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Synthesis of novel spiro-fused cyclopropa[a]pyrrolizines and 3-azabicyclo[3.1.0]hexanes and evaluation their antitumor activity

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Oncological diseases are one of the most common public health problems and a major cause of mortality. Increasing drug resistance and development of tumor resistance as well as severe side-effects of chemotherapeutic agents reduce the clinical efficacy of currently used anticancer drugs and therapies. Despite the increasing use of targeted drugs and methods of immunotherapy of oncological diseases, the development of cytostatic agents with broad range of actions is an important challenge for the treatment of cancer. Naturally occurring products and their synthetic analogous are excellent sources for new drug candidates, especially for anticancer therapy. The spirooxindole, azabicyclohexane, spirocyclopropapyrrolizine or indenoquinoxaline units are heterocyclic systems that form the core of large families of naturally occurring products with strong bioactivity and interesting structural properties. Significant recent advances in the synthesis of such fused heterocyclic systems led to increased interest in the development of related compounds as potential medicinal agents or biological probes. We have developed a simple and efficient synthesis of complex spirocyclic compounds via stereoselective one-pot three-component 1, 3-dipolar cyclo addition of *in situ* generated azomethine ylides onto cyclopropenes. The desired spiro [3-aza bicyclo[3.1.0]hexanes] and spiro [cyclopropa[a]pyrrolizines] were produced in good to high yields (up to 96%) and excellent diastereoselectivity (as a single diastereomer) in most cases. The azomethine ylides were *in situ* generated from 11H-indeno [1, 2-b]quinoxalin-11-one derivatives or isatins and amines, such as N-substituted and N-unsubstituted α-amino acids, various benzylamines, and also peptides (dipeptide Gly-Gly and tripeptide Gly-Gly-Gly). Antitumor activity against erythroleukemia (K562), cervical carcinoma (HeLa) as well as standard fibroblast cell line 3T3B and SV40-transformed 3T3B SV40 cell lines was evaluated *in vitro* by MTS-assay or flow cytometry. Cell cycle, cell viability and actin cytoskeleton structure were also investigated.

Recent Publications

1. Filatov A S, Knyazev N A, Molchanov A P, Panikorovsky T L, Kostikov R R, Larina A G, Boitsov V M and Stepakov A V (2017) Synthesis of functionalized 3-spiro[cyclopropa[a]pyrrolizine] and 3-spiro[3-azabicy-clo[3.1.0]hexane]oxindoles from cyclopropenes and azomethine ylides via [3+2]-cycloaddition. Journal of Organic Chemistry 82:959-975.
2. Filatov A S, Knyazev N A, Ryazantsev M N, Suslonov V V, Larina A G, Mol-chanov A P, Kos-tikov R R, Boitsov V M and Stepakov A V (2018) A highly dia-stereoselective one-pot three-component 1,3-dipolar cycloaddition of cyclo-propenes with azomethine ylides generated from 11H-Indeno[1,2-b]-quinoxalin-11-ones. Organic Chemistry Frontiers 5(4):595-605.

Biography

Vitali M Boitsov is an Associate Professor in the Saint-Petersburg Academic University, Russian Federation. He has completed his PhD in Organic Chemistry in 2005 from the Saint-Petersburg State University, Russian Federation.

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