Muhanned A. Mahmoud et al /J. Pharm. Sci. & Res. Vol. 10(11), 2018, 2836-2840

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

New molecules building between 5,5-diphenyl-imidazolidine-2,4-dione with many heterocyclic moieties and studying their antibacterial activities

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Abstract:
This study aimed to prepare a series of Hybrid compounds between phenytoin and Oxazepines, . Diazepines and Quinazolin .The target compounds were prepared by three steps: First step comprise synthesis of Schiff base from reaction of 4-(dimethylamino)benzaldehyde with *p*-chloroaniline, In the second step: cyclization reaction between Schiff base and phthalic anhydride ,phthalic imide and anthranilic acid to obtain Oxazepines, Diazepines and Quinazolin compounds. Final step: include Alkylation of the phenytoin salt with the product of the second step to obtain Hybrid phenytoin compounds. The chemical structures of all prepared compounds were established by FT-IR,^{1}H and ^{13}C-NMR. Some the test compounds showed potent antibacterial activity, especially against Escherichia coli .

Keywords : phenytoin, Schiff base, Oxazepines, . Diazepines

1. INTRODUCTION:

Oxazepines compounds are significant unsaturated seven-membered heterocyclic rings because of their wide variety of application . the biological activities of oxazepine compounds were establish in the pharmaceutical fields as having antihistaminic and antiallergic agents[1] hypnotic muscle relaxation [2] and anti-inflammatory effects[3].further more , these compounds with metals have shown antibacterial and antifungal activity [4]central depressant [5] , analgesic[6].

Hybrid pharmacophore program depend on the use of two or more pharmacophores, each with potential pharmacological activity to be merged in one molecule, target that this hybridization could produce yields with better pharmacological profile.

phenytoin compounds are important antiepileptic drug that act through inhibition of brain sodium channels [7], has been chosen for its efficacy against partial and generalized seizures [8]. Previous studies showed that compounds including thiosemicarbazide pharmacophore in their structure, constitute a class of compounds with potential anticonvulsant properties [9,10]. Additionally , numerous compounds containing 1,3,4-oxadiazole [11-13], 1,3,4-thiadiazole [14-16] or 1,2,4-triazole ring [17,18] in their chemical structure have been observe anticonvulsant activity. Also many of phenytion derivatives uses as anticonvulsant activity [19,20].

The specific objective of this study was to synthesis of new hybrid phenytion compounds with Oxazepines, Diazepines and Quinazolin compounds and test the antibacterial activity against tow type of bacterial

2. EXPERIMENTAL PART

2.1 General

All chemicals used were of synthetic grade. The purity of compounds was checked by TLC on silica plates using iodine vapors and UV light as detecting agents. The melting points of the synthesized compounds were determined by open capillary method and are uncorrected. The IR spectra of synthesized compounds were recorded on a SHIMADZU FT-IR 8400S spectrophotometer by using KBr disc(ν,cm^{-1}).. The ^{1}H-NMR were recorded in DMSO-d_6 using a NMR (Bruker 400MHz) MHz spectrometer and chemical shifts (δ) are given in parts per millions (ppm) downfield from tetramethylsilane (TMS) as an internal standard.

2.2 Synthesis of Schiff base (1).

Equimolar amounts (0.01 mol) of appropriate aldehyde 4-(dimethylamino) benzaldehyde and the amine *p*-chloroaniline) in EtOH 99% (15ml) with (3) drops of(CH_3COOH) was ref. in H_2O bath for Three hours. The product was then let to cool at R.T, and the precipitate was filtered and dried, recrystallized from ethanol to give yellow crystal.

4-(((4-chlorophenyl)imino)methyl)-N,N-dimethylaniline (1): yellow . m.p : 165-167 °C, yield 80% , IR (KBr, cm^{-1}): aromtic C-H_{str}(3062), aliphatic C-H_{str} (2893, 2850), C=N_{str}(1600), aromatic C=C_{str} (1577, 1550 , 1477, 1431), C-N_{str} (1230), C-Cl_{str} (732), ^{1}HNMR (dmso-d_6) δ ppm : 2.24 (s , 6H , 2CH_3), 6.69-7.74 (m,4H,Ar-H) 8.39 (s, 1H, N=CH),. ^{13}CNMR (DMSO-d6) δ ppm : 43.5(2CH_3) ,111, 114.3 , 116.2 , 124.5 , 126.7 ,134.1 , 137.1153 (Aromatic -C's), 161.1(CH=N of imine),

2.3 Synthesis of compounds (2,3,4).

Equimolar amounts (0.01) of Schiff base and (phthalic anhydride ,phthalic imide, anthranilic acid)respectively in dry C_6H_6 was refluxed for (4-5) hours, the solvent was removed by roatory evaporater and resulting colored solid was recrystallized from dry dioxane to give the title compounds.

4-(4-chlorophenyl)-3-(4-(dimethylamino)phenyl)-3,4-dihydrobenzo[e][1,3]oxazepine-1,5-dione (2): white . m.p : 212-214 °C, yield 72% , IR (KBr, cm^{-1}): aromtic C-H_{str}(3062), aliphatic C-H_{str} (2920, 2816), ester C=O_{str} (1712), amide C=O_{str}(1658), aromatic C=C_{str} (1581, 1550 , 1492, 1436), C-N_{str} (1230, 1172), C-O_{str} (1273), C-Cl_{str} (736), ^{1}H-NMR (dmso-d_6) δ ppm : 2.93 (s , 6H , 2CH_3), 6.63-8.39 (m, 12H, Ar-H), ^{13}CNMR (dmso-d_6) δ ppm : 45.5(2CH_3) 98.5(CH) , 111.58 , 111.94 , 124.5 , 126.7 ,129.5 , 130.9,153.3,155.5(Aromatic -C's), 161.1(C=O ester of Oxazepine ring),179.9(C=O amide of Oxazepine ring).

4-(2-chlorophenyl)-3-(4-(dimethylamino)phenyl)-3,4-dihydro-1H-benzo[e][1,3]diazepine-1,5(2H)-dione (3): white . m.p : 291-293 °C, yield 88% , IR (KBr, cm^{-1}): N-H_{str}(3190), aromtic C-H_{str}(3062), aliphatic C-H_{str} (2899, 2854), ester C=O_{str} (1774), amide C=O_{str}(1751), aromatic C=C_{str} (1577, 1550 , 1481, 1431), C-N_{str} (1230, 1165), C-Cl_{str} (732), ^{1}H-NMR (dmso-d_6) δ ppm : 2.92 (s , 6H , 2CH_3), 6.72-8.39 (m, 12H, Ar-H), 11.31 (s , 1H , CO-NH Diazepine ring), ^{13}CNMR (dmso-d_6) δ ppm : 42.5(2CH_3) 83.53(CH) , 111.93 , 123.06 , 124.55 , 125.04 ,129.52 , 130.97,131.13,132.86,150.42,151.66(Aromatic -C's), 162.78(O=C-N amide of Diazepin ring),169.78(HN-C=O amide of Diazepin ring).

3-(4-chlorophenyl)-2-(4-(dimethylamino)phenyl)-2,3-dihydroquinazolin-4(1H)-one (4): dark yellow . m.p : 277-279 °C, yield 75% , IR (KBr, cm^{-1}): N-H_{str}(3183), aromtic C-H_{str}(3070, 3032), aliphatic C-H_{str} (2924, 2854), C=O_{str} (1678), aromatic C=C_{str} (1597, 1581 , 1481, 1435), C-N_{str} (1288, 1226, 1168), C-Cl_{str} (821),), ^{1}H-NMR (dmso-d_6) δ ppm : 2.96 (s , 6H , 2CH_3), 6.68-8.40 (m, 12H, Ar-H), 9.29 (s , 1H , CH-NH Quinazolin ring), ^{13}CNMR (dmso-d_6) δ ppm :

44.6($2CH_3$) 70.5(CH) , 111.95 , 124.06 , 128.55 , 129.04 ,129.52 , 130.97,133.13,134.86,140.42,151.66(Aromatic -C's), 169.78(O=C-N amide of Quinazolin ring).

2.3 Synthesis of hybrid phenytion (5,6,7).

(0.05 mol) of **phenytion** salt was dissolved in absolute ethanol (15 ml) with Oxazepines, . Diazepines and Quinazolin (0.05 mol) respectively in round flask (50 ml) and reflux condenser. The mixture was refluxed for (4-7 hours) and filtered directly to get colored products of the precipitated salt the filtered sample was cooled and recrystallized from ethanol. Table (1) shows the physical properties of the prepared compounds.

) 3-(4-dimethylamino)phenyl)-4-(4-(2,5-dioxo-4,4-diphenylimidazolidin-1-yl)phenyl)-3,4-dihydrobenzo[e][1,3]oxazepine-1,5-dione (5): white . m.p : 285-287 °C, yield 77% , IR (KBr, cm^{-1}): amide N- H_{str}(3209), aromtic C-H_{str}(3070), aliphatic C-H_{str} (2951, 2796), ester C=O_{str} (1770), amide C=O_{str}(1739), imidazolidine C=O_{str}(1720) aromatic C=C_{str} (1539, 1492 , 1450), C-N_{str} (1226, 1195), C-O_{str} (1284), ^{1}H-NMR (dmso-d_6) δ ppm : 2.98 (s , 6H , $2CH_3$), 6.49-8.45 (m, 22H, Ar-H), 9.62 (s , 1H ,imidazolidine NH), ^{13}CNMR (dmso-d_6) δ ppm : 41.3($2CH_3$) ,75.5 imidazolidine CH), 97.5(N-CH) , 111.57 , 112.06 , 115.7 , 123.7 ,125.5 , 129.1, 129.4,129.7,131.3, 131.4,148(Aromatic -C's), 153.1, 158.1 (C=O of imidazolidine ring),161.04 , 170.2(C=O ester and amide of Oxazepine ring).

) 3-(4-(dimethylamino)phenyl)-2-(4-(2,5-dioxo-4,4-diphenylimidazolidin-1-yl)phenyl)-3,4-dihydro-1H-benzo[e][1,3]diazepine-1,5(2H)-dione (6): dark yellow . m.p : 310-312 °C, yield 83% , IR (KBr, cm^{-1}): amide N-H_{str}(3271,3209), aromtic C-H_{str}(3070), aliphatic C-H_{str} (2885, 2850), ester C=O_{str} (1770), amide C=O_{str}(1739), phenytoin C=O_{str}(1716) aromatic C=C_{str} (1577, 1550 , 1446, 1404), C-N_{str} (1230, 1172), ^{1}H-NMR (dmso-d_6) δ ppm : 2.43 (s , 6H , $2CH_3$), 6.39-8.55 (m, 22H, Ar-H), 9.29 (s , 1H ,imidazolidine NH), 11.08 (s , 1H , NH amide of diazepine ring), ^{13}CNMR (dmso-d_6) δ ppm : 40.2($2CH_3$) , 70.71(imidazolidine CH), 77.5(N-CH) , 112.57 , 113.06 , 116.7 , 124.7 ,127.5 , 128.1, 129.4,129.7,132.3, 133.4,140(Aromatic -C's), 154.1, 160.1 (C=O of imidazolidine ring),165.04 , 174.2(C=O amide of diazepine ring).

)3-(4-(2-(4-(dimethylamino)phenyl)-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)phenyl)-5,5-diphenylimidazolidine-2,4-dione (7): dark yellow . m.p : 297-299 °C, yield 81% , IR (KBr, cm^{-1}): amide N- H_{str}(3271,3224), aromtic C-H_{str}(3070, 3035), aliphatic C-H_{str} (2939, 2877), ester C=O_{str} (1766), amide C=O_{str}(1739), phenytoin C=O_{str}(1720) aromatic C=C_{str} (1539, 1492 , 1450), C-N_{str} (1222, 1199, 1280), ^{1}H-NMR (dmso-d_6) δ ppm : 2.49 (s , 6H , $2CH_3$), 6.59-8.65 (m, 22H, Ar-H), 9.29 (s , 1H ,imidazolidine NH), 11.08 (s , 1H , NH of Quinazolin ring), ^{13}CNMR (dmso-d_6) δ ppm : 42.2($2CH_3$) , 70.7 imidazolidine CH), 73.07(N-CH) , 112.57 , 113.06 , 116.7 , 124.7 ,126.5 , 130.1, 129.5,129.8,131.5, 132.4,149(Aromatic -C's), 155.1, 162.1 (C=O of imidazolidine ring), 170.2(C=O amide of Quinazolin ring).

3. RESULTS AND DISCUSSION

The present study comprise three reactions: the first reaction, Schiff base (1) were synthesized according to the reaction of 4-(dimethylamino)benzaldehyde with *p*-chloroaniline in the presence of absolute ethanol . The structure of the prepared compounds (1) was established on the basis of ^{1}H-^{13}C-NMR and The Infrared spectroscopy. TLC of the product showed the presence of one single spot referring to only one product. The IR spectra of compound (1) exhibited absorption bands, at (3062 cm^{-1} and 2893 cm^{-1}) which attributed to the C-H Aromatic and aliphatic group respectively . While the bands at (1577,1550,1477,1431 cm^{-1}) and (1600 cm^{-1}) are attributed to C=C and C=N stretching frequency respectively . The Infrared spectrum of compound (1) displayed band at (732 cm^{-1}) which assigned to C-Cl str.. In ^{1}H-NMR spectrum of compound (1) displayed signal at (δ 2.24 ppm) which assigned to($2 CH_3$) Methyl protons. and signal at (8.39 ppm) for (N=CH) imine group . The ^{13}C-NMR spectrum of compound (1) displayed signals at(δ 153and 146 ppm) which assigned to the group (benzene C-N$(CH_3)_3$) and (benzene C-N=CH) respectively . and signals at range (111-137 ppm) which assigned to the aromatics carbons. while signal at (161ppm) which assigned to the imine carbons(CH=N) .In the second reaction, Compound (1) was reaction with (phthalic anhydride ,phthalic imide and anthranilic acid) respectively in dry benzene to give Oxazepines, Diazepines and Quinazolin compounds (2,3,4) respectively. The structure of compounds (2,3,4) was confirmed by FT-IR and ^{1}H-^{13}C-NMR spectroscopy, The The Infrared spectra of prepared compounds exhibited absorption bands at (3062-3070)cm^{-1} was attributed to the C-H aromatic group and the bands at (2920-2899) cm^{-1} was attributed to the C-H aliphatic group . The Infrared spectra of synthesized compounds showed disappeared absorption band at (1600 cm^{-1}) which attributed to C=N imine stretching frequency of compounds (1) which indicate the success of the cyclization reaction. Also, appeared the absorption bands at (1774-1658 cm^{-1}) which assigned to C=O (ester and amid) stretching frequency indicated the occurs the cyclization reaction. The The Infrared spectra of compounds(3,4) exhibited absorption bands at (3183)cm^{-1} was attributed to the N-H stretching frequency. In third reaction , compounds(2,3,4) react with phenytion salt with stirring to obtain hybrid phenytion compounds (5,6,7). The structure of compounds (5.6.7) was confirmed by FT-IR and ^{1}H-^{13}C-NMR spectroscopy,, The The Infrared spectra of prepared compounds exhibited absorption bands at (3070.68-3070.58)cm^{-1} was attributed to the C-H aromatic group and the bands at (2951-2939) cm^{-1} was attributed to the C-H aliphatic group The IR spectra of compounds 5,6,7 Also, appeared the absorption bands at (1774-1716 cm^{-1}) which assigned to C=O (imidazolidine ,ester and amid) stretching frequency indicated the occurs the hybrid reaction.. The The Infrared spectra of synthesized compounds showed disappeared absorption band at (732-821 cm^{-1}) which attributed to C-Cl stretching frequency of compounds (2,3,4) which indicate the success of the hybrid reaction. In ^{1}H-NMR spectra of compounds (5,6,7) exhibited signal at (δ 2.98 , 2.43 and 2.49 ppm) which assigned to($2 CH_3$) methyl protons respectively. and signals at (9.62 , 9.29 and 9.29 ppm) for (N-H) imidazolidine group respectively . while compounds (6,7) appears signals at (11.08 ppm) for (N-H) Diazepines and Quinazolin ring . The ^{13}C-NMR spectra of compound (5,6,7) exhibited signals at rang (δ 153-154 and 158-161ppm) which attributed to the 2 C=O imidazolidine ring and (161.04 and 170.2),(165.04 and 174.2) and (170.2) which attributed to the 2 C=O Oxazepines , Diazepines and Quinazolin ring respectively . and signals at range (111-130 ppm) which attributed to the aromatics carbons. The reaction proceeds according to the Scheme 1

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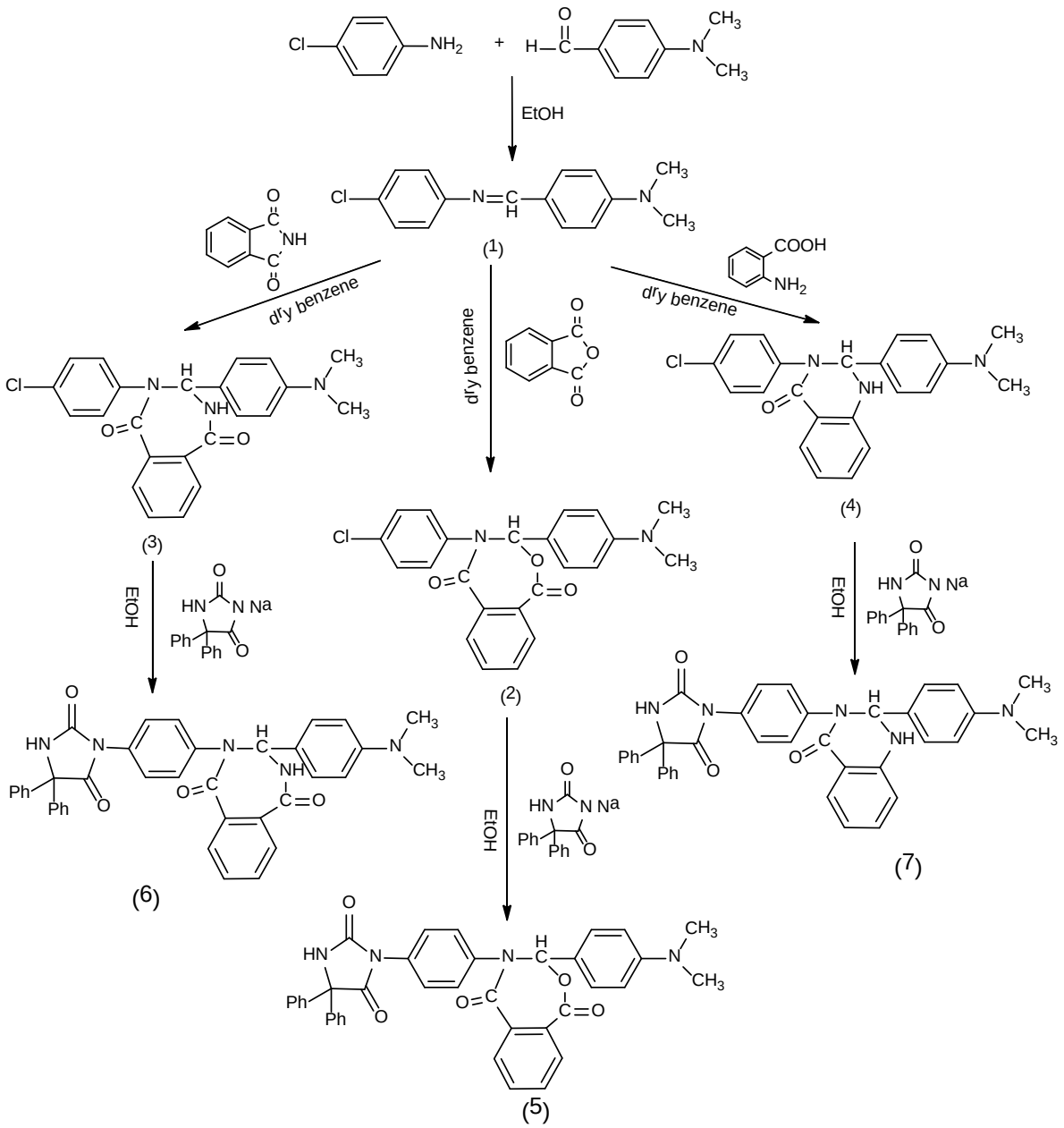
Table 1. Physical properties of the compounds.

Comp no	M.p (°C)	M . wt (g /mole)	M . Formula	Color	Yield %
1	165- 167	258.75	$C_{15}H_{15}ClN_2$	yellow	80%
2	212-214	406.86	$C_{23}H_{19}ClN_2O_3$	white	72%
3	291-293	405.88	$C_{23}H_{20}ClN_3O_2$	white	88%
4	277-279	377.87	$C_{22}H_{20}ClN_3O$	dark yellow	75%
5	285-287	622.67	$C_{38}H_{30}N_4O5$	white	77%
6	310-312	621.68	$C_{38}H_{31}N_5O_4$	dark yellow	83%
7	297-299	593.67	$C_{37}H_{31}N_5O_3$	dark yellow	81%



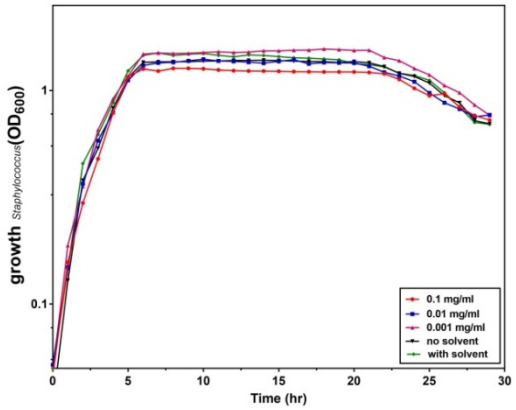
Scheme 1 : Synthetic route of synthesized compounds

4. ANTIBACTERIAL ACTIVITY

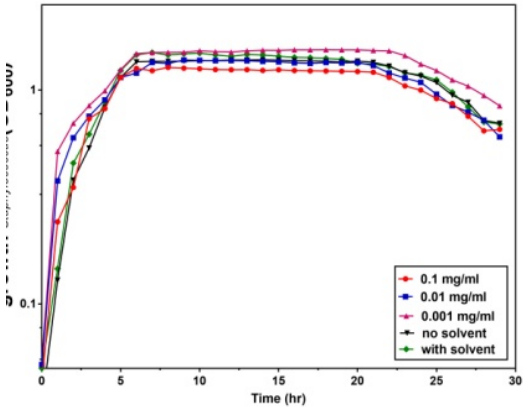
The biological activity of the compounds that were created, was examined on two types of Gram positive bacteria (Staphylococcus) and Gram negative bacteria (Escherichia coli) in the Biological Biology Lab at the Department of Biology, College of Science for Women, Baghdad University. The method of work included the preparation of three concentrations for each compound which was manufactured (0.1 mg / ml) (0.01 mg / ml) (0.001 mg / ml), in addition to measuring the growth of bacteria without any addition (negative control) and by adding solvent only (DMSO). Using the nutrient broth medium, bacteria which was attended and sterilized according to the instructions of the fitted company (Difco) installed on the box.The flasks were placed at a 37 ° C incubator shaker and 1 ml of the medium per flask (from each concentration as well as control and solvent flask) was taken every hour and up to 29 hours. Absorption was measured at a wavelength of 600 nm.Results were recorded and a prism 7 graphpad was used to draw the growth curve for each bacteria and for the three concentrations of each compound in addition to control and bacteria solution with only solvent.

The results showed that there was an effect on Escherichia coli. The addition of the compounds that were created to the bacterial solution at all concentrations used, inhibit the growth of the bacteria and arrival to the death stage was earlier than the absence of compounds in the medium where the bacteria live, The reason for this effect may be due to privation peptide-claikane in the walls of gram-positive bacteria cells and thus the thickness of the cell wall is less and may have led to the ease of penetration by the materials created or may have some effect on the life processes of gram-negative bacteria. In Staphylococcus, the results showed that there were no differences between the presence of the created compounds at all concentrations used and their absence in the medium of Gram positive bacteria

C 1



C5



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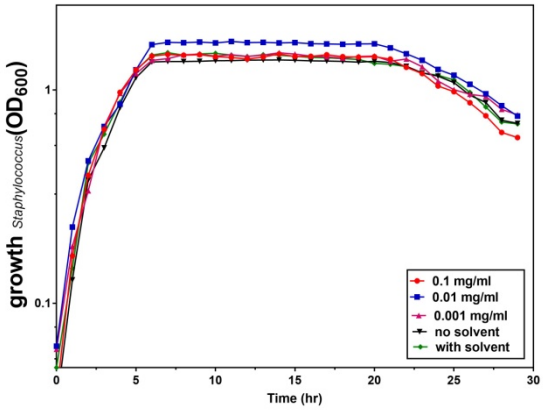
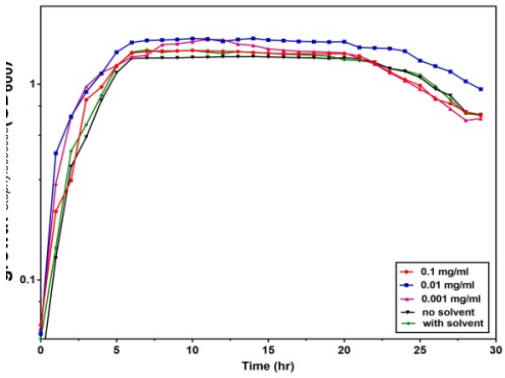
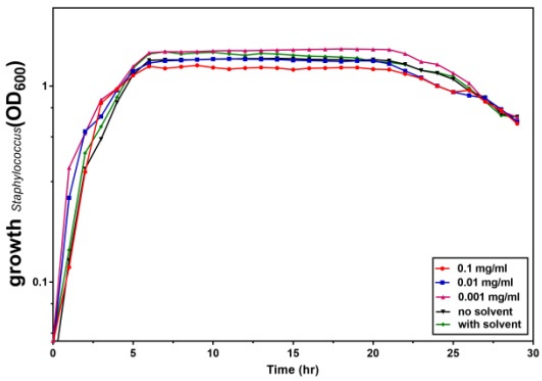


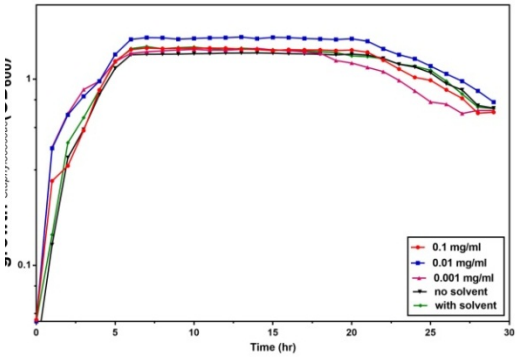
C6



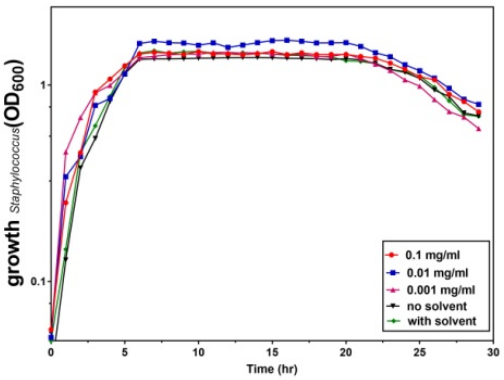
C 3



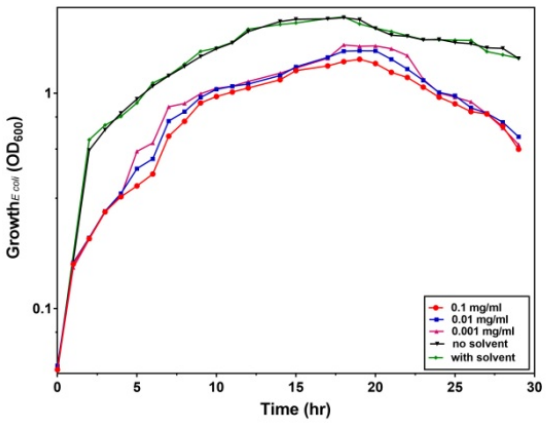
C 7

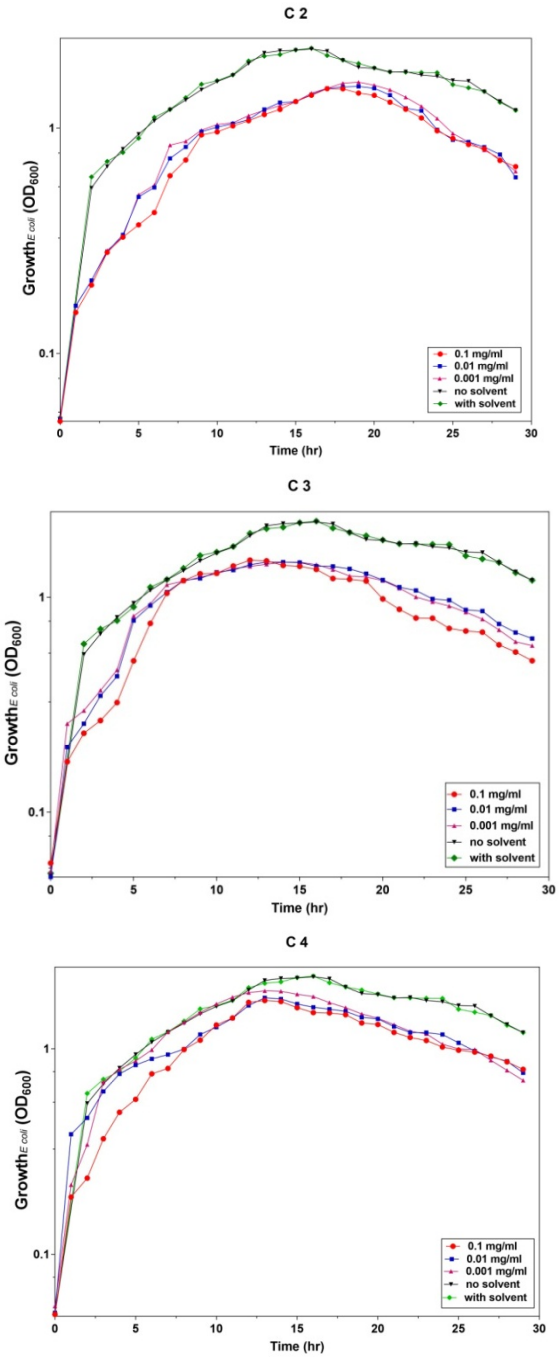


C 4



C1





CONCLUSION:

A new series of phenytion derivatives containing Oxazepines , Diazepines and Quinazolin ring were prepared . Some of the newly synthesized compounds exhibit importance antibacterial activity.

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