زانکۆی سەلاحەدین - هەولێر
Salahaddin University-Erbil

Synthesis, and Pharmaceutical Applications of Several Mefenamic acid Derivatives

Research Project
Submitted to the department of (Chemistry) in partial fulfillment of the Requirement for the degree of B.Sc. In chemistry
Chemistry department

by:

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Supervisor recommendation

I am the student's supervisor, [**Gardin Abdulrahman Qadir]**.

I support that the student has completed all the requirements for submitting the research drawn entitled [**Synthesis, and Pharmaceutical Applications of Several Mefenamic acid Derivatives]**according to the numbered administrative order 3/1/5/1972 on 9th oct. 2022 in accordance with the instructions of Salahaddin university quality assurance and it is ready for discussion.

Supervisor full name with (**Assist. Laect.Hawzhin Yassin Hussen**)

Signature with date :2023-04-05

project lecturer
Dr. Dler D. Kurda

Dedication

I sincerely dedicate this study to my beloved parents, whose kindness I will always be unable to repay. Likewise, to all the professors who have grown weary of me ever since I was a student. And devoted to all of my friends, family, and loved ones.

Acknowledgment

First of all, thank God for helping us to conduct this research that nothing can be done without God's help, Then I would like to thank Assist. Laect. Hawzhin Yassin Hussen and Dr. Dler D.Kurda for their support and help in carrying out this project, and finally, thank you to all those who helped me, even if it was a little thing. Finally, thank you.

Abstract

This research is consisting of the synthesis and pharmaceutical applications of several derivatives of Mefenamic acid. The synthesis of these derivatives involved the modification of the carboxylic acid functional group, the substitution of the phenyl ring, and the introduction of heterocyclic moieties. The pharmaceutical applications of the derivatives include their use as anti-inflammatory, analgesic, and antipyretic agents. In addition, some derivatives have exhibited potential for the treatment of other conditions such as cancer, Alzheimer's disease, and cardiovascular diseases. To overcome these limitations, several Mefenamic acid derivatives were synthesized using different chemical reactions. These derivatives were synthesized anti-inflammatory activity, and analgesic effects.

Keyword: mefenamic acid, synthesis of Derivatives, anti-inflammatory**.**

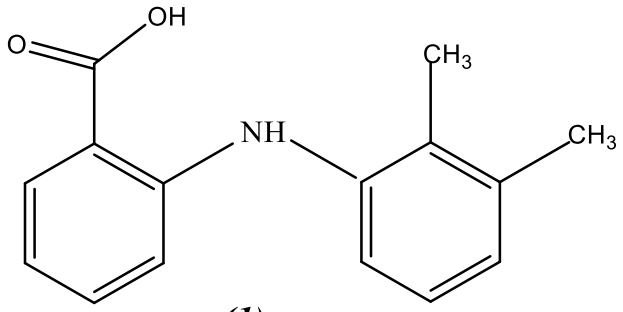
1..1. Introduction

Mefenamic acid is a non-steroidal anti-inflammatory drug (NSAID) that is widely used for the treatment of pain and inflammation associated with a variety of conditions. However, due to its limited aqueous solubility and bioavailability, the pharmaceutical applications of Mefenamic acid are restricted. To overcome these limitations, researchers have synthesized several Mefenamic acid derivatives with improved physicochemical and pharmacological properties.

The synthesis of Mefenamic acid derivatives involves the modification of the parent compound's structure to enhance its solubility, stability, and pharmacological properties. These modifications can be achieved by introducing functional groups, altering the position of substituents, or by changing the heterocyclic ring system. The resulting compounds may exhibit enhanced anti-inflammatory, analgesic, and antipyretic activities, making them potential candidates for the development of new drugs.

Pharmaceutical applications of Mefenamic acid derivatives include the treatment of various inflammatory diseases such as rheumatoid arthritis, osteoarthritis, and menstrual cramps. Some Mefenamic acid derivatives have also been shown to possess anticancer and antiviral activities. Due to their anti-inflammatory, analgesic, and antipyretic effects, nonsteroidal anti-inflammatory medicines (NSAIDs) are among the most commonly prescribed medications and mean Nonsteroidal anti-inflammatory drugs.(Burian and Geisslinger, 2005)

Mefenamic acid (**1**), an NSAID sold as Ponstel in the US, is approved for the treatment of inflammatory illnesses as well as menstrual cramps, migraines, and rheumatoid arthritis. However, the usage of Mefenamic acid is limited because of its low solubility and side effects, mostly gastrointestinal negative effects, such as bleeding, ulceration, or perforation of the stomach or intestines, which can occasionally be fatal.(Fiorucci et al., 2007)



(1)

A subset of these medications is available without a prescription in various countries. The therapeutic mode of action of NSAIDs is greatly attributed to an inhibitory effect on cyclooxygenase (COX), the essential enzyme for the production of prostaglandins, the substances that take part in inflammatory processes. NSAIDs are weak organic acids that are grouped into a few classes based on their various chemical structures. Because the majority of non-steroidal anti

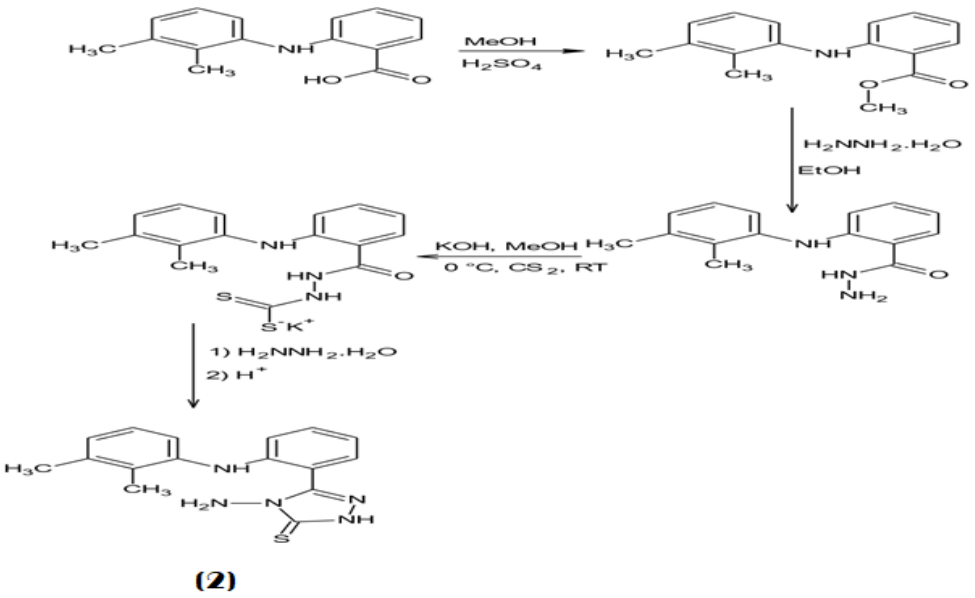
inflammatory drugs block both of the two different forms of COX (COX2 is responsible for inflammation and fiver, whereas COX1 is incurred for stomach protection from natural acids during the digestion), the main potential health issues from using these medications are linked to gastrointestinal side-effects, as well as adverse effects on the level of the cardiovascular system and kidneys.(Burian and Geisslinger, 2005)

1.2. History

It gets its name from the chemical compound dimethyl phenyl amino benzoic acid. In the 1960s, Parke-Davis found it and commercialized it. It was made generic in the 1980s and is sold all over the world under numerous brand names, including Metal. Mefenamic acid is an NSAID used to treat essential dysmenorrhea and mild to moderate pain lasting for around seven days. Mefenamic acid is a member of the fen mate family of nonsteroidal painkillers and is an anthracitic corrosive derivative (NSAIDs). It demonstrates reducing, numbing, and antipyretic exercises. Mefenamic corrosive represses prostaglandin synthetize, just like other NSAIDs. (Branka B.2020)

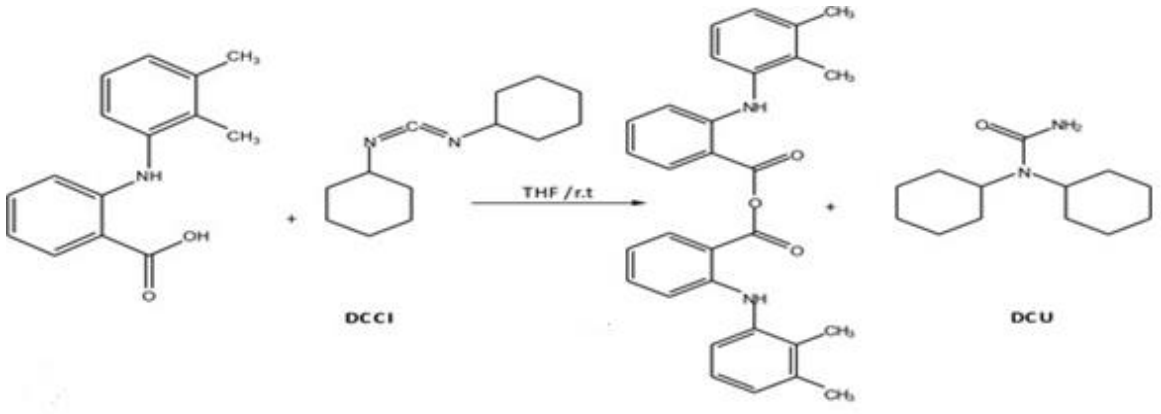
2. Synthesis of some Mefenamic acid derivatives:

This compound **(2)** was synthesized starting from mefenamic acid (MFA) according to the following general steps and use as a ligand Scheme 1.(Ahmadi, 2015)

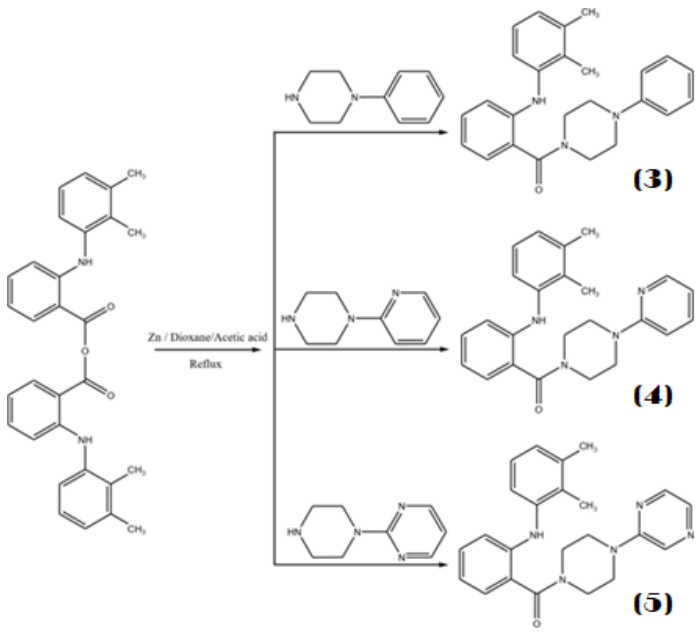


Scheme 1. Synthesis of the compound **(2)**.

New piperazine derivatives of Mefenamic acid (3), (4) & (5) were successfully synthesized as shown in Schemes 2 and 3. The conversion of the carboxylic acid group of Mefenamic acid to benzamine group by conjugating the selected moiety of the heterocyclic compounds may produce new nonsteroidal **anti-inflammatory agents.** (Ahmadi, 2015)

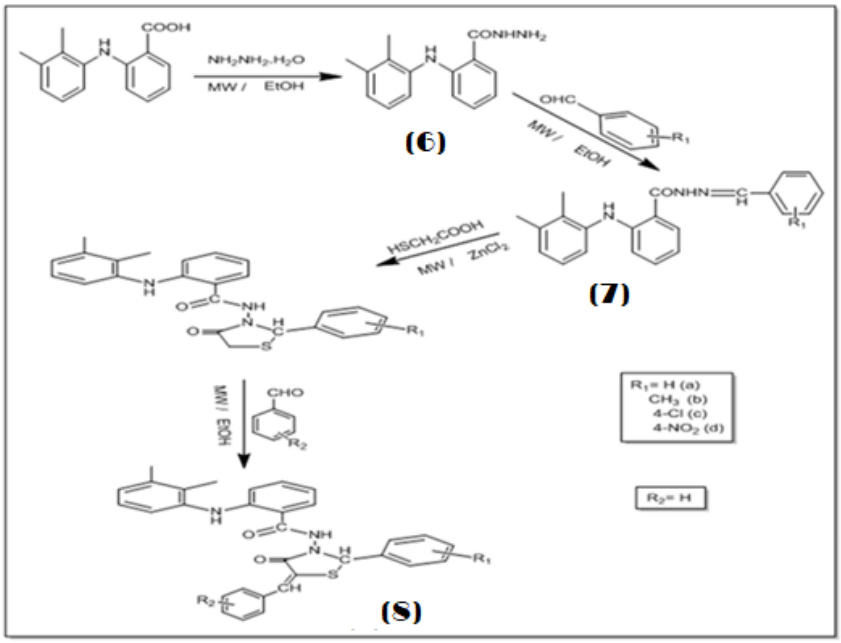


Scheme2.synthesis of intermediate



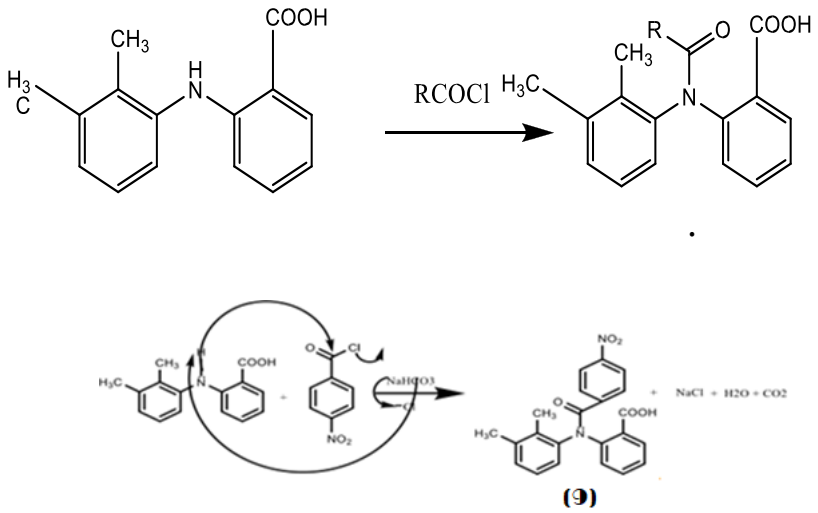
Scheme 3. Scheme of the synthesis of the final compounds (**3,4&5**)

The reaction carried out by microwave oven, the first step included replacement hydroxyl group of acid by hydrazine, then the aromatic aldehyde were condensed with the acyl hydrazide compound to give Schiff base **(6)** was reacted with mercaptan acetic acid to produce five membered heterocyclic compound of thiazolidine **(8)** and then condensate with benzaldehyde to give chalcone **(7)** compounds then this compound **(8)** was used as a **antibacterial activity**.(Al-Dulimia et al., 2016)



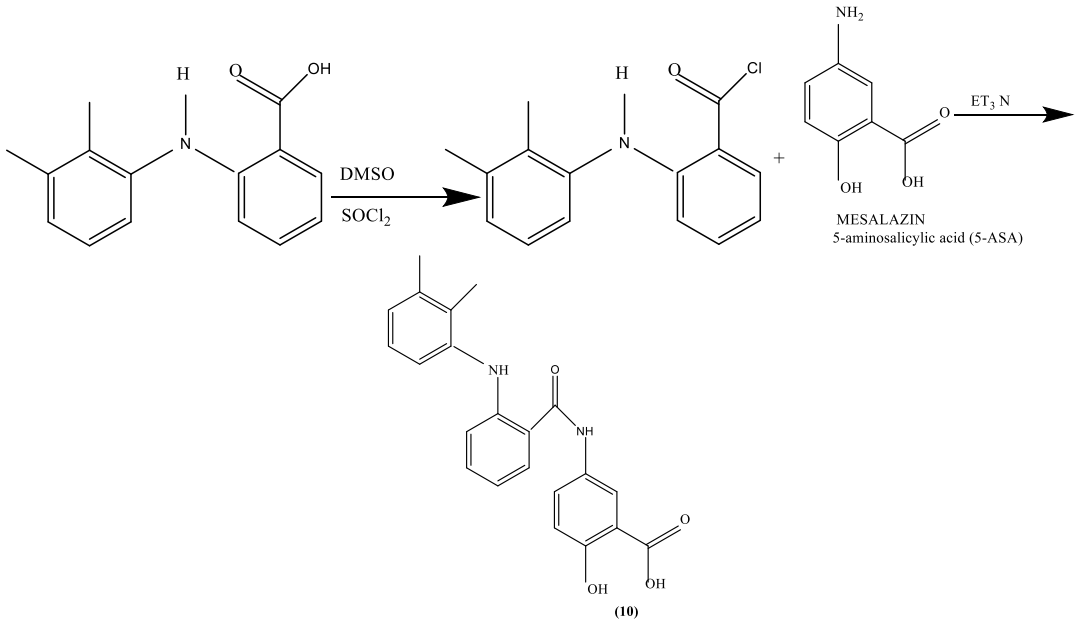
Scheme 4. Synthesis of the compound **(6), (7) & (8)**.

This compound of Mefenamic Acid derivate, 4-nitrobenzoyl-mefenamic acid (9) has been synthesized by benzoylation reaction between mefenamic acid and 4-nitrobenzoyl chloride after prediction by in silico study/molecular approach. This derivative was used as analgesic.(Puspaningtyas, 2017)



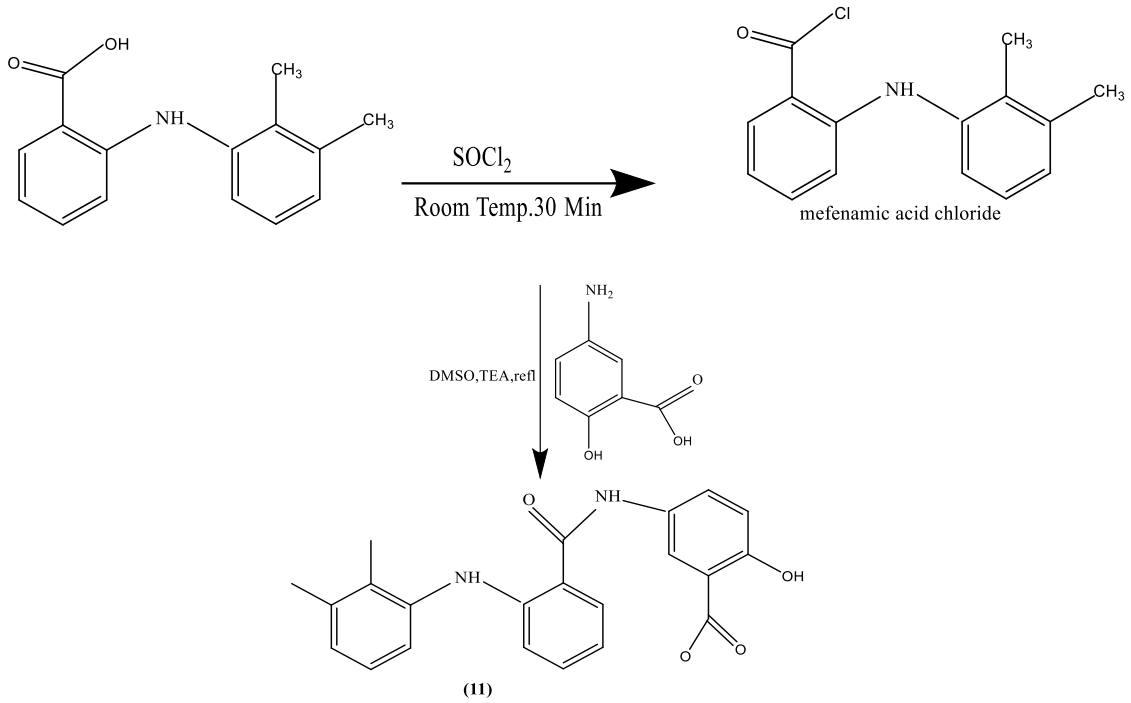
Scheme 5. Scheme of the synthesis of the compounds (**9**)

The derivatives (10) were synthesized starting by combined two drugs together mefenamic acid with mesalazin to give new binary drug compound. This compound used as a starting material to design new tertiary drugs system.(Mohammed and Kareem, 2020)



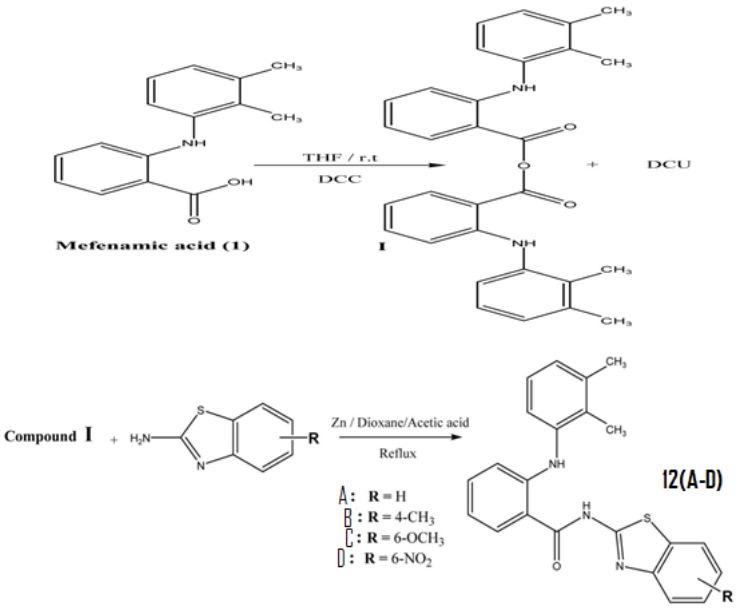
Scheme 6: synthesis of compound (**10**)

The derivative (**11**) was refluxed with 5-amino- 2-hydroxyle benzoic acid for (1hr). (Disher and Kareem, 2021)



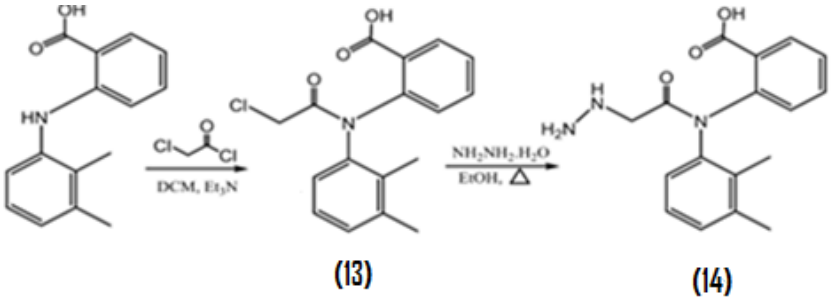
Scheme 7: Synthesis of derivatives (**11**)

The amino benzothiazole derivatives (12) of mefenamic acid were synthesized with potential analgesic and anti-inflammatory properties. (Baghernejad, 2021)



Scheme 8: Synthesis of derivatives {**12 (a-d)**}

The derivative **(14)** was synthesized by reacted of Synthesis of 2-[2-chloro-N-(2,3-dimethylphenyl) acetamido] benzoic acid (1**3**) and hydrazine hydrate in ethanol was refluxed for 4 hours. Then this compound use as **anti-cancer activity**. (Sabah et al., 2023)



Scheme 9. Synthesis of the compound **(13) & (14)**.

3.Conclusion

The synthesis and pharmaceutical application of several Mefenamic acid derivatives have shown promising results. Various modifications have been made to the chemical structure of Mefenamic acid to enhance its pharmacological profile. These modifications have been successful in increasing the efficacy and reducing the side effects of Mefenamic acid-based drugs. These advancements in Mefenamic acid derivatives have opened new avenues for the treatment of various inflammatory conditions, including arthritis and menstrual pain. Overall, the synthesis and pharmaceutical applications of Mefenamic acid derivatives hold great potential for future drug development and patient care.

4.Reference

AHMADI, A. 2015. Synthesis and anti-inflammatory evaluation of novel piperazine derivatives of mefenamic acid. *BULGARIAN CHEMICAL COMMUNICATIONS,* 47**,** 626-630.

AL-DULIMIA, A. A. A., AL-HASANI, R. A. & YOUSIF, E. A. 2016. Synthesis, characterization, theoretical studies and photostabilization of mefenamic acid derivative with some divalent metal ions. *Eur. Chem. Bull,* 5**,** 456-464.

BAGHERNEJAD, B. 2021. Synthesis, Analgesic and Anti-Inflammatory Activities of Aminobenzothiazole Derivatives of Mefenamic Acid. *Pharmaceutical Chemistry Journal,* 55**,** 355-360.

BURIAN, M. & GEISSLINGER, G. 2005. COX-dependent mechanisms involved in the antinociceptive action of NSAIDs at central and peripheral sites. *Pharmacology & therapeutics,* 107**,** 139-154.

DISHER, A. A. & KAREEM, M. M. 2021. Synthesis, Characterization And Biological Activity Applications Of New Mefenamic Acid Derivatives. *NVEO-NATURAL VOLATILES & ESSENTIAL OILS Journal| NVEO***,** 1964-1977.

FIORUCCI, S., SANTUCCI, L. & DISTRUTTI, E. 2007. NSAIDs, coxibs, CINOD and H2S-releasing NSAIDs: what lies beyond the horizon. *Digestive and Liver Disease,* 39**,** 1043-1051.

MOHAMMED, I. A. & KAREEM, M. M. Synthesis, characterization and study of some of new mefenamic acid derivatives as cytotoxic agents. Journal of Physics: Conference Series, 2020. IOP Publishing, 012081.

PUSPANINGTYAS, A. 2017. Drug Development of Mefenamic Acid Derivatives as Analgesic by Molecular Approach. *International Journal of Pharmaceutical and Clinical Research,* 9**,** 123-130.

SABAH, A. A., MHAIBES, R. M., JARALLAH, A. L., DAWOOD, S. & SALMAN, M. S. A.-R. 2023. Study the Toxicity and Anticancer Activity of Some New Derivatives of Mefenamic Acid.