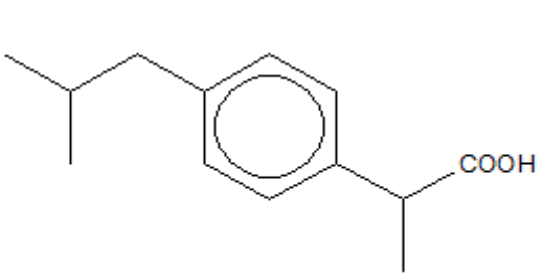
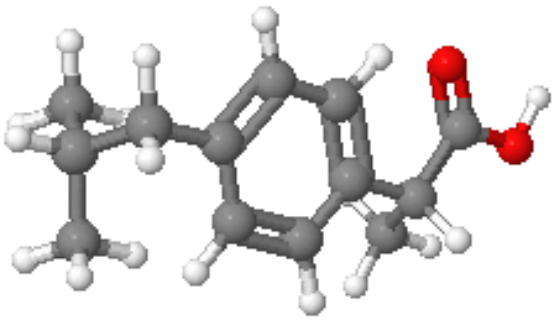
Drug Development
Ibuprofen

Introduction

Ibuprofen is a drug that possesses analgesic (**pain-relieving**) and antipyretic (**fever-reducing**) properties. It is particularly known for its use in **pain relief from arthritis**.

Ibuprofen is also an **anti-inflammatory** drug and it is classed as a non-steroidal anti-inflammatory drug(**NSAID**).





Principle

Like acetylsalicylic acid (aspirin), another NSAID, and acetaminophen, ibuprofen works by **inhibiting** the activity of a class of **enzymes** called **cyclooxygenase (COX)**,which **catalyses** the synthesis(conversion) of a compound called arachidonic acid into **prostaglandins**.

Prostaglandins are sometimes called **local hormones** because they act close to where they are produced rather than all over the body. They have a remarkably wide range of effects, both positive and negative, for example, Prostaglandins are protective against the development of stomach ulcers, but they can also **cause inflammation** (as well as the **pain response**).

There is more than one human COX enzymes of them—definitely two, and probably at least three. Ibuprofen and aspirin both inhibit COX-1 and COX-2, but they do it in different ways. Ibuprofen binds non-covalently to a COX enzyme and thus competes with the enzyme's natural substrate. (This is referred to as reversible inhibition.) On the other hand, aspirin forms a covalent bond to a serine residue in the enzyme, and this bond cannot be broken. (This is called irreversible inhibition.)

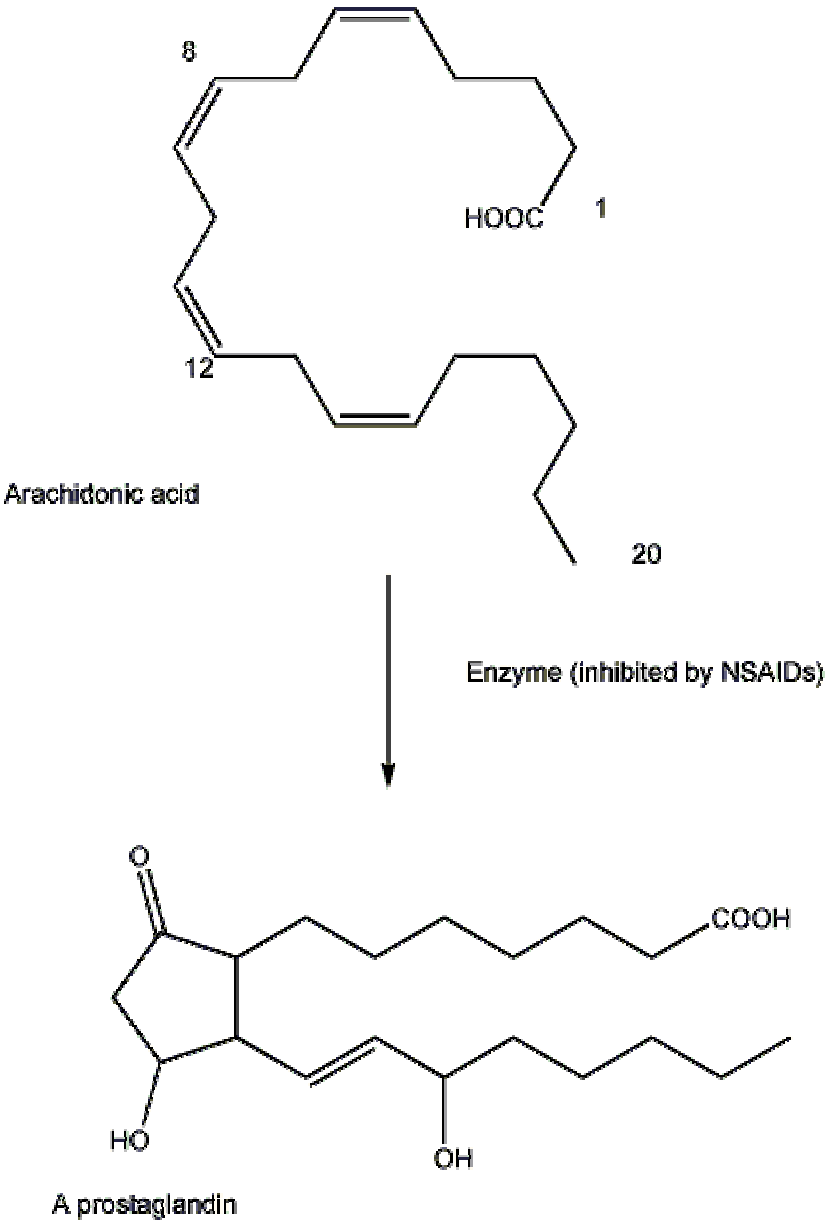


Figure 0: Prostaglandin synthesis

Lead compound discovery

Ibuprofen was developed and discovered as a drug by the Boots Company.

Boots' method of making ibuprofen described in their patent starts from the compound **2-methylpropylbenzene** (isobutylbenzene).

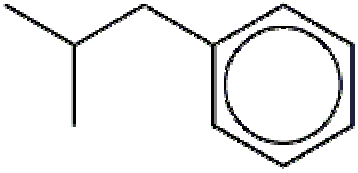


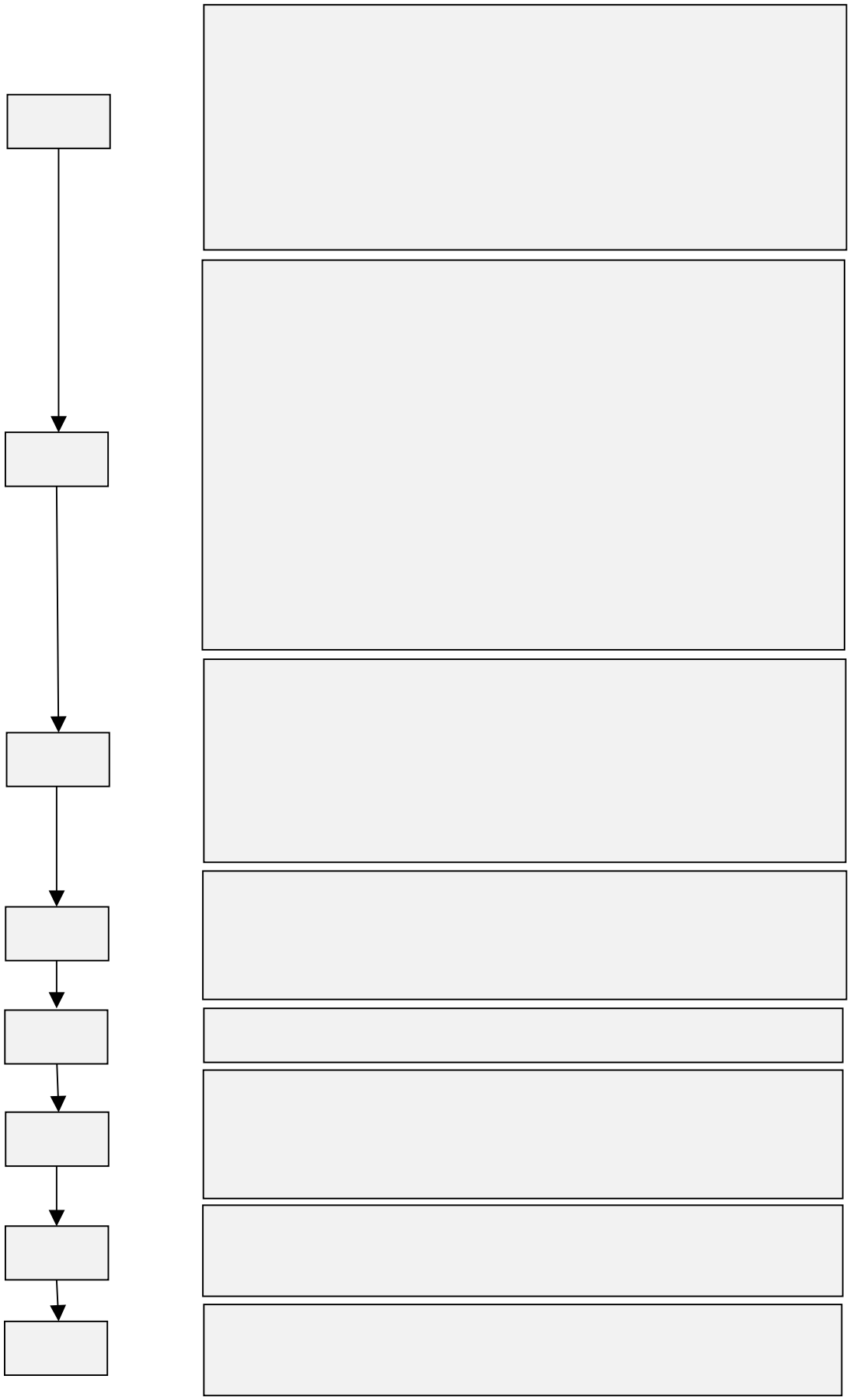
Figure 1: Structure of 2-methylpropylbenzene

2-methylpropylbenzene can be made from compounds separated from crude oil and has a similar carbon skeleton to that of ibuprofen.

Ibuprofen was developed and discovered as a drug by the research team at the Boots Company. The leaders of the team were Dr Stewart Adams and his colleagues John Nicholson and Colin Burrows during the 1960s.

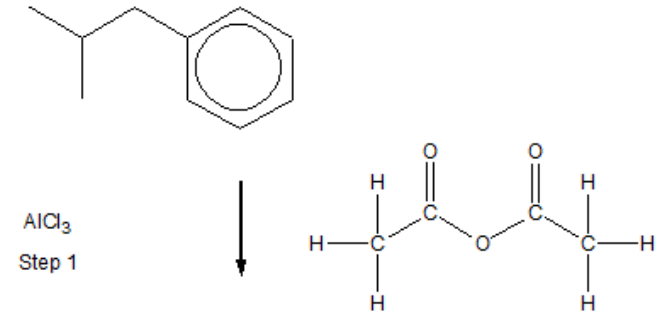
Figure 2: Stewart Adams, John Nicholson and Colin Burrows, the discoverers of ibuprofen
(Courtesy of the International Ibuprofen Foundation)

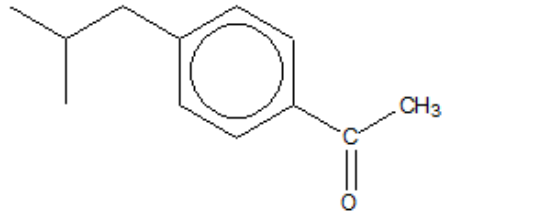
Timeline:

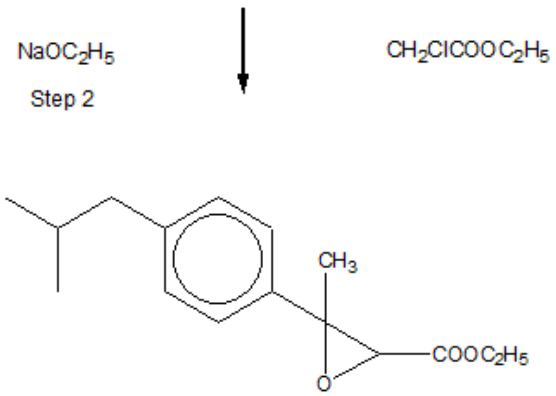


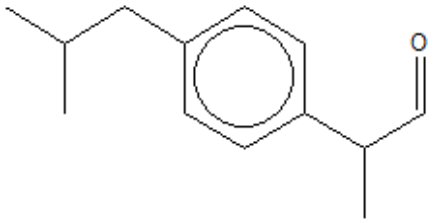
Molecular modification

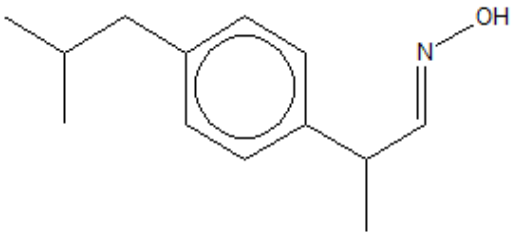
A) The **original** Boots synthesis of ibuprofen



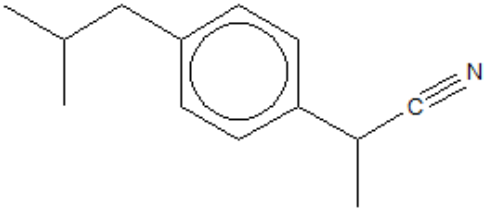




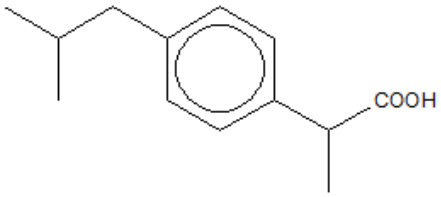




Step 5

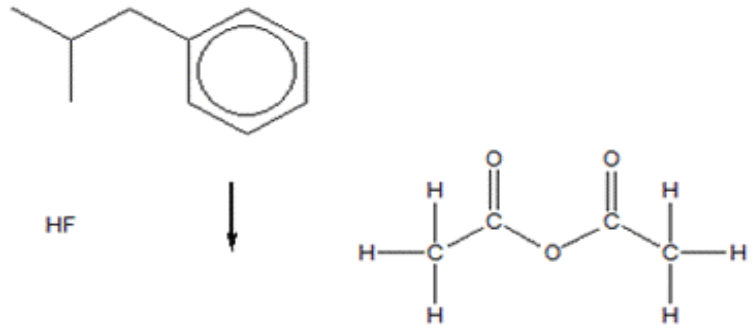


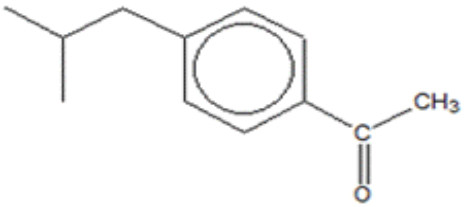
Step 6

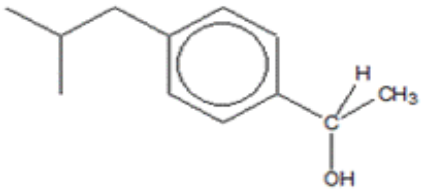


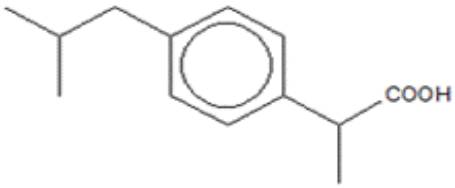
B) The 'green' synthesis of ibuprofen

The Boots' synthesis has been replaced by a **new, more efficient synthesis** shown in Figure 4. It starts with the same compound but has fewer steps - it has been described as the **'green' synthesis**.









Formulation Development

"Ibuprofen 200mg" means the dose of ibuprofen contained in a normal strength tablet is 200 mg (0.2 g). However, **it contains many other components** apart from the active ingredient ibuprofen. It should be noted that 200mg is a very small amount and would be difficult to handle and pick up. As a consequence, extra ingredients are included **to make it bulky in size so that it is easy to take up**. For the whole tablet containing 200mg Ibuprofen, it weighs about 1000 mg.

Ibuprofen tablets consist of a core and a coat. The coat contains sugar for taste and a pigment to give the tablet an acceptable colour.

Component	Function	Location
Ibuprofen	Active ingredient	Core
Croscarmellose sodium	Disintegrant	Core
Stearic acid	Lubricant	Core
Sodium laurylsulfate	Lubricant	Core
Sodium citrate	Buffering agent	Core
Colloidal anhydrous silica	Anticaking agent	Core
Carmellose sodium	Coating agent	Coat
Carnuba wax powder	Coating agent	Coat
Calcium sulfate dihydrate	Diluent	Coat
Acacia spray dried	Binding agent	Coat
Sucrose	Binding agent	Coat
Titanium dioxide	Pigment	Coat
Purified water	Diluent	Coat

Safety Test

(I) Pre-clinical testing

Experiment is carried out with cats and rats. It showed that ibuprofen, in doses which gave an anti-inflammatory effect, had **no effect on the cardiovascular system**. Also, it did **not affect the arterial pressure, frequency and strength of cardiac contractions**.

It also found that ibuprofen did **not adversely affect respiration** as the frequency and depth of the respiratory movements remained the same. Examinations of the EEG of cats and rabbits revealed **no departures from the normal whatsoever following administration of the drug**. Ibuprofen in concentration of 10^{-9} g ml^{-1} to 10^{-4} g ml^{-1}did not affect the tonus of the smooth muscle of the small intestine in guinea pig intestines or rat uterus. Moreover, it had **no effect on the spasmogenic effects of acetylcholine, serotonin and bradykinin.**

(II) Human trials

Ibuprofen has undergone extensive clinical trials. Most investigators have found that ibuprofen to **possess high therapeutic activity**, and it was stressed that it is better tolerated than acetylsalicylic acid, indomethacin and other NAID, even by patients with lesions of the gastrointestinal tract.

The high therapeutic activity of ibuprofen is **apparent in the treatment of ankylosing spondylitis and juvenile rheumatoid arthritis, lumbago, and nonspecific hyperpyrexia.** Clinical trials on patients with rheumatism, rheumatoid arthritis, osteoarthritis deformans, and systemic scleroderma showed that in most patients receiving ibuprofen in daily doses of 800-1200mg for adults and 200-600 mg for children, there was a **clear improvement in the general condition, reduction in joint pain, morning stiffness, swelling of the joints, and symptoms of carditis, and a reduction in the ESR** and other laboratory indices characteristic of the rheumatic process.

Approval for marketing

Ibuprofen was approved by the FDA in 1974. The pill has been through trials and clinical testing thoroughly. After excessive research the drug was approved for sale in the US and other states and its treatment considered effective. The sole use of this drug is to **relieve pains of bones and muscles** and is also used as a **painkiller for inflammation.**

It is distributed as coated tablets of 200 mg. the recommended initial dose is 600-1200 mg daily. **In acute conditions** and exacerbations of the process, it is desirable to **increase the daily dose to 1600 mg**. Indications for use are rheumatism, rheumatoid arthritis, osteoarthritis, and similar conditions. The drug should be used with **great care in patients suffering from bronchial asthma.**

By Chan Tsz Wa
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