Novel 4(3H)-Quinazolinone Containing Biologically Active Thiazole, Pyrazole, 1,3-dithiazole, Pyridine, Chromene, Pyrazolopyrimidine and Pyranochromene of Expected Biological Activity

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Abstract: Diazotization of 2-cyano-N-(6-iodo-2-methyl-4-oxoquinazolin-3(4H)-yl) acetamide 2 with the desired diazonium chloride gave quinazolinone hydrazono derivatives 3a, b. Reactions of 2 with carbon disulfide, 1,2-dibromoethane or 1,3-dibromopropane, isothiocyanates afforded the thio products 4-10. Cyclocondensation of the acryl amide 10 with hydrazine hydrate furnished 5-amino-N-(6-iodo-2-methyl-4-oxoquinazolin-3(4H)-yl)-3-(phenylamino)-1H-pyrazole-4-carboxamide 11 When product 11 was refluxed with acetylacetone; the pyrazolo[1,5-a]pyrimidine derivative 12 was afforded. Thermal fusion of 2 with acetylacetone in the presence of piperidine cyclocondensation reaction occurred and 4,6-dimethyl-2-pyridine derivative 13 was obtained. One-pot reactions of 2 with malononitrile and (formaldehyde or acetaldehyde) (1:1:1 molar ratio) under reflux afforded the 2-pyridone derivatives 14a, b respectively. The 2-pyridone derivatives 15a, b and 16 were obtained via reaction of cyanacetamide 2 with some arylidene malononitrile or with ter-phthalaldehyde & malononitrile upon heating under reflux in the presence of a catalyst. Cyclocondensation reaction of 2 with salicylaldehyde or 2-hydroxynaphtho-aldehyde or 7-hydroxy-5-methoxy-2-methyl-4-oxo-4H-chromene-6-carboxaldehyde in ethanol containing ammonium acetate furnished 2-imino-N-(6-iodo-2-methyl-4-oxoquinazolin-3(4H)-yl)-2H-chromene-3-carboxamide 17,2-imino-N-(6-iodo-2methyl-4-oxoquinazolin-3(4H)-yl)-2H-benzol[h]chromene-3-carboxamide 18 and 2-imino-N-(6-iodo-2-methyl-4-oxoquinazolin-3(4H)-yl)-5-methoxy-8-methyl-6-oxo-2,6-dihydro pyrano[3,2-g]chromene-3-carboxamide 19 respectively. Screening for some selected compounds was carried for their potential antitumor and antifungal activity.

Key words: Quinazolinone  ·  Pyrazole  ·  1,3-dithiazole  ·  Chromene  ·  Pyranochromene  ·  Antitumor and antifungal activity

INTRODUCTION

The chemistry of 4(3H)-quinazolinone system has received an increasing interest because of its biological significance. Many derivatives of this system showed antifungal [1], antibacterial [2], anticancer [3], anti-inflammatory [4], anticonvulsant [5], immunotropic [6], hypolipidemic [7], antiulcer [8], analgesic [9] and antiproliferative [10] 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 antiviral [11], antibacterial [12, 13], herbicidal [14], plant growth regulators [15], anti-inflammatory [16], anti-tumor [17] and analgesic properties [18]. Therefore, it was aimed in the present investigation to synthesize and characterize newer quinazolinone derivatives for their expected antitumor and / or antimicrobial activities.

MATERIALS AND METHODS

All melting points are uncorrected. Microanalyses were carried out by the Microanalytical Laboratory, National Research Center, Cairo, Egypt and the Microanalytical Research Center, Cairo University. Infrared spectra (Kbr-disc) were recorded using a Jasco
(3b): 2-(6-Iodo-2-methyl-4-oxoquinazolin-3(4H)-ylamino)-2-oxo-N-p-tolylacetohydrazonoyl cyanide: IR: ν/cm⁻¹: 3230 (NH), 2218 (C=O) and 1689 (C=O). ¹HNMR (DMSO-d₆): δ/ppm: 2.31(s, 3H, CH₃), 2.40(s, 3H, CH₃), 7.15 (d, 2H, J= 8.08 Hz, AB system), 7.50 (d, 1H, J= 8.57 Hz, ArH at C₆-H), 7.61 (d, 2H, J= 8.08 Hz, AB system), 8.10 (d, 1H, J= 8.57 Hz, ArH at C₆-H), 8.40 (s, 1H, ArH at C₆-H), 11.15 (b, 1H, NH), 12.30 (b, 1H, NH). Anal. calcd for C₉H₈IN₂O₂: C, 46.93; H, 3.11; N, 17.28. Found: C, 46.90; H, 3.10; N, 17.30%.

2-Cyano-N-(1,3-dithian-2-ylidene)-N-(6-iodo-2-methyl-4(3H)-quinoxalinone)-N〫(3H)-acylamide (4): To a stirred suspension of finely powdered potassium hydroxide (0.02 mole) in dry DMF (10ml) cyanoacetamide 2 (0.01 mole) was added. The resulted mixture was cooled at 10 °C in an ice bath, then (0.01 mol) carbon disulfide was added slowly over the course of 10 min. After complete addition, stirring of the reaction mixture was continued for additional 2 h. Then dibromomethane (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 benzene/ethanol to give 4 as yellow brownish crystals, yield 70%, m.p 243-245 °C. IR: ν/cm⁻¹: 3266 (NH), 2971 (CH₃), 1689, 1666 (C=O). ¹HNMR (CDCl₃): δ/ppm: 2.44(s, 3H, CH₃), 3.75 (s, 4H, 2CH₂), 7.50 (d, 1H, J= 8.10 Hz, ArH at C₆-H), 8.20 (d, 1H, J= 8.10 Hz, ArH at C₆-H), 8.42 (s, 1H, ArH at C₆-H), 11.20 (s, 1H, NH, D₂O-exchangeable); MS, m/z 470(M⁺); 22.2% 170 (100), 471 (2.8%), 172 (17.2%), 75 (16.5%). Anal. calcd for C₆H₈IN₂O₂S: C, 38.31; H, 2.36; N, 11.91. Found: C, 38.30; H, 2.40; N, 11.90%.

2-Cyano-N-(1,3-dithian-2-ylidene)-N-(6-iodo-2-methyl-4(3H)-quinoxalinone)-acetamide (5): Compound 5 was synthesized as mentioned above in synthesis of 4: When using dibromopropane instead of dibromoethane the resulting product was crystallized from benzene/ethanol to give 5 as yellow brownish crystals, yield 75%, m.p 238-240°C. IR: ν/cm⁻¹: 3242 (NH), 2926 (CH₃), 2200 (C=O) and 1703, 1665 cm⁻¹ (C=O). ¹HNMR (CDCl₃): δ/ppm: 2.20(p, 2H, J= 6.80 Hz, CH₂), 2.50 (s, 3H, CH₃), 3.05 (t, 2H, J= 6.60 Hz, CH₂), 2.10 (t, 2H, J= 6.60 Hz, CH₂), 7.42 (d, 1H, J= 8.50 Hz, ArH at C₆-H), 8.14 (d, 1H, J= 8.50 Hz, ArH at C₆-H), 8.35 (s, 1H, ArH at C₆-H), 11.06 (s, 1H, NH, D₂O-exchangeable). Anal. calcd for C₆H₈IN₂O₂S: 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(3H)-quinazolinone-3-yl)-3,3-bis(methylthio)acrylamide (6): Also compound 6 was synthesized as mentioned above in synthesis of 4:
When using dimethylsulfate instead of dibromoethane. The resulting product was crystallized from methanol to give 6 as yellow brownish crystals, yield 60%, m.p.173-175 °C IR: v/cm⁻¹: 3212 (NH), 2964, 2926 (CH₆), 2200 (C=O) and 1688 (C=O); MS, m/z (IR%) 472(M⁺, 22.2%), 301 (100%), 473 (M+1; 2%), 368 (30.9%), 328 (37.8%), 271 (49%), 216 (16.9%), 172 (14.8%), 116 (18.6%), 75 (43.8%). Anal. calcd for C₆H₈N₂O₅S: C, 46.40; H, 2.60; N, 12.90%. Found: C, 46.40; H, 2.60; N, 12.90%.

2-Cyano-N-(6-iodo-2-methyl-4(3H)-quinazolinon-3-yl)-4-(30-ethylthio)-3-(phenyl-amino) acrylamide (10): To suspension of potassium hydroxide (0.01 mole) in dry DMF (10ml) cyanoacetamide 2 (0.01 mol) was added during stirring, phenylisothiocyanate (0.01 mol) was dropped slowly to the reaction mixture. After complete addition, stirring of the reaction was continued for 5 h. and dimethylsulfate (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, yield 70%, m.p.144-145 °C. IR: v/cm⁻¹: 3244(NH), 2194 (C=H) and 1658 (C=O). HNMR (DMSO-d₆): 2.50 (s, 6H, 2CH₃), 2.63 1.93 (s, 3H, CH₃)[thiazole], 1.93 (s, 3H, CH₃)[thiazole], 7.52 (d, 1H, J= 8.10 Hz, ArH at C=H), 7.66 (m, 5H, ArH), 8.17 (d, 1H, J= 8.10 Hz, ArH at ArCH₂), 8.40 (s, 1H, ArH at ArCH₂), 9.93 (s, 1H, NH, DO-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 C₂₂H₁₉N₂O₅S: C, 48.80; H, 3.00; N, 12.90%.

5-Amino-N-(6-iodo-2-methyl-4(3H)-quinazolinon-3-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, yield 65%, m.p. >300°C. IR: v/cm⁻¹: 3311, 3199, 3159(NH, NH₂) and 1684 (C=O) HNMR (DMSO-d₆): δ/ppm: 2.6 (s, 3H, CH₃), 5.8 (s, 2H, NH), 6.8-8.4 (m, 8H, ArH), 9.1 (s, 1H, NH, NHPh D O- exchangeable) 11.78 (s, 1H, NH, CONH DO-exchangeable). MS: m/z 517(M⁺) 127 (100 %). Anal. calcd for C₂₀H₁₅N₄O₅S: C, 45.52; H, 3.22; N, 19.56. Found: C, 45.40; H, 3.10; N, 19.60%.
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 C₉H₃N₂O₃: C, 50.99; H, 3.57; N, 17.34
Found: C, 51.00; H, 3.60; N, 17.30%.

1-(6-Iodo-2-methyl-(4H)-quinazolinon-3-yl)-4,6-dimethyl-2-oxo-1,2-dihydro-pyridine-3-carbonitrile (13): A mixture of cyanoacetamide 2 (0.01 mol), acetyl acetone (0.012) and pipredine (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, yield 85%, m.p >300 °C IR: ν/cm⁻¹: 2958 (Ch₅n), 2218 (C≡N) and 1680 (C=O) °HNMR (DMSO-d₆): δ/ppm: 2.20 (s, 3H, CH₃-quinazoline), 2.50 (s, 3H, CH₃-pyridine), 7.53 (d, 1H, J= 8.40 Hz, ArH at C-H), 8.15 (d, 1H, J= 8.70 Hz, ArH at C-H), 8.41 (s, 1H, ArH at C-H); MS, m/z 550 (M°), 421 (38.3%), 434 (67.7%), 290 (7.8%), 257 (6.6%), 216 (19.8%), 116(15.0%), 75 (36.1%) Anal. calcd for C₅H₁₂INO₃: C, 47.24; H, 3.03; N, 12.96. Found: C, 47.20; H, 3.00; N, 13.00%.

6-Amino-1-(6-ido-2-methyl-(4H)-quinazolinon-3-yl)-4-alkyl-2-oxo-1,2-dihydro-pyridine-3,5-dicarbonitrile (14a,b)
General Procedure: To a mixture of 2-cyanoacetamide 2 (0.01 mol), formaledohyde or acetaldehyde (0.01 mol) and malononitrile (0.01 mol) in ethanol (30 ml), few drop of pipredine 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 20 as yellow crystals.

(14a): 6-Amino-1-(6-ido-2-methyl-4-oxoquinazolin-3(4H)-yl)-2-oxo-1,2-dihydro-pyridine-3,5-dicarbonitrile: M.P. 197-195°C, yield (70%), IR: ν/cm⁻¹: 3353, 3204 (NH), 2214 (C≡N) and 1690 (C=O); MS, m/z 596 (M°), 341 (100%). Anal. calcd for C₉H₆INO₃: C, 44.56; H, 2.42; N, 18.40. Found: C, 44.60; H, 2.40; N, 18.40%.

6-Amino-1-(6-ido-2-methyl-(4H)-quinazolinon-3(4H)-yl)-4-(aryl)-2-oxo-1,2-dihydro-pyridine-3,5-dicarbonitriles (15a,b)
General Procedure: 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 pipredine. 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

(15a): 6-Amino-1-(6-ido-2-methyl-4-oxoquinazolin-3(4H)-yl)-4-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile: (benzene) M.P. 178-180°C, yield (55%), IR: ν/cm⁻¹: 3300, 3150(NH), 2214 (C≡N) and 1690(C≡O); MS, m/z 550 (M°) 508(100), 551 (28.2 %), 552 (6.6%). Anal. calcd for C₁₇H₁₈INO₅: C, 50.20; H, 2.75; N, 15.27. Found: C, 50.20; H, 2.75; N, 15.30%.

(15b): 6-Amino-4-(4-chlorophenyl)-1-(6-ido-2-methyl-4-oxoquinazolin-3(4H)-yl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile: (ethanol) M.P. >300°C, yield (65%) IR: ν/cm⁻¹: 3285, 3200(NH), 2219 (C≡N) and 1695(C≡O). °HNMR (DMSO-d₆): δ/ppm: 2.40(s, 3H, CH₃); 7.53 (d, 1H, J= 8.10 Hz, ArH at C₂-quinazoline), 7.70 (m, 4H, ArH, ArH), 8.20 (d, 1H, J= 8.10 Hz, ArH at C₂′-quinazoline), 8.43 (s, 1H, ArH at C₂′-quinazoline), 9.40 (b, 2H, NH₂, D₂O-exchangeable). Anal. calcd for C₂₉H₂₃INO₇: C, 47.63; H, 2.18; N, 15.15. Found: C, 47.60; H, 2.20; N, 15.10%.

6-Amino-4-(4-(2,2-dicyanovinylphenyl)-1-(6-ido-2-methyl-(3H)-quinazolinon-3-yl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (16): To a mixture of 2-cyanoacetamide 2 (0.01 mol), tert-phthaledehyde (0.01 mol) and malononitrile (0.02 mol) in ethanol (30 ml), few drop of pipredine 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, yield 85%, m.p 258-261 °C IR: ν/cm⁻¹: 3444, 3340, 3158 (NH), 2212 (C≡N) and 1644 (C≡O). MS, m/z 596(M°); 341 (100 %). 286 (77.8%), 246 (34.3%), 114 (35.0%), 90 (17.7%). Anal. calcd for C₂₇H₂₆INO₇: C, 52.37; H, 2.20; N, 18.79. Found: C, 52.40; H, 2.20; N, 18.80%.

2-Imino-N-(6-ido-2-methyl-(3H)-quinazolinon-3-yl)-4a,8a-dihydro-2H-chromene-3-carboxamide (17): A mixture cyanoacetamide 2 (0.01 mol) and salicylaldehyde (0.3 gm) was heated under reflux for 0.5 hrs. The obtained solid product which formed while hot was collected by...
filtration and crystallized from ethanol/dioxan to give 17 as greenish crystals, yield 80%, m.p. 219-221 °C. IR: \(\nu/cm^{-1}: 3242 (NH)\) and 1682 (C=O). 1H NMR (DMSO-\(d_6\)): \(\delta 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-H), 8.10 (d, 1H, J = 8.10 Hz, ArH at C-H), 8.40 (s, 1H, ArH at C-H), 9.10 (s, 1H, CH-chromene), 10.60 (b, 1H, NH, D,O-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_{19}IN_{10}O_6: C, 49.33; H, 2.93; N, 9.60. Found: C, 48.30; H, 3.80; N, 9.90%.

Synthesis of 2-imino-N-(6-iodo-2-methyl-4(3H)-quinazolinon-3-yl)-4a,10b-dihydro-2H-benzo [I] chromene-3-carboxamide (18): Compound 18 was synthesized as mentioned above in synthesis of 17: When using \(\beta\)-naphthaldehyde instead of salicylaldehyde the resulting product was crystallized from ethanol/dioxan to give 18 as greenish crystals, yield 85%, m.p 254-256 °C. IR: \(\nu/cm^{-1}: 3284 (NH)\) and 1680 (C=O). 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-H), 8.40 (s, 1H, ArH at C-H), 9.10(s, 1H, CH-chromene), 10.60 (b, 1H, NH, D,O-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_{19}IN_{10}O_6: C, 49.33; H, 2.93; N, 9.60. Found: C, 48.30; H, 3.80; N, 9.90%.

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(3H)-quinazolinone 1[19] (above its melting point) with ethyl 2-cyanoacetate afforded 2-cyano-N-(6-iodo-2-methyl-4-oxoquinazolin-3(4H)-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 quinazolinoine hydrazono derivatives 3a, b were obtained. Structure of the acetamide 2 and the hydrazono derivatives 3a, b was inferred from correct analytical analyses and spectral determinations. IR spectrum of product 2 showed absorption bands at 3210 (NH), 2264 (C=O) and 1690 cm\(^{-1}\) (C=O). Its 1H NMR spectrum in (DMSO-\(d_6\)) revealed the following signals: 2.39(s, 3H, CH_3), 4.10 (m, 2H,CH), 7.43 (d, 1H, J= 8.40 Hz, ArH at C-H), 8.15 (d,1H, J= 8.40 Hz, ArH at C-H), 8.37 (s,1H, ArH at C-H), 11.57 (s,1H, NH, D,O-exchangeable). Its mass spectrum exhibited a molecular ion peak at: m/z = 472 (base peak). 1H NMR spectrum of 3b showed two singlet at 11.15, 12.30 for 2NH. 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 1,2-dibromopropane yielded 2-cyano-2-(1,3-dithiolan-2-ylidene)-N-(6-iodo-2-methyl-4-oxoquinazolin 3-(4H)-yl)-acetamide 4 and 2-cyano-2-(1,3-dithian-2-ylidene)-N-(6-iodo-2-methyl-4-oxoquinazino lin-3(4H)-yl) acetamide 5 respectively in good yield. Furthermore, reaction of 2 with CS_2 in the presence of KOH and dimethylsulfate while stirring and cooling: 2-cyano-N-(6-iodo-2-methyl-4-oxoquinazolin-3(4H)-yl)-3,3bis (methylthio) acrylamide 6 was afforded smoothly (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 bands for NH, CH-aliphatic, C=N and C=O groups. 1HNMR spectrum of the compound 4 showed signal at 3.75 (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%). 1HNMR spectrum of compound 5 showed signals for dithiene moiety at: 2.20 (p, 2H, J= 6.80 Hz, CH_2), 3.05 (t, 2H, J= 6.60 Hz, CH_3), 3.21 (t, 2H, J= 6.60 Hz, CH.). Mass spectrum of 6 showed a molecular ion peak at: m/z = 472 with a base peak at: m/z = 301 (100%).
Scheme 1:

The reactivity of oxoquinazolin-cyanoacetamide 2 toward isothiocyanates was investigated. Thus, when 2 was left to react with phenyl isothiocyanate in the presence of dilute 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 \textit{in situ} heterocyclization through nucleophilic addition of secondary amino group to carbonyl group of chloroacetone to yield the cyclic product: 2-cyano-N-(6-ido-2-methyl-4-oxoquinazolin-3(4H)-yl)-2-(4- methyl-3-phénylthiazol-2(3H)-ylidene)acetamide 8. Similarly, the novel 2-cyano-N-(6-ido-2-methyl-4-oxoquinazolin-3(4H)-yl)-2-(4-oxo-3-phenylthiiazol-2-ylidene)acetamide 9 was synthesized from reaction of 2 with phenyl isothiocyanate in the presence of potassium hydroxide followed by \textit{in situ} heterocyclization of the resulting adduct with ethylchloroacetate. Also, when 2-cyano-N-(6-ido-2-methyl-4-oxoquinazolin-3(4H)-yl)-2-(methylthio)-3-(phenyl amino)acryl amide 10 was afforded. Cyclocondensation of the acryl amide 10 with hydrazine hydrate in refluxing ethanol furnished 5-amino-6-iodo-2-methyl-4-oxoquinazoline (13) smoothly.

It is well known that many 2-pyridone derivatives exhibited diverse biological activities e.g. as cardiotoxic agents, potential HIV-1 specific reverse transcriptase inhibitors [20, 21] and elastase inhibitors [22]. The present study was continued to report the reactivity of cyanoacetamide derivative 2 towards certain nucleophilic reagents. Thus, when 2 was thermally fused with acetylaceton 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-ido-2-methyl-4-oxoquinazolin-3(4H)-yl)-4,6-dimethyl-2-oxo1,2-dihydropyridine 3-carbonitrile 13 (Scheme 3).

IR spectrum of the pyridine 13 exhibited bands at 2958 (CH-aliphatic), 2218 (C=O). Its \textsuperscript{1}HNMR spectrum (DMSO-\textit{d}_6) displayed the following signals: 2.25 (m, 6H, 2CH), 2.48 (s, 3H, CH), 6.67 (s, 1H, ArH), 7.54 (d, 1H, J=8.40 Hz, ArH at C_6-H), 8.25 (d, 1H, J=8.40 Hz, ArH at C_7-H), 8.41 (s, 1H, ArH at C_8-H). Mass spectrum revealed a molecular ion peak at: m/z = 432 corresponding to a molecular formula C_9H_7IN_2O_3 together with a base peak at: m/z = 416 (100 %).

One-pot reactions of the cyanooacetamide 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-pyridone derivatives 14a, b respectively. On the other hand, the 2-pyridone derivatives 15a, b and 16 were obtained via reaction of cyanooacetamide 2 with 2-(4-chlorobenzylidene) malononitrile or 2-(4-methoxybenzylidene) malononitrile (1:1 molar ratio) or with ter-p-phthaldehyde and malononitrile (1:1:2 molar ratio) upon heating under reflux in the presence of a catalyst. Structural assignment of the pyridones 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 for NH group. \textsuperscript{1}HNMR spectrum of 14b revealed signal at 2.20 (s,3H,CH_3-quniazoline),
Scheme 3:

2.50(s,3H,CH$_3$-pyridine), 7.53(d,1H, $J$ = 8.40 Hz, ArH at C$_2$-H), 8.15(d,1H, $J$ = 8.70 Hz, ArH at C$_2$-H), 8.40(s,1H, ArH at C$_2$-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 peaks 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-containing ammonium acetate furnished smoothly 2-pyridone 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$_1$_{1}N$_{8}$O$_2$ 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 [23, 24]. Some derivatives play also a vital role in electro photographic and electroluminescent devices [25]. Moreover, many other derivatives are well known for their considerable biological and medicinal activities [26]. Cyclocondensation reaction of 2 with salicylaldehyde or 2-hydroxynaphthaldehyde or 7-hydroxy-5-methoxy-2-methyl-4-oxo-4H-chromone-6-carboxaldehyde in ethanol containing ammonium acetate furnished smoothly 2-imino-N-(6-iodo-2-methyl-4-oxoazolin-3(4H)-yl)-2H-chromene-3-carboxamide 17, 2-imino-N-(6-iodo-2-methyl-4-oxoazolin-3(4H)-yl)-2H-chromene-3-carboxamide 18 and 2-imino-N-(6-iodo-2-methyl-4-oxoazolin-3(4H)-yl)-5-methoxy-8-methyl-6-oxo-2,6-dihydropyran[3,2-g]chromene-3-carboxamide 19 respectively (Scheme 4).
1HNMR spectrum of 17 showed characteristic signals at: 9.11 for CH-chromene and at 10.60 for NH ppm. Mass spectrum of 17 exhibited a molecular ion peak at: m/z = 472 (100%). Mass spectrum of compound 18 exhibited a molecular ion peak at: m/z = 522 (100%). 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 584 (100%).

**Antitumor Activity:** Some selected compounds 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 (EAC) 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.

**Antimicrobial Activity:** The preliminary *in vitro* antifungal activity screening for some selected examples of the synthesized compounds was carried out using paper disc method [27] against *Aspergillus ochraceus wilhelm* and *Fusarium oxysporium* fungi. Fresh stock solutions (1mg/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 6.25µg/ml. The incubation for impregnated discs was 72 h at 28 °C. The antibiotic 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 *Aspergillus ochraceus wilhelm* with inhibition zones (18mm) and (16mm) respectively compared with (20mm) Nystatin inhibition zone. All the other tested compounds showed no activity towards the used fungi.

**CONCLUSION**

Novel 4(3H)-quinazolinone derivatives having thiazole, pyrazole, 1,3-dithiazole, pyridine, chromene, pyrazolopyrimidine and pyranochromene moieties were synthesized and characterized. Screening for some selected compounds was carried for their potential antitumor and antifungal activity. (Z)-2-cyano-N-(6-iodo-2-methyl-4-oxoquinazolin-3(4H)-yl)-2-(4-methyl-3-phenylthiazol-2(3H)ylidene)acet-amide 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 (18mm) compared with (20mm) Nystatin inhibition zone.

**REFERENCES**


