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: 8 | August 2024 - Peer Reviewed Journal

MINI REVIEW ON PIROXICAM DERIVATIVES SYNTHESIS IN THE LAST 10 YEARS

Hussien Ali Karim[a*], Mohammed Hasan AL-Dahlaki[b]
[a] *Department of Pharmaceutical Chemistry, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq.*
[b] *Department of Pharmaceutical Chemistry, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq.*

**Corresponding Author.*

Article DOI: https://doi.org/10.36713/epra17905
DOI No: 10.36713/epra17905

ABSTRACT
Today the focus is on reducing the likelihood of creating a potentially hazardous substance by concentrating on the synthesis of derivatives from approved medications. Non-steroidal anti-inflammatory medicines (NSAIDs) are a popular class of medications used to treat painful arthritis. The medication piroxicam is a non-steroidal anti-inflammatory. Piroxicam has been the basis for the synthesis of several derivatives with various biological activity in recent years. This mini review aims to describe the biological activities of these derivatives that have emerged in the previous ten years.

KEY WORDS: *piroxicam , non-steroidal anti-inflammatory, anti-glycation , anti-nociceptive , anti-HIV.*

INTRODUCTION

The first medication in the "oxicam" class, piroxicam (4-hydroxy-2-methyl-2H-1,2-benzothiazine-1-(N-(2-pyridinyl)carboxamide)-1,1-dioxide) is an NSAID that was discovered in 1972 and released into the market by Pfizer in 1982. [(1)] Used in soft-tissue disorders, acute gout, postoperative pain, rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gout, and rheumatoid arthritis, including juvenile idiopathic arthritis. However, systemic usage in Europe is currently limited to chronic painful and inflammatory conditions. [(2,3)] An enolized β-dicarbonyl moiety is responsible for the somewhat acidic nature of oxicams, a class of NSAIDs that are defined by the absence of a carboxyl group. They are structurally either thienothiazine-3-carboxylic acid amides or benzothiazine-3-carboxylic acid amides (e.g., meloxicam, piroxicam). It has been demonstrated that piroxicam and meloxicam block angiogenesis and the proliferation of cancer cells, as well as the emergence of secondary tumors caused by surgery. [(4)] Piroxicam belongs to a class of pharmaceuticals called non-steroidal anti-inflammatory drugs (NSAIDs), which are widely used to treat inflammatory illnesses that are both acute (such as fever and discomfort) and chronic (such as rheumatoid arthritis). [(5)] Additionally, it has been demonstrated that NSAIDs offer defense against a number of dangerous diseases, including cancer and heart attacks. [(6)] Non-steroidal anti-inflammatory medications (NSAIDs) work by inhibiting the cyclooxygenase enzyme (COX1,2), which is essential for the manufacture of prostaglandins, which play a major role in inflammation. [(7-10)] Non-steroidal anti-inflammatory drugs (NSAIDs) have the potential to cause peptic ulcer disease, small bowel enteropathy, and symptoms in the foregut even though they are often used. Such an iatrogenic harm may be made worse by gastrointestinal tract perforations and hemorrhage. Lowering the dosage of NSAIDs or taking them in conjunction with proton pump inhibitors (PPIs) decreases the risk of issues, dyspepsia, and peptic ulcer therapy. [(11)] Improved bioavailability can result from the use of prodrugs containing ester; the ester functions are removed by either spontaneous hydrolysis or enzyme catalysis. [(12)] A paper published in 2014 stated that derivatives of piroxicam containing ester group had been synthesized and showed minimizing in the toxicity to the stomach and retention the anti-inflammatory activity by converting the enolic group to ester group. [(13)]

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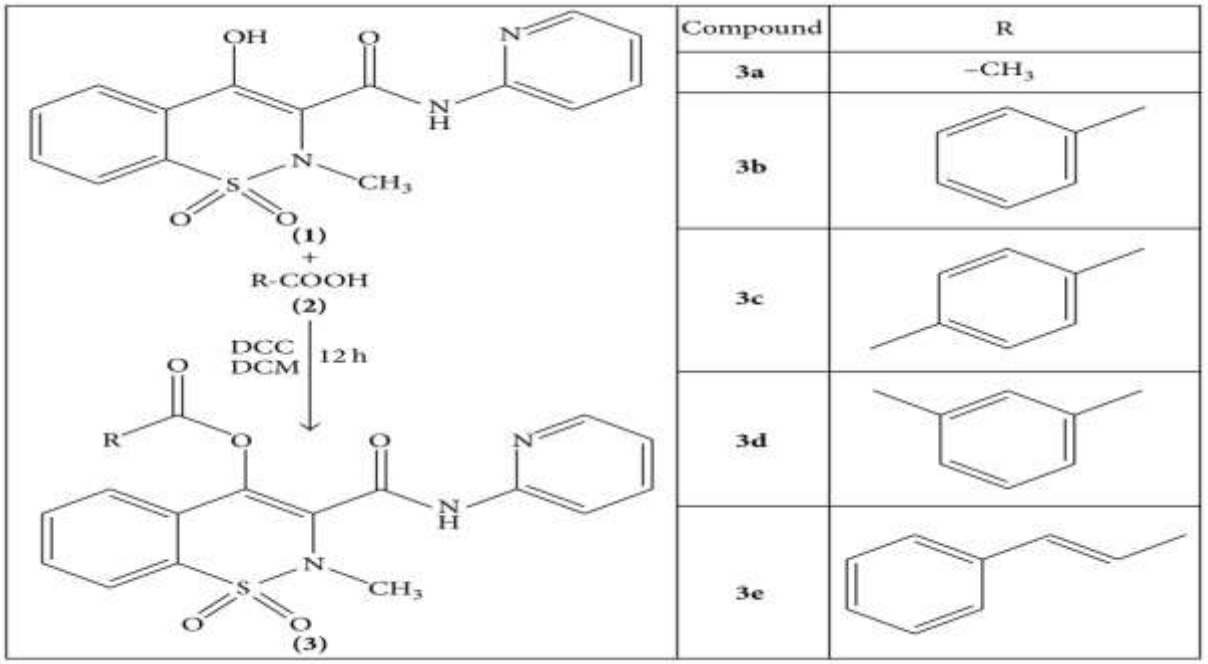
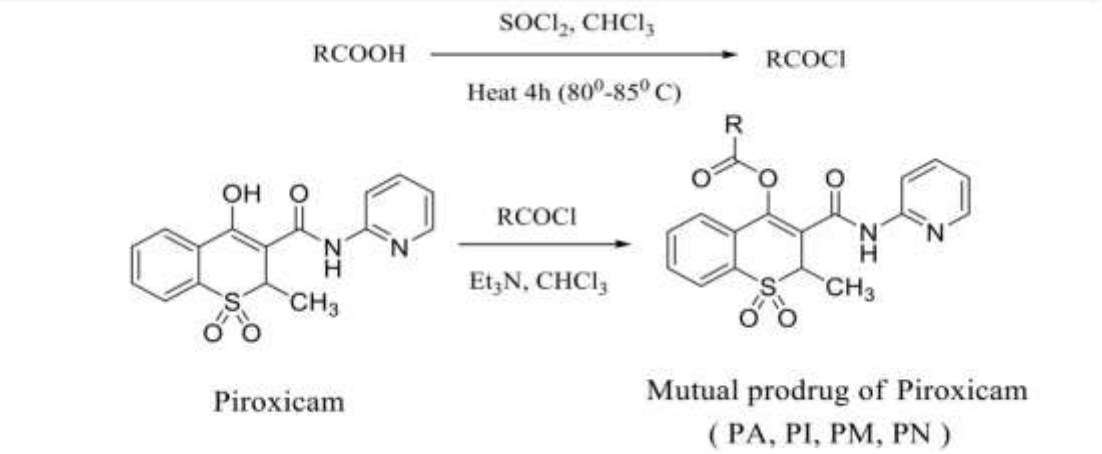


Scheme 1: Synthesis of Ester Derivatives from Piroxicam [13]

The scientific community is very interested in prodrug techniques in the difficult drug development program. Molecules having little to no biological activity on their own that activate to become pharmacologically significant are referred to as "prodrugs." After being delivered, the prodrug may undergo chemical or enzymatic processing before exhibiting pharmacological activity. Mutual prodrugs is one of the various varieties of prodrugs. The primary benefit of mutual prodrugs lies in their ability to release two or more active molecules at the same level (the target tissue) after administration and bioconversion, hence utilizing a synergistic effect. Sometimes the second pharmacophore targets a separate biological activity of the parent chemical, giving it additional benefits. Other times, it acts as a carrier to direct the parent drug to a particular region of action. [14,15] In 2016 a research article showed the synthesis of mutual prodrugs from piroxican and some of other NSAIDs. This approach increased the therapeutic effectiveness of piroxicam under two lines; firstly, masking of enolic hydroxyl group through acids and converting them to esters and secondly, utilizing the known NSAIDs for achieving the synergistic effect.[16]



Scheme 2: Synthesis of Mutual Prodrug from Piroxicam [16]

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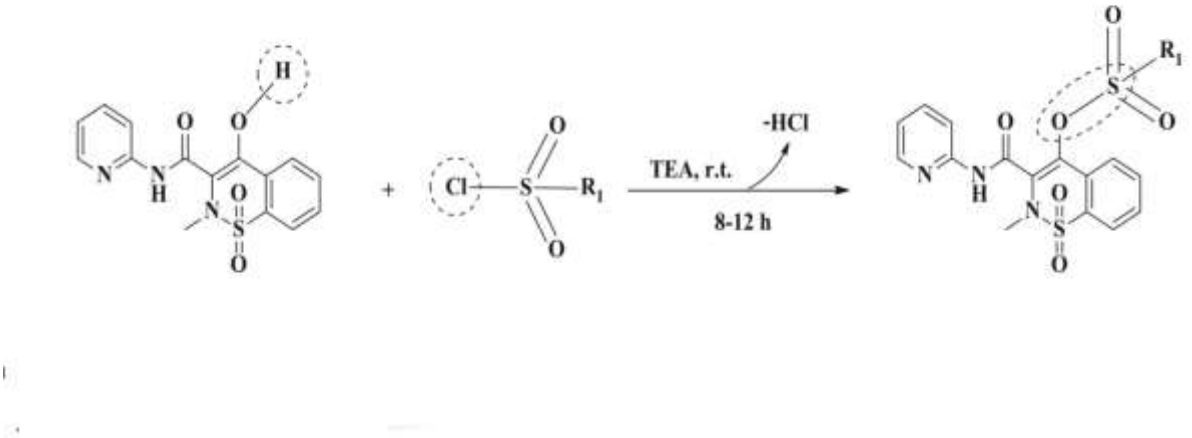
Neuropathic pain and inflammatory pain are two different conditions that can cause clinical pain. Neuropathic pain results from injury to the nerve system. The presence of spontaneous pain, hyperalgesia (an increase in reaction to noxious stimuli), and allodynia (pain in response to ordinarily harmless stimuli) are the characteristics of this type of pain. Painful stimuli are recognized by unique sensory receptors known as nociceptive receptors, and the brain receives a signal from these receptors to initiate the process of nociception, which causes pain perception. [17,18] Chronic diabetes mellitus is a highly frequent condition that is linked to non-enzymatic protein glycation and oxidative stress. Because hyperglycemia speeds up the production of advanced glycation endproducts (AGEs), it has been proposed that inhibiting AGE development could delay the onset of diabetes complications and slow down the aging process. [19,20] Sulfonates are a crucial group in chemical synthesis because they are simple to make and can be transformed into carbanions, which allows them to go through processes similar to those of aldols and alkylation. [21] In 2016 and 2021 two papers published synthesized solfonates derivatives from piroxicam act as anti-nociceptive agent or as anti-glycation agent. [22,23]



Scheme 3: Synthesis of Sulfonate Derivatives from Piroxicam. [22,23]

HIV integrase is an enzyme that is necessary for viral replication and viron generation. It integrates the double-stranded DNA product that is produced when viral RNA is reverse-transcribed into the host genome. One possible target for HIV infection treatment is the inhibition of this enzyme. [24,25] In 2022 an article published synthesized analogues of piroxicam some of them act as good anti-HIV integrase activity.[26]

CONCLUSION

piroxicam drug is a non-steroidal anti-inflammatory drug but can be used to synthesize derivatives that may improve effectiveness or give different types of activities like anti-glycation, anti-nociceptive and anti-HIV. So 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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