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# Discovery of Highly Potent Dual $CysLT_1$ and $CysLT_2$ Antagonist

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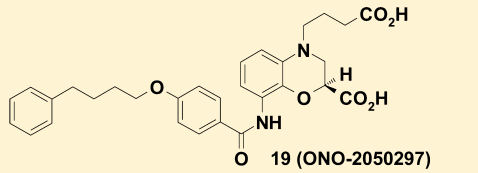
Supporting Information

**ABSTRACT:** The benzoxazine derivative, (2*S*)-4-(3-carboxypropyl)-8-{[4-(4-phenylbutoxy)benzoyl]amino}-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylic acid (**19**, ONO-2050297), was identified as the first potent dual $CysLT_1$ and $CysLT_2$ antagonist with $IC_{50}$ values of 0.017 $\mu$M ($CysLT_1$) and 0.00087 $\mu$M ($CysLT_2$), respectively.




**KEYWORDS:** *Cysteinyl leukotrienes, $CysLT_1$, $CysLT_2$, dual antagonist, asthma*

Cysteinyl leukotrienes (CysLTs), $LTC_4$, $LTD_4$, and $LTE_4$ are lipid mediators derived from arachidonic acid.[1−4] Pharmacological studies revealed that at least two classes of receptors exist, namely, $CysLT_1$ and $CysLT_2$ receptors.[5,6] $CysLT_1$ selective antagonists have been launched as clinically useful drugs for treating bronchial asthma and allergic rhinitis (Figure 1). However, it is known that these $CysLT_1$ antagonists

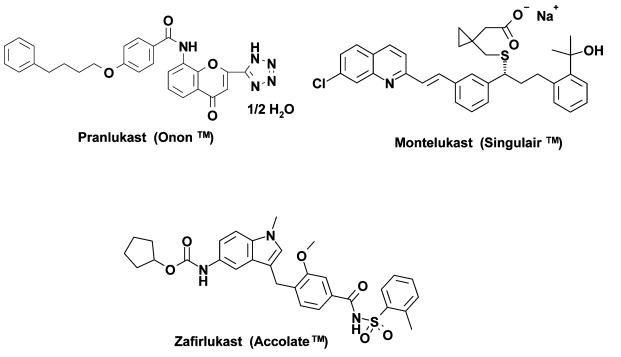



**Figure 1.** $CysLT_1$ selective antagonists.

are effective for mild or moderate bronchial asthma relative to severe ones. It is also known that in some nonresponders, $CysLT_1$ antagonists do not have sufficient effects in mild or moderate bronchial asthma. Thus, more effective drugs are needed for treating bronchial asthma.[7]

It is reported that $CysLT_2$ is also expressed on airway smooth muscle cells,[6] inflammatory cells,[8−11] and vascular endothelial cells[12] similar to $CysLT_1$. Moreover, it is also reported that $LTE_4$, which is a metabolite of $LTD_4$, is elevated in urine for aspirin-sensitive asthmatics and severe asthma.[13−18] That is why $CysLT_2$, which shows low affinity against $LTD_4$, may participate in some kinds of asthmatic patients. Therefore, a dual $CysLT_1$ and $CysLT_2$ antagonist would be useful for nonresponders and severe asthma.

HAMI3379 and $BayCysLT_2$ (Figure 2) were reported as potent $CysLT_2$ selective antagonists, and with these compounds, the cardiac effects of CysLTs were shown to be predominantly mediated by the $CysLT_2$ receptor.[19,20] BAY-u9773 was reported as a dual $CysLT_1$ and $CysLT_2$ antagonist and a partial agonist of $CysLT_2$ (Figure 3).[21,22] Ohishi and Nishide reported dual $CysLT_1$ and $CysLT_2$ antagonists.

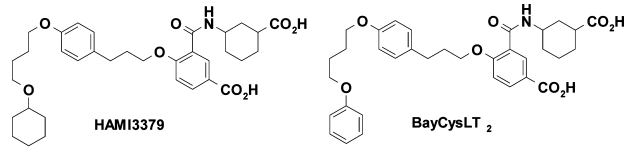



**Figure 2.** $CysLT_2$ selective antagonists.

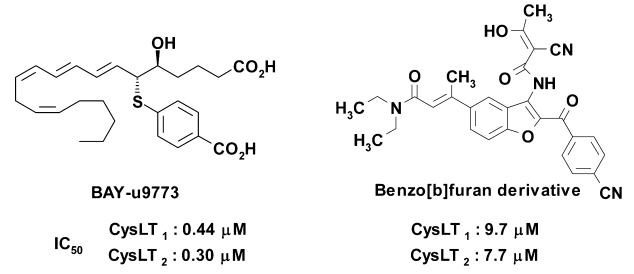



**Figure 3.** Dual $CysLT_1$ and $CysLT_2$ antagonists.

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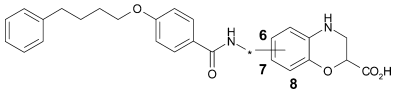
However, their reported dual $CysLT_1$ and $CysLT_2$ antagonists showed weak antagonist activities for both receptors (Figure 3).[23−25] So far, a potent dual $CysLT_1$ and $CysLT_2$ antagonist has not yet been identified.

A high-throughput screening (HTS) campaign of our in-house compound library yielded monocarboxylic acid derivative **1**, which showed micromolar $CysLT_2$ antagonist activity and potent $CysLT_1$ antagonist activity (Table 1). As shown in Table 1, the effect of the amide chain positions was investigated and revealed that substitution at position 8 in **1** was most favored, with both **2** (position 7) and **3** (position 6) showing less potent antagonist activities for both $CysLT_1$ and $CysLT_2$. Therefore, we varied the *N*-substituent of hit compound **1** to increase $CysLT_2$ antagonist activity.

**Table 1. Effect of the Amide Chain Position on Activity Profile**

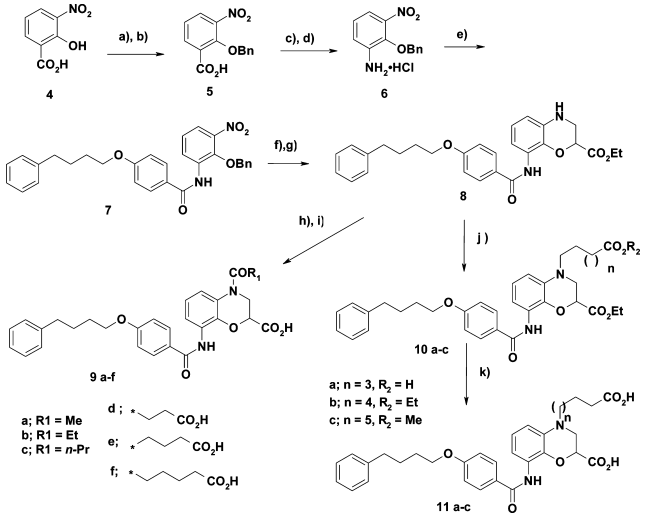


| | | $IC_{50}$ ($\mu$M)[a] | |
|---|---|---|---|
| cmpd | position | $CysLT_1$ | $CysLT_2$ |
| **1** | 8 | 0.054 | 4.6 |
| **2** | 7 | 4.6 | 36% @10 $\mu$M |
| **3** | 6 | 0.84 | 25% @10 $\mu$M |

[a]Assay protocols are provided in the Supporting Information. $IC_{50}$ values represent the mean of at least two experiments.

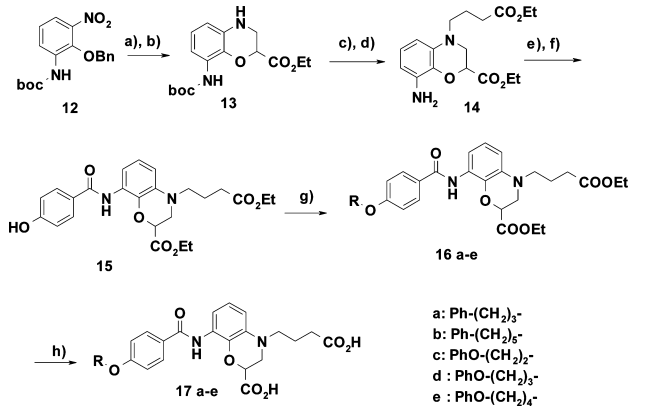
The synthesis of **9a−9f** and **11a−11c** is described in Scheme 1. Commercially available 3-nitrosalicylic acid **4** was reacted with benzyl bromide. Subsequent deprotection of the benzoyl group afforded carboxylic acid **5**, which upon Curtius rearrangement and deprotection of the Boc group afforded **6**. Acylation of **6** afforded **7**. Reduction and deprotection of **7** followed by cyclization with ethyl 2,3-bromopropanoate afforded **8**. Acylation of **8** followed by hydrolysis provided **9a−9f**. Reductive amination of ester **8** provided **10a−10c**, which were then converted to carboxylic acids **11a−11c** by alkaline hydrolysis.

**Scheme 1. Synthesis of 9a−9f and 11a−11c**[a]




[a]Reagents and conditions: (a) BnBr, $K_2CO_3$, KI, DMF, 60 °C; (b) NaOH aq, MeOH−THF, 50 °C, 59% (2 steps); (c) DPPA, $Et_3N$, dioxane, rt, then $^t$BuOH, 80 °C, 87%; (d) HCl aq, dioxane, 91% (2 steps); (e) 4-(4-phenylbutoxy)-benzoyl chloride, pyridine, $CH_2Cl_2$, rt, 86%; (f) $H_2$, Pd−C, MeOH-THF, rt; (g) ethyl 2,3-dibromo-propionate, $K_2CO_3$, acetone, 50 °C, 64% (2 steps); (h) AcCl, Et−COCl, *n*-PrCOCl, or $CO_2Et-CH_2-(CH_2)_n-COCl$ ($n$ = 1, 2, and 3), pyridine, rt; (i) NaOH aq, EtOH−THF, rt, 47−75% (2 steps); (j) $CO_2R_2-CH_2-(CH_2)_n-CHO$ ($n$ = 1, 2, and 3; $R_2$ = H, Me, Et), $H_2$, Pd−C, EtOH; or $NaBH(OAc)_3$, AcOH, THF, rt, 68−81%; (k) NaOHaq, EtOH−THF, rt, 64−88%.

**Scheme 2. Synthesis of 17a−17e**[a]




[a]Reagents and conditions: (a) $H_2$, Pd−C, EtOH, rt; (b) ethyl 2,3-bromo-propionate, $K_2CO_3$, DMF, 50 °C, 34% (2 steps); (c) ethyl 4-oxobutanoate, $NaBH(OAc)_3$, AcOH, THF, rt, 85%; (d) TMSOTf, $Et_3N$, $CH_2Cl_2$, 0 °C, 100%; (e) 4-benzyloxybenzoyl chloride, pyridine, DMF; (f) $H_2$, Pd−C, EtOH−THF, rt, 66% (2 steps); (g) $R-(CH_2)_n-Br$ or $R-(CH_2)_n-OH$ ($n$ = 3, 4, and 5; R = Ph or OPh), ADDP, $PPh_3$, $CH_2Cl_2$ or $K_2CO_3$, DMF, rt, 81−95%; (k) NaOH aq, EtOH−THF 64−97%.

The synthesis of **17a−17e** is described in Scheme 2. Reduction of **12** with Pd/C and subsequent cyclization with ethyl 2,3-bromopropanoate afforded **13**. Reductive amination of **13** followed by deprotection of the Boc group afforded **14**. Acylation of **14** with 4-benzyloxybenzoyl chloride and subsequent deprotection afforded common intermediate **15**. *O*-Alkylation of **15** with the corresponding bromide using $K_2CO_3$ as base or Mitsunobu reaction conditions with the corresponding alcohols afforded **16a−16e**, which were then converted to carboxylic acids **17a−17e** by hydrolysis.

The effect of *N*-substituents was investigated (Table 2). Monocarboxylic acid derivatives **9b** and **9c** demonstrated weak antagonist activities for $CysLT_1$ and $CysLT_2$, while **9a** demonstrated nearly equipotent antagonist activities for $CysLT_1$ and $CysLT_2$ relative to hit compound **1**. Since monocarboxylic acid derivatives showed weak $CysLT_2$ antagonist activity, substituents that interact with the $CysLT_2$ receptor might be necessary to improve $CysLT_2$ antagonist activity. We focused on the structural features of $LTD_4$ and $LTC_4$. As shown in Figure 4, $LTD_4$ and $LTC_4$, which show high affinities for $CysLT_2$, possess two or three carboxylic acid moieties. To increase $CysLT_2$ antagonist activity, at least two acidic groups might be needed.[26] Therefore, our investigations focused on structure−activity relationships (SARs) for dicarboxylic acid derivatives to increase $CysLT_2$ antagonist activity while retaining $CysLT_1$ antagonist activity. *N*-Acyl derivatives **9d**, **9e**, and **9f** demonstrated slightly improved antagonist activities for $CysLT_2$ relative to **1**. Among them, **9d**


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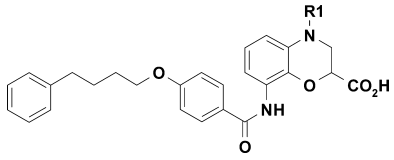
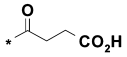
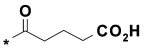
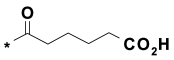
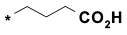
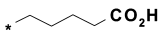
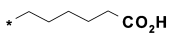
**Table 2. Activity Profile of *N*-Substituted Derivatives**



| cmpd | $R_1$ | $IC_{50}$ (μM)[a] | |
|---|---|---|---|
| | | $CysLT_1$ | $CysLT_2$ |
| **1** | H | 0.054 | 4.6 |
| **9a** |  | 0.013 | 3.6 |
| **9b** |  | 0.15 | 5.2 |
| **9c** |  | 0.30 | 3.7 |
| **9d** |  | 0.0014 | 0.89 |
| **9e** |  | < 0.0010 | 1.8 |
| **9f** |  | 0.012 | 0.89 |
| **11a** |  | 0.011 | 0.0025 |
| **11b** |  | 0.044 | 0.17 |
| **11c** |  | 0.13 | 0.29 |

[a]Assay protocols are provided in the Supporting Information. $IC_{50}$ values represent the mean of at least two experiments.

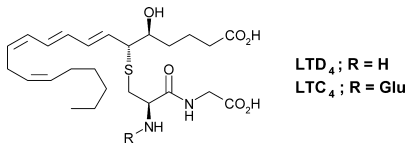


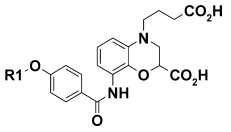

**Figure 4.** Endogenous ligands of $CysLT_1$ and $CysLT_2$.

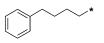
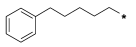
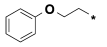
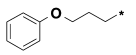
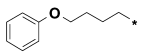
and **9e** demonstrated significantly more potent $CysLT_1$ antagonist activities than **1**. However, *N*-alkyl derivatives **11a**−**11c** demonstrated different SAR from the *N*-acyl derivatives. *N*-Alkyl derivatives **11a**, **11b**, and **11c** demonstrated significantly more potent $CysLT_2$ antagonist activities than **1**. Especially, *N*-alkyl derivative **11a** demonstrated 1840-fold more potent antagonist activity for $CysLT_2$ than hit compound **1**. Moreover, *N*-alkyl derivative **11a** demonstrated >350-fold more potent antagonist activity for $CysLT_2$ than *N*-acyl derivative **9d**, which possesses an amide linkage to the benzoxazine ring.

As shown in Table 3, the effect of side chain length between the terminal phenyl and internal phenyl rings of **11a** was investigated. Compound **11a** with a 4-phenylbutyl moiety demonstrated >10-fold more potent $CysLT_1$ antagonist activity than **17a** with a 3-phenylpropyl and **17b** with a 5-phenylpentyl moiety. With respect to $CysLT_2$ antagonist activity, **17a**, **17b**, **17d**, and **17e** demonstrated potent $CysLT_2$ antagonist activities, and only **17e** demonstrated potent dual $CysLT_1$ and $CysLT_2$ antagonist activity that approached the activity **11a**. As a result, the side chain of **11a** was determined to have the optimal length.

In general, it is hard to discover selective antagonists for the same family of receptors. However, it seems to be different in this series. So far, a number of potent $CysLT_1$ antagonists were

**Table 3. Activity Profile of *O*-Substituted Derivatives**



| cmpd | $R_1$ | $IC_{50}$(μM)[a] | |
|---|---|---|---|
| | | $CysLT_1$ | $CysLT_2$ |
| **17a** |  | 1.3 | 0.068 |
| **11a** |  | 0.011 | 0.0025 |
| **17b** |  | 0.12 | 0.00062 |
| **17c** |  | 3.0 | 1.5 |
| **17d** |  | 0.29 | 0.016 |
| **17e** |  | 0.032 | 0.017 |

[a]Assay protocols are provided in the Supporting Information. $IC_{50}$ values represent the mean of at least two experiments.

discovered; however, they did not show potent $CysLT_2$ antagonist activity. HAMI3379 with potent $CyLT_2$ antagonist activity did not show any $CysLT_1$ antagonist activity. According to the data of Tables 2 and 3, there are three important factors to achieve dual potent $CysLT_1$ and $CysLT_2$ antagonist activities, that is, two acidic moieties and the correct length of both the *N*-substituent and the *O*-substituent. With respect to $CysLT_1$ antagonist activity, different lengths of the *N*-substituent were tolerated somewhat (Table 2), while variation in the length of the *O*-substituent was not tolerated. In contrast, with respect to $CysLT_2$ antagonist activity, variation in the length of the *N*-substituent was not tolerated at all, although different lengths of the *O*-substituent were well tolerated. As a result, compounds with potent dual $CysLT_1$ and $CysLT_2$ antagonist activities possessed both a butyl carboxylic acid moiety as the *N*-substituent and a 4-phenylbutyl (or phenoxybutyl) moiety as the *O*-substituent.

Since racemic **11a** demonstrated highly potent dual antagonist activity for $CysLT_1$ and $CysLT_2$; the two enantiomers of **11a** were separated using a chiral column and evaluated (Table 4). The configuration of **19** and **18** was confirmed by X-ray crystal structure analysis of a precursor of **19**. The detailed data are summarized in the Supporting Information. Enantiomer **19** (*S*-form) demonstrated more potent $CysLT_1$ and $CysLT_2$ antagonist activities than enantiomer **18** (*R*-form) with $IC_{50}$ values of 0.017 and 0.00087 μM for $CysLT_1$ and $CysLT_2$, respectively.

The pharmacokinetic profile of racemic compound **11a** was evaluated. Unfortunately, **11a** demonstrated a poor PK profile with bioavailability of only 1.5% in rat (Table 5). Further optimization of compound **11a** to improve its PK profile will be reported in due course.

In summary, we have discovered **19** (**ONO-2050297**) as the first potent dual $CysLT_1$ and $CysLT_2$ antagonist. Our results indicate that it is essential to possess two acidic moieties for dual $CysLT_1$ and $CysLT_2$ antagonist activity and that the lengths of *O*- and *N*-substituents are also important factors.


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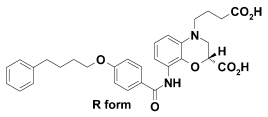
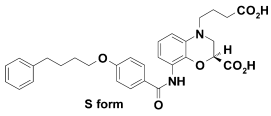
**Table 4. Activity Profile of Enantiomers of 11a**

| cmpd | Structure | $IC_{50}$ (μM)[a] | |
|---|---|---|---|
| | | $CysLT_1$ | $CysLT_2$ |
| **18** |   | 0.051 | 0.055 |
| **19** |   | 0.017 | 0.00087 |

[a]Assay protocols are provided in the Supporting Information. $IC_{50}$ values represent the mean of at least two experiments.

**Table 5. Pharmacokinetics Profile of 11a in Rat**

| i.v. dosing (1 mg/kg) | | oral dosing (30 mg/kg) | |
|---|---|---|---|
| CL (mL/min/kg) | $T_{1/2}$ (h) | AUC (μg h/mL) | $F$ (%) |
| 4.7 | 3.4 | 1.6 | 1.5 |

Compound **19** (**ONO-2050297**), which is the *S*-enantiomer of **11a**, demonstrated the most potent dual $CysLT_1$ and $CysLT_2$ antagonist activity with $IC_{50}$ values of 0.017 and 0.00087 μM, respectively.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental preparation of compounds, characterization, and conditions for the biological assays. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES


(1) Samuelsson, B. Leukotrienes: Mediators of immediate hypersensitivity reactions and inflammation. *Science* **1983**, *220*, 568−575.

(2) Evans, J. F. Cysteinyl leukotriene receptors. *Prostaglandins Other Lipid Mediators* **2002**, *68*−*69*, 587−597.

(3) Bäck, M. Functional characteristics of cysteinyl-leukotriene receptor subtypes. *Life Sci.* **2002**, *71*, 611−622.

(4) Capra, V.; Thompson, M. D.; Sala, A.; Cole, D. E.; Folco, G.; Rovati, G. E. Cysteinyl-leukotrienes and their receptors in asthma and other inflammatory diseases: Critical update and emerging trends. *Med. Res. Rev.* **2007**, *27*, 469−527.

(5) Lynch, K. R.; O'Neill, G. P.; Liu, Q.; Im, D. S.; Sawyer, N.; Metters, K. M.; Coulombe, N.; Abramovitz, M.; Figueroa, D. J.; Zeng, Z.; Conolly, B. M.; Bai, C.; Austin, C. P.; Chateauneuf, A.; Stocco, R.; Greig, G. M.; Kargman, S.; Hooks, S. B.; Hosfield, E.; Williams, D. L., Jr.; Ford-Hutchinson, A. W.; Caskey, C. T.; Evans, J. F. Characterization of the human cysteinyl leukotriene $CysLT_1$ receptor. *Nature* **1999**, *399*, 789−793.

(6) Heise, C. E.; O'Dowd, B. F.; Figueroa, D. J.; Sawyer, N.; Nguyen, T.; Im, D.-S.; Stocco, R.; Bellefeuille, J. N.; Abramovitz, M.; Cheng, R.; Williams, D. L., Jr.; Zeng, Z.; Liu, Q.; Ma, L.; Clements, M. K.; Coulombe, N.; Liu, Y.; Austin, C. P.; George, S. R.; O'Neill, G. P.; Metters, K. M.; Lynch, K. R.; Evans, J. F. Characterization of the human cysteinyl leukotriene 2 receptor. *J. Biol. Chem.* **2000**, *275*, 30531−30536.

(7) Tanaka, H.; Saito, T.; Kurokawa, K.; Teramoto, S.; Miyazaki, N.; Kaneko, S.; Hashimoto, M.; Abe, S. Leukotriene (LT)-receptor antagonist is more effective in asthmatic patients with a low baseline ratio of urinary LTE4 to 2,3-dinor-6-keto-prostaglandin $(PG)F_{1\alpha}$. *Allergy* **1999**, *54*, 489−494.

(8) Figueroa, D. J.; Borish, L.; Baramki, D.; Philip, G.; Austin, C. P.; Evans, J. F. Expression of cysteinyl leukotriene synthetic and signalling proteins in inflammatory cells in active seasonal allergic rhinitis. *Clin. Exp. Allergy* **2003**, *33*, 1380−1388.

(9) Mita, H.; Hasegawa, M.; Saito, H.; Akiyama, K. Levels of cysteinyl leukotriene receptor mRNA in human peripheral leucocytes: significantly higher expression of cysteinyl leukotriene receptor 2 mRNA in eosinophils. *Clin. Exp. Allergy* **2001**, *31*, 1714−1723.

(10) Mellor, E. A.; Frank, N.; Soler, D.; Hodge, M. R.; Lora, J. M.; Austen, K. F.; Boyce, J. A. Expression of the type 2 receptor for cysteinyl leukotrienes (CysLT2R) by human mast cells: Functional distinction from CysLT1R. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 11589−11593.

(11) Gauvreau, G. M.; Plitt, J. R.; Baatjes, A.; MacGlashan, D. W. Expression of functional cysteinyl leukotriene receptors by human basophils. *Biochem. Biophys. Res. Commun.* **2000**, *274*, 316−322.

(12) Sjöström, M.; Johansson, A.-S.; Schröder, O.; Qiu, H.; Palmblad, J.; Haeggström, J. Z. Dominant expression of the CysLT2 receptor accounts for calcium signaling by cysteinyl leukotrienes in human umbilical vein endothelial cells. *Arterioscler. Thromb. Vasc. Biol.* **2003**, *23*, e37−e41.

(13) Montuschi, P. Role of leukotrienes and leukotriene modifiers in asthma. *Pharmaceuticals* **2010**, *3*, 1792−1811.

(14) Dahlen, S. E. Treatment of asthma with antileukotrienes: First line or last resort therapy? *Eur. J. Pharmacol.* **2006**, *533*, 40−56.

(15) Kumlin, M. Measurement of leukotrienes in humans. *Am. J. Resp. Crit. Care Med.* **2000**, *161*, S102−S106.

(16) Higashi, N.; Taniguchi, M.; Mita, H.; Kawagishi, Y.; Ishii, T.; Higashi, A.; Osame, M.; Akiyama, K. Clinical features of asthmatic patients with increased urinary leukotriene E4 excretion (hyperleukotrienuria): Involvement of chronic hyperplastic rhinosinusitis with nasal polyposis. *J. Allergy Clin. Immunol.* **2004**, *113*, 277−283.

(17) Abraham, B.; Antó, J. M.; Barreiro, E.; Bel, E. H. D.; Bousquet, J.; Castellsagud, J.; Chanez, P.; Dahién, B.; Dahién, S. E.; Dews, Ń.; Djukanovic, R.; Fabbri, L. M.; Folkerts, G.; Gaga, M.; Gratziou, C.; Holgate, S. T.; Howarth, P. H.; Johnston, S. L.; Kanniess, F. The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. *Eur. Respir. J.* **2003**, *22*, 470−477.

(18) Green, S. A.; Malice, M. P.; Tanaka, W.; Tozzi, C. A.; Reiss, T. F. Increase in urinary leukotriene $LTE_4$ levels in acute asthma: correlation with airflow limitation. *Thorax* **2004**, *59*, 100−104.

(19) Wunder, F.; Tinel, H.; Kast, R.; Geerts, A.; Becker, E. M.; Kolkhof, P.; Hütter, J.; Ergüden, J.; Härter, M. Pharmacological characterization of the first potent and selective antagonist at the cysteinyl leukotriene2 ($CysLT_2$) receptor. *Br. J. Pharmacol.* **2010**, *160*, 399−409.

(20) Ni, N. C.; Yan, D.; Ballantyne, L. L.; Barajas-Espinosa, A.; St. Amand, T.; Pratt, D. A.; Funk, C. D. A selective cysteinyl leukotriene receptor 2 antagonist blocks myocardial ischemia/reperfusion injury and vascular permeability in mice. *J. Pharmacol. Exp. Ther.* **2011**, *339*, 768−778.

(21) Nothacker, H.-P.; Wang, Z.; Zhu, Y.; Reinscheid, R. K.; Lin, S. H. S.; Civelli, O. Molecular cloning and characterization of a second

human cysteinyl leukotriene receptor: Discovery of a subtype selective agonist. *Mol. Pharmacol.* **2000**, *58*, 1601−1608.
(22) Bäck, M.; Jonsson, E. W.; Dahlén, S. E. The cysteinyl-leukotriene receptor antagonist BAY u9773 is a competitive antagonist of leukotriene C4 in the guinea-pig ileum. *Eur. J. Pharmacol.* **1996**, *317*, 107−113.
(23) Akai, Y.; Tabuchi, Y.; Ando, K.; Ito, A.; Sakata, Y.; Kawasaki, I.; Ohishi, T.; Yamashita, M.; Ohta, S.; Nishide, K.; Ohishi, Y. Preparation of benzo[b]furans having five-membered heterocycles at the 2-position and 2-(4-alkylcarbamoylbuta-1,3-dienyl)benzo[b]furans, and their cysteinyl leukotriene receptor ($CysLT_1$, $CysLT_2$) inhibitory activity. *Chem. Pharm. Bull.* **2012**, *60*, 1461−1467.
(24) Tsuji, E.; Ando, K.; Kunitomo, J.; Yamashita, M.; Ohta, S.; Kohno, S.; Ohishi, Y. Preparation of 3-acetoacetylaminobenzo[b]furan derivatives with cysteinyl leukotriene receptor 2 antagonistic activity. *Org. Biomol. Chem.* **2003**, *1*, 3139−3141.
(25) Ando, K.; Tsuji, E.; Ando, Y.; Kuwata, N.; Kunitomo, J.; Yamashita, M.; Ohta, S.; Kohno, S.; Ohishi, Y. Syntheses of 3-acetoacetylaminobenzo[b]furan derivatives having cysteinyl leukotriene 2 receptor antagonistic activity. *Org. Biomol. Chem.* **2004**, *2*, 625−635.
(26) Dong, X.; Zhao, Y.; Huang, X.; Lin, K.; Chen, J.; Wei, E.; Liu, T.; Hu, Y. *Eur. J. Med. Chem.* **2013**, *62*, 754−763.