

Short Note

Ethyl 6-Methyl-2-oxo-4-{4-[(1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy]phenyl}-1,2,3,4-tetrahydropyrimidine-5-carboxylate

Itamar Luís Gonçalves ¹, Gabriel Oliveira de Azambuja ¹, Leonardo Davi ¹,
Guilherme Arraché Gonçalves ¹, Luciano Porto Kagami ¹, Gustavo Machado das Neves ¹,
João Pedro Silveira ¹, Rômulo Faria Santos Canto ^{1,2} and Vera Lucia Eifler-Lima ^{1,*}

¹ Laboratório de Síntese Orgânica Medicinal (LaSOM[®]), Faculty of Pharmaceutical Sciences, Federal University of Rio Grande do Sul, Ipiranga Avenue, Porto Alegre, RS 2752, Brazil

² Laboratório de Química Medicinal de Compostos de Selênio (QMCSe), Federal University of Health Sciences of Porto Alegre, Sarmento Leite Street, Porto Alegre, RS 245, Brazil

* Correspondence: veraeifler@ufrgs.br; Tel.: +55-51-3308-5362

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Abstract: The Biginelli reaction is an acid-catalyzed, three-component reaction between an aldehyde, a hydrogen methylene active compound, and urea (or its analogue) and constitutes a rapid and easy synthesis of highly functionalized heterocycles. Synthesis of ethyl 6-methyl-2-oxo-4-{4-[(1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy]phenyl}-1,2,3,4-tetrahydropyrimidine-5-carboxylate, identified by our laboratory code LaSOM[®] 293, was achieved using the Biginelli reaction as the key step, followed by the Huisgen 1,3-dipolar cycloaddition in a convergent four-step route. The product LaSOM[®] 293 was obtained with a yield of 84%.

Keywords: Biginelli reaction; 3,4-dihydropyrimidinone; triazole; LaSOM[®] 293

1. Introduction

The synthesis of 3,4-dihydropyrimidinones (DHPMs) was reported by the Italian chemist Pietro Biginelli, in 1893, using the one-pot multicomponent reaction of benzaldehyde, urea, and ethyl acetoacetate and employing hydrochloric acid as the catalyst [1]. In recent decades, important advances in this field have been reported, allowing for the structural diversification of this heterocycle class. The structural diversity of this reaction renders it a powerful tool using very simple building blocks [2].

Furthermore, the pharmacological effect of DHPMs has been widely investigated, mainly focusing on anticancer drug development [3]. Monastrol is a DHPM identified as a kinesin-5 inhibitor, involved in the separation of genetic material during mitosis. The inhibition of this enzyme leads to cell cycle arrest at the G₂/M phase and activation of signaling ways, which leads to cellular apoptosis [4]. Recent investigations have reported that the monastrol derivatives with an aromatic ring at N1 position showed improved activity against rat and human glioma cell lines [5].

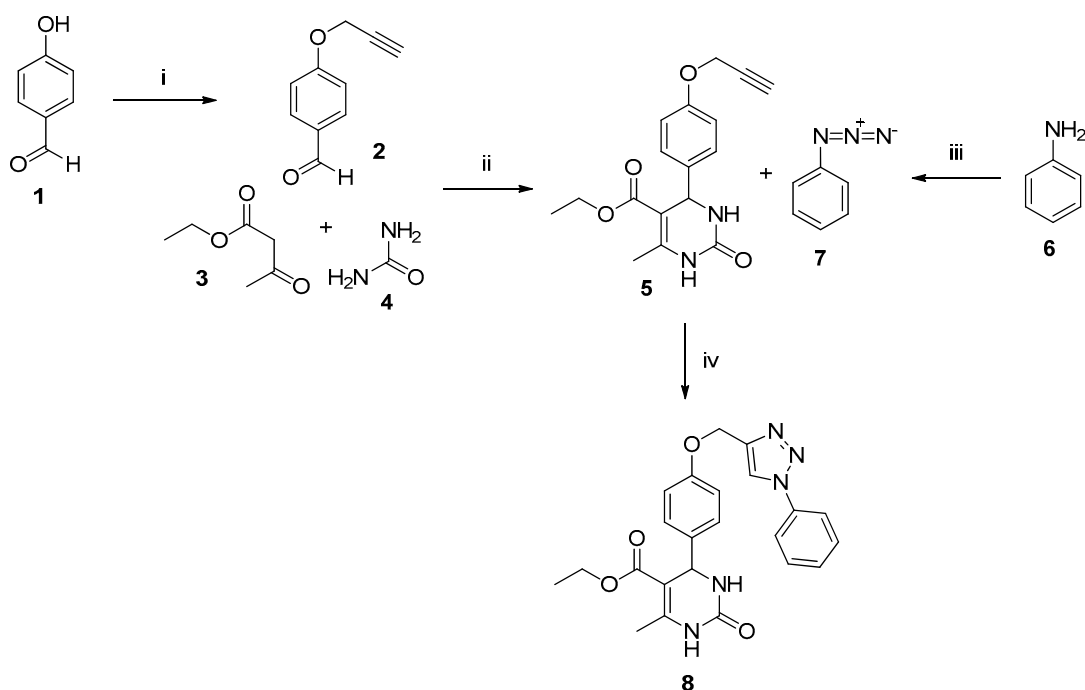
Triazole is another important scaffold in medicinal chemistry. This is due to its ability to interact with a wide number of receptors in biological systems through different non-covalent interactions, and thus exhibit versatile pharmacological profiles [6,7]. Another relevant aspect of 1,2,3-triazole is the ease with which it can be obtained from an azide and an alkyne using the Huisgen 1,3-dipolar cycloaddition [8]. Hybrid compounds have recently gained increased attention, combining parts of two pharmacophores in a single molecule [9]. The current study reports a four-step synthesis of the highly functionalized hybrid DHPM-triazole LaSOM[®] 293. This is part of an investigation to identify

novel compounds with anticancer properties using the Biginelli reaction followed by 1,3-dipolar cycloaddition.

2. Results and Discussion

The title compound was synthesized using the convergent route described in Scheme 1. The synthesis of hybrid triazole-dihydropyrimidinone started with the nucleophilic substitution reaction between 4-hydroxybenzaldehyde (**1**) and propargyl bromide in acetone reflux and potassium carbonate, yielding 4-(prop-2-yn-1-yloxy)benzaldehyde (**2**). The Biginelli reaction, catalyzed by *p*-toluenesulfonic acid, allowed the condensation of aldehyde (**2**) previously prepared, ethyl acetoacetate (**3**), and urea (**4**) leading to the already reported 3,4-dihydropyrimidinone (**5**) [10]. Compound (**5**) was used as the reagent in [3+2] cycloaddition with azide (**7**) previously prepared from aniline (**6**). The target compound LaSOM[®] 293 was obtained as an amorphous yellow solid in an 84% yield. Very similar compounds to those reported here were obtained in a previous work with similar yields [10,11].

The molecular structure of compound (**8**) was established by spectroscopic experiments, using ¹H and ¹³C NMR, HRMS, and infrared spectroscopy (the spectral data may be accessed in the Supplementary Materials). From the ¹H NMR spectra (Figure S3), two broad singlets of the NH proton of the DHPM core appeared at 7.67 ppm and 9.16 ppm. The triazole hydrogen produced a signal at 8.94 ppm, confirmed by HSQC experiment in Figure S5. The aromatic protons on the two benzene rings produced the next group of signals at 6.98–7.97 ppm. The pyrimidyl CH produced a signal at 5.11 ppm and near this signal, at 5.21 ppm, the methylene protons were localized between the triazole and the phenolic oxygen, in the form of a singlet. In addition, signals characteristic of DHPMs were observed at 2.24 ppm, the singlet of 6-methyl, and at 1.09 ppm and 3.98 ppm appeared a triplet and a quartet corresponding to the H₃CCH₂ system.



Scheme 1. Synthesis of hybrid 3,4-dihydropyrimidinone-triazole **8**. (i) K₂CO₃, acetone, reflux, propargyl bromide, 4 h 89%; (ii) TsOH 0.30 eq ethanol, reflux, 48 h 78%; (iii); HCl, water, NaNO₂, NaN₃ 90%; (iv) CuSO₄, *t*-butanol, water (1:1), MW 18 W, 70 °C, 15 min 84%.

3. Materials and Methods

3.1. Chemical Analysis

All chemicals were purchased as reagent grade and used without further purification. Melting points were determined on a Fisatom 431 apparatus (Fisatom, São Paulo, SP, Brazil), and were uncorrected. Carbon and proton nuclear magnetic resonance spectra were recorded in a Bruker Ascend NMR (Bruker, Massachusetts, USA) with standard pulse sequences operating at 400 MHz for ^1H NMR and 100 MHz for ^{13}C NMR using $\text{DMSO-}d_6$ or CDCl_3 as a solvent.

3.2. Synthesis of Aromatic Azide (7)

In a three-neck round-bottomed flask equipped with a magnetic stirrer, aniline (1 mmol, 92 μL) was dissolved in 10 mL of HCl 10% at room temperature. After the solution reached 0 $^\circ\text{C}$, 1 mL of sodium nitrite solution 1M was then added and the reaction kept at this temperature under stirring for 10 min. Sodium azide 1.1 mmol (71.5 mg) solubilized in 1 mL of water was added dropwise to the neck of the round-bottomed flask and the reaction was stirred for 2 h. The product was extracted with ethyl acetate 3 times and washed with a saturated NaCl solution. The organic layer was dried with anhydrous sodium sulphate and the solvent was removed under reduced pressure.

3.3. Synthesis of 4-(Prop-2-yn-1-yloxy)benzaldehyde (2)

A mixture of 4-hydroxybenzaldehyde (1 mmol, 122 mg), potassium carbonate (4 mmol 552 mg), and propargyl bromide 80% wt (4 mmol, 0.340 mL) was refluxed in acetone over 4 h. After the total consumption of 4-hydroxybenzaldehyde was monitored by TLC, the acetone was removed and the solid obtained was suspended in water and extracted using methylene chloride. The solid obtained was used in the consecutive step without previous purification [10].

3.4. Synthesis of 3,4-Dihydropyrimidinone (5)

In a round-bottomed flask equipped with a magnetic stirrer, aldehyde (2) (160 mg, 1 mmol), urea (72 mg, 1.2 mmol), ethyl acetoacetate (0.125 mL, 1 mmol), and *p*-toluenesulfonic acid monohydrate (57 mg, 0.3 mmol) were added to ethanol (3 mL). The mixture was heated at 60 $^\circ\text{C}$ for 2 days, cooled, and poured into cold water, and the precipitate was filtered off and dried [10].

Ethyl 6-methyl-2-oxo-4-[4-(prop-2-yn-1-yloxy)phenyl]-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5): ^1H NMR (400 MHz, CDCl_3 , δ ppm): 1.16 (t, $J = 7.1$ Hz, 3H); 2.31 (s, 3H); 2.52 (t, $J = 2.4$ Hz, 1H); 4.12–4.02 (m, 2H); 4.66 (d, $J = 2.4$ Hz, 1H); 5.34 (d, $J = 2.6$ Hz, 1H); 6.16 (s, 1H); 6.89 (d, $J = 8.7$ Hz, 2H); 7.23 (d, $J = 8.7$ Hz, 2H); 8.64 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3 , δ ppm): 14.2 (CH_3); 18.5 (CH_3); 55.0 (CH); 55.8 (CH_2); 60.0 (CH_2); 75.6 (CH); 78.8 (C); 101.4 (C); 114.4 (CH); 127.8 (CH); 137.1 (C); 146.4 (C); 154.1 (C); 157.2 (C); 165.7 (C). Yield 78% (244 mg).

3.5. Synthesis of Hybrid 3,4-Dihydropyrimidinone-triazole LaSOM[®] 293 (8)

The aromatic azide (7) (1.10 mmol, 131 μL), $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (0.03 mmol, 8 mg), and sodium ascorbate (0.10 mmol, 20 mg) in 1.5 mL of a mixture of *tert*-butanol–water (1:1) were charged in a round-bottomed flask under magnetic stirring. The 3,4-dihydropyrimidinone (5) (1 mmol 314 mg) was then added. The flask was exposed to microwave radiation in a CEM Discover microwave reactor (CEM Corporation, Matthews, NC, USA) using the parameters 18 W at 70 $^\circ\text{C}$ for 15 min. The reaction was poured into water and extracted with ethyl acetate 3 times. The organic layer was dried with sodium sulphate anhydrous and concentrated under reduced pressure. The solid obtained was recrystallized in ethanol.

Ethyl 6-Methyl-2-oxo-4-[4-[(1-phenyl-1H-1,2,3-triazol-4-yl)methoxy]phenyl]-1,2,3,4-tetrahydropyrimidine-5-carboxylate (8): ^1H NMR (400 MHz, $\text{DMSO-}d_6$): 1.08 (t, $J = 7.2$ Hz, 3H); 2.24 (s, 3H); 3.97 (q, $J = 7.1$ Hz, 2H); 5.10 (s, 1H); 5.20 (s, 2H); 7.02 (d, $J = 8.7$ Hz, 2H); 7.17 (d, $J = 8.7$ Hz, 2H); 7.49 (t, $J = 7.4$ Hz, 1H); 7.59 (t, $J = 7.8$ Hz, 2H); 7.59 (t, $J = 7.8$ Hz, 2H); 7.67 (s, 1H); 7.90 (d, $J = 7.7$ Hz, 2H); 8.94 (s, 1H); 9.16 (s, 1H). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$): 14.1 (CH_3); 17.8 (CH_3); 53.4 (CH); 59.2 (CH_2); 61.0 (CH_2); 99.6 (C); 114.6 (CH); 120.2 (CH); 122.9 (CH); 127.5 (CH); 128.8 (CH); 129.9 (CH); 136.6 (C); 137.6 (C); 143.9 (C); 148.1 (C); 152.2 (C); 157.2 (C); 165.4 (C). HRMS/MS (m/z): calcd. $\text{C}_{23}\text{H}_{23}\text{N}_5\text{O}_4$ [$\text{M} + \text{H}$] $^+$: 434.1823, found

434.1808. FT-IR (ATR, cm^{-1}): 3259 (NH), 3139 (NH), 1702 (C=O), 1510 (C=C), 1224 (C–O), 1097 (C–O). Ultraviolet-visible: λ_{max} : 250 nm. Yield 84% (364 mg), melting point: 184–186 °C (EtOH).

Supplementary Materials: The following are available online: Figure S1: ^1H NMR spectrum (400 MHz, CDCl_3) of compound (5), Figure S2: ^{13}C NMR (100 MHz, CDCl_3) and APT spectrum of compound (5), Figure S3: ^1H NMR spectrum (400 MHz, $\text{DMSO}-d_6$) of compound (8), Figure S4: ^{13}C NMR (100 MHz, CDCl_3) and APT spectrum of compound (8), Figure S5: HSQC experiment for compound (8), Figure S6: HRMS spectra of compound (8), Figure S7: FT-IR spectrum of compound (8), Figure S8: UV-visible spectrum of compound (8) in ethyl acetate.

Author Contributions: Synthesis of compounds and NMR spectra characterization: G.O.d.A., I.L.G., L.D., and G.A.G.; Design of compound, L.P.K., G.M.d.N., J.P.S., and V.L.E.-L.; Writing—original draft preparation, I.L.G., R.F.S.C., and V.L.E.-L.; Writing—review, R.F.S.C. and V.L.E.-L.; Supervision and project administration, V.L.E.-L.

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

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