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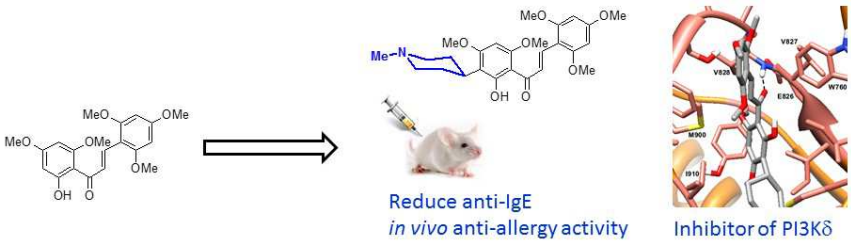


Piperidinyl-Embeded Chalcones Possessing anti PI3Kδ Inhibitory Properties Exhibit Anti-atopic Properties in Preclinical Models

Charles Dumontet,[a,b] Guillaume Beck,[c] Fabrice Gardebien,[c] Romain Haudecoeur,[d] Doriane Mathé,[a] Eva-Laure Matera,[a] Anne Tourette,[a] Eve Mattei,[a] Justine Esmenjaud,[a] Cédric Boyere,[d] Alessandra Nurisso,[e] Marine Peuchmaur,[d] Basile Peres,[d] Grégory Bouchaud,[f,g] Antoine Magnan,[f,g] Guillaume Monneret,[b] and Ahcène Boumendjel[d,*]

[a]INSERM 1052/CNRS 5286/University of Lyon – Cancer Research Center of Lyon

[b]Hospices Civils de Lyon

[c]Biologie Intégrée du Globule Rouge UMR_S1134, Inserm, Univ. Paris Diderot, Sorbonne Paris Cité, Univ. de la Réunion, Univ. des Antilles; Laboratoire d'Excellence GR-Ex, Paris, France; Faculté des Sciences et Technologies, Saint Denis Messag, F-97715 La Réunion, France

[d]Univ. Grenoble Alpes, DPM UMR 5063, F-38041 Grenoble, France; CNRS, DPM UMR 5063, F-38041 Grenoble, France

[e]School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, CH-1211 Geneva 4, Switzerland

[f]INSERM, CNRS, UNIV Nantes, l'institut du thorax, Nantes, France; CHU Nantes, France.

[g]INRA, UR1268, BIA, Nantes, France

ABSTRACT: Phosphatidylinositide 3-kinases (PI3Ks) are widely expressed enzymes involved in membrane signalization pathways. Attempts to administer inhibitors with broad activity against different isoforms have failed due to toxicity. Conversely the PI3Kδ isoform is much more selectively expressed, enabling therapeutic targeting of this isoform. Of particular interest PI3Kδ is expressed in human basophils and its inhibition has been shown to reduce anti-IgE induced basophil degranulation, suggesting that PI3Kδ inhibitors could be useful as anti-allergy drugs. Herein, we report for the first time the activity of compounds derived from chalcone scaffolds as inhibitors of normal human basophil degranulation and identified the most active compound with anti-PI3Kδ properties that was investigated in preclinical models. Compound **18**, namely 1-[2-hydroxy-4,6-dimethoxy-3-(*N*-methylpiperidin-4-yl)phenyl]-3-(2,4,6-trimethoxyphenyl)-prop-2-en-1-one, was found to inhibit normal human basophil degranulation in a dose-dependent manner. In a murine model of ovalbumin-induced asthma, compound **18** was shown to reduce expiratory pressure while its impact on the inflammatory infiltrate in alveolar lavage and total lung was dependent on the route of administration. In a DNFB-induced model of atopic dermatitis compound **18** administered systemically proved to be as potent as topical betamethasone. These results support the anti-atopic and allergic properties of the title compound and warrant further clinical development.

Key words: PI3Kδ, Chalcones, Basophil Degranulation, Allergic Properties, Anti-atopic Activity

1. Introduction

Phosphatidylinositide 3-kinases (PI3Ks) constitute a family of enzymes involved in several functions such as cell growth, proliferation, differentiation, motility, survival and intracellular trafficking. PI3Ks are involved in signal transduction through the phosphorylation of the hydroxyl group at position 3 of the inositol ring of phosphatidylinositol (PtdIns), which may be reduced by the phosphatase enzyme PTEN [1,2].

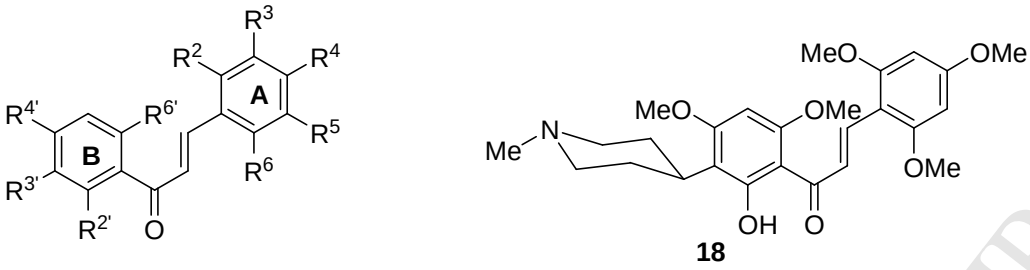
The PI3K family is divided into four different classes, based on the primary structure, regulation, and *in vitro* lipid substrate specificity [2]. Class I PI3Ks are activated by G protein-coupled receptors and tyrosine kinase receptors. They are heterodimeric molecules composed of a regulatory (p85) and a catalytic (p110) subunit. There are three variants of the p110 catalytic subunit designated p110α, β, or δ catalytic subunit, expressed by separate genes. While the first two catalytic isoforms are ubiquitously expressed in all cell types, the p110δ is expressed primarily in white blood cells [3]. PI3Kδ is particularly expressed in B cells, leading to its targeting in B cell malignancies. PI3Kδ has presently essentially been targeted in onco-hematology indications [4]. Idelalisib (CAL-101, GS-1101), an oral agent, is the first inhibitor of PI3Kδ that has recently been approved for the treatment of lymphoid malignancies such as chronic lymphocytic leukemia. Since then, a number of other PI3Kδ inhibitors have been reported to be active in preclinical models against B cell malignancies and/or in auto-immune diseases [5].

However PI3K has also been considered as a potential target in asthma [6,7] and the PI3Kδ isoform has been found to be specifically involved in allergic reactions [8]. A phase 1 study of idelalisib (NCT00836914) has been performed, demonstrating good tolerance, increased activity against allergic responses in patients with allergic rhinitis in comparison to placebo and a reduced percentage of *ex vivo* stimulated basophils [9]. A clinical trial with the related compound CAL-263 (NCT01066611) has been initiated in patients with allergic rhinitis.

Given potential applications in neoplasia, allergy, autoimmunity and inflammatory diseases, there has been significant interest to identify novel PI3K inhibitors through screening of chemical libraries or by optimization of clinically used drugs [10-13]. In this regard, benzimidazole-based inhibitors were developed [14]. High throughput screening of chemical libraries was also used to generate lead inhibitors [15,16]. More recently, Ferguson and co-workers showed that a series of 5,11-Dihydro-6*H*-benzo[e]pyrimido[5,4-b][1,4]diazepin-6-ones were selective PI3Kδ/gamma inhibitors [17]. Finally, Hoegenauer and co-workers have developed novel pyrrolidineoxy-substituted heteroaromatics [18]. Interestingly xanthine-derived compounds, such as caffeine and theophylline, have also been shown to have direct effects on PI3Kδ [19].

Being interested by the discovery of easily synthesizable scaffolds, acting as anti-allergy agents with *in vivo* effectiveness, we screened a large series of compounds belonging to flavonoids derivatives, including flavones, aurones and chalcones as inhibitors of the normal human basophil degranulation. The choice of these chemical scaffolds was motivated by their reported effect on human kinases and their therapeutic potential [20,21]. In addition, the computational analysis of a collection of compounds derived from chalcones demonstrates that the collection covers structural features for the inhibition of PI3K enzymes, especially chalcones were the most promising compounds and that these scaffolds have never been explored on this target. Herein, we report the activity of a selection of chalcones bearing methoxyl and piperidinyl groups. The latter susbtituents were reported to contribute to the biological activity of chalcones, allowed us to limit our investigation to chalcones bearing these two groups [22-24]. The most active compounds revealed by the basophil degranulation test were investigated for their inhibition effect on PI3Kδ, then the most active derivative was tested in two preclinical models: a murine ovalbumin-induced asthma assay and a murine DNFB-induced atopic dermatitis assay. The selected compound (**18**) displays selective anti-

PI3Kδ activity and possesses therapeutic activity in preclinical murine models of allergy or atopy.



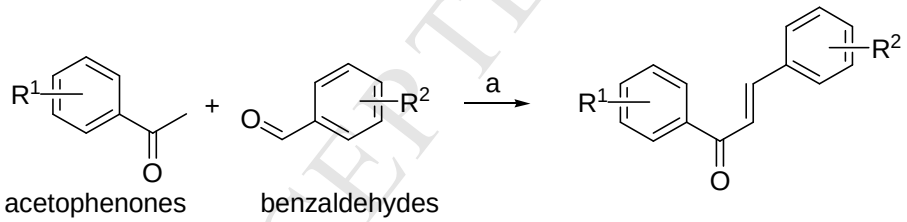
18

Figure 1. General structure of the studied compounds and the most active lead compound.

2. Results

2.1. Chemistry. The synthesis of chalcones (summarized in Table 1) were prepared according to Scheme 1, through the condensation of acetophenone derivatives with substituted benzaldehydes in the presence of KOH at 90 °C [22,23]. The benzaldehydes and acetophenones required for the synthesis of derivatives **1-17** were all commercially available.

Scheme 1. General scheme for the synthesis of chalcones.[a]

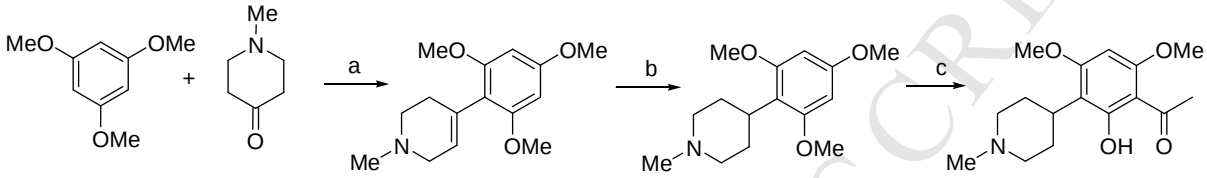


[a]Reagents and conditions: (a) for compounds **1-19**: KOH (50% in H_2O), MeOH, 90 °C, 24 h. For compound **20**: NaOH in MeOH (3%, w/v), rt, 12 h.

The acetophenone derivative required for the synthesis of compounds **18-20** was accomplished as shown in Scheme 2 [24]. The condensation of trimethoxybenzaldehyde and 1-methyl-4-piperidinone in the presence of gaseous HCl produced compound **21** with 90%

yield. Compound **21** was reduced under catalytic hydrogenation with H_2 in a mixture of AcOH/H_2O to provide the expected compound **22** with 94%. The acylation of **22** with acetic anhydride in the presence of an excess of $BF_3.Et_2O$ was achieved, giving the acetophenone derivative **23** in 57% yield.

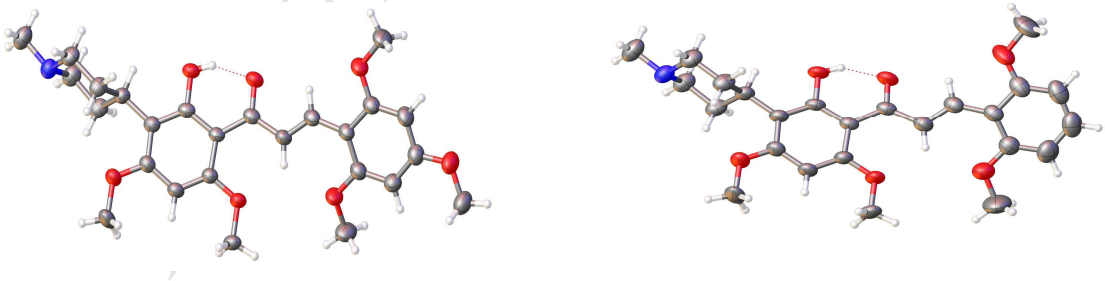
Scheme 2. Synthesis of acetophenone **23** required for the preparation of chalcones **18-20**.



21 **22** **23**

[a]Reagents and conditions: (a) HCl (gas), glacial AcOH, 24h at rt then 3h at 100 °C; (b) H_2, Pd/C, AcOH/H_2O, rt, 16h; (c) Ac_2O, $BF_3.Et_2O$, CH_2Cl_2, rt, 24 h.

In agreement with the report of Liu et al. [24], it was found that the acylation process led to a partial demethylation of the methoxy group positioned between the *N*-methylpipeirine and the carbonyl. The demethylation regioselectivity was assessed by NMR NOESY experiments and confirmed by X-ray diffraction analysis, conducted on derivatives **18** and **19** (Figure 2).



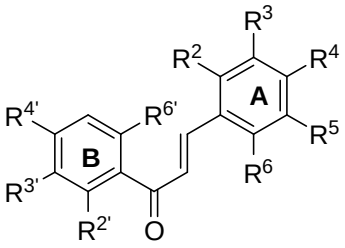
18 **19**

Figure 2. ORTEP drawing of compounds **18** and **19**

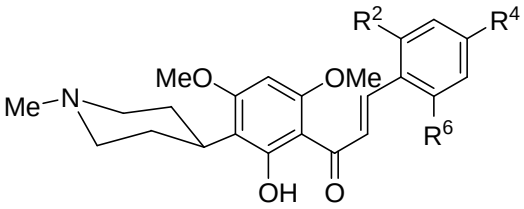
2.2. Biological Evaluation.

2.2.1. Effect of chalcones on normal human basophil degranulation. The selected chalcones were tested for their ability to reduce overexpression of the activation markers CD63 and CD203c in normal human basophils induced by anti-IgE cross-linking. The results are representative of three experiments with three different normal donors. As shown in Table 1, tested chalcones possessed very different inhibitory properties on the expression of CD63 and CD203c markers. Overall, the effect of the most potent compounds was more pronounced on CD63 rather than on CD203c expression. As it could be expected, the substition pattern played a crucial role. The first structural feature to be highlighted is the positive effect due to the presence of at least three methoxy groups on either the A or B-ring (compounds **12**, **13**, **14**, **16** and **17**). The most marked effect was obtained with compounds bearing a *N*-methylpiperidinyl moiety (**18**, **19** and **20**). The importance of the *N*-methylpiperidinyl substituent could be clearly seen by comparing the inhibitory effect of **11** and **19** that share the same substitution pattern except for the presence of the *N*-methylpiperidinyl in **19**. It should be highlighted that the replacement of the A-ring of compounds (**18**, **19** and **20**) by heteroaryl groups led to inactive compounds (results not shown). Thus, it can be concluded that the presence of the *N*-methylpiperidinyl is essential but not sufficient and the all substitution pattern of the chalcone scaffold is important. Finally it should be noticed that the chlorhydrate salts of the most active compounds (compound **18**) was deleterious for the activity.

Table 1. Screening of chalcone derivatives (at 100 μM) for their ability to inhibit IgE-induced degranulation of normal human basophils.



1 - 17



18: $R^2 = R^4 = R^6 = OMe$
19: $R^2 = OMe$, $R^4 = H$, $R^6 = OMe$
20: $R^2 = Cl$, $R^4 = H$, $R^6 = Cl$

Entry	R^2	R^3	R^4	R^5	R^6	$R^{2'}$	$R^{3'}$	$R^{4'}$	$R^{6'}$	CD63	CD203c
1	OMe	H	H	H	OMe	OMe	H	H	OMe	94	96
2	OMe	H	OMe	H	OMe	OH	H	OMe	H	95	91
3	H	OMe	OMe	OMe	H	OH	H	OMe	H	92	93
4	H	H	H	OMe	H	OMe	H	H	OMe	100	82
5	OMe	H	OMe	H	OMe	OMe	H	H	OMe	78	81
6	OMe	H	OMe	H	OMe	OMe	H	OMe	OMe	67	68
7	OMe	H	OMe	H	OMe	H	OMe	OMe	H	91	95
8	H	H	CF_3	H	H	OMe	H	H	OMe	64	81
9	OMe	H	OMe	H	OMe	OMe	H	NH_2	OMe	63	75
10	OMe	H	OMe	H	OMe	OMe	H	OMe	H	76	86
11	OMe	H	H	H	OMe	OH	H	OMe	OMe	81	85
12	H	OH	OMe	H	H	OMe	H	OMe	OMe	40	54
13	OMe	H	OMe	OMe	H	OMe	H	OMe	OMe	53	51
14	OMe	H	H	H	H	OMe	H	OMe	OMe	48	65
15	OMe	H	OMe	OMe	H	H	OMe	OMe	OMe	66	70
16	H	OH	OMe	H	H	H	OMe	OMe	OMe	49	62
17	OMe	H	H	H	H	H	OMe	OMe	OMe	55	65
18										2	7
19										4	41
20										6	24

2.2.2. Inhibition of PI3K isoforms by compound 18. The inhibition of PI3K isoforms by compound **18** and two reference inhibitors (idelalisib and duvelisib) was assessed (Table 2). These results show that derivative **18** is a weaker inhibitor of PI3Kδ than idelalisib or

duvelisib, with IC_{50} values in the micromolar range versus nanomolar ranges for idelalisib and duvelisib. However **18** displayed only weak effect on the other isoforms with IC_{50} values higher than 10 μM, while idelalisib and duvelisib remained quite potent against these isoforms in the micromolar or submicromolar range.

Table 2. Inhibition activity of compound **18**, Idelalisib and Duvelisib on PI3K isoforms

Compound	**PIK3**	**IC_{50} (μM)**
18	PI3KCα/PIK3R1	> 10
18	PI3KCβ/PIK3R1	> 10
18	PIK3Cδ/PIK3R1	7.2
18	PI3KCγ	10
Idelalisib	PI3KCα/PIK3R1	2
Idelalisib	PI3KCβ/PIK3R1	0.6
Idelalisib	PI3KCδ/PIK3R1	0.017
Idelalisib	PI3KCγ	0.25
Duvelisib	PI3KCα/PIK3R1	0.4
Duvelisib	PI3KCβ/PIK3R1	0.049
Duvelisib	PI3KCδ/PIK3R1	0.0023
Duvelisib	PI3KCγ	0.012

2.2.3. Activity of chalcone 18 in the ovalbumin-induced murine asthma model. In a first series, compound **18** was administered intraperitoneally (90 mg/kg daily) and compared to sodium cromoglycate (10 mg/kg) and in a second series, aerosolized **18** was compared to buffer and aerosolized dexamethasone (10 mg/kg). Dexamethasone and DSCG are highly potent drugs and the dose of 10 mg/kg is a standard dose which has been widely used in preclinical models. We do not expect a higher dose to have a more pronounced effect in our assay. For the experimental drug **18** which has never been used in the clinic, the dose of 90 mg/kg was chosen for reasons of solubility and thus may be a suboptimal dose for this compound.

As shown in Figure 3 (A and B), compound **18** reduced lung resistance following increasing dose of metacholine whereas sodium cromoglycate did not, with an effect comparable to that of dexamethasone in the aerosolized administration regimen.

Systemically administered **18** significantly reduced the total leukocytic infiltrate in BAL (Figure 3C) and in lungs (data not shown). Analysis of subpopulations suggested that the most striking effect of **18** was on the eosinophilic infiltrate (Figure 3E). Conversely in the aerosolized regimens, the analysis of the cellular infiltrate showed important differences between animals receiving **18** and those treated with dexamethasone. While mice receiving steroids displayed a strong decrease in their cellular infiltrate, **18** did not modify the total number of cells present in BAL (Fig 3D) while analysis of leukocyte subpopulations did not show an impact of **18** on leukocytic subpopulations (Figure 3F).

Taken together, these results support a dual role of **18** both on bronchoconstriction and on the inflammatory infiltrate observed in the ovalbumin-induced asthma model. It is likely that the effect of **18** on inflammation is dose-related and that stronger concentrations could also be active by aerosolization.

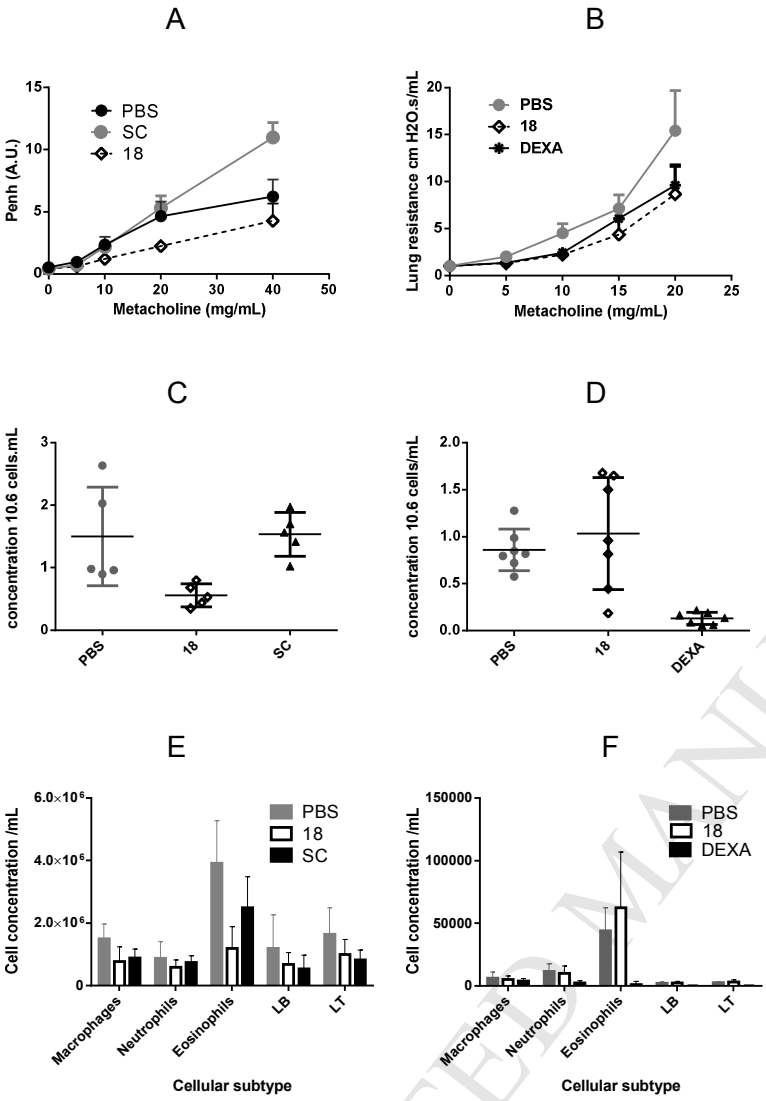


Figure 3. Effect of lead compound (**18)** and reference compounds in a murine model of OVA-induced asthma. (A) Plethysmographic analysis in mice treated intraperitoneally with **18** or cromoglycate. (B) Flexivent analysis of lung resistance in mice treated with nebuilized **18** or dexamethasone. (C) Total cell infiltrate in lung in mice treated intraperitoneally with **18** or cromoglycate. (D) Total cell infiltrate in lung in mice treated with nebuilized **18** or dexamethasone. (E) Plethysmographic analysis in mice treated intraperitoneally with **18** or cromoglycate. (F) Flexivent analysis of lung resistance in mice treated with nebuilized **18** or dexamethasone. *CM: cromoglycate; DEXA: dexamethasone; LB: B lymphocytes; LT: T lymphocytes.*

2.2.4. Activity of 18 on murine atopic dermatitis model. As shown in Figure 4, **18** was found to exert a significant protective effect when administered systemically in the DNFB-induced atopic dermatitis model. This effect appeared to be prolonged (up to three days after

exposure to the inducing agent) and was significantly different from that observed with a reference agent, topical steroids.

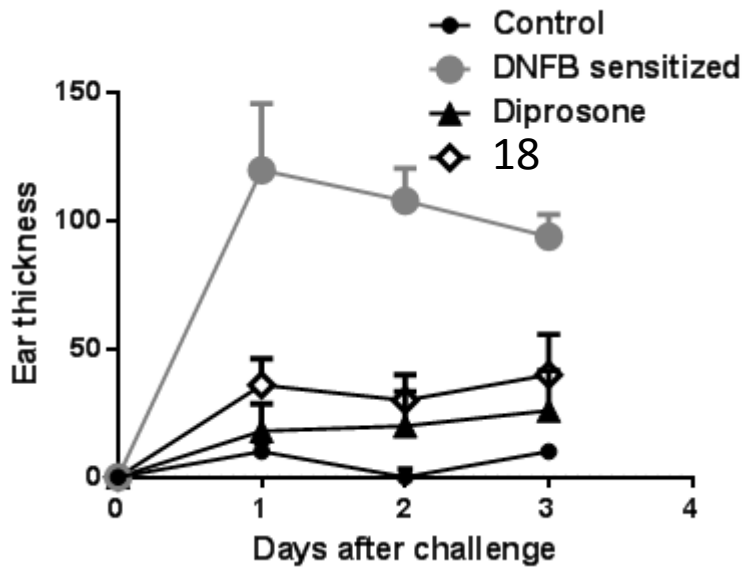


Figure 4. Effect of systemically administered **18** and topical diprosone in a murine model of atopic dermatitis. Control: mice unexposed to DNFB; DNFB sensitized: mice sensitized and challenged with DNFB; Diprosone: mice sensitized and challenged with DNFB then treated with diprosone; **18**: mice sensitized and challenged with DNFB then treated with **18**.

3. Discussion

With the aim of developing new chemical scaffolds active against allergy through the inhibition of PI3Kδ requiring simple and straightforward synthesis, we investigated a library of 20 chalcones, selected from a large series of derivatives. These compounds were selected on the basis of their substitution features and due to their therapeutic potential [25,26].

In order to identify lead compounds as candidates for *in vivo* studies and development, we performed a screening of chalcones on normal human basophil degranulation. In response to FcεRI stimulation, basophil activation was assessed through increased CD63 or CD203c expression. CD63 is anchored in the basophilic granule membrane (which contains histamine) and its exposure on the outside of the cells reflects cell degranulation due to fusion between

granules and plasma membranes [27]. CD203c is a basophil-specific surface antigen for which the expression is rapidly upregulated after stimulation with the appropriate allergen or after crosslinking of FcεRI with anti-IgE antibodies [27]. Both levels of expression were investigated in whole blood as recommended by manufacturers. The three most active chalcones on human basophil degranulation share a common chemical feature, the 6'-hydroxy-2',4'-dimethoxy-3"-(1-methylpiperidinyl) group. The 3 compounds induced high basophil degranulation with a marked effect on CD63 expression.

Our study shows that the selected chalcone, **18** possesses anti- PI3Kδ inhibitory activity. While the IC_{50} values are significantly higher than those of reference compounds such as idelalisib or duvelisib, an interesting feature of our compound is that it has little effect on other PI3K isoforms such as the α and β isoenzymes, a property which could prove to be important in terms of tolerance. This is of particular importance since idelalisib has been shown to be associated with some severe side effects in some cases [28].

Aiming to rationalize the binding of chalcone **18** to the active site of PIK3δ, we performed a prediction of the orientation (or pose) of **18** in the binding site of PI3Kδ. Among the 11 poses generated by the GOLD and rDOCK docking softwares [29,30], one of these, shown in Figure 5, has the top rank when rescoring by using each of the methods XSCORE [31], ITScore [32], and ID-Score [33].

In this predicted geometry, ligand **18** interacts with the core of the six residues that are usually found in interaction with known PI3K inhibitors (W760, E826, V827, V828, M900 and I910). The central ring along with the enone moiety fit into the adenine pocket; the carbonyl group forming a first hydrogen bond with V828. A second hydrogen bond is found between the protonated nitrogen of the 1-methylpiperidinyl moiety and D911; this ligand moiety, which is critical for the activity as revealed by our experimental assays, occupies the affinity pocket and participates in hydrophobic contacts with I910 [34]. The 1-methylpiperidinyl moiety,

which is critical for the activity as revealed by experimental assays, occupies the affinity pocket making hydrophobic contacts with I910 and could potentially form another hydrogen bond with D911 through its protonated nitrogen.

From the chalcone orientation shown in Figure 5, we can also understand the structure-activity relationships for compounds **19** and **20**. Indeed, the methoxy group in para position of the trimethoxyphenyl moiety in **18** points outside the binding site of the protein and forms no contacts in the predicted orientation. Hence, the removal of this group in **19** is not expected to have a large impact on the activity measured for this chalcone in comparison to that for **18**. In chalcone **20**, the two chlorine atoms can form similar van der Waals contacts with the protein as for the two methoxy groups found as counterparts in **18**, again accounting for the similar activities measured for these two chalcones.

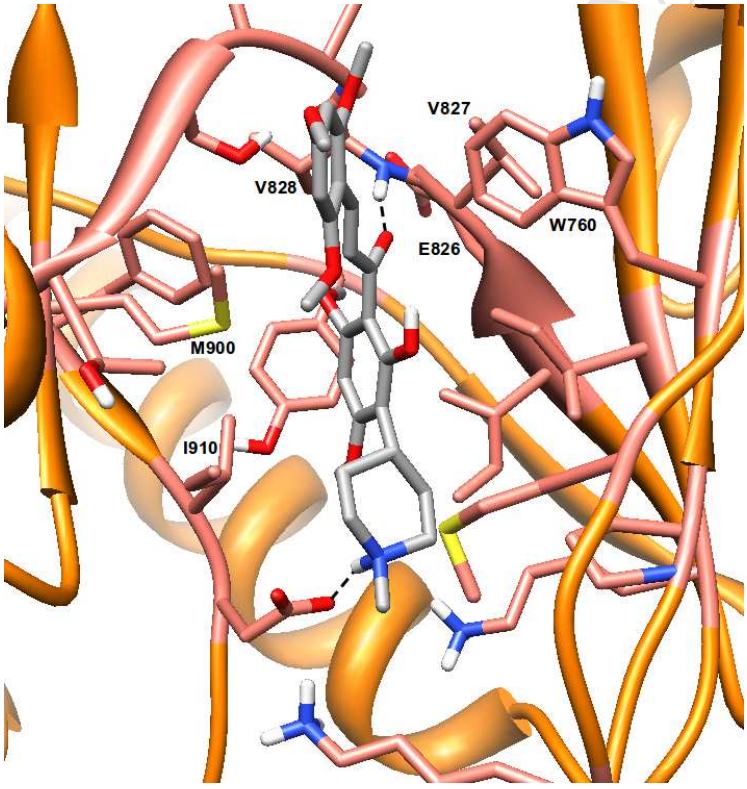


Figure 5. Prediction of the orientation of lead compound **18** in the binding site of PI3Kδ. The carbon atoms of the ligand are displayed in gray. For the protein, the residues that form at least one contact (measured by atomic distances less than 4 Å) with the ligand are displayed in salmon; the other residues are in orange. The hydrogen bonds that the ligand forms with the residues V828 and D911 are represented as dashed lines.

Importantly, the *in vivo* studies show that systemic administration of **18** is associated with anti-allergic effects and that therapeutic concentrations can therefore be reached. Of interest, chalcone **18** was administered intraperitoneally and intravenously up to doses of 90 mg/kg, 3 to 5 five times weekly, up to 4 weeks with no observed effect on animal well-being or weight (data not shown). Compound **18** displayed potent activity in both the murine atopic dermatitis model and in the asthma models, with effects close to or similar to reference steroids. In the atopic dermatitis model intraperitoneal administration of **18** displayed a protective effect comparable to topical betamethasone. In the asthma model, the lead compound proved to reduce bronchial airway resistance both after intraperitoneal administration and after aerosolization. Analysis of the cellular infiltrate in the asthma model suggests that the compound had a strong effect on total leukocytic infiltrate, in particular on eosinophilic cells. Interestingly Doukas et al. found that aerosolized administration of the PIK3δ inhibitor, PI3KTG100-115, proved to be beneficial in murine asthma model and induced a decrease of the eosinophilic infiltrate [35]. When **18** was administered by aerosolization, we did not observe a strong effect on the inflammatory infiltrate while steroids induced a decrease of all leukocytic subpopulations. In spite of this aerosolized-administration mode, **18** was associated with a decrease in lung hyperresponsiveness to metacholine. Whether this is due to reduced release of cytokines by basophils or other leukocytic cells or to an alternate mechanism remains to be determined. However this observation suggests that the compound might not induce immunosuppression, as it is commonly observed with steroids. It is likely that the

aerosolization conditions were not optimized in our study, preventing us from observing the same BAL modifications as those observed after systemic administration of **18**.

The potential consequences of chronic PI3Kδ inhibition constitute an important aspect since anti allergic agents are likely to be administered over prolonged periods of time. As PI3Kδ has been shown to be an important actor in the differentiation and/or function of various types of leucocytes, it is possible that chronic inhibition may be deleterious. Guo et al. reported that PI3Kδ plays a critical role in Natural Killer (NK) cell maturation and cytokine release [36]. PI3Kδ has also been shown to affect neutrophil function either directly or via its expression in endothelial cells [37-39]. Okeke et al. have recently shown that deficiency of PI3Kδ signaling could lead to diminished number of regulatory T cells as well as increased neutrophil activity in the context of sepsis [40]. While the clinical relevance of these observations in patients receiving PI3Kδ inhibitors is unclear, it will be important to determine whether chronic administration of these agents has to be modulated in the context of sepsis.

4. Conclusions

Our results show that judiciously functionalized chalcone derivatives administered systemically (or by inhalation in the asthma model) possess protective activity in preclinical allergy or atopy models. The observed activity is tightly linked to the inhibition of PI3Kδ. The docking studies reveals that the scaffold of chalcone **18** fits well within the active site of the PI3Kδ structure. The relevant *in vivo* activity of the lead compound, its safety at the active doses, the easy synthesis and scale-up (4 steps and 38% overall yield) warrant further optimization and development of the title compound in allergy and asthma management.

5. Experimental Section

5.1. Chemistry. All reagents were purchased from commercial sources and were used directly without further purification. Synthetic grade solvents were purchased and were used without further distillation. NMR spectra were recorded on Bruker Advance-400 instrument (400 MHz) using $CDCl_3$ as the solvent. The chemical shifts (δ) were reported in parts per million (ppm). ESI-MS spectra were recorded at the mass spectrometry facility of the Institut de Chimie Moléculaire de Grenoble (ICMG, FR 2607) using an Esquire 300 Plus Bruker Daltonis instrument with a nano spray inlet. Thin-layer chromatography (TLC) were performed on Merck silica gel F-254 plates (thickness 0.25 mm).

5.2. General procedure for the synthesis of intermediates 21 - 23

1-(*N*-methylpiperidin-3,4-en-4-yl)-2,4,6-trimethoxybenzene (21) [24]. *N*-methylpiperidin-4-one (10.0 g, 59.5 mmol) was added to a solution of trimethoxybenzene (6.72 g, 59.5 mmol) in glacial acetic acid (80 mL). Gaseous HCl was generated by the dropwise addition of HCl (37%, 50 mL) to concentrated H_2SO_4 (50 mL). The flux of HCl was bubbled into the solution containing the reagents, under stirring and for 1 h. The reaction mixture was stirred for 24 h at room temperature then for 3 h à 100 °C. The solvent was removed under reduced pressure and the residue was dissolved in H_2O. The obtained solution was alkalinized by adding NaOH (1 M), then extracted 3 times with ethyl acetate. The organic solution was dried over $MgSO_4$ and the solvent was evaporated to provide compound **21** as a white solid (14.12 g). Yield 90%. The compound was used without purification for the next step.

1-(*N*-methylpiperidin-4-yl)-2,4,6-trimethoxybenzene (22). Compound **21** (14.12 g, 53.7 mmol) was dissolved in a mixture of acetic acid (400 mL) and water (40 mL). Palladium on charcoal (10%, 1.4 g, 0.1 eq) was added (without stirring during the addition of Pd/C). The mixture was stirred under hydrogen atmosphere for 16 h, then filtered over Celite. After

filtration, the solvent was removed under reduced pressure to provide 13.37 g of compound **22** with satisfactory purity (94% yield).

2,4-Dimethoxy-6-hydroxy-3-(*N*-methylpiperidin-4-yl)acetophenone (**23**). Boron trifluoride diethyl etherate ($BF_3.Et_2O$, 71.67 g, 505 mmol, 10 eq) was dropwise added to a solution of compound **22** (13 g, 49 mmol) in dichloromethane (210 mL) at 0 °C. Acetic anhydride (50 mL) was then added dropwise and the mixture was stirred at rt for 24 h. The mixture was diluted with H_2O, alkalinized with Na_2CO_3 then extracted with dichloromethane. The organic layer was dried over $MgSO_4$ then evaporated under reduced pressure. The obtained solid was dissolved in a mixture of ethyl acetate/cyclohexane, heated up to 90 °C then immediately filtered. The residue was dissolved in small amount of methanol then a small volume of H_2O was added. The solid formed was filtered on filter paper. The solid was dried under reduced pressure to provide compound **23** as a light green powder (8.45 g). Yield 57%.

5.3. General procedure for the synthesis of chalcones 1-19. The acetophenone (10 mmol) and the benzaldehyde derivatives (1 eq.) were solubilized in methanol (200 mL). Potassium hydroxide (10 mL, 50%) was added and the solution was stirred at 90 °C for 24 h. The solution was evaporated to dryness and the residue was suspended in H_2O. The solid formed was filtered, washed with H_2O then dried in oven at 40 °C and reduced pressure to give the desired chalcone as yellow pale solids which were fully characterized by NMR and mass spectrometry analyses.

3-(2,6-Dichlorophenyl)-1-[2-hydroxy-4,6-dimethoxy-3-(N-methylpiperidin-4-yl)phenyl]-prop-2-en-1-one (20) was prepared as previously reported [24].

Synthesis and characterization of compounds **1-6**, **8-11** and **14** were reported in our previous papers.[22,23] Compound **7** was described in references [41,42]. Compound **16** was described in

reference [43]. Compound **12** is commercially available (available from Sigma-Aldrich company). Compound **13**, **15** and **17** were previously reported [44,45].

1-[2-Hydroxy-4,6-dimethoxy-3-(*N*-methylpiperidin-4-yl)phenyl]-3-(2,4,6-trimethoxyphenyl)-prop-2-en-1-one (18). Yield 60%; ^{1}H NMR ($CDCl_3$) δ 14.51 (s, 1H), 8.27 (d, 1H, *J* = 15.8 Hz), 8.18 (d, 1H, *J* = 15.8 Hz), 6.12 (s, 2H), 5.97 (s, 1H), 3.91 (s, 3H), 3.89 (s, 6H), 3.86 (s, 3H), 3.85 (s, 3H), 3.15 (dt, 1H, *J* = 12.3, 3.6 Hz), 2.92 (m, 2H), 2.43 (qd, 2H, *J* = 12.6, 3.6 Hz), 2.29 (s, 3H), 2.02 (m, 2H), 1.49 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 194.7, 164.6, 163.8, 162.9, 161.7, 161.2, 133.9, 127.7, 113.3, 107.3, 107.1, 90.7, 86.9, 57.3, 55.9, 55.7, 55.5, 55.3, 47.0, 32.1, 29.3. MS (ESI) m/z 472 $(M+H)^+$.

3-(2,6-Dimethoxyphenyl)-1-[2-hydroxy-4,6-dimethoxy-3-(*N*-methylpiperidin-4-yl)phenyl]-prop-2-en-1-one (19). Yield 35%; ^{1}H NMR ($CDCl_3$) δ 14.49 (s, 1H), 8.28 (s, 2H), 7.27 (t, 1H, *J* = 8.4 Hz), 6.58 (d, 2H, *J* = 8.4 Hz), 5.98 (s, 1H), 3.93 (s, 3H), 3.91 (s, 9H), 3.24 (m, 1H), 3.10 (m, 2H), 2.61 (m, 2H), 2.45 (br s, 3H), 2.29 (s, 2H), 1.55 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 194.8, 164.5, 164.1, 161.5, 160.4, 133.4, 131.2, 130.6, 113.6, 112.7, 107.0, 103.9, 86.9, 57.0, 55.9, 55.7, 55.4, 46.4, 31.7, 28.7. MS (ESI) m/z 442 $(M+H)^+$.

3-(2,6-Dichlorophenyl)-1-[2-hydroxy-4,6-dimethoxy-3-(N-methylpiperidin-4-yl)phenyl]-prop-2-en-1-one (20). Yield 30%; ^{1}H NMR ($CDCl_3$) δ 14.20 (s, 1H), 8.00 (d, 1H, *J* = 16.0 Hz), 7.85 (d, 1H, *J* = 16.0 Hz), 7.37 (d, 2H, *J* = 8.0 Hz), 7.17 (t, 1H, *J* = 8.0 Hz), 5.97 (s, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.27 (dt, 1H, *J* = 12.2, 3.6 Hz), 3.19 (m, 2H), 2.70 (m, 2H), 2.53 (s, 3H), 2.42 (m, 2H), 1.57 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 192.8, 165.1, 164.6, 162.0, 135.8, 135.4, 135.3, 133.2, 129.6, 129.0, 111.9, 106.4, 86.9, 56.5, 56.0, 55.6, 45.4, 31.0, 27.6. MS (ESI) m/z 450 $(M+H)^+$.

5.3. Biology.

5.3.1. Effect on normal human basophil degranulation. Cells were incubated with a crosslinking anti-FcεRI antibody in addition with various potential PI3Kδ inhibitors. Flow2 CAST assay (Buhlmann, Schönenbuch, Switzerland) was used for assessing CD63 expression (basophils were identified on the basis of CCR3 expression) whereas Allergenicity kit (Beckman Coulter, Hialeah, FL) was used for CD203c expression measurement (basophils were identified through CRTH2+/CD3- expressions). Results, recorded as means of fluorescence intensities (MFI), were expressed as percentages of maximal Ig-E mediated effect (i.e., that obtained without kinase inhibitors).

5.3.2. Murine asthma model. Analyses of the activity of chalcone derivatives in preclinical models of asthma were performed by the Therassay platform in Nantes, France. In this ovalbumin-based model, mice are sensitized by intraperitoneal administration of OVA together with alum as adjuvant on days 1 to 21 then intra-nasally exposed to OVA on days 27 to 29 andanalyzed the day after. Two series of tests were performed. In a first series, groups of 10 mice received intraperitoneal injections of PBS, compound **18** or cromoglycate (considered to be an inhibitor of basophil degranulation). Non-invasive whole body plethysmography was performed in response to metacholine, a bronchoconstrictor. Broncho-alveolar lavage was obtained from 5 mice in each group.

In a second series, groups of 15 mice received nebulization of PBS, of compound **18** or of dexamethasone. 7 to 8 mice per group were then analyzed by Flexivent®, an invasive forced oscillation method to determine respiratory function while broncho alveolar lavage was performed on the remaining animals.

5.3.3. Murine atopic dermatitis model. The murine atopic dermatitis model was obtained as previously described using DNFB (1-fluoro-2,4-dinitrobenzène, Sigma: D1529), diluted in a mixture of acetone and olive oil (4:1) [46]. Briefly mice were sensitized by application of DNFB on their abdomen then sensitized by topical administration of DNFB on their ears. To evaluate the protective effect of compounds, each mouse was used as its own control with groups receiving excipient as a negative control, topical steroid (Diprosone™) or chalcone **18** (at 90 mg/kg intraperitoneally). Ear thickness was then measured daily with a caliper in groups of 5 mice.

5.4. Molecular Modeling Calculations

The PI3Kδ structure taken from the Protein Data Bank [43] (PDB code 2WXF, resolution 1.90 Å) [34] was used for the search of the pose of the compound **18**. This search was performed with docking calculations using GOLD and rDOCK softwares [29,30] followed by geometry optimization of the poses generated by using CHARMM program [48] and binding energy evaluations for all of these relaxed poses by three scoring methods. The protein was prepared using Chimera (original ligand and water molecules were removed) [49]. During the docking experiments, a hydrogen bond with the backbone NH bond of residue V828 was used as a pharmacophore restraint since all known ligands of this protein exhibit such a hydrogen bond. Among the generated poses by GOLD and rDOCK, those with the best scores were compared and 14 of the non-redundant poses were chosen for the next step of geometry optimization. Prior to this optimization, each of the protein-ligand predicted structures were immersed in a sphere of water molecules of 20-Å radius. This sphere size is sufficient to provide a hydration shell around the binding site of the complex. A potential was imposed at the water-vacuum boundary to avoid evaporation. The force field CHARMM36 was used for the protein and the CGenFF parameters were used for the ligand [50]. First, only the water

molecules were subjected to energy minimization (gradient tolerance of 0.5 kcal/mol/Å) while the protein and ligand atoms were kept fixed. Second, the protein and the solvent were harmonically restrained while the ligand was energy-minimized (gradient tolerance of 0.1 kcal/mol/Å). Third, only the harmonical restraints on the ligand and on the solvent were applied while the protein was energy-minimized (gradient tolerance of 0.1 kcal/mol/Å). Fourth, all the atoms of the system were subjected to energy minimization (gradient tolerance of 0.1 kcal/mol/Å).

The binding energy of interaction of each of the poses we generated were then rescored by three methods: XSCORE [31], ITScore [32], and ID-Score [33]. Only one pose, which is discussed in the text, was ranked as number one in every of these rescoring methods.

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Highlights

- Chalcones inhibit normal human basophil degranulation.
- Piperidinyl unit contribute to the inhibition of the PI3Kδ isoform
- Reduction of expiratory pressure with piperidinyl-embeded chalcones
- Anti-atopic properties as potent as topical betamethasone