

Synthesis of Novel 3H-Quinazolin-4-ones Containing Pyrazolinone, Pyrazole and Pyrimidinone Moieties

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Abstract: The diazonium salt of 3-(4-aminophenyl)-2-methyl-3H-quinazolin-4-one (**2a**) and its 6-bromo derivative **2b** reacted with some active methylene compounds, namely ethyl acetoacetate (**3**), ethyl cyanoacetate (**4**) and acetylacetone (**5**), to afford the corresponding hydrazono quinazolinone derivatives **6-8**. Treatment of **6a,b** with hydrazine hydrate or phenyl hydrazine in refluxing ethanol afforded the corresponding pyrazolin-5-one derivatives of 3H-quinazolin-4-one **9a-d**. Cyclization of **7a,b** with hydrazine hydrate yielded the corresponding products **10a,b**. Reaction of **8a,b** with phenyl hydrazine or with urea afforded the corresponding derivatives **11a,b** and **12a,b**, respectively. Compounds **6-12** were identified by C,H,N analysis, IR, ¹H-NMR, ¹³C-NMR and mass spectroscopy.

Keywords: 3-(4-Aminophenyl)-2-methyl-3H-quinazolin-4-one; bromo derivative; active methylene compounds; cyclization; nitrogen nucleophiles.

Introduction

3H-Quinazolin-4-ones and their derivatives have been reported to possess significant activity as antihypertensive [1], antifibrillatory, choleric, antiphlogistic [2], antimitotic anticancer [3], antifungal [4,5] and anticonvulsant agents [6]. They have also been successfully tested as CNS depressants [7], muscle relaxants [8] and for their antineoplastic activity [9]. On the other hand, various therapeutic activities have been reported for both pyrazole [10-12] as well as pyrimidine moieties [13,14]. As a part of our continued program on the chemistry of 3H-quinazolin-4-one ring systems, we recently developed a simple and efficient approach to a wide range of such derivatives [15-20]. These results prompted us to synthesize a series of novel 3H-quinazolin-4-one derivatives containing a pyrazolinone, pyrazole or pyrimidinone ring, with the aim of obtaining some novel heterocyclic systems with potentially enhanced biological properties.

Results and Discussion

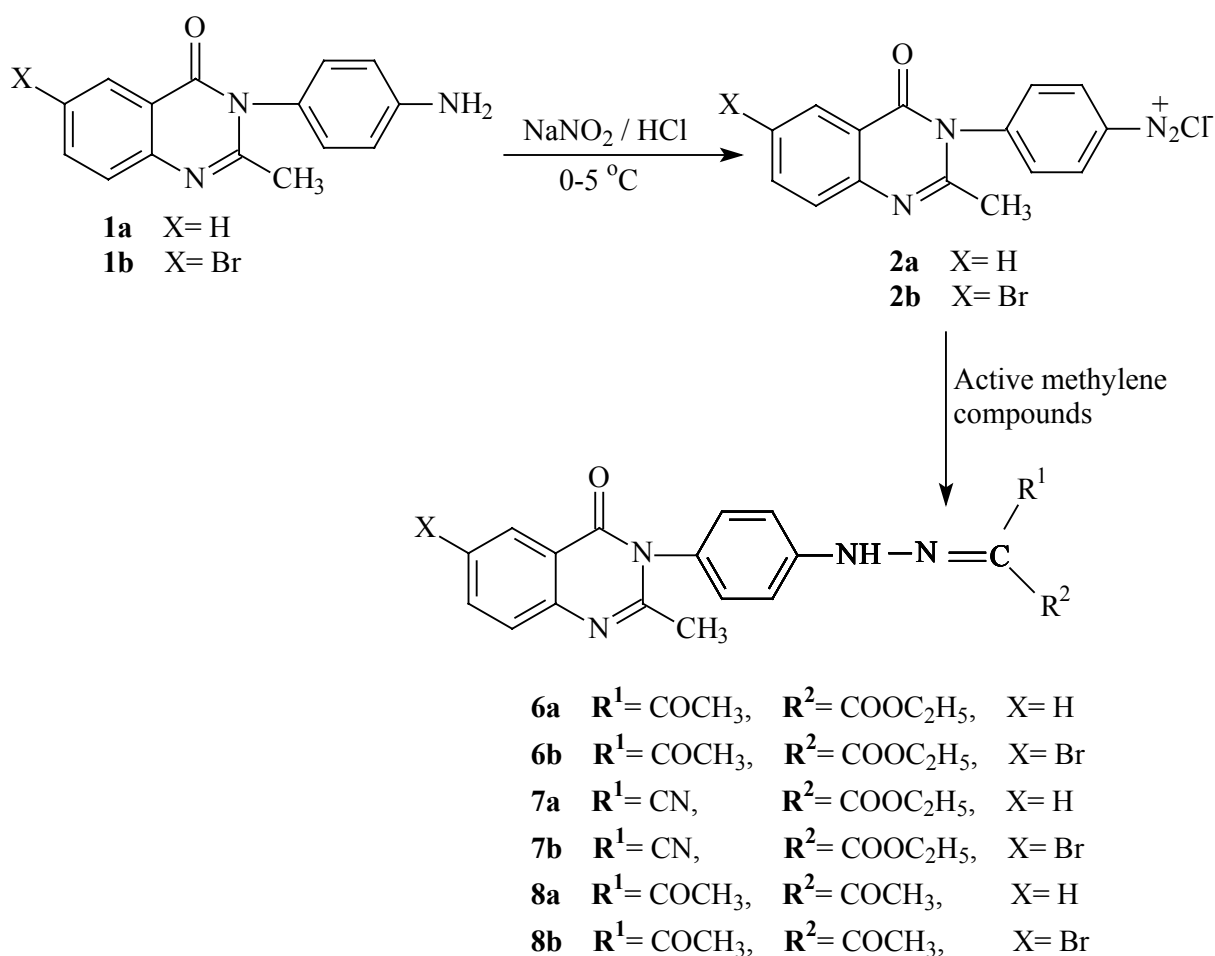
3-(4-Aminophenyl)-2-methyl-3H-quinazolin-4-one (**1a**) and its 6-bromo derivative **1b** were prepared according to the literature procedures [21,22]. The diazonium chlorides **2a,b** were synthesized by diazotisation of **1a,b** using a mixture of sodium nitrite and HCl at 0-5 °C. The diazonium salts thus obtained were treated in ethanol in the presence of sodium acetate with calculated amounts of some active methylene compounds, namely ethyl acetoacetate (**3**), ethyl cyanoacetate (**4**) and acetylacetone (**5**) to afford the corresponding hydrazone derivatives **6-8** (Scheme 1).

Compounds **6-8** were characterized by their elemental analysis, IR, ¹H-NMR, ¹³C-NMR and MS data (see Experimental). For example, the IR spectrum of **6a** shows an absorption band at 3431 cm⁻¹, corresponding to the vibration of the NH group, a band at 1773 cm⁻¹, characteristic of the carboxylic ester moiety, while bands at 1713 cm⁻¹ 1649 cm⁻¹ correspond to the characteristic acetyl and for quinazolinone C=O groups, respectively.

Proton assignments in ¹H-NMR spectra for compounds **6-8**, which are listed in the Experimental section, were made by ¹H-¹H homonuclear shift correlated (COSY) 2D-NMR, D₂O exchange and double resonance experiments. The ¹H-NMR of **6a** showed signals at δ 11.60 (s, 1H, NH), 7.41-8.10 (m, 8H, Ar-H), 4.31 (q, 2H, CH₂), 2.40 (s, 3H, COCH₃), 2.15 (s, 3H, CH₃ at position 2) and 1.28 (t, 3H, CH₃ for carboxylic ester). The ¹³C-NMR of **7a** and **7b** showed the CH₂ and CN carbons at 57.5, 58.3 and 117.3, 118.2 ppm, respectively, while the CH₃ at the 2 position of the quinazolinone moiety and the CH₃ of the carboxylic acid ester appeared at 22.7, 23.2 and 13.5, 13.8, respectively.

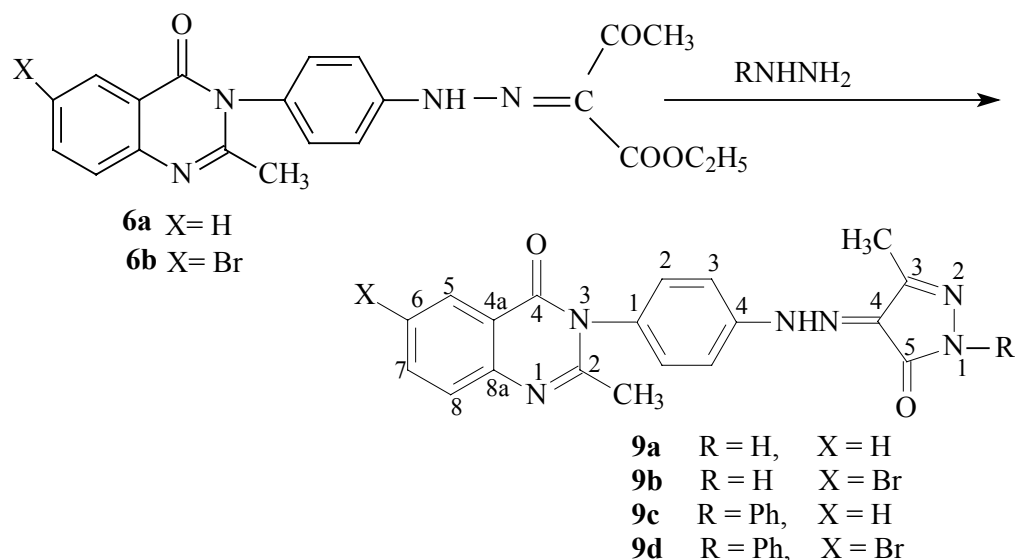
The mass spectra of all compounds containing bromine atoms (**6b**, **7b** and **8b**) showed fragments corresponding to the typical bromine isotope (⁷⁹Br and ⁸¹Br) patterns. Thus, the mass spectrum of **8a** shows its M+1 and M⁺ peaks at *m/z* 363 (19.38 %) and 362 (78.94 %), respectively (see Experimental for details).

Scheme 1



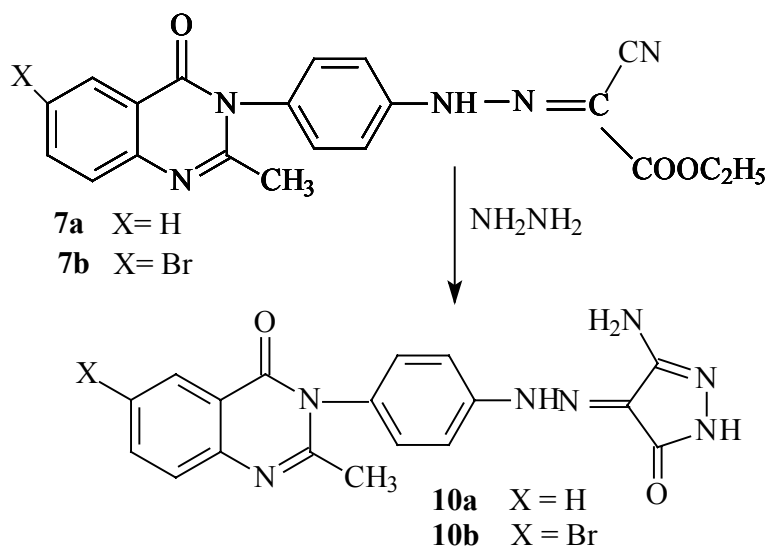
Hydrazone derivatives **6a,b** were cyclized with hydrazine or phenyl hydrazine in boiling ethanol was expected to lead to the formation of the corresponding pyrazolin-5-one derivatives of 3H-quinazolin-4-one **9a-d** (Scheme 2). The structures of the new compounds **9a-d** were confirmed by analytical data, IR, ^1H -NMR, ^{13}C -NMR and mass spectra (see Experimental). Their IR spectra showed the disappearance of the characteristic bands of the acetyl carbonyl group and carboxylic acid ester and the appearance of strong bands in the $3325\text{--}3458\text{ cm}^{-1}$ region, attributed to NH group stretching and the bands of the quinazolinone and pyrazolinone ring C=O groups appearing at 1674 and 1680 cm^{-1} , respectively. The ^1H -NMR spectra of **9a-d** showed the absence of the signals for the ethyl group, while the pyrazolinone CH_3 signal appeared at δ 2.52 - 2.75 ppm. The ^{13}C -NMR of **9a**, for example, confirmed the absence of the acetyl C=O and carboxylic acid ester groups and the appearance of two methyl group signal in the high field region. The other carbon atoms of quinazolinone, pyrazolinone and phenyl moieties all appeared at the expected chemical shifts (see Experimental). The structure of **9b** was also confirmed by its mass spectrum, that shows molecular ion peaks (M^+) at m/z 439 (34.84 %, ^{79}Br) and m/z 441 (35.00 %, ^{81}Br).

Scheme 2



3-{4-[N'-(3-Amino-5-oxo-1,5-dihydropyrazol-4-ylidene)hydrazino]phenyl}-2-methyl-3H-quinazolin-4-one (**10a**) and its bromo derivative **10b** were synthesized via cyclization of **7a,b** with hydrazine (see Scheme 3).

Scheme 3

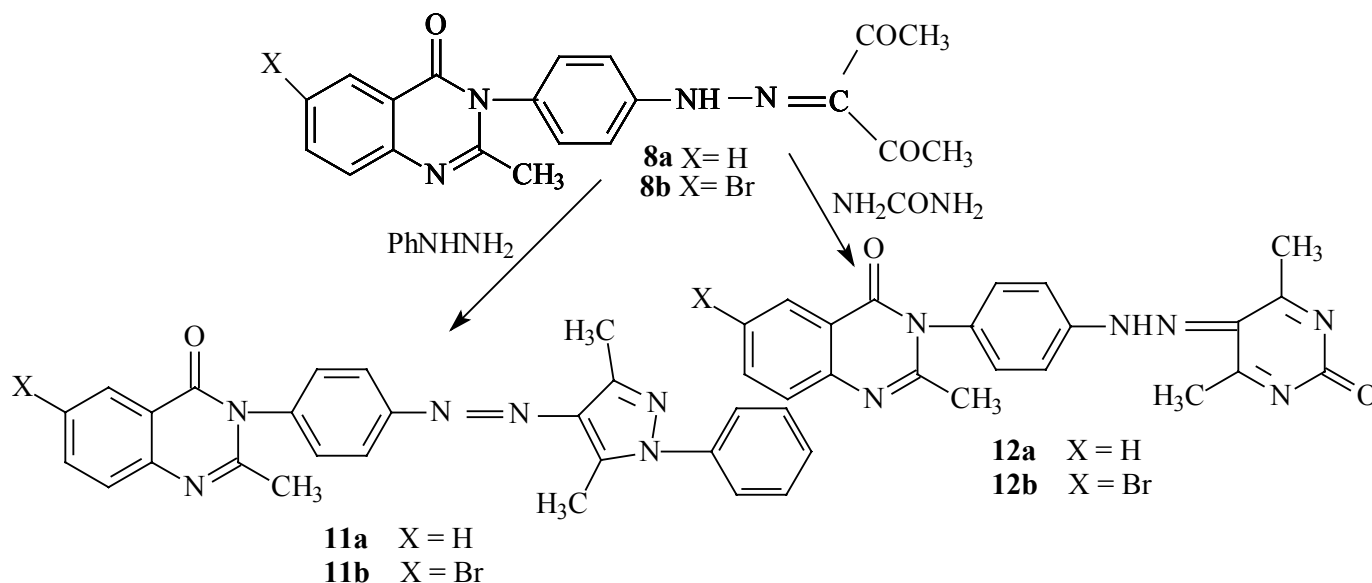


Assignment of the structures of compounds **10a,b** was obtained by elemental analysis and IR, ^1H -NMR and mass spectra. The IR spectra of **10a,b** were characterized by the disappearance of the ν CN band and the appearance of a band at $3312 - 3318\text{ cm}^{-1}$ attributed to the stretching vibration of the NH_2 group (see Experimental). Diagnostically important signals in the ^1H -NMR spectrum of **10a** were two singlet signals at 9.72 and at 12.10 attributed to the two NH groups and a singlet at 5.05 - 5.18

attributable to the NH₂ protons. As expected for the proposed structure, in the presence of deuterium oxide, the signals of the NH and NH₂ groups disappeared and the other signals not change.

3-[4-(Dimethyl-1-phenyl-1H-pyrazol-4-ylazo)-phenyl]-2-methyl-3H-quinazolin-4-one (**11a**) and its bromo derivative **11b** were obtained by thermal cyclization of **8a,b** with phenyl hydrazine in glacial acetic acid (Scheme 4). The IR spectra of **11a,b** were characterized by the disappearance of the ν NH and acetyl group ν C=O absorption bands and the presence of bands at 1678 - 1674 (quinazolinone C=O), 1456 and 1450 cm⁻¹ (N=N). The ¹H-NMR spectra of **11a,b** showed the presence of three methyl groups and the aromatic protons all appeared at the expected chemical shifts (see Experimental). The mass spectrum of **11a** showed a M + 1 peak at m/z 435, a peak at m/z 434 assigned to the molecular ion, a peak at m/z 264 assigned to 3-(4-diazenyl-phenyl)-2-methyl-3H-quinazolin-4-one and a peak at m/z 171 corresponding to 3,5-dimethyl-1-phenyl-pyrazole (see Experimental).

Scheme 4



Reaction of the hydrazono derivatives **8a,b** with urea in ethanol under reflux conditions for 5 hours gave solid products of molecular formula C₂₁H₁₈N₆O₂, which may be formulated as **12a**, or C₂₁H₁₇BrN₆O₂, corresponding to the bromo derivative **12b**, respectively (Scheme 4). Compound **12a** displayed bands in the IR spectrum at 3424 (NH), 1676 (quinazolin-4-one C=O), 1592 (pyrimidin-2-one C=O) cm⁻¹. Structure **12a** was also indicated by the ¹³C-NMR spectra which provided conclusive evidence for the quinazolin-4-one and pyrimidin-2-one structures. Thus, it showed signals at δ 152.3, 160.6, 120.5, 126.1, 125.3, 133.8, 126.6 and 145.4 (quinazolin-4-one C-2, C-4, C-4a, C-5, C-6, C-7, C-8 and C-8a, respectively) and at δ 157.3, 165.7, 149.7 and 166.7 (pyrimidin-2-one C-2, C-4, C-5 and C-6 respectively). The ¹³C-NMR data were assigned based on the comparison of the data obtained for **12a** with those reported in the literature for 3H-quinazolin-4-one [23] and pyrimidin-2-one [24] ring systems.

Experimental

General

Melting points were determined on an Electrothermal MEL-TEMP II melting point apparatus and are reported uncorrected. IR spectra were recorded on a Unicam SP 1200 spectrophotometer using KBr discs. ^1H - and ^{13}C -NMR spectra were recorded for DMSO- d_6 solutions with a Bruker AC 250 FT spectrometer operating at 250 MHz for ^1H - and 62.9 MHz for ^{13}C - measurements. Chemical shifts are reported in ppm relative to tetramethylsilane. The mass spectral data were obtained with a Micro Spectrometer model 7070 at 70 eV and a 90°C inlet temperature. All analytical samples were homogeneous by thin layer chromatography, which was performed on EM Silica gel 60 F₂₅₄ sheets (0.2 mm) using 5: 2 (v: v) chloroform - acetone or 3: 1 (v: v) petroleum ether – ethyl acetate as eluents. The spots were detected with a model UVGL-58 UV lamp. Elemental analyses were obtained from the Central Microanalysis Laboratory Service of Cairo University, Cairo, Egypt.

Diazotization of 6-substituted 2-methyl-3-(4-aminophenyl)-3H-quinazolin-4-ones 1a,b.

A mixture of **1a** or **1b** (0.01 mole) in concentrated HCl (3 ml) was cooled to 0 - 5°C under ice, and cooled sodium nitrite solution (1.5 g in 10 mL of water) added to it dropwise during 10 minutes. The reaction mixture was then stirred for 30 minutes.

General procedure for the preparation of hydrazone derivatives 6-8

To an ice-cold mixture of the appropriate active methylene compound (ethyl acetoacetate, ethyl cyanoacetate or acetylacetone) (0.01 mole) and sodium acetate (4.10 g; 0.05 mole) in ethanol (50 mL), was added dropwise with stirring a solution of diazonium salt compound **2a** or **2b** (0.01 mole) over 15 minutes. The stirring was continued for 30 minutes and the reaction mixture then left for 2 hours at room temperature. The solid product was collected and recrystallized from ethanol to give the corresponding hydrazone derivatives **6-8**. The following hydrazones were prepared in this manner:

2-{{[4-(2-Methyl-4-oxo-4H-quinazolin-3-yl)-phenyl]hydrazone}-3-oxo-butyric acid ethyl ester (6a). Pale yellow crystals; yield 2.04 g (52 %); M.p. 190-192°C; Calculated for C₂₁H₂₀N₄O₄ (392.41): 64.28 % C, 5.14 % H, 14.28 % N. Found: 64.39 %, 5.32 % H, 13.98 % N; IR, ν cm⁻¹: 3431 (NH), 3089, 2968 (Ar-H), 1773, 1713, 1649 (C=O), 1608, 1603, 1524, 1479 (C=N, C=C); ^1H -NMR δ : 11.60 (1H, s, NH), 7.41-8.10 (8H, m, Ar-H), 4.31 (2H, q, CH₂), 2.40 (3H, s, COCH₃), 2.15 (3H, s, quinazolinone CH₃), 1.28 (3H, s, carboxylic ester CH₃); ^{13}C -NMR δ : 167.3 (acetyl C=O), 164.1 (ester C=O), 161.4 (C-4), 154.5 (C-2), 147.3 (C-8a), 142.8 (Ph C-1), 134.5 (C-7), 129.6 (2C, Ph C2,6), 128.5 (Ph C-4), 126.6 (C-5), 126.4 (C-8), 126.3 (2C, Ph C3,5), 126.2 (C-6), 118.9 (C-4a), 61.2 (CH₂), 23.9 (quinazolinone CH₃), 21.4 (acetyl CH₃), 13.9 (ester CH₃).

2-{[4-(6-Bromo-2-methyl-4-oxo-4H-quinazolin-3-yl)-phenyl]hydrazono}-3-oxo-butyric acid ethyl ester (**6b**). Pale yellow crystals; yield 2.73 g (58 %); M.p. 234-236°C; Calculated for $C_{21}H_{19}BrN_4O_4$ (471.31): 53.52 % C, 4.06 % H, 11.89 % N. Found: 53.63 %, 3.88 % H, 11.67 % N; IR, ν cm^{-1} : 3442 (NH), 3080, 3048 (Ar-H), 1768, 1718, 1676 (C=O), 1608, 1607, 1548, 1460 (C=N, C=C); 1H -NMR δ : 11.40 (1H, s, NH), 7.46-8.57 (7H, m, Ar-H), 4.24 (2H, q, CH_2), 2.42 (3H, s, $COCH_3$), 2.28 (3H, s, quinazolinone CH_3), 1.27 (3H, s, ester CH_3); MS, m/z (Ir,%): 472 (M^+ for ^{81}Br , 32.43), 470 (M^+ for ^{79}Br , 32.62), 316 (52.12), 314 (51.85), 301 (12.32), 299 (13.14), 224 (15.37), 222 (16.00).

Cyano-{[4-(2-methyl-4-oxo-4H-quinazolin-3-yl)-phenyl]hydrazono}acetic acid ethyl ester (**7a**). Pale yellow crystals; yield 2.44 g (65 %); M.p. 128-130°C; Calculated for $C_{20}H_{17}N_5O_3$ (375.38): 63.99 % C, 4.56 % H, 18.66 % N. Found: 63.78 %, 4.77 % H, 18.35 % N; IR, ν cm^{-1} : 3430 (NH), 3115, 3032 (Ar-H), 2366 (CN), 1762, 1674 (C=O), 1605, 1603, 1545, 1458 (C=N, C=C); 1H -NMR δ : 12.11 (1H, s, NH), 7.30-8.32 (8H, m, Ar-H), 4.30 (2H, q, CH_2), 2.23 (3H, s, quinazolinone CH_3), 1.22 (3H, s, carboxylic ester CH_3); ^{13}C -NMR δ : 163.8 (ester C=O), 160.7 (C-4), 154.9 (C-2), 147.6 (C-8a), 143.3 (C-1 of Ph), 134.7 (C-7), 128.8 (2C, Ph C2,6), 128.5 (Ph C-4), 127.0 (C-5), 126.6 (C-8), 126.4 (2C, Ph C3,5), 126.0 (C-6), 119.2 (C-4a), 117.3 (CN), 61.4 (CH_2), 23.4 (quinazolinone CH_3), 13.5 (ester CH_3).

{[4-(6-Bromo-2-methyl-4-oxo-4H-quinazolin-3-yl)-phenyl]hydrazono}cyano-acetic acid ethyl ester (**7b**). Pale yellow crystals; yield 3.09 g (65 %); M.p. 173-175°C; Calculated for $C_{20}H_{16}BrN_5O_3$ (454.28): 52.88 % C, 3.55 % H, 15.42 % N. Found: 52.61 %, 3.83 % H, 15.09 % N; IR, ν cm^{-1} : 3439(NH), 3110, 3000 (Ar-H), 2367 (CN), 1769, 1681 (C=O), 1607, 1602, 1547, 1450 (C=N, C=C); 1H -NMR δ : 11.74 (1H, s, NH), 7.62-8.74 (7H, m, Ar-H), 4.33 (2H, q, CH_2), 2.27 (3H, s, quinazolinone CH_3), 1.28(3H, s, ester CH_3); ^{13}C -NMR δ : 164.1 (ester C=O), 162.5 (C-4), 158.4 (C-2), 142.8 (C-8a), 140.6(Ph C-1), 135.0 (C-7), 129.3 (2C, Ph C2,6), 128.8 (Ph C-4), 127.6 (C-5), 125.9 (C-8), 125.3 (2C, Ph C3,5), 125.1 (C-6), 120.6 (C-4a), 118.2 (CN), 61.7 (CH_2), 23.7 (quinazolinone CH_3), 13.8 (ester CH_3); MS m/z (Ir,%): 455 (M^+ for ^{81}Br , 16.73), 453 (M^+ for ^{79}Br , 16.54).

3-{[4-(2-Methyl-4-oxo-4H-quinazolin-3-yl)phenyl]hydrazono}-pentane-2,4-dione (**8a**). Pale yellow crystals; yield 2.17 g (60 %); M.p. 153-155°C; Calculated for $C_{20}H_{18}N_4O_3$ (362.38): 66.29 % C, 4.97 % H, 15.46 % N. Found: 66.42 %, 5.01 % H, 15.62 % N; IR, ν cm^{-1} : 3499 (NH), 3039, 2921 (Ar-H), 1712, 1662 (C=O), 1607, 1605, 1567, 1475 (C=N, C=C); 1H -NMR δ : 13.90 (1H, s, NH), 7.40-8.20 (8H, m, Ar-H), 2.44 (6H, s, 2 x $COCH_3$), 2.25 (3H, s, quinazolinone CH_3); ^{13}C -NMR δ : 169.2 (2C, 2 x acetyl C=O), 161.4 (C-4), 155.2 (C-2), 147.2 (C-8a), 142.8 (Ph C-1), 135.0 (C-7), 128.2 (2C, Ph C2,6), 127.8 (Ph C-4), 127.2 (C-5), 126.8 (C-8), 126.6 (2C, Ph C3,5), 126.2 (C-6), 118.5 (C-4a), 23.7 (quinazolinone CH_3); MS, m/z (Ir,%): 363 ($M^+ + 1$, 19.38), 362 (M^+ , 78.74), 319 (20.95), 264 (42.12), 250 (36.46), 236 (31.91), 221 (4.66), 144 (17.06), 143 (100), 115 (4.43), 89 (4.9), 77 (7.53).

3-{[4-(6-Bromo-2-methyl-4-oxo-4H-quinazolin-3-yl)phenyl]hydrazono}-pentane-2,4-dione (**8b**). Pale yellow crystals; yield 2.91 g (66 %); M.p. 165-167 °C; Calculated for $C_{20}H_{17}BrN_4O_3$ (441.28): 54.44 % C, 3.88 % H, 12.70 % N. Found: 54.23 %, 4.02 % H, 12.45 % N; IR, ν cm^{-1} : 3494 (NH), 3040, 2923

(Ar-H), 1718, 1665 (C=O), 1609, 1568, 1477 (C=N, C=C); $^1\text{H-NMR}$ δ : 13.75 (1H, s, NH), 7.43-8.16 (7H, m, Ar-H), 2.45 (6H, s, 2 x COCH_3), 2.27 (3H, s, quinazolinone CH_3); $^{13}\text{C-NMR}$ δ : 168.7 (2C, 2 x acetyl C=O), 161.5 (C-4), 154.6 (C-2), 147.5 (C-8a), 142.2 (Ph C-1), 135.4 (C-7), 128.3 (2C, Ph C2,6), 127.7 (Ph C-4), 127.4 (C-5), 127.0 (C-8), 126.5 (2C, Ph C3,5), 126.0 (C-6), 118.8 (C-4a), 23.6 (quinazolinone CH_3); MS, m/z (Ir, %): 442 (M^+ for ^{81}Br , 32.18), 440 (M^+ for ^{79}Br , 32.12).

General Procedures for the Cyclization Reactions

Method A: With Hydrazine Hydrate

A mixture of the appropriate **6a,b** or **7a,b** (0.005 mole) and hydrazine hydrate (0.32 mL, 0.01 mole) in ethanol (30 mL) was heated under reflux for 4-6 hours. The solvent was concentrated and the reaction product was allowed to cool. The separated product was filtered off, washed with water, dried and recrystallized from ethanol. The following title compounds were prepared as just described:

2-Methyl-3-{4-[N'-(3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)hydrazino] phenyl}-3H-quinazolin-4-one (9a). Orange yellow crystals; yield 1.12 g (62 %); M.p. 261-263°C; Calculated for $\text{C}_{19}\text{H}_{16}\text{N}_6\text{O}_2$ (360.37): 63.37 % C, 4.48 % H, 23.32 % N. Found: 63.11 %, 4.27 % H, 23.26 % N; IR, ν cm^{-1} : 3325, 3452 (NH), 3044, 2927 (Ar-H), 1680, 1674 (C=O), 1606, 1573, 1475 (C=N, C=C); $^1\text{H-NMR}$ δ : 12.36 (1H, s, hydrazino NH), 9.65 (1H, s, pyrazolinone NH), 7.38-8.26 (8H, m, Ar-H), 2.52 (3H, s, pyrazolinone CH_3), 2.30 (3H, s, quinazolinone CH_3); $^{13}\text{C-NMR}$ δ : 160.8 (C-4), 158.6 (pyrazolinone C-5), 156.5 (pyrazolinone C-4), 154.6 (C-2), 151.3 (pyrazolinone C-3), 148.2 (C-8a), 143.0 (Ph C-1), 136.5 (C-7), 128.7 (2C, Ph C2,6), 128.0 (Ph C-4), 127.7 (C-5), 126.8 (C-8), 126.3 (2C, Ph C3,5), 125.7 (C-6), 118.5 (C-4a), 23.4 (quinazolinone CH_3), 21.2 (pyrazolinone CH_3).

6-Bromo-2-methyl-3-{4-[N'-(3-methyl-5-oxo-1,5-dihydropyrazol-4-ylidene)hydrazino]phenyl}-3H-quinazolin-4-one (9b). Orange yellow crystals; yield 1.50 g (68 %); M.p. 308-310°C; Calculated for $\text{C}_{19}\text{H}_{15}\text{BrN}_6\text{O}_2$ (439.27): 51.95 % C, 3.44 % H, 19.13 % N. Found: 51.69 %, 3.65 % H, 19.10 % N; IR, ν cm^{-1} : 3331, 3446 (NH), 3047, 2927 (Ar-H), 1683, 1672 (C=O), 1604, 1576, 1468 (C=N, C=C); $^1\text{H-NMR}$ δ : 12.24 (1H, s, hydrazino NH), 9.56 (1H, s, pyrazolinone NH), 7.32-8.42 (7 H, m, Ar-H), 2.68 (3H, s, pyrazolinone CH_3), 2.34 (3H, s, quinazolinone CH_3); MS, m/z (Ir, %): 441 (M^+ for ^{81}Br , 35.00), 439 (M^+ for ^{79}Br , 34.84), 331 ($\text{C}_{15}\text{H}_{12}^{81}\text{BrN}_3\text{O}^+$, 13.24), 329 ($\text{C}_{15}\text{H}_{12}^{79}\text{BrN}_3\text{O}^+$, 13.42), 316 ($\text{C}_{15}\text{H}_{11}^{81}\text{BrN}_2\text{O}^+$, 100), 314 ($\text{C}_{15}\text{H}_{11}^{79}\text{BrN}_2\text{O}^+$, 100), 275 (23.95), 273 (23.94), 198 (10.23), 196 (10.20), 110 ($\text{C}_4\text{H}_4\text{N}_3\text{O}^+$, 42.36), 96 ($\text{C}_3\text{H}_2\text{N}_3\text{O}^+$, 7.40).

3-{4-N'-(3-Amino-5-oxo-1,5-dihydropyrazol-4-ylidene)hydrazino]phenyl}-2-methyl-3H-quinazolin-4-one (10a). Orange yellow crystals; yield 0.87 g (48 %); M.p. 180-182°C; Calculated for $\text{C}_{18}\text{H}_{15}\text{N}_7\text{O}_2$ (361.36): 59.83 % C, 4.18 % H, 27.13 % N. Found: 59.52 %, 4.29 % H, 27.04 % N; IR, ν cm^{-1} : 3426, 3450 (NH), 3312 (NH_2), 3186, 2923 (Ar-H), 1680, 1674 (C=O), 1603, 1601, 1508, 1464 (C=N, C=C); $^1\text{H-NMR}$ δ : 12.10 (1H, s, hydrazino NH), 9.72 (1H, s, pyrazolinone NH), 7.30-8.05 (8H, m, Ar-H),

5.05 (2H, s, NH₂), 2.27 (3H, s, quinazolinone CH₃); MS, m/z (Ir, %): 362 (M⁺ +1, 4.32), 361 (M⁺, 27.53), 251 (C₁₅H₁₃N₃O⁺, 17.10), 236 (C₁₅H₁₂N₂O⁺, 100), 195 (24.14), 118 (2.75), 111 (C₃H₃N₄O⁺, 54.26), 77 (38.38).

3-{4-N'-(3-Amino-5-oxo-1,5-dihydropyrazol-4-ylidene)hydrazino}phenyl}-6-bromo-2-methyl-3H-quinazolin-4-one (10b). Orange yellow crystals; yield 1.17 g (53 %); M.p. 244-246°C; Calculated for C₁₈H₁₄BrN₇O₂ (440.25): 49.11 % C, 3.21 % H, 22.27 % N. Found: 49.37 %, 3.51 % H, 22.10 % N; IR, ν cm⁻¹: 3428, 3451 (NH), 3318 (NH₂), 3176, 2927 (Ar-H), 1681, 1675 (C=O), 1606, 1603, 1511, 1473 (C=N, C=C); ¹H-NMR δ : 12.46 (1H, s, hydrazino NH), 9.82 (1H, s, pyrazolinone NH), 7.42-8.38 (7H, m, Ar-H), 5.12 (2H, s, NH₂), 2.31 (3H, s, quinazolinone CH₃).

Method B: With Phenyl Hydrazine

To a solution of the appropriate **6a,b** or **8a,b** (0.01 mole) in glacial acetic acid (30 mL) was added phenyl hydrazine (1.30 g, 0.012 mole) and anhydrous sodium acetate (0.82 g, 0.01 mole). The reaction mixture was heated under reflux for 4 hours. The mixture was poured into ice-cold water and stored in a refrigerator. The crude product, which separated, was washed with water, dried and recrystallized from methanol. The following title compounds were prepared as just described:

2-Methyl-3-{4-[N'-(3-methyl-5-oxo-1-phenyl-1,5-dihydropyrazol-4-ylidene)hydrazino}phenyl}-3H-quinazolin-4-one (9c). Orange yellow crystals; yield 2.00 g (46 %); M.p. 302-304°C; Calculated for C₂₅H₂₀N₆O₂ (436.47): 68.80 % C, 4.62 % H, 19.25 % N. Found: 69.13 %, 4.88 % H, 19.54 % N; IR, ν cm⁻¹: 3458 (NH), 3189, 2928 (Ar-H), 1682, 1672 (C=O), 1604, 1602, 1512, 1468 (C=N, C=C); ¹H-NMR δ : 13.35 (1H, s, hydrazino NH), 7.51-8.38 (13H, m, Ar-H), 2.54 (3H, s, pyrazolinone CH₃), 2.27 (3H, s, quinazolinone CH₃); MS, m/z (Ir, %): 437 (M⁺ +1, 7.32), 436 (M⁺, 41.50).

6-Bromo-2-methyl-3-{4-[N'-(3-methyl-5-oxo-1-phenyl-1,5-dihydropyrazol-4-ylidene)hydrazino}phenyl}-3H-quinazolin-4-one (9d). Orange yellow crystals; yield 2.16 g (42 %); M.p. 259-261°C; Calculated for C₂₅H₁₉BrN₆O₂ (515.36): 58.26 % C, 3.72 % H, 16.31 % N. Found: 58.34 %, 3.92 % H, 16.18 % N; IR, ν cm⁻¹: 3455 (NH), 3185, 2922 (Ar-H), 1680, 1673 (C=O), 1606, 1603, 1517, 1470 (C=N, C=C); ¹H-NMR δ : 13.40 (1H, s, hydrazino NH), 7.43-8.28 (12H, m, Ar-H), 2.60 (3H, s, pyrazolinone CH₃), 2.25 (3H, s, quinazolinone CH₃); MS, m/z (Ir, %): 517 (M⁺ +1 for ⁸¹Br, 10.25), 515 (M⁺ +1 for ⁷⁹Br, 10.25), 516 (M⁺ for ⁸¹Br, 43.50), 514 (M⁺ for ⁷⁹Br, 43.50).

3-[4-(3,5-Dimethyl-1-phenyl-1H-pyrazol-4-ylazo)phenyl]-2-methyl-3H-quinazolin-4-one(11a). Orange crystals; yield 2.60 g (60 %); M.p. 205-207°C; Calculated for C₂₆H₂₂N₆O (434.50): 71.87 % C, 5.10 % H, 19.34 % N. Found: 72.03 %, 4.09 % H, 19.15 % N; IR, ν cm⁻¹: 3051, 2923, 2852 (Ar-H), 1678 (C=O quinazolinone), 1596 (C=N), 1450 (N=N); ¹H-NMR δ : 7.50-8.18 (13H, m, Ar-H), 2.66, 2.51 (6H, 2 s, 2 x pyrazole CH₃), 2.23 (3H, s, quinazolinone CH₃); MS, m/z (Ir, %): 435 (M⁺ +1, 5.24), 434

(M^+ , 16.42), 264 ($C_{15}H_{12}N_4O^+$, 37.36), 263 ($C_{15}H_{11}N_4O^+$, 28.80), 171 ($C_{11}H_{11}N_2^+$, 52.33), 95 ($C_5H_7N_2^+$, 100).

6-Bromo-3-[4-(3,5-dimethyl-1-phenyl-1H-pyrazol-4-ylazo)phenyl]-2-methyl-3H-quinazolin-4-one (11b). Orange crystals; yield 2.29 g (64 %); M.p. 238-240°C; Calculated for $C_{26}H_{21}BrN_6O$ (513.39): 60.83 % C, 4.12 % H, 16.37 % N. Found: 60.98 %, 4.93 % H, 16.53 % N; IR, ν cm^{-1} : 3052, 2925, 2850 (Ar-H), 1674 (C=O quinazolinone), 1602, 1594, 1547, 1450, 1421 (C=N, C=C, N=N); 1H -NMR δ : 7.53-8.26 (12H, m, Ar-H), 2.68, 2.52 (6H, 2 s, 2 x pyrazole CH_3), 2.21 (3H, s, quinazolinone CH_3).

Method C: With Urea

A mixture of hydrazono derivatives **8a,b** (0.005 mole) and urea (0.6 g, 0.01 mole) in ethanol (40 mL) was heated under reflux for 5 hours. After cooling to room temperature, crushed ice was added and the mixture was stirred for 1 hour. The separated product was collected by filtration and recrystallized from aqueous ethanol. The following title compounds were prepared as just described:

3-{4-[N'(4,6-Dimethyl-2-oxo-2H-pyrimidin-5-ylidene)hydrazino]phenyl}-2-methyl-3H-quinazolin-4-one (12a). Orange yellow crystals; yield 0.83 g (43 %); M.p. 285-286°C; Calculated for $C_{21}H_{18}N_6O_2$ (386.41): 65.27 % C, 4.70 % H, 21.75 % N. Found: 64.97 %, 4.88 % H, 21.82 % N; IR, ν cm^{-1} : 3424 (NH), 3052 (Ar-H), 1688, 1676 (C=O), 1592, 1565, 1481 (C=N, C=C), 1284 (N-N=C); 1H -NMR δ : 13.28 (1H, s, hydrazino NH), 7.42-8.26 (8H, m, Ar-H), 2.58 (6H, s, 2 x pyrimidin-5-one CH_3), 2.27 (3H, s, quinazolinone CH_3); ^{13}C -NMR δ : 166.7 (pyrimidin-5-one C-6), 165.7 (pyrimidin-5-one C-4), 160.6 (quinazolinone C-4), 157.3 (pyrimidin-5-one C-2), 152.3 (quinazolinone C-2), 149.7 (pyrimidin-5-one C-5), 145.4 (C-8a), 140.6 (Ph C-1), 133.8 (C-7), 128.0 (2C, Ph C2,6), 127.6 (Ph C-4), 126.6 (C-8), 126.1 (C-5), 126.0 (2C, Ph C3,5), 125.3 (C-6), 120.5 (C-4a), 23.7 (quinazolinone CH_3), 20.8 (2C, 2 x pyrimidin-5-one CH_3).

6-Bromo-3-{4-[N'(4,6-dimethyl-2-oxo-2H-pyrimidin-5-ylidene)hydrazino]phenyl}-2-methyl-3H-quinazolin-4-one (12b). Orange yellow crystals; yield 1.09 g (47 %); M.p. 210-212°C; Calculated for $C_{21}H_{17}BrN_6O_2$ (465.21): 54.21 % C, 3.68 % H, 18.06 % N. Found: 53.89 %, 3.97 % H, 18.31 % N; IR, ν cm^{-1} : 3427 (NH), 3063, 2928 (Ar-H), 1692, 1679 (C=O), 1579, 1507, 1429 (C=N, C=C), 1282 (N-N=C); 1H -NMR δ : 13.68 (1H, s, hydrazino NH), 7.36-8.35 (7H, m, Ar-H), 2.55 (6H, s, 2 x pyrimidin-5-one CH_3), 2.25 (3H, s, quinazolinone CH_3); MS, m/z (Ir, %): 467 (M^+ +1 for ^{81}Br , 4.45), 465 (M^+ +1 for ^{79}Br , 4.45), 466 (M^+ for ^{81}Br , 27.75), 464 (M^+ for ^{79}Br , 27.75).

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