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

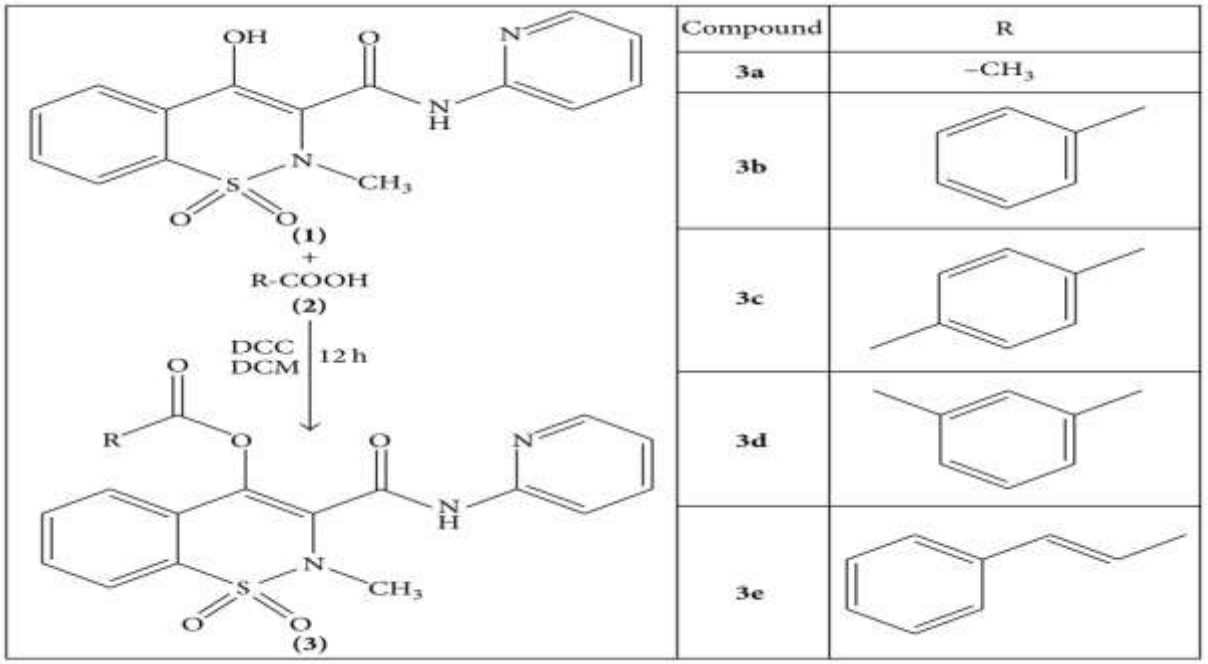
ABSTRACT
Today the focus is on reducing the likelihood of creating a potentially hazardous substance by concentrating on the synthesis of derivatives from approved medications. Non-steroidal anti-inflammatory medicines (NSAIDs) are a popular class of medications used to treat painful arthritis. The medication 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

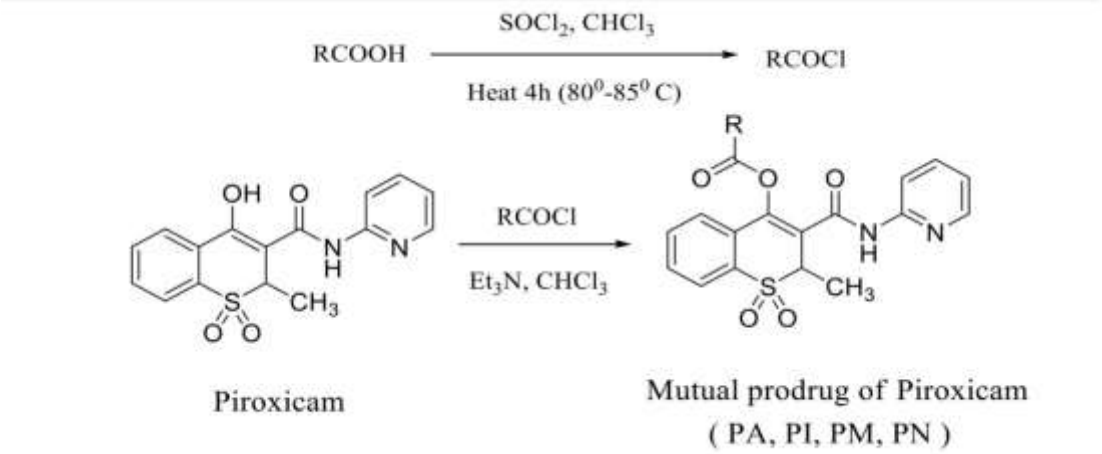
The first medication in the "oxicam" class, piroxicam (4-hydroxy-2-methyl-2H-1,2-benzothiazine-1-(N-(2-pyridinyl)carboxamide)-1,1-dioxide) is an NSAID that was discovered in 1972 and released into the market by Pfizer in 1982. [(1)] Used in soft-tissue disorders, acute gout, postoperative pain, rheumatoid 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)]

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



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

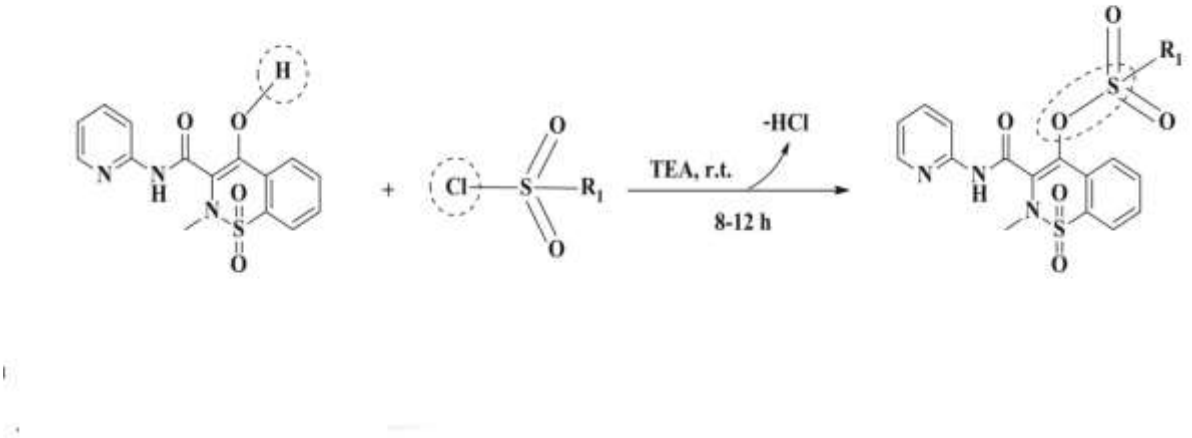
The scientific community is very interested in prodrug techniques in the difficult drug development program. Molecules having little to no biological activity on their own that activate to become pharmacologically significant are referred to as "prodrugs." After being delivered, the prodrug may undergo 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]

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

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.

REFERENCES

1. *De Miranda AS, Júnior WB, Da Silva YK, Alexandre-Moreira MS, Castro RD, Sabino JR, Lião LM, Lima LM, Barreiro EJ. Design, synthesis, antinociceptive and anti-inflammatory activities of novel piroxicam analogues. Molecules. 2012 Nov 28;17(12):14126-45.*
2. *Mostafa GA, Al-Dosseri AS, Al-Badr AA. Piroxicam. InProfiles of Drug Substances, Excipients and Related Methodology 2020 Jan 1 (Vol. 45, pp. 199-474). Academic Press.*
3. *Dimofte A, Dinu MV, Anghel N, Doroftei F, Spiridon I. Xanthan and alginate-matrix used as transdermal delivery carrier for piroxicam and ketoconazole. International Journal of Biological Macromolecules. 2022 Jun 1;209:2084-96.*

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

4. *Krzystek-Korpacka, M., Szczęśniak-Sięga, B., Szczuka, I., Fortuna, P., Zawadzki, M., Kubiak, A., Mierzchała-Pasierb, M., Fleszar, M.G., Lewandowski, Ł., Serek, P. and Jamrozik, N., 2020. L-arginine/nitric oxide pathway is altered in colorectal cancer and can be modulated by novel derivatives from oxicam class of non-steroidal anti-inflammatory drugs. Cancers, 12(9), p.2594.*
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. *Raauf AM, Rasheed HA, Abdulhaleem F. Novel antimicrobial sulfonamides derived from nabumetone. Organic Preparations and Procedures International. 2020 Nov 16;53(1):95-9.*
10. *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.*
11. *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.*
12. *Lavis LD. Ester bonds in prodrugs. ACS chemical biology. 2008 Apr 18;3(4):203-6.*
13. *Redasani VK, Shinde AB, Surana SJ. Anti-Inflammatory and Gastroprotective Evaluation of Prodrugs of Piroxicam. Ulcers. 2014;2014(1):729754.*
14. *Ciaffaglione V, Modica MN, Pittalà V, Romeo G, Salerno L, Intagliata S. Mutual prodrugs of 5-fluorouracil: From a classic chemotherapeutic agent to novel potential anticancer drugs. ChemMedChem. 2021 Dec 6;16(23):3496-512.)(Ohlan S, Nanda S, Pathak DP, Jagia M. Mutual prodrugs–A swot analysis. International Journal of Pharmaceutical Sciences and Research. 2011 Apr 1;2(4):719.*
15. *Nudelman A. Mutual Prodrugs-Codrugs. Current Medicinal Chemistry. 2023 Nov 1;30(38):4283-339.*
16. *Redasani VK, Bhalerao OC, Kalaskar MG, Surana SJ. Synthesis and evaluation of novel mutual prodrugs of Piroxicam. Journal of Pharmaceutical Chemistry. 2017 Jan 31;4(1):1-4.*
17. *Cury Y, Picolo G, Gutierrez VP, Ferreira SH. Pain and analgesia: The dual effect of nitric oxide in the nociceptive system. Nitric oxide. 2011 Oct 30;25(3):243-54.*
18. *Willis WD. Nociceptive pathways: anatomy and physiology of nociceptive ascending pathways. Philosophical Transactions of the Royal Society of London. B, Biological Sciences. 1985 Feb 19;308(1136):253-68.*
19. *Ramkissoon JS, Mahomoodally MF, Ahmed N, Subratty AH. Antioxidant and anti–glycation activities correlates with phenolic composition of tropical medicinal herbs. Asian Pacific journal of tropical medicine. 2013 Jul 1;6(7):561-9.*
20. *Chinchansure AA, Korwar AM, Kulkarni MJ, Joshi SP. Recent development of plant products with anti-glycation activity: a review. RSC Advances. 2015;5(39):31113-38.*
21. *Simpkins NS. Sulphones in organic synthesis. Elsevier; 2013 Oct 22.*
22. *Ullah S, Saeed M, Halimi SM, Fakhri MI, Khan KM, Khan I, Perveen S. Piroxicam sulfonates biology-oriented drug synthesis (BIODS), characterization and anti-nociceptive screening. Medicinal Chemistry Research. 2016 Jul;25:1468-75.*
23. *Ullah S, Saeed M, Ullah I, Halimi SM, Khan KM, Jahan S, Mohani SN, Khan S, Khan A. Synthesis and characterization of novel piroxicam derivatives and their antiglycation activity. Journal of Molecular Structure. 2021 Sep 5;1239:130470.*
24. *Kim HK, Lee HK, Shin CG, Huh H. HIV integrase inhibitory activity of Agastache rugosa. Archives of Pharmacal Research. 1999 Oct;22:520-3.*
25. *Sanna C, D'Abrosca B, Fiorentino A, Giammarino F, Vicenti I, Corona A, Caredda A, Tramontano E, Esposito F. HIV-1 Integrase Inhibition Activity by Spiroketals Derived from Plagius flosculosus, an Endemic Plant of Sardinia (Italy) and Corsica (France). Pharmaceuticals. 2023 Aug 8;16(8):1118.*
26. *Imani A, Soleymani S, Vahabpour R, Hajimahdi Z, Zarghi A. Piroxicam analogs: design, synthesis, docking study and biological evaluation as promising anti-HIV-1 agents. Medicinal Chemistry. 2022 Feb 1;18(2):209-19.*