# Proton Pump Inhibitors (PPI)

Pharmaceutical Chemistry IV

PHA 482

# Proton Pump Inhibitors (PPI)

- Inhibition of Histamine receptor does not fully prevent acid secretion because Ach and gastrin also separately promote acid secretion.
- But all these 3 regulators ultimately act on proton pump. The pump can also be independently inhibited which fully inhibits acid secretion.
- Hence, PPI have stronger acid suppression and are thus favored over $H_2$-antagonists.
- PPI are **irreversible antagonists** too, which means once they bind to a pump it cannot regain it's function anymore and is thus destroyed and replaced by a new one which takes time. This makes their effect stronger and longer (drug action persists even after it disappears from blood!)
- Also they have demonstrated antibacterial activity which is an advantage against H.pylori infection.
- Because they prevent acid secretion very strongly than $H_2$ antagonists, they interfere absorption of drugs needing acidic condition like antifungals, Iron salts, Digoxin, Ampicillin.

# How PPI's work?

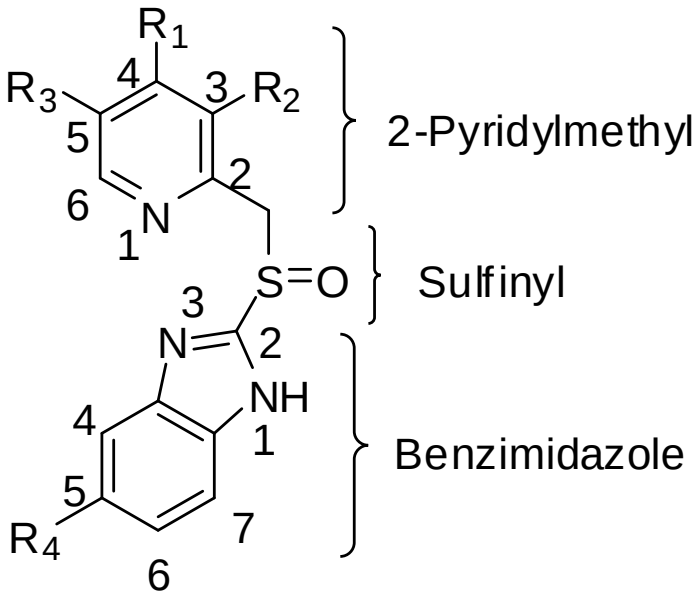
1) Benzimidazole PPI's are prodrug that are converted into sulphenamide within the acidic environment of parietal cells in stomach.

2) The sulfonamide then covalently and irreversibly interacts with sulphahydryl groups in cysteine amino acid of the binding site of the proton pump to create a disulphide bond.

- The disulphide bond between drug and pump is not completely irreversible. There are enzymes capable of reactivating the pump by breaking this disulphide bond. But if this bond is made with a particular cysteine in the binding site, cysteine 822, then is ensures maximum resistance to such reduction thus incurring longer duration of action.

- **They are made into delayed release or enteric coated formulation which prevents their release in the stomach. This is done because if they are activated in the stomach then the charged sulphonamide form won't be easily absorbed.**

# Structure-Activity Relationships




- Pyridine and benzimidazole rings important for the activity, should not be changed.
- Both rings should be connected by position 2.
- $-CH_2-S-$ is not active in vitro but active in vivo conditions; it is suggested that sulfiniyl oxides to sulfoxide moiety in vivo.
- Electron donating substituents on the pyridine ring increase pyridine nitrogen nucleophilicity and enhance activity.

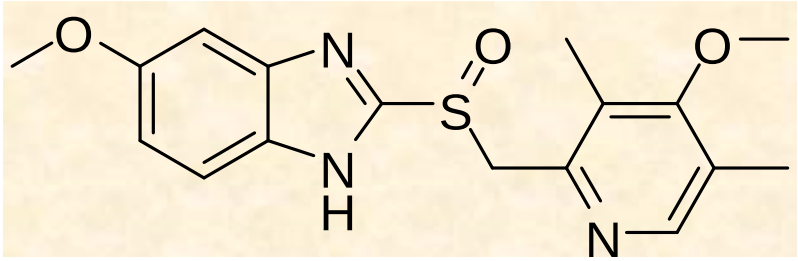
  E.g., $R_1$=OR; $R_2$ and/or $R_3$= $CH_3$
- Electron donating substituents at benzimidazole C5 increase C2 electrophilicity and enhance activity.

  E.g., $R_4$=$OCH_3$
- Electron withdrawing substituents at any substitution site decreases activity ;

  E.g., $R_2$=$OCH_3$ ; $R_4$=$OCHF_2$

# Omeprazole

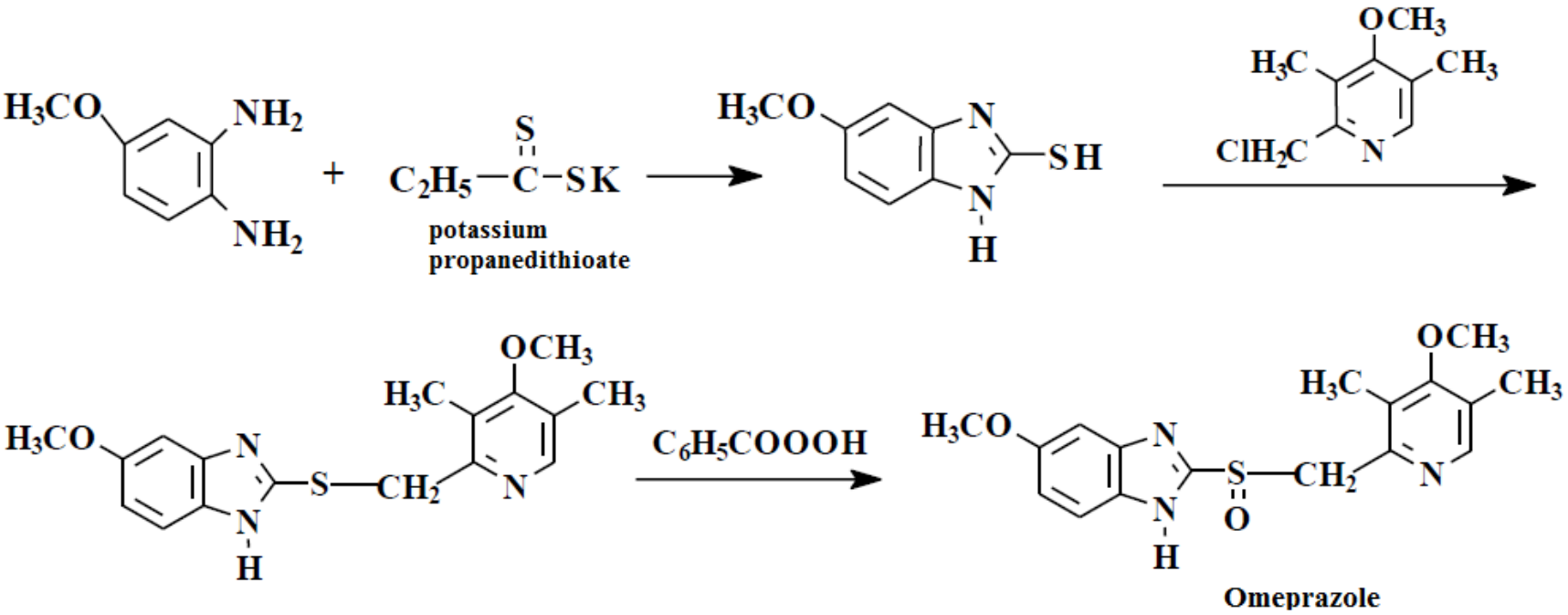
OMEPROL, OMEPRAZİD, LOSEC, GASTROMAX



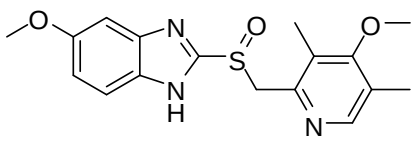

5-methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl)methylsulfinyl]-1*H*-benzimidazole

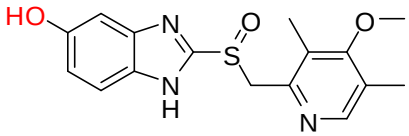
- It is an benzimidazole prodrug proton pump inhibitor
- It's acid inhibition activity is far stronger than $H_2$ antagonists such that it is incompatible with drugs needing acidic condition for absorption
- It duration of action is 24-72 hrs, even after it has cleared from plasma due to its irreversible
- It's **S enantiomer is called esomeprazole and has more** potency and 3 times lower clearance than the **R isomer.** Esomeprazole can be used against NSAIDS induced ulcer.
- Uses;
  - Peptide ulcer, GERD, heart burn, Zollinger-Ellision syndrome

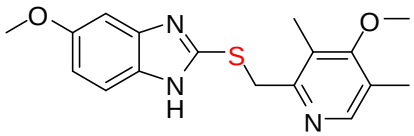
# Synthesis of omeprazole

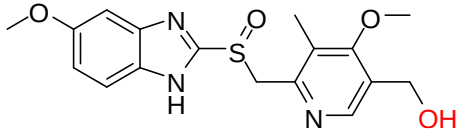


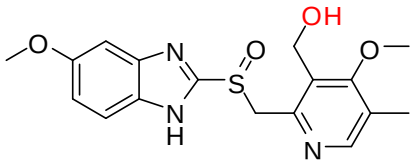
# Metabolism of Omeprazole

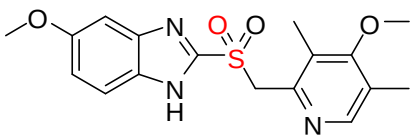


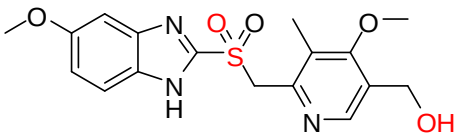




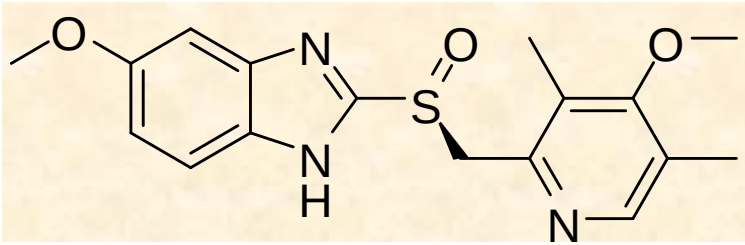








# **Esomeprazol** (NEXIUM)

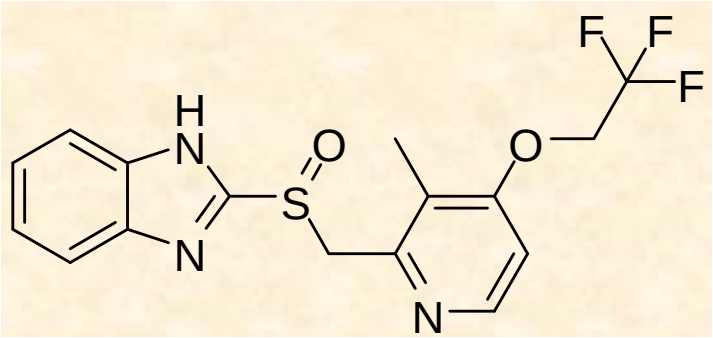



5-methoxy-2-[(*S*)-(4-methoxy-3,5-dimethylpyridin-2-yl)methylsulfinyl]-1*H*-benzimidazole

- **S enantiomer of omeprazole**
- **has more** potency and 3 times lower clearance than the **R isomer.**
- can be used against NSAIDS induced ulcer.

# Lansoprazole

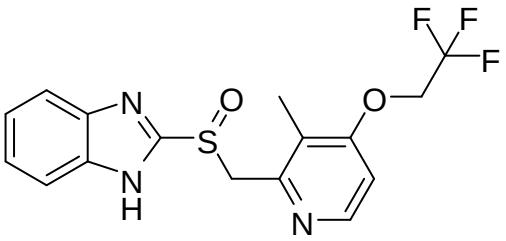
LANSOR, OGASTRO, DEGASTROL, APRAZOL

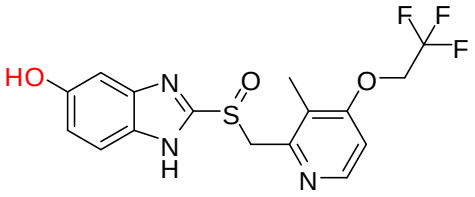


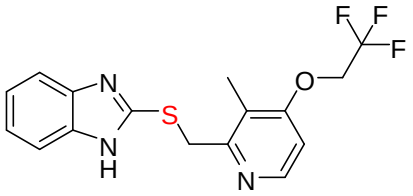

2-[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methylsulfinyl]-1*H*-benzimidazole

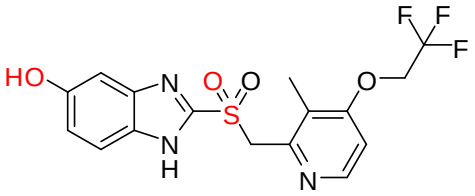
- It is an benzimidazole prodrug proton pump inhibitor.
- Lansoprazole is a racemic mixture of (R)- and (S)-isomers.
- It's acid inhibition activity is far stronger than $H_2$ antagonists such that it is incompatible with drugs needing acidic condition for absorption
- It is highly plasma bound but bioavailability is double than omeprazole
- Uses
  - Peptide ulcer, GERD, heart burn, Zollinger-Ellision syndrome, **NSAIDS induced ulcers**

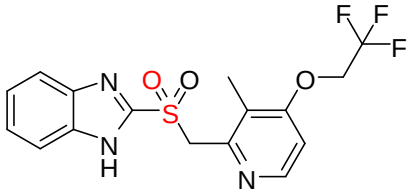
# Metabolism of **Lansoprazole**





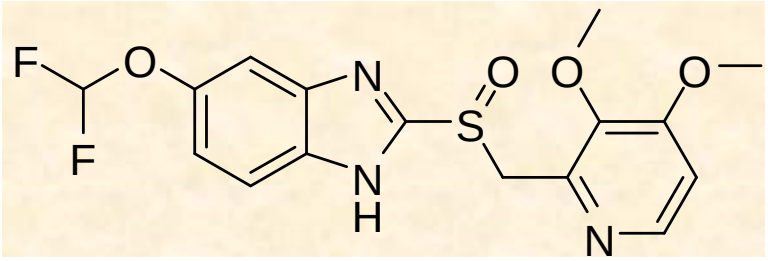






# Pantoprazole

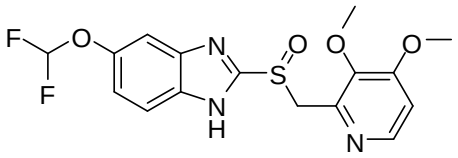
## PANDEV, PANTO, PANTPAS, PROTECH

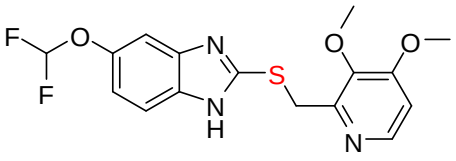


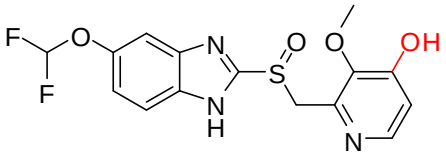

5-(difluoromethoxy)-2-[(3,4-dimethoxypyridin-2-yl)methylsulfinyl]-1*H*-benzimidazole

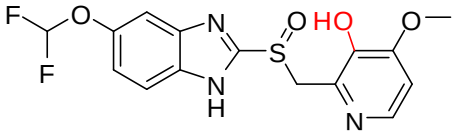
- It is an benzimidazole prodrug proton pump inhibitor
- It's acid inhibition activity is far stronger than H2 antagonists such that it is incompatible with drugs needing acidic condition for absorption
- It is highly plasma bound and has better bioavailability than omeprazole and is also extensively liver metabolized
- Uses
  - Peptide ulcer, GERD, heart burn, Zollinger-Ellision syndrome

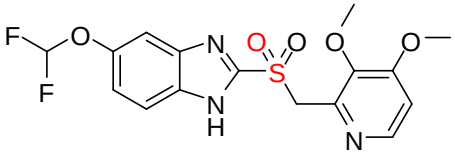
# Metabolism of **Pantoprazole**

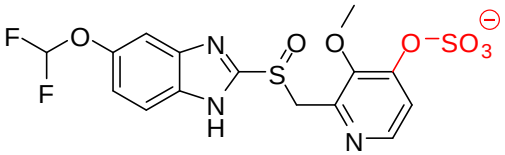






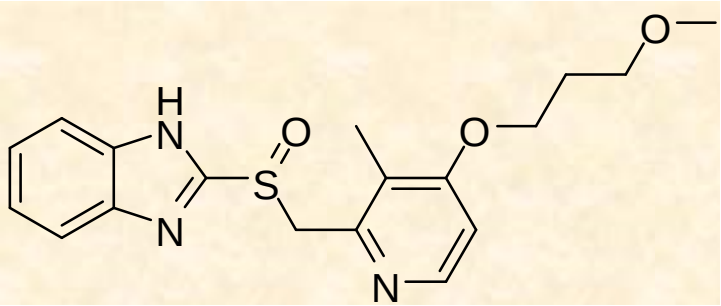






# Rabeprazole

## PARIET, PRABEX, RANEX, RAZOGEN



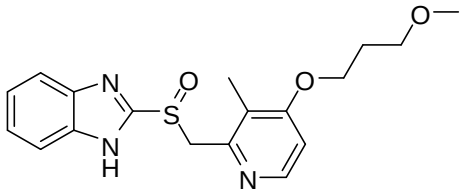

2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methylsulfinyl]-1*H*-benzimidazole

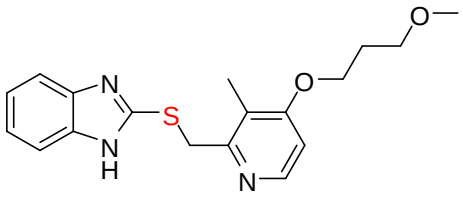
- It is an benzimidazole prodrug proton pump inhibitor
- It's acid inhibition activity is far stronger than H2 antagonists such that it is incompatible with drugs needing acidic condition for absorption
- It is highly plasma bound and has better bioavailability than omeprazole and is also extensively liver metabolized
- Uses
  - Peptide ulcer, GERD, heart burn, Zollinger-Ellision syndrome

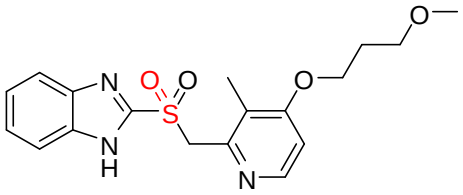
MOA- It activates into sulphamide form in the acid environment and bonds to sulphahydryl groups of cysteine amino acids in the binding site of the proton pump

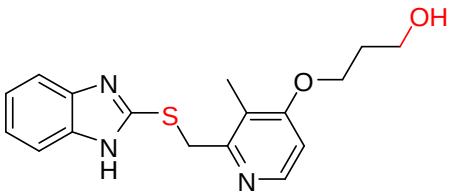
Rabeprazole therapy is associated with a low rate of transient and asymptomatic serum aminotransferase elevations and is a rare cause of clinically apparent liver injury.

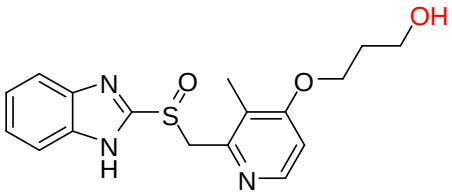
# Metabolism of **Rabeprazole**

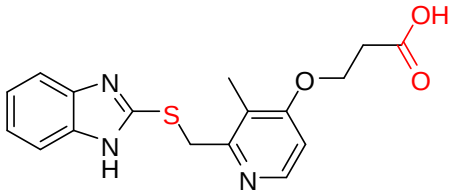






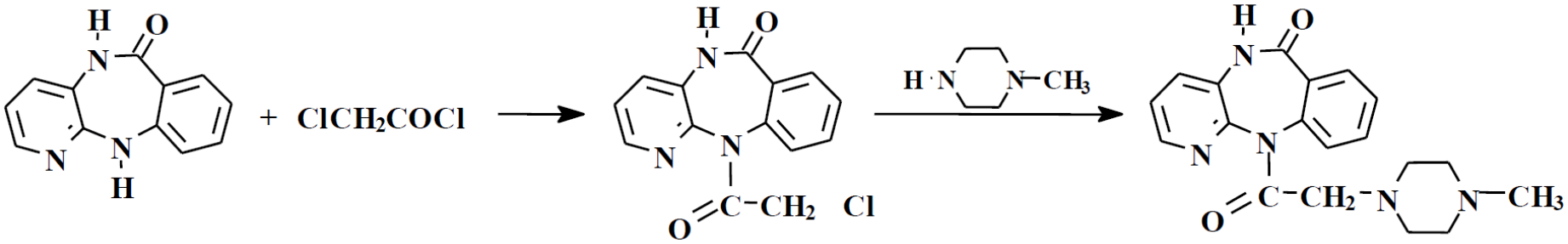






# Anticholinergic Compounds:

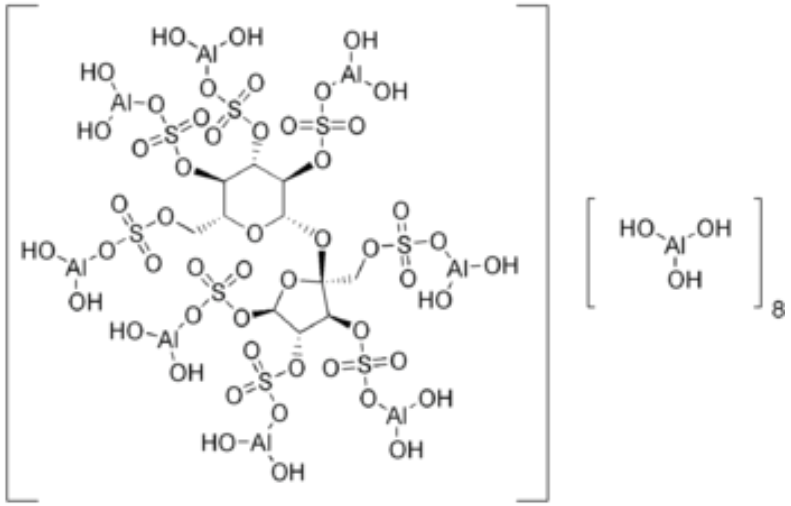
## Pirenzepine

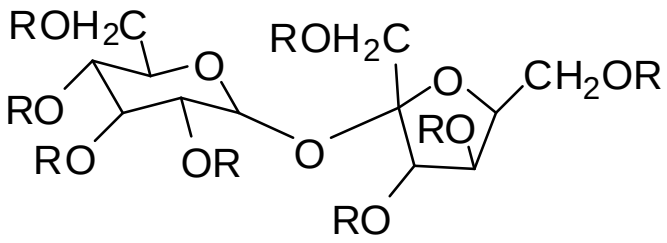



11-[2-(4-methylpiperazin-1-yl)acetyl]-5*H*-pyrido[2,3-b][1,4]benzodiazepin-6-one

It promotes the healing of duodenal ulcers and due to its cytoprotective action is beneficial in the prevention of duodenal ulcer recurrence. It also potentiates the effect of other antiulcer agents such as cimetidine and ranitidine. It is generally well tolerated by patients.

# Ulcer protectives: Sucralfate






R= $SO_3[Al_2(OH)_5]$

## Ulcer protectives:

# Bismuth subcitrate
# (Bismuth tripotassium dicitrate)