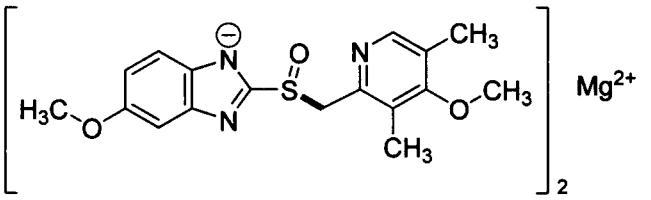
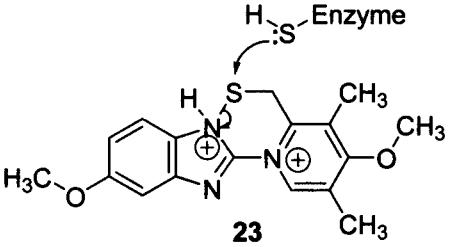


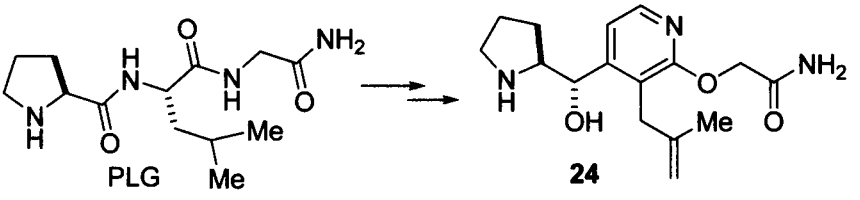
22, esomeprazole

Omeprazole (Prilosec, **21**), the first H^+/K^+-ATPase inhibitor, also known as a proton pump inhibitor (PPI), was marketed as a treatment for gastric ulcers since 1988. It functions by preventing acid production in the mucosa. Omeprazole was the best-selling drug for several years until its patent expiration in 2001, at which time, esomeprazole (Nexium, **22**), the (*S*)-enantiomer of racemic omeprazole (**21**), was launched. The mechanism of action of omeprazole (**21**), the "omeprazole cycle" was investigated.[7,8] Omeprazole (**21**) behaves more like a prodrug because pyridinium sulfydryl **23** is the actual inhibitory species in the "omeprazole cycle."



23

The 2,3,4-trisubstituted pyridine derivative **24** was designed as a potential L-Pro-L-Leu-Gly-NH_2 (PLG) tripeptidomimetic scaffold based on conformational and electrostatic comparison with the natural peptide.[9] Compound **24** exhibits higher potency with enhanced the response of the dopamine agonist *N*-propylapomorpholine (NPA) at human D_2 receptors compared to PLG in a cell-based assay.



PLG **24**

10.1.2 Potential Liabilities for Pyridine-Containing Drugs

2,6-Unsubstituted pyridines bearing sterically unencumbered ring nitrogen are well known to bind tightly via chelation to the heme iron of CYP450