Completed projects for 2018-2020.
Grant project No. AP05134198 "Study of biosynthesis of terpenoids in plants and the search for new pharmacologically active bimolecular compounds".

For chemical modification the following were isolated and developed: sesquiterpene lactones estafiatin from *Achillea nobilis* L., artemisinin from *Artemisia annua* L., argracin from *Artemisia aralensis* Krasch., arglabin and argolide from *Artemisia glabella* Kar. et Kir., grossmisin from *Artemisia leucodes* Schrenk., grossheimin from *Chartolepis intermedia* Boiss. and flavonoids quercetin from *Hypericum perforatum* L., pinostrobin from buds of *Populus balsamifera* L., and alkaloid anabasine from *Anabasis aphylla* L.

The search for bimolecular compounds was carried out in the sums of extractive substances from *Artemisia santolinifolia* Turcz. ex Besser, *Ferula akitschkensis* B. Fedtsch. ex Koso-Pol., *Ferula ferulaeoides* (Steud.) Eug. Kor., *Ferula kelleri* Koso-Pol., *Ferula krylovii* Korovin, *Ferula ovina* Boiss., *Ferula songarica* Pall. ex Spreng, Handelia trichophylla (Schrenk ex Fisch. & C.A.Mey.) Heimerl.), *Ligularia heterophylla* Rupr. The dimeric sesquiterpene lactone handelin, phenolterpenoid ester ferocinin and 3-methoxy-4,5-methylenedioxypropiophenone were isolated and identified. For the first time, the stereochemistry of the crystal structures of the molecules of ferocinin, 3-methoxy-4,5-methylenedioxypropiophenone, α-cytisinylgrossheimin was established by the X-ray diffraction method. Structural data were deposited in the Cambridge Crystallographic Database, respectively, under the numbers SSDC 1978204, 1978205, 1578031.

For the first time, 11 new hybrid derivatives based on plant sesquiterpene lactones grossheimin and arglabin were synthesized. The structure of the new derivatives was established based on the data of IR-, UV-, mass, ^{1}H, ^{13}C NMR spectroscopy and X-ray structural analysis.

Moderate antimicrobial activity against gram-positive test strains of *Bacillus subtilis* and *Staphylococcus aureus* was demonstrated by samples of 3 hybrid molecules (chloroacetylgrossheimin, cytisinylgrossheimin and cytisinylargolide).

In *in vivo* experiments, the anthelmintic activity of 4 hybrid derivatives (anabasinylarglabin, α-cytisinylarglabin, hydrochlorides of anabasinylgrossheimin and cytisinylgrossheimin) against helminthiasis in dogs was studied. A substance based on α-cytisinylgrossheimin hydrochloride is recommended for the development of a new anthelmintic agent against helminths of the *Nematodae* family. Laboratory regulations for the preparation of α-cytisinylgrossheimin hydrochloride LR-40761819-01-20 were developed.

For the first time, in the leaves and buds, as well as the leaves of a regenerant plant in vivo and its callus tissues *in vitro* of an intact plant of *Artemisia glabella* Kar. et Kir., by molecular genetic methods the presence of three sesquiterpene synthases was revealed: germacrene A synthase (GAS), germacrene A oxidase (GAO) and costunolide synthase (COS), encoding the initial stages of the biosynthetic pathway of sesquiterpene lactones arglabin, argolide, dihydroargolide in plant's body. Their nucleotide sequences were established by Sanger sequencing and deposited in the National Center for Biotechnological Information (NCBI, USA) under the numbers MT276314, MT276315, MT276313, respectively. As a result, a model of arglabin biosynthesis in the body of *Artemisia glabella* Kar. et Kir was developed.

Molecular docking of 9 sesquiterpene lactones and their bimolecular derivatives for antiviral activity was carried out.

Cytotoxicity of 10 natural sesquiterpene lactones and their bimolecular derivatives against human acute monocytic leukemia cells THP-1 was studied. Chloroacetylgrossheimin showed high cytotoxicity against acute monocytic leukemia cells (*in vitro*).

Based on the results obtained during the period of the project implementation in 2018-2020, 19 papers were published, including 5 articles in peer-reviewed foreign journals with an impact factor, indexed in the Web of Science and Scopus databases, 2 articles in the journal recommended by CCES, abstracts of 10 reports in the materials of international conferences, including 7 foreign ones. An application for obtaining a title of protection has been submitted to the National Institute of Intellectual Property of the Ministry of Justice of the Republic of Kazakhstan. For a complete list, see the "Scientific Publications" section.

According to the results of research carried out in 2019, the executor A.S. Kishkentayeva successfully defended her thesis for the degree of Doctor of Philosophy (PhD) in the specialty "Technology of pharmaceutical production".

Completed projects for 2018-2020.
Grant project No. AP05133096 “Pharmacognostic studies of plants and chemosystematics of taxa of the family *Asteraceae*”.

The anatomical, morphological and diagnostic characters of 7 plant species of the genus *Saussurea* DC., 6 plant species of the subgenus *Artemisia* Less., 5 plant species of the subgenus *Dracunculus* (Bess.) Rydb and 10 species of the subgenus *Seriphidium* (Bess.) Rouy were determined.	Based on the results of a chemical study of the aerial parts of 7 plant species of the genus *Saussurea* DC., it was determined that the sesquiterpene lactone cynaropicrin is a chemotaxonomic marker of plants of the genus *Saussurea* DC. For plants of the subgenus *Artemisia* Less. and *Dracunculus* (Bess.) Rydb. sesquiterpene lactones and coumarins were identified as chemotaxonomic markers of the taxa under study. For 10 plant species of the subgenus *Seriphidium* (Bess.) Rouy. the chemotaxonomic marker is eudesman sesquiterpene lactone α-santonin, and in essential oil - monoterpenoids 1,8-cineole and camphor.	Regulatory documents for the buds of *Populus balsamifera* L. were presented in the NCEM MH RK.
For the first time, histochemical analyzes were carried out to determine the localization of sesquiterpene lactones, flavonoids, coumarins and essential oil in the tissues of organs of the studied plant species.		
Areas of growth were identified, and the operational reserves of 7 species were evaluated: plants of the genus *Saussurea* DC in Eastern and Central Kazakhstan, *Artemisia annua* L. in the territory of Almaty region and *Artemisia leucodes* Schrenk. on the territory of Almaty and Zhambyl regions; the good quality and merchandising parameters of 7 species of the genus *Saussurea* DC., 6 species of the subgenus *Artemisia* Less., 5 species of the subgenus *Dracunculus* (Bess.) Rydb. and 10 species of the subgenus *Seriphidium* (Bess.) Rouy were determined.	The good quality of plant raw materials was determined, merchandising parameters were established, and the quantitative contents of microelements in plants of the genus *Saussurea* DC., subgenera *Artemisia* Less., *Dracunculus* (Bess.) Rydb., *Seriphidium* (Bess.) Rouy were determined. It was determined that the raw materials of the studied plant species are safe and environmentally friendly.	For the period 2018-2020, 6 scientific papers were published, of which 2 articles in peer-reviewed foreign editions with an impact factor included in the Scopus database, 2 articles in a peer-reviewed domestic edition recommended by CCES, abstracts of the report in the materials of an international conference, 2 applications have been submitted to NIIP MJ RK for obtaining a title of protection. For a complete list, see “Scientific Publications” section.
	A pharmacognostic study and standardization of raw materials of *Peganum harmala* L., *Populus balsamifera* L. were carried out, and analytical normative documents were developed for raw materials of “*Peganum harmala* L., roots” and “*Populus balsamifera* L., buds”.	

Completed projects for 2018-2020.
Grant project No. AP05130476 “Technology of water-soluble substances and finished dosage forms based on natural flavonoids and terpenoids”.

The optimal compositions of water-soluble substances of pinostrobin oxime and natural arglabin were selected, their physicochemical parameters were determined. 23 mechanocomplexes of pinostrobin oxime and 24 mechanocomposites of natural arglabin were synthesized. The effect of mechanochemical treatment on the water solubility of the pinostrobin oxime and natural arglabin substance was studied.	The technological parameters of mechanocomplexes of pinostrobin oxime and natural arglabin with polyvinylpyrrolidone, disodium glycyrrhizic acid and magnesium carbonate were determined.	Developed and approved 6 laboratory and pilot industrial regulations for the production of a mechanocomplex of pinostrobin oxime with disodium salt of glycyrrhizic acid (LR-40761819-02-19 and PIR FD65005037R-05-19); mechanocomposite of native arglabin with polyvinylpyrrolidone (LR-40761819-03-19 and PIR FD65005037R-06-19), capsules with mechanocomposite of natural arglabin (LR-40761819-04-20) and mechanocomplex of pinostrobin oxime (,LR-40761819-05-20).
A one-stage technology for obtaining water-soluble substances of pinostrobin oxime and arglabin by mechanochemical treatment was developed. The technology of obtaining a mechanocomplex of pinostrobin oxime with a disodium salt of glycyrrhizic acid and a mechanocomposite of natural arglabin with polyvinylpyrrolidone was optimized.	The compositions of the dosage form were selected and pilot batches of granules with a mechanocomposite of natural arglabin of three models and a mechanocomplex of pinostrobin oxime of six models were developed. The optimal technological parameters of model mixtures of granules of water-soluble substances of the mechanocomposite of natural arglabin and the mechanocomplex of pinostrobin oxime were determined.	During the reporting period, a patent of the Republic of Kazakhstan was received, an application for a title of protection was filed to the NIIP MJ RK, three articles were published in editions with a non-zero impact factor according to Scopus and RSCI databases, two articles in domestic scientific journals recommended by the CCES MES RK and theses of two reports in the materials of international conferences. For a complete list, see “Scientific Publications” section.

Completed projects for 2018-2020.
Grant project No. AP05130956 “Pharmacogenetic study of terpenoid molecules and molecular genetic mechanisms of their action”.

Biomaterials obtained from 100 patients aged 29 to 78 years diagnosed with breast cancer (BC) stage II and III of the disease were studied, including 31 patients who received treatment with the drug “Arglabin”. The postoperative material of breast cancer was studied for the determination of HRas oncoproteins by the immunohistochemical method and by the method of Western-blot hybridization.	Analysis of the correlation relationship between the percentage of HRAS protein obtained by the Western-blot method and the qPCR (real-time PCR) threshold cycles for the HRAS gene showed an inverse relationship with a correlation coefficient of -0.78 ($p < 0.0001$, Spearman). The level of protein expression and the level of gene expression have direct correlation dependence by 78%.	Based on the results obtained during the period of the project in 2018-2020, an application for a title of protection was submitted to the NIIP MJ RK, 12 scientific papers were published, of which 4 articles in peer-reviewed foreign journals with an impact factor indexed in the Web of Science and Scopus databases, 2 articles in the RSCI database, 1 article in a journal recommended by CCES, abstracts of 3 reports in the materials of international conferences. For a complete list, see “Scientific Publications” section.
When studying the expression of HRAS oncoproteins by Western-blot hybridization, it was found that 43% of patients had a positive expression and 57% had a negative expression.	With combined treatment with AC and Arglabin, the level of H-RAS expression increases by 3.16 times.	
It was found for the first time that HRAS oncoproteins were not found in the group of patients who received therapy with drug “Arglabin” and the standard AC regimen (doxorubicin + cyclophosphamide). In the group of patients with monotherapy with Arglabin (n=31), the studied proteins were found in 33.5% of cases, while in 66.5% of cases the studied protein was not detected. It was established that monotherapy with the drug "Arglabin" showed a fairly high efficiency in the absence of HRAS oncoproteins, the frequency of the overall effect was 72.8%.	In patients with a positive expression of HRAS, as a result of therapy with drug “Arglabin”, there was a statistically significant increase in relapse-free survival up to 16.5±1.1 months compared to the standard AC regimen (13.5 ± 1.1 months) ($p<0.05$), the addition of Arglabin to the standard AC regimen also increased this indicator to 16.4±1.2 months ($p<0.05$).	The responsible executor of the project A.M. Zhumakayeva in 2020 successfully defended her dissertation for the degree of Doctor of Philosophy (PhD) in the specialty “Medicine”.

Completed projects for 2018-2020.
Grant project No. AP05134907 “Molecular docking and bioscreening of new natural compounds”.

For a targeted search for “compounds-candidates”, a computer prediction of biological activity for 17 flavonoids molecules and their derivatives was carried out using the PASS online computer program. As a result of PASS-prediction, it was established that all the presented compounds possess pharmacological activity, in particular, antitumor, hepatoprotective, antioxidant, anti-inflammatory, antiviral, antiprotozoal, antibacterial activity. Based on the data of computer prediction, biological studies of the selected flavonoids were carried out in model systems *in vitro* and *in vivo.*	The *in vitro* cytotoxicity of 8 alkaloids, 6 sesquiterpene lactones and their derivatives in the survival test of the larvae of crustaceans *Artemia salina* (Leach) was determined.	The analgesic activity of samples of alkaloids 2-F-chalcone derivative of harmine and cytisine was established on the model of chemical irritation of the peritoneum *in vivo.* Antimicrobial activity of 6 samples of natural sesquiterpene lactones and their derivatives in *in vitro* experiments was determined.
The specific cytotoxic activity of sesquiterpene lactones against the culture of cancer cells was confirmed in models of transplanted tumors *in vivo.*	Molecular docking of molecules of alkaloids, sesquiterpene lactones on key enzyme targets and specific receptors was carried out, according to the results of which compounds were selected that demonstrated relatively high and potentially promising values of the binding energy E_{bnd} (G-score) of the molecule with the receptor. It was revealed that the alkaloids ((*E*)-1-(7-methoxy-1-methyl-9*H*-pyrido[3,4-b] indol-8-yl)-3-(2,4-dimethoxyphenyl)prop-2-en-1-one, 8-acetylharmine, cytisine and lappaconitine exhibit neurotropic effects in models of experimental stress *in vivo.*	During the reporting period, an application for a patent of the Republic of Kazakhstan was submitted to the NIIP MJ RK and 5 scientific papers were published in domestic and foreign periodicals, of which one article in a journal with an impact factor, indexed in the Scopus databases. For a complete list, see “Scientific Publications” section.

Completed projects for 2018-2020.

Grant project No. AP05130575 “Development of effective methods for the isolation and identification of new biologically active compounds from essential oils of plants”.

For the first time, using modern methods of gas chromatography with a flame-ionization detector and mass spectrometry (GC-FID and GC/MS), the component composition of essential oils of 33 plant species was studied, belonging to the genus: *Artemisia* L., *Archangelica* Hoffm., *Ajania* Poljak., *Betula* L., *Centaurea* L., *Doronicum* L., *Ferula* L., *Hippophae* L., *Ligularia* Cass., *Nepeta* L., *Pulicaria* Gaertn., *Saussurea* DC., *Schrenkia* Fisch. et Mey., *Spiraeanthus* Maxim., *Tanacetum* L., *Teucrium* L., *Thymus* L., *Viola* L. of flora of Kazakhstan and at the same time, 1571 compounds were identified.

Samples of essential oils were studied for antimicrobial, anti-inflammatory, antifungal, antioxidant activity and on a model of Alzheimer's disease.
Based on the results of screening for biological activity, essential oils of *Artemisia santolinifolia* Turcz. ex Bess., *Artemisia transiliensis* Poljakov, *Ajania fastigiata* (C.Winkl.) Poljak., *Ferula Kelleri* Koso-Pol., *Ferula songarica* Pall. ex Spreng., *Ferula ovina* (Boiss.) *Ferula akitschkensis* B. Fedtsch. ex Koso-Pol, *Ligularia heterophylla* Rupr. and *Pulicaria prostrata* (Gilib.) Aschers showed pronounced antimicrobial and anti-inflammatory activity. Essential oil of *Ferula foetida* L. shows pronounced antifungal activity.

Essential oils of *Artemisia glabella* Kar. et Kir., *Doronicum altaicum* Pall., *Ferula ceratophylla* Regel et Schmalh, *Ferula ovina* (Boiss), *Nepeta cataria* L., *Pulicaria prostrata* (Gilib.) Aschers., *Teucrium scordioides* L. and CO_2-extracts of *Artemisia rupestris* L., *Artemisia tianschanica* Krasch. et Poljak *Pulicaria prostrata* (Gilib.) Aschers. on a model of Alzheimer's disease showed an inhibitory effect on the enzyme acetylcholinesterase.

Laboratory regulations were developed for the isolation of essential oil from the roots of *Ferula akitschkensis* B. Fedtsch. ex Koso-Pol. (LR-40761819-02-20).

By the method of rectification of essential oils of *Origanum vulgare* L. and *Thymus marschallianus* Willd. with subsequent chromatographic purification, the monoterpenoids thymol and carvacrol were isolated. From essential oil of *Ligularia heterophylla* Rupr. a sesquiterpene lactone was isolated. From essential oil of *Ferula foetida* Linn., 2,3,4,5-tetramethylthiophene and guaiol were isolated and identified.

Essential oils of *Artemisia glabella* Kar. et Kir., *Doronicum altaicum* Pall., *Ferula ceratophylla* Regel et Schmalh, *Nepeta cataria* L. and CO_2-extracts of *Artemisia rupestris* L., *Pulicaria prostrata* (Gilib.) Aschers. have antioxidant activity.

During the reporting period, an application for a title of protection was filed to NIIP MJ RK, 15 scientific papers were published, of which 5 articles in peer-reviewed foreign journals with an impact factor indexed in the Web of Science and Scopus databases, 4 articles in journals recommended by CCES, abstracts of 5 reports in materials international conferences. For a complete list, see “Scientific Publications” section.

Completed projects for 2018-2020.
Grant project No. AP05133718 “Synthesis, structure and biological activity of new water-soluble derivatives of polyoxysteroids”.

During the reporting period, chemical screening was carried out of 11 plant species of the flora of Kazakhstan of the *Garyophyllaceae* Juss. and *Chenopodiaceae* Vent. families, including 5 endemic species for ecdysteroid content. It was established that 3 species of saltbush (*Atriplex patula* L., *Artiplex verrucifera* Bieb. and *Atriplex tatarica* L.) contain ecdysterone.	As a result of bioscreening, among the synthesized compounds, substances were found with pronounced anti-inflammatory and analgesic activity, exceeding the reference drug “Diclofenac sodium”.	During the reporting period, 12 articles were published, 5 of them in editions included in the Scopus and Web of Science databases, abstracts of 9 reports in the materials of international conferences. For a complete list, see “Scientific Publications” section.
Polyoxysteroids: 20-hydroxyecdysone (20E), 2-deoxyecdysone, 3-epi-2-deoxyecdysone and 2-deoxy-20-hydroxyecdysone were isolated from *Silene wolgensis* (Hornem.) Bess. ex Spreng, *Serratula coronata* L., *Acanthophyllum gispophiloides* Regel. and *Silene fruticulosa* (Pall.) Schischk and new supramolecular complexes based on them with α-, β-, γ- and 2-hydroxypropyl-β-cyclodextrins were synthesized. The fine structures of new water-soluble complexes of polyoxysteroids and polyol were fully confirmed by the data of two-dimensional correlations of ^{1}H-^{1}H NMR TOCSY, ^{1}H-^{1}H ROESY, ^{1}H-^{13}C HMQC and ^{1}H-^{13}C HMBC spectra.	Laboratory regulations were developed for the isolation of polyoxysteroids from raw materials of *Silene wolgensis* (Hornem.) Bess. and obtaining water-soluble forms on their basis (LR-40761819 dated October 19, 2020).	

Completed projects for 2018-2020.
Grant project No. AP05130781 “Isolation from plants, identification and structural modification of flavonoids - the basis of new medicinal substances”.

Chemical screening of 30 plant species of the flora of Kazakhstan for the content of flavonoids was carried out. At the same time, the qualitative composition and quantitative content of flavonoid compounds in plant extracts were determined.	Chemical study of *Origanum vulgare* L., Carduus nutans L., *Polygonum aviculare* L., *Tanacetum vulgare* L., buds of *Populus balsamifera* L., *Artemisia glabella* Kar. Et Kir., *Serratula coronata* L., *Helichrysum arenarium* L. and *Ajania fruticulosa* (Ledeb.) Poljak was carried out. At the same time, samples of 10 flavonoids were isolated and developed: chrysin, apigenin, pinostrobin, tectochrizin, pinocembrin, naringenin, cirsilineol, artemisetin, pectolinarigenin, quercetin.	Laboratory regulations weredeveloped for the production of pinostrobin acetate (LR-40761819-01-19) and for the production of apigenin from *Serratula coronata* L. (LR-40761819-02-20).
Relatively promising plant sources of flavonoid compounds were revealed, namely: *Centaurea lasiopoda* Popov & Kult. (flavonoid content 2.69% based on air-dry raw materials), *Centaurea iberica* Trevir. & Spreng. (2.40%), *Hieracium pilosella* F.W.Schultz & Sch.Bip. (2.20%), *Hypericum perforatum* L. (1.98%), *Helichrysum arenarium* L. (containing flavonoid apigenin – 2.86%), *Bupleurum aureum* Fisch. ex Hoffm. (rutin – 3.24%, myricetin – 1.63%), *Serratula coronata* L. (apigenin – 3.7%), *Polygonum aviculare* L. (rutin – 1.71%), *Bidens tripartita* L. (rutin – 3.08%) and *Artemisia absinthium* L. (artemisetin – 1.25%).	In terms of obtaining biologically active compounds based on flavonoids, 15 new derivatives were synthesized, the structures of which were established by spectral methods (IR-, UV-, PMR, ^{13}C NMR) of analysis. Biological screening of samples of flavonoids and their derivatives was carried out. It was established that the studied compounds have antioxidant, hepatoprotective and antiradical activity.	Based on the results of the studies, an application for a patent of the Republic of Kazakhstan was submitted to the NIIP MJ RK, 3 articles were published in international editions with an impact factor included in the Scopus database, 1 article in a journal recommended by the CCES MES RK; abstracts of 3 reports in the materials of international and republican scientific conferences. For a complete list, see “Scientific Publications” section.

Completed projects for 2018-2020.
Grant project No. AP05135304 “Chemical study of alkaloid-bearing plants as promising sources of biologically active substances”.

A chemical study of 11 plant species of the families *Ranunculaceae* Juss., *Asteraceae* Dumort., *Gentianaceae* Juss., *Papaveraceae* Juss. for the content of alkaloids was carried out, while 16 alkaloids were isolated and identified. For the first time, from *Gentiana decumbens* L. a pyridine alkaloid - gentianine, indole alkaloid - harmine; from *Aconitum monticola* Steinb. - diterpene alkaloid - delphinofoline; from *Aconite anthoroideum* DC. - delcosin were isolated and identified.	Biological screening of isolated alkaloids and their derivatives for neurotropic, analgesic, antimicrobial, cytotoxic activity was carried out. The results of the study showed that the diterpene alkaloid delphinofoline has a pronounced neurotropic activity; delcosin and lappaconitine - antimicrobial, 8-acetylhydrazone harmine - a pronounced analgesic activity.	The laboratory regulations were developed for the obtaining of alkaloid echinopsine from *Echinops albicaulis* Kar. & Kir. (LR-40781819-07-20).
A chemical modification of cytisine and harmine molecules was carried out, on the basis of which 16 new derivatives were synthesized. The structure of molecules of new compounds was established on the basis of elemental analysis and spectral data (UV-, IR-, ^{1}H-, ^{13}C-NMR) and XRD.	According to the results of an experiment on a model of Alzheimer's and Parkinson's disease, it was revealed that harmine derivatives have an inhibitory effect on the enzymes of acetylcholinesterase and tyrosinase.	Based on the results of studies, an application for a patent of the Republic of Kazakhstan was submitted to the NIIP MJ RK, 7 scientific papers were published, of which 2 article in peer-reviewed scientific journals indexed in the Scopus database, 2 articles in a domestic edition recommended by CCES and abstracts of 3 reports. For a complete list, see “Scientific Publications” section.