1

History of Drug Discovery

Jie Jack Li

1 Introduction

The history of drug discovery is as ancient as our glorious history of humanity. Shen Nung, *The Divine Farmer*, is fabled to have sampled 365 herbs himself to evaluate their medicinal value as early as 2337 B.C. in China. In 400 B.C. in Greece, Hippocrates, *The Father of Medicine*, decreed the *Hippocratic Oath*, in which a physician is to pledge "I will preserve the purity of my life and my arts". Another Greek Physician, Galen (129–199), influenced 45 generations with his teachings of medicine, transforming medicine from art to science. During the Renaissance, Paracelsus (1493–1541) from Switzerland represented the pinnacle of Western medicine. Since then, a parade of luminaries began to unveil the myth of life. Andreas Vesalius (1514–1564) of Brussels founded the *Science of Anatomy*. William Harvey (1578–1657) of England made one of the greatest discoveries in medicine—*Circulation of Blood*. Dutchman Antonie von Leeuwenhoek (1632–1723) opened our eyes to a whole new world of microbes by inventing the microscope.

The intellectual contributions of these great men established the foundation of modern medicine and heralded the golden age of contemporary drug discovery.

2 Antibacterials

2.1 Lister and Carbolic Acid

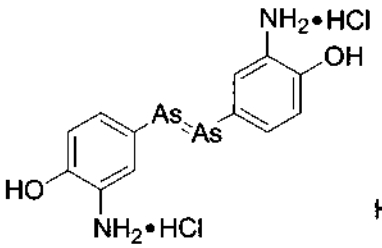
Although many contributed to the *germ theory*, French chemist Louis Pasteur (1822–1895) transformed medicine with his well-designed experiments and a treatise entitled *Organized Corpuscles Existing in Atmosphere* published in 1855.[1] Pasteur's *tour de force* officially introduced and cemented germ theory within mainstream science. The pasteurization process, heating the food at a specific temperature for a certain time and then cooling it immediately, is still the standard practice. Merely one year later, Joseph Lister (1827–1912) in England successfully applied the germ theory by using carbolic acid (phenol) as an antiseptic during surgery to kill bacteria.

As a surgeon, Lister was appalled at the postsurgical infections, which killed patients with an astonishing 40–60% mortality rate. However, simple and direct application of the pasteurization process would not be acceptable during surgery—after all one could not simply boil the patient in hot water! Inspired by anecdotal success stories of carbolic acid (an ingredient

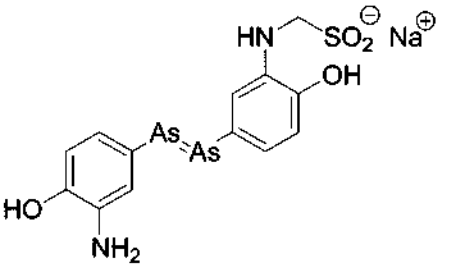
isolated from coal tar, a waste from coal gas production) in deodorizing sewage and in controlling typhoid, Lister introduced carbolic acid as an antiseptic in surgery.[2] It works by solubilizing the phospholipids in cell membranes, thus disrupting the cell membranes. Today, *asepsis* has largely replaced *antisepsis* in the operating rooms.

2.2 Dr. Ehrlich's Magic Bullet

In the 1890s, together with Emil von Behring, Paul Ehrlich (1854–1915) developed a horse serum antitoxin to quell diphtheria. The vaccine saved thousands of children's lives during the 1891 outbreak, for which he won the Nobel Prize in 1908. Since 1910, working with his Japanese associate Sachachio Hata, Ehrlich experimented with numerous chemicals to treat syphilis.[3] They had some success with an arsenic compound atoxyl, which was efficacious but was too toxic. His chemist Alfred Bertheim (1879–1914) at first elucidated the chemical constitution of atoxyl and later synthesized innumerable arsenobenzene compounds including arsphenamine (Ehrlich's 606), which was efficacious with an acceptable safety profile.[4] Ehrlich licensed the drug to Hoeschst, who sold it under the trade name Salvarsan. To find less toxic and more water-soluble ant-syphilitics, Bertheim synthesized neoarsphenamine (Neosalvarsan). Both Salvarsan and Neosalvarsan had a tremendous impact on fighting syphilis, wiping out half of the syphilis infections in Europe in a mere five years (although syphilis was not completely eradicated until the introduction of penicillin in the 1940s).



Ehrlich's 606
arsphenamine
(Salvarsan)



neoarsphenamine
(Neosalvarsan)

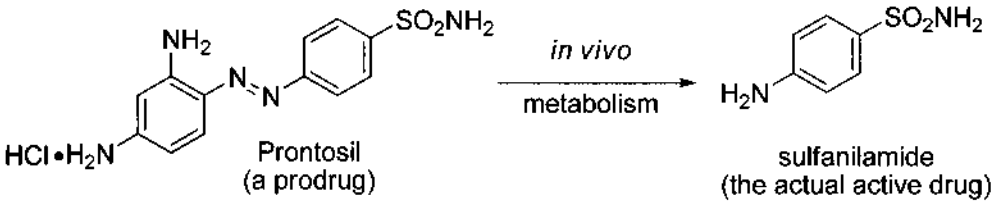
Ehrlich was also the first to propose the *side chain theory* and the *receptor theory* to explain how drugs worked. While he is immortalized as *the father of chemotherapy* and with his concept of *magic bullets*, Bertheim, probably the first medicinal chemist in history, is largely forgotten. In addition to his important contributions to the discovery of Salvarsan and Neosalvarsan, Bertheim also published a book *Ein Handbuch der organischen Arsenverbindungen* (*A Handbook of Organic Arsenic Compounds*).

2.3 Domagk and Sulfa Drugs

In 1932, Gerhard Domagk (1895–1964), the head of the Bacteriology Laboratory of I. G. Farbenindustrie Aktiengesellschaft (I. G. Farben), experimented with different dyes available to him in search of antibacterial drugs.[5] Looking for antibacterials from dyes was most likely influenced by Ehrlich's experiences with staining. By injecting dyes in mice infected with

Streptococcus pyogenes bacterium, Domagk discovered that 2′,4′-diaminoazobenzene-4-sulfonamide, later branded as Prontosil, was effective in killing the bacterium without unacceptable toxic effects. The dye was prepared by Josef Klarer (1898–1953), a chemist at the Bayer Company, a branch of I. G. Farben. Later on, another Bayer chemist, Fritz Mietzsch (1896–1958), prepared the salt of Prontosil, enabling liquid formulation that was more amenable for injection. After Domagk's first disclosure in 1935, Prontosil quickly became widely prescribed for streptococcal infections.

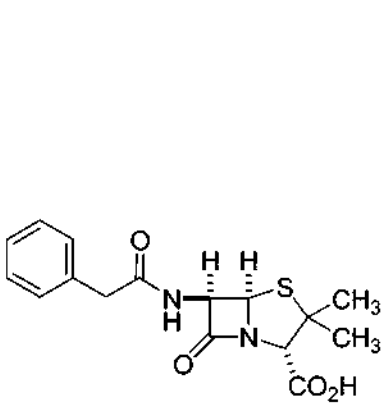
In 1935, a French husband and wife team, Professor Jacques Tréfouël and Madame Therèse Tréfouël, discovered that Prontosil was not active *in vitro*. The real active ingredient for its antibacterial activity is sulfanilamide (mistakenly being called sulfonamide even today), which is generated from *in vivo* metabolism of Prontosil. The mechanism of action (MOA) of sulfanilamides (antimetabolites) is through folate antagonism. Since the structure of sulfanilamide is similar to that of *para*-aminobenzoic acid (PABA), an essential ingredient for cell synthesis, it interrupts bacterial growth.



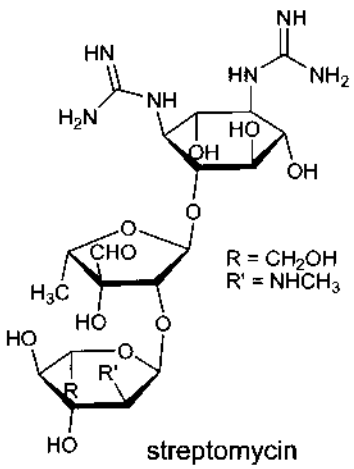
Prontosil (a prodrug) sulfanilamide (the actual active drug)

Domagk was bestowed the Nobel Prize in 1939. He received numerous letters from patients and doctors, expressing their gratitude for his discovery of Prontosil. In contrast, Klarer, the chemist who first synthesized it, received none.

2.4 *Fleming, Florey, Chain, and Penicillin*



penicillin G



streptomycin

Alexander Fleming (1881–1955)[6] actually discovered penicillin in 1928 in England, 4 years before Domagk's Prontosil. However, more than 15 years elapsed until Howard Florey (1898–1968)[7] and Ernst Chain (1907–1979)[8] isolated enough penicillin and demonstrated its curative effects in both mice and humans. Penicillin quickly replaced Ehrlich's 606 and Domagk's sulfa drugs as the most widely used antibiotic. It works for Gram-positive bacterial infections, including strep and staph infections, pneumonia, gangrene, meningitis, as well as gonorrhea (now, however, a resistant form has emerged) and syphilis. The MOA of penicillin is through inhibition of cell wall synthesis. Because animals, including humans, lack a cell wall, penicillin exerts a bactericidal action selectively on growing or multiplying germs.

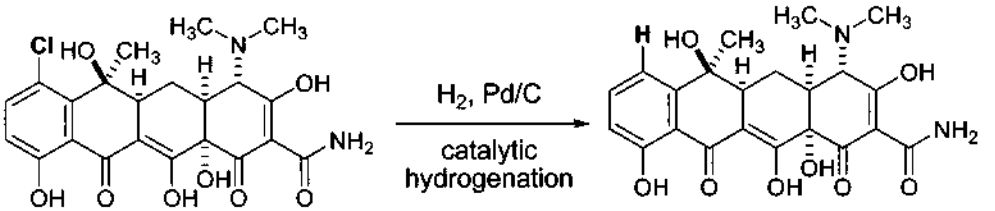
2.5 *Waksman, Schatz, and Streptomycin*

Inspired by Fleming's success with penicillin, Selman A. Waksman (1888–1973), a professor of soil microbiology at Rutgers College, began to look for antibiotics in soil in 1939.[9] At first his group isolated a small molecule antibiotic, actinomycin, and then streptothricin. Although both of them killed Gram-negative bacteria, they were so toxic that they also killed test animals. In October 1943, Waksman's student Albert Schatz isolated streptomycin, an aminosugar. With assistance from Merck for large-scale production and the Mayo Clinic for animal testing and clinical trials, streptomycin was proven to be both safe and effective in treating tuberculosis. Astonishingly, only 3 years elapsed from its discovery to the first successful treatment of a human patient. Nowadays, it generally takes 12 years and over $1.3 billion to bring a drug to the market.

Streptomycin was the first drug to be effective against Gram-negative bacteria. It was particularly interesting at the time because of its activity against human *tubercle bacillus*, which made it the first specific agent effective in treating tuberculosis. Streptomycin works by inducing the binding of "wrong" tRNA-amino-acid complexes, resulting in synthesis of false protein.

2.6 *Duggar, Conover, and Tetracyclines*

In 1945, 73 year old botanist Benjamin M. Duggar was a consultant for Lederle and led their screening efforts in the hunt for antibiotics. Coincidently, a sample from the University of Missouri, where Duggar taught botany 40 years earlier, yielded an antibiotic later named chlortetracycline. Lederle sold chlortetracycline under the brand name of Aureomycin in 1948. Nowadays, Benjamin Duggar is considered the pioneer of tetracycline antibiotics.[10]



chlortetracycline (Aureomycin) tetracycline (Terramycin)

In 1949, a yellow powder with strong antibiotic properties was isolated by Pfizer scientists from a soil sample. The soil organism was *Streptomyces rimosus* and the compound was generically known as oxytetracycline. Backtracking revealed that the soil sample was collected at

the Terre Haute factory in Indiana owned by Pfizer, which later sold oxytetracycline under the brand name Terramycin.

Later on, Lloyd Conover at Pfizer stunned his colleagues by preparing another powerful antibiotic *chemically* from chlortetracycline. Under carefully controlled catalytic hydrogenation conditions, Conover converted Lederle's chlortetracycline to tetracycline. That was the first example of a semisynthetic compound with antibiotic activities.

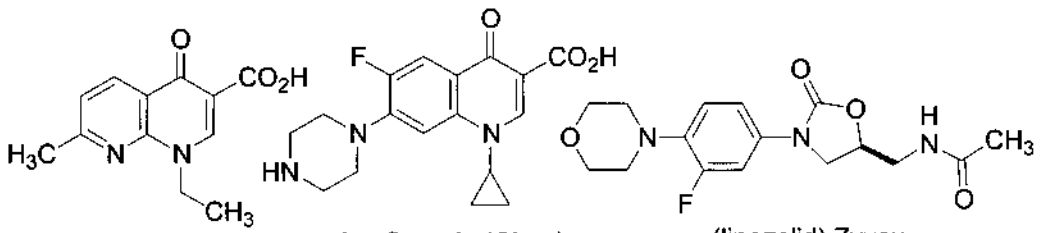
Tetracyclines are inhibitors of protein synthesis by inhibiting the binding of tRNA-amino-acid complexes. They are bacteriostatic.

2.7 Quinolones and Zyvox

In 1946, while pursuing better antimalarial drugs by synthesizing chloroquine, George Y. Lesher (1926–1990) at Sterling Winthrop Research Institute at Rensselaer isolated a by-product, nalidixic acid.[11] It was found to be an antibacterial agent during routine screening. But it did not become popular until 1962 when Lesher introduced it into clinical practice for kidney infections. It was also used to treat urinary tract infections because it was excreted via urine in high concentration. Shortly after, the quinolone antibacterial field flourished, rendering thousands of 4-quinolone derivatives as represented by pipemidic acid. Nalidixic acid and pipemidic acid are considered the first-generation quinolone antibacterials. The drawbacks of these drugs were their moderate activity toward susceptible bacteria and poor absorption by the body.

In the early 1980s, fluorinated quinolone (fluoroquinolone) antibacterials were discovered to possess longer half-lives and better oral efficacy than the first-generation quinolones. These so-called second-generation quinolone antibacterials are exemplified by norfloxacin (the first fluoroquinolone discovered in 1980) and ciprofloxacin (Cipro).[12]

The third generation of quinolone antibacterials is still being actively investigated and is urgently needed due to the rapid development of resistance by bacteria toward existing antibacterial drugs. Examples of the third generation of quinolone antibacterials include fleroxacin and tosufloxacin. They are endowed with sufficiently long half-lives to enable a once-daily regimen, along with enhanced activity toward a variety of bacteria.



nalidixic acid ciprofloxacin (Cipro) (linezolid) Zyvox

The MOA of quinolones is through inhibition of bacterial gyrase (topoisomerase II), thus inhibiting DNA function. Quinolones do not affect human cells because topoisomerase II only exists in bacteria.

Another important category of antibacterial agents is the oxazolidinones as exemplified by linezolid (Zyvox).[13] The genesis of Zyvox began in 1978 when a DuPont patent described some novel oxazolidinones for controlling fungal and bacterial plant pathogens. These compounds and two subsequently optimized drug candidates, DuP 721 and DuP 105, did not

become marketed drugs due to their unacceptable toxicities. Steven J. Brickner, a medicinal chemist working at Upjohn, was intrigued by some attributes of this class of compounds after learning of Dupont's exploits in 1987. He immediately began an exploratory oxazolidinone project. Working with two other groups led by Michael R. Barbachyn and Douglas K. Hutchinson, they prepared eperezolid and linezolid and commenced clinical trials for both compounds in 1995. Since linezolid was more advantageous than eperezolid in terms of its pharmacokinetics, linezolid was selected to move forward and won FDA approval in 2000. Pharmacia, which took over Upjohn in 1995, sold it under the trade name Zyvox.

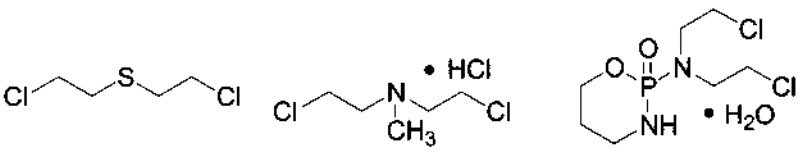
Zyvox works by inhibition of the initial phase of bacterial protein synthesis. It is also a MAO (monoamine oxidase)-B inhibitor but without significant blood pressure liability—bringing an interesting closure to the origin of MAO inhibitors for depression, which came about from the improvement in mood in patients with tuberculosis treated with the original MAO inhibiting agents (see Section 6.2).

3 Cancer Drugs

3.1 The Origin of Cancer

Today, the oncogene theory prevails for explaining the origins of cancer.[14,15] The current view is that cancer is a multistep process, characterized by mutations in several oncogenes and the loss of function of *tumor-suppressing genes*. Oncogenes are activated by either an inherited defect or exposure to an outside agent, a carcinogen. However, oncogenes are normally kept inactive by tumor-suppressing genes. In some cases those controlling genes may be mutated, or removed, allowing oncogenes to run rampant. For a tumor to develop, a subject has to lose one tumor-suppressing gene in addition to having two or more oncogenes.

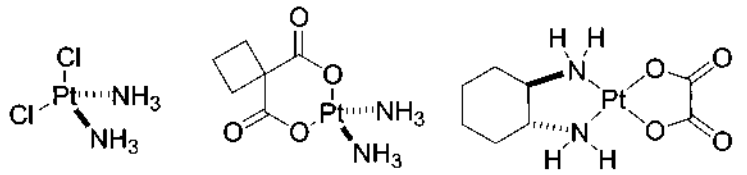
3.2 Chemotherapy



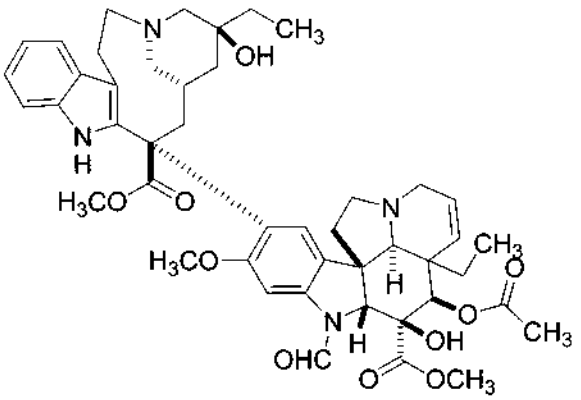
Mustard gas | mechlorethamine (Nitrogen mustard) | cyclophosphamide (Cytoxan)

Chemotherapy, despite its devastating side effects, saves lives. Yet it originated at first from a chemical weapon, mustard gas. During WWII, the USS *John Harvey* loaded with 100 tons of mustard gas was sunk by Luftwaffe Ju-88 bombers at the Bari Harbor on the Adriatic Sea. Subsequent autopsies of 617 victims revealed that mustard gas destroyed most of their white blood cells,[16] which suggested that it attacked bone marrow preferentially. Since fast division of cells is a hallmark of cancer, mustard-gas-based drugs could be applicable in cancer treatment because they slow the rate of cancer cell division. Nitrogen mustard was invented because mustard gas was impossible to administer due to its volatility. Its mechanism of action is through alkylation of DNA. Subsequently, more elaborate alkylating agents, such as cyclophosphamide (Cytoxan), discovered at Asta–Werke AG in Germany in 1956, have become the staple of chemotherapy.

Cisplatin's chemotherapeutic effect was discovered by Barnett Rosenberg, a physics professor at Michigan State University in 1967.[17] While experimenting with the effects of electric fields on cell growing in culture, he observed that an electric current interfered with cell divisions of *E. coli* bacteria in suspension. Further investigation revealed that the electric current generated by the platinum electrodes resulted in the formation of cationic platinum. Rosenberg tested cisplatin as a drug against intestinal bacteria first and tumors later. Bristol-Myers Squibb (BMS) successfully developed cisplatin and won the FDA's approval in 1978. Cisplatin (Platinol) has become one of the most widely used chemotherapeutics in treating metastatic testicular cancer, ovarian tumors, and bladder cancer. BMS developed a follow-up to cisplatin in collaboration with Johnson Matthey: carboplatin. Sanofi-Aventis licensed oxaliplatin from Switzerland's Debiopharm and developed it for treating colorectal cancer. Approved in 2002 in the U.S. under the name Eloxatin, it is usually administered with 5-fluorouracil and leucovorin in a combination called Folfox. During the past 40 years, a few thousand platinum complexes have been evaluated and about 30 have reached the clinic, but none has surpassed the three original ones which possess superior efficacy and safety profiles.



cisplatin (Platinol) carboplatin (Paraplatin) oxaliplatin (Eloxatin)

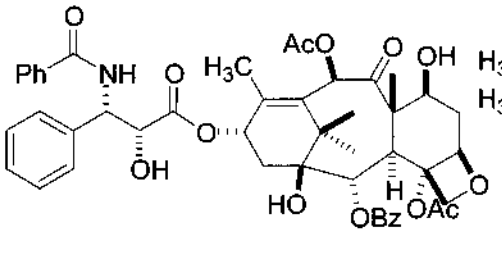


vinblastine (Velban)

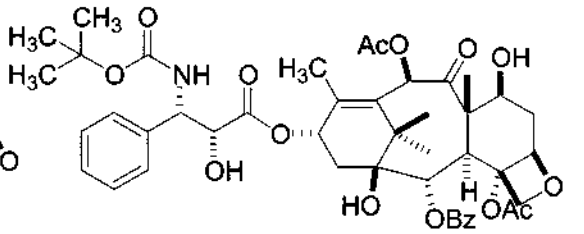
In 1958, during their pursuit of diabetes drugs, R. L. Noble and C. T. Beer at the University of Western Ontario in London, Ontario, tested extracts from Madagascar periwinkle (*Vinca rosea*) on rabbits. The animals subsequently developed critically low counts of white blood cells, leaving them with damaged bone marrow and defenseless against bacterial infections. Noble and Beer then tried the plant extract on animals with transplanted tumors because again cancer is characterized by abnormal proliferation of white blood cells. After seeing tumor shrinkage, they further investigated and isolated two important cancer drugs from vinca alkaloids:

vincristine and vinblastine.[18] The vinca alkaloids work by serving as a "spindle poison". They bind to tubulin, one of the key constituents of microtubules, thus preventing the cell from making the spindles it needs to divide. Thanks to vincristine (Oncovin) and vinblastine (Velban), Hodgkin's disease patients now have a 90% chance of survival.

Vinca alkaloids are not the only class of anticancer drugs derived from plants. Taxol is another prominent example. In 1962, Arthur Barclay, under the aegis of the NCI-USDA (National Cancer Institute-United States Department of Agriculture) plant-screening program, traveled to the Gifford Pinchot Forest in Washington State. He collected samples of twigs, leaves, and fruits of a then little known pacific yew tree, *Taxus brevifolia*, and shipped them to the NCI.[19] One of the NCI's contractors was the Wisconsin Alumni Research Foundation, which tested the extracts and found them to be cytotoxic. In 1966, after being rejected by many other laboratories for fear of toxicity, the stem barks found their way to the hands of Monroe E. Wall, chief chemist of the Fractionation and Isolation Laboratory at the Research Triangle Institute in North Carolina. Wall and his colleague, Mansukh C. Wani, isolated the active principle using the "bioactivity-directed fractionation" process. They also elucidated the compound's intricate structure and christened it taxol. The interest in taxol was greatly piqued when Susan Howitz, a professor at the Albert Einstein College of Medicine, discovered that taxol had a completely novel mechanism of action. It exerts its action by stabilizing microtubules (one of the components of the cytoskeleton), resulting in inhibition of mitosis and induction of apoptosis.



paclitaxel (Taxol)



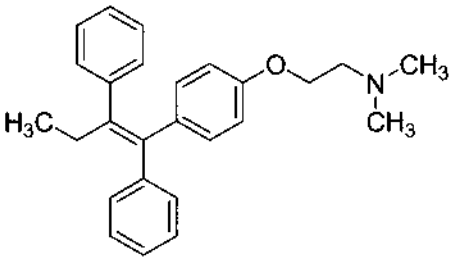
docetaxel (Taxotere)

The NCI commenced the Phase I clinical trials of taxol in 1984 and Phase II trials in 1987 with positive results. BMS, the only major U.S. pharmaceutical company to have made a bid, was awarded the molecule. BMS successfully carried out the Phase III trials for taxol. The FDA approved taxol for use in refractory ovarian cancer in 1992, for breast cancer in 1994, and later for non-small-cell lung cancer and Kaposi's sarcoma. Meanwhile, French company Rhône-Poulenc marketed a competing drug docetaxel (Taxotere), discovered by French chemist Pierre Potier, who invented docetaxel by a minor modification of taxol (replacing the benzyl amide group on taxol with a *tert*-butoxyl-carbamate group).

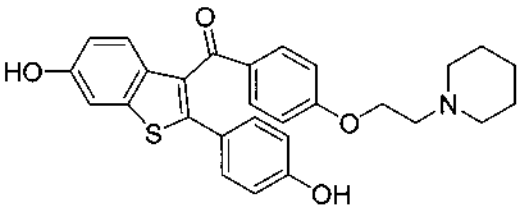
3.3 Hormone Treatment

The correlation between sex hormones and cancer has been well established. Breast cancer in particular is linked to estrogen abnormality. Tamoxifen, the most frequently prescribed anticancer drug in the world, was initially made as a contraceptive. In the 1960s, Imperial Chemical Industries Ltd. (ICI) chemist Dora M. Richardson discovered ICI-147,741, the *trans*-isomer of triphenylethylene, which would later become tamoxifen. Although it was shown to be an effective

contraceptive in rats, it induced ovulation in women, exactly the opposite of what it did to rats. Fortunately, Arthur Walpole along with his endocrinologist colleague Michael J. K. Harper included cancer as an indication in tamoxifen's clinical trials.[20] Tamoxifen was found to be efficacious. It was marketed in the UK as a breast cancer treatment (1973) and as an inducer of ovulation (1975). In 1978, the FDA approved tamoxifen for treatment of estrogen receptor-positive metastatic breast cancer in the US.



tamoxifen (Nolvadex)



raloxifene (Evista)

Tamoxifen is a *s*elective *e*strogen *r*eceptor *m*odulator (SERM). It modulates the estrogen hormone level by mimicking estrogen. Therefore it is especially effective in treating hormone-receptor-positive breast cancer. A newer SERM, raloxifene (Evista), marketed by Eli Lilly as an osteoporosis drug, renders a 58% reduction of breast cancer.

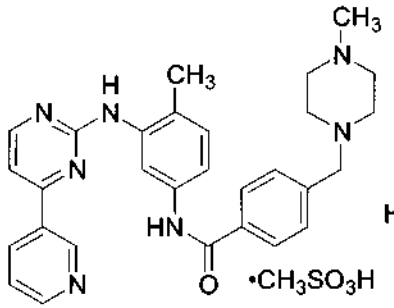
3.4 Small-Molecule Protein Kinase Inhibitors

In contrast to the carpet-bombing approach of old chemotherapy, protein kinase inhibitors, as targeted cancer drugs, are a more effective method for cancer treatment with fewer side effects. Protein kinases are enzymes inside the cell that are capable of donating phosphate groups to target proteins. Protein kinases comprise a family of more than 150 members. They are responsible for signal transduction, turning on and off the switches that control cancer cell growth. Many protein kinases have been implicated in cancer. It has been shown that blocking the functions of protein kinases can stop cancer growth.

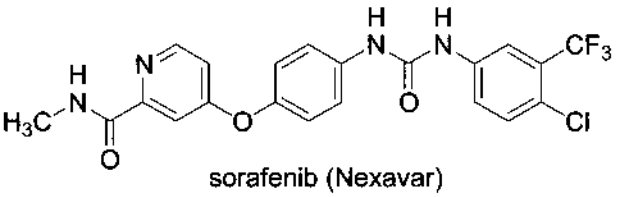
Trastuzumab (Herceptin), a bioengineered human monoclonal antibody developed by Genentech, was approved for the treatment of breast cancer in 1998.[21] The success of Herceptin inspired the pursuit of small-molecule protein kinase inhibitors. Using a protein kinase C-α inhibitor as a starting point, Ciba-Geigy chemist Jürg Zimmermann carried out methodical structure-activity relationship (SAR) investigations.[22] From among over 300 analogs emerged imatinib (Gleevec), a selective Bcr-Abl-tyrasine kinase inhibitor. It was launched in 2001 for the treatment of chronic myeloid leukemia (CML). Later study revealed that Gleevec actually blocks a panel of at least 8 protein kinases, including Bcr-Abl, platelet-derived growth factor receptor (PDGFR), and c-kit.

AstraZeneca's gefitinib (Iressa) and OSI's erlotinib (Tarceva), both EGFR inhibitors, entered the market in 2003. Sugen's sunitinib (Sutent) exhibits potent antiangiogenic activity through the inhibition of multiple receptor tyrosine kinases (RTKs). Specifically sunitinib inhibits vascular endothelial growth factor receptors VEGFR1, VEGFR2, and VEGFR3 and platelet-derived growth factor receptors PDGFR-α and PDGFR-β. In addition, sunitinib also targets receptors implicated in tumerogenesis, including fetal liver tyrosine kinase receptor 3 (Flt3) and

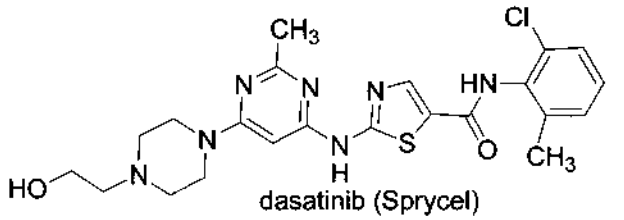
stem cell factor receptor (c-KIT). Bayer's sorafenib (Nexavar), launched in 2005, is a VEGFR inhibitor. Similar to Gleevec, BMS's dasanitib (Sprycel) and Narvotis's nilotinib (Tasignal) came to market in 2006 and 2007, respectively. They both block the Bcr-Abl kinase, which is largely responsible for causing chronic myeloid leukemia (CML).



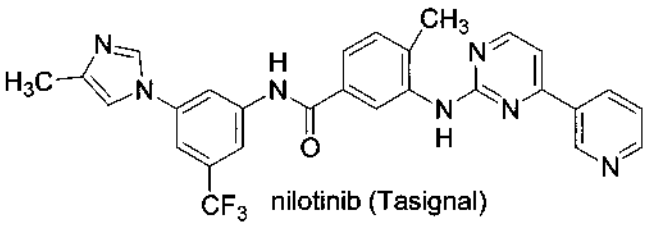
imatinib mesylate (Gleevec)



sorafenib (Nexavar)



dasatinib (Sprycel)



nilotinib (Tasignal)

4 Cardiovascular Drugs

British physician William Harvey's (1578–1657) discovery of the circulation of blood is considered one the greatest discoveries made in physiology.[23] His most celebrated monograph, *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus* (*Anatomical Exercise on the Motion of the Heart and Blood of Animals*) was published in 1628. Over a century later, another Englishman, William Withering, discovered the medicinal use of foxglove in treating cardiac diseases.

4.1 Withering and Digitalis

William Withering (1741–1799), a physician in Birmingham, bought from a Gypsy lady the secret formula of her special herbal tea, which showed remarkable results in treating dropsy (similar to today's congestive heart failure).[24] Through careful investigation, Withering correctly concluded that among 20 or so ingredients in the herbal tea, purple foxglove was the active ingredient. Withering spent the next decade exploring the curative effects of digitalis, the major principle. Digitalis, as well as many cardiac glycosides, is toxic when taken in large doses. If the dose is too low, then it is ineffective. Digitalis is only effective when administered at or near toxic dose, so finding the correct dosage is very important. Withering's finding in choosing the precise dosage propelled digitalis to become one of the most valuable cardiac drugs ever discovered.

Digitalis was originally prepared from the powdered leaves of foxglove. Nowadays, digitalis isolated from foxglove leaves is further crystallized to afford cardiac glycosides such as digoxin and digitoxin, which are more easily quantified.

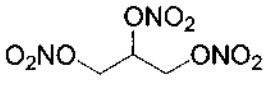
4.2 Sobrero, Nobel, and Nitroglycerin

Italian chemist Ascanio Sobrero (1812–1888) first synthesized nitroglycerin in 1847,[25] by nitration of glycerol using a cold mixture of nitric acid and sulfuric acid. When he tasted it, he found it sweet, pungent, and aromatic; but a very minute quantity put upon the tongue produced a violent headache for several hours. That was the first recorded vasodilating effect attributed to a drug.

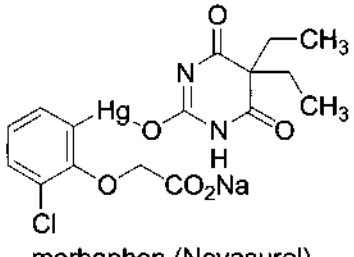
Alfred Nobel (1833–1896) from Stockholm created dynamite using a porous silica gel to absorb the unstable nitroglycerin. The patented detonator made a fortune for the Nobel family. In explosive production plants, munitions workers often experienced facial flush and severe headache when they returned to work after being away from the factory over the weekend. Further investigation revealed that nitroglycerin was a powerful vasodilator which led to its use as a circulatory system vasodilator.

The MOA of nitroglycerin's treatment of angina was not known until the 1980s. It turns out that soluble guanylated cyclase could be activated by free radicals such as nitric oxide (NO) generated from nitroglycerin. Nitric oxide is a signaling molecule in the cardiovascular system.

In addition to nitroglycerin, many organic nitrates are used to treat angina pectoris. These organic nitrates are typically prepared by nitration of polyols (molecules with many alcohol functionalities). Examples include isosorbide dinitrate (ISDN), pentaerythritol tetranitrate, and erythrityl tetranitrate.



nitroglycerin



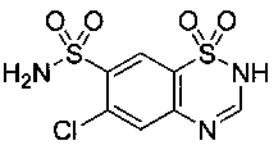
merbaphen (Novasurol)

4.3 Vogl and Diuretics

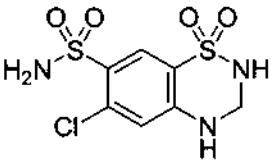
Diuretics, also known as *water pills*, and β-blockers are the most prescribed drugs for heart conditions. Serendipity played an important role in the discovery of the first mercurial diuretic.

In 1919, Alfred Vogl, a third-year medical student in Vienna, gave a new mercurial anti-syphilitic, merbaphen (Novasurol), to treat a patient's congenital syphilis.[26] To his astonishment, the patient's urine output was 5–6 times the normal amount. By removing fluid, the pressure on the heart was removed. Mercurial diuretics revolutionized the treatment of severe edema from congestive heart failure and were the primary treatment for this disease until the late 1950s and the emergence of thiazide diuretics.

In 1957, in pursuit of diuretic agents, Merck chemist Frederick C. Novello wanted to make some analogs of an older sulfa drug, dichlorophenamide.[27] Surprisingly, the reaction gave the ring formation product rather than the linear derivatization product. The bicyclic ring formed was a benzothiadiazine derivative, chlorothiazide. Further testing proved it to be a potent diuretic without elevation of bicarbonate excretion, an undesired side effect. Chlorothiazide was the first ever nonmercurial, orally active diuretic drug whose activity was not dependent on carbonic anhydrase inhibition, such as acetazolamide.



chlorothiazide (Diuril)



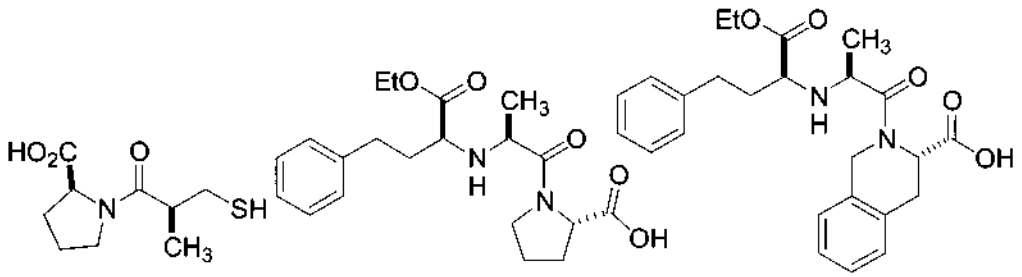
hydrochlorothiazide (HydroDiuril)

Currently the most frequently prescribed diuretic is hydrochlorothiazide discovered by Ciba scientists led by George deStevens.[28] In 1957, George deStevens became aware of the research of Frederick Novello on the synthesis of disulfonamides in general and chlorothiazide in particular. A simple modification from a double bond on chlorothiazide to a single bond gave him a hydrochlorothiazide that was 10-fold more potent than the prototype. Hydrochlorothiazide was introduced into medical practice in 1959 and within a short time became the drug of choice in the treatment of mild hypertension.

4.4 Snake Venom and ACE Inhibitors

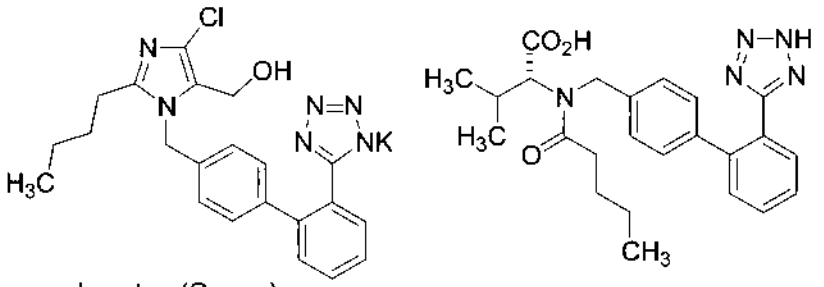
*A*ngiotensin *c*onverting *e*nzyme (ACE) inhibitors are widely used in treating hypertension, congestive heart failure, and heart attacks. In 1967, John Vane at Oxford University and his colleague Mick Bakhle tested a poisonous venom extract of the Brazilian pit viper *Bothrops jararaca*.[29] It was found to be a potent ACE inhibitor *in vitro*.

Vane suggested to the Squibb Institute that they study snake venom extract for its effects on the cardiovascular system. Biochemist David Cushman and organic chemist Miguel A. Ondetti at Squibb isolated a nonapeptide, teprotide. Using teprotide as a starting point, Cushman and Ondetti curtailed the molecule and replaced its carboxylate group with a thiol (–SH) and achieved a 2,000-fold increase in potency in ACE inhibition. The resulting drug became the first *oral* ACE inhibitor, captopril (Capoten).



captopril (Capoten) enalapril (Vasotec) quinapril (Accupril)

To improve on captopril, which suffered some side effects due to the presence of the thiol group, Merck scientists led by Arthur A. Patchett started by replacing the thiol group with the original carboxylate due to thiol's liabilities.[30] The loss in potency of the carboxylate was compensated by modification of the molecule elsewhere. They arrived at enalaprilat, which suffered poor oral bioavailability. They simply converted the acid into its corresponding ethyl ester, creating enalapril, a prodrug of enalaprilat, with excellent oral bioavailability. One advantage of a prodrug is the delay in onset of action, which can be beneficial for a drug to treat blood pressure. The longer duration of action also allows a once-daily dosage. It is also devoid of the side effects associated with the thiol group, including bone marrow growth suppression (due to a decrease in circulating white blood cells), skin rash, and loss of taste. In 1981, Merck sold enalapril using the brand name Vasotec, which became its first billion-dollar drug in 1988. Another popular ACE inhibitor is quinapril hydrochloride (Accupril), discovered by Parke–Davis.



losartan (Cozarr) valsartan (Diovan)

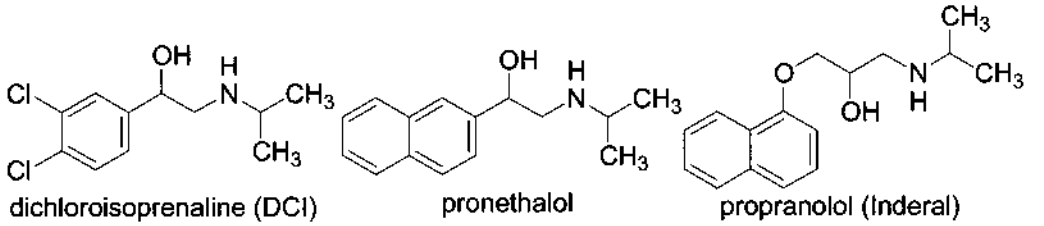
Since angiotensin II is a potent vasoconstrictor, blocking its action would result in vasodilation. Dupont–Merck Pharmaceuticals exploited the angiotensin II receptor in the early 1980s. The fruit of the effort was losartan (Cozaar), which quickly became one of the most important drugs for the treatment of high blood pressure after its launch in 1995. Other angiotensin II receptor antagonists (also known as *a*ngiotensin *r*eceptor *b*lockers, ARBs) include Novartis's valsartan (Diovan), Sanofi-Synthélabo's irbesartan (Avapro), AstraZeneca's candesartan (Atacand), and Boehringer Ingelheim's telmisartan (Micardis). They proved to be superior to ACE inhibitors because they did not cause the irritating cough that occurs in a small percentage of patients taking ACE inhibitors.

4.5 Black and Beta-Blockers

As early as 1948, Raymond P. Ahlquist at the Medical College of Georgia speculated that there were two types of adrenergic receptors (adrenoceptors in short), which he termed α-adrenoceptor and β-adrenoceptor. In 1957, Irwin H. Slater and C. E. Powell at Eli Lilly prepared dichloroisoprenaline (DCI, the *di*chloro analog of *iso*prenaline) and it was later demonstrated to be the first selective β-adrenoreceptor blocking reagent, also known as a β-blocker. However, DCI was not further pursued as a drug because it had a marked undesirable stimulant effect on the heart, an *i*ntrinsic *s*ympathomimetic *a*ction (ISA).

Ahlquist's theory of two adrenergic receptors inspired British pharmacologist James Black to look for drugs with β-receptor blocking properties in a systematic way later known as *rational drug design.* Before then, drugs were mostly discovered by screening compounds randomly against animal models.

Black famously said, "The most fruitful basis for the discovery of a new drug is to start from an old drug."[31] At Imperial Chemical Industries (ICI) Pharmaceutical Division, together with chemist James Stephenson, Black led a team to look for β-blockers that were devoid of the stimulant effect on the heart since 1958. In 1962, Stephenson and his colleagues succeeded in making a β-blocker pronethalol using DCI as the starting point (pronethalol replaced the dichlorobenzene ring with a naphthaline ring). Unfortunately, pronethalol was withdrawn from further development when it was found to cause thymic tumors in mice. In 1964 ICI eventually produced the drug propranolol (Inderal), which possessed a better efficacy and safety profile. Propranolol is now widely used in the management of angina, hypertension, arrhythmia, and migraine headaches. Two additional β-blockers, atenolol (Tenormin) and practolol (Dalzic), were later discovered and marketed by ICI.



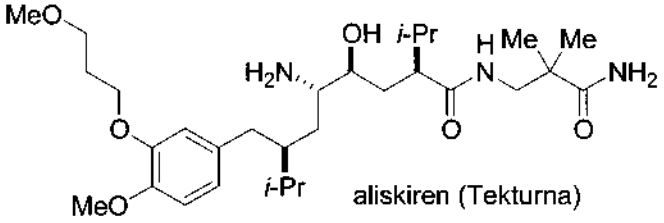
At one point or another, almost all the major pharmaceutical companies had a me-too β-blocker on the market. It brought a windfall to the drug industry.

4.6 Renin Inhibitor

Since renin is extremely specific for angiotensinogen and the first and rate-limiting enzyme of the renin-angiotensin system (RAS), renin inhibition was recognized for decades as an attractive approach for the treatment of hypertension and hypertension-related target organ damage.[32]

Ciba-Geigy was a pioneer in the rennin field in the race to develop orally available renin inhibitors, but the clinical development of aliskiren was in jeopardy following the merger of Ciba-Geigy and Sandoz to form Novartis in 1996 and the successful launch of the antihypertensive angiotensin receptor blocker (ARB) valsartan (Diovan) in 1997. A group of former Ciba-Geigy

employees convinced Novartis to out-license the Phase I/II development of aliskiren and formed the biopharmaceutical company Speedel to accomplish this task.[33] Speedel was successful in developing a commercially viable process and demonstrating clinical proof of concept (POC), and Novartis exercised a call-back option in 2002. Following an extensive Phase III development program, aliskiren (Tekturna) has been on the market for treatment of hypertension since 2007.



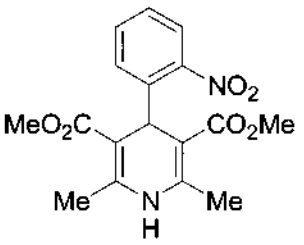
aliskiren (Tekturna)

4.7 *Fleckenstein and Calcium Channel Blockers*

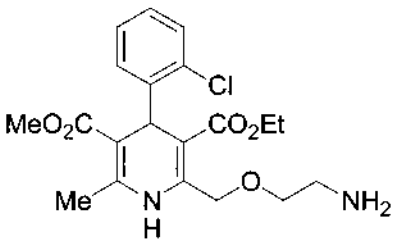
Calcium channel blockers (CCBs), also known as calcium channel antagonists or calcium entry blockers, are drugs that inhibit the influx of Ca^{2+} ions into cells without affecting inward Na^{+} or outward K^{+} currents to a significant degree. They are widely used in the treatment of high blood pressure, angina, and rapid heartbeat (tachycardia), including arterial fibrillation.

In 1963, Albrecht Fleckenstein at the University of Freiburg in Germany investigated two newly synthesized coronary vasodilators, prenylamine and verapamil, which had unexplained cardiodepressant side effects.[34] Fleckenstein and his colleagues observed that both compounds exerted a negative inotropic effect caused by calcium. They concluded that this negative inotropism was due to an ability of these drugs to block excitation-induced calcium influx. In 1966 Fleckenstein then coined the term "calcium antagonists" because both drugs mimicked the cardiac effects of simple calcium withdrawal.

In 1969, Professor Kroneberg, the leading pharmacologist of Bayer Company, handed Fleckenstein Bay-a-1040 and Bay-a-7168. Both compounds were strong coronary vasodilators and exerted significant negative inotropic effects on the myocardium. Fleckenstein also found that the mechanism of action of those two drugs appeared to be similar to that of verapamil. Later on Bay-a-1040 and Bay-a-7168 were given generic names nifepidine and niludipine, respectively. Nifepidine (Adalat) and niludipine heralded the beginning of one of the most important classes of calcium antagonists: 1,4-dihydropyridines.[35]



nifedipine (Adalat)



amlodipine (Norvasc)

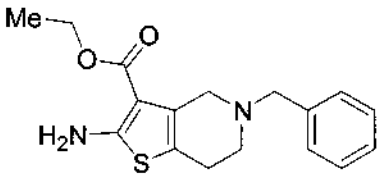
Bayer's nifepidine is a short-acting calcium channel blocker and thus has to be taken several times a day. On the other hand, Pfizer's amlodipine (Norvasc) has a high bioavailability and a longer half-life in plasma; thus it can be taken once daily.

4.8 Blood Thinners, from Heparin to Plavix

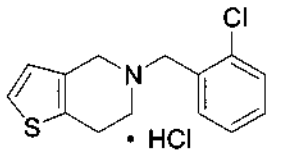
Thrombosis and embolus take place when platelets are overactive, causing promotion of blood coagulation. Blood thinners attenuate the functions of platelets and fibrin to prevent thrombosis or embolus. The first blood thinner in clinical use was heparin, acidic sulfated polysaccharides. Jay McLean (1890–1957), working in the laboratories of Prof. William Henry Howell (1860–1945) at the Johns Hopkins University, discovered the anticoagulation substance from dog's liver isolate in 1917. Two years later, Howell and his student L. Emmett Holt, Jr. further purified the anticoagulation substance and christened it *heparin*.[36] Charles Best of the insulin fame returned at the University of Toronto and embarked on a journey to produce purified heparin since 1929. Working with organic chemists Arthur Charles and David Scott, they prepared the barium and later the sodium salt of heparin, which rendered uniformly consistent composition and potency. That, in turn, enabled Best and Gordon Murray to carry out clinical trials with purified heparin in 1935. Nowadays, small-molecular-weight heparin fractions are used in clinics because only a fraction of the heparin molecule is active in *blocking blood clotting factor Xa* (heparin's MOA).

Heparin, highly sulfated glycosaminoglycan, has to be given intravenously. The first identified oral anticoagulant was warfarin, discovered by Karl Paul Link (1901–1978) at the University of Wisconsin in the 1940s. In 1933, Link began to investigate the cause of cattle death due to internal hemorrhage after ingestion of sweet clovers. By 1939, his group isolated and characterized the active principle as dicumarol. In analogy to hemorrhage of cows, Link sought to look for rodenticide from the dicumarol analogs to kill rats by hemorrhage. One of them, WARF-42, emerged as the best rat poison in 1948.[37] In the early 1950s, clinical trials for warfarin as a blood thinner commenced. It now is the most used oral anticoagulant in history. The MOA of warfarin is inhibition of VKORC1 (vitamin K epoxide reductase complex, subunit 1) and vitamin K epoxide reductase.

Aspirin was synthesized in 1897 by Bayer's Felix Hoffmann as an analgesic. In the 1940s, Lawrence Craven, a family doctor in California, observed aspirin's anticlotting properties. Harvey J. Weiss at Columbia University was one of the first to discover aspirin's antiplatelet effect in 1967. Since 1985, an aspirin a day has been a popular prophylaxis to prevent a second heart attack. Aspirin works by inhibiting prostaglandin synthetase, which explains most of its antiplatelet, antipyretic, and anti-inflammatory properties.



tinoridine (Nonflamin)



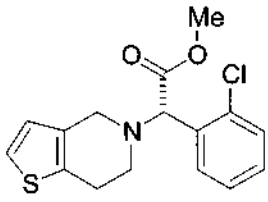
ticlopidine hydrochloride (Ticlid)

In 1972, Jean-Pierre Maffrand of Sanofi made analogs of Yoshitomi's tinoridine (Nonflamin) to find drugs with improved anti-inflammatory properties. But the compounds they

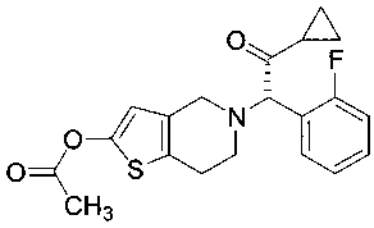
made had no anti-inflammatory properties at all. Further scrutiny revealed that they inhibited blood platelet aggregation. Immediately realizing the important roles that platelets played in myocardial infarction and brain ischemia, the team set out to find a platelet aggregation inhibitor superior to aspirin. The fruit of labor was ticlopidine (Ticlid). Unfortunately, a rare but potentially fatal side effect called thrombotic thrombocytopenic purpura (TTP) and several other side effects severely limited ticlopidine's use in patients.[38]

To overcome ticlopidine's shortcomings, Sanofi carried out extensive SAR investigations. PCR 4099, a racemate, was synthesized in 1980. Although more potent and better tolerated than ticlopidine, it caused convulsions in rats, mice, and baboons for certain high dosages. A decision was made to replace PCR 4099 with one of its enantiomers, clopidogrel bisulfate, when clopidogrel was found to have superior safety profile. Sanofi and its American development partner BMS won the FDA approval for clopidogrel (Plavix) in 1997. In 2008, Plavix was the second best-selling drug ever, with sales of $8 billion.[39]

In 2009, Daiichi Sankyo and Eli Lilly began to market a *me-too* of clopidogrel: prasugrel (Effient).



clopidogrel (Plavix)



prasugrel (Effient)

5 Cholesterol Drugs

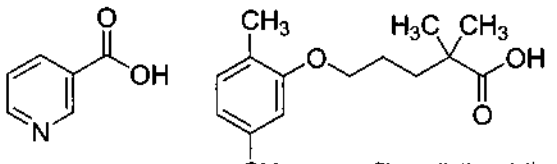
Too much cholesterol, especially the *l*ow-*d*ensity *l*ipoprotein (LDL) cholesterol, has been identified as a major *risk factor* for cardiovascular disease by experimental, genetic, and epidemiological evidence.

5.1 Early Cholesterol Drugs: Niacin and Fibrates

In the early 1950s, Canadian pathologist Rudolf Altschul at the University of Saskatchewan found that large doses of nicotinic acid decreased serum cholesterol levels in rabbits. Working with Drs. Abram Hoffer and J. D. Stephen at Regina General Hospital, they carried out clinical trials that successfully showed this link. By 1955, nicotinic acid (niacin) in gram doses became the first agent employed for the purpose of lowering cholesterol.[40] The MOA of nicotinic acid is through activation of endothelial lipoprotein lipase as a result of its binding to the *nicotinic acid receptor*, a G-protein-coupled receptor.

In 1954, ICI discovered that clofibrate (Atromid-S) possessed high cholesterol-lowering activity and marketed it in 1958. Parke–Davis's gemfibrozil (Lopid) was the second fibrate on the market. In order to find safer analogs of clofibrate, Parke–Davis screened over 8000 compounds similar to clofibrate using animals.[41] Gemfibrozil was discovered by Paul L. Creger in 1969 and was launched in 1982. Abbott's fenofibrate (Tricor) is also a clofibrate analog. Recently, fibrates

were found to be PPARα (*p*eroxisome *p*roliferator-*a*ctivated *r*eceptor-*α*) agonists, which have been used in treating type II diabetes since the late 1990s.



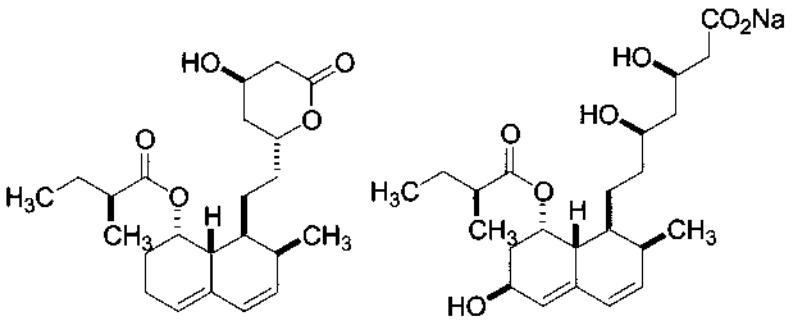
nicotinic acid gemfibrozil (Lopid)

Recent studies have also shown that risk of drug-drug interactions increases 1400-fold if statins are combined with fibrates. Therefore, fibrates should not be taken with statins (see Section 5.4).

5.2 *Endo, Mevastatin, and Pravachol*

Konrad E. Bloch at Harvard elucidated the biosynthetic pathways of cholesterol in the 1960s. During 1958–1959, it was shown that the conversion of HMG-CoA into mevalonic acid is the major rate-limiting step in cholesterol biosynthesis. Therefore, blocking HMG-CoA reductase would be an ideal approach to stop the synthesis of cholesterol in liver.

Also inspired by Fleming's success in identifying penicillin, Akira Endo of Sankyo Pharmaceuticals began in 1971 to screen microbial metabolites for HMG-CoA reductase inhibitory activity. Over a two-year period, Endo's team tested more than 6000 microbial strains for their ability to block lipid synthesis. In August 1973, mevastatin, the first statin, was isolated from the fungus *Penicillium citrium*. Endo's group isolated only 23 mg of crystalline mevastatin by extracting 600 L of the culture filtrate.[42] In 1976, A. G. Brown at Beecham Pharmaceuticals also isolated mevastatin from *Penicillium brevicompactum*. They named it compactin and elucidated its structure by X-ray crystallography, confirming that compactin and mevastatin were indeed the same molecule.[43]



mevastatin = compactin pravastatin (Pravacol)

In 1976, Endo tested mevastatin in laying hens, dogs, and monkeys and observed efficacy in lowering cholesterol. Akira Yamamoto at Osaka University gave low doses of mevastatin to several of his patients with familial hypercholesterolemia (FH) and saw good results, which

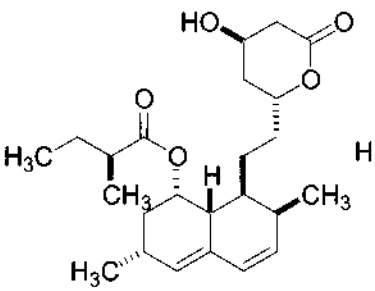
encouraged Sankyo to embark on a small clinical trial in early 1979 for patients with severe hypercholesterolemia. But by the mid-1980s, Sankyo halted the trials because long-term safety studies on dogs revealed that some of them started to show intestinal tumors at high doses.[44]

Despite mevastatin's failure to reach the market, Endo's pravastatin, first isolated from the urine of dogs that had been fed mevastatin, succeeded to reach market. Sankyo carried out the clinical trials for pravastatin in 1984. After the successful completion of the trials, Sankyo comarketed pravastatin (Pravachol) with BMS since 1991.

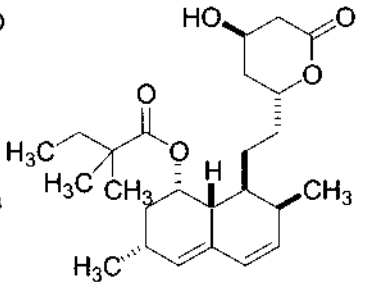
5.3 Merck's Mevacor and Zocor

Under the leadership of Roy Vagelos, Merck embarked on efforts to find HMG-CoA reductase inhibitors in 1978 with Alfred W. Albert as the *Product Champion.* Just a few days after the HMG-CoA project began, they found that the 18th microorganism produced the active principle of the broth, which potently inhibited HMG-CoA reductase. Back-tracking the sample, they identified the microorganism from the culture broth of *Aspergillus terreusi,* a common fungus found around the world. The compound was isolated and characterized and would become lovastatin (Mevacor), which reached the market in 1987 as the first statin. Ironically, nothing with a better profile was ever discovered from screening additional thousands of samples.[45]

Robert L. Smith and his colleagues at Merck synthesized simvastatin, an analog of lovastatin with an extra methyl group on the sidechain. Simvastatin (Zocor), 2.5 times more potent and longer lasting than lovastatin, was launched in 1991.



lovastatin (Mevacor)



simvastatin (Zocor)

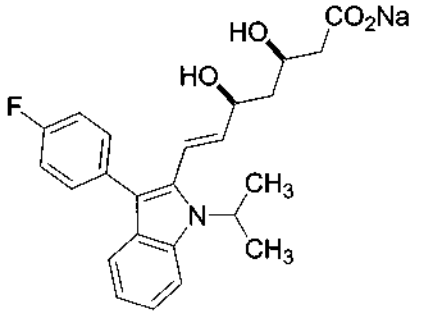
5.4 Lescol, Lipitor, Baycol, and Crestor

In the 1980s, Merck's Alvin K. Willard, Gerald E. Stokker, and their colleagues disclosed their synthetic HMG-CoA reductase inhibitors in which Mevacor's hexahydronaphthalene core structure was replaced with a diphenyl group with four substituents.[46] This demonstrated that it was not necessary to have fermentation products to have the activity against HMG-CoA reductase.

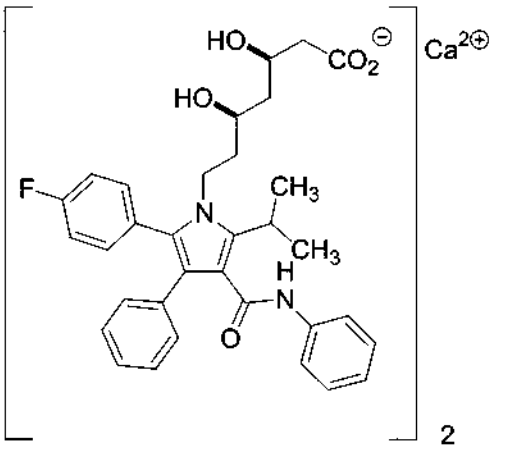
The fourth statin on the U.S. market, Sandoz's fluvastatin sodium (Lescol), was the first synthetic statin. In 1984 Faizulla G. Kathawala at Sandoz replaced mevastatin's hexahydronaphthalene core structure with an indole ring. Unlike mevastatin, Mevacor, and Zocor, Lescol's sidechain was a sodium carboxylate salt instead of a lactone ring.[47]

In the mid-1980s, Bruce D. Roth at Parke–Davis chose the pyrrole ring to replace mevastatin's hexahydronaphthalene core.[48] Initial halogenated pyrroles had similar potency to

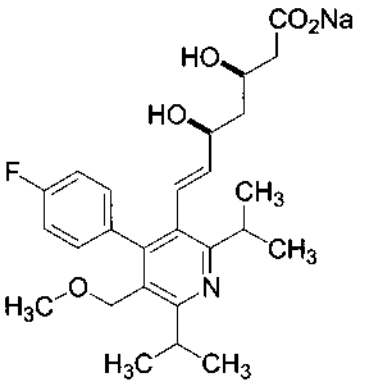
mevastatin but was toxic to rats. But the pentasubstituted pyrrole with the chiral sidechain (CI-981, atorvastatin) proved both efficacious and with similar toxicology profile to known statins. Although CI-981 was only equipotent to Mevacor in dogs, biologist Roger S. Newton convinced the management to move CI-981 to the clinics. Surprisingly, the Phase I trials showed it had superior efficacy to all known statins. Atorvastatin (Lipitor), the fifth statin on the market since 1997, is also the best in its class, becoming the best-selling drug ever with annual sales of $13 billion in 2008. Lipitor's patent expired on November 31, 2011, which will change the statin landscape significantly as generic atorvastatin floods the market.



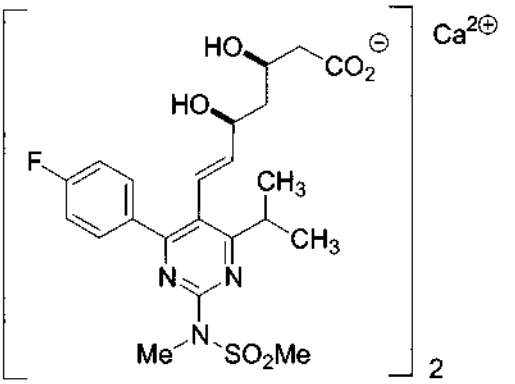
fluvastatin (Lescol)



atorvastatin calcium (Lipitor)



cerivastatin (Baycol)



rosuvastatin (Crestor)

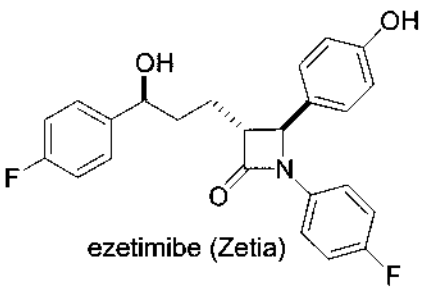
Cerivastatin (Baycol) was discovered by Bayer scientists led by medicinal chemist Rolf Angerbauer and biologist Hilmar Bischoff in the late 1980s. It was on the market in 1997 but was withdrawn in 2001 when it was reported that Baycol's serious rhabdomyolysis was about 15–60 times as frequent as with the other statins. A Baycol fatality tended to occur in patients taking

higher doses of the drug and in those also taking fibrates, especially gemfibrozil (Lopid).[49] Recent studies have shown that the risks of drug-drug interactions increase 1400 times if statins are combined with fibrates. Both statins and fibrates are metabolized by CYP 3A4 (see Section 5.1).

AstraZeneca licensed rosuvastatin (Crestor), the seventh statin on the market, from Japanese company Shionogi & Co. Ltd. In clinical trials, Crestor lowered levels of LDL by more than 53% and raised levels of HDL by nearly 15%.[50] In 2003, the FDA approved Crestor in 5–40-mg doses, but not the 80-mg dose because of concerns about its risk to the muscles and kidneys.

5.5 Zetia and Vytorin

In 1990, Schering-Plough began to work on acyl CoA cholesterol acyltransferase (ACAT) inhibitors to treat atherosclerosis. Because the *in vitro* ACAT inhibition do not correalate *in vivo* animal model efficacy, the medicinal chemists opted to use the onerous route of establishing the SAR guided solely by the *in vivo* animal model. The series of 2-azetidinones afforded ezetimibe (Zetia), a potent inhibitor of cholesterol absorption in several animal models including hamster, dog, and monkey. In humans, ezetimibe reduced LDL cholesterol levels by just 18–20%. Although not as efficacious as statins, it also exhibits desirable effects on triglyceride, apolipoprotein B, and C-reactive protein (CRP) levels.[51]



ezetimibe (Zetia)

Because no significant effects on liver enzyme levels have been observed in animals or during the clinical trials of ezetimibe, it is ideal for combination therapies with a statin. Therefore, Merck/Schering-Plough subsequently developed a fixed combination of Zetia and Zocor, which was approved by the FDA in July of 2004. The combined drug is sold under the trade name Vytorin,[52] which quickly became their biggest product. Unfortunately, in 2008, a long-awaited trial showed their cholesterol drug Vytorin failed to slow progression of heart disease better than a cheaper drug, the generic simvastatin (Zocor).[53] The advantage of Vytorin over generic simvastatin has since been questioned.

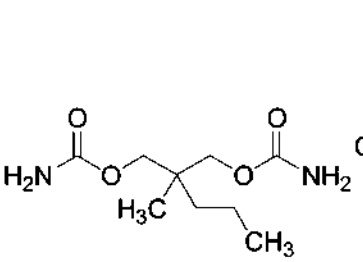
6 CNS Drugs

Humans have dabbled with mind-altering medicines for millennia. Alcohol was invented and consumed as early as 5000 B.C. Psychedelic effects of wild mushrooms were recorded in many ancient literatures. Caffeine, nicotine, marijuana, and opium have intertwined with our culture throughout history.

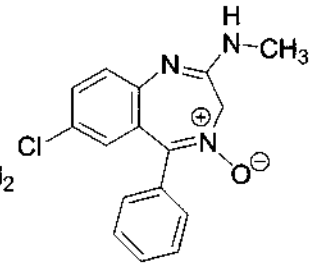
6.1 Sternbach, Valium, and Minor Tranquilizers

In 1945, working with chief chemist William Bradley, Frank M. Berger at the Wallace Laboratories investigated a variety of compounds to find an antibacterial for Gram-negative bacteria. One of the drugs, meprobamate (Miltown), synthesized in 1950, caused mice to become paralyzed and their muscles relaxed. It soon proved to be an excellent minor tranquilizer with a preferable safety profile.[54] On the market since 1955, it rapidly achieved outstanding commercial success as an anxiolytic agent.

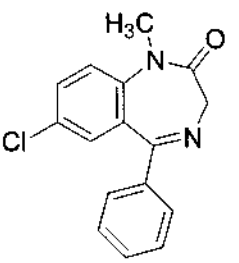
In 1955, to search new tranquilizers, Leo Henryk Sternbach at Roche prepared 24 benzodiazepines, which he studied for his Ph.D. thesis on azo dyes and dyestuff intermediates. None were active. Just when he was moved to another project, he submitted the last two additional analogs for pharmacologic testing. One of them, chlordiazepoxide (Librium), did well in mice, showing strong hypnotic effects. Subsequently, chlordiazepoxide was tested to be a better tranquilizing agent than Miltown in all species, indicating its phenomenal sedative, muscle-relaxant, and anticonvulsant properties. Librium, on the market in 1960, was followed by diazepam (Valium) three years later. Valium, another benzodiazepine also discovered by Sternbach, is five times more efficacious than Librium.[55] Their MOA is now believed to be through facilitation of synaptic transmission at the γ-aminobutyric acid (GABA) receptor. The benzodiazepine-GABA receptor complex has since been isolated and characterized.



meprobamate (Miltown)



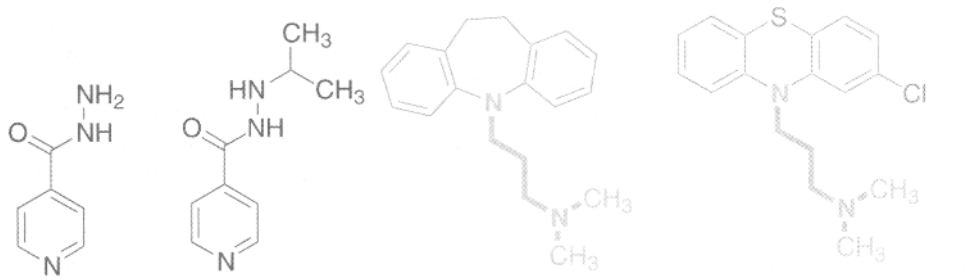
chlordiazepoxide (Librium)



diazepam (Valium)

6.2 Antidepressants

Hoffmann-La Roche discovered isoniazid in 1951 for the treatment of tuberculosis. In 1952, Herbert H. Fox and John T. Gibas at Roche prepared many derivatives of isoniazid, including iproniazid (Marsilid). During the clinical trials of iproniazid, three groups, including Nathan S. Kline's simultaneously observed improvement of mood for chronically depressed, hospitalized patients also suffering from tuberculosis. They convinced Roche to put Marsilid on the market to treat depressed patients. After a conference in 1957, an article in the *New York Times* touted Marsilid's miraculous mood elevation effects. Almost overnight, Marsilid found widespread use in treating depression as an off-label prescription. However, some patients who took Marsilid developed jaundice due to liver toxicity. Roche voluntarily withdrew Marsilid from the U.S. market in 1961 with the conviction of quickly finding a safer drug, which never materialized.[56] Iproniazid works by inhibiting monoamine oxidase (MOA, see Section 2.7).

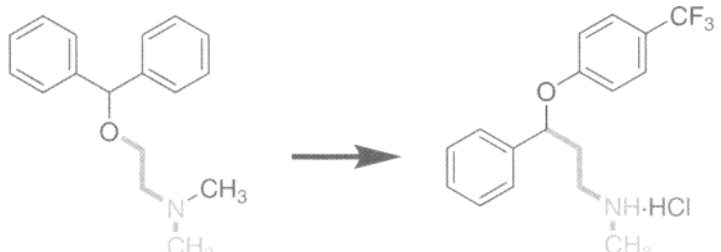


isoniazid iproniazid (Marsilid) imipramine (Tofranil) chlorpromazine (Thorazine)

In 1950, Roland Kuhn tested some of Geigy's antihistamines for possible hypnotic properties, which none of them had. Five years later, the tranquillizing properties of chlorpromazine (Thorazine) became known and heralded the first highly effective antischizophrenic drug. Kuhn remembered that some of Geigy's antihistamines he tested produced effects similar to those of chlorpromazine. He then wrote several letters to Geigy and suggested that further studies of those antihistamines for central nervous system diseases were warranted. G22355 (imipramine) was synthesized and sent to Kuhn for testing. Although it did not show any antipsychotic effects on 300 schizophrenics, the clinical trials then moved to test the effects of imipramine on severe depression. After treating their first three cases, it was already clear that the substance, later known as imipramine, had an antidepressant action.[57] The emergence of imipramine (Tofranil) in the spring of 1958 ushered in the use of tricyclic antidepressants. Imipramine works by inhibiting noradrenaline reuptake at the adrenergic endings and serotonin to a lesser extent.

Initially, AB Astra discovered and marketed an inhibitor for serotonin reuptake, zimeldine, the prototype of the *s*elective *s*erotonin *r*euptake *i*nhibitors (SSRIs). Unfortunately, a rare but serious side effect, Guillain-Barré syndrome, started to surface after zimeldine was approved and administered in a large patient base. Astra pulled it off the market in the early 1980s.

Eli Lilly was the first to put an SSRI on the market in 1988 with fluoxetine hydrochloride (Prozac).



diphenhydramine (Benadryl) fluoxetine (Prozac)

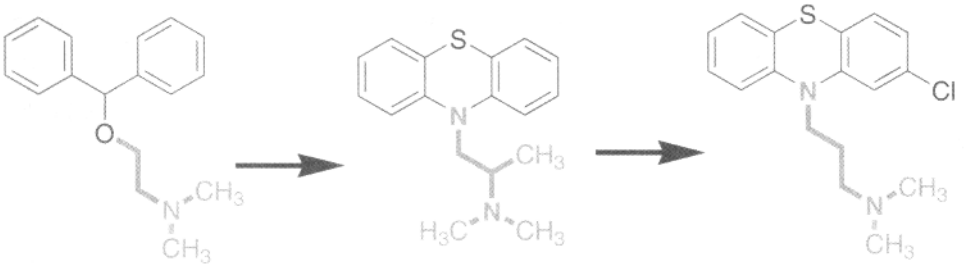
In collaboration with biologist Robert Rathburn, Lilly's medicinal chemists Bryan Molloy and David Wong looked for antidepressants without acetylcholine modulation, which was the culprit of tricyclic antidepressants' side effects.[58] Using diphenhydramine (Benadryl) as their starting point, they arrived at the phenoxypropylamine series in 1970, which were devoid of the

effect of acetylcholine. One of them, fluoxetine, selectively blocked the removal of serotonin while sparing most other biogenic amines. Unlike some of the earlier compounds, it was relatively inactive in the reserpine-induced hypothermia test in mice. In clinical trials, fluoxetine was found to have a favorable side-effect profile and was much safer in overdose relative to the tricyclics. Fluoxetine (Prozac) rapidly transformed debilitating depression into a manageable disease for many patients. Additional widely known SSRIs are sertraline hydrochloride (Zoloft) and paroxetine hydrochloride (Paxil).

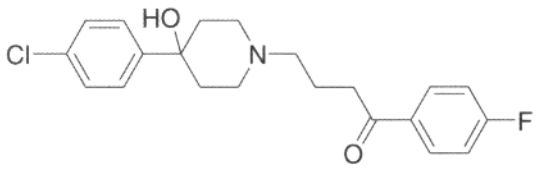
Behaving similarly to SSRIs, venlafaxine (Effexor) is one of the serotonin and norepinephrine reuptake inhibitors (SNRIs), whereas bupropion (Wellbutrin) is one of the norepinephrine and dopamine reuptake inhibitors (NDRIs)—which are also used to help smokers quit.

6.3 Antipsychotics

In 1944, Rhone-Poulenc synthesized and marketed an antihistamine, promethazine (Phena).[59] A surgeon in the French Navy, Henri Laborit found that promethazine was superior to other drugs of the time. Rhone-Poulenc sought to enhance promethazine's "side effects" in the central nervous system. Their SAR investigations led to the synthesis of RP-3277 (chlorpromazine) in 1950. Further clinical trials were then carried out under the direction of Jean Delay and Pierre Deniker, two psychiatrists at the L'Hôpital Sainte-Anne de Paris. Under the influence of chlorpromazine, their patients became "disinterested" as well. More importantly, chlorpromazine subdued the hallucinations and delusions of psychotic patients. Chlorpromazine (Thorazine), introduced in 1954 in the US, was the first typical antipsychotic. In the first eight months, over two million patients were administered the drug, contributing to an 80% reduction of the resident population in mental hospitals.



diphenhydramine (Benadryl) promethazine chlorpromazine (Thorazine)

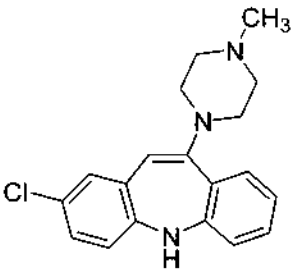


haloperidol (Haldol)

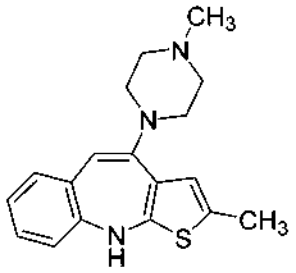
Also a typical antipsychotic haloperidol (Haldol) is 50–100 times more potent than chlorpromazine with fewer side effects such as *extra*pyramidal *s*ymptoms (EPS), including Parkinsonian symptoms, akathisia, dyskinesia, and dystonia. It was synthesized in 1958 by Bert

Hermans under the direction of Paul A. J. Janssen.[60] It was many times more potent than chlorpromazine and was both faster and longer acting. Haloperidol was potent orally as well as parenterally. More importantly, it was almost devoid of the antiadrenergic and other autonomic effects of chlorpromazine. Numerous chronic inpatients were able to leave the hospital and live at home thanks to haloperidol. Haloperidol remained one of the most prescribed neuroleptics 40 years after its discovery, until the emergence of atypical antipsychotics.

Clozapine, the first atypical antipsychotic, was developed in 1959 by the small Swiss company Wander AG.[61] During the clinical trials, clozapine showed strong sedating effects and proved to be efficacious for schizophrenia, but it also showed some liver toxicity. Wander received approval to market it in a few European countries in 1971, although liver toxicity limited its widespread use. Clozapine was removed from the market in 1975 due to rare but potentially fatal drug-associated agranulocytosis. Clozapine was reintroduced in 1990 by Sandoz and is now used as a second-line treatment requiring extensive monitoring of the patient's blood cell count.

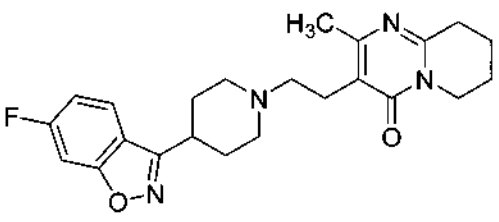


clozapine (Clozaril)

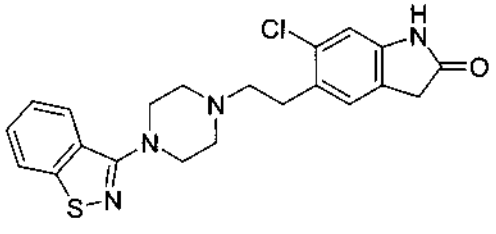


olanzapine (Zyprexa)

The second atypical antipsychotic was risperidone (Risperdal) introduced by Janssen in 1993.[62] Intrigued by the success of a combination therapy of haloperidol and ritanserin (a serotonin antagonist), Janssen initiated a medicinal chemistry program led by chemist Anton Megens. Based on the neuroleptics lenprone and benperidol, they explored a series of benzisoxazole derivatives and ultimately discovered risperidone. It showed a desired combination of very potent serotonin and potent dopamine antagonism.

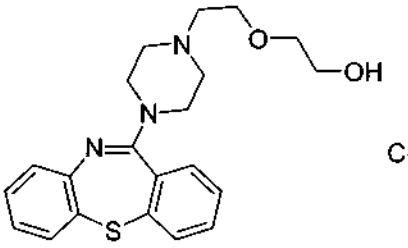


risperidone (Risperdal)

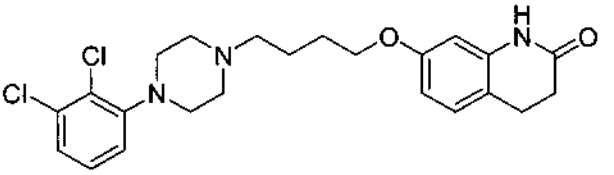


ziprasidone (Geodon)

Additional atypical antipsychotics are Eli Lilly's olanzapine (Zyprexa), AstraZeneca's quetiapine (Seroquel), Pfizer's ziprasidone (Geodon), and Bristol-Myers Squibb's aripiprazole (Abilify). One advantage of Geodon and Abilify is that they have less weight gain side effect.



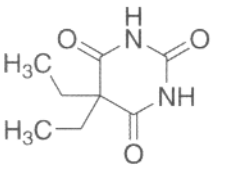
quetiapine (Seroquel)



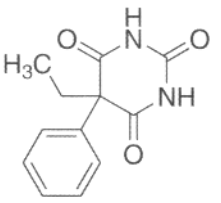
aripiprazole (Abilify)

6.4 *Drugs for Epilepsy and Bipolar Disorder*

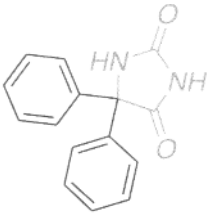
The first drug for epilepsy was phenobarbital (Luminal), discovered by Bayer in 1910. It was the fruit of a larger effort of Bayer's to take advantage of the barbiturates first discovered by Adolf von Baeyer in 1864.



barbital (Veronal)



phenobarbital (Luminal)



phenyltoin (Dilantin)

In 1939, Parke–Davis introduced phenyltoin (Dilantin) as a treatment for epilepsy shortly after its efficacy was discovered by Tracy Jackson Putnam and H. Houston Merritt of Boston City Hospital. In 1954, a chemical and biological research team including L. M. Long, G. M. Chen, and C. A. Miller at Parke–Davis developed phensuximide (Milontin), an anticonvulsant for the control of petit mal epilepsy. Three years later, Parke–Davis introduced another epilepsy drug, methsuximide (Celontin). By then, Parke–Davis's Dilantin, Milontin, and Celotin covered each of the three major types of epileptic seizure (motor symptoms, sensory symptoms, and mental symptoms).[63]

The discovery of lithium for the treatment of manic-depressive disorder was made by John F. Cade at the Bundoora Repatriation Mental Hospital. In 1948, Cade was surprised to notice that lithium urate seemed to have a profound sedative effect on the guinea pigs, which became lethargic after 2 h of latent period. Subsequently, he injected guinea pigs with lithium carbonate and observed the same outcome. He then administered lithium carbonate to 10 of his manic patients and was rewarded with an astonishing triumph: All the patients were cured, and some even went back to work.[64]

Very few people took notice of Cade's pioneering findings except a few Australian psychiatrists. More than 20 years would elapse until 1955 when Danish doctor Mogens Schou reintroduced Cade's discovery to the world and enthusiastically touted the therapeutic power of lithium. Schou's validation and extension of Cade's original observations resulted in wide acceptance of lithium as the gold standard for treating manic patients—it is now the first drug prescribed after a diagnosis of bipolar disorder. Although its mechanism of action is still unknown, it may reverse a major psychotic reaction by boosting the level of serotonin.

7 Anti-inflammatory Drugs

7.1 Cortisone

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by pain, swelling, and subsequent destruction of joints. In 1949, Philip S. Hench (1896–1965), a rheumatologist at the Mayo Clinic, worked with his colleague, biochemist Edward C. Kendall (1886–1972), and isolated the active principle that relieved RA symptoms.[65] He named it cortisone to signify the adrenal *cort*ex steroid hor*mone*. Initially Lewis H. Sarett and Max Tishler at Merck synthesized the first 100 g of cortisone from bile acid.[66] Cortisone became available to every researcher and physician in the United States. Clinical trials showed dramatic effects of cortisone on patients incapacitated by rheumatoid arthritis.

In 1949, Chemist Durey H. Peterson and microbiologist H. C. Murray at Upjohn succeeded in converting progesterone to hydroxyprogesterone by introduction of oxygen at carbon-11 by the microorganism *Rhizopus nigricans*.[67] Using 11α-hydroxyprogesterone, Upjohn chemists, led by John A. Hogg, accomplished a practical total synthesis of cortisone in 11 steps, which was commercialized, enabling a commercially viable process for the industrial production of cortisone.

In 1953, Josef Fried and his associate Elizabeth Sabo at the Squibb Institute synthesized 9-fluorocortisol, which not only was much more potent than cortisone but also possessed appreciable mineralocorticoid activity similar to that of cortisone.[68]

7.2 Nonsteroidal Anti-Inflammatory Drugs

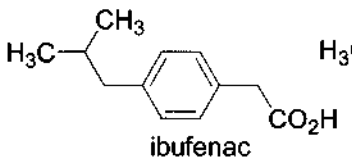
Salicylic acid, a component in the bark of willow tree, is aspirin's precursor. The Ebers Papyrus referenced willow's medicinal properties in general and its treatment of rheumatism in pregnant women in particular. In Greece the father of medicine, Hippocrates, recommended using the bark of the willow tree as an analgesic. In 1753, Reverend Edward Stone in England experimented

with the extraordinarily bitter willow bark in treating ague (fever from malaria) and intermitting disorders with satisfactory results.

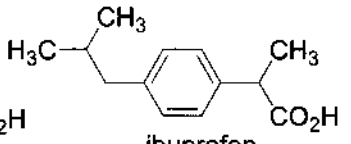
Charles Gerhardt in France and Karl Johann Kraut in Germany synthesized aspirin in 1853 and in 1869, respectively. In 1897, Felix Hoffmann at Bayer prepared a more pure form of aspirin using an improved route. Arthur Eichengrün tested aspirin on himself and did not suffer any heart malady. After aspirin's success in clinics, Heindrich Dreser discovered that aspirin is a prodrug of salicylic acid.[69]

In 1971, John R. Vane (1924–2004) discovered that aspirin works by blocking cyclooxygenase, thus preventing the synthesis of prostaglandins.[70] Another popular analgesic, acetaminophen (e.g., Tylenol), is not an NSAID. It is biologically active as an analgesic possibly through inhibition of cyclooxygenase-3 (COX-3), a subtype of the cyclooxygenase enzyme not identified until just a few years ago.

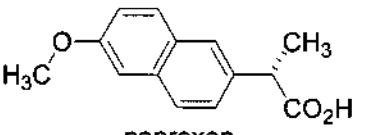
Charles Winter at Merck, Sharp, and Dohme developed the cotton string granuloma test as a model of inflammatory pain. Using this model, Merck screened about 350 indole compounds and identified indomethacin as a potent anti-inflammatory drug. Indomethacin was initially synthesized by medicinal chemist T. Y. Shen as a plant growth regulator.[71] Indomethacin was introduced in 1964, and is still regarded as a gold standard that combines both anti-inflammatory and analgesic activities.



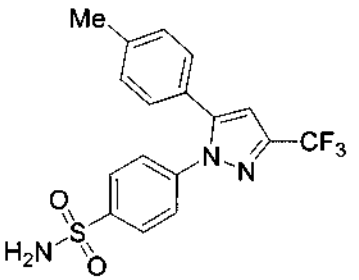
ibufenac



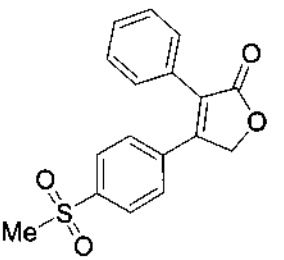
ibuprofen



naproxen



celecoxib (Celebrex)



rofecoxib (Vioxx)

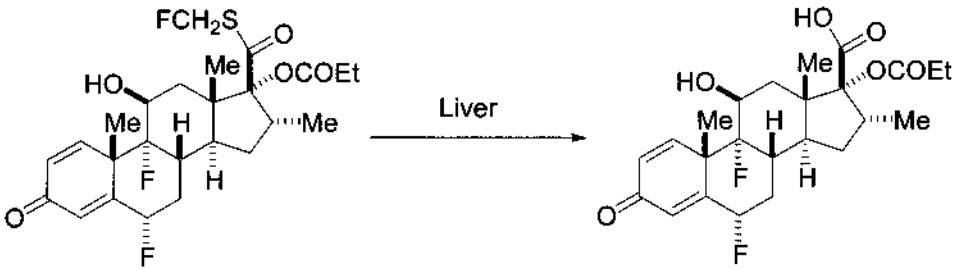
At Boots Company in the UK, pharmacologist Stewart S. Adams screened over 600 phenoxylalkanoic acids since 1956 but did not find any analgesics more potent than aspirin. In 1960, chemist John Nicholson synthesized *tert*-butylphenylacetic acid, which was proven to be effective for the treatment of rheumatoid arthritis but caused rash in some patients. A very similar drug, isobutylphenylacetic acid (ibufenac) did not cause a rash but caused liver toxicity in a small number of patients after long-term use. Finally, *isobut*ylphenyl*pro*pionic acid (ibuprofen, Motrin) was found to possess the best safety profile although it was not the most potent one.[72] In the same class, naproxen (Aleve), introduced by Syntex in 1976, was also a propionic acid with similar

pharmacology to ibuprofen. Naproxen is twice as potent as ibuprofen and has a much longer half-life in the body.

Under the leadership of Philip Needleman, G. D. Searle came up with the first COX-2 selective inhibitor celecoxib (Celebrex), first synthesized in 1993. Searle began comarketing it with Pfizer since June 1999.[73] Six months later Merck received approval from the FDA to market their version of a COX-2 selective inhibitor, rofecoxib (Vioxx).[74] Both Celebrex and Vioxx quickly became blockbuster drugs for the treatment of osteoarthritis (OA) and rheumatoid arthritis (RA). But Vioxx was withdrawn from the market in 2004 when it was found that it increased the risk of myocardial infarction and stroke in comparison to naproxen.

7.3 Antiasthmatics

The first inhaled glucocorticoid, beclomethasone dipropionate (BDP), demonstrated that topical delivery to the lung resulted in reduced systemic side effects (adrenal suppression, oseteoporosis and growth inhibition) typically seen with oral steroid treatments. Unfortunately, glucocorticoids such as BDP have significant bioavailability, and when one considers the surface area of the tracheobronchial mucosa, significant plasma levels and systemic side effects occur at therapeutic doses.



fluticasone propionate 17β-carboxylic acid

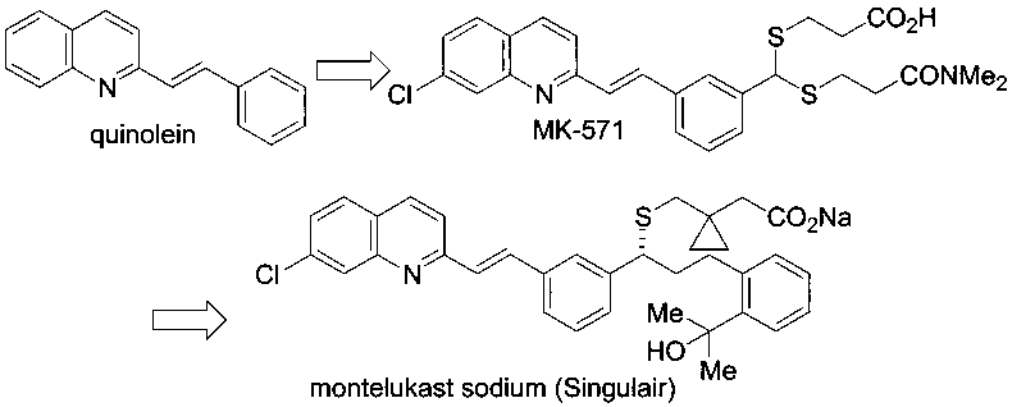
GlaxoSmithKline's fluticasone propionate (Flonase), a prodrug, has a much lower systemic bioavailability. SAR studies led to a series of carbothioates, which were very active *in vivo* when topically applied to rodents but were inactive after oral administration. It was shown that fluticasone propionate underwent first-pass metabolism in the liver to the corresponding inactive 17β-carboxylic acid. Fluticasone is a 100-fold more active than BDP and thousands-fold more active than cortisol, the active form of cortisone. Moreover, Flonase was designed to be pulmonary selective. As a consequence, fluticasone only has 1% oral bioavailability, whereas cortisol has 80% oral bioavailability.

Another asthma drug, salmeterol xinafoate (Serevent),[75] a β-adrenoceptor agonist, works through a different MOA from that of Flonase. It works by dilating the lung's bronchial tubes, which become constricted and make it difficult for asthmatics to breathe. While β-blockers are excellent drugs to lower blood pressure, β-adrenergic agonists are the most prescribed class of drugs for the treatment of asthma. β-Adrenergic agonists are preferred both for the rapid relief of symptoms and for the level of bronchodilation achieved in patients with bronchial asthma. They have now become standard bronchodilators for emergency rooms, and as day-to-day reliever

medicine. GlaxoSmithKline combined two asthma drugs with different mechanisms and arrived at Advir, which is comprised of Serevent (a β-adrenergic agonist) and Flonase (a glucocorticoid).

The newest therapy available for the treatment of asthma arises from the recognition of the role of the leukotrienes in the initiation and propagation of airway inflammation. Merck's montelukast sodium (Singulair) is an antagonist of leukotriene receptors.

In 1981, Merck Frosst established biological assays and animal models for modulation of leukotriene receptors in search of a treatment of asthma.[76] To find leukotriene receptor antagonists, they hand screened tens of thousands of compounds from Merck's compound library. They then selected quinolein as their lead compound for their studies on structure-activity relationship (SAR). They arrived at MK-571, which is a 1000-fold more potent than quinolein. The clinical trials in 1989 demonstrated that leukotriene receptor antagonists were effective for treating asthma, thereby confirming the pivotal role of leukotrienes in respiratory disease clinically. Unfortunately, MK-571 caused large increase of liver weight in mice. Merck Frosst scientists discovered that only one enantiomer of MK-571 had the liver side effect. In April 1991, they finally produced montelukast sodium, which possessed desirable attributes, such as high intrinsic potency, good oral bioavailability, and long duration of action for a once daily regimen for asthma.



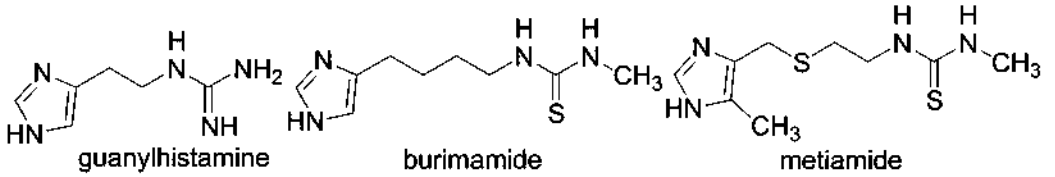
Two additional asthma drugs work via the same MOA as that of Singulair. They are AstraZeneca's zafirlukast (Accolate) and Ono Pharmaceutical's pranlukast (Onon).

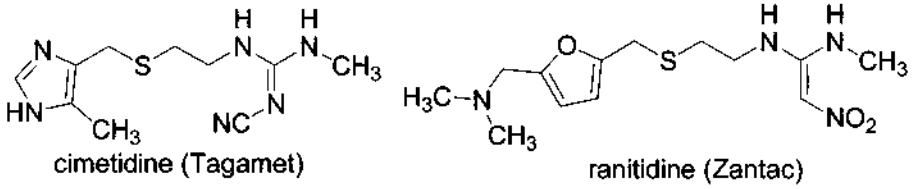
8 Antiulcer drugs

8.1 James Black and the Discovery of Tagamet

In 1963, soon after the discovery of propranolol (see Section 4.5), James Black moved from ICI to SK&F and shifted his interests to the effects of histamine. In analogy to β-receptors, Black hypothesized that selectively blocking one of the two histamine receptor would give a drug to treat ulcers. Working with a team of chemists led by C. Robin Ganellin, they did not find a compound that showed any blocking activity in the assays for the first 5 years.[77] From 1968 to 1970, the team, grappling with difficult syntheses, investigated the SAR of the guanyl-histamines. They replaced the strongly basic guanidine group with a thiourea, which in 1970 led to the discovery of

burimamide, the first *bona fide* pure H_2 antagonist without agonist effects. Another compound, metiamide, was 10 times more potent than burimamide and healed peptic ulcers in tests on humans, but it caused agranulocytosis. Replacing the thiourea group with cyanoguanidine, they synthesized cimetidine in 1972. It was shown to relieve symptoms and promote healing of lesions in a majority of patients with peptic ulcer disease and did not cause agranulocytosis. Marketed in the US in 1977, cimetidine (Tagamet) became the first blockbuster drug ever in medical history in 1985.

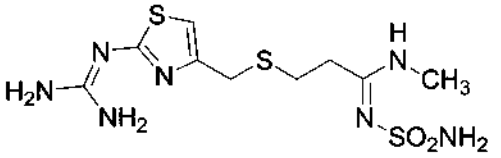


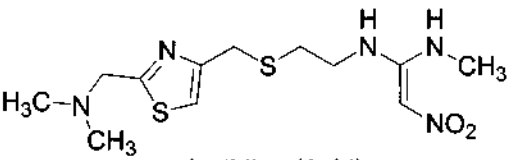


8.2 Zantac, Pepcid, and Axid

In 1972, David Jack and his pharmacologist colleague Roy Thomas Brittain at Allen & Hanburys attended a lecture by James Black, who revealed that burimamide inhibited histamine-induced acid secretion in animals and man. Jack redirected their Peptic Ulcer Project Group to solely focus on the H_2 antagonists using burimamide as the starting point.[78] They struggled for four years in attempts to replace SK&F's imidazole with nonbasic heterocyles without success until chemist John Clitherow carried out a Mannich reaction to install the dimethylaminomethylfuran. At the time, SK&F disclosed that 1,1-diamino-2-nitroethene was a good bioisostere for cyanoguanidine. Allen & Hanburys chemists then attached the nitrovinyl fragment into their own dimethylaminomethylfuran scaffold. The resulting drug AH19065, first prepared in early August 1976, was 10-times more potent in rats than cimetidine and it was also less toxic. AH19065 (ranitidine) was a poorly soluble solid. Its hydrochloride salt (Zantac) was prepared in 1977. Clinical trials subsequently confirmed its efficacy and safety.

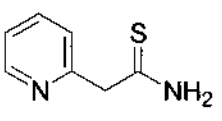
In the mid-1970s, a team at Yamanouchi led by Isao Yanagisawa replaced Tagamet's imidazole core with the guanidinothiazople. The guanidinothiazople moiety was initially discovered by ICI in its tiotidine, which was not marketed due to toxic manifestations. Meanwhile, they also replaced Tagamet's cyanoguanidine sidechain with carbamoyl-amidine. The resulting drug was the most potent histamine H_2 antagonist at the time, but it was not stable enough to be manufactured. Replacing the carbamoyl-amidine moiety with an unorthodox sulfamoyl-amidine afforded famotidine (Pepcid). Lilly's nizatidine (Axid), was the fourth histamine H_2 antagonist in the U.S. market.

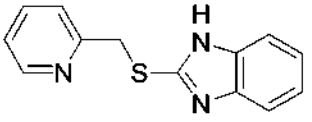

famotidine (Pepcid)

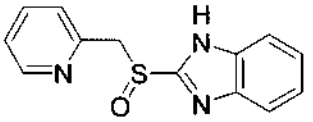

nizatidine (Axid)

8.3 Prilosec and Nexium

In 1967, Ivan Östholm, a research director at Astra Hässle (now part of AstraZeneca), initiated a program in the gastrointestinal field[79] called it "Gastrin Project." Black and his colleagues at SK&F demonstrated that imidazole was important for acid control by H_2 histamine receptors. Hässle chemists wisely selected benzimidazole moiety to replace the toxic thioamide portion on Servier's CMN 131. This decision would prove critical. Combining features on CMN 131 and Tagamet gave rise to H 124/26, which was both efficacious and safe. Unfortunately, a Hungarian patent already patented the same compound for the treatment of tuberculosis. The team later isolated timoprazole, an oxidative metabolite isolated from dogs' urine, which was even more active than H 124/26. In 1974, timoprazole was found to cause toxicities in thymus and thyroid by blocking the uptake of iodine to the thyroid gland in rats. In 1976, they arrived at picoprazole, which had antisecretory activity in both rats and dogs but without toxic effect.


CMN 131

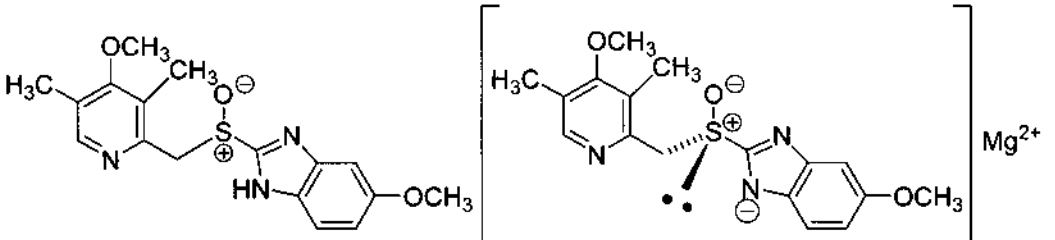

H 124/26


H 83/69 (timoprazole)

In the summer of 1977, Erik Fellenius, a biochemist from Hässle, met George Sachs from Alabama at a conference. The ensuing collaboration revealed that timoprazole's MOA is through inhibition of H^+,K^+-ATPase, the proton pump of the stomach. Sachs and his postdoc Berglindh demonstrated that timoprazole and picoprazole were prodrugs but were converted to the active form after accumulation in the acidic secretory canaliculus of the parietal cells.[80] That was the beginning of proton pump inhibitors (PPIs).

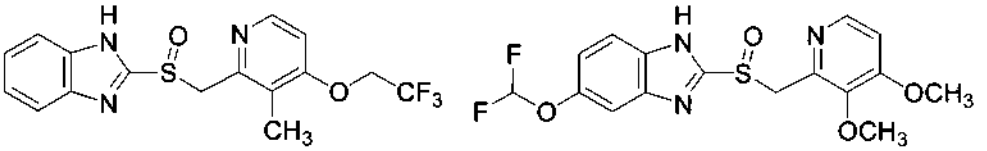
Meanwhile, medicinal chemists kept optimizing the substitutions on the core structure. In January 1979, Ylva Örtengren prepared H168/68,[81] which would eventually become omeprazole (Prilosec). Since 3,5-dimethyl-4-methoxy-pyridine was known to increase the basicity of a pyridine ring, in their enthusiasm to prepare a very potent compound, they went ahead and had Örtengren prepare it without systematically exploring the structure-activity relationship. However, by a stroke of good luck, omeprazole gave higher *in vivo* activity than any other combinations. As a matter of fact, omeprazole was the most powerful inhibitor of stimulated gastric acid secretion in experimental animals at the time. The drug had no sign of serious toxicity in animal models.

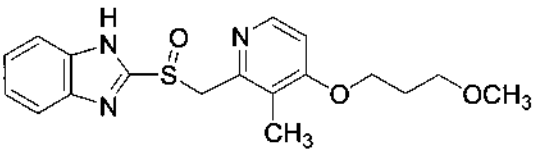
Omeprazole (Prilosec) was approved as a treatment for duodenal ulcers and reflux esophagitis in Sweden in 1988 and in the U.S. in 1990.



In 1987, a group led by Gunnel Sundén embarked on a focused program in finding an omeprazole backup with better bioavailability. Among all the compounds in their hands, only one was better than omeprazole. It was the *S*-(–)-enantiomer of omeprazole, esomeprazole (Nexium). When tested in rats, esomeprazole was 4–5 times more bioavailable than the *R*-enantiomer.[82] Another lucky break was that they tested esomeprazole directly in man and saw similar effects to what they observed with rats. Later on, when the two isomers were tested on dogs, no significant difference of efficacy was detected for the two isomers. In this case, rat was a better animal model than dog. If they used dogs for their initial *in vivo* tests, they probably would never have found esomeprazole. Esomeprazole (Nexium) was approved in Sweden in 2000 and in the U.S. in early 2001, just when Prilosec's U.S. patent expired in April.

Lansoprazole (Prevacid) is another proton pump inhibitor sold by TAP Pharmaceuticals, a joint venture of Abbott Laboratories and Takeda. Two other PPIs are pantoprazole (Protonix)[83] and rabeprazole (Aciphex).

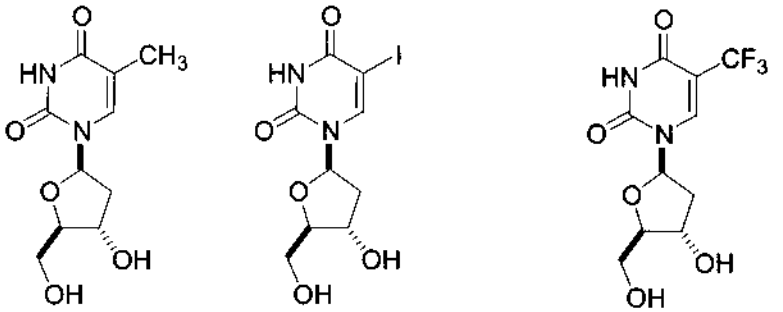




9 Antiviral Drugs

The first clinically effective antiviral did not become available in 1962 until 5-iodo-2′-deoxyuridine (IDU) became the first antiviral drug for the treatment of the most common corneal infection of humans: herpes keratitis. It was synthesized by William H. Prusoff at Yale in 1959 as a potential anticancer drug.[84] Since it was not a selective inhibitor of virus replication, it was highly toxic, most noticeably bone marrow suppression. Herbert Kaufman demonstrated IDU

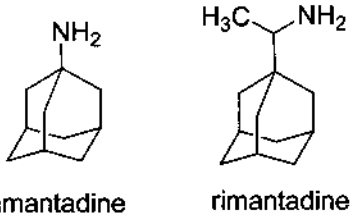
could be used for herpes simplex virus (HSV) infection in the eye.[85] He also found trifluorothymidine (TFT, Viroptic) with similar applications in 1964.



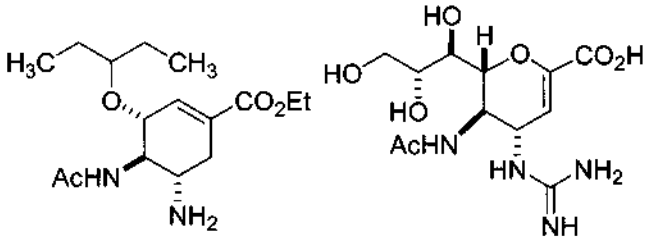
thymidine iododeoxyuridine (IDU) trifluorothymidine (TFT, Viroptic)

9.1 *Influenza Drugs*

Currently, there are four drugs available for the treatment or prophylaxis of influenza infections: the adamantanes, including amantadine and rimantadine. The adamantanes act as M_2 ion channel inhibitors and interfere with viral un-coating inside the cell.[86] They are effective only against influenza A and are associated with several toxic effects as well as drug resistance.



amantadine rimantadine



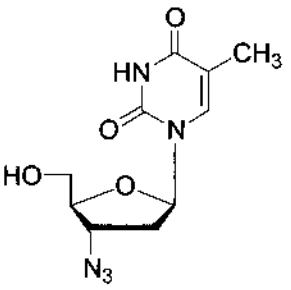
oseltamivir (Tamiflu) zanamivir (Relenza)

The neuraminidase inhibitors, including oseltamivir (Tamiflu) and zanamivir (Relenza), are newer drugs that have shown greater efficacy for both influenza A and B and are associated with fewer side effects in comparison to the adamantanes. The influenza neuraminidase is one of two major glycoproteins located on the influenza virus membrane envelope. Oseltamivir, the first orally active neuraminidase inhibitor, was discovered by Choung U. Kim and co-workers at

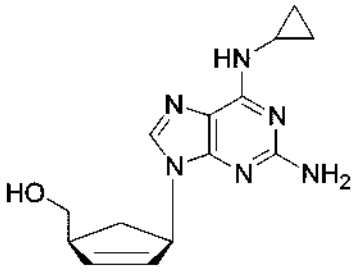
Gilead Sciences in 1995.[87] Gilead and Roche began codeveloping it in 1995 and the FDA approved it in 1999. On the other hand, zanamivir was discovered by Biota Holdings, a small Australian biotechnology concern.[88] In the United States, Biota established an alliance with GlaxoSmithKline for development and marketing of zanamivir .

9.2 HIV Drugs

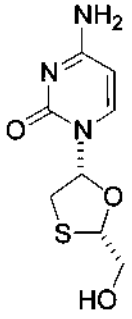
In 1984, the NCI began to screen antiviral agents as possible treatments for AIDS. In February 1985, one of the compounds, AZT (zidovudine, Retrovir), was found to be active *in vitro*.[89] AZT itself was synthesized by a group led by Jerome Horowitz of the Michigan Cancer Foundation in 1964 as a possible anticancer drug. Burroughs Wellcome acquired the right to AZT and explored the possibility of using it to treat the herpes virus under the guidance of Gertrude Elion, although it did not make it to the market. Wellcome patented AZT as an antiviral drug in 1985 and promptly commenced the clinical trials. The FDA approved the use of AZT in 1987. AZT is a prodrug—it is not active *in vitro*, but its triphosphate is the active agent *in vivo*. Its MOA is the blockade of the HIV reverse transcriptase activity.



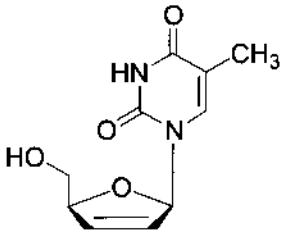
azidothymidine (AZT)



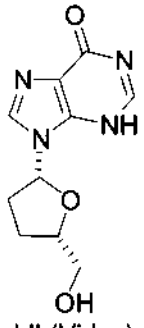
abacavir (Ziagen)



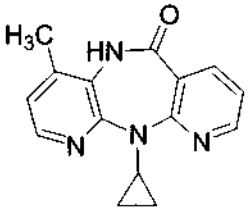
3TC (Epivir)



d4t (Zerit)



ddI (Videx)



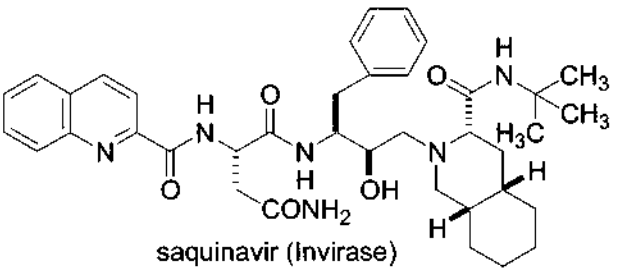
nevirapine (Viramune)

Among the newer reverse transcriptase inhibitors, abacabir (Ziagen) represents a vast improvement over AZT, a nucleotide whose gycosidic core structure is metabolized rapidly.[90] By replacing the oxygen on AZT with a methylene group, carbocyclic nucleoside analogs such as Ziagen are metabolized much slower by the body. Ziagen was developed by GlaxoWellcome (now part of GlaxoSmithKline) using a technology developed by Robert Vince of the University

of Minnesota, who licensed the patent to GlaxoWellcome in 1993.

In addition to AZT and Ziagen, many HIV reverse transcriptase inhibitors exist. An organic chemistry professor at Emory University, Dennis Liotta, and his virologist colleague Raymond Schinazi discovered another reverse transcriptase inhibitor, 3TC (lamivudine, Epivir), which allows a once daily regimen.[91] Additional HIV reverse transcriptase inhibitors are BMS's d4T (stavudine, Zerit),[92] 2′-3′-dideoxyinosine (ddI, didanosine, Videx),[93] and Boehringer Ingelheim's nevirapine (Viramune),[94] a nonnucleoside inhibitor.

Saquinavir (Invirase) by Roche was the first HIV protease inhibitor on the U.S. market.[95] In 1986, Roche undertook an ambitious international collaboration to tackle the HIV protease. The chemistry team in Welwyn led by Ian B. Duncan and Sally Redshaw designed some inhibitors using the "transition-state mimic" concept, which was highly successful in producing their potent renin inhibitors. They found that a tripeptide was ideal considering both potency and bioavailability. The Roche team fine tuned the tripeptide, exploring their lead compound systematically by modifying each amino acid residue in turn. In 1991, they arrived at Ro 31-8959 (saquinavir). Roche carried out the clinical trials, led by Keith Bragman, Roche's top European virologist. Saquinavir (Invirase) became the first HIV protease inhibitor for the treatment of AIDS when it was approved by the FDA in December 1995.



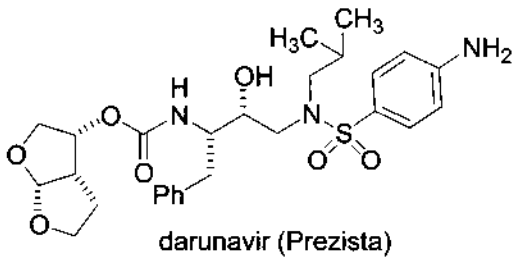
saquinavir (Invirase)

Abbott's team for protease inhibitors was led by an X-ray crystallographer, John Erickson, and a medicinal chemist, Dale Kempf.[96] Instead of screening their renin inhibitors like most drug firms did at the time, they took advantage of Erickson's X-ray crystallography work on the HIV protease, integrating structure-based drug design (SBDD) and traditional medicinal chemistry. They prepared a series of symmetry-based inhibitors to match the C_2-symmetric nature of the HIV protease. Using that approach, they arrived at A-77003, a tetrapeptide. Although A-77003 was potent in binding and cellular assays, it was not bioavailable with extremely high human biliary clearance. By reducing the molecular weight and replacing the existing amino acids with more soluble ones, they achieved an increase in bioavailability. They also identified that the pyridine termini were oxidized into *N*-oxide by hepatic cytochrome P450. Simply replacing the pyridines with thiazoles and fine tuning gave rise to ritonavir, whose bioavailability was 78% in comparison to 26% for the pyridyl analog. Interestingly, while many other protease inhibitors are metabolized by hepatic cytochrome P450 3A4 (a major isozyme), ritonavir (Norvir) is a potent inhibitor of P450 3A4. As a result, dual protease inhibitor therapy has proven to be a powerful regimen in terms of efficacy and minimizing drug resistance.

Merck began their research on protease inhibitors in 1986 with Irving Sigal as the project champion. Merck's medicinal chemistry team was led by Joel Huff.[97] They initially screened their renin inhibitors for HIV protease inhibition and then carried out rational drug design by taking advantage of the known crystal structure of HIV-1 protease. In 1990 Wayne Thompson

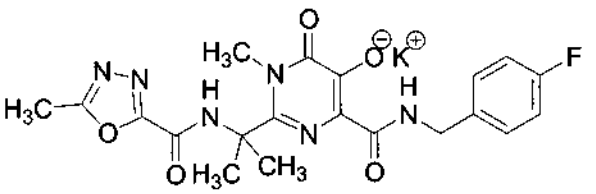
arrived at L-689,502, which was active in inhibiting the HIV protease but devoid of renin activity. Unfortunately it was not bioavailable and only effective by injection. Inspired by saquinavir's success, Joseph Vacca successfully incorporated a fragment of saquinavir into L-689,502. Bruce Dorsey, a new hire in 1989 in Vacca's group, and his associate Rhonda Levin succeeded in synthesizing L-735,524 (indinavir). However, in the monotherapy trials HIV developed resistance to indinavir in some patients after six month. Fortunately, it was found that the combination of indinavir and AZT or 3TC was effective in substantially suppressing the virus levels. Merck's studies of combination therapy were the first to prove the efficacy of the cocktail approach and became the standard for the industry. After filing with the FDA in January 1996, indinavir (Crixivan) received approval in March in an accelerated review process.

Other important HIV protease inhibitors include nelfinavir (Viracept) and amprenavir (Agenerase). In 2006, another HIV protease inhibitor darunavir (Prezista) was approved for the treatment of HIV/AIDS patients who are harboring drug-resistant HIV that does not respond to other therapies. The drug was discovered by Arun K. Ghosh at Purdue University, who started the effort strictly as an educational project.[98] They used structure-based drug design, based on X-ray crystallographic analysis of inhibitor-bound HIV protease structures, to optimize inhibitor binding to the backbone. Some older HIV protease inhibitors primarily targeted the protease's amino acid sidechain, which the virus could modify more easily.

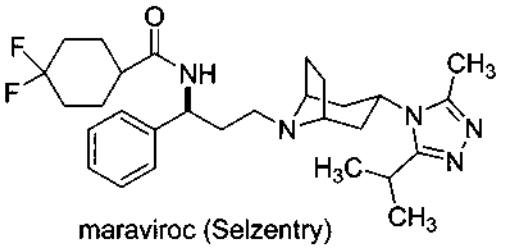


darunavir (Prezista)

In addition to HIV reverse transcriptase inhibitors and HIV protease inhibitors, several other mechanisms yielded successful treatments in the clinics. Merck's raltegravir (Isentress) is the first FDA-approved inhibitor of HIV integrase.[99] Pfizer's maraviroc (Selzentry) is the first-in-class CCR5 antagonist for the treatment of HIV.[100]



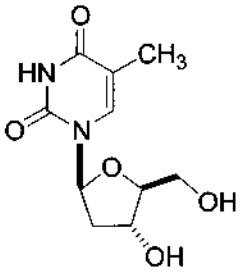
raltegravir (Isentress)



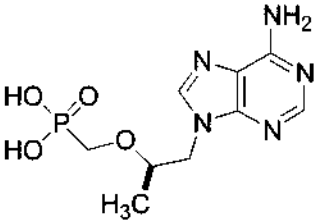
maraviroc (Selzentry)

9.3 Hepatitis Virus Drugs

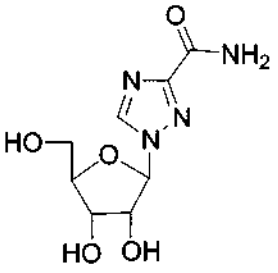
For the treatment of chronic hepatitis B, interferon and five nucleos(t)ides have been approved in many parts of the world. 3TC (lamivudine, Epivir) was the first antiviral drug for HBV. Tenofovir disoproxil fumarate (tenofovir DF) is an orally administered ester prodrug of tenofovir, a nucleotide reverse transcriptase inhibitor that shows potent *in vitro* activity against both hepatitis B virus (HBV) and HIV-1. Current treatments for HBV also include adefovir dipivoxil (Hepsera) and BMS's entecavir (Baraclude). Interferon, unfortunately, is effective only in a subset of patients It is often poorly tolerated, requires parenteral administration, and is expensive.[101]



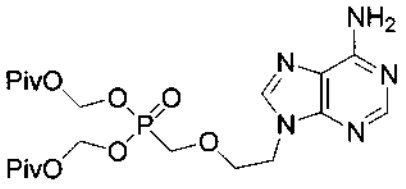
telbivudine (Tyzeka)



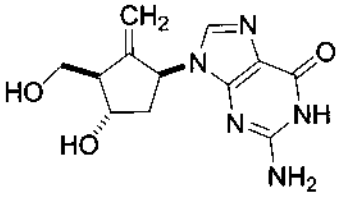
tenofovir (Viread)



ribavirin (Rebetol)



adefovir dipivoxil (Hepsera)

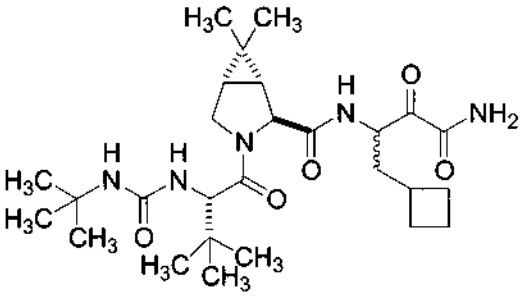


entecavir (Baraclude)

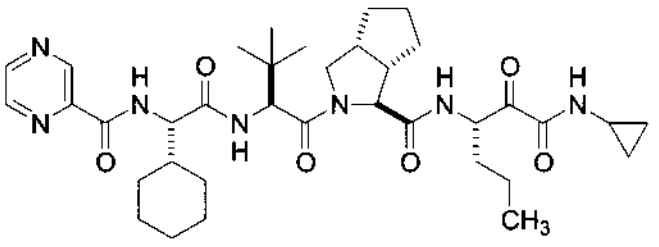
Current therapy for hepatitis C virus (HCV) includes pegylated interferon-α (PEG-Intron) alone or in combination with ribavirin (Rebetol).[102] However, the antiviral activity of interferons is indirect, and ribavirin is a nonspecific agent with inhibitory activity toward some host proteins, a circumstance that has contributed to the considerable effort being expended to identify and develop specifically targeted antiviral therapy for HCV.[103] They include HCV NS2

and NS3/4 protease inhibitors, NS3 helicase inhibitors, NS4B and NS5A, and NS5B replication factor inhibitors, as well as HCV NS5B polymerase inhibitors.

Excitingly, two HCV drugs were approved by the FDA in May 2011 during preparation of the manuscript. Both are HCV NS3–4A serine protease inhibitors. One is boceprevir (Victrelis) by Schering-Plough/Merck and the other is telaprevir (Incivek) by Vertex. These two innovative medicines now avail patients with HCV safe, efficacious, and convenient treatment options.



boceprevir (Victrelis)



telaprevir (Incivek)

Due to space restraint, I cannot even begin to cover many of the most exciting discoveries going on in the laboratories around the world. History is being written every day in human's crusade to defeat diseases. The ensuing chapters will give an overview of some major aspects in drug discovery.

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