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Synthesis of Imidazopyridines and Purines as Potent Inhibitors of Leukotriene A_4 Hydrolase

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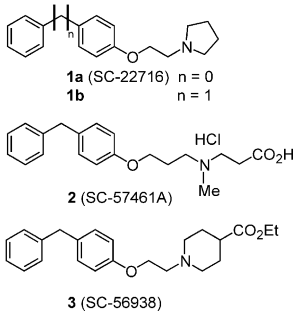
Abstract—The synthesis and biological evaluation of a series of heterocyclic analogues of the previously reported LTA_4 hydrolase inhibitor **1b** are described. Imidazopyridine and purine analogues are specifically highlighted with several demonstrating excellent potency in our in vitro assays, as well as good oral activity in a mouse ex vivo assay.

Leukotriene B_4 (LTB_4) is a potent, pro-inflammatory mediator implicated in the pathogenesis of a number of diseases including inflammatory bowel disease (IBD), psoriasis, rheumatoid arthritis and asthma. A key enzyme in the biosynthesis of LTB_4 is LTA_4 hydrolase, a zinc-containing enzyme which stereospecifically catalyzes the hydrolysis of LTA_4 to LTB_4. LTA_4 hydrolase is an attractive target since the action of this enzyme is the rate limiting step in the production of LTB_4. We, along with several others have reported a number of inhibitors over the past several years.[1] Our previous efforts focused on the exploration of a series of analogues related to screening hit **1a** (SC-22716) and resulted in the identification of potent analogues such as **1b**.[2] These non-peptidic analogues 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 acyclic and cyclic amino acid analogues that demonstrated potent inhibition of the LTA_4 hydrolase enzyme. More significantly, these analogues also showed good oral activity in a mouse ex vivo whole blood LTB_4 production assay, and led to the identification of clinical candidates **2** (SC-57461A)[3–5] and **3** (SC-56938).[6,7]



To further investigate the SAR around the amine moiety of this series, we incorporated a number of nitrogen-containing heterocycles as replacements for the pyrrolidine group in the core molecule **1b**. Since the excellent oral efficacy demonstrated with **2** and **3** was attributed in part to the presence of the carboxylate moiety, we also investigated the incorporation of additional polar functionality into these heterocyclic series. The moderate potency demonstrated with imidazole **4**, led us to explore a series of bicyclic imidazole-containing

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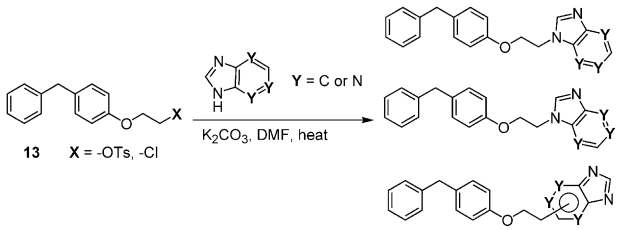
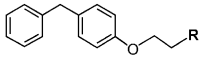


Scheme 1. General synthesis of imidazopyridine and purine analogues.

analogues, most notably, imidazopyridines and purines. The general synthesis of these analogues is outlined in Scheme 1. Heating either tosylate **13a** or chloride **13b**[2] with the appropriate nitrogen-containing heterocycle and potassium carbonate in DMF, as previously described,[2] provided the desired alkylation product(s). In the case of the imidazopyridine and purine analogues, all possible regioisomeric products were obtained and were separated by flash chromatography. In general, further functionalization of the imidazopyridine adducts could be carried out as described in Scheme 2. Oxidation with *m*-CPBA provided *N*-oxide **14**. Treatment with trifluoroacetic anhydride[8] yielded pyridone **15**, whereas treatment with TMSCN[9,10] gave nitrile **16**. The unfunctionalized analogues were 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 and the data is detailed in Table 1.[4,5] In general, most analogues showed similar potency to **1b** in both enzyme and whole blood assays. However, within each series, there were specific regioisomers that stood out in terms of enzyme potency (i.e., **6b**, **7c**, **8b** and **8c**). Although we saw no improvement in mouse ex vivo potency with **4**, **5** and **6a**/**b**/**c** (relative to **1**), we did see significant potency improvements with **7b**/**c** and **8a**/**b**/**d**, up to 72 and 76% inhibition of LTB_4 production at a 10 mg/kg dose for **8d** and **7c**, respectively. The results for several functionalized imidazopyridine analogues are shown in Table 2. In general, all of these analogues showed a significant increase in potency in both the enzyme assay and whole blood assays, with nitrile **12** showing subnanomolar potency in the enzyme assay. In addition, several of the analogues demonstrated an improvement in potency in the mouse ex vivo assay, with **9a**, **9b**, **10**, and **11** all inhibiting LTB_4 production >70% at a 10 mg/kg oral dose.

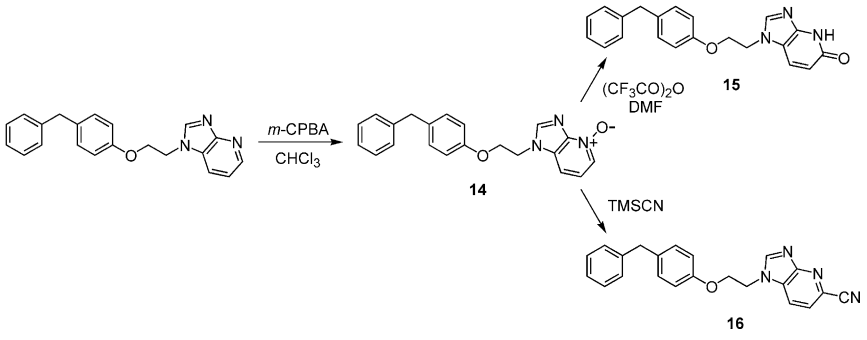
Table 1. In vitro and ex vivo data of heterocyclic analogues



Compd	R	IC_{50} (μM)[a]		Mouse ex vivo % inhib @10 mg/kg
		rhLTA_4 hydrolase	Human whole blood	
1b		0.026	0.12	35
4		0.12	1.34	29
5		2.0 (2)	13.2 (2)	46
6a		>3 (2)	9.15 (2)	[b]
6b		0.008 (2)	0.33	18
6c		0.14	0.69	22
7a		0.56	0.73	39
7b		0.12	0.33	64
7c		0.011	0.074	76
8a		0.73	0.14	60
8b		0.047	0.79	57
8c		0.04	0.14	[b]
8d		0.18	0.46	72

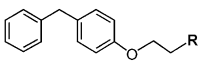
[a]Average of at least three determinations except where noted in parentheses.
[b]Not determined.

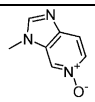
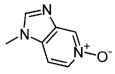
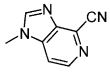
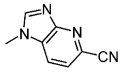
In summary, we have described a series of nitrogen-containing heterocyclic analogues of some of our previously reported LTA_4 hydrolase inhibitors. We have demonstrated that we can replace the cyclic amine moiety from the earlier series with these heterocycles and



Scheme 2. Functionalization of imidazopyridines.

Table 2. In vitro and ex vivo data of functionalized heterocyclic analogues



Compd	R	IC_{50} (μM)[a]		Mouse ex vivo % inhib @10 mg/kg
		$rhLTA_4$ hydrolase	Human whole blood	
9a		0.036	0.065 (2)	81
9b		0.082	0.32 (2)	72
10		0.50	0.94 (2)	72
11		0.031	0.10	84
12		0.0008	0.15	21

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

maintain good potency in both the enzyme and human whole blood assays. Several of these heterocyclic analogues also exhibited an increase in potency in the mouse ex vivo assay. In addition, we have demonstrated that further functionalization of these heterocycles improved enzyme inhibitory potency, as well as mouse ex vivo potency.

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