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Short Note

4-(1*H*-Tetrazol-5-yl)-2-(*p*-tolyl)quinoline

Angelika Lásiková * and Daniel Végh

Department of Organic Chemistry, Institute of Organic Chemistry, Catalysis and Petrochemistry, Faculty of Chemical and Food Technology, Slovak University of Technology, Radlinského 9, 812 37 Bratislava, Slovakia; daniel.vegh@stuba.sk

* Correspondence: angelika.lasikova@stuba.sk

Abstract: The synthesis of 4-(1*H*-tetrazol-5-yl)-2-(*p*-tolyl)quinoline **4** as a possible modification of the biphenyltetrazole substructure of losartan **1** is described. The transformation of 2-(*p*-tolyl)quinoline-4-carbonitrile **3** to the corresponding tetrazole **4** was carried out by the reaction of trimethysilyl azide and dibutyltin oxide as a catalyst in refluxing toluene. The title compound (**4**) was characterized by IR, ^{1}H NMR, ^{13}C NMR, and HRMS.

Keywords: angiotensin II receptor antagonists; analog of losartan; 2,4-disubstituted quinoline; synthesis of tetrazolylquinoline

1. Introduction

Non-peptidic angiotensin II (AII) receptor antagonists, called angiotensin receptor blockers (ARBs), are a very popular group of antihypertensive drugs. They are highly effective human hypertension drugs with minimal side effects [1,2].

Intensive research into structure–activity relationships by DuPont Merck led to the synthesis of effective, specific, and orally active AII receptor antagonists, of which losartan **1** became the prototype [3,4].

The structure of **1** can be divided into two parts, the nitrogen heterocycle—(2-butyl-4-chloro-1*H*-imidazol-5-yl)methanol and the biphenyl-tetrazole moiety 2′-(5-tetrazolyl)-1,4-biphenyl (BPT) connected by a methylene group as a linker (Figure 1).

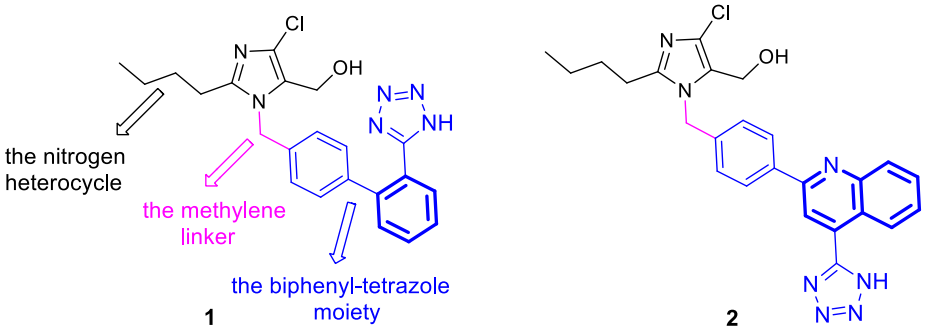

Figure 1. Structure of losartan **1** and a potential AII receptor antagonist with tetrazolylquinoline substructure **2**.

We decided to design several new modifications of the biphenyl part that could meet the prerequisites for binding to the receptor. We suggested a modification in which the terminal phenyl ring is replaced by a quinoline moiety, with the tetrazole group attached at the 4-position of the quinoline (structure **2**, Figure 1). Quinoline derivatives are an important class of structural motif that is posed with diverse chemotherapeutic activities like antimicrobial [5], antiviral [6], antimalarial [7], anti-inflammatory [8], and antibacterial [9–12]. The

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2-phenylquinoline-4-carboxamide derivatives have been identified as potent and selective non-peptide competitive agonists for human neurokinin-3 receptor [13].

Moreover, substituted quinolines attached through an oxygen, oxymethylene, sulfur, or methylenethio bridge to BPT moiety are known and useful as angiotensin II antagonists [14–17]. Quinoline ring also successfully replaced the central phenyl of BPT moiety and the resulting structure showed an excellent bioactivity [18].

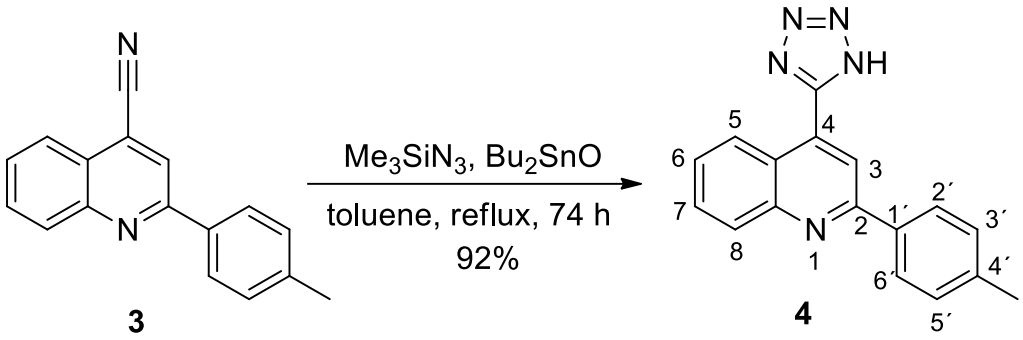
The tetrazole group acts as an isostere of a carboxylic acid, which provides greater metabolic stability and increased absorption compared to a carboxylic acid, and from this point of view, it has great importance in medicinal chemistry [19].

Herein, we want to report the preparation of the hitherto unknown 4-tetrazolyl derivative of quinoline **4** as a possible subunit of losartan-like structures.

2. Results and Discussion

Synthesis

The tetrazole **4** was synthesized by a method for the preparation of 5-substituted tetrazoles [20] from nitriles using trimethylsilyl azide in the presence of catalytic dialkyltin oxide in excellent yield 92% Scheme 1.



Scheme 1. Formation of tetrazole function in subunit **4** of losartan-like structure **2** from nitrile **3**.

This method has several advantages; the use of trimethylsilyl azide as the azide source greatly reduces the hazard posed by the in situ generation of hydroazoic acid. Sterically hindered tetrazoles are obtained in very good yields, and the separation of tetrazoles is very convenient since the reaction takes place in toluene, which can be easily distilled from the reaction mixture in contrast to classical conditions where DMF as a solvent is often used. By applying this method, the spectrally pure compound was obtained without further purification, which can be used directly in the subsequent reaction.

The nitrile **3** was prepared according to the described procedures (see Supplementary Materials) [21,22].

Tetrazole **4** was identified by IR, ^{1}H, ^{13}C NMR, and HRMS. The typical characteristic change in the nitrile functional group (CN) to tetrazole was manifested in IR spectra. The band of the CN group at 2227 cm^{-1} disappeared and the broad band appeared at 2800–2200 cm^{-1} characteristic for N-H in tetrazole and the weak band appeared at 1553 cm^{-1} caused by the vibration of the C=N bond in tetrazole.

3. Materials and Methods

3.1. General

The melting point (uncorrected) was determined on a Kofler hot-stage microscope. The FTIR spectra were obtained on a Nicolet 5700 spectrometer (Thermo Electron, Thermo Fisher Scientific, Waltham, MA, USA) equipped with a Smart Orbit (diamond crystal ATR) accessory using the reflectance technique (4000–400 cm^{-1}). The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Inova-AS600, (Varian, Inc., Paolo Alto, CA, USA) at 600 MHz and 150 MHz, respectively; chemical shifts (ppm) were referenced to the residual amounts of undeuterated solvent. High-resolution mass spectra (HRMS) were recorded on

an OrbitrapVelos mass spectrometer (Thermo Scientific, Waltham, MA, USA) with a heated electrospray ionization (HESI) source. The mass spectra (MS) were recorded on an MS 902 mass spectrometer using a direct injection system. The ionizing energy was maintained at 70 eV and the electron current was 100 μA.

3.2. Synthesis of 4-(1H-Tetrazol-5-yl)-2-(p-tolyl)quinoline (**4**)

To a solution of the nitrile **3** (1.34 g, 5.5 mmol) and trimethylsilyl azide (1.27 g, 11 mmol, 2 eq.) in anhydrous toluene (11 mL) was added dibutyltin oxide (0.14 g, 0.55 mmol, 0.1 eq.) and the mixture was refluxed for 74 h. The reaction mixture was concentrated in vacuo. The residue was dissolved in methanol and reconcentrated. The residue was then partitioned between ethyl acetate (25 mL) and 10% sodium bicarbonate solution (25 mL). The organic phase was extracted with an additional portion of 10% sodium bicarbonate solution (25 mL). The combined aqueous extracts were acidified to pH 2 with a 10% hydrochloric acid solution and then extracted with ethyl acetate (2 × 25 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated to give the crude product **4**. The crude product **4** was further purified by crystallization from water and isolated as a white solid (1.45 g, 92%), m.p. 234–235 °C, IR (ATR): 3000 (w), 2800–2200 (brs, γ(N-H), 2000–1650 (brs), 1596 (s), 1553 (w, tetrazole), 1512 (m), 1423(m), 1403 (m), 1304 (m), 1237 (m), 1183 (s), 811 (s), 762 (s) cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6, ppm): δ 8.79 (d, *J* = 8.3 Hz, 1H), 8.61 (s, 1H), 8.26 (d, *J* = 8.1 Hz, 2H), 8.20 (d, *J* = 8.3 Hz, 1H), 7.90 (t, *J* = 8.1 Hz, 1H), 7.74 (t, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 7.9 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6, ppm): δ 20.8, 118.9, 123.1, 125.6, 127.2, 127.8, 129.7, 129.8, 130.7, 135.1, 140.0, 148.3, 154.8, 155.7; HRMS (ESI) calcd for $C_{17}H_{13}N_5H^+$ $[M+H]^+$: 288.1244, found: 288.1244.

Supplementary Materials: The following supporting information can be downloaded online. Experimental procedure and IR spectrum, ^{1}H, and ^{13}C NMR spectrum for compound **3**; and IR spectrum, ^{1}H, and ^{13}C NMR spectrum for compound **4**.

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Data Availability Statement: The data are contained within the article and Supplementary Materials.

Conflicts of Interest: The authors declare no conflicts of interest.

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