SESQUITERPENE LACTONES OF PLANTS – PROMISING GROUP OF NATURAL ISOPRENOID COMPOUNDS

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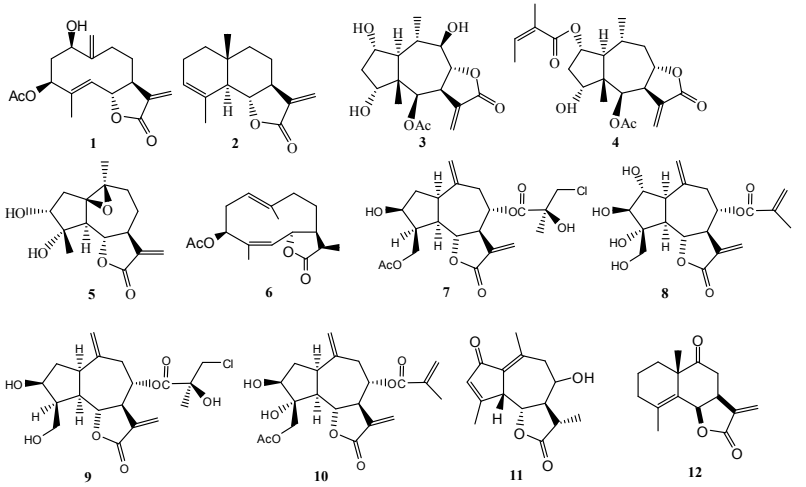
Isoprenoids take an important place among natural compounds of plants. A promising group of them is formed by biologically active sesquiterpene γ-lactones having a practical value as a potential source of new medications. Study of their biological properties *revealed many* types of activities. Besides, sesquiterpene lactones are important as chemotaxonomic markers for solution of complex and confusing problems of systematization and

Search for raw material, rich by specified sesquiterpene lactones as renewed chemical material, promotes development of a basis for subsequent synthetic researches directed to the obtaining of biologically active derivatives of terpenoids. At the same time, finding new representatives of the series and their physiological estimation enriches existing database for structure-activity relationships studies, which are very important for better efficiency of drug design.

Over 300 species of plants, basically belong to *Asteraceae (Compositae)* family, were investigated for the content of sesquiterpene lactones at JSC «International research and production holding «Phytochemistry»». Presence of sesquiterpene lactones in plant extracts was defined via absorption band at 1740–1800 cm^{-1} in IR-spectra that is characteristic for carbonyl γ-lactone group. The extracts were obtained from the plant samples by extraction with chloroform, hot water and ethanol. Extracts were analyzed by HPLC method with use of authentic markers of sesquiterpene lactones.

Resulting from the screening, 34 species of plants being representatives of genera of *Artemisia, Jurinea*, *Lepidolopha, Phalacrachena*, *Rhaponticum, Tanacetopsis, Tanacetum* were chosen as perspective sources of sesquiterpene lactones. Additional criterion for final choice of research objects was availability of raw-material. As a result, 100 sesquiterpene lactones were isolated and characterized. Twenty six new sesquiterpene lactones were determined in the vegetative objects. It was found that all of them belong to four structural types – germacranolides, eudesmanolides, guaianolides and pseudo guaianolides. For instance, new sesquiterpene lactones, which have not been described before (1-12), were isolated from *Artemisia subchrysolepis* Filatova, *Ajania fruticulosa* (Ldb.) Poljak., *Tanacetum vulgare* L., *Artemisia tournefortiana* Rchb., *Artemisia filatovii* A.Kuprijanov sp. Nova, *Rhaponticum serratuloides* (Georgi.) Bobr. and *Artemisia leucodes* Schrenk. Their structures were determined by spectral methods, including X-ray analysis, and by chemical conversions.

For the first time reactions of acidolysis, bromination, amination, alkylation, oxidation, and rearrangement were carried out on epoxy-group of sesquiterpene lactones. 600 derivatives were synthesized and their bioscreening was carried out. Structure of modified compounds was determined on the basis of their physical and chemical constants, data of element analysis, IR-, UV-, mass-, NMR ^{1}H, ^{13}C- spectra, two-dimensional NMR spectroscopy ^{1}H-^{1}H, ^{13}C-^{1}H, HPLC and X-ray analysis.



As a result of the investigations, it was established that endemic Central Kazakhstan plant *Artemisia glabella* Kar. et Kir. is a source of sesquiterpene lactone arglabin, which has not been described before. The lyophilized dosage form for parenteral injection of preparation «Arglabin», possessing high antitumor, radio-sensitizing and immunomodulating activity was developed on the basis of chemically modified derivative arglabin.

Another innovative product is the original hypolipidemic preparation «Aterolid» of plant origin based on guaiane sesquiterpene lactone leucomisin isolated from *Artemisia leucodes* Schrenk.

Pre-clinic studies showed good prospects for development of new preparation «Sausalin» for treatment of parasitosis of hepatobiliary system based on the sum of sesquiterpene lactones from *Saussurea salsa* (Pall.) Spreng.

A new method for isolation of sesquiterpene lactones arglabin, leucomisin and achillin from raw material was developed. It includes preparative centrifugal partition and preparative high-performance liquid chromatography. The advantage of this method is high productivity, absence of toxic solvents, full automation and significant reduction of process duration.

Thus, results on isolation and determination of structure of sesquiterpenoids from plants of Kazakhstan, chemical modification directed to the synthesis of new physiologically active derivatives of these natural compounds, are the prerequisite for development of the effective preparations possessing wide spectrum of pharmacological action for medicine.