Novel 1-(Pyridylphenyl)-1-phenyl-2-imidazolylethanols with Topical Antiinflammatory Activity

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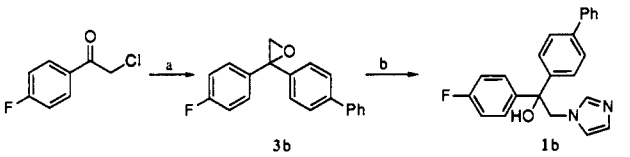
The synthesis, biological evaluation, and structure-activity relationships of a series of 1-(pyridylphenyl)-1-phenyl-2-imidazolylethanols are described. These compounds show potent dose-dependent topical antiinflammatory activity in murine models of skin inflammation. This effect is likely due to inhibition of cytochrome P450 and consequent reduction in levels of 12*R*-HETE in the skin. These compounds were examined for their ability to inhibit the oxidative metabolism of arachidonic acid; they specifically inhibit the formation of prostacyclins in mouse macrophages. To study the effects of structure on the in vivo activity, three general features of the molecules were varied: the position of attachment of the pyridine nucleus (A), the second aromatic residue (B), and the nitrogen base on the ethanol chain (C). 1-[4-(4-Pyridyl)phenyl]-1-(4-fluorophenyl)-2-imidazolylethanol (**2a**, DuP 983) shows a very attractive profile of antiinflammatory activity and has been selected for clinical evaluation as a topical antiinflammatory agent.

Introduction

A variety of inflammatory skin diseases are characterized by increased levels of proinflammatory arachidonic acid metabolites. These metabolites include those derived from the 5-lipoxygenase (5-LO) and 12-lipoxygenase (12-LO) pathway.[1] Conventional non-steroidal antiinflammatory drugs, such as indomethacin, inhibit cyclooxygenase (CO) and the biosynthesis of prostaglandins and thromboxanes but do not improve the condition of inflammatory skin diseases such as contact dermatitis or psoriasis.[2] Recently, 5-lipoxygenase inhibition has been described as an approach for the treatment of inflammatory skin diseases.[3] Psoriatic skin, in particular, has been found to contain elevated levels of leukotrienes and 12*R*-HETE. The 12*R*-HETE is synthesized by a P450-dependent monoxygenase[4] and it is chemotactic to PMNL.[5] Other inflammatory cells typically produce 12*S*-HETE[6] but not the *R*-isomer. Thus a P450 inhibitor will be of value in the treatment of psoriasis. There remains an unmet medical need for drugs effective in the treatment of inflammatory skin diseases, since the current therapies (glucocorticosteroids, anthralin, and psoralen with UV-A irradiation) possess significant toxic effects, are inconvenient or cosmetically unacceptable, or are only partially efficacious.[7]

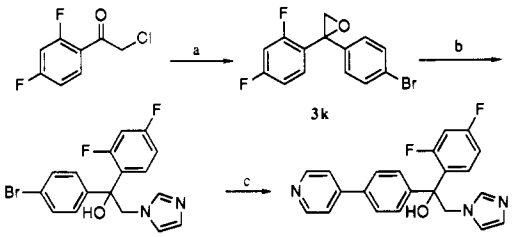
In this paper we describe studies of the topical antiinflammatory activity of 1-(pyridylphenyl)-1-(phenyl)-2-imidazolyl-1-ethanols (**2**). Structurally similar to known antifungal agents that inhibit P450, these compounds display activity in several models of murine skin inflammation. One example from this series, DuP 983 [1-[4-(4-pyridyl)phenyl]-1-(4-fluorophenyl)-2-imidazolyl-1-ethanol, **2a**], has been selected for clinical evaluation as a topical antiinflammatory agent on the basis of its complete pharmacological profile.[8] The synthesis and biological

Scheme I. Synthesis of 1,1-Diaryl-2-imidazolethanols (1)



(a) 4-PhC_6H_4Li, THF, -78°; (b) imidazole, KO*t*Bu, DMF, 90°

Scheme II. Route A. Variation of Pyridine Isomer



(a) 4-BrC_6H_4Li; THF; -78°; (b) imidazole, KO*t*Bu, DMF, 90°; (c) 4-$(CH_3)_3SnC_5H_4N$, $Pd(PPh_3)_2Cl_2$, Et_3N, DMF, 70°

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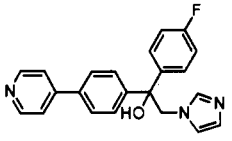


2a

activity of these compounds are described, and the structure–activity relationships (SARs) are discussed with respect to three key features of these compounds (see Figure 1): (1) the presence and position of the pyridine ring (A), (2) the nature of the second aryl residue (B), and (3) the nitrogen base on the ethanol chain (C).

Chemistry

A variety of diarylimidazolylethanols (1) were initially prepared to broadly define the SAR for these molecules in the two aromatic substituents A and B. These compounds, shown in Table I, were prepared by the reaction of an aryllithium reagent with an 2-chloroacetophenone to yield a 1,1-diaryl epoxide (3), which upon treatment with imidazole and potassium *tert*-butoxide afforded the desired product (Scheme I).[9] Because of the modest topical antiinflammatory activity noted with 1,1-bis(4-fluorophenyl)-2-imidazolyl-1-ethanol (1j), this compound was chosen as a point of departure for further variation. A novel structure with much improved activity was noted when one of the 4-fluorophenyl residues in 1j was replaced with a pyridylphenyl residue, and this series was examined in greater detail.

The (pyridylphenyl)imidazolylethanols 2 were synthesized by any one of three methods. The first method (route A) that was used to prepare these compounds built upon the chemistry described above, and is outlined in Scheme II using the preparation of 2e as an example. This route permitted the systematic variation of the pyridine isomer attached to the phenyl ring (A) at the last step in the synthesis. In this route, a (bromophenyl)arylimidazolylethanol 1k was prepared and coupled with the appropriate pyridyltrimethylstannane[10] in the presence of triethylamine and $Pd(PPh_3)_2Cl_2$ to afford the desired phenylpyridyl product 2.[11] The palladium-catalyzed bromoarene–stannylpyridine coupling reaction could be successfully applied to any of the three isomeric (trimethylstannyl)pyridines with either 3- or 4-bromoarenes, but could not be successfully applied to the synthesis of

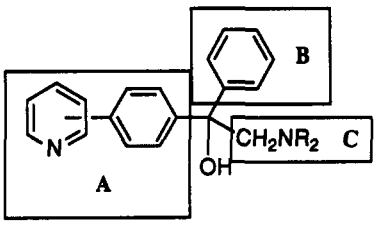
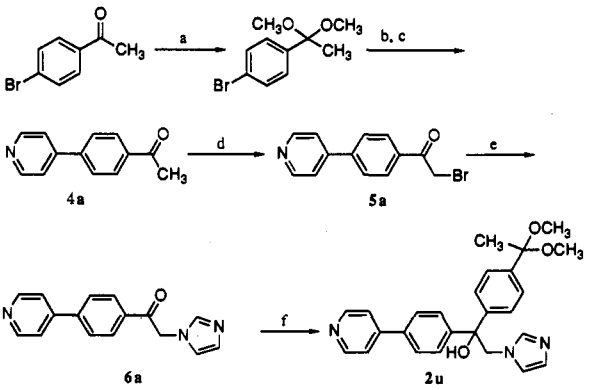


Figure 1.

Scheme III. Route B. Variation of Aryl Residue



(a) $HC(OCH_3)_3$, CH_3OH, Dowex-50, 65°; (b) (i) n-BuLi, Et_2O, -25°, (ii) $ZnCl_2$, THF, 15°, (iii) $Ni(PPh_3)_2Cl_2$, DIBAL-H, 4-BrC_5H_4N, 20°; (c) HCl, H_2O, Me_2CO, 20°. (d) Br_2, HBr, HOAc, 20°; (e) $C_3H_4N_2$, THF, 20°; (f) 4-$CH_3(CH_3O)_2CC_6H_4Li$, $CeCl_3$, THF, 20°

compounds with the pyridine ring attached to the 2-position of the arene ring.

Two new methods (routes B and C) were developed to allow efficient preparation of analogs for further SAR studies. These routes were chosen to facilitate the systematic variation of either the second aryl residue (B) or the nitrogen base on the methylene group (C) in a divergent fashion at the last step of synthesis. In addition, both synthetic routes were designed to begin with a common intermediate, 4-(4-pyridyl)acetophenone (4a). This ketone was prepared from 4-bromoacetophenone and 4-bromopyridine by the transition metal catalyzed coupling of 4-bromopyridine with the organozinc derivative of protected 4-bromoacetophenone (Scheme III).[12] This was accomplished by conversion of 4-bromoacetophenone to its dimethyl ketal, followed by treatment with *n*-butyllithium to form the lithium derivative, which was converted to the zinc derivative by transmetalation with zinc chloride.[13,14] Treatment of the arylzinc derivative with a catalyst prepared from either $Pd(PPh_3)Cl_2$ or $Ni(PPh_3)_2Cl_2$ and DIBAL-H, followed by a solution of 4-bromopyridine, gave the ketone 4a in greater than 90% yield after extractive workup and deprotection.[15] This route was successfully applied to the preparation of other

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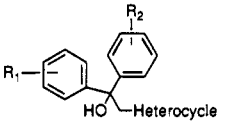
(13) Zinc chloride was dried by fusion over a free flame, followed by pouring the melt into a mortar containing carbon tetrachloride, crushing the resulting solid, and drying in vacuo.

(14) Later experimentation showed that the ketone 7a could be prepared from the Grignard derivative of 4-bromoacetophenone dimethyl ketal and 4-bromopyridine directly by nickel-catalyzed coupling, without conversion of the Grignard reagent to the arylzinc derivative.

(15) While the palladium catalyst was used initially, the nickel catalyst was found to be equally effective as the palladium catalyst.

Table I. Physical Data and in Vivo Activity for Imidazolylethanols 1 and 2



no.	R_1	R_2	heterocycle	mp, °C	recryst[a]	yield,[b] %	method	analysis[c]	PMA ear edema: % inhibn[d]	log P[e]
1a	4-F	4-Br	1-imdz[f]	176–178	A	65		$C_{17}H_{14}BrFN_2O$	29	3.42
1b	4-F	4-C_6H_5	1-imdz	221–223	A	22		$C_{23}H_{19}FN_2O$	25	4.23
1c	4-F	3-Br	1-imdz	185–187	A	30		$C_{17}H_{14}BrFN_2O$	38	3.30
1d	2,4-F_2	3-Br	1-imdz	183–185	A	27		$C_{17}H_{13}BrF_2N_2O$	42	3.60
1e	H	4-Br	1-imdz	182–184	A	52		$C_{17}H_{15}BrN_2O$	37	3.35
1f	2-Cl	4-Br	1-imdz	219–221	A	42		$C_{17}H_{14}BrClN_2O$	26	3.87
1g	4-CH_3O	4-Br	1-imdz	199–201	A	5		$C_{18}H_{17}BrN_2O_2$	31	4.02
1h	4-CH_3	4-Br	1-imdz	199–201	A	4		$C_{18}H_{17}BrN_2O$	18	3.55
1i[g]	4-F	4-F	1-imdz	181–183	B	59		$C_{18}H_{16}F_2N_2O$	52	3.13
1j	4-F	4-F	1-imdz	201–203	A	21		$C_{17}H_{14}F_2N_2O$	50	2.95
1k	2,4-F_2	4-Br	1-imdz	218–219	A	55		$C_{17}H_{13}BrF_2N_2O$	22	3.44
2a	4-F	4-(4-pyridyl)	1-imdz	205–207	A/M	64	C	$C_{22}H_{18}FN_3O$	72	2.47
2b	2,4-F_2	4-(2-pyridyl)	1-imdz	190–192	D/M	17	A	$C_{22}H_{17}F_2N_3O$	51	3.65
2c	4-F	4-(2-pyridyl)	1-imdz	206–208	D/M	20	A	$C_{22}H_{18}FN_3O$	63	3.58
2d	2,4-F_2	4-(3-pyridyl)	1-imdz	202–203	D/M	13	A	$C_{22}H_{17}F_2N_3O$	52	3.31
2e	2,4-F_2	4-(4-pyridyl)	1-imdz	190–192	E/W	26	A	$C_{22}H_{17}F_2N_3O$	73	2.54
2f	4-F	3-(2-pyridyl)	1-imdz	172–173	D/H	28	A	$C_{22}H_{18}FN_3O$	61	3.34
2g	4-F	3-(3-pyridyl)	1-imdz	196–197	D/M	34	A	$C_{22}H_{18}FN_3O$	64	3.22
2h	4-F	3-(4-pyridyl)	1-imdz	174–175	D/H	23	A	$C_{22}H_{18}FN_3O$	74	2.91
2i	H	4-(4-pyridyl)	1-imdz	183–185	D/H	18	A	$C_{22}H_{19}N_3O$	69	2.29
2j	2-Cl	4-(4-pyridyl)	1-imdz	212–214	D/H	42	A	$C_{22}H_{18}ClN_3O$	41	3.37
2k	4-CH_3	4-(4-pyridyl)	1-imdz	184–186	D/B/H	31	A	$C_{23}H_{21}N_3O$	62	3.13
2l	4-CH_3O	4-(4-pyridyl)	1-imdz	202–203	D/B/H	19	A	$C_{23}H_{21}N_3O_2$	74	3.55
2m	4-CF_3	4-(4-pyridyl)	1-imdz	221–223	A	16	B	$C_{23}H_{18}F_3N_3O$	58	3.11
2n	4-Cl	4-(4-pyridyl)	1-imdz	211–213	A	14	B	$C_{22}H_{18}ClN_3O$	58	3.27
2o	4-C_6H_5	4-(4-pyridyl)	1-imdz	123–125	A	13	B	$C_{28}H_{23}N_3O$	49	3.86
2p	4-CHO	4-(4-pyridyl)	1-imdz	209–211	A	14	B	$C_{23}H_{19}N_3O_2$	67	2.38
2q	4-CH_3CO	4-(4-pyridyl)	1-imdz	218–220	A	12	B	$C_{24}H_{21}N_3O_2$	78	2.41
2r	4-$(CH_3)_2N$	4-(4-pyridyl)	1-imdz	105–107	A/B	7	B	$C_{24}H_{24}N_4O$	34	3.29
2s	4-CH_2OH	4-(4-pyridyl)	1-imdz	173–175	D/M	60	B	$C_{23}H_{21}N_3O_2$	24	2.40
2t	4-CH_3CO_2	4-(4-pyridyl)	1-imdz	225–227	A	70	B	$C_{24}H_{21}N_3O_3$	62	2.61
2u	4-$C_4H_9O_2$[h]	4-(4-pyridyl)	1-imdz	65–67 dec	A	25	B	$C_{26}H_{27}N_3O_3$	61	3.45
2v	4-OH	4-(4-pyridyl)	1-imdz	197–199	A	3	B	$C_{22}H_{19}N_3O_2$	37	2.49
2w	4-F	4-(4-pyridyl)	1-$C_7H_5N_2$[i]	206–207	A	45	C	$C_{26}H_{20}FN_3O$	40	2.06
2x	4-F	4-(4-pyridyl)	1-C_4H_4N[j]	186–187	A	35	C	$C_{23}H_{19}FN_2O$	58	2.35
2y	4-F	4-(4-pyridyl)	1-$C_2H_2N_3$[k]	119–120	A	58	C	$C_{21}H_{17}FN_4O$	53	1.67
2z	4-F	4-(4-pyridyl)	1-$C_3H_3N_2$[l]	164–166	A	54	C	$C_{22}H_{18}FN_3O$	28	2.14
2aa	4-F	2-(4-pyridyl)	1-imdz	208–209	A	68	C	$C_{22}H_{18}FN_3O$	86	2.51
2bb	4-F	2-(3-pyridyl)	1-imdz	138–139	A	23	C	$C_{22}H_{18}FN_3O$	62	3.26
2cc	4-F	4-(4-pyridyl)	1-C_4H_8N[m]	58–59	A	52	C	$C_{23}H_{23}FN_2O$	24	3.84
2dd	4-F	4-(4-pyridyl)	1-C_4H_8NO[n]	124–125	A	38	C	$C_{23}H_{23}FN_3O_2$	41	2.82

[a] Key: A = acetonitrile; B = *n*-butyl chloride; D = dichloromethane; E = ethanol; H = hexanes; M = methanol; W = water. [b] Isolated yields of purified material. [c] Elemental analyses (C, H, N) were within ±0.4% of the theoretical value. [d] Dose of 100 μg/ear; averages of two or more determinations; the standard errors average 10% of the values shown. [e] Experimental values from HPLC. [f] 1-Imidazolyl. [g] 2-Imidazole-1-propanol. [h] Dimethyl ketal of 2q. [i] 1-Benzimidazolyl. [j] 1-Pyrrolyl. [k] 1-(1,2,4-Triazolyl). [l] 1-Pyrazolyl. [m] 1-Pyrrolidinyl. [n] 1-Morpholinyl.

pyridylphenyl ketones, including the 2-(pyridyl)phenyl substitution pattern that was inaccessible by the stannane coupling.

Systematic variations of the second aryl residue (B) at the last step of synthesis starting with ketone **4a** was accomplished as shown in Scheme III, showing the preparation of **2u** as an example. Bromination of the ketone to the α-bromo ketone **5a** hydrobromide was carried out in the presence of hydrogen bromide to prevent the polymerization of the free base of **5a**, which occurred extremely rapidly at temperatures of −20 °C or higher. The nonhygroscopic hydrobromide salt of **5a** was stable indefinitely and was conveniently handled. Conversion of **5a** to the (pyridylphenacyl)imidazole **6a** required the use of a substantial excess of imidazole (6 equiv) to serve as a hydrogen bromide acceptor, as well as to suppress the facile polymerization of **5a** or further reaction of **5a** with **6a**. This ketone was then treated with an arylmetal derivative to afford the product **2**.[16] The use of an aryllithium derivative gave exclusive enolization of the (pyridylphenacyl)imidazole **6a**, which was recovered unchanged following workup of the reaction mixture. Enolization of **6a** could be partially suppressed by the use of aryl Grignard reagents, which generally gave mixtures of approximately equal parts of recovered **6a** and desired product. Use of the arylcerium reagent gave exclusively the alcohol **2**.[17]

The systematic variation of the nitrogen base (C) at the last step of synthesis proceeded from the ketone **4a** as

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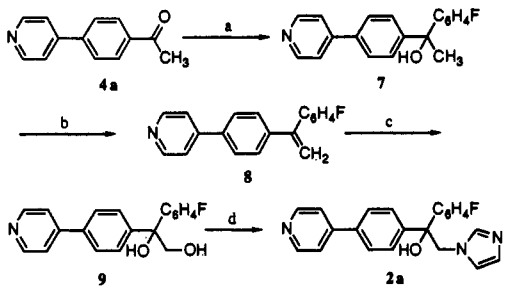
Scheme IV. Route C. Variation of Nitrogen Base



(a) 4-FC_6H_4MgBr, THF, 0°; (b) p-TsOH, $CHCl_3$, 80°; (c) OsO_4, NMMO, pyridine, Me_2CO, H_2O, 60°; (d) (i) MsCl, Et_3N, CH_2Cl_2, (ii) imidazole, KOtBu, DMF, 95°

shown in Scheme IV, which shows the synthesis of **2a** as an example. The ketone was treated with (4-fluorophenyl)magnesium bromide to yield the alcohol **7**. Again, use of the corresponding aryllithium reagent resulted in considerable enolization of the starting material and the isolation of a mixture of **4a** and **7**. This alcohol underwent smooth dehydration upon heating with acid with azeotropic removal of water to afford the olefin **8**. Chloroform was found to be an especially suitable solvent for this transformation as it readily dissolved the *p*-toluenesulfonate salts of **7** and **8**. Attempts to oxidize the olefin to the corresponding epoxide with a variety of reagents were unsuccessful, with competing N-oxidation and epoxide opening being serious side reactions. Attempts to form the bromohydrin from **8** were likewise unsuccessful and in this case oxidative cleavage of the olefin occurred to yield the corresponding diaryl ketone. The olefin **8** was converted to the diol **9** by treatment with *N*-methylmorpholine *N*-oxide (NMMO) and a catalytic amount of osmium tetraoxide. The final traces of osmium were conveniently removed from the product (as determined by atomic absorption analysis) by treatment of the crude diol with hydrogen sulfide following extraction; the residual osmium was deposited as OsS_2 and was filtered with the drying agent.[18] This diol was converted to the primary methanesulfonate using standard conditions[19] and the crude methanesulfonate was treated with the appropriate nitrogen base with heating to give **2**. During the course of these last two reactions, the methanesulfonate usually underwent some transformation to the epoxide, which could be isolated and characterized. This route was selected as the most convenient route for larger scale work. The physical data for the 1-(pyridylphenyl)-1-(phenyl)-2-imidazolylethanols prepared are summarized in Table I.

Pharmacology

The 1-(pyridylphenyl)-1-phenyl-2-imidazolylethanols were examined for their ability to inhibit various enzymes thought to play a role in inflammatory skin diseases. The standard error of the mean for these determinations averaged less than 10%. They were found as a class to be inactive as inhibitors of cyclooxygenase[20] (bovine seminal vesicles, IC_{50} generally > 750 μM), PLA_2[21] (*Crotalus adamanteus*, IC_{50} generally > 1 mM), and 5-lipoxygenase[22] (RBL-1 cell line, IC_{50} generally > 25 μM). The ability of **2a** to inhibit the oxidative metabolism of arachidonic acid in mouse resident peritoneal macrophages was also studied. It was found to inhibit the biosynthesis of prostacyclins, specifically the formation of the stable metabolite 6-keto-$PGF_{1\alpha}$, with an IC_{50} of 0.7 μM following a 15-min pretreatment of the cells with **2a**.[23] As PGI_2 synthetase is thought to be a P450-dependent enzyme system,[24] **2a** was then examined for its ability to bind to mouse liver microsomal P450.[25] It was found to bind to microsomes with a Type II binding pattern in a dose-dependent manner (K_i = 1.6 μM), which is consistent with liver microsomal P450 inhibition.[26] Following topical application, **2a** was also found to lower by 80% the increased levels of 12*R*-HETE in A23187-challenged murine ear skin. The P450 inhibitory activity of **2a** is most likely related to the presence of the imidazolylethanol moiety, as structurally

Table II. Data for Standard Drugs and Selected 1-(Pyridylphenyl)-1-phenyl-2-imidazolylethanols

	ED_{50}[g]			IC_{50}[h]		
compound	PMA ear[a]	A23187 ear[b]	AA ear[c]	PLA_2[d]	CO[e]	5-LO[f]
indomethacin	10%	254	902	>1000	0.43	>25
ketoconazole	34	8%	10%	>1000	>750	>25
lonapalene	15%	32	103	>1000	>750	0.74
DuP 654	764	5	7	>1000	>750	0.019
2a	4.6	21	543	>1000	>750	>25
2k	13.2	13	16%	>1000	>750	>25

[a] PMA mouse ear edema assay. [b] A23187 mouse ear edema assay. [c] Arachidonic acid mouse ear edema assay. [d] PLA_2 inhibition. [e] Cyclooxygenase inhibition. [f] 5-Lipoxygenase inhibition. [g] Values listed as percentages are percent inhibition vs control at a dose of 100 μg/ear; averages of two or more determinations; the standard errors average 10% of the values shown. ED_{50} values are averages of two or more determinations. [h] Values listed in μM concentration; averages of two or more determinations.

(18) Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*, 4th ed.; Wiley: New York, 1980; p 906. Later experimentation showed that the olefin **11** could be converted to the epoxide **13** without the use of transition metal salts under essentially neutral conditions by the use of MCPBA in a reaction mixture buffered with disodium hydrogen phosphate.

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(24) Haurand, M.; Ullrich, V. Isolation and Characterization of Thromboxane Synthetase from Human Platelets as a Cytochrome P450 Enzyme. *J. Biol. Chem.* **1985**, *260*, 15059–15067.

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(26) Jefcoate, C. R. Measurement of Substrate and Inhibitor Binding to Microsomal Cytochrome P-450 by Optical-Difference Spectroscopy. *Methods Enzymol.* **1978**, *52*, 258–278. Complete inhibition of 6-keto-$PGF_{1\alpha}$ release was observed at approximately 100 μM. In the same experiment, **2a** was much less efficient at inhibiting leukotriene release (IC_{50} = 100 μM).

similar imidazole containing compounds of interest as antifungal agents are known to inhibit cytochrome P450.[27,28] Taken together, this data suggests that **2a** derives its topical antiinflammatory activity by inhibition of cytochrome P450 in the skin, resulting in the subsequent inhibition of 12*R*-HETE biosynthesis.

The topical antiinflammatory activities of these compounds (**1** and **2**) were determined by inhibition of murine skin inflammation induced by either phorbol myristyl acetate,[29] the calcium ionophore A23187,[30] or arachidonic acid.[31] Each test was run in duplicate in separate experiments with groups of 10 animals. The compounds show relatively poor inhibition in the lipoxygenase-sensitive arachidonic acid ear edema model,[32] as would be expected from their enzyme-inhibitory profile. By contrast, the compounds show good inhibition of mouse ear edema induced either by phorbol myristyl acetate (PMA) or the ionophore A23187.[33] Results obtained from the in vivo tests are given in Table I. Data for several standard drugs are shown in Table II. Indomethacin was selected as a typical cyclooxygenase inhibitor, while lonapalene and DuP 654 (2-benzyl-1-naphthol) were selected as topically effective 5-lipoxygenase inhibitors.[34] Ketoconazole was chosen as a typical azole-containing cytochrome P450 inhibitor.[35]

Structure–Activity Relationships

The compounds that were first prepared to evaluate this series (**1a–k**) were largely devoid of topical antiinflammatory activity. Inhibition of PMA ear edema varied from 18% to 42% in this series, with the exception of **1i** and **1j**, which gave 52% and 50% inhibition, respectively. The replacement of one fluorine in **1j** with a pyridine ring (**2a**, **2c**) resulted in a considerable improvement in the in vivo activity of this series and led to the exploration of the 1-(pyridylphenyl)-1-phenyl-2-imidazolylethanols **2** as potential topical antiinflammatory agents.

Within the 1-(pyridylphenyl)-1-phenyl-2-imidazolylethanol series, the most noticeable SAR feature is the relative insensitivity of in vivo activity to the position of attachment of the pyridine nucleus to the phenyl ring comprising the pyridylphenyl moiety (**2a**, **2h**, and **2aa**). This result is somewhat surprising as the gross change in the overall molecular structure is quite substantial, but it suggests that the site of action of these compounds in vivo is fairly flexible in its steric requirements away from the 1,1-diaryl-2-imidazolylethanol moiety. In each case the compounds show quite potent in vivo activity. The topical potency of compounds with the pyridylphenyl group (**2a**, **2k**) is increased by 1 order of magnitude or more over compounds with similar structures and physical properties (**1i**). By contrast, the particular pyridine isomer at any given point of attachment to the phenyl ring appears to be of some importance, as an improvement in activity in vivo is seen in the series 2-pyridyl < 3-pyridyl < 4-pyridyl. The reason for this is not entirely clear, but this trend may be reflective of the compounds ability to penetrate the skin. Compound **2aa**, in fact, appears to be perhaps the most efficacious in this series. This compound was not selected for further development, however, largely because of the tedious purification of intermediates encountered in large scale synthesis.

The substituents placed on the second aryl residue (B) also appear to play an important role in determining the in vivo topical antiinflammatory activity. In particular, highly lipophilic substituents such as phenyl (**2o**) appear to be detrimental to the in vivo activity. Carbonyl-containing electron-withdrawing substituents such as formyl (**2p**), acetyl (**2q**), and carbomethoxy (**2t**) maintain good in vivo activity. Other electron-withdrawing substituents, such as trifluoromethyl (**2m**) and chloro (**2n**), are somewhat less active. Strongly electron releasing, hydrogen-bonding substituents such as dimethylamino (**2r**) and hydroxy (**2v**) diminish the in vivo activity, as does a carbinol (**2s**). These substituents may facilitate the metabolism and subsequent elimination of these compounds, resulting in their lower in vivo activity. By contrast, the corresponding methoxy derivative (**2l**) retains good activity. Incorporation of a chlorine substituent at the 2-position (**2j**) appears to have a negative effect on the activity, which may be due to a conformational change relative to other members of this series. Other substituents at the 4-position such as halogen, alkyl, and alkoxy appear to have relatively minor effects upon the topical activity of these compounds, in contrast to their effect in the earlier compounds in this series (**1a–k**).

The nitrogen base attached to the ethanol chain (C) is of critical importance in determining the topical antiinflammatory activity of these compounds. The presence of the imidazole moiety can be seen to be essential for in vivo activity. Replacement of the imidazole ring by other 5-membered ring aromatic nitrogen containing heterocycles such as pyrrole (**2x**), 1,2,4-triazole (**2y**), or pyrazole (**2z**), or by saturated nitrogen heterocycles such as pyrrolidine (**2cc**) or morpholine (**2dd**) leads to a substantial loss of in vivo activity. That the imidazole ring is critical for activity is consistent with the observed binding of **2a** to P450.

Most of the compounds examined in this study were racemic mixtures. To investigate the potential for enantiospecificity in the topical antiinflammatory activity, the enantiomers of **2a** were separated by HPLC (Chiracel OD column, 20 × 250 mm; 65:35 hexane/2-propanol; 4.5 mL

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(33) Results obtained in the A23187 ear edema assay parallel results obtained in the PMA ear edema assay in all cases in which a comparison was made.

(34) See ref 7a.

(35) Bossche, H. Vanden; Lauwers, W.; Willemsens, G.; Cools, W. Ketoconazole, An Inhibitor of the Cytochrome P-450 Dependent Testosterone Biosynthesis. *Prog. Clin. Biol. Res.* **1985**, *185A*, 187–196.

min^{-1}). An assignment of absolute configuration was not possible as attempts to grow an X-ray quality crystal of either enantiomer were unsuccessful. However, in vivo tests showed that (−)-**2a** was significantly more active in the PMA ear edema model than (+)-**2a** (76% vs 26% inhibition at 100 μg/ear).[36]

A strucutral feature that appears to be of considerable significance in determining the topical antiinflammatory activity of these compounds is their lipophilicity, as measured by the log *P* values for these compounds. It can be seen from Table I that the in vivo activity roughly correlates with the log *P* values for these compounds, as determined by HPLC.[37] Imidazole-containing compounds with lower log *P* values (log $P < 3.0$) are generally more active in the PMA ear edema test (>65% inhibition) than those with higher log *P* values, with the exception of the previously discussed pyridylphenyl compounds with strongly electron releasing, hydrogen-bonding substituents on the second aryl residue (B). This is shown particularly well with **2o**, which is considerably more lipophilic than **2a**, and which suffers a loss of in vivo activity. This dependence of in vivo activity upon lipophilicity is likely due to skin penetration effects. That the relative lipophilicity is of more importance than steric factors is supported by the observation that the 2-pyridylphenyl, 3-pyridylphenyl, and 4-pyridylphenyl derivatives are all active despite the great changes that are incurred in molecular size and shape, while **1b**, which is expected to be of exactly the same size and shape as **2a**, is inactive in vivo. In the absence of functional groups that are readily susceptible to metabolic processes in vivo (**2p**, **2r**, **2s**, **2t**, **2v**) and hence complicate the interpretation of in vivo results, the optimal log *P* for activity in the PMA ear edema model appears to lie in the range of 2.4–3.0. These observations suggest that the ability of these compounds to penetrate the skin can vary substantially, and that skin penetration is favored by optimizing the lipophilicity of these compounds.

Conclusion

1-(Pyridylphenyl)-1-phenyl-2-imidazolylethanols (**2**) are topical antiinflammatory agents that are active in the PMA mouse ear edema assay. This activity appears to be largely dependent upon the presence of the 2-imidazolylethan-1-ol moiety in a molecule with suitable lipophilicity characteristics. Such lipophilicity is conveniently introduced with the concurrent formation of a novel structure by the use of the pyridylphenyl group. Other structural features which are of secondary importance in determining the topical antiinflammatory profile are the particular pyridyl isomer and the nature of the substituent on the second aryl residue.

Compound **2a** (DuP 983) is a cytochrome P450 inhibitor which does not affect the other enzymes of the arachidonic acid cascade (Table II). It is an efficacious antiinflammatory agent when administered topically in the mouse PMA ear edema model. DuP 983 has also been shown to inhibit the biosynthesis of 12*R*-HETE in inflamed murine skin. Because of this activity, and because of its potency in other skin inflammation models, notably delayed-type hypersensitivity to 2,4-dinitrofluorobenzene in the mouse,[38] this compound has been selected for clinical evaluation as a topical antiinflammatory agent on the basis of its complete pharmacological profile.

Experimental Section

^{1}H NMR spectra were recorded on Varian Gemini 200 (200 MHz) or IBM 200 SY (200 MHz) spectrometers using tetramethylsilane as an internal standard. Infrared spectra were recorded as neat films or KBr pellets as noted on a Perkin-Elmer 1710 FT spectrometer. Mass spectral data was recorded on Finnigan-MAT 8230 or Du Pont DP-1 instruments, using the indicated ionization techniques. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Microanalyses were performed by Quantitative Technologies, Inc., Bound Brook, NJ, and were within 0.4% of the calculated values. Thin-layer chromatography was carried out with E. Merck 15327 silica gel plates.

All reactions were carried out with continuous magnetic stirring under an atmosphere of dry nitrogen. All solutions were dried over anhydrous magnesium sulfate unless otherwise noted; all evaporations were carried out on a rotary evaporator at ca. 30 Torr. Commercial reagents were used as received without additional purification. Ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Organolithium reagents were titrated against *N*-benzylbenzamide at 0 °C in THF. Diisobutylaluminum hydride solutions were titrated by reaction with an excess of dry acetophenone in toluene at −78 °C, warming to room temperature, workup, and ^{1}H NMR examination of the product mixture.

Preparation of 1,1-Diaryl-2-imidazolethanols (1). 1-(4-Fluorophenyl)-1-(4-phenylphenyl)epoxyethane (3b). A solution of 10.0 g (42.5 mmol) of 4-bromobiphenyl and 7.3 g of 2-chloro-4′-fluoroacetophenone in 100 mL of THF was cooled in a −78 °C bath, and *n*-butyllithium (1.6 M, 26.5 mL, 42.5 mmol) was added dropwise at such a rate as to maintain the internal temperature below −60 °C. Upon completion of the addition, the cooling bath was removed and the mixture was allowed to warm to 0 °C. The mixture was poured into 800 mL of water and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with water (3 × 300 mL) and brine (1 × 100 mL), then dried (Na_2SO_4), and concentrated to give 13.3 g of a yellow oil. This was chromatographed on silica (9:1 hexane/EtOAc) to give a yellow oil that was crystallized from hexane to afford 7.1 g (58%) of white crystals: mp 80–82 °C; ^{1}H NMR ($CDCl_3$) δ 7.59 (d, 4 H), 7.52–7.33 (m, 7 H), 7.07 (t, 2 H), 3.32 (d of d, 2 H); CIMS (CH_4) $m/z = 291$ ($M + H^+$). Anal. ($C_{20}H_{15}FO$) C, H.

1-(4-Fluorophenyl)-1-(4-phenylphenyl)-2-(1-imidazolyl)-1-ethanol (1b). A solution of the epoxide **3b** (6.44 g, 22 mmol) in 70 mL of DMF was treated with imidazole (3.78 g, 55.5 mmol) followed after 10 min with *t*-BuOK (6.22 g, 55.5 mmol). The mixture was heated for 20 h at 90 °C and then was cooled and poured into 350 mL of water. The mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were washed with water (6 × 50 mL) and brine (100 mL), dried (Na_2SO_4), and concentrated. The residue was digested with MeCN, filtered hot, and allowed to crystallize. The collected crystals (3.1 g, 39%, mp 218–220 °C) were recrystallized from MeCN to yield 1.75 g (22%) of white crystals: mp 221–222 °C; ^{1}H NMR (DMSO-d_6) δ 7.69–7.56 (m, 5 H), 7.54–7.46 (m, 2 H), 7.42–7.30 (m, 4 H), 7.12 (t, 2 H), 6.85 (s, 1 H), 6.67 (s, 1 H), 6.31 (s, 1 H), 4.86 (d of d, 2 H); CIMS (CH_4) $m/z = 359$ ($M + H^+$); IR (Nujol) 3400–3000 cm^{-1}. Anal. ($C_{23}H_{19}FN_2O$) C, H, N.

Preparation of (Pyridylphenyl)imidazolylcarbinols by Stannane Coupling: Method A. 1-(2,4-Difluorophenyl)-1-(4-bromophenyl)epoxyethane (3k). A solution of 20.0 g (80 mmol) of 1,4-dibromobenzene in 200 mL of THF was cooled in

(36) (−)-**2a** had an optical rotation of −32.4° ($c = 0.31$, EtOH); (+)-**2a** had an optical rotation of +38.0° ($c = 0.28$, EtOH).

(37) (a) Veith, G. D.; Morris, R. T.; Austin, N. M. A Rapid Method for Estimating Log P for Organic Chemicals. *Water Res.* **1979**, *13*, 43–47. (b) Veith, G. D.; Morris, R. T. A Rapid Method for Estimating Log P for Organic Chemicals. U.S. Environmental Protection Agency Report EPA-600/3-78-049 (May 1978). log *P* for **1a–2dd** was determined using a calibration curve which was prepared using measured octanol/water (shake flask method) log *P* values for eight pyridines. log *P* was calculated from the measured HPLC retention time as described in the reference. A plot of (log RT) vs (log *P*) determined by this method for **1a–2dd** yielded a straight line; corr 0.992.

(38) Ackerman, N. R.; Arner, E. C.; Galbraith, W.; Harris, R. R.; Jaffee, B. D.; Mackin, W. M. In *Advances in Prostaglandin, Thromboxane and Leukotriene Research*; Zor, U., et al., Eds.; Raven: New York, 1986; Vol. 6, p 47.

a −78 °C bath and treated with *n*-butyllithium (1.6 M, 50.0 mL, 80 mmol) dropwise, while the internal temperature was kept below −70 °C. After completion of the addition, the mixture was stirred for 1 h at −78 °C, after which a solution of 15.2 g (80 mmol) of 2′,4′-difluorophenyl-2-chloroacetophenone in 50 mL of THF was added dropwise, again while the internal temperature was maintained below −70 °C. The reaction mixture was kept at −78 °C for 1 h more. The cold reaction mixture was poured into 500 mL of water and extracted with EtOAc (4 × 100 mL). The combined extracts were washed with water (3 × 100 mL) and brine (100 mL), dried (Na_2SO_4), and concentrated to give 32.2 g of oil. This was purified by chromatography (9:1 hexane/EtOAc) to give 17.6 g (71%) of a pale yellow oil: ^1H NMR ($CDCl_3$) δ 7.51–7.40 (m, 3 H), 7.12 (m, 2 H), 6.97–6.80 (m, 2 H), 3.31 (d, 1 H), 3.17 (d, 1 H); CIMS (CH_4) m/z = 311, 313 (M + H^+); HRMS calcd for $C_{14}H_9BrF_2O$ (^{79}Br) 309.9804, found 309.9823.

1-(2,4-Difluorophenyl)-1-(4-bromophenyl)-2-(1-imidazolyl)-1-ethanol (1k). The epoxide **3k** (11.0 g, 35 mmol) in 100 mL of DMF was treated with imidazole (6.0 g, 88 mmol) and was stirred for 15 min. Potassium *tert*-butoxide (9.9 g, 88 mmol) was added in one portion and the mixture was heated at 90 °C for 20 h. The mixture was cooled and poured into water (1000 mL) and extracted with EtOAc (3 × 200 mL). The combined organic extracts were washed with water (5 × 100 mL) and brine (100 mL), dried (Na_2SO_4), and concentrated. The residue was triturated with ether and the solid residue was recrystallized from MeCN to give 7.3 g (55%) of white crystals: mp 218–219 °C; ^1H NMR (DMSO-d_6) δ 7.57–7.46 (m, 3 H), 7.34–7.19 (m, 2 H), 7.17–6.96 (m, 2 H), 6.76 (s, 1 H), 6.66 (s, 1 H), 6.55 (s, 1 H), 4.85 (d of d, 2 H); CIMS (CH_4) m/z = 379, 381 (M + H^+). Anal. ($C_{17}H_{13}BrF_2N_2O$) C, H, N.

1-(2,4-Difluorophenyl)-1-[4-(4-pyridyl)phenyl]-2-(1-imidazolyl)-1-ethanol (2e). A solution of the bromide **1k** (2.40 g, 6.2 mmol) in 36 mL of DMF was treated sequentially with triethylamine (4 mL, 29 mmol), 4-pyridyltrimethylstannane (2.24 g, 9.2 mmol), and $Pd(PPh_3)_2Cl_2$ (0.70 g, 1 mmol). The resulting mixture was heated to 70 °C for 120 h, cooled, and filtered through Celite, and the solids were washed with CH_2Cl_2. The filtrate was concentrated to dryness and the residue was taken up in CH_2Cl_2 (250 mL) and washed with water (2 × 100 mL). The organic phase was then extracted with 1 M HCl (5 × 50 mL), and the combined acid extracts were washed with ether (2 × 75 mL). The ethereal washes were discarded, and the aqueous solution was made strongly alkaline with 15 M NH_4OH. This was extracted with CH_2Cl_2 (3 × 75 mL), and the combined extracts were washed with water (2 × 70 mL) and brine (70 mL), dried (Na_2SO_4), and concentrated to yield 1.80 g of a dark oil. Flash chromatography on silica (9:1 CH_2Cl_2/MeOH) afforded a solid that was triturated with ether, filtered and recrystallized from EtOH/water to give 0.60 g (26%) of white crystals: mp 190–192 °C; ^1H NMR ($CDCl_3$) δ 8.61 (d, 2 H), 7.73–7.56 (m, 4 H), 7.54–7.45 (m, 4 H), 6.93–6.75 (m, 2 H), 6.62 (m, 2 H), 4.81 (d of d, 2 H); CIMS (CH_4) m/z = 378 (M + H^+), 360 (M + H^+ − H_2O). Anal. ($C_{22}H_{17}F_2N_3O$) C, H, N.

Preparation of (Pyridylphenyl)imidazolylcarbinols by Organocerium Chemistry: Method B. 2-Bromo-4′-(4-pyridyl)acetophenone Hydrobromide (5a). To a solution of 4a (9.85 g, 50 mmol) in 500 mL of glacial acetic acid was added 50 mL of 30% HBr in acetic acid, followed after 15 min by 50 mL of freshly prepared 1 M Br_2 in acetic acid. The mixture was stirred at 20 °C for 30 min, at 70 °C for 5 min, cooled to 20 °C, and stirred for 5 h. The mixture was concentrated, and the residue was thoroughly suspended in 250 mL of toluene and the mixture again concentrated. This process was repeated and the residue was dried under vacuum to yield 17.4 g (97%) of yellow crystals: mp 294 °C dec; ^1H NMR (CD_3OD) δ 8.93 (d, 2 H), 8.41 (d, 2 H), 8.26 (d, 2 H), 8.10 (d, 2 H), 4.75 (s, 2 H); CIMS (CH_4) m/z = 276, 278 (M + H^+). Anal. ($C_{13}H_{11}Br_2NO$) C, H, N.

2-(1-Imidazolyl)-4′-(4-pyridyl)acetophenone (6a). A solution of 40.04 g (0.59 mol) of imidazole in 250 mL of THF was added over 3 min to a suspension of 35.0 g (98 mmol) of the bromo ketone **5a** in 600 mL of THF with mechanical stirring. The mixture was stirred at 20 °C for 24 h and then concentrated. The residue was partitioned between water (500 mL) and CH_2Cl_2 (300 mL), and the water was saturated with Na_2CO_3 and extracted twice more with CH_2Cl_2 (100 mL). The combined CH_2Cl_2 extracts were dried (Na_2SO_4) and concentrated to give 21.2 g of crude product. This was flash chromatographed on silica (9:1 CH_2Cl_2/MeOH) and the crude product evaporated with toluene (2 × 100 mL) to afford 17.2 g (66%) of white crystals: mp 144–146 °C; ^1H NMR ($CDCl_3$) δ 8.76 (d, 2 H), 8.11 (d, 2 H), 7.83 (d, 2 H), 7.57 (m, 3 H), 7.20 (s, 1 H), 6.99 (s, 1 H), 5.80 (s, 2 H); CIMS (CH_4) m/z = 264 (M + H^+). Anal. ($C_{16}H_{13}N_3O$) C, H, N.

1-[4-(1,1-Dimethoxyethyl)phenyl]-1-[4-(4-pyridyl)-phenyl]-2-(1-imidazol-yl)-1-ethanol (2u). Cerium(III) chloride heptahydrate (9.35 g, 38 mmol) was dried[12a] and suspended in 25 mL of THF and cooled to −78 °C. A solution of 1,1-dimethoxy-1-(4-bromophenyl)ethane (9.30 g, 38 mmol) in 25 mL of THF was cooled to −78 °C, treated with *n*-butyllithium (1.6 M, 23.7 mL, 38 mmol), and kept at −78 °C for 30 min. The solution was transferred to the cold $CeCl_3$ suspension by a dry ice cooled cannula. This mixture was stirred at −78 °C for 1 h, after which a solution of **6a** (2.00 g, 7.6 mmol) in 60 mL of THF was added and the cooling bath was removed. The mixture was stirred for 16 h at 20 °C, quenched by the addition of 60 mL saturated NH_4Cl, and poured into EtOAc (300 mL). The emulsion was filtered through Celite, and the EtOAc was separated, washed with brine (150 mL), dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica (9:1 $CHCl_3$/MeOH) and the product was recrystallized from MeCN to give 0.50 g (25%) of white crystals: mp 65–67 °C; ^1H NMR (DMSO-d_6) 8.61 (d, 2 H), 7.79–7.60 (m, 6 H), 7.52 (d, 2 H), 7.38 (d, 2 H), 7.30 (s, 1 H), 6.84 (s, 1 H), 6.65 (s, 1 H), 6.30 (s, 1 H), 4.90 (d of d, 2 H), 3.35 (s, 3 H), 3.06 (s, 6 H); CIMS (CH_4) m/z = 430 (M + H^+); IR (Nujol) 3300–2700 (OH) cm^{-1}. Anal. ($C_{26}H_{27}N_3O_3$) C, H, N.

Preparation of Pyridylphenylimidazolylcarbinols by Diaryl Carbinol Chemistry: Method C. 1-(4-Fluorophenyl)-1-[4-(4-pyridyl)phenyl]-1-ethanol (7). A solution of (4-fluorophenyl)magnesium bromide (prepared from 25.4 mL (90 mmol) of 4-bromofluorobenzene and 2.19 g (90 mmol) of magnesium turnings) in 35 mL of THF was added to a suspension of **4a** (14.80 g, 75 mmol) in 55 mL of THF at 0 °C. The mixture was stirred for 30 min at 0 °C and for 30 min at 23 °C and then was poured into saturated NH_4Cl. The mixture was extracted with ether (150 mL), the organic phase was washed with water (2 × 70 mL) and brine (70 mL), dried, and concentrated to give 45 g of crude material. This was recrystallized from benzene (60 mL) to give 19.8 g (90%) of colorless needles: mp 168 °C; ^1H NMR ($CDCl_3$) 8.61 (d, 2 H), 7.60 (m, 2 H), 7.53 (m, 2 H), 7.42 (m, 2 H), 7.33 (d of d, 2 H), 7.06 (t, 2 H), 1.98 (s, 3 H); CIMS (CH_4) m/z 294 (M + H^+), 276 (M + H^+ − H_2O); IR (KBr) 3600–3000 (OH) cm^{-1}; HRMS calcd for $C_{19}H_{16}FNO$ 293.1216, found 293.1216. Anal. ($C_{19}H_{16}FNO$) C, H, N.

1-(4-Fluorophenyl)-1-[4-(4-pyridyl)phenyl]ethene (8). A solution of 7 (19.1 g, 65 mmol) and *p*-toluenesulfonic acid hydrate (24.77 g, 0.13 mol) in $CHCl_3$ (475 mL) was heated to boiling. Water and $CHCl_3$ were removed by azeotropic distillation, with additional $CHCl_3$ added to maintain the volume as needed. After 30 min, the mixture was cooled, concentrated to about 200 mL, and washed with 1 M NaOH (2 × 150 mL), water (150 mL), and brine (150 mL). The solution was dried and concentrated to provide a yellow oil. This was crystallized by scratching with hexane and was filtered and dried to give 13.96 g (78%) of white powder: mp 82 °C; ^1H NMR ($CDCl_3$) δ 8.65 (d, 2 H), 7.60 (d, 2 H), 7.51 (d, 2 H), 7.43 (d, 2 H), 7.33 (d of d, 2 H), 7.03 (t, 2 H), 5.51 (s, 1 H), 5.47 (s, 1 H); CIMS (CH_4) m/z = 276 (M + H^+); IR (KBr) 1596 (Ar) cm^{-1}. Anal. ($C_{19}H_{14}FN$) C, H, N.

1-(4-Fluorophenyl)-1-[4-(4-pyridyl)phenyl]-1,2-dihydroxyethane (9). A solution of the olefin 8 (13.80 g, 50 mmol) in 100 mL of acetone was treated with *N*-methylmorpholine *N*-oxide hydrate (8.27 g, 61 mmol) and water (33 mL). The resulting solution was treated with pyridine (17 mL) and a few crystals of osmium tetraoxide, and was heated at reflux for 24 h. Additional *N*-methylmorpholine *N*-oxide hydrate (0.83 g) was added, and the solution was heated for an additional 16 h. The mixture was cooled to room temperature, diluted with EtOAc (250 mL), and washed with water (150 mL). The water was back-extracted with EtOAc (100 mL), and the combined organic phases were washed with 0.2 M $NaHSO_3$ (100 mL), 95:5 water/glycerin (2 × 100 mL), water (2 × 100 mL), and brine (100 mL) and dried while being treated with a stream of hydrogen sulfide for 5 min. The solution was concentrated and the residue was taken up in

toluene (100 mL) and concentrated. The crude product was recrystallized from MeCN (or EtOH) to yield 10.4 g (66%) of white crystals: mp 99–101 °C; ^{1}H NMR ($CDCl_3$) δ 8.53 (d, 2 H), 7.62–7.51 (m, 4 H), 7.47–7.41 (m, 4 H), 7.08 (t, 2 H), 4.18 (d of d, 2 H); CIMS (CH_4) m/z 310 (M + H$^+$), 292 (M + H$^+$ – H_2O); IR (KBr) 3700–2400 (OH) cm^{-1}. Anal. ($C_{19}H_{16}FNO_2$) C, H, N.

1-(4-Fluorophenyl)-1-[4-(4-pyridyl)phenyl]-2-(1-imidazolyl)-1-ethanol (2a, DuP 983). The diol **9** (5.00 g, 16 mmol) was stirred in 80 mL of anhydrous $CHCl_3$ and cooled to 0 °C. Triethylamine (11.1 mL, 80 mmol) was added, followed by methanesulfonyl chloride (1.92 mL, 25 mmol). After 30 min, the reaction was complete by TLC analysis (both the methanesulfonate and epoxide were observed). The solution was washed with water (5 × 50 mL) and brine (50 mL), dried, and concentrated, and the residue was dissolved in 50 mL of toluene and concentrated. The crude methanesulfonate/epoxide mixture was dissolved in 65 mL of DMF and treated with imidazole (2.18 g, 32 mmol) and KOtBu (3.59 g, 32 mmol), and the mixture was heated at 95 °C for 18 h. The mixture was then cooled, poured into 500 mL of water, and extracted with EtOAc (3 × 125 mL). The combined extracts were washed with water (5 × 75 mL) and brine (75 mL), dried, and concentrated. The crystalline residue was recrystallized from MeOH/MeCN to give 3.66 g (64%) of white crystals: mp 205–207 °C; ^{1}H NMR ($CDCl_3$) δ 8.63 (d, 2 H), 7.75 (d, 2 H), 7.69 (d, 2 H), 7.61 (d, 2 H), 7.54 (m, 2 H), 7.10 (t, 2 H), 6.83 (s, 1 H), 6.68 (s, 1 H), 6.39 (s, 1 H), 4.83 (s, 2 H); CIMS (CH_4) m/z = 360 (M + H$^+$); IR (KBr) 3600–2600 (OH), 1594 (Ar) cm^{-1}. Anal. ($C_{22}H_{18}FN_3O$) C, H, N.

Preparation of Pyridylacetophenones by Nickel-Catalyzed Coupling. 4-(4-Pyridyl)acetophenone (4a): Step 1. A solution of 4-bromoacetophenone (75.0 g, 0.375 mol) and trimethyl orthoformate (210 mL, 1.875 mol) in 210 mL of MeOH was treated with 7.5 g of Dowex 50X2 (400 mesh) ion exchange resin (acid form) and heated under reflux for 1 h. The mixture was cooled, filtered through a pad of Celite, and concentrated. The residue was distilled to provide 70.9 g (77%) of the dimethyl ketal as a colorless liquid: bp 70° (1 torr); ^{1}H NMR ($CDCl_3$) δ 7.55–7.32 (m, 4 H), 3.15 (s, 6 H), 1.51 (s, 3 H). It was used without additional characterization.

Step 2. A mixture of *n*-butyllithium (2.5 M, 13.0 mL, 32.6 mmol) in 15 mL of ether was cooled to –25 °C and treated with the ketal prepared in step 1 (8.00 g, 32.6 mmol) added dropwise over 3 min. The mixture was stirred for 5 min longer at –25 °C and then at 20 °C for 20 min, after which a solution of freshly fused $ZnCl_2$ (5.10 g, 37.5 mmol) in 75 mL of THF was added by cannula. The mixture was stirred at 15 °C for 1 h. During this time, a catalyst solution was prepared in a separate flask by treating a suspension of 0.75 g (1.15 mmol) of $Ni(PPh_3)_2Cl_2$ in 40 mL of THF with DIBAL-H (1 M in hexanes, 2.50 mL, 2.5 mmol). A solution of 4-bromopyridine in toluene was also prepared by adding 7.29 g (37.5 mmol) of 4-bromopyridine hydrochloride to 100 mL of toluene and a solution of 11.92 g (112 mmol) of Na_2CO_3 in 75 mL of water. After all of the hydrochloride salt had dissolved, the water was saturated with NaCl, the layers were separated, and the toluene was dried and concentrated to 50 mL. After the arylzinc mixture had stood for 1 h at 15 °C, the nickel catalyst solution was added by cannula followed promptly by the bromopyridine in toluene solution. The dark reaction mixture was stirred for 16 h, then was quenched with 6 M NaOH (70 mL), and stirred open to the air for 45 min, after which the dark color had been discharged and all of the nickel had precipitated as $Ni(OH)_2$. The mixture was filtered through Celite and the Celite was washed with a little MeOH. The filtrate was separated and the THF layer was diluted with ether (150 mL). The ethereal solution was washed with water (2 × 70 mL) and brine (70 mL), dried, and concentrated. The residual oil was taken up in 100 mL of acetone and treated with 35 mL of 3 M HCl and 35 mL of water. This was stirred for 1 h at 20 °C and then was concentrated and the aqueous solution was washed with ether (2 × 75 mL). These washes were discarded, and the aqueous solution was made alkaline with KOH pellets and extracted with CH_2Cl_2 (3 × 50 mL) and ether (50 mL). These extracts were dried and concentrated to give 6.23 g (97%) of white crystals: mp 93–94 °C; ^{1}H NMR ($CDCl_3$) δ 8.74 (d, 2 H), 8.07 (d, 2 H), 7.75 (d, 2 H), 7.54 (d, 2 H), 2.67 (s, 3 H); CIMS (CH_4) m/z = 198 (M + H$^+$). Anal. ($C_{13}H_{11}NO$) C, H, N.

Ear Edema Assays. Groups of 10 male CF_1 mice (18–20 g) were used. Solutions of test compounds were prepared in acetone and were applied to both ears just prior to challenge with inflammogen. Inflammation in the ear skin was induced by the application of either 1 μg of tetradecanoylphorbol acetate, 10 μg of A23187, or 1 μg of arachidonic acid, each dissolved in 10 μL of acetone to the inner surface of one ear. The unchallenged ear served as the control. At various times after the application of the inflammogen, the animals were euthanized by cervical dislocation. Disks (6 mm) were removed from each ear with a skin biopsy punch and the weights were determined. The edema was measured as the difference in weight between the punches from the challenged and unchallenged ears; this value varied less than 10% between repeat experiments. Percent inhibition was calculated by using $[(C - T)/C] \times 100\%$, where C is the positive control swelling and T is the drug-tested swelling. Statistical significance was determined by Student's t test. The standard errors of the values reported averaged (for a large selection of the compounds) less than 10% of these values.

Evaluation of 12*R*-HETE Biosynthesis Inhibition by 2a. Mice were dosed with the drug and challenged with inflammogen as described above for the ear edema assays. Following euthanization, the ears were clamp frozen with plates cooled to –196 °C, removed, pulverized, and extracted. The extracts were analyzed by reversed-phase HPLC (Rainin SD column; eluting with a gradient of 35% to 85% acetonitrile in 0.1% aqueous acetic acid; 1.0 mL min^{-1}). Chiral separation of 12*R*-HETE and 12*S*-HETE was accomplished using a DNPG column (98:2 hexane/2-propanol; 0.8 mL min^{-1}).

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Supplementary Material Available: Synthetic details and spectral data for (a) pyridylacetophenones **4** prepared by nickel-catalyzed coupling, (b) α-bromo ketone hydrobromides **5**, (c) (pyridylphenacyl)imidazoles **6**, and (d) 2-, 3-, and 4-pyridyltrimethylstannanes, as well as topical antiinflammatory activity data for **1a–k** and **2a–dd** in A23187 mouse ear edema, arachidonic acid mouse ear edema, and delayed type hypersensitivity in the mouse (5 pages). Ordering information is given on any current masthead page.