

49. Ibuprofen

CHEMICAL NAME = 2-(4-isobutylphenyl)propanoic acid

CAS NUMBER = 15687-27-1

MOLECULAR FORMULA = $C_{13}H_{18}O_2$

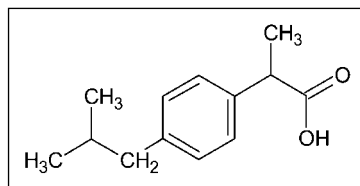
MOLAR MASS = 206.3 g/mol

COMPOSITION = C(75.7%) H(8.8%) O(15.5%)

MELTING POINT = 77°C

BOILING POINT = decomposes

DENSITY = 1.0 g/cm³ (calculated)



Ibuprofen is a white, crystalline anti-inflammatory drug used in numerous medications. It is the active ingredient marketed under various trade names including Advil, Motrin, and Nurofen. Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) used as a pain reliever (analgesic), fever reducer (antipyretic), and inflammation reducer. Inflammation is a general physiological response to tissue damage characterized by swelling, pain, and heat. Ibuprofen was developed while searching for an alternative pain reliever to aspirin in the 1950s. It and related compounds were synthesized in 1961 by Stewart Adams, John Nicholson, and Colin Burrows who were working for the Boots Pure Drug Company in Great Britain. Adams and Nicholson filed for a British patent on ibuprofen in 1962 and obtained the patent in 1964; subsequent patents were obtained in the United States. The patent of Adams and Nicholson was for the invention of phenylalkane derivatives of the form shown in Figure 49.1, where R₁ could be various alkyl groups, R₂ was hydrogen or methyl, and X was COOH or COOR, with R being alkyl or aminoalkyl groups. The first clinical trials for ibuprofen were started in 1966. Ibuprofen was introduced under the trade name Brufen in 1969 in Great Britain. It was introduced in the United States in 1974. Ibuprofen was initially offered by prescription, but it became available in over-the-counter medications in the 1980s.

Ibuprofen works by inhibiting the enzyme cyclooxygenase (COX), which in turn interferes with the synthesis of prostaglandins. COX exists as several coenzyme forms that are similar in structure: COX-1, COX-2, COX-3; ibuprofen is a nonselective inhibitor of both COX-1

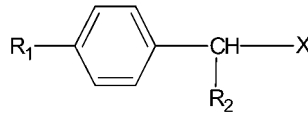


Figure 49.1 General structure of anti-inflammatory drugs.

and COX-2. COX-1 is continually produced in mammalian cells throughout the body in response to physiological stimuli. It is responsible for the production of prostaglandins, which get their name because it was originally believed they were synthesized in the prostate gland. In fact, prostaglandins are synthesized throughout the body and act like hormones by stimulating action in target cells. Prostaglandins, which are fatty acid compounds consisting of a 20-carbon chain including a 5 carbon ring, are involved in numerous physiological processes including renal function, blood clotting, and stomach mucus production. COX-2 is synthesized only in specific parts of the body (kidneys, brain, trachea) as needed and is therefore called an induced enzyme. COX-2 produces prostaglandins in response to tissue damage and inflammation. Inflammatory prostaglandins produce swelling, pain, and fever.

A common goal in the development of pain and inflammation medicines has been the creation of compounds that have the ability to treat inflammation, fever, and pain without disrupting other physiological functions. General pain relievers, such as aspirin and ibuprofen, inhibit both COX-1 and COX-2. A medication's specific action toward COX-1 versus COX-2 determines the potential for adverse side effects. Medications with greater specificity toward COX-1 will have greater potential for producing adverse side effects. By deactivating COX-1, nonselective pain relievers increase the chance of undesirable side effects, especially digestive problems such as stomach ulcers and gastrointestinal bleeding. COX-2 inhibitors, such as Vioxx and Celebrex, selectively deactivate COX-2 and do not affect COX-1 at prescribed dosages. COX-2 inhibitors are widely prescribed for arthritis and pain relief. In 2004, the Food and Drug Administration (FDA) announced that an increased risk of heart attack and stroke was associated with certain COX-2 inhibitors. This led to warning labels and voluntary removal of products from the market by drug producers; for example, Merck took Vioxx off the market in 2004. Although ibuprofen inhibits both COX-1 and COX-2, it has several times the specificity toward COX-2 compared to aspirin, producing fewer gastrointestinal side effects.

World production of ibuprofen is estimated to be 15,000 tons per year, which is approximately one-third the use of aspirin. Ibuprofen is commonly used for headaches (migraines), muscle pain, dental pain, cold, flu, fever, and menstrual cramps. Ibuprofen is most often sold as tablets, but it is also sold as liquid capsules, effervescent, chewable tablets, and liquid suspensions. Tablets commonly contain 200 mg of ibuprofen and a 1,200 mg per day limit taken over several dosages is recommended for adults. Child dosages are based on weight, but are commonly 10 mg or less per kilogram (2.2 pounds) of body weight. Ibuprofen is not recommended for pregnant women. Common side effects associated with ibuprofen are stomach pains, heartburn, constipation, headache, blurry vision, and ear-ringing. More serious side effects often associated with high prolonged doses are stomach ulcers, gastrointestinal bleeding, and renal malfunction. Increased risk of heart attack is sometimes mentioned when taking ibuprofen, but research is inconclusive as to whether ibuprofen increases the chance of a heart attack.