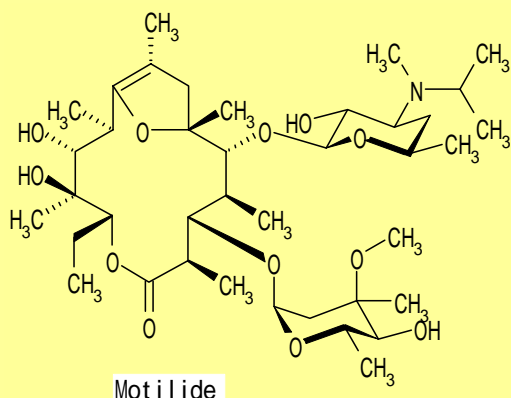


Structure



Motilide

Origin: semi-synthetic

CAS Registry Number: 110480-13-2

CA Index Name: 8,9-Didehydro-N-demethyl-9-deoxy-6-deoxy-6,9-epoxy-N-(1-methylethyl)-Erythromycin

Appearance: white powder

Molecular Formula/ Weight: C₃₉H₆₉NO₁₂=743.98

Melting Point: 110-112 Purity: >97% by HPLC

Solubility: Sol. Inso.

pKa:

log P:

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 K_d 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 located in the gastric antrum. We applied a rational computational procedure consisting of conformational analysis and a novel superposing method. Furthermore, EM574 has an orexigenic activity with affinity for growth-hormone secretagogue receptor (GSH-R).

Handling and Storage:

Store at -20 °C.

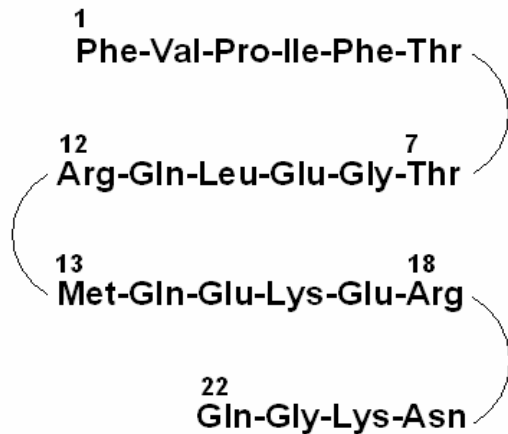
References:

1. S. Omura et al., *J. Antibiot.*, **38**, 1631-1632 (1985)
2. S. Omura et al., *J. Med. Chem.*, **30**, 1941-1943 (1987)
3. K. Tsuzuki et al., *Chem. Pharm. Bull.*, **37**, 2687-2700 (1989)

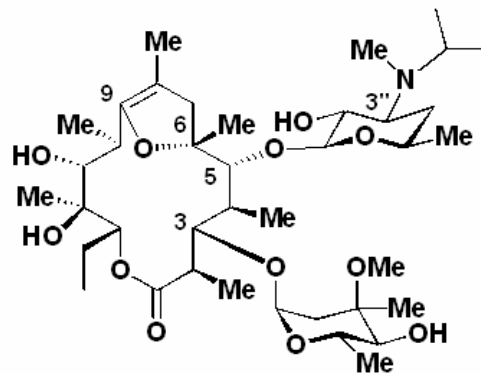
Synthesized by Organic Chemistry Group, The Kitasato Institute.

(ID#: 110480132S)

Structure of Motilin and EM 574 (Motilide)



Motilin ¹⁾



EM 574 ²⁾

1) J. C. Brown et al., *Can. J. Biochem.*, **51**, 533 (1973)

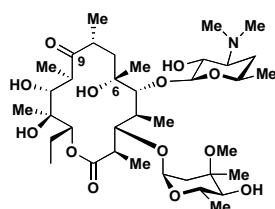
2) S. Omura et al., *J. Med. Chem.*, **30**, 1941 (1987)

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

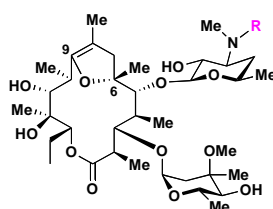
Compound	Antibacterial activity (MIC, µg/ml) ¹⁾	GMS activity ²⁾
EM A	0.2	1
EM 201	50	10
EM 523	>100	18
EM 574	>100	248
EM 536	>100	2890

1) *Staphylococcus aureus* ATCC 6538P, agar dilution method.

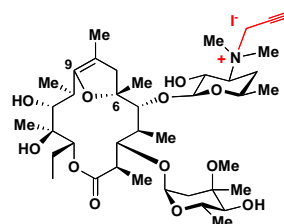
2) GMS activity was estimated by 2 X 2 points parallel line assay.



Erythromycin A (EM A)

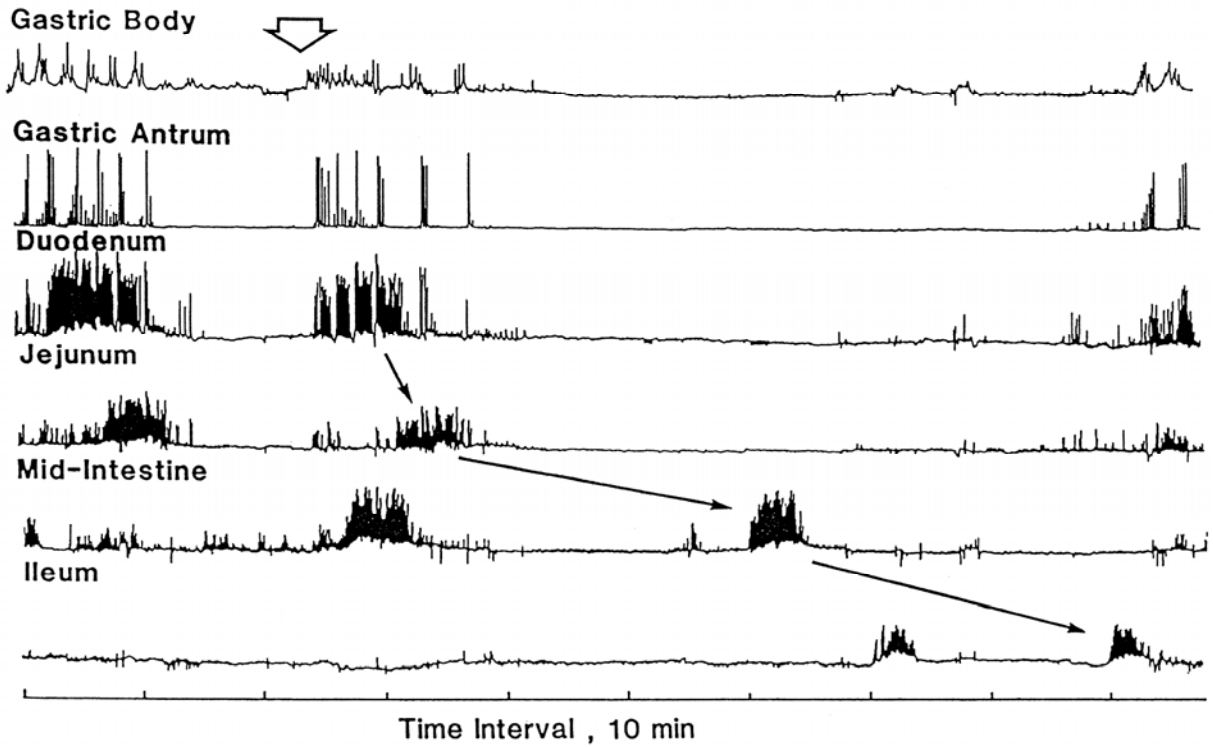


EM 201 R = Me
EM 523 R = Et
EM 574 R = *i*-Pr



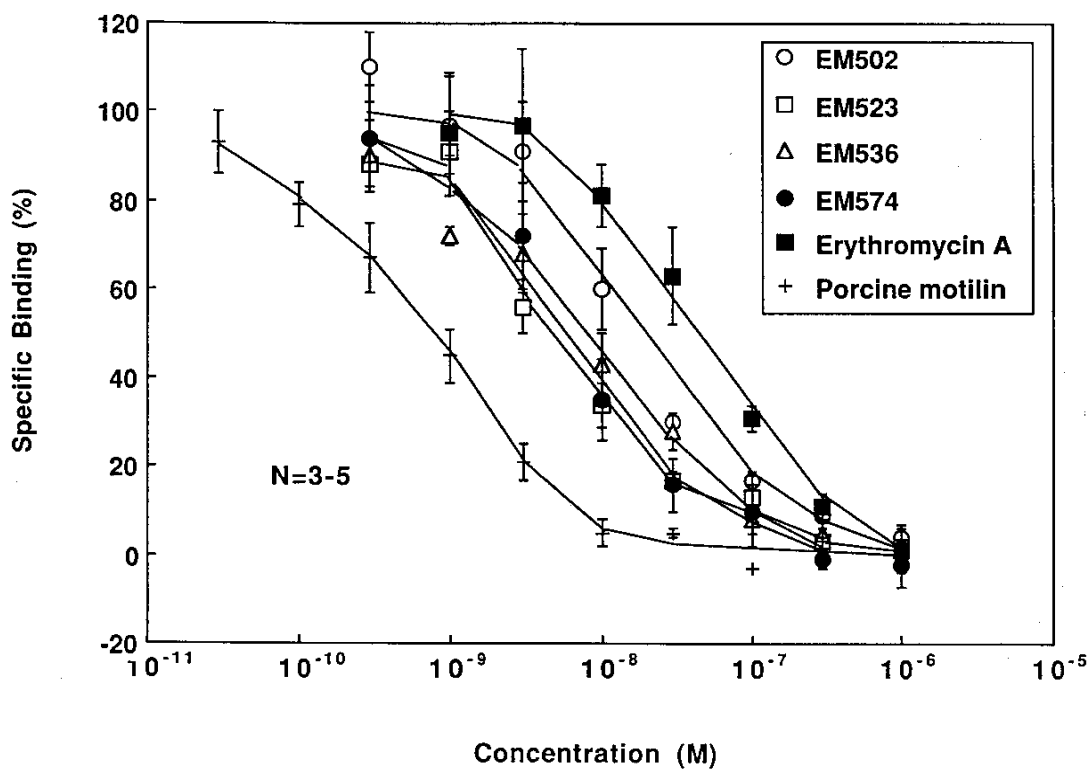
EM 536

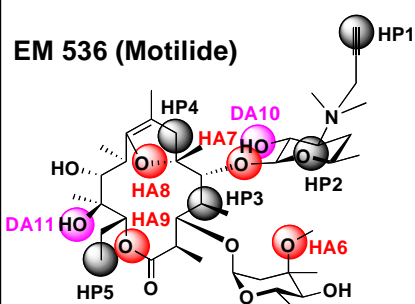
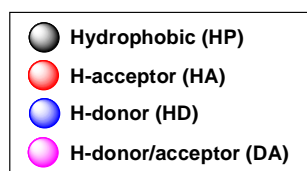
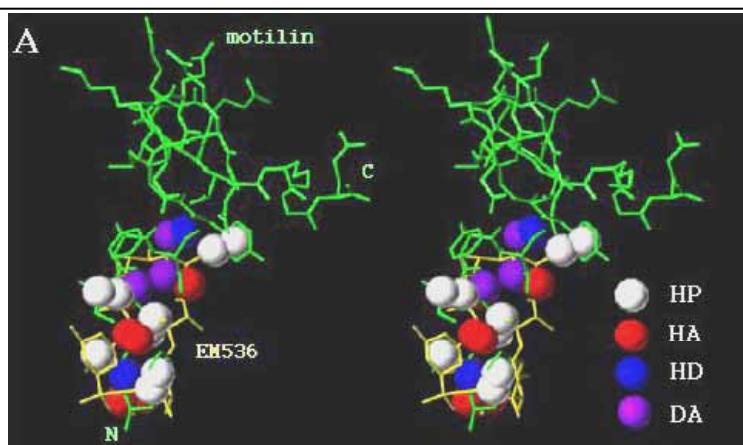
EM 574 (30 μ g/Kg)



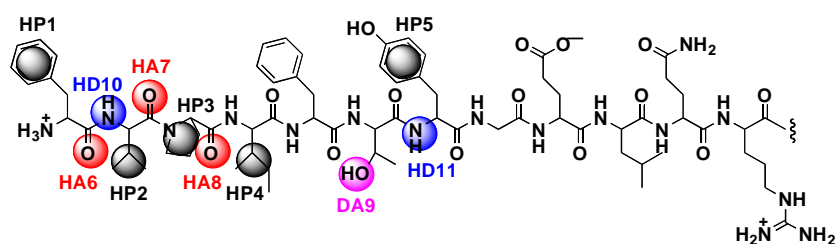
Gastrointestinal Constriction Induced by EM 574 (30 μ g/Kg)

Displacement of Iodinated Motilin Binding of Motilides





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)