ABSTRACT

of the dissertation work by Khamitova Akzhonas Ermekovna entitled “Synthesis and study of active pharmaceutical substances based on nitrogen-containing heterocyclic compounds”, submitted for the degree of Doctor of Philosophy (PhD) in the specialty 8D10102 – “Pharmacy”

Relevance of the research topic

One of the key directions outlined in the Comprehensive Plan for the Development of the Pharmaceutical and Medical Industry of the Republic of Kazakhstan for 2020-2025 and in the strategic document "Kazakhstan Development Strategy until 2030: Problems and Ways of Their Solution" is to increase the volume of pharmaceutical production and increase the share of domestically produced medicines. Achieving these goals requires the development of new pharmaceutical substances that expand the range of effective and safe medicines.

According to literary and analytical sources, the pharmaceutical market of the Republic of Kazakhstan is characterized by a high degree of import dependence. The share of imported medicines is about 80-88%, while domestic production covers only 12-20% of the market. The assortment of domestic manufacturers is represented mainly by generics (up to 70-85%), while the share of original medicines remains low (about 15%). The lack of own production of pharmaceutical substances and the predominance of generics in the structure of domestic production determine the dependence of the industry on foreign suppliers, which limits the development of the domestic pharmaceutical industry.

In this regard, an urgent task is the synthesis and study of new compounds with pharmacological activity. A special place among promising research objects is occupied by heterocyclic compounds, which are part of many drugs and are characterized by a wide spectrum of biological action. Most antibacterial, antiviral, antifungal, anti-inflammatory and antitumor agents, by their chemical nature, belong to heterocyclic compounds. Among the most common heterocyclic fragments are piperidine and morpholine.

Piperidine and morpholine are of interest as reactive heterocyclic compounds widely used as structural fragments in the synthesis of new compounds. The presence of a nitrogen atom in the ring determines their pronounced nucleophilic properties and ability to participate in various chemical transformations, including reactions of formation of amides, hydrazides and imines. In this regard, these heterocycles can be considered as universal synthetic blocks used in the construction of more complex molecular structures. Their high reactivity provides the possibility of targeted modification and obtaining compounds with desired physicochemical and pharmacological characteristics.

Piperidine derivatives are represented in various pharmacotherapeutic groups, including antiallergic, anti-inflammatory, analgesic, antioxidant, antipsychotic, antidiabetic, antitumor, antibacterial, antimalarial and antifungal agents.

Compounds containing a morpholine ring exhibit analgesic, anti-inflammatory, antitumor, antidepressant, antiplatelet, antifungal, antiparasitic, hypolipidemic and hypocholesterolemic effects.

Hydrazides and hydrazones are characterized by relative simplicity of synthesis, availability of starting reagents and the possibility of structural modification through condensation reactions of carbonyl compounds with hydrazines. The presence of reactive hydrazide and hydrazone groups determines their participation in further chemical transformations, which determines their widespread use as intermediate compounds in the synthesis of more complex molecules. A wide range of pharmacological activity has been described for these classes of compounds, including analgesic, anti-inflammatory, antimicrobial, antituberculosis and antitumor effects, which determines sustained scientific interest in their study.

Thus, the synthesis of hydrazides and hydrazones of piperidine and morpholine, as well as the study of their biological properties, aimed at expanding the arsenal of effective and safe medicines, is relevant.

Objective of the dissertation research. Synthesis of pharmaceutical substances based on piperidine and morpholine derivatives and determination of their biological activity.

Research objectives:

1. *In silico* prediction of biological activity, toxicity and ADME parameters of hydrazides and hydrazones of α-methyl-β-(*N*-piperidyl)- or -(N-morpholinyl) propanoic acid.
2. Synthesis of hydrazides of α-methyl-β-(*N*-piperidyl)- or -(*N*-morpholinyl) propanoic acid.
3. Synthesis of hydrazones of α-methyl-β-(*N*-piperidyl)- or -(*N*-morpholinyl) propanoic acid.
4. Determination of the chemical structure of the synthesized compounds using IR spectrometry and ^{1}H NMR spectroscopy.
5. Standardization and stability studies of hydrazones of β-aminopropanoic acid.
6. Evaluation of safety and biological activity of hydrazones of β-aminopropanoic acid.

Research methods: computer modeling, chemical synthesis, physicochemical, pharmacopoeial, pharmacological (biological activity evaluation) and statistical methods.

Objects of the study: hydrazides and hydrazones of α-methyl-β-(*N*-piperidyl)- or -(*N*-morpholinyl)propanoic acid.

Subject of the study: synthesis, standardization, and determination of biological activity of hydrazones of α-methyl-β-(*N*-piperidyl)- or -(*N*-morpholinyl) propanoic acid.

Main provisions submitted for defense

1. Results of *in silico* prediction of biological activity, toxicity, and ADME parameters of hydrazides and hydrazones of β-aminopropanoic acid derivatives of α-methyl-β-(*N*-piperidyl)- or -(*N*-morpholinyl) substitution.

2. Results of development and optimization of synthesis conditions for hydrazides and hydrazones of β-aminopropanoic acid derivatives of α-methyl-β-(*N*-piperidyl)- or -(*N*-morpholinyl) substitution.

3. Results of standardization of hydrazones of α-methyl-β-(*N*-piperidyl)- or -(*N*-morpholinyl)propanoic acid - quality specifications and stability study results.

4. Results of safety and pharmacological activity studies of hydrazides and hydrazones of β-aminopropanoic acid derivatives of α-methyl-β-(*N*-piperidyl)- or -(*N*-morpholinyl) substitution.

Description of main research results

As a result of the conducted *in silico* prediction, it was established that the investigated piperidine and morpholine derivatives possess a broad spectrum of biological activity. The most pronounced probability of analgesic activity was predicted for hydrazide of α-methyl-β-(*N*-piperidyl)propanoic acid, hydrazide of α-methyl-β-(*N*-morpholinyl)propanoic acid, and 3-methoxy-4-hydroxybenzylidene hydrazide of α-methyl-β-(*N*-piperidyl)propanoic acid, whereas the compounds 4-dimethylaminobenzylidene hydrazide of α-methyl-β-(*N*-piperidyl)propanoic acid, 4-dimethylaminobenzylidene hydrazide of α-methyl-β-(*N*-morpholinyl)propanoic acid, and 3,4-dihydroxybenzylidene hydrazide of α-methyl-β-(*N*-piperidyl)propanoic acid demonstrated antitubercular and antimycobacterial activity.

According to the toxicity classification provided by the Pro-Tox II program, the toxicity assessment showed that most compounds belong to toxicity classes IV–V and do not exhibit hepatotoxic, cytotoxic, or mutagenic effects, with the exception of 2-hydroxy-3-nitrobenzylidene hydrazide of α-methyl-β-(*N*-piperidyl)propanoic acid.

The results of ADME prediction indicate a high level of gastrointestinal absorption, suggesting their potential for the development of orally administered medicinal products. It was established that most compounds do not inhibit cytochrome P450 isoenzymes, thereby reducing the risk of drug–drug interactions, except for 4-dimethylaminobenzylidene hydrazide of α-methyl-β-(*N*-piperidyl)propanoic acid, which exhibits inhibitory activity toward CYP2D6.

It was established that the investigated compounds are characterized by favorable pharmacokinetic parameters, including optimal volume of distribution, moderate clearance, and a high probability of an extended half-life, indicating their potential for prolonged action. The obtained results justify the feasibility of further experimental studies and confirm the promising nature of these compounds as potential pharmacologically active substances.

Intermediate products for the synthesis of hydrazones were obtained, including esters of α-methyl-β-(*N*-piperidyl)propanoic acid and α-methyl-β-(*N*-morpholinyl) propanoic acid, as well as hydrazides of α-methyl-β-aminopropanoic acid of piperidine and morpholine. Based on the conducted studies, optimal conditions for hydrazone synthesis were selected, including reaction under stirring with heating to 80 °C for 4 hours, which ensured the formation of target products. A technological scheme for the production of piperidine and morpholine hydrazones was developed. The synthesis technology was validated according to key technological parameters. The obtained results showed an RSD value of 2,0 %, which meets the established

acceptance criterion (RSD ≤ 2) and confirms the stability of the technological process.

The chemical structure of the synthesized compounds was confirmed by IR spectrometry and NMR spectroscopy, where characteristic signals corresponding to protons of the hydrazone fragment and substituents in aromatic and heterocyclic environments were identified in the NMR spectra. Mass spectrometry data confirmed the molecular masses of the compounds and their agreement with the proposed structures. According to HPLC-UV analysis, the synthesized compounds exhibited different purity levels. It was established that for 3-methoxy-4-hydroxybenzylidene hydrazide of α-methyl-β-(*N*-morpholinyl)propanoic acid, 3,4-dihydroxybenzylidene hydrazide of α-methyl-β-(*N*-morpholinyl)propanoic acid, p-cyanobenzylidene hydrazide of α-methyl-β-(*N*-morpholinyl)propanoic acid, and 2-hydroxy-3-nitrobenzylidene hydrazide of α-methyl-β-(*N*-piperidyl)propanoic acid, the content of the main substance was 72.0 %, 62.6 %, 52.3 %, and 53.6 %, respectively. These compounds were excluded from further studies due to non-compliance with generally accepted acceptance criteria for active substance content.

Standardization of the synthesized compounds was carried out in accordance with the requirements of the State Pharmacopoeia of the Republic of Kazakhstan. Quality assessment included pharmacopeial parameters such as description, solubility, identification, melting point, pH, related substances, residual organic solvents, loss on drying, sulfate ash, heavy metals content, microbiological purity, and assay.

Based on the obtained data, quality specifications were developed for 3-methoxy-4-hydroxybenzylidene hydrazide of α-methyl-β-(*N*-piperidyl)propanoic acid, 4-dimethylaminobenzylidene hydrazide of α-methyl-β-(*N*-piperidyl)propanoic acid, and 4-dimethylaminobenzylidene hydrazide of α-methyl-β-(*N*-morpholinyl)propanoic acid. Validation characteristics of analytical methods were studied and confirmed: the HPLC-UV method for related substances and the UV-spectrophotometric assay method were validated in terms of specificity, linearity, and accuracy, confirming their suitability for quality control.

Stability studies showed that storage of the substances in a dry, light-protected, cool place at 8–15 °C for 24 months did not lead to significant changes in quality parameters. This allowed substantiation of a 24-month retest period and confirmed the stability of the synthesized compounds under the specified conditions.

Non-clinical studies demonstrated that a single enteral administration of the investigated compounds at doses up to 1500 mg/kg did not result in animal mortality or changes in general condition, indicating low acute toxicity (LD50 > 1500 mg/kg) and allowing classification into toxicity class III (State 12.1.007-76). In chronic toxicity assessment, no irreversible changes in internal organs were observed, and the detected effects were dose-dependent and minor.

In analgesic activity studies, piperidine hydrazide, morpholine hydrazide and 3-methoxy-4-hydroxybenzylidene hydrazide of α-methyl-β-(*N*-piperidyl)propanoic acid at a single intramuscular dose of 1 mg/kg demonstrated pronounced analgesic effects in the “hot plate” and “tail immersion in hot water” tests. In the tail immersion test, morpholine hydrazide increased the latency period of pain response by 3.7-fold,

while the 3-methoxy-4-hydroxybenzylidene hydrazide of α-methyl-β-(*N*-piperidyl)propanoic acid increased it by 3.6-fold compared to metamizole sodium.

According to antimycobacterial activity results, compound 4-dimethylamino-benzylidene hydrazide of α-methyl-β-(*N*-piperidyl)propanoic acid (1.4) showed pronounced activity against *M. bovis* BCG and *M. tuberculosis* H37Rv with MIC_{90} values of 26.4 μg/mL and 30.74 μg/mL, respectively, and reduced the growth of *M. abscessus*. Compound 4-dimethylaminobenzylidene hydrazide of α-methyl-β-(*N*-morpholinyl)propanoic acid (2.4) reduced *M. abscessus* growth to 68 % viability. According to preliminary prediction, 3,4-dihydroxybenzylidene hydrazide of α-methyl-β-(*N*-piperidyl)propanoic acid showed a moderate probability (0.556) of antimycobacterial activity, higher than compounds 1.4 (0.441) and 2.4 (0.428), however, this activity was not confirmed experimentally.

Justification of scientific novelty

For the first time:

- Biological activity, toxicity, and ADME parameters of hydrazides and hydrazones of β-aminopropanoic acid derivatives of α-methyl-β-(*N*-piperidyl)- or -(*N*-morpholinyl) substitution were evaluated by *in silico* prediction;
- The reaction conditions for the synthesis of hydrazides of α-methyl-β-(*N*-piperidyl)- or -(*N*-morpholinyl)propanoic acid were developed and optimized;
- Hydrazones of α-methyl-β-(*N*-piperidyl)- or -(*N*-morpholinyl)propanoic acid were synthesized. A certificate of entry into the state register of copyright-protected objects No. 62278 dated 19.09.2025 was obtained;
- Standardization of β-aminopropanoic acid hydrazones was carried out, and quality specifications were developed;
- Stability of β-aminopropanoic acid hydrazones was studied, and the storage period was established;
- Safety and biological activity of hydrazides and hydrazones of β-amino-propanoic acid were evaluated within non-clinical studies, including analgesic and antimycobacterial activity. The novelty of the results is confirmed by invention patent No. 37466 dated 08.08.2025 and utility model patents No. 11302 dated 27.08.2025 and No. 11415 dated 29.08.2025.

Practical significance of the research results:

During the course of the study, new compounds with analgesic and antimycobacterial activity were synthesized. The obtained results are protected by intellectual property objects. In particular:

- a patent for invention No. 37466 dated 08.08.2025 entitled “Use of hydrazide of 2-methyl-3-N-morpholylpropanoic acid as an agent possessing analgesic activity” was obtained;
- utility model patents No. 11302 dated 27.08.2025 entitled “Compound 3-methoxy -4-hydroxybenzylidene hydrazide of α-methyl-N-piperidyl propanoic acid possessing analgesic activity” and No. 11415 dated 29.08.2025 entitled “Compound 4-dimethylaminobenzylidene hydrazide of α-methyl-N-piperidyl propanoic acid possessing antimycobacterial activity” were registered;
- copyright certificates No. 62278 dated 19.09.2025 entitled “General scheme for the synthesis of hydrazides and hydrazones of β-aminopropanoic acid

of piperidine and morpholine" and No. 62350 dated 23.09.2025 entitled "Synthesis and study of active pharmaceutical substances based on nitrogen-containing heterocyclic compounds" were obtained.

The research results have been implemented in the educational process in the disciplines "Pharmaceutical Chemistry" and "Chemistry and Technology of Synthetic Medicinal Substances" at NJSC "Asfendiyarov Kazakh National Medical University" (Implementation Act No. 1 dated 25.12.2023, No. 2 dated 26.12.2023).

Personal contribution of the PhD-student

The personal contribution of the doctoral student consists in the independent execution of all key stages of the dissertation research. The doctoral student independently carried out *in silico* prediction and interpretation of the obtained results for the evaluation of biological activity, toxicity, and ADME parameters of the studied compounds. The synthesis of the studied compounds, their purification, and quality control using modern physicochemical analysis methods were performed personally by the doctoral student.

The author independently performed validation of analytical methods, including the method for determination of related impurities and the method for quantitative determination, as well as carried out statistical processing of validation results.

In addition, the author conducted studies on safety evaluation and determination of the pharmacological activity of the obtained compounds.

All experimental and calculated data were processed, systematized, and interpreted personally by the doctoral student, on the basis of which substantiated main provisions submitted for defense were formulated.

Conclusions:

1. In accordance with the modern concept of developing new medicinal substances based on priority computational analysis of molecular structures, *in silico* prediction of biological activity, toxicity, and ADME parameters of hydrazides and hydrazones of β-aminopropanoic acid derivatives of piperidine and morpholine was performed for the first time. Biological activity was evaluated using the PASS online platform. According to the results of biological activity prediction, hydrazide of α-methyl-β-(*N*-piperidyl)propanoic acid, hydrazide of α-methyl-β-(*N*-morpholinyl)propanoic acid, and 3-methoxy-4-hydroxybenzylidene hydrazide of α-methyl-β-(*N*-piperidyl)propanoic acid may exhibit analgesic activity with probabilities of 0.609, 0.649, and 0.625, respectively. It was established that 4-dimethylaminobenzylidene hydrazide of α-methyl-β-(*N*-piperidyl)propanoic acid, 4-dimethylaminobenzylidene hydrazide of α-methyl-β-(*N*-morpholinyl)propanoic acid, and 3,4-dihydroxybenzylidene hydrazide of α-methyl-β-(*N*-piperidyl)propanoic acid may demonstrate antitubercular activity with probabilities of 0.583, 0.622, and 0.566, respectively, as well as antimycobacterial activity with probabilities of 0.568, 0.579, and 0.556, respectively. These probability values fall within the prognostically significant range in the applied software and justify further experimental investigation of these compounds.

According to the toxicity classification provided by the Pro-Tox II program, toxicity prediction showed that all investigated compounds are assumed to belong to toxicity class IV and are characterized as low-toxic substances. An exception is

represented by hydrazide of α-methyl-β-(*N*-morpholinyl)propanoic acid and 2-hydroxy-3-nitrobenzylidene hydrazide of α-methyl-β-(*N*-piperidyl)propanoic acid, which were assigned to toxicity class V, indicating an even higher safety profile and allowing them to be characterized as non-toxic substances.

ADME prediction results indicate that all studied compounds exhibit a high rate of gastrointestinal absorption in humans and may be considered for the development of orally administered medicinal products. All compounds are characterized by optimal pharmacokinetic parameters: volume of distribution (V_d = 0.702–1.138 L/kg) indicates a pronounced ability to distribute into tissues, clearance (Cl = 5.03–8.33 mL/min·kg) is moderate, and the predicted half-life ($T_{½}$ > 3 h with probability > 0.68) suggests a potential for prolonged action.

Reproducible synthetic methods for hydrazide of α-methyl-β-(*N*-piperidyl) propanoic acid and hydrazide of α-methyl-β-(*N*-morpholinyl)propanoic acid were developed. Optimal reaction conditions were established: the reaction between the corresponding ester of α-methyl-β-(*N*-piperidyl) or (*N*-morpholinyl)propanoic acid and hydrazine hydrate is carried out at a molar ratio of 1 : 1.1, under heating with constant stirring for 4 hours at 80 °C without the use of a catalyst.

3. Hydrazones of β-aminopropanoic acid of piperidine and morpholine were synthesized: 3-methoxy-4-hydroxybenzylidene hydrazide of α-methyl-β-(*N*-piperidyl)propanoic acid; 4-dimethylaminobenzylidene hydrazide of α-methyl-β-(*N*-piperidyl)propanoic acid; 3,4-dihydroxybenzylidene hydrazide of α-methyl-β-(*N*-piperidyl)propanoic acid; 4-dimethylaminobenzylidene hydrazide of α-methyl-β-(*N*-morpholinyl)propanoic acid; 3,4-dihydroxybenzylidene hydrazide of α-methyl-β-(*N*-morpholinyl)propanoic acid; p-cyanobenzylidene hydrazide of α-methyl-β-(*N*-morpholinyl)propanoic acid; and 2-hydroxy-3-nitrobenzylidene hydrazide of α-methyl-β-(*N*-morpholinyl)propanoic acid. A technological scheme for the production of piperidine and morpholine β-aminopropanoic acid hydrazones was developed. The synthesis method of hydrazides and hydrazones of β-aminopropanoic acid of piperidine and morpholine was registered as an intellectual property object in the State Register of Copyrights under certificate No. 62278 dated 19.09.2025, and implemented into the educational process of the Department of Pharmaceutical and Toxicological Chemistry, Pharmacognosy and Botany of Asfendiyarov Kazakh National Medical University (implementation acts No. 1 dated 25.12.2023 and No. 2 dated 26.12.2023).

4. The structures of the obtained compounds were confirmed by modern physicochemical methods: IR spectrometry and ^{1}H NMR spectroscopy. Characteristic absorption bands corresponding to functional groups (–NH–NH_2, –N=NH, C=O, >C–N, C–O–C) were observed in IR spectra, while ^{1}H NMR data confirmed the proposed structures.

Identification and purity were evaluated by HPLC with UV detection and confirmed by mass spectrometry, where molecular ions corresponding to theoretical molecular masses were observed. According to HPLC analysis, the content of the main substance for 3-methoxy-4-hydroxybenzylidene hydrazide, 3,4-dihydroxybenzylidene hydrazide, p-cyanobenzylidene hydrazide of α-methyl-β-(*N*-morpholinyl)propanoic acid and 2-hydroxy-3-nitrobenzylidene hydrazide of

α-methyl-β-(N-piperidyl)propanoic acid was 72.0 %, 62.6 %, 52.3 %, and 53.6 %, respectively. These compounds were excluded from further studies due to non-compliance with acceptance criteria for active substance content.

5. Standardization of the synthesized substances was performed in accordance with the State Pharmacopoeia of the Republic of Kazakhstan and the general monograph "Substances". Quality specifications were developed for 3-methoxy-4-hydroxybenzylidene hydrazide, 4-dimethylaminobenzylidene hydrazide of α-methyl-β-(*N*-piperidyl)propanoic acid and 4-dimethylaminobenzylidene hydrazide of α-methyl-β-(*N*-morpholinyl)propanoic acid.

Stability studies were conducted; samples were stored in colorless glass containers with tightly closed caps. A stability specification was developed. A 24-month retest period was established at 8–15 °C and relative humidity not exceeding 60 ± 5 %.

6. Safety evaluation showed that hydrazides and hydrazones of β-aminopropanoic acid of piperidine and morpholine belong to toxicity class III according to State 12.1.007-76. Non-clinical pharmacological studies demonstrated pronounced analgesic activity of piperidine hydrazide, morpholine hydrazide and 3-methoxy-4-hydroxybenzylidene hydrazide of α-methyl-β-(*N*-piperidyl)propanoic acid. In the tail immersion test, morpholine hydrazide increased the latency period of pain response by 3.7-fold, while the 3-methoxy-4-hydroxybenzylidene hydrazide of α-methyl-β-(*N*-piperidyl)propanoic acid increased it by 3.6-fold compared to metamizole sodium. The novelty of the study is confirmed by invention patent No. 37466 and utility model patent No. 11302 dated 27.08.2025.

Antimycobacterial activity results showed that 4-dimethylaminobenzylidene hydrazide of α-methyl-β-(*N*-piperidyl)propanoic acid exhibited activity against *M. bovis* BCG and *M. tuberculosis* H37Rv with MIC_{90} values of 26.4 μg/mL and 30.74 μg/mL, respectively. 4-dimethylaminobenzylidene hydrazide of α-methyl-β-(N-morpholinyl)propanoic acid inhibited the growth of *M. abscessus* at 68 % viability. The novelty was confirmed by utility model patent No. 11415 dated 29.08.2025.

Thus, within the framework of the modern concept of drug development based on computational analysis of molecular structures and subsequent chemical synthesis, new compounds were developed: 3-methoxy-4-hydroxybenzylidene hydrazide of α-methyl-β-(*N*-piperidyl)propanoic acid, 4-dimethylaminobenzylidene hydrazide of α-methyl-β-(*N*-piperidyl)propanoic acid, and 4-dimethylaminobenzylidene hydrazide of α-methyl-β-(*N*-morpholinyl)propanoic acid, which are promising for the development of pharmaceutical substances with potential analgesic and antimycobacterial activity.

Approbation of the dissertation results:

The main provisions of the dissertation were presented and published in the proceedings of: the International Scientific and Practical Conference "Modern Pharmacy: New Approaches and Current Research", held within the framework of the "University Days" of NJSC "Asfendiyarov Kazakh National Medical University", dedicated to the 30th anniversary of Independence of the Republic of Kazakhstan, the 70th anniversary of the School of Pharmacy, and the 25th anniversary of the

Association for Support and Development of Pharmaceutical Activity of the Republic of Kazakhstan, 2021; the XIII International Scientific and Practical Conference "Priorities of Pharmacy and Dentistry: From Theory to Practice", 2024; the VII International Scientific and Practical Conference within the framework of ANaMed UniForum, dedicated to the 80th anniversary of Professor R. Dilbarkhanov "Formation and Prospects for the Development of the Scientific School of Pharmacy: Continuity of Generations", 2025.

Publications:

Based on the research results, 12 scientific works have been published, including:

- articles in international peer-reviewed scientific journals indexed in the Scopus and Web of Science Core Collection databases – 2;
- articles in journals recommended by the Committee for Quality Assurance in Science and Higher Education of the Ministry of Science and Higher Education of the Republic of Kazakhstan – 3;
- articles in the proceedings of international scientific and practical conferences – 1;
- article in foreign journals – 1;
- patent for invention – 1;
- utility model patents – 2;
- copyright certificates – 2.

Scope and structure of the dissertation:

The dissertation is presented on 185 pages of typed text and consists of an introduction, a literature review, a section devoted to materials and research methods, three sections containing the results of original research, 119 references, a conclusion, and 17 appendices. The work is illustrated with 45 figures and 35 tables.