REACTIONS OF ALKYLATION OF BIOLOGICALLY INTERESTING TRIAZOLO[4,5-g]QUINOLINES AND TRIAZOLO[4,5-g]QUINOLINE-1-OXIDES WITH ELECTROPHILIC REAGENTS

Antonio Carta,* Angela Sias, Sandra Piras, and Giuseppe Paglietti

Department of Medicinal and Toxicological Chemistry, University of Sassari, Via Muroni 23, 07100 Sassari, Italy; e-mail: acarta@uniss.it

Abstract – With the aim to improve the biological activities discovered for compounds containing the triazolo[4,5-g]quinoline nucleus, we describe the chemical behaviour of 4-chlorotriazolo[4,5-g]quinolines (1a,b) and some its triazolo-N1-oxide derivatives (1c-e and II) with electrophilic reagents in order to optimize the synthetic pathways for obtaining both mixtures of N1,2,3-alkyl isomers and selectively N1-O-alkyl derivatives.

INTRODUCTION

[1,2,3]Triazolo[4,5-g]quinoline (I) (here named triazolo[4,5-g]quinoline) is a new linear heterocycle prepared for the first time in 2000 by ring closure diazotization of 5,6-diaminoquinoline with HNO2 at rt.1 Further derivatives of this N-tricyclic system were successively synthesized1-3 and its chemistry has been extensively reviewed very recently.4 Nevertheless, the synthetic pathways followed to obtaining various triazoloquinoline derivatives have been described by some of us and the use of purposely prepared intermediates was also reported in 2006.5

In order to investigate the biological properties of this new class of compounds, some of them were tested against ssRNA+ and ssRNA- viruses. Interestingly, we have discovered that 4,9-dihydro-1H-triazolo[4,5-g]quinoline-1-oxide (II)3 exhibited selective activity against HIV-1, resulting non-toxic and able to prevent not only wild-type HIV-1 replication in acutely infected cells but also to be active against the most frequently observed clinically mutant forms (K103N, Y181C, and the double mutant K103N/Y181C).6 From this preliminary investigation, which prompted us to patent a series of variously substituted triazolo[4,5-g]quinolines,7 emerged the mixture in 1:1 ratio of 1,3-bis-(4-chloro-1H-triazolo[4,5-g]quinolin-1-yl)propan-2-one and 1,3-bis-(4-chloro-3H-triazolo[4,5-g]quinolin-3-yl)propan-2-one (III) for its potent antiflaviviridae activity, thus opening a new route to fight clinically significant diseases in humans and animals due to this family of viruses which includes Hepatitis C virus (HCV), the
major cause of human hepatitis. In Figure 1 are reported the chemical structures of compounds I, II and III.

![Chemical structures of compounds I, II, and III](image)

**Figure 1**

Now, in the light of the importance of this findings from a medicinal chemistry point of view, we have undertaken an investigation on the chemical behaviour of 4-chlorotriazolo[4,5-g]quinoline (1a)\(^1\) and some its derivatives (1b-e and II),\(^1\)-\(^3\) with electrophilic reagents in order to optimize the synthetic pathways for the alkylation of the positions 1, 2, 3 and 8.

![Chemical structures of compounds 1a-d and 1e](image)

**Figure 2**

1a) \(R = H, R_1 = \text{none}\)
1b) \(R = \text{OH}, R_1 = \text{none}\)
1c) \(R = H, R_1 = \text{O}\)
1d) \(R = \text{OH}, R_1 = \text{O}\)
1e) \(\text{NO}_2\)

**RESULTS AND DISCUSSION**

In our previous work\(^3\) we reported that the reaction of 1a with chloroacetonitrile in dry dimethylformamide (DMF) and KOH afforded both [4-chloro-1\(H\)-triazolo[4,5-g]quinolin-1-yl]acetonitrile and [4-chloro-3\(H\)-triazolo[4,5-g]quinolin-3-yl]acetonitrile but not the corresponding 2-yl substituted derivative. On the other hand, by reaction with acetic anhydride 1-acetyl-4-chloro-1\(H\)-triazolo[4,5-g]quinoline was the sole derivative obtained.
No further attempts at alkylation of the triazolo moiety in the triazolo[4,5-g]quinoline ring have been reported so far. Thus, we have studied the reaction of compounds 1a-e and II with several electrophilic reagents (methyl and ethyl sulphate, chloroacetonitrile, benzyl chloride, 4-nitrobenzyl chloride) in dry DMF (or without solvent) and in the presence of Cs₂CO₃ between 18-60 °C for 1-24 h and the results are here described. As reported in Scheme 1, when alkylation of 1a was carried out with ethyl sulphate (in DMF and Cs₂CO₃) at 60 °C for 6 h, we obtained all the expected N-ethyl derivative isomers 2a, 3a and 4a, as in the case of alkylation of the simple benzotriazole.⁸

A different behavior was observed as 4-chloro-3H-triazolo[4,5-g]quinoline-1-oxide (1c) underwent alkylation, with both methyl and ethyl sulphate, chloroacetonitrile, benzyl chloride and 4-nitrobenzyl chloride, where we recorded a case of high selectivity for all the reagents as reported in Scheme 2. That was not surprising since the oxygen atom exists in tautomeric equilibrium with N₁-OH form and afforded the 1-alkoxyderivatives (5a-e) in good yield (68-88%). It is evident that by means of these procedures from either 1a or 1c it is possible to obtain alternatively both mixtures of N₁,₂,₃-alkyl isomers and selectively N₁-O-alkyl derivatives.
 Scheme 2
The reactions reported in Scheme 3 show that this type of derivatives (compounds 6-8) can be selectively obtained in 31-68% yield.

 Scheme 3
On the ground of these results, we have further investigated whether, under the same conditions, other 3H-triazolo[4,5-g]quinoline-1-oxides, as 4,9-dihydro-1H-triazolo[4,5-g]quinoline-1-oxide (II) and 4-chloro-9-nitro-3H-triazolo[4,5-g]quinoline-1-oxide (1e), were able to afford N1-O-alkyl derivatives.
Analogously, when we submitted 4-chloro-8-hydroxytriazolo[4,5-g]quinoline (1b) to reaction with ethyl sulphate, under the same conditions, both the three expected N\textsubscript{1,2,3} and C\textsubscript{8}-O ethyl derivatives (9\textsubscript{a},10\textsubscript{a},11\textsubscript{a}) were obtained. Unexpectedly using benzyl chloride the reaction afforded only the derivatives 9\textsubscript{b} and 11\textsubscript{b} (Scheme 4). The failure of alkylation at N\textsubscript{2} position is possibly due to the higher reactivity of N\textsubscript{1} and N\textsubscript{3} rather than N\textsubscript{2} atom towards this halide reagent and is similar to the previously reported case of the described reaction with chloroacetonitrile.\textsuperscript{3} Furthermore, alkylation of the triazolo moiety certainly occurs prior to the oxygen atom in C\textsubscript{8}.

\[
\text{Scheme 4}
\]

Finally, selective O\textsubscript{1}-alkylation was observed in the case of reaction of 4-chloro-8-hydroxy-3\textit{H}-triazolo[4,5-g]quinoline-1-oxide (1d), under the same conditions, with the above mentioned electrophiles that led to compounds 12\textsubscript{a-d} (Scheme 5). However, it is worthwhile to note that the reaction with ethyl sulphate was conditioned upon the reaction temperature. In fact carrying out the reaction condition at rt for 6 h it afforded exclusively the N\textsubscript{1}-ethyl compound (12\textsubscript{b}) in 77% yield, whereas carrying out the reaction at 60 °C a mixture of 13 (24%) and 12\textsubscript{b} (46%) was obtained. Interestingly compound 12\textsubscript{b} at 100 °C afforded 13 in almost quantitative yield.
From these experiments it is interesting to observe that the N-Oxide function makes the oxygen atom in position 8, under certain conditions, unreactive towards the electrophilic reagents with the sole exception of ethyl sulphate. However, the Cs8-OH group in 1b can be easily replaced by chlorine by means of POCl3 to give the dichloro derivative 14 in good yield (78%) (Scheme 6). This represents a synthone to design new molecules of pharmaceutical interest owing to its susceptibility to undergo both nucleophilic and electrophilic substitutions.

Confirmation of the proposed structures came from both analytical and spectroscopic data. The exact position of the alkyl or benzyl groups in the case of N1-derivatives was deduced mainly by the examination of 1H-NMR NOE spectra. In particular, in the case of the compound 9a by irradiation of the CH2 linked to the N1 a decrease of 6.2 % of integral value of H-9 was recorded, whereas no effect was observed in the case of the compounds 10a and 11a. The other two isomers (N2 and N3) were identified by the analysis of the chemical shifts of both the 13C atom linked to the nitrogen in 2 or 3 position. In these cases, in 13C spectrum we observed that the resonance of the CH2 linked to the N2 of 10a is located at lower downfield (δ = 53.06 ppm) than that of the CH2 linked to the N3 of 11a (δ = 45.24 ppm), all these experiments were in accordance with our previous observations.8
EXPERIMENTAL

Melting points are uncorrected and were taken in open capillaries in a Digital Electrothermal IA9100 melting point apparatus. $^1$H- and $^{13}$C-NMR spectra were recorded at 200 MHz using a Varian XL-200 spectrometer. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane as internal standard. Column chromatography was performed using 70-230 mesh (Merck silica gel 60). The progress of the reactions and the purity of the final compounds were monitored by TLC using Merck F-254 commercial plates.

**Liquid chromatography/mass spectrometry**

Chromatographic separation was performed on an Agilent 1100 LC System that included a binary pump, Diode-Array Detector, column thermostat, degasser and HTS-PAL autosampler (Agilent Technologies, Palo Alto CA USA). The HPLC column was a Luna C18 (2) (4.6 × 150 mm, 3 µm) from Phenomenex (Torrance, CA, USA) with a security guard cartridge (4 × 2 mm). The mobile phase consisted of Eluent A water with 0.1% acetic acid and Eluent B acetonitrile. The flow rate was set at 0.5 mL/min and the column temperature was 33 °C. Total run time was 30 min.

**Table 1. Gradient program**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Phase A (%)</th>
<th>Phase B (%)</th>
<th>Flow (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>60</td>
<td>40</td>
<td>0.5</td>
</tr>
<tr>
<td>20</td>
<td>20</td>
<td>80</td>
<td>0.5</td>
</tr>
<tr>
<td>30</td>
<td>10</td>
<td>90</td>
<td>0.5</td>
</tr>
</tbody>
</table>

The Diode Array Detector was set at 280 and 220 nm Bw=4 Reference 800. Elemental analysis were performed Agilent ChemStation HP A.10.02.
Starting materials

Triazolo[4,5-g]quinolines (1a-e and II) were prepared following the procedure previously described by us.1-3,5

General procedure for condensation reaction of triazolo[4,5-g]quinolines with methyl and ethyl sulphate, chloroacetonitrile, benzyl chloride and 4-nitrobenzyl chloride.

Method A: alkyl sulphate.

i) A solution of triazolo[4,5-g]quinolines (1a-e and II) (5.0 mmol) in 25 mL of DMF was added of Cs₂CO₃ (5.0 mmol) and heated at 60 °C (rt for 1d) under stirring for 15 min. After then, a solution of ethyl sulphate (5.0 mmol) in solvent (10 mL), was slowly added dropwise and the stirring continued for 6 h (24 h in the case of II). Once the reactions were completed, the mixtures were cooled to rt, the excess of Cs₂CO₃ filtered off, and the DMF was removed \textit{in vacuo}. The crude solid obtained was purified by silica gel column chromatography eluting with Et₂O to give the O₁-alkylated compounds 5a, 5b, 6, 7, 12a, 13.

In the case of the mixtures of N-alkylated isomers 2a-4a and 9a-11a, we isolated in sequence 4a, 3a, 2a, and 11a, 10a, 9a, respectively.

ii) When 1d was reacted under the above conditions at 60 °C for 6 h a mixture of dialkyl derivative 13 (24%) and monoalkyl derivative 12b (46%) was obtained;

iii) When monoalkyl derivative 12b, obtained using the conditions described under i), was heated at 100 °C with one mole equivalent of ethyl sulfate for 24 h afforded the dialkyl derivative (13) in 98% yield;

iv) Alkylation of 1c with methyl sulphate using the same conditions as under i) gave 5a.

v) Alkylation of 1d with methyl sulphate using the same conditions as under i) gave 12a.

Melting points, yields, analytical and spectroscopical data are reported below;

4-Chloro-1-ethyl-1H-triazolo[4,5-g]quinoline (2a). This compound was obtained in 23 % yield; mp 180-182 °C (acetone); TLC (EtOAc-light petroleum 7:3): Rf 0.43; ¹H-NMR (CDCl₃): δ 9.05 (d, 1H, J = 4.0 Hz, H-6), 8.30 (d, 1H, J = 8.6 Hz, H-8), 7.86 (s, 1H, H-9), 7.46 (dd, 1H, J = 8.6 and 4.0 Hz, H-7), 4.82 (q, 2H, J = 7.2 Hz, CH₂), 1.72 (t, 3H, J = 7.2 Hz, Me); ¹³C-NMR (CDCl₃): δ 151.07 (d), 144.66 (s), 139.70 (s), 136.80 (s), 131.39 (s), 128.31 (s), 124.54 (s), 121.68 (d), 103.88 (d), 43.75 (t), 14.72 (q); LC/MS: 234 (M+H); Anal. Calcd for C₁₁H₉ClN₄: C, 56.78; H, 3.90; Cl, 15.24; N, 24.08. Found C, 57.02; H, 3.65; N, 23.88.

4-Chloro-2-ethyl-2H-triazolo[4,5-g]quinoline (3a). This compound was obtained in 21 % yield; mp 108-110 °C (Et₂O); TLC (EtOAc-light petroleum 7:3): Rf 0.65; ¹H-NMR (CDCl₃): δ 9.03 (d, 1H, J = 4.1 Hz, H-6), 8.33 (d, 1H, J = 8.2 Hz, H-8), 8.26 (s, 1H, H-9), 7.33 (dd, 1H, J = 8.2 and 4.1 Hz, H-7), 4.99 (q,
2H, J = 7.2 Hz, CH₂), 1.85 (t, 3H, J = 7.2 Hz, Me); ¹³C-NMR (CDCl₃): δ 152.57 (d), 143.34 (s), 141.21 (s), 140.43 (s), 137.96 (d), 130.46 (s), 127.96 (s), 120.29 (d), 116.63 (d), 53.09 (t), 16.78 (q); LC/MS: 234 (M+H); Anal. Calcd for C₁₁H₉ClN₄: C, 56.78; H, 3.90; Cl, 15.24; N, 24.08. Found C, 56.51; H, 3.81; N, 24.41.

4-Chloro-3-ethyl-3H-triazolo[4,5-g]quinoline (4a). This compound was obtained in 32 % yield; mp 114-116 °C (Et₂O); TLC (EtOAc-light petroleum 7:3): Rₖ 0.70; ¹H-NMR (CDCl₃): δ 9.11 (d, 1H, J = 4.0 Hz, H-6), 8.38 (d, 1H, J = 8.4 Hz, H-8), 8.26 (s, 1H, H-9), 7.46 (dd, 1H, J = 8.4 and 4.0 Hz, H-7), 5.21 (q, 2H, J = 7.2 Hz, CH₂), 1.71 (t, 3H, J = 7.2 Hz, Me); ¹³C-NMR (CDCl₃): δ 151.94 (d), 145.23 (s), 142.70 (s), 141.93 (s), 137.46 (d), 130.46 (s), 125.76 (s), 120.29 (d), 114.42 (d), 45.24 (t), 15.10 (q); LC/MS: 234 (M+H); Anal. Calcd for C₁₁H₉ClN₄: C, 56.78; H, 3.90; Cl, 15.24; N, 24.08. Found C, 56.39; H, 4.11; N, 24.19.

4-Chloro-1-methoxy-1H-triazolo[4,5-g]quinoline (5a). This compound was obtained in 88 % yield; mp 182-184 °C (acetone); ¹H-NMR (DMSO-d₆): δ 9.08 (d, 1H, J = 4.0 Hz, H-6), 8.57 (d, 1H, J = 8.6 Hz, H-8), 8.37 (s, 1H, H-9), 7.62 (dd, 1H, J = 8.6 and 4.0 Hz, H-7), 4.50 (s, 3H, Me); LC/MS: 235 (M+H); Anal. Calcd for C₁₀H₇ClN₄O: C, 51.19; H, 3.01; N, 23.88. Found C, 51.00; H, 3.21; N, 24.17.

4-Chloro-1-ethoxy-1H-triazolo[4,5-g]quinoline (5b). This compound was obtained in 70 % yield; mp 120-122 °C (acetone); ¹H-NMR (DMSO-d₆): δ 9.12 (d, 1H, J = 4.1 Hz, H-6), 8.66 (d, 1H, J = 8.6 Hz, H-8), 8.57 (s, 1H, H-9), 7.70 (dd, 1H, J = 8.6 and 4.1 Hz, H-7), 4.75 (q, 2H, J = 7.0 Hz, CH₂), 1.47 (t, 3H, J = 7.0 Hz, Me); LC/MS: 249 (M+H); Anal. Calcd for C₁₁H₉ClN₄O: C, 53.13; H, 3.65; N, 22.53. Found C, 53.41; H, 3.42; N, 22.90.

1-Ethoxy-4,9-dihydro-1H-triazolo[4,5-g]quinoline (6). This compound was obtained in 32 % yield; mp 144-145 °C (acetone); ¹H-NMR (CDCl₃): δ 8.57 (d, 1H, J = 4.6 Hz, H-6), 7.64 (d, 1H, J = 8.0 Hz, H-8), 7.23 (dd, 1H, J = 8.0 and 4.6 Hz, H-7), 4.59 (q, 2H, J = 7.0 Hz, O-CH₂), 4.31 (m, 2H, C₄-H₂), 4.09 (m, 2H, C₉-H₂), 1.47 (t, 3H, J = 7.0 Hz, Me); LC/MS: 217 (M+H); Anal. Calcd for C₁₁H₁₂N₄O: C, 61.10; H, 5.59; N, 25.91. Found C, 61.32; H, 5.69; N, 25.78.

4-Chloro-1-ethoxy-9-nitro-1H-triazolo[4,5-g]quinoline (7). This compound was obtained in 31 % yield; mp 110-112 °C (Et₂O); ¹H-NMR (CDCl₃): δ 9.15 (d, 1H, J = 4.1 Hz, H-6), 8.79 (d, 1H, J = 8.6 Hz, H-8), 7.65 (dd, 1H, J = 8.6 and 4.1 Hz, H-7), 4.75 (q, 2H, J = 7.0 Hz, CH₂), 1.62 (t, 3H, J = 7.0 Hz, Me); LC/MS: 293 (M⁺); Anal. Calcd for C₁₁H₈ClN₅O₃: C, 44.99; H, 2.75; N, 23.85. Found C, 50.30; H, 2.79; N, 24.07.

4-Chloro-8-ethoxy-1-ethyl-1H-triazolo[4,5-g]quinoline (9a). This compound was obtained in 18 % yield; mp 130-132 °C (Et₂O); TLC (CHCl₃-MeOH 95:5): Rₖ 0.42; ¹H-NMR (CDCl₃): δ 8.90 (d, 1H, J = 4.5 Hz, H-6), 8.27 (s, 1H, H-9), 6.24 (d, 1H, J = 4.5 Hz, H-7), 4.85 (q, 2H, J = 7.0 Hz, N-CH₂), 4.37 (q,
2H, $J = 7.0$ Hz, O-CH$_2$), 1.74-1.60 (m, 6H, 2 Me); $^{13}$C-NMR (CDCl$_3$): $\delta$ 161.77 (s), 152.43 (d), 144.38 (s) 141.54 (s), 129.35 (s), 125.48 (s), 118.07 (s), 99.81 (d), 99.02 (d), 64.85 (t), 43.75 (t), 14.94 (q), 14.37 (q); LC/MS: 277 (M+H); Anal. Calcd for C$_{13}$H$_{13}$ClN$_4$O: C, 56.42; H, 4.74; N, 20.25. Found C, 56.80; H, 4.91; N, 20.51.

4-Chloro-8-ethoxy-2-ethyl-1$H$-triazolo[4,5-g]quinoline (10a). This compound was obtained in in 35 % yield; mp 122-124 °C (Et$_2$O); TLC (CHCl$_3$-MeOH 95:5): R$_f$ 0.55; $^1$H-NMR (CDCl$_3$): $\delta$ 8.88-8.82 (m, 2H, H-6 + H-9), 6.62 (d, 1H, $J = 5.0$ Hz, H-7), 4.98 (q, 2H, $J = 7.0$ Hz, O-CH$_2$), 4.34 (q, 2H, $J = 7.0$ Hz, N-CH$_2$), 1.84 (t, 3H, $J = 7.0$ Hz, 2 O-CH$_2$Me), 1.63 (t, 3H, $J = 7.0$ Hz, 2 N-CH$_2$Me); $^{13}$C-NMR (CDCl$_3$): $\delta$ 161.47 (s), 153.17 (d), 142.13 (s) 141.55 (s), 122.10 (s), 118.05 (s), 111.15 (s), 109.84 (d), 98.24 (d), 64.69 (t), 53.06 (t), 14.94 (q), 14.42 (q); LC/MS: 277 (M+H); Anal. Calcd for C$_{13}$H$_{13}$ClN$_4$O: C, 56.42; H, 4.74; N, 20.25. Found C, 56.09; H, 4.70; N, 20.04.

4-Chloro-8-ethoxy-3-ethyl-1$H$-triazolo[4,5-g]quinoline (11a). This compound was obtained in in 21 % yield; mp 195-198 °C (acetone); TLC (CHCl$_3$-MeOH 95:5): R$_f$ 0.73; $^1$H-NMR (CDCl$_3$): $\delta$ 8.97-8.90 (m, 2H, H-6 + H-9), 6.73 (d, 1H, $J = 5.0$ Hz, H-7), 5.20 (q, 2H, $J = 7.0$ Hz, O-CH$_2$), 4.36 (q, 2H, $J = 7.0$ Hz, N-CH$_2$), 1.84-1.60 (m, 6H, 2 Me); $^{13}$C-NMR (CDCl$_3$): $\delta$ 162.96 (s), 153.82 (d), 144.88 (s) 144.19 (s), 140.86 (s), 131.11 (s), 120.43 (s), 112.05 (s), 110.94 (d), 98.24 (d), 64.69 (t), 53.06 (t), 15.21 (q), 14.42 (q); LC/MS: 277 (M+H); Anal. Calcd for C$_{13}$H$_{13}$ClN$_4$O: C, 56.42; H, 4.74; N, 20.25. Found C, 56.56; H, 4.59; N, 19.91.

4-Chloro-8-hydroxy-1-methoxy-1$H$-triazolo[4,5-g]quinoline (12a). This compound was obtained in 60% yield; mp 186-188 °C (acetone); $^1$H-NMR (DMSO-d$_6$): $\delta$ 11.55 (s, 1H, OH), 8.45 (s, 1H, H-9), 7.98 (d, 1H, $J = 7.6$ Hz, H-6), 6.11 (d, 1H, $J = 7.6$ Hz, H-7), 4.46 (s, 3H, Me); LC/MS: 251 (M+H); Anal. Calcd for C$_{10}$H$_7$ClN$_4$O$_2$: C, 47.92; H, 2.82; N, 22.35. Found C, 48.30; H, 3.02; N, 22.11.

4-Chloro-1-ethoxy-8-hydroxy-1$H$-triazolo[4,5-g]quinoline (12b). This compound was obtained in 77 and 46 % yield by ethylation of 1b at rt and 60 °C respectively; mp 174-176 °C (acetone); $^1$H-NMR (CDCl$_3$+DMSO-d$_6$): $\delta$ 11.29 (s, 1H, OH), 8.56 (s, 1H, H-9), 7.92 (d, 1H, $J = 7.6$ Hz, H-6), 6.21 (d, 1H, $J = 7.6$ Hz, H-7), 4.71 (q, 2H, $J = 7.0$ Hz, CH$_2$), 1.54 (t, 3H, $J = 7.0$ Hz, Me); LC/MS: 265 (M+H); Anal. Calcd for C$_{11}$H$_9$ClN$_4$O$_2$: C, 49.92; H, 3.43; N, 21.17. Found C, 50.15; H, 3.61; N, 21.03.

4-Chloro-1,8-diethoxy-1$H$-triazolo[4,5-g]quinoline (13). This compound was obtained in 24 % yield by ethylation of 1b at 60 °C and in 98 % yield by ethylation of 12b at 100 °C; mp 161-163 °C (acetone); $^1$H-NMR (CDCl$_3$): $\delta$ 8.92 (d, 1H, $J = 5.0$ Hz, H-6), 8.34 (s, 1H, H-9), 6.77 (d, 1H, $J = 5.0$ Hz, H-7), 4.74 (q, 2H, $J = 7.0$ Hz, N-CH$_2$), 4.36 (q, 2H, $J = 7.0$ Hz, O-CH$_2$), 1.67 (t, 3H, $J = 7.0$ Hz, 2 N-CH$_2$Me), 1.57 (t, 3H, $J = 7.0$ Hz, 2 O-CH$_2$Me); LC/MS: 293 (M+H); Anal. Calcd for C$_{13}$H$_{13}$ClN$_4$O$_2$: C, 53.34; H, 4.48; N, 19.14. Found C, 53.02; H, 4.71; N, 18.89.
Method B: benzyl chloride.

To a solution of 1c, 1d or 1e (5.0 mmol) in 40 mL of DMF, Cs₂CO₃ (5.0 mmol) and 4-nitrobenzyl chloride (15.0 mmol) were added and the mixture heated at 60 °C under stirring for 24 h. After the reactions were completed, the mixtures were cooled to rt and the excess of Cs₂CO₃ filtered off. The resulting mother liquors were diluted with 250 mL of water, then kept at 0 °C overnight. The precipitate formed was filtered off, washed with water, dried and purified by column chromatography on silica gel eluting with a mixture of chloroform-methanol in 85:5 ratio, to give respectively:

1-Benzyl-8-benzyloxy-4-chloro-1H-triazolo[4,5-g]quinoline (9b). This compound was obtained in 30 %; mp 98-100 °C (Et₂O); TLC (CHCl₃-MeOH 98:2): Rf 0.61; ¹H-NMR (CDCl₃): δ 8.89 (d, 1H, J = 5.2 Hz, H-6), 8.10 (s, 1H, H-9), 7.46-7.20 (m, 10H, 10 phenyl-H), 6.80 (d, 1H, J = 5.2 Hz, H-7), 5.97 (s, 2H, N-CH₂), 5.31 (s, 2H, O-CH₂); ¹³C-NMR (CDCl₃): δ 161.31 (s), 152.21 (d), 135.10 (s) 134.05 (s), 131.06 (s), 128.02 (s), 128.98 (d), 128.88 (d), 128.76 (d), 128.59 (d), 127.92 (s), 127.76 (d), 127.47 (d), 126.32 (s), 122.85 (s), 100.42 (d), 99.79 (d), 70.74 (t), 52.74 (t); LC/MS: 401 (M+H); Anal. Calcd for C₂₃H₁₇ClN₄O: C, 68.91; H, 4.27; N, 13.98. Found C, 69.22; H, 4.09; N, 14.32.

3-Benzyl-8-benzyloxy-4-chloro-1H-triazolo[4,5-g]quinoline (11b). This compound was obtained in 17 %; mp 188-190 °C (Et₂O); TLC (CHCl₃-MeOH 98:2): Rf 0.71; ¹H-NMR (CDCl₃): δ 9.05 (d, 1H, J = 5.2 Hz, H-6), 8.95 (s, 1H, H-9), 7.50-7.25 (m, 10H, 10 phenyl-H), 6.83 (d, 1H, J = 5.2 Hz, H-7), 6.35 (s, 2H, N-CH₂), 5.38 (s, 2H, O-CH₂); ¹³C-NMR (CDCl₃): δ 162.44 (s), 153.64 (d), 144.74 (s) 143.48 (s), 136.16 (s), 134.96 (s), 128.72 (d), 128.69 (d), 128.53 (d), 128.03 (d), 127.69 (s), 127.31 (d), 127.17 (d), 127.47 (d), 126.32 (s), 122.85 (s), 100.42 (d), 99.79 (d), 70.74 (t), 52.74 (t); LC/MS: 401 (M+H); Anal. Calcd for C₂₃H₁₇ClN₄O: C, 68.91; H, 4.27; N, 13.98. Found C, 69.22; H, 4.09; N, 14.32.

1-Benzyloxy-4-chloro-1H-triazolo[4,5-g]quinoline (5c). This compound was obtained in 69 %; mp 135-136 °C (acetone); ¹H-NMR (DMSO-d₆): δ 9.09 (d, 1H, J = 4.1 Hz, H-6), 8.60 (d, 1H, J = 8.6 Hz, H-8), 8.30 (s, 1H, H-9), 7.67 (dd, 1H, J = 8.6 and 4.1 Hz, H-7), 7.55 (m, 2H, H-2’ + H-6’), 7.55 (m, 3H, H-3’ + H-4’ + H-5’), 5.27 (s, 2H, CH₂); LC/MS: 311 (M+H); Anal. Calcd for C₁₆H₁₁ClN₄O: C, 61.84; H, 3.57; N, 18.03. Found C, 61.49; H, 3.75; N, 17.80.

1-Benzzyloxy-4-chloro-8-hydroxy-1H-triazolo[4,5-g]quinoline (12c). This compound was obtained in 43 % yield; mp 212-214 °C (acetone); ¹H-NMR (DMSO-d₆): δ 11.51 (s, 1H, OH), 8.17 (s, 1H, H-9), 7.96 (d, 1H, J = 7.2 Hz, H-6), 7.47-7.31 (m, 5H, 5 phenyl-H), 6.07 (d, 1H, J = 7.2 Hz, H-7), 5.70 (s, 2H, CH₂); LC/MS: 327 (M+H); Anal. Calcd for C₁₆H₁₁ClN₄O₂: C, 58.82; H, 3.39; N, 17.15. Found C, 59.20; H, 3.27; N, 17.39.
Method C: 4-nitrobenzyl chloride.

A solution of 1c, 1d or 1e (5.0 mmol) in 40 mL of DMF was added of Cs$_2$CO$_3$ (5.0 mmol) and 4-nitrobenzyl chloride (15.0 mmol), heated at 60 °C under stirring for 24 h. After the reactions were completed the mixtures obtained were cooled to rt and the excess of Cs$_2$CO$_3$ filtered off. The resulting mothers liquid were diluted with 250 mL of water, kept at 0 °C overnight, and the precipitate obtained was filtered off, washed with water, dried and purified by column chromatography on silica gel eluting with a mixture of chloroform-methanol 85:5, to give respectively:

4-Chloro-1-(4-nitrobenzyloxy)-1H-triazolo[4,5-g]quinoline (5d). This compound was obtained in 88 %; mp 190-192 °C (acetone); $^1$H-NMR (DMSO-d$_6$): $\delta$ 9.11 (d, 1H, $J$ = 4.1 Hz, H-6), 8.64 (d, 1H, $J$ = 8.2 Hz, H-8), 8.45 (s, 1H, H-9), 8.29 (d, 2H, $J$ = 8.0 Hz, H-3' + H-5'), 7.89 (d, 2H, $J$ = 8.0 Hz, H-2' + H-6'), 7.68 (dd, 1H, $J$ = 8.2 and 4.1 Hz, H-7), 5.90 (s, 2H, CH$_2$); LC/MS: 356 (M+H); Anal. Calcd for C$_{16}$H$_{10}$ClN$_5$O$_3$: C, 54.02; H, 2.83; N, 19.69. Found C, 54.40; H, 3.02; N, 19.47.

4-Chloro-8-hydroxy-1-(4-nitrobenzyloxy)-1H-triazolo[4,5-g]quinoline (12d). This compound was obtained in 32 %; mp 218-220 °C (acetone); $^1$H-NMR (DMSO-d$_6$): $\delta$ 11.56 (s, 1H, OH), 8.27 (m, 3H, H-9 + H-3' + H-5'), 7.96 (d, 1H, $J$ = 7.2 Hz, H-6), 7.89 (d, 2H, $J$ = 7.6 Hz, H-2' + H-6'), 6.09 (d, 1H, $J$ = 7.2 Hz, H-7), 5.87 (s, 2H, CH$_2$); LC/MS: 372 (M+H); Anal. Calcd for C$_{16}$H$_{10}$ClN$_5$O$_4$: C, 51.70; H, 2.71; N, 18.84. Found C, 52.03; H, 2.50; N, 19.21.

4-Chloro-9-nitro-1-(4-nitrobenzyloxy)-1H-triazolo[4,5-g]quinoline (8). This compound was obtained in 68 %; mp 228-230 °C (acetone); $^1$H-NMR (DMSO-d$_6$): $\delta$ 9.22 (d, 1H, $J$ = 4.1 Hz, H-6), 8.86 (d, 1H, $J$ = 8.8 Hz, H-8), 8.34 (d, 2H, $J$ = 8.6 Hz, H-3' + H-5'), 7.890 (m, 3H, H-7 + H-2' + H-6'), 5.89 (s, 2H, CH$_2$); LC/MS: 401 (M+H); Anal. Calcd for C$_{16}$H$_9$ClN$_6$O$_5$: C, 47.95; H, 2.26; N, 20.97. Found C, 47.61; H, 2.37; N, 21.22.

Method D: chloroacetonitrile.

A mixture of 4-chloro-3H-triazolo[4,5-g]quinoline-1-oxide (1c) (5.0 mmol) and chloroacetonitrile (10 mL) was added of Cs$_2$CO$_3$ (5.0 mmol) and heated at 60 °C under stirring for 1 h. After the reaction was completed the mixture of reaction was cooled to rt, the excess of Cs$_2$CO$_3$ filtered off, and the excess of chloroacetonitrile was removed in vacuo. The crude solid obtained was purified by column chromatography on silica gel eluting with a mixture of CHCl$_3$-MeOH 9:1, to give:

2-(4-Chloro-1H-triazolo[4,5-g]quinolin-1-yloxy)acetonitrile (5e). This compound was obtained in 68 %; mp > 300 °C (acetone); $^1$H-NMR (DMSO-d$_6$): $\delta$ 9.16 (d, 1H, $J$ = 4.0 Hz, H-6), 8.60 (d, 1H, $J$ = 8.2 Hz, H-8), 8.61 (s, 1H, H-9), 7.76 (dd, 1H, $J$ = 8.2 and 4.0 Hz, H-7), 5.49 (s, 3H, CH$_3$); LC/MS: 259 (M+H); Anal. Calcd for C$_{11}$H$_6$ClN$_5$O: C, 50.88; H, 2.33; N, 26.97. Found C, 50.50; H, 2.47; N, 26.71.
Preparation of 4,8-dichloro-3H-triazolo[4,5-g]quinoline (14). A suspension of 4-chlorotriazolo-8-hydroxy-[4,5-g]quinoline (1b) (6.2 mmol) in 20 mL of phosphorus(V)oxychloride (99%) was refluxed under stirring for 40 h. The reaction mixture was then cooled to rt and poured onto 200 g of crushed ice and the crude solid obtained was filtered off, washed with water and dried, to give 14 in 74% yield; mp > 300 °C (acetone); 1H-NMR (DMSO-d6): δ 16.60 (s, 1H, NH), 9.02 (d, 1H, J = 4.4 Hz, H-6), 8.78 (s, 1H, H-9), 7.91 (d, 1H, J = 4.4 Hz, H-7); LC/MS: 238 (M+H); Anal. Calcd for C9H4Cl2N4: C, 45.22; H, 1.69; N, 23.44. Found C, 44.89; H, 1.77; N, 23.28.

REFERENCES AND NOTES