SJIF Impact Factor (2024): 8.675| ISI I.F. Value: 1.241| Journal DOI: 10.36713/epra2016 ISSN: 2455-7838(Online)
EPRA International Journal of Research and Development (IJRD)
Volume: 9 | Issue: 7 | July 2024 - Peer Reviewed Journal

REVIEW ON NABUMETONE DERIVATIVES SYNTHESIS IN THE LAST 10 YEARS

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Article DOI: https://doi.org/10.36713/epra17806
DOI No: 10.36713/epra17806

ABSTRACT

The focus today is on the synthesis of derivatives from the approved drugs, so decrease the chance of synthesizing a potentially toxic compound. One of the commonly used drugs is the non-steroidal anti-inflammatory drugs for the treatment of painful arthritis. Nabumetone is a non-steroidal anti-inflammatory drug. In recent years many of derivatives having different biological activities have been synthesized from nabumetone. The purpose of this review is giving sight to these derivatives in the last 10 years and the biological activities of them.

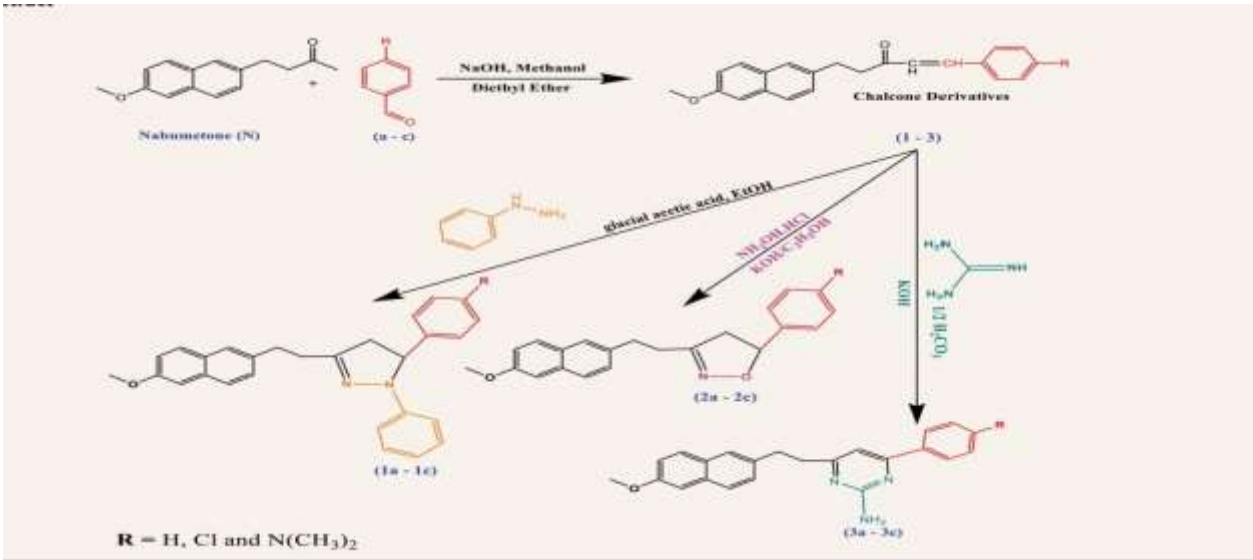
KEY WORDS: *nabumetone , non-steroidal anti-inflammatory, anti-inflammatory , anti-cancer, anti-bacterial.*

introduction

As a non-steroidal prodrug that reduces inflammation, nabumetone works pharmacologically through the metabolite 6-methoxy-2-naphthylacetic acid (6-MNA). The non-acidic drug nabumetone itself is extensively metabolized in the first pass after absorption to produce the primary circulating active metabolite (6-MNA), which is a far more effective inhibitor of cyclooxygenase (COX)-2.[1,2]The primary purpose of nabumetone treatment is to relieve arthritic pain.[3] The enhanced gastrointestinal (GI) tolerability of this medication is believed to be attributed to its non-acidic nature, prodrug formulation, and absence of biliary secretion of its active metabolite, 6-methoxy-2-naphthylacetic acid. [4] Nabumetone is one of a class of medications known as non-steroidal anti-inflammatory drugs (NSAIDs), which are used extensively to treat both acute (like fever and discomfort) and chronic (like rheumatoid arthritis) inflammatory diseases. [5] NSAIDs have also been shown to provide protection against a variety of serious illnesses, such as cancer and heart attacks. [6] By blocking the cyclooxygenase enzyme(COX1,2), non-steroidal anti-inflammatory drugs prevent prostaglandins from being biosynthesised, which has a significant inflammatory function in inflammation.[7,8]

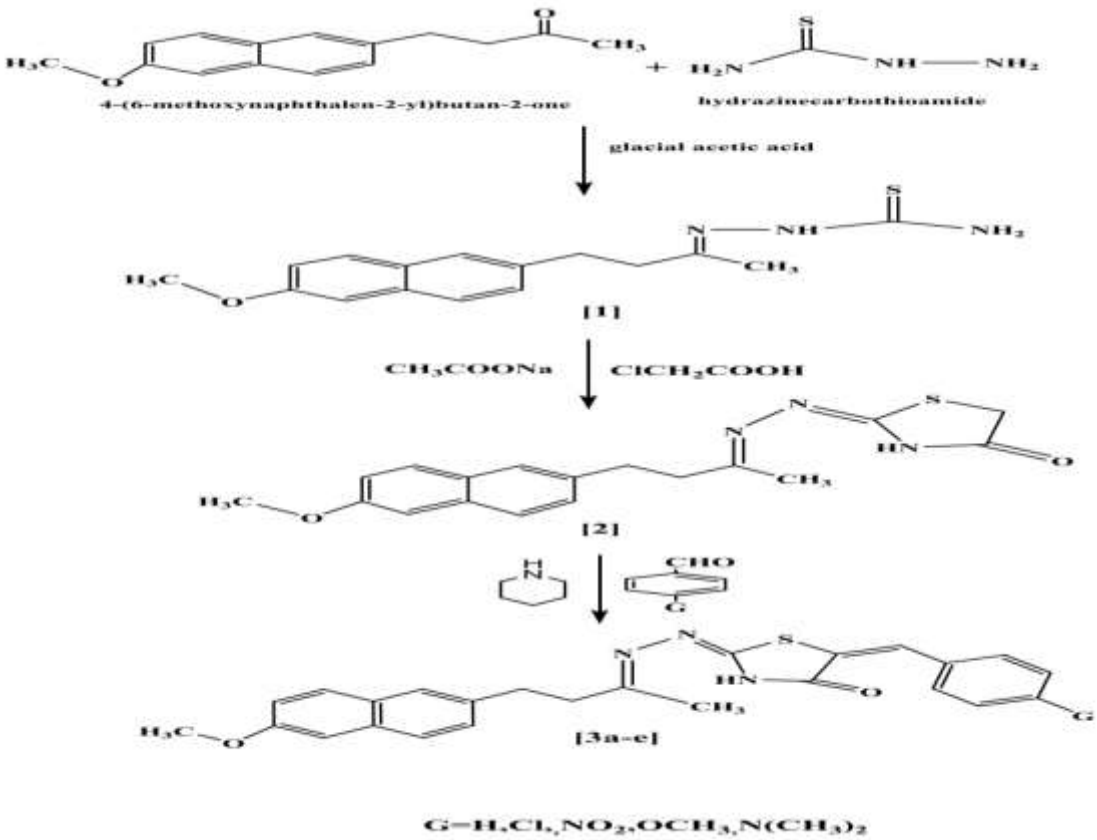
Although they are often used, non-steroidal anti-inflammatory medicines (NSAIDs) have the potential to cause small bowel enteropathy, peptic ulcer disease, and foregut symptoms. Perforations and bleeding into the gastrointestinal tract may exacerbate such an iatrogenic damage. Reducing the amount of NSAIDs taken or using them together with proton pump inhibitors (PPIs) lowers the incidence of problems, dyspepsia, and peptic ulcer disease.[9] Nitrogen-containing 5-membered heterocyclic compounds, or pyrazolines, are widely recognized and significant chemicals. Several synthetic routes have been developed for them. The discovery that many pyrazoline derivatives have significant biological activities has sparked interest in this area of study. Their antibacterial, antimycobacterial, antifungal, anti-amoebic, anti-inflammatory, analgesic, antidepressant, and anticancer properties are only a few of their notable effects. [10,11] Nitrogen and oxygen are found in the five-membered heterocyclic compounds known as isoxazoles and isoxazolines. As an antibacterial, antifungal, anti-inflammatory, anti-tubercular, anti-cancer, and anti-neoplastic drug, isoxazoline has demonstrated remarkable efficacy in clinical trials. [12,13] Pyrimidine is a nitrogen-containing, six-membered heterocyclic molecule that occurs naturally in vitamin B1 and nucleic acid components (uracil, thymine, and cytosine). Pyrimidines and their derivatives are useful for pharmaceuticals and agricultural chemicals. Numerous pyrimidine derivatives have been shown to have anti-inflammatory, antitumor, antiviral, anticancer, and antibacterial properties. [14,15] There is an article published in 2019 stated that a number of derivatives had been synthesized containing pyrazoline , isoxazoline and pyrimidine rings and using nabumetone as starting material. This paper showed that increase in the anti-inflammatory effect of nabumetone by adding these rings. [16]

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Scheme 1: (synthesis of some new pyrazoline, isoxazoline and pyrimidine derivatives bearing nabumetone moiety) [16]

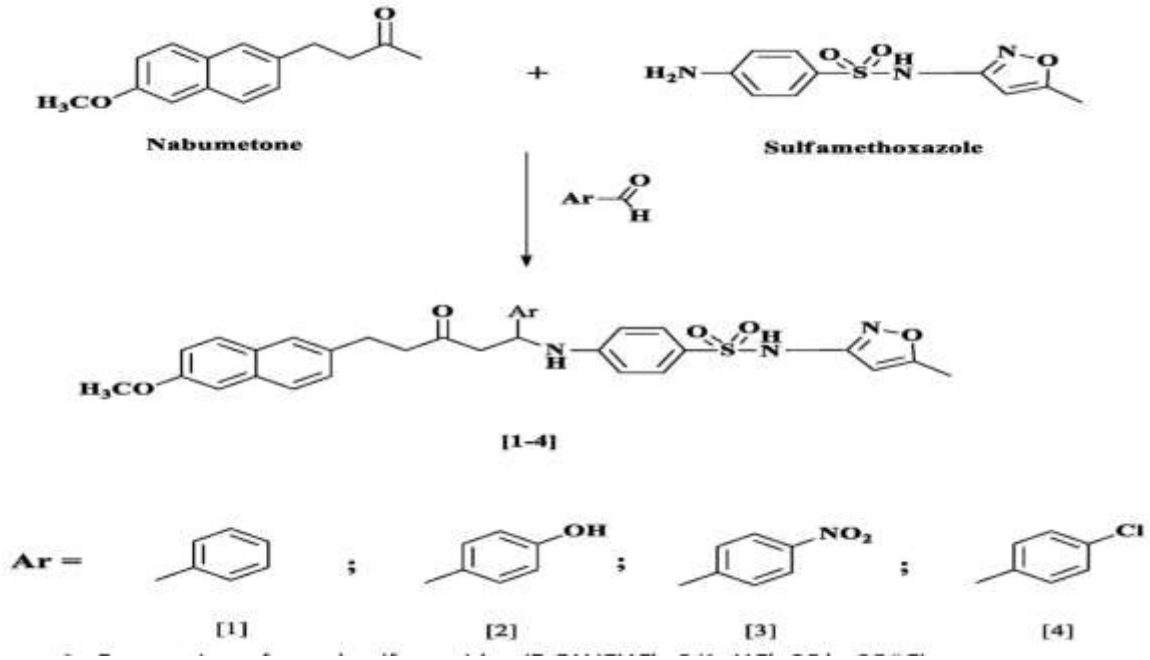
Another heterocyclic compound with biological significance is thiazolidinone, which has a carbonyl group at positions 2, 4, or 5, a nitrogen atom at position 3, and a sulfur atom at position 1. The 4-thiazolidinone moiety, also referred to as the "wonder nucleus," is a magical component with a broad range of biological actions, including antiviral, antibacterial, anti-inflammatory, and anti-tubercular properties. [17,18] There is another article published in 2019 showed that a number of derivatives had been synthesized containing this group by using nabumetone as starting material. This paper described that these derivatives had some anti-bacterial and anti-fungal properties. [19]



Scheme 2: (Synthesis of some New 4-Thiazolidinones Derivatives from nabumetone.) [19]

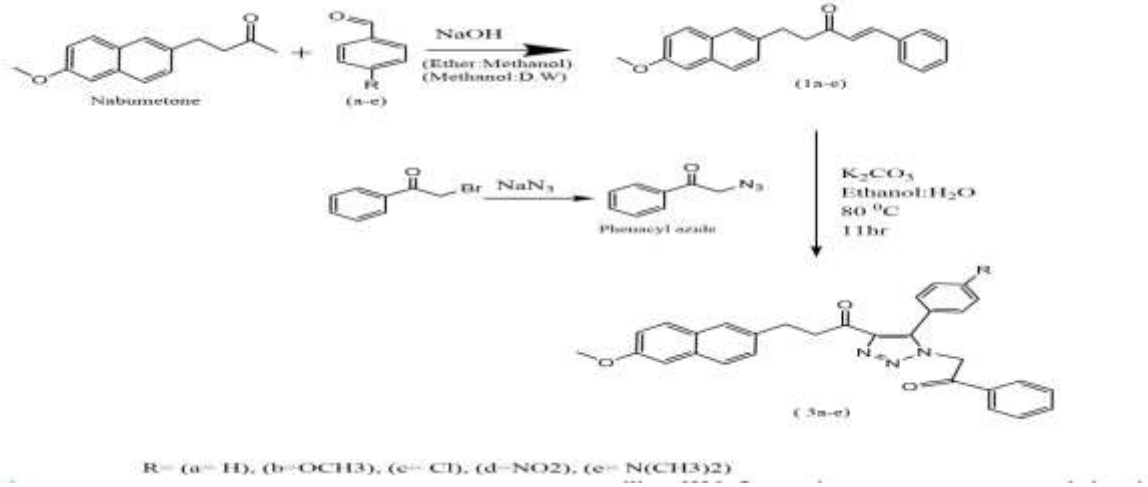
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One of the most well-known antimicrobial medications is sulfonamide. The amino group at the para position of the benzene ring and the sulfonamide group make up the basic structure of sulfonamides. A growing number of bioactive compounds with the sulfonamide subunit have been developed due to their significant biological effects, including anti-tumor, antioxidant, anti-bacterial, and anti-fungal characteristics. [20,21] A research paper published in 2020 talked about the synthesis of derivatives containing sulfonamide and nabumetone. These derivatives had good anti-bacterial activity comparing to sulfamethoxazole. [22]



Scheme3: (synthesis of some sulfonamides derivatives from nabumetone.)[22]

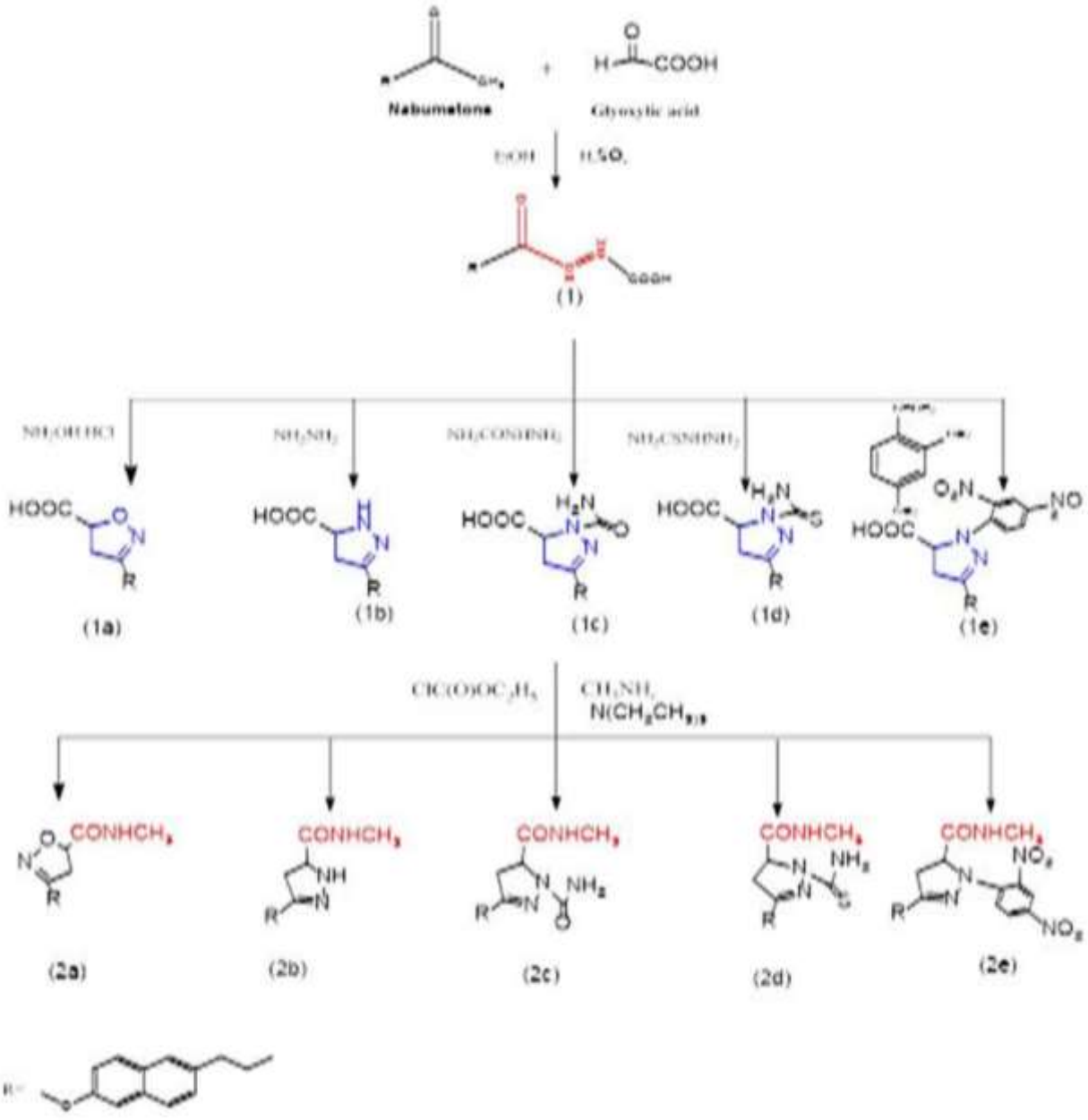
Triazole compounds, which include three nitrogen atoms and two carbon atoms, exhibit a wide range of biological activity because they can bind to different enzymes and receptors in the biological system. Several therapeutic classes, including antibacterial, antifungal, anticancer, antioxidant, antiviral, anti-inflammatory, analgesic, antiepileptic, antihypertensive, antidepressant, anti-diabetic, anti-anxiety, and anti-tubercular, contain the triazole nucleus as a key structural component. [23,24] A paper published in 2021 showed the enhancement in the anti-inflammatory effect of nabumetone by using it in the synthesis of number of derivatives containing triazole ring. [25]



Scheme 4: (Synthesis of some new triazole derivatives bearing nabumetone moiety.) [25]

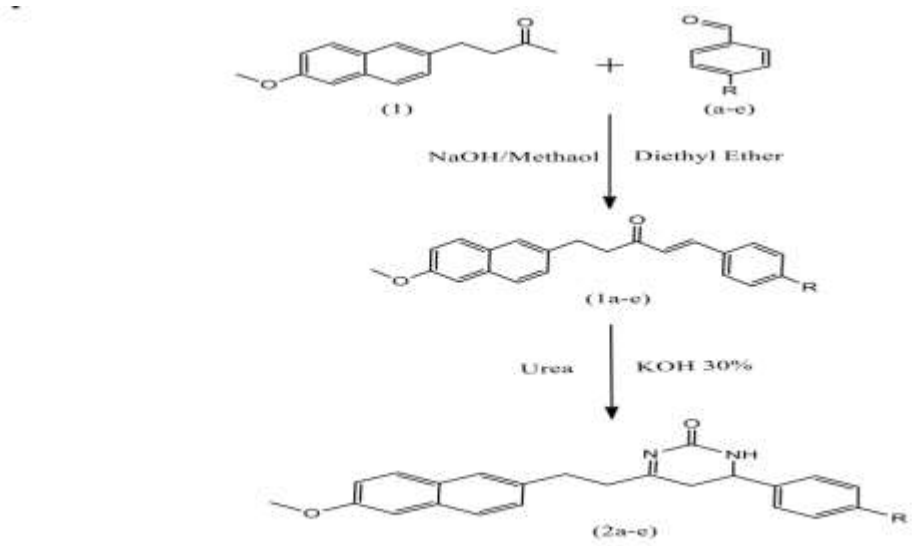
Also in 2021 a research paper showed that a number of derivatives had been synthesized from nabumetone , these derivatives bearing different five membered heterocyclic ring systems and some of these derivatives have a good anti-proliferative activity . [26]

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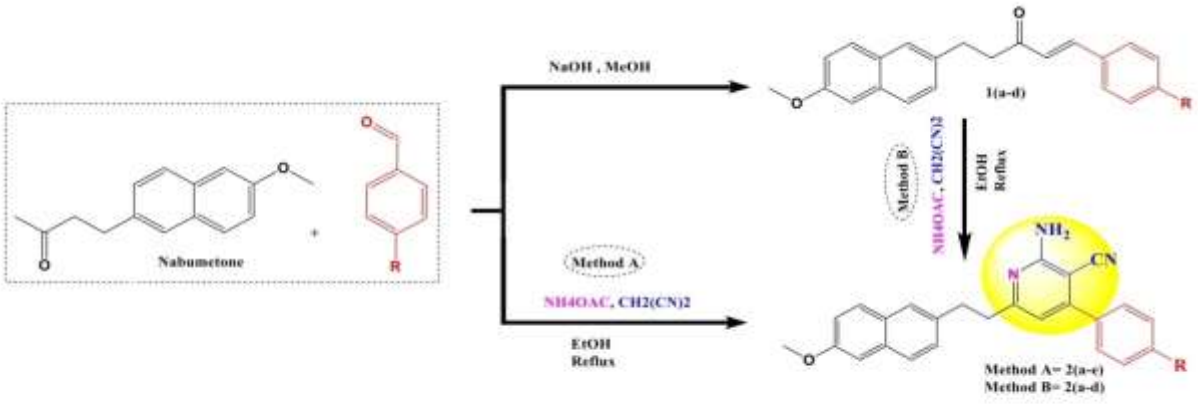
Scheme 5: (synthesis of some new five-member ring heterocyclic compounds from nabumetone.) [26]
In 2023 a research showed that enhancement in the anti-inflammatory activity of nabumetone occurred when using it in the synthesis of some derivatives containing pyrimidine ring. [27]

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Scheme 6: (synthesis of some pyrimidine derivatives from nabumetone)

An isostere of benzene called pyridine (C5H5N) is utilized as a precursor in the synthesis of target agrochemicals and medicines. Antimicrobial, antiviral, anticancer, anti-diabetic, antifungal, anti-inflammatory, and anti-mycobacterial properties. [28,29] An article published in 2023 stated the synthesis of a number of derivatives (containing pyridine moiety) from nabumetone and some these derivatives showed good anti-cancer activity against lung cancer cells. [30]



Scheme 7: (Synthesis of new pyridine derivatives of nabumetone.) [30]

Conclusion

Nabumetone drug is non-steroidal anti-inflammatory drug but can be used to synthesize derivatives that either have enhanced anti-inflammatory activity or different type of activity like anti-bacterial, anti-fungal, anti-proliferative and anti-cancer. Also it may be investigated to design derivatives have different types of activities other than listed above.

Acknowledgements

The authors are greatly thankful to management and principal, Department of Pharmaceutical Chemistry/ College of Pharmacy/ Mustansiriyah University for their help and support.

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