DRUGS PROFILE

5.1 LAFUTIDINE

Fig 5.1: Chemical Structure of Lafutidine


Molecular Formula: C_{22}H_{29}N_{3}O_{4}S

Molecular Weight: 431.55

PKa Value: 3.9


Mechanism of Action: Lafutidine has multimodal mechanism of action. It has been reported that the gastro protective effect of Lafutidine is independent of its acid antisecretory activity (Ichikawa et al. 1998). Lafutidine not only suppresses gastric acid secretion, but also has cytoprotective properties by the virtue of its property to induce the collagen synthesis in the gastric mucosa. In addition to being a potent H₂ receptors antagonist LAF also activates capsaicin-sensitive afferent neurons and stimulates the release of calcitonin gene-related peptide (CGRP), which inhibits acid secretion and stimulates mucosal blood flow. It is also found to stimulate mucin biosynthesis and promote the reconstitution of damaged mucosa (Fujisawa et al. 2004, Shimatani et al. 2006, Itoh et al. 2002).

Therapeutic uses: Lafutidine is a second generation histamine H₂- receptor antagonist used as anti-ulcerative agent. Antisecretory drugs are used in the treatment and prophylaxis of peptic ulcer disease, some are also employed in other disorders.
associated with gastric hyperacidity such as gastro-esophageal reflux disease (GERD) and dyspepsia.

5.2 DOMPERIDONE

Fig 5.2: Chemical Structure of Domperidone (DOM)

Chemical Name: 5-chloro-1-[1-[3-(2, 3-dihydro-2-oxo-1H-benimidazol-1-yl) propyl]-4-piperidinyl]-1, 3-dihydro-2H-benimidazol-2-one.

Molecular Formula: \( \text{C}_{22}\text{H}_{24}\text{ClN}_{5}\text{O}_{2} \)

Molecular Weight: 425.911g/mol

PKa value: 4.1

Therapeutic Categories: Antiemetic (O’Neil Mjb 2006).

Mechanism of Action: Domperidone is a dopamine antagonist with antiemetic properties. It stimulates gastro-intestinal motility. Domperidone is a peripheral dopamine (D2) and (D3) receptor antagonist. It provides relief from nausea by blocking receptors at the chemo-receptor trigger zone (a location in the nervous system that registers nausea) at the floor of the fourth ventricle (a location near the brain). It increases motility in the upper gastrointestinal tract to a moderate degree and increases lower esophageal sphincter pressure by blocking dopamine receptors in the gastric antrum and the duodenum. A low dose of Domperidone (10 mg iv) was able to increase the LES pressure to 275% above the basal pressure. This effect was rapid and prolonged and not mediated bay gastrin. (Bron & Massih 1980, Goodman & Gilman’sa 2006).

Therapeutic Uses: It is used as an antiemetic for the short-term treatment of nausea and vomiting (I.P. 2010, B.P. 2010).

Rationale of combinational therapy: Antacids, Antireflux Agents & Antiulcerants
5.3 DARUNAVIR ETHANOLATE

Fig 5.3: Chemical Structure of Darunavir Ethanolate

Chemical Names: [(1R,5S,6R)-2,8-dioxabicyclo[3.3.0]oct-6-yl] N-[(2S,3R)-4-[(4-aminophenyl)sulfonyl-(2-methylpropyl)amino]-3-hydroxy-1-phenyl-butan-2-yl] carbamate

Molecular Formula: C₂₇H₃₇N₃O₇S

Molecular Weight: 547.665 g/mol

Therapeutic Categories

Protease inhibitor drug used to treat HIV infection (O’Neil MJc 2006).

Mechanism of Action: Darunavir is a HIV protease inhibitor which prevents HIV replication by binding to the enzyme's active site, thereby preventing the dimerization and the catalytic activity of the HIV-1 protease. Darunavir selectively inhibits the cleavage of HIV encoded Gag-Pol polyproteins in virus-infected cells, which prevents the formation of mature infectious virus particles. Structural analyses suggests that the close contact that darunavir has with the main chains of the protease active site amino acids (Asp-29 and Asp-30) is an important contributing factor to its potency and wide spectrum of activity against multi-protease inhibitor resistant HIV-1 variants. Darunavir can also adapt to the changing shape of a protease enzyme because of its molecular flexibility. Darunavir is known to bind to two distinct sites on the enzyme: the active site cavity and the surface of one of the flexible flaps in the protease dimer.

Therapeutic Uses: Darunavir has robust interaction with the protease enzyme from many strains of HIV, including strains from treatment-experienced patients with multiple resistance mutations to protease inhibitors.
5.4 RITONAVIR

Chemical Name

1,3-thiazol-5-ylmethylN-[(2S,3S,5S)-3-hydroxy-5-[(2S)-3-metyl-2-[[methyl([2-(propan-2-yl)-1,3-thiazol-4-yl]methyl)carbamoyl]amino]butanamido]-1,6-diphenylhexan-2-yl]carbamate.

Molecular formula: C$_{37}$H$_{48}$N$_6$O$_5$S$_2$

Molecular weight: 720.94 USP

Pka: 13.68

Therapeutic Categories: Antiretroviral; HIV protease inhibitor (O’Neil MJ$^\circ$ 2006).

Mechanism of action: Ritonavir inhibits the HIV viral proteinase enzyme which prevents cleavage of the gag-pol polyprotein, resulting in noninfectious, immature viral particles (http://www.drugbank.ca/drugs/DB00503).

Therapeutic uses: Treats Human Immunodeficiency Virus (HIV) infection. HIV causes acquired immune deficiency syndrome (AIDS). Ritonavir does not cure HIV or AIDS, but it may slow the progress of the disease. This drug is used with other HIV medications to help control HIV infection. It helps to decrease the amount of HIV in the body so the immune system can work better. This lowers your chance of getting HIV complications and improves your quality of life.

Rationale of combinational therapy: Low-dose Ritonavir is used in conjunction with other Protease inhibitors to decrease metabolism and increase plasma concentrations of the other protease inhibitors regimens containing low-dose Ritonavir with certain other Protease
5.5 AZITHROMYCIN

**Fig 5.5: Chemical Structure of Azithromycin**

**Chemical Names:** (2R,3S, 4R, 5R, 8R, 10R, 11R, 12S, 13S,14S)-11-((2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2Hpyran-2-yloxy)-2-ethyl-3,4,10-trihydroxy-13-((2S,4R,5S)-5-hydroxy-4methoxy4hyltetrahydro-2H-Pyran-2-yloxy)-3,5,6,8,10,12,14-heptamethyl-1-oxa 6cyclopentade-can-5-one1,

**Molecular Formula:** C$_{38}$H$_{72}$N$_2$O$_{12}$

**Molecular Weight:** 748.98 g/mol (O’Neil MJ® 2006)

**PKa Value:** 7.34 (Sandra B. 2007)

**Therapeutic Categories:** Synthetic Macrolide antibiotic related to Erythromycin. Azithromycin is derived from erythromycin; however, it differs chemically from erythromycin in that a methyl-substituted nitrogen atom is incorporated into the lactone ring.

**Mechanism of Action:** Macrolide antibiotics are bacteriostatic agents that inhibits protein synthesis by binding reversibly to 50S ribosomal subunits of sensitive microorganisms, at or very near the sites that binds chloramphenicol.

**Therapeutic uses:** S. pneumonia, Community-acquired pneumonia' due to C. pneumoniae, Pharyngitis or tonsillitis, skin and skin structure infections, sexually transmitted diseases, Urethritis and cervicitis due to C. trachomatis, used in acute bacterial exacerbations of chronic obstructive pulmonary disease due to H. influenzae, M. catarrhalis, Acute otitis media (Goodman and Gillman’s® 2006).
5.6 OFLOXACIN

**Chemical Structure of Ofloxacin**

![Chemical Structure of Ofloxacin](image)

**Chemical Name:** 9-Fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyridol[1,2,3-de]-1,4-benzoazaine-6-carboxylic acid

**Molecular Formula:** $\text{C}_{18}\text{H}_{20}\text{FN}_{3}\text{O}_{4}$

**Molecular Weight:** 316.37 g/mol

**PKa value:** 5.45

**Therapeutic Categories:** Broad spectrum Fluorinated quinolones antibacterial (O’Neil Mj\(^b\) 2006).

**Mechanism of Action:** Ofloxacin acts on DNA gyrase and topoisomerase IV, enzymes which, like human topoisomerase, prevents the excessive supercoiling of DNA during replication or transcription. By inhibiting their function, the drug thereby inhibits normal cell division.

**Therapeutic uses:** used in Acute bacterial exacerbations of chronic bronchitis, Community-acquired pneumonia, Uncomplicated skin and skin structure infections, Nongonococcal urethritis and cervicitis, Mixed Infections of the urethra and cervix Acute pelvic inflammatory disease, Uncomplicated cystitis, Complicated urinary tract infections, Prostatitis, Acute, uncomplicated urethral and cervical gonorrhea. (Goodman and Gillman’s\(^b\) 2006).

**Rationale of combinational therapy:** MDR typhoid (Christopher M. Parry 2007).
5.7 CEFPODOXIME PROXETIL

Chemical Names: (6R,7R)-7-[(2Z)-(2-Amino-4-thiazolyl) (methoxyimino) acetyl] amino]-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-carboxylic acid 1-[(1-methylmethoxy) carbonyl][oxy]ethyl ester. Basically it is available as a recemic mixture due to $R$ and $S$ isomers.

Molecular Formula: $C_{21}H_{27}N_5O_9S_2$

Molecular Weight: 557.61g/mol (O’Neil MJb, 2006)

PKa Value: 3.22

Therapeutic Categories: Broad spectrum, Orally absorbed third generation cephalosporin antibiotics.

Mechanism of Action: Cefpodoxime is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis by inhibiting the final transpeptidation step of peptidoglycan synthesis in cell walls. Cefpodoxime has activity in the presence of some beta-lactamases, both penicillinases and cephalosporinases, of Gram-negative and Gram-positive bacteria.

Therapeutic uses: Acute otitis media, Pharyngitis and/or tonsillitis, Community-acquired pneumonia, Acute bacterial exacerbation of chronic bronchitis, Acute, uncomplicated urethral and cervical gonorrhea, Acute, uncomplicated ano-rectal infections in women, Uncomplicated skin and skin structure infections (Goodman and Gillman’s, 2006).

5.8 LEVOFLOXACIN

Chemical Name: (S) 9-Fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H- pyridol[1,2,3-de]-1,4 benzoxazine -6-carboxylic acid, hemihydrate

Molecular Formula: $C_{18}H_{20}FN_3O_4 \cdot 1/2 H_2O$
Molecular Weight: 316.37g/mol 370.37

PKa value: 6.05 and 8.22 (Jigar A Goswami 2013)

Therapeutic Categories: Broad spectrum Fluorinated quinolones antibacterial. Levofloxacin, a fluoroquinolone antiinfective, is the optically active L-isomer of Ofloxacin. (O’Neil MJ, 2006)

Mechanism of Action: Like other fluorinated quinolones Levofloxacin acts on DNA gyrase and topoisomerase IV, enzymes which, like human topoisomerase, prevents the excessive supercoiling of DNA during replication or transcription. By inhibiting their function, the drug thereby inhibits normal cell division. Levofloxacin inhibits bacterial type II topoisomerases, topoisomerase IV and DNA gyrase.

Therapeutic uses: Levofloxacin is used in acute bacterial exacerbations of chronic bronchitis, bacterial conjunctivitis, sinusitis, community-acquired pneumonia and pneumonia caused by penicillin-resistant strains of Streptococcus pneumonia, uncomplicated skin and skin structure infections, nongonococcal urethritis and cervicitis, mixed infections of the urethra and cervix acute pelvic inflammatory disease, uncomplicated cystitis, complicated urinary tract infections, prostatitis, acute uncomplicated urethral and cervical gonorrhea (Goodman and Gillman’sb 2006).

Rationale of combinational therapy: The combined dosage forms of Ofloxacin and Cefpodoxime Proxetil are available in the market and used as antibacterial drugs. The combination of Cefpodoxime Proxetil and Ofloxacin has unique dual mode of action, Ofloxacin prevents nucleic acid synthesis, while Cefpodoxime Proxetil inhibits cell wall synthesis and work synergistically with improved patient compliance (dmpharma.co.in/cefpodoxime+Ofloxacin.html dated 01/01/2015).