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The reaction of 3-*N*-(2-mercapto-4-oxo-4*H*-quinazolin-3-yl)acetamide (**1**) with hydrazine hydrate yielded 3-amino-2-methyl-3*H*-[1,2,4]triazolo[5,1-*b*]quinazolin-9-one (**2**). The reaction of **2** with *o*-chlorobenzaldehyde and 2-hydroxy-naphthaldehyde gave the corresponding 3-arylidene amino derivatives **3** and **4**, respectively. Condensation of **2** with 1-nitroso-2-naphthol afforded the corresponding 3-(2-hydroxy-naphthalen-1-yl-diazenyl)-2-methyl-3*H*-[1,2,4]triazolo[5,1-*b*]quinazolin-9-one (**5**), which on subsequent reduction by $SnCl_2$ and HCl gave the hydrazino derivative **6**. Reaction of **2** with phenyl isothiocyanate in refluxing ethanol yielded thiourea derivative **7**. Ring closure of **7** subsequently cyclized on refluxing with phencyl bromide, oxalyl dichloride and chloroacetic acid afforded the corresponding thiazolidine derivatives **8**, **9** and **10,** respectively. Reaction of 2-mercapto-3-phenylamino-3*H*-quinazolin-4-one (**11**) with hydrazine hydrate afforded 2-hydrazino-3-phenylamino-3*H*-quinazolin-4-one (**12**). The reactivity **12** towards carbon disulphide, acetyl acetone and ethyl acetoacetate gave **13**, **14** and **15**, respectively. Condensation of **12** with isatin afforded 2-[*N*-(2-oxo-1,2-dihydroindol-3-ylidene)hydrazino]-3-phenylamino-3*H*-quinazolin-4-one (**16**). 2-(4-Oxo-3-phenylamino-3,4-dihydroquinazolin-2-ylamino)isoindole-1,3-dione (**17**) was synthesized by the reaction of **12** with phthalic anhydride. All isolated products were confirmed by their ir, ^{1}H nmr, ^{13}C nmr and mass spectra.

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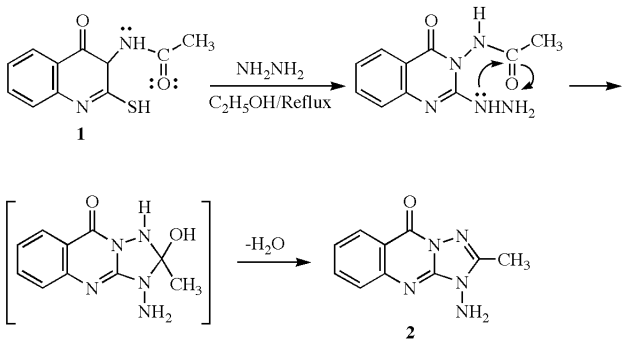
Substituted 3*H*-quinazolin-4-ones are known to possess a wide range of pharmacological activities. Several aminoquinazolinones are found to be active on the central nervous system of mice [1] and as antitubercular agents [2]. A number of diazo, hydrazide and hydrazine derivatives are also found to be good CNS active, monoamine oxidase inhibitors [3,4] and antibacterial agents [5,6]. It was also found that some 1,2,4-triazole derivatives have been reported to possess significant antifungal, antibacterial and insecticidal properties [7-9]. Additionally, several of the thiazolidine derivatives have shown biological activity against antimicrobial [10], anticancer [11], Central Nervous System activity [12], antibacterial agents [13,14] and anti-inflammatory activity [15,16]. Thus it seemed of interest to combine the 3*H*-quinazolin-4-one system with triazole ring and thiazolidine ring in a single molecule as compounds of this type may possess biologically activity. Herein and in continuation of our work [17-22] we synthesized some 3*H*-quinazolin-4-one derivatives hoping that they may have biological interest.

Compound **1** was prepared from isatoic anhydride and acetyl hydrazide followed by reaction with CS_2 in refluxing ethanol [23]. The reaction of **1** with hydrazine hydrate was heated under reflux in methanol for 3 hours to afford the new heterocylic 3-amino-2-methyl-3*H*-[1,2,4]triazolo[5,1-*b*]quinazolin-9-one (**2**) (Scheme 1). It was suggested that the hydrazino compound was obtained in the first step, then an internal nucleophilic attack by the NH group on the electron deficient carbonyl carbon atom took place, followed by elimination of water to give the cyclized compound **2** (Scheme 1).

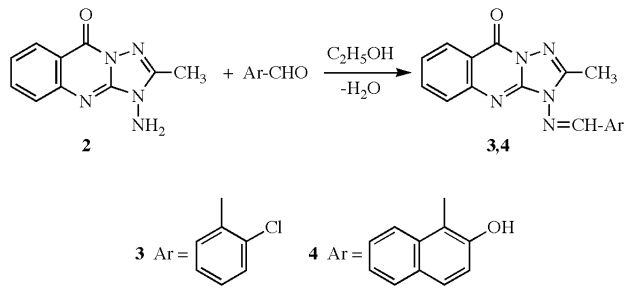
Compound **2** was characterized by elemental analysis, ir and ^{1}H nmr (see Experimental). The ^{1}H nmr spectrum of **2** confirms with the assigned structure. The NH_2 and CH_3 protons appeared as two singlet peaks at δ 6.00 and 2.48, respectively (see Experimental).

Scheme 1



3-[(2-Chlorobenzylidene)amino]-2-methyl-3*H*-[1,2,4]-triazolo[5,1-*b*]quinazolin-9-one (**3**) and 3-[(2-hydroxy-naphthalen-1-ylmethylene)amino]-2-methyl-3*H*-[1,2,4]triazolo[5,1-*b*]quinazolin-9-one (**4**) were obtained, respectively by the reaction of **2** with *o*-chlorobenzaldehyde and

Scheme 2



2-hydroxy-naphthaldehyde in refluxing ethanol for 5-6 hours (Scheme 2).

The ir spectra of **3** and **4** revealed the disappearance of the absorption band due to NH_2 group. The strong absorption band at 3425 cm^{-1} was due to the (OH) group in **4**.

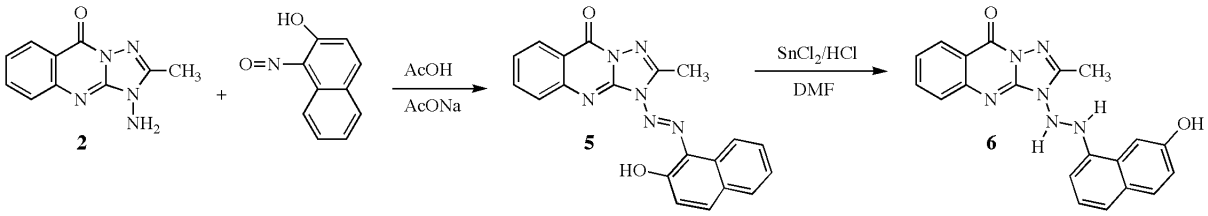
The mass spectrum of **3** containing chlorine atom showed fragments to the typical pattern chlorine isotopes (^{35}Cl and ^{37}Cl). The molecular ion peak M^+ appeared at *m/z* = 337 (^{35}Cl, 33.3%) and m /z = 339 (^{37}Cl, 11.1%) with the ratio 3: 1 for ^{35}Cl and ^{37}Cl, respectively. The base peak appeared at *m/z* = 200 (100%) related to 2-methyl-3*H*-[1,2,4]triazolo[5,1-*b*]quinazolin-9-one ($C_{10}H_8N_4O^+$) (see Experimental for details). Also the mass spectrum of **4** was characterized by the molecular ion peak M^+ appeared at *m/z* = 369 (44.4 %), the base peaks that appeared at *m/z* = 200 (100%) was related to ($C_{10}H_8N_4O^+$) and *m/z* = 169 (100 %) was related to 2-hydroxy-naphthalene-1-carbonitrile ($C_{11}H_7NO^+$). The ^1H and ^{13}C nmr spectra of **3** and **4** could not be recorded because of their insolubility in common solvents.

Condensation of **2** with 1-nitroso-2-naphthol furnished the corresponding 3-(2-hydroxy-naphthalene-1-yl-diazenyl)-2-methyl-3*H*-[1,2,4]triazolo[5,1-*b*]quinazolin-9-one (**5**), which on subsequent reduction by stannous chloride and hydrochloric acid yielded 3-[*N*'-(2-hydroxy-naphthalen-1-yl)hydrazino]-2-methyl-3*H*-[1,2,4]triazolo [5,1-*b*]quinazolin-9-one (**6**) (Scheme 3).

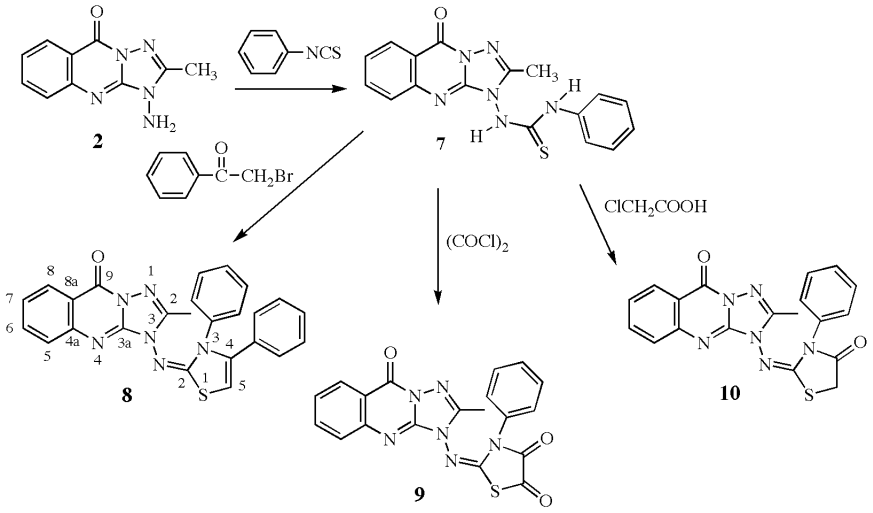
The ir spectrum of **5** showed three absorption bands at 3385, 1687 and 1556 cm^{-1} corresponding to ν_{OH}, $\nu_{C=O}$ and $\nu_{N=N,}$ respectively. The ^1H nmr spectrum of **5** showed two-singlet signals corresponding to CH_3 at δ 2.52, as well as exchangeable singlet corresponding to the OH at δ 5.81 ppm and a multiplet at δ 7.10-8.12 ppm region due to ten aromatic protons. The ir spectrum of **6** exhibited a broad band 3540-3380 cm^{-1} due to ν_{NH} and $\nu_{OH.}$ The absence of a band at 1556 cm^{-1} (previously found in the ir spectrum of **5**) confirmed the reduction of -N=N- of **5** to form the hydrazino group (-NH-NH-) in **6**. The ^1H nmr spectrum of **6** exhibited a multiplet (10 H) at δ 7.09-8.10 ppm assignable to aromatic protons (see Experimental).

Reaction of **2** with phenyl isothiocyanate in refluxing ethanol yielded 1-(2-methyl-9-oxo-9*H*-[1,2,4]triazolo-[5,1-*b*]quinazolin-3-yl)-3-phenylthiourea (**7**) (Scheme 4). The ir spectrum of **7** displayed NH and C=S stretching bands at 3375 and 1372 cm^{-1}, respectively, in addition to the carbonyl of quinazolinone ring at 1675 cm^{-1}. The ^1H nmr spectrum of **7** showed the two NH protons as two singlet peaks at δ 9.10 and 10.3 ppm. The ^{13}C nmr spectrum of **7** showed a signal peak at δ 180.6 ppm corresponding to C=S and signal at 162.4 corresponding to C=O of quinazolinone (see Experimental for details). The mass spectrum of **7** was characterized by the molecular ion peak M^+ that appeared at *m/z* = 350 and the peak corresponding to the loss of the thiourea moiety (M^+-151). The base ion

Scheme 3



Scheme 4



peak appeared at *m/z* = 200 (100%) was related to ($C_{10}H_8N_4O^+$) (see Experimental for details).

Compound **7** was cyclized with phenacyl bromide to the corresponding 3-(3,4-diphenyl-3*H*-thiazol-2-ylideneamino)-2-methyl-3*H*-[1,2,4]triazolo[5,1-*b*]quinazolin-9-one (**8**). 2-(2-Methyl-9-oxo-9*H*-[1,2,4[triazolo[5,1-*b*]quinazolin-3-ylimino)-3-phenyl-thiazolidine-4,5-dione (**9**) was synthesized *via* cyclization of **7** with oxalyl dichloride. Alternatively, 2-methyl-3-(4-oxo-3-phenylthiazolidin-2-ylideneamino)-3*H*-[1,2,4]triazolo[5,1-*b*]quinazolin-9-one (**10**) was prepared by cyclization of **7** with chloroacetic acid (Scheme 4).

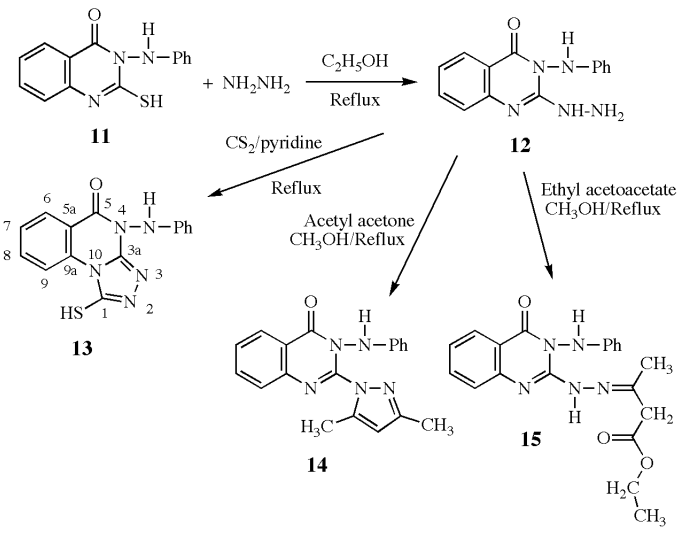
The structures of the new compound **8-10** were established on the basis of their elemental microanalyses and spectral data. The ir spectra revealed the disappearance of ν_{NH} at 3375 cm^{-1} and $\nu_{C=S}$ at 1372 cm^{-1} (previously found in the ir spectrum of **7**) confirmed the formation of the 1,3-thiazole ring. The ^1H nmr spectrum of **8** also lacked the NH signals and showed a new singlet signal at δ 5.65 ppm integrated for one proton attributed to the C_5-H of 1,3- thiazole ring. The ^1H nmr spectrum of **10** also showed a sharp singlet signal at δ 4.18 ppm, assignable to the methylene protons at C-5 of a 1,3-thiazole ring. The ^{13}C nmr data for **8** and **10** supported the formation of thiazole ring when they were compared with the data for **7**. In spectrum of **8** the C=S resonance was replaced by signals at δ 151.5, 112.8 and 167.2 ppm, which assigned to C-4, C-5, and C-2 of a 1,3- thiazole ring, respectively. The ^{13}C nmr data were assigned on the basis of comparing the data obtained for **8** and **10** with those repoted in the literature for 3*H*-quinazolin-4-one [20] and 1,3-thiazole ring system [24]. Complete information about ir, nmr and mass spectra is presented in the experimental part.

The reaction of 2-mercapto-3-phenylamino-3*H*-quinazolin-4-one (**11**) [22] with hydrazine hydrate in refluxing ethanol for 6 hours afforded the corresponding 2-hydrazino-3-phenylamino-3*H*-quinazolin-4-one (**12**) (Scheme 5). The presence of two strong bands at 3423 and 3334 cm^{-1} due to the presence of NH hydrazino and NH_2 characterized the ir spectrum of **12**, respectively. The ^1H nmr and ^{13}C nmr of **12** show the presence of the expected protons, in agreement with the proposed structure (see Experimental).

The hydrazino compound **12** has been used as the key starting material for the preparation of some other heterocyclic compounds. Thus, **12** reacts with carbon disulfide, acetyl acetone or ethyl acetoacetate to give 1-mercapto-4-phenylamino-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-one (**13**), 2-(3,5-dimethyl-pyrazol-1-yl)-3-phenylamino-4*H*-quinazolin-4-one (**14**) and 3-[4-oxo-3-phenylamino-3,4-dihydroquinazolin-2-yl)hydrazono]butyric acid ethyl ester (**15**), respectively as in Scheme 5.

Assignment of cyclic structures **13-15** was based on the observation that NH_2 groups were absent in their ir and ^1H nmr spectra and the presence of ν_{NH} and $\nu_{C=O}$ at 3430-3420 and 1699-1687 cm^{-1} in ir spectra, respectively. The ^1H nmr spectrum of **13** was characterized by two signals peak appeared at δ 8.98 and 10.26 ppm attributed to the NH and SH, respectively. The two-methyl groups' proton signals in compound **14** appeared at 2.60 and 2.85 ppm, in addition, the signal which appeared at 5.96 ppm region was due to the CH proton in the pyrazole ring. The ^1H nmr of **15** exhibited two signals for six protons of two methyl group at 1.98 ppm as triplet and another methyl group at 1.23 ppm as singlet and the ^{13}C signals at 14.5 and 17.2 ppm, respectively, while the four protons of the two CH_2 groups appeared at 3.40 and 3.82 ppm and the ^{13}C signals at 37.2 and 60.0 ppm, respectively. The mass spectra of **14** and **15** were characterized by the molecular ion peaks M^+ that appeared at m/z =331 (27.08%) for **14** and at m/z = 379 (63.97%) for **15**. The base peak appeared at m/z = 76 (100%) for **14** and at m/z = 292 (100%) for **15**. Complete information about the ir, ^1H nmr, ^{13}C nmr and mass spectra is presented in the experimental part.

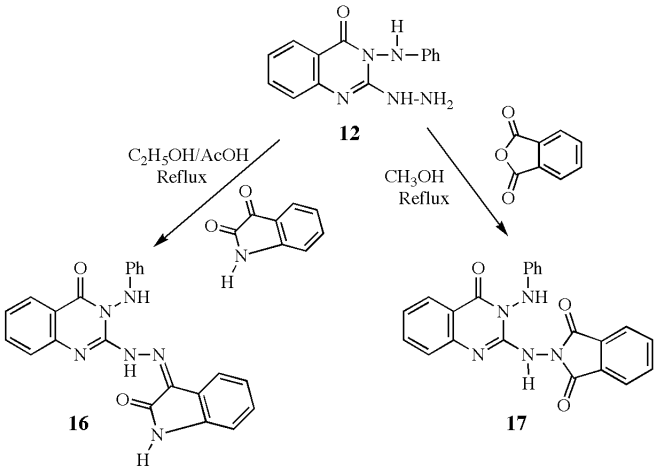
Scheme 5



Condensation of **12** with isatin in ethanol in the presence of acetic acid as a catalyst afforded 2-[*N*'-(2-oxo-1,2-dihydroindol-3-ylidene)hydrazino]-3-phenylamino-3*H*-quinazolin-4-one (**16**) as indicated in Scheme 6. The ir spectrum of **16** showed absorption function group at 3427 (ν_{NH}) and at 1708, 1668 cm^{-1} due to the two carbonyl groups ($\nu_{C=O}$). The ^1H nmr of **16** was characterized by three singlet signal peaks at δ 11.43 (s, 1H, NH of isatin), 10.53 (s, 1H, NH of hydrazino) and 8.79 ppm (s, 1H, NH attached to phenyl at position 3). The aromatic protons appeared at the expected field (see Experimental). The ^{13}C nmr of **16** showed the quinazolinone carbon atoms, the four carbon types of the phenyl and the isatin carbon atoms (see Experimental).

2-(4-Oxo-3-phenylamino-3,4-dihydroquinazolin-2-yl-amino)-isoindole-1,3-dione (**17**) was synthesized by the reaction of **12** with phthalic anhydride in refluxing methanol for 6 hours (Scheme 6).

Scheme 6



The structure of **17** was estimated by elemental analysis and spectral data (ir, ^{1}H nmr and ^{13}C nmr) (see Experimental). The ir spectrum of **17** showed functional absorption bands at 3378 (ν_{NH}) and 1731, 1693 cm^{-1} ($\nu_{C=O}$). The ^{1}H nmr spectrum of **17** showed two singlet peaks at δ 10.35 (s, 1H, NH of hydrazino) and 9.30 ppm (s, 1H, NH attached to phenyl group).

EXPERIMENTAL

All melting points are uncorrected. They were performed by open capillary method using electrothermal melting MEL-TEMP II apparatus. The infrared spectra were recorded with Unicam SP 1200 spectrophotometer using pellet technique KBr discs (ν in cm^{-1}). The ^{1}H nmr spectra were recorded with Bruker AC 250 FT spectrometer (250 MHz). The ^{13}C nmr spectra were recorded with Bruker AC-250 FT spectrometer (62.9 MHz). TMS was used as an internal standard and chemical shifts are expressed in δ ppm values. The mass spectral data were obtained with micro mass spectrometer model 7070 at energy of 70 eV and inlet temperature 90° C. Elemental analyses (C, H, N) were performed by the Microanalysis Center, Cairo University and Central Laboratory Service of Microanalysis Tanta University, Egypt.

3-Amino-2-methyl-3*H*-[1,2,4]triazolo[5,1-*b*]quinazolin-9-one (**2**).

A mixture of 3-*N*-(2-mercapto-4-oxo-4*H*-quinazolin-3-yl)acetamide (**1**) (2.35 g, 0.01 mole) and hydrazine hydrate (2 ml) in methanol (50 ml) was refluxed for 3 hours on water bath. After cooling the solid product was collected, washed with little methanol, dried and recrystallized from DMF to give compound **2** as colorless needles. Yield, 1.72 g (80 %); mp >300 °C; ir (KBr): 3319 (NH_2), 3195 (Ar-H), 1695 (C=O quinazolinone), 1622, 1466 (C=N, C=C) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ_H 2.48 (s, 3H, CH_3, *J* = 7.0 Hz), 6.00 (s, 2H, exchangeable with D_2O, NH_2), 7.33 (t, 1H, H-7, *J* = 8.2 Hz), 7.61 (d, 1H, H-5, *J* = 8.2 Hz), 7.75 (t, 1H, H-6, *J* = 8.2 Hz), 8.20 (d, 1H, H-8, *J* = 8.2 Hz).

Anal. Calcd. for $C_{10}H_9N_5O$ (215.2): C, 55.81; H, 4.19; N, 32.56. Found: C, 56.00; H, 4.12; N, 32.97.

3-[(2-Chlorobenzylidene)amino]-2-methyl-3*H*-[1,2,4]triazolo[5,1-*b*]quinazolin-9-one (**3**).

A solution of **2** (2.15 g, 0.01 mole) and *o*-chlorobenzaldehyde (1.4 g, 0.01 mole) in ethanol (60 ml) was refluxed for 4 hours in the presence of 2 drops of acetic acid as catalyst. The solvent was concentrated and the reaction product was allowed to cool. The separated product was collected by filtration, washed with water, dried and crystallized from methanol to give compound **3**. Yield, 17.5 g (52 %); mp 262-264 °C; ir (KBr): 3070 (Ar-H), 1708 (C=O quinazolinone), 1612, 1459, 1402 (C=N, C=C) cm^{-1}; ms: *m/z* (ion, relative intensity): 339 (M^+, 11.1 for ^{37}Cl), 337 (M^+, 33.3 for ^{35}Cl), 302 (7.4), 200 (100), 171 (17.9), 145 (14.1), 132 (25.9), 105 (14.8), 103 (14.8), 67 (17.9).

Anal. Calcd. for $C_{17}H_{11}ClN_5O$ (336.7): C, 60.71; H, 3.27; N, 20.83. Found: C, 60.88; H, 3.21; N, 21.14.

3-[(2-Hydroxynaphthalen-1-ylmethylene)amino]-2-methyl-3*H*-[1,2,4]triazolo[5,1-*b*]quinazolin-9-one (**4**).

Compound **4** was prepared in the same manner as described for **3**, using compound **2** (2.15 g, 0.01 mole) and 2-hydroxynaphthaldehyde (1.72 g, 0.01 mole). The product was crystallized from ethanol to furnish compound **4**. Yield 1.70 g (46 %); mp; 255- 256 °C; ir (KBr): 3425 (OH), 2923 (Ar-H), 1696(C=O quinazolinone), 1611, 1593, 1462 (C=N, C=C) cm^{-1}; ms: *m/z* (ion, relative intensity): 369 (M^+, 44.4), 279 (7.0), 302 (7.4), 200 (100), 169 (100), 145 (7.2), 119 (14.8), 105 (9.3), 67 (14.8).

Anal. Calcd. for $C_{21}H_{15}N_5O_2$ (369.4): C, 68.29; H, 4.07; N, 18.97. Found: C, 68.60; H, 4.20; N, 19.10.

3-(3-Hydroxy-naphthalene-1-yl-diazenyl)-2-methyl-3*H*-[1,2,4]triazolo[5,1-*b*]quinazolin-9-one (**5**).

Compound (**2**) (2.15 g, 0.01 mole) and 1-nitroso-2-naphthol (1.73 g, 0.01 mole) were taken in glacial acetic acid and the reaction mixture was refluxed for 2 hours. The solid that separated on adding water was collected by filration and recrystallized from 40 % aqueous ethanol to yield compound **5**. Yield, 2.52 g (68 %); mp 219-221 °C; ir (KBr): 3385 (OH), 3183 (Ar-H), 1697 (C=O quinazolinone), 1622, 1556,1466 (C=N, N=N, C=C) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ_H 2.52 (s, 3H, CH_3, *J* = 7.2 Hz), 5.81 (s, H, exchangeable with D_2O, OH), 7.10-8.12 (m, 10H , quinazolinone and naphthalene).

Anal. Calcd. for $C_{20}H_{14}N_6O_2$ (370.4): C, 64.86; H, 3.81; N, 22.69. Found: C, 65.11; H, 3.96; N, 22.61.

3-[*N*'-(2-Hydroxy-naphthalen-1-yl)hydrazino]-2-methyl-3*H*-[1,2,4]triazolo[5,1-*b*]quinazolin-9-one (**6**).

To a solution of **5** (3.7 g, 0.01 mole) in DMF (25 ml) were added $SnCl_2$ (5.69 g, 0.03 mole) and HCl (5 ml) and the reaction mixture was refluxed for 6 hours, and filtered while hot. The filtrate was cooled and poured over crushed ice water (100 ml). The solid thus separated was collected by filtration and recrystallized from ethanol-benzene to give compound **6**. Yield, 2.52 g (61 %); mp 196-198 °C; ir (KBr): 3548-3374 (NH and OH), 3194 (Ar-H), 1697 (C=O quinazolinone), 1620, 1469 (C=N, C=C), 1212 (O-H bending) cm^{-1} ; ^{1}H nmr (DMSO-d_6): δ_H = 2.54 (s, 3H, CH_3, *J* = 7.0 Hz), 7.09-8.10 (m, 10H, quinazolinone and naphthalene), 9.20-8.70 (m, 3H, exchangeable with D_2O, OH and 2 x NH).

Anal. Calcd. for $C_{20}H_{16}N_6O_2$ (372.4): C, 64.51; H, 4.33; N, 22.57. Found: C, 64.77; H, 4.63; N, 22.80.

1-(2-Methyl-9-oxo-9*H*-[1,2,4]triazolo[5,1-*b*]quinazolin-3-yl)-3-phenylthiourea (**7**).

To a solution of **2** (2.15 g, 0.01 mole) in absolute ethanol (30 ml), phenyl isothiocyanate (1.35 g, 0.01 mole) was added. The reaction mixture was heated under reflux for 4 hours, the solvent was concentrated under vacuum and the residue was allowed to cool. The crude product, which separated, was collected by filtration, washed with ethanol and crystallized from ethanol to give compound **7**. Yield 2.70 g (77%); mp 213-214 °C; ir (KBr): 3375 (*NH*), 1675 (CO), 1622 , 1542 (C=N, C=C), 1372 (C=S) cm^{-1}; ^1H nmr (DMSO-d_6): δ_H 2.40 (s, 3H, CH_3, *J* = 7.0 Hz), 7.30 (t, 1H, H-7, *J* = 8.0 Hz), 7.58 (d, 1H, H-5, *J* = 8.0 Hz), 7.72 (t, 1H, H-6, J = 8.0 Hz), 8.18 (d, 1H, H-8), 6.66-7.15 (m, 5H, Ph), 9.10 (s, 1H, exchangeable with D_2O, NH), 10.3 (s, 1H, exchangeable with D_2O, *NH*); ^{13}C nmr (DMSO-d_6): δ_C 14.2 (CH_3), 120.3, 121.7, 124.5, 126.3, 128.3, 128.8, 129.5, 137.2, 137.8, 143.3, 148.6, 153.7 (C_{arom}), 162.4 (C=O), 180.6 (C=S); ms: *m/z* (ion, relative intensity): 350 (M^+, 12.7), 273 (M^+-Ph, 5.0), 200 ($C_{10}H_8N_4O^+$, 100), 199 (M^+-NHCSNHPh, 24.7), 152 ($PhNHCSNH_2^+$, 9.0), 145 (4.6), 119(13.0), 105 (17.6), 77 (43.2).

Anal. Calcd. for $C_{17}H_{14}N_6OS$ (350.4): C, 58.27; H, 4.03; N, 23.98. Found: C, 58.54; H, 4.23; N, 24.23.

3-(3,4-Diphenyl-3*H*-thiazol-2-ylideneamino)-2-methyl-3*H*-[1,2,4]triazolo[5,1-*b*]quinazolin-9-one (**8**).

A mixture of thiourea derivative **7** (1.75 g, 0.005 mole), phencyl bromide (1.0 g, 0.005 mole) and freshly fused sodium acetate (0.41 g, 0.005 mole) in ethanol (25 ml) was heated under reflux for 5 hours. The solvent was concentrated and the reaction product was allowed to cool. The separated product was collected by filtration, washed with water and crystallized from methanol/petroleum ether (3:1) to give compound **8**. Yield 1.85 g (82%); mp 331-333 °C; ir (KBr): 1683 (C=O quinazolinone), 1625 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ_H 2.48 (s, 3H, CH_3, *J* = 7.2 Hz), 5.65 (s, 1H, thiazolidine proton C_5-H), 7.05-8.28 (m, 14H, Ar-H); ^{13}C nmr (DMSO-d_6): δ_C 14.8 (CH_3), 119.7, 122.4, 124.8, 126.5, 127.5, 128.4, 128.7, 128.8, 129.2, 129.7, 134.3, 136.6, 137.5, 143.4, 149.0, 155.1 (C_{arom}), 164.6 (C=O), 112.8, 151.5, 167.2 (3C, C-5, C-4, C-2 of thiazolidine ring, respectively).

Anal. Calcd. for $C_{25}H_{18}N_6OS$ (450.5): C, 66.65; H, 4.03; N, 18.65. Found: C, 66.47; H, 4.25; N, 18.34.

2-(2-Methyl-9-oxo-9*H*-[1,2,4]triazolo[5,1-*b*]quinazolin-3-ylimino)-3-phenyl-thiazolidine-4,5-dione (**9**).

Oxalyl dichloride (1.26 g, 0.01 mole) was added dropwise to a solution of thiourea derivative (3.5 g, 0.01 mole) **7** in saturated sodium bicarbonate solution (10 ml) and methylenedichloride (25 ml) under cooling in ice-cold water. There after, the reaction mixture was stirred for 7 hours at room temperature. The CH_2Cl_2 layer was separated, washed with water, dried over anhydrous $MgSO_4$ and evaporated to dryness. The residue was crystallized from DMF/ethanol (1:4) to give compound **9**. Yield 1.78 g (44%); mp 179-182 °C; ir (KBr): 1768, 1736 (C=O thiazolidone), 1692 (C=O quinazolinone), 1632 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ_H 2.52 (s, 3H, CH_3, *J* = 7.0 Hz), 7.23-8.46 (m, 9H, Ar-H).

Anal. Calcd. for $C_{19}H_{12}N_6O_3S$ (404.4): C, 56.43; H, 2.99; N, 20.78. Found: C, 56.70; H, 2.84; N, 20.89.

2-Methyl-3-(4-oxo-3-phenylthiazolidin-2-ylideneamino)-3*H*-[1,2,4]triazolo[5,1-*b*] quinazolin-9-one (**10**).

A mixture of thiourea derivative **7** (3.5 g, 0.01 mole), chloroacetic acid (0.94 g, 0.01 mol) and freshly fused sodium acetate (1.23 g, 0.015 mole) in absolute ethanol (25 ml) was heated under reflux for 10 hours. The reaction mixture was poured onto ice-cold water (400 ml) and the separated product was collected by filtration and recrystallized from ethanol to yield compound **10**. Yield 2.65 g (68%); mp 279-280 °C; ir (KBr): 1724 (C=O 4-oxothiazolidine) 1688 (C=O quinazolinone), 1630 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ_H 2.45 (s, 3H, CH_3, *J* = 7.0 Hz), 4.18 (s, 2H, CH_2, 4-oxothiazolidine), 7.14-8.05 (m, 9H, Ar-H); ^{13}C nmr (DMSO-d_6): δ_C 14.4 (CH_3), 120.1, 122.0, 125.2, 125.8, 127.4, 128.6, 129.0, 136.7, 134.5, 142.5, 147.8, 154.2 (C_{arom}), 163.7 (C=O), 58.7, 166.4, 192.2 (3C, C-5, C-2, C-4 of thiazolidine ring, respectively).

Anal. Calcd. for $C_{19}H_{14}N_6O_2S$ (390.4): C, 58.45; H, 3.61; N, 21.53. Found: C, 58.18; H, 3.42; N, 21.74.

2-Hydrazino-3-phenylamino-3*H*-quinazolin-4-one (**12**).

A mixture of 2-mercapto-3-phenylamino-3*H*-quinazolin-4-one (**11**) (2.69 g, 0.01 mole) and hydrazine hydrate (2 ml) in ethanol (100 ml) was refluxed for 6 hours. After cooling the precipitate was collected, washed with ethanol and recrystallized from methanol to yield compound **12**. Yield 1.20 g (45%); mp 175 °C; ir (KBr): 3423 (NH), 3334 (NH_2), 1665 (C=O quinazolinone), 1591, 1482 (C=N, C=C) cm^{-1}; ^1H nmr (DMSO-d_6): δ_H 4.06 (s, 2H, NH_2), 6.63-7.13 (m, 5H, Ph), 7.14 (t, 1H, H-6), 7.36 (d, 1H, H-8), 7.61 (t, 1H, H-7), 7.86 (d, 1H, H-5), 8.58 (s, 1H, NH), 8.83 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ_C 116.9, 120.3, 121.7, 124.5, 126.3, 128.8, 133.0, 137.5, 146.5, 148.9, 152.7 (C_{arom}), 160.2 (C=O).

Anal. Calcd. for $C_{14}H_{13}N_5O$ (267.3): C, 62.91; H, 4.90; N, 26.20. Found: C, 63.20; H, 5.00; N, 26.40.

1-Mercapto-4-phenylamino-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-one (**13**).

A mixture of compound **12** (2.67 g, 0.01 mole) and carbon disulfide (5 ml) in 30 ml of pyridine was refluxed for 5 hours, until the odour of hydrogen sulfide was ceased. The reaction mixture was cooled and poured into ice-water (250 ml), a yellow precipitate was obtained, dried and recrystallized from ethanol to give compound **13**. Yield 1.85 g (60%); mp. 260 °C; ir (KBr): 3430 (NH), 3307 (SH), 1693 (C=O quinazolinone), 1602, 1550 (C=N, C=C) cm^{-1}; ^1H nmr (DMSO-d_6): δ_H 6.32-6.84 (m, 5H, Ph), 7.10 (t, 1H, H-8, *J* = 8.2 Hz), 7.12 (t, 1H, H-7, *J* = 8.2 Hz), 7.52 (d, 1H, H-9, *J* = 8.2 Hz), 8.20 (d, 1H, H-6, *J* = 8.2 Hz), 8.98 (s, 1H, NH), 10.26 (s, 1H, SH); ^{13}C nmr (DMSO-d_6): δ_C 112.8, 115.00, 116.7, 117.5, 118.7, 119.9, 126.9, 128.7, 134.1, 146.0, 150.2 (C_{arom}), 135.5 (C-1 triazole), 162.3 (C=O).

Anal. Calcd. for $C_{15}H_{11}N_5OS$ (309.3): C, 58.25; H, 3.56; N, 22.65. Found: C, 58.60; H, 3.70; N, 23.00.

2-(3,5-Dimethylpyrazol-1-yl)-3-phenylamino-3*H*-quinazolin-4-one (**14**).

A mixture of the hydrazino derivative **12** (2.67 g, 0.01 mole) and acetyl acetone (1.0 g, 0.01 mole) was refluxed for 3 hours. The reaction mixture was cooled and the product that separated out was collected by filtration, dried and recrystallized from ethanol to give compound **14**. Yield 2.00 g (60%); mp 218 °C; ir (KBr): 3420 (NH), 1699 (CO), 1603, 1561 (C=N, C=C) cm^{-1}; ^1H nmr (DMSO-d_6): δ_H 2.60 (s, 3H, CH_3,), 2.85 (s, 3H, CH_3), 5.96

(s, 1H, CH-pyrazole ring), 6.59-7.13 (m, 5H, Ph), 7.63 (t, 1H, H-8, *J* = 8.2 Hz), 7.79 (t, 1H, H-6, *J* = 8.2 Hz), 7.92 (t, 1H, H-7, J = 8.2 Hz), 8.17 (d, 1H, H-5, *J* = 8.2 Hz), 8.97 (s, 1H, exchangeable with D_2O, NH); ms: *m/z* (ion, relative intensity): 331 (M^+, 27.08), 316(M^+-Me, 1.48), 301(316-Me, 2.73), 239 (M^+-NHPh, 15.25), 145 (239-$C_5H_6N_2$, 15.62), 119 (144-CN, 20.10), 104 (119-NH, 3.14), 76 (104-CO, 100).

Anal. Calcd. for $C_{19}H_{17}N_5O$ (331.4): C, 68.87; H, 5.17; N, 21.13. Found: C, 69.10; H, 5.00; N, 21.43.

3-[(4-Oxo-3-phenylamino-3,4-dihydroquinazolin-2-yl)hydrazono]butyric Acid Ethyl Ester (**15**).

A mixture of hydrazino compound **12** (2.67 g, 0.01 mole) and ethyl acetoacetate (3.0 ml, 0.023 mole) was refluxed in methanol (20 ml) for 3 hours. The reaction mixture was cooled and the solvent was evaporated to dryness. The residue was recrystallized from benzene/petroleum ether to give compound **15** as yellow crystals. Yield 1.90 g (50%); mp 79-80 °C; ir (KBr): 3425 (NH), 1726 (CO ester), 1687 (CO quinazolinone), 1623 , 1548 (C=N, C=C) cm^{-1}; ^1H nmr (DMSO-d_6): δ_H 1.23 (s, 3H, CH_3), 1.98 (t, 3H, CH_3 of ester, *J* = 7.0 Hz), 3.40 (s, 2H, CH_2), 3.82 (q, 2H, CH_2, *J* = 7.0 Hz), 6.10-7.97 (m, 9H, Ar-H), 8.20 (s, 1H, exchangeable with D_2O, NH), 10.25 (s, 1H, exchangeable with D_2O, *NH*); ^{13}C nmr (DMSO-d_6): δ_C 14.5 (CH_3), 17.2 (CH_3), 37.2 (CH_2), 60.0 (CH_2), 113.5, 120.0, 120.3, 122.2, 122.2, 128.0, 129.1, 129.1, 135.6, 136.5, 148.0 (C_{arom}) 158.2 (-N=C-), 160.1 (C=O quinazolinone), 169.4 (C=O butyric ethyl ester); ms: *m/z* (ion, relative intensity): 379 (M^+, 63.97), 364 (M^+-Me, 7.35), 334 (364-CH_2O, 7.35), 292 (334-C_2H_2O, 100), 236 (292-$C_2H_3N_2$, 25.75), 145 (33.08), 119(19.55), 104 (7.00), 77 (33.08).

Anal. Calcd. for $C_{20}H_{21}N_5O_3$ (379.4): C, 63.31; H, 5.58; N, 18.46. Found: C, 63.60; H, 5.60; N, 18.73.

2-[*N*'-(2-Oxo-2-dihydroindol-3-ylidene)-hydrazino-3-phenylamino-3*H*-quinazolin-4-one (**16**).

A mixture of hydrazino compound **12** (2.67, 0.01 mol) and isatin (1.47 g, 0.01 mol) in ethanol (50 ml) in the presence of 2 drops of glacial acetic acid as catalyst was refluxed for 4 hours. During this period, the product was separated from the reaction mixture as yellow precipitate. The precipitate was collected by filtration and recrystallized from butanol to give compound **16**. Yield 3.2 g (80%); mp 276 °C; ir (KBr): 3427(NH), 2922 (C-H aromatic), 1708 (CO), 1668 (CO), 1618, 1546 , 1462 (C=N, C=C) cm^{-1}; ^1H nmr (DMSO-d_6): δ_H 6.62-8.20 (m, 13H, Ar-H), 8.79 (s, 1H, exchangeable with D_2O, NH), 10.53 (s, 1H, exchangeable with D_2O, NH of hydrazino), 11.43 (s, 1H, exchangeable with D_2O, NH of isatin); ^{13}C nmr (DMSO-d_6): δ_C 154.1, 165.6, 123.1, 127.9, 127.4, 135.4, 117.4 and 145.7 (C-2, C-4, C-4a, C-5, C-6, C-7, C-8 and C-8a (quinazolinone carbon atoms, respectively), 142.7, 109.5, 128.8 and 112.2 (phenyl carbon atoms due to *ipso*, *ortho*, *meta* and *para*, respectively), 159.7, 146.8, 119.3, 128.8, 121.2, 131.0, 114.4 and 138.8 (C-2, C-3, C-3a, C-4, C-5, C-6, C-7 and C-7a (isatin carbon atoms, respectively).

Anal. Calcd. for $C_{22}H_{16}N_6O_2$ (396.4): C, 66.66; H, 4.07; N, 21.20. Found: C, 66.68; H, 4.10; N, 21.29.

2-(4-Oxo-3-phenylamino-3,4-dihydroquinazolin-2-ylamino)-isoindole-1,3-dione (**17**).

πA mixture of hydrazino compound **12** (2.67 g, 0.01 mole) and phthalic anhydride (1.48 g, 0.01 mole) in methanol (50 ml) in the presence of 2 drops of glacial acetic acid as catalyst was refluxed for 6 hours. After cooling the precipitate was collected, washed with ethanol, dried and recrystallized from ethanol to give compound **17**. Yield 2.8 g (70%); mp 280-282 °C; ir (KBr): 3378 (NH), 3049 (C-H aromatic), 1731 (CO), 1693 (CO), 1605, 1518 (C=N, C=C) cm^{-1}; ^1H nmr (DMSO-d_6): δ_H 6.92-8.02 (m, 13H, Ar-H), 9.30 (s, 1H, exchangeable with D_2O, NH), 10.35 (s, 1H, exchangeable with D_2O, *NH* of hydrazino); ^{13}C nmr (DMSO-d_6): δ_C 150.6, 166.0, 124.2, 127.0, 127.4, 136.0, 121.6 and 148.1 (C-2, C-4, C-4a, C-5, C-6, C-7, C-8 and C-8a (quinazolinone carbon atoms, respectively), 136.0, 114.4, 129.6 and 118.6 (phenyl carbon atoms due to *ipso*, *ortho*, *meta* and *para*, respectively), 160.6, 147.2, 126.0, 129.6, 121.6, 130.0, 114.4, 135.5 (C-1, C-3, C-3a, C-4, C-5, C-6, C-7 and C-7a (isoindole carbon atoms, respectively).

Anal. Calcd. for $C_{22}H_{15}N_5O_3$ (397.4): C, 66.49; H, 3.80; N, 17.62. Found: C, 66.90; H, 3.60; N, 18.00.

REFERENCES AND NOTES

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[1] F. K. Kirchnov and A. W. Zalay, *US Patent*, **3**, 217,005 (1965); *Chem. Abstr*., **64**, 3570 (1966).

[2] K. Kar, J. Chatterjee and B. Mukherji, *J. Sci & Ind. Research*, **85**, 159 (1960); *Chem. Abstr*., **55**, 6704 (1961).

[3] V. Z. Gorkin and R. S. Krivchenkova, *Vop Med. Khim*, **14**, 428 (1967); *Chem. Abstr*., **67**, 87675 (1967).

[4] I. Ahmad, *J. Indian Chem. Soc*., **65**, 362 (1988).

[5] G. H. F. Nuttal, *Proc. Camb. Phil. Soc*., **15**, 53 (1909); *Chem. Abstr*., **3**, 1301 (1909).

[6] I. A. Mazur, R. S. Kalkewick and P. N. Steplywle, *Farmzho*, **4**, 34 (1980); *Chem. Abstr*., **94**, 47258 (1981).

[7] G. Tanaka, Japan Kokai, 7495, 973 (1974); *Chem. Abstr*., **82**, 156320 (1975).

[8] K. Spirkova, S. Stankovsky and J. Homacek, *Collect. Czech. Chem. Commun*., **59**, 243 (1994).

[9] A. A. Bekhit and M. A. Khalil, *Pharmazie*, **53**, 539 (1998).

[10] A. M. E. Omar, H. M. Salama and N. H. Eshba, *Farmaco Ed. Sci*., **40**, 49 (1985).

[11] M.. Rajopadhye and F. D. Popp, *J. Heterocyclic Chem*., **24,** 1637 (1987).

[12] T. Szirtes, L. Kisfaludy, E. Palosi and L. Szporny, *J. Med. Chem*., **29**, 1654 (1986).

[13] K. Mogilaiah and R. B. Rao, *Indian J. Chem*., Sec.B, **37**, 894 (1998).

[14] G. Coppi, A. Falcone and S. Manzardo, *Arzneim Forsch*, **44**, 12a, 1417 (1994).

[15] R. Lesyke, O. Vladzimirska, B. Zimenkovsky, M. Horishny and I. Nektegayev, *Boll. Chem. Farm*., **137**, 210 (1998).

[16] N. S. Habib, S. Fahmy, S. M. El- Khawass and T. A. Aziem, *Pharmazie*, **55** (12), 900 (2000).

[17] M. F. Abdel-Megeed, G. A. El-Hiti, M. A. Abdo and M. A.Saleh , *Revue Roumaine De Chimie*, **45**, 545 (2000).

[18] M. A. Saleh, Y. A. Abbas, F. E. Abdel-Hai and S. A. Youssef, *Nucleosides, Nucleotides & Nucleic Acids*, **20**, 1891 (2001).

[19] M. A. Saleh, M. F. Abdel-Megeed, M. A. Abdo and A. M. Shokr, *Nucleosides, Nucleotides & Nucleic Acids*, **21**, 93 (2002).

[20] M. A. Saleh, M. F. Abdel-Megeed, M. A. Abdo and A. M. Shokr, *J. Heterocyclic Chem*., **40**, 85 (2003).

[21] M. A. Saleh, M. F. Abdel-Megeed, M. A. Abdo and A. M. Shokr, *Molecules*, **8**, 363 (2003).

[22] M. A. Saleh and M. F. Abdel-Megeed, *J. Carbohydr. Chem*., **22**, 79 (2003).

[23] H. K Gakhar, S. C. Gupta and N. Kumar, *Indian J. Chem*., Sec.B, **20**, 14 (1981).

[24] R. Umarani, *Magn. Reson. Chem*., **30**, 1027 (1992).