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REVIEW article

Chemistry, pharmacology, and chiral separation of proton pump inhibitor drugs

Khadidja Addadi [*], **Nasser Belboukhari**, and **Khaled Sekkoum**

Bioactive Molecules and Chiral Separation Laboratory, Faculty of Exact Sciences,
Tahri Mohammed's University, Istiklal street, PO 417, Bechar 08000, Algeria
[*] Author to whom correspondence should be addressed

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Abstract: A chiral sulfoxide is an important group in many bioactive molecules, and its absolute configuration often has substantial effects on its biological activity. Compounds that contain tri-coordinated sulfur atoms in a pyramidal structure can exist in different optically active forms. Omeprazole is a highly successful sulfoxide drug and the first registered substance in the proton pump inhibitor class, whose chirality may significantly impact its interaction with biological targets. The R-enantiomer of omeprazole is rapidly metabolized. In contrast, the clearance of the S-enantiomer occurs at a much slower rate. Viewing this, further attention should be paid to the pharmacological and toxicological studies of individual enantiomers of chiral drugs, and thus led to an exigent demand for enantioseparation.

Introduction

Chiral sulfoxides are in extremely high demand in nearly every sector of the chemical industry concerned with the design and development of new synthetic reagents, drugs, and functional materials [1]. The sulfoxide functional group is found in a large number of molecules of biological interest, many of which have application as pharmaceuticals for the treatment of a wide range of conditions [2]. Their chirality may play an important role in the interaction with biological targets and should be taken into consideration in drug design [3], Drug enantiomers often have different physiological actions. While much of this work centers on carbon chirality, sulfur has also been of concern. Many drugs and drug candidates containing sulfur have been synthesized or obtained as natural products [4]. This chapter centers around chiral sulfoxide drugs, covering their pharmacology, synthesis, and chiral separation.

Sulfoxides: Chiral sulfoxides are used as a precursor of new chiral compounds, with interesting therapeutic properties. Sulfoxides constitute an important class of organosulfur compounds [3]. Such compounds feature a sulfinyl (S=O) functional group attached to two carbon atoms [5]. Though this structural motif is typically represented in Lewis structures as analogous to a carbonyl moiety, the sulfur atom of the sulfoxide is in fact a stereogenic centre when R1≠R2 (**Figure 1**).

Figure 1: Lewis structures of sulfoxide group

The oxygen and sulfur do not share a typical p-orbital pi bond which would enforce a planar conformation, but rather the oxygen donates electron density from a lone pair into a d-orbital of sulphur [6]. Chirality at pyramidal centers can be specified as (*R*) or (*S*) by the usual Cahn-Ingold-Prelog (CIP) system. To do so, valence bond structures are defined. If these structures are not self-evident, four conventions are used to define an appropriate valence-bond approximation for unsaturated compounds. Convention (b) states that contributions by d orbitals to bonds of quadriligant atoms are neglected. The *absent* ligand, normally alone electron pair, is assigned an atomic number of zero and in determining the sequence order of precedence, has the lowest priority. Thus, for methyl propyl sulfoxide, the priority sequence is $O > C_3H_7 > CH_3$. lone electron pair; the (2) enantiomer has the (*R*) configuration 1a-1c, **Figure 2**, [4].

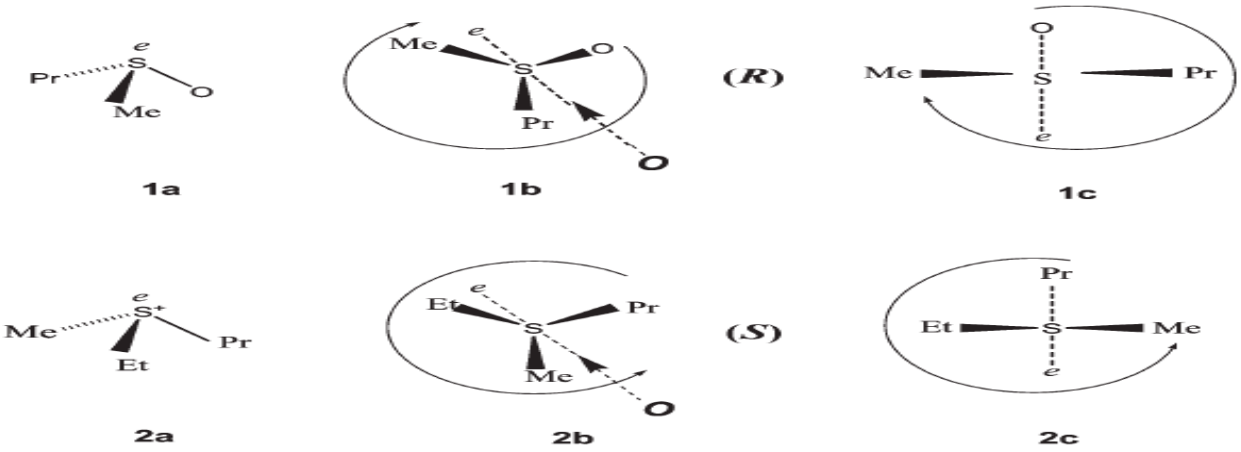


Figure 2: Configurational assignments for sulfoxides and sulfonium salts

In this and subsequent figures, ***e*** indicates a lone electron pair
In 1b and 2b, the group of lowest priority, ***e***, is positioned away from the observer, ***O***

Natural sulfoxide: Methionine S-oxide and biotin S-oxide: Sulfoxides contribute to unique bioactive (e.g., antioxidative, antimicrobial) properties of species from the *Allium* genus, particularly garlic and onion, which are long known and used in traditional medicine. Isolation, identification of these compounds, and revealing the mechanism of their action is of importance for the future design of pharmaceuticals **Figure 3**, [3].

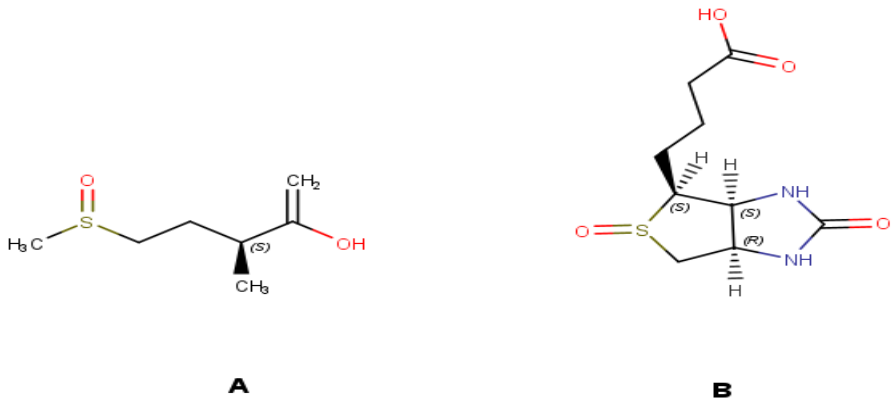


Figure 3: Structure of **A**: Methionine S-oxide and B: biotin S-oxide

Sulforaphane: Sulforaphane, a compound within the isothiocyanate group of organosulfur compounds, is a phytochemical commonly found in cruciferous vegetables such as broccoli, brussels sprouts and cabbage [7, 9]. Sulforaphane (1-isothiocyanate-4-methyl-sulfinylbutane), **Figure 4** is a redox-active natural molecule isolated for the first time in 1958 from the leaves of hoary cress (*Lepidium draba*). Afterwards, in 1992, it was found in plants from the Brassicaceae family [8].

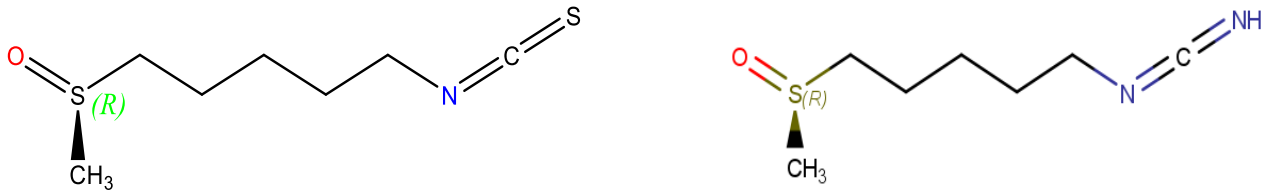


Figure 4: Structure of sulforaphane

Sulforaphane, which possesses antiproliferative, anti-inflammatory, anti-oxidant, and anti-cancer activities [9]. This compound has regulatory effects on the tumor cell cycle, apoptosis, and angiogenesis by modulation of the related signaling pathways and genes [3].

α-*amanitin:* Amanitins are members of the amatoxin family, toxic bicyclic octapeptides with molecular weights of about 900 g/mol, contained in certain fungi. Currently, three major families of fungi are known to contain these toxins: the amanita (*Amanita sp.*), the galerina (*Galerina* sp.), and the lepiota (*Lepiota*sp) [10]. α-amanitin **(Figure 5**) is a representative toxin found in the *Amanita* genus of mushrooms [11], and the consumption of mushrooms containing α-amanitincan lead to severe liver damage [12]. Due to its high selective inhibition of RNA polymerase II which is directly linked to its high toxicity, particularly to hepatocytes, α-amanitin received increased attention as a toxin-component of antibody drug conjugates in cancer research [13, 14].

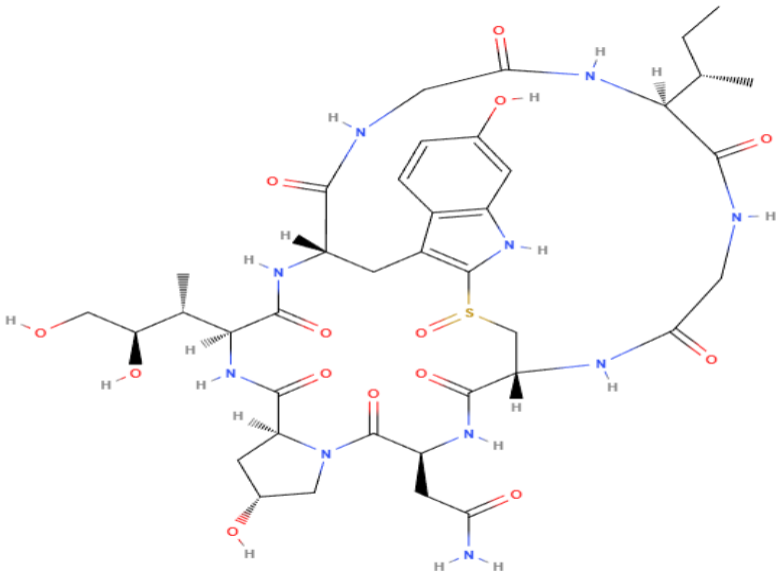


Figure 5: Structure of $\boldsymbol{\alpha}$-amanitin

Synthetised sulfoxide: Dimethylsulfoxide (DMSO) was first discovered in the 19th century as a byproduct at a chemical factory in Germany that was producing paper from wood pulp. In 1867, Russian chemist Alexander Saytzeff described the solvent characteristics of DMSO. Although it remained inconspicuous from the 1940s to 1950s, industrial researchers later uncovered that DMSO, when used as a solvent, could reinforce the permeability of herbicides, bactericides, antibiotics, and phytohormones, thereby boosting the growth of plants by 15.0%-20.0%. These findings demonstrated the efficacy of DMSO for food production and plant growth [15]. DMSO is an aprotic, amphiphilic solvent commonly used in biological studies to dissolve compounds with low solubility in water for in *vitro* and in *vivo* studies; it also serves as a cryopreservation agent [3]. DMSO has been used in several human therapeutic situations. In 1978, it received approval by the United States Food and Drug Administration (FDA) for use in the treatment of interstitial cystitis, by intravesical

instillation. Its effects do not seem to be related to a detectable histamine release from mast cells. It has been used successfully in the treatment of dermatological, urinary, pulmonary, rheumatic, and renal manifestations of amyloidosis. Basically, through its anti-inflammatory and reactive oxygen species scavenger actions, its use has been proposed in several gastrointestinal diseases [16, 17]. An improvement in the diffusion of a metal complex by coordination of a DMSO ligand was noted (**Figure 6**). In a search for a more selective alternative to cisplatin and its analogs, high hopes were put on NAMI-A, a ruthenium (III) complex [ImH] [trans-RuCl4(DMSO) (Im)] (Im=imidazole) bearing S-coordinated dimethylsulfoxide [3].

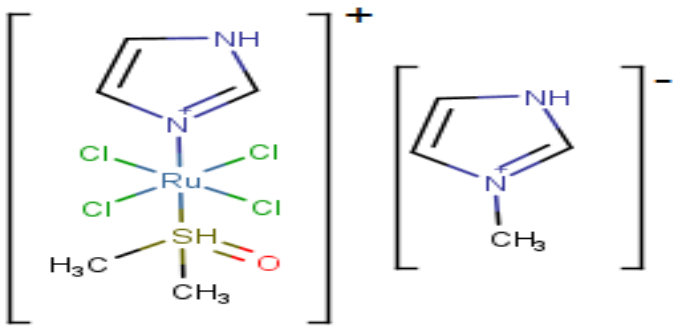


Figure 6: Complexes containing dimethylsulfoxide ligand(s) NAMI-A

Modafinil: **Figure 7**, Modafinil (*d, l*-2- [(diphenyl methyl) sulfinyl] acetamide; is a novel wake promoting agent is for oral administration [18], first marketed in France in the early 1990s, as a treatment for the excessive somnolence as a feature of narcolepsy. In 2008 approved by the United States FDA as a schedule IV agent to treat excessive daytime sleepiness in narcolepsy, shift work sleep disorder, and obstructive sleep apnea/hypopnea syndrome [19].

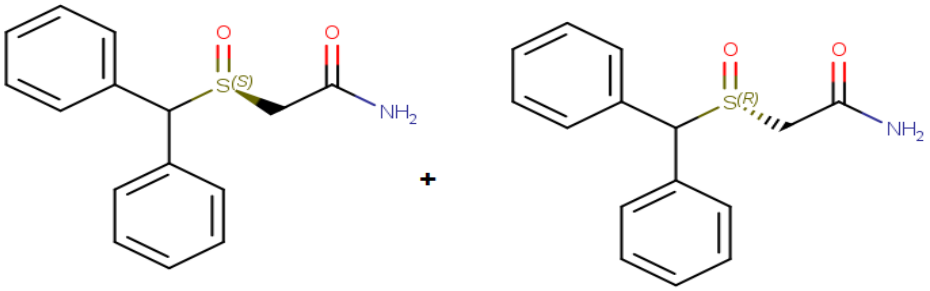


Figure 7: Structure of modafinil

It is a white to off-white crystalline solid that is practically insoluble in water and cyclohexane and slightly soluble in methanol and acetone. The molecular formula is $C_{15}H_{15}NO_2S$ and the molecular weight is 273.4 [18]. Although typically prescribed in racemic form, both enantiomers are biologically active. However, the isomers exhibit different pharmacokinetic profiles. The *S*-isomer has a relatively short terminal elimination half-life of 4-5 hrs, compared with that of the *R*-isomer, which is approximately 3-4 times longer (~15 hours). The (*S*)-isomer is eliminated from the body at a rate three times faster than that of the *R*-isomer [20, 21].

Sulindac: **Figure 8**, Sulindac{(Z)-5-fluoro-2-methyl-I-[4-(methylsulphinyl) phenyl] methylene]-1H-indene-3-acetic acid; is a nonsteroidal anti-inflammatory drug (NSAID) structurally similar to indomethacin [22]. The anti-inflammatory drug sulindac is employed in the treatment of arthritic conditions and has, over the past ten years, gained interest as an anti-cancer treatment. Four neurokinin antagonists have been investigated for their potential for use in treatments against depression, urinary incontinence and asthma [2].

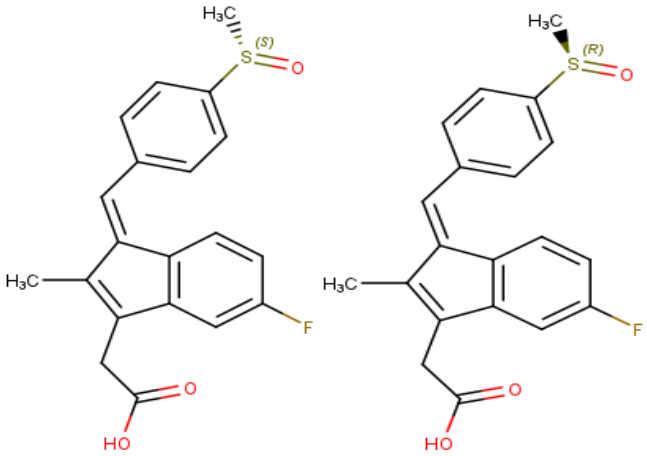


Figure 8: Structure of sulindac

Cenicriviroc: (S)-8-[4-[2-(butoxy) ethoxy] phenyl]-1-isobutyl-N-[4-[[(1-propyl-1H-imidazol-5-yl) methyl] sulfinyl] phenyl]-1,2,3,4-tetrahydro-1-benzazocine-5-carboxamide methane sulfonate (**Figure 9**) [23].

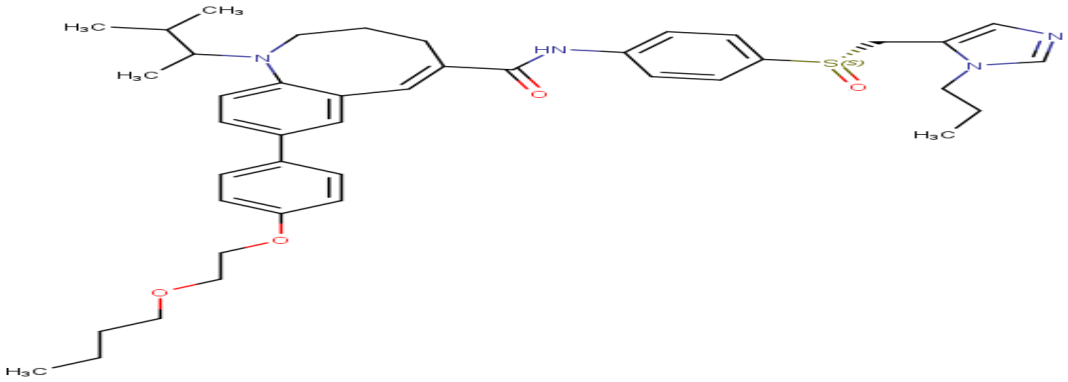


Figure 9: Structure of cenicriviroc

Cenicriviroc is a drug candidate developed by Takeda Pharmaceutical Company as an orally bioavailable inhibitor of two chemokine receptors CCR2 and CCR5 with potent anti-HIV-1 activity with a favorable pharmacokinetic profile in humans. The ability to inhibit macrophages in the peripheral fat tissue led to its evaluation for the treatment of nonalcoholic steatohepatitis (ASH), a progressive form of non-alcoholic fatty liver disease (NAFLD) [3].

Adezmapimod: It is a tri-substituted imidazole based p38 MAP kinase inhibitor in the pyridinyl imidazoleclass that is widely used in the literature as an ATP-competitive ref [24], and it is an anti-inflammatory drug [25]. In the 1990s, a series of pyridylimidazoles were developed at SmithKline Beecham as kinase inhibitors, and a sulfoxide derivative (**Figure 10**) was identified as a potent inhibitor of stress-activated p38 mitogen-activated protein kinase (MAPK) [3].

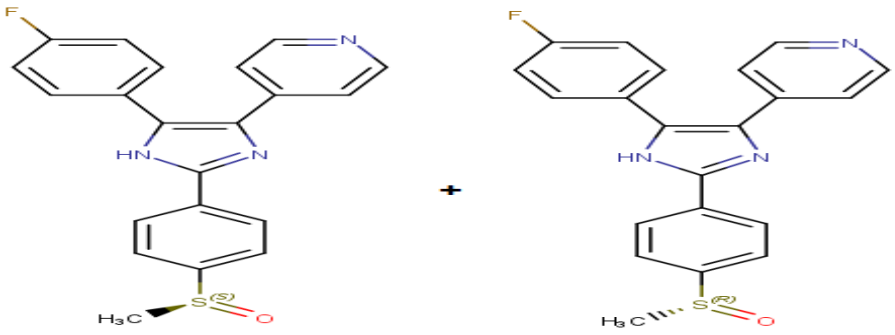


Figure 10: Structure of Adezmapimod

Sulfoxides as proton pump inhibitors: Sulfoxides bearing bezimidazole and pyridine moieties have evolved as first-line treatment of peptic ulcers and gastroesophageal reflux disease. We will thoroughly explore this specific category of medications in the next section.

Proton pump inhibitor drugs; Synthesis and pharmacology, a very successful sulfoxide drug is the proton pump inhibitor, omeprazole. Investigated in the late 1970s, it was marketed as Losec1 (Europe, 1988) and as prilosec1 (USA, 1990). Sales quickly approached US $6 billion per annum, and Prilosec1 is now available over the counter in the USA. Omeprazole, marketed as a racemate, is a prodrug, the active agent being an achiral sulfenamide formed by biotransformation [4]. The first representatives of this group, timoprazole, picoprazole, and omeprazole were developed in the late 1970s, and the latter was finally selected, followed by lansoprazole, pantoprazole, and rabeprazole, **Figure 11**, [3].

Compounds which contain tricoordinated sulfur atoms in a pyramidal structure can exist in different optically active form, omeprazole, 5-methoxy-2-(((4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl) sulfinyl)-1Hbenzimidazole [26], is a well-known gastric proton pump inhibitor (PPI) used in the treatment of gastric-acid related diseases [27]. Omeprazole was first approved as a racemic mixture, but the (*S*)-enantiomer was later introduced to the market. The major difference is that (*S*)-omeprazole is metabolized more slowly and reproducibly than the (*R*)-omeprazole and racemic omeprazole. Ilaprazole is a new PPI, designed for the treatment of gastric ulcers developed by Il-Yang Pharmaceutical [28]. Pantoprazole, (5-(difluoromethoxy) -2-[(3,4-dimethoxy-2-pyridyl) methylsulfinyl]-1H-benzimidazole) (**Scheme 1**) [29], and Lansoprazole (2- [[3 methyl-4-(2,2,2-trifluoroethoxy) pyridin2-yl] methylsulfinyl]-1H benzimidazole) [30].

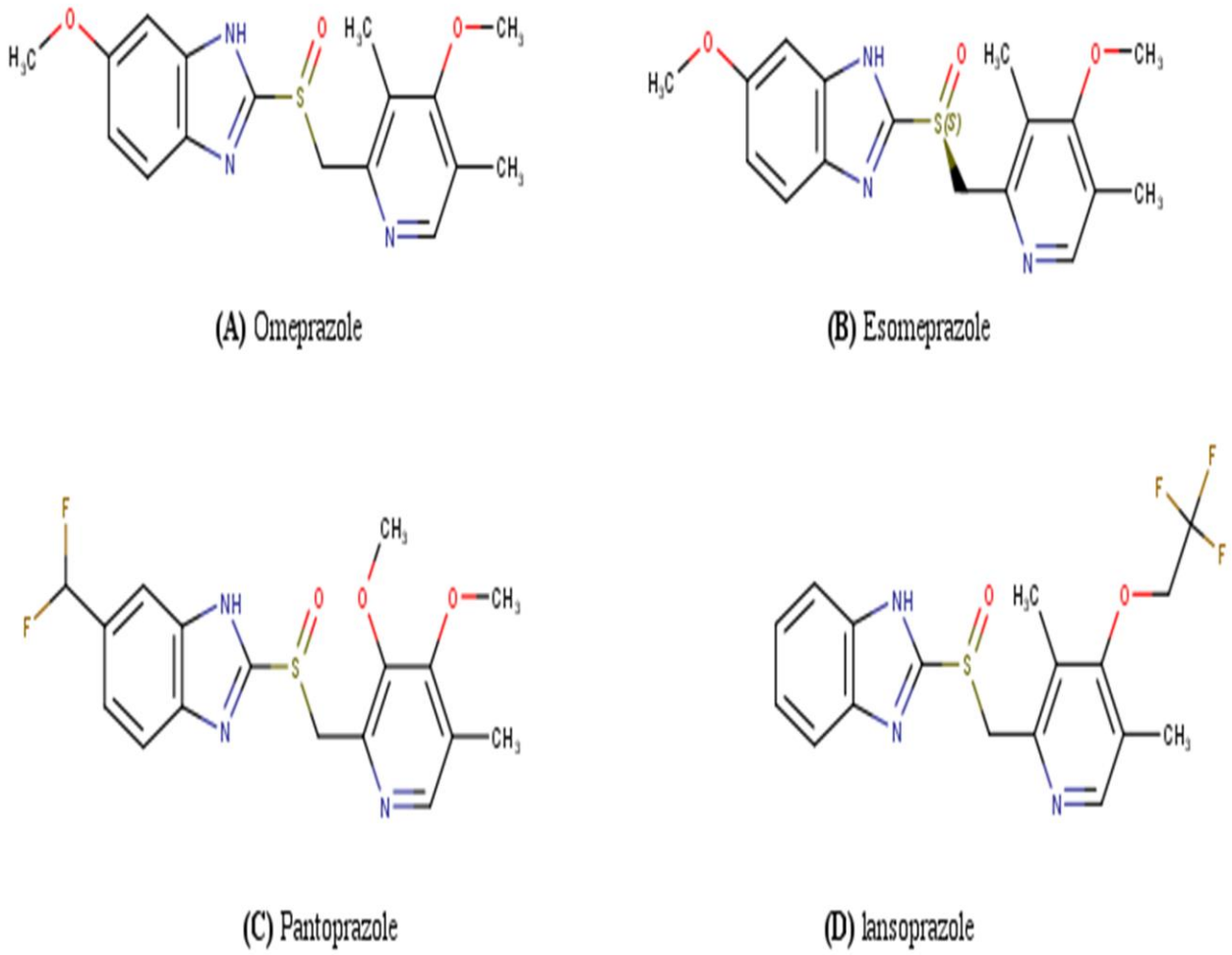
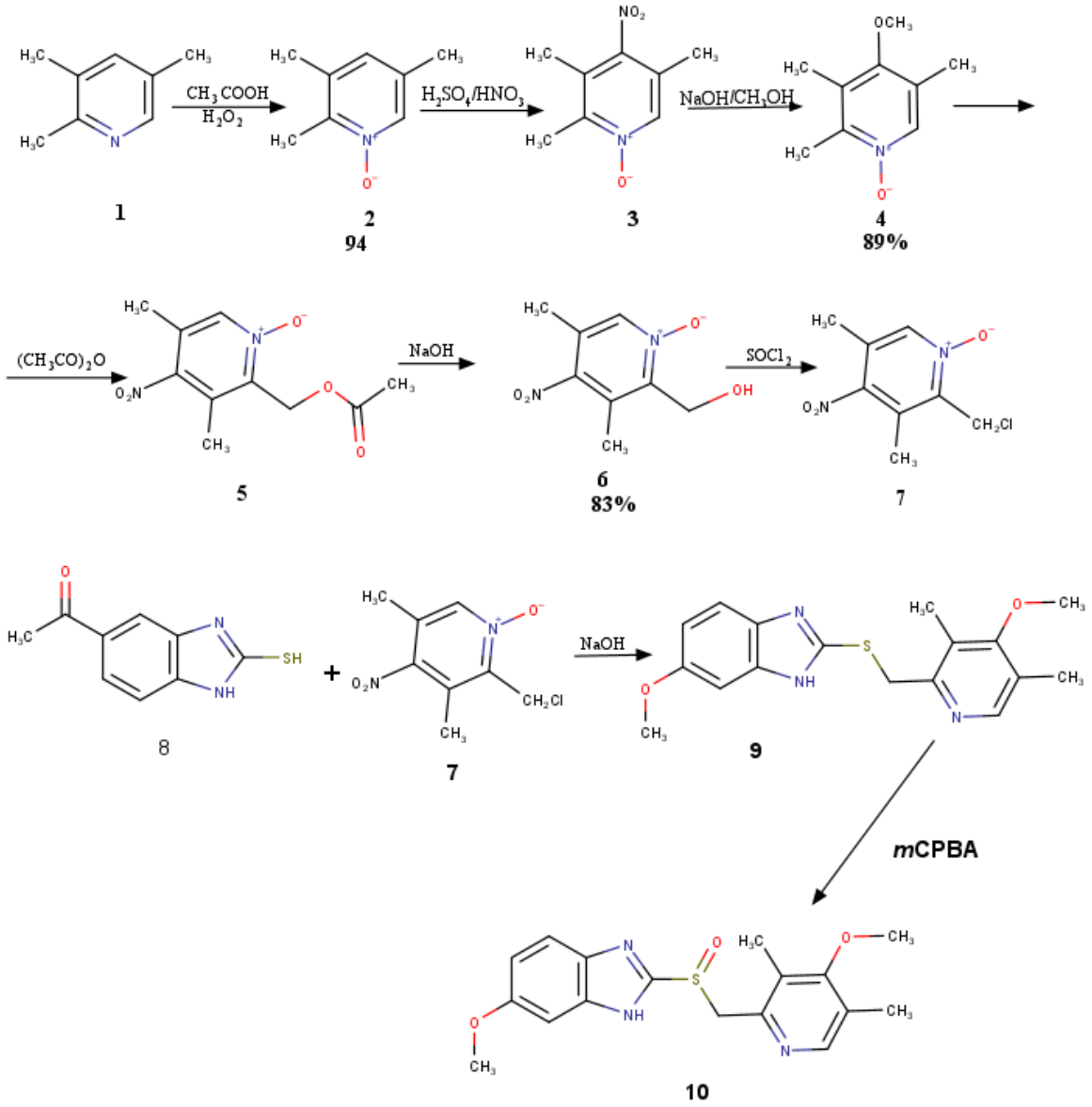


Figure 11: Chemical structures of drugs IPP (**A**) omeprazole (**B**)esomeprazole (**C**) pantoprazole and (**D**) lansoprazole

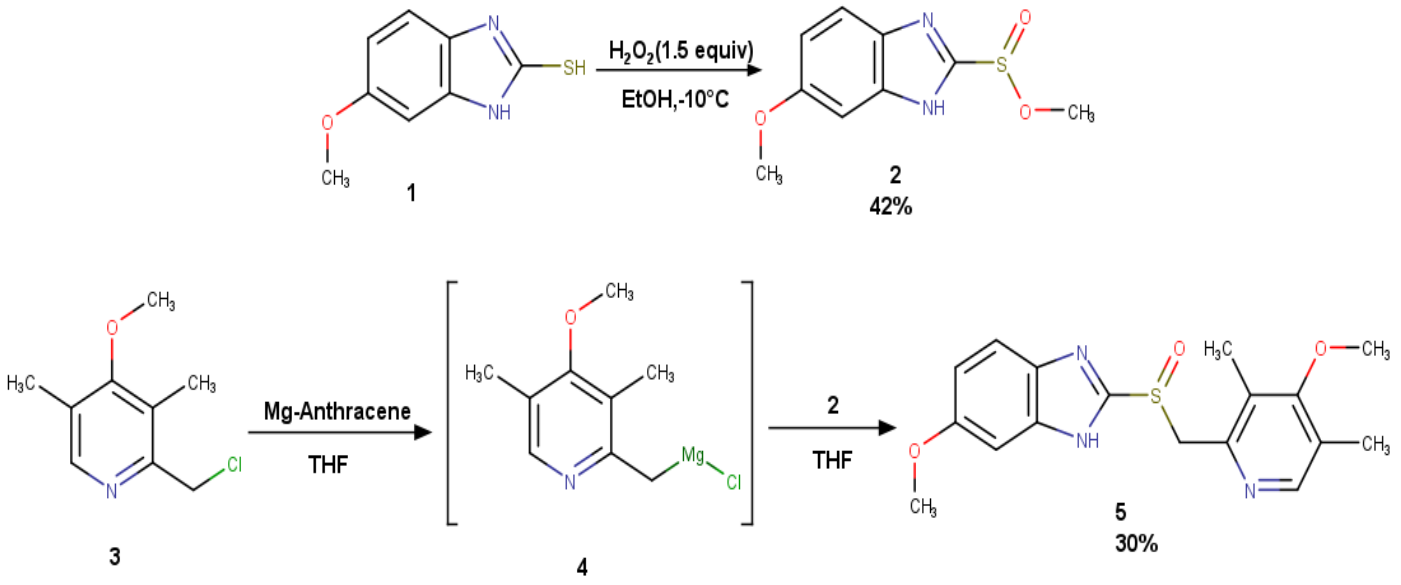
Synthesis: In 1986, Branstrom *et al*., who developed omeprazole at Astra Pharmaceuticals, published a process for the preparation of omeprazole and its intermediates in the United States (**Scheme 1**) [2].



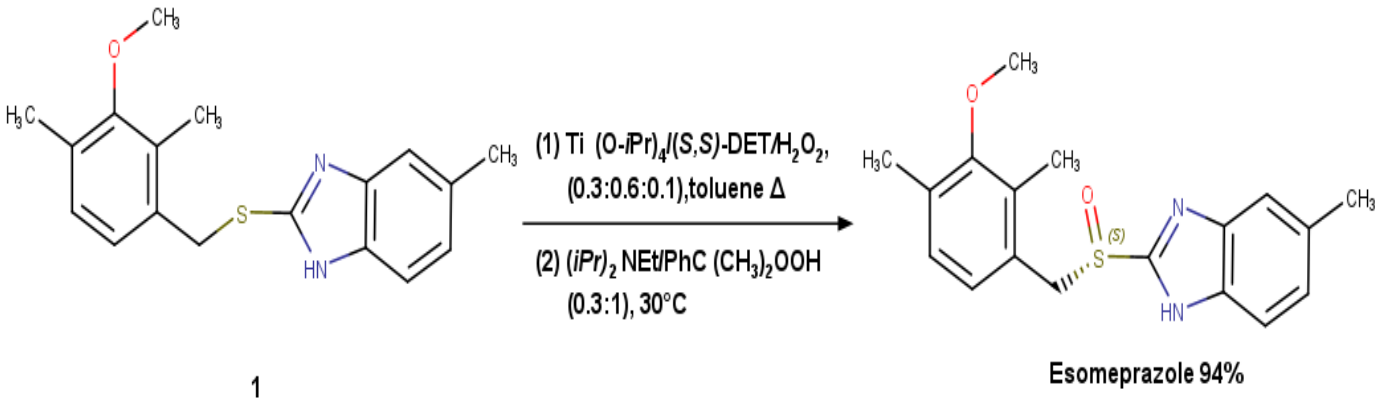
Scheme 1: Synthesis of omeprazole through Branstrom *et al*

2,3, Trimethyl pyridine **1** was oxidized by hydrogen peroxide in acetic acid to give the N-oxide **2**, and the latter was nitrated using a mixture of sulfuric acid and nitric acid to give the 4-nitro derivative **3 [2, 31]**. The nitro group in **3** was displaced by hydroxymethylation to yield **4**. Treatment of compound **4** with acetic acid anhydride reduces the ring and forms an ester derivative **5**. The corresponding alcohol **6** was formed by the treatment with base, followed by displacement of the hydroxyl group with a chloride using thionyl chloride to give 2-chloromethyl-4-methoxy-2,3,5-trimethyl pyridine **7**. Omeprazole **10** was obtained through the reaction of thiol **8** with pyridine **7** in the presence of NaOH; oxidation of pyrmetazole sulfide with *m*CPBA gave **10** as a racemic mixture [2, 31]. Bhalero and coworkers reported a novel synthetic route to omeprazole **5**, via the formation of the benzimidazole ester **2** and subsequent *in situ* reaction with the pyridyl Grignard intermediate **4** (**Scheme 2**) [2]. Cotton et *al*. described an innovative method for the asymmetric synthesis of esomeprazole. The (*S*)-enantiomer of omeprazole was synthesized through the asymmetric oxidation of prochiral sulfide 5-methoxy-2-[[(4-methoxy-3,5-dimethyl pyridin-2-yl) methyl] thio]-1H-benzimidazole **1** (**Scheme 3**) [2, 31].

The key step involved titanium-mediated oxidation using cumene hydroperoxide in the presence of (*S, S*)-diethyl tartarate (DET). Enantioselectivity was achieved by carefully preparing the titanium complex in the presence of sulfide **1** at an elevated temperature and/or during an extended preparation time. Additionally, performing the oxidation of sulfide 1 in the presence of an amine further contributed to the impressive enantioselectivity, resulting in a remarkable 94.0% enantiomeric excess (ee) [2, 31].



Scheme 2: Synthesis of omeprazole via the formation of the benzimidazole ester



Scheme 3: Asymmetric synthesis of *S*-omeprazole

Large-scale oxidations from the pharmaceutical industry, giving omeprazole**4** from pyrmetazole**1** have been reported which use inorganic oxidants such as sodium perborate, sodium hydrochloride, or sodium percarbonate in the presence of Mo catalysts (**Scheme 4)** [2].

Pharmacology and mechanism of action: Proton-pump inhibitors (PPIs) have emerged as the drug class of choice for treating patients with acid-related diseases, including gastroesophageal reflux disease (GERD), duodenal ulcer, and gastric ulcer. PPIs are also effective in treating patients with Barrett's esophagus and Zollinger-Ellison syndrome [32]. The stimulation of proton pump (H^+, K+-ATPase) in the parietal cell represents the final step of acid secretion and this knowledge has led to the development of a class of drugs, the proton pump inhibitors (PPIs), which are targeted at blocking this enzyme [28, 33-38], **Figure 12**. Chemically, all the available PPIs consist of a benzimidazole ring and a pyridine ring, but vary in the specific side ring substitution. As a class, they are the most potent inhibitors of gastric acid secretion available [37].

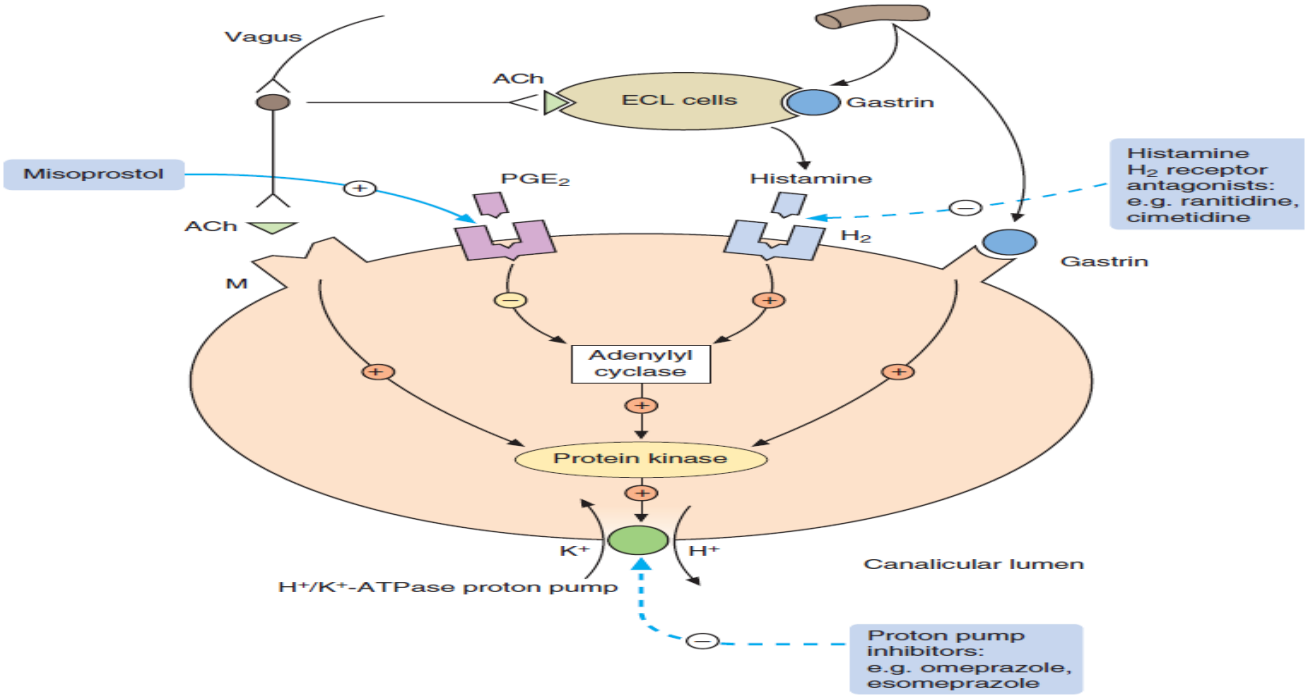


Figure 12: Control of gastric acid secretion from the parietal cell

Acid secretion from the parietal cell is stimulated by acetylcholine (ACh), histamine and gastrin. Gastrin and ACh also reinforce acid secretion by causing the release of histamine from the enterochromaffin-like (ECL) cells, which lie close to the parietal cells in the gastric pits. Prostaglandin E2 (PGE2) reduces acid secretion. The sites of action of the main drugs used to inhibit acid secretion from the parietal cell are shown. There are no useful inhibitors of gastrin action, and the gastric-selective muscarinic receptor (M-1) antagonist pirenzepine is no longer available in the United Kingdom. *H2*, Histamine type 2 receptor [38]. Under acid conditions omeprazole **1** is transformed to the spiro intermediate **2** which arises as a result nucleophilic attack of the pyridine nitrogen on the C2-position of the protonated benzimidazole **3**. Aromatization to the sulfenic acid**4**is followed by dehydration to the tetracyclic sulfenamide**5**which reacts with the target enzyme and deactivates it via formation of the disulfide complex **6** (**Scheme 5**) [2].

Pharmacodynamics and pharmacokinetics of IPPS drugs: All PPIs suppress gastric acid secretion by blocking the gastric acid pump, H^+/K^+-ATPase [39]. **Figure 13**, which was analyzed by Besancon, illustrates the variations in the rate of inhibition of H+/K+-ATPase activity with four PPIs [39, 40].

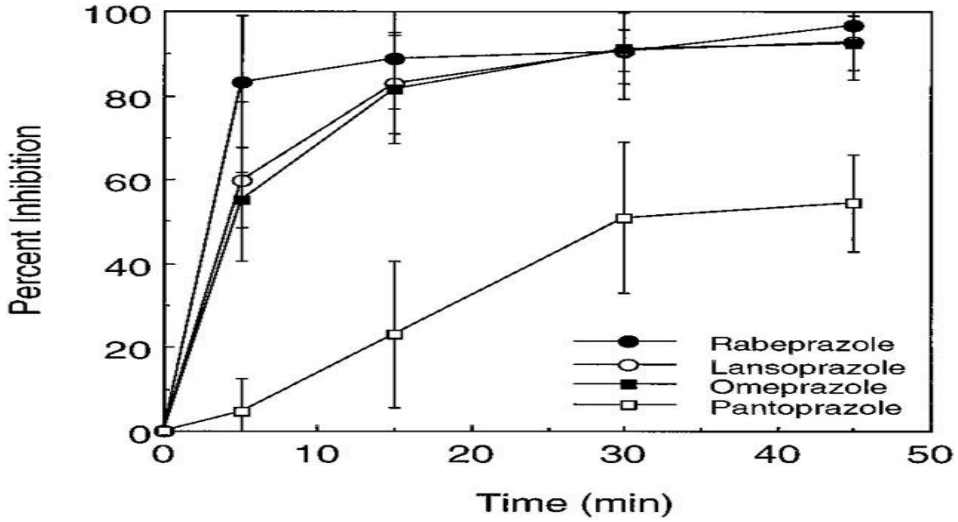
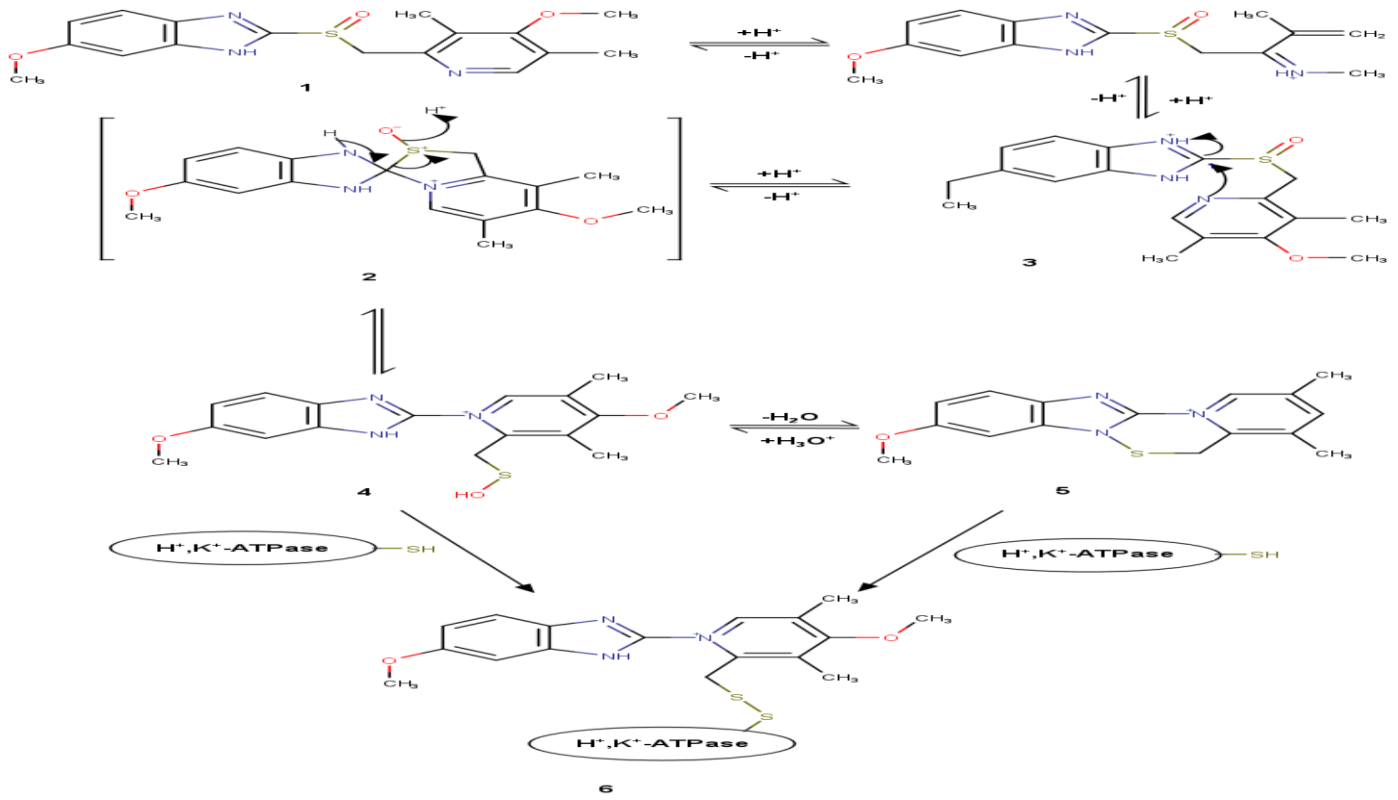


Figure 13: The rate of inhibition of the gastric H^+, K^+-ATPase under acid-transporting conditions by rabeprazole, omeprazole, lansoprazole, and pantoprazole. The vesicles were incubated in 150 mM KCl, with 1 mg/ml valinomycin in buffer at pH 6.8 in the presence of 10 mM compound and the reaction started by the addition of MgATP [40].



Scheme 5: Omeprazole under acid conditions [2]

The study results showed that Rabeprazole achieved the fastest inhibition, followed by Lansoprazole and omeprazole, and then pantoprazole [40]. Several factors must be considered to understand the pharmacodynamics of PPIs: accumulation of PPI in the parietal cell, proportion of the pump enzyme located at the canaliculus, de novo synthesis of new pump enzyme, metabolism of PPI, amounts of covalent binding of PPI in the parietal cell and the stability of PPI binding [41]. The PPIs have relatively short elimination half-lives; however, this has minimal bearing on their pharmacodynamic properties in that covalent binding to the H^+/K^+-ATPase enzyme predominately influences the duration of antisecretory action. Specifically, covalent binding to the cysteine residues of the proton pump leads to a duration of action that is substantially longer than would be predicted based strictly on the plasma concentration profile [42]. PPIs are unstable in acid and are given orally as enteric-coated formulations. Esomeprazole, omeprazole and pantoprazole are also available as intravenous formulations. Elimination is by hepatic metabolism. They have short plasma half-lives, but because of the irreversible mechanism of action, these bear no relationship to the long duration of action [38]. The PPIs also have stereoselective metabolism. When omeprazole is given as a racemic mixture, the *R*-enantiomer is rapidly cleared by the liver, whereas the clearance of the *S*-enantiomer is much slower. When esomeprazole is given, one is giving only the S-enantiomer of omeprazole and thus it has slower clearance as compared with the racemic mixture [42].

Enantioseparation of PPIS by HPLC: HPLC enantioseparation of omeprazole, lansoprazole, and pantoprazole drugs has been performed on various types of chiral stationary phases (CSPs), especially derivatives of cellulose and amylose, under normal phase, polar organic phase, and reversed phase. In 2004, Bonato PS colleagues reportedthe chiral HPLC-UV separation of omeprazole using five different columns: Chiralpak®IA, Chiralpak® AD, Chiralpak® AS, Chiralcel®OD-H and Chiralcel®OB-H. Among the evaluated chiral columns, only Chiralcel® OJ-R did not achieve complete resolution (Rs=1.1) of omeprazole [43]. In 2010, Zanitti L. and al achieved enantioseparation of omeprazole on the immobilized-type Chiralpak®IA chiral stationary phase (CSP) under both polar organic and normal-phase conditions at 25°C. The method has shown high selectivity ($\alpha \geq 1$) and efficiency in enantioseparation of omeprazole [44]. In 2011, Vyas S and colleagues conducted an HPLC study on the chiral separation of the same drug under normal phase conditions at 40°C, using Chiralcel®OD-H. The optimization of methanol content in the mobile phase was investigated across a

range from 0.0% to 10.0%, and the best result (Rs=1.85) was obtained with 10.0% methanol [45]. In 2016, Ferretti R and his collaborator published two papers in the same courses, one of them for omeprazole and the second about lansoprazole. The chromatographic conditions for enantioseparation of omeprazole are: Chiralpak®AGP columns, mobile phase ACN–pH 6 phosphate buffer (87: 13, v/v) [47], and for lansoprazole are: Chiralpak® IC, mobile phase n-hexane/ethanol/DEA 60:40:0.1 v/v/v [46]. Both methods demonstrated high selectivity in the enantioseparation of the studied drugs, with an enantiomeric separation factor (α) of 2.72 for omeprazole and 1.81 for lansoprazole. After one year, Rahman and colleagues [47] achieved a good resolution (RS=1.85) for omeprazole drugs using HPLC. The chromatographic separation was accomplished with a mobile phase consisting of n-hexane/2-propanol/acetic acid/triethylamine (80: 20: 0.2: 0.05, v/v). They employed a Chiralcel®OD-H. column and detected the compounds at a wavelength of 300 nm [47, 48]. In 2018 Xiong and others [49] reported the enantioseparation of some chiral sulfoxide drugs including omeprazole drug and lansoprazole drugs by HPLC using Chiralpak® AD-H and Chiralcel®OD-Hcolumns. The study shed light on the stereochemistry and chiral recognition mechanisms of these important drugs. Finally, in 2020, Papp LA and al, reported an enantioseparation of pantoprazole using HPLC coupled with circular dichroism (CD) detection, HPLC-CD. They employed a teicoplaninaglycone stationary phase under reversed-phase conditions [50]. The recent methods effectively separated the enantiomers of pantoprazole with a resolution factor (Rs) of at least 1.5. This achievement provided valuable insights into the stereochemistry and chiral recognition mechanisms of pantoprazole [51].

Conclusion: Biologically active sulfoxides are found in a number of natural products and pharmaceuticals. Chirality is also possible in certain sulfur compounds; just as with carbon, there can be differences in the physiological behavior of chiral sulfur compounds. The PPIs are an important advance in the management of acid-related disorders. They share a common core structure, a similar mechanism of action, and many clinical characteristics. They are highly potent suppressors of gastric acid secretion and are agents of choice for the treatment of many acid-related disorders. On the other hand, Resolution of racemic enantiomers PPIs can be simple and rapid with Chromatographic methods which provide materials in high enantiopurity. However, electrophoresis also demonstrates a good resolution of these drugs.

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