Bioorganic & Medicinal Chemistry Letters 23 (2013) 3175–3179

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Conformational restriction in a series of GPR119 agonists: Differences in pharmacology between mouse and human

James S. Scott *, Katy J. Brocklehurst, Hayley S. Brown, David S. Clarke, Helen Coe, Sam D. Groombridge, David Laber, Philip A. MacFaul, Darren McKerrecher, Paul Schofield

Cardiovascular & Gastrointestinal Innovative Medicines Unit, AstraZeneca, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG, UK

ARTICLE INFO

Article history:
Received 4 March 2013
Revised 28 March 2013
Accepted 2 April 2013
Available online 10 April 2013

Keywords:
G-protein coupled receptors
GPR119 agonists
Pharmacology
Partial agonists

ABSTRACT

A series of conformationally restricted GPR119 agonists were prepared based around a 3,8-diazabicyclo[3.2.1]octane scaffold. Examples were found to have markedly different pharmacology in mouse and human despite similar levels of binding to the receptor. This highlights the large effects on GPCR pharmacology that can result from small structural changes in the ligand, together with inter-species differences between receptors.

G-protein coupled receptor 119 (GPR119) is a class A type receptor expressed predominantly in pancreatic islets and intestinal enteroendocrine cells.[1] Research has demonstrated that agonism of the GPR119 receptor results in secretion of incretins from the gut (e.g., glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) release from L-cells)[2] and release of insulin from β-cells in the pancreas.[3] Taken together, these effects represent a potential mechanism for modulation of glucose homeostasis and a novel approach to the treatment of type 2 diabetes.[4]

A number of chemical series displaying GPR119 agonism have been disclosed from Arena,[5] Astellas,[6] Boehringer Ingelheim,[7] GSK,[8] Pfizer,[9] Merck,[10] and Sanwa Kagaku Kenkyusho.[11] Data has recently been reported from the first example of a GPR119 agonist to enter trials, APD-597 (JNJ-38431055). Results indicated elevation of GLP-1, GIP and peptide YY levels although decreases in glucose excursion or insulin secretion were not significant.[12]

Many of the reported chemical series share a common structural motif incorporating a carbamate or heterocycle capped piperidine linked via a spacing group to an aryl group with a strong acceptor (pyridyl, sulphone, heterocycle). A pharmacophore model has been proposed that encapsulates these features.[13] Work from Pfizer,[9a,e] together with a recent disclosure from researchers from the College of Pharmacy of Kangwon National University,[14] have highlighted the importance of conformational restriction of the piperidine portion in controlling human GPR119 pharmacology. Examples of conformationally restricted piperidines are shown in Figure 1.

We herein report our own findings in this area around a series of 3,8-diazabicyclo[3.2.1]octanes and the divergent nature of the effects on human and mouse pharmacology relative to piperazine matched pairs. In accordance with previous reports[9a] we postulate conformational restriction, leading to an inability of the bridged compounds to access an 'agonist conformation', as a likely source of these effects in mouse. As part of this work we developed an assay that allowed us to assess the strength of the ligand–receptor binding interaction.[16] These results were compared with EC_{50} values derived from a functional cAMP assay.[17]

Initial exploration around the piperazine core **1** had shown that methyl substitution, piperazine **2**, brought increases in both human and mouse binding potency (Table 1). This was reflected by an increase in human potency (cAMP EC_{50}) and intrinsic activity (IA) for this compound although no corresponding improvement in the mouse. Further exploration around ethylene bridging proximal to each of the nitrogens in the piperazine gave isomeric 3,8-diazabicyclo[3.2.1]octanes **3** and **4** which showed marked differences. In particular, compound **4** was around two orders of magnitude more potent in both human and mouse binding assays than the unsubstituted piperazine **1**. In the human cAMP assay this compound had a lower EC_{50} and a larger intrinsic effect than piperazine **1** but in stark contrast, it had no discernible effect in the mouse cAMP assay and no EC_{50} could be determined. Similarly the alternative bridged isomer **3** showed no effect in mouse despite a full agonist profile in human.

* Corresponding author. Tel.: +44 (0)1625 232567; fax: +44 (0)1625 516667.
E-mail address: jamie.scott@astrazeneca.com (J.S. Scott).

0960-894X/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmcl.2013.04.006

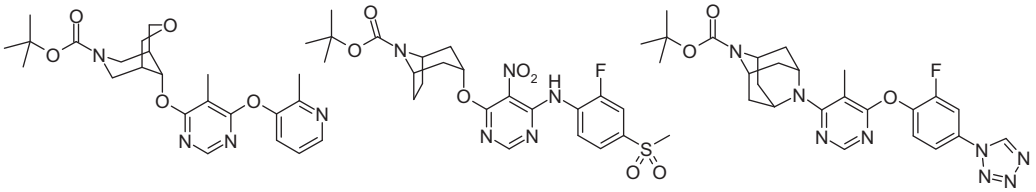
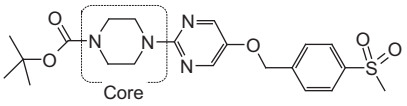


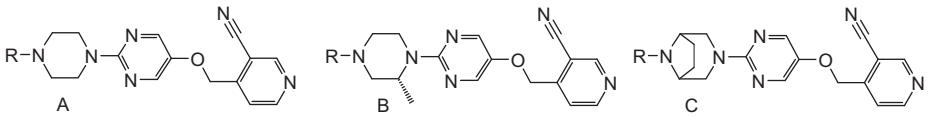
Figure 1. Examples of conformationally restricted piperidine based GPR119 agonists.

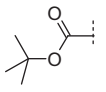
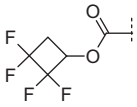
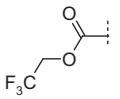
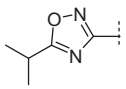
Table 1
GPR119 binding and cAMP data for aryl sulphones **1–4**



Compd	Core	Human binding IC_{50} (μM)	mouse binding IC_{50} (μM)	Human cAMP EC_{50} (μM)	Human cAMP IA (%)	Mouse cAMP EC_{50} (μM)	Mouse cAMP IA (%)
1		0.351	0.543	0.065	83	0.041	99
2		0.017	0.129	0.019	150	0.084	101
3		0.092	0.072	0.079	133	NA	0
4		0.003	0.005	0.011	166	NA	0

Table 2
GPR119 binding and cAMP data for cyanopyridines **5–16**



Compd	R	Core	Human binding IC_{50} (μM)	Mouse binding IC_{50} (μM)	Human cAMP EC_{50} (μM)	Human cAMP IA (%)	Mouse cAMP EC_{50} (μM)	Mouse cAMP IA (%)
5		A	0.010	0.507	0.021	155	0.120	102
6		B	0.001	0.100	0.005	171	0.036	97
7		C	0.001	0.009	0.004	250	NA	5
8		A	0.025	0.758	0.020	251	0.252	98
9		B	0.006	0.694	0.006	182	0.084	54
10		C	0.009	0.065	0.007	183	NA	9
11		A	0.018	4.985	0.047	193	0.698	101
12		B	0.031	1.827	0.020	132	0.246	76
13		C	0.008	0.104	0.009	203	0.020	31
14		A	0.012	2.716	0.019	167	0.242	74
15		B	0.003	0.568	0.008	269	0.056	92
16		C	0.004	0.122	0.011	229	0.045	41

Intrigued by the lack of effect in the mouse cAMP assay with the bridged piperazines, we prepared a series of compounds in a cyanopyridyl subseries of compounds with a range of capping groups (**5–16**) as shown in Table 2.

Compounds **5–7** are matched molecular pairs of **1**, **3** and **4** with the aryl sulphone replaced with a cyanopyridyl group. The same structure–activity relationship was observed with the bridged compound **7** having the lowest EC_{50} value and high intrinsic activity in the human cAMP assay and minimal effect in the murine cAMP assay despite being the most potent in the binding assay in both species.[18] Further variation of the carbamate to the tetrafluoro cyclobutyl (compounds **8–10**) and the trifluoroethyl (compounds **11–13**) showed similar trends in both human and mouse. Compound **13** was notable for the fact that it was the first bridged compound to show a measurable EC_{50} in the mouse but with intrinsic activity that was significantly lower than either the unsubstituted (**11**) or methyl (**12**) piperazine, indicating that this was only a partial agonist. Switching to an isopropyl 1,2,

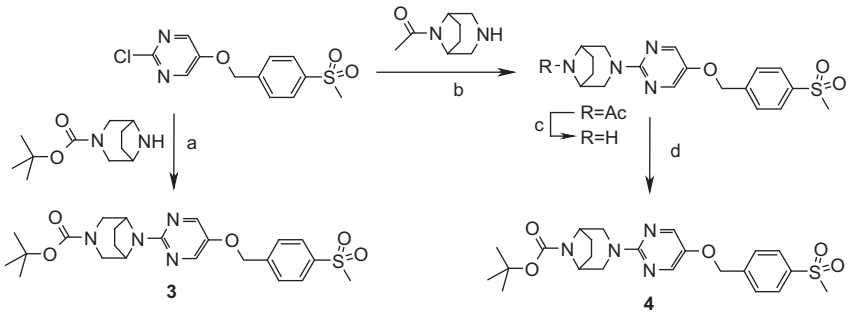
4-oxadiazole (compounds **14**–**16**) maintained the trends previously observed with compound **16** showing full agonism in human and only partial agonism in mouse.

Synthesis of isomeric bridged compounds in the sulphone series was achieved by nucleophilic displacement of the 2-chloro substituent of a pyrimidine.[19] In the case of compound **3** this was achieved directly by displacement of the Boc substituted bridged piperazine. In the case of compound **4**, the regioisomeric acetyl bridged piperazine was used for the initial displacement. The acetyl group was then removed using forcing acidic conditions and the resultant amine capped with a *tert*-butyl carbamate (Scheme 1).

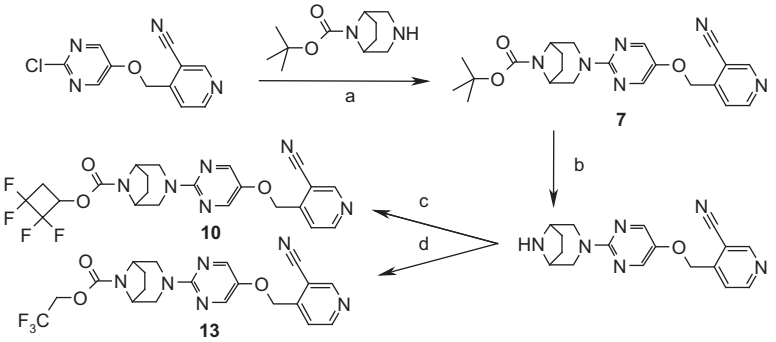
In the cyanopyridyl series, a similar strategy was employed with nucleophilic displacement with the Boc substituted bridged piperazine affording compound **7** directly. Alternative carbamates were introduced by removing the Boc group and then reacting the resultant amines with appropriately substituted phenylcarbamates to give **10** and **13** (Scheme 2).

For oxadiazole **16** the strategy was modified with the pyridyl substituted with a bromine rather than a cyano group to avoid any chemoselctivity issues with the later hydroxylamine addition. Displacement of the 2-chloro pyrimidine and removal of the Boc group was carried out as before to give the amine which was transformed into the cyanamide using cyanogen bromide. Addition of hydroxylamine followed by capping with isobutyric acid and ring closure gave the oxadiazole. Subsequent conversion of the bromide to the cyano group was achieved under palladium catalysed conditions with zinc cyanide to afford **16** (Scheme 3).

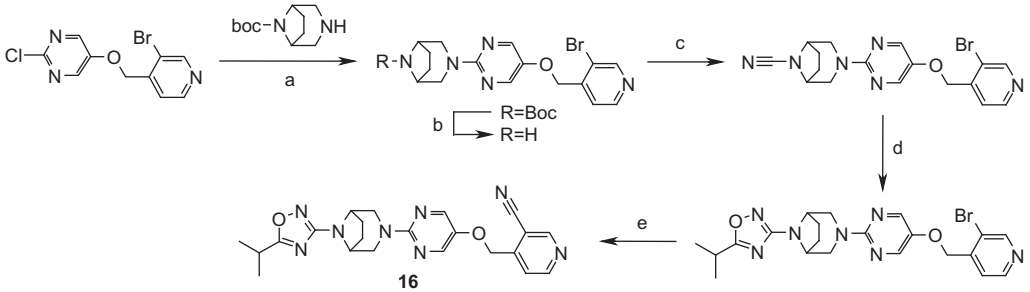
Compounds **11**–**13** were profiled further to assess the impact of the piperazine modifications on the properties of the compounds (Table 3). The log$D_{7.4}$ values showed no significant changes for addition of the methyl group in **12** or the ethylene bridge in **13**. This was reflected in the similar values for free drug levels for the three compounds measured in both mouse and rat. Notably the solubility of the methyl compound **12** was higher than either



Scheme 1. Synthesis of sulphones **3** and **4**. Reagents and conditions: (a) K_2CO_3, ^{n}BuCN, 165 °C, μW, 4 h, 28%; (b) ^{i}Pr$_2$NEt, K_2CO_3, ^{n}BuCN, 160 °C, μW, 8 h, 29%; (c) 2 M HCl, 85 °C, 6 h, 70%; (d) (^{t}BuO)$_2$CO, K_2CO_3, 1,4-dimethylaminopyridine, 20 °C, 4 d, 14%.



Scheme 2. Synthesis of cyano pyridines **7**, **10** and **13**. Reagents and conditions: (a) K_2CO_3, CH_3CN, 150 °C, μW, 8 h, 81%; (b) HCl, 1,4-dioxane/CH_2Cl_2, 20 °C, 18 h, 100%; (c) $C_4H_3F_4OCO_2Ph$, NEt_3, $CHCl_3$, 90 °C, 18 h, 30%; (d) $CF_3CH_2OCO_2Ph$, NEt_3, $CHCl_3$, 100 °C, 36 h, 73%.



Scheme 3. Synthesis of oxadiazole **16**. Reagents and conditions: (a) K_2CO_3, CH_3CN, 150 °C, μW, 8 h, 50%; (b) HCl, 1,4-dioxane/CH_2Cl_2, 20 °C, 3 h, 89%; (c) CNBr, $NaHCO_3$, CH_2Cl_2/H_2O, 0–25 °C, 2 h, 78%; (d) (i) $NH_2OH{\cdot}HCl$, Na_2CO_3, DMF, 80 °C, 1 h; (ii) ^{i}PrCOOH, ^{i}Pr$_2$NEt, HOBt, EDAC, DMF, 20 °C, 16 h; (iii) toluene, 120 °C, 1 h, 61%; (e) $Zn(CN)_2$, $Pd(dba)_2$, Xantphos, DMF, 130 °C, μW, 2 h, 46%.

Table 3
Physical properties for compounds **11**–**13**

Compd	log$D_{7.4}$[a]	Mouse PPB[b] (% free)	Rat PPB[b] (% free)	Solubility[c] (μM)	MDCK permeability[d] Papp ($\times 10^{-6}$ cm s^{-1})	CYPS[e] IC_{50} (μM)	hERG[f] IC_{50} (μM)	Rat Heps Clint (μL/min/10^6 ells)
11	3.0	9.4	5.1	3.3	32 (A–B); - (B–A)	All >30	10	12
12	3.0	11	4.4	23	19 (A–B); 10 (B–A)	All >30	12	27
13	3.0	9.6	6.5	3.8	25 (A–B); 20 (B–A)	All >30	13	13

[a] Distribution coefficient between 1-octanol and aqueous phosphate buffer at pH 7.4.
[b] % Free compound measured when dialysed with appropriate plasma proteins.
[c] Solubility of compounds in aqueous phosphate buffer at pH 7.4 after 24 h at 25 °C (μM).
[d] Compounds were incubated at 10 μM in cultured MDCK cells. Permeability was measured in both the A–B and B–A direction.
[e] Inhibition of cytochrome P450 enzymes IC_{50} (μM).
[f] Inhibition of hERG channel IC_{50} (μM) in a electrophysiology (IonWorks™) assay

Table 4
Pharmacokinetic parameters for compounds **11**–**13**[a]

Compd	Clp (mL/min/kg)	Vdss (L/kg)	PO half-life (h)	IV half-life (h)	AUC (μM h)	Bioavailability (%)
11	22	5.3	2.1	3.9	4.0	48
12	14	1.1	2.2	1.4	3.2	27
13	11	1.0	2.6	1.7	2.1	17

[a] Compounds were dosed at 2 mg/kg (IV) and 5 mg/kg (po) in 5% DMSO:95% hydroxylpropyl beta cyclodextrin, and a 0.1% pluronic F127 suspension, respectively at volumes of 5 mL/kg.

Table 5
Oral glucose tolerance test (OGTT) results for compounds **8** and **10**–**13**[a]

Compd	Mouse GPR119 EC_{50} (μM)	Mouse GPR119 IA (%)	Mouse GPR119 binding (μM)	% Reduction in OGTT blood glucose AUC[a]
8	0.252	98	0.758	30
10	NA	9	0.065	3
11	0.698	101	4.985	21
12	0.246	76	1.827	10
13	0.020	31	0.104	6

[a] Compounds administered 30 min prior to a glucose load of 2 g/kg and glucose levels monitored out to 90 min.

the piperazine or bridged compound, perhaps reflecting the disruption to the crystal packing by this axial methyl group observed in previous work.[15a] All three compounds were highly permeable as measured in a Madin-Darby Canine Kidney (MDCK) epithelial cell line and showed no inhibition against five isoforms of the cytochrome P450 enzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4). Compounds showed similar activity against the hERG channel and were moderately stable in rat hepatocytes.

Profiling of the compounds in rat showed similar profiles for all three matched cores (unsubstituted, methyl and bridged) with low to moderate clearance and bioavailabilities and a difference in AUC of less than twofold (Table 4).

In order to assess the relevance of the mouse cAMP results in vivo, we selected compounds for profiling in a mouse (C57BL6/JAX) oral glucose tolerance test (OGTT) at a fixed dose of 50 mg/kg. Our expectation that the compounds with lower intrinsic activities in the mouse cAMP assay would be less efficacious was borne out by the results shown in Table 5 whereas significant glucose lowering was observed for those compounds with high mouse intrinsic activities (**8**, **11**).

In conclusion, we have reported conformationally restricted piperazines which bind strongly to the GPR119 receptor. Marked differences were observed between human and mouse in vitro pharmacology in a cAMP assay. The compounds were full agonists in the human assay but showed no or partial agonism in the mouse assay. This was confirmed by profiling selected compounds in vivo.

Acknowledgements

Wendy Snelson and Jules Hudson are thanked for synthetic contributions. Alastair Brown is thanked for his contributions to the development of the binding assays and Rob Garcia and Steve Bloor are thanked for the generation of in vitro data. Jo Teague and Laraine Gregory are thanked for contributions to in vitro OGTT data generation.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2013.04.006.

References and notes

1. Fredriksson, R.; Höglund, P. J.; Gloriam, D. E. I.; Lagerström, M. C.; Schiöth, H. B. *FEBS Lett.* **2003**, *554*, 381.
2. Chu, Z.; Carroll, C.; Alfonso, J.; Gutierrez, V.; He, H.; Lucman, A.; Pedraza, M.; Mondala, H.; Gao, H.; Bagnol, D.; Chen, R.; Jones, R. M.; Behan, D. P.; Leonard, J. *Endocrinology* **2008**, *149*, 2038.
3. Chu, Z.; Jones, R. M.; He, H.; Carroll, C.; Gutierrez, V.; Lucman, A.; Moloney, M.; Gao, H.; Mondala, H.; Bagnol, D.; Unett, D.; Liang, Y.; Demarest, K.; Semple, G.; Behan, D. P.; Leonard, J. *Endocrinology* **2007**, *148*, 2601.
4. (a) Fyfe, M. C. T.; McCormack, J. G.; Overton, H. A.; Procter, M. J.; Reynet, C. *Expert Opin. Drug Discov.* **2008**, *3*, 403; (b) Shah, U. *Curr. Opin. Drug Discov. Dev.* **2009**, *12*, 519; (c) Jones, R. M.; Leonard, J. N. In *Annual Reports in Medicinal Chemistry*; Macor, John E., Ed.; Academic Press, 2009; Vol. 44, pp 149–170; (d) Shah, U.; Edmondson, S.; Szewczyk, J. W. In *New Therapeutic Strategies for Type 2 Diabetes*; Jones, Rob M., Ed.; RSC Drug Discovery Series, 2012; Vol. 27, pp 177–214.
5. (a) Semple, G.; Fioravanti, B.; Pereira, G.; Calderon, I.; Uy, J.; Choi, K.; Xiong, Y.; Ren, A.; Morgan, M.; Dave, V.; Thomsen, W.; Unett, D. J.; Xing, C.; Bossie, S.; Carroll, C.; Chu, Z.; Grottick, A. J.; Hauser, E. K.; Leonard, J.; Jones, R. M. *J. Med. Chem.* **2008**, *51*, 5172; (b) Semple, G.; Ren, A.; Fioravanti, B.; Pereira, G.; Calderon, I.; Choi, K.; Xiong, Y.; Shin, Y.; Gharbaoui, T.; Sage, C. R.; Morgan, M.; Xing, C.; Chu, Z.; Leonard, J. N.; Grottick, A. J.; Al-Shamma, H.; Liang, Y.; Demarest, K. T.; Jones, R. M. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3134; (c) Semple, G.; Lehmann, J.; Wong, A.; Ren, A.; Bruce, M.; Shin, Y.; Sage, C. R.; Morgan, M.;

Chen, W.; Sebring, K.; Chu, Z.; Leonard, J. N.; Al-Shamma, H.; Grottick, A. J.; Du, F.; Liang, Y.; Demarest, K.; Jones, R. M. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1750.
6. (a) Yoshida, S.; Ohishi, T.; Matsui, T.; Tanaka, H.; Oshima, H.; Yonetoku, Y.; Shibasaki, M. *Biochem. Biophys. Res. Commun.* **2010**, *402*, 280; (b) Yoshida, S.; Ohishi, T.; Matsui, T.; Shibasaki, M. *Biochem. Biophys. Res. Commun.* **2010**, *400*, 437; (c) Yoshida, S.; Tanaka, H.; Oshima, H.; Yamazaki, T.; Yonetoku, Y.; Ohishi, T.; Matsui, T.; Shibasaki, M. *Biochem. Biophys. Res. Commun.* **2010**, *400*, 745; (d) Yoshida, S.; Ohishi, T.; Matsui, T.; Tanaka, H.; Oshima, H.; Yonetoku, Y.; Shibasaki, M. *Diabetes Obes. Metab.* **2011**, *13*, 34; (e) Negoro, K.; Yonetoku, Y.; Maruyama, T.; Yoshida, S.; Takeuchi, M.; Ohta, M. *Bioorg. Med. Chem.* **2012**, *20*, 2369; (f) Negoro, K.; Yonetoku, Y.; Misawa-Mukai, H.; Hamaguchi, W.; Maruyama, T.; Yoshida, S.; Takeuchi, M.; Ohta, M. *Bioorg. Med. Chem.* **2012**, *20*, 5235; (g) Negoro, K.; Yonetoku, Y.; Moritomo, A.; Hayakawa, M.; Iikubo, K.; Yoshida, S.; Takeuchi, M.; Ohta, M. *Bioorg. Med. Chem.* **2012**, *20*, 6442.
7. Wellenzohn, B.; Lessel, U.; Beller, A.; Isambert, T.; Hoenke, C.; Nosse, B. *J. Med. Chem.* **2012**, *55*, 11031.
8. (a) Wu, Y.; Kuntz, J. D.; Carpenter, A. J.; Fang, J.; Sauls, H. R.; Gomez, D. J.; Ammala, C.; Xu, Y.; Hart, S.; Tadepalli, S. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2577; (b) Katamreddy, S. R.; Carpenter, A. J.; Ammala, C. E.; Boros, E. E.; Brashear, R. L.; Briscoe, C. P.; Bullard, S. R.; Caldwell, R. D.; Conlee, C. R.; Croom, D. K.; Hart, S. M.; Heyer, D. O.; Johnson, P. R.; Kashatus, J. A.; Minick, D. J.; Peckham, G. E.; Ross, S. A.; Roller, S. G.; Samano, V. A.; Sauls, H. R.; Tadepalli, S. M.; Thompson, J. B.; Xu, Y.; Way, J. M. *J. Med. Chem.* **2012**, *55*, 10972.
9. (a) McClure, K. F.; Darout, E.; Guimarães, C. R. W.; DeNinno, M. P.; Mascitti, V.; Munchhof, M. J.; Robinson, R. P.; Kohrt, J.; Harris, A. R.; Moore, D. E.; Li, B.; Samp, L.; Lefker, B. A.; Futatsugi, K.; Kung, D.; Bonin, P. D.; Cornelius, P.; Wang, R.; Salter, E.; Hornby, S.; Kalgutkar, A. S.; Chen, Y. *J. Med. Chem.* **2011**, *54*, 1948; (b) Mascitti, V.; Stevens, B. D.; Choi, C.; McClure, K. F.; Guimarães, C. R. W.; Farley, K. A.; Munchhof, M. J.; Robinson, R. P.; Futatsugi, K.; Lavergne, S. Y.; Lefker, B. A.; Cornelius, P.; Bonin, P. D.; Kalgutkar, A. S.; Sharma, R.; Chen, Y. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1306; (c) Kalgutkar, A. S.; Mascitti, V.; Sharma, R.; Walker, G. W.; Ryder, T.; McDonald, T. S.; Chen, Y.; Preville, C.; Basak, A.; McClure, K. F.; Kohrt, J. T.; Robinson, R. P.; Munchhof, M. J.; Cornelius, P. *Chem. Res. Toxicol.* **2011**, *24*, 269; (d) Sharma, R.; Eng, H.; Walker, G. S.; Barreiro, G.; Stepan, A. F.; McClure, K. F.; Wolford, A.; Bonin, P. D.; Cornelius, P.; Kalgutkar, A. S. *Chem. Res. Toxicol.* **2011**, *24*, 2207–2216; (e) Darout, E.; Robinson, R. P.; McClure, K. F.; Corbett, M.; Li, B.; Shavnya, A.; Andrews, M. P.; Jones, C. S.; Li, Q.; Minich, M. L.; Mascitti, V.; Guimarães, C. R. W.; Munchhof, M. J.; Bahnck, K. B.; Cai, C.; Price, D. A.; Liras, S.; Bonin, P. D.; Cornelius, P.; Wang, R.; Bagdasarian, V.; Sobota, C. P.; Hornby, S.; Masterson, V. M.; Joseph, R. M.; Kalgutkar, A. S.; Chen, Y. *J. Med. Chem.* **2013**, *56*, 301; (f) Futatsugi, K.; Mascitti, V.; Guimarães, C. R. W.; Morishita, N.; Cai, C.; DeNinno, M. P.; Gao, H.; Hamilton, M. D.; Hank, R.; Harris, A. R.; Kung, D. W.; Lavergne, S. Y.; Lefker, B. A.; Lopaze, M. G.; McClure, K. F.; Munchhof, M. J.; Preville, C.; Robinson, R. P.; Wright, S. W.; Bonin, P. D.; Cornelius, P.; Chen, Y.; Kalgutkar, A. S. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 194.
10. (a) Szewczyk, J. W.; Acton, J.; Adams, A. D.; Chicchi, G.; Freeman, S.; Howard, A. D.; Huang, Y.; Li, C.; Meinke, P. T.; Mosely, R.; Murphy, E.; Samuel, R.; Santini, C.; Yang, M.; Zhang, Y.; Zhao, K.; Wood, H. B. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2665; (b) Xia, Y.; Chackalamannil, S.; Greenlee, W. J.; Jayne, C.; Neustadt, B.; Stamford, A.; Vaccaro, H.; Xu, X.; Baker, H.; O'Neill, K.; Woods, M.; Hawes, B.; Kowalski, T. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3290.
11. (a) Sakairi, M.; Kogami, M.; Torii, M.; Kataoka, H.; Fujieda, H.; Makino, M.; Kataoka, D.; Okamoto, R.; Miyazawa, T.; Okabe, M.; Inoue, M.; Takahashi, N.; Harada, S.; Watanabe, N. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5123; (b) Sakairi, M.; Kogami, M.; Torii, M.; Makino, M.; Kataoka, D.; Okamoto, R.; Miyazawa, T.; Inoue, M.; Takahashi, N.; Harada, S.; Watanabe, N. *Chem. Pharm. Bull.* **2012**, *60*, 1093.
12. (a) Katz, L. B.; Gambale, J. J.; Rothenberg, P. L.; Vanapalli, S. R.; Vaccaro, N.; Xi, L.; Polidori, D. C.; Vets, E.; Sarich, T. C.; Stein, P. P. *Clin. Pharmacol. Ther.* **2011**, *90*, 685; (b) Katz, L. B.; Gambale, J. J.; Rothenberg, P. L.; Vanapalli, S. R.; Vaccaro, N.; Xi, L.; Sarich, T. C.; Stein, P. P. *Diabetes Obes. Metab.* **2012**, *14*(8), 709.
13. Zhu, X.; Huang, D.; Lan, X.; Tang, C.; Zhu, Y.; Han, J.; Huang, W.; Qian, H. *Eur. J. Med. Chem.* **2011**, *46*, 2901.
14. Yang, Z.; Fang, Y.; Pharm, T. N.; Lee, J.; Park, H. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1519.
15. (a) Scott, J. S.; Birch, A. M.; Brocklehurst, K. J.; Broo, A.; Brown, H. S.; Butlin, R. J.; Clarke, D. S.; Davidsson, Ö.; Ertan, A.; Goldberg, K.; Groombridge, S. D.; Hudson, J. A.; Laber, D.; Leach, A. G.; MacFaul, P. A.; McKerrecher, D.; Pickup, A.; Schofield, P.; Svensson, P. H.; Sörme, P.; Teague, J. *J. Med. Chem.* **2012**, *55*, 5361; (b) Scott, J. S.; Birch, A. M.; Brocklehurst, K. J.; Brown, H. S.; Goldberg, K.; Groombridge, S. D.; Hudson, J. A.; Leach, A. G.; MacFaul, P. A.; McKerrecher, D.; Poultney, R.; Schofield, P.; Svensson, P. H. *Med. Chem. Commun.* **2013**, *4*, 95.
16. The assay used was a radioligand filter binding assay where compounds compete for binding sites on the receptor with a standard [^{3}H]-labelled standard GPR119 agonist. The human or mouse receptor was overexpressed with a Gs protein in a baculovirus system, from which membranes were prepared. All binding data is the mean of at least two determinations. See Supplementary data for full details.
17. Full details of the cAMP assay are described in Ref. 15a. The intrinsic activity was expressed as the percent effect compared to that of the control, 50 μM oleoylethanolamide, defined as 100%. All human cAMP data is the mean of at least two determinations. All mouse cAMP data is the mean of at least two determinations with the exception of compounds **3**, **4**, **7**, **8** and **11** which is $n = 1$ data. A typical standard deviation in $\log EC_{50}$ when a compound is repeated is 0.20 and 0.27 for the human and mouse assays respectively. This translates to 95% of EC_{50} values within 2.5-fold (human) and 3.5-fold (mouse) of a compound's 'true' EC_{50}.
18. Some elevation above baseline (<5%) was observed however this was not of sufficient magnitude to be able to determine an EC_{50} value. This led us to conclude that these were not inverse agonists, but we did not confirm their antagonist status in mouse.
19. The synthesis of compounds **1**, **2**, **5**, **6**, **11**, **12**, **14** and **15** are described in PCT Int. Appl. (2011), WO 2011030139 A1.