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# REVIEW ON NABUMETONE DERIVATIVES SYNTHESIS IN THE LAST 10 YEARS

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**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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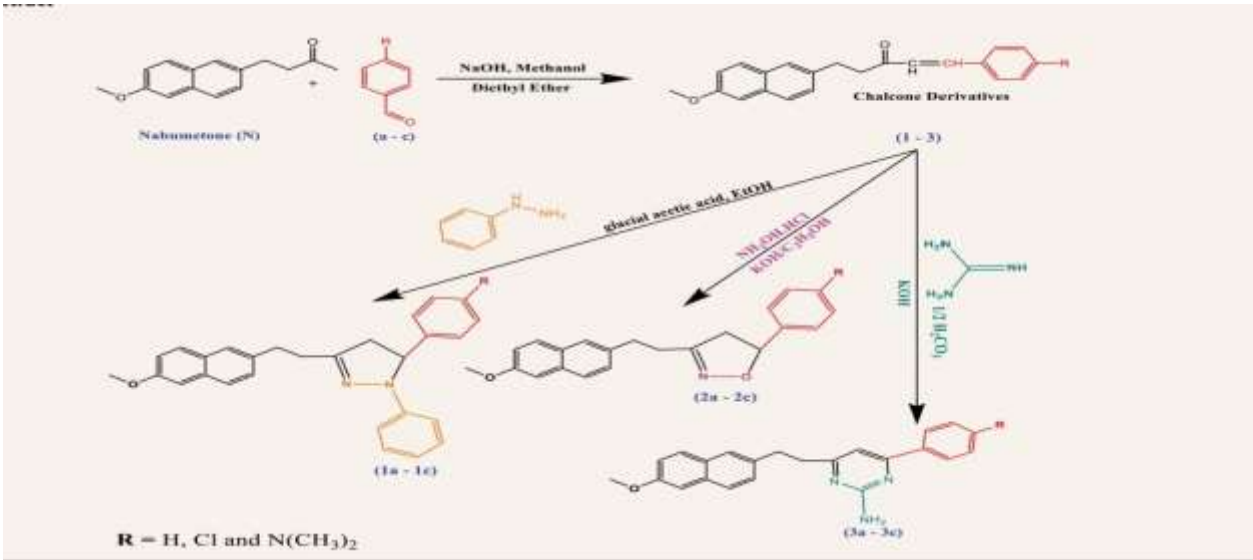
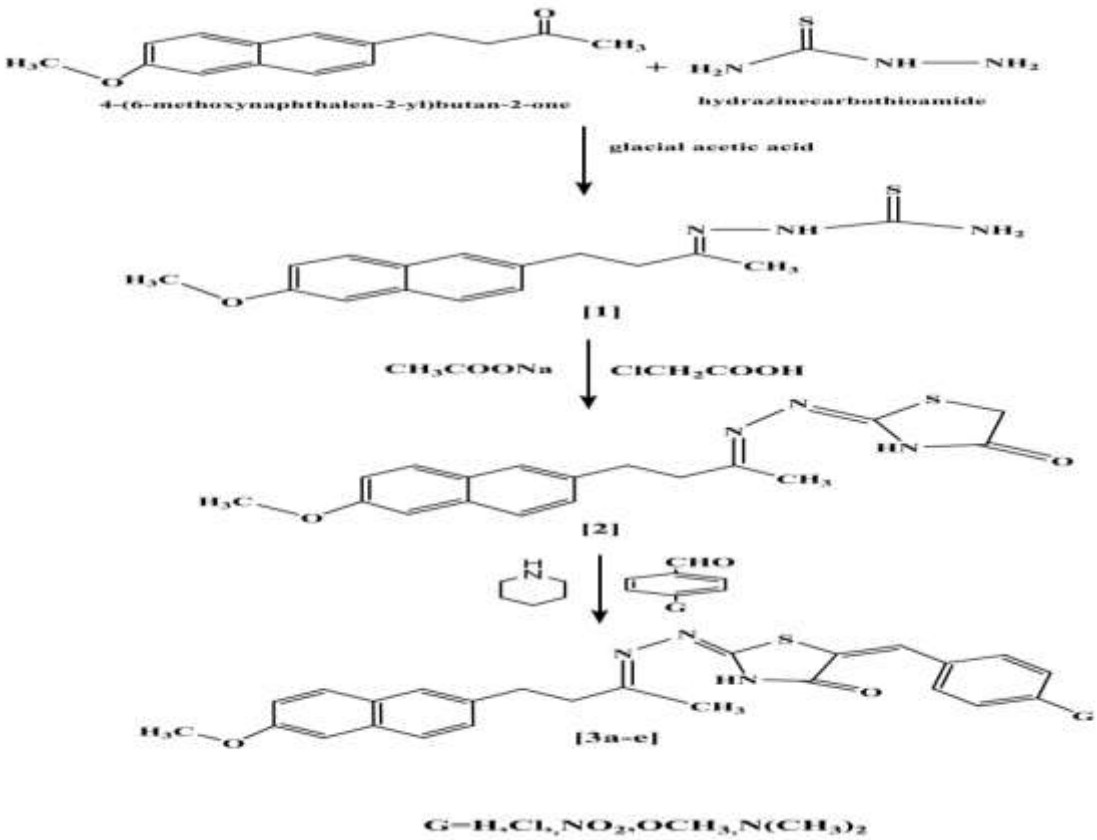



**Scheme 1:** (synthesis of some new pyrazoline, isoxazoline and pyrimidine derivatives bearing nabumetone moiety) [16]

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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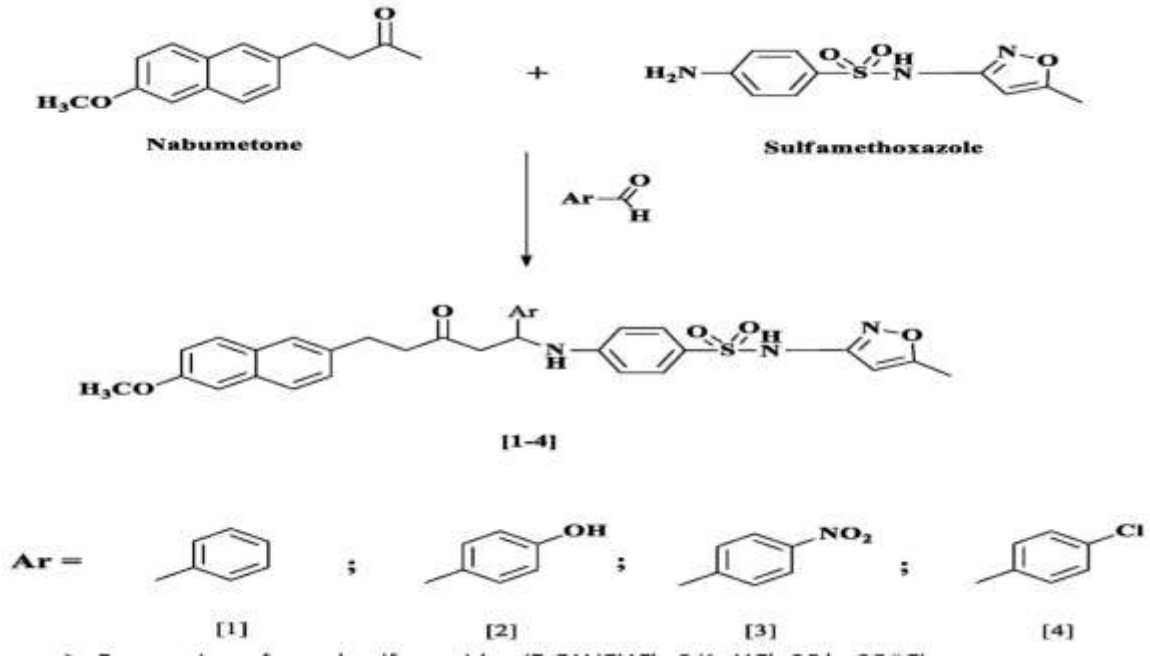
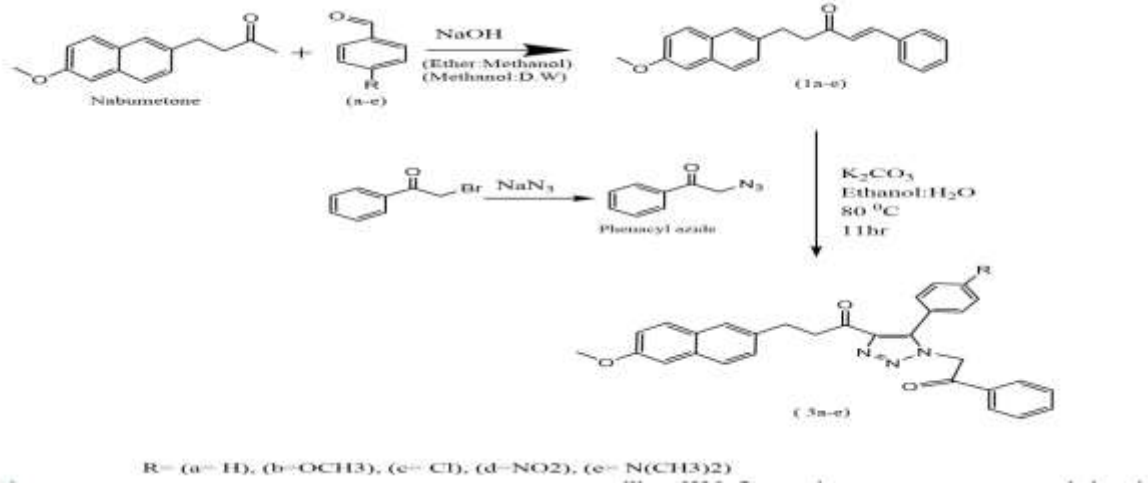
One of the most well-known antimicrobial medications is sulfonamide. The amino group at the para position of the benzene ring and the sulfonamide group make up the basic structure of sulfonamides. A growing number of bioactive compounds with the sulfonamide subunit have been developed due to their significant 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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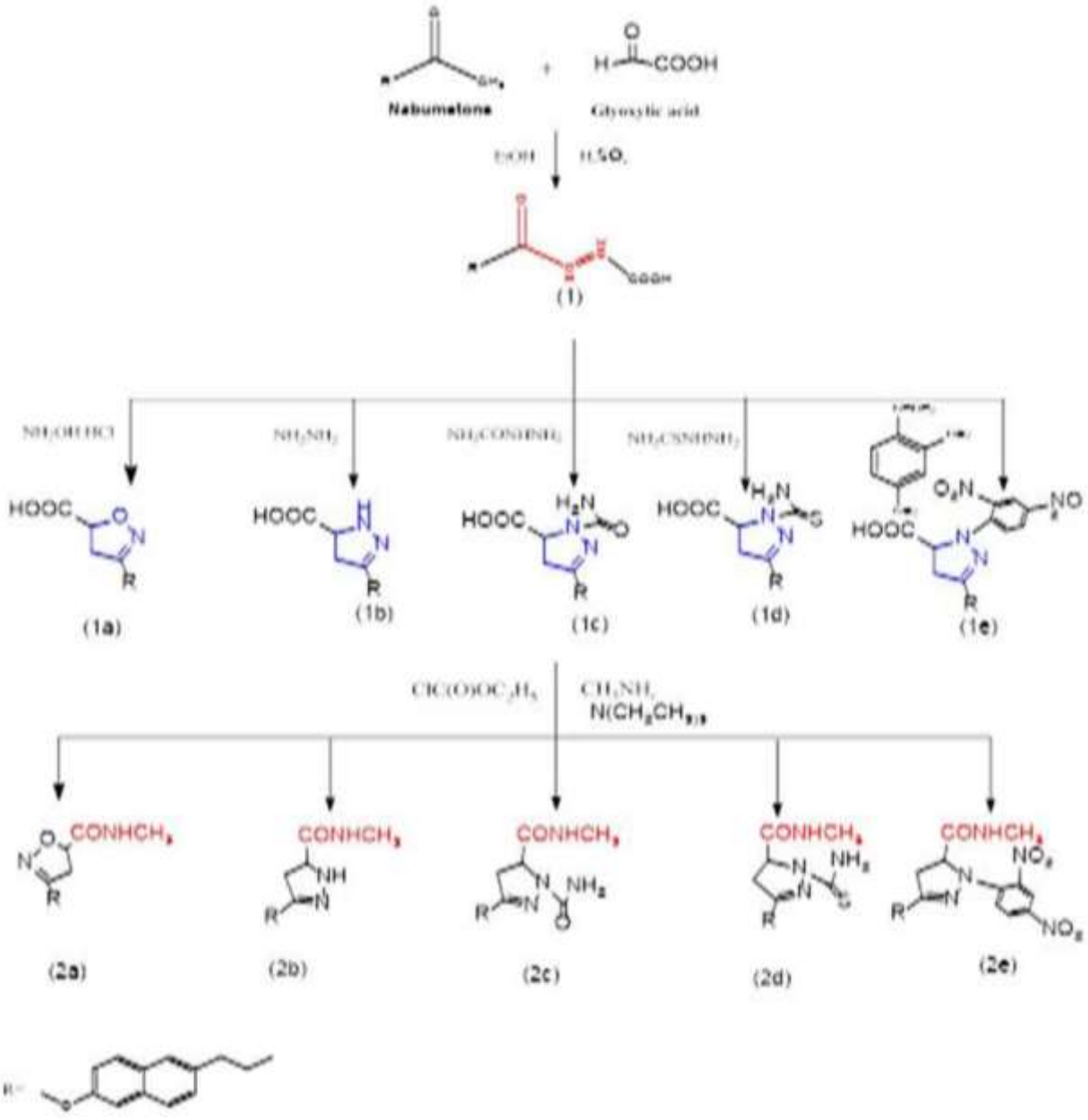


**Scheme 5:** (synthesis of some new five-member ring heterocyclic compounds from nabumetone.) [26]
In 2023 a research showed that enhancement in the anti-inflammatory activity of nabumetone occurred when using it in the synthesis of some derivatives containing pyrimidine ring. [27]

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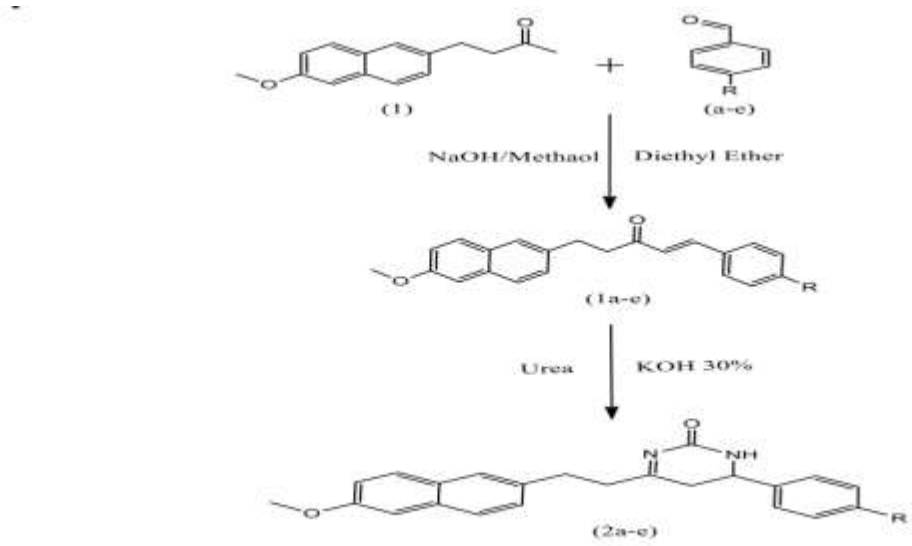
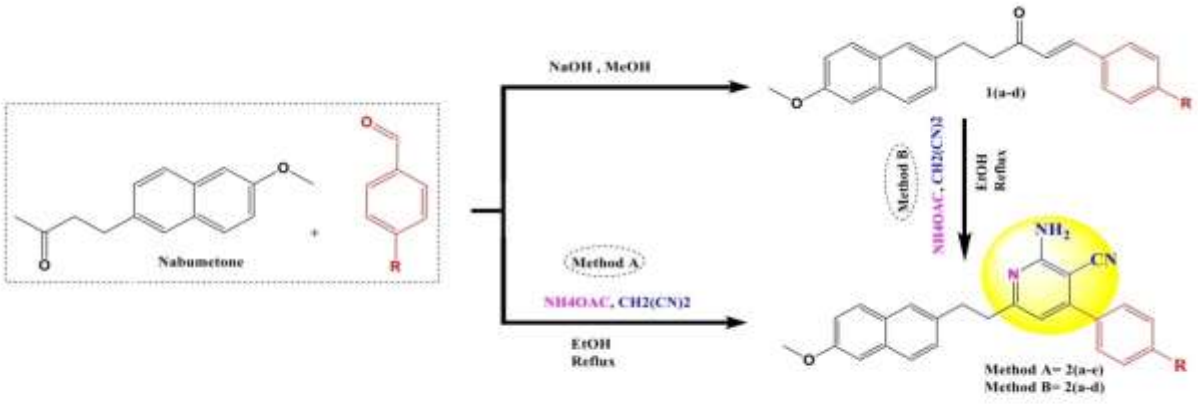



**Scheme 6:** (synthesis of some pyrimidine derivatives from nabumetone )

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.

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## REFERENCES

1. *Hedner T, Samulesson O, Währborg P, Wadenvik H, Ung KA, Ekbom A. Nabumetone: therapeutic use and safety profile in the management of osteoarthritis and rheumatoid arthritis. Drugs. 2004 Oct;64:2315-43.*
2. *Gonzalo-Garijo MA, Cordobés-Duran C, Lamilla-Yerga AM, Moreno-Gastón I. Severe immediate reaction to nabumetone. Journal of Investigational Allergology and Clinical Immunology. 2007 Jan 1;17(4):274.*
3. *Moore RA, Derry S, Moore M, McQuay HJ. Single dose oral nabumetone for acute postoperative pain in adults. Cochrane Database of Systematic Reviews. 2009(4).*
4. *Bannwarth B. Safety of the nonselective NSAID nabumetone: focus on gastrointestinal tolerability. Drug safety. 2008 Jun;31(6):485-503.*
5. *Robb CT, Goepp M, Rossi AG, Yao C. Non-steroidal anti-inflammatory drugs, prostaglandins, and COVID-19. British Journal of pharmacology. 2020 Nov;177(21):4899-920.*
6. *Bindu S, Mazumder S, Bandyopadhyay U. Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: A current perspective. Biochemical pharmacology. 2020 Oct 1;180:114147.*
7. *Drożdżal, S., Lechowicz, K., Szostak, B., Rosik, J., Kotfis, K., Machoy-Mokrzyńska, A., Białecka, M., Ciechanowski, K. and Gawrońska-Szklarz, B., 2021. Kidney damage from nonsteroidal anti-inflammatory drugs—Myth or truth? Review of selected literature. Pharmacology research & perspectives, 9(4), p.e00817.*
8. *Musaa LA, Karim HA, Ahmeda AM. Selection of the best solvent and pH indicator for the acid-base titration of indomethacin in laboratories for pharmacy college students. inflammation. 2022 Aug 2;9:10.*
9. *Tai FW, McAlindon ME. Non-steroidal anti-inflammatory drugs and the gastrointestinal tract. Clinical Medicine. 2021 Mar 1;21(2):131-4.)( Khamroev BS. RESULTS OF TREATMENT OF PATIENTS WITH BLEEDING OF THE STOMACH AND 12 DUO FROM NON-STEROIDAL ANTI-INFLAMMATORY DRUGS-INDUCED OENP. Journal of Pharmaceutical Negative Results. 2022 Nov 19:1901-10.*
10. *Kumar S, Bawa S, Drabu S, Kumar R, Gupta H. Biological activities of pyrazoline derivatives-A recent development. Recent patents on anti-infective drug discovery. 2009 Nov 1;4(3):154-63.*
11. *Marella A, Ali R, Alam T, Saha R, Tanwar O, Akhter M, Shaquiquzzaman M, Mumtaz Alam M. Pyrazolines: a biological review. Mini reviews in medicinal chemistry. 2013 May 1;13(6):921-31.*
12. *Pandhurnekar CP, Pandhurnekar HC, Mungole AJ, Butoliya SS, Yadao BG. A review of recent synthetic strategies and biological activities of isoxazole. Journal of Heterocyclic Chemistry. 2023 Apr;60(4):537-65.*
13. *Wang X, Hu Q, Tang H, Pan X. Isoxazole/Isoxazoline skeleton in the structural modification of natural products: a review. Pharmaceuticals. 2023 Feb 2;16(2):228.*
14. *Natarajan R, Anthoni Samy HN, Sivaperuman A, Subramani A. Structure-activity relationships of pyrimidine derivatives and their biological activity-a review. Medicinal Chemistry. 2023 Jan 1;19(1):10-30.*
15. *Mohana KN, Kumar BN, Mallesha L. Synthesis and biological activity of some pyrimidine derivatives. Drug invention today. 2013 Sep 1;5(3):216-22.*
16. *Yousif, O.A., Mahdi, M.F. and Raauf, A.M., 2019. Design, synthesis, preliminary pharmacological evaluation, molecular docking and ADME studies of some new pyrazoline, isoxazoline and pyrimidine derivatives bearing nabumetone moiety targeting cyclooxygenase enzyme. Journal of Contemporary Medical Sciences, 5(1).*
17. *Alheety KA, Jamel NM, Tomma JH, Alheety KA. Synthesis and biological activity of some new thiazolidinone derivatives. Sys Rev Pharm. 2020 Mar 1;11:490-4.*
18. *Mech D, Kurowska A, Trotsko N. The bioactivity of thiazolidin-4-ones: A short review of the most recent studies. International Journal of Molecular Sciences. 2021 Oct 26;22(21):11533.*
19. *Taha DE, Raauf AM, Ali KF. Design, Synthesis, Characterization, Biological Activity and ADME Study of New 5-arylidene-4-Thiazolidinones Derivatives Having. Al Mustansiriyah Journal of Pharmaceutical Sciences. 2019 Dec 1;19(4):77-88.*
20. *Azevedo-Barbosa H, Dias DF, Franco LL, Hawkes JA, Carvalho DT. From antibacterial to antitumour agents: a brief review on the chemical and medicinal aspects of sulfonamides. Mini Reviews in Medicinal Chemistry. 2020 Nov 1;20(19):2052-66.*
21. *Tačić A, Nikolić V, Nikolić L, Savić I. Antimicrobial sulfonamide drugs. Advanced technologies. 2017;6(1):58-71.*
22. *Raauf AM, Rasheed HA, Abdulhaleem F. Novel antimicrobial sulfonamides derived from nabumetone. Organic Preparations and Procedures International. 2020 Nov 16;53(1):95-9.*
23. *Dixit D, Verma PK, Marwaha RK. A review on 'triazoles': Their chemistry, synthesis and pharmacological potentials. Journal of the Iranian Chemical Society. 2021 Oct;18(10):2535-65.*
24. *Sahu JK, Ganguly S, Kaushik A. Triazoles: A valuable insight into recent developments and biological activities. Chinese journal of natural medicines. 2013 Sep 1;11(5):456-65.*
25. *Karim HA, Raauf AM, Ali KF. Synthesis and preliminary pharmacological evaluation of some new triazole derivatives bearing nabumetone moiety targeting cyclooxygenase enzyme. Systematic Reviews in Pharmacy. 2021 Jan 1;12(1):190-5.*
26. *Alawad, K.M., Mahdi, M.F. and Raauf, A.M., 2021. Molecular docking, synthesis, characterization and adme studies of some new five-member ring heterocyclic compounds with in vitro antiproliferative evaluation. Journal of Hunan University (Natural Science Edition), 48(9).*
27. *Karim HA, Raauf AM, Ali KF. Synthesis and preliminary pharmacological evaluation of some new pyrimidine derivatives bearing nabumetone moiety targeting cyclooxygenase enzyme. HIV Nursing. 2023 Jan 19;23(2):457-62.*

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28. *De S, SK AK, Shah SK, Kazi S, Sarkar N, Banerjee S, Dey S. Pyridine: the scaffolds with significant clinical diversity. Rsc Advances. 2022;12(24):15385-406.*
29. *Patil P, Sethy SP, Sameena T, Shailaja K. Pyridine and its biological activity: a review. Asian Journal of Research in Chemistry. 2013;6(10):888-99.*
30. *Jameel BK, Raauf AM, Abbas WA. Synthesis, characterization, molecular docking, in silico ADME study, and in vitro cytotoxicity evaluation of new pyridine derivatives of nabumetone. Al Mustansiriyah Journal of Pharmaceutical Sciences. 2023 Jul 20;23(3):250-62.*