Preparation of 2-, 3-, 4- and 7-(2-alkylcarbamoyl-1-alkylvinyl)benzo[*b*]furans and their BLT_1 and/or BLT_2 inhibitory activities†‡

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Received 17th July 2007, Accepted 26th October 2007
First published as an Advance Article on the web 29th November 2007
DOI: 10.1039/b710935k

Several 2-alkylcarbamoyl-1-alkylvinylbenzo[*b*]furans were designed to find a selective leukotriene B_4 (LTB_4) receptor antagonist. 2-(2-Alkylcarbamoyl-1-alkylvinyl)benzo[*b*]furans having a substituent group at the 3-position, 4-(2-alkylcarbamoyl-1-methylvinyl)benzo[*b*]furans having a substituent group at the 3-position, and 7-(2-alkylcarbamoyl-1-methylvinyl)benzo[*b*]furans and 3-(2-alkylcarbamoyl-1-alkylvinyl)benzo[*b*]furans were prepared and evaluated for LTB_4 receptor (BLT_1 and BLT_2) inhibitory activities. (*E*)-3-Amino-4-[2-[2-(3,4-dimethoxyphenyl)ethylcarbamoyl]-1-methylvinyl]benzo[*b*]furan ((***E*)-17c**) showed potent and selective inhibitory activity for BLT_2. On the other hand, (*E*)-7-(2-diethylcarbamoyl-1-methylvinyl)benzo[*b*]furan ((***E*)-27a**) showed potent inhibitory activity for both BLT_1 and BLT_2.

Introduction

Leukotriene B_4 (LTB_4), a dihydroxy fatty acid formed from arachidonic acid by the 5-lipoxygenase pathway, is a potent chemoattractant of leukocytes, which are involved in various inflammatory diseases. The LTB_4 receptor is a target for anti-inflammatory drugs, and many antagonists of it have been developed and are being evaluated but none have yet been approved for clinical use.[1]

Recently, two G-protein-coupled receptors for LTB_4 have been identified.[2–6] BLT_1 is a high affinity receptor exclusively expressed in leukocytes, while BLT_2 is a low affinity receptor expressed more extensively. Current studies on LTB_4 receptors (BLT_1, BLT_2) suggest the possibility of new clinical drugs being developed for the treatment of asthma,[7–9] pancreatic cancer,[10,11] arteriosclerosis[12,13] and rheumatoid arthritis.[14–16]

We previously reported preparation of various (*E*)-2- and 4-(2-alkylcarbamoyl-1-methylvinyl)benzo[*b*]furans (type **A** and **B** compounds) (Fig. 1) and inhibitory activities of their selective LTB_4 receptors (BLT_1, BLT_2).[17,18] The study revealed a significant relationship between the conformation of the (*E*)-2-alkylcarbamoyl-1-methylvinyl group and BLT_1 and/or BLT_2 inhibitory activity. The type **A** compound, in which the (*E*)-2-(2-alkylcarbamoyl-1-methylvinyl) group lies on nearly the same plane as the benzo[*b*]furan ring, shows selective BLT_2 inhibitory activity. On the other hand, the type **B** compound having some torsion angle (*ca.* 46°) between the (*E*)-4-(2-alkylcarbamoyl-1-methylvinyl) group and the benzo[*b*]furan ring shows both BLT_1 and BLT_2 inhibitory activities. These findings encouraged us to prepare several new series of 2-alkylcarbamoyl-1-alkylvinylbenzo[*b*]furans to find more potent and selective BLT_1 and/or BLT_2 inhibitors.

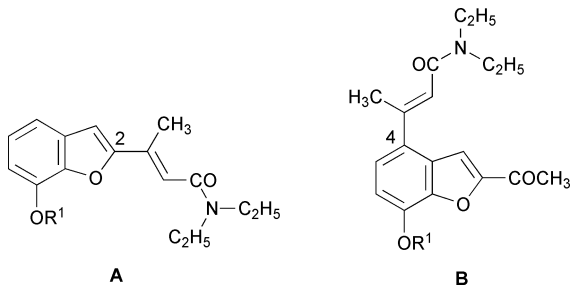

Fig. 1

We designed type **C**, **D**, **E**, **F** and **G** compounds (Fig. 2) on the basis of lead compounds **A** and **B**. Type **C** and **E** compounds have a substituent group neighboring the 2-alkylcarbamoylvinyl group. This neighboring group may force the 2-alkylcarbamoylvinyl group into a twisted steric position. On the type **D** compound, the methyl group on the 2-alkylcarbamoyl-1-methylvinyl group of type **A** compound was replaced with a hydrogen atom or a phenyl group. Type **F** and **G** compounds have the 2-alkylcarbamoyl-1-methylvinyl group at the 3- and 7-positions, respectively.

We describe here the preparation of the designed compounds and their inhibitory activities for BLT_1 and/or BLT_2.

Results and discussion

Chemistry

Preparation of type C compound. Preparations of the starting materials (**3**, **7**) used to prepare the type **C**, **D**, **F** and **G** compounds are shown in Scheme 1 and 2.

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† Electronic supplementary information (ESI) available: Physical data and yields of compounds **2**, **3**, **5–15**, **17–21** and **23–31**. See DOI: 10.1039/b710935k

‡ CCDC reference numbers 662142 and 664905. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b710935k

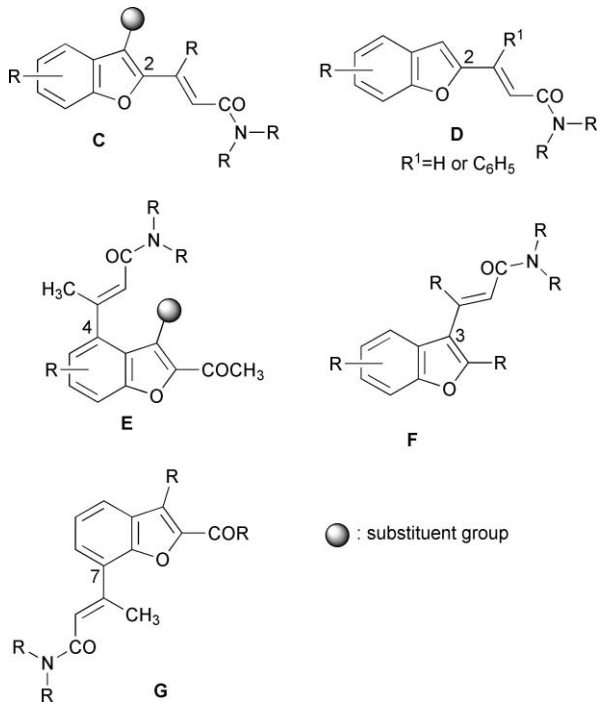
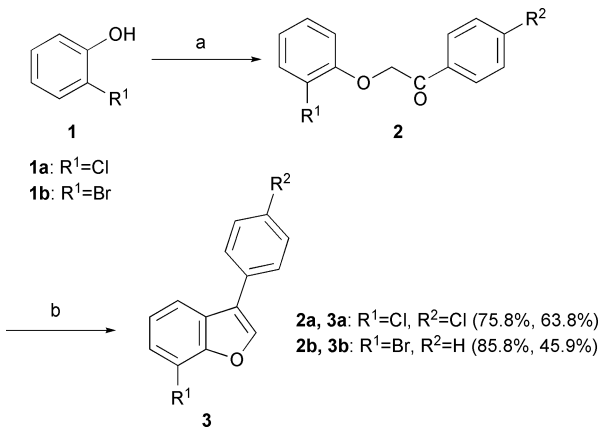


Fig. 2



Scheme 1 (a) $BrCH_2COC_6H_4$(4-H or Cl), K_2CO_3, acetone; (b) PPA.

Alkylation of phenols (**1a**, **1b**) by using phenacyl bromides afforded **2a** and **2b**, which were converted to 3-phenylbenzo[*b*]furans (**3a**, **3b**) by heating with polyphosphoric acid (Scheme 1).[19,20]

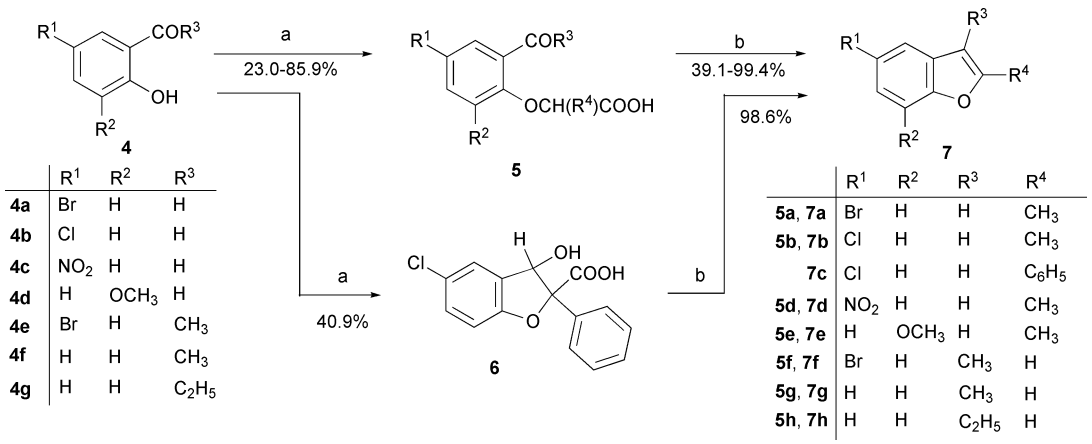
Several 2- or 3-alkylbenzo[*b*]furans (**7**) were prepared from the corresponding 2-acylphenols (**4**) according to the procedure reported by Brady *et al.*[21,22] Salicylaldehydes (**4a–4d**) were treated with ethyl 2-bromopropionate to give the corresponding *O*-alkyl compounds, which were hydrolyzed to carboxylic acids (**5a**, **5b**, **5d**, **5e**). On the other hand, a reaction of **4b** with ethyl 2-bromophenylacetate afforded 2,3-dihydro-3-hydroxybenzo[*b*]-furan (**6**). Ring closure reaction of compounds (**5a**, **5b**, **5d**, **5e**) with sodium acetate and acetic anhydride gave 2-alkylbenzo[*b*]furans (**7a**, **7b**, **7d**, **7e**). 2,3-Dihydroxy-3-hydroxybenzo[*b*]furan (**6**) was converted to 2-phenylbenzo[*b*]furan (**7c**) under the same conditions. Similarly, 3-alkylbenzo[*b*]furans (**7f–7h**) were prepared starting from 2-acylphenols (**4e–4g**) *via* *O*-alkyl compounds (**5f–5h**) (Scheme 2).

The conformation of the 2-alkylcarbamoyl-1-methylvinyl group of the lead compounds **A** and **B** affected the inhibitory activities of BLT_1 and/or BLT_2.[17,18] Thus, we prepared 3-alkyl-2-[(2-alkylcarbamoyl)-1-alkylvinyl]benzo[*b*]furans (type **C** compound, **9**, **11**) with steric hindrance between the 3-substituent group and the 2-alkylcarbamoylvinyl group at the 2-position (Scheme 3).

Acylation of 3-alkylbenzo[*b*]furans (**3a**, **3b**, **7f**) with acyl chlorides gave 3-alkyl-2-acylbenzo[*b*]furans (**8a–8d**). Treatment of **8** with several *N*-alkyl diethylphosphonoacetamides in the presence of NaH under the Horner–Wadsworth–Emmons (HWE) reaction conditions[23–25] afforded 3-alkyl-2-(2-alkylcarbamoyl-1-alkylvinyl)benzo[*b*]furans ((***E*/*Z***)-**9a–9g**) as a mixture of *E*- and *Z*-isomers. Each predominant *E*-isomer (**9a–9g**) was isolated from the mixture by column chromatography.

E-Isomers ((***E***)-**11a**, **11b**) were selectively prepared from 2-bromobenzo[*b*]furans (**10**) under the Heck reaction conditions.[26,27] Bromination of 3-ethylbenzo[*b*]furan (**7h**) with NBS gave 2-bromo-3-ethylbenzo[*b*]furan (**10**) which was treated with *N*-alkylcrotonamides prepared in our laboratory[17,18] in the presence of palladium acetate, tri-*o*-tolylphosphine and triethylamine to selectively afford (*E*)-2-(2-alkylcarbamoyl-1-methylvinyl)-3-ethylbenzo[*b*]furans (**11a**, **11b**) (Scheme 3).

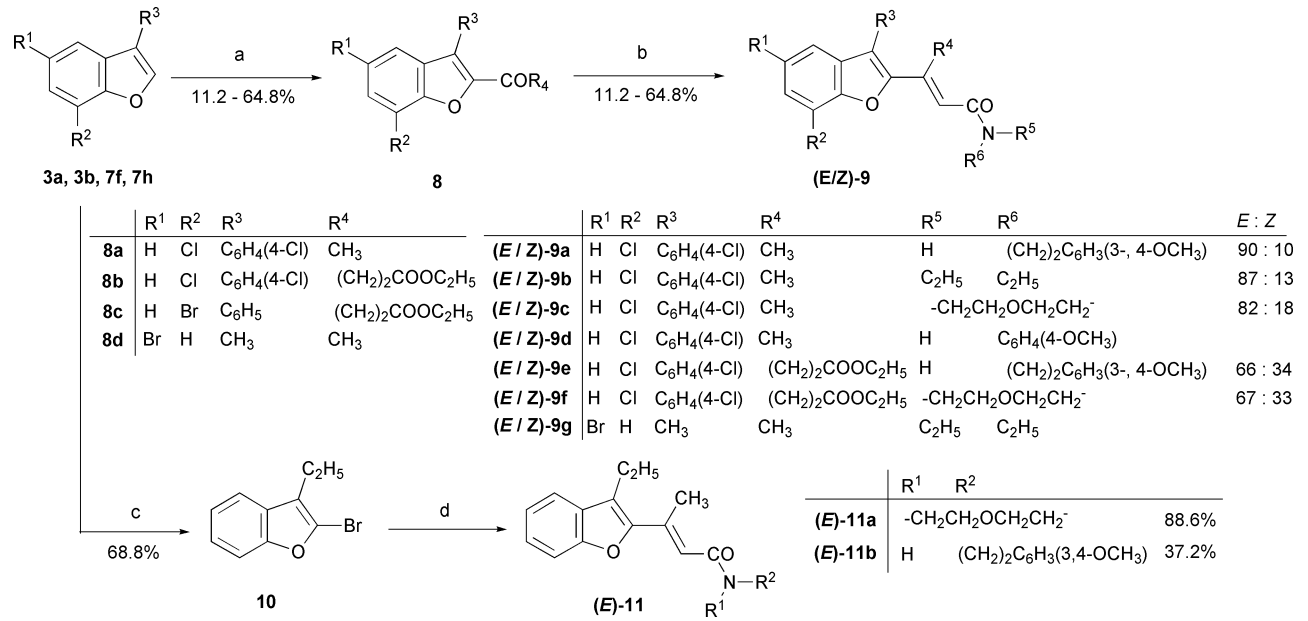
Preparation of type D compound. To examine the effect of the substituent group on the olefinic carbon of the type **A**



	R^1	R^2	R^3
4a	Br	H	H
4b	Cl	H	H
4c	NO_2	H	H
4d	H	OCH_3	H
4e	Br	H	CH_3
4f	H	H	CH_3
4g	H	H	C_2H_5

	R^1	R^2	R^3	R^4
5a, **7a**	Br	H	H	CH_3
5b, **7b**	Cl	H	H	CH_3
7c	Cl	H	H	C_6H_5
5d, **7d**	NO_2	H	H	CH_3
5e, **7e**	H	OCH_3	H	CH_3
5f, **7f**	Br	H	CH_3	H
5g, **7g**	H	H	CH_3	H
5h, **7h**	H	H	C_2H_5	H

Scheme 2 (a) (i) $BrCH(R^4)COOC_2H_5$, K_2CO_3, CH_3CN; (ii) K_2CO_3, H_2O, CH_3OH; (b) CH_3COONa, $(CH_3CO)_2O$.



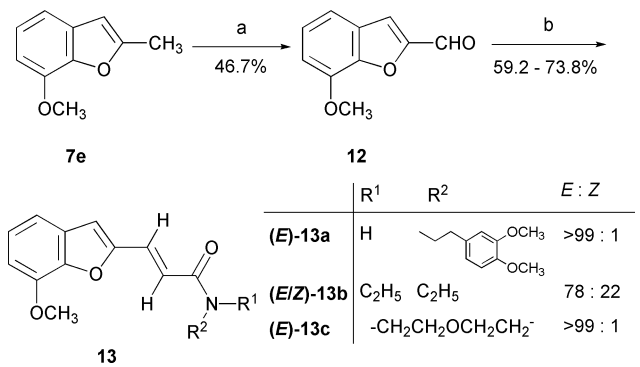
	R^1	R^2	R^3	R^4
8a	H	Cl	C_6H_4(4-Cl)	CH_3
8b	H	Cl	C_6H_4(4-Cl)	$(CH_2)_2COOC_2H_5$
8c	H	Br	C_6H_5	$(CH_2)_2COOC_2H_5$
8d	Br	H	CH_3	CH_3

	R^1	R^2	R^3	R^4	R^5	R^6	*E* : *Z*
(*E* / *Z*)-9a	H	Cl	C_6H_4(4-Cl)	CH_3	H	$(CH_2)_2C_6H_3$(3-, 4-OCH_3)	90 : 10
(*E* / *Z*)-9b	H	Cl	C_6H_4(4-Cl)	CH_3	C_2H_5	C_2H_5	87 : 13
(*E* / *Z*)-9c	H	Cl	C_6H_4(4-Cl)	CH_3	$-CH_2CH_2OCH_2CH_2-$		82 : 18
(*E* / *Z*)-9d	H	Cl	C_6H_4(4-Cl)	CH_3	H	C_6H_4(4-OCH_3)	
(*E* / *Z*)-9e	H	Cl	C_6H_4(4-Cl)	$(CH_2)_2COOC_2H_5$	H	$(CH_2)_2C_6H_3$(3-, 4-OCH_3)	66 : 34
(*E* / *Z*)-9f	H	Cl	C_6H_4(4-Cl)	$(CH_2)_2COOC_2H_5$	$-CH_2CH_2OCH_2CH_2-$		67 : 33
(*E* / *Z*)-9g	Br	H	CH_3	CH_3	C_2H_5	C_2H_5	

	R^1	R^2	
(*E*)-11a	$-CH_2CH_2OCH_2CH_2-$		88.6%
(*E*)-11b	H	$(CH_2)_2C_6H_3$(3,4-OCH_3)	37.2%

Scheme 3 (a) R^4COCl, $AlCl_3$, $CHCl_3$; (b) $(C_2H_5O)_2POCH_2CONR^5R^6$, NaH, THF; (c) NBS, CH_3CN; (d) $CH(CH_3)$=$CHCONR^1R^2$, $Pd(CH_3COO)_2$, P(*o*-tolyl)$_3$, $N(C_2H_5)_3$.

compound on the inhibitory activity for BLT_1 and/or BLT_2, 2-(2-alkylcarbamoylvinyl) compounds (**13**) and 2-(2-alkylcarbamoyl-1-phenylvinyl) compounds (**15**), both type **D** compounds, were prepared (Scheme 4, 5).



	R^1	R^2	*E* : *Z*
(*E*)-13a	H		>99 : 1
(*E*/*Z*)-13b	C_2H_5	C_2H_5	78 : 22
(*E*)-13c	$-CH_2CH_2OCH_2CH_2-$		>99 : 1

Scheme 4 (a) SeO_2, 1,4-dioxane; (b) $(C_2H_5O)_2POCH_2CONR^1R^2$, NaH, THF.

Oxidation of 2-methylbenzo[*b*]furan (**7e**) using SeO_2[28] gave 2-formylbenzo[*b*]furan (**12**) which was treated with *N*-alkyl diethylphosphonoacetamides under the HWE reaction conditions to selectively afford (*E*)-2-(2-alkylcarbamoylvinyl)benzo[*b*]furans ((***E*)-13a–13c**) (Scheme 4).

Ring closure reactions of salicylaldehydes (**4a**, **4d**) with phenacylbromides were achieved to afford 2-benzoylbenzo[*b*]furans (**14a–14f**).[29–31] 2-Benzoyl compounds (**14**) were treated with *N*-alkyl diethylphosphonoacetamides under the HWE reaction conditions to afford a corresponding mixture of *E*- and *Z*-isomers of 2-(2-alkylcarbamoyl-1-phenylvinyl)benzo[*b*]furans ((***E*/*Z*)-15a–15l**), in which the *Z*-isomers (***Z*-15**) were preferentially prepared (Scheme 5). On the contrary, the 2-acetylbenzo[*b*]-furans (**8**) predominantly gave the *E*-isomers (**9**) (see Scheme 3).

Preparation of type E compound. Preparation of 4-(2-alkylcarbamoyl-1-methylvinyl)benzo[*b*]furans (type **E** compounds **17**, **19**) having a substituent group at the 3-position is shown in Scheme 6. 3-Amino-4-bromobenzo[*b*]furans (**16a**, **16b**)[32] were treated with *N*-alkylcrotonamides under Heck reaction conditions to obtain (*E*)-3-amino-4-(2-alkylcarbamoyl-1-methylvinyl)-benzo[*b*]furans ((***E*)-17a–17f**). X-Ray analysis of (***E*)-17c** was examined to check the steric effect of the 3-amino group on conformation of the 2-alkylcarbamoyl-1-methylvinyl group at the 4-position. The stereostructure of (***E*)-17c** was determined by X-ray analysis as shown in Fig. 3.[33] The torsion angle between the 2-[2-(3,4-dimethoxyphenyl)ethylcarbamoyl]-1-methylvinyl group and the benzo[*b*]furan ring of (***E*)-17c** was 87.0°. Introduction of the amino substituent group at the 3-position forced the 2-[2-(3,4-dimethoxyphenyl)ethylcarbamoyl]-1-methylvinyl group at the 4-position to be orthogonal to the benzo[*b*]furan ring plane.

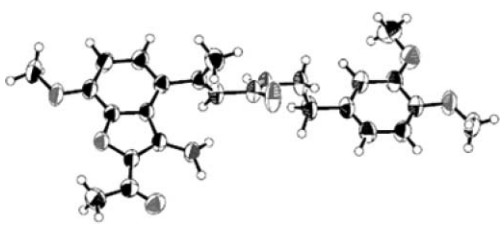
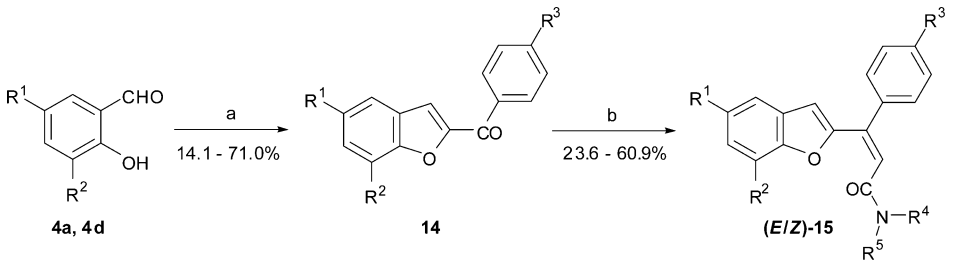


Fig. 3 X-Ray structures of (*E*)-**17c**.

Acylation of **16** with acyl chlorides gave 3-acylamino-4-bromobenzo[*b*]furans (**18**). Treatment of **18** with several *N*-alkylcrotonamides under Heck reaction conditions afforded the corresponding (*E*)-3-acylamino-4-(2-alkylcarbamoyl-1-methlvinyl)-benzo[*b*]furans ((***E*)-19a–19j**) (Scheme 6).

Preparation of type F compound. Type **A–E** compounds have a 2-alkylcarbamoyl-1-alkylvinyl group at the 2- and 4-positions.

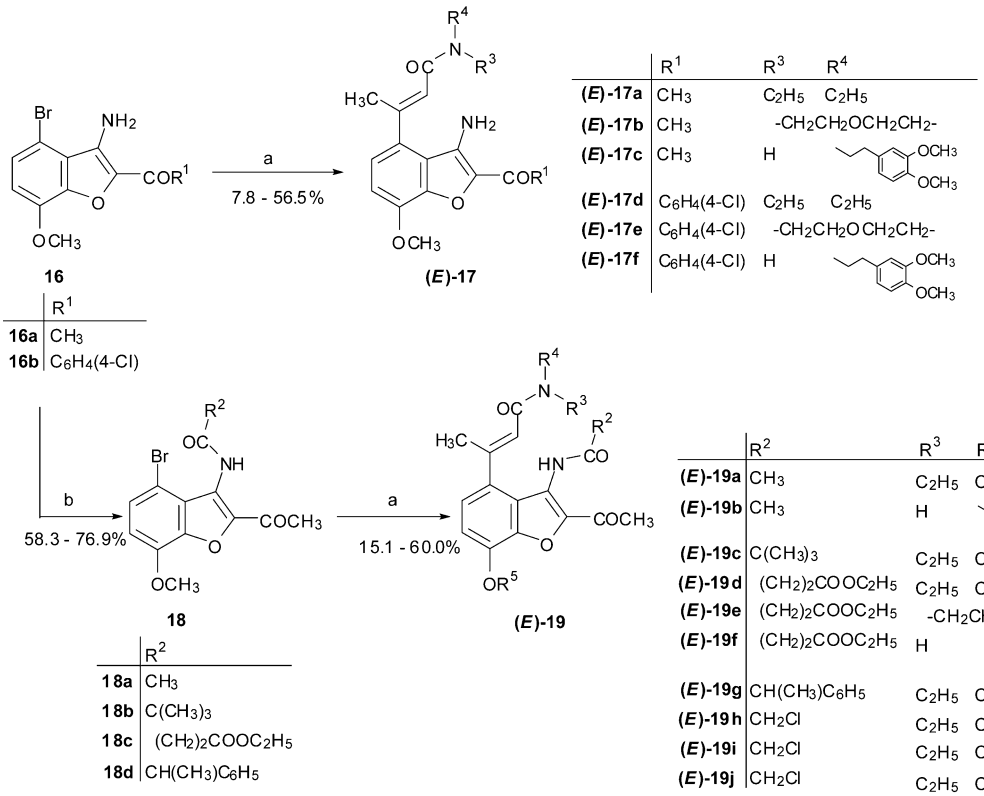


	R^1	R^2
4a	Br	H
4d	H	OCH_3

	R^1	R^2	R^3
14a	Br	H	Cl
14b	Br	H	OCH_3
14c	H	OCH_3	OCH_3
14d	H	OCH_3	Cl (c)
14e	H	OH	Cl
14f	H	$OCH(CH_3)C_6H_5$	Cl (d)

	R^1	R^2	R^3	R^4	R^5	$E:Z$
(E/Z)-15a	Br	H	Cl	H	$C_6H_4(3\text{-}OCH_3)$	25 : 75
(E/Z)-15b	Br	H	Cl	C_2H_5	C_2H_5	20 : 80
(E/Z)-15c	Br	H	Cl	$-CH_2CH_2OCH_2CH_2-$		31 : 69
(E/Z)-15d	Br	H	OCH_3	H	$CH_2CH_2C_6H_4(3\text{-}OCH_3)$	30 : 70
(E/Z)-15e	Br	H	OCH_3	H	$C_6H_4(3\text{-}OCH_3)$	7 : 93
(E/Z)-15f	Br	H	OCH_3	C_2H_5	C_2H_5	1 : >99
(E/Z)-15g	Br	H	OCH_3	$CH_2CH_2OCH_2CH_2$		12 : 88
(E/Z)-15h	H	OCH_3	OCH_3	H	$CH_2CH_2C_6H_4(3\text{-}OCH_3)$	35 : 65
(E/Z)-15i	H	OCH_3	OCH_3	H	$C_6H_3(4\text{-}OCH_3)$	38 : 62
(E/Z)-15j	H	OCH_3	OCH_3	C_2H_5	C_2H_5	21 : 79
(E/Z)-15k	H	OCH_3	OCH_3	$CH_2CH_2OCH_2CH_2$		20 : 80
(E/Z)-15l	H	$OCH(CH_3)C_6H_5$	Cl	C_2H_5	C_2H_5	39 : 61

Scheme 5 (a) $BrCH_2COC_6H_4R^3$, K_2CO_3, CH_3CN; (b) $(C_2H_5O)_2POCH_2CONR^4R^5$, NaH, THF; (c) $C_{12}H_{25}SH$, $AlCl_3$, $CHCl_3$; (d) $BrCH(CH_3)C_6H_5$, K_2CO_3, CH_3CN.



	R^1
16a	CH_3
16b	$C_6H_4(4\text{-}Cl)$

	R^1	R^3	R^4
(E)-17a	CH_3	C_2H_5	C_2H_5
(E)-17b	CH_3	$-CH_2CH_2OCH_2CH_2-$	
(E)-17c	CH_3	H	3,4-dimethoxyphenethyl
(E)-17d	$C_6H_4(4\text{-}Cl)$	C_2H_5	C_2H_5
(E)-17e	$C_6H_4(4\text{-}Cl)$	$-CH_2CH_2OCH_2CH_2-$	
(E)-17f	$C_6H_4(4\text{-}Cl)$	H	3,4-dimethoxyphenethyl

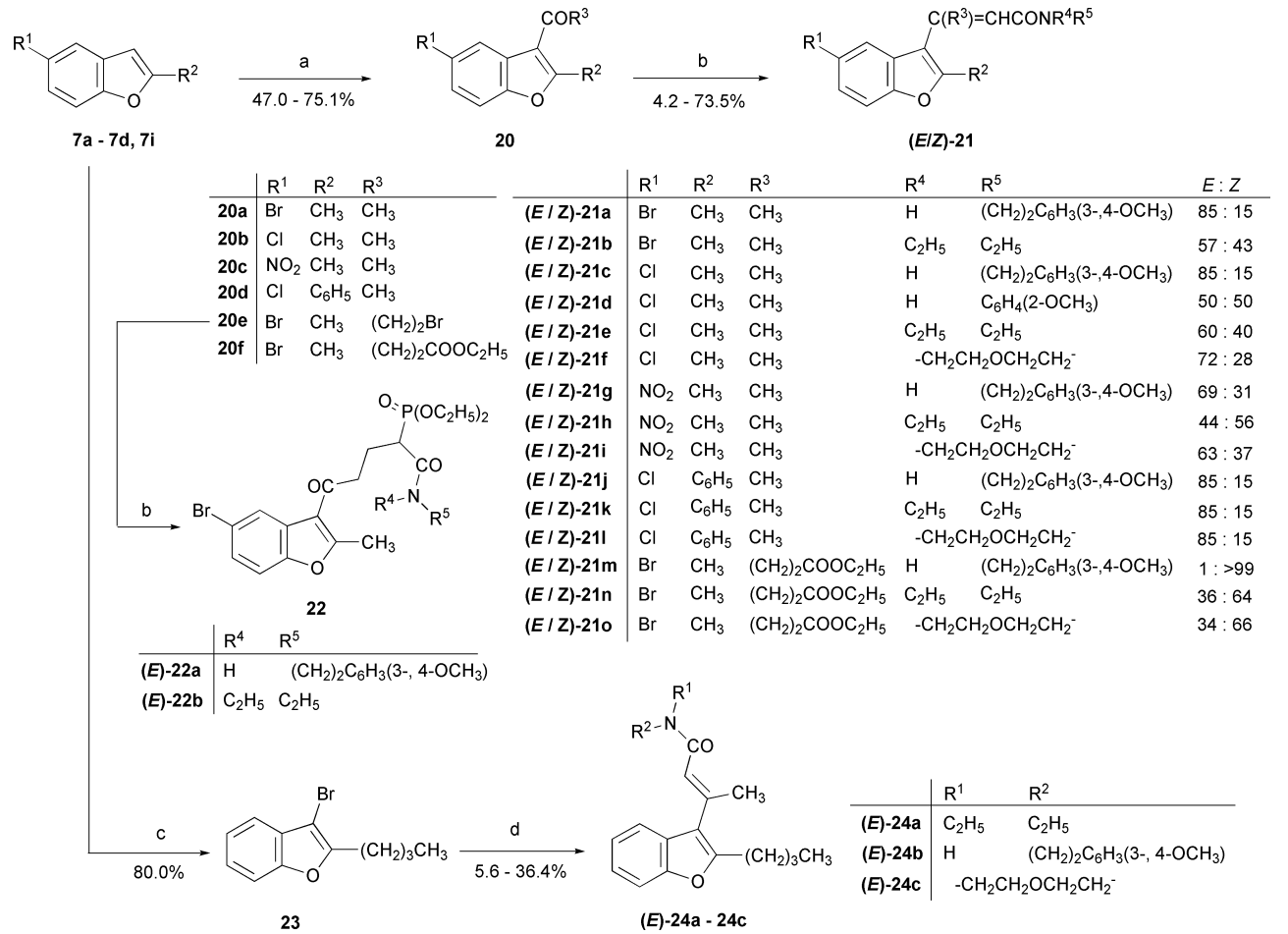
	R^2
18a	CH_3
18b	$C(CH_3)_3$
18c	$(CH_2)_2COOC_2H_5$
18d	$CH(CH_3)C_6H_5$

	R^2	R^3	R^4	R^5
(E)-19a	CH_3	C_2H_5	C_2H_5	CH_3
(E)-19b	CH_3	H	3,4-dimethoxyphenethyl	CH_3
(E)-19c	$C(CH_3)_3$	C_2H_5	C_2H_5	CH_3
(E)-19d	$(CH_2)_2COOC_2H_5$	C_2H_5	C_2H_5	CH_3
(E)-19e	$(CH_2)_2COOC_2H_5$	$-CH_2CH_2OCH_2CH_2-$		CH_3
(E)-19f	$(CH_2)_2COOC_2H_5$	H	3,4-dimethoxyphenethyl	CH_3
(E)-19g	$CH(CH_3)C_6H_5$	C_2H_5	C_2H_5	CH_3
(E)-19h	CH_2Cl	C_2H_5	C_2H_5	CH_3 (c)
(E)-19i	CH_2Cl	C_2H_5	C_2H_5	H
(E)-19j	CH_2Cl	C_2H_5	C_2H_5	$CH(CH_3)C_6H_5$ (d)

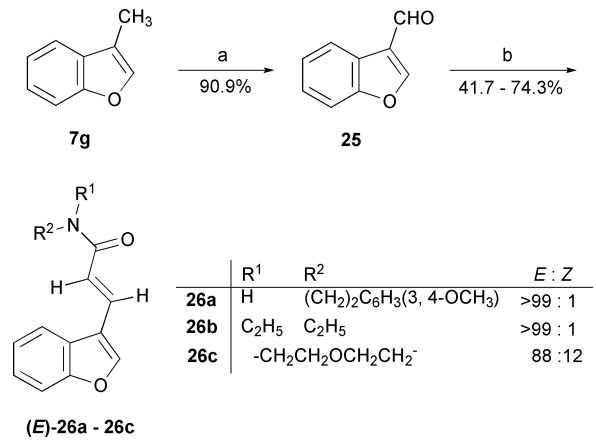
Scheme 6 (a) $CH(CH_3)=CHCONR^3R^4$, $Pd(CH_3COO)_2$, $P(o\text{-tolyl})_3$, $N(C_2H_5)_3$; (b) R^2COCl, THF; (c) $C_{12}H_{25}SH$, $AlCl_3$, $CHCl_3$; (d) $BrCH(CH_3)C_6H_5$, K_2CO_3, CH_3CN.

Preparation of the novel type **F** compound having a 2-alkylcarbamoyl-1-alkylvinyl group at the 3-position was achieved as shown in Scheme 7, 8.

Friedel–Crafts acylation of **7a–7d** afforded 3-aceyl-(**20a–20d**), 3-(3-bromopropionyl)-(**20e**) and 3-(3-ethoxycarbonylpropionyl)-benzo[*b*]furans (**20f**). Treatment of acyl compounds (**20a–20d**,



Scheme 7 (a) R^3COCl, $AlCl_3$, $CHCl_3$; (b) $(C_2H_5O)_2POCH_2CONR^4R^5$, NaH, THF; (c) NBS, CH_3CN; (d) $CH(CH_3)=CHCONR^4R^5$, $Pd(CH_3COO)_2$, P(*o*-tolyl)$_3$, N $(C_2H_5)_3$.



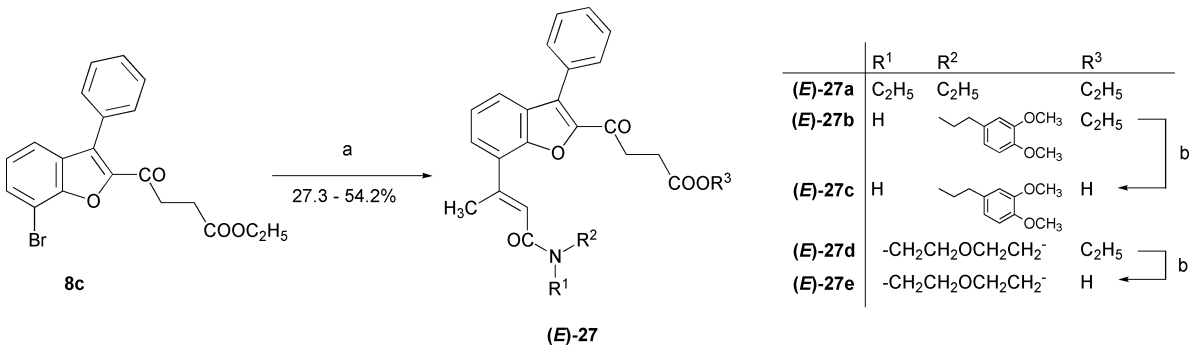
Scheme 8 (a) SeO_2, 1,4-dioxane; (b) $(C_2H_5O)_2POCH_2CONR^1R^2$, NaH, THF.

20f) with *N*-alkyl diethylphosphonoacetamides under HWE reaction conditions afforded a mixture of *E*- and *Z*-isomers of 3-(2-alkylcarbamoyl-1-alkylvinyl)benzo[*b*]furans ((***E*/*Z***)-**21a–21o**). Interestingly, 5-bromo-3-[4-(diethoxyphosphoryl)-4-alkylcarbamoylbutyryl]-2-methylbenzo[*b*]furans (**22a**, **22b**) were obtained by treatment of 3-(3-bromopropionyl)benzo[*b*]furan (**20e**) with *N*-alkyl diethylphosphonoacetamides under similar conditions (see Scheme 7). Alkyl bromide (**20e**) reacted with the active methylene group of *N*-alkyl diethylphosphonoacetamides in the presence of NaH and formed a carbon–carbon bond.[34]

Bromination of 2-*n*-butylbenzo[*b*]furan (**7i**) with NBS gave 3-bromo-2-*n*-butylbenzo[*b*]furan (**23**). The compound (**23**) was treated with *N*-alkylcrotonamides under Heck reaction conditions to selectively afford (*E*)-3-(2-alkylcarbamoyl-1-methylvinyl)-2-*n*-butylbenzo[*b*]furans ((***E*-24a–24c**) (Scheme 7).

Oxidation of 3-methylbenzo[*b*]furan (**7g**) using SeO_2 afforded 3-formylbenzofurane (**25**). Treatment of **25** with several *N*-alkyl diethylphosphonoacetamides under HWE reaction conditions afforded the corresponding (*E*)-3-(2-alkylcarbamoylvinyl)benzo-[*b*]furans ((***E*-26a–26c**), similar to the preparation of **13**.

Preparation of type G compound. The novel type **G** compounds (**27**, **31**) having a 2-alkylcarbamoyl-1-methylvinyl group at the 7-position were prepared as follows. Treatment of 7-bromo-2-(3-ethoxycarbonylpropionyl)-3-phenylbenzo[*b*]furan (**8c**) with *N*-alkylcrotonamides under Heck reaction conditions selectively afforded the corresponding (*E*)-7-(2-alkylcarbamoyl-1-methylvinyl)-3-phenylbenzo[*b*]furans ((***E*-27a**, **27b**, **27d**) (Scheme 9).



	R^1	R^2	R^3
(*E*)-27a	C_2H_5	C_2H_5	C_2H_5
(*E*)-27b	H	3,4-dimethoxyphenylethyl	C_2H_5
(*E*)-27c	H	3,4-dimethoxyphenylethyl	H
(*E*)-27d	$-CH_2CH_2OCH_2CH_2-$		C_2H_5
(*E*)-27e	$-CH_2CH_2OCH_2CH_2-$		H

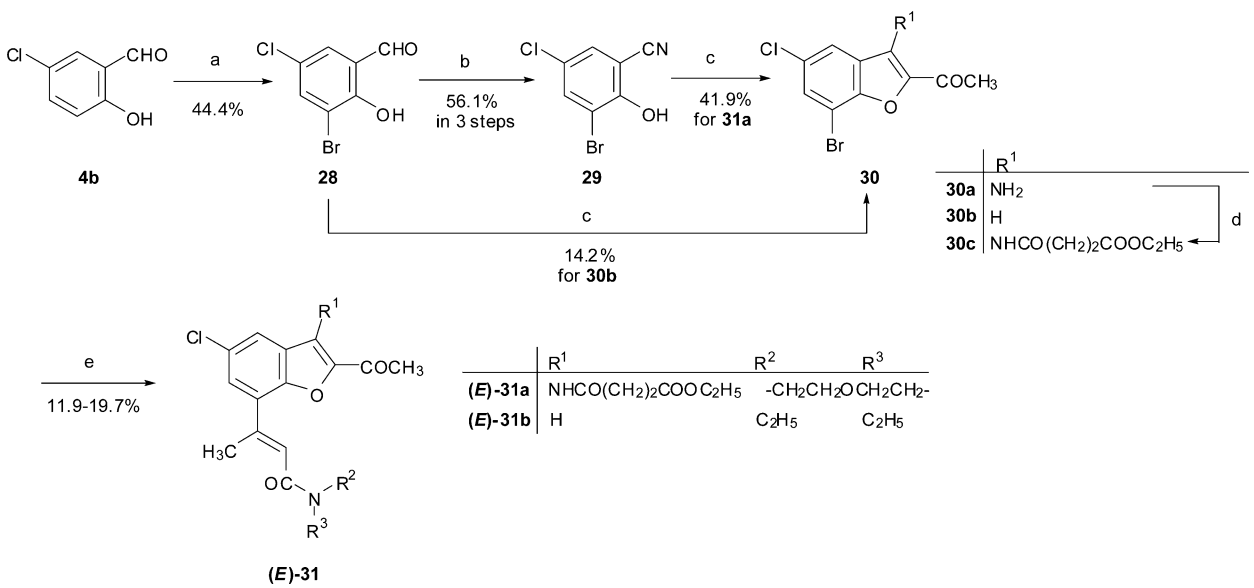
Scheme 9 (a) $CH(CH_3)$=$CHCONR^1R^2$, $Pd(CH_3COO)_2$, P(*o*-tolyl), $(C_2H_5)_3N$; (b) NaOH, H_2O, CH_3OH.

Bromonation of 5-chlorosalicylaldehyde (**4b**) gave 3-bromo-5-chloro-2-hydroxybenzaldehyde (**28**) which was converted to 3-bromo-5-chloro-2-hydroxybenzonitrile (**29**).[35,36] Reaction of **29** with chloroacetone afforded 3-aminobenzo[*b*]furan (**30a**) which was treated with ethyl succinyl chloride to give 2-acetyl-7-bromo-3-ethoxycarbonylpropionylaminobenzo[*b*]furan (**30c**). Reaction of **28** with chloroacetone afforded 3-acetylbenzo[*b*]furan (**30b**). Treatment of **30b** and **30c** with *N*-alkylcrotonamides under Heck reaction conditions afforded the corresponding (*E*)-7-(2-alkylcarbamoyl-1-methylvinyl)benzo[*b*]furans ((***E*)-31a**, **31b**), respectively (Scheme 10).

Biological activity

The compounds prepared were evaluated for LTB_4 receptor inhibitory activity by measurement of the inhibition of calcium mobilization in both CHO cells overexpressing human BLT_1 (BLT_1) and human BLT_2 (BLT_2) at the concentration of 10 μM.[2,4,17,18]

We checked the effectiveness of introducing a substituent group at the 3-position of the 4-(2-alkylcarbamoylvinyl-1-methylvinyl)benzo[*b*]furans for BLT_1 and/or BLT_2 inhibitory activities (Table 1, type **E** compound). 4-[2-[2-(3,4-Dimethoxyphenyl)ethylcarbamoyl]-1-methylvinyl]benzo[*b*]furan ((***E*)-36**,[18] type **A** compound) having no substituent group at the 3-position showed only weak inhibitory activities (BLT_1, 10.8% inhibition; BLT_2, 29.7% inhibition). Interestingly, 3-amino-4-[2-[2-(3,4-dimethoxyphenyl)ethylcarbamoyl] - 1 - methylvinyl]benzo[*b*]furan ((***E*)-17c**) showed potent activity and 12-fold selectivity for BLT_2 over that for BLT_1 (BLT_1, 7.4% inhibition; BLT_2, 92.6% inhibition). The torsion angle of (***E*)-17c** was 87.0° on the basis of the X-ray analysis as described above. We previously reported that the 3-unsubstitued-4-(2-alkylcarbamoyl-1-methylvinyl) compound (type **B** compound, (***E*)-35**, **-36**[18]) had the torsion angle (*ca.* 46°) between the 2-alkylcarbamoyl-1-methylvinyl group and the benzo[*b*]furan ring plane. The torsion angle of (***E*)-17c** was larger than that of the type **B** compounds. Introduction of the substituent group at the 3-position forced the 2-[2-(3,4-dimethoxyphenyl)ethylcarbamoyl]-1-methylvinyl group at the 4-position to twist more. The compound ((***E*)-17c**) having the larger torsion angle (87.0°) inhibited BLT_2 selectively; on the other hand, the type **B** compounds bearing the smaller torsion angle (*ca.* 46°) inhibited both BLT_1 and BLT_2.



	R^1	R^2	R^3
30a	NH_2		
30b	H		
30c	$NHCO(CH_2)_2COOC_2H_5$		

	R^1	R^2	R^3
(*E*)-31a	$NHCO(CH_2)_2COOC_2H_5$	$-CH_2CH_2OCH_2CH_2-$	
(*E*)-31b	H	C_2H_5	C_2H_5

Scheme 10 (a) NBS, $CHCl_3$; (b) (i) $HONH_2$·HCl, pyridine, CH_3OH; (ii) CH_3COONa, $(CH_3CO)_2O$; (iii) K_2CO_3, H_2O, CH_3OH; (c) $ClCH_2COCH_3$, K_2CO_3, CH_3CN; (d) $ClCOCH_2CH_2COOC_2H_5$, THF; (e) $CH(CH_3)$=$CHCONR^2R^3$, $Pd(CH_3COO)_2$, P(*o*-tolyl), $N(C_2H_5)_3$.

Table 1 Evaluations of 4-[(*E*)-2-alkylcarbamoylvinyl]benzo[*b*]furans ((***E*)-17**, **-19**, **-35**, **-36**) for LTB_4 receptor (BLT_1, BLT_2) inhibitory activity[a]

Compound	Type	R^1	R^2	R^3	R^4	R^5	Inhibition (%)/10 μM		IC_{50}/μM	
							BLT_1	BLT_2	BLT_1	BLT_2
(*E*)-**17a**	**E**	CH_3	—	—	C_2H_5	C_2H_5	N. I.	11.9		
(*E*)-**17b**	**E**	CH_3	—	—	-$(CH_2)_2O(CH_2)_2$-		N. I.	16.1		
(*E*)-**17c**	**E**	CH_3	—	—	H	$(CH_2)_2C_6H_3(3,4\text{-}OCH_3)$	7.4	92.6		
(*E*)-**17d**	**E**	$C_6H_4(4\text{-}Cl)$	—	—	C_2H_5	C_2H_5	15.8	47.3		
(*E*)-**19b**	**E**	—	CH_3	—	H	$(CH_2)_2C_6H_3(3,4\text{-}OCH_3)$	N. I.	3.4		
(*E*)-**19d**	**E**	—	$(CH_2)_2COOC_2H_5$	—	C_2H_5	C_2H_5	4.5	N. I.		
(*E*)-**19e**	**E**	—	$(CH_2)_2COOC_2H_5$	—	-$(CH_2)_2O(CH_2)_2$-		N. I.	N. I.		
(*E*)-**35**[b]	**B**	—	—	$CH(CH_3)C_6H_5$	C_2H_5	C_2H_5	92.6	92.8	0.42	0.48
(*E*)-**36**	**B**	—	—	$CH(CH_3)C_6H_5$	H	$(CH_2)_2C_6H_3(3,4\text{-}OCH_3)$	10.8	29.7		

N. I.: not inhibited. [a] Effect of calcium mobilization by LTB_4 (300 nM) in CHO-hBLT_1 and CHO-hBLT_2 cells, unless otherwise noted. [b] Stimulated by LTB_4 at 100 nM.

(*E*)-7-(2-Alkylcarbamoyl-1-methylvinyl)-2-ethoxycarbonylpropionylbenzo[*b*]furans (type **G** compound, (***E*)-27**, **-31**) were found to be potently active against LTB_4 receptors (Table 2). The 3-ethoxycarbonylpropionyl moiety present in these compounds is effective for displaying the inhibitory activity in our current study.[1,2] The compound ((***E*)-27a**), having a 2-diethylcarbamoyl-1-methylvinyl group at the 7-position, was the most active against both BLT_1 and BLT_2 (BLT_1, 73.7% inhibition, BLT_2, 95.7% inhibition). In contrast, (*E*)-7-[2-[2-(3,4-dimethoxyphenyl)-ethylcarbamoyl]-1-methylvinyl]benzo[*b*]furan ((***E*)-27b**) showed an approximately 6-fold potency for BLT_2 over that for BLT_1 (BLT_1, 14.7% inhibition; BLT_2, 86.3% inhibition). The acidic compound (***E*)-27e** was inactive. The compound (***E*)-31a** having the ethoxycarbonylpropionyl moiety at the 3-position also showed moderate activity. The type **G** compound showed more potent activity for BLT_2 than for BLT_1.

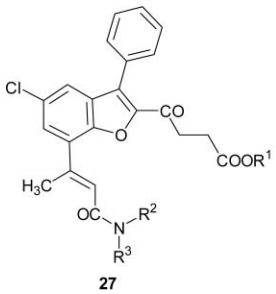
Here let us consider the efficacy of introducing a substituent group at the 3-position of 2-alkylcarbamoylvinylbenzo[*b*]furans for the inhibitory activity for BLT_1 and/or BLT_2 (Table 3). The compound (***E*)-33**,[18] having a 2-(4-methoxyphenylcarbamoyl)-1-methylvinyl group at the 2-position, showed no inhibitory activity. (***E*)-9d**, having the same functional group at the 2-position as (***E*)-33**, was given a phenyl group at the 3-position. (***E*)-9d** did not show any activity either. Unfortunately, introduction of the substituent group at the 3-position did not enhance the inhibitory activity.

Replacement of the methyl group (type **A** compound, (***Z*)-34**[18]) by a phenyl group (type **D** compound, (***Z*)-15b**, **-15c**, **-15f**) did not enhance the inhibitory activity (Table 3). In the preparation of (***E*/*Z*)-15**, *Z*-isomers were preferentially formed and isolated. We previously reported that the *Z*-isomer of type **A** showed lower inhibitory activity than the *E*-isomer (Table 3, (***E*)-34**[18] and **(Z)-34**). The *Z*-isomers of type **D** might also have lower activity than the *E*-isomers, similar to the case of the type **A** compound. Unfortunately, (***E*)-21**, **-24**, **-26** (type **F**), having a 2-alkylcarbamoylvinyl group at the 3-position, prepared in this study were inactive (Table 4).

LTB_4 receptor antagonists have been reported to show anti-pancreatic cancer activity.[10,11] Therefore, we tested representative compounds ((***Z*)-15f**, (***E*)-17a**, (***E*)-21c**, **22b**) and a selective BLT_2 inhibitory compound (**32**)[17,18] for anti-pancreatic cancer activity using a human pancreatic cancer cell line (MiaPaCa-2). However, none of the compounds showed any growth inhibition of MiaPaCa-2 at 10 μM (data not shown). Human pancreatic cancer cells have been reported to express both BLT_1 and BLT_2.[11] Inhibitors of both BLT_1 and BLT_2 will be advantageous for displaying growth inhibitory activity against human pancreatic cancer cells. Both the BLT_1 and BLT_2 inhibitory compounds prepared in our current study are being tested for anti-pancreatic cancer activity.

In summary, selective BLT_2 inhibitors (type **A**) and both BLT_1 and BLT_2 inhibitors (type **B**) showed a significant relationship between the conformation of the (*E*)-2-alkylcarbamoyl-1-methylvinyl group and BLT_1 and/or BLT_2 inhibitory activity in our previous study. In this study, type **C** and **E** compounds, having a substituent group at the 3-position, which may affect the conformation of the 2-alkylcarbamoyl-1-methylvinyl group, were prepared. As expected, 4-(2-alkylcarbamoyl-1-methylvinyl)benzo[*b*]furan (type **E**, (***E*)-17c**), with a substituent group introduced at the 3-position, has a larger torsion angle

Table 2 Evaluations of 7-[(*E*)-2-alkylcarbamoyl-1-methylvinyl]benzo[*b*]furans ((***E*)-27**, **-31**) for LTB_4 receptors (BLT_1, BLT_2) inhibitory activity[a]



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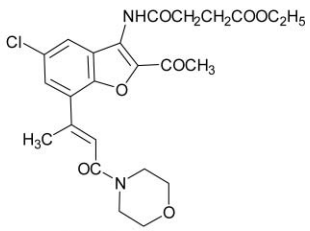
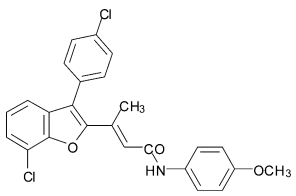


(*E*)-31a

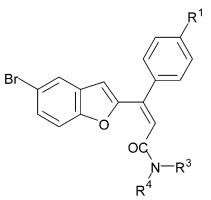
Compound	Type	R^1	R^2	R^3	Inhibition (%)/10 μM BLT_1	Inhibition (%)/10 μM BLT_2	IC_{50}/μM BLT_1	IC_{50}/μM BLT_2
(*E*)-**27a**	**G**	C_2H_5	C_2H_5	C_2H_5	73.7	95.7	7.05	2.54
(*E*)-**27b**	**G**	C_2H_5	H	$(CH_2)_2C_6H_3$(3,4-OCH_3)	14.7	86.3		
(*E*)-**27e**	**G**	H	-$(CH_2)_2O(CH_2)_2$-		N. I.	3.1		
(*E*)-**31a**	**G**				43.9	81.9		

N. I.: not inhibited.[a] Effect of calcium mobilization by LTB_4 (300 nM) in CHO-hBLT_1 and CHO-hBLT_2 cells.

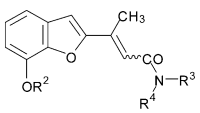
Table 3 Evaluations of 3-[(*E*)-2-alkylcarbamoylvinyl]benzo[*b*]furans ((***E*)-9d**, (***Z*)-15**, (***E*)-32**, **-33**, (***E*/*Z*)-34**) for LTB_4 receptor (BLT_1, BLT_2) inhibitory activity[a]



(*E*)-9d



(*Z*)-15



(*E*)-32, -33, (*E*/*Z*)-34

Compound	Type	R^1	R^2	R^3	R^4	Inhibition (%)/10 μM BLT_1	Inhibition (%)/10 μM BLT_2	IC_{50}/μM BLT_1	IC_{50}/μM BLT_2
(*E*)-**9d**	**C**					6.5	20.8		
(*Z*)-**15b**	**D**	Cl	—	C_2H_5	C_2H_5	7.8	37.3		
(*Z*)-**15c**	**D**	Cl	—	-$(CH_2)_2O(CH_2)_2$-		N. I.	15.4		
(*Z*)-**15f**	**D**	OCH_3	—	C_2H_5	C_2H_5	1.4	18.4		
(*E*)-**32**	**A**	—	$CH(CH_3)C_6H_5$	C_2H_5	C_2H_5	69.9	>100	2.88	0.68
(*E*)-**33**	**A**	—	$O(CH_2)_3COOC_2H_5$	H	C_6H_4(4-OCH_3)	1.7	6.6		
(*E*)-**34**	**A**	—	$O(CH_2)_3COOC_2H_5$	C_2H_5	C_2H_5	21.9	88.1		
(*Z*)-**34**	**A**	—	$O(CH_2)_3COOC_2H_5$	C_2H_5	C_2H_5	9.2	34.4		

N. I.: not inhibited.[a] Effect of calcium mobilization by LTB_4 (300 nM) in CHO-hBLT_1 and CHO-hBLT_2 cells.

(87.0°) than the original compound (type **B**). But, (*E*)-**17c** showed surprising selectivity for BLT_2, unlike the original type **B** compound. The inhibitory potency and selectivity of the type **E** compound might be affected by not only the conformation of the 2-alkylcarbamoyl-1-methyvinyl group, but also the chemical properties of the substituent group at the 3-position.

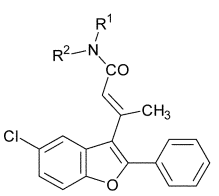
The novel 7-(2-alkylcarbamoyl-1-methylvinyl) compound (type **G**, (*E*)-**27a**) showed potent inhibitory activity for both BLT_1 and BLT_2; as did the 4-(2-alkylcarbamoyl-1-methylvinyl) compound (type **B**, (*E*)-**35**). The 2-alkylcarbamoyl-1-methylvinyl group of both (*E*)-**27a** and (*E*)-**35** are neighboring with the furan ring. This common stereochemical characteristic might exert similar inhibition activity.

Evaluation of the BLT_1 and/or BLT_2 inhibitors prepared in our current study is in progress to find novel anti-pancreatic cancer agents.

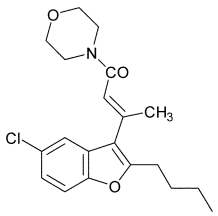
Experimental

All melting points were determined using a Yanako microscopic hot-stage apparatus and are uncorrected. ^{1}H-NMR, ^{13}C-NMR and HMBC, HMQC spectra were obtained with a JEOL JNM-ECP400, JEOL JNM-ECP500 and a JEOL PMX60FT spectrometer with tetramethylsilane as an internal standard. MS spectra (MS, HRMS) were obtained using a JEOL JMS-700 EIMS spectrometer. Elemental analyses (EA) were performed using a

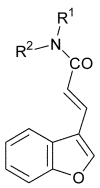
Table 4 Evaluations of 3-[(*E*)-2-alkylcarbamoylvinyl]benzo[*b*]furans ((***E***)-**21**, -**24**, -**26**) for LTB_4 receptor (BLT_1, BLT_2) inhibitory activity[a]



(*E*)-21



(*E*)-24c



(*E*)-26

Compound	Type	R^2	R^3	Inhibition (%)/10 μM	
				BLT_1	BLT_2
(***E***)-**21j**	**F**	H	$(CH_2)_2C_6H_3(3,4\text{-}OCH_3)$	N. I.	44.9
(***E***)-**21k**	**F**	C_2H_5	C_2H_5	N. I	28.8
(***E***)-**24c**	**F**			2.0	8.9
(***E***)-**26b**	**F**	C_2H_5	C_2H_5	N. I.	N. I.
(***E***)-**26c**	**F**	$-(CH_2)_2O(CH_2)_2-$		N. I.	5.7

N. I.: not inhibited.[a] Effect of calcium mobilization by LTB_4 (300 nM) in CHO-hBLT_1 and CHO-hBLT_2 cells.

CHN CORDER MT-3 (Yanako). All organic extracts were dried over anhydrous $MgSO_4$. Column chromatography was carried out on Wakogel C-200. Thin layer chromatography was performed on a Merck silica gel plate (0.5 mm, 60F-254).

2-Acetyl-7-chloro-3-(4-chlorophenyl)benzo[*b*]furan (8a)

General procedure for 8b–8d, 20a–20f. To a suspension of $AlCl_3$ (2.0 g, 15 mmol) in chloroform (15 ml) was added dropwise acetyl chloride (0.20 ml, 2.8 mmol) under a N_2 atmosphere at 5 °C with stirring. A solution of **3a** (1.0 g, 3.8 mmol) in chloroform (10 ml) was added dropwise to the mixture at 5 °C, and the mixture was stirred at the same temperature for 1.5 h. The mixture was poured into ice water, and extracted with ethyl acetate. The organic layer was washed with brine and dried. The solvent was evaporated off. The residue was recrystallized from ethanol to give **8a** (0.45 g, 39.0%) as an orange solid (found: C, 62.83; H, 3.18. $C_{16}H_{10}Cl_2O_2$ requires C, 62.97; H, 3.30%); mp 145.6–146.8 °C; δ_H (60 MHz; $CDCl_3$; Me_4Si) 2.64 (3H, s, C*H*$_3$), 7.25–7.28 (1H, m, 5-H), 7.46–7.54 (6H, m, 4-, 6-H, phenyl H); *m*/*z* (EI) 306 (M + 4, 10.83%), 304 (M + 2, 64.67), 304 (M^+, 100.00).

In a similar manner to that described above, **3a** gave **8b**, **3b** gave **8c**, **7f** gave **8d**, **7a** gave **20a**, **20e**, **20f**, **7b** gave **20b**, **7d** gave **20c**, **7c** gave **20d**.

(*E*)-7-Chloro-3-(4-chlorophenyl)-2-[diethylcarbamoyl-1-methylvinyl]benzo[*b*]furan ((*E*)-9b)

General procedure for 9a, 9c–9g, 21a–21o. To a suspension of NaH (60% in oil, 0.13 g, 3.3 mmol) in THF (10 ml) was added dropwise a solution of *N*,*N*-diethyl diethylphosphonoacetamide (0.74 g, 2.9 mmol) in THF (10 ml) under a N_2 atmosphere at −5 °C with stirring. The solution was stirred at the same temperature until it became clear. A solution of **8a** (0.50 g, 1.6 mmol) in THF (10 ml) was added dropwise to the clear solution at 15 °C, and the mixture was stirred at 20 °C for 5 h. The reaction mixture was then quenched with saturated NH_4Cl solution and extracted with chloroform. The organic layer was washed with brine and dried. The solvent was evaporated off, giving a residue which was recrystallized from ethyl acetate to give (***E***)-**9b** (0.23 g, 34.8%) as yellow needles (found: C, 65.54; H, 5.22; N, 3.48. $C_{22}H_{21}Cl_2NO_2$ requires C, 65.68; H, 5.26; N, 3.48%); mp 136.9–139.2 °C; δ_H (500 MHz; $CDCl_3$; Me_4Si) 1.05 (3H, t, *J* 7.1, CH_2CH_3), 1.15 (3H, t, *J* 7.1, CH_2CH_3), 2.17 (3H, d, *J* 1.4, C=C(C*H*$_3$)), 3.22 (2H, q, *J* 7.3, CH_2CH_3), 3.42 (2H, q, *J* 7.8, CH_2CH_3), 6.60 (1H, q, *J* 1.4, C=C*H*), 7.15 (1H, t, *J* 7.8, 5-H), 7.22 (1H, dd, *J* 7.8 and 0.9, 6-H), 7.33 (1H, dd, *J* 7.6 and 1.2, 4-H), 7.38 (2H, d, *J* 8.7, 2′-, 6′-H or 3′-, 5′-H), 7.46 (2H, d, *J* 8.2, 2′-, 6′-H or 3′-, 5′-H); *m*/*z* (EI) 401 (M^+, 63.46), 329 (100.00).

In a similar manner to that described above, **8a** gave **9a**, **9c**, **9d**, **8b** gave **9e**, **9f**, **8d** gave **9g**, **20a** gave **21a**, **21b**, **20b** gave **21c–21f**, **20c** gave **21g–21i**, **20d** gave **21j–21l**, **20f** gave **21m–21o**.

2-Bromo-3-ethylbenzo[*b*]furan (10)

To a solution of **7h** (1.0 g, 6.9 mmol) in chloroform (20 ml) was added dropwise *N*-bromosuccinimide (1.3 g, 7.5 mmol) in CH_3CN (20 ml) at −8 °C. The reaction mixture was stirred at the same temperature for 1 h. The reaction mixture was poured into water and extracted with chloroform. The organic layer was washed with brine and dried. The solvent was evaporated off, giving a residue which was purified by silica gel column chromatography (hexane) to give **10** (1.1 g, 68.8%) as a colorless oil: δ_H (60 MHz; $CDCl_3$; Me_4Si) 1.24 (3H, t, *J* 7.32, CH_2CH_3), 2.67 (2H, q, *J* 7.32, CH_2CH_3), 7.00–7.60 (4H, m, 4-, 5-, 6-, 7-H); *m*/*z* (EI) 226 (44.12), 224 (M^+, 44.12), 102 (100.00).

Compound (**23**) was prepared from **7i** according to the procedure described for **10**.

(*E*)-2-[2-[2-(3,4-Dimethoxyphenyl)ethylcarbamoyl]-1-methylvinyl]-3-ethylbenzo[*b*]furan ((*E*)-11b)

General procedure for 11a, 24a–24c. A mixture of **10** (0.63 g, 2.8 mmol), (*E*)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-2-butenamide (1.4 g, 5.6 mmol), palladium acetate (30 mg, 0.13 mmol), tri-*o*-tolylphosphine (90 mg, 0.30 mmol) and triethylamine (2.0 ml, 19.8 mmol) was heated at 90–100 °C for 7 h. The mixture was treated with ethyl acetate, and the insoluble portion was removed

by filtration. The filtrate was evaporated to dryness. The residue was poured into ice water, and extracted with ethyl acetate. The organic layer was washed with brine and dried. The solvent was evaporated off. The residue was purified with silica gel column chromatography [hexane–ethyl acetate (10 : 1)] to give a yellow solid. This solid was recrystallized from ethyl acetate to give (***E***)-**11b** (0.51 g, 46.4%) as pale yellow needles (found: C, 72.99; H, 7.06; N, 3.58. $C_{24}H_{27}NO_4$ requires C, 73.26; H, 6.92; N, 3.56%); mp 131.0–135.0 °C; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.29 (3H, t, *J* 7.3, CH_2CH_3), 2.63 (3H, d, *J* 1.5, CH=CCH_3), 2.84 (2H, t, *J* 7.0, NCH_2CH_2), 2.90 (2H, q, *J* 7.3, CH_2CH_3), 3.61 (2H, m, NCH_2CH_2), 3.87 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 5.60 (1H, t, *J* 5.5, $NHCH_2CH_2$), 6.27 (1H, d, *J* 1.1, CH=CCH_3), 6.76–6.78 (2H, m, 2′-, 6′-H), 6.83 (1H, d, *J* 8.4, 5′-H), 7.20–7.31 (2H, m, 5-, 6-H), 7.39 (1H, d, *J* 8.4, 7-H), 7.53 (1H, d, *J* 7.7, 4-H); *m*/*z* (EI) 393 (M^+, 12.86), 164 (100.00).

In a similar manner to that described above, **10** gave **11a**, **23** gave **24a–24c**.

2-Formyl-7-methoxybenzo[*b*]furan (12)

A mixture of **7e** (2.8 g, 17 mmol) and SeO_2 (3.8 g, 34 mmol) in 1,4-dioxane (50 ml) was heated at 75 °C for 92 h. After the insoluble portion was filtered off, the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography [hexane–ethyl acetate (10 : 1)] to give a pale yellow solid. This solid was recrystallized from ethyl acetate to give **12** (1.42 g, 46.7%) as yellow needles: mp 41.0–43.9 °C; δ_H (60 MHz; $CDCl_3$; Me_4Si) 4.03 (3H, s, OCH_3), 7.04–7.53 (4H, m, 3-, 4-, 5-, 6-H), 9.91 (1H, s, CHO); *m*/*z* (EI) 176 (M^+, 100.00).

Compound (**25**) was prepared from **7g** according to the procedure described for **12**.

(*E*)-2-Diethylcarbamoylvinyl-7-methoxybenzo[*b*]furan (13b)

General procedure for 13a, 13c, 26a–26c. To a suspension of NaH (60% in oil, 0.14 g, 3.4 mmol) in THF (10 ml) was added dropwise a solution of *N*,*N*-diethyl diethylphosphonoacetamide (0.77 g, 3.1 mmol) in THF (10 ml) under a N_2 atmosphere at −8 °C with stirring. The solution was stirred until it became clear. A solution of **12** (0.3 g, 1.7 mmol) in THF (10 ml) was added dropwise to the clear solution at 20 °C, and the mixture was stirred at the same temperature for 4 h. The mixture was then quenched with saturated NH_4Cl solution and extracted with ethyl acetate. The organic layer was washed with brine and dried. The solvent was evaporated off, giving a residue which was recrystallized from ethyl acetate to give (***E***)-**13b** (0.30 g, 63.8%) as white needles (found: C, 70.29; H, 7.24; N, 5.07. $C_{16}H_{19}NO_3$ requires C, 70.31; H, 7.01; N, 5.12%); mp 86.6–88.7 °C; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.22–1.27 (6H, m, CH_2CH_3 × 2), 3.51 (4H, q, *J* 6.9, CH_2CH_3 × 2), 4.03 (3H, s, OCH_3), 6.85 (1H, m, Ar H), 6.86 (1H, s, 3-H), 7.02 (1H, d, *J* 15.0, vinyl H), 7.13–7.18 (2H, m, Ar H), 7.59 (1H, d, *J* 15.1, vinyl H); *m*/*z* (EI) 273 (M^+, 46.62), 201(100.00).

In a similar manner to that described above, **12** gave **13a**, **13c**, **25** gave **26a–26c**.

2-(4-Chlorobenzoyl)-7-hydroxybenzo[*b*]furan (14e)

To a mixture of $AlCl_3$ (3.7 g, 28 mmol) and 1-dodecanethiol (3.3 ml, 14 mmol) in chloroform (100 ml) was added dropwise a solution of **14d** (1.0 g, 3.5 mmol) in chloroform (50 ml) at −4 °C with stirring. The mixture was stirred at 20 °C for 22 h. The mixture was poured into water and extracted with chloroform. The organic layer was washed with brine and dried. The solvent was evaporated off, giving a residue which was purified by silica gel column chromatography [hexane–ethyl acetate (20 : 1)] to give **14e** (0.25 g, 26.3%) as a yellow solid: mp 212.2–217.5 °C; δ_H (60 MHz; acetone-d_6; Me_4Si) 7.11–8.20 (8H, m, Ar H), 9.23 (1H, s, O*H*); *m*/*z* (EI) 274 (M + 2, 37.96%), 272 (M^+, 100.00), 139 (62.44).

Compound (**19i**) was prepared from **19h** according to the procedure described for **14e**.

2-(4-Chlorobenzoyl)-7-(2-phenylethoxy)benzo[*b*]furan (14f)

A mixture of **14e** (0.2 g, 0.74 mmol), K_2CO_3 (0.2 g, 1.5 mmol), and (1-bromoethyl)benzene (0.15 ml, 1.1 mmol) in CH_3CN (100 ml) was stirred at 75 °C for 2.5 h. After the insoluble portion was filtered off, the filtrate was distilled under reduced pressure. The residue was purified by silica gel column chromatography [hexane–ethyl acetate (10 : 1)] to give **14f** (0.20 g, 71.4%) as a pale yellow oil: δ_H (60 MHz; $CDCl_3$; Me_4Si) 1.76 (3H, d, *J* 6.4, $CHCH_3$), 5.61 (1H, q, *J* 5.9, $CHCH_3$), 6.79–8.17 (13H, m, Ar H); *m*/*z* (EI) 378 (M + 2, 16.61), 376 (M^+, 46.81), 105 (100.00).

Compound (**19j**) was prepared from **19i** according to the procedure described for **14f**.

(*Z*)-5-Bromo-2-[1-(4-chlorophenyl)-2-diethylcarbamoylvinyl]benzo[*b*]furan (15b)

General procedure for 15a, 15c–15l. To a suspension of NaH (60% in oil, 0.12 g, 3.0 mmol) in THF (10 ml) was added dropwise a solution of *N*,*N*-diethyl diethylphosphonoacetamide (2.0 g, 4.1 mmol) in THF (40 ml) under a N_2 atmosphere at −8 °C with stirring. The solution was stirred until it became clear. A solution of **14a** (0.50 g, 1.5 mmol) in THF (20 ml) was added dropwise to the clear solution at 8 °C, and the mixture was stirred at the same temperature for 1.5 h. The mixture was then quenched with saturated NH_4Cl solution and extracted with ethyl acetate. The organic layer was washed with brine and dried. The solvent was evaporated off, giving a residue which was recrystallized from ethyl acetate to give (***Z***)-**15b** (0.20 g, 31.3%) as white needles (found: C, 58.29; H, 4.43; N, 3.19. $C_{21}H_{19}BrClNO_2$ requires C, 58.29; H, 4.43; N, 3.24%); mp 106.7–109.8 °C; δ_H (500 MHz; $CDCl_3$; Me_4Si) 1.08 (3H, t, *J* 7.2 CH_2CH_3), 1.27 (3H, t, *J* 6.9, CH_2CH_3), 3.39 (2H, q, *J* 7.4, CH_2CH_3), 3.52 (2H, q, *J* 7.4, CH_2CH_3), 6.26 (1H, s, C=CHCO), 6.63 (1H, s, 3-H), 7.25–7.27 (2H, m, 6- and 7-H), 7.38–7.39 (4H, br m, phenyl H), 7.64 (1H, d, *J* 1.8, 4-H); *m*/*z* (EI) 435 (M + 4, 19.34), 433 (M + 2, 73.51), 431 (M^+, 54.93), 361 (100.00).

In a similar manner to that described above, **14a** gave **15a**, **15c**, **14b** gave **15d–15g**, **14c** gave **15h–15k**, **14f** gave **15l**.

(*E*)-2-Acetyl-3-amino-4-[2-[2-(3,4-dimethoxyphenyl)ethylcarbamoyl]-1-methylvinyl]-7-methoxybenzo[*b*]furan ((*E*)-17c)

General procedure for 17a, 17b, 17d–17f, 19a–19g. A mixture of **16a** (0.60 g, 2.1 mmol), (*E*)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-2-butenamide (0.63 g, 2.5 mmol), palladium acetate (24 mg, 0.10 mmol), tri-*o*-tolylphosphine (64 mg, 0.21 mmol) and triethylamine (20 ml) was heated at 90–100 °C for 31 h. The mixture was

treated with chloroform, and the insoluble portion was removed by filtration. The filtrate was evaporated to dryness. The residue was poured into ice water and extracted with chloroform. The organic layer was washed with brine and dried. The solvent was evaporated off, giving a residue which was purified by silica gel column chromatography [chloroform–ethyl acetate (10 : 1)] to give (***E***)-**17c** (0.28 g, 29.2%) as yellow needles (found: C, 66.16; H, 6.30; N, 6.23. $C_{25}H_{28}N_2O_6$ requires C, 66.36; H, 6.24; N, 6.19%); mp 176.4–177.7 °C; δ_H (500 MHz; $CDCl_3$; Me_4Si) 2.51 (3H, s, $COCH_3$), 2.60 (3H, d, *J* 1.4, $CH{=}CCH_3$), 2.81 (2H, t, *J* 6.8, NCH_2CH_2), 3.60 (2H, m, NCH_2CH_2), 3.86 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.01 (3H, s, OCH_3), 5.55 (1H, brt, *J* 5.6, $NHCH_2CH_2$), 5.72 (2H, brs, NH_2), 5.74 (1H, q, *J* 1.4, $CH{=}CCH_3$), 6.73–6.75 (2H, m, 2′-, 6′-H), 6.81 (1H, d, *J* 8.7, 5′-H), 6.91 (1H, d, *J* 8.3, 6-H), 6.97 (1H, d, *J* 8.3, 5-H); *m*/*z* (EI) 452 (M^+, 17.77), 244 (100.00).

In a similar manner to that described above, **16a** gave **17a**, **17b**, **16b** gave **17d–17f**, **18a** gave **19a**, **19b**, **18b** gave **19c**, **18c** gave **19d–19f**, **18d** gave **19g**.

2-Acetyl-3-acetylamino-4-bromo-7-methoxybenzo[*b*]furan (18a)

General procedure for 18b–18d, 19h, 30c. A mixture of **16a** (1.0 g, 3.5 mmol) and acetyl chloride (0.37 g, 5.3 mmol) in tetrahydrofuran (50 ml) was heated at 60 °C for 8.5 h. The reaction mixture was poured into ice water, and the resulting precipitate was collected by filtration, then recrystallized from ethyl acetate to give **18a** (0.84 g, 73.0%) as pale yellow needles (found: C, 47.86; H, 3.70; N, 4.26. $C_{13}H_{12}BrNO_4$ requires C, 47.87; H, 3.71; N, 4.29%); mp 235.3–237.4 °C; δ_H (60 MHz; $CDCl_3$; Me_4Si) 2.25 (3H, s, $COCH_3$), 2.59 (3H, s, $COCH_3$), 4.02 (3H, s, OCH_3), 6.88 (1H, d, *J* 8.4, 6-H), 7.37 (1H, d, *J* 8.5, 5-H), 8.49 (1H, brs, N*H*); *m*/*z* (EI) 327 (M + 2, 20.51%), 325 (M^+, 20.88), 283 (100.00).

In a similar manner to that described above, **16a** gave **18b–18d**, **17a** gave **19h**, **30a** gave **30c**.

5-Bromo-3-[4-(diethoxyphosphoryl)-4-diethylcarbamoylbutyryl]-2-methylbenzo[*b*]furan (22b)

To a suspension of NaH (60% in oil, 69 mg, 1.7 mmol) in THF (10 ml) was added dropwise a solution of ethyl diethylphosphonoacetamide (0.39 g, 1.6 mmol) in THF (10 ml) under a N_2 atmosphere at −10 °C with stirring. The solution was stirred until it became clear. A solution of **20e** (0.30 ml, 0.87 mmol) in THF (20 ml) was added dropwise to the clear solution at 27 °C, and the mixture was stirred at the same temperature for 5 h. The mixture was then quenched with saturated NH_4Cl solution and extracted with ethyl acetate. The organic layer was washed with brine and dried. The solvent was evaporated off, giving a residue which was purified by silica gel column chromatography [chloroform–ethyl acetate (20 : 1)] to give (***E***)-**22b** (0.13 g, 63.8%) as pale yellow needles (found: C, 50.96; H, 6.09; N, 2.68. $C_{22}H_{31}BrNO_6P$ requires C, 51.17; H, 6.05; N, 2.71%); mp 92.7–95.6 °C; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.13 (3H, t, *J* 7.2, NCH_2CH_3), 1.19 (3H, t, *J* 7.2, NCH_2CH_3), 1.32 (3H, t, *J* 6.8, OCH_2CH_3), 1.34 (3H, t, *J* 7.0, OCH_2CH_3), 2.32–2.51 (2H, m, $COCH_2CH_2$), 2.76 (3H, s, CH_3), 2.83–2.93 (1H, m, $COCH_2CH_2$), 3.06–3.14 (1H, m, $COCH_2CH_2$), 3.22–3.38 (2H, m, NCH_2CH_3), 3.45–3.55 (2H, m, NCH_2CH_3, C*H*), 3.61–3.70 (1H, m, NCH_2CH_3), 4.11–4.22 (4H, m, OCH_2CH_3 × 2), 7.30 (1H, d, *J* 8.8, 7-H), 7.39 (1H, dd, *J* 8.6 and 2.0, 6-H), 8.08 (1H, d, *J* 2.2, 4-H); *m*/*z* (EI) 517 (M + 2, 30.34), 515 (M^+, 30.23), 72 (100.00).

Compound (**22a**) was prepared from **20e** according to the procedure described for **22b**.

(*E*)-7-[2-[2-(3,4-Dimethoxyphenyl)ethylcarbamoyl]-1-methylvinyl]-2-ethoxycarbonylpropionyl-3-phenylbenzo[*b*]furan (27b)

General procedure for 27a, 27d, 31a, 31b. A mixture of **8c** (0.43 g, 1.1 mmol), (*E*)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-2-butenamide (0.40 g, 1.6 mmol), palladium acetate (12 mg, 0.052 mmol), tri-*o*-tolylphosphine (32 mg, 0.11 mmol) and triethylamine (8.0 ml) was heated at 90–100 °C for 16 h. The mixture was treated with $CHCl_3$, and the insoluble portion was removed by filtration. The filtrate was evaporated to dryness. The residue was poured into water, and extracted with chloroform. The organic layer was washed with brine and dried. The solvent was evaporated off. The residue was purified by silica gel column chromatography [chloroform–ethyl acetate (5 : 2)] to give a yellow solid. This solid was recrystallized from methanol to give **27b** (0.18 g, 29.5%) as yellow needles (found: C, 71.27; H, 6.22; N, 2.48. $C_{34}H_{35}NO_7 \cdot 1/4H_2O$ requires C, 71.13; H, 6.23; N, 2.44%); mp 145.6–147.4 °C; δ_H (500 MHz; $CDCl_3$; Me_4Si) 1.23 (3H, m, OCH_2CH_3), 2.69 (2H, t, *J* 6.8, CH_2CH_2), 2.75 (3H, d, *J* 0.9, $CH{=}CCH_3$), 2.87 (2H, t, *J* 7.3, NCH_2CH_2), 3.25 (2H, t, *J* 6.9, CH_2CH_2), 3.62–3.66 (2H, m, NCH_2CH_2), 3.86 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.12 (2H, q, *J* 7.3, OCH_2CH_3), 5.92 (1H, t, *J* 5.5, N*H*), 6.51 (1H, d, *J* 0.9, $CH{=}CCH_3$), 6.77–6.84 (3H, m, 2′-, 5′-, 6′-H), 7.31 (1H, t, *J* 7.8, 5-H), 7.44–7.60 (7H, m, 4-, 6-H, phenyl H); *m*/*z* (EI) 569 (M^+, 5.82%), 164 (100.00).

In a similar manner to that described above, **8c** gave **27a**, **27d**, **30b** gave **31b**, **30c** gave **31a**. **27c** and **27e** were obtained in the usual manner from **27b** and **27d**, respectively.

Measurement of calcium mobilization in CHO cells

Evaluation for BLT_1 and BLT_2 receptor inhibitory activity was carried out according to a procedure reported previously.[17,18]

Acknowledgements

This work was supported in part by a grant from the Ministry of Education, Culture, Sports, Science and Technology of Japan for a "University–Industry Joint Research" Project (2004–2008). The authors thank the staff of the Instrument Analysis Center of Mukogawa Women's University for the ^{1}H-NMR and MS measurements and element analyses.

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33 Compound (***E***)-**17c** formula: $C_{25}H_{28}N_2O_6$, formula weight: 452.51, crystal color, habit: colorless, needle, crystal dimensions: 0.35 × 0.20 × 0.10 mm, crystal system: monoclinic, lattice type: C-centered, indexing images: 3 oscillations @ 180.0 seconds, detector position: 127.40 mm, pixel size: 0.100 mm, lattice parameters: $a = 33.4101(8)$ Å, $b = 5.07911(13)$ Å, $c = 27.9188(7)$ Å, $\beta = 101.8321(14)°$, $V = 4637.0(2)$ Å^3, space group: $C2/c$ (#15), Z value: 8, D_{calc}: 1.296 g cm^{-3}, F_{000}: 1920.00, μ(CuKα): 7.671 cm^{-1}, $R1 = 0.0448$ for 4197 observations, 50% probability chosen for the ellipsoids.
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