Novel Selective Orally Active CRTH2 Antagonists for Allergic Inflammation Developed from in Silico Derived Hits

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Abstract: Hits from an in silico derived focused library for CRTH2 were transformed into highly selective antagonists with favorable ADME properties. Oral administration of 4-bromo-2-(1-phenyl-1*H*-pyrazole-4-carbonyl)phenoxyacetic acid (**19**) inhibited peribronchial eosinophilia and mucus cell hyperplasia in a mouse model of allergic asthma, supporting the therapeutic potential of this novel compound class. In addition, this selective pharmacological tool compound provides further evidence for CRTH2 as a relevant therapeutic target for treatment of Th2- and eosinophil-related inflammation.

Prostaglandin D_2 (PGD_2) is the major prostanoid released by IgE-activated mast cells, and it has been implicated as a major contributor in various inflammatory conditions, including asthma and allergic diseases.[1,2] PGD_2 interacts with two G-protein-coupled 7TM[a] receptors, i.e., the DP (DP1) receptor that was the first receptor for PGD_2 to be identified[3] and the DP2 or CRTH2 receptor that was discovered later.[4] The DP1 receptor belongs to the classical prostanoid receptor cluster, and it is found on mucus-secreting goblet cells, bronchial epithelia, Th2 cells, and eosinophils. The CRTH2 receptor is selectively expressed on Th2 cells, eosinophils, and basophils, all of which are implicated in asthma and allergic reactions.[4] In addition to PGD_2 a number of other arachidonate metabolites activate the receptor, i.e., the thromboxane A_2 (TXA_2) metabolite 11-dehydro-TXB_2,[5] Δ^{12}-PGJ_2, and 15-deoxy-$\Delta^{12,14}$-PGJ_2,[6] which may contribute to allergic inflammation. The Th2 cells are known as central orchestrators of allergic asthma, driving IgE response and eosinophilia. Notably, PGD_2-induced chemotaxis in Th2 cells, eosinophils, and basophils is mediated by CRTH2 but not DP1.[4] These observations support the rational for development of selective CRTH2 antagonists for treatment of asthma and other allergic diseases.[7] DP antagonists displaying efficacy in in vivo models of allergy and asthma have been developed,[8] but in vivo activity of selective antagonists for the CRTH2 receptor is yet to be seen.

We have recently described a physicogenetic approach to identify relationships between 7TM receptors with respect to the physicochemical nature of the ligand binding site in the 7TM bundle.[9] When applied to CRTH2, we identified angiotensin AT1 and AT2 as related receptors and incorporated this information in the design of a pharmacophore that was used for in silico screening.[9] Here, we describe the identification of ligands, their transformation into drugable molecules, and their characterization as highly selective CRTH2 ligands with a favorable ADME profile. Furthermore, we show that oral administration of a selective CRTH2 antagonist effectively inhibited peribronchial eosinophilia and mucus cell hyperplasia in a mouse model of allergic asthma, supporting their therapeutic potential.

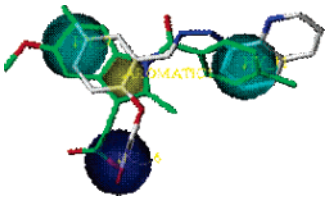

Figure 1. Indomethacin (light-green) and compound **1** (light-gray) superimposed with pharamacophore: green, hydrophobic; yellow, aromatic; blue, negative site.

Table 1. Hit Rate of Different Compound Collections from First and Second Round Libraries

size	no.	chemical class	hits <10 μM	hits <1 μM
143	first	third-party libraries	26 (18%)	3 (2.1%)
456	first	in-house library	31 (6.8%)	8 (1.8%)
40	first	AT antagonists	10 (25%)	0
12	first	indomethacin analogues	5 (42%)	0
30	first	aromatic acids	0	0
231	second	in-house hit analogues	33 (14%)	7 (3.0%)
174	second	in-house library	53 (30%)	8 (4.6%)

A pharmacophore model was derived using the information of how angiotensin AT1 and AT2 ligands where modeled to bind in their respective receptors and the corresponding binding site information of the CRTH2 receptor. The pharmacophore contains a negatively charged site and three hydrophobic regions, which can encompass the previously described CRTH2 agonist ligand indomethacin (Figure 1).[10]

When the pharmacophore model was applied on AT antagonists, 78 of 132 were accepted by the model. In silico mining of about 1.2 million compounds from a selection of compounds from third party vendors with this pharmacophore identified 1742 hits that were filtered with respect to molecular weight, log *P*, and unwanted chemical groups to about 800 compounds from which 143 were manually selected to provide a high diversity. In addition, 456 compounds were retrieved from the in-house collection by the pharmacophore query when applying somewhat more relaxed requirements. A set of angiotensin antagonists, indomethacin analogues, and aromatic carboxylic acids were included in this first round library to investigate the potential of using alternative approaches to identify chemical starting points.

The outcome of screening this compound collection is detailed in Table 1. The public and the in-house derived libraries (599 compounds) produced 11 hits (1.8%) with IC_{50} <1 μM affinity in receptor binding and an overall hit rate of 9.5% with a cutoff of <10 μM. The acid reference set produced no binders, but a large number of indomethacin-related and angiotensin ligands with affinities of <10 μM were found. It is also notable that the pharmacophore-retrieved compounds show no strong affinity for the AT1 (Figure 2) or AT2 receptor (data not shown).

The in-house collection contained two hits with IC_{50} < 100 nM, of which the phenoxyacetic acid **1** was one (Table 2 and

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[a] Abbreviations: CRTH2, chemoattractant receptor-homologous molecule expressed on Th2 cells; 7TM, seven transmembrane.

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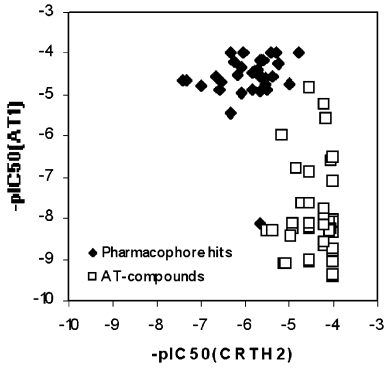
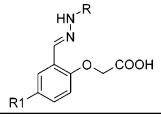
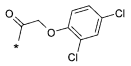
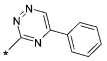
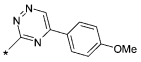
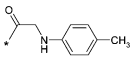
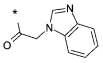


Figure 2. Selectivity of CRTH2 vs angiotensin AT1 receptor for pharmacophore hits (◆) and angiotensin antagonists (□).

Table 2. Binding Affinity and Functional Antagonism on hCRTH2 of Primary Hits Retrieved by in Silico Screening of Compound Collections[c]



compd	R1	R	IC_{50},[a] nM binding[b]	BRET[c]
1	Br		54 ± 1	643 ± 37
2	Br		255 ± 26	3490 ± 866
3	H		555 ± 49	6,320 ± 1,610
4	Br		89 ± 10	3,210 ± 449
5	H		1,580 ± 57	>100,000
6	H		3,660 ± 790	60,200 ± 14,600
7	H		12,800 ± 538	81,700 ± 7,490
8	H		11,200 ± 1530	>100,000

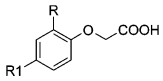
[a] Data are given as the mean of triplicates ± SEM. [b] [^{3}H]PGD_2 equilibrium competition binding. [c] Antagonistic activity as inhibition of β-arrestin translocation measured in a BRET assay.

Figure 1). The close analogue **2** also showed appreciable affinity. However, the two hits contain an unwanted hydrazone moiety that needs to be modified into a more drugable entity.

From our in-house collection, we retrieved additional 231 structural analogues to the hits from the different series and 174 compounds using the pharmacophore query combined with hit information. This second round library produced 86 compounds (21% "hit rate") with activities better than 10 μM and 15 compounds (3.7%) with IC_{50} < 1 μM and gave additional SAR information that was used in the following work.

A reasonable number of additional hits belonging to the phenoxyacetic acid class were identified (Table 2). The acylhydrazone **3** displayed appreciable binding affinity for the CRTH2 receptor. The positive influence of the para-bromo substituent was indicated when comparing **4** with **5** even if the influence of the methoxy group also could contribute to the lower activity of **5**. The other des-bromo derivatives, **6**−**8**, showed modest affinity in the primary screen, and in this light the activity of the acylhydrazone **3** is even more encouraging. All compounds besides **1** show a modest or poor functional

Table 3. Binding Affinity and Functional Antagonism on hCRTH2 of Small Phenoxyacetic Acid Derivatives



compd	R1	R	IC_{50},[a] nM binding[b]	BRET[c]
9	H	HCO−	1970 ± 498	50000 ± 16400
10	Br	HCO−	124 ± 43	481 ± 157
11	Br	CH_3CO−	510 ± 72	4520 ± 1060
12	Br	PhCO-	53 ± 2.4	437 ± 28
13	Br		391 ± 100	2650 ± 742
14	Br	*t*-Bu	61 ± 3.7	423 ± 116
15	Br	$HOCH_2$−	886 ± 82	6870 ± 1150

[a] Data are given as the mean of triplicates ± SEM. [b] [^{3}H]PGD_2 equilibrium competition binding. [c] Antagonistic activity as inhibition of β-arrestin translocation measured in a BRET assay.

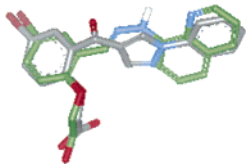


Figure 3. Original hit **1** (light-green) superimposed with pyrazole **19** (gray).

activity using a bioluminescence resonance energy transfer (BRET) assay.[11]

To broaden the SAR in this substance class, additional simple members were identified and investigated (Table 3). It is interesting that the simple formyl derivatives **9** and **10** show substantial binding affinity, the para-bromo derivative being functionally much more active. Notably, the acetyl **11** and isoxazole analogue **13** display slightly lower activity than the corresponding formyl derivative **10**. The benzoyl **12** and *tert*-butyl derivative **14** showed pronounced activity, whereas the primary alcohol **15** was less active. Thus, a picture was emerging of para-substituted phenoxyacetic acid as a scaffold with strong inherent affinity for the CRTH2 receptor, whereas the R group in the 2-position could vary considerably in size.

On the basis of this structural information, we explored various 2-substituted phenoxyacetic acid derivatives and made flexible superimpositions with the most potent hits as templates. We investigated compounds having a carbonyl moiety attached to the phenoxy group and a steric match with **1**. For example, we found the 2-(1-phenyl-1*H*-pyrazole-4-carbonyl)phenoxyacetic acid class (**VI**) to overlay effectively with the first hit **1** as shown in Figure 3. The distal phenyl group in **VI** is perfectly positioned over the pyridyl part of the quinoline in **1**, which is not possible with the less potent **2**.

A number of these compounds **VI** were synthesized according to Scheme 1. The pyrazole core was made by base-catalyzed condensation of arylhydrazines **III** with the 3-formylchromones **II**, which were obtained from the corresponding acetophenones **I** under Vilsmeyer−Haack conditions by a known method.[12] The unmasked phenol group in **IV** was alkylated under standard conditions with ethyl bromacetate to produce **V**, which were hydrolyzed with lithium hydroxide to give the desired compound class. The 4-phenyl derivatives **23**−**25** were obtained by Suzuki coupling of **26** and the corresponding phenylboronic acids at conditions giving simultaneous hydrolysis of the esters.

Most of the compounds possessed high binding and functional antagonistic activity for the CRTH2 receptor (Table 4). The results from the two assays for all 31 compounds correlated

Scheme 1

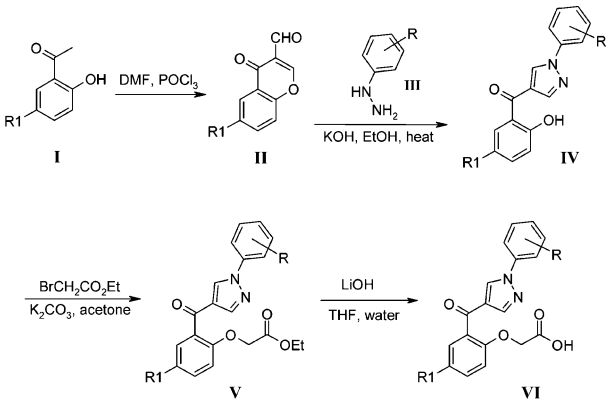
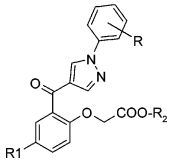


Table 4. Binding Affinity and Functional Antagonism on hCRTH2 of Designed Pyrazoles **VI**



				IC_{50},[a] nM	
compd	R_2	R1	R	binding[b]	BRET[c]
16	H	H	H	510 ± 24	5350 ± 1650
17	H	F	H	108 ± 24	1320 ± 105
18	H	Cl	H	15 ± 1.4	185 ± 10
19	H	Br	H	1.5 ± 0.5	24 ± 10
20	H	Me	H	48 ± 3.3	587 ± 140
21	H	OMe	H	151 ± 37	4200 ± 810
22	H	NO_2	H	47 ± 11	236 ± 34
23	H	Ph	H	42 ± 7.8	485 ± 24
24	H	4-ClC_6H_4	H	37 ± 8.3	448 ± 59
25	H	3,5-$F_2C_6H_3$	H	13 ± 2.9	147 ± 4.4
26	Et	Br	H	165 ± 93	3000 ± 607
27	H	Br	*p*-OMe	3.6 ± 1.1	53 ± 15
28	H	Br	*p*-Cl	1.5 ± 0.7	17 ± 2.1
29	H	Br	*p*-Br	1.4 ± 0.5	13 ± 1.7
30	H	Br	*m*-Br	3.4 ± 1.1	31 ± 3.3
31	H	Br	*o*-Br	1.9 ± 0.6	12 ± 1.7

[a] Data are given as the mean of triplicates ± SEM. [b] [^{3}H]PGD_2 equilibrium competition binding. [c] Antagonistic activity as inhibition of β-arrestin translocation measured in a BRET assay.

well with a slope close to unity (log BRET = 1.03 logBind + 1.01; r^2 = 0.96). For the series **VI**, the influence of the para substituent R1 was clearly seen with bromo **19** being more potent than chloro **18**, which again was more potent than fluoro **17**, with unsubstituted derivative **16** being the least active compound. The methyl **20** and the nitro **22** derivatives were equipotent and slightly more active than methoxy **21**. A large substituent was also allowed in the para position, as evidenced by the phenyl derivatives **23**−**25** of which the 3,5-difluoro derivative **25** was the best. The ethyl ester **26** was 100-fold less active than the corresponding acid **19**, which is in line with the expected requirement from the pharmacophore used (cf. negative site in Figure 1).

Various substituents (*R*) were also investigated in the Northern phenyl ring, and the para-halogen derivatives **28** and **29** were slightly more active than the para-methoxy **27** in the functional assay. The ortho-, meta-, and para-bromo derivatives (**29**, **30**, and **31**) showed comparable activity.

The parent compound **19** was further characterized with respect to its receptor selectivity and ADME profile to determine its potential for further investigations in allergic in vivo models. Thus, **19** showed less than 30% inhibition toward 43 receptors and transporters at 10 μM and <20% inhibition of the lipid mediator converting enzymes PLA_2, COX-1, COX-2, 12-LO, and 15-LO at 10 μM. The IC_{50} for the other PGD_2 receptor DP1 was over 100 μM, and no affinity was seen for the physicogenetically related AT1 and AT2 receptors. The high receptor binding affinity was also verified for the mouse CRTH2 receptor (IC_{50} = 3.2 nM).

Table 5. In Vitro and in Vivo ADME Profile of **19**

aqueous solubility (PBS, pH 7.4), μM	200
aqueous solubility (pH 1), μM	80
log *D* (water/*n*-octanol, pH 7.4)	0.64
Caco-2 (A to B), cm/s	8.7×10^{-6}
Caco-2 (B to A), cm/s	13×10^{-6}
metabolic stab. (S-9, rat) remaining, %	92
metabolic stab. (S-9, human) remaining, %	93
half-life (rat), h	2.7
bioavailability (rat), %	84

The ADME profile of **19** is shown in Table 5. The compound has suitable properties for oral administration with low log *D* value, good solubility, good metabolic stability in rat and human S9 fraction, and a bioavailability of 84% in rat. There were no indications of active transporters because the two Caco-2 parameters had comparable magnitudes.

The favorable properties of **19** prompted the exploration of its therapeutic potential in inflammatory airway disease. Mice were immunized by intraperitoneal injection of OVA using established protocols.[13] On the first day of the experiment and 14 days later mice were exposed once daily to aerosolized saline or OVA for 2 days. **19** (5 mg/kg) and vehicle control were given orally by gavage twice daily 1 h before each allergen challenge and 4 h after each challenge. Lung tissue specimens were collected and eosinophils were detected by histochemical visualization of cyanide-resistant eosinophil peroxidase activity. For histochemical detection of mucus-containing cells in lungs, fixed cryosections were stained with periodic acid Schiff (PAS) reagent to produce distinct purple-red granules in the mucus-containing cells. As shown in Figure 4, **19** significantly reduced the number of infiltrating eosinophils in the lung tissue, supporting its anti-inflammatory role in vivo. Furthermore, the number of mucus cells was significantly reduced compared to the vehicle group (Figure 4), indicating an effect on an early remodeling marker belonging to the characteristic features of asthma.

In conclusion, the present study shows efficient use of in silico screening of large compound collections to produce small target-specific libraries from which novel chemotypes of CRTH2 antagonist hits were identified. We also show the conversion of the initially found phenoxyacetic acid hits into druglike compounds having highly selective action on CRTH2 and good ADME properties. The in vivo studies clearly show the potential of this novel class of compounds for treatment of inflammatory disorders such as asthma. This report also provides additional evidence, by the use of selective pharmacological tool com-

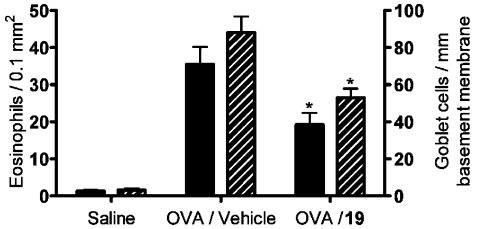


Figure 4. Inhibition of peribronchial eosinophilia (solid bars) and goblet cell hyperplasia (striped bars) in mice after oral administration of 5 mg/kg **19**.

pounds, that CRTH2 is a promising therapeutic target for limiting Th2- and eosinophil-related inflammation.

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Supporting Information Available: Synthetic procedures and compound characterization data, procedures for receptor cloning and transfection, binding assay, BRET assay, and in vivo models of OVA-induced allergic inflammation in mice. This material is available free of charge via the Internet at http://pubs.acs.org.

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