

Short Note

2-(4-Chlorophenyl)-4-(3,4-dimethoxy-phenyl)-6-methoxy-3-methylquinoline

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Abstract: A 2,4-diarylquinoline derivative, 2-(4-chlorophenyl)-4-(3,4-dimethoxyphenyl)-6-methoxy-3-methylquinoline, was synthesized in a conventional two-step procedure from *p*-anisidine, *p*-chlorobenzaldehyde and methyl isoeugenol as available starting reagents through a sequence of BF₃·OEt₂-catalyzed Povarov cycloaddition reaction/oxidative dehydrogenation aromatization processes under microwave irradiation conditions in the presence of a green oxidative I₂-DMSO system. The structure of the compound was fully characterized by FT-IR, ¹H and ¹³C-NMR, ESI-MS, and elemental analysis. Its physicochemical parameters (Lipinski's descriptors) were also calculated using the Molinspiration Cheminformatics software. The diarylquinoline molecule obtained is an interesting model with increased lipophilicity and thus permeability, an important descriptor for quinoline-based drug design. Such types of derivatives are known for their anticancer, antitubercular, antifungal, and antiviral activities.

Keywords: 2,4-diarylquinoline; methyl isoeugenol; Povarov reaction; oxidative dehydrogenation aromatization process; Lipinski's descriptors



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1. Introduction

Quinoline and its derivatives are of imperative significance to medicinal and agricultural chemistry, exhibiting a broad array of exciting biological properties [1–5]. In particular, diaryl-substituted quinoline scaffolds are an integral component of various bioactive agents, displaying a wide range of biological activity, such as antithyroid cancer, antifungal, analgesic, antimalarial, antibacterial, anti-inflammatory, anti-tuberculosis, and antiproliferative activity, as well as inhibitory properties against a diverse set of important enzyme targets, such as EGFR/FAK kinase, Human Ecto-5'-nucleotidase, cyclooxygenase-2, etc. [6–11]. Among them, 2,4-diarylquinolines have been proven to be especially important because of their potential biological activity (Figure 1) [12–16]. Besides pharmacological activity, compounds containing a diarylquinoline substructure have found many applications in functional material chemistry [17–21].

Therefore, the synthesis and study of polyfunctionalized diarylquinolines are a continuous focus of interest. Aryl substitution on the quinoline skeleton may increase lipophilicity, thereby increasing cell permeability, which has displayed a significant effect on quinoline-based drug design. Hence, a large number of synthetic protocols are being constantly developed for the preparation of 2,4-diarylquinolines [15,22–27].

Considering the above-stated aspects, and as a continuation of our efforts in the preparation of new bioactive quinoline-based molecules [27–30], we designed, synthesized, and characterized the above-mentioned 2-(4-chlorophenyl)-4-(3,4-dimethoxyphenyl)-6-methoxy-3-methylquinoline. Thus, in this work, we describe a practical method for the synthesis of the title compound using a one-pot three-component strategy/oxidative dehydrogenation aromatization process sequence through the reaction between arylamine,

benzaldehyde, and activated (methyl isoeugenol) by using $\text{BF}_3 \cdot \text{OEt}_2$ as a homogeneous catalyst and a microwave-assisted aromatization reaction with the oxidative I_2 -DMSO system. The drug-like nature of the final product is also investigated by predicting its pharmacokinetic properties.

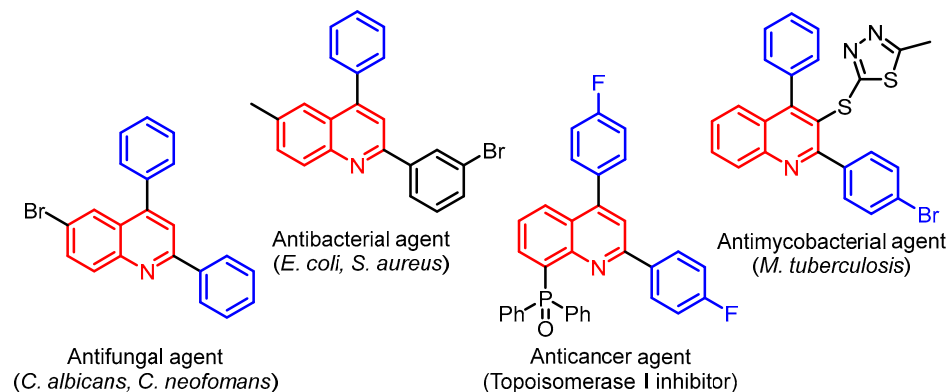
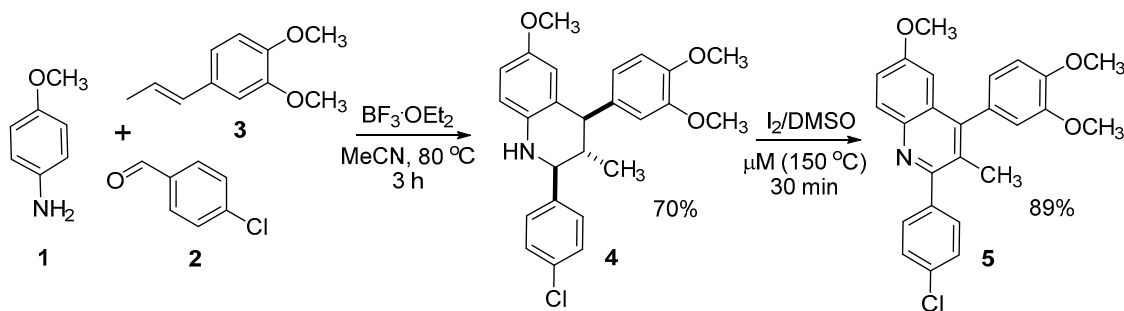


Figure 1. Structure of pharmacological agents based on the 2,4-diarylquinoline skeleton.

2. Results and Discussion

The title quinoline derivative (**5**) was easily prepared through a conventional two-step procedure from commercially available *p*-anisidine (**1**), *p*-chlorobenzaldehyde (**2**), and methyl isoeugenol (**3**) as an activated dienophile, using a $\text{BF}_3 \cdot \text{OEt}_2$ -catalyzed three-component cycloaddition reaction (Povarov reaction) [31,32] to give *cis*-2,4-diaryl-*r*-3-methyl-1,2,3,4-tetrahydroquinoline (**4**) [33], which was subjected to a dehydrogenation aromatization process under microwave irradiation conditions in the presence of a green oxidative I_2 -DMSO system [34,35], which allowed us to obtain the desired target 2,4-diarylquinoline molecule (**5**) as a white stable powder with a high degree of purity and yield (89%) (Scheme 1).



Scheme 1. Synthesis of 2-(4-chlorophenyl)-4-(3,4-dimethoxyphenyl)-6-methoxy-3-methylquinoline (**5**) from commercially available *p*-anisidine (**1**), *p*-chlorobenzaldehyde (**2**), and methyl isoeugenol (**3**) using Povarov cycloaddition reaction/oxidative dehydrogenation aromatization sequence.

The structural elucidation of the compound (**5**) was achieved based on spectroscopic data, and the results are presented in the experimental section and in the electronic supporting information (ESI). Analyzing its IR spectrum (ESI, Figure S7), we could note the disappearance of bands corresponding to NH tension (3332 cm^{-1}) and vibrational peaks at 1023 cm^{-1} (C–N) and 808 cm^{-1} (N–H) of the tetrahydroquinoline precursor (**4**) (ESI, Figure S1). Instead of this, –C=N– stretching at 1619 cm^{-1} and strong additional –C=C– stretching within the zone at $1560\text{--}1480\text{ cm}^{-1}$ were also observed, confirming the success of the aromatization of the system. The structure of (**5**) was verified by ^1H , ^{13}C NMR, and DEPT-135 spectra (Figures S8 and S9). Observing the ^1H -NMR spectrum, from high fields a singlet could be observed at 2.18 ppm corresponding to the signal from the methyl group at C-3. It was also noted that its multiplicity and position had changed compared

to that of the tetrahydroquinoline precursor (**4**) (ESI, Figures S2–S4). At lower fields, the signals at 3.75, 3.91, and 4.02 ppm corresponded to the methoxy groups which did not undergo any significant alteration. On the other hand, in the aromatic region, a doublet could be observed at 8.05 ppm ($J = 9.1$ Hz), which corresponded to the 8-H proton since it was the most unprotected proton of the molecule. The data provided by the COSY spectrum revealed that the signal at 7.33 ppm ($J = 9.1, 2.8$ Hz) corresponded to the 7-H proton; furthermore, the multiplicity and the coupling constants corroborate this fact. The signal at 6.74 ppm ($J = 2.8$ Hz) agreed with the 5-H proton since it had a coupling constant equal to that of the 7-H proton with which it was coupling, as expected given the structure of the molecule. Analyzing the same signal pattern and taking the coupling constants as a reference, it was possible to assign the signals at 7.07 ppm ($J = 8.1$ Hz), 6.88 ppm ($J = 8.1, 1.9$ Hz), and 6.83 ppm ($J = 1.9$ Hz) to the 5'-H, 6'-H, and 2'-H protons of the C-4-aryl ring, respectively. Finally, the signals at 7.57 ppm and 7.47 ppm corresponded to the equivalent 3''-H(5''-H) and 2''-H(6''-H) protons of the C-2-aryl ring, respectively (Figure S8).

To complete the characterization, the ^{13}C -NMR and DEPT-135 spectra shown in Figure S9 were analyzed. The signals located at 157.7, 157.0, 149.1, 148.5, 146.6, 142.4, 140.0, 134.0, 130.2, 128.3, and 127.0 ppm in the ^{13}C -NMR spectrum disappeared in the DEPT-135 spectrum, from which it could be concluded that these correspond to the 11 quaternary carbons of the molecule. The signals at 130.9, 130.5, 128.4, 121.6, 121.0, 112.3, 111.4, and 104.0 ppm corresponded to the CH_{Ar} carbons, among which the signals at 130.5 and 128.4 ppm corresponded to the two equivalent carbon signals of the molecule. In total, 23 signals could be observed, which was in line with our expectations due to the aromatic 2,4-arylquinoline structure. The mass spectrum also confirmed the condensed formula of the target product (**5**): the molecular ion (M^+) at $m/z = 419.59$, corresponding to its mass, was quite intensive, exhibiting the isotopic contribution of ^{37}Cl in the ratio of 1:3 ($^{37}\text{Cl}/^{35}\text{Cl}$). In general, the mass spectrum presented a poor fragmentation pattern (ESI, Figure S10), which is characteristic of heteroaromatic compounds.

Given that the pharmacological activity of organic molecules is strictly related to their hydrophilic/lipophilic nature, we easily calculated some of the physicochemical properties (molecular weight, lipophilicity (LogP), hydrogen bond acceptor and donor properties, polar surface area and rotatable bonds, and so-called Lipinski descriptors [36]) of the title compound and its closest precursor. Calculations were performed using the Molinspiration software, available online [37]. Exploring the physicochemical properties obtained in the *in silico* study for the target 2,4-diarylquinoline compound (**5**) and its 2,6-diaryl-tetrahydroquinoline precursor (**4**), we could note that these molecules possessed a more pronounced lipophilic character (cLogP 6.59 and cLogP 5.86, respectively) (Table S1). This particular descriptor was above the lipophilicity optimum interval ($0 < \text{LogP} < 3$). This means that high lipophilic parameters could compromise the compounds' absorption properties. On the other hand, both (tetrahydro)quinoline compounds (**4** and **5**) could achieve good hematoencephalic barrier permeation according to Veber's rules (the total molecular polar surface area, $\text{TPSA} < 140 \text{ \AA}^2$) [38] (Table S1). Although the synthesized compounds did not meet the Lipinski "rule of five" (RO5), failing in terms of the lipophilicity parameter, they are important and interesting models for the development of new antifungal, anticancer, and above all antibacterial/antitubercular agents. These latter agents exhibit a specific physicochemical profile that usually differs from other drugs, i.e., they have higher molecular weight, larger total polar surface area, and lesser lipophilicity as compared to other drugs utilized for human diseases [29,39].

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 Infracum spectrophotometer (FT-02, Lumex Co., Solon, OH, USA) in KBr. ^1H -NMR spectra were recorded on a 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)] (for comp. (4)). Mass spectrum of comp. (5) was obtained in ultrascan mode using a Hitachi LaChrom Elite HPLC liquid chromatography instrument coupled to a Bruker Daltonics AmaZon-X mass-selective detector equipped with electrospray ionization (ESI) in positive mode and a quadrupole ion trap (QIT) analyzer. 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's progress was monitored using thin-layer chromatography on a Silufol UV254 TLC aluminum sheet (Merck KGaA, Darmstadt, Germany).

3.2. Synthesis of 2-(4-chlorophenyl)-4-(3,4-dimethoxyphenyl)-6-methoxy-3-methylquinoline (5)

Step 1. In a clean, dry 20 mL vial, 0.39 g (2.80 mmol) of aniline (1) and 0.34 g (2.80 mmol) of aldehyde (2) were added, followed by 3 mL of acetonitrile. The mixture was stirred for 15 min at room temperature, and then 0.40 g (2.80 mmol) of $\text{BF}_3 \cdot \text{OEt}_2$ was added, followed by 0.50 g (2.80 mmol) of methyl isoeugenol (3) dropwise. The vial was sealed, and the system was subjected to heating in an oil bath at 80 °C for 3 h, monitoring the progress of the reaction by thin-layer chromatography (TLC). Once the reaction was complete, liquid–liquid extraction was carried out with dichloromethane (3×30 mL) and the crude product of the reaction was purified by column chromatography using mixtures of petroleum ether–ethyl acetate (10:1), thus obtaining the pure tetrahydroquinoline precursor (4) as a white, crystalline solid (70%). Mp: 201–202 °C; $R_f = 0.5$ (1:1 petroleum ether/ethyl acetate); IR (KBr, disk): 3332 $\nu(\text{NH})$, 2959 $\nu(\text{O-CH}_3)$, 2826 (CH Aliphatic), 1259 $\nu(\text{C-O})$, 808 $\nu(\text{NH})$ cm^{-1} . ^1H NMR (400 MHz, CDCl_3) $\delta(\text{ppm})$ 7.40 (2H, d, $J = 8.5$ Hz, H_{Ar}), 7.36 (2H, d, $J = 8.5$ Hz, H_{Ar}), 6.84 (1H, d, $J = 8.1$ Hz, H_{Ar}), 6.80 (1H, dd, $J = 8.2, 1.9$ Hz, H_{Ar}), 6.69 (1H, d, $J = 1.9$ Hz, H_{Ar}), 6.64 (1H, ddd, $J = 8.7, 2.9, 0.8$ Hz, H_{Ar}), 6.52 (1H, d, $J = 8.6$ Hz, H_{Ar}), 6.23 (1H, dd, $J = 2.9, 1.1$ Hz, H_{Ar}), 4.07 (1H, d, $J = 9.9$ Hz, 2-H), 3.90 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.73 (1H, d, $J = 10.9$ Hz, 4-H), 3.61 (3H, s, OCH_3), 2.17 (1H, m, 3-H), 0.59 (3H, d, $J = 6.5$ Hz, CH_3). ^{13}C -NMR (101 MHz, CDCl_3) $\delta(\text{ppm})$ 152.2, 149.1, 147.7, 141.3, 139.0, 136.6, 133.4, 129.2 (2), 128.7 (2), 126.9, 122.0, 115.8, 114.7, 111.8, 111.0, 113.0, 113.0, 63.6, 55.9, 55.8, 55.7, 52.4, 41.8, 16.4. MS m/z (%): 425.49 (6), 424.50 (32), 423.50 (M^+ , 30), 422.50 (100), 421.50 (16), 388.55 (10). Anal. Calcd. (%) for $[\text{C}_{25}\text{H}_{26}\text{ClNO}_3]$: C, 70.83; H, 6.18; N, 3.30; found (%): C, 70.66; H, 6.25; N, 3.37.

Step 2. In a clean and dry 20 mL vial, 0.59 g (1.40 mmol) of comp. (4) was added and 3 mL of dimethylsulfoxide was added. Subsequently, 0.35 g (1.40 mmol) of molecular iodine (I_2) was added and the vial was sealed and placed inside a Biotage Initiator+[®] microwave reactor. The reaction system was subjected to heating with microwave energy for 30 min. Once the reaction was complete, liquid–liquid extraction was carried out with ethyl acetate (3×30 mL) and the crude product of the reaction was purified by column chromatography using mixtures of petroleum ether–ethyl acetate (10:1), thus obtaining the quinoline (5) as a white, crystalline solid (89%). Mp: 178–179 °C; $R_f = 0.4$ (1:1 petroleum ether/ethyl acetate); IR (KBr, disk): 3077 $\nu(\text{C}_{\text{Ar}}\text{-H}_{\text{Ar}})$, 2959 (OCH_3), 2836 (CH_3), 1619 $\nu(\text{C=N})$, 1253 (C-O) cm^{-1} . ^1H -NMR (400 MHz, CDCl_3) $\delta(\text{ppm})$ 8.05 (1H, d, $J = 9.2$ Hz, H_{Ar}), 7.57 (2H, m, H_{Ar}), 7.47 (2H, m, H_{Ar}), 7.33 (1H, dd, $J = 9.2, 2.8$ Hz, H_{Ar}), 7.07 (1H, d, $J = 8.1$ Hz, H_{Ar}), 6.88 (1H, dd, $J = 8.1, 1.9$ Hz, H_{Ar}), 6.83 (1H, d, $J = 1.9$ Hz, H_{Ar}), 6.74 (1H, d, $J = 2.8$ Hz, H_{Ar}), 4.01 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 2.18 (3H, s, CH_3). ^{13}C -NMR (101 MHz, CDCl_3) $\delta(\text{ppm})$ 157.7, 157.0, 149.1, 148.5, 146.6, 142.4, 140.0, 134.0, 130.9, 130.5 (2), 130.2, 128.4 (2), 128.3, 121.0, 127.0, 112.3, 111.4, 104.0, 56.0, 55.9, 55.4, 18.6. ESI-MS m/z (%): 667.73 (38), 633.64 (28), 421.59 (30), 419.59 (M^+ , 100). Anal. Calcd. (%) for $[\text{C}_{25}\text{H}_{22}\text{ClNO}_3]$: C, 71.51; H, 5.28; N, 3.34; found (%): C, 71.46; H, 5.35; N, 3.27.

4. Conclusions

We have successfully synthesized a new compound, 2-(4-chlorophenyl)-4-(3,4-dimethoxyphenyl)-6-methoxy-3-methylquinoline, using a one-pot three-component strategy/dehydrogenation aromatization process sequence through the reaction between arylamine, benzaldehyde, and activated (methyl isoeugenol) by using $\text{BF}_3 \cdot \text{OEt}_2$ as a homogeneous catalyst and a microwave-assisted aromatization reaction with the green oxidative I_2 -DMSO system. The 2,4-diarylquinoline derivative that was synthesized in our work is an interesting biological model for pharmacological agent research, especially regarding antibacterial and antifungal drug design.

Supplementary Materials: The following are available online, FT-R, ^1H -, ^{13}C -NMR, and GC-MS for compounds (4) and (5).

Author Contributions: D.A.R.E. and C.E.P.G. conceived the experiments; V.V.K. designed the experiments and wrote the paper. All three authors analyzed and discussed the results and data. All authors have read and agreed to the published version of the manuscript.

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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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