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Azabenzthiazole inhibitors of leukotriene A_4 hydrolase

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ABSTRACT

Previously, benzthiazole containing LTA_4H inhibitors were discovered that were potent (**1**–**3**), but were associated with the potential for a hERG liability. Utilizing medicinal chemistry first principles (e.g., introducing rigidity, lowering *c*Log *D*) a new benzthiazole series was designed, congeners of **1**–**3**, which led to compounds **7a**, **7c**, **12a**–**d** which exhibited LTA_4H IC_{50} = 3–6 nM and hERG Dofetilide Binding IC_{50} = 8.9–> >10 μM.

Leukotriene A_4 hydrolase (LTA_4H) is a zinc-containing cytosolic enzyme with both hydrolase and aminopeptidase activity, the crystal structure of which was published in 2001.[1] LTA_4H is a key enzyme in the arachidonic acid cascade downstream of 5-lipoxygenase (5-LO) and 5-lipoxygenase-activating protein (FLAP) as seen in Fig. 1. The leukotrienes LTC_4, LTD_4 and LTE_4, known as cysteinyl leukotrienes,[2] are also produced from LTA_4.

LTA_4H stereospecifically catalyzes the hydrolysis of the unstable epoxide LTA_4, affording the proinflammatory mediator leukotriene B_4 (LTB_4). LTB_4 is a potent chemoattractant of neutrophils, eosinophils, macrophages, mast cells, T-cells, dendritic cells, smooth muscle cells and keratinocytes, and also activates neutrophils.[3] This inflammatory mediator has been implicated in a plethora of disorders, including inflammatory bowel disease (IBD),[4] chronic obstructive pulmonary disease (COPD),[5] cancer,[6] rheumatoid arthritis (RA),[7] asthma,[8] and cardiovascular disease.[9] LTA_4H also functions as an anion-dependent aminopeptidase, efficiently processing arginyl di- and tri-peptides. Recently, a role for this aminopeptidase activity in the degradation and inactivation of the tripeptide proline-glycine-proline (PGP) was described.[10]

The lipoxins, LXA_4 and LXB_4, derived from arachidonic acid and LTA_4, are endogenous anti-inflammatory agents that are thought to participate in the resolution phase of inflammation (not shown). We surmised that an inhibitor of LTA_4H may have certain advantages[11] over 5-LO or FLAP inhibitors which prevent the formation of LTA_4, a source of the lipoxins.[12] In contrast, the inhibition of LTA_4H would not block the production of the lipoxins, as it acts downstream of this branch point in the cascade. Inhibiting LTB_4 formation eliminates the potential challenges associated with antagonizing two LTB_4 receptors, BLT1 and BLT2, which may be needed in order to achieve full efficacy in vivo.[13] Rao et al.[11] previously reported that a LTA_4H inhibitor **1** (Fig. 2) selectively blocked LTB_4 production in a zymosan-induced peritonitis model without affecting cysteinyl leukotriene production and maintained the production of the anti-inflammatory mediator LXA_4.

In our previously disclosed report,[14] the benzthiazole left hand portion of **1** was held constant, while focusing modification efforts on the right hand portion. These efforts resulted in a series of potent and selective LTA_4H inhibitors represented by **1**, **2**, and **3** (Fig. 2), having excellent PK/PD properties.[14]

The data in Table 1 show potent LTA_4H inhibitory activity and good inhibition of LTB_4 production in stimulated mouse whole blood for **1**, **2**, and **3**.[14] Compounds **1** and **2** also exhibit a relative lack of potency inhibiting dofetilide binding to the hERG channel (hERG binding).[14] Compounds **1**, **2**, and **3** were evaluated in the murine arachidonic acid-induced ear inflammation model and were found to have good activity as measured by the % inhibition of LTB_4 production in blood, and the % inhibition of myeloperoxidase activity (MPO) as a measure of neutrophil influx into the ear tissue.[15] In a rat PK study (10 mg/kg:2 mg/kg po:iv) compound **2** had a reasonable %F (65%) and $t_{1/2}$ (5.6 h), and showed a C_{max} of

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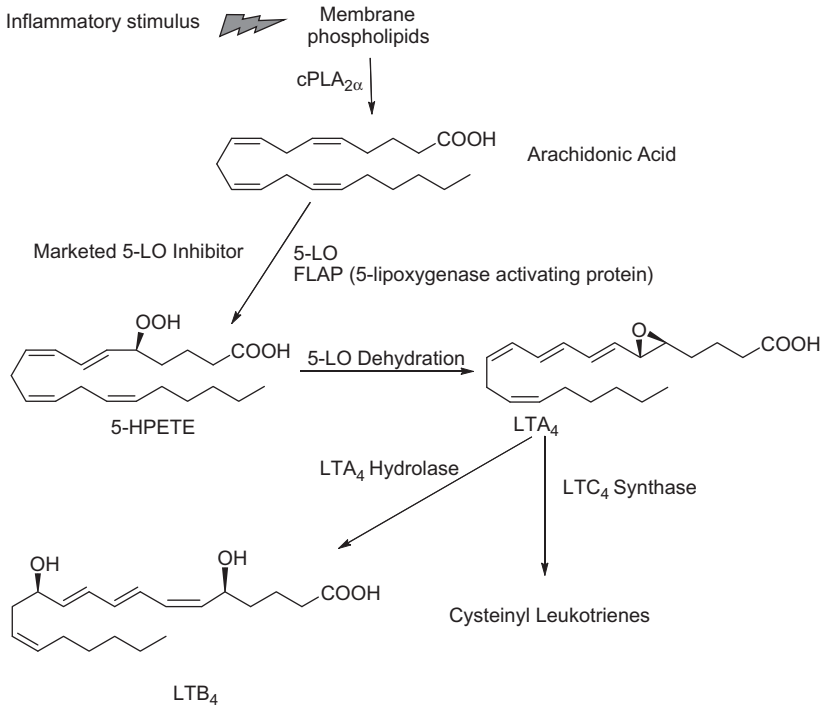


Figure 1. Biosynthetic pathway of the leukotrienes.

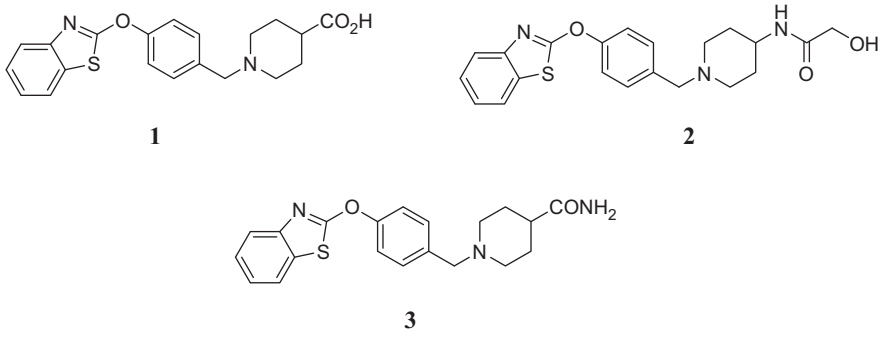


Figure 2. Benzthiazole containing LTA_4H inhibitor leads.

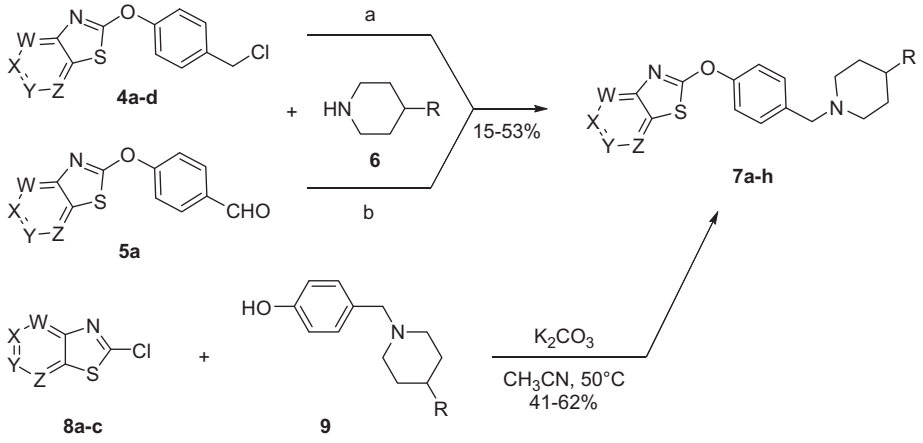
Table 1
In vitro and in vivo data for LTA_4H inhibitors **1**, **2**, and **3**

Compd.	LTA_4H IC_{50} (nM) [d,g]	MWB[a] LTA_4H IC_{50} (nM)[d,g]	% Inh[b,g] LTB_4/MPO	hERG DB[c] IC_{50} (μM)	%F/ $t_{1/2}$[e]	C_{max}[f]
1	11 ± 9	88 ± 24	80/82	>10	—	—
2	13 ± 12	104 ± 100	94/75	9.9	65/5.6 h	2.2
3	17 ± 11	151 ± 156	93/87	1.5	—	—

[a] Mouse whole blood diluted 1:15 with media is stimulated with calcium ionophore, A23187, and then assayed for LTB_4 production.
[b] Mouse arachidonic acid-induced ear inflammation model 30 mg/kg.
[c] DB = dofetilide binding.
[d] Data expressed as IC_{50} ± std dev in nM.
[e] Rat PK 10 mg/kg: 2 mg/kg po:iv.
[f] Rat PK 10 mg/kg: 2 mg/kg po:iv, μMol/L.
[g] For assay details see Ref. 14.

2.2 μmol/L.[14] However, when the potential for a hERG liability was further investigated, it was found that **2** exhibited a 74% inhibition at 3 μM, when measured in the hERG-mediated K^+ current in a voltage clamp assay.[14] Continued exploration was deemed appropriate in order to optimize the in vitro and in vivo activity, while reducing a potential hERG liability.

Some of the principles for reducing a hERG liability are reasonably well understood, such as introducing rigidity into flexible, relatively linear molecules.[16] Reducing the lipophilicity, as measured by Log *D*, can be associated with a lowering of hERG interaction and a potential reduced cardiovascular risk, but the trends are not strong, particularly with basic compounds.[17] Given these notions,



Scheme 1. The syntheses of thiazolo[4,5-*b*]pyridine, thiazolo[4,5-*c*]pyridine, thiazolo[5,4-*c*]pyridine, and thiazolo[5,4-*b*]pyridine congeners of 1-carbon linked analogs **1**, **2** and **3** via alkylation and reductive amination.

Table 2
Compounds prepared with the chemistry of Scheme 1

Entry	Starting compd.	Product	Yield (%)	W	X	Y	Z	R
1	**5a**	7a	53	N	CH	CH	CH	$CONH_2$
2	**4a**	7b	15	CH	CH	CH	N	$CONH_2$
3	**4b**	7c	44	N	CH	CH	CH	H
4	**4c**	7d	20	CH	CH	N	CH	H
5	**4d**	7e	36	CH	N	CH	CH	H
6	**8a**	7f	53	N	CH	CH	C–CH_3	H
7	**8b**	7g	41	N	CH	C–Cl	CH	H
8	**8c**	7h	62	N	CH	C–F	CH	H

Table 3
In vitro and in vivo IC_{50} Data for Thiazolo-Pyridines **7a–h**

Compd.	LTA_4H IC_{50} (nM)[d]	MWB[a] LTA_4H IC_{50} (nM)[d]	% Inh[b] LTB_4/MPO	hERG DB[c] IC_{50} (μM)
7a	6 ± 0.6	37 ± 48	85/89	8.9
7b	733 ± 161	2043 ± 702	ND	ND
7c	3 ± 0.6	14 ± 16	67/48	>10
7d	614 ± 135	723 ± 327	ND	ND
7e	1800*	ND	ND	ND
7f	33 ± 8	82 ± 31	12/42	8.1
7g	40 ± 10	245 ± 204	ND	>10
7h	29 ± 12	38 ± 16	15/53	>10

[a–d] See Table 1 for details. (*) Single determination; ND = not determined.

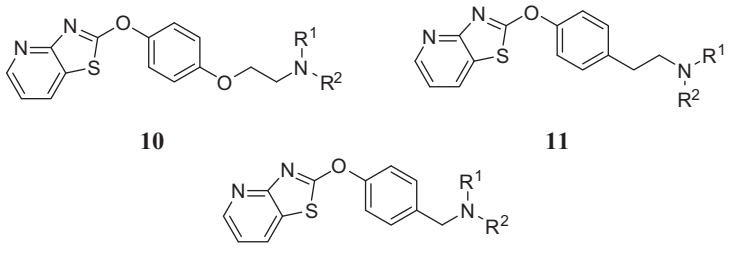
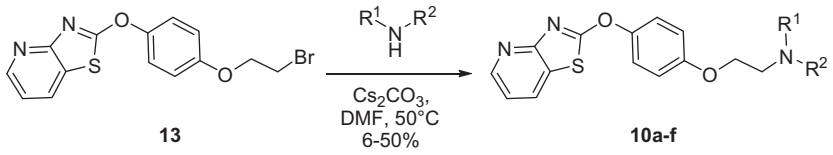


Figure 3. Thiazolo[4,5-*b*]pyridine containing targets—impact of polarity/flexibility on biological activity/hERG.

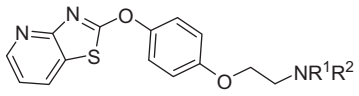
follow-up efforts were initiated by examining the addition of some polarity to the relatively lipophilic benzthiazole left hand portion of molecules such as **1**, **2**, or **3**.

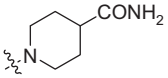
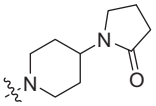
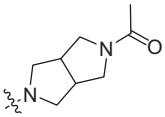
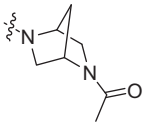
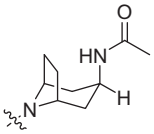
The initial focus was on the simple paradigm of substitution of a nitrogen into the aryl ring of the benzthiazole of **1**, **2**, and **3**. Scheme 1 and Table 2 illustrate two construction methods.



Scheme 2. The synthesis of 3-atom linker containing thiazolo[4,5-*b*]pyridines **10**.

Table 4
In vitro and in vivo IC_{50} data for 3-atom linker thiazolo-pyridines **10a–f**



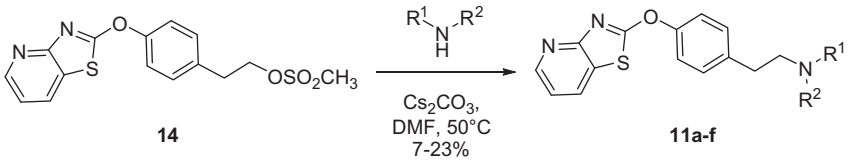
Compd.	NR^1R^2	Yield (%)	LTA_4H IC_{50} (nM)[d]	MWB[a] LTA_4H IC_{50} (nM)[d]	% Inh[b] LTB_4 /MPO	hERG DB[c] IC_{50} (μM)
10a		31	8 ± 3	18 ± 2	65/62	>10
10b		50	16 ± 12	30 ± 4	80/71	>10
10c		47	6 ± 3	20 ± 6	89/76	>10
10d		6	7 ± 3	30 ± 20	81/86	>10
10e		26	7 ± 5	18 ± 10	84/72	>10
10f		29	4 ± 2	24 ± 10	85/74	>10

[a–d] See Table 1 for details.

The first method utilizes either the alkylation of thiazolo-pyridine benzylic halides **4a–d**[18] or the reductive amination of the related benzaldehyde **5a**,[18] whereas the second method outlines an alternative synthetic sequence in which a more complex right hand half **9**[15,18] is coupled with 2-chloro-thiazolopyridines **8a–c**[18] to provide the target thiazolo-pyridines **7a–h**. Preliminary biological examination of **7a–h** was then conducted to determine if the pyridyl nitrogen would be tolerated, if there was a positional preference, and if the alteration in *c*Log*D* would impact hERG. The data for these compounds is presented in Table 3.

The data presented in Table 3 indicate that the thiazolo[5,4-*b*]pyridine nucleus of **7b** and the thiazolo[4,5-*c*]pyridine nucleus of **7e** are detrimental to LTA_4H inhibitory activity. A direct comparison of the positional isomers **7c**, **7d**, and **7e** identifies the thiazolo[4,5-*b*]pyridine of **7c** as the preferred isomer. This substitution (**7a**, **7c**) is associated with both potent LTA_4H inhibitory activity and good inhibition of LTB_4 production in stimulated mouse whole blood, as well as good activity in the murine arachidonic acid-induced ear inflammation model as measured by the inhibition of LTB_4 production and the inhibition of MPO. The addition of a substituent, such as the methyl of **7f**, or the halogens of **7g** or **7h** offers no obvious benefit. The lack of hERG binding associated with **7c** (IC_{50} > 10 μM) is noteworthy as **7c** does not possess the polar carboxylic acid of **1** or the hydroxyacetamide of **2**. As a starting point, compound **7c** exhibits a moderate *c*Log*D* value of 2.80 considering the lack of polar or ionizable groups present in **1** and **2** (*c*Log*D* values of 1.43 and 2.58 respectively).[19] These data, when taken in concert with the in vitro and in vivo data of Table 3, clearly support the choice of the thiazolo[4,5-*b*]pyridine nucleus of **7c** for inclusion in a more highly developed series of molecules.

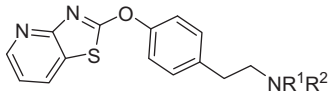
As this study proceeded, the importance of in vitro and in vivo assessments of biological activity (Tables 1 and 3) were considered, while the impact of the changes upon the potential hERG liability was examined. In order to ascertain the potential impact of a decrease in molecular flexibility, in addition to the polarity alterations made in Table 3, the construction of molecules with 3-, 2-, and 1-atom tethers (Fig. 3, **10–12**) between the central aryl

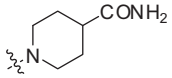
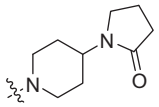
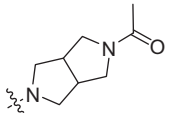
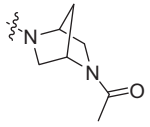
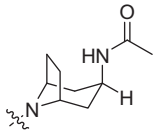


14 11a-f

Scheme 3. The synthesis of 2-atom linker containing thiazolo[4,5-*b*]pyridines **11**.

Table 5
In vitro and in vivo IC_{50} data for 2-atom linker thiazolo-pyridines **11a–f**



Compd.	NR^1R^2	Yield (%)	LTA_4H IC_{50} (nM)[d]	MWB[a] LTA_4H IC_{50} (nM)[d]	% Inh[b] LTB_4 /MPO	hERG DB[c] IC_{50} (μM)
11a		21	3 ± 1	24 ± 22	70/36	>10
11b		23	11 ± 6	50 ± 9	76/60	>10
11c		22	14 ± 3	65 ± 44	86/75	>10
11d		7	6 ± 5	22 ± 19	86/79	>10
11e		8	14 ± 3	30 ± 12	90/68	>10
11f		8	0.3 ± 0.2	43 ± 29	85/78	8.3

[a–d] See Table 1 for details.

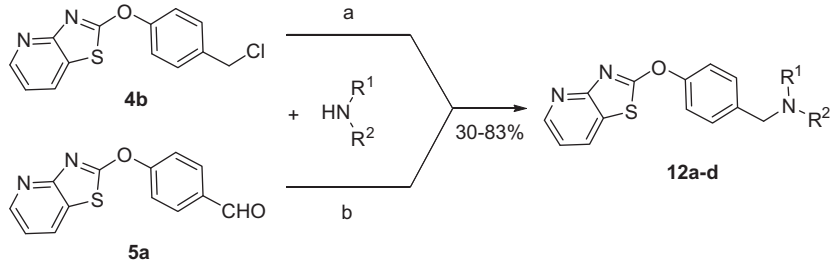
ring and the polar right hand functionality was desired. Flexibility will decrease as the tether length decreases and additional rigidity can be introduced by changing the amines of **10**, **11**, and **12** (Fig. 3) from simple cyclic amines to fused and bridged bicyclo[3.3.0], bicyclo[2.2.1] and bicyclo[2.2.2] diamines.

The syntheses of a selection of 3-atom linker analogs **10**, possessing the thiazolo[4,5-*b*]pyridine left hand ring system are shown in Scheme 2. Bromide **13**[18b] was treated with a variety of amines (Cs_2CO_3, DMF, 50 °C) ranging from piperidine to 3-acetamido-tropane[18] to give amines **10a–f** in modest yields (Table 4).

The target 2-atom tethered analogs were assembled in a similar fashion, as shown in Scheme 3. The mesylate **14**[18b] was treated with the amines utilized in Scheme 2 (Cs_2CO_3, DMF) to give amines **11a–f** in poor yields for the bicyclic amines (7–8%) to modest yields for the mono-cyclic amines (21–23%; Table 5). In the case of the bicyclic amines (**11d–f**, Table 5) elimination to the corresponding styrene was found to be a major competing side reaction.

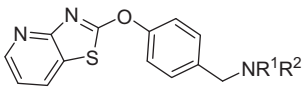
The desired 1-atom tethered analogs **12** were constructed utilizing only the bicyclic amines of Schemes 2 and 3, as the piperidinyl and piperidinyl-4-carboxamide variants had been described earlier (Scheme 1; compounds **7c** and **7a** respectively). The syntheses of these molecules, via alkylative and reductive amination protocols, are shown in Scheme 4. As expected, the utilization of the reactive benzylic halide **4b**[18] as well as the reactive benzaldehyde **5a**[18] in this sequence afforded modest to excellent yields (30–83%) of compounds **12a–d** (Table 6), in contrast to the generally lower yields reported in Schemes 2 and 3.

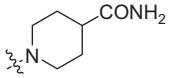
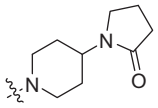
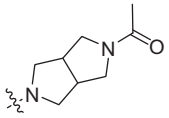
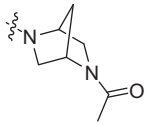
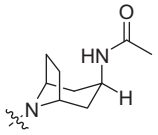
A review of the data associated with the 3-atom linker thiazolo-pyridines **10** (Table 4) shows that **10a–f** exhibit uniformly excellent enzymatic inhibitory activity (IC_{50} of 4–16 nM) as well as stimulated mouse whole blood activity (IC_{50} of 18–30 nM). The first differentiation in this series was observed when **10a–f** were examined in vivo in the murine arachidonic acid-induced ear inflammation model. In this assessment, the simple piperidine **10a** performed poorly, inhibiting the production of LTB_4 and MPO activity to the extent of 68% and 62% respectively. The remaining compounds of Table 4 inhibit the production of LTB_4 from 80% to 89%, and inhibit MPO from 71% to 86%. This series of molecules is the most flexible of those prepared, as a consequence of their 3-atom tether. All of the compounds of Table 4 are inactive (IC_{50} > 10 μM) in the hERG binding assay, however, differentiation of them begins in the hERG patch clamp assay.[20] Compounds **10b**,



Scheme 4. The synthesis of 1-atom linker containing thiazolo[4,5-*b*]pyridines **12**. Ragents and conditions: (a) K_2CO_3, CH_3CN, 50 °C; (b) $NaBH(OAc)_3$, $ClCH_2CH_2Cl$, rt.

Table 6
In vitro and in vivo IC_{50} data for 1-atom linker thiazolo-pyridines **7c**, **7a** and **12a–d**



Compd.	NR^1R^2	Yield (%)	LTA_4H IC_{50} (nM)[d]	MWB[a] LTA_4H IC_{50} (nM)[d]	% Inh[b] LTB_4 /MPO	hERG DB[c] IC_{50} (μM)
7c		44	3 ± 0.6	14 ± 16	67/48	>10
7a		53	6 ± 0.6	37 ± 48	85/89	8.9
12a		49	6 ± 2	27 ± 19	81/88	>10
12b		30	3 ± 0.6	10 ± 1	57/95	>10
12c		53	5 ± 2	7 ± 5	92/88	>10
12d		83	1 ± 1	20 ± 17	81/70	>10

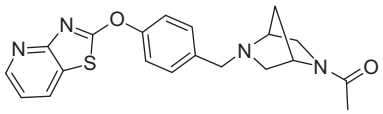
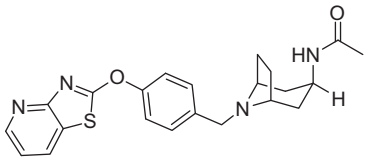
[a–d] See Table 1 for details.

10e, and **10f** have IC_{50} > 10 μM in this assay, while compounds **10c** (IC_{50} = 2.5 μM) and **10d** (IC_{50} = 3 μM) demonstrate greater hERG liability.

The 2-atom tether analogs (Table 5) **11a–f** are associated with excellent LTA_4H inhibitory activity, with IC_{50} values of 0.3–14 nM. The mouse whole blood LTA_4H assessment provides a broader range of IC_{50} values (22–65 nM) in this series than in the 3-atom tether **10a–f** (Table 4). As was the case for the **10a–f** series, further differentiation was seen in this 2-atom tether series when **11a–f** were studied in vivo in the murine arachidonic acid-induced ear inflammation model. Compounds **11a** and **11b** were only moderately active, with the in vivo assessment showing LTB_4 and MPO inhibition of <80% for each measurement. Compounds **11c–f** exhibit a better balance of LTB_4 and MPO inhibitory activity. Compounds **11a–e** exhibit IC_{50} > 10 μM for hERG binding, whereas **11f** shows a small hERG DB signal with an IC_{50} of 8.3 μM. Compounds **11c–f**, were examined in a hERG patch clamp assay and the results were most interesting.[20] The 4-pyrrolidinone-piperidine **11c** (IC_{50} = 2.8 μM) and the tropane **11f** (IC_{50} = 4.3 μM) were surprisingly active in this assay.

The final series of this study, the 1-atom tethered amines **7c**, **7a**, and **12a–d** were evaluated (Table 6). With the least backbone flexibility of all of the molecules described herein, these compounds provide the best opportunity to collect all of the desired attributes in a single entity. In the in vitro LTA_4H enzymatic assessment, all of the compounds of Table 6 exhibited excellent potency (1–6 nM). A greater range of IC_{50} values (7–37 nM) was observed in the mouse whole blood LTA_4H assessment, as was the case with **11a–f**. In the in vivo assessment of LTA_4H target engagement, the activity of **7c** was disappointing. In contrast, the piperidinyl-4-acetamide **7a**,

Table 7
Rat pharmacokinetic data for 1-atom linker thiazolo-pyridines **12c** and **12d**

Compd.	Structure	IV (2 mg/kg)			PO (10 mg/kg)	
		$t_{1/2}$ (h)	Cl (L/h/kg)	V_{ss} (L/kg)	%F	C_{max} (μM)
12c		3.3	0.42	1.4	125	3.3
12d		2	1.2	3.5	65	1.2

4-pyrrolidinone **12a** and the 2,5-diazabicyclo[2.2.1]heptane acetamide **12c** are noteworthy for their good LTB_4/MPO inhibitory activities. Compound **7a** inhibited dofetilide binding to the hERG channel with an IC_{50} = 8.9 μM, while compounds **12a–d** could not be readily differentiated in this assay, presenting IC_{50} values of >10 μM. An examination of these five compounds in a hERG patch clamp assay was also unrevealing as each is associated with an IC_{50} > 10 μM.[20] In an attempt to discern the impact on enzymatic inhibitory activity of alternative asymmetry (2,5-diazabicyclo[2.2.1]heptane acetamide) and axial vs equatorial preference (tropane acetamide), these amines (not exemplified) were utilized in place of those shown in Table 6 (**12c** and **12d**) to provide compounds which were identical in their in vitro and in vivo activity to those exemplified (**12c** and **12d**).

Compounds **7a** and **12a–d** (Table 6) all present a desirable collection of attributes. As an example, compounds **12c** and **12d** were further evaluated in rat PK (Table 7). These compounds exhibit low to moderate clearance and a moderate to high steady state volume of distribution. Both **12c** and **12d** display high oral bioavailability and moderate intravenous half-lives.

In order to discern the impact of backbone flexibility, compounds **10c** (*c*Log*D* 3.28), **11c** (*c*Log*D* 2.86) and **12a** (*c*Log*D* 3.21) were compared. As the tether length is decreased, there is no smooth progression in *c*Log*D* due to the electronic impact of structural variation. However, the hERG patch clamp assay for these compounds shows the effect of decreasing backbone flexibility with the 3-atom tether **10c** IC_{50} of 2.5 μM, while the 2-atom tether **11c** has an IC_{50} of 2.8 μM, and the least flexible 1-atom tether **12a** is associated with an IC_{50} > 10 μM. Within the 1-atom tether series (Table 6), the *c*Log*D* values range from 1.21 to 3.21, varying as additional rigidity is introduced in the form of a bicyclo-[3.3.0] moiety (**12b**, *c*Log*D* 2.82), a bicyclo-[2.2.1] subunit (**12c**, *c*Log*D* 2.89), and a bicyclo-[3.2.1] fragment (**12d**, *c*Log*D* 1.21). Five of the six compounds of Table 6 (**7a**, **12a–d**) were examined in a hERG patch clamp assay and all compounds had IC_{50} > 10 μM. Clearly, restricting backbone flexibility by shortening the tether and introducing amines with additional polarity and/or rigid cage structures, while keeping within a relatively narrow range of *c*Log*D*, has a positive effect on the hERG patch clamp outcome.

The data of Table 6 suggest that the design plans to continue to optimize the desirable LTA_4H activity while minimizing potential liabilities has been realized. Reducing flexibility appears to have greatly reduced the potential for a hERG liability, as measured in a patch clamp assay. This stands in contrast to the more standard hERG binding assessment, which for this series did not allow for sufficient prioritization. The 1-atom linker molecules may offer the best combination of properties to warrant further investigation.

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References and notes

1. Thunnissen, M. M.; Nordlund, P.; Haeggstrom, J. Z. *Nat. Struct. Biol.* **2001**, *8*, 131.
2. Brocklehurst, W. E. *Prog. Allergy* **1962**, *6*, 539.
3. (a) Del Prete, A.; Shao, W.-H.; Mitola, A.; Santoro, G.; Sozzani, S.; Haribabu, B. *Blood* **2007**, *109*, 626; (b) Goetzl, E. J.; Goldman, D. W.; Naccache, P. H.; Sha'afi, R. I.; Pickett, W. C. *Adv. Prostaglandin, Thromboxane, Leukotriene Res.* **1982**, *9*, 273; (c) Goodarzi, K.; Goodarzi, M.; Tager, A. M.; Luster, A. D.; von Andrian, U. H. *Nat. Immunol.* **2003**, *4*, 965; (d) Haeggstrom, J. Z.; Kull, F.; Rudberg, P. C.; Tholander, F.; Thunnissen, M. M. *Prostaglandins Other Lipid Mediat.* **2002**, *68–69*, 495; (e) Heller, E. A.; Liu, E.; Tager, A. M.; Sinha, S.; Roberts, J. D.; Koehn, S. L.; Libby, P.; Aikawa, E. R.; Chen, J. Q.; Huang, P.; Freeman, M. W.; Moore, K. J.; Luster, A. D.; Gerszten, R. E. *Circulation* **2005**, *112*, 578; (f) Iizuka, Y.; Yokomizo, T.; Terawaki, K.; Komine, M.; Tamaki, K.; Shimizu, T. *J. Biol. Chem.* **2005**, *280*, 24816; (g) Lundeen, K. A.; Sun, B.; Karlsson, L.; Fourie, A. M. *J. Immunol* **2006**, *177*, 3439; (h) Munoz, N. M.; Douglas, I.; Mayer, D.; Herrnreiter, A.; Zhu, X.; Leff, A. R. *Am. J. Respir. Crit. Care Med.* **1997**, *155*, 1398; (i) Ott, V. L.; Cambier, J. C.; Kappler, J.; Marrack, J. P.; Swanson, B. J. *Nat. Immunol.* **2003**, *4*, 974.
4. (a) Jupp, J.; Hillier, K.; Elliott, D. H.; Fine, D. R.; Bateman, A. C.; Johnson, P. A.; Cazaly, A. M.; Penrose, J. F.; Sampson, A. P. *Inflamm. Bowel Dis.* **2007**, *13*, 537; (b) Rask-Madsen, J. *Drugs Today* **1998**, *34*, 45; (c) Sharon, P.; Stenson, W. F. *Gastroenterology* **1984**, *86*, 453.
5. (a) Marian, E.; Baraldo, S.; Visentin, A.; Papi, A.; Saetta, M.; Fabbri, L. M.; Maestrelli, P. *Chest* **2006**, *129*, 1523; (b) Barnes, P. J. *Nat. Rev. Drug Disc.* **2002**, *1*, 437; (c) Gompertz, S.; Stockley, R. A. *Chest* **2002**, *122*, 289.
6. (a) Chen, X.; Wang, S.; Wu, N.; Yang, C. S. *Curr. Cancer Drug Targets* **2004**, *4*, 267; (b) Gao, P.; Guan, L.; Zheng, J. *Biochem. Biophys. Res. Commun.* **2010**, *402*, 308; (c) Ihara, A.; Wada, K.; Yoneda, M.; Fujisawa, N.; Takahashi, H.; Nakajima, A. J. *Pharmacol. Sci.* **2007**, *103*, 24; (d) Jeong, C. H.; Bode, A. M.; Pugliese, A.; Cho, Y. Y.; H. Kim, H. G.; Shim, J. H.; Jeon, Y. J.; Li, H.; Jiang, H.; Dong, Z. *Cancer Res.* **2009**, *69*, 5584; (e) Larre, S.; Tran, N.; Fan, C.; Hamadeh, H.; Champigneulles, J.; Azzouzi, R.; Cussenot, O.; Mangin, P.; Olivier, J. L. *Prostaglandins Other Lipid Mediat.* **2008**, *87*, 14; (f) Oi, N.; Jeong, C. H.; Nadas, J.; Cho, Y. Y.; Pugliese, A.; Bode, A. M.; Dong, Z. *Cancer Res.* **2010**, *70*, 9755; (g) Tong, W. G.; Ding, X. Z.; Talamonti, M. S.; Bell, R. H.; Adrian, T. E. *Biochem. Biophys. Res. Commun.* **2005**, *335*, 949; (h) Tsuji, F. H. M.; Enomoto, H.; Aono, H. *Curr. Top. Pharmacol.* **2005**, *9*, 71.
7. (a) Griffiths, R. J.; Pettipher, E. R.; Koch, K.; Farrell, C. A.; Breslow, R.; Conklyn, M. J.; Smith, M. A.; Hackman, B. C.; Wimberly, D. J.; Milici, A. J. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 517; (b) Shao, W. H.; Del Prete, A.; Bock, C. B.; Haribabu, B. *J. Immunol.* **2006**, *176*, 6254; (c) Tsuji, F.; Oki, K.; Fujisawa, K.; Okahara, A.; Horiuchi, M.; Mita, S. *Life Sci.* **1999**, *64*, PL51; (d) Chen, M.; Lam, B. K.; Kanaoka, Y.; Nigrovic, P. A.; Audoly, L. P.; Austen, K. F.; Lee, D. M. *J. Exp. Med.* **2006**, *203*, 837.
8. (a) Lemiere, C.; Pelissier, S.; Tremblay, C.; Chaboillez, S.; Thivierge, M.; Stankova, J.; Rola-Pleszczynski, M. *Clin. Exp. Allergy* **2004**, *34*, 1684; (b) Luster, A. D.; Tager, A. M. *Nat. Rev. Immunol.* **2004**, *4*, 711; (c) Montuschi, P.; Sala, A.; Dahlen, S. E.; Folco, G. *Drug Discov. Today* **2007**, *12*, 404; (d) Rubin, P.; Mollison, K. W. *Prostaglandins Other Lipid Mediat.* **2007**, *83*, 188; (e) Terawaki, K.; Yokomizo, T.; Nagase, T.; Toda, A.; Taniguchi, M.; Hashizume, K.; Yagi, T.; Shimizu, T. *J. Immunol.* **2005**, *175*, 4217; (f) Duroudier, N. P.; Tulah, A. S.; Sayers, I. *Allergy* **2009**, *64*, 823; (g) Fourie, A. M. *Curr. Opin. Investig. Drugs* **2009**, *10*, 1173; (h) Montuschi, P. *Pharmaceuticals* **2010**, *3*, 1792; (i) Montuschi, P.; Peters-Golden, M. L. *Clin. Exp. Allergy* **2010**, *40*, 1732; (j) Rao, N. L.; Riley, J. P.;

Banie, H.; Xue, X.; Sun, B.; Crawford, S.; Lundeen, K. A.; Yu, F.; Karlsson, L.; Fourie, A. M.; Dunford, P. J. *Am. J. Respir. Crit. Care Med.* **2010**, *181*, 899.
9. (a) Back, M.; Bu, D. X.; Branstrom, R.; Sheikine, Y.; Yan, Z. Q.; Hansson, G. K. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 17501; (b) Back, M.; Hansson, G. K. *Ann. Med.* **2006**, *38*, 493; (c) Friedrich, E. B.; Tager, A. M.; Liu, E.; Pettersson, A.; Owman, C.; Munn, L.; Luster, A. D.; Gerszten, R. E. *Arterioscler. Thromb. Vasc. Biol.* **2003**, *23*, 1761; (d) Funk, C. D. *Nat. Rev. Drug Disc.* **2005**, *4*, 664; (e) Helgadottir, A.; Manolescu, A.; Thorleifsson, G.; Gretarsdottir, S.; Jonsdottir, H.; Thorsteinsdottir, U.; Samani, N. J.; Gudmundsson, G.; Grant, S. F.; Thorgeirsson, G.; Sveinbjornsdottir, S.; Valdimarsson, E. M.; Matthiasson, S. E.; Johannsson, H.; Gudmundsdottir, O.; Gurney, M. E.; Sainz, J.; Thorhallsdottir, M.; Andresdottir, M.; Frigge, M. L.; Topol, E. J.; Kong, A.; Gudnason, V.; Hakonarson, H.; Gulcher, J. R.; Stefansson, K. *Nat. Genet.* **2004**, *36*, 233; (f) Jala, V. R.; Haribabu, B. *Trends Immunol.* **2004**, *25*, 315; (g) Qiu, H.; Gabrielsen, A.; Agardh, H. E.; Wan, M.; Wetterholm, A.; Wong, C.-H.; Hedin, U.; Swedenborg, J.; Hansson, G. K.; Samuelsson, B.; Paulsson-Berne, G.; Haeggstrom, J. Z. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 8161; (h) Riccioni, G.; Back, M.; Capra, V. *Curr. Drug Targets* **2010**, *11*, 882; (i) Sanchez-Galan, E.; Gomez-Hernandez, A.; Vidal, C.; Martin-Ventura, J. L.; Blanco-Colio, L. M.; Munoz-Garcia, B.; Ortega, L.; Egido, J.; Tunon, J. *Cardiovasc. Res.* **2009**, *81*, 216; (j) Subbarao, K.; Jala, V. R.; Mathis, S.; Suttles, J.; Zacharias, W.; Ahamed, J.; Ali, H.; Tseng, M. T.; Haribabu, B. *Arterioscler. Thromb. Vasc. Biol.* **2004**, *24*, 369.
10. Snelgrove, R. J.; Jackson, P. L.; Hardison, M. T.; Noerager, B. D.; Kinloch, A.; Gaggar, A.; Shastry, S.; Rowe, S. M.; Shim, Y. M.; Hussell, T.; Blalock, J. E. *Science* **2010**, *330*, 90.
11. Rao, N. L.; Dunford, P. J.; Xue, X.; Jiang, X.; Lundeen, K. A.; Coles, F.; Riley, J. P.; Williams, K. N.; Grice, C. A.; Edwards, J. P.; Karlsson, L.; Fourie, A. M. *J. Pharmacol. Exp. Ther.* **2007**, *321*, 1154.
12. Serhan, C. N.; Hamberg, M.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 5335.
13. Mathis, S. P.; Jala, V. R.; Lee, D. M.; Haribabu, B. *J. Immunol.* **2010**, *185*, 3049.
14. Grice, C. A.; Tays, K. L.; Savall, B. M.; Wei, J.; Butler, C. R.; Axe, F. U.; Bembenek, S. D.; Fourie, A. M.; Dunford, P. J.; Lundeen, K.; Coles, F.; Xue, X.; Riley, J. P.; Williams, K. N.; Karlsson, L.; Edwards, J. P. *J. Med. Chem.* **2008**, *51*, 4150.
15. Miko, T.; Ligneau, X.; Pertz, H. H.; Arrang, J.-M.; Ganellin, C. R.; Schwartz, J.-C.; Schunack, W.; Stark, H. *Bioorg. Med. Chem.* **2004**, *12*, 2727.
16. (a) Cavalli, A.; Poluzzi, E.; De Ponti, F.; Recanatini, M. *J. Med. Chem.* **2002**, *45*, 3844; (b) Anghelescu, A. V.; DeLisle, R. K.; Lowrie, J. F.; Klon, A. E.; Xie, X.; Diller, D. J. *J. Chem. Inf. Model.* **2008**, *48*, 1041; (c) Zachariae, U.; Giordanetto, F.; Leach, A. G. *J. Med. Chem.* **2009**, *52*, 4266.
17. Waring, M. J.; Johnstone, C. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1759.
18. (a) Bacani, G.; Chrovian, C. C.; Eccles, W.; Fourie, A. M.; Gomez, L.; Grice, C. A.; Kearney, A. M.; Landry-Bayle, A. M.; Lee-Dutra, A.; Santillan, A.; Tanis, V. M.; Wiener, J. J. M. WO 2010132599A1.; (b) Bacani, G. M.; Broggini, D.; Cheung, E. Y.; Chrovian, C. C.; Deng, X.; Fourie, A. M.; Gomez, L.; Grice, C. A.; Kearney, A. M.; Landry-Bayle, A. M.; Lee-Dutra, A.; Liang, J. T.; Lochner, S.; Mani, N. S.; Santillan, A.; Sappey, K. C.; Sepassi, K.; Tanis, V. M.; Wickboldt, A. T.; Wiener, J. J. M.; Zinser, H. WO 2009126806A2.
19. Calculated with ACD Labs Software v12.0.
20. Determined by AVIVA using PatchXpress™.