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Revisiting Aspirin, Paracetamol and Ibuprofen: Discovery of Synthetic Procedures and Mode of Actions



Santarupa Thakurta*

Department of Chemistry, Prabhu Jagatbandhu College, India

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*Corresponding author: Santarupa Thakurta, Department of Chemistry, Prabhu Jagatbandhu College, India

Abstract

In this article, we will outline the historical background of the popular medicines Aspirin, Paracetamol and Ibuprofen which have been widely used for decades for their desired therapeutic effects as Analgesics, Antipyretics and Anti-inflammatory agents. We will discuss the synthetic procedures and mechanism of actions of these well-known drugs, achieved through systematic research on medicinal chemistry as well as cellular biology and pharmacology.

Keywords: Aspirin; Paracetamol; Ibuprofen; Discovery; Metabolism

Introduction

By the end of the nineteenth century, scientific approach towards development of medicine made it possible to isolate drugs like Quinine, Ipecacuanha, and Aspirin etc. which were mainly derivatives of Natural Products. In modern times, screening of synthetic drug and lead chemical identification is an extremely complex process which requires active participation of disciplines like organic chemistry, biochemistry, microbiology, physiology, pharmacology. Even after discovery, it takes ages for the candidate drug to come for marketing. It has often been seen that establishment of proper mechanism of action of therapeutic effects involves collaborations of different research groups, from different countries, even from different time periods. In this article, we will outline the developmental process of the popular medicines Aspirin, Paracetamol and Ibuprofen which have been widely used for decades for their desired therapeutic effects as Analgesics, Antipyretics and Anti-inflammatory agents. The terms Analgesics and Analgetic drugs are often used interchangeably to describe a diverse group of pain medications. Antipyretics are the drugs that lower body temperature increased by infections or other diseases but have no effect on normal body temperature. Anti-inflammatory agents are the drugs used to diminish or reduce inflammation and pain associated with it. Here we will highlight the discovery of the laboratory synthetic procedures and mechanism of actions of these well-known drugs.

Aspirin

Willow bark extract was recognised as folk medicine from the mid-eighteenth century for treatment of fever and pain. Salicylic acid derived from willow bark is one of the oldest analgesics. However, its use can cause gastric irritation and bleeding due to the free phenolic group. This is overcome by masking the phenol as an ester. The compound acetylsalicylic acid known as Aspirin was tested and introduced into medicine by Bayer in Germany in the late 1890s. Heinrich Dreser, Arthur Eichengrün and Felix Hoffmann are recognised as pioneers in the development of acetylsalicylic acid as the drug Aspirin. Bayer's brand name, Aspirin was named by taking a from acetyl and spirin, comes from an old name for salicylic or spiric acid, derived from its natural source of spirea plants. Synthetically, Salicylic acid is converted to its prodrug Aspirin by acetylation of the phenolic hydroxy group. In human body, Aspirin is mainly converted to salicylic acid by esterases after absorption from the GI tract. This reduces the degree of stomach irritation because lesser amount of salicylic acid encounters the gut wall lining. The drug became popular worldwide and it was sold over the counter in the form of tablets since 1915. It is a common remedy for the relief of headache, muscular pain, rheumatic states, gout, and toothache [1].

Chemical name: Acetylsalicylic acid

Common names: ASPRO, DISPRIN, CARDIPRIN

To prepare aspirin, salicylic acid is reacted with an excess of acetic anhydride. A small amount of a strong acid is used as

a catalyst which speeds up the reaction (Figure 1). The product will appear as a solid mass when crystallization is complete, and crystals are collected through vacuum filtration.

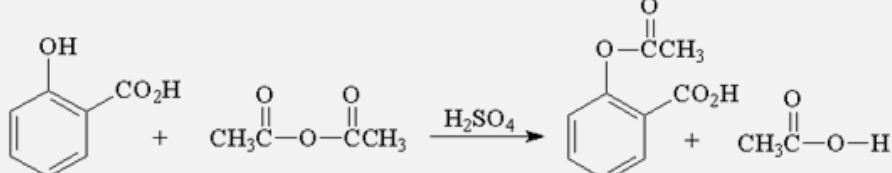


Figure 1: Scheme of synthesis of Aspirin.

Investigations were continued to understand the basic mechanism of Aspirin's action while clinical trials and other studies in 1960s established that it reduces the risk of heart attack. In 1971, John R. Vane from the Wellcome Research Laboratories, UK discovered the mechanism by which Aspirin exerts its anti-inflammatory, analgesic and antipyretic effects [2]. He proved that Aspirin and other non-steroid anti-inflammatory drugs (NSAIDs) inhibit the activity of the enzyme now called cyclooxygenase (COX) which leads to the production of Prostaglandins (PGs), responsible for sensations of pain and processes of fever and inflammation. Aspirin acts by acetylating the hydroxyl of a serine

residue in the active site of the COX enzyme. This makes Aspirin different from other NSAIDs (such as Diclofenac and Ibuprofen), which are reversible inhibitors. Moreover, Cyclooxygenase is required for synthesis of Thromboxane, responsible for the aggregation of platelets that form blood clots. So, Aspirin can also function as an efficient anti-clotting agent by irreversibly blocking the formation of Thromboxane in platelets. This entire process is depicted in Figure 2. For discoveries concerning Prostaglandin, the Nobel Prize in medicine in 1982 was awarded jointly to Sune K. Bergström, Bengt I. Samuelsson and John R. Vane.

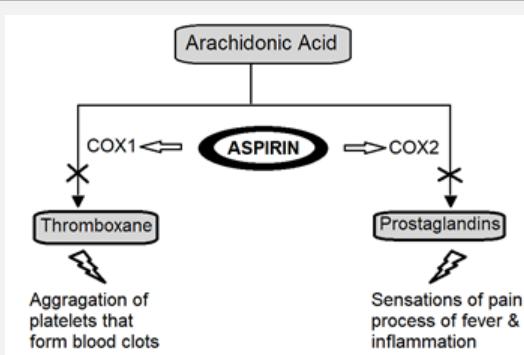


Figure 2: Scheme of action of Aspirin.

Paracetamol

Paracetamol is a common household drug for pain reliever and fever reducer [3]. This aniline derivative is popularly known as Paracetamol (from para-acetyl-amino-phenol) in Europe and most of the rest of the world and as Acetaminophen (from N-acetyl-para-aminophenol) in the United States and Japan. The compound was first prepared in 1877 by Harmon Northrop Morse at Johns Hopkins University, but clinically tested on humans by von Mering during 1887. From a historical perspective, Acetaminophen/Paracetamol and the related drugs such as Acetanilide (Antifebrin:

1886), Phenacetin (1887) were introduced into the market about the same time as Aspirin and the other salicylates. The sale of Aspirin was overshadowed by Phenacetin which established Bayer as a leading pharmaceutical company that time. About half a century later, it was rediscovered that Paracetamol is the active metabolite of both Phenacetin and Acetanilide [4]. After this breakthrough, Paracetamol was successfully marketed in 1953 by Sterling-Winthrop Co. as Panadol. This medicine still continues to be the most widely used analgesic antipyretics with few side-effects and little interaction with other pharmaceutical agents.

The drug inhibits COX activities in the central nervous system, but it lacks an anti-inflammatory effect because it cannot inhibit COX in the peripheral tissues. So, unlike Aspirin and salicylates, it does not cause gastrointestinal problems or prolonged bleeding time. This family of drug is on the World Health Organization's List of Essential Medicines, the safest and most effective medicines needed in a health system. Doses of Paracetamol greater than the recommended ones can cause severe liver damage [5].

Common names: ANACIN-3, CALPOL, CROCINE, PANADOL,

TYLENOL

For production of Paracetamol, phenol is used as the starting material which is reacted with sodium nitrate giving a mixture of two isomers of which the desired nitration product, 4-nitrophenol (BP: 279°C) can easily be separated by steam distillation. The nitro group is then reduced to amine, giving 4-aminophenol. Industrially direct hydrogenation is used, but in the laboratory scale sodium borohydride serves. Finally, the amine is acetylated with acetic anhydride. The synthesis reaction is shown in Figure 3.

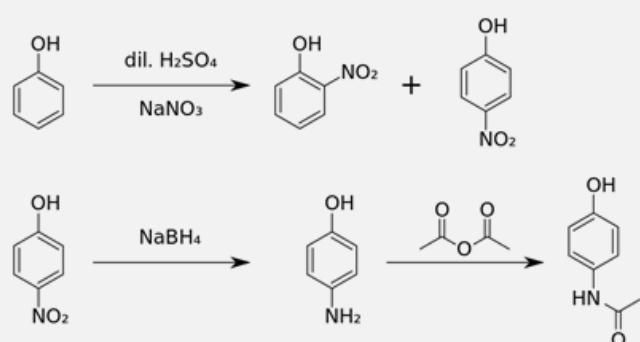


Figure 3: Scheme of synthesis of Paracetamol.

Ibuprofen

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) belonging to the family of synthetic 2-arylpropionic acids (Profens) that is used for treating pain, fever and inflammation. It is mainly effective for the pain and swelling associated with arthritis. It is a reversible, non-selective COX inhibitor, lowering the level of Prostaglandins via blocking the metabolism of Arachidonic acid

in the body. Ibuprofen is administered as a racemic mixture. The human body can convert the inactive (R) form into the active (S) form, so eventually 100% of the Ibuprofen taken becomes active.

Chemical name: $[(\pm)\text{-}2\text{-}(4\text{-isobutylphenyl})]\text{ propionic acid}$

Common names : BRUFEN, FENLONG, NOVAPRIN, EMFLAM, ADVIL, MOTRIN

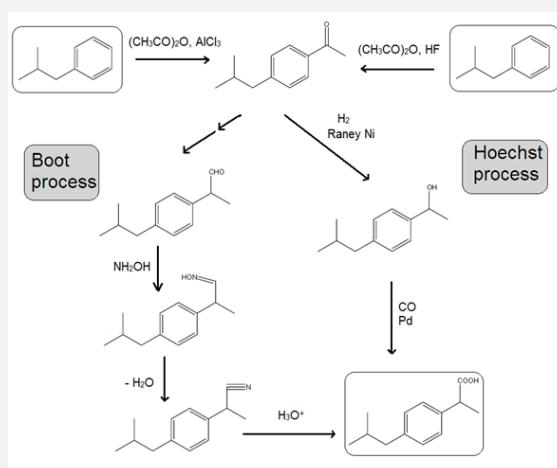


Figure 4: Scheme of synthesis of Ibuprofen.

The two most popular ways to obtain ibuprofen are the Boot process and the Hoechst process. The Boot process is an older commercial process developed by the Boot Pure Drug Company

and patented in 1960s [6]. This synthesis consists of six steps and resulted in unwanted by-products as shown in Figure 4. The Boots-Hoechst-Celanese (BHC) synthesis serves as a model that has

genuinely contributed to green chemistry [7]. In 1992, the BHC Company developed a new, sustainable synthesis that reduced the number of synthetic steps to half (total three steps) of that in the original Boots Company method (Figure 4). It is noteworthy that the synthesis began with the same first step, e.g. acylation of isobutylbenzene, but utilized anhydrous hydrogen fluoride as both a catalyst and solvent. The reduced amount of unwanted waste due to the generation of only one molecule of water as the byproduct is another achievement of the BHC method. Ibuprofen is the first pharmaceutical compound that was recognized by the U.S. Environmental Protection Agency Presidential Green Chemistry Challenge Awards in 1997.

Conclusion

During the past century, Aspirin and Paracetamol have occupied a central role in the treatment of fever and pain. Non-steroidal anti-inflammatory drugs (NSAIDs) have proved to be highly efficient for getting instant relief from pain and inflammation and Ibuprofen remains the first choice for this. With evolving research on biological activity, traditional role of Aspirin has been re-defined leading to the appropriate use of this agent in clinical practice. The green synthesis of Ibuprofen has emerged resulting improved and economical yield. We can conclude that the field of medicinal chemistry based on the studies on cellular biology and

pharmacology has covered a long journey to understand the mode of operation and metabolism of these synthetic drugs in the body.

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