OBC
www.rsc.org/obc

Preparation of 3-acetoacetylaminobenzo[*b*]furan derivatives with cysteinyl leukotriene receptor 2 antagonistic activity

Eriko Tsuji,[a] Kumiko Ando,[a] Jun-ichi Kunitomo,[a] Masayuki Yamashita,[b] Shunsaku Ohta,[b] Shigekatsu Kohno[b] and Yoshitaka Ohishi*[a]

[a] *School of Pharmaceutical Sciences, Mukogawa-Women's University, 11-68 Koshien Kyuban-cho, Nishinomiya 663-8179, Japan. E-mail: yohishi@mwu.mukogawa-u.ac.jp; Fax: +798 41 2792; Tel: +798 45 9953*

[b] *Kyoto Pharmaceutical University, Misasagi, Yamashinaku, Kyoto 607-8412, Japan*

Received 1st July 2003, Accepted 5th August 2003
First published as an Advance Article on the web 15th August 2003

Novel 3-acetoacetylaminobenzo[*b*]furan derivatives with a modified triene system at the 3-position were prepared through acylation of the 3-aminobenzo[*b*]furans with 5-methylisoxazole-4-carboxylic acid chloride followed by basic cleavage of the isoxazole ring and several of these compounds showed moderate cysteinyl leukotriene receptor 2 antagonistic activity.

The cysteinyl leukotrienes (cysLTs) are potent biological mediators in the pathophysiology of inflammatory disorders, in particular asthma. Studies of cysLTs receptors indicated the existence of at least two types of cysLTs receptors, designated cysLT1 and cysLT2. The cysLT1 receptor was cloned, and the cysLT2 receptor has been cloned and characterized recently.[1] BAY u9773 (**1**)[1b] and DUO-LT (**2**)[2] were reported to be dual cysLT1 and cysLT2 antagonists. Discovery of the stable dual antagonist and/or selective cysLT2 antagonist may lead to possible therapeutic opportunities.

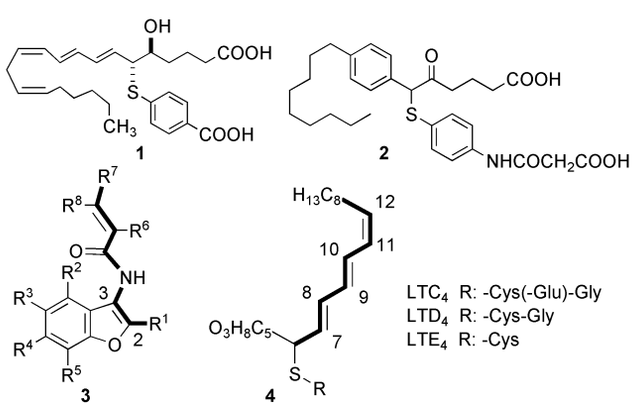


Fig. 1

In this communication, we report the synthesis of 3-acetoacetylaminobenzo[*b*]furans (**3**) and their antagonistic activities to cysLT1 and cysLT2. π-Conjugation and planarity of the bold-line portion of **3** may be kept as shown in Fig. 1. It was also considered that the modified triene system (the bold-line portion) of **3** might be exactly simulated in the C7–C12 portion of cysLTs (**4**) (Fig. 1).[3]

3-Amino-5-bromobenzo[*b*]furan derivatives (**7a**–**d**) were prepared starting with 4-bromo-2-cyanophenol (**5**) *via* the intermolecular cyclization of 4-bromo-2-cyanophenylmethylether derivatives (**6**).[4] The bromides (**6b** and **7d**) were subjected to the Heck reaction with *N*,*N*-diethylcrotonamide in the presence of $Pd(OAc)_2$ and tri-*o*-tolylphosphine to afford successfully the corresponding Heck products **8b** and **9d**. Treatment of **8b** with NaH afforded **9b**. Heck reaction of **6a** under similar conditions afforded **9a** accompanied by cyclization. The obtained 3-aminobenzo[*b*]furans (**7** and **9**) were acylated with 5-methylisoxazole-4-carboxylic acid chloride to give the corresponding amides (**10**), isoxazole rings of which were easily cleaved by treatment with Et_3N to afford the corresponding enol isomers (**11**) of the 3-acetoacetylaminobenzo[*b*]furan derivatives (Scheme 1).

On the other hand, the primary amino group of 3-aminobenzo[*b*]furans showed an enamine property, for example, treatment of 3,5-diamino-2-ethylbenzo[*b*]furan[5] with hydrochloric acid afforded 5-amino-2-ethyl-3(2*H*)-benzo[*b*]furanone as a hydrolysis product. The enamine property of **11** may assist in keeping the conjugation and planarity of the C2 substituent through the C3 side-chain of **11** as shown in Fig. 1. The stereostructure of **11g** was determined by X-ray analysis as shown in Fig. 2,[6] which clearly shows the conjugation and planarity of the C2 substituent through the C3 side-chain as we expected.

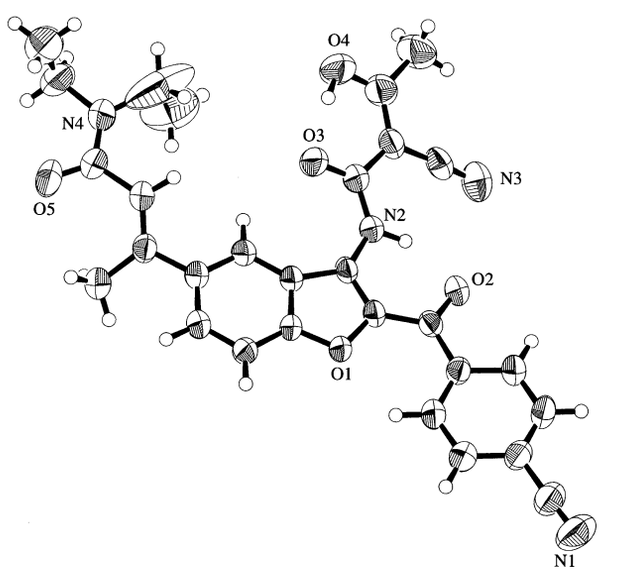


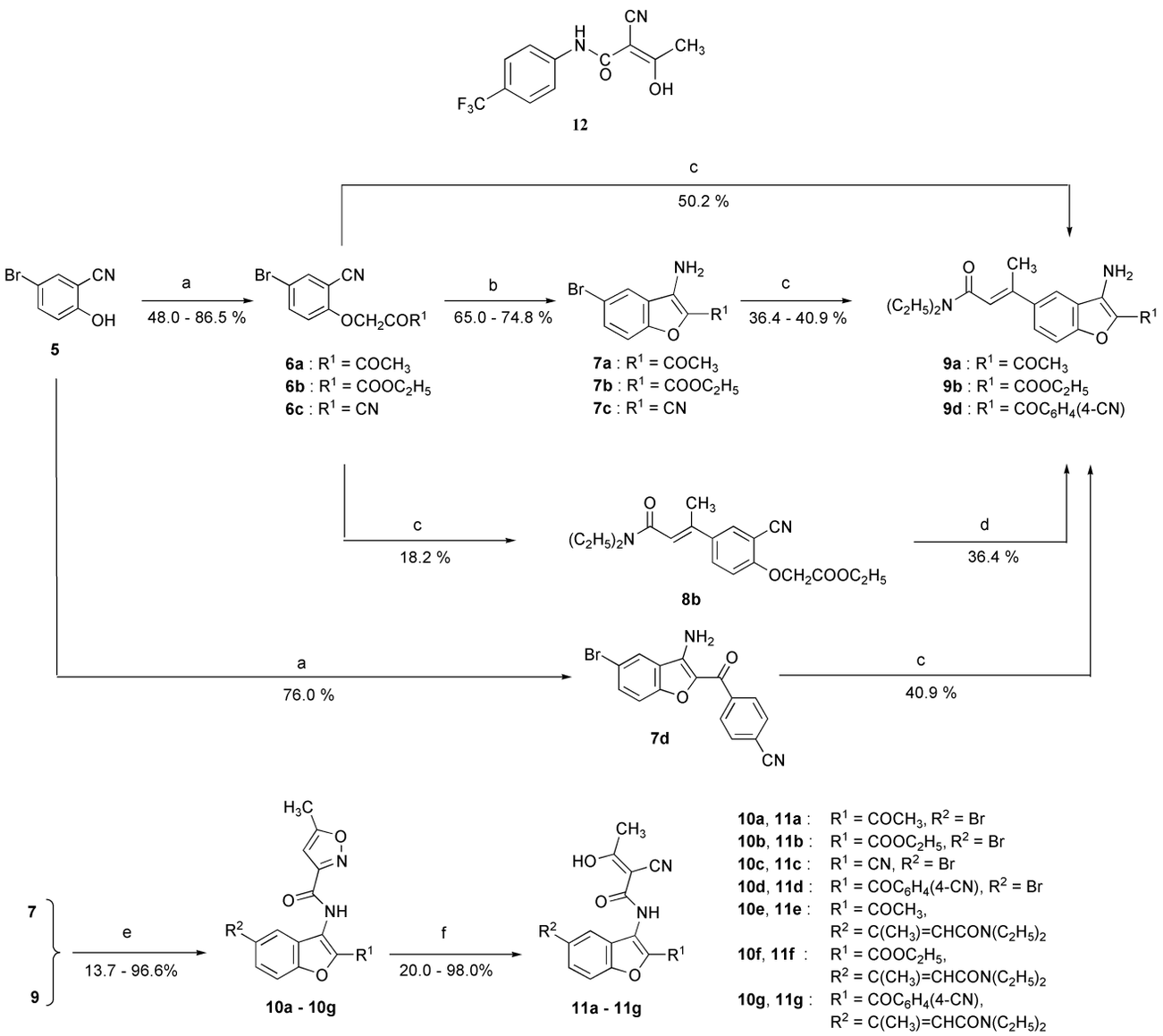
Fig. 2 X-Ray structure of **11g**.

The prepared enol isomers (**11**) were evaluated for their cysLT1 and cysLT2 antagonistic activity (Table 1).[7] The novel 3-acetoacetylaminobenzo[*b*]furan derivatives (**11b**,**d**,**g**) showed valuable antagonistic activities, especially **11d** which demonstrated specific activity for cysLT2. In contrast, **12**[8] was inactive on the Ca assay which reveals a significant role for the benzo[*b*]furan ring in the appearance of antagonistic activity. Among these compounds, we selected **11d**, which showed valuable activities as a lead compound for structure-optimization. Investigations along this line are underway in our laboratory.

DOI: 10.1039/b307468d

Table 1 Antagonistic activities

	Ca Assay				Binding assay	
	Inhibition (%)				Inhibition (%)	
	(10 μM)		IC_{50}/μM		(10 μM)	IC_{50}/μM
Compound	cysLT1	cysLT2	cysLT1	cysLT2	cysLT2	cysLT2
11b	49.8	61.4	>10	>10	9.5	>10
11d	52.1	67.1	>10	4.8	85	3.7
11g	51.0	57.6	9.7	7.7		
BAY u9773			0.44	0.30 [1a]		0.597 ± 0.297 [1b]
12	16.1	2.3	>10	>10		



Scheme 1 *Reagents*: (a) $ClCH_2COCH_3$ or $BrCH_2CO_2C_2H_5$ or $ClCH_2CN$ or $ClCOCH_2C_6H_4(4\text{-}CN)/K_2CO_3$; (b) $(C_2H_5)_3N$ or NaH; (c) $Pd(OAc)_2/[(2\text{-}CH_3)C_6H_4]_3P/(C_2H_5)_3N/(E)\text{-}CH_3CH{=}CHCON(C_2H_5)_2$/THF; (d) NaH; (e) ClC(O)–C=N–O–C(CH$_3$)=CH; (f) $(C_2H_5)_3N$.

Experimental

5-Bromo-2-(4-cyanobenzoyl)-3-(5-methylisoxazol-4-carbonyl)-aminobenzo[*b*]furan (10d)

To a solution of **7d** (0.2 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 a N_2 atmosphere with vigorous stirring at 26 °C. The solution was stirred at 65 °C for 7 h. The mixture was cooled to room temperature, a resulting precipitate was collected by filtration. The precipitate was recrystallized from MeOH to give **10d** (850 mg, 34%) as yellow needles. Mp 236 °C. ^{1}H-NMR ($CDCl_3$): δ 2.90 (3H, s, CH_3), 7.42 (1H, d, J = 9.1 Hz, 7-H), 7.70 (1H, dd, J = 9.1, 1.9 Hz, 6-H), 7.86–7.88 (2H, m, 3′-, 5′-H), 8.32–8.35 (2H, m, 2′-, 6′-H), 8.71 (1H, s, isoxazole-H), 8.91 (1H, d, J = 1.9 Hz, 4-H), 11.30 (1H, bs, NH). MS: *m*/*z* 449 (M^+, 56.56), 341 (100.00). HRMS: $C_{21}H_{12}BrN_3O_4$, *m*/*z* 449.0001 (calc. 449.0012).

5-Bromo-2-(4-cyanobenzoyl)-3-[*Z*-(2-cyano-3-hydroxybut-2-enoyl)amino]benzo[*b*]furan (11d)

A solution of **10d** (0.8 g, 1.8 mmol) and Et_3N (2.4 mL) in anhydrous THF (30 mL) was heated at 68 °C for 6 h, and the solvent was evaporated off. 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. Evaporation of the extract gave a residue which was recrystallized from CH_3CN to give **11d** (0.66 g, 82%) as colorless needles. Mp 269 °C. ^{1}H-NMR (DMSO-d_6): δ 2.19 (3H, s, CH_3), 7.61 (1H, d, J = 8.7 Hz, 7-H), 7.71 (1H, dd, J = 8.7, 2.0 Hz, 6-H), 8.05 (2H, m, 2′-, 6′-H or 3′-, 5′-H), 8.16 (2H, m, 2′-, 6′-H or 3′-, 5′-H), 8.66 (1H, d, J = 2.1 Hz, 4-H), 12.53 (1H, bs, NH). MS: *m*/*z* 449 (M^+, 55.84), 340 (100.00). HRMS: $C_{21}H_{12}BrN_3O_4$, *m*/*z* 449.0011 (calc. 449.0012).

Acknowledgements

We thank staff of the instrumental analysis centre of Mukogawa Women's University for ^{1}H NMR and MS.

Notes and references

1 (*a*) H.-P. Nothacker, Z. Wang, Y. Zhu, R. K. Reinscheid, S. H. S. Lin and O. Civelli, *Mol. Pharmacol.*, 2000, **58**, 1601–1608; (*b*) C. E. Heise, B. F. O'Dowd, D. J. Figueroa, N. Sawyer, T. Nguyen, D.-S. Im, R. Stocco, J. N. Bellefeuille, M. Abramovitz, R. Cheng, D. V. Williams Jr., Z. Zeng, Q. Liu, L. Ma, M. K. Clements, N. Coulombe, Y. Liu, C. P. Austin, S. R. George, G. P. O'Neill, K. M. Metters, K. R. Lynch and J. F. Evans, *J. Biol. Chem.*, 2000, **275**, 30531–30536; (*c*) H. M. Sarau, R. S. Ames, J. Chambers, C. Ellis, N. Elshourbagy, J. J. Foley, D. B. Schmidt, R. S. Muccitelli, O. Jenkins, P. R. Murdock, N. C. Herrity, W. Halsey, G. Sathe, A. I. Muir, P. Nuthulaganti, G. M. Dytko, P. T. Buckley, S. Wilson, D. J. Bergsma and D. W. P. Hay, *Mol. Pharmacol.*, 1999, **56**, 657–663.

2 American Thoracic Society – 98th International Conference (May 2002, Atlanta) [D38] [Poster F4], *Characterization of DUO-LT: A novel Dual Cysteinyl Receptor Antagonist* .

3 I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, Wiley, NY, 1976, pp. 58.

4 K. Gewald and H. J. Kaensch, *J. Prakt. Chem.*, 1973, **315**, 779–785; V. P. Baidya, S. B. Mahajam and Y. S. Agasimundin, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 1981, **20**, 391–393; W. K. R. W. Mederski, M. Osswald, D. Dorsch, M. Christadler, C.-J. Schmitges and C. Wilm, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 619–622; S. Rádl, P. Hezký, J. Urbánková, P. Váchal and I. Krejcf, *Collect. Czech. Chem. Commun.*, 2000, **65**, 280–297; S. Rádl, P. Hezký, P. Konvicka and I. Krejcf, *Collect. Czech. Chem. Commun.*, 2000, **65**, 1093–1108; S. S. Sangapure and S. Y. Agasimundin, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 1976, **14**, 6886–6891.

5 3,5-Diamino-2-ethylbenzo[*b*]furan was obtained by catalytic hydrogenation of 2-ethyl-3,5-dinitrobenzo[*b*]furan over Pd/C in EtOH.

6 Formula $C_{29}H_{26}N_4O_5$, formula weight = 522.56, monoclinic, space group $P2_1/c$ (no. 14), a = 17.709(3), b = 7.553(2), c = 19.656(2) Å, β = 100.926(8)°, V = 2581.5(7) Å^3, T = 296 K, Z = 4, D_c = 1.344 g cm^{-3}, F_{000} = 1096.00, μ(Cu-Kα) = 7.65 cm^{-1}. 5184 reflections measured, 4619 (2θ < 135.15), R_{int} = 0.016, R_1 = 0.058 (R_w = 0.170). CCDC reference number 214287. See http://www.rsc.org/suppdata/ob/b3/b307468d/ for crystallographic data in CIF or other electronic format.

7 The assays were achieved according to the procedure reported by Nothacker *et al*. (ref. 1*a*).

8 E. Kuo, P. Hambleton, D. Kay, P. Evans, S. Matharu, E. Little, C. McDowall, B. Jones, C. Hedgecock, C. Yea, A. Chan, P. Hairsine, I. Ager, W. Tully, R. Williamson and R. Westwood, *J. Med. Chem.*, 1996, **39**, 4608–4621; S. Greene, K. Watanabe, J. Braatz-Trulson and L. Lou, *Biochem. Pharmacol.*, 1995, **50**, 861–867.