

Abstract

Study of Cytotoxicity of Spiro-Fused [3-Azabicyclo[3.1.0]hexane]oxindoles against Tumor Cell Lines [†]

Anton A. Kornev ¹, Stanislav V. Shmakov ¹, Alexey S. Klyuchnikov ¹, Alexey V. Artemov ^{1,2}, Alexander V. Stepanov ³ and Vitali M. Boitsov ^{1,*} 

¹ Laboratory of Nanobiotechnologies, Saint Petersburg National Research Academic University of the Russian Academy of Sciences, Saint Petersburg 194021, Russia

² Department of Chemistry, Saint Petersburg State University, Saint Petersburg 199034, Russia

³ Laboratory of Structural Dynamics, Stability and Folding of Proteins, Institute of Cytology RAS, Saint Petersburg 194064, Russia

* Correspondence: bovitalli@yandex.ru

[†] Presented at the 8th International Electronic Conference on Medicinal Chemistry, 1–30 November 2022;

Available online: <https://ecmc2022.sciforum.net/>.

Abstract: Oncological diseases are one of the most common public health problems and the second leading cause of death after cardiovascular disease. Natural products or synthetic compounds derived from natural products continue to be excellent sources for new drug candidates. Recent advances in synthesis of complex heterocyclic systems have led to significant increase in interest in development of efficient methods for synthesis of thereof as potential drugs or biological probes. Oxindole, azabicyclohexane and pyrrolizine units are known heterocyclic motifs that form the core of a large family of alkaloid natural products with strong bioactivity profiles. Series of heterocyclic compounds containing 3-spiro[3-azabicyclo[3.1.0]hexane]oxindole framework have been studied for their antiproliferative activity against K562, Jurkat, HeLa, and CT26 cell lines. These spiro-fused adducts are readily available via one-pot three-component 1,3-dipolar cycloaddition reactions of cyclopropanes and azomethine ylides (generated in situ from amino acids and oxindoles). In agreement with DNA cytometry studies, the tested compounds have achieved significant cell-cycle perturbation with higher accumulation of cells in G0/G1 phase. Using confocal microscopy, we found that actin filaments disappeared and granular actin was distributed diffusely in the cytoplasm in up to 40% of treated cells. In addition, we discovered that the number of cells with filopodium-like membrane protrusions was significantly reduced after treatment with some of the tested compounds (from 92% in control cells up to 36% after treatment). The obtained results support the antitumor effect of the studied compounds and encourage the extension of the study in order to improve the anticancer activity and reduce the toxicological risks of the obtained compounds.

Keywords: antiproliferative activity; tumor cell lines; morphological changes (cytoskeleton); cell death; cell cycle; spiro-fused [3-azabicyclo[3.1.0]hexane]oxindoles



Citation: Kornev, A.A.; Shmakov, S.V.; Klyuchnikov, A.S.; Artemov, A.V.; Stepanov, A.V.; Boitsov, V.M. Study of Cytotoxicity of Spiro-Fused [3-Azabicyclo[3.1.0]hexane]oxindoles against Tumor Cell Lines. *Med. Sci. Forum* **2022**, *14*, 8. <https://doi.org/10.3390/ECMC2022-13653>

Academic Editor: Maria Emilia Sousa

Published: 16 November 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2022 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 (<https://creativecommons.org/licenses/by/4.0/>).

Supplementary Materials: The following are available online at <https://www.mdpi.com/article/10.3390/ECMC2022-13653/s1>.

Author Contributions: Investigation, A.A.K., S.V.S., A.S.K., A.V.A., A.V.S., V.M.B.; Writing, V.M.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research was financially supported by a grant from the Russian Science Foundation, RSF 20-15-00332.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available on request from the corresponding authors.

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