Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters 18 (2008) 2023–2027
Bioorganic & Medicinal Chemistry Letters

Substituted 2,2-bisaryl-bicycloheptanes as novel and potent inhibitors of 5-lipoxygenase activating protein

Dwight Macdonald,* Christine Brideau, Chi Chung Chan, Jean-Pierre Falgueyret, Richard Frenette,† Jocelyne Guay, John H. Hutchinson,‡ Hélène Perrier, Peptiboon Prasit,‡ Denis Riendeau, Philip Tagari,§ Michel Thérien, Robert N. Young¶ and Yves Girard

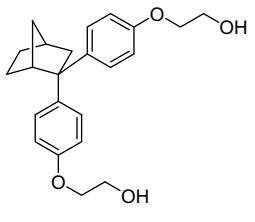
Department of Medicinal Chemistry, Merck Frosst Centre for Therapeutic Research, 16711 Trans Canada Hwy., Kirkland, Que., Canada H9H 3L1

Received 22 November 2007; revised 28 January 2008; accepted 29 January 2008
Available online 2 February 2008

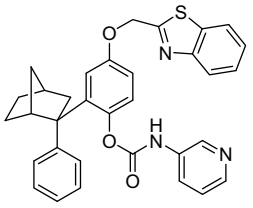
Abstract—The discovery and SAR of a novel series of substituted 2,2-bisaryl-bicycloheptane inhibitors of 5-lipoxygenase activating protein (FLAP) are herein described. SAR studies have shown that 2,5-substitution on the exo-aryl group is optimal for potency. The most potent compounds in this series have an ortho-nitrogen aryl linked with a methyleneoxy as the 5-substituent and a polar group such as a urethane as the 2-substituent. One of the most potent compounds identified is the 5-benzothiazolymethoxy-2-pyridinylcarbamate derivative **2** (FLAP IC_{50} = 2.8 nM) which blocks 89% of ragweed induced urinary LTE_4 production in dogs (at an I.V. dose of 2.5 μg/kg/min). This compound inhibits calcium ionophore stimulated LTB_4 production in both human polymorphonuclear (PMN) leukocytes and human whole blood (IC_{50} = 2.0 and 33 nM, respectively).

Leucotrienes (LT's) are potent inflammatory mediators involved in the pathogenesis of diseases such as asthma and atherosclerosis.[1,2] The first step in the conversion of arachidonic acid to the LT's is catalyzed by the enzyme 5-lipoxygenase (5-LO).[3] The enzyme 5-LO may be inhibited either by the direct interaction with an inhibitor or by the binding of an inhibitor to the 5-lipoxygenase activating protein (FLAP).[4] Clinical trials have demonstrated that the FLAP inhibitor **MK-0591** is an effective treatment for asthma.[5,6] FLAP inhibitors have also been shown to be protective in animal models of cardiovascular disease.[1]

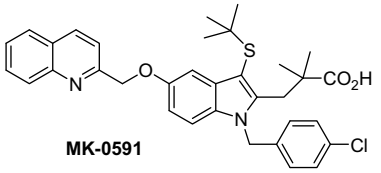
By screening a large number of diverse chemical structures, obtained from various sources, for their ability to prevent the production of LTB_4 by human polymorphonuclear (PMN) leukocytes when stimulated with calcium ionophore,[7] we discovered a potent inhibitor, **1** (IC_{50} = 60 nM). This 2,2-bis(oxyaryl)-bicycloheptane was also found to be a potent FLAP inhibitor[8] (IC_{50} = 387 nM) while not inhibiting the purified 5-LO (IC_{50} > 8 μM).



1



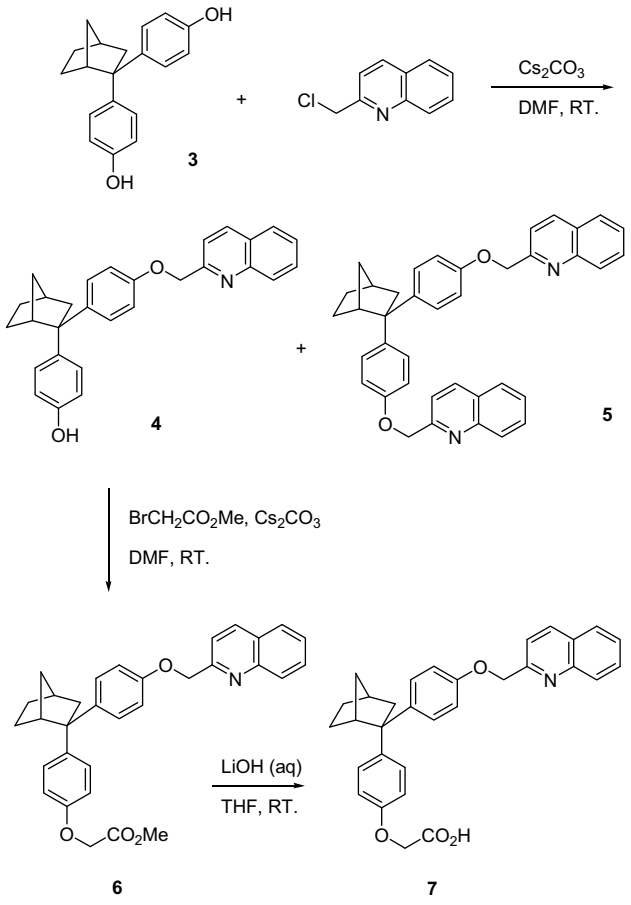
2



MK-0591

Keywords: 5-LO; FLAP; LT; Asthma; Inflammatory bowel disease; Rheumatoid arthritis; Psoriasis; Atherosclerosis.
* Corresponding author. Tel.: +1 514 428 3089; fax: +1 514 428 4900; e-mail: dwight_macdonald@merck.com
† Present address: Neurochem Inc., 275 Armand-Frappier Blvd., Laval, Que., Canada H7V 4A7.
‡ Present address: Amira Pharmaceuticals, 9535 Waples St., Suite 100, San Diego, CA 92121, USA.
§ Present address: Chemistry Research and Discovery, Amgen, Inc., One Amgen Center Drive, Thousand Oaks, CA 91320, USA.
¶ Present address: Department of Chemistry, Simon Fraser University, Burnaby, BC, Canada V5A 1S6.

0960-894X/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2008.01.105



Scheme 1. [10] Synthesis of compounds **3**–**7**.

Structure–activity relationship (SAR) study of this FLAP inhibitor has led to the identification of the 5-benzothiazolymethoxy-2-pyridinylcarbamate derivative **2** which has shown excellent potency in an in vivo model for blocking the production of systemic LT's. The SAR studies and synthesis of this novel series of FLAP inhibitors is herein described.

The initial direction of our SAR studies was led by the observation that other FLAP inhibitors such as **MK-0591** have two structural features which are important for their high potency.[9] These two functional groups, namely the quinolinylmethoxy and a carboxylic acid, were then introduced at the most convenient locations on the core of the lead compound **1** (Scheme 1). The commercially available 2,2-bis(hydroxyphenyl)-bicycloheptane **3** was alkylated with one equivalent of 2-chloromethylquinoline in DMF using cesium carbonate as base, to yield both the mono-quinolinyl and the bis-quinolinyl compounds **4** and **5**. The mono quinolinyl phenol was then coupled to methyl bromoacetate under the same conditions. Hydrolysis of the resulting methyl ester **6** then afforded the required carboxylic acid **7**. All the compounds described in this paper were isolated as mixtures of stereoisomers except where noted otherwise.

In order to more closely mimic the position of the quinolinyl and acid groups of **MK-0591**, these two groups were also placed on the same aromatic ring of the bisarylbicycloalkane. The synthesis of the 2-phenyl-2-(2,5-alkoxyphenyl) bicycloalkanes followed the procedure shown in Scheme 2. Phenylmagnesium bromide was added to norbornanone **8**, which resulted in production of only the exo-phenyl tertiary alcohol **9**. Friedel-Crafts alkylation of hydroquinone with the tertiary alcohol **9** gave the required diphenol **10** in modest yield (27%). Only the product from exo addition to the bicyclo system was observed. The 2,5-diphenol **10** was deprotonated with 1 equivalent of *t*-BuOK followed by alkylation with a halomethyl-aryl to produce the bis (not shown) and mono-alkylated product **11**. Further functionalization of monophenol **11** with Cs_2CO_3 and various halides in DMF or with an aryl isocyanate in toluene supplied the compounds shown in Scheme 2. Similar chemistry was used to prepare the corresponding 2,4-diphenol products (Scheme 3) and monocyclic 5 and 6-member compounds (Scheme 4). The Friedel-Crafts alkylation gave good yields for the bicyclo 2,4-diphenol but very poor yields for the monocyclic compounds. The monocyclic compounds were best prepared from the corresponding alkenes as shown in Scheme 4. The methyl benzoate derivative **12r** was prepared by converting phenol **11a** to a triflate, followed by Pd catalyzed carbonylation (Scheme 2).

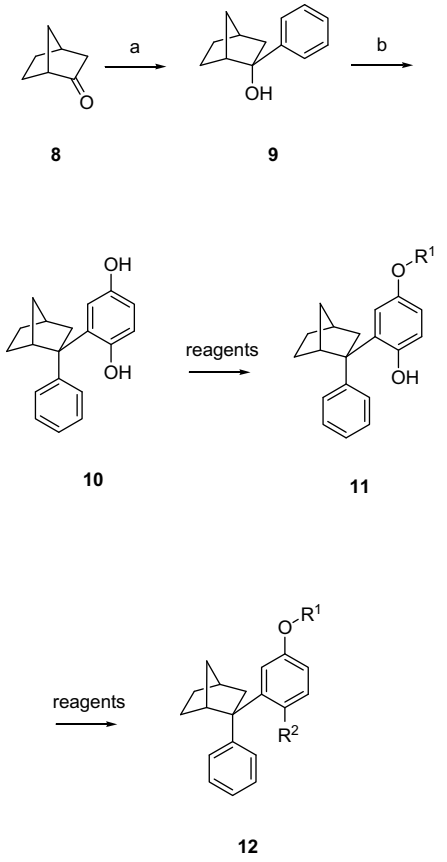
The in vitro evaluation of the compounds was as follows: (a) Each compound was evaluated in a 5-lipoxygenase activating protein (FLAP) binding assay. This assay determines the ability of the compound to displace the radio-labeled ligand [^{125}I]-L-691,831.[8]

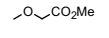
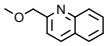
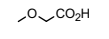
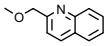
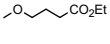
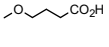
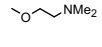
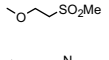
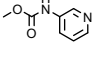
(b) The compounds were screened in a calcium-ionophore-activated human polymorphonuclear (PMN) leukocyte and a human whole blood assay for their ability to inhibit LTB_4 production.[7]

(c) Direct inhibition of recombinant 5-LO of selected compounds was evaluated using a spectrophotometric assay monitoring 5-hydroperoxyeicosatetraenoic acid production.[12]

Introduction of a quinoline and a carboxylic acid function to the core of the lead structure at the two para positions of the phenyl rings **7**, produced an encouraging fourfold enhancement of the FLAP potency over that of the lead compound **1** (Scheme 1, Table 1). The bis-quinolinyl **5**, quinolinyl-phenol **4**, and the quinolinyl-ester **6** were also more potent than the lead compound. This enhancement in potency by the introduction of the quinolinyl, especially if an acid is added **7**, is analogous to the effects of these groups in other FLAP inhibitors such as **MK-0591**.[9]

Placement of the quinolinyl and acid groups on the same phenyl ring of the lead compound core structure is a better mimic of the position of these groups on more potent known inhibitors, such as **MK-0591** (Scheme 2, Table 1). A 30-fold enhancement in FLAP binding potency over **1** is observed when the quinolinyl and the

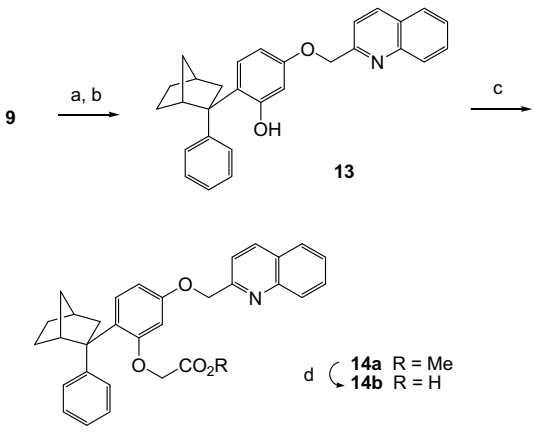


Compound	Reagents	R^1	R^2
11a	c		
12a	c,d		
12b	d,c		
12c	c,d,e		
12d	d,c,e		
12e	c,f		
12f	c,f,e		
12g	c,g		
12h	c,h		
12i	c,i		
12j	c,j		
12k	c,k		
12l	c,l		
12m	m,l		
12n	n,l		
12o	o,l		
12p	p,l		
12q	q,l		
2	q,o		
12r	c,r,s		
12s	c,r,s,t		

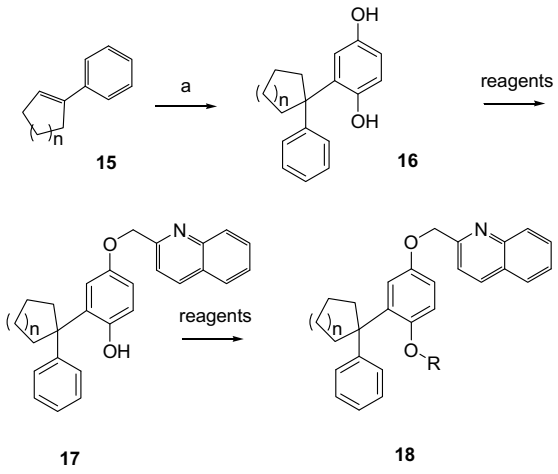
Scheme 2. [10] Synthesis of compounds **10**–**12**. Reagents and conditions: (a) PhMgBr, THF, −60 to 25 °C; (b) Hydroquinone, p-TSA monohydrate, toluene, reflux, 3 h, 27%; (c) *t*-BuOK, DMF, 2-(chloromethyl)quinoline, 25 °C, 18 h, 32% mono, 17% bis; (d) Cesium carbonate, DMF, methyl bromoacetate, 25 °C, 18 h; (e) LiOH(aq), THF, 25 °C, 18 h; (f) Cesium carbonate, DMF, ethyl-4-bromobutyrate, 25 °C, 18 h; (g) Cesium carbonate, DMF, MeI, 25 °C, 18 h; (h) Cesium carbonate, DMF, bromobutane, 25 °C, 18 h; (i) Cesium carbonate, DMF, benzyl bromide, 25 °C, 18 h; (j) Cesium carbonate, DMF, *N*,*N*-dimethylamino ethylchloride, 25 °C, 18 h; (k) Triton-B, THF, methyl vinyl sulfone, 25 °C, 18 h. (l) Cesium carbonate, DMF, 2-picolyl chloride, 25 °C, 18 h; (m) *t*-BuOK, DMF, 2-picolyl chloride, 25 °C, 18 h; (n) *t*-BuOK, DMF, 3-picolyl chloride, 25 °C, 18 h; (o) 3-pyridyl isocyanate (in situ from refluxing nicotinyl azide in toluene 30 m), DIPEA, toluene, reflux, 3 h, 63%; (p) *t*-BuOK, DMF, 5-chloromethylfuro[3,2-B]pyridine, 25 °C, 18 h; (q) *t*-BuOK, DMF, 2-(chloromethyl)-1,3-benzothiazole, 25 °C, 18 h, 24% mono, 10% bis; (r) Tf_2O, pyridine, 0–25 °C, 18 h; (s) Palladium (II) acetate, dppf, TEA, CO(1 atm), DMF, MeOH, 80 °C, 18 h, 26%; (t) KOH(aq), THF, 1,2-propanediol, 110 °C, 18 h, 59%.

acid are in the 5 and 2 positions of the aryl, respectively, **12c**. An even more interesting observation is that ester **12a** is more potent than the acid, with its FLAP potency 80-fold more than the lead compound. If the position of the acid/ester and the quinoline are exchanged, the potency is much less, 20-fold with ester **12b** and 200-fold with acid **12d**. The relatively small differences in the FLAP potency between the ester and acid pairs reported in this paper (one to threefold) are in agreement with compounds related to **MK-0591**, where a neutral group in place of an acid led to a potency within threefold of the acid compound.[9]

The corresponding 2,4-substituted compounds are significantly less potent than the 2,5-substituted compounds (Scheme 3, Table 1). Using a longer 3-carbon



Scheme 3. [10] Synthesis of compounds **13**–**14**. Reagents and conditions: (a) Resorcinol, 3-mercaptopropionic acid, HCl (conc), 1 h, 41%; (b) *t*-BuOK, DMF, 2-(chloromethyl)quinoline, 25 °C, 18 h; (c) Cesium carbonate, DMF, methyl bromoacetate, 25 °C, 18 h; (d) LiOH(aq), THF, 25 °C, 18 h.



Compound	Reagents	n	R
17a	b	1	
18a	b,c	1	CO_2Me
18b	b	1	
18c	b,d	1	
18d	b,e	1	
18e	b,c	2	CO_2Me
18f	b	2	

Scheme 4. [11] Synthesis of compounds **16**–**18**. Reagents and conditions: (a) Hydroquinone, p-TSA monohydrate, toluene, reflux, 3 h, ~7%; (b) *t*-BuOK, DMF, 2-(chloromethyl)quinoline, 25 °C, 18 h; (c) Cesium carbonate, DMF, methyl bromoacetate, 25 °C, 18 h; (d) *t*-BuOK, DMF, 3-picolyl chloride, 25 °C, 18 h; (e) 3-picolyl isocyanate (in situ from refluxing nicotinyl azide in toluene, 30 min), DIPEA, toluene, reflux, 3 h.

chain to connect the acid/ester to the phenol gave compounds **12e** and **12f** that have similar FLAP potency to the 1-carbon linked ester **12a**. The most interesting contrast between the long and short chain compounds is that the long chain ester and acid have only a two-fold difference in potency in the human whole blood assay (WBA) while the short chain compounds have more than a 10-fold difference. If the acid/ester is directly attached to the aryl (**12r** and **12s)** then the potency profile is similar to the 2-atom linked compounds. We have thus obtained several compounds (**12a**, **12e**, **12f**, and **12r**) with a similar in vitro potency profile to that of the clinically effective **MK-0591**.

Further SAR study on the 2-oxyaryl substituent (Scheme 2, Table 1) shows that a polar group is important for potency in the whole blood assay. The amine **12j**, sulfone **12k**, and 2-pyridyl **12l** are quite potent in the WBA (100–300 nM) while the methyloxy, butyloxy and benzyloxy analogs (**12g**, **12h**, and **12i**, respectively) are >1000 nM. One of the best polar groups is the 3-pyridinylcarbamate, as in **2** (WBA IC_{50} = 33 nM). Replacement of the quinoline with other heterocycles is possible, provided that an ortho-nitrogen is present (compare **12m** to **12n**, Scheme 2, Table 1). This observation is analogous to compounds related to **MK-0591**, where a naphthyl in place of the quinoline gave a much less potent compound.[9] The benzothiazole proved to be equivalent to the quinoline, and when combined with a 3-pyridinylcarbamate derivative, provided the extremely potent and orally bioavailable **2**. When dosed orally in rats at 20 mg/kg as a solution in PEG400, the bioavailability was 19% with a C_{max} of 1.1 μM at 6 h. These compounds were resolved on Chiralpak® AD (eluted with 4:1 hexane/2-propanol) and the enantiomers (+)**2** and (−)**2** were found to have similar potency. This small difference in potency between the enantiomers is similar to that of a chiral compound related to **MK-0591**(L-674,636), where there was only a twofold potency difference.[9] Compound **2** was also very potent for inhibiting ragweed induced urinary LTE_4 production in dogs (89% inhibition at an I.V. dose of 2.5 μg/kg/min).[13] Both the PK and the in vivo efficacy studies were preformed on the racemate of compound **2**.

The corresponding monocyclic 5 and 6-member ring compounds have similar potency and SAR to the bicyclo series (Scheme 4, Table 1). The similar potency of the monocyclic compounds to the corresponding bicyclic compounds, in addition to the similar potency of the enantiomers (+)**2r** and (−)**2r**, suggests that the bicyclic and monocyclic moiety is either solvent exposed, lipid exposed, or in a large hydrophobic pocket when these molecules are bound to FLAP.

In conclusion, a highly potent series of FLAP inhibitors (2,2-bisaryl-bicycloheptanes) has been discovered. A representative compound **2** has a FLAP, HPMN, and human whole blood IC_{50} of 2.8, 2.0 and 33 nM, respectively. This compound also blocks 89% of ragweed induced urinary LTE_4 production in dogs at an I.V. dose of 2.5 μg/kg/min.

Table 1. Summary of in vitro assay data

Compound	FLAP IC_{50}[a] (nM)	HPMN IC_{50}[a] (nM)	5-LO IC_{50}[a] (nM)	HWBA IC_{50}[a] (nM)
MK-0591	1.6 ± 0.3	3.1 ± 0.5	—	510 ± 50
1	387 ± 50	60 ± 20	>8000	—
2(±)	2.8 ± 0.1	2.0 ± 1.0	—	33 ± 10
2(+)	2.5 ± 0.2	1.8 ± 0.5	—	86 ± 10
2(−)	2.4 ± 0.6	3.0 ± 0.5	—	37 ± 10
4	145 ± 50	186 ± 50	—	—
5	127 ± 15	>1800	—	—
6	182 ± 15	169 ± 50	—	—
7	98 ± 50	44 ± 2	>6300	—
10	2070 ± 700	418 ± 250	—	—
11a	13.2 ± 0.1	19 ± 14	5000	580 ± 50
12a	5.0 ± 1.0	5.0 ± 05	>6000	290 ± 160
12b	94 ± 1	5.9 ± 3.0	—	—
12c	14 ± 1	16 ± 2	—	>3000
12d	3155 ± 1000	282 ± 70	—	—
12e	3.7 ± 0.1	42 ± 8	—	150 ± 20
12f	3.5 ± 0.5	8 ± 4	—	300 ± 30
12g	8.6 ± 1.0	9.0 ± 1.5		1100 ± 100
12h	6 ± 2	80 ± 40	—	>3000
12i	8.6 ± 0.4	217 ± 100	—	>3000
12j	6.5 ± 1.5	8.7 ± 4.0	—	335 ± 50
12k	5.5 ± 1.2	4.2 ± 1.0	—	114 ± 60
12l	4.1 ± 0.2	7.0 ± 2.5	—	225 ± 100
12m	18.3 ± 6.0	3.9 ± 0.7	—	275 ± 75
12n	134 ± 9	24 ± 1	—	—
12o	181 ± 23	—	—	>3000
12p	4.9 ± 0.5	2.2 ± 0.8	—	80 ± 10
12q	7.6 ± 0.2	7.0 ± 4.0	—	220 ± 50
12r	5.6 ± 1.0	2.6 ± 0.5	—	140 ± 20
12s	12.4 ± 1.0	9.5 ± 1.0	—	—
13	980 ± 200	>2372	—	—
14a	776 ± 50	47 ± 16	—	—
14b	3595 ± 275	152 ± 50	—	—
17a	22 ± 3	5.0 ± 0.5	—	1920 ± 200
18a	9.3 ± 1.5	1.7 ± 0.5	—	890 ± 100
18b	4.5 ± 0.6	10.2 ± 3	—	1080 ± 100
18c	2.5 ± 0.1	4.1 ± 1	—	200 ± 20
18d	2.4 ± 0.3	<1.3	—	52 ± 4
18e	3.7 ± 0.3	1.8 ± 0.5	—	200 ± 200
18f	4.2 ± 0.5	6.1 ± 1	—	∼3000

[a] Values are means of at least two experiments, ±standard error.

References and notes

1. Funk, C. D. *Nat. Rev. Drug Disc.* **2005**, *4*, 664.
2. (a) Friesen, R. W.; Riendeau, D. *Ann. Rep. Med. Chem.* **2005**, *40*, 199; (b) Osher, E.; Weisinger, G.; Limor, R.; Tordjman, K.; Stern, N. *Mol. Cell. Endocrinol.* **2006**, *252*, 201.
3. Radmark, O.; Samuelsson, B. *Biochem. Biophys. Res. Commun.* **2005**, *338*, 102.
4. Ferguson, A. D.; McKeever, B. M.; Shihua, X.; Wisniewski, D.; Miller, D. K.; Yamin, T.-T.; Spencer, R. H.; Chu, L.; Ujjainwalla, F.; Cunningham, B. R.; Evans, J. F.; Becker, J. W. *Science* **2007**, *317*, 510.
5. Diamant, Z. et al. *J. Allergy Clin. Immunol.* **1995**, *95*, 42.
6. Young, R. *Eur. J. Med. Chem.* **1999**, *34*, 671.
7. Brideau, C.; Chan, C.; Charleson, S.; Denis, D.; Evans, J. F.; Ford-Hutchinson, A. W.; Fortin, R.; Gillard, J. W.; Guay, D.; Guévremond, D.; Hutchinson, J. H.; Jones, T. R.; Léger, S.; Mancini, J. A.; McFarlane, C. S.; Pickett, C.; Piechuta, H.; Prasit, P.; Riendeau, D.; Rouzer, C. A.; Tagari, P.; Vickers, P. J.; Young, R. N.; Abraham, W. M. *Can. J. Physiol. Pharmacol.* **1992**, *70*, 799.
8. Charleson, S.; Prasit, P.; Léger, S.; Gillard, J. W.; Vickers, P. J.; Mancini, J. A.; Charleson, P.; Guay, J.; Ford-Hutchinson, A. W.; Evans, J. F. *Mol. Pharmacol.* **1992**, *41*, 873.
9. Prasit, P.; Belley, M.; Blouin, M.; Brideau, C.; Chan, C.; Charleson, S.; Evans, J. F.; Frenette, R.; Gauthier, J. Y.; Guay, J.; Gillard, J. W.; Grimm, E.; Ford-Hutchinson, A. W.; Hutchinson, J. H.; Fortin, R.; Jones, T. R.; Mancini, J.; Leger, S.; McFarlane, C. S.; Piechuta, H.; Riendeau, D.; Roy, P.; Tagari, P.; Vickers, P. J.; Young, R. N.; Zamboni, R. *J. Lipid Mediators* **1993**, *6*, 239.
10. Chu, L.; Goulet, M. T.; Ujjainwalla, F.; Frenette, R.; Girard, Y.; Therien, M.; Macdonald, D.; Hutchinson, J. H.; Chang, L. Patent: WO 2005/009951 A2, 2005.
11. Armstrong, H. M.; Chang, L. L.; Frenette, R Macdonald, D.; Ok, H. O.; Therien, M.; Ujjainwalla, F. Patent: WO 2006/098912 A1, 2006.
12. Falgueyret, J.-P.; Denis, D.; Macdonald, D.; Hutchinson, J. H.; Riendeau, D. *Biochemistry* **1995**, *34*, 13603.
13. Tagari, P.; Becker, A.; Brideau, C.; Frenette, R.; Sadl, V.; Thomas, E.; Vickers, P.; Ford-Hutchinson, A. *J. Pharmacol. Exp. Ther.* **1993**, *2651*, 416.