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Discovery of GSK345931A: An EP_1 receptor antagonist with efficacy in preclinical models of inflammatory pain

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ABSTRACT

Herein we describe the medicinal chemistry programme to identify a potential back-up compound to the EP_1 receptor antagonist GW848687X. This work started with the lipophilic 1,2-biaryl benzene derivative **4** which displayed molecular weight of 414.9 g/mol and poor in vivo metabolic stability in the rat and resulted in the identification of compound **7i** (GSK345931A) which demonstrated good metabolic stability in the rat and lower molecular weight (381.9 g/mol). In addition, **7i** (GSK345931A) showed measurable CNS penetration in the mouse and rat and potent analgesic efficacy in acute and sub-chronic models of inflammatory pain.

Prostaglandin E_2 (PGE_2) is a proinflammatory mediator that has been linked with a causative role in pain and inflammation[1] and exerts its physiological action by activating four G-protein coupled receptors, EP_{1-4}.[2] Antagonists of the EP_1 receptor subtype have shown efficacy in preclinical models of inflammatory pain.[3] Thus further EP_1 antagonists with preclinical efficacy are needed to assess this mechanism of action in a clinical setting.

Following the publication of our initial work to discover novel EP_1 receptor antagonists[4] we have subsequently reported the optimization of the pyrrole series,[5] which led to the identification of compounds such as GW855454X (**1**),[5c] and the cyclopentene derivative GW848687X (**2**)[6] which was selected as a development candidate (Fig. 1).

GW848687X was efficacious in acute and sub-chronic preclinical models of inflammatory pain,[6] namely the Complete Freund's Adjuvant (CFA) model of inflammatory pain[5a,6] and a joint pain model of inflammatory pain.[6,7] However, we previously reported that close structural analogues of GW848687X, such as GW845706X (**3**), Figure 1, failed to show efficacy in the joint pain sub-chronic model of inflammatory pain. Studies to understand this lack of efficacy in a sub-chronic model of inflammatory pain will be the subject of future publications.

As part of an ongoing programme we wished to identify a potential back-up compound to GW848687X which also demonstrated efficacy in both acute and sub-chronic preclinical models of inflammatory pain but also offered some form of structural diversity over GW848687X.

Extensive profiling of GW848687X had shown oxidation of the allylic position of the cyclopentene ring to be one of the metabolic routes. Thus in order to address the above, we elected to use the 1,2-biarylbenzene lead compound **4**[4] as our starting point (Fig. 2).

Compound **4** showed good in vitro activity in both [^{3}H]-PGE_2 binding[4] and functional[4] (mobilization of intracellular Ca^{2+} measured by FLIPR) assays, IC_{50} 50 nM and K_i 32 nM, respectively. Despite showing low intrinsic clearance in rat and human liver microsomes, the rat in vivo pharmacokinetic (PK) profile was not optimal. Furthermore the compound was highly lipophilic, with a *c*log*P* of 7.0 (measured log*D* 2.2 at pH 7.4). Thus, our goals were to investigate the SAR of this template and to optimize EP_1 activity whilst improving the in vivo DMPK profile.

Initial structure–activity relationships (SAR) established that the Cl-atom on the A-ring (X-group) was not critical for activity, compare **4** to **5a** (Table 1) but if moved (Y-position), **5b**, was detrimental to activity (Table 1). Substitution of the central phenyl ring (B-ring) revealed that only the 4-position was amenable to substitution, compound **5e**, although this did not increase EP_1 affinity. This result

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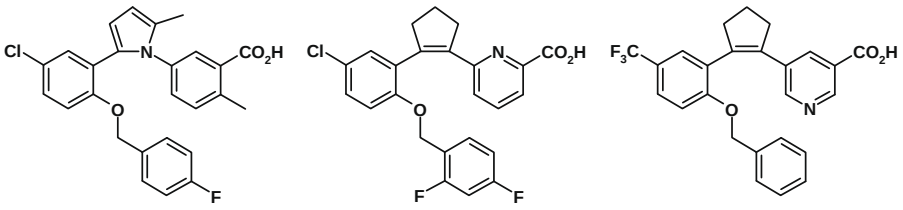


Figure 1. Selected published GSK EP_1 receptor antagonists GW855454X (**1**), GW848687X (**2**) and GW845706X (**3**).

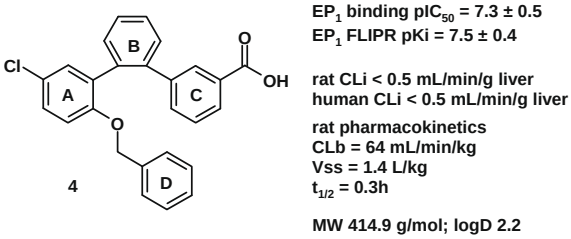


Figure 2. Profile of lead compound **4**.

is in line with results in the related pyrrole series, where it was found a methyl group was tolerated in an analogous position.[4,5a] It was also found that the acid group could be moved from the *meta*- to the *ortho*-position without affecting activity, whereas translocation to the *para*-position drastically reduced activity (Table 1).

We next investigated substitution of the benzoic acid (C-ring). Substitution in the 2-, 4- or 6-position generally resulted in a decrease in EP_1 affinity, **6a–c**, (Table 2). The effect of substitution at the 6-position is in contrast to the SAR in the related pyrrole series where substitution of the 6-position was well tolerated.[5c] Substitution at the 5-position was best tolerated. The addition of acylamino groups generally increased affinity **6e–i**; propylacetamide **6g** increased the affinity by more than 10-fold.

Although a good level of affinity was achieved with these substitutions (Tables 1 and 2), the physicochemical properties of these compounds were not optimal, as already seen in the related pyrrole series.[5b,c]

As we had found that the C-ring could be replaced by aromatic heterocycles in the cyclopentene series, and that this change had resulted in compounds with good oral bioavailability and in vivo efficacy we decided to investigate a similar change in the current series.

Thus, the phenyl ring (C-ring) in compound **4** was replaced with pyridine to give compound **7a** (Table 3) which resulted in a slight increase in the EP_1 affinity.

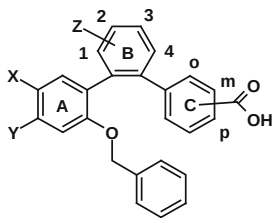
Further SAR investigation of the R-group on the A-ring revealed that benzyl group could be substituted with halogenated benzyl groups (**7b**–**h**). As in the cyclopentene series the 2,4-difluorobenzyl derivative (**7c**) was the most preferred benzyl derivative (Table 3).

As we had found that the benzyl group could be replaced by alkyl groups, and in particular an *iso*-butyl group, in the pyrrole series[5a] we decided to investigate similar modifications in the current series. Thus compounds **7i**–**l** were prepared. The SAR showed that the *iso*-butyl group proved optimal (compound **7i**) and was considerably better than any of the other groups investigated (**7j**–**l**) (Table 3).

Based on structural differentiation over GW848687X and its overall profile, including in vitro activity data, CYP450 inhibition data (CYP450 IC_{50} values, 1A2 >100 μM, 2C19 62 μM, 2C9 25 μM, 2D6 >100 μM, 3A4 89 μM) and good in vitro metabolic stability (Table 4),[8] compound **7i** (GSK345931A) was selected for further evaluation.

In terms of solubility, GSK345031A (sodium salt) showed moderate aqueous solubility, low solubility in simulated gastric fluid (SGF) and good solubility in fasted and fed state simulated intestinal fluid (FaSSIF and FeSSIF), Table 5.[9] The compound displays two pK_a values, 4.8 and 1.3, which were attributed to the carboxylic acid and pyridyl N-atom, respectively.[10]

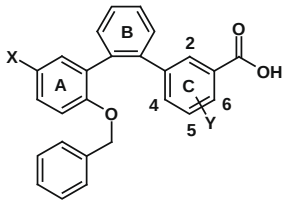
Table 1
In vitro binding data for compounds **4** and **5a–h**



Compound	X	Y	Z	Acid	Binding pIC_{50}[a]
4	Cl	H	H	m	7.3 ± 0.5
5a	H	H	H	m	7.7 ± 0.0
5b	H	Cl	H	m	6.5 ± 0.1
5c[b]	Cl	H	2-Me	m	<6
5d[b]	Cl	H	3-Me	m	<6
5e[b]	Cl	H	4-Me	m	7.0 ± 0.0
5f[b]	Cl	H	3-Cl	m	<6
5g	Cl	H	H	o	7.7 ± 0.1
5h	Cl	H	H	p	6.1 ± 0.0

[a] Values are the means of at least three experiments.
[b] Sodium salt.

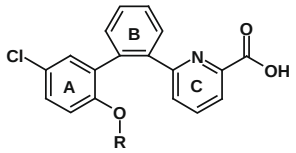
Table 2
In vitro binding data for compounds **6a–i**



Compound	X	Y	Binding pIC_{50}[a]
4	Cl	H	7.3 ± 0.5
5a	H	H	7.7 ± 0.0
6a	H	2-Me	6.3 ± 0.3
6b	H	4-F	7.1 ± 0.1
6c	H	6-Cl	6.9 ± 0.1
6d	H	5-F	7.2 ± 0.1
6e	Cl	5-NHAc	8.0 ± 0.0
6f	Cl	5-NHCOEt	8.2 ± 0.1
6g	Cl	5-NHCOPr	8.7 ± 0.1
6h	Cl	5-NHCO*i*-Pr	8.0 ± 0.1
6i	Cl	5-$NHCOCH_2OMe$	8.4 ± 0.1

[a] Values are the means of at least three experiments.

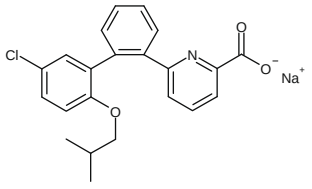
Table 3
In vitro binding data for compounds **7a–l**



Compound	R	Binding pIC_{50}[a]
4	n/a	7.3 ± 0.5
7a	Bn	8.0 ± 0.2
7b	4-F Bn	8.3 ± 0.3
7c	2,4-diF Bn	8.4 ± 0.2
7d[b]	2-Cl, 4-F Bn	7.2 ± 0.1
7e[b]	2-F, 4-Br Bn	7.3 ± 0.0
7f[b]	2-F, 4-Cl Bn	7.7 ± 0.1
7g[b]	2,4,6-triF Bn	7.9 ± 0.1
7h[b]	2-F Bn	7.4 ± 0.1
7i[b]	*i*-Bu	7.8 ± 0.1
7j[b]	Bu	7.0 ± 0.1
7k[b]	Pr	6.6 ± 0.1
7l[b]	Cyclopentylmethyl	6.8 ± 0.2

[a] Values are the means of at least three experiments.
[b] Sodium salt.

Table 4
In vivo pharmacokinetic data for **7i** (GSK345931A)



7i: GSK345931A

Species	Mouse	Rat	Dog	Monkey	Human
CLi[a]	0.6	0.7	⩽0.5	8.0	1.9

[a] Intrinsic clearance in liver microsomes (mL/min/g liver), values are the mean of three experiments.

Table 5
Solubility data for **7i** (GSK345931A)[a]

Medium	Water	SGF[b]	FaSSIF[c]	FeSSIF[d]
Solubility at 2 h	499	33	1030	1217
Solubility at 24 h	612	11	1052	1143

[a] Units = μg/mL.
[b] Simulated gastric fluid.[9]
[c] Fasted state simulated intestinal fluid.[9]
[d] Fed state simulated intestinal fluid.[9]

Table 6
In vivo pharmacokinetic data for **7i** (GSK345931A)

Species	CLb[a] (mL/min/kg)	Vss[a] (L/kg)	$t½$[a] (h)	Fpo[b]
Rat	11 ± 2	1.9 ± 0.6	3.5 ± 1.3,	95 ± 19%
Cynomolgus monkey	26 ± 5	0.5 ± 0.1	0.8 ± 0.5	34 ± 18%

[a] 1 mg/kg intravenous dose. Vehicle = 2% (v/v) DMSO added to saline solution containing 10% (w/v) Kleptose. Data are the mean from three animals.
[b] 3 mg/kg oral dose. Vehicle = 1% (w/v) methycellulose aq. Data are the mean from three animals.

GSK345931A also displays good oral bioavailability in the rat and moderate bioavailability in the cynomolgus monkey (Table 6).

Despite being a carboxylic acid, GSK345931A shows measurable CNS penetration in both the mouse and the rat with brain-to-blood (Br:Bl) ratios of 0.24 and 0.33, respectively (Table 7).

In the rat, GSK345931A displayed a low unbound fraction in both blood and brain tissue (Fu Bl = 0.50 ± 0.14%, Fu Br = 0.53 ± 0.07%, Kbb = 0.93).[11]

When tested in Complete Freund's Adjuvant (CFA) model of inflammatory pain,[5,6] GSK345931A produced a dose related reversal of hypersensitivity with calculated ED_{50} values of 1.6 and 2.4 mg/kg (when dosed at 1, 2 and 3 mg/kg or 1, 3 and 10 mg/kg, respectively).

Bioanalysis from both studies revealed a dose-proportional increase in exposure (Table 8). The overlapping dose groups (1 and 3 mg/kg) provided comparative exposure. The CNS penetration, as measured by brain-to-blood ratio (Br:Bl), was similar to that found in the steady state studies (Table 7). This data shows that despite being a carboxylic acid, GSK345931A demonstrates reasonable CNS penetration and good whole brain concentrations (Table 8).

On consideration of free brain concentrations (Table 9), the efficacy in this model appears to be driven by peripheral concentra-

Table 7
In vivo CNS penetration data for **7i** (GSK345931A)

Species	Blood conc. (nM)	Brain conc. (nM)	Br:Bl
Mouse[a]	1120 ± 406	277 ± 154	0.24 ± 0.04
Rat[b,c]	1663 ± 20	550 ± 55	0.33 ± 0.05

[a] 3 mg/kg oral dose. Samples taken 0.5 h post-dose.
[b] Steady state penetration study. Compound dosed at a rate of 0.28 mg/kg/h free acid over 18 h via femoral vein cannula. Steady state CLb 8 mL/min/kg.
[c] For comparison, GW848687X (**2**) was found to have a Br:Bl of 0.20 in the rat at steady state.

Table 8
Bioanalysis of blood and brain samples from CFA studies with GSK345931A

Dose	Study[a]	Blood conc.[b] (nM)	Brain conc.[c] (nM)	Br:Bl[d]
1 mg/kg	A	1633 ± 518	425 ± 61	0.27 ± 0.07
2 mg/kg	A	2139 ± 423	645 ± 240	0.22 ± 0.07
3 mg/kg	A	3330 ± 1042	1477 ± 184	0.72 ± 0.64[e]
1 mg/kg	B	948 ± 118	317 ± 12	0.36 ± 0.05
3 mg/kg	B	4274 ± 693	1719 ± 214	0.47 ± 0.17
10 mg/kg	B	15418 ± 2453	7261 ± 1073	0.48 ± 0.19

[a] Study A conducted at doses of 1, 2 and 3 mg/kg p.o., study B conducted at doses of 1, 3 and 10 mg/kg p.o. Samples taken 1 h post-dose.
[b] Mean of seven values.
[c] Mean of three values.
[d] Mean of three values where the blood and brain samples were taken from the same three animals.
[e] One rat displayed significantly higher Br:Bl. Individual ratios were 0.30, 0.39 and 1.46.

Table 9
Calculated free concentrations in blood and brain from CFA studies

Dose	Study[a]	Calc. free Blood conc.[b] (nM)	Calc. free brain conc.[b] (nM)
1 mg/kg	A	8.2	2.3
2 mg/kg	A	10.7	3.4
3 mg/kg	A	16.7	7.8
1 mg/kg	B	4.7	1.7
3 mg/kg	B	21.4	9.1
10 mg/kg	B	77.1	38.5

[a] Study A conducted at doses of 1, 2 and 3 mg/kg p.o., study B conducted at doses of 1, 3 and 10 mg/kg p.o. Samples taken 1 h post-dose.
[b] Calculated from data in Table 8 using rat percentage unbound data (0.50% in blood and 0.54% in brain).

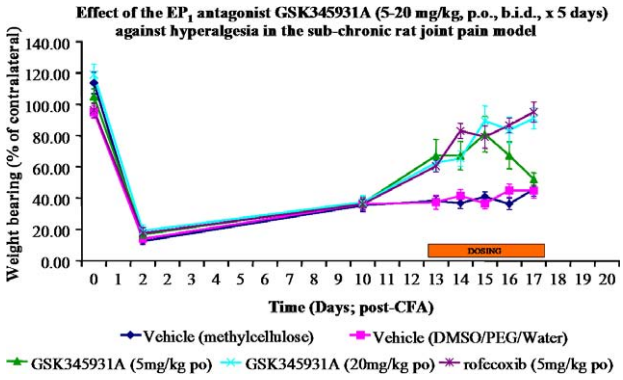


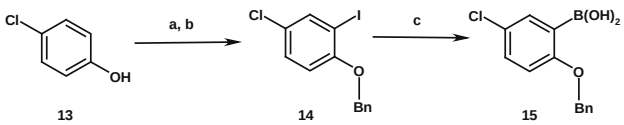
Figure 3. Effect of 5 mg/kg p.o. b.i.d. and 20 mg/kg p.o. b.i.d. GSK345931A (**7i**) in the sub-chronic rat joint pain assay versus vehicle (methylcellulose) and positive control (rofecoxib 5 mg/kg p.o.) and positive control vehicle (DMSO/PEG/water).

tions (binding pIC_{50} 7.8, i.e., IC_{50} 16 nM at the human receptor, binding pIC_{50} 7.9, i.e., IC_{50} 12.6 nM at the rat receptor) as the free brain concentrations are below the in vitro IC_{50} value at doses that proved efficacious.

Based on its overall profile GSK345931A (**7i**) was evaluated in a sub-chronic rat joint pain model[7] at doses of 5 and 20 mg/kg (b.i.d.) and showed efficacy equivalent to rofecoxib (Fig. 3).

Blood samples were taken 1 h post-dose on day one from a satellite study group, and terminal blood and brain samples were taken 1 h post-dose from both satellite and treatment groups (Table 10). The data show that the blood concentrations were higher on day 1 than day 5 for both dose groups. Conversion of the whole blood and brain concentrations to free blood and brain concentrations helps to explain the lack of efficacy in the 5 mg/kg group on the fifth day of dosing (Table 10) as both the free blood and brain concentrations are below the in vitro IC_{50} value (rat IC_{50} 12.6 nM). Based on the blood concentration for the 5 mg/kg satellite group on day 1, it would be expected that this dose group would have a free blood and brain concentration in excess of the in vitro IC_{50} value which may explain the observed efficacy in the earlier phase of this study. Taken together these results are consistent with the thesis that the free drug concentrations drive efficacy in this model, however it is not possible to conclude the site of action (i.e., peripheral or central) from the current data as both the free blood and brain concentrations are below the in vitro IC_{50} value for the 5 mg/kg dose group on day 5 of dosing. Further work to delineate the site of action for EP_1 antagonists will be the subject of future publications.

Limited selectivity data was collected as related compounds had not shown any significant activity at related prostanoid receptors, with the exception of the thromboxane A_2 (TP) receptor.[5,6] Thus, GSK345931A shows good selectivity over the EP_3 receptor in a functional assay, EP_1 FLIPR pK_i 8.6, EP_3 FLIPR pK_i 5.7, and ~100-fold selectivity over the TP receptor, TP FLIPR pIC_{50} 5.8 pK_i 6.5, no activity at the $PGF_{2\alpha}$ receptor (FP), FLIPR $pIC_{50} < 5$, and no

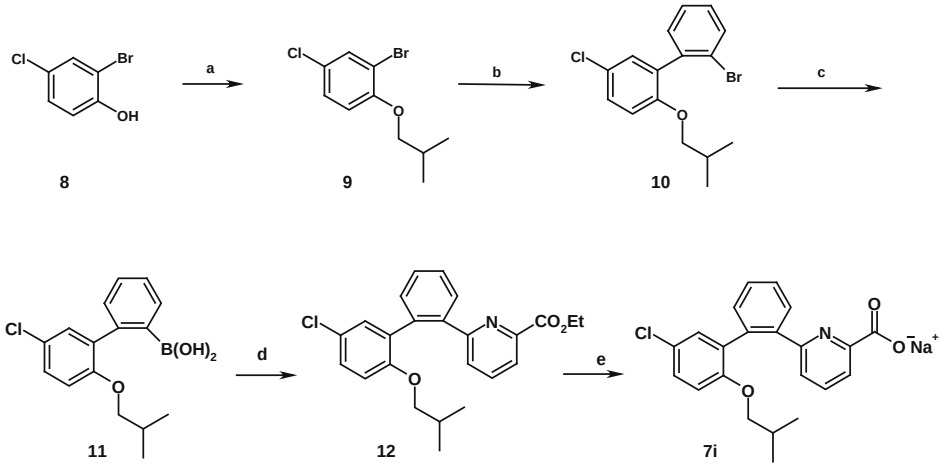


Scheme 2. Reagents and conditions: (a) BnBr, K_2CO_3, Me_2CO, reflux. (b) I_2, Selectfluor™, CH_3CN (c) *n*-BuLi, THF, −100 °C, $B(Oi\text{-}Pr)_3$, −78 °C–rt., 2 M HCl.

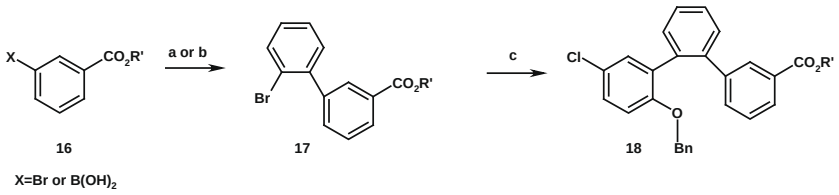
Table 10
Bioanalysis data and calculated free brain concentrations from the rat sub-chronic joint pain efficacy study (Fig. 3)

Dose	Study group[a]	Blood conc.[b] (nM)	Brain conc.[b] (nM)	Br:Bl	Calc. free blood conc.[c] (nM)	Calc. free brain conc.[c] (nM)
5 mg/kg	A, day 1	5266 ± 1149	[d]n/t	n/t	26.3	n/t
5 mg/kg	A, day 5	1665 ± 459	822 ± 181	0.54	8.3	4.4
5 mg/kg	B, day 5	1630 ± 462	1074 ± 298	0.57	8.2	5.7
20 mg/kg	A, day 1	25900 ± 1916	[d]n/t	n/t	129.5	n/t
20 mg/kg	A, day 5	6771 ± 2467	3627 ± 996	0.50	33.9	19.2
20 mg/kg	B, day 5	5526 ± 2409	3213 ± 1483	0.45	27.6	17.0

[a] Study group A = satellite animals, values are the mean from five animals. Study group B = treatment group, values are the mean from seven animals.
[b] Samples taken 1 h post-dose.
[c] Calculated using rat percentage unbound data (0.50% in blood and 0.54% in brain).
[d] n/t, not tested.



Scheme 1. Reagents and conditions: (a) *iso*-butyl bromide, K_2CO_3, DMF, 80 °C, 94%. (b) (2-bromophenyl)boronic acid, $Pd(PPh_3)_4$, K_2CO_3, PhMe-EtOH, 90 °C, 47%. (c) *n*-BuLi, THF, −100 °C; $B(Oi\text{-}Pr)_3$, −78 °C–rt; 2 M HCl, 83%. (d) Ethyl 6-bromo-2-pyridinecarboxylate, $Pd(PPh_3)_4$, K_2CO_3, PhMe-EtOH, 90 °C, 100%. (e) EtOH, 2 M NaOH, 96%.



Scheme 3. Reagents and conditions: (a) 1,2-dibromobenzene, $Pd(PPh_3)_4$, K_2CO_3, PhMe-EtOH, 90 °C. (b) (2-bromophenyl)boronic acid, $Pd(PPh_3)_4$, K_2CO_3, PhMe-EtOH, 90 °C. (c) **15**, $Pd(PPh_3)_4$, K_2CO_3, PhMe-EtOH, 90 °C.

activity at hERG cardiac channel (^{3}H-dofetilide binding assay $pIC_{50} < 4.5$). Counter screening against the peroxisome proliferator-activated (PPAR) receptors revealed GSK345931 had no activity at the α- or δ-isoforms ($pEC_{50} < 5$, binding $pK_i < 4.7$ at PPAR-α and PPAR-δ) and very weak activity at the PPAR-γ receptor (pEC_{50} 5.4, binding pK_i 4.9).

Overall the data presented support further development of GSK345931A.

GSK345931A was prepared on a 50 g scale as described in Scheme 1. Alkylation of phenol **8** gave ether **9** which underwent Suzuki reaction[12] to give **10**. Lithium–halogen exchange, trapping with tri-isopropyl borate and hydrolysis gave boronic acid **11** which underwent a second Suzuki reaction[12] to give **12**. Saponification of **12** yielded **7i** (GSK3435931A) as the sodium salt (Scheme 1). Full experimental procedures and characterising data have been published.[13]

For the synthesis of analogues, a slightly modified procedure was employed. 4-Chlorophenol was alkylated then iodinated in the presence of Selectfluor™[14] to give **14**. Iodine–lithium exchange then reaction with tri-isopropyl borate and hydrolysis gave boronic acid **15** (Scheme 2).

Derivatives with a benzoic acid derivative on the right hand side could be prepared by the versatile route outlined in Scheme 3.

In summary we have taken the lipophilic lead compound **4**, log*D* 2.2, MW 414.9 g/mol and reduced the molecular weight and lipophilicity to give compound **7i** (GSK345931 A), log*D* 1.9, MW 381.9 g/mol which shows considerably improved pharmacokinetic parameters in addition to excellent in vivo efficacy in acute and sub-chronic models of inflammatory pain. The data reported herein support the further development of GSK345931A.

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