ANNOTATION

of the dissertation of Duisenali Aidana Maksutkyzy, a candidate for the degree of Doctor of Philosophy (PhD) under the educational program 8D07105 – «Chemical Technology of Organic Substances», entitled: «Technology for the Synthesis of Biologically Active Compounds Based on β-Aminopropioamidoximes».

General description of the work. The dissertation is intended to solve a pressing scientific and practical problem in the field of medicinal chemistry and organic synthesis: the development of technological methods for obtaining new biologically active compounds based on β-aminopropioamidoximes. The relevance of this topic is due to the increasing resistance of pathogens to existing antibiotics and the need to create new effective chemotherapeutic agents, which are based on the synthesis of new biologically active compounds.

The research work used a complex of modern research and analysis methods aimed at solving scientific problems: IR spectroscopy, UV spectroscopy, 1H and 13C NMR spectroscopy, elemental analysis, X-ray structural analysis, HPLC-dad chromatography, in vitro studies of sensitive and resistant pathogens.

Relevance of the research work. Currently, the resistance of pathogenic microorganisms to existing antibiotics is increasing. This situation reduces the effectiveness of the treatment of infectious diseases and is becoming an urgent problem in the healthcare system. As a solution to this, amidoximes, as universal building blocks, open up wide opportunities for the synthesis of various heterocyclic systems. The studied class of β-aminopropioamidoximes is of particular interest due to its multifunctionality, since on their basis it is possible to obtain linear derivatives (O-aroyl-β-aminopropioamidoximes and 5-aryl-1,2,4-oxadiazoles), as well as products of aryl- and alkylsulfochlorination of unique spirocyclic structures.

The purpose of the work: Targeted synthesis of new derivatives of β-aminopropioamidoximes, elucidation of their structures using modern physicochemical methods of analysis, and evaluation of their biological activity *in vitro.*

To achieve the set goal, the following tasks were solved:

– To improve the synthesis of pharmacologically acceptable salts of O-toluoyl-β-(morpholin-1-yl)propioamidoxime and 5-aryl-3-β-(piperidin-1-yl)ethyl-1,2,4-oxadiazoles by separately obtaining a hydroxylamine base solution for reaction with β-aminopropionitriles.

– Tosylation of β-aminopropioamidoximes, isolation of 2-aminospiropyrazolyl ammonium sulfonates formed as a result of intramolecular N–N(+)-heterocyclization, synthesis of new chlorides and hexafluorophosphates by ion exchange reaction, determination of their structure by IR, NMR spectroscopy and X-ray structural analysis (XRD).

– Study of the alkyl sulfochlorination of β-aminopropioamidoximes, in particular, using β-(morpholin-1-yl)- and β-(4-Ph-piperazin-1-yl)propioamidoximes, with elucidation of the role of an external tertiary base.

– Study of the antimicrobial and antifungal activity of the synthesized compound groups on panels of sensitive and resistant bacterial and fungal strains (Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Candida albicans, Basillus subtilis), determination of their minimum inhibitory concentrations and comparison of their efficacy with reference drugs. Determination of the antimicrobial and antifungal activity of the obtained O-alkylsulfonyl-β-(morpholin-1-yl)propioamidoxime and O-alkylsulfonyl-β-(4-Ph-piperazin-1-yl)propioamidoxime derivatives.

– Production technological proposal and material balance calculation for the production of new promising compounds.

Object of study: 2-aminospiropyrazolyl ammonium sulfonates, chlorides and hexafluorophosphate salts, O-alkylsulfonyl-β-(morpholin-1-yl)propioamidoxime and O-alkylsulfonyl-β-(4-Ph-piperazin-1-yl)propioamidoxime and O-toluoyl-β-(morpholin-1-yl)propioamidoxime, 5-aryl-3-β-(piperidin-1-yl)ethyl-1,2,4-oxadiazoles, formed as a result of aryl- and alkylsulfochlorination and intramolecular N–N(+)-heterocyclization.

Research methods: delicate organic synthesis, melting point determination, elemental analysis, IR and NMR spectroscopy, X-ray diffraction analysis, purity verification by HPLC-DAD, in vitro biological activity determination.

Scientific novelty of the research work

The scientific novelty and originality of the dissertation work are as follows:

– The synthesis of pharmacologically acceptable salts of O-toluoyl-β-(morpholin-1-yl)propioamidoxime and 5-aryl-3-β-(piperidin-1-yl)ethyl-1,2,4-oxadiazoles was improved by separately obtaining a hydroxylamine base solution for reaction with β-aminopropionitriles.

– Tosylation of β-aminopropioamidoximes, isolation of 2-aminospiropyrazolyl ammonium sulfonates as a result of intramolecular N–N(+)-heterocyclization, and new chlorides and hexafluorophosphates were obtained by ion exchange reaction.

– Alkyl sulfochlorates of new β-aminopropioamidoximes were obtained from β-aminopropioamidoximes using β-(morpholin-1-yl)- and β-(4-Ph-piperazin-1-yl)propioamidoximes, elucidating the role of the external tertiary base.

– The antimicrobial and antifungal activity of the synthesized new compounds on a panel of sensitive and resistant bacterial and fungal strains (Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Candida albicans, Basillus subtilis) was studied, their minimum inhibitory concentrations were determined, and their efficacy was compared with reference drugs.

– The material balance of the production and production of new promising compounds was calculated and a technological scheme was proposed.

The main provisions submitted for defense:

1. Sulfonates of 2-aminospiropyrazolium compounds of β-aminopropioamidoximes, when reacted with an ethereal solution of HCl in ethanol, lead to the formation of 2-aminospiropyrazolium ammonium chlorides in yields of 55–97%, and in a double ion exchange reaction with ammonium hexafluorophosphate in ethanol at room temperature, to the formation of 2-aminospiropyrazolium ammonium hexafluorophosphates in yields of 55–90%;

2. Alkyl sulfochlorination of β-(morpholin-1-yl)- and β-(4-F-piperazin-1-yl)propioamidoximes at room temperature without an external base leads to the formation of protonated nitrogen atoms of the heterocycles in the β-position and protonated nitrogen atoms of the imidomid group, and their counterions are complex compounds of the chloride anion and alkyl sulfonate anion in a 1:2 ratio with a yield of 52–74%;

3. The new compound 2-amino-1,5-diazaspiro[4.5]dec-1-en-5-ium hexafluorophosphate exhibits 6.67 times greater biological activity as an antifungal agent *in vitro* than the reference fluconazole against a resistant strain of *Aspergillus fumigatus*.

Compliance with scientific development directions or state programs.

This dissertation was carried out in accordance with the scientific development priorities approved by the Higher Scientific and Technical Commission under the Government of the Republic of Kazakhstan: 5. Scientific research in the field of natural sciences.

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Approbation of practical results of the work. The results obtained in the dissertation were presented and discussed at conferences:

Al-Farabi Kazakh National University Beremzhanov International Conference on Chemistry and Chemical Technologies, Almaty, Kazakhstan. December 4-6, 2024;

Mississippi University 7th World Congress on Medicinal and Aromatic Plants for Human and Animal Welfare, Oxford, USA. March 3-5, 2024.

Saint Petersburg State University 21st International School Conference "Magnetic Resonance and Its Applications - SPINUS-2024" dedicated to the 300th anniversary of Saint Petersburg State University, Russia, Saint Petersburg. April 1-5, 2024;

Tomsk Polytechnic University 25th International Scientific and Practical Conference of Students and Young Scientists named after outstanding chemists L.P. Kulev and N.M. Kizhner dedicated to the 100th anniversary of the birth of Professor V.P. Lopatinsky, Russia, Tomsk. May 20-24, 2024;

Ionian University Proceedings of the 20th Anniversary Symposium on Medicinal Chemistry, Greece, Karolos Papoulias. April 3-5, 2025;

Publications. As a result of the research conducted on the topic of the dissertation, the author's association published 10 scientific works, including 3 articles, 1 patent, 6 theses:

- one article in the international journal *Molecules* on the Scopus database (Q1, 83% percentile);
- 2 articles included in the list of journals of the Committee for Quality Assurance in Science and Higher Education of the Ministry of Science and Higher Education of the Republic of Kazakhstan;
- 6 abstracts of reports at international and republican conferences and symposia.
- one patent for a utility model of the «National Institute of Intellectual Property» of the Republic of Kazakhstan.

The individual contribution of the doctoral student to the preparation of each publication: in the independent planning and execution of the experimental part of the study, as well as in the interpretation and processing of the obtained data, as well as the author worked together with scientific advisors to eliminate problems and discuss the results of the study.

1. Kayukova L., Vologzhanina A., Dorovatovskii P., Yergaliyeva E., Uzakova A., Duisenali A. N-N(+) Bond-forming intramolecular cyclization of O-tosyloxyβ-aminopropioamidoximes and ion exchange reaction for the synthesis of 2-aminospiropyrazolilammonium chlorides and hexafluorophosphates // International Journal of Molecular Sciences – 2023. – Vol. 24. - 11315. (Biochemistry&MolecularBiology, IF 6,208,CiteScoreQ1, 85%). Conducting research, gathering resources and conducting formal analysis.

2. Kayukova L.A., Yerlanuly A., Duisenali A.M., Vologzhanina A.V. The base use in the alkylsulfochlorination of β-(4-phenylpiperazin-1-yl)-andβ-(benzimidazol-1-yl)-propioamidoximes in the chloroform and in the water // Chemical Journal of Kazakhstan. – 2024. – 2(86). – P. 36-41. https://doi.org/10.51580/2024-2.2710-1185.19 Creation of the experimental section, carrying out physicochemical analyses of the obtained compounds, processing and collection of literature.

3. Kayukova L.A., Seidakhmetova R.B., Duisenali A.M., Yerlanuly A., Sartoeva A.B. Search for drugs effective against pathogenic flora in the series of derivatives of para-toluoyl-β-(morpholin-1-yl)propioamidoxime and 5-aryl-3-β-(piperidin-1-yl)ethyl-1,2,4-oxadiazoles // Chemical Journal of Kazakhstan. – 2025. - No. 1(89). – P.129-139. DOI: https://doi.org/10.51580/2025-1.2710-1185.13
Creation of an experimental section, conducting physicochemical analyses of the obtained compounds, processing, collection of literature.

4. Patent for a utility model 26.05.2025 RK No. 2025/0772.2. The use of the compound 2-amino-1,5-diazaspiro[4.5]dec-1-en-5-ium hexafluorophosphate as an antifungal agent against mold fungi Aspergillus fumigatus ATCC 625 / Kayukova L.A., Duisenali A.M., Ospanov M.A., Elibayeva N.S. The dissertationist contributed to the preparation of the application in accordance with the current requirements, corrections, translations, and was also a correspondent.

5. In the materials of scientific conferences and symposium reports: obtaining and describing experimental data, obtaining and discussing the results of the analysis, preparing materials and participating in international conferences by the doctoral student.

Structure and scope of the dissertation. The dissertation consists of 121 pages of typewritten text and consists of an introduction, 3 sections, a conclusion, a list of references containing 26 tables, 57 figures, 11 drawings, 171 titles, and 10 pages of appendices.