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Potent, Selective, and Orally Active CRTh2 Antagonists for Allergic Disease

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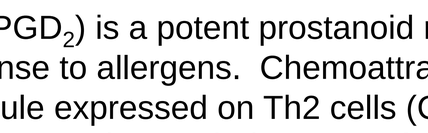
Abstract

Prostaglandin D_2 (PGD_2) is a potent prostanoid released from mast cells in response to allergens. Chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTh2, also known as DP2), a G-protein coupled receptor for PGD_2 and related metabolites, mediates chemotaxis/activation of basophils, eosinophils and Th2 lymphocytes along with production of IL-4, IL-5 and IL-13 from this subset of lymphocytes. Selective antagonism of CRTh2 offers a therapeutic approach for the treatment of allergic disease and, accordingly, drug discovery efforts were initiated. A set of substituted phenyl acetic acids were prepared and evaluated for binding affinity to the CRTh2 receptor. Selectivity over related prostanoid receptors was also evaluated. In the event, compound **2x** (2-(4-(4-(4-chlorophenethylcarbamoyl)phenoxy)-3-cyanophenyl)acetic acid) was identified as a potent, selective, functionally active CRTh2 antagonist. Moreover, compound **2x** demonstrated good plasma exposure in rodents upon oral dosing and provided protection from inflammation in a murine model of delayed-type hypersensitivity.



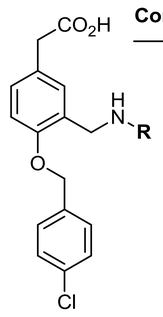
Compound **2x**
CRTh2 IC_{50} = 44 nM

Background

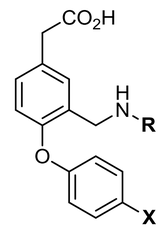
- Prostaglandin D_2 (PGD_2) is a potent prostanoid released upon mast cell activation and links early and late phase allergen responses[1]
- CRTh2 is the biologically relevant receptor for PGD_2 and its more stable metabolites[2]
- Current therapies do not modulate PGD_2 release or its actions
- CRTh2 is expressed on esoinophils, basophils & Th2 cells
  - CRTh2 activation results in chemotaxis
  - CRTh2 stimulation yields IL-4, 5 & 13 from Th2 cells without co-stimulation
- CRTh2 KO mice have diminished responses to allergic challenge with decreased IL-4, IL-13, IgE, mucus production, eosinophil migration & airway hyperresponsiveness versus wild type
- A weak, non-selective CRTh2 antagonist with modest efficacy, is approved for allergic rhinitis in Japan (Ramatroban®)
- Selective CRTh2 antagonists that are in clinical development have reported positive results in allergic disease indications[3]
  - FEV_1 improvements over baseline and versus placebo in asthma patients
  - Improvements in peak expiratory flow in asthma patients
  - Reduced serum IgE levels and sputum eosinophil counts in asthma patients
  - Improved nasal symptom scores in allergic rhinitis patients[4]

1. R. Pettipher, T. T. Hansel, R. Armer, *Nature Rev. Drug Discovery* 2007, **6**, 313.
2. G. Philip, J. van Adelsberg, T. Loeys, N. Liu, P. Wong, E. Lai, B. Dass, T. F. Reiss, *J. Allergy Clin. Immunol.* 2009, **124**, 942.
3. N. Barnes, I. Pavord, A. Chuchalin, J. Bell, M. Hunter, M. Payton, L. P. Collins, R. Pettipher, J. Steiner, M. Perkins, *Abstract 3267*, ERS Meeting, Vienna, Austria, 2009.
4. Actelion press release, May 23, 2011.

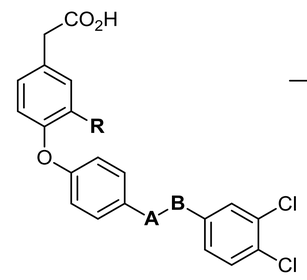
Structure Activity Relationships (vs. CRTh2 receptor binding in 0.1% BSA)



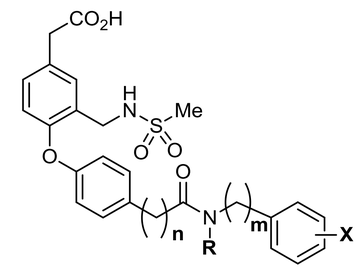
Compound	R	CRTh2 IC_{50} (nM)
1a	COPh	3574
1b	COPh (4-Cl)	4325
1c	COPh (2-Cl)	2980
1d	CO(4-Pyridine)	2800
1e	CO(3-Pyridine)	500
1f	$COCH_2Ph$(4-Cl)	2488
1g	$COCH_2Ph$(2,4-diCl)	650
1h	SO_2Ph(4-F)	1690



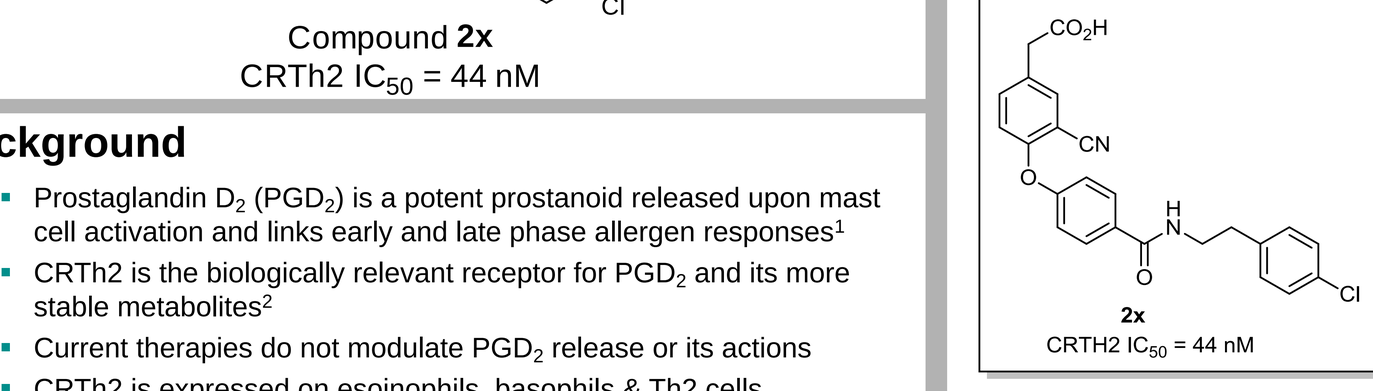
Compound	R	X	CRTh2 IC_{50} (nM)
2a	SO_2Ph(4-F)	H	6324
2b	SO_2Me	H	>25,000
2c	COMe	H	>25,000
2d	CO(4-Pyridine)	H	>25,000
2e	CO(3-Pyridine)	H	1986
2f	SO_2Ph(4-F)	Cl	820
2g	SO_2Ph(4-F)	NH(CO)Ph(4-Cl)	849
2h	SO_2Ph(4-F)	NH(CO)Ph(3-Cl)	294
2i	SO_2Me	NH(CO)Ph(3,4-Cl_2)	20
2j	SO_2Ph(4-F)	NH(CO)Ph(3,4-Cl_2)	20
2k	COMe	NH(CO)Ph(3,4-Cl_2)	18
2l	CO(4-Pyridine)	NH(CO)Ph(3,4-Cl_2)	40
2k	CO(3-Pyridine)	NH(CO)Ph(3,4-Cl_2)	15



Cmpd	R	A-B	CRTh2 IC_{50}	tPSA	MW	Caco-2 (Pe AB; BA)
2i	$CH_2N(H)SO_2Me$	N(H)CO	20 nM	122	523	1.4; 4.3 x10^{-6} cm/s
2l	$CH_2N(H)SO_2Me$	CO(NH)	40 nM	122	523	10.4; 5.2 x10^{-6} cm/s
2m	CN	N(H)CO	33 nM	99	441	2.2; 15.9 x10^{-6} cm/s
2n	Cl	N(H)CO	60 nM	75	450	11.6; 18.1 x10^{-6} cm/s
2o	CN	CON(H)	16 nM	99	441	69.6; 27.5 x10^{-6} cm/s



Cmpd	n	m	R	X	CRTh2 IC_{50}
2p	0	0	H	H	561 nM
2q	0	1	H	H	2265 nM
2r	0	2	H	H	99 nM
2s	1	0	H	H	6854 nM
2t	1	1	H	H	259 nM
2u	1	1	CH_3	H	2541 nM
2v	1	2	H	H	736 nM
2w	0	2	H	Cl	15 nM



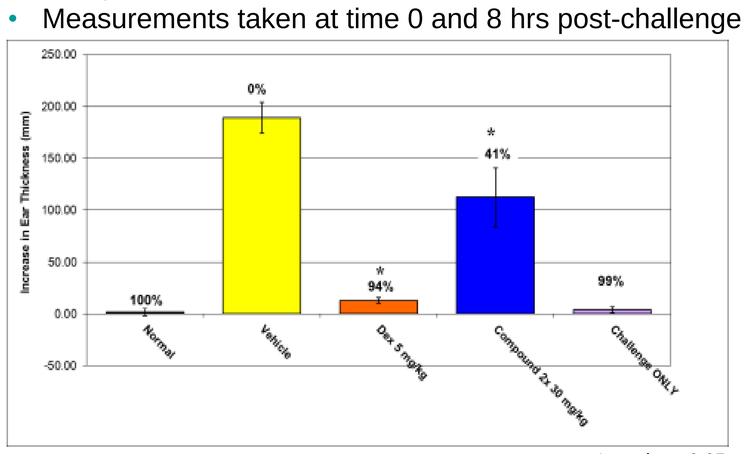
2x
CRTH2 IC_{50} = 44 nM

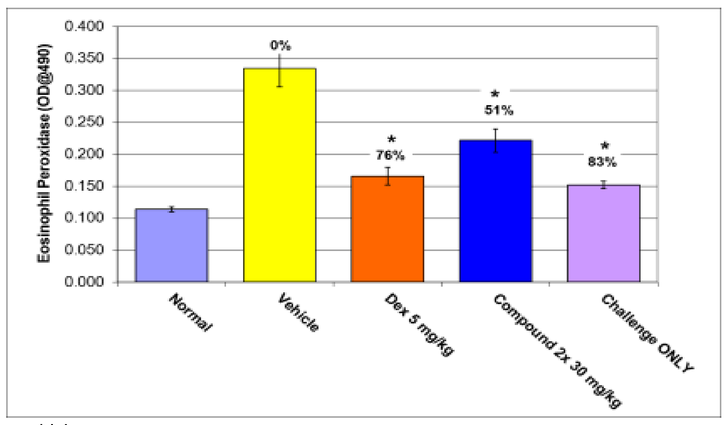
Enzyme or Receptor	Activity at 10 μM
COX-1	6%
COX-2	0%
CysLT1	14%
DP	8%
EP2	31%
EP4	2%

	Rat (1 mg/kg IV; 10 mg/kg PO)	Mouse (2 mg/kg IV; 20 mg/kg PO)
IV Cl (mL/min/kg)	6.97	9.07
PO Cmax (μg/mL)	0.52	4.13
PO AUCinf (μg-hr/mL)	8.49	30.7
F (%)	35.5	50.5

Murine Delayed-Type Hypersensitivity

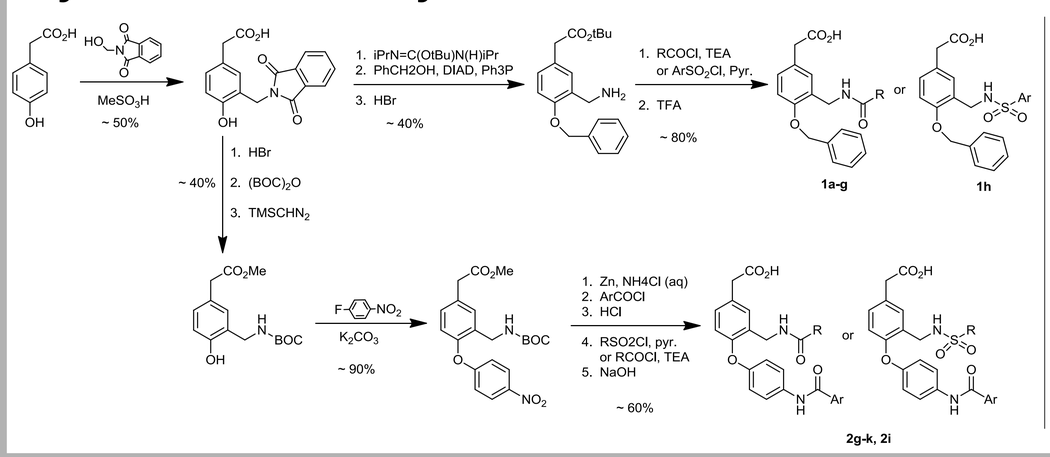
- Female Balb/c mice were sensitized to FITC with 0.5% solution on abdomen Day 0 and Day 1 (or not) then challenged with a 1.0% solution of FITC on the right ear on Day 7
- Animals (10 mice/group) were dosed (po) 30 min before treatment with either vehicle, Dexamethasone (Dex) or Compound **2x**
- Measurements taken at time 0 and 8 hrs post-challenge

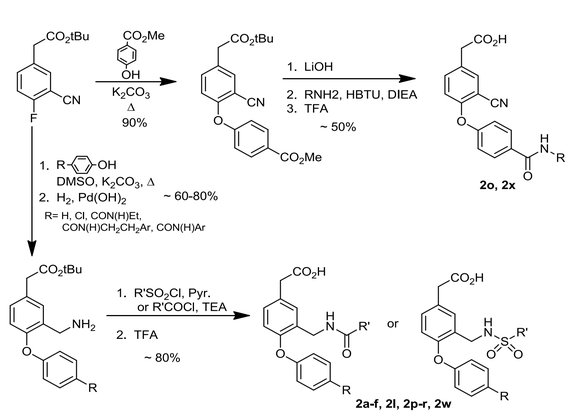




* p value <0.05 vs. vehicle

Synthetic Chemistry





Conclusions and Follow-up

Potent, selective and orally bioavailable CRTh2 antagonists based on a substituted biphenyl ether-acetic acid template have been discovered. Compound **2x** demonstrated good pharmacokinetics in rat and mouse along with efficacy in a mouse model of delayed-type hypersensitivity.

Additional drug discovery efforts led to the identification even more potent and selective CRTh2 antagonists, one of which* advanced to clinical studies.

* See S. Bell et al. "Safety, PK and PD of ARRY-502, a CRTh2 Antagonist, in Healthy Subjects with a History of Seasonal Allergies." As presented at the European Respiratory Society Annual Congress 2010, Barcelona, Spain, September 2010 (poster available at www.arraybiopharma.com)