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Ibuprofen: A Cornerstone of Pain Relief - A Review of Established Synthetic Approaches

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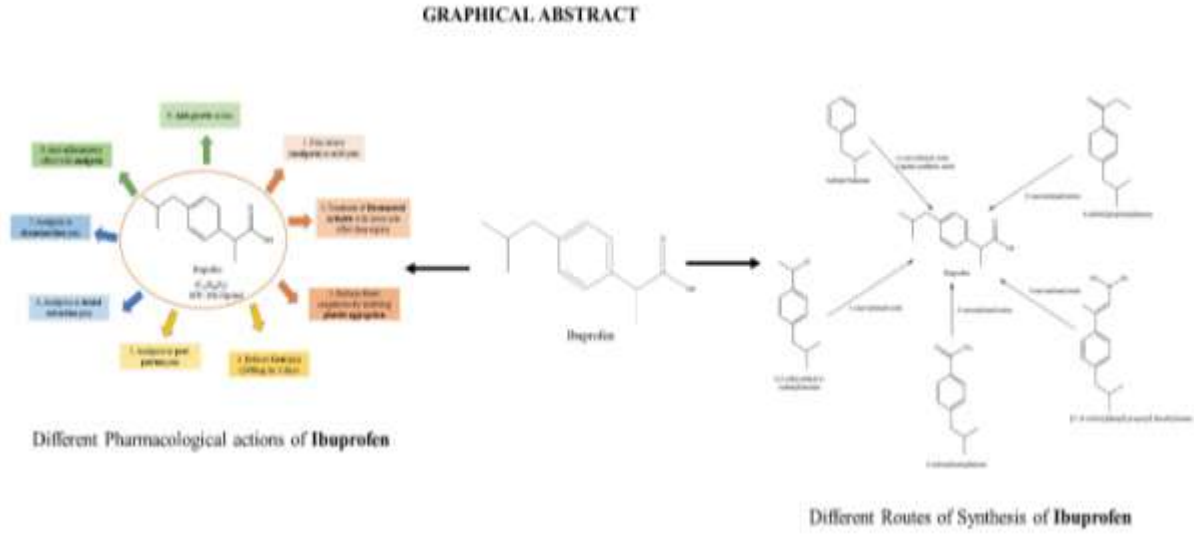
Highlights:

- This article compiles the different established routes of synthesis of Ibuprofen
- The comparative evaluation of different routes of synthesis has also been illustrated
- The advantages of Green Synthetic routes of Ibuprofen has been mentioned
- The atom economy of the Green Synthetic Routes has been discussed

ABSTRACT: Drug synthesis is the most vital challengesfaced bya Pharmaceutical Chemist. Scientists often focus on identifying different routes for synthesizing the same drug candidate. The main aim is to reduce the number of by-products and obtain maximum yield. Industries often face huge loss if the yield percentage of the followed synthetic route is less. Ibuprofen is a widely used Non-Steroidal anti-inflammatory drug (NSAIDs). It acts by non-selective inhibition of COX or Cyclooxygenase enzymes. Various synthetic routes of Ibuprofen have been identified and some of them have been patented. The different identified routes can be grouped as conventional routes or green synthetic routes. Green Synthesis of Ibuprofen is a promising route of synthesis due to its higher yield and lesser energy usage than conventional synthesis. The photochemical synthesis and BHC company synthesis have optimized the yield percentage and atom efficiency to a large extent. This review deals with various routes of synthesis of Ibuprofen that have been identified, including conventional synthesis as well as Green Synthesis.

Graphical Abstract:



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

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I. INTRODUCTION

Synthetic chemistry have instrumental and pivotal role in Pharmaceutical Industries [1]. Ranging from developing innovative routes of synthesis of Active Pharmaceutical ingredient to excipient synthesis of formulations, synthesis has wide role [1]. Thus, synthetic chemistry is termed to be the prerequisite of modern society[2]. The thirst and curiosity of scientist to find new ways to synthesize a molecule, has led to development of multiple route of synthesis for any complex molecule [2].

Ibuprofen is one of the widely used NSAIDs, which have multiple developed routes of synthesis [3]. Ibuprofen is a derivative of propionic acid [4]. IUPAC name of Ibuprofen is (RS)-2-(4-(2-methylpropyl)phenyl)propanoic acid [5]. It belongs to the substituted phenyl alkanoic acids [6](Figure 01). It is used as a racemic mixture [5].

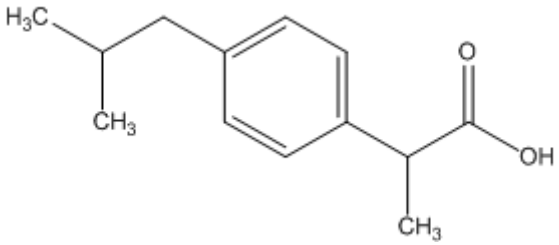

Figure 01: Structure of Ibuprofen

The main Pharmacological mechanism of Ibuprofen to act as an anti-inflammatory drug is by inhibiting Cyclooxygenase (COX) pathway [7]. It causes reversible inhibition of two isoenzymes of Cyclooxygenase enzyme –COX-1 and COX-2 [7]. The S-isomer contains anti-inflammatory effect while R-isomer is converted to S-isomer in-vivo [5] (Figure 02).

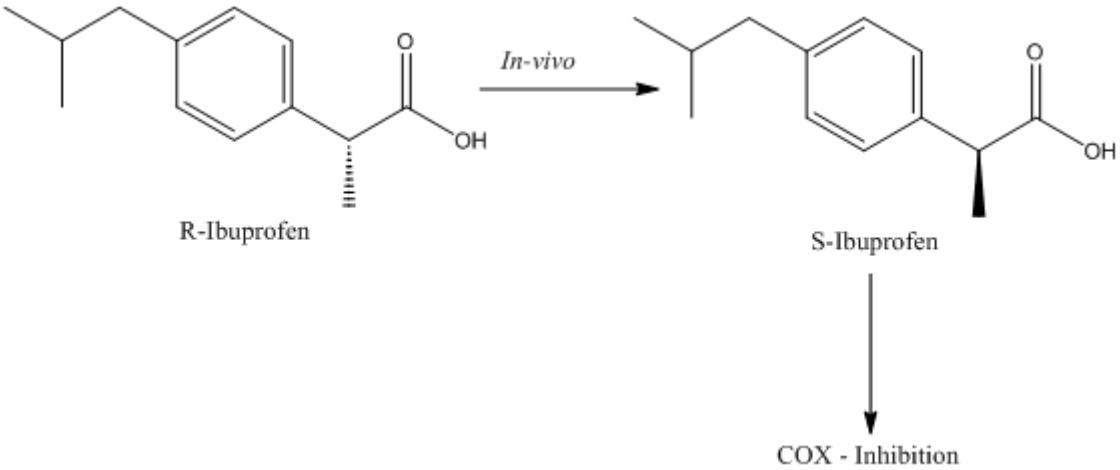

Figure 02: In-vivo conversion of R-Ibuprofen to S-Ibuprofen

Physical and Chemical Properties

Ibuprofen which is widely used as API for NSAIDs, has CAS registration number 15687-27-1 [8]. It has molecular weight 206.29g/mol and molecular formula $C_{13}H_{18}O_2$. It appears to be colourless to white crystalline solid powder with a characteristic odour. The melting point of Ibuprofen was found to be at 75-77.5 ºC and shows its boiling point at 157ºC. It is sparingly soluble 21mg/L (at 25 °C) in water, but has higher solubility in organic solvent like ethanol and methanol. It has density about 1.009g/cc. The vapour pressure has a value of 4.74×10^{-5} mm Hg at 25 °C. The log P or the n-octanol – water partition coefficient value of Ibuprofen was found to be 3.97 [9].

Mechanism of Action

Prostaglandins and Leukotrienes are derivatives of 20-Carbon chain polyunsaturated

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fatty acids. They are released from phospholipid bilayer of cell membrane [10]. Prostaglandins are biological derivatives of prostanoic acid (Figure 03), though they are not biologically found in our body [10].

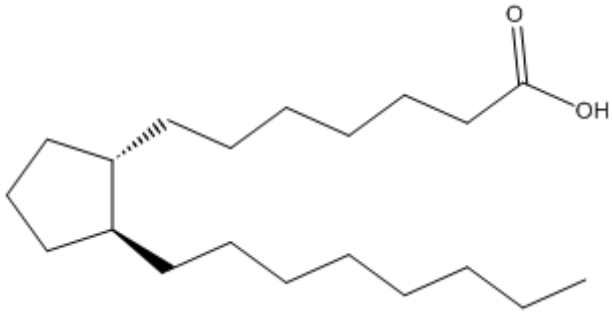

Figure 3: Prostanoic acid

Depending on the ring structure and substituents, Prostaglandins and Thromboxanes has been designated names A to I [8]. These Prostaglandins are synthesized from arachidonic acid [5].

The Cyclooxygenase enzyme produces eicosanoids with ring structure (PG and TX), while Lipoxygenase enzyme produce open chain compound (LT) [11].

The primary action of ibuprofen is due to its role in inhibition of COX (Cyclooxygenase) enzyme. The two isoenzymes of COX are COX-1 and COX-2 enzymes [10]. This in turn prevents the synthesis of endoperoxidases and short lived prostaglandins – PGE_2 and PGF_2 [12] (Figure 04). Ibuprofen structurally has free carboxyl group. This causes it to make ionic interaction with the arginine residue, which is positively charged, present at COX- active site (Arg120 in COX1 and Arg106 in COX2) [5].

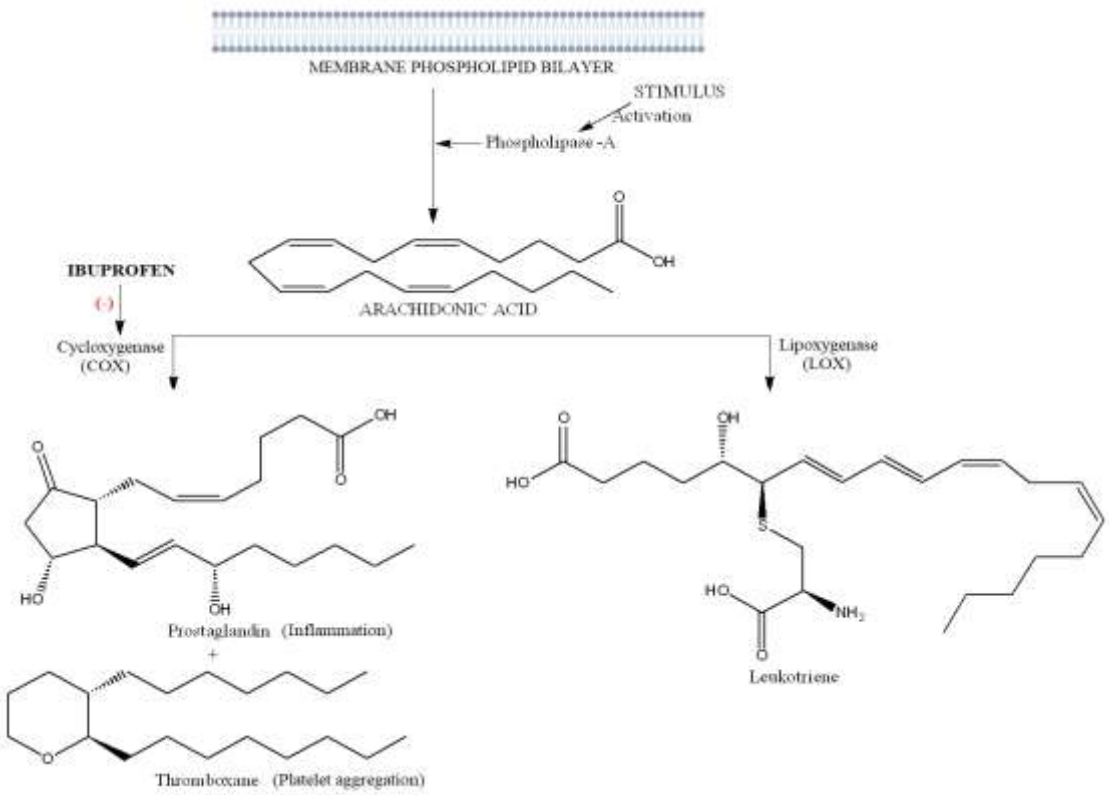

Figure 04: Chemical aspect of Mechanism of action of Ibuprofen

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Pharmacological Effects of Ibuprofen

The main Pharmacological actions of Ibuprofen includes anti-inflammation and causing analgesia. Multiple clinical trials of Ibuprofen has been done [13]. Compared to aspirin, Ibuprofen has lower side effects, when treated in Rheumatoid Arthritis [5,14]. From the clinical studies, it was evident that anti-inflammatory effect of aspirin and ibuprofen in treatment of Rheumatoid arthritis had no significant effects [15]. Ibuprofen has a well marked effect on aggregation of platelets and on bleeding time [16]. Ibuprofen inhibits aggregation of platelet, which causes increased bleeding time [16]. Ibuprofen when co-administered with aspirin reduces cardioprotective effect of aspirin by binding to COX-1 isoenzyme of platelet and interfere with aspirin's activity of inhibition of TXA2 synthesis in platelet [5]. Clinical efficiency in treatment of osteoarthritis was found similar to aspirin, but with better effectiveness to toxicity ratio [17].

Ibuprofen has also shown to be effective in pain-relieve of gout, by treating the patient with 2400mg for 3 days [18]. It is also effective to cause analgesia in post partum pain, dental extraction pain and dysmennorhea[19, 20, 21]. Its effectiveness in treatment of severe pain has not been established (Figure 05).

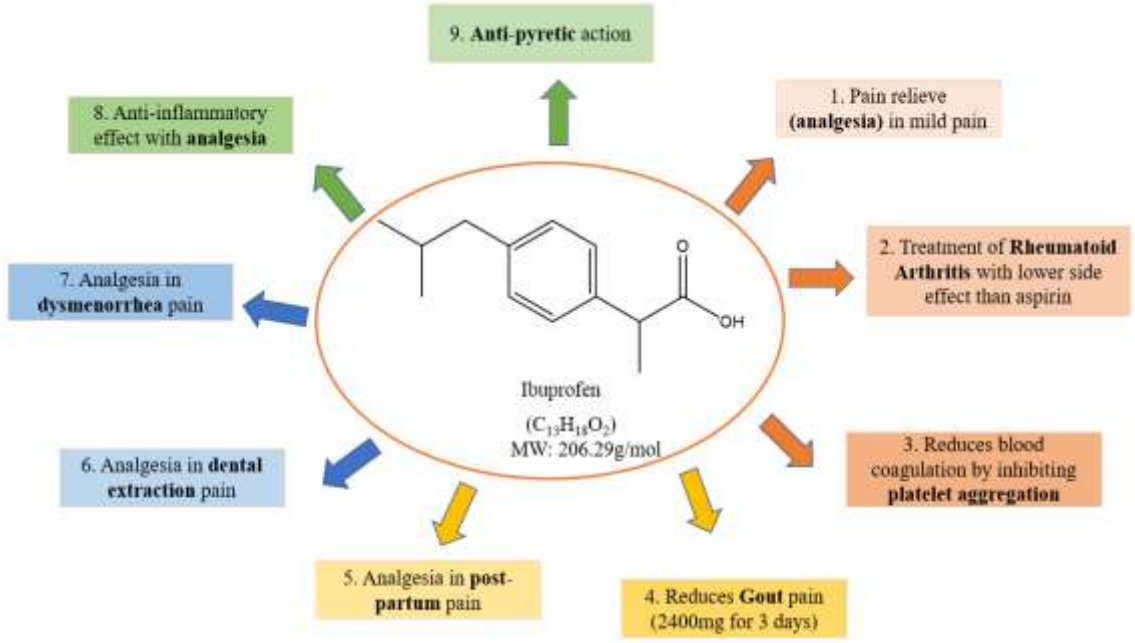

Figure 05: Different Pharmacological effects of Ibuprofen

SYNTHETIC ROUTES OF IBUPROFEN

In laboratory scale, there are multiple synthetic routes for Ibuprofen as API. The different routes of synthesis for any drug molecule can be classified into two broad heads – conventional methods and green method. Conventional synthesis can be defined as those methods which adopts traditional routes of synthesis with multiple steps, linear route, multiple by-product formation, hazardous waste and environmental waste formations[22]. These processes seems to be less economical than Green Chemistry process, which have lesser number of steps, by-products and wastes[23]. Moreover, Green synthesis process lead to much lesser environmental pollution and has greater atom economy[24].

CONVENTIONAL METHODS OF SYNTHESIS

Conventional methods of synthesis, involves molecular reactions with higher number of steps, which results in production of more number of by products and higher waste generation[25]. This results in environmental pollution. Synthesis by conventional route, due to production multiple toxic by-product increases risk of health hazards. These methods are also quite less economical. So, with time different green synthesis procedures are employed [26].

There are some very simple approaches or synthetic routes for synthesis of Ibuprofen as API.

International Journal of Pharmaceutical Research and Applications
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In both laboratory scale and industrial scale, these methods are implemented.

Route 1 – By Friedel Craft Acylation

Friedel Craft acylation is a reaction which involves introduction of a acyl moiety to the ring by help of acyl chloride and aluminium chloride as a catalyst [27]. Typically, FC acylation is considered as an example of intermediate catalyst theory. For synthesis of ibuprofen, the starting material used is isobutylbenzene (1). This isobutylbenzene is acetylated using acetyl chloride to produce an intermediate (2), which on reaction with sodium cyanide produces nitrile (3). This nitrile is acid hydrolysed to yield ibuprofen [28] (Figure 06)

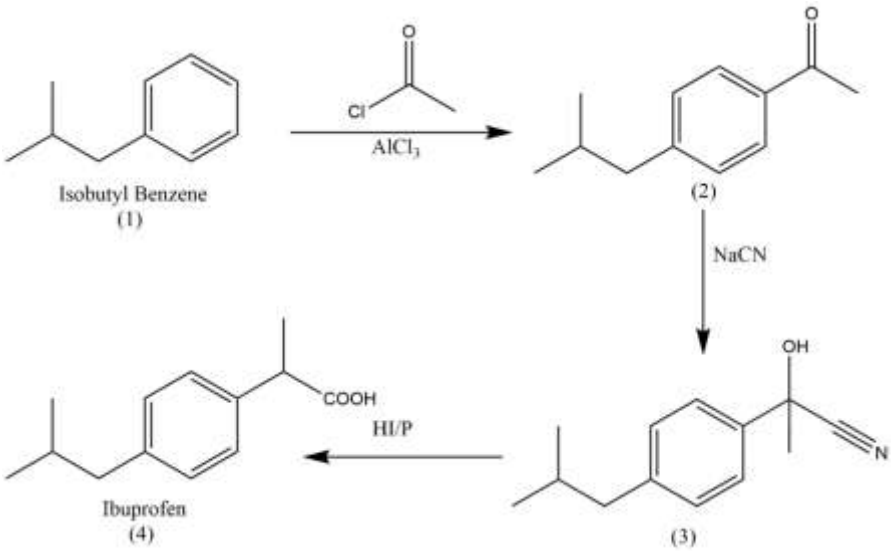

Figure06: Reaction Scheme of synthesis of Ibuprofen by Route 1

Route 2 – Synthesis from 2-(4-isobutylphenyl)-propionitrile

This is a linear synthesis route of two steps[29]. Being two step synthesis, it can be assumed, that the yield percentage of the product will be quite higher than an elongated chain reaction [30]. In first step, 1-(1-chloroethyl)-4-isobutylbenzene (5) is treated with sodium cyanide to replace the chloride group with -CN moiety. This forms 2-(4-isobutylphenyl)-propionitrile (6). Hydrolysis of (6) with Sodium hydroxide and ethanol forms Ibuprofen (7) in the last step of synthesis [29] (Figure 07)

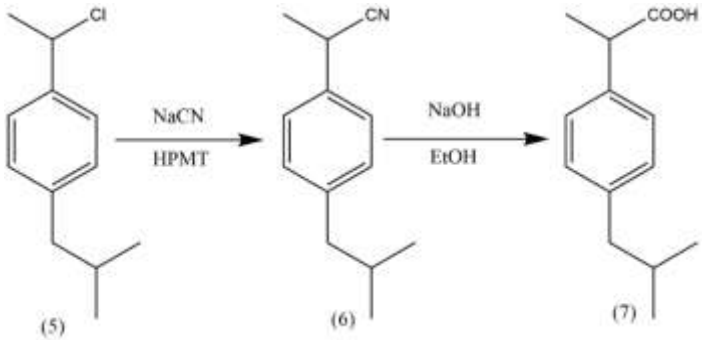

Figure 07: Synthesis of Ibuprofen by Route 2

Route 3 – By Dow's Process

This is a named process of synthesis of Ibuprofen. It is a multi-steped linear synthesis which uses isobutyl benzene (8) as its starting material. It is often used as a strategy of synthesizing Ibuprofen in industries. Isobutylbenzene is chlorinated by HCl, carbonic acid and methanol to 2-(4-isobutylphenyl)-methylchloride (9). Reaction of (9) with sodium cyanide (NaCN) and Methyl chloride (CH_3Cl)

International Journal of Pharmaceutical Research and Applications
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successively followed by hydrolysis with Sodium hydroxide forms Sodium carboxylate derivative of Ibuprofen (10). Further treatment of it with HCl forms Ibuprofen (11) [31](Figure 08).

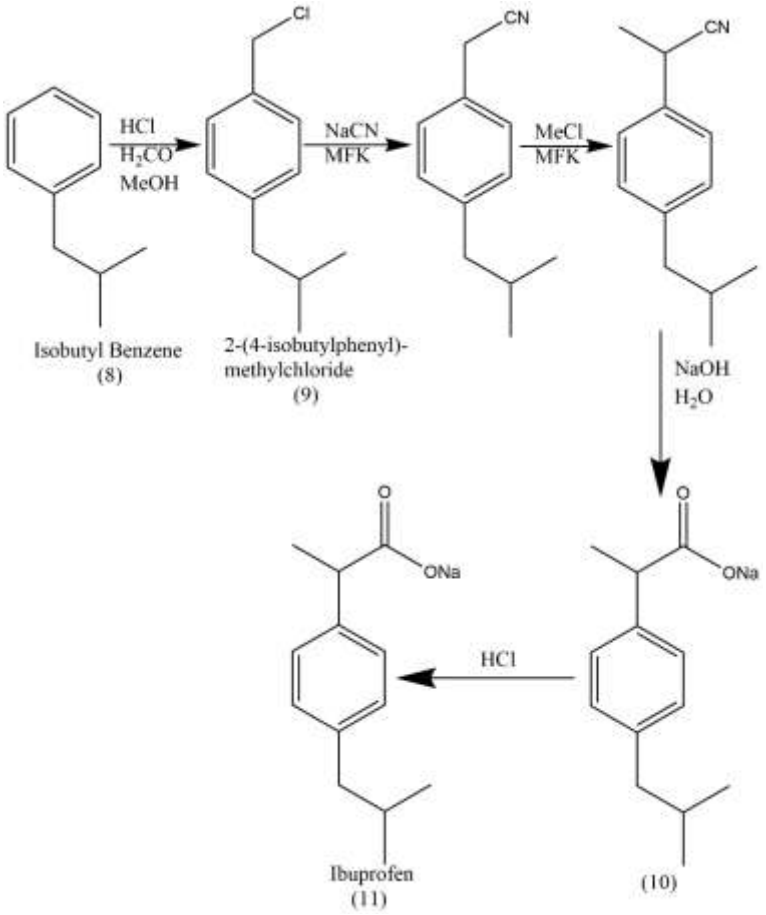

Figure 08: Synthesis of Ibuprofen by Route 3

The first step of the synthesis is chlorination step. This is generally done on isobutyl benzene, which is a substituted benzene. Reacting substituted benzene at 20 to 75°C (preferably 40 to 65°C) with chloromethyl ester in presence of solvent using acid/ acidic metal catalyst yields chlorinated derivative. This entire method is patented [31].

Route 4 – Synthesis from alkyl aryl glycidate

Reaction of 4-isopropylacetophenone (12) with methylchloroacetate forms glycidate (13). With further reactions with tribluoroboron and Methanol and further hydrolysis with Sodium Hydroxide forms Ibuprofen (14) [32]. One of the major limitation of this process of Ibuprofen synthesis is use of unique and not readily available reagents (Figure 09).

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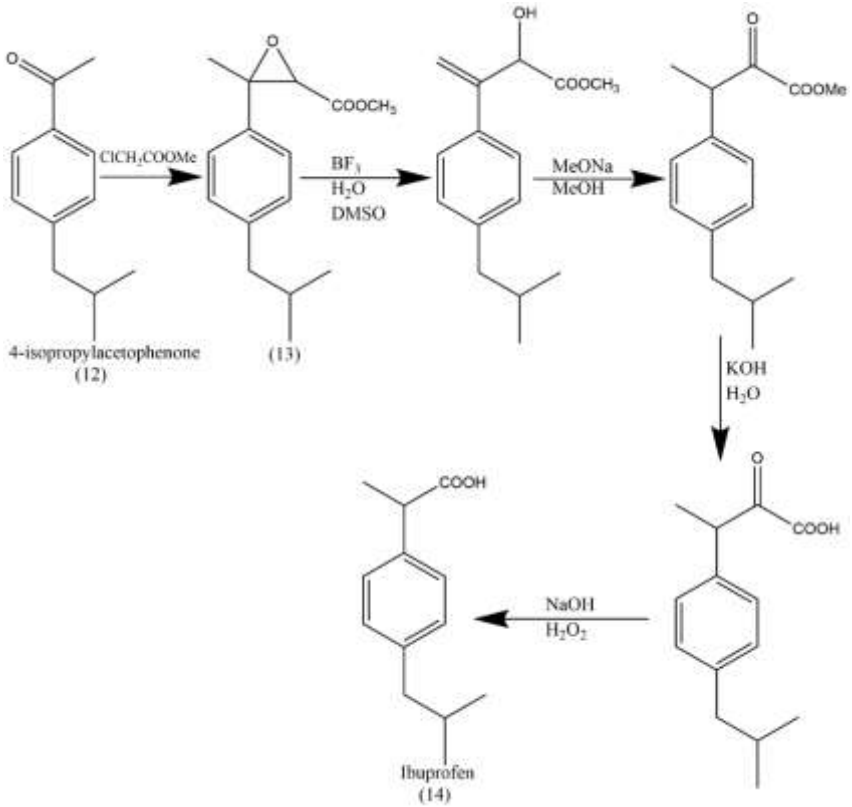

Figure 09: Synthesis of Ibuprofen using Route 4

Route 5 – From Cyanohydrin

The starting material for synthesis is 4-isobutylacetophenone (15). Addition of hydrogen cyanide to 4-isobutylacetophenone, and the hydrolysis of the cyanohydrin formed (16) and the hydrogenolysis of the hydroxyl group can be obtained with ibuprofen (17) [29] (Figure 10)

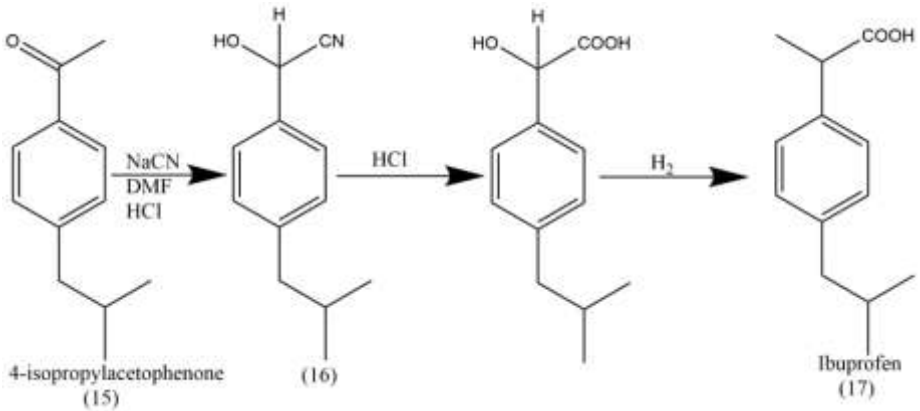

Fig 10: Synthesis of Ibuprofen from Route 5

Route 6 – From aryl alkyl ketone

Reaction of 4-isobutylacetophenone (18) with aniline and sodium cyanide forms an intermediate (19).This intermediate, followed by successive hydrolytic treatment of sodium hydroxide and Hydrochloric acid produces ibuprofen (20). [29, 33] (Figure 11)

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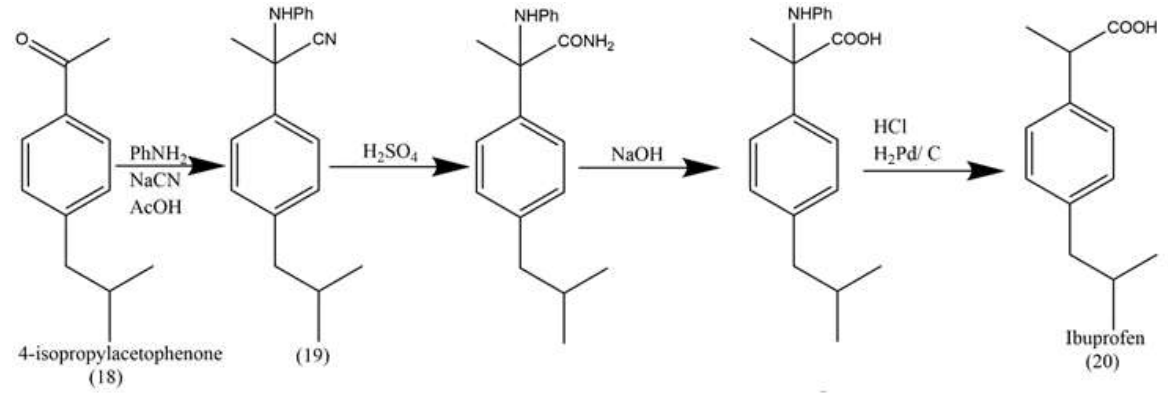

Fig 11: Synthesis of Ibuprofen from Route 6

Route 7 – From enamine

The enamine is converted to ibuprofen by this route of synthesis. When enamine, [2- (4-isobutylphenyl) propenyl] dimethylamine (21) is hydrolysed with hydrochloric acid, the corresponding aldehyde is formed (22). This aldehyde converted to ibuprofen (23) by oxidation with silver nitrate[29] (Figure 12)

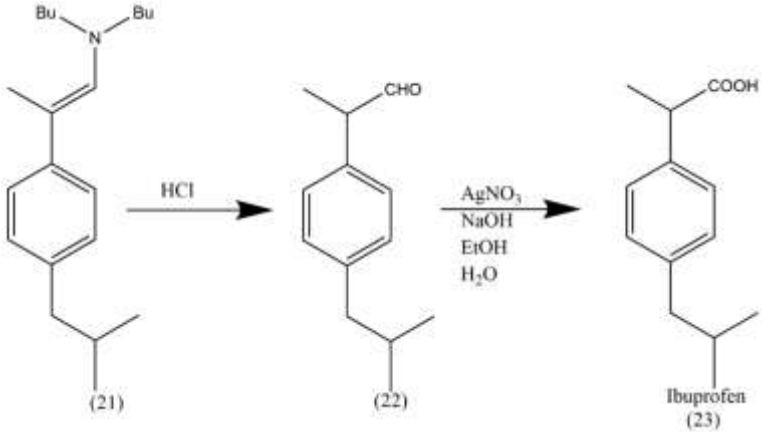

Figure 12: Synthesis of Ibuprofen from Route 7

Route 8 – Modified Friedel Craft acylation

Ethyl lactate when reacted with triethylamine at $0^{o}C$ forms ethyl-2-(methylsulphonyloxy) propanoate (24). The organic layer was collected in a separating funnel. Crude compound (24) was obtained by drying it with Na_2SO_4 and concentrating with reduced pressure. Treatment of (24) with aluminium chloride and isobutylbenzene at 273K forms ethyl-2-(4-isobutylphenyl) propanoate (25). To it,methanol and solution of KOH in was added. It formed a solution. In room temperature, it was stirred, forming the resultant product, ibuprofen (26) [34] (Figure 13).

International Journal of Pharmaceutical Research and Applications
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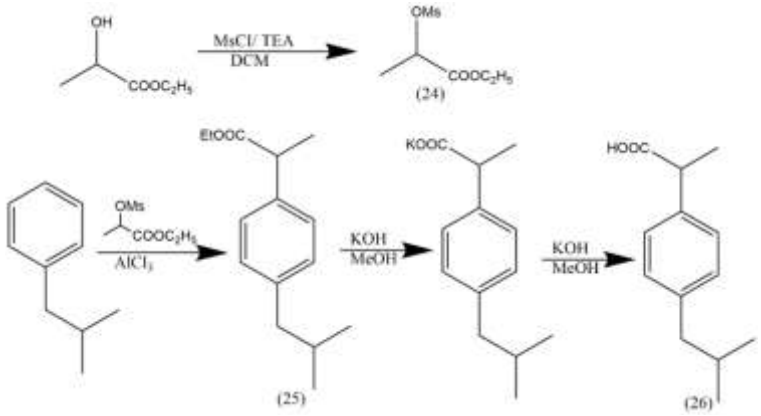

Figure 13: Synthesis of Ibuprofen from Route 8

Route 9 – From p-isobutylacetophenone

Metal hydrides are effective reducing agents specific to carbonyl compounds with no effect on Carbon – Carbon π-bond. Sodium borohydride is one of them[35, 36]. Sodium borohydride is used to reduce p-isobutylacetophenone (27) in methanol. Corresponding chloride (28) was formed by shaking with HCl in separating funnel [37] (Figure 14)

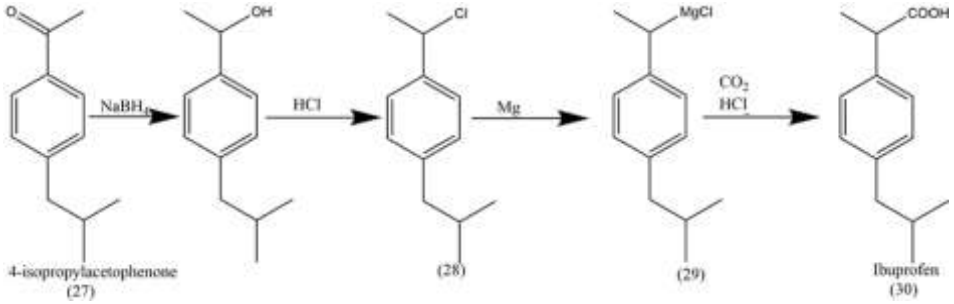

Figure 14: Synthesis of Ibuprofen from Route 9

This results in formation of alkyl chloride. Using Grignand's reagent (29), it was heated under reflux using Tetrahydrofuran (THF) as solvent, with a small amount of 1,2-dibromoethane. Adding carbon dioxide and sodium hydroxide forms ibuprofen (30). [37]

Isobutylbenzene (31) is converted to the corresponding arylol acetate (32). This is followed by the reaction with the methylmalonic acid derivative to form organometallic compound, a Meldrum acid derivative (33) is obtained which, after hydrolysis and decarboxylation, is converted into ibuprofen (34) [38] (Figure 15).

Route 10 – Via Organometallic compound

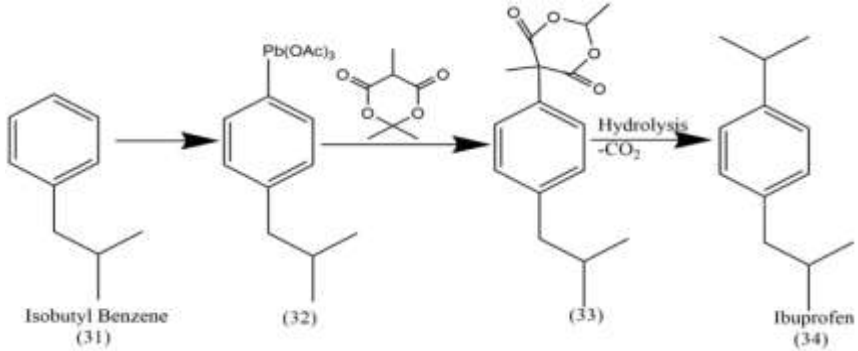

Figure 15: Synthesis of Ibuprofen from Route 10

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 810-824 www.ijprajournal.com ISSN: 2456-4494

Route 11 – Rearrangement of polyvalent iodide derivative

A polyvalent iodide compound (36) is obtained from 4-isobutylpropionophenone (35). The rearrangement of the polyvalent iodide compound (36) results in ibuprofen methyl ester (37) formation. This methyl ester is converted to ibuprofen (38) by hydrolytic reaction [39] (Figure 16).

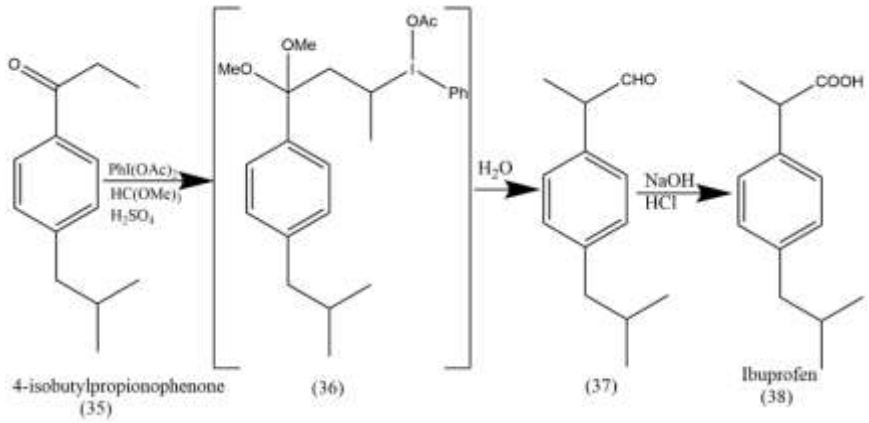

Figure 16: Synthesis of Ibuprofen from Route 11

SYNTHESIS BASED ON GREEN CHEMISTRY

Synthesis involving Green Chemistry create none or minimum by-products which pollute the atmosphere[40]. Apart from producing lesser amount of waste, Green Chemistry seems to be more energy saving, because it focuses on renewable energy sources. This makes it more economical.This in turn lowers the cost of synthesis. Fewer by-products produced implies lesser health hazards.[40]. In Green Chemistry, atom economy is a important principle. According to it, maximum amount of all materials should be incorporated to final product, reducing component loss as side products [41]. Green Chemistry is also called sustainable chemistry

Route 12 –Photo-Favorskii approach towards ibuprofen

Any reaction which is catalysed using photon or light is called photochemical reactions. The efficiency of photochemical reaction is given by quantum yield. As per Stokes Einstein Law, the quantum yield ideally should be equal to 1 [42].

It is rearrangement of α-halopropiophenonesto produce arylpropionic acid. This is the main scaffold present in ibuprofen.

Isobutyl benzene (39) is acylated using chloropropionyl chloride by FC acylation in presence of aluminium chloride. This is a regioselective reaction – higher para orienting reaction.

Next it uses UV-150 photo-reactor. At range of 80 – 150W, α-halopropiophenones forms Ibuprofen (40) via a series of reaction (Figure 17).[29, 43]

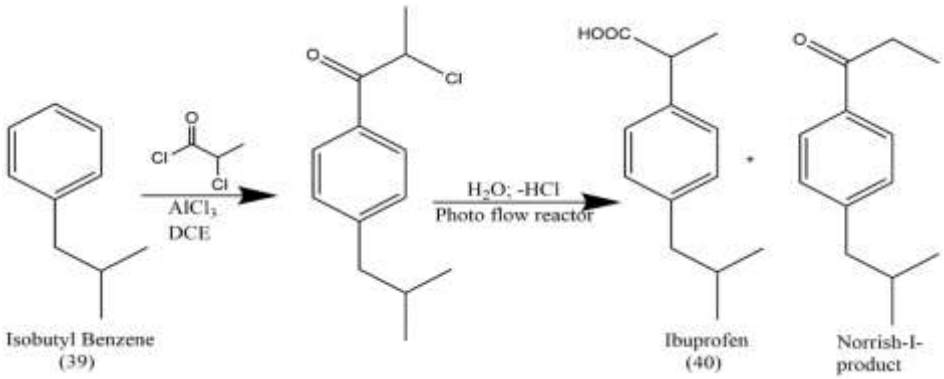

Figure 17: Synthesis of Ibuprofen from Route 12

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 810-824 www.ijprajournal.com ISSN: 2456-4494

Route 13 – McQuade Continuous flow

This synthesis is based on the principle of continuous flow reactors. Isobutylbezene (41) and propionic acid are taken. Separately triflic acid is taken. The reaction is allowed to pass through submerged oil bath at 150°C[44].

To the outlet of the first reactor ethylene tetrafluoroethylene (ETFE) tee was attached. A solution of (Diacetoxyiodo)benzene and Trimethyl orthoformate in methanol was placed. The organic extracts were washed, dried using sodium sulphate and light orange solid yield was found. Crystals were obtained by removing the filtrate. This is ibuprofen (42) [44](Figure 18).

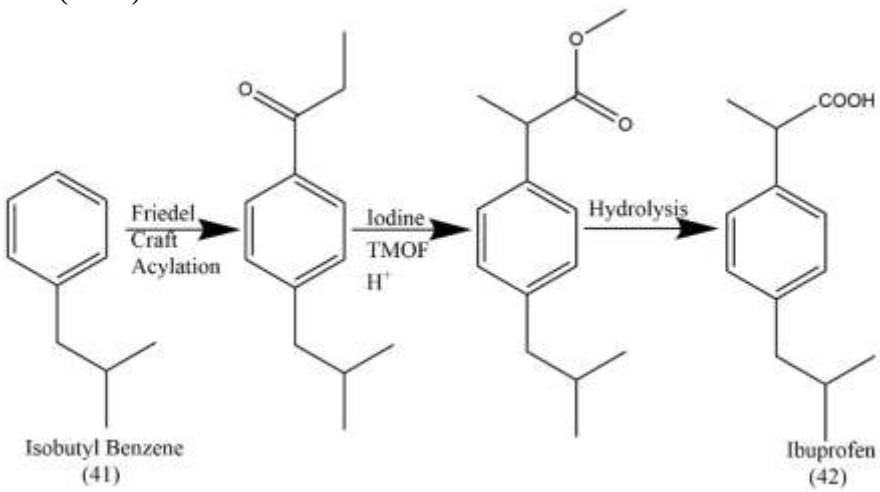

Figure 18: Synthesis of Ibuprofen from Route 13

Route 14 – Boot's Process of Ibuprofen synthesis (Brown Method)

Isobutylbenzene (43) is the starting reagent for this method. Friedel Craft acylation of (43) with acetyl chloride produces intermediate (44). Aiming to convert the p-acetyl group to propionic acid, the acetyl group is first converted to α,β-epoxy ester (45). This is an example of Dalzen reaction, where reactant is ethyl chloroacetate. Hydrolysis and decarboxylation forms aldehyde (46), successive condensation and dehydration forms nitrile (48). Hydrolysis of (48) forms ibuprofen (49) [45] (Figure 19).

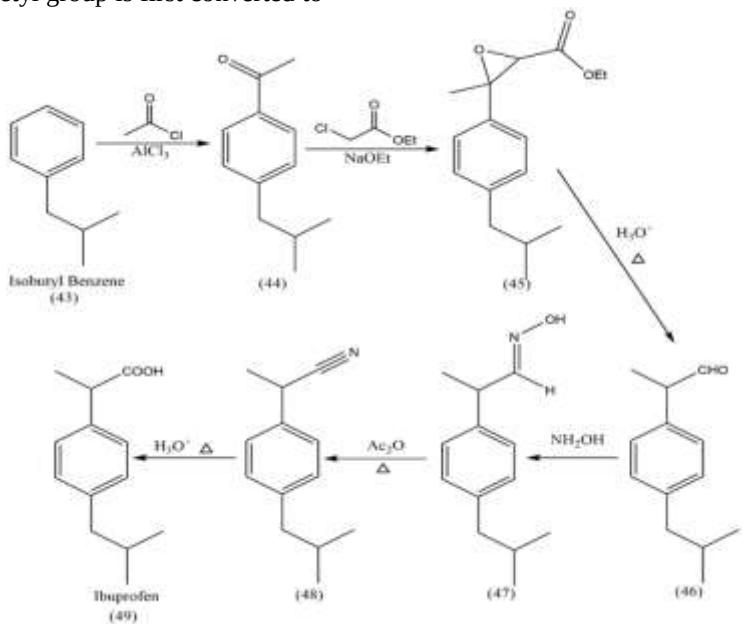

Figure 19: Synthesis of Ibuprofen from Route 14

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 810-824 www.ijprajournal.com ISSN: 2456-4494

Route 15 – Boots-Hoechst-Celanese Process

4'-isobutylacetophenone (51) was synthesized from isobutylbenzene (50) by FC acylation reaction. It is then converted to alcohol (52) by catalytic hydrogenation. Carbonylation of alcohol using carbon monoxide and palladium catalyst forms ibuprofen (53) [46, 47] (Figure 20)

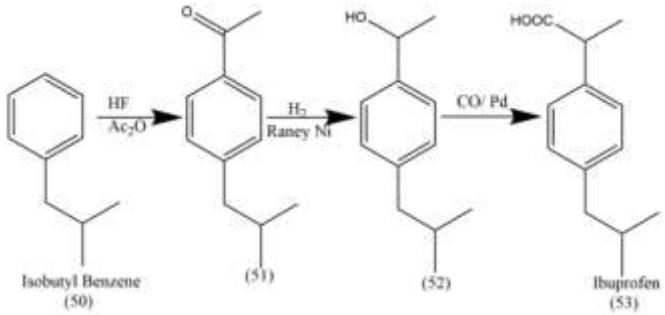

Fig 20: Synthesis of Ibuprofen from Route 15

II. DISCUSSION

The conventional methods, being the traditional methods, are of longer steps, linear routes, and hence forms more by-products, more hazardous wastes, and environmental pollutants. The atom economy is also less as compared to Green Chemistry. [45]

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
ND- Not Described

The route 1, the most famous route of synthesis of Ibuprofen in laboratory, shown to have the yield of 50 – 60% (Table 01). [29]

Dow process, or route 4 showed the yield of ibuprofen compared to the baseline Isobutyl benzene is about 42% which is quite less for industrial manufacturing. [32]

Route 6, which describes synthesis of Ibuprofen from aryl alkyl ketone, shows yield of 80% which is very nearly similar to the yield of route 10, via organometallic compound. The yield percentage of route 10, was also found to be >80%. [29]

Synthesis of Ibuprofen by Route 11, Rearrangement of polyvalent iodide derivative has a quite high yield of about 94%[39].

In BHC process or Route 15, Ibuprofen is synthesized from Isobutylbenzenein three-steped reaction, but Boots process (Route 14) requires six steps [47]. This indicates the formation of higher number of by-products in Boot's process.

Atom economy is a very important factor in Green Chemistry. Atom Economy (AE) can be calculated by:

$$\text{AE} = \frac{\text{mass of atoms in desired product}}{\text{mass of reactants}} \times 100\%$$

Thus, the atom economy of the BHC process (Route 15)is higher, and almost twice (~80%) of the original Boots process (~40%) (Route 14).[45, 47]

III. CONCLUSION

Continuous development of new synthetic route for all drugs are being done. The main aim to design different routes of synthesis is to find an easy and less toxic alternative route. Ibuprofen has multiple different routes of synthesis, including conventional and Green synthetic routes. Among them, Green synthesis routes were found to be producing less by-product. Photochemical or microwave synthesis has higher yield. Atom economy was also found to be more in case of Green Synthetic routes.

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COMPETING INTERESTS

The Authors declare that there is no competing interests.

AUTHOR'S CONTRIBUTION

Amitesh Chakraborty: Data curation; Formal analysis; Resources; Methodology; Roles/Writing - original draft.

Tushar Adhikari: Conceptualization; Investigation; Project administration; Supervision; Validation; Writing - review & editing

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