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Synthesis, Characterization And Biological Activity Applications Of New Mefenamic Acid Derivatives

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Abstract: In this study, novel mefenamic acid derivatives were prepared as binary and tertiary molecule drug delivery system binding by hydrazide as a bridge. The compound AY1 was used as a starting material for the production of tri-molecule pharmaceutical compounds by reacting it firstly with hydrazide to give AY1H,which reacted with four different carboxylic drugs (Naproxen, Ibuprofen, Captopril, Methyldopa) to produce the new compounds (AY20-AY23) respectively. All the prepared compounds were characterizedby FT-IR,^{1}HNMR and ^{13}CNMR. The physical properties of the synthesized compounds were also determined and their solubility in different solvents. The biological activity as antibacterial effect against different bacteriawas studied and showed bactericidal effect.

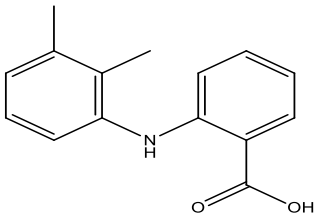
Keywords: Mefenamic acid,Mesalazine, antibacterial activity, Naproxen, Ibuprofen, Captopril, Methyldopa

Introduction

Millions of people suffer from infections around the world[1]. Increasing body temperature, swelling, and pain are some of the most common symptoms associated with most infections. Non-steroidal anti-inflammatory drugs (NSAIDs) can be used to treat the symptoms of infections[2]. NSAIDs are widely used to treat arthritis[3] , pain, fever[4], community-acquired pneumonia[5], Heavy menstrual bleeding[6], and low back pain[7, 8]. Many studies indicate the use of non-steroidal drugs as anti-cancer agents, such as breast and prostate cancer etc.[9]. The use of non-steroidal medicines for long periods can lead to a set of adverse effects [30-47] that the patient may suffer from, such as cardiovascular risk[10]gastrointestinal toxicity, renal failure, heart failure and increasing blood pressure[11]. Non-steroidal drugs relieve pain and treat swelling and fever by reducing the action of the cyclooxygenase (COX) enzymes responsible for converting arachidonic acid into prostaglandins, the latter being responsible for pain and swelling[12–15].

Mefenamic acid (mef) is a NSAID[16, 17] and is known to be a derivative of anthranilic acid[18, 19], and is classified under the fenamate class of NSAIDs[20]. Mefenamic acid (fig.

1) is an analgesic[21] and antipyretic drug[22] widely utilized to treat moderate and light pain and also utilized for treating rheumatoid arthritis, osteoarthritis and muscular-skeletal conditions[23]. Depending on the difference in solubility and stability, mefenamic acid is divided into three types (I, II, III), the first type is the most stable in SATP conditions , the second type is stable at temperatures above 160 ^{o} C, and the third type is unstable in the SATP conditions and quickly turns into type I [24].



Mefenamic acid

A prodrug is a molecule that does not have a biological function, butthat can be enzymatically catalyzed and converted into a drug at any step of its metabolism[25]. The prodrug could be made up of two or more medicines that are joined by a covalent bond[22].

In this work, we prepared new prodrugs consists of three drugs in one macromolecule by using mefenamic acid as the main molecule in all prepared compounds. All synthesized compounds were tested as antibacterial agents.

EXPERIMENTAL SECTION:

Material methods

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

Biological activity:

For each of the synthesized compounds (AY20 –AY23) the biological activity was determined against gram +ve and gram -ve bacteria.

Synthesis mefenamic acid derivatives:

Preparation of AY1

An excess of thionyl chloride was added to (10gm, 41.4mmol) of mefenamic acid.The mixture was left at (20-25) ^{o}C for (0.5hr.) min) with stirring. A yellow precipitate of the acid chloride was produced. the product was dissolved in (10ml) of DMSO and then it was added to the round bottom flask containing (6.34gm, 41.4mmol) of 5-aminosalicylic acid dissolved in (10 ml) of DMSO. The mixture was refluxed for (3hrs). After that, (4.2gm, 41.4mmol) of triethylamine was added, and the reflux was continued for (1hr). The progress of the reaction was monitored by TLC. The contents of the round flask were poured into cold ice water afforded dark brown precipitate, then filtered under vacuum pressure. The product was washed by water and then it was dried[22](scheme 1). FT-IR and ^{1}H-NMR were used to characterize AY1. Solid, Color: Dark brown, molecular formula:$C_{22}H_{20}N_2O_4$, M.wt=376.41gm/mol , yield=88% , m.p=160-164°C, R_f=0.86(Acetone8:Hexane2).

Preparation of AY1H(2-((2,3-dimethylphenyl)amino)-N-(3-(hydrazinecarbonyl)-4-hydroxyphenyl)benzamide)

An excess of thionyl chloride was added to (5gm, 13.3 mmol) AY1, the mixture was left at (20-25) ^{o}C for (30 mins) with stirring. To this mixture (15 ml) of methyl alcohol was added drop by drop at room temperature with stirring. Then (15 ml) of $NH_2NH_2.H_2O$ solution in ethanol was added to above mixture dropwise at room temperature with stirring. The result mixture reaction was refluxed for (4 hrs.). The progress of the reaction was monitored by TLC. The contents of the round flask were poured into ice cold water. Gray precipitate was formed and then filtered under vacuum pressure. the product was washed by water and then it was dried[26] (scheme 2). FT-IRwas used to characterize AY1-$NHNH_2$. Solid, Color: gray, molecular formula:$C_{22}H_{22}N_4O_3$, M.wt=390.44gm/mol , yield=88% , m.p=204-208^{o}C, R_f=0.74(Acetone9:Hexane1).

Synthesis of AY20-AY23

An excess of thionyl chloride was added to (0.5 mmol) of naproxen(0.16 gm), ibuprofen (0.1 gm), captopril (0.11 gm), and methyldopa (0.11 gm) respectively and left at room temperature for (30 mins) with stirring. (0.5 mmol, 0.2 gm) of AY1H in DMSO was added to above mixtures and refluxed for (1.5 hr). triethylamine(TEA) was added and the mixture was refluxed for (30min). The progress of reactions was monitored by TLC. The round flask contents were poured in cooledice water. Solid precipitates were formed and filtered under vacuum pressure. The products were washed with water and dried (scheme 3). All products were characterized by FTIR and ^{1}HNMR.

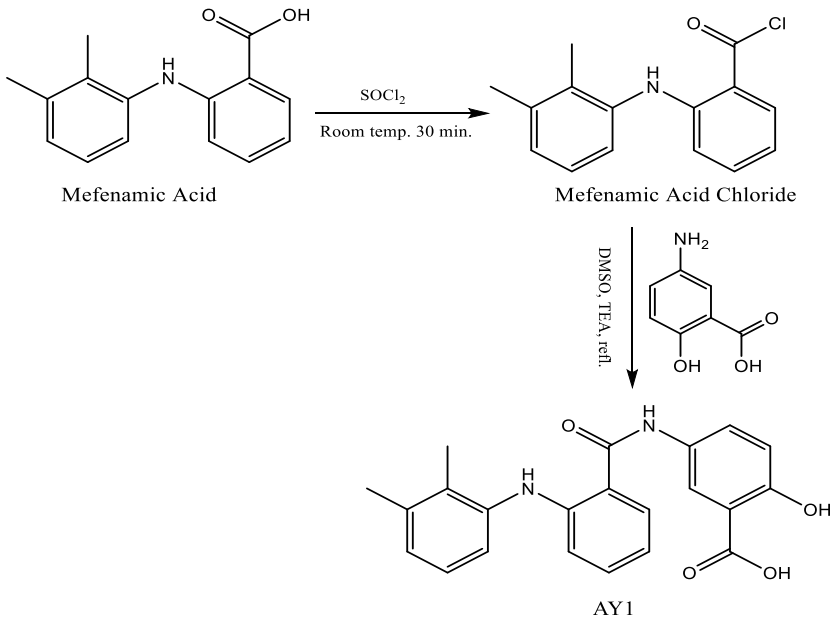
AY20:2-((2,3-dimethylphenyl)amino) -N-(4-hydroxy-3- (2-(3-(6-methoxynaphthalen-2-yl)butanoyl)hydrazinecarbonyl)phenyl)benzamide,Molecular formula: $C_{37}H_{36}N_4O_5$,M.wt= 616.71gm/mol, color: Dark brawn, yield =97.2%(0.3gm), m.p= (256-257) ^oC, R_f= 0.69 (9:1 acetone/hexane).

AY21:2-((2,3-dimethylphenyl)amino)-N-(4-hydroxy-3-(2-(2-(4-isobutylphenyl)propanoyl)hydrazinecarbonyl)phenyl)benzamide**,** molecular Formula: $C_{35}H_{38}N_4O_4$, M.wt=578.70 gm/mol, color: brawn, yield= 96.7(0.28gm). m.p =(181-182) ^oC, R_f = 0.65(9:1 acetone/hexane).

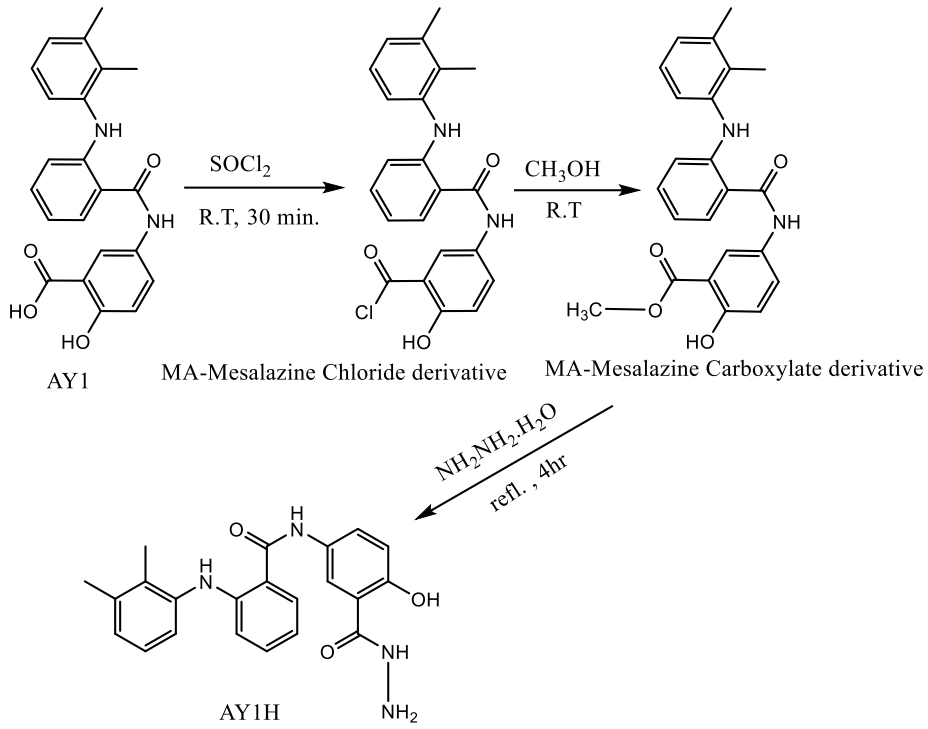
AY22:2-((2,3-dimethylphenyl)amino)-N-(4-hydroxy-3-(2-(1-(3-mercapto-2-methyl-propanoyl)pyrrolidine-2-carbonyl)hydrazinecarbonyl) phenyl)benzamide, molecular formula: $C_{31}H_{35}N_5O_5S$, M.wt= 589.71gm/mol, color: brawn, yield=94.9%(0.28gm). m.p= (235-237) ^oC,R_f= 0.67(9:1 acetone/hexane).

AY23:(S)-N-(3-(2-(2-amino-3-(3,4-dihydroxyphenyl)-2methylpropanoyl) hydrazine- carbonyl)-4-hydroxyphenyl)-2-((2,3-dimethylphenyl)amino) benzamide, molecular formula: $C_{32}H_{33}N_5O_6$, M.wt= 583.63gm/mol, color: dark brawn, yield= 82.2%(0.24gm), m.p= 277-280 ^oC, R_f= 0.72(9:1 acetone/hexane).

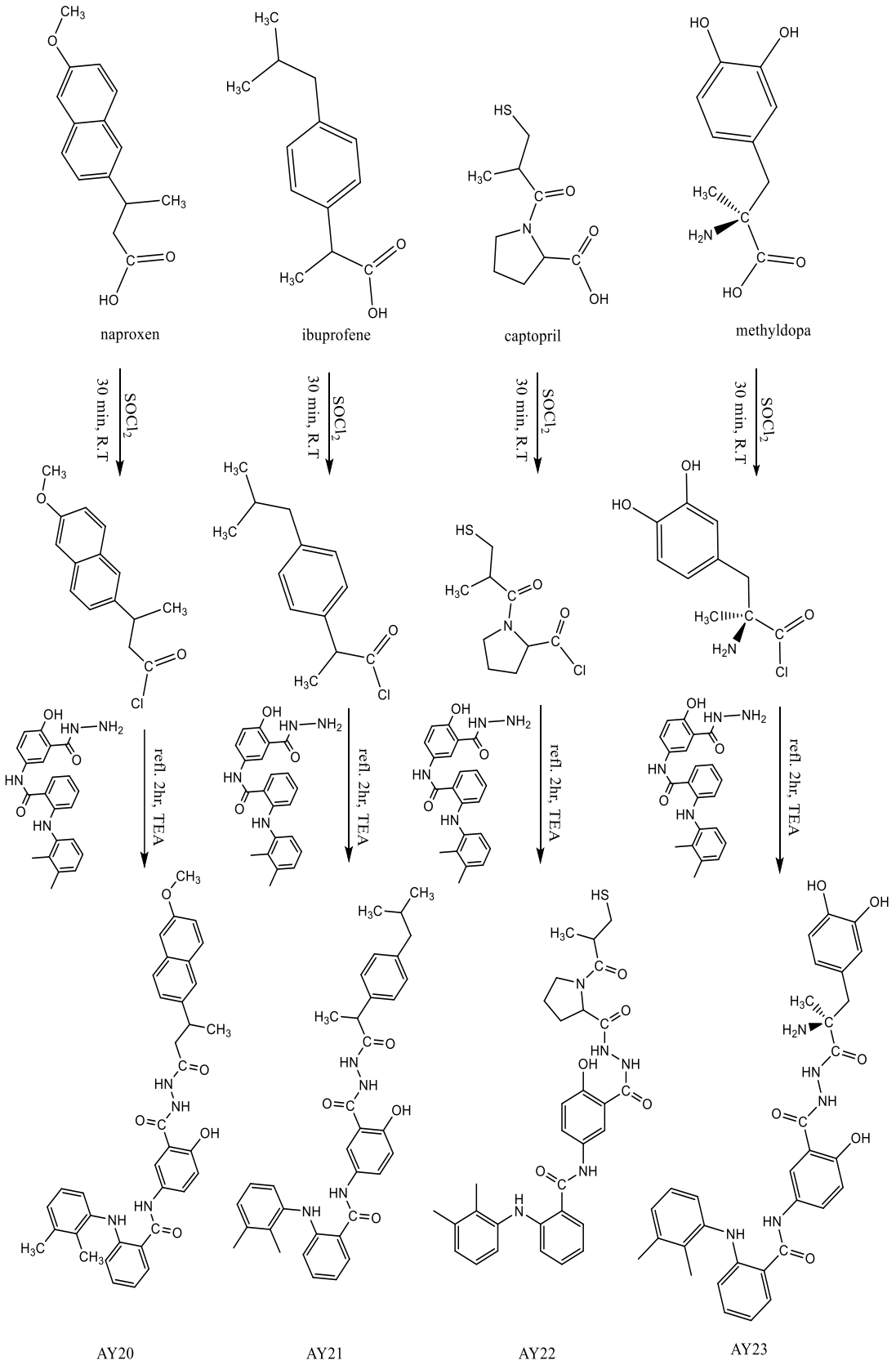
The solubility of all synthesized derivatives in different solvents was studied and listed in Table1.Biological activity against Staphylococcus aureus and Escherichia (E. coli) for all synthesized compounds was studied and recorded in Table 2.



Scheme 1: Synthesis of AY1



Scheme 2: Synthesis of AY1H



Scheme 3: Synthesis of AY20-AY23

Results and discussion:[26-29]

The reaction between mefenamic acid and mesalazine (5-ASA) lead to produce a bi-molecular compound (AY1) that was used as starting material to produce new tri-molecular drug systems consist of three different drugs molecules (AY20-AY23). All synthesized compounds were identified and confirmed by FTIR and ^{1}HNMR spectrum.

FT-IR spectrum for AY1 showed the following values (V_{max} cm^{-1}): 3272 and 3246(N-H str. groups) ,1573(N-H bend),1353(C-N str. aryl),1667(C=O str. carboxyl), 1622(CO str. amide), 3272-2489 (O-H str. groups), 3061(C-H str. Sp^2 aromatic), 2874 and 2942(C-H str. Sp^3), 1313 and 1244(C-O str.), 1433(O-H bend). ^{1}H-NMR (500 MH, δ ppm): 10.52(O-H , carboxyl), 8.63(N-H ,aromatic amid), 2.27(N-H, aromatic amine), 6.94(O-H, phenol), 8.02; 7.40; 7.52; 8.20; 7.72; 7.12; 7.1; 7.81; 7.39; 7.58(C-H, aromatic), 2.43 and 2.73(C-H, methyl), 2.51(DMSO).

For AY20, FTIR spectrum showed the following values (V_{max} cm^{-1}): 3291(O-H str., phenol), 3273- 3193(N-H str. groups), 3141-3067(C-H str. Sp^2 aromatic), 2995-2847(C-H str. SP^3 alkane), 1660 ; 1620(C=O str. amid), 1595 ; 1484(C=C str. aromatic), 1316(C-N str. aryl), 1572(N-H bend, amine), 1533(N-H bend, amide),1218 ; 1187(C-O str.). ^{1}H-NMR (500 MH, δ ppm):a- 10.43(N-H,sec.amide), b- 8.18(N-H, sec.amide), c- 8.01(N-H, sec. amide), d- 7.91-7.00(C-H,aromatic), e- 6.86(O-H phenol), f- 4.04(N-H aromatic amine), g- 3.78(O-C-H), h-3.45(C-H, methine), i- 2.47(C-H, methyl), j- 2.41(C-H, methyl), k-2.14(CH_2, methylene), l-1.20(C-H, methyl), 2.50(DMSO).

FTIR spectrum for AY21 showed the following values (V_{max} cm^{-1}): 3291(OH str., phenol), 3273; 3234(NH str., amine and amide), 3150- 3045(CH str., aromatic), 2953-2848(CH str., alkyl groups), 1689;1622(C=O str.), 1595, 1462(C=C str., aromatic), 1570; 1533(NH bend, amine and amide), 1313(C-N str. aryl), 1381(CH_3 bend), 1219(C-O str. phenol). ^{1}H-NMR (500 MH, δ ppm): a- 10.42(N-H, sec.amide), b- 8.18(N-H, sec.amide), c- 8.01(N-H, sec.amide), d-7.91- 7.08(C-H, benzene), e- 6.73(O-H, phenol), f- 3.87(N-H, aromatic amine), g- 3.62(C-H, methine), h- 2.46(CH_2, methylene), i- 2.40(C-H, methyl), j- 2.13(C-H, methyl), k- 1.79(C-H, methine), l- 1.34(C-H, methyl), m- 0.84(C-H, methyl), 2.50(DMSO).

The following values (V_{max} cm^{-1}) were obtained from FTIR spectrum for AY22: 3291(O-H str., phenol), 3273-3191(N-H str., amine and amide), 3138-3013(C-H str., aromatic, sp^2), 2992-2874(C-H str., alkyl groups, sp^3), 2559(S-H str., mercaptans), 1679; 1621(C=O str., amides), 1596; 1484(C=C str., aromatic), 1310(C-N str., aryl), 1571; 1533(N-H bend, amine and

amide), 1466(CH_2 bend), 1382(CH_3 bend), 1221(C-O str., phenol). ^{1}H-NMR (500 MH, δ ppm): a- 10.43(N-H, sec.amide), b- 8.18(N-H, sec.amide), c- 8.00(N-H, sec.amide), d- 7.91-7.08(C-H, benzene), e- 6.67(O-H, phenol), f- 4.81(C-H, pyrrolidine), g- 4.23(N-H, aromatic amine), h- 3.87;3.40(CH_2, pyrrolidine), i- 2.97(CH_2, methylene), j- 2.71(C-H, methine), k- 2.47(C-H, methyl), l- 2.40(C-H, methyl), m- 2.13(CH_2, pyrrolidine), n- 1.92(CH_2, pyrrolidine), o- 1.48(S-H, thiol), p- 1.15(C-H, methyl), 2.50(DMSO).

FTIR spectrum for AY23 showed the following values (V_{max} cm^{-1}): 3290(O-H str., phenol), 3274- 3151(N-H str., amine and amide), 3100-3012(C-H str., aromatic,sp^2), 2979-2918(C-H str., alkyl, sp^3), 1677;1620(C=O str., amide), 1597;1484(C=C str., aromatic), 1349(C-N str., aryl), 1036(C-N str., alkyl), 1571;1533(N-H bend, amine and amide), 1234-1187(C-O str.), 1467(CH_2 bend), 1383(CH_3 bend). ^{1}H-NMR (500 MH, δ ppm): a- 10.42(N-H, sec.amide), b- 8.18(N-H, sec.amide), c- 8.00(N-H, sec.amide), d- 7.90-7.07(C-H, benzene), e- 6.48(O-H, phenol), f- 4.82(NH_2, amine), g- 4.69(O-H, phenol), h- 4.61(O-H, phenol), i- 4.44(N-H, aromatic amine), j- 3.40(CH_2, methylene), k- 2.46(C-H, methyl), l- 2.40(C-H, methyl), m- 1.21(C-H, methyl), 2.50(DMSO).

Solubility of synthesized compounds:

Table 1: solubility of synthesized compounds in different solvents

Comp.	H_2O	EtOH	$(CH_3)_2O$	CH_2Cl_2 DCM	$C_4H_8O_2$ Et.ac.	$(C_2H_5)_2O$ ether	Pet.ether	DMSO
AY20	-	+	+	-	partial	-	-	+
AY21	-	+	+	-	partial	-	-	+
AY22	-	+	+	partial	partial	-	-	+
Ay23	-	+	+	partial	Partial	-	-	+

+ = dissolved, - = undissolved

The antibacterial activity: Table 2 represents the results of the antibacterial activity test for new derivatives (Ay20-AY23), these derivatives have the ability to prevent the diffusion of bacteria more than mef and the other medicines that are utilized in the synthesis of these new derivatives (Ay20-AY23). Dimethylsulfoxide was used to dissolve compounds. agar disc-diffusion method was used to determine the biological activity for prepared compounds versus two classes of bacteria; Staphylococcus aureus (gram +ve), and Escherichia (E. coli) (gram -ve).

Table-2: anti-bacterial activity for AY20-AY23 and MEF at 1mg/ml concentration.

Inhibition aria (mm) for studied bacteria			Inhibition aria (mm) for studied bacteria		
Comp.s	Gram +ve (Staphylococcus aureus)	Gram –ve (E- coli)	Pure drug	Gram +ve (Staphylococcus aureus)	Gram -ve (E- coli)
AY20	23	13	Naproxen	32	30
Ay21	24	0	Ibuprofen	6	14
Ay22	20	6	Captopril	4	12
AY23	14	12	Methyldopa	0	8
MEF	0	0			
DMSO	0	0			

CONCLUSION:

Novel tertiary molecules drug systems were developed to enhance mefenamic acid with new therapeutic properties. Mefenamic acid was bound with various carboxylic drugs in addition to meslazin. FTIR and ^{1}H-NMR were used to identifyproduced compounds .The biological activity of the prepared compounds was indicated and showed bactericidal effect.

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