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Structure–activity relationships of 1,5-biaryl pyrroles as EP_1 receptor antagonists

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Abstract—The preliminary SAR of a series of novel 1,5-biaryl pyrrole EP_1 receptor antagonists derived from compound **1** is described. Replacement of the benzyl group of **1** with isosteric groups was investigated. The most effective replacement was found to be the isobutyl group. The cyclopentylmethyl and cyclohexylmethyl groups were also effective benzyl replacements. The cyclohexylmethyl derivative **19** demonstrated the lowest metabolic clearance within this series. In addition, several high affinity substituted benzyl analogues were also identified. Compound **39** was found to have good bioavailability in rats and demonstrated efficacy in the established FCA preclinical model of inflammatory pain with a calculated ED_{50} of 9.2 mg/kg.
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Prostaglandin E_2 (PGE_2) is a pro-inflammatory mediator[1] that exerts its physiological actions by activating four 7-transmembrane receptor subtypes, EP_{1-4}.[2] Studies with prostaglandin E synthase (PGES) knockout (KO) mice have shown that PGE_2 plays an important role in pain[1] and EP_1 receptor KO mice have implicated the EP_1 receptor subtype in the sensation of PGE_2-mediated allodynia[3] and inflammatory pain.[4] In conjunction with this, EP_1 receptor antagonists have shown efficacy in preclinical models of postoperative pain,[5] neuropathic pain[6] and allodynia.[7] There is also evidence to suggest that PGE_2mediated pyrexia is controlled by the EP_1 receptor.[8] Furthermore, a recent report described the efficacy of the AstraZeneca compound ZD6416 in a human model of visceral hypersensitivity.[9] Thus, an EP_1 receptor antagonist has the potential to deliver efficacy in various pain states. By sparing the beneficial effects of PGE_2, at other EP receptors, and the synthesis of prostaglandin I_2 (PGI_2) and thromboxane A_2 (TxA_2),[10] an improved side-effect profile over COX-2 inhibitors may be achieved.

Several EP_1 antagonists are known in the literature, such as ZD6416,[11] ONO-8713[12] and ONO-8711,[13] SC-51322[14] and analogues[15] and the 2,3-biaryl thiophenes from Merck Frosst.[16]

We recently disclosed the structures of several novel EP_1 receptor antagonists, such as the pyrrole **1**.[17]

Herein we describe the initial structure–activity relationships (SAR) in this series.

Compound **1**[17] showed good in vitro activity at the EP_1 receptor, 8 nM in a [^{3}H]PGE_2 binding assay in CHO cells and 0.7 nM in a functional assay (FLIPR) in CHO cells.[17,18] It has also shown low intrinsic clearance in both rat and human liver microsomes (Fig. 1). However, the rat in vivo pharmacokinetic profile was not optimal. Thus, our goals were to explore the SAR of this template and to optimise EP_1 activity,whilst improving the in vivo DMPK profile, which we hoped would lead to in vivo efficacy in preclinical models of inflammatory pain.

Keywords: EP_1 antagonist; Pyrrole; Isostere; Pain; Established FCA.
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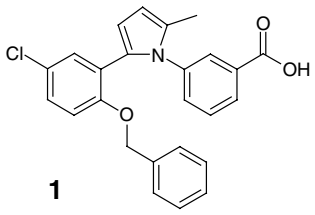


EP_1 binding pIC_{50} = 8.1
EP_1 functional pKi = 9.15

rat CLi = 1.4 mL/min/g liver
human CLi = 1.6 mL/min/g liver

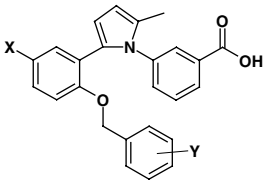
rat pharmacokinetics
CLb = 67 mL/ming/kg
Vss = 3.0 L/kg
$t_{1/2}$ = 0.5h

Figure 1. Profile of lead compound **1**.

One of the first areas we sought to investigate was the role of the chlorine atom, *para* to the benzyloxy group. Initial data suggested that the bromo analogue **2** had an improved in vivo DMPK profile relative to **1**. Hence, we were interested in exploring whether replacement of the chlorine atom would improve EP_1 receptor affinity,whilst simultaneously optimising the pharmacokinetic parameters of the series. Results show that the chlorine atom can be replaced by isosteric electron-withdrawing moieties such as Br and CF_3 and even the larger methyl sulfone group, compounds **2**–**4**. Deletion of this electron-withdrawing moiety appeared to have little effect on activity, as evidenced by compound **5**. However, replacement by aromatic groups such as phenyl or thiophenyl led to a marked decrease in activity, compounds **6** and **7**, Table 1. Despite the fact that **5** was essentially equipotent with analogues **1**–**3**, we chose the Cl, Br and CF_3 substituents for further exploration.

Next, we investigated substitution of the pyrrole ring. We had previously discovered that the methyl group on the pyrrole ring could be removed without effecting activity, compound **8**.[17] In this instance, replacement of the Me group by CF_3 led to a substantial decrease in activity, compounds **9** and **10**, compared to the analogous methyl derivatives **14** and **15**. This may be due to the increased steric nature of the CF_3 group relative to the Me group as it was found that the Me group could be replaced by a chlorine atom, compound **11**, therefore implying that electron-withdrawing groups are tolerated in this position. The steric restrictions of this region of the molecule were further highlighted

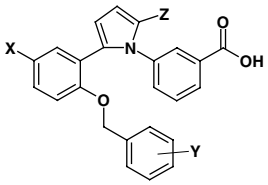
Table 1. In vitro EP_1 binding data for compounds **1**–**7**



Compound	X	Y	Binding pIC_{50}[a]
1	Cl	H	8.1 ± 0.4
2	Br	H	8.1 ± 0.2
3	CF_3	H	8.3 ± 0.1
4	SO_2Me	H	7.6 ± 0.1
5	H	H	7.7 ± 0.3
6	Ph	H	6.4 ± 0.5
7	Thiophen-3-yl	H	6.2 ± 0.7

[a] Mean of at least three experiments.

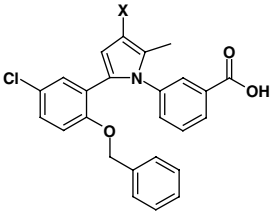
Table 2. In vitro binding data for compounds **8**–**15**



Compound	X	Y	Z	Binding pIC_{50}[a]
8	Cl	H	H	8.0 ± 0.1
9	Cl	4-F	CF_3	6.7 ± 0.1
10	Cl	2,4-DiF	CF_3	7.0 ± 0.1
11	Cl	H	Cl	7.6 ± 0.1
12	Cl	H	Et	7.0 ± 0.2
13	Br	H	Et	7.1 ± 0.1
14	Cl	4-F	Me	8.2 ± 0.2
15	Cl	2,4-DiF	Me	8.4 ± 0.2

[a] Mean of at least three experiments.

Table 3. In vitro binding data for compounds **16**–**18**



Compound	X	Binding pIC_{50}[a]
16	Cl	<6
17	Br	6.1 ± 0.2
18	Ph	<6

[a] Mean of at least three experiments.

when the methyl group was replaced by an ethyl group, compounds **12** and **13**, which resulted in a considerable loss of activity, approximately 10-fold, relative to the corresponding methyl analogues (compounds **1** and **2**), Table 2.

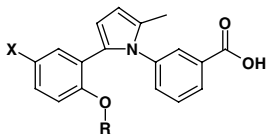
Further substitution of the pyrrole ring by addition of a halogen atom or a phenyl group led to a marked decrease in EP_1 activity, compounds **16**–**18**, hence no further analogues were pursued in this series, Table 3.

We were interested in exploring the role of the benzyl group in binding to the EP_1 receptor and its potential in modulating the intrinsic clearance and CYP450 profile of compounds.

To this end, we synthesized a range of analogues where the benzyl group was replaced by potential non-aromatic isosteric groups, Table 4.

We were pleased to find that the benzyl group could be replaced by a cyclohexylmethyl group, compounds **19**–**21**, with a modest decrease in activity (5- to 16-fold). Furthermore, the cyclohexyl ring could be replaced by a tetrahydropyran (**22**) ring without further affect on

Table 4. In vitro EP_1 binding data for compounds **19**–**29**



Compound	X	R	Binding pIC_{50}[a]
19	Cl	CH_2Cyclohexyl	6.9 ± 0.5
20	Br	CH_2Cyclohexyl	7.4 ± 0.1
21	CF_3	CH_2Cyclohexyl	7.5 ± 0.2
22	Cl	CH_2tetrahydropyran-4-yl	7.4 ± 0.2
23	Cl	CH_2Cyclopentyl	7.6 ± 0.3
24	Br	CH_2Cyclopentyl	7.8 ± 0.3
25	Cl	CH_2tetrahydrofuran-2-yl	7.4 ± 0.2
26	Cl	*i*-Bu	8.3 ± 0.1
27	Br	*i*-Bu	8.3 ± 0.1
28	Br	(5-Methyl-3-isoxazolyl) methyl	7.6 ± 0.1
29	Br	(3,5-Dimethyl-4-isoxazolyl) methyl	6.7 ± 0.1

[a] Mean of at least three experiments.

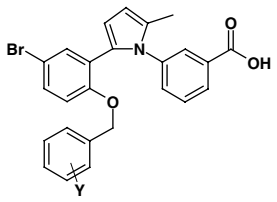
activity. Replacement of the benzyl group by the less bulky cyclopentylmethyl moiety yielded more promising analogues (**23** and **24**), with activity 2- to 3-fold lower than their benzyl analogues. Again, we found that an oxygen atom could be incorporated into the ring with minimal detriment to binding affinity, compound **25**. The most potent analogues were obtained when the benzyl group was replaced by an *iso*-butyl group, (**26** and **27**), as these compounds were equipotent with the original benzyl analogues. These results suggest that the benzyl group forms a lipophilic interaction with the receptor, but that the environment may be limited sterically, as the bulky cyclohexylmethyl group has lower activity than the sterically less demanding cyclopentylmethyl group and the smaller *iso*-butyl group. These results demonstrate the utility of the cyclohexylmethyl, cyclopentylmethyl and *iso*-butyl groups as isosteres for the benzyl group in this instance.

We also investigated replacement of the phenyl moiety of the benzyl group by aromatic heterocycles such as isoxazole, (**28** and **29**). Results show that **28** was well tolerated indicating that the 5-methylisoxazol-3-yl group is a good isostere for a phenyl ring in this instance.

Synthesis of substituted benzyl analogues was undertaken in the bromo series as compound **2** had previously demonstrated lower metabolic clearance than **1** in rat in vivo study, Table 5.

The addition of both electron-donating and electron-withdrawing substituents was explored. In general, electron-withdrawing groups were well tolerated. Addition of a halogen atom to the 2-position, **38**, the 4-position, **47**, and the 2,4-position, **48**, was well tolerated. The most preferred substitution patterns were the 2,6- and the 2,4,6-positions. The 2,6-difluoro derivative **43** showed excellent activity with an IC_{50} of 1 nM making it the most potent compound in this series.

Table 5. In vitro EP_1 binding data for compounds **2** and **30**–**53**



Compound	Y	Binding pIC_{50}[a]
2	H	8.0 ± 0.2
30	2-Me	7.7 ± 0.2
31	4-Me	8.6 ± 0.1
32	3-CF_3	6.6 ± 0.1
33	4-CF_3	7.4 ± 0.1
34	3-OMe	7.3 ± 0.0
35	4-OMe	7.3 ± 0.3
36	3-$OCHF_2$	7.1 ± 0.1
37	4-OCF_3	7.8 ± 0.0
38	2-F	8.5 ± 0.1
39	4-F	8.2 ± 0.1
40	3,4-DiF	8.3 ± 0.2
41	2,5-DiF	8.1 ± 0.1
42	2,3-DiF	8.2 ± 0.1
43	2,6-DiF	9.0 ± 0.3
44	2,4,6-TriF	8.8 ± 0.5
45	2-Cl	7.9 ± 0.2
46	3-Cl	8.0 ± 0.2
47	4-Cl	8.0 ± 0.2
48	2,4-DiCl	8.3 ± 0.2
49	3,4-DiCl	7.0 ± 0.3
50	2-Cl, 4-F	7.8 ± 0.1
51	2-Cl, 6-F	7.9 ± 0.3
52	2-F, 4-CF_3	7.9 ± 0.1
53	2-F, 6-CF_3	7.0 ± 0.2

[a] Mean of at least three experiments.

The pharmacokinetic parameters of several compounds were assessed in vivo in a rat iv pharmacokinetic screen. Results are summarized in Table 6.

The data in Table 6 show that substitution of the benzyl group could be used to modulate the rate of clearance of the compounds although the cyclohexylmethyl derivative (**19**) showed the lowest blood clearance. Derivative **39** also showed similar metabolic stability to analogue **2** and displayed a good CYP450 profile (IC_{50} values all $\geqslant$17 μM, except the 2C9 isoform which displayed an IC_{50} of 3.9 μM). When administered orally to rats in 1% (w/v) methylcellulose aqueous formulation at a dose of 3 mg/kg, **39** was found to have 44% bioavailability. Due to these encouraging results, **39** was tested in Freund's complete adjuvant (FCA) model of inflammatory pain.[19] A dose-related effect was observed, 1 h post-dose, at doses of 3, 10 and 30 mg/kg with a calculated ED_{50} of 9.2 mg/kg, Figure 2.[20]

Compounds were synthesized as described in Schemes 1–5. Full experimental details and characterizing data for key compounds have been described.[18]

The methyl-pyrrole derivatives were prepared as outlined in Scheme 1.[21] Briefly, chlorosalicylaldehydes were

Table 6. In vivo pharmacokinetic data for selected compounds[a]

Compound	CLb (mL/min/kg)	Vss (L/kg)	$t_{1/2}$ (h)
1	67	3.0	0.5
2	41	0.6	0.3
14	48	0.9	nd
15	62	0.9	nd
17	54	1.0	0.3
19	28	0.5	0.4
39	42	0.7	nd
47	51	0.8	0.2
50	48	0.8	0.3

[a] Compounds administered intravenously in 0.9% and (w/v) saline solution containing 2% (v/v) DMSO and 10% (w/v) hydroxypropyl-β-cyclodextrin at a dose of 1 mg/kg.

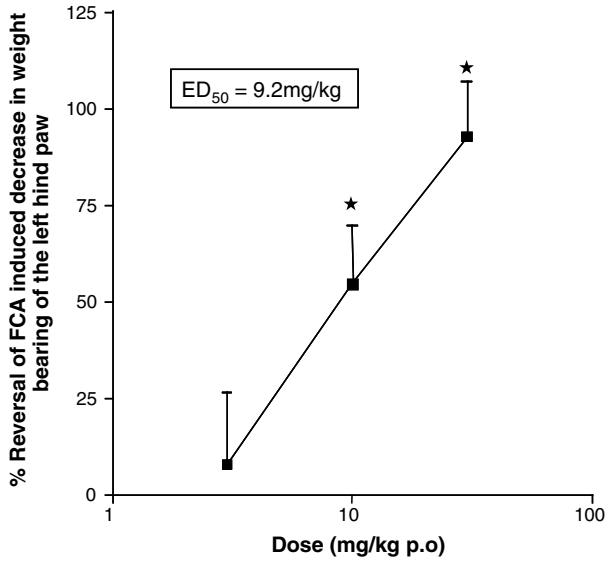
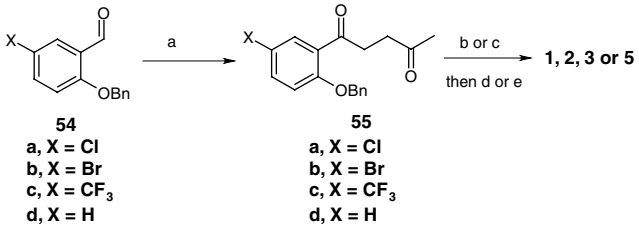


Figure 2. Dose–response graph for compound **39** in FCA.



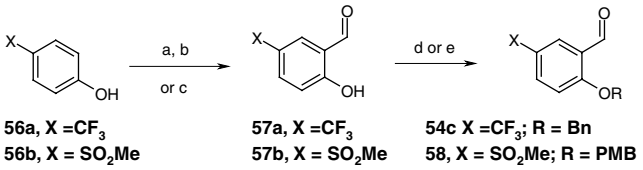
Scheme 1. Reagents and conditions: (a) MVK, TEA, 3-ethyl-5-(2-hydroxyethyl)-4-methyl-thiazolium bromide, reflux; (b) ethyl 3-aminobenzoate, PhMe, pTSA, reflux; (c) ethyl 3-aminobenzoate, reacti-vial, 145 °C; (d) 2 M NaOH, EtOH, reflux; (e) 2 M NaOH, EtOH, reacti-vial, 100–200 °C.

alkylated with benzyl bromide (K_2CO_3, DMF, 60 °C) to give 2-benzyloxy-5-chlorobenzaldehyde **54a–d**. Implementation of the Stetter reaction[22] with methylvinylketone (MVK) gave the corresponding 1,4-diketones **55a–d** which underwent Paal–Knorr condensation[23] with ethyl-3-aminobenzoate to give the requisite pyrroles **1–3** and **5**, upon basic hydrolysis of the esters, Scheme 1 and Table 7. The ethyl ester of Br-derivative **2** underwent Suzuki reaction with phenylboronic and thiophene-3-boronic acid to give derivatives **6** and **7**, respectively, under standard conditions (PhMe–EtOH, $Pd(PPh_3)_4$, K_2CO_3, reflux). The ethyl pyrrole derivatives **12** and **13** were prepared in an analogous fashion to the corresponding methyl derivatives **1** and **2** using ethylvinylketone (EVK).

Table 7. Yields for the synthesis of compounds **1–3** and **5**

Compound	X	Yields
1	Cl	81%,[a] 60%,[b] 100%[d]
2	Br	78%,[a] 55%,[b] 100%[d]
3	CF_3	32%,[a] 56%,[c] 96%[e]
5	H	72%,[a] 88%,[b] 91%[e]

[a] Yield for conditions a.
[b] Yield for conditions b.
[c] Yield for conditions c.
[d] Yield for conditions d.
[e] Yield for conditions e.

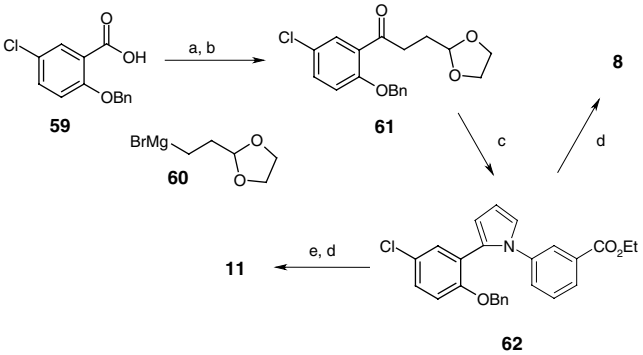


Scheme 2. Reagents and conditions: (a) 3,4-dihydro-2*H*-pyran, DCM, HCl in dioxane, 78%; (b) *n*-BuLi, TMEDA, −15 °C then DMF, −15 °C to rt, then aq HCl, 75%; (c) HMTA, TFA, 100 °C; (d) BnBr, K_2CO_3, DMF, 60 °C; (e) PMBCl, K_2CO_3, DMF, 70 °C.

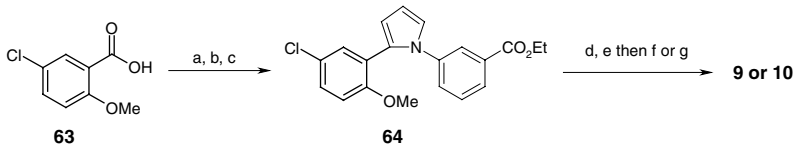
Table 8. Yields for the synthesis of compounds **54c** and **58**

Compound	X	Yields
54c	CF_3	78%,[a] 75%,[b] 19%[d]
58	SO_2Me	30%,[c] 100%[e]

[a] Yield for conditions a.
[b] Yield for conditions b.
[c] Yield for conditions c.
[d] Yield for conditions d.
[e] Yield for conditions e.



Scheme 3. Reagents and conditions: (a) DCM, $SOCl_2$, reflux; (b) **60**, THF, −60 °C to rt, 65%; (c) ethyl 3-aminobenzoate, NMP, pTSA, 150 °C, microwave 10 min, 50%; (d) 2M NaOH, EtOH, 100 °C, microwave 2 min, 100%; (e) NCS, THF, 100%.



Scheme 4. Reagents and conditions: (a) DCM, $SOCl_2$, reflux; (b) **57**, THF, −60 °C to rt; (c) ethyl 3-aminobenzoate, NMP, pTSA, 150 °C, microwave 12 min, 92%; (d) ICF_3, 30% H_2O_2, $FeSO_4{\cdot}7H_2O$, DMSO, 43%; (e) NaSMe, DMF, 100 °C, 4h; (f) 4-fluorobenzyl bromide, KI, K_2CO_3, MeOH, 60 °C; (g) 2,4-difluorobenzyl bromide, KI, K_2CO_3, MeOH, 60 °C.

The ester of compound **1** could be chlorinated or brominated with NCS or NBS to yield **16** and **17**, respectively, upon saponification. Suzuki reaction of **17** with phenylboronic acid, under standard conditions, furnished **18.**

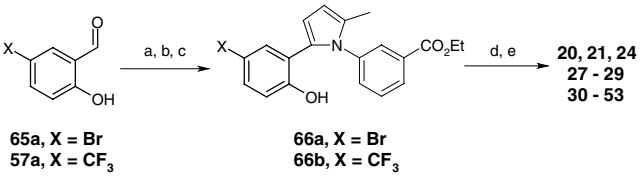
2-Benzyloxy-5-trifluoromethylbenzaldehyde **57a** was prepared from 4-trifluoromethylphenol **56a** as described by Schäfer.[24] Alkylation under standard conditions furnished **54c**, Scheme 2. 2-*para*-Methoxybenzyl-5-methylsulfoxidebenzaldehyde was prepared from 4-(methylsulfonyl)-phenol **56b** by Duff reaction[25] with hexamethylenetetramine (HMTA) to give salicylaldehyde derivative **57b** which was alkylated with *para*-methoxybenzyl chloride to give **58** as illustrated in Scheme 2 and Table 8.

The des-methyl pyrrole **8** was prepared as outlined in Scheme 3.[26] 2-Benzyloxy-5-chlorobenzoic acid **59** was converted to the corresponding acid chloride and reacted with the Grignard reagent **60**[26] to give the protected acetal **61**. Condensation with ethyl 3-aminobenzoate led directly to **62** which underwent base-mediated ester hydrolysis to give **8**, Scheme 3.

The Cl-pyrrole **11** was prepared by chlorination of **62** with NCS in THF followed by ester hydrolysis, Scheme 3.

The CF_3 pyrrole derivatives **9** and **10** were prepared as described in Scheme 4. 5-Chloro-2-methoxybenzoic acid **63** was converted to the corresponding acid chloride and reacted with Grignard reagent **60** then ethyl 3-aminobenzoate to give pyrrole **64**. The CF_3 group was installed by reaction with CF_3I in the presence of $FeSO_4{\cdot}7H_2O$ and H_2O_2 in DMSO.[21] Simultaneous deprotection of the methyl ether and ethyl ester was achieved by reaction with sodium thiomethoxide. Selective alkylation of the phenol, in the presence of the carboxylic acid, was achieved by reaction with the requisite benzyl bromide derivative in methanol with KI and K_2CO_3 as base, Scheme 4.

The analogues described in Tables 4 and 5 were prepared as detailed for the CF_3- and Br-derivatives in Scheme 5. The requisite salicylaldehyde derivatives **65a** and **57a** were protected as their *para*-methoxybenzyl derivatives, then subjected to the Stetter reaction[22] to give the analogous 1,4-diketones. Refluxing in toluene with pTSA followed by addition of ethyl 3-aminobenzoate and further heating effected a one-pot deprotection of the PMB ether and pyrrole formation to give **66a** and **b**. Sequential alkylation and ester hydrolysis furnished the desired compounds, Scheme 5.



Scheme 5. Reagents and conditions: (a) PMBCl, K_2CO_3, DMF, 60 °C; (b) MVK, TEA, 3-ethyl-5-(2-hydroxyethyl)-4-methyl-thiazolium bromide, reflux; (c) PhMe, pTSA, reflux 4–6 h then ethyl 3-aminobenzoate, reflux, 53% (X = Br), 74% (X = SO_2Me); (d) substituted benzyl bromide derivative, alkyl halaide or alkyl tosylate, K_2CO_3, DMF, 60 °C; (e) 2 M NaOH, EtOH, reflux or 2 M NaOH, EtOH, 100 °C, microwave 2 min or 2 M NaOH, EtOH, reacti-vial, 100–200 °C.

In summary we have described the SAR of a range of novel pyrrole EP_1 receptor antagonists. The most potent analogue **43** displayed an IC_{50} of 1 nM. We have also shown that the Me group on the pyrrole ring could be effectively replaced by a Cl-atom but not a CF_3 group. In addition, we have described several isosteric replacements for the benzyl group of **1** and have shown that replacement of this benzyl group by a cyclohexylmethyl group, to give **19**, resulted in lower metabolic clearance. Finally, compound **39** showed good bioavailability in rats and efficacy in a preclinical model of inflammatory pain.

Acknowledgments

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