Preparation of 3-(4-chlorophenyl)-2-(2-aminothiazol-4-yl)-5-methoxybenzo[*b*]furan derivatives and their leukotriene B_4 inhibitory activity†

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A series of 3-(4-chlorophenyl)-2-(2-aminothiazol-4-yl)benzo-[*b*]furan derivatives 6–10 were prepared and their leukotriene B_4 inhibitory activity was evaluated. We found that several compounds showed strong inhibition of calcium mobilization in CHO cells overexpressing human BLT_1 and BLT_2 receptors. Among them, 3-(4-chlorophenyl)-2-[5-formyl-2-[(dimethylamino)methyleneamino]thiazol-4-yl]-5-methoxybenzo[*b*]furan 9b showed the most potent and selective inhibition for the human BLT_2 receptor, and its IC_{50} value was smaller than that of the selected positive control compound, ZK-158252.

Introduction

Leukotriene B_4 (LTB_4), a dihydroxy fatty acid produced mainly by macrophages and neutrophils, has been shown to be a potent mediator of the inflammatory process, playing important physiological roles in leukocyte trafficking to the site of infection and clearance of invading microorganisms.[1] However, elevated levels of LTB_4 have been observed in patients with various inflammatory diseases.[2]

Much work has been done to develop LTB_4 receptor antagonists for clinical use as an anti-inflammatory drug.[3] The structures of representative compounds are shown in Fig. 1.[4] However, no antagonist has yet been developed for clinical applications. Recently, a second LTB_4 receptor (BLT_2) was found and its molecular cloning established.[5] The results encouraged new studies to find novel BLT_1 and/or BLT_2 inhibitors, which may lead to the development of new clinical drugs for immunosuppression of allograft rejection in organ transplantation,[6] arteriosclerosis,[7] psoriasis,[8] cancer,[9] and rheumatoid arthritis.[10]

In a previous paper, we reported the preparation of 2- and 4-[(2-alkylcarbamoyl)-1-methylvinyl]benzo[*b*]furan derivatives **1** and **2**, and their selective LTB_4 receptor (BLT_1, BLT_2) inhibitory activities.[11] We also demonstrated that several furo[2,3,4-*jk*][2]benzazepin-4(3*H*)-one derivatives **3** showed moderate human BLT_2 receptor inhibitory activity (Fig. 2).[12] From these studies, we suggested that the torsion angle between the benzo[*b*]furan ring plane and the (2-alkylcarbamoyl)-1-methylvinyl functional group

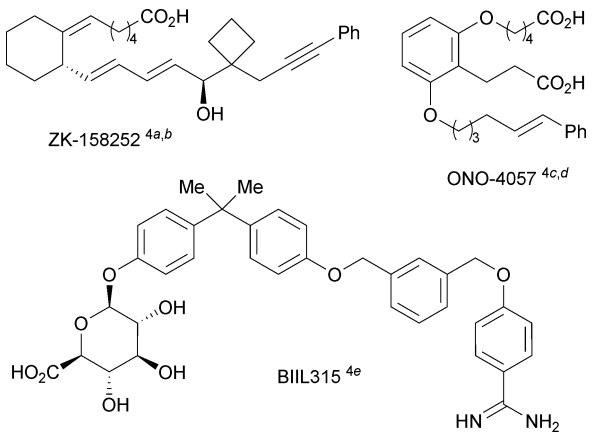

Fig. 1 Structures of representive LTB_4 receptor antagonists.

may affect the inhibitory potency and the selectivity for BLT_1 and/or BLT_2.

In the present study, the (*E*)-2-alkylcarbamoyl-1-methylvinyl group, the conjugated chain functional group, was modified to an aromatic five-membered heterocyclic ring with the (dimethylamino)methyleneamino group. The thiazole ring may be advantageous to various types of receptors,[13] including leukotriene D_4.[14] 2-(2-Aminothiazol-4-yl)benzo[*b*]furan was prepared as the key intermediate and several derivatives were prepared to investigate their activity for the LTB_4 receptor.[15]

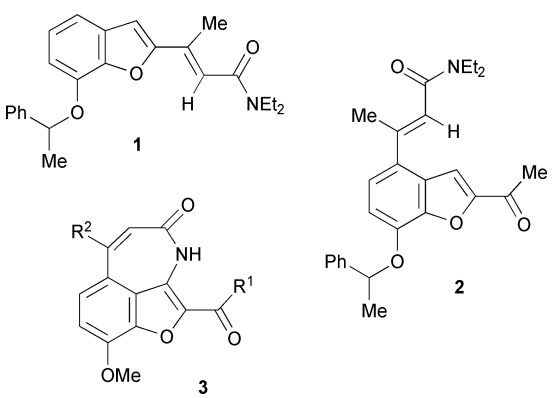

Fig. 2 Structures of reported LTB_4 receptor inhibitory benzo[*b*]furan derivatives.

Here we describe the preparation of 2-(2-aminothiazol-4-yl)benzo[*b*]furan derivatives and the evaluation of their inhibitory potency and selectivity for BLT_1 and/or BLT_2.

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Chemistry

In the literature, only a few examples of the preparation of 2-(2-aminothiazol-4-yl)benzo[*b*]furan derivatives have been reported.[16] We planned the preparation of a series of 2-(2-aminothiazol-4-yl)benzo[*b*]furan derivatives by applying Hantzsch thiazole synthesis as a key step to construct the thiazole moiety at the 2-position of the benzo[*b*]furan ring by using 2-(chloroacetyl)benzo-[*b*]furan **5** and thiourea (Scheme 1).[17]

Chloromethyl ketone **5** was prepared by the reaction of chloroacetyl chloride with 3-(4-chlorophenyl)-5-methoxybenzo-[*b*]furan **4**, which was easily obtained from 1-(4-chlorophenyl)-2-(4-methoxyphenoxy)ethanone by dehydration with polyphosphoric acid.[18] Thiazole ring formation by treatment of the chloromethylketone **5** with thiourea proceeded smoothly in refluxing EtOH to give 2-(2-aminothiazol-4-yl)-3-(4-chlorophenyl)-5-methoxybenzo[*b*]furan **6** in 56% yield as a crystalline compound. Acylation of the aminothiazole **6** with acetyl chloride or 5-methylisoxazole-4-carbonyl chloride gave the corresponding carboxamides **7a** and **7b** in 77% and 31% yields, respectively. Treatment of the 5-methylisoxazol-4-yl derivative **7b** with Et_3N in refluxing THF afforded the characteristic (*Z*)-2-cyano-3-hydroxybut-2-enoyl compound **8** in 50% yield by opening of the isoxazole ring followed by enolization of the α-cyano-β-ketoamide. The structure of **8** was supported by the observation of enol OH proton at 14.49 ppm in the ^{1}H-NMR spectrum.[19]

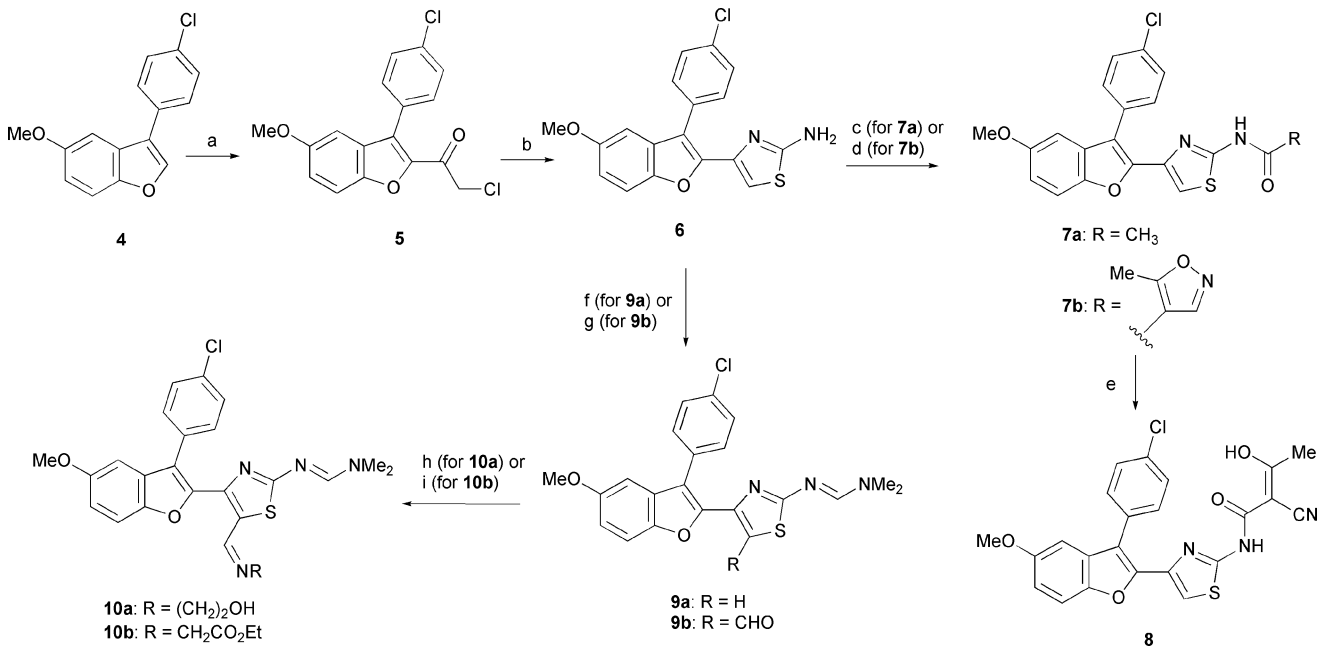
In order to formylate the 5-position of the thiazole ring, aminothiazole **6** was treated with 2 equiv. of $POCl_3$ in DMF at −10 to −5 °C. The reaction proceeded smoothly and selectively only at the primary amino group of the 2-position on the thiazole ring to give the *N*,*N*-dimethylformimidamide product **9a** in 74% yield. However, the same reaction using a large excess (8 equiv.) of $POCl_3$ at room temperature provided the *N*′-(5-formylthiazol-2-yl)-*N*,*N*-dimethylformimidamide **9b** in 60% yield as the sole product. Although the *N*,*N*-dimethylformimidamide group derived from 2-amino-4-phenylthiazole has been reported to be relatively sensitive to hydrolysis conditions,[20] the 3-(4-chlorophenyl)-2-[5-formyl-2-[(dimethylamino)methyleneamino]thiazol-4-yl]-5-methoxybenzo-[*b*]furan **9b** that we prepared was stable enough to allow evaluation of its biological activities.

The imine derivatives **10a** and **10b** were obtained by condensation of the aldehyde **9b** with 2-aminoethanol or glycine ethyl ester in 72% and 17% yields, respectively.

Biological study

The prepared 2-(2-aminothiazol-4-yl)-3-(4-chlorophenyl)-5-methoxybenzo[*b*]furan derivatives **6**, **7a**, **7b**, **8**, **9a**, **9b**, **10a** and **10b** were evaluated for their LTB_4 inhibitory activity by inhibition of calcium mobilization in both CHO cells overexpressing human BLT_1 (CHO-hBLT_1) and human BLT_2 (CHO-hBLT_1)[21] together with **1** and **2**.[11] First, all thiazolyl derivatives were evaluated at a concentration of 10 μM, with the results shown in Table 1. Six 2-(2-aminothiazol-4-yl)benzo[*b*]furans **7a**, **8**, **9a**, **9b**, **10a** and **10b** prepared in this study showed more than 70% inhibition of calcium mobilization in CHO-hBLT_2 cells. In contrast, the 5-methylisoxazole-4-yl carboxamide **7b** was inactive to both hBLT_1 and hBLT_2. All of the active 2-(2-aminothiazol-4-yl)benzo[*b*]furan compounds **6**, **7a**, **8**, **9a**, **9b**, **10a** and **10b** were more potent for CHO-hBLT_2 than CHO-hBLT_1.

The 2-cyano-3-hydroxy-2-butenamide **8** and *N*,*N*-dimethyl-*N*′-(2-thiazolyl)formamidines **9b**, **10a** and **10b** were selected based on the results of screening at a concentration of 10 μM, and were evaluated at five concentrations (1, 10, 100 nM, 1 and 10 μM) in comparison with ZK-158252.[4a] All of the evaluated compounds



Scheme 1 Preparation of a series of 2-(2-aminothiazol-4-yl)benzo[*b*]furan derivatives. *Reagents and conditions*: (a) $ClCH_2COCl$, $AlCl_3$, $CHCl_3$, reflux, 79%. (b) $H_2NC(S)NH_2$, EtOH, reflux, 56%. (c) CH_3COCl, THF, reflux, 77% (**7a**). (d) 5-methylisoxazole-4-carbonyl chloride, THF, reflux, 31% (**7b**). (e) Et_3N, THF, reflux, 50% (from **7b**). (f) 2 equiv. $POCl_3$, DMF, −10 to −5 °C, 74% (**9a**). (g) 8 equiv. $POCl_3$, DMF, rt, 60% (**9b**). (h) $NH_2CH_2CH_2OH$, EtOH, reflux, 72% (**10a**). (i) $NH_2CH_2CO_2Et$·HCl, EtOH, 3 Å molecular sieves, reflux, 17% (**10b**).

Table 1 Evaluation of prepared compounds for LTB_4 receptor (BLT_1, BLT_2) inhibitory activities[a]

	% Inhibition (10 μM)		IC_{50}/μM	
Compound	CHO-hBLT_1	CHO-hBLT_2	CHO-hBLT_1	CHO-hBLT_2
6	4.8	70.6	—	—
7a	11.2	68.7	—	—
7b	N.I.[b]	N.I.[b]	—	—
8	13.6	82.1	—	3.29
9a	11.6	72.0	—	—
9b	24.4	97.9	3.55	0.19
10a	51.3	>100	3.19	0.20
10b	49.4	88.3	6.81	0.35
1	69.9	>100	2.88	0.48
2[c]	92.6	92.8	0.42	0.68
ZK158252	—	—	1.70	1.18

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

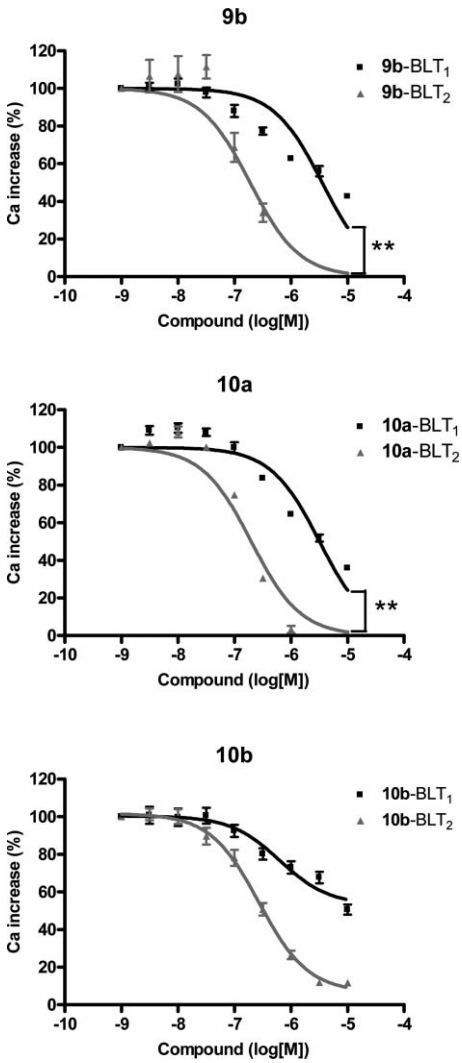


Fig. 3 Effect of **9a**, **10a** and **10b** on calcium mobilization by LTB_4 (300 nM) in CHO-hBLT_1 and CHO-hBLT_2 cells (mean ± S.D., $n = 3,4$). * $p < 0.001$ (two-way ANOVA).

exhibited dose-dependent inhibition of hBLT_1 and hBLT_2 (Fig. 3), and IC_{50} values are summarized in Table 1.

Three of the compounds tested, **9b**, **10a** and **10b**, showed potent inhibitory activity to the LTB_4 receptor, and inhibited BLT_2 16.0–19.5 times more potently than BLT_1. In contrast, ZK-158252 showed nearly equal inhibition of BLT_1 and BLT_2. Compounds **9b**, **10a** and **10b** inhibited BLT_2 3.4–6.0 times more strongly than ZK-158252. In comparison with **1**, found in our current study to be a BLT_2-selective compound, the test compounds **9b**, **10a** and **10b** were more potent and selective inhibitors of BLT_2. These three compounds showed lower inhibitory activity than ZK-158252 to BLT_1.

In summary, among the 2-(2-aminothiazol-4-yl)benzo[*b*]furans **6–10**, the 2-[2-[(dimethylamino)methyleneamino]-5-substituted-thiazol-4-yl]benzo[*b*]furans **9b**, **10a** and **10b** show highly potent and significantly selective inhibitory activity to BLT_2. These results indicate that substituents at both the 2- and 5-positions on the thiazolyl group (at the 2-position of the benzo[*b*]furan skeleton) have a significant effect on the selective and potent BLT_2 inhibitory activity of these compounds.

Conclusion

Several 2-(2-aminothiazol-4-yl)benzo[*b*]furan derivatives **6–10** were prepared in order to find more potent and selective BLT_2 inhibitors on the basis of 2- and 4-[(2-alkylcarbamoyl)-1-methylvinyl]benzo[*b*]furan derivatives **1** and **2**. The potent and selective inhibitors **9b**, **10a**, **10b** were found. A common structural feature of these compounds is the 2-[(dimethylamino)-methyleneamino]thiazole group with substituents at the 5-position. Their inhibitory potencies towards BLT_2 were 6.2–3.4 times higher than ZK-158252. Further experiments to confirm these preliminary results are in progress, with the ultimate aim of developing them as agents for clinical purposes.

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