Dual Acting Antihistaminergic Agents

R.T. Scannell*[a], E. Differding[b] and P. Talaga[b]

[a]*UCB Research Inc. 840 Memorial Drive, Cambridge, MA 02139, USA*

[b]*UCB S.A. Pharma Sector, Chemin du Foriest, B-1420 Braine-l'Alleud, Belgium*

Abstract: Histamine is a primary mediator in allergic response and acts in concert with other agents to impact disease progression. Respiratory disorders such as asthma, rhinitis and dermatological conditions such as urticaria involve histamine along with other mediators. An antihistamine that possesses an additional property of counteracting the effects mediated by these other mediators should offer some therapeutic benefit over a selective antihistaminergic agent.

Keywords: Dual H_1 antihistamine, 5-LO, LTD_4, H_2 antihistamine, H_3 antihistamine, H_4 antihistamine, PAF, Neurokinin, Tachykinin, Thromboxane A_2, Bradykinin B_2.

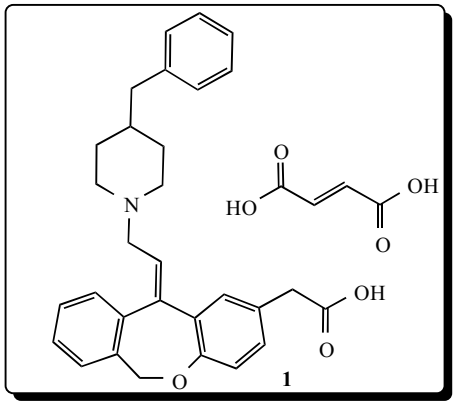
INTRODUCTION

The histamine H_1 receptor is a G protein coupled receptor (GPCR) that mediates its actions by coupling to the $G_{q/11}$ family of G proteins [1] with subsequent cleavage of phospholipids by phospholipase C to yield inositol-1,4,5-triphosphate (IP_3) and diacylglycerol (DAG). Intracellular stores of Ca^{2+} are subsequently mobilized. These receptors are found both in the periphery and in the CNS. In the periphery, they affect smooth muscle and endothelial cell contraction in the respiratory and gastrointestinal system as well as causing vasodilatation and increased vascular permeability. The H_1 receptors that are localized in the CNS can produce sedation.

Antagonists to the histamine H_1 receptor are useful for relieving the symptoms of an allergic reaction such as bronchoconstriction, rhinitis, urticaria, atopic dermatitis, and asthma [1]. Due to the presence of additional inflammatory and bronchoconstrictive mediators during an allergic reaction, an antihistaminergic agent that affects some of the biochemical pathways induced by such agents would be of potential benefit. Thus, several research groups have developed programs aimed at identifying compounds that possess dual activities against "disease mediators" involving both histamine and other inflammatory agents. This review discusses efforts to develop agents that would possess a dual activity combining histamine H_1 receptor antagonism with an inhibitory effect against another inflammatory mediator system. Approaches involving a combination of two discrete agents are not discussed here.

DUAL HISTAMINE H_1 RECEPTOR ANTAGONIST-THROMBOXANE A_2 RECEPTOR ANTAGONIST OR SYNTHESIS INHIBITOR

The prostanoid, thromboxane A_2 (TXA_2), plays a role in vascular smooth muscle contraction, bronchoconstriction and airway hyperresponsiveness [2-4]. This mediator has also been implicated in the bronchial hyperresponsiveness associated with asthma [5]. Kyowa Hakko Kogyo [6] developed a series of dual acting H_1 and TXA_2 receptor antagonists based upon a dibenzooxepine scaffold. The fumarate half salt, KF15766 (**1**), was identified as a lead compound in this series displaying affinity at both the TXA_2/PGH_2 guinea pig platelet receptor (K_i = 740 nM) and the guinea pig cerebellum histaminergic H_1 receptor (K_i = 20 nM). Oral administration of this compound inhibited the passive cutaneous anaphylaxis reaction in rats with an ED_{50} of 0.73 mg/kg. Moreover, bronchoconstriction in guinea pigs induced by either histamine or the thromboxane mimetic, U-46619, was inhibited by KF15766 at an oral dose of 0.3 mg/kg and 10 mg/kg, respectively.



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Kyoto Pharmaceutical Industries developed a series of indoles possessing both H_1 receptor antagonistic activity and inhibitory activity against thromboxane A_2 synthase [7]. KY-234 (**2**) was identified as the lead candidate from this series. The sodium salt of KY-234 inhibited TXA_2 production in rabbit platelets with an IC_{50} of 50 nM and inhibited H_1-mediated contraction of guinea pig trachea with an IC_{50} of 8 nM.

DUAL ACTING LEUKOTRIENE MODIFYING AGENTS - H_1 RECEPTOR ANTAGONISTS

The leukotrienes are potent inflammatory mediators derived from the metabolism of arachidonic acid (Fig. **1**). Through the action of the 5-lipoxygenase (5-LO) enzyme and

*Address correspondence to this author at UCB Research Inc. 840 Memorial Drive, Cambridge, MA 02139, USA; Tel: (617).547.0033, ext. 236; Fax: (617).547.8481; E-mail: ralph.scannell@ucb-group.com

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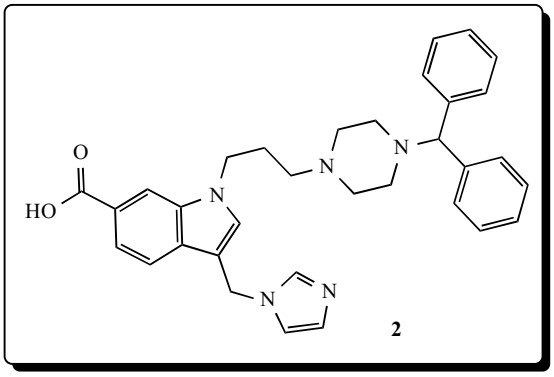
the 5-lipoxygenase activating protein (FLAP), arachidonic acid participates in a cascade leading to the formation of the chemoattractant leukotriene, LTB_4 and the bronchoconstricting cysteinyl leukotrienes, LTC_4, LTD_4 and LTE_4 [8].



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LTB_4 binds to the B-LT receptor on neutrophils and acts as a chemoattractant and activator resulting in the liberation of other inflammatory mediators, proteases and reactive oxygen species. The peptidyl leukotrienes, LTC_4, LTD_4 and LTE_4 bind to the Cys-LT_1 receptor on smooth muscle and result in pronounced bronchoconstriction in the airways. These leukotrienes induce mucus secretion, plasma extravasation and recruitment of eosinophils [9].

The chemotactic properties of LTB_4 indicate that this leukotriene plays a role in diseases such as asthma, inflammatory bowel disease, psoriasis and arthritis. The cysteinyl leukotrienes have been shown to play a prominent role in asthma, and study of these agents has led to the development of several drugs that show promise in the treatment of these diseases. Thus, Abbott laboratories developed zileuton, a 5-lipoxygenase inhibitor that is effective in preventing the initiation of the arachidonic acid cascade [10]. Several drugs have emerged that are Cys-LT_1 receptor antagonists and are employed in the management of asthma. These are montelukast from Merck, zafirlukast from AstraZeneca and pranlukast from Ono [11].

The asthmatic response is complex and involves a variety of inflammatory and bronchoconstricting mediators. In allergic asthma, antigen-induced dimerization of IgE on mast cells leads to the liberation of histamine, tryptase, leukotrienes and other inflammatory agents. This early phase is followed by a late phase response where inflammatory cells are recruited into the airway, thus contributing to the

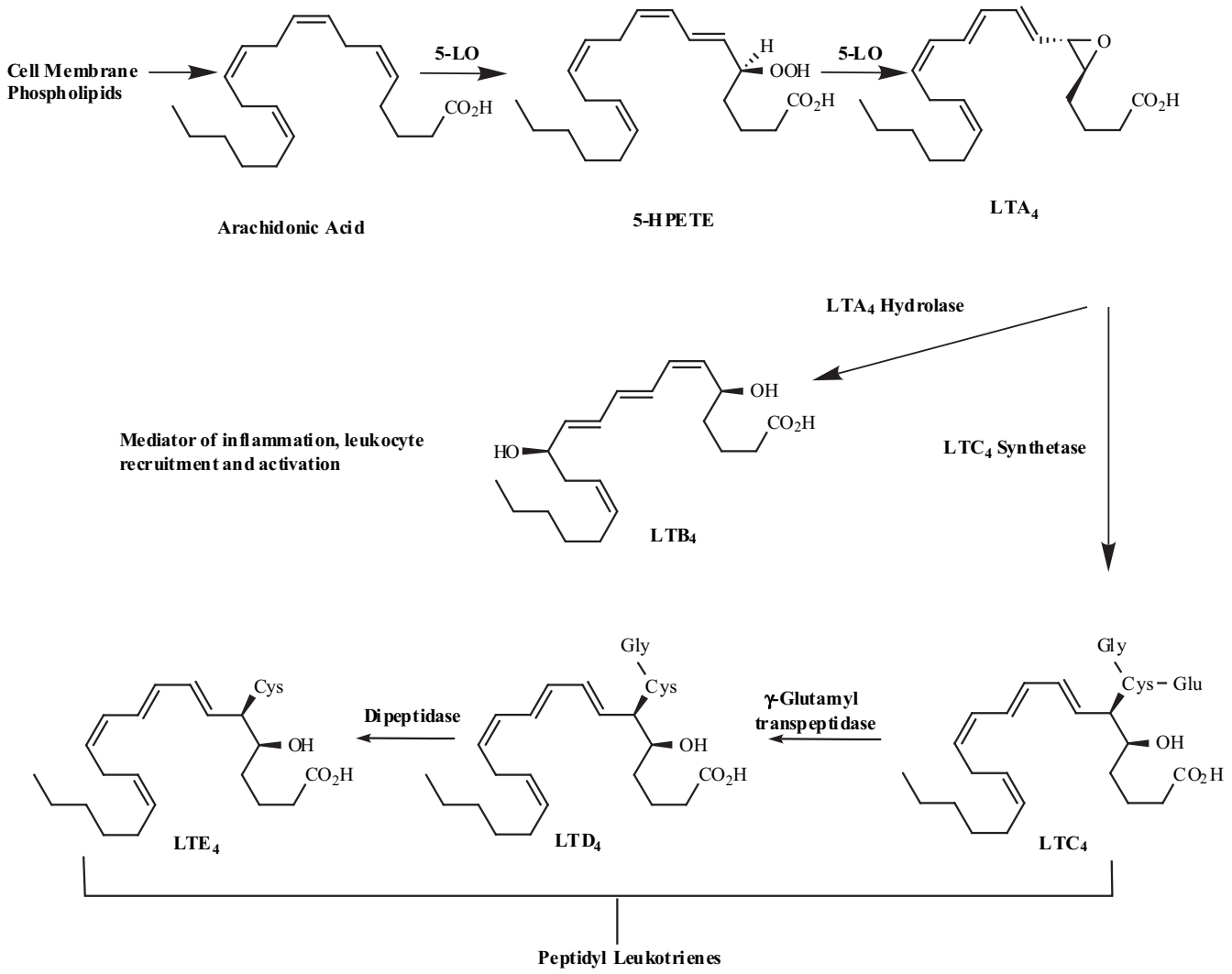
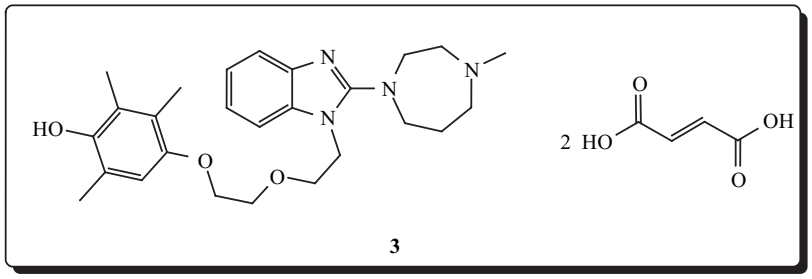


Fig. (1).



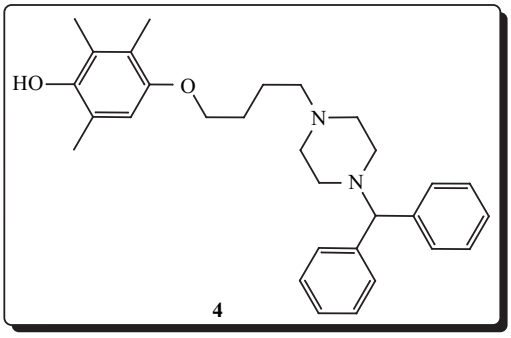
3

formation of the bronchoconstricting leukotrienes. A dual acting agent that would act on both early (histaminergic mediated) and late (leukotriene mediated) phases of the disease should offer an increased benefit over an agent affecting only a single mediator.

Several universities and pharmaceutical companies have mounted an effort to identify dual acting agents that would be effective both at inhibiting the binding of histamine to its cognate receptor as well as interfering with the arachidonic acid cascade or the products of this inflammatory pathway.

Nakano *et al.* [12, 13] reported the identification of benzimidazole derivatives that possess both H_1 receptor antagonism and 5-lipoxygenase inhibition. *In vitro*, their lead candidate (**3**) displayed a pA_2 of 7.49 at inhibition of the histamine-induced contraction of an isolated guinea pig ileum, and inhibited the 5-LO enzymatic activity by 74% at a concentration of 1 μM in an RBL-1 cell assay. Since the lipoxygenase inhibition was derived from a redox reaction associated with the phenolic nature of the molecule, it was not surprising that **3** also inhibited the NADPH-dependent lipid peroxidation induced by Fe^{3+}-ADP in rat liver microsomes. This molecule was also found to inhibit the release of histamine from rat peritoneal mast cells that were activated by an antigen-antibody driven reaction.

Kawasaki *et al.* [14] also reported the use of trimethylhydroquinones oxygen-tethered to a benzhydrylpiperazine moiety. Their most potent compound, identified as **4**, inhibited the 5-LO enzyme in the RBL-1 cell assay with an IC_{50} of 358 nM while displaying a pA_2 of 7.11 against histamine-induced contractions in the guinea pig ileum. Oral administration of **4** at 100 mg/kg in ovalbumin-sensitized guinea pigs treated with mepyramine, demonstrated an improvement in breathing resistance.



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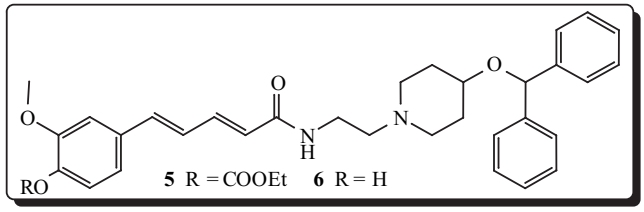
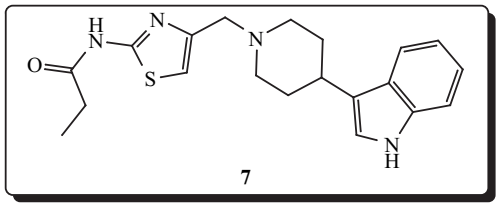
Terumo [15] developed a dual 5-LO inhibitor and H_1 receptor antagonist, linazolast (TMK688, **5**) for asthma and reported on its active metabolite, **6** (TMK777). In the mouse mastocytoma cell line, **5** and **6** inhibited the 5-LO enzymatic activity with an IC_{50} of 0.32 nM and 0.017 nM, respectively. The active metabolite most likely employed the phenol in a redox manner to inactivate the enzyme. Moreover, TMK688 and TMK777 inhibited the histamine-induced contraction of an isolated guinea pig trachea with pD'_2 values of 7.28 and 7.98, respectively. TMK688 significantly inhibited bronchoconstriction at 10 mg/kg in an ovalbumin sensitized guinea pig bronchoconstriction model, confirming a beneficial effect on the early phase of the inflammatory process. This early phase is thought to be a histamine-driven response with TMK688 being able to blunt this process due to its antihistaminergic activity. Looking at the late phase of the process, TMK688 inhibited the increase in airway resistance evoked by ovalbumin at an oral dose of 3.2 mg/kg. This late phase process is thought to be mediated by activation of the cysteinyl leukotriene pathway.



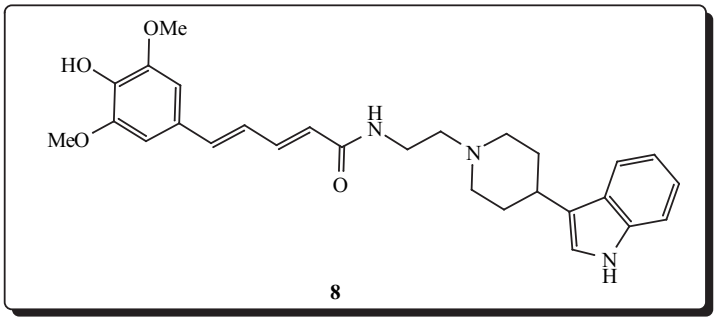
5 R = COOEt **6** R = H

Fujisawa [16] developed a series of indoles that possessed both antihistaminergic activity and 5-LO inhibitory activity. Indole **7** was active in the histamine-induced guinea pig ileum contraction assay with an IC_{50} of 76 nM and was inhibitory at the 5-LO enzyme with an IC_{50} of 244 nM. This indole was later modified to incorporate the phenolic 5-LO inhibitory pharmacophore of TMK777, **6**. Following extensive structure activity modification, indole **8** was identified as the most active compound in the series with an IC_{50} of 34 nM for 5-LO inhibition. This compound also inhibited the histamine-induced contraction of guinea pig ileum with an IC_{50} of 55 nM.



7

Sepracor [17] recently disclosed their work on dual acting 3-hydroxyquinazolin-4-ones of which **9** is a representative structure. The hydroxyquinazolin-4-one group seems to be of crucial importance for the 5-LO inhibitory activity displayed by this type of compound, while the piperidinyl-benzamidazole moiety acts as the H_1 receptor antagonist pharmacophore. Such molecules display affinity for the H_1



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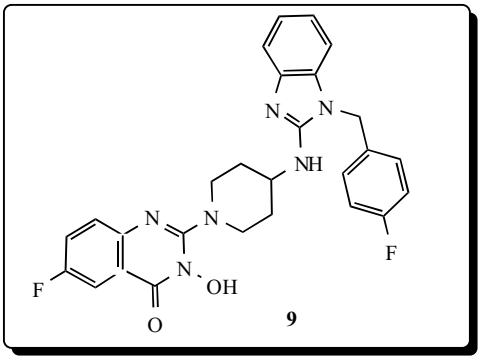
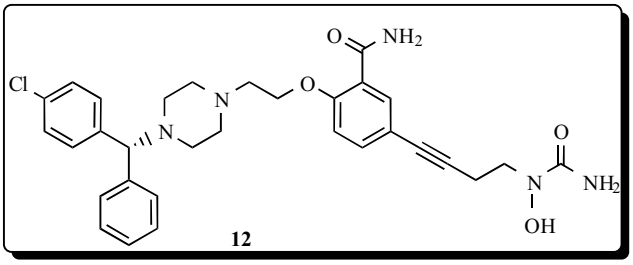
histamine receptor (IC_{50} < 0.1 μM), as well as a potent 5-LO inhibitory activity (IC_{50} <1 μM).

In the same patent, other scaffolds (**10** and **11**) possessing alternative H_1 binding pharmacophores were disclosed. Nevertheless, their activities toward the H_1 histaminergic / 5-LO mediated pathways were much less potent than those reported for **9**.



9

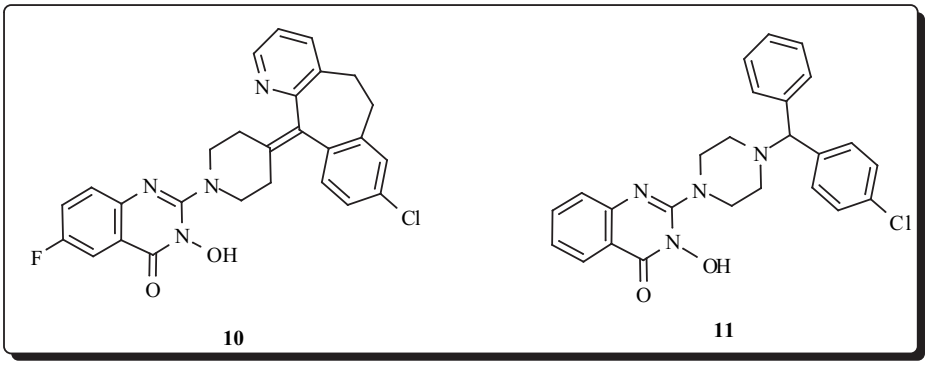
UCB Pharma has recently identified a series of *N*-hydroxyureas that posses both 5-LO inhibitory as well as H_1 receptor binding properties [18-21]. The lead candidate in this series is ucb-35440 (**12**), which exhibited affinity for the human H_1 histaminergic receptor transfected in CHO cells (K_i = 114 nM). Moreover, **12** inhibited the activity of 5-LO in an RBL-2H3 cell extract assay with an IC_{50} of 106 nM. In an *ex vivo* model for the inhibition of LTB_4 formation in the guinea pig, **12** administered orally at a dose of 2 mg/kg, showed a 46% inhibitory effect after 6 hours. In the histamine induced bronchoconstriction guinea pig model, oral administration of 5 mg/kg of **12** displayed 76% inhibition after six hours. Moreover, in ovalbumin sensitized guinea pigs, oral dosing at 5 mg/kg gave an 81% inhibition of antigen-induced bronchoconstriction after three hours.



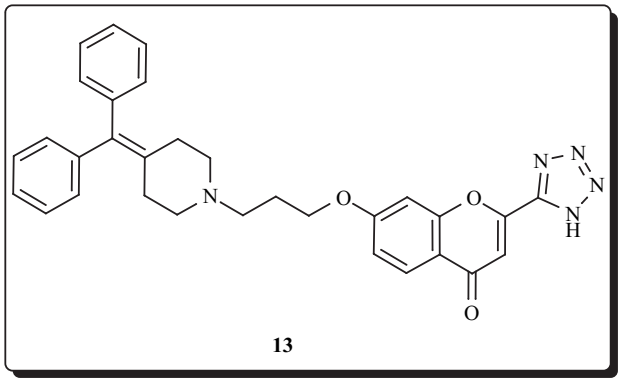
12

An alternative to 5-LO inhibition to impact the leukotriene cascade would be an agent designed to interact with a later significant mediator. Thus LTD_4, a bronchoconstricting cysteinyl leukotriene, has been demonstrated to be important in the asthmatic response. Drugs that block its action at the Cys-LT_1 receptor have been shown to be efficacious in pathologies such as asthma and/or rhinitis.

Timmerman *et al*. [22] developed a series of piperidinylalkoxychromones that exhibited potent antihistamine H_1 as well as Cys-LT_1 receptor antagonism. The most potent compound in the series was **13** displaying a K_D for the H_1 and the Cys-LT_1 receptors in guinea pig lung membranes of 5.89 nM and 2.34 μM respectively. This compound inhibited histamine- and LTD_4-induced contraction in the guinea pig ileum with a K_B of 3.6 nM and an IC_{50} of 190 nM respectively. The chromone **13** was also evaluated in an animal model to confirm these interesting *in vitro* findings. Thus, when administered intraperitoneally at 10 mg/kg, **13** inhibited the histamine-induced increase in vascular permeability in the guinea pig. In a similar model using LTD_4 as the provoking agent [22], a 30% inhibitory effect was observed when **13** was administered i.p. at a dose of 10 mg/kg while a higher dose of 50 mg/kg resulted in 56% inhibition of the vascular permeability induced by LTD_4.

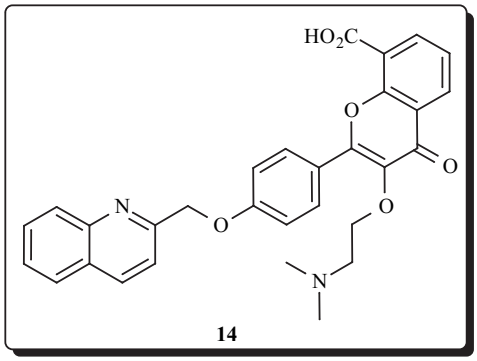


10 **11**



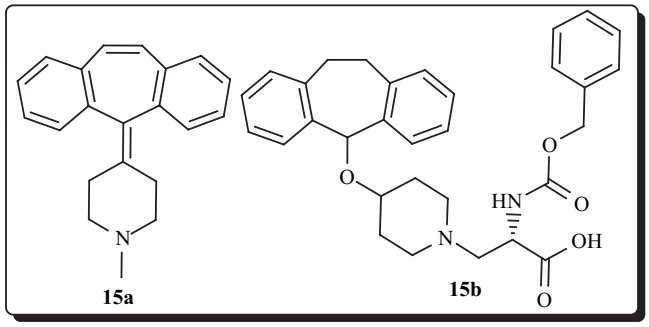
13

In a study evaluating the steric requirements of a group of flavones for Cys-LT_1 receptor binding, Timmerman *et al.* [23] identified one flavone (**14**) that displayed potent H_1 receptor binding affinity but poor Cys-LT_1 receptor activity. Using a guinea pig lung membrane preparation, **14** inhibited the binding of [^{3}H] mepyramine with a K_D of 10 nM while poorly competing with the binding of [^{3}H] LTD_4 (K_D = 4000 nM) to its receptor. Although this demonstrated the possibility of incorporating dual anti-H_1/LTD_4 activities within the same compound, clearly much work remains to be done to improve the Cys-LT_1 potency and also to balance each activity.



14

Timmerman *et al.* [24] also reported a study where a dual acting H_1 receptor antagonist displaying weak Cys-LT_1 antagonistic activity was modified in order to improve this latter property. First, a panel of antihistamines was screened in order to find a substance that would possess some Cys-LT_1 antagonistic properties. In this series, cyproheptadine (**15a**), at a concentration of 10 μM, displayed 50% inhibitory activity in the LTD_4-induced (10 nM) guinea pig ileum contraction assay. This compound became the lead compound in this series and was developed into VUF4876 (**15b**), a dual-acting H_1-Cys-LT_1 antagonist with reasonably balanced activity. VUF4876 inhibited histamine-induced contraction of the guinea pig ileum with a K_B of 110 nM. When the guinea pig ileum was subjected to LTD_4 induced contractions, VUF4874 inhibited the effect with an IC_{50} of 890 nM. In competition binding experiments using [^{3}H] mepyramine (guinea pig cerebellum preparation) and [^{3}H] LTD_4 (guinea pig lung membrane preparation), **15b** (*S* isomer) displayed a K_D of 410 nM and 1550 nM, respectively. Interestingly, the *R* isomer of **15b** displayed a lower K_D value (27 nM) in the guinea pig cerebellum preparation, compared to the one observed (> 100 μM) in the lung preparation.

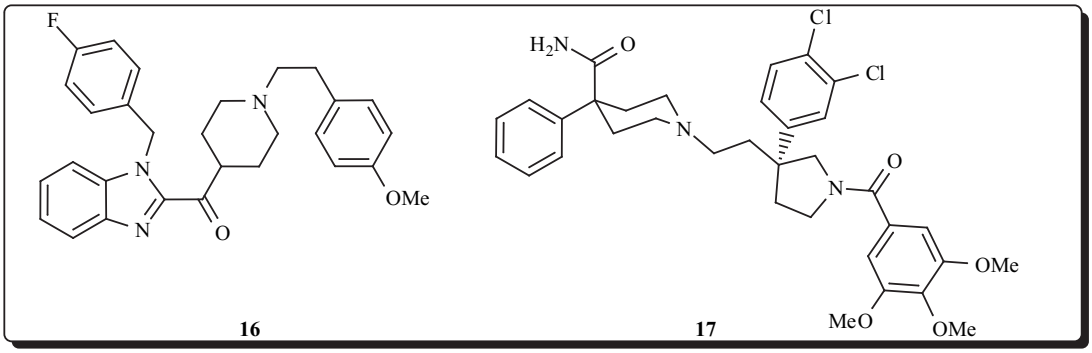


15a **15b**

DUAL ACTING TACHYKININ AND HISTAMINE H_1 RECEPTOR ANTAGONISTS

The tachykinins are a group of closely related neuropeptides which bind to G-protein coupled receptors. There are three receptor subtypes that have been designated as NK_1, NK_2 and NK_3 [25]. The tachykinin, substance P (SP), which binds more potently to the NK_1 receptor has been associated with some of the symptoms found in allergic rhinitis. Release of SP from airway nerve terminals can result in bronchoconstriction and mucus secretion. In animal models [26, 27] and human subjects with allergic rhinitis [28, 29], SP produced nasal obstruction, increased nasal blood flow, microvascular leakage, mucus secretion and recruitment of inflammatory cells. Since SP produces many of the same effects as those induced by histamine, the development of a molecule that would posses both NK_1 and histamine H_1 receptor antagonistic activity may offer a potential therapeutic benefit in allergic diseases.

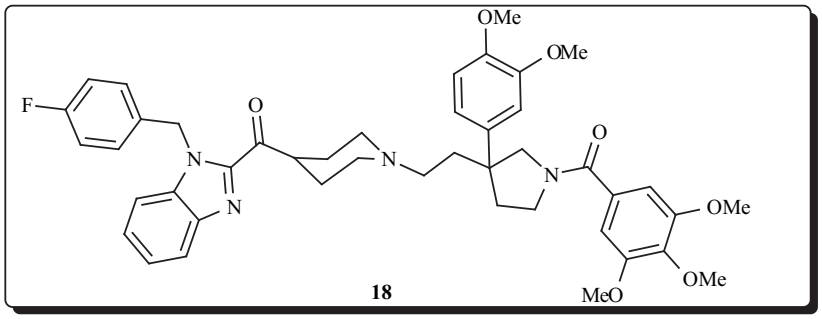
In order to design a molecule that would have both H_1 and NK_1 receptor antagonistic activities, Aventis [30] combined the structures of their astemizole based H_1 receptor antagonist, MDL 28,163 (**16**), with the NK_1/NK_2 receptor antagonist, MDL 105,212 (**17**). Support for constructing such a dual acting compound that would possess H_1 receptor antagonistic properties at one end of the molecule and NK_1 receptor antagonism on the other was supplied by Comparative Molecular Field Analysis (CoMFA) for receptor binding affinities, and overlays of crystal structures of several antagonists [31]. The lead candidate that evolved from this study was compound **18**. Binding affinity at the human H_1 receptor transfected into a Chinese hamster ovary (CHO) cell line gave an IC_{50} of 309 nM. Compound **18** also displayed a high affinity for the NK_1 receptor (IC_{50}: 31 nM, guinea pig lung preparation). In the guinea pig ileum assay, **18** inhibited contractions induced by histamine with a pA_2 of 7.52. Moreover, it inhibited the SP-induced increases in phosphatidylinositol turnover in UC11 cells with a pA_2 of 7.19. Although this compound demonstrated balanced and potent *in vitro* activity, oral administration of the maleate salt of **18** as a solution in 40% hydroxypropyl-β-cyclodextrin, showed rather poor activity (ED_{50} = 18.9 mg/kg) in the histamine-induced guinea pig skin wheal assay. The poor *in vivo* potency was attributed to low aqueous solubility (<0.1 μg/mL in 50 mM pH 7.4 phosphate buffer) and high lipophilicity (calculated log P = 4.72). Continued structural manipulation resulted in the identification of MDL 108,207DA (**19**), of which the *R* enantiomer is being developed [32]. Binding to human H_1 receptors in CHO cells gave an IC_{50} of 233 nM while



binding to NK_1 receptors from guinea pig lung gave an IC_{50} of 17 nM. Binding to the H_1 receptor was not stereoselective. On the other hand, NK_1 receptor binding did show some stereoselectivity, where the *S* enantiomer of **19** displayed an IC_{50} of 241 nM and the *R* enantiomer showed an increased affinity for this receptor (IC_{50} = 17 nM). MDL 108,207DA dose dependently inhibited histamine-induced contraction of guinea pig ileum (pA_2 = 8.02) and inhibited SP-induced phosphatidylinositol turnover in UC11 cells (pA_2 = 8.01). Oral administration of **19** in a solution of 40% hydroxypropyl-β-cyclodextrin inhibited microvascular leakage (ED_{50} = 1.95 mg/kg) in the histamine-induced guinea pig skin wheal assay. When *i.v.* administered, this compound displayed more potent activity (ED_{50} = 0.75 mg/kg). In the antigen-induced microvascular leakage guinea pig model, often used to reveal dual anti-histamine and anti-substance P potencies, **19** inhibited leakage with an ED_{50} of 0.14 mg/kg, when administered intravenously.

have been identified. Both are G protein-coupled surface receptors, which activate phospholipase A_2, C and D. Subsequently, inositol triphosphate and diacylglycerol are released resulting in intracellular calcium mobilization [35]. The B_2 receptor is constitutively expressed and is found on a variety of cell types. This receptor is also responsible for the majority of the inflammatory effects of bradykinin. On the other hand, the B_1 receptor is expressed as a result of an inflammatory stimulus and can be activated by bradykinin and its metabolites. The B_1 receptor is responsible for the production of prostaglandins, leukocyte trafficking, edema, pain and the release of TNFα and IL-1 from macrophages [36].

Kinins have been found in the bronchoalveolar lavage fluid of asthmatic subjects following allergen challenge and have been associated with the symptoms of sore throat associated with rhinitis [36].



DUAL ACTING BRADYKININ B_2 AND HISTAMINE H_1 ANTAGONISTS

Bradykinin is a nonapeptide that has been identified as a potent inflammatory mediator and a bronchoconstricting agent in asthmatic patients [33]. It has been associated with several diseases such as asthma, rhinitis, allergy and pain [34]. This kinin mediates its action through the activation of the bradykinin receptor of which two subtypes, B_1 and B_2,

In a study to identify non-peptide bradykinin B_2 antagonists, the second-generation antihistamine, cetirizine (**20**) was found to have weak B_2 antagonistic activity. Cetirizine at a dose of 100 nM provided a 51% inhibition of histamine-induced contractions of isolated guinea pig ileum and also displayed a 27% inhibition of bradykinin-induced contractions of isolated rat ileum [37]. Structural modifications of the ethoxy chain of cetirizine gave

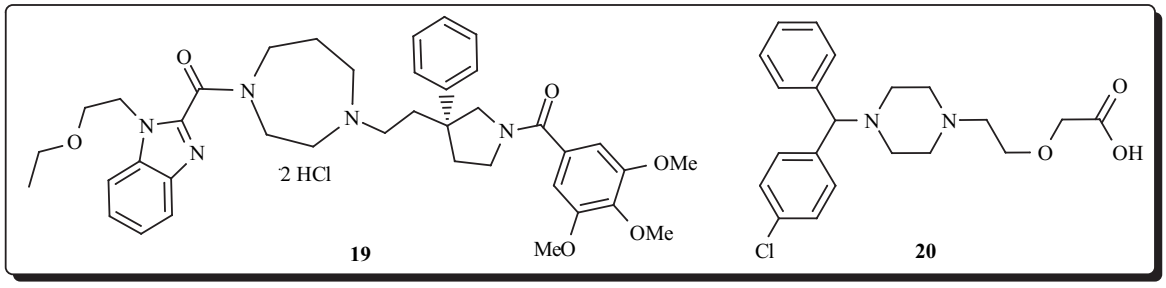
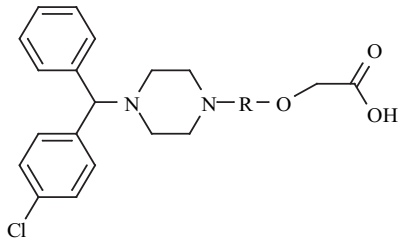
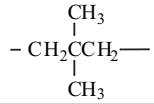
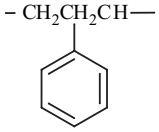
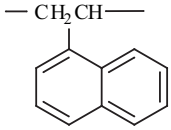


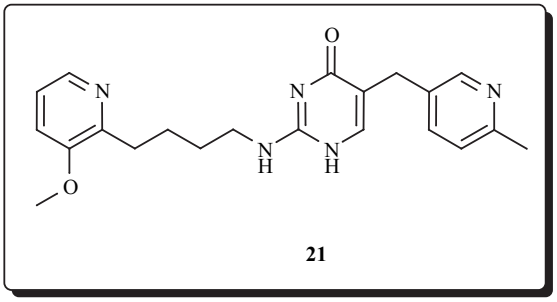
Table 1.



R	Inhibition of histamine-induced contractions of isolated guinea pig ileum[a]	Inhibition of bradykinin-induced contractions of isolated rat ileum[a]
	43%	33%
	53%	25%
	57%	27%

a. Inhibition at 100 nM Concentration

compounds with comparable activity at both receptors (see Table **1**).



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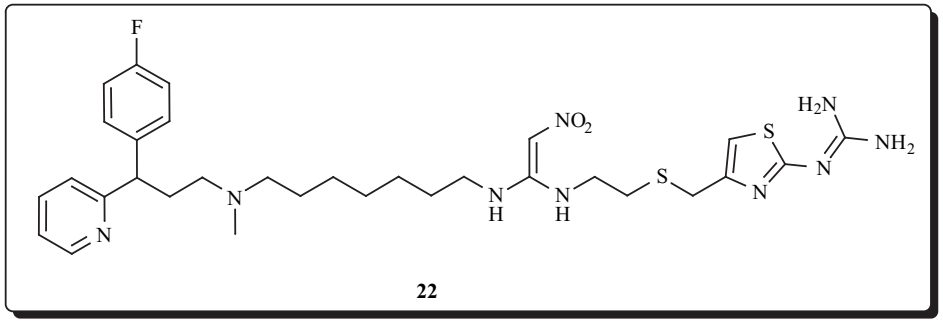
DUAL HISTAMINE H_1-H_2 RECEPTOR ANTAGONISTS

The various effects mediated via the histamine H_2 receptor involve different intracellular mediators. Thus, this subtype of the receptor primarily couples to the adenylyl-cyclase production of cAMP; and seems also to be involved in the breakdown of phosphoinositides, intracellular Ca^{++} levels, as well as the regulation of phospholipase A_2 activity [38].

Both histamine H_1 and H_2 receptors have been detected in blood vessels of the skin and are often involved simultaneously in a number of pathophysiological conditions. Clinical studies have indeed shown that the combined application of H_1 and H_2 receptor antagonists reduced skin lesions and itching in chronic urticaria more effectively than a H_1 receptor antagonist alone [39-40].

Icotidine (SK&F 93319, **21**) was the first compound that displayed both H_1 and H_2 receptor antagonist activities across a similar concentration range [41]. Schunack and co-workers have published a rational approach to dual acting H_1/H_2 receptor antagonists by connecting structural parts of classical H_1-receptor antagonists with H_2-receptor antagonist elements [42-45]. This approach was based on initial work by Buschauer [46], and Christiaans *et al.* [47], relating to the design of dual H_2 receptor agonists/H_1 receptor antagonists for the treatment of arrhythmias. Such compounds were predicted to display an added therapeutic benefit due to their additional anti-H_1 histaminergic activity,



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thus potentially conferring some protection against H_1-mediated effects after histamine release under various clinical conditions. One of the most potent compound within this series (**22**) displayed pK_B of 8.78 at the H_1 receptor (guinea pig ileum), and 8.08 at the H_2 receptor (guinea pig right atrium).

DUAL HISTAMINE H_1-H_3 RECEPTOR ANTAGONISTS

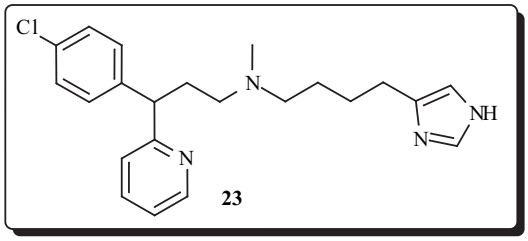
The histamine H_3 receptor is a presynaptic autoreceptor that controls the release of histamine as well as other neurotransmitters such as acetylcholine and norepinephrine [48]. This receptor has been identified in the central and peripheral nervous system and on various non-neural cell lines. An increasing number of H_3 receptor antagonists have been discovered (for reviews, see references [48-51]).

Some of the initial H_3 antagonists have been found to possess a dual H_1/H_3 antagonist property [52]. It has been demonstrated that the combination of the selective H_1 antagonist chlorpheniramine with the selective H_3 receptor antagonist thioperamide prevented congestion in a histamine-driven model of nasal congestion in the cat [53]. It has been suggested that histamine may induce nasal congestion through the activation of inhibitory prejunctional H_3 receptors on sympathetic nerves [54]. This would then decrease the release of norepinephrine, thus causing subsequent vasodilatation with nasal vascular engorgement. A combination of a histamine H_1- and H_3-receptor antagonist could reduce nasal airflow resistance and increase nasal cavity airspace volumes. These observations led researchers at Schering-Plough to investigate dual antagonists of these receptors, in which H_1 antagonist pharmacophores have been linked to the imidazole heterocycle [53, 55-61].

One of the identified lead compounds, **23**, displays very good binding affinities for both the H_1 and H_3 receptor (7 and 15 nM, respectively).

DUAL HISTAMINE H_1-H_4 RECEPTOR ANTAGONISTS

Screening of libraries as well as public databases for histaminergic subtype H_3-like fragments led to the cloning and characterization of what is now referred to as the H_4 receptor [62-64]. This receptor, displaying a 37 to 43% homology to the H_3 subtype shows highest levels of expression in bone marrow and leukocytes (particularly eosinophils and neutrophils). It has been recently reported that the histaminergic H_4 receptor mediates chemotaxis and calcium mobilization of mast cells [65]. Due to the importance of inhibition of inflammatory processes and immunomodulatory potencies, one can easily expect future therapeutic approaches based on the antagonism of this type of receptor. The first selective H_4 agonist, **24** [66], and selective H_4 antagonist, **25** [67] have been recently reported and will help to further elucidate the physiological roles of this new receptor.



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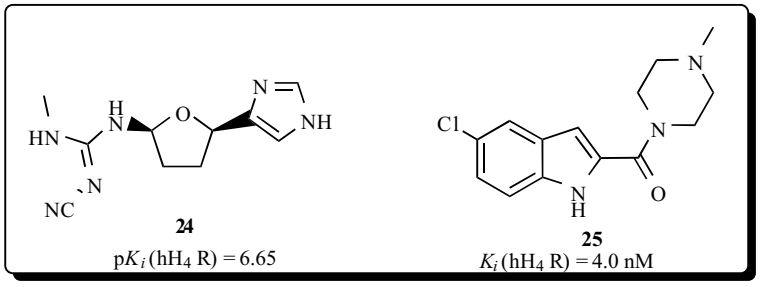
Pfizer recently reported the combination of a histamine H_1 receptor antagonist and a selective histamine H_4 receptor antagonist as apotential treatment for allergic diseases such as rhinitis and asthma [68]. Interestingly, using a cell-based assay, they showed that histamine-induced chemotaxis of human eosinophils appears to be mediated by the histamine H_4 receptor rather than by the histamine H_3 subtype.

DUAL HISTAMINE H_1 RECEPTOR-PAF RECEPTOR ANTAGONISTS

PAF is a biologically active ether phospholipid that is released from a variety of cells involved in the pathogenesis of the allergic and inflammatory response (for a recent reference see [69]). These cells include basophils, mast cells, neutrophils, macrophages, eosinophils and endothelial cells. PAF is formed from a specific phosphatidylcholine species by the sequential action of phospholipase A_2 and acetyltransferase activities. Both *in vitro* and *in vivo*, PAF shares with histamine the ability to induce bronchoconstriction, chemotaxis and vascular permeability. Consequently, it has been implicated as a mediator in a variety of respiratory and inflammatory diseases [69]. PAF may play a role in asthma, especially since it has been shown to cause bronchial hyperreactivity in man [70].

An intensive effort has been made by researchers at Schering-Plough to discover compounds, which antagonize the action of both mediators. The starting points were azatadine and loratadine, potent histamine H_1 receptor antagonists, which have been found to exhibit very weak PAF receptor antagonism.

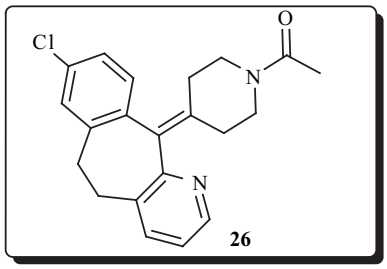
This work [71] initially culminated in the discovery of Sch 37370 (**26**), which possesses affinity for both the PAF receptor (IC_{50} = 610 nM) and the H_1 receptor (K_i = 320 nM), and which potently inhibits PAF- or histamine-



24 pK_i (hH$_4$ R) = 6.65

25 K_i (hH$_4$ R) = 4.0 nM

induced bronchospasm in the guinea pig (ED_{50} = 0.6-0.7 mg/kg).



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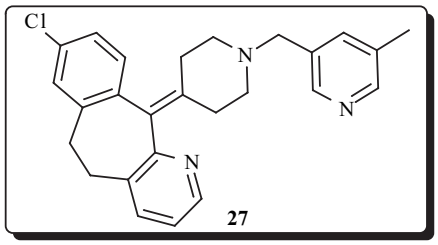
Structure-activity relationships around Sch 37370 revealed that a relatively small hydrophobic substituent at C-3 on the aromatic ring, conformational rigidity, and the presence of both nitrogen atoms are required for optimum PAF receptor affinity and activity [71-74].

Modification of the nitrogen substituent of the original piperidinylidene series by Uriach produced UR-12592, rupatadine (**27**) [75-76], a more potent dual antagonist than Sch 37370. Rupatadine is currently undergoing clinical trials, and is expected to be introduced in Spain in 2003 for the treatment of allergic rhinitis.



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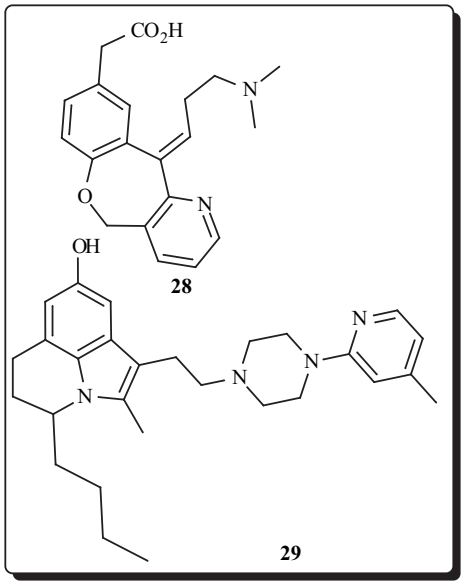
Other compounds that have been reported to display dual anti-histamine and anti-PAF receptor activity include olopatine (**28**) [77] and derivatives of KC 11404 (**29**) [78].



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CONCLUSION

In the near future, the Consensus Group of New Generation Antihistamines (CONGA), a group composed of leading histamine investigators, will outline the criteria that must be met before a compound can be called a "third generation antihistamine". Interestingly, examples of such compounds may include dual acting antihistamines [79], with optimal pharmacokinetic properties, lacking drug-drug interactions and completely devoid of CNS effects. It can be reasonably expected that dual H_1-X drug discovery approaches, like those reported in this review, could potentially lead to compounds that will have the right to be designated third generation antihistamines.

LIST OF ABBREVIATIONS

K_i	=	Concentration of a competing ligand that would occupy 50% of the receptor if no radioligand present in a competition binding assay
pA_2	=	Negative logarithm to base 10 of the molar concentration of an antagonist that makes it necessary to double the concentration of agonist needed to elicit the original sub-maximal response
pD_2, pEC_{50}	=	The negative logarithm to base 10 of the EC_{50} (molar concentration of an agonist that produces 50% of the maximal possible effect)
K_B, pK_B	=	Dissociation equilibrium constants
K_D	=	Dissociation equilibrium constant for ligand-receptor interactions
ED_{50}	=	The dose of a drug that produces, on average, a specified all-or-none response in 50% of a test population
IC_{50}	=	The molar concentration of an antagonist that reduces a specified response to 50% of its former value.
PAF	=	Platelet Activating Factor
i.p.	=	Intraperitoneal

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