

ANNOTATION

on the dissertation work «Synthesis, transformations and properties of fluorine-containing divinylketones» for the degree of Doctor of Philosophy (PhD)

on educational program 8D05301 – «Chemistry»

by Koshetova Zhanargul Abdrakhmanovna

Research topic: Synthesis, transformations and properties of fluorine-containing divinylketones.

Aim of the Research: The development of methods for the synthesis of fluoro- and trifluoromethyl-substituted divinylketones based on piperidin-4-ones, study of their chemical transformations and biologically active properties.

Research objectives:

- To synthesize fluorine-containing divinyl ketones via aldol–crotonic condensation (Claisen–Schmidt reaction) of 1-(2-ethoxyethyl)- and 1-(*N*-benzyl)piperidin-4-ones with *o*-, *m*-, and *p*-fluorobenzaldehydes, namely: 1-(*N*-benzyl)-3,5-di(*o*-, *m*-, *p*-fluorobenzylidene)piperidin-4-one and 1-(2-ethoxyethyl)-3,5-di(*o*-, *m*-, *p*-fluorobenzylidene)piperidin-4-one.

- To introduce a fluoroalkyl substituent into the aromatic ring via aldol–crotonic condensation of the aforementioned piperidin-4-ones with *o*-, *m*-, and *p*-trifluoromethylbenzaldehydes, affording the corresponding trifluoromethyl-substituted derivatives.

- To increase structural complexity of the synthesized compounds through heterocyclization with fluorophenyl- and phenylhydrazines (Wolff–Kishner reaction), leading to the formation of piperidine–pyrazoline derivatives.

- To establish the composition and structure of the synthesized compounds using a комплекс of physicochemical analytical methods.

- To evaluate the biological activity of the obtained compounds and analyze the results to identify the most active structures.

Research methods: The composition and structure of the obtained compounds were determined by physicochemical methods. Infrared spectra (IR) were recorded on KBr tablets on a Nicolet 5700 spectrometer, nuclear magnetic resonance spectra (^1H and ^{13}C NMR) on hydrogen nuclear in a CDCl_3 solution on a JNM-ECA Jeol - 400 spectrometer with operating frequencies of 399.78 and 100.53 MHz. The individuality of the compounds and the direction of the reaction were determined by thin-layer chromatography (TLC) on a Silufol UV-254 plate. Eluent: benzene:dioxane (7:1), hexane:diethyl ether (1:2). For purification, column chromatography on aluminum oxide was used.

Key provisions submitted for defense (substantiated scientific hypotheses and conclusions constituting new knowledge):

1. Novel 4-oxopiperidines bearing 3,5-disubstituted arylidene fragments have been synthesized, namely: 1-(2-ethoxyethyl)-3,5-di(*o*-, *m*-, *p*-fluorobenzylidene)-, 1-(2-ethoxyethyl)-3,5-di(*o*-, *m*-, *p*-trifluoromethylbenzylidene)-, 1-(*N*-benzyl)-3,5-di(*o*-, *m*-, *p*-fluorobenzylidene)-, and 1-(*N*-benzyl)-3,5-di(*o*-, *m*-, *p*-trifluoromethylbenzylidene)piperidin-4-ones.

2. The reaction of aromatic hydrazines with piperidine dienones afforded, in good yields, the corresponding pyrazoline derivatives: 5-benzyl-7-(*o*-, *m*-, *p*-fluorobenzylidene)-2,3-bis(*o*-, *m*-, *p*-fluorophenyl)-3,3a,4,5,6,7-hexahydro-2H-pyrazolo[4,3-*c*]pyridine; 5-benzyl-7-(*o*-, *m*-, *p*-trifluoromethylbenzylidene)-2,3-bis(*o*-, *m*-, *p*-fluorophenyl)-3,3a,4,5,6,7-hexahydro-2H-pyrazolo[4,3-*c*]pyridine; 5-(2-ethoxyethyl)-7-(*o*-, *m*-, *p*-fluorobenzylidene)-2,3-bis(*o*-, *m*-, *p*-fluorophenyl)-3,3a,4,5,6,7-hexahydro-2H-pyrazolo[4,3-*c*]pyridine; and 5-(2-ethoxyethyl)-7-(*o*-, *m*-, *p*-trifluoromethylbenzylidene)-2,3-bis(*o*-, *m*-, *p*-fluorophenyl)-3,3a,4,5,6,7-hexahydro-2H-pyrazolo[4,3-*c*]pyridine.

3. A novel complex of a fluorinated pyrazolopiperidine derivative—5-benzyl-7-(2-fluorobenzylidene)-2,3-bis(2-fluorophenyl)-3,3a,4,5,6,7-hexahydro-2H-pyrazolo[4,3-*c*]pyridine hydrochloride (PP·HCl)—with beta-cyclodextrin (PPβCD) was synthesized and characterized as a potential therapeutic agent for the treatment of chemotherapy-induced myelosuppression and lymphopenia. Encapsulation of PP in β-cyclodextrin increased its aqueous solubility by approximately 3.4-fold and enhanced the dissolution rate by 2.8-fold compared to the free compound.

4. Biological studies demonstrated that some of the newly synthesized compounds exhibit plant growth-stimulating and retardant properties, as well as erythropoiesis-, thrombopoiesis-, and leukopoiesis-stimulating activities, thereby influencing blood composition.

Relationship of the dissertation topic to Research activities and national/state programs: The dissertation work was completed in accordance with the research program of the A.B. Bekturov Institute of Chemical Sciences on the following topics: Targeted development of preventative agents and/or adaptogens for plants from elemental organic systems» (AP05131025, 2018-2020), “Targeted modification of polyfunctional azaheterocycles - derivatives of piperidine and piperazine - into new bioactive molecular systems for agriculture and/or medicine” (AP08856051, 2020-2022), “Targeted modification of natural alkaloids and their synthetic analogues into agents of a given type of action” (AP 23484420 2024-2026).

Justification of the novelty and significance of the obtained results and their alignment with scientific development priorities and state programs:

1. For the first time, a method for the synthesis of 3,5-difluoro- and trifluoromethyl-substituted diarylidene ketones based on 1-(2-ethoxyethyl)- and 1-(N-benzyl)piperidin-4-one has been developed and experimentally validated.

2. For the first time, a series of piperidine-pyrazole derivatives containing a curcumin-like α,β-unsaturated carbonyl fragment has been obtained via heterocyclization of the synthesized piperidine dienones with fluorophenyl- and phenylhydrazines (Wolff-Kishner reaction).

3. The composition, structure, and structural features of the synthesized fluorinated divinyl ketones and their heterocyclization products were determined and thoroughly characterized using a комплекс of modern physicochemical methods, including ¹H and ¹³C NMR spectroscopy, IR spectroscopy, elemental analysis, and TLC.

4. Based on the results of biological screening, it was demonstrated that some of the synthesized fluorine-containing heteroorganic compounds exhibit plant growth-regulating activity (SAV-52) and inhibitory activity (SAV-41), as well as pronounced stimulatory effects on erythropoiesis, thrombopoiesis, and leukopoiesis (BIV-152).

Description of the doctoral candidate's contribution to the preparation of each publication (the candidate's share is indicated as a percentage of the total text):

Based on the results of the dissertation work published 14 scientific works.

Articles in international scientific journals included in the Scopus database of scientific materials (Eurasian Chem.-Technol. J. Q4 29%, Molecules J. Q1 87%) - 2 (two):

1. Novel 7-Aryliden-3,3a,4,5,6,7-(hexahydro-5-(2-ethoxyethyl)-2-phenyl-3-aryl-2H-pyrazolo[4,3-c]pyridine hydrochloride: Synthesis and Structure // Eurasian Chem.-Technol. J. - 2022. – Vol. 24. -P. 43–50.<https://doi.org/10.18321/ectj1147> (Koshetova Zh.A. 85%, birlesken author V.K. Yu., T. Iskakova., N.A. Zhumanova., K. Beketov., A.E. Malmakova A., K.D. Praliev., T. Seilkhanov, K. Berlin).

2. Design, Characterization, and Hematopoietic Efficacy of a Fluorinated Pyrazolopiperidine Inclusion Complex // Molecules 2025, Volume 30, Issue 20, 4047 (Koshetova Zh.A. 80%, birlesken author Daulet G., Ten A., Koyshaiganova R., Baktybaeva G., Zharkynbek T., A. Zazybin., T. Seilkhanov., Zhumanova N., Yu V).

Articles in international scientific journals included in the Web of Science database of scientific materials - 1 article and 1 international patent:

1. Novel 3,5-bis(fluorobenzylidene)piperidin-4-ones as regulators of wheat growth // International Journal of Biology and Chemistry 14 No. 2 117-122. <https://doi.org/10.26577/ijbch.2021.v14.i2.016>. (2021) (Koshetova Zh.A. 85%, Praliev K.D., Yu V.K., Li T.E., Zhumanova N.A., Ersen Turaç).

2. New 1-(2-ethoxyethyl)-3,5-di[2-(trifluoromethyl)benzylidene]piperidin-4-one in combination with β cyclodextrin having hemopoiesis-stimulating activity. халықаралық патент A61K-031/465. Praliev K.D., Koshetova Z.A., Fisher D.E., Yu V.K., Zhumanova N.A., Baktybaeva L.K., Daulet G.D.

One article was published in journals recommended by the Committee for Quality Assurance in Science and Higher Education of the Ministry of Education and Science of the Republic of Kazakhstan.

1. 3,5-Bis (arylidene) piperidin-4-ones as synthetic curcumin analogues // Chemical Journal of Kazakhstan. 2019. No. 2. pp. 49-55 (Koshetova Zh.A. 75%, co-authors Zhumanova N.A., Malmakova A.E., Zhumakova S.S., Makasheva D., Praliev K.D., Yu V.K).

Six abstracts of reports have been published in the collections of proceedings of domestic and international scientific and practical conferences:

1. Approaches to new biologically active synthetic analogues of curcumin // XX International scientific and practical conference of students and young scientists named after L. P. Kulev "Chemistry and chemical technology in the 21st century". May 20-23, 2019, Tomsk. (Koshetova Zh.A.60%, Zhumakova S.S., Makashova D).

2. Triazabicycles as potential antispasmodics // XXI Mendeleev Congress on General and Applied Chemistry, September 9-13, 2019. St. Petersburg. - Volume 3. - P. 316. (Koshetova Zh.A.70%, Malmakova A.A., Zhumanova N.A., Zhumakova S.S., Seilkhanov T.M., Yu V.K., Praliev K.D).

3. Triazabicycles as potential // Book of abstracts of the XXI Mendeleev Congress on general and applied chemistry, September 9-13. – Saint Petersburg, 2019. -Volume 5.

-P. 299 (Koshetova Zh.A. 70%, Malmakova A.A., Zhumanova N.A., Zhumakova S.S., Seilkhanov T.M., Yu V.K., Praliev K.D).

4. New derivatives of pyrazoline piperidines as potential serotonin modulators and/or anti-inflammatory agents // X International Beremizhanovsky Congress on Chemistry and Chemical Technology, October 24-25, Almaty, -2019. - P. 136-137. (Koshetova Zh.A. 70%, Zhumanova N.A., Malmakova A.E., Praliev K.D., Seilkhanov T.M., Yu V.K).

5. Biopolymer Materials Containing New Synthesized Curcumin-Like 3,5-Bis-Arylidenpiperidones // "Ankarada düzenlenen 4 Uluslararası Gevher Nesibe Sağlık Bilimlerine kongresine katılmıştır" Turkiya 2019 (Zh.A. Koshetova. 80%, N.A.Zhumanova., S.S. Zhumakova., A.E. Malmakova, Zh. Rakhimbekov., Ersen Turaç., V.K. Yu).

6. Synthetic Curcumin-like Remedies //Materials of the 6th International Russian-Kazakh scientific and practical conference "Chemical technology of functional materials". - June 15-16, 2020. "Kazakh Universities" 2020. Almaty, pp. 81-85. (Koshetova Zh.A. 75%, Malmakova A.E, Zhumanova N.A, Seilkhanov T.M, Praliev K.D, Yu V.K).

In the Republic of Kazakhstan, 1 (one) patent for a utility model and 2 (two) patents for inventions were received:

1. 1-(2-ethoxyethyl)-3,5 -di-(2-fluorobenzylidene)-piperidin-4-one with growth-stimulating activity Utility Model Patent. April 30, 2021 No. 6025.

2. Complex of 5-(2-ethoxyethyl)-7-(4-fluorobenzylidene)-3-(4-fluorophenyl)-2-phenyl-3,3a,4,5,6,7-hexahydro-2H-pyrazolo[4,3-c]pyridine s-cyclodextrin hydrochloride with β -cyclodextrin having myelostimulating activity. Patent for invention March 5, 2021. No. 34931.

3. Complex of N-Benzyl 3,5-di(n-fluorobenzylidene)piperidin-4-one with β -cyclodextrin, having retardant properties Patent for invention April 22, 2022 No. 35617.

Structure and scope of work. The dissertation consists of standard sections: normative references, designations and abbreviations, introduction, literature review, practical part, research results and their discussion, as well as a list of references.

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