A Convenient Synthesis of 1,2-Dihydro-1,2,4-triazolo[3,2-*b*]quinazolin-9(1*H*)-ones and Their 1,2,4-Triazolo Derivatives

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A range of 1,2-dihydro-1,2,4-triazolo[3,2-*b*]quinazolin-9(1*H*)-ones (**3**) has been synthesized in very good yields by the reaction of 3-amino-2-anilino-4(3*H*)-quinazolinone (**1**) with aromatics aldehydes in the presence of excess piperidine as a base. The 1,2,4-triazolo[3,2-*b*]quinazolin-9(1*H*)-ones could be obtained in very good yields by dehydrogenation of compounds **3** with thionyl chloride. Reaction of **1** with active methylene compounds (diethyl malonate and acetylacetone) resulted in the production of condensed products. These condensed products could be cyclized to 1,2,4-triazolo[3,2-*b*]quinazolin-9(1*H*)-one by heating above the melting point. Acetylation of **1** by acetic anhydride was found to be dependent on the reaction conditions. The acetyl derivative 3-acetamido-2-anilino-4(3*H*)-quinazolinone formed under mild conditions, while dimerization took place under strong conditions to give a pentacyclic compound in very good yield.

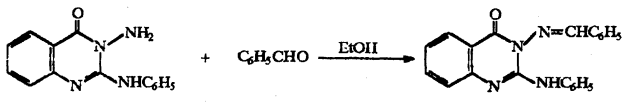
Quinazoline and its synthetic analogues have been found to exhibit interesting biological activities.[1] Some of these activities include antimicrobial,[2] antimalarial,[3] anticonvulsive,[4] antidepressant,[5] antihistamines,[6] stimulant,[5] biocidal,[7] plant-growth regulating[8] anticancer,[9] antiinflammatory properties,[10] etc. The range of biological activities and characteristic chemical structures have made synthetic studies of quinazolines very attractive.

The introduction of a triazole ring to the quinazoline system is expected to influence the biological activities significantly. Hence, it was thought desirable to synthesize a system having both ring systems, in order to evaluate the biological activities of the resulting triazoloquinazoline system. While this work was in progress, antimicrobial,[11] antibacterial,[12] and nervous system agents[13] have been reported for some triazoloquinazolines.

In the present work, I report an efficient synthetic approach to the title dihydroquinazolinones from the condensation reaction of 3-amino-2-anilino-4(3*H*)-quinazolinone (**1**) with aromatic aldehydes in the presence of piperidine. However, it is reported in the literature that a reaction of compound **1** with benzaldehyde under nearly the same reaction conditions gives the benzylidene derivative **2** (Scheme 1).[14]

Results and Discussion

3-Amino-2-anilino-4(3*H*)-quinazolinone (**1**) was prepared according to the literature procedure.[14]

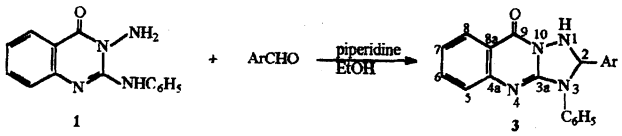


1 2

Scheme 1.

Reactions of compound **1** with a range of aromatic aldehydes in boiling absolute ethanol in the presence of excess amounts of piperidine as a base resulted in the production of 2-aryl-3-phenyl-1,2-dihydro-1,2,4-triazolo[3,2-*b*]quinazolin-9(1*H*)-one derivatives **3a—h** (Scheme 2) in very good yields (Table 1).

The products were expected to be Schiff bases, as reported in the literature,[14] but a ring-forming reaction was seen to occur. Thus, the melting point of dihydrotriazolo derivative **3a** (221—222 °C) is completely different from the melting point of the corresponding benzylidene derivative **2** (153—



1 3

Scheme 2.

Table 1. Synthesis of 2-Aryl-3-phenyl-1,2-dihydro-1,2,4-triazolo[3,2-*b*]quinazolin-9(1*H*)-one Derivatives (**3a—h**) According to Scheme 2[a]

Compound	Ar	Yield (%)[b]
3a	C_6H_5	76
3b	2-HOC_6H_4	80
3c	4-HOC_6H_4	81
3d	4-$NO_2C_6H_4$	75
3e	4-$(CH_3)_2NC_6H_4$	77
3f	4-$CH_3OC_6H_4$	75
3g	3-ClC_6H_4	80
3h	4-ClC_6H_4	85

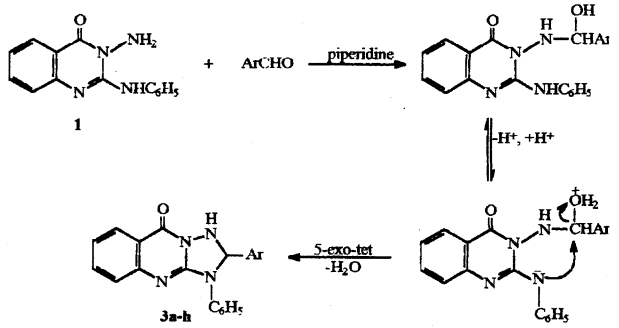
a) See experimental section for details. b) Yields reported are for isolated, purified materials.

155 °C). Cyclization from the Schiff base would be contrary to the forward pathway according to Baldwin.[15] The ^{1}H NMR spectra of compounds **3a**—**h** were characterized by a doublet located at $\delta = 6.5$—6.9 region, assigned to the CH proton at position 2, which, after shaking with D_2O, converts to a singlet. This is an indication of the presence of a CH–NH linkage, supporting the cyclic nature of compounds **3a**—**h**.

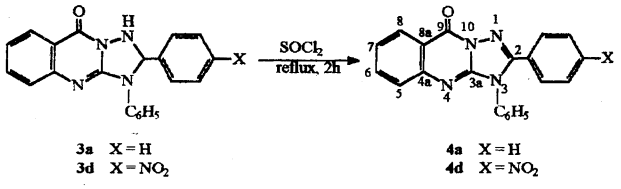
A possible pathway leading to compounds **3**, which is in consistent with Baldwin rules, is shown in Scheme 3.

Compounds **3** can now be used as starting materials for other transformations. As a demonstration of this, we have converted two examples, **3a**,**d**, into the corresponding triazoloquinazolin-9(1*H*)-ones (**4a**,**d**) in 81 and 80% isolated yields, respectively (Scheme 4), by reaction with thionyl chloride.

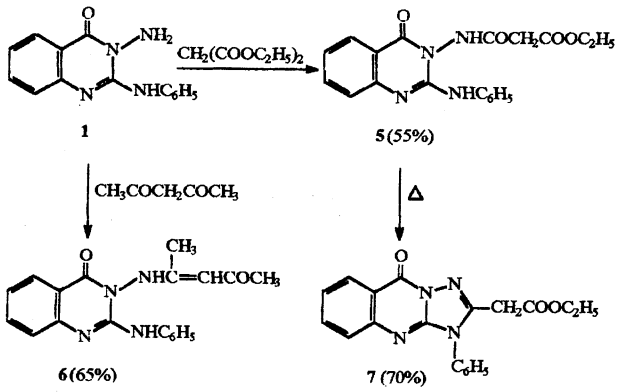
In an attempt to produce to triazoloquinazolinones directly, compound **1** was reacted with other carbonyl compounds, diethyl malonate, acetylacetone and acetic anhydride. However, none led to triazoles directly. Reactions of compound **1** with active methylene compounds such as (diethyl malonate and acetylacetone) resulted in the production of condensation products **5** and **6** in 55 and 65% isolated yields, respectively (Scheme 5). However, the attempt to convert compound **5**



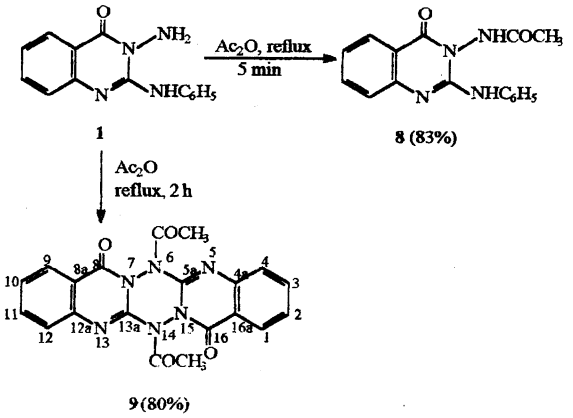
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

into the triazolo derivative **7** was successful. Compound **7** was obtained in 70% isolated yield (Scheme 5) by heating **5** above its melting point.

The ^{1}H NMR spectrum of compound **5** shows interesting features, in which the two hydrogen atoms of the CH_2 group occur as independent, coupled signals, suggesting that they are diastereotopic (see Experimental section). We have observed related phenomena in spectra of some compounds produced via lithiation and electrophilic trapping of 2-alkyl- and 2-unsubstituted 3-acylamino-4(3*H*)-quinazolinones,[16,17] and 3-amino-2-alkyl-4(3*H*)-quinazolinones.[18] The effect results from the presence of a chiral axis associated with the N–N bond and a high barrier to rotation about that bond in such diacylhydrazines.[19]

The structure of the acetylated product of compound **1** was found to be dependent on the conditions of the acetylation process. Acetylation of **1** with acetic anhydride under mild conditions (5 min reflux) caused simple acetylation of the amino group at position 3 without affecting the anilino group at position 2, leading to compound **8** in 83% isolated yield (Scheme 6). The reaction with boiling acetic anhydride for 2 h, however caused dimerization to give the pentacyclic structure **9** in 80% isolated yield (Scheme 6). Compound **9** was also obtained via reaction of the dilithio reagent of 3-acetamido-4(3*H*)-quinazolinone with iodine and is identical in all respects with that prepared according to Scheme 6.[17]

The ^{1}H NMR spectrum of compound **9** is characterized by the lack of any NH proton. Its FAB mass spectrum shows a pseudo molecular ion peak (MH^+) at 403, and a base peak at 202.

Conclusion

The one-step reaction of 3-amino-2-anilino-4(3*H*)-quinazolinone with a range of aromatic aldehydes in the presence of piperidine as a base provides a convenient route for the preparation of a number of 1,2-dihydro-1,2,4-triazolo[3,2-*b*]quinazolin-9(1*H*)-one derivatives, some of which would be tedious to prepare otherwise. The derivatives are now available for further transformation as shown by the conversion into the corresponding triazoloquinazoline derivatives. This should be beneficial for the synthesis of analogues with potentially useful pharmacological properties.

Experimental

Melting points were determined on an electrothermal MEL-TEMP II melting apparatus and are reported uncorrected. Elemental analyses were obtained from the central laboratory service of microanalysis, Tanta University. IR spectra were recorded on a Unicam SP 1200 spectrophotometer using KBr discs. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C measurements. Chemical shifts are recorded relative to tetramethylsilane. Assignments of signals are based on coupling patterns and expected chemical shift values and have not been rigorously confirmed. Signals with similar characteristics might be interchanged. Low resolution mass spectra were recorded on Quattro II triple quadrupole mass spectrometer, electron impact (EI) at 70 eV and chemical ionization (CI) by use of ammonia as ionization gas. FAB (LSIMS) spectrum was recorded on a VG-Autospec instrument. Accurate mass data were obtained on a VG ZAB-E instrument. The solvents were purified by standard procedures.[20,21] IR spectra were in agreement with the assigned structures.

General Procedure for the Synthesis of 2-Aryl-3-phenyl-1,2-dihydro-1,2,4-triazolo[3,2-*b*]quinazolin-9(1*H*)-ones (3a—h). To a solution of compound **1** (5.0 mmol; 1.26 g) in absolute ethanol (20 ml), the appropriate aromatic aldehydes (6.0 mmol) and piperidine (1.0 ml) were added. The mixture was heated under reflux for 2 h. After cooling, the precipitate which separated was collected by filtration, then washed with ethanol to give compounds **3a—h**. Yields are recorded in Table 1. Melting points, analyses and accurate mass spectral data are recorded in Table 2. The NMR spectral data are recorded in Table 3.

Synthesis of 2-Aryl-3-phenyl-1,2,4-triazolo[3,2-*b*]quinazolin-9(1*H*)-one Derivatives 4a,d. Compounds **3a** or **3d** (1.0 mmol) in thionyl chloride (10 ml) was refluxed for 2 h. The excess thionyl chloride was removed in vacuo and the solid obtained was crystallized from 1-butanol to give yellow crystals of **4a** or **4d**.

Table 2. Melting Points, Analyses, Mass and Accurate Mass Spectral Data of **3a—h**

Product	Mp	Analyses Calcd/Found			MS[a]	Acc. mass of M^+ Calcd/Found
	°C	C	H	N		
3a	221—222	74.09	4.74	16.47	340	340.1324
		73.97	4.87	16.51		340.1324
3b	230—231	70.78	4.53	15.72	357[b]	357.1352
		70.56	4.31	15.71		357.1352
3c	235—236	70.78	4.53	15.72	357[b]	357.1352
		70.66	5.43	15.67		357.1352
3d	260—261	65.45	3.92	18.17	385	385.1175
		65.33	4.09	18.01		385.1175
3e	177—178	72.03	5.52	18.27	383	383.1746
		71.95	5.51	18.09		383.1746
3f	218—219	71.32	4.90	15.13	370	370.1430
		71.19	5.01	15.00		370.1430
3g	210—211	67.36	4.04	14.97	374	374.0934
		67.31	3.98	15.02		374.0934
3h	185—186	67.36	4.04	14.97	374	374.0934
		67.25	3.95	15.11		374.0934

a) Unless otherwise indicated, all spectra were recorded using electron impact. b) Chemical ionization (M+1 peak).

2,3-Diphenyl-1,2,4-triazolo[3,2-*b*]quinazolin-9(1*H*)-one (4a). Mp 241—242 °C; **4a** is highly insoluble in DMSO-d_6. ^{1}H NMR (DMSO-d_6) δ = 8.16 (d, J = 8.0 Hz, 1H, H-8), 8.12—7.32 (m, 13H, H-5, H-6, H-7, and 2 Phs); MS (EI) m/z (%) 338 (M^+; 17), 261 (20), 235 (40), 192 (10), 179 (12), 102 (20), 77 (100). HRMS Found: m/z 338.1168. Calcd for $C_{21}H_{14}N_4O$:M, 338.1168. Found: C, 74.40; H, 4.10; N, 16.42%. Calcd for $C_{21}H_{14}N_4O$: C, 74.53; H, 4.14; N, 16.57%.

2-(4-Nitrophenyl)-3-phenyl-1,2,4-triazolo[3,2-*b*]quinazolin-9(1*H*)-one (4d). Mp 281—282 °C; ^{1}H NMR (DMSO-d_6) δ =

Table 3. NMR Chemical Shifts (ppm)[a] for Compounds **3a—h**

Cpd	^{1}H NMR parameteres	^{13}C NMR parameters
3a	9.17 (br, exch., 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.72—7.01 (m, 13H), 6.64 (d, J = 8.2 Hz, 1H)	156.45, 148.65, 148.35, 137.26, 136.70, 134.06, 129.30, 128.98, 128.84, 127.22, 125.93, 125.64, 124.34, 123.57, 120.94, 119.11, 75.32
3b	10.01 (br, exch., 1H), 8.02 (d, J = 7.9 Hz, 1H), 7.73—6.88 (m, 13H), 6.74 (d, J = 8.4 Hz, 1H)	156.24, 155.53, 148.58, 148.09, 137.26, 133.61, 130.02, 128.65, 127.15, 125.71, 125.42, 123.64, 123.11, 122.64, 119.88, 118.96, 118.92, 115.80, 70.99
3c	10.30 (br, exch., 1H), 9.64 (br, exch., 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.91—6.70 (m, 12H), 6.59 (d, J = 9.6 Hz, 1H)	156.22, 158.15, 148.58, 148.35, 137.13, 133.65, 131.52, 128.60, 128.15, 126.19, 125.74, 125.37, 124.66, 119.02, 115.29, 75.54
3d	8.38—7.11 (m, 14H), 6.80 (d, J = 8.4 Hz, 1H)	156.24, 148.41, 147.52, 144.18, 136.91, 133.85, 128.93, 128.39, 125.78, 125.57, 124.23, 123.85, 123.69, 120.35, 118.99, 73.80
3e	8.79 (br, exch., 1H), 8.03—6.80 (m, 13H), 6.54 (d, J = 8.6 Hz, 1H), 3.04 (s, 6H)	156.40, 153.26, 148.86, 148.73, 146.38, 137.32, 134.22, 128.81, 128.41, 126.77, 125.52, 125.06, 122.50, 122.37, 119.25, 111.33, 76.08, 39.88
3f	9.05 (br, exch., 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.70—6.82 (m, 12H), 6.62 (d, J = 9.6 Hz, 1H), 3.72 (s, 3H)	158.61, 156.70, 148.95, 148.80, 137.51, 134.23, 129.51, 129.10, 128.40, 126.25 125.80, 124.72, 123.69, 121.73, 119.40, 114.42, 75.71, 55.43
3g	8.04 (d, J = 8.0 Hz, 1H), 7.76—7.11 (m, 13H), 6.72 (d, J = 8.6 Hz, 1H)	156.24, 148.44, 147.75, 139.19, 136.97, 133.80, 133.37, 130.54, 129.10, 128.06, 128.80, 125.77, 125.51, 123.41, 122.80, 120.57, 119.01, 74.25
3h	8.03 (d, J = 8.0 Hz, 1H), 7.73—7.10 (m, 13H), 6.70 (d, J = 7.3 Hz, 1H)	156.22, 148.48, 147.86, 136.99, 135.69, 133.85, 133.77, 128.96, 128.81, 128.68, 125.76, 125.49, 124.21, 123.36, 120.75, 119.00, 74.43

a) Spectra recorded in DMSO-d_6.

8.31—8.19 (m, 3H, H-8 and 2H of Ar), 7.80—7.74 (m, 3H, H-6 and 2H of Ar), 7.61—7.37 (m, 7H, H-5, H-7 and Ph); ^{13}C NMR (DMSO-d_6) δ = 155.43 (s, C-9), 149.10 (s, C-3a), 148.80 (s, C-4a), 148.76 (s, C-4 of Ar), 148.41 (s, C-2), 147.71 (s, C-1 of Ar), 134.26 (d, C-6), 132.27 (s, C-1 of Ph), 130.51 (d, C-2 of Ar), 129.72 (d, C-2 of Ph), 129.63 (d, C-3 of Ar), 128.05 (d, C-8), 126.54 (d, C-7), 125.81 (d, C-5), 125.81 (d, C-4 of Ph), 123.71 (d, C-3 of Ph), 117.21 (s, C-8a); MS (EI) *m/z* (%) 383 (M^+; 37), 336 (20), 102 (22), 77 (100). HRMS Found: *m/z* 383.1019. Calcd for $C_{21}H_{13}N_5O_3$: M, 383.1018. Found: C, 65.66; H, 3.50; N, 18.38%. Calcd for $C_{21}H_{13}N_5O_3$: C, 65.78; H, 3.42; N, 18.28%.

Synthesis of Compounds 5 and 6. A mixture of compound **1** (5.0 mmol; 1.26 g) and an active methylene compound (diethyl malonate or acetylacetone) was heated under reflux for 1 h. After cooling, the precipitate which separated was collected by filtration and recrystallized from ethanol.

2-Anilino-3-[(2-ethoxycarbonylacetyl)amino]-4(3*H*)-quinazolinone (5). Mp 218—219 °C; ^{1}H NMR (DMSO-d_6) δ = 11.12 (s, exch., 1H, NHCO), 8.02 (d, J = 8.0 Hz, 1H, H-5), 7.80—7.08 (m, 8H, H-6, H-7, H-8, and Ph), 4.10 (q, J = 7.5 Hz, 2H, C*H*$_2$CH$_3$), 3.70 (2d, J = 17.0 Hz, 2H, CH$_2$CO), 1.14 (t, J = 7.5 Hz, 3H, CH$_3$); ^{13}C NMR (DMSO-d_6) δ = 167.87 (s, NHCO), 166.23 (s, COO), 159.32 (s, C-4), 148.23 (s, C-2), 147.56 (s, C-8a), 138.54 (d, C-1 of Ph), 135.27 (d, C-7), 128.84 (d, C-2 of Ph), 126.83 (d, C-5), 125.54 (d, C-6), 124.04 (d, C-8), 123.47 (d, C-4 of Ph), 122.22 (d, C-3 of Ph), 117.92 (s, C-4a), 61.38 (t, *C*H$_2$CO), 41.16 (t, *C*H$_2$CH$_3$), 14.27 (q, CH$_2$*C*H$_3$); MS (EI) *m/z* (%) 366 (M^+; 15), 348 (100), 276 (60), 252 (47), 236 (99), 221 (52), 43 (27). HRMS Found: *m/z* 366.1328. Calcd for $C_{19}H_{18}N_4O_4$: M, 366.1328. Found: C, 62.15; H, 5.01; N, 15.18%. Calcd for $C_{19}H_{18}N_4O_4$: C, 62.27; H, 4.95; N, 15.30%.

2-Anilino-3-[(1-methyl-3-oxo-1-butenyl)amino]4(3*H*)-quinazolinone (6). Mp 188—189 °C; ^{1}H NMR (DMSO-d_6) δ = 11.22 (s, exch., 1H, NHC=C), 9.11 (s, exch., 1H, PhNH), 7.99—7.10 (m, 9H, H-5, H-6, H-7, H-8, and Ph), 5.51 (s, 1H, CH), 2.10 (s, 3H, CH$_3$CO), 1.74 (s, 3H, CH$_3$C=C); ^{13}C NMR (DMSO-d_6) δ = 167.12 (s, NHCO), 161.42 (s, C-4), 148.13 (s, C-2), 147.99 (s, C-8a), 138.56 (d, C-1 of Ph), 134.82 (d, C-7), 128.24 (d, C-2 of Ph), 126.53 (d, C-5), 125.24 (d, C-6), 123.62 (d, C-8), 122.95 (d, C-4 of Ph), 122.52 (d, C-3 of Ph), 117.82 (s, *C*=CH), 117.64 (s, C-4a), 100.70 (d, CH), 29.64 (q, *C*H$_3$CO), 17.48 (q, *C*H$_3$C=C); MS (EI) *m/z* (%) 334 (M^+; 2), 276 (100), 252 (38), 221 (22), 77 (50), (CI), 335 (MH^+; 17), 277 (100), 253 (46), 238 (40). HRMS Found: *m/z* 335.1508. Calcd for $C_{19}H_{19}N_4O_2$: M, 335.1508. Found: C, 68.14; H, 5.47; N, 16.61%. Calcd for $C_{19}H_{18}N_4O_2$: C, 68.26; H, 5.39; N, 16.77%.

Synthesis of Ethyl 9-Oxo-3-phenyl-1,2,4-triazolo[3,2-*b*]quinazolin-2-acetate (7). Compound **5** (0.36 g; 1.0 mmol) was heated on an oil bath beyond its melting point for 15 min. The residue obtained was purified by column chromatography (ethyl acetate/diethyl ether in 20/80 volume) to give compound **7** (0.24 g; 0.7 mmol; 70%). Mp 212—214 °C; ^{1}H NMR (DMSO-d_6) δ = 8.15 (d, J = 8.1 Hz, 1H, H-8), 7.74 (t, J = 8.1 Hz, 1H, H-6), 7.62—5.59 (m, 5H, Ph), 7.49 (d, J = 8.1 Hz, 1H, H-5), 7.38 (t, J = 8.1 Hz, 1H, H-7), 4.05 (s, 2H, C*H*$_2$COO), 3.95 (q, J = 7.1 Hz, 2H, C*H*$_2$CH$_3$), 1.05 (t, J = 7.1 Hz, 3H, CH$_3$); ^{13}C NMR (DMSO-d_6) δ = 160.30 (s, C=O), 158.20 (s, C-9), 148.71 (s, C-3a), 148.41 (s, C-2), 147.17 (s, C-4a), 134.07 (d, C-6), 131.35 (s, C-1 of Ph), 129.97 (d, C-8), 129.69 (d, C-2 of Ph), 127.95 (d, C-3 of Ph), 126.48 (d, C-7), 125.72 (d, C-5), 123.18 (d, C-4 of Ph), 119.50 (d, C-8a), 61.22 (t, *C*H$_2$COO), 31.99 (t, *C*H$_2$CH$_3$), 13.68 (q, CH$_2$*C*H$_3$); MS (EI) *m/z* (%) 348 (M^+; 100), 333 (1), 303 (10), 275 (60), 102 (35), 77 (55). HRMS Found: *m/z* 348.1222. Calcd for $C_{19}H_{16}N_4O_3$: M, 348.1222. Found: C, 65.47; H, 4.67; N, 15.97%. Calcd for $C_{19}H_{16}N_4O_3$: C, 65.49; H, 4.63; N, 16.09%.

Synthesis of 3-Acetamido-2-anilino-4(3*H*)quinazolinone (8). A mixture of compound **1** (1.01 g; 4.0 mmol) and acetic anhydride (7 ml) was refluxed for 5 min, in which a white precipitate was formed while on hot. After cooling the precipitate was filtered off, washed with ethanol, then recrystallized from 1-butanol to give compound **8** (0.98 g; 3.3 mmol; 83%). Mp 275—276 °C; ^{1}H NMR (DMSO-d_6) δ = 10.65(s, exch., 1H, NHCO), 9.03 (s, exch., 1H, PhNH), 7.96 (d, J = 8.0 Hz, 1H, H-5), 7.76 (t, J = 7.4 Hz, 2H, H-2 of Ph), 7.65 (t, J = 8.0 Hz, 1H, H-7), 7.34 (m, 3H, H-8 and H-3 of Ph), 7.22 (t, J = 8.0 Hz, 1H, H-6), 7.11 (t, J = 7.4 Hz, 1H, H-4 of Ph), 2.15 (s, 3H, CH$_3$); ^{13}C NMR (DMSO-d_6) δ = 170.21 (s, C=O), 159.13 (s, C-4), 148.01 (s, C-2), 147.81 (s, C-8a), 138.34 (s, C-1 of Ph), 134.77 (d, C-7), 128.19 (d, C-2 of Ph), 126.37 (d, C-5), 125.04 (d, C-6), 123.51 (d, C-8), 122.82 (d, C-3 of Ph), 122.41 (d, C-4 of Ph), 117.69 (s, C-4a), 21.43 (q, CH$_3$); MS (EI) *m/z* (%) 294 (M^+; 100), 276 (42), 252 (44), 236 (38), 221 (50), 77 (42), (CI), 295 (MH^+; 100), 277 (5), 238 (6). HRMS Found: *m/z* 294.1117. Calcd for $C_{16}H_{14}N_4O_2$: M, 294.1117. Found: C, 65.27; H, 4.67; N, 18.97%. Calcd for $C_{16}H_{14}N_4O_2$: C, 65.28; H, 4.80; N, 19.04%.

Synthesis of 6,14-Diacetyl-1,2,4,5-tetrazino[3,2-*b*:6,5-*b*′]-diquinazolin-8,16(6*H*,14*H*)-dione (9). The procedure was very similar to that described for compound **8**, in which compound **1** (1.01 g; 4.0 mmol) in acetic anhydride (10 ml) was refluxed for 2 h. The crude material obtained was purified by recrystallization from ethanol to give compound **9** (0.64 g; 1.6 mmol; 80%). Mp 254—255 °C (lit, 255—257 °C).[17]

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