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LETTER

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Optimization of the Central Core of Indolinone−Acetic Acid-Based CRTH2 (DP2) Receptor Antagonists

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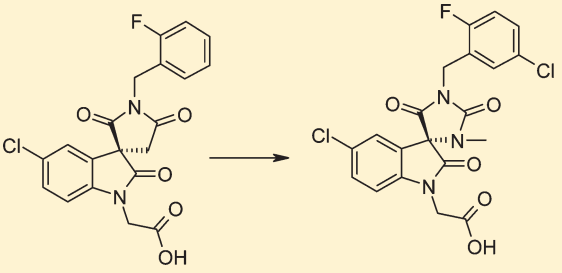
Supporting Information

ABSTRACT: New spiroindolinone antagonists of CRTH2 are described. Following identification of insufficient stability in human plasma as an important liability of the lead compounds, replacement of the spirosuccinimide core with a spirohydantoin or spiropyrrolidinone structure has yielded a compound that is fully stable in human plasma and with good potency in a human whole blood assay (IC_{50} = 69 nM) but shows a much lower oral bioavailability (6−9% in rodents) than the earlier compounds. Successive optimization aimed at restoring an acceptable oral bioavailability has yielded compound (*S*)-**17a**, which exhibits both stability in human plasma and a good oral bioavailability in rat (37%) and mouse (39%). This compound is also active in a mouse model of ovalbumin-induced lung inflammation following oral dosing at 30 mg/kg.



KEYWORDS: CRTH2 receptor, prostaglandin D2, antagonist, indolinone, asthma, atopic dermatitis

Prostaglandin D2 (PGD2) (**1**) (Figure 1) is the major prostanoid species produced by mast cells in response to stimulation by allergens and plays a key role in inflammatory processes. PGD2 exerts its effect through two high-affinity G protein-coupled receptors: the classical PGD2-receptor (DP or DP1) and the more recently discovered chemoattractant receptor homologous expressed on Th2 lymphocytes (CRTH2 also known as DP2). In humans, CRTH2 is predominantly expressed by Th2 cells, eosinophils, and basophils, all known to play a key role in allergic diseases.[1] Activation of the Gi-coupled CRTH2 by PGD2 or the selective agonist DK-PGD2 stimulates chemotaxis of human Th2 cells, eosinophils, and basophils in vitro and in vivo,[2,3] suggesting that the CRTH2 receptor may directly mediate the recruitment of inflammatory cells in allergic diseases such as asthma, allergic rhinitis, and atopic dermatitis. CRTH2 is expressed by antigen-specific Th2 cells in allergic individuals supporting this notion that CRTH2 receptor is important in the recruitment of Th2 in allergic diseases in humans.[4] Indeed, atopic dermatitis subjects or those with sensitivity to pollen or to dust mite antigens have significantly increased levels of $CD4^+$ T cells expressing CRTH2 receptors,[2,5] and severity of atopic dermatitis has been correlated with increased numbers of circulating Th2 cells.[6] Finally, sequence variants of the CRTH2 receptor that confer increased mRNA stability are associated with a higher degree of bronchial hyper-responsiveness and the occurrence of fatal asthma.[7]

Further data in animal models likewise point to a central role for CRTH2 in allergic disorders. CRTH2 receptor activation induces the release of eosinophils from guinea pig bone marrow.[8] In mouse models of allergic asthma and atopic dermatitis, CRTH2 receptor activation promotes eosinophilia and exacerbates pathology.[9] Intratracheal administration of PGD2 in rats, pretreated or not with systemic IL-5 injection, induces eosinophil trafficking into the airways. This effect is mimicked by selective CRTH2 receptor agonists but not by a DP (DP1) selective agonist.[3,10] Furthermore, inhibition by selective small molecules of the CRTH2 receptor but not of the DP or TP receptor abolishes inflammatory responses in mouse models of acute and chronic contact hypersensitivity as well as eosinophilic airway inflammation.[11−14] Recently, it has been postulated that DP and CRTH2 might have opposing effects in complex inflammatory processes, so that inhibition of CRTH2 may have the added benefit of leaving the anti-inflammatory effects mediated by DP1 unopposed.[15]

PGD2 is enzymatically and nonenzymatically metabolized into many different products, several of which are biologically active.[15,16] The thromboxane A2 antagonist ramatroban (**2**) (Figure 1), a drug marketed for allergic rhinitis, has also been shown to possess CRTH2 antagonistic properties. In addition, the finding that indomethacin was able to activate CRTH2, among other pharmacological actions, was the starting point for the discovery of other indole acetic acid derivatives and further spurred much effort in the pharmaceutical industry aimed at discovering selective agents to modulate its action.[17,18]

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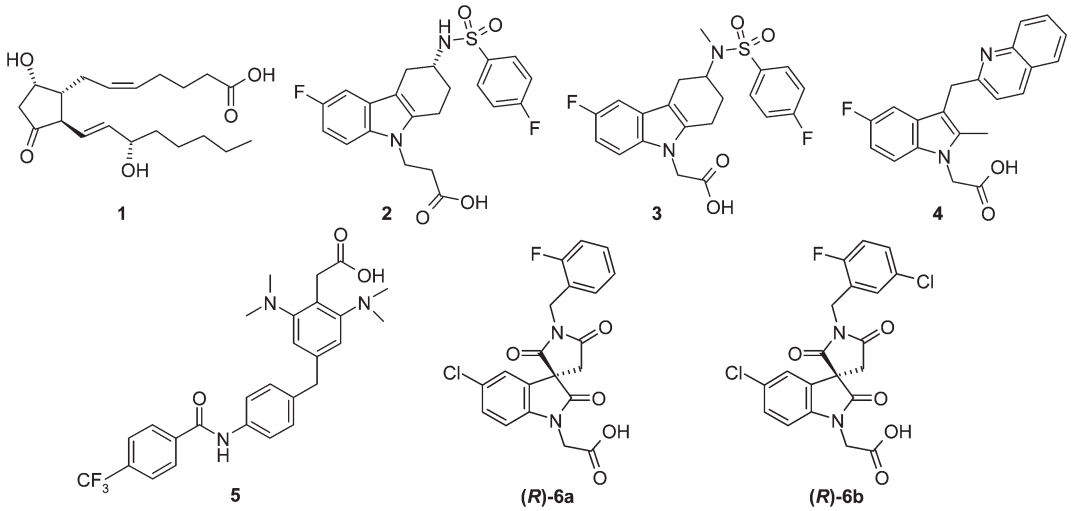

Figure 1. Structures of prostaglandin D2 (PGD2) (**1**), ramatroban (**2**), representative CHTH2 antagonists (**3**−**5**), and the previously described lead compounds [(*R*)-**6a** and (*R*)-**6b**].

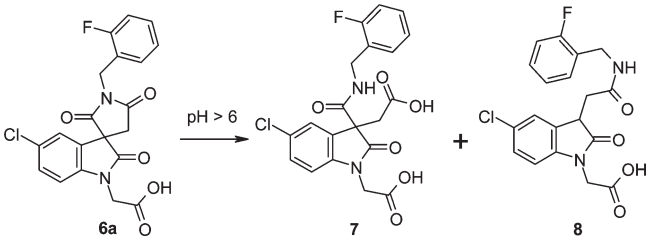

Figure 2. Degradants of **6a** at pH > 6.

In a preceding paper of this series,[19] we disclosed two novel, potent DP2 antagonists. Spirosuccinimides (*R*)-**6a** and (*R*)-**6b** showed not only excellent potencies on CRTH2 in both binding as well as functional assays but also showed a good pharmacokinetic (PK) profile in rodents and dog. These two compounds were further profiled to establish their potential for use as therapeutic agents for atopic diseases. A key weakness was soon identified: pH stability studies demonstrated that the compounds were prone to significant degradation at neutral and basic pH [25% degradation after 24 h at pH 7.4 and 50% degradation after 24 h at pH 8 for (*R*)-**6a**]. The two main degradants were identified as being products **7** and **8**, both derived from opening of the succinimide ring, with subsequent decarboxylation for derivative **8** (Figure 2). It was hypothesized that the succinimide moiety was particularly prone to ring opening due to the strain caused by the spiro system.

This chemical instability had a negative impact on the development potential of the compounds, since the preparation of different salts [potassium or 4-(2-hydroxyethyl)-morpholine salts, for example] led to an unacceptable level of degradation, leaving only the parent form of the compound as suitable for preclinical and clinical studies. However, no significant impact had been determined in the rodent and dog PK experiments, which exhibited medium/low clearance values, in keeping with the good stability exhibited by the compounds in the presence of rat and mouse plasma. In contrast, the compounds were found to have low stability ($t_{1/2} \sim 1$ h) in the presence of human plasma, precluding the possibility of the compounds showing a favorable PK profile in humans. The same degradation products found during the pH stability studies were apparent, clearly indicating that the plasma degradation was also taking place on the succinimide group.

To obtain new analogues with substantially improved stability in human plasma, two strategies to stabilize the CO−N bonds of the succinimide ring were envisioned, removal of either of the carbonyl groups of the succinimide to give more stable spiropyrrolidinones or replacement of the succinimide ring with a hydantoin. The synthesis of the spiropyrrolidinones **9** and **10** has been described in our previous work.[19] Spirohydantoins **11a**−**c** could be prepared as described in Scheme 1.

Following alkylation of chloroisatin with *tert*-butyl bromoacetate, the hydantoin ring could be assembled in one step by reaction with KCN and $(NH_4)_2CO_3$. Alkylation with various benzyl bromides using $NaHCO_3$ in *N*,*N*′-dimethylformamide (DMF) was found to exclusively alkylate on the most acidic NH group, giving the desired intermediates **15a**−**c**. Deprotection with trifluoroacetic acid afforded the desired spirohydantoin compounds. Separation of the two enantiomers was accomplished for the most potent analogues by preparative high-performance liquid chromatography (HPLC) on a chiral stationary phase.[20]

Comparison of the activities of these compounds showed that two of the succinimide replacements maintained a good level of potency on the receptor. Hydantoins **11a**−**c** were found to be active, as well as one of the pyrrolidinone regioisomers (**9**). In contrast, the other pyrrolidinone regioisomer (**10**) was found to be significantly less active than its succinimide counterpart, suggesting that the carbonyl in the 5-position of the succinimide ring is important for the binding to the receptor. Both new scaffolds proved to be more stable than the corresponding succinimides: Both (*S*)-**11b** and (*S*)-**9b** were found to be stable in human plasma (<15% degradation after 24 h). In pH stability experiments, (*S*)-**9b** proved to be completely stable (<5% degradation) up to pH 9, whereas (*S*)-**11b** was stable at pH 8 (<5% degradation) but not at pH 9 (45% degradation). The improved stability allowed for the development of salt forms for both types of compounds, and both were found stable in a number of formulations.

A comparison of the profiles of two of the most potent analogues for each of the spiropyrrolidinone and spirohydantoin

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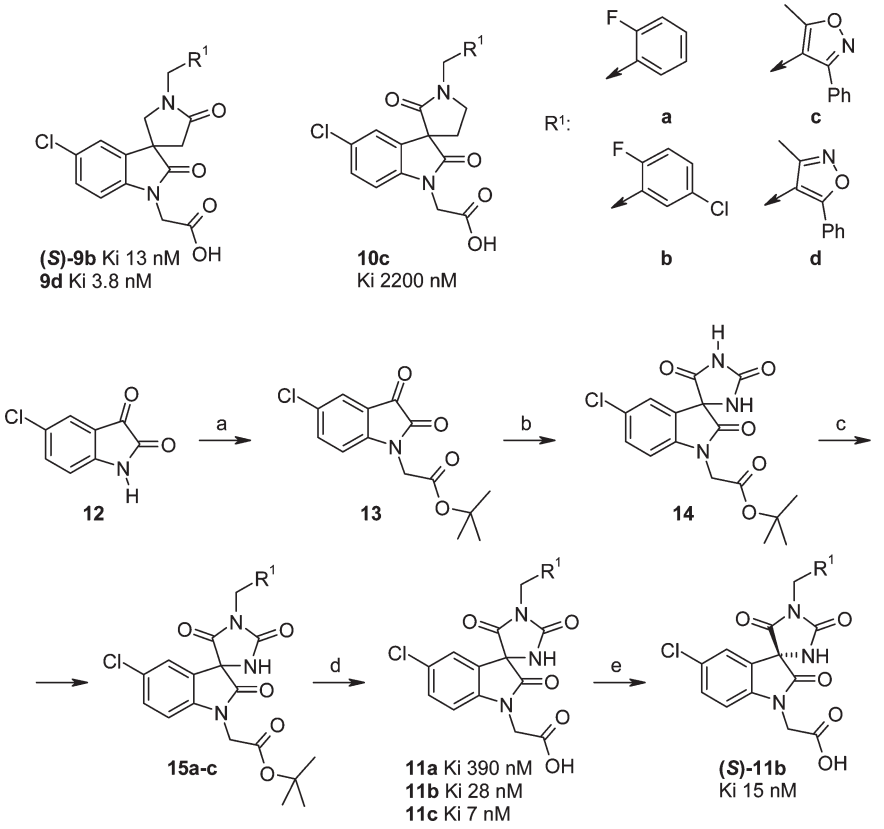
Scheme 1[a]



[a] Reagents: (a) K_2CO_3, *tert*-butyl bromoacetate, room temperature, 65%. (b) KCN, $(NH_4)_2CO_3$, $EtOH/H_2O$, reflux, 92%. (c) $NaHCO_3$, R^1CH_2Br, 59%. (d) CF_3COOH, CH_2Cl_2, 0 °C to room temperature, 93%. (e) Chiral HPLC for **11b**.

Table 1. Comparison of (*S*)-9b and (*S*)-11b

	(*S*)-**9b**	(*S*)-**11b**
K_i (hCRTH2) (nM)	13	15
eosinophil chemotaxis IC_{50} (nM)	62	7.4
hWB assay IC_{50} (nM)	1800	69
Fu (h, r, m, %)	<1%/ ND/ND	2.3/3.0/6.3
Caco-2 permeation Papp (cm/s)	1.8×10^{-6}	0.2×10^{-6}
clearance in rat (L/kg/h)	0.72	0.15
oral bioavailability in rat (Fz, %)	5	6

series can be found in Table 1. For both series, the compounds substituted with an isoxazole substituent (**9d** and **11c**) were found to be highly potent on the receptor and showed excellent activities in a human whole blood assay (hWB assay, inhibition of eosinophil shape change induced by 10 nM PGD2) but had very high clearance in rodent PK experiments and were not further characterized. The (2-fluoro-4-chloro)benzyl-substituted compounds showed similar potencies in the binding assay but different activities in the functional assays, with hydantoin (*S*)-**11b** being significantly more potent in both the eosinophil chemotaxis assay (7.4 vs 62 nM) and especially in the hWB assay (69 vs 1800 nM). The difference in activity in human whole blood could be at least in part attributed to the higher unbound fraction in human plasma [Fu 2.3% for (*S*)-**11b** vs Fu <1% for (*S*)-**9b**]. The rat PK data also showed that among the two compounds (*S*)-**11b** had the better profile, with a low clearance of 0.15 vs 0.72 L/kg/h for (*S*)-**9b**. This was in keeping with low clearance values in both human microsomes (<1 μg/mL/h) and human hepatocytes (2 μg/mL/h) for (*S*)-**11b**. Both compounds showed low oral bioavailability (Fz), 6% for (*S*)-**11b** vs 5% for (*S*)-**9b**.

PK experiments in various animal species (mouse, dog, guinea pig, and monkey) confirmed that (*S*)-**11b** could be considered as a low-clearance compound. However, the low oral bioavailability observed in the rat was confirmed in mouse (9%), guinea pig (7%), and monkey (10−15%), while the dog, with an oral bioavailability of 71%, was an outlier. The in vitro profiling of (*S*)-**11b** identified two parameters that could explain the poor oral bioavailability. First, the compounds exhibited a very low solubility in simulated gastric fluid (SGF) of 0.01 mg/mL (vs a solubility in fasted state simulated intestinal fluid, Fassif, of 1.5 mg/mL). Even more importantly, (*S*)-**11b** had a very poor permeability in the Caco-2 assay (Papp = 0.2×10^{-6} cm/s), ca. 100-fold lower than the corresponding succinimide (*R*)-**6b** (Papp = 26×10^{-6} cm/s), which showed a more satisfactory Fz of 32% in rat. To determine the cause for the low oral bioavailability, an experiment was performed in rats by administering the compound via different routes. The high bioavailability after portal vein administration (90%) ruled out the possibility that first-pass metabolism could play a major role in reducing oral bioavailability. In contrast, the low bioavailability after intraduodenal administration (11%) confirmed that low permeability of the compound, and not a possible precipitation in the stomach, was the main determinant of the low oral bioavailability.

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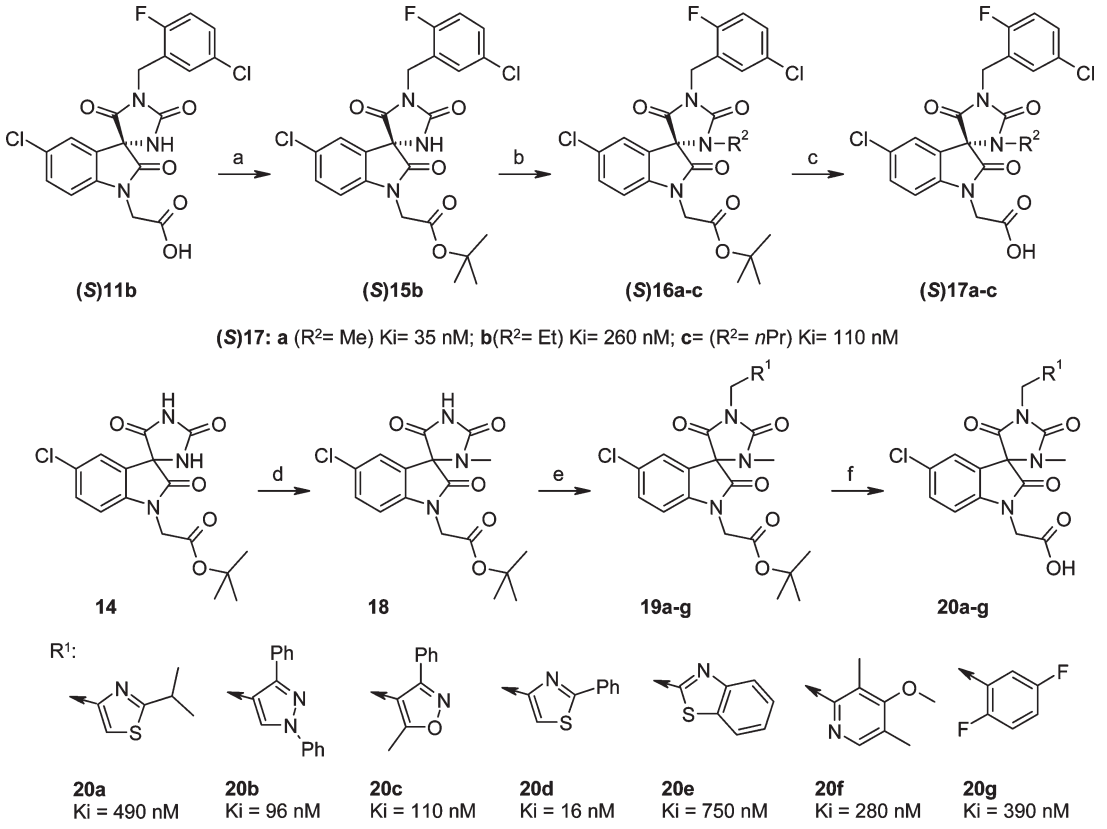
Scheme 2[a]



[a] Reagents: (a) *tert*-Butyl *N*,*N*′-diisopropylimidocarbamate, THF, room temperature, 61%. (b) R^2I, K_2CO_3, DMF, room temperature. (c) CF_3COOH, CH_2Cl_2, 0 °C to room temperature. (d) CH_3I, $[(CH_3)_3Si]_2NLi$, THF, 0 °C to room temperature, 47%. (e) R^1CH_2Br or R^1CH_2Cl, $NaHCO_3$, KI, DMF, 80 °C. (f) HCl, dioxane, 0 °C to room temperature.

Table 2. Comparison of (*S*)-17a and (*S*)-11b

	(*S*)-**17a**	(*S*)-**11b**
K_i (hCRTH2) (nM)	35	15
eosinophil chemotaxis IC_{50} (nM)	47	7.4
hWB assay IC_{50} (nM)	150	69
Fu (h, r, m, %)	2.0/1.9/5.0	2.3/3.0/6.3
Caco-2 permeation Papp (cm/s)	0.6	0.2×10^{-6}
clearance in mouse (L/kg/h)	0.8	0.8
oral bioavailability in mouse (Fz, %)	39	9
AUC po (5 mg/kg) (h ng/mL)	2400	580

Comparing the structures of (*R*)-**6b** and (*S*)-**11b**, the important difference in permeability could be tentatively attributed to the presence of an extra hydrogen bond donor (HBD) in hydantoin (*S*)-**11b**. To obtain compounds combining the plasma and pH stability of the hydantoin compounds and the permeability of the succinimide compounds, it was decided to mask the HBD function by alkylating the second hydantoin nitrogen atom. A small series of *N*-alkyl derivatives (*S*)-**17a**−**c** could be prepared by alkylation of the *tert*-butyl ester (*S*)-**16** (Scheme 2).

Compound (*S*)-**17a** showed an activity on the receptor, which, albeit slightly reduced as compared to (*S*)-**11a**, was still acceptable (Table 2). In contrast, introducing even slightly larger substituents, such as ethyl and propyl, quickly led to compounds having K_i over 100 nM. A limited SAR was also performed on the R^1 substituent (Scheme 2), a position that had been extensively studied on the succinimide derivatives. A number of groups were explored, but only the phenyl thiazole derivative **20d** showed potency comparable to (*S*)-**17a**. Further profiling of **20d** showed that potency in the hWB assay (IC_{50} = 3940 nM) as well as mouse PK parameters (Cl 3.63 L/kg/h, Fz <5%) were unfavorable, and further development of this compound was not pursued.

Characterization of (*S*)-**17a** (Table 2) showed that the compound retained stability in human plasma as well as in human and rat microsomes (Clint <10 μL/min/mg in both species). In the Caco-2 experiment, (*S*)-**17a** was still found to be poorly permeable, with a Papp $<1 \times 10^{-6}$ cm/s, far below the corresponding succinimide (*R*)-**6b** (Papp = 26×10^{-6} cm/s). However, in a mouse PK experiment, (*S*)-**17a** had a similar, moderate clearance (Cl = 0.8 L/kg/h) as shown by (*S*)-**11a** in the same species but with an improved oral bioavailability (Fz = 39% vs Fz = 9% for (*S*)-**11a** in mouse), resulting in a much-improved AUC after oral dosing (2400 vs 580 h ng/h/mL at 5 mg/kg po). A similar improvement of the oral bioavailability was observed in the rat [Fz = 37% vs Fz = 6% for (*S*)-**11a**]. The stability in human and rodent plasma was retained. The protein binding of (*S*)-**17a** was found to be very similar to that of (*S*)-**11a**, so rather unsurprisingly the potency in the hWB assay was found to follow the same trend as the affinity for the receptor, with an IC_{50} ca. 2-fold higher than for (*S*)-**11a** (IC_{50} = 150 vs 69 nM). The combination of good potency in the hWB assay and favorable PK

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in mice indicated that (*S*)-**17a** should be active in CRTH2-dependent animal models after oral dosing. This was verified by testing the compound in a lung eosinophilia model in mice: (*S*)-**17a** was found to inhibit lung eosinophilia induced by aerosolized ovalbumin (67 ± 11% inhibition following oral dosing at 30 mg/kg, $P < 0.05$, vs 83 ± 8% inhibition by dexamethasone dosed at 1 mg/kg ip, $P < 0.01$).

The undesirable off-target activity of (*S*)-**17a** (at a concentration of 10 μM) was also evaluated; among other prostanoid receptors, EP1 and EP2 were weakly inhibited (respectively, 32 and 34% inhibition in a binding assay). Inhibition of PGD2 binding to DP1 or of PGD2-mediated cyclic adenosine monophosphate (cAMP) increase in DP1-expressing human embryonic kidney cells was found to be of less than 30% [up to 20 μM of (*S*)-**17a**]. No significant activity was found on a panel of 50 different enzymes and receptors, including the K_v11.1 (hERG) channel, with the exception of the enzyme aldose reductase (IC_{50} = 150 nM). The compound was also tested in a cytotoxicity assay, both on primary rat hepatocytes and on human hepatocellular carcinoma (HepG2) cells, and found to be noncytotoxic up to the highest concentration tested (750 μM). Finally, no significant inhibition of the major cytochrome P450 (CYP) isoforms was observed (CYP1A2, -2C19, -2C8, -2C9, -2D6, and -3A4; $IC_{50} > 10$ μM).

In conclusion, the lack of stability of the initial lead compounds in neutral and mildly basic conditions and especially in human plasma could be substantially improved by modifying the succinimide ring. Of the modifications attempted, both yielded compounds with good affinity for the receptor, but only the use of a hydantoin group allowed the discovery of an antagonist with high potency in the human whole blood assay, but its low oral bioavailability across several species prevented its development as an oral agent for atopic dermatitis or asthma. Further optimization to improve the oral bioavailability led to the identification of compound (*S*)-**17a**, which shows good potency in the hWB assay as well as good PK parameters in rodents, including a acceptable oral bioavailability, translating to activity in a mouse model of ovalbumin-induced lung inflammation following oral dosing.

■ ASSOCIATED CONTENT

Supporting Information. Experimental details for biological assays and for the synthesis and characterization of **11a**−**c**, **17a**−**c**, and **20a**−**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) While the absolute configuration for the enantiomers of **11b** could not be determined due to the difficulty to obtain crystals suitable for X-ray diffraction, the absolute configuration of the most potent (on CRTH2) enantiomer (+)-**11b** was deduced by analogy with known (*R*)-**6a** and (*R*)-**6b** to be of (*S*) configuration.