CHAPTER 9

Developments and Advances in Gastrointestinal Prokinetic Agents

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Contents

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1. INTRODUCTION

The quality of life for many people suffering from functional gastrointestinal disorders (FGIDs) is significantly reduced when compared with the general population. The symptoms suffered by these people cover a wide spectrum including abdominal discomfort, bloating, nausea, regurgitation, vomiting, early satiety, fatigue, tenderness, diarrhea, and constipation. These disorders encompass several conditions: functional dyspepsia, irritable bowel syndrome with constipation (IBS-C), gastro-esophageal reflux disease (GERD), chronic constipation (CC) or chronic idiopathic constipation (CIC), and idiopathic (I-GP) or diabetic gastroparesis (D-GP). These conditions, together with post-operative ileus (POI) and the treatment of the critically ill, who often suffer delayed gastric emptying (GE) and may require naso-gastric feeding, represent the possible indications that can be targeted with prokinetics. As such, one can appreciate the need for efficacious prokinetic agents, which increase the frequency or strength of GI contractions, thereby aiding, or enhancing gut motility.

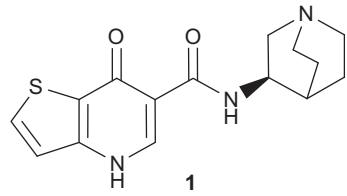
This review serves as an update to the 2006 article in these annals by Sandham and Pfannkuche [1], and as a supplement to other recent reviews in the prokinetic arena [2]. The aim of this review is to highlight the advances made in the area of gastrointestinal (GI) prokinetics in both the clinical and early discovery phases between 2006 and 2010, with an emphasis placed on the more recent developments. It does not cover in any great detail opioid receptor modulators, as this subject matter has been discussed in depth by Hipkin and Dolle in 2010 [3].

2. KEY CLINICAL DEVELOPMENTS

2.1. Serotonin 5-HT receptor modulators

2.1.1. 5-HT_3 receptor partial agonists

5-Hydroxytryptophan (5-HT) acts on GPCRs within the GI tract to modulate gut motility in either a pro- or antipropulsive manner, depending on the GPCR subtype and its anatomical location [4]. Pumosetrag, **1**, a 5-HT_3 partial agonist, has been shown to be moderately efficacious in promoting bowel motility in a small study of patients with constipation and has shown improvements in ''overall response'' in IBS-C patients, yet its development for these indications was reported to have been discontinued [5–7]. Nevertheless, in late 2010, it was reported that recruitment for a Phase 2 trial in GERD had begun [8]; no other 5-HT_3 agonists appear to be in active clinical studies for GI indications.



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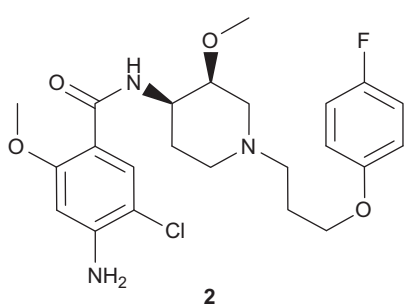
2.1.2. 5-HT$_4$ receptor agonists

Agonism of 5-HT$_4$ receptors is an established prokinetic mechanism, mediating smooth muscle contractions *via* action on cholinergic and ganglionic neurons. Four molecules have been marketed; however, cisapride, **2**, was withdrawn in 2000 for its well-documented cardiovascular safety profile. In the current review period, tegaserod, **3**, has also been voluntarily withdrawn due to an increased incidence of cardiovascular ischemic events in a pooled analysis of clinical trial data from circa. 11,000 patients [9]. Interestingly, an analysis carried out subsequently has provided a contrasting view of the cardiovascular risks associated with this molecule [10]. Mosapride, **4**, remains available for gastritis and GERD and has been shown in a recent study in Japan to ameliorate constipation in diabetic patients [11]. Prucalopride, **5**, the latest 5-HT$_4$ agonist to reach the market, was approved in 2010 for the treatment of CC in adults and is currently in Phase 3 development for IBS-C. Three separate 12-week Phase 3 studies consistently showed significant and improved bowel function, associated symptoms, and satisfaction in chronically constipated patients treated with prucalopride [12–14]. All trials achieved the primary endpoint of drug-treated individuals achieving three or more complete spontaneous bowel movements (SBMs) per week. Further, in an open-label follow-up study, patients from the previous double-blinded studies who continued to receive prucalopride treatment maintained their satisfaction with bowel function for up to 18 months [15]. Various other 5-HT$_4$ agonists are in late-stage clinical development. Naronapride, **6**, is an oral 5-HT$_4$ receptor agonist in Phase 2b clinical trials for GI disorders. Significant metabolism of naronapride occurs *via* esterases rather than CYP450s, so it avoids the drug–drug interactions (and high exposure risk) associated with cisapride. Modest effects of naronapride on GE have been observed in healthy volunteers [16]. Moreover, the number of SBMs were improved *versus* placebo in patients with CIC receiving an 80 mg *bid* dose of naronapride during a Phase 2b clinical study [17]. Velusetrag, **7**, is also in Phase 2 trials and was well tolerated and efficacious in patients with CIC, also achieving increased SBM frequency compared with patients receiving placebo [18]. Finally, a further 5-HT$_4$ agonist, M-0003 is reportedly entering Phase 2 for GP and GERD although its structure has not been disclosed [7].



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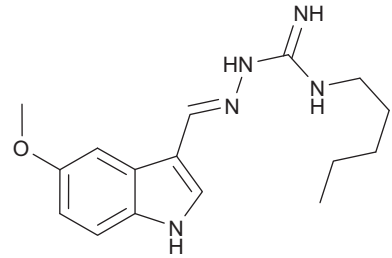

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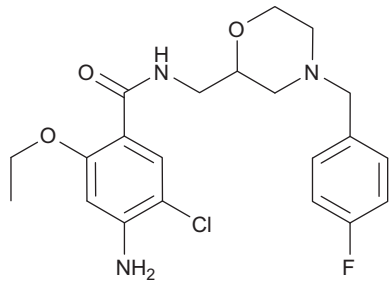

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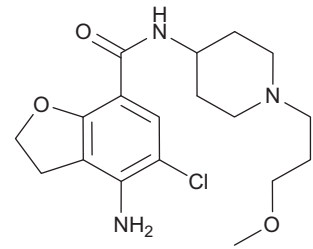

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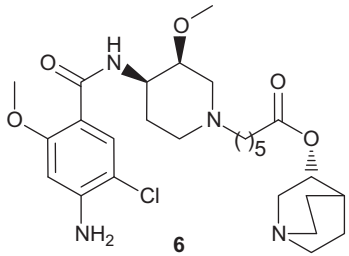

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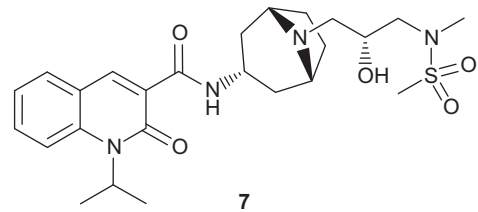

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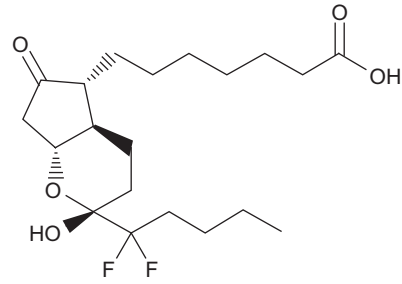
2.2. Type-2 chloride channel activators

Type-2 chloride channel (ClC-2) is a chloride ion channel which is located on the apical side of epithelial cells lining the gut lumen. Activation of ClC-2 drives chloride ions into the gut lumen inducing intestinal fluid secretion, and leads to increased intestinal motility [19]. The ClC-2 activator lubiprostone, **8**, has been launched for the treatment of CC and IBS-C, and the results from several clinical trials have now been reported. Notably, in a combined analysis of two Phase 3 trials in patients with IBS-C

($n = 1171$), the number of responders based on patient-rated assessments of symptoms was significantly greater (17.9% *vs*. 10.1%; $P = 0.001$) for the lubiprostone (8 μg, *bid*) group compared with those who received placebo [20]. This data reinforced the findings of an earlier Phase 2 trial in IBS-C [21]. In trials for CC, improved SBMs were consistently observed in drug-treated groups compared with placebo. Additionally, Phase 2 studies are reported to be ongoing in opioid-induced bowel dysfunction [7,22,23].



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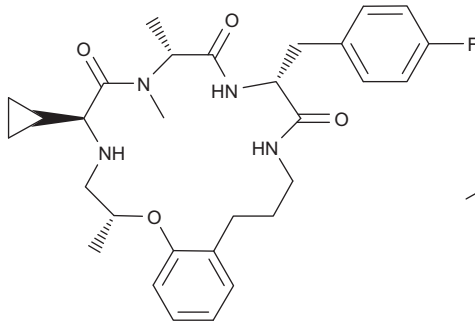
2.3. Ghrelin receptor agonists

Ghrelin, an *n*-octanoylated 28-amino acid peptide hormone, is the endogenous ligand of the growth hormone (GH) secretagogue receptor (GHS-R1a) [24,25]. Ghrelin is produced in the gastric mucosa by enteroendocrine cells and is a prokinetic which has been demonstrated to stimulate GE in healthy human volunteers when administered intravenously [26]. Moreover, several small clinical trials have shown efficacy of ghrelin in increasing GE in patients with D-GP ($n = 10$), neurogenic GP (which includes D-GP, $n = 6$), or I-GP, although no further development has been reported for ghrelin in these indications [27–29]. Nevertheless, there has been significant recent interest in the role of ghrelin receptor agonists as prokinetic agents. Ulimorelin, **9**, a potent GI prokinetic agent delivered *via* intravenous administration, is in development for the treatment of GP and POI. So far, positive clinical data in GP in diabetics has been reported in three studies. In patients with moderate to severe symptoms, a pilot study showed a statistically significant improvement in GE [30]. A larger follow-up study showed significant improvements in the patient-rated Gastroparesis Cardinal Symptom Index (GCSI) Loss of Appetite and Vomiting scores ($P = 0.034$ and 0.006, respectively) at the 80 μg/kg dose [31]. In a further study, in a subset of patients with severe nausea and vomiting, significant effects at the 80 μg/kg dose were also observed on the GCSI Vomiting score ($P < 0.008$) and the GCSI Nausea

and Vomiting subscale ($P < 0.001$) *versus* placebo [32]. Additionally, the efficacy of ulimorelin has been demonstrated in POI patients after partial colectomy in a Phase 2b placebo-controlled trial, accelerating the time to first bowel movement in all treatment groups [33]. TZP-102 (structure undisclosed) is an orally delivered molecule that is also being developed. Results of a Phase 2 study stated the compound to be safe, well tolerated and effective in significantly improving disease symptoms in patients with D-GP [34]. While both ulimorelin and TZP-102 appear to be ahead in the clinic, other new molecular entities are advancing such as EX-1314, **10**, for which an investigational new drug (IND) application has been filed for use in patients with D-GP. The pentapeptide ipamorelin, **11**, completed a Phase 2 trial in 2009 to determine its safety and effectiveness in the management of POI [35]. However, at the time of writing, no results had been posted. The prokinetic effects of ghrelin agonists were the subject of a recent review [36].



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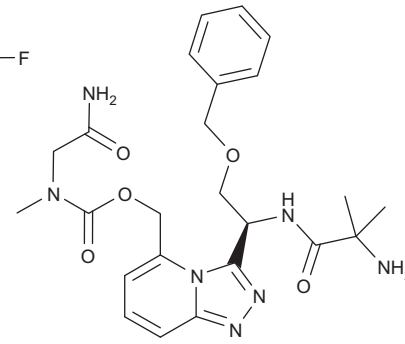

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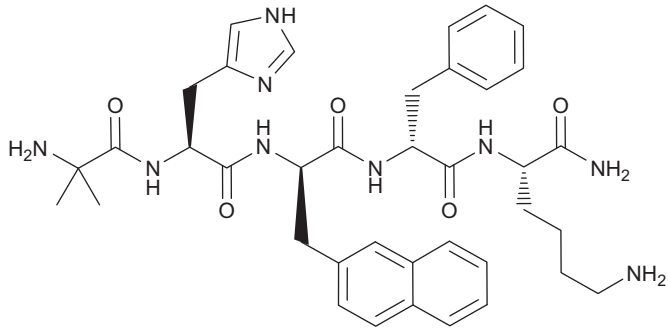

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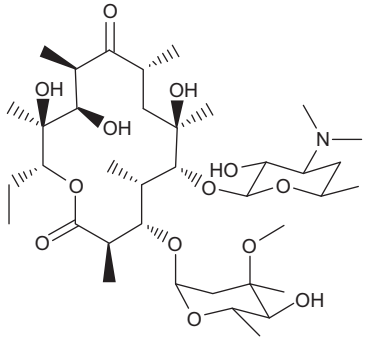
2.4. Motilin receptor agonists

The 22-amino acid peptide motilin, found in endocrine M-cells of the duodenum and jejunum mucosa, is released during fasting and promotes GE by stimulation of antral contractions through engagement of the motilin receptor in the gut. Agonism of the motilin receptor is thus an attractive prokinetic approach [37]. The macrolide antibiotic erythromycin, **12**, has been shown to be a potent motilin agonist making it a powerful prokinetic, and there have been numerous published clinical studies examining its use for enhancing motility. A recent example has shown it, and the related macrolide azithromycin, to be efficacious at stimulating antral activity in patients with GP [38]. Erythromycin has been widely used to treat feeding intolerance in critical care patients [39]. A study comparing erythromycin to the D2 agonist metoclopramide concluded that erythromycin is the more effective agent in the short-term treatment of feeding intolerance; successful gastric feeding had been achieved after 24 h in 87% of patients taking erythromycin *versus* 62% in the metoclopramide arm. However, tachyphylaxis can develop rapidly, and both treatments were significantly less effective after 3 days. Combination therapy was highly effective and sustained in patients who had failed monotherapy (92% achieving successful enteral feeding after 24 h) thus indicating the combination successfully prevented tachyphylaxis [40]. Concerns have been expressed that the use of erythromycin, for its prokinetic properties, may promote the emergence of macrolide-resistant bacteria. For this reason, significant efforts have been invested in the development of macrolides which retain the prokinetic activity but have reduced antibiotic activity (motilides) [41]. Clinical results to date with the motilides in patients with GP have been mixed, likely due to the induction of tachyphylaxis. For instance, a 28-day trial of mitemcinal demonstrated a significant change in post-treatment meal-retention time at 4 h for drug-treated patients compared to placebo; however, no significant improvement was seen in the gastroparetic symptom score for any treatment group compared with placebo [42]. However, in a separate 16-week study *versus* placebo, positive results were obtained for mitemcinal where a 10.6% ($P = 0.05$) increase in relieving GP symptoms was observed at a dose of 10 mg/kg [43]. No recent development has been reported for mitemcinal. Away from the macrolide arena, recent developments include the non-macrolide motilin agonist GSK-962040, **13**, which reached Phase 2 clinical trials in patients with D-GP and also those with enteral feeding intolerance in critical care (although no data has yet been reported) [44,45]. A follow-up compound, GSK-1322888, also entered Phase 1 for GP at the end of 2010 [46].



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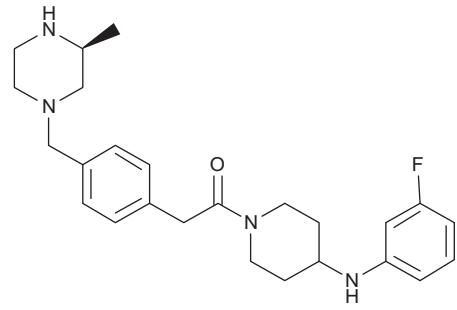

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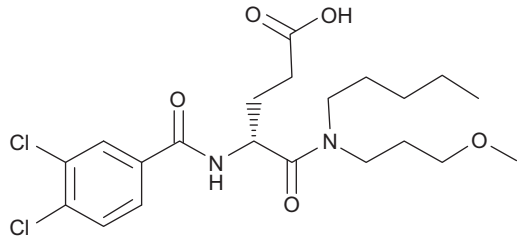
2.5. Cholecystokinin 1 (CCK-1) receptor antagonists

CCK is a peptide hormone which is made from prepro-CCK, a 115-aa peptide, and is found in both the periphery and the CNS [47]. In humans, CCK-8 and CCK-58 are the predominant forms [48]. CCK is released within the intestinal tract from endocrine cells and regulates gut function in response to food intake by binding to CCK receptors located on, but possibly not restricted to, vagal neurons [49]. As such, CCK antagonists represent an attractive opportunity for treating FGIDs. The development of the selective CCK-1 antagonist dexloxiglumide, **14**, had seemingly stalled after its failure to show a significant difference to placebo in two 12-week Phase 3 IBS trials. However, a further Phase 3 study was published in 2008, where in an innovative trial design, a randomized ''withdrawal study'' was conducted. Approximately 400 IBS-C patients, classed as ''responders'' to drug over an 8–12-week period, were subsequently randomized and treated with drug or placebo for a further 24 weeks. The outcome of the study was a statistically significant 16.2% difference in the maintenance of response seen for those on drug compared with those who received placebo [50]. No other significant clinical developments appear to have been reported over the review period for CCK antagonists in GI indications.



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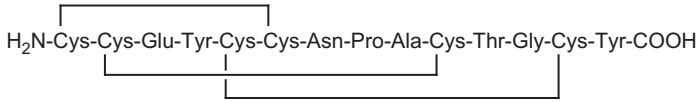
2.6. Guanylate cyclase 2C agonists

Uroguanylin and guanylin are peptide hormones which bind to the guanylate cyclase C (GC-C) receptor in the gut epithelium. This results in cGMP synthesis and elicits a large increase in the secretion of chloride and bicarbonate anions through activated CFTR channels, thereby increasing fluid secretion into the gut and enhancing motility [51]. These observations have stimulated interest in analogues of uroguanylin and guanylin as prokinetic agents. The orally delivered linaclotide, **15**, is a 14-mer peptidic guanylate cyclase 2C agonist in Phase 3 clinical trials for IBS-C and CC [52]. This compound is thought to act locally on the receptors at the luminal surface of the intestine and shows minimal systemic exposure. Recently published Phase 2b data demonstrated that treatment with linaclotide at doses ranging from 75 to 600 μg once daily for 12 weeks significantly improved disease symptoms, including abdominal pain and bowel symptoms, in patients with IBS-C [53]. Additionally, in a 4-week Phase 2b study in patients with CC, a significant increase in the number of SBMs (primary endpoint), as well as other symptoms, was seen for patients on linaclotide compared to placebo [54]. Moreover, recent company press releases disclose two positive Phase 3 trials for each targeted indication (IBS-C and CC), and an IND application is expected to be filed during 2011 [55]. Another guanylate cyclase 2C agonist in clinical trials is the uroguanylin analogue guanilib (plecanatide), for which a positive outcome in a Phase 2a study in CC patients was reported in October 2010 [56].



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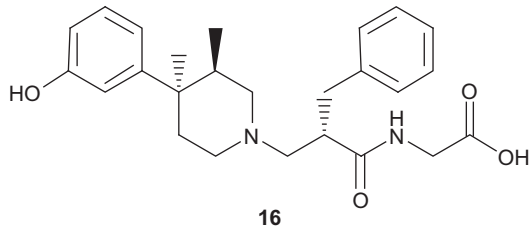
2.7. Ileal bile acid transporter inhibitors

The first in class ileal bile acid transporter (IBAT) inhibitor, A-3309 (structure undisclosed), has shown positive results in a double-blind placebo-controlled Phase 2b study for the oral treatment of CIC [57]. At doses of 10 and 15 mg, once daily, the primary endpoint of statistically significant increases in SBMs over baseline during treatment week 1 was achieved. The compound has minimal systemic exposure and is believed to act locally in the gut to inhibit the re-uptake of bile acids, which in turn increases motility.

2.8. μ-Opioid receptor antagonists

Several Phase 3 trials have now been reported for the peripherally acting μ-opioid antagonist alvimopan, **16**, in patients undergoing major abdominal surgery. Alvimopan counteracts the reduction in intestinal tract motility caused by endogenous opioids released in the gut as a result of the stress of surgery, as well as by administered opioids commonly given as analgesics to these patients. The poor CNS penetration of alvimopan, however, ensures that the analgesic effect of systemic opioids is not affected [58]. A pooled analysis of Phase 3 clinical studies demonstrated that alvimopan significantly accelerates GI recovery and is an effective treatment for POI following bowel resection. The compound was approved by the FDA in 2008 for this use [59].



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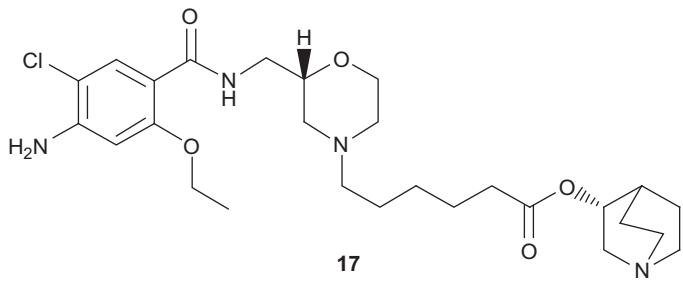
3. RECENT MEDICINAL CHEMISTRY DEVELOPMENTS

3.1. Serotonin 5-HT$_4$ agonists

A series of benzamide analogues have been reported in the patent literature as 5-HT$_4$ receptor agonists for the treatment of GP disorders. Compounds were evaluated in a rat 5-HT$_4$ radioligand binding assay using tissue isolated from rat striatum. Compound **17** (IC_{50}: 24 nM) has been shown to have comparable activity to **6** (IC_{50}: 23 nM) in this assay. Structure activity relationships show that the *S*-enantiomers have higher binding affinities, and optimal activity is achieved when the alkyl linker is pentyl [60].



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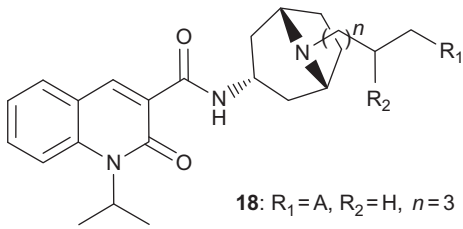
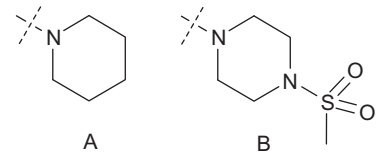
Developed using a ''multivalent'' optimization strategy, a family of potent 5-HT_4 receptor agonists was prepared with high selectivity over the 5-HT_3 receptor [61–63]. Initial work led to the identification of quinolinone, indazole, and benzimidazoline scaffolds while access to a secondary binding pocket was achieved *via* alkylation of the aza-bicycle. Introduction of a piperidine, **18**, or a piperazine sulfonamide, **19**, led to striking selectivity over the 5-HT_{3A} receptor (8100- and 2800-fold, respectively). A related example, **20**, was orally bioavailable in the rat (*F* 38%) and exhibited hERG inhibition of 38% at 3 μM. Optimization afforded, **21**, a potent (pK_i: 7.9) and selective (7400-fold) antagonist with reduced hERG activity (4% at 3 μM); its *R*-isomer, **22**, showed reduced activity (pK_i: 7.3) and selectivity (1300-fold). Compound **21** demonstrated efficacy in an isolated guinea-pig colon longitudinal muscle strip assay with pEC_{50} of 8.6 [intrinsic activity (*i.a.*): 63% of the maximal response of 5-HT] and was efficacious at 3 mg/kg (*s.c.*) in a guinea-pig model of colonic GI transit [64].



18: R_1 = A, R_2 = H, n = 3

19: R_1 = B, R_2 = H, n = 3

20: R_1 = B, R_2 = H, n = 1



A B

21: R_1 = B, R_2 =  , n = 1

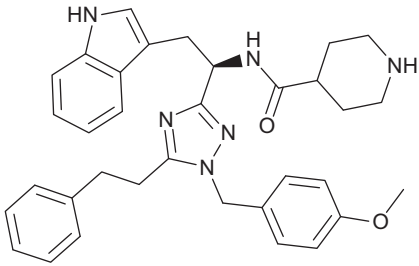
22: R_1 = B, R_2 =  , n = 1

3.2. Ghrelin receptor agonists

A peptidomimetic strategy has been successfully applied to the modification of the peptide frameworks of the GH-secretagogues through inclusion of amide-bond isosteres. The exploration of a 1,2,4-triazole motif within the backbone generated antagonists, partial agonists, and full agonists within a subset of closely related analogues [65]. Moreover, following the replacement of an amino-*iso*-butyryl amide (Aib) motif with an *iso*-nipecotic carboxamide, a series of full agonists was identified, including **23**. When given by *s.c.* injection, **23** was able to stimulate food intake and GH secretion in infant rats, and also potentiate hexarelin-stimulated food intake [66].

An alternative amide isostere, a 1,5-disubstituted tetrazole, was exploited upon recognition that the conformational restriction imparted by this 5-membered heterocycle could still realize potent GH-secretagogues. The retention of an Aib motif and inclusion of the tetrazole enabled

the discovery of an *N1*-cyanoethyltetrazole, **24**, which had good oral bioavailability in rat and dog (*F* 56% and 75%, respectively) and was efficacious at increasing GH mean peak levels in beagle dogs at 10 mg/kg. More notably, BMS-317180, **25**, the *N1*-alkyl carbamate-based tetrazole, is a potent (EC_{50}: 1.9 nM), highly water soluble (>100 mg/mL) and orally active compound advanced into development for the treatment of cancer cachexia and wasting syndrome. The compound displays low to moderate oral bioavailability (*F* 9%, 12%, and 40%) in rat, monkey, and dog, respectively; its superior exposure in dog is attributed to a decrease in clearance. So far, development for GI indications has not been reported [67,68]. More recently, **25** has been further optimized through successful replacement of the benzyloxy-group with a *gem*-difluoropropyl benzene, giving **26**, which has an increased *in vitro* potency (EC_{50}: 0.27 nM), better efficacy, and improved exposure and oral bioavailability in rat (*F* 26%) when compared to **25** [69].



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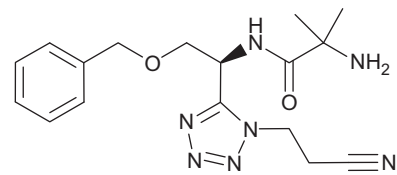

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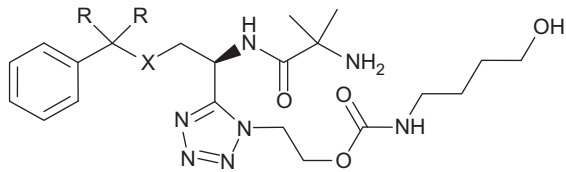
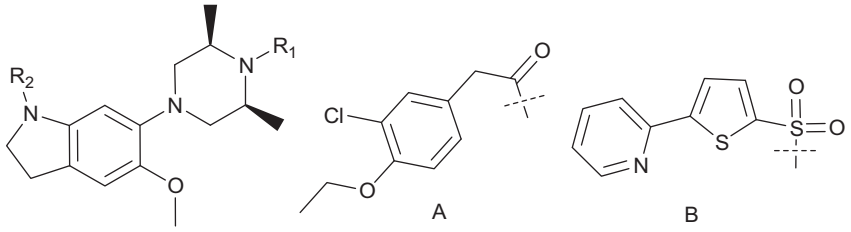


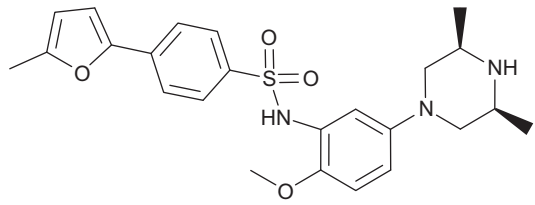
25: R = H, X = O **26**: R = F, X = CH_2

A high-throughput screening (HTS) approach was used to identify agonists of the ghrelin receptor which were devoid of the peptide-like nature of privileged fragments seen thus far [70]. The indoline hit **27**, originally a 5-HT_{1B} receptor antagonist (5-HT_{1B} pK_i: 7.9), was optimized to give SB-791016, **28**, a potent ghrelin agonist with good intrinsic activity (*i.a.*: 0.9). This compound showed significant acceleration of GE after *s.c.* dosing in rat with an ED_{50} of 0.1 mg/kg. However, after oral dosing, it had very low exposure, likely due to its high lipophilicity and low solubility. Subsequent optimization, which included ring opening of the

indoline, use of an intramolecular H-bond to maintain permeability, and optimization of the sulfonamide group, led to the identification of GSK-894490A, **29**. This compound is a potent, orally bioavailable full agonist (*F* 75% in rat) which was shown to stimulate an increase in food intake in rat at 3 mg/kg following oral dosing [71].

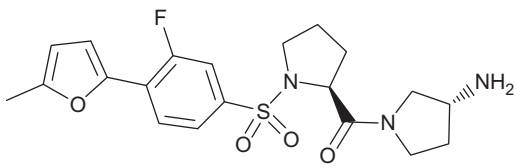


27: R_1 = Me, R_2 = A **28**: R_1 = H, R_2 = B

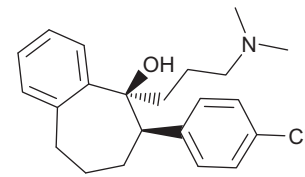


29

In a more recent publication from the same group, the spacer between the sulfonyl group and the basic piperazine has been investigated and has led to the discovery of a 3-amino-pyrrolidinyl amide derivative, **30**, that has an encouraging *i.v.* PK profile (CL 25 mL min/kg, and VD_{ss} 3.5 L/kg). Further optimization is required to achieve the necessary exposure for the *in vivo* evaluation of this class of ghrelin agonist [72].



30



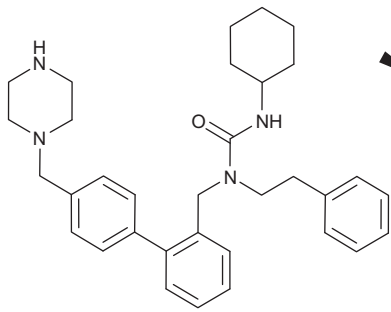
31

A series of potent benzocycloheptane and benzoxepine GHS-R1 agonists has been reported in the patent literature. The most efficacious of the compounds disclosed was **31**, which increased GE and stimulation of small intestine propulsion in NMRI mice at 0.63 mg/kg following *s.c.* dosing

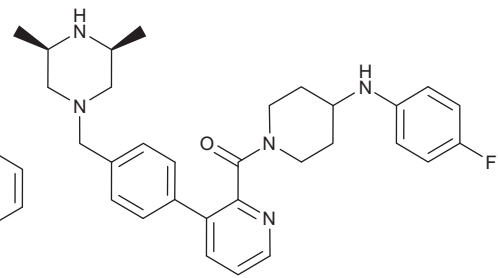
compared with vehicle-treated animals. In a further study, it was also shown that the compound had no effect on GE in GHS-1R$^{-/-}$ knock-out mice [73].

3.3. Motilin receptor agonists

A prospective 7-TM receptor pharmacophore library screened within the context of a HTS campaign yielded the hit compound **32** [74]. Subsequent modifications yielded **33**, which showed gastric prokinetic-like activity in the potentiation of neuronal-mediated contractions in isolated rabbit antrum tissue in the 0.3–10 μM range. Compound **33** also showed exposure in rat and dog after oral dosing (*F* 13%, 58%, respectively). However, **33** only shows a fivefold selectivity when compared to its activity at the ghrelin receptor (MTL-R pEC_{50}: 7.7, GHS-1R pEC_{50}: 7.0) [75]. Subsequent optimization was required to address its selectivity, CYP3A4 time-dependent inhibition (TDI), high molecular weight, and lipophilicity, and to improve its PK profile. As such, **13** (MTL-R pEC_{50}: 7.9 (*i.a.*: 0.9)) was identified with optimal oral PK properties (*F* (rat) 48%; (dog) 51%), no CYP TDI, good selectivity over the ghrelin receptor (GHS-1R pEC_{50}: <6.0), and good solubility as its HCl salt (>1 mg/mL) [44]. Compound **13** has also been demonstrated to activate the motilin receptor in rabbit and human isolated stomach and is active *in vivo* in the conscious rabbit, suggesting that it has the potential to increase GE in humans [76].

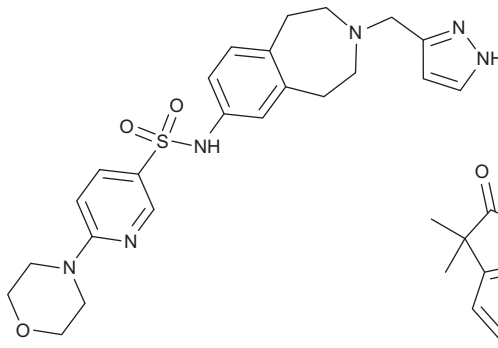


32

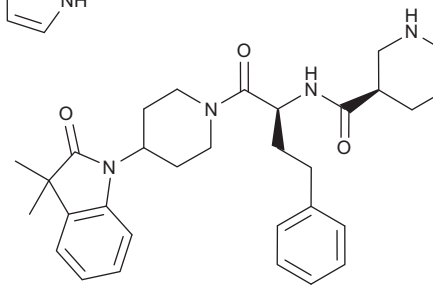


33

A FLIPR-based HTS, carried out by the same group, identified a series of benzazepine sulfonamides as novel motilin agonists. Initial screening activity was confirmed using tissue isolated from rabbit gastric antrum. Optimization led to the morpholine-substituted compound **34**, which displayed superagonist efficacy in the rabbit tissue strip assay (E_{max}: 476% at 1 μM); however, further optimization of this series was stopped due to persistent inhibition of CYP2D6 (<1 μM for compound **34**) [77].



34

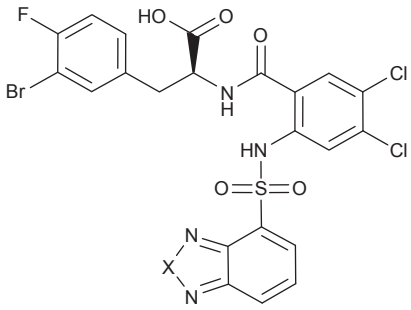


35

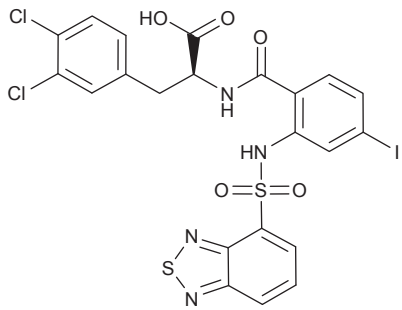
RQ-00201894 is a motilin peptidomimetic with potent agonist activity in CHO cells (EC_{50} 0.26 nM). When tested *in vivo* following oral dosing, the compound induced MMC-like contractions in the upper GI tract in fasted dogs, and dose-dependently increased GE in conscious dogs and cynomolgus monkeys up to 3 mg/kg [78]. The structure of RQ-00201894 has yet to be disclosed; however, a recent patent described a series of oxindoles, of which **35** is the most potent example [79].

3.4. Cholecystokinin dual (CCK-1/2) receptor antagonists

A series of aryl sulfonamide dual CCK-1 and CCK-2 antagonists has been reported for the potential treatment of GERD [80]. Antagonism of CCK-1 accelerates GE through improved lower esophageal sphincter function, while CCK-2 inhibition regulates gastric acid secretion. The investigators observed that selectivity between CCK-1 and CCK-2 could be modulated, and efforts were made to optimize activities at both receptors [81]. The [2,1,3]-benzothiadiazole moiety of compound **36** (CCK-1/2 pK_i: 6.8/8.0) could be replaced with a quinoxaline while maintaining potency and dual CCK activities (compound **37**, pK_i: 6.8/8.2). Although metabolism in human liver microsomes was comparable, both series suffered from high efflux in a Caco-2 permeability assay, which impacted oral bioavailability. Nevertheless, compound **36** was selected for *in vivo* studies and inhibited pentagastrin-stimulated gastric acid secretion with an ED_{50} of 1 mg/kg *p.o.* [82]. CCK-2-mediated contractility was assessed using guinea-pig corporeal muscle in the presence of 2-NAP; here compound **38** demonstrated a pK_B of 8.8 [80].



36: X = S **37**: X = CH = CH



38

4. CONCLUSIONS

In recent years, there have been numerous clinical advances in the field of prokinetic agents, which offer great potential for patients who suffer from FGIDs. Specifically, the launches of prucalopride and lubiprostone provide new treatment options for those with CC and IBS-C. Major advances are evident in the area of GP, where the ghrelin agonists ulimorelin and TZP-102 hold much promise, and in the related motilin field, where the low molecular weight agonist GSK-962040 has also reached the clinic. In the CIC arena, the first in class IBAT inhibitor A-3309 is a highlight. The most significant setback over the review period has been the voluntary withdrawal of the 5-HT_4 agonist tegaserod. In an interesting approach, the potential of dexloxiglumide for the treatment of IBS-C was maximized through an innovative trial design. Given the complex nature of FGIDs, and specifically the low treatment responses *versus* placebo often observed in clinical trials, it is clear that the design of these trials is critical in ensuring success and ultimately enabling new molecular entities to reach patients.

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