HETEROCYCLES, Vol. 75, No. 10, 2008, pp. 2493 - 2505. © The Japan Institute of Heterocyclic Chemistry
Received, 22nd April, 2008, Accepted, 26th May, 2008, Published online, 29th May, 2008. COM-08-11415

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-mal: 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-N_1-oxide derivatives (**1c-e** and **II**) with electrophilic reagents in order to optimize the synthetic pathways for obtaining both mixtures of $N_{1,2,3}$-alkyl isomers and selectively N_1-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 HNO_2 at rt.[1] Further derivatives of this *N*-tricyclic system were successively synthesized[1-3] 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-1*H*-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-1*H*-triazolo[4,5-*g*]quinolin-1-yl)propan-2-one and 1,3-bis-(4-chloro-3*H*-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**.

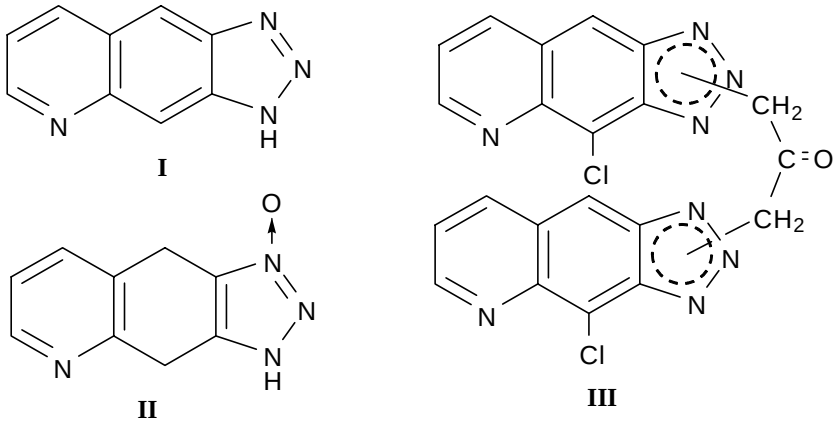
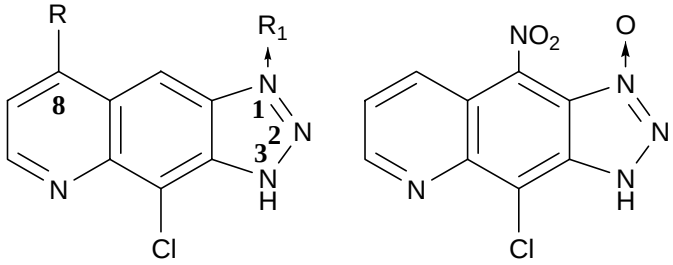


Figure 1

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.



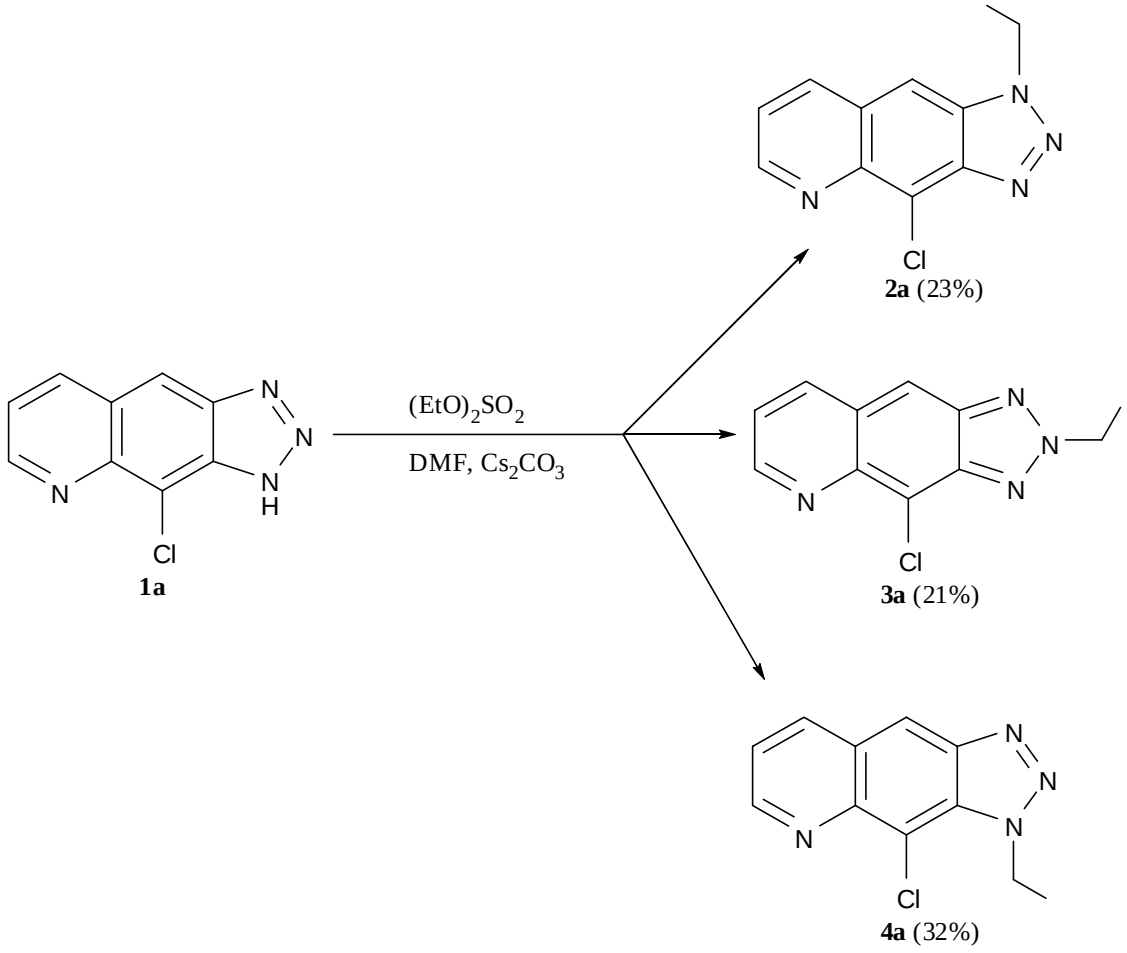
1a) R = H, R_1 = none
1b) R = OH, R_1 = none
1c) R = H, R_1 = O
1d) R = OH, R_1 = O

Figure 2

RESULTS AND DISCUSSION

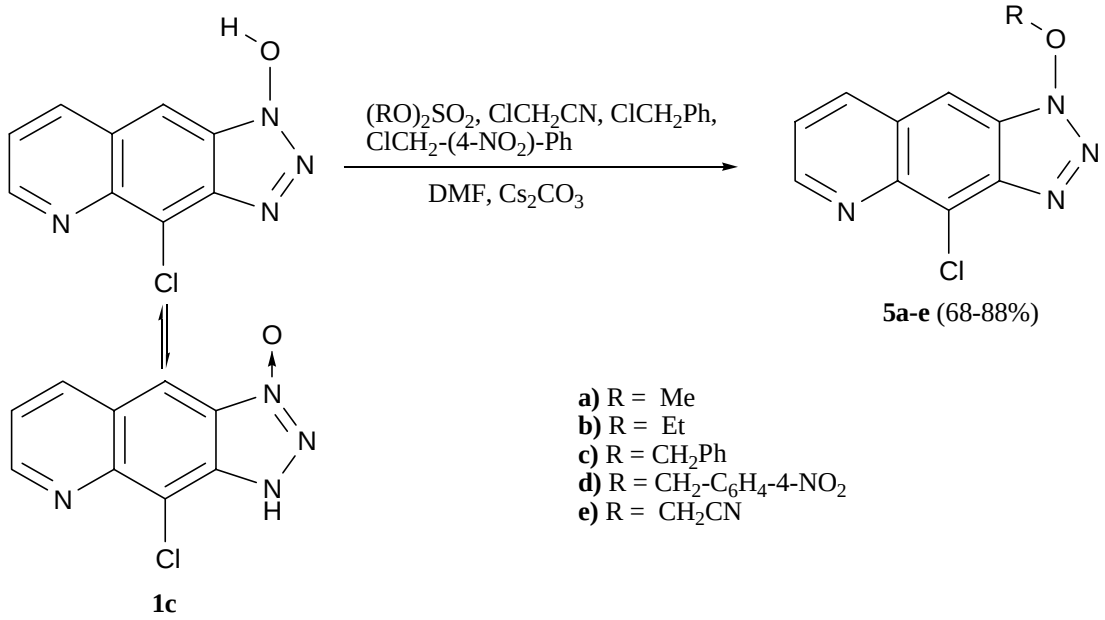
In our previous work[3] we reported that the reaction of **1a** with chloroacetonitrile in dry dimethylformamide (DMF) and KOH afforded both [4-chloro-1*H*-triazolo[4,5-*g*]quinolin-1-yl]acetonitrile and [4-chloro-3*H*-triazolo[4,5-*g*]quinolin-3-yl]acetonitrile but not the corresponding 2-yl substituted 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 Cs_2CO_3 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 Cs_2CO_3) 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]



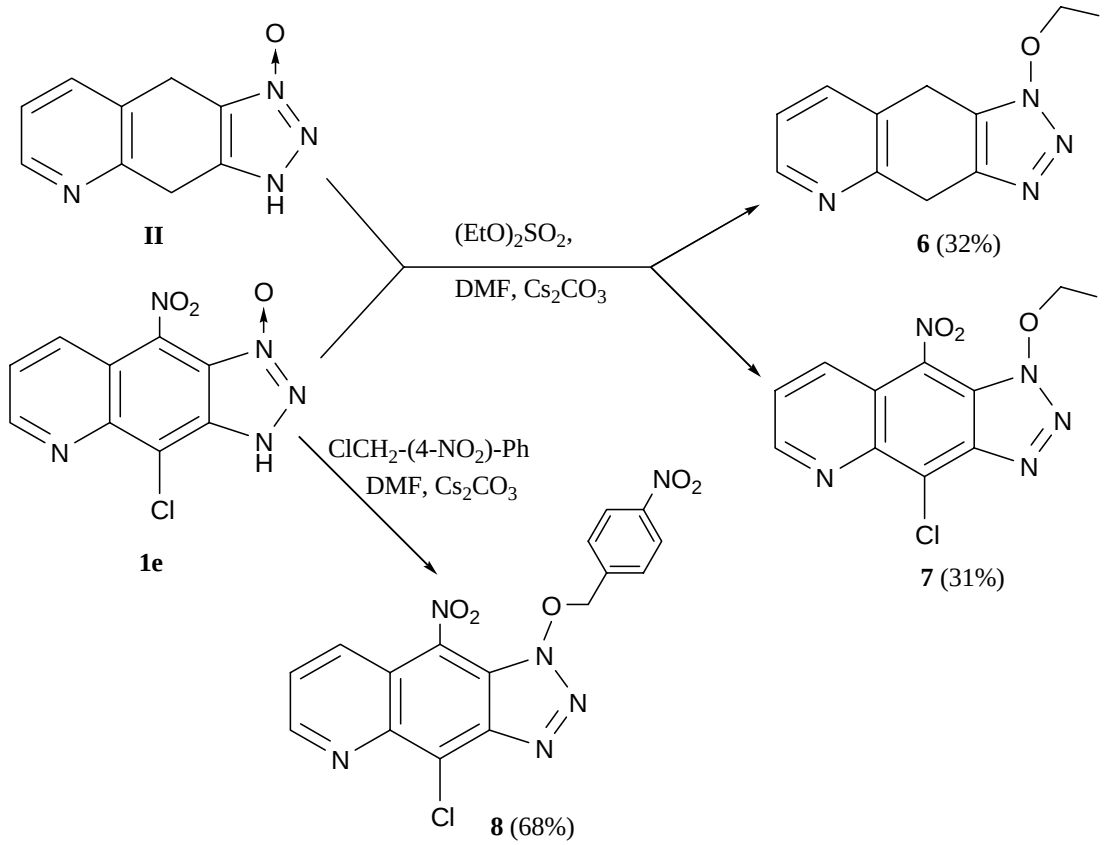
Scheme 1

A different behavior was observed as 4-chloro-3*H*-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 N_1-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 $N_{1,2,3}$-alkyl isomers and selectively N_1-O-alkyl derivatives.



Scheme 2

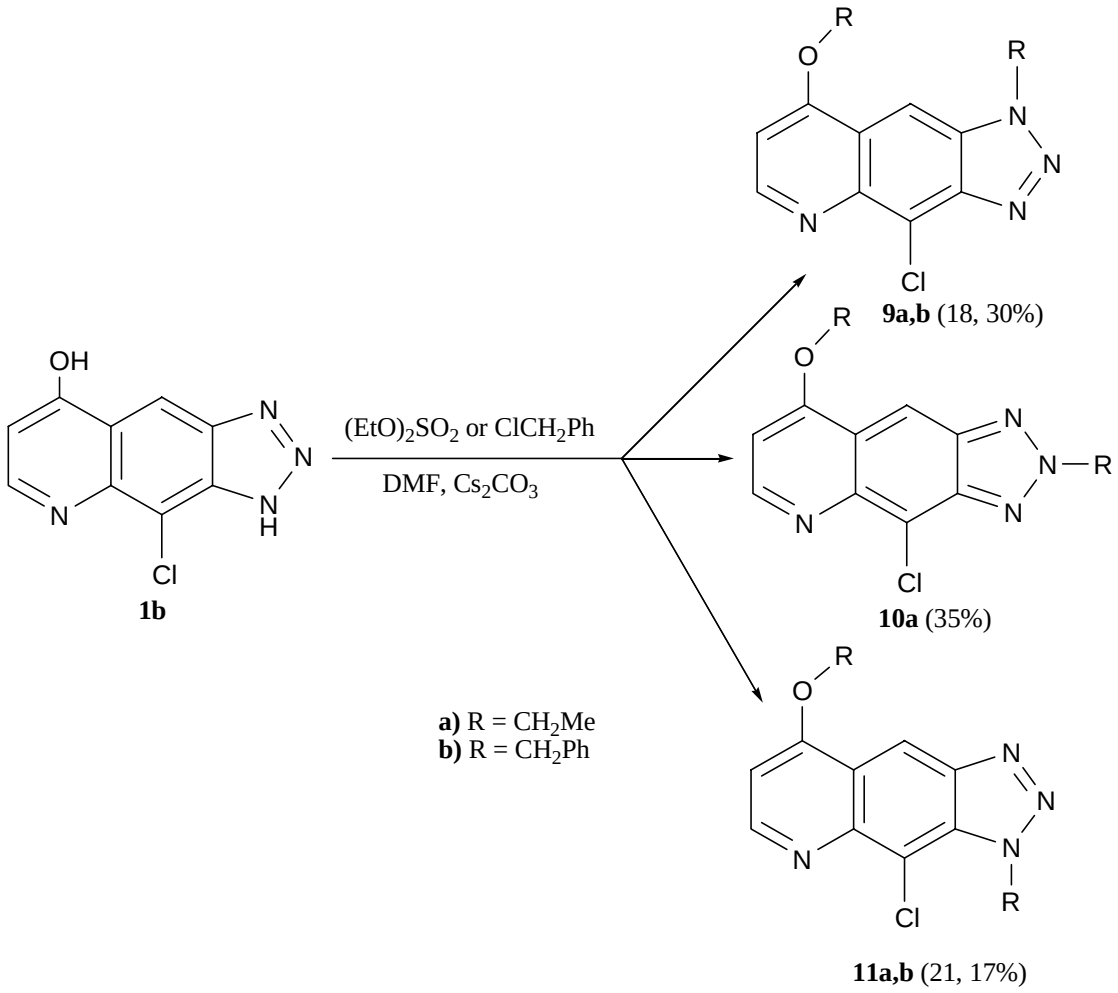
The reactions reported in **Scheme 3** show that this type of derivatives (compounds **6-8**) can be selectively obtained in 31-68% yield.



Scheme 3

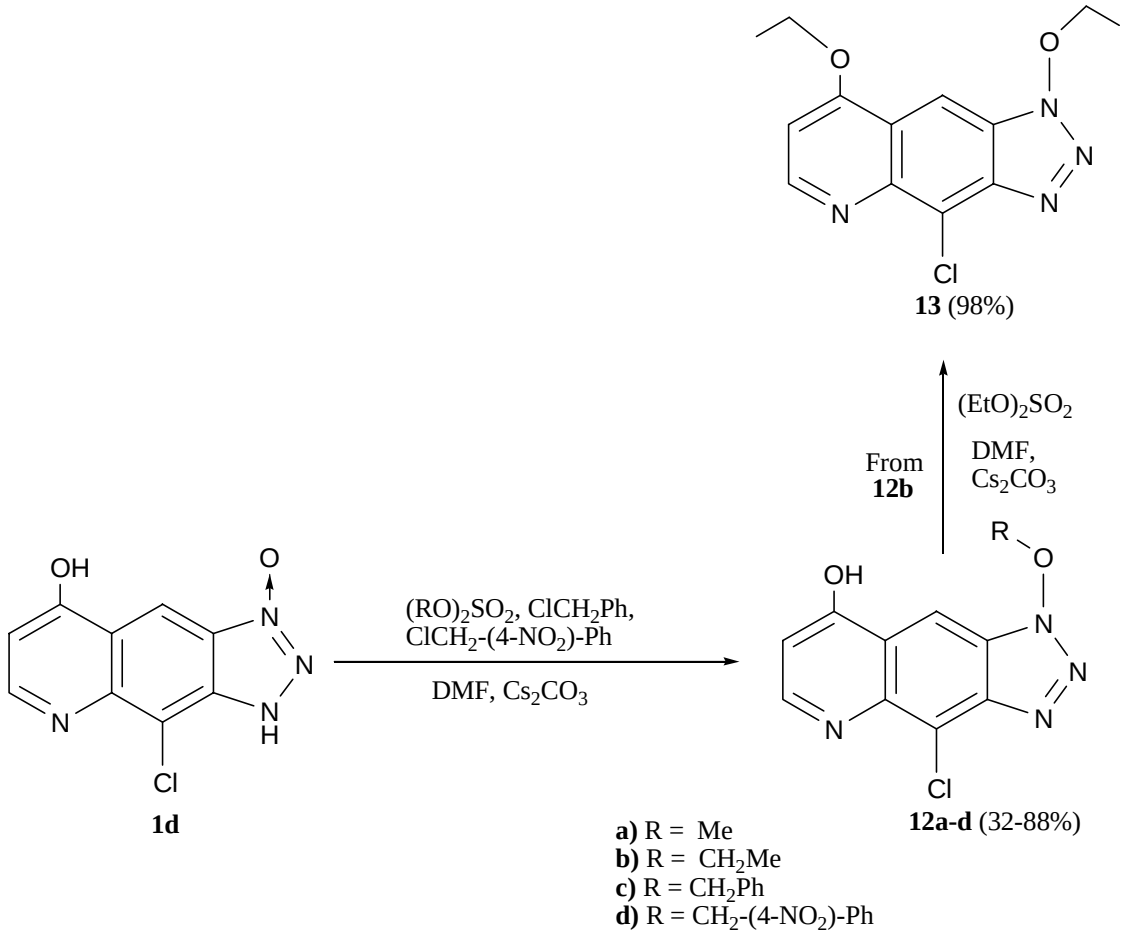
On the ground of these results, we have further investigated whether, under the same conditions, other 3*H*-triazolo[4,5-*g*]quinoline-1-oxides, as 4,9-dihydro-1*H*-triazolo[4,5-*g*]quinoline-1-oxide (**II**) and 4-chloro-9-nitro-3*H*-triazolo[4,5-*g*]quinoline-1-oxide (**1e**), were able to afford N_1-O-alkyl 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 $N_{1,2,3}$ and C_8-O ethyl derivatives (**9a**,**10a**,**11a**) were obtained. Unexpectedly using benzyl chloride the reaction afforded only the derivatives **9b** and **11b** (**Scheme 4**). The failure of alkylation at N_2 position is possibly due to the higher reactivity of N_1 and N_3 rather than N_2 atom towards this halide reagent and is similar to the previously reported case of the described reaction with chloroacetonitrile.[3] Furthermore, alkylation of the triazolo moiety certainly occurs prior to the oxygen atom in C_8.



Scheme 4

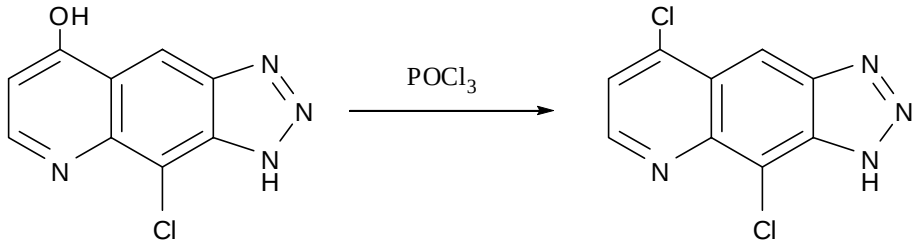
Finally, selective O_1-alkylation was observed in the case of reaction of 4-chloro-8-hydroxy-3*H*-triazolo[4,5-*g*]quinoline-1-oxide (**1d**), under the same conditions, with the above mentioned electrophiles that led to compounds **12a-d** (**Scheme 5**). However, it is worthwhile to note that the reaction 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_1-ethyl compound (**12b**) in 77% yield, whereas carrying out the reaction at 60 °C a mixture of **13** (24%) and **12b** (46%) was obtained. Interestingly compound **12b** at 100 °C afforded **13** in almost quantitative yield.



Scheme 5

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 C_8-OH group in **1b** can be easily replaced by chlorine by means of $POCl_3$ 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 N_1-derivatives was deduced mainly by the examination of ^{1}H-NMR NOE spectra. In particular, in the case of the compound **9a** by irradiation of the CH_2 linked to the N_1 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 (N_2 and N_3) were identified by the analysis of the chemical shifts of both the ^{13}C atom linked to the nitrogen in 2 or 3 position. In these cases, in ^{13}C spectrum we observed that the resonance of the CH_2 linked to the N_2 of **10a** is located at lower downfield (δ = 53.06 ppm) than that of the CH_2 linked to the N_3 of **11a** (δ = 45.24 ppm), all these experiments were in accordance with our previous observations.[8]



1b **14** (74%)

Scheme 6

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

Time (min)	Phase A (%)	Phase B (%)	Flow (mL/min)
0	60	40	0.5
20	20	80	0.5
30	10	90	0.5

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 Cs_2CO_3 (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 Cs_2CO_3 filtered off, and the DMF was removed *in vacuo*. The crude solid obtained was purified by silica gel column chromatography eluting with Et_2O to give the O_1-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-1*H*-triazolo[4,5-*g*]quinoline (2a). This compound was obtained in 23 % yield; mp 180-182 °C (acetone); TLC (EtOAc-light petroleum 7:3): R_f 0.43; ^{1}H-NMR ($CDCl_3$): 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, CH_2), 1.72 (t, 3H, *J* = 7.2 Hz, Me); ^{13}C-NMR ($CDCl_3$): δ 151.07 (d), 144.66 (s), 139.70 (s), 136.80 (d), 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 $C_{11}H_9ClN_4$: 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-2*H*-triazolo[4,5-*g*]quinoline (3a). This compound was obtained in 21 % yield; mp 108-110 °C (Et_2O); TLC (EtOAc-light petroleum 7:3): R_f 0.65; ^{1}H-NMR ($CDCl_3$): 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, CH_2), 1.85 (t, 3H, *J* = 7.2 Hz, Me); ^{13}C-NMR ($CDCl_3$): 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 $C_{11}H_9ClN_4$: 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-3*H*-triazolo[4,5-*g*]quinoline (4a). This compound was obtained in 32 % yield; mp 114-116 °C (Et_2O); TLC (EtOAc-light petroleum 7:3): R_f 0.70; ^{1}H-NMR ($CDCl_3$): 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, CH_2), 1.71 (t, 3H, *J* = 7.2 Hz, Me); ^{13}C-NMR ($CDCl_3$): 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 $C_{11}H_9ClN_4$: 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-1*H*-triazolo[4,5-*g*]quinoline (5a). This compound was obtained in 88 % yield; mp 182-184 °C (acetone); ^{1}H-NMR (DMSO-d_6): 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 $C_{10}H_7ClN_4O$: C, 51.19; H, 3.01; N, 23.88. Found C, 51.00; H, 3.21; N, 24.17.

4-Chloro-1-ethoxy-1*H*-triazolo[4,5-*g*]quinoline (5b). This compound was obtained in 70 % yield; mp 120-122 °C (acetone); ^{1}H-NMR (DMSO-d_6): 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, CH_2), 1.47 (t, 3H, *J* = 7.0 Hz, Me); LC/MS: 249 (M+H); Anal. Calcd for $C_{11}H_9ClN_4O$: C, 53.13; H, 3.65; N, 22.53. Found C, 53.41; H, 3.42; N, 22.90.

1-Ethoxy-4,9-dihydro-1*H*-triazolo[4,5-*g*]quinoline (6). This compound was obtained in 32 % yield; mp 144-145 °C (acetone); ^{1}H-NMR ($CDCl_3$): 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-CH_2), 4.31 (m, 2H, C_4-H_2), 4.09 (m, 2H, C_9-H_2), 1.47 (t, 3H, *J* = 7.0 Hz, Me); LC/MS: 217 (M+H); Anal. Calcd for $C_{11}H_{12}N_4O$: 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-1*H*-triazolo[4,5-*g*]quinoline (7). This compound was obtained in 31 % yield; mp 110-112 °C (Et_2O); ^{1}H-NMR ($CDCl_3$): 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, CH_2), 1.62 (t, 3H, *J* = 7.0 Hz, Me); LC/MS: 293 (M^+); Anal. Calcd for $C_{11}H_8ClN_5O_3$: 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-1*H*-triazolo[4,5-*g*]quinoline (9a). This compound was obtained in in 18 % yield; mp 130-132 °C (Et_2O); TLC ($CHCl_3$-MeOH 95:5): R_f 0.42; ^{1}H-NMR ($CDCl_3$): 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-CH_2), 4.37 (q,

2H, *J* = 7.0 Hz, O-CH_2), 1.74-1.60 (m, 6H, 2 Me); ^{13}C-NMR ($CDCl_3$): δ 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 $C_{13}H_{13}ClN_4O$: 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_2O); TLC ($CHCl_3$-MeOH 95:5): R_f 0.55; ^{1}H-NMR ($CDCl_3$): δ 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_2Me), 1.63 (t, 3H, *J* = 7.0 Hz, 2 N-CH_2Me); ^{13}C-NMR ($CDCl_3$): δ 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), 15.21 (q), 14.42 (q); LC/MS: 277 (M+H); Anal. Calcd for $C_{13}H_{13}ClN_4O$: 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 ($CDCl_3$): δ 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), 1.74-1.60 (m, 6H, 2 Me); ^{13}C-NMR ($CDCl_3$): δ 162.96 (s), 153.82 (d), 144.88 (s) 144.19 (s), 140.86 (s), 131.11 (s), 120.43 (s), 112.05 (d), 98.85 (d), 64.85 (t), 45.24 (t), 16.90 (q), 14.41 (q); LC/MS: 277 (M+H); Anal. Calcd for $C_{13}H_{13}ClN_4O$: 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): δ 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 $C_{10}H_7ClN_4O_2$: 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): δ 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 $C_{11}H_9ClN_4O_2$: 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 ($CDCl_3$): δ 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_2Me), 1.57 (t, 3H, *J* = 7.0 Hz, 2 O-CH_2Me); LC/MS: 293 (M+H); Anal. Calcd for $C_{13}H_{13}ClN_4O_2$: 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, Cs_2CO_3 (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 Cs_2CO_3 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-1*H*-triazolo[4,5-*g*]quinoline (9b). This compound was obtained in 30 %; mp 98-100 °C (Et_2O); TLC ($CHCl_3$-MeOH 98:2): R_f 0.61; ^{1}H-NMR ($CDCl_3$): 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-CH_2), 5.31 (s, 2H, O-CH_2); ^{13}C-NMR ($CDCl_3$): 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 $C_{23}H_{17}ClN_4O$: 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-1*H*-triazolo[4,5-*g*]quinoline (11b). This compound was obtained in 17 %; mp 188-190 °C (Et_2O); TLC ($CHCl_3$-MeOH 98:2): R_f 0.71; ^{1}H-NMR ($CDCl_3$): 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-CH_2), 5.38 (s, 2H, O-CH_2); ^{13}C-NMR ($CDCl_3$): 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 $C_{23}H_{17}ClN_4O$: C, 68.91; H, 4.27; N, 13.98. Found C, 6859; H, 4.41; N, 14.07.

1-Benzyloxy-4-chloro-1*H*-triazolo[4,5-*g*]quinoline (5c). This compound was obtained in 69 %; mp 135-136 °C (acetone); ^{1}H-NMR (DMSO-d_6): 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, CH_2); LC/MS: 311 (M+H); Anal. Calcd for $C_{16}H_{11}ClN_4O$: C, 61.84; H, 3.57; N, 18.03. Found C, 61.49; H, 3.75; N, 17.80.

1-Benzyloxy-4-chloro-8-hydroxy-1*H*-triazolo[4,5-*g*]quinoline (12c). This compound was obtained in 43 % yield; mp 212-214 °C (acetone); ^{1}H-NMR (DMSO-d_6): 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, CH_2); LC/MS: 327 (M+H); Anal. Calcd for $C_{16}H_{11}ClN_4O_2$: 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_2CO_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_2CO_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)-1*H*-triazolo[4,5-*g*]quinoline (5d). This compound was obtained in 88 %; mp 190-192 °C (acetone); ^{1}H-NMR (DMSO-d_6): δ 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 $C_{16}H_{10}ClN_5O_3$: 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)-1*H*-triazolo[4,5-*g*]quinoline (12d). This compound was obtained in 32 %; mp 218-220 °C (acetone); ^{1}H-NMR (DMSO-d_6): δ 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 $C_{16}H_{10}ClN_5O_4$: 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)-1*H*-triazolo[4,5-*g*]quinoline (8). This compound was obtained in 68 %; mp 228-230 °C (acetone); ^{1}H-NMR (DMSO-d_6): δ 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 $C_{16}H_9ClN_6O_5$: 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-3*H*-triazolo[4,5-*g*]quinoline-1-oxide (**1c**) (5.0 mmol) and chloroacetonitrile (10 mL) was added of Cs_2CO_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_2CO_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-1*H*-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): δ 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_2); LC/MS: 259 (M+H); Anal. Calcd for $C_{11}H_6ClN_5O$: C, 50.88; H, 2.33; N, 26.97. Found C, 50.50; H, 2.47; N, 26.71.

Preparation of 4,8-dichloro-3*H*-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 %; mp > 300 °C (acetone); ^{1}H-NMR (DMSO-d_6): 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 $C_9H_4Cl_2N_4$: C, 45.22; H, 1.69; N, 23.44. Found C, 44.89; H, 1.77; N, 23.28.

REFERENCES AND NOTES

1. P. Sanna, A. Carta, and G. Paglietti, *Heterocycles*, 2000, **53**, 423.
2. A. Carta, G. Boatto, G. Paglietti, G. Poni, M. G. Setzu, and P. Caredda, *Heterocycles*, 2003, **60**, 833.
3. A. Carta and G. Paglietti, *Arkivoc*, 2004, **5**, 66.
4. A. Carta and G. Paglietti, in "Triazolo[4,5-*g*]quinoline, imidazo[4,5-*g*]quinoline, pyrido[2,3-*g*]quinoxaline and [4,7]phenantroline. An easy pathway for the syntheses of these *N*-Tricycles derived from quinolines" from *Modern Approaches to the Synthesis of O- and N-Heterocycles*, ed. By T. S. Kaufman and E. L. Larghi, Vol. 1 Chapter 7, Ed. Research Signpost Keral, India, 2007, pp. 173-185, and references cited therein.
5. A. Carta, M. Palomba, and Paola Corona, *Heterocycles*, 2006, **68**, 1715.
6. S. Pricl, M. Ferrone, P. Posocco, M. Fermeglia, G. Sanna, G. Collu, P. La Colla, R. Loddo, A. Sias, S. Piras, and A. Carta, *Global Antiviral Journal*, 2006, **2**, 63.
7. A. Carta, P. La Colla, R. Loddo, and G. Paglietti, 2006, U.S. Patent 60,871,352.
8. A. Carta, P. Sanna, G. Paglietti, and F. Sparatore, *Heterocycles*, 2001, **55**, 1133, and references cited therein.