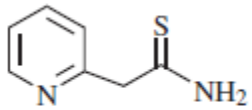
PROTON ACTIVATION

The antiulcer drugs cimetidine and ranitidine lowered gastric acid secretion by antagonizing the H2 histamine receptor. But there is another way of lowering gastric acid secretion i.e. by inhibition of the enzyme *H+, K+- ATPase* (also known as the proton pump), which is responsible for acid secretion by the parietal cell, the cell in the gastric mucosa responsible for acidification of the stomach.

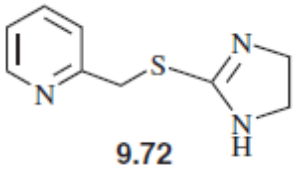
This enzyme catalyzes a one-to-one exchange of proton and potassium ions, there by increasing the acidity in the stomach; Hence, inhibition of this enzyme *(H+, K+- ATPase)* could lead to a new class of antiulcer drugs.

In 1972, the Swedish pharmaceutical company Hässle was searching for a compound that could block gastric acid secretion and discovered a lead compound 9.71 in a random screen.



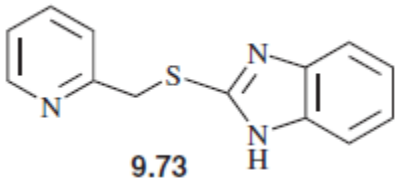
9.71

The liver toxicity caused by this compound was attributed to the thioamide group, so other sulfur-containing analogs were made, and 9.72 emerged with good antisecretory activity.



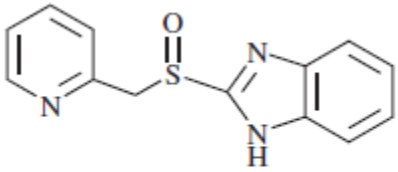
9.72

A series of analogs of 9.72 with different heterocycles led to 9.73 with high activity.



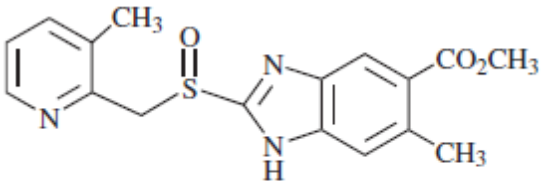
9.73

A metabolism study in dogs demonstrated that the corresponding sulfoxide (9.74, timoprazole) was more potent, but it also blocked the uptake of iodine into the thyroid gland, so it could not be used in humans.



Timoprazole
9.74

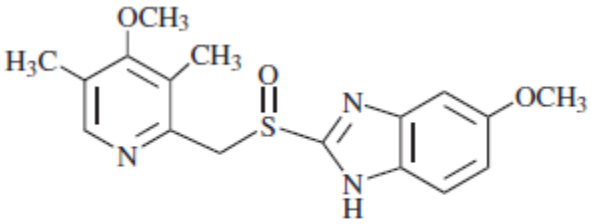
Hence, A variety of analogs of timoprazole were synthesized, and (picoprazole, 9.75) was found to have antisecretory activity without the iodine blockage activity.



Picoprazole
9.75

In 1977, it was found that picoprazole inhibited the enzyme H+,K+-ATPase.

The SAR of analogs of picoprazole showed that electron-donating groups on the pyridine ring, which increased the pKa of the pyridine ring, also increased the potency as an inhibitor of H+,K+-ATPase, and the best analog was **omeprazole**



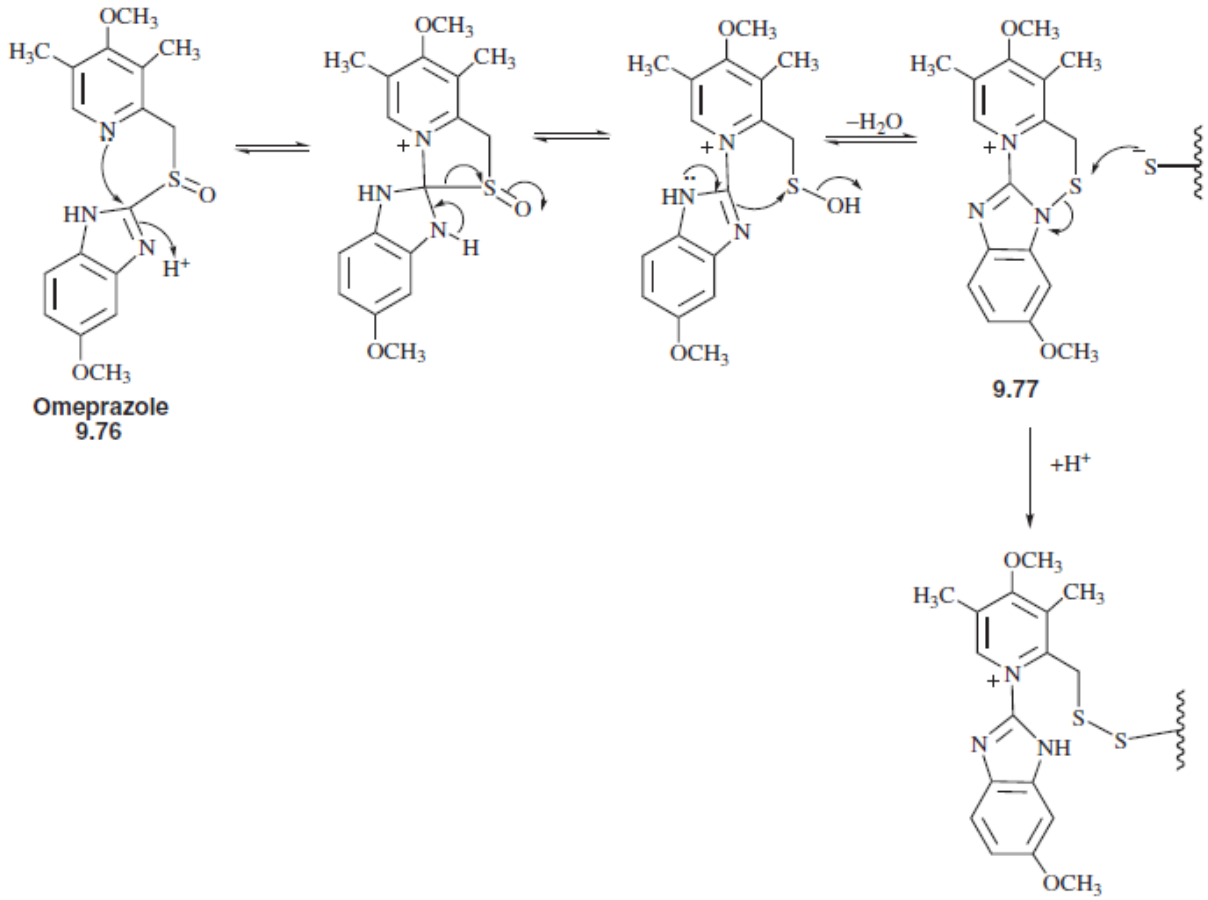
Omeprazole
9.76

Studies with 3H-labeled omeprazole showed that the compound concentrated in the gastric mucosa.

Later it was found to be bound to the enzyme H+,K+-ATPase in parietal cells. Omeprazole is a relatively weak base, having a p*K*a of only about 4.

Therefore, the pyridine ring is not protonated at physiological pH, so it is lipid permeable and able to diffuse into the secretory canaliculus of the parietal cell.

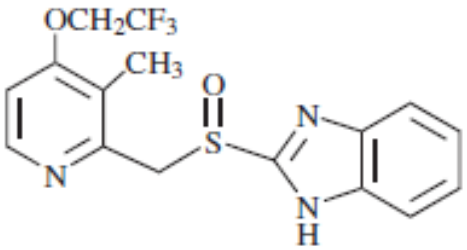
However, the pH in the parietal cell is below 1, so omeprazole becomes protonated *inside* the canaliculus of the cell, where it becomes trapped and then undergoes a proton-initiated transformation to **9.77**, which reacts covalently with a cysteine residue of H+,K+-ATPase (Scheme 9.17).



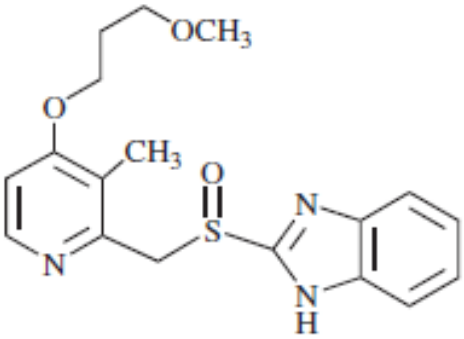
SCHEME 9.17 Mechanism of inactivation of H+,K+-ATPase by omeprazole

Omeprazole also inhibits human carbonic anhydrase isozymes I and II in erythrocytes and isozyme IV selectively in gastric mucosa. Inhibition of carbonic anhydrase has been shown to be another mechanism for lowering gastric acid secretion.

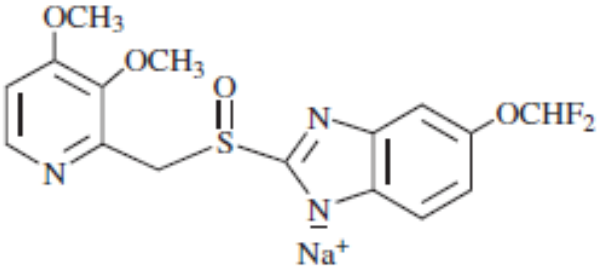
This indicates that omeprazole may have a twofold mechanism of action, which may explain the greater effectiveness of the substituted benzimidazole class of antiulcer drugs compared to other classes of antiulcer drugs. Related analogs that are comparable to omeprazole include lansoprazole (**9.78**, Prevacid), rabeprazole (**9.79**, Aciphex), and pantoprazole sodium (**9.80**, Protonix).



Lansoprazole
9.78



Rabeprazole
9.79



Pantoprazole sodium
9.80