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Computer-assisted design of novel leukotriene C_4 receptor antagonists

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Structural features of the agonist leukotriene C_4 (LTC_4) derived from conformational analysis has led to the development of an intuitive receptor model and the design of potential LTC_4 antagonists. These compounds are modelled, in which either phenoxymethyleneoxadiazole, N-phenylbenzamide or phenyloxymethylenetetrazole functionality is incorporated as a planar equivalent of LTC_4. The trifluoromethyl group is introduced at the lipophilic binding pocket of the agonist.

Enzymic oxidation of arachidonic acid via the lipoxygenase pathway gives rise to a group of biologically important mediators, the peptide leukotrienes (pLTs) **C, D** and **E** (LTC_4, LTD_4 and LTE_4) which have been identified as important components of slow reacting substances of anaphylaxis (SRS-A)[1,2]. These leukotrienes are reported as potent mediators of allergic, inflammatory and other pathological events[2]. Leukotriene C_4 has been shown to cause potent bronchoconstriction[3], increased microvascular permeability[4], and airway mucous secretion[5]. Development of antagonists of leukotriene C_4 is of immense pharmacological interest to treat allergic asthma and other inflammatory diseases.

In the present paper, we report an application of the computer-assisted molecular modelling (CAMM) to develop a novel series of compounds possessing LTC_4 antagonist properties. Since no structural information is available about the receptor active site, an indirect approach was adopted to understand the important interactions necessary for binding. Based on the natural agonist and on the structure-activity relationships (SAR) of known LTC_4 antagonists, we have studied the conformational properties of the LTC_4. Each of the conformer was evaluated and compared in search for agonist binding conformation. Six torsion's were considered most critical to the conformation of the molecule[6] (Figure 1). Four conformers extracted from the potential energy wells within 5 kcal/mol of the lowest energy were selected as shown in Figure 2.

Conformational analysis revealed the existence of folded conformations. The hydrophilic portion of the peptide chain tends to curl upon the triene portion of the molecule. Similarly, the hydrophobic tail also curls back towards the triene at the methylene between the two *cis* double bonds. Thus, the three important components of the agonists are: an acidic hydrophilic group at one end, hydrophobic region at the other end and the third part represented by a central planar triene[6,7]. On the basis of these structural features and interatomic distances, the lowest energy conformer was identified as an active conformation and used in the design of potential LTC_4 antagonists.

Methods

All molecules in this study were built using QUANTA[8] version 4.0 and charges were assigned by Gasteiger method[9]. Each compound was energy minimized using steepest descent until energy changes for the entire structures were smaller than

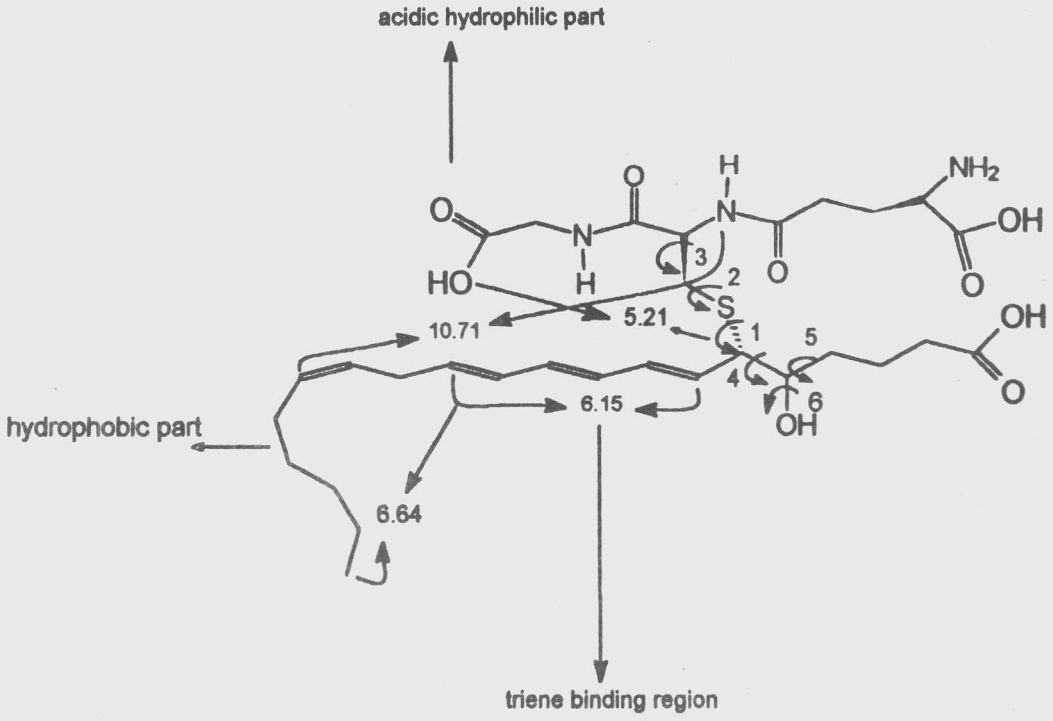

Figure 1 — Receptor binding model of LTC_4 showing the torsions rotated during grid search.

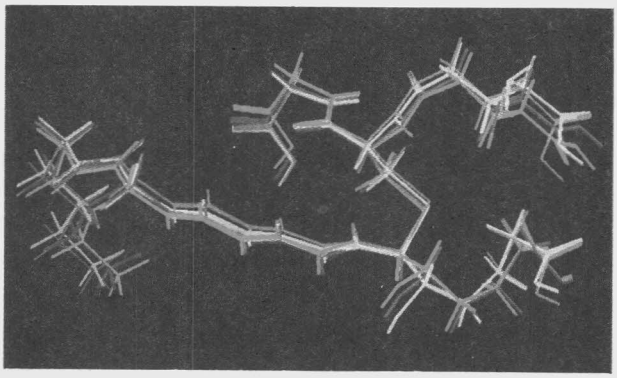

Figure 2 — Super imposition of low energy conformations of LTC_4.

0.01 kcal/mol per 250 steps. This was followed by application of the Adopted-Basis Newton-Raphson (ABNR) minimization until energy tolerance of 0.001 kcal/mol was satisfied. In general, this required 500 ABNR minimization steps. Minimization of agonist (LTC_4) was performed by using 500 steps of steepest descent 1000 steps of ABNR minimization methods. The conformational space[10] of the agonist and modelled structures was explored with systematic (Grid scan) search algorithm[11] within QUANTA. Number of conformers generated for agonist were 729 (steps of 30° increment) and for modelled structures were 256. The lowest energy conformer was chosen for flexible fitting method. All calculations were performed using CHARMm[12] version 22 running on Silicon Graphics IRIS 4D/20 workstation.

Molecular Modelling Study

Compound design. Since the structure of the LTC_4 receptor has not been known, our design of antagonists binding to this receptor was based on molecular modelling of the natural agonist and on the structural features of known receptor antagonists. ONO-RS-347 and ONO-RS-411 (Figure 3) belonging to the series of 8-(benzoylamino)-2-(tetrazol-5yl)-1, 4-benzodioxans and 8-(benzoylamino)-2(tetrazol-5yl)-4-oxo-4H-1-

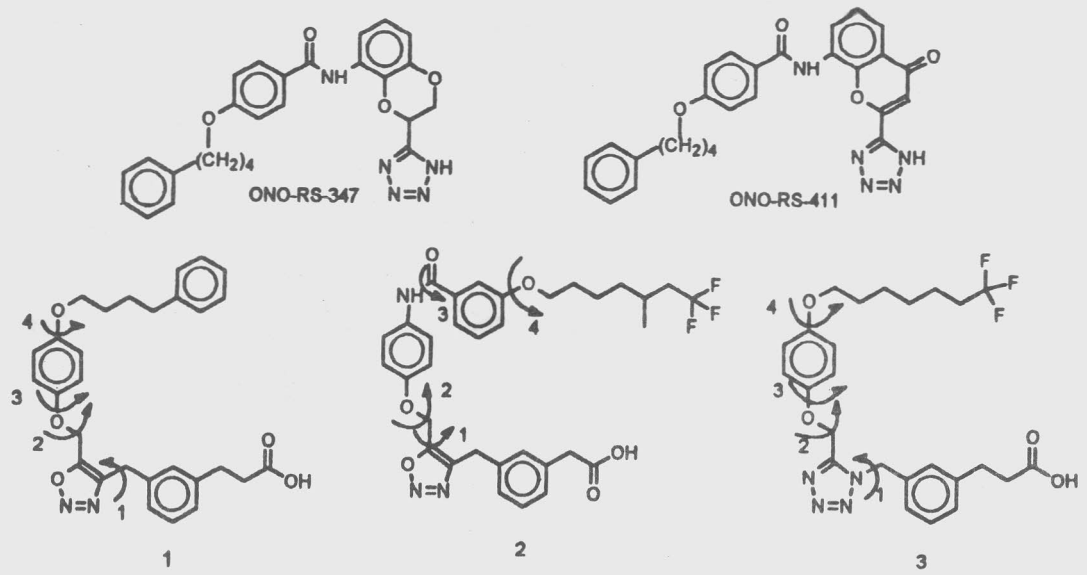

Figure 3

benzopyrans were shown to be potent antagonists of LTC_4 receptor[13]. The hydrophobic phenylbutoxy chain, present in these compounds was incorporated in compound **1**, and the N-phenylbenzamide functionality was introduced in compound **2** to mimic the planar triene region. On the basis of interatomic distance 5.80Å and molecular modelling of possible groups that fill the triene portion, led to the selection of phenyloxymethylene substited 1,2,3-oxadiazole. It is well documented that the compounds containing oxadiazole unit exhibit anti-inflammatory activity[14]. Hence, we incorporated the oxadiazole group with an aim to obtain potential antagonists of LTC_4. The trifluoromethyl group was introduced based on two criteria: firstly, the replacement of hydrogen atoms by fluorine in biologically active molecules found to have significance on activity[15] and secondly, the ability of fluorinated group to change the lipophilicity and electronic character. Presence of a fluorine containing group in the lipophilic side chain would increase antagonistic activity by increasing lipopilicity. The phenyloxymethylene tetrazole group of compound **3** occupies the planar triene region, with a distance of 6.17Å. The rationale for the addition of an acidic functional group, a carboxylic acid, is based on the molecular features of the LTC_4. Thus, three compounds **1, 2, 3** shown in Figure 3 have been designed.

Results and Discussion

Conformational search analyses of Leukotriene C4(LTC_4). The conformational space of LTC_4 was explored using grid scan. At each grid point dihedral angles were constrained to a specific grid value, thus 729 conformers were generated. Four conformers which were within 5 kcal/mol of the lowest energy conformation (Table I) were extracted from the potential energy wells and subjected to 500 iterations of Adopted-Basis Newton-Raphson minimization. The low energy conformers were superimposed by flexible fitting method. The weighted root mean square deviation (RMS) of all superimpositions was 0.41Å.

Conformational search analyses of LTC_4 antagonists. Low energy conformations ((Table II) of each of the antagonists were obtained by using grid search. Number of conformers generated were 256 per compound followed by a 500 step minimization using Adopted-Basis Newton-Raphson method. The C-O torsion angle of **1** was rotated by 179° from –60° (the change in bond angle was 0°) in order to get a distance similar in range to that of LTC_4, the distance of the acid binding region now being 5.28Å. The small change resulted in 1.13 kcal/mol increase in conformational energy when calculated *in vacuo*. The energy difference however, does not preclude this conformation from being an active

Table 1 — Conformational data of LTC_4

Conf.	Energy kcal/mol	ϕ_1	ϕ_2	ϕ_3	ϕ_4	ϕ_5	ϕ_6
1.	−74.90	29.52	60.20	60.35	29.66	59.89	59.97
2.	−72.746	29.76	60.23	60.37	29.48	59.76	30.40
3.	−71.718	29.42	60.21	60.13	29.77	30.15	60.03
4.	−70.776	29.57	60.01	60.13	29.91	30.14	30.09

Table II — Conformational data for low energy structures of LTC_4 antagonists

Compd	Energy kcal/mol	ϕ_1	ϕ_2	ϕ_3	ϕ_4
1.	40.14	89.984	89.923	60.084	60.034
2.	34.31	59.937	30.165	− 0.056	89.925
3.	−22.09	60.143	60.102	0.138	60.047
ONO-RS-347	15.99	0.136	29.911	60.116	89.951

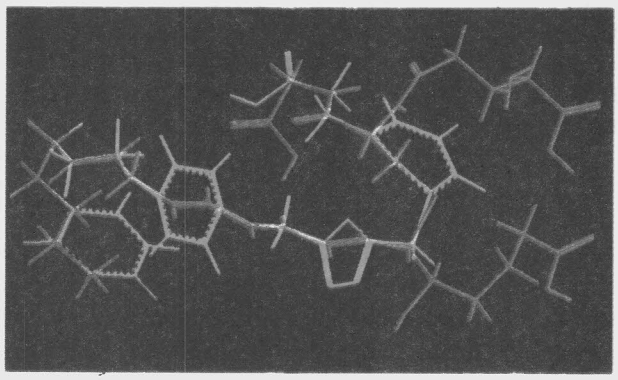

Figure 4 — Superimposition of **1** (red) on LTC_4 (blue) by torsional flexible fitting.

conformation. For all other compounds, the lowest energy conformers had distances similar to that of the agonist; therefore the torsion angles were left unaltered. Each of these conformers were taken for torsional flexible fit with the agonist (Figure 4). In all cases RMS values were between 0.15 and 0.2 Å.

Conclusions

A hypothetical model for leukotriene C_4 receptor was deduced from the conformational and structure analysis of an agonist and on the basis of known receptor antagonists. The three important components of the receptor model were identified: a lipophilic binding region, an acid binding region and a planar triene region. Based on the principle of complementarity in shape and properties that is essential for receptor recognition, we have designed three compounds with such features as potential receptor antagonists. Phenoxymethylenetetrazole and phenoxymethyleneoxadiazole were incorporated as receptor binding equivalents of the triene unit of LTC_4 and trifluoromethyl substituent as lipophilic side chain. The structures of potential receptor antagonists having been derived, the low energy conformers were superimposed on LTC_4 and examined for similarity. The low RMS values of torsional flexible fit with LTC_4 indicate that the three compounds modelled may exhibit potential LTC_4 receptor antagonist activity.

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References

1 Nelson N A, Kelly R C & Jonhson R A, *Chem Eng News*, 16, **1982**, 30.
2 Lewis R A, Austen K F & Soberman R J, *N Engl J Med*, 323, **1990**, 644.
3 Dahlan J E, Hedquist P, Harmmarstrom S & Samuelson B, *Nature*, 288, **1980**, 484.
4 Woodward D F, Weichmann B, Gill C A & Wasserman M A, *Prostaglandins*, 25, **1983**, 131.
5 Maron Z, Shelhaman J H, Bach M K, Mortani D R & Kaliner M, *Am Rev Respir Dis*, 126, **1982**, 449.
6 Harper R W, Herron D K, Bollinger N G, Sawyer J S, Baldwin R F, Roman C R, Rinkema L E & Fleisch J H, *J Med Chem*, 35, **1992**, 1191.
7 Hariprasad V & Kulkarni V M, *J Comput-Aided Mol Design*, 10, **1996**, 284.
8 QUANTA version 4.0 (Polygen Corp., Molecular Simulations Inc., 200 Fifth Ave. Waltham, MA 02154) 1994.
9 Gaseiger J & Marsilli M, *Tetrahedron*, 36, **1980**, 3219.
10 Hariprasad V & Kulkarni V M, *J Mol Recogn*, 9, **1996**, 95.
11 QUANTA Simulations Search and Analysis, (Molecular Simulations Inc.) 1994, 106.
12 Brooks B R, Bruccoleri R E, Olafson B D, States D J, Swaminathan S & Karplus M, *J Comput Chem*, 4, **1983**, 187.
13 Nakai R, Konno M, Kosuge S Sakuyama S, Toda M, Arai Y, Obata T, Katsube N, Miyamoto T, Okegawa T & Kawasaki A, *J Med Chem*, 31, **1988**, 84.
14 Palazzo G, Travella M, Strani G & Silversini B, *J Med Pharm Chem*, 4, **1961**, 351.
15 Filler R & Kobayashi Y, *Biomedicinal aspects of fluorine chemistry*, (Elsevier, Amsterdam) 1982, 246.