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# EXPLORING IBUPROFEN: KEY ASPECTS OF PAIN RELIEF - A REVIEW OF ESTABLISHED SYNTHETIC METHODS

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**ABSTRACT:**
Drug synthesis poses significant challenges for pharmaceutical chemists, who often seek multiple synthesis routes for the same drug candidate to minimize by-products and maximize yield. Low yield percentages in the synthetic process can lead to substantial losses in the industry. Ibuprofen, a widely used non-steroidal anti-inflammatory drug (NSAID), functions through non-selective inhibition of cyclooxygenase (COX) enzymes. Various synthetic routes for ibuprofen have been identified, with some being patented. These routes can be categorized as either conventional or green synthetic routes. The green synthesis of ibuprofen is particularly promising due to its higher yield and lower energy consumption compared to conventional methods. Notably, photochemical synthesis and BHC company's synthesis have significantly optimized yield percentage and atom efficiency. This review explores the various identified routes for ibuprofen synthesis, encompassing both conventional and green synthetic methods.

**Keyword:** Synthetic routes, Ibuprofen, Conventional synthesis, Green synthesis, NSAIDs

## INTRODUCTION

Synthetic chemistry plays a critical and pivotal role in the pharmaceutical industry [1]. It encompasses the development of innovative synthesis routes for active pharmaceutical ingredients and the synthesis of excipients for formulations, highlighting its broad impact. In modern society, synthetic chemistry is considered essential, driven by scientists' continuous exploration to discover new methods for synthesizing complex molecules [2].

Ibuprofen, a widely used non-steroidal anti-inflammatory drug (NSAID), is synthesized through multiple established routes [3]. Chemically, ibuprofen is a derivative of propionic acid [4] with the IUPAC name (RS)-2-(4-(2-methylpropyl)phenyl)propanoic acid [5]. It falls under the category of substituted phenyl alkanoic acids [6] (Figure 01). Ibuprofen is utilized as a racemic mixture [7].

 

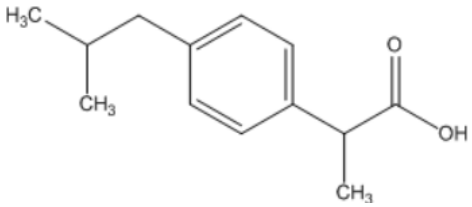

Figure 01: Structure of Ibuprofen

The primary pharmacological mechanism of Ibuprofen as an anti-inflammatory drug involves inhibiting the Cyclooxygenase (COX) pathway. It exerts reversible inhibition on two isoenzymes of the Cyclooxygenase enzyme, namely COX-1 and COX-2 [8]. The S-isomer of Ibuprofen exhibits anti-inflammatory effects, while the R-isomer is converted to the S-isomer in vivo [5] (Figure 02).

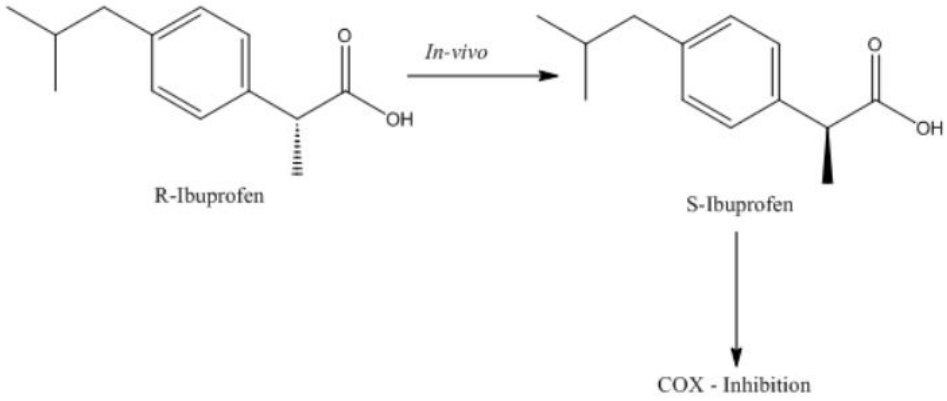

Figure 02: In-vivo conversion of R-Ibuprofen to S-Ibuprofen

**Physical and Chemical Properties**

Ibuprofen, widely used as an active pharmaceutical ingredient (API) in NSAIDs, is identified by CAS registration number 15687-27-1. It has a molecular weight of 206.29 g/mol and the molecular formula C13H18O2. Ibuprofen appears as a colorless to white crystalline solid powder with a characteristic odor. Its melting point ranges from 75 to 77.5 ℃, and it boils at 157℃. Ibuprofen is sparingly soluble in water, approximately 21 mg/L at 25°C, but exhibits higher solubility in organic solvents such as ethanol and methanol. It has a density of about 1.009 g/cc and a vapor pressure of 4.74×10-5 mm Hg at 25°C. The log P or n-octanol-water partition coefficient value of Ibuprofen is 3.97 [9].

**Mechanism of Action**

Prostaglandins and leukotrienes are derivatives of 20-carbon chain polyunsaturated fatty acids, released from the phospholipid bilayer of cell membranes [10]. Prostaglandins are biological derivatives of prostanoic acid (Figure 03), although they are not naturally occurring in the body.

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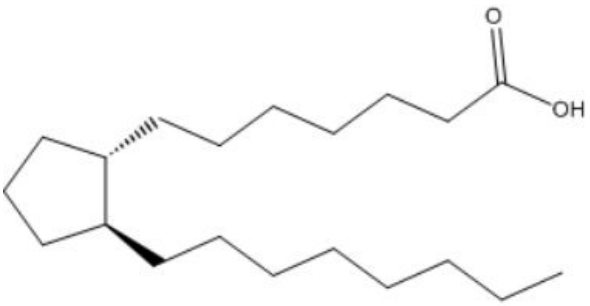


Figure 3: Prostanoic acid

Dependence on the ring structure and substituents, Prostaglandins and Thromboxanes have been designated names A to I. These Prostaglandins are synthesized from arachidonic acid [5]. The Cyclooxygenase enzyme produces eicosanoids with ring structure (PG and TX), while Lipoxygenase enzyme produces open chain compounds (LT) [11].

Prostaglandins and thromboxanes are categorized into types A through I based on their ring structure and substituents. They are synthesized from arachidonic acid [5]. The enzyme cyclooxygenase (COX) synthesizes eicosanoids with ring structures (PG and TX), while lipoxygenase synthesizes open-chain compounds (LT).

The primary action of ibuprofen is due to its role in inhibiting the COX (cyclooxygenase) enzyme. The two isoenzymes of COX are COX-1 and COX-2 enzymes [10]. This, in turn, prevents the synthesis of endoperoxides and short-lived prostaglandins such as PGE2 and PGF2 (Figure 04).

Ibuprofen structurally contains a free carboxyl group. This allows it to form ionic interactions with the positively charged arginine residue present at the active site of COX (Arg120 in COX1 and Arg106 in COX2).

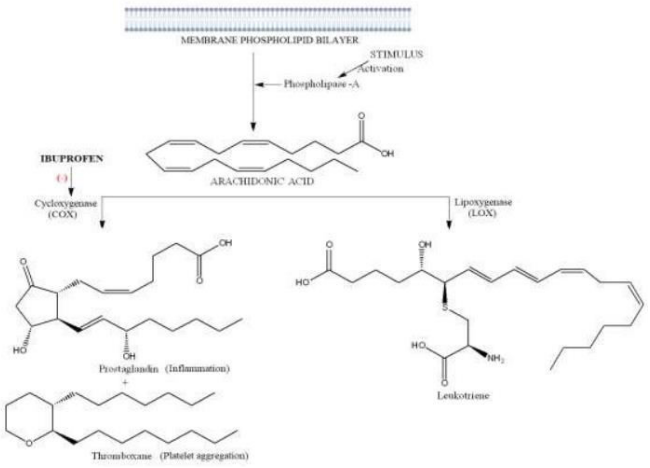


Figure 04: Chemical aspect of Mechanism of action of Ibuprofen

 

**Pharmacological Effects of Ibuprofen**

The main pharmacological actions of Ibuprofen include anti-inflammation and analgesia. Numerous clinical trials have investigated Ibuprofen. Compared to aspirin, Ibuprofen demonstrates fewer side effects in the treatment of rheumatoid arthritis. Clinical studies have shown that the anti-inflammatory effects of aspirin and Ibuprofen in the treatment of rheumatoid arthritis do not significantly differ. Ibuprofen significantly affects platelet aggregation and bleeding time by inhibiting platelet aggregation, thereby prolonging bleeding time.

When co-administered with aspirin, Ibuprofen reduces aspirin's cardioprotective effect by binding to the COX-1 isoenzyme of platelets and interfering with aspirin's inhibition of TXA2 synthesis [5]. Clinical efficacy in treating osteoarthritis is similar to aspirin but with a better effectiveness-to-toxicity ratio

Ibuprofen has also been found effective in relieving pain in gout patients when administered at a dose of 2400 mg for 3 days. It is also effective in providing analgesia for postpartum pain, dental extraction pain, and dysmenorrhea. However, its efficacy in treating severe pain has not been firmly established (Figure 05).

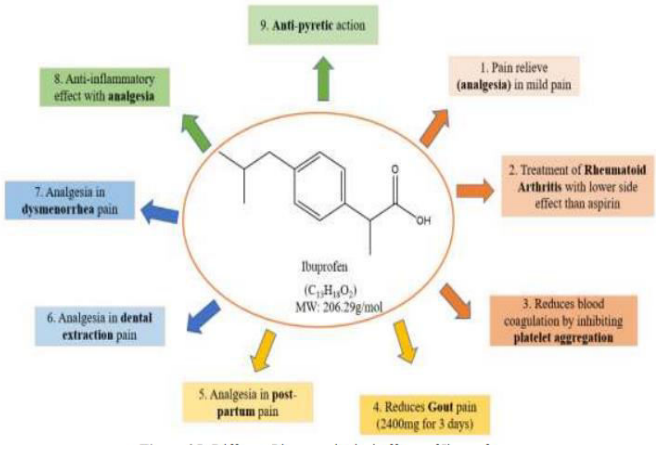


Figure 05: Different Pharmacological effects of Ibuprofen

**DISCUSSION**

Conventional methods, characterized by their traditional approach, typically involve longer steps and linear routes, resulting in higher production of by-products, hazardous wastes, and environmental pollutants. Additionally, conventional methods often have lower atom economy compared to Green Chemistry.

| Route | % yield | Route | % yield | Route | % yield |
|---|---|---|---|---|---|
| Route 1 | 50-60% [29] | Route 6 | 80% [29] | Route 11 | 94%[39] |
| Route 2 | ND | Route 7 | ND | Route 12 | >80% [29] |
| Route 3 | 40% [31] | Route 8 | ND | Route 13 | ND |
| Route 4 | 42% [32] | Route 9 | ND | Route 14 | ND |
| Route 5 | ND | Route 10 | >80% [29] | Route 15 | >70% [47] |

Table 01: Brief comparison between percentage yield found by various routes of synthesis

**Route Comparisons for Ibuprofen Synthesis**

Route 1, the most renowned laboratory synthesis method for Ibuprofen, demonstrates a yield of 50–60% (Table 01) [29].

The Dow process, or Route 4, shows an Ibuprofen yield of approximately 42% compared to the baseline Isobutyl benzene, which is considered relatively low for industrial manufacturing

Route 6 involves the synthesis of Ibuprofen from aryl alkyl ketone, achieving a yield of 80%, which is comparable to Route 10 using organometallic compounds, also yielding >80% [29].

Route 11, involving the rearrangement of a polyvalent iodide derivative, boasts a high yield of about 94%.

## CONCLUSION

Continuous efforts are underway to develop new synthetic routes for all drugs. The primary goal is to design alternative routes that are simpler and less toxic. Ibuprofen, in particular, offers multiple synthesis routes, including both conventional and green synthetic methods. Among these, green synthesis routes have shown promise by producing fewer by-products. Techniques such as photochemical or microwave synthesis have demonstrated higher yields, and green synthetic routes generally exhibit better atom economy.

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