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Aryl sulphonyl amides as potent agonists of the growth hormone secretagogue (ghrelin) receptor

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ABSTRACT

As part of an on-going lead optimisation effort, a cross screening exercise identified an aryl sulphonyl amide hit that was optimised to afford a highly potent series of ghrelin receptor agonists.

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] Previously we described the systematic optimisation of a high-throughput screening hit (HTS) to yield a series of small molecule orally bioavailable ghrelin receptor agonists (Scheme 1).[5,6]

As part of our on-going lead optimisation efforts, a routine cross screening exercise of all newly prepared GSK compounds identified (**2**) as a hit worthy of further investigation. Herein we report the subsequent SAR optimisation and preliminary in vivo properties of these compounds.

Our initial evaluation of the lead (**2**) focussed on understanding the stereochemical preference at both asymmetric centres. Interestingly, whilst the S-isomer of the pipecolinic acid was essential for potency (cf **3** and **4** with **5** and **6**) there was no stereochemical influence of the 3-aminopyrrolidinyl amine (cf **5** and **6**) (Tables 1 and 2).

Given the structural similarity to the previously disclosed aryl sulphonamide lead (**1**) we then sought to determine whether we could exploit the previous SAR findings from this series. As in the aryl sulphonamide series a biaryl moiety appeared essential for high inhibitory potency (cf **6** and **7**) and further optimisation of this side chain afforded dramatic improvements in potency which was also consistent with our original lead series (cf **8**, **9** and **11**). The preferred furanyl substituent was confirmed to be an optimal

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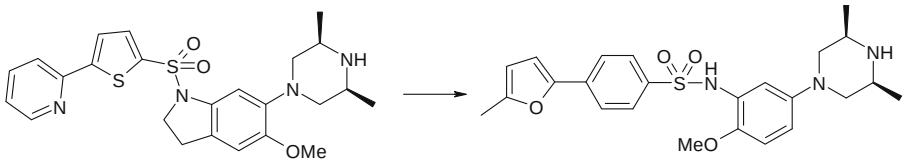
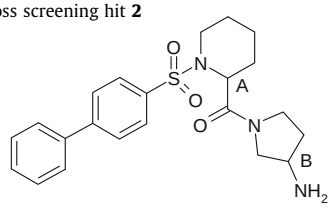


Scheme 1. Identification of potent orally bioavailable ghrelin receptor agonists.

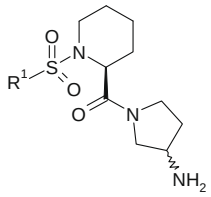
Table 1
Stereo isomers of cross screening hit **2**



Compound	A (*R*/*S*)	B (*R*/*S*)	GHSR pEC50 (IA)[7]
2	Racemic		7.5 (0.8)
3	*R*	*S*	<5.3
4	*R*	*R*	<5.3
5	*S*	*S*	8.1 (1.1)
6	*S*	*R*	7.8 (1.1)

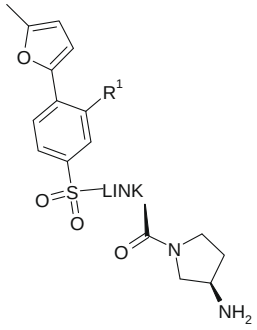
substituent in both the *R* and *S* amino pyrrolidinyl amine series (**11** and **12**) but could also be replaced by a suitably functionalised aryl moiety (e.g., **17** and **18**). Consistent with the aryl sulphonamide

Table 2
Side chain SAR



Compound	*R*/*S*	R^1	GHSR pEC50 (IA)[7]
7	*R*	4-Br-Ph	6.4 (0.7)
8	*R*	(2-Furanyl)-4-Ph	7.5 (1.2)
9	*R*	(5-Me-2-furanyl)-4-Ph	9.6 (1.3)
10	*R*	(2-Furanyl)-4-(3-F-Ph)	8.5 (0.9)
11	*R*	(5-Me-2-furanyl)-4-(3-F-Ph)	10.3 (1.3)
12	*S*	(5-Me-2-furanyl)-4-(3-F-Ph)	9.8 (1.3)
13	*S*	PhCONH-4-Ph	7.7 (1.1)
14	*S*	(2-F-Ph)CONH-4-Ph	8.4 (1.3)
15	*S*	(3-MeO-Ph)CONH-4-Ph	8.7 (1.3)
16	*S*	(3-Pyridyl)-4-Ph	6.5 (0.6)
17	*R*	(2,5-diF-Ph)-4-Ph	9.0 (1.2)
18	*R*	(2,5-diCl-Ph)-4-Ph	9.5 (1.2)

Table 3
Template SAR



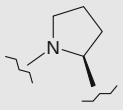
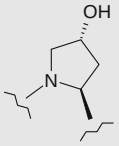
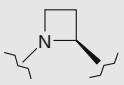
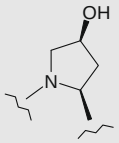
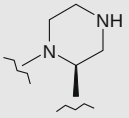
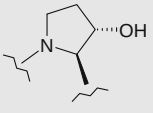
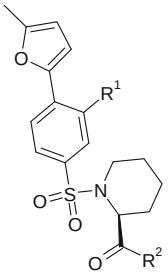
Compound	LINK	R^1	*c*log*P*	GHSR pEC50 (IA)[7]	Compound	LINK	R^1	cLogP	GHSR pEC50 (IA)[7]
19		F	3.4	9.4 (1.2)	**22**		F	1.8	9.3 (1.1)
20		F	2.4	7.8 (1.1)	**23**		F	1.8	8.3 (1.2)
21		H	2.6	8.9 (1.1)	**24**		F	2.0	9.7 (1.2)

Table 4
Amine SAR



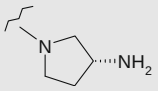
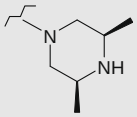
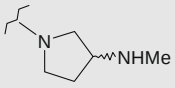
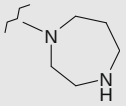
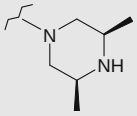
Compound	R^1	R^2	GHSR pEC50 (IA)[7]
11	F		10.3 (1.3)
25	H		8.2 (1.2)
26	H		8.0 (0.9)
27	H		8.1 (0.9)
28	F		8.6 (1.2)

Table 5
Rat pharmacokinetic profile for compound **19** in male Sprague–Dawley rats

i.v. Bolus at 1 mg/kg		3 mg/kg po (n = 3, ±SD)	
CLb (mL/min/kg)	25	Cmax (μM)	0.151 ± 0.024
Vss (L/kg)	3.5	Tmax* ((h))	4.0 (4.0–4.1)
Cmax (μM)	0.762	AUC (0–t)/dose** (min kg/L)	5 ± 1
t½ (h)	2.4		
MRT (h)	2.4		

* Tmax expressed as median and range.
** t for AUC ($0 \rightarrow t$) is 6 h or the time of the last quantifiable blood concentration.

series, introduction of polarity led to a reduction in potency (cf **5** and **16**) however the finding that a linker group was tolerated between the two aryl rings was a surprising result (e.g., **14** and **15**) given this was poorly tolerated in our initial lead series (data not published).

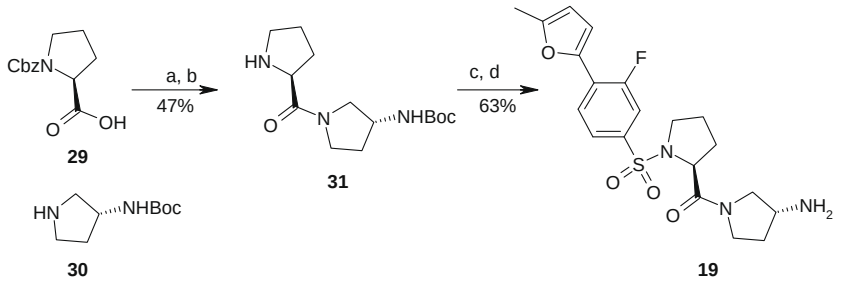
Having established the stereochemical preferences and side chain SAR we turned our attention to establishing the role of the central template in order to ascertain whether this part of the molecule could be utilised to modulate the overall lipophicity of the series which had previously been difficult to achieve with our early lead series (SB-791016-A and **1** *c*log*P*s 4.1 and 4.9, respectively). Gratifyingly, whilst the six-membered pipecolinic acid moiety was confirmed as the optimal ring size (cf **11** with **19** and **20**) (Table 3), a wide range of groups were tolerated which potentially allows for the fine tuning of the physicochemical properties of these molecules and the identification of compounds with substantially lower *c*log*P*s than our initial lead series (e.g., **19–20** cf **SB-791016** and **1**).

Having established the preliminary preferences of both the side chain and the central core we sought to examine the structural requirements of the amine group. Previous SAR exploration in the arylsulphonamide series had demonstrated that this part of the molecule was highly sensitive to modification. Interestingly, we again confirmed the *cis*-2,6-dimethylpiperazine moiety as having good potency albeit this was not the optimal amine substituent (cf **28** and **11**) (Table 4). In general this series was more tolerant to changes in the amine functionality than in the aryl sulphonamide series.[5]

Given the initial promising SAR findings of this cross screening hit we decided to profile one of our more potent compounds. Whilst compound **19**, displayed an encouraging profile following iv dosing with low to moderate in vivo clearance the systemic exposure was low following oral dosing and would need to be optimised prior to further in vivo evaluation (Table 5).

The pyrrolidinyl analogue **19** was obtained starting with the coupling of the commercially available Cbz protected L-proline **29** and Boc protected (3*R*)-pyrrolidinyl amine **30** to afford, after hydrogenolysis, the amine **31**. Sulphonylation of the secondary amine followed by Boc deprotection afforded the desired analogue **19** in good overall yield (Scheme 2).

In summary, having identified a hit from a cross screening exercise, we have explored the initial structural requirements for optimal potency. In common with our previously published aryl sulphonamide series, and literature the SAR around the natural ligand ghrelin, an appropriately placed lipophilic side chain is essential for optimal potency. Furthermore, replacement of the pipecolinic acid core and aminopyrrolidinyl side chain is well tolerated giving encouragement for further optimisation of the pharmacokinetic properties of this series.



Scheme 2. Reagents and conditions: (a) HOAt, EDC, DCM, 25 °C; (b) H_2, Pd/C, EtOH, 25 °C; (c) (5-Me-2-furanyl)-4-(2-F-Ph)-SO_2Cl, pyridine, DCM, 25 °C; (d) HCl·dioxane (63%, two steps).

References and notes

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7. GHSR Agonist BACMAM FLIPR assay was used to determine the potency and efficacy of the test compounds. Media is 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 (IA) expressed relative to human ghrelin.