# Non-Steroidal Anti-inflammatory Drugs (NSAIDs): Synthesis of Ibuprofen, Naproxen and Nabumetone

**Ayad M. R. Raauf *, Sura S. Raoof *,Nehad Kanaan Abed* , Hala Ayad M*.**
***Department of Pharmaceutical Chemistry, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq.**

**DOI:** https://doi.org/10.32947/ajps.19.03.0409

Article Info:

Received 21 May 2019
Accepted 16 Jun 2019
Published 1 Aug 2019

Corresponding Author email:
Pharm.dr.ayad@uomustansiriyah.edu.iq
orcid: https://orcid.org/0000-0002-8957-2093

## Abstract:

This review paper covers the major synthetic approaches attempted towards the synthesis of some Non-Steroidal Anti-Inflammatory Drugs (Naproxen, Ibuprofen and Nabumetone)

**Key words:** synthesis, Naproxen, Ibuprofen and Nabumetone

**الادوية المضادة للالتهابات الغير ستيرويدية (مضادات الاتهابات الغير ستيرويدية) :تخليق الايبوبروفين، نابروكسين ونابوميتون**

**اياد محمد رشيد رؤوف*، سرى صادق رؤوف*، نهاد كنعان عبد*، هالة اياد محمد رشيد ***
****فرع الكيمياء الصيدلانية ، كلية الصيدلة ، الجامعة المستنصرية***

**الخلاصة:**
هذة المقالة تتضمن التركيب الرئيسي لتخليق الادوية المضادة للالتهابات الغيرستيرويدية (نابروكسين ،إيبوبروفين ونابوميتون) .

**الكلمات المفتاحية:** تخليق ، نابروكسين، ايبوبروفين ونابوميتون

## Introduction

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are the most prescribed therapeutic drugs for the treatment of pain and inflammation [1]. One of the major approaches to develop novel drugs is by modifying a well-known non-selective NSAIDs [2,3]. Derivatization of the carboxylate function of representative NSAIDs was shown by different studies that it could enhance the anti-inflammatory activity while minimizing the gastrointestinal side effects [4-7].

The mechanism of action principally responsible for most of the NSAIDs seems to act by inhibition of prostaglandin (PG) synthesis causing almost complete blockade of the activity of the precursor enzymes, cyclooxygenases which are the rate limiting enzymes for Prostaglandin synthesis [8,9].

NSAIDs can be classified as traditional non-steroidal anti-inflammatory drugs, preferential COX-2 inhibitors, analgesic /antipyretic with poor anti-inflammatory NSAIDs and COX-2 selective inhibitors (Coxibs). Traditional NSAIDs can be further sub classified into a carboxylic acid, enolic acids & non-acidic compounds as shown in Figure (1) [10].

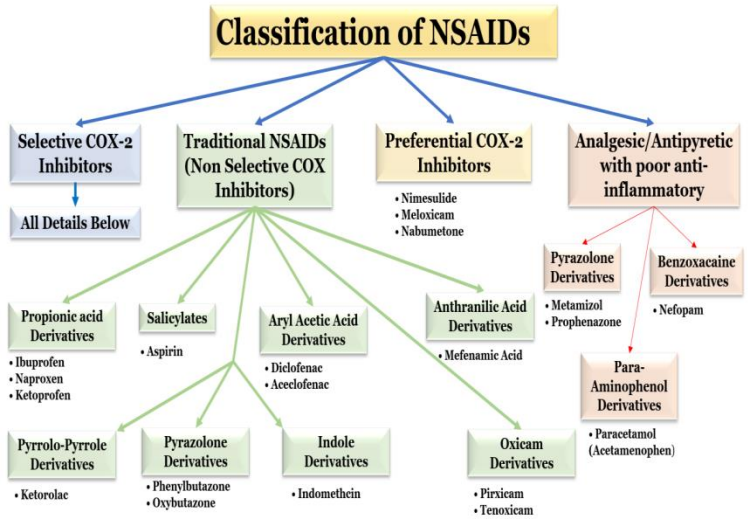



**Figure (1): Classification and representative chemical structures of the traditional nonsteroidal anti-inflammatory drugs (NSAIDs)**

Aspirin (acetylsalicylic acid) was introduced in 1899 as the first efficient drug that treats rheumatic diseases. Later on, at the time between 1960 and 1980, various anti-inflammatory agents were developed and marketed, e.g. ibuprofen, indomethacin, diclofenac and naproxen, as shown in Figure (2) [11].

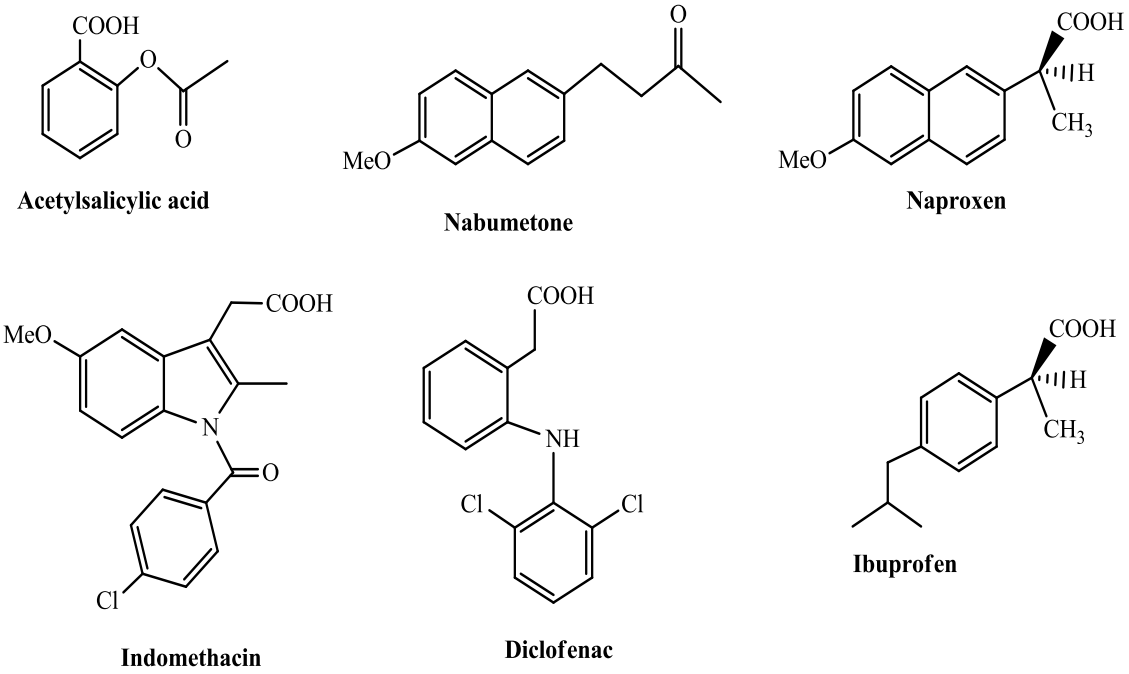



**Figure (2): Some examples of classical NSAIDs**

**Synthesis of ibuprofen:**

Ibuprofen-(+/)2(4-iso-butyl-phenyl) also known as, propionic acid, Figure3, is considered among the most common anti-inflammatory drugs used world-wide. It's the synthetic family of 2-arylpropionic acids prototype, a subclass from Non-Steroidal Anti-Inflammatory drugs.

It's not before 1960s that ibuprofen was discovered by Andrew Dunlop, whose early usage of the drug was meant as a hangover cure.

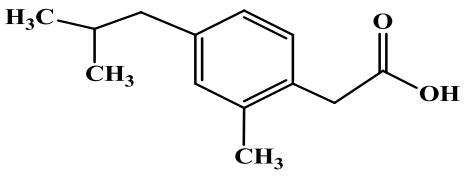
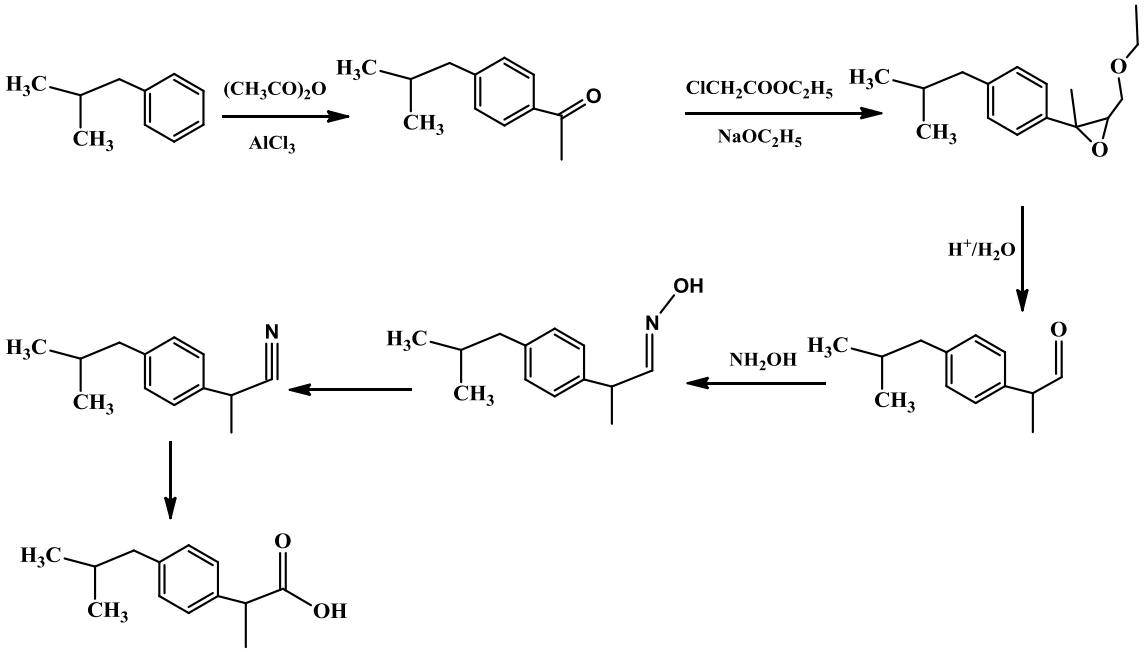


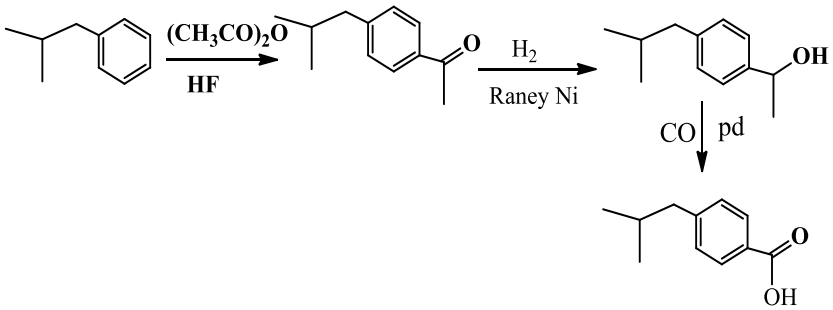
**Figure (3): Ibuprofen structure**

Boots drug company patented the procedure to synthesize the drug in the 1960s Scheme (1). A chemical-waste was considerably produced as a result of applying a complicated several-step synthetic procedure [12]. Ibuprofen was discovered in 1961 by Stewart Adams and initially marketed as Brufen [13].



**Scheme (1): A synthetic method by Boots to yield Ibuprofen. The first published route to Ibuprofen.**

In 1992, Boots unearthed an alternative process of synthesizing ibuprofen Scheme (2) that was found to be more friendly to the environment [14].

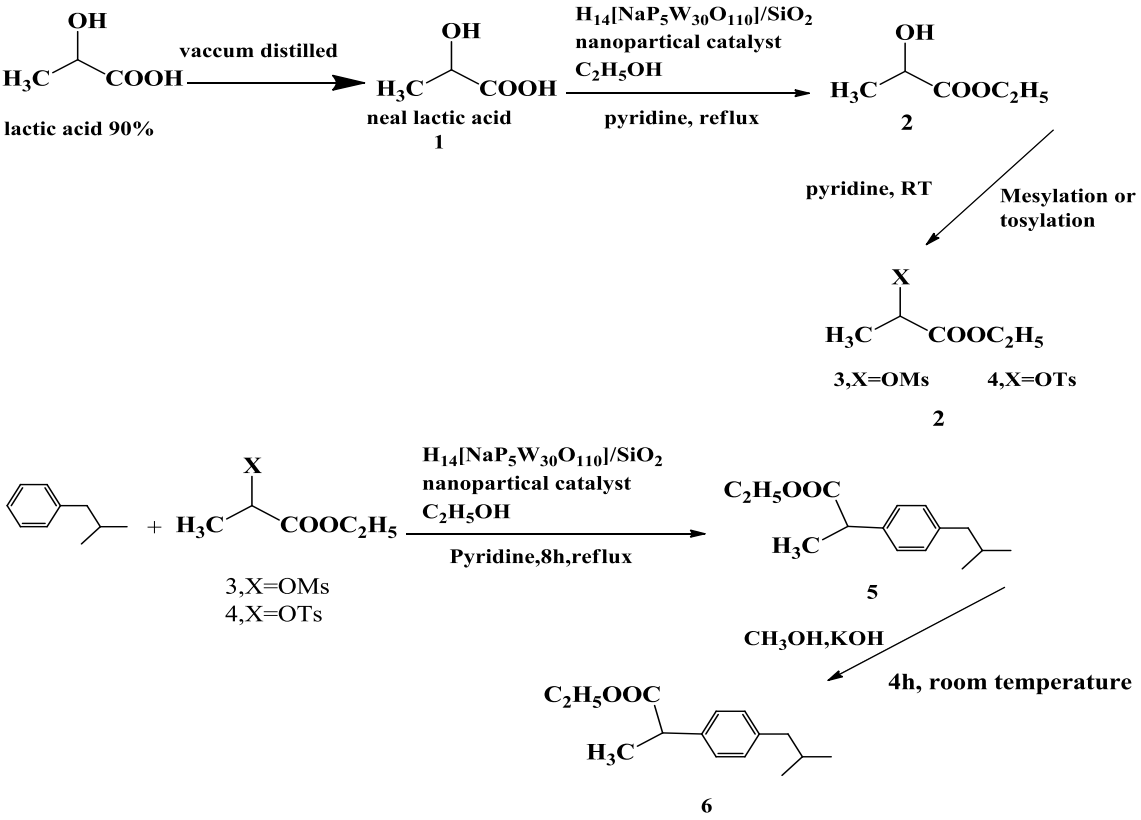


**Scheme (2): Boots procedure to synthesize ibuprofen. A green synthetic route to ibuprofen.**

Silica Preyssler Nanoparticles, also known as(H-14[Na-P5-W30-O110SiO2) (SPNPs), was used as a simple and alternative procedure to synthesize Ibuprofen. Among its many advantages it's found to be inexpensive, efficient-catalyst and economically convenient compound. This protocol later found to produce high yields through a simple operation and easy workup procedure. Thermal-stability and

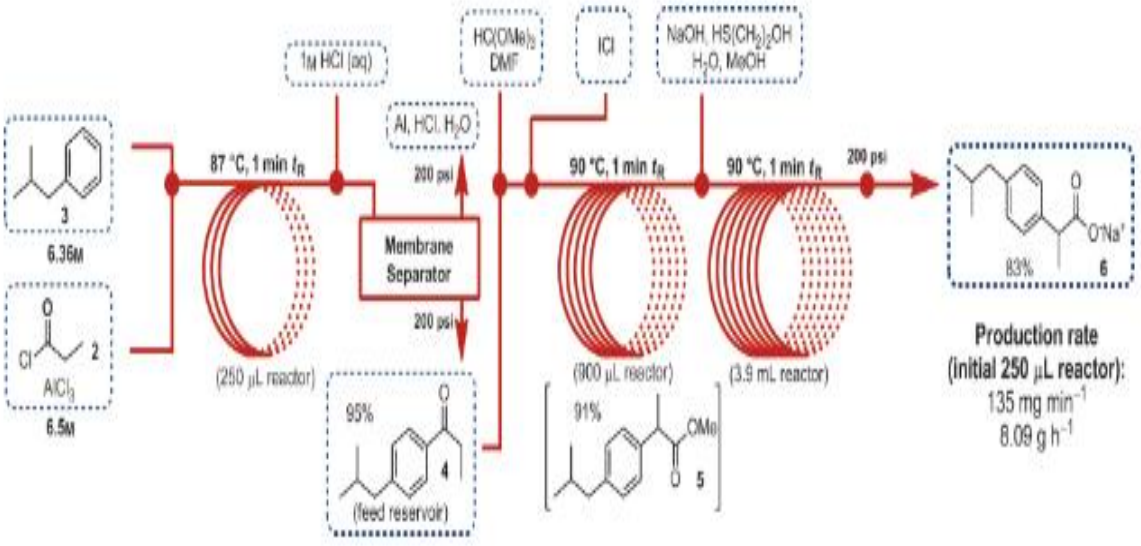
higher hydrolytic characteristic of the compound offered more advantages. The salient features of Preyssler's anion are non- toxicity, availability and reusability.

Vacuum-distillation method was applied to dehydrate Lactic-acid 90% and then refluxed with ethanol in the presence of Silica Supported Preyssler Nanoparticles by azeotropic water removal to maintain 82 % ethyl-lactate (2) yield, (Scheme 1). ethyl-lactate undergo Tosylation and Methylation in the presence of pyridine or triethyl-amine at 25°C had a role in keeping the corresponding ethyl-2-(methylsulphonyloxy) propanoate (3) and ethyl2-(tosyloxy) propanoate (4). Friedel-Crafts-alkylation of mesylate or tosylate with isobutyl benzene for a solo step synthesis of ethyl-2-(4-isobutylphenyl) propanoate was conducted via heating with Silica-Supported -Preyssler-Nanoparticles while reaction conditions remained neat. Ethyl-2-(4-isobutylphenyl) propanoate (5) formed in 65% yield, that was hydrolyzed with KOH in methanol to obtain the racemic Ibuprofen (6) in 97% yield Scheme (3) [15].




**Scheme (3): Ibuprofen Synthesis by silica-supported-Nanoparticles (H14-[NaP5-W30-O110]/SiO2) (SPNPs)**

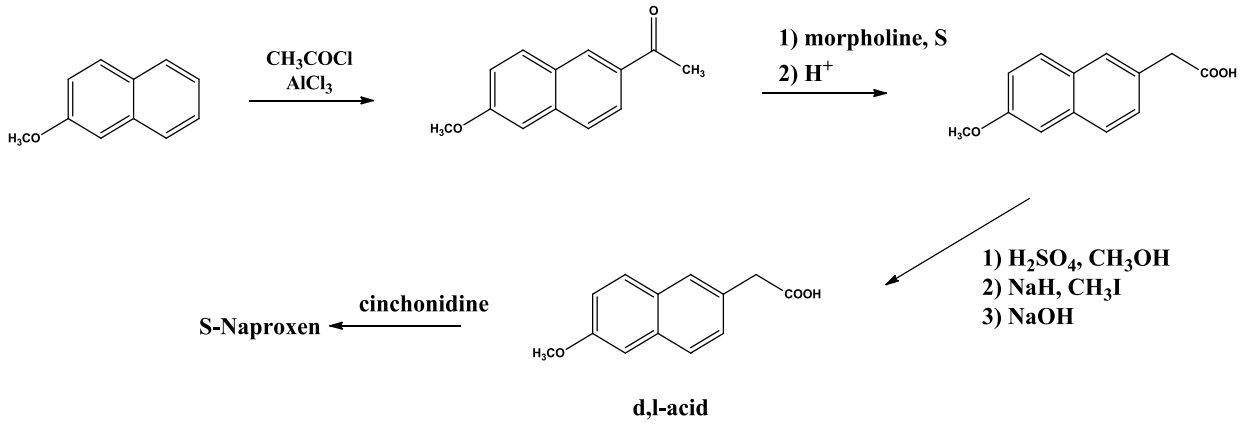
Flow procedures were implemented continuously to handle rough conditions in Ibuprofen production. Three operations were used sequentially; each one-step reaction was complete in a matter of a minute. A yield of 83 % was reached for the three-minute synthesis Scheme (4). Inexpensive, simple and quickly available reagents were used like aluminum chloride and (diacetoxy) iodo-benzene with iodine-monochloride. The exothermic Friedel–Crafts reaction was conducted not only at elevated temperature, but also without external solvent [16].




**Scheme (4): The three-minute ibuprofen synthesis**

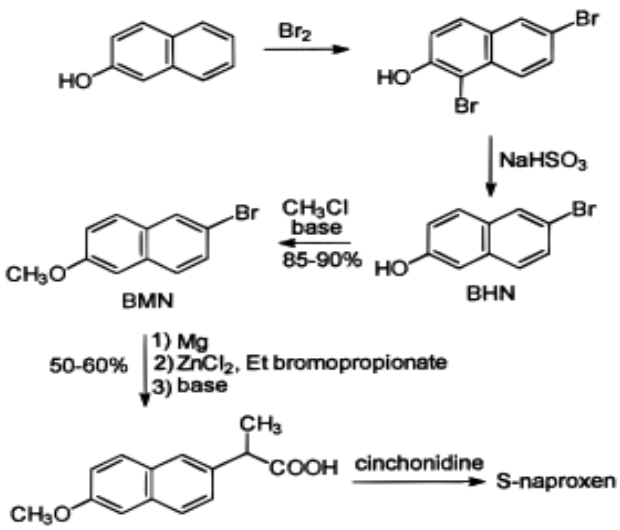
**Synthesis of Naproxen:**

Naproxen is a member of the 2-arylpropionic acid (profen) family of NSAIDs. naproxen was produced in a large-scale-synthesis for first time in a yield of 500kg of material in 1970 Scheme (5). Friedel- Crafts-acylation of 2-methoxynaphthalene (nerolin) supplied 2-acetyl-6-methoxynaphthalene (MAN), which in turn converted to a naphthylacetic acid via the Willgerodt reaction. α-Methy-lation produces the d,l -acid, that can be efficiently settled using cinchonidine to synthesize S-naproxen [17].




**Scheme (5): First large-scale naproxen process (500 kg)**

The initial manufacturing step of Naproxen, around 1972-1975, was conducted through a radically different Scheme (6). α-Naphthol was brominated in methylene chloride to produce 1,6-dibromonaphthol. Bisulfite was used to remove labile bromine at the 1-position. Thereafter the product of 2-bromo-6-hydroxynaphthalene (BHN) was methylated by methyl-chloride in water-2-propanol. The resultant product of 2-bromo-6-methoxynaphthalene (BMN) found 85-90% from α -naphthol. BMN was converted to a Grignard reagent, then zinc-chloride had been used to transmetalate the reagent and then naphthylzinc coupled with ethyl bromopropionate. Hydrolysis of the ester yielded *d,l*-acid [18].




**Scheme (6): First large-scale manufacturing process, 1972-1975**

**Synthesis of nabumetone:**

Nabumetone[4-(6-methoxy-2-naphthalenyl)-2-butanone] Figure (4) is a novel nonacidic broad-spectrum anti-inflammatory, analgesic, and antipyretic agent, Nabumetone was first synthesized in 1973 by Chatterjee, J. N. et al [19].

Its activity is greater than that of aspirin and comparable to naproxen and indomethacin [20].

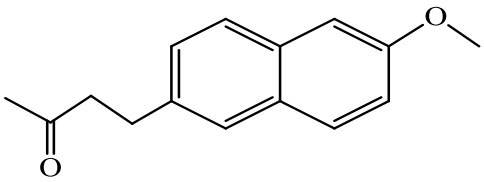
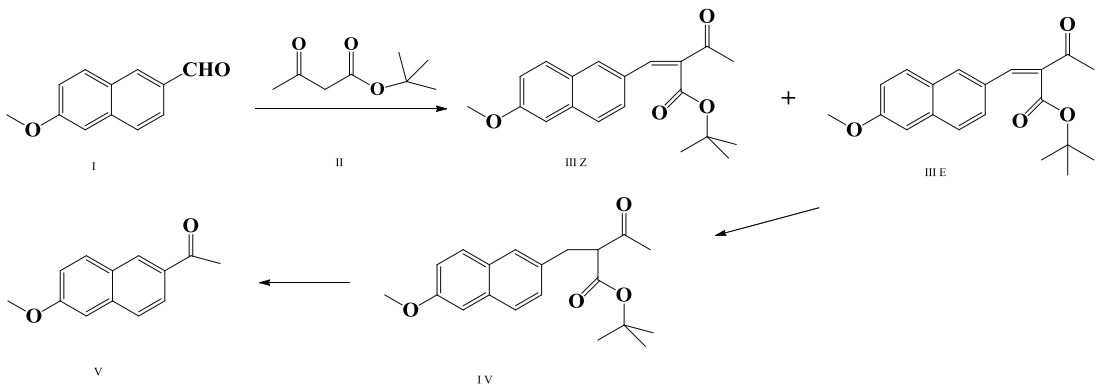


**Figure 4: Nabumetone structure**

The active metabolite of nabumetone was found to be the compound initially responsible for the therapeutic effect. Comparatively, the parent-drug is a poor inhibitor of COX-2 by-products, particularly prostaglandins. Nonetheless, it may be less nephrotoxic than indomethacin [21].

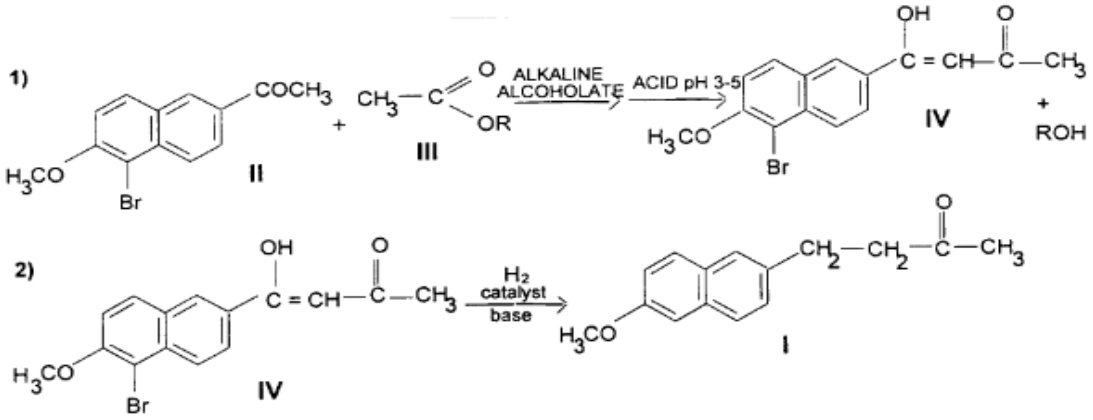
A process was improved to prepare Nabumetone, which consist of the next steps Scheme (7):

A condensation reaction between 6-methoxy-naphthaldehyde I and t-butyl acetoacetate II, to produce an E/Z mixture of 3-t-butoxycarbonyl 4-(6'-methoxy-2-naphthyl)-but-3-en-2-one III; a palladium catalyst promoted the hydrogenation of III, to gain 3-t-butoxycarbonyl-4-(6'-methoxy-2-naphthyl)-butan-2-one IV; the t-butyl ester was cleaved by acid catalysis; while the crude compound re-crystallization was achieved with methanol [22].



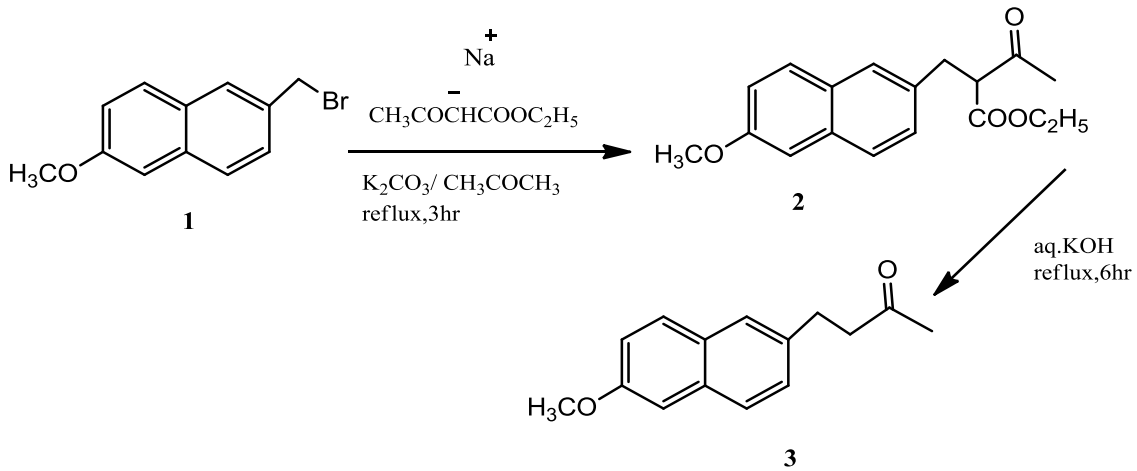

**Scheme 7: synthesis of nabumetone**

Other synthetic processes of nabumetone have been described by reacting 2-acetyl-5-bromo-6-methoxynaphthalene with ethyl acetate in presence of 80% sodium hydride as an oily dispersion to gain the salt of sodium 4(5-bromo-6-methoxy-2-naphthyl)-4-hydroxybut-3-en-2-one, which is reduced to 4-(6-methoxy-2-naphthyl)butan-2-one by using 10% palladium on carbon as catalyst resulting in a catalytic hydrogenation while an excess of sulfuric acid was presented with respect to the amount necessary to liberate the 4-(5-bromo-6-methoxy-2-naphthyl)-4-hydroxybut-3-en-2-one Scheme (8) [23].




**Scheme (8)**

Convenient method for synthesis of nabumetone from readily accessible precursor,2-(bromoethyl)-6-methoxynaphthalene 1. Refluxing a mixture of 1 and sodium acetoacetic ester in acetone in the presence of $K_2CO_3$ followed by usual work up afforded ethyl-2-acetyl-3-(6-methoxy-2-naphthyl) propionate 2 as a brown syrup. Hydrolysis of 2 in presence of 40% KOH finished nabumetone in 73% yield Scheme (9) [24].




**Scheme (9)**

## Conclusions:

In summary, the synthesis of some Non-Steroidal Anti-Inflammatory Drugs (Naproxen, Ibuprofen and Nabumetone) can be achieved by a number of pathways.

**Acknowledgments:**

The authors are grateful to chairman and members of department of Pharmaceutical Chemistry, College of Pharmacy, Mustansiriyah University for their help and support.

## References:

1- Da Costa BR, Reichenbach S, Keller N, Nartey L, Wandel S, Jüni P, Trelle S. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. The Lancet. 2017;390(10090): e21-33.

2- L.J. Marnett, A.S. Kalgutkar, Current Opinion in Chemical Biology 1998, 2(4), 482-490.

3- Takahashi M, Ogawa T, Kashiwagi H, Fukushima F, Yoshitsugu M, Haba M, Hosokawa M. Chemical synthesis of an indomethacin ester prodrug and its metabolic activation by human carboxylesterase 1. Bioorganic & medicinal chemistry letters. 2018 ;28(6):997-1000.

4- Mahdi MF, Mohammed MH, Jassim AA. Design, synthesis and preliminary pharmacological evaluation of new non-steroidal anti-inflammatory agents having a 4-(methylsulfonyl) aniline pharmacophore.Molecules. 2012;17(2):1751-63.

5- Kalgutkar AS, Rowlinson SW, Crews BC, Marnett LJ. Amide derivatives of meclofenamic acid as selective cyclooxygenase-2 inhibitors. Bioorganic & medicinal chemistry letters. 2002 ;12(4):521-4.

6- Kalgutkar AS, Crews BC, Saleh S, Prudhomme D, Marnett LJ. Indolyl esters and amides related to indomethacin are selective COX-2 inhibitors. Bioorganic & medicinal chemistry. 2005;13(24):6810-22.

7- Khanna S, Madan M, Vangoori A, Banerjee R, Thaimattam R, Basha SJ, Ramesh M, Casturi SR, Pal M. Evaluation of glycolamide esters of indomethacin as potential cyclooxygenase-2 (COX-2) inhibitors. Bioorganic & medicinal chemistry. 2006 Jul 15;14(14):4820-33.

8- Ashutosh Kar (Ed.): Medicinal Chemistry (4th ed). New Age International Publishers, New Delhi, 2007; 522-535.

9- Laurance, D.R.; Bennett, P.N. and Brown, M.J. (Eds.): Clinical pharmacology (9th ed.). Churchill Livingstone, London, 2003; pp. 280.

10- Modified from Harris E, Budd R, Firestein G, et al [eds] "Kelley's Textbook of Rheumatology, 7th ed" Philadelphia, WB Saunders, 2005.

11- Howard, Patricia A.: Nonsteroidal anti-inflammatory drugs and cardiovascular Risk. J Am Coll Cardiol. 2004; 43: 519-25.

12- Nicholson JS, Adams SS GB Patent 971,700, 1964; U.S. Patent 3228831, 1966; U.S. Patent 3,385,886, 1968.

13- Joha Stuart Nicholson and Stewart Sanders Adams, phenyl proponic acids USA Patent 3,385,886.

14- Trost BM (1991) The atom economy—a search for synthetic efficiency. Science 254:1471–1477.

15- Ali Gharib, Nader Noroozi Pesyan, Leila Vojdani Fard, and Mina Roshan Synthesis of Ibuprofen Using Silica-Supported Preyssler Nanoparticles (H14[NaP5W30O110]/SiO2) as an Eco-Friendly, Inexpensive, and Efficient Catalyst, Hindawi Publishing Corporation Organic Chemistry International 2014, 1-6.

16- David R. Snead and Timothy F. Jamison A Three-Minute Synthesis and Purification of Ibuprofen: Pushing the Limits of Continuous-Flow Processing Angew. Chem. Int. Ed. 2014, 53, 1– 6.

17- Harrison, I. T.; Lewis, B.; Nelson, P.; Rooks, W.; Roszkowski, A.; Tomolonis, A.; Fried, J. H. Nonsteroidal Antiinflammatory Agents. I. 6- Substituted 2-Naphthylacetic Acids' J. Med. Chem. 1970,13, 203-205.

18- Peter J. Harrington and Eric Lodewijk Twenty Years of Naproxen Technology Organic Process Research & Development 1997, 1, 72-76.
19- Chatterjea, et al., "Condensation of Mannich Base Salts with Phenols: Orientation of Adducts", Indian Journal of Chem., vol. 11, Mar. 1973, pp. 214–218.
20- Prabhakar C, Reddy GB, Reddy CM, Nageshwar D, Devi AS, Babu JM, Vyas K, Sarma MR, Reddy GO. Process research and structural studies on nabumetone. Organic Process Research & Development. 1999 Mar 19;3(2):121-5.
21- Olsen NV, Jensen NG, Hansen JM, Christensen NJ, Niels FA, Kanstrup IL. Non-steroidal anti-inflammatory drugs and renal response to exercise: a comparison of indomethacin and nabumetone. Clinical Science. 1999 Oct 1;97(4):457-65.
22- Walter Cabri, Rozzano; Domenico Magrone, Milan; Roberto Angelini, Milan; Erminio Oldani, Milan PROCESS FOR THE PREPARATION OF 4-(6'-METHOXY-2'-NAPHTHYL) BUTAN-2-ONE, USOO5955635A, 1999.
23- Process for the synthesis of nabumetone EP 0 792 860 B1, 2001.
24- G Srinivasulu, A Raghupthi Reddy, Ch Nagaraju, p Pratap Reddy and M Stayanarayana Reddy, A convenient synthesis of Nabumetone an anti-inflammatory drug candidate, Indian J. of Chem.,44B,205, 207-208