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STRUCTURAL ANALYSIS OF LEUKOTRIENE B4 (LBT_4) RECEPTOR (BLT_1 AND BLT_2) ANTAGONISTS

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The structural characteristics typical of highly and moderately effective antagonists of BLT_1 and BLT_2 receptors were identified and the extents of their influences on the target property were evaluated. Two models for predicting inhibitory activity were constructed for series of sulfur-, nitrogen- and oxygen-containing heterocyclic compounds with significant prognostic levels of greater than 80% using two methods based on sample recognition theory. These structural patterns can be used for virtual screening of potential drugs for antiallergic activity associated with blockade of leukotriene LTB_4-sensitive BLT_1 and BLT_2 receptors.

Keywords: Structure-properties relationships, leukotriene LTB_4, BLT_1 and BLT_2 receptors, structural descriptors.

Leukotrienes LTB_4 are mediators of allergic and inflammatory processes in living organisms (purulent inflammation, rheumatoid arthritis) [1, 2]. They are formed by oxidative metabolism of arachidonic acid by the lipoxygenase enzyme system [1, 2]. The effects of leukotrienes LTB_4 on the development of inflammation in cells are mediated by two G-coupled receptors: BLT_1 and BLT_2 [3 – 6]. Antagonists of BLT_1 and BLT_2 receptors can prevent the development of inflammatory and allergic processes, including bronchial asthma, acute respiratory failure, and chronic bronchitis. Thus, the practical task is to study structure-activity interactions in a series of natural and synthetic blockers of BLT_1 and BLT_2 receptors for predicting new effective antagonists of these receptors. The first stage in performing these studies consists of constructing mathematical models to predict and recognize a target activity, and this is the aim of the present work.

CALCULATIONS FOR SIMULATION EXPERIMENT

Studies of structure-activity relationship were run in the SARD-21 (Structure Activity Relationship & Design) computer environment [7]. The main SARD-21 procedures were used to construct two models for the prediction and recognition of highly effective blockers of BLT_1 and BLT_2 receptors - M1 and M2. Two training sets were formed at the first stage of the study, based on 216 biologically active substances, including synthetic and natural BLT_1 and BLT_2 antagonists [3 – 6, 8 – 23]. The structures of the compounds used in each of the training sets were classified into two groups with alternative properties (highly effective – moderately effective BLT_1 and BLT_2 receptor antagonists) using the IC_{50} parameter determined experimentally by measurements of the functional activity of BLT_1 and BLT_2 receptors (chemotaxis of human neutrophils) to construct model M1 and ligand binding (radioligand binding of BLT_1 and BLT_2 receptors from polymorphonuclear cells) for model M2. Training series A for model M1 consisted of 44 highly effective BLT_1 and BLT_2 receptor antagonists ($IC_{50} \le 1$ μM), while series B included 43 compounds of moderate and low effectiveness, with $IC_{50} > 1$ μM. The training set for model M2 included 81 highly effective BLT_1 and BLT_2 receptor antagonists ($IC_{50} < 1$ μM) (class A) and 48 moderately effective compounds with $IC_{50} > 1$ μM (class B). Typical structures of compounds in the training sets for models M1 and M2 are shown in Table 1, along with IC_{50} values.

The structures of chemical compounds were then represented in fragment descriptor (FD) language [7]. Three types of FD were used: 1) unit fragments, including elements of

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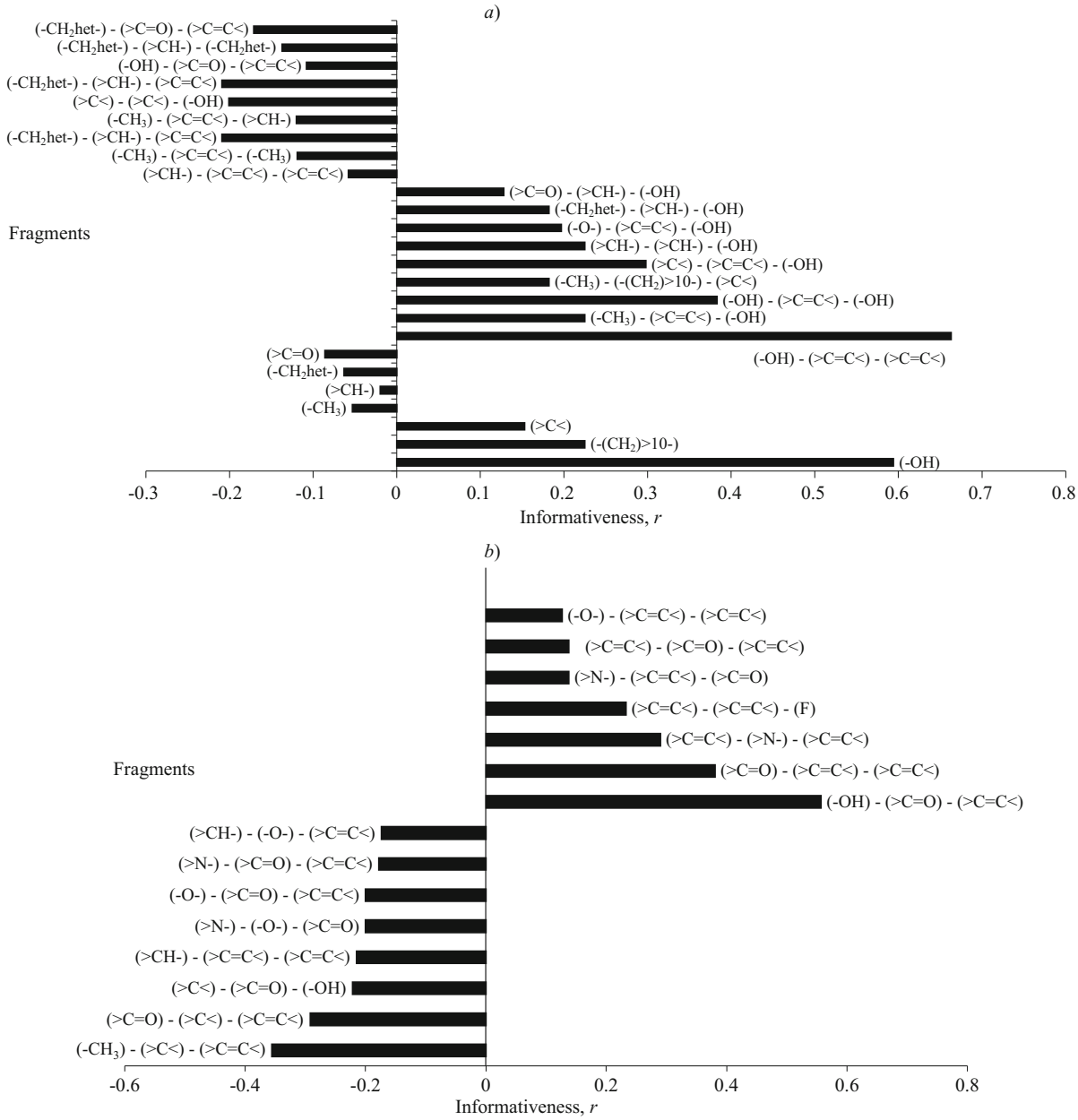


Fig. 1. Influences of acyclic fragments on the effective of antagonist activity in relation to BLT_1 and BLT_2, data from models M1 (*a*) and M2 (*b*).

cyclic systems, as well as the cyclic systems themselves; 2) substructural descriptors consisting of several chemically bound unit fragments; 3) logical combinations (conjunctions, disjunctions, strict disjunctions) generated on the basis of these two types of descriptors [7].

The nature of the influences of FD on the effectiveness of blockade of BLT_1 and BLT_2 receptors was evaluated using the coefficient of informativeness *r* [7]:

$$r = \frac{n_1 \cdot n_4 - n_2 \cdot n_3}{\sqrt{N_1 \cdot N_2 \cdot N_3 \cdot N_4}},$$

where n_1 and n_2 are the numbers of structures of active (more toxic) compounds of group A which contain and do not contain the fragment of interest, n_3 and n_4 are the same for inactive (less toxic) compounds of group B; N_1 and N_2 are the numbers of structures in groups A and B; $N_3 = n_1 + n_3$; $N_4 = n_2 + n_4$.

The value of *r* varied over the range $-1 < r < 1$, and the greater the absolute value of the informativeness measure, the greater the probability that this feature would influence the occurrence of the target property (positive and negative, designated respectively by the "+" and "–" signs) [7].

The complete descriptor description of the study groups of compounds was excessive. Dimensionality was therefore decreased to the optimum level and the most significant factors for evaluating activity were identified, yielding the deci-

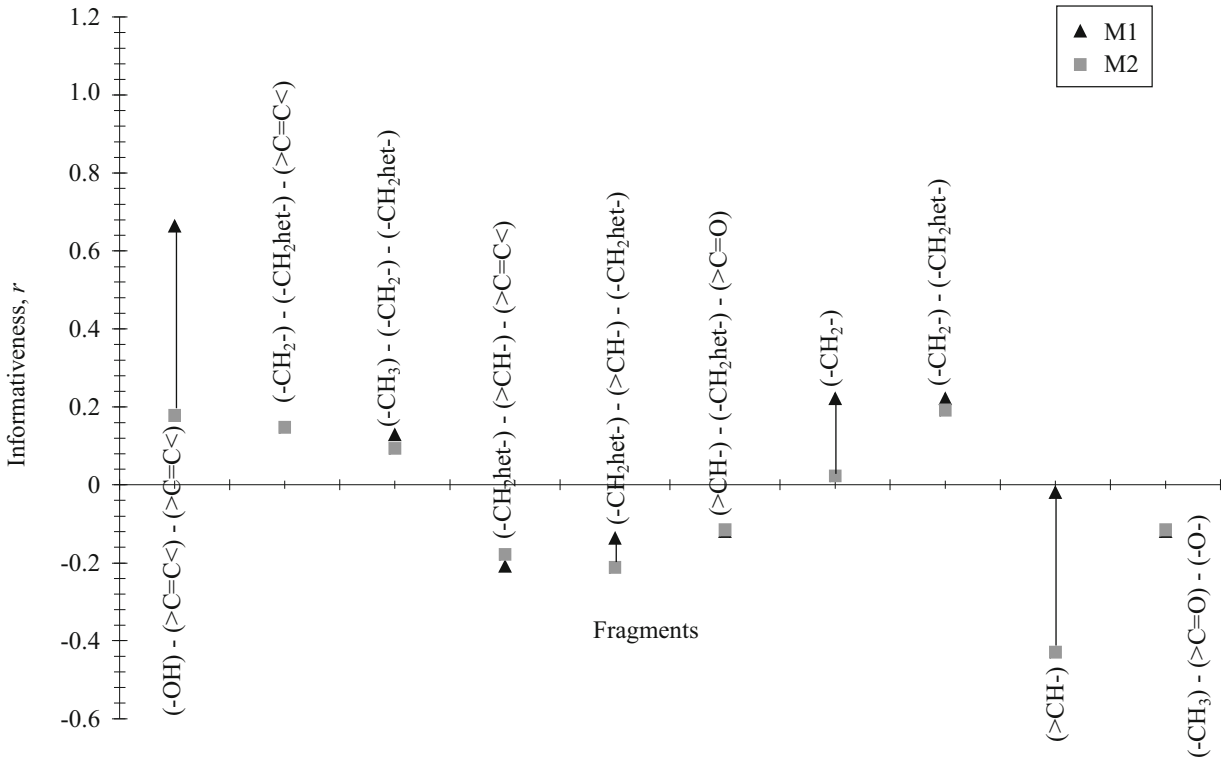
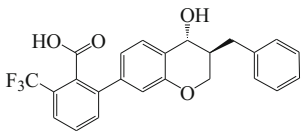
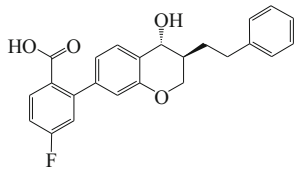
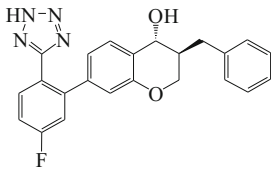
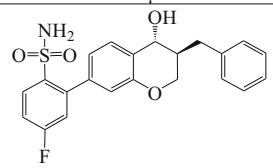
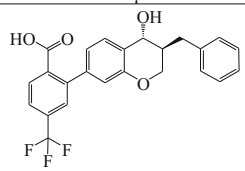
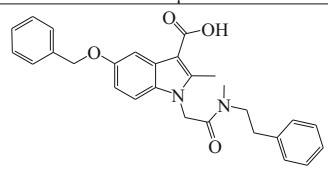
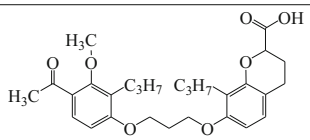
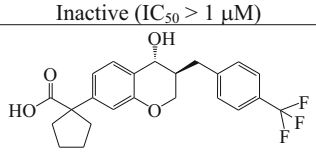
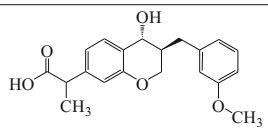
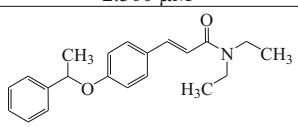
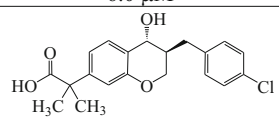
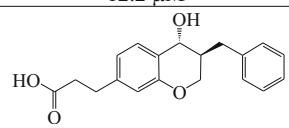


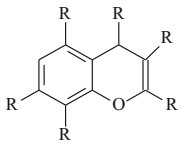
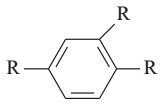
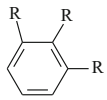
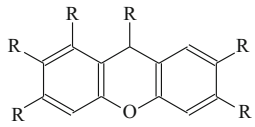
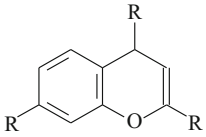
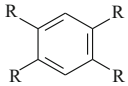
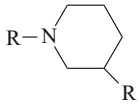
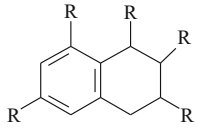
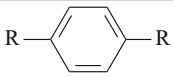
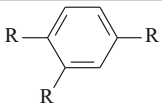
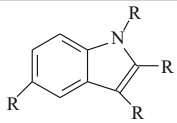
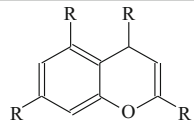
Fig. 2. Acyclic fracture typical of highly and moderately effective blockers of BLT_1 and BLT_2 receptors.

TABLE 1. Typical Structures of Learning Sets M1 and M2

Active (IC_{50} < 1 μM)		
 0.024 μM[f]	 0.032 μM[f]	 0.110 μM[f]
 0.037 μM[b]	 0.056 μM[b] 0.0024 μM[f]	 0.090 μM[b]
Inactive (IC_{50} > 1 μM)		
 2.300 μM[f]	 6.0 μM[f]	 12.2 μM[f]
 1.6 μM[b]	 4.0 μM[b]	 12.0 μM[b]

[f]IC_{50} determined by measuring functional activity of BLT_1 and BLT_2 receptors (human neutrophil chemotaxis); [b]IC_{50} determined by radioligand binding to receptors from polymorphonuclear cells.

TABLE 2. Cyclic Features Typical of Highly and Moderately Effective BLT_1 and BLT_2 Blockers

 507*	 121*	 192*	 514*
 517*	 243*	 327	 508
 143	 290	 511	 513

* Features typical of highly effective compounds.
Numbers indicate the codes used for cyclic structures in calculations.

TABLE 3. Decision Set of Features (M1)

Feature No.	Content of feature	*r*
1	{(-OH)-(1,2,4,5-tetrasubstituted benzene)}#{(>C=C<)-(1,2,3,6,8-pentasubstituted-1,2,3,4-tetrahydronaphthalene)}	0.770
2	{(-OH)-(>C=C<)}#{(>C=C<)-(1,2,3,6,8- pentasubstituted -1,2,3,4-tetrahydronaphthalene)}	0.770
3	{(-O-)-(1,2,4,5-tetrasubstituted benzene)}#{(>C=C<)-(1,2,3,6,8-pentasubstituted -1,2,3,4-tetrahydronaphthalene)}	0.770
4	(F)#(2,3,5,7-tetrasubstituted-4H-chromene)#(-CH_2het-)	0.000
5	(>CH-)#(2,4-tetrasubstituted-chromane)#(1,2,4-trisubstituted benzene)	– 0.613
6	(1,2,3,6,8- pentasubstituted-1,2,3,4-tetrahydronaphthalene)#(2-substituted-1,3-benzoxaole)#(1,2,4-trisubstituted benzene)	– 0.634

sion set of features (DSF). Criteria for inclusion of features in the DSF were a maximal level of informativeness, a minimal level of interactivity, and an optimum recognition of the identifiable chemical structures. The models for theoretical assessment of the target activity were formed by simultaneous use of the DSF and structure recognition algorithms: a geometric approach and a "voting" method. In the geometric approach assignment of the structure of interest to the active compounds group or the inactive compounds group (groups A and B) was performed after determining the distance of the structure in Euclidean space to the calculated standards of groups A and B. In the "voting" method, the numbers of features of alternative groups from the DSF coinciding with structural features were counted and compared.

RESULTS AND DISCUSSION

These theoretical studies established that the extent and nature of the influences of structural features on the appearance of antagonistic activity in relation to BLT_1 and BLT_2 receptors depended both on their chemical nature and on how they were bonded (Fig. 1). In addition, the extent of antagonistic activity and, thus, the nature of the influences of structural features depended on the method used to measure activity. In particular, data from model M1 indicated that the carbonyl group has a small negative informativeness (Fig. 1*a*), i.e., did not have a significant influence on blockade of BLT_1 and BLT_2 receptors. Sequential combination of the carbonyl and hydroxyl groups with an ethylene fragment had marked negative actions on the appearance of antagonistic activity against BLT_1 and BLT_2 receptors on the basis of data from model M1 (Fig. 1*a*), though this same combination was typical of highly effective blockers of BLT_1 and BLT_2 receptors on the basis of data from model M2 (Fig. 1*b*). The unit consisting of a chemically bonded carbonyl group, a methyl fragment, and a hydroxyl group made a positive contribution to the presence of antagonistic activity in relation to this receptor (Fig. 1*a*). An analogous comment can be made regarding the influence of the hydroxyl group. Combination of the carbonyl group with two ethylene fragments was predominantly found in the class of highly effective compounds, though substitution of one of the ethyl-

TABLE 4. Decision Set of Features (M1)

Feature No.	Content of feature	*r*
1	{(-CH_2Het-)-(-CH_2het-)}-!-{(>C=C<)-(2,3,4,5,7 pentasubstituted chromane)}-!-{(-CH_2-)-(-CH_2het-)}	0.680
2	{(>C=O)-(-OH)}-&-{(>C=O)-(>C=C<)}-&-{(-CH_2het-)-(>C=C<)}	0.642
3	{(-OH)-(>C=O)-(>C=C<)}	0.557
4	(1,3-disubstituted pyridine)-#-(2,3,4,5,7-pentasubstituted chromane)-#-(-CH_3)	0.521
5	(-(CH_2)$_3$-)-#-(2,3,4,5,7-pentasubstituted chromane)-#-(-CH_3)	0.511
6	(-OH)-#-(>C<-#-(2,2,5,6,7,8-hexasubstituted chromane)	0.493
7	(1,2,4,5 tetrasubstituted benzene)-#-(N-)-#-(-CH_3)	– 0.364
8	(2,3,4,5,7-pentasubstituted chromane)-#-(1,4-disubstituted benzene)-#-(-CH_2-)	– 0.394
9	(F)-#-(2,3,4,5,7-pentasubstituted chromane)-#-(1,4-disubstituted benzene)	– 0.558
10	{(>CH-)-(>C=C<)}-#-{(>C=C<)-(2,3,4,5,7-pentasubstituted chromane O-)-(1,2,4,3-substituted benzene)}	– 0.582
11	(>CH-)-#-(1,2,4,3-substituted benzene)-#-(-N=N-)	– 0.615

& – indicates conjunction (logical "and"); ! indicates disjunction (logical "or"); # indicates strict disjunction (logical "nor")

TABLE 5. Results of Recognition of the Training and Test Sets Using the Decision Set of Features (DSF)

Recognition result, %, method	Training set M1			Test set (27 structures)	Training set M2			Test set (26 structures)
	Series A	Series B	Whole set		Series A	Series B	Whole set	
Geometrical	88.6	88.4	88.5	81.5	86.4	95.8	91.1	77.0
Voting	86.4	88.4	87.4	81.5	88.9	72.9	80.9	80.8

ene fragments with an oxygen atom led to inversion of the target property (Fig. 1*b*).

Thus, as shown in Fig. 1, the calculation results can not only differ significantly, but can be contradictory. Thus, refinement of the relationships found using data from the two methods was sought by further complex analysis of the structural features of the two models, M1 and M2. As an example, Fig. 2 shows acyclic features typical of highly and moderately effective antagonists of BLT_1 and BLT_2 receptors. The cyclic fragments typical of effective blockers of BLT_1 and BLT_2 receptors are shown in Table 2.

During further investigations, the DSF was formed and two mathematical models for predicting and recognizing blockers of BLT_1 and BLT_2 receptors were constructed for series of nitrogen-, oxygen-, and sulfur-containing heterocyclic organic compounds (Tables 3 and 4). Automatic selection using the program algorithm placed fragment features and their logical combinations potentially responsible for the presence or absence of antagonistic activity in the DSF. The significance of these relationships was verified by testing the DSF against compounds of the training sets and the test sets, containing 27 and 26 structures of compounds with known effectiveness as antagonists of BLT_1 and BLT_2 receptors for models M1 and M2 respectively. The level for significant prediction of the target property was greater than 80% for compounds in the training set and about 80% for structures in the test sets using the "voting" and geometrical approaches (Table 5). The structural patterns found can be used for virtual screening of potential drugs for the presence of antagonist activity as blockers of BLT_1 and BLT_2 receptors.

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