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Synthesis and Antibacterial Assessment of New Mefenamic Acid-Derived Polymers

[1*]Ayad A. Disher, [2*]Mohanad Mousa Kareem, [3]Abbas Jasim Atiyah Lafta

[1,2,3]Department of Chemistry, College of Science, University of Babylon, P.O. Box 4, Hilla, Iraq.

*Corresponding authors: E-mail: sci.ayad.ali@uobabylon.edu.iq
sci.mohanad.mousa@uobabylon.edu.iq

Abstract:

Because of its ability to inhibit prostaglandin production by inhibiting the COX enzymes, mefenamic acid plays an important role in pain relief and anti-inflammatory treatment. Three new monomers and three new homopolymers based on mefenamic acid were synthesized in this work. The monomers HZ1, HZ2, and HZ3 were made by converting mefenamic acid to mefenamic acid chloride (acyl chloride), which converted to a mefenamic acid ester (Y1) by ethanol and concentrated sulfuric acid, then (Y1) was converted to mefenamic hydrazide(Y2) by reaction with hydrazine hydrate, and finally (Y2) was reacted with methylnadic anhydride, malic anhydride, and dodecenylsuccinic anhydride to form the above monomers respectively. These monomers were polymerized to the corresponding homopolymers HZ4, HZ5, and HZ6 in toluene using BPO as the initiator. All synthesized compounds were identified by FTIR, ^{1}H-NMR, and ^{13}C-NMR. Physical data for all synthesized compounds were recorded, and the antibacterial activity of selected compounds was evaluated.

Keywords: Mefenamic Acid, Dodecenylsuccinic Anhydride, Malic Anhydride, Methylnadic Anhydride, Homopolymerization, Maleimide.

Introduction:

NSAIDs are recommended to relieve pain and treat some infections [1], [2]. NSAIDs inhibit cyclooxygenase enzymes (COX1 and COX2), thereby affecting arachidonic acid metabolism and prostaglandin synthesis.[3]–[5]. The adverse effects of NSAID abuse are cardiovascular problems, gastrointestinal complications, renal failure, and hypersensitivity reactions.[6]–[10]. In recent decades, Polymer Therapeutics (PT) has gained prominence. The possibility of finely modifying drug properties by altering the polymer structure or its interactions with the drug is one of the key reasons for its development. According to Ringsdorf's model of polymer-based drug delivery systems, the optimal objective is the development of a smart, functionalized polymer capable of performing multiple tasks through rational design of its structure [11]. New delivery systems, especially biomedical polymers used to develop unique targeting drug delivery systems, are used to overcome problems such as undesirable chemical and physical properties, like shorter half-life, lower bioavailability, and drug resistance, and high doses of low molecular weight, which lead to severe adverse effects. The use of modern drug delivery systems is highly beneficial because it is increasingly difficult and costly to discover and develop new active molecules [12]. Mefenamic acid (MA) or [2- [(2,3-dimethyl phenyl) amino] benzoic acid] or Ponstan (Fig. 1) is considered an anthranilic acid derivative and used to alleviate moderate to severe pain [13], [14]. MA has poor solubility in water but high permeability, which plays a very important role in ensuring drug absorption [15]. MA is an active pharmaceutical compound that exists in different polymorphic forms. These forms exhibit varying solubility and stability behaviors [16]. Due to its ability to inhibit prostaglandin production by inhibiting the COX enzymes, mefenamic acid plays an important role in pain relief and anti-inflammatory treatment [17].

In 2020, Ali Sabah *et al*. synthesized a range of mefenamic acid amic acid derivatives to reduce the local effects of mefenamic acid on the gastrointestinal tract. They prepared tetracyclic and pentacrylate compounds, such as azetidine-2-one, thiazolidine-4-one, and imidazolidine-4-one[18]. In 2021, Ayad A. Disher and Mohanad Mousa used mefenamic acid to prepare new derivatives by reacting it with 5-aminosalicylic acid, thereby forming a novel binary drug system. This system served as a basis for reacting with naproxen, ibuprofen, captopril, and methyldopa to produce tertiary delivery systems. The solubility of the prepared derivatives in various solvents was studied, and some of their physical properties were determined[19]. In 2023, Ali Sabah *et al.* prepared 1,3-oxazepine derivatives of mefenamic acid with anhydrides (succinic, malic, phthalic, and 3-nitrophthalic)[20]. In 2024, Aseel Fadhil *et al.* used mefenamic acid to obtain three chemical compounds as mefenamic acid derivatives by introducing it via a cyclization reaction, Schiff bases, and a diazotization reaction[21].

Here, we report the synthesis of new monomers and polymers based on mefenamic acid, and we evaluate the anti-inflammatory activity of some of them.

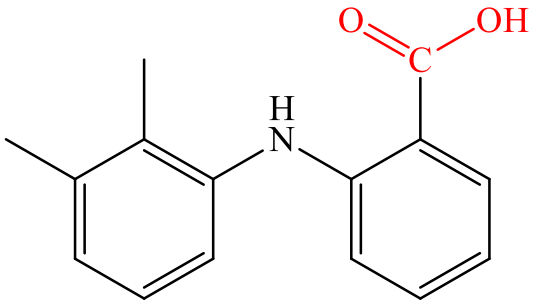
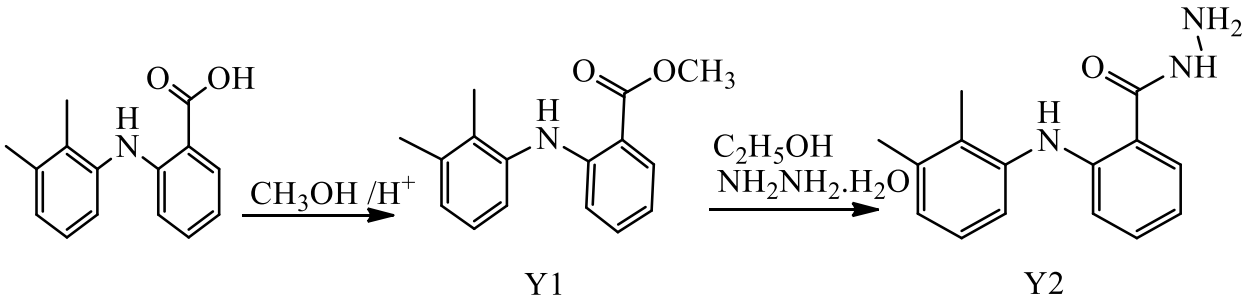
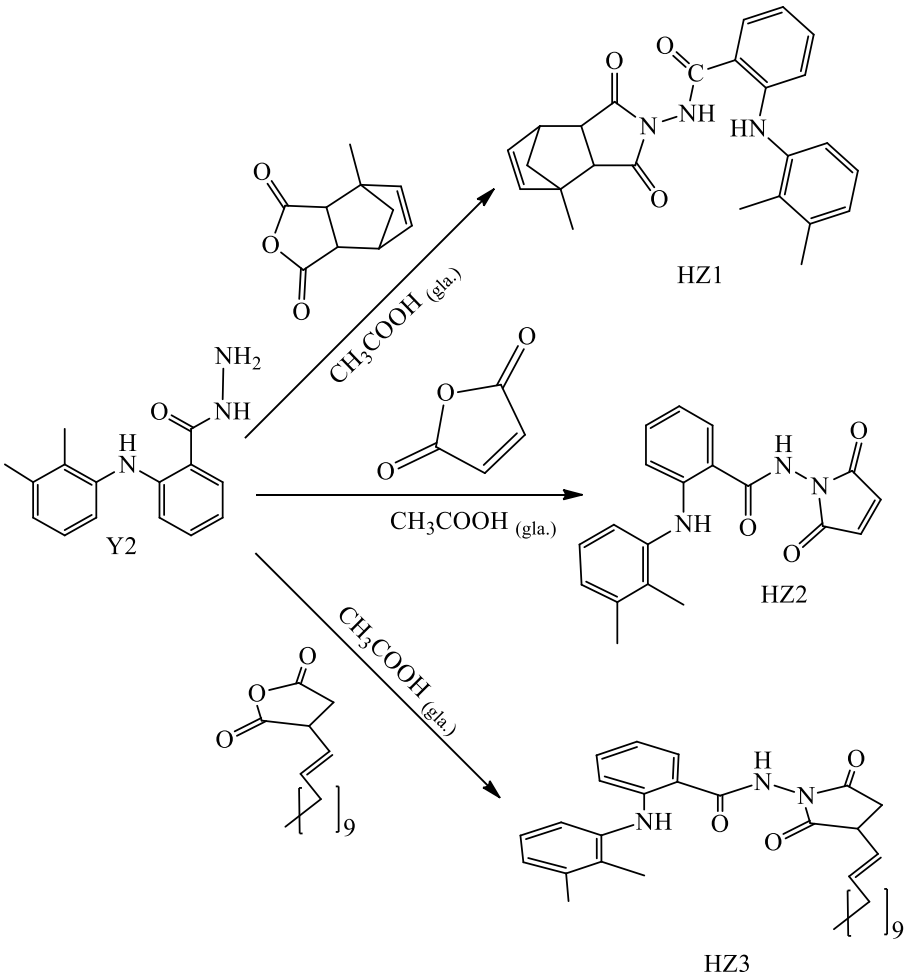


Figure 1: Chemical structure of mefenamic acid.

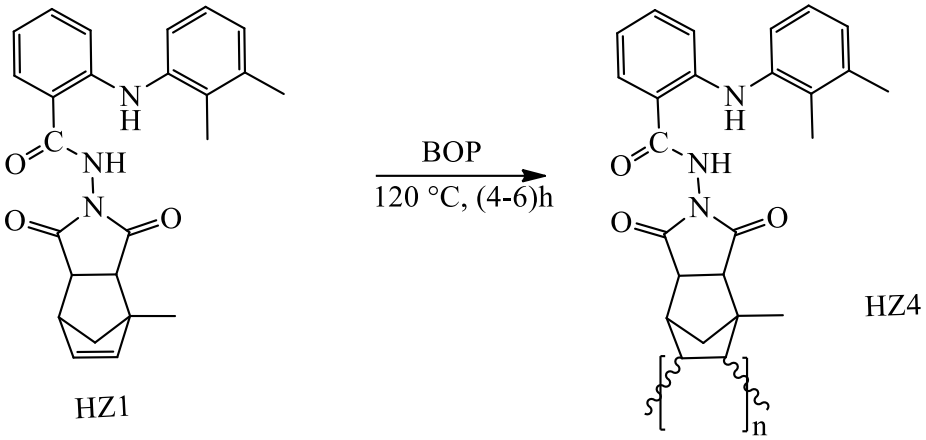


Y1 Y2

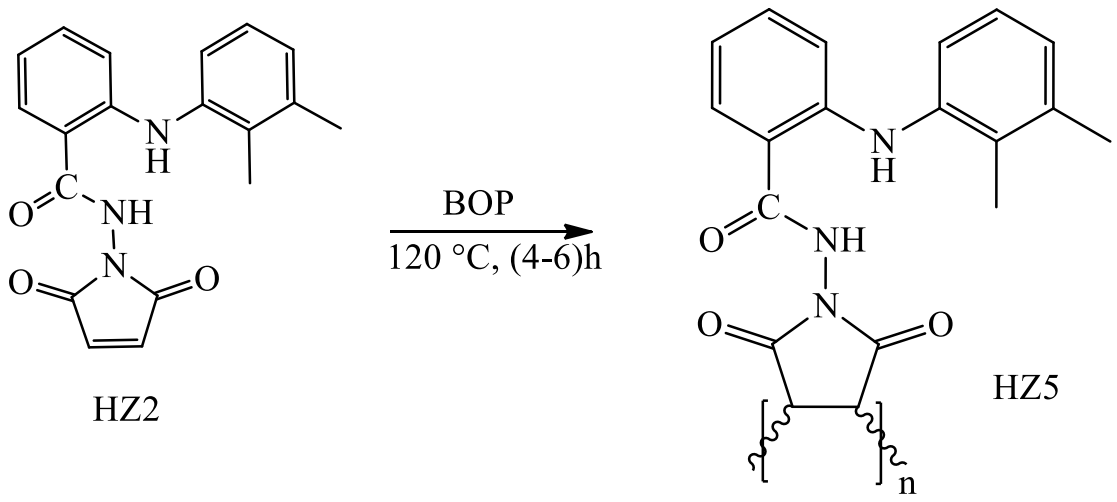
Scheme (1) preparation of Y1 and Y2



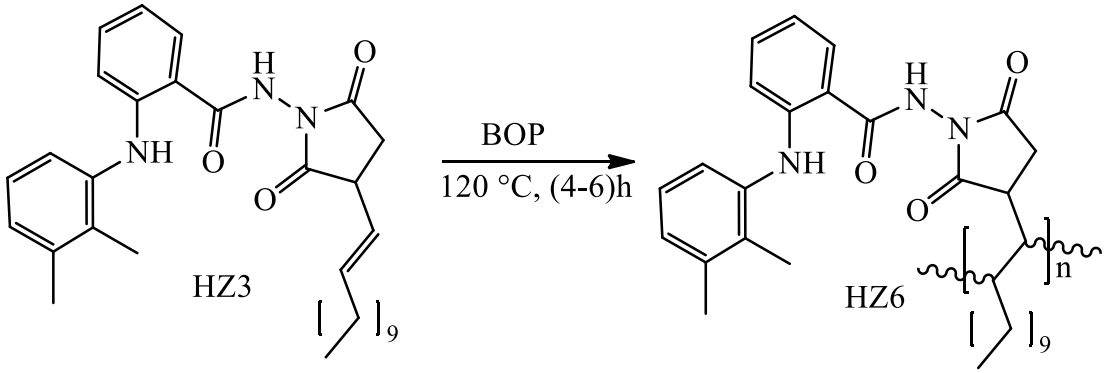
Scheme (2) synthesis of monomers HZ1, HZ2, and HZ3



Scheme (3) synthesis of polymer HZ4



Scheme (4) synthesis of polymer HZ5



Scheme (5) synthesis of polymer HZ6

EXPERIMENTAL SECTION:

Material and methods

The chemical compounds used are of the highest purity available. Sigma-Aldrich and Fluka supported all of the chemicals used in this research. Samarra Company for drug production produced mefenamic acid. On a Gallenkamp MFB-600 melting-point Stuart apparatus, melting points of the prepared compounds were determined, and FTIR spectra were recorded on a Bruker spectrometer. 1H NMR was recorded using a Bruker AC 400 spectrometer at 500 MHz. All chemical shifts (δ) are expressed in parts per million (ppm) relative to tetramethylsilane (TMS) as a default (δ=0.0 ppm).

Biological activity:

For the synthesized compounds HZ1, HZ4, and HZ5, biological activity was evaluated against the Gram-negative bacterium Escherichia coli and the Gram-positive bacterium Staphylococcus aureus.

Preparation of mefenamic acid ester (Y1):

Mefenamic acid (10 gm, 41.5 mmol) was dissolved in 25 mL of methyl alcohol. Then (3 mL) of concentrated H_2SO_4 is gradually added. For 17-18 hrs at 60-70 °C, the mixture was refluxed. To check the reaction, TLC was used. When the reaction stopped, and after removing the solvent by evaporation, distilled water was added to the product. Then, NaOH (2 mol L^{-1}) was used to neutralize the acidic solution. The two layers were separated by chloroform (3 x 25 mL). The organic phase was washed with salt solution, and then dried with Na_2SO_4, and condensed under reduced pressure (Scheme 1)[22].

The target product was collected as a solid white substance (8.8 g, 34.8 mmol), yield = 84%, m.p. = 98°C, Rf = 0.70 (9:1 acetone/n-hexane).

Preparation of mefenamic acid hydrazide (Y2):

Excess NH2NH2 · H2O (80%) was added dropwise, with stirring, to the mefenamic acid ester (Y1) solution (5 g, 19.6 mmol) in ethanol. The mixture was refluxed for 5 hours, and the reaction temperature was steadily increased to 97 °C. The ice-cold water was poured over the flask contents (scheme 1)[22], [23].

A solid yellow compound was collected after recrystallization from ethanol (4 g, yield=80%), m.p = (117- 120) °C, R_f =0.35 (7:3 acetone/ n-hexane).

Synthesis of new monomers HZ1, HZ2, and HZ3:

The compound Y2 (1 gm, 3.9 mmol) was dissolved in glacial A.A. with continues stirred at (25 °C) for tow hour, then refluxed for 4-6 hours at (120 °C) with (3.9 mmol) of each of methylnadic anhydride (0.69gm), malic anhydride (0.38gm), and dodecenylsuccinic anhydride (1.03gm), with continues stirring until colored solid precipitate was formed, the reaction was ended according to the vanishing of TLC reactant spot[24] (Scheme 2).

HZ1: 2-((2,3-dimethylphenyl)amino)-N-(4-methyl-1,3-dioxo-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindol-2(3H)-yl)benzamide solid, green, $C_{25}H_{25}N_3O_3$, M. Wt.=415.48, (1.4gm, Yield =86.4%), m. p= (88-90) °C, R_f= 0.68 (8: 2 Acetone/ n-hexane). FTIR spectrum for HZ1showed the following values (V_{max} cm^{-1}): 3294 (NH of sec. amine), 3249 (N-H amid), 3014 (C-H str. Ar), 2956; 2918 (C-H str.sp^3), 1728(C=O maleimide), 1683(C=O amid), 1666 (C=C str. alkene), 1634; 1452 (C=C str. Ar), 1571 and 1505 (N-H bend), 1317(C-N Str. Aromatic amine). ^{1}H-NMR (500 MH, δ ppm): a-10.44 (NH sec. amid), b- 8.13-6.64 (CH benzene), c- 5.76 (CH, cyclopentene), d- 5.28 (CH, cyclopentene), e- 4.67 (NH, sec. aromatic amine), f- 3.95 (CH, succinimide), g- 3.39 (CH, succinimide), h- 2.99 (H_2O), i- 2.77 (CH, succinimide), j- 2.44 (DMSO), k- 2.35 (CH_3, methyl), l- 2.13 (CH_3, methyl), m- 2.07;1.84 (CH_2, cyclopentene), n- 1.31 (CH_3, methyl). ^{13}C-NMR (125 MH, δ ppm): a- 178.22 (C, 1-amide), b- 167.18 (C, 1-amide), c-150.12- 112.60 (C, 1-benzene), d- 141.90 (CH, 2-norbornene), e- 135.88 (CH, 2-norbornene), f- 59.23 (C, 2-norbornene), g- 54.80 (CH, 2-norbornene), h- 53.22 (CH_2, 2-norbornene), i- 49.80 (CH, 2-norbornene), j-48.60 (CH, 2-norbornene), k- 40.13 (DMSO), l- 21.62 (CH_3, methyl), m- 19.64 (CH_3, methyl), n- 18.57 (CH_3, methyl).

HZ2: 2-((2,3-dimethylphenyl)amino)-N-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzamide Gumy, brawn, $C_{19}H_{17}N_3O_3$, M. Wt.=335.36, (0.96gm, Yield=73.3%), Rf =0.70 (8: 2 Acetone/ n-hexane).

FTIR spectrum for HZ2 showed the following values (in cm^{-1}): 3292 (NH str. sec. amine), 3174 (NH str. amid), 2980; 2916 (C-H str. alkane), 1709 (C=O str. maleimide), 1676 (C=O str. amid), 1623 (C=C str. alkene), 1591; 1453 (C=C str., aromatic), 1571;1508 (N-H bend), 1313 (C-N Str. Aromatic amine). ^{1}H-NMR for HZ2 (500 MH, δ ppm): a- 10.45 (NH, amid), b- 8.18- 6.67 (CH, 1-benzene), c-6.26 (CH, 1-ethylene), d- 4.38 (NH, sec. amine, aromatic), e- 3.04 (H_2O), f- 2.52 (DMSO), g- 2.35 (CH_3, methyl), h- 2.21 (CH_3, methyl). ^{13}C-NMR (125 MH, δ ppm): a- 164.67 (C, 1-amide), b- 163.46 (C, 1-amide), c- 148.79- 118.66 (C, 1-benzene), d- 134.74 (CH, 1-ethylene), e- 40.24- 39.41 (DMSO), [f- 21.19, g- 18.45] (CH_3, methyl).

HZ3: (E)-2-((2,3-dimethylphenyl)amino)-N-(3-(dodec-1-en-1-yl)-2,5-dioxopyrrolidin-1-yl)benzamide Gumy, brawn, $C_{31}H_{41}N_3O_3$, M. Wt.=503.68, (1.52gm, Yield=77.3%), R_f = 0.62 (8: 2 Acetone/ n-hexane).

FTIR for HZ3 showed the following values (in cm^{-1}): 3215 (N-H str.), 2958-2871 (C-H str. aliphatic), 1726 (C=O str. maleimide), 1679 (C=O str. amid), 1622 (C=C str. alkene), 1602; 1452 (C=C str., aromatic), 1577; 1504 (NH bend), 1372 (C-N Str. Aromatic amine). ^{1}H-NMR (500 MH, δ ppm): a- 10.50 (N-H, amide), b- 8.29- 6.69 (C-H, benzene), c- 5.80 (C-H, 1-ethylene), d- 5.64 C-H, 1-ethylene), e- 4.29 (N-H, aromatic amine), f- 3.98 (CH, succinimide), g- 3.03 (H_2O), h- 2.50 (DMSO), i- 2.38 (CH_3, methyl), j- 2.24 (CH_2, succinimide), k- 2.14 (CH_3, methyl), l- 1.94 (CH_2, succinimide), [m- 1.88, n- 1.81, o- 1.73, p- 1.17] (CH_2, methylene), q- 0.80 (CH_3, methyl). ^{13}C-NMR (125 MH, δ ppm): a- 172.40 (C, 1-amide), b- 169.19 (C, 1-amide), c- 168.59 (C, 1-amide), d- 147.52- 118.62 (C, 1- benzene), e- 128.08 (C-H, 1-ethylene), f- 127.25 (C-H, 1-ethylene), g- 45.99 (CH, aliphatic), h- 40.50- 39.45 (DMSO), [i- 33.79, j- 33.00, k- 32.51, l- 30.83, m- 30.59, n- 30.35, o- 29.88, p- 25.36] (CH_2, aliphatic), [q- 21.44, r- 20.83, s- 15.15] (CH_3, methyl).

Synthesis of new homopolymers HZ4, HZ5, and HZ6:

In a round-bottom flask, (0.5 gm) of synthesized monomers (HZ1, HZ2, and HZ3) were dissolved respectively in (15 ml) of toluene. Then (0.05 gm) of benzoyl peroxide (BPO) was added as an initiator. The mixture was heated at 120 °C for 4-6 hours in the presence of N_2 gas, which passed through one of two nicks of the round-bottom flask. After the end of the reaction, the solid precipitates were filtered and then washed with diethyl ether and dried at 50 °C (Scheme-3,4,5)[25].

HZ4: solid, black, m. p=140°C, R_f = 0.63(9:1 Acetone/ n-hexane).

For HZ4, FTIR spectrum showed the following values($V_{max}$$cm^{-1}$): 3294 (NH str.), 3014 (CH str. aromatic), 2968-2873 (CH str. aliphatic), 1728 (C=O, maleimide), 1684 (C=O, amid), 1621; 1452 (C=C str., aromatic), 1572 (N-H bend, amid), 1502(N-H bend, aromatic amine).^{1}H-NMR (500 MH, δ ppm): a- 10.43 (NH amide), b- 8.17- 6.73 (CH benzene), c- 4.72 (NH aromatic sec. amine), [d- 3.79. f- 2.82, i- 2.17, k-1.94, l- 1.61] (CH cyclohexane), m-1.52;1.53 (CH_2 cyclopentane), [h- 2.33, j- 2.12, n- 1.14] (CH_3 methyl), e- 3.33(H_2O), g- 2.47 (DMSO). ^{13}C-NMR (125 MH, δ ppm): a- 178.23 (C, 1-amide), b- 167.21 (C, 1-amide), c- 150.15- 112.60 (C, 1-benzene), [d- 48.92, f- 46.50,

g- 46.01, h- 45.96, j- 35.10] (CH, norbornane), e- 46.98 (C, norbornane), i- 40.58- 39.46 (DMSO), k- 34.07 (CH_2, norbornane), [l- 21.63, m- 19.67, n- 18.69] (CH_3, methyl).

HZ5: Gumy, dark brown, R_f = 0.69(9:1Acetone/ n-hexane).

FTIR spectrum for HZ5 showed the following values (V_{max} cm^{-1}): 3297 (NH str.), 3065 (CH str. Aromatic), 2995-2846 (CH str. aliphatic), 1724 (C=O str. Maleimide), 1680 (C=O str. Amid), 1596;1452 (C=C str. Aromatic), 1574; 1506 (NH bend), 1282 (C-N Str. Aromatic amine). ^{1}H-NMR (500 MH, δ ppm): a- 10.44 (NH amide), b- 8.21-6.68 (CH aromatic), c- 4.41 (NH aromatic sec. amine), d- 3.07 (H_2O), e- 2.99 (2CH succinimide), f- 2.49 (DMSO), [g- 2.38, h- 2.23] (CH3 methyl). ^{13}C-NMR (125 MH, δ ppm): a- 181.67 (C, 1-amide), b- 167.80 (C, 1-amide), c- 149.86- 129.11 (C, 1-benzene), d- 52.97 (CH, aliphatic), e- 40.44- 39.41 (DMSO), [f- 20.82, g- 18.99] (CH_3, methyl).

HZ6: Gumy, dark brawn, R_f =0.61(9:1 Acetone/ n-hexane).

For HZ6, the FTIR spectrum showed the following values (in cm^{-1}): 3192 (NH str.), 2958, 2873 (CH str. aliphatic), 1708 (C=O maleimide), 1687 (C=O str. amide), 1601, 1453 (C=C str. aromatic), 1573, 1511 (NH bend). ^{1}H-NMR (500 MH, δ ppm): a- 10.48 (NH amide), b- 8.18- 6.65 (CH aromatic), c- 4.27 (NH aromatic sec. amine), d- 3.04 (H_2O), e- 2.50 (DMSO), f- 2.37 (CH3 methyl), g- 2.23 (CH succinimide), h- 2.16 (CH3 methyl), [i- 2.10, j- 2.05] (CH_2 succinimide), [k- 1.95, l- 1.88] (CH aliphatic), [m- 1.82, n- 1.52, o- 1.43, p- 1.17] (CH_2 methylene), q- 0.80 (CH_3 methyl). ^{13}C-NMR (125 MH, δ ppm): [a- 172.41, b- 169.12, c- 168.52] (C, 1-amide), d- 147.45- 119.17 (C, 1-benzene), [e- 45.91, f- 43.54, i- 34.91] (CH, aliphatic), g- 40.41-39.39 (DMSO), [h-35.64, j- 33.68, k-32.51, l- 30.85, m- 30.60, n- 30.33, o- 27.45, p- 25.62] (CH_2, aliphatic), [q- 21.47, r- 20.87, s- 15.10] (CH_3, methyl).

RESULT AND DISCUSSION:

Macromolecules are widely used as carriers of medication due to their bulk properties and surfaces. Thus, they are used for medication delivery and medication preparation. Polymers used in drug carrier systems provide a major benefit of drug delivery systems, owing to optimized drug packing and release properties[26], [27]. To prepare new mefenamic acid derivatives, hydrazine hydrate (80%) was mixed with mefenamic acid ester to give compound Y2 (Scheme 1). Y2 was combined with different anhydrides (methyl nadic anhydride, malic anhydride, and dodecenyl succinic anhydride) to produce compounds HZ1, HZ2, and HZ3, respectively, as a starting material for creating new drug systems (Scheme 2). HZ4, HZ5, and HZ6 (schemes 3, 4, 5) were formed by polymerizing these derivatives. Due to the existence of an electron-withdrawing carbonyl group on both sides of the maleimide ring, the double bond of the maleimide ring, which is an electron-deficient bond, will be varied. Polymaleimides can be produced by polymerizing the double bond of the maleimide, or they can be created by polymerizing the double bond with nucleophilic difunctional reagents. FT-IR, ^{1}H-NMR, and ^{13}C-NMR were used to characterize the structure of these compounds.

The solubility of the synthesized compounds was studied and recorded in Table 1.

Table-1: Solubility of synthesized monomers and polymers

Solvents / Comps.	H_2O	EtOH	$(CH_3)_2CO$	CH_2Cl_2	ether	n-hexane	DMSO
HZ1	+	+	Partial	Partial	_	_	+
HZ2	+	+	+	Partial	_	_	+
HZ3	+	+	Partial	Partial	_	_	+
HZ4	+	Partial	_	Partial	_	_	+
HZ5	+	Partial	_	Partial	_	_	+
HZ6	+	_	_	Partial	_	_	+

The antibacterial activity

Table 2 shows the antibacterial activity of the synthesized compounds HZ1, HZ4, and HZ5. The agar disc-diffusion method was used to measure this activity against negative gram bacteria, Escherichia coli, and positive gram bacteria, Staphylococcus aureus. The compounds used in this test were dissolved in DMSO. The results of this study indicate that these compounds had a bactericidal effect.

Table-2: anti-bacterial activity for HZ1, HZ4, HZ5, and MA at 1mg/ml concentration.

Inhibition area (mm) for the studied bacteria		
compounds	Gram-positive (Staphylococcus aureus)	Gram–negative (Escherichia coli)
HZ1	9	11
HZ4	7	9
HZ5	10	10
MA	0	8
DMSO	0	0

CONCLUSION:

The new monomers and homopolymers were successfully prepared from mefenamic acid and exhibit therapeutic properties distinct from those of the materials used in their preparation, as the results showed they have greater antibacterial activity than mefenamic acid and the anhydrides used in the preparation. All the prepared compounds are completely soluble in water, which increases their potential for therapeutic applications.

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