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# The discovery of 6-[2-(5-chloro-2-{[(2,4-difluorophenyl)-methyl]oxy}phenyl)-1-cyclopenten-1-yl]-2-pyridinecarboxylic acid, GW848687X, a potent and selective prostaglandin $EP_1$ receptor antagonist for the treatment of inflammatory pain

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**Abstract**—The discovery of a series of selective $EP_1$ receptor antagonists based on a 1,2-diarylcyclopentene template is described. After defining the structural requirements for $EP_1$ potency and selectivity, heterocyclic rings were incorporated to reduce log *D* and improve in vitro pharmacokinetic properties. The 2,6-substituted pyridines and pyridazines gave an appropriate balance of potency, in vivo pharmacokinetic properties and a low potential for inhibiting a range of CYP450 enzymes. From this series, GW848687X was shown to have an excellent profile in models of inflammatory pain and was selected as a development candidate.


Prostaglandin $PGE_2$ is a key mediator of pain and inflammation.[1] Non-steroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors that interrupt the biosynthesis of $PGE_2$ and other prostaglandins (PGs) are first-line treatments for inflammatory pain,[2] including pain associated with osteoarthritis, rheumatoid arthritis and chronic low back pain.[3] Although selective COX-2 inhibitors have been successful in reducing gastrointestinal side effects associated with NSAIDs,[4] there remain significant safety issues as evidenced by the recent withdrawal from the market of Vioxx.[5] $PGE_2$ acts downstream on four G-protein coupled 7-transmembrane receptors, $EP_{1-4}$.[6] Studies with $EP_1$ knock-out mice have suggested a central role of the $EP_1$ receptor in $PGE_2$-mediated allodynia[7] and inflammatory pain;[8] and there is evidence that $PGE_2$ acts on $EP_1$ receptors located both peripherally and in the CNS.[9] $EP_1$ receptor antagonists have shown efficacy in preclinical models of postoperative pain,[10] neuropathic pain[11] and allodynia[12] and it is hypothesised that, by sparing the synthesis of PGs, $EP_1$ receptor antagonists may have an improved safety profile. A number of selective $EP_1$ receptor antagonists have been reported in the literature (Fig. 1). The Searle group have described acylhydrazides such as SC51322[13] **1**; AstraZeneca have highlighted the efficacy of ZD6416 **2** in a human model of visceral hyperalgesia,[14] Ono have reported ONO-8713 **3**[15] and Merck Frosst have identified a series of thiophene analogues **4**.[16] As part of a long-standing interest in prostaglandin receptors, we sought to discover $EP_1$ receptor antagonists as potentially clinically effective analgesics. We focused our initial approach on exploring 1,2-substituted cyclic templates[17] and this paper describes the optimisation of the 1,2-diarylcyclopentene series **5** and discovery of

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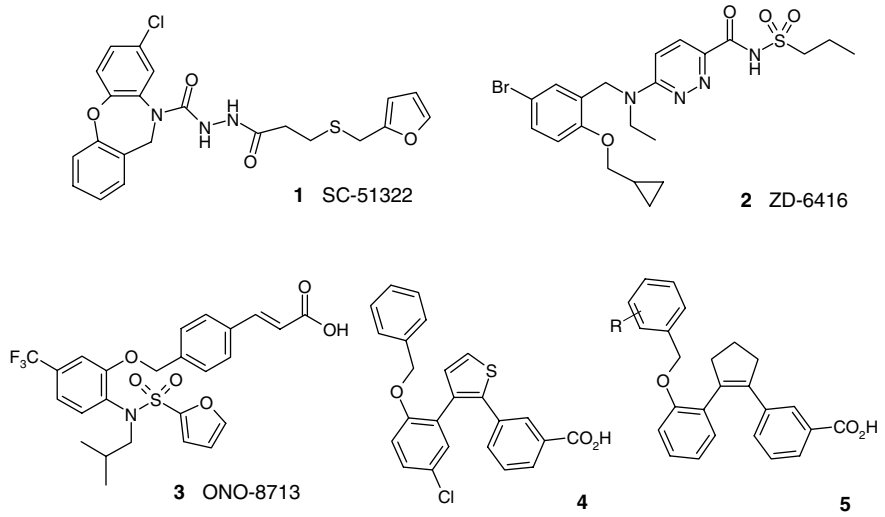


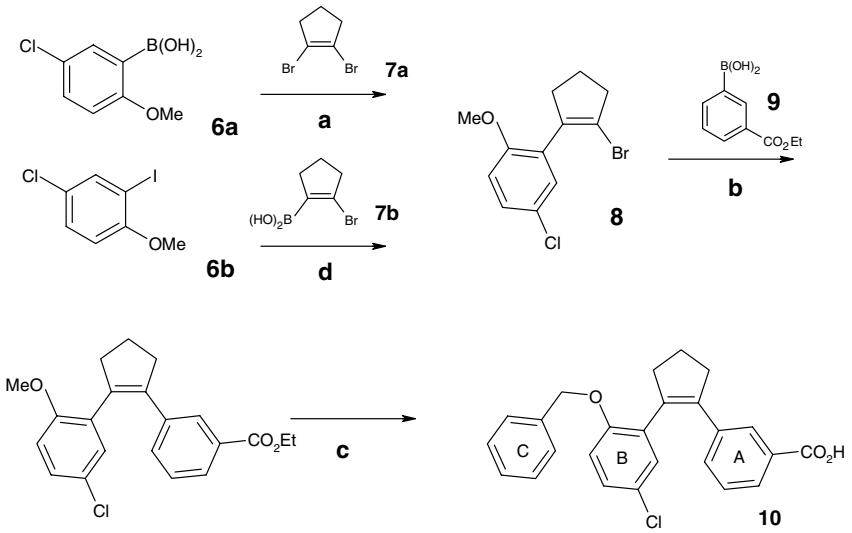

**Figure 1.** $EP_1$ antagonists (1) Searle, (2) AstraZeneca, (3) Ono, (4) Merck-Frosst and (5) GSK.

GW848687X, a candidate for the treatment of inflammatory pain.

The synthetic route to the cyclopentene analogues is shown in Scheme 1.[18] We identified commercially available dibromocyclopentene **7a** as a potentially versatile building block. Appropriately substituted aryl boronic acids **6a** were reacted under carefully controlled Suzuki conditions with 4 equiv of 1,2-dibromocyclopentene **7a** to furnish the bromocyclopentene **8**. A second Suzuki coupling with the *meta* substituted boronic acid ester **9** installed the second aromatic ring. Subsequent cleavage of the methyl ether and ethyl ester with sodium methylthiolate, followed by benzylation and saponification of the ester, gave the target compound **10**. An alternative first step that utilizes the novel 2-bromo-1-cyclopenteneboronic acid **7b** was developed. This route allowed better control of the first Suzuki coupling with iodo-benzenes such as **6b**, requiring just one molar equivalent of **7b**. It is noteworthy that the novel boronic acid **7b** is an air stable solid at room temperature that shows no evidence of self-coupling under Suzuki reaction conditions.

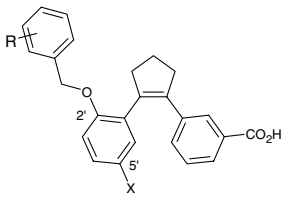
Evaluation of the aromatic substitution patterns around the A and B phenyl rings (see structure **10**) confirmed that a *meta*-acid substituent in the A-ring and an *ortho*-benzyloxy substituent in the B ring were optimal for $EP_1$ potency.[19] Detailed exploration of the requirements for $EP_1$ activity was initially focused on the role of the benzyl substitution pattern and the 5′-substituent (Table 1).

The 5′-substituent is important for potency. For unsubstituted C-ring analogues, the rank order of potency is X = Cl, H > Br > MeS,$MeSO_2$, CN (analogues **10**, **11**, **16**, **23**, **26**, and **29**). When X = H, the unsubstituted benzyl analogue **11** is most potent. The 2,4-difluorobenzyl analogue **12** is the next most active. For each of the other B-ring 5′-substituents the 2,4-difluorobenzyl analogue is




**Scheme 1.** Synthesis of cyclopentene $EP_1$ antagonists. Reagents and conditions: (a) $Pd(PPh_3)_4$, DME-$H_2O$, 80 °C; (b) $Pd(PPh_3)_4$, DME-$H_2O$, 80 °C; (c) i—MeSNa; ii—benzyl bromide, $K_2CO_3$; iii—NaOH, EtOH; (d) $Pd(PPh_3)_4$, 1:1 toluene–ethanol, 90 °C.

**Table 1.** SAR of phenyl acid analogues




| Compound | X | R | hEP$_1$ pIC$_{50}$ |
|---|---|---|---|
| **11** | H | H | 8.2 ± 0.2 |
| **12** | H | 2,4-Difluoro | 7.6 ± 0.1 |
| **13** | H | 3,4-Dichloro | 6.4 ± 0.1 |
| **14** | H | 2-Fluoro, 4-chloro | 7.3 ± 0.1 |
| **15** | H | 4-Methoxy | 7.0 ± 0.0 |
| **10** | Cl | H | 8.3 ± 0.2 |
| **16** | Br | H | 7.9 ± 0.3 |
| **17** | Br | 4-Chloro | 7.9 ± 0.2 |
| **18** | Br | 4-Fluoro | 7.7 ± 0.4 |
| **19** | Br | 3,4-Dichloro | 7.0 ± 0.2 |
| **20** | Br | 2,4-Difluoro | 8.3 ± 0.3 |
| **21** | Br | 2-Fluoro, 4-chloro | 8.6 ± 0.2 |
| **22** | Br | 4-Methoxy | 7.4 ± 0.4 |
| **23** | MeS | H | 7.2 ± 0.1 |
| **24** | MeS | 4-Fluoro | 7.5 ± 0.2 |
| **25** | MeS | 2,4-Difluoro | 7.8 ± 0.2 |
| **26** | $MeSO_2$ | H | 7.1 ± 0.1 |
| **27** | $MeSO_2$ | 4-Fluoro | 7.1 ± 0.2 |
| **28** | $MeSO_2$ | 2,4-Difluoro | 7.8 ± 0.2 |
| **29** | CN | H | 7.0 ± 0.2 |
| **30** | CN | 4-Fluoro | 6.4 ± 0.1 |
| **31** | CN | 2,4-Difluoro | 7.4 ± 0.2 |
| **32** | CN | 4-Chloro | 6.7 ± 0.2 |

Values are means of four experiments ±SD. All compounds were inactive (functional pIC$_{50}$ < 5.5) at the human EP$_3$ receptor.

most potent, suggesting this substitution pattern is important for high EP$_1$ affinity. In order to characterise the in vivo pharmacokinetics of this series, selected analogues were administered intravenously to rats (Table 2). These compounds had low volumes of distribution, moderate-to-high blood clearance and very short half-lives. Low volume of distribution and short half-life are typical properties of lipophilic acids (e.g., NSAIDs) but we hypothesised that reduction of log *D* may reduce clearance and extend half-life. Selected compounds were assessed in human recombinant CYP450 assays and it was found that inhibitory activities (IC$_{50}$) across a panel of human CYP450 enzymes were generally in excess of 10 μM with the exception of CYP2C9.

A-ring heterocyclic replacements were investigated in an attempt to lower log *D* and to improve in vitro and in vivo pharmacokinetic profiles. During the course of this work we were able to establish that a $CF_3$ group was an acceptable replacement for halogen substituents in the B-ring, Table 3 compounds **33** and **35**. Compounds were screened for rate of metabolism (intrinsic clearance, CLi) in a rat microsomal assay and for CYP450 inhibition in a human 2C9 CYP450 isozyme assay.

**Table 2.** Rat iv pharmacokinetics (1 mg/kg) for selected analogues

| Compound | CLb (ml/min/kg) | $V_d$ (L/kg) | $t_{1/2}$ (h) |
|---|---|---|---|
| **10** | 54 | 0.8 | 0.5 |
| **16** | 52 | 1.0 | 0.3 |
| **17** | 33 | 0.4 | NT |
| **18** | 46 | 0.7 | 0.2 |
| **20** | 35 | 0.6 | 0.2 |

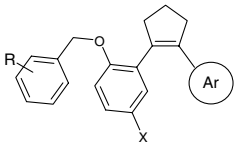
NT, not tested.

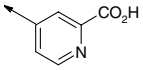
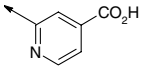
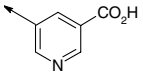
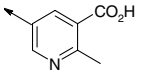
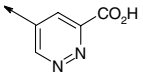
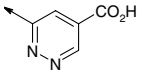
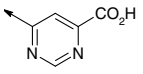
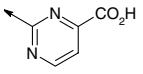
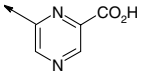
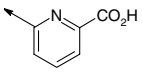
A-ring pyridine analogues gave high EP$_1$ potency with the exception of the 2,4-isomer **33**. The pyridazine analogue **37** showed low EP$_1$ activity but its isomer, compound **38**, possessed almost 10-fold higher potency. Disappointingly pyridazine analogue **38** had high intrinsic clearance in rat microsomes and was a potent inhibitor of the 2C9 CYP450 isozyme. Pyrimidines **39** and **40** showed low EP$_1$ potency however the pyrazine analogue **41** had high potency with low intrinsic clearance in rat microsomes and acceptable 2C9 activity. Analogues **35** and **42** had much reduced rat in vivo clearance and improved half-life. Selected compounds were tested in the Freund's complete adjuvant rat model of acute inflammatory pain.[20] Compounds were either assayed in a single dose study at 5 mg/kg *po* or in a 3 point dose response assay for which an ED$_{50}$ (dose that would give 50% reversal of hypersensitivity) was calculated (see Table 3). Whereas analogues **36** and **41** had modest potency and failed to show full reversal of hypersensitivity, analogues **35** and **42** gave a low ED$_{50}$ and full reversal of hypersensitivity in this acute model of inflammatory pain. Subsequent evaluation of pyridine analogues **35** and **42** in a chronic rat model of joint pain[21] clearly differentiated these compounds. Nicotinic acid analogue **35** showed no significant antihyperalgesic effect (data not shown) when dosed for 5 days at 30 mg/kg b.i.d. However, picolinic acid analogue **42** at the same dose showed complete reversal of the anti-hyperalgesic effect with a response equivalent to rofecoxib (Fig. 2).

On the basis of this profile, compound **42** 6-[2-(5-chloro-2-{[(2,4-difluorophenyl)methyl]oxy}phenyl)-1-cyclopenten-1-yl]-2-pyridinecarboxylic acid, GW848687X, was selected for further evaluation. GW848687X is a competitive antagonist at the EP$_1$ receptor with a pA$_2$ 9.1. It has >400-fold selectivity relative to the other EP receptor subtypes, the DP receptor and the IP (prostacyclin) receptor. It has 30-fold selectivity over the TP (thromboxane A$_2$) receptor, acting as a functional antagonist at this receptor.[22] It shows no significant effect at a range of other receptors and enzymes in the CEREP screen at 1 μM. GW848687X has an excellent oral pharmacokinetic profile; oral bioavailability is 54% in the rat and 53% in dog. It has a half-life of 2 h in both species. These data suggest that GW848687X may have benefit for treating both acute and chronic pain conditions.

In conclusion, we have identified a novel series of EP$_1$ receptor antagonists based on a 1,2-disubstituted cyclopentene template. Optimising in vitro and in vivo activities has led to the identification of GW848687X, a selective EP$_1$ receptor antagonist as a candidate for the treatment of acute and chronic inflammatory pain.

**Table 3.** A-ring heterocyclic analogues




| Compound | R | X | Ar | hEP$_1$ pIC$_{50}$ | Rat CLi (ml/min/g) | CYP 2C9 IC$_{50}$ (μM) | log *D* | Rat CLb (ml/min/kg) | Rat $t_{1/2}$ (h) | Rat FCA |
|---|---|---|---|---|---|---|---|---|---|---|
| **33** | H | $CF_3$ |  | 7.4 ± 0.2 | NT | NT | NT | NT | NT | NT |
| **34** | 4-Fluoro | Br |  | 8.5 ± 0.0 | 20 | 5 | 2.7 | NT | NT | NT |
| **35** | H | $CF_3$ |  | 8.0 ± 0.1 | 2.2 | 14 | 2.7 | 22 | 4.1 | $ED_{50}$ 1.3 mg/kg |
| **36** | 4-Fluoro | Cl |  | 8.8 ± 0.1 | 3.8 | 9 | 2.7 | NT | NT | <30% at 5 mg/kg |
| **37** | H | Cl |  | 7.4 ± 0.2 | NT | NT | NT | NT | NT | NT |
| **38** | 2,4-Difluoro | Cl |  | 8.2 ± 0.2 | 14 | 5.4 | 1.2 | NT | NT | NT |
| **39** | H | Cl |  | 6.7 ± 0.2 | NT | NT | 1.2 | NT | NT | NT |
| **40** | H | Cl |  | 6.8 ± 0.1 | NT | NT | 0.8 | NT | NT | NT |
| **41** | 2,4-Difluoro | Cl |  | 8.7 ± 0.1 | 2.6 | 12 | 1.6 | NT | NT | 52% at 5 mg/kg |
| **42** | 2,4-Difluoro | Cl |  | 8.6 ± 0.1 | 2.9 | 14 | 2.6 | 7 | 2.2 | $ED_{50}$ 1.3 mg/kg |

NT, not tested. For the rat FCA model, data are presented as either an $ED_{50}$ values corresponding to the dose calculated to show a 50% reduction in hypersensitivity; or a percentage reversal of hypersensitivity at a given oral dose.

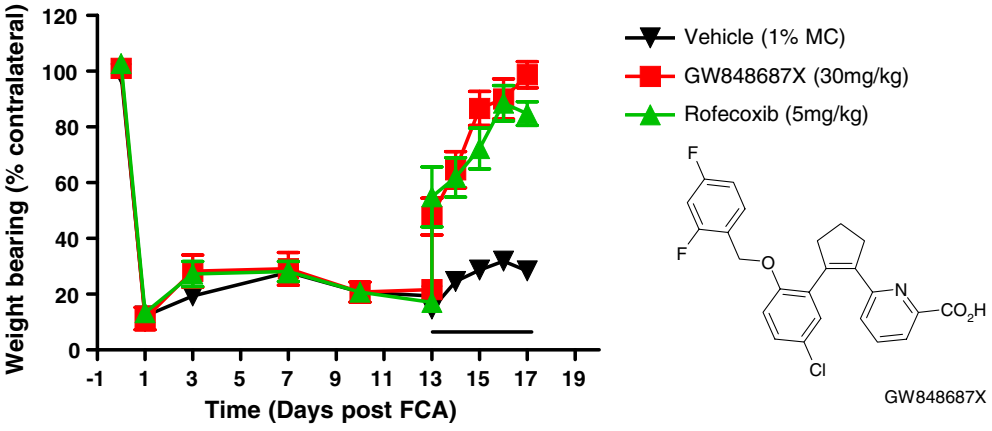



**Figure 2.** Analogue **42**, GW848687X, shows anti-hyperalgesic activity (red) in an FCA induced joint pain model of inflammatory pain. GW848687X was orally dosed at 30 mg/kg per day in a 1% methylcellulose vehicle over 5 days and compared with rofecoxib (Vioxx) 5 mg/kg (green).

## References and notes


1. (a) Murakami, M.; Nakatani, Y.; Tanioka, T.; Kudo, I. *Prostaglandins Other Lipid Mediat.* **2002**, *68–69*, 383; (b) Claveau, D.; Sirinyan, M.; Guay, J.; Gordon, R.; Chan, C.-C.; Bureau, Y.; Riendeau, D.; Mancini, J. A. *J. Immunol.* **2003**, *170*, 4738; (c) Trebino, C. E.; Stock, J. L.; Gibbons, C. P.; Naiman, B. M.; Wachtmann, T. S.; Umland, J. P.; Pandher, K.; Lapointe, J.-M.; Saha, S.; Roach, M. L.; Carter, D.; Thomas, N. A.; Durtschi, B. A.; McNeish, J. D.; Hambor, J. E.; Jakobsson, P.-J.; Carty, T. J.; Perez, J. R.; Audoly, L. P. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 9044; (d) Kamei, D.; Yamakawa, K.; Takegoshi, Y.; Mikami-Nakanishi, M.; Nakatani, Y.; Oh-ishi, S.; Yasui, H.; Azuma, Y.; Hirasawa, N.; Ohuchi, K.; Kawaguchi, H.; Ishikawa, Y.; Ishii, T.; Uematsu, S.; Akira, S.; Murakami, M.; Kudo, I. *J. Biol. Chem.* **2004**, *279*, 33684; (e) Mabuchi, T.; Kojima, H.; Abe, T.; Takagi, K.; Sakurai, M.; Ohmiya, Y.; Uematsu, S.; Akira, S.; Watanabe, K.; Ito, S. *Neuro Report* **2004**, *15*, 1395.
2. (a) Camu, F.; Shi, L.; Vanlersberghe, C. *Drugs* **2003**, *63*(suppl. 1), 1; (b) Bianchi, M.; Broggini, M. *Drugs* **2003**, *63*(suppl. 1), 37; (c) Jeger, R. V.; Greenberg, J. D.; Ramanathan, K.; Farkouh, M. E. *Exp. Rev. Clin. Immunol.* **2005**, *1*, 37; (d) Lee, Y.; Rodriguez, C.; Dionne, R. A. *Curr. Pharm. Des.* **2005**, *11*, 1737.
3. (a) Akarca, U. S. *Curr. Pharm. Des* **2005**, *11*, 1779; (b) Sheen, C. L.; MacDonald, T. M. *Exp. Opin. Pharmacother.* **2002**, *3*, 265.
4. (a) Hawkey, C. J.; Jackson, L.; Harper, S. E.; Simon, T. J.; Mortensen, E.; Lines, C. R. *Aliment. Pharmacol. Ther.* **2001**, *15*, 1; (b) Bombardier, C.; Laine, L.; Reicin, A.; Shapiro, D.; Burgos-Vargas, R.; Davis, B.; Day, R.; Bosi Ferraz, M.; Hawkey, C. J.; Hochberg, M. C.; Kvien, T. K.; Schnitzer, T. J. *N. Eng. J. Med.* **2000**, *343*, 1520; (c) Silverstein, F. E.; Faich, G.; Goldstein, J. L.; Simon, L. S.; Pincus, T.; Whelton, A.; Makuch, R.; Eisen, G.; Agrawal, N. M.; Stenson, W. F.; Burr, A. M.; Zhao, W. W.; Kent, J. D.; Lefkowith, J. B.; Verburg, K. M.; Geis, G. S. *JAMA* **2000**, *284*, 1247.
5. Meagher, E. A. *Curr. Pharm. Des.* **2004**, *10*, 603.
6. (a) Coleman, R. A.; Smith, W. L.; Narumiya, S. *Pharmacol. Rev.* **1994**, *46*, 205; (b) Breyer, R. M.; Bagdassarian, C. K.; Myers, S. A.; Breyer, M. D. *Annu. Rev. Pharmacol. Toxicol.* **2001**, *41*, 661; (c) Narumiya, S.; Sugimoto, Y.; Ushikubi, F. *Physiol. Rev.* **1999**, *79*, 1193; (d) Coleman, R. A.; Kennedy, I.; Humphrey, P. P. A.; Bunce, K.; Lumley, P.. In *Comprehensive Medicinal Chemistry*; Pergamon: Oxford, UK, 1990; Vol. 3, p 643.
7. (a) Minami, T.; Nakano, H.; Kobayashi, T.; Sugimoto, Y.; Ushikubi, F.; Ichikawa, A.; Narumiya, S.; Ito, S. *Br. J. Pharmacol.* **2001**, *133*, 438; (b) Mebane, H.; Turnbach, M. E.; Randich, A. *J. Pain* **2003**, *4*, 392.
8. Stock, J. L.; Shinjo, K.; Burkhardt, J.; Roach, M.; Taniguchi, K.; Ishikawa, T.; Kim, H-S.; Flannery, P. J.; Coffman, T. M.; McNeish, J. D.; Audoly, L. P. *J. Clin. Invest.* **2001**, *107*, 325.
9. Hata, A. N.; Breyer, R. M. *Pharmacol. Ther.* **2004**, *103*, 147, and references therein.
10. (a) Omote, K.; Kawamata, T.; Nakayama, Y.; Kawamata, M.; Hazama, K.; Namiki, A. *Anesth. Analg.* **2001**, *92*, 233; (b) Omote, K.; Yamamoto, H.; Kawamata, T.; Nakayama, Y.; Namiki, A. *Anesth. Analg.* **2002**, *95*, 1708.
11. Kawahara, H.; Sakamoto, T.; Takeda, S.; Onodera, H.; Imaki, J.; Ogawa, R. *Anesth. Analg.* **2001**, *93*, 1012.
12. Maruyama, T.; Koketsu, M.; Yamamoto, H.; Yamamoto, K.; Yamamoto, L. T.; Hayashida, K-i.; Ohuchida, S.; Kondo, K. *Prostaglandins Other Lipid Mediat.* **1999**, *59*, 217.
13. Hallinan, E. A.; Stapelfeld, A.; Savage, M. A.; Reichman, M. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 509.
14. (a). *Expert Opin. Ther. Patents* **2004**, *14*, 435; (b) Breault, G.A. WO9700863A1, 1997.
15. Watanabe, K.; Kawamori; Nakatsugi, S.; Ohta, T.; Ohuchida, S.; Yamamoto, H.; Maruyama, T.; Kondo, K.; Narumiya, S.; Sugimura, T.; Wakabayashi, K. *Cancer Lett.* **2000**, *156*, 57.
16. Ducharme, Y.; Blouin, M.; Carrière, M-C.; Chateauneuf, A.; Côté, B.; Denis, D.; Frenette, R.; Greig, G.; Kargman, S.; Lamontagne, S.; Martins, E.; Nantel, F.; O'Neill, G.; Sawyer, N.; Metters, K. M.; Friesen, R. W. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1155.
17. Hall, A.; Bit, R. A.; Brown, S. H.; Chaignot, H. M.; Chessell, I. P.; Coleman, T.; Giblin, G. M. P.; Hurst, D. N.; Kilford, I. R.; Lewell, X. Q.; Michel, A. D.; Mohamed, S.; Naylor, A.; Novelli, R.; Skinner, L.; Spalding, D. J.; Tang, S. P.; Wilson, R. J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2666.
18. Full synthetic details, including spectral characterization of all final compounds are disclosed in: Giblin, G.M.P.; Hall, A.; Hurst, D.N.; Kilford, I.R.; Lewell, X.Q.; Naylor, A.; Novelli, R. WO2003084917A1.
19. Analogues with methoxy replacing benzyloxy and analogues with acid as a *para* ring substituent showed no significant activity ($pIC_{50} < 5.5$) in $EP_1$ binding assay (data not shown).
20. (a) Iadarola, M. J.; Douglass, J.; Civelli, O.; Naranjo, J. R. *Brain Res.* **1988**, *455*, 205; (b) Hay, C. H.; Trevethick, M. A.; Wheeldon, A.; Browers, J. S.; De Belleroche, J. S. *Neuroscience* **1997**, *78*, 843, Briefly one hind paw was treated with FCA and 24 h later, when an inflammatory reaction and associated hypersensitivity had become established, animals were treated with a single oral dose of test compound from a 1% methylcellulose formulation. A percentage inhibition of hypersensitivity was measured by weight bearing for each dose tested and, where appropriate, an $ED_{50}$ calculated.
21. Wilson, A. W.; Medhurst, S. J.; Dixon, C. I.; Bontoft, N. C.; Winyard, L. A.; Brackenborough, K. T.; De Alba, J.; Clarke, C. J.; Gunthorpe, M. J.; Hicks, G. A.; Bountra, C.; McQueen, D. S.; Chessell, I. P. *Eur. J. Pain* **2006**, *10*, 537.
22. The activity of GW848687X at the prostaglandin FP and $CRTH_2$ receptors has not been characterised.