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Short Note

[4-(3,4-Dimethoxyphenyl)-3,6-dimethyl-2-phenyl-3,4-dihydroquinolin-1(2*H*)-yl)](furan-2-yl)methanone

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Abstract: A *N*-(2,4-diaryltetrahydroquinolin-1-yl) furan-2-carboxamide derivative, [4-(3,4-dimethoxyphenyl)-3,6-dimethyl-2-phenyl-3,4-dihydroquinolin-1(2*H*)-yl)](furan-2-yl)methanone, was synthesized in a two-step procedure from *p*-toluidine, benzaldehyde, and *trans*-methyl-isoeugenol as commercial starting reagents through a sequence of Povarov cycloaddition reaction/*N*-furoylation processes. The structure of the compound was fully characterized by IR, ^{1}H, ^{13}C-NMR, and X-ray diffraction data. Such types of derivatives are known as relevant therapeutic agents exhibiting potent anticancer, antibacterial, antifungal, anti-inflammatory, and immunological modulator properties.

Keywords: 2,6-diaryl-tetrahydroquinolines; *trans*-methyl-isoeugenol; green Povarov reaction; deep eutectic solvents; *N*-furoylation; *N*-(tetrahydroquinolin-1-yl) furancarboxamides

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1. Introduction

The tetrahydroquinoline (THQ) moiety is present in various natural products [1–5], which exhibit a broad range of biological activities; it is used in the production of new materials, and it is an important precursor for more complex molecules with bio-utilities [6–9]. Due to these reasons, interest in small THQ molecules and their *N*-acyl derivatives has remained, mainly to understand biological processes, as they are pharmacologically relevant therapeutic agents (Figure 1). In particular, *N*-(tetrahydroquinolin-1-yl) amide compound **A** can be used as NF-κB inhibitors, which could be useful in anticancer drug research; additionally, retinoid nuclear modulators **B** are important agents for the treatment of metabolic and immunological diseases, and lipopolysaccharide (LPS)-induced inflammatory mediators **C** and **D** might have a beneficial impact on various brain disorders where neuroinflammation involving microglial activation plays a crucial role in the pathogenesis of these diseases [10–12]. Additionally, nicainoprol **E**, a THQ-based 3-pyridinyl amide derivative, is an antiarrhythmic drug [13,14]. On the other hand, furan-2-carboxamide derivatives exhibited interesting antihyperlipidemic, anti-breast cancer, antibacterial, antimicrobial, and antifungal activities [15–18]. Therefore, the importance of the generation of new pathways for the rapid and efficient construction of molecular libraries based on bioactive natural products has pushed our research toward new synthetic methods in order to construct the privileged 1,2,3,4-THQ core. Due to the great importance of the THQ nucleus in the search for drug candidates and medicinal chemistry, the development of new synthetic methodologies continues to be an active area. The 1,2,3,4-THQ ring can be formed through various synthetic strategies that involve the reduction process of the respective quinoline derivatives [14,19–21] or the THQ ring construction from aminobenzene precursors using a formation of one or two bounds simultaneously or alternately. Out of the set of tactics, the Povarov reaction is undoubtedly the most powerful tool in the generation of *N*-heterocycle systems, with excellent *regio*-, *diastereo*-selective control [22–29]. The preparation of *N*-acylated THQs through the *N*-acylation reaction is the most widely used

method for the formation of amide bonds [30–32]. However, the examples regarding the synthesis and characterization of *N*-acylated 2,6-diaryl-3-methyl-THQs are still very scarce.

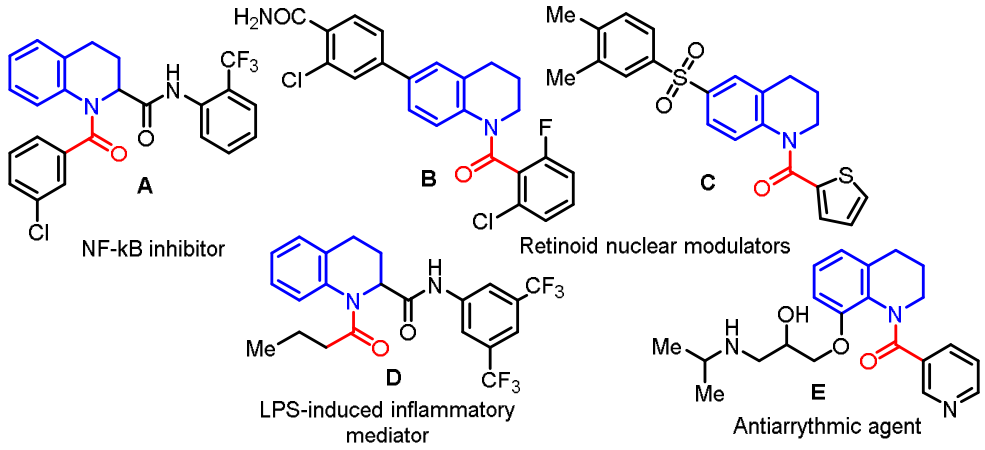
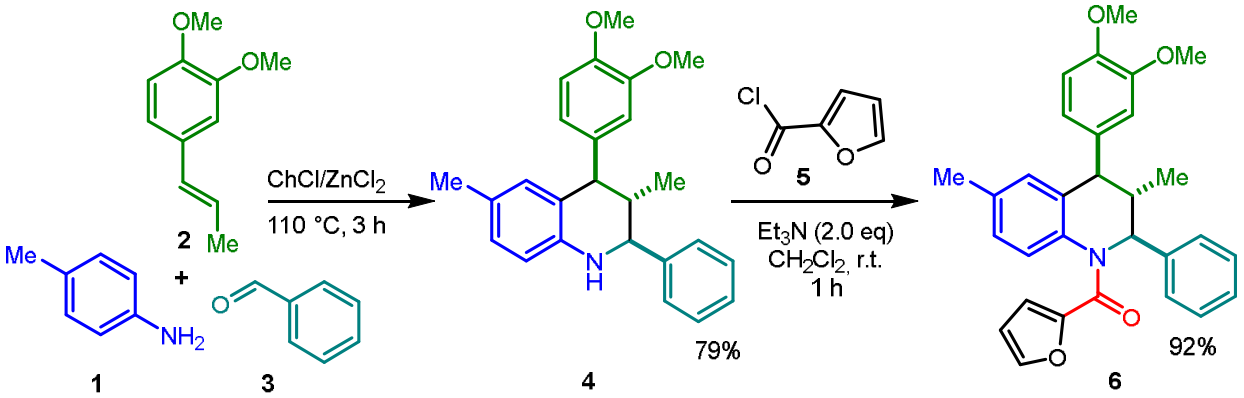


Figure 1. Structure of pharmacological agents based on the *N*-(tetrahydroquinolin-1-yl) amide skeleton.

Considering the above-stated aspects, and as a continuation of our efforts to prepare new bioactive quinoline-based molecules, we designed, synthesized, and characterized the above-mentioned, [(4-(3,4-dimethoxyphenyl)-3,6-dimethyl-2-phenyl-3,4-dihydroquinolin-1(2*H*)-yl)](furan-2-yl)methanone. Therefore, in this work, we describe a practical method for the synthesis of the title compound using a one-pot, three-component strategy/*N*-furoylation process sequence through the reaction between arylamine benzaldehyde and activated olefin (methyl isoeugenol) by using choline chloride-zinc chloride deep-eutectic solvent (ChCl-$ZnCl_2$, DES) as a homogeneous deep eutectic mixture, which serves as a promotor and a green reaction medium to give the 2,4-diAr-3-Me-THQ precursor, and its subsequent *N*-acylation reaction with the respective acid chloride.

2. Results and Discussion

The title *N*-(tetrahydroquinolin-1-yl) furan-2-carboxamide derivative (**6**) was easily prepared through a conventional two-step procedure from commercially available *p*-toluidine (**1**), *trans*-methyl-isoeugenol (**2**) as activated dienophile, and benzaldehyde (**3**), following a previously reported method by our group [29], in which the selected DES are used as the reaction medium using a three-component Povarov reaction as a key step of the procedure (Scheme 1).



Scheme 1. Synthesis of 4-(3,4-dimethoxyphenyl)-3,6-dimethyl-2-phenyl-3,4-dihydroquinolin-1(2*H*)-yl)(furan-2-yl)methanone (**6**) from *p*-toluidine (**1**), *trans*-methylisoeugenol (**2**), and benzaldehyde (**3**), using Povarov cycloaddition reaction under DES medium (step 1) and *N*-furoylation (step 2).

In this case, the $ChCl/ZnCl_2$ eutectic mixture readily promoted the formation of 2,4-diaryl-3-Me-1,2,3,4-THQ intermediate (**4**), which was easily obtained in good yield (79%) as a white solid in only 3 h of reaction. It is noteworthy that the isolated THQ product is a diastereoisomer with all three equatorial C-2-Ar,C-3-Me,C-4-Ar substituents (2e,3e,4e-form), where the Ar groups are in the *cis*-configuration with respect to each other [9,33]. Its *N*-furoylation reaction under mild conditions using 2-furoyl chloride (**5**) and triethylamine as a base in dichloromethane allowed us to obtain the desired target *N*-(2-furoyl)-THQ molecule (**6**) in excellent yield (92%) as a white crystalline solid (Scheme 1).

The structural elucidation of the compound (**6**) was achieved based on spectroscopic data, and the results are presented in the experimental section and in the electronic supporting information (ESI). In its infrared spectra, the different absorption bands associated with the functional groups present in its structure are recorded (ESI, Figure S5). C_{Ar}-H and C=C-H vibrations could be observed at 3015 cm^{-1}. Methoxy substituents of the aromatic rings could be appreciated due to the symmetric and asymmetric strain vibration bands in the region between 2979–2831 cm^{-1}. C=O and C=C strain vibrations appeared in 1638 and 1578 cm^{-1}, respectively. Asymmetric and symmetric tension vibrations of the C-O bond were shown in 1251 and 1029 cm^{-1}, respectively.

The structure of (**6**) was verified by ^1H, ^{13}C, and ^{13}C-APT NMR spectra (ESI, Figures S6–S8). First, the analysis of the ^1H-NMR spectra indicated the presence of the signals generated by the methyl hydrogens of the 3,6-dimethyl (0.97 and 2.21 ppm) and the methoxy (3.87–3.95 ppm) groups in the 2,4-diAr-3-Me-THQ skeleton. Secondly, the three different signals from THQ aliphatic hydrogens, 2-H, 3-H, and 4-H, were observed: the doublet at 5.13 ppm (^3J = 8.7 Hz), doublet of doublets of doublets (ddd) at 2.21 ppm (^3J = 11.6, 8.6, 6.5 Hz), and a doublet at 3.63 ppm (^3J = 11.6 Hz), respectively (ESI, Figure S6). Comparing the vicinal coupling constants ^3J between hydrogens 3-H and 4-H (11.6 Hz), and 2-H and 3-H (8.6–8.7 Hz) confirmed the stereochemistry given by the *trans* arrangement of these in the THQ ring, and thus, the stereochemistry of the THQ fragment. In the aromatic region of the spectrum, the following signals are observed in their order: at 6.29 ppm, there is a doublet of doublets corresponding to hydrogen 4″ in the furan ring, and it has coupling constants of 3.5 and 1.7 Hz. At 6.39, a doublet corresponding to the hydrogen 3″ with a coupling constant of 3.5 Hz is found. The signals of the hydrogens 7-H, 8-H, 5′-H, 6′-H, 5″-H, *m*-H, *m*′-H, *o*-H, *o*′-H, 5-H, and 2′-H are in the region of 6.60 to 7.32 ppm.

To complete the characterization, the ^{13}C-NMR and ^{13}C-APT spectra, shown in Figures S7 and S8, were analyzed. The signals located at 159.39, 149.30, 148.11, 147.71, 143.73, 138.60, 135.90, 135.60, and 131.47 ppm in the positive phase of the ^{13}C-APT NMR spectrum belong to the nine signals from the quaternary carbons of the molecule. Whereas the signals at 128.43, 127.69, 127.22, 127.18, 126.78, 125.31, 116.31, 111.46, and 111.02 corresponded to the C_{Ar}-H, the signals at 65.73, 56.10, 55.98, 49.52, 47.48, 21.46, and 18.21 ppm were appropriate to methoxy carbons and C-H from the aliphatic core of the THQ (**6**). In total, 26 signals were observed, which was in line with our expectations due to the structure of the *N*-furoyl-THQ molecule (**6**).

All the proton resonance data mentioned above indicated that the final product has the THQ half-chair conformation, where the Ar substituents are in the *cis*-configuration with each other, occupying the equatorial arrangement. The 3-Me group is also in the equatorial disposition; therefore, this group is in the *trans*-configuration with respect to both Ar groups, and therefore it follows that the *N*-furoyl-THQ possesses all three equatorial substituents and is a *trans*-2,4-diaryl-*r*-3-methyl-diastereoisomer, like the NH-THQ precursor (**4**).

Finally, crystals of compound (**6**) obtained from slow chloroform evaporation as prepared were directly suitable for X-ray diffraction, and the resulting molecular structure is shown in Figure 2A. The X-ray diffraction analysis evidenced the stereochemistry of the tetrahydroquinoline ring formed through the high stereospecificity of the Povarov reaction in this implemented methodology, for which the substituents at positions C-2, C-3, and C-4 of the aliphatic part of the THQ skeleton are found in *pseudo*-equatorial arrangements.

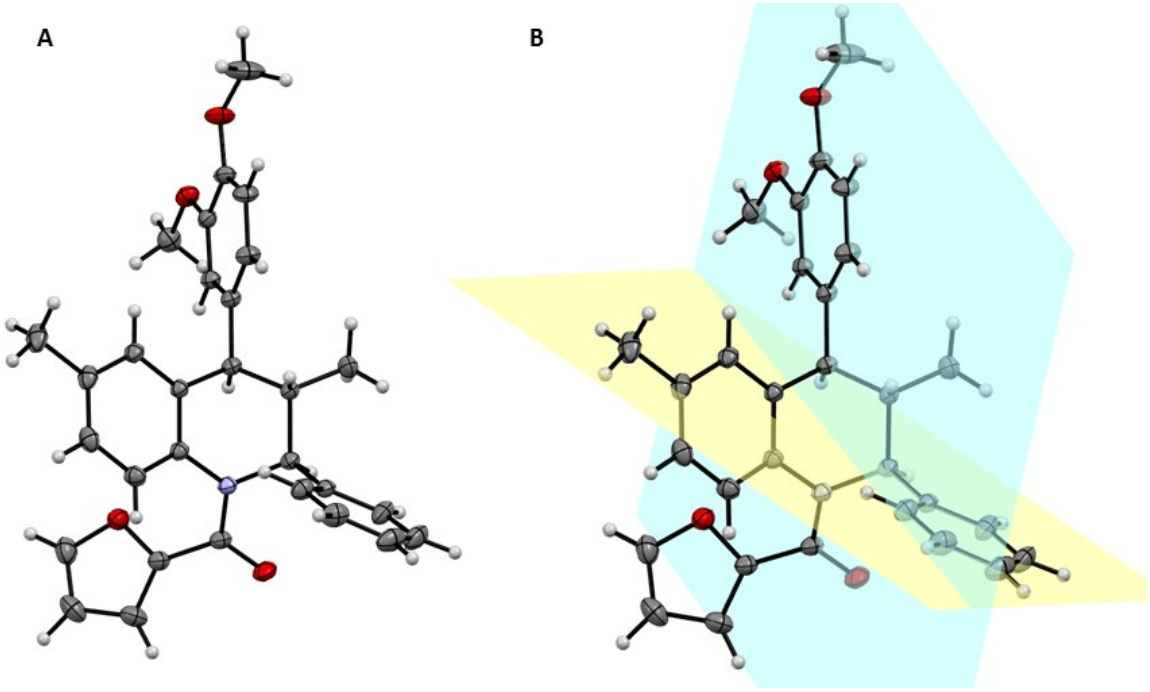


Figure 2. (**A**) ORTEP view of the molecular structure of compound (**6**) showing the stereochemistry of the THQ ring with the two aromatic rings in *pseudo*-equatorial conformation (thermal ellipsoids at 25% level). (**B**) Planes between aromatic rings that are part of its structure. CCDC 2184176 deposition number.

The arrangement of the aromatic ring substituents that make up the molecular carcass of compound (**6**) can be seen by adding a plane to each of them. Figure 2B displays the planes that go through each of these aromatic rings, i.e., the ring from the isoeugenyl fragment, and the benzene ring in position C-2 of the THQ skeleton.

3. Materials and Methods

3.1. Chemical Analysis

The reagents and solvents used in the synthesis of the intermediate and final compounds were of purity grade for synthesis. The composition and monitoring of the reactions, as well as the preliminary analysis of the purity of the synthesized compounds, were carried out by thin-layer chromatography (TLC) on Silufol UV254 plates of 0.25 mm thickness, revealed in a UV light chamber of 254 nm or in an ethanolic solution of phosphomolybdic-sulfuric acids. The melting points of the products were determined in a Fisher–Jöns melting point apparatus and the values were not corrected, reporting the average of three measurements. Infrared spectra (FT–IR) were obtained on a Thermo Scientific Nicolet iS50 FT–IR spectrophotometer with Fourier transform, with attenuated total reflectance (ATR) module, acquisition range: 4000–400 cm^{-1} (256 scans, resolution of 2 cm^{-1}). The acquisition of nuclear magnetic resonance spectra ^{1}H, ^{13}C–APT, and 2D variants was performed in a Bruker Avance–400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) using deuterated chloroform ($CDCl_3$, 99.8% Merck®) as the solvent. Chemical shift values (δ) are expressed in ppm. In ^{1}H-NMR spectra, the scale was adjusted from the residual chloroform signal (7.26 ppm). Similarly, the ^{13}C-APT spectra were scaled from the signal characteristic for the solvent ($CDCl_3$), and the phase of the signals was assigned as a (+) positive phase and (-) negative phase. The coupling constants (^{n}J) are described at *n* bonds and are given in Hz; the multiplicity of signals is expressed by the following abbreviations: (s) singlet, (d) doublet, (dd) doublet of doublets, (ddd) doublet of doublet of doublets, (t) triplet, and (m) multiplet.

The crystal data collection of compound (**6**) was done as follows: a colorless lath crystal (Et_2O) was used to record 3417 (CuKα radiation, θ_{max} =74.61 °) reflections with I > 2σ(*I*) on a Rigaku AF11 diffractometer. Accurate unit cell parameters were determined by the least-squares techniques from the θ values of 13,769 reflections, with a θ range of 3.96–74.61°. The final refinement converged with *R*1 = 0.188, *R*ω2 = 0.011 on F^2 for all data. The structure was solved by direct methods and refined by full-matrix least-squares against F^2 (SHELXL, Version 2014/7) [34,35]. The software used to prepare the material for publication was PLATON [36] and MERCURY. The data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/getstructures (accessed on 4 July 2022) with the CCDC 2184176 deposition number.

*3.2. Synthesis of [4-(3,4-Dimethoxyphenyl)-3,6-dimethyl-2-phenyl-3,4-dihydroquinolin-1(2H)-yl)](furan-2-yl)methanone (**6**)*

Step 1. Three-component Povarov reaction: In a clean, dry, 10 mL vial, choline chloride (ChCl, 8 mmol) and zinc chloride ($ZnCl_2$, 16 mmol) were added as a eutectic mixture. The mixture was heated at 110 °C to obtain a liquid media. Then, *p*-toluidine **1** (1 mmol), *trans*-methyl-isoeugenol **2** (1.5 mmol), and benzaldehyde **3** (1.5 mmol) were combined. Before 3 h of reaction time, the formation of 2,4-diaryl-tetrahydroquinoline **4** was confirmed by TLC. The reaction mixture was diluted with ethyl acetate and was washed with distilled water (50 mL). The reaction crude was placed in an Erlenmeyer flask over anhydrous sodium sulfate. Finally, the solvent was removed by distillation, and the organic residue that remained was purified by column chromatography on silica gel, using an isocratic mixture of ethyl acetate–petroleum ether at 20% as eluent. Yield = 79%. The spectral data of compound **4** is available in ESI.

Step 2. *N*-Furoylation reaction: In a clean, dry, 20 mL vial, THQ **4** (1 mmol), 2-furoylchloride **5** (2 mmol), triethylamine (2 mmol), and 5 mL of dichloromethane were added. The reaction was carried out at room temperature for 1 h. The solvent was removed by distillation, and crude was purified by column chromatography on silica gel using an isocratic mixture of ethyl acetate–petroleum ether at 30% as eluent. Compound **6** was obtained in a yield of 92% as a white solid, Mp = 194–195 °C, R*f* = 0.19 (30% ethyl acetate–petroleum ether). IR [ATR, $\overline{\nu}$ (cm^{-1})] = 3105, 2979, 2944, 2926, 2896, 2831, 1638, 1578, 1515, 1493, 1348, 1251, 1165, 1029, 751, 707. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm = 7.32–7.25 (m, 6H, *p*-H, 7-H, 8-H, 5′-H, 6′-H, 5″-H), 6.93 (t, *J* = 8.3 Hz, 2H, *m*-H, *m*′-H), 6.82 (t, *J* = 7.0 Hz, 2H, *o*-H, *o*′-H), 6.74 (s, 1H, 5-H), 6.60 (s, 1H, 2′-H), 6.39 (d, ^3J = 3.5 Hz, 1H, 3″-H), 6.29 (dd, ^3J = 3.5, 1.7 Hz, 1H, 4″-H), 5.13 (d, ^3J = 8.7 Hz, 1H, 2-H), 3.95 (s, 3H, 3′-OCH_3), 3.87 (s, 3H, 4′-OCH_3), 3.63 (d, ^3J = 11.6 Hz, 1H, 4-H), 2.27 (s, 3H, 6-CH_3), 2.21 (ddd, ^3J = 11.6, 8.6, 6.5 Hz, 1H, 3-H), 0.97 (d, ^3J = 6.5 Hz, 3H, 3-CH_3). ^{13}C-APT (100 MHz, $CDCl_3$) δ ppm = 159.39 (+), 149.30 (+), 148.11 (+), 147.71 (+), 143.91 (−), 143.73 (+), 138.60 (+), 135.90 (+), 135.60 (+), 131.47 (+), 128.43 (−), 127.69 (−), 127.22 (−), 127.18 (−), 126.78 (−), 125.31 (−), 116.31 (−), 111.46 (−), 111.02 (−), 65.73 (−), 56.10 (−), 55.98 (−), 49.52 (−), 47.48 (−), 21.46 (−), 18.21 (−). Anal. Calcd. (%) for [$C_{30}H_{29}NO_4$]: C, 77.07; H, 6.25; N, 3.00; found (%): C, 77.25; H, 6.12; N, 3.11. X-ray diffraction analysis data of furan-2-carboxamide (**6**) with the (2*S*,3*S*,4*R*)-configuration: Colorless crystal obtained from a slow chloroform evaporation, $C_{30}H_{29}NO_4$ (*MW* = 467.57 g/mol), triclinic space group P–1, unit cell dimensions: *a* = 9,9318(3), *b* = 12,1531(5), *c* = 12,3695(7) Å, α = 64,515(5)°, β = 79,358(4)°, γ = 70,990(3)°, *V* = 272,51(11) Å^3, *Z* = 2, T = 293 K.

4. Conclusions

We have successfully synthesized a new *N*-(tetrahydroquinolin-1-yl) furancarboxamide, [4-(3,4-dimethoxyphenyl)-3,6-dimethyl-2-phenyl-3,4-dihydroquinolin-1(2*H*)-yl)](furan-2-yl)methanone, as a 2e,3e,4e THQ diastereoisomer with an overall yield of 73%, using a two-step strategy of Povarov cycloaddition and *N*-furoylation process sequence through the reaction between *p*-toluidine, *trans*-methyl-isoeugenol, and benzaldehyde to achieve a tetrahydroquinoline core. The synthesized *N*-furoyl-THQ derivative is an inter-

esting biological model for pharmacological agent research, especially regarding anticancer and antibacterial or antifungal drug design.

Supplementary Materials: The following are available online, FT-IR, ^{1}H- and ^{13}C-NMR, and X-ray data (.CIF) for compounds (**4**) and (**6**).

Author Contributions: S.M.B.-C. and A.F.V.-M. conceived the experiments; V.V.K. designed the experiments; A.F.V.-M. and V.V.K. 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, analysis, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results.

Sample Availability: Samples of the compounds (**5**) and (**6**) are available from the authors.

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