Assignment

You should pick one of the top selling small molecule drugs of 2014, as published in the American Chemical Society 'Top 50 Drugs of 2014'.

In your report you should include and discuss the following:

1. **The structure of the drug**
2. **The disease area it has been developed for and its target**
3. **Discuss the physico-chemical properties of the drug: does it conform to the Lipinski 'Rule of 5'?**
4. **The stereochemistry of the drug**
4. **The synthesis of the drug**

Solution:

I picked Nexium (esomeprazole) of the 20th top selling small molecule drugs of 2014, as published in the American Chemical Society 'Top 50 Drugs of 2014' (http://cen.acs.org/content/dam/cen/supplements/CEN-supplement092014.pdf).

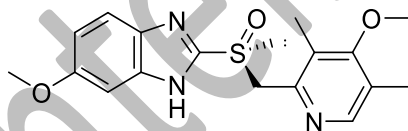**Nexium (esomeprazole)**

1. The structure of the Nexium

Figure 1: Chemical structure of Esomeprazole

Esomeprazole is a proton pump inhibitor and a single enantiomer of omeprazole. Proton pump inhibitor are very useful in different indications and are widely prescribed drugs for Gastroesophageal Reflux Disease (GERD) and Erosive Esophagitis (EE). It inhibits the proton pump and reduces the gastric acid secretion from parietal cells [1].

Esomeprazole is having *S*- stereochemistry at the sulphur atom in form of sulfoxide functional group having lone pair of electrons [2]. It rotates plane polarized light to left and regarded with negative sign and called as laevorotatory. Chemically its name will be 6-methoxy-2-[(*S*)-(4-methoxy-3,5-dimethylpyridin-2-yl)methylsulfinyl]-1H-benzimidazole (Figure 1). It is having methoxy substitution on benzimidazole ring to one side of sulfoxide and other side with substitutes pyridine ring. The heteroaryl and substituted imidazole interact as hydrophobic group and steric interactions involve via alkyl substitutions.

Omeprazole drug is as a racemic mixture and used for the similar indications like gastroesophageal reflux disease (GERD), Zollinger–Ellison syndrome and peptic ulcer disease [3]. The development of

proton pump inhibitors was beginning in 1970 by Astra (AstraZeneca) and first proton pump inhibitor i.e., Omeprazole was discovered in 1979 and was launched in 1988 [4]. This is found better in controlling the gastric acid secretion than the H2 receptor antagonist and became blockbuster drug as highest selling drug in 2004. When the patent of omeprazole was near to expire than its single enantiomer i.e., esomeprazole was patented (1993) and launched by AstraZeneca for the treatment of GERD in 2001 as a one of the chiral switches branded as "Nexium" [5,6]. It is known as "purple pill" and one of the most prescribed medicine in USA and available as OTC (Over the counter) from 2014. Now in 2020 its generic drug is approved by FDA with respect of ANDA filed by Dr. Reddy Lab India [7].

2. The disease area it has been developed for and its target

Esomeprazole is a proton pump inhibitor which block the gastric acid secretion from parietal cells and useful in the treatment of gastroesophageal reflux disease (GERD), Zollinger–Ellison syndrome and peptic ulcer disease. It is a *S*- enantiomer and proven to be good than its racemate omeprazole, because of better bioavailability than *R*-enantiomer. Esomeprazole covalently binds with cysteine amino acid residues at the α subunit of H+/K+ ATPase enzyme via disulfide brond [1].

Thereby it inhibits the H+/K+ ATPase pump which in turn inhibits the gastric acid secretion or formation of hydrochloric acid in parietal cells.

An initial development was beginning with CMN131 as antisecretory agent by Servier, however it showed acute toxicity which may be due to presence of thioamide group. Later with addition of benzimidazole heterocycle to H124/126, Timoprazole, Picoprazole and omeprazole (Figure 2) [8].
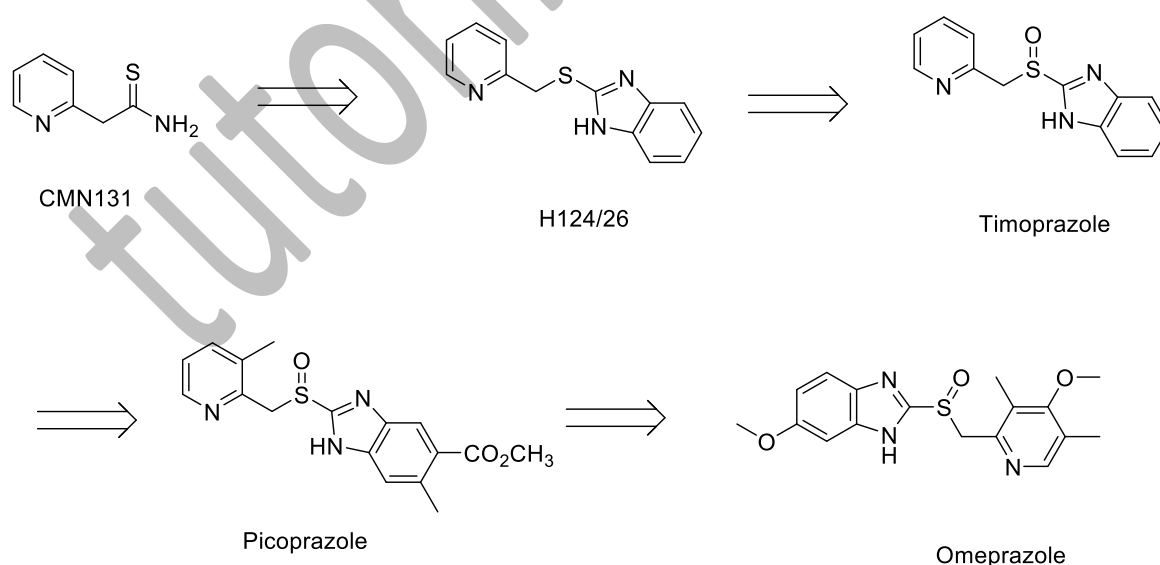

Figure 2: Development of proton pump inhibitors

As discussed, earlier Esomepraozole was patented as S-enantiomer of Omeprazole and marketed as Nexium. Esomprazole available in different salt form and among them mostly are sodium or magnesium salt.

It is white crystalline powder and slightly soluble in water. Melting point reported for it to be 155 °C. It is stable in alkaline conditions while degrades in acidic conditions. Its pKa is - 4.78 [9].

Lipinski 'Rule of 5' also known as Pfizer's rule presenting the physicochemical properties of drug like molecule such as [10]:

1. Molecular weight less than or equal to 500
2. Number of hydrogen bond donor less than or equal to 5
3. Number of hydrogen bond acceptor less than or equal to 10
4. Partition coefficient or CLogP less than or equal to 5

HA = hydrogen bond acceptor
HD = hydrogen bond donor
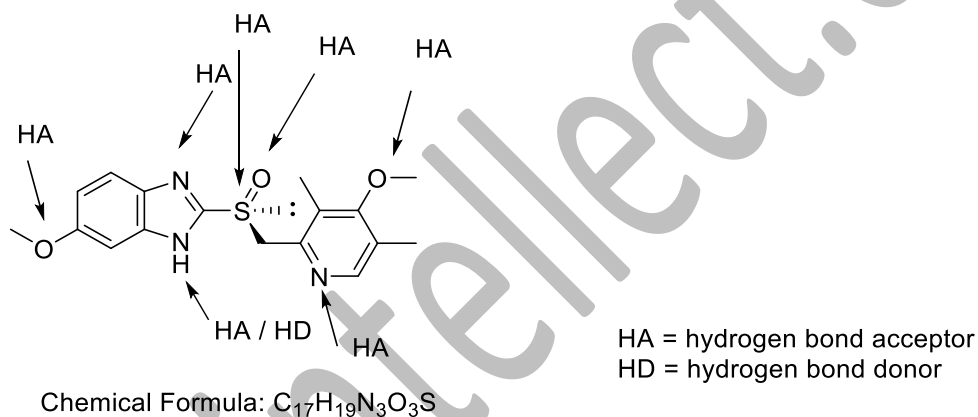
Chemical Formula: $C_{17}H_{19}N_3O_3S$

Molecular Weight: 345.42

Figure 3: Possible hydrogen bond and acceptor in Esomeprazole

1. Molecular weight = 345.42 (its less than 500)
2. Number of hydrogen bond donor = 1
3. Number of hydrogen bond acceptor = 7
4. Partition coefficient or CLogP = 1.66

The above all satisfies the Lipinski's rule of 5 and do not shao any deviation. Therefore, it can be said to have drug likeliness.

3. The stereochemistry of the drug:

Esomeprazole is a *S*-enantiomer of Omeprazole. Omeprazole is having a chiral center at sulphur atom and thus presenting two enantiomers as shown below in figure 4 [1]. The *S*-enantiomer is found more potent than its counterpart *R*-enantiomer of Omeprazole. It is suggested that *S*-enantiomer has more bioavailability.
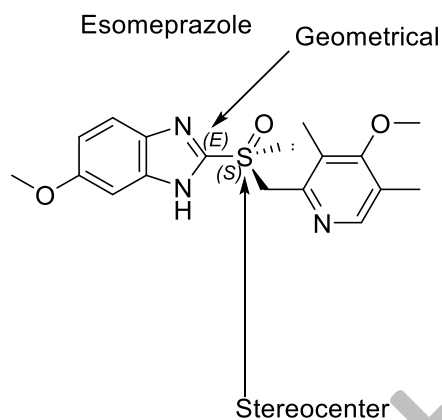

Figure 4: Stereocenter in Esomeprazole

4. The synthesis of the drug:

AstraZeneca developed the industrial synthesis of Esomeprazole. The synthesis of esomeprazole (developed by AstraZeneca) begins with pyrmethyl alcohol which is chlorinated via displacement of hydroxyl group using thionyl chloride (SOCl$_2$) in toluene. This reaction is a SN2 type of reaction. Pyrmethyl chloride is obtained as hydrochloride salt with pyridine ring which is neutralized using aqueous solution of sodium hydroxide by dissolving it in methanol and reacted with metmercazole via SN2 reaction again at chloride with sulfide functional group producing pyrmetazole in good yields [11].
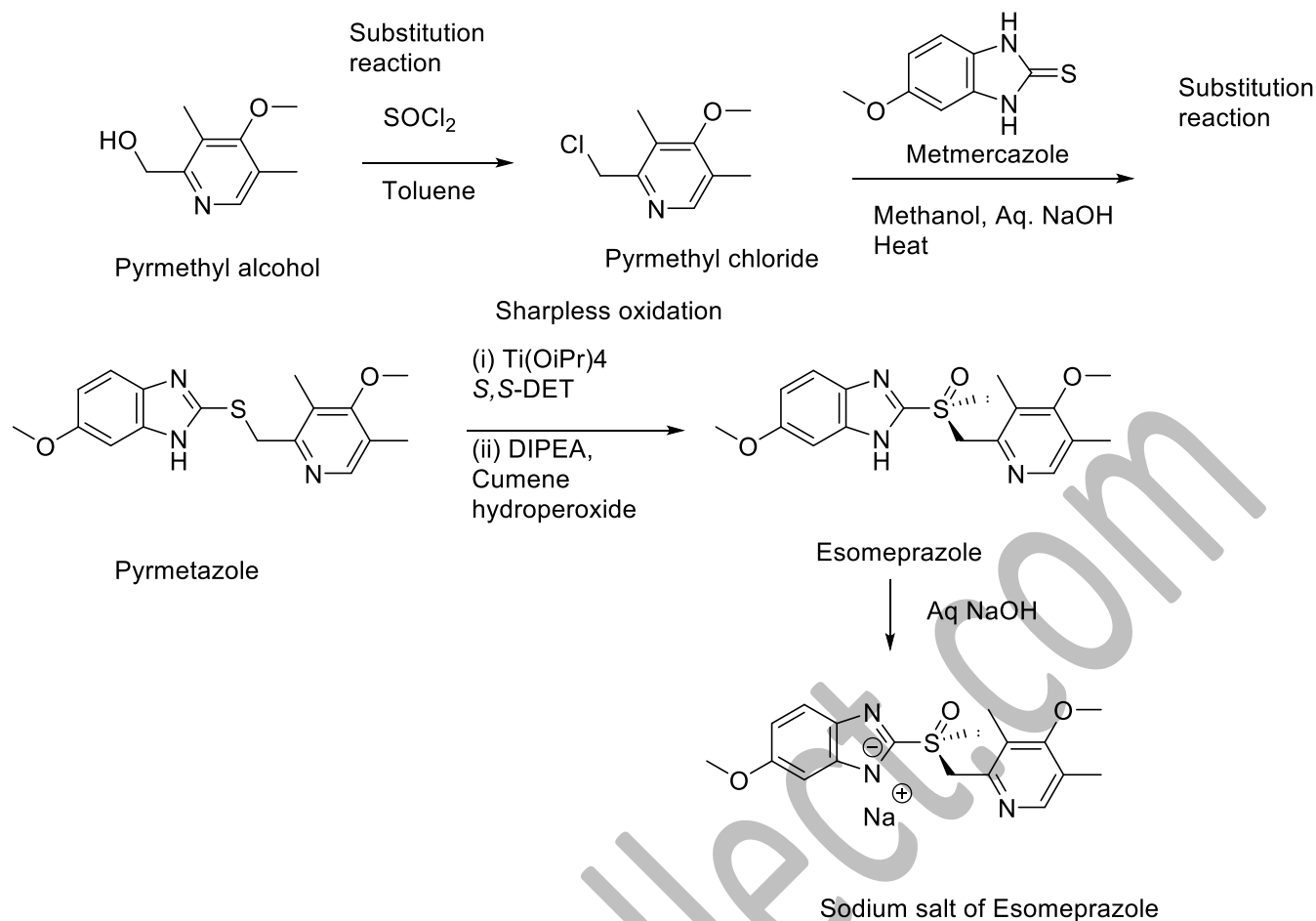
Figure 5: Synthesis of Esomeprazole (AstraZeneca).

Further Esomeprazole was prepared using the reaction conditions similar to Sharpless asymmetric epoxidation. Pyrmetazole is mixed with titanium tetraisopropoxide [Ti(O^{i}Pr)$_4$], and (*S,S*)-diethyl tartrate (*S,S*-DET) and later with diisopropyl ethyl amine (DIPEA as base) and cumene hydroperoxide (an oxidant). At the end it was transformed into sodium slat as white precipitate with the treatment of sodium hydroxide.

References:

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