Bioorganic & Medicinal Chemistry Letters 18 (2008) 6423–6428

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Identification of small molecule agonists of the motilin receptor

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ARTICLE INFO

Article history:
Received 11 September 2008
Revised 15 October 2008
Accepted 16 October 2008
Available online 19 October 2008

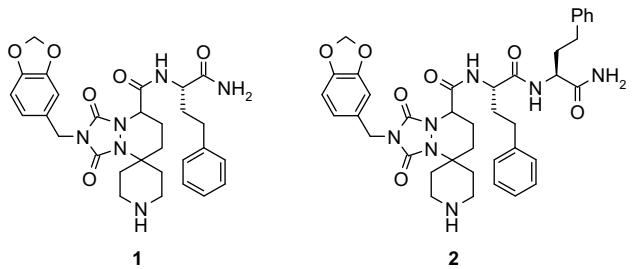
Keywords:
Motilin
Receptor
Agonist
GPCR

ABSTRACT

High-throughput screening resulted in the identification of a series of novel motilin receptor agonists with relatively low molecular weights. The series originated from an array of biphenyl derivatives designed to target 7-transmembrane (7-TM) receptors. Further investigation of the structure–activity relationship within the series resulted in the identification of compound (**22**) as a potent and selective agonist at the motilin receptor.

Motilin, a 22-amino acid peptide found in endocrine cells within the gut mucosa, can enhance gastrointestinal motility and promote gastric emptying in both animals and humans.[1] The macrolide antibiotic erythromycin mimics the effects of motilin, and has been used clinically for the treatment of motility disorders including post-operative ileus.[2] These effects have been shown to result from agonist activity at the motilin receptor (previously known as GPR38), providing attractive clinical validation of the receptor as a target for small molecule therapeutic intervention,[3] and prompting the development of a family of non-antibiotic macrolides known as motilides, exemplified by KC11458, ABT229 and mitemcinal (GM-611).[4] Until recently the motilides were the only non-peptide agonists of the motilin receptor, and despite success in demonstrating enhanced gastric emptying in humans, some have encountered difficulties during clinical development.[5] However two molecules of this class, mitemcinal from Roche/Chugai and PF-0454803/KOS2197 from Pfizer/Kosan, are currently progressing in clinical trials.[6] In 2004 a series of non-motilide motilin receptor agonists was disclosed (Fig. 1), represented by compounds (**1**) and (**2**), possessing molecular weights in the range 560–720, multiple chiral centres and a relatively complex synthesis.[7]

At GSK we initiated a programme towards the discovery of small molecule rather than motilide agonists of the human motilin receptor. A FLIPR (Fluorescence Imaging Plate Reader) based high-throughput screen[8] of the in-house compound collection using cells recombinantly expressing the human motilin receptor identified a series of biphenylmethyl piperazine analogues with promising agonist activity. These screening hits originated from a large array of biphenyl containing compounds which had been prospectively designed to contain the 3D display of pharmacophoric elements known to be important in small molecule interactions with 7-TM receptors. We have described previously a subset of compounds from this array which led to the discovery of a series of selective $5HT_{5a}$ receptor antagonists.[9] The identification of a



1 2

Figure 1. Non-macrolide motilin receptor agonists.

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doi:10.1016/j.bmcl.2008.10.071

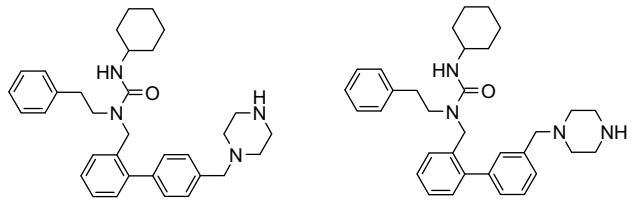


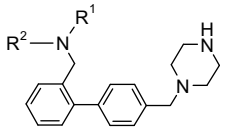
Figure 2. Motilin receptor agonist potency of regioisomeric 4- and 3-piperazinyl derivatives. HTS FLIPR data[8] on array compounds from DMSO solution.

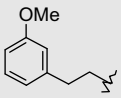
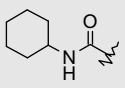
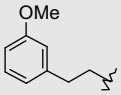
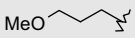
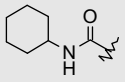
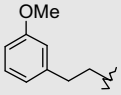
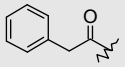
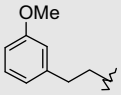
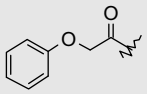
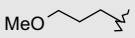
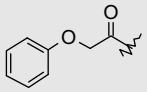
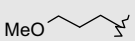
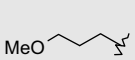
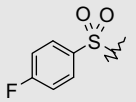
second subset of compounds from the same array which has motilin receptor agonist activity provides clear validation of this prospective design approach.

The significant number of close analogues in the array allowed rapid generation of SAR without the need for further synthesis. Thus, the data for regioisomeric analogues (**3**) and (**4**) indicated a clear preference for the piperazinylmethyl group to be linked in a 1,4-orientation with respect to the first phenyl ring of the biphenyl core (Fig. 2).

The SAR around the most potent hit from the array, urea (**3**), is shown in Table 1. Removal of the cyclohexyl urea (**5**) effectively abolished activity, whilst replacement of the methoxyphenethyl group with the smaller, less lipophilic methoxypropyl group (**6**) gave a fivefold reduction in activity. Replacement of the urea with amides (**7**)–(**10**) or a sulfonamide (**11**) was tolerated.

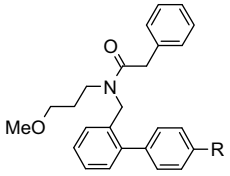
Table 1
Motilin receptor agonist potency of analogues of HTS hit (**3**). HTS FLIPR data[8] on array compounds from DMSO solution.

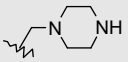
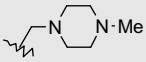
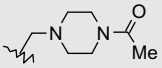
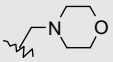
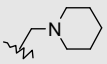
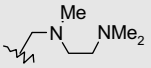
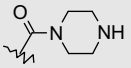


Compound	R^1	R^2	Motilin R pEC_{50}[a]
3			7.0
5			5.3
6			6.3
7			6.0
8			6.6
9			6.4
10			6.2
11			6.2

[a] All compounds $n = 2$.

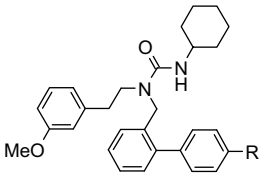
Table 2
Motilin receptor agonist potency of piperazine analogues (**12**)–(**18**). FLIPR data8 on compounds from solid.

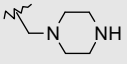
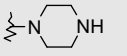
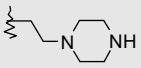
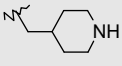
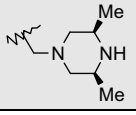


Compound	R	Motilin R pEC_{50} (IA)[a]
12		6.1 (0.7)
13		<4.9
14		<4.9
15		<4.9
16		<4.9
17		5.5 (0.4)
18		<5.5

[a] All compounds $n \geqslant 3$ except (**12**), (**13**) and (**17**) where $n = 2$. *IA* = intrinsic activity.[8]

Table 3
Motilin receptor agonist potency of piperazine analogues (**3**) and (**19**)–(**22**). FLIPR data[8] on compounds from solid.



Compound	R	Motilin R pEC_{50} (IA)[a]
3		7.3 (0.9)
19		5.3 (0.9)
20		<4.9
21		6.4 (0.6)
22		8.0 (1.0)

[a] All compounds $n \geqslant 3$ with SEM $\leqslant 0.1$ except (**21**) where $n = 2$. *IA* = intrinsic activity.[8]

Table 4
Concentration-dependent potentiation of the Electrical Field Stimulated (EFS) contractile response in rabbit isolated gastric antrum by compound **22**.

Compound	Max response % increase	Conc (uM)[a]	$T_{½}$ (min)	*n*
Rabbit motilin	506 ± 112	0.3	9	4
Erythromycin	490 ± 117	3	23	5
22	182 ± 56	10	39	3

[a] Concentration of agonist at which maximum response was observed.

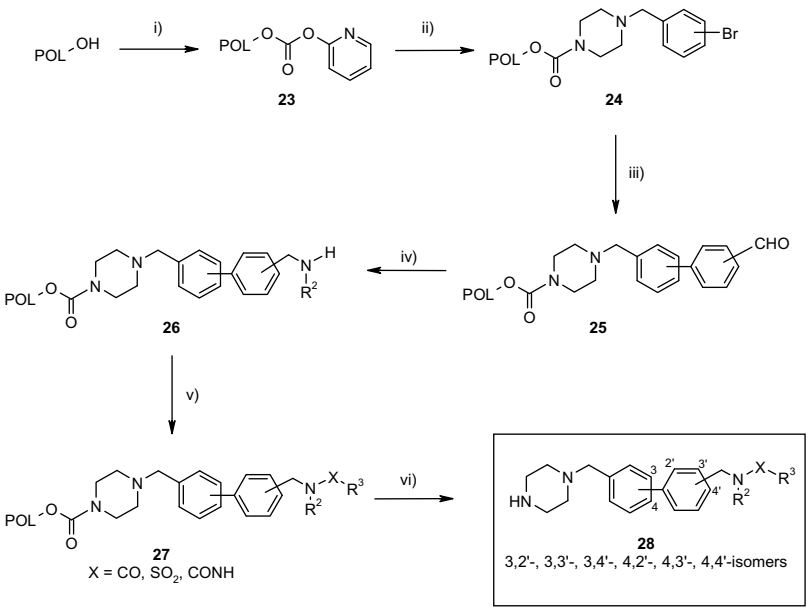
Since the piperazinyl ring had been the point of attachment to the solid phase in the original array, there were no existing analogues of this group, and hence the early chemistry program focused on generating diverse SAR in this region of the molecule. Amide (**12**) was chosen as the starting point for these modifications, as although not the most potent analogue, its relatively low molecular weight would allow incorporation of larger piperazine replacements without overly compromising physicochemical properties. A 96-member solution phase array was prepared using reductive alkylation chemistry, and screened in the FLIPR assay.[8] The results indicated that the NH of the piperazine was essential for agonist activity (Table 2). Methylation (**13**), or acetylation (**14**) of the terminal piperazine nitrogen abolished activity, as did replacement by oxygen (**15**) or methylene (**16**). The only analogue showing measurable but weak activity was the trimethyl ethylenediamine (**17**). Replacement of the methylene linker between the phenyl ring and the piperazine with a carbonyl group (**18**), also abolished activity, suggesting that both of the piperazine nitrogens need to be basic.

Following these results, a series of more conservative modifications were made in this region of the molecule, using the side chains of the most potent urea (**3**) as the starting point (Table 3). The narrow SAR observed for the diversity array was confirmed. Shortening the methylene linker to a bond (**19**) or lengthening to ethylene (**20**) effectively abolished activity and replacement of the proximal piperazine nitrogen with carbon (**21**) reduced activity by ~10-fold. However, addition of methyl groups flanking the terminal piperazine nitrogen (**22**) led to a significant increase in potency.

The dimethylpiperazine (**22**) was selected for further profiling and >100-fold selectivity was demonstrated against a panel of over 100 receptor and enzyme targets. When tested against the closely related ghrelin receptor (previously known as the growth hormone secretagogue receptor) in a similar human recombinant FLIPR assay (**22**) had a pEC_{50} of 6.9, representing ~10-fold selectivity.[10] In experiments to assess the potential for gastric prokinetic-like activity (measuring an ability to enhance neuronally mediated contractions evoked by electrical field stimulation of isolated rabbit gastric antrum[11]), (**22**) significantly enhanced the contractile response. The enhancement is partial in magnitude compared to motilin and erythromycin, and interestingly shows a longer duration (Table 4). This profile is encouraging in the light of speculation that the lack of clinical efficacy of motilides such as ABT-229 in functional dyspepsia and diabetic gastroparesis may arise from their potential to evoke tachyphylaxis.[5]

The synthesis of the hit generation array, including analogues (**3**)–(**11**), was carried out using solid phase chemistry (Scheme 1). Wang resin was activated with the 2-pyridylcarbonate group (**23**), then nucleophilic displacement with the regioisomeric bromobenzyl piperazines gave the carbamates (**24**). Suzuki coupling with 2-, 3- or 4-formylbenzeneboronic acid was followed by reductive amination to give the regioisomeric biphenylmethylamines (**26**). Treatment with the appropriate acid chloride or sulfonyl chloride in the presence of triethylamine, or with the appropriate isocyanate gave the resin bound final products (**27**). TFA-mediated cleavage from the resin and purification then gave the library of piperazinylmethyl biphenyl methyl amides, sulfonamides and ureas respectively, represented by (**28**). Array compounds for which data are shown in Table 1 exceeded 80% purity (LC/MS and ^{1}H NMR) and were screened without further purification.

The solution phase piperazine analogue array, including compounds (**12**)–(**17**), was prepared according to Scheme 2. Hence, 2-bromobenzaldehyde was reacted with 3-methoxypropylamine under reductive amination conditions, and the resulting secondary amine was acylated with phenyl–acetyl chloride to give amide (**29**). Suzuki coupling of (**29**) with 4-formylbenzeneboronic acid gave the biphenylaldehyde (**30**). Reductive amination using sodium triacetoxyborohydride with 80 diverse amines followed



Scheme 1. Reagents and conditions: (i) Wang resin (1.7 mmol/g), $(2\text{-PyO})_2C{=}O$, Et_3N, DCM; (ii) 3- or 4-bromobenzylpiperazine, DCM; (iii) 2-, 3- or 4-formylbenzeneboronic acid, $Pd(Ph_3P)_4$, Na_2CO_3, 1,2-dimethoxyethane-water (9:1), 80 °C under argon; (iv) R^2NH_2, $NaBH(OAc)_3$, AcOH, Na_2SO_4, 1,2-dichloroethane; (v) R^3COCl, Et_3N; R^3SO_2Cl, Et_3N; or R^3NCO in DCM; (vi) 1:4 TFA/CH_2Cl_2.

by solid phase cation exchange purification and HLPC gave the target biphenylmethylamines represented by (**31**). The amide (**18**) was prepared by oxidation of aldehyde (**30**) followed by standard amide coupling with *N*-Boc-piperazine and deprotection.

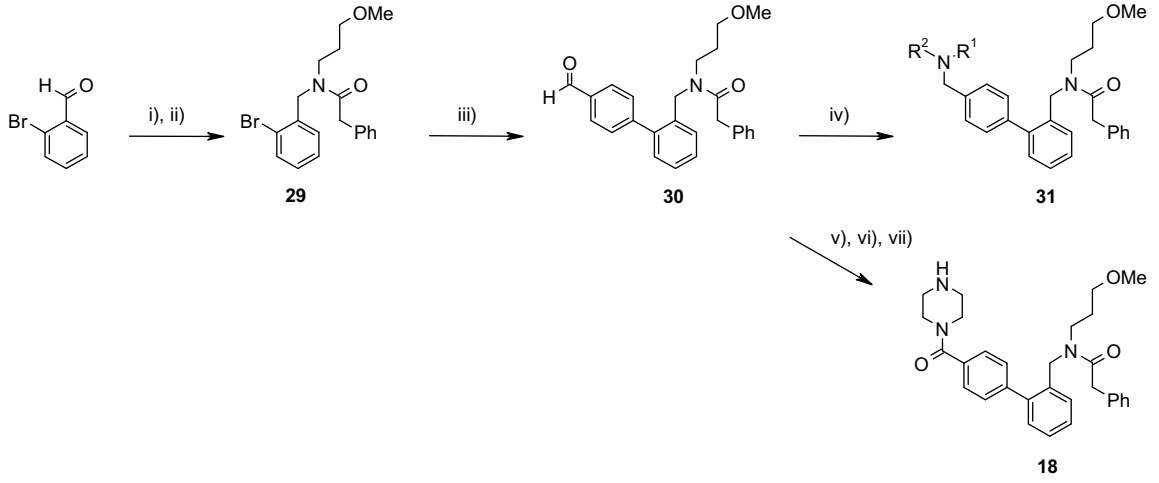
Synthesis of the phenylpiperazine analogue (**19**) is shown in Scheme 3. Protection of 4-bromophenyl piperazine and subsequent Suzuki coupling with 2-formylboronic acid yielded the aldehyde (**33**) which was treated with (3-methoxy)phenethylamine under reductive amination conditions to give amine (**34**). Reaction of (**34**) with cyclohexyl isocyanate and final deprotection yielded target compound (**19**) (Scheme 3).

Synthesis of the ethylene-linked analogue (**20**) started from *N*-Boc-piperazine, which was coupled with 4-bromophenylacetic acid to give amide (**35**) (Scheme 4). Reduction with borane/THF complex followed by basic work up to avoid hydrolysis of the Boc group yielded compound (**36**), which was converted to (**20**) following the same synthetic pathway described in Scheme 3.

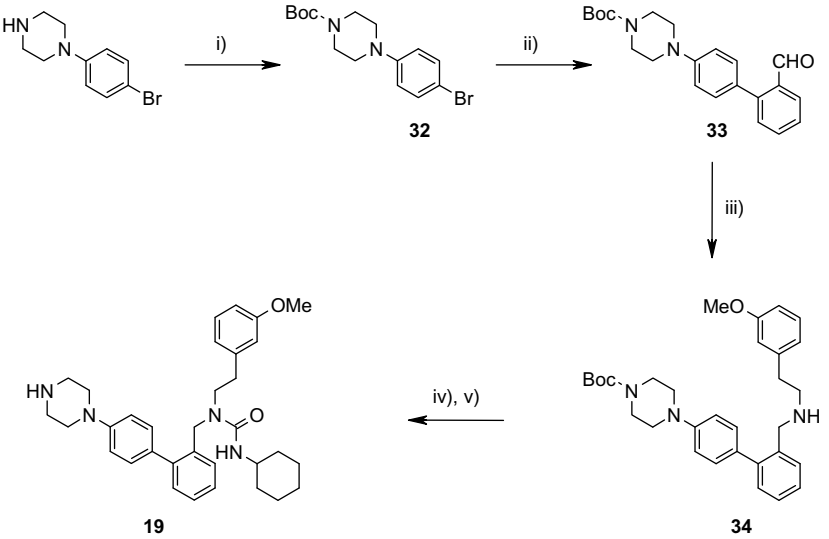
Synthesis of piperidine analogue (**21**) was carried out according to Scheme 5. Reductive amination of 2-bromobenzaldehyde with 3-methoxyphenylethylamine followed by electrophilic trapping with cyclohexylisocyanate gave the bromobenzyl urea (**38**). Suzuki coupling with 4-formylbenzeneboronic acid gave the biphenylaldehyde (**39**), which was reduced with sodium borohydride, converted to the bromide with phosphorus tribromide, and then to the triphenylphosphonium bromide Wittig precursor (**40**). Deprotonation of (**40**) with butyllithium followed by reaction with *N*-Boc-4-oxopiperidine, then hydrogenation of the resulting alkene and acidic deprotection gave the target compound (**21**).

Compound (**22**) was prepared in 67% yield from the biphenylaldehyde (**39**) (Scheme 5), via reductive amination with *cis*-2,6-dimethylpiperazine using the same conditions as in the preparation of the array compounds (**31**).

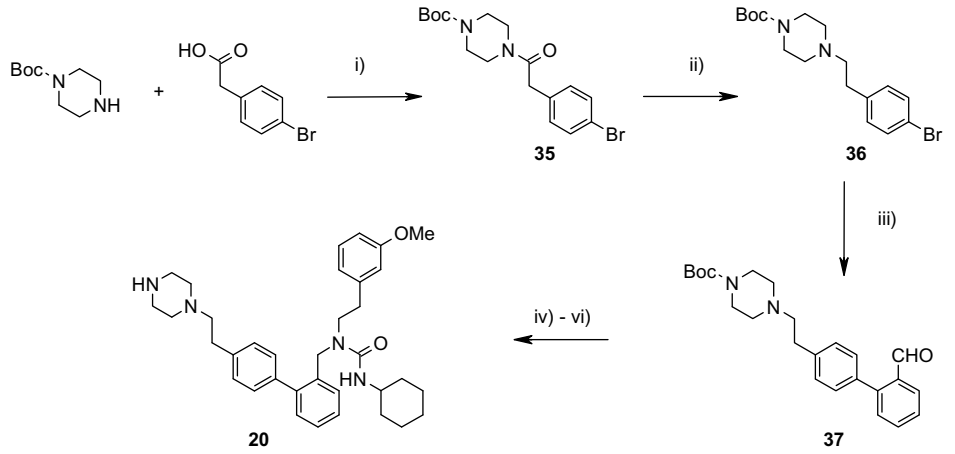
In summary, following the discovery of a series of biphenylmethyl piperazine analogues from a high-throughput screen, subsequent optimisation has identified compound (**22**) as a potent and selective motilin receptor agonist with prokinetic-like activity in a native tissue assay. Compound (**22**)[12] represents a lead which has



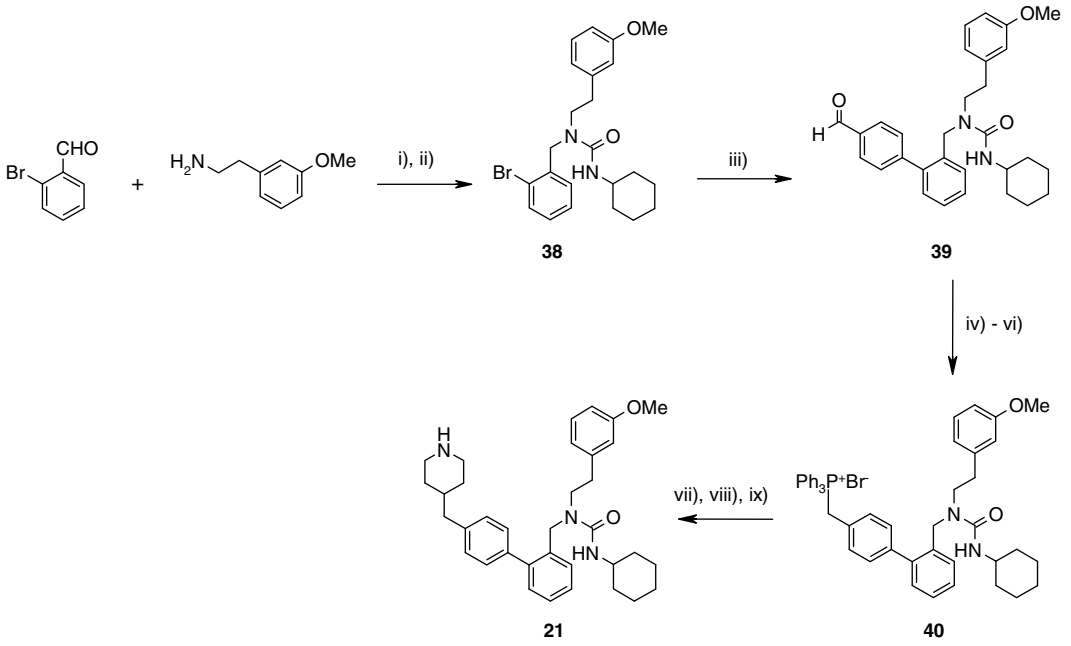
Scheme 2. Reagents and conditions: (i) 3-methoxypropyl-1-amine, $NaBH(OAc)_3$, THF, rt, 37%; (ii) phenyl–acetyl chloride, Et_3N, DCM, 0 °C, 64%; (iii) 4-formylbenzeneboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, DME, H_2O, reflux, 82%; (iv) R^1R^2NH, $NaBH(OAc)_3$, DCM, rt, 5–75%; (v) H_2NSO_3H, $NaClO_2$, THF, H_2O, rt, 54%; (vi) 1-Boc-piperazine, EDCI.HCl, HOBt, Et_3N, DCM, rt; (vii) TFA, DCM, rt, 59% (2 steps).



Scheme 3. Reagents and conditions: (i) $(Boc)_2O$, NaOH, *t*-BuOH/H_2O (2:1), rt, quant.; (ii) 2-formyl-benzeneboronic acid, $Pd(PPh_3)_4$, 2M Na_2CO_3, DME, 80 °C, 65%; (iii) 3-$MeOPh(CH_2)_2NH_2$, DCM, 4 Å mol. sieves, rt, 6 h then $NaBH(OAc)_3$, rt, 42%; (iv) CyNCO, DCM, rt, quant.; (v) 2.0 M HCl in Et_2O, DCM, rt, quant.



Scheme 4. Reagents and conditions: (i) HOBt, NMM, EDCI·HCl, DMF, rt, 98%; (ii) BH_3.THF, THF, 50 °C then rt, 83%; (iii) 2-formyl-benzeneboronic acid, $Pd(PPh_3)_4$, 2M Na_2CO_3, DME, 80 °C, 74%; (iv) 3-MeOPh$(CH_2)_2NH_2$, DCM, 4 Å mol. sieves, rt, 6 h then $NaBH(OAc)_3$, rt, 90%; (v) CyNCO, DCM, rt, 60%; (vi) 2.0 M HCl in Et_2O, DCM, rt, quant.



Scheme 5. Reagents and conditions: (i) 2-BrPhCHO, MeOH, rt, 16 h, then $NaBH_4$, 1 h, rt, 85%; (ii) CyNCO, THF, rt, quant. (crude); (iii) 4-formylbenzeneboronic acid, $Pd(PPh_3)_4$, 3 M Na_2CO_3, DME, 80 °C, 86%; (iv) $NaBH_4$, EtOH, 0 °C, quant. (crude); (v) PBr_3, DCM, 0 °C–rt, 98%; (vi) PPh_3, toluene, reflux, 90%; (vii) *n*BuLi, THF, 0 °C–rt, then 4-oxo-*N*-Boc-piperidine, rt, 77%; (viii) H_2/Pd/C, MeOH, 20 psi, rt, 96%; (ix) 2.0 M HCl in Et_2O, DCM, rt, 88%.

the potential for further optimization to provide orally active small molecule motilin receptor agonists for the treatment of gastric motility disorders such as gastroparesis, functional dyspepsia, post-operative ileus, and others. Further development of structure–activity relationships and DMPK properties of the series are described in the succeeding paper.[13]

References and notes

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8. High-throughput screening was carried out using recombinant human motilin receptor stably expressed in a HEK293 cell line. Subsequent SAR analysis was carried out using recombinant human motilin receptor stably expressed in a CHO cell line. Assay conditions for the latter are as follows. Briefly, cells were seeded onto 384-well black-walled, clear bottom microtitre plates (Greiner) (10,000 cells/well) and incubated for 24 h. On the day of assay, media was aspirated from cell plates using a cell washer (leaving 10 μl of media). Cells

were 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. Master compound plates were prepared in 100% DMSO. A top concentration of 3 mM was used (giving 12 μM final concentration in assay) and this was serially diluted 1 in 4. One microliter from the master plate was transferred to a daughter plate, to which 50 μl of compound dilution buffer (Tyrodes + 1 mg/mL BSA + 1.5 mM $CaCl_2$) was added. 10 μl from the compound plates was then added immediately to cell plates using a FLIPR 3 calcium imaging instrument and changes in fluorescence were measured over a 1 min timeframe. Maximum change in fluorescence over baseline was used to determine agonist response and concentration-response curves were constructed, using a 4-parameter logistic equation. The intrinsic activity of target compounds was calculated by using the maximum asymptote of its concentration-response curve relative to the maximum asymptote of the motilin concentration-response curve.

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10. It is unlikely that the activity observed for Compound **22** in the rabbit gastric antrum assay is partly or wholly due to action on the ghrelin receptor: other analogues in the series with no activity at the ghrelin receptor showed comparable or greater activity in the antrum assay (unpublished data); and ghrelin itself does not show enhancement of EFS mediated contractions in rabbit gastric antrum, see Dass, N. B.; Hill, J.; Muir, A.; Testa, T.; Wise, A.; Sanger, G. J. *Brit. J. Pharmacol.* **2003**, *140*, 948; Depoortere, I.; Thijs, T.; Theelemans, L.; Robberecht, P.; Peters, T. L. *J. Pharmacol. Exp. Ther.* **2003**, *305*, 660.
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12. Characterising data for (**22**): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.29–7.38 (5H, m), 7.23 (1H, m), 7.21 (2H, d, *J* 8.0 Hz), 7.15 (1H, t, *J* 7.8 Hz), 6.73 (1H, m), 6.66 (1H, d, *J* 7.5 Hz), 6.62 (1H, m), 4.35 (2H, s), 3.86 (1H, d, *J* 7.7 Hz), 3.76 (3H, s), 3.56 (2H, s), 3.52 (1H, m), 3.35 (2H, m), 3.03 (2H, m), 2.83 (2H, m), 2.65 (2H, m), 1.76 (4H, m), 1.56 (3H, m), 1.28 (2H, m), 1.10 (6H, d, *J* 6.4 Hz), 1.07 (1H, m), 1.86 (2H, m). MS: (ES^+) 569 (MH^+).
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