European Journal of Chemistry 2 (4) (2011) 455-462

European Journal of Chemistry

Journal homepage: www.eurjchem.com

Novel 4(3*H*)-quinazolinones containing biologically active thiazole, pyridinone and chromene of expected antitumor and antifungal activities

Khairy Abdel Hameed Mohsen El-Bayouki[a], Wahid Mohamed Basyouni[a], Yahia Abdel Fatah Mohamed[b], Mohsen Mohamed Aly[b] and Samir Youssef Abbas[a,*]

[a] *Organometallic and Organometalloid Chemistry Department, National Research Centre, Cairo, 12311, Egypt*
[b] *Department of Chemistry, Faculty of Science, Al-Azhar University, Cairo, 11884, Egypt*

**Corresponding author at: Organometallic and Organometalloid Chemistry Department, National Research Centre, Cairo, 12311, Egypt. Tel.: +202.33335929; fax: +202.33370931. E-mail address: samiryoussef98@yahoo.com (S.Y. Abbas).*

ARTICLE INFORMATION

Received: 16 June 2010
Received in revised form: 19 January 2011
Accepted: 03 February 2011
Online: 31 December 2011

KEYWORDS

4(3*H*)-Quinazolinone
Thiazole
Pyridinone
Chromene
Antitumor
Antifungal activity

ABSTRACT

Novel 4(3*H*)-quinazolinone derivatives with biologically active moieties were synthesized. Reactions of 2-cyano-*N*-(6-iodo-2-methyl-4-oxoquinazolin-3(4*H*)-yl) acetamide with carbon disulfide, isothiocyanates followed by cycloalkylation afforded acrylamide, 1,3-dithiazole, 1,3-dithiane, thiazole and pyrazole derivatives. The 2-pyridone derivatives were obtained via reaction of cyanoacetamide with some acetylacetone or arylidenes. Cyclocondensation reaction of cyanoacetamide with *o*-hydroxy aldehydes furnished chromene derivatives. Screening for some selected compounds was carried for their potential antitumor and antifungal activities. 2-Cyano-*N*-(6-iodo-2-methyl-4-oxoquinazolin-3(4*H*)-yl)-2-(4-methyl-3-phenyl-thiazol-2(3*H*)ylidene)-acetamide with 3-side chain incorporated with substituted thiazole moiety was found to be of high to moderate activity towards cells. Also, the latter product showed high activity against *Aspergillus ochraceus* Wilhelm with inhibition zone (18 mm) compared with (20 mm) Nystatin inhibition zone.

1. Introduction

The chemistry of 4(3*H*)-quinazolinone system has received an increasing interest because of its biological significance. Many derivatives of this system showed antifungal [1], antibacterial [2], antitumor [3], antiinflammatory [4], anticonvulsant [5-7], analgesic [8,9] and anti-tuberculosis [10,11] activities. Cyanoacetamides are highly reactive compounds. The carbonyl and the cyano functions of these compounds are suitably situated to enable reactions with common reagents to form a variety of heterocyclic compounds. Also, the active methylene of cyanoacetamide can take part in a variety of condensation and substitution reactions. Moreover, cyanoacetamides and their related heterocyclic derivatives have generated great attention due to their interesting biological, therapeutic value and pharmaceutical activities e.g. as herbicidal [12] plant growth regulators [13] anti-inflammatory [14] anti-tumor [15] and analgesic properties [16]. Therefore, it was aimed in the present investigation to synthesize and characterize newer 4(3*H*)-quinazolinone derivatives for their expected antitumor and antimicrobial activities.

2. Experimental

2.1. Instrumentation

All melting points are uncorrected. Microanalyses were carried out by the Microanalytical Laboratory, National Research Centre, Cairo, Egypt and the Microanalytical Center, Cairo University. Infrared spectra (KBr disc) were recorded using a Jasco FT/IR-300E spectrophotometer and FTIR 5300 spectrometer (ν, cm^{-1}). ^1H NMR spectra were recorded using Varian mercury 300 MHz or Varian Gemini 200 MHz with chemical shift in δ from Me_4Si and Jeol 270, 500 MHz. Mass spectra were recorded on GC/MS Finnigan SSQ 7000 spectrophotometer &or GC Ms-QP 1000 EX mass spectrometer at 70 eV.

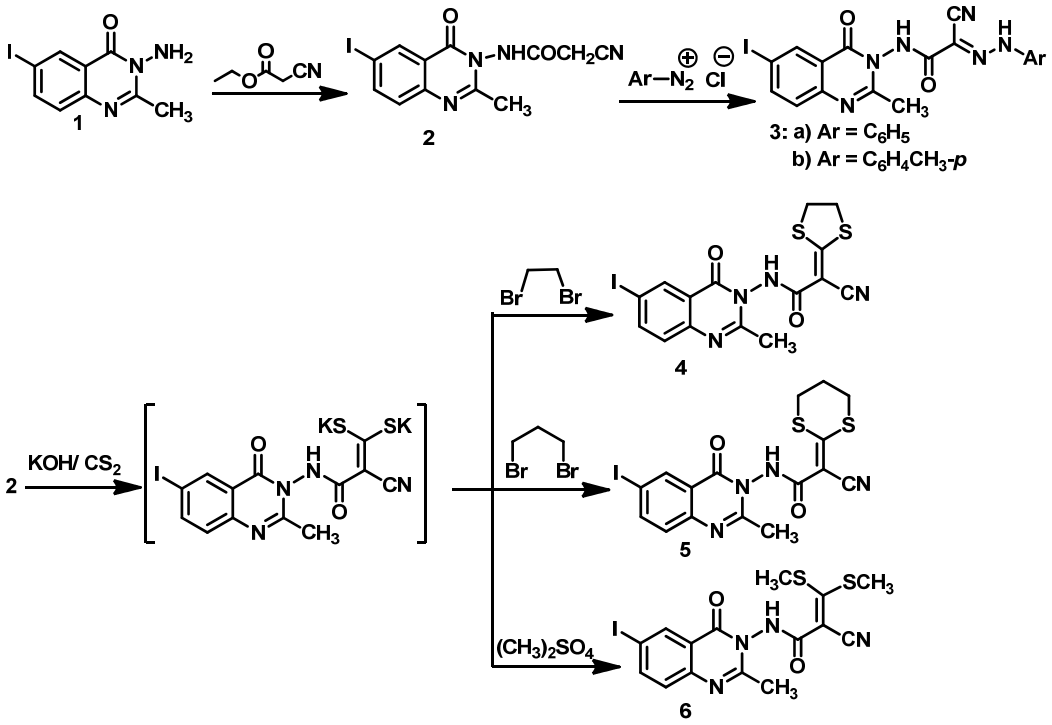
2.2. Synthesis

2.2.1. 2-Cyano-N-(6-iodo-2-methyl-4(3H)-quinazolinon-3-yl) acetamide (2)

3-Amino-quinazolinone, **1**, (0.01 mol) was fused with excess ethyl cyanoacetate at ~210 °C in an oil-bath for 40 min. Excess ethyl cyanoacetate was evaporated under vacuum. The solid product remained was triturated with ethanol (20 mL) then filtered. The ethanolic filtrate was poured onto crushed ice. The solid product obtained was filtered and crystallized from toluene:ethyl acetate (1:1) to give **2** as yellow brownish crystals (Scheme 1). Yield: 80%. M.p.: 215-217 °C. FT-IR (ν, cm^{-1}): 3210 (NH), 2264 (C≡N), 1690 (C=O). ^1H NMR (DMSO-d_6, δ, ppm): 2.39 (s, 3H, CH_3), 4.10 (m, 2H, CH_2), 7.43 (d, 1H, *J* = 8.40 Hz, ArH at C_8-H), 8.15 (d, 1H, *J* = 8.40 Hz, ArH at C_7-H), 8.37 (s, 1H, ArH at C_5-H), 11.57 (s, 1H, NH, D_2O-exchangeable). MS (*m/z*, %): 368 (M^+; 100). Anal. calcd for $C_{12}H_9IN_4O_2$: C, 39.15; H, 2.46; N, 15.22. Found: C, 39.10; H, 2.50; N, 15.20%.

2.2.2. General procedure for the syntheses of 2-(6-iodo-2-methyl-3(4H)-quinazolinonylamino)-2-oxo-N'-p-arylaceto-hydrazonoylcyanide (3a,b)

ISSN 2153-2249 (Print) / ISSN 2153-2257 (Online)
DOI:10.5155/eurjchem.2.4.455-462.171



Scheme 1

To aromatic amine (0.01 mole) concentrated HCl (3 mL) was added and cooled to ~0-5 °C in ice bath then cooled sodium nitrite solution (1.0 g in 10 mL of water) was added to the mixture drop wise during 10 minutes. The reaction mixture was then stirred for 10 minutes. A cold mixture of the cyanoacetamide derivative **2** (0.01 mole) and sodium acetate (4.10 g; 0.05 mole) in ethanol (50 mL), was then added drop wise to the reaction mixture with stirring. The stirring was continued for 30 minutes and the reaction mixture was left for 1 hour at room temperature. The solid product obtained was collected by filtration and crystallized from ethanol to give the corresponding hydrazono derivatives, **3a**,**b**, as yellow crystals (Scheme 1).

2-((6-iodo-2-methyl-4-oxoquinazolin-3(4H)-yl)amino)-2-oxo-N'-phenylacetohydrazonoyl cyanide (**3a**): Yield: 80%. M.p.: 234-236 °C. FT-IR (ν, cm^{-1}): 3228 (NH), 2216 (C≡N), 1686 (C=O). MS (*m/z*, %): 472 (M^+; 8.4), 301 (100), 473 (3.2%), 301 (18.5), 245 (9.7), 172 (4.0), 111 (5.4). Anal. calcd. for $C_{18}H_{13}IN_6O_2$: C, 45.78; H, 2.77; N, 17.80. Found: C, 45.80; H, 2.70; N, 17.80%.

2-(6-Iodo-2-methyl-4-oxoquinazolin-3(4H)-ylamino)-2-oxo-N'-p-tolylacetohydrazonoyl cyanide (**3b**): Yield: 90%. M.p.: >300 °C. FT-IR (ν, cm^{-1}): 3230 (NH), 2218 (C≡N), 1689 (C=O). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.31 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 7.15 (d, 2H, *J* = 8.08 Hz, AB system), 7.50 (d, 1H, *J* = 8.57 Hz, ArH at C_8-H), 7.61 (d, 2H, *J* = 8.08 Hz, AB system), 8.10 (d, 1H, *J* = 8.57 Hz, ArH at C_7-H), 8.40 (s, 1H, ArH at C_5-H), 11.15 (b, 1H, NH), 12.30 (b, 1H, NH). Anal. calcd. for $C_{19}H_{15}IN_6O_2$: C, 46.93; H, 3.11; N, 17.28. Found: C, 46.90; H, 3.10; N, 17.30%.

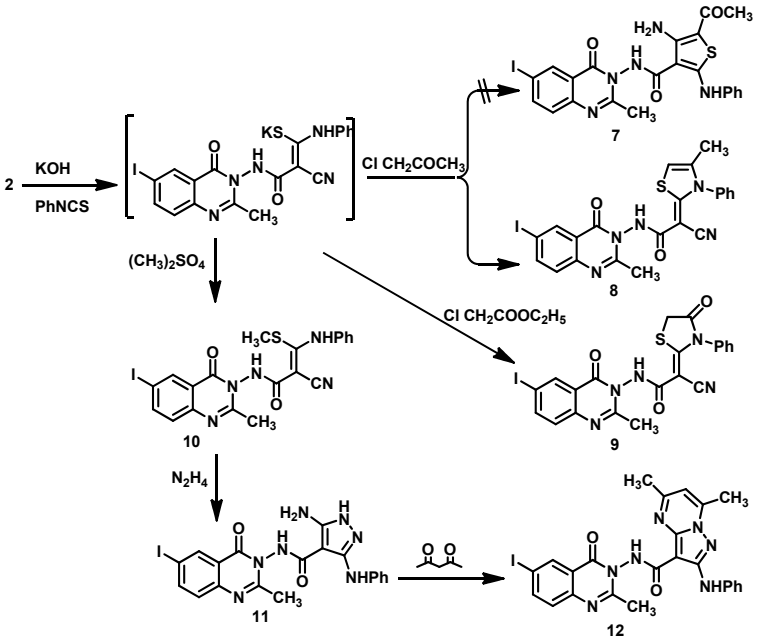
2.2.3. General procedure for synthesizing 2-cyano-2-(substituted)-N-(6-iodo-2-methyl-4(3H)quinazolinonyl) acetamides (4,5 and acrylamide 6)

To a stirred suspension of finely powdered potassium hydroxide (0.02 mole) in dry DMF (10 mL) cyanoacetamide **2** (0.01 mole) was added, the resulted mixture was cooled at 10 °C in an ice bath, then carbon disulfide (0.01 mol) was added slowly over the course of 10 min (Scheme 1). After complete addition, stirring of the reaction mixture was continued for additional 2 h. Then dibromoethane, dibromopropane or dimethylsulfate (0.01 mol) was added to the mixture while cooling (~15 °C) and stirring for 1 h. then poured into crushed ice, the resulting precipitate was filtrated off, dried and crystallized from the proper solvent to give:

2-Cyano-2-(1,3-dithiolan-2-ylidene)-N-(6-iodo-2-methyl-4-oxoquinazolin-3(4H)-yl)acetamide (**4**): As yellow brownish crystals (benzene:ethanol; 1:1). Yield: 70%. M.p.: 243-245 °C. FT-IR (ν, cm^{-1}): 3266 (NH), 2971 (CH_{aliph}), 2204 (C≡N), 1696, 1666 (C=O). ^{1}H NMR ($CDCl_3$, δ, ppm): 2.44 (s, 3H, CH_3), 3.75 (s, 4H, $2CH_2$), 7.50 (d, 1H, *J* = 8.10 Hz, ArH at C_8-H), 8.20 (d, 1H, *J* = 8.10 Hz, ArH at C_7-H), 8.42 (s, 1H, ArH at C_5-H), 11.20 (s, 1H, NH, D_2O-exchangeable). MS (*m/z*, %): 470 (M^+, 22.2), 170 (100), 471 (2.8), 172 (17.2), 75 (16.5). Anal. calcd. for $C_{15}H_{11}IN_4O_2S_2$: C, 38.31; H, 2.36; N, 11.91. Found: C, 38.30; H, 2.40; N, 11.90%.

2-Cyano-2-(1,3-dithian-2-ylidene)-N-(6-iodo-2-methyl-4-oxoquinazolin-3(4H)-yl)acetamide (**5**): As yellow brownish crystals (benzene:ethanol; 1:1). Yield: 75%. M.p.: 238-240 °C. FT-IR (ν, cm^{-1}): 3242 (NH), 2926 (CH_{aliph}), 2200 (C≡N), 1703, 1665 (C=O). ^{1}H NMR ($CDCl_3$, δ, ppm): 2.20 (p, 2H, *J* = 6.80 Hz, CH_2), 2.50 (s, 3H, CH_3), 3.05 (t, 2H, *J* = 6.60 Hz, CH_2), 3.21 (t, 2H, *J* = 6.60 Hz, CH_2), 7.42 (d, 1H, *J* = 8.50 Hz, ArH at C_8-H), 8.14 (d, *J* = 8.50 Hz, 1H, ArH at C_7-H), 8.35 (s, 1H, ArH at C_5-H), 11.06 (s, 1H, NH, D_2O-exchangeable). Anal. calcd. for $C_{16}H_{13}IN_4O_2S_2$: C, 39.68; H, 2.71; N, 11.57. Found: C, 39.70; H, 2.70; N, 11.60%.

2-Cyano-N-(6-iodo-2-methyl-4-oxoquinazolin-3(4H)-yl-3,3-bis(methylthio)acrylamide (**6**): As yellow brownish crystals (methanol). Yield: 60%. M.p.: 173-175 °C. FT-IR (ν, cm^{-1}): 3212 (NH), 2964, 2926 (CH_{aliph}), 2200 (C≡N), 1688 (C=O). MS (m/z, %): 472 (M^+, 22.2), 368 (30.9), 328 (37.8), 271 (49.0), 216 (16.9), 172 (14.8), 116 (18.6), 75 (43.8). Anal. calcd. for $C_{15}H_{13}IN_4O_2S_2$: C, 38.14; H, 2.77; N, 11.86. Found: C38.10, H, 2.80; N, 11.90%.



Scheme 2

2.2.4. 2-Cyano-N-(6-iodo-2-methyl-4(3H)-quinazolinon-3-yl)-2-(substituted) acetamide (8,9)

To a stirred suspension of finely powdered potassium hydroxide (0.01 mole) in dry DMF (10 mL) cyanoacetamide **2** (0.01 mole) was added, and then phenyl isothiocyanate (0.01 mol) was added slowly (Scheme 2). After complete addition, stirring of the reaction mixture was continued for additional 5 h. Then chloroacetone or ethyl chloroacetate (0.01 mole) was added to the mixture and the reaction mixture was stirred for 2 h. The reaction mixture was poured into crushed ice. The resulting precipitate was filtrated off, dried and crystallized to give:

2-Cyano-N-(6-iodo-2-methyl-4-oxoquinazolin-3(4H)-yl-2-(4-methyl-3-phenylthiazol-2(3H)ylidene)acetamide (**8**): As yellow brownish crystals (acetic acid). Yield: 75%. M.p.: 248-250 °C. FT-IR (ν, cm^{-1}): 2973, 2926 (CH_{aliph}), 2181 (C≡N), 1708 (C=O). ^{1}H NMR (DMSO-d_6, δ, ppm): 1.93 (s, 3H, CH_3 [thiazole]), 2.40 (s, 3H, CH_3 [quinazoline]), 7.03 (s, 1H, CH [thiazole]), 7.52 (d, 1H, *J* = 8.10 Hz, ArH at C_8-H), 7.66 (m, 5H, ArH), 8.17 (d, 1H, *J* = 8.10 Hz, ArH at C_7-H), 8.40 (s, 1H, ArH at C_5-H), 9.93 (s, 1H, NH, D_2O-exchangeable). MS (*m/z*, %): 541(M^+, 1.8), 214 (100), 327 (48.2), 243 (45.7), 187 (8.2), 116 (11.0), 75 (17.5). Anal. calcd. for $C_{22}H_{16}IN_5O_2S$: C,48.81; H, 2.98; N, 12.94. Found: C, 48.80; H, 3.00; N, 12.90%.

2-Cyano-N-(6-iodo-2-methyl-4-oxoquinazolin-3(4H)-yl)-2-(4-oxo-3-phenylthiazolidin-2-ylidene)acetamide (**9**): As yellow brownish crystals (ethanol:dioxane; 2:1). Yield: 70%. M.p.: 193-195 °C. FT-IR (ν, cm^{-1}): 3188 (NH), 2924 (CH_{aliph}), 2220 (C≡N), 1688 (C=O). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.35 (s, 3H, CH_3), 4.00 (s, 2H, CH_2[thiazole]), 7.30-7.70 (m, 6H, [Ph-H , ArH at C_8-H]), 8.10 (d, 1H, *J* = 8.10 Hz, ArH at C_7-H), 8.35 (s, 1H, ArH at C_5-H), 10.60 (s, 1H, NH, D_2O-exchangeable). Anal. calcd. for $C_{21}H_{14}IN_5O_2S$: C, 46.42; H, 2.60; N, 12.89. Found: C, 46.40; H, 2.60; N, 12.90%.

2.2.5. 2-Cyano-N-(6-iodo-2-methyl-4-oxoquinazolin-3(4H)-yl)-3-(methylthio)-3-(phenylamino)acrylamide (10)

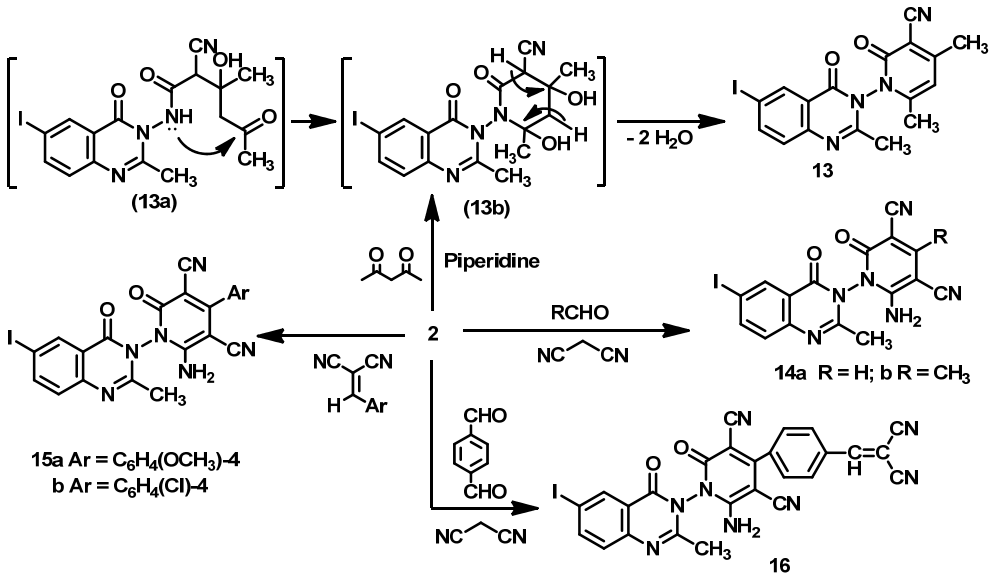
To suspension of potassium hydroxide (0.01 mole) in dry DMF (10 mL) cyanoacetamide **2** (0.01 mole) was added during stirring, phenyl isothiocyanate (0.01 mol) was dropped slowly to the reaction mixture. After complete addition, stirring of the reaction was continued for 5 h. and dimethyl sulfate (0.01 mol) was added. The reaction mixture was stirred for 2 h. then, poured into crushed ice. The resulting precipitate was filtrated off, dried and crystallized from benzene to give **10** as yellow brownish crystals (Scheme 2). Yield: 70%. M.p.: 144-145 °C. FT-IR (ν, cm^{-1}): 3244 (NH), 2194 (C≡N), 1658 (C=O). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.30 (s, 3H, SCH_3), 2.45 (s, 3H, CH_3), 7.35 (d, 1H, *J* = 8.50 Hz, ArH at C_8-H), 7.46 (m, 5H, ArH), 8.20 (d, 1H, *J* = 8.50 Hz, ArH at C_7-H), 8.41 (s, 1H, ArH at C_5-H), 10.81 (s, 1H, NH, NHPh D_2O-exchangeable), 11.78 (s, 1H, NH, CONH, D_2O-exchangeable). MS (*m/z*, %): 517 (M^+), 127 (100). Anal. calcd. for $C_{20}H_{16}IN_5O_2S$: C, 46.43; H, 3.12; N, 13.54. Found: C, 46.40; H, 3.10; N, 13.50%.

2.2.6. 5-amino-N-(6-iodo-2-methyl-4-oxoquinazolin-3(4H)-yl)-3-(phenylamino)-1H-pyrazole-4-carboxamide (11)

A mixture of **10** (0.01 mol) and hydrazine hydrate (0.012 mol) in ethanol (30 mL) was heated under reflux for 3 hrs and allowed to cool. The solid product obtained was filtrated and crystallized from acetic acid to give **11** as yellow crystals (Scheme 2) Yield: 65%. M.p.: 300 °C. FT-IR (ν, cm^{-1}): 3311, 3199, 3159 (NH, NH_2), 1684 (C=O). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.6 (s, 3H, CH_3), 5.8 (s, 2H, NH_2), 6.8-8.4 (m, 8H, ArH), 9.1 (s, 1H, NH), 9.2 (s, 1H, NH), 10.0 (s, 1H, NH). Anal. calcd. for $C_{19}H_{16}IN_7O_2$: C, 45.52; H, 3.22; N, 19.56. Found: C, 45.50; H, 3.20; N, 19.60%.

2.2.7. N-(6-iodo-2-methyl-4-oxoquinazolin-3(4H)-yl)-5,7-dimethyl-2)phenylamino)pyrazolo[1,5-a]pyrimidine-3-carboxamide (12)

A mixture of compound **11** (0.01 mol) and acetyl acetone (0.01 mol) was heated under reflux in glacial acetic acid (20 mL) for 3 hrs then left to cool. The obtained solid product was filtrated and crystallized from dioxane to give **12** as yellow brownish crystals (Scheme 2). Yield: 65%. M.p.: >300 °C. FT-IR (ν, cm^{-1}): 3253 (NH), 1705, 1656 (C=O).



Scheme 3

^{1}H NMR (DMSO-d_6, δ, ppm): 2.50 (s, 6H, 2CH_3), 2.63 (s, 3H, CH_3), 6.90 (t, 1H, *J* = 7.55 Hz, ArH at C_4 of phenyl ring), 7.11 (s, 1H, CH-pyrimidine), 7.35 (t, 2H, *J* = 7.55 Hz, ArH at $C_{3,5}$ of phenyl ring), 7.48 (d, 1H, *J* = 8.40 Hz, ArH at C_8-H of quinazoline), 7.74 (d, 2H, *J* = 8.40 Hz, ArH at $C_{2,6}$ of phenyl ring), 8.15 (d, 1H, *J* = 8.40 Hz, ArH at C_7 of quinazoline), 8.38 (s, 1H, ArH at C_5 of quinazoline), 9.11 (b, 1H, NH), 10.37 (b, 1H, NH). MS (*m/z*, %): 565 (28.0), 265 (100), 566 (6.9), 238 (9.6), 174 (2.6), 134(7.8). Anal. calcd. for $C_{24}H_{20}IN_7O_2$: C, 50.99; H, 3.57; N, 17.34. Found: C, 51.00; H, 3.60; N, 17.30%.

2.2.8. 1-(6-iodo-2-methyl-4-oxoquinazolin-3(4H)-yl)-4,6-dimethyl-2-oxo-1,2-dihydro-pyridine3-carbonitrile (13)

A mixture of cyanoacetamide **2** (0.01 mol), acetyl acetone (0.012 mol) and pipridine (few drops) was placed in a conical flask and fused for 15 min. then allowed to cool. The mixture was triturated with ethanol (20 mL) and the solid obtained was collected by filtration and crystallized from dioxane to give **13** as pale grey crystals (Scheme 3). Yield: 85%. M.p.: >300 °C. FT-IR (ν, cm^{-1}): 2958 (CH_{aliph}), 2218 (C≡N), 1680 (C=O). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.25 (m, 6H, 2CH_3), 2.48 (s, 3H, CH_3), 6.67 (s, 1H, Ar-H), 7.54 (d, 1H, *J* = 8.40 Hz, ArH at C_8-H), 8.25 (d, 1H, *J* = 8.40 Hz, ArH at C_7-H), 8.41 (s, 1H, ArH at C_5-H). MS (*m/z*, %): 432 (M^+), 416 (100), 433 (38.3), 434 (6.7), 290 (7.8), 257 (6.6), 216 (19.8), 116(15.0), 75 (36.1). Anal. calcd. for $C_{17}H_{13}IN_4O_2$: C, 47.24; H, 3.03; N, 12.96. Found: C, 47.20; H, 3.00; N, 13.00%.

2.2.9. General procedure for the syntheses of 6-amino-1-(6-iodo-2-methyl-4(3H)-quinazolin-3-yl)-4-alkyl-2-oxo-1,2-dihydro-Pyridine-3,5-dicarbonitrile (14a,b)

To a mixture of 2-cyanoacetamide **2** (0.01 mol), formaledehyde or acetaldehyde (0.01 mol) and malononitrile (0.01 mol) in ethanol (30 mL), few drop of pipridine was added. The reaction mixture was heated under reflux for 3 hrs. The solid product which formed while hot was collected by filtration and crystallized from dioxane to give **14a**,**b** as yellow crystals (Scheme 3).

6-Amino-1-(6-iodo-2-methyl-4-oxoquinazolin-3(4H)-yl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (**14a**): M.p.: 197-195 °C. Yield: 70%. FT-IR (ν, cm^{-1}): 3353, 3204 (NH_2), 2191 (C≡N), 1694 (C=O). MS (m/z, %): 444 (M^+, 1.5), 286 (100). Anal. calcd. for $C_{16}H_9IN_6O_2$: C, 43.26; H, 2.04; N, 18.92. Found: C, 43.30; H, 2.00; N, 18.90%.

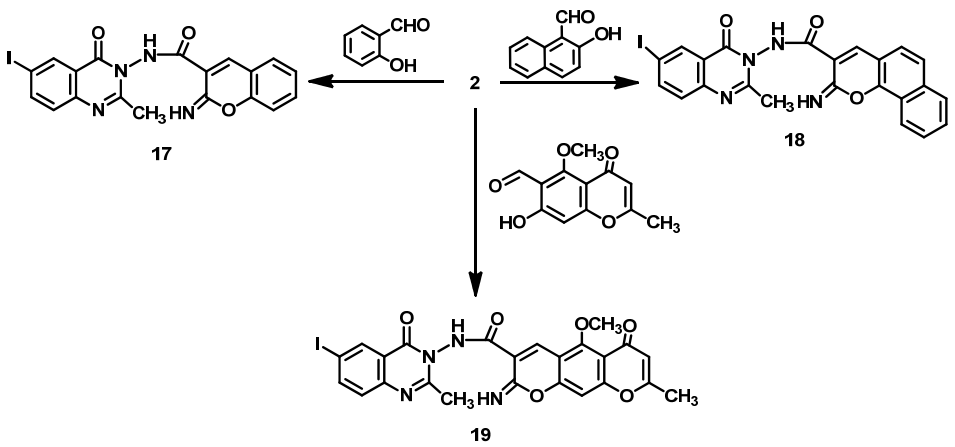
6-Amino-1-(6-iodo-2-methyl-4-oxoquinazolin-3(4H)-yl)-4-methyl-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (**14b**): M.p.: 277-280°C. Yield: 75%. FT-IR (ν, cm^{-1}): 3302, 3143 (NH2), 2218 (C≡N), 1696 (C=O). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.20 (s, 3H, CH_3-quinazoline), 2.50 (s, 3H, CH_3- pyridine), 7.53 (d, 1H, *J* = 8.40 Hz, ArH at C_8-H), 8.15 (d, 1H, *J* = 8.70 Hz, ArH at C_7-H), 8.40 (s, 1H, ArH at C_5-H), 9.22 (b, 2H, NH_2). Anal. calcd. for $C_{17}H_{11}IN_6O_2$: C, 44.56; H, 2.42; N, 18.34. Found: C, 44.60; H, 2.40; N, 18.40%.

2.2.10. General procedure for the syntheses of 6-amino-1-(6-iodo-2-methyl-4(3H)-quinazolinonyl)-4-(aryl)-2-oxo-1,2-dihydro-pyridine-3,5-dicarbonitriles (15a,b)

To equimolar amounts of 2-cyanoacetamide **2** and 2-(4-(chloro or methoxy) benzylidene) malononitrile, (0.01 mol) in ethanol (30 mL) it was added few drop of pyridine. The reaction mixture was heated under reflux for 3 hrs then allowed to cool and poured into cold diluted HCl solution. The obtained product was collected by filtration and crystallized from the proper solvent to give pyridinone derivatives **15a**,**b** (Scheme 3).

6-Amino-1-(6-iodo-2-methyl-4-oxoquinazolin-3(4H)-yl)-4-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (**15a**): M.p.: 178-180 °C. Yield: 55%. FT-IR (ν, cm^{-1}): 3300, 3150 (NH_2), 2214 (C≡N), 1690 (C=O). MS (m/z, %): 550 (M^+, 94.7), 508 (100), 551 (28.2), 552 (6.6). Anal. calcd. for $C_{23}H_{15}IN_6O_3$: C, 50.20; H, 2.75; N, 15.27. Found: C, 50.20; H, 2.75; N, 15.30%.

6-Amino-4-(4-chlorophenyl)-1-(6-iodo-2-methyl-4-oxo-quinazolin-3(4H)-yl)-2-oxo-1,2-dihydropyridine-3,5-dicarbo-nitrile (**15b**): M.p.: >300 °C. Yield: 65%. FT-IR (ν, cm^{-1}): 3285, 3200 (NH_2), 2219 (C≡N), 1695 (C=O). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.40 (s, 3H, CH_3), 7.53 (d, 1H, *J* = 8.10 Hz, ArH at C_8-quinazoline), 7.70 (m, 4H, ArH), 8.20 (d, 1H, *J* = 8.10 Hz, ArH at C_7- quinazoline), 8.43 (s, 1H, ArH at C_5-quinazoline), 9.40 (b, 2H, NH_2, D_2O-exchangeable). Anal. calcd. for $C_{22}H_{12}ClIN_6O_2$: C, 47.63; H, 2.18; N, 15.15. Found: C, 47.60; H, 2.20; N, 15.10%.



Scheme 4

2.2.11. 6-amino-4-(4-(2,2-dicyanovinyl)phenyl)-1-(6-iodo-2-methyl-4-oxoquinazolin-3(4H)-yl-2-oxo-1,2dihydropyridine-3,5-dicarbonitrile (16)

To a mixture of 2-cyanoacetamide **2** (0.01 mol), *ter*-phthaledehyde (0.01 mol) and malononitrile (0.02 mol) in ethanol (30 ml), few drop of pyridine was added. The reaction mixture was heated under reflux for 3 hrs. The solid product which formed while hot was collected by filtration and crystallized from dioxane to give **16** as red crystals (Scheme 3). Yield: 85%. M.p.: 258-261 °C. FT-IR (ν, cm^{-1}): 3444, 3320, 3158 (NH_2), 2212 (C≡N), 1644 (C=O). MS (*m/z*, %): 596 (M^+, 1.6), 341 (100), 286 (77.8), 246 (34.3), 114 (35.0), 90 (17.7) Anal. calcd. for $C_{26}H_{13}IN_8O_2$: C52.37; H, 2.20; N, 18.79. Found: C, 52.40; H, 2.20; N, 18.80%.

2.2.12. General procedure for the syntheses of chromene-3-carboxamide derivatives (17-19)

A mixture cyanoacetamide **2** (0.01 mol) and salicylaldehyde, β-naphthaldehyde or 7-hydroxy-5-methoxy-2-methyl-4-oxo-4*H*-chromone-6-carboxaldehyde (0.01 mol) in ethanol (30 mL) containing ammonium acetate (0.3 g) was heated under reflux for 0.5 hrs (Scheme 4). The obtained solid product which formed while hot was collected by filtration and crystallized from ethanol:dioxane (2:1) to give:

2-Imino-N-(6-iodo-2-methyl-4-oxoquinazolin-3(4H)-yl)-2H-chromene-3carboxamide (**17**): As greenish crystals. Yield: 80%. M.p.: 219-221 °C. FT-IR (ν, cm^{-1}): 3242 (NH), 1682 (C=O). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.50 (s, 3H, CH_3), 6.90-7.50 (m, 5H, [Ar-H + NH]), 7.90 (d, 1H, *J* = 8.10 Hz, ArH at C_8-H), 8.10 (d, 1H, *J* = 8.10 Hz, ArH at C_7-H), 8.40 (s, 1H, ArH at C_5-H), 9.10 (s, 1H, CH-chromene), 10.60 (b, 1H, NH, D_2O-exchangeable). MS (*m/z*, %): 472 (M+), 301 (100), 474 (2.3), 396 (2.4), 368 (5.0), 245 (19.6), 137 (20.5), 145 (12.6), 75 (11.7). Anal. calcd. for $C_{19}H_{13}IN_4O_3$: C48.32; H, 2.77; N, 11.86. Found: C, 48.30; H, 3.80; N, 11.90%.

2-Imino-N-(6-iodo-2-methyl-4-oxoquinazolin-3(4H)-yl)-2H-benzo[h]chromene-3carboxamide (**18**): As greenish crystals (ethanol:dioxane; 2:1). Yield: 85%. M.p.: 254-256 °C. FT-IR (ν, cm^{-1}): 3284 (NH), 1680 (C=O). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.50 (s, 3H, CH_3), 6.90-7.50 (m, 5H, [Ar-H + NH]), 7.90 (d, 1H, *J* = 8.10 Hz, ArH at C_8-H), 8.10 (d, 1H, *J* = 8.10 Hz, ArH at C_7-H), 8.40 (s, 1H, ArH at C_5-H), 9.10 (s, 1H, CH-chromene), 10.60 (b, 1H, NH, D_2O-exchangeable). MS (*m/z*, %): 522 (M^+), 301 (100), 523 (M+1; 24.5), 494 (90.3), 477 (38.7), 222 (78.7), 193 (55.3), 139 (37.6), 111 (20.6), 75 (46.6). Anal. calcd. for $C_{23}H_{15}IN_4O_3$: C, 52.89; H, 2.89; N, 10.73. Found: C, 52.90; H, 2.90; N, 10.70%.

2-Imino-N-(6-iodo-2-methyl-4-oxoquinazolin-3(4H)-yl)-5-methoxy-8-methyl-6-oxo-2,6-dihydropyrano[3,2-g]chromene-3carboxamide (**19**): As yellow crystals (dioxane). Yield: 80%. M.p.: 254-356 °C. FT-IR (ν, cm^{-1}): 3186 (NH), 1718, 1690 (C=O). MS (m/z, %): 584 (M^+), 325 (100), 555 (31.0), 490 (13.6), 286 (75.9), 245 (33.0), 145 (3.5), 90 (7.1). Anal. calcd. for $C_{24}H_{17}IN_4O_6$: C, 49.33; H, 2.93; N, 9.60. Found: C, 49.30; H, 2.90; N, 9.59%.

2.3. Antitumor activity against Ehrlich Ascites Carcinoma cells (EAC) [17]

In vitro short term cytotoxic activity of the compounds was determined using *Ehrlich Ascites Carcinoma* (EAC) cells. The EAC cells that were collected from the animal peritoneum by aspiration were washed repeatedly with phosphate buffered saline (PBS) solution to free it from blood. The viability of the cells was checked in a haemocytometer. The cells (2.5 x 10^5 tumor cells/mL PBS) were incubated in clean sterile tubes with the test compounds (25, 50, 100 µg/mL in dimethylsulfoxide (DMSO)) for 2h at 37 °C, keeping the final volume at 0.9 mL. The volume of DMSO was pegged below 0.1% of the total volume. The control tube had 10 µL of solvent. The final volume was made up to 0.9 mL with PBS. To each tube100 µL of Tryphan blue solution was added. The live (without stain) and dead (with blue stain) cells were counted using haemocytometer and percent cell death was calculated. Exclusion test was carried out to calculate the percentage of nonviable cells.

$$\% \text{ Cytotoxicity} = \frac{(T_{dead} - C_{dead})}{T_{total}} \text{ X } 100 \quad (1)$$

where T_{dead} is the number of dead cells in the treated group, C_{dead} is that in the control group and T_{total} is the total number of dead and live cells in the test compound treated group. *Cis*-platin was used as the standard.

2.4. Antifungal activity of some selected synthesized compounds

Two test organisms were used: *Aspergillus ochraceus* Wilhelm and *Fusarium oxysporium* (local strainidentified in Regional Center for fungi and its applications in Al-Azher University). Sterilized discs method [18] was used. Fresh stock solutions (1 mg/mL) of the synthesized compounds were prepared in redistilled dimethylsulfoxide according to the required concentrations. The discs were impregnated in DMSO.

Each disc was impregnated with 0.1 mL DMSO, so total amount of compound contained in each disk was 100 µg. Media: Dox agar was prepared and sterilized by autoclaving for 15 min at 121 °C, then the medium was cooled to 50 °C inoculated with the previously prepared fungi suspension and poured in sterilize petri dishes. The medium was allowed to solidify after a simple circular movement of the plates. Paper discs previously impregnated with the solution of compounds to be tested were placed on the plates. The plates were then incubated for 72 h at 28 °C. On each plate an appropriate reference Nystatin disc was applied. To ensure that the solvent had no effect on fungi growth; a control test was performed with test medium supplemented with DMSO as the same procedures as used in the experiments. DMSO showed no inhibition zones.

Dilution method: To determine the MIC for highly active compounds dilution method [19] was used. The compounds were dissolved and then diluted using DMSO, two-fold serial concentrations of the compounds were employed to determine the MIC ranging from 100 to 6 µg/mL. The MIC-value was determined as the lowest concentration of the compound that completely inhibited macroscopic growth of microorganism.

3. Results and discussion

The solvent-free reaction of aryl amines with ethyl cyanoacetate is well known to constitute one of the most widely used synthetic methods. Thermal fusion of 3-amino-4(3*H*)-quinazolinone [20], **1**, (above its melting point) with ethyl 2-cyanoacetate afforded 2-cyano-*N*-(6-iodo-2-methyl-4-oxoquinazolin-3(4*H*)-yl) acetamide, **2**. In order to probe the reactivity of the latter cyanoacetamide having active methylene moiety, its diazotization reaction was tried. Thus, upon its reaction with the desired diazonium chloride (obtained in situ by diazotization of the desired aromatic amine using a mixture of sodium nitrite and HCl) in the presence of sodium acetate; the corresponding quinazolinone hydrazono derivatives, **3a**,**b**, were obtained. Structures of the acetamide **2** and the hydrazono derivatives **3a**,**b** were inferred from correct analytical analyses and spectral determinations. IR spectrum of product **2** showed absorption bands at 3210 (NH), 2264 (C≡N) and 1690 cm^{-1} (C=O). Its ^{1}H NMR spectrum revealed the following signals at δ: 2.39 (s, 3H, CH_3), 4.10 (m, 2H, CH_2), 7.43 (d, 1H, *J* = 8.40 Hz, ArH at C_8-H), 8.15 (d, 1H, *J* = 8.40 Hz, ArH at C_7-H), 8.37 (s, 1H, ArH at C_5-H), 11.57 (s, 1H, NH, D_2O-exchangeable). Its mass spectrum exhibited a molecular ion peak at m/z = 368 (base peak). ^{1}H NMR spectrum of **3b** showed two singlet at 11.15 and 12.30 ppm for 2 NH. Mass spectrum of **3a** revealed a molecular ion peak at *m/z* = 472 (8.4%) with a base peak at m/z = 301.

Upon stirring the cyanoacetamide **2** with carbon disulfide in the presence of potassium hydroxide in *N*,*N*-dimethylformamide followed by cycloalkylation with 1,2-dibromoethane afforded 1,3-dithiolane derivative, **4**. Also, stirring of **2** under the same reaction conditions with 1,3-dibromopropane yielded 2-cyano-2-(1,3-dithian-2-ylidene)-*N*-(6-iodo-2-methyl-4-oxo-quinazolin-3(4*H*)-yl) acetamide, **5**, in good yield. Furthermore, reaction of **2** with CS_2 in the presence of KOH, followed by addition of dimethyl sulfate while stirring and cooling, afforded 2-cyano-*N*-(6-iodo-2-methyl-4-oxoquinazolin-3(4*H*)-yl)-3,3-bis(methylthio)acrylamide, **6** (Scheme 1). Elemental analyses and spectroscopic data accorded well the proposed structures of the acetamide derivatives, **4**, **5** and **6**. IR spectra of compounds **4**, **5** and **6** showed characteristic bands for NH, CH-aliphatic, C≡N and C=O groups. ^{1}H NMR spectrum of the compound **4** revealed signal at δ 3.75 ppm (s, 4H, $2CH_2$-dithiolane), mass spectrum of compound **4** showed a molecular ion peak at *m/z* = 470 (22.2%) with a base peak at *m/z* = 170 (100%). ^{1}H NMR spectrum of compound **5** showed signals for dithiene moiety at δ 2.20 ppm (p, 2H, *J* = 6.80 Hz, CH_2), 3.05 (t, 2H, *J* = 6.60 Hz, CH_2), 3.21 (t, 2H, *J* = 6.60 Hz, CH_2). Mass spectrum of **6** showed a molecular ion peak at *m/z* = 472 with a base peak at m/z = 301 (100%).

The reactivity of 3(4*H*)-quinazolinone cyanoacetamide, **2**, toward isothiocyanates was investigated. Thus, when **2** was left to react with phenyl isothiocyanate in the presence of solution of potassium hydroxide at room temperature and then chloroacetone was added; the corresponding 4-methylthiazole derivative, **8**, was obtained, as a clean cut product, in good yield without affording the expected thiophene structure of type **7**. Probably the reaction mechanism is assumed to proceed via initial alkylation followed by *in situ* heterocyclization through nucleophilic addition of secondary amino group to carbonyl group of chloroacetone to yield the cyclic product: 2-cyano-*N*-(6-iodo-2-methyl-4-oxoquinazolin-3(4*H*)-yl)-2-(4-methyl-3-phenylthiazol-2(3*H*)-ylidene)acetamide, **8**. Similarly, the novel 2-cyano-*N*-(6-iodo-2-methyl-4-oxoquinazolin-3(4*H*)-yl)-2-(4-oxo-3-phenylthiazolidin-2-ylidene)-acetamide, **9**, was synthesized from reaction of **2** with phenyl isothiocyanate in the presence of potassium hydroxide followed by *in situ* heterocyclization of the resulting adduct with ethyl chloroacetate. Also, when 2-cyano-*N*-(6-iodo-2-methyl-4-oxoquinazolin-3(4*H*)-yl) acetamide, **2**, was left to react with the same isothiocyanate in the presence of $(CH_3)_2SO_4$ in alkaline medium, the corresponding 2-cyano-*N*-(6-iodo-2-methyl-4-oxoquinazolin-3(4*H*)-yl)-3-(methyl-thio)-3-(phenylamino)-acrylamide, **10**, was afforded. Cyclocondensation of the acryl amide, **10**, with hydrazine hydrate in refluxing ethanol furnished 5-amino-*N*-(6-iodo-2-methyl-4-oxoquinazolin-3(4*H*)-yl)-3-(phenylamino)-1*H*-pyrazole-4-carboxamide, **11**.

Presumably, formation of the aminopyrazole **11** is assumed to proceed via Michael addition of the hydrazino amino group to the ethylenic bond side chain in **10** with elimination of SCH_3 group followed by intramolecular cyclization at the cyano group. When product **11** was heated under reflux with acetylacetone in glacial acetic acid; the pyrazolo[1,5-a]pyrimidine derivative, **12**, was afforded (Scheme 2). ^{1}H NMR spectrum (DMSO-d_6) of **8** displayed the following signals at δ 1.93 (s, 3H, CH_3 [thiazole]), 2.40 (s, 3H, CH_3 [quinazoline]), 7.03 (s, 1H, CH [thiazole]), 9.93 ppm (s, 1H, NH, D_2O-exchangeable). Its mass spectrum revealed a molecular ion peak at m/z = 541 with a base peak at m/z = 214 (100%). ^{1}H NMR spectrum of **9** revealed signals at δ = 4.00 (s, 2H, CH_2[thiazole]), 10.60 ppm (s, 1H, NH (D_2O-exchangeable)). ^{1}H NMR spectrum of **10** displayed the following signals at δ = 2.30 (s, 3H, SCH_3), 2.45 (s, 3H, CH_3), 10.81 ppm (s, 1H, NH, NHPh (D_2O- exchangeable)), 11.78 (s, 1H, NH, CONH-(D_2O-exchangeable)). Mass spectrum of **10** revealed a molecular ion peak at *m/z* = 517 with a base peak at *m/z* = 127.

IR spectrum of **11** showed bands at 3311, 3199, 3159 (NH, NH_2) and 1684 (C=O) cm^{-1}. Its ^{1}H NMR spectrum showed signals at δ = 2.6 (s, 3H, CH_3), 5.8 (s, 2H, NH_2), 6.8-8.4 (m, 8H, ArH), 9.1 (s, 1H, NH), 9.2 (s, 1H, NH), 10.0 ppm (s, 1H, NH). ^{1}H NMR spectrum (DMSO-d_6) of **12** displayed signals a δ = 2.50 (s, 6H, $2CH_3$), 2.63 (s, 3H, CH_3), 6.90 (t, 1H, *J* = 7.55 Hz, ArH at C_4 of phenyl ring), 7.11 (s, 1H, CH-pyrimidine), 7.35 (t, 2H, *J* = 7.55 Hz, ArH at $C_{3,5}$ of phenyl ring), 7.48 (d, 1H, *J* = 8.40 Hz, ArH at C_8 of quinazoline), 7.74 (d, 2H, *J* = 8.40 Hz, ArH at C2,6 of phenyl ring), 8.15 (d, 1H, *J* = 8.40 Hz, ArH at C_7 of quinazoline), 8.38 (s, 1H, ArH at C_5 of quinazoline), 9.11 (b, 1H, NH), 10.37 (b, 1H, NH). Its Mass spectrum revealed a molecular ion peak at *m/z* = 566 with a base peak at *m/z* = 265.

It is well known that many 2-pyridone derivatives exhibited diverse biological activities e.g. as cardiotonic agents, potential HIV-1 specific reverse transcriptase inhibitors [21,22] and elastase inhibitors [23]. The present study was continued to report the reactivity of cyanoacetamide derivative **2** towards certain nucleophilic reagents. Thus, when **2** was thermally fused with acetylacetone in the presence of a catalytic amount of piperidine cyclocondensation reaction occurred and the 4,6-dimethyl-2-pyridine derivative **13** was smoothly afforded. It

can be postulated that the reaction initially proceeds via a nucleophilic attack to form Michael adduct (**13a**) which in turn cyclized to the adduct (**13b**) then lost two water molecules affording 1-(6-iodo-2-methyl-4-oxoquinazolin-3(4*H*)-yl)-4,6-dimethyl-2-oxo-1,2-dihydro-pyridine-3-carbonitrile, **13**, (Scheme 3).

IR spectrum of the pyridine, **13**, exhibited bands at 2958 (CH-aliphatic), 2218 (C≡N) and 1680 (C=O) cm^{-1}. Its ^1H NMR spectrum displayed the following signals 2.25 (m, 6H, $2CH_3$), 2.48 (s, 3H, CH_3), 6.67 (s, 1H, Ar-H), 7.54 (d, 1H, *J* = 8.40 Hz, ArH at C_8-H), 8.25 (d, 1H, *J* = 8.40 Hz, ArH at C_7-H), 8.41 (s, 1H, ArH at C_5-H). Mass spectrum revealed a molecular ion peak at *m/z* = 432 corresponding to a molecular formula $C_{17}H_{13}IN_4O_2$ together with a base peak at *m/z* = 416 (100%).

One-pot reactions of the cyanoacetamide derivative, **2**, with malononitrile and (formaldehyde or acetaldehyde) (1:1:1 molar ratio) at reflux temperature in ethanol in the presence of piperidine afforded the 2-pyridinone derivatives, **14a**,**b**, respectively. On the other hand, the 2-pyridinone derivatives **15a**,**b** and **16** were obtained *via* reaction of cyanoacetamide, **2**, with 2-(4-chlorobenzylidene) malononitrile or 2-(4-methoxy-benzylidene)malononitrile (1:1:1 molar ratio) or with *ter*-phthaldehyde and malononitrile (1:1:2 molar ratio) upon heating under reflux in the presence of a catalyst. Structural assignment of the pyridinones **14a**,**b**, **15a**,**b** and **16** was confirmed on the basis of correct elemental analyses and spectral determination. IR spectrum of **14b** showed bands at 3353, 3204 cm^{-1} for NH_2 group. ^1H NMR spectrum of **14b** revealed signal at 2.20 (s, 3H, CH_3-quniazoline), 2.50 (s, 3H, CH_3-pyridine), 7.53 (d, 1H, *J* = 8.40 Hz, ArH at C_8-H), 8.15 (d, 1H, *J* = 8.70 Hz, ArH at C_7-H), 8.40 (s, 1H, ArH at C_5-H), 9.22 (b, 2H, NH_2) ppm. Mass spectrum of **15a** showed a molecular ion peak at *m/z* = 550 (94.70%) with base beaks at m/z = 508. Also, one pot reaction of cyanoacetamide derivative **2** with *ter*-phthaldehyde and malononitrile (1:1:2 molar ratio) at reflux temperature in ethanol in the presence of piperidine (few drops) afforded the 2-pyridinone derivative, **16**, (Scheme 3). Mass spectrum of **16** showed a molecular ion peak at m/z = 596 (1.6%) corresponding to a molecular formula, $C_{26}H_{13}IN_8O_2$, with a base peak at *m/z* = 341 (100 %).

Chromene derivatives are widely used for production of highly effective fluorescent dyes for synthetic fibers and daylight fluorescent pigments [24,25]. Some derivatives play also a vital role in electro photographic and electroluminescent devices [26] Moreover, many other derivatives are well known for their considerable biological and medicinal activities [27]. Cyclocondensation reaction of **2** with salicylaldehyde or 2-hydroxynaphthaldehyde or 7-hydroxy-5-methoxy-2-methyl-4-oxo-4*H*-chromone-6-carboxaldehyde in ethanol containing ammonium acetate furnished smoothly 2-imino-*N*-(6-iodo-2-methyl-4-oxoquinazolin-3(4*H*)-yl)-2*H*-chromene-3-carbox-amide, **17**, 2-imino-*N*-(6-iodo-2-methyl-4-oxoquinazolin-3(4*H*)-yl)-*2H*-benzo[*H*]chromene-3-carbox amide, **18**, and 2-imino-*N*-(6-iodo-2-methyl-4-oxoquinazolin-3(4*H*)-yl)-5-met-hoxy-8-methyl-6-oxo-2,6-dihydropyrano[3,2-g]- chromene-3-carboxamide, **19**, respectively (Scheme 4).

^1H NMR spectrum of **17** showed characteristic signals at 9.11 for CH-chromene and at 10.60 ppm for NH. Mass spectrum of **17** exhibited a molecular ion peak at m/z = 472. Mass spectrum of compound **18** exhibited a molecular ion peak at *m/z* = 522. IR spectrum of the pyrano-chromene **19** showed absorption bands at 3186 and 1718 cm^{-1} for NH and C=O, respectively. Its mass spectrum revealed molecular ion peak at *m/z* = 584.

Some selected examples from the synthesized products were tested using the short term in vitro cytotoxicity towards *Ehrlich ascites carcinoma* cells (EAC) as a preliminary screening technique of tryphan blue exclusion method (cell viability test) for their potential cytotoxicity activity using 100, 50 and 25 µg/mL concentrations. Structure activity relationship (SAR) indicated that the thio compounds **4**, **8** and **10** showed that the quinazolinone derivative **4** with C-3 side chain having dithiolane moiety was found of no activity at the used concentrations. Product **8** with 3-side chain incorporated with substituted thiazole moiety was found to be of high to moderate activity towards cells at 100 (50%) and 50 (20%) µg/mL, respectively. Presumably the activity showed by compound **8** was due to the presence of the thiazole ring in its structure. On the other hand, product **10** with methyl mercapto group attached in its 3-position was of low activity (10%) only at 100 µg/mL (Table 1).

Table 1. Antitumor activity of the screened compounds.

Compound No.	% Cell death at different concentrations (µg/mL) after 2 h		
	100	50	25
4	0	0	0
8	50	20	0
10	10	0	0

The preliminary in vitro antifungal activity screening for some selected examples of the synthesized compounds was carried out using paper disc method against *Aspergillus ochraceus* Wilhelm and *Fusarium oxysporium* fungi. Fresh stock solutions (1 mg/mL) of the tested compounds were prepared in redistilled DMSO according to the required concentrations. Serial concentrations of the compounds were employed to determine the (MIC) ranging from 100 to 6.25 µg/mL. The incubation for impregnated discs was 72 h at 28 °C. The antifungal Nystatin and the DMSO solvent were used as positive and negative controls, respectively. The results showed compound **8** incorporating a thiazole moiety and the chromene product **19** were only of high activity against *Fusarium oxysporium* with inhibition zones (18 mm) and (16 mm), respectively, compared with (20 mm) Nystatin inhibition zone. MIC of compounds 8, 19 was 12.5 µg/mL. All the other tested compounds showed no activity towards the used fungi (Table 2).

Table 2. Antimicrobial activities data of some synthesized compounds.

Compound No.	Fungi	
	Asperg. Sp.	*Fuzarium sp.*
8	0	18 (12.5)
13	0	0
15a	0	0
19	0	16 (12.5)
Nystatin	12	20

4. Conclusion

Novel 4(3*H*)-quinazolinone derivatives bearing thiazole, pyrazole, 1,3-dithiazole, pyridine, pyrazolopyrimidine, chromene and pyranochromene moieties were synthesized and characterized. Screening of some selected compounds was carried for their potential antitumor and antifungal activity. 2-Cyano-*N*-(6-iodo-2-methyl-4-oxoquinazolin-3(4*H*)-yl)-2-(4-methyl-3-phenyl-thiazol-2(3*H*)ylidene)-acetamide, **8**, with 3-side chain incorporated with substituted thiazole moiety was found to be of high to moderate activity towards EAC cells at 100 (50%) and 50 (20%) µg/mL respectively. Also, the latter product showed high activity against *Aspergillus ochraceus* Wilhelm with inhibition zone (18 mm) compared with (20 mm) Nystatin inhibition zone.

References

[1]. Tiwari, A. K.; Singh, V. K.; Bajpai, A.; Shukla, G.; Singh, S.; Mishra, A. K. *Eur. J. Med. Chem.* **2007**, *42*, 1234-1238.
[2]. Grover, G.; Kini, S. G. *Eur. J. Med. Chem.* **2006**, *41*, 256-262.
[3]. Cao, S. L.; Feng, Y.-P.; Jiang, Y. Y. *Biorg. Med. Chem. Lett.* **2005**, *15*, 1915-1917
[4]. Giri, R. S.; Thaker. H. M.; Giordano, T.; Williams, J.; Rogers, D.; Sudersanam, V.; Vasu, K. K. *Eur. J. Med. Chem.* **2009**, *44*, 2184-2189.
[5]. El-Helby, A. G. A.; Abdel Wahab, M. H. *Acta Pharm.* **2003**, *53*, 127-138.
[6]. Kadi, A. A.; El-Azab, A. S.; Alafeefy, A. M.; Abdel-Hamide, S. G. *Al-Azhar J. Pharm. Sci.* **2006**, *34*, 147-158.

[7]. Jatav, V.; Mishra, P.; Kashaw, S. *Eur. J. Med. Chem.* **2008**, *43*, 1945-1951.
[8]. Van Zyl, E. F. A. *Forensic Sci. Int.* **2001**, *122*, 142-149.
[9]. Kumar, A.; Sharma, S.; Bajaj, A. K.; Sharma, S.; Panwar, H.; Singh, N.; Srivastava, V. K. *Bioorg. Med. Chem.* **2003**, *11*, 5293- 5299.
[10]. Mohamed, M. S.; Ibrahim, M. K.; Alafeefy, A. M.; Abdel-Hamide, S. G. *J. Appl. Sci*. **2004**, *4*, 302-307.
[11]. Mohamed, M. S.; Ibrahim, M. K.; Alafeefy, A. M.; Abdel-Hamide, S. G. *Int. J. Pharmacol.* **2005**, *1*, 261-265.
[12]. Geissler, A. E.; Huppatz J. L.; Phillips, J. N. *Pesticide Sci.* **1980**, *11(4)*, 432-438.
[13]. Wayne, J. W. O.; Seidel M. C.; Harlow, W. L. *US Patent*, (1977) 4, 038, 065, Chem. Abstr. 1977, 87: 152034y.
[14]. Roifman, C. M.; Aviv G.; Alexander, L. *PCT Int . Appl. WO Patent*, (2000) 0055, 128, Chem. Abstr. (2000)133: 237695h.
[15]. Fahmy, H. T.; Rostom, S. A.; Bekhit, A. A. *Archiv der Pharmazie* **2002**, *335(5)*, 213-222.
[16]. Ismail, M. M. F.; Ammar, Y. A.; El-Zahaby, H. S. A.; Eisa S. I.; Barakat, S. E. *Archiv der Pharmazie* **2007**, *340*, 476-482.
[17]. Sathisha, M. P.; Shetti, U. N.; Revankar, V. K.; Pai, K. S. R. *Eur. J. Med. Chem.* **2008**, *43(11)*, 2338-2346.
[18]. NazAgh-Atabay, M.; Dulger, B.; Gucin, F. Microbiological Methods, sixth Ed. Butterworths Co. Ltd., London, (1989).
[19]. Performance Standards for Antimicrobial Disk Suspectibility Tests, Approved Standard NCCLS Publication M2-A5, Villanova, PA, USA, 1993, pp. 1-32.
[20]. Mohamed, Y. A.; Aziza, M. A. E.; Salama, F. M.; Alafify, A. M. *J. Serb. Chem. Soc.* **1992**, *57(10)*, 629-633.
[21]. Dolle, V.; Fan, E.; Ngugen, C. H.; Aubertin, A. M.; Bisagui, E. A. *J. Med. Chem.* **1995**, *38*, 4679-4686.
[22]. Wai, J. S.; Williams, T. M.; Bamberey, D. L.; Anderson, P. S. *J. Med. Chem.* **1993**, *36*, 249-255.
[23]. Veale, C. A.; Bernstein P. R.; Brynat, C.; Cessorelli, C.; Woolson, S. *J. Med. Chem.* **1995**, *38*, 98-108.
[24]. Zhang, Y. Y.; Meng, X. M.; Wang, X. L.; Xu, L. X. *Dyes and Pigment* **2003**, *56*, 189-194.
[25]. Christie R. M.; Chih-Hung, L. *Dyes and Pigments* **1999**, *42*, 85-93.
[26]. Sasaki, K. *Jpn. Kokai Tokkyo Koho* (**1994**) 23 05, 190, 902; Chem. Abst. **1994**, 120:310929a
[27]. Melagraki, G.; Afantitis, A.; Igglessi-Markopoulou, O.; Detsi, A.; Koufaki, M.; Kontogiorgis, C.; Hadjipavlou-Litina D. J. *Eur. J. Med. Chem.* **2009**, *44*, 3020-3026.