New AZO Compounds Derivatives Based on 4- chloro-2-((5-formyl-2-hydroxy-3-methoxyphenyl) diazenyl)benzenesulfonamide: Preparation, diagnostic, Spectroscopic, Antioxidant and Antimicrobial efficiency

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Abstract:

In this study, two series of compounds have been prepared based on azo compound 4-chloro-2-((5-formyl-2-hydroxy-3-methoxyphenyl)153iazinyl) benzene sulfonamide (**A1**) which prepared by diazotization of 2-amino-4-chlorobenzen sulfonamide and 4-hydroxy -3-methoxy benzaldehyde (vanillic aldehyde). The new azo (**A1**) subsequently reacted with amine and sulfa drugs such as 4-bromoaniline, sulfanilamide, sulfadiazine, and sulfathiazole to form corresponding azo-azomethine compounds as a first series. The reaction of this new azo-azomethine with thioglycolic acid with the participation of zinc chloride afforded thiazolidinone (**MO** and **MS**) as a second series. The prepared materials have been diagnosed with elemental analysis and various spectroscopic methods, spectroscopic techniques, such as IR, ^{1}HNMR, ^{13}CNMR, and Mass. All the new compounds were evaluated for their antioxidant using the free radical scavenging (DPPH) method. The antibacterial activities were studied in in-vitro as opposed to gram-positive (staphylococcus aureus) and gram-negative (Escherichia coli) by utilizing an agar diffusion process, at different concentrations to calculate MIC. Furthermore, the antifungal potential opposed to fungal strains such as candida albicans was studied and showed good to moderate activity.

Keywords: Amines, Antibacterial, Antioxidant, Azo, Azo-azomethine, Thiazolidine, Vanillic aldehyde.

Introduction

Sulfa drugs or sulfonamide, which is considered a primary viable substance that is generally popular as specific chemotherapeutic instruments in the pharmaceutical field because they are established as elegant and remarkable antimicrobial drugs for various diseases, especially skin diseases and acute inflammation. Sulfonamides, such as sulfadiazine, sulfamerazine, sulfanilamide, and sulfathiazole possess special properties within their chemical composition, that they own a component parallel to para-aminobenzoic acid [PABA], which is estimated for the creation of folic acid to continue the process of synthesis and production DNA in microorganism (1). Recent studies. Many molecules containing the sulfonamide structure have been created since its discovery, yielding improved formulations with greater effectiveness and less toxicity. Sulfa drugs are still widely used to treat various types of medical conditions as, antileprotic, antiepileptic, antibacterial, anti-parasitic, antiretroviral, oral hypoglycemic, and applied diuretic. Azo compounds are one of the significant classes of natural dyes. These organic compounds are characterized by occupying the common constitution $R_1N=N-R_2$, that R1 R2 could be either an aromatic group (aryl)or (alkyl) comparand. The more stable compounds that azo moiety conjugated with two aromatic rings or

hetero aromatic substructure. In as much as their exceptional biological and physico-chemical properties, they are distinguished by general attention in food, pharmaceutical, beauty products, and analytical chemistry (2). The first red azo-dye sulfonamide is prontosil (prontosil rubrum), which was shown by Domagk to prevent mortality in mice infected with *streptococcus bacteria* (3). The dye is a prodrug in vivo metabolism and under the action of cellular enzymes converts it into the sulfa drug sulfanilamide, the active antibiotic agent (4). Currently, studies, establish that sulfonamides can obstruct cancerous cells and smash them (5). Hugo Schiff initially described Schiff bases in 1864, which are condensation byproducts of carbonyl compounds and primary amine. Schiff bases can be utilized for their biological efficiency which includes, antibacterial, antiproliferative, antiviral, antifungal, and anti-inflammatory characteristics (6). Various studies have proven that the therapeutic properties of sulfa drugs became more efficient and effective when changed to Schiff bases especially those that contain hetrocyclic rings which can be used as hard tonics and diuretic substances (7). On the other hand, azo-azomethine are organic pigment. Coutain the characteristic chromophore advantage category group [-N=N-] and [-CH=N-]. Recently many studies have proven that compounds combine azo and azomethine moieties showing excellent pharmacological action and possessing many therapeutic properties (8). Thiazolidine is one of the main classes in organic and medicinal chemistry. Thiazolidines are a significant skeleton known to be utilized in different biological potential. Many and varied biological compounds contain active molecules that have within their chemical structure a five-membered ring that has within composition more than one hetero atom, such as sulfur atom at position, and nitrogen atom in position 3, as well carbonyl moiety at position 4 Although, thiazolidine derivatives mostly includes customarily antibiotic compounds such as penicillin which contains an important moiety, thiazolidine ring in its structure. These compounds possess broad application in therapeutic procedures, such as agents and anti-HIV agents (9).

Experimental

Materials

Each chemical used in this occupation was reagent grade and purified before use. 2-amino-4-chlorobenzene sulfonamide supplied from Merck, 4-bromo aniline, sulfanilamide, sulfadiazine and Sulfathiazole purchased from Sigma-Aldrich, vanillin (4-hydroxy-3 methoxy benzaldehyde) was supplied from BDH, Sodium nitrate, hydrochloric acid, 2,2-Diphenyl-1-picrylhydrazyl (DPPH) and Citric acid were supplied from fluka company.

Instrumentations

The IR spectra for all preparing compounds were recorded at Shimadzu FT-IR type 8400 S spectrophotometer in KBr discs within an arrangement of 400-4000 cm^{-1}. The ^{1}H-NMR and ^{13}CNMR were measured in DMSO-d6 as a standard solvent, with internal standard (TMS) as the internal standard using a Brucker spectrophotometer (400MHZ). The chemical shift δ is given in ppm. The elemental analysis (CHN) was performed with the micro analyzer instrument Elemental Euro Vector EA-300. Mass spectra were captured by the use of a Technologies 5975 C spectrometer at 70 ev. Reaction monitoring and the check of purity were done with TLC on silica gel-protected aluminum sheets.

Synthesis of 4-chloro-2-((5-formyl-2-hydroxy-3-methoxyphenyl) 154iazinyl)benzensulfonamide (A1).

A solution of 2-amino-4-chlorobenzen Sulfonamide 2 mmol (0.4133 gm) in 2N of HCl (10ml) was stirred until a clear solution was obtained. The mixture was cooled to 0-5c, and another solution of Sodium nitrate 6 mmol (0.4139 gm) which dissolved in 4ml of water was prepared at the same temperature and added dropwise with stirring, the diazonium salt was

obtained. The mixture was stirred for an additional 30 min. At the same time, vanillin 2mmol (0.3043gm) was dissolved in 15 ml of aqueous solution containing 10 mmol (1.05 gm) of sodium Carbonate and added gradually to the solution of the cold diazonium salt. The resulting mixture was stirred for 2h at 0-5^{0}C and maintained PH at 6-7. The elementary precipitate was filtered, washed with cold water, and recrystallized from absolute ethanol to obtain the required azo compound – The purity was checked by TLC methanol/acetone (3:7) as eluent (10, 11).

Orange crystals were obtained in 86% yield. Rf = 0.36, m.p. 228-230 ^{0}C. Elemental analysis for $C_{14}H_{12}N_3O_5SCl$: Calculated C45.47, H3.27,N11.36. Found: C45,82, H3.29, N11.40. IR (KBr) Cm^{-1}: 3510 (O-H), 3421 (N-H), 3055 ($CH_{Arom.}$), 2966 ($CH_{Aliph.}$), 1589 (N=N), 1026(C-O), 1392 ($SO_{2\ Asy.}$), 1199 ($SO_{2\ Sym.}$), 949 (S-N). ^{1}HNMR (DMSO-d_6-400MHZ) δ/ppm: 10.48 (s, 1H$_a$, CHO), 9.67 (s, 1H$_e$, OH), 8.83 (s, 2H$_i$, NH$_2$), 7.90 (s, 1H$_c$, Arom-H), 7.53 (s, 1H$_d$, Arom-H), 7.15 (s, 1H$_h$, Arom-H), 6.94 (d, 1H$_f$, Arom-H), 6.35 (d, 1H$_g$, Arrom-H), 3.89 (s, 3H$_b$, OCH_3). ^{13}CNMR (DMSO-d_6-400MHZ):188.38 (C=O), 154.83, 150.49, 147.04, 135.83, 134.09, 129.37, 114.52, ($CH{=}C_{Arom.}$), 52.02 (OCH_3). The El-MS (m/s): 369 $[M]^+$, 341 $[C_{14}H_{12}NO_5SCl]^+$, 306 $[C_{13}H_{12}N_3O_4S]^+$, 258 $[C_{13}H_7N_2O_2Cl]^+$, 213 $[C_{12}H_{11}N_3O]^+$, 185 $[C_6H_7N_3O_2S]^+$, 121 $[C_6H_6N_3]^+$, 68 $[C_4H_6N]^+$.

General procedure for Synthesis (A1B1, A1B2, A1B3, A1B4) of azo-azomethines.

The compounds were prepared following the procedure in the literature method (12) The Schiff base (**A1B1-A1B4**) was set by the typical condensation reaction, that equimolar (0.337g; 1mmol) of compound **A1** and 1mmol of substituted aniline (i.e-4-bromoaniline, sulfanilamide, sulfadiazine and sulfathiazole) were dissolved in 25 ml of absolute ethanol, also (2-3) drops of sulphuric acid was added and refluxed for 24h, the configure of desired product was tested by TLC using ethanol /ethyl acetate (3:7). The reaction mixture was poured into crushed ice to obtain the required compounds. The resulting solid product collected filtration, washed with cold absolute methanol, and recrystallized from ethanol to yield the corresponding azo-azomethine compounds.

2-((5-(€-(4-bromophonyl) imino) methyl)-2-hydroxy-3-methony phenyl) 155iazinyl)-4-chlorobenzene Sulfonamide (A1B1).

Light pink solid. Yield 88%, Rf=0.68, m.p. 120-122^{0}C. Elemental analysis for $C_{20}H_{16}BrCl\ N_4O_2S$: Calculated C45.86, H3.08, N10.70. Found: C46.10, H3.1, N10.74. IR(KBr) Cm^{-1}: 3506 (O-H), 3420 (N-H), 3090 ($CH_{Arom.}$), 2928 ($CH_{Aliph.}$) 1631(CH=N), 1589(N=N), 1226 ($SO_{2\ Asy.}$), 1203 ($SO_{2\ Sym.}$), 1068 (C-O), 918(S-N). ^{1}HNMR (DMSO-d_6-400MHZ) δ/ppm: 10.47 (s, 1H$_b$, OH) 8.61 (s, 1H$_e$, HC=N), 7.50 (dd, 2H$_{gg'}$, Arom-H) 7.35 (dd, 2H$_{ff'}$, Arom-H), 7.17 (d, 1H$_h$, Arom-H), 7.11 (s, 1H$_j$, Arom-H), 6.99 (d, 1H$_i$, Arom-H), 6.97 (s, 1H$_d$, Arom-H), 6.91 (s, 1H$_c$, Arom-H), 6.24 (s, 2H$_k$, NH$_2$), 3.89 (s, 3H$_a$, OCH_3). ^{13}C NMR (DMSO-d_6-400 MHZ) S/ppm; δ 170.69 (CH=N), 146.33, 135.33, 134.34, 132.79, 129.39, 124.09, 120.71, 118.28, ($CH{=}C_{Arom.}$), 40.74 (OCH_3).

4-chloro-2-((2-hydroxy-3-methoxy-5(€ – ((4-sulfamoylphenyl) imino) methyl) phenyl)155iazinyl) benzenesulfonamide(A2B2) .

Dark yellow solid. Yield 61%, Rf = 0.67, m.p. 118-120^{0}C. Elemental analysis for $C_{20}H_{18}N_5O_6S_2Cl$: Calculated, C47.88, H3.35, N16.29. Found: C46.12, H3.47, N13.42. IR (KBR) Cm^{-1}: 3529(O-H), 3425 (N-H), 3063 ($CH_{Arom.}$), 2920 ($CH_{Aliph.}$), 1639 (CH=N), 1404 (N=N), 1249 ($SO_{2\ Asy.}$), 1165 ($SO_{2\ Sym.}$), 1068 (C-O), 999 (S-N). ^{1}HNMR (DMSO-d_6-400MHZ) δ/PPm: 10.41 (s, 1H$_b$, OH) 8.49 (s, 1H$_e$, HC=N), 7.78 (dd, 2H$_{gg'}$, Arom-H), 7.76 (dd, 2H$_{ff'}$, Arom-H), 7.57 (s, 1H$_d$, Arom-H), 7.40 (s,1H$_c$, Arom-H), 7.29 (s, 1H$_j$, Arom-H), 7.20 (d, 1H$_h$, Arom-H) 6.98 (d, 1H$_i$, Arom-H), 6.35 (s, 4H$_{kk'}$, NH$_2$), 3.83 (s, 3H$_a$, OCH_3). ^{13}CNMR (DMSO-d_6-

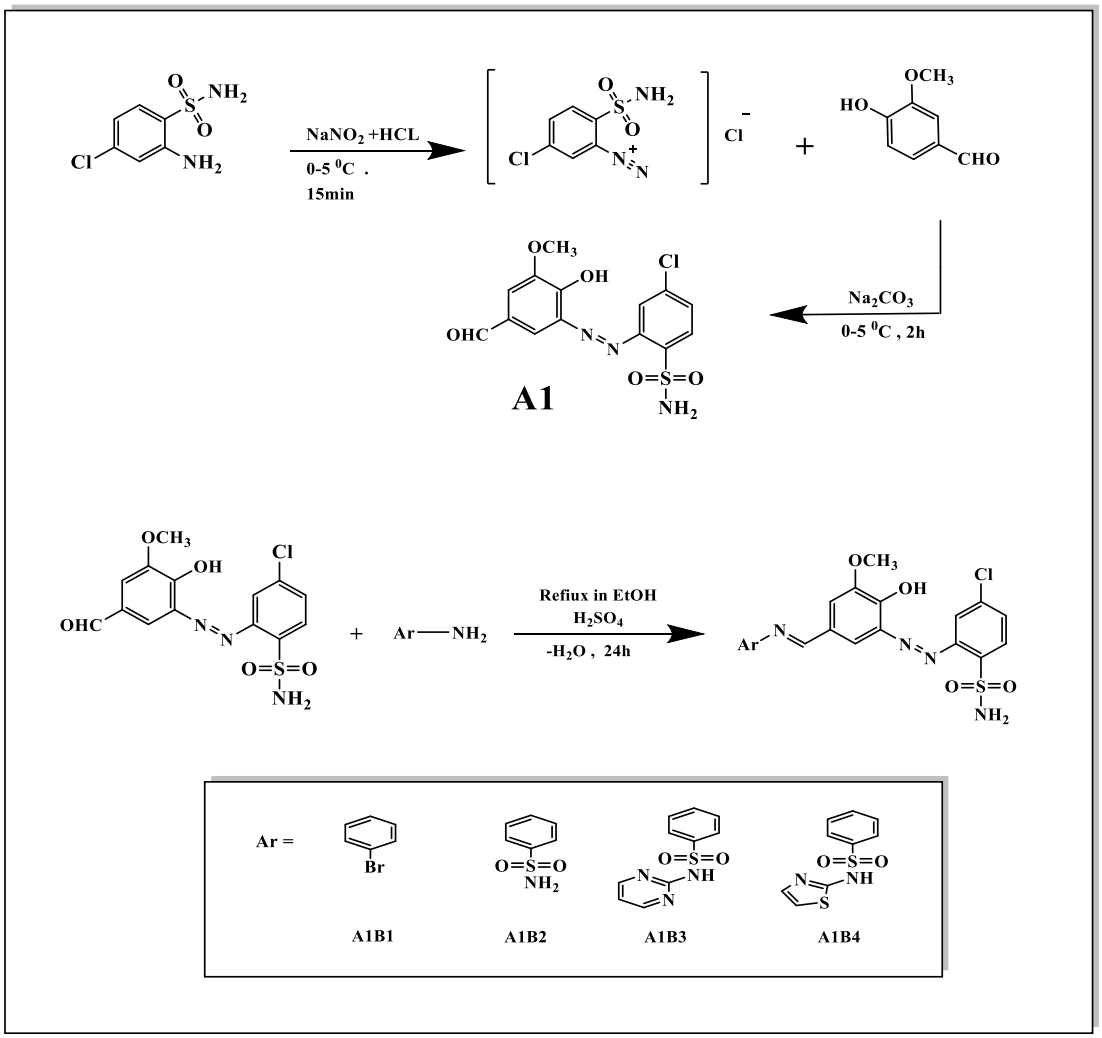
400 MHZ) S/PPM: 170.77 (CH=H), 143.26, 137.82, 135.34, 127.80, 124.02, 119.14, 113.41, (CH=$C_{Arom.}$), 43.86 (OCH_3). The ET -MS (m/s): 523 $[C_{20}H_{18}N_5O_6S_2Cl]^+$, 443$[C_{20}H_{16}N_4O_4SCl]^+$, 398$[C_{19}H_{15}N_4O_2SCl]^+$, 203 $[C_6H_4N_2O_2Cl]^+$, 200 $[C_8H_{10}O_3NS]^+$, 108 $[C_6H_8N_2]^+$, 64 $[SO_2]^+$.

4-((€-3-((5-chloro-2-sulfamoylphenyl)156iazinyl)-4-hydroxy-5-methoxybenzylidene)amino)-N-(pyrimidin-2-yl)benzenesulfonamide (A1B3).

Dark orange Solid. Yield 66%, Rf = 0.58, m.p. 180-182^{0}C Elemental analysis for $C_{24}H_{20}N_6O_3SCl$: Calculated C47.88, H3.35, N16.29. Found: C 48.08, H3-38, N16.34. IR (KBr) Cm^{-1}: 3429(O-H), 3363(N-H), 3090 ($CH_{Arom.}$), 2931($CH_{Aliph.}$), 1647 (CH=N), 1585 (N=N), 1323 ($SO_{2\ Asy}$), 1153 ($SO_{2\ Sym}$), 1087 (C-O), 937(S-N). ^{1}HNMR (DMSO-d_6-400 MHZ),δ/ppm : 10.95 (s, 1H_b, OH), 9.19 (s, 1H_e, HC=N), 8.16 (s, 1H_o, NH), 7.30 (dd, 2$H_{f,f'}$, Arom-H), 7.14 (dd, 2$H_{g,g'}$, Arom-H),7.03 (s, 1H_c, Arom-H), 6.93 , (d, 1H_d, Arom-H), 6.68 (d,1H_i, Arom-H), 6.66 (d, 1H_j, Arom-H), 6.52 (s, 1H_j, Arom-H), 6.34 (dd, 1$H_{l,l'}$, Arom-H), 6.25 (t, 1H_m, Arom-H), 5.94 (s, 2H_k, NH_2), 3.89 (s, 3H_a, OCH_3). ^{13}CNMR (DMSO-d_6-400 MHZ), δ/ppm: 170.67 (CH=N), 157.66, 153.20, 146.54, 140.24, 130.24, 125.55, 116.26, 114.81, 112.83, (CH=$C_{Arom.}$), 40.47 (OCH_3). The EI – Mass (m/s).: 602 $[C_{24}H_{20}N_7O_6S_2Cl]^+$, 551 $[C_{24}H_{21}N_7O_5S_2]^+$, 507 $[C_{24}H_{20}N_6O_3SCl]^+$, 368 $[C_{18}H_{16}N_4O_3S]^+$, 231 $[C_{12}H_{10}N_3Cl]^+$, 185 $[C_6H_7N_3O_2S]^+$, 97 $[C_5H_9N_2]^+$, 55$[C_3H_5N]^+$.

4-((€-3-((5-chloro-2-sulfamoylphenyl)156iazinyl)-4-hydroxy-5-methoxybenzylidene)amino)-N-(thiazol-2-yl)benzenesulfonamide (A1B4) .

Orange Solid. Yield 82%, Rf = 0.705, m.p. = 109-110 ^{0}C. Elemental analysis for $C_{23}H_{19}N_6O_6S_3Cl$: Calculated C45.51, H3.15, N13.84. Found: C45.76, H3.15, N13.89. IR (KBr) Cm^{-1}: 3479 (O-H), 3463 (N-H), 3093 ($CH_{Arom.}$), 2982 ($CH_{Aliph.}$), 1643 (CH=N), 1519 (N=N), 1265 ($SO_{2\ Asy}$), 1211 ($SO_{2\ Sym}$), 1072(C-O), 925 (S-N).^{1}HNMR (DMSO-d_6-400MHZ) δ/ppm: 8.51 (s, 1H_e, HC=N), 7.93 (s, 1H_l, NH), 7.51 (dd, 2$H_{ff'}$, Arom-H),7.45 (dd, 2$H_{gg'}$, Ar-H), 7.44 (s, 1H_d, Ar-H), 7.35(s, 1H_c, Ar-H), 7.33 (s, 1H_j, Arom-H), 7.25 (d, 2H_h, Arom-H), 7.16 (d, 1H_i, Arom-H), 7.03(d, 1H_n, Arom-H) 7.02(d, 1H_m, Arom-H), 6.58(s, 1H_b, OH), 5.96 (s 2H_K, NH_2), 3.98 (s, 3H_a, OCH_3). ^{13}CNMR (DMSO-d6-400MHZ) δ/PPM: 181.85 (S-C=N) , 169.03 (CH=N) , 136.36, 128.03, 124.96, 119.51, 116.65, 111.30 (CH=$C_{Arom.}$) , 43.27 (OCH_3) .The EI – Mass (m/s) : 607 $[C_{23}H_{19}N_6O_6S_3Cl]^+$, 507 $[C_{20}H_{16}N_4O_6S_2Cl]^+$, 368 $[C_{14}H_{13}N_4O_4SCl]^+$, 279 $[C_{12}H_8N_2O_2SCl]^+$, 156 $[C_6H_6NSO_2]^+$, 111 $[C_6H_4Cl]^+$, 64 $[SO_2]^+$.



Schema (1) general pathways for synthesis of compound A1 & A1B1-A1B4

General procedure for preparation of thiazolidinone (MO, MS).

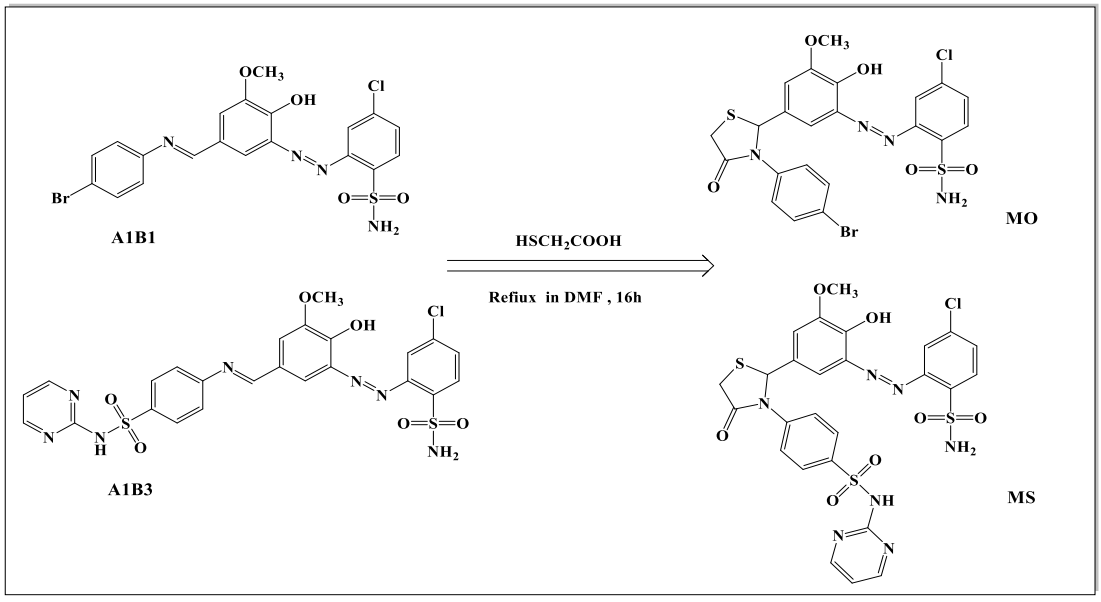
A solution of Schiff base, **A1B1** (0.523g, 1mmol), and **A1B2** (0.601g, 1mmol) in 20 ml of DMF was prepared and (0.08g, 1mmol) of thioglycolic acid was added dropwise with stirring. The amount of $ZnCl_2$ as catalyst (0.4g, 3mmol) in 10ml of DMF was added slowly to the stirring solution of Schiff bases. A previous mixture was refluxed for 12-14 hrs. The reaction was monitored by TLC using methanol/chloroform (3:7)(13, 14). The resulting mixture was infusion in crushed ice to obtain the required compounds. The precipitate of each compound was neutralized by sodium bicarbonate to bring out the residue of thioglycolic acid. The stiff material to every prepared reagent has been collected with the filtration method, later washed several times with water, and recrystallized from ethanol to produce the conformable compounds.

2-((5-(3-(4-bromophenyl)-2-oxothiazolidin-4-yl)-2-hydroxy-3-methoxyphenyl)diazenyl)-4-chlorobenzenesulfonamide (MO).

Dark yellow solid: Yield 73%, Rf = 0.67, m.p. = 270-272 ^{0}C. Elemental analysis for $C_{22}H_{18}N_4O_5S_2BrCl$: Calculated C44.20, H3.03, N9.37. Found: C44.61, H3.05, N9.42. IR (KBr) Cm^{-1}: 3520 (O-H), 3100 ($CH_{Arom.}$), 2928 ($CH_{Asy\ aliph.}$), 2862 ($CH_{Sym,\ aliph.}$), 1620 (C=O), 1581 (N=N), 1234 (C-N), 1090 (C-O), 902 (S-N).^{1}HNMR (DMSO-d_6-400MHZ) δ/ppm: 9.19 (s, 1H$_b$, OH), 8.17 (s, 1H$_e$, CH-N), 7.46 (dd, 2H$_{g,g'}$, Arom-H), 7.28 (dd, 2H$_{h,h'}$, Arom-H), 7.03 (s, 1H$_d$, Arom-H), 6.46 (s, 1H$_c$, Arom-H), 6.02 (s, 1H$_k$,

Arom-H), 5.90 (d, $1H_i$, Arom-H), 5.73 (d, $1H_j$, Arom-H), 5.50 (s, $2H_L$, NH_2), 4.49 (s, $2H_f$, S-CH_2), 3.84 (s, $3H_a$, OCH_3).^{13}CNMR (DMSO-d6-400MHZ) δ/PPM: 189.55 (C=O), 149.01, 146.35, 140.68, 135.25, 129.35, 126.44, 126.44, 121.94, 117.94, (CH=$C_{Arom.}$), 50.16 (CH-S), 40.49 (OCH_3), 26.72 (CH_2).The EI - Mass (m/s) : 597 $[C_{22}H_{18}N_4O_5S_2ClBr]^+$, 532 $[C_{22}H_{17}N_3O_4S_2Br]^+$, 430 $[C_{16}H_{19}N_4O_4S_2Cl]^+$, 341 $[C_{13}H_{12}N_3O_4SCl]^+$, 256 $[C_{14}H_{16}N_4O]^+$, 213 $[C_{13}H_{15}N_3]^+$, 149 $[C_7H_5N_2S]^+$, 69 $[C_4H_7N]^+$.

4-(2-(3-((5-chloro-2-sulfamoylphenyl)diazenyl)-4-hydroxy-5-methoxyphenyl)-4-oxothiazolidin-3-yl)-N-(pyrimidin-2-yl)benzenesulfonamide (MS). Brown solid: Yield 87%, Rf = 0.88, m.p. = 260-260 ^{0}C. Elemental analysis for $C_{26}H_{22}N_7O_7S_3Cl$: Calculated C46.19, H3.28, N14.50. Found: C46.54, H3.29, N14.54. IR (KBr) Cm^{-1}: 3550 (O-H), 3414 (N-H), 3100 ($CH_{Arom.}$), 2924 ($CH_{Asy\ aliph.}$), 2858 ($CH_{Sym\ aliph.}$), 1604 (C=O), 1504 (N=N), 1384 (C-N), 1045 (C-O), 945(S-N). ^{1}HNMR (DMSO-d_6-400MHZ) δ/ppm : 11.77 (s, $1H_i$, NH), 10.25 (s, $1H_b$, OH), 9.13 (s, $1H_e$, CH-N), 8.06 (dd, $2H_{l,l'}$, Arom-H), 8.02 (t, $1H_k$, Arom-H), 7.94 (dd, $2H_{h,h'}$, Arom-H), 7.61 (dd, $2H_{g,g'}$, Arom-H), 7.17 (s, $2H_p$, NH_2), 7.13 (s, $1H_d$, Arom-H), 7.02 (s, $1H_c$, Arom-H), 6.84 (s, $1H_o$, Arom-H), 6.71 (d, $1H_m$, Arom-H), 6.64 (d, $1H_n$, Arom-H), 4.76 (s, $2H_f$, S-CH_2), 3.78 (s, $3H_a$, OCH_3). ^{13}CNMR (DMSO-d6-400MHZ) δ/PPM: 173.76 (C=O), 145.08, 143.49, 136.10, 131.28, 123.71, 116.02, 114.51, (CH=$C_{Arom.}$), 46.84, (CH-S), 43.42 (OCH_3), 32.36 (CH_2) .The EI - Mass (m/s): 675 $[C_{26}H_{22}N_7O_7S_3Cl]^+$, 532 $[C_{26}H_{22}N_7O_2SCl]^+$, 341 $[C_{13}H_{12}N_3O_4SCl]^+$, 292 $[C_{14}H_{17}N_4ClO]^+$, 224 $[C_{13}H_{12}N_4]^+$, 149 $[C_7H_5N_2S]^+$, 69 $[C_4H_7N]^+$.



Schema (2) general pathways for synthesis of compound MO&MS

Antimicrobial activity

Antimicrobial spectrum has been established in vitro for all proposed compounds. The variety of organisms used as Pathogens are *Gram-positive Staphylococcus aureus (ATCC 25923)* and *Gram-negative Escherichia coli (ATCC 25912)* bacterium, also fungal strain *candida albicans*. Dimethyl sulfoxide (DMSO) was used as a negative monitoring disc, furthermore, utilized as a solvent. All studied compounds as well as sulfathiazole, amoxicillin, and nystatin have been applied as reference drugs, and it was compared with antimicrobial strain. The operation requires the reveal of the locality of inhibition towards the pervasive microorganisms. A.0.2 ml of bacteria inocula, as well as fungal inocula, have been settled on the surface of -(SDA)- Sabouraucl Dextrose Agar and -(NA)- Nutrient Agar medium. Cautiously L-shape glass rod was used for propagation. The decker was put up for 10 mins. All studied reagents as well as drugs have been dissolved in DMSO using different concentrations (100, 50, 25 mg/ml) to calculate the (MIC) value of minimum inhibition concentration. The synthesized azo compounds were set up into centric pores that included 0.1ml. The fungal plates were incubated (25 ± 2^0C), while the bacterial discs were incubated (37 ± 2^0C) for 24 hours under aerobic conditions. The zones of inhibition to every isolate have been determined by using millimeter extent (15). In addition, the value of (MIC) for the compounds were recorded (16, 17)

Antioxidant activity

The radical scavenging efficiency for new azo-azomethine was detected with the used DPPH (Diphenyl-1-1-picrylhydrazy) as a free radical scavenging assay. The organic compounds [DPPH] have been used as standard owing to the fact it's stability as well as widely characterized solid radical source. The method strategy involves using the free radicals present in the reaction to evaluate the potential of these substances as antioxidant scavengers or by having the ability of these substances to donate hydrogen atoms when the solution of these prepared substances is mixed with DPPH. The free radical scavenging efficiency of DPPH is appreciated particularly in ethanol or methanol via measuring the absorbance drop at 515-517nm. At room temperature the DPPH free radical solution is characterized by a typical violet color with an absorption at the range of 515 nm, changing this color to pale yellow or colorless when mixed with radical scavengers, later visual monitoring of the color change is available to track the progress of the reaction as well as to determine the number of initial radicals present via knowing the quantity of color change at the fixed absorption range. The activity of prepared compounds was studied depending on the procedure of Shub Baba, also Malik [18]. 0.2ml for every substance at a concentration [0.78, 1.56,1.56,3.12, 6.25, 12.5, 25,50,100] µg/ml were added to 3.8 ml of (100 µg/ml) DPPH. The resulting mixture has been incubated in a dark place at room temperature, for 30 minutes. The negative control solution contains all the reagents except the sample, moreover, the methanol solution has been used as a blank. Through using the UV-vis spectroscopy process, the DPPH radical scavenging efficiency has been determined at the range of 515nm. The results were confirmed as IC_{50}. In addition, the reduction efficiency of results was confirmed as an azo compound (**A1**), and new azo-azomethine substances were determined with some adjustments. Also, the effectiveness of ascorbic acid (vitamin C) was calculated for comparison purposes. Inhibition percentage of the prepared substances was evaluated using the equation below: -

Inhibition activity (%) = [Ab - Am/Ab] x100

Knowing that Ab represents the control solution absorption, while Am represents the sample absorption Also the results are given IC_{50}.

Results and Discussion

Fourier transform infrared spectra (FT-IR)

Sulfa drug derivative (2-amino-4-chlorobenesulfonamide has been diazotized with $NaNO_2$ and HCl to form corresponding diazonium

salt, and then treated with 4-hydroxy-3-methoxybenzaldehyde at 0-5^{0}C, resulting in the formation of azo compound **A1**. The four azo-azomethines (**A1B1, A1B2, A1B3** and**A1B4**) were prepared by the condensation reaction of equimolar quantities of **A1**, and 4-bromo aniline, sulfanilamide, sulfadiazine, and sulfathiazole, in ethanol (Scheme 1). Also, cyclo condensation of Schiff bases (**A1B1** and **A1B3**) with thioglycolic acid in the presence of Zine chloride afforded thiazolidine derivatives, **MO** and **MS**. (Scheme 2). The elemental analysis of all the synthesis compounds agrees with the empirical formulae (see, Experimental Section).

The prepared compounds are stable solids and non-hygroscopic. They were recognized by FT-IR spectroscopy. The infrared spectra of all synthesized compounds displayed broad bands between 3350-3429 cm^{-1}, which can be attributed to the stretching vibration of OH. The appearance of the azo (-N=N-) band at (1589-1404 cm) confirmed that all the synthesized compounds contained the azo group in their structure. The FT-IR spectra of all the azo-azomethine shows the absence of bonds around 3250 cm^{-1} and 1620 cm^{-1} due to ν NH_2 group of aromatic amines and ν C=O of azo-aldehyde. Instead of these, a new prominent band appeared at 1631-1647 cm^{-1} due to azomethine ν CH=N linkage indicating that condensation between HC=O moiety of azo-aldehyde and that of amino group of aromatic amines has taken place resulting in the formation of azo-azomethine compounds. On other hand the absence of bands of azomethine around 1631cm^{-1} and 1644cm^{-1} in compounds **A1B1** and **A1B3** and instead of these, new prominent bands at 1581-1604cm^{-1}and 1384-1234cm^{-1} due to stretching vibration of the carbonyl group ν C=O and ν C-N appeared in compounds MO and MS indicated that the ring closure has taken place resulting into the formation of thiazolidinone (19). Furthermore, the IR spectra of all synthesized compounds showed medium bands due to the stretching vibration of phenolic C-O between 1087-1026cm^{-1}, and absorption bands at the range 1392-1226cm^{-1} and 1203-1141cm^{-1}, which assigned to asymmetrical and symmetrical stretching vibration respectively of (SO_2) moiety see Experimental section.

^{1}HNMR and ^{13}CNMR spectra

The ^{1}HNMR and ^{13}CNMR spectra of all synthesized compounds were carried out in a DMSO-d_6 solution and chemical shifts of the different signals are declared in the experimental section. The ^{1}HNMR and ^{13}CNMR analysis appeared to support the preparation of the azo-azomethine and thiazolidinone. Compound **A1** slowed a signal at δ 10.48 ppm attributed to HC=O of azo aldehyde, the absence of the aldehyde band and the appearance of the imine HC=N signal at around δ 9.19-8.49 ppm indicated the formation of Schiff base. The ^{1}HNMR spectra of all synthesized compounds show a broad signal lying at δ 6.58-10.95 ppm range giving evidence that they are due to the phenolic OH group attached to the phenyl ring. The signals in the ^{1}HNMR spectra of all the synthesized compounds that appeared at δ3.98 3.78 ppm can be attributed to the hydrogen proton of the OCH_3 group. Also, the signals of a singlet resonance at δ 5.50-8.83 ppm can be assigned to the two protons of the NH_2 group that are attached to the SO_2 moiety (20). The multiple signals around δ5.73-8.06ppm are due to aromatic protons. In addition, the thiazolidinone compounds MO and MS are characterized by showing singlet signals at δ8.17-9.13 ppm, which can be attributed to the proton of CH-N moiety, also the two protons of the S-CH_2 group in thiazolidinone ring can be observed as a singlet signals in the range of δ4.49-4.76 ppm(21).

In ^{13}CNMR spectra of the compounds, **A1B1, A1B2, A1B3** and **A1B4** the azo-azomethine carbons appear between δ 196.03-170.77 ppm, while the C=O of azo-aldehyde in compound **A1** appear at 188.38 ppm. In all the synthesized compounds, the methoxy group carbon atom was observed at the range δ 40.47-52.02 ppm (22, 23) .Additionally the ^{13}CNMR spectra of the compounds MO and MS, the signals at δ 189.55 ppm and δ 173.70 ppm can be assigned to carbon atoms of C=O. Also, the signals of the carbon atoms

of the CH-S moiety in the thiazolidinone ring can be observed at δ 50.6 ppm and δ 46.84 ppm respectively. Signals of carbon atoms of the aromatic rings appeared within the expected range. Both ^{1}H and ^{13}C spectra confirm the validity of the proposed structures of the newly synthesized compounds, Experimental section, and figs (1-33) Supplementary file.

EI-mass:

Mass spectrometry (**MS**) is a powerful qualitative and quantitative analytical technique that employs ionization and mass analysis of compounds to determine the mass, formula, and structure of the compound being analyzed. The mass principle consists of ionizing chemical compounds to generate charged molecules or molecule fragments and measurement of their mass-to-charge. From the mass spectra, the molecular ion $[M]^+$ of each synthesized Compound can be observed with great acceptance (24). The suggested potential fragments of ion and the proposed fragmentation can be observed in the scheme (3-8) in the supplementary file. Also, the stability of the fragments and the base peaks of each compound can be indicated via the peak's intensity. The mass spectra of compound **A1** shows several fragmentation peaks at m/z 341, 306,258,185 and 68, which can be assigned to $[C_{14}H_{12}NO_5SCl]^+$ $[C_{13}H_{12}N_3O_4S]^+$, $[C_{13}H_7N_2O_2Cl]^+$, $[C_6H_7N_3O_2S]^+$ and $[C_4H_6N]^+$ respectively. Also, the mass spectrum of **A1B2** shows an important fragmentation peaks at m/z 443,398,203 and 64 which can be attributed to $[C_{20}H_{16}N_4SCl]^+$, $[C_{19}H_{15}N_4O_2SCl]^+$, $[C_6H_4N_2O_2Cl]^+$ and $[SO_2]^+$, respectively. Also, the compound **A1B3** and **A1B4** show several fragmentation peaks at m/z 551, 368, 185, and 55 which can be assigned to $[C_{24}H_{21}N_7O_5S_2]^+$,$[C_{18}H_{16}N_4O_3S]^+$,$[C_6H_7N_3O_2S]^+$ and $[C_3H_5N]^+$, while the compound **A1B4** shows fragmentation peaks at m/z 507,367,279 and 64, that can be attributed to$[C_{20}H_{16}N_4O_6S_2Cl]^+$,$[C_{14}H_{13}N_4O_4SCl]^+$, $[C_{12}H_8N_2O_2SCl]^+$ and $[SO_2]^+$, respectively. Furthermore, the mass spectrum of compound **MO** is characterized by the appearance of many fragmentation peaks at m/z 532,430,341,256, 149 and 69 which can be assigned to $[C_{22}H_{17}N_3O_4S_2Br]^+$, $[C_{16}H_{19}N_4O_4S_2Cl]^+$, $[C_{13}H_{12}N_3ClO_4S]^+$, $[C_{14}H_{16}N_4O]^+$, $[C_7H_5N_2S]^+$ and $[C_4H_7N]^+$. On the other hand, the Compound MS shows several fragmentation peaks at m/z, 530,341,224, and 69 which can be attributed to $[C_{26}H_{21}N_7O_2SCl]^+$, $[C_{13}H_{12}N_3O_4SCl]^+$, $[C_{13}H_{12}N_4]^+$ and $[C_4H_7N]^+$, respectively.

Biological activity: **antifungal and antibacterial**

In vitro, studies of the antibacterial and antifungal activities of the investigated compounds against *gram-positive staphylococcus aureus*, *gram-negative live Escherichia coli*, and fungi *candida albicause* were carried out using a well diffusion method. Amoxicillin, sulfathiazole, and Nystatin were used as reference antibiotics.

Almost all the compounds exhibited antibacterial activity against the studied microbes at different concentrations (25, 50, 100 mg/L). The investigation of antibacterial testing data showed that the synthesized compounds are more effective against *Gram-negative Escherichia-Coli* than *Gram-positive staphylococcus* aureus even within the lowest concentration. It was found that compounds **AlB4** and **A1B3** are more effective against *E-Coli* with an IZ-19mm and I2 = 17mm at concentration l00mg/L while the same compounds shown least effective with an IZ=16mm and IZ=13mm against *S. Coccus*. Also, the compound **MO** was found to be more effective against *E. coli* with an IZ=17.8mm than the compound **MS** even though it's from the same thiazolidinone group. In comparison with the standard amoxicillin compounds **A1B4**, **A1B3,** and **A1B2** showed appreciable activity especially at the concentration of 50 mg/L against *E. Coli* and *S. Coccus*, while the same compounds showed moderate effectiveness towards the same studied microbes at the concentration 25mg/L.

The antifungal activity against *candida albicause* shows that **A1B4** was the most active of all the compounds with an IZ=22mm. Also, compound **A1B3** showed good activity with an IZ=20 mm,

while the compounds **A1B2** and **A1B1** showed moderate activity with an IZ=18mm and IZ=16mm, respectively. Furthermore, compounds **A1, MO,** and **MS** showed weak activity with an IZ=6mm, for each one of them even at a concentration of 100 mg/L. The results of antimicrobial testing data are presented in Table 1 and Figs (28-30).

Azo-azo compounds that contain azomethine components within their structure help to clarify the mechanism of transamination and racemization reactions in biological processes. The practice of action of these compounds may include the formation of a hydrogen bond via an azomethine moiety with the active centers of various cellular constituents, resulting in interference with normal cellular processes (25). Also, all the prepared compounds contain within their skeleton composition a sulfonamide derivative and the mode of action of the sulfonamide involves competitive inhibition to synthesize the essential enzyme, dihydropteroate synthetase, hence the bacterial DNA synthesis stops and they can no longer proliferate by using sulfonamides. The bacterial dihydropteroate synthetase accepts the sulfonamides into its active, site instead of para-aminobenzoic acid due to the similar in structure between sulfonamide and para-aminobenzoic acid, and once bound, it prevents para-amino acid from binding, therefore dihydropteroate synthesis is inhibited. Because sulfonamides inhibit bacterial growth, therefore they are bacteriostatic (26). Furthermore, compounds consisting of the -N=N- group played a significant role in antibacterial activity. The azo derivatives which include the -N=N- moiety in their structure can protonate it under acidic conditions by reacting with the phosphate group on the polysaccharide peptidoglycan layer of bacteria, which impedes the formation of the cell wall (10).

Table (1) Antimicrobial activity results of prepared azo and azo-azomethine

Compound	*Staphylococcus aureus* Concentration (mg/ml)			*Escherichia Coli* Concentration (mg/ml)			MIC	*Candida albicane* Concentration (mg/ml)		
	100	50	25	100	50	25		100	50	25
A1	6	9	6.2	11	15	13	25	6	6	6
A1B1	6.5	9	8	6.5	14	13	25	16	6	6
A1B2	11	15	13	16	16	15	25	18	6	6
A1B3	13	16.3	12	17	17	16	25	20	6	6
A1B4	16	17	13	19	18	15	25	22	6	6
MO	9	15	13	13	17.8	14.5	25	6	6	6
MS	10	15.5	13.4	11.5	17	16	25	6	6	6
Sulfathiazole	14	15	13.5	18	13.2	9	25	7	6	6
Amoxicillin	30	28	20	42	25	18	25	9	8	7
Nystatin	0	0	0	0	0	0	25	35	22	12

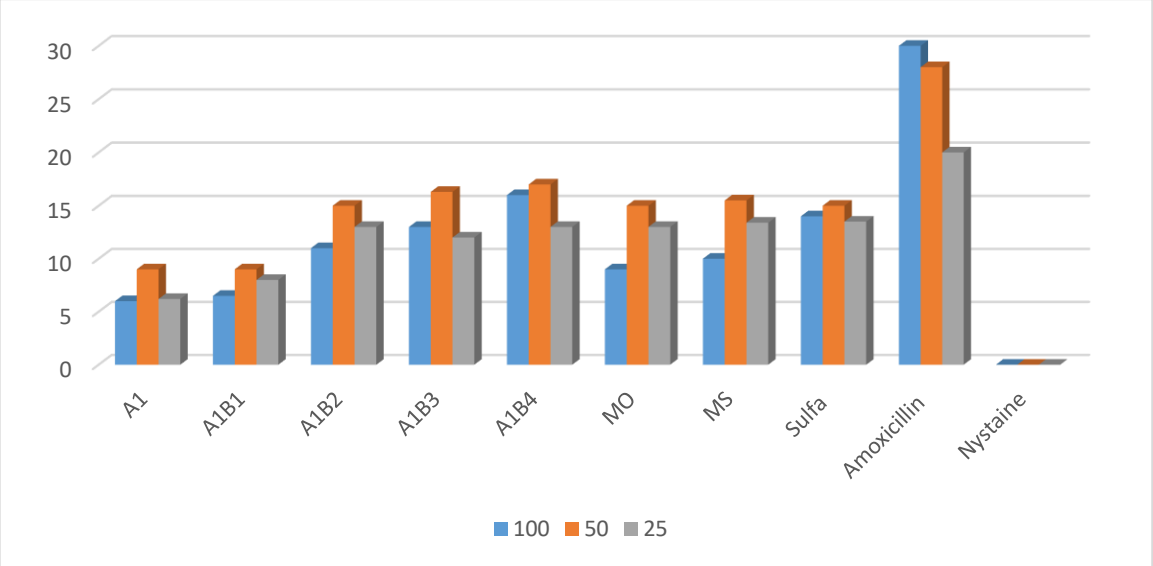


Fig 28: *Staphylococcus aureus* concentration (mg/ml)

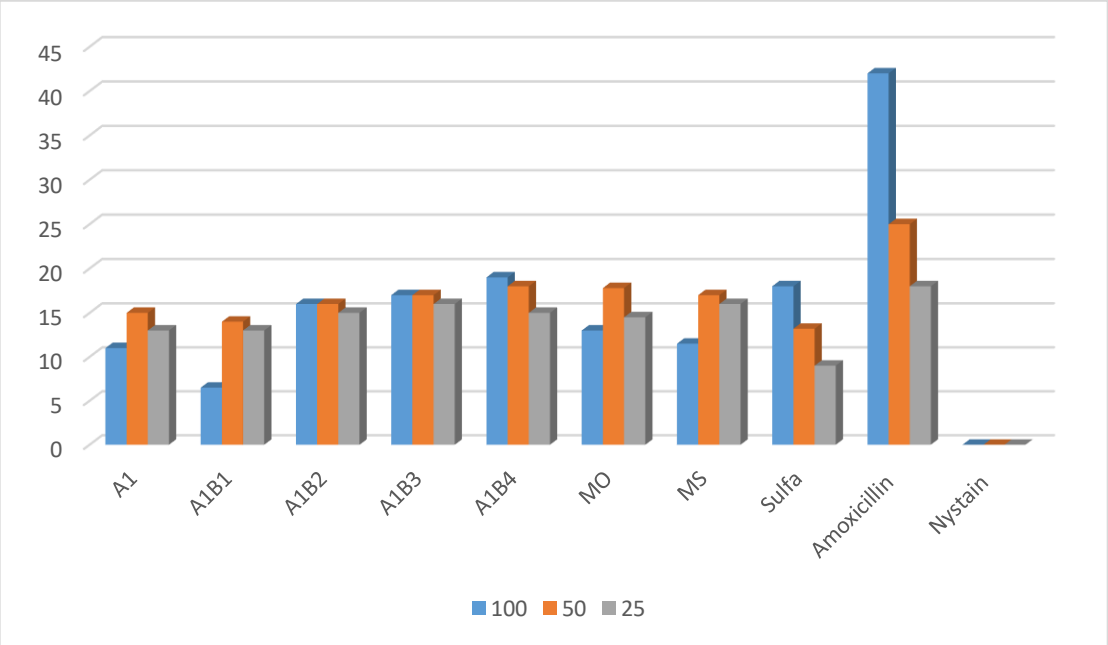


Fig 29: *Escherichia Coli* concentration (mg/ml)

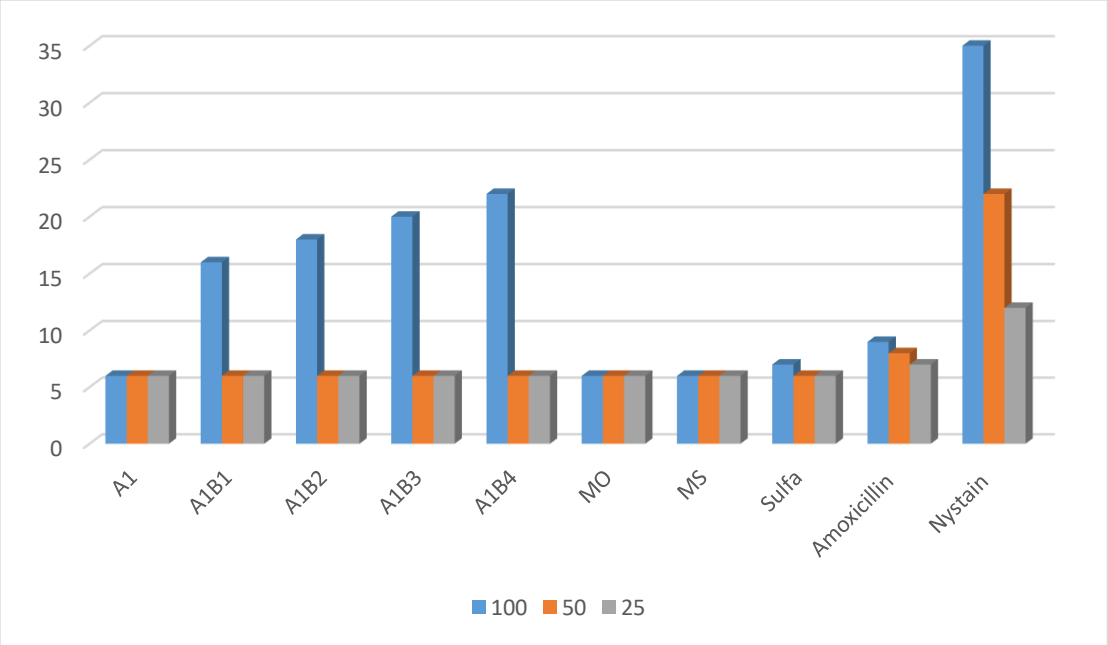


Fig 30: *Candida albicane* concentration (mg/ml)

Antioxidant activity

In this study, the DPPH radical scavenging method was used to assess the determination of potential radical scavenging activities of the synthesized compounds (**A1-MS**). Table 2 and figs (31-32) illustrate DPPH scavenging activity as IC_{50}. The antioxidant activity of antioxidants was attributed to various mechanisms, involving the prevention of continued hydrolysts, reductive capacity, decomposition of peroxides, and radical scavenging (10). Free radical scavenging activities of azo-azomethines **A1B1** are higher than other compounds, followed by the potency effectiveness of the compound **A1B2**. Also compounds **A1B4** and **MO** show moderate efficiency. However, DPPH free radical scavenging of the synthesized compounds shows low activity when compared with vitamin C as a positive control (27). The efficiency of our synthesized compounds could be assigned to demesne these new compounds' phenolic hydroxyl group, which have proficiency in scavenging free radicals. In addition, phenolic compounds are considered inhibitors in the process of oxidation, ordinarily, they possess an aromatic ring with a hydroxyl group as part of their molecular structure. This feature allows for excellent conjugation. Molecules containing conjugated systems recognize a better delocalization of π- electrons across all the adjacent atoms, thus a conjugated system of phenolic compounds allow the ready donation of hydrogen atoms or electrons from phenolic hydroxyl group to free radicals, which generate phenoxide free radical (Aro^{-}) which stabilize by resonance (1). On the other hand, all the synthesized compounds possess a methoxy group as part of the molecular structure, that stabilizes the free radical generated during oxidation process by correlating the introduction of electron donor substituent (28). Therefore, the antioxidant active order of these compounds take this way:

A1B1>A1B2>A1B4>A1B3>A1>MS>MO

Table (2) DPPH Scavenging capacities (IC_{50}µm) of the synthesized compounds

Compound	Concentration (µg/ml)								R^2	IC_{50} µg.ml
	0.78	1.56	3.12	6.25	12.5	25	50	100		
A1	0.7	1.6	4.3	14.8	24.2	29.3	46.4	61.3	0.9321	614.007
A1B1	38.59	42.44	42.77	42.77	43.41	42.77	46.4	47.59	0.8657	42.16
A1B2	7	13.2	11.6	44.8	62	70.1	71.7	75.1	0.9004	98.3152
A1B3	6.3	9.6	8.3	10.6	17.3	39.5	59.5	67.9	0.8393	381.887
A1B4	5.5	9.8	8.6	22.6	47.4	62.8	68.6	77.9	0.9329	141.673
MO	2.3	6.8	8.6	12.8	20.3	33.1	40.1	43	0.9547	1704.53
MS	2.4	4.4	12.8	15.4	21.1	30.7	40.5	52.1	0.9586	1080.47
Vit. C	7.2	24.1	41.4	64.5	89.3	94.8	95.2	95.2	0.8982	4.374

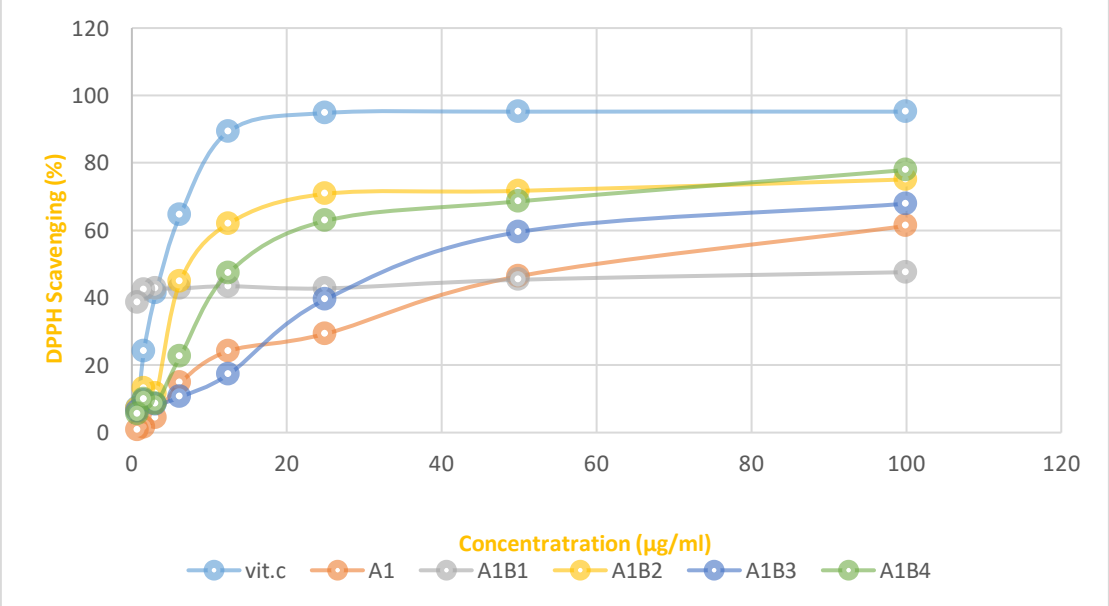


Fig (31) DPPH Scavenging activity of synthesized compounds A1, A1B1, A1B2, A1B3 & A1B4

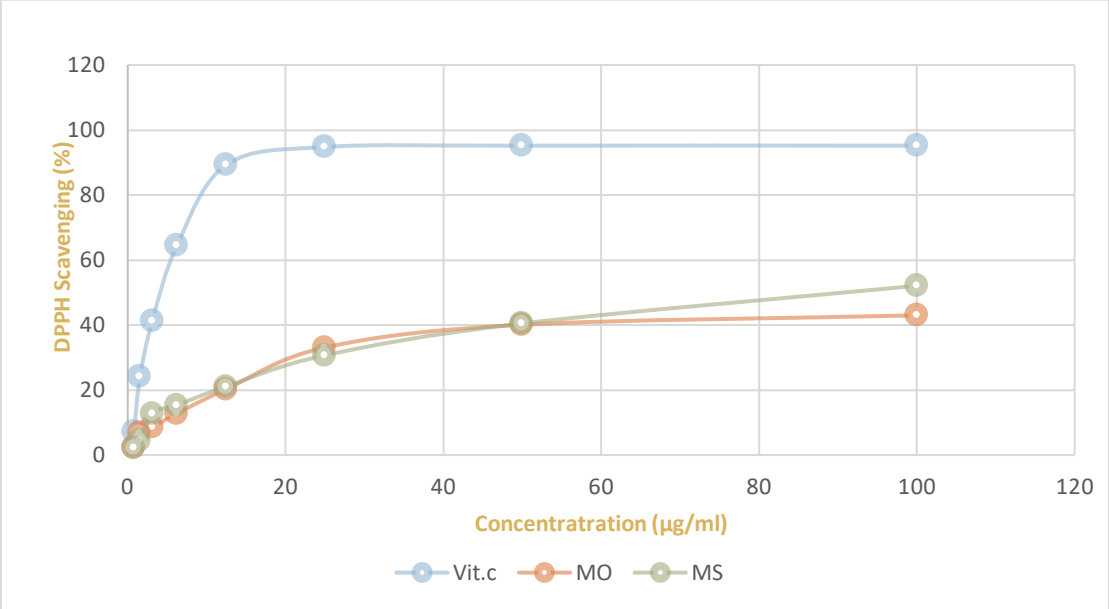


Figure (32) DPPH Scavenging activity of synthesized compounds MO&MS

Conclusion

New azo-azomethine and thiazolidinone were successfully synthesized using chemical methods. These compounds are derived from different amines such as sulfa drugs. The synthesized compounds were diagnosed with CHN which confirms the chemical structure, while FT-IR, ^{1}HNMR,^{13}CNMR spectroscopy, and mass have been confirming the components' moieties. Especially -N=N- as well as H-C=N imine moieties. The antioxidant activity was evaluated by using the DPPH radical scavenging method. The compound **A1B1** shows excellent activity followed by compound **A1B2**. The biological efficiency of the prepared substances was screened by using two pathogenic bacterial strains and fungi. The prepared substances displayed moderate efficiency and little activity as antifungal efficacy.

Additional Information

A document file including copies of synthetic azo and amides FT-IR, ^{1}HNMR,^{13}CNHR (400MHZ, DMSO-d6), and mass spectra.

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Conflict of interest

The author declares that he has no conflict of interest.

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Author Contributions

Dania Mohammed conducted the experiments. Bushra Kamil and Dania conducted the calculations. Bushra Kamel wrote and revised the manuscript, and all authors agreed to the final version of this manuscript.

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