CHAPTER 8

Recent Advances in the Discovery and Development of CRTh2 Antagonists

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Contents

1. INTRODUCTION

Prostaglandin D_2 (PGD_2, **1**), produced from arachidonic acid *via* cyclooxygenase and prostaglandin synthases, is a potent mediator of allergic inflammation. Primarily released from mast cells in response to immunoglobulin E (IgE)-mediated degranulation, this prostanoid undergoes rapid metabolism. Both parent PGD_2 and the resulting metabolites possess proinflammatory actions contributing to early and late phase inflammatory events. The function of these mediators appears to be largely unaffected by existing therapeutics, and it has been postulated that if the proinflammatory actions of PGD_2 could be mitigated, significant

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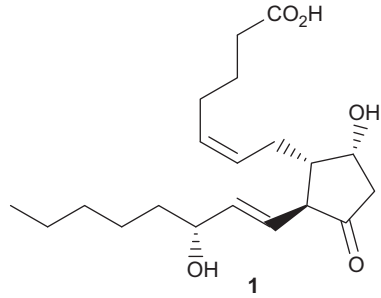
benefit could be realized for patients suffering from allergic diseases. Indeed, the pharmacology of PGD_2 and attempts to control it *via* receptor antagonism have been reviewed [1].



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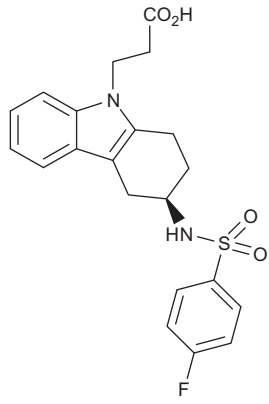
PGD_2 is recognized by two G-protein-coupled seven transmembrane receptors, DP (also known as DP1) and CRTh2 (*c*hemoattractant *r*eceptor-homologous molecule expressed on *Th2* cells; also known as DP2 or GPR44 or CD294). Several PGD_2 metabolites formed *in vivo* lose significant affinity for DP and retain affinity for CRTh2. Thus, of these two, CRTh2 has emerged as the relevant receptor mediating the prolonged proinflammatory activity of PGD_2 [2]. The recent disclosure that a selective DP antagonist provided no benefit in two clinical studies in asthma and allergic rhinitis further supports the focus on CRTh2 as the therapeutically relevant PGD_2 receptor in allergic disease [3]. CRTh2 is expressed on eosinophils, basophils, and Th2 effector T cells and mediates the activation and chemotaxis of these cell types. Specifically, the PGD_2/CRTh2 system regulates respiratory burst and degranulation of eosinophils [4], histamine release from basophils [5], and the production of IL-4, IL-5, and IL-13 from $CD4^+$ $CRTh2^+$ T cells without a costimulatory signal [6]. Such pathophysiology has been strongly associated with asthma, allergic rhinitis, and atopic dermatitis—three diseases that afflict millions of patients worldwide. A safe and effective CRTh2 antagonist could provide benefit to these patients.

Ramatroban (**2**), an indole propionic acid with moderate CRTh2 antagonism activity ($K_i = 137$ nM), is approved for use in allergic rhinitis in Japan [7]. Clinical studies comparing it to antihistamine treatment demonstrated that ramatroban provided a significant improvement in the control of signs and symptoms of perennial allergic rhinitis, particularly nasal obstruction [8]. While primarily a thromboxane receptor antagonist, the CRTh2 antagonism also provided by this drug has been speculated to contribute to this efficacy. Accordingly, selective CRTh2 antagonists have demonstrated efficacy in preclinical models of allergic rhinitis. In an ovalbumin (OVA)-sensitized mouse model involving intranasal challenges, both the early and late phase response as measured by changes in respiratory frequency were inhibited with a potent and

selective CRTh2 antagonist, ARRY-005 (IC_{50} = 35 nM; structure not disclosed) [9]. Reduced levels of IL-4, IL-5, and IL-13 were also noted in nasal tissue compared to controls. Thus, while ramatroban has provided benefit to allergic rhinitis patients, perhaps more potent and selective CRTh2 antagonists will supply even greater benefit.

CRTh2 antagonists have also shown benefit in several rodent models of asthma; not only with OVA and cockroach antigen-based protocols but also in house dust mite induced allergic responses [10]. Unlike other allergens commonly used in preclinical models of allergy, house dust mite allergen is clinically relevant and reproduces signs and symptoms of the human disease including structural remodeling of the airway [11]. In this model, pulmonary inflammation, mucus hypersecretion and mucus cell metaplasia were inhibited by AM156 (*vide infra*) at a dose of 10 mg/kg. Clinically, several human studies have been completed or are underway to evaluate the potential for CRTh2 antagonism in allergic asthma. In a 4-week study treating mild to moderate asthmatics with daily doses of an oral CRTh2 antagonist, OC000459 (identified by others as structure **3** [12]), a significant increase in forced expiratory volume in one second (FEV_1) was noted versus placebo along with decreased serum IgE and sputum eosinophil counts [13]. These results spurred the initiation of a second trial in a greater number of patients involving 17 weeks of daily oral dosing but results have not been published [14]. Another CRTh2 antagonist, AZD1981 (structure not disclosed), is presently being evaluated in a worldwide asthma study involving over 1000 patients of varying disease severity [15]. Ultimately, patient selection criteria could significantly influence clinical study outcomes. To date, about half the trials have not selected for any degree of asthma severity among enrolled patients, while the other half have targeted mild to moderate asthmatics. Recently, levels of PGD_2 were shown to be increased in lung fluid of severe asthmatics and correlated with disease severity suggesting that these patients may benefit from a CRTh2 antagonist [16].



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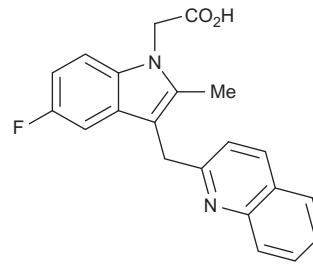


3

The cutaneous allergic response in rodents can also be controlled *via* CRTh2 modulation. In one murine model, involving epicutaneous sensitization of tape-stripped skin (mimicking scratching) in OVA-sensitized animals, skin PGD_2 levels, infiltration of inflammatory cells, and Th2 cytokine mRNA were significantly increased 24 h after the mechanical injury. Applying this same model to CRTh2−/− mice, the inflammatory infiltrate and cytokine message were significantly decreased [17]. A comparable study utilizing a selective CRTh2 antagonist in mice with functional CRTh2 produced similar results [18]. In yet another study, a selective CRTh2 antagonist controlled various skin endpoints and pruritus in the Nc/Nga mouse model of atopic dermatitis [9]. Additional data that demonstrate upregulation of CRTh2 expression in Th2 T cells and eosinophils isolated from atopic dermatitis patients compared to healthy subjects provide further support for the role of CRTh2 in skin disease; however, there have been no reports of clinical studies designed to explore CRTh2 antagonism for dermal indications [19,20].

CRTh2 antagonism may also provide benefit to patients suffering from chronic obstructive pulmonary disease (COPD). In a mouse model involving exposure to cigarette smoke, CRTh2 antagonism reduced cellular inflammation, mucus cell metaplasia, and epithelial hyperplasia in the airway [21]. While these results are encouraging, it is also important to note that murine neutrophils express CRTh2 under basal conditions while human neutrophils do not. However, based on precedence in cystic fibrosis and other human cellular studies, it might be expected that human neutrophils could upregulate CRTh2 [22]. Indeed, CRTh2 upregulation in lipopolysaccharide- and formyl peptide (fMLP)-stimulated neutrophils was recently disclosed [23]. There have also been clinical studies in COPD involving treatment with a CRTh2 antagonist, but no results have been reported [24].

The clinical studies involving CRTh2 antagonists were recently reviewed [12]. In addition to efficacy studies, several clinical trials involving CRTh2 antagonists have been designed to explore safety, specifically drug–drug interactions and CYP induction [25]. These appear to have been designed to explore compound specific properties and are probably not related to antagonism of the PGD_2/CRTh2 system.

2. CRTH2 ANTAGONISTS

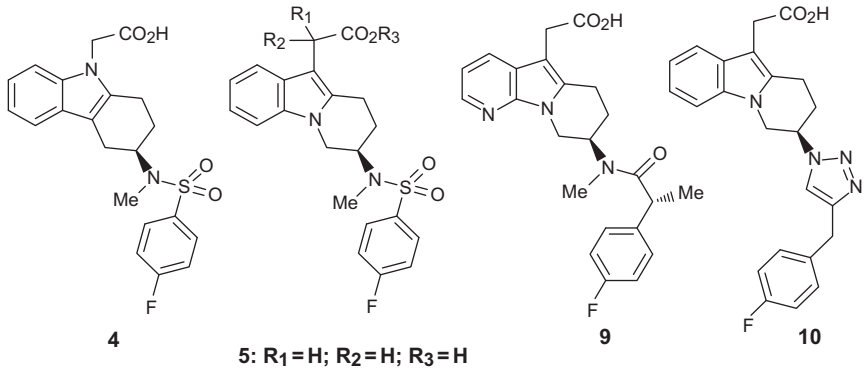
CRTh2 antagonists are typically assessed for receptor affinity using standard membrane binding assays and are reported here as either an IC_{50} or a K_i. Almost all CRTh2 antagonists disclosed to date can be broadly classified as hydrophobic acids [26]. Since hydrophobic organic anions of medium size (100–600 Da) often bind nonspecifically (and strongly) to

serum proteins like albumin, the concentration of exogenous protein in these binding assays is important to note when making comparisons among compounds so that protein shifts can be put into context [27]. Ideally, the use of 4% human serum albumin (HSA) in assay media would mimic a human whole blood setting [28]; however, lower concentrations of HSA or BSA (bovine serum albumin) are often employed. An additional method for evaluating the functional activity of CRTh2 antagonists is eosinophil shape change (ESC). In response to PGD_2, human eosinophils prepare for chemotaxis by activating intracellular motile machinery resulting in a shape change that is readily assessed by flow cytometry. ESC is mediated by CRTh2 and can be effectively antagonized; furthermore, when conducted in human whole blood, this assay provides meaningful context to an antagonist's potency.

2.1. Indole acetic acids

Several leads based on the structure of ramatroban have been disclosed. It was reported that contracting the carboxylic acid tether, retaining the *R* absolute stereochemistry and methylation of the sulfonamide results in a much more potent and selective CRTh2 antagonist (**4**, single enantiomer; $K_i = 1.5$ nM) [29]. Building upon those results, it was found that reversing the indole maintained potency and selectivity to provide MK-7246 (**5**, $K_i = 2.5$ nM; ESC $IC_{50} = 2.2$ nM). This compound was profiled extensively and advanced to Phase 1 clinical studies [7]. MK-7426 was characterized as a reversible, full antagonist and demonstrated moderate inhibition of CYP 2C9 *in vitro* ($IC_{50} = 9.4$ μM), low to moderate plasma clearance *in vivo* with a moderate terminal half-life and oral bioavailabilty of >57% in rat, dog, and rhesus monkey. The major metabolite of MK-7426 was acyl glucuronide (**6**). This metabolite was observed in plasma of all species dosed with MK-7426 and was most predominant in nonhuman primates (~50–150% of parent). In an attempt to reduce the potential reactivity of any resulting glucuronides, analogs bearing a substituent alpha to the carboxylic acid (**7**, **8**) were prepared but were found to lose ~100-fold affinity for CRTh2. There are very few examples of potent CRTh2 antagonists that incorporate α-substitution relative to the carboxylic acid; however, when such structural features are incorporated into carboxylic acids, lower reactivity of the corresponding glucuronide metabolites with protein or peptide nucleophiles is observed [30]. As a backup to MK-7246, aza-indole **9** was identified as having no CYP inhibition and improved off-target selectivity while retaining high potency ($K_i = 3.4$ nM; ESC $IC_{50} = 1.2$ nM) and similar pharmacokinetics upon oral dosing [31]. Compound **9** also demonstrated less nonspecific covalent binding *in vivo* as compared to MK-7426, and this was proposed to be due to the replacement of the aryl sulfonamide with a benzamide, thereby reducing

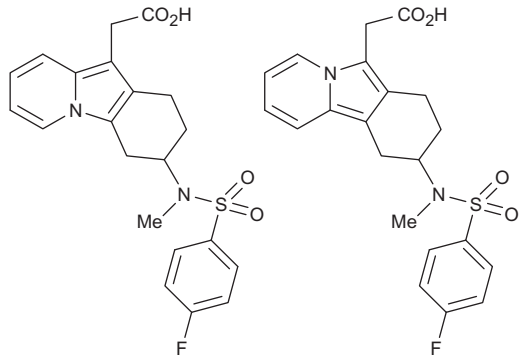
potential electrophilicity. A triazole moiety (see **10**, $K_i < 5$ nM) can also replace the MK-7426 sulfonamide [32].



4 **9** **10**

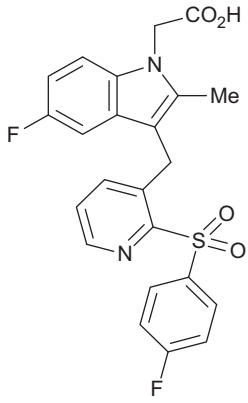
5: R_1 = H; R_2 = H; R_3 = H
6: R_1 = H; R_2 = H; R_3 = glucuronic acid
7: R_1 = R_2 = spiro-cyclopropyl; R_3 = H
8: R_1 = H; R_2 = Me; R_3 = H

The same nitrogen shift strategy that produced MK-7426 was extended. Recently, disclosed CRTh2 antagonists **11** and **12** are also based on the tetrahydrocarbazole substructure of ramatroban, in which the nitrogen is shifted to bridgehead positions. These racemic compounds are reported to have an IC_{50} of less than 300 nM [33].



11 **12**

Ramatroban's tetrahydrocarbazole architecture can be disconnected in favor of less conformationally constrained substructures that still provide potent CRTh2 antagonism. Pyridyl sulfone **13** is potent ($K_i = 2$ nM; ESC $IC_{50} = 2.5$ nM) [34]. The pyridine ring can also be replaced with several other heterocycles including a thiophene (**14**; $K_i = 0.8$ nM) [35]. A related disconnection/reconnection strategy provides sultams **15** and **16** [36]. While the unsubstituted sultam, **15**, is weakly potent ($K_i = 2.8$ μM), the isoxazole substituted sultam **16** is much more so ($K_i = 12$ nM). Along with other reported SAR, this suggests the importance of a strategically placed hydrogen bond acceptor.



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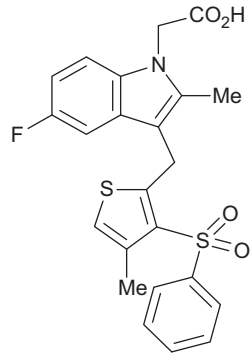

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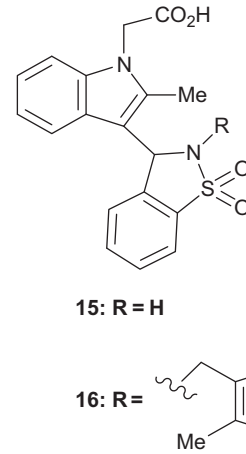
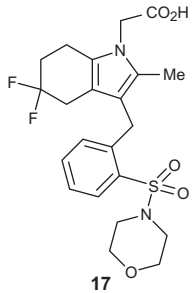


2.2. Heteroaryl acetic acids

While indole acetic acids have provided an effective template for CRTh2 antagonists, other heteroaromatic systems are also viable. Pyrrole-based antagonists such as sulfonamide **17** and sulfone **18** are potent in human whole blood assays ($IC_{50} < 5$ nM) [37]. Thiazole and pyrimidine templates (exemplified by **19** and **20**) which originated from *in silico* screening efforts have also been explored. Thiazole **19** and pyrimidine **20** demonstrated potent antagonism ($IC_{50} = 3.7$ and 1.9 nM, respectively) with no exogenous protein added [38]. Analogs of these antagonists along with molecular modeling studies have led to a proposed pharmacophore and binding alignment that involves a crucial interaction of the carboxylic acid with Lys210, a hydrogen bond to Ser266, and a hydrophobic subpocket consisting of an array of aromatic residues [39].



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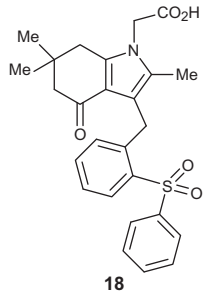

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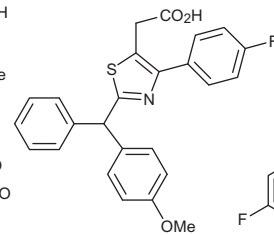

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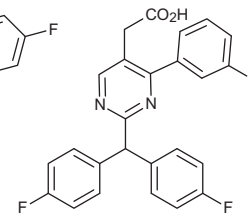
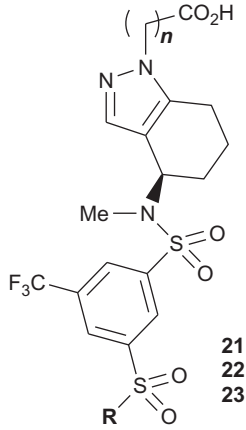


20

A series of pyrazole acetic acids have been disclosed including **21** and **22** which possess CRTh2 binding IC_{50}s of 3 nM [40]. Interestingly, several

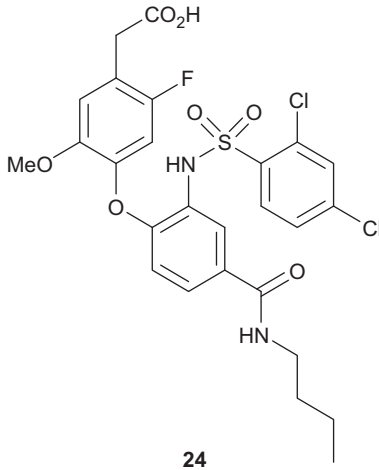
propionic acid analogs, exemplified by **23**, maintained high CRTh2 affinity (binding $IC_{50} = 3$ nM). While phenoxy acetic acids have shown high affinity for the CRTh2 receptor (*vide infra*), corresponding carbon analogs (*i.e.*, aryl propionic acids) are typically less potent.



21: R = cyclopentyl; *n* = 1
22: R = (4-methyl)phenyl; *n* = 1
23: R = (4-methyl)phenyl; *n* = 2

2.3. Phenyl acetic acids

A plethora of CRTh2 antagonists based on the phenyl acetic acid template have recently been disclosed, and they fall, generally, into three structural categories: biphenyl ethers, benzophenones, and biphenyls. Of the biphenyl ether class, compound **24** ($IC_{50} = 3$ nM in buffer; $IC_{50} = 28$ nM in human plasma) was one of the first to enter clinical trials. Ultimately, compound **24** was abandoned in favor of AMG-853 (**25**) because of a reduced plasma shift. AMG-853 has been extensively profiled and also advanced to clinical studies [41]. AMG-853 is potent in both buffer ($IC_{50} = 3$ nM) and human plasma ($IC_{50} = 8$ nM) and also possesses affinity for the DP receptor ($IC_{50} = 35$ nM) [42]. In preclinical pharmacokinetic studies, this dual CRTh2/DP antagonist showed low to moderate clearance across species, excellent oral absorption, and low potential for drug–drug interactions as indicated by CYP inhibition and induction studies. In single oral dose, first-in-human clinical studies, AMG-853 pharmacokinetics were approximately dose proportional (*i.e.*, 100 mg: $C_{max} \sim 500$ ng/mL; 400 mg: $C_{max} \sim 3000$ ng/mL) and the drug was well tolerated [43]. The major metabolite was the corresponding acyl glucuronide, and this was observed at levels (based on AUC) approximating 70% of parent. As a pharmacodynamic endpoint, CRTh2 receptor internalization in response to *ex vivo* PGD_2 stimulation demonstrated that oral doses of 200 or 400 mg of AMG-853 could only suppress this phenomenon for approximately 8–10 h, suggesting that this drug may benefit from a BID dosing regimen.



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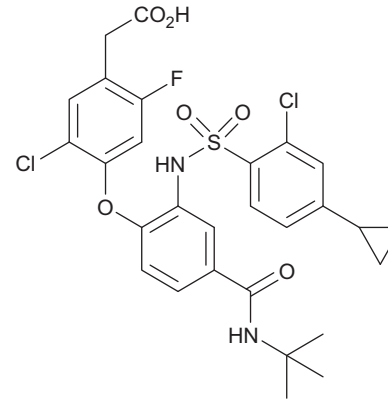
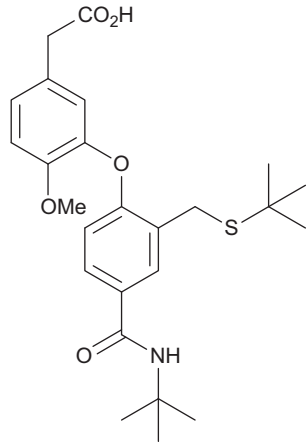


25

Another series of structurally related biphenyl ether-based phenyl acetic acid CRTh2 antagonists includes **26**, **27**, and **28** (all IC_{50}s < 300 nM) [44]. It is interesting to note that the reverse amide, **27**, and its analogous diphenyl methane, **28**, both retain CRTh2 affinity. These results suggest that the nature of the linker (benzamide *vs.* anilide or ether *vs.* alkyl) is not crucial and, comparing to AMG-853, there seems to be flexibility in the position of the linker relative to the acetic acid substituent (*i.e.*, *meta* versus *para*). The preferential use of the *tert*-butyl amide in both series of compounds also suggests a similar binding mode to AMG-853.



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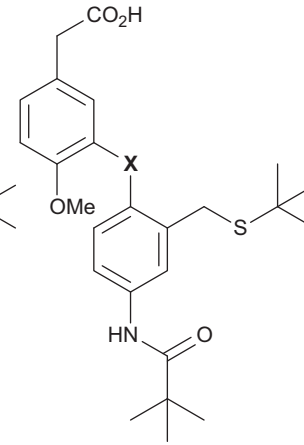
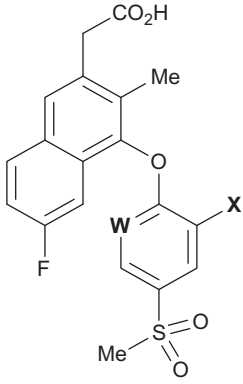
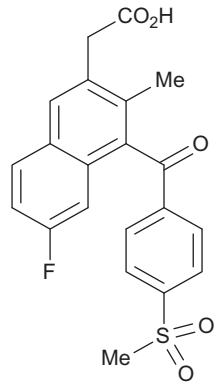


27: X = O
28: X = CH_2

A very potent series of biphenyl ether-containing phenyl acetic acid CRTh2 antagonists was recently disclosed [45]. Compounds **29**–**32** incorporate a 6-fluoro-3-methyl naphthalene core and utilize either an ether (**29**; $IC_{50} = 2.3$ nM) or a keto-linker without loss of affinity (**31**; $IC_{50} = 2.1$ nM) [46]. The terminal aryl sulfone can also be replaced as a piperidinesulfonamide (**32**; $IC_{50} = 2.4$ nM), a common functional group in many CRTh2 antagonists. In particular, compound **30**, which incorporates a bromo-substituted pyridine, demonstrates very high affinity for CRTh2 ($IC_{50} = 0.02$ nM).



29: W = CH; X = H
30: W = N; X = Br



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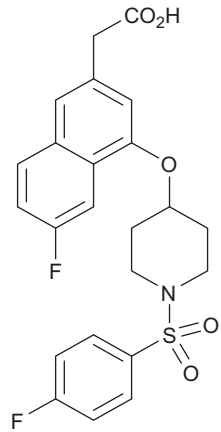
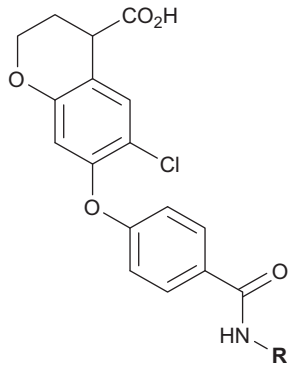
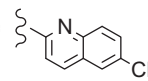
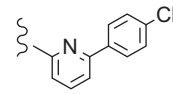


32

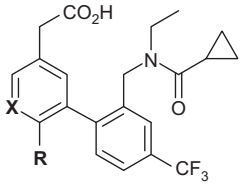
A series of chroman-based compounds that incorporate a biphenyl ether have also been reported to be potent CRTh2 antagonists [47]. Single enantiomers of these chiral phenyl acetic acids were prepared, and a significant difference in affinity for CRTh2 was demonstrated (**33**, eutomer; $IC_{50} = 84$ nM; distomer $IC_{50} = 4000$ nM). One of the more potent, single enantiomer antagonists in this series incorporates a pyridyl-containing biphenyl motif (**34**; $IC_{50} = 22$ nM).



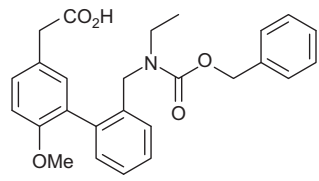
33: R = 

34: R = 

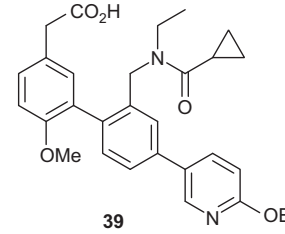
Additional phenyl acetic acid CRTh2 antagonists that incorporate a biaryl arrangement are represented by several active compounds related to previously disclosed AM156 (**35**; $IC_{50} = 24$ nM) [48]. CRTh2 activity is maintained when a pyridine is used in place of phenyl as evident in this series (**36**, **37**; $IC_{50} < 300$ nM). Carbamate **38** was quite potent ($IC_{50} = 8$ nM; ESC $IC_{50} = 5$ nM), demonstrated good selectivity over other prostanoid receptors and good pharmacokinetics in rat ($t_{1/2} = 8.7$ h, $F = 77\%$) and dog ($t_{1/2} = 7.4$ h, $F = 89\%$). This compound also provided similar efficacy (at a dose of 10 mg/kg) to dexamethasone (also at a dose of 10 mg/kg) in a murine model of allergic rhinitis. The carbamate was later identified as a metabolic and potential toxicological liability. In an effort to eliminate this functionality, the biphenyl was elaborated to a pyridyl-containing triarene, and the cyclopropyl amide was reintroduced to provide AM432 (**39**; $IC_{50} = 31$ nM) [49]. AM432 was considered as a clinical development compound and profiled extensively in animal models. At an orally administered dose of 10 mg/kg, AM432 provided protection from upper airway distress in a murine model of allergic rhinitis and also reduced neutrophil influx in the lower airway in a murine model of COPD involving cigarette smoke exposure. In addition to potent CRTh2 activity and selectivity over related prostanoid receptors, AM432 was also found to be devoid of agonist and antagonist activity at three isoforms of the PPAR receptor up to concentrations of 250 μM. Reports of CRTh2 antagonist selectivity screening versus nuclear hormone receptors have been rare; however, several clinical CYP induction and drug–drug interaction studies have been disclosed that may be linked to this activity [25].



35: X = CH, R = OMe
36: X = N, R = H
37: X = N, R = OMe



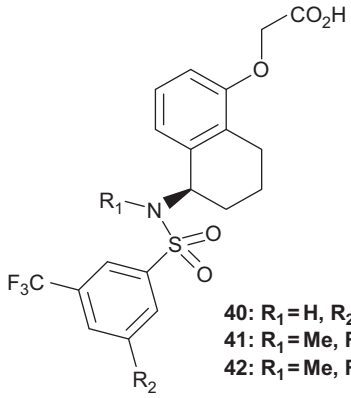
38



39

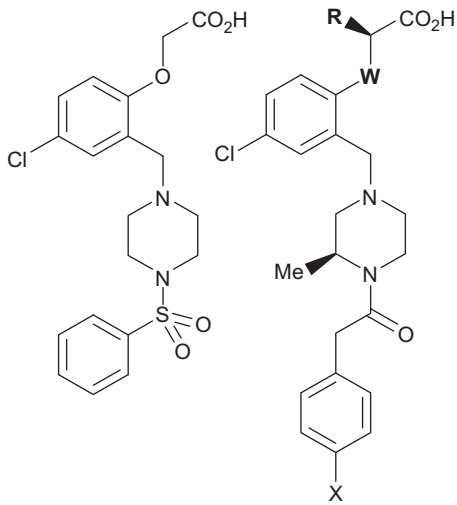
2.4. Phenoxy acetic acid

A variety of phenoxy acetic acid-based CRTh2 antagonists have been recently disclosed including a series of tetrahydronaphthalene sulfonamides [50]. Unsubstituted sulfonamide **40** is potent ($IC_{50} = 6$ nM), while the methyl-substituted analog loses affinity (**41**; $IC_{50} = 74$ nM). Introduction of a sulfone (**42**) restores the CRTh2 affinity ($IC_{50} = 3$ nM).



40: R_1 = H, R_2 = CF_3
41: R_1 = Me, R_2 = CF_3
42: R_1 = Me, R_2 = SO_2-cyclopentyl

Based on the ramatroban structure, a virtual screen identified compound **43** (IC_{50} = 16 nM) as a CRTh2 antagonist lead [51]. Subsequent lead optimization (including side-chain modification and specific stereochemical substitutions along with physiochemical property improvements) provided amide **44** (IC_{50} = 0.5 nM) which demonstrated reasonable rat pharmacokinetics (Cl = 15 mL/min/kg; Vss = 1.6 L/kg; F = 22%). An interesting feature of these compounds is the incorporation of a basic amine (pK_a = 6.8) resulting in zwitterions. This might explain the volume of distribution of **44**, which is generally higher than most CRTh2 antagonists that could be generally classified as lipophilic acids. It is worth noting that phenoxy acetic acid **44** could be substituted alpha to the carboxylic acid without much loss of affinity (**45**; IC_{50} = 1.3 nM); meanwhile, the carbon analog of **44**, propionic acid **46**, was significantly less potent (IC_{50} = 79 nM) despite having the same atom count.

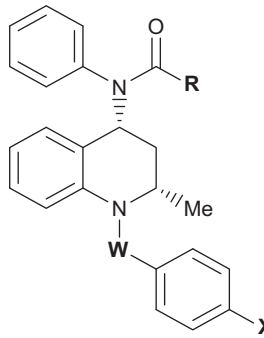


43

44: R = H; W = O; X = Cl
45: R = Me; W = O; X = Cl
46: R = H; W = CH_2; X = H

2.5. Noncarboxylic acids

There have been sporadic reports of CRTh2 antagonist structures that lack a carboxylic acid or mimic thereof. Recently, optimization of *cis*-substituted, racemic tetrahydroquinoline **47** (IC_{50} = 43 nM), identified through high-throughput screening, provided **48** (IC_{50} = 26 nM) [52]. The enantiomers of **48** were isolated and the more active single enantiomer provided potent CRTh2 affinity in the presence of 50% human plasma (IC_{50} = 106 nM) and good rat pharmacokinetics (Cl = 12 mL/min/kg; F = 38%). Interestingly, the sulfonamide analog, **49**, lost all affinity for CRTh2 (IC_{50} > 10,000 nM) while introduction of a carboxylic acid greatly enhanced CRTh2 affinity (**50**; IC_{50} = 5 nM).



47: W = CO; X = H; R = Me
48: W = CO; X = OCF_3; R = Me
49: W = SO_2; X = H; R = Me
50: W = CO; X = H; R = $(CH_2)_2CO_2H$

3. CONCLUSIONS

While pharmacophore models have been put forward for CRTh2 antagonists, common structural features are evident from the reports summarized herein. Two lipophilic aryl ring systems oriented in an appropriate spatial arrangement relative to the carboxylic acid seem required. Linking these systems through an amide or sulfonamide is preferred and may provide a hydrogen bond interaction with the receptor. On the other hand, ether, keto, and biphenyl linkages can also be employed, with an apparent requirement for reintroduction of another amide or sulfonamide system. In general, potent affinity for CRTh2 can be engendered along with selectivity relative to other prostanoid receptors; however, additional selectivity screening is rarely reported. Differential selectivity profiles may impact the clinical progression of these antagonists. Protein binding data are also scant but will certainly play a role, particularly given the nonspecific binding typical of carboxylic acids [27]. Preclinical pharmacokinetics disclosed to date have been quite good for CRTh2 antagonists, and this seems to be translating well into human studies.

Ultimately, clinical profiles consistent with once daily dosing are expected to be advantageous over twice daily dosing regimens given the chronic nature of allergic disease and the need for patient adherence. Additional human efficacy data that could benchmark the scope of the single agent anti-inflammatory activity of CRTh2 antagonists relative to existing therapies (*i.e.*, corticosteroids) and in combination are anxiously awaited.

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