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Non-acidic pyrazole EP_1 receptor antagonists with in vivo analgesic efficacy

Adrian Hall,* Andy Billinton, Susan H. Brown, Nicholas M. Clayton, Anita Chowdhury, Gerard M. P. Giblin, Paul Goldsmith, Thomas G. Hayhow, David N. Hurst, Ian R. Kilford, Alan Naylor, Barry Passingham and Lisa Winyard

Neurology Centre of Excellence for Drug Discovery, GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex, CM19 5AW, UK

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Abstract—Replacement of the carboxylic acid group in a series of previously described methylene-linked pyrazole EP_1 receptor antagonists led to the discovery of amide, reversed amide and carbamate derivatives. Two compounds, **10a** and **10b**, were identified as brain penetrant compounds and both demonstrated efficacy in the CFA model of inflammatory pain.

Antagonists for the prostaglandin E_2 (PGE_2) receptor EP_1 have shown efficacy in preclinical models of inflammatory pain.[1,2]

Several lines of evidence suggest that EP_1 receptors are present in the central nervous system (CNS) as well as in the periphery.[3]

Most known EP_1 receptor antagonists and, indeed, prostaglandin receptor ligands in general, contain a carboxylic acid or surrogate which has been proposed to bind to an arginine residue in the seventh transmembrane region (TM7) of the prostaglandin receptors.[1,4] Acidic compounds generally exhibit low levels of CNS penetration.[5]

Thus, it would be of interest to identify non-acidic EP_1 antagonists, that can access the CNS, as pharmacological tools.

Recently, several groups, including ourselves, have disclosed their efforts to identify non-acidic EP_1 receptor antagonists.[6–9] Thus, we replaced the carboxylic acid in compound **1** with amides to give derivatives **2** and **3** (Fig. 1).[6] Although these compounds had high affinity for the EP_1 receptor, they were extremely lipophilic, and as a result, displayed poor properties which hampered further development. Subsequently, we discovered the methylene-linked pyrazole derivatives exemplified by **4** and **5** (Fig. 1).[10] Compound **5** was found to be considerably less lipophilic than compound **1** (measured log *D* 1.0 vs 2.5, respectively).[11]

Thus, we sought to investigate whether the carboxylic acid in compounds from the methylene-linked pyrazole series could be replaced by amides and carbamates and whether these derivatives would retain EP_1 affinity (binding $pIC_{50} \geqslant 7.5$, i.e., $IC_{50} \geqslant 32$ nM) with lower lipophilicity.

This work led to the identification of two brain penetrant carbamate derivatives which are the first non-acidic EP_1 receptor antagonists to demonstrate in vivo efficacy in the CFA model of inflammatory pain when dosed orally.[12,13]

All compounds reported herein were tested in [^{3}H]-PGE_2 binding assay.[14,15]

Replacement of the acid in compound **5** with a primary amide (compound **6a**) led to a 10-fold decrease in affinity and a substantial gain in lipophilicity. As we had found that the benzyl group could be replaced by an iso-butoxy group (i.e., template 6 could be replaced by

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* Corresponding author. Tel.: +44 1279 643464; e-mail: adrian.2.hall@gsk.com

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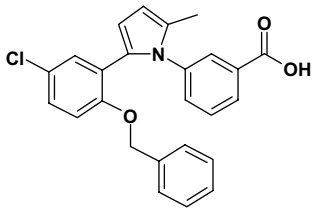
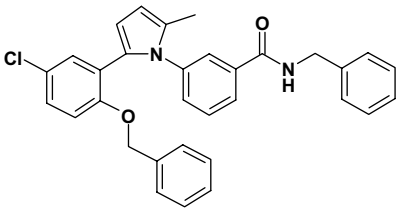
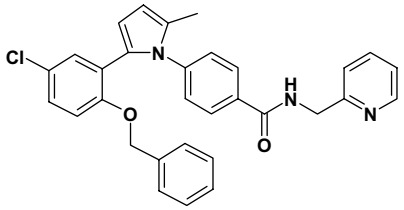


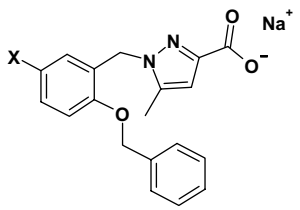
1; binding pIC_{50} 8.1
logD 2.5



2; binding pIC_{50} 7.6



3; binding pIC_{50} 8.6



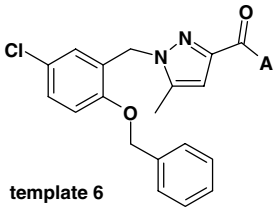
4; X = Br, binding pIC_{50} 8.2, logD 1.2
5; X = Cl, binding pIC_{50} 8.0, logD 1.0

Figure 1. Selected GSK EP_1 receptor antagonists.

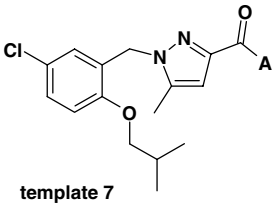
template 7)[2a] compound **7a** was prepared and found to have equal affinity to its benzyl analogue (**6a**) but considerably lower lipophilicity (log*D* 3.1 vs log*D* 3.7, respectively) (Table 1).

Alkyl amides (**6b** and **c**) showed no improvement in affinity. However, anilide **6d** displayed slightly higher affinity than the primary or alkyl amides. Monosubstitution of the phenyl ring of the anilide had little impact on affinity or appeared detrimental (**6e** and **f**); however, the 2,6-difluoroanilide (**6g**) displayed affinity equivalent to the starting acid (**5**). The phenyl ring of the anilide could be replaced by pyridine (**6h**), albeit with a slight decrease in affinity. The benzyl amide (**6i**) maintained affinity equivalent to anilide (**6d**). Again, the phenyl ring could be replaced by pyridines (**6j–l**) with the 2-pyridyl (**6j**) isomer having the highest affinity of the pyridyl isomers. Finally, attempts to lower the lipophilicity by installing a weakly basic centre (**7b** and **c**) resulted in weak activity (Table 1).

Table 1. SAR for amides **6a–l** and **7a–c**



template 6



template 7

Compound	A	Binding pIC_{50}[a]	log*D*[b]
5[c]	OH	8.0 ± 0.2	1.0
6a	NH_2	6.9 ± 0.0	3.7
6b	NHMe	7.0 ± 0.1	>3.7
6c	NH-*i*-Pr	6.9 ± 0.1	>3.7
6d	NHPh	7.4 ± 0.4	>3.7
6e	NH(3-FPh)	6.7 ± 0.1	2.8
6f	NH(4-FPh)	7.1 ± 0.1	3.0
6g	NH(2,6-diF)Ph	8.0 ± 0.1	3.7
6h	NH-(2-pyridyl)	6.9 ± 0.1	>3.7
6i	$NHCH_2Ph$	7.4 ± 0.2	>3.7
6j	$NHCH_2$(2-pyridyl)	7.6 ± 0.1	>3.7
6k	$NHCH_2$(3-pyridyl)	7.3 ± 0.1	>3.7
6l	$NHCH_2$(4-pyridyl)	7.1 ± 0.2	>3.7
7a	NH_2	6.9 ± 0.1	3.1
7b	NH-(1-piperidinyl)	6.7 ± 0.2	3.3
7c	NH-(1-morpholinyl)	6.6 ± 0.1	3.1

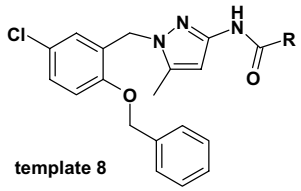
[a] See Refs. 14 and 15.
[b] See Ref. 11.
[c] See Fig. 1 for structure.

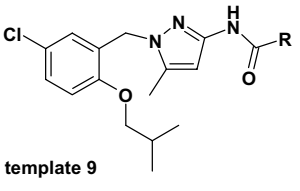
Disappointingly, the potent amide derivatives in Table 1 were very lipophilic and the high lipophilicity generally resulted in compounds with poor metabolic stability both in vitro and in vivo, see later (Table 4).

We next turned our attention to reversed amides (Table 2). Again, it was found that the benzyl and *iso*-butyl groups were generally interchangeable in terms of affinity (compare template 8, i.e., **8d**, to template 9, i.e., **9b**). The SAR revealed that some affinity was achievable with small alkyl groups (**8a**) and that affinity could be increased by moving to larger groups (**8b** and **c**). Cycloalkyl groups (**8d** and **9a**) were well tolerated and resulted in potent compounds. The cyclohexylmethyl derivative **8e** was the most potent analogue of the compounds shown in Table 2. Cyclic ethers (**8f–h**) displayed approximately similar affinity to their alkyl analogues. Benzamide **8i** displayed high affinity, however, substitution of the benzamide had little effect on affinity (**8j**). Homologation to the phenethylamide (**8k**) did not increase affinity. Pyridines were generally well tolerated (**8l–n**).

Most of the reversed amide analogues discussed above were found to have poor metabolic stability in vitro, see Table 4. Therefore, in an attempt to improve metabolic stability the benzylic position of several analogues

Table 2. SAR for reversed amides **8a**–**r** and **9a**





Compound	R	Binding pIC_{50}[a]	log *D*[b]
8a	Me	6.5 ± 0.1	>3.7
8b	*i*-Pr	7.6 ± 0.1	>3.7
8c	CH_2*t*-Bu	8.0 ± 0.2	>3.7
8d	Cyclopentyl	7.8 ± 0.2	3.5
8e	CH_2cyclohexyl	8.2 ± 0.1	3.2
8f	2-THF[b]	7.4 ± 0.0	>3.7
8g	3-THF[c]	7.4 ± 0.1	>3.7
8h	4-THP	7.2 ± 0.0	>3.7
8i	Ph	7.8 ± 0.1	>3.7
8j	2,6-diF-Ph	7.9 ± 0.2	>3.7
8k	CH_2Ph	7.9 ± 0.1	>3.7
8l	CH_2pyridin-2-yl	7.7 ± 0.1	>3.7
8m	CH_2pyridin-3-yl	7.4 ± 0.1	>3.7
8n	CH_2pyridin-4-yl	7.3 ± 0.1	>3.7
8o	CMe_2phenyl	7.2 ± 0.2	>3.7
8p	$C(Me)_2$pyridin-2-yl	7.8 ± 0.1	>3.7
8q	CF_2Ph	7.4 ± 0.1	>3.7
8r	CF_2pyridin-2-yl	7.6 ± 0.2	3.1
9a	Cyclohexyl	7.5 ± 0.4	>3.7
9b	Cyclopentyl	7.6 ± 0.1	>3.7

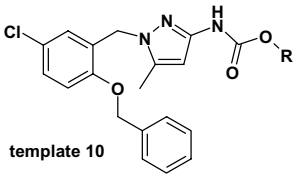
[a] See Refs. 14 and 15.
[b] See Ref. 11.
[c] Racemic.

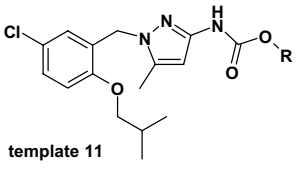
was blocked by methyl or fluorine substitution (**8o**–**r**); however, this had little impact on metabolic stability; **8p** CLi > 50 mL/min/g liver, **8q** CLi 10.0 mL/min/g liver, **8r** 24.0 mL/min/g liver (all rat microsomes),[16] implying that this is not a major site of metabolism. Furthermore, the reversed amides generally displayed similar lipophilicity to that of the amides described in Table 1. It should be noted that accurate measurement of log *D* values was problematic as most compounds displayed log *D* values at, or in excess of, the upper limit of the assay.

Based on the reversed amide results, we investigated the activity of carbamates (Table 3). The *t*-butyl carbamates (**10a** and **11a**) met our target affinity, again highlighting that the benzyl and *iso*-butyl groups were interchangeable in terms of in vitro affinity. The *iso*-propyl carbamates (**10b** and **11b**) also showed good activity. A range of carbamates were thus investigated (**10c**–**g** and **11c**–**e**) and the data revealed that a range of R groups were tolerated, although affinity decreased with decreasing R size (compounds **10e**–**g**). It was also possible to combine the steric requirements for affinity whilst adding some polarity as shown by the cyclic ethers (**10g** and **11d**) (Table 3). Again accurate measurement of log *D* values was problematic as most compounds displayed log *D* values at, or in excess of, the upper limit of the assay.

In the final aspect of the SAR investigation, we explored the role of the methyl group on the pyrazole ring, Figure 2. We were interested to see if the methyl group could be removed, in order to decrease lipophilicity and to remove a potential site for metabolism. However, as results show (Fig. 2), removal of the methyl group caused approximately a 10-fold decrease in affinity. This is in line with observations in the corresponding acid series.[19]

Table 3. SAR for carbamates **10a**–**h** and **11a**–**d**





Compound	R	Binding pIC_{50}[a]	log *D*[b]
10a	*t*-Bu	7.6 ± 0.2	>3.7
10b	*i*-Pr	7.5 ± 0.0	>3.7
10c	Bn	7.1 ± 0.1	3.1
10d	CH_2(2-pyridyl)	7.1 ± 0.1	3.1
10e	*i*-Bu	7.6 ± 0.1	3.3
10f	Et	7.1 ± 0.1	>3.7
10g	Me	6.7 ± 0.1	>3.7
10h	3-(S)-THF	7.1 ± 0.1	2.7
11a	*t*-Bu	7.5 ± 0.1	>3.7
11b	*i*-Pr	7.3 ± 0.1	>3.7
11c	$C(Me)_2CF_3$	7.3 ± 0.3	3.5
11d	4-THP	7.2 ± 0.1	3.4

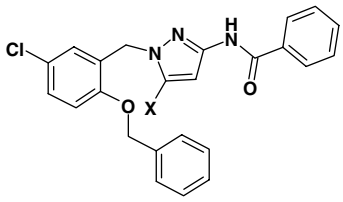
[a] See Refs. 14 and 15.
[b] See Ref. 11.

The desmethyl pyrazoles **12** and **13** (Fig. 2) showed similar metabolic stability to their analogous methyl derivatives, **8i** and **8k**, respectively, implying that the methyl group on the pyrazole is not a major site of metabolism.

Further data from in vitro metabolic stability studies in rat liver microsomes and rat in vivo pharmacokinetic studies are shown in Table 4. Most compounds displayed high intrinsic clearance values in rat liver microsomes (CLi > 5 mL/min/g liver, equivalent to >60% turnover in 30 min).[16] Carbamates **10a** and **10b** showed the best in vitro metabolic stability. This translated into a good in vivo pharmacokinetic profile for **10a**, which coupled a balance of moderate blood clearance with a large volume of distribution (**10b** and **11a** were not assessed via iv administration due to the structural similarity to **10a** and similar in vitro metabolic stability to **10a**). This improved metabolic stability is not due to lower lipophilicity as both compounds **10a** and **10b** have similar or higher log *D* values than other compounds in Table 4.

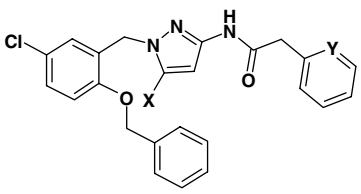
Based on the above data, compounds **10a** and **10b** were selected for further profiling.

Thus compounds **10a** and **10b** were tested in a functional assay where the increasing concentrations of both compounds showed a concentration-dependent rightward shift of the PGE_2 dose–response curve. Schild analysis[20] showed both compounds to be competitive antagonists with a slope of 1 (Fig. 3 and Table 5).



8i; X = Me, binding pIC_{50} 7.8 ± 0.1
rat CLi = 7.3 mL/min/g liver

12; X = H, binding pIC_{50} 6.6 ± 0.1
rat CLi = 7.0 mL/min/g liver



8k; X = Me, Y = CH binding pIC_{50} 7.9 ± 0.1
rat CLi = 17.0 mL/min/g liver

13; X = H, Y = CH, binding pIC_{50} 6.8 ± 0.1
rat CLi = 11.0 mL/min/g liver

8l; X = Me, Y = N, binding pIC_{50} 7.7 ± 0.1

14; X = H, Y = N, binding pIC_{50} 6.4 ± 0.1

Figure 2. Comparison of 5-methyl and 5-desmethyl pyrazole amides (**8i** vs **12**) and reversed amides (**8k** vs **13** and **8l** vs **14**).

In order to assess the distribution characteristics of these non-acidic compounds a steady state CNS penetration study was conducted with **10a** in the rat (Table 6). Data show that the compound readily penetrated the brain with a brain-to-blood ratio (Br:Bl) of 3.44:1. The level of CNS penetration could possibly be attributed to the low molecular weight (428 g/mol) and low polar surface area (PSA, 65.4 $Å^2$).

Having identified compound **10a** as a promising tool compound, we were interested in investigating its efficacy in the CFA model of inflammatory pain.[12] However, we wished to dose the compound orally and were concerned about its acid stability. Thus we conducted a stability study in simulated gastric fluid (SGF, 0.4% NaCl in 0.1 M HCl). Sampling was conducted by LC/MS every 30 min for 2 h and showed minor degradation (1.5% loss of parent). The major degradant (0.9% after 2 h) appeared to correspond to the aminopyrazole derivative **16** (see synthetic Scheme 2). These data showed **10a** to be stable in moderately acidic media and suitable for oral administration.

Table 4. Rat intrinsic clearance data[16] and intravenous pharmacokinetic data[17] for selected compounds

Compound	CLi[a]	CLb[b] (mL/min/kg)	Vss[b] (L/kg)	$t1/2$[b] (h)
6d	12.0	n.d.[c]	n.d.[c]	n.d.[c]
6i	15.0	75	9.3	4.6
6j	30.0	68	3.6	1.3
8h	9.1	55	3.3	1.0
9a	15.0	68	3.5	1.7
8i	7.3	50	4.1	2.5
8k	17.0	59	7.5	2.9
10a	2.2	42	8.6	3.0
11a	3.0	n.d.[c]	n.d.[c]	n.d.[c]
10b	3.4	n.d.[c]	n.d.[c]	n.d.[c]
10d	8.4	98	3.0	n.d.[c]
10e	8.2	124	3.9	n.d.[c]
10h	11.0	86	3.7	0.8
11d	17.0	n.d.[c]	n.d.[c]	n.d.[c]

[a] Rat intrinsic clearance measured in rat liver microsomes (mL/min/g liver).[16]
[b] 1 mg/kg iv infusion.
[c] n.d., not determined.

Having assessed the acid stability of **10a**, compounds **10a** and **10b** were profiled in the CFA model of inflammatory pain[12] (Table 7). Both compounds showed excellent efficacy in this model and gave equivalent reversal of hypersensitivity equivalent to celecoxib. The analysis of blood and brain samples from these studies demonstrated a Br:Bl of 2.26–2.73:1 and 1.73–2.20:1 for **10a** and **10b**, respectively, which was in good agreement to the ratio observed with **10a** at steady state (Table 6).

Compounds **10a** and **10b** were found to be potent antagonists in an EP_1 Ca^{2+} mobilization assay (FLIPR),[14,21] **10a** pK_i 7.8, **10b** pK_i 7.3. Both compounds displayed good selectivity over the EP_3 receptor, **10a** and **10b** FLIPR $pK_i < 5$. Furthermore, neither compound showed any activity at the TP receptor (FLIPR $pIC_{50} < 5$, $pK_i < 5.4$). Both compounds were found to have low CYP inhibition potential at five major isoforms, **10a** $IC_{50} > 100$ μM (1A2), >100 μM (2C19), 16 μM (2C9), >100 μM (2D6), >100 μM (3A4), **10b** IC_{50} 7.8 μM (1A2), 69 μM (2C19), 17 μM (2C9), >100 μM (2D6), ⩾81 μM (3A4).

Compounds were synthesized as shown in Schemes 1–4. Full experimental procedures and characterizing data for key compounds have been published.[21] The free acid version of compound **5** (**5a**) was converted to the amide derivatives described in Table 1 as exemplified in Scheme 1.

The carbamates described in Table 3 were prepared as outlined in Scheme 2. Carboxylic acid **5a** underwent Curtius rearrangement[22] using *tert*-butanol as solvent to give compound **10a**. Deprotection of **10a** gave aminopyrazole **16** which allowed the synthesis of further carbamates, for example **10b**, by reaction with the requisite chloroformate (Scheme 2). Alternatively, analogous carbamates could be prepared directly from the analogous carboxylic using the Curtius rearrangement[22] and the requisite alcohol in either toluene or dioxan as a solvent (Scheme 2).

The trimethylsilyl carbamate (e.g., compound **17**) was found to offer better yields during the deprotection step,

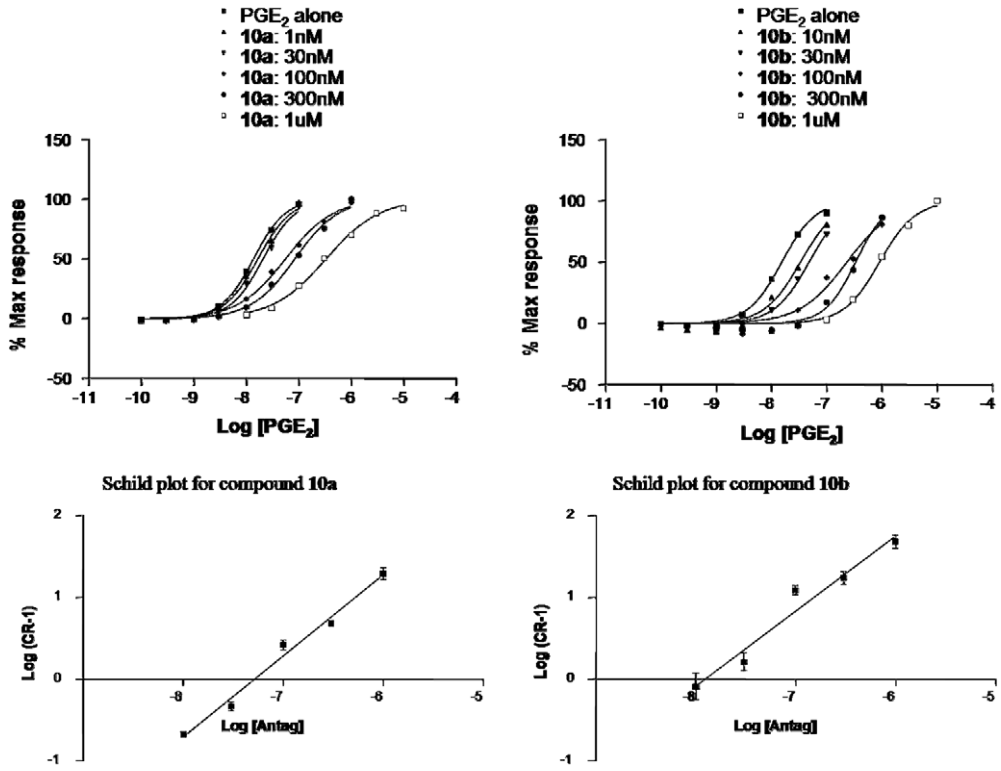


Figure 3. Representative graphs for Schild analysis with **10a** and **10b**.

Table 5. Schild analysis for **10a** and **10b**[20]

Compound	pA_2[a]	Slope[a]	Binding pIC_{50}[b]
10a	7.3 ± 0.1	0.9 ± 0.1	7.6 ± 0.2
10b	8.1 ± 0.2	1.0 ± 0.1	7.5 ± 0.0

[a] Mean of four experiments.
[b] See Refs. 14, 15, and 21.

Table 6. Steady state CNS penetration data for compound **10a**

Compound	CLb[a] (mL/min/kg)	Brain Css[a] (μM)	Blood Css[a] (μM)	Br:Bl[a]
10a	54	1.403	0.408	3.44:1

[a] Steady state (18 h) iv infusion. See Ref. 18 for details.

than the corresponding *tert*-butyl analogue and was thus used more routinely. Derivative **17** was prepared from carboxylic acid **15**, by Curtius rearrangement.[22] Deprotection with TBAF delivered aminopyrazole **18** which underwent standard amide formation, as described in Scheme 3.

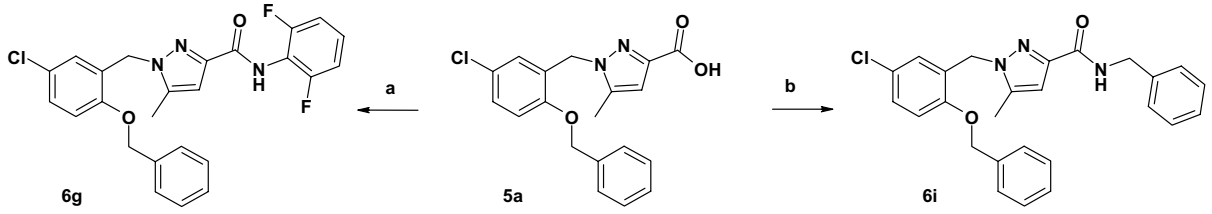
The carboxylic acids for the synthesis of derivatives **8o–r** were prepared as outlined in Scheme 4. Ethyl-2-pyridylacetate (**19**) was dialkylated with methyl iodide and hydrolyzed to give carboxylate derivative **21**. The α-difluoro derivatives **24** and **25** were prepared by difluorination of methyl phenylacetate (**18**) or ethyl-2-pyridyl acetate (**19**) followed by saponification. Carboxylates **21** and **24–25** were then coupled with aminopyrazole **16** as described in Scheme 3 (1-hydroxybenzotriazole, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride) using DMF (derivatives **21** and **25**) or CH_2Cl_2 as solvent to give compounds **8o–r**.

In conclusion, we have investigated amide, reversed amide and carbamate analogues of our original acidic series. Although the compounds were generally of lower affinity than the carboxylic acids we identified several potent antagonists. Further investigation highlighted two carbamate derivatives as competitive antagonists with good pharmacokinetic profiles and significant brain

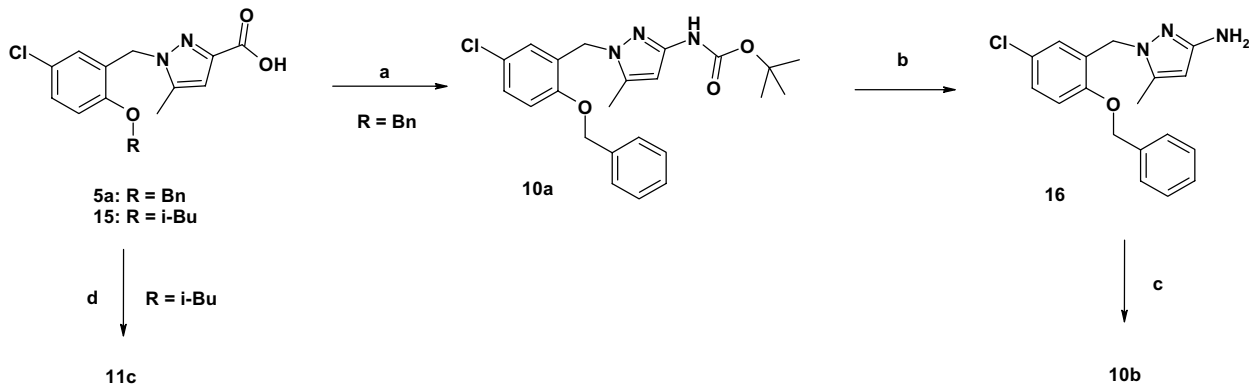
Table 7. CFA data for **10a** and **10b**

Compound	ED_{50}[a] (mg/kg)
10a	5.36[b]
10b	4.6,[c] 1.89[d]

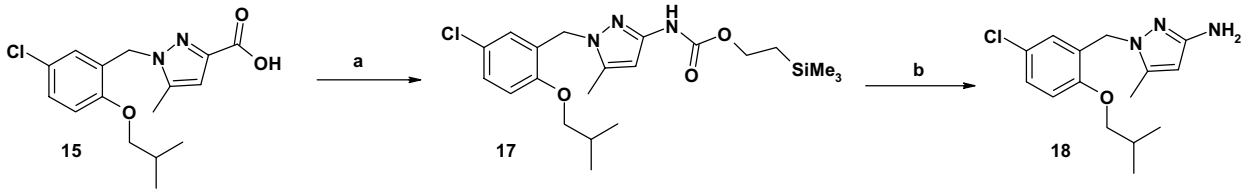
[a] Oral doses of 1, 3 and 10 mg/kg or 1, 3, 10 and 30 mg/kg, efficacy readout (weight bearing) and samples taken 1 h post-dose.
[b] Vehicle = 2% DMSO and 20% Kleptose water. Doses of 1, 3, 10 and 30 mg/kg gave blood concentrations of 57 nM, 210 nM, 302 nM and 299 nM, respectively (values are the mean from seven rats). Doses of 1, 3, 10 and 30 mg/kg gave mean brain concentrations of 106 nM (mean of two rats), 473 nM (mean of three rats), 781 nM (mean of three rats) and 836 nM (mean of three rats), respectively, giving a Br:Bl of 2.66, 2.66, 2.26 and 2.73, respectively (average of three rats except the 1 mg/kg dose group which is the mean of two rats).
[c] Vehicle = 2% NMP, 2% miglyol, and 2% solutol–Kleptose in water. Doses of 1, 3 and 10 mg/kg gave blood concentrations of 153 nM, 749 nM and 1401 nM, respectively (mean of seven rats). The dose of 10 mg/kg gave a mean brain concentration of 3.328 μM (mean of three rats), giving a Br:Bl of 2.2 (mean of three rats).
[d] Vehicle = 1% DMSO, 66% PEG400, 33% water, Br:Bl 1.73 from 10 mg/kg dose group (mean of seven rats).



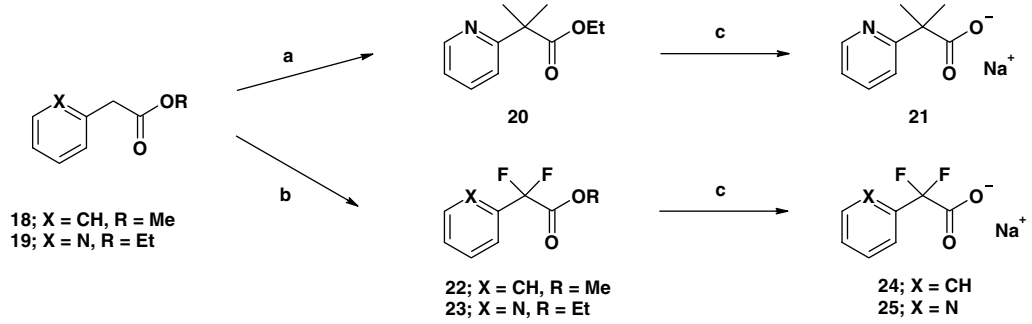
Scheme 1. Reagents and conditions: (a) i—CH_2Cl_2, $(COCl)_2$, rt, 2 h, evaporation; ii—CH_2Cl_2, NEt_3, 2,6-difluoroaniline, rt, 2 h; (b) $BnNH_2$, HOBt, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride, CH_2Cl_2, rt.



Scheme 2. Reagents and conditions: (a) **5a**, diphenylphosphoryl azide, NEt_3, *t*-BuOH, reflux; (b) i—CH_2Cl_2–CF_3CO_2H (1:1), rt, 3 h then evaporation; ii—EtOH–2 M NaOH (2:1), 60 °C, 1 h; (c) *iso*-propyl chloroformate, CH_2Cl_2, pyridine, rt, 2 h; (d) **15**, diphenylphosphoryl azide, PhMe, NEt_3, 90 °C, 30 min, then 1,1,1-trifluoro-2-propanol, 90 °C, 4 h.



Scheme 3. Reagents and conditions: (a) PhMe, diphenylphosphoryl azide, NEt_3, 2-(trimethylsilyl)-ethanol, 100 °C, 3 h; (b) TBAF, THF, 50 °C, 1 h.



Scheme 4. Reagents and conditions: (a) THF, *t*-BuOK, rt, 10 min, then MeI, cooling (water bath), 1 h; (b) THF, potassium bis(trimethylsilyl)amide, −78 °C, 45 min, then $MnBr_2$, 30 min, then *N*-fluorobenzenesulfonamide, −78 °C for 30 min then warmed to rt the stirred 3 h; (c) 2 M NaOH, rt.

penetration in the rat. Both of these compounds demonstrated efficacy in the CFA model of inflammatory pain and as such are the first non-acidic EP_1 receptor antagonists to show efficacy in this preclinical model of inflammatory pain. Furthermore, both compounds readily penetrate the CNS and may therefore prove useful pharmacological tools. It should be noted that EP_1 receptor antagonists with extremely low levels of CNS penetration have shown activity in the CFA model of inflammatory pain.[23]

Acknowledgment

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18. Compound **10a** was formulated as a solution in 0.9% (w/v) saline containing 2% (v/v) DMSO and 20% (w/v) Kleptose and administered as an intravenous infusion over 18 h at a dose rate of 5 mL/kg/h (0.518 mg/kg/h) to a male Sprague–Dawley rat. Serial blood samples were taken every 15 min over the last hour of infusion to confirm steady state concentrations had been achieved. After the 18 h period a blood sample was taken and the rat was culled, the brain removed and homogenized. Brain and blood samples were analysed for compound **10a** by LC/MS/MS.
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