**Short Note**

5-(4-Bromophenyl)-7-(2,4-dimethoxyphenyl)-4,7-dihydrotetrazolo[1,5-\(a\)]pyrimidine

Kautsar Ul Haq, Mareta Dewi Liawati, Abdulloh Abdulloh and Hery Suwito *

Department of Chemistry, Faculty of Science and Technology, Airlangga University, Surabaya 60115, Indonesia; kautsar.ul.haq@fst.unair.ac.id (K.U.H.); mareta.dewi.liawati-2014@fst.unair.ac.id (M.D.L.); abdulloh@fst.unair.ac.id (A.A.)

* Correspondence: herys08032002@yahoo.com; Tel.: +62-31-5936502

Received: 30 November 2018; Accepted: 12 December 2018; Published: 17 December 2018

**Abstract:** A derivative of dihydrotetrazolopyrimidine has been successfully synthesized through a cyclocondensation reaction between a chalcone derivative with 5-aminotetrazole. The molecular structure of the title compound was established based on Fourier transform infrared spectra (FTIR), high-resolution mass spectrometry (HRMS), 1D and 2D nuclear magnetic resonance (NMR) spectrum.

**Keywords:** cyclocondensation; tetrazolopyrimidine; fused heterocyclic

1. Introduction

Compounds with pyrimidine ring scaffold are well known for their biological and interesting pharmacological activity [1,2]. The pyrimidine ring can merge with other heterocyclic rings to build a fused pyrimidine ring. Purine is an example of a fused pyrimidine ring exhibiting an attractive biological activity [3]. Tetrazolopyrimidine ring is an example of a fused heterocyclic ring that belongs to the purin analog, showing various biological activities [4] such as antioxidant, antimicrobial [5], anti-inflammation [6], antiviral [7], and anticancer [8]. Due to its broad spectrum of biological activity, developing a convenient and efficient synthesis method of tetrazolopyrimidine becomes an attractive challenge.

The research focused on the synthesis and activity of dihydrotetrazolopyrimidine (DHTPM) derivatives, which are carried out extensively. Generally, DHPMT can be synthesized using two methods. First is cyclization of a substrate possessing pyrimdine ring, such as ring closure in azidopyrimidine [9]. The second is cyclocondensation of a substrate possessing tetrazole ring, like a cyclocondensation reaction between chalcone [10] with 5-aminotetrazole or using a multicomponent reaction (Biginelli reaction) [5,11,12].

2. Results

Firstly, the synthesis of the title compound was conducted by a one step multicomponent Biginelli reaction between 4′-bromoacetophenone, 5-aminotetrazole, and 2,4-dimethoxybenzaldehyde in ethanol as solvent, using pTsOH as catalyst [12]. However, we did not get the product. Therefore, we tried to synthesize the title compound in a two step reaction.

The first reaction is a Claisen–Schmidt condensation to furnish chalcone 1 using the procedure reported by Suwito et al. [13] followed by cyclocondensation with 5-aminotetrazole in a basic condition to produce the title compound (2) as white crystal (167 mg, 47.5%) after recrystallization with ethanol. The reaction equation is presented in Scheme 1. The advantage of the cyclocondensation method is that we obtain dihydropyrimidine derivative possessing two aromatic rings at one reaction step. In this article we discuss only compound 2 because compound 1 has published previously [14].
The appearance of two peaks with a nearly equivalent intensity of high-resolution mass spectrometry (HRMS) (ESI) spectra at m/z: 436.0377 and 438.0350 showed that the compound contained bromine atom and possessed 13 degrees of unsaturated (Supplementary Materials, Figure S1). The results of the infrared (IR) spectrum analysis showed that the title compound has secondary amide N–H group, C–H aromatic, C–H aliphatic, C=C alkene, C=C aromatic, CAlkyl–O–Carly ether, and C-Br groups, which were represented by the bands at (cm⁻¹) 3184, 3065, 2933, 1609, 1591, 1211, and 734, consecutively (Supplementary Materials, Figure S2).

Based on ¹H-NMR analysis, the existence of a 4,7-dihydrotetrazolo [1,5-a]pyrimidine skeleton was proved by three proton signals: a broad signal at 10.40 ppm indicated the existence of an amide-type –NH proton, while two other doublet signals formed an AX spin system at δC 151.1 (C-1) and 97.3 (C-4) (see Table 1). The existence of 4,7-dihydrotetrazolo[1,5-a]pyrimidine is also supported by the results of HMBC experiment (Figure 1), where proton of H-5 (δH 6.64) correlated to olephinic carbon atom (δC 134.1 (C-3) and 97.3 (C-4)); proton C-4 (δH 5.17) showed a correlation with carbon atom δC 134.1 (C-3) and 54.6 (C-5); and proton H-2 (10.40 ppm) correlated to C atom of δC 151.1 (C-1) and 97.3 (C-4) (see Table 1).

The fragment of 2,4-dimethoxyphenyl attached at C-5 could be observed from the correlation of proton H-5 with three carbon atoms (δC 120.6 (C-6), 157.8 (C-7) and 129.0 (C-11), whereas 4-bromophenyl fragment attached at C-3 was assigned by correlation of proton H-2'/H-6' with carbon atom C δC 134.1 (C-3) (Supplementary Materials, Figure S6).
Figure 1. (a) Structure numbering, and (b) high-resolution mass spectrometry (HMBC) correlations of the prepared compound.

Table 1. Nuclear magnetic resonance (NMR) data of the target compound (2) in DMSO-$d_6$.

<table>
<thead>
<tr>
<th>No.</th>
<th>Atom</th>
<th>$\delta_H$ (ppm), mult, $J$ (Hz)</th>
<th>$\delta_C$ (ppm)</th>
<th>HMBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>10.40 (s, 1H)</td>
<td>151.1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>5.17 (d, $J = 3.7$ Hz, 1H)</td>
<td>97.3</td>
<td>C-3, C-5</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>6.64 (d, $J = 3.7$ Hz, 1H)</td>
<td>54.6</td>
<td>C-3, C-4, C-6, C-7, C-11</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>105.2</td>
<td>131.5</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>128.0</td>
<td>129.0</td>
<td>C-5, C-7, C-9</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>122.2</td>
<td>131.5</td>
<td>C-1′, C-3′/C-5′, C-4′</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>133.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>157.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>160.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. Materials and Methods

3.1. General

All reagents and solvents were provided from commercial sources (E.Merck, Darmstadt, Germany or Sigma Aldrich, St. Louis, MO, USA) and used without prior purification. The reaction progress was monitored via a Thin Layer Chromatography (TLC) experiment using an aluminum silica gel plate GF254 (0.25 mm) employing different solvents. The melting point was determined using a Thermo Scientific Fisher-Johns melting point apparatus 220 VAC (Waltham, MA, USA) and it is uncorrected. The TLC spot was detected using UV light ($\lambda = 254$ nm). The Fourier transform infrared (FTIR) spectrum was recorded on a IRTracer100 spectrophotometer (Shimadzu, Kyoto, Japan) using a diffuse reflectance method, whereas the mass spectrum was recorded on a HRESIMS QTOF microTOF-Q II Bruker Compass (Billerica, MA, USA). The nuclear magnetic resonance (NMR) spectrum ($^1$H-, and $^{13}$C-APT) was recorded on a JEOL JNM-ECS400 spectrometer (at 400 and 100 MHz) (JEOL Ltd., Tokyo, Japan) with CDCl$_3$ as the solvent and internal standard.

3.2. Synthesis of Chalcone Derivative 1

The synthesis of chalcone derivative was conducted following the procedure reported by Suwito et al. [13]. A mixture of 6 mmol 4′-bromoacetophenone (1.195 g), 6 mmol 2,4-dimetoxybenzaldehyde (0.997 g), and 30 mL ethanol was placed in a three neck round bottom flask (equipped with a reflux
condenser, thermometer, and dropping funnel), stirred, and cooled under 10 °C. To the reaction mixture, 6 mL NaOH 40% solution was added dropwise and the temperature was kept under 10 °C, stirred for 1 h, and then stirred at room temperature for a further 5 h. The precipitate was filtered off and recrystallized using aqueous ethanol. The chalcone 1 was isolated as a yellow crystal (1.792 g, 86%).

3.3. Synthesis of Target Compound

A mixture of 1 mmol of chalcone 1 (350 mg), 2 mmol 5-aminotetrazole (210 mg), and a solution of ethanolic KOH (1 mmol potassium hydroxide, 17 mL ethanol, and 1 mmol PEG200) were put in a three neck round bottom flask. The mixture was stirred and refluxed at 70 °C for 30 h, cooled at room temperature, and white precipitate was observed. The precipitate was then filtered off and recrystallized on ethanol.

5-(4-Bromophenyl)-7-(2,4-dimethoxyphenyl)-4,7-dihydrotetrazolo[1,5-a]pyrimidine: white crystal (0.1969 g, 47.5%); m.p 268–270 °C, Rf (n-hexane:ethyl acetate = 3:2) = 0.41. HRMS (ESI): [M + Na]⁺ calcd for C₁₈H₁₇BrN₅O₂Na⁺, 436.0385 found 436.0377. IR (DRS, KBr, cm⁻¹): 3184 (m, N–H amide type), 3065 (m, C–H aromatic), 2933 (m, C–H aliphatic), 1609 (str, C=C alkene), 1591, 1551, 1506 (str, C=C aromatic), 1211 (str, C₆H₅–O–C₆H₅ ether), 734 (m, C-Br).

1H-NMR (400 MHz, DMSO-d₆) δH (ppm): 10.40 (s, 1H), 7.62 (d, J = 8.6 Hz, 2H), 7.56 (d, J = 8.6 Hz, 2H), 7.04 (d, J = 8.5 Hz, 1H), 6.64 (d, J = 3.7 Hz, 1H), 6.60 (d, J = 2.3 Hz, 1H), 6.52 (dd, J = 8.5, 2.3 Hz, 1H), 5.17 (d, J = 3.7 Hz, 1H), 3.75 (s, 3H), 3.73 (s, 3H).

13C-NMR (101 MHz, DMSO-d₆) δC (ppm): 160.9 (C), 157.8 (C), 151.1 (C), 134.1 (C), 131.1 (C), 131.5 (CH), 129.0 (CH), 128.0 (CH), 122.2 (C), 120.6 (C), 105.2 (CH), 99.0 (CH), 97.3 (CH), 55.8 (CH₃), 55.3 (CH₃), 54.6 (CH).

4. Conclusions

A new compound of dihydrotetrazolopyrimidine derivative that is 5-(4-bromophenyl)-7-(2,4-dimethoxyphenyl)-4,7-dihydrotetrazolo[1,5-a]pyrimidine has been successfully synthesized under basic cyclocondensation reaction.

Supplementary Materials: The Supplementary Materials are available online. The HRESIMS, FTIR, 1H-NMR, 13C-NMR, HMQ, HMBC spectra are reported in the Supplementary Materials as Figures S1–S6, respectively, and the structure refinement in Table S1.

Author Contributions: K.U.H. brought the idea, performed the structure elucidation and wrote the manuscript. M.D.L. performed the synthesis, while H.R.S. brought the idea and managed the research, A.A. corrected the manuscript. All the authors have read the draft.

Funding: This research was funded by Universitas Airlangga through Penelitian Dosen Pemula 2018 research scheme, grant number 1889/UN3.1.8/LT/2018.

Acknowledgments: The authors acknowledge Lembaga Penelitian & Inovasi and the Faculty of Science & Technology, Airlangga University for the funding support. Furthermore, the authors acknowledge Preecha Phuwapraisirisan from the Department of Chemistry, Chulalongkorn University and Rico Ramadhan from the Department of Chemistry, Airlangga University for the high-resolution mass spectroscopy measurement.

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

References

1. Sandhu, J.S. Past, present and future of the Biginelli reaction: A critical perspective. Arkivoc 2012, 66–133. [CrossRef]


© 2018 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).