Synthesis of [1,2,4]Triazoloquinazoline and [1,2,4]-Triazolo-1,4-benzodiazepine Derivatives

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Some [1,2,4]triazolo[1,5-*c*]quinazolin-5(6*H*)-ones **7**, the corresponding isomers [1,2,4]triazolo[4,3-*c*]quinazolin-5(6*H*)-ones and the 5-amino derivatives **8**, **9** and **11** have been synthesized starting from the acylamidrazones **5**. The preparation of 5*H*-[1,2,4]triazolo[1,5-*d*]-1,4-benzodiazepin-6(7*H*)-ones **15** and of 5-cyclicaminomethyl-[1,2,4]triazolo[1,5-*c*]quinazolines **16** and **17** is also reported.

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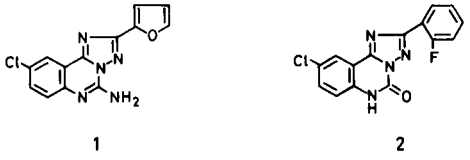
Compounds containing the triazoloquinazoline moiety have recently attracted considerable attention due to their remarkable adenosine and benzodiazepine receptors affinity. Particularly, the 5-amino-9-chloro-2-(2-furyl)-[1,2,4]triazolo[1,5-*c*]quinazoline **1** was discovered to be a highly potent adenosine antagonist [1], while the 9-chloro-2-(2-fluorophenyl)-[1,2,4]triazolo[1,5-*c*]quinazolin-5(6*H*)-one **2** displayed a very significant benzodiazepine binding activity [2].



1 2

Figure 1

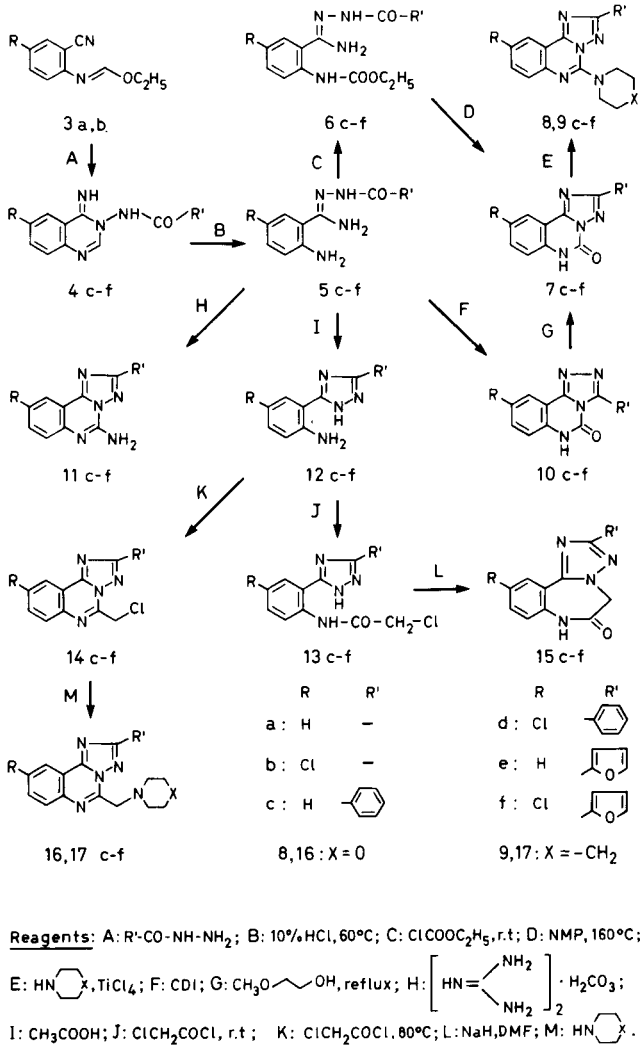
This current pharmacological interest has led us to seek novel methods to the synthesis of such tricyclic systems, in order to prepare new and biologically active molecules.

The synthetic pathways to compounds here reported are summarized in Scheme 1.

The starting *N*-ethoxymethylene-2-aminobenzonitriles **3** were reacted with benzhydrazide or 2-furoic acid hydrazide in refluxing ethanol to give the 3-acylamino-4-imino-3,4-dihydroquinazolines **4**. Pyrimidine ring opening, by heating in 10% hydrochloric acid at 60°, afforded the key acylamidrazones **5**, which, by reaction with ethyl chlorocarbonate at room temperature, gave the 2-[imino(2-ethoxycarbonylaminophenyl)methyl]hydrazides **6**.

The proposed structures for **4**, **5** and **6** were supported by the following spectral features: the ir spectra of **4** showed the absence of any nitrile band in the 2200 cm^{-1} region; the ^{1}H-nmr spectrum of **5c** (R = H; R′ = phenyl, cited as an example) showed two NH_2 signals at δ 6.50 and 6.80 and a broad signal for the hydrazide NH proton at δ 10.10, whereas the corresponding **6c** was characterized by a NH_2 signal at δ 6.87 and by two broad singlets at δ 10.10 and 11.30 for the hydrazide and carbamic NH respectively. Furthermore in the ^{13}C-nmr spectrum of **5c** the aromatic carbon bearing the NH_2 gave a signal at 148.1 ppm; the same carbon of **6c** was shifted at 137.7 ppm owing to the *N*-ethoxycarbonylation. Moreover the peaks of the car-

Scheme 1



Reagents: A: R′-CO-NH-NH_2; B: 10% HCl, 60°C; C: $ClCOOC_2H_5$, r.t; D: NMP, 160°C; E: HN⟨X⟩, $TiCl_4$; F: CDI; G: CH_3O⟨⟩OH, reflux; H: $\left[HN{=}\langle^{NH_2}_{NH_2}\rangle\right]_2 \cdot H_2CO_3$; I: CH_3COOH; J: $ClCH_2COCl$, r.t; K: $ClCH_2COCl$, 80°C; L: NaH, DMF; M: HN⟨X⟩.

bons in *ortho* and *para* to NH_2 of **5c** (115.9 and 114.3 ppm) appeared rightly shifted at a higher field from the same signals of **6c** (121.6 and 119.1 ppm).

Heating the urethanes **6** in 1-methyl-2-pyrrolidone at 160° produced the [1,2,4]triazolo[1,5-*c*]quinazolin-5(6*H*)-ones **7** in nearly quantitative yields. The latter ones by reaction with titanium tetrachloride and morpholine or piperidine in anhydrous toluene afforded the 5-cyclicamino derivatives **8** and **9**.

Treatment of compound **5** with carbonyldiimidazole in anhydrous tetrahydrofuran at room temperature led, by a double cyclization, to the 3-substituted-1,2,4-triazolo[4,3-*c*]quinazolin-5(6*H*)-ones **10** in one step.

It is noteworthy that a synthesis of 3-(4-chlorophenyl)-[1,2,4]-triazolo[4,3-*c*]quinazolin-5(6*H*)-one has recently been reported [3]. However, on the basis of the melting point and the ir (ν CO = 1750 cm^{-1}) and ^{1}H-nmr (NH s at δ 12.32 ppm) spectral data, identical to those successively described for the corresponding [1,2,4]triazolo[1,5-*c*] isomer [2], it could seem likely that Dimroth-type rearrangement [4] had occurred under the synthetic conditions, and that the product isolated should not be the claimed 1,2,4-triazolo[4,3-*c*]quinazolinone but the isomeric [1,5-*c*] derivative.

Compounds **10** crystallized with water of crystallization, ascertained by a micro Karl-Fischer determination and by the presence of a sharp peak at *ca* δ 3.20 in the ^{1}H-nmr spectra. They presented an ill-defined melting point because of the loss of water at 130-150° and subsequent formation at 250-270° of new and different crystals which melted above 300°.

By refluxing in ethylene glycol monomethyl ether compounds **10** were easily and quantitatively converted to the isomers **7** in agreement with literature reports for similar structures [5].

The structure of compounds **10** was supported and characterized by elemental analyses, ir (a strong carbonyl adsorption shifted of 15-20 cm^{-1} to lower frequencies than the ν CO of the corresponding **7**), ^{1}H-nmr (a broad singlet for the amide NH group at δ 10.95-11.00 *vs* 12.30-12.40 of **7**), ^{13}C-nmr and mass spectra (expected molecular peak).

The acylamidrazones **5** fusion with guanidine carbonate under somewhat reduced pressure gave the 5-amino-2-substituted-[1,2,4]triazolo[1,5-*c*]quinazolines **11**, while by refluxing in 5% ethanolic acetic acid provided the 5-(2-aminophenyl)-3-substituted-1*H*-triazoles **12**.

Some of compounds **7**, **11** and **12** have already been reported in the literature: their preparation involved the reaction of 2-(ethoxycarbonylamino)benzonitriles with hydrazides to obtain **7** [2], the hydrolysis of **7** with sodium hydroxide to obtain **12** [1], and finally treatment of **12** with cyanamide to afford **11** [1]. Therefore our procedures represent new and alternative methods for the synthesis of such compounds.

The triazolo derivatives **12** were found to react with chloroacetyl chloride in acetic acid: at room temperature the only products that have been isolated were the 5-[(2-chloroacetylamino)phenyl]-3-substituted-1*H*-[1,2,4]triazoles **13**, while at 80-90° the 5-chloromethyl-[1,2,4]triazolo-[1,5-*c*]quinazolines **14** were obtained in fair to excellent yields. Ring closure of **13** to triazolo[1,5-*d*][1,4]benzodiazepin-6(7*H*)-ones **15** was accomplished by sodium hydride in anhydrous dimethylformamide.

Finally, reaction of chloro derivatives **14** with morpholine or piperidine furnished the 5-cyclicaminomethyl-[1,2,4]triazolo[1,5-*c*]quinazolines **16** and **17**.

In the experimental ir, ^{1}H-nmr, ^{13}C-nmr and mass spectral data of the most significant compounds (with R = H and R′ = phenyl) are reported.

EXPERIMENTAL

Melting points are uncorrected. The ^{1}H-nmr spectra were determined on a Varian T-60 instrument with TMS as internal standard; ^{13}C-nmr spectra were obtained on a Bruker AMX 400 spectrometer; ir and uv spectra were recorded on a Perkin-Elmer 580 and on a Perkin-Elmer 554 spectrophotometer respectively; electron ionization mass spectra were determined on a Finnigan 5100 apparatus. Column chromatography was performed on silica gel Merck (70-230 mesh). Purity of each compound was checked on silica gel Carlo Erba 60_{F254} plates and the spots were located by uv light. Sodium sulfate was used to dry organic solutions.

N-Ethoxymethylene-2-aminobenzonitriles **3a,b**.

A solution of 2-aminobenzonitrile (11.8 g, 0.1 mole) or 2-amino-5-chlorobenzonitrile (15.2 g, 0.1 mole) in triethylorthoformate (100 ml) was refluxed until tlc (ethyl acetate/hexane 1:1) indicated that the starting material has been converted. Excess orthoformate was removed *in vacuo*, and the resultant nearly pure **3** were used without further purification.

General Procedure for the Preparation of 3-Acylamino-4-imino-3,4-dihydroquinazolines **4c-f**.

A suspension of **3** (20 mmoles) and benzhydrazide (2.9 g, 22 mmoles, to obtain **4c,d**) or 2-furoic acid hydrazide (2.8 g, 22 mmoles, to obtain **4e,f**) in ethanol (50 ml) was refluxed with stirring for 1 hour. After few minutes, a precipitate began to separate from the initially clear solution. The mixture was filtered, while still hot, and the solid obtained was rinsed with ethanol to give pure samples.

3-Benzoylamino-4-imino-3,4-dihydroquinazoline (**4c**).

This compound was obtained from **3a** in 67% yield, mp 209-211° (ethanol); ^{1}H-nmr (DMSO-d_6): δ 9.13 (broad, 1H, deuterium oxide-exchangeable, =NH), 8.53 (bs, 1H, deuterium oxide-exchangeable, NH-CO), 8.42 (s, 1H, 2-CH), 8.32-7.20 (m, 9H, aromatic protons).

Anal. Calcd. for $C_{15}H_{12}N_4O$: C, 68.17; H, 4.58; N, 21.20. Found: C, 68.00; H, 4.74; N, 21.41.

3-Benzoylamino-6-chloro-4-imino-3,4-dihydroquinazoline **4d**.

This compound was obtained from **3b** in 76% yield, mp 243-

245° (ethanol).

Anal. Calcd. for $C_{15}H_{11}ClN_4O$: C, 60.31; H, 3.71; N, 18.75. Found: C, 60.42; H, 3.70; N, 18.75.

3-(2-Furoylamino)-4-imino-3,4-dihydroquinazoline **4e**.

This compound was obtained from **3a** in 70% yield, mp 229-231° (ethanol).

Anal. Calcd. for $C_{13}H_{10}N_4O_2$: C, 61.41; H, 3.96; N, 22.04. Found: C, 61.60; H, 3.89; N, 21.94.

6-Chloro-3-(2-furoylamino)-4-imino-3,4-dihydroquinazoline **4f**.

This compound was obtained from **3b** in 61% yield, mp 228-230° (ethanol).

Anal. Calcd. for $C_{13}H_9ClN_4O_2$: C, 54.09; H, 3.14; N, 19.40. Found: C, 53.86; H, 3.07; N, 19.58.

General Procedure for the Preparation of 2-[Imino(2-aminophenyl)methyl]hydrazides **5c-f**.

A suspension of each compound **4** (10 mmoles) in 10% hydrochloric acid (300 ml) was stirred at 60° for *ca* 2 hours to give a homogeneous solution. After cooling the *p*H was adjusted to 7-8 with 10% sodium carbonate and the solid which had formed was filtered and crystallized.

2-[Imino(2-aminophenyl)methyl]benzhydrazide **5c**.

This compound was obtained from **4c** in 65% yield, mp 176-178° (ethanol); ^{1}H-nmr (DMSO-d_6): δ 10.10 (bs, 1H, deuterium oxide-exchangeable, NH-CO), *ca* 6.80 and *ca* 6.50 (bs, 4H, deuterium oxide-exchangeable, partially overlapped by aromatic protons, 2 NH_2); ^{13}C-nmr (DMSO-d_6): 163.1 (N-C=N), 153.2 (CO), 148.1 (C-2'), 134.5 (C-1), 130.9 (C-4), 129.8 (C-4' and C-6'), 128.2 (C-3 and C-5), 127.7 (C-2 and C-6), 115.9 (C-3' or C-5'), 114.6 (C-1'), 114.3 (C-3' or C-5').

Anal. Calcd. for $C_{14}H_{14}N_4O$: C, 66.12; H, 5.55; N, 22.04. Found: C, 66.29; H, 5.71; N, 22.18.

2-[Imino(2-amino-5-chlorophenyl)methyl]benzhydrazide **5d**.

This compound was obtained from **4d** in 59% yield, mp 178-180° (ethanol).

Anal. Calcd. for $C_{14}H_{13}ClN_4O$: C, 58.24; H, 4.54; N, 19.40. Found: C, 58.03; H, 4.51; N, 19.50.

2-[Imino(2-aminophenyl)methyl]-(2-furoic acid)hydrazide **5e**.

This compound was obtained from **4e** in 50% yield, mp 169-171° (ethanol).

Anal. Calcd. for $C_{12}H_{12}N_4O_2$: C, 59.01; H, 4.95; N, 22.94. Found: C, 58.96; H, 4.96; N, 22.88.

2-[Imino(2-amino-5-chlorophenyl)methyl]-(2-furoic acid)hydrazide **5f**.

This compound was obtained from **4f** in 50% yield, mp 207-209° (ethanol).

Anal. Calcd. for $C_{12}H_{11}ClN_4O_2$: C, 51.72; H, 3.98; N, 20.10. Found: C, 51.81; H, 3.88; N, 20.01.

General Procedure for the Preparation of 2-[Imino(2-ethoxycarbonylaminophenyl)methyl]hydrazides **6c-f**.

Ethyl chlorocarbonate (10 ml, 0.1 mole) was added to a suspension of each compound **5** (10 mmoles) in ethanol (100 ml) and the mixture was stirred at room temperature for 2 hours. The solvent was concentrated *in vacuo* (maximum bath temperature 40°) to a solid residue which was crystallized.

2-[Imino(2-ethoxycarbonylaminophenyl)methyl]benzhydrazide **6c**.

This compound was obtained from **5c** in 74% yield, mp 194-196° (ethanol); ^{1}H-nmr (DMSO-d_6): δ 11.34 (bs, 1H, deuterium oxide-exchangeable, NH), 10.10 (bs, 1H, deuterium oxide-exchangeable, NH), 8.33-7.00 (m, 9H, aromatic protons), 6.90 (bs, 2H, deuterium oxide-exchangeable, NH_2); ^{13}C-nmr (DMSO-d_6): 163.1 (N-C=N), 154.0 (COO), 153.4 (CO), 137.7 (C-2'), 134.1 (C-1), 131.0 (C-4), 130.1 (C-4'), 128.7 (C-3 and C-5), 127.9 (C-6'), 127.6 (C-2 and C-6), 121.6 (C-3' or C-5'), 120.6 (C-1'), 119.1 (C-3' or C-5').

Anal. Calcd. for $C_{17}H_{18}N_4O_3$: C, 62.57; H, 5.56; N, 17.17. Found: C, 62.77; H, 5.58; N, 17.51.

2-[Imino(5-chloro-2-ethoxycarbonylaminophenyl)methyl]benzhydrazide **6d**.

This compound was obtained from **5d** in 66% yield, mp 200-202° (ethanol).

Anal. Calcd. for $C_{17}H_{17}ClN_4O_3$: C, 56.59; H, 4.75; N, 15.53. Found: C, 56.68; H, 4.88; N, 15.17.

2-[Imino(2-ethoxycarbonylaminophenyl)methyl]-(2-furoic acid)hydrazide **6e**.

This compound was obtained from **5e** in 58% yield, mp 180-182° (ethanol).

Anal. Calcd. for $C_{15}H_{16}N_4O_4$: C, 59.96; H, 5.10; N, 17.71. Found: C, 59.65; H, 4.90; N, 17.70.

2-[Imino(5-chloro-2-ethoxycarbonylaminophenyl)methyl]-(2-furoic acid)hydrazide **6f**.

This compound was obtained from **5f** in 56% yield, mp 192-194° (methanol).

Anal. Calcd. for $C_{15}H_{15}ClN_4O_4$: C, 51.36; H, 4.31; N, 15.97. Found: C, 51.50; H, 4.15; N, 15.63.

General Procedure for the Preparation of [1,2,4]Triazolo[1,5-*c*]quinazolin-5(6*H*)-ones **7c-f**.

A stirred solution of **6** (10 mmoles) in 1-methyl-2-pyrrolidone (NMP, 40 ml) was heated at 160° (oil bath temperature) for 5 hours. The reaction mixture was cooled and stirred in water (150 ml) over 30 minutes. The solid was collected, washed with water then crystallized.

2-Phenyl-[1,2,4]triazolo[1,5-*c*]quinazolin-5(6*H*)-one **7c**.

This compound was obtained from **6c** in 90% yield, mp >300° (dimethylformamide/ethanol) (lit [2] mp 311-313°); ^{13}C-nmr (DMSO-d_6): 162.8 (C-2), 153.3 (C-5), 143.8 (C-10b), 137.0 (C-6a), 132.7 (C-8), 130.3 (C-4'), 129.8 (C-1'), 128.9 (C-3' and C-5'), 126.8 (C-2' and C-6'), 124.1 (C-10), 123.5 (C-9), 116.0 (C-7), 110.3 (C-10a).

Anal. Calcd. for $C_{15}H_{10}N_4O$: C, 68.69; H, 3.84; N, 21.37. Found: C, 68.67; H, 3.83; N, 21.57.

9-Chloro-2-phenyl-[1,2,4]triazolo[1,5-*c*]quinazolin-5(6*H*)-one **7d**.

This compound was obtained from **6d** in 92% yield, mp >300° (dimethylformamide) (lit [2] mp >340°).

Anal. Calcd. for $C_{15}H_9ClN_4O$: C, 60.72; H, 3.06; N, 18.88. Found: C, 60.65; H, 3.16; N, 18.53.

2-(2-Furyl)-[1,2,4]triazolo[1,5-*c*]quinazolin-5(6*H*)-one **7e**.

This compound was obtained from **6e** in 76% yield, mp >300° (dimethylformamide).

Anal. Calcd. for $C_{13}H_8N_4O_2$: C, 61.90; H, 3.20; N, 22.21. Found: C, 61.79; H, 3.45; N, 22.14.

9-Chloro-2-(2-furyl)-[1,2,4]triazolo[1,5-*c*]quinazolin-5(6*H*)-one **7f**.

This compound was obtained from **6f** in 90% yield, mp >300° (dimethylformamide) (lit [2] mp >340°).

Anal. Calcd. for $C_{13}H_7ClN_4O_2$: C, 54.47; H, 2.46; N, 19.54. Found: C, 54.18; H, 2.49; N, 19.54.

General Procedure for the Reaction of Compounds **7** with Titanium Tetrachloride and Morpholine or Piperidine.

To a stirred and ice-cooled solution of morpholine (5 g, 60 mmoles to obtain **8**) or piperidine (5 g, 60 mmoles, to obtain **9**) and anisole (1 ml) in anhydrous toluene (150 ml) was cautiously added titanium tetrachloride (1.1 ml, 10 mmoles) followed by each compound **7** (10 mmoles). The reaction mixture was allowed to warm to room temperature, then heated to reflux for 3 hours. After cooling, the insoluble material was filtered off; the filtrate was rotary evaporated onto 10 g of silica gel, applied to the top of a chromatographic column, and eluted with ethyl acetate to give pure **8** or **9**.

5-(4-Morpholinyl)2-phenyl-[1,2,4]triazolo[1,5-*c*]quinazoline **8c**.

This compound was obtained by reaction of **7c** with morpholine in 55% yield, mp 182-184° (methanol).

Anal. Calcd. for $C_{19}H_{17}N_5O$: C, 68.86; H, 5.17; N, 21.14. Found: C, 68.94; H, 5.14; N, 21.00.

9-Chloro-5-(4-morpholinyl)2-phenyl-[1,2,4]triazolo[1,5-*c*]quinazoline **8d**.

This compound was obtained by reaction of **7d** with morpholine in 48% yield, mp 198-200° (ethanol).

Anal. Calcd. for $C_{19}H_{16}ClN_5O$: C, 62.38; H, 4.41; N, 19.14. Found: C, 62.11; H, 4.25; N, 18.98.

2-(2-Furyl)-5-(4-morpholinyl)-[1,2,4]triazolo[1,5-*c*]quinazoline **8e**.

This compound was obtained by reaction of **7e** with morpholine in 45% yield, mp 201-203° (methanol).

Anal. Calcd. for $C_{17}H_{15}N_5O_2$: C, 63.54; H, 4.70; N, 21.80. Found: C, 63.20; H, 4.91; N, 21.50.

9-Chloro-2-(2-furyl)-5-(4-morpholinyl)-[1,2,4]triazolo[1,5-*c*]quinazoline **8f**.

This compound was obtained by reaction of **7f** with morpholine in 50% yield, mp 228-231° (ethanol).

Anal. Calcd. for $C_{17}H_{14}ClN_5O_2$: C, 57.39; H, 3.97; N, 19.68. Found: C, 57.13; H, 3.93; N, 19.39.

2-Phenyl-5-(1-piperidinyl)-[1,2,4]triazolo[1,5-*c*]quinazoline **9c**.

This compound was obtained by reaction of **7c** with piperidine in 67% yield, mp 123-125° (ethanol).

Anal. Calcd. for $C_{20}H_{19}N_5$: C, 72.92; H, 5.81; N, 21.26. Found: C, 72.66; H, 5.64; N, 20.98.

9-Chloro-2-phenyl-5-(1-piperidinyl)-[1,2,4]triazolo[1,5-*c*]quinazoline **9d**.

This compound was obtained by reaction of **7d** with piperidine in 59% yield, mp 207-209° (ethanol).

Anal. Calcd. for $C_{20}H_{18}ClN_5$: C, 66.02; H, 4.99; N, 19.25. Found: C, 65.98; H, 4.88; N, 19.08.

2-(2-Furyl)-5-(1-piperidinyl)-[1,2,4]triazolo[1,5-*c*]quinazoline **9e**.

This compound was obtained by reaction of **7e** with piperidine in 48% yield, mp 127-129° (methanol).

Anal. Calcd. for $C_{18}H_{17}N_5O$: C, 67.69; H, 5.37; N, 21.93. Found: C, 67.69; H, 5.09; N, 21.73.

9-Chloro-2-(2-furyl)-5-(1-piperidinyl)-[1,2,4]triazolo[1,5-*c*]quinazoline **9f**.

This compound was obtained by reaction of **7f** with piperidine in 52% yield, mp 169-171° (ethanol).

Anal. Calcd. for $C_{18}H_{16}ClN_5O$: C, 61.11; H, 4.56; N, 19.79. Found: C, 60.98; H, 4.51; N, 19.79.

General Procedure for the Preparation of [1,2,4]Triazolo[4,3-*c*]-quinazolin-5(6*H*)-ones **10c-f**.

1,1'-Carbonyldiimidazole (1.6 g, 10 mmoles), was added to a stirred suspension of each compound **5** (5 mmoles) in anhydrous tetrahydrofuran (50 ml). The mixture was allowed to stir at room temperature and monitored by tlc (ethyl acetate) to ascertain when the starting material was converted into a more polar compound, which fluoresced differently under uv light. In general the reaction was complete after about 2 hours. The insoluble material was filtered, the solvent was evaporated *in vacuo* at room temperature and the residue was chromatographed on a silica gel column by elution with 10% methanol in ethyl acetate. The appropriate uv-absorbing fractions were evaporated *in vacuo* at room temperature. Methanol was added to the residue and the solid, which had formed, was filtered to afford compounds **10** as colourless prisms.

3-Phenyl-1,2,4-triazolo[4,3-*c*]quinazolin-5(6*H*)-one **10c**.

This compound was obtained from **5c** in 45% yield, mp >300° (methanol); ir: ν CO 1710 cm^{-1}; uv (methanol): λ max 224 (log ϵ 4.65), 308 (3.66); ^{1}H-nmr (DMSO-d_6): δ 10.40 (broad, 1H, deuterium oxide-exchangeable, NH), 8.27-8.00 (m, 3H, aromatic protons), 7.65-7.30 (m, 4H, aromatic protons), 7.20-7.00 (m, 2H, aromatic protons); ^{13}C-nmr (DMSO-d_6): 166.0 (C-3), 152.2 (C-5), 148.3 (C-10b), 137.4 (C-6a), 133.1 (C-8), 132.2 (C-4'), 131.8 (C-1'), 128.5 (C-3' and C-5'), 127.9 (C-2' and C-6'), 126.8 (C-10), 122.4 (C-9), 115.2 (C-7), 114.4 (C-10a); ms: (m/z) 262 (M^+).

Anal. Calcd. for $C_{15}H_{10}N_4O\cdot H_2O$: C, 64.27; H, 4.32; N, 19.99. Found: C, 64.00; H, 4.17; N, 19.82.

9-Chloro-3-phenyl-1,2,4-triazolo[4,3-*c*]quinazolin-5(6*H*)-one **10d**.

This compound was obtained from **5d** in 39% yield, mp >300° (methanol).

Anal. Calcd. for $C_{15}H_9ClN_4O\cdot H_2O$: C, 57.24; H, 3.52; N, 17.80. Found: C, 57.39; H, 3.64; N, 18.01.

3-(2-Furyl)-1,2,4-triazolo[4,3-*c*]quinazolin-5(6*H*)-one **10e**.

This compound was obtained from **5e** in 44% yield, mp >300° (methanol).

Anal. Calcd. for $C_{13}H_8N_4O_2\cdot H_2O$: C, 57.77; H, 3.73; N, 20.73. Found: C, 57.79; H, 3.74; N, 20.67.

9-Chloro-3-(2-furyl)-1,2,4-triazolo[4,3-*c*]quinazolin-5(6*H*)-one **10f**.

This compound was obtained from **5f** in 36% yield, mp >300° (methanol).

Anal. Calcd. for $C_{13}H_7ClN_4O_2\cdot H_2O$: C, 51.25; H, 2.98; N, 18.39. Found: C, 51.27; H, 3.04; N, 18.45.

General Procedure for the Preparation of 5-Amino-[1,2,4]triazolo-[1,5-*c*]quinazolines **11c-f**.

Each compound **5** (5 mmoles) was finely ground with guanidine

carbonate (3.6 g, 20 mmoles) in a mortar. The mixture was heated at 170-180° under reduced pressure (100 mm) for 2 hours. After cooling, the mixture was vigorously stirred in boiling water (50 ml) over 30 minutes, then filtered. The solid was collected, washed with water and cold methanol, then crystallized.

5-Amino-2-phenyl-[1,2,4]triazolo[1,5-*c*]quinazoline **11c**.

This compound was obtained from **5c** in 48% yield, mp 286-289° (dimethylformamide/ethanol).

Anal. Calcd. for $C_{15}H_{11}N_5$: C, 68.95; H, 4.24; N, 26.81. Found: C, 69.21; H, 4.30; N, 26.97.

5-Amino-9-chloro-2-phenyl-[1,2,4]triazolo[1,5-*c*]quinazoline **11d**.

This compound was obtained from **5d** in 54% yield, mp 295-297° (dimethylformamide/ethanol).

Anal. Calcd. for $C_{15}H_{10}ClN_5$: C, 60.92; H, 3.41; N, 23.68. Found: C, 60.71; H, 3.43; N, 23.87.

5-Amino-2-(2-furyl)-[1,2,4]triazolo[1,5-*c*]quinazoline **11e**.

This compound was obtained from **5e** in 45% yield, mp 294-296° (dimethylformamide/ethanol) (lit [1] mp 282-285°).

Anal. Calcd. for $C_{13}H_9N_5O$: C, 62.14; H, 3.61; N, 27.88. Found: C, 61.90; H, 3.63; N, 27.97.

5-Amino-9-chloro-2-(2-furyl)-[1,2,4]triazolo[1,5-*c*]quinazoline **11f**.

This compound was obtained from **5f** in 50% yield, mp 281-284° (dimethylformamide/ethanol) (lit [1] mp 279-281°).

Anal. Calcd. for $C_{13}H_8ClN_5O$: C, 54.65; H, 2.82; N, 24.51. Found: C, 54.33; H, 2.69; N, 24.53.

General Procedure for the Preparation of 5-(2-Aminophenyl)-1*H*-1,2,4-triazoles **12c-f**.

To a suspension of **5** (10 mmoles) in ethanol (50 ml) was added acetic acid (1 ml) and the mixture was heated at reflux for 6 hours. The solution was concentrated to dryness at reduced pressure and the residue was treated with diluted ammonium hydroxide. The formed precipitate was then crystallized.

5-(2-Aminophenyl)-3-phenyl-1*H*-1,2,4-triazole **12c**.

This compound was obtained from **5c** in 78% yield, mp 178-180° (methanol) (lit [6] mp 257-258°).

Anal. Calcd. for $C_{14}H_{12}N_4$: C, 71.16; H, 5.12; N, 23.72. Found: C, 71.05; H, 5.24; N, 24.02.

5-(2-Amino-5-chlorophenyl)-3-phenyl-1*H*-1,2,4-triazole **12d**.

This compound was obtained from **5d** in 80% yield, mp 262-265° (ethanol) (lit [6] mp 257-258°).

Anal. Calcd. for $C_{14}H_{11}ClN_4$: C, 62.10; H, 4.09; N, 20.70. Found: C, 61.79; H, 4.19; N, 20.82.

5-(2-Aminophenyl)-3-(2-furyl)-1*H*-1,2,4-triazole **12e**.

This compound was obtained from **5e** in 74% yield, mp 210-212° (ethanol).

Anal. Calcd. for $C_{12}H_{10}N_4O$: C, 63.70; H, 4.46; N, 24.77. Found: C, 64.03; H, 4.61; N, 25.03.

5-(2-Amino-5-chlorophenyl)-3-(2-furyl)-1*H*-1,2,4-triazole **12f**.

This compound was obtained from **5f** in 66% yield, mp 252-254° (dimethylformamide/ethanol) (lit [1] mp 246-248°).

Anal. Calcd. for $C_{12}H_9ClN_4O$: C, 55.29; H, 3.48; N, 21.49. Found: C, 55.18; H, 3.66; N, 21.56.

General Procedure for the Reaction of **12** with Chloroacetyl Chloride.

Chloroacetylchloride (1.6 ml, 20 mmoles) was dropwise added to a stirred cooled solution of **12** (10 mmoles) in glacial acetic acid (50 ml). The mixture was allowed to stir for 3 hours at room temperature for **13** or heated at 80-90° for 4 hours for **14**. Compounds **13** were obtained by addition of water (200 ml) to the reaction mixture followed by filtration of the precipitate product; compounds **14** were isolated by removing acetic acid *in vacuo*, then by adding water and sodium carbonate to achieve alkalinity, and finally by filtering the solid which had formed. The crude products were then crystallized.

5-(2-Chloroacetylaminophenyl)-3-phenyl-1*H*-1,2,4-triazole **13c**.

This compound was obtained from **12c** in 62% yield, mp 191-193° (ethyl acetate).

Anal. Calcd. for $C_{16}H_{13}ClN_4O$: C, 61.44; H, 4.19; N, 17.91. Found: C, 61.07; H, 4.07; N, 17.69.

5-(5-Chloro-2-chloroacetylaminophenyl)-3-phenyl-1*H*-1,2,4-triazole **13d**.

This compound was obtained from **12d** in 69% yield, mp 206-208° (ethyl acetate).

Anal. Calcd for $C_{16}H_{12}Cl_2N_4O$: C, 55.35; H, 3.48; N, 16.14. Found: C, 55.65; H, 3.41; N, 16.45.

5-(2-Chloroacetylaminophenyl)-3-(2-furyl)-1*H*-1,2,4-triazole **13e**.

This compound was obtained from **12e** in 74% yield, mp 188-190° (methanol).

Anal. Calcd. for $C_{14}H_{11}ClN_4O_2$: C, 55.55; H, 3.66; N, 18.51. Found: C, 55.77; H, 3.89; N, 18.37.

5-(5-Chloro-2-chloroacetylaminophenyl)-3-(2-furyl)-1*H*-1,2,4-triazole **13f**.

This compound was obtained from **12f** in 62% yield, mp 198-200° (ethyl acetate).

Anal. Calcd. for $C_{14}H_{10}Cl_2N_4O_2$: C, 49.87; H, 2.99; N, 16.62. Found: C, 49.66; H, 2.96; N, 16.60.

5-Chloromethyl-2-phenyl-[1,2,4]triazolo[1,5-*c*]quinazoline **14c**.

This compound was obtained from **12c** in 69% yield, mp 199-202° (ethyl acetate).

Anal. Calcd. for $C_{16}H_{11}ClN_4$: C, 65.20; H, 3.76; N, 19.01. Found: C, 64.95; H, 3.83; N, 19.10.

9-Chloro-5-chloromethyl-2-phenyl-[1,2,4]triazolo[1,5-*c*]quinazoline **14d**.

This compound was obtained from **12d** in 77% yield, mp 192-194° (ethanol).

Anal. Calcd. for $C_{16}H_{10}Cl_2N_4$: C, 58.38; H, 3.06; N, 17.02. Found: C, 58.49; H, 3.18; N, 17.25.

5-Chloromethyl-2-(2-furyl)-[1,2,4]triazolo[1,5-*c*]quinazoline **14e**.

This compound was obtained from **12e** in 82% yield, mp 188-190° (ethanol).

Anal. Calcd. for $C_{14}H_9ClN_4O$: C, 59.06; H, 3.19; N, 19.68. Found: C, 58.89; H, 3.26; N, 19.66.

9-Chloro-5-chloromethyl-2-(2-furyl)-[1,2,4]triazolo[1,5-*c*]quinazoline **14f**.

This compound was obtained from **12f** in 75% yield, mp 188-190° (ethanol).

Anal. Calcd. for $C_{14}H_8Cl_2N_4O$: C, 52.69; H, 2.53; N, 17.56. Found: C, 52.92; H, 2.41; N, 17.57.

General Procedure for the Preparation of 5*H*-[1,2,4]Triazolo[1,5-*d*]benzodiazepin-6(7*H*)-ones **15c-f**.

Each compound **13** (5 mmoles) was dissolved in dry dimethylformamide (20 ml) and added dropwise to a cooled and stirred suspension of sodium hydride (0.3 g, 50% oil dispersion, 6 mmoles) in dimethylformamide (60 ml). The mixture was allowed to warm to room temperature and stirred for 4 hours. The reaction mixture was carefully diluted with water and extracted with ethyl acetate. The solvent was removed and the resulting residue crystallized.

2-Phenyl-5*H*-[1,2,4]triazolo[1,5-*d*]benzodiazepin-6(7*H*)-one **15c**.

This compound was obtained from **13c** in 80% yield, mp 250-252° (ethyl acetate).

Anal. Calcd. for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.25; H, 4.36; N, 20.11.

10-Chloro-2-phenyl-5*H*-[1,2,4]triazolo[1,5-*d*]benzodiazepin-6(7*H*)-one **15d**.

This compound was obtained from **13d** in 77% yield, mp 285-287° (ethyl acetate).

Anal. Calcd. for $C_{16}H_{11}ClN_4O$: C, 61.84; H, 3.57; N, 18.03. Found: C, 61.92; H, 3.72; N, 18.20.

2-(2-Furyl)-5*H*-[1,2,4]triazolo[1,5-*d*]benzodiazepin-6(7*H*)-one **15e**.

This compound was obtained from **13e** in 74% yield, mp >300° (ethanol).

Anal. Calcd. for $C_{14}H_{10}N_4O_2$: C, 63.15; H, 3.79; N, 21.04. Found: C, 62.95; H, 3.73; N, 20.84.

10-Chloro-2-(2-furyl)-5*H*-[1,2,4]triazolo[1,5-*d*]benzodiazepin-6(7*H*)-one **15f**.

This compound was obtained from **13f** in 70% yield, mp 278-280° (ethanol).

Anal. Calcd. for $C_{14}H_9ClN_4O_2$: C, 55.92; H, 3.02; N, 18.63. Found: C, 55.59; H, 3.20; N, 18.66.

General Procedure for the Reaction of **14** with Morpholine or Piperidine.

Each compound **14** (5 mmoles) in morpholine (5 g, 60 mmoles) or piperidine (5 g, 60 mmoles) was stirred and heated at 100° for 12 hours. Excess of the amine was removed *in vacuo* and the resulting residue directly crystallized.

5-(4-Morpholinylmethyl)-2-phenyl-[1,2,4]triazolo[1,5-*c*]quinazoline **16c**.

This compound was obtained from **14c** and morpholine in 68% yield, mp 167-169° (methanol).

Anal. Calcd. for $C_{20}H_{19}N_5O$: C, 69.55; H, 5.54; N, 20.28. Found: C, 69.64; H, 5.73; N, 20.07.

9-Chloro-5-(4-morpholinylmethyl)-2-phenyl-[1,2,4]triazolo[1,5-*c*]-quinazoline **16d**.

This compound was obtained from **14d** and morpholine in 69% yield, mp 176-178° (methanol).

Anal. Calcd. for $C_{20}H_{18}ClN_5O$: C, 63.24; H, 4.78; N, 18.44. Found: C, 63.60; H, 4.91; N, 18.37.

2-(2-Furyl)-5-(4-morpholinylmethyl)-[1,2,4]triazolo[1,5-*c*]quinazoline **16e**.

This compound was obtained from **14e** and morpholine in 68% yield, mp 158-160° (methanol).

Anal. Calcd. for $C_{18}H_{17}N_5O_2$: C, 64.47; H, 5.11; N, 20.88. Found: C, 64.39; H, 4.90; N, 20.61.

9-Chloro-2-(2-furyl)-5-(4-morpholinylmethyl)-[1,2,4]triazolo[1,5-*c*]-quinazoline **16f**.

This compound was obtained from **14f** and morpholine in 62% yield, mp 198-200° (methanol).

Anal. Calcd. for $C_{18}H_{16}ClN_5O_2$: C, 58.46; H, 4.36; N, 18.94. Found: C, 58.54; H, 4.43; N, 19.25.

2-Phenyl-5-(1-piperidinylmethyl)-[1,2,4]triazolo[1,5-*c*]quinazoline **17c**.

This compound was obtained from **14c** and piperidine in 69% yield, mp 163-165° (methanol).

Anal. Calcd. for $C_{21}H_{21}N_5$: C, 73.44; H, 6.16; N, 20.39. Found: C, 73.16; H, 6.34; N, 20.14.

9-Chloro-2-phenyl-5-(1-piperidinylmethyl)-[1,2,4]triazolo[1,5-*c*]-quinazoline **17d**.

This compound was obtained from **14d** and piperidine in 61% yield, mp 127-129° (methanol).

Anal. Calcd. for $C_{21}H_{20}ClN_5$: C, 66.75; H, 5.33; N, 18.53. Found: C, 67.04; H, 5.40; N, 18.50.

2-(2-Furyl)-5-(1-piperidinylmethyl)-[1,2,4]triazolo[1,5-*c*]quinazoline **17e**.

This compound was obtained from **14e** and piperidine in 70% yield, mp 133-135° (methanol).

Anal. Calcd. for $C_{19}H_{19}N_5O$: C, 68.45; H, 5.74; N, 21.01. Found: C, 68.30; H, 5.73; N, 21.28.

9-Chloro-2-(2-furyl)-5-(1-piperidinylmethyl)-[1,2,4]triazolo[1,5-*c*]-quinazoline **17f**.

This compound was obtained from **14f** and piperidine in 68% yield, mp 168-170° (methanol).

Anal. Calcd. for $C_{19}H_{18}ClN_5O$: C, 62.04; H, 4.93; N, 19.04. Found: C, 62.01; H, 4.81; N, 18.82.

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