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Novel Phthalimide Derivatives, Designed as Leukotriene D_4 Receptor Antagonists

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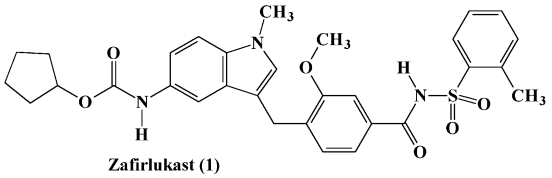
Abstract—A series of phthalimide acid derivatives was synthesized and evaluated as leukotriene D_4 receptor antagonists. The tetrazolephthalimide LASSBio 552 (**7**) was shown to be able to inhibit the contractile activity induced by 100 nM of LTD_4 in guinea-pig tracheal strips with an $IC_{50} = 31.2\,\mu M$. In addition, LASSBio 552 (**7**) has been showed to present a better efficacy than zafirlukast (**1**) used as standard.

Asthma is the most rapidly growing therapeutic market in the world, reflecting the world-wide increase in prevalence of this pathology and the increasing recognition that chronic treatment is needed for many patients.[1,2] Cysteinyl-leukotrienes C_4, D_4, and E_4 are products of the 5-lipoxygenase pathway of arachidonic acid metabolism, which were characterized as the major constituents of the slow-reacting substance of anaphylaxis.[3,4] These substances are believed to be involved in the development of immediate airways hyperresponsiveness, bronchoconstriction, and inflammatory response associated with asthma.[5–8] Recent development of antiasthmatic drugs representing an important therapeutic innovation, the most important in the last 20 years, are cysteinyl leukotriene receptor antagonists. Zafirlukast (**1**), is an example, of selective and competitive leukotriene D_4 (LTD_4) receptor antagonist that has been recently developed.[9–11]



Zafirlukast (1)

In the course of a research program aiming at design, synthesis, and pharmacological evaluation of new lead candidates useful for asthma treatment,[12] we describe in this paper the design, synthesis and inhibitory contractile effect, in guinea-pig tracheal strips induced by LTD_4, of novel phthalimide derivatives, structurally planned as LTD_4 receptor antagonists (**2**–**8**). These new derivatives were planned by applying molecular simplification approach in the prototypes (**9**–**10**),[13–16] searching for a new possible bioisosteric relationship between the quinoline and phthalimide rings (Chart 1). In addition, the highly rigid LTD_4 receptor antagonist VUF5017 (**9**) was used as template to obtain the interatomic distances between nitrogen atom of the quinoline moiety and carboxylate group that are previously designated as pharmacophoric moieties.[16,17]

The measured interatomic distances between oxygen atom of the phthalimide group and ionizable nitrogen atom of tetrazole moiety of compound **7** (LASSBio 552) are in the same range of those showed by VUF5017 (**9**) (Fig. 1), as well to all new derivatives (**4**–**8**), except for compounds **2** and **3**.

These novel phthalimide derivatives **2**–**8** were synthesized by the route illustrated in Scheme 1,[18] based on condensation of phthalic anhydride with tyramine [4-(2-aminoethyl)phenol] in the presence of acetic acid at reflux, furnishing the key intermediate (**12**) in 80% yield. Subsequent treatment of phenolic derivative (**12**) with appropriated alkyl bromides in different *O*-alkylation

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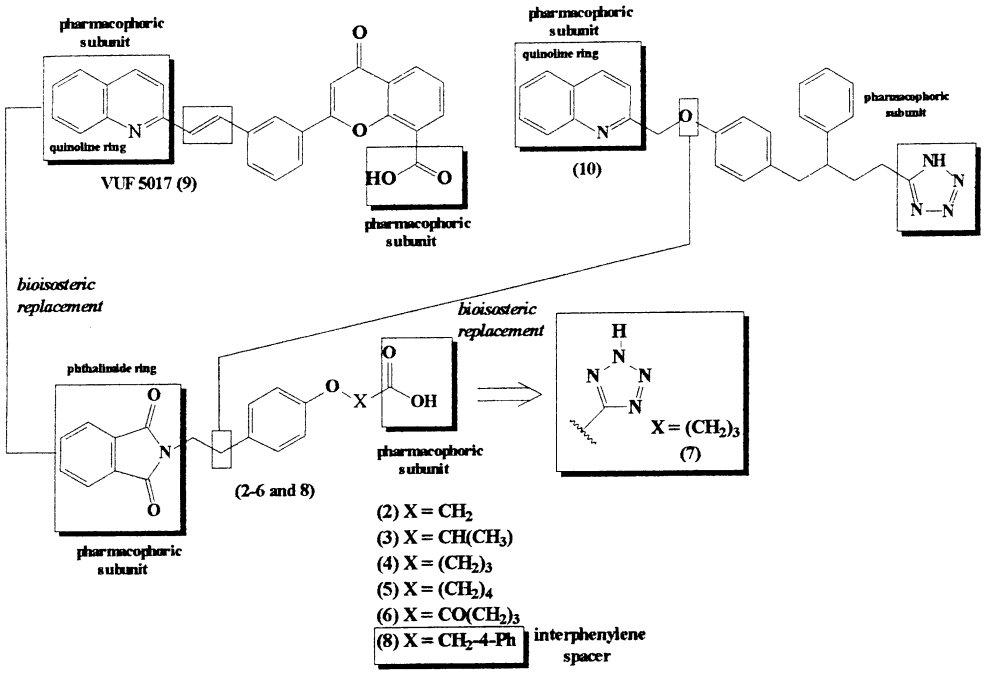
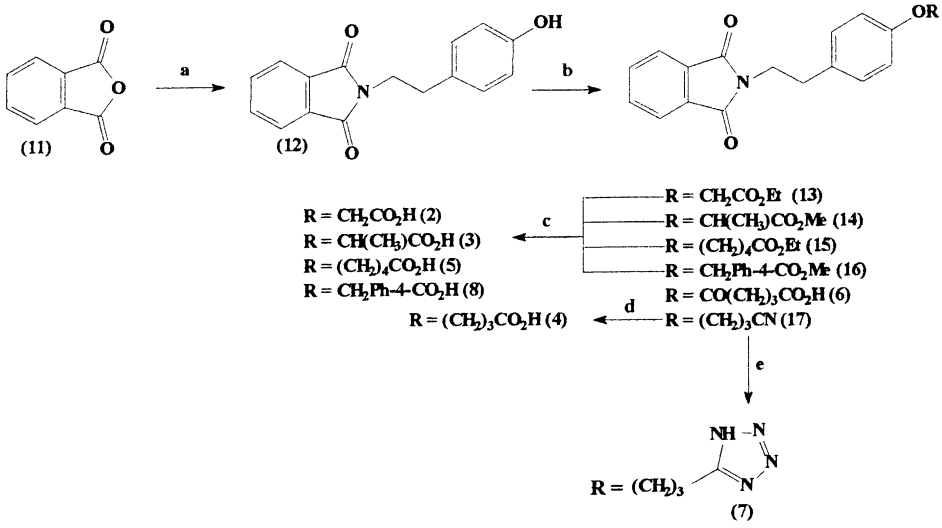


Chart 1.



Scheme 1. Reagents and conditions: (a) [4-(2-aminoethyl)phenol], AcOH, 140 °C, 30 min, 80%; (b) Alkyl-bromides, DMF, K_2CO_3, rt, 2–24 h, 63–92%; (c) HCl:AcOH (1:1), rt, 4–8 h, 72–84%; (d) HCl:AcOH (1:1), 60 °C, 30 min, 72%; (e) NaN_3, NH_4Cl, DMF, 120 °C, 72 h, 80%.

conditions, as previously described,[19] allowed to obtain esters (**13**–**16**) and nitrile (**17**) in good yields. Following our synthetic route, these derivatives were submitted to acidic hydrolysis with a mixture of hydrochloric acid and acetic acid at room temperature or at reflux,[20] to obtain the desired phthalimide-acid derivatives (**2**–**5** and **8**) in adequate yields. Finally, we prepared the tetrazole derivative (**7**) in 80% yield, by the reaction of nitrile intermediate (**17**) with sodium azide and ammonium chloride in dimethylformamide at reflux.[21]

The pharmacological results obtained for the novel phthalimide derivatives (**2**–**8**) are compiled in Table 1.

All compounds were evaluated in vitro using the LTD_4 induced contraction of guinea-pig trachea strips bioassay,[22,23] and zafirlukast (**1**) as standard (Table 1). The analysis of these screening data showed a significant inhibitory activity for compounds **4** (LASSBio 553) and **6** (LASSBio 483), and a highlighting activity observed for compound **7** (LASSBio 552) (Table 1). Encouraged by these results, LASSBio 552 (**7**) was selected to study the concentration–response relationship to inhibit the contractile activity induced by 100 nM of LTD_4, presenting an $IC_{50} = 31.2\ \mu M$ (10 nM–400 μM). Although, LASSBio 552 has been showed to be less potent than zafirlukast ($IC_{50} = 1.03$ nM [0.1 nM–100 μM]), it was able to evoke a maximum inhibitory response, contrasting with zafirlukast that presented a maximum response of effect in the range of 58% (Table 2).[24] These results suggest that LASSBio 552 presented a better efficacy profile than the standard zafirlukast.

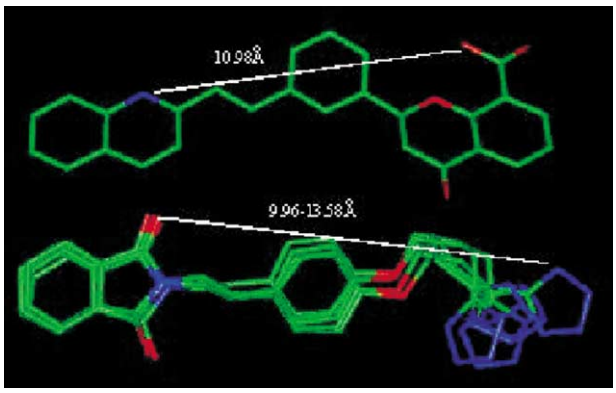


Figure 1. Interatomic distances between the main pharmacophore groups of the VUF5017 and LASSBio 552 (**7**) (showing the superimposition of the most stable conformations). Hydrogen atoms are not shown for clarity.

Table 1. Inhibitory contractile effect of phthalimide derivatives (**2**–**8**) in guinea-pig tracheal strips induced by LTD_4 (100 nM)

Compd (100 μM)	n[a]	% Contraction[b]	% Inhibition[c]
Control	26	100.0±0.0	0.0 n.s.[d]
Zafirlukast (**1**)	04	41.3±7.2	58.7*
LASSBio 482 (**2**)	03	101.5±0.8	−1.5 n.s.[d]
LASSBio 485 (**3**)	03	91.4±3.7	8.6*
LASSBio 553 (**4**)	05	80.3±7.6	19.7*
LASSBio 484 (**5**)	03	97.6±11.9	2.4 n.s.[d]
LASSBio 483 (**6**)	05	73.9±7.9	26.1*
LASSBio 552 (**7**)	06	52.4±6.4	47.6*
LASSBio 551 (**8**)	05	93.7±5.2	6.3 n.s.[d]

[a]n = number of independent experiments.
[b]% of contraction, considering contraction obtained in the vehicle presence 100.0%.
[c]% of inhibition obtained by comparison with control group.
[d]n.s., not significant.
*$P<0.05$ (Student's t-test). Results are expressed as mean±SEM.

Table 2. Comparison of the pharmacological effects of zafirlukast (**1**) and LASSBio 552 (**7**), using the LTD_4 (100 nM) induced contraction of guinea-pig tracheal strips bioassay

Compd	E_{max}[a]	IC_{50}[b]
Zafirlukast (**1**)	58.7%	1.03×10^{-9} M
LASSBio 552 (**7**)	100.0%	31.2×10^{-6} M

[a]E_{max}, maximum effect.
[b]IC_{50}, concentration to produce 50% of effect.

In summary, we were able to design a new phthalimide derivative possessing adequate structural requirements to antagonize the contractile effect of LTD_4 in guinea-pig tracheal strips, in a dose dependent manner, establishing a new bioisosteric relationship between phthalimide ring, present in LASSBio 552 (**7**) and quinoline ring present in prototypes (**9**–**10**).

Acknowledgements

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