a defined combination of substituents confers appropriate polarity and charge distribution for good activity.

Chemistry

The key step in the synthesis of imidazoles **I** and **II** involves reaction of tosylmethyl isocyanide (TosMIC) with an imine, in which the presence of the electron-withdrawing 4-methylsulfonyl group allows the reaction to take place in good yield. The reaction is performed in the presence of K_2CO_3, which initiates a two-step anionic 1,3-dipolar cycloaddition.[19] In cases where the reaction needs to be performed with 4-methylsulfanyl imines, and thus no electron-withdrawing group is present, the more reactive benzotriazol-1-yl-methyl isocyanide (BetMIC)[20] must be used.

As shown in Scheme 1, 1-(4-methylsulfonylphenyl) imidazoles **9** were obtained using these conditions in good to high yield from imines **8**, which were prepared by reaction of 4-methylsulfonylaniline **6** with the corresponding aldehydes **7** under Dean−Stark conditions. Amine **6** was obtained in 75% yield and high purity, by reaction of 4-methylmercaptoaniline with H_2O_2 in the presence of Na_2WO_4.[21] The use of other oxidizing agents afforded higher quantities of amino-oxidation byproducts (mainly the azoxy and nitro derivatives). Aldehydes **7** were commercially available or were synthesized from the corresponding acids by successive conversion to the ethyl ester, reduction ($LiAlH_4$), and Swern oxidation. Finally, chlorination of **9** was effected with *N*-chlorosuccinimide (NCS) in acetonitrile to give 4-chloroimidazoles **10** (Tables 3 and 4) in 80−90% yield. This reaction was highly regioselective, since only small amounts of the 2-chloro (i.e., **14**, around 2%) and dichloro derivatives (i.e., **18**, around 5%) were generally observed. Both were separated from **10** either by crystallization or flash chromatography.

Scheme 2[a]



a: R_1 = Me; **b:** R_1 =Et; **c:** R_1 = Allyl; **d:** R_1 =Bn; **e:** R_1 = Pent

[a] (i) IR_1, $ClNEt_3Bn$, CH_2Cl_2, NaOH, 1−5 h, −20−0 °C; (ii) TosMIC, K_2CO_3, DME, MeOH, reflux, 3 h.

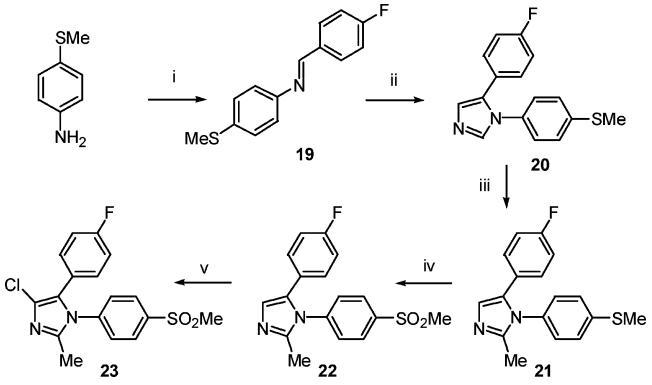
4-Bromoimidazole **11** (Table 1) was obtained from **9a** in a similar way using *N*-bromosuccinimide (NBS) and the dichloro derivative **18** was obtained from **9a** using 2 equiv of NCS. The 4-alkylimidazoles **13a**−**e** were obtained by reaction of imine **8a** with the corresponding alkyl-substituted isocyanides **12**. These were prepared, as depicted in Scheme 2, by phase-transfer alkylation of TosMIC using the conditions previously described.[22] In our hands, the alkylation with the more reactive benzyl and allyl bromides had to be performed at −20 °C in order to avoid formation of dialkylated products.

The 2-substituted imidazoles **15** and **16** (Table 1) were regioselectively prepared on treatment of **9a** with PhCOCl/NEt_3[23] and aqueous formaldehyde[24] respectively. Chlorination of **16** with NCS gave **17** in 80% yield.

As shown in Scheme 3, the synthesis of the 4-chloro-2-methyl derivative **23** required the preparation of the sulfanyl imidazole **20**. Formation of imine **19** was effected as described above for **8**, but in this case the reaction with TosMIC provided a complex mixture of products. However, when BetMIC[20] was used, **20** was isolated in 59% yield. Alkylation of **20** with BuLi and IMe in THF[25] afforded **21** in 36% yield, which was finally transformed into **23** by oxidation with *m*-chloroperbenzoic acid (MCPBA) and chlorination with NCS.

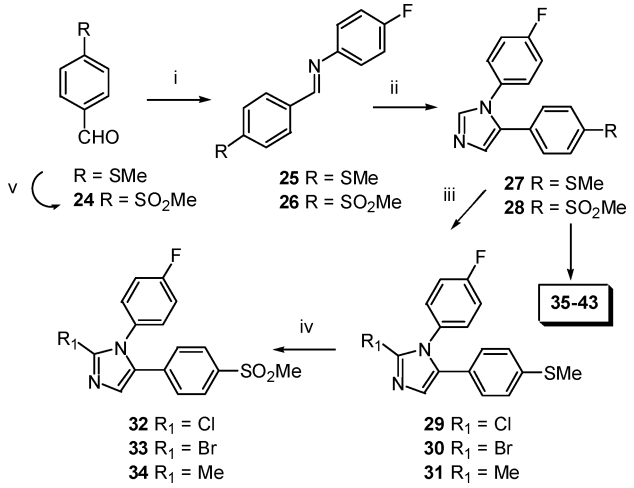
The 1-(4-fluorophenyl)imidazoles (**II**) were prepared, as shown in Scheme 4, using similar methods as described above for their regioisomers. The 2-substituted derivatives **32**−**34** were obtained from 4-methylsulfanylphenylimidazole **27**, which was prepared upon successive imine formation and cyclization with BetMIC. Reaction of **27** with LDA and the corresponding electrophile (NCS, NBS or MeI) gave compounds **29**−

Scheme 3[a]



[a] (i) Toluene, Dean−Stark, 110 °C, 24−48 h; (ii) BetMIC (**23**), KOBu^t, DMSO, 75 °C, 1 h; (iii) LDA, IMe, THF, −20−20 °C, 1.5 h; (iv) MCPBA, CH_2Cl_2, 20 °C, 2 h; (v) NCS, acetonitrile, 81 °C, 24 h.

Scheme 4[a]



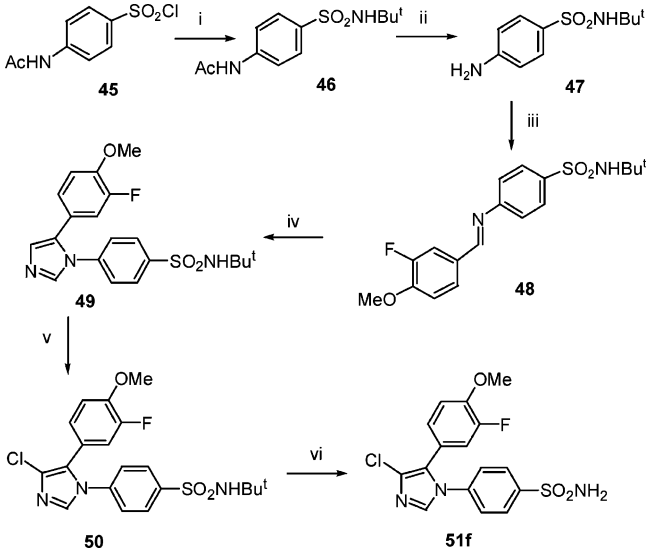
[a] (i) Toluene, Dean−Stark, 110 °C, 24−48 h; (ii) BetMIC (**23**), KOBu^t, DMSO, 75 °C, 1 h or TosMIC (**24**), K_2CO_3, DME, MeOH, reflux, 3 h; (iii) LDA, NCS (or NBS or IMe), THF, −20 to 20 °C, 1.5 h; (iv) MCPBA, CH_2Cl_2, 20 °C, 2 h; (v) MCPBA, CH_2Cl_2, 25 °C, 2 h.

31, which were finally oxidized to afford **32**−**34**, respectively. The remaining compounds in Table 2 were obtained from imidazole **28**. This was converted to **35** and **40** as described above for **16** and **15**, respectively. Reaction of **35** with diethylaminosulfur trifluoride (DAST) afforded compound **36** and oxidation of **35** with MnO_2 gave a mixture of aldehyde **37** and methyl ester **38**. Aldehyde **37** was converted to nitrile **39** on treatment with hydroxylamine-*O*-sulfonic acid in the presence of pyridine.[26] Compounds **41**−**44** were obtained following similar methods to those described previously.

Sulfonamides **51** (Table 5) were initially prepared as described in the experimental part for compound **51a**. The sulfonamide functionality was introduced using the transformation of sulfinyl derivatives previously described for related compounds.[27]

A more direct method was developed for the synthesis of sulfonamide **51f**, as described in Scheme 5. Treatment of 4-(acetylamino)sulfonyl chloride **45** with *tert*-butylamine yielded **46**, which on deprotection with potassium hydroxide gave **47**. Reaction of **47** with 4-methoxy-3-fluorobenzaldehyde gave imine **48**, which was cyclized with TosMIC to afford imidazole **49**. Regioselective

Scheme 5[a]



[a] (i) NH_2Bu^t/DME, reflux, 4 h; (ii) KOH/MeOH/H_2O, 100 °C, 4 h; (iii) 4-methoxy-3-fluorobenzaldehyde, toluene, Dean−Stark, 110 °C, 24 h; (iv) TosMIC, K_2CO_3, DME, MeOH, reflux, 3 h; (v) NCS, acetonitrile, 81 °C, 24 h; (vi) 6 N HCl, reflux, 3 h.

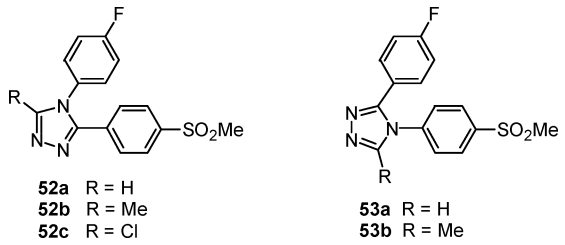


Figure 3.

chlorination with NCS and deprotection of the sulfonamide group yielded **51f** in 40% overall yield.

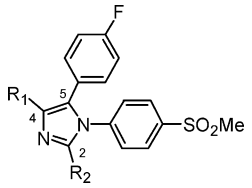
Some triazoles **52a**−**c** and **53a**,**b** (Figure 3) were also prepared following a route previously described for similar compounds.[28]

Results and Discussion

The activity and selectivity of the new compounds was first evaluated in vitro by obtaining their IC_{50} in human cell lines expressing COX-1 and COX-2. The COX-2 activity was also determined in a human whole blood (HWB) assay. Percent inhibition at 10 μM was initially determined and active compounds were also tested at 1 μM. All compounds showing more than 60% inhibition at 10 μM were tested orally in the rat carrageenan-induced paw edema assay (CPE) at 10 mg/kg (Tables 1−5).[29] The most potent derivatives were also tested in the carrageenan-induced air pouch model[30] to estimate PG production at 1 mg/kg po and in the hyperalgesia model[31] at 3 mg/kg po (Table 6).

The 1-methylsulfonylimidazole **I**, in which a 4-fluorophenyl group was present in position 5, was initially selected to explore the SAR around the imidazole nucleus (Table 1). Whereas the parent unsubstituted compound (**9a**) was completely inactive, a substantial increase in activity was seen on introduction of small substituents in position 4. 4-Halo derivatives **10a** and **11** showed remarkable potency and selectivity in both in vitro tests, similar to that of reference compounds **2** and **3**. The chloro derivative **10a** also showed good

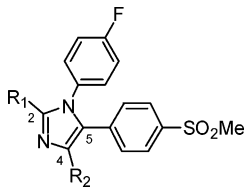
Table 1. 5-(4-Fluorophenyl)-1-(4-methylsulfonyl)imidazoles **9**−**23**



					h cell lines IC_{50}[c]		HWB COX-2,[d] % inhib		CPE[e] % inhib,
compd	R_1	R_2	mp,[a] °C	formula[b]	COX-1 (μM)	COX-2 (μM)	10 μM	1 μM	10 mg/kg
9a	H	H	151−155	$C_{16}H_{13}FN_2O_2S$	>10	>10	56.9	-	NT[f]
10a	Cl	H	167	$C_{16}H_{12}ClFN_2O_2S$	>10	0.014	100	89.0	41.2
11	Br	H	148	$C_{16}H_{12}BrFN_2O_2S$	>10	0.036	100	85.2	23.0[g]
13a	Me	H	143	$C_{17}H_{15}FN_2O_2S\cdot0.25H_2O$	>10	0.144	86.5	34.5	35.1[g]
13b	Et	H	168−169	$C_{18}H_{17}FN_2O_2S\cdot0.5H_2O$	>10	>10	3.8	-	NT
13c	Allyl	H	114−115	$C_{19}H_{17}FN_2O_2S\cdot0.25H_2O$	>10	>10	3.4	-	NT
13d	CH_2Ph	H	173	$C_{23}H_{19}FN_2O_2S\cdot0.25H_2O$	>10	>10	60.5	-	NT
13e	Pent	H	103	$C_{21}H_{13}FN_2O_2S$	>10	>10	64.4	-	NT
14	H	Cl	162−166	$C_{16}H_{12}ClFN_2O_2S$	>10	>10	-	-	NT
15	H	COPh	225−227	$C_{23}H_{17}FN_2O_3S\cdot0.75H_2O$	>10	>10	0	-	NT
16	H	CH_2OH	208−211	$C_{17}H_{15}FN_2O_3S\cdot0.75H_2O$	>10	>10	27.4	-	NT
17	Cl	CH_2OH	199−202	$C_{17}H_{14}ClFN_2O_3S\cdot0.5H_2O$	>10	>10	2.4	-	NT
18	Cl	Cl	194	$C_{16}H_{11}Cl_2FN_2O_2S$	>10	>10	0	-	NT
23	Cl	Me	188−199	$C_{17}H_{14}ClFN_2O_2S\cdot HCl$	>10	>10	27.5	-	NT
1	indomethacin				0.002	0.009	100	67.9	66.2
2	celecoxib				5.1	0.079	96.4	67.0	35.7
3	rofecoxib				>10	0.012	100	84.1	33.3

[a] Melting points correspond generally to chromatographed compounds. [b] Elemental analyses for C, H, N, and S were within 0.4% of the theoretical values indicated. [c] IC_{50} for human COX activity in U-937 cells (COX-1) and 143982 cells (COX-2). Assays were performed in duplicate. [d] Percentage inhibition of COX-2 activity in human whole blood (at 10 and 1 μM). Assays were performed in duplicate. [e] Carrageenan paw edema test (10 mg/kg, po). [f] NT: not tested. [g] Percentage of inhibition at 30 mg/kg.

Table 2. 1-(4-Fluorophenyl)-5-(4-methylsulfonyl)imidazoles **28**−**44**



					h cell lines IC_{50}[c]		HWB COX-2,[d] % inhib		CPE[e] % inhib,
compd	R_1	R_2	mp,[a] °C	formula[b]	COX-1 (μM)	COX-2 (μM)	10 μM	1 μM	10 mg/kg
28	H	H	133−134	$C_{16}H_{13}FN_2O_2S$	>10	>10	63.4	-	NT[f]
32	Cl	H	218−220	$C_{16}H_{12}ClFN_2O_2S\cdot0.25H_2O$	>10	0.014	100	85.6	20.4
33	Br	H	207−208	$C_{16}H_{12}BrFN_2O_2S$	>10	0.048	92.8	56.2	40.4
34	CH_3	H	160−162	$C_{17}H_{15}FN_2O_2S\cdot0.5H_2O$	>10	0.051	68.0	-	21.7
35	CH_2OH	H	211−212	$C_{17}H_{15}FN_2O_3S$	>10	>10	8.1	-	NT[f]
36	CH_2F	H	152−154	$C_{17}H_{14}F_2N_2O_2S\cdot0.75H_2O$	>10	>10	16.8	-	NT[f]
37	CHO	H	198	$C_{17}H_{13}FN_2O_3S\cdot0.5H_2O$	>10	> 1	70.9	-	27.5
38	COOMe	H	192−194	$C_{18}H_{15}FN_2O_4S\cdot1.25H_2O$	>10	>10	39.1	-	NT[f]
39	CN	H	192	$C_{17}H_{12}FN_3O_2S\cdot0.25H_2O$	>10	0.051	100	74.0	28.5
40	COPh	H	225−226	$C_{23}H_{17}FN_2O_3S\cdot0.25H_2O$	>10	0.030	95.0	59.1	9.8[g]
41	H	Cl	133−134	$C_{16}H_{12}ClFN_2O_2S$	>10	>10	15.3	-	NT[f]
42	H	Br	187−189	$C_{16}H_{12}BrFN_2O_2S$	>10	>10	36.0	-	NT[f]
43	Cl	Cl	211−212	$C_{16}H_{11}Cl_2FN_2O_2S$	>10	>10	51.6	-	NT[f]
44	Cl	Me	201−205	$C_{17}H_{14}ClFN_2O_2S\cdot0.25H_2O$	>10	>10	42.6	-	NT[f]

[a−g] See footnotes a−g of Table 1.

activity in vivo, similar to **2** and **3** and superior to that of **11**. Among the 4-alkyl derivatives, only **13a** showed some activity, but inferior to that of **10a**. Elongation of the chain led to a complete loss of activity (**13b**−**e**). Substitution in the 2-position of the imidazole ring was clearly detrimental (**14**−**16**, **17**, **18**, **23**).

The SAR around the imidazole nucleus of 5-methylsulfonylimidazole **II** was also performed with a 4-fluorophenyl group in position 1 (Table 2). Again, the parent unsubstituted compound **28** was devoid of activity, but on introduction of small substituents in position 2 (α to the 4-fluorophenyl group) activity increased substantially. The 2-chloro derivative, **32**, was the most potent in vitro, showing a similar trend to that observed in the case of its regioisomer **10a**. The bromo derivative **33** as well as the methyl **34** and the 2-carbonitrile **39** also exhibited high in vitro potency. In this case, the activity in the CPE test was superior for the bromo- and carbonitrile derivatives **33** and **39**. The replacement of the methyl group with hydroxymethyl (**35**), fluoromethyl

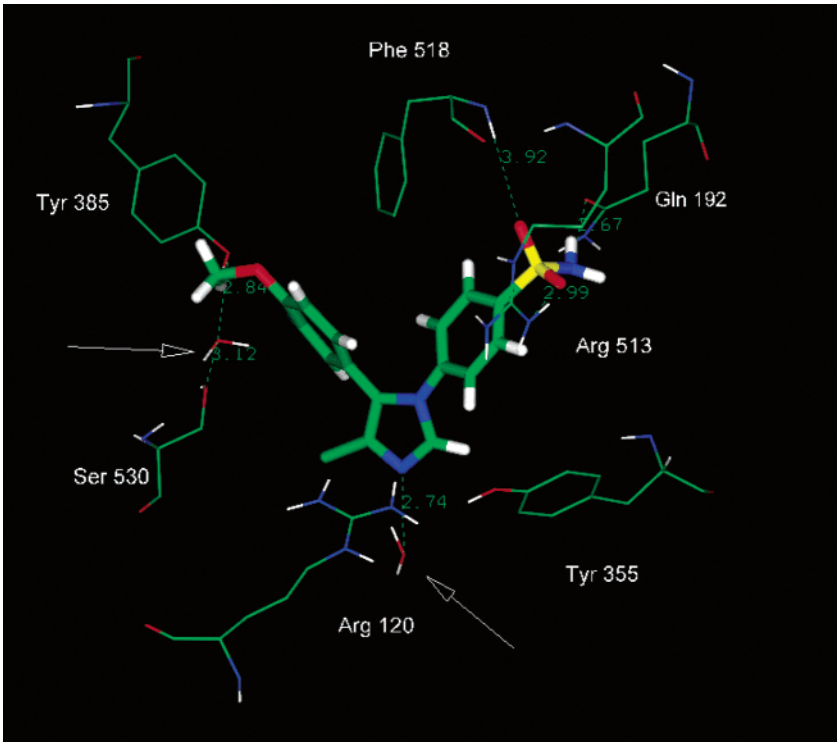


Figure 4. Proposed binding mode of compound **51f** inside the active site of COX-2, resulting from a molecular dynamics simulation. The most important amino acids are shown together with their respective numbers. The inhibitor only forms hydrogen bonds with the enzyme through its sulfonamide moiety (to Gln 192, Arg 513, and Phe 518). Two structural water molecules hydrating the imidazole ring and bridging Tyr 385 to Ser 530 are marked with arrows.

(**36**), and methyl ester (**38**) led to a complete loss of activity, while aldehyde **37** retained some potency. As in the case of isomers **I**, the introduction of substituents in the position α to the 4-methylsulfonylphenyl group led to a complete loss of activity (**41**−**44**).

An interesting result was obtained on introduction of a benzoyl group in position 2 (**40**), which provided excellent activity in vitro, although low potency in vivo. This compound probably occupies the same space in the active site of COX-2 as other related compounds,[32] in which a large lipophilic residue and a carbonyl group are present in similar positions.

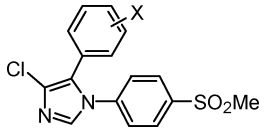
The introduction of a third nitrogen atom (Figure 3) in the position occupied by the chlorine of **10a** was explored with triazole **53a**, which was devoid of activity. The same result was obtained with the regioisomeric triazole **52a**. Compounds **52b** and **52c**, which can be regarded as aza analogues of **34** and **32**, respectively, were also completely inactive. Clearly the introduction of a third nitrogen atom is detrimental, either because of its electronegative nature or as a result of its hydrogen bond acceptor properties.

Methyl triazole **53b** was also inactive at 10 μM. Although it is sterically similar to the potent COX-2 inhibitor valdecoxib (**4**), their different H-bonding capacities or electronic features may explain their different activity. In the case of both regioisomeric imidazoles **23** and **44**, the introduction of a methyl substituent vicinal to the methylsulfonylphenyl group, provided also completely inactive compounds. However, introduction of methyl groups in similar positions of rofecoxib (i.e., in the lactone methylene) maintains potency.[33] Clearly this indicates the danger of drawing up general rules to explain the main interactions and derive a generic pharmacophore for COX-2 selective inhibitors. Thus, although many compounds have similar or even identical topologies, their electronic distributions may play a key role in determining their activities at two levels.[15,16] First, the active site of COX-2 is very flexible, and some key amino acids could shift the orientation of their lateral chains depending on the inhibitor, leading to changes in the interaction pattern. Second, the active site is at the bottom of a long and buried channel, sterically restricted and mainly lipophilic, and therefore the free energy of desolvation of the inhibitors as well as their van der Waals interaction with the amino acids lining the channel wall must also have an impact on activity.

This has recently been studied for both celecoxib derivatives and 1,5-diarylimidazoles.[15] In the case of celecoxib, elimination of the trifluoromethyl group leads to a dramatic decrease of activity mainly due to a change in desolvation energy (the presence of CF_3 reduces the desolvation of the molecule upon binding) and to a decrease of the drug−protein van der Waals interaction. Also in the case of 1,5-diarylimidazoles, elimination of the chlorine atom on the heterocycle again has a negative impact on biological activity since the presence of this halogen decreases the desolvation of the molecule and increases the drug−protein van der Waals contacts.

The predicted binding mode of **51f** (Figure 4) is similar to that of other compounds within this series.[15] It shows a very strong van der Waals contact with many of the amino acids lining the bottom of the active site, but the inhibitor only hydrogen bonds to the enzyme through its phenylsulfonamide moiety (the oxygen atoms with Phe518 and Arg513, the amino group with Gln192).

Table 3. Phenyl-Substituted Sulfones of Formula **10**



compd	X	yield %	mp,[a] °C	formula[b]	*h* cell lines IC_{50}[c] COX-1 (μM)	*h* cell lines IC_{50}[c] COX-2 (μM)	HWB COX-2,[d] % inhib 10 μM	HWB COX-2,[d] % inhib 1 μM	CPE[e] % inhib, 10 mg/kg
10a	4-F	80	167	$C_{16}H_{12}ClFN_2O_2S$	>10	0.014	100	89.0	41.2
10b	3-F	62	177−179	$C_{16}H_{12}ClFN_2O_2S{\cdot}HCl$	>10	0.065	100	51.9	22.8
10c	2-F	65	177−178	$C_{16}H_{12}ClFN_2O_2S{\cdot}HCl{\cdot}0.5H_2O$	100	0.028	100	66.2	21.5
10d	H	51	145−146	$C_{16}H_{13}ClN_2O_2S{\cdot}0.25H_2O$	>10	0.123	96	82.6	29.2
10e	4-Cl	55	222−223	$C_{16}H_{12}Cl_2N_2O_2S{\cdot}HCl{\cdot}0.25H_2O$	>10	0.018	100	88.4	9.1
10f	4-Me	76	182	$C_{17}H_{15}ClN_2O_2S{\cdot}0.25H_2O$	>10	0.016	100	90.5	21.6
10g	4-OMe	63	205	$C_{17}H_{15}ClN_2O_3S{\cdot}0.5H_2O$	1.3	0.011	100	100	33.4
10h	4-OEt	65	207	$C_{18}H_{17}ClN_2O_3S{\cdot}HCl$	>10	0.004	100	100	16.3
10i	4-OPr	60	161−163	$C_{19}H_{19}ClN_2O_3S{\cdot}HCl{\cdot}0.5H_2O$	>10	10.0	NT[f]	0	NT[f]
10j	4-OPr^i	80	153	$C_{19}H_{19}ClN_2O_3S{\cdot}0.25H_2O$	>10	>10	NT[f]	NT[f]	NT[f]
10k	4-OCF_3	73	136−138	$C_{17}H_{12}ClF_3N_2O_3S{\cdot}HCl$	>10	10.0	NT[f]	NT[f]	NT[f]
10l	4-Pr	76	151	$C_{19}H_{19}ClN_2O_2S$	>10	0.100	91.9	60.0	0
10m	4-Pr^i	65	161	$C_{19}H_{19}ClN_2O_2S{\cdot}0.25H_2O$	>10	0.039	100	70.0	17.0
10n	4-SMe	15	216−220	$C_{17}H_{15}ClN_2O_2S_2{\cdot}0.75H_2O$	0.9	0.011	88.5	49	21.7
10o	4-SEt	34	181−185	$C_{18}H_{17}ClN_2O_2S_2{\cdot}0.5H_2O$	>10	0.053	97.3	76.7	12.3
10p	4-SO_2Et	80	-	$C_{18}H_{17}ClN_2O_4S_2$	>10	>10	NT[f]	NT[f]	NT[f]
10q	4-NH_2	85	170	$C_{16}H_{14}ClN_3O_2S{\cdot}H_2O$	>10	0.187	71.6	NT[f]	15.3
10r	4-AcNH	65	238−241	$C_{18}H_{16}ClN_3O_3S{\cdot}0.5H_2O$	>10	>10	NT[f]	NT[f]	NT[f]
10s	4-NEt_2	70	207−209	$C_{20}H_{22}ClN_3O_2S{\cdot}0.5H_2O$	>10	0.080	100	9.7	24.2
10t	2,4-di-F	45	183−184	$C_{16}H_{11}ClF_2N_2O_2S$	23.8	0.007	100	79.6	8.6
10u	4-OMe-2-F	61	176−198	$C_{17}H_{14}ClFN_2O_3S{\cdot}HCl{\cdot}0.25H_2O$	0.11	0.015	100	100	33.0
10v	3,4-di-Cl	74	156−157	$C_{16}H_{11}Cl_3N_2O_2S$	9.0	0.006	100	93.8	23.5
10w	4-OMe-3-F	73	196	$C_{17}H_{14}ClFN_2O_3S$	>10	0.004	100	79	24.2
10x	4-Me-3-F	48	176	$C_{17}H_{14}ClFN_2O_2S{\cdot}HCl{\cdot}0.5H_2O$	>10	0.006	100	75.1	22.6
10y	4-OMe-3-Me	73	198	$C_{18}H_{17}ClN_2O_3S{\cdot}HCl$	>10	0.013	100	100	21.4
10z	4-Me-3-OMe	71	178	$C_{18}H_{17}ClN_2O_3S{\cdot}HCl$	>10	0.015	100	77.1	9.2
10aa	4-Cl-3-Me	76	181−182	$C_{17}H_{14}Cl_2N_2O_2S{\cdot}HCl$	4.0	0.011	100	-	NT[f]
10ab	4-NMe_2−3-Cl	75	169	$C_{18}H_{17}Cl_2N_3O_2S$	1.9	0.027	98.9	64.6	33.3
10ac	4-OMe-3-Cl	70	191−192	$C_{17}H_{14}Cl_2N_2O_3S$	>10	0.008	100	84.1	31.4
10ad	4-OEt-3-Cl	76	218−219	$C_{18}H_{16}Cl_2N_2O_3S{\cdot}0.5H_2O$	>10	0.007	100	47.7	2.0
10ae	4-OEt-3-F	84	199−203	$C_{18}H_{16}ClFN_2O_3S{\cdot}0.75H_2O$	>10	0.025	95.2	96.5	14.1
10af	4-F-3-OMe	60	178−179	$C_{17}H_{14}ClFN_2O_3S$	>10	0.016	92.6	97.4	25.0
10ag	4-OMe-3,5Cl	75	230	$C_{17}H_{13}Cl_3N_2O_3S$	>10	0.007	99.8	37.3	16.5
10ah	3,5-di-OEt	60	227−231	$C_{20}H_{21}ClN_2O_4S{\cdot}HCl$	>10	>10	0	NT[f]	NT[f]
10ai	3,5-diF	80	196	$C_{16}H_{11}ClF_2N_2O_2S$	>10	0.075	61.6	NT[f]	NT[f]

[a−f] See footnotes a−f of Table 1.

When the most potent compounds identified so far (**10a**, **11**, **32**, **33**, and **39**), were submitted to other tests in vivo (Table 6), compound **10a** emerged as the most potent derivative. For this reason the 4-chloro-1-methylsulfonylphenylimidazole nucleus was selected for studying the SAR around the aryl group in position 5 (Tables 3 and 4), the only portion in the molecule yet to be explored. Similar analogues of compounds **32** and **39** were also prepared, but none of them showed increased potency in vivo (results not shown).

Changing the fluorine position of **10a** decreased potency both in vitro and in vivo (**10b**,**c**). The unsubstituted derivative **10d** was less potent, as confirmed in the air-pouch model (Table 6). The 4-chloro and methyl derivatives **10e** and **10f**, although highly potent in vitro, were less so in vivo. The 4-methoxy derivative **10g** was potent in the CPE test, but was less selective than **10a**. However elongation of the alkoxy chain to ethoxy (**10h**) increased selectivity, possibly caused by the occupation of an additional pocket in the COX-2 enzyme by the longer alkyl chain.[15] This pocket may be easier to achieve in the case of these 4-chloroimidazoles than in other related structures such as the pyrazoles represented by Celecoxib, where the ethoxy group only produced a loss in potency.[9]

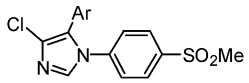
Further elongation of the alkoxy chain (**10i**−**j**), as well as introduction of fluorine atoms (**10k**), blocked all activity. Maintaining the same chain length, the oxygen atom was replaced by sulfur (**10n,o**), sulfone (**10p**), CH_2 (**10l**), and CHMe (**10m**). The effect of an electron-withdrawing sulfone (**10p**) was clearly negative, and although the remaining compounds retained potency in vitro, they were all less potent in vivo than their alkoxy counterparts.

The poor in vitro potency of the 4-amino and acetylamino derivatives **10q** and **10r** was improved upon substitution (**10s**), although this compound failed to show sufficient activity in vivo (Table 6).

Disubstitution of the phenyl ring was initially explored by introduction of fluorine in the 2-position of **10a** and **10g**. In the first case (**10t**), the in vivo activity was lost and in **10u** selectivity decreased. Among the 3,4-disubstituted derivatives (**10v**−**af**) highly potent compounds were identified, which were submitted to additional tests in vivo (Table 6). The trisubstituted and the 3,5-disubstituted derivatives were poorly active both in vivo (**10ag**) and in vitro (**10ah,ai**).

Replacing the phenyl ring in position 5 by other heterocycles was also explored (Table 4). The naked 3-pyridyl and 4-pyridyl derivatives **10aj** and **10ap**

Table 4. Aryl Sulfones of Formula **10**



					h cell lines IC_{50}[c]		HWB COX-2[d]		CPE[e]
		Yield	Mp[a],		COX-1	COX-2	% Inh		% Inh.
Comp	Ar	%	°C	Formula[b]	(μM)	(μM)	10 μM	1 μM	10 mpk
10aj	3-pyridyl	32	187	$C_{15}H_{12}ClN_3O_2S.0.25H_2O$	>10	>10	100	74.9	19.0
10ak	6-Me-3-pyridyl	63	-	$C_{16}H_{14}ClN_3O_2S.2HCl.0.5H_2O$	>100	0.284	100	58.4	28.9
10al	6-Cl-3-pyridyl	45	223	$C_{15}H_{11}Cl_2N_3O_2S$	>10	0.043	100	76.6	29.0
10am	6-EtO-3-pyridyl	70	186-188	$C_{17}H_{16}ClN_3O_3S$	10.8	0.274	97.5	74.2	24.7
10an	6-OH-3-pyridyl	60	198-200	$C_{15}H_{12}ClN_3O_3S.H_2O$	>10	>1	66.4	-	NT[f]
10ao	6-NEt_2-3-pyridyl	30	200-202	$C_{19}H_{21}ClN_4O_2S$	>10	>1	90.9	-	NT[f]
10ap	4-Pyridyl	68	189-190	$C_{15}H_{12}ClN_3O_2S$	>10	10.0	82.4	54.5	31.7
10aq		71	221	$C_{17}H_{13}ClN_2O_4S.0.5H_2O$	>10	0.006	100	60.5	30.6
10ar		64	227	$C_{18}H_{15}ClN_2O_3S$	0.11	0.009	65.5	69.9	29
10as		74	212-216	$C_{19}H_{15}ClN_2O_3S.H_2O$	>10	0.074	59.9	NT[f]	NT[f]
10at		66	127-131	$C_{20}H_{15}BrClN_2O_3S$	>1	>1	NT[f]	NT[f]	NT[f]
1010au		78	215	$C_{18}H_{13}ClN_2O_3S.0.25H_2O$	>1	>1	NT[f]	NT[f]	NT[f]

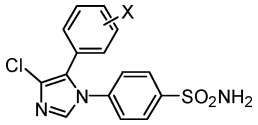
[a–f] See footnotes a–f of Table 1.

showed poor activity in the whole cell assay but a surprisingly high activity in the HWB test. The 4-methyl, 4-chloro and 4-ethoxy derivatives **10ak**−**am** showed good activity in the CPE test, but not in the air-pouch or hyperalgesia models. Compound **10aq** was the most potent and selective of all the heterocycle variations studied.

We next replaced the SO_2Me group by a SO_2NH_2, which has been shown to improve the activity in vivo by enhancing bioavailability.[9] As shown in Table 5 the selectivity of the sulfonamide derivatives was generally lower than their sulfone counterparts. Three of them (**51a**,**b**,**g**) showed a diminished potency in the HWB test, which may be explained by a high percentage of binding to serum proteins. Although some compounds (**51i**−**j**) failed to improve activity in vivo, others were highly potent COX-2 inhibitors both in vitro and in vivo (Tables 5 and 6).

The highly lipophilic and insoluble character of the diarylheterocycle class of COX-2 inhibitors together with lack of hepatic elimination routes may explain the prolonged half-lives described for some of these compounds.[34] For this reason early pharmacokinetic evaluation in rats was performed for the most active compounds (Table 6). The 4-fluoro derivatives **10a** and **51a** showed long half-lives in this species, which were hardly diminished in the unsubstituted **10d** and **51b**. Introduction of metabolizable methyl groups decreased the half-lives (**10f** and **51c**), but in vivo activity was also reduced. The pyridyl derivative **10al** also had a long half-life, suggesting that N-oxidation was not an effective elimination route. It is known that substitution of aromatic rings with electron-releasing groups such as alcoxy or alkylamino increases metabolic elimination, either by increasing the potential for hydroxylation of such rings or by giving dealkylated products, which are more easily eliminated. These assumptions were accomplished in our series, where introduction of electron-releasing groups gave compounds with shorter half-lives (**10w**, **10ab**, **10ac**, **10aq**, **51d**, **51f**). Compounds **10ab** and **10ac** were discarded due to their inferior in vivo activity and the remaining four compounds were submitted to in vitro evaluation of cytochrome inhibition.[35] Compound **10aq** was discarded due to high CYP3A4 inhibi-

Table 5. Phenyl-Substituted Sulfonamides of Formula **51**



compd	X	mp,[a] °C	formula[b]	*h* cell lines IC_{50}[c] COX-1 (μM)	*h* cell lines IC_{50}[c] COX-2 (μM)	HWB COX-2[d] % inhib 10 μM	HWB COX-2[d] % inhib 1 μM	CPE[e] % inhib, 10 mg/kg
51a	4-F	223	$C_{15}H_{11}ClFN_3O_2S\cdot0.25H_2O$	3.1	0.018	61.4	NT[f]	38.6
51b	H	235	$C_{15}H_{12}ClN_3O_2S\cdot0.25H_2O$	5.1	0.009	59.5	NT[f]	36.3
51c	4-Me	255	$C_{16}H_{14}ClN_3O_2S\cdot0.25H_2O$	2.7	0.003	100	76.1	32.6
51d	4-OEt	265	$C_{17}H_{16}ClN_3O_3S\cdot0.25H_2O$	2.2	0.002	100	100	29.2
51e	3,4-Cl	251	$C_{15}H_{10}Cl_3N_3O_2S\cdot0.5H_2O$	0.6	0.002	100	93.5	29.6
51f	4-OMe-3-F	211	$C_{16}H_{13}ClFN_3O_3S$	3.3	0.005	100	100	31.0
51g	4-F-3-OMe	191	$C_{16}H_{13}ClFN_3O_3S$	> 1	0.008	79.3	NT[f]	14.3
51h	4-OEt-3-F	236	$C_{17}H_{15}ClFN_3O_3S$	76.0	0.020	100	57.0	30.3
51i	4-OMe-3-Cl	245	$C_{16}H_{13}Cl_2N_3O_3S$	1.2	0.005	99.9	-	24.0
51j	4-OEt-3-Cl	272	$C_{17}H_{15}Cl_2N_3O_3S$	15.5	0.007	99.9	26.8	18.5
51k	4-Cl-3-Py[g]	276−277	$C_{14}H_{10}Cl_2N_4O_2S$	> 10	0.042	97.6	19.6	18.1

[a−f] See footnotes a,b,c,d,e of Table 1. [g] X-Ph = 4-Chloro-3-pyridyl.

Table 6. In Vivo Data of Selected Compounds

UR	air pouch,[a] % inhib (1 mg/kg, po)	rat[b] half-life (h)	hyperalgesia[a] % inhib (3 mg/kg, po)
2[c]	93.4	NT[e]	86.7
3[d]	95.3	NT[e]	83.4
10a	98.1	21	NT[e]
10d	83.2	17	NT[e]
10f	65.5	1.7	NT[e]
10s	64.1	NT[e]	64.1
10x	18.5	NT[e]	NT[e]
10y	75.6	NT[e]	NT[e]
10w	89.5	2.2	80.0
10ab	43.0	1.2	63.8
10ac	71.1	3.6	66.6
10af	15.1	NT[e]	20.4
10ak	66.6	NT[e]	NT[e]
10al	91.4	26	NT[e]
10am	70.1	NT[e]	62.9
10ap	50.2	NT[e]	69.4
10aq	NT[e]	3.5	69.9
11	91.4	NT[e]	NT[e]
13a	45.0	NT[e]	NT[e]
32	55.2	NT[e]	NT[e]
33	35.5	NT[e]	NT[e]
39	79.0	NT[e]	NT[e]
51a	93.2	17	NT[e]
51b	96.3	26	NT[e]
51c	62.3	5.2	NT[e]
51d	98.9	2.2	82.8
51f	98.2	2.9	83.4
51g	58.9	3.8	38.0

[a] See Experimental Section. [b] Half-life in rat after iv administration of compounds in DMSO solution at 1 mg/kg. [c] Celecoxib. [d] Rofecoxib. [e] Not tested.

tion, and the remaining compounds, **10w**, **51d,** and **51f** were selected for further evaluation (Table 7).

Gastric toxicity was assessed using the ^{51}Cr leakage test.[36] In this assay imidazoles **10w** and **51d** and **51f** did not induce gastric bleeding at 100 mg/kg bid. In contrast, indomethacin produced a 7.5% leakage at a much lower dose (5 mg/kg bid). In the adjuvant arthritis model, compounds **51d** and **51f** were more potent than **10w** and comparable to the reference compounds **2** and **3**. Compound **51f** showed a reduction in total radiographic scores and secondary paw swelling (ID_{50}: 0.18 mg/kg) in a dose-dependent manner.

Compound **51f** was selected for further development after pharmacokinetic evaluation in other species. It showed 90% binding to human serum proteins, good bioavailability in rats (53%) and dogs (81%) and pharmacokinetic behavior suggestive of one daily dosing in man. Compound **51f** (UR-8880)[37] has successfully completed preclinical development as it is now finishing phase I clinical trials for the treatment of osteoarthritis and pain.

Table 7. Pharmacological Data of Selected Compounds

compd	COX-2 HWB, IC_{50} (nM)	adjuvant arthritis, % inhib[b]	^{51}Cr leakage[c] 100 mg/kg, bid, 5 days (%)
indomethacin (**1**)	640	94	7.5[d]
celecoxib (**2**)	600	89	0.7
rofecoxib (**3**)	280	87	0.6
10w	156	86	0.4
51d	27	97	0.5
51f	66	93	0.9

[a] Inhibition of contralateral paw swelling after oral treatment for 28 days (1 mg/kg od). [b] Percentage of ^{51}Cr secreted in feces.[37] [c] Dose: 5 mg/kg, bid.

In summary, we have described the structure activity relationships of two isomeric imidazole cores, which has led to the identification of a highly selective COX-2 inhibitor, **51f**. This compound showed high potency in all inflammation tests assayed together with good pharmacokinetics, which led to its selection as a clinical candidate.

Experimental Section

Melting points were determined with a Mettler FP 80 central processor melting point apparatus and are uncorrected. ^{13}C (75 MHz) NMR spectra and ^{1}H (300 MHz) NMR spectra were recorded on a Brücker Avance DPX-300 spectrometer. They are reported in ppm on the δ scale, from the reference indicated. Combustion analyses were performed with a Carlo Erba 1106 analyzer. Liquid chromatography was performed with a forced flow (flash chromatography) of the indicated solvent system on SDS silica gel Chromagel 60 ACC (230−400 mesh). Analytical thin-layer chromatography (TLC) was performed with Macherey-Nagel 0.25 mm silica gel SIL G-25 plates.

4-Methylsulfonylaniline (6). A mixture of Na_2WO_4 (0.067 g), 8 drops of acetic acid, and H_2O (19 mL) was placed in a flask and heated to 65 °C. 4-Methylthioaniline (19 mL, 153 mmol) was added followed by dropwise addition of H_2O_2 (34.5 mL, 337 mmol). The mixture was stirred at 65 °C for 1.5 h and, after cooling, 800 mL of 1 N HCl and 500 mL of $CHCl_3$

were added. The layers were separated, and the aqueous phase was washed with more $CHCl_3$. The aqueous phase was basified with 25% NaOH and extracted with $CHCl_3$. The organic phase was washed with brine and dried over $MgSO_4$. The solvent was removed to give **6** as a white solid (19.80 g, 75%): mp 134 °C; ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS) 2.97 (s, 3 H), 4.04 (s, 2 H), 6.66 (d, J = 9 Hz, 2 H), 7.56 (d, J = 9 Hz, 2 H).

***N*-(4-Fluorobenzylidene)-4-methylsulfonylaniline (8a).** A mixture of **6** (19.60 g, 115 mmol), 4-fluorobenzaldehyde (12.19 mL, 115 mmol), and toluene (590 mL) was refluxed in a Dean−Stark for 2 days. The solvent was removed, and the crude **8a** thus obtained was directly used in the next reaction.

A sample was recrystallized from Et_2O to give the analytically pure compound: mp 142 °C; ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS) 3.08 (s, 3 H), 7.20 (m, 2 H), 7.30 (m, 2 H), 7.98 (m, 4 H), 8.38 (s, 1 H).

5-(4-Fluorophenyl)-1-(4-methylsulfonylphenyl)imidazole (9a). A mixture of **8a** (31.8 g, 115 mmol), tosylmethyl isocyanide (33.4 g, 172 mmol), K_2CO_3 (31.7 g, 229 mmol), MeOH (795 mL), and DME (340 mL) was refluxed for 2 h. The solvent was removed, and the residue was redissolved in a CH_2Cl_2/brine mixture. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and concentrated. The crude product was washed with Et_2O and recrystallized from EtOAc/hexane to afford **9a** as a creamy solid (27.5 g, 75%): mp 151−155 °C; ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS) 3.10 (s, 3 H), 7.05 (m, 2 H), 7.13 (m, 2 H), 7.26 (s, 1 H), 7.36 (d, J = 9 Hz, 2 H), 7.75 (s, 1 H), 7.99 (d, J = 9 Hz, 2 H); Anal. ($C_{16}H_{13}FN_2O_2S$) C, H, N, S.

5-(6-Ethoxy-3-pyridyl)-1-(4-methylsulfonylphenyl)imidazole (9am). A mixture of **9al** (0.20 g, 0.6 mmol), 18-crown-6 (0.007 g), KOH (0.079 g, 1.2 mmol), EtOH (0.1 mL), and toluene (10 mL) was refluxed in a Dean Stark for 12 h. The mixture was poured on ice, and the layers were separated. The aqueous phase was extracted with EtOAc, and the organic phases were dried over $MgSO_4$ and concentrated. Chromatography on silica gel (hexane−AcOEt mixtures) afforded **9am** as a yellow solid (0.20 g, 100%): mp 167−169 °C; ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS) 1.40 (t, J = 7.5 Hz, 3 H), 3.10 (s, 3 H), 4.35 (q, J = 7.5 Hz, 2 H), 6.65 (d, J = 8.5 Hz, 1 H), 7.30 (m, 2 H), 7.38 (d, J = 8.5 Hz, 2 H), 7.79 (m, 1 H), 8.02 (m, 3 H); Anal. ($C_{17}H_{17}N_3O_3S\cdot0.5H_2O$) C, H, N, S.

4-Chloro-5-(4-fluorophenyl)-1-(4-methylsulfonylphenyl)-imidazole (10a). A mixture of **9a** (27.2 g, 86 mmol), *N*-chlorosuccinimide (12.05 g, 90 mmol), and $CHCl_3$ (81 mL) was refluxed for 18 h. The solvent was removed, and the residue was redissolved in CH_2Cl_2 and washed with 1 N HCl, 1 N NaOH, and brine. The organic phase was dried over $MgSO_4$ and concentrated to a residue, which was chromatographed on silica gel (hexane−AcOEt mixtures) to afford **10a** as a white solid (24.0 g, 80%): mp 167 °C; ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS) 3.13 (s, 3 H), 7.12 (m, 2 H), 7.20 (m, 2 H), 7.32 (d, J = 9 Hz, 2 H), 7.71 (s, 1 H), 8.02 (d, J = 9 Hz, 2 H); Anal. ($C_{16}H_{12}ClFN_2O_2S$) C, H, N, S.

Following a similar procedure, but using NCS, NBS, or 2 equiv of NCS, and starting from the corresponding imidazoles, compounds **11**, **18**, **23**, **41**, **42**, **43**, and **44** were obtained.

5-(4-Aminophenyl)-4-chloro-1-(4-methylsulfonylphenyl)-imidazole (10q). A mixture of 4-chloro-1-(4-methylsulfonylphenyl)-5-(4-nitrophenyl)imidazole (1.14 g, 3 mmol), $SnCl_2$ (2.88 g, 15 mmol), and EtOH (21 mL) was refluxed for 1.5 h. The solvent was removed, and the residue was basified with 25% NaOH and extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated. Chromatography on silica gel (hexane−AcOEt mixtures) afforded **10q** as a yellow solid (0.85 g, 81%): mp 170 °C; ^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD δ TMS) 3.08 (s, 3 H), 4.0 (s, 2 H + H_2O), 6.60 (d, J = 8.5 Hz, 2 H), 6.90 (d, J = 8.5 Hz, 2 H), 7.35 (d, J = 8.5 Hz, 2 H), 7.66 (s, 1 H), 7.93 (d, J = 8.5 Hz, 2 H); Anal. ($C_{16}H_{14}ClN_3O_2S\cdot H_2O$) C, H, N, S.

5-(4-Acetylaminophenyl)-4-chloro-1-(4-methylsulfonylphenyl)imidazole (10r). A mixture of **10q** (0.15 g, 0.4 mmol) and Ac_2O (0.15 mL) was refluxed for 4 h. The solvent was removed, and the residue was chromatographed on silica gel (hexane−AcOEt mixtures) to afford **10r** as a yellow solid (0.028 g, 18%): mp 238−241 °C; ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS) 2.31 (s, 3 H), 3.11 (s, 3 H), 5.32 (s, 1 H), 7.14 (d, J = 8.5 Hz, 2 H), 7.32 (d, J = 8.5 Hz, 2 H), 7.37 (d, J = 8.5 Hz, 2 H), 7.70 (s, 1 H), 8.02 (d, J = 8.5 Hz, 2 H); Anal. ($C_{18}H_{16}ClN_3O_3S\cdot0.5H_2O$) C, H, N, S.

4-Chloro-5-(3-chloro-4-dimethylaminophenyl)-1-(4-methyl-sulfonylphenyl)imidazole (10ab). Following a similar procedure to that described for the preparation of **10a**, but starting from 5-(4-dimethylaminophenyl)-1-(4-methyl-sulfonylphenyl)imidazole and using 2 equiv of *N*-chlorosuccinimide, compound **10ab** was obtained as a yellow solid (45%): mp 169 °C; ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS) 2.85 (s, 6 H), 3.09 (s, 3 H), 6.9 (m, 2 H), 7.2 (m, 1 H), 7.35 (d, J = 8.6 Hz, 2 H), 7.64 (s, 1 H), 8.00 (d, J = 8.6 Hz, 2 H). Anal. ($C_{18}H_{17}Cl_2N_3O_2S$) C, H, N, S.

5-(4-Fluorophenyl)-4-methyl-1-(4-methylsulfonylphenyl)imidazole (13a). Following a similar procedure to that described for the preparation of **9a**, but using α-tosylethyl isocyanide[22] (**12a**) instead of tosylmethyl isocyanide, **13a** was obtained as a white solid (45%): mp 143−143 °C; ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS) 2.31 (s, 3 H), 3.08 (s, 3 H), 7.05 (m, 4 H), 7.27 (d, J = 9 Hz, 2 H), 7.71 (s, 1 H), 7.93 (d, J = 9 Hz, 2 H); Anal. ($C_{17}H_{15}FN_2O_2S\cdot0.25H_2O$) C, H, N, S.

Compounds **13b**−**e** were obtained in a similar way from the corresponding tosyl isocyanides (**12b**−**e**), which were prepared as described for **10**.[22]

***N*-(4-Methylsulfanylbenzyliden)-4-fluoroaniline (23).** A mixture of 4-fluoroaniline (10.0 g, 90 mmol), 4-methylsulfanylbenzaldehyde (16.5 g, 90 mmol), and benzene (500 mL) was refluxed in a Dean−Stark for 2 days. The solvent was removed and the crude product obtained was directly used in the following reaction. A sample was recrystallized from Et_2O to give analytically pure **25**: mp 93 °C; ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS) 2.54 (s, 3 H), 7.07 (m, 2 H), 7.20 (m, 2 H), 7.31 (d, J = 9 Hz, 2 H), 7.79 (d, J = 9 Hz, 2 H), 8.38 (s, 1 H).

4-Methylsulfonylbenzaldehyde (24). To a solution of 4-methylthiobenzaldehyde (5 g, 33 mmol) in CH_2Cl_2 (132 mL) was added, at 0 °C, *m*-chloroperbenzoic acid (20.61 g, 66 mmol). The mixture was stirred for 3 h at room temperature and was poured over $CHCl_3$, washed with saturated $NaHCO_3$ solution, and dried over $MgSO_4$. The solvent was removed, and the residue was chromatographed on silica gel (hexane−AcOEt mixtures) to afford **24** as a white solid (3.96 g, 65%): mp 157−159 °C; ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS) 3.10 (s, 3 H), 8.09 (m, 4 H), 10.14 (s, 1 H).

In a similar manner, compound **19** was obtained from 4-methylsulfanylaniline and 4-fluorobenzaldehyde.

1-(4-Fluorophenyl)-5-(4-methylsulfanylphenyl)imidazole (27). A mixture of **25** (6 g, 24.5 mmol), benzotriazolylmethylisocyanide (3.87 g, 24.5 mmol), potassium *tert*-butoxide (5.49 g, 49 mmol), and DMSO (98 mL) was heated to 75 °C for 1 h. After cooling, Et_2O was added, and it was washed with H_2O. The organic phase was dried over $MgSO_4$, and the solvent was removed. The residue thus obtained was chromatographed on silica gel (hexane−AcOEt mixtures) to afford **27** as a white solid (4.06 g, 58%): mp 96−99 °C; ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS: 2.46 (s, 3 H), 7.0−7.3 (m, 9 H), 7.67 (s, 1 H); Anal. ($C_{16}H_{13}FN_2S\cdot0.5H_2O$) C, H, N, S.

In a similar manner, compound **20** was obtained from **19**.

1-(4-Fluorophenyl)-5-(4-methylsulfonylphenyl)imidazole (28). Following a similar procedure to that described for the preparation of **9a**, but starting from **24** and 4-fluoroaniline, **28** was obtained as a white solid (70%): mp 133−134 °C; ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS) 3.05 (s, 3 H), 7.20 (m, 4 H), 7.31 (d, J = 9 Hz, 2 H), 7.41 (s, 1 H), 7.73 (s, 1 H), 7.83 (d, J = 9 Hz, 2 H); Anal. ($C_{16}H_{13}FN_2O_2S$) C, H, N, S.

2-Chloro-1-(4-fluorophenyl)-5-(4-methylsulfanylphenyl)-imidazole (29). To a solution of diisopropylamine (0.35 mL, 2.5 mmol) in THF (8.5 mL) was added, at −20 °C, BuLi (1.6 M in hexane, 1.57 mL, 2.5 mmol), and the mixture was stirred for 10 min. Compound **27** (0.56 g, 2 mmol) in THF (14 mL) was added, and after stirring for 30 min, *N*-chlorosuccinimide

(0.78 g, 5.8 mmol) in THF (8 mL) was added. The mixture was stirred for 30 min at −20 °C and for 1.5 h at room temperature. The solvent was removed, and the residue was dissolved in an EtOAc−H_2O mixture. The layers were separated, and the aqueous phase was extracted with EtOAc. The organic phase was dried over $MgSO_4$, and the solvent was removed to give a residue, which was chromatographed on silica gel (hexane−AcOEt mixtures). Compound **29** was obtained as a white solid (0.23 g, 37%): ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS) 2.43 (s, 3 H), 6.9−7.2 (m, 8 H), 7.67 (s, 1 H).

Following a similar procedure but using NBS or methyl iodide instead of NCS, compounds **30** and **31** were obtained. Following a similar procedure, but starting from compound **20** and using methyl iodide instead of NCS, compound **21** was obtained.

2-Chloro-1-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-imidazole (32). Following a similar procedure to that described for the preparation of **24**, but starting from **29**, compound **32** was obtained as a white solid (80%): mp 218−220 °C; ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS) 3.04 (s, 3 H), 7.1 (m, 6 H), 7.32 (s, 1 H), 7.82 (d, J = 8.5 Hz, 2 H); Anal. ($C_{16}H_{12}Cl_2FN_2O_2S\cdot0.25H_2O$) C, H, N, S.

In a similar manner compounds **33**, **34**, and **22** were obtained from **30**, **31**, and **21**, respectively.

1-(4-Fluorophenyl)-2-hydroxymethyl-5-(4-methylsulfonylphenyl)imidazole (35). A mixture of **28** (2.0 g, 6.3 mmol) and CH_2O (40% in H_2O, 10 mL) was heated at 130 °C for 72 h. The solvent was removed, and the residue was dissolved in a EtOAc−H_2O mixture. The layers were separated, and the aqueous phase was extracted with EtOAc. The organic phase was dried over $MgSO_4$, and the solvent was removed to give a residue which was chromatographed on silica gel (hexane−AcOEt mixtures). Compound **35** was obtained as a white solid (0.94 g, 43%): mp 211−212 °C; ^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD δ TMS) 3.07 (s, 3 H), 3.8 (s, 1 H + H_2O), 4.45 (s, 2 H), 7.2 (m, 7 H), 7.80 (d, J = 8.2 Hz, 2 H); Anal. ($C_{17}H_{15}FN_2O_3S$) C, H, N, S.

2-Fluoromethyl-1-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)imidazole (36). To a solution of **35** (0.2 g, 0.6 mmol) in CH_2Cl_2 (4 mL) was carefully added diethylaminosulfur trifluoride (0.14 g, 0.9 mmol), and the mixture was stirred at room temperature for 2 h. Water was added, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, and the solvent was removed to give a residue, which was chromatographed on silica gel (hexane−AcOEt mixtures). Compound **36** was obtained as a white solid (0.06 g, 28%): mp 152−154 °C; Anal. ($C_{17}H_{14}F_2N_2O_2S\cdot0.75H_2O$) C, H, N, S.

1-(4-Fluorophenyl)-5-(4-methylsulfonylphenyl)imidazol-2-carboxaldehyde (37) and Methyl 1-(4-Fluorophenyl)-5-(4-methylsulfonylphenyl)imidazol-2-carboxylate (38). A mixture of **35** (0.2 g, 0.6 mmol), MnO_2 (1.26 g, 14.5 mmol), 3 Å molecular sieves (0.100 g), MeOH (6.5 mL), and THF (4 mL) was stirred at room temperature for 24 h. The resulting suspension was filtered through Celite and washed with hot THF. The solvent was removed, and the crude product was chromatographed on silica gel (hexane−AcOEt mixtures) to give the following:

37: (0.073 g, 36%); mp 198 °C; ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS) 3.05 (s, 3 H), 7.1 (m, 6 H), 7.62 (s, 1 H), 7.85 (d, J = 8.5 Hz, 2 H), 9.84 (s, 1 H); Anal. ($C_{17}H_{13}FN_2O_3S\cdot0.5H_2O$) C, H, N, S.

38: (0.061 g, 28%); mp 192−194 °C; ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS) 3.03 (s, 3 H), 3.87 (s, 3 H), 7.1 (m, 6 H), 7.50 (s, 1 H), 7.87 (d, J = 8.5 Hz, 2 H); Anal. ($C_{18}H_{15}FN_2O_4S\cdot1.25H_2O$) C, H, N, S.

1-(4-Fluorophenyl)-5-(4-methylsulfonylphenyl)imidazol-2-carbonitrile (39). A mixture of **37** (0.24 g, 0.7 mmol), hydroxylamine-*O*-sulfonic acid (0.155 g, 1.4 mmol), pyridine (3 mL), and EtOH (30 mL) was stirred under reflux for 18 h. The mixture was poured over $CHCl_3$ and washed with saturated $NaHCO_3$ solution. It was dried over $MgSO_4$, and the solvent was removed, affording a crude product, which was chromatographed on silica gel (hexane−AcOEt mixtures). Compound **39** was obtained as a white solid (0.090 g, 37%): mp 192 °C; ^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD δ TMS) 2.99 (s, 3 H), 7.1 (m, 6 H), 7.39 (s, 1 H), 7.75 (d, J = 8.5 Hz, 2 H); Anal. ($C_{17}H_{12}FN_3O_2S\cdot0.25H_2O$) C, H, N, S.

2-Benzoyl-1-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)imidazole (40). To a solution of **28** (0.20 g, 0.6 mmol) in acetonitrile (1 mL), NEt_3 (0.08 mL, 0.6 mmol), and benzoyl chloride (0.07 mL, 0.6 mmol) was added, and the mixture was stirred at room-temperature overnight. The mixture was poured over H_2O and extracted with EtOAc. The organic phase was washed with 1 N HCl and H_2O, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel (hexane−AcOEt mixtures) to give **40** as a white solid (0.060 g, 22%): mp 225−226 °C; ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS) 3.05 (s, 3 H), 7.0−7.5 (m, 10 H), 7.85 (d, J = 8.5 Hz, 2 H), 8.25 (d, J = 8.5 Hz, 2 H); Anal. ($C_{23}H_{17}FN_2O_3S\cdot0.25H_2O$) C, H, N, S.

Following a similar procedure, but starting from compound **9a**, compound **15** was obtained.

***N-tert*-Butyl-4-acetylaminobenzenesulfonamide (46).** To a suspension of 4-acetylaminobenzenesulfonyl chloride (10 g, 43 mmol) in DME (103 mL) was added, at 0 °C, *tert*-butylamine (9 mL, 86 mmol) in DME (103 mL). The bath was removed, and the mixture was stirred for 5 h at reflux. The solvent was concentrated, and $CHCl_3$ was added to the residue. The suspension thus obtained was filtered, and the solid was washed with $CHCl_3$, H_2O, and Et_2O and vacuum-dried. Compound **46** was obtained as a white solid (8.1 g, 70%): mp 200−201 ° C; ^{1}H NMR ($CDCl_3$ + CD_3OD δ TMS): 1.15 (s, 9 H), 2.12 (s, 3 H), 4.21 (s, 2 H + CD_3OD), 7.66 (d, J = 9 Hz, 2 H), 7.75 (d, J = 9 Hz, 2 H); Anal. ($C_{12}H_{18}N_2O_4S$) C, H, N, S.

***N-tert*-Butyl-4-aminobenzenesulfonamide (47).** A solution of **46** (8.0 g, 30 mmol), KOH (8.3 g, 148 mmol), H_2O (6 mL), and MeOH (24 mL) was heated at 100 ° C during 2 h. Water (24 mL) was added and heating continued for 2 h more. The mixture was allowed to cool, H_2O was added, and the pH was adjusted to 8 with 1 N HCl. The suspension thus obtained was extracted with AcOEt and dried over Na_2SO_4. The solvent was removed to afford **47** as a white solid (6.0 g, 89%): mp 127 ° C; ^{1}H NMR ($CDCl_3$ + CD_3OD δ TMS): 1.19 (s, 9 H), 3.74 (s, CD_3OD + 1 H), 6.67 (d, J = 9 Hz, 2 H), 7.60 (d, J = 9 Hz, 2 H); Anal. ($C_{10}H_{16}N_2O_2S$) C, H, N, S.

***N*-(3-Fluoro-4-methoxybenzylidene)-4-(*tert*-butylaminosulfonyl)aniline (48).** Following a similar procedure to that described for the preparation of **8a**, but starting from **47**, compound **48** was obtained as a yellow solid (100%): mp 129−131 ° C; ^{1}H NMR ($CDCl_3$ δ TMS): 1.23 (s, 9 H), 3.98 (s, 3 H), 4.65 (s, 1 H), 7.04 (t, J = 8.1 Hz, 1 H), 7.21 (d, J = 6.7 Hz, 2 H), 7.58 (m, 1 H), 7.73 (dd, J_{H-F} = 11.8 Hz, J = 2 Hz, 1 H), 7.90 (d, J = 6.7 Hz, 2 H), 8.33 (s. 1 H); Anal. ($C_{18}H_{21}FN_2O_3S$) C, H, N, S.

1-(*tert*-Butylaminosulfonylphenyl)-5-(3-fluoro-4-methoxyphenyl)imidazole (49). Following a similar procedure to that described for the preparation of **9a,** but starting from **48**, compound **49** was obtained as a white solid (87%): mp 229 °C; ^{1}H NMR ($CDCl_3$ δ TMS): 1.24 (s, 9 H), 3.89 (s, 3 H), 4.51 (s, 1 H), 6.90 (m, 3 H), 7.23 (s, 1 H), 7.29 (d, J = 8.7 Hz, 2 H), 7.73 (s, 1 H), 7.94 (d, J = 8.7 Hz, 2 H); Anal. ($C_{20}H_{22}FN_3O_3S$) C, H, N, S.

1-(*tert*-Butylaminosulfonylphenyl)-4-chloro-5-(3-fluoro-4-methoxyphenyl)imidazole (50). Following a similar procedure to that described for the preparation of **10a,** but starting from **49**, compound **50** was obtained as a white solid (82%): mp 209 °C; ^{1}H NMR ($CDCl_3$ δ TMS): 1.24 (s, 9 H), 3.89 (s, 3 H), 4.51 (s, 1 H), 6.90 (m, 3 H), 7.23 (d, J = 8.7 Hz, 2 H), 7.63 (s, 1 H), 7.92 (d, J = 8.7 Hz, 2 H); Anal. ($C_{20}H_{21}ClFN_3O_3S$) C, H, N, S.

4-[4-Chloro-5-(3-fluoro-4-methoxyphenyl)imidazol-1-yl]benzenesulfonamide (51f). A mixture of **50** (37.0 g, 85 mmol), concd HCl (200 mL), and H_2O (200 mL) was heated under reflux for 3 h. The mixture was allowed to cool and basified with 6 N NaOH at pH = 6. The precipitate thus obtained was filtered and washed with H_2O and $CHCl_3$. The solid thus obtained was crystallized from acetonitrile to give

51f as a white solid (27. 1 g, 84%): mp 211−212 °C; ^{1}H NMR ($CDCl_3$ + CD_3OD δ TMS) 3.90 (s, 3 H), 4.16 (s, CD_3OD + 2 H), 6.93 (m, 3 H), 7.30 (d, J = 8.6 Hz, 2 H), 7.73 (s, 1 H), 7.95 (d, J = 8.6 Hz, 2 H); Anal. ($C_{16}H_{13}ClFN_3O_3S$) C, H, N, S.

4-[4-Chloro-5-(4-fluorophenyl)imidazol-1-yl]benzenesulfonamide (51a).

Step 1: 4-Methylsulfinylaniline. To a solution of 4-methylsulfanylaniline (20 g, 144 mmol), CH_2Cl_2 (420 mL), and MeOH (80 mL) at 0 °C was added magnesium monoperoxyphthalate hexahydrate (46.6 g, 75 mmol), and the mixture was stirred at room temperature for 3 h. The suspension thus obtained was filtered and concentrated. The residue was dissolved in CH_2Cl_2 and washed with 1 N NaOH until basic. The organic phase was dried over $MgSO_4$ and concentrated. A crude product was obtained, which was washed with Et_2O to afford 4-methylsulfinylaniline as a creamy solid (20.1 g, 90%): ^{1}H NMR (300 MHz, $CDCl_3$ δ TMS) 2.68 (s, 3 H), 4.02 (s, 2 H), 6.75 (d, J = 8.7 Hz, 2 H), 7.45 (d, J = 8.7 Hz, 2 H).

Step 2: 1-[4-(Acetoxymethylsulfanyl)phenyl]-5-(4-fluorophenyl)imidazole. A mixture of 1-[4-(methylsulfonyl)-phenyl]-5-(4-fluorophenyl)imidazole (obtained from 4-methylsulfonylaniline and 4-fluorobenzaldehyde after heating with toluene and cyclization with TosMIC, as described for **9a**, 1.6 g, 5.3 mmol), Ac_2O (16 mL), and NaOAc (1.60 g, 20 mmol) was stirred at reflux under a nitrogen for 8 h. The solvent was removed, and the crude product was chromatographed on silica gel (hexane−AcOEt mixtures) to give the desired product as a foamy solid (1.6 g, 84%).

Step 3: 1-[4-(Acetoxymethylsulfanyl)phenyl]-4-chloro-5-(4-fluorophenyl)imidazole. Following a similar procedure to that described for the preparation of **10a**, but starting from 1-[4-(acetoxymethylsulfanyl)phenyl]-5-(4-fluorophenyl)imidazole the title compound was obtained (0.9 g, 51%).

Step 4: Sodium [4-Chloro-5-(4-fluorophenyl)imidazol-1-yl]benzenesulfinate. To a solution of the previous compound (0.9 g), CH_2Cl_2 (8 mL), and MeOH (4 mL) at 0 °C was added magnesium monoperoxyphthalate hexahydrate (1.5 g, 2.6 mmol), and the mixture was stirred at room-temperature overnight. A 5% $NaHCO_3$ solution (12 mL) was added, and the mixture was extracted with CH_2Cl_2. The solvent was removed, and the residue was dissolved in a mixture of THF (8 mL) and MeOH (4 mL). After the mixture was cooled to 0 °C, a 1 N NaOH solution (2.6 mL) was added. The mixture was stirred for 1 h at room temperature and was then concentrated. Water was removed by azeotropic distillation with EtOH/toluene mixtures. The residue was dried in vacuo, to give the title compound (0.9 g, 100%).

Step 5: 4-[4-Chloro-5-(4-fluorophenyl)imidazol-1-yl]-benzenesulfonamide (51a). A mixture of sodium [4-chloro-5-(4-fluorophenyl)imidazol-1-yl]benzenesulfinate (0.9 g), H_2O (13 mL), NaOAc (0.21 g, 2.7 mmol), and hydroxylamine-*O*-sulfonic acid (0.3 g, 2.7 mmol) was stirred overnight at room temperature. The resulting suspension was filtered, and the solid was washed with EtOAc and H_2O. The layers were separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were concentrated, and the residue was chromatographed on silica gel (hexane−AcOEt mixtures) to give **51a** as a white solid (0.42 g, 48%): mp 223 °C; ^{1}H NMR ($CDCl_3$ δ TMS) 4.84 (s, 2 H), 7.05 (m, 2 H), 7.18 (m, 2 H), 7.26 (d, J = 8.6 Hz, 2 H), 7.65 (s, 1 H), 7.96 (d, J = 8.6 Hz, 2 H); Anal. ($C_{15}H_{11}ClFN_3O_2S\cdot0.25H_2O$) C, H, N, S.

Air Pouch Model of Inflammation. Determination of PGE_2 in Exudate.[30] Male Lewis rats (175−200 g) were used. Air cavities were produced by a subcutaneous injection of sterile air (20 mL) into the intracapsular area. Every 2 days air (10 mL) was injected into the cavity to keep the space open. Seven days after the first injection, lambda-carrageenan (Sigma) in saline (2 mL of a 1% solution) was injected into the air pouch to produce an inflammatory reaction. The compounds were administered by oral route as a suspension in carboxymethyl cellulose and Tween-80 at 1% (10 mL/kg), 0.5 h before carrageenan injection. The animals were killed 6 h later, and the exudate volume was measured. Cells were pelleted by centrifugation at 1200*g* for 5 min at 4 °C, and PGE_2 was determined in the supernatant by specific ELISA.

Hyperalgesia Test.[31] The analgesic activity was measured in the inflammatory hyperalgesia model. Oedema was induced by injection of 1% carrageenan suspension (0.1 mL) in the right hind foot pad of male Sprague−Dawley rats. Three hours later, test compounds, suspended in 1 mL of tween-80 (1%), were administered orally via a gavage needle. Thirty minutes after dosing, hyperalgesic stimulus was induced by a heat source under the inflamed paw. The withdrawal latency in seconds was recorded for the control and treated groups. Percentage inhibition of the stimulus-induced decrease in withdrawal latency was determined and compared with measurement taken in the left (untreated) paw.

Adjuvant-Induced Arthritis (AIA) in Rat. AIA was induced in the right hind foot pad of Lewis rats (140−170 g, 7 weeks old) by an intradermal injection of 0.5 mg of *Mycobacterium butyricum* (Difco Laboratory, Detroit, MI) in light mineral oil. Ten rats were injected with incomplet adjuvant and served as nonadjuvant controls. Animals were distributed randomly into groups of 10 and dosed with 1 mg/kg po of tests compounds daily for 28 days beginning the day of adjuvant injection. Foot volume of left rat hind paws was measured plethysmographically at the end of the experiment. The mean increase in paw volume of treated animals was compared with that of controls, and results were expressed as inhibition percentage.

Gastrointestinal Lesion in Rats.[36] Ulcerogenicity of test compounds was evaluated by a modified version of the ^{51}Cr excretion method (2) in rats. **a. Red Blood Cell Labeling.** Blood from a donor rat was collected 1:7 in ACD anticoagulant (30 mM citric acid, 80 mM sodium citrate, 60 mM dextrose). A red blood cell (RBC) pellet was obtained by centrifugation and washed twice with ACD saline solution (5.4 mM citric acid, 12.2 mM sodium citrate, 9.5 mM dextrose, 0.9% sodium chloride, pH 6.50). RBCs were resuspended up to the original volume in saline solution and incubated with 14 Ci/mL sodium 51-chromate (CJS11, Amersham PharmaciaBiotech). Unincorporated ^{51}Cr was washed away, and radioactivity was measured in aliquots of resuspended labeled-RBC in a gamma-counter (Wallac). A volume of 0.5 mL of ^{51}Cr-RBC (about 7 Ci) was subsequently iv injected into the animal. **b. Fecal Drug-Induced Bleeding**. Drugs (control, 5 mg/kg indomethacin, 10 mg/kg diclofenac, 100 mg/kg UR-8880, and 100 mg/kg celecoxib, bid) were administered by gavage for 4 days. Feces were collected daily, and radioactivity was quantified and corrected for background and isotope decay. Data are expressed as percentage of injected radioactivity.

Molecular Modeling. Compound **51f** was modeled inside the active site of COX-2 from the crystal structure of murine COX-2 complex with the celecoxib analogue SC558. Atomic charges for this inhibitor were calculated in a two-step procedure using Spartan (Wave function Inc.): (i) geometry optimization at the AM1[38] semiempirical level; (ii) ab initio single point calculation at the HF/6-31G(d) level to obtain the molecular electrostatic potential (MEP) from which ESP charges were derived.

Only one monomer of the enzyme was modeled. The protein−inhibitor system was hydrated with TIP3P water molecules[39] and equilibrated by a series of minimizations interspersed by short 10 ps molecular dynamics simulations using the Cornell et al. all atom force field[40] implemented in the program TINKER.[41] Only atoms within 20 Å of the inhibitor were allowed to move. The equilibrated system was subject to a 1.0 ns molecular dynamics simulation at a constant temperature of 300 K. The nonbonded pair-list was updated every 20 steps (nonbonded cutoff was set to 14 Å). SHAKE[42] was used together with a time step of 2 fs. Visualization was performed with the Insight II package (Accelrys Inc.).

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Supporting Information Available: Description of the synthesis and experimental data for the preparation of triazoles **52a**−**c** and **53a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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