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Tetrahydroquinoline derivatives as CRTH2 antagonists

Jiwen Liu *, Yingcai Wang, Ying Sun, Derek Marshall, Shichang Miao, George Tonn, Penny Anders, Joel Tocker, H. Lucy Tang, Julio Medina

Amgen Inc., 1120 Veterans Boulevard, South San Francisco, CA 94080, USA

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ABSTRACT

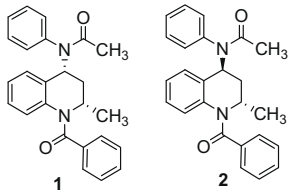
A series of tetrahydroquinoline-derived inhibitors of the CRTH2 receptor was discovered by a high throughput screen. Optimization of these compounds for potency and pharmacokinetic properties led to the discovery of potent and orally bioavailable CRTH2 antagonists.

CRTH2 (chemoattractant receptor-homologous molecule expressed on Th2 cells), also known as DP_2, is a G-protein coupled receptor related to the *N*-formyl peptide receptor (FPR) subfamily of chemoattractant receptors. Its endogenous ligand is prostaglandin D_2 (PGD_2). PGD_2 is the major cyclooxygenase product formed and secreted by activated mast cells during allergic reactions.[1–3] PGD_2 also signals through prostanoid D (DP or DP_1) receptor. The DP receptor is primarily expressed on airway epithelium, smooth muscle and platelets, while CRTH2 is selectively expressed on Th2 cells, T cytotoxic type 2 (Tc2) cells, eosinophils, and basophils.[4–6] Stimulation of CRTH2 by PGD_2 mediates multiple inflammatory responses, such as chemotaxis of eosinophils, basophils and Th2 cells, eosinophil activation and degranulation, cytokine production from Th2 T cells, and leukotriene production by mast cells.[7–13] Therefore, blockade of CRTH2 is likely to be beneficial in the treatment of allergic diseases triggered by PGD_2.

Several research groups, including ours, discovered that tetrahydroquinoline derivatives are potent CRTH2 antagonists.[14–19] These compounds were of special interest to us, because to our knowledge, it was the only series of CRTH2 antagonists devoid of a carboxylic acid moiety. Here we report the discovery, optimization and structure activity relationship (SAR) of the tetrahydroquinoline derivatives.

Tetrahydroquinoline **1** (Table 1), discovered in a high throughput screen, inhibited the binding of ^{3}H-PGD_2 to hCRTH2 receptors on 293 cells with an IC_{50} of 0.043 μM (Table 1).[20] Compound **1** also inhibited CRTH2 mediated cell migration in response to PGD_2 with an EC_{50} of 11 nM using hCRTH2 stably transfected CEM cells.[21] The

Table 1



1 2

Compd	Chiral Center	CRTH2 IC_{50}[a] in buffer (μM)	CRTH2 IC_{50}[a] in plasma (μM)
1	Racemic	0.043	1.05
2	Racemic	>10	
1a[b]	(2*S*,4*R*)	0.017	0.44
1b[b]	(2*R*,4*S*)	0.42	>10

[a] Displacement of ^{3}H-PGD_2 from the CRTH2 receptor expressed on 293 cells. Assay run in buffer containing 0.5% BSA or in 50% plasma. See Ref. 20 for assay protocol. Values are means of three experiments, standard deviation is ±30%.
[b] ee >99%.

* Corresponding author.
E-mail address: jiwenl@amgen.com (J. Liu).

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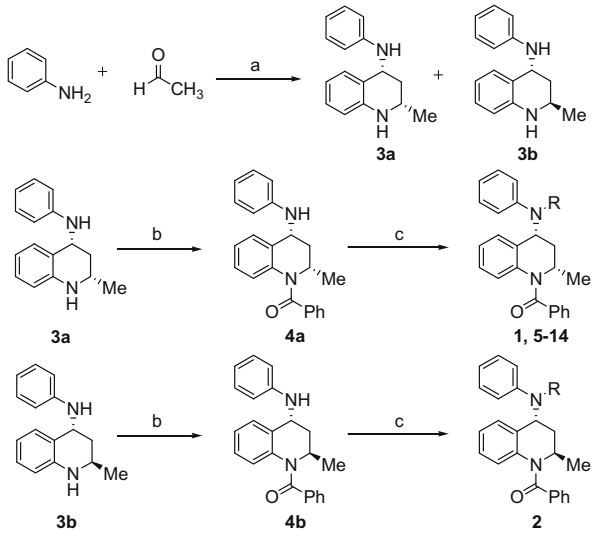
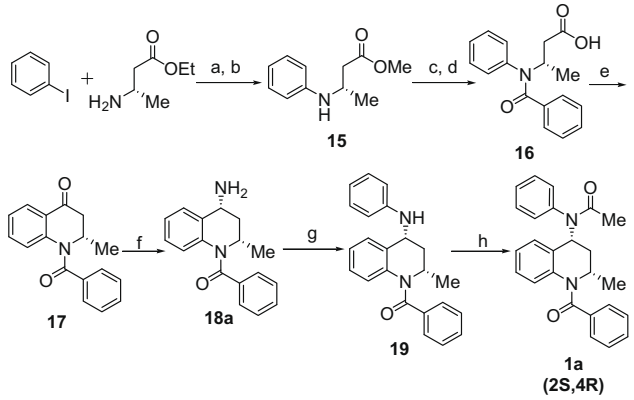
structure of compound **1** was determined to be *cis* by synthesis[22] (Scheme 1) and NMR studies.[23] Conversely, the *trans* isomer (**2**) had weak CRTH2 activity. Furthermore, the stereo-selective synthesis (Scheme 2) indicated the (2*S*,4*R*) enantiomer **1a** was responsible for the majority of the CRTH2 activity of racemic compound **1** (Table 1).

Compound **1** was synthesized according to Scheme 1. Reaction of aniline with acetaldehyde in ethanol at room temperature afforded a mixture of *cis*–*trans* isomers **3a** and **3b** in >95% yield. Separation of the *cis* isomers **3a** was achieved in 35% yield by recrystallization from 10% EtOAc/Hex. The *trans* isomer **3b** was obtained in 30% yield from the purification of the mother liquor using silica column chromatography. Selective acylation of **3a** and **3b** with benzoyl chloride at 1-*N* position afforded amides **4a** and **4b**, respectively, in 90% yield. Reaction of **4a** and **4b** with acetyl chloride afforded **1** and **2**, respectively, in 85% yield. Compounds **5–14** (Table 2) were synthesized from *cis* intermediate **4a** using reductive amination, sulfonylation or acylation.

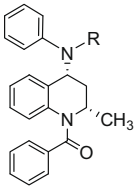


Scheme 1. Racemic synthesis of **1**, **2** and **5–14**. Reagents and conditions: (a) EtOH, rt, 24 h, 35% for compound **6** after recrystallization in 10% EtOAc/hexanes; (b) PhCOCl, triethylamine, DCM, rt, 24 h, 90%; (c) for amines: aldehydes, $Na(OAc)_3BH$, $ClCH_2CH_2Cl$, rt, 20 h, ~80%; for sulfonamides: sulfonyl chloride, DMAP, pyridine, rt, 3 h, 60%; for amides, acid chlorides, NaH, THF, rt, 20 h, 85%.



Scheme 2. Stereo-selective synthesis of **1a**. Reagents and conditions: (a) CuI, potassium carbonate, DMF, water, 90 °C, 48 h, 70%; (b) $SOCl_2$, MeOH, rt, 12 h, 90%; (c) PhCOCl, triethylamine, DCM, rt, 24 h, 90%; (d) LiOH, THF/MeOH/water, rt 4 h, 95%; (e) oxalyl chloride, DMF, DCM, 0 °C–rt, 3 h, then $AlCl_3$, DCM, 0 °C–rt, 12 h, 60%; (f) ammonium acetate, sodium cyanoborohydride, MeOH, 70 °C, 2 days, 85%; (g) phenyl boronic acid, pyridine, DMF, copper(II) acetate, air, 60 °C, overnight, 20%; (h) acetyl bromide, NaH, THF, 0 °C–rt, 3 h, 85%.

Table 2



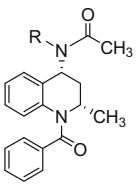
Compd[a]	R	CRTH2 IC_{50}[b] in buffer (μM)
1	–COMe	0.043
4a	–H	>50
5	$-CH_2CH_3$	3.17
6	$-SO_2Ph$	5.50
7	–COPh	0.105
8	$-CO(CH_2)_3CH_3$	0.064
9	$-CO(CH_2)_2CO_2H$	0.005
10	$-CO(CH_2)_2CO_2NH_2$	0.029
11	$-COCH_2CO_2H$	0.54
12	$-CO(CH_2)_3CO_2H$	0.022
13	$-COCH{=}CHCO_2H$	2.28
14	$-CO(1,3\text{-}Ph)CO_2H$	40.3

[a] Mixture of racemic mixture of (2*S*,4*R*) and (2*R*,4*S*) enantiomers.
[b] Displacement of ^{3}H-labeled PGD_2 from the CRTH2 receptor expressed on 293 cells. See Ref. 20 for assay protocol. Values are means of three experiments, standard deviation is ±30%.

The stereo-selective synthesis (Scheme 2) of **1a** began with a CuI catalyzed coupling of iodobenzene with the (*S*)-β-amino acid ester.[24] Amide formation of the coupling product (**15**) with benzoyl chloride followed by ester hydrolysis yielded acid **16**. Conversion of the carboxylic acid to the acid chloride followed by an intramolecular Friedel–Crafts acylation provided ketone **17**.[25] Reductive amination with ammonium hydroxide produced primary amine **18a**, which was coupled with phenyl boronic acid in the presence of copper acetate to give compound **19**.[14] Reaction of **19** with acetyl bromide afforded compound **1a** ((2*S*,4*R*)-enantiomer) with >99% ee. Compound **1b** ((2*R*,4*S*)-enantiomer) was obtained from chiral HPLC separation of racemate **1**.[26]

Compounds **22, 24** and **25** (Table 3) were synthesized according to Scheme 3. Reductive amination of ethyl acetoacetate with aniline afforded ester **20**. Saponification of **20** followed by intramolecular Friedel–Crafts acylation afforded ketone **21**.[27] Amide formation with benzoyl chloride followed by a reductive amination yielded compound **18**. Finally, compound **22** was obtained from acetamide formation of **18** with acetyl bromide. Compounds **24**

Table 3



Compd[a]	R	CRTH2 IC_{50}[b] in buffer (μM)
1	Ph	0.043
22	H	3.62
24	Et	0.25
25	Bn	0.43

[a] Mixture of racemic mixture of (2*S*,4*R*) and (2*R*,4*S*) enantiomers.
[b] Displacement of ^{3}H-labeled PGD_2 from the CRTH2 receptor expressed on 293 cells. See Ref. 20 for assay protocol. Values are means of three experiments, standard deviation is ±30%.