BULGARIAN ACADEMY OF SCIENCES
INSTITUTE OF ORGANIC CHEMISTRY WITH CENTRE OF PHYTOCHEMISTRY

Habilitation report for scientific contributions

of the publications of Assist. Prof. Dr. Tsvetelina Doncheva

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For application in the procedure for "Associate professor" in professional field 4.2. Chemical sciences, scientific discipline "Bioorganic chemistry, chemistry of natural and physiologically active compounds" for the needs of Laboratory "Chemistry of Natural Compounds", announced in the Bulgarian State Official Journal, no. 102/8.12.2023

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The author's report for the scientific contributions was made on **19** scientific publications (outside the PhD thesis). Publications [**B1-B6**] are equated to habilitation work (group of indicators B) are presented as an equal equivalent number of articles according to criteria "B", and the remaining **13** articles [**Г1 - Г13**] are presented according to criteria "Г", in accordance with the requirements of the Law on the Development of the Academic Staff of the Republic of Bulgaria and the rules for the terms and conditions for the acquisition of scientific degrees and academic positions at the Institute of Organic Chemistry with the Center for Phytochemistry (IOCCP, BAS). At the time of filing the documents, a total of **200** citations (**150** of them on Scopus/WoS) were noticed, the h-index is **7** (Scopus, without the auto-citations)

In general, the scientific work reflected in these publications is in the field of chemistry of natural compounds. The aim in the most of them is to clarify the alkaloid composition, the associated biological activity and the possibilities for application in modern medical practice of alkaloid biosynthesizing medicinal plants. Furthermore, the identified alkaloids as characteristic secondary metabolites in plants have been used to enrich the information related to the chemotaxonomy of species from different geographical areas. Only one of the publications investigated the triterpene composition of the plant species *Gentiana cruciata* [Г9], and in the publication [Г11] subject of the study was amphibians of the species *Triturus ivanbureschi*.

The scientific contributions presented in this competition are the result of interdisciplinary research, which can be summarized in the following directions:

1. Study of the composition, structure and biological activity of secondary metabolites isolated from unexplored, rare and/or endemic plant species and organisms.

2. Comparative analysis of the alkaloid composition of plants of the genus *Fumaria*, *Glaucium*, *Coridalis* and *Hypecoum* and derivation of chemotypical and taxonomical relationships.

3. Alkaloid composition of *in vitro* cultivated and *ex vitro* adapted endemic plants.

1. Study of the composition, structure and biological activity of secondary metabolites isolated from unexplored, rare and/or endemic plant species and organisms [B2, B3, Г2, Г5, Г6, Г8, Г9, Г10, Г11, Г12 and Г13].

Plants are an indispensable source of raw material and new biologically active compounds for the pharmaceutical industry. Many of them are the only source for obtaining important substances for medical practice that have no synthetic substitutes.

Alkaloids are an important class of N-heterocyclic natural products with diverse pharmacological and biological activities. A number of studies have shown that these compounds are responsible for the medicinal properties of some plants from families - Papaveraceace, Berberidaceace, Fumariaceae, Menispermaceae, Rutaceae, Ranunculacea, Amaryllidaceae, etc. To date, more than 27 000 alkaloids have been isolated and identified from plant sources, and some of them, such as the analgesic morphine, the antimalarial quinine or the bronchodilator ephedrine, are actively used as medicine.

My investigations on the composition and structure of natural substances are mainly related to the isolation and structural characterization of alkaloids from plant species belonging to the genera: *Leptopyrum*, *Hypecoum*, *Papaver*, *Pandanus* and *Thalictrum* [B2, B3, Г5, Г6, Г8 and Г10]. Thirty-four individual compounds are isolated using modern chromatographic techniques, of which 23 were discovered for the first time in the respective species, and 3 were new natural compounds identified by spectral methods (^{1}H and ^{13}C NMR, ^{1}H-^{1}H COSY, ^{1}H -^{13}C HSQC, ^{1}H -^{13}C HMBC, NOESY, UV, IR and MS). Publications **Г**2, **Г**12 and **Г**13 presented summarized data on the structure and biological activity of the alkaloids identified from the species of the genus *Hypecoum* and *Leptopyrum*, as well as a classification of tropane alkaloids from different plant sources. In one of the publications, the alkaloid composition of skin secretions of amphibians of the *Triturus ivanbureschi* species was investigated [**Г**9], and in a publication [**Г**11], the triterpene composition of the plant species *Gentiana cruciata* L. was investigated for the first time.

1.1. Study of the composition and structure of biologically active alkaloids isolated from species of the genera *Leptopyrum*, *Hypecoum*, *Papaver*, *Pandanus* and *Thalictrum* [B2, B3, Г5, Г6, Г8 and Г10].

Leptopyrum fumarioides L. is the only representative in the genus *Leptopyrum* belonging to the family Ranunculaceae. The species is distributed in the northeastern parts of Asia-Siberia, Mongolia, China and North Korea. The aerial parts of the plant are used in

Mongolian and Tibetan traditional medicine to treat fever, typhoid, high blood pressure, liver, cardiovascular and gastrointestinal diseases. The species of the Ranunculaceae family are known to produce a large amount of alkaloids with diverse biological activity. In the search for new biologically active compounds, the alkaloid composition of the species *L. fumarioides* was investigated for the first time [B2 and Г8]. Four isoquinoline-type alkaloids were isolated and characterized - **protopine, talifoline, leptopyrine and leptofumarin**. The last two alkaloids are new natural compounds. **The leptopyrine is the first example of a dimeric alkaloid containing a benzyltetrahydroisoquinoline moiety linked to 3,4-dihydroisoquinoline**. **Leptofumarin is a dimeric alkaloid composed of an aporphine and a benzylisoquinoline unit**. In the literature, only aporphine-benzylisoquinoline alkaloids possessing one ether bridge have been identified so far, while in leptofumarin the two parts of the molecule are **connected by two ether bridges, the connection being "head-to-head" and "tail-to-tail"**. **The two new compounds were found to have potential anti-inflammatory and immunomodulatory effects [B2]**[1].

The genus *Hypecoum* L., belonging to the Papaveraceae family, is widespread in the Mediterranean region, South-West and Central Asia. The plants from the genus are used in Tibetan medicine as an antipyretic, analgetic and anti-inflammatory remedy. These effects are due to the biologically and pharmacologically active isoquinoline alkaloids. In Flora of Bulgaria, 3 species of *Hypecoum* are known, among which *H. ponticum* has been determined as endemic for the Balkan Peninsula. **Investigating the crude alkaloid mixture of the species, 6 isoquinoline alkaloids were isolated and determined, four of which are quaternary (hippepontine, sanguinarine, N-methylcanadine, N-methylstylopine) and two tertiary (protopine, N-methylsecoglucine) [Г5]. N-Methylcanadine and N-methylstylopine are identified for the first time in the species *Hypecoum* and the alkaloid hipepontine is a new natural compound.** The tertiary and quaternary alkaloid mixtures as well as the isolated alkaloids were evaluated for their antibacterial and antifungal activity. The result revealed that **the crude alkaloid mixture containing quaternary isoquinoline alkaloids, hypepontin, N-methylcanadine and N-methylstylopine showed potent antifungal and antibacterial activity and can be used in future pharmacological tests [Г5]**[1]. The antibacterial activity of all individual compounds was lower compared to their activity in a mixture, which is probably due to synergistic interactions between the identified alkaloids.

[1] The tests on anti-inflammatory, immunomodulatory and antibacterial activity were carried out by colleagues at the Institute of Microbiology ‘Stefan Angelov’-BAS.

Papaver degenii (Pyrin poppy) is a perennial herbaceous plant of the Papaveraceae family. The Pirin poppy is a local endemic plant localized in the high mountain belt of the Pirin Mountains at an altitudes of 2,100 to 2,900 m. The species is protected by the Biological Diversity Act and is included in the Red Data Book of Bulgaria. Phytochemical investigation of the alkaloid composition in Bulgarian endemic species was made for the first time. **Fourteen alkaloids were isolated and determined. Two of them are simple tetrahydroisoquinolines (O-methylcorypaline and salsolidin), three are benzylisoquinolines (laudanozoline, codamine and tetrahydroscholamine), four are protopines (alocryptopine, protopine, muramine and cryptopine), three are isopavines (O-methylisopavine, amurensine and amurensine), one is benzophenantridine (chelidonine) and one is morphinane alkaloid (O-methylavinanthine)** [**B3**]. The alkaloid composition of the species is similar to those of the other species of genus *Papaver*. This fact, as well as that *Papaver degenii* is a glacial relic species whose speciation took place in exclusively severe environmental and habitat conditions, indicate a relative genetic stability of the representatives of this genus.

Pandanus plants are widespread in tropical and subtropical regions, such as Southeast Asia and North Australia. They have been used in traditional medicine for centuries in various ethnic societies in Vietnam, Taiwan, Thailand and Indonesia for the treatment of rheumatism, hyperglycemia and epilepsy, acting to strengthen the liver and inhibit tumour growth. Together with colleagues from the Vietnamishe Academy of Science and Technology, a **phytochemical study of the alkaloid composition of the species *Pandanus amaryllifolius* Roxb and *Pandanus tectorius* Parkinson was carried out and nine pandane alkaloids were isolated and determined** [**Г10**]. **The alkaloids pandamarilactonine B, N-acetylnorpandamarilactonine A and pandamarilactonine G were found for the first time in *P. tectorius*.** The total alkaloid mixtures and alkaloid fractions of the species were evaluated for their anti-inflammatory activity using *in vitro* experimental models. [**Г10**][1]. It has been established that the alkaloid mixtures and fractions of the species inhibit macrophage activation by reducing the proinflammatory cytokines TNF-α and IL-6. The total alkaloid mixtures are more effective than their sub fractions. These positive outcomes are probably due to synergistic interactions between the alkaloids. At the same time, ConA-induced IL-10 secretion by macrophages and lymphocytes has been enhanced in the presence of alkaloid mixture of *P. tectorius* and was not affected in the presence of alkaloid mixture of *P. amaryllifolius*. The alkaloid profile of *P. tectorius* is poorer than *P. amaryllifolius*, which

means that some of the molecules identified in *P. amaryllifolius* may have an antagonistic effect on alkaloids (pandamarilactonin B, N-acetylnorpandamarilactonin A and pandamarilactonin G) identified in *P. tectorius*.

The dimeric aporphine benzylisoquinoline alkaloid - talicarpine was isolated from the species *Thalictrum minus* ssp. *mayus* (family Ranunculaceae) [Г6]. According to literature data, this alkaloid is known to have antitumor, hypotensive and antimicrobial effects. With the cooperation of colleagues from the Faculty of Physics and the Faculty of Biology at SU "St. Kliment Ohridski" the prooxidant and antimicrobial effects of TiO_2 nanoparticles in combination with the isolated talicarpine were evaluated. It was established that **thalicarpine and its combination with TiO_2 nanoparticles exhibit pronounced antioxidant activities at pH 8.5 which are lost and transformed into well-presented prooxidant effects at pH 7.4. Thalicarpine, in combination with TiO2, showed even synergetic antibacterial effect.** The obtained results are relevant to the pharmaceutical industry, considering the use of nanoparticles as carriers of medicinal products in the diagnosis and treatment of various diseases.

1. **2. Summarized data on the structure and biological activity of alkaloids from various plant sources [Г2, Г12 and Г13]**

Summarized data on the structure and biological activity of alkaloids are presented in review papers published in scientific journals and books (by invitation), concerning:

1.2.1. Chemical composition and biological activity of the alkaloids identified in the genus *Hypecoum* and *Leptopyrum*. Particular attention was paid to the newly discovered natural compounds and the possibilities for their future application [Г2 and Г12].

1.2.2. Summarized data on the structures and classification of tropane alkaloids. According to the biosynthetic pathways, tropane alkaloids was classified into four groups, derivatives of tropinone, ecgoninone, 4-benzyltropanone and pyronotropanes [Г13].

1. **3. Studies on the composition of amphibian skin secretions of the species *Triturus ivanbureschi* [Г11].**

Amphibians are known to produce secretions containing alkaloids that protect them from the harmful effects of the environment. The alkaloids found in amphibian skin are represented in over 20 structural classes and have diverse biological activities. While the chemical composition of the skin secretions of some species, such as the Fire salamander (*Salamandra salamandra*) is relatively well studied, the data on newts of the genus *Triturus* are limited. In this regard, samples of skin secretions from 95 specimens of *Triturus*

ivanbureschi were collected by colleagues from IBEI-BAS and provided to us for study of their alkaloid content [Г11]. **The samples were analyzed by GC-MS analysis and found that they did not contain alkaloids, but only sterol compounds representing their biosynthetic precursors.** Given the small sample sizes and scant research in this area, the chemical composition of newt skin secretions is a topic that needs more research in the future.

1. 4. Studies on the triterpene composition of *Gentiana cruciata* L. [**Г9**].

Gentiana cruciata L. is a medicinal herb often used as tonics for improving digestion. It was established that the extract of the species mainly contains of secoiridoid, xanthone and flavonoid glucosides. Bitter constituents belonging to the class of secoiridoid glycosides are typical chemical metabolites for the genus *Gentiana*. Triterpenes, mainly in dammarane, ursane and oleanane types, which are also bioactive compounds with important pharmacological applications, have been also identified. To date, no detailed investigations have been reported on triterpenoid composition of the species *G. cruciata*. In connection with the implementation of the tasks under the National scientific program BioActivMed, the triterpene profile of two samples of *G. cruciata* (commercial and native) was investigated [**Г9**]. **Nine pentacyclic triterpenoids of the ursane and oleanane types were identified, with 3-formyl oleanolic acid being identified for the first time from a natural source, and 3-formyl ursolic acid and methyl ester of ursolic acid being new for the genus *Gentiana*.** It is important to note that formyl oleanolic and formyl ursolic acids are characterized for the first time as silylated derivatitives by GC-MS, which could be useful in respect to theirfurther rapid identification in plant extracts.

2. Comparative analysis of the alkaloid composition of plants of the genus *Fumaria, Glaucium, Coridalis* and *Hypecoum* and derivation of chemotypical and taxonomical relationships [**B1, B4, B5, B6, Г1 and Г4**]**.**

Alkaloids as characteristic secondary metabolites for species have been used to derive chemotaxonomic relationships, as well as to trace the influence of various environmental factors on plant development.

Studies of the alkaloid composition of plants of the genera *Glaucium*, *Fumaria*, *Coridalis*, *Alkanna* and *Hypecoum* led to the identification of 246 alkaloids, of which 86 were discovered for the first time in the respective species. Depending on the geographical location of the populations of the genera *Glaucium* and *Fumaria*, the differences in their alkaloid composition were traced and were made conclusions about their existing chemotypes in Bulgaria [B1, B4 and B6**]**. The results of the comparative analyzes of the alkaloid composition of the species of the genus *Coridalis*, *Alkanna* and *Hypecoum* was examined

from a chemotaxonomic point of view to clarify the taxonomic status of some endemic species, as *C. slivenesis*, *A. primuliflora*, *A. stribrnyi*, *A. graeca* and *H. ponticum* [B5, Г1 and Г4].

Glaucium flavum Crantz. (Yellow hornpoppy) is a herbaceous plant with gray-green leaves living in coastal sands, rocky places on highly eroded soils, up to 500 m altitude. The species is an important medicinal plant containing isoquinoline alkaloids. Glaucine is the most common alkaloid in *G.flavum*, and because of its bronchodilator activity is used as anticough agent in Bulgaria and in other East European countries. Different studies have shown that the composition of the alkaloids identified in the species is highly variable depending on the plant's distribution areas. However, such data are lacking for *Glaucium* species distributed in Bulgaria, although they are particularly needed, considering their use as a source of glaucine.

Nine alkaloids were identified in *G. flavum* collected from four different natural populations in Bulgaria [B6]. **In accordance with the particular content and composition of alkaloids in the localities of the species three alkaloid chemotypes were suggested. The first one contains aporphines and protopines with a main alkaloid glaucine. The second chemotype contains again aporphine and protopine alkaloids but the main alkaloid is isocorydine and the third chemotype contains besides these two types of alkaloids and the morphinane alkaloid salutaridine.** It is noteworthy that two of the populations have a similar alkaloid profile and fall into one chemotype group, although one is located in the coastal zone and the other is located inside the country. We assume that in this case the development of chemotype does not depend only on the geographical location and environmental factors but the regulation of the different alkaloid biosynthetic pathways is genetically determined.

In collaboration with colleagues from the University of M'Silla, Algeria, a comparative analysis of the alkaloid composition of the species ***Glaucium corniculatum*** **of Bulgarian and Algerian origin** was carried out, and a total of 17 alkaloids of protopine, aporphine, benzophenanthridine, protoberberine, benzylisoquinoline and spirobenzylisoquinoline type were identified [B4]. **Comparative analysis of alkaloid profiles showed that plants of Bulgarian origin produce benzophenathridine alkaloids (chelerythrine and sanguinarine), similar to the plants growing in other regions with a continental climate.** In the samples from Algeria, where the climate is tropical, this type of alkaloids was not detected. This suggests that the biosynthesis of benzophenathridine alkaloids in *G. corniculatum* depends of the geographical region the plant is growing and could be used as chemotaxonomic markers to help identify the source of the plants.

Fumaria plants are distributed all over the world, and most widely in Mediterranean region The plants are used in traditional medicine for treating of gastrointestinal disorders, hepatobiliary dysfunction, rheumatism, fever, some skin diseases, syphilis and leprosy. Their biological activity is associated with the presence of isoquinoline alkaloids. In publication [B1] the alkaloid pattern of four *Fumaria* species (*F. kralikii*, *F. rostellata*, *F. schleicherii* and *F. thuretii*) growing in Bulgaria were investigated by GC-MS and twenty isoquinoline alkaloids were determined. Many of the alkaloids are described for the first time for the corresponding species. The main alkaloid in most of the analyzed samples is protopine in amount of 23% to 43%. According to literature data, the species of the genus *Fumaria* belongs to three chemotypes formed depending on the content of the main alkaloids. In our investigation plants of one and the same species as *F. kralikii* grown under various environmental conditions (habitats, altitudes) biosynthesized various main alkaloids. Considering these data it seems that the types of isoquinoline alkaloids could be more useful in respect to the chemotypical conclusions than the main alkaloids. According to that we suggest the formation of **two new chemotypical groups**. **To group A belong species *F. kralikii, F. rostellata* and *F. thuretii* containing more than 50% spirobenzylisoquinoline alkaloids of the crude alkaloid mixtures. To group B belong species *F. rostellata* and *F. schleicherii* containing more than 40% protopine alkaloids and relatively high percentage phthaldeisoquinoline alkaloids (11-19%).**

Genus *Corydalis* is represented by 300 species in the poppy family (Papaveraceae). In Bulgarian flora it is represented by only four of them: *C. bulbosa*, *C. marschalliana*, *C. slivenensis* and *C. solida*. The taxonomic status of the bulgarien endemic species *C. slivenesis* is not clearly determined and some authors consider that *C. slivenesis* is a variety or subspecies of *C. solida*. **As a result of the studies of the alkaloid composition of *C. slivenesis* and *C. solida*, a total of 21 isoquinoline-type alkaloids were identified (19 alkaloids from *C. slivenensis* and 8 alkaloids from *C. solida*) [B5]. *C. slivenesis* plants were found to have a more complex alkaloidal profile due to the presence of a large number of aporphine and protoberberine alkaloids.** Furthermore the benzylisoquinoline alkaloids papaverine and N-methyllaurothetanine were identified only in *C. solida*, and the benzophenanthridine alkaloid sanguinarine in *C. slivenesis*. The obtained results are important from a chemotaxonomic point of view and would contribute to clarifying the taxonomic status of the species in the genus.

The genus *Alkanna* belongs to the family Boraginaceae, subfamily Boraginoidae. *Alkanna* species are distributed in the southern part of the Balkan Peninsula, in the Mediterranean region and in the subtropical regions of the world and the plants are represented by a large number of local and regional endemics. Six *Alkanna* species are found in the Bulgarian flora and five of them are either Balkan or Bulgarian endemics. *Alkanna primuliflora* Griseb., *A. stribrnyi* Velen. and *A. graeca* Boiss. & Spruner are Balkan endemics, while *A. stojanovii* Kožuharov and *A. jordanovii* Kožuharov are two Bulgarian endemics. In collaboration with colleagues from the Agricultural University in Plovdiv and IBER-BAS, were studied the reproductive capacity and the alkaloid composition of the Balkan endemics *A. primuliflora*, *A. stribrnyi* and *A. graeca* of Bulgarian origin, which are with limited distribution and are included in the European Ecological Network NATURA 2000 [**Г1**]. Eight pyrrolizidine alkaloids were identified by GC-MS analysis of the crude alkaloid mixtures: **7-angeloylretronesine, 9-angeloylretronesine, 7-tigloylretronesine, 9-tigloylretronesine, triangularine, triangularine, dihydroxytriangularine, and dihydroxytriangularine. The main alkaloid in all investigated *Alkanna* species is triangularine. All three species were found to have similar alkaloid profiles, with differences in alkaloid content mainly related to the absence or presence of some minor components.** In addition, minimal differences were observed in the alkaloid profiles of plants from different natural populations and at different developmental stages, proving that environment and ontogeny have little influence on alkaloid biosynthesis in the genus. The results of the study are important for the knowledge of endemic species with limited distribution in Bulgaria and will facilitate opportunities for their conservation.

In a comparative study of the alkaloid composition of some *Hypecoum* species (*H. procumbens* L., *H. ponticum* Velen and *H. imberbe* Sm.), ten isoquinoline alkaloids were identified: tertiary - protopine, N-methylsecoglucine, stylopine, dihydroprotopine, N-methylcoclaurine and dihydrochelirubin and quaternary - sanguinarine, N-methylstylopine, N-methylcanadine, hipepontine [**Г4**]. **It was established that *H. ponticum*, which some authors consider to be a synonym of *H. procumbens*, is well separated from the other species - *H. procumbens* and *H. imberbe* due to the presence of a large number of quaternary isoquinoline alkaloids.**

3. Alkaloid composition of in vitro cultivated and ex vitro adapted endemic plants [Г3 and Г7].

The endemic *Papaver degenii* (Urum. & Jav.) Kuzmanov occurs in limited places in the alpine zone of the Pirin Mountains. Due to difficult reproduction and the short growing season preventing the ripening of the seeds, the species has a limited distribution. This necessitates measures to preserve it through some *in situ* and *ex situ* conservations. In collaboration with colleagues from IBER-BAS, *in vitro* cultures were grown by somatic embryogenesis with the addition of different elicitors, as well as *in vitro* cultures from seeds that were *ex vitro* adapted and acclimatized in natural conditions [Г3 and Г7]. **A significant increase in alkaloid content (5 to 6 times) was found in the *in vitro* cultivated and *ex vitro* adapted plants (aerial parts and roots) compared to the wild-growing plants.** This difference may be related to the fact that the cultivating plants in laboratory conditions, far from those in their natural habitats, can cause stress and lead to increased levels of alkaloids produced.

Four isoquinoline alkaloids, amurensine, O-methylthalisopavine, allocryptopine and protopine, were isolated from the regenerated plants. **The main alkaloid in all analyzed samples was the alkaloid amurensine, representing 63.4% of the crude alkaloid mixture in the *in vitro* cultures and 88.1% in the aerial parts of the *ex vitro* adapted plants [Г3]**. It was found that the addition of elicitors (methyljasmonic acid) in the media during the induced indirect somatic embryogenesis had a positive effect on the alkaloid content, but did not cause significant changes in the alkaloid composition [Г7].

The obtained results are a good example of the successful application of biotechnological methods for conservation of rare and endangered species. The *ex vitro* adapted *P. degenii* plants could be cultivated as a source of biologically active compounds, such as the alkaloid amurensine, with application in the treatment of neurological diseases, such as Parkinson's and Alzheimer's.

Guidelines for future research:

Over the next three years, I intend to:

- Phytochemical studies of medicinal, endemic and unexplored plants with the aim of discovering new biologically active compounds (alkaloids) and searching for possible structure-biological activity relationships;

- Studies related to tracking the influence of various environmental factors on the alkaloid content in plants;

- Development of methods for obtaining biologically active substances from medicinal plants using modern extraction techniques;

- Continuation of collaborations, both with the Bulgarian scientific community (IBER-BAS, IM'Stefan Angelov'-BAS, Agricultural University, etc.), and with the international one with Mongolian Academy of Sciences, Vietnam Academy of Science and Technology, etc.

- Searching for opportunities to apply for national and international programs for funding scientific research.

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