Drugs of the Future 1999, 24(11): 1178-1183

CCC: 0377-8282/99

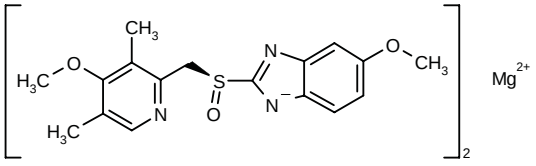
Esomeprazole Magnesium

Prop INNM

H^+/K^+-ATPase Inhibitor
Antiulcer
Treatment of GERD

(–)-Omeprazole Magnesium
Perprazole (formerly)
(*S*)-Omeprazole Magnesium
H-199/18
Nexium™

5-Methoxy-2-[(*S*)-(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole magnesium salt



$2C_{17}H_{18}N_3O_3S.Mg$ Mol wt: 713.1314

CAS: 202742-32-3
CAS: 119141-88-7 (as free acid)
CAS: 217087-10-0 (as dihydrate)
CAS: 217087-09-7 (as trihydrate)
CAS: 161796-85-6 (as calcium salt)
CAS: 161796-84-5 (as potassium salt)
CAS: 161796-83-4 (as lithium salt)
CAS: 161796-78-7 (as sodium salt)

EN: 272598

Synthesis

Esomeprazole can be obtained by several related ways:

1) The NaOH-mediated condensation of 2-(chloromethyl)-4-methoxy-3,5-dimethylpyridine (II), obtained by reaction of the hydroxymethylpyridine (I) with $SOCl_2$, with 5-methoxy-1*H*-benzimidazole-2-thiol (V), obtained by cyclization of 4-methoxy-*o*-phenylenediamine (III) with potassium ethylxanthate (IV), gives 5-methoxy-2-(4-methoxy-3,5-dimethylpyridin-2-ylmethylsulfanyl)-1*H*-benzimidazole (VI), which is oxidized with *m*-chloroperbenzoic acid, yielding racemic omeprazole (VII) (1). The optical resolution of (VII) can be performed by chiral chromatography using several different chiral stationary phases (2-9), or by stereoselective bioreduction of the undesired (+)-enantiomer with a purified preparation of DMSO reductase from *Rhodobacter capsulatus* DSM 938 that, after reversed phase HPLC separation of the reduced sulfanyl derivative (VI), affords an enantiomerically enriched (15:85) mixture of the (+)- and (–)-enantiomers (10). Finally, this mixture is submitted to chiral HPLC separation (10) or fractional crystallization in either acetonitrile, 2-butanone or acetone (11). Scheme 1.

2) The asymmetric oxidation of the pro-chiral sulfide (VI) carried out by biooxidation with various microorganisms; among them, the best results (>99% ee) were obtained with *Penicillium frequentans* BPFC 386, *Penicillium frequentans* BPFC 585, and *Brevibacterium praffinoliticum* ATCC 21195 (12). Scheme 1.

3) The asymmetric oxidation of the pro-chiral intermediate (VI) performed with titanium(IV) isopropoxide and cumene hydroperoxide in the presence of (–)-diethyl D-tartrate and DIEA in toluene (11, 13). Scheme 1.

4) The reaction of racemic omeprazole (VII) with formaldehyde in dichloromethane gives, after crystallization in acetonitrile, 1-(hydroxymethyl)-6-methoxy-2-(4-methoxy-3,5-dimethyl-2-pyridinylmethylsulfinyl)-1*H*-benzimidazole (VIII), which is treated with $SOCl_2$ in dichloromethane to afford, after crystallization in acetonitrile, the corresponding chloromethyl derivative (IX) (14). The condensation of (IX) with (*R*)-2-hydroxy-2-phenylacetic acid (X) by means of NaOH and tetrabutylammonium hydrogen sulfate in water gives the corresponding ester (XI) as a diastereomeric mixture, that is resolved by reverse phase chromatography. Finally, the suitable isomer is hydrolyzed to esomeprazole by treatment with NaOH in methanol (15, 16, 17). Scheme 2.

Esomeprazole magnesium can be obtained by three different ways: i) by reaction of esomeprazole with mag-

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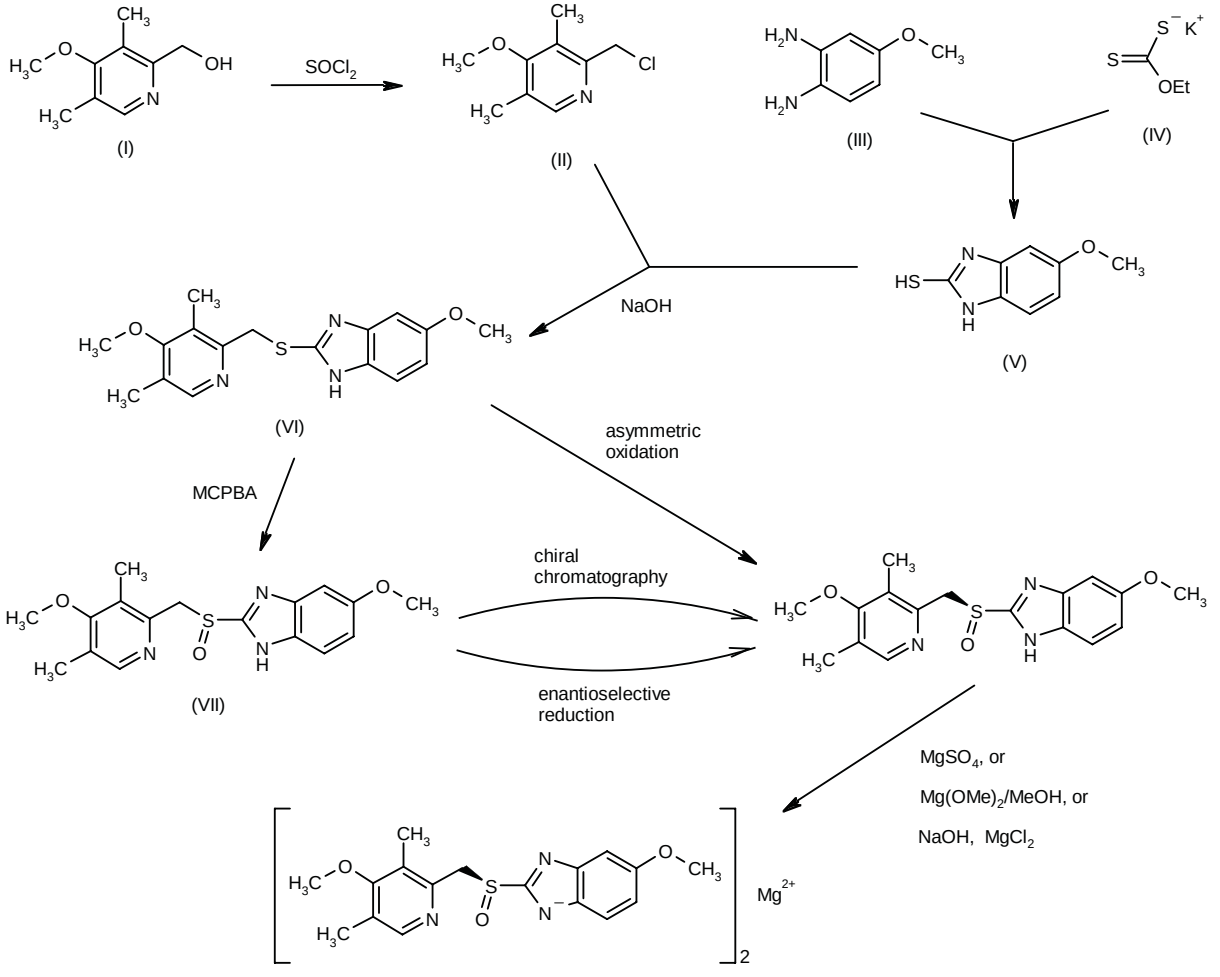
Scheme 1: Synthesis of Esomeprazole Magnesium



nesium sulfate heptahydrate in aqueous ammonia (18); ii) by reaction of esomeprazole with magnesium methoxide in methanol (19) or iii) by reaction of esomeprazole sodium, obtained by treatment of esomeprazole with NaOH in 2-butanone, with hydrated magnesium chloride in water (15, 16).

Description

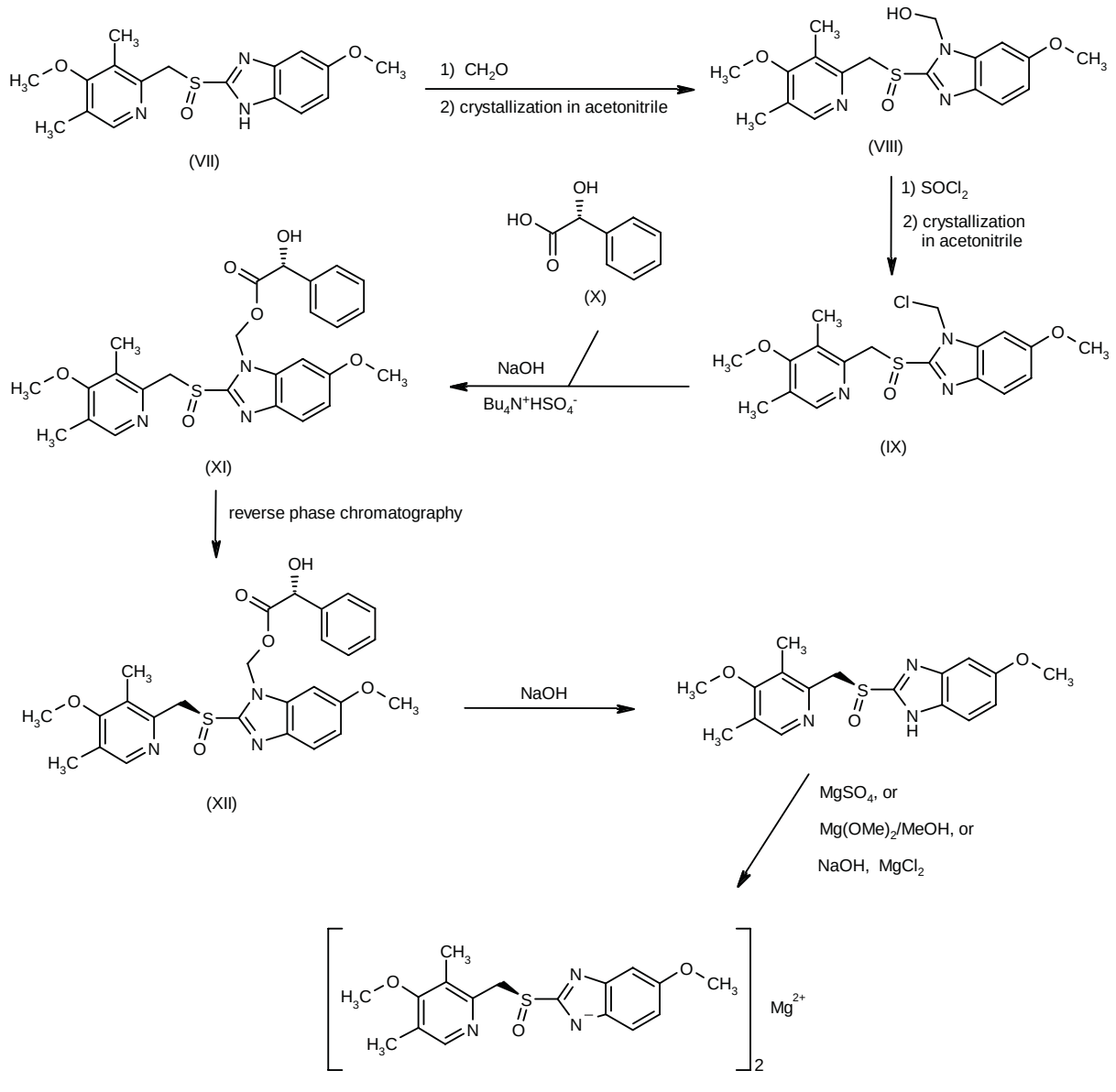
Magnesium salt: $[\alpha]_D^{20}$ –131.5° (c 0.5, MeOH) (15), $[\alpha]_D^{20}$ –128.2° (c 1, MeOH) (15, 16); sodium salt: $[\alpha]_D^{20}$ +42.8° (c 0.5, H_2O) (15, 16).

Introduction

Gastric H^+/K^+-ATPase (the so-called "proton pump") is the enzyme responsible for the transport of gastric acid into the lumen stomach and is an important target for peptic ulcer therapy. Inhibitors of H^+/K^+-ATPase block acid secretion at the final step of its production, independent of the way in which it is stimulated. In 1988, Astra won the race to market the first H^+/K^+-ATPase inhibitor with the launch of omeprazole (Losec) in Sweden. Since 1988, omeprazole – which is marketed in the U.S. as Prilosec – has become one of the world's largest-selling drugs. The efficacy of omeprazole in the treatment of peptic ulcer is well documented in the literature. The drug has also been used with considerable success in the treatment and prevention of other gastric acid-related diseases, including gastroesophageal reflux disease (GERD), gastritis, duodenitis, gastric ulcer and duodenal ulcer, and in the prevention of gastrointestinal irritation associated with NSAIDs, to name just a few.

Following the launch of omeprazole in 1988, several other H^+/K^+-ATPase inhibitors reached the market, while others are progressing through clinical development. The structures of compounds available and under development are shown in Table I, and the proton

Scheme 2: Synthesis of Esomeprazole Magnesium



pump-inhibitory activity of selected compounds is given in Table II.

Astra's substance patent for omeprazole began to expire in the first countries in 1999, although in most countries AstraZeneca has obtained Patent Term Extensions or Supplementary Protection Certificates (until April 2001 in the U.S., until 2002-2004 in European countries and until 2004 in Japan) (20). In view of the eventual expiration of their patents on omeprazole, Astra began conducting further research soon after the drug was first launched in an effort to develop an improved version of the proton pump inhibitor and at the same time protect its proprietary position. The result of these efforts was the discovery of esomeprazole, the active (–)-enantiomer of omeprazole (21).

Pharmacokinetics and Metabolism

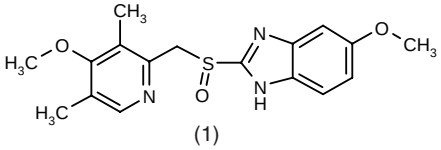
In spite of its documented safety and efficacy, omeprazole does have at least one known drawback: polymorphic metabolism. Approximately 3% of all Caucasian patients and some 15-20% of Oriental patients metabolize omeprazole more slowly than the general population. In slow metabolizers, plasma concentrations of the drug are higher than the average. Since

Table I: H^+/K^+-ATPase inhibitors available and under development (Prous Science Ensemble database).

Launched
1. Omeprazole (1988)
2. Lansoprazole (1991)
3. Pantoprazole sodium (1994)
4. Rabeprazole sodium (1997)

Clinical Trials
5. Esomeprazole magnesium
6. Leminoprazole
7. IY-81149
8. Tenatoprazole

Preclinical Studies
9. YJA-20379-1
10. YJA-20379-5
11. YJA-20379-8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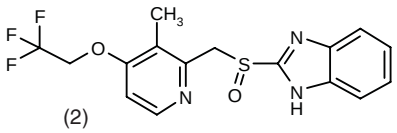
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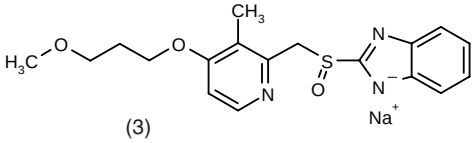
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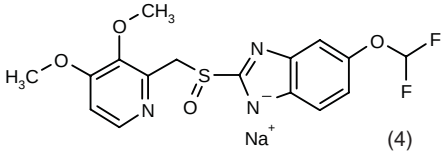
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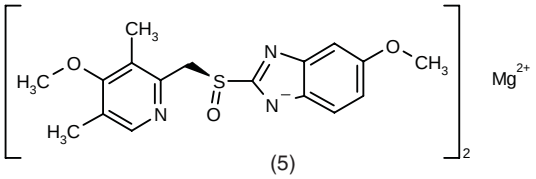
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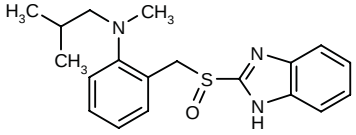
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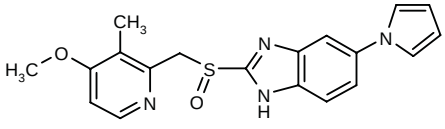
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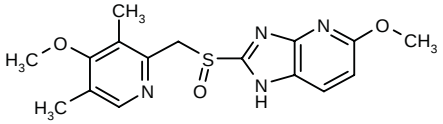
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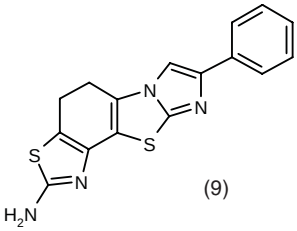
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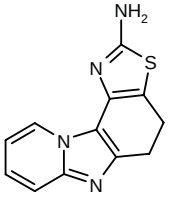
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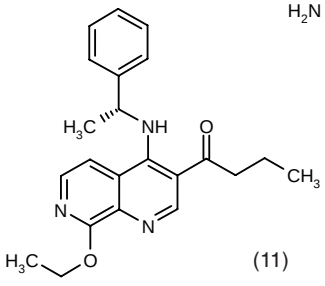
(11)

the inhibition of gastric acid secretion is correlated to the plasma concentration AUC, these slow metabolizers can be expected to experience a more pronounced effect from the drug. As such, the search began for an improved version of omeprazole with less interindividual variation and that would produce higher plasma levels. This search led to the identification of esomeprazole (formerly called perprazole) as an improved alternative to omeprazole (21).

Omeprazole is metabolized primarily in the liver via the cytochrome P450 system (CYP) – a superfamily of enzymes – and more specifically by the polymorphically expressed enzyme CYP2C19 (22). *In vitro* studies demonstrated that esomeprazole undergoes less metabolic transformation by CYP2C19 than the racemic drug and, as a result, shows less variation in plasma levels between slow and rapid metabolizers (21).

A study was conducted in 10 healthy subjects, 5 of whom were classified as extensive metabolizers and 5 as poor metabolizers, with the aim of confirming the above. Subjects were first classified as slow or rapid metabolizers through *S*-mephenytoin phenotyping and then administered a single 20-mg dose of omeprazole following an overnight fast. Plasma concentrations of the parent drug, the (+)- and (–)-enantiomers and the principal metabolites of omeprazole (5-hydroxyomeprazole and omeprazole sulfone) were determined over the next 10 h. The results indicated that the mean AUC over the first 8 h postdosing for the (+)-enantiomer of omeprazole was 7.5 times higher in poor metabolizers than in extensive metabolizers and the AUC_{0-8} for the 5-hydroxy metabolite of the (+)-enantiomer was 3.8 times lower; as a result, the mean AUC_{0-8} ratio for (+)-omeprazole/(+)-5-hydroxyomeprazole was about 30-fold higher in poor than in extensive

Table II: Inhibition of H^+/K^+-ATPase by selected proton pump inhibitors (Prous Science MFLine® database).

Compound	Inhibitory activity (IC_{50}, μM)	Tissue source	Ref.
IY-81149	6.0	Rabbit parietal cells	29
Lansoprazole	2.7	Dog stomach	30
	0.4	Rabbit gastric glands	31
Leminoprazole	5.3	Dog stomach	32
Omeprazole	2.8	Dog stomach	30
	2.4	Pig stomach (mucosa)	33
	0.5	Rabbit gastric glands	31
Pantoprazole sodium	1.0	Rabbit gastric glands	31
Rabeprazole sodium	0.3	Dog stomach	30
	0.2	Pig stomach (mucosa)	33
Tenatoprazole	7.0	Dog stomach	34
YJA-20379-1	21.0	Pig stomach (mucosa)	35
YJA-20379-8	28.0	Rabbit stomach (mucosa)	36
YJA-20379-5	43.0	Pig stomach	37

metabolizers. In contrast, the (–)-enantiomer showed an AUC_{0-8} that was also higher, but significantly less so (3.1-fold), in poor metabolizers than in extensive metabolizers. Furthermore, concentrations of the corresponding (–)-5-hydroxy metabolite did not show the interindividual variation seen with the (+)-enantiomer (22).

Clinical Studies

Although no clinical studies have yet been published, AstraZeneca's U.S. patent for esomeprazole summarizes the results of an early efficacy study conducted in 38 patients with symptomatic GERD. Most importantly, the study concluded that the interindividual variation in AUC, and hence in antisecretory effect, was significantly lower for the (–)-enantiomer than for the racemate (21).

Preliminary results were presented in October of 1998 from the first clinical efficacy study conducted within an extensive research program evaluating esomeprazole in the short-term treatment of reflux esophagitis. This study demonstrated significant clinical superiority for esomeprazole over omeprazole, with especially favorable results obtained in patients with severe disease (23).

Most recently, during a presentation of the company's R&D pipeline, AstraZeneca reported that, during pivotal studies in reflux esophagitis, healing time was reduced significantly with esomeprazole as compared to omeprazole. The healing rate for esomeprazole after 4 weeks of treatment was comparable to that of omeprazole after 8 weeks. A similarly accelerated healing effect was seen in patients with GERD, together with a sustained duration of effect. Complete sustained freedom from heartburn was achieved in almost half the treatment time required for omeprazole. Furthermore, on-demand treatment with esomeprazole represents a new, efficient, symptom-driven approach to the management of patients with GERD. Satisfactory healing of *H. pylori*-associated duodenal ulcers and eradication of *H. pylori* was also reported following 1 week of triple drug therapy incorporating esomeprazole, without the need for follow-up antisecretory monotherapy (24).

AstraZeneca recently filed the first marketing application for esomeprazole magnesium in Sweden, which will act as rapporteur country in the European Union's mutual recognition procedure. Filing was made in the U.S. in December, and will follow soon in other countries (24-26). The first indications documented for esomeprazole magnesium are the initial treatment for healing of reflux esophagitis; daily long-term treatment for preventing relapse of esophagitis; initial treatment for the resolution of heartburn and other symptoms of GERD; long-term on-demand treatment for controlling recurrent heartburn and other symptoms of GERD; and, in combination with appropriate antibiotics, healing of *H. pylori*-associated duodenal ulcers and *H. pylori* eradication for preventing recurrence of *H. pylori*-associated peptic ulcers (24).

Formulation

A patent has been published claiming a multiple-unit tablet dosage form of omeprazole or esomeprazole and their alkaline salts for oral use in the treatment of gastric acid-related diseases in humans (19). Other patents claiming oral pulsed-release (27) and enteric-coated extended-release (28) dosage forms of esomeprazole magnesium have been published.

Manufacturer

AstraZeneca plc (GB).

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