Quantitative Structure-Activity Relationships of Benzamide Derivatives for Anti-Leukotriene Activities†

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To determine the structural requirements of the benzamide derivatives reported by Nakai et al. (*J. Med. Chem.* 1988, *31*, 84-91) for antileukotriene activity, we studied their conformational characteristics in comparison with those of leukotriene. By superimpositions of the conformations of antagonists on that of leukotriene, we found that the conformations of the conjugated benzamide moiety, tetrazole ring, and benzopyran or benzodioxan ring of the antagonists correspond to the triene moiety, peptide carboxylic acid residue, and cysteine residue of leukotriene, respectively, but that no moiety of the antagonists corresponds to the terminal aliphatic carboxylic acid moiety of leukotriene. Furthermore, the stable conformations of alkyl and alkoxy groups of the antagonists were quite different from that of the ω-chain of leukotriene. However, conformational analyses taking all the possible rotations of these flexible chains into consideration showed that antagonists in which these flexible chains can most feasibly adopt the same lengths as those of the ω-chain exhibit potent antagonist activity. From these results, we deduced the structural features of benzamide derivatives necessary for potent antileukotriene activity.

Introduction

Peptidoleukotrienes (LTs; for chemical structures, see Chart I) are mediators of asthma, and show potent bronchoconstriction activity.[1] Thus, their antagonists are expected to be therapeutically effective in treatments of allergic asthma and other hypersensitivity diseases.[2,3] The hydroxyacetophenone (HAP) compound FPL-55712[4] has long been known to be an antagonist of the slow-reacting substance of anaphylaxis (SRS-A). As SRS-A itself is a mixture of LTs,[5] attempts have been made to develop effective LT antagonists by modification of HAP.[6-12] The most commonly used antagonist developed by this method is probably LY-171883,[7] and L-649,923[9] and L-648,051[10] are under clinical trial. Another approach in developing LT antagonists is modifications of the chemical structure of LTs,[13-16] SK&F-104,353[14] and U-19052[15] being representative examples of drugs developed in this way.

There are also other effective antagonists that do not contain the HAP moiety or do not seem to contain a structure common to LTs such as L-660,711[17-19] and ICI-198,615.[20-22] Thus, these antagonists may belong to a third category of LT antagonists. Recently, the group of Toda and Nakai[23,24] reported that benzamide derivatives such as ONO-1078 (cf. Chart I) have potent anti-LT activities. The structures of these compounds have no superficial similarity with those of LTs, although Nakai et al.[24] designed these compounds to contain common hydrophobic and hydrophilic regions to those of LTs.

We were interested in the structural requirements for the anti-LT activities of benzamide derivatives of ONO-1078, such as *N*-(4′-substituted benzoyl)-8-amino-2-(tetrazol-5″-yl)-4*H*-1-benzopyran-4-one (BPs; cf. Chart II), and *N*-(4′-substituted benzoyl)-8-amino-2-(tetrazol-5″-yl)benzodioxan (BDs; cf. Chart II). We introduced various alkyl or alkyl ether chains at the C(4′) position of the

Chart I. Chemical Structures of Leukotrienes and Their Antagonist

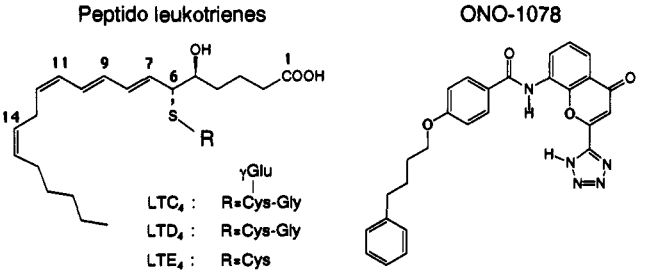
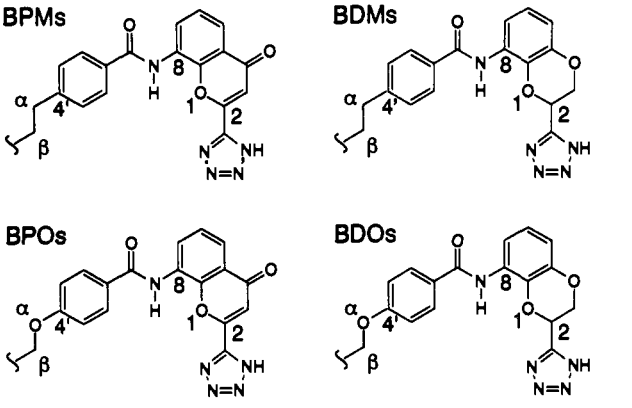


Chart II. Chemical Structures of Benzamide Leukotriene Antagonists



† Abbreviations: LT(s), leukotriene(s); nor-LT, 2-norleukotriene; BP(s), *N*-(4′-substituted benzoyl)-8-amino-2-(tetrazol-5″-yl)-4*H*-1-benzopyran-4-one(s); BPM(s), *N*-(4′-alkylbenzoyl)-8-amino-2-tetrazol-5″-yl)-4*H*-1-benzopyran-4-one(s); BPO(s), *N*-(4′-alkoxybenzoyl)-8-amino-2-(tetrazol-5″-yl)-4*H*-1-benzopyran-4-one(s); BD(s), *N*-(4′-substituted benzoyl)-8-amino-2-(tetrazol-5″-yl)-benzodioxan(s); BDM(s), *N*-(4′-alkylbenzoyl)-8-amino-2-(tetrazol-5″-yl)benzodioxan(s); BD(s), *N*-(4′-alkoxybenzoyl)-8-amino-2-(tetrazol-5″-yl)benzodioxan(s); HAP, hydroxyacetophenone.

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Table I. Biological Activities and Physicochemical Parameters of Benzamide-Type LT Antagonists

antagonist	pI_{50}[a]	L[b]	B_4[c]	π[d]	DL[e]
BDM6	6.68	12.44	5.87	5.26	1.312
BDM7	7.15	13.38	6.39	5.80	0.193
BDM8	7.00	14.49	7.33	6.34	0.197
BDM9	6.80	15.43	7.85	6.88	0.580
BDM10	6.30	16.54	8.79	7.42	0.977
BDO5	7.00	12.33	5.73	4.25	1.381
BDO6	7.89	13.27	6.23	4.79	0.172
BDO7	8.05	14.40	7.16	5.33	0.221
BDO8	7.85	15.34	7.66	5.87	0.594
BDO9	7.70	16.46	8.60	6.41	0.997
BPM6	7.82	12.44	5.87	5.26	1.312
BPM7	8.38	13.38	6.39	5.80	0.193
BPM8	8.26	14.49	7.33	6.34	0.197
BPM9	8.15	15.43	7.85	6.88	0.580
BPO6	9.07	13.27	6.23	4.79	0.172
BPO7	9.30	14.40	7.16	5.33	0.221
BPO8	8.26	15.34	7.66	5.87	0.594
BPO9	8.13	16.42	8.60	6.41	0.997

[a] Negative logarithm of the concentration of benzamide-type antagonists required for 50% inhibition of LTC_4-induced contraction of guinea pig ileum reported by Nakai et al.[24] These values were means for several runs, and their deviations were about 10% (T. Miyamoto, personal communication). [b] STERIMOL parameter representing the chain length. [c] STERIMOL parameter representing the maximum chain width. [d] Hydrophobic substituent coefficient. [e] Determined by eq 9.

benzoyl ring of these benzamide derivatives; for simplicity, we refer to their alkyl derivatives as BPMs and BDMs, and

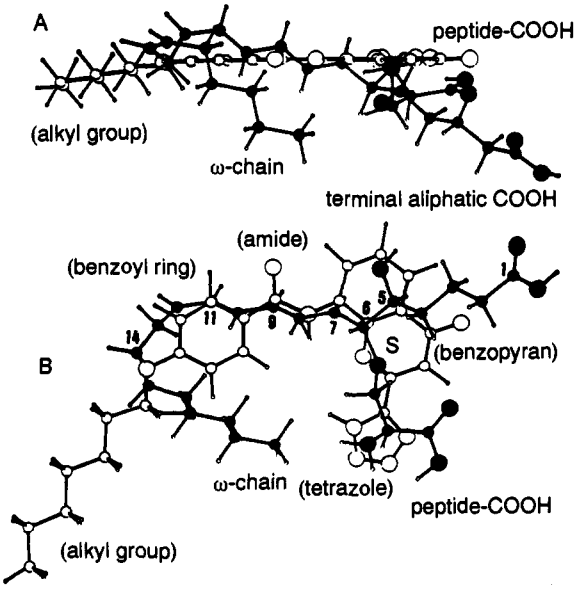

Figure 1. Superimposition of BPO7 on leukotriene E_4: (A) side view, (B) top view. Closed and open circles represent LTE_4 and BPO7 molecules, respectively. The moieties of BPO7 are shown in parentheses.

to their alkoxy derivatives as BPOs and BDOs. The structures of these derivatives are shown by the number

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of C atoms (n) of the alkyl (C_nH_{2n+1} in the BPM and BDM series) or alkoxy (OC_nH_{2n+1} in the BPO and BDO series) group at the end of BPM, BPO, BDM, or BDO; e.g., BPM7 represents BPM with a heptyl chain. The length of the alkyl or alkoxy group is also shown by the number of C atoms, such as C_7 for the heptyl group, and OC_7 for the heptyl ether group. We found that a similar conformation of antagonists to that of LTs, except in the terminal aliphatic carboxyl chain of the latter, is important for their antagonist activities.

Results

1. Hansch–Fujita Analyses. We analyzed the LT antagonist activities of BPs and BDs against guinea pig ileum contraction induced by LTD_4 reported by Nakai et al.[24] by the method of Hansch and Fujita.[25-27] We found that the following relationship, analyzed in terms of the Verloop's STERIMOL parameter L,[28] was the most significant:

$$pI_{50} = \underset{(\pm 8.356)}{-25.895} - \underset{(\pm 0.040)}{0.163L^2} + \underset{(\pm 1.167)}{4.643L} + \underset{(\pm 0.135)}{0.769I_O} + \underset{(\pm 0.136)}{1.082I_{BP}} \quad (1)$$

$$(n = 18, r = 0.952, s = 0.283)$$

where the indicator variable I_O is 1 with alkoxy groups and 0 with alkyl groups, and I_{BP} is 1 with benzopyran derivatives (BPs) and 0 with benzodioxans (BDs). Values in parentheses represent 95% confidence intervals, and n, r, and s are the number of antagonists used in the analysis (cf. Table I), the correlation coefficient and the standard deviation, respectively. The optimum value of the chain length L of the alkyl or alkoxy group was 14.24, corresponding to C_8 for an alkyl group and to OC_7 for an alkoxy group.

Use of the STERIMOL parameter B_4 instead of L gave a similar correlation. When anti-LT activities were analyzed in terms of the hydrophobic substituent coefficient π of the alkyl group (BPMs and BDMs) and the alkoxy group (BPOs and BDOs), a significant correlation, but lower than that in eq 1, was obtained as shown in eq 2:

$$pI_{50} = \underset{(\pm 4.031)}{-0.574} - \underset{(\pm 0.119)}{0.243\pi^2} + \underset{(\pm 1.395)}{2.732\pi} + \underset{(\pm 0.198)}{0.669I_O} + \underset{(\pm 0.182)}{1.079I_{BP}} \quad (2)$$

$$(n = 18, r = 0.916, s = 0.370)$$

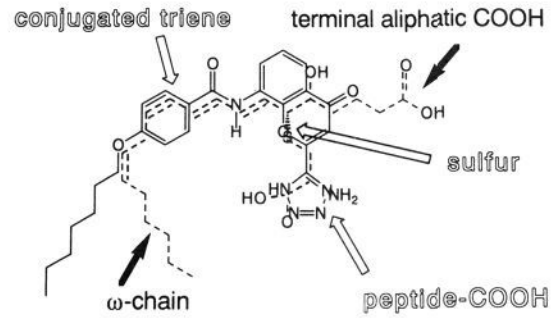

Figure 2. Comparison of the conformation of BPO7 with that of LTE_4. Structures shown by broken and continuous lines represent LTE_4 and BPO7, respectively, and open arrows represent moieties or the atoms of LTE_4 that fitted those of BPO7. Closed arrows represent moieties of LTE_4 that did not fit those of BPO7.

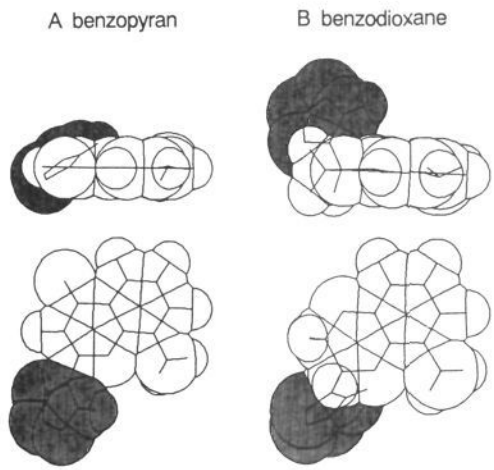

Figure 3. Space-filling models of the conformations of 8-amino-2-(tetrazol-5′-yl) derivatives of benzopyran-4-one (A) and benzodioxan (B). Upper models show side-view conformations, and lower models show top-view conformations. Shaded moieties represent the tetrazole ring.

In eqs 1 and 2, the value of the coefficient with an I_O of 0.769 or 0.669 indicates that the alkoxy group is about 6 times more favorable than the alkyl group with the corresponding chain length for exerting high activity. Furthermore, the value 1.082 or 1.079 of the coefficient with I_{BP} shows that the benzopyran ring is more than 10 times as effective as the benzodioxan ring. As the van der Waals volumes of these two rings are about the same, some other factor(s) seems important.

2. Stable Conformations of Antagonists and LT. To obtain more detailed information about the structural requirement for the anti-LT activities of the benzamides, we next compared the most stable conformations of these antagonists with that of LTE_4. We used LTE_4 as a representative LT because of its structural simplicity. Ball and stick models of the conformations of BPO7 and LTE_4 are compared in Figure 1. The atoms O(1), C(8), amide carbonyl-C, C(2′), and O(α) of BPO7 were found to correspond to the sulfur atom of the sulfide bond, C(7), C(9) and C(11) of the conjugated triene moiety, and the C(14) atom of LTE_4, respectively. Namely, the conjugated benzamide moiety seemed to be equivalent to the conjugated triene moiety, and O(1) in the benzopyran ring and the C–NH moiety of the tetrazole ring of the antagonist superimposed well on the sulfur atom and the peptide COOH group in LTE_4. However, there was no structural moiety of BPO7 that fitted the terminal aliphatic COOH chain between C(1) and C(5) of LTE_4. Furthermore, the

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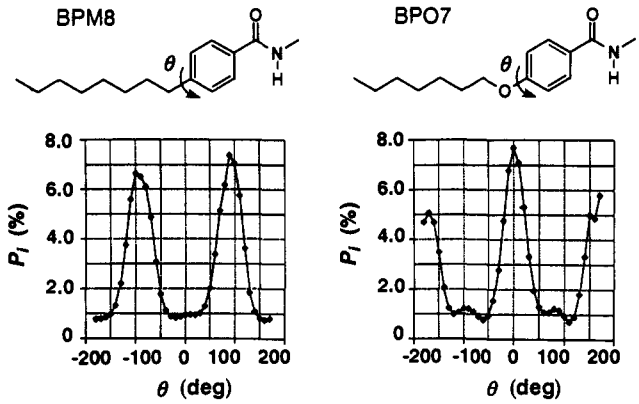


Figure 4. Conformational probability of the C(4′)–C(α) and C(4′)–O(α) bonds of BPM8 and BPO7, respectively. Calculations were performed by generating various conformations of these bonds, but fixing angles of the other bonds of alkyl and alkyl ether chains. P_i: probability of the generated conformation i of these bonds. θ: dihedral angle.

conformation of the alkoxy group at the 4′-position of the benzoyl ring of BPO7 was quite different from that of the ω-chain of LTE_4. These features are summarized in Figure 2. Similar structural characteristics to those of BPO7 were also observed in BDM8, BDO7, and BPM8.

According to eq 1, the benzopyran ring was more effective than the benzodioxan ring for antagonist activity. As the hydrophobicities and the van der Waals volumes of these rings are very similar, we next examined the conformations of these rings to determine why the benzopyran ring is favorable to the benzodioxan ring. We used 8-amino-2-(tetrazol-5′-yl) derivatives of benzopyran-4-one and benzodioxan as models of BPs and BDs, respectively. We determined the most stable conformations of these compounds by molecular orbital calculation, taking into consideration their conjugated structures. Figure 3 shows space-filling models of the stable conformations of these compounds. Interestingly, the tetrazole and benzopyran rings are almost coplanar (A), but the tetrazole ring is not coplanar with the benzodioxan ring (B). Thus, the conformational coplanarity of the former two rings is favorable for the C–NH moiety of the tetrazole ring to be located at a similar position to that of the peptide COOH of LTs. This conformational similarity would be a reason why BPs showed higher LT-antagonistic activities than the corresponding BDs. Other structural factors such as the carbonyl group at C(4) and the double bond between C(2) and C(3) in the benzopyran ring could also be favorable for the higher biological activity of BPs.

3. Rotation of Alkyl and Alkyl Ether Chains of Antagonists. QSAR analysis by eq 1 showed the importance of the lengths of alkyl and alkoxy groups for anti-LT activity, although the structures of stable conformers were quite different from that of the ω-chain of LTE_4. It is important to know whether similar conformations of these flexible chains of antagonists to those of the ω-chain of LTs are required for their antagonist activities.

We determined the conformational distributions of the alkyl and alkyl ether chains as functions of the torsional rotation angle θ about the C(4′)–C(α) bond of the alkyl chain and about the C(4′)–O(α) bond of the alkyl ether chain. We defined θ as 0° and ±180°, when the benzoyl ring and the C(α)–C(β) or the O(α)–C(β) bond were in the same plane, and as ±90°, when they were perpendicular to one another. Figure 4 shows the probabilities of various conformations of BPM8 and BPO7 as functions of θ. The conformational distribution for BPM7 was symmetric with

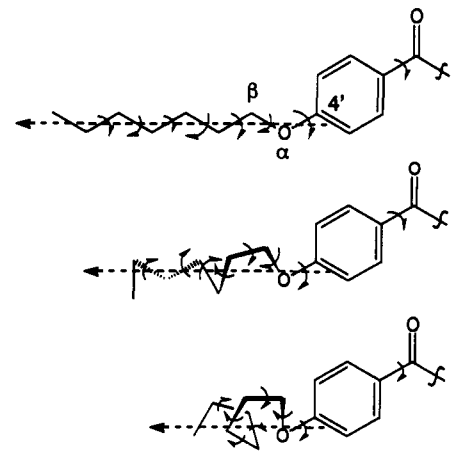


Figure 5. Possible conformations of alkyl ether chains attached to the 4′-position of the benzoyl ring of LT antagonist.

minima at θ = 0° and ±180° and maxima at θ = ±90°, but the distribution for BPO7 was just the opposite with minima at about θ = ±90° and maxima at θ = 0° and ±180°. These results indicate that the C(α)–C(β) bond is perpendicular to the benzoyl ring, but the O(α)–C(β) bond is in the same plane as the benzoyl ring. Other compounds with different lengths of alkyl and alkyl ether chains showed similar results.

The conformations of the other bonds in these chains were found to be the same. Thus, the conformations of these chains were governed by those of the bond between C(4′) of the benzoyl ring and the α-atoms. Accordingly, it can be concluded that the α-atom of alkyl and alkoxy groups working as hinges regulates the rotations of these groups. Possibly, the coplanar conformation allows the alkyl ether chain to take similar conformations to those of the ω-chains of LTs more easily than the perpendicular conformation of the alkyl chain. This could explain why BPOs and BDOs are more effective than BPMs and BDMs with corresponding chain lengths for induction of anti-LT activity.

4. Effects of Alkyl and Alkoxy Groups on Anti-LT Activity. Next we examined whether antagonists with chains of similar lengths to that of the ω-chain exhibited potent anti-LT activities. For this purpose, we determined the probabilities of occurrence of conformations of alkyl and alkoxy groups as functions of their chain lengths relative to that of the ω-chain of LTE_4 (RL) by eq 7 (cf. Methods): A value of RL = 1 indicates an identical chain length to that of the ω-chain at a certain conformation of these moieties. We took the length of the ω-chain in its most stable conformation as a reference, because this chain can be assumed to take the most extended conformation when it binds to its receptor. In this computation, various conformations were generated randomly according to the Monte Carlo approach, taking all possible torsional angles of the rotatable single bonds of the antagonists into account. Some of the possible conformations of the alkyl ether chain are shown in Figure 5, and the results with BPOs are shown in Figure 6, in which binomial distributions of conformations were observed.

To quantitate the similarities in the chain lengths of alkyl and alkoxy groups to that of the ω-chain of LTs, we determined the feasibilities of these chains to take the same length as that of the ω-chain of LTE_4. We determined this feasibility by summation of the probability of occurrence of conformations in the range of RL of 0.80–1.2, shown by the shadowed area in Figure 6. This area is referred to as F_s, and its negative logarithm was defined as DL according to eqs 8 and 9. A greater F_s and smaller

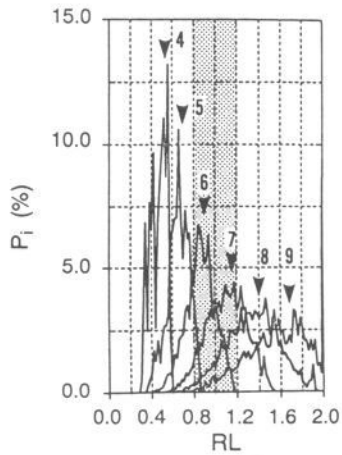


Figure 6. Conformation probability (P_i) of alkyl ether chains of BPOs as a function of their lengths relative to that of the ω-chain of LTE_4 (*RL*). The number beside each distribution curve is the C number of the alkyl ether chain of the BPO. The shaded region represents the *RL* region between 0.8 and 1.2.

DL are measures of closer coincidence of alkyl and alkyl ether chain lengths with the ω-chain length: complete coincidence corresponds to $F_s = 1.0$ and $DL = 0$, and 10% coincidence corresponds to $F_s = 0.1$ and $DL = 1$. Values of *DL* are summarized in Table I. The *DL* value of the alkyl group of C_n was about the same as that of the alkoxy group of OC_{n-1}, indicating that the feasibilities of these corresponding chains to have the same length as the ω-chain are very similar. The smallest *DL* values were observed with chains of C_8 and OC_7.

We analyzed the antagonist activities of these benzamides in terms of *DL*, and obtained the significant correlation shown in eq 3:

$$pI_{50} = \underset{(\pm 0.143)}{-7.315} - \underset{(\pm 0.146)}{0.662DL} + \underset{(\pm 0.125)}{0.730I_O} + \underset{(\pm 0.127)}{1.095I_{BP}} \quad (3)$$

$$(n = 18,\ r = 0.955,\ s = 0.265)$$

The negative sign of the coefficient with *DL* indicates that the antagonist activity increased as *DL* decreased: similar lengths of alkyl and alkoxy groups to that of the ω-chain of LTs are important for their activities. It is noteworthy that the coefficients with indicator variables I_O and I_{BP} in eq 3 are very similar to those in eq 1.

DL correlated with the STERIMOL parameter *L* in a parabolic manner with relatively high significance, as shown in eq 4, and correlation of *DL* with the hydrophobic substituent π was less. Thus, the "dynamic parameter"

$$DL = \underset{(\pm 6.620)}{49.485} - \underset{(\pm 0.032)}{0.236L^2} - \underset{(\pm 0.924)}{6.823L} \quad (4)$$

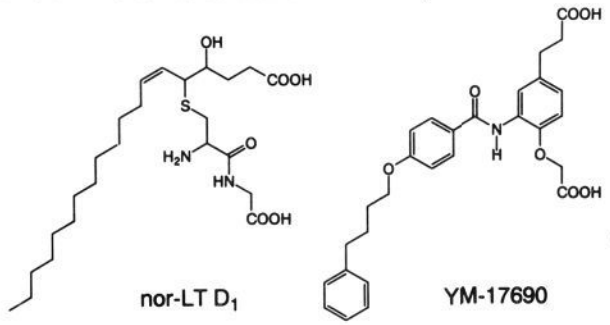
$$(n = 18,\ r = 0.886,\ s = 0.228)$$

DL is regarded to represent similar natures to *L* or π to a considerable extent, but not to be identical with these static parameters. As the conformations of these chains were geometrically quite different from that of LTs, as shown in Figures 1 and 2, the roles of these chains in induction of antagonist activities cannot be understood with the use of *L*. *DL* could be a more useful parameter with flexible groups.

Discussion

We studied the structural characteristics of the benzamide type LT antagonists BPs and BDs. We found that the major geometric conformations of these antagonists are essentially the same as that of LTs: (1) the conjugated benzamide moiety of antagonists corresponds to the triene moiety of LTs, (2) the O(1) in the benzopyran and benzodioxan rings of antagonists corresponds to the sulfur atom of the sulfide bond of LTs, (3) the acidic C–NH moiety of the tetrazole ring of antagonists corresponds to the peptide COOH group of LTs, and (4) the alkyl and alkoxy groups can take similar conformations to that of the ω-chain of LTs. These features can be regarded as important for antagonist activity.

Chart III. Chemical Structures of Nor-LTD_1 and YM-17690



The present results also showed that the following structures of benzamide type antagonists are required for potent anti-LT activity: (1) a similar chain length of the alkyl or alkoxy group to that of the ω-chain, (2) an ether O(α) rather than a methylene C(α) in these chains, and (3) a benzopyran ring rather than a benzodioxan ring. The main role of the ether O(α) is to enable the C(4′)–O(α) bond to be coplanar to the benzoyl ring. This would be favorable for the alkyl ether chain, rather than the alkyl chain, to take a similar conformation to that of the ω-chain of LTs. Furthermore, the benzopyran ring could induce the acidic C–NH moiety of the tetrazole ring to take a similar conformation to that of the peptide COOH of LTs. For this, the coplanar conformation of the tetrazole and benzopyran rings could be favorable, but the conformational coplanarity of the tetrazole and benzodioxan rings is lost.

No moiety in BPs and BDs fitted the terminal aliphatic COOH chain of LTs, suggesting that the conformational and electronic structures of the terminal aliphatic COOH of LTs are decisive for their agonist activity. This prediction is supported by the finding that nor-LT (SK&F-101,132; cf. Chart III), in which the terminal aliphatic COOH chain is one carbon shorter than that of LTs, showed antagonist activity.[13] In this connection, it is interesting to note that the benzamide derivative YM-17690 (cf. Chart III), showed LT-agonist activity in such a manner as that it shares a common binding site with LTs at the LT receptor(s),[22,29] although its chemical structure including the carboxymethoxy group (OCH_2COOH) in the aniline ring is similar to those of the benzamide antagonists. This would be owing to the presence of the propionic acid moiety (CH_2CH_2COOH), which has a similar structural feature to that of the terminal aliphatic COOH chain of LTs. Thus, compounds that possess similar structural and electronic properties to LTs other than those of the terminal aliphatic COOH chain of LTs exhibit potent anti-LT activities. More rigorous structural requirements for induction of agonist and antagonist activities will be reported in the subsequent paper.

In this study, *DL*, derived from the distribution probability of conformations, was used as a descriptor to ex-

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press the structural properties of the freely rotatable flexible alkyl and alkyl ether chains. For induction of biological activity of a flexible compound, its stable conformation, in which steric energy is minimal, is not always effective, because the stability of the active conformer is dependent on the conformational entropy. Thus, the feasibility of conformational fluctuation should be taken into account especially for compounds with flexible groups. *DL* is a descriptor that represents the conformational stability of bioactive compounds. However, in this study superiority of *DL* to the static parameters such as *L* was not demonstrated, the correlation of pI_{50} with *DL* being about the same as that with *L*. Further study is necessary to show the usefulness of *DL* as a denominator to represent the structure of flexible groups.

Methods

The inhibitory effects of BPs and BDs on LTD_4-induced contraction of guinea pig ileum reported by Nakai et al.[24] were taken as measures of their antagonist activities. Their activities are summarized in Table I as pI_{50} values (negative logarithms of their concentrations for 50% inhibition).

Quantitative structure–antagonist activity relationships were studied by the method of Hansch and Fujita,[25-27] using the reported values of structural parameters summarized in Table I.[26-28]

Molecular mechanics calculation was performed according to the MM2PRIME program[30,31] in a FACOM M760, at the Computer Center, University of Tokushima. The empirical parameters for the nitrogen atoms in pyridine and amide were taken from the MMP2[32] and MMPEP,[33] respectively. Molecular orbital calculations by the AM1 method were performed with MOPAC[34] in a FACOM M760 computer. The initial arbitrary configurations were generated from their partial structures determined by X-ray crystallography taken from the Cambridge Structural Database of the Computer Center, Tokyo University. The most stable conformation of LTE_4 was determined by optimizing with MM2PRIME of the conformer that showed the lowest van der Waals potential among conformers generated randomly by rotating all their single bonds. Molecular superimpositions on LTE_4 of the antagonist in their stable conformations were performed by the least-squares method.

The conformational distribution of antagonist was analyzed statistically with 10^4 conformations, in which the torsional angles of all the rotatable single bonds were varied randomly at 30° increments and their energies were calculated by the method of MM2PRIME.[31] When the interatomic distance became less than 0.8 Å in the computation, this conformation was omitted. Their thermal fluctuations were analyzed at an absolute temperature *T* of 3000 K by the Monte Carlo approach. The steric energy E_i of the *i*th conformation was determined, and the probability of occurrence of its conformation P_i was calculated by eq 5 according to Boltzmann statistics:[35]

$$P_i = \exp(-E_i/RT) / \sum_{i=1}^{N} \exp(-E_i/RT) \quad (5)$$

where *R* is the gas constant and N ($=10^4$) is the number of conformational states generated.

The distribution maps of these conformations were determined by plotting their probabilities as functions of the torsional rotation angle θ of the C(4′)–C(α) bond or C(4′)–O(α) bond of the antagonist. In the calculation, the conformations of the alkyl or alkyl ether chain generated were assumed to be rigid ellipsoids, and their longest axis was taken as their principal axis. The covariance value λ of the generated conformations was defined by eq 6:

$$\lambda = \sum_{j=1}^{m} |\mathbf{u}_j - \bar{\mathbf{u}}|^2 \quad (6)$$

where vector $\mathbf{u}_j$ is the coordinate of the *j*th atom of these chains on orthogonal axes, vector $\bar{\mathbf{u}}$ is the coordinate of the gravity center of these chains, and *m* is the total number of O and C atoms in the chain.

The extent of coincidence of alkyl and alkyl ether chain lengths in the conformation generated with the ω-chain length *RL* was expressed by eq 7:

$$RL = \lambda_i/\lambda_{LT} \quad (7)$$

where λ_{LT} is the covariance value of the ω-chain of LTE_4 in its most stable conformation.

The probability of occurrence of the generated conformations in the region $0.8 < RL < 1.2$ was determined by summation of the numbers of conformations generated in this *RL* region, and this value was expressed as F_s as shown in eq 8:

$$F_s = \sum_i P_i \qquad (0.8 \text{ L } RL < 1.2) \quad (8)$$

For use of F_s as a denominator to represent the feasibility of conformational fluctuation, we defined *DL* as shown in eq 9:

$$DL = -\log F_s \quad (9)$$

Namely, *DL* was taken as a measure of the feasibility of conformational fluctuation of the alkyl and alkyl ether chains to adopt the same length as that of the ω-chain.

Registry No. BDM6, 103195-06-8; BDM7, 103195-07-9; BDM8, 103195-08-0; BDM9, 103176-00-7; BDM10, 103176-01-8; BDO5, 103177-97-5; BDO6, 103176-15-4; BDO7, 103176-16-5; BDO8, 103176-17-6; BDO9, 103176-07-4; BPM6, 103177-39-5; BPM7, 103177-40-8; BPM8, 103177-41-9; BPM9, 103177-42-0; BPO6, 103177-16-8; BPO7, 103177-17-9; BPO8, 103177-19-1; BPO9, 103177-18-0; ONO 1078, 103177-37-3.

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