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Novel 4(3*H*)-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(4*H*)-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(4*H*)-yl)-3-(phenylamino)-1*H*-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 cyanoacetamide 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-hydroxynaphtha-aldehyde *or* 7-hydroxy-5-methoxy-2-methyl-4-oxo-4*H*-chromone-6-carboxaldehyde in ethanol containing ammonium acetate furnished 2-imino-*N*-(6-iodo-2-methyl-4-oxoquinazolin-3(4*H*)-yl)-2*H*-chromene-3-carboxamide **17**,2-imino-*N*-(6-iodo-2methyl-4-oxoquinazolin-3(4*H*)-yl)-2*H*-benzo[*h*]chromene-3-carboxamide 18 and 2-imino-*N*-(6-iodo-2-methyl-4-oxoquinazolin-3(4*H*)-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(3*H*)-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

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FT/IR-300E spectrophotometer and FTIR 5300 spectrometer (ν, cm^{-1}). ^1H NMR spectra were recorded using Varian mercury 300 MHz & Varian Gemini 200 MHz with chemical shift in δ from Me_4Si and Jeol 270, 500 MHz. Mass spectra were recorded on GC/MS Finnegan SSQ 7000 spectrophotometer & GC Ms-QP 1000 EX mass spectrometer at 70 ev.

2-Cyano-*N*-(6-iodo-2-methyl-4(3*H*)-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, yield 80%, m.p 215-217°C. IR: ν/cm^{-1}: 3210 (NH), 2264 (C≡N) and 1690 (C=O). ^{1}HNMR (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-(6-Iodo-2-methyl-4-oxoquinazolin-3(4H)-ylamino)-2-oxo-N'-p-arylacetohydrazonoyl cyanide (3): 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.

(3a): 2-(6-Iodo-2-methyl-4-oxoquinazolin-3(4H)-ylamino) -2-oxo-N'-phenylacetohydrazonoyl cyanide: IR: ν/cm^{-1}: 3228 (NH), 2216 (C ≡ N) and 1686 (C=O). MS, m/z (%) 472 (M^+; 8.4%) 301(100) 473, 367(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%.

(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≡N) and 1689 (C=O). ^{1}HNMR (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-Cyano-2-(1,3-dithiolan-2-ylidene)-*N*-(6-iodo-2-methyl-4(3*H*)quinazolinonyl)-acetamide (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 dibromoethane (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 (CH_{aliph}), 2204 (C≡N) and 1696, 1666 (C=O). ^{1}HNMR ($CDCl_3$): 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(3*H*)-quinazolinonyl)-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 (CH_{aliph}), 2200 (C≡N) and 1703, 1665 cm^{-1} (C=O). ^{1}HNMR ($CDCl_3$): 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(3H)-quinazolinon-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: ν/cm^{-1}: 3212 (NH), 2964, 2926 (CH_{aliph}), 2200 (C≡N) 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 $C_{15}H_{13}IN_4O_2S_2$: C, 38.14; H, 2.77; N, 11.86. Found: C38.10, H, 2.80; N, 11.90%.

2-Cyano-N-(6-iodo-2-methyl-4(3H)-quinazolinon-3-yl)-2-(4-methyl-3-phenyl-thiazol-2(3H)-ylidene)acetamide(8): To a stirred suspension of finely powdered potassium hydroxide (0.01 mole) in dry DMF (10ml) cyanoacetamide 2 (0.01 mole) was added, then (0.01 mol) phenylisothiocyanate was added slowly. After complete addition, stirring of the reaction mixture was continued for additional 5 h. Then chloroacetone (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 from acetic acid to give 8 as yellow brownish crystals, yield 75%, m.p 248-250 °C. IR: ν/cm^{-1}: (NH), 2973, 2926 (Ch_{aliph}) 2181 (C≡N) and 1708 (C=O). ^{1}HNMR (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 $C_{22}H_{16}IN_5O_2S$: C48.81,; H, 2.98; N, 12.94. Found: C, 48.80; H, 3.00; N, 12.90%.

2-Cyano-N-(6-iodo-2-methyl-3(4H)-quinazolinon-3-yl)-2-(4-oxo-3-phenylthiazo-lidin-2-ylidene) acetamide (9): Compound 9 was synthesized as mentioned for synthesis of 7: When using ethylchloroacetate instead of chloroacetone the resulting product was crystallized from ethanol/dioxan to give 9 as yellow brownish crystals, yield 70%, m.p 193-195°C. IR: ν/cm^{-1}: 3188 (NH), 2924 (CH_{aliph}) 2220 (C≡N) and 1688 (C=O). ^{1}HNMR (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-Cyano-*N*-(6-iodo-2-methyl-4(3*H*)-quinazolinon-3-yl)-3-(methylthio)-3-(phenyl-amino) acrylamide (10): To suspension of potassium hydroxide (0.01 mole) in dry DMF (10ml) cyanoacetamide 2 (0.01 mole) 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: ν/cm^{-1}: 3244 (NH), 2194 (C≡N) and 1658 (C=O). ^{1}HNMR (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%.

5-Amino-*N*-(6-iodo-2-methyl-4(3*H*)-quinazolinon-3-yl)-3-(phenylamino)-1*H*-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. >300ºC. IR: ν/cm^{-1}: 3311, 3199, 3159(NH, NH_2) and 1684 (C=O) ^{1}HNMR (DMSO-d_6): δ/ppm: 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 (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%.

***N*-(6-iodo-2-methyl-3(4*H*)-quinazolin-3-yl)-5,7-dimethyl-2(phenylamino)pyra-zolo[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 3hrs. then left to cool. The obtained solid product was filtrated and crystallized from dioxane to give 12 as yellow brownish crystals, yield 65%, m.p >300 °C. IR: ν/cm^{-1}: 3253(NH) and 1705, 1656 (C=O) ^{1}HNMR (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%.

1-(6-Iodo-2-methyl-4(3H)-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 (Ch_{aliph}) 2218 (C≡N) and 1680 (C=O) ^{1}HNMR (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; H3.00; N, 13.00%.

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)

General Procedure: 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 20 as yellow crystals.

(14a): 6-Amino-1-(6-iodo-2-methyl-4-oxoquinazolin-3(4H)-yl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile: M.P. 197-195°C, yield (70%), IR: ν/cm^{-1}: 3353, 3204(NH_2), 2191(C≡N) and 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%.

(14b): 6-Amino-1-(6-iodo-2-methyl-4-oxoquinazolin-3(4H)-yl)-4-methyl-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile: M.P. 277-280°C, yield (75%) IR: ν/cm^{-1}: 3302, 3143 (NH_2), 2218 (C≡N) and 1696 (C=O). ^{1}HNMR (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%.

6-Amino-1-(6-iodo-2-methyl-4(3H)-quinazolinonyl)-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 pipridine. 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-iodo-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_2), 2214 (C≡N) and 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%.

(15b): 6-Amino-4-(4-chlorophenyl)-1-(6-iodo-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_2), 2219 (C≡N) and 1695(C=O). ^{1}HNMR (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%.

6-Amino-4-(4-(2,2-dicyanovinyl)phenyl)-1-(6-iodo-2-methyl-4(3H)-quinazolinon-3-yl)-2-oxo-1,2-dihydropyridine-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 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, 3320, 3158 (NH_2), 2212 (C≡N) and 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 $C_{26}H_{13}IN_8O_{\frac{1}{2}}$ C52.37; H, 2.20; N, 18.79. Found: C, 52.40; H, 2.20; N, 18.80%.

2-Imino-N-(6-iodo-2-methyl-4(3*H*)-quinazolinon-3-yl)-4a,8a-dihydro-2*H*-chrom-ene-3-carboxamide (17): A mixture cyanoacetamide 2 (0.01 mol) and salicylaldehyde (0.01 mol) in ethanol (30 ml) containing ammonium acetate (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: ν/cm^{-1}: 3242 (NH) and 1682 (C=O). ^{1}HNMR (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%.

Synthesis of 2-imino-N-(6-iodo-2-methyl-4(3*H*)-quinazolinon-3-yl)-4a,10b-dihydro-2*H*-benzo [*H*] chromene-3-carboxamide (18): Compound 18 was synthesized as mentioned above in synthesis of 17: When using β-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: ν/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_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%.

Synthesis of 2-imino-N-(6-iodo-2-methyl-4(3*H*)-quinazolinon-3-yl)-5-methoxy-8-methyl-6-oxo-2,6-dihydropyrano[3,2-*g*]chromene-3-carboxamide (19): Compound 19 was synthesized as mentioned above in synthesis of 17: When using (7-hydroxy-5-methoxy-2-methyl-4-oxo-4*H*-chromone-6-carboxaldehyde) instead of salicylaldehyde the resulting product was crystallized from dioxin to give 19 as yellow crystals, yield 80%, m.p 254-356 °C. IR: ν/cm^{-1}: 3186 (NH) and 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%.

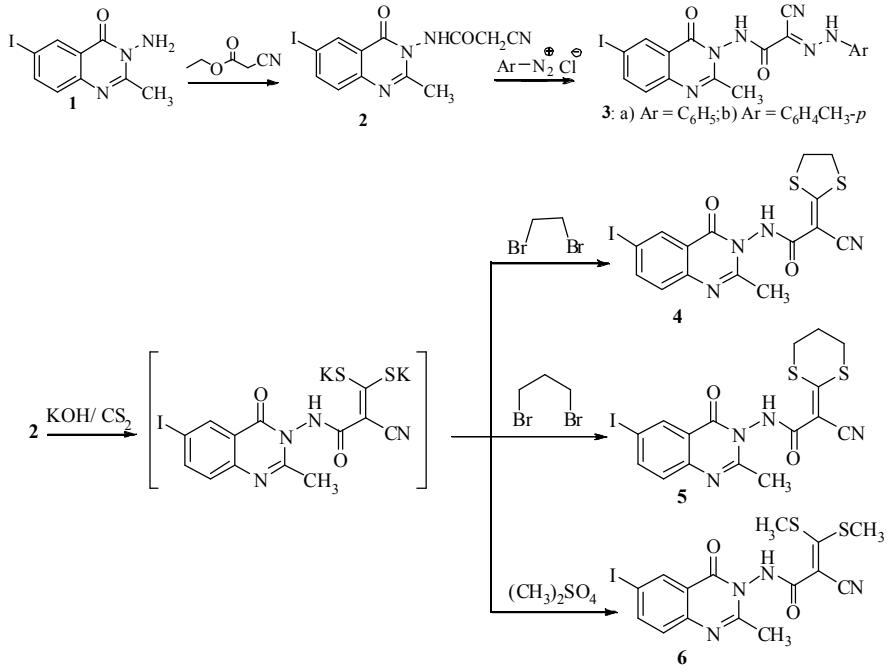
RESULTS AND DISCUSSION

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 1[19] (above its melting point) with ethyl 2-cyanoacetate afforded 2-cyano-*N*-(6-iodo-2-methyl-4-oxoquinazolin-3(4*H*)-yl) acetamide 2.

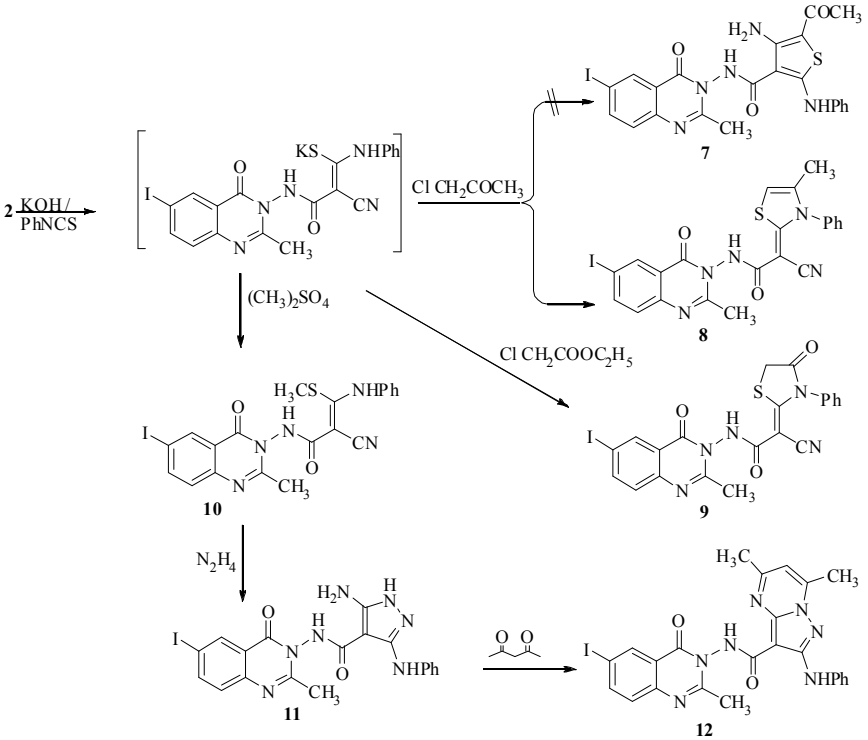
In order to probe the reactivity of the latter cyanoacetamide having active methylene moiety, its diazotization reaction was tried. Thus, upon its reaction with the desired diazonium chloride (obtained *in situ* by diazotization of the desired aromatic amine using a mixture of sodium nitrite and HCl) in the presence of sodium acetate; the corresponding quinazolinone hydrazono derivatives 3a, b were obtained. 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≡N) and 1690 cm^{-1} (C=O). Its ^{1}HNMR spectrum in (DMSO-d_6) revealed the following signals: 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}HNMR 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-dibromoethan or 1,3-dibromopropane yielded 2-cyano-2-(1,3-dithiolan-2-ylidene)-*N*-(6-iodo-2-methyl-4-oxoquinazolin 3-(4*H*)-yl)-acetamide 4 and 2-cyano-2-(1,3-dithian-2-ylidene)-N-(6-iodo-2-methyl-4-oxoquinazo lin-3(4*H*)-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(4*H*)-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. ^{1}HNMR 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%). ^{1}HNMR 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_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%).



Scheme 1:



Scheme 2:

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 *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(4H)-yl)-2-(4-oxo-3-phenylthiazolidin-2-ylidene)acet- amide 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 ethylchloroacetate. 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-(methylthio)-3-(phenyl amino)acryl amide 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-(phenyl amino)-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.

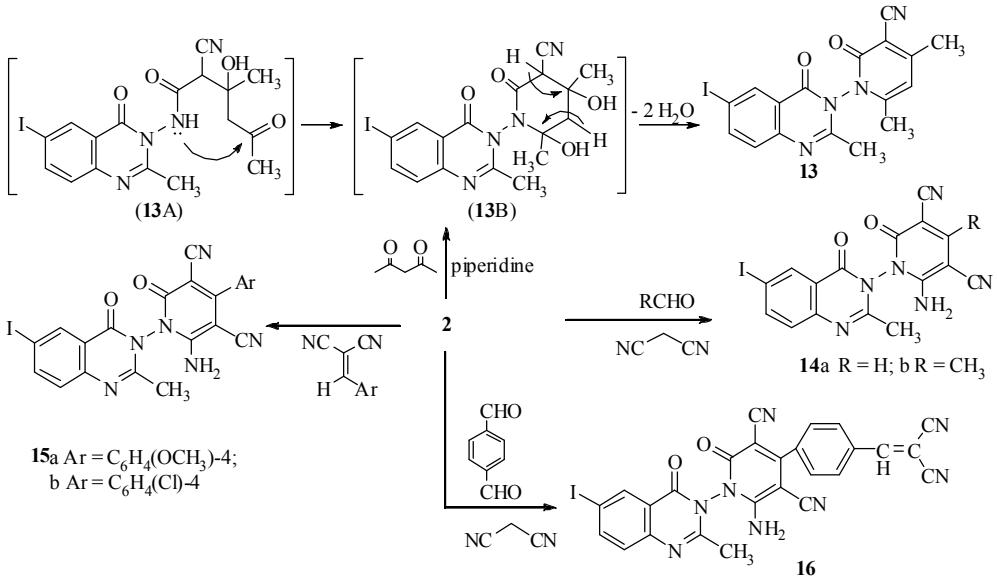
^{1}HNMR spectrum (DMSO-d_6) of 8 displayed the following signals at: δ = 1.93 (s, 3H, CH_3[thiazole]), 2.40 (s, 3H, CH_3[quinazoline]), 7.03 (s, 1H, CH [thiazole]), 9.93 (s, 1H, NH, D_2O-exchangeable). Its mass spectrum revealed a molecular ion peak at: *m/z* = 541with a base peak at: m/z = 214 (100%). ^{1}HNMR spectrum of 9 revealed signal at: δ = 4.00 (s,2H, CH_2[thiazole]),10.60(s,1H,NH,D_2O-exchangeable). ^{1}HNMR spectrum of 10 displayed the following signals at: δ = 2.30 (s, 3H, SCH_3), 2.45 (s, 3H, CH_3), 10.81 (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 (100 %).

IR spectrum of 11 showed bands at 3311, 3199, 3159(NH, NH_2) and 1684cm^{-1} (C=O). Its ^{1}HNMR spectrum (DMSO-d_6) 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 (s, 1H, NH). ^{1}HNMR spectrum (DMSO-d_6) of 12 displayed signals at: 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 $C_{2,6}$ 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). Its Mass spectrum revealed a molecular ion peak at: *m/z* = 566 (M + 1; 9.6%) with a base peak at: m/z = 265 (100 %).

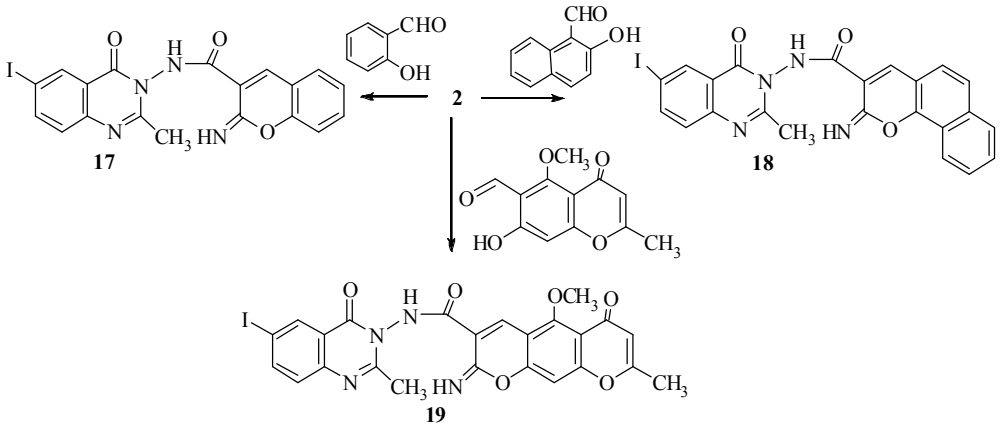
It is well known that many 2-pyridone derivatives exhibited diverse biological activities e.g. as cardiotonic agents, potential HIV-1 specific reverse transcriptase inhibitors [20, 21] and elastase inhibitors [22]. The present study was continued to report the reactivity of cyanoacetamide derivative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

IR spectrum of the pyridine 13 exhibited bands at 2958 (CH-aliphatic), 2218 (C≡N) and 1680 cm^{-1} (C=O). Its ^{1}HNMR spectrum (DMSO-d_6) 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-pyridone derivatives 14a, b respectively. On the other hand, the 2-pyridone derivatives 15a, b and 16 were obtained *via* reaction of cyanoacetamide 2 with 2-(4-chlorobenzylidene) malononitrile or 2-(4-methoxybenzy-lidene) 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 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_2 group. ^{1}HNMR spectrum of 14b revealed signal at 2.20 (s,3H,CH_3-quniazoline),



Scheme 3:



Scheme 4:

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-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 $C_{26}H_{13}IN_8O_2$ 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 [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-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-carboxamide 17, 2-imino-*N*-(6-iodo-2-methyl-4-oxoquinazolin-3(4*H*)-yl)-2*H*-benzo[*h*]chromene-3-carboxamide 18 and 2-imino-*N*-(6-iodo-2-methyl-4-oxoquinazolin-3(4*H*)-yl)-5-methoxy-8-methyl-6-oxo-2,6-dihydropyrano[3,2-*g*]chrom-ene-3-carboxamide 19 respectively (Scheme 4).

^{1}HNMR 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 reavealed 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 relation ship (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(3*H*)-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.

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