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PREPARATION OF 9-DEOXO-4″-DEOXY-6,9-EPOXYERYTHROMYCIN LACTAMS "MOTILACTIDES": POTENT AND ORALLY ACTIVE PROKINETIC AGENTS

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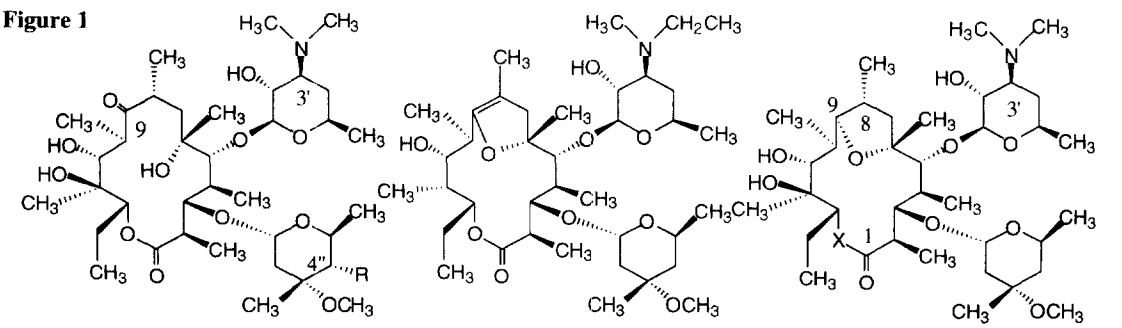
Abstract: A series of new, highly potent and orally active "motilactides", 9-deoxo-4″-deoxy-6,9-epoxyerythromycin lactams was designed, synthesized, and evaluated for their gastrointestinal motor stimulating activity. These compounds were acid stable and showed good oral efficacy.

Motilin is a gastrointestinal peptide hormone involved in the generation of interdigestive migrating contractions that originate in the stomach and migrate to the ileum in man and dog.[1] Erythromycin A (**1**, EryA), a well known macrolide antibiotic, is a motilin receptor agonist[2] and it has been reported to induce such contractions in humans when administered at low doses.[3] However, its antibacterial properties and low prokinetic activity limit its application for the treatment of GI disorders. Recently, several EryA (**1**) derivatives (Figure 1) referred to as motilides have been reported to be free of antibacterial activity, but retain the capacity to produce well coordinated contractions of the gastrointestinal tract.[4] Among them, ABT-229 (**2**),[5] an orally active motilin receptor agonist, is under clinical development for the treatment of gastroesophageal reflux disease and diabetic gastroparesis.

Figure 1



EryA: **1** R = OH
4 R = H

ABT 229: **2**

3 X = O
Motilactide: **10** X = NH

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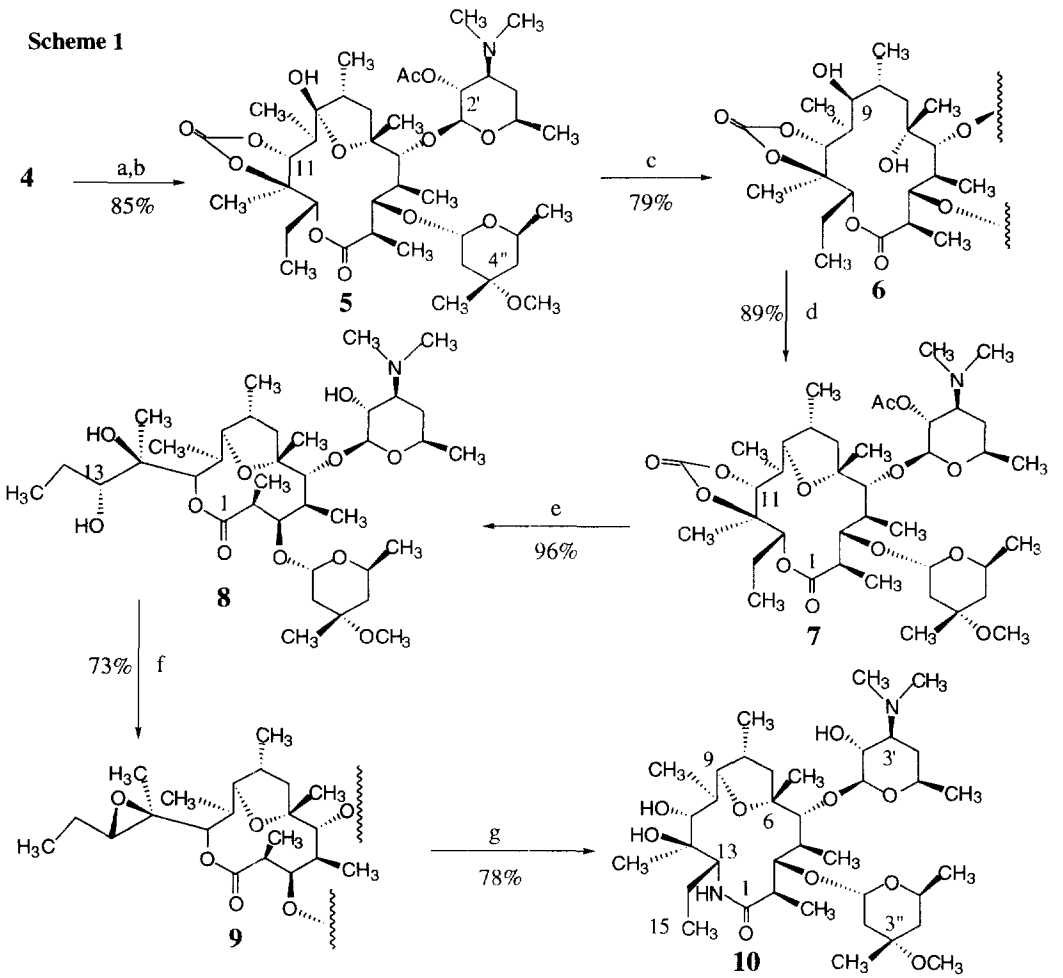
The 6,9-enol ether structural feature of the motilides, is most recognized as responsible for their high prokinetic potency. However, it is also implicated in their instability under the acidic conditions of the stomach,[6] resulting in loss of potency and erratic oral bioavailability. Recently, we have demonstrated[7] that the 6,9-enol ether can be successfully replaced by 6,9-epoxy functionality without loss of pharmacological activity. However, 8(*R*),9(*R*)-9-deoxo-4″-deoxy-6,9-epoxyerythromycin A (**3**) resulting from such replacement, showed a poor bioavailability profile in dog despite good in vitro potency.

Scheme 1

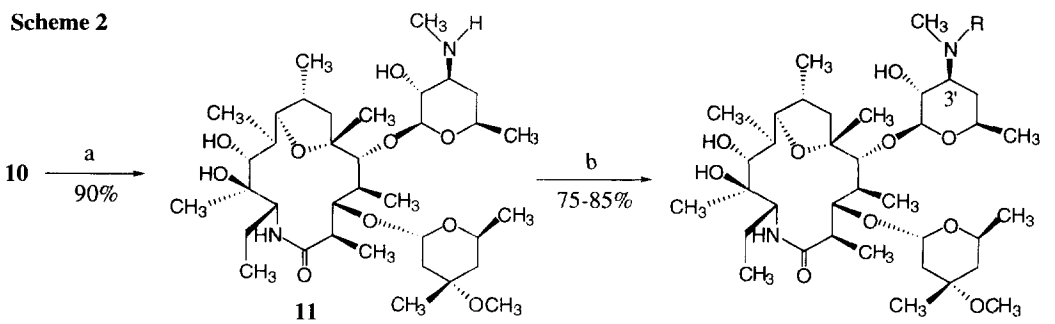


(a) Ac_2O, CH_2Cl_2. (b) CDI, DMAP, 80 °C, toluene. (c) $NaBH_4$, 2-propanol. (d) Tf_2O, pyridine, 0 °C, CH_2Cl_2. (e) K_2CO_3, 70 °C, CH_3OH, H_2O. (f) Martin sulfurane, CH_2Cl_2. (g) NH_3, 100 °C, CH_3OH.

In our quest to understand the SAR of the 6,9-epoxy derivatives with 8(*R*),9(*R*) configurations, we studied the transformation of the macrolactone ring in **3** to a novel and more stable macrolactam to generate novel potent compounds, motilactides with good oral bioavailability.

4″-Deoxy-erythromycin A (**4**) was prepared according to the published procedure[8] (Scheme 1). Treatment of **4** with acetic anhydride followed by carbonyl diimidazole gave the 11,12-cyclic carbonate-6,9-hemi-acetal intermediate **5** in excellent yield.[9] Reduction of the C-9 hemiketal of **5** with sodium borohydride gave the desired 9(*S*)-dihydro-erythromycin (**6**), thus placing the C-6 hydroxyl and the C-9 carbon within close proximity.[10] No formation of the 9(*R*)-epimer was observed with this substrate. Treatment of **6** with trifluoromethanesulfonic anhydride, led to the 6,9-epoxy (**7**) with 8(*R*),9(*R*) configuration, in 89% yield as requisite for in vitro potency.[7] The triflate formed in situ is apparently displaced by the near C-6 hydroxyl group.[11] Base treatment of cyclic carbonate **7** with potassium carbonate gave cleanly the fully unprotected ring contracted material **8** in almost quantitative yield via a *trans* lactonisation between the hydroxyl group at C-11 and C-1 lactone. Treatment of **8** with Martin sulfurane[12] gave epoxide **9** (73% yield), thus setting the stage for the key ring expansion. This ring expansion was effected by treating epoxide **8** with hot methanolic ammonia. To give lactam **10** in 78% yield.[13] Lactam **10** was further treated with I_2/NaOAc in the presence of light to give the desired **11** (Scheme 2). Further modification of the 3′-amino group led to compounds **12** to compounds **17** (Scheme 2) in excellent yields.

Scheme 2



12 R = CH_2CH_3 **15** R = $CH(CH_3)_2$
13 R = CH_2CH_2F **16** R = $CH_2CH(CH_3)_2$
14 R = CH_2CH_2OH **17** R = $CH_2CHOHCH_3$

(a) I_2, NaOAc, hv, CH_3OH. (b) RX, diisopropylethylamine, 80 °C, CH_3CN.

Prokinetic activity of lactams **10** to **17** was studied in vitro as smooth muscle contractility using isolated rabbit duodenum[14] (Table 1).

Table 1. In vitro Activities of Selected Compounds

Compd	pED_{50}
1	5.85
2	7.22
3	7.80
8	4.35
10	7.50
11	7.25
12	7.11
13	6.30
14	6.60
15	8.00
16	6.88
17	6.60

The results indicated that the dramatic transformation of the macrolactone ring to a macrolactam did not lead to loss of in vitro potency. Modification of the 3′-amine also influenced activity[15] in the 6,9-epoxylactam series. In a series of *N*-alkyl-*N*-methyl derivatives, the *N*-isopropyl-*N*-methyl derivative **15** was the most potent. Further extension of the alkyl carbon chain or introduction of an alkanol group decreased the in vitro activity delineating a limit in the binding region with respect to their target protein or receptor.

Compounds **10** and **15** fulfilled our requirement of in vitro potency. In order to test the macrolactam stability hypothesis behind these studies, we evaluated the bioavailability of compounds **10** and **15** in dog. Table 2 shows the pharmacokinetic data[16] for **3**, **10**, and **15**.

Table 2. Pharmacokinetics of Selected Compound in Dog

	pharmacokinetics	
Compd	$t_{1/2}$ (h)	bioavailability (%)
3	4.0	5.0
10	3.3	40.0
15	3.8	60.5

On the basis of excellent oral bioavailability and potent in vitro potency, the in vivo activity of **15** was studied in an intact animal model by measuring GI smooth muscle contraction after oral administration in the conscious dog.[17] Compound **15** revealed potency following an oral dose with an ED_{50} of 0.036 mg/Kg.

Compound **15** represents a novel and unique class of prokinetic agents with excellent in vitro activity. The compound demonstrates good oral bioavailability and efficacy in dog. These properties identify **15** for further evaluation and modification in our laboratories.

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13. Data for **10**: mp 139 to 142 °C; $[\alpha]_D$ –57.8 (*c* 0.68, $CHCl_3$); ^{13}C NMR (75.48 Mhz, $CDCl_3$) δ(ppm) 178.6 (C-1), 48.8 (C-2), 14.1 (2-CH_3), 75.9 (C-3), 42.6 (C-4), 11.5 (4-CH_3), 83.0 (C-5), 83.0 (C-6), 27.7 (6-CH_3), 43.5 (C-7), 32.7 (C-8), 14.7 (8-CH_3), 88.7 (C-9), 32.2 (C-10), 8.6 (10-CH_3), 70.1 (C-11), 75.6 (C-12), 16.7 (12-CH_3), 57.1 (C-13), 21.4 (C-14), 11.5 (C-15), 101.9 (C-1′), 70.8 (C-2′), 65.7 (C-3′), 40.2 (3′-NCH_3), 28.6 (C-4′), 68.8 (C-5′), 21.2 (C-6′), 95.1 (C-1″), 33.8 (C-2″), 70.7 (C-3″), 49.5 (3″-OCH_3), 25.7 (3″-CH_3), 45.8 (C-4″), 61.3 (C-5″), 21.6 (C-6″); HRMS: calcd for $C_{37}H_{68}N_2O_{10}$ 700.4873, found 700.4871.

14. In vitro prokinetic activity was studied as smooth muscle contractility in isolated rabbit duodenum. Longitudinal smooth muscle of the duodenum of male New Zealand white rabbits was bluntly separated from circular smooth muscle in a balanced electrolyte solution (pH 7.4). Isolated muscle (~30 mg) was mounted in a tissue bath and attached to force transducers. A dose–response curve was generated with the test compound and results expressed as fractional activity relative to the response observed in the presence of 10^{-6} M methacholine. From the dose–response profile, a pED_{50} (–log concentration yielding half-maximal contraction) was calculated as a comparative parameter for evaluating potency.

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16. Pharmacokinetics of selected compounds: 2 mg/mL solution of the lactobionate salt, were administered to groups of fasted beagles dogs (male/female) either at a 0.5 mg/kg iv or a 1 mg/kg po dose. Blood samples were collected over the 12 h postdosing intervals. The parent compounds were extracted from an alkalinized plasma aliquots using a mixture of EtOAc and C_6H_{14} (1:1). The desired compounds were separated from plasma contaminants on a 10 cm/4.6 mm Spherisorb ODS-AQ column (YMC Inc.). Analysis and quantitation was performed by electrochemical detection in the oxidative mode.

17. In vivo activity was assessed in fasted conscious female beagle dogs. The animals were surgically prepared by applying strain gauge transducers to the serosal surfaces of the stomach, antrum, duodenum, and jejunum. Smooth muscle motility responses were recorded and the results scored as the area under the force/time curve for 60 min following oral dosing.