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Short Note

5-Chloro-8-{[1-(2-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl]methoxy}quinoline

Luz Karime Luna Parada and Vladimir V. Kouznetsov *

Laboratorio de Química Orgánica y Biomolecular, CMN, Parque Tecnológico Guatiguará, Km 2 vía refugio, Universidad Industrial de Santander, Piedecuesta A.A. 681011, Colombia; luzkarimeluna@gmail.com

* Correspondence; kouznet@uis.edu.co; Tel.: +57-7-6349069

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Abstract: The title quinoline derivative, 5-chloro-8-{[1-(2-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl]methoxy} quinoline, was synthesized in a common three-step procedure from 5-chloro-8-hydroxyquinoline using *O*-propargylation reaction/copper-catalyzed 1,3-dipolar cycloaddition sequence. The structure of the compound was fully characterized by FT-IR, ^{1}H- and ^{13}C-NMR, GC-MS, and elemental analysis. Its physicochemical parameters (Lipinski's descriptors) were also calculated using the Molinspiration Cheminformatics software. The hybrid obtained could be an interesting model for antifungal bio-essays or a suitable precursor in the synthesis of more complex triazolyl-quinoline hybrids, potential pharmacological agents.

Keywords: 4-chloro-8-hydroxyquinoline; triazoles; conjugated triazolyl-quinoline hybrid; CuAAC; Lipinski' descriptors

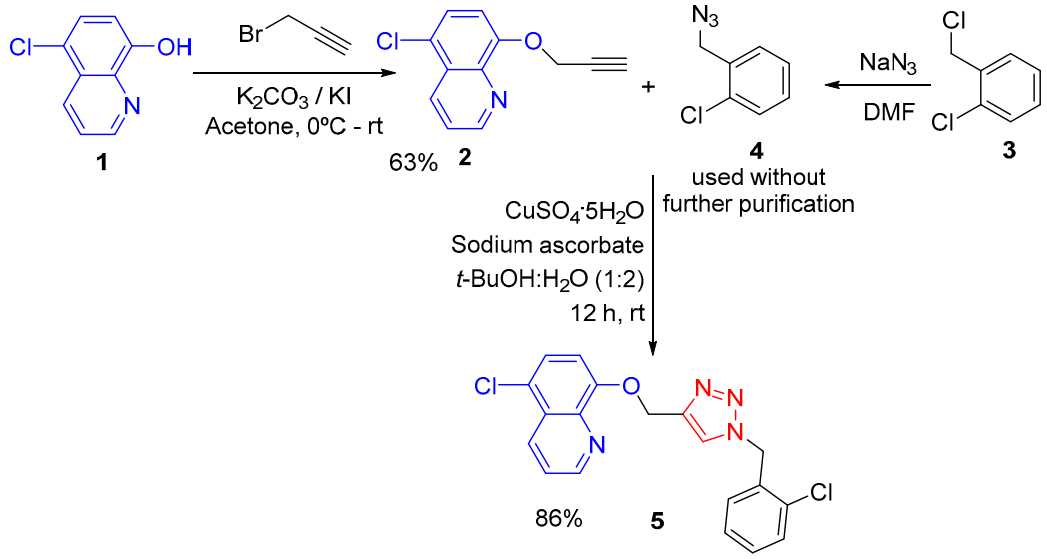
1. Introduction

Quinolines and 1,2,3-triazoles are of great relevance to medicinal and agricultural chemistry displaying a broad array of interesting biological properties [1–4]. Therefore, the combination of both pharmacophoric rings in a single molecule to form fused or conjugated triazol-quinoline hybrids with an enriched biological profile could offer a rapid access to new chemical entities, hybrid molecules, which are needed in bioactive molecules research [5,6]. Rapid progress in research on synthesis and biological evaluations of triazoles that are linked to quinoline derivatives is due to the recent developments in copper-catalyzed 1,3-dipolar cycloaddition (CuAAC), known as a click reaction [7,8]. Among diverse triazol-quinoline hybrids, conjugated 1,2,3-triazole hybrids that are based on 8-hydroxyquinoline skeleton are particularly interesting. Recently, these hybrids disclosed potent inhibitory properties against *Candida* spp [9] and selective antiproliferative activity toward ovarian (OVCAR-03) cancer cells [10]. Moreover, 8-[(benzimidazol-2-yl)methoxy]-5-chloroquinoline derivatives exhibited promising antibacterial activity against *Salmonella typhimurium* and *Staphylococcus aureus* [11]. Other chloroquinoline derivatives form part of known antimalarial (chloroquinine) and antimicrobial (chlorquinaldol) drugs [12,13]. In this context, in continuation with our studies that are focused on bioprospecting different heterocyclic hybrids, a new conjugated triazolquinoline containing two chlorine atoms was designed and synthesized.

2. Results and Discussion

The title compound triazolyl-quinoline hybrid **5** was easily prepared through three step synthesis from commercially available 5-chloro-8-hydroxyquinoline (**1**) and 1-chloro-2-(chloromethyl)benzene (**3**) using *O*-propargylation of (**1**) to obtain quinoline alkyne (**2**) and S_N2 substitution of (**3**) with NaN_3 to give aralkylazide (**4**), which was used without further purification (Scheme 1). After synthesizing

the two main components, alkyne (**2**) and azide (**4**), we performed its CuAAC using Sharpless-Fokin protocol [7] to obtain the desired target molecule (**5**) with a high degree of purity and yield (86%).



Scheme 1. Synthesis of 5-chloro-8-((1-(2-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy) quinoline (**5**) from 5-chloro-8-hydroxyquinoline (**1**) using *O*-propargylation reaction/copper-catalyzed 1,3-dipolar cycloaddition sequence.

The structural elucidation of the compound (**5**) was made based on spectroscopic data, and the results are displayed in the experimental section and in the electronic supporting information. From the ^{1}H-NMR spectra (Figure S2), aromatic hydrogens of the three rings produced a group of several signals at 7.17–8.95 ppm that corresponds to 10 aromatic H. The benzylic hydrogen of O-CH_2-Triazol group produced a signal at 5.63 ppm, while another singlet of benzylic hydrogen from N-CH_2-Ar fragment resonated at 5.53 ppm. The proton in the C-5 position of the triazole ring of this hybrid presented one singlet signal at δ 7.77 ppm, indicating its 1,4-regioisomeric nature. In the ^{13}C-NMR spectrum (Figure S3), the most representative signals were the methylene carbons at 51.6 and 63.1 ppm, corresponding to N-CH_2-Ar and O-CH_2-Triazol systems, respectively.

When considering that the pharmacological activity of organic molecules is strictly related to its hydrophilic/lipophilic nature, we easily calculated some physicochemical properties (molecular weight, lipophilicity (LogP), hydrogen bond acceptor and donor properties, polar surface area and rotatable bonds, and Lipinski descriptors [14] of the title compound. Calculations were performed by Molinspiration software available online [15]. Analyzing physicochemical properties obtained in silico study for of hybrid (**5**), we could note that this triazolquinoline molecule obeyed the Lipinski's rule of five and displayed good drug-likeness scores. Calculations predict good bioavailability properties as no violation to the Lipinski' rule of five was observed (Table S1). However, it should be noted that the values of the calculated partition coefficient (LogP) are above the lipophilicity optimum interval ($0 < \text{LogP} < 3$). This means that high lipophilic parameters (cLogP = 4.86) of the title compound (**5**) could compromise its absorption properties. Interestingly, quinoline precursors (**1**) and (**2**) could be less lipophilic molecules (cLogP = 2.61 and 3.04, respectively), and thus more hydrophilic substances. All three quinoline compounds (**1**, **2**, and **5**) could have a good hematoencephalic barrier permeation according to Veber's rules (TPSA < 140 A^2) [16] (Table S1). This short study pointed to the triazolquinoline hybrid synthesized in our work as an interesting biomodel for pharmacological agents' research.

3. Materials and Methods

3.1. Chemical Analysis

The melting points (uncorrected) were determined on a Fisher-Johns melting point apparatus (00590Q, Thermo Scientific, Waltham, MA, USA). The IR spectra were recorded using an Infralum spectrophotometer (FT-02, Lumex Co., Solon, OH, USA) in KBr. ^{1}H-NMR spectra were recorded on Bruker Avance-400 spectrometer (Bruker, Hamburg, Germany). Chemical shifts are reported in ppm (δ) relative to the solvent peak ($CHCl_3$ in $CDCl_3$ at 7.24 ppm for protons). Signals are designated, as follows: s, singlet; d, doublet; dd, doublet of doublets; m, multiplet. A Hewlett Packard 5890a series II Gas Chromatograph interfaced to an HP 5972 Mass Selective Detector (MSD) with an HP MS Chemstation Data system (PerkinElmer, Akron, OH, USA) was used for MS identification at 70 eV using a 60 m capillary column that was coated with HP-5 [5%-phenyl-poly(dimethyl-siloxane)]. Elemental analyses were performed on a Perkin Elmer 2400 Series II analyzer (PerkinElmer, Akron, OH, USA) and were within ±0.4 of theoretical values. The reaction progress was monitored using thin layer chromatography on a silufol UV254 TLC aluminum sheet (Merck KGaA, Darmstadt, Germany).

*3.2. Synthesis of 5-Chloro-8-{[1-(2-chlorobenzyl)-1H-1,2,3-triazol-4-yl]methoxy}quinoline (**6**)*

Step 1. To a solution of 5-chloro-8-hydroxiquinoline (**1**) (0.99 g, 5.51 mmol) in 15 mL of acetone, potassium carbonate (1.27 g, 9.19 mmol), and potassium iodide (0.07 g, 0.46 mmol) was added and the mixture was cooled to 0 °C. Propargyl bromide (0.54 g, 4.59 mmol) in acetone was added dropwise and the solution was allowed to warm to room temperature and stirred overnight. The progress of the reaction was monitored by TLC using petroleum ether: ethyl acetate (5:1, *v*/*v*) as the mobile phase. After the completion of the reaction, the reaction mixture was quenched with water. Compounds were extracted with ethyl acetate (3 × 20 mL) and the organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure. The obtained crude product was purified by column chromatography on silica gel. Starting product, 5-chloro-8-(prop-2-yn-1-yloxy)quinoline (**2**) was obtained in 63% yields. Product was identified by a comparison of their GC-MS, FT-IR, and ^{1}H-NMR with literature data.

Step 2. 1-Chloro-2-(chloromethyl)benzene (**3**) (1 mmol) was added to sodium azide (2 mmol) dissolved in anhydrous DMF (5 mL). The mixture was stirred overnight at 80 °C. After completion of the reaction, the reaction mass was quenched with water and extracted with ethyl acetate (3 × 20 mL). Organic fractions were washed with brine (3 × 50 mL) and dried over Na_2SO_4. The solvent was removed under vacuum obtaining crude azide (**4**) that was used without further purification.

Step 3. Benzyl azide (**4**) (1.3 mmol) and alkyne (**2**) (1 mmol) were dissolved in *tert*-butanol/water (1:2) mixture, and then $CuSO_4 \cdot 5H_2O$ (0.05 mmol) and sodium ascorbate (0.40 mmol) were added to this solution. The resulting mixture was stirred overnight at room temperature. The reaction mixture was quenched with brine and extracted with ethyl acetate (3 × 20 mL) and dried over anhydride Na_2SO_4. The crude was purified by column chromatography (eluent–dichloromethane and methanol, 9:1) to give 5-chloro-8-{[1-(2-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl]methoxy}quinoline (**6**) (960 mg, 86%) as colorless powder, m.p. 102–103 °C, R_f: 0.3 (Ethyl acetate: Petroleum ether = 2:1). IR: γ_{max} (KBr, cm^{-1}): 1589, 1465, 1373, 1234, 1095, 786, 755. Anal. Calcd for $C_{19}H_{14}Cl_2N_4O$: C, 59.24; H, 3.66; N, 14.54. Found: C, 59.55; H, 3.78; N, 14.35. GC-MS: t_R = 18.21 min, (EI), *m*/*z* (%): *m*/*z* 385 ($M^{+\cdot}$). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.93 (1H, dd, *J* = 4.2, 1.6 Hz, 2-H_Q), 8.49 (1H, dd, *J* = 8.6, 1.6 Hz, 4-H_Q), 7.75 (1H, s, 3′-H_{TA}), 7.51 (1H, dd, *J* = 8.6, 4.2 Hz, 3-H_Q), 7.48 (1H, d, *J* = 8.5 Hz, 6-H_Q), 7.38 (1H, dd, *J* = 7.9, 1.3 Hz, 10′-H_{Ar}), 7.27 (1H, td, *J* = 7.6, 1.9 Hz, 8′-H_{Ar}), 7.25 (1H, d, *J* = 8.5 Hz, 7-H_Q), 7.21 (1H, td, *J* = 7.9, 1.3 Hz, 9′-H_{Ar}), 7.15 (1H, dd, *J* = 7.5, 1.9 Hz, 7′-H_{Ar}), 5.61 (2H, s, 1′-CH_2), 5.51 (2H, s, 5′-CH_2). ^{13}C-NMR (101 MHz, $CDCl_3$): δ 153.02, 149.87, 143.96, 140.78, 133.63, 133.23, 132.18, 130.57, 130.43, 130.03, 127.68, 127.14, 126.56, 123.83, 122.89, 122.46, 110.10, 63.06, 51.61.

4. Conclusions

We have successfully synthesized a new compound 5-chloro-8-{[1-(2-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl]methoxy}quinoline through a common three-step procedure from 5-chloro-8-hydroxyquinoline using *O*-propargylation reaction/copper-catalyzed 1,3-dipolar cycloaddition sequence. The triazolquinoline hybrid that was synthesized in our work is an interesting biomodel for pharmacological agents' research.

Supplementary Materials: The following are available online, FT-R, ^{1}H-, ^{13}C-NMR, and GC-MS for compound (**5**).

Author Contributions: L.K.L.P. conceived the experiments; V.V.K. designed the experiments. Both authors analyzed the data and wrote the paper.

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Conflicts of Interest: The authors declare no conflict of interest. The founding sponsors had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results.

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