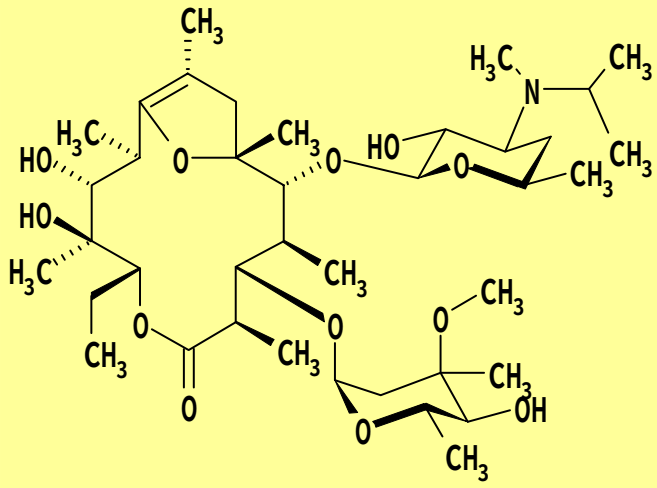
EM574 [Motilide] [Idremcinal]	Cat.# BLS0510

Structure



Origin: semi-synthetic from Erythromycin	
CAS Registry Number: 110480-13-2	
CA Index Name: 8,9-Didehydro-N-demethyl-9-deoxo-6-deoxy-6,9-epoxy-N-(1-methylethyl)-Erythromycin Idremcinal	
Appearance: white powder	
Molecular Formula/ Weight: $C_{39}H_{69}NO_{12}$=743.98	
Melting Point: 110-112°C	**Purity:** >97% by HPLC
Solubility: Sol. in MeOH, DMSO, Chloroform, EtOH, EtOAc, Acetone, Acetonitrile Insoluble in water, Hexane	

Background Information:

Motilides are a series of erythromycin derivatives (especially EM 522, EM 523, EM536 and EM 574) (Table 1) which showed gastrointestinal motor stimulating (GMS) activity without antibacterial activity[1-4]. The GMS activity is very similar to the effect caused by the hormone motilin (Fig. 1).

Motilides induce phase III-like contractions, which are similar to those induced by motilin, in the human gastrointestinal tract during the interdigestive state in dogs and humans. EM574 is a motilin receptor agonist in the human gastric antrum in vitro, using contraction studies of muscle strips and isolated myocytes, receptor binding assay and tissue section autoradiography. EM574 stimulated contractions of muscle strips in a concentration-dependent manner (10-7-10-5 M), and this contractile effect was unaffected by pretreatment with atropine or tetrodotoxin. Isolated myocytes contracted in response to EM574 with a peak shortening at 10-7 M, which was comparable to the response to motilin[5-10].

EM574 displaced specifically 125I-motilin bound to smooth muscle homogenates with a Kd value of 7.8 x 10-9 M, compared with 4.5 x 10-9 M for motilin. Film autoradiograms showed that 125I-motilin-binding sites were localized in the muscle layers, and that the labeling disappeared in the presence of a 1,000 times molar concentration of EM574. EM574 directly stimulates smooth muscle cell contraction by acting on motilin receptors in the human gastric antrum in vitro[11] (Fig. 2).

We applied a rational computational procedure consisting of conformational analysis and a novel superposing method to investigate the 3D structure-activity relationship between motilide (EM536) and motilin. The HA9, DA10, and DA11 atoms for EM536 were superposed on the DA9, HD10, and HD11 atoms for motilin, respectively. We have proposed common 3D structural features between these molecules, which may be related to for their activity[12] (Fig. 3).

Furthermore, EM574 has an orexigenic activity with affinity for growth-hormone secretagogue receptor (GSH-R), which Ghrelin binds[13].

Handling and Storage:

Store at -20°C.

References:

1. S. Ōmura et al., J. Antibiot., **38**, 1631-1632 (1985).
2. S. Ōmura et al., J. Med. Chem., **30**, 1941-1943 (1987).

3. K. Tsuzuki et al., Chem. Pharm. Bull., **37**, 2687-2700 (1989).
4. T. Sunazuka et al., Chem. Pharm. Bull., 37, 2701-2709 (1989)
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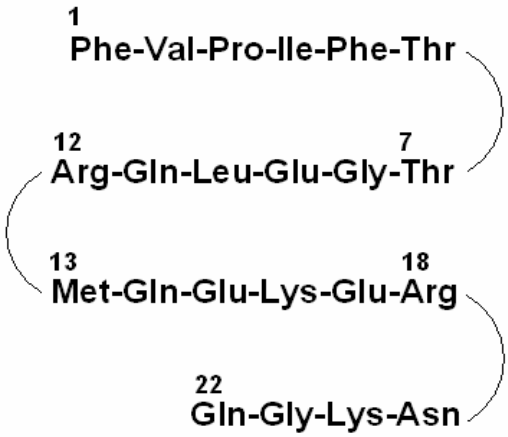
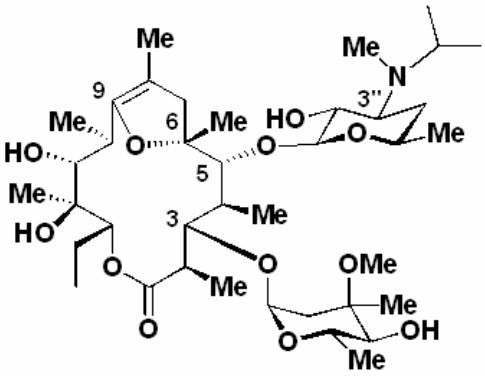
11. Y. Kondo et al., Biochem. Biophys. Res. Commun., 150, 877-882 (1988)
12. H. Gouda et al., Chem. Pharm. Bull., 48, 1835-1837 (2000)
13. A. Asakawa et al., J. Gastroenterology and Hepatology, 18, 881-882 (2003)

Synthesized by Organic Chemistry Group, The Kitasato Institute.

Structure of Motilin and EM 574 (Motilide)





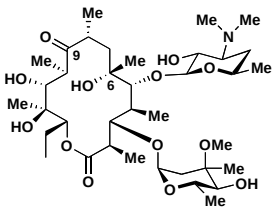
Motilin [1)] **EM 574** [2)]

1) J. C. Brown *et al.*, *Can. J. Biochem.*, 51, 533 (1973)
2) S. Ōmura *et al.*, *J. Med. Chem.*, 30, 1941 (1987)

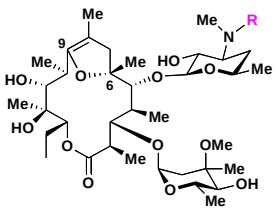
Antibacterial Activity and Gastrointestinal Motor Stimulating (GMS) Activity of Motilides

Compound	Antibacterial activity (MIC, μg/ml)[1)]	GMS activity[2)]
EM A	0.2	1
EM 201	50	10
EM 523	>100	18
EM 574	>100	248
EM 536	>100	2890

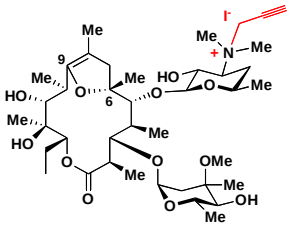
1) *Staphylococcus aureus* ATCC 6538P, agar dilution method.
2) GMS activity was estimated by 2 X 2 points pallel line assay.



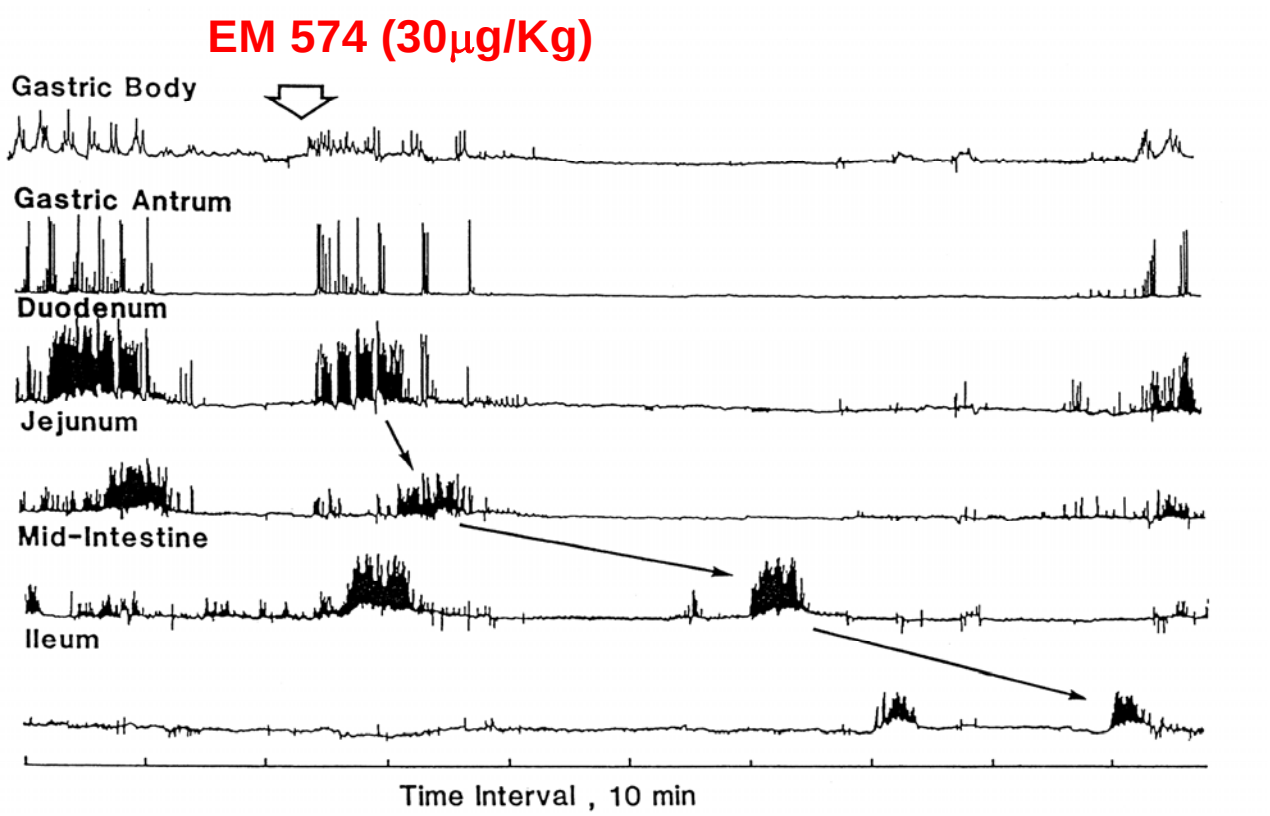
Erythromycin A (EM A)



EM 201 R = Me
EM 523 R = Et
EM 574 R = *i*-Pr

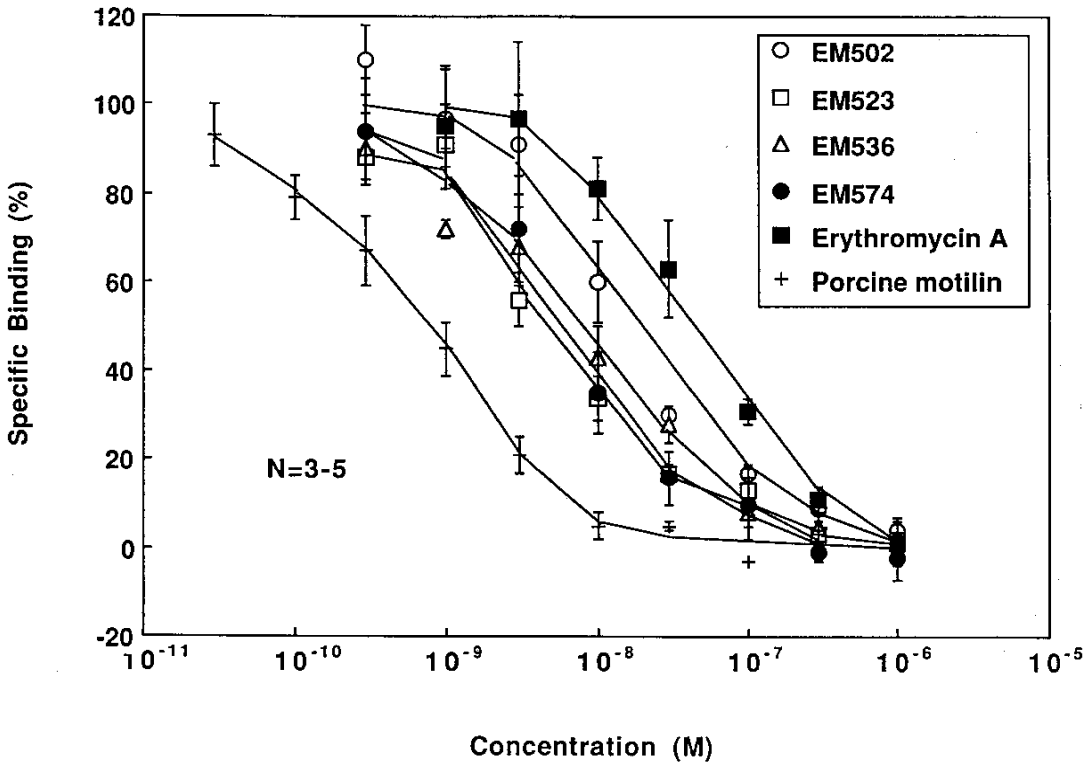


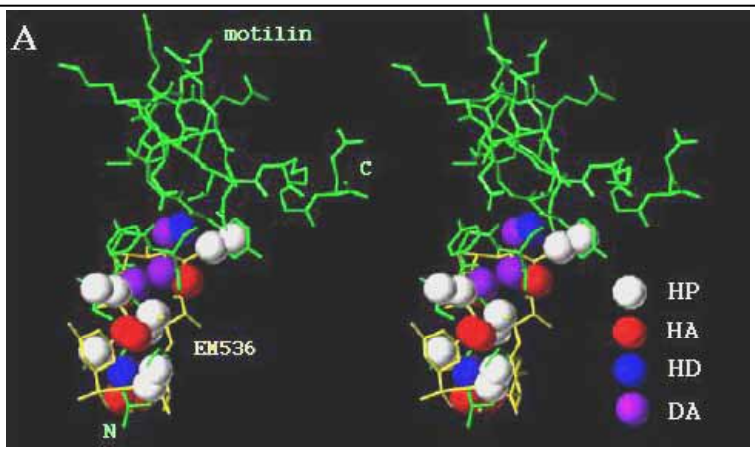
EM 536



Gastrointestinal Constraction Induced by EM 574 (30μg/Kg)

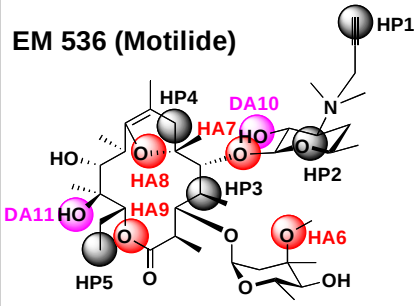
Displacement of Iodinated Motilin Binding of Motilides



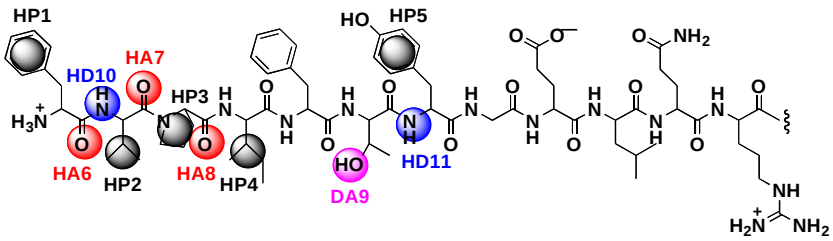


Hydrophobic (HP)
H-acceptor (HA)
H-donor (HD)
H-donor/acceptor (DA)

EM 536 (Motilide)



Motilin



Three-dimensional Structure-activity Relationship Analysis between Motilin and Motilide Using Conformational Analysis and a Novel Molecular Superposing Method

H. Gouda et al., *Chem.Pharm.Bull*, *48*,1835 (2000)