molbank

MDPI

Short Note

6-[(4-Chlorophenyl)(1*H*-1,2,4-triazol-1-yl)methyl]-3-methyl-2(3*H*)-benzoxazolone

Mariana S. Gerova [1,*], Yordanka B. Ivanova [2], Christo D. Chanev [1] and Ognyan I. Petrov [1]

[1] Department of Pharmaceutical and Applied Organic Chemistry, Faculty of Chemistry and Pharmacy, Sofia University "St. Kliment Ohridski", 1 James Bourchier Blvd., Sofia 1164, Bulgaria; hchanev@chem.uni-sofia.bg (C.D.C.); opetrov@chem.uni-sofia.bg (O.I.P.)

[2] Department of Plant Pathology and Chemistry, Faculty of Ecology and Landscape Architecture, University of Forestry, 10 Kliment Ohridsky Blvd., Sofia 1756, Bulgaria; yordanka_b_ivanova@abv.bg

* Correspondence: mgerova@chem.uni-sofia.bg; Tel.: +359-2-8161-313; Fax: +359-2-9625-438

Academic Editor: Norbert Haider

Received: 18 April 2016; Accepted: 19 May 2016; Published: 1 June 2016

Abstract: A new hybrid molecule containing a triazole and a benzoxazolone ring was synthesized. The structure of 6-[(4-chlorophenyl)(1*H*-1,2,4-triazol-1-yl) methyl]-3-methyl-2(3*H*)-benzoxazolone was confirmed by IR, ^{1}H-, ^{13}C-NMR, MS and elemental analysis.

Keywords: triazole; 2(3*H*)-benzoxazolone; aromatase inhibitors; antifungal agents

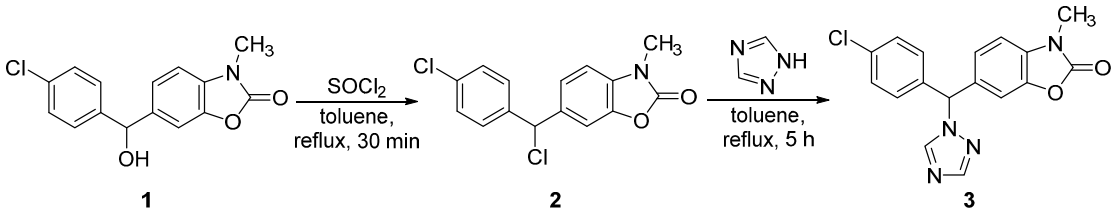
1. Introduction

Triazoles are an important class of heterocyclic compounds with antimicrobial, antimycotic, antimycobacterial, antiprotozoal, anticonvulsant and anticancer activity [1]. Commonly used triazole antifungal drugs include *fluconazole*, *itraconazole* and *voriconazole* [2,3]. These compounds have a broad spectrum of activity against both superficial and invasive fungal infections [4]. Other clinically useful triazole derivatives, such as *anastrozole*, *letrozole* and *vorozole*, act as non-steroidal aromatase inhibitors and find use in the treatment of estrogen dependent breast cancer [5,6].

Given the wide presence of the triazole moiety in bioactive compounds with diverse mechanisms of action, here, we propose the synthesis of 6-[(4-chlorophenyl)(1*H*-1,2,4-triazol-1-yl) methyl]-3-methyl-2(3*H*)-benzoxazolone (**3**). Structurally related hybrid compounds combining an imidazole fragment with a benzazole ring have been previously synthesized as aromatase inhibitors [7–9] and antifungal agents [10,11]. However, fewer molecules containing the triazole and benzoxazolone moieties have been reported. As a third ring in the target molecule, we chose the 4-chlorophenyl moiety, as the presence of chlorine atom on aromatic positions 2 or 4 in some cases improved the effectiveness in azole antifungal agents [12]. To the best of our knowledge, triazole derivative **3** has not been previously prepared.

2. Results

The synthesis of the title compound **3** was achieved in two steps, as presented in Scheme 1. Reaction of secondary alcohol **1** [8,11] with thionyl chloride led to the corresponding chloride **2**, which was used in the second stage without further purification. Treatment of **2** with an excess of 1,2,4-triazole provided **3** and triazole hydrochloride as a by-product. Compound **3** was isolated in good yield and purified by recrystallization. Compounds **1–3** possess a chiral center and can exist as a pair of enantiomers. We used racemic reagent **1** and the target compound **3** was correspondingly obtained as a mixture of both enantiomers. Their separation could be achieved by HPLC methods using polysaccharide-based stationary phases [13,14].



Scheme 1. Synthesis of 6-[(4-chlorophenyl)(1*H*-1,2,4-triazol-1-yl)methyl]-3-methyl-2(3*H*)-benzoxazolone (**3**).

The structure of **3** was confirmed by IR, ^{1}H- and ^{13}C-NMR, MS and elemental analysis. All data are in accordance with the assumed structure. In the ^{1}H-NMR spectrum two singlets corresponding to the triazole protons (7.98 and 8.03 ppm) were observed. In addition to the signals for aromatic protons in the 6.95–7.36 ppm range, a characteristic singlet for the methine proton was observed at 6.74 ppm. A singlet corresponding to the methyl group of benzoxazolone heterocycle was observed at 3.40 ppm (Figure S1).

3. Experimental Section

3.1. General Information

All reagents were used as received without further purification. Compound **1** was prepared by reduction of the corresponding ketone with sodium borohydride as described previously [8,11]. The reaction was monitored by thin-layer chromatography (TLC) on silica gel plates (Kieselgel 60 F_{254}), using cyclohexane/ethyl acetate (3:2) and ethyl acetate/isopropranol (3:1) as eluents. The purity of the final compound **3** was determined by GC-MS analyses on an Agilent 6890 system with MSD 5973, using electron-impact ionization (EI) at 70 eV on a HP-5MS column (30 m × 0.25 mm × 0.25 μm). Helium was used as a carrier gas with 0.8 mL/min flow rate. The temperature programmed mode was used (from 60 °C for 2 min, then with 10 °C/min to 300 °C for 10 min). The sample was introduced in splitless injection mode. IR spectrum ($CHCl_3$) was recorded on a Shimadzu FTIR-8400S spectrometer (Kyoto, Japan). NMR spectra were obtained on a Bruker Avance III HD 500 (Rheinstetten, Germany) in $CDCl_3$. Chemical shifts are given in parts per million (δ) relative to the solvent peak (δ 7.26 ppm for ^{1}H; δ 77.16 ppm for ^{13}C). Coupling constants (*J*) were measured in hertz (Hz). Elemental analysis (C, H, N) was performed on a VARIO EL III Elemental analyzer (Hanau, Germany) and the obtained results were within ±0.4% of the theoretical values. Melting point of **3** was determined on a Boetius hot-stage microscope and was uncorrected.

3.2. Synthesis of 6-[(4-Chlorophenyl)(1H-1,2,4-triazol-1-yl)methyl]-3-methyl-2(3H)-benzoxazolone (**3**)

Thionyl chloride (1 mL, 14 mmol) was added to a solution of 6-[(4-chlorophenyl)(hydroxy) methyl]-3-methyl-2(3*H*)-benzoxazolone (**1**, 1.40 g, 5 mmol) in toluene (10 mL). The mixture was refluxed for 30 min and then the access of thionyl chloride was evaporated under reduced pressure. The obtained oil of **2** was dissolved in toluene (15 mL) and 1,2,4-triazole (0.7 g, 10 mmol) was added. The mixture was refluxed for 5 h (TLC) and the solvent was evaporated *in vacuo*. Water (20 mL) was added and the obtained precipitate was filtered off and dried. Recrystallization from toluene afforded **3** (68%, 1.15 g) as white crystals, m.p.: 185–186 °C. IR ($CHCl_3$): 1755 (C=O) cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.40 (s, 3H, NCH_3), 6.74 (s, 1H, CH), 6.95 (d, 1H, arom. H, *J* = 8.0 Hz), 6.99–7.01 (m, 2H, arom. H), 7.06 (d, 2H, arom. H, *J* = 8.4 Hz), 7.36 (d, 2H, arom. H, *J* = 8.4 Hz), 7.98 (s, 1H, triazole H), 8.03 (s, 1H, triazole H). ^{13}C-NMR (125.8 MHz, $CDCl_3$): δ 28.2 (NCH_3), 66.7 (CH), 108.2, 109.9, 123.9, 129.2, 129.3, 132.2, 132.3, 134.9, 136.2, 142.9 (arom. C), 143.4, 152.6 (triazole C), 154.5 (CO). Anal. calcd. for $C_{17}H_{13}ClN_4O_2$ (340.77): C, 59.92; H, 3.85; N, 16.44. Found: C, 60.25; H, 3.58; N, 16.23. MS (EI): $[M]^+$ *m/z* = 340(38), $[M + 2]^+$ *m/z* = 342(13), 272(100), 274(32), 152(35), 178(21), 207(20), 236(19).

Supplementary Materials: Copies of the ^{1}H-, ^{13}C-NMR and MS spectra as well as the molfile for compound **3** can be found at http://www.mdpi.com/1422-8599/2016/2/M901.

Acknowledgments: The authors are thankful to the Sofia University Scientific Research Fund (grant 117/2016) for the financial support.

Author Contributions: O.I.P. designed the experiments; M.S.G. and Y.B.I. performed the experiments and contributed to manuscript; M.S.G. and O.I.P. analyzed the NMR spectral data and wrote the manuscript; C.D.C. provided and analyzed the mass spectra. All authors read and approved the final manuscript.

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

References

1. Kumar, S.S.; Kavitha, H.P. Synthesis and biological applications of triazole derivatives—A review. *Mini-Rev. Org. Chem.* **2013**, *10*, 40–65. [CrossRef]
2. Shalini, K.; Kumar, N.; Drabu, S.; Sharma, P.K. Advances in synthetic approach to and antifungal activity of triazoles. *Beilstein J. Org. Chem.* **2011**, *7*, 668–677. [CrossRef] [PubMed]
3. Fromtling, R.A. Overview of medically important antifungal azole derivatives. *Clin. Microbiol. Rev.* **1988**, *1*, 187–217. [PubMed]
4. Chen, S.C.A.; Sorrell, T.C. New Drugs, Old Drugs. Antifungal agents. *Med. J. Aust.* **2007**, *187*, 404–409. [PubMed]
5. Hamilton, A.; Piccart, M. The third–generation non-steroidal aromatase inhibitors: a review of their clinical benefits in the second-line hormonal treatment of advanced breast cancer. *Ann. Oncol.* **1999**, *10*, 377–384. [CrossRef] [PubMed]
6. Goss, P. Anti-aromatase agents in the treatment and prevention of breast cancer. *Cancer Control.* **2002**, *9*, 2–8. [PubMed]
7. Marchand, P.; Le Borgne, M.; Palzer, M.; Le Baut, G.; Hartmann, R.W. Preparation and pharmacological profile of 7-(α-azolylbenzyl)-1*H*-indoles and indolines as new aromatase inhibitors. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1553–1555. [CrossRef]
8. Nativelle-Serpentini, C.; Moslemi, S.; Yous, S.; Park, C.H.; Lesieur, D.; Sourdaine, P.; Séralini, G.-E. Synthesis and evaluation of benzoxazolinonic imidazoles and derivatives as non-steroidal aromatase inhibitors. *J. Enz. Inh. Med. Chem.* **2004**, *19*, 119–127. [CrossRef] [PubMed]
9. Park, C.H.; Yous, S.; Nativelle-Serpentini, C.; Seralini, G.-E.; Chang, S.-J.; Lesieur, D. Use of Benzothiazinones and Related Compounds as Aromatase Inhibitors in Treatment of Psoriasis and Neoplasm, and Their Preparation. FR 2860235, 1 April 2005. *Chem. Abstr.* **2005**, *142*, 355274.
10. Botta, M.; Corelli, F.; Manetti, F.; Mugnaini, C.; Tafi, A. Rational design and synthesis of homochiral azole antifungal agents. *Pure Appl. Chem.* **2001**, *73*, 1477–1485. [CrossRef]
11. Petrov, O.; Gerova, M.; Petrova, K.; Ivanova, Y. New imidazole derivatives of 2(3*H*)-benzazolones as potential antifungal agents. *J. Heterocycl. Chem.* **2009**, *46*, 44–48. [CrossRef]
12. Rani, N.; Sharma, A.; Gupta, G.K.; Singh, R. Imidazoles as potential antifungal agents: A review. *Mini-Rev. Med. Chem.* **2013**, *13*, 1626–1655. [CrossRef] [PubMed]
13. Danel, C.; Foulon, C.; Park, C.; Yous, S.; Bonte, J.-P.; Vaccher, C. Enantiomeric resolution of new aromatase inhibitors by liquid chromatography on cellulose chiral stationary phases. *J. Sep. Sci.* **2005**, *28*, 428–434. [CrossRef] [PubMed]
14. Danel, C.; Foulon, C.; Guelzim, A.; Park, C.H.; Bonte, J.-P.; Vaccher, C. Preparative Enantiomeric separation of new aromatase inhibitors by HPLC on polysaccharide-based chiral stationary phases: Determination of enantiomeric purity and assignment of absolute stereochemistry by X-ray structure snalysis. *Chirality* **2005**, *17*, 600–607. [CrossRef] [PubMed]