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**Review Article**

# Nabumetone Derivatives Synthesized Over the Past Decade a Comprehensive Review

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**Abstract:** The modification of approved drugs is an established medicinal-chemistry approach that can reduce some of the uncertainty associated with completely new chemical entities while providing opportunities to improve activity or introduce additional biological effects. Nabumetone is a non-acidic non-steroidal anti-inflammatory prodrug used mainly for painful inflammatory disorders such as osteoarthritis and rheumatoid arthritis. During the last decade, its chemically accessible framework has been employed in the synthesis of structurally diverse derivatives containing pyrazoline, isoxazoline, pyrimidine, thiazolidinone, sulfonamide, triazole, pyridine, and other five-membered heterocyclic systems. The reported compounds exhibited anti-inflammatory, antibacterial, antifungal, antiproliferative, and anticancer activities. This review summarizes their synthetic relationships, structural diversity, biological importance, and the principal considerations that should guide further investigation of nabumetone-derived compounds.

**Keywords:** Nabumetone, Non-Steroidal Anti-Inflammatory Drugs, Anti-Inflammatory Activity, Anticancer Activity, Antibacterial Activity, Heterocyclic Derivatives.

## INTRODUCTION

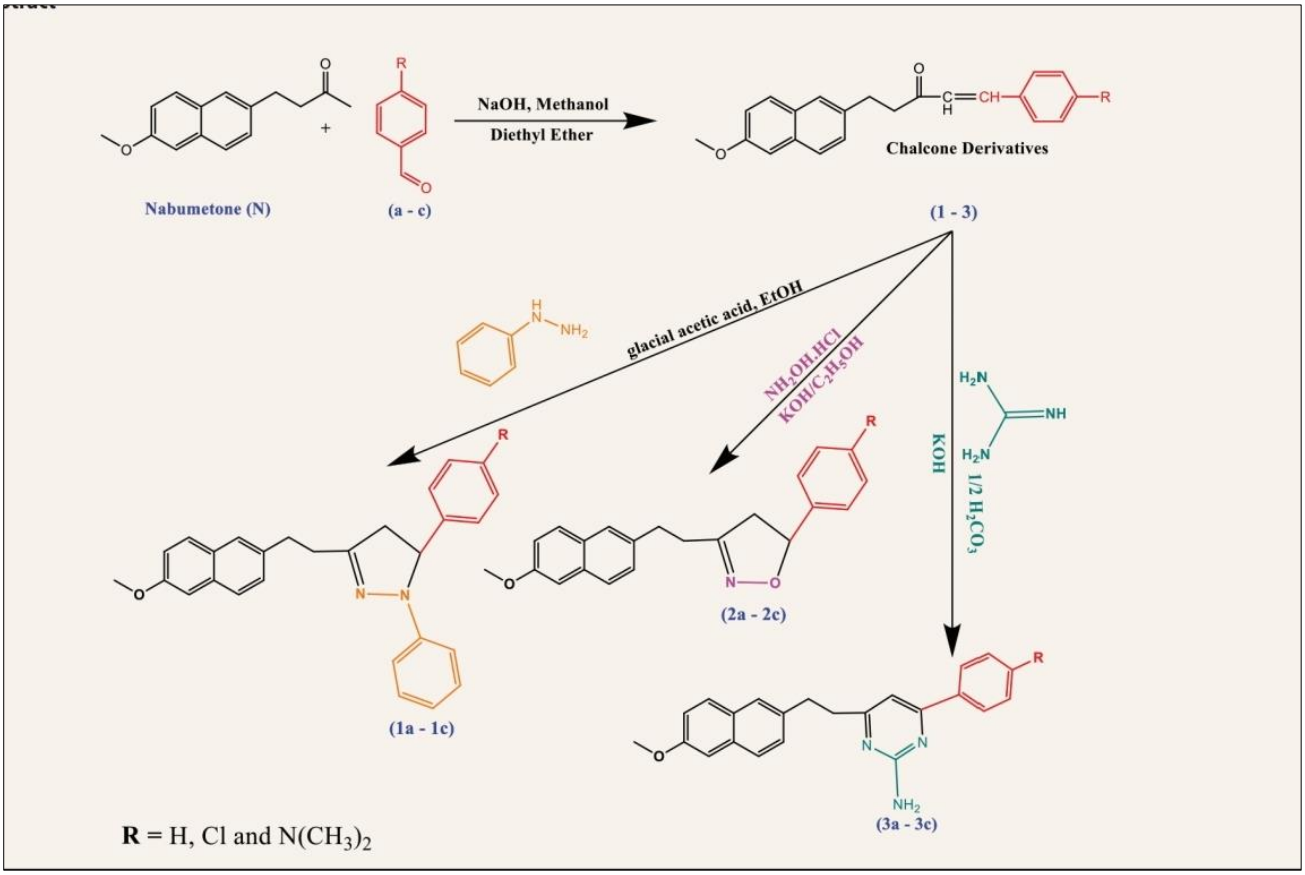
Nabumetone is a non-steroidal anti-inflammatory prodrug whose therapeutic action is mainly attributed to the active metabolite 6-methoxy-2-naphthylacetic acid (6-MNA). Following oral absorption, the non-acidic parent drug undergoes extensive first-pass metabolism, producing 6-MNA as the major circulating active species. This metabolite is a more effective cyclooxygenase inhibitor than nabumetone itself and shows comparatively greater inhibition of COX-2 under relevant conditions [1, 2]. Clinically, nabumetone is used primarily to relieve pain and inflammation associated with arthritic disorders [3]. Its non-acidic parent structure, prodrug behavior, and the absence of substantial biliary secretion of 6-MNA have been proposed as factors contributing to its gastrointestinal tolerability [4].

NSAIDs are widely prescribed for acute pain, fever, and chronic inflammatory diseases, including rheumatoid arthritis [5]. Their main pharmacological effect results from inhibition of cyclooxygenase enzymes, particularly COX-1 and COX-2, which decreases the biosynthesis of prostaglandins involved in pain and inflammation [7, 8]. Although this mechanism explains their efficacy, it also contributes to adverse effects involving the gastrointestinal tract, kidneys, and other organs [6-9]. Gastrointestinal injury may range from dyspepsia and mucosal irritation to ulceration, bleeding, or perforation. Strategies such as lowering the NSAID dose or using proton-pump inhibitors can reduce, but not completely remove, these risks [9].

The medicinal-chemistry modification of nabumetone therefore has two broad aims: to enhance or better direct its anti-inflammatory action and to exploit its aromatic ketone framework as a starting point for derivatives with different biological activities. The naphthalene ring provides a hydrophobic region, whereas the side chain can be transformed into conjugated intermediates and several heterocyclic systems. The following studies illustrate how these transformations have been used to create new chemical series while retaining a recognizable nabumetone-derived moiety.

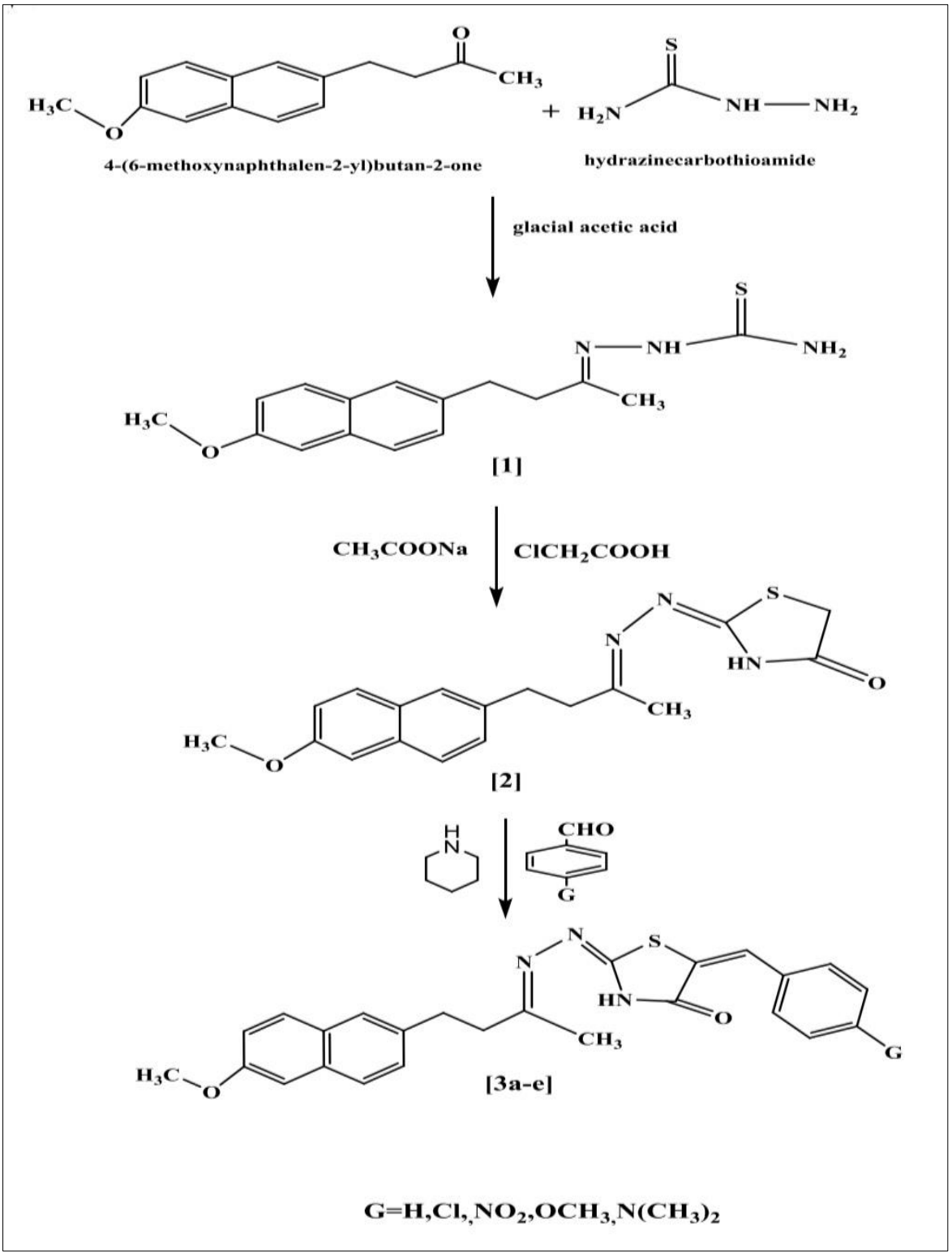
Pyrazolines are important five-membered nitrogen-containing heterocycles. Considerable interest in this class arises from the antibacterial, antimycobacterial, antifungal, anti-amoebic, anti-inflammatory, analgesic, antidepressant, and anticancer activities reported for many substituted pyrazolines [10, 11]. Isoxazoles and isoxazolines are related five-membered rings containing both nitrogen and oxygen, and members of these classes have demonstrated antibacterial, antifungal, anti-inflammatory, antitubercular, anticancer, and antineoplastic properties [12, 13]. Pyrimidine is a six-membered nitrogen-containing heterocycle found in vitamin B1 and in the nucleobases uracil, thymine, and cytosine. Pyrimidine derivatives are important in pharmaceutical and agrochemical research and have been associated with anti-inflammatory, antitumor, antiviral, anticancer, and antibacterial effects [14-15].

In 2019, Yousif and co-workers described nabumetone-related derivatives containing pyrazoline, isoxazoline, and pyrimidine rings [16]. A chalcone-type intermediate served as a versatile precursor for ring formation, allowing several heterocyclic pharmacophores to be introduced into the nabumetone framework. The study combined synthesis and characterization with molecular docking, ADME prediction, and preliminary pharmacological evaluation. The reported findings indicated that selected derivatives produced stronger anti-inflammatory effects than the parent drug. These observations support the idea that heterocyclic modification may change molecular recognition and physicochemical behavior; however, the activity of each derivative remains dependent on its complete substitution pattern rather than on the heterocyclic ring alone.



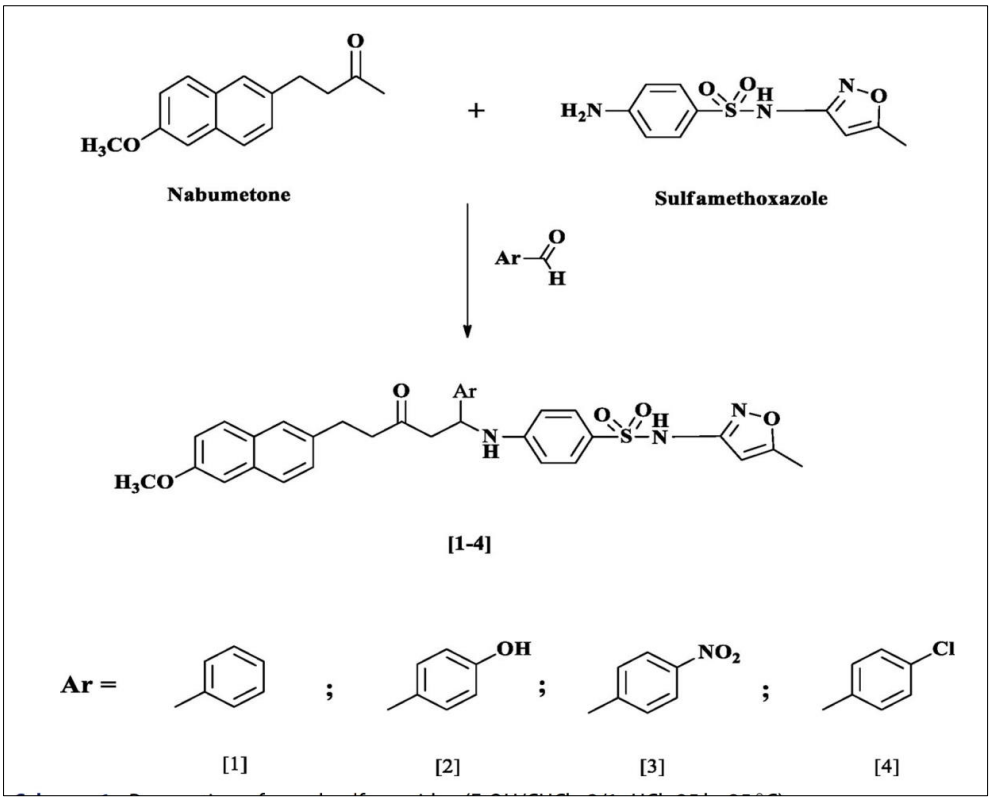

**Scheme 1: Synthesis of pyrazoline, isoxazoline, and pyrimidine derivatives bearing a nabumetone moiety [16]**

Thiazolidinones represent another biologically important heterocyclic family. Their ring system contains sulfur at position 1, nitrogen at position 3, and a carbonyl group that may occur at position 2, 4, or 5. The 4-thiazolidinone nucleus has attracted sustained attention because derivatives of this scaffold have been investigated for antiviral, antibacterial, anti-inflammatory, and antitubercular properties [17, 18]. A 2019 study used a nabumetone-related precursor to prepare a series of 5-arylidene-4-thiazolidinone derivatives [19]. The synthesized compounds were evaluated for antibacterial and antifungal effects, and some showed measurable activity. The variation in activity across aromatic substituents suggests that electronic character, lipophilicity, and molecular size may influence interaction with microbial targets and passage through microbial membranes.



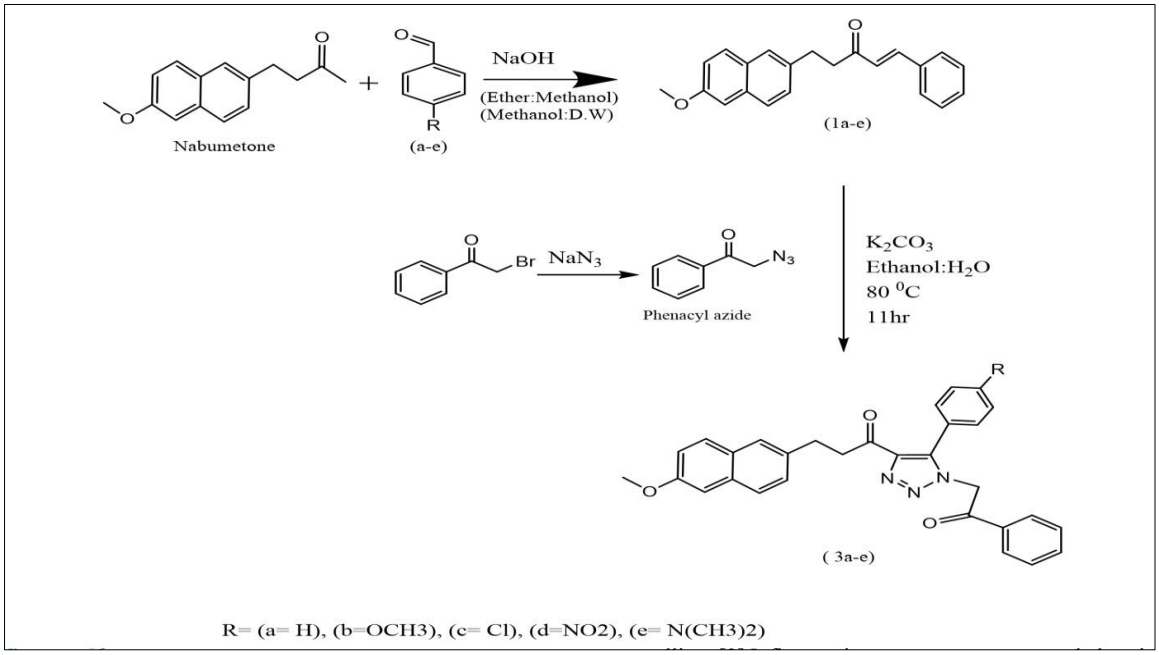

**Scheme 2: Synthesis of new 4-thiazolidinone derivatives from nabumetone [19]**

Sulfonamides are among the most historically important antimicrobial drug classes. Their core pharmacophore contains a sulfonamide group, commonly connected to an aromatic system, and many classical antibacterial sulfonamides also contain a para-amino group. Beyond antibacterial use, sulfonamide-containing compounds have been studied for antitumor, antioxidant, antibacterial, and antifungal effects [20, 21]. In 2020, nabumetone-derived sulfonamides were synthesized and screened for antimicrobial activity [22]. Some members of the series displayed favorable antibacterial effects when compared with sulfamethoxazole. Linking the nabumetone-derived region with a sulfonamide pharmacophore created hybrid molecules that combine a hydrophobic aromatic portion with a strongly polarized sulfur-containing group.



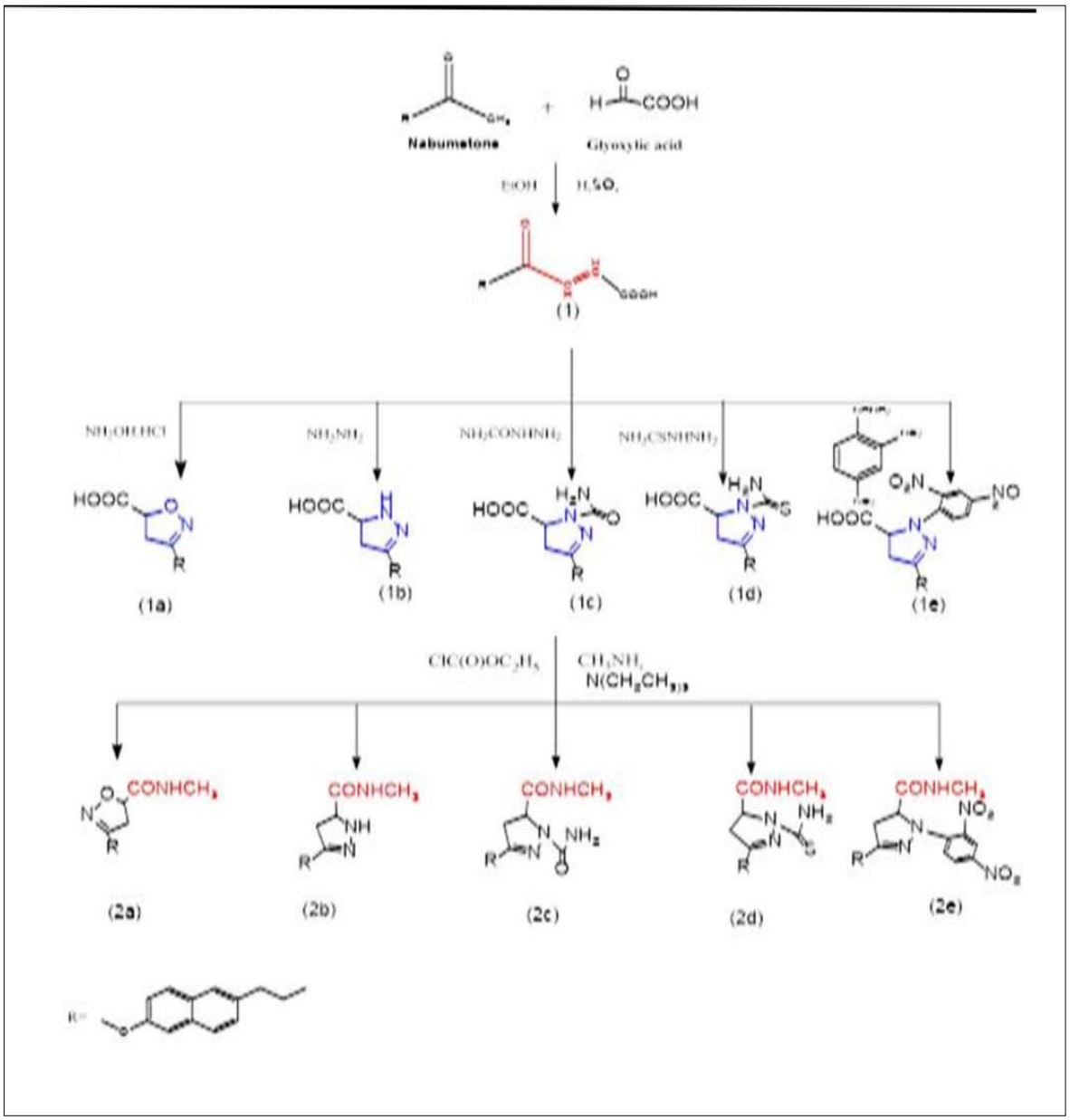

**Scheme 3: Synthesis of sulfonamide derivatives from nabumetone [22]**

Triazoles are five-membered aromatic heterocycles composed of three nitrogen atoms and two carbon atoms. Their high nitrogen content and stable aromatic structure allow them to interact with a variety of enzymes and receptors. The triazole nucleus occurs in compounds reported to possess antibacterial, antifungal, anticancer, antioxidant, antiviral, anti-inflammatory, analgesic, antiepileptic, antihypertensive, antidepressant, antidiabetic, anxiolytic, and antitubercular activities [23, 24]. In 2021, Karim and co-workers prepared triazole derivatives bearing a nabumetone moiety and examined their potential as cyclooxygenase-targeted anti-inflammatory compounds [25]. The preliminary results suggested that triazole incorporation could improve anti-inflammatory activity, while differences among individual analogues emphasized the importance of substituent identity and overall molecular architecture.



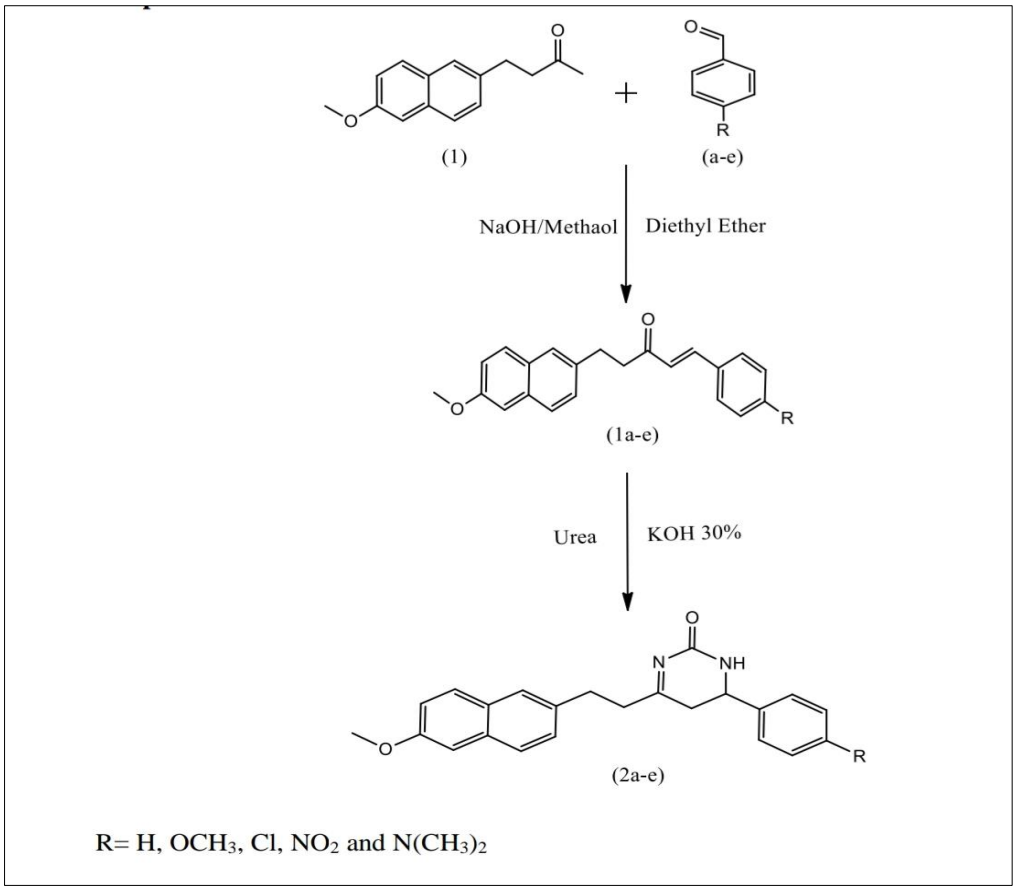

**Scheme 4: Synthesis of new triazole derivatives bearing the nabumetone moiety [25]**

Another investigation published in 2021 extended nabumetone chemistry toward several five-membered heterocyclic systems and related amide derivatives [26]. The compounds were designed with the aid of molecular docking and were evaluated for antiproliferative activity against the A549 lung cancer cell line. Selected derivatives produced promising inhibitory effects, and one compound was reported to show an IC50 value comparable with the reference drug used in that study. These findings broaden the possible biological relevance of nabumetone-derived scaffolds beyond inflammation, although cell-based activity should be supported by target-specific experiments, testing against nonmalignant cells, and additional mechanistic studies.



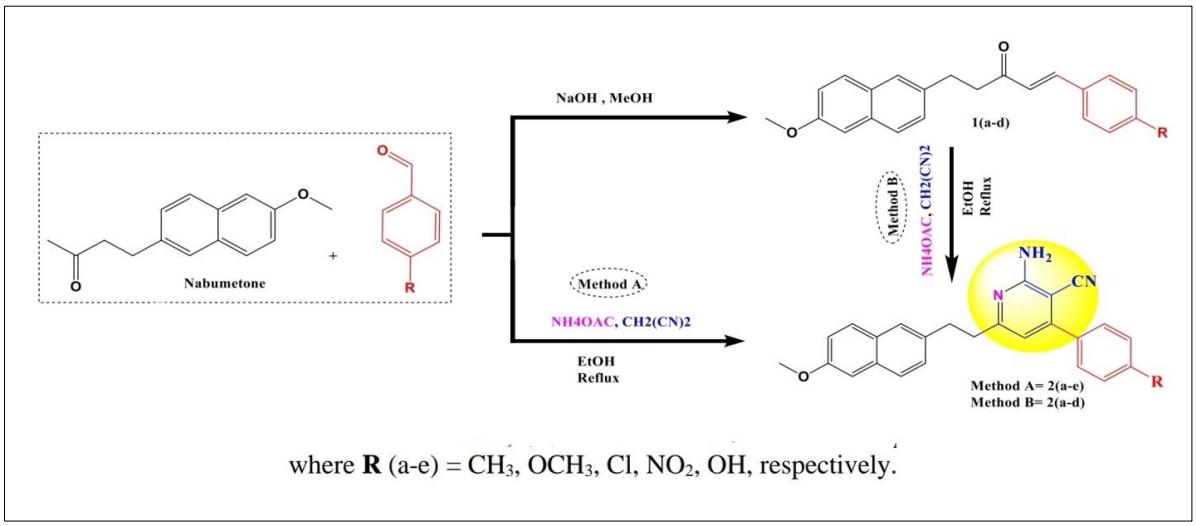

**Scheme 5; Synthesis of five-membered heterocyclic compounds derived from nabumetone [26]**

Further work published in 2023 returned to pyrimidine-containing nabumetone derivatives [27]. The pyrimidine ring offers two nitrogen atoms capable of serving as hydrogen-bond acceptors and provides a relatively rigid aromatic framework that can support different substituents. The reported pharmacological evaluation indicated enhanced anti-inflammatory activity for selected derivatives. When considered together with the earlier pyrimidine series [16], these results suggest that the pyrimidine scaffold is a useful direction for nabumetone modification, although broader compound series and direct measurements of COX-1 and COX-2 inhibition would be needed to establish a detailed structure-activity relationship.




**Scheme 6: Synthesis of pyrimidine derivatives from nabumetone [27]**

Pyridine is an aromatic benzene bioisostere in which one carbon-hydrogen unit is replaced by nitrogen. This structural change preserves aromaticity while adding a basic, hydrogen-bond-accepting site and altering the electronic and physicochemical properties of the ring. Pyridine derivatives are widely represented among pharmaceuticals and agrochemicals and have been associated with antimicrobial, antiviral, anticancer, antidiabetic, antifungal, anti-inflammatory, and antimycobacterial activities [28, 29]. In 2023, Jameel and co-workers synthesized new pyridine derivatives of nabumetone and evaluated them through molecular docking, in silico ADME prediction, and in vitro cytotoxicity testing [30]. Some compounds showed promising activity against lung cancer cells. The 2-amino and 3-cyano functions of the pyridine system may contribute useful interaction sites, while aromatic substituents can modify hydrophobic and electronic properties.




**Scheme 7: Synthesis of new pyridine derivatives of nabumetone [30]**

A comparison of the seven reported synthetic directions shows a consistent medicinal-chemistry strategy. The methoxy-substituted naphthalene portion of nabumetone is generally retained as a hydrophobic structural unit, whereas the carbonyl-containing side chain is modified to generate chalcones, hydrazones, sulfonamide hybrids, or heterocyclic rings. Pyrazoline, isoxazoline, pyrimidine, and triazole derivatives were primarily examined for anti-inflammatory potential [16-27], whereas thiazolidinone and sulfonamide analogues were directed toward antimicrobial activity [19-22]. Other five-membered rings and pyridine systems extended the biological scope toward antiproliferative and cytotoxic activity [26-30]. Thus, the reviewed work demonstrates that changing the side-chain pharmacophore can redirect the biological profile while preserving the central nabumetone-derived aromatic framework.

The collected studies also indicate that the biological response cannot be attributed to the presence of a heterocyclic ring alone. Substituents attached to each ring influence electron distribution, steric requirements, lipophilicity, solubility, and the ability of the compound to form interactions with a biological target. Molecular docking and predicted ADME properties were useful for preliminary prioritization in several reports [16-30], but these computational findings are most informative when considered together with experimental pharmacological data. The available results therefore provide a foundation for future systematic structure-activity studies rather than a final ranking of the derivative classes.

# CONCLUSION

Nabumetone is established as a non-steroidal anti-inflammatory prodrug, but its structure also provides a useful platform for the preparation of chemically diverse derivatives. During the reviewed period, the nabumetone framework was incorporated into pyrazoline, isoxazoline, pyrimidine, thiazolidinone, sulfonamide, triazole, pyridine, and other five-membered heterocyclic systems. The reported compounds displayed enhanced anti-inflammatory effects or additional antibacterial, antifungal, antiproliferative, and anticancer activities. Collectively, the studies demonstrate the versatility of nabumetone as a starting scaffold. Nevertheless, most findings remain preliminary, and future work should include larger and systematically substituted compound series, quantitative biological assays, target confirmation, toxicity testing, and pharmacokinetic evaluation.

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