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Original Article

Study the Toxicity and Anticancer Activity of Some New Derivatives of Mefenamic Acid

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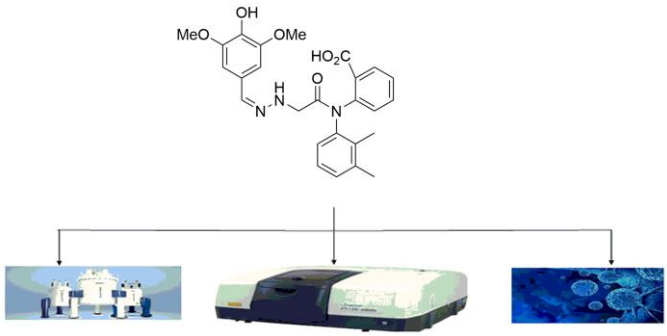
ABSTRACT

The new 1,3-Oxazepine derivatives **(IV$_{a-d}$)** were manufactured from the response of *N*-Arylhydrazone (**III**) based on Mefenamic acid with various cyclic carboxylic acid anhydrides such as (succinic, maleic, phthalic, and 3-nitrophthalic) anhydride by using dry benzene under reflex via (2+5) cycloaddition reaction. These compounds 1,3-Oxazepine (**IV**) were obtained via a four-steps- sequence reactions in good yields. Condensation reaction of mefenamic acid with chloroacetyl chloride to give 2 -[2-chloro-N-(2,3-dimethylphenyl) acetamido] benzoic acid (**I**), which on amination with hydrazine hydrate in ethanol to give a corresponding acid hydrazid (**II**). The acid hydrazide was used as the starting materials on condensation with syringe aldehyde afforded newly *N*-Arylhydrazone (**III**) in a good yield. Finally, the later compound reacted with different type of acid anhydrides to get new derivatives of 1,3-Oxazepine. The new compounds were characterized by using FT-IR, ^{1}H-NMR, and mass spectroscopy. In addition, the potential antibacterial activities for the certain compounds were investigated by using three species of bacteria: *Staphylococcus aureus, Klebsiella pneumoniae*, and *Escherichia coli* which most of the target derivatives have exhibited a good efficacy compared with ampicillin (as antibacterial). Besides the cytotoxic effect by using various concentrations of the derivatives (**IV$_c$**) and (**IV$_d$**) were assessed by human breast carcinoma cells (MCF-7), which have been exhibited a high effect on the concentration of 400 µl/ml with IC50 =80.20 and IC50=82.80. A tiered approach to investigate the toxicity utilized mice to estimate its acute toxicity and the result confirmed the non-toxicity of these compounds

GRAPHICAL ABSTRACT



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Introduction

In drug chemistry, Mefenamic acid is known as anthranilic acid derivatives brand of nonsteroidal anti-inflammatory drugs (NSAID) that inhibits the synthesis of pain-causing prostaglandins and is useful as pain reliever [1, 2]. The unique structure of mefenamic acid synthetically leads to a large number of the derivatives class of (NSAID), which based on pharmacological findings represent their interference with prostaglandin biosynthesis. It has been used for the rheumatoid treatment and degeneration of joint cartilage disease [3, 4]. Recently, it has been found that (NSAID) can be used to treat musculosketal pain. An important aspect in the literature is that prepared many Mefenamic acid derivatives containing heterocyclic moiety, which have been useful in medicine and cytotoxic activities [5-7].

Various synthetic routes to 1,3-Oxazepine derivatives have been synthesised based on different strategies for the construction of the heterocyclic ring [8-10]. These strategies led to 1,3-oxazepine carrying suitable position of mefenamic acid which open the way for synthesis of new heterocyclic rings [11-13].

A wide range of heterocyclic derivatives was reported and has been developed including pharmaceutical molecules. The aims of this research project was to initially carry out some novel 1,3-oxazepine derivatives of Mefenamic acid as pro-drug moieties which have a more therapeutic efficacy and a lower toxicity.

Materials and Methods

All chemicals used were purchased from Sigma-Aldrich, and Merck Chemicals. ^{1}H-NMR spectra were recorded through Ultra Shield (Bruker) 300 MHz. The Fourier Transform Infrared Spectrometer (FT-IR) spectra were registered on Shimadzu (Ir prestige-21). Mass spectra were performed by Electron Impact (EI) (70) eV mass through the Model: 5973 spectrometer.

*Synthesis of 2-[2-chloro-N-(2,3-dimethylphenyl) acetamido] benzoic acid (**I**)*

A mixture of Mefenamic acid (2.41 g, 0.01 mol) and chloroacetyl chloride (0.035 mol) were refluxed for 2 hours on a water bath. 2-propanol and water (2:2 mL) were added to the mixture and stirring was continued overnight, and then toluene (10 mL) was added and extracted with 10% $NaHCO_3$, dried with $MgSO_4$, and recrystallized by ethanol that was resulted in a pale-yellow solid. Yield 75%, mp 135-137 °C [14].

*Synthesis of 2- (N-(2,3-dimethylphenyl) -2-hydrazineylacetamido) benzoic acid (**II**)*

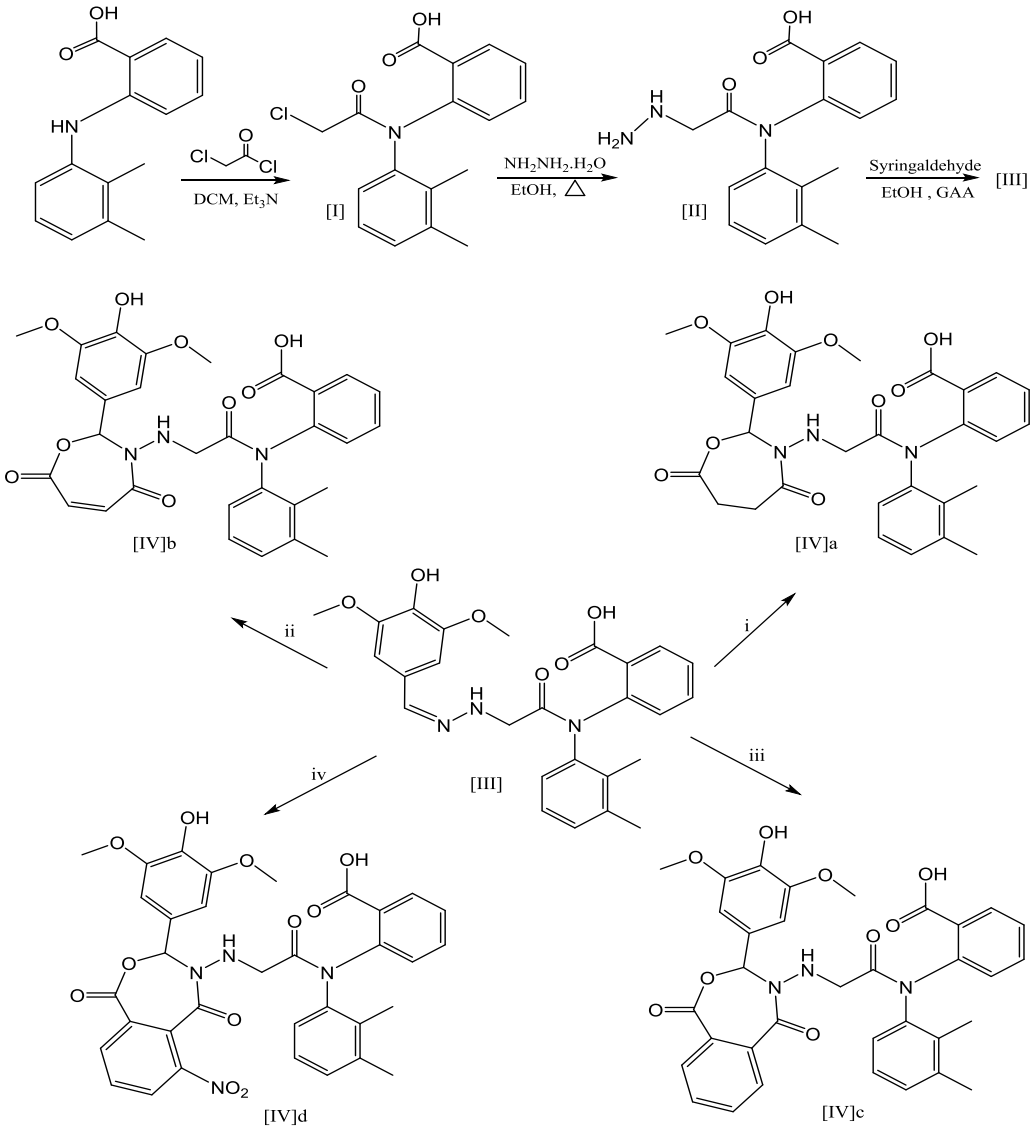
A mixture of compound (**I**) (3.17 g, 0.01 mol) and hydrazine hydrate (0.01 mol) in ethanol (20 mL) was refluxed for 4 hours. After cooling the resulting solid was filtered, dried, and recrystallized from methanol to give light yellow solid. Yield 80%, mp 155-158 °C [15].

*Synthesis of 2-(N-(2,3-dimethylphenyl)-2-(2-(4-hydroxy-3,5-dimethoxybenzylidene) hydrazineyl) acetamido) benzoic acid (**III**)*

Equal moles of compound (**II**) and syringaldehyde were mixed in 20 mL of ethanol, with (GAA) and heated for 8 hours. Then, the hydrazone precipitate was filtered and dried. Dark yellow powder, yield 70%, mp l10-112 °C [16].

*Procedure of 1, 3-oxazepine compounds (**IV**$_{a-d}$)*

A mixture of synthesized hydrazone (**III**) (4.78 g, 0.01 mol) and 0.01 mol of different acid anhydride in 20 mL of benzene was heated for 7 hours [17]. The precipitate was formed which has been recrystallized from 1, 4-dioxane. Our successful routes to synthesize the new derivatives are illustrated in Scheme 1.



Scheme 1: Synthesis of target derivatives (**I-IV$_{a-d}$**)

Biological study

Anti-bacterial activity

The new oxazepine (**I-IV$_{a-d}$**) were examined (*in vitro*) against *Staphylococcus aureus (G+), Klebsiella pneumoniae (G-)* and *Escherichia coli (G-)* employing the agar diffusion method [18]. The bacterial isolation and purification were carried out in the Biology Department of the University of Baghdad, Iraq. The prepared agar and petri dishes were sterilized by autoclaving for 20 min at 121 °C. The agar was surface inoculated uniformly from the both culture of the tested microorganisms, the three types of previous bacteria were activated in a nutrient growth medium at for 24 hours. In the soloidified medium, suitably spaced apart holes were made (6 mm in diameter). These holes were filled up with the prepared compounds dissolved in DMSO to give concentration 200 µg/ml. These plates were incubated at 37 °C for 24 hours. The formed inhibition zones were measured in millimeter and compared with ampicillin as a common antibiotic.

Cytotoxicity assay

The cytotoxicity of new 1,3-oxazepine derivatives of mefenamic acid (**IV$_c$**) and (**IV$_d$**) was examined against MCF-7 cell line [19] at the Biotechnology Research Center, Al-Nahrain University. The cells have been seeded at 200 µl of cell suspension and

filled in 96 well culture plates, sealed at Para film and incubated at 37 °C for one day with 5% CO_2 gas and medium completed with (1% penicillin/streptomycin blend +10% bovine serum) till the cells fielded confluence. The cells were examined for impurity and cultured at various concentrations (10-500 µg/Ml). However, 200 µl of sustenance medium were filled to monitor group, after that closed firmly incubated. The cytotoxicity was executed after 48 hours, and then 150 µL of dimethyl sulfoxide was added up to the solution, and then it was shaken [20]. Thereafter, the absorbance values registers to enumerate the inhibition rate of cell growth [21].

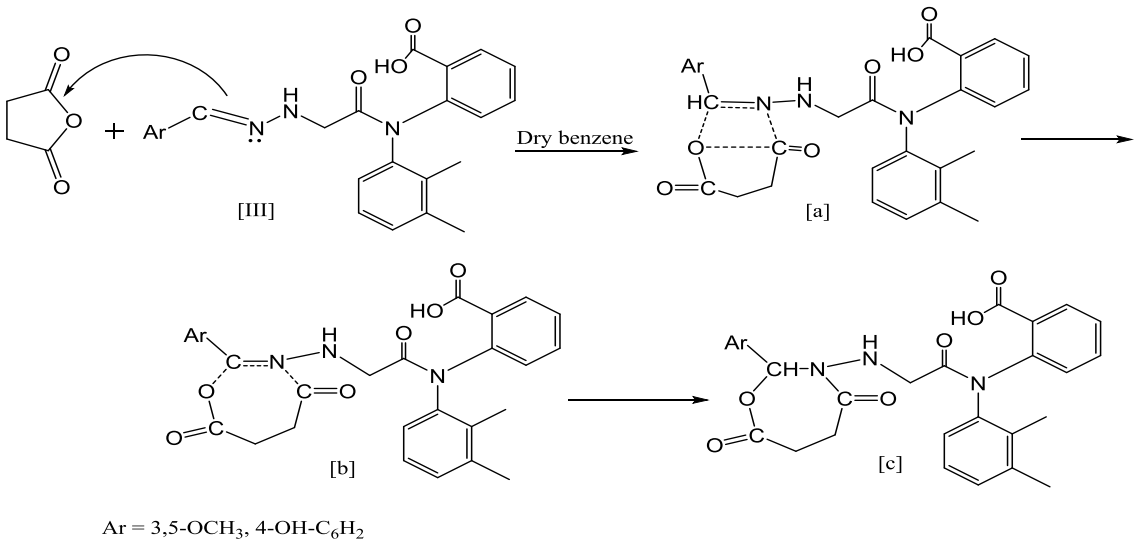
Acute toxicity test

Three sets of forty-five albino mice were utilized to examine the acute toxicity of new1,3-oxazepine derivatives (**IV$_c$**) and (**IV$_d$**) by using the Lorke-written method [19]. The three groups were fasted for eighteen hours with approaching to water before experiment. The derivatives were resolved in distilled H_2O and handled via the oral route gently. After two weeks of feeding, the internal organs mice such as the heart, kidneys, and brain were weighed and compared with the control group and weighed with the monitoring of vital signs.

Results and Discussion

Chemistry

This research project is to initially carry out the synthesis of 7-membered cyclic ring oxazepine derivatives (**IV$_{a-d}$**) based on Mefenamic acid. The newly 1,3-oxazepine (**IV$_{a-d}$**) were obtained by (2+5) cycloaddition reaction of novel Schiff base (**III**) with five atoms cyclic anhydride including: (succinic, maleic, phthalic, or 3-nitrophthalic) anhydride in the presence of dry benzene as a solvent. The mechanism includes the addition of σ bond of C-O group of acid anhydride to π bond of imine group to yield four-membered hetero ring and five-membered cyclic ring in the same $[T.S]_{a,b,c}$, which unlocks into acid anhydride to afford seven-membered heterocyclic ring. The proposed mechanism has been summarized in Scheme 2 [17].



Scheme 2: The suggested mechanism of composing1,3-oxazepine derivatives

Compounds (**IV$_{a-d}$**) have been perfectly characterized and correlated with their structures by using the spectroscopic analysis. The physical properties are illustrates in following for all derivatives (**IV$_{a-d}$**) [22-25].

*N-(2,3-dimethylphenyl)-2-((2-(4-hydroxy-3,5-dimethoxyphenyl)-4,7-dioxo-1,3-oxazepan-3-yl)amino)acetamido)benzoic acid (**IV$_a$**)*

Beige, yield 81%, $C_{30}H_{31}N_3O_9$, mp 262-264 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3361, 3313, 3072, 2979, 2847, 1747, 1653, 1608, 1576, 1508. ^{1}H-NMR (300

MHz, DMSO): δ 2.10-2.29 (s, 6H, $2CH_3$), 1.34-1.36 (m, 4H, CH_2-CH_2), 3.84 (s, 6H, $2OCH_3$), 4.33 (s, 2H, CO-CH_2), 6.88-7.90 (m, 9H, Ar-H), 8.58 (s, 1H, CH-N), 9.49 (s, 1H, NH), 9.70 (s, 1H, OH), 11.98 (s, 1H, COOH).

2-(N-(2,3-dimethylphenyl)-2-((2-(4-hydroxy-3,5-dimethoxyphenyl)-4,7-dioxo-4,7-dihydro-1,3-oxazepin-3(2H)-yl)amino)acetamido)benzoic acid (***IV$_b$***)

Bright yellow, yield 78%, $C_{30}H_{29}N_3O_9$, mp 120-122 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3300, 3263, 3010, 2987, 2922, 1732, 1685, 1657, 1601, 1527, 1329, 1255. ^{1}H-NMR (300 MHz, DMSO): δ 2.20-2.29 (s, 6H, $2CH_3$), 3.75 (s, 6H, $2OCH_3$), 4.25 (s, 2H, CO-CH2), 6.20-6.41 (m, 2H, CH=CH), 6.75-8.07 (m, 9H, Ar-H), 8.09 (s, 1H, CH-N), 9.31(s, 1H, NH), 9.18 (s, 1H, OH), 11.12 (broad, 1H, COOH).

*2-(N-(2,3-dimethylphenyl)-2-((3-(4-hydroxy-3,5-dimethoxyphenyl)-1,5-dioxo-1,5-dihydrbenzo [e][1,3]oxazepin-4(3H)-yl)amino)acetamido) benzoic acid (**IV$_c$**)*

Pale yellow, yield 82%, $C_{34}H_{31}N_3O_9$, mp 198-200 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3467, 3346, 3066, 2918, 2860, 1741, 1653, 1625, 1574, 1502, 1329, 1254. ^{1}H-NMR (300 MHz, DMSO): δ 2.10-2.29 (s, 6H, $2CH_3$), 3.83 (s, 6H, $2OCH_3$), 3.33 (s, 2H, CO-CH_2), 6.68-7.37 (m, 13H, Ar-H), 7.89 (s, 1H, CH-N), 9.18 (s, 1H, NH), 9.45 (s, 1H, OH), 12.98 (broad, 1H, COOH).

*2-(N-(2,3-dimethylphenyl)-2-((3-(4-hydroxy-3,5-dimethoxyphenyl)-6-nitro-1,5-dioxo-1,5-dihydrobenzo[e][1,3]oxazepin-4(3H)-yl) amino)acetamido)benzoic acid (**IV$_d$**)*

Yellow, yield 80%, $C_{34}H_{30}N_4O_{11}$, mp 146-148 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3410, 3370, 3012, 2933, 2843, 1763, 1718, 1601, 1510, 1462, 1514, 1336. ^{1}H-NMR (300 MHz, DMSO): δ 2.09-2.38 (s, 6H, $2CH_3$), 3.37 (s, 6H, $2OCH_3$), 4.50 (s, 2H, CO-CH_2), 6.69-7.91 (m, 12H, Ar-H), 8.06 (s, 1H, CH-N), 9.20 (s, 1H, NH), 9.45 (s, 1H, OH), 12.97 (broad, 1H, COOH).

Mass spectrum of hydrazine (**III**): $C_{26}H_{27}N_3O_6$ (M.Wt.=477.19) showed the base peak at (m\z = 367%). Furthermore, characteristic peaks were indicated for independent fragments by m/z (Rel. Int. in %): (m\z = 293(75%), 268(24%), 194(18%), 161(25%), 121(15%), and 46(20%)). This data confirmed the hydrazone structure.

Finally, the mass spectra of compound (**IV$_d$**): $C_{34}H_{30}N_4O_{11}$ (M.Wt.=670.19), Scheme (3) showed the base peak at m/z=293 (100%). Too characteristic peaks were shown for independent fragments represented by m/z=657 (5%), 309 (22%), 293 (100%), 267 (50%), 163 (30%), 135 (27%), which agrees with the molecular weight of the structure inspired by for compound (**IV$_d$**) [26, 27].

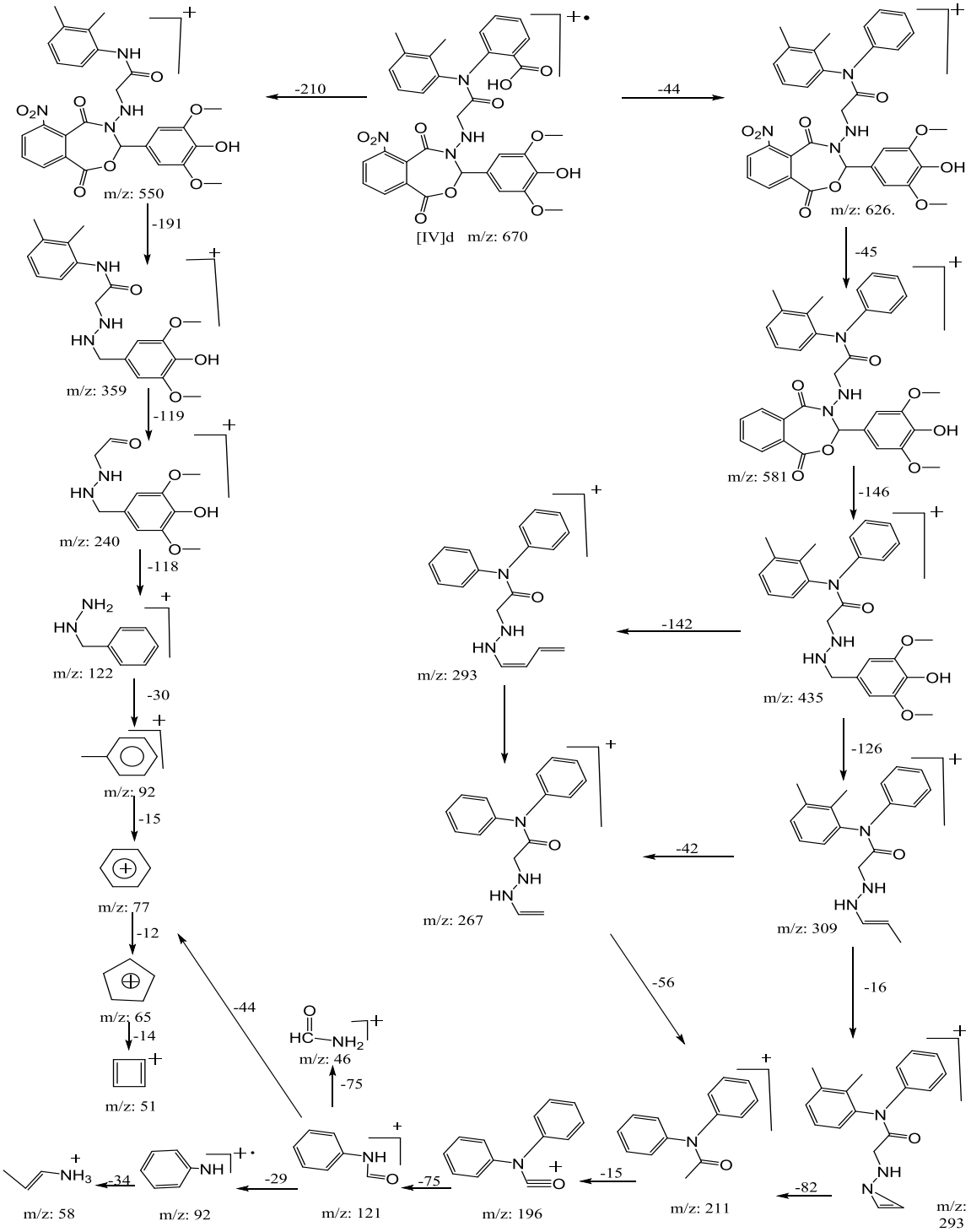
Biological activity

Antibacterial activity

All prepared derivatives have been tested *in vitro* against pathogenic bacteria [18]. The inhibition zones of the target compounds are presented in Table 4 and most of the derivatives possess the high or moderate biological activity against bacteria compared with ampicillin an antibiotic drug. This could be due to the presence of the oxazepine ring and NO_2 group, as displayed in Figure 1 [28, 29].

Cytotoxicity assay

Compounds (**IV$_c$**) and (**IV$_d$**) have been screened for their cytotoxicity activity (*In vitro*) by using MCF-7 (human breast carcinoma cells). Freshney's protocol [19] has been employed for cell culture media. The MCF-7 viability after adding different concentrations of (**IV$_c$**) and (**IV$_d$**) were recorded in ELISA reader at 575 nm. Compound (**IV$_c$**) showed the significant effects at concentration of 400 µl/mL, whereas the viability cells were (38.63%, 25.78%,13.99, 6.34%, 5.98%, and 6.09%) in (400, 200, 100, 50, 25, and 12.5) µg/ml, with IC50=80.20. In addition, compound (**IV$_d$**) possess important effects at concentration of 400 µl/mL vs. cells line, whereas the viability cells were (50.99%, 50.54%, 28.23 %, 18.98%, 13.09%, and 6.98%) in the same concentrations, respectively, and IC50=82.80.



Scheme 3: Mass fragments of compound (**IV$_d$**)

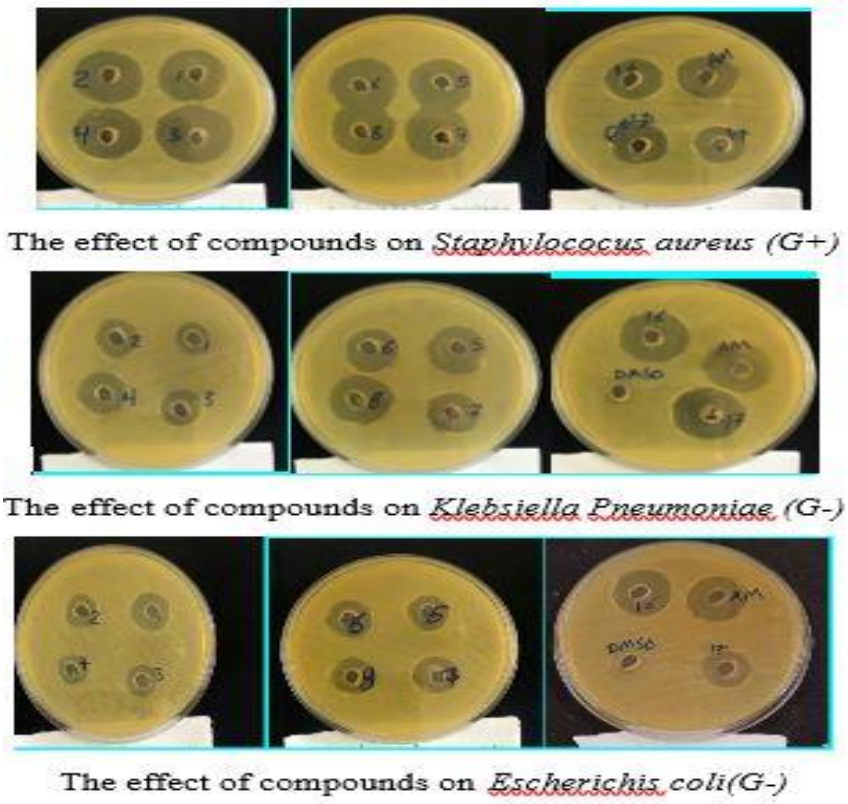


Figure 1: The effect of compounds against bacteria

Table 4: The zone of inhibition in (mm) for oxazepine derivatives $[IV]_{a-d}$

Compound No.	Staph. aureus	Klebsiella pneumoniae	Escherichis coli
(IV_a)	20	12	12
(IV_b)	21	16	10
(IV_c)	24	20	10
(IV_d)	21	22	10
Ampicillin	22	22	20

Acute Toxicity Test

The object mice showed no symptoms of toxicity, behavior change, or mortality with doses (5 and 10 g/kg) body weight between the control and the handler groups. Moreover, mice were weighed daily for both groups and for the next two weeks. Certainly, the organs (cervical, liver, kidneys, and heart) were weighted after sacrificed some of theme and showed normal cases and weight [19].

Conclusion

Finally, the synthetic route described of new 1,3-oxazepine derivatives based on mefenamic acid with the expected biological activity to attain better action and low gastric side effects. The objective compounds showed a broad range of antimicrobial activities. Compounds (**IV_c**) and (**IV_d**) display the anticancer activity on MCF-7 *(in vitro)*, this could be related to the presence of the oxazepine ring with NO_2 group in its molecule structure, so they are prospective to be very promising origin compounds for the design a new pharmaceutical drug over and above pharmacological project and reduce the more side effects of mefenamic acid.

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Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

The author declared that they have no conflict of interest.

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