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2,4,5- TRIARYLIMIDAZOLE INHIBITORS OF IL-1 BIOSYNTHESIS

Timothy F. Gallagher,*† Susan M. Fier-Thompson,† Ravi. S. Garigipati,† Margaret E. Sorenson,† Juanita M. Smietana,† Dennis Lee,† Paul E. Bender,† John C. Lee,‡ Jeffrey T. Laydon,‡ Don E. Griswold,§ Marie C. Chabot-Fletcher,§ John J. Breton,§ and Jerry L. Adams†

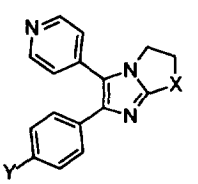
Departments of Medicinal Chemistry,† Cellular Biochemistry‡ and Pharmacology,§ SmithKline Beecham Pharmaceuticals, King of Prussia, PA 19406-0939, USA.

Abstract. As part of an effort to define the pharmacophore and discover the mechanism by which the anti-inflammatory dual cyclooxygenase / 5-lipoxygenase inhibitors SK&F 86002 and SK&F 105809 inhibit IL-1 biosynthesis, a series of substituted 2,4,5-triarylimidazole derivatives were prepared and evaluated as inhibitors of IL-1 and 5-lipoxygenase biosynthesis.

Introduction

Monocytic phagocytes in response to a variety of stimuli produce interleukin-1 (IL-1) as two structurally distinct proteins, IL-1α and IL-1β.[1] Both proteins have similar biological activities[2] which include, but are not limited to, stimulation of prostaglandins and collagenase produced by synovial cells,[3] induction of tumor necrosis factor[4] and IL-6,[5] stimulation of osteoclasts toward bone resorption,[6] stimulation of acute phase proteins by hepatocytes[7] and regulation of body temperature.[8] As a natural consequence of its myriad of activities, IL-1 has long been suggested to be a contributing factor in a host of inflammatory and other disease processes. More recently, studies with IL-1 receptor antagonists[9] and small molecule inhibitors of IL-1 synthesis or release[10] have demonstrated activity in a variety of disease models. IL-1 receptor antagonist protein is presently in phase II clinical trials for rheumatoid arthritis and other diseases.[11]

We have been interested for some time in a class of pyridylimidazole anti-inflammatory compounds which include SK&F 86002 and SK&F 105809. These compounds were initially designed as dual cyclooxygenase / 5-lipoxygenase inhibitors and were only later found to be inhibitors of IL-1 biosynthesis *in vitro*.[12] Their unique activities in animal models of inflammation suggested that inhibition of IL-1 may be an important property of these compounds *in vivo*.[13] The precise mechanism of action by which these compounds inhibit IL-1 synthesis is not known but has been shown to be at the translational level.[14]



SK&F 86002: X= S, Y= F
SK&F 105809: X= CH_2, Y= $S(O)CH_3$
SK&F 105561: X = CH_2, Y = SCH_3

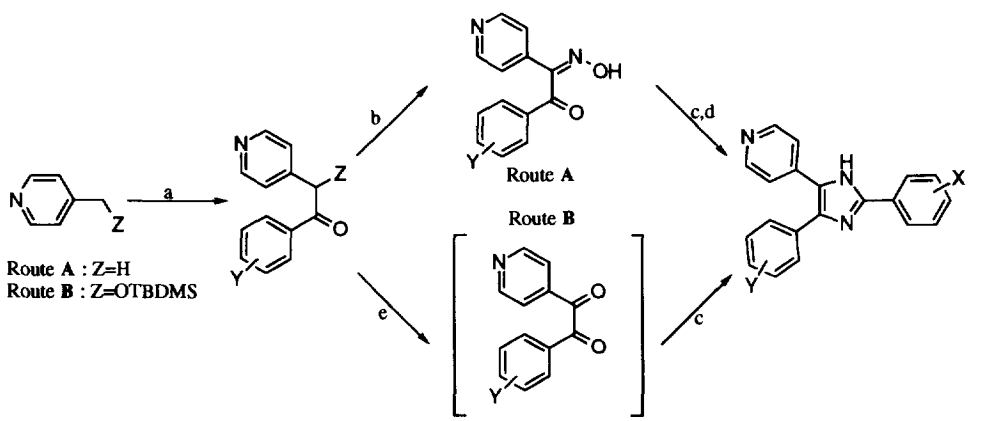
Evaluation of SK&F 86002, SK&F 105809 and existing analogs led to a hypothesis that the essential feature of the pharmacophore for IL-1 inhibition is a 4-pyridyl group attached to an imidazole ring β to an unalkylated imidazole nitrogen[15] All of the compounds evaluated, however, were prepared to optimize inhibition of eicosanoid production and, consequently, evaluation of the pharmacophore was incomplete.

We decided, therefore, to undertake and SAR study with the goal of optimizing IL-1 inhibition. By employing such an approach, we hoped to demonstrate that inhibition of IL-1 was specific and unrelated to 5-lipoxygenase inhibition,[16] enhance our understanding of pharmacophore for IL-1 inhibition and prepare more potent inhibitors of IL-1 biosynthesis. In addition, we felt that knowledge of the structural features affecting potency and selectivity could be used to design radiolabelled and radio-photoaffinity labelled probes to aid in the identification of the molecular target.

Results and discussion

Replacement of the pyrrole ring of SK&F 105809 with a phenyl ring at the 2-position of the imidazole was initially explored, since we felt that this portion of the molecule was probably not crucial for IL-1 activity and that placement of a phenyl ring at the 2-position would allow for the facile preparation of a large number of substituted phenyl analogs to probe for differences in pharmacophores.

Scheme I

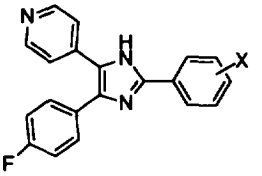


a) LDA, THF, Y-PhN(OMe)Me; b) $NaNO_2$, HCl, H_2O; c) X-PhCHO, NH_4OAc; d) $P(OMe)_3$; e) $Cu(OAc)_2$

All of the triarylimidazoles of this type (Tables 1-3), except for compounds **4** and **60**,[17] were prepared according to the synthetic sequence outlined in Scheme I. Route **A** is nearly identical to processes outlined in the literature[18] with the only modification being the use of N,O-dimethylbenzamides[19] instead of the corresponding esters. In our hands, the Weinreb amides afforded better yields of the corresponding deoxybenzoins. Route **B**, which produces triarylimidazoles directly from siloxybenzoins, represents a significant improvement in both yield and practicality compared with methods detailed in the literature which require synthesis and isolation of the intermediate α-hydroxyketone[20] or diketone.[18]

The results in Tables 1-3 show that for 2,4,5-triarylimidazoles, inhibition of IL-1 synthesis does not depend upon or correlate with 5-lipoxygenase inhibition (Fig. 1). A non-specific antioxidant mechanism can also be discounted as no correlation is observed between redox potential and IL-1 inhibition (Table 4). Furthermore, subtle changes in inhibitor structure can lead to dramatic differences in potency. For instance, three series of sulfides (**1**,**5**,**8**), sulfoxides (**2**,**4**,**9**) and sulfones (**3**,**7**,**10**) (Table 1) were prepared differing only in the position of the group around the 2-phenyl ring. When placed at the 4 position and not the 2 or 3

Table 1. 2-Phenyl Substituents



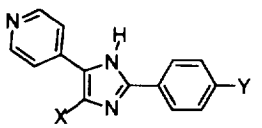
Compound No.	X	IL-1[c] IC_{50} (μM)	5-LO[d] IC_{50} (μM)[b]	Compound No.	X	IL-1[c] IC_{50} (μM)[b]	5-LO[d] IC_{50} (μM)
1	4-SCH_3	0.58	2.7	**22**	4-NO_2	0.05	8.0
2	4-$S(O)CH_3$	0.08	58	**23**	4-$NHSO_2CH_3$	0.27	52%
3	4-SO_2CH_3	0.20	24	**24**	4-$CH_2NHSO_2CH_3$	0.50	58%
4	4-$S(O)CH_3$[a]	0.65	-	**25**	4-$CH_2C[N(CN)]NH_2$	0.42	3.8
5	3-SCH_3	0.93	-	**26**	4-$CH_2N(CH_3)CH_2Ph$	2.3	0.80
6	3-$S(O)CH_3$	0.70	-	**27**	4-CH_2NHCHO	0.12	-
7	3-SO_2CH_3	0.62	-	**28**	4-CH_2-N-morpholino	0.55	33%
8	2-SCH_3	0.82	-	**29**	4-N_3	0.44	-
9	2-$S(O)CH_3$	0.71	-	**30**	4-CN	0.10	66%
10	2-SO_2CH_3	0.74	-	**31**	4-CO_2H	0.50	3%
11	H	0.30	53%	**32**	4-CO_2Et	1.0	2.4
12	4-OCH_3	0.40	7.6	**33**	4-CO_2Me	0.37	5.3
13	4-OH	0.05	68%	**34**	4-C(O)NHOH	0.12	4.7
14	3,5-dimethyl,4-OH	0.60	3.1	**35**	4-$C[N(OH)]NH_2$	0.19	46%
15	2-OH	3.0	4.1	**36**	4-SO_2NH_2	0.05	47%
16	3,5-di-t-butyl,4-OH	>5.0	62%	**37**	4-[SO_2(N-Me-piperdine)]	0.74	-
17	4-$O(CH_2)_3N(CH_3)_2$	0.29	49	**38**	4-$[CH(CH_3)N(OH)C(O)NH_2]$	0.35	6.2
18	4-CH_2NH_2	0.05	62%	**39**	4-$CH_2N(OH)C(O)NH_2$	0.20	-
19	4-$CH_2N(CH_3)_2$	0.08	38%	**40**	4-(oxadiazol-5-one-3-yl)	0.86	42%
20	4-$N(CH_3)_2$	0.35	5.6	**41**	4-(5,5-dimethyloxadiazol-3-yl)	6.8	7.2
21	4-NH_2	0.05	38%	**42**	4-(5-methyloxadiazol-3-yl)	1.32	70%

[a] Imidazole is methylated α to the pyridine. [b]or percent inhibition @ 20 μM. [c]Inhibition determined using intact human monocytes.[21] [d]Assay employs semi-purified enzyme from RBL-1 cells.[22]

position, the more polar sulfoxide leads to enhanced potency. In contrast, it was shown that placement of a sulfoxide moiety at the 4 position of the 4-phenyl ring in the pyrroloimidazole series produces an inactive prodrug, SK&F 105809, to the active sulfide metabolite, SK&F 105561. Placement of other polar functionalities at the 4 position of the 2-phenyl ring also led to compounds exhibiting enhanced potency (e. g. **13**, **18** and **36**). In contrast, other substituents at this position, including sterically demanding ones, are tolerated but do not lead to more potent compounds.

A different but equally rigid SAR exists with respect to substitution around the 4-phenyl ring (Table 2). The requirement for an aromatic ring at this position is illustrated by the lack of activity exhibited by the 4-ethyl derivative **43.** Of the analogs prepared, only the 3-chlorophenyl analog, **44,** exhibited potency equal to its corresponding 4-fluorophenyl derivative **2.** Increasing either the size or the polarity of substituents led to diminished potency.[23]

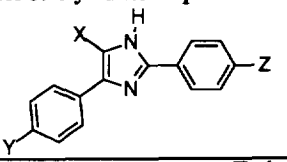
Table 2. 4-Fluorophenyl Replacements



Cmpd. No.	X	Y	IL-1 IC_{50} (μM)	5-LO IC_{50} (μM)[a]
12	4-FPh	OCH_3	0.40	7.6
43	CH_2CH_3	OCH3	>5	-
2	4-FPh	$S(O)CH_3$	0.08	58
44	3-ClPh	$S(O)CH_3$	0.08	43%
45	3-CH_3OPh	$S(O)CH_3$	0.59	22%
46	2-CH_3OPh	$S(O)CH_3$	1.14	5%
47	3-CH_3SO_2NHPh	$S(O)CH_3$	>5	-
48	1-Naphthyl	$S(O)CH_3$	0.65	-
49	2-Naphthyl	$S(O)CH_3$	0.77	-
1	4-FPh	SCH_3	0.58	2.7
50	3-$CH_3C(O)NHPh$	SCH_3	4.32	-
51	3-NO_2Ph	SCH_3	2.77	-
52	3-NH_2Ph	SCH_3	0.68	-
53	3-CH_3SO_2NHPh	SCH3	>5	62%
29	4-FPh	N_3	0.44	-
54	3-I	N_3	0.64	-

[a] or percent inhibition @ 20 μM.

Table 3. Pyridine Replacements



Cmpd. No.	X	Z	IL-1 IC_{50} (μM)	5-LO IC_{50} (μM)[a]
22	4-Pyridyl	NO_2	0.05	8.0
55[b]	Ph	NO_2	>5	-
2	4-Pyridyl	$S(O)CH_3$	0.08	58
56[c]	2-CH_3-4-Pyridyl	$S(O)CH_3$	0.43	23%
57[c]	4-Quinolyl	$S(O)CH_3$	0.71	7.2
30	4-Pyridyl	CN	0.10	66%
58[c]	4-Quinoyl	CN	0.60	-

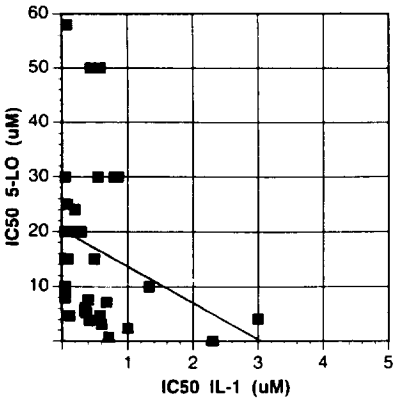
[a] or percent inhibition @ 20 μM
[b] Y = H; [c] Y = F

The importance of the 4-pyridyl moiety for IL-1 inhibitory activity which had been established for SK&F 86002 and SK&F 105809 was confirmed by the lack of activity displayed by the phenyl analog **55** (Table 3). However, substitution of the 4-pyridyl with two six-membered heterocyclic rings containing a basic nitrogen in place of the pyridyl nitrogen, namely, 2-methylpyridyl (**56**) and 4-quinolyl (**57** &**58**), produced compounds which were active, albeit less potent, as IL-1 inhibitors.

Table 4. Redox Potentials

Cmpd. No.	Red. Pot. (eV)	IL-1 IC_{50} (μM)
12	1.00, 1.32	0.42
13	0.78, 1.1	0.05
16	0.90, 1.25	>5
18	0.92, 1.22	0.05
30	1.40	0.10
31	0.87, 1.38	0.5
58	1.20, 1.58	0.06

Fig. 1
Scatter Plot of Inhibition of IL-1 vs. 5-LO production



R = 0.008

Summary

We have been able to show that for a series of 2,4,5-triarylimidazoles, IL-1 inhibition does not correlate with 5-LO inhibition and is not a function of non-specific antioxidant activity suggesting a unique molecular target as the site of action for these compounds. In addition, we have expanded our knowledge of the pharmacophore for IL-1 inhibition and have identified several potent inhibitors with $IC_{50's} < 0.1$ μM. Radiolabeled **13** (SB 202190) has recently been used to develop a binding assay and a radioiodinated photoaffinity label based upon the aryl azide **54** has been employed to help identify the molecular target as a novel stress induced MAP kinase homologue.[24] Compound **2** (SB 203580) has been found by Cuenda et al. to be a selective inhibitor of this kinase (or a very close homologue).[25] Future publications will explore the pharmacology of the triaryl imidazoles along with further refinements of our pharmacophore model.

Acknowledgement

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