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Zwitterionic CRTh2 Antagonists

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Supporting Information

ABSTRACT: A novel series of zwitterions is reported that contains potent, selective antagonists of the chemoattractant receptor-homologous expressed on Th2 lymphocytes receptor (CRTh2 or DP2). A high quality lead compound 2 was discovered from virtual screening based on the pharmacophore features present in a literature compound 1. Lead optimization through side chain modification and preliminary changes around the acid are disclosed. Optimization of physicochemical properties (log D, MWt, and HBA) allowed maintenance of



high CRTh2 potency while achieving low rates of metabolism and minimization of other potential concerns such as hERG channel activity and permeability. A step-change increase in potency was achieved through addition of a single methyl group onto the piperazine ring, which gave high quality compounds suitable for progression into in vivo studies.

INTRODUCTION

Chemoattractant receptor-homologous expressed on Th2 lymphocytes (CRTh2) has been identified as a G proteincoupled receptor, expressed on human Th2 cells, eosinophils, and basophils. Prostaglandin D_2 (PGD₂) is the principal prostanoid released by immunoglobulin E (IgE)-activated mast cells during asthmatic and allergic reactions. PGD₂ has long been associated with inflammatory conditions and is considered an important mediator in asthma and allergic diseases.¹ The first PGD₂-specific receptor to be discovered was the DP receptor,² but PGD₂ is now also known to be an endogenous agonist of the CRTh2 receptor and promotes chemotaxis of inflammatory cells.³ Studies have shown that this chemotaxis, as well as that induced by the CRTh2-selective metabolite 13,14-dihydro-15keto-PGD₂ (DK-PGD₂), is blocked by selective CRTh2 antagonists. Therefore, it is expected that a CRTh2 antagonist would be useful for the treatment of asthma and allergic rhinitis.⁴

Ramatroban⁵⁻⁷ (1, Figure 1), an indole-1-propionic acid, was originally developed as a thromboxane A2 antagonist for the treatment of thrombosis and coronary artery disease but was later shown to be a relatively potent CRTh2 antagonist. It is possible that the biological efficacy of 1 is at least in part mediated through CRTh2, and the compound has gained approval in Japan for the treatment of allergic rhinitis.

Compounds from the AstraZeneca collection with hints of structural similarity to Ramatroban were identified by virtual screening using a speculative pharmacophore consisting of an acidic group connected to an aryl ring by 1-3 atoms. These virtual hits were selected for CRTh2 potency determination to discover novel antagonists. Interestingly, compound 2 was identified (Figure 1), which, despite its very different molecular

framework, contained a carboxylic acid and sulfonamide at a broadly comparable spatial arrangement to compound 1. Surprisingly, 2 was subsequently found to be a highly potent CRTh2 antagonist ($IC_{50} = 16$ nM). We and others have recently disclosed unrelated CRTh2 antagonists that also contain the phenoxyacetic acid unit.8 The discovery of 2 was strategically important as it offered the intriguing possibility of delivering a zwitterionic drug candidate (measured base pK_a 6.8). This is a novel discovery within the PGD₂ prostanoid area, as the vast majority of candidate drugs are monoacids. The discovery of zwitterion 2 was therefore viewed as an opportunity to deliver substantial changes to absorption-distribution-metabolismexcretion (ADME), selectivity, and toxicity profiles.9 We now disclose the synthesis and CRTh2 structure-activity relationship (SAR) around this new series of zwitterions and how it led to the discovery of exceptionally potent and selective compounds with the superior properties suitable for progression into in vivo toxicology studies.

CHEMISTRY

The phenoxyacetic acid-derived zwitterions were assembled using the routes highlighted in Scheme 1. Alkylation of 2-hydroxybenzaldehydes with a bromoacetate ester afforded intermediate 3. This chemistry was tolerant of α -substitution, enabling installation of monomethyl ($R^3 = Me$) and dimethyl (not shown) groups adjacent to the carboxylic ester. The protected amine side chains were subsequently installed either through reductive amination chemistry or via a reduction/mesylation/alkylation

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Figure 1. Structures of Ramatroban (1) and novel CRTh2 antagonist (2) from pharmacophore overlays and virtual screening.

sequence to afford 4. Diversification was then possible through selective removal of the *tert*-butyloxycarbonyl (BOC) group followed by the introduction of R^6 via the use of a wide variety of amidations and sulfonylations. Ester hydrolysis afforded final target molecules (9–33).

The complete side chains (8), already containing the R° group required for the final targets, could also be synthesized independently from 7. Reaction of 8 with aldehyde 3 afforded 6 directly, leaving only the final ester hydrolysis step to deliver the desired zwitterions. Target compounds incorporating amine side chains other than piperazine were constructed using analogous procedures from suitably functionalized amines (e.g., 1-BOChomopiperazine).

The synthesis of acetic acid analogues is summarized in Scheme 2. Reduction of 2-iodo-4-chloro-benzoic acid gave the corresponding benzylic alcohol, which was then homologated to the acetic ester **35**. The desired carboxylic acid functional handle required for side chain installation (**37**) was introduced using palladium-catalyzed carbonylation chemistry that conveniently generated carbon monoxide in situ from acetic anhydride and sodium formate.¹⁰ The desired target molecules **40** and **46** were then constructed from **38** using similar transformations to those used for the phenoxyacetic acid analogues in Scheme 1.

Heck chemistry was used to access the propionic acid homologues (Scheme 3). The 2-hydroxybenzaldehyde was converted to the corresponding triflate **41** and cross-coupled with methyl acrylate. Hydrogenation over platinum on carbon reduced both the double bond and the aldehyde without reduction of the aryl chloride to afford key intermediate **43**. Similar chemistry to earlier analogues (Schemes 1 and 2) completed the construction of the target zwitterions **45**.

BIOLOGICAL RESULTS

Gratifyingly, the initial hit 2 was highly potent (Table 1), and so, a matrix of close structural changes was rapidly prepared to unravel the CRTh2 SAR present within the series. It was found that both *para*-chlorine and *para*-CF₃ substituents on the phenoxyacetic acid ring were of similar potency (9 vs 2), and both aryl- and benzyl-sulfonylpiperazine side chains were potent (2, 9, and 10). The side chain sulfonamide group could be successfully replaced by the corresponding amide (11 and 12) with only limited potency erosion. This was important SAR, as it was expected that these highly charged acids would require control of polar surface area (PSA) to maintain good oral pharmacokinetic profiles.¹¹

Replacement of the piperazine ring was possible (13 and 14) but only if the distal sulfonamide nitrogen was retained surprisingly, sulfone 15 was not active at CRTh2. Clearly, this molecular change alters the H-bond geometry, with the SO_2 group in 15 now joined to the six-membered ring via a tetrahedral carbon as compared to a trigonal nitrogen in **2**. This modification concomitantly increases the basicity of the benzylic nitrogen proximal to the phenoxyaryl ring (**15**: measured base $pK_a = 7.8$) and a combination of such effects may well be implicated within the potency SAR. Accordingly, the homopiperazine phenylsulfonamide **13** was also of increased basicity and lower potency as compared to **2** and therefore may lend some credence to the latter hypothesis, although the benzylsulfonamide analogue (**14**) was able to reverse this SAR.

Halogen substitution on the distal aryl ring was tolerated with the 4-fluorophenyl (16) having excellent potency. The benzylsulfonamides (10 and 14) were less metabolically stable in rat hepatocytes and, given their increased molecular weight (MWt) and PSA, were viewed as somewhat less promising leads than the corresponding arysulfonamide and amide derivatives.

Several classes of nonprostanoid acids are known to function as CRTh2 agonists,¹² and so, these zwitterions were also characterized in functional assays (Table 1). Hit 2 and all other analogues were shown to be inactive in an eosinophil shape change agonism assay, a response known to be mediated through CRTh2.¹³ Inactivity (IA) in this assay was defined as <10% of the response of the selective CRTh2 agonist DK-PGD2, which represented the minimum statistically meaningful response detectable. The compounds were also shown to behave as functional antagonists and block PGD_2 -mediated Ca^{2+} flux in CHO cells expressing human CRTh2. The potency ranking in this functional screen was broadly similar to that observed from the radioligand binding screen, with any drop in IC₅₀ generally attributable to interaction with bovine serum albumin (BSA) present in the cell assay. Representative compounds (2 and 10) were shown to have high (>1000 \times) selectivity over receptors and enzymes from the prostanoid area including DP1, thromboxane A₂, and cyclo-oxygenase 1.

Given the novelty of the piperazine side chain, this was selected as a key area of focus for further optimization (Table 2). Interestingly, the addition of a single methyl, initially in racemic form, onto the piperazine ring adjacent to the sulfonamide gave a modest 2-fold increase in potency over the unsubstituted analogue (17 vs 2). However, when the single enantiomers (18 and 19) were prepared, a 35-fold potency separation was found, with the (S)-enantiomer 18 being an incredibly potent subnanomolar antagonist. Given the strong stereochemical bias, this step change in potency (>1 log improvement for a 0.5 log P increase) would appear to be from a specific interaction with the receptor. The expected conformational effect of this structural change would be to broadly preserve the sulfonyl orientation but place the chiral methyl group into an axial environment through allylic strain.¹⁴ Other unrelated drug discovery programs have also found that this structural change has led to significant potency increases,15 highlighting the wider value of this conformational effect. A similar potency increase was also observed within the amide subseries (20 and 25). However, substitution at the carbon adjacent to the benzylic nitrogen gave no potency increase (21). Increasing the size of the chiral piperazine substituent to ethyl (22) or *n*-propyl (23) also gave highly potent compounds but no additional increase in potency for the increasing lipophilicity.

Small substituents were tolerated on the pendant aryl of the amide (26-29), with halides in the para-position being more potent and metabolically stable. Finally, the CF₃ compound **30** again maintained similar activity to the corresponding chloro

Scheme 1^a



^{*a*} Reagents: (a) $BrCH_2CO_2R^2$ or $TsOCH(Me)CO_2R^2$, K_2CO_3 . (b) R^4 -(R^5)-piperazine, NaBH(OAc)₃, NMP or R^4 -(R^5)-piperazine, NaBH(OAc)₃, MgSO₄, THF. (c) NaBH₄, MeOH. (d) MeSO₂Cl, iPr₂EtN, CH₂Cl₂, then R^4 -(R^5)-piperazine, NaI, DMF. (e) CF₃COOH, CH₂Cl₂. (f) Sulfonyl chloride, NaHCO₃, CH₂Cl₂, water/acid chloride, Et₃N, THF/aryl or alkyl acid, iPr₂EtN, HATU or Pybrop, DMF or THF. (g) R^2 = tBu: CF₃COOH, CH₂Cl₂ or HCl, dioxane, R^2 = Me or Et: NaOH (aq), THF.

Scheme 2^{*a*}



^{*a*} Reagents: (a) BH₃·THF, THF. (b) SOCl₂, DMF_{cat} CH₂Cl₂. (c) NaCN, DMF. (d) KOH (aq), 100 °C. (e) Me₃SiCl, MeOH. (f) Pd₂(dba)₃, LiCl, HCO₂Na, iPr₂EtN, Ac₂O, DMF, 80 °C. (g) BH₃·THF, THF. (h) MeSO₂Cl, Et₃N, CH₂Cl₂ then 1-R⁶-(2S)-2-(R⁴)-piperazine, K₂CO₃, DMF. (i) NaOH (aq), THF.

Scheme 3^{*a*}



^{*a*} Reagents: (a) Tf₂NPh, Et₃N, DMF. (b) Methyl acrylate, Pd(dppf)Cl₂, Et₃N, THF, 67 °C. (c) Pt/C, H₂, ethyl acetate. (d) MeSO₂Cl, Et₃N, CH₂Cl₂, then R^6 -(R^4)-piperazine, K₂CO₃, DMF or EtOH. (e) NaOH (aq), THF, MeOH.

Table 1. Preliminary SAR of Compounds 2 and 9-16



Cpd.	R^1	R ²	CRTh2 binding IC ₅₀ ^a (nM)	Log D _{7.4}	Rat Hep Cl _{int} ^b	Hum Mic Cl _{int} ^c	Agonism Eos Shape change ^d	$\begin{array}{c} \text{CRTh2} \\ \text{Ca}^{2+} \\ \text{IC}_{50}^{\text{e}} \\ \text{(nM)} \end{array}$
1		-	77	0.6	-	-	IA	461
2	Cl	↓ N SO₂Ph	16	0.5	<3	4	IA	201
9	CF ₃	}_N_N−SO₂Ph	18	0.4	<4	6	IA	517
10	Cl	↓ N N SO ₂ CH ₂ Ph	6	0.3	9	5	IA	18
11	CF ₃	k N N − K Ph	316	-	<3	5	-	-
12	Cl	↓N_NPh	100	-	-	-	-	1082
13	Cl	₹-N_N-SO ₂ Ph	631	1.0	5	<3	-	4093
14	Cl	k −N N−SO ₂ CH ₂ Ph	79	1.0	18	5	IA	89
15	Cl	k −N −SO ₂ Ph	IA at 1 μM	-	<3	<3	-	-
16	Cl	≩−N_N−SO₂(Ph-4-F)	10	1.0	<3	11	IA	-

^{*a*} Radiometric binding assay, n > 2 measurements. ^{*b*} Rat hepatocyte intrinsic clearance (μ L/min/1 × 10⁶ cells). ^{*c*} Human liver microsomes intrinsic clearance (μ L/min/mg). ^{*d*} Agonism in eosinophil shape change, IA refers to <10% response of DK-PGD₂. ^{*e*} Antagonism of PGD₂-mediated Ca²⁺ flux in human CHO cells, n > 2 measurements.

analogue 26, but substitution on the benzylic position of the amide led to a reduction of potency and metabolic stability (31).

Again, virtually all zwitterions in this set were devoid of agonist activity and behaved as functional antagonists with only compound (**30**) identified as a partial agonist in the eosinophil shape change assay (\sim 40% of DK-PGD₂ efficacy).

Changes to the acid side chain were investigated to sterically block conjugative metabolism and/or modulate the carboxylate acidity. The preferred aim was to minimize the difference between the acid and the base pK_a values to limit zwitterionic character at physiological pH and thus hopefully mitigate the bioavailability risks often present in zwitterionic compounds. These changes are summarized in Table 3.

A single methyl substituent was well tolerated adjacent to the carboxylate (32 vs 27); however, the addition of a second methyl group resulted in substantial potency loss (33). Encouragingly, the less acidic acetic acids (40 and 46) maintained potency and metabolic stability with both the amide and the sulfonamide side chains. By contrast, the propionic acid 45 lost significant potency despite the chain length and proportion of ionization at physiological pH being similar to the original oxyacetic acids. Finally, bioisosteric replacement of the carboxylic acid by an



		R	1					
Cpd.	\mathbb{R}^1	\mathbb{R}^2	CRTh2 binding IC ₅₀ ^a (nM)	Log D _{7.4}	Rat Hep Cl _{int} ^b	Hum Mic Cl _{int} ^c	Agonism Eos Shape change ^d	$\begin{array}{c} \text{CRTh2} \\ \text{Ca}^{2+} \\ \text{IC}_{50}^{\text{e}} \\ \text{(nM)} \end{array}$
17	Cl	k N−SO ₂ Ph	4.5	0.3	-	-	IA	31
18	C1	k N−SO ₂ Ph Me	0.8	-	<3	5	IA	16
19	C1	k N_N−SO ₂ Ph Me	28	-	8	8	IA	240
20	Cl	k − N − V − V − V − V − V − V − V − V − V	71	-0.1	-	-	IA	199
21	Cl	k N−SO ₂ Ph Me	28	0.7	7	<3	IA	71
22	Cl	ξ−N_N−SO₂Ph Et	4.5	0.4	4	9	IA	31
23	C1	k N−SO ₂ Ph	1.3	1.0	10	11	IA	13
24	Cl	k − N − N − O Me − Ph	71	0.7	20	<3	IA	3840
25	Cl		3.3	0.2	4	<3	IA	26
26 27 28 29	Cl	k→N N→O Me R ³ 4-F 4-Cl 2-Cl 3-Cl	1.0 0.5 5.6 6.8	- 1.2 1.1 0.8	<3 <3 13 12	<3 <3 7 <3	IA IA IA IA	9 9 16 27
30	CF ₃		0.3	0.8	<3	<3	yes	-
31	C1		20	-	9	<3	IA	39

^{*a*} Radiometric binding assay, n > 2 measurements. ^{*b*} Rat hepatocyte intrinsic clearance (μ L/min/1 × 10⁶ cells). ^{*c*} Human liver microsomes intrinsic clearance (μ L/min/mg). ^{*d*} Agonism in eosinophil shape change, IA refers to <10% response of DK-PGD₂. ^{*e*} Antagonism of PGD₂-mediated Ca²⁺ flux in human CHO cells, n > 2 measurements.

Table 3. Side Chain SAR of Compounds 32, 33, 40, and 45-47



Cpd.	\mathbf{R}^1	\mathbf{R}^{6}	CRTh2 IC ₅₀ ^a (nM)	Log D _{7.4}	Rat Hep Cl _{int} ^b	Hum Mic Cl _{int} ^c	Agonism Eos Shape change ^d	$\begin{array}{c} \text{CRTh2} \\ \text{Ca}^{2+} \\ \text{IC}_{50}^{e} \\ (\text{nM}) \end{array}$
32	Me O	€	1.3	1.7	<3	<3	IA	-
33		≹—SO₂Ph	708	0.5	17	5	-	1442
40	CO ₂ H	€ CI	2.2	1.7	<3	<4	IA	18
45	CO ₂ H		79	1.5	<3	<3	IA	547
46	CO ₂ H	∳─SO₂CH₂Ph	0.6	1.1	9	<3	IA	11
47	C(O)NHSO ₂ Me	↓−SO₂CH₂Ph	50	0.4	4	9	IA	486

^{*a*} Radiometric binding assay, n > 2 measurements. ^{*b*} Rat hepatocyte intrinsic clearance (μ L/min/1 × 10⁶ cells). ^{*c*} Human liver microsomes intrinsic clearance (μ L/min/mg). ^{*d*} Agonism in eosinophil shape change, IA refers to <10% response of DK-PGD₂. ^{*e*} Antagonism of PGD₂-mediated Ca²⁺ flux in human CHO cells, n > 2 measurements.

acylsulfonamide (47) maintained modest CRTh2 potency, although this was also at the expense of increased MWt and PSA.

From this rapid lead optimization program, a range of high quality antagonists were generated, which met our original aspirations of high CRTh2 potency, high lipophilic ligand efficiency (LLE), and low rates of metabolism. The best compounds from the series demonstrated acceptable plasma protein binding, as well as no significant CYP P450 inhibition and high selectivity against the human ether-a-go-go-related gene (hERG) channel. These compounds were progressed into in vivo rat pharmacokinetic studies, and a representative selection is summarized in Table 4.

Gratifyingly, the compounds had moderate clearances as expected from the low in vitro rates of metabolism. They also displayed moderate volumes of distribution, certainly larger than one might expect for monoacids, and more in keeping with the zwitterionic nature of these compounds. These parameters drove encouraging terminal half-lives of 3-5 h. Compounds 2 and 27 had moderate permeability in Caco-2 screens [P_{app} A–B (1 × 10^{-6} cm/s): 2, 1.7; 27, 5.8] and high solubility (both >80 μ M), which produced moderate levels of oral bioavailability. Encouragingly, the less acidic 40 as hoped had complete bioavailability and a long terminal half-life. On the basis of these results, preclinical

Table 4. Rat Pharmacokinetic Properties of Key Analogues

compd	Rat iv ^a Cl (mL/min/kg)	Rat iv Vss (L/kg)	Rat iv $t_{1/2}$ (h)	Rat po ^b F %
2	23	4.6	3.3	46
27	15	1.6	3.2	22
40	9	3.5	5.3	110
¹ Intraveno	us dose. 1 mg/kg.	^b Oral dose, 4	(2) or $3 \text{mg}/$	kg (2 7 and 40).

candidates were selected for additional pharmacokinetic and toxicity profiling.

CONCLUSIONS

We have identified a novel series of zwitterionic CRTh2 antagonists. The initial lead compound **2** was optimized through a mixture of changes to the basic and acidic side chains to deliver compounds of exceptional quality. A key chiral methyl group delivered a surprising step-change increase in potency. Control of physicochemical properties afforded low rates of metabolism and promising selectivity profiles (no CYP, hERG). Careful molecular design enabled the discovery of zwitterions with encouraging

pharmacokinetic profiles, and candidates from the series were successfully progressed into more detailed in vivo studies.

EXPERIMENTAL SECTION

Chemistry. Reagents were obtained from commercial suppliers and used without purification. Unless otherwise stated, reactions were carried out at ambient temperature (18-25 °C) and under positive nitrogen pressure with magnetic stirring. Flash chromatography was performed on E. Merck 230-400 mesh silica gel 60. Solvent mixtures used as eluents are volume/volume ratios unless otherwise stated. Preparative reverse phase (RP) HPLC purifications were performed on Waters Symmetry, Novapak, or Xterra columns eluting with a gradient of acetonitrile or methanol in aqueous ammonium acetate, ammonia, or trifluoroacetic acid solution. Routine ¹H NMR spectra were recorded on a Varian UnityInova spectrometer at a proton frequency of either 300 or 400 MHz. Chemical shifts are expressed in ppm. Mass spectra were measured on an Agilent 1100 MSD G1946D spectrometer using electrospray ionization, atmospheric pressure chemical ionization, or Agilent Multimode ionization; only ions that indicate the parent mass are reported.

The purity of all test compounds was determined by RPHPLC conducted on an Agilent 1100 LC/MS system, using UV detection and a gradient of 5–95% acetontirile in either aqueous ammonium acetate (0.1% w/v) (conditions a) or trifluoroacetic acid (0.1% v/v) (conditions b) over 2.5 min on 2.1 mm \times 5 mm columns packed with Waters Symmetry C8 or Waters Symmetry C18 or 2.0 mm \times 50 mm columns packed with Phenomemex Max-RP. Column and solvent details for each compound are given in the Supporting Information. All test compounds unless otherwise indicated showed \geq 95% purity. For all key molecules, high resolution mass spectrometry or microanalysis data were also generated.

(4-Chloro-2-formylphenoxy)acetic Acid, 1,1-Dimethylethyl Ester (**3a**) ($R^1 = CI$, $R^2 = {}^tBu$, and $R^3 = H$). Potassium carbonate (5.0 g, 36 mmol) was added to a solution of 2-hydroxy-5-chlorobenzaldehyde (5.2 g, 33 mmol) and *tert*-butylbromoacetate (4.8 mL, 33 mmol) in *N*,*N*-dimethylformamide (DMF) (20 mL). The reaction was stirred for 16 h. Aqueous sodium hydroxide was added (1 N, 100 mL), and the mixture was extracted with diethyl ether (3×). The combined organics were washed with water and brine and dried (MgSO₄), and the solvent was removed in vacuo. The resulting solid was triturated with *iso*-hexane to give **3a** (7.2 g, 81%). ¹H NMR (CDCl₃) δ : 10.5 (1H, s), 7.81 (1H, d), 7.47 (1H, dd), 6.82 (1H, d), 4.64 (2H, s), 1.48 (9H, s).

(2S)-4-[[5-Chloro-2-[2-(1,1-dimethylethoxy)-2-

oxoethoxy]phenyl]methyl]2-methyl-1-piperazine Carboxylic Acid, 1,1-Dimethylethyl Ester (**4a**) $[R^1 = Cl, R^2 = {}^tBu, R^3 = H, R^4 = BOC, and R^5 =$ (2S)-Me]. To a solution of (2S)-2-methyl-1-piperazinecarboxylic acid 1,1-dimethylethyl ester (6.7 g, 33.4 mmol) and 3a (9.1 g, 33.6 mmol) in tetrahydrofuran (THF) (350 mL) was added magnesium sulfate (18 g), and the reaction was stirred at room temperature for 20 h. Sodium triacetoxyborohydride (11.7 g, 54 mmol) was added portion-wise, and the reaction was stirred for 20 h. The reaction was diluted with toluene, and the volatiles were removed in vacuo. Water was added, and the mixture was extracted with ethyl acetate $(2 \times)$. The combined organics were washed with brine and dried (Na_2SO_4) , and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel, eluting with iso-hexane/ethyl acetate (6:1-4:1) to give 4a (9.2 g, 61%). LRMS: $m/z 455/7 [M + H]^+$. ¹H NMR (CDCl₃) δ : 7.44 (1H, d), 7.12 (1H, dd), 6.64 (1H, d), 4.49 (2H, s), 4.20 (1H, bs), 3.80 (1H, d), 3.55 (2H, s), 3.10 (1H, dt), 2.77 (1H, d), 2.65 (1H, d), 2.23 (1H, dd), 2.09 (1H, m), 1.48 (9H, s), 1.46 (9H, s), 1.28 (3H, d).

[4-Chloro-2-[[(3S)-3-methyl-1-piperazinyl]methyl]phenoxy]acetic Acid, 1,1-Dimethylethyl Ester Trifluoroacetate Salt (**5a**) [$R^1 = Cl$, $R^2 = {}^tBu$, $R^3 = H$, $R^4 = H$, and $R^5 = (3S)$ -Me]. To a solution of **4a** (3.8 g, 8.4 mmol) in dichloromethane (40 mL) was slowly added trifluoroacetic acid (13 mL). The reaction was stirred until complete consumption of starting material (~50 min, LCMS analysis of crude reaction). The reaction was immediately diluted with a similar volume of toluene (this step is critical to ensure no loss of 'Bu ester during solvent removal), and the volatiles were removed in vacuo. Further toluene was added, and the mixture was concentrated to dryness to give **5a** as a brown oil that slowly solidified (3.8 g). This was used in crude form in the next step. LRMS: m/z 455/7 $[M + H]^+$.

[4-Chloro-2-[[(3S)-4-[(4-chlorophenyl)acetyl]-3-methyl-1-piperazinyl]methyl]phenoxy]acetic Acid, 1,1-Dimethylethyl Ester (**6a**) $[R^1 =$ Cl, $R^2 = {}^tBu$, $R^3 = H$, $R^5 = (3S)$ -Me, and $R^6 = 4$ -Chlorobenzeneacetyl]. To 5a (1.2 g, 2.6 mmol) were added dichloromethane (30 mL), water (30 mL), and sodium hydrogencarbonate (1.3 g, 15.5 mmol), and the mixture was vigorously stirred. 4-Chlorobenzeneacetyl chloride (0.58 g, 3.1 mmol) was added dropwise, and the mixture was stirred for 16 h. The mixture was extracted with dichloromethane, and the combined organics were washed with water and dried (Na2SO4), and the solvent was removed in vacuo to give crude 6a as an oil (0.9 g). This was used in the next step without further purification. An aliquot from an identical preparation was purified by column chromatography on silica gel, eluting with *iso*-hexane/diethyether (1/2-1/3) to give analytically pure **6a** for characterization. LRMS: m/z 451 $[M + H - {}^{t}Bu]^{+}$. ¹H NMR (CDCl₃) δ: 7.40 (1H, d), 7.28 (2H, d), 7.18 (2H, d), 7.14 (1H, dd), 6.64 (1H, d), 4.81-4.38 (3H, m), 4.03-3.93 (0.5H, m), 3.71-3.63 (2H, m), 3.52 (2H, s), 2.88-2.59 (3H, m), 2.24-1.89 (2.5H, m), 1.47 (9H, s), 1.28 (3H, d).

[4-Chloro-2-[[(3S)-4-[(4-chlorophenyl)acetyl]-3-methyl-1-piperazinyl]methyl]phenoxy]acetic Acid (**27**). To **6a** (0.9 g crude, 1.8 mmol) was added trifluoroacetic acid (6 mL), and the reaction was stirred for 16 h. Toluene was added, and the volatiles were removed in vacuo. The crude product was purified by RPHPLC. Solvent removal followed by redissolution in methanol and evaporation to dryness gave **27** as a white foam. HPLC analysis: 99.7% purity (conditions b, Phenomemex Max-RP). LRMS: m/z 451 [M + H]⁺. ¹H NMR [dimethyl sulfoxide (DMSO)- d_6] δ : 7.40–7.32 (3H, m), 7.28–7.19 (3H, m), 6.93 (1H, d), 4.65 (2H, s), 4.54 (1H, m), 4.20 (1H, m), 3.69 (2H, s), 3.53 (2H, s), 3.24 (1H, m), 2.84 (1H, m), 2.69 (1H, m), 2.12 (1H, m), 1.98 (1H, m), 1.19 (3H, m). Anal. (C₂₂H₂₄Cl₂N₂O₄ • 0.70H₂O) C, H, N.

4-Chloro-2-iodo-benzeneacetonitrile (34). Borane-THF complex (24 mL of a 1 M solution in THF, 24 mmol) was added to a solution of 4-chloro-2-iodobenzoic acid (2.4 g, 8.5 mmol) in THF (15 mL), and the reaction was heated at 50 °C for 1 h. After it was cooled to room temperature, the reaction mixture was cautiously quenched with methanol, and then, volatiles were removed in vacuo. Methanol was added, and the volatiles were removed in vacuo (repeated twice) to give a white solid. This was dissolved in a mixture of dichloromethane (20 mL) and DMF (1 mL). Thionyl chloride (0.93 mL, 16.8 mmol) was added dropwise, and the reaction was stirred for 1 h. The solvents were removed in vacuo, and the residue was partitioned between diethyl ether and aqueous NaHCO3. The organic layer was separated and dried (MgSO₄), and the solvents were removed in vacuo. The residue was dissolved in DMF (8 mL), sodium cyanide (0.81 g, 17.0 mmol) was added, and the reaction mixture was stirred at room temperature for 3 h. Ice was added, and the solid was collected by filtration to give 34 (2.65 g, wet) as a beige solid. LRMS: $m/z 276 [M - H]^-$.

4-Chloro-2-iodophenyl)acetic Acid (**35**). Nitrile **34** (2.4 g) was dissolved in aqueous KOH (14 mL of 3.4 M solution) and heated at 100 °C for 24 h. After it was cooled to room temperature, the aqueous mixture was washed with diethylether (discarded), acidified, and extracted with ethyl acetate (2×). The combined organic extracts were dried (Na₂SO₄), and the solvents were removed in vacuo to give **35** (1.93 g, 82% overall) as a yellow solid. ¹H NMR (CDCl₃) δ : 7.85 (1H, d), 7.32 (1H, dd), 7.22 (1H, d), 3.83 (2H, s).

Methyl (4-Chloro-2-iodophenyl)acetate (**36**). Chlorotrimethylsilane (2 mL, 15.6 mmol) was added to a solution of **35** (1.93 g, 6.5 mmol) in MeOH (50 mL), and the reaction was stirred for 48 h. The solvents were removed in vacuo, and the residue was purified by column chromatography on silica gel, eluting with diethyl ether to give **36** (1.93 g, 96%) as a yellow oil. ¹H NMR (CDCl₃) δ : 7.84 (1H, d), 7.31 (1H, dd), 7.21 (1H, d), 3.78 (2H, s), 3.72 (3H, s).

5-Chloro-2-(2-methoxy-2-oxoethyl)benzoic Acid (**37**). Sodium formate (0.66 g, 9.7 mmol), *N*,*N*-diisopropylethylamine (1.12 mL, 6.4 mmol), acetic anhydride (0.61 mL, 6.44 mmol), and DMF (3.8 mL) were charged to a flask and stirred under nitrogen for 1 h. A solution of **36** (1.0 g, 3.2 mmol), tris(dibenzylidineacetone)dipalladium(0) (75 mg, 2.5 mol %), and lithium chloride (0.412 g, 9.7 mmol) in DMF (7.6 mL) was added, and the reaction was stirred at 80 °C for 16 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and washed with aqueous 2 M HCl (3×). The organic layer was dried (Na₂SO₄), and then, the solvents were removed in vacuo. The residue was purified by column chromatography on silica gel, eluting with isohexane/ethyl acetate (20/1-6/1) and then ethyl acetate to give **37** as a yellow oil, yield (0.4 g, 54%). ¹H NMR (DMSO-*d*₆) δ : 7.88 (1H, d), 7.62 (1H, dd), 7.41 (1H, d), 4.01 (2H, s), 3.58 (3H, s).

Methyl [4-Chloro-2-(hydroxymethyl)phenyl]acetate (**38**). Borane— THF complex (3.7 mL of a 1 M solution in THF, 3.7 mmol) was added dropwise to a solution of **37** (0.40 g, 1.74 mmol) in THF (5 mL) at 0 °C. The temperature was then allowed to reach room temperature, and the stirring continued for 2 h. The reaction mixture was quenched with water, acidified (pH 3), and extracted with ethyl acetate (3×). The combined organic extracts were dried (Na₂SO₄), and the solvents were removed in vacuo. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate, to give **38** (0.34 g, 89%) as a yellow oil. ¹H NMR (CDCl₃) δ : 7.43 (1H, d), 7.25 (1H, dd), 7.17 (1H, d), 4.65 (2H, s), 3.72 (2H, s), 3.71 (3H, s).

(2S)-1-[(4-Chlorophenyl)acetyl]-2-methyl-piperazine Trifluoroacetate Salt (**8a**) $[R^4 = (2S)$ -Me, and $R^6 = 4$ -Chlorobenzeneacetyl]. To a vigorously stirred mixture of (3S)-3-methyl-1-piperazinecarboxylic acid 1,1-dimethylethyl ester (3.5 g, 17.5 mmol) and sodium hydrogencarbonate (4.41 g, 52.5 mmol) in dichloromethane (25 mL)/water (25 mL) was added 4-chloro-benzeneacetyl chloride (3.97 g, 21 mmol) dropwise at 0 °C, and the reaction was warmed to room temperature and stirred for 3 h. The mixture was diluted with water and dichloromethane, and the organic layer was separated. The aqueous layer was extracted with dichloromethane $(2\times)$, the combined organics were dried (MgSO₄), and the solvent was removed in vacuo. The residue was triturated with iso-hexane to give crude 7a as a white solid. This solid was dissolved in dichloromethane (40 mL), trifluoroacetic acid (20 mL) was added, and the mixture was stirred for 2 h. Toluene was added, and the volatiles were removed in vacuo. The resulting oil was dissolved in the minimum MeOH. Dilution with diethyl ether and iso-hexane followed by removal of solvents in vacuo gave 8a as a white solid (4.63 g, 72% overall). LRMS: $m/z 253 [M + H]^+$.

[4-Chloro-2-({(3S)-4-[(4-chlorophenyl)acetyl]-3-methylpiperazin-1-yl} methyl) phenyl]acetic Acid Methyl Ester (**39**). To **38** (0.28 g, 1.3 mmol) in dichloromethane (5 mL) was added triethylamine (0.34 mL, 2.4 mmol) followed by methanesulfonyl chloride (0.15 mL, 1.9 mmol), and the reaction was stirred for 2 h. Diethyl ether and water were added, and the organic layer was separated, washed with water, and dried (MgSO₄). Solvent removal in vacuo gave a crude mesylate/chloride mixture as a yellow oil (~0.3 g). To this were added **8a** (0.28 g, 0.77 mmol), K₂CO₃ (0.26 g, 2.1 mmol), and DMF (3 mL), and after flushing with nitrogen, the mixture was heated at 60 °C for 3 h. The reaction was cooled to room temperature, and ethyl acetate and water were added. The organic layer was separated, washed with brine, dried (MgSO₄), and concentrated in vacuo. The residue was purified on SCX ion-exchange resin eluting sequentially with ethyl acetate, acetonitrile, and MeOH and then 7 N

NH₃ in MeOH to afford the product. Further purification by column chromatography on silica gel, eluting with *iso*-hexane/diethyl ether (3/7-0/1), gave **39** (0.127 g, 22%) as a colorless glass. LRMS: m/z 449 [M + H]⁺.

[4-Chloro-2-({(3S)-4-[(4-chlorophenyl)acetyl]-3-methylpiperazin-1-yl} methyl) phenyl]acetic Acid (**40**). Ester **39** (125 mg, 0.3 mmol) was dissolved in a mixture of THF (3 mL) and aqueous NaOH (3 mL of 25% w/v) and stirred for 1 h at 50 °C. The reaction was cooled to room temperature, acidified with acetic acid (10 mL), and then concentrated in vacuo. The residue was purified by RPHPLC to give **40** (90 mg, 74%). HPLC analysis: 98.9% purity (conditions a, Symmetry C18). LRMS: m/z 433 [M - H]⁻. ¹H NMR (DMSO- d_6) δ : 7.31 (3H, m), 7.24 (4H, m), 4.37 (1H, s), 3.90 (1H, s), 3.72 (1H, d), 3.69 (1H, d), 3.66 (1H, d), 3.63 (1H, d), 3.45 (1H, d), 3.39 (1H, d), 3.01 (1H, m), 2.67 (1H, d), 2.58 (1H, d), 2.08 (1H, dd), 1.89 (1H, td), 1.14 (3H, d). Anal. (C₂₂H₂₄Cl₂N₂O₃·0.30H₂O) C, H, N.

Biology. Preparation of Cell Membranes. HEK293 cells were transfected with human CRTh2 cDNA, previously cloned into the eukaryotic expression vector pGenIRESneo2. Populations of Geneticin (Invitrogen)-resistant, stably transfected cells were selected. HEK293 cells expressing recombinant human CRTh2 were grown in 225 cm² tissue culture flasks containing Dulbecco's modified Eagle's medium supplemented with 10% fetal calf serum (FCS), 1% nonessential amino acids, 1% L-glutamine, and 2% G418 at 37 °C, 5% CO₂. Cells were disrupted using a Polytron homogenizer for 2 × 20 s bursts keeping the tube in ice. Unbroken cells were removed by centrifugation (220g for 10 min at 4 °C), and the membrane fraction was pelleted by centrifugation at 90000g for 30 min at 4 °C. The final pellet was resuspended in 20 mM HEPES, pH 7.4, containing 1 mM ethylenediamineteraacetic acid, 0.1 mM phenylmethylsulfonyl fluoride, 0.1 mg/mL bacitracin, and 0.1 mM dithiothreitol and stored at -80 °C.

CRTh2 Radioligand Binding Assay. A scintillation proximity assay (SPA) was used to quantify displacement of [³H]PGD₂ binding. Prior to assay, HEK cells membranes containing CRTh2 were coated onto wheat germ agglutinin-coated polylvinyl toluene SPA beads (Amersham) at a ratio of $25-50 \,\mu g$ membrane protein per mg of SPA beads for 12-18 h at 4 °C with constant agitation. The beads were pelleted by centrifugation (800g for 10 min at 4 °C), washed once with assay buffer (50 mM HEPES, pH 7.4, containing 5 mM magnesium chloride), and finally resuspended in assay buffer at a bead concentration of 10 mg beads/mL. Binding assays were performed in white 96-well clear-bottomed plates (Corning). To each well, 5 μ L of test compound (or assay buffer containing 10% DMSO for determination of total binding) was added, followed by 20 µL of 6.25 nM [³H]-PGD₂ (Perkin-Elmer/NEN, 210 Ci/mmol) and 25 µL of membrane-coated beads prepared as above. Nonspecific binding was determined by adding 5 µL of 100 µM DK-PGD₂ (Cayman Chemical Co.) in place of test compound. Plates were incubated for 2 h at room temperature, and radioactivity bound to SPA beads was measured on a Wallac Microbeta counter using a ³H protocol for 4 min per well.

Determination of Agonist Potential at CRTh2 Using Human Blood Eosinophil Shape Change. Human blood (20 mL) was taken by venipuncture from healthy volunteers into heparin as an anticoagulant. Assays were performed in deep well 96-well plates with a final assay volume of 100 μ L. Compounds (10 μ L at 10× the required final concentration) or vehicle (assay buffer containing 1% DMSO) were added to wells followed by 90 μ L of cells. Compounds were spot tested at 1 and 10 μ M, which represented concentrations at which compounds would near maximally occupy CRTh2. The plate was shaken for 30 s to thoroughly mix the contents and incubated in a water bath at 37 °C for 4 min. After incubation, the cells were fixed by addition of 100 μ L of Optilyse B (Immunotech, Coulter), shaken again for 30 s, and left for 10 min at room temperature. Red blood cells were lysed by the addition of 1 mL of water, and the mixture was left at room temperature for 45 min. Plates were centrifuged for 5 min at 375g, the supernatant was discarded, and cells were resuspended in 400 μ L of assay buffer. Finally, the fixed cells were transferred to polypropylene tubes (12 mm \times 75 mm) suitable for use with the flow cytometer. Shape change was determined using a Coulter FC500. Granulocytes were gated on their forward scatter/side scatter profile, and eosinophils were distinguished from neutrophils on the basis of higher natural autofluorescence. Changes in the median value in forward scatter were recorded as a measure of shape change. The efficacy ratio for agonist compounds was expressed as fraction relative to the maximal DK-PGD₂ response.

Antagonism of PGD₂-Mediated Calcium Flux in CHO Cells Expressing Human CRTh2. AequoScreen CRTh2 CHO-K1 cells were purchased from Perkin-Elmer and cultured in Hams F12 supplemented with glutamax and containing 10% FCS, 1 mg/mL geneticin (G418), and 250 µg/mL zeocin. Cells were cultured under standard tissue culture conditions (37 °C, 5% CO₂, and 95% humidity) and harvested when \sim 80% confluent. The assay procedure required cells to be used directly from frozen stocks at 1.25×10^8 cells in 4.5 mL vials stored at -80 °C. Cells were defrosted quickly in a water bath at 37 °C, washed once with 50 mL of complete media, and adjusted to 5×10^{6} cells/mL in assay buffer [Dulbecco's modified Eagle's medium/Hams F12 nutrient mixture 1:1 without phenol red, 1% (w/v) BSA, 0.1% (v/v) Pluronic F68]. Coelentrazine h (DiscoverX) was added to a final concentration of at 5 μ M, and cells were loaded with the dye overnight on a revolving mixer at 6 rpm and at room temperature in the dark. For use, cells were diluted to 1.6×10^6 cells/mL in assay buffer without coelentrazine and allowed to "rest" for 2 h in the dark before plating. Assays were carried out in 1536-well plates. Test compound (25 nL at 180 times the desired final concentration in DMSO) or vehicle control was preincubated with 4.5 µL of dye-loaded cells for 15 min at room temperature in the dark. Ca²⁺ flux measurements were made using a FLIPR Tetra instrument fitted with a 1536 head used to add an equal volume of agonist (PGD_2) at 750 nM, which was found to produce an EC₈₀ concentration in the assay. Data analysis was set to use the area under the curve over the read times between 6 and 23 reads.

ASSOCIATED CONTENT

Supporting Information. Analytical data for final compounds **2**, **9**–**33**, **40**, and **45**–**47**, experimental procedure for the synthesis of compounds **2**, **45**, and **47**, and references for in vitro rat hepatocyte and human microsome screens and in vivo rat pharmacokinetic studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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ABBREVIATIONS USED

ADME, absorption-distribution-metabolism-excretion; BOC, *tert*-butyloxycarbonyl; BSA, bovine serum albumin; CRTh2,

chemoattractant receptor-homologous expressed on Th2 lymphocytes, also known as DP2; DK-PGD₂, 13,14-dihydro-15-keto-PGD₂; DMF, *N*,*N*-dimethylformamide; DMSO, dimethyl sulfoxide; FCS, fetal calf serum; HATU, *O*-(7-azabenzotriazol-1-yl)-*N*, *N*,*N'*,*N'*-tetramethyluronium hexafluorophosphate; HBA, hydrogen bond acceptor; hERG, human ether-a-go-go-related gene; IgE, immunoglobulin E; IA, inactive; LLE, lipophilic ligand efficiency; MWt, molecular weight; NMP, 1-methyl-2-pyrrolidinone; PGD₂, prostaglandin D₂; PSA, polar surface area; PyBroP, bromotrispyrrolidinophosphonium hexafluorophosphate; RP, reverse phase; SAR, structure—activity relationship; SPA, scintillation proximity assay; THF, tetrahydrofuran

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