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Discovery of novel biaryl heterocyclic EP_1 receptor antagonists

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Abstract—We describe the generation of novel EP_1 receptor antagonists by investigation of thiophene isosteres. In addition, we disclose preliminary in vitro and in vivo DMPK for selected compounds.

Non-steroidal anti-inflammatory drugs (NSAIDs), which inhibit both cyclooxygenase-1 (COX-1) and -2 (COX-2) and, more recently, selective inhibitors of (COX-2) have demonstrated efficacy in the treatment of inflammatory pain.[1] Although NSAIDs are effective analgesic agents, as a class they suffer from gastrointestinal (GI) toxicity as a common side-effect liability upon chronic dosing, which hampers their use in the treatment of chronic pain conditions such as rheumatoid arthritis (RA) and osteoarthritis (OA).[2] Whilst selective COX-2 inhibitors have been shown to have an improved GI side-effect profile relative to NSAIDs,[3] there has recently been concern over the cardiovascular safety of one of these agents which has resulted in the recent withdrawal from the market of Vioxx (Rofecoxib).[4] Prostaglandin E_2 (PGE_2) has been shown to be the major pro-inflammatory mediator from the arachidonic acid cascade.[5] Studies with mice lacking prostaglandin E synthase (PGES) have shown that PGE_2 plays an important role in pain.[5] The physiological actions of PGE_2 are attributed to agonism at four 7-transmembrane (7-TM) receptor subtypes, EP_{1-4}.[6] Studies with knock-out (KO) mice have implicated the EP_1 receptor in the generation of PGE_2-mediated allodynia[7] and inflammatory pain.[8] EP_1 receptor antagonists have shown efficacy in preclinical models of postoperative pain,[9] neuropathic pain[10] and allodynia.[11] There is also evidence to suggest that PGE_2-mediated pyrexia is controlled by the EP_1 receptor.[12] Furthermore, a recent report described the efficacy of the AstraZeneca compound ZD6416 in a human model of visceral hypersensitivity.[13] Thus, an EP_1 receptor antagonist has the potential to deliver efficacy in various pain states. Hence, we sought to identify potent selective, bioavailable EP_1 receptor antagonists as potential analgesics.

A survey of the literature revealed several reports of known EP_1 antagonists (Fig. 1).

Published compounds include ZD6416 (**1**)[14] from AstraZeneca, ONO-8713 (**2**)[15] and ONO-8711[16] (not shown), SC-51322 (**3**)[17] and analogues[18] from Searle and thiophene **4** from Merck Frosst.[19]

The replacement of ring systems and functional groups by isosteric groups is known.[20–22] Therefore, we sought

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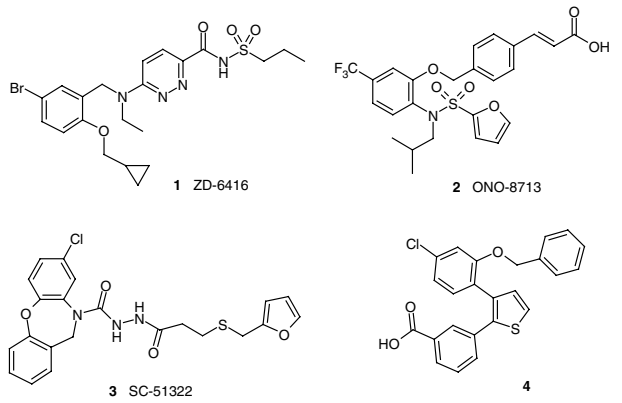


Figure 1. Literature EP_1 antagonists disclosed by AstraZeneca (**1**), Ono (**2**), Searle (**3**) and Merck Frosst (**4**).

to replace the thiophene of **4** with isosteric ring systems and investigate the effect of these changes on EP_1 activity and physicochemical properties.

Hence, we initiated an early stage programme to establish the role of the thiophene in these ligands, and to determine if this heterocycle could be replaced to generate potent EP_1 antagonists with good pharmacokinetic properties.

Various analogues were synthesized and tested in a [^{3}H]-PGE_2 binding assay.[23] Selected compounds were also tested in a functional assay (FLIPR).[24] Results are summarized in Table 1.

Thiophene **4** was found to be a potent EP_1 antagonist with a binding IC_{50} of approximately 5 nM and a functional K_i of approximately 0.3 nM, which is in good agreement with data published by Merck Frosst (binding $K_i = 4$ nM, functional $K_b = 7$ nM).[19]

We were pleased to find that the thiophene could be replaced by a cyclopentene or pyrrole ring with no decrease in activity, as shown by compounds **5**–**7**.

Although the initial pyrrole derivatives had an additional Me-group on the pyrrole ring, this substitution was found to be unnecessary for activity, as demonstrated by the activity of compound **8**. Addition of a second *N*-atom to **8** gave the pyrazole **10**, which was approximately 10-fold less active. The regioisomeric pyrazole **11** showed no measurable affinity up to a concentration of 1 μM. These results show that lipophilic ring systems are preferred, however, some polarity can be tolerated on the right-hand side of the central ring, but not on the left-hand side.

The pyrrole derivative **9** was considerably less active than its regioisomer **6**, indicating electronic or steric considerations are important as compounds **6** and **9** are of similar lipophilicity. Of the imidazole isomers prepared, compound **12** showed moderate activity, whereas analogue **13** was inactive.

Addition of a third *N*-atom to give the triazoles **14** and **15** resulted in complete loss of activity.

As it had been found that the thiophene ring in the COX-2 inhibitor DuP-697 could be replaced by a butenolide to give rofecoxib,[20e] we investigated a similar modification. We found that lactone **16** was well tolerated, whereas the regioisomer **17** was inactive, again demonstrating that polarity can be tolerated on the right-hand side of the central ring, but not the left-hand side.

Taken together these results show that the central ring needs to be lipophilic as the more hydrophilic rings such as triazole showed weaker activity whereas the most lipophilic rings, such as cyclopentene and pyrrole, showed the highest activity. Polarity can be tolerated in this central ring on the right-hand side but not the left-hand side, as shown by comparing pyrazole **10** with **11** and butenolide **16** with **17**.

We also sought to replace the thiophene with a six-membered ring and were encouraged to find that the phenyl derivative **18** displayed good activity. Its slightly diminished activity relative to the cyclopentene **5** and thiophene **4** could possibly be attributed to its narrower bond vector angle: 60° for the phenyl ring versus 69° for the cyclopentene and 2,3-disubstituted thiophene.

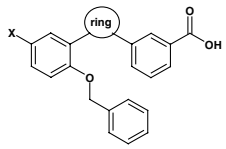
Replacement of the phenyl ring with a pyridine to give compounds **19**–**22** revealed an interesting trend. Compounds **19** and **21** showed good activity in both binding and functional assays. Compound **22** displayed somewhat weaker activity in the binding assay but good activity in the functional assay. Isomer **20** was essentially inactive in the binding assay but displayed high activity in the functional assay. The reasons for the discrepancy in assay results are not clear but could be due to an allosteric mode of action or modulation of other cellular pathways which affect intracellular calcium concentration. Replacement of the phenyl ring to give the pyrazine **23** led to a marked decrease in activity, again highlighting the preference for lipophilicity in this region, although a detrimental interaction with the polar nitrogen atoms cannot be ruled out.

The results shown in Table 1 show a similar trend to that observed for the phenyl acetic acid analogues of compound **4**, as described by Merck Frosst.[19]

Since several analogues displayed good affinity for the EP_1 receptor, selected compounds were profiled in vitro and in vivo to assess their pharmacokinetic parameters. Compounds were first screened for CYP450 interactions and metabolic stability (intrinsic clearance).

With the exception of pyrrole **9**, all compounds showed good metabolic stability in rat microsomes and displayed good CYP450 profiles, although all interacted with CYP2C9 to some degree (Table 2). To investigate how the in vitro metabolic stability results would translate into the in vivo situation, selected compounds were administered via intravenous injection to male Sprague–

Table 1. SAR for compound **4** and synthesized analogues **5–23**



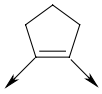
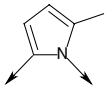
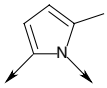
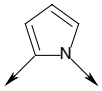
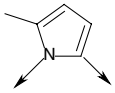
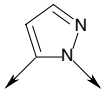
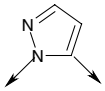
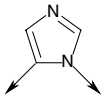
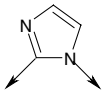
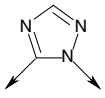
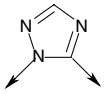
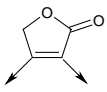
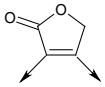
Compound	Ring	X	Binding pIC_{50}[a]	Functional pK_i[b,c]
4		Cl	8.2 ± 0.2 (12)	9.51 ± 0.15 (4)
5		Cl	7.9 ± 0.4 (12)	8.37 ± 0.14 (2)
6		Cl	8.1 ± 0.4 (16)	9.15 ± 0.01 (2)
7		Br	8.1 ± 0.2 (7)	n/t
8		Cl	8.0 ± 0.1 (12)	9.23 ± 0.89 (4)
9		Cl	6.7 ± 0.2 (8)	7.81 ± 0.18 (2)
10		Cl	7.1 ± 0.2 (4)	n/t
11		Cl	<6 ± 0 (4)	n/t
12		Cl	6.9 ± 0.4 (8)	8.45 ± 0.33 (2)
13		Cl	<6 ± 0 (8)	<6 (2)
14		Cl	<6 ± 0 (7)	<6 (2)
15		Cl	<6 ± 0 (8)	<6 (2)
16		Cl	7.1 ± 0.2 (3)	n/t
17		Cl	<6 ± 0.1 (8)	n/t
18		Cl	7.3 ± 0.5 (16)	7.54 ± 0.42 (4)

Table 1. (*continued*)

Compound	Ring	X	Binding pIC_{50}[a]	Functional pK_i[b,c]
19		Cl	7.0 ± 0.2 (8)	8.18 ± 0.01 (2)
20		Cl	<6 ± 0.1 (8)	7.28 ± 0.50 (2)
21		Cl	7.1 ± 0.1 (4)	6.86 ± 0.01 (2)
22		Cl	6.5 ± 0.2 (8)	7.55 ± 0.16 (2)
23		Cl	6.4 ± 0.2 (4)	n/t

[a] See Ref. 23.
[b] See Ref. 24.
[c] n/t, not tested.

Table 2. In vitro pharmacokinetic data for compounds **5–9** and **12**, **18**, **19**, and **21**

Compound	Rat CLi[a]	Human CLi[a]	CYP450[b,c] (IC_{50} at isozyme)
5	4.1	8.4	5.7 μM (2C9)
6	1.4	1.6	6.5 μM (2C9)
7	2.1	1.8	6.8 μM (2C9)
8	2.6	1.5	7.3 μM (2C9)
9	5.9	7.9	n/t
12	1.7	0.96	1.9 μM (2C9), <1 μM (3A4)
18	<0.5	<0.5	3.9 μM (2C9)
19	1.3	<0.5	All >50 μM
21	3.6	1.4	4.3 μM (2C9), 1.4 μM (3A4)

[a] Intrinsic clearance values measured in microsomes (mL/min/g liver).
[b] In vitro CYP450 assay results using Gentest protocol for isozymes 1A2, 2C9, 2C19, 2D6 and 3A4. Data quoted only for isozymes with IC_{50} < 10 μM.
[c] n/t, = not tested.

Dawley rats at a target dose of 1 mg/kg to assess blood clearance, volume of distribution and half-life (Table 3).

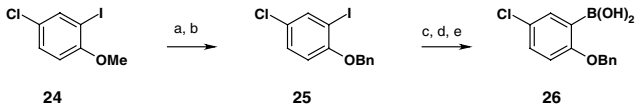
Most compounds displayed a relatively short half-life, due to a combination of a low volume of distribution and moderate to high blood clearance. Although phenyl derivative **18** appeared much more stable in vitro than the cyclopentene **5** and pyrrole **6** analogues, their in vivo

Table 3. In vivo pharmacokinetic data for compounds **5–7** and **18**

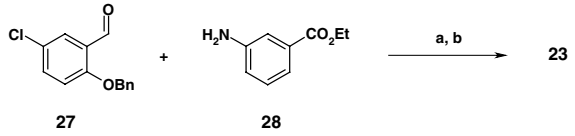
Compound	CLb (mL/min/kg)	V_{ss} (L/kg)	$t_{1/2}$ (h)
5	54	0.8	0.5
6	67	3.0	0.5
7	41	0.6	0.3
18	64	1.4	0.3

blood clearance values are high. This may be indicative that the major metabolic route is phase 2 metabolism (possibly glucuronidation) of the carboxylic acid. It is also interesting to note that it was possible to reduce the blood clearance in the pyrrole series by simple modification, changing a chlorine atom to a bromine atom, **6** versus **7** (Table 3). On the basis of these results and excellent EP_1 activity, the cyclopentene **5**, pyrroles **6** and **7** and benzene **18** were selected for further optimization. The results of these studies will be reported in future publications.

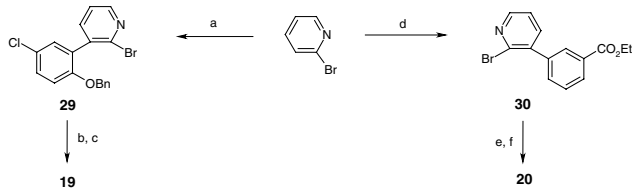
Compounds were synthesized according to literature procedures or as outlined in Schemes 1–4. Full experimental details and characterizing data for key compounds have been described.[25]



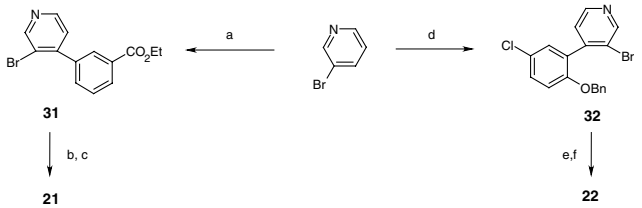
Scheme 1. Reagents and conditions: (a) BBr_3, DCM, −78 °C to rt, 91%; (b) BnBr, K_2CO_3, Me_2CO, 60 °C, 86%; (c) *n*-BuLi, THF, −100 °C; (d) B(O*i*-Pr)$_3$, −78 °C to rt; (e) 2 M HCl, 53% for three steps.



Scheme 2. Reagents and conditions: (a) glyoxal, AcOH, NH_4OAc, 100 °C, 2 h, 17%; (b) 2 M NaOH, EtOH, reflux.



Scheme 3. Reagents and conditions: (a) LDA, THF, $ZnCl_2$, −95 °C to rt, then **25**, $Pd(PPh_3)_4$, reflux, 83%; (b) 3-ethoxycarbonylphenylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, PhMe–EtOH 90 °C, 84%; (c) 2 M NaOH, EtOH, 60 °C, 78%; (d) LDA, THF, $ZnCl_2$, −95 °C to rt, then ethyl-3-iodoacetate, $Pd(PPh_3)_4$, reflux, 76%; (e) **26**, $Pd(PPh_3)_4$, K_2CO_3, PhMe–EtOH 90 °C, 75%; (f) 2 M NaOH, EtOH, rt, 78%.



Scheme 4. Reagents and conditions: (a) LDA, THF, $ZnCl_2$, −95 °C to rt, then ethyl-3-iodoacetate, $Pd(PPh_3)_4$, reflux, 44%; (b) **26**, $Pd(PPh_3)_4$, K_2CO_3, PhMe–EtOH 90 °C, 79%; (c) 2 M NaOH, EtOH, rt, 83%; (d) LDA, THF, $ZnCl_2$, −95 °C to rt, then **25**, $Pd(PPh_3)_4$, reflux, 32%; (e) 3-(ethoxycarbonylphenyl)boronic acid, $Pd(PPh_3)_4$, K_2CO_3, PhMe–EtOH 90 °C, 75%; (f) 2 M NaOH, EtOH, rt, 77%.

Scheme 1 depicts the synthesis of 2-benzyloxy-5-chloroiodobenzene **25** and 2-benzyloxy-5-chlorophenylboronic acid **26** which proved useful intermediates in the synthesis of several analogues.

Cyclopentene **5**, butenolide **17** and benzene **18** were prepared by sequential Suzuki reactions[26] with either 3-ethoxycarbonylphenylboronic acid or 3-*tert*-butoxycar bonylphenylboronic acid followed by **26** as described for related compounds.[20a,20c,27] Butenolide **16** and pyrazine **23** were prepared in a similar fashion by sequential Suzuki reactions[26,27] with **26** and 3-ethoxycarbonylphen ylboronic acid.

The methyl-pyrrole derivatives **6**, **7** and **9** were prepared via sequential Stetter reaction[28] with methylvinylketone (MVK) and Paal–Knorr condensation[29] in an analogous manner to published analogues.[20d] The des-methyl pyrrole **8** was prepared via literature procedures.[30] The pyrazoles **10** and **11** were prepared by known procedures.[20f] Imidazoles **12** and **13** were prepared via reaction of the requisite Schiff base with van Leusen's reagent (TosMIC)[20h,31] followed by ester hydrolysis. Imidazole **23** was prepared in two steps by condensation of aldehyde **27** with aniline **28** and glyoxal in the presence of ammonium acetate, followed by ester hydrolysis (Scheme 2).

Triazoles **14** and **15** were synthesized by standard methods.[32]

Synthesis of the four pyridine isomers employed the chemistry developed by Gallagher and co-workers.[33] *ortho*-Lithiation of 2-bromopyridine or 3-bromopyridine and trapping with $ZnCl_2$ followed by Negishi coupling[34] with **25** and ethyl-3-iodobenzoate gave **29** and **30**, respectively. Suzuki coupling[25] with 3-ethoxycarbonylphenylboronic acid and **26** followed by basic hydrolysis gave **19** and **20**, respectively (Scheme 3).

Pyridines **21** and **22** were prepared in a similar fashion, but starting from 3-bromopyridine (Scheme 4).

In summary, we have discovered several novel, potent, EP_1 antagonists by replacing the thiophene ring of **4** with alternative isosteric ring systems. The most promising analogues were profiled in vivo and the data generated support their use as lead compounds. Details of the optimization of these templates will be the subject of future publications.

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23. Compound potencies were determined using a radioligand binding assay where the ability of compounds to compete with tritiated prostaglandin E_2 ($[^3H]$-PGE_2) binding to the human EP_1 receptor was measured in Chinese hamster ovary-K1 (CHO-K1) cells into which a stable vector containing the EP_1 cDNA had previously been transfected. Cell membranes, competing compounds and $[^3H]$-PGE_2 (3 nM final assay concentration) were incubated in a final volume of 100 μL for 30 min at 30 °C. The radioactivity retained was measured by liquid scintillation counting in Packard TopCount scintillation counter.
24. The antagonist properties of compounds were assessed by their ability to inhibit the mobilisation of intracellular calcium ($[Ca^{2+}]_i$) in response to activation of the EP_1 receptor by prostaglandin E_2 (PGE_2). The amount of calcium produced was assessed using a calcium-sensitive fluorescent dye such as Fluo-3, AM and a suitable instrument such as a Fluorimetric Imaging Plate Reader (FLIPR).
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