Bioorganic & Medicinal Chemistry Letters 20 (2010) 1181–1185

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Novel selective thiazoleacetic acids as CRTH2 antagonists developed from in silico derived hits. Part 2

Marie Grimstrup, Øystein Rist, Jean-Marie Receveur, Thomas M. Frimurer, Trond Ulven [†], Jesper M. Mathiesen, Evi Kostenis [‡], Thomas Högberg [*]

7TM Pharma A/S, Fremtidsvej 3, DK-2970 Hørsholm, Denmark

ARTICLE INFO

Article history:
Received 1 November 2009
Revised 2 December 2009
Accepted 2 December 2009
Available online 6 December 2009

Keywords:
CRTH2 antagonists
Chemoattractant receptor-homologous molecule expressed on Th2 cells
PGD2
Chemical libraries
Hit-to-lead
Structure–activity relationships
Molecular modeling

ABSTRACT

Structure–activity relationships have been established by exploring the eastern and western side of 5-thiazolyleacetic acids as CRTH2 (chemoattractant receptor-homologous molecule expressed on Th2 cells) antagonists. Benzhydryl motifs in the 2-position of the thiazole was found to be most advantageous. The 4-thiazole position should either carry 3- or 4-fluorophenyl rings or a 4-pyridyl suitably substituted in the flanking 2-position. Several compounds with single digit nanomolar binding affinity and full antagonistic efficacy for human CRTH2 receptor were obtained. The compound series display a good PK profile and selectivity over a large number of other targets.

Prostaglandin D_2 (PGD_2) and one of its receptors CRTH2 (chemoattractant receptor-homologous molecule expressed on Th2 cells) have been implicated in the pathogenesis of various inflammatory conditions.[1] The CRTH2 receptor is expressed on various inflammatory cells, including Th2 cells, mediating their chemotaxis in response to PGD_2 and a number of other arachidonate metabolites such as 13,14-dihydro-15-keto-PGD_2, PGJ_2, $\Delta^{12}PGJ_2$, 15-deoxy-PGJ_2 and 11-dehydro-TXB_2.[1–3] The Th2 cells play a central role in allergic asthma, driving IgE response, eosinophilia and release of proinflammatory cytokines.[1,4] Activation of the CRTH2 receptor also mediates the release of histamine from basophils[1,5], induces respiratory burst and degranulation of eosinophils.[1,6] and affects apoptosis of Th2 cells.[7] Thus, CRTH2 antagonists are under development for the treatment of asthma and allergic disease.[8–10]

We have earlier described the hit-to-lead process of hits obtained from screening an in silico derived library that successfully delivered some novel chemotypes of CRTH2 antagonists (Fig. 1).[11–13] In this communication we describe and extension of the structure–activity relationships and the subsequent optimization of the thiazole derivatives **2**–**4** into selective and orally available compounds.

The compounds **2** and **3** have large lipophilic moieties on the western side whereas **4** on the eastern side. Superimpositions of the molecules when **2** and **3** are rotated around the thiazole-

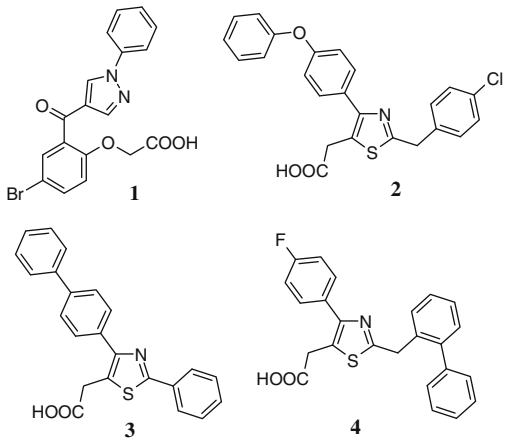


Figure 1. Representative chemotypes identified after hit to lead process of in silico screening hits. CRTH2 receptor binding IC_{50}: **1** (4 nM)[12], **2** (3.7 nM)[13], **3** (38 nM) and **4** (24 nM).[13]

* Corresponding author. Tel.: +45 3925 7760; fax: +45 3925 7776.
E-mail address: th@7tm.com (T. Högberg).
† Present address: Department of Physics and Chemistry, University of Southern Denmark, Campusvej 55, DK-5230 Odense, Denmark.
‡ Present address: Institute of Pharmaceutical Biology, University of Bonn, Nussallee 6, D-53155 Bonn, Germany.

0960-894X/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2009.12.015

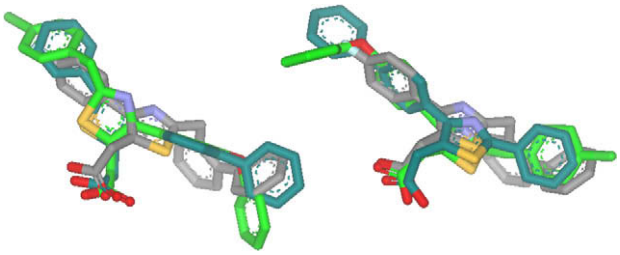


Figure 2. Superimpositions of the CRTH2 antagonists **2** (light green), **3** (dark green – kept in fixed position) and **4** (grey) in rotated low energy conformations (left) and in receptor-bound conformations (right).

carboxyl axis show a reasonable overlap of the essential carboxylic function interacting with ^{210}Lys and the larger aromatic clusters (Fig. 2 left). However, inspection of the likely receptor-bound conformations of **2**–**4** also invoking a critical interaction between the thiazole nitrogen and ^{266}Ser implies separate pharmacophoric features in eastern and western sides (Fig. 2 right). Hence, we decided first to explore the lipophilic eastern side pocket further by making a diverse library of derivatives shown in Table 1.

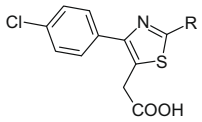
The thiazoles were prepared from 3-bromo-4-oxo-butyric acid derivatives and thioamides in accordance with the procedure described earlier by microwave assisted heating in DMF (Scheme 1).[13] The compounds were characterized with respect to binding affinity and functional antagonistic activity using a bioluminescence resonance energy transfer (BRET) assay in HEK385-7 cells (Table 2).[12–14]

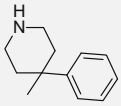
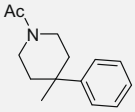
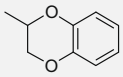
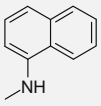
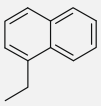
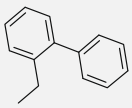
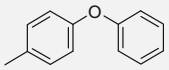
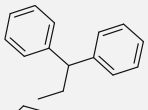
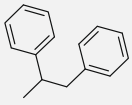
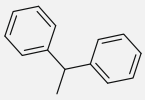
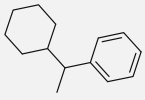
The smaller eastern R groups NH_2 (**5**), methyl (**6**) and 2-furanyl (**7**) gives no or a poor activity. A phenyl and a benzyl moiety (**8,9**) give submicromolar binding affinity, but ethyl substitution of the benzyl carbon leads to loss of functional activity (**10**). Notably, the piperidine substituted benzyl lacks functional activity whereas the N-acetylated analogue displays good affinity and functional activity (**11** vs **12**). The nitrogen derivatives **13–15** with different linker length display activities comparable to benzyl derivative **9** and the amide **16** as well. The oxymethylene linked molecule **19** has considerable higher affinity than the sulfur analogues **17** and **18**. Constraining the oxymethylene linker into the bicyclic **20** leads to reduced potency. The naphthyl derivative **21** has affinity comparable to the phenyl analogue **13**, but it has a poor functional efficacy. However, the corresponding carba analogue **22** has full antagonistic efficacy. A number of compounds **23–27** having two phenyl rings attached in conformationaly less constrained combinations display good binding affinities with the benzydryl **27** being a potent and full functional antagonist. Notably, changing one phenyl with a cyclohexyl (**28**) leads to a considerable loss in affinity and a complete loss in functional activity This finding is corroborated by docking a compound with benzhydryl showing a tight interaction with aromatic residues (Phés, Trp, Tyr) in the hydrophobic pocket (vide infra Fig. 3).

We decided to further explore the benzhydryl series by making a large set of compounds with substitutions that could affect physicochemical properties and metabolic behavior (Table 2). The compounds were synthesized according to the method in Scheme 1 from the appropriate 3-bromo-4-oxo-buturic acid derivative or by Suzuki coupling of the 4-thiazolyltriflate as outlined in Scheme 2. The required 4-hydroxy-thiazol-5-ylacetic acid was obtained by condensation with 2-mercapto-succinic acid and bis(4-fluorophenyl)acetonitrile in a modest yield.

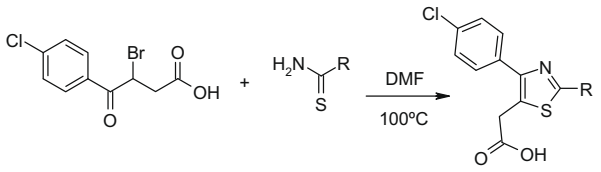
Initially, the **27** lead compound was modified by making *para* chloro, fluoro and methoxy derivatives (**29–32**), which showed retained affinity and functional activity in contrast to the 2-pyridyl modification **33** that lost in activity. Introduction of a pyridyl system in the methoxy compound (**34**) gave a reduced activity

Table 1
Binding affinity and functional antagonism on hCRTH2 of 4-(*p*-chlorophenyl)thiazoleacetic acids



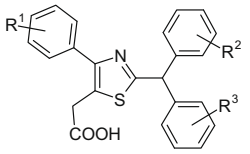
No.	R	IC_{50} bind[a] (μM)	IC_{50} BRET[b] (μM)
5	NH_2	>100	>100
6	Me	5.5	41
7	2-Furanyl	5.1	3.8
8[d]	Ph	0.55	0.96
9[d]	CH_2-Ph	0.18	4.1
10	CH(Et)-Ph	0.19	>100
11		2.9	>100
12		0.052	0.55
13[d]	NH-Ph	0.10	1.3
14	NH–CH_2-Ph	0.44	2.3
15	NH–CH_2–CH_2-Ph	0.65	0.39
16	NH–CO-Ph	0.52	0.87
17	CH_2–S-Ph	0.25	0.45[c]
18	CH_2–SO_2–(*p*-Cl-Ph)	1.5	0.73
19	CH_2–O–(*p*-Cl-Ph)	0.032	0.37
20		0.50	2.0
21		0.15	0.096[c]
22[d]		0.041	0.57
23[d]		0.041	0.51
24[d]		0.093	1.3
25		0.34	32[c]
26		0.056	0.51
27		0.014	0.060
28		0.53	>100

[a] [^{3}H]PGD_2 equilibrium competition binding in hCRTH2 transfected HEK385-7 cells; except for **6**, **7** and **9** which were tested in hCRTH2 transfected COS7 cells.
[b] Antagonistic activity as inhibition of β-arrestin translocation measured in a bioluminescence resonance energy transfer (BRET) assay in HEK385-7 cells. All compounds displayed efficacy above 50% unless noted. All values are single or mean of double determinations.
[c] Compounds having 30–35% antagonistic efficacies.
[d] Compounds described in Part 1.[13]



Scheme 1.

Table 2
Binding affinity and functional antagonism on hCRTH2 of (2-benzhydryl-4-phenyl-thiazol-5-yl)acetic acids



No.	R^1	R^2	R^3	IC_{50} bind[a] (nM)	IC_{50} BRET[b] (μM)
27	4-Cl	H	H	14	0.060
29	4-Cl	4-Cl	H	45	0.075
30	4-Cl	4-F	H	17	0.036
31	4-Cl	4-F	4-F	9.7	0.18
32	4-Cl	4-OMe	H	8.4	0.076
33	4-Cl	2-py[e]	H	810	1.9[c]
34	4-Cl	2-py[e]	4-OMe	61	0.31
35	4-Cl	6-Cl, 2-py[e]	H	3200	>100
36	H	H	H	570	0.37
37	H	4-F	4-F	16	0.24
38	4-F	H	H	8.7	0.077
39	3-F	H	H	2.9	0.029
40	4-OMe	H	H	370	0.91[c]
41	3,4-F_2	H	H	4.1	0.043
42	4-CF_3	H	H	1100	>100
43	2-OMe, 5-Cl	H	H	9400	>100
44	2,5-OMe_2	H	H	>10^5	>100
45	4-F	4-Cl	H	14	0.079
46	4-F	3,4-F_2	H	10	0.064
47	4-F	4-OMe	H	3.6	0.031
48	4-F	4-OH	H	3.4	0.030
49	4-F	4-OMe	4-OMe	3.9	0.031
50	4-F	4-F	4-F	7.5	0.072
51	3-F	4-F	4-F	1.4	0.018
52	3,4-F_2	4-F	4-F	3.5	0.041
53	3,5-F_2	4-F	4-F	35	0.34
54	4-CN	4-F	4-F	150	1.5[d]
55	3-CN	4-F	4-F	20	0.22
56	4-F, 3-CN	4-F	4-F	57	0.52
57	4-H_2NSO_2	4-F	4-F	1500	>100
58	3-H_2NSO_2	4-F	4-F	140	0.71[c]
59	3-$MeSO_2$	4-F	4-F	590	6.3[d]
60	3-$MeSO_2NH$	4-F	4-F	40	0.37

[a] As in Table 1, but all compounds displayed efficacy above 80% unless noted.
[b] As in Table 1, but all compounds displayed efficacy above 80% unless noted.
[c] Compound having 55–60% antagonistic efficacy.
[d] Compound having 30–35% antagonistic efficacy.
[e] One phenyl ring replaced with 2-pyridyl system.

and the chloropyridyl derivative **35** lost substantially in activity. The importance of the halogen substituent in the western ring was evidenced by comparing the unsubstituted **36** and the methoxy **40** compounds with the chloro (**27**) and fluoro derivatives (**38**, **39** and **41**). Introduction of *p*-fluoro groups (**37**) gave an increase in affinity but not functional activity over **36**. The larger pseudo halogen trifluoromethoxy derivative **42** and the *ortho* methoxy derivatives (**43**, **44**) are devoid of functional activity. Thus, a set of western mono fluoro derivatives **45**–**51** all showed very high binding affinity and full functional antagonistic activity. Notably, methoxy and hydroxyl groups are allowed in the *para*

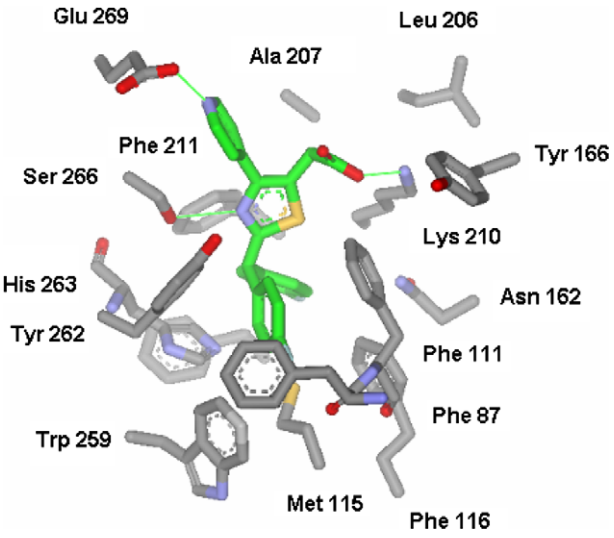
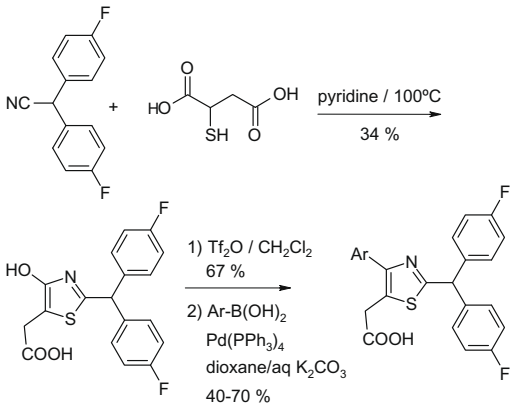


Figure 3. Docking of 4-pyridyl derivative **67** in hCRTH2 receptor.

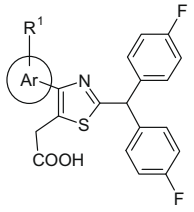


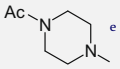
Scheme 2.

positions of the eastern phenyl rings. The 3,4-difluorinated compound **52** displays comparably high activity whereas a 10-fold is lost for the 3,5-diflouro derivative **53**. A *p*-cyano compound **54** drops more in activity than the *m*-cyano compounds **55** and **56**. The difference in *meta* and *para* substitution with polar groups are also shown by comparing the aminosulfonyl derivatives **57** and **58**. The corresponding methylsulfone **59** displays a poor functional and only partial activity, but the sulfonamide **60** is reasonably active.

As an extension of the exploration the western side we made a number of aromatic heterocyclic five- and six-ring systems using the Suzuki coupling method in Scheme 2 (Table 3). The 2-and 3-furanyl derivatives **61** and **62** had reasonable activity comparable to the 4-pyrazole derivative **63**. The methyl substituted 4-pyrazolyl **64** and the 3-pyrazolyl **65** were less active. The 3-pyridyl **66** was comparable to the best five-membered heterocycles whereas the 4-pyridyl compound **67** showed superior potency and full functional antagonistic activity. Docking studies also indicate the 4-pyridyl to be better positioned than 3-pyridyl to interact with ^{269}Glu in the receptor (cf. Fig. 3). Hence, we explored the 4-pyridyl subclass further by making modifications especially in the 2-position *ortho* to the pyridyl nitrogen (**68**–**80**). The 2-chloro **69** is comparable to the unsubstituted compound **67** whereas the 2-fluoro **68** is a 10-fold more active with subnanomolar binding affinity and 5 nM full functional antagonistic activity. Although,

Table 3
Binding affinity and functional antagonism on hCRTH2 of (4-aryl-2-benzhydryl-thiazol-5-yl)acetic acids

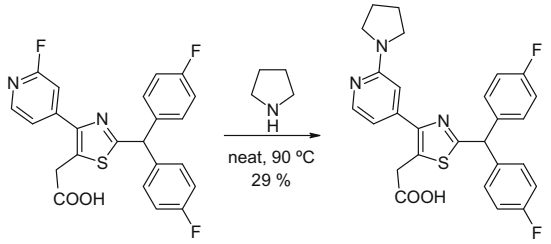


No.	Ar	R^1	IC_{50} bind[a] (nM)	IC_{50} BRET[b] (μM)
61	2-Furanyl	H	18	0.14
62	3-Furanyl	H	14	0.13
63		H	16	0.22
64		H	1300	3.5
65		H	280	3.3[d]
66		H	68	0.51
67		H	5.3	0.040
68	4-Pyridyl	2-F	0.48	0.0047
69	4-Pyridyl	2-Cl	3.1	0.039
70	4-Pyridyl	2,6-F_2	5.4	0.11
71	4-Pyridyl	2-Me	3.1	0.053
72	4-Pyridyl	2-MeO	29	0.38[c]
73	4-Pyridyl	2-OH	68	0.89[c]
74	4-Pyridyl	2-NH_2	4.8	0.064
75	4-Pyridyl	6-F, 2-NH_2	220	1.4[d]
76	4-Pyridyl	2-NHMe	25	0.17
77	4-Pyridyl	2-NMe_2	380	>100
78	4-Pyridyl		660	>100
79	4-Pyridyl		230	>100
80	4-Pyridyl		360	>100
81	3-Pyridyl	6-NH_2	100	0.50[c]
82	3-Pyridyl	5-Me, 6-NH_2	880	>100
83	3-Pyridyl	5-F	71	0.30

[a] As in Table 1, but all compounds displayed efficacy above 80% unless noted.
[b] As in Table 1, but all compounds displayed efficacy above 80% unless noted.
[c] Compound having 60–70% antagonistic efficacy.
[d] Compound having 30–35% antagonistic efficacy.
[e] Substituent in 2-pyridyl position.

we cannot explain the dramatic potency increase at present, it may be speculated that an irreversible binding mode is a contributing factor. This reactivity was also utilized by making some of the 2-substituted derivatives exemplified by the pyrrolidine derivative **79** (Scheme 3).

The 2-chloro derivative is also potentially subject to chemical instability which makes the potent 2-methyl **71** more attractive also with respect to masking the pyridyl against potential CYP interactions. The 2-methoxy (**72**) and 2-hydroxy (**73**) show 10-fold lower activity. The activity of the amines ranks according to alkylation degree with the primary amine **74** being more potent than the secondary amine **76** while the tertiary amines (**77**–**80**) lack functional activity. Finally, we explored some 3-pyridyl derivatives with 6-amino (**81**, **82**) with rather poor functional activity. The 5-flouro compound **83** was equipotent with the parent compound **66**.



Scheme 3.

Table 4
In vitro and in vivo ADME profile of representative compounds

	27	**47**
Aqueous solubility (PBS, pH 7.4)	154 μM	197 μM
Aqueous solubility (pH 1)	30 μM	3.4 μM
Log D (water/*n*-octanol, pH 7.4)	2.6	2.1
Plasma protein binding (rat)	98.5%	97.8%
Caco-2 (A to B)	69×10^{-6} cm/s	24×10^{-6} cm/s
Metabolic stab. (S-9, rat) Remain	27%	62%
Metabolic stab. (S-9, h) Remain	n.d.	40%
CYP2D6 inhibition (1 μM)	3%	6%
CYP3A4 inhibition (1 μM)	0%	0%
Half-life (rat)	3.3 h	5.8 h
Clearance (rat)	4.4 mL/min/kg	8.5 mL/min/kg
Bioavailability (rat)	70%	81%

The compound **27** having only a *p*-chlorophenyl group in the western side was further characterized with respect to its receptor selectivity showing less than 33% inhibition towards 41 receptors and transporters at 10 μM concentration. Furthermore, it showed less than 20% inhibition of the lipid mediator converting enzymes PLA_2, COX-1, COX-2, 12-LO and 15-LO at 10 μM concentration. The IC_{50} value for the other PGD_2 receptor DP1 was over 100 μM. Importantly no affinity was seen for the physicogenetically related AT1 and AT2 receptors that provided input to the pharmacophore used for the in silico generation of hits.[11,12] The ADME properties for **27** and **47** having an eastern 4-methoxy substituted are shown in Table 4. Both compounds display a favorable in vitro profile with good membrane permeability and physicochemical properties. The oral bioavailability and half-life are appreciable for both compounds, indicating that the methoxy group represents no metabolic liability as supported by a hepatic clearance of about 10% of hepatic blood flow for **47**. No CYP inhibitions were indicated for the 2D6 and 3A4 isoforms.

In summary, we have extensively explored the eastern and western side of 5-thiazolyleacetic acids. Functionalisation with substituted benzhydryl motifs in the 2-position of the thiazole was found to be most advantageous. The docking of this benzhydryl series also fit nicely into a pocket containing several aromatic residues. The 4-thiazole position should either carry 3- or 4-fluorophenyl rings or a 4-pyridyl suitably substituted in the flanking 2-position with a methyl group. The series display a good PK profile warranting further in vivo PD studies in inflammation and allergy models that will be described in subsequent reports.

Acknowledgments

The authors thank Joan Gredal, Stina Hansen, Rokhsana Andersen, Ann Christensen and Helle Zancho Andresen, for excellent technical assistance.

References and notes

1. Reviews with relevant references therein: (a) Pettipher, R. *Br. J. Pharmacol.* **2008**, *153*, S191; (b) Pettipher, R.; Hansel, T. T.; Armer, R. *Nat. Rev. Drug Disc.* **2007**, *6*, 313; (c) Kostenis, E.; Ulven, T. *Trends Mol. Med.* **2006**, *12*, 148; (d) Herlong, J. L.; Scott, T. R. *Immunol. Lett.* **2006**, *102*, 121; (e) Moore, M. L.; Peebles, R. S., Jr *J. Allergy Clin. Immunol.* **2006**, *117*, 1036.
2. (a) Nagata, K.; Hirai, H.; Tanaka, K.; Ogawa, K.; Aso, T.; Sugamura, K.; Nakamura, M.; Takano, S. *FEBS Lett.* **1999**, *459*, 195; (b) Hirai, H.; Tanaka, K.; Yoshie, O.; Ogawa, K.; Kenmotsu, K.; Takamori, Y.; Ichimasa, M.; Sugamura, K.; Nakamura, M.; Takano, S.; Nagata, K. *J. Exp. Med.* **2001**, *193*, 255.
3. Bohm, E.; Sturm, G. J.; Weiglhofer, I.; Sandig, H.; Shichijo, M.; McNamee, A.; Pease, J. E.; Kollroser, M.; Peskar, B. A.; Heinemann, A. *J. Biol. Chem.* **2004**, *279*, 7663.
4. Xue, L.; Gyles, S. L.; Wettey, F. R.; Gazi, L.; Townsend, E.; Hunter, M. G.; Pettipher, R. *J. Immunol.* **2005**, *175*, 6531.
5. Yoshimura-Uchiyama, C.; Iikura, M.; Yamaguchi, M.; Nagase, H.; Ishii, A.; Matsushima, K.; Yamamoto, K.; Shichijo, M.; Bacon, K. B.; Hirai, K. *Clin. Exp. Allergy* **2004**, *34*, 1283.
6. Gervais, F. G.; Cruz, R. P.; Chateauneuf, A.; Gale, S.; Sawyer, N.; Nantel, F.; Metters, K. M.; O'Neill, G. P. *J. Allergy Clin. Immunol* **2001**, *108*, 982.
7. Xue, L.; Barrow, A.; Pettipher, R. *J. Immunol* **2009**, *182*, 7580.
8. Reviews: (a) Ulven, T.; Kostenis, E. Curr. *Top. Med. Chem* **2006**, *6*, 1427; (b) Ly, T. W.; Bacon, K. B. *Exp. Opin. Invest. Drugs* **2005**, *14*, 769.
9. (a) Stearns, B. A.; Baccei, C.; Bain, G.; Broadhead, A.; Clark, R. C.; Coate, H.; Evans, J. F.; Fagan, P.; Hutchinson, J. H.; King, C.; Lee, C.; Lorrain, D. S.; Prasit, P.; Prodanovich, P.; Santini, A.; Scott, J. M.; Stock, N. S.; Truong, Y. P. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4647; (b) Sandham, D. A.; Adcock, C.; Bala, K.; Barker, L.; Brown, Z.; Dubois, G.; Budd, D.; Cox, B.; Fairhurst, R. A.; Furegati, M.; Leblanc, C.; Manini, J.; Profit, R.; Reilly, J.; Stringer, R.; Schmidt, A.; Turner, K. L.; Watson, S. J.; Willis, J.; Williams, G.; Wilson, C. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4794; (c) Royer, J. F.; Schratl, P.; Carrillo, J. J.; Jupp, R.; Barker, J.; Weyman-Jones, C.; Beri, R.; Sargent, C.; Schmidt, J. A.; Lang-Loidolt, D.; Heinemann, A. *Eur. J. Clin. Invest.* **2008**, *38*, 663; (d) Crosignani, S.; Page, P.; Missotten, M.; Colovray, V.; Cleva, C.; Arrighi, J.-F.; Atherall, J.; Macritchie, J.; Martin, T.; Humbert, Y.; Gaudet, M.; Pupowicz, D.; Maio, M.; Pittet, P.-A.; Golzio, L.; Giachetti, C.; Rocha, C.; Bernardinelli, G.; Filinchuk, Y.; Scheer, A.; Schwarz, M. K.; Chollet, A. *J. Med. Chem.* **2008**, *51*, 2227; (e) Uller, L.; Mathiesen, J. M.; Alenmyr, L.; Korsgren, M.; Ulven, T.; Högberg, T.; Andersson, G.; Persson, C. G. A.; Kostenis, E. *Respir. Res.* **2007**, 8. http://respiratory-research.com /content/pdf/1465-9921-8-16.pdf.
10. Clinical studies: (a) AZD1981 from AstraZeneca in asthma and COPD; http://www.clinicaltrials.gov (b) OC000459 from Oxagen in asthma and allergic rhinoconjunctivitis; http://www.clinicaltrials.gov (c) ADC3680 reported from Argenta. (d) AM211 reported from Amira Pharmaceuticals.
11. Frimurer, T. M.; Ulven, T.; Elling, C. E.; Gerlach, L.-O.; Kostenis, E.; Högberg, T. *Bioorg. Med. Chem. Lett* **2005**, *15*, 3707.
12. Ulven, T.; Receveur, J.-M.; Grimstrup, M.; Rist, Ø.; Frimurer, T. M.; Gerlach, L.-O.; Mathiesen, J. M.; Kostenis, E.; Uller, L.; Högberg, T. *J. Med. Chem.* **2006**, *49*, 6638.
13. Rist, Ø.; Grimstrup, M.; Receveur, J.-M.; Frimurer, T. M.; Ulven, T.; Kostenis, E.; Högberg, T. *Bioorg. Med. Chem. Lett.* **2009**. doi:10.1016/j.bmcl.2009.12.008.
14. Vrecl, M.; Jørgensen, R.; Pogacnik, A.; Heding, A. *J. Biomol. Screen.* **2004**, *9*, 322.