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Pyrrolidine and Piperidine Analogues of SC-57461A as Potent, Orally Active Inhibitors of Leukotriene A_4 Hydrolase

Thomas D. Penning,[a,*] Nizal S. Chandrakumar,[a] Bipin N. Desai,[a] Stevan W. Djuric,[a,†] Alan F. Gasiecki,[a] Chi-Dean Liang,[a] Julie M. Miyashiro,[a] Mark A. Russell,[a] Leslie J. Askonas,[b] James K. Gierse,[b] Elizabeth I. Harding,[b] Maureen K. Highkin,[b] James F. Kachur,[b] Suzanne H. Kim,[b] Doreen Villani-Price,[b] E. Yvonne Pyla,[b] Nayereh S. Ghoreishi-Haack[b] and Walter G. Smith[b]

[a]*Department of Medicinal Chemistry, Pharmacia Corporation, 4901 Searle Parkway, Skokie, IL 60077, USA*
[b]*Departments of Inflammatory Diseases Research and Molecular Pharmacology, Pharmacia Corporation, 4901 Searle Parkway, Skokie, IL 60077, USA*

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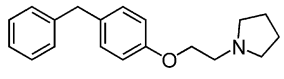
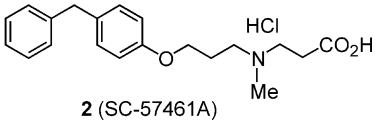
Abstract—The synthesis and biological evaluation of a series of functionalized pyrrolidine- and piperidine-containing analogues of our lead LTA_4 hydrolase inhibitor, SC-57461A, is described. A number of compounds showed excellent potency in our in vitro screens and several demonstrated good oral activity in a mouse ex vivo assay. These efforts led to the identification of SC-56938 (**14**) as a potent, orally active inhibitor of LTA_4 hydrolase.

Leukotriene B_4 (LTB_4) is a potent, pro-inflammatory mediator synthesized by a number of cell types and implicated in the pathogenesis of a number of diseases including inflammatory bowel disease (IBD), psoriasis, rheumatoid arthritis and asthma. LTA_4 hydrolase is a zinc-containing enzyme which stereospecifically catalyzes the hydrolysis of the unstable epoxide LTA_4 to LTB_4. LTA_4 hydrolase represents an attractive target since the action of this enzyme is the rate limiting step in the production of LTB_4. A number of inhibitors of this enzyme have been reported over the past several years.[1] Our previous efforts focused on the exploration of a series of analogues related to screening hit SC-22716 and resulted in the identification of potent analogues such as **1**.[2] The analogues within this non-peptidic series are unique in that they do not appear to bind zinc as most other previously reported inhibitors. Extensive structure–activity studies around this structural class resulted in the identification of a series of α-, β-, and γ-amino acid analogues that demonstrated potent inhibition of the LTA_4 hydrolase enzyme, as well as good oral activity in a mouse ex vivo whole blood LTB_4 production assay. These efforts led to the identification of clinical candidate SC-57461A (**2**).[3–5]



1



2 (SC-57461A)

The excellent oral efficacy that was demonstrated with SC-57461A we have attributed, at least in part, to the presence of the carboxylate moiety. Based on this assumption, we sought to incorporate various polar functional groups into the cyclic amine moiety of **1** and **12** in an effort to improve upon the generally poor oral activity demonstrated in this non-functionalized class. A series of substituted pyrrolidine- and piperidine-containing analogues were synthesized to validate this hypothesis. In general, all analogues described could be synthesized as shown in Scheme 1.

*Corresponding author. Tel.: +1-847-982-7563; fax: +1-847-982-4714; e-mail: thomas.d.penning@pharmacia.com
†Currently at Abbott Laboratories, Abbott Park, IL, USA.

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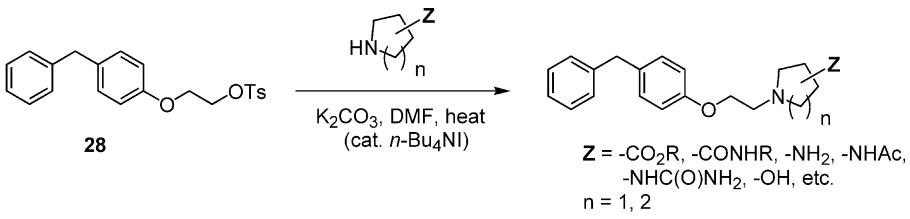
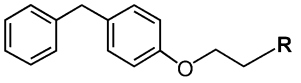
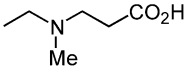
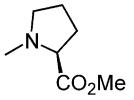
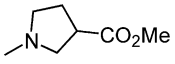
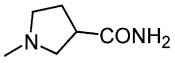
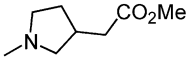
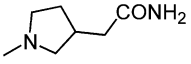
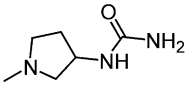
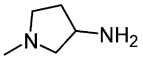
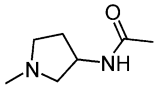
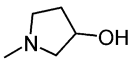


Scheme 1. General synthesis of functionalized analogues.

Heating tosylate **28**[2] with a variety of functionalized amines and potassium carbonate in DMF (with catalytic *n*-Bu_4NI optionally added), as previously described,[2] provided, after purification by flash chromatography, the desired cyclic amines. Additional functionalized analogues were readily accessible by appropriate functional group manipulation. The substituted pyrrolidine analogues highlighted in Table 1 were synthesized and evaluated in our recombinant human LTA_4 hydrolase enzyme assay, human whole blood LTB_4 production assay and mouse ex vivo whole blood LTB_4 production assay.[4,5] Several analogues showed significant potency in the enzyme and whole blood assays with two analogues in particular, **6** and **8**, also showing good potency when dosed orally in the mouse ex vivo assay. However, neither analogue demonstrated the level of potency that

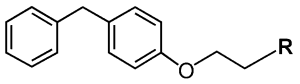
Table 1. In vitro and ex vivo data for pyrrolidino analogues

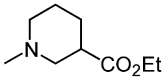
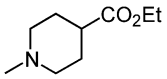
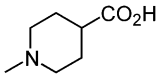
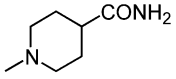
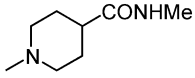
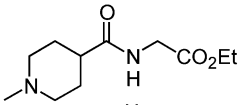
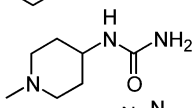
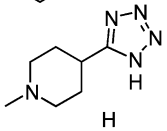
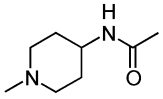
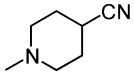
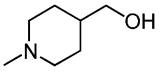
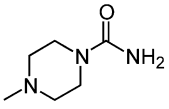
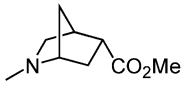
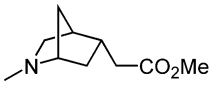
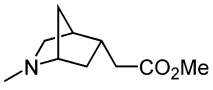


Compd	R	IC_{50} (μM)[a]		Mouse ex vivo % inhib @10 mg/kg (ED_{90})
		rhLTA_4 hydrolase	Human whole blood	
1		0.026	0.12	35
2 (SC-57461A)		0.0025	0.049	>98 (1–3 mg/kg)
3		0.45 (2)	1.86	0
4		4.1	0.23	75
5		0.016	0.36	60
6		0.39	0.24 (2)	75 (3–10 mg/kg)
7		0.21	0.40	4
8		0.081	0.35	92
9		0.02	0.29	57
10		0.21	0.42	22
11		0.03 (2)	0.19	50

[a]Average of at least three determinations except where noted in parentheses.

Table 2. In vitro and ex vivo data for piperidino analogues



Compd	R	IC_{50} (μM)[a]		Mouse ex vivo % inhib @10 mg/kg (ED_{90})
		rhLTA$_4$ hydrolase	Human whole blood	
12		0.055 (2)	0.17	8
13		> 3 (1)	1.65 (2)	[b]
14 (SC-56938)		1.8	0.82	97 (3 mg/kg)
15		0.28	0.29	80
16		0.13	0.64	95 (3–10 mg/kg)
17		0.057	0.13 (2)	92
18		0.11	0.70 (2)	91 (3–10 mg/kg)
19		0.087	0.44	72
20		0.24	0.30	91 (3 mg/kg)
21		0.05 (2)	0.18	49
22		0.47	0.41	56
23		0.052	0.58	85
24		1.1	2.4 (2)	44
25		0.047	0.20	50
26		0.015	0.11	80 (≥10 mg/kg)
27		0.21	0.79 (2)	70

[a]Average of at least three determinations except where noted in parentheses.
[b]Not determined.

was seen with **2**. Overall, there was a trend towards improved oral activity (relative to **1**) when a polar functional group was introduced into the core structure of **1**. However, it appeared that this alone was not sufficient to impart significant oral activity to the molecule, as evidenced by the complete lack of oral efficacy demonstrated by **3**. Although we attributed poor oral efficacy, at least in part, to poor oral absorption, this was not confirmed by any detailed pharmacokinetic studies.[6]

The results for a series of functionalized piperidine-containing analogues are detailed in Table 2. In general, 3-substituted piperidines such as **13** showed diminished potency in the enzyme and whole blood assays relative to the parent structure **12**. On the other hand, 4-substituted analogues **14**–**23** all showed potencies roughly equivalent to **12** in the in vitro assays. In addition, all of the 4-functionalized piperidine analogues demonstrated significantly improved potency in the mouse ex vivo assay (relative to **12**) including several (**14**, **16**, **18**, and **20**) with ED_{90} values in the 3–10 mg/kg range. Several functionalized bicyclic analogues **25**–**27** also showed improved oral efficacy.

Although not particularly potent in our in vitro assays, but based on the excellent potency demonstrated in the mouse ex vivo assay, **14** (SC-56938) was chosen for further pharmacological evaluation. In a rhesus monkey ex vivo assay, SC-56938 showed excellent potency when dosed orally, inhibiting the production of LTB_4 with an ED_{90} of <10 mg/kg. In addition, SC-56938 was orally efficacious in a rat peritoneal LTB_4 production model,[7] with an $ED_{50} = 3$ mg/kg and an $ED_{90} = 30$ mg/kg. Significant oral efficacy was also demonstrated in a rat reversed passive dermal arthus model,[7] with an $ED_{90} = 3$–10 mg/kg.

In summary, we have demonstrated that we can significantly improve the oral activity of a series of LTA_4 hydrolase inhibitors based on **1** and **12** by incorporation of a polar functional group into the pyrrolidine or piperidine ring system. In general, the 4-carboxypiperidine derivatives showed the best overall profile in this study, with the acid or acid isosteres, ester, and various amides all demonstrating good oral efficacy in the mouse ex vivo assay. As a result of this study, SC-56938 was chosen for further biological characterization. Based on encouraging efficacy data, SC-56938 was identified as a potential clinical candidate and was positioned as a backup to the lead LTA_4 hydrolase inhibitor, SC-57461A.

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6. Pharmacokinetic data is available for **2**, which had an oral bioavailability of 25% and a half-life of 1.1 h in mouse. However, the pharmacodynamic half-life as demonstrated in the mouse ex vivo assay exceeded 24 h, possibly due to its extensive distribution.
7. Askonas, L. J.; Kachur, J. F.; Villani-Price, D.; Harding, E. I.; Pyla, E. Y.; Highkin, M. K.; Liang, D. C.; Desai, B. N.; Russell, M. A.; Smith, W. G. 8th International Congress of the Inflammation Research Association, Hersey, PA, 1996; Abstract 84.