Synthesis of Some Quinazoline-2(1*H*),4(3*H*)-dione Derivatives

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Several quinazoline-2(1*H*),4(3*H*)-dione derivatives were synthesized from pyrimidine-2(1*H*),4(3*H*)-dione derivative.

Keywords: Quinazoline-2(1*H*),4(3*H*)-dione derivatives.

INTRODUCTION

Synthesis of quinazoline-2,4-diones with various substituents has been reported.[1] The characterization and cycloaddition reaction of 5,6-dihydro-1,3-dimethyl-6-methylene-5-(substituted amino) methylenopyrimidine-2(1*H*),4(3*H*)-diones with olefinic dienophiles was carried out in highly regio- and stereoselective ways to give quinazoline derivatives.[2] Novel 4-substituted 2-piperazinylquinazolines as potent anticonvulsive and antihypoxic agents have been reported.[3] Novel quinazoline derivatives based on cycloaddition between 2,4-disubstituted pyrimidine *ortho*-quinodimethanes and suitable dienophiles have been reported.[4] Quinazoline derivatives often lead to very interesting biological and pharmaceutical activities.[5-10] In continuation of previous work, the pyrimidine derivative[11] **1** was used as precursor for the synthesis of some quinazoline-2(1*H*),4(3*H*)-dione derivatives which are expected to have biological activity.

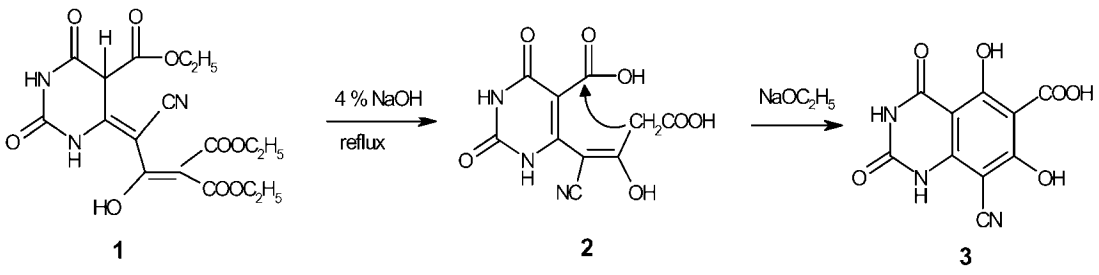
RESULTS AND DISCUSSION

Pyrimidine derivative **1** was refluxed in 4% sodium hydroxide solution to afford 6-[1-(cyano)-2-(hydroxyl)ethenyl acetic acid]pyrimidine-2(1*H*),4(3*H*)-dione-5-carboxylate **2** whose ^{1}H NMR spectra revealed an enol hydrogen at 13.4 ppm, two carboxylic hydrogens at 10.2, 10.7 ppm, methylene hydrogen at 2.65 ppm and the absence of the characteristic signals for ethyl moity.

On the treatment of **2** with sodium ethoxide it yielded compound **3** whose ^{1}H and ^{13}C NMR spectra showed the absence of a characteristic signal for methylene group, and its mass spectra revealed a parent peak at 263 for M^+. Since only one set of signals is observed in the ^{1}H NMR spectra, it is assumed that if tautomerism exists, it is fast on the NMR timescale.[12] The structures of the prepared compounds are in agreement with their spectral data (cf experimental, Scheme I).

Several 6-substituted-5,7-dihydroxy-8-cyanoquinazoline-2(1*H*),4(3*H*)-dione derivatives were synthesized through the reaction of **3** with appropriate reagents. Thus, compound **3** reacted with hydrazine hydrate afforded **4** which on the reaction with triethylorthoformate yielded **5**. Also, the reaction of **3** with phenylenediamine or ethylenediamine afforded **6**, **7**, respectively. Decarboxylation of **3** was maintained by treatment with orthophosphoric acid at room temperature to

Scheme I



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afford **8** (cf experimental, Scheme II).

Compound **8** was subjected to further reactions affording 6-substituted-5,7-dihydroxy-8-cyanoquinazoline-2(1*H*),4(3*H*)-dione derivatives. Thus, compound **8** reacted with formaldehyde and piperazine to yield **9**. The reaction of **8** with formaldehyde in the presence of dimethylamine yielded **10**. Nitration of **8** with 20% HNO_3 afforded **11**. Compound **8** reacted with diazonium salt of *p*-chloroaniline to yield the dye **12** which on treatment with zinc in acetic acid afforded **13**.

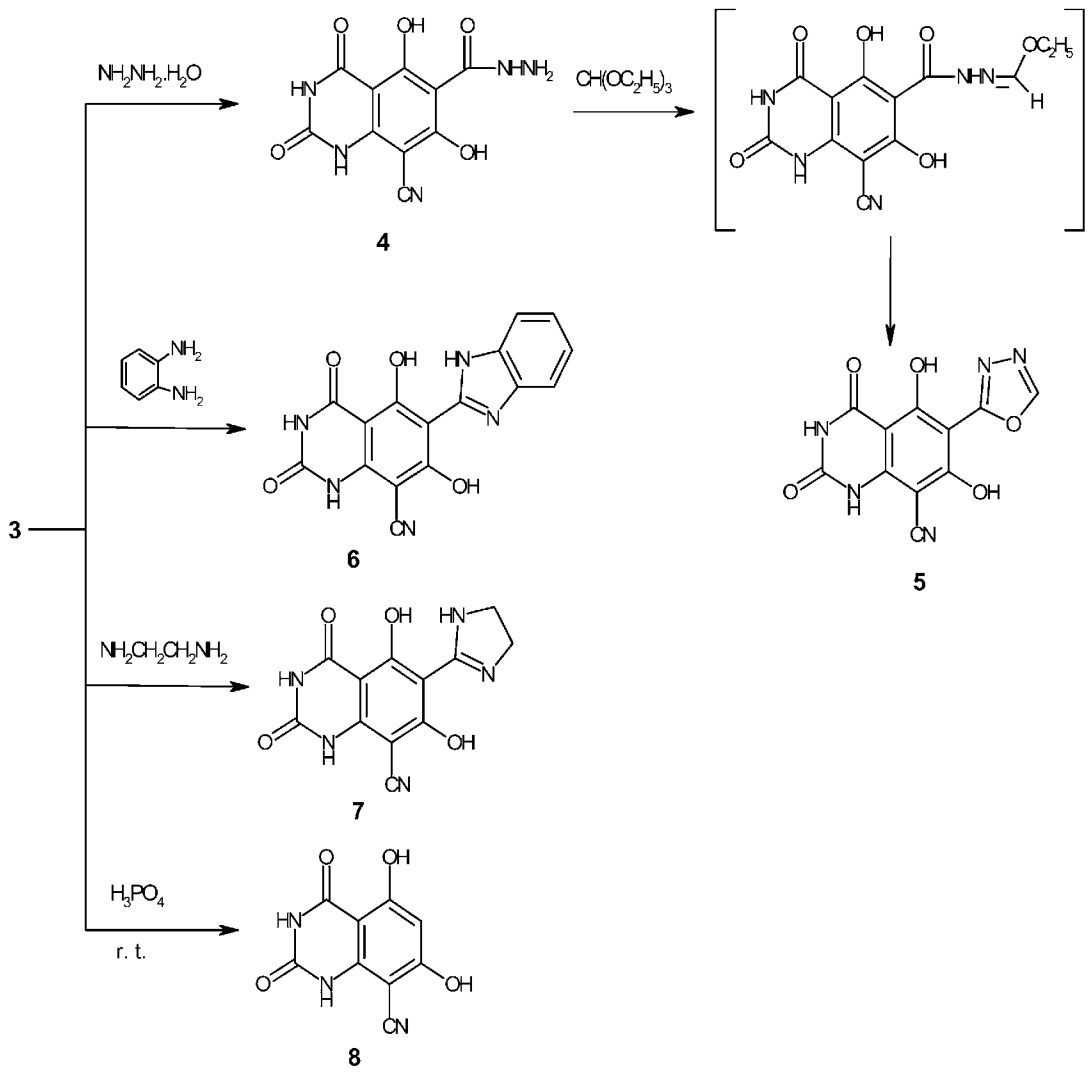
Quinazoline-2(1*H*),4(3*H*)-dithione derivative **14** was synthesized by the reaction of **8** with phosphorouspentasulphide. Compound **14** was methylated by the reaction with methyl iodide and sodium hydroxide affording **15** which was oxidized using concentrated nitric and sulfuric acids to yield **16**. Pyrano[2,3-*a*]benzo[3,4-*d*]pyrimidine derivatives **17**, **18** were synthesized by the treatment of **8** with diethylmalonate and ethylcyanoacetate, respectively.

The treatment of **8** with phosphorousoxychloride afforded **19**. By applying the Reiman-Tiemann reaction using an alkaline solution of **8**, compound **20** was obtained which, when treated with hydrazine hydrate, afforded **21**. The structures of the prepared compounds are in agreement with their spectral data (cf experimental, Scheme III).

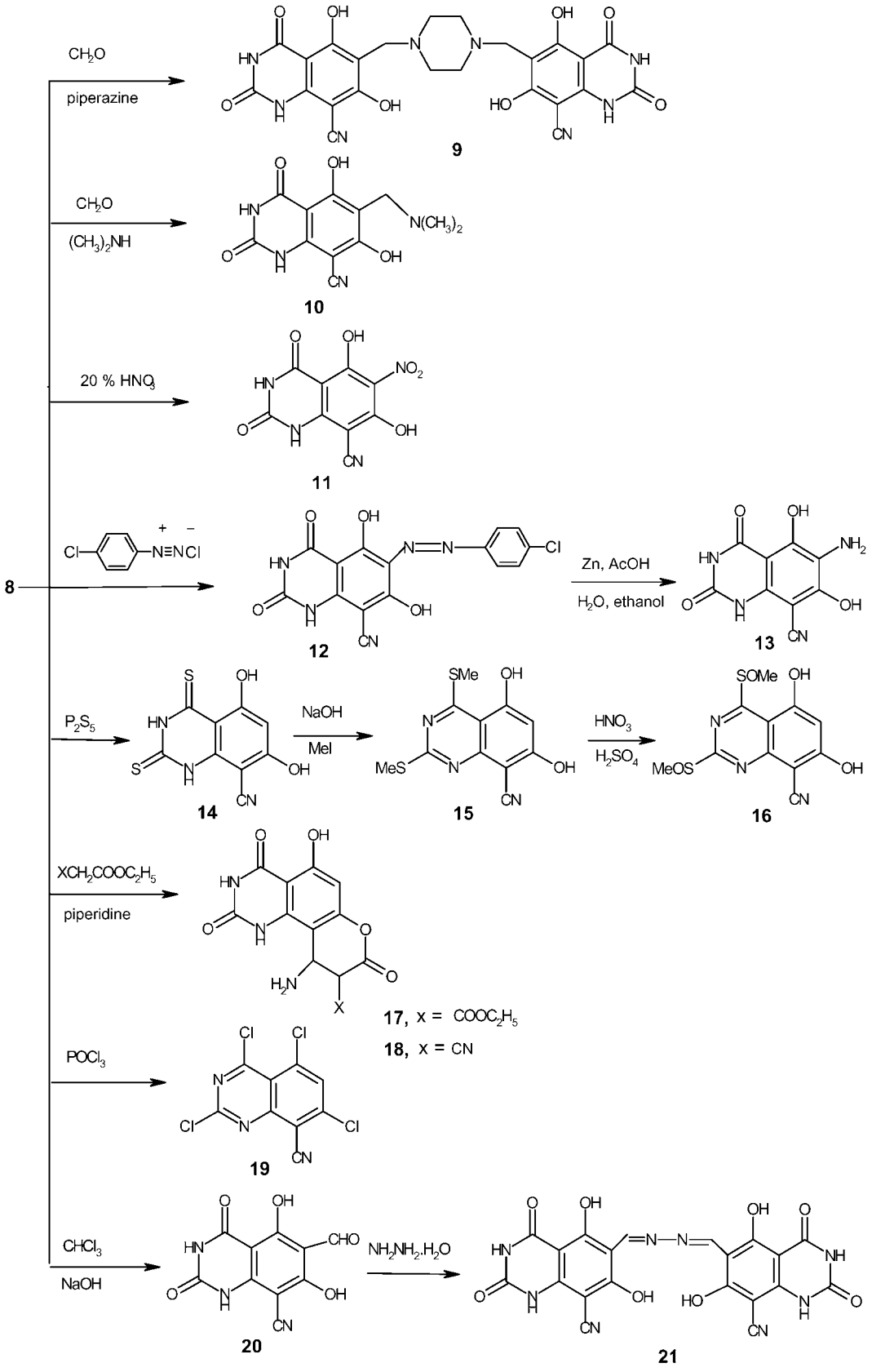
EXPERIMENTAL

Melting points were determined on a Gallenkamp electrothermal apparatus and are uncorrected. The IR spectra

Scheme II



Scheme III


8
CH2O
piperazine
9
CH2O
(CH3)2NH
10
20 % HNO3
11
12
Zn, AcOH
H2O, ethanol
13
P2S5
14
NaOH
MeI
15
HNO3
H2SO4
16
XCH2COOC2H5
piperidine
17, x = COOC2H5
18, x = CN
POCl3
19
CHCl3
NaOH
20
NH2NH2.H2O
21

were recorded on a Pye-Unicam SP 110 spectrophotometer as KBr disks. The ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini NMR spectrometer 300 (300 MHz for ^1H, 75.5 MHz for ^{13}C) using Me_4Si as an internal reference. Mass spectra were measured on a Hitachi 80-B spectrometer at 70 eV. The progress of the reaction was monitored by TLC using precoated silica gel plates (F254, Merck, Darmstadt).

Preparation of 6-[1-(cyano)-2-(hydroxyl)ethenyl acetic acid]pyrimidine-2(1*H*),4(3*H*)-dione-5-carboxylate 2

Compound **1** (4.08 g, 0.01 mole) was refluxed with 1 N NaOH[13] (50 mL) for 4 h. Monitor the reaction by tlc (1 drop of the reaction mixture was added to two drops of 5 N HCl; this aqueous sample was extracted with ten drops of ethyl acetate, and the ethyl acetate extracted was spotted on the tlc plate, which was eluted with hexane:ethyl acetate 1:1) for the disappearance of the starting material. The reaction mixture was cooled, triturated with water, acidified to pH 2 with conc. HCl, then extracted with ethyl acetate to remove the organic impurities. The resulting aqueous mixture was concentrated. This concentrate was stored in a freezer for about 24 h, and the resulting crystals were collected by filtration and then dried. 2.33 g (83%); m.p. > 300 °C; IR (KBr) ν_{max}/cm^{-1}: 1730 (CO), 2224 (CN), 3355 (NH), 1605 (C=C); ^1H NMR ($CDCl_3$) δ/ppm: 8.2, 9.5 (br, s, H, NH) D_2O exchangeable, 10.2, 10.7, 13.4 (br, 1H, OH), 2.65 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ: 28.7 (CH_2), 117.8 (CN), 132.3 (C), 134.9 (C), 138.2 (C), 139.6 (C), 162.7, 163.5, 169.3, 170.4 (CO); MS *m/z*: 281 (M^+, 16%).

Anal. Calc. For $C_{10}H_7N_3O_7$ (M_r = 281.18): C, 42.72; H, 2.51; N, 14.94%, found C, 42.66; H, 2.45; N, 14.83%.

Preparation of 8-cyano-5,7-dihydroxyquinazoline-2(1*H*),4(3*H*)-dione-6-carboxylate 3

A solution of **2** (2.81 g, 0.01 mol) in ethanolic sodium ethoxide [prepared from sodium (0.04 g) in dry ethanol (20 mL)] was refluxed for 6 h. To the reaction mixture was added water (30 mL) and the product was collected by filtration. Further purification was accomplished by recrystallization from chloroform. 1.959 g (83%); m.p. > 300 °C; IR (KBr) ν_{max}/cm^{-1}: 1726 (CO), 2225 (CN), 3353 (NH), 1610 (C=C ring stretch); ^1H NMR ($CDCl_3$) δ/ppm: 8.3, 9.5 (br, s, 1H, NH) D_2O exchangeable, 10.4, 10.6, 12.7 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ: 117.2 (CN), 130.6 (C), 131.7 (C), 132.5 (C), 134.4 (C), 138.0 (C), 140.3 (C), 162.4, 162.7, 169.5 (CO); MS *m/z*: 263 (M^+, 45%).

Anal. Calc. For $C_{10}H_5N_3O_6$ (M_r = 263.17): C, 45.64; H, 1.92; N, 15.97%, found C, 45.58; H, 1.88; N, 15.89%.

Preparation of 8-cyano-6-carboxylic acid hydrazide-5,7-dihydroxyquinazoline-2(1*H*),4(3*H*)-dione 4

A solution of compound **3** (2.63 g, 0.01 mol) in H_2O (50 mL) and hydrazine hydrate (5 mL) were heated under reflux for 2 h. After cooling, the precipitate formed is collected and crystallized from ethanol. 2.52 g (91%); m.p. 286 °C; IR (KBr) ν_{max}/cm^{-1}: 1720 (CO), 2222 (CN), 3362 (NH), 3244 (NH_2), 1608 (C=C ring stretch); ^1H NMR ($CDCl_3$) δ/ppm: 8.4 (br, s, 1H, NH) D_2O exchangeable, 10.4, 10.5 (s, 1H, OH), 8.4, 9.2, 9.8 (s, 1H, NH), 6.5 (s, 2H, NH_2); ^{13}C NMR ($CDCl_3$) δ: 117.5 (CN), 130.2 (C), 132.3 (C), 132.8 (C), 134.4 (C), 138.5 (C), 139.3 (C), 162.2, 162.5, 163.0 (CO); MS *m/z*: 277 (M^+, 27%).

Anal. Calc. For $C_{10}H_7N_5O_5$ (M_r = 277.20): C, 43.33; H, 2.55; N, 25.26%, found C, 43.24; H, 2.44; N, 25.19%.

Preparation of 8-cyano-5,7-dihydroxy-6-(1,3,4-oxadiazol-2-yl)quinazoline-2(1*H*),4(3*H*)-dione 5

A mixture of **4** (2.77 g, 0.01 mol), an equimolar amount of triethylorthoformate[14] (1.48 g, 0.01 mole) and acetic anhydride (15 mL) was refluxed for 5 h. The solvent was removed under reduced pressure. Water was added to the resulting solid product followed by filtration. Further purification was accomplished by recrystallization from chloroform. 2.38 g (83%); m.p. 267 °C; IR (KBr) ν_{max}/cm^{-1}: 1695 (CO), 2225 (CN), 3346 (NH), 1610 (C=C ring stretch); ^1H NMR ($CDCl_3$) δ/ppm: 8.7, 9.4 (br, s, 1H, NH) D_2O exchangeable, 10.5, 10.8 (s, 1H, OH), 7.31 (s, 1H, oxadiazole-H); ^{13}C NMR ($CDCl_3$) δ: 118.7 (CN), 128.6 (CH), 129.0 (C), 130.5 (C), 131.8 (C), 132.6 (C), 134.3 (C), 138.6 (C), 139.9 (C), 162.2, 162.8 (CO); MS *m/z*: 287 (M^+, 19%).

Anal. Calc. For $C_{11}H_5N_5O_5$ (M_r = 287.19): C, 46.00; H, 1.75; N, 24.39%, found C, 45.92; H, 1.68; N, 24.30%.

Preparation of 8-cyano-5,7-dihydroxy-6-(benzoimidazol-2-yl)quinazoline-2(1*H*),4(3*H*)-dione 6

A mixture of **3** (2.63 g, 0.01 mol), phenylene diamine (1.08 g, 0.01 mol) and freshly fused sodium acetate (0.3 g) in glacial acetic acid (40 mL) was refluxed for 3 h. The reaction mixture was cooled and the precipitate solid was filtered, dried and crystallized from dilute acetic acid. 2.64 g (79%); m.p. 251 °C; IR (KBr) ν_{max}/cm^{-1}: 1715 (CO), 2222 (CN), 3358 (NH), 1612 (C=C ring stretch); ^1H NMR ($CDCl_3$) δ/ppm: 8.4, 8.8, 9.8 (br, s, 1H, NH) D_2O exchangeable, 10.4, 10.6 (s, 1H, OH), 7.10 (dd, *J* = 8, Ar-H), 7.65 (dd, *J* = 8, 1H, Ar-H), 8.20 (d, *J* = 8, Ar-H), 8.75 (d, *J* = 8, Ar-H); ^{13}C NMR ($CDCl_3$) δ: 117.8 (CN), 128.4 (C), 129.3 (C), 129.7 (C), 130.5 (C), 130.9 (2C), 131.8 (C), 132.5 (2C), 133.6 (C), 135.9 (C),

138.0 (C), 138.8 (C), 162.7, 163.2 (CO); MS *m/z*: 335 (M^+, 44%).

Anal. Calc. For $C_{16}H_9N_5O_4$ (M_r = 335.28): C, 57.32; H, 2.71; N, 20.89%, found C, 57.24; H, 2.66; N, 20.83%.

Preparation of 8-cyano-5,7-dihydroxy-6-(4,5*H*-imidazol-2-yl)quinazoline-2(1*H*),4(3*H*)-dione 7

A mixture of **1** (0.01 mol), ethylene diamine (0.66 mL, 0.01 mol) and freshly fused sodium acetate (0.3 g) in glacial acetic acid (30 mL) was refluxed for 3 h. The reaction mixture was cooled and the precipitate solid was filtered, dried and crystallized from dilute acetic acid. 2.35 g (82%); m.p. 277 °C; IR (KBr) ν_{max}/cm^{-1}: 1708 (CO), 2224 (CN), 3360 (NH), 1606 (C=C ring stretch); ^{1}H NMR ($CDCl_3$) δ/ppm: 8.3, 9.3 (br, s, 1H, NH), 11.6 (t, *J* = 4.6, 1H, NH) D_2O exchangeable, 10.3, 10.7 (s, 1H, OH), 4.4 (t, *J* = 10, 2H, CH_2), 1.7 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ: 19.6, 19.8 ($2CH_2$), 116.8 (CN), 126.4 (C), 130.8 (C), 131.7 (C), 132.3 (C), 134.4 (C), 138.7 (C), 139.5 (C), 162.8, 163.4 (CO); MS *m/z*: 287 (M^+, 58%).

Anal. Calc. For $C_{12}H_9N_5O_4$ (M_r = 287.24): C, 50.18; H, 3.16; N, 24.38%, found C, 50.09; H, 3.05; N, 24.29%.

Preparation of 8-cyano-5,7-dihydroxyquinazoline-2(1*H*),4(3*H*)-dione 8

A mixture of **3** (2.63 g, 0.01 mol) and orthophosphoric acid (2 mL) was stirred at room temperature for 10 h. The reaction mixture was cooled, filtered, washed with water and recrystalized from ethanol. 1.7 g (78%); m.p. > 300 °C; IR (KBr) ν_{max}/cm^{-1}: 1716 (CO), 2226 (CN), 3345 (NH), 1608 (C=C ring stretch); ^{1}H NMR ($CDCl_3$) δ/ppm: 8.6, 9.5 (br, s, 1H, NH) D_2O exchangeable, 9.8, 10.2 (s, 1H, OH), 7.25 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ: 116.7 (CN), 130.6 (CH), 131.7 (C), 132.3 (C), 134.5 (C), 138.5 (C), 139.7 (C), 162.9, 163.2 (CO); MS *m/z*: 219 (M^+, 21%).

Anal. Calc. For $C_9H_5N_3O_4$ (M_r = 219.16): C, 49.33; H, 2.30; N, 19.17%, found C, 49.26; H, 2.22; N, 19.06%.

Preparation of 1*N*,4*N*-bis(8-cyano-5,7-dihydroxyquinazoline-2(1*H*),4(3*H*)-dione-6-methyleno)piperazine 9

A mixture of **8** (2.19 g, 0.01 mol), formaline (37%, 1 mL) and piperazine (0.8 g) in ethanol (20 mL) was stirred at room temperature for 6 h. The product was cooled, filtered, washed with water and recrystallized from ethanol. 4.0 g (73%); m.p. 226 °C; IR (KBr) ν_{max}/cm^{-1}: 1734 (CO), 2228 (CN), 3367 (NH), 1630 (C=C ring stretch); ^{1}H NMR ($CDCl_3$) δ/ppm: 8.8, 9.7 (br, s, H, NH) D_2O exchangeable, 11.4, 11.9 (s, 1H, OH), 3.36-3.60 (m, 2H, CH_2), 3.11 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ: 20.8 ($2CH_2$), 22.5 ($4CH_2$), 119.7 (2CN), 130.6 (2C), 131.8 (2C), 132.3 (2C), 134.9 (2C), 138.2 (2C), 139.6 (2C), 162.6, 163.7 (4CO); MS *m/z*: 548 (M^+, 36%).

Anal. Calc. For $C_{24}H_{20}N_8O_8$ (M_r = 548.48): C, 52.56; H, 3.68; N, 20.43%, found C, 52.49; H, 3.59; N, 20.33%.

Preparation of 8-cyano-5,7-dihydroxy-6-dimethylamino-methylquinazoline-2(1*H*),4(3*H*)-dione 10

A mixture of **8** (2.19 g, 0.01 mol) formaline (37%, 1 mL) and dimethylamine hydrochloride (0.41 g) in ethanol (20 mL) was stirred at room temperature for 6 h. The product was cooled, filtered, washed with water and recrystallized from ethanol. 2.23 g (81%); m.p. 196 °C; IR (KBr) ν_{max}/cm^{-1}: 1718 (CO), 2220 (CN), 3348 (NH), 1610 (C=C ring stretch); ^{1}H NMR ($CDCl_3$) δ/ppm: 8.0, 9.3 (br, s, H, NH) D_2O exchangeable, 10.8, 11.5 (s, 1H, OH), 5.46 (s, 2H, CH_2), 3.34 (s, 3H, NMe_2); ^{13}C NMR ($CDCl_3$) δ: 22.5 (CH_2), 34.4 ($2CH_3$), 116.7 (CN), 130.4 (C), 131.7 (C), 132.7 (C), 134.9 (C), 138.2 (C), 139.8 (C), 162.2, 162.8 (2CO); MS *m/z*: 276 (M^+, 48%).

Anal. Calc. For $C_{12}H_{12}N_4O_4$ (M_r = 276.25): C, 52.17; H, 4.38; N, 20.28%, found C, 52.09; H, 4.32; N, 20.23%.

Preparation of 8-cyano-5,7-dihydroxy-6-nitroquinazoline-2(1*H*),4(3*H*)-dione 11

Compound **8** (2.19 g, 0.01 mol) and HNO_3 (20%, 2 mL) were refluxed for 2 hours. After cooling, the product was filtered, washed with water and recrystallized from chloroform. 2.29 g (87%); m.p. 291 °C; IR (KBr) ν_{max}/cm^{-1}: 1726 (CO), 2223 (CN), 3352 (NH), 1560, 1378 (N=O), 1605 (C=C ring stretch); ^{1}H NMR ($CDCl_3$) δ/ppm: 8.3, 9.6 (br, s, H, NH) D_2O exchangeable, 11.3, 11.7 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ: 118.5 (CN), 130.8 (C), 131.7 (C), 132.4 (C), 134.7 (C), 138.5 (C), 139.4 (C), 162.3, 162.8 (CO); MS *m/z*: 264 (M^+, 33%).

Anal. Calc. For $C_9H_4N_4O_6$ (M_r = 264.16): C, 40.92; H, 1.53; N, 21.21%, found C, 40.83; H, 1.46; N, 21.14%.

Preparation of 8-cyano-6-(*p*-chlorophenylazo)-5,7-dihydroxy-quinazoline-2(1*H*),4(3*H*)-dione 12

To a well stirred solution of *p*-chloroaniline (1.27 g, 0.01 mol) in concentrated hydrochloric acid (10 mL) and water (20 mL) cooled in an ice bath slowly was added a solution of sodium nitrite (0.92 g, 0.013 mol) in water (20 mL). A light yellow solution resulted. After stirring at 0 °C for 10 minutes, this cooled solution of p. chlorobenzenediazonium chloride[15] was added dropwise to a mixture containing **8** (2.19 g, 0.01 mol) buffered with sodium acetate (14 g) and acetic acid (50 mL) in water (100 mL). A yellow precipitate appeared. The mixture was allowed to stir at room temperature for 24 h. The

precipitate brown solid was filtered, washed with water and dried. This material was used in the next step without any further purification. An analytical sample was prepared by flash column chromatography (2:1 hexane-acetone) followed by recrystallization from hexane/acetone. 3.219 g (90%); m.p. 184 °C; IR (KBr) ν_{max}/cm^{-1}: 704 (C-Cl), 1722 (CO), 2224 (CN), 1815 (N=N), 3352 (NH), 1650 (C=C ring stretch); ^1H NMR ($CDCl_3$) δ/ppm: 8.6, 9.6 (br, s, H, NH) D_2O exchangeable, 10.4, 10.6 (s, 1H, OH), 7.58 (d, *J* = 8, 2H, Ar-H), 7.72 (d, *J* = 8, 2H, Ar-H); ^{13}C NMR ($CDCl_3$) δ: 117.4 (CN), 128.6 (CH), 128.9 (CH), 129.4 (CH), 129.8 (CH), 130.7 (C), 131.7 (C), 132.3 (C), 134.8 (C), 135.7 (C), 136.4 (C), 138.3 (C), 139.5 (C), 162.4, 162.8, (2CO); MS *m/z*: 359 (M^+, 42%).

Anal. Calc. For $C_{15}H_8N_5O_4Cl$ (M_r = 357.71): C, 50.36; H, 2.25; N, 19.57%, found C, 50.29; H, 2.18; N, 19.48%.

Preparation of 6-amino-8-cyano-5,7-dihydroxy-quinazoline-2(1*H*),4(3*H*)-dione 13

A suspension of **12** (3.57 g, 0.01 mol), zinc dust (4.00 g, 75 mg-atoms) in acetic acid (3 mL) and water was refluxed under nitrogen for 4 h. The excess zinc was filtered from the still-warm solution and washed with ethanol. The dark filtrate and washings were evaporated in vacuo. Traces of water were azeotropically removed with benzene. The brown residue was purified by flash column chromatography (2:1 hexane/acetone). 2.01 g (86%); m.p. > 300 °C; IR (KBr) ν_{max}/cm^{-1}: 1725 (CO), 2224 (CN), 3347 (NH), 2353 (NH_2), 1610 (C=C ring stretch); ^1H NMR ($CDCl_3$) δ/ppm: 8.5, 9.4 (br, s, H, NH) D_2O exchangeable, 10.2, 10.4 (s, 1H, OH), 6.3 (br, s, 2H, NH_2); ^{13}C NMR ($CDCl_3$) δ: 118.4 (CN), 130.8 (C), 131.7 (C), 132.3 (C), 135.3 (C), 138.2 (C), 139.5 (C), 162.7, 163.3 (2CO); MS *m/z*: 234 (M^+, 18%).

Anal. Calc. For $C_9H_6N_4O_4$ (M_r = 234.17): C, 46.16; H, 2.58; N, 23.93%, found C, 46.07; H, 2.51; N, 23.86%.

Preparation of 8-cyano-5,7-dihydroxyquinazoline-2(1*H*),4(3*H*)-thione 14

To a solution of **8** (2.19 g, 0.01 mol) in xylene (30 mL), phosphorouspentasulphide[16] (4.44 g, 0.02 mole) was added and the reaction mixture was refluxed for 2 h. After cooling, the reaction was shaken vigorously with aqueous sodium hydroxide solution (10%, 10 mL). The alkaline extract was cooled and acidified with conc. HCl. The product was filtered and crystallized from ethanol. 1.96 g (78%); m.p. 276 °C; IR (KBr) ν_{max}/cm^{-1}: 1175 (CS), 2222 (CN), 3353 (NH), 1605 (C=C ring stretch); ^1H NMR ($CDCl_3$) δ/ppm: 7.8, 8.7 (br, s, H, NH) D_2O exchangeable, 9.8, 10.3 (s, 1H, OH), 7.22 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ: 117.8 (CN), 130.8 (C), 131.8 (C), 132.5 (C), 134.9 (C), 138.0 (C), 139.7 (C), 180.4, 180.7 (2CS); MS *m/z*: 251 (M^+, 17%).

Anal. Calc. For $C_9H_5N_3O_2S_2$ (M_r = 251.29): C, 43.02; H, 2.01; N, 16.72%, found C, 42.95.24; H, 1.91; N, 16.66%.

Preparation of 8-cyano-5,7-dihydroxy-2,4-methylthio-quinazoline 15

A stirred solution of compound **14** (2.51 g, 0.01 mol) in NaOH solution (1 N, 10 mL) and methyl iodide[17] (3.2 g, 1.4 mL, 0.022 mol) was heated at 40 °C for 1 h. After cooling, the product was purified by filtration, washed with water and recrystallized from ethanol. 2.15 g (77%); m.p. 193 °C; IR (KBr) ν_{max}/cm^{-1}: 1612 (C=N), 2224 (CN), 1634 (C=C); ^1H NMR ($CDCl_3$) δ/ppm: 2.67 (s, 3H, Me), 9.7, 10.0 (s, 1H, OH), 7.22 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ: 14.8 ($2CH_3$), 118.5 (CN), 130.8 (C), 131.9 (C), 132.5 (C), 135.7 (C), 138.0 (C), 140.2 (C); MS *m/z*: 279 (M^+, 35%).

Anal. Calc. For $C_{11}H_9N_3O_2S_2$ (M_r = 279.34): C, 47.30; H, 3.25; N, 15.04%, found C, 47.23; H, 3.21; N, 14.93%.

Preparation of 8-cyano-5,7-dihydroxy-2,4-methylsulfinyl-quinazoline 16

Compound **15** (2.79 g, 0.01 mol) was dissolved in 96% sulphuric acid (3 mL) at 0 °C. The nitrating mixture[18] (fuming nitric acid, d = 1.5 g/mL, 0.16 mL, 3.6 mmole of nitric acid and 0.16 mL of conc. sulphuric acid) was then added dropwise at 0-5 °C within ten minutes and then the reaction mixture was poured onto ice water and neutralized at 0 °C with 25% aqueous ammonia. The solid was filtered off, washed with cooled water and air dried. The product was recrystallized from methanol. 2.148 g (69%); m.p. 210 °C; IR (KBr) ν_{max}/cm^{-1}: 1630 (C=C ring stretch), 2220 (CN), 1025 (S=O); ^1H NMR ($CDCl_3$) δ/ppm: 2.85 (s, 3H, Me), 9.8, 10.5 (s, 1H, OH), 7.24 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ: 14.5 ($2CH_3$), 116.7 (CN), 125.7 (C), 126.4 (C), 130.8 (C), 131.7 (C), 132.3 (C), 134.9 (C), 138.2 (C), 140.5 (C); MS *m/z*: 311 (M^+, 22%).

Anal. Calc. For $C_{16}H_9N_3O_4S_2$ (M_r = 311.34): C, 42.44; H, 2.91; N, 13.50%, found C, 42.37; H, 2.85; N, 13.42%.

Preparation of 10-amino-9-carboxyethyl-5-hydroxy-8-oxo-4,5H-pyrano[2,3-h]quinazoline-2(1*H*),4(3*H*)-dione 17

A mixture of **8** (2.19 g, 0.01 mol) and diethylmalonate (1.5 mL, 0.01 mol) was refluxed in ethanol (50 mL) for 3 h. The reaction mixture was cooled, triturated with H_2O, filtered and recrystallized from ethanol. 2.78 g (83%); m.p. 216 °C; IR (KBr) ν_{max}/cm^{-1}: 1735 (CO), 2345 (NH_2), 3348 (NH), 1606 (C=C ring stretch); ^1H NMR ($CDCl_3$) δ/ppm: 8.5, 9.4

(br, s, H, NH) D_2O exchangeable, 11.2 (s, 1H, OH), 7.30 (s, 2H, NH_2), 8.4 (1H, d, J = 4.8 $CHNH_2$), 9.8 (d, J = 7, 1H, $CHCOOC_2H_5$), 7.15 (s, 1H, H-6), 4.48 (q, 2H, J = 8, $COOCH_2CH_3$), 1.24 (t, 3H, J = 6, $COOCH_2CH_3$); ^{13}C NMR ($CDCl_3$) δ: 124.6 (CH), 126.8 (CH), 130.6 (C), 131.7 (C), 132.5 (C), 134.7 (C), 138.6 (C), 139.6 (C), 163.4, 164.7, 164.8, 165.3 (4CO); MS *m/z*: 335 (M^+, 14%).

Anal. Calc. For $C_{14}H_{13}N_3O_7$ (M_r = 335.28): C, 50.15; H, 3.91; N, 12.53%, found C, 50.07; H, 3.84; N, 12.44%.

Preparation of 10-amino-9-cyano-5-hydroxy-8-oxo-4,5*H*-pyrano[2,3-h]quinazoline-2(1*H*),4(3*H*)-dione 18

A mixture of **8** (2.19 g, 0.01 mol), ethylcyanoacetate (1.06 mL, 0.01 mol) was refluxed in ethanol (50 mL) for 3 h. The reaction mixture was cooled, triturated with H_2O, filtered and recrystallized from ethanol. 2.50 g (87%); m.p. 224 °C; IR (KBr) ν_{max}/cm^{-1}: 1727 (CO), 2226 (CN), 3350 (NH), 2345 (NH_2), 1610 (C=C ring stretch); ^{1}H NMR ($CDCl_3$) δ/ppm: 8.6, 9.5 (br, s, H, NH) D_2O exchangeable, 11.3 (s, 1H, OH), 7.44 (s, 2H, NH_2), (d, J = 4.8, 1H, $CHNH_2$), 10.3 (d, J = 7 CHCN), 7.18 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ: 119.7 (CN), 124.6 (CH), 125.8 (CH), 130.8 (C), 131.8 (C), 132.6 (C), 134.5 (C), 138.7 (C), 139.8 (C), 162.7, 163.8, 164.9 (3CO); MS *m/z*: 288 (M^+, 26%).

Anal. Calc. For $C_{12}H_8N_4O_5$ (M_r = 288.22): C, 50.01; H, 2.80; N, 19.44%, found C, 57.24; H, 2.66; N, 20.83%.

Preparation of 8-cyano-2,4,5,7-tetrachloroquinazoline 19

A mixture of **8** (2.19 g, 0.01 mol), 20 mL of phosphorousoxychloride and 2 mL of *N,N*-dimethylaniline[19] was refluxed for 3 h. After removal of the excess of phosphorousoxychloride, to the residue was added 200 mL of ice water. The precipitate was collected by filtration and recrystallized from ethanol. 2.577 g (88%); m.p. 116 °C; IR (KBr) ν_{max}/cm^{-1}: 725 (C-Cl), 2228 (CN), 1628 (C=C ring stretch); ^{1}H NMR ($CDCl_3$) δ/ppm: 6.92 (s, 1H, H-6), ^{13}C NMR ($CDCl_3$) δ: 116.6 (CN), 125.6 (C), 126.5 (C), 130.6 (C), 131.6 (C), 132.3 (C), 135.7 (C), 138.2 (C), 140.4 (C); MS *m/z*: 292 (M^+, 52%).

Anal. Calc. For $C_9HN_3Cl_4$ (M_r = 292.94): C, 36.90; H, 0.34; N, 14.34%, found C, 36.80; H, 0.29; N, 14.26%.

Preparation of 8-cyano-5,7-dihydroxy-6-formylquinazoline-2(1*H*),4(3*H*)-dione 20

Riemer-Tiemann reaction was carried out using an alkaline solution of **8**. Thus, a mixture of **8** (2.19 g, 0.01 mol), NaOH (10%, 20 mL), and chloroform (50 mL) was refluxed at 60 °C for 4 h. After cooling, the excess of chloroform was distilled off. Acidifying the residual liquid with sulphuric acid, and then steam-distilling it leaves behind compound **20**. 2.0 g (81%); m.p. 278 (chloroform); IR (KBr) ν_{max}/cm^{-1}: 1735 (CO), 2220 (CN), 3350 (NH), 1607 (C=C ring stretch); ^{1}H NMR ($CDCl_3$) δ/ppm: 8.7, 9.6 (br, s, H, NH) D_2O exchangeable, 10.7, 11.3 (s, 1H, OH), 9.8 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$) δ: 118.7 (CN), 130.4 (C), 131.9 (C), 132.7 (C), 135.9 (C), 138.7 (C), 139.8 (C), 162.7, 163.5, 182.5 (3CO); MS *m/z*: 247 (M^+, 28%).

Anal. Calc. For $C_{10}H_5N_3O_5$ (M_r = 247.17): C, 48.59; H, 2.04; N, 17.00%, found C, 48.51; H, 2.00; N, 16.89%.

Preparation of *N,N′*-(bis-5,7-dihydroxy-8-cyanoquinazoline-2(1*H*),4(3*H*)-dione-6-methylidine)hydrazine 21

A solution of compound **20** (2.47 g, 0.01 mol) in H_2O (50 mL) and hydrazine hydrate (5 mL) were heated under reflux for 2 h. After cooling, the precipitate formed is collected and crystallized from ethanol. 4.216 g (86%); m.p. 242; IR (KBr) ν_{max}/cm^{-1}: 1738 (CO), 2230 (CN), 3366 (NH), 1640 (C=C ring stretch); ^{1}H NMR ($CDCl_3$) δ/ppm: 8.8, 9.5 (br, s, H, NH) D_2O exchangeable, 10.0, 10.6 (s, 1H, OH), 8.6 (s, 1H, CH=N); ^{13}C NMR ($CDCl_3$) δ: 119.6 (2CN), 126.8 (2CH), 130.4 (2C), 131.9 (2C), 132.9 (2C), 136.1 (2C), 138.4 (2C), 141.3 (2C), 162.8, 163.7 (4CO); MS *m/z*: 490 (M^+, 21%).

Anal. Calc. For $C_{20}H_{10}N_8O_8$ (M_r = 490.34): C, 48.99; H, 2.05; N, 26.10%, found C, 48.88; H, 2.00; N, 26.02%.

CONCLUSION

Quinazoline-2,4-diones with various substituents on aromatic rings were obtained from pyrimidine-2(1*H*),4(3*H*)-dione derivative. Decarboxylation of compound **3** makes it easier to prepare several 6-substituted quinazoline-2(1*H*),4(3*H*)-dione derivatives in high yields. These derivatives would facilitate researchers' studies to target them for cancer therapy and inhibition of tumor activity.

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