ANNOTATION

of the dissertation for the degree of Doctor of Philosophy (PhD)
in the specialty 6D060600 – «Chemistry»

Satpayeva Zhanarkul Bolsynbekovna

Directed synthesis of new biologically active substances based on hydrazides of *o*- and *p*-hydroxybenzoic acids

The dissertation work is devoted to the synthesis and search for new biologically active substances based on *o*- and *p*-hydroxybenzoic acid hydrazides; to establish the regularities of the mechanisms of the reaction of heterocyclization of hydrazide derivatives; to study the bioactivity of synthesized compounds to identify the relationship "chemical structure-bioactivity". The structure of the synthesized new compounds was established by modern physical and chemical methods-IR, ^{1}H and ^{13}C NMR spectroscopy, as well as data from two-dimensional NMR COSY (^{1}H-^{1}H) and HMQC (^{1}H-^{13}C) spectroscopy, elemental and X-ray diffraction analysis with determination of the crystal lattice parameters of substances.

Relevance of the research topic. Currently, for the pharmaceutical industry of our republic, the problem of finding and creating a wide range of biologically active substances with antibacterial and antiviral properties is of particular relevance. At the same time, the key role belongs to the so-called functionalized organic substances and materials with a certain set of properties that meet the requirements of the most diverse areas of possible practical application in medicine.

In spite of the widespread popularity of hydrazides in medicine as the antibacterial drugs, the search is continued for their new bioactive derivatives.By now, a sufficiently large number of hydrazide derivatives of *o*- and *p*-hydroxybenzoic acids were patented, however, the structural features and breadth of the spectrum of their antibacterial and antiviral properties allow them to be used as building blocks to obtain the new classes of pharmacologically active compounds.

This search is necessary, because one of the main reasons that reduce the effectiveness of treatment is the primary drug resistance of the pathogen and toxic-allergic reactions caused by drugs during long-term treatment and limited monitoring of compliance with the chemotherapy regimen. The problem of drug resistance appeared simultaneously with the introduction of antibiotics and chemotherapy drugs into practice. Drug resistance of bacteria and viruses develops to almost all existing antiviral and antibacterial drugs and is a natural adaptation of species to the environment. Such studies are an integral part of the WHO Program to Combat Various Infections. This important social problem requires a constant search and expansion of the arsenal of new highly effective and low-toxic drugs.

Due to the importance of this problem, scientific and experimental requirements for the development of synthesis methods and the search for new potentially physiologically active medicinal substrates are also increasing.

In this regard, the study of methods for the synthesis of new biologically active compounds obtained on the basis of hydrazine and hydroxybenzoic acid derivatives, which are the structural units of many synthetic pharmacological substances, is of important practical and scientific interest.

All of the above determines the relevance and prospects of developing strategies for the synthesis of bioactive derivatives of *o*- and *p*-hydroxybenzoic acid hydrazides, establishing their structure, studying structural features and reactivity, as well as evaluating biological activity. Currently, there is still a wide range of possibilities for modifying hydrazides and, accordingly, prospects for adding new derivatives to this interesting class of compounds.

The degree of development of the problem. Derivatives of hydrazides are studied in various schools of organic chemistry and attract the attention of many researchers engaged in the search for new antiviral, antibacterial and anti-tuberculosis drugs. Achievements in the field of chemistry of hydrazide and its derivatives are summarized in a number of monographs and review articles (A. P. Grekov (1966), V. E. Kolla (1976), I. S. Berdinsky (1976), Yu.P. Kitaev (1977), V. O. Kozmina (1993), I. I. Semina (2002), A. K. Brel, S. V. Lisina (2007). In Kazakhstan, research in the field of synthesis and the study of the properties of hydrazide derivatives is carried out at the A. B. Bekturov Institute of Chemical Sciences of the Ministry of Education and Science of the Republic of Kazakhstan (K. D. Praliev, K. B. Yerzhanov), the Institute of Organic Synthesis and Coal Chemistry of the Republic of Kazakhstan (S. D. Fazylov, O. A. Nurkenov). The hydrazine class is an inexhaustible source for creating unique pharmacologically active compounds with different structures and a wide range of bioactivity. One of the important topical problems of pharmaceutical chemistry is the production of water-soluble drugs and ensuring the prolongation of the drug in the gastrointestinal tract of the body with natural starch oligomers.In this direction, the development of methods for obtaining supramolecular complexes will contribute to solving the above problems. Research in this area appeared at the Karaganda University named after E. A. Buketov in the Laboratory of Organic Chemistry and Polymers under the leadership of Corresponding Member of the National Academy of Sciences of the Republic of Kazakhstan Burkeev M. Zh. and Academician of the National Academy of Sciences of the Republic of Kazakhstan Fazylov S. D. Creation of new nanostructured supramolecular complexes of water-soluble bioactive substances the study of their physical and chemical properties and the relationship "structure-bioactivity" is currently a new scientific direction in pharmaceutical chemistry.

Connection with the work with the plan of state scientific programs. This work is part of the research carried out within the framework of grant projects: "Development of scientific foundations and effective methods for the synthesis of new polyfunctional pyridine compounds in order to search for

potential biologically active substances for medicine based on them" for 2015-2017 (state registration No.AP05131054).

The aim of the dissertation research is to develop optimal conditions for the synthesis of new functionally substituted derivatives of *o*- and *p*-hydroxybenzoic acid hydrazides, to study the mechanisms of their formation reactions, as well as to comprehensively study their structure and conduct biological tests of the synthesized compounds for antibacterial, antioxidant, antimicrobial, etc. types of activity.

Within the framework of this goal, the following tasks were solved:

1. Search and development of methods for obtaining and optimal conditions for the synthesis of new hydrazones, thiosemicarbazides, S, N-heterocycles and cyclodextrin water-soluble complexes based on *o*- and *p*-hydroxybenzoic acid hydrazides, study of the mechanisms of their formation reactions, and determination of their structure.

2. Study of the structure of the synthesized compounds by IR, ^{1}H and ^{13}C NMR spectroscopy, elemental and X-ray diffraction analysis, as well as data from two-dimensional NMR spectroscopy COSY (^{1}H-^{1}H) and HMQC (^{1}H-^{13}C). Description of cyclodextrin complex compounds by the TG/DSC method.

3. Computer bioprognosis according to the PASS program for the selection of the most promising pharmacologically active derivatives of *o*- and *p*-hydroxybenzoic acid hydrazides and their development for extended bioassays.

4. Conducting biological tests of synthesized compounds to identify patterns of the structure-bioactivity relationship.

The object of research are the hydrazides of *o*- and *p*-hydroxybenzoic acids, hydrazones, thiosemicarbazides, products of heterocyclization of thiosemicarbazides, cyclodextrins.

The subject of the research is the development of synthesis methods and the study of new derivatives of *o*- and *p*-hydroxybenzoic acid hydrazides, the synthesis of their oligomeric water-soluble complexes, as well as the identification of the structure of the synthesized compounds.

The scientific novelty of the work is determined by the fact that:

- previously undescribed hydrazone, thiosemicarbazide, 1,3,4-thiadiazole, 1,2,4-triazole-thione derivatives of *o*- and *p*-hydroxybenzoic acid hydrazides of various structures were synthesized for the first time;

- supramolecular complexes of inclusion of hydrazides and hydrazone derivatives of *o*- and *p*-hydroxybenzoic acids with natural cyclodextrins were synthesized, their characteristics were determined by the TG/DSC method;

- The structural data of the synthesized compounds are described by IR, ^{1}H and ^{13}C NMR spectroscopy, elemental analysis, and two - dimensional NMR COSY (^{1}H-^{1}H) and HMQC (^{1}H-^{13}C) spectroscopy;

-the quantum-chemical parameters of the molecule are calculated in comparison with the experimental data of the XRD;

- the spatial structures of the synthesized crystalline 5-ti compounds were confirmed by X-ray diffraction, C_{if} files of the new compounds were deposited in the Cambridge Crystal Structure Data Bank;

- biological screening studies of the synthesized compounds for antibacterial, anti-radical and inhibitory activities were carried out, among the synthesized compounds a number of substances were identified that have high practically useful properties.

Practical significance. As a result of the dissertation research, 47 new derivatives based on *o*- and *p*-hydroxybenzoic acid hydrazides were synthesized, of which 32 compounds were screened for various types of biological activity. Among the synthesized derivatives, 4 compounds with pronounced antioxidant activity were found, 3 of which were patented: 1 Patent for invention No. 32855 of 14.05.2018; 1 Patent for utility model No. 4696 of 19.02.2020. Three compounds have moderate antimicrobial activity (Application A); another 3 compounds showed a weak antiradical effect (Application B); 4 compounds inhibit the activity of neutrophil elastase (Application C).

The author's personal contribution consists in the analysis and generalization of literature data, the implementation of experimental studies on the synthesis of new hydrazide derivatives of *o*- and *p*-hydroxybenzoic acids, the interpretation and generalization of the results obtained, and the development of substances for bioscreening.

Methodological basis of the study. In the dissertation work, modern physical and chemical methods were used, such as IR, ^{1}H - and ^{13}C-NMR spectroscopy, data from two-dimensional NMR spectroscopy COSY (^{1}H-^{1}H) and HMQC (^{1}H-^{13}C), DG/DSC, elemental and X-ray diffraction analysis, quantum chemical calculations, molecular docking, as well as methods for predicting the biological activity of PASS and experimental bioscreening of new synthesized compounds.

The main provisions of the dissertation submitted for defense:

- the developed ways and synthesis conditions of the new hydrazone, thiosemicarbazide, 1,2,4-triazole-5-thione derivatives of *o*- and *p*-hydroxybenzoic acids;

- the established patterns of reactivity and mechanisms of heterocyclization of thiosemicarbazides of *o*- and *p*-hydroxybenzoic acids, and the structure features of their cyclic derivatives such as 1,2,4-triazole-3-thiones and 1,3,4-thiadiazole;

-the results of the targeted synthesis of the glycosyl-containing thiosemicarbazide derivatives;

- the synthesis conditions for oligomeric β-cyclodextrin inclusion complexes of the hydrazide derivatives;

- the test results for the antiradical (antioxidant) and antiviral activity of some synthesized compounds.

The reliability and validity of the results and conclusions is due to the complex use of modern physical and chemical research methods, such as elemental analysis, IR spectroscopy, one-dimensional and two-dimensional NMR ^{1}H spectroscopy COSY, HMQC, X-ray diffraction analysis used to determine the structure, personality, and conformational features of synthesized compounds. The

practical useful properties of bioactive substances identified during bioscreening confirm the validity of the scientific results.

Approbation of the work. The results of the dissertation work were presented at the international scientific and practical conferences "Science, Education and Production in the conditions of the Fourth Industrial Revolution" (Karaganda, 2018); Proceedings of the VIII International symposium on speciality polymers (Karaganda, 2019).

Publications. 12 papers were published on the topic of the dissertation, including: 5 articles in republican publications (Izvestiya NAS RK, Vestnik KarSU and Vestnik NAS RK), 2 articles in the international scientific journal included in the Web of Science database (Russian Journal of General Chemistry, Russian Journal of Bioorganic Chemistry), as well as theses of 2 reports at international scientific conferences. One article was published in the European journal - East European Scientific Journal. 1 Patent of the Republic of Kazakhstan for invention No. 32855 "N-phenyl-2-(2-hydroxybenzoyl)hydrazine carbothioamide with pronounced antioxidant activity" and 1 utility model patent No. 4696 "Ethylthiosemicarbazide derivatives of hydrazides of 2- and 4-hydroxybenzoic acids with a pronounced antioxidant activity (options)" (Application D).

The structure of the dissertation consists of an introduction, the main part-experimental data, the results of experimental studies and discussion, conclusion, list of sources used, appendix. The volume of the dissertation consists of 108 pages, 20 tables and 41 figures. The number of sources used is 203. The 3 applications contain acts of bio-testing of new compounds.

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