Synthesis of Drugs containing Heterocyclic Compounds

The history of mankind has witnessed significant milestones such as invention of wheel, fire, astronomy, laws of physics and chemistry, industrial revolution, theory of evolution, understanding of the human physiology, germ theory of infections, telephones, television, transistors, semiconductors, computers, mobile phones etc.

These advances have been primed by curiosity of mankind as well as the desire to better his living standards, lead health lifestyles and prolong living. The attempts to enhance our health and longlevity is evidenced by advances in biomedical research leading to proposition of the germ theory, history of drug discovery and advances in biomedical instrumentation and clinical practices.

In the middle of the 19the century, French chemist and microbiologist, Louis Pasteur showed that fermentation occurs due to microorganisms. This led to the discovery a microbial world that was invisible to the naked eye. Along with this, the fact that we inhabit this world with microorganisms was understood, although the malefic implications of this was not completely understood. In the latter half of the 19th century, English surgeon Joseph Lister revolutionized surgical practices minimizing risks from microbial infections to patients. German physician Robert Koch discovered lethal germs and advanced the "germ theory". Germ theory proposed that certain diseases, if not all are caused by the invasion of the body by microorganisms, organisms too small to be seen except through a microscope. The acceptance of the germ theory was a significant milestone in medical sciences and redefined the field of pathology.

Before World War I, inspite of the understanding of significance of germ theory, bacterial infections leading to septicemia was a leading cause of death. The quest to combat these microorganisms, led to the emergence of chemotherapy, the use of chemicals as therapeutic agents against microorganisms. In the early part of the 20th century, German physician and scientist Paul Erlich attempted to use dyes and other known organic chemicals as chemotherapeutic agents. The discovery of organoarsenic compound, "salvarsan" in 1910 against syphilis was a significant milestone in chemotherapy. Salvarsan was widely used in World War I and till 1930s, till it was displaced by an azo dye named prontosil discovered by Gerhard Domagk (1895-1964) in 1932. He discovered that the dye was effective *in-vivo* when administered to subjects, but not *in-vitro* against bacterium in test tubes.

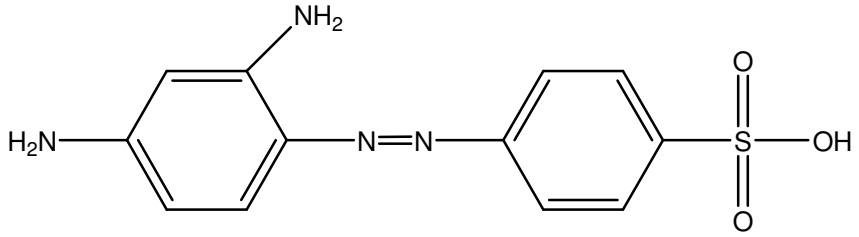


Figure 1: Prontosil, an azo dye that was also effective against bacterial infections

Prontosil was a precursor molecule (prodrug) to what came to be called as sulfa drugs. When administered to patients, microorganisms in the intestines hydrolyze the protonsil to sulfanilamide. It is

the sulfanilamide and not the prontosil that is active against bacteria. When the prontosil was used in test tubes, the absence of intestinal bacteria prevents its conversion to sulfanilamide. This leads to lack of its ineffectiveness as an antibacterial drug. Sulfa drugs were widely used as antibacterial agents, till the development of penicillins as antibiotic agents.

In 1928, Alexander Fleming discovered Penicillin, a biologically produced compound secreted by mold (microganisms) with antibiotic activity against bacteria. This was a significant breakthrough in field of chemotherapy and led to the area of modern antibiotics. The large-scale fermentative production of penicillin and the synthetic modification of the molecule led to the emergence of semisynthetic penicillins as antibiotic agents.

Apart from antibacterials, other drugs have also been developed. Drugs can be subdivided into small molecules and biomolecues. Small molecules are chemically synthesized entities with < 500 D molecular weight. In contrast, biomolecules also known as biologics are large molecules and usually proteins such as insulin that are difficult to chemically synthesize.

Almost 90% of the drug market is dominated by small molecules. The research process that leads to identification of an effective therapeutic treatment is largely based on mimicking nature by "fooling" it in a very subtle way. Because heterocycles are the core elements of a wide range of natural products such as nucleic acids, amino acids, carbohydrates, vitamins, and alkaloids, medicinal chemistry efforts often evolve around simulating such structural motifs. However, heterocycles play a much bigger role in the modern repertoire of medicinal chemists. Some of the drug properties that can be modulated by a strategic inclusion of heterocyclic moiety into the molecule include: 1) potency and selectivity through bioisosteric replacements, 2) lipophilicity, 3) polarity, and 4) aqueous solubility.

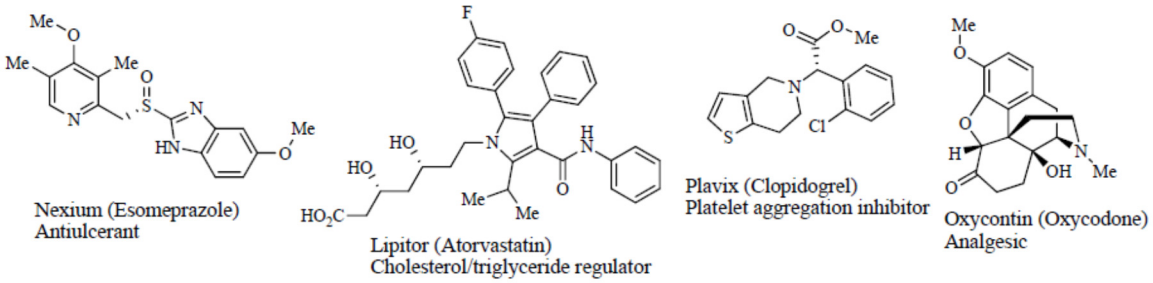


Figure: Examples of famous drugs from US market that contain heterocyclic rings

An example of heterocyclic moiety bearing drug are sulfa drugs. This is used as an example below.

Sulfa Drugs

These drugs are para-amino benzene sulfonic acids and derivatives. They are active against gram positive and gram negative strains of bacteria and are therefore used as antibacterials.

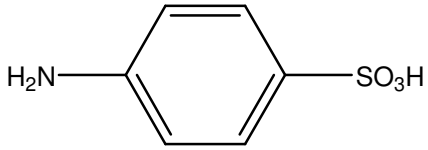


Figure 2: Para-amino benzene sulfonic acid

Examples of sulfa drug synthesis

Sulfanilamide

Sulfanilamide is an antibacterial drug. It is prepared by acetylating aniline to acetanilide (n-acetyl-aniline). This steps protects the amine from getting oxidized further. The acetanilide upon treatment with chlorosulfonic acid ($ClSO_3H$), gives N-acetyl sulfanyl chloride. This upon treatment with ammonia produces N-acetyl sulfanilamide. The protection on the amino group can be hydrolyzed to produce sulfanilamide as shown in figure 3 below.

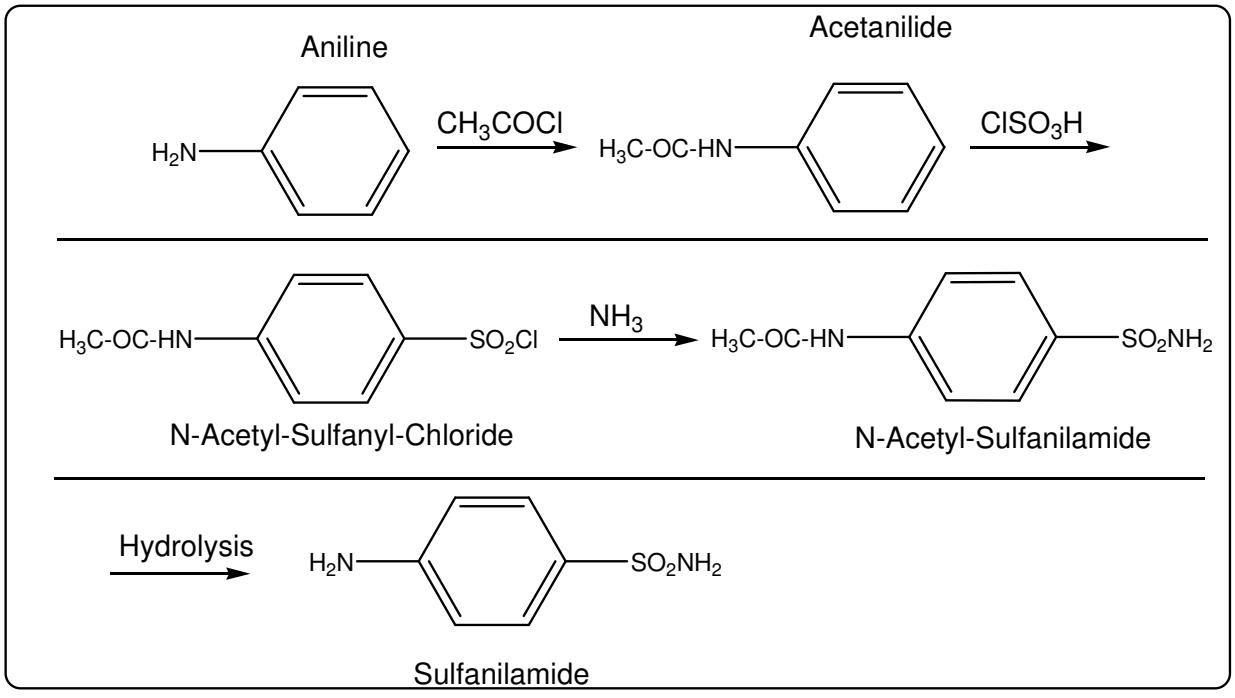


Figure 3: Synthesis of Sulfanilamide

Mode of Action

This is a basic sulfa drug used against infections. Sulfonamide antibiotic block the synthesis of dihydrofolic acid needed for synthesis of folic acid in bacteria. This is achieved by inhibiting the enzyme dihydropteroate synthase. Human subjects are unaffected as we lack the enzyme, dihydropteroate synthase and acquire our folic acid requirements through food.

SulfaPyridine

Sulfapyridine was one of the first generation of sulphonamide antibiotics. It was reported to be the first chemotherapeutical agents against pneumonia. It was used widely during the World War II. It was later superseded by penicillin and other sulfa drugs. . It is a bacteriostatic antibiotics with a wide spectrum against most gram-positive and many gram-negative organisms. However, many strains of an individual species may be resistant. It inhibits multiplication of bacteria by acting as competitive inhibitors of *p*-aminobenzoic acid (PABA) in the folic acid metabolism cycle.

Preparation

It is prepared starting with aniline. The amino group is protected against oxidation by acetylating it with acetyl chloride. The acetylated aniline is treated with chlorosulfonic acid to form a para-chlorosulfonyl dertivate (N-Acetyl-Chlorosulfonyl Chloride). This on treatment with 2-aminopyridine followed by the hydrolysis of the N-protecting acetyl group forms sulfapyridine as shown in figure 4.

Uses: It is used against dermatitis. It can crystallize in the body and is not used orally.

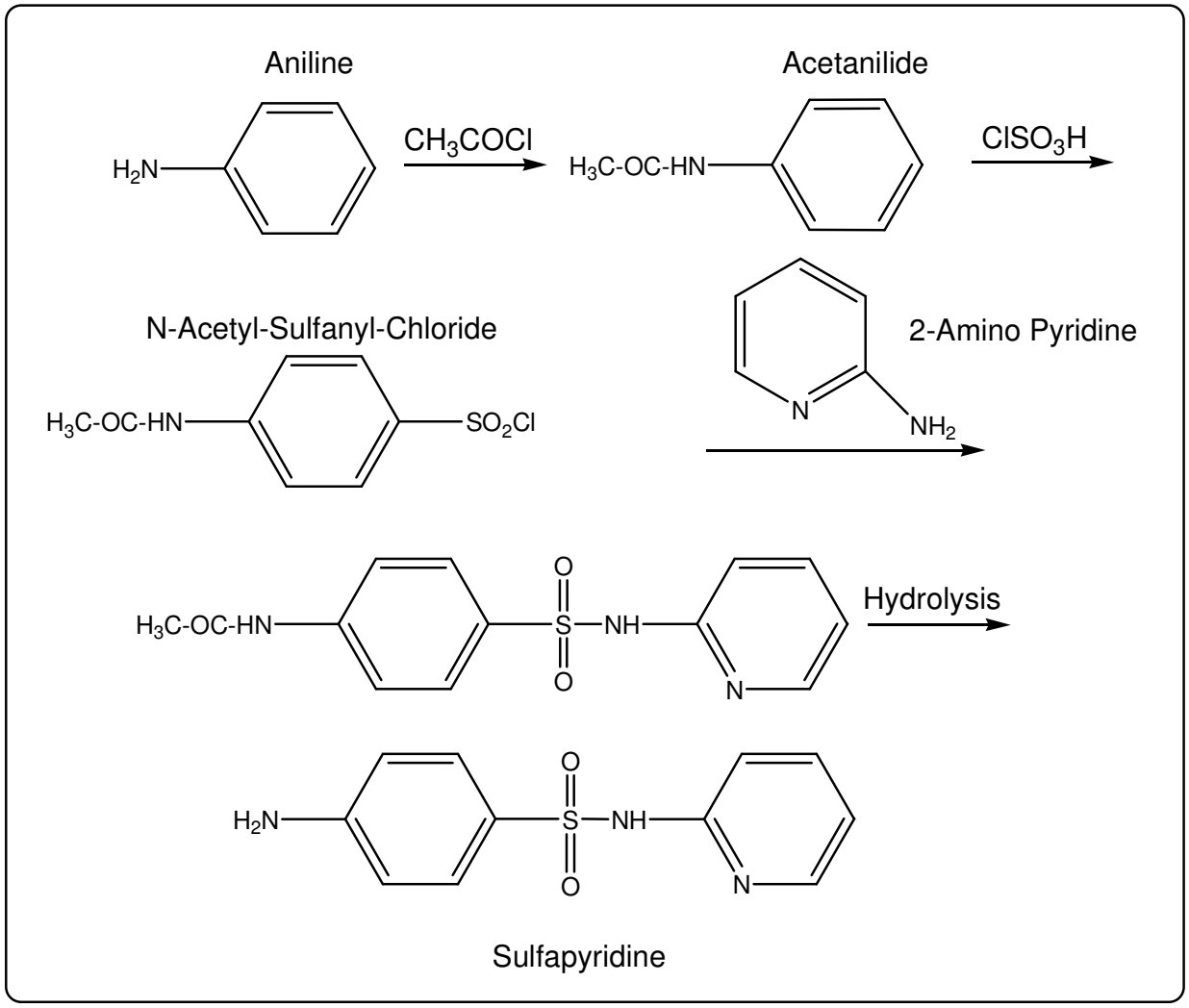


Figure 4: Synthesis of Sulfapyridine

Other Sulfa Drugs

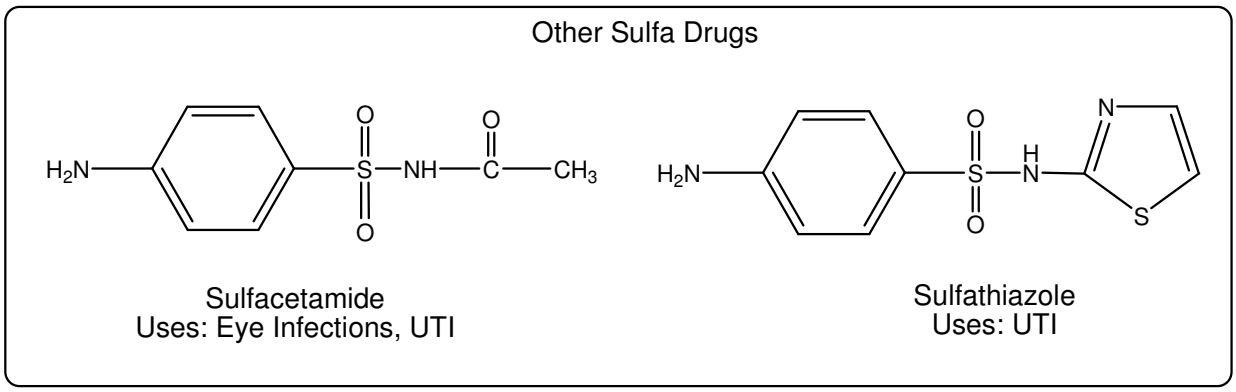


Figure 5

Antimalarials

Malaria is a tropical disease that is transmitted by female anopheles mosquito vector. The bite of this mosquito transmits *Plasmodium falciparium, Plasmodium vivax and Plasmodium ovale* parasites into the blood stream that spreads systemically, resides and reproduces in the liver. This infects red blood cells leading to more reproduction of the bursting of the cells and subsequent effects.

Symptoms include fever, fatigue, vomiting, headaches and shivering. Treatment may be prophylactic with mosquito nets and repellents. It may also be treated with drugs such as quinine, promoquinone, chloroquinone, artemisnin, doxycycline *etc*.

Synthesis of Quinine

The quinine molecule is extracted from the bark of the chinchona tree and is still the major source of this drug. Synthetic methods have been discovered, but long drawn procedures have hindered their commercialization.

The molecule consists of quinoline with a 6-methoxy substituent and a 3-vinyl substituted quiniclidine skeleton is bridged by a methylene group containing a hydroxyl group as shown in figure 5.

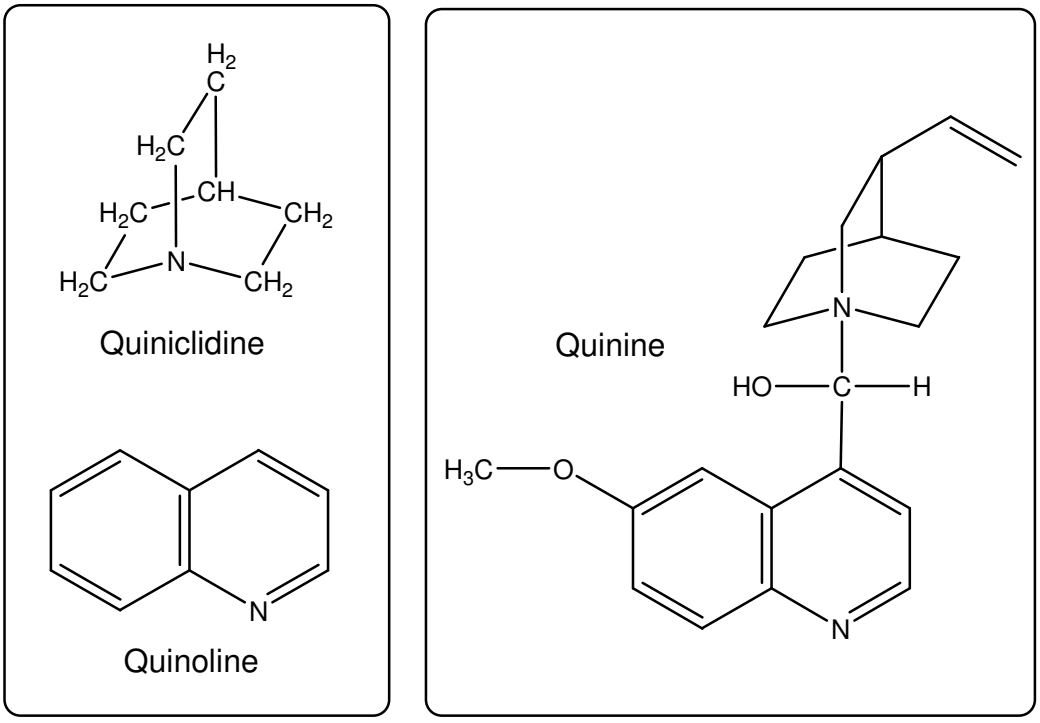


Figure 5: Quinine

Synthesis of Quinine from Quinitoxine (Smith and Williams, 2008)

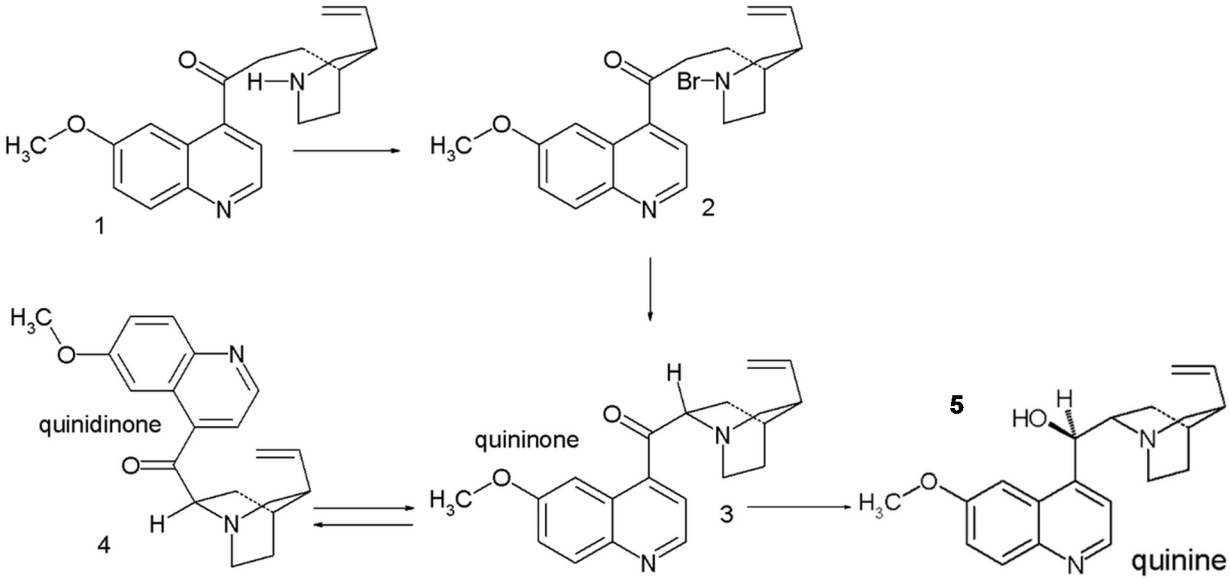


Figure 6: Conversion of *d*-quinotoxine to quinine. In the figure above: 1. Quinitoxine 2. N-bromoquinitoxine 3. Quunininone 4. Quinidinone 5. Quuninine

The Quinotoxine when treated with a solution of freshly-made sodium hypobromite (NaOBr, NaOH, HCl (aq), Diethylether) results in approximately 55% crude product, “N-bromoquinotoxine”. This is an unstable substance and is immediately treated with sodium ethoxide in ethanol (NaOEt, EtOH) to effect quinuclidine cyclization with 88% yield of crude cyclization products. However, this provides a mixture of quininone and quinidinone. In the last step, the cyclization products when treated with Aluminum powder and sodium ethoxide in ethanol produces quinine.

Qunine Analogs

Inspite of synthetic methods, quinine from chinchona bark is the primary drug against malaria. In the quest for discovering more potent drugs, in the 1920s and 1930s, German companies such as Bayer started working on synthesizing and testing analogs of quinine. The success of naturally available quinine as a prophylactic against malaria suggested that analogs might be more potent than quinine. Some of the successful analogs were primaquine, pamaquine, mepaquine, sontoquine, chloroquine as shown in figure 7. We shall be concentrating on only two analogs primaquine, chloroquine.

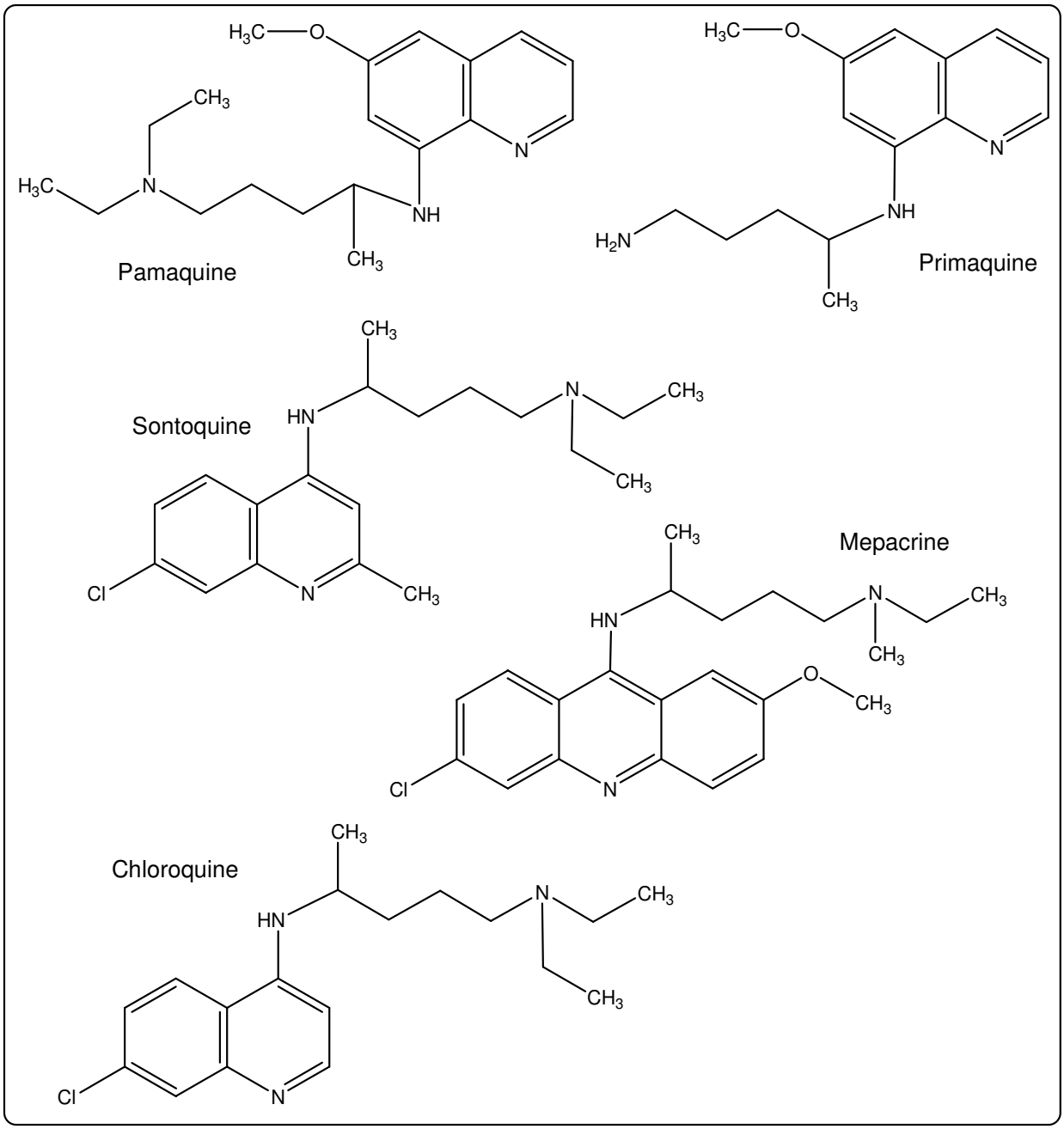


Figure: Quinine Analogs

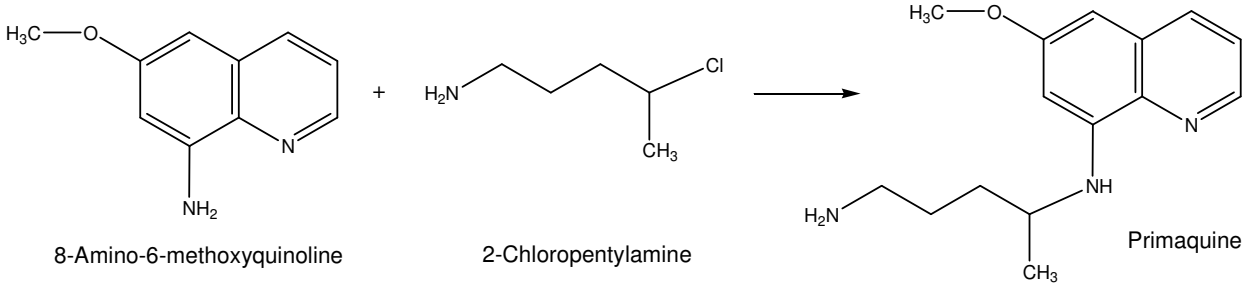
Primaquine

It is 8-[(4-Amino-1-methylbutyl) amino]-6-methoxyquinoline synthetic analog of quinine. It is used in the treatment of malaria and Pneumocystis pneumonia. It is a member of the 8-aminoquinoline group of drugs such as pamaquine. It was first synthesised by Robert Elderfield of Columbia University in the

1940s. It is on the World Health Organization's List of Essential Medicines, the most important medications needed in a basic health system.

Primaquine is mainly used to treat *Plasmodium vivax* or *Plasmodium ovale* induced malaria. It acts on the active forms of this parasite in the bloodstreams, but it is more potent on its action against dormant forms in the liver. Other forms of quinines are potent against blood stream parasites and are used first followed by primaquine to counter dormant forms in other tissues such as liver. Hence, it prevents relapse of the disease. It has some side effects such as nausea, vomiting, and stomach cramps. The most dangerous adverse effect of primaquine is hemolysis, ie lysis of red blood cells in patients with Glucose-6-Phosphate Dehydrogenase deficiency.

Synthesis of Primaquine



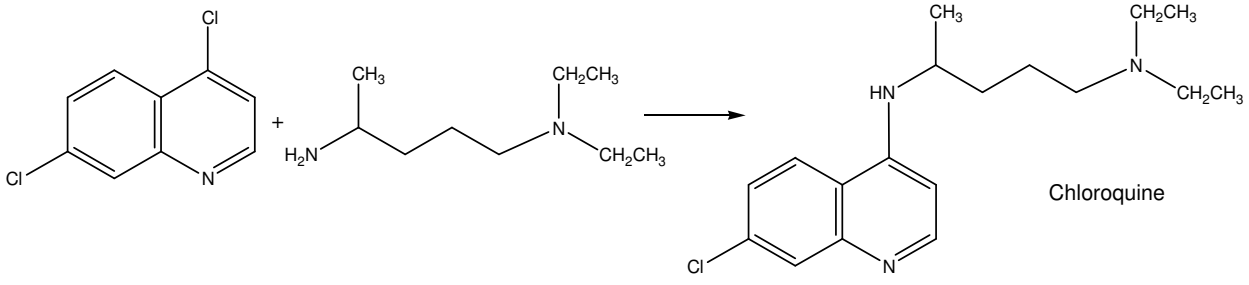
8-Amino-6-methoxyquinoline 2-Chloropentylamine Primaquine

Primaquine is synthesized by condensation of 2-chloropentylamine with 8-amino-6-methoxyquinoline as shown in the figure.

Chloroquine (Aralen) 7-Chloro-4-[4-diethylamino]-1-methyl] butyl]-amino)-quinoline

Chloroquine is one of the 4-aminoquinoline drug used in the treatment or prevention of malaria.

It is synthesized by condensation of 4,7-dichloroquinoline and diethylaminopentane.



4,7-Dichloroquinoline 4-Amino-1-Diethylaminopentane Chloroquine