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

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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.

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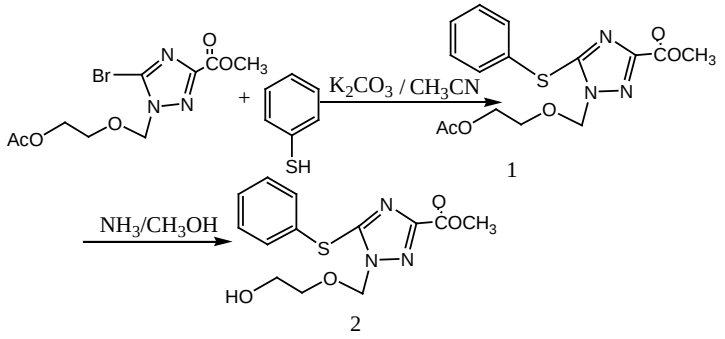
Well-known nucleoside drugs include the antiviral drugs ribavirin, acyclovir, and zidovudine, and the most commonly used anticancer nucleoside drugs include gemcitabine and cladribine. We have been engaged in a program to develop structurally diverse triazole nucleoside analogs. These nucleosides contain 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**.

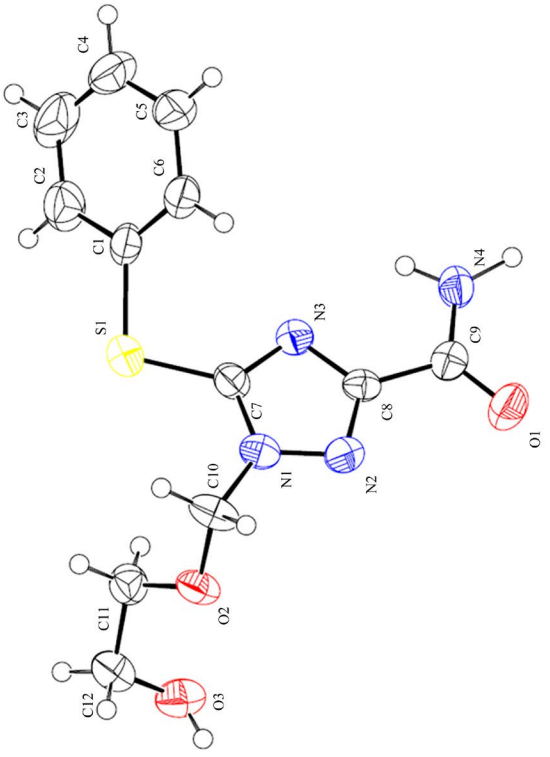


Figure 1. The single crystal structure of compound 2.

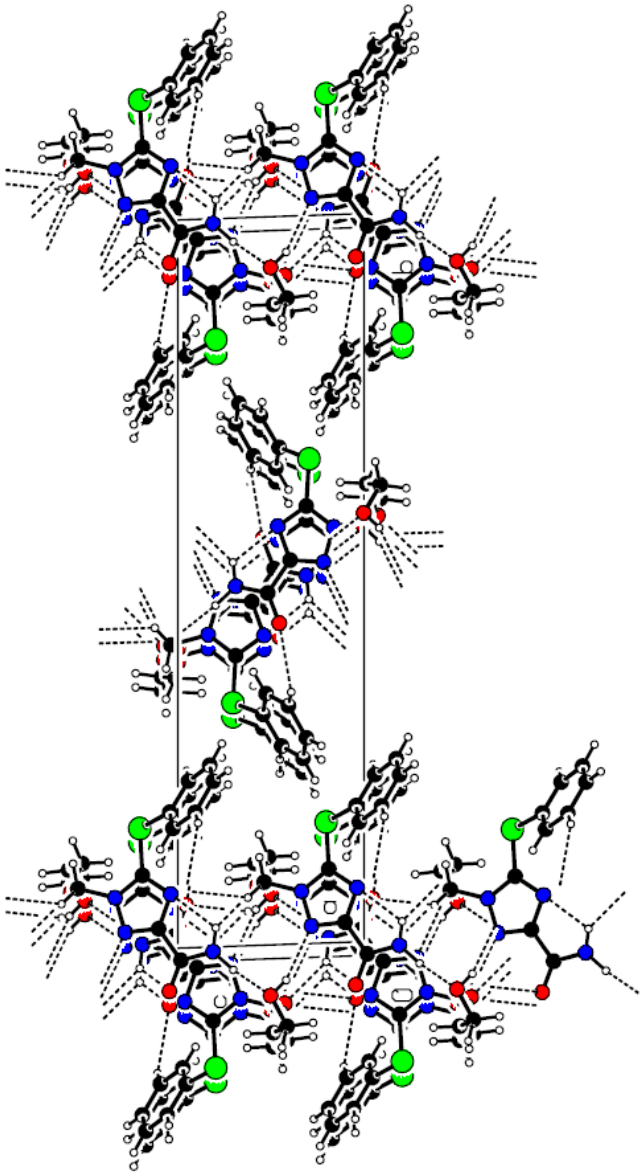


Figure 2. Three-dimensional molecular-packing diagram of the title compound.

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 CH_3CN 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 NH_3/MeOH (18 mL) was added to a flask contammg 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 ^{1}H NMR was recorded on a Mercury Plus-400 spectrometer with TMS as internal reference and $CDCl_3$ 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 date 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 MoKa radiation (λ = 0.71073 Å) on a Bruker Smart Apex-CCD diffactometer 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: $C_{12}H_{14}N_30_4S$, M = 294.33, Triclinic, space group P2(1)/n, a = 7.347(2) Å, b = 26.952(7) Å, c = 7.708(2) Å, α = 90˚, β = 116.505(5)˚, γ = 90˚, V = 1365.7(6) $Å^3$, Z = 4, Dc = 1.431 Mg/m^3. 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. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 - 7.54 (m, 2H, phenyl-H), 7.36 - 7.38 (m, 3H, phenyl-H), 5.66 (s, 2H,-OCH_2N-), 4.13 (t, 2H, J = 4.7 Hz, -OCH_2CH_2OAc), 3.99 (s, 3H, -OCH_3), 3.76 (t, 2H, J = 4.7 Hz, -OCH_2CH_2OAc), 2.05 (s, 3H, -C(O)CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): 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 $C_{15}H_{18}N_3O_5S^+$ 352.0962, found 352.0951.

Compound of 2. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (br s, 1H, -C(O)NH_2), 7.70 (br s, 1H, -C(O)NH_2), 7.39 - 7.51 (m, 5H, phenyl-H), 5.66 (s, 2H, -OCH_2N-), 4.74 (t, 1H, J = 5.4 Hz, -OH), 3.51 - 3.55 (m, 2H, -OCH_2CH_2OH), 3.44 - 3.47 (m, 2H, -OCH_2CH_2OH); ^{13}C 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 $C_{12}H_{15}N_4O_3S^+$ 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 ^{1}H NMR. Both have great potential to bind aromatic guest molecules. Further studies on their binding properties are in progress.

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