Synthesis and Identification of New Chalcone, pyrazoline, isoxazoline and pyrimidine and Study their Antibacterial, Antioxidant, Cytotoxicity assay and Electrochemical oxidation effect

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Abstract:

Throughout this work new of chalcones, pyrazolines, isoxazolines and pyrimidines derivatives were prepared by click reaction of N-propargyl saccharin with *p*-Acetyl azido benzene in the presence of $CuSO_4.5H_2O$ and sodium ascorbate produce N-[1-{(*p*-acetylphenyl)-1,2,3-triazol-4-yl} methyl] saccharin. Condensation of 1,2,3-triazole derivative with some aromatic aldehyde in the presence of 40%ethanol:KOH give the corresponding of chalcone compounds. Cyclization of chalcone compounds hydrazine hydrate, hydroxylamine hydrochloride, urea and thiourea gave the corresponding pyrazoline, isoxazoline, pyrimidine and thiopyrimidine derivatives. All prepared compounds were identified by FT-IR, ^{1}HNMR and ^{13}CNMR spectra and some of synthesized compounds showed antibacterial activity, electrochemical oxidation and cytoxicity effect.

Key words: (saccharin; chalcone; isoxazoline; pyrazoline; pyrimidine; click reaction).

تحضير وتشخيص أنواع جديدة من الجالكون والبايرازولين والايزواوكسازولين والبريميدين ودراسة فعاليتها كمضادات للجراثيم ومضادات للأكسدة والسمية وتأثير الأكسدة الكهروكيميائية

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الملخص:

خلال هذا العمل ، تم تحضير مشتقات جديدة من الجالكون ، والبايرازولين ، والإيزواوكسازولين ، والبيريميدين عن طريق تفاعل N-بروبرجيل سكرين مع بارا-اسيتايل ازيدو بنزين في وجود $CuSO_4.5H_2O$ وأسكوربات الصوديوم N-١-((بارا اسيتايل فنيل)-١و٢و٣-ترايازول-٤-يل)مثيل سكرين, تكثيف مشتق ٣،٢،١-تريازول مع بعض الألديهايدات العطرية بوجود ٤٠٪ إيثانول وهيدروكسيد البوتاسيوم: يعطي المشتق المقابل

لمركبات الجالكون. حوقلت الجلكونات باستخدام الهيدرازين وهيدروكسيل أمين هيدروكلورايد واليوريا والثايويوريا مشتقات البيرازولين والإيزوكسازولين والبيريميدين والثايوبيريميدين. تم تشخيص جميع المركبات المحضرة بواسطة أطياف FT-IR و ^{1}HNMR و ^{13}CNMR وأظهرت بعض المركبات المحضرة نشاطًا كمضادات للبكتيريا والاكسدة الكهروكيميائية وتأثير السمية الخلوية.

الكلمات الأساسية: (السكرين ، كالكون ، إيزوكسازولين ، بيرازولين ، بيريميدين ، تفاعل النقر).

Introduction:

Saccharin is a weak acid, and easily forms salt with different basic active pharmaceutical ingredient therefore resulting very soluble saccharinates, which may be used in pediatric medication, also Saccharin used in the formation of phenolic ether prod rugs[(1)]. Chalcones are products of condensation of simple or substituted aromatic aldehydes or ketones with various aryl ketones under base conditions (ethanolic KOH or NaOH solution) that forms the central core for a variety of important biological compounds[(2)]. chalcones and their derivatives have a wide range of biological activities such as anti-microbial and anti-tumor[(3)], anticancer[(4)], anti-proliferative[(5)], anti-alzheimer and anti-HIV1[(6)]. Pyrazoline derivatives possess a wide range of biological activities, such as antimicrobial, anticancer, anti-inflammatory, anti-depressant, anticonvulsant, anti-hypertensive, antiepileptic, anti-tumor, and analgesic[(7)]. Pyrimidine derivatives are of particular interest due to their promising biological activity, Compounds possessing the Pyrimidine nucleus, have attracted a considerable attention by interest from the chemical and pharmacological community. oxazole derivatives could be applied as hypoglycaemic and in agrochemical as soil fungicidal activity, insecticides, pesticides and also used as lubricants, electric insulating oils, pigments[(8)]. In the literature, several effective strategies to their synthesis have been reported[(9)] such as anticancer, anti-inflammatory[(10)], anti-proliferative[(11)], anti-tubercular[(12)] and anti-HCV agents[(13)].

Experimental Methods:

All chemicals were purchased from BDH, Fluka and Merck and M.p. is recorder use electrothermal (m.p) apparataus. The FT-IR spectral data were recorded on a Shimadzu FT-IR8400S spectro-photometer in the Department of Chemistry, College of Science, University of Baghdad. ^{1}H-NMR and ^{13}C-NMR spectra are recorder on central laboratory of Isfahan University, 400MHz, using DMSO and tetramethylsilane (TMS) as an internal standard**.**

Synthesis of N-[1-{(*p*-acetylphenyl)-1,2,3-triazol-4-yl} methyl] saccharin [1][(14)]

N-Propargyl saccharin (20, 0.01 mole) was add drop wise with stirring to a solution containing *p*-Acetyl azido benzene (0.01 mole) [(15)]. The sodium ascorbate (0.0009 mole) was added and $CuSO_4.5H_2O$ (0.0045 mole) in (25 mL) DMF, then the solutaion was refluxed overnight at 75^{o}C, after cooling (25 mL) of distilled water

was added and extracted with ether (3x25 mL), the organic layers were dried over magnesium sulfate, and evaporate under reduced pressure, the formed pale brown precipitate was filtered, recrystallized from absolute ethanol. To give triazole derivatives [1] pale brown , 72%, M.P. (198-200)^{o}C

Synthesis of chalcones derivatives [2-9][(16)]

(1g, 0.0027 mole) of compound [1] was stirred in (10 mL) absolute ethanol with equimolar of some substituted benzaldehyde such as benzaldehyde, *p*-methyl benzaldehyde, *p*-chloro benzaldehyde, *p*-hydroxy benzaldehyde, *m*-nitro benzaldehyde, *p*-nitro benzaldehyde and *p*-dimethyl amino benzaldehyde (0.0027 mole), then 40% KOH (10 mL) was added drop wise. The mixture was refluxed for (8-10) h., then it was poured on (50 mL) ice-water, with continuous stirring for 1 h. The mixture was neutralized by concentration of hydrochloric acid. The precipitate obtained was filtered, washed, air dried and recrystallized from ethanol to give the corresponding chalcones [2-9].

***o*-[N-{1-(4-(phenylacryloyl)phenyl)-1,2,3-triazol-4-yl}methylsulfamoyl] benzoic acid [2]**

Off White, Yield 74%, m.p. 151-153 ^{o}C, IR (KBr) cm^{-1} 3479 (O-H), 3149 (N-H), 3029 (C-H) Arom, 1708 (C=O) Acid, 1662 (C=O) Ketone, (SO_2) Asym. 1298 Sym. 1164

***o*-[N-{1-(4-(3-(*p*-nitrophenyl)acryloyl)phenyl)-1,2,3-triazol-4-yl}methyl sulfamoyl] benzoic acid [3]**

Deep Brown, Yield 75%, m.p. 260-263 ^{o}C, IR (KBr) cm^{-1} 3446 (O-H), 3143 (N-H), 3080 (C-H) Arom, 1708 (C=O) Acid, 1635 (C=O) Ketone, (NO_2) Asym.1517 Sym.1324, (SO_2) Asym.1342 Sym.1164

***o*-[N-{1-(4-(3-(*m*-nitrophenyl)acryloyl)phenyl)-1,2,3-triazol-4-yl}methyl sulfamoyl] benzoic acid [4]**

Brown, Yield 72%, m.p. 192-194 ^{o}C, IR (KBr) cm^{-1} 3463 (O-H), 3147 (N-H), 3083 (C-H) Arom, 1712 (C=O) Acid, 1665 (C=O) Ketone, (NO_2) Asym. 1529 Sym. 1348, (SO_2) Asym. 1348 Sym.1164

***o*-[N-{1-(4-(3-(*p*-chlorophenyl)acryloyl)phenyl)-1,2,3-triazol-4-yl}methyl sulfamoyl] benzoic acid [5]**

Pale Brown, Yield 49%, m.p. 158-160 ^{o}C, IR (KBr) cm^{-1} 3448 (O-H), 3147 (N-H), 3068 (C-H) Arom, 1685 (C=O) Acid, 1655 (C=O) Ketone, (SO_2) Asym. 1323 Sym.1164, 1056 (C-Cl)

***o*-[N-{1-(4-(3-(*p*-bromophenyl)acryloyl)phenyl)-1,2,3-triazol-4-yl}methyl sulfamoyl] benzoic acid [6]**

Pale Brown, Yield 49%, m.p. 184-186^{o}C, IR (KBr) cm^{-1} 3458 (O-H), 3147 (N-H), 3080 (C-H) Arom, 1687 (C=O) Acid, 1642 (C=O) Ketone, (SO_2) Asym. 1336 Sym.1164, 1045

***o*-[N-{1-(4-(3-(*p*-tolyl)acryloyl)phenyl)-1,2,3-triazol-4-yl}methylsulfamoyl] benzoic acid [7]**

Pale Green, Yield 53%, m.p. 126-127^{o}C, IR (KBr) cm^{-1} 3458 (O-H), 3147 (N-H), 3031 (C-H) Arom, 1716 (C=O) Acid, 1662 (C=O) Ketone, (SO_2) Asym. 1332 Sym.1166

***o*-[N-{1-(4-(3-(*p*-hydroxyphenyl)acryloyl)phenyl)-1,2,3-triazol-4-yl}methyl sulfamoyl] benzoic acid [8]**

Brown, Yield 51%, m.p. 201-204^{o}C, IR (KBr) cm^{-1} 3446 (O-H), 3159 (N-H), 3049 (C-H) Arom, 1716 (C=O) Acid, 1641 (C=O) Ketone, (SO_2) Asym. 1326 Sym.1163

***o*-[N-{1-(4-(3-(*p*- (dimethylamino)phenyl)acryloyl)phenyl)-1,2,3-triazol-4-yl} methyl sulfamoyl] benzoic acid [9]**

Brown, Yield 51%, m.p. 184-186^{o}C, IR (KBr) cm^{-1} 3452 (O-H), 3149 (N-H), 3072 (C-H) Arom, 1716 (C=O) Acid, 1639 (C=O) Ketone, (SO_2) Asym. 1330 Sym.1164

Synthesis of pyrazoline derivatives [10-14][(17)]

To mixture of chalcone compounds [2-6] (0.01 mole), dissolved in (20 mL) absolute ethanol containing (0.5 mL) acetic acid, (1 mL) hydrazine hydrate 99% was added the mixture was refluxed for 8 h. and left with continuous stirring overnight. After that the mixture was poured into (50 mL) ice water and neutralized by diluted hydrochloric acid . The solid formed was filtered, washed and recrystallized from ethanol. To give pyrazoline derivatives [10-14].

***o*-[N-{1-(4-(5-phenyl-4,5-dihydro-1H-pyrazoline-3-yl)phenyl)-1,2,3-triazol-4-yl}methylsulfamoyl] benzoic acid [10]**

Deep Yellow, Yield 97%, m.p. 215-217 ^{o}C, IR (KBr) cm^{-1} 3461-3421 (O-H), 3267, 3141 (N-H), 3062 (C-H) Arom, 1714 (C=O) Acid, 1685 (C=N)

***o*-[N-{1-(4-(5-(*p*-nitrophenyl)-4,5-dihydro-1H-pyrazoline-3-yl)phenyl)-1,2,3-triazol-4-yl}methylsulfamoyl] benzoic acid [11]**

Off White, Yield 60%, m.p. 352-354 ^{o}C, IR (KBr) cm^{-1} 3461-3379 (O-H), 3219, 3195 (N-H), 3080 (C-H) Arom, 1728 (C=O) Acid, 1685 (C=N), ν(NO_2) Asym.1515 Sym.1344

***o*-[N-{1-(4-(5-(*m*-nitrophenyl)-4,5-dihydro-1H-pyrazoline-3-yl)phenyl)-1,2,3-triazol-4-yl}methylsulfamoyl] benzoic acid [12]**

Off White, Yield 40%, m.p. 282-284 ^{o}C, IR (KBr) cm^{-1} 3440-3434 (O-H), 3205, 3153 (N-H), 3093 (C-H) Arom, 1688 (C=O) Acid, 1627 (C=N), ν(NO_2) Asym. 1527 Sym. 1350

***o*-[N-{1-(4-(5-(*p*-chlorophenyl)-4,5-dihydro-1H-pyrazoline-3-yl)phenyl)-1,2,3-triazol-4-yl}methylsulfamoyl] benzoic acid [13]**

Off White, Yield 73%, m.p. 230-232^{o}C, IR (KBr) cm^{-1} 3539-3434 (O-H), 3276, 3153 (N-H), 3082 (C-H) Arom, 1712 (C=O) Acid, 1635 (C=N), 1056 (C-Cl)

***o*-[N-{1-(4-(5- *p*-bromophenyl)-4,5-dihydro-1H-pyrazoline-3-yl)phenyl)-1,2,3-triazol-4-yl}methyl sulfamoyl] benzoic acid [14]**

Pale Yellow, Yield 66%, m.p. 152-154^{o}C, IR (KBr) cm^{-1} 3614-3425 (O-H), 3271, 3145 (N-H), 3064 (C-H) Arom, 1703 (C=O) Acid, 1652 (C=N), 1043 (C-Br)

Synthesis of isoxazoline derivatives [15-19][(17)]

To a mixture of compounds [2-6] (0.01 mole), hydroxylamine hydrochloride (0.69 g, 0.01 mole) anhydrous sodium acetate (0.67 g, 0.01 mole) in absolute ethanol (20 mL) was added. The mixture was refluxed for 6-8 h. after cooling to room temperature and let overnight. Finally the mixture was poured onto ice water,

the formed solid was filtered and recrystallized from absolute ethanol to give isoxazoline derivatives [16-20].

***o*-[N-{1-(4-(5-phenyl-4,5-dihydroisoxazoline-3-yl)phenyl)-1,2,3-triazol-4-yl} methyl ulfamoyl] benzoic acid [15]**

Off White, Yield 70%, m.p. 241-243^{o}C, IR (KBr) cm^{-1} 3458-3423 (O-H), 3276 (N-H), 3064 (C-H) Arom, 1714 (C=O) Acid, 1652 (C=N), 1296 (N-O)

***o*-[N-{1-(4-(5-(*p*-nitrophenyl)-4,5-dihydroisoxazoinel-3-yl)phenyl)-1,2,3-triazol-4-yl}methylsulfamoyl] benzoic acid [16]**

Brown, Yield 39%, m.p. 170-172^{o}C, IR (KBr) cm^{-1} 3471-3390 (O-H), 3145 (N-H), 3080 (C-H) Arom, 1714 (C=O) Acid, 1637 (C=N), (NO_2) Asym.1514 Sym.1394, 1296 (N-O)

***o*-[N-{1-(4-(5-(*m*-nitrophenyl)-4,5-dihydroisoxazoline-3-yl)phenyl)-1,2,3-triazol-4-yl}methylsulfamoyl] benzoic acid [17]**

Brown, Yield 73%, m.p. 161-163^{o}C, IR (KBr) cm^{-1} 3467-3379 (O-H), 3145 (N-H), 3085 (C-H) Arom, 1714 (C=O) Acid, 1629 (C=N), (NO_2) Asym.1527 Sym.1394, 1253 (N-O)

***o*-[N-{1-(4-(5-(*p*-chlorophenyl)-4,5-dihydroisoxazoline-3-yl)phenyl)-1,2,3-triazol-4-yl}methylsulfamoyl] benzoic acid [18]**

Brown, Yield 69%, m.p. 160-162^{o}C, IR (KBr) cm^{-1} 3463-3440 (O-H), 3149 (N-H), 3050 (C-H) Arom, 1685 (C=O) Acid, 1639 (C=N), 1296 (N-O), 1054 (C-Cl)

***o*-[N-{1-(4-(5-(*p*-bromophenyl)-4,5-dihydroisoxazoline-3-yl)phenyl)-1,2,3-triazol-4-yl}methylsulfamoyl] benzoic acid [19]**

Pale Yellow, Yield 87%, m.p. 242-244^{o}C, IR (KBr) cm^{-1} 3471-3365 (O-H), 3151 (N-H), 3083 (C-H) Arom, 1718 (C=O) Acid, 1642 (C=N), 1249 (N-O), 1041 (C-Br)

Synthesis of pyrimidin and thiopyrimidine derivatives [20-29][(18)]

A mixture of chalcones [2-6] (0.025 mole) and (0.05 mole) of (urea or thiourea) dissolved in an aqueous sodium hydroxide solution (15 mL, 30%) and (75 mL) ethanol was refluxed for 8 h. and left with stirring over night. The mixture was poured on (100 mL) of distilled water, and left for 15 min. The mixture was filtered off, the filtrate was cooled in an ice-bath and acidified with concentrated hydrochloric acid. The formed precipitate was filtered, washed with distilled water and recrystallized from ethanol to give pyrimidine [20-24] and thiopyrimidine[25-29] derivatives respectively.

***o*-[N-{1-(4-((6-phenyl)-2-oxo-1,5-dihydropyrimidin-5-yl)phenyl)-1,2,3-triazol-4-yl}methylsulfamoyl] benzoic acid [20]**

Brown, Yield 55%, m.p. 196-198^{o}C, IR (KBr) cm^{-1} 3490-3421 (O-H), 3292, 3149 (N-H), 3083 (C-H) Arom, 1716 (C=O) Acid, 1685 (C=O) Amide, 1631 (C=N)

***o*-[N-{1-(4-(6-(*p*-nitrophenyl)-2-oxo-1,5-dihydropyrimidin-5-yl)phenyl)-1,2,3-triazol-4-yl}methylsulfamoyl] benzoic acid [21]**

Deep Red, Yield 34%, m.p. 156-158^{o}C, IR (KBr) cm^{-1} 3465-3431 (O-H), 3167 (N-H), 3024 (C-H) Arom, 1701 (C=O) Acid, 1681 (C=O) Amide, 1681 (C=N), (NO_2) Asym.1515 Sym.1340

***o*-[N-{1-(4-(6-(*m*-nitrophenyl)-2-oxo-1,5-dihydropyrimidin-5-yl)phenyl)-1,2,3-triazol-4-yl}methylsulfamoyl] benzoic acid [22]**

Deep Red, Yield 19%, m.p. 320-322°C, IR (KBr) cm^{-1} 3479-3436 (O-H), 3192 (N-H), 3082 (C-H) Arom, 1710 (C=O) Acid, 1703 (C=O) Amide, 1658 (C=N), (NO_2) Asym.1519 Sym.1321

***o*-[N-{1-(4-(6-(*p*-chlorophenyl)-2-oxo-1,5-dihydropyrimidin-5-yl)phenyl)-1,2,3-triazol-4-yl}methylsulfamoyl] benzoic acid [23]**

Brown, Yield 60%, m.p. 148-150°C, IR (KBr) cm^{-1} 3463-3382 (O-H), 3149 (N-H), 3097 (C-H) Arom, 1685 (C=O) Acid, 1662 (C=O) Amide, 1631 (C=N), 1054 (C-Cl)

***o*-[N-{1-(4-(6-(*p*-bromophenyl)-2-oxo-1,5-dihydropyrimidin-5-yl)phenyl)-1,2,3-triazol-4-yl}methylsulfamoyl] benzoic acid [24]**

Pale Brown, Yield 39%, m.p. 180-182°C, IR (KBr) cm^{-1} 3465 (O-H), 3276 (N-H), 3078 (C-H) Arom, 1727 (C=O) Acid, 1683 (C=O) Amide, 1649 (C=N), 1056 (C-Br)

***o*-[N-{1-(4-(6-phenyl-2-thioxo-1,5-dihydropyrimidin-5-yl)phenyl)-1,2,3-triazol-4-yl}methylsulfamoyl] benzoic acid [25]**

Pale Brown, Yield 76%, m.p. 158-160°C, IR (KBr) cm^{-1} 3440 (O-H), 3145 (N-H), 3062 (C-H) Arom, 2613 (C=S), 1716 (C=O), 1633 (C=O) Amide

***o*-[N-{1-(4-(6-(*p*-nitrophenyl)-2-thioxo-1,5-dihydropyrimidin-5-yl)phenyl)-1,2,3-triazol-4-yl}methylsulfamoyl] benzoic acid [26]**

Deep Red, Yield 17%, m.p. 364-366°C, IR (KBr) cm^{-1} 3467 (O-H), 3185 (N-H), 3064 (C-H) Arom, 2613 (C=S), 1704 (C=O), 1637 (C=O) Amide, (NO_2) Asym.1513 Sym.1326

***o*-[N-{1-(4-(6-(*m*-nitrophenyl)-2-thioxo-1,5-dihydropyrimidin-5-yl)phenyl)-1,2,3-triazol-4-yl}methylsulfamoyl] benzoic acid [27]**

Deep Red, Yield 58%, m.p. 340-342°C, IR (KBr) cm^{-1} 3433 (O-H), 3141 (N-H), 3070 (C-H) Arom, 2594 (C=S), 1712 (C=O), 1631 (C=O) Amide, (NO_2) Asym.1514 Sym.1326

***o*-[N-{1-(4-(6-(*p*-chlorophenyl)-2-thioxo-1,5-dihydropyrimidin-5-yl)phenyl)-1,2,3-triazol-4-yl}methylsulfamoyl] benzoic acid [28]**

Brown, Yield 77%, m.p. 141-143°C, IR (KBr) cm^{-1} 3463 (O-H), 3190 (N-H), 3099 (C-H) Arom, 2507 (C=S), 1785 (C=O), 1638 (C=O) Amide, 1053 (C-Cl)

***o*-[N-{1-(4-(6-(*p*-bromophenyl)-2-thioxo-1,5-dihydropyrimidin-5-yl)phenyl)-1,2,3-triazol-4-yl}methylsulfamoyl] benzoic acid [29]**

Deep Brown, Yield 55%, m.p. 184-186°C, IR (KBr) cm^{-1} 3471 (O-H), 3147 (N-H), 3093 (C-H) Arom, 2566 (C=S), 1685 (C=O), 1652 (C=O) Amide, 1054 (C-Cl)

Anti-microbial activity[19]

Several synthesized compounds were tested for their in vitro growth inhibitory activity the compounds tested against ***Escherichia coli***, ***Klebsiella pneumonia***, ***Staphylococcus aureus*** and ***Streptococcus pneumonia*** bacteria by applying cup plate method using nutrient agar medium and DMSO that used as a sample solution.

The test organisms were first cultured in nutrient broth and incubated for (24) hours at temperature 37°C and then freshly prepared bacterial cells were spread onto the nutrient agar. Then the tested compounds were previously dissolved in DMSO then (0.1 ml) of each compound as known concentration was added in the cups and the

petri dishes were subsequently incubated at temperature 37^{o}C for 24 h. Inhibition zone produced by each compound was measured in (mm).

Electrochemical oxidation effect of synthesized compounds [1,9, 13, 17 & 22] on Mercury ions in blood serum using Cyclic Voltammetry[20]:

The mechanical method by using direct attachment, about twenty times of carbon nanotube CNT powder with modified GCE with abrasively adhere CNT piratical and then add compound sample test. Moreover this modification of G C E was done every run of CV because of avoid dropping CNT molecules from the surface of GCE electrode into the solution of blood serum.

Antioxidant (DPPH Radical Scavenging Activity) [21]:

The antioxidant activity of compounds [1, 9, 13, 17 & 22] was determined using 2, 2-diphenyl-1-picrylhydrazyl (DPPH). The principle of the assay is based on reduction of DPPH via hydrogen donation from antioxidant, by which the color change can be spectrophotometrically recorded. It is widely used to detect the scavenging activates of agents. Moreover, (1 mL) of the samples was mixed with an equal volume of the solution of DPPH (60 µM). After 30 min. incubation at temperature 37°C in darkness, the absorbance was recorded at 517 nm spectrophotometrically (Perkin-Elmer Lambda 25, Germany). L-ascorbic acid was used as a positive control. The measurements were carried out in triplicate. Inhibition of free radicals by DPPH was calculated by the following equation:

$$\text{DPPH radical scavenging activity (\%)} = \left(\frac{\text{Ac} - \text{As}}{\text{AC}}\right) \times 100\%$$

Where, Ac = control absorbance and As= samples absorbance

Measurement of cell viability[22]:

For cell viability detection the colorimetric 3-(4,5-dimethylthiazol-z-yl)-2,5-diphenyltetrazolium (MTT) assay. Cells were seeded in 96-well plates at a concentration of 1×10^5 cell/ml. Then after 48 h of incubation, 100 µL of of compounds [1, 9, 13, 17 & 22] at concentrations of 10, 50, 100, 150, 200, 220, 240 and 280 µg/ ml was added to each well and incubated for 24, 48 and 72h. After the incubation period, 10 µL of (MTT) solution (5 mg/ ml) was added to each well and plates were further incubated at temperature 37°C for 4 h. Finally, 50 µL of DMSO was added to each well and incubated for 10 min. Cells in medium without synthesis compounds solution served as control. Then the absorbance was measured at 550 nm using micro plate reader (VersaMaxTM, Molecular Devices, Sunnyvale, CA). Percent of inhibition ratio was calculated according to the following formula:

$$\text{GI\%} = \frac{(OD\ of\ control\ wells - OD\ of\ test\ wells)}{OD\ of\ control\ wells} \times 100.$$

Where GI = growth index and OD = optical density

Results and discussion:

Cyclization of N-Propargyl saccharin [1] with p- acetyl azido benzene via click reaction in the precence $CuSO_4.5H_2O$ and sodium ascorbate to give N-[1-{(*p*-acetylphenyl)-1,2,3-triazol-4-yl} methyl] saccharin [1].

FT-IR spectra showed the disappearance of the absorption bands at (3276)cm^{-1} and at (2125)cm^{-1} for acetylenic ν(C-H) and ν(C≡C). In addition to disappearance the absorption bands at (2131-2106)cm^{-1} for ν(N_3) groups, while the appearance of new bands for ν(N=N) at (1595-1521)cm^{-1} which indicate to formation of 1,2,3-triazole derivatives [1]. While ^{1}H-NMR spectra of compound [1] showed the following characteristic signals δ(ppm): 1.85(s, 3H,C<u>H</u>$_3$); 3.92(s, 2H,C<u>H</u>$_2$); 6.50-7.98(m,8H,Ar-H); 8.06(N-C-<u>H</u> triazole)[23,24].

The synthesis of substituted chalcones carried out via crossed aldol. Available compound [1] that represent the mother compound which condensation with same substituted benzaldehyde in presence of 40% KOH in absolute ethanol to give corresponding chalcone derivatives as in Scheme (2).

FT-IR spectra of synthesized chalcon compounds [2-9] were proves by the appearance of the starching bands at (3479-3146)cm^{-1}, (3149-3143)cm^{-1}, (1716-1616)cm^{-1} and (1666-1633) due to ν(O-H) acid, ν(N-H), ν(C=O) acid and α,β-unsaturated (C=O) respectively. While the disappearance starching bands at (1735)cm^{-1} and (1680)cm^{-1} which due to (C=O) amide and (C=O) ketone respectively. That was indicate the formation of chalcone compounds [2-9]. While ^{1}H-NMR spectrum of compound [2] showed the following characteristic signals δ(ppm): 3.32(s, 2H, C<u>H</u>$_2$); 5.85-6.81(m,2H,C<u>H</u>=C-<u>H</u>); 7.15-7.73(m,13H,Ar-H); 8.24(N-C-<u>H</u> triazole);8.45 (s,1H,N-<u>H</u>); 12.62(s,1H,-O-<u>H</u>).

^{1}H-NMR spectrum of compound [3] showed the following characteristic signals δ(ppm): 3.17(s, 2H, C<u>H</u>$_2$); 5.42-6.95(m,2H,C<u>H</u>=C-<u>H</u>); 7.01-7.71(m,13H,Ar-H); 9.67(N-C-<u>H</u> triazole);9.81 (s,1H,N-<u>H</u>); 12.28 (s,1H,-O-<u>H</u>).

^{1}H-NMR spectrum of compound [5] showed the following characteristic signals δ(ppm): 3.73(s, 2H, C<u>H</u>$_2$); 6.74-6.83(m,2H,C<u>H</u>=C-<u>H</u>); 7.18-7.92(m,12H,Ar-H); 8.34(N-C-<u>H</u> triazole);8.48 (s,1H,N-<u>H</u>); 12.64(s,1H,-O-<u>H</u>).

^{1}H-NMR spectrum of compound [7] showed the following characteristic signals δ(ppm): 1.19(s,3H,C<u>H</u>$_3$); 3.37(s, 2H, C<u>H</u>$_2$); 6.05-6.91(m,2H,C<u>H</u>=C-<u>H</u>); 7.01-8.22(m,12H,Ar-H); 8.26(N-C-<u>H</u> triazole);8.42 (s,1H,N-<u>H</u>); 12.33(s,1H,-O-<u>H</u>).

^{1}H-NMR spectrum of compound [8] showed the following characteristic signals δ(ppm): 3.58(s, 2H, C<u>H</u>$_2$); 5.61-6.02(m,2H,C<u>H</u>=C-<u>H</u>); 6.70(s, 2H, Ar-O<u>H</u>); 6.73-7.96(m,12H,Ar-H); 8.57(N-C-<u>H</u> triazole);8.63 (s,1H,N-<u>H</u>); 12.41(s,1H,-O-<u>H</u>).

The pyrazoline derivatives [10-14] were synthesized from cyclization of chalcone derivatives [2-6] with hydrazine hydrate 99% in absolute ethanol which containing a few drop of glacial acetic acid under refluxing[25] as shown in Scheme (2).

FT-IR spectra of the synthesized pyrazoline derivatives [10-14] show the absence of ν(C=O) ketone group at (1662-1635)cm^{-1}. While the appearance starching bands of ν(C=N) at (1685-1620)cm^{-1} indicate to formation of compounds [10-14]. While ^{1}H-NMR spectrum of compound [10] showed the following characteristic signals δ(ppm): 3.75(s, 2H, N-C<u>H</u>$_2$); 3.76-3.91(m, 3H, C<u>H</u> pyrazoline); 6.49-7.76(m,13H,Ar-H); 8.05(N-C-<u>H</u> triazole);8.31 (s,1H,N-<u>H</u>); 12.45(s,1H,-O-<u>H</u>).

^{1}H-NMR spectrum of compound [13] showed the following characteristic signals δ(ppm): 3.40(s, 2H, N-C<u>H</u>$_2$); 3.66-3.80(m, 3H, C<u>H</u> pyrazoline); 6.44-7.72(m,12H,Ar-H); 8.09(N-C-<u>H</u> triazole);8.42 (s,1H,N-<u>H</u>); 12.07(s,1H,-O-<u>H</u>).

A mixture of chalcone derivatives [2-6] with hydroxyl amine hydrochloride and anhydrous sodium acetate in absolute ethanol under reflux condition gave the target isoxazoline derivatives [15-19] **(25)** as in Scheme (2).

FT-IR spectra of isoxazoline derivatives [15-19] show disappearance of absorption band of ν(C=O) ketone group at (1716-1641)cm^{-1} and appearance absorption bands for ν(C=N) at (1639-1629)cm^{-1}. In addition to the absorption of ν(N-O) band at (1296-1249)cm^{-1} which were indicate to produce isoxazoline derivatives [15-19]. While ^{1}H-NMR spectrum of compound [16] showed the following characteristic signals δ(ppm): 3.32-4.82(m,3H, isoxazoline); 4.32(s, 2H, C$\underline{H}_2$); 7.25-7.73(m,12H,Ar-H); 8.48(N-C-$\underline{H}$ triazole); 8.87 (s,1H,N-$\underline{H}$); 12.51(s,1H,-O-$\underline{H}$).

^{1}H-NMR spectrum of compound [17] showed the following characteristic signals δ(ppm): 3.61-4.02(m,3H, isoxazoline); 6.53-7.73(m,12H,Ar-H); 8.11(N-C-$\underline{H}$ triazole);8.52 (s,1H,N-$\underline{H}$); 12.46(s,1H,-O-$\underline{H}$).

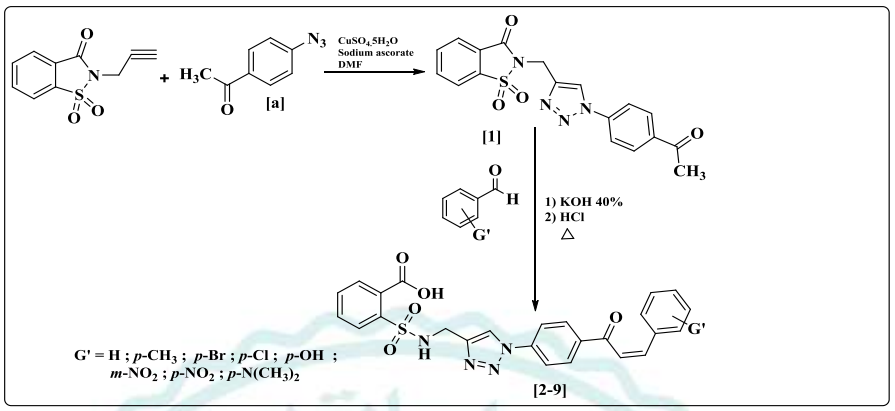
Cycloaddition of chalcone derivatives [2-6] with urea in the presence of sodium hydroxide under reflux condition produce pyrimidin-2-one derivatives [20-24] **(26)** as in Scheme (2).

FT-IR spectra of pyrimidine-2-one derivatives [20-24] show anew stretching bands due to (C=O) amide and (C=N) groups at (1703-1662)cm^{-1} and at (1681-1631)cm^{-1} respectively which were indicate to formation pyrimidine-2-one derivatives [20-24]. While ^{1}H-NMR spectrum of compound [20] showed the following characteristic signals δ(ppm): 3.32(s, 2H, N-C$\underline{H}_2$); 4.28(s, 1H, C$\underline{H}$ pyrimidine); 6.76-7.78(m,13H,Ar-H); 8.02(N-C-$\underline{H}$ triazole); 10.26 (s,1H,N-$\underline{H}$); 10.61 (s,1H,-O-$\underline{H}$); 12.69(s,1H,O=C-O-$\underline{H}$).

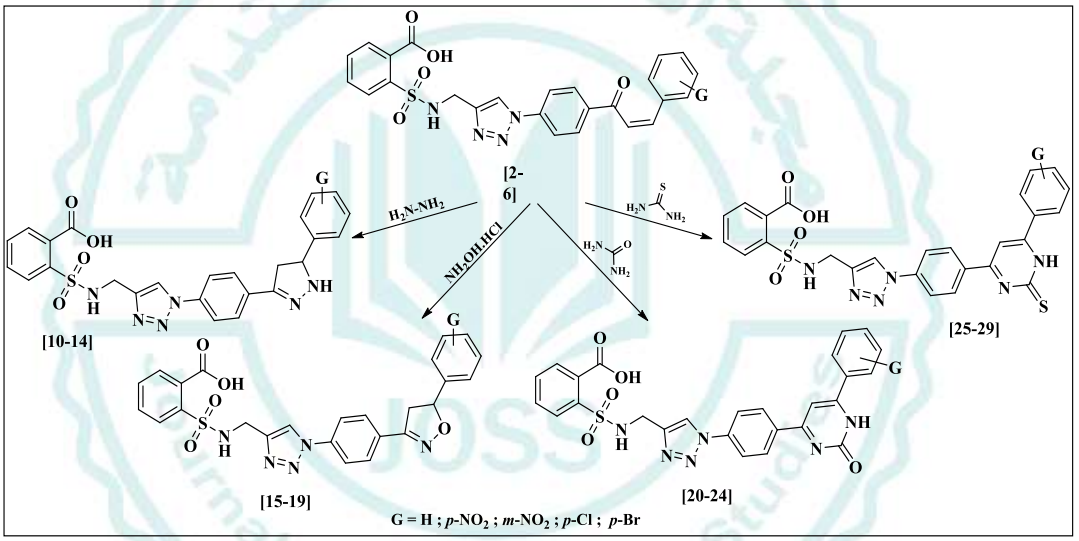
pyrimidin-2-thiol derivatives [25-29] were synthesized via the reaction of chalcone derivatives [2-6] with thiourea in the presence of sodium hydroxide under reflux condition**(26)** as in Scheme (2).

FT-IR spectra of pyrimidine-2-thiol derivatives [25-29] show disappearance of ν(C=O) ketone group at (1665-1641)cm^{-1}. Further the appearance of absorption bands at (2623-2507)cm^{-1}, and (1652-1631)cm^{-1} due to ν(S-H) and ν(C=N) respectively which were indicate to formation pyrimidin-2-thiol derivatives [25-29]. While ^{1}H-NMR spectrum of compound [25] showed the following characteristic signals δ(ppm): 1.25(s,1H,S=C-N$\underline{H}$); 2.53(s, 2H, N-C$\underline{H}_2$); 4.37(s, 1H, C$\underline{H}$ pyrimidine); 6.77-7.84(m,13H,Ar-H); 8.26(N-C-$\underline{H}$ triazole); 9.67 (s,1H,N-$\underline{H}$); 10.63 (s,1H,S-$\underline{H}$); 12.70(s,1H,-O-$\underline{H}$).

^{1}H-NMR spectrum of compound [27] showed the following characteristic signals δ(ppm): 1.19(s,1H,S=C-N$\underline{H}$); 3.37(s, 2H, N-C$\underline{H}_2$); 4.27(s, 1H, C$\underline{H}$ pyrimidine); 6.74-8.17(m,12H,Ar-H); 8.25(N-C-$\underline{H}$ triazole); 10.15 (s,1H,N-$\underline{H}$); 10.65 (s,1H,S-$\underline{H}$); 12.65(s,1H,-O-$\underline{H}$).



Scheme (1)



Scheme (2)

Applications:

Antibacterial activities:

The synthesized compounds were tested against different species of bacteria such as; ***Staphylococcus aureus*** and ***Streptococcus pneumonia*** which represented to Gram positive bacteria, while ***Escherichia coli*** and ***Klebsiella pneumonia*** that represent to Gram negative bacteria. The synthesized compounds were evaluated against four types of bacteria and the results showed all the tested of the synthesized compounds [1, 2, 3, 4, 5, 6,8, 9, 13, 16, 17, 18, 20, 22, 25 and 26] possess moderate and good antibacterial activities as shown as Table (1). Compounds (1, 3, 5, 9, 13, 16, 17, 22 and 26) possess a moderate activities against Gram negative bacteria (***Escherichia coli*** and ***Klebsiella pneumonia***) while it have a strong activities against Gram positive bacteria (***Staphylococcus aureus*** and ***Streptococcus pneumonia***). At the other hand in general compounds (2, 4, 5, 8, 17, 18, 20, and 25)

have a moderate activities against Gram negative and Gram negative bacteria but less than the others.

Table (1): Antibacterial activity test of some prepared compounds

No.	*Escherichia coli*	*Klebsilla*	*Staphylococcus aureus*	*Streptococcus pneumoniae*
1	13	14	12	14
2	11	11	10	14
3	10	11	13	12
4	12	14	10	11
5	10	11	12	12
6	11	11	15	14
8	11	11	13	13
9	10	10	13	16
13	16	13	12	13
16	12	10	14	13
17	11	11	15	13
18	11	10	11	14
20	13	11	13	11
22	12	13	14	13
25	13	12	11	13
26	10	10	13	13
Ceftriaxone	16	14	12	11
control	-	-	-	-

[Control]: 100µg/mL; Solvent: dimethylsolfoxide

Inhibition Zone: (-) no inhibition; (6-10) weak; (11-18) moderate; (19-30) strong; (30>) very strong.

Electrochemical oxidation effect of synthesized compounds [1, 9, 13, 17 & 22] on Mercury ions in blood serum using Cyclic Voltammetry:

In this study some of the synthesized compounds [1, 2, 3, 4, 5, 6,8, 9, 13, 16, 17, 18, 20, 22, 25 and 26] that have a good antibacterial as shown as in Table (1). Some of them were a good antioxidant and medium degree, where the others are not suitable for being as antioxidant. A fabricated and modificated glassy carbon electrode (GCE) as a biosensors with mechanical attachment by carbon nanotubes to detect the effect of several compounds [1, 9, 13, 17 & 22] on mercury ions in blood serum of human healthy.

The aim of this studies were made to find a therapeutic agents capable of minimizing genoxicty of various natural and man-made compounds.

Cyclic Voltammogram was show the effect of the oxidation current peaks of Hg^{+2} with blood serum, by modified (GCE), carbon nanotube CNT as a working electrode using Cyclic Voltammogram (CV) method which enhances the oxidation current peak at CV analysis study. Compounds [1, 9, 13, 17 & 22] arrange in terms of their effectiveness as antioxidant from high antioxidant to low antioxidant respectively, as follows:

22 > 13 > 17 > 1 > 9.

The result of test compound [1] indicated that considered a good antioxidant compound and has no side effect when it used as a medicine due to presence of two oxidation peaks at (-0.5)v and (+0.5)v as well as the presence of three redaction peaks at (-250)mv, (0)v and (+1.25)v respectively. Thus the reduction more than oxidation as shown as Figure (1).

Compound [9] has three oxidation peaks at (-250)mv, (+500)mv and (+750)mv. Also has one reduction peak at (-250)mv as shown in Figure (2). Morever, this compound is not recommended for use as a medicinal compound.

Compound [13] considered very good antioxidant where it's found only one peak at (+1)v and also two redactive peaks at (-350)mv and (+750)mv. Therefor the redation are more than oxidation as shown in Figure (3) and it's good for medical uses.

Form the chart of Cyclic Voltammogram of compound [17] presented a good antioxidant as it was found through analysis tested which were contain two oxidation peaks at (-200)mv and (+250)mv in addition to three redaction peaks at (-200)mv, (-750)mv and (+1.25)v as shown in Figure (4). The redaction values are higher than the oxidation values. Thus, there are no pose risk in its therapeutic uses.

Compound [22] resulted very good antioxidant with medical uses for contain one oxidation peak at (-200)mv, when the figure appear two reduction peaks at (-400)mv and (-1.25)v as shown in Figure (5). Thus the redaction more than oxidative stress and it can be extracted by liver easily without side effects.

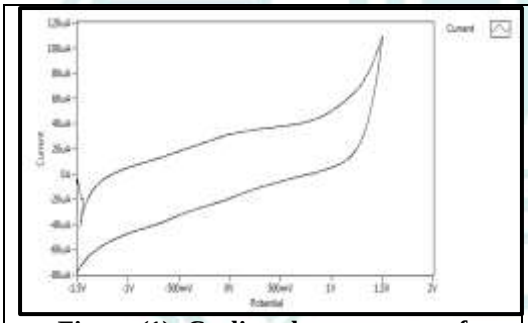


Figure (1): Cyclic voltammogram of compound [1] at 1000 µ/L concentration in blood serum medium using GCE/CNT and Ag/AgCl as a reference electrods.

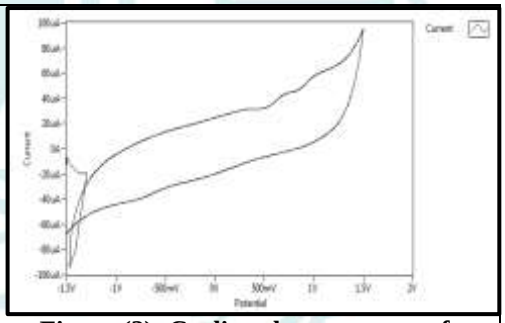


Figure (2): Cyclic voltammogram of compound [9] at 1000 µ/L concentration in blood serum medium using GCE/CNT and Ag/AgCl as a reference electrods.

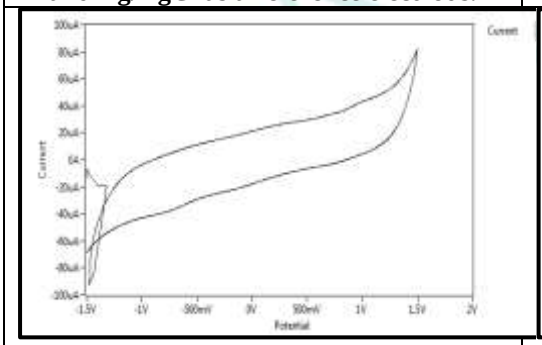


Figure (3): Cyclic voltammogram of

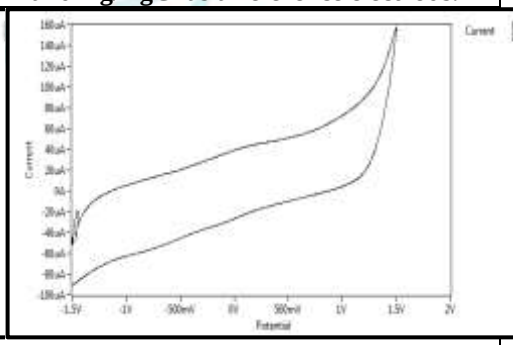


Figure (4): Cyclic voltammogram of

compound [13] at 1000 µ/L concentraction in blood serum medium using GCE/CNT and Ag/AgCl as a reference electrods.	compound [17] at 1000 µ/L concentraction in blood serum medium using GCE/CNT and Ag/AgCl as a reference electrods.

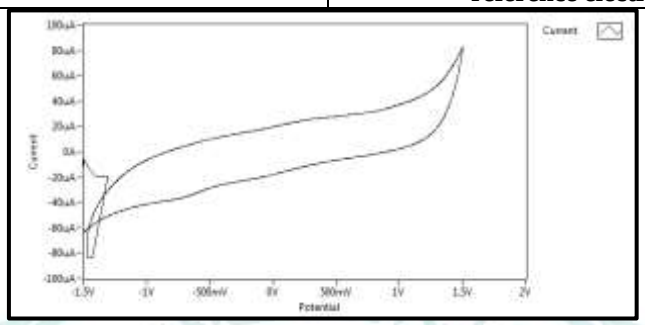


Figure (5): Cyclic voltammogram of compound [22] at 1000 µ/L concentraction in blood serum medium using GCE/CNT and Ag/AgCl as a reference electrods.

Antioxidant activity:

The results of selective compounds tests using DPPH showed in all selective compounds a concentration-dependent radical scavenging activity. Higher activity was observed at 280 µg/ ml in compound [9], while the lowest activity was observed in compound [22] at same concentration compared with the ascorbic acid control Figure (6).

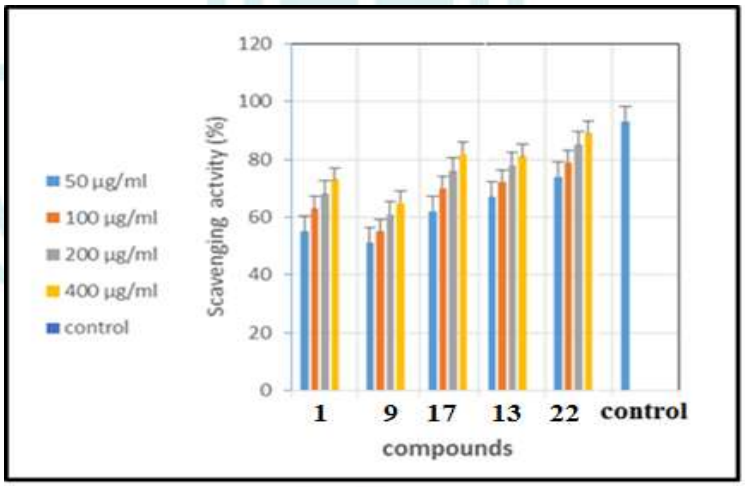


Figure (6): DPPH free radical scavenging activity. The inhibition percentage of different concentrations of derivative compounds at different concentrations (50-400 µg/ml) at 517 nm. Values presented are means ± SE (n = 3). L-ascorbic acid served as control.

Cytotoxicity assay:

In this study, the MTT results on HEK293 cell line revealed that for the compound [1], the relative cell viability after 24 hours of treatment is in an moderate grade and after 48 and 72 hours of treatment, the cell viability decreased by the rate of 10- 23

%; therefore, this sample is moderate in vitro results. In contrast, the relative cell viability of compound [22], [9] and compound [17] after 24 hours of treatment is in a low grade (not good for in vitro and in vivo phases), but not recommended for total experiments of in vivo phases; and after 48 and 72 hours of treatment, the cell viability decreased by the rate of 9 to 13 %; therefore, this sample is not recommended for in vivo phases, however, it is moderate in vitro results. Moreover, based on the results on HEK293 cell line for compound [13], the relative cell viability after 24 hours of treatment is in an average grade (good for in vitro and also moderate for in vivo phases with the concentrations optimizations); and after 48 and 72 hours of treatment, the cell viability decreased dramatically by the rate of 16 to 52 %; therefore, this sample is dose and time-dependent manner, and more experiments should be conducted for extra information, Figure (7-11).

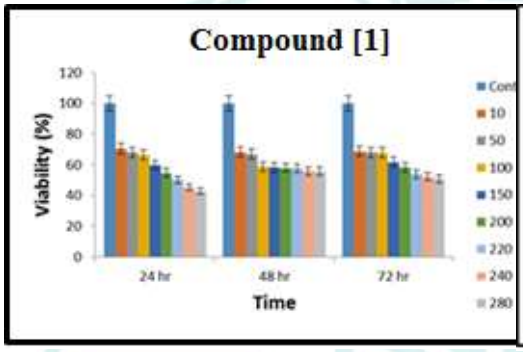


Figure (7): Growth inhibition of HEK294 cell lines treated with different concentrations (10-280 µg/ml) using MTT assay after 24, 48 and 27h of treatment. Values presented are means ± SE.

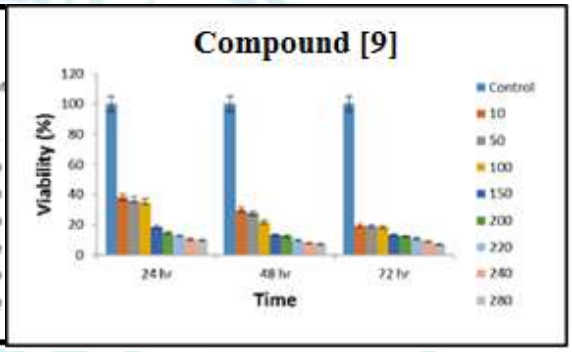


Figure (8): Growth inhibition of HEK294 cell lines treated with different concentrations (10-280 µg/ml) using MTT assay after 24, 48 and 27h of treatment. Values presented are means ± SE.

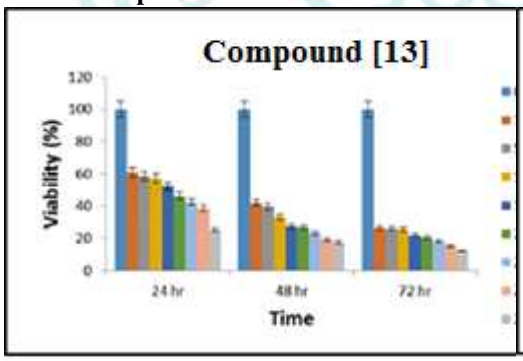


Figure (9): Growth inhibition of HEK294 cell lines treated with different concentrations (10-280 µg/ml) using MTT assay after 24, 48 and 27h of treatment. Values presented are means ± SE.

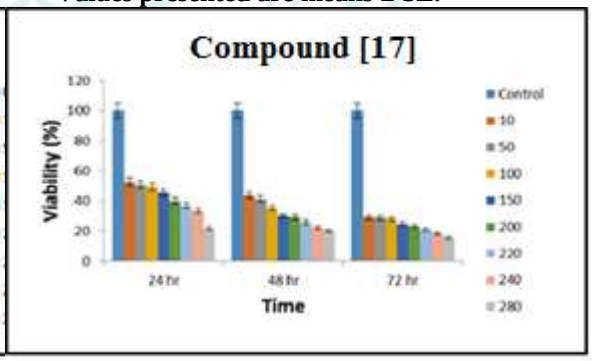


Figure (10): Growth inhibition of HEK294 cell lines treated with different concentrations (10-280 µg/ml) using MTT assay after 24, 48 and 27h of treatment. Values presented are means ± SE.

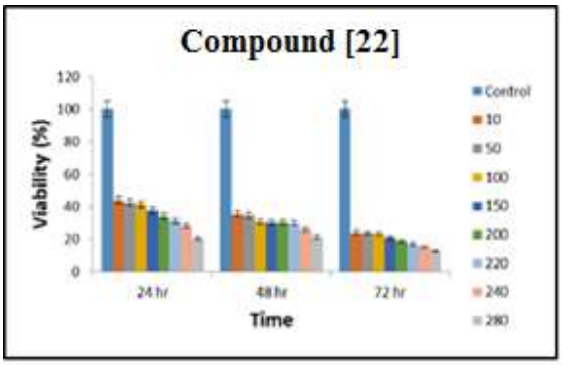


Figure (11): Growth inhibition of HEK294 cell lines treated with different concentrations (10-280 µg/ml) using MTT assay after 24, 48 and 27h of treatment. Values presented are means ± SE

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