Bioorganic & Medicinal Chemistry Letters 18 (2008) 4027–4032

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Discovery of brain penetrant, soluble, pyrazole amide EP_1 receptor antagonists

Adrian Hall [a,*], Andy Billinton [a], Alan K. Bristow [b], Susan H. Brown [a], Anita Chowdhury [a], Leanne Cutler [a], Gerard M. P. Giblin [a], Paul Goldsmith [a], Thomas G. Hayhow [a], Ian R. Kilford [a], Alan Naylor [a], Barry Passingham [a], D. Anthony Rawlings [a]

[a] Neurolosciences Centre of Excellence for Drug Discovery, GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK
[b] Pharmaceutical Development, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK

ARTICLE INFO

Article history:
Received 21 April 2008
Revised 28 May 2008
Accepted 31 May 2008
Available online 5 June 2008

Keywords:
Non-acidic EP_1 antagonist
Amide EP_1 antagonist
Brain penetration
CNS penetration
Solubility
Improved solubility
Oral exposure
Oral absorption

ABSTRACT

We describe the discovery of a series of pyrazole amide EP_1 receptor antagonists with good aqueous solubility and CNS penetration. In order to achieve solubility we investigated the incorporation of a basic group in the region of the molecule previously occupied by a carboxylic acid, which was known to be a key element of the pharmacophore. This study led to the identification of compounds such as **4h**, **4j** and **10b** which demonstrated brain-to-blood ratios of 0.8:1–2.0:1 in addition to good solubility and metabolic stability.

Prostaglandin E_2 (PGE_2) is produced in various tissues where it has been shown to activate four G-protein-coupled receptors (GPCRs) known as EP_1, EP_2, EP_3 and EP_4.[1] Several lines of evidence indicate that PGE_2 is the main prostanoid responsible for pain and inflammation[2] and that these undesirable effects arise via activation of the EP_1 receptor subtype, thus, EP_1 receptor antagonists have the potential to act as analgesics.[3]

In support of this hypothesis we have demonstrated several series of EP_1 receptor antagonists have analgesic properties in preclinical models of inflammatory pain, such as Complete Freund's Adjuvant model of inflammatory pain.[4]

We have previously reported on pyrazole EP_1 receptor antagonists, for example **1**[5] (Fig. 1). We found that it was possible to replace the carboxylic acid in **1** by non-acidic groups, such as amides and reversed amides, as exemplified by compounds **2** and **3**.[6] These analogues were able to mimic the carboxylic acid in terms of EP_1 pharmacology despite the fact that it has been construed that the acid in prostaglandin ligands forms a key ionic interaction with the receptor.[1a] Furthermore, despite the absence of a key pharmacophore, these compounds retained a good binding efficiency index (BEI)[7] and good ligand efficiency (LE)[8] (Fig. 1).

Despite this encouraging in vitro pharmacology, we found that replacing the carboxylic acid by non-ionisable functional groups unmasked the intrinsic lipophilicity of these compounds, which was undesirable, and resulted in high lipophilicity (e.g., compounds **2** and **3** log*D* >3.7, Fig. 1) and poor solubility (see Table 4).

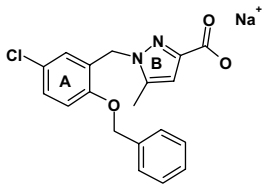
As part of an ongoing medicinal chemistry programme we were interested in identifying further non-acidic EP_1 receptor antagonists with lower lipophilicity and better solubility. In addition, we wished to identify compounds that could penetrate the central nervous system (CNS) and thus we wanted to identify compounds without a carboxylate group.

To improve the solubility of the pyrazole amide series, we used compounds **2** and **3** as a starting point and attempted to introduce a basic group in order to aid solubility. In SAR investigations with related templates we had found this to be a difficult challenge as the EP_1 receptor has a strong preference for lipophilic ligands and incorporation of even mild basicity or polarity was poorly tolerated (data not shown).

Based on the data in Figure 1, we first started this work with the reversed amide **3**, as it had shown more encouragement in terms of metabolic stability. We also switched the benzyloxy group on the A-ring to the isobutoxy group as we had found this to result in equipotent compounds but with reduced lipophilicity.[6] The results for this segment of work are summarized in Table 1.

* Corresponding author. Tel.: +44 1279 643464.
E-mail address: adrian.2.hall@gsk.com (A. Hall).

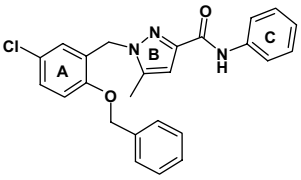
0960-894X/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2008.05.118



1; EP_1 binding pIC_{50} 8.0 ± 0.2
logD 1.0

BEI: 22.4

LE: 0.44

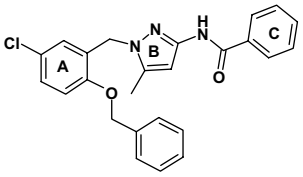


2; EP_1 binding pIC_{50} 7.4 ± 0.4
logD >3.7

rCLi 12.0 mL/min/g liver

BEI: 17.1

LE: 0.33



3; EP_1 binding pIC_{50} 7.8 ± 0.1
logD >3.7

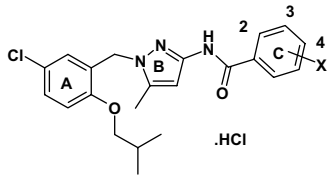
rat CLi 7.3 mL/min/g liver
rat CLb 50 mL/min/kg, Vdss 4.1 L/kg
rat t½ 2.5 hours

BEI: 18.1

LE:0.35

Figure 1. Selected GSK methylene-linked pyrazole EP_1 receptor antagonists.

Table 1
SAR for 3-substituents, compounds **4a–l**



Compound	X	Binding pIC_{50}[a]
3[b]	H	7.8 ± 0.1
4a	2-CH_2OH	7.6 ± 0.1
4b	3-CH_2NHEt	6.3 ± 0.1
4c	3-CH_2NMe_2	6.2 ± 0.1
4d	3-CH_2pyrrolidin-1-yl	6.9 ± 0.3
4e	3-CH_2piperidin-1-yl	6.3 ± 0.1
4f	3-CH_2morpholin-4-yl	6.6 ± 0.2
4g	4-CH_2OH	7.9 ± 0.2
4h	4-CH_2NHEt	7.0 ± 0.1
4i	4-CH_2NMe_2	7.0 ± 0.2
4j	4-CH_2-pyrrolidin-1-yl	7.3 ± 0.2
4k	4-CH_2piperidin-1-yl	7.4 ± 0.0
4l	4-CH_2morpholin-4-yl	7.3 ± 0.1

[a] See Ref. 4a or 9.
[b] Benzyloxy substituent on A-ring, see Figure 1.

Compounds were tested in [^{3}H]-PGE_2 binding assay, selected compounds were also tested in a functional assay (FLIPR).[4a,9]

Our strategy was to introduce a basic group joined by a methylene linker to the phenyl ring (C-ring) and to systematically investigate its placement around the phenyl ring. We initiated our investigation at the 2-position. Disappointingly, chemistry issues prevented us from testing the methylamino derivatives,[10] however we were able to test the intermediate hydroxymethyl derivative (**4a**) which indicated that we could at least introduce polarity into this region of the molecule (Table 1).

Next, we turned our attention to the 3-position of the benzamide moiety. Disappointingly addition of basic groups to this position consistently decreased binding affinity by ~10-fold (**4b–f**), compared to the parent unsubstituted compound **3** (Table 1).

We then turned our attention to the 4-position of the benzamide and were pleased to find, like the 2-position, that the hydroxymethyl group was tolerated (**4g**). Addition of a range of primary and secondary methylamino groups was tolerated (**4h–l**) and had little effect on binding affinity, leading us to conclude that this group was not making any particular interaction with the receptor. Compounds also showed activity in a functional antagonism assay (FLIPR), e.g., **4h** pK_i 6.8 ± 0.1, **4j** pK_i 6.8 ± 0.6.

Despite the addition of the basic groups several compounds retained reasonable binding efficiency, **4h** BEI 16.3 and LE 0.32, **4j** BEI 15.6 and LE 0.30.

Based on the success of the SAR summarized in Table 1 we went on to investigate substitution of the benzylic position of the methylamino group, compounds **5a** and **5b** (Fig. 2). Addition of the methyl group was well tolerated in terms of binding affinity.

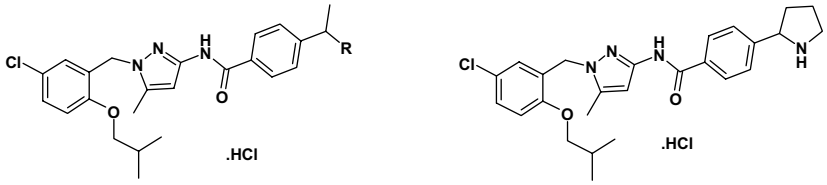
Following on from this result, we found that the group on the amine could be tied back onto the benzylic position to generate phenyl pyrrolidine derivative **6**, FLIPR pK_i 7.0 ± 0.7 (Fig. 2).

We also investigated the effect of tying the amine substituent back to the 3-position of the phenyl ring as exemplified by the tetrahydroisoquinolines (**7a** and **7b**), **7a** FLIPR pK_i 6.9 ± 0.2, and benzazepines (**8a** and **8b**), **8b** FLIPR pK_i 7.3 ± 0.2 (Fig. 3).

Next, we sought to transfer the SAR from the reversed amide series to the amide series (Table 2). Thus, substitution of the anilide phenyl ring (C-ring) was only investigated in the 4-position, however, analogues were made with both the iso-butoxy and benzyloxy groups on the phenyl A-ring, and as Table 2 shows, both groups generally resulted in equipotent compounds. Interestingly, although the parent amide series (e.g., **2**) displayed slightly lower affinity in general than the reversed amide series (e.g., **3**) the 4-substituted amide derivatives were generally slightly more potent than their reversed amide analogues. Thus, the 4-hydroxymethyl derivative **9a** (FLIPR pK_i 7.8 ± 0.4) retained activity of the parent unsubstituted compound (**2**) whereas **10a** (FLIPR pK_i 7.4 ± 0.2) displayed slightly higher affinity. Again, it was found that a range of secondary and tertiary amino groups were tolerated (**9b–g** and **10b–g**), **9b** FLIPR pK_i 7.1 ± 0.2, **10b** FLIPR pK_i 6.9 ± 0.2, **10g** FLIPR pK_i 7.1 ± 0.1. It was even found that further polarity could be introduced in addition to the amino group, such as the hydroxyethyl group (**9h**, FLIPR pK_i 7.0 ± 0.0) and dihydroxyethyl group (**9i**, FLIPR pK_i 7.1 ± 0.0).

Several of the analogues in Table 2 retained good binding efficiency/ligand efficiency, for example **9b** BEI 18.4 and LE 0.36, **10b** BEI 16.6 and LE 0.32.

Based on a combination of in vitro potency, in vitro metabolic stability[11] and CYP450 profile, the in vivo pharmacokinetic profiles of compounds **4h**, **4j** and **10b** were assessed in the rat via intravenous administration (Table 3). Despite the fact all three showed improved in vitro stability relative to compounds **2** and **3** their in vivo metabolic stability was similar as shown by the blood clearance values (CLb). However, all three showed moderate blood clearance and volumes of distribution (Vdss) which resulted in half-lives between 1.4 and 3.0 h.

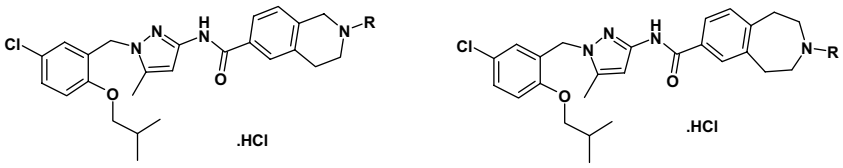


5a; R = NHi-Bu
binding pIC_{50} 7.3 ± 0.1

5b; R = pyrrolidin-1-yl
binding pIC_{50} 7.3 ± 0.2

6; binding pIC_{50} 7.0 ± 0.0
FLIPR pKi 7.0 ± 0.7

Figure 2. Further 4-aminomethyl derivatives.



7a; R = H
binding pIC_{50} 7.4 ± 0.1
FLIPR pKi 6.9 ± 0.2

7b; R = i-Pr
binding pIC_{50} 7.0 ± 0.4

8a; R = H
binding pIC_{50} 7.1 ± 0.2

8b; R = Et
binding pIC_{50} 7.3 ± 0.1
FLIPR pKi 7.3 ± 0.2

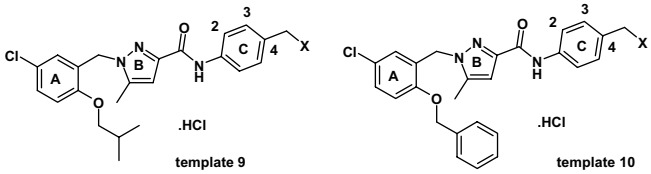
Figure 3. Tetrahydroisoquinoline and benzazepeine derivatives.

We also assessed the solubility of several derivatives (Table 4) as we had hypothesized that increasing the solubility, whilst maintaining metabolic stability, would ultimately lead to improved oral bioavailability.

As Table 4 shows, most compounds had moderate to good solubility in the media tested,[12] which was markedly better than the two starting compounds (**2** and **3**). In particular, several derivatives demonstrated good solubility in all four media.

Solubility data (Table 3) revealed that the amides generally had better solubility than the corresponding reversed amides (cf. **9c** to **4h**). Within the amide series, the iso-butoxy derivatives had better solubility than their benzyloxy analogues (cf. **9b** to **10b** and **9f** to **10f**).

Table 2
SAR for 4-substituted anilides **9a–i** and **10a–g**



Compound	X	Binding pIC_{50}[a]
2[b]	n/a	7.4 ± 0.4
9a	OH	7.5 ± 0.1
9b	NHMe	8.1 ± 0.1
9c	NHEt	8.1 ± 0.1
9d	NMe_2	8.3 ± 0.0
9e	Pyrrolidin-1-yl	8.2 ± 0.1
9f	Piperidin-1-yl	8.2 ± 0.1
9g	Morpholin-4-yl	8.1 ± 0.1
9h	$NHCH_2CH_2OH$	7.6 ± 0.3
9i	$N(CH_2CH_2OH)_2$	7.8 ± 0.2
10a	OH	8.2 ± 0.3
10b	NHMe	7.9 ± 0.1
10c	NHEt	7.9 ± 0.2
10d	NMe_2	8.1 ± 0.3
10e	Pyrrolidin-1-yl	7.9 ± 0.1
10f	Piperidin-1-yl	7.9 ± 0.2
10g	Morpholin-4-yl	8.0 ± 0.1

[a] See Ref. 4a or 9.
[b] For structure, see Figure 1.

Table 3
Rat microsomal intrinsic clearance data and intravenous pharmacokinetic data for compounds **2**, **3**, **4h**, **4j** and **10b**

Compound	CLi[a]	CLb (mL/min/kg)[b]	Vdss (L/kg)[b]	*t*1/2 (h)[b]
2	12.0	n.d.[c]	n.d.[c]	n.d.[c]
3	7.3	50	4.1	2.5
4h	1.8	29	6.3	2.8
4j	3.2	46	4.6	1.4
10b	1.8	46	9.7	3.0

[a] Intrinsic clearance measured in rat liver microsomes (mL/min/g liver)[11].
[b] 1 mg/kg iv infusion.
[c] Not determined.

Table 4
Solubility data for selected compounds[a]

Compound	H_2O	SGF[b]	FaSSIF[c]	FeSSIF[d]
2[e]	0	0	0	0
3[e]	2	2	38	50
4h[f]	690	62	14	154
4j[f]	>1000	n.d.[g]	n.d.[g]	520
4k[f]	>1000	30	90	240
9b	474	364	483	589
9c	>1000	905	812	>1000
9f	811	662	164	315
10b	253	n.d.[g]	57	185
10f	373	n.d.[g]	n.d.[g]	64

[a] 1 h, units = μg/mL.
[b] Simulated gastric fluid.[12]
[c] Fasted state simulated intestinal fluid.[12]
[d] Fed state simulated intestinal fluid.[12]
[e] 0.5 h.
[f] 2 h.
[g] Not determined.

Based on the pharmacokinetic data (Table 3) and solubility data (Table 4) the CNS penetration of compounds **4h**, **4j** and **10b** was assessed in the rat (Table 5).

Table 5
Rat CNS penetration assay[a]

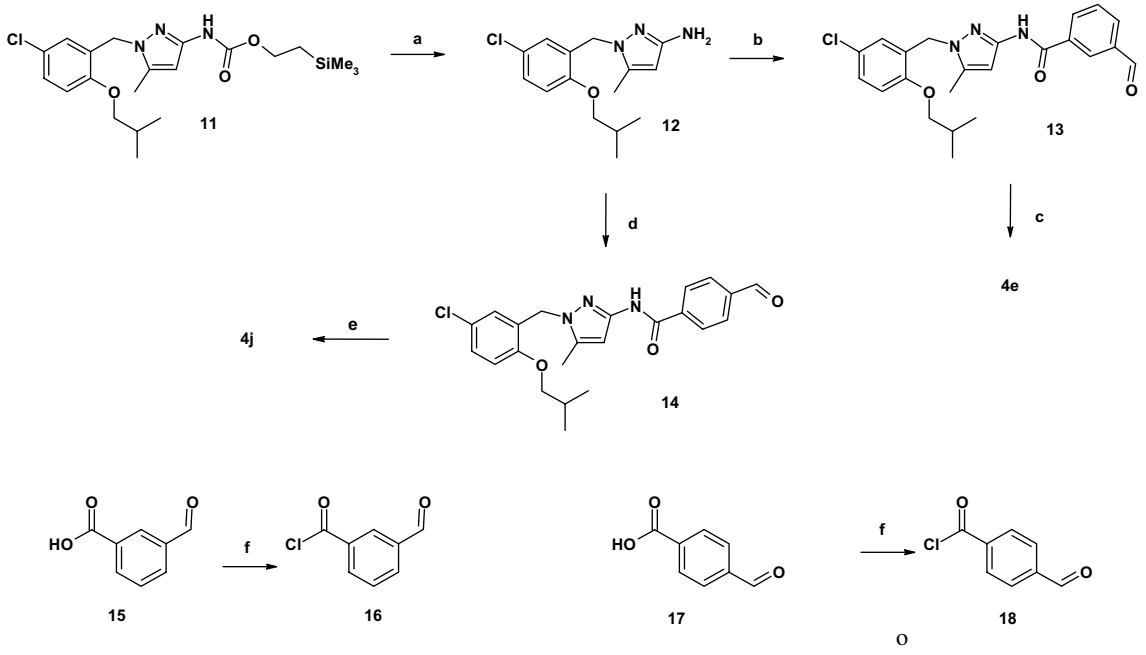
Compound	Br:Bl	Blood concentration (nM)	Brain concentration (nM)
4hA[b]	0.8:1[c]	107[d]	60[e]
4h[f]	0.9:1[c]	114[c]	92[c]
4j[b]	1.2:1[c]	25[d]	43[e]
4j[g]	2.0:1	21	41
10b[h]	1.4:1	145	201

[a] Rats dosed orally and blood and brain samples taken 1 or 3 h post-dose.
[b] 10 mg/kg dose, samples taken 1 h post-dose.
[c] Ratio is an average from three animals where blood and brain samples taken from same animal.
[d] Value is a mean from seven animals.
[e] Value is a mean from three animals.
[f] 3 mg/kg dose, samples taken 3 h post-dose, values are the mean from three animals.
[g] 3 mg/kg dose, samples taken 3 h post-dose, values are the mean from two animals.
[h] 5 mg/kg dose, samples taken 3 h post-dose, values are the mean from three animals.

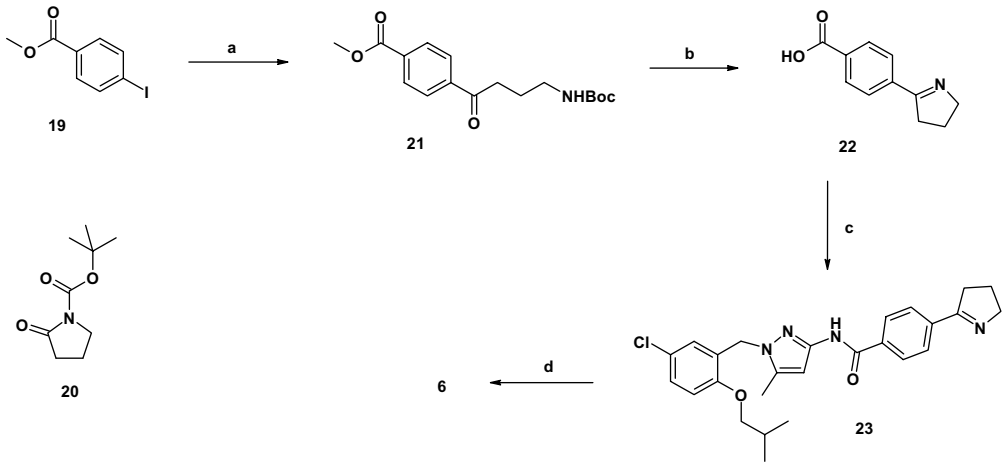
Although all three compounds had good brain-to-blood ratios all exhibited low systemic exposure after oral dosing.

As the blood clearance was moderate, we hypothesized that the low exposure was possibly due to poor absorption, even though the in vitro permeability was good.[13,14] To prove this hypothesis a hepatic portal vein (HPV) study was conducted with **4j** and **10b** and demonstrated that the pre-systemic and systemic concentrations of both compounds were low, thus discounting the possibility that the low oral exposure was due to hepatic extraction and demonstrating the low exposure was due to poor absorption.

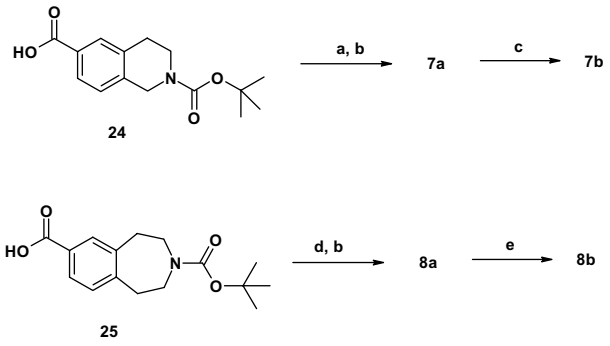
No further work was conducted to decipher whether the poor absorption was due to permeability or solubility. Related compounds with improved solubility relative to **4h**, **4j** and **10b**, failed to yield higher exposures after oral administration suggesting that low exposure was not due to poor solubility.



Scheme 1. Conditions and reagents: (a) TBAF, THF, 50 °C, 1 h, 92%; (b) **16**, CH_2Cl_2, 4-(dimethylamino)pyridine, NEt_3, 23%; (c) piperidine, CH_2Cl_2, AcOH then $NaBH(OAc)_3$, MeOH, 1M HCl in Et_2O, 17%; (d) **18**, CH_2Cl_2, 4-(dimethylamino)pyridine, NEt_3, 21%; (e) pyrrolidine, CH_2Cl_2, AcOH, $NaBH(OAc)_3$, MeOH, 1 M HCl in Et_2O, 73%; (f) PhMe, $SOCl_2$, reflux, 16 h, then evaporation.



Scheme 2. Conditions and reagents: (a) THF, *i*-PrMgCl, −60 °C to −45 °C, then **20**, warm to rt, 65%; (b) THF, 5 M HCl, 70 °C, 1 h, 29%; (c) **12**, CH_2Cl_2, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride, 1-hydroxy-7-azabenzotriazole, rt, 22%; (d) CH_2Cl_2, AcOH, $NaBH(OAc)_3$ then 1 M HCl in Et_2O, 93%.



Scheme 3. Conditions and reagents: (a) **12**, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride, 1-hydroxy-7-azabenzotriazole, CH_2Cl_2, 77%; (b) 4 M HCl in dioxan, 100%; (c) CH_2Cl_2, AcOH, Me_2CO, $NaBH(OAc_3)$, then 1 M HCl in Et_2O, 35%; (d) **12**, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride, 1-hydroxy-7-azabenzotriazole, CH_2Cl_2, 81%; (e) CH_2Cl_2, AcOH, MeCHO, $NaBH(OAc_3)$, 46%.

Compounds were synthesized as outlined in Schemes 1–4. Full experimental details and characterizing data for key compounds has been described.[9]

Reversed amides such as **4e** and **4j** were prepared as outlined in Scheme 1. Carbamate **12** was generated from the corresponding carboxylic acid[6,9] via Curtius rearrangement[15] in the presence of trimethylsilyl ethanol. Subsequent deprotection delivered amino pyrazole **12**. Reaction with acid chlorides **16** and **18** gave aldehydes **13** and **14**, respectively. Reductive amination with **13** and piperidine provided compound **4e**, whereas reductive amination with pyrrolidine and **14** provided **4j**.

Compounds **5a** and **5b** were prepared in an analogous manner to that described in Scheme 1, via reductive amination with the corresponding acetophenone.

The synthesis of **6** started from methyl 4-iodobenzoate (**19**) (Scheme 2). Reaction with *i*-PrMgCl under Knochel's conditions[16] and quenching with 1-Boc-pyrrolidinone (**20**) gave **21**(Scheme 2). Heating **21** in THF with HCl effected ester hydrolysis, amine deprotection and cyclisation to give imine **22**. Amide formation with **12**, to give**23**, followed by imine reduction delivered compound **6**.

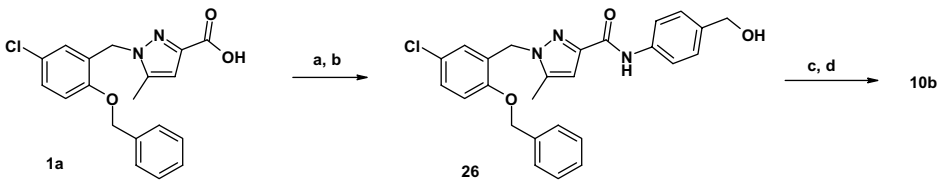
Tetrahydroisoquinoline (**7a**) was prepared as outlined in Scheme 3, **7b** in turn was prepared from **7a** via reductive amination. Derivatives **8a** and **8b** were prepared from **25** (Scheme 3) via analogous procedures.

The anilides described in Table 2 were prepared as shown for derivative **10b** (Scheme 4). Carboxylic acid **1a**[5,6,9] was converted to the corresponding acid chloride and reacted with 4-aminobenzyl alcohol to give **26**. Dess–Martin oxidation,[17] reductive amination and salt formation gave **10b** (Scheme 4).

In conclusion, we have modified a series of amides and reversed amides to incorporate a basic solubilising group. In doing this, we succeeded in placing the basic group in the region of the molecule where a carboxylic acid normally forms a key interaction. Despite this, compounds still maintained high BEI and LE. In so doing we identified several compounds with good solubility, good pharmacokinetic properties and good CNS penetration. Despite these desirable characteristics, these compounds failed to show acceptable oral exposure. This low oral exposure was attributed to poor absorption from the gastrointestinal tract.

Acknowledgements

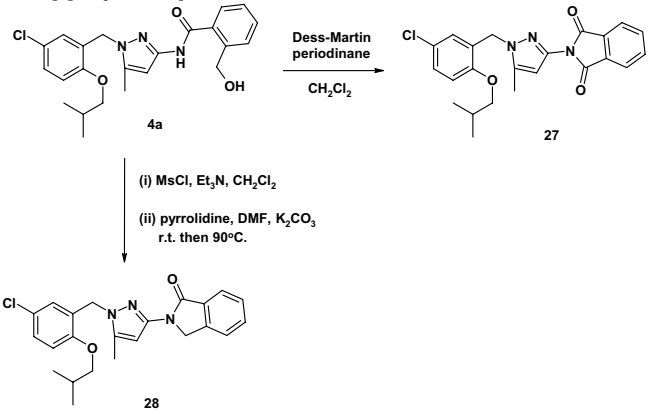
We thank Shiyam Mohamed and Sadhia Mahmood for permeability measurements.



Scheme 4. Conditions and reagents: (a) $(COCl)_2$, DMF, CH_2Cl_2, rt, 90% (b) 4-aminobenzyl alcohol, CH_2Cl_2, NEt_3, rt, 67–98% (c) **12**, Dess–Martin periodinane, CH_2Cl_2, rt, 86%; (d) methylamine, CH_2Cl_2, AcOH, $NaBH(OAc)_3$ then CH_2Cl_2, 1 M HCl in Et_2O, 39%.

References and notes

1. (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.
2. (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.
3. Hall, A.; Billinton, A.; Giblin, G. M. P. *Curr. Opin. Drug Discov. Dev.* **2007**, *10*, 597.
4. (a) Hall, A.; Atkinson, S. A.; Brown, S. H.; Chessell, I. P.; Chowdhury, A.; Coleman, T.; Giblin, G. M. P.; Gleave, R. J.; Hammond, B.; Healy, M. P.; Johnson, M. R.; Michel, A. D.; Naylor, A.; Novelli, R.; Spalding, D. J.; Tang, S. P. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3657; (b) Giblin, G. M. P.; Bit, R. A.; Brown, S. H.; Chaignot, H. M.; Chowdhury, A.; Chessell, I. P.; Clayton, N. M.; Coleman, T.; Hall, A.; Hammond, B.; Hurst, D. N.; Michel, A. D.; Naylor, A.; Novelli, R.; Spalding, D. J.; Tang, S. P.; Wilson, A. W.; Wilson, R. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 385; (c) Hall, A.; Brown, S. H.; Chessell, I. P.; Chowdhury, A.; Clayton, N. M.; Coleman, T.; Giblin, G. M. P.; Hammond, B.; Healy, M. P.; Johnson, M. R.; Metcalf, A.; Michel, A. D.; Naylor, A.; Novelli, R.; Spalding, D. J.; Sweeting, J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 732; (d) Hall, A.; Brown, S. H.; Chessell, I. P.; Chowdhury, A.; Clayton, N. M.; Coleman, T.; Giblin, G. M. P.; Hammond, B.; Healy, M. P.; Johnson, M. R.; Metcalf, A.; Michel, A. D.; Naylor, A.; Novelli, R.; Spalding, D. J.; Sweeting, J.; Winyard, L. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 916; (e) Hall, A.; Atkinson, S.; Brown, S. H.; Chessell, I. P.; Chowdhury, A.; Giblin, G. M. P.; Goldsmith, P.; Healy, M. P.; Jandu, K. S.; Johnson, M. R.; Michel, A. D.; Naylor, A.; Sweeting, J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1200.
5. McKeown, S. C.; Hall, A.; Giblin, G. M. P.; Lorthioir, O.; Blunt, R.; Lewell, X. Q.; Wilson, R. J.; Brown, S. H.; Chowdhury, A.; Coleman, T.; Watson, S. P.; Chessell, I. P.; Pipe, A.; Clayton, N. M.; Goldsmith, P. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4767.
6. Hall, A.; Bit, R. A.; Brown, S. H.; Chowdhury, A.; Giblin, G. M. P.; Hurst, D. N.; Kilford, I. R.; Lewell, X.; Naylor, A.; Scoccitti, T. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1592.
7. Abad-Zapatero, C.; Metz, J. T. *Drug Discov. Today* **2005**, *10 7*, 464.
8. Hopkins, A. L.; Groom, C. R.; Alex, A. *Drug Discov. Today* **2004**, *9*, 432.
9. Conway, E. A.; Giblin, G. M. P.; Gibson, M.; Hall, A.; Hayhow, T. G. C.; Healy, M. P.; Hurst, D. N.; Kilford, I. R.; McKeown, S. C.; Naylor, A.; Price, H. S.; Rawlings, D. A. WO2006/114313A1, 2006.
10. Attempts to oxidise the benzylic alcohol **4a** resulted only in formation of phthalimide **27**(oxidation with PDC was also attempted but resulted in no detectable aldehyde formation). Attempts to convert the hydroxyl group to a leaving group and displace with amines resulted in formation of lactam **28**



.
11. Clarke, S. E.; Jeffrey, P. *Xenobiotica* **2001**, *31*, 591.
12. (a) Kostewicz, E. S.; Wunderlich, M.; Brauns, U.; Becker, R.; Bock, T.; Dressman, J. B. *J. Pharm. Pharmacol.* **2005**, *56*, 43; (b) Galia, E.; Nicolaides, E.; Horter, D.; Löbenberg, R.; Reppas, C.; Dressman, J. B. *Pharm. Res.* **1998**, *15*, 698.
13. Permeability for compounds in MDCK cells: **4h** 521 nm/s, **4j** 360 nm/s, **10b** 318 nm/s.
14. Studies with *mdr*1a/b knockout mice (in the presence and absence of GF120918, a potent P-gp and BCRP inhibitor) indicated the poor oral exposure of **4j** was not due to P-gp or BCRP-mediated efflux.
15. Saunders, J. H.; Slocombe, R. J. *Chem. Rev.* **1948**, *43*, 205.
16. Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed* **2003**, *42*, 4302.
17. Dess, D. B.; Martin, J. C. *J. Org. Chem* **1983**, *48*, 4155.