

Synthesis and X-Ray Structure of New Anticancer Nucleosides Based on 1-((2-Hydroxyethoxy)methyl)-5-(phenylthio)-1H-1,2,4-triazole-3-carboxamide

Yulong Lei¹, Dehua Zhang^{1*}, Yang Liu², Guanghui Tian², Hongguang Ge²

¹College of Chemistry and Chemical Engineering & Hubei Key Laboratory of Pollutant Analysis & Reuse Technology, Hubei Normal University, Huangshi, China

²School of Chemistry & Environmental Science, Shaanxi University of Technology, Hanzhong, China
Email: zhangdehua200@163.com

Received 17 April 2014; revised 16 May 2014; accepted 16 June 2014

Copyright © 2014 by authors and Scientific Research Publishing Inc.

This work is licensed under the Creative Commons Attribution International License (CC BY).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

Abstract

A pair of new anticancer nucleosides based on 1,2,4-triazole nucleosides and 1-((2-hydroxyethoxy)methyl)-5-(phenylthio)-1H-1,2,4-triazole-3-carboxamide have been synthesized, and have given the corresponding products in excellent yields. Its structures and conformations were confirmed by single crystal X-ray diffraction.

Keywords

Anticancer Nucleosides, Triazole Nucleosides, Excellent Yields

1. Introduction

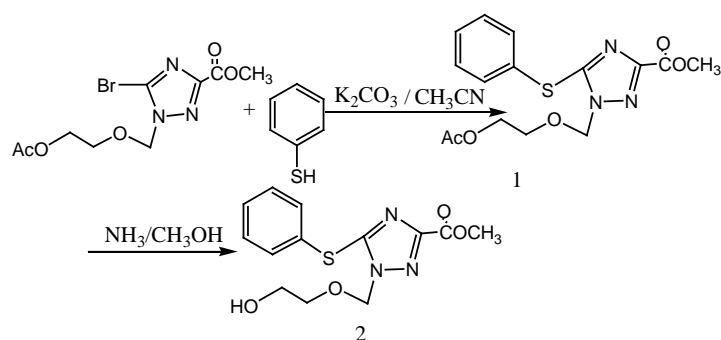
Synthetic nucleoside analogs with modified nucleobase and/or sugar moieties are of considerable importance in the search for promising candidates leads endowed with antiviral, anticancer, and antibacterial activities [1] [2]. Nucleoside analogs with modified sugar and/or base moieties can mimic natural nucleosides and serve as building units or inhibitors that interfere in nucleic acid synthesis or block nucleoside-dependent biological processes.

*Corresponding author.

Well-known nucleoside drugs include the antiviral drugs ribavirin, acyclovir, and zidovudine, and the most commonly used anticancer nucleoside drugs include gemcitabine and cladribine. We have been engaged in a program to develop structurally diverse triazole nucleoside analogs. These nucleosides contain triazole as nucleobase and aromatic groups have been appended on the nucleobases [3] [4], with a view to identifying new structural leads exhibiting biologically interesting activity. Pancreatic cancer is one of the most lethal forms of human cancer, and drug resistance develops extremely fast. The current first-line treatment for pancreatic cancer is based on gemcitabine, which is only moderately effective, with a median survival period of 5 months and a five-year survival rate as low as 3% [5] [6]. Consequently, there is an urgent need to develop more efficacious drug candidates to treat pancreatic cancer [7].

We report on the synthesis of S-arylated triazole acyclonucleoside analogue, using a simple and efficient S-arylation procedure without catalyst, giving the corresponding products in excellent yields.

The synthesis of the title new anticancer nucleosides **2** is shown in **Scheme 1**. The structures and conformations of compound **2** were further elucidated by their single crystal X-ray diffraction, as shown in **Figure 1**. Three-dimensional molecular-packing diagram of the title compound was shown in **Figure 2**.



Scheme 1. Synthesis of the anticancer nucleosides intermediate **2**.

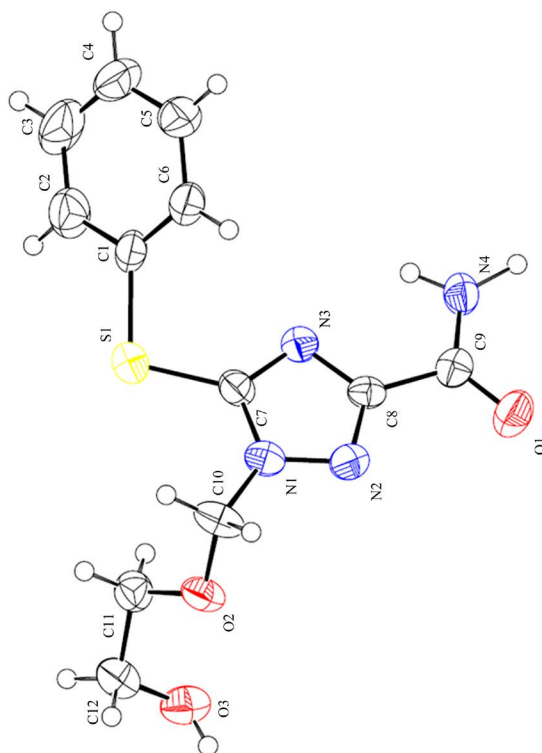


Figure 1. The single crystal structure of compound **2**.

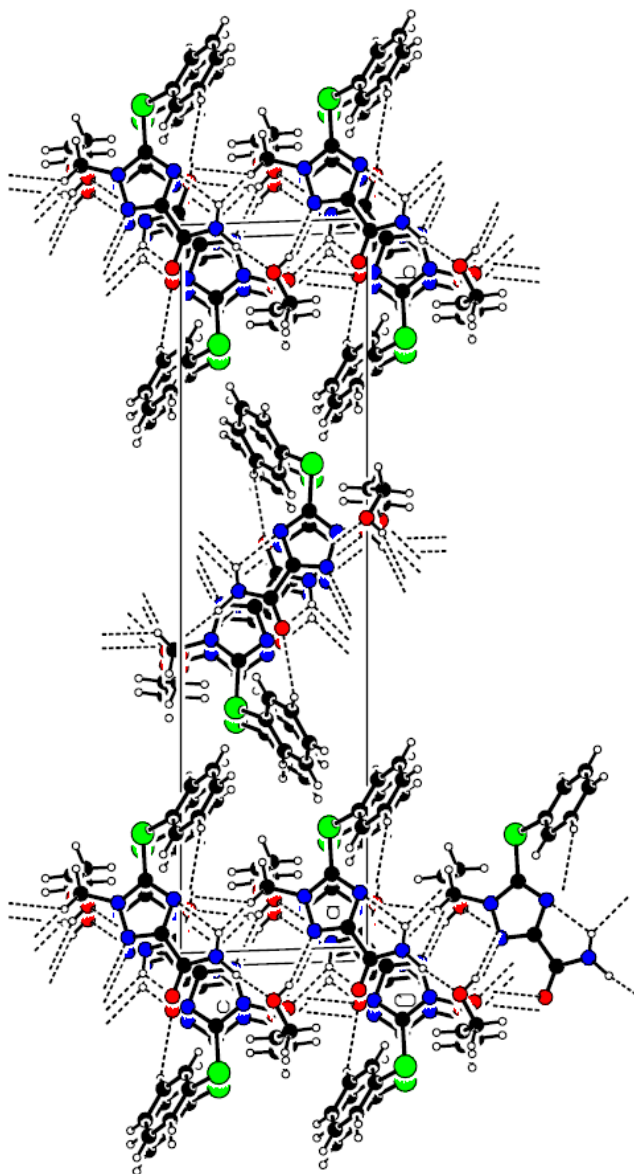


Figure 2. Three-dimensional molecular-packing diagram of the title compound.

The crystals of **2** were obtained by slow evaporation of their solution in ethyl acetate/petroleum ether (3:1, v/v) mixtures. The crystal structures of **2** clearly revealed that it has well-defined geometry due to the rigidity that the fused rings confer on the molecule. Its structures and conformations were confirmed by single crystal X-ray diffraction. The dihedral angle between the benzene and the other triazole rings (N2, N1, C7, N3, C8) is 52.94° . The molecular conformation is stabilized by N---H...O hydrogen bond. The crystal packing is governed by C---H...O and C---H...N hydrogen interactions resulting in a three-dimensional network. These values are suitable for the complexation of an aromatic ring by π - π stacking interactions.

2. Experimental Details

2.1. Preparation of **1** [8]

Methyl 1-((2-acetoxyethoxy)methyl)-5-bromo-1H-1,2,4-triazole-3-carboxylate (32.2 mg, 0.1 mmol), the corresponding 4-benzenethiol (0.12 mmol), and K_2CO_3 (27.6 mg, 0.2 mmol) were suspended in 2 mL of fresh dis-

tilled CH₃CN under argon. The vessel was sealed and the reaction was carried out under microwave irradiation at 100°C for 30 min, and then cooled to room temperature. The reaction mixture was concentrated under reduced pressure and the crude residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 2:1). The purified material was dried in vacuo to afford the corresponding product as colorless oil, an amount of 35.2 mg of compound 2 was obtained with a excellent yield of 99%.

2.2. Preparation of 2 [9]

The solution of NH₃/MeOH (18 mL) was added to a flask containing compound 1 (90.6 mg, 0.258 mmol), and the mixture was stirred at room temperature until two days. After removal of the solvent, the compound 4 (63.9 mg, 84%) was obtained as a white solid.

White crystals suitable for XRD formed after a few days of slow evaporation of the solvent at room temperature over several days. Yellow single crystals of the title compound are shown in **Figure 1**. The crystal structures of 1 clearly revealed that it has well-defined geometry due to the rigidity that the fused rings confer on the molecule.

2.3. Characterization

All reagents obtained from commercial sources were of AR grade. Melting points were determined with XT4A micromelting point apparatus and were uncorrected. The ¹H NMR was recorded on a Mercury Plus-400 spectrometer with TMS as internal reference and CDCl₃ as solvent. IR were recorded on a Perkin-Elmer PE-983 IR spectrometer as KBr pellets with absorption in cm⁻¹. MS were obtained with Finnigan Trace MS instrument using EI method. Elemental analyses were carried out on a Vario EL III instrument.

3. Results and Discussion

3.1. Single Crystal X-Ray Diffraction Analysis

Single crystal X-ray diffraction studies were carried out on the grown crystals. The X-ray data were collected using X-ray diffractometer (Model: Bruker Smart APEX-CCD). A white crystal of the title compound 4 was each mounted on a glass fibre in a random orientation at 298(2) K. The determination of the unit cell and the data collection were performed with MoK α radiation ($\lambda = 0.71073$ Å) on a Bruker Smart Apex-CCD diffractometer with a ψ - ω scan mode. The structure was solved by direct methods with SHELXS-97 program and expanded by Fourier technique. The non-hydrogen atoms were refined anisotropically, and the hydrogen atoms were placed at the calculated positions.

Crystal data for 2: C₁₂H₁₄N₃O₄S, *M* = 294.33, Triclinic, space group P2(1)/n, *a* = 7.347(2) Å, *b* = 26.952(7) Å, *c* = 7.708(2) Å, $\alpha = 90^\circ$, $\beta = 116.505(5)^\circ$, $\gamma = 90^\circ$, *V* = 1365.7(6) Å³, *Z* = 4, *D*_c = 1.431 Mg/m³. Reflections collected: 8719, independent reflections: 2675 [*R*_{int} = 0.1147, Final *R* indices [*I* > 2 *sigma*(*I*)]: *R*¹ = 0.0686, *wR*² = 0.1291. *R* indices (all data): *R*¹ = 0.1183, *wR*² = 0.1475.

3.2. The Structure Characterized

Compound of 1. ¹H NMR (300 MHz, CDCl₃): δ 7.51 - 7.54 (m, 2H, phenyl-H), 7.36 - 7.38 (m, 3H, phenyl-H), 5.66 (s, 2H, -OCH₂N-), 4.13 (t, 2H, *J* = 4.7 Hz, -OCH₂CH₂OAc), 3.99 (s, 3H, -OCH₃), 3.76 (t, 2H, *J* = 4.7 Hz, -OCH₂CH₂OAc), 2.05 (s, 3H, -C(O)CH₃); ¹³C NMR (150 MHz, CDCl₃): δ 170.9, 159.9, 154.6, 153.5, 132.3, 129.8, 129.2, 78.4, 67.9, 62.8, 53.1, 21.0; Maldi-MS: *m/z* 352.1 [*M* + *H*]⁺; HRMS: calcd. for C₁₅H₁₈N₃O₅S⁺ 352.0962, found 352.0951.

Compound of 2. ¹H NMR (300 MHz, CDCl₃): δ 7.93 (br s, 1H, -C(O)NH₂), 7.70 (br s, 1H, -C(O)NH₂), 7.39 - 7.51 (m, 5H, phenyl-H), 5.66 (s, 2H, -OCH₂N-), 4.74 (t, 1H, *J* = 5.4 Hz, -OH), 3.51 - 3.55 (m, 2H, -OCH₂CH₂OH), 3.44 - 3.47 (m, 2H, -OCH₂CH₂OH); ¹³C NMR (75 MHz, DMSO-*d*₆): δ 160.5, 157.7, 151.4, 131.7, 130.9, 130.3, 129.2, 78.7, 71.8, 60.4; Maldi-MS: *m/z* 295.1 [*M* + *H*]⁺; HRMS: calcd. for C₁₂H₁₅N₄O₃S⁺ 295.0859, found 295.0853.

4. Conclusion

A pair of new 1-((2-hydroxyethoxy)methyl)-5-(phenylthio)-1H-1,2,4-triazole-3-carboxamide derived from 1,2,4-

triazole nucleoside have been synthesised. Their structures and conformations were confirmed by single crystal X-ray diffraction and ^1H NMR. Both have great potential to bind aromatic guest molecules. Further studies on their binding properties are in progress.

Acknowledgements

We thank the Hubei provincial Department of Education (Grant No. D20112503), Hubei Key Laboratory of Pollutant Analysis & Reuse Technology (Grant No. KL2013G06), the Shanxi provincial Department of Education (Grant No. 2013JK0659) and Shanxi University of Technology (SLGQD13-2) for financial support.

References

- [1] Claire, S. (2001) *Nucleoside Mimetics: Their Chemistry and Biological Properties* (Advanced Chemistry Texts). Gordon and Beach Science, UK.
- [2] Herdewijn, P., Ed. (2008) *Modified Nucleosides in Biochemistry, Biotechnology and Medicine*. Wiley-VCH, Weinheim. <http://dx.doi.org/10.1002/9783527623112>
- [3] Xia, Y., Liu, Y., Wan, J.Q., Wang, M.H., Rocchi, P., Qu, F.Q., Iovanna, J.L. and Peng, L. (2009) Novel Triazole Ribonucleoside Down-Regulates Heat Shock Protein 27 and Induces Potent Anticancer Activity on Drug-Resistant Pancreatic Cancer. *Journal of Medicinal Chemistry*, **52**, 6083-6096. <http://dx.doi.org/10.1021/jm900960v>
- [4] Wan, J.Q., Xia, Y., Liu, Y., Wang, M.H., Rocchi, P., Yao, J.H., Qu, F.Q., Neyts, J., Iovanna, J.L. and Peng, L. (2009) Discovery of Novel Arylethynyltriazole Ribonucleosides with Selective and Effective Antiviral and Antiproliferative Activity. *Journal of Medicinal Chemistry*, **52**, 1144-1155. <http://dx.doi.org/10.1021/jm800927r>
- [5] Rivera, F., López-Tarruella, S., Vega-Villegas, M.E. and Salcedo, M. (2009) Treatment of Advanced Pancreatic Cancer: From Gemcitabine Single Agent to Combinations and Targeted Therapy. *Cancer Treatment Review*, **35**, 335-339. <http://dx.doi.org/10.1016/j.ctrv.2008.11.007>
- [6] Pierantoni, C., Pagliacci, A., Scartozzi, M., Berardi, R., Bianconi, M. and Cascinu, S. (2008) Pancreatic Cancer: Progress in Cancer Therapy. *Critical Reviews in Oncology/Hematology*, **67**, 27-38. <http://dx.doi.org/10.1016/j.critrevonc.2008.01.009>
- [7] Wong, H.H. and Lemoine, N.R. (2009) Pancreatic Cancer: Molecular Pathogenesis and New Therapeutic Targets. *Nature Reviews Gastroenterology and Hepatology*, **6**, 412-422. <http://dx.doi.org/10.1038/nrgastro.2009.89>
- [8] Liu, Y., Xia, Y., Li, W., Maggiani, A., Leyssen, P., Qu, F.Q., Neyts, J. and Peng, L. (2010) S-Aryltriazole Acyclonucleosides: Synthesis and Biological Evaluation against Hepatitis C Virus. *Bioorganic & Medicinal Chemistry Letters*, **20**, 3610-3613. <http://dx.doi.org/10.1016/j.bmcl.2010.04.115>
- [9] Narik, S.R., Witkowski, J.T. and Robins, R.K. (1974) Synthesis of Nucleosides of 5-Substituted-1,2,4-triazole-3-carboxamides. *Journal of Heterocyclic Chemistry*, **11**, 57-61. <http://dx.doi.org/10.1002/jhet.5570110112>

Scientific Research Publishing (SCIRP) is one of the largest Open Access journal publishers. It is currently publishing more than 200 open access, online, peer-reviewed journals covering a wide range of academic disciplines. SCIRP serves the worldwide academic communities and contributes to the progress and application of science with its publication.

Other selected journals from SCIRP are listed as below. Submit your manuscript to us via either submit@scirp.org or [Online Submission Portal](#).

