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The discovery and optimisation of benzazepine sulfonamide and sulfones as potent agonists of the motilin receptor

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ABSTRACT

Optimisation of a series of benzazepine sulfonamide hit compounds identified from high throughput screening led to the discovery of a new series of tractable, potent motilin receptor agonists.

Motilin is a 22 amino acid peptide which on interaction with the motilin G protein-coupled receptor (GPCR) is involved in regulating the motor activity of the digestive system.[1,2] Specifically, activation of the motilin receptor increases contractile activity of the gastrointestinal smooth muscle[3] and promotes gastric emptying.[4,5] Motilin plays a key role in regulating the migrating motor complexes (phase III), which are a series of peristaltic contractions emanating from the stomach to the small intestine which serve to clear this tract of residual content in the interdigestive state.[2,6] Motilin is produced by endocrine cells in the upper small intestinal mucosa and is related to another gastrointestinal hormone, ghrelin.[1,7,8] The human motilin receptor was cloned and characterised in 1997 and has a 52% overall amino acid sequence identity to the ghrelin receptor.[9,10]

Several gastrointestinal disorders involve delayed gastric emptying, for example in diabetic gastroparesis patients and some subsets of functional dyspepsia patients. In these cases administration of a gastroprokinetic agent such as a motilin receptor agonist could alleviate symptoms. However the pathophysiology underlying these conditions is complex, being affected by multiple factors.[11] The macrolide antibiotic erythromycin is well established as a motilin receptor agonist which increases gastric emptying,[12,13] and is frequently used in the clinic for the treatment of gastric stasis. However, in addition to its antibiotic activity, erythromycin also possesses other undesirable properties such as acid instability, increased cardiac risk factors and potential for drug–drug interactions.[14] Various macrolide erythromycin derivatives, or motilides, have been developed which maintain the motilin receptor agonist activity whilst eradicating antibiotic activity. Clinical trials in gastroparesis and functional dyspepsia patients with some of the early motilides have yielded mixed results.[15,16] However, more recently, the motilide mitemcinal[17] (**1**, Fig. 1) has shown promise in clinical trials by improving the rate of gastric emptying[18] and alleviating symptoms in gastroparesis patients.[19]

As part of our ongoing program,[20] we sought to identify low molecular weight motilin receptor agonists for use in conditions where reduced gastric emptying is a factor. There are limited examples of non-macrolide motilin receptor agonists, for example, **2**[21] and GSK962040 **3** from our laboratories.[20c] In this Letter, we disclose the discovery and optimisation of a novel series of low molecular weight benzazepine sulfonamide and sulfone motilin receptor agonists.

A high throughput screen (HTS) against the motilin receptor conducted in FLIPR format[22] on the GSK compound collection produced several potential series of interest. Prioritisation of these

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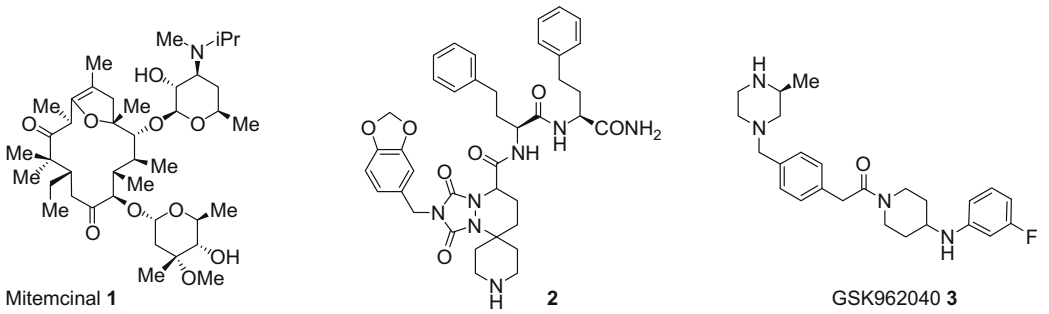


Figure 1. Various known motilin receptor agonists.

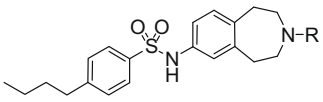
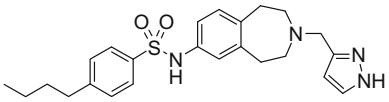


Figure 2. Benzazepine template **4**.



Potency:
h-motilin R: pEC_{50} 8.6 (0.7)

Efficacy:
Rabbit native tissue bath:
E_{max} 47% at 1μM

Selectivity:
h-ghrelin R pEC_{50} 7.1 (0.7),
$5HT_6$ fpKi 7.7,
D_2/D_3 pKi 7.0 / 8.4
hERG pIC_{50} 5.6

Developability:
MW 439, clogP 4.9

Aq. Sol. 10 mg/mL (pH 7.4)

CLi (mL/min/g): rat 33, hum 22

P450 enzyme inhibition (IC_{50} μM):
1A2 29, 2C9 0.6, 2C19 8.8,
2D6 <0.1, $3A4_{DEF}$ 0.8, $3A4_{PPR}$ 1.9

Figure 3. Benzazepine compound **18**.

series, for example by profiling compounds in our rabbit isolated gastric antrum native tissue assay,[23] identified a number of compounds based on the benzazepine sulfonamide template (Fig. 2) as a suitable starting point for our chemistry programme.

We first investigated the effect of substitution on the benzazepine nitrogen, complemented by analogue searching of the GSK compound collection following the HTS (Table 1). The unsubstituted benzazepine **5** was only very weakly active, bulky alkyl groups showed a small increase in potency, with cyclopentyl **6** the most active. More polar saturated groups such as THF **7** and piperidines **8** or **9** were generally not well tolerated. A range of benzyl substituents were investigated, and were weakly active or inactive, for example the parent benzyl compound **10**. Interestingly, the most potent compound from this set was phenylacetamide **11** possessing hydrogen bond donor capabilities. A similar pattern was observed for thiophenes **12** and **13**, where the appropriately positioned acetamide endowed good potency and efficacy compared with the unsubstituted parent. To explore this effect further, a series of H-bond donor capable heterocycles were prepared. Thus, imidazoles **14** and **15** displayed excellent potency and efficacy whereas imidazole **16**, in which the methyl group sterically hinders the hydrogen bond donor sites, showed a marked decrease in potency. N-Me compound **17** had no hydrogen bond donor capability and therefore displayed low potency. This SAR strongly suggests that good hydrogen bond donor capability affords good motilin receptor agonist activity in this series. The more potent imidazoles **14**–**16** all showed activity at the ghrelin receptor, albeit as partial agonists, but switching to pyrazole **18** was encouraging with this being one of our most potent compounds to date, and it also showed >30-fold selectivity towards the ghrelin receptor.[24]

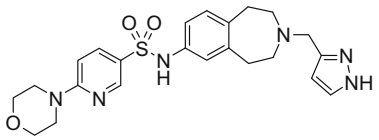
Compound **18** was a good starting point in terms of potency; but a lack of GPCR selectivity, a poor DMPK profile,[25] and only weak efficacy in our native tissue assay (Fig. 3) meant it required further optimisation. To this end, we next focused on variation of the lipophilic phenyl group (Table 2), in the hope that modification would engender selectivity against other GPCR receptors and improve efficacy in the rabbit native tissue assay. Reduction of log *P* by introduction of more polar groups here was also expected to improve the DMPK profile.

Isopropyl sulfonamide **19** was inactive and benzyl sulfonamide **20** was weakly active, suggesting that more bulky substitution here was poorly tolerated. A variety of phenyl sulfonamides were then investigated and these displayed a range of potencies. For example, the cyanophenyl analogue **21** was inactive whereas chlorophenyl **22** was weakly potent. The 3-chloro-4-methylphenyl analogue **23** displayed moderate potency and efficacy, although this compound also showed considerable affinity for the ghrelin, $5HT_6$ and D_3 receptors.

para-Substituted phenyl sulfonamides generally displayed good motilin receptor agonist potency and efficacy, with bulkier substituents performing best. The 4-4′-biphenyl compound **24**, 4-isopropoxyphenyl **25** and chroman **26** all displayed high potency and efficacy although potency against the D_3 receptor was a concern, as was rising ghrelin activity for the two ethers. All three compounds also had high *c* log *P* values, leading to the hypothesis that lipophilicity in the tail was required for motilin activity. Benzoxazine **27** fueled our concerns, as the more polar compound was almost a log unit less active than ether **26**. Another bicyclic compound, pyridinylthiophene **28**, exhibited high potency and efficacy and performed well in the native tissue assay (E_{max} 190% at 3 μM). Furthermore, selectivity was good but unfortunately intrinsic clearance remained high (rat = 32, human = 15 mL/min/g). Morpholinylpyridine **29** displayed similar potency to **28**, and had an excellent effect in the rabbit native tissue assay (E_{max} 476% at 1 μM). Moreover, compared to *n*-butylphenyl **18**, both selectivity and intrinsic clearance were greatly improved (rat = 3.8, human = 6.6 mL/min/g). These results were very gratifying, as it showed that an excellent activity profile could be obtained for a compound with low *c* log *P*.

Pyridines **28** and **29** gave two of our most efficacious compounds to date, **29** also showed a much improved developability profile over **18** (Fig. 4).

However there were still issues to address with the series, in particular the CYP2D6 activity of all but two of the compounds measured in Table 2 was $\leqslant$1 μM, leading to a potential for drug–drug interactions in the clinic. We reasoned that the pyrazole group which imparts potency could also be accountable for interaction with the



Potency:
h-motilin R: pEC_{50} 8.2 (1.0)

Efficacy:
Rabbit native tissue bath:
E_{max} 476% at 1μM

Selectivity:
h-ghrelin R pEC_{50} <6,
$5HT_6$ fpKi 6.2,
D_2/D_3 pKi <5.5 / 6.2
hERG pIC_{50} <4.8

Developability:
MW 468, clogP 2.4, CHI $logD_{7.4}$ 1.2

Aq. Sol. 371 μg/mL (pH 7.4)

CLi (mL/min/g): rat 3.8, hum 6.6

P450 enzyme inhibition (IC_{50} μM):
2D6 <1, Rest >8

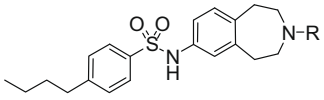
Mouse PK (10 mg/kg oral) $t_{½}$ 1.5 h;
T_{max} 2.0 h; C_{max} 273 ng/mL.

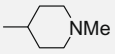
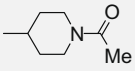
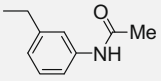
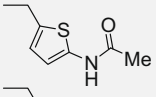
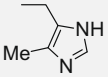
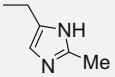
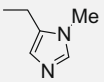
Figure 4. Benzazepine compound **29**.

heme core of the 2D6 enzyme.[26] Analysis of other non-aromatic groups in the series showed none had a comparable profile to the pyrazole in **29** (cf. Table 1), so we initiated further investigation around the sulfonamide core to try and improve potency and efficacy in the absence of the aromatic NH donor (Table 3).

Compounds were prepared as NH benzazepines in either the *n*-butylphenyl series cf. **18** or the pyridyl morpholine series cf. **29**. Sulfonamides **30** and **31** were only weakly active without the donor pyrazole. Reversing the linker as in **32** had no effect on potency, but switching from sulfonamide to amide resulted in a total loss of activity as demonstrated in **33**–**36**. Sulfone **37** showed a modest increase in potency compared to sulfonamide **30**, however replacement with the *n*-butylphenyl series gave **38**, which was 10-fold more potent than **5** on which it was based. This result encouraged us to expand the SAR further around this aromatic sulfone template.

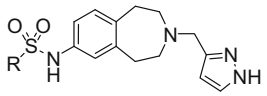
Table 1
Agonist activity at motilin and ghrelin receptors for pyrazole analogues

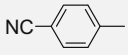
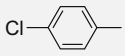
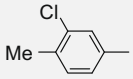
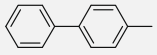
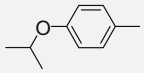
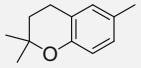
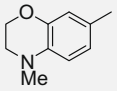
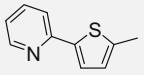
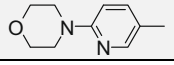


Compound	R	h-MotilinR pEC_{50} (IA)[a]	h-GhrelinR pEC_{50} (IA)[b]
5	H	5.8 (0.8)	–
6		6.7 (0.8)	<6
7		5.7 (0.96)	<6
8		<4.9	–
9		<5.6	–
10		<5.5	–
11		6.3 (0.7)	<5
12		5.6 (0.9)	<6
13		7.3 (0.9)	<6
14		8.1 (0.8)	8.4 (0.4)
15		8.5 (0.8)	8.4 (0.6)
16		7.2 (0.7)	7.7 (0.5)
17		5.5 (0.7)	–
18		8.6 (0.7)	7.1 (0.7)

[a] IA refers to intrinsic activity compared to human motilin.
[b] IA refers to intrinsic activity compared to human ghrelin.

Table 2
Profile of compounds for replacement of the *n*-butylphenyl group



Compound	R	h-MotilinR pEC_{50} (IA)	h-GhrelinR pEC_{50} (IA)	5HT6 fpKi	D2 pK_i binding	D3 pK_i binding	*c* log *P*	P450 (IC_{50} μM)
19		<4.9	–	–	–	–	2.0	2D6 16
20		5.6 (0.8)	<6.0	–	–	–	2.8	–
21		5.1 (1.0)	–	–	–	–	2.9	2C9 2.5 2D6 7.9
22		6.1 (0.9)	<5	–	–	–	3.8	–
23		7.4 (0.7)	7.1 (0.7)	8.2	6.4	7.0	4.3	–
24		8.0 (0.9)	5.8 (0.7)	6.9	6.2	7.5	4.7	3A4, 2D6 <0.1
25		8.4 (1.0)	6.8 (0.6)	6.7	6.2	7.7	3.9	2D6 1.3
26		8.3 (1.2)	6.2 (0.7)	–	–	–	4.6	2D6 0.5
27		7.5 (0.8)	<5	7.8	<6.0	6.2	3.4	–
28		8.1 (1.0)	<5	6.8	<6.1	6.7	3.6	2C9 0.4 2D6 0.2
29		8.2 (1.0)	<6	6.2	<5.5	6.2	2.4	2D6 0.2

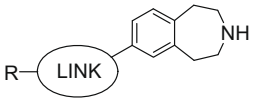
Removal of the *n*-butyl group in **38** gave unsubstituted phenyl sulfone **39** which was inactive at the motilin receptor (Table 4). Addition of *t*-butyl or the fused naphthyl ring system **40** and **41** restored some potency at the expense of lipophilicity. This early SAR suggested a more linear group was preferred, and this was confirmed when a boost in activity came with the addition of the 4-substituted biphenyls **42–44**. In this way the sulfone SAR followed that of the earlier sulfonamides (cf. Table 2). We were pleased to see low microsomal clearance for the three biphenyls, although they still showed sub-μM potency at CYP 2D6. It was felt that the high *c* log *P* (⩾4) was a contributing factor here, so further compounds were designed to raise the PSA and reduce *c* log *P* in an effort to address this. Pleasingly, the pyridyl analogues **45** and **46** were equipotent with the best pyrazole sulfonamides **28** and **29**. 4-F substitution seemed to offer the best profile, reducing *c* log *P* to a reasonable level (3.3) and a suggestion of lower 2D6 inhibition. More polar acceptors such as CN on the biaryl group were not well tolerated.

In an effort to raise the PSA further, addition of a polar linker between the pyridyl and 4-fluorophenyl rings, in the form of amide **48** or phenyl ether **49** resulted in a 100-fold drop in activity. This effect was reversed somewhat with smaller alkyl ethers **50** and **51**, suggesting a lack of space at this end of the ligand–receptor complex. Smaller amine substituents were also tolerated, with the N-linked piperidine **52** performing best. We were surprised to see that replacing this with 4-fluoroaniline gave a 20 nM compound **53**, 25-fold more potent than the ether analogue **49**.

Two of the best compounds were tested in the rabbit native tissue assay, with modest results; Compound **43** gave E_{max} 166% at 3 μM and **46** 54% at 1 μM. Ultimately however all compounds suffered the same fate—the more active compounds tended to be more lipophilic, which correlated to high levels of inhibition at CYP 2D6, and as such were not progressed further. This is clearly illustrated by comparing piperidine **52** (*c* log *P* = 2.4, 2D6 IC_{50} = 1.1 μM) with morpholine **37** (*c* log *P* = 1.1, 2D6 IC_{50} = 16 μM), a marked difference for such a simple change. This would suggest the earlier heme H-bonding proposal may not be involved, or at least be the only binding mode within the CYP2D6 receptor for these benzazepine ligands. More studies may be needed to evaluate these findings further.

The synthesis of the benzazepine sulfonamides used standard conditions beginning with sulfonylation of the known benzazepine **54**[27] using commercially available sulfonyl chlorides. Removal of the Boc group and reductive amination then gave the final products. This chemistry is exemplified by the synthesis of the 4-*n*-butylphenyl analogues (Scheme 1). The final step was a reductive amination array (dimensions 1 × 60) utilizing borohydride resin which facilitated the reaction work up. Purification was achieved

Table 3
Effect of linker changes



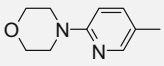
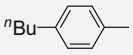
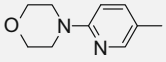
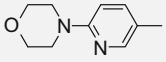
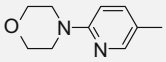
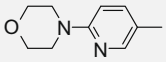
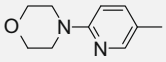
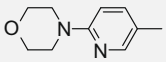
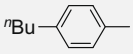
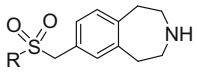
Compound	R	LINK	h-MotilinR pEC_{50} (IA)
30			5.8 (0.65)
31			5.6 (0.4)
32			5.6 (0.6)
33			<4.9
34			<4.9
35			<4.9
36			<4.9
37			6.3 (0.8)
38			6.9 (1.0)

Table 4
Benzazepine sulfone SAR



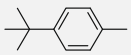
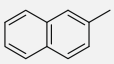
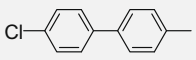
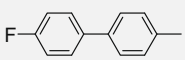
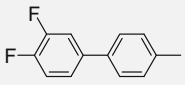
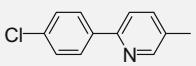
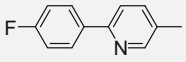
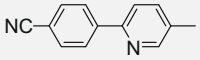
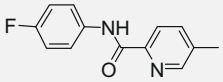
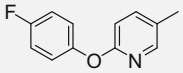
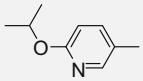
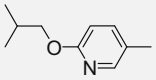
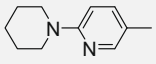
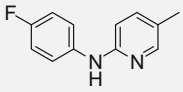
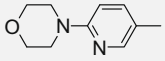
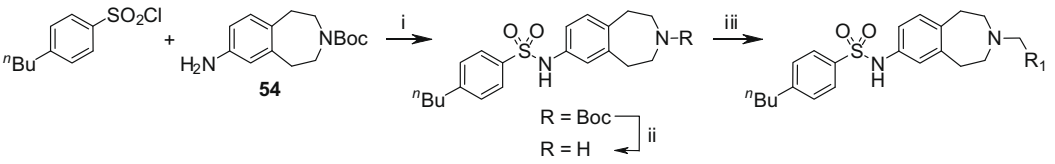
Compound	R	h-MotilinR pEC_{50} (IA)	h-GhrelinR pEC_{50}	*c* log *P*	P450 2D6 (IC_{50} μM)	CLi rat (mL/min/g)	CLi human (mL/min/g)
39		<4.9	<6	1.9	–	–	–
40		5.5 (1.0)	<5	3.8	–	–	–
41		5.9 (0.7)	<5	3.1	–	–	–
42		7.7 (1.1)	<5	4.6	<0.1	<0.5	<1
43		7.9 (1.1)	<5	4.0	0.2	<1	<1
44		7.6 (1.5)	<5	4.1	0.1	1.1	1.0
45		8.1 (1.3)	<6	3.9	<0.1	<1	<1

Table 4 (*continued*)

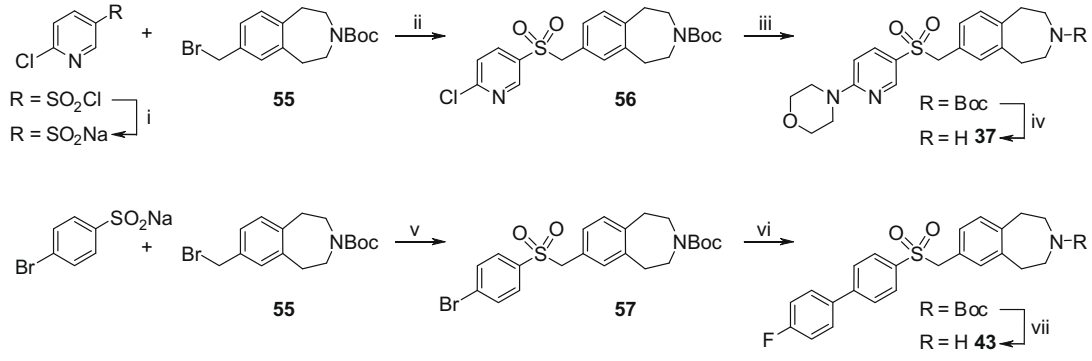
Compound	R	h-MotilinR pEC_{50} (IA)	h-GhrelinR pEC_{50}	*c* log *P*	P450 2D6 (IC_{50} μM)	CLi rat (mL/min/g)	CLi human (mL/min/g)
46		8.3 (1.0)	<6	3.3	0.6	<0.5	<1
47		6.8 (1.1)	<6	2.6	–	–	–
48		5.7 (0.7)	–	2.8	–	–	–
49		6.3 (0.8)	<6	3.3	1.7	–	–
50		6.8 (0.8)	<6	2.7	1.6	–	–
51		7.4 (0.8)	<6	3.3	–	–	–
52		7.2 (0.9)	<6	2.4	1.1	–	–
53		7.7 (0.8)	<6	3.8	0.3	<0.5	<1
37		6.3 (0.8)	<6	1.1	16	<1	<0.5



Scheme 1. Reagents and conditions: (i) diisopropylethylamine, CH_2Cl_2, rt, 74%; (ii) trifluoroacetic acid, 1,3-dimethoxybenzene, CH_2Cl_2, rt, 99%; (iii) R^1CHO, MP-$BH(OAc)_3$ resin, THF/DMF, rt; PL-NCO resin; SCX cartridge; further purification as necessary, for example, mass directed auto purification using reverse phase HPLC.

using isocyanate scavenging resin and strong cation exchange cartridges. Compound purity was assessed at this point and further purification was carried out as necessary, for example by mass directed auto purification using reverse phase HPLC.

The methylene sulfone compounds were readily prepared using sulfinate chemistry.[28] Thus conversion of 6-chloro-3-pyridinesulfonyl chloride to the sodium sulfinate salt, followed by alkylation with the known bromide **55**[29] gave methylene sulfone



Scheme 2. Reagents and conditions: (i) Na_2SO_3, Na_2HPO_4, EtOH, H_2O, 55 °C; (ii) $^nBu_4N^+Br^-$, DME, 85 °C, 69% over two steps; (iii) morpholine, $^iPr_2NEt$, THF, DMF, 100 °C (microwave), 81%; (iv) 4 M HCl/dioxan, DCM, rt, 75%; (v) $^nBu_4N^+Br^-$, DME, 85 °C, 53%; (vi) 4-fluorophenyl boronic acid, $Pd(PPh_3)_4$, $NaHCO_3$, toluene, EtOH, H_2O, reflux, 86%; (vii) 4 M HCl/dioxan, DCM, rt, 100%.

56 in good yield (Scheme 2). Nucleophilic displacement under thermal conditions followed by deprotection then gave compounds such as morpholine **37** as shown. The biphenyl compounds were prepared in a similar manner. Thus commercially available sodium bromobenzenesulfinate and bromide **55** were reacted to form sulfone **57**. Suzuki coupling and deprotection gave biphenyl compounds as exemplified by **43**.[30]

In conclusion, we report here for the first time a series of small molecule motilin receptor agonists, based on a chemically tractable benzazepine sulfonamide or sulfone core. When compared to the 4-*n*-butylphenylsulfonamide compound **1**, promising new leads have displayed higher levels of potency, selectivity and efficacy in a disease relevant tissue assay. Morpholinylpyridine compound **29**[30] additionally had a promising oral pharmacokinetic profile in mice. Switching to methylene sulfone linkers gave good potency in the absence of the pyrazole donor group, and had the positive effect of reducing the MW to below 400.[31] Further progression of the series was precluded due to the sub-μM CYP 2D6 activity. However their nM potency makes them valuable tools for further investigation, and provide yet more evidence that small molecule agonists of peptide GPCRs are a realisable goal.

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30. *Characterisation data for* **29**: ^{1}H NMR (400 MHz, MeOH-d_4) δ (ppm): 8.34 (1H, d, *J* 2.4 Hz), 7.71 (1H, dd, *J* 9.2, 2.4 Hz), 7.56 (1H, d, *J* 2.0 Hz), 6.91–6.95 (1H, m), 6.82–6.86 (2H, m), 6.70 (1H, d, *J* 9.2 Hz), 6.30 (1H, d, *J* 2.2 Hz), 3.68–3.76 (6H, m), 3.54–3.59 (4H, m), 2.79–2.86 (4H, m), 2.59–2.67 (4H, m). MS: (ES$^+$) 469 (MH$^+$). *Characterisation data for* **43**: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.16 (1H, s), 7.91 (2H, d, *J* 8 Hz), 7.84–7.80 (4H, m), 7.37 (2H, app. t, *J* 8 Hz), 7.16 (1H, d, *J* 8 Hz), 7.05–7.01 (2H, m), 4.66 (2H, s), 3.18–2.98 (8H, m). MS: (ES$^+$) 396 (MH$^+$).
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