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Perspective

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Update on the Development of Antagonists of Chemoattractant Receptor-Homologous Molecule Expressed on Th2 Cells (CRTH2). From Lead Optimization to Clinical Proof-of-Concept in Asthma and Allergic Rhinitis

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1. INTRODUCTION

Chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2, also known as DP_2) is a G protein-coupled receptor that plays an increasingly recognized role in the initiation and the perpetuation of allergic diseases. Prostaglandin D_2 (PGD_2) was identified as a ligand for CRTH2 in 2001,[1] and there has been a dramatic increase in the number of published articles and patents describing the identification and optimization of potent CRTH2 antagonists in recent years. The biology of CRTH2 and the pharmacology and medicinal chemistry of the early CRTH2 antagonists were reviewed extensively in 2007,[2] but since that time the field has developed considerably as highlighted by Ulven and Kostenis,[3] Norman,[4] and Chen and Budelsky.[5] At least 13 distinct CRTH2 antagonists have entered clinical trials and early encouraging proof-of-concept trials in asthma and allergic rhinitis have recently been disclosed.

2. CRTH2 BIOLOGY

In humans, CRTH2 is selectively expressed by Th2 cells, eosinophils, and basophils[6] and mediates chemotactic activation of these cells in response to prostaglandin D_2 (PGD_2).[1] Prostaglandin D_2 is produced by the sequential action of cyclooxygenases and PGD_2 synthase and is produced in high quantities by mast cells, particularly during IgE-dependent allergic responses. Prostaglandin D_2 has been detected in high concentrations in a number of settings where allergic individuals have been challenged with allergen.[2] The interaction between immunologically activated mast cells and Th2 lymphocytes plays a key role in the pathogenesis of allergic disorders, and recent evidence suggests that CRTH2 plays a dominant role in mediating this interaction. IgE-dependent activation of human mast cells leads to the elaboration of soluble factors that stimulate both the migration of Th2 cells and their subsequent activation to produce cytokines such as interleukins 4, 5, and 13. These effects are completely inhibited by selective CRTH2 antagonists.[7,8] Furthermore, in immunologically activated human nasal polyp tissue, CRTH2 is up-regulated and plays a functional role in mediating activation of Th2 cells in response to supernatants from these tissues.[9] Studies in CRTH2 knockout mice support the view that CRTH2 plays a central role in mast cell dependent activation of Th2 cells in allergic disease. In a mouse model of skin inflammation, genetic ablation of CRTH2 was associated with diminished recruitment of eosinophils and lymphocytes, reduced tissue swelling, and a reduction in the levels of serum IgE.[10] Reduction in circulating IgE was also observed in CRTH2-deficient mice exposed to intranasal Japanese cedar pollen, an effect associated with reduced inflammation of the nasal mucosa and signs of rhinitis.[11] The effects of CRTH2 gene ablation are mimicked by small molecule CRTH2 antagonists. Both the ramatroban analog **2** (TM30089) and an Actimis pyrimidinylacetic acid compound are effective in reducing allergen-induced airway inflammation in mice,[12,13] and an Oxagen indole acetic acid derivative ablated eosinophil accumulation in the airways of allergen-challenged guinea pigs.[14] Recently, it has been discovered that activation of CRTH2 acts as a survival signal for Th2 lymphocytes, a process involving the PI3 kinase pathway.[15] This suggests that CRTH2 antagonists may not only inhibit the recruitment and activation of Th2 cells but also accelerate apoptosis and clearance of these cells from inflamed tissue, thereby promoting the resolution of allergic inflammation. PGD_2 also binds with high affinity to the DP_1 receptor, which is linked to elevation of cAMP and mediates vasodilatation and bronchodilatation.[2] Although it is possible that DP_1 may contribute to increased blood flow to sites of allergic inflammation, activation of this receptor inhibits the function of a number of key leukocyte populations, which is likely to lead to suppression of allergic responses.[2,14] The clinical effects of selective DP_1 antagonists and dual DP_1/CRTH2 antagonists are discussed later. It is also of interest that PGD_2 is converted to a number of metabolites such as 13,14-dihydro-15-keto-PGD_2, Δ^{12}-PGD_2, and Δ^{12}-PGJ_2, which retain activity on CRTH2 but have only weak DP_1 activity.[2] It is likely that at sites of allergic inflammation, where PGD_2 is actively metabolized, that the effects of CRTH2 will dominate over that of DP_1.

The encouraging preclinical data has led to a number of companies advancing selective CRTH2 antagonists into clinical development. AstraZeneca's lead compound **33** (AZD1981) is in phase II trials in asthma and COPD (some of which have been completed, see Clinical Status section for details), and AstraZeneca has also advanced back-ups (AZD5985 and AZD8075, structures not disclosed) to phase 1, but these have since been discontinued. Actelion has completed phase II trials in asthma and allergic rhinitis with **17** (setipiprant, formerly ACT129968). Novartis has studied the effect of QAV680

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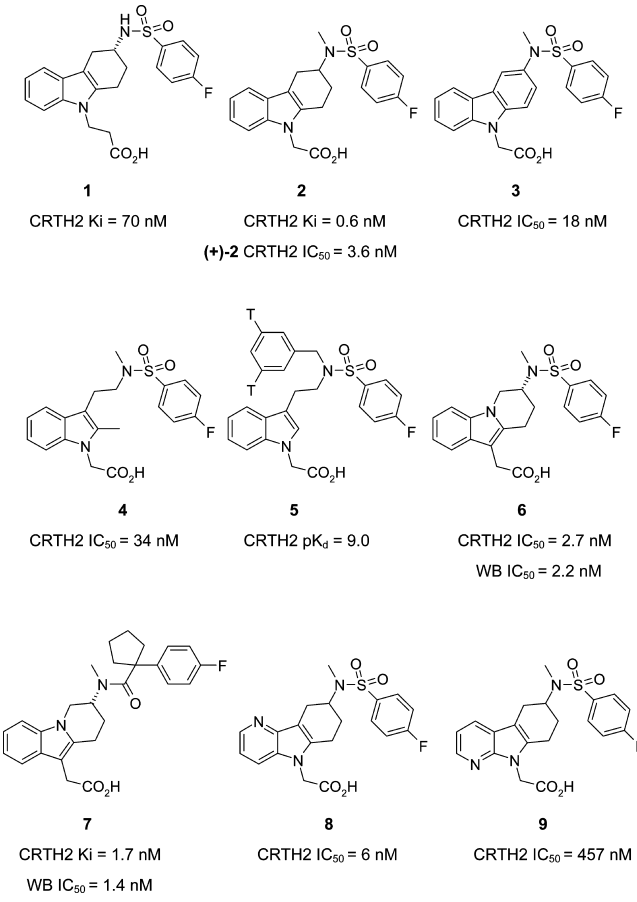
(structure not disclosed) in allergic rhinitis and has completed a trial with this drug in combination with cetirizine. Boehringer Ingelheim has completed a number of trials in asthma and allergic rhinitis with **72** (BI671800). Amira (**59** [AM211] and AM461, structure not disclosed), Array Biopharma (ARRY-502, structure not disclosed), Merck (**6**, MK-7246), Roche (RG-7185, structure not disclosed), and Pulmagen (ADC3680, structure not disclosed) have all completed phase I trials, and Oxagen's lead compound **29** (OC000459) has completed a number of trials in asthma and allergic rhinitis. In addition, Amgen has completed a phase II trial in asthma with the dual DP_1/CRTH2 antagonist **65** (vidupiprant, formerly AMG853), although this compound has been subsequently been discontinued. Both Actelion and Oxagen have reported on positive proof-of-concept data in asthma and allergic rhinitis. In the case of Oxagen's lead compound **29**, this drug was effective in reducing airway inflammation and improving lung function and symptoms in subjects with moderate persistent asthma.[16] The rapidity by which CRTH2 antagonists have been identified and developed is a reflection of both compelling biology and the relative ease in identifying low molecular weight drug-like ligands for this receptor. This review summarizes the properties of the most promising CRTH2 antagonists discovered to date.

3. RAMATROBAN ANALOGS

Compound **1** (ramatroban) was originally identified as a thromboxane (TP) antagonist by Bayer and is marketed in Japan under the trade name Baynas for the treatment of allergic rhinitis. It is now recognized that **1** also has moderate CRTH2 antagonist activity (K_i = 70 nM), and this is the most likely reason for its efficacy in allergic rhinitis. This finding provided, at the same time, both an excellent validation of the therapeutic approach and a drug-like chemical starting point for further medicinal chemistry. 7TM Pharma has demonstrated that only minor structural modifications were required to improve CRTH2 activity and abolish unwanted binding to TP.[17] Replacement of the propionic acid moiety with acetic acid and N-methylation of the sulfonamide (**2**) increased CRTH2 binding (K_i = 0.6 nM), and this racemic compound is essentially devoid of TP activity (K_i > 10 000 nM). The single (+)-enantiomer of compound **2**, together with a series of analogues, is claimed in a patent application from Shionogi[18] that predates the 7TM Pharma publication. Shionogi made modifications to the 1,2,3,4-tetrahydrocarbazole ring system of compound **2** and found that both the unsaturated carbazole analogue **3** and the "ring-opened" indole analogue **4** lost CRTH2 antagonist activity in comparison to the parent compound **2**.[18] Based on a related Shionogi compound, the radioligand **5** has been recently prepared as an alternative to radiolabeled PGD_2.[19] Both Merck[20] and Amira[21] have shown that other selected minor structural modifications of **1** can also give rise to CRTH2 antagonists.

Merck claims CRTH2 antagonist activity for analogues of **2** such as **6**[20] in which the indole moiety is inverted. Compound **6** has been shown to be selective for CRTH2 over other prostanoid receptors, to be active in a human whole blood (WB) assay and to inhibit the late phase airway response in allergic sheep.[22] Compound **6** was found to be devoid of CYP liabilities (except weak inhibition of 2C9) and underwent less covalent binding than other related compounds in the series, although such covalent interaction was clearly apparent in both rat and human liver microsomes.[23] Compound **6** has an acceptable PK profile in a range of species including



non-human primates[23] and has entered phase 1 clinical trials. The Merck group has recently reported on an efficient synthetic route to the N-fused tricyclic indole core for the preparation of analogues of **6** with an electron-withdrawing group para to the indolyl nitrogen.[24] A series of amide analogues of **6** have been investigated because of concerns about potential hypersensitivity reactions (e.g., fever, skin rashes, GI disturbances, and liver toxicity) in patients who have previously exhibited an adverse immune response to treatment with sulfonamide antibiotics.[25] A few amide analogues such as compound **7** were found to be equipotent to **6** in the eosinophil shape change assay performed in whole blood. This compound is devoid of CYP 2C9 inhibitory activity and is orally available in the rat (F = 74%, $t_{1/2}$ = 2.2 h).[25] Amira has prepared a series of analogues of **2** in which other variations to the scaffold have been investigated. It was found that for a series of azaindole analogues the regioisomer **8** was more potent than other regioisomers investigated such as **9**.[21] Inversion of the azaindole moiety of **8** abolishes CRTH2 antagonist activity for regiosiomer **10**. Amira also investigated the indolizine analogues **11** and **12**[21] and found that although regioisomer **11** is more potent in a receptor binding assay than regioisomer **12**, in the presence of human serum albumin (HSA), the compounds exhibit similar potency. These results show that subtle changes to the electronics of the tricyclic ring system of compound **2** can have a significant effect on CRTH2 antagonist activity and plasma protein binding. A motivation for investigation of changes to the electronics of the tricyclic ring system by Stearns et al. was the observation of glutathione adduct formation for related DP_1 receptor antagonists from Merck[26] and the finding that **1** also forms reactive metabolites.[21]

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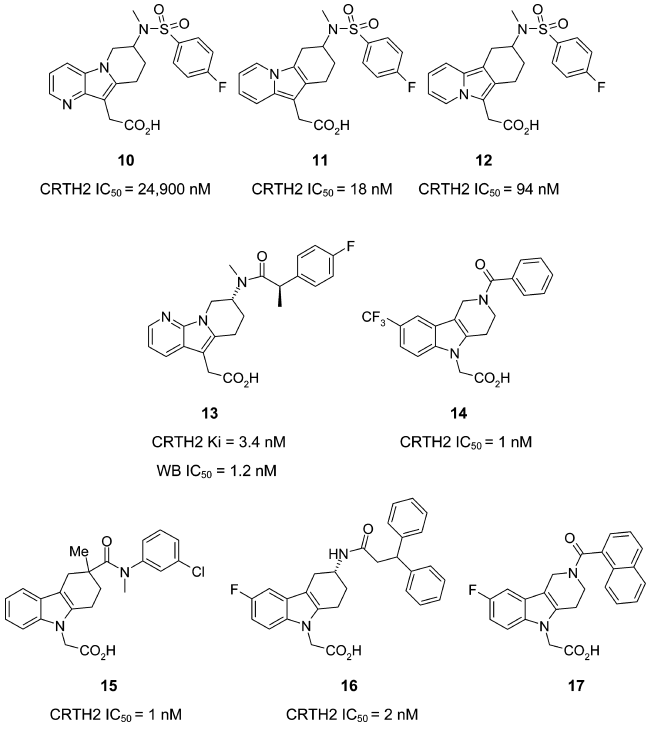


Compound **1** was shown to form an adduct with glutathione, but compound **8** and other analogs (as well as competitor compounds from Actimis, Oxagen, and 7TM Pharma) were found to lack this potential liability, illustrating that it should be possible to avoid idiosyncratic toxicity in this series.

Merck has reported a similar study on azaindole ramatroban analogues[27] to that of Amira[21] from which they concluded a strong preference for the 7-azaindole analogues over other regioisomers evaluated. From this work, Merck has identified a 7-azaindole derivative **13** as a potential backup compound to **6** where the sulfonamide linker is replaced with an amide bond. The advantage of 7-azaindole **13** over **6** is that it displayed both a lower time dependent inhibition of CYP3A4 and lower in vivo covalent binding.[27]

Researchers at Actelion have published a number of patent applications[28−30] describing analogues of **2** with potent CRTH2 antagonist activity. Compound **14**[28] features modification to the tricyclic scaffold, and in compound **15**,[29] the sulfonamide of **2** is replaced by a reverse amide. Although the separate enantiomers are not described, it is possible that the methyl group at the 3-position of the 1,2,3,4-tetrahydrocarbazole may have been introduced to block potential racemization that could occur in its absence. Actelion has also prepared straightforward amide analogues of **2** such as compound **16**.[30] Actelion's clinical candidate **17**, an analogue of the achiral compound **14**,[28] has successfully completed phase II trials in asthma (most likely a bronchial allergen challenge study) and allergic rhinitis according to information contained on the Actelion Web site (http://www.actelion.com/en/scientists/mechanisms-of-action/crth2-receptor-antagonism.page?).

Therefore, ramatroban-like carbazole derivatives represent a promising series with potent CRTH2 activity, drug-like properties, and the potential to deliver clinical efficacy.

4. INDOLE ACETIC ACIDS

4.1. Indole-3-Acetic Acids. The first indication that indole-3-acetic acids could be used to target the CRTH2 receptor came from the observation that **18** (indomethacin) bound to the receptor and, surprisingly, had agonist activity.[31,32] Reports of the potency of **18** differ widely depending on the assay conditions, particularly the concentration of protein, in assay buffer, which is likely to affect the availability of free drug. Figure 1 shows the results of a previously unpublished

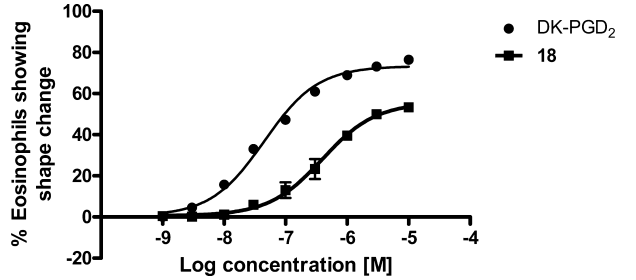
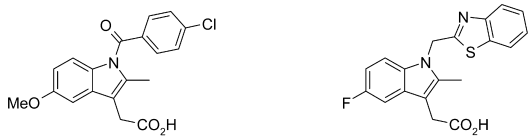


Figure 1. Effect of **18** and DK-PGD_2 on activation of isolated eosinophils as measured by shape change (gated autofluorescence forward scatter).

experiment designed to define the potency and efficacy of **18** as a CRTH2 agonist in a system where the concentration of protein is controlled. Isolated human eosinophils were incubated with **18** or 13,14-dihydro-15-keto-PGD_2, a metabolite of PGD_2 that is a selective CRTH2 agonist, in medium containing 10% fetal calf serum, and induced shape change of the eosinophils was measured by FACS.[33]

Compound **18** induced eosinophil shape change with moderate potency (EC_{50} = 389 nM) but with reduced efficacy compared with DK-PGD_2. DK-PGD_2 itself has slightly reduced efficacy compared with PGD_2.[33] These data suggested that **18** acts as a partial agonist at the CRTH2 receptor and provided a hint that modifications to the structure of **18** might lead to antagonist activity.



Indeed, at around the same time, Pfizer published a screening patent application[34] that disclosed the benzothiazole indole acetic acid derivative **19** as a CRTH2 antagonist with selectivity over DP_1. While **19** has reasonable intrinsic potency, high concentrations are required to antagonize the effects of PGD_2 on eosinophil shape change in human whole blood suggesting it was unlikely to be very potent in vivo. The Oxagen team investigated SAR for CRTH2 activity for a series of analogues of **18** and found that for the 1*H*-indolyl-3-yl acetic acid core the 5-fluoro, 2-methyl, and carboxylic acid groups were important for CRTH2 antagonist activity.[35] Substitution of the indole N-substituent led to compounds with improved potency, particularly in whole blood assays. The indole *N*-sulfonyl analog **20** displayed reasonably potent and selective activity in a range of binding and functional assays and, importantly, had >20-fold more potent activity than **19** in human whole blood.

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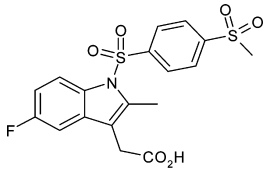


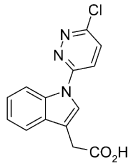
20

CRTH2 Ki = 68 nM

WB IC_{50} = 106 nM

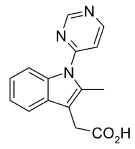
Compound **20** was found to be negative in genotoxicity assays (both Ames' and CHO clastogenicity tests) and to be selective when tested in a battery of >85 receptors and enzymes (including COX1 and COX2). Compound **20** also had acceptable pharmacokinetic properties: it was stable in human and rat microsomes, showed no inhibition of CYP 3A4, 2D6, 2C9, 2C19, or 1A2, and was well absorbed after oral dosing of the rat (F = 56%) with a plasma $t_{1/2}$ of 5.5 h.

The 7TM group conducted a pharmacophore-based virtual screen that led to the identification of the indole-3-acetic acid derivative **21** (TM27632) as an inhibitor of PGD_2 binding to CRTH2,[36] while researchers at AstraZeneca starting from **18** identified a structurally related compound **22** as a partial agonist and compound **23** as a competitive antagonist, which like **18** is a potent cyclooxygenase inhibitor.[37]



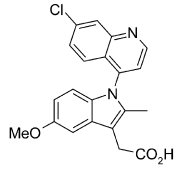
21

CRTH2 IC_{50} = 2,400 nM



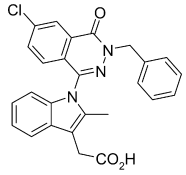
22

CRTH2 IC_{50} = 5,200 nM



23

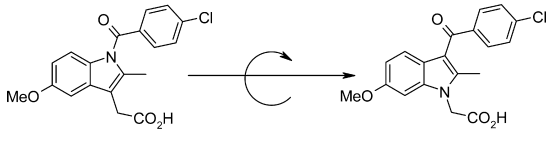
CRTH2 IC_{50} = 180 nM



24

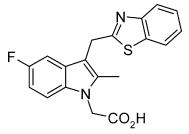
More recently workers from Pfizer have published a synthetic route to analogues of **23** such as 3,4-dihydrophthalazin-1-yl **24**. No activity data is given but it is interesting to note that compound **24** exists as enantiomers, due to atropisomerism, with a racemisation half-life of 19 days at 25 °C.[38]

4.2. N1-indole acetic acids. There is precedence for inverting the indole scaffold to N1-indole acetic acids and retaining pharmacological activity, as in the case of **25** (clomethacin), which is an inverse analogue of **18**. It should be noted that a related indole inversion strategy was also used by Merck in deriving **6** from the ramatroban analog **2**



18 **25**

described above. Switching the position of the benzothiazole and acetic acid substituents of compound **19**, but not the 5-substituent of the indole ring (methoxy in **18**, fluoro in compound **19**), leads to a 7-fold improvement in intrinsic potency and whole blood activity (**26** compared with **19**). A similar improvement in activity

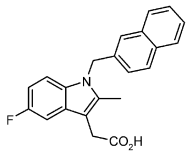


26

CRTH2 Ki = 6 nM

WB IC_{50} = 343 nM

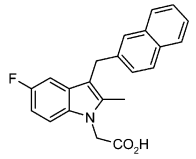
observed for compound **26** was also seen with other substituents at the C3 position. The C3 naphthalene derivative **28** maintained CRTH2 antagonist activity in whole blood while the corresponding N1-napthalene **27** had potent CRTH2 binding activity but undesirable agonist effects. Substitution of quinoline for



27

CRTH2 Ki = 9 nM

Agonist activity

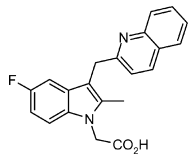


28

CRTH2 Ki = 15 nM

WB IC_{50} = 812 nM

naphthalene in the C3 position (**29**) dramatically increased whole blood activity (pK_B = 7.5).



29

CRTH2 Ki = 13 nM

WB IC_{50}=100 nM

WB pK_B = 7.5

Quinoline derivative **29** inhibits PGD_2-mediated activation of eosinophils and Th2 cells including chemotaxis, cytokine production, and the ability to prevent the antiapoptotic activity of PGD_2 (Table 1). Such activity is likely to inhibit the initiation of allergic responses and to accelerate the resolution of established disease by promoting the clearance of apoptotic T cells.

In addition, **29** is a highly selective CRTH2 antagonist. No significant binding or functional activity was detected for other prostanoid receptors or against a panel of 75 receptors, ion channels, or enzymes (including COX1 and COX2), with the exception of aldose reductase, which was modestly inhibited (IC_{50} = 550 nM). Compound **29** was stable in human and rat microsomes, showed no inhibition of CYP 3A4, 2D6, 2C9, 2C19, or 1A2, and was well absorbed after oral dosing of the rat (F = 100%) with a plasma $t_{1/2}$ of 3.5 h. After completion of a standard battery of ADMET tests, **29** was nominated as a

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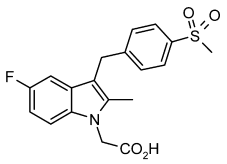
Table 1. Potency (IC_{50} or EC_{50} (nM)) of Compound 29 in Inhibiting CRTH2-Dependent Activation of Eosinophils and Th2 Cells

eosinophil shape change	Th2 cell chemotaxis	IL-13 production by Th2 cells	promotion of Th2 cell apoptosis
24	28	19	35

development candidate in May 2004 and entered phase 1 trials in 2005. Compound **29** has subsequently completed phase IIa proof-of-concept studies in asthma and allergic rhinoconjunctivitis as discussed later.



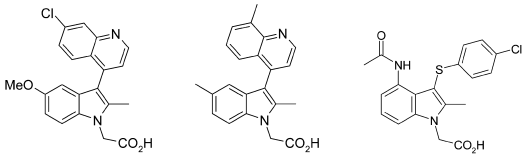
30

CRTH2 Ki = 7 nM

WB IC_{50} = 8 nM

As in the case of the C3 indole acetic series, addition of a sulfone moiety increases whole blood potency as shown for **30**. The N1-indole acetic acids **26**, **28**, **29**, and **30** were first disclosed in a PCT patent application filed by Oxagen.[39] AstraZeneca has also investigated a number of related N1-indole acetic acid derivatives. Switching the position of the quinoline and the acetic acid substituents of the quinoline derivative **23** but not the methoxy moiety gave an analogue **31** with improved antagonist activity.[37] Further, variation thereof gave rise to compound **32** with a preferred profile: on testing in 153 assays, activity was seen only against rat aldose reductase (IC_{50} = 150 nM) and the serotonin transporter (IC_{50} = 2 μM). Importantly, no activity was observed against both COX-1 and COX-2 when tested at 3 μM. Bioavailability in the dog was 100% with a clearance of 1 mL/(min·kg), half-life of 5.3 h, and a volume of distribution of 0.2 L/kg.[37]

Another N1-indole acetic acid derivative of particular note is the 4-carboxamide derivative **33**, which was originally exemplified in a composition of matter patent application,[40] featured as a single compound in a process patent,[41] and of which the discovery and SAR have been recently described.[42] AstraZeneca's lead CRTH2 antagonist, **33**, was derived from analog generation around a 3-thioaryl indol-2-yl acetic acid screening hit. This led to a set of more potent 3-thioaryl indol-1-yl acetic acid derivatives. A key goal was to reduce or eliminate inhibitory activity against both human aldehyde reductase and human aldose reductase that was present in some of the early analogues. Activity against these enzymes was perceived to be a potential liability on the basis of their role in detoxification of aldehydes. Both replacement of the carboxylic acid by tetrazole and methylation α to the carboxylic acid were poorly tolerated, whereas CRTH2 affinity was maintained by a variety of substituents of the fused phenyl ring of the indole and of the thioaryl ring. For chlorine, there is a preference for substitution at the 4- or 5-positions of the indole over that at the 6- or 7-positions and in the 3- or 4-positions of the thiophenyl group. Concern over CYP 2C9 inhibition led to a focus on compounds with lower lipophilicity including investigation of compounds with alternative sulfone and ether linkers at the indole 3-position. The thioaryl derivative **33**, which features the polar acetamide moiety at the 4-position of the indole core scaffold, was selected for development based on its potent CRTH2 affinity, therapeutic window versus inhibition of human aldehyde reductase (IC_{50} = 794 nM) and human aldose reductase (IC_{50} = 2512 nM), lack of CYP inhibition (IC_{50} > 10 μM), and promising oral PK profile (Rat F = 63%, $t_{1/2}$ = 1.9 h).[42] Compound **33** is being clinically evaluated both in asthmatics not controlled by inhaled corticosteroids and in COPD patients (www.clinicaltrials.gov).



31

CRTH2 IC_{50} = 50 nM

32

CRTH2 IC_{50} = 2.6 nM

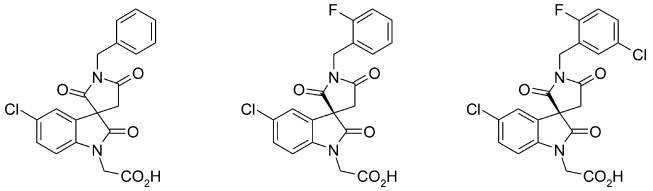
WB IC_{50} = 92 nM*

33

CRTH2 IC_{50} = 4.3 nM

*Test conducted by Oxagen. The potency in inhibiting eosinophil shape change (as measured by gated autofluorescence forward scatter) in heparinised human blood in response to PGD_2 (10 nM) using methods previously described.[33]

Merck Serono has identified spiroindolinone N1 acetic acids from a high-throughput screening campaign.[43] A promising hit, **34**, was optimized to yield **35** and **36**, which possessed acceptable CRTH2 antagonist activities and PK properties in rats and dogs. However, it was subsequently discovered that these compounds had low plasma and pH stability due to opening of the succinimide ring both at neutral and at basic pH. Pyrrolidinone derivatives such as isoxazole **37** were investigated as alternatives to the succinamide, but this compound exhibited high clearance in vivo in the rat. The stability liability of the succinimide derivatives was overcome by synthesis of a hydantoin derivative, **38**, in which the second hydantoin nitrogen was alkylated to improve bioavailability.[44] The methyl-substituted hydantoin derivative **38** was absorbed in rats (F = 37%) and mice (F = 39%) following oral administration and was active in a mouse model of allergic airway inflammation when administered at an oral dose of 30 mg/kg.[44]



34

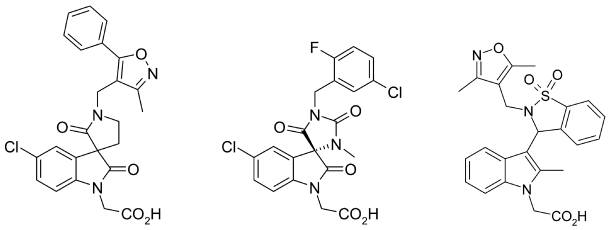
CRTH2 Ki = 196 nM

35

CRTH2 Ki = 23 nM

36

CRTH2 Ki = 5.3 nM



37

CRTH2 Ki = 3.8 nM

38

CRTH2 Ki = 35 nM

WB IC_{50} = 150 nM

39

CRTH2 Ki =12 nM

Another example of how the SAR around carbazoles and indole acetic acids has converged is the indentification of

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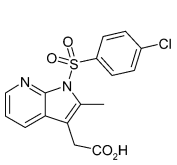
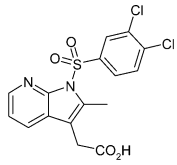
3-indolyl sultams as CRTH2 antagonists,[45] where the carbazole N1 acetic acid is converted to an N1 acetic acid with a bicyclic sulfonamide in the 3 position.[45] Unsubstituted indolyl sultams had weak activity, but this potency was dramatically improved by adding substituents to the sultam nitrogen; particularly dimethyl isoxazole, as in derivative **39**, which was selective for CRTH2 over DP_1 and TP. It is hypothesized that the potency enhancement achieved with dimethyl isoxazole is due to the formation of one or more key hydrogen bonds with the receptor.[45] For this compound series, resolution of the sultam enantiomers has not been reported.

5. AZAINDOLES

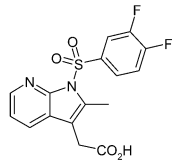
AstraZeneca,[46] Novartis, and Oxagen have claimed various series of azaindole (as well as indazole and benzimidazole) compounds, but for the most part only limited details are available from the patent literature. Researchers at Novartis have identified 7-azaindole-3-acetic acid derivatives with potent and selective CRTH2 antagonist activity.[47] From a HTS campaign, 7-azaindole **40** was discovered as a starting point from which the more potent analogue **41** was prepared. However, compound **41** exhibited suboptimal whole blood activity, and based on the hypothesis that lowering logD would reduce plasma protein binding and so increase whole blood potency, **42** was identified as a particularly promising analogue.



40
CRTH2 K_i = 103 nM
WB IC_{50} = NT

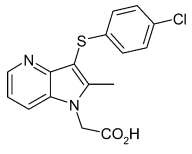


41
CRTH2 K_i = 52 nM
WB IC_{50} = 629 nM

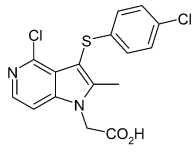


42
CRTH2 K_i = 31 nM
WB IC_{50} = 17 nM

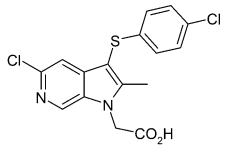
This compound, which has potent whole blood activity, has proven to be selective in an extensive battery of in vitro receptor and enzyme tests. The compound was clean in a number of key in vitro ADMET assays (e.g., hERG, genetox, CYP inhibition) and inactive against COX-1, COX-2, a panel of six prostanoid receptors, and a broader set of 46 GPCRs. Bioavailability of 7-azaindole **42** in the rat was 54% with a clearance of 20 mL/(min·kg), half-life of 1.8 h, and a volume of distribution of 4.9 L/kg.[47] For this series, the changes made to the original hit **40** to provide the more optimal analogue **42** are relatively minor but nicely illustrate that such subtle changes can have a significant impact on whole blood potency for CRTH2 antagonists.



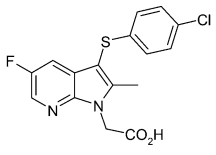
43
CRTH2 K_i = 143 nM



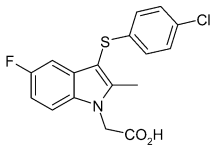
44
CRTH2 K_i = 58 nM



45
CRTH2 K_i = 106 nM



46
CRTH2 K_i = 337 nM

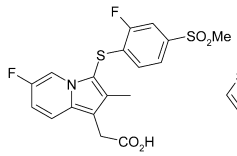


47
CRTH2 K_i = 5 nM

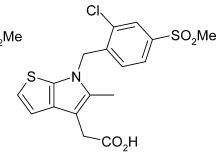
In contrast to the Novartis compounds, which feature a C3-acetic acid, Oxagen has claimed series of 4-azaindoles[48] (e.g., **43**), 5-azaindoles[49] (e.g., **44**), 6-azaindoles[50] (e.g., **45**), and 7-azaindoles[51] (e.g., **46**) with an N1-acetic acid moiety. However, these compounds offer no advantage over the parent indole compound **47** (Pettipher et al., unpublished results). AstraZeneca has independently evaluated compounds **44** and **47** and similarly reported that the 5-fluoroindole derivative **47** exhibits greater CRTH2 affinity than the 4-azaindole **44**.[42]

6. INDOLIZINE AND THIENOPYRROLE ACETIC ACIDS

Replacements for the indole scaffold have been sought. Pulmagen (formerly Argenta) has published a number of patent applications on indolizine acetic acids with similar structural features to the indole acetic acids and azaindoles described above. Compound **48** is a potent example of a CRTH2 antagonist from the indolizine series,[52] displaying a number of structural features (acetic acid, methyl group on heterocycle adjacent to acetic acid, and aryl fluorine substituent) that were also found to be optimal for activity in the indole acetic acid series. Pulmagen's lead compound ADC3680 has completed phase I trials (http://www.clinicaltrials.gov/ct2/show/NCT01173770?term=ADC3680&rank=1) although the structure of this compound has not been disclosed.



48
CRTH2 Ki = 0.2 nM



49
CRTH2 IC_{50} = 10 nM

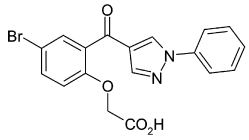
Abbott has recently described a series of thienopyrrole acetic acid derivatives.[53] Two regioisomers were investigated along with methyl substitution of this new core scaffold. Methyl substitution α to the pyrrole nitrogen improved affinity for the CRTH2 receptor in contrast to substitution of the thiophene ring. Sulfone **49** was the most potent analogue in the series and exhibited no activity at the DP_1 receptor and promising metabolic stability.[53]

7. PHENOXYACETIC ACIDS AND PHENYLACETIC ACIDS

7TM Pharma was one of the first companies to identify phenoxyacetic acid derivatives as CRTH2 antagonists.[54] From virtual screening, phenoxyacetic acid hits were identified. Subsequent optimization led to compound **50**, which is selective with respect to a panel of 43 receptors, transporter, and lipid converting enzymes, is orally available (Rat F = 84%, $t_{1/2}$ 2.7 h), and significantly reduced the number of infiltrating eosinophils in ovalbumin-sensitized mice after oral administration at 5 mg/kg.[54]

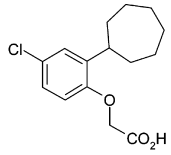
Researchers at Novartis identified a series of 2-cycloalkyl phenoxyacetic acids by high-throughput screening.[55] Based on receptor binding and functional inhibition of eosinophil shape change responses, **51** was selected for further profiling, was found to possess no CYP inhibition liability (3A4, 2D6, 1A2, 2C19, and 2C9). This compound was well absorbed in the rat after oral dosing (F = 58%) with clearance of 7.3 mL/(min·kg), half-life of 71 min, and a volume of distribution of 0.52 L/kg. However, the compound was later reported to exhibit negligible activity in a human whole blood assay.[47] This may be due to its high level of protein binding (>99.9%).

dx.doi.org/10.1021/jm2013997 | J. Med. Chem. 2012, 55, 2915−2931



50

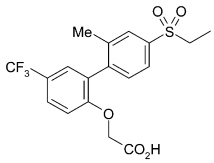
CRTH2 IC_{50} = 1.5 nM



51

CRTH2 Ki = 59 nM

WB IC_{50}>10,000 nM



52

CRTH2 IC_{50} = 0.9 nM

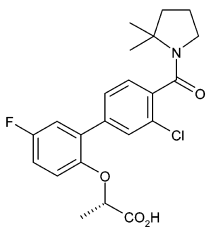
AstraZeneca has recently published on the discovery of biaryl phenoxyacetic acid derivative **52** starting from a dinitro biaryl phenoxyacetic acid screening hit.[56] Using an assay to measure up-regulation of the adhesion molecule CD11b in human eosinophils, it was found that subtle structural changes switched efficacy between antagonism and agonism. Replacement of the carboxylic acid moiety by tetrazole resulted in an antagonist with greatly reduced CRTH2 affinity. The introduction of a single methyl group α to the carboxylic acid gave a potent antagonist where the stereochemistry was *R*- but the alternative *S*-enantiomer exhibited weaker CRTH2 affinity and borderline agonism in the CD11b assay. There was a further loss of CRTH2 affinity for the gem dimethyl analogue. Biaryl phenoxyacetic acid derivative **52** gave high potency in a CHO cell calcium flux assay performed in the presence of serum albumin (IC_{50} 29 nM) suggesting an acceptable level of protein binding. It was selective against a panel of prostanoid targets (DP1, TP, and COX-1), a general panel of 111 receptor and enzyme assays, and five CYP isoforms. Furthermore, it displayed promising PK (Rat F = 42%, $t_{1/2}$ = 1.1 h; Dog F = 46%, $t_{1/2}$ = 9.8 h). Compound **52** has been identified as AZ11805131 and reported to be effective in reducing airway inflammation and tissue remodeling in mice exposed to tobacco smoke.[57]

AstraZeneca also holds patent applications on other phenoxyacetic acid CRTH2 antagonists. A patent application from AstraZeneca[58] describes scale-up synthesis, salts, and polymorphs of compound **53** suggesting that this compound may be a development candidate, possibly AZD5985, which entered phase 1 clinical studies but was discontinued because of safety issues (www.clinicaltrials.gov).

The AstraZeneca compound **54** is one of the most potent phenoxy acetic acids so far described.[59] The introduction of a methyl piperazinyl substituent was found to be advantageous with the (*S*)-enantiomer being significantly more potent than the (*R*)-enantiomer. A unique feature of compound **54** and its analogues is their zwitterionic nature. This compound was shown to be stable in human liver microsomes and to possess oral bioavailability in the rat (F = 22%). The volume of distribution of compounds tested in the rat in this zwitterionic series is generally higher (V_{ss} = 1.6−4.6 L/kg) than that observed for acidic CRTH2 antagonists.

From a focused screen of 8500 compounds selected on the basis of substructure similarity to known CRTH2 antagonists, followed by initial analoging, Merck Serono identified arylalkynylphenoxyacetic acid derivative **55**.[60] Lead optimization starting from compound **55** focused on the reduction of protein binding and led to the identification of alkylsulfone **56** with a significant activity improvement in an eosinophil shape change assay performed in human whole blood. The Merck Serono group has reported extensive SAR obtained during this optimization process. Key findings include a preference for chloro para to the oxyacetic acid moiety over other substituents evaluated in the first aryl ring. The introduction of a single methyl group α to the carboxylic acid is tolerated but larger alkyl groups and gem dimethylation at this position give a significant loss of CRTH2 affinity. Sulfone **56** was subjected to detailed profiling and did not give significant activity when tested against a panel of 50 receptors and ion channels. However, weak affinity was observed for the DP_1 receptor (K_i 1.58 μM) and submicromolar potency was observed for the inhibition of aldose reductase (IC_{50} 172 nM). The latter was not a concern to the Merck Serono group because aldose reductase is an intracellular target for which more potent inhibitors have been evaluated in man for the treatment of diabetes. Sulfone **56** is orally available in the mouse (F = 80%, $t_{1/2}$ = 3.9 h) and was found to exhibit statistically significant efficacy in mouse models of asthma (ovalbumin-induced lung eosinophilia) and atopic dermatitis (fluorescein isothiocyanate-mediated contact hypersensitivity) at doses of 10 mg/kg.[60]

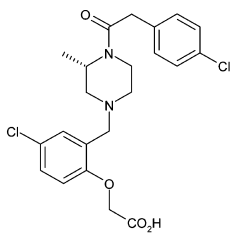
Amira has claimed a large number of phenylacetic acid derivatives as CRTH2 antagonists.[61] One of these, **57** (AM156), retains potent activity in whole blood and has been shown to be effective in reduced airway inflammation in mice exposed to tobacco smoke.[62] Amira has recently published SAR studies that led to the identification of biarylacetic acid



53

CRTH2 pIC_{50} = 8.4

WB IC_{50} = 44 nM*

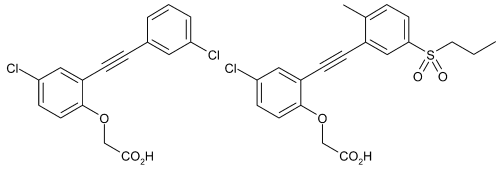


54

CRTH2 IC_{50} = 0.5 nM

*Test conducted by Oxagen. The potency in inhibiting eosinophil shape change (as measured by gated autofluorescence forward scatter) in heparinised human blood in response to PGD_2 (10 nM) using methods previously described.[33]

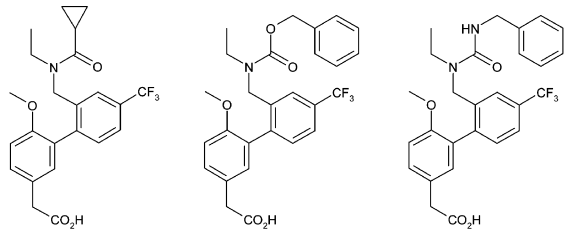
dx.doi.org/10.1021/jm2013997 | *J. Med. Chem.* 2012, 55, 2915−2931



55
CRTH2 Ki = 29 nM
WB IC_{50} = 6,900 nM

56
CRTH2 Ki = 2.0 nM
WB IC_{50} = 80 nM

derivative **58** from a structurally related screening hit.[63] This carbamate derivative is free of significant CYP and hERG inhibition, is orally available (rat F = 77%, $t_{1/2}$ = 8.7 h; Dog F = 89%, $t_{1/2}$ = 7.4 h) and exhibits comparable oral efficacy to dexamethasone in a mouse model of allergic rhinitis.[63] A related phenylacetic acid compound, **59**, has been shown to possess potent whole blood activity, to be well absorbed after oral dosing in the rat and to be effective in reducing antigen-induced airway inflammation in guinea pigs and mice.[64] Phase 1 clinical studies have been completed with **59**.[65] Plasma exposure and eosinophil shape responses in whole blood ex vivo were measured after single doses of 0.3, 3, 10, 30, 100, 300, and 600 mg. Plasma concentrations of drug were only detectable at doses of 30 mg or higher, and doses in excess of 100 mg were required to cause



57
CRTH2 Ki = 13.5 nM
WB IC_{50} = 6.5 nM

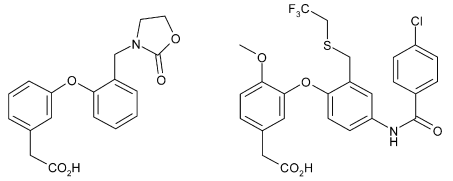
58
CRTH2 IC_{50} = 4 nM
WB IC_{50} = 5 nM

59
CRTH2 IC_{50} = 4.9 nM
WB IC_{50} = 2.7 nM

substantial inhibition of eosinophil shape change responses ex vivo measured at 24 h after dosing. Based on this information, the therapeutic once daily doses of **59** are likely to be in range of 100−300 mg, although only the 30 mg dose was tested in the multiple dosing regimen. This compound and details of its clinical evaluation are given in a patent application in which the sodium salt of compound **59** is specifically claimed.[65]

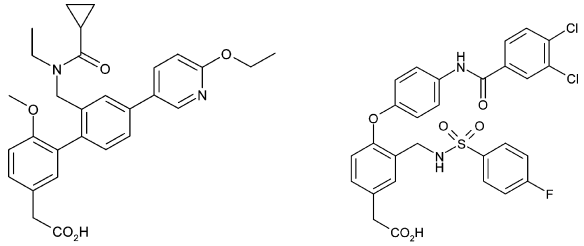
Patent applications from Amira also claim aryl ether phenyl acetic acids[66] such as **60** and more recently 6-methoxy derivatives with the aryl group substituted with sulfide, sulfoxide, and sulfone-linked aromatic groups,[67] of which **61** is an example. Amira investigated a set of analogues of **59** in which the CF_3 group is replaced by a third aryl moiety.[68] From this study, **62** (AM432) was identified as a potent and selective CRTH2 antagonist that retains high potency in whole blood and has a slow off-rate from the CRTH2 receptor, which may be important in delivering prolonged receptor blockade in vivo.[68] Compound **62** also possessed good PK properties in rats and dogs and did not demonstrate any significant CYP or hERG liabilities.

A patent application from Array Biopharma[69] contains a large number of examples of phenoxyphenylacetic acids, each with CRTH2 binding IC_{50} less than 1 μM. Compound **63** is one example, and many other examples contain different substitution of the sulfonamide. Array Biopharma's clinical



60 **61**

candidate, ARRY-502, which inhibits eosinophil shape change in whole blood (IC_{50} = 58 nM), has completed phase 1 trials.[70] Doses of 100, 200, and 400 mg resulted in high plasma exposures and significant inhibition of PGD_2-mediated eosinophil activation in blood ex vivo. Plasma levels of approximately 300 ng/mL or greater were required to maximally inhibit eosinophil shape change ex vivo, and PK/PD modeling studies indicated that a once-a-day dose of 400 mg was required to achieve >50% receptor blockade at C_{min}.



62
CRTH2 Ki = 6 nM
WB IC_{50} = 5 nM

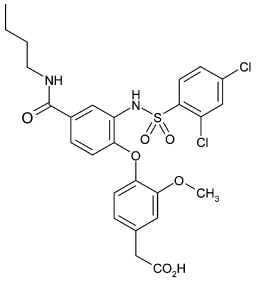
63
CRTH2 Ki<1000nM

Researchers at Tularik (now Amgen) have identified 2-(benzenesulfonamidyl)phenoxyphenylacetic acid derivatives as potent CRTH2 antagonists.[71] Exploration of the SAR led to the finding that when the acetic acid is para to the oxygen linker dual CRTH2/DP_1 activity was apparent as in compound **64** (AMG009). Compound **64** was ~150× less active on DP_1 compared with CRTH2 but was well absorbed after oral administration in the rat, dog, and cynomolgus monkey and had acceptable PK properties. Further optimization of compound **64** led to the discovery of analogue **65**, which demonstrated improved activity on CRTH2 and DP_1 in human whole blood, although **65** still has approximately 25-fold more potent activity on CRTH2 compared with DP_1.[72] Analysis of SAR shows that the bis-aryl ether linker is preferred over sulfide, sulfoxide, sulfone, and amine linkers while for methylene potencies were maintained. Compound **65** was well absorbed after oral administration in several species and demonstrated low to moderate clearance (Rat F = 87%, MRT = 3.9 h; Dog F = 100%, MRT = 3.0 h; Cyno F = 79%, MRT = 1.0 h). A clinical study of compound **65** in asthmatics poorly controlled by inhaled corticosteroids (ICS) has been completed (http://www.clinicaltrials.gov/ct2/show/NCT01018550?term=AMG-853&rank=1), and development of this compound has been discontinued. It remains to be determined whether dual CRTH2/DP_1 antagonists offer any therapeutic advantage over selective CRTH2 antagonists. Although there are theoretical benefits of DP_1 blockade in allergic disease, clinical results with Merck's DP_1 antagonist laropiprant indicate that DP_1 does not play an important role in either asthma or allergic rhinitis.[73] However, activation of DP_1

dx.doi.org/10.1021/jm2013997 | J. Med. Chem. 2012, 55, 2915−2931

provides an anti-inflammatory function in suppressing leukocyte activation, so any benefits of CRTH2 antagonism may be offset by DP_1 blockade. Furthermore, since DP_1 is expressed by platelets and blood vessels where it can mediate platelet antiaggregatory and vasodilator effects, it is possible that DP_1 blockade may pose a cardiovascular risk. The results of clinical trials comparing efficacy and safety profiles of dual CRTH2/DP_1 antagonists to selective CRTH2 antagonists are awaited with interest.

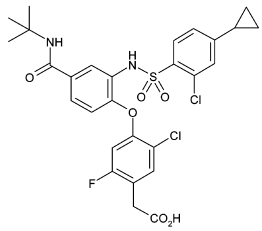
Researchers at Amgen have identified potent phenylacetic acid derivatives substituted with benzodiazepinone in the meta-position



64

CRTH2 WB IC_{50} = 1 nM

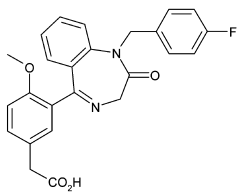
DP_1 WB IC_{50} = 148 nM



65

CRTH2 WB IC_{50} = 0.2 nM

DP_1 WB IC_{50} = 4.7 nM



66

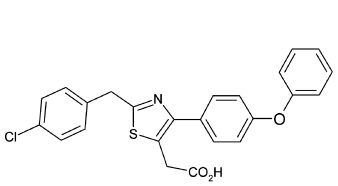
CRTH2 Ki = 3 nM

WB pK_B = 8.7

relative to the acetic acid moiety as in compound **66**.[74] The benzodiazepinone was introduced to increase the rigidity of the molecule based on the activity of a phenylsulfonamido-benzophenone for which hydrogen bonding between the sulfonamide and carbonyl groups was suspected. Interestingly, replacement of the benzodiazepinone with quinazolinone led to dramatic loss of activity. The potent activity of compound **66** was retained in 50% plasma and a favorable pharmacokinetic profile was observed in mice.

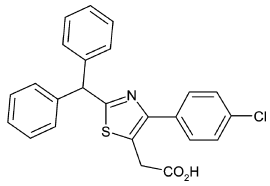
8. THIAZOLE ACETIC ACIDS

7TM Pharma has described the optimization of thiazole acetic acid derivatives as CRTH2 antagonists. Analog derivatization around in silico-derived hits led to the identification of a number active molecules including the 2-benzyl-4-phenyl-thiazoleacetic acid **67**.[75] Thiazole **67** demonstrated functional CRTH2 antagonist activity in a recombinant cell-based assay (IC_{50} = 12 nM) and had negligible DP_1 binding. Further optimization identified analogue **68** as a potent and selective CRTH2 antagonist with an acceptable PK profile.[76]Thiazole **68** acted as a functional CRTH2 antagonist (IC_{50} = 60 nM) and was selective versus a battery of enzymes and receptors including COX1, COX2, and DP_1. Thiazole **68** did not inhibit CYP 2D6 and 3A4 and, although relatively unstable in rat microsomes, was well absorbed after oral dosing in the rat (F = 70%), exhibiting a half-life of 3.3 h and clearance of 4.4 mL/(min·kg). Further investigations of SAR within this series have shown that both methylation of the benzhydryl carbon as in analogue **69** or replacement with nitrogen as in



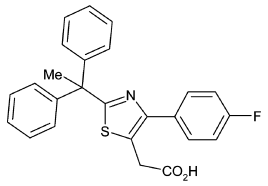
67

CRTH2 IC_{50} = 3.7 nM



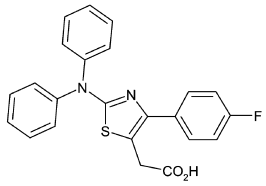
68

CRTH2 IC_{50} = 14 nM



69

CRTH2 IC_{50} = 7.9 nM



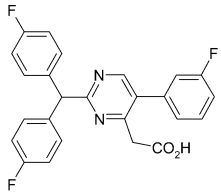
70

CRTH2 IC_{50} = 15 nM

the 2-aminothiazole derivative **70** are both tolerated changes. In contrast replacement of the thiazole by imidazole leads to complete loss in potency (attributed to the formation of an internal hydrogen bond between the acetic acid and the imidazolyl NH).[77]

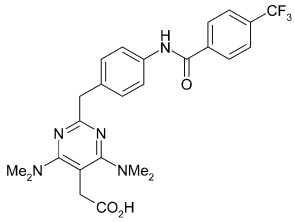
9. PYRIDIMINYL ACETIC ACID DERIVATIVES

7TM Pharma has further shown that replacement of the thiazole scaffold as in compound **70** with pyrimidine as in analogue **71** is tolerated. This compound did not display significant activity against DP_1 and TP receptors. In contrast to the thiazole core, CRTH2 affinity was lost on replacement of the benzhydryl carbon with nitrogen.[77]



71

CRTH2 IC_{50} = 1.9 nM



72

CRTH2 Ki = NT

WB IC_{50} = 626 nM*

*Test conducted by Oxagen. The potency in inhibiting eosinophil shape change (as measured by gated autofluorescence forward scatter) in heparinised human blood in response to PGD_2 (10 nM) using methods previously described.[33]

Researchers at Actimis have identified a different class of pyrimidinyl acetic acid derivatives compared with the CRTH2 antagonists from 7TM Pharma. Patent filings describing polymorphs[78] and polymorphs of ethylene diamine salts[79] suggest that Actimis' lead compound AP761 is the salt form of, or is closely related to, compound **72**. Compound **72** or compounds closely related to it have been reported to be effective in reducing allergic inflammation in skin[80] and lungs.[13] However, high doses are likely to be required in the clinic to reduce allergic responses, given its low potency in human blood. Compound **72** has been licensed to Boehringer Ingelheim, and the Boehringer Ingelheim candidate may be

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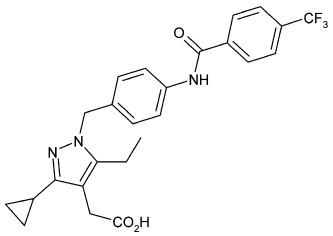
72 or an analog of this compound. A number of trials in asthma and allergic rhinitis have been completed with this compound.

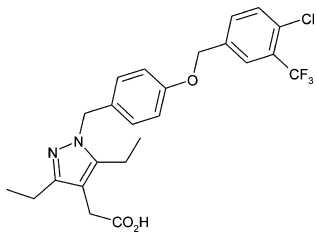
10. PYRAZOLE ACETIC ACIDS

Boehringer Ingelheim has published a patent application[81] that discloses a number of pyrazole derivatives with highly potent CRTH2 antagonist activity of which compound **73** is an example. Binding data are reported for these compounds, and it is claimed that these compounds are active in a range of in vitro functional tests including whole blood eosinophil shape change assays, but no details are reported. The majority of compounds that exemplify this patent application feature a 4-aminobenzyl linking group between the heterocycle bearing the acetic acid group and an aryl lipophilic moiety as in **72** and pyrazole **73**. Compounds that feature alternative linkers, such as ether **74**, lacking the potentially undesirable aniline functionality, tend to be less potent on the basis of the activity data provided.[81]



73

CRTH2 Ki = 0.5 nM

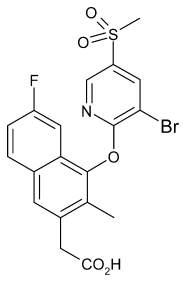


74

CRTH2 Ki = 4.8 nM

11. 6,6-BICYCLIC ACETIC ACIDS

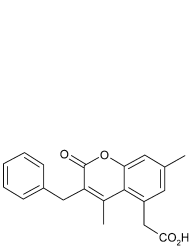
A number of companies have investigated the potential of fused 6,6-bicyclic acetic acid derivatives as CRTH2 antagonists. Roche has published patent applications on fluorinated naphthalene-2-acetic acids with a number of substitutions in the 4-position that are well tolerated.[82−84] One of the most potent examples is **75**, which includes a sulfone group that may be important for whole blood activity as shown in the Oxagen series. Likewise the presence of a fluorine naphthyl substituent appears to be required for optimal activity. From the data provided, it seems that the methyl substituent on naphthyl gives a smaller enhancement of CRTH2 affinity to that provided by the 2-methyl substituent in the indolyl acetic acid series of antagonists. Roche has evaluated a variety of alternative linking atoms to the ether oxygen of naphthalene **75**, but none offers a potency advantage.



75

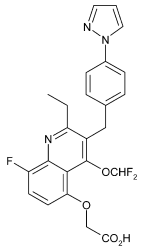
CRTH2 IC_{50} = 0.02 nM

Pulmagen (formerly Argenta) has disclosed both 2-oxochromene acetic acids and quinolineoxy acetic acids,[85−90] of which **76** and **77** are examples. Array has claimed a series of 7-phenoxychroman carboxylic acid derivatives,[91,92] for example, analogue **78**, for which a protein shift CRTH2 receptor binding assay has been used. The other enantiomer of phenoxychroman **78** was over 100-fold less active in this assay.



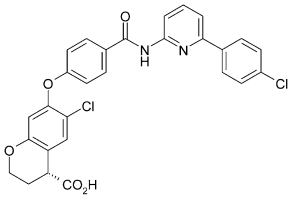
76

CRTH2 Ki = 32 nM



77

CRTH2 Ki = 5.4 nM



78

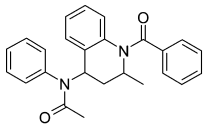
CRTH2 4% HSA IC_{50} = 22 nM

12. COMPOUNDS LACKING A CARBOXYLIC ACID

As can be seen, all of the CRTH2 antagonists reviewed above feature a carboxylic acid moiety, and attempts to introduce carboxylic acid isosteres (e.g., tetrazole, acylsulfonamides) have resulted in a loss of CRTH2 antagonist activity.[55,59,93] However, there are a few patent applications on compounds that lack an acidic group. For example, tetrahydroquinoline compounds have been identified as CRTH2 antagonists. Millennium was the first to file a patent application on tetrahydroquinolines,[94] and Warner-Lambert,[95] Kyowa Kakko,[96] and Amgen[97] have also described CRTH2 antagonists of this structural type. Amgen identified tetrahydroquinoline **79** as a screening hit and subsequently determined that the (2*S*,4*R*)-isomer was most potent.[97] An analogue, **80**, was profiled in more detail and was shown to be selective for CRTH2 over DP_1, and orally available in the rat (F = 38%) with a terminal half-life of 5.1 h. Interestingly, the introduction of a propionic acid amide substituent at the 4-position of the tetrahydroquinoline scaffold in compound **81** gave approximately 10-fold enhancement of CRTH2 affinity. It was found that there is a strong preference for the ethylene linker between the carboxylic acid and the amide carbonyl, as in compound **81**, over one carbon or three carbon linkers. Millennium has filed a patent application on a series of tetrahydroisoquinoline analogues some of which include an alkyl carboxylic acid as a substituent from the benzamide moiety, but it is unclear from the data given whether this confers any potency advantage.[98] There has not been much patent activity regarding tetrahydroquinolines in recent years, and no compounds of this class are believed to be in development.

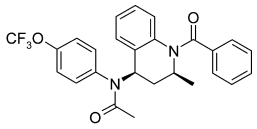
The Serono group identified a series of pyrazine sulfonamides as CRTH2 antagonists as exemplified by compound **82**.[99] For this compound with modest CRTH2 affinity, in silico assessment suggests that the pyrazine sulfonamide moiety is weakly acidic ($pK_a \approx 5.5$).

dx.doi.org/10.1021/jm2013997 | J. Med. Chem. 2012, 55, 2915−2931



79

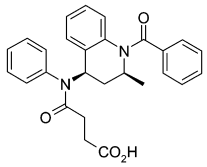
CRTH2 IC_{50} = 43 nM



80

CRTH2 IC_{50} = 25 nM

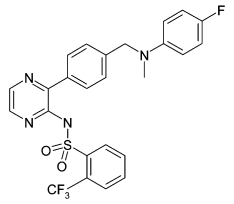
WB IC_{50} = 48.8 nM



81

CRTH2 IC_{50} = 3 nM

WB IC_{50} = 0.77 nM



82

CRTH2 Ki = 380 nM

13. GENERALIZATION OF THE STRUCTURAL FEATURES OF CRTH2 ANTAGONISTS AND THEIR ADMET PROPERTIES

It is clear from the above discussion of currently known CRTH2 antagonists that there is a very strong preference for a carboxylic acid moiety as a key pharmacophore group (Figure 2). From CRTH2 receptor modeling and antagonist docking studies, the 7TM group has suggested that the key interaction made by the carboxylic acid group of antagonists is with a lysine on transmembrane helix V.[77] This follows from earlier work of Hata and co-workers[100,101] who showed that the K209A mutation of CRTH2 abolished agonist activity of both PGD_2 and **18** whereas functional activity was maintained for a K209R mutation. Based on these and other mutation results, a model was built for CRTH2 based on homology and de novo techniques, and this suggested that **1** and **18** bind in a similar manner to the CRTH2 receptor binding pocket by interacting with an overlapping but distinct set of residues compared with PGD_2.[101] To date, isosteric replacements of the key carboxylic acid moiety have without exception resulted in a loss in CRTH2 affinity. For example, replacing the carboxylic acid with tetrazole in the Amgen series of phenyl acetic acid derivatives gives a >500-fold loss in CRTH2 affinity.[71] There is generally a preference for a methylene moiety adjacent to the carboxylic acid group. Although a subset of CRTH2 antagonists feature the carboxylic acid moiety directly attached to a saturated heterocyclic ring system (e.g., **78**), for the phenoxy acetic acid subclass mono substitution, but not disubstitution, by methyl α to the carboxylic acid is tolerated[59] whereas for ramatroban analogues, such as **6**, such adjacent substitution is not tolerated.[23] This loss in CRTH2 affinity is also the case for α methylation in the Amgen series of phenylacetic acid derivatives.[71] These modifications have been investigated because of concerns that metabolic activation of the carboxylic acid moiety could give rise to idiosyncratic liver toxicity via acyl-glucuronide[102,103] or acyl-CoA thioester[104,105] formation and subsequent covalent adduct formation with protein (as indeed is observed for **6**). The introduction of α substitution adjacent to carboxylic acids has been previously demonstrated as an effective strategy for the limitation of covalent binding of acidic drugs.[106,107]

It is usual for the acetic acid moiety to be attached either directly to an aryl or to a heteroaryl scaffold, and in the case of an aryl scaffold optionally by an ether oxygen linker. The aryl or heteroaryl scaffold is often part of a larger fused ring system and typically features one large broadly lipophilic substituent and often a smaller halogen substituent. Both the scaffold and its substituents affect potency. The electronics of the aryl or heteroaryl scaffold affect receptor affinity. For example, differences in activity are observed for azaindole analogues in both the rematroban-like (e.g., **6** and **8** vs **9**) and indole acetic acid series (e.g., **47** vs **46**). Furthermore, as seen above, subtle changes in the nature of the larger substituent of the core scaffold can have significant effects on potency in the whole blood assay (e.g., **30** vs **28** and **42** vs **41**) presumably due to changes in the extent or kinetics of protein binding. In the case of the subset of CRTH2 antagonists with an indole scaffold, the introduction of a 2-methyl substituent confers a strong potency advantage. For example, in the Athersys 3-indolyl sultam series 2-methyl substitution of the indole scaffold gave improved CRTH2 affinity over the 2-des-methyl analogue. This was attributed to a specific hydrophobic pocket encompassing the 2-position of the indole ring.[45] Other workers have suggested that

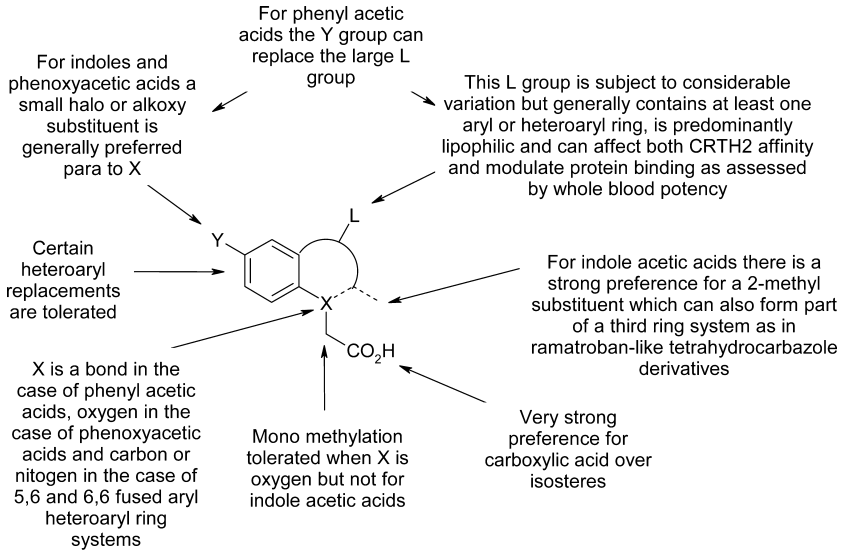


Figure 2. Generalization of key features for CRTH2 antagonists illustrating tight SAR around carboxylic acid moiety and core scaffold.

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the role of the 2-methyl indolyl substituent is to correctly orientate the neighboring acetic acid moiety for optimal receptor interaction.

Boehringer Ingelheim has derived a set of specific "drug-like property" rules for a carboxylate-containing oral drug candidate:[108] molecular weight < 400, H-bond donors < 3, H-bond acceptors ≤ 6, rotatable bonds ≤ 9, clogP < 3, −1.5 < clogD (pH 7.4) < 1.5, 60 Å^2 < TPSA < 140 Å^2, cpKa (COOH) > 3, with COOH-containing compounds not violating more than two of these parameters. The chemical structure is known for eight CRTH2 antagonist compounds that have progressed to clinical trials (compound **1** and compounds from Table 2), and these broadly satisfy the criteria with key exceptions that six out of eight compounds have molecular weights above 400 and all compounds have clogP values in excess of 3. Therefore, the majority of CRTH2 antagonists can be classified as lipophilic carboxylic acids, and they tend to have, similar to acidic NSAIDs, physicochemical and pharmacokinetic properties characteristic of BCS class II drugs; e.g., low aqueous solubility but satisfactory permeability.[109] CRTH2 antagonists are likely to compete in the clinic with the leukotriene receptor antagonist montelukast, which is also a lipophilic carboxylic acid but which has both a molecular weight and clogP outside the Boehringer Ingelheim "drug-like property" rules for carboxylate-containing oral drug candidates. Salt formation between the carboxylic acid motif and a pharmaceutically acceptable counterion has been a strategy adopted for a number of CRTH2 antagonists as a means to enhance dissolution. Lipophilic acid CRTH2 antagonists that have been characterized in more detail generally exhibit satisfactory to good oral bioavailability, high plasma protein binding, low volume of distribution, and half-life sufficient for twice daily or perhaps even once daily dosing in man. The tendency for high protein binding has been addressed in many CRTH2 antagonist drug discovery programs by utilization of whole blood based assays as the primary means to drive SAR optimization. There has been no analysis of in vivo efficacy of CRTH2 antagonists from the perspective of free drug concentration,[110] and there are no clear generic SAR learnings for protein binding. However, both we[35] and others[68] have found that sulfonyl alkyl substituents, incorporated into position L of the generic structure depicted in Figure 2, can give rise to improved potency in whole blood based assays. Achievement of high potency in such assays allied to good pharmacokinetic properties should enable low doses to be achieved in humans that will negate any concerns regarding potential for idiosyncratic toxicity[111,112] associated with the carboxylic acid functionality. An advantage of the presence of a carboxylic acid group is the general lack of any hERG liability for CRTH2 antagonists.[113,114]

Table 2. Summary of CRTH2 Antagonists in Clinical Development

compound	company	indication	status
17	Actelion	asthma	phase 2
		allergic rhinitis	phase 2
65	Amgen	asthma	phase 2 discontinued
59	Amira		phase 1
AM461	Amira		phase 1
ARRY-502	Array Biopharma		phase 1
33	AstraZeneca	asthma	phase 2
		COPD	phase 2
AZD5985	AstraZeneca		phase 1 discontinued
72	Boehringer Ingelheim	asthma	phase 2
		allergic rhinitis	phase 2
6	Merck		phase 1
29	Oxagen	asthma	phase 2
		allergic rhinitis	phase 2
ADC3680	Pulmagen		phase 1
RG-7185	Roche		phase 1

14. CLINICAL STATUS

One of the most advanced CRTH2 antagonists in development is **29**. This compound has been tested in a large number of both healthy subjects and patients suffering from asthma and allergic rhinitis. In steroid naïve moderate persistent asthmatics treatment with **29** (200 mg bid) for 4 weeks led to a significant reduction in airway inflammation (as measured by sputum eosinophilia) compared with placebo.[16] This reduction in airway inflammation was associated with a steady improvement in lung function and reduction in asthma symptoms. The degree of improvement in lung function is comparable to that of low-dose inhaled corticosteroids, and it is anticipated that longer term treatment will lead to further therapeutic benefit. Compound **29** has recently completed a 3-month dose-ranging phase IIb trial in asthma, which included once-a-day dosing arms of 25 and 200 mg (http://www.clinicaltrials.gov/ct2/show/NCT00890877?term=oc000459&rank=5).

The Actelion CRTH2 antagonist **17** has also been reported to be effective in improving lung function in mild asthmatics (http://www.actelion.com/en/scientists/mechanisms-of-action/crth2-receptor-antagonism.page?). It is likely that this crossover study has evaluated the effect of **17** on responses to inhaled allergen (http://www.respiratoryclinicaltrials.co.uk/publications.htm) and the therapeutic effect reported highlights the proposed role for CRTH2 in the late phase airway response.[14]

A key unmet medical need in current asthma therapy is to provide improved asthma control in those patients not adequately treated by inhaled corticosteroids. Astra-Zeneca has completed the OLIVE trial, which studied the effect of **33** in asthma patients not controlled by inhaled corticosteroids. Compound **33** was administered at doses up to 1000 mg twice daily for 1 month (http://www.clinicaltrials.gov/ct2/show/NCT00758589?term=AZD-1981&rank=6). Although the results of OLIVE have not been disclosed, it would appear that the outcome was encouraging since Astra-Zeneca has undertaken a 3 month trial with **33** in a similar patient population using a broad range of doses from 10 mg twice a day to 400 mg twice a day and including some once-a-day doses (http://www.clinicaltrials.gov/ct2/show/NCT01197794?term=AZD-1981&rank=4).

The effects of **72** at doses up to 400 mg bid has been studied in both steroid naïve asthmatics (compared with fluticasone) and patients not controlled by ICS (compared with placebo). Another 6 week trial of **72** in uncontrolled asthmatics (compared with montelukast) has also been completed. A trial of **17** in asthmatics not controlled by ICS is ongoing. As mentioned earlier, Amgen has conducted a 3 month trial with the dual CRTH2/DP$_1$ antagonist **65** in poorly controlled asthmatics. Compound **65** was dosed twice-a-day at doses up to 100 mg and included a once-a-day 200 mg dose as a comparison (http://www.clinicaltrials.gov/ct2/show/NCT01018550?term=AMG-853&rank=1). Compound **65**

has been discontinued, but the reason for this has not been disclosed.

Astra-Zeneca has also conducted one month trials with **33** in patients with COPD, one of these trials involving a biopsy, presumably to assess the effect of drug on leukocyte accumulation into bronchial tissue (http://www.clinicaltrials.gov/ct2/show/NCT00690482?term=AZD-1981&rank=10; http://www.clinicaltrials.gov/ct2/show/NCT00766415?term=AZD-1981&rank=11).

Although COPD is not generally thought to be a Th2-dependent disease, it is becoming increasingly apparent that eosinophilic airway inflammation is present in a significant number of COPD patients. In eosinophilic COPD, it is possible that CRTH2 might mediate eosinophil accumulation in response to PGD_2 produced from activated macrophages within the lung.

Proof-of-concept trials have also been conducted with CRTH2 antagonists in allergic rhinoconjunctivitis. The effect of **29** has been studied in an allergen challenge chamber.[115] Treatment with **29** (200 mg bid) reduced nasal and ocular symptoms in allergic subjects exposed to grass pollen. Actelion has disclosed that **17** is effective in reducing daytime symptoms in subjects with seasonal allergic rhinitis, and a phase III trial comparing **17** with cetirizine is planned in subjects as young as 12 years of age (http://www.clinicaltrials.gov/ct2/show/NCT01484119?term=ACT129968&rank=3). The effects of the Novartis compound QAV680 have been evaluated in an environmental exposure chamber where allergic subjects were exposed to rag weed allergen in a controlled fashion (http://www.clinicaltrials.gov/ct2/show/NCT00784732?term=QAV680&rank=4). The effects of QAV680 on nasal and ocular symptoms and levels of eosinophils and cytokines in nasal lavage were studied although the results are not yet disclosed. QAV680 has been studied further in this setting in comparison to, and in combination with, the antihistamine cetirizine (http://www.clinicaltrials.gov/ct2/show/NCT01103050?term=QAV680&rank=3). This is an important study since it is anticipated that combined blockade of the histamine-mediated early phase response and the CRTH2-mediated late phase allergic response would have superior benefit to current oral therapies especially in patients with more severe disease or in those patients where relatively antihistamine-resistant nasal obstruction is particularly troublesome.

Phase 1 trials have been completed for a number of CRTH2 antagonists including **59**, AM461, ADC3680, **6**, ARRY-502, and RG7185. The clinical status of CRTH2 antagonists in currently in development is summarized in Table 2.

15. CONCLUSIONS

Since the discovery of PGD_2 as the ligand for CRTH2 in 2001 there has been significant progress in defining the role of this receptor in allergic disease and the identification of small molecular weight antagonists with drug-like properties. With **1**, **18**, and various high-throughput screening hits as starting points for medicinal chemistry programs, a number of companies have identified lipophilic carboxylic acids as highly potent and selective CRTH2 antagonists. Armed with the knowledge of the known liabilities of carboxylic acids such as the formation of reactive metabolites leading to covalent binding, it has proved possible to select clinical candidates with acceptable pharmacodynamic, pharmacokinetic, metabolic, and safety profiles. Early proof-of-concept clinical studies indicate that CRTH2 antagonists are effective in treating the signs and symptoms of both asthma and allergic rhinitis and possess features that are differentiated from existing therapies for these indications. One of the most important properties of CRTH2 antagonists demonstrated in preclinical models is inhibition of Th2 cytokine production. Therefore, recent clinical trials with anti-IL5 and anti-IL13 antibodies may be informative in highlighting those patient populations that may be most responsive to CRTH2 antagonists and the magnitude of clinical improvement that might be expected. The anti-IL5 antibody mepolizumab has been tested in patients with refractory eosinophilic asthma and shown to reduce exacerbations and improve quality of life over 1 year of treatment.[116] The anti-IL5 antibody reslizumab has also been shown to be effective in treating eosinophilic asthmatics where clinically meaningful improvements in lung function and asthma control were demonstrated over a 15 week dosing period, especially in subjects with comorbid nasal polyps.[117] The anti-IL13 antibody lebrikizumab was also shown to be effective in improving lung function in asthmatics with a Th2 phenotype as defined by the presence of the biomarker periostin in blood or a combination of high circulating eosinophils and IgE.[118] It is anticipated that such patients groups would also be highly responsive to CRTH2 antagonists, which have advantages over the anti-Th2 antibodies in terms of cost and convenience of dosing. It seems likely that CRTH2 antagonists will ultimately find utility as novel antiallergic drugs; the challenge is to identify compounds that are effective when dosed once a day and prove to have an acceptable safety profile in long-term studies.

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Biographies

Roy Pettipher is Director of Pharmacology at Oxagen where he was involved in the initiation of the CRTH2 drug discovery program. He has over 25 years experience in anti-inflammatory drug discovery having previously worked at Pfizer (1990−1997) and Wellcome (1984−1990). He has been involved in the initiation and management of a number of drug discovery programs that have yielded clinical candidates and has published extensively in the field of inflammation biology. He holds a degree in Pharmacology from the University of Bath and a Ph.D. in Pharmacology from the University of London.

Mark Whittaker is Senior Vice President Drug Discovery at Evotec where he is involved in a number of collaborative drug discovery projects. This previously included a collaboration with Oxagen that led to the discovery of the CRTH2 antagonist OC000459. He joined Evotec in 2001 after 13 years at British Biotech where he was initially a group leader in medicinal chemistry and subsequently became Head of Medicinal Chemistry (1993−1997), Director of Medicinal Chemistry (1997−2000), and Director of Chemistry (2000−2001). Mark obtained a D.Phil. in chemistry from the University of York in 1982 and conducted postdoctoral research with Prof. C. C. Leznoff at York University, Toronto (1982−1985), and with Prof. S. G. Davies at the University of Oxford (1985−1987).

ABBREVIATIONS USED

CRTH2, chemoattractant receptor-homologous molecule expressed on Th2 cells; DP_1, prostaglandin D_2 receptor type 1; DP_2, prostaglandin D_2 receptor type 2; PGD_2, prostaglandin D_2; IgE, immunoglobulin E; TP, thromboxane receptor; CYP, cytochrome P450; DK-PGD_2, 13,14-dihydro-15-keto-prostaglandin D_2; COX, cyclooxygenase; IL, interleukin; HTS,

high-throughput screening; ADMET, absorption, distribution, metabolism, excretion, and toxicity; hERG, human ether-à-go-go-related gene; PK, pharmacokinetics; BCS, biopharmaceutics classification system; COPD, chronic obstructive pulmonary disease; WB, whole blood; ICS, inhaled corticosteroids; MRT, mean residence time; TPSA, total polar surface area

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