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Facile Synthesis, Characterization of Novel Schiff Bases and N-Nucleosides Bearing Quinazoline Moiety and Evaluation Their Antimicrobial effects

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ABSTRACT

The present work describes convenient synthesis of the novel Schiff bases 4, 5 and 6 by reaction of each of the previously synthesized quinazolinones 1, 2 and 3 with p-methoxybenzaldehyde. [2+2] Cycloaddition Reaction of the former Schiff bases within phenylisothiocyanate affording azatedine derivatives 7 and 8. Also, the quinazolines 1 and 2 could be reacted with α-bromoglucose tetraacetate giving peracetylated N-glycosides of quinazolinones 9 and 10 which were then deacetylated to afford N-glycosylated quinazolinones 11 and 12 respectively. On the other hand, Dapsone was reacted with p-methoxyacetophenone to afford 4-[(4-aminophenyl) sulfonyl]-N-[(1E)-1-(4-methoxyphenyl)ethylidene]aniline 15 which was, in turn, reacted with 4-chloro-2-ethoxyquinazoline 16 affording Schiff base 17. The latter was reacted with 2-furoyl chloride affording Schiff base 18. The structures of the novel Schiff bases and N-glycosides were confirmed by the IR, 1H-NMR, 13C-NMR, MS and elemental analysis. The antimicrobial activity for these synthesized compounds could outline, the moderate activity was observed with new quinazoline compounds which proved to possess marked activity against E. coli, S. aureus and C. albicans. The strong activity has observed nearly with the most synthesized compounds .

Introduction

Quinazoline as N-heterocycles have received considerable attention in the literature as a consequence of their exciting biological properties and their role as pharmacophore[1-4]. Some of quinazolinones were screened in vitro for their antimicrobial activity and the energy gap between HOMO and LUMO has been calculated to reflect the chemical reactivity and kinetic stability of compounds [5]. A Novel series of N-substituted-2-phenylquinazolin-4-ones bearing different anilines at the N-3 of quinazolin-4-one scaffold *via* acetyl-flexible linker as anticancer agents with the compounds were synthesized by insertion of methylene (CH_2) bridge at C4-position of quinazoline moiety to provide a flexibility that increase their anti-proliferative activity against three human tumor cells[6].

Similarly, heterocycles containing the quinazoline moiety are of interest because they show some pharmacological and biological activities [7-9]. Quinazoline derivatives were reported to posses anticonvulsant[10], antitumor[11,12], antihypertensive[13], antithrombotic[14], antidiabetic[15], antitrypanosomal[16], and anti-inflammatory[17]. Olaparib (Anticancer Agent), Zopolrestat and Ponalrestat (Anti-diabetic Agent), Azelastine and Flezelastine (Anti-histaminic Agent) could have benzyl moiety directly attached to quinazoline precursors. From this view the authors could be decided and prompted us to synthesize the quinazoline derivatives bearing benzyl moiety to evaluate their antimicrobial effects.

Experimental

All melting points recorded are uncorrected. The IR spectra were recorded on a Pye Unicam SP 1200 spectrophotometer using the KBr wafer technique. The ^{1}H- and ^{13}C-NMR spectra were determined on a Varian FT-200, Brucker AC-200 MHz spectrophotometry experiment using

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TMS as an internal standard. Chemical shifts (δ) are expressed in ppm. The mass spectra were determined by MP model NS-5988 and Shimadzu single focusing mass spectrometer (70 eV). All solvents used were of HPLC / Analar grade.

2.1.General Procedure for the Synthesis of the quinazoline-4(3H)-one* 1-3*:

A mixture of 3,1-Benzoxazin-4-one (0.01 mol) and *p-phenylene diamine, 4,4\-benzidine and/or 2,2\-dimethyl,4,4\-benzidine* (0.01 mol) was heated under reflux in absolute ethanol (20 ml) for 6h. The resulting mixture was cooled and then poured onto an ice/water mixture. The separated solid was filtered, washed with water, air-dried and crystallized from ethanol to give colorless crystals of products.

2.1.1. 2-(4- Aminophenyl)-4-(4-methoxy)benzylquinazolin-4(3H)-one (*1*):

m.p. 168-170 ºC; yield 76 %; Anal. for $C_{22}H_{19}N_3O_2$ (m.w. 357). Anal: Calcd: C, 73.94; H, 5.32; N, 11.76; Found: C, 73.93; H, 5.34; N, 11.75. IR υ (cm^{-1}) 1666 (C=O), 1610 (C=N), 2993 (CH); MS: *m/z* (int. %) $[M+H]^+$ 357(27.9); ^{1}H-NMR (DMSO-d6) δ 3.22 (s, 3H, O*CH*$_3$), 4.02 (s, 2H, CH_2Bz), 6.3(s, 2H, NH_2), 7.18-7.92 (m, 12 H, 3Ph-*H*); ^{13}C-NMR: 15.01, 55.79, 114.41, 114.39, 120.81, 122.48, 122.51, 126.59, 126.68, 127.31, 128.72, 129.59, 129.62, 130.18, 131.18, 133.41, 146.92, 147.58, 154.01, 160.02, 160.60, 162.90.

2.1.2. 2-(4-Amino-[1,1'-biphenyl]-4-yl) 4-(4-methoxy)benzylquinazolin-4(3H)-one (2):

m.p. 182-184 ºC; yield 68 %; Anal. for $C_{28}H_{23}N_3O_2$ (m.w. 433), Calcd: C, 77.59; H, 5.31; N, 9.69; Found: C, 77.57; H, 5.34; N, 9.69. IR υ (cm^{-1}) 1668 (C=O), 1622 (C=N), 2992 (CH). MS: *m/z* (int. %) $[M^+]$433(35.7); ^{1}H-NMR (DMSO-d6) δ 3.41 (s, 3H, O*CH*$_3$), 4.04 (s, 2H, *CH*$_2$*Bz*), 6.23(s, 2H, NH_2), 6.95-7.90 (m, 16H, PhH); ^{13}C-NMR: 15.01, 64.91, 114.41, 120.82, 122.01, 122.69, 125.11, 126.19, 126.61, 126.72, 127.32, 128.69, 130.21, 130.21, 131.01, 131.01, 132.12, 133.39, 134.42, 134.78, 137.21, 140.11, 146.89, 150.01, 154.00, 160.58, 160.00, 162.91.

***2.1.3. 2-(4-Amino-3,3'-dimethyl -[1,1'-biphenyl]-4-yl)-4-(4-methoxy)benzylquinazolin-4(3H)-one* (3):**

m.p. 188-190 ºC; yield 68 %; Anal. for $C_{30}H_{27}N_3O_2$ (m.w. 461), Calcd: C, 78.09; H, 5.85; N, 9.11; Found: C, 78.07; H, 5.84; N, 9.09. IR υ (cm^{-1}) 1668 (C=O), 1622 (C=N), 2992 (CH). MS: *m/z* (int. %) $[M^+]$ 461(6.6); ^{1}H-NMR (DMSO-d6) δ 2.19, 2.41 (2s, 2H, 2*CH*$_3$ of biphenyl), 3.84 (s, 3H, -O*CH*$_3$), 4.52 (s, 2H, -*CH*$_2$Bz), 6.95-7.50 (m, 4H, PhH), 7.33-8.10 (m, 6H, biphenyl), 7.48-8.19 (m, 4H, qui); ^{13}C-NMR: 15.01, 17.59, 18.61, 55.80, 114.41, 120.82, 122.01, 122.69, 125.11, 126.19, 126.61, 126.72, 127.32, 128.69, 130.21, 130.21, 131.01, 131.01, 132.12, 133.39, 134.42, 134.78, 137.21, 140.11, 146.89, 150.01, 154.00, 160.58, 160.00, 162.91.

2.2.General Procedure for the Synthesis of the Schiff Bases* 4-6*:

A mixture of compounds **1**, **2**, and/or **3**(0.01 mol) and *p*-methoxybenzaldehyde (0.01 mol) was heated under reflux in absolute ethanol (20 ml) for 6 h. The resulting mixture was cooled and then poured onto an ice/water mixture. The separated solid was filtered, washed with water, air-dried and crystallized from ethanol to give colorless crystals of products.

2.2.1. 4-(4-Methoxy)benzyl -2-(4-((4-methoxybenzylidene) amino) phenyl)quinazolin-4(3H)-one (*4*):

m.p. 200-202 ºC; yield 80 %; Anal. for $C_{30}H_{25}N_3O_3$ (m.w. 475). Anal: Calcd: C, 75.78; H, 5.26; N, 8.84; Found: C, 75.76; H, 5.24; N, 8.85. IR υ (cm^{-1}) 1666 (C=O), 1610 (C=N), 2993 (CH); MS: *m/z* (int. %) $[M^+]$ 475 (40); ^{1}H-NMR (DMSO-d6) δ 3.64, 3.82 (2s, 6H, 2O*CH*$_3$), 4.26 (s, 2 H, *CH*$_2$Bz), 7.18-7.78 (m, 12 H, 3Ph-*H*), 7.34-8.19 (m, 4 H, qui), 8.68 (s, 1H, =*CH*-); ^{13}C-NMR: 15.01, 55.79, 64.89, 114.41, 114.49, 120.81, 122.48, 122.51, 126.59, 126.68, 127.31, 134.39, 140.81, 142.48, 142.51, 146.59, 148.68, 149.31, 151.72, 153.59, 155.62, 160.18, 161.18, 163.41, 164.92, 167.58, 168.01, 170.02, 170.60, 172.90.

***2.2.2. 4-(4-Methoxy)benzyl-2-(4'- (4-methoxybenzylidene) amino)- [1,1'-biphenyl]-4-yl)quinazolin-4(3H) -one* (5):**

m.p. 212-214 ºC; yield 74 %; Anal. for $C_{36}H_{29}N_3O_3$ (m.w. 551), Calcd: C, 78.40; H, 5.26; N, 7.62; Found: C, 78.37; H, 5.24; N, 7.59. IR υ (cm^{-1}) 1668 (C=O), 1622 (C=N), 2992 (CH). MS: *m/z* (int. %) $[M^+]$ 551 (35.7); ^{1}H-NMR (DMSO-d6) δ 3.62, 3.84 (2s, 6H, 2O*CH*$_3$), 4.52 (s, 2H, *CH*$_2$Bz), 6.95-7.50 (m, 8H, PhH), 7.33-8.10 (m, 8H, biphenyl), 7.48-8.19 (m, 4H, qui), 8.72 (s, 1H, =*CH*-); ^{13}C-NMR: 15.01, 17.59, 18.61, 55.80, 64.91, 114.41, 114.41, 120.82, 122.01, 122.69, 125.11, 126.19, 126.61, 126.72, 127.32, 128.69, 130.21, 130.21, 131.01, 131.01, 132.12, 133.39, 134.42, 134.78, 137.21, 140.11, 146.89, 150.01, 154.00, 160.58, 160.00, 162.91, 167.58, 168.01, 170.02, 170.60.

***2.2.3. 4-(4-Methoxy)benzyl-2-(4'-(4-methoxybenzylidene) amino)-3,3'-dimethyl -[1,1'-biphenyl]-4-yl) phth -alazin-1(2H)-one* (6):**

m.p. 222-224 ºC; yield 70 %; Anal. for $C_{38}H_{33}N_3O_3$ (m.w. 579), Calcd: C, 78.75; H, 5.69; N, 7.52; Found: C, 78.73; H, 5.67; N, 7.50. IR υ (cm^{-1}) 1668 (C=O), 1622 (C=N), 2992 (CH). MS: *m/z* (int. %) $[M^+]$ 579 (35.7); ^{1}H-NMR (DMSO-d6) δ 2.19, 2.41 (2s, 6H, 2*CH*$_3$ of biphenyl), 3.64, 3.84 (2s, 6H, 2O*CH*$_3$), 4.52 (s, 2H, *CH*$_2$Bz), 6.95-7.50 (m, 8H, PhH), 7.33-8.10 (m, 6H, biphenyl), 7.48-8.19 (m, 4H, phthala), 8.72 (s, 1H, =*CH*-).

2.3. Synthesis of Compounds 7-8:

Equimolar amounts of **4** and/or **5** (0.01 mol) and phenyl isothiocyanate in 25 mL toluene was refluxed for 6 h. The solvent was distilled off and the residue was washed with ethanol followed by water, and the product was crystallized from ethanol as yellow crystals.

***2.3.1. 2-(4-[2-(4-Methoxyphenyl)-3-phenyl-4-thioxo-1,3-diazetidin-1-yl]phenyl)amino-2-(4-methoxy benzyl)quinazolin-4(3H)-one* (7):**

m.p. 278-280 °C, yield 68 %. Anal. for $C_{37}H_{30}N_4O_3S$ (m.w. 610); Calcd: C, 72.78 ; H, 4.91; N, 9.18; S, 5.24; Found: C, 72.76; H, 4.87; N, 9.15; S, 5.23; IR υ (cm^{-1}) 1319 (C=S), 1519 (C=N), 1669 (C=O), 3318, 3443 (CH);; MS: *m/z* (int. %) [M^+] 610 (59.1); ^{1}H-NMR (DMSO-d6) δ 3.46, 3.76 (2s, 6H, 2OCH_3), 4.37 (s, 2H; CH_2Bz), 6.70-7.15(m, 8H, 2C_6H_4OCH$_3$), 7.18-7.30(m, 5H, -C_6H_5), 7.32-7.40(m, 4H, X = Ar), 7.44-8.20 (m, 4H, qui).

2.3.2. 2-(4-[2-(4-Methoxyphenyl)-3-phenyl-4-thioxo-1,3-diazetidin-1-yl] -[1,1'-biphenyl])amino-2-(4-methoxybenzyl)quinazolin-4(3H)-one (8):

m.p. 284-286 °C, yield 72 %. Anal. for $C_{43}H_{33}N_4O_3S$ (m.w. 685); Calcd: C, 75.32; H, 4.81; N, 8.17; S, 4.67; Found: C, 75.30; H, 4.83; N, 8.18; S, 4.69; IR υ (cm^{-1}) 1322 (C=S), 1522 (C=N), 1671 (C=O), 3327, 3433 (CH);; MS: *m/z* (int. %) [M^+] 685 (66.3); ^{1}H-NMR(DMSO-d6) δ 3.52(s, 3H, O*CH3*), 3.76 (s, 3H, -O*CH3*), 4.45 (s, 2H; CH_2Bz), 7.17-7.33 (m, 5H, -C_6H_5), 6.70-6.95 (m, 8H, 2C_6H_4OCH$_3$), 7.0, 7.28(m, 8H, X =Ar), 7.30-8.20 (m, 4H, qui).

***2.4. Synthesis of Acetylated Derivatives* 9 *and* 10 *and Deacetylated Derivatives* 11 *and* 12:**

A crude mixture of quinazolinones **1** and/or **3** (0.05 mol) and α-bromoglucose tetraacetate (0.01 mol) in 100 mL 1, 4-dioxane was heated with frequent stirring under reflux for 4h. The mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate, washed sequentially with saturated $NaHCO_3$ and dried over $MgSO_4$. The purification and separation was achieved by column chromatography (3:1 EtOAc: Hexane) giving the acetylated products **9** and **10** as a white solid which was later on recrystallized using dichloromethane- diethyl ether – hexane solvents. A solution of **9** or **10** in MeOH (50 mL) was treated with sodium carbonate solution (0.05 mol). A white solid syrupy began to settle. The residue was then purified by column chromatography (3:1, EtOAc:Hexane) giving the deacetylated derivatives each as a white solid, which was crystallized by dichloromethane-diethyl ether-hexane solvents affording **11** or **12** respectively**.**

***2.4.1. (2R, 3R, 4S, 5R, 6S)-2-(Acetoxymethyl)-6-((4-(4-methoxybenzyl-1-oxoquinazolin-2-yl) phenyl) amino) tetrahydro-2H-pyran-3, 4, 5-triyl triacetate* (9):**

m.p. 124- 126 ºC; yield 58 %. Anal. for $C_{36}H_{37}N_3O_{11}$ (m.w. 687): Calcd: C, 62.88; H, 5.38; N, 6.11; Found: C, 62.84; H, 5.38; N, 6.08. IR υ (cm^{-1}) 1662, 1738 (C=O), 2988 (CH), 3334 (NH); MS: *m/z* (int. %) [M^+] 687(1.4); ^{1}H-NMR (DMSO-d6) δ) 2.05-2.06 (s, 12H, 4Ac-H), 3.45(s, 3H, OCH$_3$), 4.00 (s, 1H, sec *NH*), 4.52 (s, 2H, CH_2Bz), 3.75-5.11 (m, 6H, H-2, H-3, H-4, H-5, H-6a, H-6b), 5.22 (d, 1H, H_{anom}), 6.70-6.95 (m, 4H, C_6H_4OCH$_3$)7.01-7.34(m, 4H, X =Ar), 7.47-8.19 (m, 4H, qui); ^{13}C-NMR: 15.01, 20.70, 21.02, 21.02, 21.02, 62.39, 64.89, 69.01, 69.38, 73.0, 77.18, 87.89, 117.89, 117.89, 120.8, 121.11, 122.42, 122.42, 126.59, 126.71, 127.32, 130.38, 130.8, 131.11, 132.42, 132.42, 136.59, 136.71, 143.19, 146.90, 154.01, 160.58, 170.20, 170.20, 170.21, 170.21.

***2.4.2.(2R,3R,4S,5R,6S)-2-(Acetoxymethyl)-6-((4'-(4-methoxybenzyl-1-oxoquinazolin-2-yl)-3,3'-dimethyl-[1, 1'-biphenyl]-4-yl)amino)tetrahydro-2H-pyran-3,4,5-triyl triacetate* (10):**

m.p. 164-166 ºC; yield 56%. Anal. for $C_{44}H_{45}N_3O_{11}$ (m.w. 789): Calcd: C, 66.92; H, 5.70; N, 5.32; Found: C, 66.93; H, 5.70; N, 5.30. IR υ (cm^{-1}) 1666, 1736 (C=O), 2992 (CH), 3334 (NH); MS: *m/z* (int. %) [M^+] 789(10.9); ^{1}H-NMR (DMSO-d6) δ 2.05-2.12 (s, 12H, 4 Ac-H), 2.29, 2.22 (2 s, 6H, 2CH_3), 3.22 (s, 3H, -OCH_3), 4.0 (s, 1H, sec-*NH*), 4.52 (s, 2H, CH_2Bz), 3.74-5.14 (m, 6H, H-2, H-3, H-4, H-5, H-6a, H-6b), 5.47 (d, 1H, anom-H), 6.66-7.72 (m, 10H, ArH), 7.50-8.19 (m, 4H, qui); ^{13}C-NMR: 15.01, 17.61, 17.89, 20.72, 21.01, 21.01, 21.01, 62.39, 64.90, 69.01, 69.39, 73.01, 77.18, 88.21, 113.89, 120.78, 122.01, 125.11, 125.68, 126.59, 126.72, 126.72, 127.29, 130.00, 131.00, 131.62, 133.41, 134.38, 134.78, 137.20, 140.78, 142.01, 145.11, 145.68, 146.59, 146.72, 147.41, 148.89, 154.00, 160.59, 170.20, 170.20, 170.20, 170.20.

***2.4.3. 4-(4-Methoxybenzyl)-3-(4-((2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)amino) phenyl) quinazolin-4(3H)-one* (11):**

m.p. 158-160 ºC; yield 48 %. Anal. for $C_{28}H_{29}N_3O_7$ (m.w. 519): Calcd: C, 64.73; H, 5.58; N, 8.09; Found: C, 64.73; H, 5.60; N, 8.03. IR υ (cm^{-1}) 1662 (C=O), 3268, 3384 (OH bonded and non-bonded); MS: *m/z* (int. %) [M^+] 519(25.2); ^{1}H-NMR (DMSO-d6) δ 3.22 (s, 3H, OCH_3), 4.00 (s, 1H, sec *NH*), 4.37 (s, 2H, CH_2Bz), 3.29-3.87 (m, 6H, H-2, H-3, H-4, H-5, H-6a, H-6b), 3.58 (m, 4H, 2'-OH, 3'-OH, 4'-OH), 3.65 (s, 6'-OH), 5.01 (d, 1H, Hanom), 7.30-7.44 (m, 8H, Ar-H), 7.32- 8.19 (m, 4H, qui); ^{13}C-NMR: 15.01, 61.89, 64.89, 71.21, 77.38, 74.11, 82.59, 91.62, 117.9, 117.9, 120.78, 121.11, 122.4, 122.4, 126.6, 126.70, 127.29, 127.79, 127.92, 130.78, 131.11, 132.4, 132.4, 133.39, 143.18, 146.90, 154.0, 160.59.

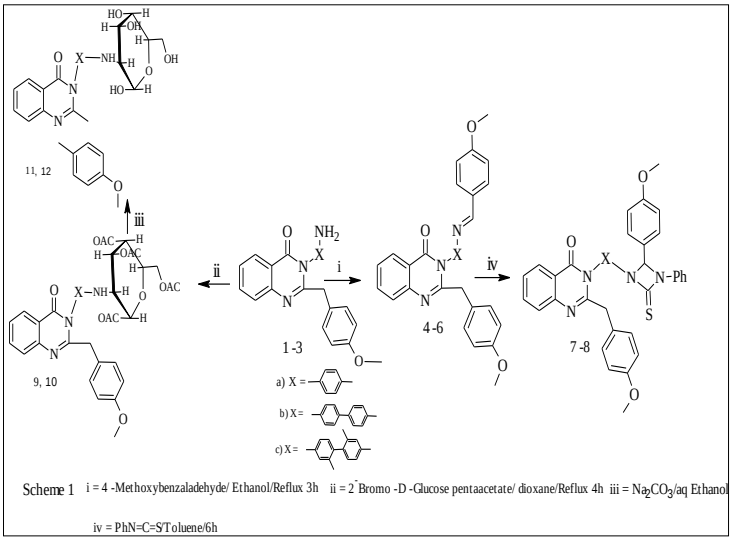
2.4.4.2-(3,3'-Dimethyl-[1,1'-biphenyl]amino-4-yl)-4-(4-methoxybenzyl)-4'-((1S,2S,3S,4R,5R)-2,3,4-trihydroxy-6-

***(hydroxymethyl)tetrahydro-2H-pyran-2-yl)- quinazolin-4(3H)-one* (12):**

m.p. 188-190 ºC; yield 48 %. Anal. for $C_{37}H_{37}N_3O_6$ (m.w. 619): Calcd: C, 71.72; H, 5.97; N, 6.78; Found: C, 71.69; H, 5.94; N, 6.73. IR υ (cm^{-1}) 1669(C=O), 3266, 3382(OH bonded and non-bonded); MS: *m/z* (int. %) [M^+] 619(34.2); ^{1}H-NMR (DMSO-d6) δ 2.34(s, 6H, $2CH_3$), 3.32 (s, 3H, O*CH*$_3$), 4.0(s, 1H, sec *NH*), 4.47 (s, 2H, O*CH*$_2$Bz), 3.33-3.67 (m, 6H, H-2, H-3, H-4, H-5, H-6a, H-6b), 3.58 (m, 3H, 2'-OH, 3'-OH, 4'-OH), 3.65 (s, 1H, 6'-OH), 5.38 (d, 1H, H_{anom}), 6.90- 7.99 (m, 10H, Ar-H), 7.29 - 8.19 (m, 4 H, qui); ^{13}C-NMR: 15.01, 17.61, 7.89, 61.92, 64.90, 71.18, 74.11, 77.38, 82.60, 91.90, 113.89, 120.78, 122.01, 125.11, 125.68, 126.59, 126.72, 126.72, 127.29, 130.00, 131.00, 131.62, 133.41, 134.39, 134.78, 137.20, 140.78, 142.01, 145.11, 145.68, 146.59, 146.72, 146.72,147.41, 148.89, 154.00, 160.59.

*2.5. Synthesis of (E)-4-((4-Aminophenyl) sulfonyl)-N-(1-(4-methoxyphenyl) ethylidene) aniline (1*5**):**

A mixture of dapsone **13** and *p*-methoxyacetophenone **14** (0.01 mol each) in 20 mL boiling absolute ethanol was heated under reflux for 4h. The resulting mixture was cooled and poured onto ice/water. The solid that separated out was filtered, washed, dried and crystallized from ethanol giving colorless crystals; m.p. 176-178 ºC; yield 63 %; Anal. for $C_{21}H_{20}N_2O_3S$ (m.w. 380): Calcd: C, 66.31; H, 5.26; N, 7.36; S, 8.42; Found: C, 66.30; H, 5.25; N, 7.31; S, 8.37. IR υ (cm^{-1}) 1160 (S=O), 1610 (C=N), 2993 (CH) and 3430 (NH); MS: *m/z* (int. %) [M^+] 380 (24.4), 382 (5.5), 383(9.1); ^{1}H-NMR (DMSO-d6) δ 2.27 (s, 3H, *CH*$_3$), 3.94 (s, 3H, O*CH*$_3$), 6.27 (s, 2H, *NH*$_2$), 6.99 - 7.88 (m, 12H, 3 ArH).



Scheme 1 i = 4 -Methoxybenzaladehyde/ Ethanol/Reflux 3h ii = 2`Bromo -D -Glucose pentaacetate/ dioxane/Reflux 4h iii = Na_2CO_3/aq Ethanol iv = PhN=C=S/Toluene/6h

2.6. 4-(4-Methoxy)benzyl-N-(4-((4-((1-(4-methoxy phenyl)ethylidene)amino)phenyl) sulfonyl) phenyl) quinazolin -1-ylamine (17)

4-Chloro-2-methoxybenzylquinazoline **16** and product 1**5** (0.01 mol each) in 20 mL absolute ethanol was heated under reflux for 6 h. The resulting mixture was cooled and poured onto ice / water. The solid that separated out was filtered, washed with water, air-dried and crystallized from ethanol to afford white crystals of **7**; m.p. 226-228 ºC; yield 58 %; Anal. for $C_{37}H_{32}N_4O_4S$ (m.w. 628): Calcd: C, 70.70; H, 5.09; N, 8.91; S, 5.09; Found: C, 70.71; H, 5.07; N, 8.88; S, 5.03. IR υ (cm^{-1}) 1158 (S=O), 1619 (C=N), 2992 (CH) and 3330 (NH); MS: *m/z* (int. %) [M^+] 628(13.22), 552(100), 553(34.0), 554(6.7), 553(2.3), 555(1.6); ^{1}H-NMR (DMSO-d6) δ 2.27 (s, 3H, *CH*$_3$), 3.57, 3.94 (2s, 6H, 2O*CH3*), 4.00 (s, 1H, sec *NH*), 4.26 (s, 2H, -*CH*$_2$), 7.25-8.08 (m, 16H, Ar-H), 7.46-8.81 (m, 4H, qui); ^{13}C-NMR: 14.79, 18.41, 55.80, 60.52, 111.89, 114.42, 114.38, 114.52, 114.52, 123.31, 123.31, 124.19, 127.49, 127.60, 128.69, 128.69, 129.11, 129.11, 129.62, 129.62, 131.41, 132.02, 132.49, 133.43, 135.32, 136.32, 137.35, 138.73, 139.90, 140.43, 145.91, 150.91, 156.29, 162.88, 165.31, 171.42, 192.80.

2.7. N-4-(4-Methoxy)benzylphthalazin-1-yl)-N-(4-((4-((1-(4-methoxyphenyl) ethylidene) amino) phenyl) sulfonyl) phenyl)furan-2-carboxamide (18):

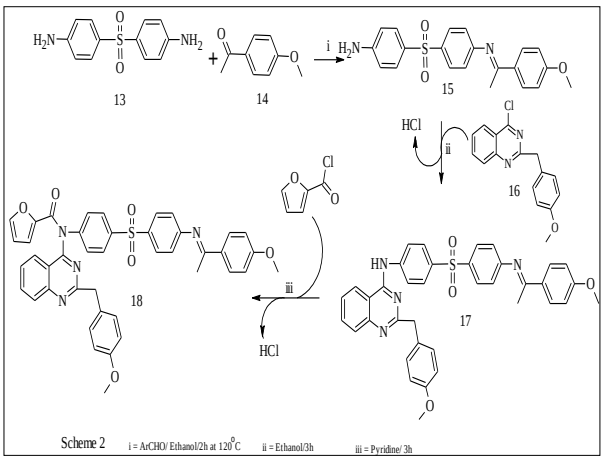
A mixture of Schiff base 1**7** (0.01 mol) and the 2-furoyl chloride (0.01 mol) was refluxed in 50 mL of dry pyridine for 3h. The excess solvent was distilled off and the reaction solution was cooled, then poured into crushed ice with frequent stirring leaving a crude product which was filtered off, washed with water, dried and crystallized from ethanol; m.p. 264-265 ºC; yield 78%. Anal. for $C_{42}H_{34}N_4O_6S$ (m.w. 722): Calcd: C, 69.80; H, 4.70; N, 7.75; S, 4.43; Found: C, 69.78; H, 4.69; N, 7.74; S, 4.39. IR υ (cm^{-1}) 1157 (S=O), 1588 (C=N), 1734 (C=O), and 2988 (CH); MS: *m/z* (int.%) [M^+] 722(23.2), 646(18.2), 119(100); ^{1}H-NMR(DMSO-d6) δ 2.21 (s, 3H, *CH*$_3$), 3.35, 3.95 (2s, 6H, 2O*CH*$_3$), 4.52 (s, 2H, *CH*$_2$), 7.28-8.33 (m, 16H, 3ArH), 7.24, 7.67, 8.41 (3dd, 3H, 3*CH* of furan), 7.55-8.83 (m, 4H, qui); ^{13}C-NMR: 14.80, 18.39, 55.82, 60.49, 111.68, 111.92, 114.40, 114.4, 115.3, 122.60, 122.60, 123.29, 123.29, 124.21, 127.48, 127.6, 128.52, 128.52, 128.68, 129.61, 129.61, 130.25, 131.54, 132.0, 132.49, 134.67, 136.34, 137.0, 139.92, 140.78, 143.78, 147.01, 147.71, 148.24, 150.89, 156.32, 157.68, 162.9, 165.31, 171.39, 172.34, 192.78.

Results and Discussion

The reaction of benzoxazin-4-one with binucleophiles afforded quinazolinone derivatives that were highly antimicrobial effects [18, 27]. Quinazolinone could be synthesized according to our previously published work [28-42]. Quinazolinone inhibitors of inosine-5-monophosphate [43] that containing methylene, phenyl, and methoxy groups. So, the authors can be decided the reaction of 3.2-benzoxazin-4-one with binucleophiles e.g. *p*-phenylenediamine, 4,4-benzidene, and 2,2-dimethyl-4,4-

benzidene afforded phthalazinone derivatives **1**-**3** synthesis of some novel quinazolinone-containing Schiff bases, with the aim of obtaining more precise information about the course of reaction. Thus, 2-(4-aminophenyl)-4-methoxy benzylquinazolin-4(3H)-one(**1),** 2-(4'-amino-[1,1'-biphenyl]–4-yl)-4-meth-oxy-benzylquinazolin-4(3H)-one(**2)** and 2-(4'-amino- 3,3'–dimethyl-[1,1'-biphenyl]–4-yl)-4-methoxy-N benzylquinazolin-4(3H)-one(**3)**, each was reacted with *p*-methoxybenzaldehyde in boiling absolute ethanol giving products **4, 5,** and **6,** respectively (Scheme 1). The IR spectra of **4, 5,** and **6** devoid any bands for the NH_2 group and the mass spectra showed molecular ion peaks at *m/z* 475, 551, and 579 for derivative **4**, **5** and **6** respectively.

On the other hand, when the amino quinazolinone derivative **4** and/or **5** was allowed to react with phenylisothiocyanate afforded azatedine derivative **7** and/or **8,** respectively [36],(scheme 1). Moreover, the reaction of quinazolinone derivatives **1** and/or **2** with α-bromoglucose tetraacetate in 1,4-dioxane gave the per-*O*-acetylated quinazolinone **9** and **10**, whose IR spectrum showed two strong peaks at 1668 and 1736 attributable for υmax of the two C=O groups of quinazolinone and peracetyl moieties, respectively, and the ^{1}H-NMR spectrum showed a singlet at δ 2.05-2.06 which is attributable for CH_3 of acetyl groups. The deacetylation of **9** and **10** by sodium carbonate and ethanol gave the deacetylated derivative **11** and **12**. The structure of **11** was assigned by its mass spectrum that showed a molecular ion peak at *m/z* 519 (M^+). The authors can be reported also, the overall reaction in Scheme 2. Dapsone was refluxed with an equimolar amount of *p*-methoxyacetophenone in boiling ethanol giving the Schiff base **15** in good yield**.** The formation of product **1**5 was confirmed by its mass spectrum showing a molecular ion peak at *m/z* 380[M^+] and its IR spectrum showing an absorption band at 1160 attributable for υmax of S=O in dapsone. The latter was reacted with 4-chloro-4-methoxybenzyl quinazoline **16** in boiling ethanol gave product **17 (**Scheme 2**).** This product could be isolated by washing the crude reaction mixture with water, to remove



any ammonium salts formed, then crystallized from ethanol. Purification of product **17** was rechecked by TLC. Formation of product **17** was confirmed by mass spectrum that showed a molecular ion peak at *m/z* 628(M^+). In its pure state, product **7** was reacted with an equimolar amount of 2-furoyl chloride in dry pyridine affording derivative **18**, whose structure was inferred by the IR spectrum that showed a strong peak at 1734 attributable for υ $cm^{-1}$of the C=O attached to the furoyl moiety. Also, the IR devoid any band for *sec*-NH. The chlorine test for **18** showed no indication for the presence of chlorine.

Biological investigation (Antimicrobial activity)

The antimicrobial screening of all the synthesized compounds was done using the agar diffusion assay. This screening was performed against the Gram-positive bacteria, Gram-negative bacteria, staphylococcus aureus atcc 06538, Escherechia coli Atcc 10536, pathogenic fungi candida albicans Atcc 1023, and Aspergills flavus. A moderate activity was observed with compounds which proved to possess marked activity against E. coli, S. aureus and C. albicans. The strong activity has observed nearly with the most synthesized compounds. The inhibitory concentration was determined for each of the active compounds along with Ampicillin, Streptomycin and Nystatin as positive control. No activity was detected for all the synthesized compound, toward Aspergillus flavus. Results are shown in the following Table 1.

Table 1 (**Antimicrobial screening results of tested compounds at 1 mg/1 mL).** (No activity (0.0), inhibition zone (< 7 mm), weak activity (7-10), moderate activity (11-15 mm), strong activity (> 15 mm), solvent $CDCl_3$ (6 mm).

Compound No.	E. coli	S. aureus	A. Flavus	C. albicans
1	14	16	14	12
2	15	12	10	11
3	12	12	16	12
4	15	14	17	11
5	13	16	11	12
6	11	14	18	12
7	13	13	15	21
8	18	21	11	10
9	16	11	14	11
10	12	18	10	12
11	12	15	11	12
12	16	12	13	11
15	12	17	12	10
16	14	13	15	11
17	16	16	12	13
18	15	14	14	12
Ampicillin	0.0	22	0.0	0.0
Streptomycin	20	21	0.0	0.0
Nystatin	0.0	0.0	0.0	22

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التشخيص والتوليف السهل لقواعد شيف الجديدة و ن-نيوكليوسايد الحاملة لمجموعة كوينازولين الفعالة و تقييم ادائها كمضاد للميكروبات

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الخلاصة :

العمل الحالي يوضح تخليق مناسب لقواعد شيف الجديدة 4،5، و6 عن طريق تفاعل كل من كوينازولين 1،2و3 المحضرة سابقا مع بارا ميثوكسي بنزالديهايد. من خلال تفاعل الاضافة]2+2[الحلقي مع قواعد شيف السابقة بوجود الفينيل ايزوثايوسايانات ادى لإنتاج مشتقات أزاتيدين 7،8. كذلك تم مفاعله الكوينازولين 1،2 مع الفا-بروموكلوكوز تترا-اسيتيت لتعطي ن-جليكوسيدات الباراسيتيل كوينازولين 9 و 10 والتي فيما بعد تم ازالة مجموعة الاسيتيت لتعطي مركبات الكوينازولينون 11 و 12 بالتعاقب. بالمقابل تم مفاعلة دابسون مع بارا اسيتوفينون لإعطاء المركب 15 والذي تم مفاعلته مع 4-كلورو-2-ايثوكسي كوينازولين 16 ليعطي قاعدة شيف17، هذا المركب الاخير (17) تم مفاعلته مع 2-فورايل كلورايد ليعطي قاعدة شيف 18. الاشكال الهيكلية لهذه القواعد الجديدة و ن-كلايكوسايد تم دراستها بواسطة ^{13}C-NMR, ^{1}H-NMR, IR و C.H.N. الفعالية االمايكروبية لهذه المركبات المصنعة تم ايجازها، حيث اظهرت مركبات الكوينازولين فعالية متوسطة ضد بكتريا *E-coli* و *S. aureus* و *C. albicans.* اقوى فعالية كانت تقريبا مع معظم المركبات المصنعة.