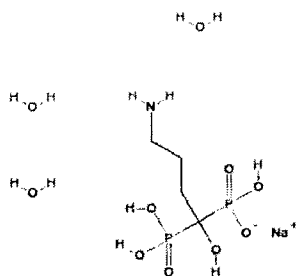


## An overview of Fosamax (alendronate sodium tablets)

### Abstract

Fosamax, developed and distributed by Merck Pharmaceuticals, Inc., is a geminal bisphosphate (BP) classified as an antiosteoporotic drug. Commonly known as alendronate, the IUPAC name for this molecule is sodium [4-amino-1-hydroxy-1-(hydroxy-oxido-phosphoryl)butyl]phosphonic acid trihydrate. First studied by Neuman and Fleisch in the 1960s, pyrophosphates were discovered in human body fluids to prevent decalcification of bones based on the structure's similarity to polyphosphates used previously. However due to the susceptibility of the compound to hydrolysis during oral administration, bisphosphonates with a more stable P-C-P structure were developed. Later synthesized by Henkel Pharmaceutical and improved upon by Ciba-Geigy, new variations of bisphosphonates were produced including the second generation BP alendronate, used to treat several diseases such as Paget's disease of the bone, hypercalcemia, myeloma, bone metastases as well as osteoporosis. The structure of bisphosphonates allows them to be selectively directed to sites of bone remineralization due to their affinity for calcium atoms of hydroxyapatite on the bone surface, to which they form chelated complexes. Variations of bisphosphonate structure can cause inhibition of bone resorption by osteoclasts on the bone surface by physico-chemical interaction or for some BPs, the disruption of the mevalonate pathway, preventing protein prenylation and function of key regulatory proteins and eventually lead to osteoclast apoptosis or cell death. Although the exact mechanism of bisphosphonate activity is still being unraveled, it has shown to be an effective treatment for reducing bone fracture risk due to osteoporosis.

### Structure



alendronate sodium (Fosamax)

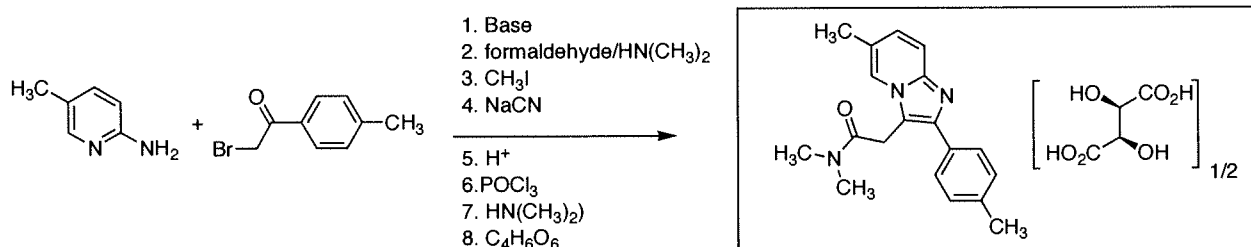
### References

- (1) Russell, R.G.G., Rogers, M.J., "Bisphosphonates: From the Laboratory to the Clinic and Back Again", *Bone* 1999(25) 97-106.
- (2) Widler, L., Jueggi, K., "Highly Potent Geminal Bisphosphates. From Pamidronate Disodium (Aredia) to Zoledronic Acid (Zometa)", *J. Med. Chem.* 2002(45) 3721-3738.
- (3) Rogers, M.J., Watts, D.J., Russell, R.G., "Overview of Bisphosphonates", *Cancer* 1997(80) 1652- 1660.
- (4) Rodan, G.A., Reszka, A.A., "Bisphosphonate Mechanism of Action", *Curr. Mol. Med.* 2002(6) 571-577.
- (5) Kotsikorou, E., Oldfield, E., "A Quantitative Structure-Activity-Relationship and Pharmacophore Modeling Investigation of Aryl-X and Heterocyclic Bisphosphonates as Bone Resorption Agents", *J. Med. Chem.* 2003(46) 2932-2944.
- (6) Dunford, J.E., Thompson, K., Coxon, F.P., et al., "Structure-activity relationships for inhibition of farnesyl diphosphate synthase in vitro and inhibition of bone resorption in vivo by nitrogen-containing bisphosphonates", *J. Pharm. Exp. Ther.*, 2001(296) 235-242.

Ambien®

Names: *N,N*-dimethyl-2-[3-methyl-8-(4-methylphenyl)-1,7-diazabicyclo[4.3.0]nona-2,4,6,8-tetraen-9-yl]acetamide (IUPAC), *N,N*, 6-trimethyl-2-p-tolyl-imidazo[1,2-*a*]pyridine-3-acetamide L-(+)-tartrate (2:1), Zolpidem, Stilnox®, Ambien CR™, Myslee®

Structure/Synthesis:



Drug Summary: Zolpidem was first synthesized under patent in 1983 at Synthelabo (now Sanofi-Aventis). This patented synthesis is briefly illustrated above. Zolpidem is classified as a sedative/hypnotic. It is issued in the treatment of short-term ( $\leq 4$  wk) insomnia. The drug is administered orally generally as a 10 mg/day dose. Zolpidem is very well received in most cases with the common side-effects being, slight psychomotor impairment and/or memory loss in the 1<sup>st</sup> 2 h, dizziness/light-headedness, drowsiness, gastrointestinal (nausea, vomiting, pain), and headache.

Mechanism of Action: Zolpidem is considered to be an agonist of the benzodiazepine (BZ) receptor component of the GABA Receptor Complex. It shows greatest affinity to the  $\omega_1$ -subunit of this receptor and enhances inhibitory effects of GABA on neuronal excitation.

Pharmacokinetics: Zolpidem is absorbed rapidly in the gut, and does suffer 1<sup>st</sup> Pass Metabolism with  $\sim 70\%$  being bioavailable. Approximately, 92% is bound to plasma proteins. Three major metabolites are generated predominately by P450s, all being benign. The metabolites are excreted renally with 79-96% being found in bile, urine or feces.

Future Direction: Ambien® goes off patent Oct. 2006. Sanofi-Aventis launched Ambien CR™ in 2005 which is a different formulation of zolpidem hemitartrate allowing for controlled release.

References:

- Kaplan, J-P., et al. U.S. Patent, 4,382,938, 1983.  
Rossey, G.; Long, D. U.S. Patent 4,794,185, 1987.  
*Drugs of the Fut.* **1987**, 12, 777.  
Langtry, H.D., et al. *Drugs.* **1990**, 40, 291.  
Holm, K.J., et al. *Drugs.* **2000**, 59, 865.  
Alaux, G., et al. European Patent, 1,064,937, 2001.

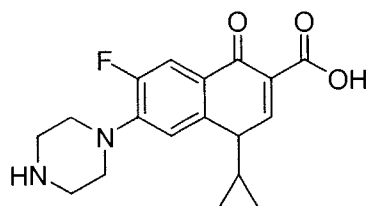
# Cipro

**Pronounced:** SIP-roh

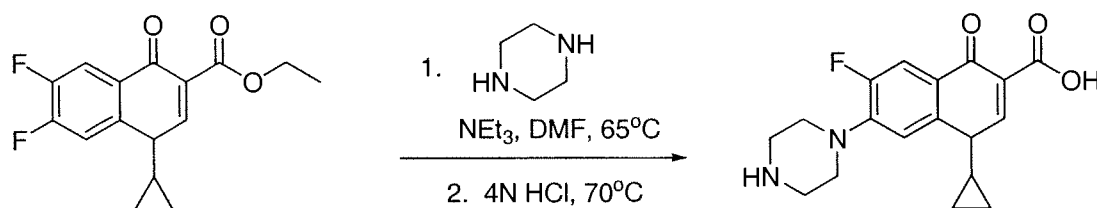
**Generic name:** Ciprofloxacin hydrochloride

**IUPAC name:** 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazine-1-ylquinoline-3-carboxylic acid

**Structure:**



**Scheme of Synthesis:**



**Abstract:**

Cipro is a fluoroquinolone antibiotic, which is available as a tablet and was put on the market by Bayer. The FDA approved Cipro as a marketable drug on August 30, 2000. Cipro is generally used to treat infections of the lower respiratory tract, the abdomen, the skin, the bones and joints, and the urinary tract, including cystitis (bladder inflammation) in women. It is also prescribed for severe sinus or bronchial infections, infectious diarrhea, typhoid fever, inhalational anthrax, infections of the prostate gland, and some sexually transmitted diseases such as gonorrhea.

Nearly 40 years ago, nalidixic acid was clinically introduced and started a wave of new quinolone antibacterial agents. Cipro is one of the analogues of nalidixic acid. Fluoroquinolones have high intracellular penetration and relatively long half-lives with good oral bio-availability. Fluoroquinolones are known to be involved in the inhibition of bacterial enzymes DNA topoisomerase IV and DNA gyrase. These two enzymes play a vital role in DNA replication. The introduction of a fluoroquinolone, such as Cipro, causes degradation of chromosomal DNA and termination of cell replication resulting in cell death. Cipro has the most potent DNA gyrase-inhibiting activity of any of the fluoroquinolones as well as in clinical efficacy.

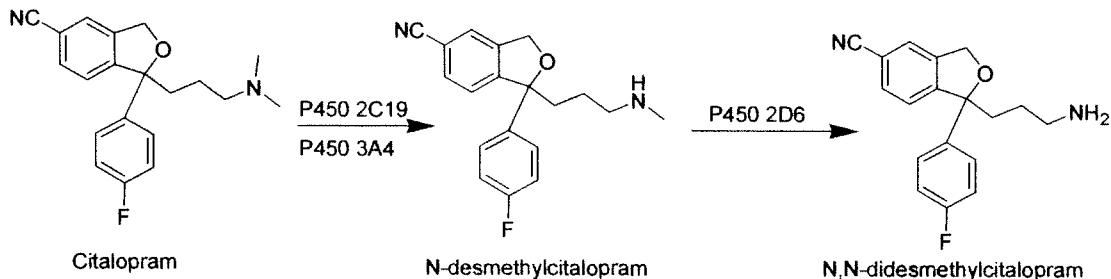
**References:**

- Baker, W.; Cai, S.; Dimitroff, M.; Fang, L.; Huh, K.; Ryckman, D.; Shang, X.; Shawar, R.; Therrien, J. *J. Med. Chem.* 2004, 47, 4693-4709.
- Jung, M.; Yang, E.; Vu, B.; Kiankarimi, M.; Spyrou, E.; Kaunitz, J.; *J. Med. Chem.* 1999, 42, 3899-3909.
- Zhi, C.; Long, Z.; Manikowski, A.; *Hybrid Antibacterials. DNA Polymerase-Topoisomerase Inhibitors*; *J. Med. Chem.* 2006, 49, 1455-1465.
- Hiasa, H.; *Biochemistry.* 2002, 41, 11779-11785.

## CELEXA

IUPAC: (RS)-1-[3-(dimethylamino)propyl]-1-(*p*-fluorophenyl)-5-phthalanarbonitrile, hydrobromide

Structure:



Abstract: Celexa (citalopram hydrobromide) is a selective serotonin reuptake inhibitor (SSRI) that, shown through clinical trials, has antidepressant activity, and is a treatment for a number of psychiatric disorders. The advantage of Celexa, and other SSRIs, which are classified as second generation antidepressants, is that it has an increased tolerability and cuts down on the enhanced sensitivity to adverse side effects in comparison with classical antidepressant medications, such as ones displayed by tricyclic antidepressants (TCCs). Celexa acts by increasing the concentration of serotonin (5-hydroxytryptamine 5-HT) in the synaptic cleft. It achieves this by inhibiting the 5-HT transporter, and thus slowing the reuptake of 5-HT. Celexa has been shown to be more selective than other SSRI's, having minimal effect on the neuronal reuptake of norepinephrine and dopamine, and minimal affinity for other neuronal receptors. It is an orally administered drug, and has 80% of the bioavailability when compared to intravenous administration, and absorption is not affected by food. Because of oral administration, Celexa is subject to the first pass effect, and is primarily metabolized by the liver (85%). These metabolic processes are carried out partially by cytochrome P450 2C19 and partially by cytochrome P450 3A4 to give N-desmethycitalopram. Further metabolism by cytochrome P450 2D6 yields N,N-didesmethycitalopram. Studies have shown that these metabolites of Celexa also inhibit the neuronal reuptake of serotonin. However, they are less potent, less selective and less abundant than parent compound in the blood plasma, and thus have minor clinical significance. The half-life of Celexa is approximately 37 hours, which allows for once-daily dosing. Dosage is usually between 20 and 40 mg, and should not exceed 60 mg, although overdosing of Celexa is relatively safe.

This presentation will focus on the effects of Celexa on depression, a detailed synthesis of the drug starting with readily available components, its metabolism/elimination, and its common side effects.

### References

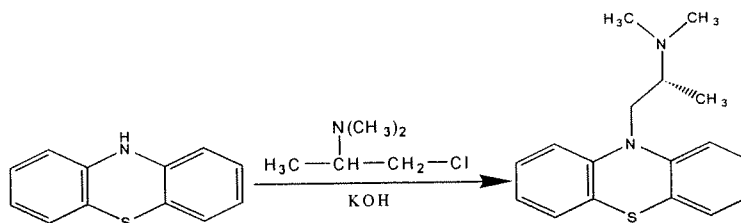
- Dorell, K., et al. *Citalopram-Induced Diplopia*. *Psychosomatics*, 2005, 46:91-93.
- Engelbrechtsen, K. M., et al. *Cardiotoxicity and late onset seizures with citalopram overdose*. *Journal of Emergency Medicine*, 2003, Volume 25, Issue 2, pp. 163-166.
- Holmgren, P, et al. *Enantioselective analysis of citalopram and its metabolites in postmortem blood and genotyping for CYD2D6 and CYP2C19*. *Journal of Analytical Toxicology*, 2004, 2:94-104
- Montgomery, S. A.; Djarv L. *The antidepressant efficacy of citalopram*. *International Clinical Psychopharmacology*. Volume 11, Issue SUPPL. 1, 1996, pp. 29-33.

# PHENERGAN<sup>®</sup>

Jacinda C. Do  
Chemistry 640, Dr. Berkman, Spring 2006

IUPAC: 10H-Phenothiazine-10-ethanamine, N,N,  $\alpha$ -trimethyl-, monohydrochloride

## Abstract



Phenergan (promethazine hydrochloride) is a phenothiazine derivative and a first-generation H<sub>1</sub> receptor antagonist (antihistamine) that is used in the treatment of allergic conditions, motion sickness, and relief of post operative nausea and vomiting. Promethazine was also found to have anti-psychotic properties, although it was not intended to function as a neuroleptic. Like other H<sub>1</sub> receptors, promethazine has anticholinergic and antiallergic, as well as sedative and antiemetic effects, and also some local anesthetic properties. Like many H<sub>1</sub> antagonists, promethazine does not prevent the release of histamine, as do cromolyn and nedocromil, but competes with free histamine for binding at H<sub>1</sub>-receptor sites. Histamine receptors in the gastrointestinal tract (GI), uterus, large blood vessels, and bronchial muscle are blocked. The relief of motion sickness and nausea or vomiting appears to be related to central anticholinergic. Sedation is significant at concentrations achieved from therapeutic dosages. Mild antitussive activity has been attributed to promethazine, but this effect probably results from anticholinergic and sedative actions. Local anesthetic activity requires higher concentrations than those required to antagonize histamine receptors. Promethazine is well absorbed from the gastrointestinal tract after oral dosing, but undergoes considerable first-pass-metabolism leading to a variable bioavailability. Promethazine is metabolized by the liver to a variety of compounds; the sulfoxides of promethazine and N-dimethylpromethazine are the predominant metabolites appearing in the urine. Lastly, drug interactions, including an increased incidence of extrapyramidal effects, have been reported when some monoamine oxidase inhibitors (MAOI) and phenothiazines are used concomitantly. Also when phenothiazine (chlorothiazine) is taken with epinephrine, epinephrine can decrease blood pressure. However, neither of these drug reactions has been reported with promethazine.

## References

- Lynch, L.; Simpson, K.H.; *Antiemetic Drugs. The Royal College of Anaesthetists*, 2001.  
Caldwell, J.B.; Moser, J.D.; Rhule, F.J. *No more than necessary: safety and efficacy of low-dose promethazine. Ann Pharmacother*, 2006.  
Katzung, B.G. *Basic and Clinical Pharmacology*. 2004, 9<sup>th</sup> Ed. pp 264-265  
RxList: The Internet Drug Index. [http://www.rxlist.com/cgi/generic/prometh\\_ad.htm](http://www.rxlist.com/cgi/generic/prometh_ad.htm)

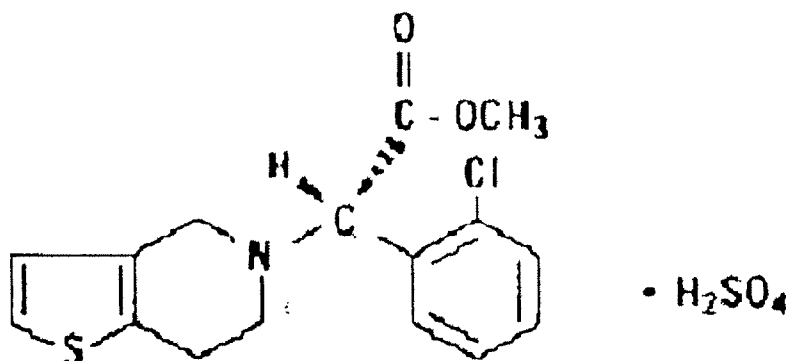
## Plavix

Alc Fboreime

Chemistry 640, Dr. Berkinan, Spring 2006

**IUPAC:** d-methyl[1'-chlorophenyl]-5-[4,5,6,7-tetrahydrothieno][3,2-c pyridinyl] acetate hydrogensulfate.

### Structure:



**Abstract:** Plavix (Clopidogrel hydrogen sulfate) is an orally-administered thienopyridine prodrug used to inhibit ADP-induced platelet aggregation. Plavix is oxidized by cytochrome P450s in the liver to an unknown metabolite that causes the inhibition of platelet aggregation. Only a small amount of Plavix is converted to its active metabolite; the majority is hydrolyzed by esterases to an inactive carboxylic acid derivative that is found circulating in the plasma one hour after administration. The metabolite of Plavix is not found in the plasma; it is believed to be oxidized twice to open the thiol ring and create a carboxyl and thiol group. It is this thiol group that reversibly binds to the P2Y<sub>12</sub> ADP-receptor on the platelet. The inhibitor works by competition with ADP to prevent it from binding to this receptor; thereby disrupting the subsequent concomitant action between two of the G protein-coupled ADP receptors, P2Y<sub>12</sub>, a G<sub>12</sub> coupled receptor, and P2Y<sub>1</sub>, a G<sub>q</sub> coupled receptor. Plavix, as well as another similar thienopyridine, ticlopidine, are continuously being clinically tested to see if there is improved efficacy over aspirin. Aspirin was the antithrombotic drug of choice to prevent blood clots in those patients who are at risk for myocardial infarction, stroke, and vascular death due to a history of symptomatic atherosclerotic disease. Now, large clinical trials have demonstrated an improved control of platelet aggregation from both plavix and ticlopidine, with Plavix providing less side-effects and no fatal complications. Plavix does not frequently cause the gastrointestinal bleeding that aspirin does. The major side-effect is a severe rash that some studies have found can be overcome through a desensitization process.

The presentation will include a discussion on ADP's three platelet receptors and their modes of action, Plavix synthesis, mechanism, structure-activity, administration, side-effects, and future directions.

### References:

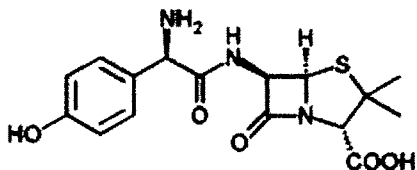
- Camara, M.G., Almeda, F.Q. *Catherterization and Cardiovascular Interventions* **2005**; 65: 525-527.
- Clarke, T. A., Waskell, L.A. *Drug Metabolism and Disposition* **2002**; 31: 53-59.
- Jin, J., Kunapuli, S. P. *Proc. Natl. Acad. Sci.* **1998**; 95:8070-8074.
- Savi, P., Labouret, C., Delesque, N., Guette, F., Lupker, J., Herbert, J.M. *Biochemical and Biophysical Research Communications* **2001**; 283: 379-383.
- Quinn, M. J., Fitzgerald, D. J. *Circulation* **1999**; 100:1667-1672.

Jason Epstein 907247411

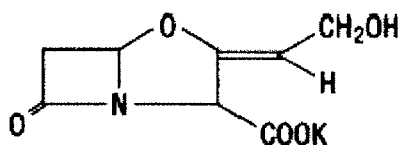
Drug Abstract

Chem 640, Spring 2004

Augmentin is an orally administered mixture of amoxicillin ((2S,5R,6R)-6-[(R)-(-)-2-Amino-2-(p-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate ) and clavulanate potassium (potassium (Z)-(2R,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]-heptane-2-carboxylate) and is manufactured by GlaxoSmithKline.



Amoxicillin is an analog of the synthetic antibiotic ampicillin, which is formed by adding an amino group to the side chain of Penicillin-G. Amoxicillin is ampicillin with a hydroxyl group at the *para* position of the benzyl ring. Amoxicillin is subject to cleavage by beta-lactamase.



Clavulanate potassium is a beta-lactamase inhibitor produced by *Streptomyces clavuligerus*.

**Usage:** Augmentin is active against a wide range of both gram positive and gram negative bacteria. It is especially useful in treating respiratory and ear infections.

**Metabolism:** Up to 90% of a dose of amoxicillin is absorbed into the serum, twice as much as with ampicillin. Up to 80% of a dose of amoxicillin exits the body intact in the urine, with 59% of clavulanate being excreted unchanged. For amoxicillin, 20%-30% is metabolized by the liver.

**Biological Activity:** Augmentin has the same clinical activity as amoxicillin, which has higher activity than ampicillin. The addition clavulanate does affect activity, nor does the clavulanate have any effect on its own. Beta-lactamase has a higher affinity for clavulanate than it does for amoxicillin, allowing the amoxicillin a greater half-life and to have a greater spectrum of activity.

#### References:

Bodey GP. *Tex Heart Inst J*. 1990; 17(4): 315-329

Bush K. *Clin Microbiol Rev*. 1988 Jan; 1(1): 109-123

Woodnutt G.; Berry V. *Antimicrob Agents Chemother*. 1999 January; 43(1): 35-40.

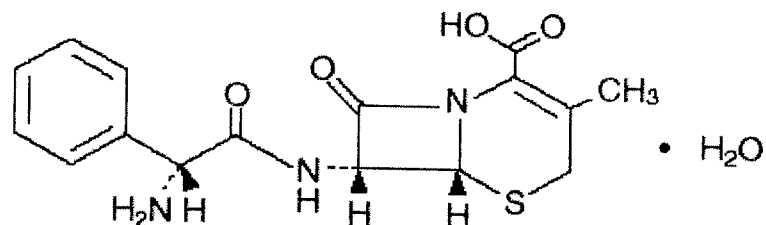
Rizwi I, Tan AK, Fink AL, Virden R. *Biochem J*. 1989 Feb 15; 258(1): 205-209

Schaad UB, Casey PA, Cooper DL. *Antimicrob Agents Chemother*. 1983 Feb; 23(2): 252-255.

Keflex®

**IUPAC:** 7-(D- $\alpha$ -amino- $\alpha$ -phenylacetamido)-3-methyl-3-cephem-4-carboxylic acid monohydrate.

**Structure:**



**Common Name:** Cephalexin Monohydrate; **MW:** 365.41

**Abstract:** Keflex (Cephalexin Monohydrate) is a semi synthetic cephalosporin antibiotic. Its structure is composed of a phenylglycine sidechain and a nucleus. It is one of several B-lactam antibiotics, and acts in the inhibition of cell wall synthesis. Cephalexin is absorbed completely (80-100%) by the proton-dependent transporter after oral administration. It is a substrate of PEPT1, a peptide transporter located in the apical membrane. The typical synthesis of cephalexin involves protection of the amino group on the acylating agent and the carboxyl group of the nucleus and the subsequent coupling of the acylating agent and the nucleus. However, other methods have been explored due to the potential low yields following many synthetic steps. One alternative is the use of cephalexin synthesizing enzyme of *Glucobacter oxydans* because it has been shown to catalyze the coupling reaction without the extensive protection and de-protection chemistry. *G. oxydans* has been demonstrated to synthesize cephalexin from D-phenylglycine methyl ester and 7-amino-3-deacetoxycephalosporanic acid by CSE. In addition to formulating alternate synthesis pathways, other studies have focused on the effects of altering the parent B-lactam ring on antimicrobial activity and ability to bind the dipeptide transporter. Cephalexin exists as a zwitterion in the intestinal lumen. Less polar analogues generally bound to the transporter and competed against cephalexin for drug uptake. However, the modifications altered their activity towards bacteria. Generally, the analogues retained their activity towards gram-positive bacteria, but their activities toward gram-negative microbes diminished. Studies such as these demonstrated the need to focus on both the antimicrobial activity and structural requirements for interaction with the transporter.

#### REFERENCES

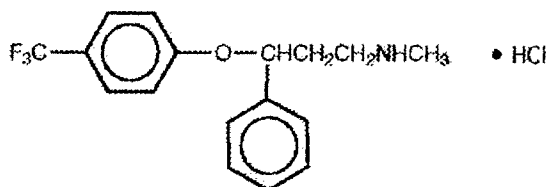
1. **Padoin, M Tod; Perret, G.; Petitjean, O. 1998.** Analysis of the Pharmacokinetic Interaction between Cephalexin and Quinapril by a nonlinear Mixed-Effect Model. *American Society for Microbiology*. P. 1463-1469
2. **Muniandy, Saravanan; Nataraj, Kalakonda Sri. 2002.** The Effect of Tablet Formulation and Hardness on in Vitro Release of Cephalexin from Eudragit L100 Based Extended Release Tablets. *Biol. Pharm. Bull.* 25:541-545
3. **Shiau, Chia-Yang; Pai, Shun-Chung. 2005.** Purification Characterization of Inducible Cephalexin Synthesizing Enzyme in *Glucobacter oxydans*. *Biosci. Biotechnol. Biochem.* 69: 463-469
4. **Snyder, Nancy J.; Tabas, Linda B; Berry, Donnis M; Duckworth, Dale C; Spry, Douglas O.; Dantzig, Anne H. 1997.** Structure-Activity Relationship of Carbacephalosporins and Cephalosporins: Antibacterial Activity and Interaction with the Intestinal Proton-Dependent Dipeptide Transport Carrier of Caco-2 Cells. *Antimicrobial Agents and Chemotherapy*. p. 1649-1657
5. **Watanabe, Kazuhiro; Toshiya, Jinriki; Sato, Juichi. 2004.** Effects of Progesterone and Norethisterone on Cephalexin Uptake in the Human Intestinal Cell Line Caco-2. *Biol. Pharm. Bull.* 27:559-563

Emily Hsu  
Chemistry 640, Medicinal Chemistry  
March 20, 2006

## Prozac

Prozac, or Fluoxetine Hydrochloride, is an orally administered selective serotonin reuptake inhibitor introduced in 1988 to treat depression, other psychiatric disorders such as bulimia nervosa and OCD, and later on to treat Premenstrual Dysphoric Disorder and other disorders as well.

Structure:



IUPAC:

(+/-)-N-methyl-3-phenyl-3-[(alpha,alpha,alpha-trifluoro-p-tolyl)oxy]propylamine hydrochloride

Fluoxetine Hydrochloride can be synthesized by various mechanisms. Two examples are by going through an azetidinium intermediate or by way of a Diels Alder mechanism. Fluoxetine Hydrochloride is absorbed well when taken orally and reaches peak plasma concentration between 6-8 hours, with its active metabolite, norfluoxetine, having a half life of 7-10 days. This allows some patients to only have to take it once a week. Prozac is more polar and less hydrophilic than fluoxetine free base and thus is less able to cross cell membrane and thus more difficult to administer transdermally than its base. But the addition of ethanol to a free base solution of fluoxetine significantly improves the permeability of the cell membrane to fluoxetine. There is now the possibility of created a drug that can be administered transdermally to bypass the first pass metabolism and elimination.

The response to Prozac is highly individualized but has been shown to be effective against all degrees of depression. Both fluoxetine and norfluoxetine are known to effect nicotinic acetylcholine channels, 5-hydroxy-tryptamine serotonin receptors, chloride ion channels as well as enhance GABAR activity. The therapeutic effects of fluoxetine have been mostly based on its ability to inhibit the 5HT Serotonin receptors resulting in an increase in the availability of 5HT in the synaptic cleft. The increase in 5-hydroxy-tryptamine in the synaptic cleft due to gestational ingestion of fluoxetine has been shown to continue to persist after birth and during adult life and reduce depressive behaviors.

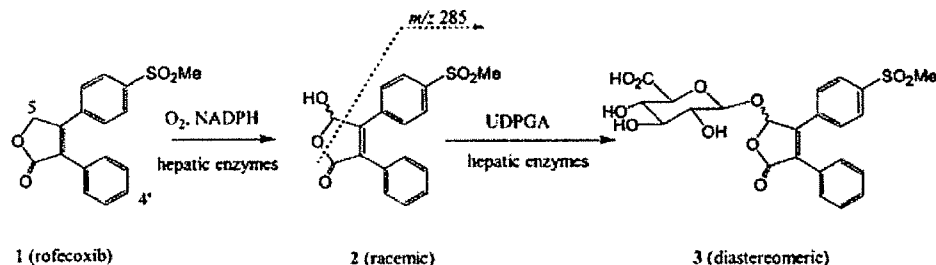
### Bibliography

- Mendes-da-Silva C, de Souza SL, et. al., Neonatal treatment with fluoxetine reduces depressive behavior induced by forced swim in adult rats. Arq. Neuro-Psiquiatr. Vol 60 (December 2002)
- Ni, Y.G., Miledi, R., Blockage of 5HT<sub>2C</sub> Serotonin Receptors by Fluoxetine (Prozac). Proc. Natl. Acad. Sci. USA. Vol. 94 (March 1997): pp 2036-2040.
- O'Brian, Peter, Philips, David W., Towers, Timothy D., An azetidinium ion approach to 3-aryloxy-3-aryl-1-propanamines, Tetrahedron Letter. Vol 43 Issue 41 (October 7, 2002): 7333-7335.
- Panunzio, Mauro, Rossi, Katia, et.al., Synthesis of enantiomerically pure (S)- and (R)-fluoxetine (Prozac<sup>®</sup>) via a hetero Diels-Alder strategy. Tetrahedron: Assymetry. Vol 15 Issue 22 (Nov. 15, 2004): 3489-3493.
- Parikh, Darshan K., Ghosh, Tapash K., Feasibility of Transdermal Delivery of Fluoxetine, AAPS PharmSciTech 2005. (September 20, 3005): Article 22.
- Robinson, Richard T., Drafts, Brandon C., Fisher, Janet L., Fluoxetine Increases GABA<sub>A</sub> Receptor Activity Through a Novel Modulatory Site, The Journal of Pharmacology and Experimental Therapeutics. (2003): 304:978-984.
- Rossi, Andrea, Barraco, Alessandra, Donda, Pietro, Fluoxetine: a review on evidence based medicine, Annals of General Hospital Psychiatry 2004. (2004): 3:2.

## Vioxx®

**IUPAC:** 4-(4'-methylsulfonylphenyl)-3-phenyl-2(5H)-furanone.

Vioxx (Rofecoxib) is a non-steroidal anti-inflammatory drug (NSAID), especially designed to selectively inhibit the enzymatic activity of cyclooxygenase(COX)-2 which is expressed for production of prostaglandins, associated with pain sensation during the inflammatory response to tissue injury. COX-1, an isoenzyme of COX-2, is involved in gastric mucosal protection from digestive injury by acid and pepsin. Due to its selective inhibition of COX-2 relative to COX-1, Vioxx shows less association with general adverse effects of NSAIDs such as gastrointestinal ulceration, dyspepsia, gastritis, bleeding, perforation and hemorrhage while having effects on controlling pain from acute tissue injury and chronic inflammatory disease such as osteoarthritis and rheumatoid arthritis. The structure and metabolism of Vioxx are shown below.



**Synthesis:** In 1999, Prasit et al. devised substituents of DuP697 to improve oral bioavailability and COX-2 selectivity. The methylsulfonyl group was replaced by a sulfonamide moiety and C-2 substituent of DuP697 was removed. The central thiophene template was replaced with a lactone moiety. Out of the methylsulfonyl series with different substituents, rofecoxib, a phenyl-substituted methylsulfone, was chosen.

**Metabolism:** Rofecoxib is oxidized by NADPH and hepatic enzymes, giving 5-hydroxy rofecoxib. With uridinediphospho-glucuronic acid and hepatic enzymes, 5-hydroxy rofecoxib generates a mixture of two diastereomeric glucuronides.

**Side effects:** It had been reported that Vioxx was associated with cardiovascular side effects until Merck and Co. voluntarily withdrew Vioxx from market after discussion with US FDA on 2004.

### References:

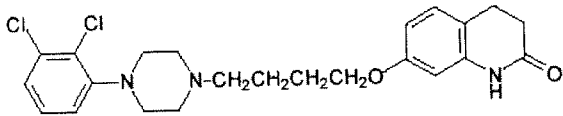
- Jüni, P., Nartey, L., Reichenbach, S., Sterchi, R., A Dieppe, P., Egger, M. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. **2004**. *The Lancet*. 364, 9450. pp 2021-2029
- MacConnachie, Rofecoxib(Vioxx)-the first of a new generation of a NSAIDs. *A.M. Intensive and Critical Care Nursing*. **2000**. 16, 201-202
- Mukherjee, D. Selective cyclooxygenase-2 (COX-2) inhibitors and potential risk of cardiovascular events. **2002**. *Biochemical Pharmacology*. 63, 5. pp 817-821.
- Nicoll-Griffith, D., Yergey, J., Trimble, L., Silva, J., Li, C., Chauret, N., Gauthier, J., Grimm, E., Léger, S., Roy, P. et al. Synthesis, characterization, and activity of metabolites derived from the cyclooxygenase-2 inhibitor rofecoxib (MK-0966, Vioxx™). **2000**. *Bioorganic & Medicinal Chemistry Letters*. 10, 23. pp 2683-2686
- Pajdo, R., Brzozowski, T., Konturek, P., Kwiecien, S., Konturek, S., Liwowski, Z., Pawlik, M., Ptak, A., Drozdowicz, D., Hahn, E. Ischemic preconditioning, the most effective gastroprotective intervention: involvement of prostaglandins, nitric oxide, adenosine and sensory nerves. **2001**. *European Journal of Pharmacology*. 427, 3. pp 263-276
- Prasit, P., Wang, Z., Brideau, C., Chan, C., Charleson, S., Cromlish, W., Ethier, E., Evans, J., Ford-Hutchinson, A., Gauthier, J. et al. The discovery of rofecoxib, [MK 966, VIOXX®, 4-(4'-methylsulfonylphenyl)-3-phenyl-2(5H)-furanone], an orally active cyclooxygenase-2 inhibitor. **1999**. *Bioorganic & Medicinal Chemistry Letters*. 9, 13, pp 1773-1778.
- Radhakrishna, T., Rao, S., Reddy, G. LC determination of rofecoxib in bulk and pharmaceutical formulations. **2001**. *Journal of Pharmaceutical and Biomedical Analysis*. 26, 4. pp 617-628

## ABILIFY®

Aripiprazole (**ABILIFY**® Bristol Myers Squibb, Otsuka America Pharmaceuticals Inc.) is an atypical antipsychotic used to treat Schizophrenia and acute manic and mixed episodes associated with Bipolar I Disorder by adjusting dopamine levels in the brain.

**UPAC:** 7-[4-[4-(2,3-dichlorophenyl)piperazin-1-yl]butoxy]-3,4-dihydro-1H-quinolin-2-one

### Structure:



**Synthesis:** “Aripiprazole is synthesised by a 2-step process. In the first step, 7-hydroxy-3,4-dihydro-2(H)-quinolinone is transformed into an intermediate, which is reacted with 1-(2,3-dichlorophenyl) piperazine hydrochloride to obtain aripiprazole”<sup>1</sup>

**Administration:** Aripiprazole tablets are available in 5-mg, 10-mg, 15-mg, 20-mg, and 30-mg strengths and as a 1 mg/mL oral solution.<sup>1,2</sup>

**Metabolism:** Aripiprazole is metabolized by the p450 enzymes CYP3A4 and CYP2D6 into dehydro aripiprazole. 3A4 works by causing N-dealkylation at nitrogen-alkyl chain bond. 2D6 causes dehydrogenation and hydroxylation of the ether bond.

**Activity:** The drug works as a partial antagonist of dopamine D-2 and serotonin 5-HT(1A) receptors in the brain.<sup>6,7</sup>

### References:

1. “Scientific Discussion.” European Medicines Agency. Mar 7, 2006. <http://www.emea.eu.int/humandocs/PDFs/EPAR/abilify/089304en6.pdf>
2. McGavin JK, Goa KL. *CNS Drugs* 2002;16(11):779-86; discussion 787-8
3. Taylor DM. *Int J Clin Pract* 2003 Jan-Feb;57(1):49-54
4. Winans E. *Am J Health Syst Pharm.* 2003 Dec 1; 60(23): 2437-45
5. “Aripiprazole.” RxList.com. Mar. 3, 2006. <http://www.rxlist.com/cgi/generic/abilify.htm>
6. “Enclosure.” Food and Drug Administration. Mar. 2 2006. [http://www.fda.gov/cder/foi/label/2002/21436\\_Abilify\\_lbl.pdf](http://www.fda.gov/cder/foi/label/2002/21436_Abilify_lbl.pdf)
7. *Neuropsychopharmacology* 1999 Jun;20(6):612-27
8. McQuade *et al.* *Int J Neuropsychopharmacol.* 2002;5(Suppl 1):S176
9. “Ambilify.” Emmanuel Saltiel, Pharm. D. Medicinenet.com. Feb 26, 2006 <http://www.medicinenet.com/aripiprazole/article.htm>

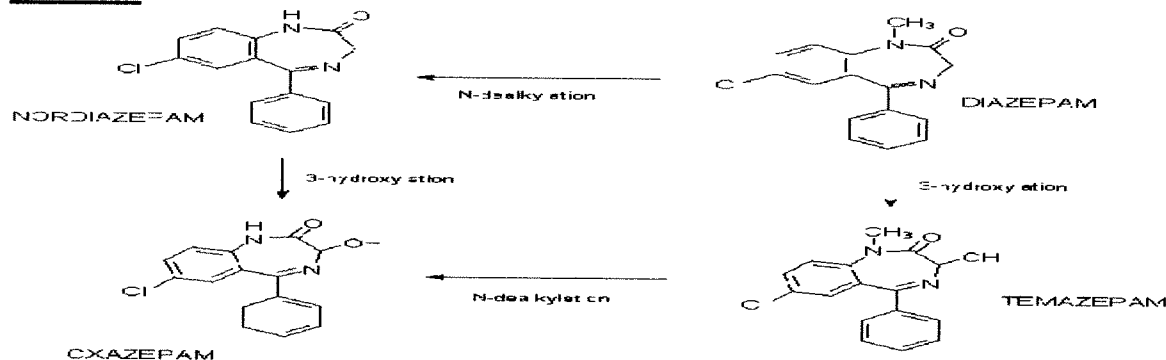
# Diazepam

Benjamin Lintner

Chemistry 640, Dr. Berkman, Spring 2006

**IUPAC:** 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one  
(MW:284.74) Formula: C<sub>16</sub>H<sub>13</sub>ClN<sub>2</sub>O

## Structure:



**Abstract:** Diazepam (Valium) is derived from benzodiazepine, which belongs to a group of psychotropic drugs with potent hypnotic and sedative action; used predominantly as antianxiety and sleep-inducing drugs. Side effects of Diazepam and these drugs may include impairment of psychomotor performance, amnesia, euphoria and dependence. Diazepam is classified under the ATC index as a Psycholeptic and Anxiolytic. The target organ is the central nervous system, causing depression of respiration and consciousness.

Diazepam can be injected for the relief of acute anxiety when rapid action is required in acute alcohol withdrawal and surgical procedures. It is also commonly used for skeletal muscle spasm, cerebral palsy, atherosclerosis, insomnia, tetanus and severe recurrent convulsive seizures. Diazepam is a benzodiazepine derivative originally developed through original research at Roche. It has a colorless crystalline compound and is insoluble in water. It can be used as a premedication, or a preanesthetic to enhance the therapeutic effect and safety of a surgical procedure. Clinical use includes an antianxiety and sedative drug used to treat acute cocaine poisoning, alcohol withdrawal and anxiety disorders. The clinical effects of Diazepam are Central nervous system depression and coma, or paradoxical excitation.

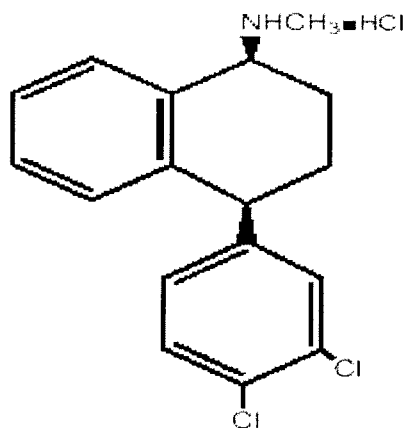
Diazepam is a synthetic compound created by Sternbach et al, 1961. Benzoyl chloride reacts with p-chloroaniline to produce 2-amino-5-chlorobenzophenone. This is converted to the oxime with hydroxylamine. After cyclization with chloroacetyl chloride and ring enlargement with alkali treatment, 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one-4-oxide is reduced and methylated to diazepam. Diazepam is primarily metabolized by hepatic enzymes. The hepatic cytochrome enzyme isozyme is responsible for hydroxylation. Hepatic n-demethylation results in the formation of the active metabolite desmethyldiazepam, which is hydroxylated to form oxazepam, which is conjugated to oxazepam glucuronide.

The toxic and therapeutic effects of diazepam are a result of its effect on CNS GABA activity. GABA (gamma-aminobutyric acid) is an important inhibitory neurotransmitter which mediates pre- and post-synaptic inhibition in all regions of the central nervous system. Diazepam and the other benzodiazepines appear to either enhance or facilitate GABA activity by binding to the benzodiazepine receptor, which is part of a complex including an aminobutyric acid receptor, benzodiazepine receptor, and barbiturate receptor. Binding at this complex results in increased CNS inhibition by GABA. The anticonvulsant and other effects of diazepam are believed to be produced by a similar mechanism, possibly involving various subtypes of the receptor.

## References:

- Ashton H. Department of Psychiatry, Newcastle Upon Tyne, England. *Drugs* 1994 Jul; 48(1):25-40
- F. A. Davis Co. *Taber's Cyclopedic Medical Dictionary*. Philadelphia, PA. 2005.
- Long, Phillip W. *Internet Mental Health*. [www.mentalhealth.com](http://www.mentalhealth.com). 2005
- Mattner, F. et al. Study of Benzodiazepine Receptors. <http://www.pubmed.com>. *Life Sci*. 2006 Feb 3
- <http://www.rxlist.com/cgi/generic/diazepam.htm>
- <http://www.toxlab.co.uk/diazmet.html>

Zoloft



Zoloft or Sertraline hydrochloride is an antidepressant belonging to the class of selective serotonin reuptake inhibitor (SSRI), which increases the amount of serotonin (5 hydroxytryptamine or 5-HT) in the synaptic gap. The chemical name of Sertraline Hydrochloride is (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride with an empirical formula of  $C_{17}H_{17}NCl_2 \cdot HCl$ . Sertraline undergoes first pass metabolism in the liver to N-desmethylsertraline. It is then oxidatively deaminated to desmethylsertraline ketone, which, in turn, undergoes hydroxylation to an alpha-hydroxyketone and alcohol. These metabolites are then conjugated and excreted in equal amount in the urine and feces. The mechanism of action of sertraline is linked to the inhibition of CNS neuronal uptake of serotonin (5HT) by the presynaptic neuron. Zoloft is manufactured and marketed by Pfizer, where Welch and Koe first synthesized the molecule by transforming tametraline, a norepinehrine reuptake inhibitor.

Reference:

- Murdoch D & Mac Tavish D (1992) Sertraline: A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in depression and obsessive-compulsive disorders. *Drugs*, 44 (4): 604-624
- Lau GT & Horowitz BZ (1996) Sertraline overdose. *Acad Emerg Med*, 3(2): 132-136
- Lejoyeux M, Ades J & Rouillon F (1994) Serotonin syndrome: incidence, symptoms and treatment. *CNS Drugs*, 2 (2): 132-143

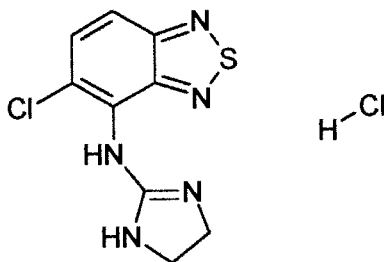
**ZANAFLEX®**

**Generic name:** Tizanidine hydrochloride

**IUPAC name:** 5-chloro-4-(2-imidazolylamino)-2,1,3-benzothiazole hydrochloride.

**Chemical Formula:** C<sub>9</sub>H<sub>8</sub>ClN<sub>5</sub>S•HCl

**Chemical Structure:**



**Usage:** Tizanidine hydrochloride reduces muscle spasms in people with multiple sclerosis, cerebral palsy, stroke and other conditions where portions of the nervous system that controls voluntary movement have been damaged. This drug provides only a short duration therapeutic effect and thus is taken when relief of spasticity is most important. Although tizanidine hydrochloride reduces spasticity, it does not reduce muscle strength. As a side effect, tizanidine hydrochloride lowers blood pressure.

**Route of administration:** Orally. 2 and 4 mg tablets and 2, 4 and 6 mg capsules available. Bioavailability is ~21% due to extensive first-pass effect.

**Metabolism:** Tizanidine hydrochloride is believed to be metabolized by cytochrome P450 1A2 in the liver. However, studies are still progressing to prove this.

**Major metabolites:**

- 1) DS-200-717 (guanidine, [(5-chloro-4-(2-imidazolylamino)-2,1,3-benzothiazole])
- 2) DS-201-341 (amide, [5-chloro-4-(guanidino)-2,1,3-benzothiazole]).

**Reaction site:**

Tizanidine hydrochloride is a centrally acting skeletal muscle relaxant and is an agonist at the  $\alpha$ -2 adrenergic receptor site. Spasticity is decreased by increasing presynaptic inhibition of motor neurons. Its effects are greatest at polysynaptic pathways.

**Similar compounds:** The anti-hypertensive drug clonidine and other  $\alpha$ -2 adrenergic agonists have the same imidazoline chemical structure.

**References**

Acorda Therapeutics. "Zanaflex Capsules™" Acorda: Pipeline: Marketed Products: Zanaflex. 2006. Acorda Therapeutics. 20<sup>th</sup> March 2006.

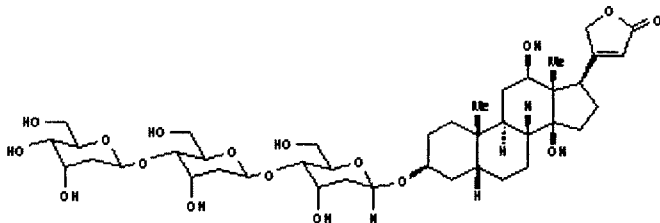
Granfors, M. et al. "Tizanidine is mainly metabolized by cytochrome P450 1A2 *in vitro*." British Journal of Clinical Pharmacology. 57.3 (2003): 349-353.

Shellenberger, M. et al. "A Controlled Pharmacokinetic Evaluation of Tizanidine and Baclofen at Steady State." Drug Metabolism and Disposition. 27.2 (1999): 201-204.

U.S. Food & Drug Administration. "Zanaflex®" 30<sup>th</sup> of August 2002. U.S. Food & Drug Administration. 17<sup>th</sup> March 2006.

## DIGOXIN

*Digoxin is a cardiac glycoside extracted from the foxglove plant, digitalis. It is widely used in the treatment of various heart conditions, and heart failure that cannot be treated by other medication. Cardiac glycosides are composed of two structural features: the sugar (glycoside) and the non-sugar (aglycone - steroid). Its nomenclature and structure are given below.*



(3 $\beta$ ,5 $\beta$ ,12 $\beta$ )-3-[(O-2,6-Dideoxy- $\beta$ -D-ribo-hexopyranosyl-(1 $\rightarrow$ 4)-O-2,6-dideoxy- $\beta$ -D-ribo-hexopyranosyl-(1 $\rightarrow$ 4)-2,6-dideoxy- $\beta$ -D-ribo-hexopyranosyl)oxy]-12,14-dihydroxycard-20(22)-enolide.

**Synthesis.** The cardiac drug digoxin, in use for more than 200 years, was discovered by an English physician William Withering who stemmed from an herbal preparation rather than from laboratory chemistry. Digoxin is extracted from the leaves of the woolly foxglove, which is a member of the snapdragon family. The dried foxglove leaves are extracted using an aqueous-alcohol solvent and they contain a number of glycosides which are the chemicals that are composed of a sugar and a cardenolide (which has a five-membered lactone ring) that are called digitalis.

**Pharmacokinetics.** Digoxin is usually given by mouth and well absorbed into blood are widely distributed to tissues including the central nervous system, but can also be given by IV injection in urgent situations. The half life is about 36 hours, digoxin is given once daily, usually in 125 $\mu$ g or 250 $\mu$ g dosing. In patients with decreased kidney function the half life is considerably longer, a reduction in dosing or a switch to a different glycoside (digitoxin). Because the safety margin of cardiac glycosides is very narrow, a minor variation in bioavailability can cause major toxicity or loss of effect. It is not extensively metabolized in humans and almost two thirds is excreted unchanged by the kidneys then be reabsorbed from the intestine.

**Pharmacodynamics.** The main action of digoxin and the other cardiac glycosides is to inhibit the sodium-potassium ATPase pump located in the membrane of myocytes (heart muscle cells). The cardiac glycosides bind to a site on the extracellular of the  $\alpha$ -subunit of the  $\text{Na}^+/\text{K}^+$  ATPase pump in the membranes of heart cells then inhibit the membrane bound  $\text{Na}^+/\text{K}^+$ -ATPase pump responsible for  $\text{Na}^+/\text{K}^+$  exchange. This causes an increase in the level of intracellular sodium ions in the myocytes, which then also leads to increase in the level of calcium. Inhibition of this removes the regulation of a low intracellular sodium ion concentration, and a high potassium ion concentration. The increase in intracellular calcium concentration activates a cascade of intracellular biochemical actions that ultimately result in an increase in the force of the myocardial contraction or a positive inotropic effect for most heart failure patients.

### References:

1. Katz AM: Effects of digitalis on cell biochemistry: Sodium Pump Inhibition. *J Am Coll Cardiol* 1985;5(Suppl A):16A
2. Katzung B: Basic and Clinical Pharmacology. 9<sup>th</sup> edition. The McGraw-Hill Companies, 2004
3. Rang, Dale, Ritter, Moore. Pharmacology (5th edition), Churchill Livingstone, 2003. ISBN 0443 071454
4. Schrier RW, Abraham WT: Hormones and hemodynamics in heart failure. *N Engl J Med* 1999;341:577
5. Zimmermann N et al: Positive inotropic effects of the calcium sensitizer CGP 48506 in guinea pig myocardium. *J Pharmacol Exp Ther* 1996;277:1572

**IUPAC:** (2 a, 6 a, 8 a, 9 a b)-octahydro-3-oxo-2, 6-methano-2H-quinolizin-8-yl-1H-indole-3-carboxylate monomethanesulfonate, monohydrate.

## Abstract

Dolasetron has been found to be a selective, and reversible antagonist of neuronal 5' hydroxytryptamine (5-HT<sub>3</sub>) receptors (1). Prescribed as an antiemetic and antiemetic, Dolasetron reduces nausea and vomiting associated with chemotherapy and postoperative effects with minimal side-effects and toxicity. Nausea and vomiting side-effects are thought to be induced by the release of serotonin by the enterochromaffin cells of the small intestine which activates the 5-HT<sub>3</sub> receptors on the vagal efferents that start the vomiting reflex. Dolasetron blocks that 5-HT<sub>3</sub> binding site of this ligand-gated ion channel, inhibiting the reflex. Dolasetron is quickly metabolized when taken orally or by IV. The primary metabolic pathway consist of carbonyl reductases that almost completely reduce the ketone group resulting in stereoselective hydrodolasetron (R+) isomer major product. The hydrodolasetron has a half life of 5.9 to 7.9 hr after reaching its maximum plasma concentration. Hydrodolasetron is then metabolized by the P450 isoenzyme CYP2D6 to 5'OH Hydrodolasetron and 6'OH Hydrodolasetron being the primary products. The 5'OH and 6'OH metabolites can be excreted as is or metabolised further to glucuronide or sulfate conjugates. In vitro testing has shown that Dolasetron, the (R+), (R-) hydrodolasetron isomers and the 5'OH and 6'OH metabolites selectively inhibit 5-HT<sub>3</sub>. The (R+) isomer is the major product and is the most active. Since the metabolism of Hydrodolasetron involves the CYP450 mixed oxidase system, drugs that affect this system may cause drug-drug interactions (1).

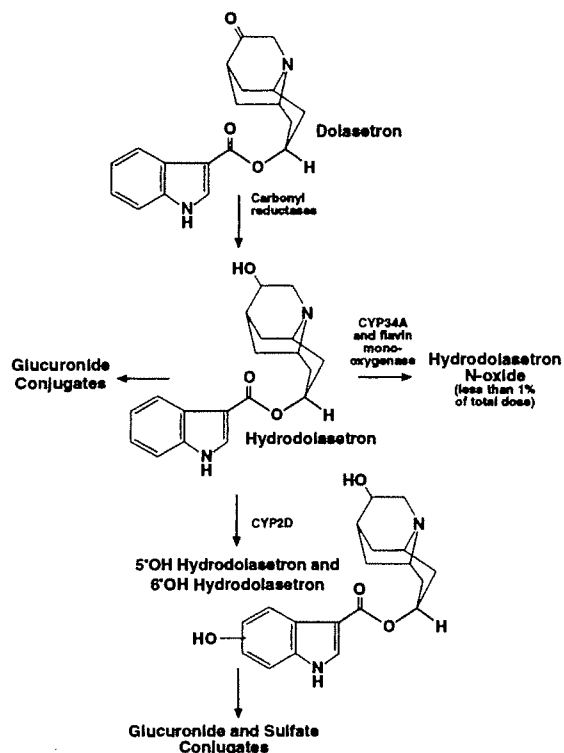
Morphine sulfate was first shown to be an antagonist of the 5-HT<sub>3</sub> receptor. 5-HT is an indole alkylamine neurotransmitter found in the central and peripheral nervous system and also in the nerves that stimulate the gut. Metoclopramide had been known to stimulate gut activity but is also a weak antagonist of 5-HT<sub>3</sub> receptors. Use of Metoclopramide as an antiemetic for cisplatin induced emesis stimulated research into 5-HT<sub>3</sub> receptor inhibition antiemetics(2).

Synthesis information for Dolasetron does not seem to be readily available.

## References

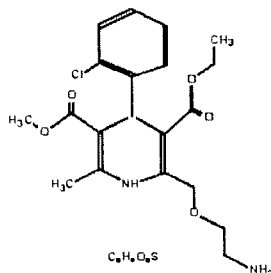
1. Robert C. Miller, Martin Galvan, Maurice W. Gittos, Paul L. M. van Giersbergen, Paul C. Moser, John R. Fozard **Pharmacological properties of dolasetron, a potent and selective antagonist at 5-HT<sub>3</sub> receptors** Drug Development Research Vol. 28, Issue 1, 1993. Pg. 87-93
2. Paul J. Hesketh\* David R. Gandara **Serotonin Antagonists: A New Class of Antiemetic Agents** JNCI Vol. 83, Num. 9 1993.
3. [www.rxlist.com](http://www.rxlist.com) website
4. <http://redpoll.pharmacy.ualberta.ca/drugbank/>

## Structure/Metabolite



**IPUAC:** 3-Ethyl-5-methyl (+/-)-2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-1, 4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate.  $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$

### STRUCTURE:



**Abstract:** Norvasc (Amlodipine besylate) is third generation calcium channel blocker (CCB) to treat hypertension and coronary artery disease (CAD). Amlodipine has a longer half-life than the first generation of CCBs, such as nifedipine, with bioavailability between 64-90% and lasting effects of more than 16 hours at daily dosage of 5-10mg. Amlodipine is administered as racemates, active S-(-)-amlodipine and non-active R-(+)-amlodipine. It has many advantages over first generation CCBs, for example, it reduces symptoms, plasma norepinephrine concentration in heart failure, morbidity and mortality.

Amlodipine has pleiotropic effects. During atherogenesis, cellular cholesterol levels increases, thus, creating cholesterol domains in the plasma membrane. The increased level alters the activation of calcium ion channels, therefore, disrupting normal gene expression and cell proliferation. Amlodipine achieves calcium ion channel blockage by binding to both dihydropyridine and nondihydropyridine binding sites present in the vascular smooth muscle and cardiac muscle. Among other pleiotropic effects, Amlodipine has a high lipophilicity which enables it to inhibit the aggregation of oxidized LDL, it has reported antioxidant properties achieved by inhibiting lipid peroxide formation at as low concentration as 10mM/L, and it stimulates endothelial NOS (eNOS) activity, an enzyme responsible for NO production in endothelial cells, where no calcium ion channels are present.

Amlodipine is deactivated by the liver's metabolism. 90% of the parent molecule is broken down into 18 metabolites, mostly pyridine derivatives, from which, 60% are secreted through the urine along with about 5% as parental molecules.

This study will concentrate in the pleiotropic effects of Amlodipine observed during the treatment of hypertension and CAD.

#### References:

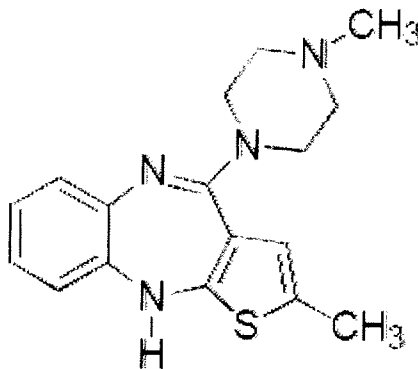
- Mason, P. R. *Mechanism for plaque stabilization for the dihydropyridine calcium channel blocker Amlodipine: review of evidence.* Atherosclerosis 2002; 165:191-1999
- Mason, P.R., Marche, P., Hintze, T.H. *Novel Vascular Third-generation L-Type Calcium Channel Antagonist: Ancillary Actions of Amlodipine.* Atherosclerosis 2003; 23: 2155-2163.
- Stopher, D.A., Beresford, A.P., Macrae, P.V., Humphrey, M.J. *The metabolism and pharmacokinetics of amlodipine in humans and animals.* J Cardiovasc Pharmacol. 1988;12 Suppl 7:855-9.
- Yamazaki, T., Komuro, I., Zou, Y., Kudoh, S., Shiojima, I., Mizuno, T., Hiroi, Y., Nagai, R., Yazaki, Y. *Efficient Inhibition of the Development of Cardiac Remodeling by a Long-Acting Calcium Antagonist Amlodipine.* Hypertension; 1998; 31:32.
- Luksa J., Josic D., Podobnik B., Furlan B., Kremser M. *Semi-preparative chromatographic purification of the enantiomers S-(-)-amlodipine and R-(+)-amlodipine.* J Chromatogr B Biomed Sci Appl. 1997; 693(2):367-75.
- Beresford AP, Macrae PV, Alker D, Kobylecki RJ. *Biotransformation of amlodipine. Identification and synthesis of metabolites found in rat, dog and human urine: confirmation of structures by gas chromatography-mass spectrometry and liquid chromatography-mass spectrometry.* Arzneimittelforschung. 1989; 39(2):201-9.
- Pieper, JA. *Evolving role of calcium channel blockers in heart failure.* Pharmacotherapy. 1996; 16(2 Pt 2):43S-49S.

## Zyprexa (Olanzapine) Eli Lilly

### **IUPAC name:**

2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*] [1,5]benzodiazepine.

### **Chemical structure:**



### *Drug metabolites:*

olanzapine 10-*N*-glucuronide; olanzapine 4'-*N*-glucuronide; 4'-*N*-desmethylolanzapine; olanzapine *N*-oxide

### **Description/Indications/Side effects:**

Zyprexa (olanzapine) is a yellow crystalline solid practically insoluble in water. It is a psychotropic drug used in the maintenance treatment of schizophrenia and to alleviate acute bipolar mania, and sometimes as maintenance therapy in bipolar disorder. It is taken orally via 2.5 to 10 mg tablets. Side effects include: constipation, weight gain, dizziness, personality disorder, akathisia (motor restlessness), dry mouth, somnolence, tremor, and asthenia (weakness).

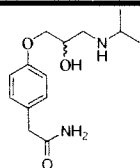
### **Suspected Mechanism of Action:**

- Antagonist of dopamine D1 receptors
- Inverse agonist at dopamine D2 receptors
- Antagonist of dopamine D3 and D4 receptors
- Antagonist of histamine H1 receptors
- Antagonist of alpha-1 adrenoceptors
- Antagonist of M1 and M5 muscarinic acetylcholine receptors

### **References:**

1. [www.zyprexa.com](http://www.zyprexa.com)
2. [www.neurotransmitter.net/drug\\_reference.html](http://www.neurotransmitter.net/drug_reference.html)
3. [http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label\\_ApprovalHistory#aphist](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#aphist)
4. <http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO2&Sect2=HITOFF&u=/netahtml/search-adv.htm&r=271&f=G&l=50&d=PTXT&s1=olanzapine&p=6&OS=olanzapine&RS=olanzapine>
5. <http://pi.lilly.com/us/zyprexa-pi.pdf>

## Atenolol

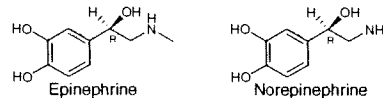


Chemical Formula:  $C_{14}H_{22}N_2O_3$   
Molecular Weight: 266.34

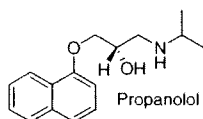
IUPAC: 4-[2'-hydroxy3'-(1-methylethyl)amino]propyl]-benzeneacetamide

### Background:

Peripheral adrenergic receptors are GPCRs that bind the catecholamines epinephrine and norepinephrine. Epinephrine is synthesized in the adrenal medulla and released into the body through the bloodstream as a result of the body's "fight or flight" response. Its effects are stimulation of the heart, dilation of blood vessels and decrease of GI activity. Norepinephrine is a neurotransmitter that is released by sympathetic nerves and is used by the body to contract skeletal muscle and constrict blood vessels. Adrenergic receptors have two main subtypes  $\alpha$  (alpha) and  $\beta$  (beta) with subclasses of each. Alpha ( $\alpha$ ) receptors are the most common sympathetic receptor and have a higher affinity for norepinephrine. Beta ( $\beta$ ) receptors are either nonspecific binders ( $\beta_1$ ) or preferentially bind epinephrine ( $\beta_2$ ). Beta-1 receptors are found in the heart while beta-2 receptors are found throughout the body on blood vessels and smooth muscle. Atenolol is a beta-1 cardio selective adrenoreceptor blocking agent. Its antagonist activity is selective towards the beta-1 receptors found in the heart. It is used to treat hypertension, angina pectoris, myocardial infarction and arrhythmias without the complications associated with non-selective beta blockers.



### Discovery:



Beta blockers were originally developed as a treatment for angina. The first beta blocker used clinically was propranolol, synthesized in 1958 by Sir James Whyte Black. While propranolol was selective towards the beta subtype of adrenergic receptor it did not differentiate between the subclasses of beta receptors. Asthmatic as well as circulatory complications seen with the use of propranolol were attributed to its beta-2 antagonist effects. Nervous system side effects were also

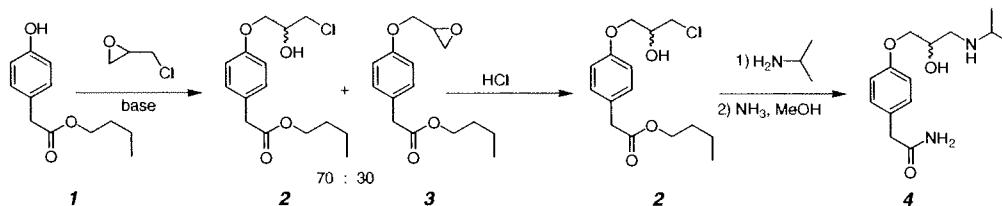
noted as being caused by propranolol's ability to cross the blood brain barrier.

A second generation of beta blockers was developed to selectively antagonize beta-1 or beta-2 receptors. Atenolol was developed by ICI in 1976 as a beta-1 selective antagonist. It was marketed by AstraZeneca as Tenormin® and today is made as a generic drug by a number of companies. To date it is the third best selling drug in the world.

### Synthesis:

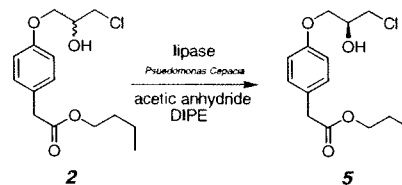
The industrial synthetic scheme is not readily available due to patent concerns. Below is a model synthesis from patent literature:

Butyl p-hydroxyphenylacetate (1) is treated with epichlorohydrin and catalytic pyridine to give a mixture of (2) and (3). This mixture is converted to the more desired product (2) by the addition of



HCl. Addition of isopropyl amine to the reactive chloride followed by formation of the terminal amide with ammonia in methanol gives the final product. Purification is accomplished through recrystallization from ethyl acetate.

Both enantiomers of atenolol are bioactive and it is synthesized and sold as a racemic mixture. Recent studies have shown that excessive heart rate reduction and other unwanted side effects may be due to the R enantiomer. A stereoselective synthesis of S-atenolol could be achieved by subjecting (2) to a lipase of *Pseudomonas Cepacia* prior to amine derivation and amide formation.



### Dosing and PK:

Atenolol is dosed orally (25-100 mg once a day) or via IV injection (10 mg once followed by oral dosing).

The following PK statistics are for oral dosing:

Bioavailability: Absorption is rapid and consistent, though it is incomplete: 50% of the drug enters circulation, the remainder is excreted in the feces.

Drug in circulation: 90% is found unchanged, 10% is present as hepatic metabolites, 6-16% plasma protein bound.

Atenolol clearance occurs renally.  $t_{1/2}$ : 6-7 h;  $t_{cmax}$ : 2-4h

### References:

PDR.net. Physician's Desk Reference - online edition. Thompson Healthcare. March 21, 2006 <<http://www.pdr.net/>>

Silverthorn, Dee Unglaub. Human Physiology: An Integrated Approach. San Francisco: Pearson Benjamin Cummings, 2004.

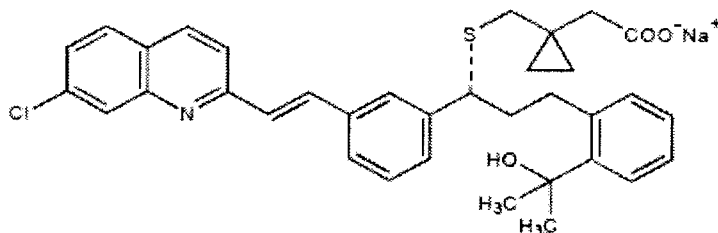
Patrick, Graham L. An Introduction to Medicinal Chemistry 3<sup>rd</sup> Ed. New York: Oxford University Press, 2005.

The Merck Index. The Merck Index 13<sup>th</sup> Edition - online. Cambridgesoft. March 21, 2006

## Singulair (MONTELUKAST SODIUM)

IUPAC: [*R*-(*E*)]-1-[[[1-[3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl]propyl]thio]methyl]cyclopropaneacetic acid, monosodium salt

Structure:



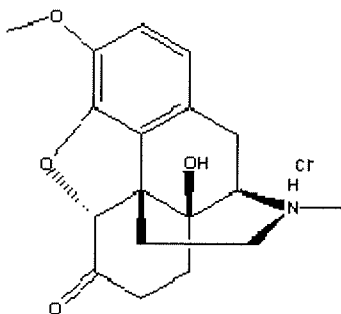
Singulair is a drug prescribed to relieve symptoms of asthma. It is advised to be used as long term care for asthma patients. It can also help to control the symptoms of allergic rhinitis. The starting point in the development of montelukast appears to be a quinoline-containing structure, likely identified as a weak random screening lead. Montelukast sodium, the active ingredient in Singulair. Montelukast sodium is a hygroscopic, optically active, white to off-white powder. Montelukast sodium is a selective and orally active leukotriene receptor antagonist that inhibits the cysteinyl leukotriene CysLT1 receptor. The CysLT type-1 (CysLT1) receptor is found in the human airway (including airway smooth muscle cells and airway macrophages) and on other pro-inflammatory cells (including eosinophils and certain myeloid stem cells). CysLTs has been shown to increase nasal airway resistance and symptoms of nasal obstruction. Montelukast is an orally active compound that binds with high affinity and selectivity to the CysLT1 receptor (in preference to other pharmacologically important airway receptors, such as the prostanoid, cholinergic, or  $\beta$ -adrenergic receptor). Montelukast inhibits physiologic actions of LTD4 at the CysLT1 receptor without any agonist activity. Montelukast causes inhibition of airway cysteinyl leukotriene receptors as demonstrated by the ability to inhibit bronchoconstriction due to inhaled LTD4 in asthmatics. Montelukast is more than 99% bound to plasma proteins. Doses as low as 5 mg cause substantial blockage of LTD4-induced bronchoconstriction. Each 10-mg film-coated Singulair tablet contains 10.4 mg montelukast sodium, which is equivalent to 10 mg of montelukast. Some of the possible side effects of Montelukast include stomach pain, intestinal upset, heartburn etc. Women who are pregnant or breast feeding shall not take Singulair.

### References:

- [http://www.fda.gov/medwatch/safety/2005/Nov\\_PI/Singulair\\_PI.pdf](http://www.fda.gov/medwatch/safety/2005/Nov_PI/Singulair_PI.pdf)
- [www.rxlist.com](http://www.rxlist.com)
- Mihaltan F., Bronchial asthma and allergic rhinitis: a new therapeutic challenge. Disfunction co-morbidities--shared therapies? PMID: 16193729 [PubMed - indexed for MEDLINE]
- Chen XJ, Cheng DY, Guan J, Wang H, Zhang Y, Xia XQ., Preventive effects of montelukast on the collagen expression of pulmonary arterioles in rats with chronic hypoxia PMID: 15807270 [PubMed - indexed for MEDLINE]

## Oxycontin

Oxycontin, an oxycodone hydrochloride controlled-release, is an oral administration that moderates to severe pains. Tablets are an opioid analgesic supplied in 10mg, 20mg, 40mg, 80mg, 160mg tablet strengths for oral administration. Its IUPAC name and structure are given below.



*4, 5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride*

**Synthesis:** OxyContin was introduced by Purdue Pharma in 1995. OxyContin is synthesis by oxidation of codeine to codeinone, formation of a dienolsilyl ether congener of codeinone in strong amine base, oxidation of the dienolsilyl ether using peracetic acid, and hydrogenation of the resulting 14-hydroxycodeinone.

**Therapeutic:** OxyContin is an opioid agonist and a Schedule II controlled substance. It is an analgesic medicine, prescribed for pain relief that is released slower over a longer period of time for cancer patients that are in extreme pain. The activity of the drug can last for 12 hours. Also, OxyContin is labeled as an abused drug because crushing, chewing, snorting, or injection of the drug can cause uncontrolled delivery of the opioid that can lead to overdose and death.

**Distribution:** When Oxycodone is released, it is absorbed and distributes to skeletal muscle, liver, intestinal tract, lungs, spleen, and brain.

**Mechanism:** The exact mechanism of the analgesic action is unknown. But, the drug binds to specific CNS opioid receptors that show activity throughout the brain and spinal cord.

**Metabolism/Elimination:** OxyContin (Oxycodone hydrochloride) is extensively metabolized to oxymorphone, noroxycodone, and their glucuronides. Both Noroxycodone and Oxymorphone are metabolized by cytochrome P450, a demethylation, and then glucuronidation. Both metabolites have small amount of activity. Noroxycodone analgesic is weaker than Oxycodone and Oxymorphone has some analgesic activity, but it is presented in the plasma in a low concentration. Noroxycodone is the major metabolite circulating through the body. These metabolites are excreted primarily through the kidney.

**Side effects/Toxicity:** The side effects of taking Oxycontin were tested using patients who are in severe pain. The side effects are constipation, nausea, somnolence, dizziness, vomiting, headache, dry mouth, sweating, and asthenia by taking daily doses ranging from 20 mg – 640 mg.

## DEMEROL

(meperidine hydrochloride, USP)

1-methyl-4-phenyl-ethyl ester, hydrochloride



Demerol is a narcotic analgesic used to relieve moderate to severe pain during childbirth or for postoperative patients. It is a synthetic opioid possessing 10-12% overall potency to that of morphine. Demerol was discovered by chance in the 1940s when chemists were studying analogues for cocaine for antispasmodic properties. To synthesize Demerol, the quasi-Favorskii rearrangement is employed. Based on intrinsic activity, Demerol is classified as an agonist whose aromatic ring and basic nitrogen are essential for activity. It interacts predominantly with the  $\mu$ -opioid receptor and its chief pharmacological action is on the central nervous system and organs composed of smooth muscle. Due to its lipid-solubility, Demerol is a fast-acting analgesic. It also has a shorter duration of action. Analgesic effects after oral and intravenous/intramuscular administration are detectable after 15 and 10 minutes, respectively. In terms of total analgesic effect, Demerol is one-third as effective when given by mouth as when administered parenterally. Use of Demerol has diminished in recent years due to concerns over metabolite toxicity. It is metabolized chiefly in the liver and undergoes P450 dependent N-demethylation to produce normeperidine, its main metabolite. Normeperidine is not an analgesic, but is a potent central nervous system excitatory agent and is associated with the adverse side effects of Demerol. Demerol analogues have been created to serve as potential selective serotonin reuptake inhibitors. Alternatively, other analogues were developed to act as potent ligands for the high-affinity cocaine binding site of the dopamine transporter in order to relate this action to cocaine abuse.

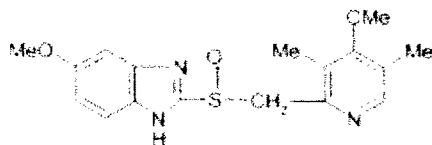
## REFERENCES

- Gilman, A., L. Goodman, T. Rall, and F. Murad. 1985. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 7<sup>th</sup> ed. New York: Eds. Macmillan Publishing Co.
- Harvard-MIT Division of Health Sciences and Technology. Opioid Pharmacology. Cambridge, MA: Harvard University and Massachusetts Institute of Technology.
- Lomenzo, S., J. Rhoden, S. Izenwasser, D. Wade, T. Kopajtic, J. Katz, and M. Trudell. 2005. Synthesis and Biological Evaluation of Meperidine Analogues at Monoamine Transporters. *J. Med. Chem.* 48: 1336-1343.
- Nursing 2001 Drug Handbook. 21<sup>st</sup> ed. Pennsylvania: Springhouse Corporation, 2001.
- Patrick, G. L. 2005. An Introduction to Medicinal Chemistry, 3<sup>rd</sup> ed. New York: Oxford University Press.
- Perlman, K., S. Myers-Phariss, and J. Rhodes. 2004. A Shift From Demerol (Meperidine) to Dilaudid (Hydromorphone) Improves Pain Control and Decreases Admissions for Patients in Sickle Cell Crisis. *J Emerg Nurs.* 30: 439-446.
- Physician's Desk Reference. New Jersey: Medical Economics Co., 2005.
- Ramirez, J., F. Innocenti, D. Flockhart, R. Santucci, and M. Ratain. 2004. Role of CYP3A4 and CYP2B6 in the In Vitro N-Demethylation of Meperidine. *Clin Pharmacol Ther.* 75: P85.
- Rhoden, J., M. Bouvet, S. Izenwasser, D. Wade, S. Lomenzo, and M. Trudell. 2005. Structure-activity studies of 3'-4'-dichloro-meperidine analogues at dopamine and serotonin transporters. *Bioorg Med Chem.* 13: 5623-5634.
- Silverman, R. B. 2004. The Organic Chemistry of Drug Design and Drug Action. 2<sup>nd</sup> ed. San Diego: Elsevier Academic Press.
- Smisson, E. and G. Hite. 1959. The Quasi-Favorskii Rearrangement. I. The Preparation of Demerol and  $\beta$ -Pethidine. *J. Med. Chem.* 81: 1201-1203.

# Omeprazole (Prilosec®)

17 Benzimidazole derivatives

Omeprazole is a substituted benzimidazole compound with potent anti-secretory properties. Administered orally, it suppresses gastric acid secretion by inhibiting the H<sup>+</sup>/K<sup>+</sup> ATPase enzyme system (proton pump) at the surface of the gastric parietal cell.



5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl] methyl] sulfinyl]-1H-benzimidazole

**Synthesis.** A substituted 2-mercaptoimidazole was readily obtained by condensation of amines with isothiocyanacetalddehyde diethyl acetal or isothiocyanates with aminoacetalddehyde diethyl acetal followed by cyclization of the resulting thioureas under acidic conditions. Next, alkylation of the substituted 2-mercaptoimidazole with *N,N*-disubstituted 2-aminobenzyl chloride under alkaline conditions yielded the desired sulfide. Furthermore, oxidation of the sulfide was effected with *m*-chloroperbenzoic acid to give the desired sulfoxide (omeprazole).

**Metabolism.** Absorption is rapid, with peak plasma levels of omeprazole occurring within 0.5 to 3.5 hours. Peak plasma concentrations of omeprazole and AUC are approximately proportional to doses up to 40 mg, but because of a saturable firstpass effect, a greater than linear response in peak plasma concentration and AUC occurs with doses greater than 40 mg. Absolute bioavailability (compared to intravenous administration) is about 30–40% at doses of 20–40 mg, due in large part to presystemic metabolism. The majority of the drug (about 77%) is eliminated in urine as at least six metabolites. Two are identified as hydroxyomeprazole and the corresponding carboxylic acid. The remainder of the drug is recoverable in feces. This implies a significant biliary excretion of the metabolites of omeprazole. Three metabolites have been identified in plasma — the sulfide and sulfone derivatives of omeprazole, and hydroxyomeprazole. These metabolites have very little or no antisecretory activity.

**Prodrug and comparative activity.** Among studies on H<sup>+</sup>/K<sup>+</sup>-ATPase inhibitors, 2-[(2-pyridylmethyl)sulfinyl]benzimidazoles (PSBs) such as omeprazole, lansoprazole, and pantoprazole have been found to have superior properties responsible for complete suppression of gastric acid secretion, and have recently been introduced as clinically useful agents. The PSBs act as prodrugs, being chemically transformed into the highly thiophilic sulfenic acid and the cyclic sulfenamide in an acidic environment such as the apical membrane of the parietal cell. The thiophilic sulfenic acid and the sulfenamide react readily with thiol groups on the enzyme to form an enzyme-inhibitor complex with a tight S-S bond.

Doria G., Passarotti C., Sala R., Magrini R., and Toti D. (1985). 7-Trans-(2-Pyridylethenyl)-5H-Thiazolo[3,2-A]Pyrimidine-5-Ones – Synthesis and Pharmacological. *Farmaco-Edizione Scientifica* 40 (12): 885-894.

Hideo T., Akihiko T., Keiko T., Keiji N., Yasuhiro S., and Yoshinori N. (1997). Nicotinamide Derivatives as a New Class of Gastric H<sup>+</sup>/K<sup>+</sup>-ATPase Inhibitors. Synthesis and Structure-Activity Relationships of *N*-Substituted 2-(Benzhydryl- and benzylsulfinyl) nicotinamides. *J Med Chem.* 40, 313-321.

Manouchehr K., Ebrahim F., Nosratollah N., Farzaneh K., and Mohammadreza R. (2006). A comparison of oral omeprazole and intravenous cimetidine in reducing complications of duodenal peptic ulcer. *BMC Gastroenterology* 2006, 6:2.

Masaki Y., Takeshi Y., Masamichi M., Tsunehiro H., Koichiro Y., Yasushi H., Mine K., and Masaki S. (1996). 2-[(2-Aminobenzyl)sulfinyl]-1-(2-pyridyl)-1,4,5,6-tetrahydrocyclopent[*d*]imidazoles as a Novel Class of Gastric H<sup>+</sup>/K<sup>+</sup>-ATPase Inhibitors. *J Med Chem.* 39, 596-604.

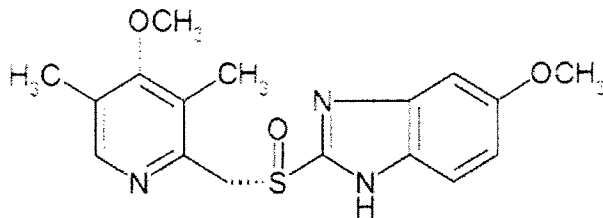
Omar A., Farghaly A., and Shamseldine S. (1975). Novel Synthesis of 2-substituted Aminobenzimidazoles From Thiourea Derivatives. *Pharmazie* 30 (2): 83-84.

Sanfilippo P., Urbanski M., Press J., and Scott C. (1988). Synthesis of (aryloxy)

### Nexium (esomeprazole magnesium)

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

**Structure:**



Nexium is a proton pump inhibitor (PPI) which inhibits the  $H^+$ ,  $K^+$ -ATPase. It is a highly effective inhibitor of gastric acid secretion used in the therapy of stomach ulcers and it also used to treat gastroesophageal reflux disease (GERD/ heartburn).

**Synthesis:** Esomeprazole which is the (S)-enantiomer of omeprazole and also known as Nexium™, a new proton pump inhibitor. Esomeprazole is synthesized via asymmetric oxidation of prochiral sulphide. The asymmetric oxidation was achieved by titanium-mediated oxidation with cumene hydroperoxide (CHP) in the presence of (S,S)-diethyl tartrate [(S,S)-DET].

**Metabolism:** Esomeprazole is metabolized in liver by the cytochrome P450 (CYP) enzyme system. The metabolites of esomeprazole lack antisecretory activity. Therefore, the major part of esomeprazole's metabolism is dependent upon the CYP2C19 isoenzyme which forms the hydroxyl and desmethyl metabolites. The remaining amount is dependent on CYP3A4 to form the sulphone metabolite.

**Comparative Activity:** Esomeprazole which is derived from the (S)-enantiomer of omeprazole is proved to be a first drug that is superior to omeprazole both as a gastric acid inhibitor and GERD disease. The earliest treatment of acid-related disease was the used of antisecretory drug cimetidine which was an antagonist of the histamine 2 ( $H_2$ ) receptor. However,  $H_2$  receptor antagonists have a short duration of action.

**Pro-drug:** Tenatoprazole which is a pro-drug of esomeprazole is converted to the active sulfonamide or sulfenic acid by acid in the secretory canaliculus of the stimulated parietal cell of the stomach. Beside, tenatoprazole is more potent than esomeprazole in exertion acid inhibition by extending the duration of acid suppression and a shorter nocturnal acid.

### References:

- Carlson, E; Lindberg, P; Olbe, L. A Proton- Pump Inhibitor Expedition: The case Histories of Omeprazole and Esomeprazole. *Nature Reviews Drug Discovery*. 2003, 2, 132
- Cotton, H; Elebring, T; Larson, Magnus; Li, L; Sorensen, H; Unge, S. V. Asymmetric Synthesis of Esomeprazole 2000, 11, 3819-3825.
- Domagala, F; Ficheux, H; Homerin, M; Sachs, G; Shin, JM. Characterization of The Inhibitory Activity of Tenatoprazole on The Gastric  $H^+$ ,  $K^+$ -ATPase in Vitro and In Vivo. *Biochemical Pharmacology*. 2006, 71, 837-849.
- Esplugues, JV. A Pharmacological Approach To Gastric Acid Inhibition. 2005, 65, 7-12.
- F, Gomollon; X, Calvet. What Is Potent Acid Inhibition and How Can It Be Achieved. 2005, 65, 13-23.