A Novel Nucleophilic Substitution with Quinoline Derivatives. Synthesis of Quinolones and Pyrazolo[4,3-*c*]quinoline Derivatives

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Novel nucleophilic substitution in quinoline system utilizing 2-chloro-4-piperidino-3-quinolinecarbonitrile (**1**) and 4-piperidino-2-oxo-1,2-dihydro-3-quinolinecarbonitrile (**2**) was reported. Some new quinolinones and pyrazolo[4,3-*c*]quinolines were synthesized.

It has been reported that several quinoline derivatives possess chemotherapeutic activity and act as antimalaria[1] and antiallergic[2,3] agents. In addition, they have some biological activities and are considered as antiinflammatory,[4] agrochemical fungicides[5] and antiviral[6] reagents. These wide pharmaceutical activities of quinoline derivatives have made them attractive targets for the synthesis over many years and prompted us to exert a great effort to synthesize new pyrazolo-[4,3-*c*]quinolines and several quinolines via the action of a variety of nucleophiles on 2-chloro-4-piperidino-3-quinolinecarbonitrile (**1**)[7] and 4-piperidino-2-oxo-1,2-dihydro-3-quinolinecarbonitrile (**2**).[7] Our approach is centered on the replacement of the piperidino group at C-4 with a nucleophile.

It has been reported that,[8,9] the hydroxyl group situated in the ortho-position of heteroaromatic nitriles can be alkylated by chloromethyl or bromomethyl carbonyl compounds and related agents to yield the corresponding ether, which undergoes cyclization in the presence of a base to give the aminofuran derivatives. However, it has been found that the hydroxy-3-quinolinecarbonitriles **2** is alkylated with ethyl bromoacetate and phenacyl bromide in the presence of potassium carbonate to afford a solid product of molecular formula $C_{19}H_{21}N_3O_3$ and $C_{23}H_{21}N_3O_3$ respectively. Two theoretically possible isomeric structures were considered (**3** and **4**, Chart 1). During our investigation of the cyclization of this product with ethanolic sodium ethoxide, we observed that its cyclization into the furoquinolines **5** did not occur. This evidence strongly supported that the ethoxycarbonylmethylation or phenacylation reaction occurred at N and not at O. Since, if the reaction took place at O, the intramolecular cyclization of the product **4** could be observed. The structure of **3** was preferred over the possible isomer **4** based on its analytical and spectral data (see Experimental). Thus, the IR spectrum of **3a** showed absorption bands at 2200, 1740, and 1630 cm^{-1} due to CN, ester carbonyl and amide carbonyl[10—12] groups, respectively. The similar three absorption bands are also shown by **3b**.

Reflux of **3a** with sodium ethoxide for 10 min resulted in the formation of 1-carboxymethyl-2-oxo-4-piperidino-1,2-dihydro-3-quinolinecarbonitrile (**6**). Beside the analytical and spectroscopic proof of the structure of **6** (see Experimental) it was also proven chemically by its conversion into the corresponding ester **3a** via the action of triethyl orthoformate. On the other hand, increasing the reaction time between **3a,b** and sodium ethoxide (6 h), they underwent nucleophilic substitution at C-4 to yield 4-hydroxy-2(1*H*)-quinolinones **7a,b**. This interesting behavior, the substitution of piperidino group with nucleophile, attracted our attention to study this phenomenon further.

Thus, compound **6** was allowed to react with other nucleophiles. Reaction of **6** with hydrazine hydrate in boiling ethanol afforded 1-carboxymethyl-4-hydrazino-2-oxo-1,2-dihydro-3-quinolinecarboxamide (**12**), via nucleophilic attack at position 4. Meanwhile on fusion at 120 °C pyrazolo[4,3-*c*]quinoline derivatives **11** was formed presumably through the nucleophilic attack of two molecules of hydrazine at position 4 and the carbonyl group in compound **6** to give the intermediate **10**, which then undergoes intramolecular cyclocondensation, via elimination of water to yield the pyrazolo-fused compound (Chart 2). Alternatively, compound **11** could be obtained on treatment of **3a** with hydrazine hydrate at 120 °C. When compound **3a** was refluxed with benzylamine, it afforded the product **13**, which indicates a similar behavior as the fusion of **6** with hydrazine hydrate.

For further investigation of the scope of this reaction and to support this view, we have studied another model system in which the piperidino group is available. Thus, 2-chloro-4-piperidino-3-quinolinecarbonitrile (**1**) was subjected to react with some nucleophiles under various conditions. Reaction of **1** with sodium azide did not yield the azido quinoline **14**, but instead, the tautomeric ring closed 5-piperidinotetrazolo[1,5-*a*]-quinoline-4-carbonitrile **15** was formed (Chart 3). The IR spectrum of **15** showed the absence of azido group. Compound **15** then reacted with hydrazine hydrate to give **16** probably by a mechanism similar to that discussed above for formation of **11**.

Similarly to the behavior of **6** with hydrazine hydrate, compound **1** reacted with benzylamine to yield the corresponding 2-aminoquinolines **17**, which reacted with hydrazine hydrate in boiling ethanol to afford **18**.

The reaction of **1** with sodium ethoxide gave 2-ethoxy-4-hydroxy-3-quinolinecarbonitrile (**19**) upon long

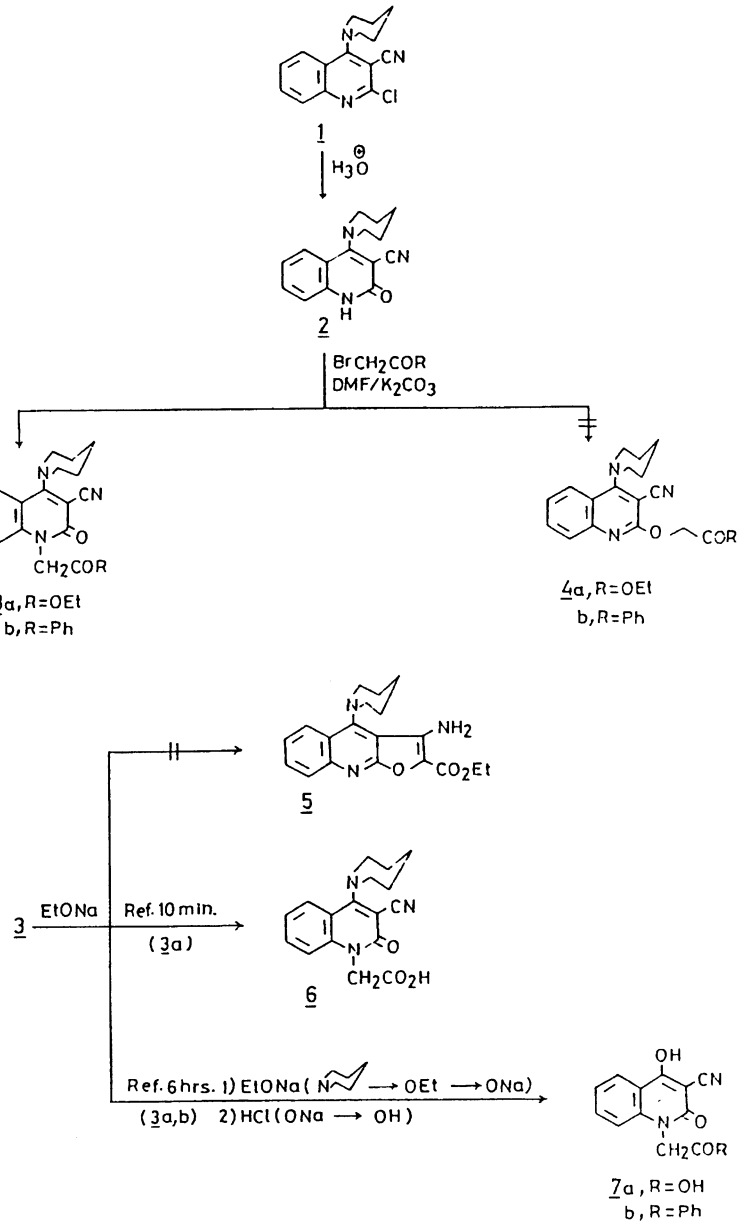

Chart 1.

reflux in ethanol, presumably by a mechanism similar to that discussed above for the formation of **7**.

In conclusion, the methodology described in this paper affords a novel and general route of nucleophilic substitution of piperidino group at C-4 in quinolines. To our knowledge the substitution of piperidino group at position 4 in quinolines by nucleophilies has not yet been reported. This nucleophilic substitution has the advantage of versatility for the preparation of these relatively complexed structures, which would be difficult to be prepared by classical synthetic routes, are assembled in a simple one-pot procedure in high yields, under mild reaction conditions, and from readily available starting materials.

Experimental

Melting points were obtained on a Gallen-Kamp Melting point apparatus (open capillary tubes) and are uncorrected. ^{1}H NMR spectra were obtained on a JEOL JNM-PMX (60 MHz) or a JEOL FX-90Q (90 MHz) spectrometer in deuterated dimethyl sulfoxide using TMS as internal standard and with chemical shifts expressed as δ values. ^{13}C NMR spectra were obtained on a Bruker WP 200 (90 MHz) spectrometer. Microanalyses were performed on a C, H, N-Automat Carlo Erba 1106 at Karl-Franzens University-Graz, Austria and by Microanalytical Laboratory, Institute of physical chemistry, Vienna University, Austria. IR spectra were recorded on a Shimadzu 470 spectrophotometer (KBr pellets). Mass spectra were determined on an MS 9 spectrometer (AEI) operating at 70 eV.

1-Ethoxycarbonylmethyl(or Phenacyl)-2-oxo-1,2-

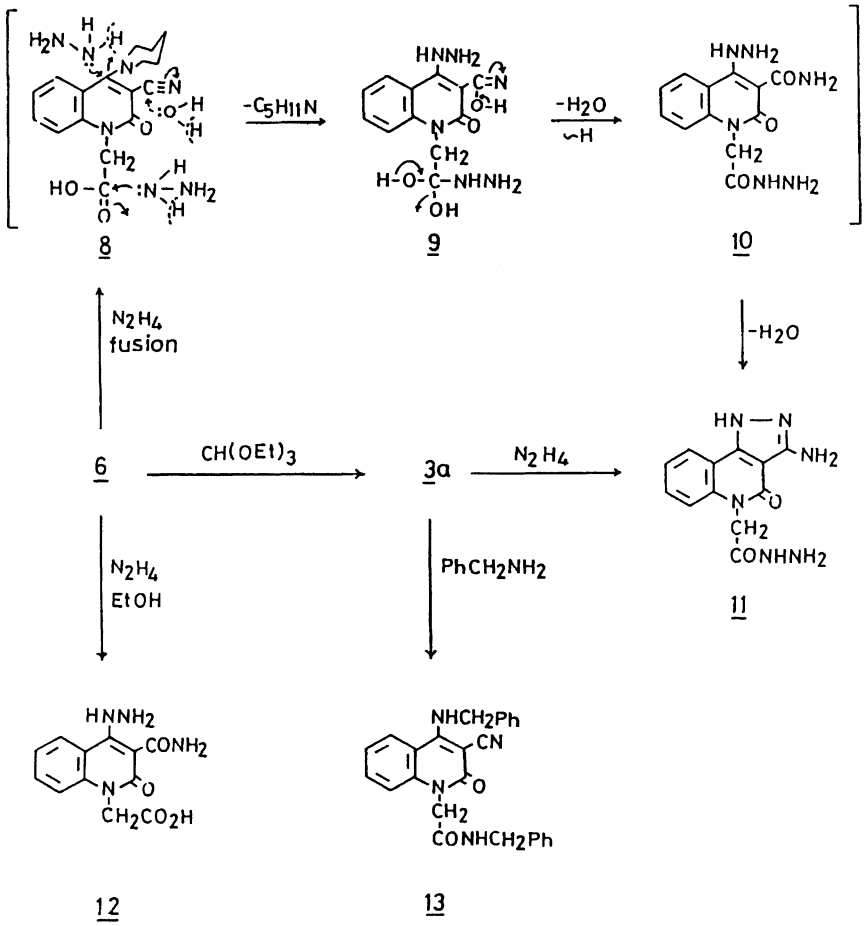

Chart 2.

dihydro-4-piperidino-3-quinolinecarbonitriles (3a,b). Method 1: (For **3a,b**): A mixture of 4-piperidino-2-oxo-1,2-dihydro-3-quinolinecarbonitrile (**2**) (1.18 mmol), ethyl bromoacetate or phenacyl bromide (1.18 mmol) and anhydrous potassium carbonate (1.18 mmol) in *N,N*-dimethylformamide (10 ml) was heated under stirring for one hour at 50—55 °C and then at room temperature (30 °C) for 5 h. Then, the reaction mixture was poured into cold water (15 ml). The resulting solid product was collected by filtration, dried and recrystallized.

Method 2: (For **3a**): A suspension of 1-carboxymethyl-2-oxo-4-piperidino-1,2-dihydro-3-quinolinecarbonitrile (**6**) (3.21 mmol) in triethyl orthoformate (30 ml) was refluxed for 10 h under stirring. After evaporation of the solvent under reduced pressure, the resulting solid product was collected by filtration and dried.

1-Ethoxycarbonylmethyl-2-oxo-4-piperidino-1,2-dihydro-3-quinolinecarbonitrile (3a). The analytical sample was recrystallized from ethanol. Yield 95%, mp 177—179 °C; IR ν=2200 (CN), 1740 (ester C=O), and 1630 cm^{-1} (amide C=O); ^{1}H NMR δ=1.2 (t, 3H, CH_3), 1.75 (br, 6H, $3CH_2$), 3.6 (br, 4H, $2CH_2$), 4.15 (q, 2H, CH_2), 5.05 (s, 2H, CH_2), and 7.3—7.9 (m, 4H, ArH). Found: C, 67.12; H, 6.18; N, 12.25%. Calcd for $C_{19}H_{21}N_3O_3$: C, 67.24; H, 6.24; N, 12.38%.

***N*-Phenacyl-2-oxo-4-piperidino-1,2-dihydro-3-quinolinecarbonitrile (3b).** The analytical sample was recrystallized from *N,N*-dimethylformamide. Yield 91%, mp 234—235°C; IR ν=2200 (CN), 1680 (benzoyl C=O), and 1630 cm^{-1} (amide C=O); ^{1}H NMR δ=1.76 (br, 6H, $3CH_2$), 3.56 (br, 4H, $2CH_2$), 5.83 (s, 2H, CH_2), 7.20—8.20 (m, 9H, ArH). Found: C, 74.25; H, 5.60; N, 11.24%. Calcd for $C_{23}H_{21}N_3O_3$: C, 74.37; H, 5.70; N, 11.31%.

1-Carboxymethyl-2-oxo-4-piperidino-1,2-dihydro-3-quinolinecarbonitrile (6). A solution of **3a** (10.3 mmol) in abs. ethanol (30 ml) containing 0.24 g of metallic sodium was refluxed for 10 min. After cooling, the reaction mixture was acidified with dil. HCl to pH=3. The resulting solid product was filtered off, dried and recrystallized from ethanol to give 1-carboxymethyl-2-oxo-4-piperidino-1,2-dihydro-3-quinolinecarbonitrile (**6**). Yield 81%, mp 256—258°C; IR ν=3450 (OH), 2200 (CN), 1730 (acid C=O), and 1630 cm^{-1} (amide C=O); ^{1}H NMR δ=1.8 (br, 6H, $3CH_2$), 2.52 (m, 4H, $2CH_2$), 4.93 (s, 2H, CH_2), 7.3—7.9 (m, 4H, ArH). ^{13}C NMR δ=23.5, 26.1, and 43.8 (piperidino carbons),[13] 53.7 (CH_2 carbon), 90.3 (C-3), 115.7 (CN), 116.4 (C-6), 117.0 (C-8), 122.3 (C-7), 126.9 (C-5), 133.5 (C-4a), 140.2 (C-8a), 160.3 (C-4), 163.6 (C-2) (lit,[13] 165.0), and 169.5 (COOH). MS *m/z* 311 [M^+]. Found: C, 65.42; H, 5.49; N, 13.66%. Calcd for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50%.

1-Carboxymethyl(or Phenacyl)-4-hydroxy-2-oxo-1,2-dihydro-3-quinolinecarbonitriles (7a,b). A solution of **3a,b** (1.84 mmol) in abs. ethanol (15 ml) containing

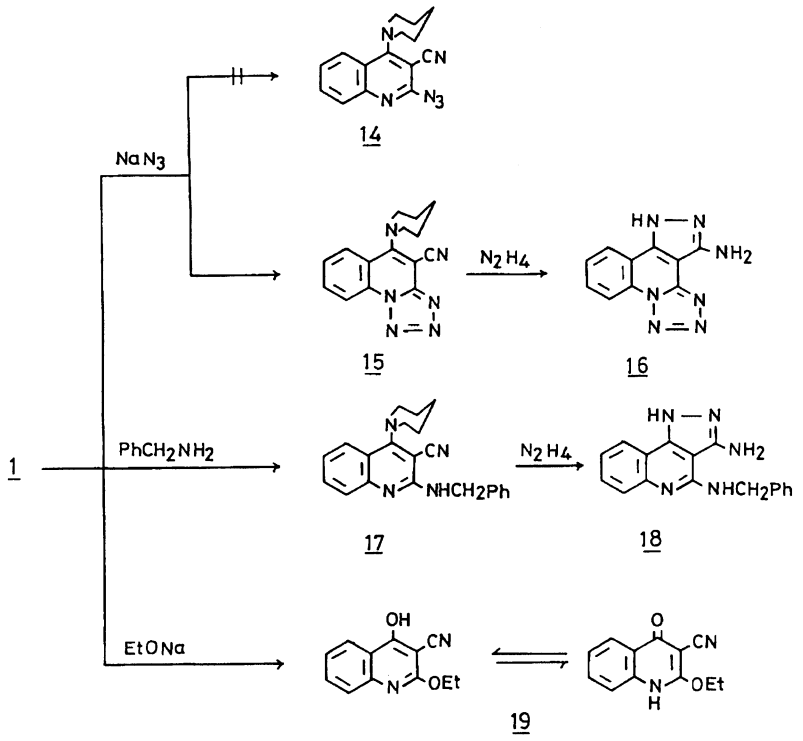

Chart 3.

0.17 g of metallic sodium was refluxed for 6 h. Then the reaction mixture was worked up as described for **6**.

1-Carboxymethyl-4-hydroxy-2-oxo-1,2-dihydro-3-quinolinecarbonitrile (7a). The analytical sample was recrystallized from ethanol. Yield 65%, mp 240—241°C; IR ν=3500 (OH), 2200 (CN), 1730 cm^{-1} (acid C=O); ^1H NMR δ=4.93 (s, 2H, CH_2), 5.19 (br, 1H, OH), 7.16—8.13 (m, 4H, ArH). Found: C, 54.87; H, 3.87; N, 10.71%. Calcd for $C_{12}H_8N_2O_4 \cdot H_2O$ (dried at 60 °C for 2 h): C, 54.96; H, 3.84; N, 10.68%.

4-Hydroxy-2-oxo-1-phenacyl-1,2-dihydro-3-quinolinecarbonitrile (7b). The analytical sample was recrystallized from DMF/water. Yield 73%, mp 261—262°C; IR ν=3400 (OH), 2200 (CN), and 1680 cm^{-1} (benzoyl C=O); ^1H NMR δ=5.8 (s, 2H, CH_2), 7.16—8.16 (m, 9H, ArH). MS *m/z* 304 [M^+]. Found: C, 71.14; H, 4.08; N, 9.18%. Calcd for $C_{18}H_{12}N_2O_3$: C, 71.04; H, 3.98; N, 9.20%.

2-Ethoxy-4-oxo-1,4-dihydro-3-quinolinecarbonitrile (19). A solution of **1** (1.84 mmol) in abs. ethanol (15 ml) containing 0.17 g of metallic sodium was refluxed for 40 h. Then the reaction mixture was worked up as described for **6**. The analytical sample was recrystallized from DMF/EtOH. Yield 88%, mp 230—232°C; IR ν=3250—2700 (NH), 2200 (CN), and 1580 cm^{-1} (γ pyridone); ^1H NMR δ=1.42 (t, 3H, CH_3), 4.53 (q, 2H, CH_2), 7.35—8.10 (m, 4H, ArH). Found: C, 67.40; H, 4.58; N, 13.08%. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.70; N, 13.07%.

Compound 11. A mixture of **3a** or **6** (1.44 mmol) and hydrazine hydrate (5 ml) was refluxed for 10 min. After cooling at room temperature, the resulting solid product was collected by filtration, washed with methanol and dried. The analytical sample was recrystallized from DMF. Yield 89%, mp>360 °C; IR ν=3440, 3300, 3200 (NH), and 1650 cm^{-1}; ^1H NMR δ=4.23 (s, 2H, NH_2), 4.80 (s, 2H, CH_2), 5.36 (br, 1H, NH), 7.13—8.0 (m, 4 ArH), 9.35 (s, 1H, NH). MS *m/z* 272 [M^+]. Found: C, 52.63; H, 4.52; N, 30.55%. Calcd for $C_{12}H_{12}N_6O_2$: C, 52.93; H, 4.44; N, 30.87%.

Compound 16. A mixture of **15** (1.44 mmol) and hydrazine hydrate (5 ml) was refluxed for 10 min. Then the reaction mixture was worked up as described for **11**. The analytical sample was recrystallized from DMF. Yield 83%, mp 332—334 °C (decomp); IR ν=3300—2800 (NH), and 1620 cm^{-1} (C=N). Found: C, 53.30; H, 3.42; N, 43.28%. Calcd for $C_{10}H_7N_7$: C, 53.33; H, 3.13; N, 43.54%.

Compound 18. A mixture of **17** (1.47 mmol) and hydrazine hydrate (5 ml) in ethanol (5 ml) was refluxed for 14 h. After evaporation to dryness under reduced pressure, the resulting oil was triturated with cold water. A solid product was collected by filtration and dried. The analytical sample was recrystallized from methanol. Yield 83%, mp 229—230 °C (decomp); IR ν=3450, 3400, 3300, 3200, 3150 (NH), and 1620 cm^{-1} (C=N); ^1H NMR δ=4.83 (d, 2H, CH_2), 5.50 (s, 2H, NH_2), 7.08 (m, 9H, 8ArH+NH), 8.0 (d, 1H, ArH), 12.68 (s, 1H, pyrazole NH). Found: C, 70.50; H, 5.30; N, 24.19%. Calcd for $C_{17}H_{15}N_5$: C, 70.57; H, 5.23; N, 24.20%.

Compound 13. A mixture of **3a** (1.47 mmol) and benzylamine (2 ml) was heated under reflux for 2h, during which a solid product was separated out. After cooling, at room temperature, it was filtered, washed with water and dried. The analytical sample was recrystallized from DMF. Yield 72%, mp 259—260 °C (decomp); IR ν=3350, 3300 (NH), 2200 (CN), and 1650 cm^{-1}; ^1H NMR δ=4.3 (d, 2H, CH_2), 4.88 (s, 2H, CH_2), 5.1 (d, 2H, CH_2), 7.2—7.4 (m, 13H, ArH), 7.67 (t, 1H, NH), 8.3 (d, 1H, ArH), 8.7 (t, 1H, NH). Found: C, 73.82; H, 5.31; N, 13.14%. Calcd for $C_{26}H_{22}N_4O_2$: C, 73.91; H, 5.21; N, 13.26%.

2-Benzylamino-4-piperidino-3-quinolinecarbonitrile (17). A mixture of **1** (1.83 mmol), anhydrous

$NaHCO_3$ (2.75 mmol) and benzylamine (2 ml) in DMF (10 ml) was refluxed for 8 h. After cooling, the reaction mixture was poured into cold water (20 ml). The precipitated product was collected by filtration and dried. The analytical sample was recrystallized from acetone. Yield 95%, mp 139—140 °C (decomp); IR ν=3350 (NH) and 2200 cm^{-1} (CN); ^1H NMR δ=1.75 (br, 6H, $3CH_2$), 3.54 (br, 4H, $2CH_2$), 4.70 (d, 2H, CH_2), 7.15—7.60 (m, 8ArH+NH), 7.80 (d, 1ArH). Found: C, 76.90; H, 6.40; N, 16.20%. Calcd for $C_{22}H_{22}N_4$: C, 77.16; H, 6.48; N, 16.36%.

1-Carboxymethyl-4-hydrazino-2-oxo-1,2-dihydro-3-quinolinecarboxamide (12). To a solution of **6** (3.21 mmol) in ethanol (10 ml), hydrazine hydrate (5 ml) was added. The reaction mixture was refluxed for 2 h. After evaporation to dryness under reduced pressure, the resulting solid product was filtered off and dried. The analytical sample was recrystallized from DMF/methanol. Yield 98%, mp 233—235 °C (decomp); IR ν=3450 (OH), 3300, 3150 (NH), and 1690 cm^{-1} (CO); ^1H NMR δ=4.95 (s, 2H, CH_2), 5.75 (br, 2H, NH_2), 7.23—8.08 (m, 5H, 4ArH+NH). Found: C, 51.95; H, 4.48; N, 20.19%. Calcd for $C_{12}H_{12}N_4O_4$: C, 52.17; H, 4.38; N, 20.28%.

5-Piperidinotetrazolo[1, 5-*a*]quinoline-4-carbonitrile (15). To a solution of **1** (1.84 mmol) in DMF (10 ml) NaN_3 (3.68 mmol) was added. The reaction mixture was stirred for 2 h. at 100—110 °C. After cooling, the reaction mixture was diluted with water (20 ml). The resulting precipitate was collected by filtration, washed well with water, dried and recrystallized from DMF. Yield 98%, mp 215—216 °C (decomp); IR ν=2200 (CN) cm^{-1}. ^1H NMR δ=1.5 (br, 6H, $3CH_2$), 3.33 (br, 4H, $2CH_2$), 7.43—8.33 (m, 4 ArH). Found: C, 64.50; H, 5.04; N, 30.32%. Calcd for $C_{15}H_{14}N_6$: C, 64.73; H, 5.07; N, 30.20%.

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