

ANNOTATION

of the dissertation for the degree of Doctor of Philosophy (PhD) in specialty
6D074800 – «Technology of pharmaceutical production»

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«Chemical development of a new substance based on modified ecdysteroids»

The dissertation is devoted to the optimization of methods for the isolation and complex extraction of polyoxysteroids from plant materials, theoretical and experimental research on the directed synthesis of new supramolecular encapsulated and hydrophilic derivatives based on them with high biological activity.

Methods of IR-, UV-, Mass-, NMR-spectroscopy, X-ray diffraction and HPLC analysis, quantum chemical calculations of reactivity and PASS-prediction of biological activity and bioscreening were used in this work.

The relevance of the topic of dissertation research.

The strategic direction of the state policy in Kazakhstan is a systematic reduction in the dependence of the Republic's health care on the import of medicinal products through a fuller use of its own production capacities, raw materials, the country's scientific and technical potential and the creation of pharmaceutical industries based on domestic science-intensive technologies. The State Register of the Republic of Kazakhstan contains more than 8000 registered medicinal products. The share of domestic drugs is 30%, in value - 10%; therefore 90% of the demand for pharmaceutical products is met through imported drugs. In the conditions of dependence of the country's pharmaceutical market on import the creation of new domestic medicines is one of the most important stages in the development of the pharmaceutical industry in Kazakhstan.

The Republic of Kazakhstan is rich in natural resources, the rational use of which will contribute solution of the objectives. One of the current objectives facing the pharmaceutical science of Kazakhstan is the search for potential sources of biologically active compounds, identification and study of their nature, physicochemical properties, determination of qualitative and quantitative significance, development of technology for pharmaceutical substances.

According to the data of the World Health Organization, at present up to eighty percent of people worldwide use medicinal plants for the treatment of diseases. This is due to the polyvalence of their pharmacological action determined by the complex composition of the plant biologically active substances. Phytopreparations are characterized by mild therapeutic effect, low toxicity, low occurrence of adverse reactions, and economic availability of raw materials from which they are made. All

this determines their advantages over synthetic drugs and makes them the drugs of choice in the therapy of many diseases.

Steroid compounds play an extremely important role in the life of plants, animals and humans. In this regard, they have attracted the attention of researchers working in the field of bioorganic chemistry, pharmaceutical chemistry, and the chemistry of supramolecular compounds in recent decades. The unique properties of molecules characterized by the presence of a wide range of biological activity, structural features and the availability of sources for their preparation made it possible for them to become practically important source of renewable material for the development of new highly effective phytopreparations based on them.

Such multi functionality is especially pronounced in a relatively new group of natural compounds, polyoxysteroids, which are a fairly large group (about 500 compounds).

However, the development of modern research is hampered by the limited availability of polyoxysteroids, the content of which in the organisms of plants and animals is low, and is also hampered by their water insolubility. Therefore, the main way to develop drugs based on them is directed organic synthesis or chemical modification. In addition, studies show that the modification of the molecules of steroid compounds sometimes leads to an increase in biological activity compared with natural analogues. This is the main reason for the need for chemical and biological studies of the vast series of polyoxysteroids.

One of the promising directions in terms of modification and creation of new water-soluble substances of medicines is supramolecular complexation-incapsulation. In the study, potentially biologically active phytoecdysteroid-ecdysterone was modified, its structure and biological activity were determined. As a result, new compounds with adaptogenic properties have been obtained and their safety has been proven. It was analyzed from a physical, chemical and economic point of view, among which the characteristics of quality, standardization, stability and safety for the most effective compound were studied.

Currently, the application of cyclodextrins (CDs) to obtain inclusion complexes of biologically active compounds (BAC) and medicines is one of the main ways of developing and creating new forms of pharmaceuticals. CDs differ in a number of advantageous properties due to their low cost and special structure among other widely known encapsulating receptors for BAC such as cucurbiturils, crown ethers, calixarenes, etc.

From the point of view of comparing similar structures, the main distinguishing feature of CDs is their ability to hydrophobically bind a guest molecule in their cavity in an aqueous medium with the formation of inclusion complexes with substrates that are less polar than water and if their geometry and structure are complementary to cavity of cyclodextrin receptor.

Available literature data on the study of ecdysteroid-containing plants, polyoxysteroids and polyols, methods for their extraction, modification and biological

activity show the promise of studying these secondary plant metabolites. In this regard, the study of polyoxysteroids and polyols from available plant materials of the Republic of Kazakhstan, the modification of their molecules with subsequent bioscreening of the compounds obtained, as well as the development of high-tech and less expensive have been obtained and their safety has been proven. It was analyzed from a physical, chemical and economic point of view, among which the characteristics of quality, standardization, stability and safety for the most effective compound were studied. technologies for creating new supramolecular encapsulated and hydrophilic forms based on them remains relevant and in demand.

Purpose of the research

Getting medication based on the modified biological availability, improved physiochemical and pharmacological properties of modified edystone.

Objectives of the research:

- To obtain new modified compounds based on the phytoecdysteroid ecdsterone with optimized physical and chemical properties;
- To study the physical and chemical properties of the new derivatives obtained;
- Carry out standardization, development of technology for obtaining and analysis of stability of new compounds;
- To study the safety and main pharmacological effect of the derivative;

Object of research

– The object of the research is a complex supramolecular substance of cyclodextrin obtained by the modification of echistone or 20-hydroxyacidone.

Methods of the research:

– physical and physicochemical, pharmacognostic, pharmaco-technological, biological, microbiological, statistical, pharmacopoeial and non-pharmacopoeial methods.

Scientific novelty

The scientific novelty of the research is that for the first Time:

- new water-soluble compounds were obtained on the basis of ecdysterone and α -, β -, γ - CD and their structures were determined by IR-, mass-, NMR ^1H and ^{13}C spectroscopy;
- optimal technology for obtaining water-soluble substance ecdisteronas β -cyclodextrin were developed and standardized according to the requirements of the State Pharmacopoeia of the Republic of Kazakhstan;
- acute toxicity, high adaptogenic and actoprotective activity and stability of the obtained substance were studied.

The main provisions of the dissertation submitted for defense:

- technology of preparation, standardization, stability research and production of dry extract of raw materials *Rhaponticum karatavicum* Rgl. et Schmalh in accordance with the requirements of the State Pharmacopoeia of the Republic of Kazakhstan;
- results of research of antiradical and antioxidant activity of dry extract of *Rhaponticum karatavicum* Rgl. et Schmalh;
- development of optimal technology for obtaining and operating a new modified substance ecdisterone with β -cyclodextrin
- results of the study of acute toxicity, adaptogenic and actoprotective activity of new and stable supramolecular complexes of polyoxysteroids with cyclodextrins.

A practical significance of the work:

- a technology of harvesting and storage of the *Rhaponticum karatavicum* Rgl. et Schmalh in accordance with the requirements of the GACP standard has been developed.
- developed technology for collecting and harvesting *Rhaponticum karatavicum* Rgl. et Schmalh in accordance with the requirements of the GACP standard;
- developed technology for the production of supramolecular complexaecdysterone with β -CD.

Reliability and validity of the research results

The work was aimed at addressing the urgent problems of the present time, with the development of domestic and world leading research sites and the study of the structure and properties of the works by modern devices.

Approbation of work

The main results of the research on the theme of the dissertation: VI XVII International Conference "Education in Science in XXI Century" (Kharkov 2016), International Conference "Prodcorporation - Potential of Future" (St. Petersburg, 2016), International Scientific and Practical Conference "Belarusian Drugs" (Minsk 2016), LX-LXI International Scientific and Practical Conference № 4-5 (46) 2017, Research Conference: Problems of Medicine (Moscow 2017), XXVI Международная научная конференция «Актуальные научные исследования в современном мире» (in absentia) issue 5 (25) part 3, May 2017. (Pereyaslav-Khmelnitsky, 2017).

Publication Info:

- According to the results of the research 10 works were published, including:
- An international journal entry into the Scopus database - 2;
 - Publication in journals recommended by the Committee for Control of Education and Science of the Republic of Kazakhstan - 4;
 - publication in materials of the international scientific-practical conference - 5;
 - Useful Pattern - 1.

The structure and scope of the dissertation

The dissertation consists of introduction, literary review, discussion of practical results, conclusion, list of used literature and appendices. The dissertation material consists of 158 pages of computer parts, 24 tables, 57 pictures, the list of used literature is 218.