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# Design, Synthesis, and Anticancer Activity Study of several New Schiff Base Imidyl Sulfa Drug Derivatives based on N-(Sulfamethoxazole-4-yl)-4-Aminomethylbenzylidene

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## Abstract

In this research, a series of new (Schiff base imidly sulfa drug) derivatives were designed and synthesized via many steps. In the first step, a sulfa drug (sulfamethoxazole) was chosen as a bioactive starting material and introduced in a condensation reaction with 4-amino acetophenone under microwave irradiation producing compound N-(sulfamethoxazole-4\-yl)-4-amino methyl benzylidene [1]. Subsequently, in the second step, compound [1] was introduced in reaction with three cyclic anhydrides, namely (succinic, maleic, and phthalic) anhydrides producing amic acid compounds [2-4], and these, inturn, introduced in the third step in a dehydration reaction via treatment with acetic anhydride and sodium acetate under reflux producing the target corresponding cyclic imide [5-7]. The work also involved a synthesis of other (Schiff base imidyl sulfa drug) derivatives (quinazoline) [8-10] via treatment of compounds [5-7] with anthranilic acid, while the treatment of compound [5-7] with phthalic anhydride afforded other new derivatives (oxazepin) [11-13]. Since molecules of the newly synthesized compound contain three biologically active segments, two of them are sulfa drug and cyclic imide. At the same time, the third segment is Schiff base in compounds [5-7], quinazoline in compounds [8-10], and oxazepin in compounds [11-13]. They are expected to possess high biological activity. Thus, the work involved also studying the anticancer activity of the prepared compounds against breast cancer, and the results are promising.

**Keywords: Schiff base, Cyclic imide, Sulfamethoxazole drug and MDA assay**

## Introduction

Breast cancer (BC) is one of the widespread cancers that impact women, and it is characterized by uncontrolled growth of cells in the breast[1, 2]. Many studies indicated that breast cancer occurs from a combination of several internal and external causes[3]; thus, the incidence of poor lifestyle choices is linked to environmental factors and social–psychological factors. Also, a research has shown that hereditary mutations and family history account for 5% to 10% of breast cancer, while modifiable variables contribute 20% to 30% of breast cancers[4]. Sulfonamide antibiotics are bacteriostatic drugs widely used in human health care and cattle production to inhibit gram-positive and gram-negative bacteria effectively[5, 6]. Sulfamethoxazole (SMX) is a member of the sulfonamide class of antibiotics[7], and due to its extensive utilization , it has been selected as the representative of this group. On the other hand, Cyclic Imides are essential types of organic compounds whose structure is composed of five or six-membered heterocycles containing only one nitrogen atom linked to two carbonyl groups[8, 9] . Since cyclic imides exhibit various biological activities, including antimicrobial, anti-inflammatory, antibacterial, anticancer, anticonvulsant, and analgesic[10-12], they are important basic modular units in a lot of pharmaceuticals, medicines, and essential parts in structures of various significant compounds such as thalidomide, isogranulatimide, granulatimide, and fumaramidmycin[13]. In addition, cyclic imides are utilized as precursors and intermediates in the synthesis of polymers[14, 15], dyes[16], anticancer drugs, and pesticides[17]. Similarly, Schiff bases are well-known important organic compounds that

were prepared for the first time by Hugo Schiff in 1864 via condensation of a carbonyl compound with a primary amine. Generally, Schiff bases have been reported to possess a broad spectrum of biological activities, such as antibacterial[18], anti-inflammatory[19], antifungal[20], antimalarial[21], analgesic, anticancer [22], pharmacological[23], and antitumor[24]. Many types of research indicated that the presence of the amino group (-C=N) in Schiff base structures is vital for all biological activities that are shown by Schiff bases[25, 26] . Both Schiff base and cyclic imides are currently attracting considerable attention in the field of cancer treatment because of their biological activity, extensive distribution[27], and ease in crossing membranes. Besides, some of these compounds are employed as carriers for anticancer drugs to deliver them to cancer cells. All the mentioned encouraged us to design and synthesize new compounds that contain these three biologically active compounds. Besides, we thought it was worth it to synthesize other new compounds that contain sulfa drugs and cyclic imides besides quinazoline or oxazepin heterocycles and then examine their effect on biological activity.

## Materials and Methods

### *Materials*

### *Chemicals*

All chemicals were supplied from different companies; Sulfamethoxazole was supplied from Sigma and Aldrich, while other pure chemicals and solvents were supplied from Merck, BDH Alfa, and Fulka

### *Apparatus*

Melting points were recorded on a hot-stage digital Stuart Scientific SMP30 melting point apparatus manufactured in the UK. Infrared spectra were recorded on a Shimadzu FT-IR—8400 spectrophotometer in the College of Science, Bagdad University; all derivatives were run in as KBr discs. In addition, $^{1}$H-NMR and $^{13}$C NMR spectra were recorded on a Bruker 400MHZ instrument in DMSO-d6 as a solvent and trimethyl silane (TMS) as an internal standard.

### *Methodology*

**Synthesis of N-(sulfamethoxazole-4\-yl)-4-amino methyl benzylidene [1]**

Compound [1] was synthesized via heating the mixture of sulfamethoxazole drug (0.5g, 0.002mol) and 4-amino acetophenone(0.27g,0.002mol) with ٢-٣ drops of glacial acetic acid inside a Microwave(50W) oven for (4-5) min[28]. The brown-coloured solid obtained was cooled, washed with ether, and then dried and recrystallized from petroleum ether (b.p.40-60) °C.

**N-(sulfamethoxazole - 4\ - yl )-4-amino methyl benzylidene [1]**

[$C_{18}H_{18}N_4O_3S$]: powder yellow; 95%; m.p.130-131 °C; recrystallization from Petroleum ether; FTIR ($cm^{-1}$): (3467,3379 ,3290 & 3228 ) (NH), 3030 (Ar-H), 2960 & 2880 (CH aliphatic), 1639& 1622 (C=N), 1595 & 1564 (C=C), 1363 (asym. $SO_2$), 1157 (sym. $SO_2$); $^{1}$HNMR (DMSO-d6, 400 MHz,) δ/ppm: 2.33 (3H, $CH_3$), 2.43 ($CH_3$C=N-), 6.07-6.15($NH_2$) protons, 6.61-7.74( Ar-H) and proton in hetero ring, 10.98($NHSO_2$) proton. $^{13}$CNMR (76 MHz, DMSO) δ/ppm: 12.54($CH_3$), 26.34($CH_3$C=N-), (95.81-154.10) aromatic carbons and carbons in hetero ring, 158.46(C=N), 170.39($CH_3$C=N-).

**Synthesis of N-[4-(N\-Sulfamethoxazole-4\-yl) methyl benzylidene Succinamic acid [2]**

The solution of compound [1] (3.7g,0.01mol) dissolved in (20 mL) dry acetone was added as drops to the solution of succinic anhydride (1.0g,0.01mol) dissolved in (10 mL) acetone with good stirring[29]. The resulting mixture was stirred for two hours at room temperature, and then the precipitate formed was filtered, washed with diethyl ether, dried, and finally recrystallized from acetone.

**N-[4- ( N\ - Sulfamethoxazole-4\-yl) methyl benzylidene Succinamic acid [2]**

[$C_{22}H_{22}N_4O_6S$]: powder orang; 91%; m.p.159-161 °C; recrystallization from acetone; FTIR ($cm^{-1}$): (3464, 3380 & 3342) (NH), 3082 (Ar-H), 2929 & 2890 (CH aliphatic), 1695 (C=O) carboxyl, 1695 (C=O) amide (overlap),1643& 1622 (C=N), 1595 (C=C), 1365 (asym. $SO_2$), 1157 (sym. $SO_2$); $^{1}$HNMR (DMSO-d6, 400 MHz,) δ/ppm: 2.14(3H, $CH_3$), 2.45($CH_3$-C=N-), 2.57-2.60(-$CH_2$-$CH_2$-), 6.1-8.0(aromatic protons and proton in hetero ring), 10.71(NH amide), 11.0($NHSO_2$), 11.43(OH carboxyl).$^{13}$CNMR (76 MHz, DMSO) δ/ppm:12.51($CH_3$), 26.90($\underline{CH_3}$C=N-), 31.16(-$CH_2$-$CH_2$-), 112.9-144.3(aromatic carbons and carbons in hetero ring), 153.7(C=N), 167.7(C=O) amide, 168.3(C=O) carboxyl.

**Synthesis of N-[4-(N\-Sulfamethoxazole-4\-yl) methyl benzylidene maleamic acid [3]**

Synthesis of compound [3] was performed by the reaction of (3.7g,0.01mol) of compound [1] with (0.98g,0.01mol) of maleic anhydride in dry acetone using the same experimental procedure that was employed in the synthesis of compound [2]. The resulting solid was filtered, washed with ether, dried, and finally recrystallized from acetone[29].

**N- [4 -(N\- Sulfamethoxazole- 4\ - yl) methyl benzylidene maleamic acid [3]**

[$C_{22}H_{20}N_4O_6S$]: powder light orang; 90%; m.p.178-179 °C; recrystallization from acetone; FTIR ($cm^{-1}$): (3477, 3386 & 3269) (NH), 3062 (Ar-H), 2940 & 2885 (CH aliphatic), 1712 (C=O) carboxyl, 1677 (C=O) amide,1633 (C=N), 1595& 1537 (C=C), 1361 (asym. $SO_2$), 1157 (sym. $SO_2$).

**Synthesis of N-[4-(N\-Sulfamethoxazole-4\-yl) methyl benzylidene phthalamic acid [4]**

Synthesis of compound [4] was performed by reaction of (3.7g,0.01mol) of compound [1] with (1.48g,0.01mol) of phthalic anhydride in dry acetone using the same experimental procedure that was employed in the synthesis of compound [2]. The resulting solid was filtered, washed with ether, dried, and finally recrystallized from acetone[29].

**N-[4-( N\ - Sulfamethoxazole -4\ -yl) methyl benzylidene phthalamic acid [4]**

[$C_{26}H_{20}N_4O_6S$]: powder deep orange; 85%; m.p.161-163°C; recrystallization from acetone; FTIR ($cm^{-1}$): (3477, 3386 & 3259) (NH), 3093 (Ar-H), 2966,2931 & 2896 (CH aliphatic), 1714 (C=O) carboxyl, 1674 (C=O)amide,1643& 1620 (C=N), 1595& 1537 (C=C), 1326 (asym. $SO_2$), 1157 (sym. $SO_2$); $^1$HNMR (DMSO-d6, 400 MHz,) δ/ppm: 2.21(3H, $CH_3$), 2.3($CH_3$-C=N-), 6.45-8.3(aromatic protons and proton in hetero ring), 9.85(NH amide), 10.45($NHSO_2$), 11.8(OH carboxyl).

**Synthesis of N-[4-(N\-Sulfamethoxazole-4\-yl) methyl benzylidene succinimide [5]**

The titled compound [5] was synthesized by reacting succinamic acid [2] (2.35g,0.005mol) with (25 mL) of acetic anhydride and (5-10) % by weight of anhydrous sodium acetate under reflux with stirring for two hours[30, 31]. After cooling to room temperature, the mixture was vigorously stirred before being poured into ice water. The resultant solid was collected via filtering, washed twice with distilled water, and recrystallized from n-Hexane.

**N-[ 4- ( N \- Sulfamethoxazole-4\-yl) methyl benzylidene succinimide [5]**

[$C_{22}H_{20}N_4O_5S$]: powder deep broen; 84%; m.p.190-192 °C; recrystallization from n-Hexane; FTIR ($cm^{-1}$): (3342 & 3139) (NH), 3055 (Ar-H), 2929 & 2850 (CH aliphatic), 1766 & 1708(C=O) imide,1608 (C=N), 1591 (C=C), 1365(C-N) imide, 1313 (asym. $SO_2$), 1163 (sym. $SO_2$); $^1$HNMR (DMSO-d6, 400 MHz,) δ/ppm:2.16(3H, $CH_3$), 2.37($CH_3$-C=N-), 2.77-2.92(-$CH_2$-$CH_2$-), 6.3-7.99(aromatic protons and proton in hetero ring), 10.99($NHSO_2$).$^{13}$CNMR (76 MHz, DMSO) δ/ppm:12.64($CH_3$), 31.2($\underline{CH_3}$C=N-), 36.2(-$CH_2$-$CH_2$-), 96.9-131.8(aromatic carbons and carbons in hetero ring), 159.5(C=N), 162.81($CH_3\underline{C=N}$-) 171.40(C=O) imide.

**Synthesis of N-[4-(N\-Sulfamethoxazole-4\-yl) methyl benzylidene maleimide [6]**

The compound [6] was synthesized by reacting maleamic acid [3] (2.34g,0.005mol) with (25 mL) of acetic anhydride in the presence of anhydrous sodium acetate, following the same procedure steps used in the synthesis of the compound [5](30) . The resultant solid was collected via filtering, washed twice with distilled water, dried, and recrystallized from n-Hexane[30, 31].

**N-[4-(N\-Sulfamethoxazole-4\-yl) methyl benzylidene maleimide [6]**

[$C_{22}H_{18}N_4O_5S$]: powder yellow; 78%; m.p.194-196 °C; recrystallization from n-Hexane; FTIR ($cm^{-1}$): (3342) (NH), 3056 (Ar-H), 2929 & 2852 (CH aliphatic), 1712(C=O) imide,1645 (C=N), 1591 & 1529 (C=C), 1367(C-N) imide, 1313 (asym. $SO_2$), 1163 (sym. $SO_2$);

**Synthesis of N-[4-(N\-Sulfamethoxazole-4\-yl) methyl benzylidene phthalimide [7]**

The compound titled [7] was synthesized via the reaction of phthalic acid [4] (2.59g,0.005mol) with (25 mL) of acetic anhydride in the presence of anhydrous sodium acetate, following the same procedure steps used in the synthesis of the compound [5]. The resultant solid was collected via filtering, washed twice with distilled water, dried, and recrystallized from n-Hexane[30, 31].

**N-[ 4 - ( N\ - Sulfamethoxazole-4\-yl) methyl benzylidene phthalimide [7]**

[$C_{26}H_{20}N_4O_5S$]: powder off white; 90%; m.p.180-182 °C; recrystallization from n-Hexane; FTIR ($cm^{-1}$): (3440) (NH), 3060 (Ar-H), 2960,2931 & 2873 (CH aliphatic), 1787 & 1720(C=O) imide,1633& 1604 (C=N), 1541 & 1512 (C=C), 1390(C-N) imide, 1342 (asym. $SO_2$), 1120 (sym. $SO_2$); $^1$HNMR (DMSO-d6, 400 MHz,) δ/ppm: 2.39(3H, $CH_3$), 2.58($CH_3$-C=N-), 6.26-8.19(aromatic protons and proton in hetero ring), 10.4($NHSO_2$).$^{13}$CNMR (76 MHz, DMSO) δ/ppm: 12.56($CH_3$), 26.96($\underline{CH_3}$C=N-), 95.82-153.79(aromatic carbons and carbons in hetero ring), 164.21C=N), 167.39($CH_3\underline{C=N}$-), 170.40(C=O) imide.

**Synthesis of 2-methyl-2-[4\-(N –succinimidly) phenyl]-3-(Sulfamethoxazole-4\-yl)-dihydroquinazoline-4-one [8]**

In a suitable round-bottomed flask (0.68g,0.005mol), anthranilic acid was dissolved in (6 mL) of dioxane and three drops of $Et_3N$ in an ice bath with stirring for (15) minutes[32, 33]. Then,

compound [5] (2.26g, 0.005mol) dissolved in (15 mL) dioxane was added in portions with good stirring. The resulting mixture was refluxed for ten hours, then cooled, and the formed solid product was filtered, dried, and then recrystallized from ethanol.

**2-methyl-2-[4\-(N –succinimidly) phenyl]-3-(Sulfamethoxazole-4\-yl)-dihydroquinazoline-4-one [8]**

[$C_{29}H_{25}N_5O_6S$]: powder deep brown; 95%; m.p.200-201 °C; recrystallization from ethanol; FTIR ($cm^{-1}$): (3420&3342) (NH), 3064 (Ar-H), 2968,2929 & 2894 (CH aliphatic), 1766 & 1704(C=O) imide, 1685(C=O) amide,1610 (C=N), 1589 & 1533 (C=C), 1390(C-N) imide, 1313 (asym. $SO_2$), 1164 (sym. $SO_2$); $^1$HNMR (DMSO-d6, 400 MHz,) δ/ppm: 2.08(3H, $CH_3$), 2.19($CH_3$-C-N-), 2.35(-$CH_2$-$CH_2$-), 3.72(NH amine), 6.18-8.08(aromatic protons and proton in hetero ring), 10.55($NHSO_2$).$^{13}$CNMR (76 MHz, DMSO) δ/ppm:12.56($CH_3$), 13.04($\underline{CH_3}$-C-N-), 24.27-24.71(-$CH_2$-$CH_2$-), 95.88-158.08(aromatic carbons and carbons in oxazole ring), 168.95C=N), 169.60($CH_3$-$\underline{C=N}$-), 170.76(C=O) amide, 173.61(C=O) imide.

**Synthesis of 2-methyl-2-[4\-(N –maleimidyl) phenyl]-3-(Sulfamethoxazole-4\-yl)-dihydroquinazoline-4-one [9]**

Compound [9] was synthesized via a reaction of anthranilic acid (0.68g,0.005mol) with compound [6] (2.25g,0.005mol) in dioxane solvent in the presence of $Et_3N$, following the same steps that are used in the synthesis of the compound [8]. The obtained solid was purified by recrystallization from ethanol[32, 33].

**2-methyl-2-[4\-(N –maleimidyl) phenyl]-3-(Sulfamethoxazole-4\-yl)-dihydro quinazoline-4-one [9]**

[$C_{29}H_{23}N_5O_6S$]: powder off white; 88%; m.p.180-182 °C; recrystallization from ethanol; FTIR ($cm^{-1}$): (3460&3276) (NH), 3060 (Ar-H), 2975 & 2860 (CH aliphatic), 1697(C=O) imide, 1681(C=O) amide,1616 (C=N), 1593 (C=C), 1338(C-N) imide, 1317 (asym. $SO_2$), 1163 (sym. $SO_2$); $^1$HNMR (DMSO-d6, 400 MHz,) δ/ppm:2.08(3H, $CH_3$), 2.14($CH_3$-C-N-), 5.77(NH amine and vinylic protons), 6.39-8.0(aromatic protons and proton in oxazole ring), 10.11($NHSO_2$).

**Synthesis of 2-methyl-2-[4\-(N –phthalimidyl) phenyl]-3-(Sulfamethoxazole-4\-yl)-dihydroquinazoline-4-one [10]**

Compound [10] was synthesized via a reaction of anthranilic acid (0.68g,0.005mol) with compound [7] (2.50g,0.005mol) in dioxane solvent in the presence of $Et_3N$, following the same steps that are used in the synthesis of the compound [8]. The obtained solid was purified by recrystallization from ethanol[32, 33].

**2-methyl-2-[4\-(N –phthalimidyl) phenyl]-3-(Sulfamethoxazole-4\-yl)-dihydro quinazoline-4-one [10]**

[$C_{33}H_{25}N_5O_6S$]: powder deep yellow; 93%; m.p.205-207 °C; recrystallization from ethanol; FTIR ($cm^{-1}$): (3475&3373) (NH), 3058 (Ar-H), 2925 & 2854 (CH aliphatic), 1741 & 1716(C=O) imide, 1677(C=O) amide,1604 (C=N), 1596 (C=C), 1384(C-N) imide, 1384 (asym. $SO_2$) overlap, 1164 (sym. $SO_2$).

**Synthesis of 2-methyl-2-[4\-(N-succinimidyl) phenyl]-3-(Sulfamethoxazole-4\-yl)-oxazepin-4,7-dione [11]**

A mixture of equimolar amount (2.26g,0.005mol) of compound [5]and (0.74g,0.005mol) of phthalic anhydride in (25 mL) of dry benzene[34, 35] was heated under reflux for eight hours with stirring. After reflux completion, the solvent was evaporated, and the obtained solid was purified by recrystallization from n-Hexane.

**2-methyl-2-[4\-(N-succinimidyl) phenyl]-3-(Sulfamethoxazole-4\-yl)-oxazepin-4,7-dione [11]**

[$C_{30}H_{24}N_4O_8S$]: powder yellow; 93%; m.p.225-227 °C; recrystallization from n-Hexane; FTIR ($cm^{-1}$): (3433) (NH), 3040 (Ar-H), 2974,2923 & 2850 (CH aliphatic), 1765 & 1718(C=O) imide, 1718(C=O) ester (overlap), 1679(C=O) amide,1606 (C=N), 1535 (C=C), 1396(C-N) imide, 1373 (asym. $SO_2$), 1164 (sym. $SO_2$).

**Synthesis of 2-methyl-2-[4\-(N-maleimidyl) phenyl]-3-(Sulfamethoxazole-4\-yl)-oxazepin-4,7-dione [12]**

Compound [12] was synthesized via a reaction of the compound [6] (2.25g,0.005mol) with phthalic anhydride (0.74g,0.005mol) in dry benzene, following the same steps that are used in the synthesis of the compound [11]. The obtained solid was purified by recrystallization from ethanol[34, 35].

**2-methyl-2-[4\-(N-maleimidyl) phenyl]-3-(Sulfamethoxazole-4\-yl)-oxazepin-4,7-dione [12]**

[$C_{30}H_{22}N_4O_8S$]: powder orang; 78%; m.p.217-219 °C; recrystallization from ethanol; FTIR ($cm^{-1}$): (3440) (NH), 3020 (Ar-H), 2927 & 2880 (CH aliphatic), 1775 & 1708(C=O) imide, 1739(C=O) ester, 1679(C=O) amide,1620 (C=N), 1539&1515 (C=C), 1396(C-N) imide, 1338 (asym. $SO_2$), 1159 (sym. $SO_2$).$^1$HNMR (DMSO-d6, 400 MHz,) δ/ppm:1.96(3H, $CH_3$), 2.19($CH_3$-C-N-), 6.0(vinylic protons), 6.61-8.53(aromatic protons and proton in oxazole ring), 11.25($NHSO_2$).

**Synthesis of 2-methyl-2-[4\-(N-phthalimidyl) phenyl]-3-(Sulfamethoxazole-4\-yl)-oxazepin-4,7-dione [13]**

Compound [13] was synthesized via a reaction of the compound [7] (2.5g,0.005mol) with phthalic anhydride (0.74g,0.005mol) in dry benzene, following the same steps that are used in the synthesis of the compound [11]. The obtained solid was purified by recrystallization from ethanol[34, 35].

**2-methyl-2-[4\-(N-phthalimidyl) phenyl]-3-(Sulfamethoxazole-4\-yl)-oxazepin-4,7-dione [13]**

[$C_{34}H_{24}N_4O_8S$]: powder deep brown; 82%; m.p.193-195 °C; recrystallization from ethanol; FTIR ($cm^{-1}$): (3420) (NH), 3015 (Ar-H), 2970 & 2814 (CH aliphatic), 1770 & 1713 (C=O) imide, 1730 (C=O) ester, 1677(C=O) amide,1622 (C=N), 1544 (C=C), 1395(C-N) imide, 1341 (asym. $SO_2$), 1152 (sym. $SO_2$).

## *In vitro cell proliferation-inhibition assay*

The MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay was used to determine the efficacy of compounds (8,9,13), which was investigated via in vitro evaluation analysis employing an MDA cell line. The analysis was conducted after establishing a monolayer confluent cell within the vessel and aspiration of the growth medium, followed by washing the cell sheet with PBS (phosphate-buffered saline). This step was followed by the addition of 2-3 mL of Trypsin/versine solution to the cells, then flipping with the gentle rocking of the vessel to ensure a complete emersion of the cells. Eventually, the vessel was incubated at 37C0 for 1-2 minutes to ensure detachment of cells from the vessel, followed by the addition of 15-20 mL RPMI medium, allowing cells to disperse by pipetting. The cells were 4 rearranged into culture growth plates at specific concentrations determined by a hemocytometer using the formula. The cells were incubated at 37 C in a 5% CO2 incubator[36] .Total cell count /mL = cell count * dilution factor * 104 After the growth of the cells, the cytotoxic analysis was conducted for the above compounds using the following concentrations (25, 50, 100, 200, and 400 µg/mL) via the employment of an MTT ready-to-use kit contains 10 vials of 1mL MTT solution and 2 bottles of 50 mL solubilization solution. Tumor cells (1x104 1x106 cells/mL) were cultured in 96-well flat-bottom micro-titer plates with a final volume of 200 µL of complete medium per well. The microplates were sealed with sterilized parafilm and gently shaken, followed by incubation at 37 °C with 5% CO2 for 24 hours. After removing the medium, two-fold serial dilutions of the desired concentrations (8,9,13) at 25, 50, 100, 200, and 400 µg/mL were added to the wells. Each concentration and control (cells treated with serum-free medium) were tested in triplicate. The plates were incubated at 37 °C with 5% CO2 for 24 hours. Afterward, 10 µL of MTT solution was added to each well, and the plates were further incubated for 4 hours under the same conditions. The media were carefully removed, and 100 µL of solubilization solution was added per well for 5 minutes. Optical density was measured at 575 nm using an ELISA reader. The data were statistically analyzed to determine the concentration of compounds required to reduce cell viability by 50% in each cell line[37] .

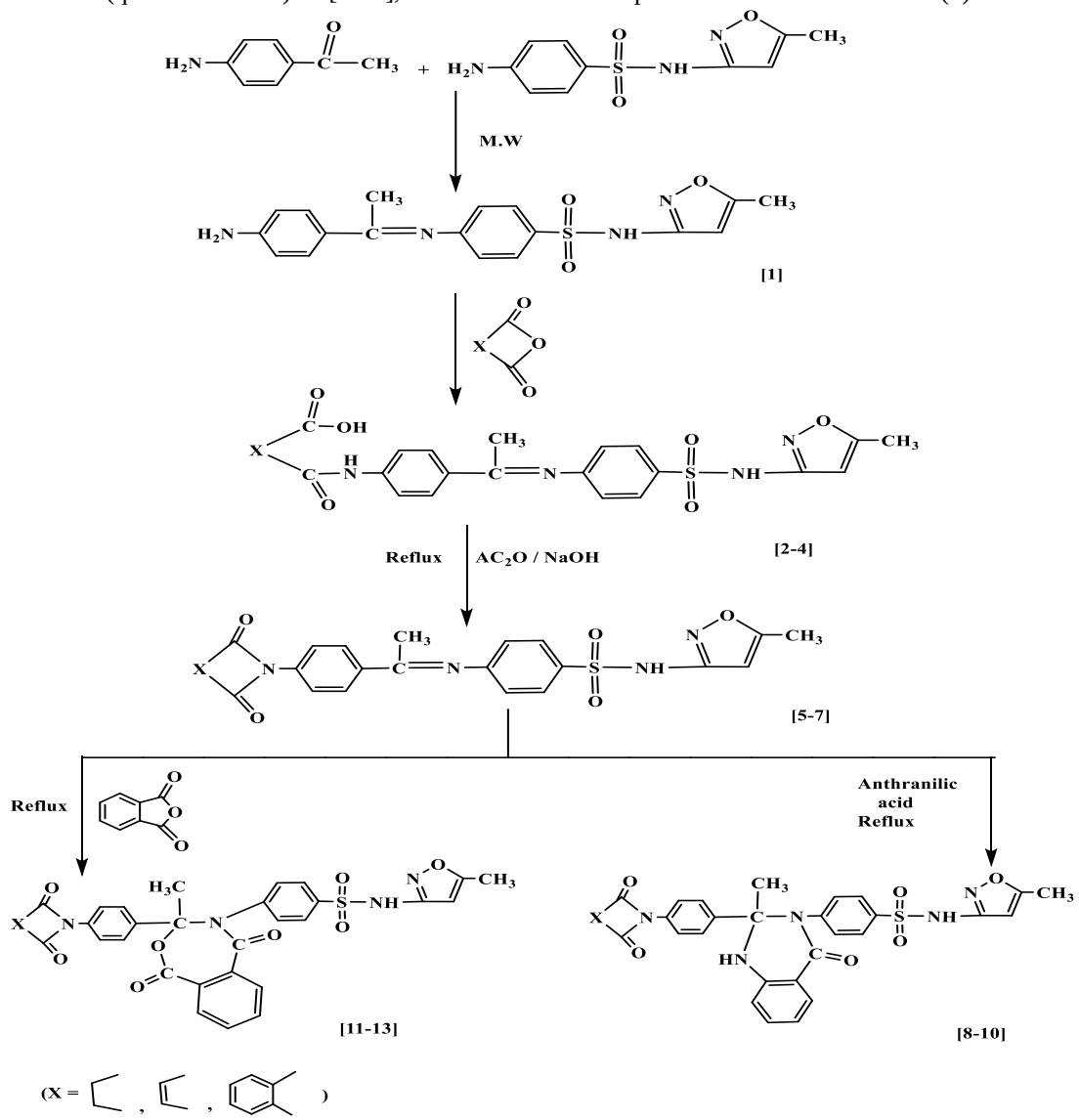
### *Statistical analysis*

The statistics were conducted in triplicate, and the data were presented as mean ± standard deviation (SD). Significant variances (ns: non-significant, *: $p \leq 0.05$, **: $p \leq 0.01$, ***: $p \leq 0.001$, ****: $p \leq 0.0001$) between each compound with Tamoxifen were analyzed by two-way ANOVA (Tukey) and student's t-test (one-tailed unpaired) using GraphPad Prism version 9.0 (GraphPad Prism software Inc., La Jolla, CA, USA)(38).

## Results and Discussion

Both cyclic imides and Schiff bases play a unique role in medicinal chemistry due to their various biological activities and widespread use in medicine and pharmacology. Thus, some of them are used as analgesics, antifungals, and anticoagulants, while others are used as anti-inflammatory and anticancer agents. Besides, sulfamethoxazole drug has been reported to be used for antimalarial, antibacterial, and antineoplastic purposes. Therefore, designing and synthesizing new molecules that contain these biologically active components seemed very worthy and a highly important task. For this purpose, in this work, we designed and synthesized new molecules that contain these active compounds by choosing sulfa drug (sulfamethoxazole) as the starting material, which is introduced in a condensation reaction with 4-amino acetophenone under Microwave irradiation producing compound [1] (sulfa drug linking to Schiff base). Compound [1] is the important key compound in this work and the valuable starting material from which all the target compounds were synthesized through many steps. In the second step, compound [1] was reacted with different cyclic anhydrides, including (succinic, maleic, and phthalic) anhydrides, giving amic acids [2-4]. Dehydration of amic acids [2-4] was performed in the third step via treatment with acetic anhydride and anhydrous sodium acetate, producing the corresponding cyclic imides [5-7][31]. The target compounds [5-7] contain three biologically active segments together in the same molecule, namely

(sulfa drug, Schiff base, and cyclic imide). For this reason, these compounds are expected to exhibit very high biological activity. Moreover, the presence of Schiff base moiety in compounds [5-7] made them ready to introduce in the subsequent reaction with anthranilic acid, which attacks the imino group (C=N), producing new Schiff base derivatives (quinazoline-one) [8-10], while treatment of compounds [5-7] with phthalic anhydride, which also attacks imino group producing other new Schiff base derivatives (oxazepins) [11-13]. Structures of compounds [8-10] and [11-13] contain the sulfa drug, cyclic imide, and bioactive heterocycles (quinazolin-one) and (oxazepin). Synthetic steps for all these new compounds are shown in scheme (1).




**Scheme 1. Synthesis Steps for the New Target Compounds [1-13]**

Chemical structures of the prepared compounds were confirmed by depending on FTIR, $^{1}$H-NMR, and $^{13}$C-NMR spectral data.

FTIR spectrum of compound [1] showed characteristic absorption bands at (3467,3379) $cm^{-1}$ due to ν ($NH_2$) and others at (3290,3228) $cm^{-1}$ due to ν (N-H) amide[39]. Other absorption bands appeared at (1639,1622) $cm^{-1}$, (1595,1564) $cm^{-1}$, (1363) $cm^{-1}$, and (1157) $cm^{-1,}$ which are attributed to ν (C=N), ν(C=C), asym. ν($SO_2$), and sym. ν ($SO_2$) respectively[39, 40]. The $^{1}$H-NMR spectrum of compound [1] showed signals at (δ = 2.33 and 2.43) ppm belonging to the protons of two $CH_3$ groups, signals at δ (6.07-6.15) ppm, (6.61-7.74) ppm, and (10.98) ppm belong to ($NH_2$) protons, aromatic protons, and ($NHSO_2$) protons respectively. The $^{13}$C-

NMR spectrum of the compound [1] showed a signal at δ = (12.54,26.3) ppm belonging to $CH_3$, a signal at δ = (95.81-154.1) ppm belonging to aromatic carbons, and signals at δ =(158.46,170.39) ppm belonging to (C=N) carbons. FTIR spectral of amic acid [2-4] showed absorption bands at (3477-3259) $cm^{-1}$ due to ν (O-H) carboxyl and ν (N-H) amide[41]The spectra also showed clear absorption bands at (1695-1714) cm-1, (1674-1695) cm-1, (1620-1643) cm-1, (1537-1595) cm-1, (1326-1365) cm-1, and (1159) cm-1, which are due to ν (C=O) carboxyl, ν (C=O) amid, ν (C=N), ν (C=C), asym. (SO2), and sym.(SO2), respectively.

On the other hand, FTIR spectra of compounds [5-7] showed absorption bands at (3139-3440) $cm^{-1}$, (1766-1787) $cm^{-1}$ and (1708-1720) $cm^{-1}$ due to ν (N-H), asym. ν (C=O) imide and sym. ν(C=O) imide. Other absorption bands appeared at (1604-1645) $cm^{-1}$, (1512-1591) $cm^{-1}$, (1365-1390) $cm^{-1}$, (1313-1342) $cm^{-1}$, and (1120-1163) $cm^{-1,}$ which are attributed to ν (C=N), ν (C=C), ν (C-N) imide, ν (C=C), asym. ($SO_2$), and sym. ($SO_2$) respectively[41].

$^1$H-NMR spectra of compounds [2]and [4] showed signals at (δ = 2.14-2.45) ppm belonging to the protons of $CH_3$ groups and signals at δ (6.1-8.3) ppm belonging to aromatic protons. Signals belonging to (NH) amide proton, ($NHSO_2$) proton, and (OH) carboxyl proton appeared at (9.85-10.71), (10.45-11.0), and (11.43-11.80) ppm. $^1$H-NMR spectrum of compound [2] showed signals at (δ= 2.57-2.6) ppm belonging to (-$CH_2$-$CH_2$-) protons. $^{13}$C-NMR spectrum of the compound [2] showed a signal that belonging to two $CH_3$, (-$CH_2$-$CH_2$-) carbons, aromatic carbons, (C=N), (C=O) amide, and (C=O) carboxyl carbons as shown in Table (11). On the other hand, $^1$H-NMR spectra of compounds [5] and [7] showed signals at (δ= 2.16-2.58) ppm belonging to protons of two CH3 groups, signal at δ = (6.26-8.19) ppm belonging to aromatic protons and signals at δ = (10.4-10.99) ppm belong to ($NHSO_2$) proton. H-NMR spectrum of compounds [5] showed a signal at (δ = 2.77-2.92) ppm belonging to (-$CH_2$-$CH_2$-) protons in the imide ring. $^{13}$C-NMR spectra of compounds [5] and [7] showed signals at ( δ = 12.56-31.2) ppm belonging to $CH_3$ carbons, signals at ( δ = 95.82-153.79) ppm belonging to aromatic carbons, signals at (δ = 159.5-167.39) ppm belonging to (C=N) carbons and signals at (δ = 170.40-171.40) ppm belonging to (C=O) imide carbons. The $^{13}$C-NMR spectrum of the compound [5] showed signals at (δ = 36.2) ppm belonging to (-$CH_2$-$CH_2$-) carbons. FTIR spectra of quinazoline derivatives [8-10] showed absorption bands at (3276-3475) $cm^{-1}$ due to ν (N-H), bands at (1741-1766) $cm^{-1}$, and (1697-1716) $cm^{-1}$ due to asym. ν (C=O) imide and sym. ν (C=O) imide respectively.

Other absorption bands appeared at (1677-1685) $cm^{-1}$,(1604-1616) $cm^{-1}$, (1533-1596) $cm^{-1}$, (1338-1384) $cm^{-1}$,(1313-1384)$cm^{-1}$ and (1163-1164) $cm^{-1,}$ which are attributed to ν (C=O) amide, ν (C=N) , ν (C=C), ν (C-N) imde, asym. ($SO_2$), and sym. ($SO_2$) respectively. [42] . $^1$H-NMR spectra of quinazoline derivatives [8]and [9] showed signals at (δ = 2.08-2.19) ppm belonging to $CH_3$ groups, signals at δ (6.18-8.08) ppm belonging to aromatic protons, and signals at (δ = 10.11-10.55) ppm belonging to ($NHSO_2$) proton[42]. Besides $^1$H-NMR spectrum of the compound [8] showed signals at (δ = 2.35) ppm and (δ =3.72) ppm, which belongs to (-$CH_2$-$CH_2$-) protons in imide ring and (NH) amine proton, respectively while H-NMR spectrum of compound [9] showed a signal at (δ=5.77) ppm belong to (NH) amine and vinylic protons. The $^{13}$C-NMR spectrum of compound [8] showed signals at ( δ = 12.56,13.04) ppm belonging to $CH_3$ group carbons, signals at ( δ = 24.27-24.71) ppm belonging to (-$CH_2$-$CH_2$-) carbons, and signals at (δ = 95.88-158.08) ppm belonging to aromatic carbons; signals belong to (C=N), ($CH_3$C-N-),(C=O) amide and (C=O) imide carbons appeared at δ= (168.95), (169.60), (170.76) and (173.61)ppm respectively[42]. FTIR spectra of compounds [11-13] showed absorption bands at (3420-3440) $cm^{-1}$, (1765-1775) $cm^{-1}$, and (1708-1718) cm-1, which are due to ν (N-H), asym. ν (C=O) imide and sym. ν(C=O) imide respectively. Other absorption bands appeared at (1718-1739) $cm^{-1}$, (1677-1679) $cm^{-1}$, (1606-1622) $cm^{-1}$, (1515-1544) $cm^{-1}$, (1395-1396) $cm^{-1}$, (1338-1373) $cm^{-1}$, and (1152-1164) $cm^{-1}$ which are attributed to ν (C=O) ester, ν (C=O) amide, ν (C=N), ν (C=C), ν (C-N) imide, asym. ($SO_2$), and sym. ($SO_2$) respectively.

The $^1$H-NMR spectrum of the compound [12] showed signals at (δ = 1.96, 2.19) ppm belonging to protons of two CH3 groups and signals at δ (6.0) ppm belonging to vinyl protons. Signals at (δ = 6.6-8.5) ppm belong to aromatic protons, and signals at (δ = 11.25) ppm belong to ($NHSO_2$) protons.

***Biological evaluation***

Compounds (8, 9, and 13) were tested for their capacity to inhibit MDA breast cancer cells in vitro using the MTT technique for the molecules that had significant inhibitory effects on growth proliferation in this experiment.

***Antiproliferative activity***

The MTT assay [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] [43] was accomplished to conclude the cytotoxic effects of

compounds 8, 9, and 13 on the MDA breast cancer cell line. The MTT Assay was conducted to calculate cell viability and inhibition rates in the tumor cell line utilizing various concentrations of compounds (8,9,13). The percentage vitality of treated cells was calculated in comparison with the normal cell line HdFn. The cytotoxic effects of chemicals (8, 9, 13) at concentrations ranging from 25 to 400 µg/ml on MDA cells after 24, 48, and 72 hours, as detailed in Tables (1), (2), and (3), respectively, demonstrated a decrease in cell viability in a dose-dependent manner in comparison with the reference significance ($p < 0.01$), as shown in Fig.6. After 24 hours, compounds 8 and 13 showed lower IC50 values (98.45 and 74.80, respectively) compared to the reference drug Tamoxifen (IC50=173.1), as illustrated in Figures 1, 2, and 4, respectively. After 48 hours, compound 13 maintained a lower IC50 value (44.79) than Tamoxifen (IC50=60.26), as shown in Figures 3 and 5. Still, after 72 hours, the IC50 values of compound 8 showed (IC50=32.59) near the value of the reference drug Tamoxifen (IC50=25.26), while compounds 9 and 13 demonstrated inadequate cytotoxicity. Data indicates that chemicals 8 and 13 exhibit significant cytotoxicity against breast cancer.

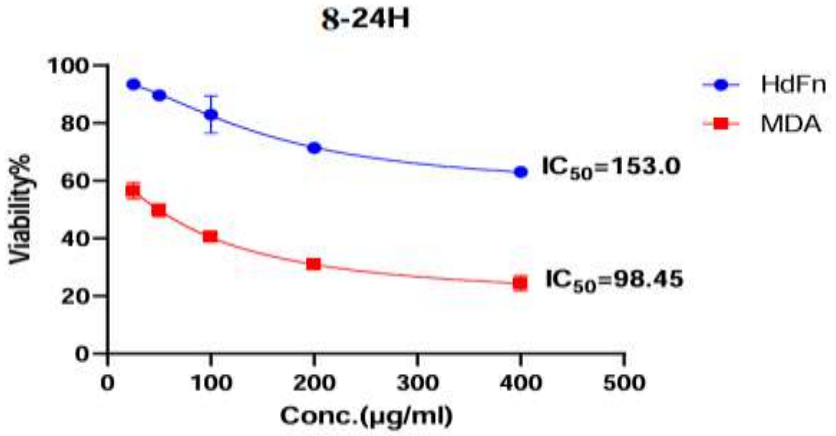



**Figure 1. Cytotoxic activities of compound 8 toward MDA and HdFn after 24h**

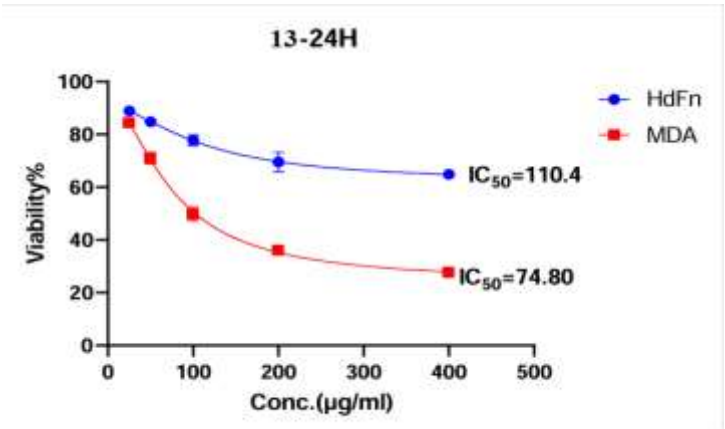



**Figure 2. Cytotoxic activities of compound 13 toward MDA and HdFn after 24h**

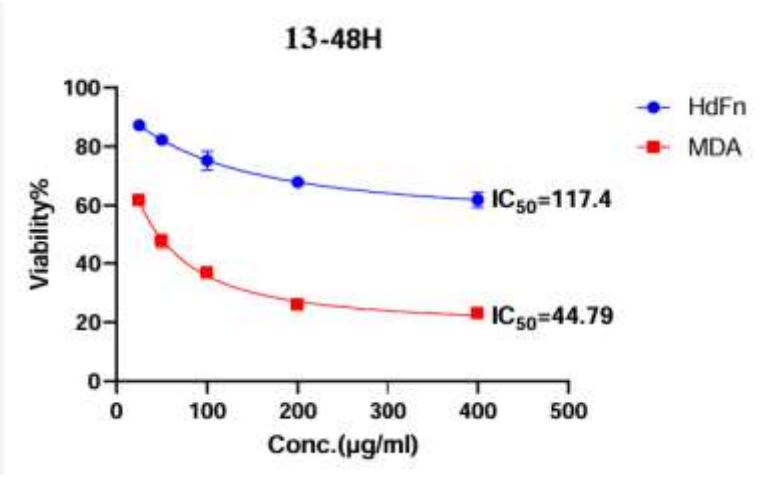



**Figure 3. Cytotoxic activities of compound 13 toward MDA and HdFn after 48h**

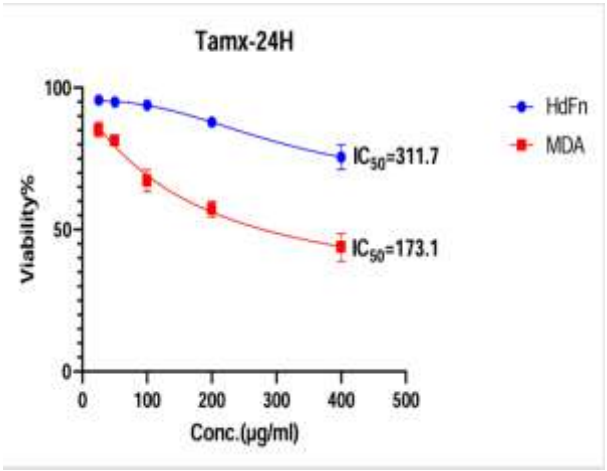



**Figure 4. Cytotoxic activities of Tamoxifen reference toward MDA and HdFn after 24h**

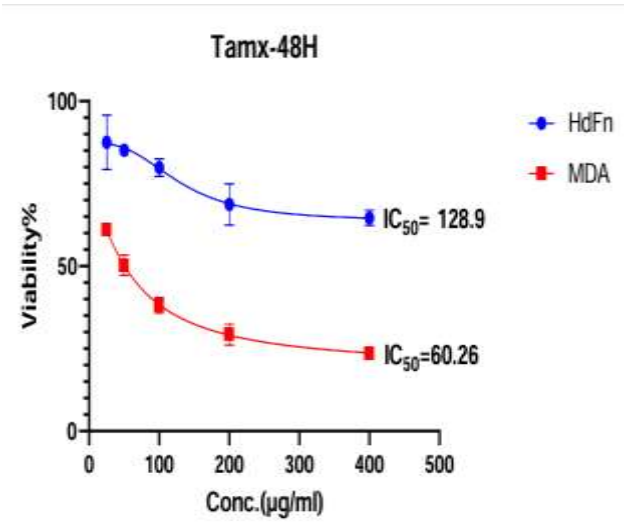



**Figure 5. Cytotoxic activities of Tamoxifen reference toward MDA and HdFn after 48h**

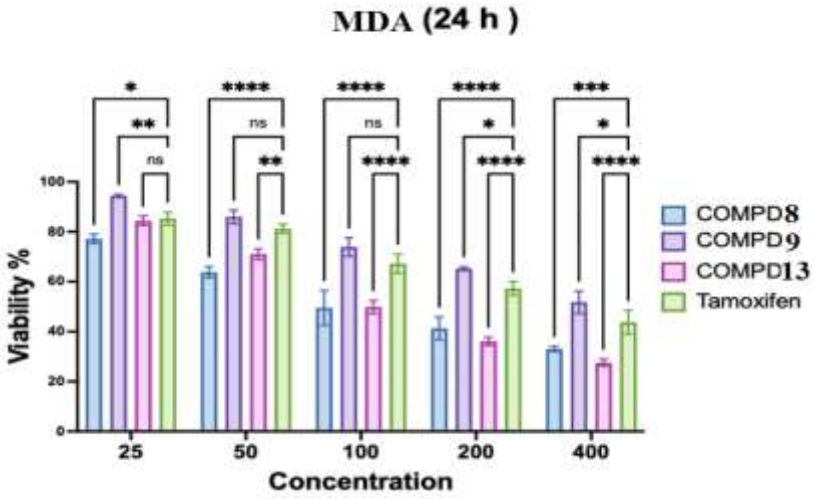



**Figure 6. shows significant differences between compounds [8,9, and 13] with Tamoxifen reference. ns: non-significant, *:p≤ 0.05,**:p ≤ 0.01,***:p ≤ 0.001 and ****:p≤ 0.0001**

**Table 1. Cytotoxicity effect of compounds [8,9, and 13] and reference drug Tamoxifen on MDA and HdFn cells after 24 hours incubation at 37C0**

| Comp. No | Con. (µg/mL) | Viable cell count of MDA cells line Mean± S.D. | Viable cell count of HdFn cell line Mean± S.D. | $IC_{50}$ of MDA cells line | Sig. | $IC_{50}$ of HdFn cells line | Sig |
|---|---|---|---|---|---|---|---|
| 8 | 400 | 33.02±1.05 | 71.02± 1.67 | 98.45 | ** | 153.0 | **** |
| | 200 | 41.28±4.63 | 74.65±1.00 | | **** | | *** |
| | 100 | 49.53±6.97 | 80.97±1.81 | | **** | | *** |
| | 50 | 63.77±2.25 | 87.73±2.95 | | **** | | ** |
| | 25 | 77.12±1.88 | 91.43±3.43 | | * | | ns |
| 9 | 400 | 51.77±4.47 | 76.77±2.38 | 110.5 | * | 164.9 | **** |
| | 200 | 65.23±0.77 | 82.52±3.91 | | * | | **** |
| | 100 | 73.88±3.67 | 92.36±2.16 | | ns | | **** |
| | 50 | 85.95±2.69 | 94.32±0.23 | | ns | | **** |
| | 25 | 94.40±0.54 | 95.98±0.87 | | ** | | *** |
| 13 | 400 | 27.54±1.45 | 64.89±1.26 | 74.80 | **** | 110.4 | **** |
| | 200 | 36.07±1.64 | 69.52±3.70 | | **** | | ns |
| | 100 | 49.84±2.60 | 77.81±2.03 | | **** | | ns |
| | 50 | 71.02±2.14 | 84.76±0.93 | | ** | | ns |
| | 25 | 84.37±1.91 | 88.85±0.63 | | ns | | ns |
| Tamx. | 400 | 43.71±4.80 | 75.54±4.27 | 173.1 | 311.7 | | |
| | 200 | 57.29±2.72 | 87.84±1.28 | | | | |
| | 100 | 67.16±3.84 | 93.86±0.30 | | | | |
| | 50 | 81.17±1.87 | 94.98±0.67 | | | | |
| | 25 | 85.30±2.57 | 95.60±0.50 | | | | |

**Table 2. Cytotoxicity effect of compounds [8,9, and 13] and reference drug Tamoxifen on MDA and HdFn cells after 48 hours incubation at 37C0**

| Comp. No | Con. (µg/mL) | Viable cell count of MDA cells line Mean± S.D. | Viable cell count of HdFn cell line Mean± S.D. | $IC_{50}$ of MDA cells line | Sig. | $IC_{50}$ of HdFn cells line | Sig |
|---|---|---|---|---|---|---|---|
| 8 | 400 | 29.35±1.39 | 66.58±1.88 | 68.16 | * | 161.9 | ns |
| | 200 | 34.87±2.93 | 74.76±6.06 | | * | | ns |
| | 100 | 43.94±2.87 | 85.68±2.96 | | * | | ns |
| | 50 | 56.67±3.25 | 91.39±1.66 | | ** | | ns |
| | 25 | 66.5\±2.66 | 94.25±0.35 | | * | | ns |
| 9 | 400 | 42.70±2.08 | 65.93±2.73 | 193.6 | **** | 219.2 | ns |
| | 200 | 53.00±2.16 | 77.08±2.25 | | **** | | * |
| | 100 | 61.07±0.96 | 86.14±0.92 | | **** | | ns |
| | 50 | 73.03±1.59 | 93.51±0.87 | | **** | | * |
| | 25 | 87.77±2.21 | 94.63±0.52 | | **** | | ns |
| 13 | 400 | 22.83±1.26 | 61.96±2.55 | 44.79 | ns | 117.4 | ns |
| | 200 | 25.89±0.71 | 67.94±1.73 | | ns | | ns |
| | 100 | 36.80±1.60 | 75.30±3.18 | | ns | | ns |
| | 50 | 47.72±2.48 | 82.33±0.24 | | ns | | ns |
| | 25 | 61.69±0.87 | 87.19±1.01 | | ns | | ns |
| Tamx. | 400 | 23.64±1.18 | 64.66±2.40 | 60.26 | 128.9 | | |
| | 200 | 29.20±3.13 | 68.71±6.25 | | | | |
| | 100 | 38.15±2.37 | 79.86±2.66 | | | | |
| | 50 | 50.30±3.13 | 85.14±1.68 | | | | |
| | 25 | 61.03±1.79 | 87.53±8.26 | | | | |

**Table 3. Cytotoxicity effect of compounds [8,9, and 13] and reference drug Tamoxifen on MDA and HdFn cells after 72 hours incubation at 37C0**

| Comp. No | Con. (µg/mL) | Viable cell count of MDA cells line Mean± S.D. | Viable cell count of HdFn cell line Mean± S.D. | $IC_{50}$ of MDA cells line | Sig. | $IC_{50}$ of HdFn cells line | Sig |
|---|---|---|---|---|---|---|---|
| 8 | 400 | 24.46±2.56 | 63.07±1.81 | 32.59 | ns | 97.59 | *** |
| | 200 | 30.78±0.72 | 71.37±1.11 | | ns | | ns |
| | 100 | 40.54±1.49 | 82.94±6.40 | | ns | | *** |
| | 50 | 49.65±2.25 | 89.58±1.90 | | * | | *** |
| | 25 | 56.55±2.85 | 93.44±0.37 | | **** | | * |
| 9 | 400 | 42.36±0.72 | 62.84±1.45 | 73.08 | **** | 136.5 | *** |
| | 200 | 54.78±2.14 | 68.40±1.28 | | **** | | ns |
| | 100 | 68.13±1.60 | 73.22±1.80 | | **** | | ns |
| | 50 | 81.21±3.81 | 82.44±5.64 | | **** | | ns |
| | 25 | 89.66±2.85 | 88.07±2.05 | | **** | | ns |
| 13 | 400 | 21.29±1.13 | 55.78±2.11 | 45.93 | ns | 658.0 | ns |
| | 200 | 24.38±0.40 | 63.31±2.08 | | *** | | ns |
| | 100 | 31.01±1.33 | 72.99±2.82 | | *** | | ns |
| | 50 | 40.39±1.59 | 75.46±1.21 | | **** | | ns |
| | 25 | 50.501.03 | 81.40±2.44 | | **** | | ns |
| Tamx. | 400 | 25.03±0.87 | 52.97±2.49 | 25.26 | 68.9 | | |
| | 200 | 33.79±4.94 | 66.58±3.30 | | | | |
| | 100 | 40.12±6.08 | 72.95±1.57 | | | | |
| | 50 | 55.67±3.54 | 79.82±4.08 | | | | |
| | 25 | 69.56±1.94 | 87.30±1.11 | | | | |

## Conclusion

This work includes the design and synthesis of novel compounds that contain three biologically active compounds (Schiff base, cyclic imide, and sulfa drug) from the sulfamethoxazole drug, in addition to quinazoline and oxazepine heterocycles compounds. The novel compounds were validated using FTIR, $^{1}$H-NMR, and $^{13}$C-NMR spectra. Furthermore, several of these compounds were assessed for their anti-proliferative activities utilizing the MTT assay with an MDA cell line and tamoxifen as a reference molecule. Consequently, it can be concluded that some of these compounds have the potential for development as anticancer medicines.

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## Conflicts of Interest

There is no conflict of interest in the manuscript.

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## Ethics Statements

This article was approved by the ethical committee of the college of biotechnology, Al-Nahrain university.

## Author Contribution

The authors confirm their contributions to the work. Every author reviewed the results and approved the manuscript's final version.

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# تصميم، تحضير ودراسة النشاط المضاد للسرطان لعدة مشتقات جديدة من (قواعد شيف ايميديل دواء سلفاميثاوكسازول-٤\-يل)-٤-امينو مثيل بنزيلدينNسلفا) تعتمد على

**سرى صادق رؤوف [١،٢] و أحلام معروف العزاوي [٢]**

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**الخلاصة**

تم في هذا البحث تصميم وتحضير سلسلة من مشتقات (قواع شف ايميديل دواء سلفا) جديدة بواسطة عدة خطوات. تم في الخطوة الأولى اختيار دواء سلفا وهو (السلفاميثاوكسازول) كمادة أولية فعالة بايولوجيا حيث تم إدخالها في تفاعل تكاثف مع المركب ٤- امينو اسيتوفينون تحت اشعة المايكروويف مما اسفر عن تكوين المركب-N [1] ( سلفاميثاوكسازول-٤\-يل)-٤-امينو مثيل بنزيلدين .بعد ذالك تم ادخال المركب [١] في تفاعل مع ثلاث انهيدريدات حلقية هي انهدريدات (السكسنك, الماليك والفثالك ) مما اسفر عن تكوين مركبات حوامض الاميك [٢-٤] وهذه بدورها تم سحب الماء منها في الخطوة الثالثة وذلك بمعاملتها مع انهدريد الخليك وخلات الصوديوم مع التصعيد مما اسفر عن تكوين المركبات الهدف وهي الايمايدات الحلقية المقابلة [٥-٧] . إضافة الى ذلك فقد تضمن العمل تحضير مشتقات أخرى جديدة وهي الكوينازولين [٨-١٠] وذلك من خلال تفاعل المركبات [٥-٧] مع حامض الانثرانيليك بينما تم تحضير المشتقات الجديدة الأخرى (اوكسازبين) [١١-١٣] من تفاعل مركبات [٥-٧] مع انهدريد الفثالك. نظرا لاحتواء جزيئات المركبات المحضرة الجديدة على ثلاث مكونات فعالة بايولوجيا اثنان منهما (دواء السلفا والايماید الحلقي) اما المكون الفعال الثالث فهو قاعدة شيف في المركبات [٧-٥] والكوينازولين في المركبات [١٠-٨] والاوكسازبين في المركبات [١٣-١١] فقد كان المركبات المحضرة ضد سرطان الثدي وقد كانت النتائج واعدة .

**الكلمات المفتاحية: قواعد شيف ، ايميد حلقي ، دواء سلفاميثاوكسازول و فحص MDA .**