IJPSR (2023), Volume 14, Issue 11 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 03 April 2023; received in revised form, 29 May 2023; accepted 31 May 2023; published 01 November 2023

SYNTHESIS AND CHARACTERIZATION OF MUTUAL PRODRUGS OF MEFENAMIC ACID WITH OTHER NSAIDS

Simran [1], Arshi Hussain [1] and Neelam Vashist [*2]

Department of Chemistry [1], Department of Pharmaceutical Sciences [2], Gurugram University, Gurugram - 122003, Haryana, India.

Keywords:

EDAC, Ester conjugates, Mutual Prodrugs, Mefenamic Acid, Paracetamol

Correspondence to Author:
Dr. Neelam Vashist

Assistant Professor,
Department of Pharmaceutical Sciences, Gurugram University, Gurugram - 122003, Haryana, India.

E-mail: neelam.vashisth@gurugramuniversity.ac.in

ABSTRACT: Inflammation and pain have all been successfully treated using nonsteroidal anti-inflammatory drugs. Today's nonsteroidal anti-inflammatory drugs (NSAIDs) are typically taken with restriction due to the gastric intolerance they create. The prodrug approach is quite effective in reducing the side effects caused by NSAIDs. Many nonsteroidal anti-inflammatory drug molecules have been modified in several ways so that they can be less hazardous to the stomach. Using the mutual prodrug concept, the side effects can be minimized by covalently bonding the NSAIDs to the second pharmacologically active carrier. The goal of the current study is to use the coupling approach to create mutual ester prodrugs of NSAIDs (MS and MP) in order to overcome the troubles, they cause, like gastrointestinal toxicity, ulcerogenic side effects, *etc*. The prodrugs were made by using a better reagent, EDAC 1-Ethyl-3-(3-Dimethylaminopropyl) carbodiimide hydrochloride, because it outperformed DCC (N, N′-Dicyclohexylcarbodiimide) as a coupling agent. The physiochemical properties were determined, and the structures of the synthesized prodrugs were confirmed and analyzed by UV, FT-IR, ^{1}HNMR, ^{13}CNMR Spectroscopy and Mass spectrometry.

INTRODUCTION: The clinical importance of NSAIDs is enormous, but there's a robust risk that they might have negative effects on the abdomen. The ability of NSAIDs to restrict the activity of the enzyme cyclooxygenase (COX) involved in prostaglandin H_2 (PGH_2) production is correlated with their pharmacological effectiveness [1, 2]. It is generally known that COX has two isoforms, COX-I and COX-II, which are controlled in various ways. In the GIT, COX-I is expressed constitutively in the stomach to provide cytoprotection, and COX-II plays a major role in the biosynthesis of prostaglandin, which is expressed in inflammatory cell [3].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.14(11).5465-71

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.14(11).5465-71

In a nutshell, the chemical structure of NSAIDs typically consists of an attached acidic group and a hydrophobic aromatic nucleus [4-5]. Since, most NSAIDs used clinically block both isoforms, there is sufficient evidence to conclude that COX-I inhibition contributes to the development of stomach ulcers when these agents are used over an extended period of time [6-8]. The relatively brief plasma half-life of certain drugs, such as ibuprofen and flurbiprofen, which is about two hours, is another drawback. This results in quick combined action and frequent dosing, producing a robust ulcerogenic impact.

An ester or amide mutual prodrug concept has been employed to overcome this drawback. Derivatization of the carboxylic acid group of NSAIDs into esters or amide prodrugs has been proven to be an effective method that lessens their gastrointestinal ulcerogenic adverse effects [9-10]. Mefenamic acid, which is a very potent anti-inflammatory drug used in several inflammatory

diseases such as mild to moderate pain, arthritis, dysmenorrhea, *etc*., is also associated with various side effects like an upset stomach, gastric irritation, and erosion of the gastroduodenal mucosa [11]. Based on the literature available, it has been concluded that co-administration of mefenamic acid with paracetamol or the other NSAIDs may reduce the possibility of NSAIDs induced gastrointestinal ulcerogenicity.

To address this issue, we can temporarily form the ester and/or amide linkages of the free carboxylic group of NSAIDs. The free carboxylic group of the NSAID was condensed with another pharmacologically active drug. To name a few mutual prodrugs, Mefenamic acid-PGA to overcome poor solubility [12], Etodolic and Thymol with reduced ulcerogenic activity [13], Piroxican with Aceclofenac, Ibuprofen and Mefenamic acid to reduce gastric side effects [14], esters of Mefenamic acid with thymol and sesamol with enhanced anti-inflammatory activity and reduced gastric toxicity [15], Mefenamic acid with a tocopherol and a tocopherol acetate to reduce the CNS toxicity and enhance therapeutic efficacy [16], Galifloxacin – Paracetamol to enhance therapeutic action [17], p-Aminosalicyclic acid and alkyl, alkoxy carbonyl to increase oral bioavailability [18], xylitol-ibuprofen ester for enhanced water solubility [19], Ibuprofen-sulphanilamide with an improved toxicity profile [20]. NSAIDs with 4-(1H-benzo[d] imidazole 2-yl) – phenol (BZ) with better anti-inflammatory potential [21], Febuxostat-NSAIDs with gastrointestinal safety profile [22].

To conceal the free carboxylic group of the NSAIDs and to produce a synergistic anti-inflammatory, analgesic and antipyretic effect, a mutual prodrug concept is used for synthesizing conjugates of two NSAIDs so that the expected adverse effect of the individual NSAIDs can be minimized as well as their therapeutic value can be increased. In the present work, we synthesized and characterized two Mutual ester prodrugs of Mefenamic acid with Paracetamol and Salicylic acid (MP and MS) to mask the free carboxylic group of Mefenamic acid in order to lessen the gastrointestinal toxicity of Mefenamic Acid by using a better coupling reagent EDAC than the one (DCC) that was used by Kamal Shah *et al*. in 2013 [23] to overcome the troubles during the purification of the product. Using EDAC, the byproduct formed during the reaction can be easily separated, making the purification process easier and ensuring a good yield of product.

MATERIALS AND METHODS: Mefenamic acid and Paracetamol were received as gift samples from Gentech Healthcare Pvt. Ltd., Sonipat, Haryana. Reagents like 1-(3-dimethylaminopropyl) -3-ethylcarbodiimide hydrochloride and N, N˙-dimethyl aminopyridine were purchased from Sisco Research Laboratories Pvt. Ltd., Mumbai, Maharashtra. The other chemicals were from Merck and Rankem, provided by Gurugram University, and all the chemicals were of analytical grade. The melting point was determined by the open capillary method and was uncorrected. The λ_{max} was determined using $BaSO_4$ pellets on a Shimadzu 3600 UV spectrophotometer at Aryabhata CIL, Maharshi Dayanand University, Rohtak. The IR spectra were recorded on RZX (Perki Elmer) KBr pellets (anhydrous) at CIL, Panjab University, Chandigarh. The ^{1}H and ^{13}C NMR spectra of the synthesized compounds were recorded in $CDCl_3$ with TMS as an internal standard and the chemical shifts were recorded in δ ppm using a Bruker Avance II 500 NMR spectrometer, SAIF, Panjab University, Chandigarh. The mass spectra were recorded on the SCIEX Triple TOF 5600.

The synthesis was done according to Steglich Esterification [24] in which EDAC was used as coupling reagent due to the limitations of DCC over EDAC. DCC must be used with great caution because it is irritating, potentially harmful to organs, and considered an allergen. It generates N, N′-dicyclohexylurea (DCU), a byproduct that is largely insoluble in many organic solvents and insoluble in water. Although the weak solubility of byproduct (DCU) makes it simple to filter out of reaction mixtures, it can be challenging to get rid of any remaining trace amounts, even using column chromatography, making purification time-consuming. Meanwhile EDAC is a solid that is even simpler to manage. It can be employed in a variety of mild solvents, such as water, DCM, THF, and DMF. The fact that the urea byproduct is water soluble and can be extracted with ease gives it an edge over DCC.

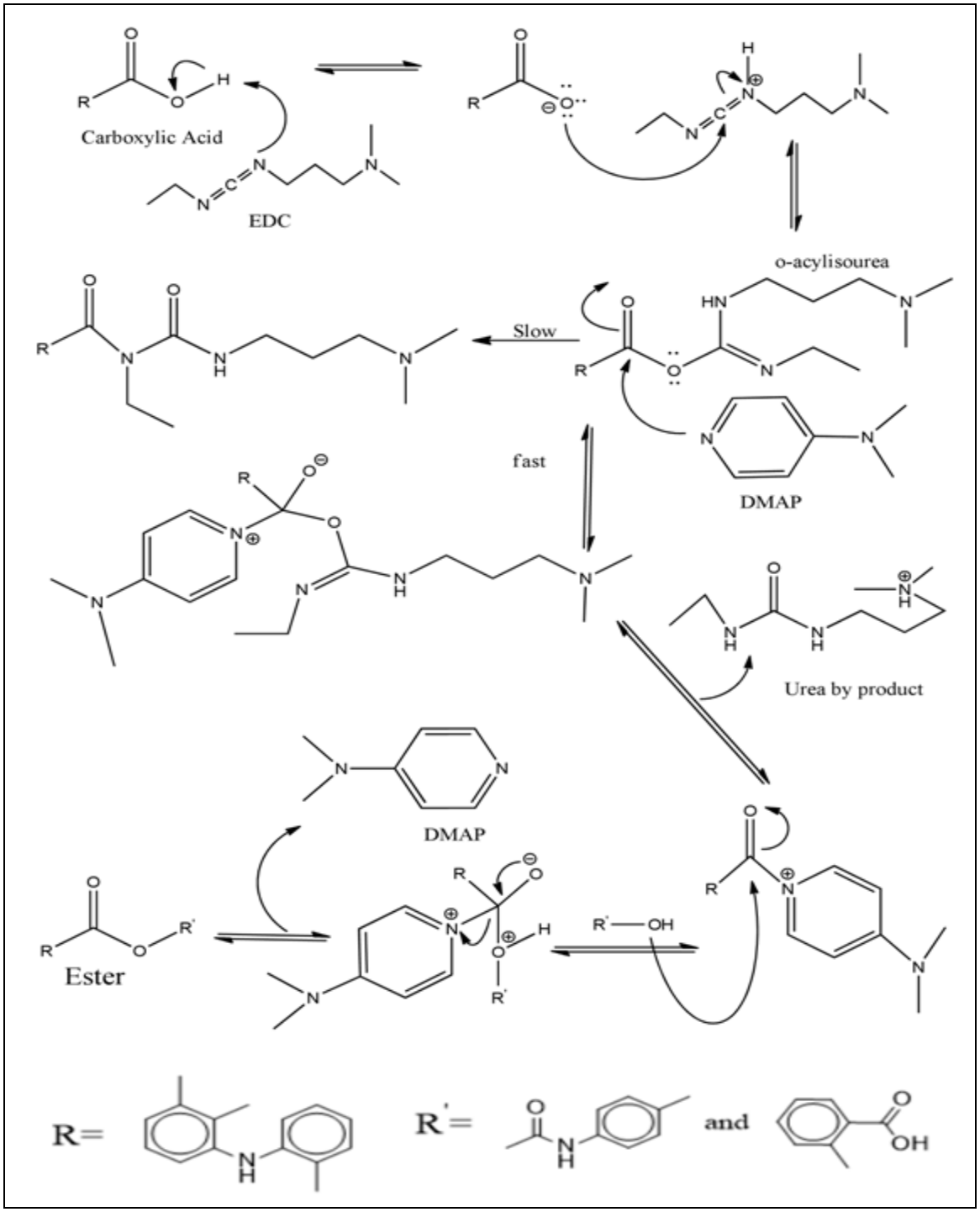

FIG. 1: MECHANISM OF STEGLICH ESTERIFICATION BY EDAC

Synthesis of Mutual Prodrug of Mefenamic acid and Paracetamol (MP) (4-acetamidocyclohexa-2,5-diene-1-yl 2-((2,3-dimethylphenyl) amino) benzoate): Mefenamic acid (30 mmol, 7.23 g), paracetamol (30 mm, 4.54 g), and dichloromethane (DCM) (100 mL) were added to a 250 mL flask with a flat bottom. The temperature of the reaction mixture was kept at 0 °C while adding 1-(3-dimethylaminopropyl) - 3-ethyl-carbodiimi-dehydrochloride (EDAC) (30 mm) and N, N'-dimethyl aminopyridine (DMAP) (30 mm) in portions. At room temperature, the reaction mixture was stirred for 4 hours. The mixture was then extracted with 5% HCl (3 × 100 mL), 5% $NaHCO_3$ (3 × 100 mL), and water (3 × 100 mL), respectively. Combining and drying the CH_2Cl_2 extracts over anhydrous Na_2SO_4. The product was recrystallized from methanol, and yellow-colored, needle-shaped crystals were obtained.

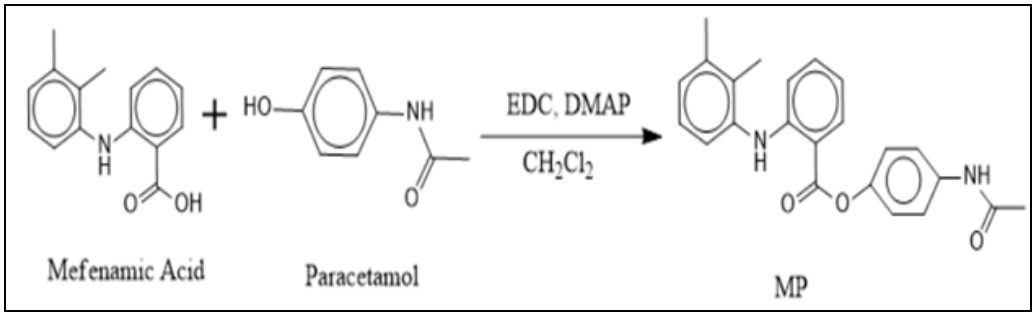

FIG. 2: SCHEME FOR SYNTHESIS OF MP

Synthesis of Mutual Prodrug of Mefenamic Acid and Salicylic Acid (MS) 2-((2,3-dimethylphenyl) amino) Benzoyl) oxy) Benzoic Acid: Mefenamic acid (20 mmol, 4.82 g) and salicylic acid (20 mmol, 2.76g) were dissolved in 50mL of dichloromethane, and then DMAP (10 mmol, 1.22 g) was added. The resulted solution was cooled in an ice/water bath to (0–5) °C, and to these stirred mixtures, EDAC (20 mmol, 3.83 g) in CH_2Cl_2 (5mL) was added dropwise over 10–15 min. After that, the reaction mixture was stirred at 0 °C for 1 hour and then kept in the dark overnight at room temperature. The mixture was then extracted with 5% HCI (3 × 100mL), 5% $NaHCO_3$ (3 × 100mL), and water (3 × 100 mL), respectively. Combining and drying the CH_2Cl_2 extracts over anhydrous Na_2SO_4.The product was recrystallized from methanol to obtain small circular crystals.

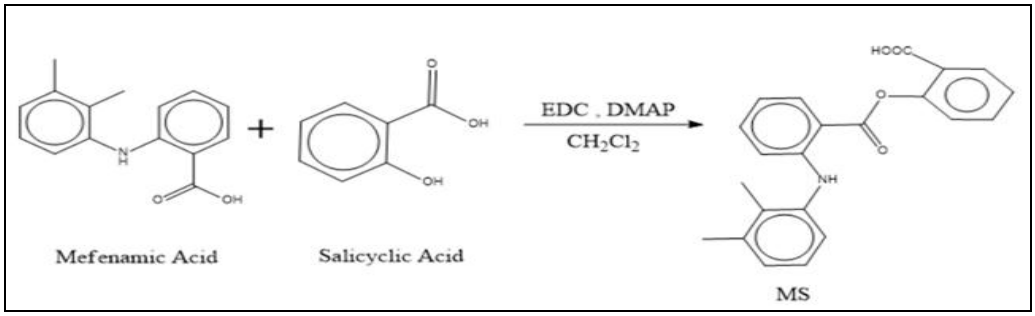

FIG. 3: SCHEME FOR SYNTHESIS OF MS

RESULTSAND DISCUSSION: The synthesis was done according to Steglich Esterification, in which EDAC (1-Ethyl-3-(3-Dimethylaminopropyl) carbodiimide hydrochloride) was used as a coupling reagent and 4-dimethylamino pyridine was used as a catalyst. The initial phase of the reaction process is the interaction between the carboxylic acid and the carbodiimide, most likely through an ion pair, to produce the O-acylisourea.

This intermediate can now either react with a different carboxylate equivalent to produce the symmetric anhydride, with alcohol to produce the ester, or it can undergo intramolecular rearrangement to produce the N-acyl urea byproduct. Since alcohols are typically significantly worse nucleophiles than amines, the degree of N-acyl urea creation is higher in esterification processes driven by carbodiimides than in amide formations. However, the addition of DMAP in catalytic quantities can counteract this tendency by rapidly reacting with O-acylisourea to produce an acyl pyridinium species that isn't capable of forming intramolecular byproducts and can combine with alcohol to produce the ester. A prodrug of mefenamic acid with Paracetamol was synthesized previously by Kamal Shah *et al.* in 2013. The synthesis of the prodrug was done with the coupling reagent dicyclohexylcarbodiimide (DCC), which had limitations.

The byproduct formed during the reaction is Dicyclohexyl urea (DCU), which is difficult to separate from the main product. In the present work, the synthesis was done using 1-Ethyl-3-(3-Dimethylaminopropyl) carbodiimide hydrochloride (EDAC) to overcome this limitation, as the byproduct formed during the reaction is urea, which is water soluble and can be separated by extraction, making purification easier and less time-consuming. The product obtained had a better yield (70.2%) as compared to the yield obtained by

Kamal Shah *et al*. which was 52.2%. The synthesized ester conjugates (MP and MS) were subjected to physio-chemical analysis, the results of which are provided in **Table 1**, and their structures were supported and verified by UV, FTIR, ^{1}H NMR,^{13} C NMR and mass spectroscopy, as shown in **Table 2.**

TABLE 1: PHYSIO-CHEMICAL PROPERTIES OF SYNTHESIZED PRODRUGS

Code	Chemical Formula	Molecular Weight (g/mole)	Appearance	Elemental Analysis (%)	% Yield	Melting Point (℃)
MP	$C_{23}H_{22}N_2O_3$	374.3	Light Yellow	C-73.5, H-6.17, N-7.46, O-12.7	70.2	139
MS	$C_{22}H_{19}NO_4$	361.3	White	C-73.1, H-5.30, N-3.88, O-17.7	66	224

TABLE 2: SPECTRAL DATA OF THE SYNTHESIZED MUTUAL ESTER PRODRUGS

1. Mefenamic Acid -Paracetamol (MP):

IR spectra	^{1}H NMR	^{13}C NMR	Mass Spectra
1611 cm^{-1} C=O ester str., 1251-1014 cm^{-1} C-O ester str., 3318 cm^{-1} N-H amide str., 1659 cm^{-1} C=O amide str., 1190 cm^{-1} C-N stretching, 3062.31cm^{-1} aromatic C-H str. , 3318 cm^{-1} N-H str, for secondary amines	δ 8.03 [s, 1H] -NH-CO, δ 6.58 [s, 1H] -CH methine, δ 7.55 [d, 2H] aromatic C-OH, δ 8.13 [s, 1H] CH-benzene, δ 7.46 [s, 1H] CH-benzene, δ 6.67 [s, 1H] CH-benzene, δ 6.90 [s, 1H] CH-benzene, δ 7.46 [s, 1H] CH-benzene, δ 7.03 [s, 1H] CH-benzene, δ 2.01 [s, 3H] -CH_3 , δ 2.19 [s, 3H] -CH_3	In benzene ring A [δ=119.8(C_1),137.7(C_2),132.9(C_3),138.4(C_4),127(C_5),126.5(C_6)]. In benzene ring B [δ=148.1(C_1), 113.4(C_2), 134.8(C_3), 118.1(C_4), 131.2(C_5), 113.5(C_6)]. δ=18.8 and 20.7 for methyl carbon attached to C_2 and $C_3$of benzene ring A. In ring C[δ=124.2(C_1), 55.6(C_2), 121.2(C_3)]. δ= 165.2 for ester group carbon. δ= 169.0 for carbon of amide group	m/z= 374(M^+), 224(M^+ = $C_8H_8O_2N$), 196 (M^+=C_7H_8ON), 135

2. Mefenamic Acid -Salicylic Acid (MS):

IR spectra	^{1}H NMR	^{13}C NMR	Mass Spectra
1647 cm^{-1} C=O ester str., 3313 cm^{-1} N-H amide str., 3012 cm^{-1} aromatic C-H str., 1256 cm^{-1} C-N str., 1256-1039 cm^{-1} C-O ester stretching,3413.99 cm^{-1}for OH of carboxylic group,3313 cm^{-1}N-H str, for secondary amine	δ 6.67 [s, 1H] CH-benzene, δ 6.71 [s, 1H] CH-benzene, δ 6.66 [s, 1H] CH-benzene, δ 2.33[s, 3H] -CH_3, δ 8.02 [s, 1H] CH-benzene, δ 7.29 [s, 1H] CH-benzene, δ 6.71 [s, 1H] CH-benzene, δ 7.16 [s, 1H] CH-benzene	In benzene ring A [δ=119.8(C_1), 137.7(C_2), 132.9(C_3), 138.4(C_4), 127(C_5), 126.5(C_6)]. In benzene ring B [δ=148.1(C_1), 113.4(C_2), 134.8(C_3), 118.1(C_4), 131.2(C_5), 113.5(C_6)]. δ=18.8 and 20.7 for methyl carbon attached to C_2 and $C_3$of benzene ring A. In ring C[δ=124.2(C_1), 55.6(C_2), 121.2(C_3)]. δ= 165.2 for ester group carbon. δ= 166.1 for carbon of carboxylic acid group	m/z = 361(M^+), 224($C_8H_8O_2N$), 120

The λ_{max} (nm) obtained for MP are 409 and for MS are 304 nm using $BaSO_4$ pellets.

An ester can be recognized if there is a strong band owing to C=O str. and C-O str. In an IR spectrum, the normal absorption band is 1750–1735 cm^{-1} for aliphatic esters, but the C=O absorption band shifts to a lower frequency when it is conjugated with a double bond, phenyl, or the ring system, and the C=O absorption frequency lies between 1600–1450 cm^{-1} [25]. The observed ester peak in MP is 1611 cm^{-1} and MS is 1647 cm^{-1} due to the conjugation of C=O with the rings. The C-O stretch appears in the range of 1256–1039 cm^{-1} for MP and 1256–1039 cm^{-1} for MS, which confirms the presence of an ester group in the prodrugs. A broad absorption for -OH of carboxylic acid also occurs in MS. The absorption frequency is around 3300 cm^{-1}for-NH of secondary amines. The anticipated structures distinctive chemical shifts were visible in the ^{1}H NMR spectra of the synthesized derivatives. The chemical shift value for the aromatic proton lies between 6.5 to 8.0 ppm as hydrogens attached to the aromatic ring are deshielded by the anisotropic field generated by theπelectrons in the ring. The chemical shift of a proton attached to an amide group is about 8.05 ppm. The chemical shift in ^{13}C-NMR for aromatic carbon is usually downfield, which is between 110 -175 as the field produced is of non-uniform density and the effect due to this is called the anisotropic effect. The carbon of the ester group also has a downfield chemical shift due to the presence of an electronegative atom, oxygen, which

is directly bonded to the carbon and deshields the carbon. The molecular mass of the synthesized prodrugs was confirmed by mass spectrometry. The m/z is observed at 374 and 361, which are the molecular ion peaks for MP and MS, respectively.

CONCLUSION: The authors would like to conclude that the prodrugs were successfully synthesized by using a better coupling reagent in a good yield and their characterization have been done through different spectroscopic methods. The masking of the free carboxylic group of the parent drug – Mefenamic Acid would reduce its side effects; this would result in the enhancement of drug usefulness. It also thus may improve the therapeutic index of the individual drugs.

ACKNOWLEDGEMENTS: The authors thank the Gurugram University, Gurugram, for providing the facilities to carry out this research work and Gentech Healthcare Pvt. Ltd. for providing the gift samples of the required drugs; the Department of Chemistry, Gurugram University, Gurugram; and SAIF, Panjab University, Chandigarh.

CONFLICTS OF INTREST: The author declares no conflict of interest.

REFERENCES:

1. Vane JR: Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nat New Biol 1971; 231(25): 232-5.
2. Vane JR and Botting RM: New Insight into the mode of action of anti-inflammatory drugs. Inflamm Res 1995; 44(1): 1-10.
3. Hla T and Neilson K: Human cyclooxygenase-2 cDNA. Proc Natl Acad Sci USA 1992; 9(16): 7384-8.
4. Arora M, Choudhary S, Singh PK, Sapra B and Silakari O: Structural investigation on the selective COX-2 inhibitors mediated cardiotoxicity: A review. Life Sci 2020; 251: 117631.
5. Crisan L, Borota A, Bora A and Pacureanu L: Diarylthiazole and diarylimidazole selective COX-1 inhibitor analysis through pharmacophore modeling, virtual screening, and DFT-based approaches. Struct Chem 2019; 30: 2311–2326.
6. Cao C, Matsumura K, Yamagata K and Watanabe Y: Endothelial cells of the rat brain vasculature express cyclooxygenase-2 mRNA in response to systemic interleukin-1 beta: a possible site of prostaglandin synthesis responsible for fever. Brain Res 1996; 733(2): 263-72.
7. Reuter BK, Asfaha S, Buret A, Sharkey KA and Wallace JL: Exacerbation of inflammation-associated colonic injury in rat through inhibition of cyclooxygenase-2. J Clin Invest 1996; 98(9): 2076-85.
8. Warner TD, Giuliano F, Vojnovic I, Bukasa A, Mitchell JA and Vane JR: Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: a full *in-vitro* analysis. Proc Natl Acad Sci USA 1999; 96(13): 7563-8.
9. Bharat V. Dhokchawle, Milind D. Kamble, Savita J. Tauro and Anil B. Bhandari Der: Synthesis, spectral studies, hydrolysis kinetics and pharmacodynamic profile of mefenamic acid prodrugs Pharma Chemica 2014; 6(3): 347-353.
10. Husain A, Ahuja P, Ahmad A and Khan SA: Synthesis, Biological Evaluation and Pharmacokinetic Studies of Mefenamic Acid - N-Hydroxymethylsuccinimide Ester Prodrug as Safer NSAID. Med Chem 2016; 12(6): 585-91.
11. Wolf JA, Plotzer R, Safina FJ, Ross M, Poppky G and Rubin W: Arch. Intern Med 1976; 136: 923.
12. Dipak Gordhan, Sadie ME. Swainson, Amanda K. Pearce and Ioanna D. Styliari: Poly (Glycerol Adipate): From a Functionalized Nanocarrier to a Polymeric-Prodrug Matrix to create Amorphous Solid Dispersion. Journal of Pharmaceutical Science 2020; 109 (3): 1347-1355.
13. Hassib STGS Hassan AA, El-Zaher MA, Fouad OAA, El-Ghafar and EA. Taha: Synthesis and biological evaluation of new prodrugs of etodolac and tolfenamic acid with reduced ulcerogenic potential. Eur J Pharm Sci 2019; 140: 105101.
14. Bharat V. Mohd Imran and Mohammad Asif: Mutual Prodrugs of Piroxicam. Acta Scientific Pharmaceutical Sciences 2019; 3(7): 27-28.
15. Nija B, Rasheed, Arun A and Kottaimuthu: Development, Characterization, and Pharmacological Investigation of Sesamol and Thymol Conjugates of Mefenamic Acid. Journal of Evolution of Medical and Dental Sciences 2020; 9: 3909-3916.
16. Ayoub R, Jarrar Q, Ali D, Moshawih S, Jarrar Y, Hakim M and Zakaria Z: Synthesis of Novel Esters of Mefenamic Acid with Pronounced Anti-nociceptive Effects and a Proposed Activity on GABA, Opioid and Glutamate Receptors. Eur J Pharm Sci 2021; 163: 105865.
17. Naser, Noor, Hussein, Sahar, Hussein, Ahmed, Alibeg, Ammar, Jasim and Zainab: Design, Synthesis and Antibacterial Study of New Gatifloxacin-Antioxidants as Mutual Prodrugs. J Biochem Tech 2020; 11(1): 32-36.
18. Hegde PV, Howe MD, Zimmerman MD, Boshoff HIM, Sharma S, Remache B, Jia Z, Pan Y, Baughn AD, Dartois V and Aldrich CC: Synthesis and biological evaluation of orally active prodrugs and analogs of para-aminosalicylic acid (PAS). Eur J Med Chem 2022; 232:114201.
19. Zappaterra, F, Tupini C, Summa D, Cristofori V, Costa S, Trapella C, Lampronti I and Tamburini E: Xylitolas a Hydrophilization Moiety for a Biocatalytically Synthesized Ibuprofen Prodrug. Int J Mol Sci 2022; 23: 2026.
20. Asghar A, Yousuf M, Mubeen H, Nazir R, Haruna K, Onawole AT and Rasheed L: Synthesis, spectroscopic characterization, molecular docking and theoretical studies (DFT) of N-(4-aminophenylsulfonyl)-2-(4-isobutylphenyl) propanamide having potential enzyme inhibition applications. Bioorg Med Chem. 2019; 27(12): 2397-2404.
21. Arora M, Choudhary S, Silakari O: In silico guided designing of 4-(1H-benzo[d]imidazol-2-yl) phenol-based mutual-prodrugs of NSAIDs: synthesis and biological evaluation. SAR QSAR Environ Res 2020; 31(10): 761-784.
22. Rashad AY, Daabees HG, Elagawany M, Shahin M, Abdel Moneim AE and Rostom SAF: Towards the Development of Dual Hypouricemic and Anti-inflammatory Candidates: Design, Synthesis, Stability Studies and Biological

Evaluation of Some Mutual Ester Prodrugs of Febuxostat-NSAIDs. Bioorg Chem 2023; 135:106502.
23. Shah K, Shrivastava SK and Mishra P: Synthesis, kinetics, and pharmacological evaluation of mefenamic acid mutual prodrug. Acta Poloniae Pharmaceutica 2013; 70(5): 905-11.
24. Neises, Bernhard, Steglich, Wolfgang: Simple method for the esterification of carboxylic acids, Angewandte Chemie Int. Edition English 1978; 17 (7): 522–524.
25. Donald L Pavia, Gary M Lampman, George S Kriz: Introduction to Spectroscopy. Third Edition. Washington: USA Press 2001; 62-63.

How to cite this article:
Simran, Hussain A and Vashist N: Synthesis and characterization of mutual prodrugs of mefenamic acid with other NSAIDs. Int J Pharm Sci & Res 2023; 14(11): 5465-71. doi: 10.13040/IJPSR.0975-8232.14(11).5465-71.