SUMMARY

to the doctoral thesis "Chemical development of a biologically active substance based onnew derivatives of n-arylalkylpiperidine"
for the degree of Philosophy Doctor (PhD)
on specialty 6D074800 – Technology of Pharmaceutical Production
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Relevance of the research tittle

In accordance with section 4 of the concept of healthcare development of the Republic of Kazakhstan until 2026 (Resolution of the Government of the Republic of Kazakhstan dated November 24, 2022 945), domestic pharmaceutical productionand the national sanitary and epidemiological service for innovative medicines ensure internal needs, independence from the global pharmaceutical market and biosafety of the population.

The Head of State set the task to bring the share of domestic production in the pharmaceutical market to 50 % by 2025. In pursuance of the Comprehensive Plan for the Development of the Pharmaceutical Industry of the Country, aimed at 2020-2025, the issue of organizing the production of chemical substans based on the territory of the Republic of Kazakhstan with different chemical compositions and broad pharmacological effects has a significant status for our state.

Implementation of the national drug policy, i.e. reducing dependence on foreign pharmaceutical products by providing the population with high-quality, effective, safe and inexpensive drugs, developing the domestic market, increasing the financial sustainability of the healthcare system, searching for new medicinal compounds, developing and introducing into practice domestic drugs drugs of natural origin is very important. In this regard, the most in-depth study of herbal medicines produced in our country has high scientific and technical significance.

The main products of pharmaceutical production in our country are generics, and the preparation of new patented drugs requires a long time and a lot of funding. Therefore, the production of new medicines is of strategic, economic and social importance for the development of the pharmaceutical sector of our country and for the Republic of Kazakhstan.

In addition, one of the important tasks of modern pharmaceutical science is the creation of new drugs and preparations to ensure national security. The achievements of drug therapy are associated not only with the creation of modern unique and safe medicines, but also with the development and improvement of the optimal composition and technology of drugs used in the pharmaceutical industry that have a wide range of effects and do not cause the appearance of resistant microorganisms.

Therefore, the research and development of new medicines, as well as the improvement of methods for assessing their quality to ensure maximum therapeutic efficacy and safety, is one of the main tasks of pharmaceutical chemistry.

New piperidine derivatives are of great interest in the search for new anti-infectious substances, which is an urgent problem of modern medicine.

Goal of the study:

Chemical development of a potentially biologically active substance based on new derivatives of a number of N-arylalkylpiperidines, development of a technological scheme for obtaining.

Objectives of the study:

1. Synthesis of various 4,4-disubstituted derivatives based on N-phenyl ethyl piperidine-4-one and their further modification in order to obtain water-soluble forms.
2. Establishment of the fine structure of synthesized compounds using modern physico-chemical methods.
3. Establishing the relationship "structure-biological activity".
4. Study of antimicrobial, antibacterial, antifungal/fungicidal and cytotoxic activity of compounds;
5. Establishing the relationship "structure-biological activity".
6. Development of a technological scheme for obtaining a biologically active substance, standardization, determination of stability and acute toxicity.

Research methods: Chemical, physico-chemical, biological, pharmaceutical-technological, pharmacological, statistical.

Objects of study: N-substituted piperidine derivatives with potential anti-infective activity, N-substituted 4-oxopiperidines, N-phenylethyl-substituted piperidoles and their 4,4-disubstituted derivatives with potentially pharmacological activity, as well as their hydrochlorides and β-cyclodextrin complexes.

The subject of the study:

Chemical processes leading to the production of multifunctional research objects and their chemical modification, as well as the study of the fine structure and properties of synthesized compounds.

Synthesis of various 4,4-disubstituted derivatives of the N-phenylethyl-piperidine series and their water-soluble salts, determination of their structure by modern physico-chemical methods, determination of antibacterial, antimicrobial, fungicidal, cytotoxic properties of compounds. Standardization of a potentially biologically active substance, development of its production technology.

Scientific novelty

For the first time:

- New 4,4-disubstituted derivatives were synthesized by introducing N-phenylethylpiperidines p-fluorophenyl-, m-fluorophenyl-, o-fluorophenyl-, 4-(trifluoromethyl) into the structures- cyclohexane-, adamantane-, naphthoyloxy-fragments that give the molecule anti-infective properties;
- their hydrochlorides and complexes with β-cyclodextrin were obtained;
- antimicrobial and fungicidal properties of synthesized compounds have been studied;
- Studies have been conducted on standardization, stability determination and acute toxicity of 1-(2-phenylethyl)-4-adamantancarbonyloxypiperidine hydrochloride (AIP-2).

The scientific novelty of the study was confirmed by obtaining a patent for a utility model under registration number No.4782 dated 06/20/2019. "1-(2-phenylethyl)-4-adamantancarbonyloxypiperidine hydrochloride with antimicrobial activity".

The main provisions submitted for protection

1. Synthesis of new derivatives of a number of N-aryl alkyl piperidines and preparation of their water-soluble forms for the purpose of chemical development of a biologically active substance;

2. Proof of the structure of synthesized compounds by modern physico-chemical analysis methods;

3. Study of the structure-activity relationship in a number of obtained substances;

4. The technology of preparation of the AIP-2 substance, quality indicators and research results to determine the shelf life and stability;

5. Creation and standardization of the effective technology of the selected product;

The practical significance of the study

- for the first time, the technology for the production of 1-(2-phenylethyl)-4-adamantancarbonyloxypiperidine hydrochloride (AIP-2) substance was developed and implemented at the Scientific Center for Anti-Infectious Drugs JSC;

- the technology of obtaining a biologically active substance (AIP-2) has been introduced in the S. D. Asfendiyarov Kazakh National Medical university " at the Department of Pharmaceutical Production Technology;

The experimental part and chemical synthesis of new derivatives of a number of N-phenylethylpiperidines within the framework of the dissertation work "Chemical development of a biologically active substance based on new derivatives of N-arylalkylpiperidine" were performed in the laboratory of chemistry of synthetic and natural medicinal substances of JSC "Institute of Chemical Sciences named after A.B. Bekturov"

- the act of determining the antimicrobial activity of the substance of JSC "National Scientific Center of Especially Dangerous Infections named after M.Aikimbayev" has been put into effect;

- AIP-2 ND project has been developed on the basis of the A.B. Bekturov Institute of Chemical Sciences;

The practical significance of the work

First of all, it consists in the accumulation and development of scientific ideas about piperidine compounds, methods of their synthesis, structure, and properties, which can later be used in the purposeful design and identification of even more complex systems and will help predict their behavior. The second, but no less important achievement of the conducted research is the prospects for the development of further research on the chemistry of 4,4-disubstituted piperidine derivatives. The synthesized compounds were tested at the Department of Pharmacology of the Kazakh National Medical University named after S.D. Asfendiyarova", in the laboratories of microbiology and virology of JSC Scientific Center for Anti-Infectious Drugs.

As a result of pharmacological screening, it was revealed that a number of compounds exhibit high anti-infective activity, and were recommended for in-depth study of their pharmacological properties.

Personal contribution of a doctoral student

On the topic of the dissertation work, the applicant independently conducted a review of domestic and foreign literature, performed practical work on all the tasks set.

This is confirmed by the results of studies obtained in laboratory and production conditions using modern devices and equipment.

The reliability and validity of the research results is confirmed by the focus on solving an urgent problem, the execution of works, regulatory documents in a modern research center and projects.

Conclusion:

1. By introducing into the structures of N-phenylethylpiperidines p-fluorophenyl-, m-fluorophenyl-, o-fluorophenyl-, 4-(trifluoromethyl)-, cyclohexane-, adamantane-, naphthoyloxy fragments, various 4,4-disubstituted derivatives were obtained. 25 derivatives have been synthesized, of which 22 compounds are new, never described in the literature. To determine their biological activity, their complexes with water-soluble hydrochloride salts and β-cyclodextrin were obtained;

2. The structure of the synthesized compounds was confirmed by a complex of physico-chemical methods, such as IR, 1H and 13C NMR spectroscopy and elemental analysis, the melting temperatures of all products were determined.

3. The direct incorporation of cyclohexane, 3-fluorophenyl fragments into the structure of N-phenethyl piperidine s led to the formation of compounds with anti-infective/antimicrobial activity.

The antimicrobial activity of 1-(2-phenylethyl)-4-(m-fluorobenzoyloxy)piperidine hydrochloride (2.11, MA-5) against the museum-sensitive test strain Staphylococcus aureus ATCC 6538-P and Escherichia coli ATCC 8739 is 2 times higher than that of the ampicillin-colored comparison drug and compound 1-(2-phenylethyl)-4-cyclohexanecarbonyloxypiperidine hydrochloride (2.12, MA-10) exceeded 4 times.

4. All synthesized compounds of the N-phenyl ethyl piperidine series, the structures of which are unambiguously confirmed, were studied in an in vitro experiment against 3 different bacteria, gram-positive and gram-negative microorganisms at the University of Mississippi, USA. As a result, among 12 compounds, only one compound under the code MAM-9 (1-(2-phenylethyl-4-naphthoyloxyperidine hydrochloride, 2.19) showed high activity against the multidrug-resistant Staphylococcus MRS, the inhibitory concentration of which was IC50 11.87 mcg/ml, thereby surpassing the comparison drug Cefotaxime by 2.6 times, in It is 3.5 times higher than Meropenem, 3.8 times higher than Methicillin, but slightly inferior to the drug Vancomycin.

5. Among the synthesized compounds, the greatest antimicrobial/fungicidal activity was shown by hydrochloride 1-(2-phenylethyl)-4-adamantancarbonyloxypiperidine (AIR-2, F-11).

The bactericidal activity of AIR-2 against staphylococcus is 8 times higher than that of the comparison drug ampicillin, the antimicrobial effect is 4 times higher against the Escherichia strain coli ATCC 8739, and the fungicidal activity against the Candida albicans strain is 20 times higher than the commercial drug fluconazole.

6. Based on the study of the antimicrobial activity of compounds at the University of Mississippi (USA), the high antifungal activity of 1-(2-phenylethyl) hydrochloride was confirmed- 4-adamantancarbonyloxypiperidine (AIR-2, F-11) and its complexes with β-cyclodextrin hydrochloride and base (MAM-1, MAM-2), composition with

humate (MAM-3).Their IC50 values for the Cryptococcus neoformans strain were <0.8 mcg/ml, 2.54 mcg/ml, 1.36 mcg/ml, <0.8 mcg/ml.

The compound (FIP-2, A-11) is 2 times superior in terms of antifungal activity to the comparison drug Amphotericin B, 7.18 times to Fluconazole. All 4 compounds that showed high fungicidal activity turned out to be adamantane derivatives based on N-phenylethylpiperidine.

7. Some structure-activity correlations have been identified:

It turned out that the combination of an adamantane fragment and a phenylethyl substituent in the pyridine cycle led to the manifestation of high fungicidal activity of the compound.

Also, the high antimicrobial activity of the compounds against the multidrug-resistant staphylococcus MRSa is explained by the presence and introduction of a fragment of the naphthoyloxygroup into the structure of T-phenylethylpiperidine.

8. Cytotoxicity in vitro of heteroorganic derivatives AIP-2, MA-1, MA-2, AIP-2 with humate, AIP-33, MA-3, MA-4, MA-5, MA-6, MA-7, MA-8, MA-9 and MA-10 A study was conducted in the MDCK cell line. Of all the studied heteroorganic derivatives, it was found that for MDCK cells, the cytotoxicity effect of compounds MA-8, AIP-2, AIP-33 and MA-9 has the lowest index.

9. The quality indicators of the AIP-2 substance have been determined, and a quality specification has been developed. A technological scheme for the production of FIP-2 substance has been developed, consisting of 5 main stages: preparation of raw materials for the production of FIP-2 substance; reaction; precipitation; separation of the product packing, packaging, labeling. The substance is standardized. With a long-term or actual study of the shelf life, all the qualitative indicators fixed in the regulatory document did not exceed the maximum sizes for the period up to now, i.e. there were no deviations. The results of the research showed that at a temperature of 25 ± 2 °With a relative humidity of 60 ± 5%, the shelf life according to research data is currently 24 months.

10. According to the results of the toxicity study, the toxicity of the substance AIP-2 according to the classification of Hodge and Sterner and K. K. Sidorov LD50 >5000 mg/kg was classified as class 5 "low-risk substances", that is, practically non-toxic substances.

Approbation of the results of the dissertation

The main results of the research carried out on the topic of the dissertation were presented at the XX international scientific and practical conference "Chemistry and Chemical Technology in the XXI century" (Tomsk, 2019); At the XIV international scientific and practical conference of young scientists and students "Scientific discussion: current problems, achievements and innovations in medicine" (Dushanbe, 2019); at the international scientific and practical conference "XXI Mendeleev Congress on General and Applied Chemistry" (St. Petersburg, 2019); at the international scientific and practical conference "XXI Mendeleev Congress on General and Applied Chemistry" (St. Petersburg, 2019); International Conference "Modern problems of chemistry and technology of organic substances and materials" (Almaty 2019), "Chemical Journal of Kazakhstan" (Almaty 2019), "Topical issues of chemical technology and environmental protection" VIII All-Russian, dedicated to the 60th

anniversary of KSK Khimprom at the conference (Cheboksary 2020);

At the III International scientific and practical conference "Formation and prospects for the development of the scientific school of pharmacy: succession of generations" (Almaty 2020); "Research Journal of Pharmacy and Technology" (Scopus, India, 2020); Patent No. 4782 for 1-(2-phenylethyl)-4-adamantancarbonyloxypiperidine hydrochloride with antimicrobial activity, under the title "Modern pharmacy: new approaches and current research" S.D. International scientific and practical conference dedicated to the Day of Asfendiyarov KazNMU University (Almaty 2021); at the scientific conference "Fine Organic Synthesis-2021" (Almaty 2021); II International Scientific and practical conference "Innovative development of education, science and technology" (Moscow 2022); International Scientific and Practical Conference of Young Scientists "Science and Innovation" (Tashkent 2022); At the international scientific and practical conference "Current trends in the development of science and education in the field of natural sciences" (Almaty 2022); At the forum with the participation of young scientists of the CIS within the framework of the program of events to celebrate the 300th anniversary of the Russian Academy of Sciences "Science without Borders" (Nizhny Novgorod, 2022); "Promising directions for the development of chemical science, technology and Ecology" by A.B. It was presented and published at an international scientific conference dedicated to the 75th anniversary of the Institute of Chemical Sciences. Bekturova (Almaty, 2022).

Publications Information

According to the results of the dissertation, 20 works were published, of which:

- in the database of foreign journals "Scopus" - 1 article;
- in journals recommended by the Committee for Control in the field of education and Science of the Ministry of Education and Science of the Republic of Kazakhstan - 3 articles;
- in collections of international and foreign conferences - 15 publications;
- Patent 1.

The relationship of national state and scientific and technical programs with the topic of the dissertation

Dissertation work "Physico-chemical foundations for the creation of inorganic, organic, polymer compounds, systems and materials with the necessary properties" according to the plan of research work at the A.B. Institute of Chemical Sciences JSC. Bekturova" (Scientific and Technical Program) No.BR05234667) (2018-2020), "Development of unique domestic innovative pharmaceutical substances (ligands) with anti-infectious activity" (grant financing project of the Ministry of Education and Science of the Republic of Kazakhstan No. AP05131065) (2018 - 2020), "Natural raw materials" and "Innovative multifunctional materials based on man-made waste" (NTP No. BR10965255) (2021-2023).

The scope and structure of the dissertation

The dissertation consists of an introduction, a literary review, a discussion of practical results, a conclusion, a list of references and appendices. The dissertation material consists of 177 pages of a computer set, 42 tables, 17 images, a list of references - 176 titles.