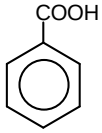
№ 33. DERIVATIVES OF BENZENE AS DRUGS

benzene

1. Benzene. Recall the characteristic features of an aromatic system.

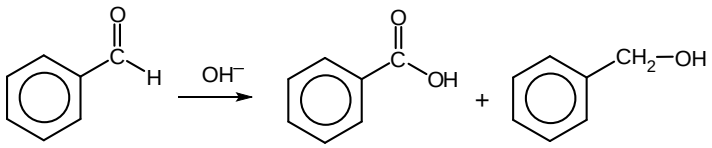
Benzene, with the molecular formula C_6H_6 , is an aromatic hydrocarbon with a continuous π-bond (6 p electrons, delocalized over 6 C atoms). It is sometimes abbreviated Ph–H. Benzene is a colorless and highly flammable liquid with a sweet smell and a relatively high melting point. Because it is a known carcinogen, its use as an additive in gasoline is now limited, but it is an important industrial solvent and precursor in the production of drugs, plastics, synthetic rubber, and dyes. Benzene is a natural constituent of crude oil, and may be synthesized from other compounds present in petroleum.

Even the short term breathing of high levels of benzene can result in death, while low levels can cause drowsiness, dizziness, rapid heart rate, headaches, tremors, confusion, and unconsciousness. The major effects of benzene are chronic (long-term) exposure. Benzene damages the bone marrow (anemia). Benzene targets liver, kidney, lung, heart and the brain and can cause DNA strand breaks, chromosomal damage etc., all related to cancer.



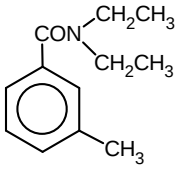
benzoic acid

2. Benzoic acid. Benzoic acid, (C_6H_5COOH), is a colorless crystalline solid and the simplest aromatic carboxylic acid. The name comes from gum benzoin (balsamic resin obtained from the bark of several species of trees), which was for a long time the only source for benzoic acid. Benzoic acid is produced commercially by partial catalytic oxidation of toluene with oxygen. The base-induced disproportionation of benzaldehyde, the Cannizzaro reaction, affords equal amounts of benzoate and benzyl alcohol.



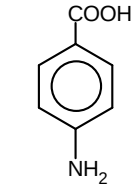
benzaldehyde benzoic acid benzyl alcohol

Benzoic acid is a weak acid. Its salts are used as a food and drinks preservative. Benzoic acid is an important precursor for the synthesis of many other organic substances. Benzoic acid inhibits the growth of mold, yeast and some bacteria. Therefore, as a food preservative it is added directly or created from reactions with its sodium, potassium, or calcium salt. After absorption of benzoic acid into the cell, if the intracellular pH changes to 5 or lower, the anaerobic enzymic fermentation of glucose is decreased by 95% which inhibits the organism growth. Acidic food and beverages like fruit juice (containing citric acid), sparkling drinks (containing carbon dioxide), soft drinks (containing phosphoric acid), pickles (containing vinegar) or other acidified food are preserved with benzoic acid and benzoates. After digestion, benzoic acid is metabolized by conjugation with glycine and excreted in the urine as hippuric acid ($C_6H_5CONHCH_2COOH$).



N,*N*-diethyl-*m*-toluamide

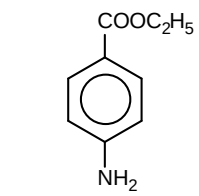
A simple amide derivative of benzoic acid, *N*,*N*-Diethyl-*meta*-toluamide, abbreviated DEET, is the most common active ingredient in insect repellents. It is intended to be applied to the skin or to clothing, and is primarily used to repel mosquitoes.



p-aminobenzoic acid (PABA)

3. 4-Aminobenzoic acid (also known as ***p**ara*-**a**mino**b**enzoic **a**cid or PABA) is a colorless, crystalline substance, slightly soluble in water compound. PABA can counteract the bacteriostatic action of sulfonamide drugs.

PABA is naturally occurring in food sources such as brewer's yeast, liver, molasses, mushrooms, spinach, whole grains substance. PABA is sometimes called vitamin Bx, but it is not a true vitamin. In humans, PABA is normally made by *E. coli* in the colon and therefore PABA from food is not normally essential to human health. PABA is an intermediate in bacterial synthesis of folate. Humans lack the ability to synthesize folate from PABA, that is also normally done by *E. coli*. The folic acid requirements of mammals must be met with preformed folic acid. PABA is sometimes marketed as an essential nutrient despite the lack of any recognized syndromes of PABA deficiency.

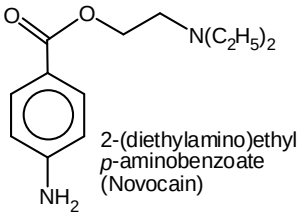


ethyl *p*-aminobenzoate (anesthesin, benzocaine)

4. Derivatives of *p*-aminobenzoic acid. Benzocaine is a local anesthetic commonly used as a topical pain reliever (surface anesthetic). It is the active ingredient in many over-the-counter anesthetic ointments (e.g. products for oral ulcers). It is also combined with antipyrine for ear pain relieve and removal of cerumen (earwax). The neutral compound is poorly soluble in water but soluble in oily phases. The hydrochloride salt is soluble in water. Such solutions are acidic (pH<7) due to hydrolysis and because of that are not used in medicine. The physiology of pain includes build-up

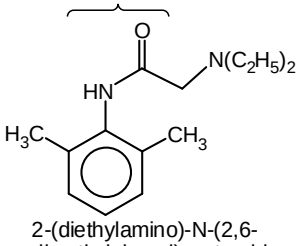
of potential from sodium ions in neurons. Esters of PABA work as a chemical barrier, stopping the sodium from being able to enter the nerve ending, thus relieving the pain.

Novocain® (trade name) or Procaine is a local anesthetic drug of the amino ester group. It is used primarily in dentistry and to reduce the pain of intramuscular injection of penicillin. Novocain stabilizes the neuronal membrane and prevents the initiation and transmission of nerve impulses, thereby effecting local anesthesia. The onset of action is very rapid (2 to 5 minutes after direct injections in gums) and the duration of action is relatively short (on average 1 to 1½ hours). The drug is readily absorbed following parenteral administration and is rapidly hydrolyzed by plasma cholinesterase to *p*-aminobenzoic acid and diethylaminoethanol. Novocain molecule may be viewed as consisting of three connected parts. A hydrophilic basic tertiary amino group is connected by a linker to lipophilic aromatic residue. The connector is an ester group that is essential for the action because it is this ester bond that is hydrolyzed during metabolic degradation and inactivation in the body. Variation of any of the three molecular portions modulate the activity and toxicity, and provide places for chemical modifications in order to obtain new drugs.

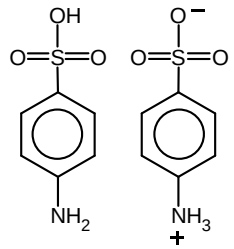


2-(diethylamino)ethyl *p*-aminobenzoate (Novocain)

Similar fragments are found in **Lidocaine**. Lidocaine or lignocaine is the first amino amide-type common local anesthetic, replacing Novocain, and antiarrhythmic drug. Lidocaine is used topically to relieve itching, burning and pain from skin inflammations. It is injected as a dental anesthetic, and in minor surgery. Formally, Lidocaine is not a derivative of *p*-aminobenzoic acid, but is an acylated aniline with residue from N,N-diethylaminoacetic acid.



2-(diethylamino)-N-(2,6-dimethylphenyl)acetamide (Lidocaine)

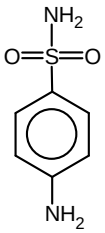


sulfanilic acid

5. Sulfanilic acid and its derivatives. Sulfanilic acid (4-aminobenzene sulfonic acid) is a colorless crystalline solid produced from sulfonation of aniline. It readily forms diazo compounds and is widely used to make dyes and sulpha drugs.

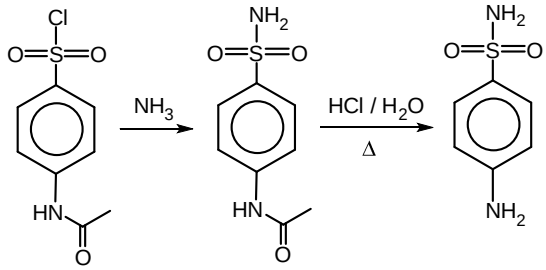
Sulphanilic acid contains a highly acidic group and a basic group, therefore exists as a **zwitterion (internal salt)** that is difference from PABA, and has an unusually high melting point.

The term sulfonamide is usually used as a generic name for many different derivatives of *p*-aminobenzenesulfonamide (sulfanilamide) with basic structure:

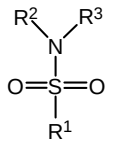


sulfanilamide

The basic structure, sulfanilamide (a trivial name), is synthesized from *p*-aminobenzenesulfonyl chloride and ammonia, requiring protection of the amino group with acetyl moiety to prevent NH_2 from attacking the sulfonyl chloride of another molecule. The protection is later removed by acid catalyzed hydrolysis.



In principal, a reaction of a sulfonyl chloride with an amine gives the corresponding **sulfonamides**, containing the functional group:



sulfonamide group

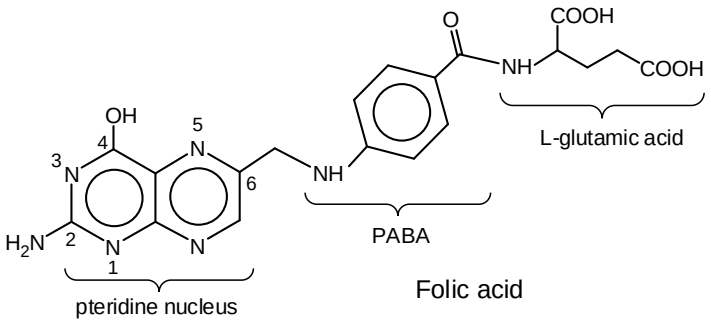
Many sulfonamides have important medicinal use as antibacterial agents and their biological activity has been studied in details.

Sulfanilamide is a molecule containing the sulfonamide functional group attached to an aniline. The term "sulfanilamides" is also used to describe a family of molecules containing these functional groups. Some examples include: Furosemide, a loop diuretic; Sulfadiazine, an antibiotic; Sulfamethoxazole, an antibiotic.

Sulfanilamides are chemically similar to PABA and their antibacterial activity is due to their ability to interfere with the conversion of PABA to folate and subsequent utilization by bacteria. Folic acid (also known as Vitamin B_9) and folate (the naturally occurring form) are forms of the water-soluble Vitamin B_9. It (folic acid and folate inclusive) is essential to numerous bodily functions ranging from nucleotide synthesis to the remethylation of homocysteine. It is especially important during periods of rapid cell division and growth. Folic acid is an important nutrient for women who may become pregnant. Both children and adults require folic acid to produce healthy red blood cells and prevent anemia. Leafy vegetables such as spinach, turnip

greens, lettuces, dried beans and peas, fortified cereal products, sunflower seeds and certain other fruits and vegetables are rich sources of folate. Liver and liver products also contain high amounts of folate, as does baker's yeast.

Folic acid's molecule includes fragments of pteridine, PABA, and glutamic acid. (Pteridine has fused rings of a pyrimidine and a pyrazine. Besides folic acid, pteridine is present in the pigments of butterfly wings.)



Folic acid

Sulfanilamides or other sulfa drugs that are similar and simulate PABA can fool the microbes into trying to use them instead of PABA, which causes the invaders to stop growing. Many sulfonamides' antibacterial action is due to competitive inhibition of enzyme involved in bacterial folate synthesis.

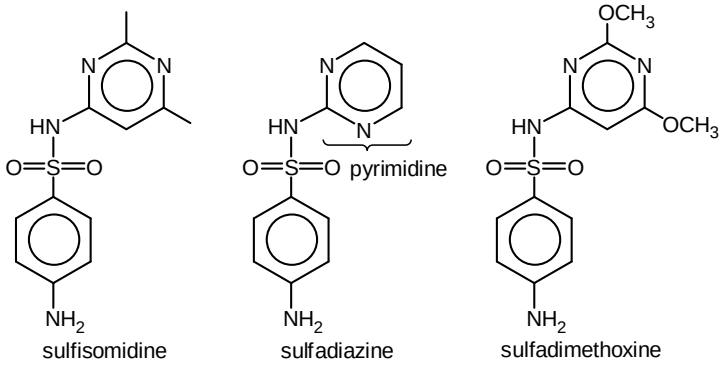
Prontosil (a prodrug releasing sulfonamide) is the first commercially available (Bayer, IG Farben) antibacterial antibiotic with a relatively broad effect against Gram-positive cocci but not against enterobacteria. This compound was the first medicine ever discovered that could effectively treat some bacterial infections inside the body. As a class of organic compounds, sulfonamide drugs were the first (before penicillin) antimicrobial drugs, and paved the way for the antibiotic revolution in medicine. For the discovery, Gerhard Domagk was awarded Nobel Prize in Physiology or Medicine1939 "for the discovery of the antibacterial effects of prontosil".

Sulfanilamide can not be used for synthesis of folate by bacteria. However, their enzymes do not distinguish between PABA and sulfanilamides causing inhibition of active folate production and the organism growth stops. The bacteria are not killed. The host body defense mechanisms can destroy the infection when the bacterial growth and reproduction is slower. Sulfanilamides do not interfere with human metabolism because we do not produce folate. It is obtained by the foodstuffs like spinach and leafy vegetables.

Many variations in the substituents on a sulfonamide framework can give valuable antibacterials with fine-tuned mode of action. Some representatives of sulfanilamides acting as antibiotics / dihydropteroate synthetase inhibitors (subdivided into classes by their mode of action) are:

Short-acting: Sulfisomidine (also known as sulphasomidine, sulfamethin and sulfaisodimidine), is a sulfonamide antibacterial.

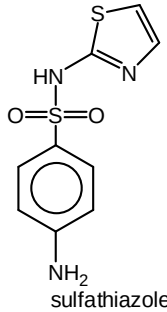
Sulfapyridine (with pyridine ring instead of pyrimidine) is not prescribed for treatment in humans any more. Winston Churchill has been successfully treated with it for bacterial pneumonia. It is a good antibacterial drug, but its water solubility is very pH dependant. Thus there is a risk of crystallization within the bladder or urethra, which could lead to pain or blockage.



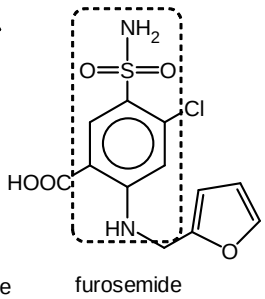
Intermediate-acting: Sulfadiazine.

It eliminates bacteria that cause infections by stopping the production of folic acid inside the bacterial cell, and is commonly used to treat urinary tract infections (UTIs).

Long-acting: Sulfadimethoxine



sulfathiazole



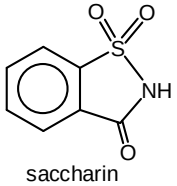
furosemide

Sulfathiazole is an old sulfa drug. It used to be a common oral and topical (on bruises) antimicrobial until less toxic alternatives were discovered.

Numerous sulfonamides and sulfanilamides posses other than antibacterial biological activity, e.g. they act as diuretics. These are compounds that increase the excretion of water.

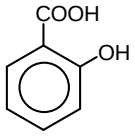
Furosemide is a loop (of Henle, in kidneys) diuretic used in the treatment of congestive heart failure and edema.

The molecular fragment mainly responsible for physiological activity is shown in dashed rectangle. Such fragment is called **pharmacophore**. A pharmacophore was first defined by Paul Ehrlich (scientist in the fields of hematology, immunology and chemotherapy) in 1909 as "a molecular framework that carries (*phoros*) the essential features responsible for a drug's (*=pharmacon's*) biological activity". This definition was updated to "a set of structural features in a molecule that is recognized at a receptor site and is responsible for the molecule's biological activity". The IUPAC definition of a pharmacophore is "an ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target and to trigger (or block) its biological response".

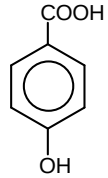


saccharin

A sulfonamide group can be found also in other compounds that are used in everyday life. Saccharin is an artificial sweetener (E954) containing sulfonamide. The substance has effectively no food energy (non-nutritive) but is much sweeter than sucrose. Nowadays other sweeteners are aspartame (E951) and sucralose (Splenda, E955).



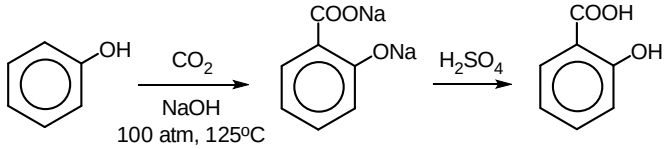
salicylic acid



p-hydroxybenzoic acid

6. Salicylic acid and its derivatives. Salicylic acid is *o*-hydroxybenzoic acid. It is stronger acid (pK_a=2.98) than benzoic acid (pK_a=4.20) and *p*-hydroxybenzoic acid (pK_a=4.50). The compound is soluble in water. Intramolecular hydrogen bonding, involving the phenolic OH is characteristic for the acid and some derivatives. The Greek physician Hippocrates wrote in the 5th century BC about a bitter powder extracted from white willow (*Salix alba*) bark that could ease aches and pains (analgesic) and reduce fevers (antipyretic). Salicylic acid possesses antiseptic properties, stops fermentation and putrification (rottening), therefore is used as food preservative.

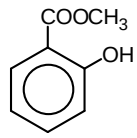
Industrial preparation of sodium salicylate is achieved by treating sodium phenolate (the sodium salt of phenol) with carbon dioxide.



carboxylation reaction

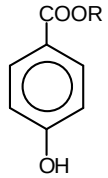
Because of high acidity salicylic acid causes digestive problems such as gastric irritation, bleeding, and is used today mainly for topical treatments. It is key ingredient in many skin-care products for the treatment of acne, psoriasis, warts. It works as a chemical exfoliant by causing the cells of the epidermis to shed more readily, preventing pores from clogging up, and allowing room for new cell growth.

Salicylic acid is the parent compound for two large groups of derivatives – esters of salicylic acid, obtained by substitution on the carboxylic group with alcohol residues, and salicylate esters of organic acids in which the COOH of salicylic acid remains intact but the phenolic OH group is substituted. For internal use, esters (on COOH) and acyl (on OH) derivatives have been tested and utilized even now. The most famous of them is Aspirin.



methyl salicylate

Methyl salicylate is found in oil of some evergreen plants. Though its source plants are not true mints, it is used as a mint in some kinds of chewing gum and candy. It also has the ability to clear plant or animal tissue samples of color, and as such is useful for microscopy and immunohistochemistry when excess pigments obscure structures or block light in the tissue being examined. It is also a potentially entertaining source of triboluminescence; when mixed with sugar and dried, it gains the tendency to build up electrical charge when ground. Direct esterification of salicylic acid with methanol in the presence of sulfuric acid is an equilibrium process and according to the Le Chatelier's principle requires large excess of methanol to proceed to completion, to the product.

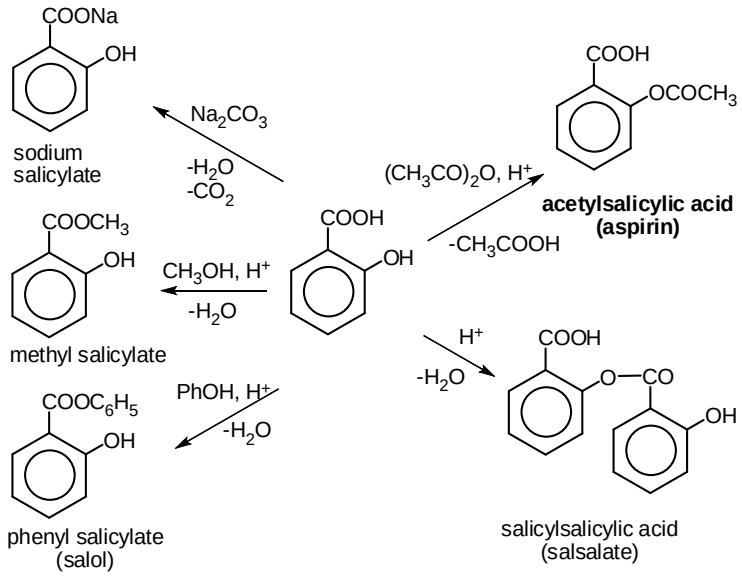


p-hydroxybenzoate (paraben)

$R=CH_3$	E218
$R=CH_2CH_3$	E214
$R=CH_2CH_2CH_3$	E216

The esters of *p*-hydroxybenzoic acid (called Parabens) are a group of chemicals widely used as preservatives in the cosmetic and pharmaceutical industries. These compounds, and their salts, are used primarily for their bacteriocidal and fungicidal properties. They can be found in shampoos, commercial moisturizers, shaving gels, topical/parenteral pharmaceuticals, spray tanning solution and toothpaste. They are also used as food additives.

The chemical reactions for preparation of salts, methyl and phenyl ester of salicylic acid, and for acylation of its OH group are combined in the following scheme:



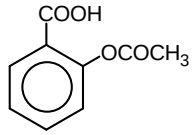
Neutralization with base is a reaction driven to completion.

Acid catalyzed esterification is an equilibrium reaction (Le Chatelier – Brown principle is applicable).

Phenyl salicylate (salol) has been used as an antiseptic that will not dissolve in the acidic gastric juice. The antibacterial activity is triggered after hydrolysis in the small intestine.

Salsalate is a salicylate type of non-steroidal anti-inflammatory drug (NSAID). It is used to reduce pain and inflammation in rheumatoid arthritis, osteoarthritis, and related rheumatic conditions.

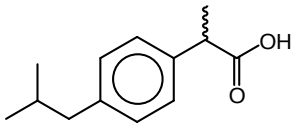
The phenolic OH group of salicylic acid reacts with acetic anhydride to give acetylsalicylic acid, better known as Aspirin.



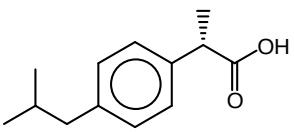
acetylsalicylic acid (aspirin)

Acetylsalicylic acid (Aspirin® - a trademark) is one of the most frequently used drugs in the treatment of mild to moderate pain, including that of migraines (analgesic action) and fever (antipyretic action). It is often combined with other (NSAID) and opioid analgesics in the treatment of moderate to severe pain.

[Additional information: In 1897, scientists at the drug and dye firm Bayer (Germany) began investigating acetylsalicylic acid as a less-irritating replacement for then common salicylate medicines. By 1899, Bayer had dubbed this drug Aspirin and was selling it around the world. Aspirin's popularity declined after the market releases of paracetamol (acetaminophen) in 1956 and ibuprofen in 1969. In 1971, British pharmacologist John R. Vane (Nobel Prize in Physiology or Medicine, 1982), showed that aspirin suppressed the production of prostaglandins and thromboxanes due to its irreversible inactivation of the cyclooxygenase (COX) enzyme. Later was established aspirin's efficacy as an anti-clotting agent that reduces the risk of clotting diseases.] Aspirin popularity revived considerably in the last decades, thanks to widespread use as a preventive treatment for heart attacks and strokes. Aspirin use has been shown to increase the risk of upper gastrointestinal (GI) bleeding. Therefore coated formulations are now offered and preferred.



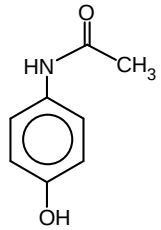
2-(4-isobutylphenyl)propanoic acid (ibuprofen), **racemic**



(S)-(+)-ibuprofen

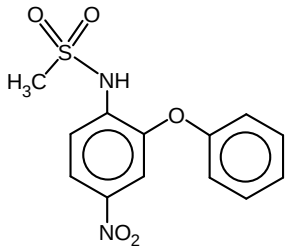
Other, modern medicines containing benzene moiety are ibuprofen and paracetamol.

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID). It is used for relief of symptoms of arthritis, fever, and as an analgesic, especially where there is an inflammatory component. Ibuprofen, like other 2-arylpropionate derivatives (including ketoprofen, flurbiprofen, naproxen, *etc*), contains a chiral carbon at the α-position to COOH. There are two possible enantiomers of ibuprofen, with the potential for different biological effects and metabolism for each enantiomer. Indeed it was found that (*S*)-(+)-ibuprofen is the active form both *in vitro* and *in vivo*. It was logical, then, that there was the potential for improving the selectivity and potency of ibuprofen formulations by marketing ibuprofen as a single-enantiomer product (as occurs with naproxen, another NSAID). However, an enzime, isomerase converts (R)- into (S)-enantiomer and most ibuprofen formulations currently marketed are racemic mixtures.



paracetamol acetaminophen

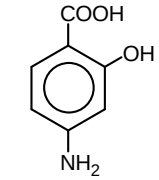
Paracetamol or **acetaminophen** is a widely used analgesic (pain reliever) and antipyretic (fever reducer). It is commonly used for the relief of fever, headaches, and other minor aches and pains, and is a major ingredient in numerous cold and flu remedies.



nimesulide

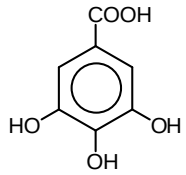
Nimesulide is non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. This compound contains ether linkage between two benzene rings – a phenolic ether. The substance was widely prescribed. Recent concerns about side effects caused warnings and withdrawal from the market.

The pharmacophore of salicylate drugs has been extensively modified on the COOH and OH in order to find more potent and less toxic drugs with similar analgesic, antipyretic and anti-inflammatory action. The substitution on the benzene ring has also been explored. An example of such substituted derivative is ***p*-aminosalicylic acid**.



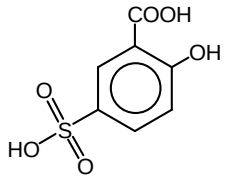
p-aminosalicylic acid

4-Aminosalicylic acid (**p**ara-**a**mino**s**alicylic acid, commonly known as **PAS**), is an antibiotic used to treat tuberculosis. The drug was introduced to clinical use in 1948. It was the second antibiotic found to be effective in the treatment of tuberculosis, after streptomycin. PAS is less potent than the current five first-line drugs (isoniazid, rifampicin, ethambutol, pyrazinamide, and streptomycin) for treating tuberculosis, but it is still useful in the treatment of multidrug-resistant tuberculosis.



3,4,5-trihydroxybenzoic acid
gallic acid

Gallic acid is representative example of a polyhydroxy aromatic acid. Gallic acid is constituent (as free or as part) of tannins which are found in tea leaves, coffee, walnuts, oak bark, and other plants. Propyl gallate is used in small quantities in foods as a preservative and antioxidant.



5-sulfosalicylic acid

Sulfosalicylic acid is used in clinical laboratory urine tests to determine urine protein content. The chemical's strong acidity causes the precipitation of dissolved proteins, which is measured from the degree of turbidity.