

ABSTRACT

of the dissertation work of
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submitted in partial fulfillment of the requirements for the degree of
Doctor of Philosophy (PhD) in the Educational Program
8D07103 – «Chemical Technology of Organic Substances» on the topic
«**DEVELOPMENT OF NEW BIOACTIVE DERIVATIVES OF AROMATIC
AND PYRIDINECARBOXYLIC ACIDS**»

General characteristics of the work. The dissertation is devoted to the development of new multifunctional derivatives based on hydrazides of pyridinecarboxylic and hydroxybenzoic acids. During the course of the research, novel compounds were synthesized, and their chemical structures were confirmed using modern physicochemical analytical techniques. In addition, the relationship between their chemical structures and biological activities was systematically investigated. A significant aspect of the study was the development of a laboratory-scale technological protocol for the preparation of a water-soluble form of 2-((2-isonicotinoylhydrazono)methyl)benzoic acid, which exhibits pronounced antiviral activity.

Relevance of the research topic. The global risk of the emergence and spread of new viral and infectious diseases continues to increase, accompanied by a growing likelihood of future pandemics. At the same time, the increasing resistance of pathogenic microorganisms to existing therapeutic agents remains one of the most pressing challenges in modern healthcare. Consequently, the discovery and development of novel biologically active compounds with high therapeutic potential has become one of the priority areas of contemporary pharmaceutical chemistry. Numerous studies have demonstrated that compounds containing a hydrazide moiety exhibit a broad spectrum of pharmacological activities. Therefore, the synthesis of new derivatives of nicotinic, isonicotinic, 2-hydroxybenzoic, and 4-hydroxybenzoic acid hydrazides, as well as their application as key intermediates for the development of biologically active compounds, is of considerable scientific and practical significance.

The aim of the dissertation research is to synthesize new multifunctional derivatives of pyridinecarboxylic and hydroxybenzoic acids, to investigate their chemical structures, reaction mechanisms, and biological properties, as well as to develop a technology for the preparation of a novel compound exhibiting pronounced biological activity.

Research objectives:

1. To synthesize new hydrazones and thiosemicarbazides based on hydrazides of nicotinic, isonicotinic, 2-hydroxybenzoic, and 4-hydroxybenzoic acids, and to investigate the pathways of their formation and their reaction behavior.

2. To prepare water-soluble inclusion complexes of derivatives of nicotinic, isonicotinic, 2-hydroxybenzoic, and 4-hydroxybenzoic acids with cyclodextrins and to elucidate the mechanisms of their formation.

3. To establish the structures of the newly synthesized compounds using IR and UV spectroscopy, one-dimensional (^1H and ^{13}C) and two-dimensional COSY (^1H - ^1H) and HMQC (^1H - ^{13}C) NMR spectroscopy, mass spectrometry, X-ray crystallographic analysis, and high-performance liquid chromatography.

4. To evaluate the synthesized compounds for a broad spectrum of biological activities, including antiviral, antimicrobial, cytotoxic, and hemorheological activities, and to develop a laboratory-scale technological protocol for the preparation of a novel biologically active substance exhibiting high biological activity.

The objects of the research are hydrazides of nicotinic, isonicotinic, and 2- and 4-hydroxybenzoic acids, newly synthesized hydrazones, their inclusion complexes with β - and γ -cyclodextrins.

Research methods. The synthesis of new compounds and the isolation of reaction products were carried out using conventional methods of organic synthesis. The biological activities of the synthesized compounds were evaluated, and their chemical structures were confirmed and characterized using modern physicochemical techniques, including IR- and UV- spectroscopy, one-dimensional (^1H and ^{13}C) and two-dimensional (COSY (^1H - ^1H) and HMQC (^1H - ^{13}C)) NMR spectroscopy, mass spectrometry, X-ray crystallographic analysis, and high-performance liquid chromatography.

Main provisions to be defended:

1. The reaction of hydrazides of nicotinic, isonicotinic, 2-hydroxybenzoic, and 4-hydroxybenzoic acids with substituted aromatic and aliphatic aldehydes enables the synthesis of novel compounds exhibiting antimicrobial and antiviral activities.

2. The reaction of hydrazide derivatives of nicotinic, isonicotinic, 2-hydroxybenzoic, and 4-hydroxybenzoic acids with 2-formylbenzoic acid proceeds and cyclization, resulting in the formation of novel phthalimidine derivatives.

3. The reaction of 2-methyl-5-nitro-6-phenylnicotinoylhydrazones with aromatic aldehydes leads to the formation of new compounds that exist as mixtures of *Z*- and *E*-configurational isomers.

4. Modification of nicotinic acid azide with the Curtius rearrangement enables the synthesis of new compounds belonging to the urethane and urea classes.

5. Hydrazones of nicotinic, isonicotinic, 2-hydroxybenzoic, and 4-hydroxybenzoic acids are capable of forming inclusion complexes with β - and γ -cyclodextrins, resulting in the formation of water-soluble inclusion complexes.

Scientific novelty of the research:

1. Efficient synthetic approaches for the preparation of novel hydrazones derived from nicotinic, isonicotinic, 2-hydroxybenzoic, and 4-hydroxybenzoic acids were developed, and the optimal reaction conditions were established. The synthesized compounds were identified as promising scaffolds for the development of antimicrobial and antiviral agents.

2. The reaction of 2-formylbenzoic acid with hydrazides of nicotinic, isonicotinic, 2-hydroxybenzoic, and 4-hydroxybenzoic acids afforded novel biologically active hydrazones and their heterocyclic derivatives, namely phthalimidines, in high yields.

3. For the first time, it was established that the synthesis of hydrazones based on 2-methyl-5-nitro-6-phenylnicotinohydrazide proceeds through the formation of a mixture of *Z*- and *E*-isomers in a 3:2 ratio.

4. For the first time, novel amides were synthesized with the reaction of nicotinic acid chloride with various naturally occurring alkaloids. In addition, synthetic methods for the preparation of novel urethanes and ureas were developed based on the reactions of nicotinic acid azide with alcohols and the alkaloid cytosine.

5. Water-soluble inclusion complexes of derivatives of nicotinic, isonicotinic, 2-hydroxybenzoic, and 4-hydroxybenzoic acids with β - and γ -cyclodextrins were synthesized. A laboratory-scale technological protocol was developed for the preparation of a water-soluble formulation of 2-((2-isonicotinoylhydrazono)methyl)benzoic acid exhibiting pronounced antiviral activity.

6. The synthesized compounds were subjected to biological screening to evaluate their antiviral and antimicrobial activities, as well as their cytotoxicity and hemorheological properties. The biological evaluation identified novel compounds with pronounced antimicrobial activity (5 compounds), antiviral activity (5 compounds), and hemorheological activity (1 compound).

Practical significance of the research. During the course of the dissertation research, synthetic methods for 66 previously undescribed compounds were developed. The obtained compounds were subjected to biological screening, resulting in the identification of promising candidates exhibiting pronounced antimicrobial, antiviral, and hemorheological activities. Based on the obtained results, a laboratory-scale technological protocol was developed for the preparation of a water-soluble formulation of 2-((2-isonicotinoylhydrazono)methyl)benzoic acid (code name Ginkasone), a compound exhibiting pronounced antiviral activity.

Author's contribution. The author actively participated in the collection and critical analysis of national and international scientific literature related to the research topic. The author independently carried out the experimental work on the synthesis of novel derivatives of nicotinic, isonicotinic, 2-hydroxybenzoic, and 4-hydroxybenzoic acid hydrazides, performed the processing and interpretation of the experimental data, and prepared the research findings for publication in scientific magazines.

22 publications have been co-authored on the topic of the dissertation, including 2 articles in the international journal *Molecules* (Q2, 81%), 1 article in the *Russian Journal of General Chemistry* (Q4, 28%), 1 article in the journal *Russian Journal of Bioorganic Chemistry* (Q4, 17%), 1 article in the Eurasian chemical-technological journal (Q4, 20%), 1 article in the Eurasian Journal of Chemistry, in journals included in the list of recommended The Committee for Quality Assurance in Science and Higher Education of the Ministry of Science and Higher Education of the Republic of Kazakhstan: 1 articles in the journal *Proceedings of the National Academy of Sciences (Academic Scientific Journal of Chemistry)*, 3 articles in the journal *Bulletin of KazUTB*, 1 monograph, as well as materials and abstracts of 9 reports at international scientific conferences. Received 2 patents of the Republic of Kazakhstan for utility model №8205 «2-((2-isonicotinoylhydrazono)methyl)benzoic acid, which has a pronounced antiviral activity» and №12361 «2-(4-

Hydroxybenzoyl)-N-(naphthalene)hydrazine-1-carbotioamide with pronounced antiviral activity».

Description of the Doctoral Student's Contribution to the Preparation of Each Publication

1. Nurkenov O.A., **Mendibayeva A.Zh.**, Fazylov S.D., Kabieva S.K., Syzdykov A.K., Vasilchenko A.S., Kulakov I.I., Alkhimova L.E., Kulakov I.V., Seilkhanov T.M., Iashnikov A.V. Synthesis, structure and biological activity of 2-methyl-5-nitro-6-phenylnicotinohydrazide-based hydrazones // *Molecules*. - 2025. - №30. - P. 169-183. (1):169. <https://doi.org/10.3390/molecules30010169> (Q2, 81%). During a research internship at Tyumen State University of the Russian Federation, the doctoral student synthesized new hydrazones based on 2-methyl-5-nitro-6-phenylnicotinohydrazide and determined their structures using NMR spectroscopy and mass spectrometry methods. The doctoral student independently analyzed the obtained results, prepared and formatted the manuscript of the scientific article, and ensured its publication in the journal «Molecules».

2. Nurkenov O.A., Muldakhmetov Z.M., Fazylov S.D., **Mendibayeva A.Zh.**, Pustolaikina I.A., Sarsenbekova A.Zh., Seilkhanov O.T., Syzdykov A.K., Kabiyeveva S.K., Nurmaganbetov Zh.S. Water-soluble inclusion complexation of naphthyl-containing thiosemicarbazides and thioureas with β -Cyclodextrin // *Molecules*. - 2026. - №31. - P. 1290-1312. <https://doi.org/10.3390/molecules31081290> (Q2, 81%). The doctoral student synthesized naphthyl-containing thiosemicarbazides and investigated methods for obtaining their complexes with cyclodextrins. During the structural characterization of the resulting complexes, the doctoral student participated in the analysis of SEM and NMR spectroscopy data. The doctoral student completed the full research cycle, including the preparation of the manuscript and the formatting of materials for publication.

3. Nurkenov O.A., Fazylov S.D., Kulakov I.V., Seilkhanov T.M., **Mendibayeva A.Zh.**, Kabieva S.K. Reaction of *o*-formylbenzoic acid with hydrazides of (Iso)nicotinic and hydroxybenzoic acids // *Russian Journal of General Chemistry*. - 2023. - Vol. 93, №9. - P. 2202-2209. <https://doi.org/10.1134/S1070363223090025> (Q4, 28%). The doctoral student carried out the condensation of *o*-formylbenzoic acid with hydrazides of isonicotinic and hydroxybenzoic acids, and also investigated the possibility of intramolecular heterocyclization of the obtained new compounds.

4. Nurkenov O.A., Fazylov S.D., Satbayeva E.M., Seilkhanov T.M., **Mendibayeva A.Zh.**, Kabieva S.K., Tursymbek Sh.N. Synthesis and study anti-inflammatory activity of nicotinic acid hydrazones // *Russian Journal of Bioorganic Chemistry*. - 2024. - Vol. 50, №5. - P. 2066-2075. <https://doi.org/10.1134/S1068162024050376> (Q4, 17%). The doctoral student synthesized new hydrazones of nicotinic acid and participated in the study of their biological activity. The obtained experimental data were analyzed and interpreted

by the doctoral student, and the preparation and formatting of the scientific article for publication were also carried out.

5. Nurkenov O.A., Fazylov S.D., Nurmaganbetov Zh.S., Seilkhanov T.M., **Mendibayeva A.Zh.**, Kabieva S.K., Satbaeva E.M. Synthesis and anti-inflammatory activity of new nicotinoyl amides // Eurasian Chemico-Technological Journal. - 2024. - №3. - P. 169 - 174. <https://doi.org/10.18321/ectj1640> (Q4, 20%). The doctoral student synthesized new amides of nicotinic acid and participated in the study of their biological activity. The obtained experimental data were analyzed and interpreted by the doctoral student, and the preparation and formatting of the scientific article for publication were also carried out.

6. Nurkenov O.A., Fazylov S.D., Seilkhanov T.M., Abulyaissova L.K., Turdybekov K.M., Zhivotova T.S., Kabieva S.K., **Mendibayeva A.Zh.** Interaction of isonicotinic acid hydrazide with carboxylic acid anhydrides // Eurasian Journal of Chemistry. - 2023. - №2. - P. 29-35. <https://doi.org/10.31489/2959-0663/2-23-1>. The doctoral student synthesized new hydrazones of isonicotinic acid hydrazide and investigated optimal methods for their preparation. The synthesized compounds were studied using IR spectroscopy, ^1H and ^{13}C NMR, as well as two-dimensional correlation methods COSY and HMQC to establish their 3D molecular configuration. The doctoral student also independently prepared the text of the scientific article.

7. Nurkenov O.A., Fazylov S.D., Nurmaganbetov Zh.S., Seilkhanov T.M., **Mendibayeva A.Zh.** Synthesis and structure of new thiourea derivatives of nicotinic acid with fragments of natural alkaloids // Proceedings of the National Academy of Sciences. Chemistry and Technology series. - 2024. - №1(458). - P. 106-115. <https://doi.org/10.32014/2024.2518-1491.211>. The doctoral student synthesized new alkaloid-containing thioureas during the course of the work and, in order to establish the structure of the obtained new compounds, recorded and analyzed their IR and UV spectra.

8. Nurkenov O.A., **Mendibayeva A.Zh.**, Seilkhanov T.M., Nurmaganbetov Zh.S., Kabieva S.K., Syzdykov A.K., Fazylov S.D. Synthesis and modification of nicotinic acid azide // Bulletin of KazUTB. - 2024. - №3 (24). - P. 201-214. <https://doi.org/10.58805/kazutb.v.3.24-499>. The doctoral student synthesized azide of nicotinic acid and participated in the development of methods for its further modification. The structures of the obtained new urethanes were analyzed by the doctoral student using ^1H and ^{13}C NMR methods.

9. Fazylov S.D., Satpayeva Zh.B., Nurkenov O.A., Bakirova R.E., Svidersky A.K., **Mendibayeva A.Zh.** Preparation of water-soluble complexes of inclusions of *o*- and *p*-hydroxybenzoic acid hydrazides and their hydrazone derivatives // Bulletin of KazUTB. - 2024. - №3 (24). - P. 250-260. <https://doi.org/10.58805/kazutb.v.3.24-501>. The doctoral student modeled hydrazone–cyclodextrin complexes using quantum chemical 3D methods, determining their geometric compatibility and

performing preliminary predictive calculations. The doctoral student also synthesized cyclodextrin complexes with o- and p-hydroxybenzoic acids.

10. **Mendibayeva A.Zh.**, Fazylov S.D., Kabieva S.K., Zhaslan R.K., Zhautikova S.B., Bogoyavlensky A.P., Nurkenov O.A. Development of technology for obtaining a water-soluble form of 2-((2-isonicotinoylhydrazono)methyl) benzoic acid in a β -oligosaccharide capsule // Bulletin of KazUTB. - 2026. - №1 (30). - P. 309-318. <https://doi.org/10.58805/kazutb.v.1.30-1455>. The doctoral student synthesized 2-((2-isonicotinoylhydrazono)methyl)benzoic acid and obtained its water-soluble complex with cyclodextrin. The doctoral student also developed a laboratory protocol for the preparation of 2-((2-isonicotinoylhydrazono)methyl)benzoic acid.

11. Patent of the Republic of Kazakhstan for utility model №8205 «2-((2-isonicotinoylhydrazono)methyl)benzoic acid with pronounced antiviral activity» / Muldakhmetov Z.M., Nurkenov O.A., Fazylov S.D., Nurmaganbetov Zh.S., **Mendibayeva A.Zh.**, Syzdykov A.K. dated 13.03.2023.

12. Patent of the Republic of Kazakhstan for utility model №12361 «2-(4-Hydroxybenzoyl)-N-(naphthalene)hydrazine-1-carbotioamide with pronounced antiviral activity» / Muldakhmetov Z.M., Nurkenov O.A., Fazylov S.D., Seilkhanov T.M., Nurmaganbetov Zh.S., Bogoyavlensky A.P., **Mendibayeva A.Zh.**, Syzdykov A.K. dated 05.06.2026.

13. Nurkenov O.A., Fazylov S.D., Seilkhanov T.M., **Mendibayeva A.Zh.**, Syzdykov A.K. Multifunctional derivatives of aromatic and pyridine carboxylic acids. Karaganda: Glasir Publ., 2024. 188 p. ISBN 978-601-7655-83-9.

14. Conference abstracts: The doctoral student synthesized new derivatives of hydrazides of nicotinic, isonicotinic, 2-hydroxybenzoic, and 4-hydroxybenzoic acids, as well as their supramolecular complexes. The obtained data were interpreted, and the preparation, formatting, and presentation of 9 conference abstracts were carried out.

Structure of the dissertation. The dissertation consists of an introduction, the main part - experimental studies and discussion of results, conclusion, list of references, and appendices. The total volume of the dissertation is 166 pages of printed text, includes 16 tables and 26 figures. The number of references is 140. The appendices contain acts of biological testing of the new compounds.