Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters 18 (2008) 2203–2205
Bioorganic & Medicinal Chemistry Letters

Potent achiral agonists of the growth hormone secretagogue (ghrelin) receptor. Part 2: Lead optimisation

Jason Witherington,[a,*] Lee Abberley,[a] Michael A. Briggs,[a] Katharine Collis,[a] David K. Dean,[a] Alessandra Gaiba,[a] N. Paul King,[a] Helmut Kraus,[a] Nicola Shuker,[a] Jon G. A. Steadman,[a] Andrew K. Takle,[a] Gareth Sanger,[b] Graham Wadsworth,[b] Sharon Butler,[c] Fiona McKay,[c] Alison Muir,[c] Kim Winborn[c] and Tom D. Heightman[d]

[a]*Department of Medicinal Chemistry & DMPK, Neurology & GI Centre of Excellence for Drug Discovery, GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK*
[b]*Department of Biology, Neurology & GI Centre of Excellence for Drug Discovery, GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK*
[c]*Molecular Discovery Research, Department of Screening and Compound Profiling, GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK*
[d]*Molecular Discovery Research, Department of Medicinal Chemistry, GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK*

Received 8 November 2007; revised 10 December 2007; accepted 11 December 2007
Available online 15 December 2007

Abstract—A series of small molecule orally bioavailable ghrelin receptor agonists have been identified through systematic optimisation of a high throughput screening hit.

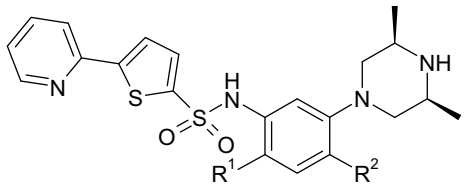
Ghrelin, a 28-amino acid gastric hormone containing a unique post-translational modification on serine 3, exhibits a wide range of biological activities via its postulated cognate receptor, the growth hormone secretagogue receptor (GHSR1a). In humans as well as in rodents, ghrelin stimulates pituitary growth hormone (GH) secretion[1] and in addition increases food intake and body weight gain and regulates energy balance.[2,3] Agents which mimic the actions of ghrelin have potential not only in growth hormone replacement therapy, but also in disorders requiring increased nutritional intake, such as cancer-induced cachexia and post-operative ileus, and in motility disorders such as neurogenic and diabetic gastroparesis.[4]

In the preceding paper, we highlighted the identification and subsequent optimisation of a series of small molecule ghrelin receptor agonists, typified by SB-791016 (**1**).[5] Whilst this represents an exciting new class of ghrelin receptor agonists, this series generally suffers from poor oral exposure which may be attributed to the relatively high lipophilicity and poor solubility. Herein we report the subsequent SAR optimisation and in vivo properties of these compounds. Previous SAR exploration around the arylsulfonamide and amine moieties had demonstrated that these parts of the molecule were highly sensitive to modifications; hence our initial efforts targeted core modifications that would lower the overall lipophilicity of the compounds (Table 1). Interestingly although removal of the indoline ring resulted in a considerable reduction of potency, compound **2** did retain appreciable potency and hence further open chain analogues were prepared. Subsequent removal of the methoxy group was also tolerated (cf. **2** and **3**), whereas replacement with an electron withdrawing led to a significant reduction in potency (cf. **2** and **4**). A range of targets whereby there is the potential to form an intramolecular hydrogen bond with the highly acidic sulfonamide moiety were also targeted with the aim of increasing the potential for good permeability and hence oral bioavailability. Gratifyingly the *ortho* methoxy

Keywords: Ghrelin; Growth hormone; Agonist.
* Corresponding author. Tel.: +44 1279 627832; fax: +44 1279 627685; e-mail: Jason_Witherington@GSK.com

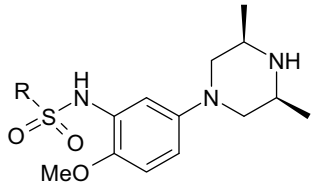
0960-894X/$ - see front matter
doi:10.1016/j.bmcl.2007.12.021

Table 1. Core modifications



#	R^1	R^2	hGHSR pEC50 (IA)[7]
2	H	OMe	7.8 (0.9)
3	H	H	7.4 (0.8)
4	H	CN	6.2 (0.9)
5	MeO	H	8.0 (1.1)
6	EtO	H	7.4 (0.8)
7	*i*PrO	H	7.0 (1.1)
8	Cl	H	7.4 (1.0)
9	F	H	7.0 (0.8)
10	MeCO	H	7.4 (0.9)
11	Me_2NCO	H	6.1 (0.9)

Table 2. Side chain SAR

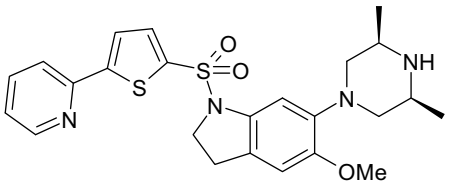


#	R^1	hGHSR pEC50 (IA)
5	(2-Pyridyl)-4-thienyl	8.0 (1.1)
12	4-Br-Ph	6.9 (0.7)
13	Ph-4-Ph	8.2 (1.0)
14	(5-OMe,2-F-Ph)-4-Ph	9.4 (1.2)
15	(3-OMe-Ph)-4-Ph	8.7 (1.0)
16	(5-Cl,2-F-Ph)-4-Ph	9.3 (1.0)
17	(1,3-Oxazol-5-yl)-4-thienyl	8.6 (0.9)
18	(4-Pyridyl)-4-Ph	6.5 (0.7)
19	(5-Pyrimidinyl)-4-Ph	6.5 (0.6)
20	(2-Oxo-1-pyrrolidinyl)-4-Ph	7.4 (0.8)
21	1*H*-Pyrazol-1-yl)-4-Ph	7.8 (0.8)
22	(2-Thienyl)-4-Ph	8.4 (1.0)
23	(2-Furanyl)-4-Ph	8.4 (0.9)
24	(5-Me-2-furanyl)-4-Ph	9.1 (1.0)
25	(2-Thienyl)-4-(2-Cl-Ph)	9.1 (0.9)
26	(2-Thienyl)-4-(2-F-Ph)	8.7 (0.9)
27	(2-Furanyl)-3-Ph	7.7 (1.0)
28	Ph-3-Ph	6.8 (1.0)
29	PhO-4-Ph	7.2 (0.9)
30	BnO-4-Ph	7.0 (0.8)

analogue **5** demonstrated encouraging potency. Attempts to replace the potential metabolically labile methoxy group with either larger alkoxy groups (**6** and **7**) or alternative hydrogen bonding substituents generally led to a reduction in potency (e.g., **9**, **10**, and **11**).

With compound **5** in hand we sought to optimise the (het)aryl sulfonamide moiety (Table 2). The presence of an (het)aryl substituent in the para position appears optimal for potency (cf. **13** with **12** and **28**) consistent with our hypothesis that an appropriately placed lipophilic group potentially mimics the octanyl group present on serine 3 of ghrelin which has been reported to be critical for potency and efficacy.[6] Further support for this hypothesis comes from the finding that introduction of polarity also leads to a reduction in potency (cf. **13** with **18**, **19** and **20**), however functionalisation of the terminal aryl ring can lead to further improvements in potency (cf. **13** with **14**, **15** and **16**). Interestingly, introduction of either a thiophene or furan group is also well tolerated (**22** and **23**) and the potency can be further enhanced by modulation of the lipophilicity around this part of the molecule (**24**, **25**, and **26**). Introduction of a linker residue between the two aromatic rings generally led to a reduction in potency (**29** and **30**).

Having identified several potent ligands we sought to determine whether they displayed improved in vivo properties relative to the indoline sulfonamides typified by SB-791016 (**1**). Encouragingly, a number of compounds displayed robust performance in a rat feeding assay[8] following oral dosing and were subsequently further profiled. Gratifyingly, compounds **22** and **24** retained a good selectivity profile over the 5-HT_{1B} receptor and displayed encouraging pharmacokinetic properties with low blood clearance and excellent bioavailability (Table 3).



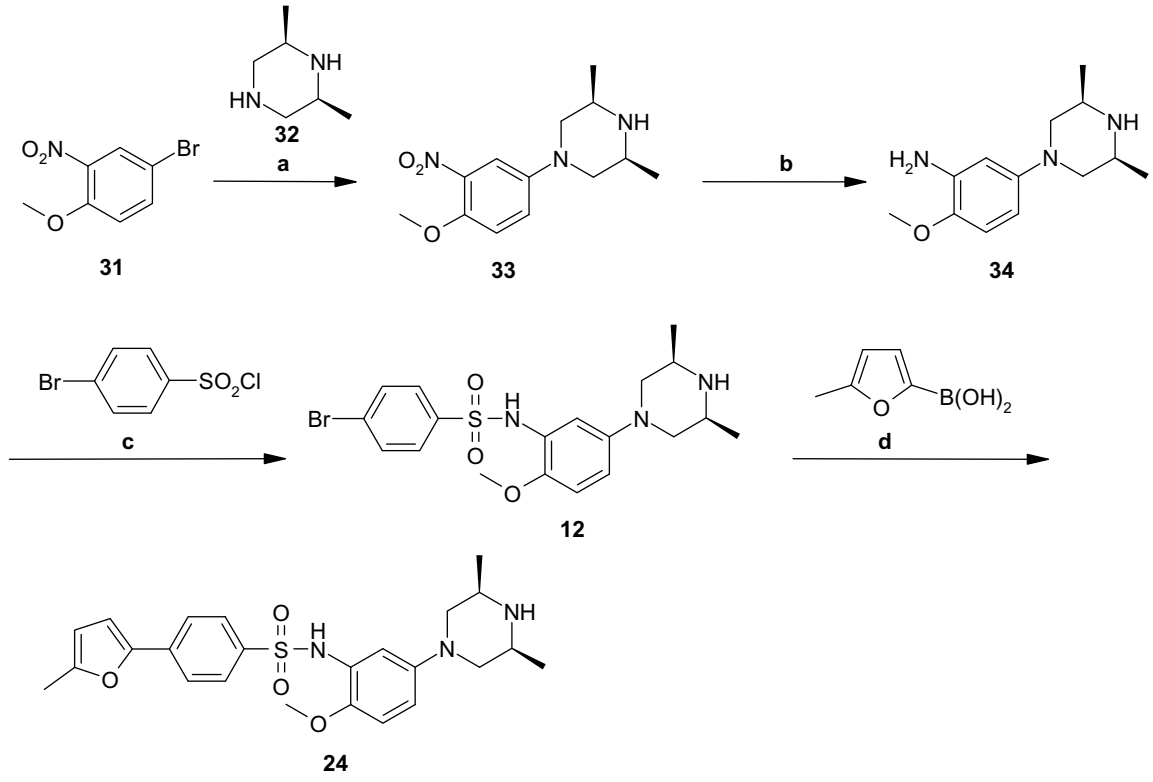
(1) SB-791016, hGHSR pEC50 (IA) 9.8 (0.9)

The furanyl analogue **24** was obtained starting with the reaction of the commercially available bromide **31** and piperazine **32** under cross coupling conditions to afford the *N*-aryl piperazine **33**. Reduction of the nitro moiety and subsequent selective sulfonylation of the resulting aniline, employing the commercially available 4-bromo benzene sulfonyl chloride, afforded the sulfonamide **12**. Finally, treatment of **12** with the commericially available

Table 3. 5-HT_{1B} selectivity and rat pharmacokinetic profiles of selected ghrelin agonists

#	5-HT_{1B} pK_i	Feeding response[a] (3 mg/kg, po)	Fpo[b,c] (%)	Cl (iv) (mL/min/kg)	$T_{1/2}$ (h)	V_{SS} (L/kg)
22	<5.5	292%	74%	26 ± 7	1.0	1.6 ± 0.1
24	<5.5	544%	75%	24 ± 4	1.9	3.3 ± 0.0

[a] Food intake measured between 0 and 2 h post-dose expressed relative to vehicle (n = 6).
[b] Male Sprague–Dawley rats (n = 1–3).
[c] Dose: iv infusion at 1 mg/kg; po at 3 mg/kg (n = 3, ±SD).



Scheme 1. Reagents and conditions: (a) Cs_2CO_3, $Pd(OAc)_2$, (*RS*)-BINAP, dioxane, reflux (68%); (b) H_2, Pd/C, EtOH, 25 °C (100%); (c) pyridine, DCM, 25 °C (85%); (d) $Pd(PPh_2)_2Cl_2$ (0.1 mol%), Na_2CO_3, DME, reflux (90%).

5-methyl furanyl boronic acid under Suzuki cross coupling conditions afforded the desired analogue **24** (GSK894490A) in good overall yield (Scheme 1).

In summary, having previously successfully identified SB-791016 as a potent agonist of the ghrelin receptor we have systematically identified the key pharmacophoric features responsible for high potency. In common with the literature the SAR around the natural ligand ghrelin, an appropriately placed lipophilic side chain is essential for optimal potency in our non peptidic agonists. Furthermore, replacement of the indoline moiety with an ortho methoxy phenyl ring led to the identification of a series of compounds that display excellent in vivo efficacy and pharmacokinetic properties.

References and notes

1. Takaya, K.; Ariyasu, H.; Kanamoto, N.; Iwakura, H.; Yoshimoto, A.; Harada, M.; Mori, K.; Komatsu, Y.; Usui, T.; Shimatsu, A.; Ogawa, Y.; Hosoda, K.; Akamizu, T.; Kojima, M.; Kangawa, K.; Nakao, K. *J. Clin. Endocrinol. Metab.* **2000**, *85*, 4908.
2. Tschop, M.; Smiley, D. L.; Heiman, M. L. *Nature* **2000**, *407*, 908.
3. Nakazato, M.; Murakami, N.; Date, Y.; Kojima, M.; Matsuo, H.; Kangawa, K.; Matsukura, S. *Nature* **2001**, *409*, 194.
4. (a) Binn, M.; Albert, C.; Gougeon, A.; Maerki, H.; Coulie, B.; Lemoyne, M.; Rabasa Lhoret, R.; Tomasetto, C.; Poitras, P. *Peptides* **2006**, *27*, 1603; (b) Murray, C. D. R.; Martin, N. M.; Patterson, M.; Taylor, S. A.; Ghatei, M. A.; Kamm, M. A.; Johnston, C.; Bloom, S. R.; Emmanuel, A. V. *Gut* **2005**, *54*, 1693.
5. Heightman, T. D.; Scott, J. S.; Longley, M.; Dean, D. K.; Elliott, R.; Hutley, G.; Witherington, J.; Abberley, L.; Passingham, B.; Berlanga, M.; Frailes, M.; Wise, A.; Powney, B.; Muir, A.; McKay, F.; Butler, S.; Winborn, K.; Gardner, C.; Darton, J.; Campbell, C.; Sanger, G. *Bio. Med. Chem. Lett.* **2007**, *17*, 6584.
6. Matsumoto, M.; Hosoda, H.; Kitajima, Y.; Morozumi, N.; Minamitake, Y.; Tanaka, S.; Matsuo, H.; Kojima, M.; Hayashi, Y.; Kangawa, K. *Biochem. Biophys. Res. Commun.* **2001**, *287*, 142.
7. GHSR Agonist BACMAM FLIPR Assay was used to determine the potency and efficacy of the test compounds. Media were aspirated from cell plates using a cell washer (leaving 10 μl of media). Cells are immediately loaded with loading buffer (Tyrodes (Elga water + 145 mM NaCl + 5 mM KCl + 20 mM HEPES + 10 mM glucose + 1 mM $MgCl_2$) + 1.5 mM $CaCl_2$ + 0.714 mg/ml probenicid (predissolved in 1 M NaOH) + 0.5 mM brilliant black + 2.5 μM Fluo 4 dye) and incubated at 37.5 °C for 1 h. Ten microliters from compound plates is then added immediately to cell plates using a FLIPR 3 calcium imaging instrument. Fluorescence measurements are then taken. Intrinsic activity is expressed relative to human ghrelin.
8. Test compounds were assessed for their effects on food intake in singly housed, freely feeding male Sprague–Dawley rats. Groups of 6 rats received either vehicle (1% (w/v) methylcellulose in water, 1 ml kg^{-1}), or test compounds (3 mg kg^{-1}) po. Total food consumption was measured up to 2 h post-dose.