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Review Article

Motilides and motilactides: design and development of motilin receptor agonists as a new class of gastrointestinal prokinetic drugs

Ramin Faghih*, Hugh N. Nellans and Jacob J. Plattner

Pharmaceutical Discovery Division, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064-3500, USA.
**Correspondence*

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Introduction

Smooth muscle motor function of the gastrointestinal (GI) tract is the result of an equilibrium between stimulatory events, predominantly regulated through acetylcholine release, and inhibitory mechanisms, regulated by dopamine. Prokinetic drugs (1) represent a limited number of structurally unrelated compounds which induce GI smooth muscle contraction, both *in vitro* and *in vivo*. Smooth muscle motor function leading to GI motility can be stimulated both by dopamine antagonists, such as metoclopramide and domperidone, and by compounds which release acetylcholine such as cisapride. A clinically useful agent in this class of prokinetic drugs is one that not only enhances smooth muscle contraction but also coordinates such activity between different sites in the GI tract. In this respect, none of the currently available agents qualify as optimal prokinetic therapeutics, in addition to their shortcomings related to variable efficacy and endocrine/CNS side effects.

Motilides and motilactides as prokinetics are members of the macrolide family (2), which refers to a wide number of compounds containing a lactone moiety in a large ring. Erythromycin, a macrolide antibacterial, has been in clinical use for the past 40 years. However, this decade has witnessed the "renaissance" of erythromycin, related to the discovery of new pharmacological actions and not to the mechanism of its antibacterial activity. In this review, we will discuss the design, development and clinical introduction of several erythromycin derived motilides and motilactides with potential for treatment of GI motility disorders.

Discovery of motilin

During the 1960s, the laboratory of J.C. Brown (3) investigated the induction of gastric motility in the dog using duodenal alkalinization. Brown hypothesized that two possible mechanisms of action could be involved in producing the observed stimulation of motor activity: blocking the release of an inhibitory substance from the duodenal mucosa, or the release of a humoral stimulating agent. In support of the latter hypothesis, in 1971 Brown and coworkers (4, 5) isolated a humoral stimulating agent from the duodenal mucosa and 2 years later, announced the complete amino acid sequence of motilin, a 22-amino acid polypeptide (6-9) with a molecular weight of 2700 (Fig. 1).

Distribution of motilin

Motilin is found predominantly in endocrine cells of the upper small intestine (10, 11). However, the existence of motilin in the CNS and in peripheral nerves has also been

Human	Phe-Val-Pro-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg -Met-Glu-Glu-Lys-Glu-Arg-Asn-Lys-Gly-Gln
Pig	Phe-Val-Pro-Ile-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Met-Glu-Glu-Lys-Glu-Arg-Asn-Lys-Gly-Gln
Dog	Phe-Val-Pro-Ile-Phe-Thr-His-Ser-Glu-Leu-Lys-Arg-Ile-Arg-Glu-Lys-Glu-Arg-Asn-Lys-Gly-Gln

Note that human motilin sequence is identical to that of porcine motilin.

Fig. 1. Amino acid sequence of motilin in various species.

suggested, with extensive studies by Beinfeld having shown motilin immunoreactivity in rat cerebellum (12) at concentrations comparable to those found in intestine. Recent autoradiographic demonstration of motilin receptors in rabbit cerebellum has also been reported by Peeters' group (13). The physiological role of motilin in the brain has not, however, been clearly elucidated.

Action of motilin in the GI tract

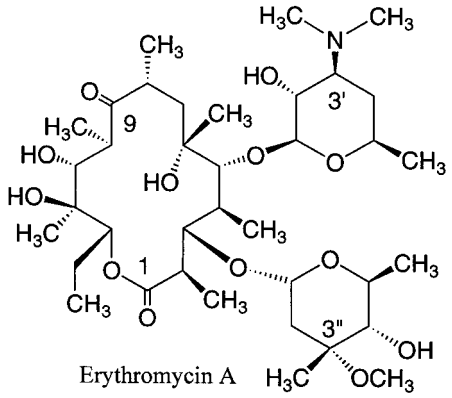
In isolated smooth muscle preparations, activity of motilin can be demonstrated in stomach and duodenum of both rabbit and humans (14-16). The action on smooth muscle appears to be direct stimulation requiring extracellular calcium (14, 15). Itoh's studies (17) have demonstrated, in both conscious dogs and human subjects, the close association of circulating motilin with the induction of phase III contraction of stomach during the interdigestive state. Soon thereafter, Itoh's laboratory described motilin stimulation of muscle contraction of the lower esophageal sphincter, sphincter of Oddi and the gallbladder. Concentrations of motilin in plasma exhibit phasic variations that are closely correlated with changes in gastric and duodenal smooth muscle motor activity (18). A rise in circulating concentration corresponds with the onset of duodenal phase III motor activity observed at regular 90- to 120-minute intervals. The phasic changes are abolished by both eating and cholinergic blockade. In addition to these findings, secretion of digestive enzymes in the stomach and pancreas has also been found to be associated with phase III smooth muscle activity, suggesting potential control by circulating motilin in both dog and man (19, 20).

Since motilin is a polypeptide, its instability at room temperature, together with a notable absence of oral efficacy, make it an unlikely candidate for commercial clinical trials. However, the recent discovery and clinical introduction of several nonpeptide motilin agonists have opened new opportunities for modulation of GI motility for the GI community.

Erythromycin as a motilin agonist

It has been known for many years that some antibiotics, including the macrolide erythromycin A (EryA), may cause GI side effects such as diarrhea, borborygmi and vomiting; however, little attention had been paid to the mechanisms involved. In 1984, two groups (21, 22), independently and nearly simultaneously, reported that EryA stimulated small intestinal contractile activity in dog. Itoh and coworkers (21) found that EryA at doses well below those required for antibacterial efficacy (0.03 mg/kg i.v.) induced a pattern of migrating contractions originating in the stomach with a frequency similar to spontaneous slow waves.

The pattern and duration of the smooth muscle activity were similar to the spontaneous activity that occurs periodically in the fasted state, *i.e.*, phase III activity of the migrating motor complex (MMC), which is a cyclical motor



Erythromycin A

pattern originating in either stomach or duodenum with migration to the terminal ileum (23). There was a striking resemblance of the EryA response to that produced by motilin. Because EryA was associated with motilin release in dog, Itoh suggested that the macrolide acted through motilin. However, subsequent findings in man suggested EryA induced phase III activity directly without requisite motilin release (24).

Peeters *et al.* (25) subsequently demonstrated that EryA acts directly on the motilin receptor in binding experiments using rabbit antral smooth muscle homogenates, where the macrolide specifically displaced bound motilin. The ability of EryA to compete with motilin for common binding sites was correlated with its potency to induce contraction in rabbit duodenal smooth muscle strips. Like motilin (26), EryA had no contractile effect on muscle strips of rat or dog duodenum, but did induce contraction in human strips (27).

These findings and earlier reports on antral motilin receptors in man led to evaluation of the effect of intravenous EryA on gastric emptying in patients with diabetic gastroparesis (28), where retarded emptying of solids and liquids was markedly accelerated. Presentation of these results at the American Gastroenterological Association meeting in Washington in 1989 marked the beginning of intense research in this area and the emergence of a new class of potent prokinetic agents (motilides and motilactides) derived from erythromycin possessing improved oral activity with no antibiotic potency.

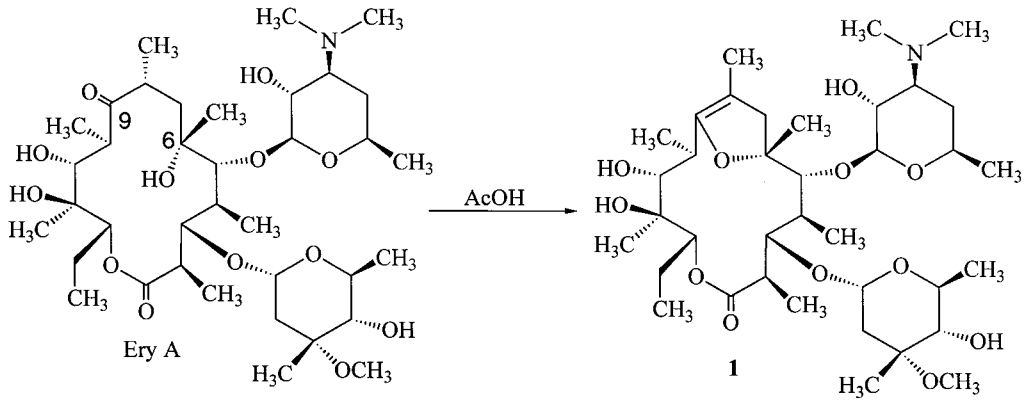
Motilides

Omura and Itoh (29) defined motilides as macrolides with: a) direct contractile effect on segments of isolated smooth muscle of rabbit duodenum, b) the capacity to induce phase III activity in conscious dog, and c) lacking antibacterial activity.

Structure-activity relationship of motilides and motilactides

Early studies in 1985 revealed that 14-membered, but not 16-membered, macrolides stimulated GI contractions in conscious dogs (21, 30, 31). Two earlier studies in the

Scheme 1: Synthesis of erythromycin A-6,9-hemiacetal



1960s noted that oleandomycin (14-membered macrolide) and EryA stimulated motor activity in the rabbit small intestine, gallbladder and the terminal bile duct, but both reports went largely unnoticed (32, 33). In 1992, Nakayoshi (34) included roxithromycin and clarithromycin in dog studies and found reduced smooth muscle stimulating activity relative to EryA, and further noted that all 16-membered compounds tested (josamycin, leucomycin, midecamycin and acetylspiramycin) failed to induce contractions.

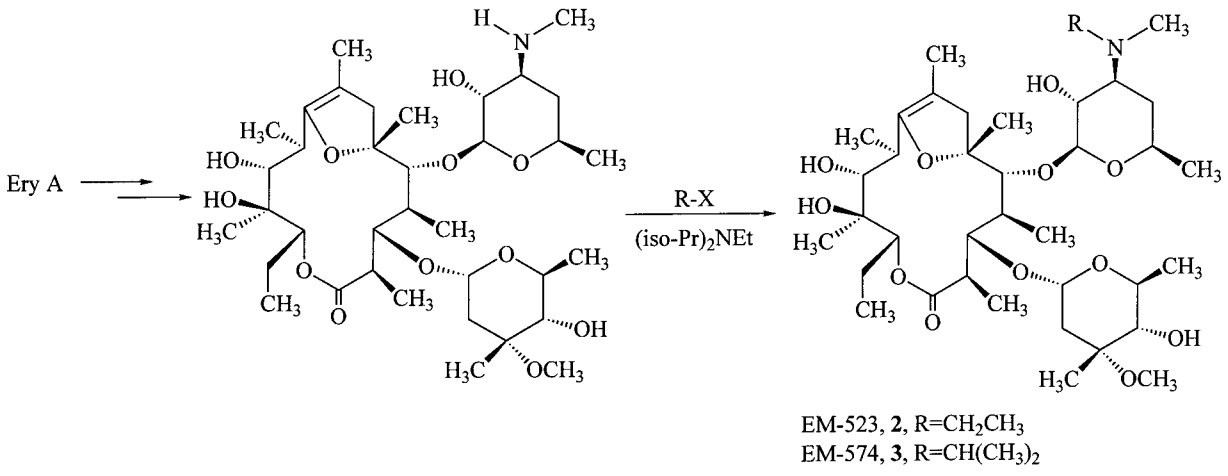
Omura *et al.* (35) demonstrated that conversion of the 9-ketone of the macrolactone ring system (Scheme 1) to an enol ether, such as **1**, led to an increase in GI motor stimulating activity (10-fold that of EryA) with a concomitant decrease in antibacterial activity. This manipulation demonstrated the feasibility of enhancing smooth muscle contractile potency with an associated decrease in antibacterial efficacy.

Substitutions on the 3'-position of the basic sugar (36, 37) also modulate potency (Scheme 2) in GI motility induction.

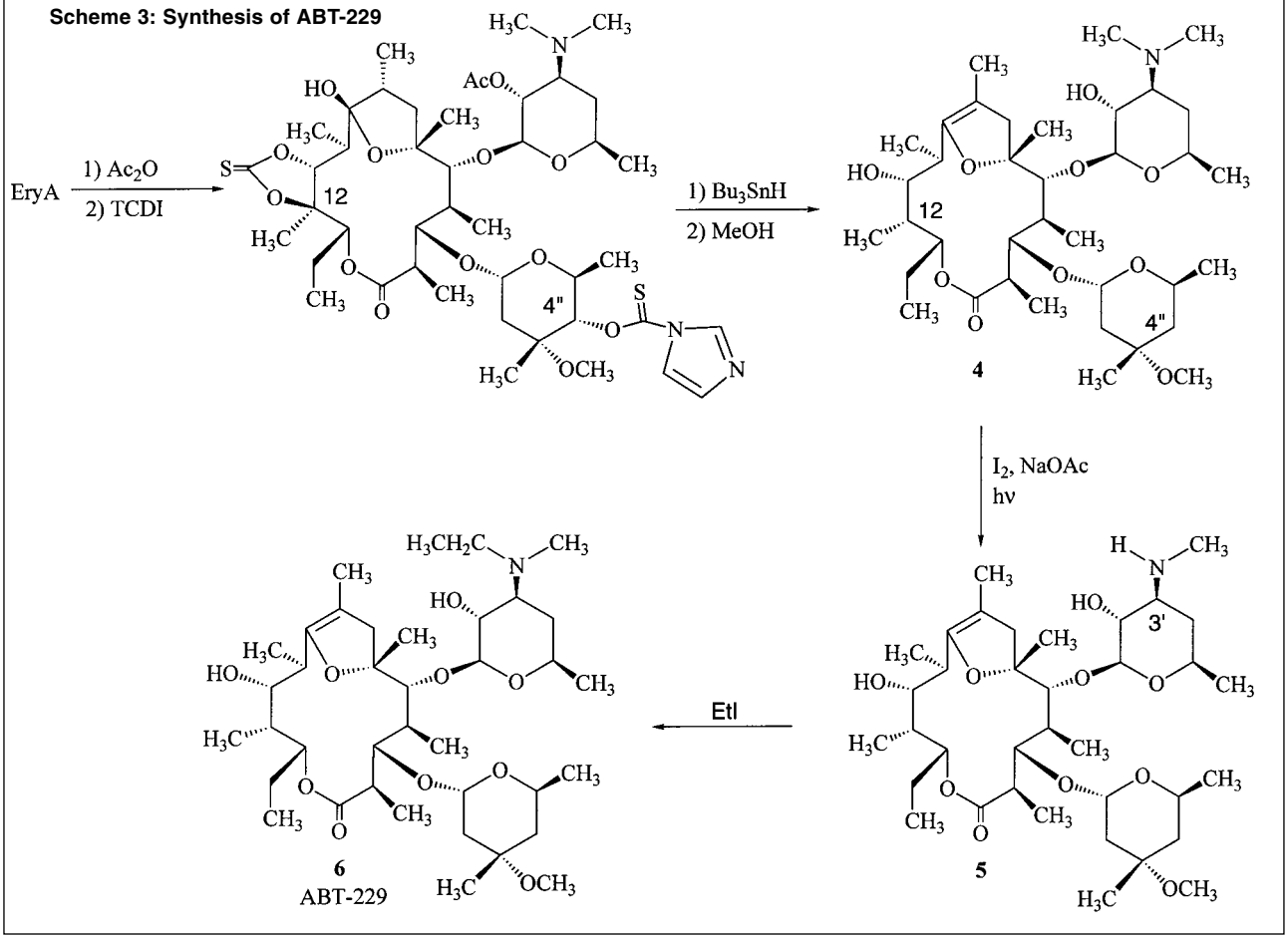
While the prokinetic potency could be increased (**2**, 18-fold and **3**, 248-fold that of EryA) with these modifications, antibacterial potency was eliminated.

Studies in our laboratories indicate that **2** and **3** have very low oral bioavailability (less than 5%) in the dog. A plausible explanation is that enol ethers of EryA, such as **2** and **3**, undergo rapid reaction involving the 12-OH to produce 6,9:9,12-spiroacetals under acidic conditions (38) in the stomach. Unlike **2** and **3**, spiroacetals have no prokinetic activity. To address this shortcoming, scientists at Abbott (39, 40) reported deoxygenation of erythromycin, at both the 12-position on the macrolactone ring and the 4"-position of the neutral sugar. These manipulations resulted in improved *in vitro* contractile potency (Scheme 3), affording an increase in prokinetic

Scheme 2: Synthesis of EM-523 and EM-574



Scheme 3: Synthesis of ABT-229



activity which led to the identification of ABT-229 (**6**). In the *in vitro* rabbit duodenum contractile assay, ABT-229 was 200-fold more potent than EryA. Excellent GI stimulatory activity was also demonstrated in the conscious dog following oral administration, with contractions observed in stomach, duodenum and ileum. ABT-229 showed promising oral activity, with an ED_{50} of 0.05 mg/kg in conscious dogs. It also revealed attractive oral bioavailability in dog (25%) and an elimination half-life of 6.0 h. Like EM-523 or EM-574 (Scheme 2), ABT-229 had no antibacterial activity.

The above SAR studies also underscore the importance of the conformation of the macrolactone at C-9 to C-12 for prokinetic potency. For example, the conformation of **6**, as determined by NMR, is superimposable on the X-ray crystal structure of **1**. On the other hand, conformation of the 12-epi congener of **6** differs considerably in the same region (40, 41), and has been shown to be much weaker than ABT-229 in contractility studies.

In a search for greater acid stability, Koga *et al.* (42) were able to protect the 12-hydroxyl group by *O*-alkylation and found that the 12-*O*-methyl derivatives, like GM-611 (**7**) (Scheme 4), exhibited less lability while retaining attractive *in vitro* potency. However, compound **7** did not show improved oral bioavailability compared to ABT-229 when examined by Abbott pharmacokineticists.

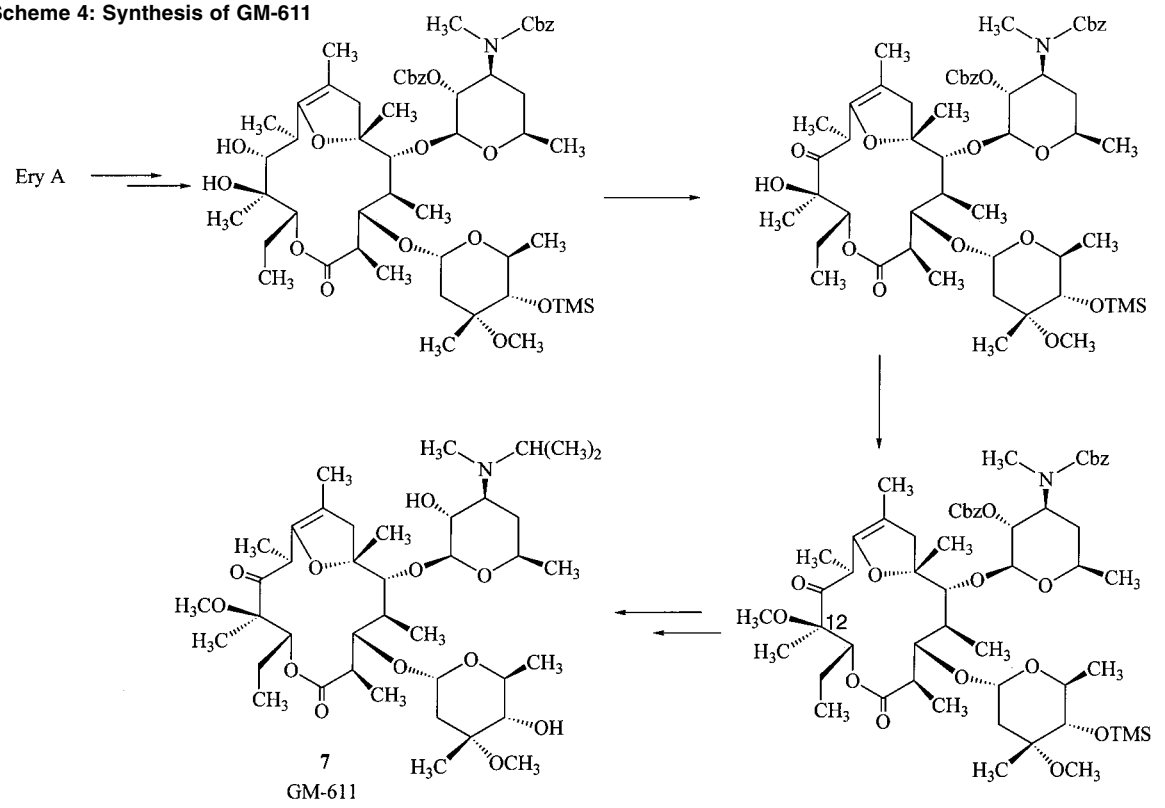
Other studies by Faghih *et al.* (43) confirmed that a key to potentiating stimulatory smooth muscle activity was to form a 6,9-epoxy ring system, as in the two epoxy derivatives **8** and **9**; both compounds were more potent (220- and 240-fold, respectively) than EryA (Schemes 5 and 6).

The presence of a 6,9-cyclic ether system is more critical for smooth muscle activity than the macrolactone ring size, as shown by Abbott investigators (44, 45) in the case of a 13-membered macrolide, A-182061 (Scheme 7).

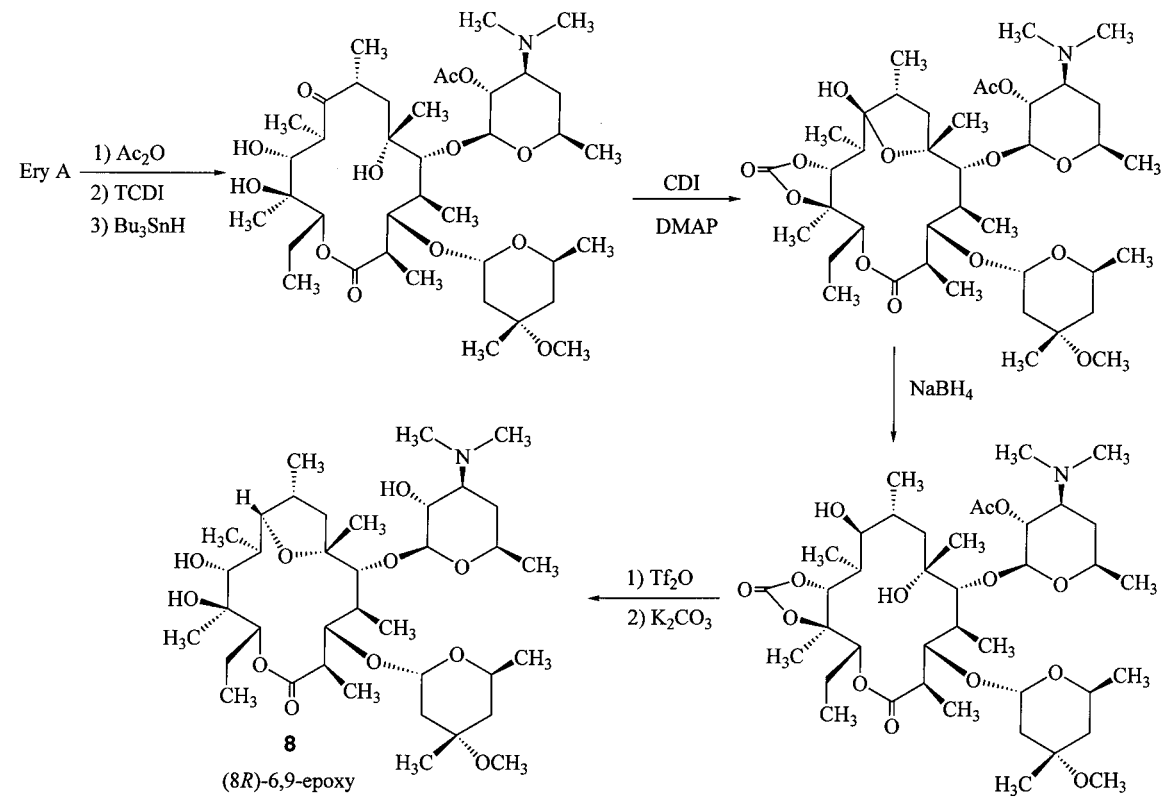
Eeckhout *et al.* (46), as well as Gregory and coworkers (47), have also confirmed that 12-membered macrolides such as KC-11458 (10) retain smooth muscle stimulating activity, although these 12- or 13-membered motilides are less potent *in vitro* than their 14-membered analogs. The 12-membered macrolides are the product of a ring rearrangement reaction of erythromycin, formed via translactonization of the 11-hydroxyl group (48).

For 14-membered 6,9-enol ether or 6,9-epoxy motilides, a conformation of the macrolactone containing a five-membered ring, which positions 11-OH close to C-1, predisposes the macrolactone ring toward intramolecular translactonization. This translactonization

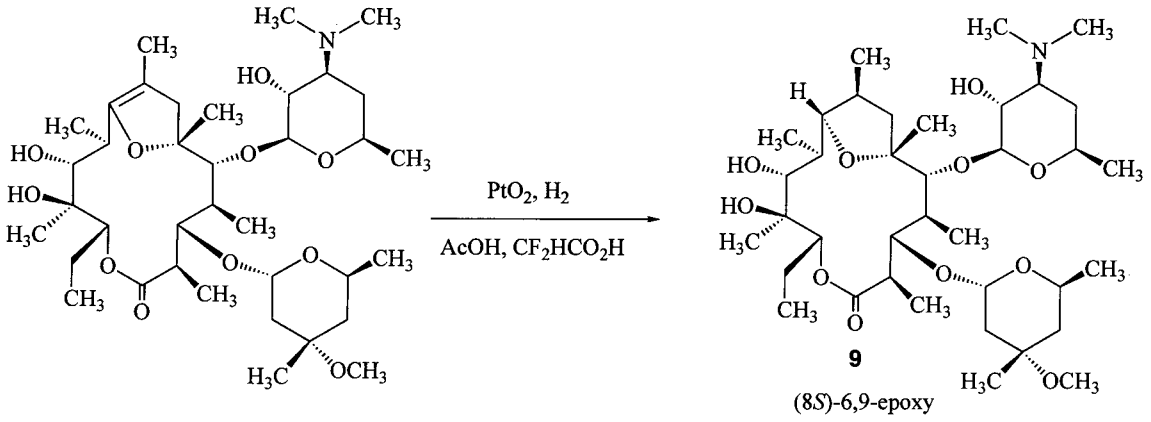
Scheme 4: Synthesis of GM-611



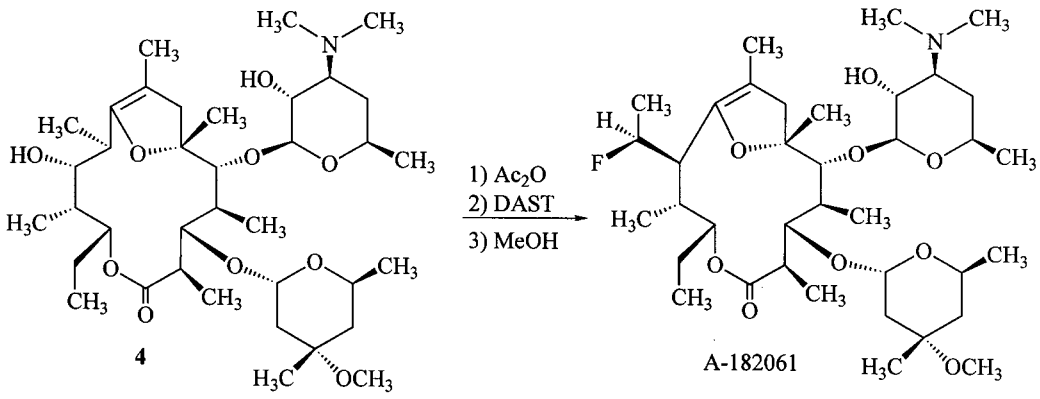
Scheme 5: Synthesis of (8*R*)-4"-deoxy-6,9-epoxyerythromycin A

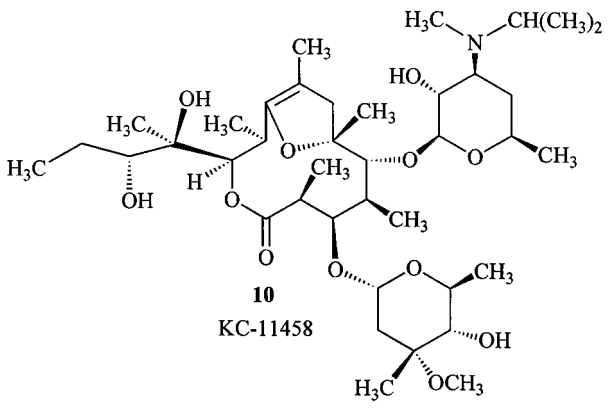


Scheme 6: Synthesis of (8*S*)-4"-deoxy-6,9-epoxyerythromycin A



Scheme 7: Synthesis of A-182061





contributes to instability of such systems. Consequently, toward the synthesis of potent and stable motilides, Abbott chemists studied the transformation of the macrolactone ring to a novel and stable macrolactam (Scheme 8).

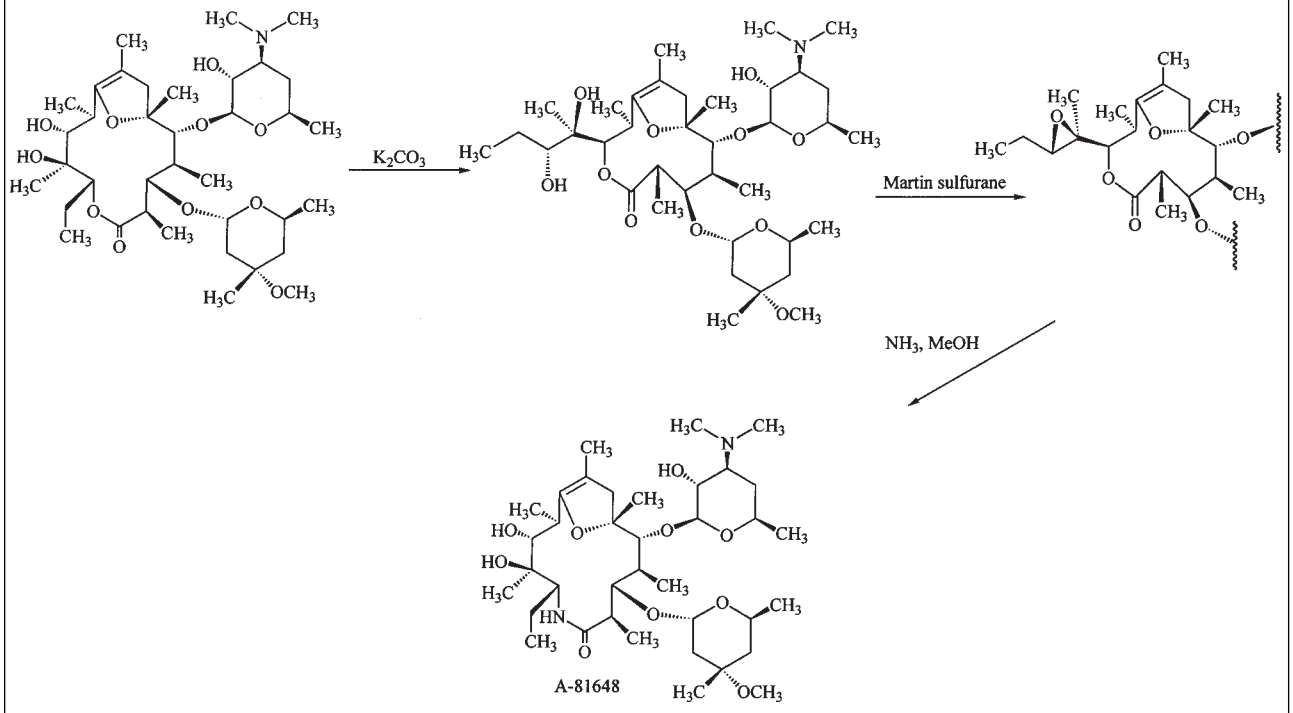
However, despite attractive *in vitro* potency (200 times that of EryA), A-81648 showed low oral bioavailability in dogs. The poor pharmacokinetic behavior may be attributed to the presence of the acid labile 6,9-enol ether. Hence, the 6,9-enol ether was replaced with an acid stable, 6,9-epoxy with 8(*R*),9(*R*) configuration (49, 50) (Scheme 9). This transformation led to a series of compounds with significantly improved bioavailability. For example, A-173508 (**11**) showed excellent *in vitro* activity (330 times that of EryA), measured as isolated rabbit duodenal smooth muscle contractility. Additional studies revealed oral bioavailability in dogs of 61%. A-173508 was also studied in conscious dog through measurement of GI smooth muscle contraction after oral administration. The compound demonstrated marked activity following oral dosing with an ED_{50} of 0.036 mg/kg. Thus, A-173508 has emerged as a member of a novel and unique class of potent and stable prokinetic agents, motilactides, with attractive oral bioavailability and efficacy.

Mode of action of motilides

Isolated tissue preparations

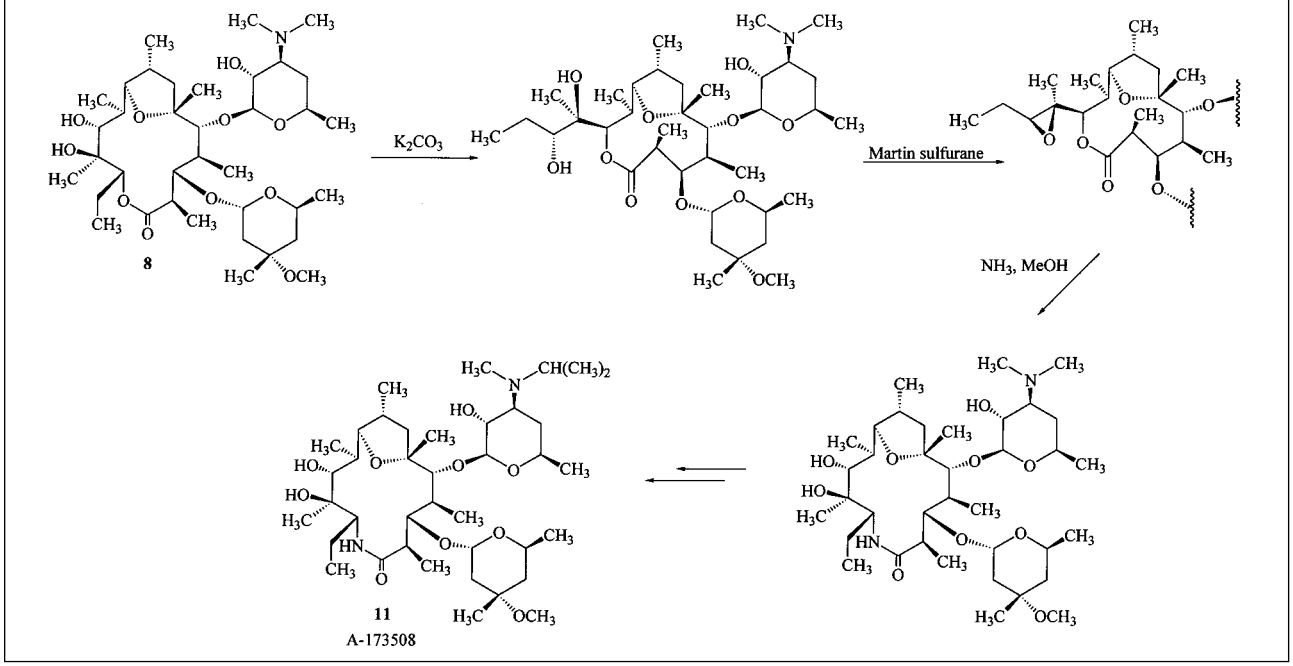
In isolated rabbit duodenal smooth muscle, motilides act directly on smooth muscle motilin receptors. This

Scheme 8: Synthesis of A-81648



receptor has been characterized in both contractility and binding studies (25). Early evidence that motilides are agonists for this smooth muscle receptor was recently confirmed by a report from Peeters' laboratory (51) employing a receptor antagonist. ANQ-11125, this 14-amino acid peptide derivative of motilin, at a concentration of 1 μm shifted the dose-response curves of motilin, EryA and motilides one order of magnitude, but

Scheme 9: Synthesis of A-173508



had no effect on substance P. More recently, Takanashi (52) reported the preparation of another antagonist, GM-109, a cyclic peptide derivative. Evidence has also surfaced for neurally mediated effects of motilides as reflected by the work of Morgan (53), Tack (54), Kitazawa (55) and others (56, 57). While binding studies of motilides have substantiated the presence of smooth muscle receptors, recent data from Poitras' laboratory (58) have also shown binding to synaptosomes in antral homogenates. Additional binding studies have also detected central (12, 13) neural motilin receptors. Consequently, the diversity of motilin receptor sites remains to be more rigorously characterized.

Intact animal studies

In vivo, most effects of erythromycin and motilides are neurally mediated, as shown by Ohtawa (59) for EM-523 (**2**) in dogs. In a series of conscious dogs implanted with force transducers, EM-523 and receptor antagonists were given intravenously during the interdigestive state. EM-523 induced phase III-like contractions in a dose-dependent manner, and the contractions were dose dependently inhibited by pretreatment with cholinergic and 5-HT_3 receptor antagonists and dopamine, but not by adrenoceptor, opiate antagonist or methysergide. Therefore, *in vivo*, EryA and motilides act on neural pathways to increase the release of acetylcholine and other excitatory transmitters. These pathways may be different in the fasting and fed states and are probably not vagally mediated, since EryA continues to accelerate gastric emptying after vagotomy in dogs (60) and man (61). Work by Morgan and Tack (53, 54) has suggested that EryA or motilin act at the level of the myenteric plexus.

These differences between *in vitro* and *in vivo* results may be due to differences in sensitivity. Recently Peeters (62) presented data suggesting that in rabbit antrum, the response toward electrical field stimulation is enhanced by motilin at much lower concentrations than those needed to induce contractions mediated via smooth muscle receptors. The neural motilin receptor may possess a higher affinity than the smooth muscle receptor, which is consistent with observations that low doses of EryA may drive neurally generated responses while high doses may directly drive muscular responses (21, 63).

Therapeutic applications of motilides

Since 1990, a large array of clinical motility disorders has been investigated using EryA as a motilin agonist with notable beneficial impact (64). With the clinical introduction of several improved erythromycin derivatives possessing improved potency and absence of antibacterial activity, the prospect of additional beneficial effects for motility disorders has been expanded.

Refux disease

Disorders of esophageal and gastric motility are the most dominant factors in the pathogenesis of gastroesophageal reflux disease (GERD). Patients with GERD have abnormal esophageal peristalsis, an incompetent lower esophageal sphincter and delayed emptying. The effect of motilides on gastric emptying and esophageal motility (66-70) suggest that motilides could find a place in the treatment of GERD. In a study with human volunteers, gastroesophageal reflux caused by white wine was reversed by EryA (71). It was also found that in patients with reflux disease, EryA shortened postprandial reflux duration. More data are needed to evaluate the potential of motilides in the treatment of gastroesophageal reflux disease.

Diabetic gastroparesis

The first demonstration of clinical utility for the prokinetic action of EryA was reported by Janssens (28). In these studies the gastric emptying of both solids and liquids was significantly accelerated in normal subjects and in patients suffering from gastroparesis due to diabetes. Intravenous, as well as orally administered (65), EryA increased emptying, and the effect was maintained for several weeks on repeated oral dosing.

Postoperative ileus

Interdigestive activity is important in postoperative patients. In postoperative ileus the frequency of phase III cycles is decreased, and it has been suggested that return of the migrating motor complex signals return to normalcy. Since motilides induce phase III activity, their potential for the treatment of this disorder is obvious. Positive results (73) have been reported with EM-523 (2).

Scleroderma

In systemic sclerosis different areas of the GI tract are affected, commonly the esophagus and small intestine and less often the stomach. When gastric emptying is delayed, migrating motor complex patterns are absent and patients develop bezoars and bacterial overgrowth. Motilides may play a role in the symptomatic treatment of this disorder (74, 75).

Gallstones

The effect on the gallbladder (76, 77) suggest that motilides may find application in patients with risk of gallstone formation, as a prophylactic to reduce recurrence or to aid fragment clearance after shock-wave lithotripsy.

Duodenal intubation

In children with the presumptive diagnosis of chronic intestinal pseudoobstruction, EryA facilitates the postpyloric passage of tubes during duodenal intubation. It is also reported that EryA facilitated the migration of antral feeding tubes (78).

Other applications

In patients with chronic idiopathic pseudoobstruction, EryA was able to induce phase III activity and improve clinical symptoms (72, 79). To empty the stomach before emergency surgery, intravenous EryA has been recommended as a quick and safe procedure (64). Also in patients with gastric stasis, intravenous EryA cleared the stomach and facilitated endoscopy (80).

Motilides in clinic

Morrison (81) studied the safety and pharmacodynamics of a single oral dose of ABT-229 (6) in 36 healthy subjects. The drug was safe and well tolerated in doses up to 64 mg and accelerated gastric emptying. Maes *et al.* (82) also studied ABT-229 in humans. Gastric emptying was evaluated using the octanoic acid breath test (83). ABT-229, after an oral dose of 4 mg, significantly increased gastric emptying of solids in man. In another study by Verhagen in 9 volunteers (84), a single oral dose of ABT-229 (4 mg) strongly stimulated postprandial antral motility. Finally, Verlinden *et al.* (85) described the dose-dependent acceleration of solid gastric emptying with ABT-229 in 132 healthy male subjects. ABT-229 accelerated gastric emptying of a solid meal in normal subjects, and was safe and well tolerated. Consistent responses across all meals required twice-daily dosing. The lowest effective dose was 2.5 mg twice daily. There was no evidence of tachyphylaxis. In light of these encouraging results, ABT-229 has entered phase IIB clinical trials.

Two other motilides from Takeda, EM-523 and EM-574, are also under clinical development. However, few clinical reports are available except for one study by Hanyu (73) and another by Nakamura *et al.* (86), showing improved gastric emptying in 6 patients with diabetic gastroparesis after intravenous administration of EM-523.

Summary

In parallel to the morphine and enkephalin relationship developed over the last 20 years, macrolide derivatives (motilides and motilactides) as highly potent agonists for receptors of the endogenous peptide, motilin, provide intriguing new possibilities for the study and treatment of motility disorders. As clinical development of this family of erythromycin derivatives continues, it is very probable that a compound with no antibacterial activity may find a major role in the therapy of gastrointestinal motility and be a useful addition to our rather limited armamentarium of effective and safe gastrointestinal prokinetic agents.

Acknowledgements

It is a distinct pleasure for us to thank all of our colleagues whose names appear in the references for their invaluable contributions to this research program.

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