molbank

Short Note

2-Furyl-6-nitro-1,2,4-triazolo [1,5-*a*]pyrimidin-7-one

Victor V. Fedotov *, Konstantin V. Savateev, Evgeny N. Ulomsky, Roman A. Drokin, Pavel A. Slepukhin and Vladimir L. Rusinov

Chemical Engineering Institute, Ural Federal University, 19 Mira St., 620002 Yekaterinburg, Russia
* Correspondence: viktor.fedotov@urfu.ru

Abstract: A sodium salt of 2-(fur-2-yl)-6-nitro-1,2,4-triazolo[1,5-*a*]pyrimidin-7-one as a close structural analogue of ZM-241385 was obtained. This heterocycle can serve as an effector for A_{2a} adenosine receptors and possesses antiseptic activity. The structures of compounds were confirmed based on the data of ^{1}H, ^{13}C NMR spectroscopy, IR spectroscopy, and an elemental analysis. The structure of sodium salt 2-furyl-6-nitro-1,2,4-triazolo[1,5-*a*]pyrimidin-7-one was confirmed by an X-ray diffraction analysis.

Keywords: azolo[1,5-*a*]pyrimidines; nitrocompounds; cyclization; sepsis

1. Introduction

Sepsis and septic shock are major healthcare problems affecting millions of people around the world each year and killing as many as one in four (and often more) [1–3]. Similar to polytrauma, acute myocardial infarction, or stroke, early identification and appropriate management in the initial hours after sepsis develops improves outcomes. The causative agents of sepsis are bacteria (95% of cases), fungi, viruses, and protozoa. Most often, sepsis develops as a complication of diseases such as abdominal trauma, perforation of an intestinal ulcer, pyelonephritis, pneumonia, and severe influenza. The secondary complications of influenza include viral or bacterial pneumonia, pulmonary distress syndrome, and septic shock, which are difficult to treat, including due to late detection, on the one hand, as well as the presence of aggravating factors in the form of an unfavorable premorbid patient background, on the other.

Recently, the European Society of Intensive Care Medicine and the Society of Critical Care Medicine revised the definitions for sepsis and septic shock. Sepsis is now defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Septic shock is a subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality [4].

Modern chemotherapy for septic conditions based on broad-spectrum antibiotics [5] and steroids [6] has limited potential, as mortality in sepsis can reach 30% and more than 50% in septic shock. It is clear that novel molecules with a different mechanism of action should be found to fight septic conditions.

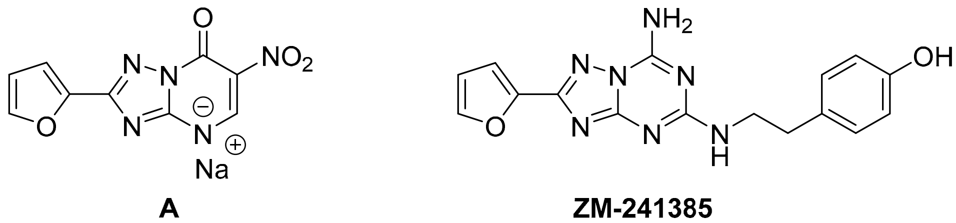
It has previously been shown that inflammation is reduced during the activation of adenosine A_{2a} receptor (A_{2a} AR), and the use of synthetic analogues of adenosine increases survival in sepsis. Moreover, A_{2A} AR gene-deficient mice are susceptible to the minimum damaging impacts that stimulate inflammation. In particular, the level of cytokine production is increased, tissues are damaged, and even the death of male species is observed; at the same time, there is no such effect under the action of the same stimuli on wild-type mice [7]. Additionally, we found that nitro-containing derivatives of azoloazine series possessed anti-septic activity in vivo [8]. They could also serve as structural analogues of known effectors for A_{2a} AR, such as 1,2,4-triazolo[1,5-*a*][1,2,4]triazine ZM 241385 [9]. The further development of more potent effectors for A_{2a} AR with antiseptic activity relies on docking

Citation: Fedotov, V.V.; Savateev, K.V.; Ulomsky, E.N.; Drokin, R.A.; Slepukhin, P.A.; Rusinov, V.L. 2-Furyl-6-nitro-1,2,4-triazolo [1,5-*a*]pyrimidin-7-one. *Molbank* **2023**, *2023*, 0. https://doi.org/

Received: 27 December 2022
Revised: 16 January 2023
Accepted: 19 January 2023
Published: 23 January 2023

studies towards the active site of this receptor. This task requires optimizing the structural geometry of potential ligands by an X-ray analysis of appropriate crystal samples.

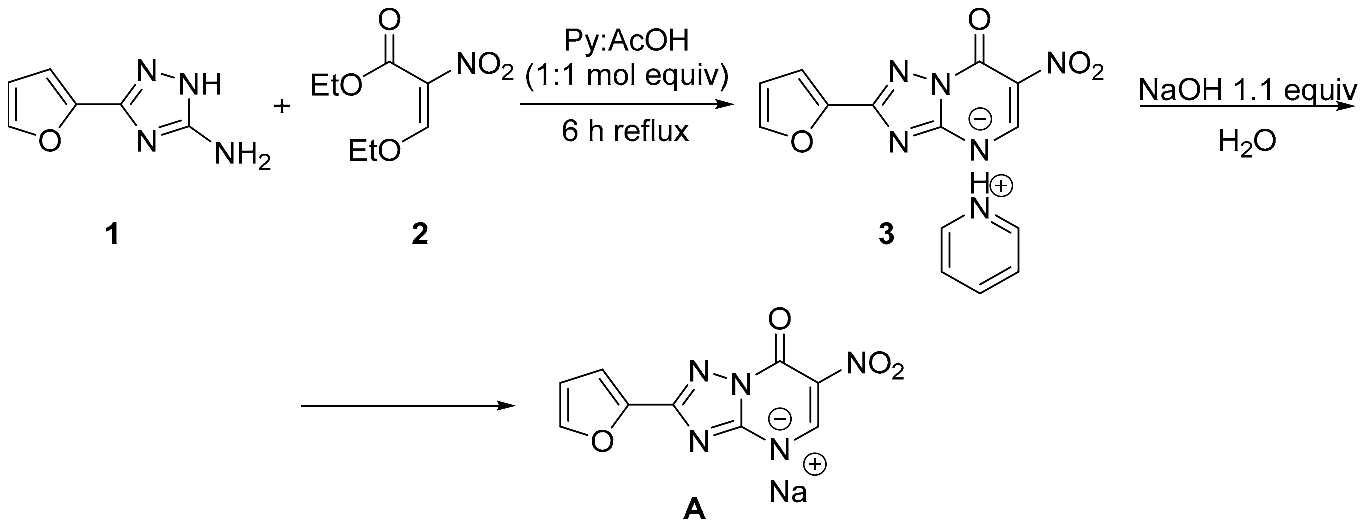
In this communication, we report the synthesis of a sodium salt of 2-(fur-2-yl)-6-nitro-1,2,4-triazolo[1,5-*a*]pyrimidin-7-one (**A**), a close structural analogue of ZM-241385 (Scheme 1). This heterocycle (**A**) can serve as an effector for A_{2a} AR and possesses antiseptic activity. We obtained a crystal sample of azolopyrimidine (**A**) that was suitable for X-ray analysis and determined the geometry of this molecule.



Scheme 1. The structure of the sodium salt 2-furyl-6-nitro-1,2,4-triazolo[1,5-*a*]pyrimidin-7-one (**A**) and ZM-241385.

2. Results

The 2-furyl-6-nitro-1,2,4-triazolo[1,5-*a*]pyrimidin-7-one **A** was obtained by a two-step reaction scheme starting from aminoazole **1** and ethoxymethylenenitroacetate **2** (Scheme 2).



Scheme 2. Synthesis of 2-furyl-6-nitro-1,2,4-triazolo[1,5-*a*]pyrimidin-7-one sodium salt **A**.

In the first step, an equimolar mixture of glacial acetic acid and dry pyridine was used as a solvent for the cyclocondensation of azole **1** and nitrocompound **2**. It was found that the isolated product is a pyridinium salt of nitroazoloazine **3**, which was confirmed by ^{1}H and ^{13}C NMR analysis (characteristic peaks of pyridine ring in downfield). This can be explained by a strong NH-acidity of the azoloazine scaffold due to the electron-withdrawing effect of the nitro group on the π-deficiency of the heterocyclic system. Subsequent treatment of the pyridinium salt 3 with aqueous solution NaOH resulted in the sodium salt of 2-(fur-2-yl)-6-nitrotriazolo[1,5-*a*]pyrimidin-7-one **A** in a good yield (70%). It should be noted that sodium salt **A** has good solubility in aqueous media, which is important for biological studies.

All compounds were fully characterized by NMR, IR spectroscopy, and elemental analysis (Figures S1–S4, Supplementary Materials). The structure of sodium salt of 2-(fur-2-yl)-6-nitrotriazolo[1,5-*a*]pyrimidin-7-one **A** was confirmed by an X-ray diffraction analysis (Figure 1). According to the XRD data, the compound is crystallized in the non-centrosymmetric space group as a hydrate (1:1). In the result of the various anion–cationic interactions, the salt forms the complicated 3D structure; however, any shortened π-π-contacts between heterocycles in the crystal are not observed.

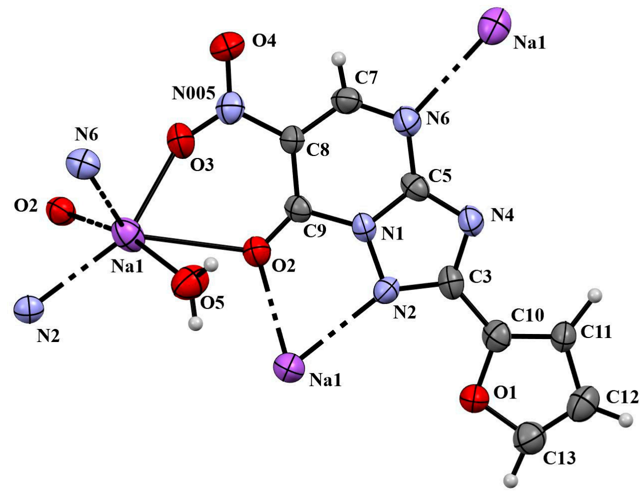


Figure 1. The molecule of compound **A** in the thermal ellipsoids of the 50% probability level and contacts with nearest atoms.

3. Materials and Methods

Commercial reagents were obtained from Sigma-Aldrich Merck Life Science LLC Valovaya Str. 35, floor 6 Moscow 115054, Russian Federation, Acros Organics Thermo Fisher Scientific Geel—Belgium, or Alfa Aesar Thermo Fisher (Kandel) GmbH Erlenbachweg 2 76870, Kandel Germany and used without any preprocessing. All workup and purification procedures were carried out using analytical-grade solvents. One-dimensional ^{1}H and ^{13}C NMR spectra were acquired on a Bruker DRX-400 instrument (400 and 101 MHz, respectively) utilizing DMSO-d_6 as a solvent and an external reference. Chemical shifts are expressed in δ (parts per million, ppm) values, and coupling constants are expressed in herts (Hz). The following abbreviations are used for the multiplicity of NMR signals: s, singlet; d, doublet; t, triplet; dd, doublet of doublet; and m, multiplet. The IR spectra were recorded on a Bruker α spectrometer equipped with a ZnSe ATR accessory. The elemental analysis was performed on a PerkinElmer PE 2400 elemental analyzer. Melting points were determined on a Stuart SMP3 (Staffordshire, UK) and are uncorrected. High-resolution mass spectra were obtained using an Agilent 1290 Infinity II high-performance liquid chromatography system equipped with a UV diode array detector and a tandem quadrupole time-of-flight accurate mass detector (Agilent 6545, Agilent Technologies Inc., Santa Clara, CA, USA). 3-(Furan-2-yl)-1*H*-1,2,4-triazol-5-amine (**1**) was prepared according to a literature procedure [10].

3.1. Pyridinium 2-(Fur-2-yl)-6-nitro-1,2,4-triazolo[1,5-a]pyrimidin-7-one (3)

Ethyl ethoxymethylenenitroacetate **2** (0.01 mol, 1 equiv) was added to a stirred solution of the 3-(furan-2-yl)-1*H*-1,2,4-triazol-5-amine (**1**) (0.01 mol, 1 equiv) in a mixture of pyridine (8.5 mL) and glacial acetic acid (6.0 mL), and the resulting solution was stirred at reflux (145 °C oil bath temperature) for 6 h. The obtained precipitate was filtered off and washed with EtOH. Yellow powder (0.65 g, yield 60%), m.p. 225–226 °C. FT-IR (neat) ν_{max} (cm^{-1}): 1689 (C=O), 1616 (NO_2), 1311 (NO_2). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 6.61 (1 H, dd, J = 3.4, 1.8 Hz, H-4′), 7.07 (1 H, d, J = 3.3 Hz, H-3′), 7.77 (1 H, d, J = 1.8 Hz, H-5′), 7.80–7.88 (2 H, m, H-3′′, H-5′′), 8.31 (1 H, t, J = 7.7 Hz, H-4′′), 8.83 (2 H, m, H-2′′, H-6′′), 9.04 (1 H, s, H-5). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ (ppm) 111.0, 111.9, 123.6, 126.7, 143.3, 143.4, 144.6, 144.8, 144.9, 146.1, 150.3, 152.3, 155.1, 157.4. Anal. Calcd. for $C_{14}H_{10}N_6O_4$: C 51.54, H 3.09, N 25.76; found: 51.48, H 3.10, N 25.80. HRMS (ESI/Q-TOF), m/z: [M+H]+ Calcd for $C_{14}H_{10}N_6O_4$ 327.0836; Found 327.0831.

3.2. 2-(Fur-2-yl)-6-nitro-1,2,4-triazolo[1,5-a]pyrimidin-7-one Sodium Salt (A)

Pyridinium salt 2-(fur-2-yl)-6-nitro-1,2,4-triazolo[1,5-*a*]pyrimidin-7-one **3** 0.33 g (0.001 mol, 1 equiv) was added to the solution of 0.064 g (0.0016 mol, 1.6 equiv) of NaOH in 10 mL of H_2O. The resulting suspension was refluxed for 10 min and cooled to 25 °C. The solid product that formed was collected by filtration and recrystallized from H_2O. Yellow crystals (0.16 g, yield 60%), m.p. 259–261 °C. FT-IR (neat) ν_{max} (cm^{-1}): 3358 (H_2O), 1661 (C=O), 1539 (NO_2), 1256 (NO_2). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 6.66 (1 H, dd, *J* = 3.4, 1.8 Hz, H-4′), 7.10 (1 H, d, *J* = 3.4, Hz H-3′), 7.86 (1 H, d, *J* = 1.8 Hz, H-5′), 9.01 (1 H, s, H-5). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ (ppm) 110.9, 111.9, 123.2, 144.5, 146.4, 150.9, 153.5, 155.6, 158.7. Anal. Calcd. for $C_9H_4N_5O_4Na{*}H_2O$: C 37.64 H 2.11 N 24.39; found: C 37.73 H 2.09 N 24.42. HRMS (ESI/Q-TOF), *m*/*z*: [M+H]+ Calcd for $C_9H_4N_5NaO_4$ 270.0233; Found 270.0232.

The XRD analysis was carried out using equipment from the Center for Joint Use "Spectroscopy and Analysis of Organic Compounds" at the Postovsky Institute of Organic Synthesis of the Russian Academy of Sciences (Ural Branch). The experiment was accomplished on the automated X-ray diffractometer «Xcalibur 3» with a CCD detector on standard procedure (MoKα-irradiation, graphite monochromator, ω-scans with 1^0 step at T = 295(2) K). Empirical absorption correction was applied. The solution and refinement of the structures were accomplished using the Olex program package [11]. The structures were solved using the method of the intrinsic phases on the ShelXT program and refined on ShelXL in anisotropic approximation by the full-matrix least-squared method for non-hydrogen atoms [12]. The H-atoms were placed in the calculated positions and refined in isotropic approximation.

Crystal Data for $C_9H_6N_5NaO_5$ (M =287.18 g/mol): orthorhombic, space group $P2_12_12_1$, a = 6.0608(9) Å, b = 13.231(2) Å, c = 13.608(2) Å, V = 1091.3(3) Å^3, Z = 4, T = 295(2) K, μ(Mo Kα) = 0.177 mm^{-1}, D_{calc} = 1.748 g/cm^3, 3615 reflections measured (7.36° $\leq 2\Theta \leq$ 54.17°), 2378 unique (R_{int} = 0.0766, R_{sigma} = 0.1364). These were used in all calculations. The final R_1 = 0.0687 (I > 2σ(I)) and wR_2 = 0.1840 (all data).

The XRD data were deposited in the Cambridge Structural Database with number CCDC 2232970. These data can be requested free of charge via www.ccdc.cam.ac.uk.

4. Conclusions

To summarize, ZM-241385 structural analogue, 2-(fur-2-yl)-6-nitro-1,2,4-triazolo[1,5-*a*]pyrimidin-7-one sodium salt **A** was synthesized. The synthesis was characterized by simplicity and the availability of the reagents. The structure of the synthesized compounds is unambiguously confirmed by the set of spectral data. The prepared structural analogue of ZM-241385 may be further used in medicine for the treatment of sepsis.

Supplementary Materials: Figures S1–S2: ^{1}H and ^{13}C NMR spectra of compounds **3**, **A**; Figures S3–S4: IR spectra of compounds **3**, **A**; Figures S5–S6: HRMS chromatogram with mass spectrum of compounds **3**, **A**.

Author Contributions: Synthesis, V.V.F. and K.V.S.; methodology, E.N.U. and V.L.R.; writing—original draft preparation, V.V.F. and K.V.S.; writing—review and editing, E.N.U. and V.L.R.; crystallographic investigation, P.A.S. and R.A.D.; project administration, V.L.R. All authors have read and agreed to the published version of the manuscript.

Funding: The research funding from the Ministry of Science and Higher Education of the Russian Federation (Ural Federal University Program of Development within the Priority-2030 Program) is gratefully acknowledged.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data are contained within the article.

Acknowledgments: The team of authors would like to thank the Laboratory for Comprehensive Research and Expert Evaluation of Organic Materials under the direction of O.S. Eltsov.

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

References

1. Angus, D.C.; Linde-Zwirble, W.T.; Lidicker, J.; Clermont, G.; Carcillo, J.; Pinsky, M.R. Epidemiology of Severe Sepsis in the United States: Analysis of Incidence, Outcome, and Associated Costs of Care. *Crit. Care Med.* **2001**, *29*, 1303–1310. [CrossRef] [PubMed]
2. Dellinger, R.P. Cardiovascular Management of Septic Shock. *Crit. Care Med.* **2003**, *31*, 946–955. [CrossRef] [PubMed]
3. Martin, G.S.; Mannino, D.M.; Eaton, S.; Moss, M. The Epidemiology of Sepsis in the United States from 1979 through 2000. *N. Engl. J. Med.* **2003**, *348*, 1546–1554. [CrossRef] [PubMed]
4. Seymour, C.W.; Liu, V.X.; Iwashyna, T.J.; Brunkhorst, F.M.; Rea, T.D.; Scherag, A.; Rubenfeld, G.; Kahn, J.M.; Shankar-Hari, M.; Singer, M.; et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *J. Am. Med. Assoc.* **2016**, *315*, 762. [CrossRef] [PubMed]
5. Rhodes, A.; Evans, L.E.; Alhazzani, W.; Levy, M.M.; Antonelli, M.; Ferrer, R.; Kumar, A.; Sevransky, J.E.; Sprung, C.L.; Nunnally, M.E.; et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med.* **2017**, *43*, 304–377. [CrossRef] [PubMed]
6. Volbeda, M.; Wetterslev, J.; Gluud, C.; Zijlstra, J.G.; van der Horst, I.C.C.; Keus, F. Glucocorticosteroids for Sepsis: Systematic Review with Meta-Analysis and Trial Sequential Analysis. *Intensive Care Med.* **2015**, *41*, 1220–1234. [CrossRef] [PubMed]
7. Ohta, A.; Sitkovsky, M. Role of G-Protein-Coupled Adenosine Receptors in Downregulation of Inflammation and Protection from Tissue Damage. *Nature* **2001**, *414*, 916–920. [CrossRef] [PubMed]
8. Savateev, K.V.; Ulomsky, E.N.; Fedotov, V.V.; Rusinov, V.L.; Sivak, K.V.; Lyubishin, M.M.; Kuzmich, N.N.; Aleksandrov, A.G. 6-Nitrotriazolo [1,5-*a*]Pyrimidines as Promising Structures for Pharmacotherapy of Septic Conditions. *Russ. J. Bioorg. Chem.* **2017**, *43*, 421–428. [CrossRef]
9. Hasko, G.; Nemeth, Z.; Bleich, D.; Deitch, E. Sepsis Prevention through Adenosine Receptor Modulation. WO Patent 2006 083949, 1 February 2006.
10. Aghazadeh Tabrizi, M.; Baraldi, P.G.; Ruggiero, E.; Saponaro, G.; Baraldi, S.; Poli, G.; Tuccinardi, T.; Ravani, A.; Vincenzi, F.; Borea, P.A.; et al. Synthesis and Structure Activity Relationship Investigation of Triazolo [1,5-*a*]Pyrimidines as CB2 Cannabinoid Receptor Inverse Agonists. *Eur. J. Med. Chem.* **2016**, *113*, 11–27. [CrossRef] [PubMed]
11. Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J.A.K.; Puschmann, H. OLEX2: A Complete Structure Solution, Refinement and Analysis Program. *J. Appl. Crystallogr.* **2009**, *42*, 339–341. [CrossRef]
12. Sheldrick, G.M. Crystal Structure Refinement with SHELXL. *Acta Crystallogr. C* **2015**, *C71*, 3–8. [CrossRef] [PubMed]