DRUG SYNTHESIS

SYNTHESIS OF SOME NEW QUINAZOLIN-4-ONE DERIVATIVES AND EVALUATION OF THEIR ANTIMICROBIAL AND ANTIINFLAMMATORY EFFECTS

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Abstract: In this work, it was of interest to synthesize new series of some 2-[(E)-2-furan-2-y]-vinyl]-quinazolin-4(*3H*)-ones incorporated into pyrazoline, isoxazoline, pyrimidine or pyrimidine-thione ring systems at position-3 of the quinazoline ring. The antimicrobial activity and antiinflammatory effect of some of these compounds were studied.

Keywords: 2-((E)-2-furan-2-yl-vinyl)-quinazolin-4(*3H*)-one derivatives, antimicrobial activity, anti-inflamma-tory activity

Many substituted-4(*3H*) quinazolines are known to possess diverse biological activities as antimalarials (1), hyponotics (2), anti-convulsant (3) and antiprotozoal agents (4). It has been reported (5) that some α , β -unsaturated ketones of quinazolines have bacteriostatic and fungistatic actions.

Also, several styryl heterocycles have been reported to exhibit antitumor activity (6), and to inhibit aerobic glycolysis (7). Blocking the sulfhydryl groups of the biologically active macromolecules changes significantly their chemical structures which in turn impair their biological function and the microorganism cell will be destroyed. 2-Vinyl, and 2-styrylquinazolines are good agents for selective modification of protein SH-groups (6).

Based on these findings, it was of interest to prepare a new series of styrylquinazolin-4-ones with possible antibacterial activity. Synthesis of these heterocycles was based on the fact that certain α , β unsaturated ketones have bacteriostatic and fungistatic action (8, 9). Also, many styrylpyrazoles and styrylisoxazoles and other related compounds are reported to possess 5-lipoxygenase and cyclooxygenase inhibitory effects (10). Several pyrazolines were reported to be nonulcerogenic, antiinflammatory agents (11).

The starting material, namely, 2-[(E)-2-furan-2-yl-vinyl]benzo[d]-[1,3]oxazin-4-one **1** was prepared in a good yield, $\approx 85\%$, by the condensation of furylacryloyl chloride with anthranilic acid in presence of pyridine (12, 13) (Scheme 1).

Compound 1 reacted with *p*-aminoacetophenone at 150° C, for 45 min., to yield the correspon-

ding product 3-(4-acetylphenyl)-2-[(E)-(2-furyl)-vinyl] (*3H*)-quinazolin-4-one **2** (Scheme 1).

Chalcones (α , β -unsaturated ketones) represent active intermediates for the preparation of several heterocyclic ring systems which possess biological activities (14-18). So, compound **2** was subjected to the Claisen-Schmidt condensation, which allowed to react with different aromatic aldehydes, namely, benzaldehyde, p-hydroxybenzaldehyde, p-methoxybenzaldehyde, p-N,N-dimethylaminobenzaldehyde and 2-thienyl carboxaldehyde in the presence of a base to give the corresponding α , β -unsaturated ketones **3a-e**, respectively (Scheme 1).

Compound **3c** was condensed with hydrazine hydrate and/or phenylhydrazine to give the corresponding $2-[(E)-2-furan-2-yl-vinyl]-3-\{4-[5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl]phenyl}-3H-quinazolin-4-one$ **4a** $and <math>2-[(E)-2-furan-2-yl-vinyl]-3-\{4-[5-(4-methoxyphenyl)-4,5-dihydro-1-phenylpyrazol-3-yl]phenyl}-3H-quinazolin-4-one$ **4b**, respectively (Scheme 2).

On the other hand, compounds **3c,d** reacted with hydroxylamine hydrochloride in ethanolic sodium hydroxide solution to yield 2-[(*E*)-2-furan-2-yl-vinyl]-3-{4-[5-(4-methoxyphenyl)-4,5-dihydroisoxazol-3-yl]-phenyl}-*3H*-quinazolin-4-one **5a** and 2-[(*E*)-2-furan-2-yl-vinyl)-3-{4-[5-(4-dimethy-laminophenyl)-4,5-dihydroisoxazol-3-yl]-phenyl}-*3H*-quinazolin-4-one **5b**, respectively (Scheme 2).

Moreover, condensation of a mixture of compound **3d** and urea in boiling ethanolic hydrochloric acid gave $3-\{4-[6-(4-dimethylaminophenyl)-2-oxo 1,2,5,6-tetrahydropyrimidin-4-yl] phenyl}-2(($ *E*)-2-



Scheme 1.

furan-2-yl-vinyl)-*3H*-quinazolin-4-one **6a** afforded in 65% yield.

Similarly, compound **3d** reacted with thiourea in boiling ethanolic potassium hydroxide solution to give $3-\{4-[6-(4-dimethylaminophenyl)-2-thioxo-$ 1,2,5,6-tetrahydropyrimidin-4-yl]-phenyl $\}-2-((E)-2$ furan-2-yl-vinyl)-*3H*-quinazolin-4-one **6b** in about 70% yield (Scheme 2).

In the present investigation, it was of interest to introduce some heterocyclic rings of interesting biological activity in one molecule of 4(3H)-quinazoline moiety to increase the biological activity of the products (19-22).

Accordingly, compounds **8a,b** were prepared by the reaction of thiosemicarbazone derivatives **7c** or **7d** with an equimolar amount of phenacylbromide.

The raction of compounds **3a-e** with malononitrile or ethylcyanoacetate in the presence of an excess of ammonium acetate yielded compounds **9 a-c** and **10 a-d**, respectively (Scheme 3).

Also, compounds **9a-c** and **10a-d** were obtained in one step synthesis by heating a mixture of equimolar ratio of **2** and the appropriate aromatic aldehydes in the presence of an excess ammonium acetate and malononitrile or ethylcyanoacetate in nbutanol (Scheme 4).

EXPERIMENTAL

All melting points are uncorrected, elemental analysis was carried out in the microanalytical unit of the National Research Center. IR spectra were recorded on FT. IR spectrometer-Nexus 670-Nicolet USA and Perkin Elmer-9712 spectrophotometer. ¹H-NMR spectra were determined on a Varian-Gemini-300 MHz. and Joel-Ex-270 MHz NMR spectrometers using TMS as an internal standard. Mass spectra were determined on Finnigan Mat SSQ 7000 apparatus (Thermo Inst. Sys. Inc. USA), mode: EI, 70 eV. The purity of the synthesized compounds was tested by thin layer chromatography (TLC) on Merck Silica gel F254 plates (0.2 mm) using solvent system chloroform/methanol (3:1, v/v) and visualization under UV lamp.

2-[(*E*)-2-Furan-2-yl-vinyl]-benzo[d][1,3]oxazine-4one (1)

Condensation of a mixture of anthranilic acid (13.7 g, 0.1 mol) and furylacryloyl chloride (31.3 g,





0.2 mol) in pyridine (300 mL). The mixture was shaken for 5 min and then set aside at room temperature for further 1 h, with occasional shaking. The reaction mixture was poured into cold water (2 L) with stirring and the precipitate was filtered off. It was washed with cold water to remove pyridine and recrystallized from dioxane to give compound **1** with m.p. 135-137°C and yield 85%. Analysis: for C₁₄H₉NO₃, M.w. 239.2. Calcd.: %C, 70.29; H, 3.79; N, 5.85. Found: %C, 70.25; H, 3.63; N, 5.69. IR: (KBr, cm⁻¹) 3303 (C-H aromatic), 1732 (C=O of quinazoline), 1630 (C=N) and at 1593 (C=C). ¹H-NMR (DMSO-d₆, δ ppm): 7.30-7.75 (11H, m, aromatic H including 3 H of the furan ring). MS (m/z): 239.37 (9.3%) – M⁺.

3-(4-Acetylphenyl)-2-[(E)-2-(2-furyl) vinyl] -(3H)-quinazolin-4-one (2)

A mixture of 1 (2.3 g, 0.0 1 mol) and p-aminoacetophenone (1.35 g, 0.01 mol) was heated at 150° C on sand bath for 45 min. After cooling, the crude mass was crystallized from ethanol twice to give reddish brown crystals with m.p. 183-185°C and yield 2.7 g (0.007 mol, 80%). Analysis: for $C_{22}H_{16}N_2O_3$, M.w. 356.37. Calcd.: %C, 74.15; H, 4.53; N, 7.86. Found: %C, 74.10; H, 4.45; N, 7.83. IR (KBr, cm⁻¹): 3303 (C-H aromatic), 1732 (C=O of quinazoline), 1670 (C=O of ketone), 1630 (C=N) and at 1593 (C=C). ¹H-NMR (DMSO-d₆, δ ppm): 2.45 (3H, s, COCH₃), 6.55-6.85 (2H, dd, CH=CH), 7.30-7.75 (11H, m, aromatic H including 3H of the furan ring). MS (m/z): 356.37 (9.1%) – M⁺., 120.9 (100%).

General procedure for the preparation of chalcones (**3a-e**)

A mixture of compound 2 (0.01 mol) the appropriate aromatic aldehyde namely, benzaldehyde, p-hydroxy, p-methoxy, p-N,N-dimethyl- benzaldehydes and/or 2-thiophenecarboxaldehyde and two drops of piperidine were heated for 2-4 h. The reaction mixture was cooled and triturated with ethanol then filtered off, air dried and then crystallized from the proper solvent to give compounds **3a-e**.



Scheme 3.

 $2-[(E)-2-Furan-2-yl-vinyl]-3-{4-[(E)-3-(4-phenyl)-acryloyl]-phenyl}-3H-quinazolin-4-one (3a)$

Crystallized from ethanol, yellowish white crystals, m.p. 195-197°C, yield 3.1 g (0.006 mole, 70%). Analysis: for $C_{29}H_{20}N_2O_3$, M.w. 444.41. Calcd.: %C, 78.36; H, 4.53; N, 6.30. Found: %C, 78.30; H, 4.48; N, 6.25. IR (KBr, cm⁻¹): 1710, 1660 (2 C=O), 1600 (C=N), 1160, 1200 (cyclic ether). MS (m/z): 444.49 (35.42%) – M⁺.

 $2-[(E)-2-Furan-2-yl-vinyl]-3-{4-[(E)-3-(4-hydroxy-phenyl)-acryloyl]-phenyl}-3H-quinazolin-4-one (3b)$

Crystallized from ethanol to give brown crystals with m.p. 218-222°C, yield 2.9 g (0.006 mol, 65%). Analysis: for $C_{29}H_{20}N_2O_4$, M.w. 460.49. Calcd.: %C, 75.64; H, 4.37; N, 6.08. Found: %C, 75.60; H, 4.31; N, 6.04. IR (KBr, cm⁻¹): 3440 (-OH), 1720 (C=O of quinazoline), 1665 (C=O of ketone) and 1610 (C=N).

2-[(*E*)-2-Furan-2-yl-vinyl]-3-{4-[(*E*)-3-(4-methoxy-phenyl)-acryloyl]-phenyl}-*3H*-quinazolin-4-one (**3c**)

Crystallized from ethanol to give dark orange crystals, m.p. > 300° C decomp., yield 3.2 g (0.006 mol, 68%). Analysis: for C₃₀H₂₂N₂O₄, M.w. 474.51.



Scheme 4.

Calcd.: %C, 75.93; H, 4.67; N, 5.90. Found: %C, 75.85; H, 4.60, N, 5.88. IR (KBr, cm⁻¹): 1700 (C=O of quinazoline), 1660 (C=O of chalcone), 1600 (C=N), 1585 (C=C) and 1160, 1230 (cyclic ether). MS (m/z): 474.4 (0.5%) M⁺, 284 (100%).

3-{4-[(*E*)-3-(4-Dimethylaminophenyl)-acryloyl]phenyl}-2-[(*E*)-2-furan-2-yl-vinyl]-*3H*-quinazolin-4-one (**3d**)

Crystallized from chloroform to give orange crystals with m.p. 205-207°C, yield 3.1 g (0.006 mol, 65%). Analysis: for $C_{31}H_{25}N_3O_3$, M.w. 487.56. Calcd.: %C, 76.37; H, 5.17; N, 8.62. Found: %C, 76.35; H, 5.11; N, 8.60. 'H-NMR (DMSO-d₆, δ ppm): 3.00 (6H, s, N(CH₃)₂), 6.60-6.80 (4H, dd, 2 CH=CH), 7.30-8.60 (15H, m, aromatic H including 3 H of the furan ring). MS (m/z): 487.2 (3.65%) -M⁺, 266.1 (100%).

2-[(*E*)-2-Furan-2-yl-vinyl]-3-{4-[(*E*)-3-thiophen-2-yl-acryloyl)-phenyl]-*3H*-quinazolin-4-one (**3e**)

Crystallized from ethanol to give dark yellow crystals, m.p. 120-122°C, yield 2.6 g (0.005 mol, 59%). Analysis: for $C_{27}H_{18}N_2O_3S$, M.w. 450.52. Calcd.: %C, 71.98; H, 4.03; N, 6.22. Found: %C, 71.90; H, 3.28; N, 6.15.

2-[(*E*)-2-Furan-2-yl-vinyl]-3-{4-[5-(4-methoxyphe-nyl)-4,5-dihydro-*1H*-pyrazol-3-yl]-phenyl}-*3H*-qui-nazolin-4-one (**4a**)

A mixture of compound **3c** (2.37 g, 0.005 mol) and hydrazine hydrate (0.005 mol, 98%) in absolute ethanol (25 mL) was heated under reflux for 8 h. After cooling, the separated solid was filtered off, air dried and crystallized from ethanol to give **4a** with m.p. 153-155°C, yield 1.3 g (0.002 mole, 55%). Analysis: for $C_{30}H_{24}N_4O_3$, M.w. 488.55. Calcd.: %C, 73.75; H, 4.95; N, 11.46. Found: %C, 73.70; H, 4.89; N, 11.40. IR (KBr, cm⁻¹): disappearance of the band at 1660 (C=O), characteristic bands at 1750 (C=O), 1635 (C=N), 1170, 1245 (cyclic ether). MS (mz): 488.55 (17.80%) – M⁺.

2-[(*E*)-2-Furan-2-yl-vinyl]-3-{4-[5-(4-methoxyphe-nyl)-4,5-dihydro-1-phenylpyrazol-3-yl]-phenyl}-*3H*-quinazolin-4-one (**4b**)

A mixture of compound 3c (2.37 g, 0.005 mol) and phenyl hydrazine (0.005 mol) in acetic acid (5 mL) was refluxed for 6 h. After cooling, ice-cold water was added and the formed solid was filtered off, washed with water, air dried and crystallized from ethanol to give **4b** with m.p. 145-147°C and yield 1.4 g) (0.002 mol, 50%). Analysis: for $C_{36}H_{28}N_4O_3$, M.w. 564.65. Calcd.: %C, 76.57; H, 4.49; N, 9.92. Found: %C, 76.45; H, 4.43; N, 9.52. IR (KBr, cm⁻¹) disappearance of the band at 1660 (C=O of chalcone) and characteristic bands at 1750 (C=O), 1631 (C=N), 1597 (C=C). ¹H-NMR spectrum (DMSO-d₆, δ ppm): 2.80 (2H, d, CH₂ of pyrazoline), 3.85 (3H, s, OCH₃), 4.75 (1H, t, CH of pyrazoline), 6.55-6.90 (2H, dd, CH=CH), 7.20-8.50 (20H, m, aromatic H interfering with 3H of the furan ring). MS (m/z): 564.65 (23.40%) – M⁺.

General procedure for the preparation of the isoxazolinyl derivatives (**5a**,**b**)

A mixture of 3c or 3d (0.005 mol) and hydroxylamine hydrochloride (0.005 mol) in sodium hydroxide solution (0.5 g NaOH in 2.5 mL of water) in ethanol (60 mL) was refluxed for 6-8 h. After cooling, the reaction mixture was diluted with ice-cold water and the formed solid was filtered off, washed with water, air dried and crystallized from ethanol.

2-[(*E*)-2-Furan-2-yl-vinyl]-3-{4-[5-(4-methoxyphe-nyl)-4,5-dihydroisoxazol-3-yl]-phenyl}-*3H*-quina-zolin-4-one (**5a**)

M.p. 245-247°C, yield 1.3 g, (0.002 mol, 55%). Analysis: for $C_{30}H_{23}N_3O_4$, M.w. 489.53. Calcd.: %C, 73.60; H, 4.73; N, 8.58. Found: %C, 73.86; H, 4.68; N, 8.55. IR (KBr, cm⁻¹): 1750 (C=O), 1559 (C=C), 1015, 1089 (cyclic ether). 'H-NMR (DMSOd₆, δ ppm): 3.80 (3H, s, OCH₃), 3.90 (2H, d, CH₂), 5.50 (1H, t, CH), 6.70-8.35 (17H, m, aromatic H including the system CH=CH and interfering with 3H of the furan ring). The mass spectrum showed the molecular ion peak (M⁺, C₃₀H₂₃N₃O₄) at m/z 489.53 (27.35%).

2-[(*E*)-2-Furan-2-yl-vinyl]-3-{4-[5-(4-dimethylaminophenyl)-4,5-dihydroisoxazol-3-yl]-phenyl}-*3H*-quinazolin-4-one (**5b**)

M.p. 236-238°C, yield 1.9 g (0.003 mol, 58%). Analysis: for $C_{31}H_{26}N_4O_3$, M.w. 502.58. Calcd.: %C, 74.08; H, 5.21; N,11.14. Found: %C, 74.02; H, 5.10; N, 11.09. IR (KBr, cm⁻¹): disappearance of the band of chalcone at 1660, characteristic bands at 1750 (C=O of quinazoline), 1630 (C=N), 1558 (C=C). MS (m/z): 502.58 (19.34%) M⁺.

3-{4-[6-(4-Dimethylaminophenyl)-2-oxo-1,2,5,6tetrahydropyrimidin-4-yl]-phenyl}-2-[(E)-2-furan-2-yl-vinyl]-*3H*-quinazolin-4-one (**6a**)

A mixture of compound 3d (0.487 g, 0.001 mol) and urea (0.1 g, 0.001 mol) in ethanol (20 mL) and conc. hydrochloric acid (5 mL) was refluxed for 7 h.

The reaction mixture was then concentrated to half of its volume, cooled and neutralized with ammonium hydroxide. The precipitated solid was filtered off, washed with water, air dried and crystallized from ethanol to give **6a** with m.p. 290-292°C, yield 0.3 g (0.0005 mol, 60%). Analysis: for $C_{32}H_{27}N_5O_3$, M.w. 529.59. Calcd.: %C, 72.57; H, 5.13; N,13.22. Found: %C, 72.62; H, 5.18; N, 13.30. IR (KBr, cm⁻¹): broad band at 3200-3600 (OH), 1720 (C=O), 1618 (C=N), 1590 (C=C). ¹H-NMR (DMSO-d₆, δ ppm): 3.00 (6H, s, N(CH₃)₂), 3.70 (2H, d, CH₂ pyrimidinone ring), 6.50-6.85 (2H, dd, CH=CH), 7.00-8.20 (16H, m, aromatic H interfering with 3 H of the furan ring and CH proton of pyrimidinone ring), 10.95 (1H, s, NH). MS (m/z): 529 (21.34%) – M⁺.

3-{4-[6-(4-Dimethylaminophenyl)-2-thioxo-1,2,5,6-tetrahydropyrimidin-4-yl]-phenyl}-2-[(*E*)-2furan-2-yl-vinyl-*3H*-quinazolin-4-one (**6b**)

A mixture of compound **3d** (0.487 g, 0.001 mol), thiourea (0.11 g, 0.001 mol) and sodium hydroxide (0.1 g) in 25 mL of 80% ethanol was refluxed for 6 h. The reaction mixture was concentrated under vaccum, cooled and neutralized with ammonium hydroxide solution. The formed solid was filtered off, washed with water, dried and then crystallized from ethanol to give **6b** with m.p. 297-299°C, yield 0.35 g (0.0006 mol, 65%). Analysis: for $C_{32}H_{27}N_5O_2S$, M.w.545.66. Calcd.: %C, 70.43; H, 4.98; N,12.83. Found: %C, 70.39; H, 4.90; N, 12.80, IR (KBr, cm⁻¹) 3221 (NH), 1753 (C=O of quinazoline), 1645 (C=N), 1590 (C=C) and at 1273 (C=S).

General method for preparation of thiosemicarbazone derivatives (7a-d)

A mixture of compound **6** (3.56 g, 0.01 mol) and (0.01 mol) of the appropriate substituted thiosemicarbazide, namely: cyclohexylthiosemicarbazide, phenylthiosemicarbazide, benzoylthiosemicarbazide or 4-chlorophenylthiosemicarbazide in absolute ethanol (25 mL) was refluxed for 6-8 h. The reaction mixture was cooled and the formed solid was filtered off, air dried and recrystallized from the proper solvent to give compounds **7a-d** in $\approx 60-65\%$ yield.

3-[4-(ω -Cyclohexylthiosemicarbazone- α ethyl)phenyl]-2-[(*E*)-2-(2-furyl)vinyl]-*3H*-quinazolin-4-one (**7a**)

Crystallized from ethanol to give dark red crystals, with m.p. $320-322^{\circ}$ C. Analysis: for $C_{29}H_{28}N_5O_2$ S, M.w. 510.64. Calcd.: %C, 68.21; H,5.52; N,13.71. Found: %C, 68.38; H, 5.59; N, 13.83, IR (KBr, cm⁻¹): 3200 (NH, str), 2200 (C=N), 1730, 1660 (2C=O), 1610 (C=N), 1580 (C=C), 1100, 1205 (cyclic ether). MS (m/z) 507.40 (0.3%) – M*-1, 120 (100%).

3-[4-(ω -Phenylthiosemicarbazone- α -ethyl) phenyl]-2-[(*E*)-2-(2-furyl)vinyl]-*3H*-quinazolin-4-one (**7b**)

Crystallized from ethanol to give dark yellow crystals, with m.p. 247-249°C. Analysis: for $C_{29}H_{23}N_5O_2S$, M.w. 505.60. Calcd.: %C, 68.89; H, 4.58; N, 13.85. Found: %C, 68.73; H, 4.36; N, 13.80. 'H NMR (DMSO-d₆, δ ppm): 6.60-6.90 (2H, dd, CH=CH), 7.15-7.95 (16H, m, aromatic H including CH proton of the pyridone ring and interfering with 3 H of the furan ring), 11.35 (1H, s, NH) and at 13.01 (1H, s, OH).

3-[4-(ω -Benzoylthiosemicarbazon- α -ethyl)phenyl]-2-[(*E*)-2-(2-furyl)vinyl]-3*H*-quinazolin-4-one (7c)

Crystallized from acetic acid to give brown crystals, with m.p. 258-260°C. Analysis: for $C_{30}H_{23}N_5O_3S$, M.w. 533.61. Calcd.: %C, 67.52; H, 4.34; N, 13.12. Found: %C, 67.61; H, 4.48; N, 13.20. MS (m/z) 538.56 (33.15%) – M⁺.

 $3-[4-(\omega-Chlorophenylthiosemicarbazone-\alpha-ethyl)phenyl]-2-[(E)-2-(2-furyl)vinyl]-3H-quina$ zolin-4-one (7d)

Crystallized from acetic acid to give yellowish brown crystals, with m.p. 265-267°C Analysis: for $C_{29}H_{22}N_5O_2SCl$, M.w. 540.04. Calcd.: %C, 64.49; H, 4.10; N, 12.96. Found: %C, 64.39; H, 4.03; N, 12.80. IR (KBr, cm⁻¹): 3400 (NH), 2200 (C=N), 1755, 1655 (2C=O), 1600 (C=N), 1570 (C=C). 'H NMR (DMSO-d₆, δ ppm): 3.80 (9H, s, 30CH₃), 6.15-6.25 (2H, dd, CH=CH), 7.15-8.05 (14H, m, aromatic H including 1H of pyridone ring and interfering with 3H of the furan ring) and at 9.45 (1H, s, NH).

General method of preparation of thiazoline derivatives (8a,b)

To a solution of compound 7c or 7d (0.01 mol) in absolute ethanol (20 mL), the phenacyl bromide (0.01 mol) was added. The reaction mixture was heated under reflux for 8 h, concentrated under reduced pressure and cooled. The formed precipitate was filtered off and recrystallized from aqueous ethanol to give the title compounds.

 $3-[4-(1-{[3-(Benzoyl)-4-phenyl-3H-thiazol-(2Z)-ylidene]-hydrazone}-ethyl) phenyl]-2-[(E)-2-(2-furan-2-yl-vinyl)]-3H-quinazolin-4-one (8a)$

M.p. 187-189°C, yield 4.3 g (0.006 mole, 68%). Analysis: for $C_{38}H_{27}N_5O_3S,\ M.w.\ 633.73.$

Calcd.: %C, 72.02; H, 4.29; N, 11.05. Found: %C, 72.12; H, 4.35; N, 11.15.

 $\label{eq:2.1} \begin{array}{l} 3-[4-(1-\{[3-(4-chlorophenyl)-4-phenyl-3H-thiazol-(2Z)-ylidene]-hydrazone\}-ethyl)-phenyl]-2-[(E)-2-furan-2-yl-vinyl]]-3H-quinazolin-4-one (8b) \end{array}$

M.p. 200-202°C, yield 4.1 g (0.006 mole, 65%). Analysis: for $C_{37}H_{26}N_5O_2SCl$, M.w. 640.17. Calcd.: %C, 69.42; H, 4.09; N, 10.93. Found: %C, 69.37; H, 3.97; N, 10.88.

General method for preparation of iminopyridens (9a-c)

A mixture of compound **2** (3.5 g, 0.01 mol), malononitrile (0.6 mL, 0.01 mol), anhydrous ammonium acetate (6.1 g, 0.8 mol) and the appropriate aldehyde, namely, benzaldehyde, p-hydroxybenzaldehyde or p-methoxybenzaldehyde (0.01 mol) in n-butanol (30 mL) was refluxed for 3-5 h. After cooling, the reaction mixture was filtered off and recrystallized from the proper solvent to give the compounds (9a-c) in \approx 65-75% yield.

6-{4-[2-(2-Furan-2-yl-vinyl)-4-oxo-*4H*-quinazolin-3-yl]-phenyl}-2-imino-4-phenyl-1,2,-dihydropyridine-3-carbonitrile (**9a**)

Crystallized from acetic acid to give brown crystals, with m.p. 218-220°C. Analysis: for $C_{32}H_{21}N_5O_2$, M. 507.55. Calcd.: %C, 75.72; H, 4.17; N, 13.79. Found: %C, 75.79; H, 4.23; N, 13.90. IR (KBr, cm⁻¹): 3120 (NH), 2200 (C=N), 1735 (C=O), 1640 (C=N), 1500 (C=C), 1100, 1240 (cyclic ether).

6-{4-[2-(2-Furan-2-yl-vinyl)-4-oxo-*4H*-quinazolin-3-yl]-phenyl}-2-imino-4-hydroxyphenyl-1,2,-dihydro-pyridine-3-carbonitrile (**9b**)

Crystallized from DMF to give reddish brown crystals, with m.p. $361-363^{\circ}$ C. Analysis: for $C_{32}H_{21}N_5O_3$, M.w. 523.54. Calcd.: %C, 73.41; H, 4.04; N, 13.38. Found: %C, 73.38; H, 4.00; N, 13.25, IR (KBr, cm⁻¹): 3480-3240 (OH), 3400 (NH), 2200 (C=N), 1740 (C=O), 1600 (C=N), 1560 (C=C). MS (m/z): 523.54 (45.50%) – M⁺.

6-{4-[2-(2-Furan-2-yl-vinyl)-4-oxo-*4H*-quinazolin-3-yl]-phenyl}-2-imino-4-methoxyphenyl-1,2,-dihydropyridine-3-carbonitrile (**9c**)

Crystallized from acetic acid to give dark brown crystals, with m.p. 340-342°C. Analysis: for $C_{33}H_{23}N_5O_3$, M.w. 537.57. Calcd.: %C, 73.73; H, 4.31; N, 13.02. Found: %C, 73.79; H, 4.4;5 N, 13.11. IR (KBr, cm⁻¹): 3360 (NH), 2200 (C§N), 1740 (C=O), 1600 (C=N), 1570 (C=C), 1120, 1255 (cyclic ether). 'H NMR (DMSO-d₆, δ ppm): 3.73 $(3H, s, OCH_3)$, 6.65-6.85 (2H, dd, CH=CH), 7.25-8.00 (16H, m, aromatic H including 1H of the iminopyridine ring and interference with 3 H of the furan ring), 9.60, 11.80 (2H, 2s, 2NH).

General method for preparation of pyridones (10a-d)

A mixture of compound **2** (0.71 g, 0.002 mol), ethyl cyanoacetate (0.23 mL, 0.002 mol), anhydrous ammonium acetate (1.24 g, 0.016 mol) and the appropriate aldehydes, namely: benzaldehyde, phydroxybenzaldehyde, p-methoxybenzaldehyde, or 3,4,5-trimethoxybenzaldehyde (0.002 mol) in nbutanol (10 mL) was refluxed for 5-7 h. The reaction mixture was concentrated to half of its volume under reduced pressure. After cooling the formed precipitate was filtered off, air dried and recrystallized from the proper solvent to give the title compounds.

6-{4-[2-(2-Furan-2-yl-vinyl)-4-oxo-*4H*-quinazolin-3-yl]-phenyl}-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile (**10a**)

Crystallized from ethanol to give brown crystals, with m.p. 170-173°C, nd yield 0.7 g (0.001 mol, 70%). Analysis: for $C_{32}H_{20}N_4O_3$, M.w. 508.54. Calcd.: %C, 75.57; H, 3.96; N, 11.01. Found: %C, 75.61; H, 3.99; N, 10.13. MS (m/z): 511.5 (2.3%) – M⁺ + 1, 121 (100%).

6-{4-[2-(2-Furan-2-yl-vinyl)-4-oxo-*4H*-quinazolin-3-yl]-phenyl}-2-oxo-4-hydroxyphenyl-1,2-dihydropyridine-3-carbonitrile (**10b**)

Crystallized from acetic acid to give dark brown powder, with m.p. 255-257°C and yield 0.7g (0.001 mol, 75%). Analysis: for $C_{32}H_{20}N_4O_4$, M.w. 524.54. Calcd.: %C, 73.27; H, 3.84; N, 10.68. Found: %C, 73.31; H, 3.90; N, 10.71. IR (KBr, cm⁻¹): 3360 (NH), 1720 (C=O), 1640 (C=N), 1610 (C=C), 1270 (C=S). ¹H NMR (DMSO-d₆, δ ppm): 2.30 (3H, s, C-CH₃), 3.05 (3H, s, NH-CH₃), 6.15-6.40 (2H, dd, CH=CH), 7.30-8.15 (11H, m, aromatic H interfering with 3H of the furan ring), 8.55, 13.25 (2H, 2s, 2NH exchangeable with D₂O).

6-{4-[2-(2-Furan-2-yl-vinyl)-4-oxo-*4H*-quinazolin-3-yl]-phenyl}-2-oxo-4-methoxyphenyl-1,2-dihydropyridine-3-carbonitrile (**10c**)

Crystallized from acetic acid to give reddish brown crystals, with m.p. $260-262^{\circ}$ C, yield 0.7 g, (0.001 mol, 75%). Analysis: for C₃₃H₂₂N₄O₄, M.w. 538.56. Calcd.: %C, 73.59; H, 4.11; N, 10.40. Found: %C, 73.50; H,;4.05; N, 10.32. IR (KBr, cm⁻¹): 3240 (NH), 1720 (C=O of quinazoline), 1680 (C=O of benzoyl), 1620 (C=N), (C=C). MS (m/z): the molecular ion peak expected at m/z 533.4 is not recorded, 120.1 (100%). 6-{4-[2-(2-Furan-2-yl-vinyl)-4-oxo-*4H*-quinazolin-3-yl]-phenyl}-2-oxo-4-(3,4,5-trimethoxyphenyl-1,2-dihydropyridine-3-carbonitrile (**10d**)

Crystallized from ethanol to give dark red crystals, with m.p. 283-285°C, yield 0.8 g, (0.001 mol, 75%). Analysis: for $C_{35}H_{26}N_4O_4$, M.w. 566.63. Calcd.: %C, 74.19; H, 4.62; N, 9.88. Found: %C, 74.10; H, 4.53; N, 9.80. 'H NMR (DMSO-d₆, δ ppm): 2.40 (3H, s, C-CH₃), 6.30-6.60 (2H, dd, CH=CH), 7.30-8.20 (15H, m, aromatic H interfering with 3H of the furan ring), 10.75, 11.65 (2H, 2s, 2NH).

BIOLOGICAL ACTIVITY

Antimicrobial activity test

Some representative samples of the prepared compounds were tested against local strains of bacteria and fungi using chloramphenicol as a control.

Escherichia coli as Gram positive and *Staphylococcus aureus* as Gram negative bacteria, *Candida albicans* as yeast and *Aspergillus niger* as fungi were used. The test was performed according to the disk-diffusion method (23).Whatman No. 1 filter paper disks (5 mm) were impregnated with the tested compounds (500 mg/disk) and were placed on the surface of the cold medium in Petri dishes, inoculated with the considered local microorganisms incubated at 5°C for 1 h to permit a good diffusion and then transferred to an incubator at 37°C for 24 h for bacteria and 28°C for 72 h for fungi.

From the data obtained (Table 1), it is clear that compounds **4a,b** and **9a,b** show moderate activity towards Gram positive bacteria compared with the control, whereas the rest of the compounds show slight activity towards the same organism. Compounds **4a** and **4b** show moderate activity towards Gram negative bacteria, whereas the rest of the tested compounds show slight activity compared with the control. All the compounds tested show slight activity towards the yeast. Moreover, compounds **9a** and **9b** show moderate activity towards fungus *A. niger* compared with the control, whereas the rest of the tested compounds show moderate activity.

ANTIINFLAMMATORY EFFECT OF SOME NEW QUINAZOLIN-4-ONE DERIVATIVES

Material and Methods

Animals

Male albino rats weighing 150 g were obtained from the animal house, National Research Centre. They were housed in air conditioned room and fed

	Microorganism / inhibition zone (nm)					
Compound	Gram positive	Gram negative	Yeast	Fungi		
No.	Escherichia. Coli	Staphylococcus aureus	Candida albicans	Aspergillus niger		
Control	+++	+++	+++	++		
1	+	+	+	+		
2	+	+	+	+		
3b	+	+	+	+		
3c	+	+	+	+		
3d	+	+	+	+		
3e	+	+	+	+		
4a	++	++	+	+		
4b	++	++	+	+		
6a	+	++	+	+		
6b	+	++	+	+		
7b	+	+	+	+		
9a	++	+	+	++		
9b	++	+	+	++		
10b	+	+	+	+		
10c	+	+	+	+		
10d	+	+	+	+		

Table 1. The results of preliminary screening test.

Control: chloramphenicol; inhibition zones: +++ = highly active (> 12 mm); ++ = moderately active (9-12 mm); + = slightly active (6-9 mm)

Group	Edema rate (%)					
	1 h	2 h	3 h	4 h		
Control	37.1 ± 5.6	62.0 ± 9.2	63.2 ± 12.4	50.5 ± 9.3		
1	25.5 ± 2.7* (31.3)	44.6 ± 13.8* (28.1)	45.1 ± 4.9* (28.6)	35.3 ± 4.2* (30.1)		
9a	38.2 ± 2.0	62.8 ± 3.4	64.4 ± 7.4	53.0 ± 9.8		
10a	36.7 ± 4.7	60.1 ± 3.8	62.1 ± 6.5	49.3 ± 8.9		
10b	$22.9 \pm 3.2*$ (38.3)	50.7 ± 5.3* (18.2)	$42.3 \pm 5.6^{*}$ (33.1)	33.4 ± 3.7* (33.9)		
10c	36.5 ± 5.8	61.2 ± 4.9	61.8 ± 3.7	50.1 ± 6.5		
Indomethacin	18.1 ± 3.6* (51.2)	38.0 ± 6.4* (38.7)	30.6 ± 6.0* (51.6)	26.1 ± 8.8* (48.3)		

Table 2. Effects of new quinazolin-4-one derivatives on carrageenan induced paw edema in rats.

Values represent the mean \pm S.D. of six animals for each group. Each value in parenthesis indicates the percentage of inhibition rate. Statistically significant from control * p < 0.005.

with a standard laboratory diet and tap water throughout the experiments.

Tested compounds

Due to water insolubility of the tested compounds, they were dissolved in DMSO. The control animals were injected (*i.p.*) with appropriate volume of DMSO. The standard drug used was indomethacin (10 mg/kg, Cairo for Pharmaceutical and Chemical Industry, Cairo Egypt).

Antiinflammatory test was performed according to the method of Winter et al. (24). Edema in the left hind paw of rat was induced by injection of 0.05 mL of 1% (w/v) carrageenan (Sigma, St. Louis, MO) in saline into the footpad, subcutaneously. The paw volume of each rat was measured before carrageenan injection and then at hourly intervals up to four times with Plethysmometer 7150 (Ugo Basile, Italy). The test compounds (9 mg/kg b.w.) were administered *i.p.* 1 h before carrageenan injection. The animals in the control group received DMSO only. Another group of rats was administered with indomethacin as standard reference. The edema rate and inhibition rate of each group were calculated (Table 2).

It was found that compounds 1 and 10b have significant anti-inflammatory activity comparable with indomethacin but compounds 9a, 10a and 10c have no significant activity of this type.

Statistical analysis

Data were expressed as the mean \pm S.D. and statistically assessed by one-way analysis of variance (ANOVA).

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