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# Syntheses of 3-acetoacetylaminobenzo[*b*]furan derivatives having cysteinyl leukotriene 2 receptor antagonistic activity †‡

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Novel 3-acetoacetylaminobenzo[*b*]furan derivatives having a modified triene system at the 3-position were synthesized starting with 3-aminobenzo[*b*]furans. The enol isomers, 3-[(3-hydroxybut-2-enonyl)amino]benzo[*b*]furans (**1**), of the 3-acetoacetylaminobenzo[*b*]furans were obtained as stable isomers owing to formation of a hydrogen bonding between the enol hydroxyl group and the amidocarbonyl group. The planarity of the C-2 substituent through the C-3 side chain suggested the existence of a modified conjugational triene system in the enol compound. Cysteinyl leukotriene 1 and 2 receptor antagonistic activities for these compounds were evaluated. 2-(4-Cyanobenzoyl or ethoxycarbonyl)-3-[(2-cyano-3-hydroxybut-2-enonyl)amino]benzo[*b*]furans (**15g**, **15o**, **15u**) were moderately active.

## Introduction

The cysteinyl leukotrienes (cysLTs) are potent biological mediators in the pathophysiology of inflammatory diseases, particularly of airway obstruction in asthma. Cysteinyl leukotriene 1 receptor (cysLT1) selective antagonists such as pranlukast, montelukast and zafirlukast, have been shown to be clinically beneficial against chronic asthma. Recently a second human cysLT receptor (cysLT2) was molecularly cloned and characterized.[2]

The synthesis of cysLT1 and/or cysLT2 antagonist remains a challenge. BAY u9773 (**5**) was reported to be a dual cysLT1 and cysLT2 antagonist[2a,3] and a partial agonist of cysLT2.[2d] DUO-LT[4] (**6**) was also shown to be a dual antagonist. Discovery of the dual antagonist and/or selective cysLT2 antagonist should be of therapeutic value.

The importance of the benzo[*b*]furan ring system in natural substances and synthetic products with various bioactivities is evident from the large number of papers published. The electron density of both C-2 and C-3 on the benzo[*b*]furan ring has been reported to be higher than that of other positions.[5] We found enamine reactivity[6] of the 2-ethyl-3,5-diaminobenzo[*b*]furan in the course of our studies,[7] which suggested olefinic as well as aromatic properties of the double bond between C-2 and C-3. As the starting point for our own investigation, we focused on the double bond between C-2 and C-3 on the benzo[*b*]furan ring. It was used to construct a modified conjugational triene system. The designed compound (**1**), the enol isomer of 3-acetoacetylaminobenzo[*b*]furans, may have the π-conjugation and planarity shown by the bold-line portions in Fig. 1. The C-7–C-12 portion of cysLTs (**4**) might be simulated as shown by the bold-line portions of **1**. Two other series compounds (**2**, **3**) were also prepared for comparison of potencies. Here, we report the synthesis of new benzo[*b*]furan derivatives (**1**, **2**, **3**) and their antagonistic activities on cysLT1 and cysLT2.

## Results and discussion

The designed compound (**1**) was synthesized starting with 3-aminobenzo[*b*]furans (**9**) as the key intermediate. Ring closure reactions of 2-cyanophenols (**7**) with several α-halogenated compounds ($XCH_2COR$, $ClCH_2CN$, $BrCH_2NO_2$) are convenient for preparing **9** having an electron withdrawing group at the 2-position.

Several 2-cyanophenols (**7b**, **7c**, **7d**, **7e**, **7f**) were prepared from the corresponding salicylaldehydes according to the procedure reported by Astles *et al.*[8]

2-Acetyl-3-aminobenzo[*b*]furans (**9a**, **9b**, **9d**, **9e**) were prepared by treatment of the 2-cyanophenols (**7a**, **7b**, **7d**, **7e**) with chloroacetone under condition **c**[9] (Scheme 1). On the other hand, treatment of **7a** with chloroacetone under condition **a** afforded only the intermediate acetyl methyl ether (**8a**) which gave the bromide (**8b**). Reaction of **8b** with $Et_3N$ (condition **d**) easily afforded 2-acetyl-3-amino-5-bromobenzo[*b*]furan (**9b**). Treatment of 4′-chloro-, 4′-cyano- and 3′,4′-methylenedioxy-2-bromoacetophenone with 2-cyanophenols (**7b**, **7c**, **7e**) under condition **b** or **c** afforded the 3-amino-2-benzoylbenzo[*b*]furans (**9g**, **9i**, **9j**, **9k**, **9l**, **9m**).[10] Under the mild condition **a**, reactions of 2-cyanophenols (**7a**, **7c**) with the 2-bromoacetophenones gave the intermediate benzoyl methyl ethers (**8c**, **8e**), respectively. Nitration of **8c** gave the nitro intermediate (**8d**). The intermediates (**8c**, **8d**) were also converted to 3-amino-2-benzoylbenzo[*b*]furans (**9f**, **9h**), respectively, by treatment with $Et_3N$ (condition **d**).

Reactions of 2-cyanophenols (**7a**, **7b**) with $ClCH_2CN$ formed mixtures [(**8f**, **9n**) and (**8g**, **9o**)] of the intermediate cyanomethyl ethers (**8**) and the 3-amino-2-cyanobenzo[*b*]furans (**9**), respectively, under condition **b**. The intermediates (**8f**, **8g**) were converted to the corresponding 3-amino-2-cyanobenzo[*b*]furans (**9n**, **9o**) under condition **e**.[11] 2-Cyanophenol (**7a**) was treated with chloroacetamide under condition **b** to give the stable intermediate (**8h**) which was converted to 3-aminobenzo[*b*]-furan-2-carboxamide (**9p**) under condition **f**.[11,12]

Treatment of 2-cyanophenol (**7a**) with ethyl bromoacetate under condition **b** gave the intermediate ethoxy carbomethyl ether (**8i**) alone without any cyclization product.[12] Bromination of **8i** gave bromide (**8j**). Ring closures of the ethoxy carbo-

† See ref. 1.
‡ Electronic supplementary information (ESI) available: Tables S1–S10 containing the physical data of compounds **8**–**10**, **12**, **14**–**16** and **18**–**27**. See http://www.rsc.org/suppdata/ob/b3/b312682j/

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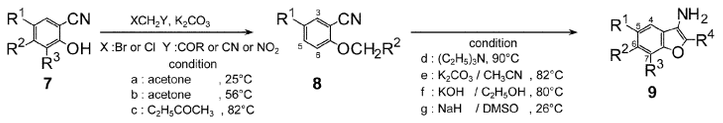



| | R1 | R2 | R3 |
|---|---|---|---|
| 7a : | H | H | H |
| 7b : | Br | H | H |
| 7c : | $NO_2$ | H | H |
| 7d : | H | $OCH_3$ | H |
| 7e : | H | H | $OCH_3$ |
| 7f : | H | H | $OC_2H_5$ |

| | R1 | R2 | condition |
|---|---|---|---|
| 8a : | H | $COCH_3$ | a |
| 8b : | Br | $COCH_3$ | - |
| 8c : | H | $COC_6H_4$(4-CN) | a |
| 8d : | $NO_2$ | $COC_6H_4$(4-CN) | - |
| 8e : | $NO_2$ | A | a |
| 8f : | H | CN | b |
| 8g : | Br | CN | b |
| 8h : | H | $CONH_2$ | b |
| 8i : | H | $COOC_2H_5$ | b |
| 8j : | Br | $COOC_2H_5$ | - |

NBS; $HNO_3$; $Br_2$

A = CO

| | R1 | R2 | R3 | R4 | condition |
|---|---|---|---|---|---|
| 9a : | H | H | H | $COCH_3$ | c |
| 9b : | Br | H | H | $COCH_3$ | c or d |
| 9c : | CN | H | H | $COCH_3$ | - |
| 9d : | H | $OCH_3$ | H | $COCH_3$ | c |
| 9e : | H | H | $OCH_3$ | $COCH_3$ | c |
| 9f : | H | H | H | $COC_6H_4$(4-CN) | d |
| 9g : | Br | H | H | $COC_6H_4$(4-CN) | c |
| 9h : | $NO_2$ | H | H | $COC_6H_4$(4-CN) | d |
| 9i : | Br | H | H | $COC_6H_4$(4-Cl) | c |
| 9j : | $NO_2$ | H | H | $COC_6H_4$(4-Cl) | b |
| 9k : | H | H | $OCH_3$ | $COC_6H_4$(4-Cl) | c |
| 9l : | H | H | $OCH_3$ | $COC_6H_4$(4-Br) | b |
| 9m : | $NO_2$ | H | H | A | b |
| 9n : | H | H | H | CN | e |
| 9o : | Br | H | H | CN | e |
| 9p : | H | H | H | $CONH_2$ | f |
| 9q : | H | H | H | $COOC_2H_5$ | g |
| 9r : | Br | H | H | $COOC_2H_5$ | g |
| 9s : | Br | H | H | $NO_2$ | b |
| 9t : | H | H | $OC_2H_5$ | $NO_2$ | b |

CuCN

**Scheme 1**

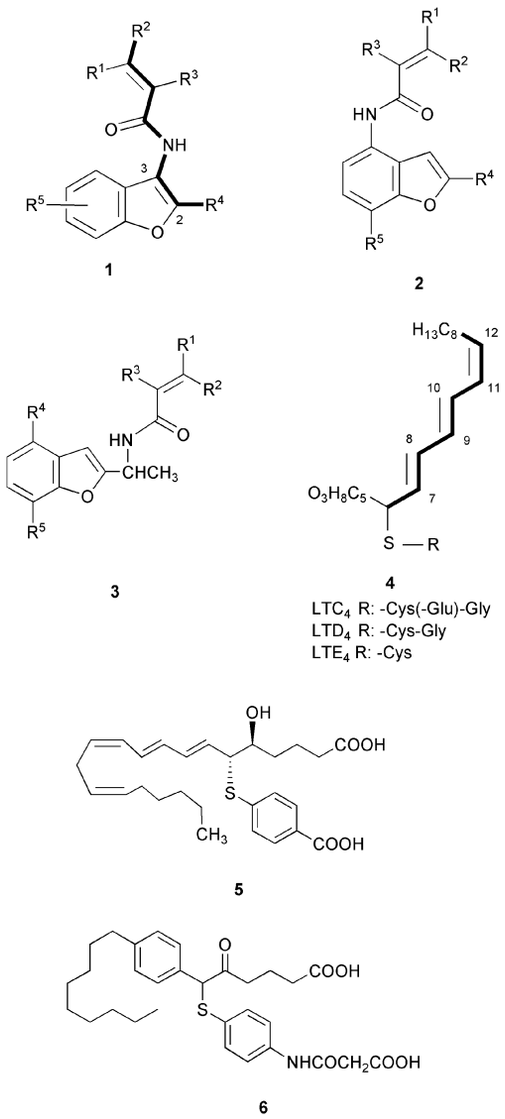



**Fig. 1**

methyl ethers (**8i**, **8j**) to the 3-amino-2-ethoxycarbonylbenzo[*b*]furans (**9q**, **9r**) were accomplished under condition **g**.

In the ring closure reactions of **8**, the acetyl- (**8a**, **8b**), benzoyl- (**8c**, **8d**, **8e**) and cyanomethyl ethers (**8f**, **8g**) easily gave the corresponding 3-aminobenzo[*b*]furans compared to cyclizations of the amide (**8h**) and the esters (**8i**, **8j**).

The 3-amino-2-nitrobenzo[*b*]furans (**9s**, **9t**) were obtained by reactions of **7b** and **7f** with $BrCH_2NO_2$ under condition **b** with low yield[13] (Scheme 1).

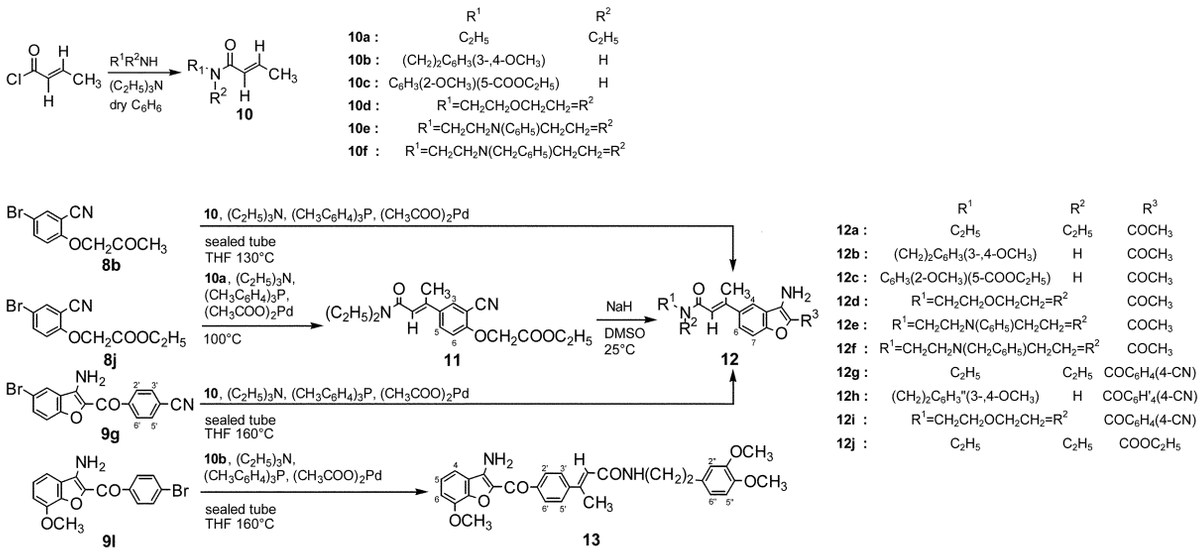
The 2-acetyl-3-aminobenzo[*b*]furans (**12a**–**12f**) having the 2-alkyl- or 2-dialkylcarbamoyl-1-methylvinyl functional group[14] at the 5-position were also prepared in one step by reaction of the acetyl methyl ether (**8b**) with six *N*-alkyl or *N*,*N*-dialkylcrotonamides (**10a**–**10f**)[15] in $Et_3N$ under modified Heck coupling conditions[14b,16] (Scheme 2). Consideration of nuclear Overhauser enhancement spectroscopy (NOESY) spectra of **12a**–**12f** (typical compound, **12a** shown in Fig. 2) led to the conclusion that **12** had an (*E*)-[(2-alkyl- or 2-dialkyl)carbamoyl-1-methylvinyl] group. 3-Amino-2-benzoylbenzo[*b*]furans (**9g** and **9l**) were also subjected to the Heck reaction to obtain the corresponding alkylcarbamoylvinyl derivatives (**12g**, **12h**, **12i** and **13**). 3-Amino-2-ethoxycarbonyl-5-(2-diethylcarbamoyl-1-methyl)vinylbenzo[*b*]furan (**12j**) was obtained by cyclization of **11** prepared from **8j** (Scheme 2).

2-Acetyl-(**14a**–**14e**, **14q**–**14t**), 2-benzoyl-(**14f**–**14j**, **14u**–**14w**, **14y**), 2-cyano-(**14k**, **14l**), 2-ethoxycarbonyl-3-(5-methylisoxazole-4-carbonyl)aminobenzo[*b*]furans (**14n**, **14o**, **14x**) and 3-(5-methylisoxazole-4-carboxyl)aminobenzo[*b*]furan-2-carboxamide (**14m**) were obtained from the corresponding 3-aminobenzo[*b*]furans (**9**, **12**, **13**) by treatment with 5-methylisoxazole-4-carboxylic acid chloride[17] (Scheme 3).

In $^1$H-NMR studies of the 3-(5-methylisoxazole-4-carbonyl)-aminobenzo[*b*]furans, except for the 2-cyano compounds (**14k**, **14l**), a significant downfield shift (Δppm: 1.11–1.21) of the H-4 signals compared to those of the corresponding 3-aminobenzo[*b*]furans was observed as shown in Table 1 [Δppm (1.21) = [{chemical shift (9.16) of **14c**} — {chemical shift (7.95) of **9c**}]], and a correlation of the NH with the only isoxazole ring H (typical compounds, **14b** and **14q** shown in Fig. 2) was detected in the NOESY spectra. The magnetic anisotropic effect caused by the amidocarbonyl and the NOE data supported the proposed conformation of these 3-(5-methylisoxazole-4-carbonyl)aminobenzo[*b*]furans as shown in Fig. 2.

In contrast, only the 2-cyano compounds (**14k**, **14l**) showed characteristic correlation between NH and both isoxazole ring H and H-4 in the NOESY spectra (**14l** in Fig. 2). This revealed that the 2-cyano compounds had the opposite conformation from the others shown in Fig. 2.

The 3-(5-methylisoxazole-4-carbonyl)aminobenzo[*b*]furans (**14a**–**14e**, **14g**, **14h**, **14j**–**14o**, **14q**–**14u**, **14y**) were rapidly convertible to the respective 2-substituted-3-(2-cyano-3-hydroxy-




**Scheme 2**

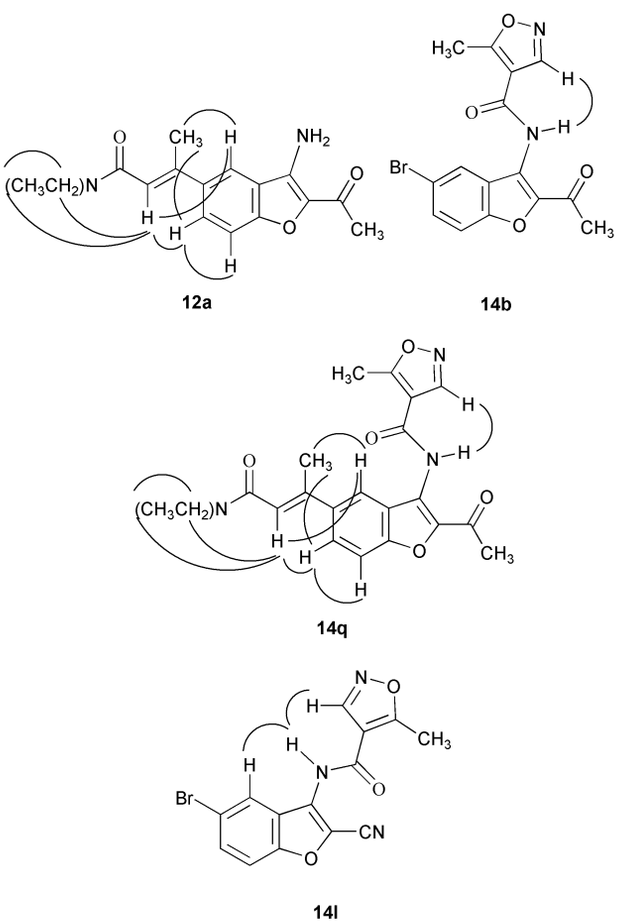



**Fig. 2** NOESY correlation and proposed conformations of **12a**, **14b**, **14q** and **14l**.

but-2-enonyl)aminobenzo[*b*]furans (**15a**–**15e**, **15g**, **15h**, **15j**–**15o**, **15q**–**15u**, **15y**), the enol isomer of the 3-acetocyanoacetylaminobenzo[*b*]furan, by treatment with $Et_3N$ (Scheme 3).[18] In their $^1$H-NMR spectra, the 3-(2-cyano-3-hydroxybut-2-enonyl)-aminobenzo[*b*]furans (**15**) showed characteristic hydroxyl signals (15.2 ppm) caused by strong hydrogen bonding with amidocarbonyl, and H-4 signals were also shifted downfield (Δppm: 0.90–1.00) owing to the magnetic anisotropic effect of the amidocarbonyl from the chemical shift of the H-4 signals of the corresponding 3-aminobenzo[*b*]furans [Δppm (0.93) = [{chemical shift (8.63) of **15b**} — {chemical shift (7.70) of **9b**}] in Table 1].

The assignments of proton and carbon signals of **15** were completed by extensive two-dimensional NMR (2D-NMR) analysis [heteronuclear multiple bond connectivity (HMBC) and heteronuclear multiple quantum coherence (HMQC)]. The possible conformations, $^1$H-NMR and $^{13}$C-NMR data of **15q** as a typical compound, are shown in Fig. 3. The stable enol isomer, 3-(2-cyano-3-hydroxybut-2-enonyl)aminobenzo[*b*]furan, due to formation of hydrogen bonds, was predominantly formed, in contrast to the keto isomer, acetocyanoacetylaminobenzo-[*b*]furan, which could not be obtained by this preparation method.

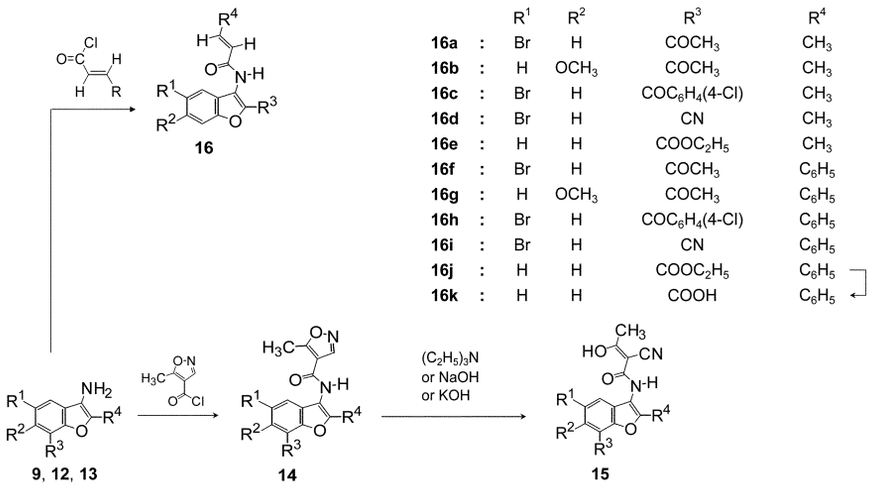
The stereostructures of representative 3-(2-cyano-3-hydroxybut-2-enonyl)aminobenzo[*b*]furans (**15b** and **15u**) were determined by X-ray analysis as shown in Fig. 4,[19] which clearly shows the conjugation and planarity of the C-2 substituent through the C-3 side chain that were as we had expected.

3-(But-2-enonyl)amino-(**16a**–**16e**) and 3-(3-phenylprop-2-enoyl)aminobenzo[*b*]furans (**16f**–**16k**), not enol analogues, were prepared from the 3-aminobenzo[*b*]furans (**9**) by treatment with crotonyl chloride or *trans*-cinnamic acid chloride (Scheme 3).

In addition, 2-acetyl-4-(2-cyano-3-hydroxybut-2-enonyl)-amino-7-methoxybenzo[*b*]furan (**22**) was prepared, starting with 2-acetyl-4-amino-7-methoxybenzo[*b*]furan (**20**) *via* **21**. 2-[1-[(2-Cyano-3-hydroxybut-2-enonyl)amino]ethyl]benzo[*b*]-furans (**26a**–**26e**), 2-[1-[(but-2-enonyl)amino]ethyl]benzo[*b*]-furans (**27a**, **27b**) and 2-[1-[(3-phenylprop-2-enonyl)amino]-ethyl]benzo[*b*]furans (**27c**, **27d**) were prepared starting with 2-(1-amino)ethylbenzo[*b*]furans (**24**) (Scheme 4). A significant NOE between the NH and the isoxazole ring H was observed in **21** and **25**, similar to that observed with **14**.

## Biological evaluation

Most of the compounds reported in this paper were first evaluated for cysLT1 and cysLT2 antagonistic activity by measurement of inhibition of agonist-induced calcium release according to the method reported by Nothacker.[2d,20] The compounds selected on the basis of calcium assay were next evaluated for their cysLT2 antagonistic activity by radioligand binding studies. In the calcium assay, three compounds (**15g**, **15o**, **15u**) showed more than 50% inhibition of the calcium release for both cysLT1 and cysLT2 at a concentration of 10 μM. The $IC_{50}$ values (μM) of the calcium assay indicated that **15g** and **15u** were more potent than **15o**, and **15g** displayed selective antagonistic activity for cysLT2 ($IC_{50}$ for cysLT2,




| | R1 | R2 | R3 | R4 |
|---|---|---|---|---|
| 16a : | Br | H | $COCH_3$ | $CH_3$ |
| 16b : | H | $OCH_3$ | $COCH_3$ | $CH_3$ |
| 16c : | Br | H | $COC_6H_4$(4-Cl) | $CH_3$ |
| 16d : | Br | H | CN | $CH_3$ |
| 16e : | H | H | $COOC_2H_5$ | $CH_3$ |
| 16f : | Br | H | $COCH_3$ | $C_6H_5$ |
| 16g : | H | $OCH_3$ | $COCH_3$ | $C_6H_5$ |
| 16h : | Br | H | $COC_6H_4$(4-Cl) | $C_6H_5$ |
| 16i : | Br | H | CN | $C_6H_5$ |
| 16j : | H | H | $COOC_2H_5$ | $C_6H_5$ |
| 16k : | H | H | COOH | $C_6H_5$ |

| | R1 | R2 | R3 | R4 |
|---|---|---|---|---|
| 14a , 15a : | H | H | H | $COCH_3$ |
| 14b , 15b : | Br | H | H | $COCH_3$ |
| 14c , 15c : | CN | H | H | $COCH_3$ |
| 14d , 15d : | H | $OCH_3$ | H | $COCH_3$ |
| 14e , 15e : | H | H | $OCH_3$ | $COCH_3$ |
| 14f : | H | H | H | $COC_6H_4$(4-CN) |
| 14g , 15g : | Br | H | H | $COC_6H_4$(4-CN) |
| 14h , 15h : | Br | H | H | $COC_6H_4$(4-Cl) |
| 14i : | H | H | $OCH_3$ | $COC_6H_4$(4-Cl) |
| 14j , 15j : | H | H | $OCH_3$ | $COC_6H_4$(4-Br) |
| 14k , 15k : | H | H | H | CN |
| 14l , 15l : | Br | H | H | CN |
| 14m , 15m : | H | H | H | $CONH_2$ |
| 14n , 15n : | H | H | H | $COOC_2H_5$ |
| 14o , 15o : | Br | H | H | $COOC_2H_5$ |
| 15p : | H | H | H | COOH |
| 14q , 15q : | $C(CH_3)$=CHCON$(C_2H_5)_2$ [a] | H | H | $COCH_3$ |
| 14r , 15r : | $C(CH_3)$=CHCOA [a] | H | H | $COCH_3$ |
| 14s , 15s : | $C(CH_3)$=CHCONCH$_2$CH$_2$OCH$_2$CH$_2$ [a] | H | H | $COCH_3$ |
| 14t , 15t : | $C(CH_3)$=CHCONCH$_2$CH$_2$N$(C_6H_5)$CH$_2$CH$_2$ [a] | H | H | $COCH_3$ |
| 14u , 15u : | $C(CH_3)$=CHCON$(C_2H_5)_2$ [a] | H | H | $COC_6H_4$(4-CN) |
| 14v : | $C(CH_3)$=CHCOA [a] | H | H | $COC_6H_4$'(4-CN) |
| 14w : | $C(CH_3)$=CHCONCH$_2$CH$_2$OCH$_2$CH$_2$ [a] | H | H | $COC_6H_4$(4-CN) |
| 14x : | $C(CH_3)$=CHCON$(C_2H_5)_2$ [a] | H | H | $COOC_2H_5$ |
| 14y , 15y : | H | H | $OCH_3$ | $COC_6H_4$'$C(CH_3)$=CHCOA [a] |

[a] *E*-form
A=NH$(CH_2)_2C_6H_3$"$(OCH_3)_2$

**Scheme 3**

Table 2). The selective activity for cysLT2 of **15g** was also supported by tentative examination using a radioligand binding assay (Table 3).

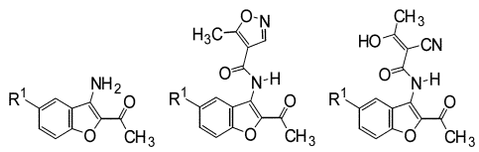
In contrast, 2-acetyl-4-(2-cyano-3-hydroxybut-2-enonyl)-amino-7-methoxybenzo[*b*]furan (**22**), 2-[1-[(2-cyano-3-hydroxybut-2-enonyl)amino]ethyl]benzo[*b*]furans (**26**) and 4-trifluoromethyl-(2-cyano-3-hydroxybut-2-enonyl)aminobenzene (**29**)[18,21], the simple control compounds, were inactive in the calcium assay (Table 2). The (2-cyano-3-hydroxybut-2-enonyl)-amino functional groups of **22** and **26** displayed no conjugation with the double bond between C-2 and C-3. Also the functional group of **29** was not conjugated with any olefinic double bonds. These findings showed that the functional group required a conjugated double bond to display activity. These results demonstrated, as we had hypothesized, a significant contribution of the double bond between C-2 and C-3 for the appearance of activity. In addition, the enol form of the 3-acetoacetylamino functional group may play a crucial role in the antagonistic activities for cysLT1 and cysLT2 because of the very poor activities of 3-(but-2-enonyl)amino-(**16a**, **16b**, **16d**, **16e**) and 3-(3-phenylprop-2-enonyl)aminobenzo[*b*]furans (**16j**, **16k**). X-ray crystallography studies of **15b** and **15u** indicated the planarity of the C-2 substituent through the C-3 side chain, which suggested the existence of a modified conjugational triene system in the designed compound (**1**), as we had expected.

Our designed compound (**1**) may be a novel lead compound as a cysLT2 antagonist, which is still moderately active. Optimization of **15g** to find more potent and selective cysLT2 antagonistic active compounds is in progress.

## Experimental

All melting points were determined using a Yanako microscopic hot-stage apparatus and are uncorrected. $^1$H-NMR, $^{13}$C-NMR, HMBC and HMQC spectra were obtained on a JEOL GSX-500 spectrometer with tetramethylsilane as an internal standard. MS spectra (MS, HRMS) were obtained using a JEOL JMS DX-303 EIMS spectrometer. Elemental analyses were performed on a CHN CORDER MT-3 (Yanako). All organic extracts were dried over anhydrous $MgSO_4$. Column chromatography was carried out on Wakogel C-200 (100–200). Thin layer chromatography was performed on an E. Merck silica gel plate (0.5 mm, 60F-254).

**Table 1** Downfield shift of H-4 of **14** and **15**



**9 ,12** **14** **15**

| Chemical shift (ppm) | Δppm (**14** ↔ **9**) | Chemical shift (ppm) | Δppm (**15** ↔ **9**) | Chemical shift (ppm) |
|---|---|---|---|---|
| **9b** 7.70 | 1.14 | **14b** 8.84 | 0.93 | **15b** 8.63 |
| **9c** 7.95 | 1.21 | **14c** 9.16 | 1.00 | **15c** 8.95 |
| Chemical shift (ppm) | Δppm (**14** ↔ **12**) | Chemical shift (ppm) | Δppm (**15** ↔ **12**) | Chemical shift (ppm) |
| **12a** 7.62 | 1.14 | **14q** 8.76 | 0.92 | **15q** 8.54 |
| **12e** 7.66 | 1.11 | **14t** 8.77 | 0.90 | **15t** 8.56 |

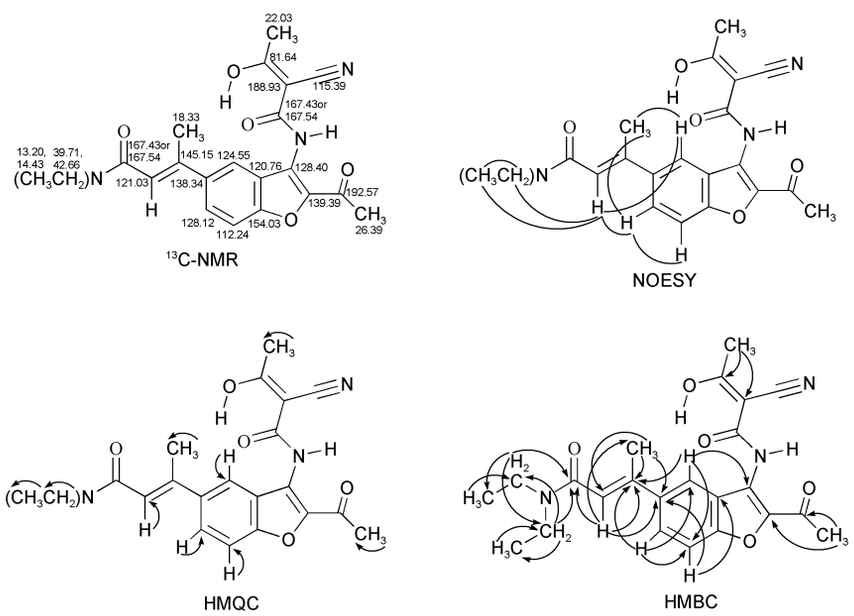
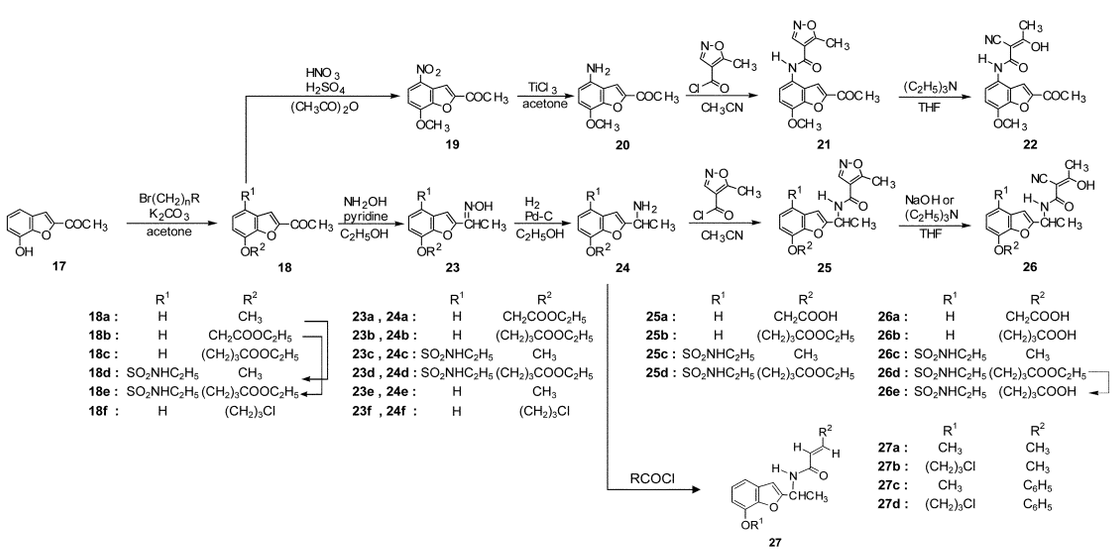


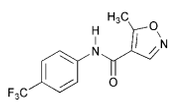

**Fig. 3** Conformation, $^{1}$H-NMR and $^{13}$C-NMR of **15q**.



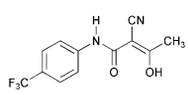

**Scheme 4**

**Table 2** Inhibition of agonist-induced calcium release

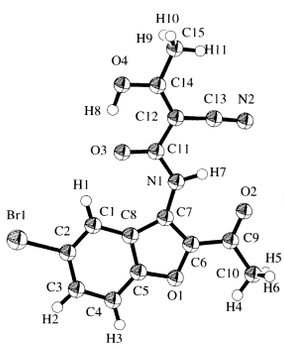
| Comp. | Inhibition (%) (10 μM) cysLT1 | Inhibition (%) (10 μM) cysLT2 | $IC_{50}$ (μM) cysLT1 | $IC_{50}$ (μM) cysLT2 | Comp. | Inhibition (%) (10 μM) cysLT1 | Inhibition (%) (10 μM) cysLT2 |
|---|---|---|---|---|---|---|---|
| **15a** | 6.5 | 24.1 | | | **14a** | 11.9 | 2.4 |
| **15b** | 36.3 | 7.5 | | | **14b** | 11.1 | 5.5 |
| **15e** | 20.1 | 0.7 | | | **14c** | 0.2 | −11.8 |
| **15g** | 52.1 | 67.1 | >10.0 | 6.0±1.6 | **14m** | −11.2 | 13.5 |
| **15h** | 23.1 | 29.1 | | | **14n** | 8.4 | 2.7 |
| **15j** | 24.5 | 1.6 | | | **14o** | 5.7 | −3.4 |
| **15k** | 6.3 | 22.1 | | | **14s** | 35.5 | 27.5 |
| **15l** | 15.7 | −11.2 | | | **14t** | 13.0 | 4.3 |
| **15m** | 8.4 | 7.8 | | | **16a** | 2.8 | 3.1 |
| **15o** | 49.8 | 61.4 | >10.0 | >10.0 | **16b** | 24.6 | 21.1 |
| **15p** | 3.3 | 3.5 | | | **16d** | 17.0 | 6.5 |
| **15q** | 11.5 | 15.0 | | | **16e** | 11.8 | −13.0 |
| **15r** | 25.7 | 16.9 | | | **16j** | 6.8 | 16.3 |
| **15t** | 35.0 | 13.3 | | | **16k** | 37.5 | 11.0 |
| **15u** | 51.0 | 57.6 | 9.7 | 7.7 | **21** | 13.3 | 7.5 |
| **28** | 18.1 | 10.1 | >10.0 | >10.0 | **22** | 15.1 | 5.7 |
| **29** | 16.1 | 2.3 | >10.0 | >10.0 | **25b** | 6.5 | −8.5 |
| **BAY u9773**[2d] | | | 0.44±0.182 | 0.30±0.092 | **25c** | 14.7 | 5.4 |
| | | | | | **26b** | 5.0 | 6.6 |
| | | | | | **26c** | 0.1 | 12.7 |
| | | | | | **27a** | −10.0 | −14.6 |
| | | | | | **27b** | 20.4 | 1.3 |
| | | | | | **27c** | 14.8 | 17.9 |
| | | | | | **27d** | 18.4 | 7.7 |



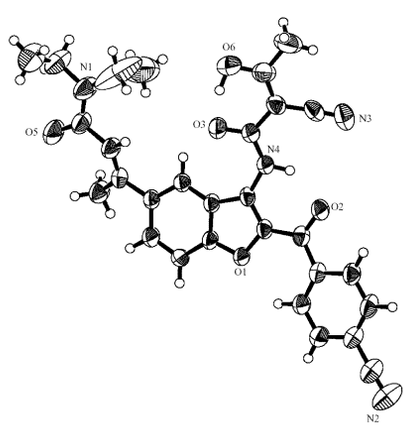
**28**



**29**



**15b**



**15u**

**Fig. 4** X-Ray structures of **15b** and **15u**.

**Table 3** Radioligand binding assay at CysLT2

| Comp. | Inhibition (%) (10μM) | $IC_{50}$ (nM) |
|---|---|---|
| **15g** | 85.0 | 3700 |
| **15o** | 9.5 | >10.0 |
| **BAY u9773**[2c] | | 597±279 |

### 2-(2-Oxopropoxy)benzonitrile (8a) General procedure for 8c, 8e (condition a)

To a solution of **7a** (5.0 g, 4.2 mmol) in dry acetone (500 ml) was added $K_2CO_3$ (11.6 g, 84.0 mmol) and chloroacetone (4.4 ml, 54.6 mmol). The reaction mixture was stirred at 25 °C for 6 h. After filtration, the filtrate was concentrated *in vacuo* to dryness to give a residue which was recrystallized from ethyl acetate to give **8a** (6.4 g) as colorless needles.

### 4-Bromo-2-(2-oxopropoxy)benzonitrile (8b)

$AlCl_3$ (18.3 g, 0.14 mol) and *N*-bromosuccinimide (24.4 g, 0.14 mol) were added to a solution of **8a** (20.0 g, 0.11 mol) in acetonitrile (150 ml). The reaction mixture was stirred at 24 °C for 1 h and poured into ice water to give a colorless powder. The powder was recrystallized from ethanol to give **8b** (29.0 g) as colorless needles.

### 2-[2-(4-Cyanophenyl)-2-oxoethoxy]-4-nitrobenzonitrile (8d)

To a solution of **8c** (0.71 g, 2.7 mmol) in acetic anhydride (135 ml) was added concentrated $H_2SO_4$ (0.20 ml) and $HNO_3$ (0.21 ml, 4.6 mmol) at 6 °C. The reaction mixture was stirred for 0.5 h and poured into ice water to give **8d** (0.77 g) as colorless prisms.

### 2-Cyanomethoxybenzonitrile (8f) General procedure for 8g–8i, 9j, 9l–9m, 9s–9t from 7 (condition b)

To a suspension of **7a** (1.0 g, 8.4 mmol) and $K_2CO_3$ (1.5 g, 10.9 mmol) in dry acetone (100 ml) was added chloroacetone (0.69 ml, 10.9 mmol) at 20 °C with stirring. The reaction mixture was heated at 56 °C, and an insoluble portion was filtered off. The filtrate was evaporated *in vacuo* to give a residue which was recrystallized from ethyl acetate to afford **8f** (0.60 g) as pale yellow needles.

### (4-Bromo-2-cyanophenoxy)acetic acid ethyl ester (8j)

$Br_2$ (0.90 g, 5.6 mmol) was added to a solution of **8i** (1.0 g, 4.9 mmol) in acetic anhydride (10 ml). The reaction mixture was stirred at 26 °C for 5 h, and poured into ice water to give a colorless powder. The powder was washed with hexane to give **8j** (0.80 g).

**2-Acetyl-3-aminobenzo[*b*]furan (9a) General procedure for 9d–9e, 9g, 9i, 9k (condition c)**

To a suspension of **7a** (1.0 g, 8.4 mmol) and $K_2CO_3$ (2.9 g, 21.0 mmol) in dry methyl ethyl ketone (50 ml) was added chloroacetone (0.64 ml, 10.1 mmol) at 25 °C with stirring. The reaction mixture was heated at 82 °C for 1 h. After an insoluble portion was filtered off, the filtrate was evaporated *in vacuo*. The residue was recrystallized from ethanol to give **9a** (1.1 g) as a pale yellow powder.

**2-Acetyl-3-amino-5-bromobenzo[*b*]furan (9b) General procedure for 9f, 9h (condition d)**

A solution of **8b** (8.0 g, 31.5 mmol) in $Et_3N$ (350 ml) was heated at 90 °C for 5 h. Evaporation of excess reagent left a yellow residue, which was recrystallized from ethanol to give **9b** (7.2 g) as pale yellow prisms.

**2-Acetyl-3-amino-5-cyanobenzo[*b*]furan (9c)**

A mixture of **9b** (1.0 g, 3.9 mmol), CuI (1.0 g, 5.3 mmol) and CuCN (0.95 g, 10.6 mmol) in DMF (25 ml) was heated at 153 °C for 8 h. After an insoluble portion was filtered off, the filtrate was poured into ice water and extracted with ethyl acetate. The organic layer was washed with brine, then dried, and evaporated to give a brown powder. The powder was recrystallized from methanol to give **9c** (70.0 mg) as yellow needles.

**3-Amino-2-cyanobenzo[*b*]furan (9n) Procedure for 9o (condition e)**

A suspension of **8f** (1.0 g, 6.3 mmol) and $K_2CO_3$ (2.2 g, 15.8 mmol) in acetonitrile (50 ml) was heated at 82 °C for 3 h. After an insoluble portion was filtered off, the filtrate was evaporated off *in vacuo*. The residue was poured into ice water, and extracted with ethyl acetate. The organic layer was washed with brine, then dried, and evaporated to give a pale brown powder which was recrystallized from ethyl acetate to give **9n** (0.65 g) as pale yellow needles.

**3-Aminobenzo[*b*]furan-2-carboxamide (9p) (condition f)**

A suspension of **8h** (6.0 g, 31.1 mmol) and KOH (4.0 g, 71.4 mmol) in ethanol (80 ml) was heated at 80 °C for 3 h. The reaction mixture was poured into ice water to give **9p** (4.6 g) as colorless needles.

**3-Amino-2-ethoxycarbonylbenzo[*b*]furan (9q) Procedure for 9r (condition g)**

A suspension of **8i** (5.0 g, 24.0 mmol) and NaH (1.0 g, 27.0 mmol) in dry DMSO (11 ml) was stirred at 25–27 °C for 10 h. The reaction mixture was poured into ice water, and extracted with ether. The ether layer was washed with brine, then dried, and evaporated to give **9q** (3.7 g) as yellow needles.

***N*,*N*-Diethyl crotonamide (10a)**

A solution of crotonyl chloride (60.0 ml, 0.63 mol) in dry benzene (160 ml) was added to a solution of diethylamine (75.0 ml, 0.73 mol) and ethydiisopropylamine (76.0 ml, 0.42 mol) in dry benzene (420 ml) at 0 °C with stirring. The mixture was allowed to stand for 4 h at room temperature, then was washed successively with 10% $Na_2CO_3$, 10% HCl solution, and brine and dried. This was fractionated under reduced pressure to give **10a** (50.8 g) as colorless oil, $b.p._8$ 88 °C.

**(*E*)-*N*-[2-(3,4-Dimethoxyphenyl)ethyl]-2-butenamide (10b) General procedure for 10c–10f**

To a mixture of 3,4-dimethoxyphenethylamine (6.9 ml, 40.0 mmol) and $Et_3N$ (5.5 ml) in dry benzene (180 ml) was added crotonyl chloride (4.2 ml, 44.0 mol) in dry benzene (40 ml) dropwise over 30 min at 0 °C. The reaction mixture was stirred at 3–5 °C for 1 h. The solvent was evaporated off. The residue was recrystallized from ethyl acetate to give **10b** (9.6 g) as colorless needles.

**(*E*)-[2-Cyano-4-(2-diethylcarbamoyl-1-methylvinyl)phenoxy]-acetic acid ethyl ester (11)**

A mixture of **8j** (1.0 g, 3.5 mmol), **10a** (0.99 g, 7.0 mmol), $Et_3N$ (7.0 ml, 50.3 mmol), palladium acetate (0.59 g, 0.26 mmol) and tri-*o*-tolylphosphine (0.11 g, 0.35 mmol) was heated at 100 °C for 3 h, and the resulting precipitate was collected by filtration. The precipitate was dissolved with ethyl acetate, and the insoluble portion was filtrated off. The filtrate was evaporated to dryness. The residue was recrystallized from ethyl acetate to give **11** (0.22 g, 18%) as pale brown needles. mp: 100 °C, $\delta_H$ ($CDCl_3$) 1.18 (6H, t, *J* 7.0, $NCH_2CH_3 \times 2$), 1.30 (3H, t, *J* 7.0, $OCH_2CH_3$), 2.25 (3H, bs, C=C–$CH_3$), 3.37 (2H, q, *J* 7.3, $NCH_2CH_3$), 3.47 (2H, q, *J* 7.0, $NCH_2CH_3$), 4.27 (2H, q, *J* 7.0, $OCH_2CH_3$), 4.77 (2H, s, $OCH_2$), 6.24 (1H, bs, C=C–H), 6.83 (1H, d, *J* 8.8, 6-H), 7.58 (1H, dd, *J* 8.8 and 2.6, 5-H), 7.66 (1H, d, *J* 2.6, 3-H). *m*/*z*: (ES) Found: 344.1736 ($M^+$). [$C_{19}H_{24}O_4N_2$] requires 344.1736. *m*/*z*: 344 ($M^+$, 72.0%), 329 (100).

**(*E*)-3-(2-Acetyl-3-aminobenzo[*b*]furan-5-yl)but-2-enoic acid diethylamide (12a) General procedure for 12b–12f**

To a solution of **8b** (3.0 g, 11.8 mmol) in acetonitrile (20 ml) was added **10a** (3.3 g, 23.6 mmol), $Et_3N$ (7.1 ml, 50.7 mmol), palladium acetate (0.13 g, 0.59 mmol) and tri-*o*-tolylphosphine (0.35 g, 1.2 mmol) in a tube. The tube was sealed and heated at 130 °C for 10 h. The reaction mixture was cooled to room temperature and an insoluble portion was filtered off. The filtrate was evaporated to dryness. The residue was poured into ice water and extracted with $CH_2Cl_2$, the extract was washed with brine and dried. The solvent was evaporated off. The residue was recrystallized from ethanol to give **12a** (1.9 g) as yellow needles.

**(*E*)-3-[3-Amino-2-(4-cyanobenzoyl)benzo[*b*]furan-5-yl]but-2-enoic acid diethyl amide (12g) General procedure for 12h–12i**

To a solution of **9g** (2.5 g, 7.0 mmol) in THF (30 ml) was added **10a** (2.0 g, 14.0 mmol), $Et_3N$ (7.0 ml, 70.2 mmol), palladium acetate (0.16 g, 0.70 mmol) and tri-*o*-tolylphosphine (0.22 g, 0.70 mmol) in a tube. The tube was sealed and heated at 160 °C for 7 h. The mixture was worked up in a similar manner as **12a**, and crude **12g** was recrystallized from ethanol as yellow needles (1.2 g).

**(*E*)-3-Amino-5-(2-diethylcarbamoyl-1-methylvinyl)benzo[*b*]-furan-2-carboxylic acid ethyl ester (12j)**

A mixture of **11** (0.66 g, 1.9 mmol) and NaH (78.0 mg, 32.5 mmol) in dry DMSO (10 ml) was stirred at 25 °C for 2 h, then poured into ice water and extracted with ether. The extract was washed with brine and dried. The solvent was evaporated off, and the residue was recrystallized from ethyl acetate to give **12j** (0.24 g) as colorless needles.

**(*E*)-3-[4-(3-Amino-7-methoxybenzo[*b*]furan-2-carbonyl)-phenyl]but-2-enyl acid [2-(3,4-dimethoxyphenyl)ethyl]amide (13)**

To a solution of **9l** (3.0 g, 8.7 mmol) in THF (50 ml), was added $Et_3N$ (10 ml), **10b** (4.3 g, 17.4 mmol), tri-*o*-tolylphosphine (0.27 g, 8.7 mmol) and palladium acetate (0.19 g, 0.87 mmol) in a tube. The tube was sealed and heated at 160 °C for 15 h. The mixture was cooled to room temperature and an insoluble portion was filtered off. The filtrate was dried up. The residue was poured into ice water and extracted with $CHCl_3$. The extract was washed with brine and dried. The solvent was evaporated, and the residue was recrystallized from ethyl acetate to give **13**

(3.6 g) as yellow prisms. mp: 198 °C, $\delta_H(CDCl_3)$ 2.59 (3H, d, *J* 1.5, C=C–$CH_3$), 2.84 (2H, t, *J* 7.0, $NHCH_2CH_2$), 3.61 (2H, q, *J* 7.0, $NHCH_2CH_2$), 3.87 (6H, s, 3″-, 4″-$OCH_3$), 4.01 (3H, s, 7-$OCH_3$), 5.58 (1H, t, *J* 5.9, CONH), 5.98 (2H, s, $NH_2$), 6.02 (1H, d, *J* 1.4, C=C–H), 6.75 (1H, d, *J* 1.8, 2″-H), 6.77 (1H, dd, *J* 8.9 and 1.8, 6″-H), 6.83 (1H, d, *J* 8.9, 5″-H), 6.99 (1H, m, 6-H), 7.19 (1H, dd, *J* 11.3, 5-H), 7.19 (1H, d, *J* 6.2, 4-H), 7.55 (2H, dd, *J* 7.0 and 1.8, 3′-, 5′-H), 8.27 (2H, dd, *J* 6.6 and 1.8, 2′-, 6′-H). *m*/*z*: (ES) Found: 514.2103 ($M^+$). [$C_{30}H_{30}O_6N_2$] requires 514.2104. MS *m*/*z*: 514 ($M^+$,17.19%), 164 (100.00).

### 5-Methylisoxazole-4-carboxylic acid chloride

Thionyl chloride (4.3 ml, 39.5 mmol) was added dropwise at 26 °C to 5-methylisoxazole-4-carboxylic acid (0.44 g, 3.4 mmol). The solution was heated at 89 °C for 1 h, and excess thionyl chloride was removed under reduced pressure to provide acid chloride as a yellow oil, suitable for use in subsequent reactions.

### 2-Acetyl-5-bromo-3-(5-methylisoxazole-4-carbonyl)aminobenzo[*b*]furan (14b) General procedure for 14a, 14c–14e, 14k–14m, 14q–14t

To a solution of **9b** (0.20 g, 0.79 mmol) in anhydrous THF (10 ml), was added dropwise 5-methylisoxazole-4-carboxylic acid chloride (0.10 g, 0.79 mmol) under $N_2$ atmosphere with vigorous stirring at 26 °C. The solution was heated at 65 °C for 2 h. The reaction mixture was cooled to room temperature and the resulting precipitate was collected by filtration. The precipitate was recrystallized from ethyl acetate to give **14b** (0.19 g) as pale yellow needles.

### 5-Bromo-2-(4-chlorobenzoyl)-3-(5-methylisoxazole-4-carbonyl)-aminobenzo[*b*]furan (14h) General procedure for 14f–14g, 14i–14j, 14u–14w, 14y

To a solution of **9i** (0.20 g, 0.57 mmol) in anhydrous THF (6 ml) was added dropwise 5-methylisoxazole-4-carboxylic acid chloride (0.14 g, 1.1 mmol) in anhydrous THF (3 ml) under $N_2$ atmosphere with vigorous stirring at 26 °C. The solution was heated at 65 °C for 7 h. After usual work up, the precipitate was recrystallized from methanol to give **14h** (0.99 g) as yellow needles.

### 2-Ethoxycarbonyl-3-(5-methylisoxazole-4-carbonyl)aminobenzo[*b*]furan (14n) Procedure for 14o

To a solution of **9q** (3.0 g, 14.6 mmol) in acetonitrile (18 ml), was added dropwise 5-methylisoxazole-4-carboxylic acid chloride (2.2 g, 17.5 mmol) in acetonitrile (2 ml) under $N_2$ atmosphere with vigorous stirring at 25 °C. The reaction mixture was stirred at 27 °C for 3 h, and the resulting precipitate was collected by filtration. The precipitate was recrystallized from ether to give **14n** (3.3 g) as colorless needles.

### 5-(2-Diethylcarbamoyl-1-methylvinyl)-2-ethoxycarbonyl-3-(5-methylisoxazole-4-carbonyl)aminobenzo[*b*]furan (14x)

To a solution of **12j** (1.0 g, 2.9 mmol) in acetonitrile (200 ml), was added dropwise 5-methylisoxazole-4-carboxylic acid chloride (1.9 g, 2.9 mmol) in acetonitrile (10 ml) under $N_2$ atmosphere with vigorous stirring at 22 °C. The solution was stirred at the same temperature for 3 h, and heated at 30 °C for 2 h. The solvent was evaporated *in vacuo*. After usual work up, the residue was recrystallized from ethanol to give **14x** (1.4 g) as colorless needles.

### 2-Acetyl-3-(*Z*)-(2-cyano-3-hydroxybut-2-enonyl)aminobenzo[*b*]-furan (15a) General procedure for 15b, 15d–15m, 15q–15u

A solution of **14a** (0.50 g, 1.8 mmol) and $Et_3N$ (2.4 ml, 0.18 mmol) in anhydrous THF (30 ml) was heated at 68 °C for 6 h, and then the solvent was evaporated. The residue was poured into ice water, and made acid with 5% HCl solution and extracted with $CHCl_3$. The extract was washed with brine and dried. The solvent was evaporated. The residue was recrystallized from acetonitrile to give **15a** (0.23 g) as colorless needles.

### 5-Bromo-3-(2-cyano-3-hydroxybut-2-enonyl)aminobenzo[*b*]-furan-2-carboxylic acid ethyl ester (15o) Procedure for 15n

A solution of **14o** (0.47 g, 1.1 mmol) and $Et_3N$ (1.5 ml, 11.1 mmol) in anhydrous THF (20 ml) was stirred at 23 °C for 1 h, then the solvent was evaporated. The residue was poured into ice water, and made acid with 5% HCl solution and extracted with ethyl acetate. The extract was washed with brine and dried. The solvent was evaporated. The residue was recrystallized from methanol to give **15o** (0.37 g) as colorless needles.

### 3-(2-Cyano-3-hydroxybut-2-enonyl)aminobenzo[*b*]furan-2-carboxylic acid (15p)

To a solution of **14n** (0.84 g, 2.7 mmol) in ethanol (30 ml) and DMSO (20 ml), was added dropwise 10% NaOH aqueous solution (17 ml) at 15 °C with stirring. The mixture was stirred at 19 °C for 1 h, and poured into ice water, and made acid with 5% HCl solution and extracted with ethyl acetate. The extract was washed with brine and dried. The solvent was evaporated. The residue was recrystallized from ethyl acetate to give **15p** (0.46 g) as colorless needles.

### 2-Cyano-3-hydroxybut-2-enyl acid [2-[4-[2-{2-(3,4-dimethoxyphenyl)ethylcarbamoyl}-1-methylvinyl]benzoyl]-7-methoxybenzo[*b*]furan-3-yl]amide (15y)

A suspension of **14y** (0.50 g, 0.80 mmol) and KOH (90.0 mg, 1.6 mmol) in THF (270 ml) was heated at 65 °C for 5 h. The solvent was evaporated *in vacuo*. The residue was poured into ice water, and made acid with 5% HCl solution, and the resulting precipitate was collected. The precipitate was recrystallized from ethyl acetate to give **15y** (0.10 g) as colorless needles.

### 2-Acetyl-5-cyano-3-(*Z*)-(2-cyano-3-hydroxybut-2-enonyl)-aminobenzo[*b*]furan (15c)

To a solution of **9c** (0.90 g, 4.5 mmol) in anhydrous THF (100 ml) was added dropwise 5-methylisoxazole-4-carboxylic acid chloride (1.9 g, 14.0 mmol) under $N_2$ atmosphere with vigorous stirring at 28 °C. The solution was heated at 66 °C for 7 h and treated with pyridine (10 ml). A resulting precipitate was collected by filtration, and recrystallized from ethanol to give **15c** (0.28 g, 20%) as colorless needles. Treatment of the filtrate gave **14c** (0.19 g, 14%) as colorless needles.

### 2-Acetyl-5-bromo-3-(but-2-enonyl)aminobenzo[*b*]furan (16a) Procedure for 16b–16e

Crotonyl chloride (0.29 ml, 3.04 mmol) was added to a solution of **9b** (0.7 g, 2.76 mmol) in anhydrous THF (20 ml) at 25 °C with stirring. The mixture was stirred at 54 °C for 3 h. The solvent was evaporated, leaving a residue. The residue was dissolved in ethyl acetate. This solution was washed with 5% NaOH aqueous solution and brine, then dried. Concentration of the solution gave a powder which was recrystallized from ethyl acetate to afford **16a** (0.61 g) as pale yellow needles.

### 2-Acetyl-5-bromo-3-(3-phenylprop-2-enonyl)aminobenzo[*b*]furan (16f) General procedure for 16g–16j

A mixture of *trans*-cinnamic acid (1.16 ml, 7.88 mmol) and thionyl chloride (5 ml) was heated at 55 °C for 3 h. The mixture was concentrated *in vacuo* to give a yellow oil. The oil was added to a solution of **9b** (1.0 g, 3.94 mmol) in anhydrous THF (30 ml). The mixture was stirred at 64 °C for 4 h and worked up according to the procedure mentioned above. The product was recrystallized from ethyl acetate to give **16f** (1.0 g) as colorless

prisms. The acid (**16k**) was obtained according to the usual manner from **16j**.

### (2-Acetylbenzo[*b*]furan-7-yloxy)acetic acid ethyl ester (18b) General procedure for 18a, 18c and 18f

A mixture of **17** (5.7 g, 34.1 mmol), $K_2CO_3$ (13.0 g, 93.9 mmol) and ethyl bromoacetate (3.8 ml, 34.1 mmol) in dry acetone (120 ml) was stirred at 54 °C for 2 h. After an insoluble portion was filtered off, the filtrate was dried. Ethyl acetate solution of the resulting residue was washed with 5% NaOH aqueous solution and brine, and dried. Concentration of the solution gave **18b** (5.1 g) as pale yellow needles.

### 2-Acetyl-7-methoxybenzo[*b*]furan-4-sulfonic acid ethylamide (18d) Procedure for 18e from 18b

The fine powder **18a** (3.0 g, 15.7 mmol) was carefully added to chlorosulfonic acid (8.4 ml, 0.13 mol) in portions at 26–30 °C over 1 h under vigorous stirring. After the mixture was stirred at the same temperature for 5 min, it was poured into ice water and extracted with ethyl acetate. The organic layer was washed with brine, then dried, and evaporated quickly to give the intermediate sulfonyl chloride (4.7 g) as a yellow solid, $R_f$ = 0.43, hexane–ethyl acetate (1 : 1), which was suitable for use in subsequent reactions. To a solution of ethylamine hydrochloride (1.7 g, 20.5 mmol) and triethylamine (5.1 ml, 36.3 mmol) in $CHCl_3$ (10 ml), was added dropwise the sulfonyl chloride in dry $CHCl_3$ (50 ml) at 27–30 °C with stirring. After the mixture was stirred at 30 °C for 0.5 h, it was poured into ice water and made acid with 5% HCl solution, then extracted with $CHCl_3$. The extract was washed with brine, then dried. The solvent was evaporated off, giving a residue which was recrystallized from methanol to give **18d** (3.1 g) as yellow needles.

### 2-Acetyl-7-methoxy-4-nitrobenzo[*b*]furan (19)

To a solution of **18a** (10.0 g, 53.0 mmol) in acetic anhydride (200 ml) was added $HNO_3$ (16.0 ml, 0.36 mmol) at 6 °C. The reaction mixture was stirred at 26 °C for 1 h, and poured into ice water to give **19** (9.7 g) as pale yellow needles.

### 2-Acetyl-4-amino-7-methoxybenzo[*b*]furan (20)

A mixture of **19** (0.21 g, 0.85 mmol) and 20% titanium trichloride solution (3.9 ml, 5.1 mmol) was evacuated to approximately 87 mmHg and stirred at 26 °C for 2.5 h. The mixture was poured into ice water and made alkaline with 10% $NH_4OH$ and extracted with $CHCl_3$. The extract was washed with brine and dried. The solvent was evaporated off to give **20** (77 mg) as pale brown needles.

### 2-Acetyl-7-methoxy-4-(5-methylisoxazole-4-carbonyl)-aminobenzo[*b*]furan (21)

To a solution of **20** (2.4 g, 8.5 mmol) in acetonitrile (15 ml), was added 5-methylisoxazole-4-carboxylic acid chloride (1.4 g, 11.0 mmol) in acetonitrile (5 ml) dropwise at 7 °C. The mixture was stirred at 20 °C for 1.5 h. After work up, the residue was recrystallized from benzene to give **21** (0.45 g) as pale brown prisms.

### 2-Acetyl-4-(2-cyano-3-hydroxybut-2-enonyl)amino-7-methoxybenzo[*b*]furan (22)

A mixture of **21** (0.20 g, 0.63 mmol) and $Et_3N$ (0.89 ml, 6.3 mmol) in anhydrous THF (30 ml) was stirred at 72 °C for 1 h. After work up, the powder was recrystallized from methanol to give **22** (0.16 g) as pale yellow needles.

### 7-Ethoxycarbonylmethyloxy-2-(1-hydroxyimino)ethylbenzo[*b*]-furan (23a) General procedure for 23b–23f

To a solution of **18b** (10.0 g, 38.2 mmol) in methanol (100 ml), was added pyridine (3.7 ml, 46.0 mmol) and hydroxylamine hydrochloride (3.2 g, 46.0 mmol). The reaction mixture was heated at 65 °C for 1 h, and then the solvent was evaporated. A solution of the residue in ethyl acetate was washed with brine, then dried, and evaporated to give a yellow powder. The powder was recrystallized from ethyl acetate to give **23a** (6.8 g) as yellow prisms.

### 2-(1-Aminoethyl)-7-ethoxycarbonylmethyloxybenzo[*b*]furan (24a) General procedure for 24b and 24d

To a mixture of **23a** (1.5 g, 5.4 mmol) and 37% HCl solution (2.0 ml) in ethanol (150 ml) was hydrogenated over 10% Pd–C (0.20 g) at 26 °C for 2 h under 5 atmospheres of hydrogen. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was poured into ice water and made acid with 5% HCl solution and washed with $CHCl_3$. The acidic aqueous solution was made alkaline with 10% NaOH aqueous solution and extracted with $CHCl_3$. The extract was washed with brine and dried. The solvent was evaporated off to give **24a** (1.1 g) as yellow oil, $R_f$ = 0.70, $CHCl_3$–ethyl acetate (5 : 2).

### [2-[1-[(5-Methylisoxazole-4-carbonyl)amino]ethyl]benzo[*b*]-furan-7-yloxy]acetic acid (25a)

5-Methylisoxazole-4-carboxylic acid chloride (0.50 g, 4.6 mmol) was added to a solution of **24a** (2.0 g, 7.6 mmol) in anhydrous THF (50 ml) at 32 °C. After the mixture was stirred at 63 °C for 1 h, the solvent was evaporated. The residue was poured into ice water and extracted with ethyl acetate. The extract was washed with 5% HCl solution and brine, then dried. Concentration of the extract gave the ester as yellow oil 1.1 g, $R_f$ = 0.72, ethyl acetate—methanol (5 : 1). The oil (ester) was treated with 37% HCl solution (0.10 ml) in acetonitrile (30 ml) at 25 °C for 2 h, and then the solvent was evaporated. The residue was poured into ice water and extracted with ethyl acetate, then washed with brine, and dried. Concentration of the extract gave an oil. The crude oil was purified on a silica gel column [$CHCl_3$–ethyl acetate (10 : 1)] to give **25a** (0.20 g) as a colorless powder.

### 4-[2-[1-[(5-Methylisoxazole-4-carbonyl)amino]ethyl]benzo[*b*]-furan-7-yloxy)]butyric acid ethyl ester (25b) General procedure for 25c and 25d

To a solution of **24b** (3.3 g, 11.3 mmol) in anhydrous THF (15 ml) was added 5-methylisoxazole-4-carboxylic acid chloride (1.5 g, 13.6 mmol) in anhydrous THF (15 ml) at 32 °C. The mixture was heated 65 °C for 1 h. After work up, the powder was recrystallized from ethanol to give **25b** (3.0 g) as pale yellow needles.

### [2-[1-(2-Cyano-3-hydroxybut-2-enonyl)amino]ethylbenzo[*b*]-furan-7-yloxy]acetic acid (26a) Procedure for 26b from 25b

To a solution of **25a** (0.30 g, 0.87 mmol) in ethanol (8 ml) was added 10% NaOH aqueous solution (12.0 ml). After the mixture was stirred for 5 min at 25 °C, the solvent was evaporated. The residue was poured into ice water and extracted with ethyl acetate. The extract was washed with 5% HCl solution and brine, then dried. Concentration of the extract gave **26a** (0.19 g) as colorless prisms.

### 4-[2-[1-[(2-Cyano-3-hydroxybut-2-enonyl)amino]ethyl]-7-methoxybenzo[*b*]furanyl]-*N*-ethylsulfonamide (26c) Procedure for 26d

To a solution of **25c** (0.50 g, 1.2 mmol) in anhydrous THF (100 ml) was added $Et_3N$ (1.7 ml, 12.2 mmol). The reaction mixture was heated at 70 °C for 12 h, and then the solvent was evaporated. The residue was usually treated to afford a pale yellow oil. The oil was purified on silica gel column chromatography [$CHCl_3$–ethyl acetate (10 : 1)] and recrystallized from acetonitrile to give **26c** (0.20 g) as colorless prisms.

**4-[2-[1-(2-Cyano-3-hydroxybut-2-enonylamino)ethyl]-4-ethylsulfamoylbenzo[*b*]furan-7-yloxy]butyric acid (26e)**

To a solution of **26d** (1.1 g, 2.2 mmol) in ethanol (60 ml) was added 10% NaOH aqueous solution (7.0 ml). The mixture was heated at 60 °C for 2.5 h, and then the solvent was evaporated. The residue was treated according the usual manner to give a yellow powder. The powder was recrystallized from ethanol to give **26e** (0.46 g) as a colorless powder.

**2-[1-(But-2-enonyl)aminoethyl]-7-methoxybenzo[*b*]furan (27a) Procedure for 27b from 23f**

Catalytic reduction of **23e** (1.5 g, 7.3 mmol) in a similar manner as for **23a** gave amine (**24e**, 0.61 g) as a yellow oil. Crotonyl chloride (0.5 ml, 4.8 mmol) was added to a solution of the oil in anhydrous THF (30 ml). After stirring at 25 °C for 6 h, the mixture was worked up in the usual way to afford a yellow powder which was recrystallized from ethyl acetate to give **27a** (0.41 g) as pale yellow prisms.

**7-Methoxy-2-[1-[(3-phenylprop-2-enonyl)]aminoethyl]benzo[*b*]-furan (27c) Procedure for 27d from 23f**

Catalytic reduction of **23e** (0.8 g, 3.9 mmol) in a similar manner as for **23a** gave the crude amine (**24e**) as a yellow oil. *trans*-Cinnamic acid chloride [prepared by treatment of *trans*-cinnamic acid (0.76 g, 4.64 mmol) with $SOCl_2$ (5 ml, 4.8 mmol)] was added to a solution of the oil in anhydrous THF (30 ml). After stirring at 65 °C for 3 h, work up in the usual way gave a yellow oil which was purified on silica gel column chromatography [hexane–ethyl acetate (10 : 1)] to give **27c** (0.73 g) as colorless prisms.

**Calcium release experiments**

Calcium mobilization assays were carried out using stably transfected HEK 293T-cysLT2R or CHO-cysLT1R cells loaded with Fura 2-AM fluorescent indicator dye (Molecular Probes, Eugene, OR) in the fluorescent imaging plate reader system (Hamamatsu Photonics, Japan). Briefly, the cells were seeded in microtiter plate at $1.0 \times 10^5$ cells/well (HEK 293T cell) or $0.4 \times 10^5$ cells/well (CHO cell) and incubated at 37 °C for 24 h (5% $CO_2$). The cells were loaded with 7.5 μM Fura 2-AM in Dulbecco's modified Eagle's medium (HEK 293T cell) or F-12 medium (CHO cell) containing 10% fetal bovine serum, 20 mM HEPES (pH 7.4) and 2.5 mM probenecid at 37 °C for 30 min. The cells were washed with Hanks' balanced salt solution containing 20 mM HEPES (pH 7.4). $LTD_4$ (100 nM) were added the cells, and fluorescence values were taken at 3-second intervals for 90 seconds. Test compounds were added 1 min before $LTD_4$ (100 nM) stimulation, and the $LTD_4$ response was obtained by calculating peak fluorescence values.

**Radioligand binding studies**

Stably transfected HEK 293T-cysLT2R cells were grown and harvested, and the membranes were prepared according to the procedure reported by Obata *et al.*[22] For competition binding studies, the membranes (125 μg of total membrane protein) were incubated with 1.0 nM [$^3$H]$LTD_4$ (Perking Elmer, Boston, MA) and various concentrations of test compounds in assay buffer (pH 7.4) containing 10 mM HEPES, 20 mM $CaCl_2$ and 20 mM L-penicillamine at room temperature for 1 h. The reactions were stopped by ice-cold wash buffer (pH 7.4) containing 10 mM HEPES and 0.01% bovine serum albumin, and the bound ligand was captured on Whatman GF/B filters. Radioactivity was quantitated by liquid scintillation counter. Non-specific binding was determined in the presence of 1 μM unlabelled $LTD_4$.

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