

## The design of paracetamol

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**ABSTRACT:** Paracetamol is a common drug used to relieve pain and treat fever. It was firstly designed in 19th century and now has various methods, including original synthesis, green synthesis and direct synthesis, to be produced. However, it can also cause severe adverse effects, such as overdose, liver damage and skin reaction.

Paracetamol, also known as acetaminophen, is a medicine used to treat moderate pain and fever. It is also used for severe pain, such as cancer pain and pain after surgery, in combination with opioid pain medication.[1] Paracetamol is generally safe under the guidance of a doctor. The recommended maximum daily dose for an adult is three to four grams, while higher doses may lead to toxicity.[2] It does not have significant anti-inflammatory activity. But how it works is not entirely clear.[3]

**KEYWORDS:** paracetamol, phenacetin, pharmacophores, liver damage, overdose.

### The structure of paracetamol

The molecular formula of paracetamol is C<sub>8</sub>H<sub>9</sub>NO<sub>2</sub>, with a molar mass of 151.165 g/mol. [fig.1][fig.2] It contains an hydroxyl functional group and an amide functional group.

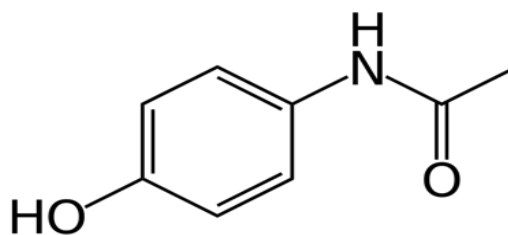


Figure 1

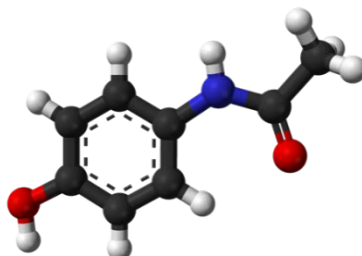


Figure 2

### The history of paracetamol

Paracetamol was first made in 1877 and then tried on humans by clinical pharmacologist in 1887. But its unacceptable toxic effects – the most alarming being cyanosis due to methemoglobinemia – prompted the search for less toxic aniline derivatives. Thus in 1893, phenacetin, another aniline derivative with slight tendency to produce methemoglobinemia, was then quickly discarded in favor of paracetamol. In 1948, scientists confirmed that paracetamol was the major metabolite of acetanilide in human blood, and established that it was just as efficacious an analgesic as its precursor. They also suggested that methemoglobinemia is produced in humans mainly by another metabolite, phenylhydroxylamine. This led to a "rediscovery" of paracetamol.[4]

Paracetamol was first marketed in the United States in 1950 under the name Triagesic, a combination of paracetamol, aspirin, and caffeine. After that, it has become a common household drug.

### The synthesis of paracetamol

The first one is original method for production[fig.3], which involves the nitration of phenol with sodium nitrate gives a mixture of two isomers, from which the wanted 4-nitrophenol (bp 279 °C) can easily be separated by steam distillation. In this electrophilic aromatic substitution reaction, phenol's oxygen is strongly activating, thus the reaction requires only mild conditions as compared to nitration of benzene itself. The nitro group is then reduced to an amine, giving 4-aminophenol. Finally, the amine is acetylated with acetic anhydride. Industrially direct hydrogenation is used, but in the laboratory scale sodium borohydride serves.[5]

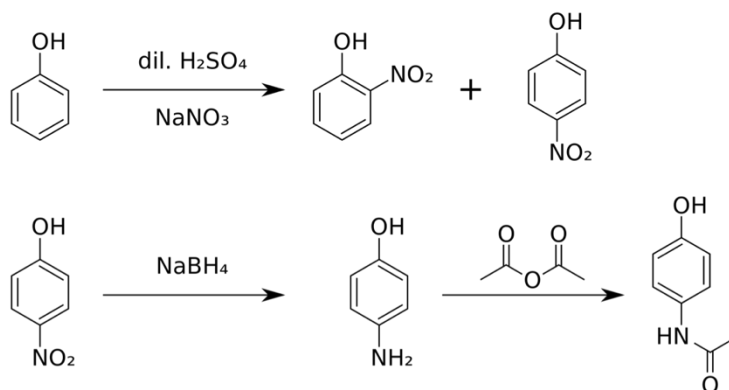


Figure 3

An alternative industrial synthesis— green synthesis[fig.4]— developed by Hoechst–Celanese involves direct acylation of phenol with acetic anhydride catalyzed by HF, conversion of the ketone to a ketoxime with hydroxylamine, followed by the acid-catalyzed Beckmann rearrangement to give the amide.

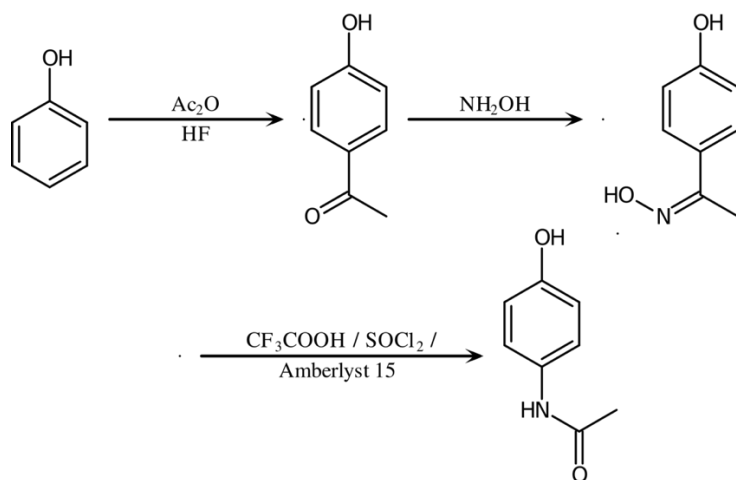


Figure 4

More recently (2014) a "one-pot" synthesis from hydroquinone has been described before the Royal Society of Chemistry.[6][7] The process called "direct synthesis" may be summarized as follows:

Hydroquinone, ammonium acetate, and acetic acid were mixed in an argon atmosphere and heated slowly to 230 °C. The mixture was stirred at this temperature

for 15 hours. After cooling the acetic acid was evaporated and the precipitate was filtered, washed with water and dried to give paracetamol as a white solid. The authors go on to claim an 88% yield and 99% purity.

### **The pharmacophores and how they were changed to make the drug better**

Despite its common use, the mechanism of action of paracetamol is not completely understood. Unlike NSAIDs such as aspirin, paracetamol does not appear to inhibit the function of any cyclooxygenase (COX) enzyme outside the central nervous system, and this appears to be the reason why it is not useful as an anti-inflammatory. It does appear to selectively inhibit COX activities in the brain, which may contribute to its ability to treat fever and pain. This activity does not appear to be direct inhibition by blocking an active site, but rather by reducing COX, which must be oxidized in order to function.

Paracetamol apparently might modulate the endogenous cannabinoid system in the brain through its metabolite, AM404, which appears to inhibit the reuptake of the endogenous cannabinoid/vanilloid anandamide by neurons, making it more available to reduce pain. AM404 also appears to be able to directly activate the TRPV1 (older name: vanilloid receptor), which also inhibits pain signals in the brain.[8]

### **The side effects of paracetamol**

Liver damage can be caused by acute overdoses of paracetamol, and that can be potentially lethal. In a 2011 Safety Warning, the FDA immediately required manufacturers to update labels of all prescription combination acetaminophen products to warn of the potential risk for severe liver injury and required that such combinations contain no more than 325 mg of acetaminophen.[9]

Paracetamol toxicity is the foremost cause of acute liver failure in the Western world. According to the FDA, in the United States, "56,000 emergency room visits, 26,000 hospitalizations, and 458 deaths per year [were] related to acetaminophen-associated overdoses during the 1990s. Within these estimates, unintentional acetaminophen overdose accounted for nearly 25% of the emergency department visits, 10% of the hospitalizations, and 25% of the deaths." [10]

The paracetamol could also cause rare and possibly fatal skin reactions such as Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Prescription-strength products would be required to carry a warning label about skin reactions, and the FDA urged manufacturers to do the same with over-the-counter products.[11]

Untreated paracetamol overdose results in a lengthy, painful illness. Signs and symptoms of paracetamol toxicity may initially be absent or non-specific symptoms. The first symptoms of overdose usually begin several hours after ingestion,

with nausea, vomiting, sweating, and pain as acute liver failure starts.[12] People who take overdoses of paracetamol do not fall asleep or lose consciousness, although most people who attempt suicide with paracetamol wrongly believe that they will be rendered unconscious by the drug.[13] The process of dying from an overdose takes from 3–5 days to 4–6 weeks. And treatment is aimed at removing the paracetamol from the body and replenishing glutathione.[14]

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