NATURAL INDANONES

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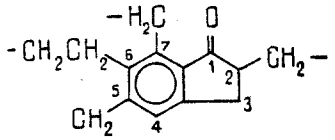
UDC 547.913.5/547.665

A review is given of the chemical structures, biosynthetic pathways, and biological properties of the pterosins — natural *l*-indanone derivatives.

In 1970, Hikino [1] isolated from the fern *Pteridium aquilinum* Khun var. *laitiusculum* a glycoside the aglycone of which was a derivative *l*-indanone. During the ten ysars that have passed since then, more than 60 substances of this type have been isolated from various species of ferns. A *l*-indanone derivative has also been detected in *Equisetum arvense* L. — a representative of the family Equisetaceae [2]. It may be thought that these substances are distributed in the vegetable kingdom considerably more widely than has so far become known.

The aim of the present review is to direct the attention of research workers to the new class of natural compounds and to systematize information on their structure and properties with the aim of facilitating identification and structural studies in whis field of chemistry of plant substances.

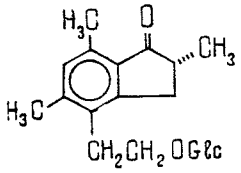
As applied to natural indanones, the term pterosins has gained wide acceptance. The chemical structure is based on the system I. Material on the chemical structure of the pterosins can conveniently be subdivided into four sections depending on the nature and position of the substituents in the basic nucleus of the molecule.



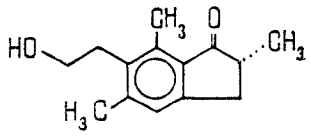
I

2,5,6,7-SUBSTITUTED INDANONES

The first representative of the indanones detected contained no substituents in positions 3 and 4. It was isolated [1] from the fern *Pteridium aquilinum* and was called pteroside B. Initially, the structure of 4-(2'-hydroxyethyl)-2(R),5,7-trimethylindanone 2'-β-glucopyranoside (II) was proposed for it. Later the corresponding aglycone — the pterosin B — was also found in the native state.



II



III

The structure of the five-membered ring followed from the presence of a carbonyl band at 1705 cm^{-1} in the IR spectrum, and the absorption of an acetophenone chromophore with maxima at 217, 260, and 304 nm. In the PMR spectrum, the methyl group at C-2 is represented by a doublet at 1.25 ppm (J = 8 Hz). The reduction of the carbonyl group with sodium tetrahydroborate led to the appearance of a new proton with a signal split into a doublet. It followed from this that the methyl and carbonyl groups were located on neighboring carbon atoms. This was also indicated by the capacity for the proton at C-2 for exchanging with deuterium

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Translated from Khimiya Prirodnykh Soedinenii, No. 1, pp. 3-14, January, 1982. Original article submitted March 2, 1981.

0009-3130/82/1801-0001$07.50

TABLE 1. 2,5,6,7-Substituted 1-Indanones

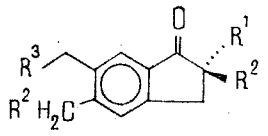
Name, properties	R	R^1	R^2	R^3	Source of isolation	Literature
						
III. Pterosin B, 107-109°C, $[\alpha]_D$ −13.5° (chloroform)	H	CH_3	H	CH_2OH	Pteridium aquilinum Kuhn var. latiusculum, Pteris setulosocostulata Hayata, Histopteris incisa (Thunb.) J. Sm., Pteris inaqualis Baker var. aequata	3, 4, 6, 7, 12, 14
IV. Pteroside B, mp 119-121° C	H	CH_3	H	CH_2OGlc	Pteridium aquilinum Kuhn var. latiusculum	1, 6, 7
V. (±)-Pterosin O,* mp 45-46°C	H	CH_3	H	CH_2OCH_3	Pteridium aquilinum Kuhn var. latiusculum	8
VI. (−)-Pterosin O,* oil, $[\alpha]_D$ −14.1° (chloroform)	H	CH_3	H	CH_2OCH_3	Pteris inaequalis Baker var. aequata	14
VII. Pterosin F, mp 66-67°C, $[\alpha]_D$ −9.2° (benzene)	H	H_3C	H	CH_2Cl	Pteridium aquilinum Kuhn var. latiusculum, Histopteris incisa (Thunb.) J. Sm.	3, 6, 7, 12
VIII. Isocrotonylpterosin B, oil	H	CH_3	H	$CH_2CO_2CH{=}CHCH_3$	Pteridium aquilinum Kuhn var. latiusculum	6, 9
IX. Palmitoylpterosin B, mp 50-51°C, $[\alpha]_D$ −3.3° (cyclohexane)	H	CH_3	H	$CH_2CO_2C_{15}H_{31}$	Pteridium aquilinum Kuhn var. latiusculum	6, 9
X. Benzoylpterosin B, mp 115-116°C, $[\alpha]_D$ +86.1° (chloroform)	H	CH_3	H	$CH_2O{-}CO_2C_6H_5$	Pteridium aquilinum Kuhn var. latiusculum	9
XI. Pterosin E, mp 160-162°C	H	CH_3	H	CO_2H	Pteridium aquilinum Kuhn var. latiusculum Histopteris incisa (Thunb.) J. Sm.	3, 6, 7
XII. Pterosin P,* mp 115-117°C, $[\alpha]_D$ +4.6° (methanol)	H	CH_3	OH	CH_2OH	Pteridium aquilinum Kuhn var. latiusculum	8

TABLE 1 (continued)

Name, properties	R	R^1	R^2	R^3	Source of isolation	Literature
XIII. Pteroside P,*, mp 191-193° C	H	CH_3	OH	CH_2OGlc	Pteridium aquilinum Kuhn var. latiusculum,	8
XIV. Pteroside (hypolein B)	CH_3	CH_3	H	CH_2OH	Pteridium aquilinum Kuhn var. latiusculum, Pityrogramma calomelanos	3, 7, 15
XV. Pteroside Z	CH_3	CH_3	H	CH_2OGlc	Hypolepis punctata Mett., Pteridium aquilinum Kuhn var. latiusculum	7, 10
XVI. Pterosin J (hypolein C), mp 56-57° C	CH_3	CH_3	H	CH_2OCH_3	Hypolepis punctata Mett.	7
XVII. Pterosin H (hypolein A)	CH_3	CH_3	H	CH_2Cl	Hypolepis punctata Mett.	7
XVIII. Pterosin A, mp 125-127°C, 129-130°C, $[\alpha]_D$ −21.8° (chloroform)	CH_3	CH_2OH	H	CH_2OH	Pteridium aquilinum Kuhn var. latiusculum	3, 6, 7
XIX. Pteroside A	CH_3	CH_2OH	H	CH_2CGlc	Pteridium aquilinum Kuhn var. latiusculum	7, 11
XX. Pterosin K, mp 85-87 °C, $[\alpha]_D$ −20.0° C (chloroform)	CH_3	CH_2OH	H	CH_2Cl	Pteridium aquilinum Kuhn var. latiusculum	6, 9
XXI. Palmitoylpterosin A, mp 50-51°C	CH_3	CH_2OH	H	$CH_2CO_2C_{15}H_{31}$	Pteridium aquilinum Kuhn var. latiusculum	6, 9
XXII. Pterosin N,* mp 165-167 °C, $[\alpha]_D$ −18.8°C (methanol)	OH	H	H	CH_2OH	Pteridium aquilinum Kuhn var. latiusculum, Pteris setuloso-costulata Hayata	8, 12
XXIII. Pterosin G	H	CH_2OH	H	CH_2OH	Pteridium aquilinum Kuhn var. latiusculum,	6

*Absolute configuration not established.

TABLE 2. 3-Hydroxyindanones

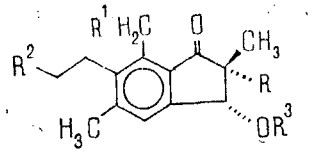
Name, properties	R	R^1	R^2	R^3	Source of isolation	Literature
						
XXIV. Pterosin C, mp 158-160°, 168-170°, $[\alpha]_D$ +60° (methanol)	H	H	OH	H	Pteridium aquilinum Kuhn var. latiusculum, Pteris wallichiana, Histopteris incisa (Thunb.) J. Sm. Pteris inaqualis Baker var. aequata	6, 7, 11, 12, 13, 17
XXV. Pteroside C	H	H	OGlc	H	Pteridium aquilinum Kuhn var. latiusculum	11, 17
XXVI. Pterosin D, mp 189-190°C, 193-194°C, $[\alpha]_D$ +4.8° (ethanol)	CH_3	H	OH	H	Pteridium aquilinum Kuhn var. latiusculum	3, 6, 7, 10
XXVII. Pteroside D	CH_3	H	OGlc	H	Pteridium aquilinum Kuhn var. latiusculum, Coniogramma japonica (Thunb.) Diels.	7, 10, 12
XXVIII. Wallichoside, mp 216-218°C, $[\alpha]_D$ +22.2° (methanol)	H	H	OH	Glc	Pteris wallichiana	18
XXIX. Pterosin J, * mp 136-137°C, $[\alpha]_D$ + 83.5° (chloroform)	H	H	Cl	H	Pteridium aquilinum Kuhn var. latiusculum, Histopteris incisa (Thunb.) J. Sm.	6, 9, 12
XXX. Acetylpterosin C, mp 115-116°C, $[\alpha]_D$ +86.1° (chloroform)	H	H	CO_2CH_3	H	Pteridium aquilinum Kuhn var. latiusculum	6. 9
XXXI. Palmitoylpterosin C, mp 95-97°C, $[\alpha]_D$ +52.8° (chloroform)	H	H	$CO_2C_{15}H_{31}$	H	Pteridium aquilinum Kuhn var. latiusculum	6, 9
XXXII. Phenylacetylpterosin C, mp 67-68°C, $[\alpha]_D$ +38.6° (methanol)	H	H	$CO_2CH_2C_6H_5$	H	Pteridium aquilinum Kuhn var. latiusculum	8

TABLE 2 (continued)

Name, properties	R	R¹	R²	R³	Source of isolation	Literature
XXXIII. Pterosin C 3-O-β-D-glucopyranoside, mp 189-190°C, $[\alpha]_D$ +29.4° (methanol)	H	H	OH	Glc	Pteris wallichiana	17
XXXIV. Pterosin C 3-O-β-L-arabinoside, mp 220-222°C, $[\alpha]_D$ +26° (methanol)	H	H	OH	Ara	Pteris oshimensis Hieron.	20
XXXV. Pterosin W, mp 134-136°C, $[\alpha]_D$ +51.1°C (methanol)	CH_3	OH	OH	H	Pteris fauriei Hieron.	13
XXXVI. Pteroside W, mp 134-136°C, $[\alpha]_D$ +3.96° (methanol)	CH_3	OH	OGlc	H	Pteris fauriei Hieron.	13
XXXVII. Pterosin L,‡ mp 139-141°C, $[\alpha]_D$ +23.7° (methanol)	CH_2OH	H	OH	H	Pteridium aquilinum Kuhn var. latiusculum, Pteris inapualis Baker var. aequata	6, 9
XXXVIII Onitisin 2'-O-β-D-glucoside, $[\alpha]_D$ −16.94° (methanol)	CH_2OH	H	OGlc	H	Pteris inaqualis Baker var. aequata	13
XXXIX. Pterosin S,* mp 118-119°C, $[\alpha]_D$ +71.1° (methanol)	H	OH	OH	H	Pteris kiuschauensis Hieron.	19
XL. Pteroside S	H	OH	OGlc	H	Pteris fauriei Hieron.	13
XLII. Pterosin T,* $[\alpha]_D$ + 91.0° (methanol)	H	H	OH	OH	Pteris kiuschauensis Hieron.	19
XLI. Pteroside T, mp 118-121°C, $[\alpha]_D$ +33° (methanol)	H	H	OGlc	OH	Pteris inaqualis Baker var. aequata	13

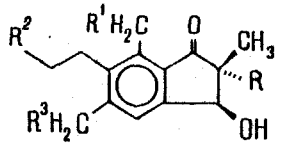
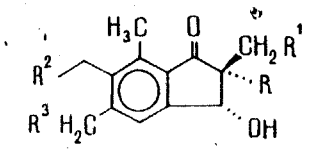
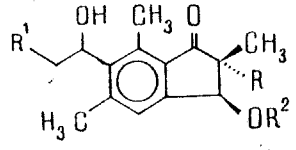


TABLE 2 (continued)

Name, properties	R	R¹	R²	R³	Source of isolation	Literature
XLIII. Pterosin U,* mp 120-130°C, $[\alpha]_D$ +73.1° (methanol)	H	OH	OH	OH	Pteris kiuschiuensis Hieron.	19
XLIV. Pteroside U,* mp 149-151°C, $[\alpha]_D$ +2.3° (methanol)	H	OH	OGlc	OH	Pteris fauriei Hieron.	13
						
XLV. Setulosopteroside, $[\alpha]_D$ +30.6° (methanol)	OH	H	CH_2OGlc	OH	Pteris setuloso-costulata Hayata	12
XLVI. Setulosopterosin, $[\alpha]_D$ +64.0°	OH	H	CH_2OH	OH	Pteris setuloso-costulata Hayata	12
XLVII. Pterosin Y, $[\alpha]_D$ +62.2° (methanol)	H	OH	CH_2OH	OH	Coniogramme japonica	12
XLVIII. Histopterosin A,‡ mp 145-151°C, $[\alpha]_D$ +1.7° (methanol)	H	H	CO_2H	H	Histopteris incisa (Thunb.) J. Sm.	12
XLIX. Pterosin X, $[\alpha]_D$ +31.1° (methanol)	CH_3	H	CH_2OH	OH	Pteris fauriei Hieron., Coniogramme japonica	12, 13
L. Pteroside X, $[\alpha]_D$ −10.3° (methanol)	CH_3	H	CH_2OGlc	OH	Pteris fauriei Hieron., Coniogramme japonica	12, 13
						
LI. Pterosin Q,* $[\alpha]_D$ +90.0° (methanol)	H	OH	H	—	Pteris kiuschiuensis Hieron., Pteris oshimensis Hieron., Histopteris incisa (Thunb.) J. Sm.	16, 19
LII. Pteroside Q, $[\alpha]_D$ +24.0° (methanol)	H	OH	Glc	—	Pteris oshimensis Hieron., Histopteris incisa (Thunb.) J. Sm.	16
LIII. 3-O-β-L-arabinopyranoside, $[\alpha]_D$ +25° (methanol)	H	OH	Ara	—	Pteris oshimensis Hieron.	20

*Mixture of 2(S), 3(S) and 2(S), 3(R) epimers.

†2(R), 3(R) epimer, see [8]. [To which compound this footnote refers to is not indicated in Russian original — Publisher.]

‡Configuration not established.

when the substance was heated with deuterotrifluoroacetic acid. The position of the single aromatic proton in the formula (II) was deduced on the basis of the fact that irradiation with the appropriate frequency in a double magnetic resonance experiment revealed a response in the signals of both aromatic methyl groups. However, it was later [3, 4] found that the nuclear Overhauser effect on the frequency of the aromatic proton was reflected in the signal of only one methyl group, which excluded the localization of a hydrogen atom between two methyl groups, as in formula (II). The introduction of a second ketonic function in position 3 greatly affected the chemical shift of the aromatic proton, and it could be assumed that it was present at C-4. The definitive choice between the possible isomeric structures was made on the basis of the fact that nitric acid oxidation gave 2,6-dimethyl-3-nitrobenzene-1,4,5-tricarboxylic acid. Thus, pterosin B is represented by structure (III). The structure of hypolepin B (pterosin Z, [14]) which is connected by chemical transformations with (III) has been confirmed by total synthesis [5].

Natural analogs of pterosin B differ from (III) by the presence of additional substituents in position 2, by various functional groups in the ethyl chain, and by the degree of oxidation of the methyl groups. The spectral characteristics given above for pterosin B are common for the whole group and permit it to be readily recognized. The structures and some properties of the 2,5,6,7-substituted indanones are given in Table 1. Attention must be drawn to the presence of a chlorine atom in each of compounds (VII), (XVII), and (XX), which is not infrequently found among metabolites of higher plants.

Many of the compounds given in Table 1 contain an asymmetric carbon atom. The absolute configuration of peterosin B was determined by chemical conversion into 2(R)-methylsuccinic acid [6]. From these results with the aid of physicochemical methods it has been possible to deduce the absolute configurations of many other pterosins.

3-HYDROXYINDANONES

Many pterosins contain a hydroxy group in position 3. Their vibrational and electronic spectra are similar to those for compounds of the first group. An assignment to the class of 3-hydroxyindanones is most reliably made from the results of PMR spectroscopy. The proton at C-3 gives a signal in the 4.7-5.1 ppm region which is displaced upfield after reduction of the ketone group. In a study of the nuclear Overhauser effect, an interaction of this proton with the proton at C-4 is detected.

Brief information on the 3-hydroxyindanones is given in Table 2. Some of these compounds contain two asymmetric centers. Their relative configurations are determined by an analysis of the spin–spin couplings in the PMR spectra. A study of the link between the protons at C-2 and C-3 under the conditions of the nuclear Overhauser effect in comparison with the CD and ORD curves, and also with the results of chemical transformations has permitted the absolute configurations of the majority of the epimeric 3-hydroxyindanones to be determined. In different compounds the two asymmetic centers may have either the R or the S configuration. Pterosins Q, S, T, J, and L are present in plants in the form of mixtures of epimers.

PHENOLIC PTEROSINS

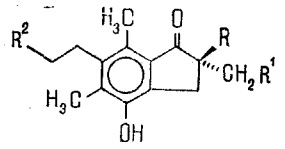
Some natural indanones (Table 3) contain a phenolic hydroxy group at C-4. Compounds of this type are readily recognized from their electronic spectra. The absorption maxima at wavelengths of 233, 277 and 322 nm observed for pterosin M (LIV) are also characteristic for other representatives of this group.

The aromatic nuclei of the phenolic pterosins do not contain protons, which complicates the determination of the structure by the methods of PMR spectroscopy. The structure of onitin (LVI) has been established on the basis of its similarity with other pterosins. The absence of a hypsochromic shift in the UV spectrum due to chelation on the addition of $AlCl_3$ excluded the alternative form with the carbonyl at C-3. In order to establish the structure of (LIV) the aglycone of this glycoside was oxidized to 2-hydroxy-3,5-dimethylbenzene-1,2,4-tricarboxylic acid [21]. The structure of onitin has also been confirmed by x-ray structural analysis [2] and by synthesis [23].

COMPOUNDS RELATED TO THE PTEROSINS

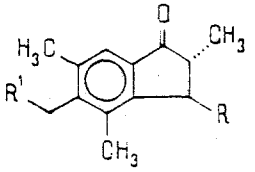
A glycoside which has been called isopteroside C has been isolated from the fern *Pteris wallichiana* Agardth. [24]. The structure (LXI) for this compound and (LXII) for the corre-

TABLE 3. Phenolic 1-Indanones

Name, properties	R	R^1	R^2	Source of isolation	Literature
					
LIV. Pterosin M, mp 187°	H	H	OH	Onychium japonicum	21
LV. Pteroside M, mp 192°C, $[\alpha]_D$ +129° (acetone–water)	H	H	OGlc	Onychium japonicum	21
LVI. Onitin, mp 210-212, 214°C	CH_3	H	OH	Onychium auratum, Equisetum arvense L.	2, 22
LVII. Onitin 2'-O-β-D-glucoside, mp 178–180°, $[\alpha]_D$ –17.7° (methanol)	CH_3	H	OGlc	Cibotium barometz (L.) J. Sm.	12
LVIII. Onitin 2'-O-β-D-alloside, $[\alpha]_D$ –24.8° (methanol)	CH_3	H	O-allo-side	Cibotium barometz (L.) J. Sm.	22
LIX. Onitisin,* mp 184°C	CH_3	OH	OH	Onychium auratum	22
LX. Pterosin R	CH_3	H	Cl	Cibotium barometz (L.), J. Sm.	12

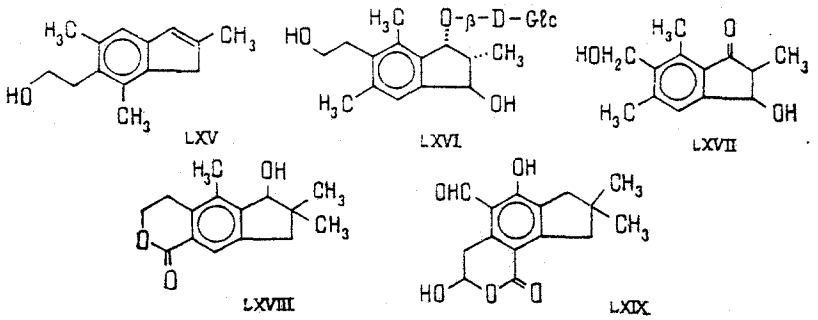
*Absolute configuration not determined.

sponding aglycone were established by comparing the PMR spectra of derivatives with the corresponding derivatives of pterosin B (III). In the isopterosin series the signal of the aromatic proton at C-7 lay in considerably weaker fields than in the pterosins. This was explained by the anisotropic influence of the carbonyl group. In actual fact, in derivatives having no carbonyl groups, such as (LXV) and (LXVI), the chemical shifts of the aromatic protons in the two nuclei were in the same region.



LXII. R = O-β-D-Glc $R^1 = CH_2OH$
LXII. R = OH; $R^1 = CH_2OH$
LXIII. R = H; $R^1 = CH_2OH$
LXIV. R = OH; $R^1 = CO_2H$

Isopterosins A, B, and C (LXII-LXIV) have been isolated from the fern *Histopteris incisa* (Thunb.) J. Sm. [12].

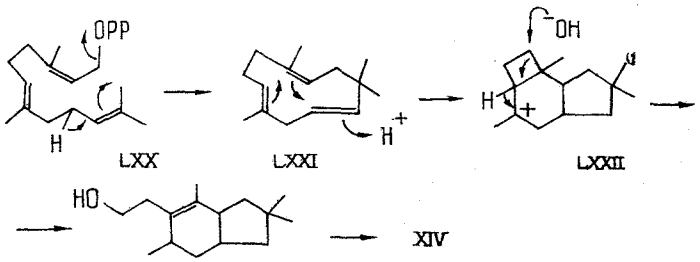


LXV LXVI LXVII LXVIII LXIX

Several natural compounds are known which are the products of metabolic oxidative or reductive transformations of the pterosins. For example, the glucoside pterosol C (LXVI) has been isolated from *Pteris wallichiana* and norpterosin C (LXVII) from *Pteridium semipinnata* [25]. Calomelanolactone (LXIII), which has been found in the fern *Pitirogramma calomelanos* together with pterosin Z (XIV), is, as it is not difficult to see, formed by the oxidation of the methyl group of the latter [15]. Lactones similar in structure, such as illudalic acid (LXIX) are present in the products of the metabolism of the mold *Clytocybe illudens* [26].

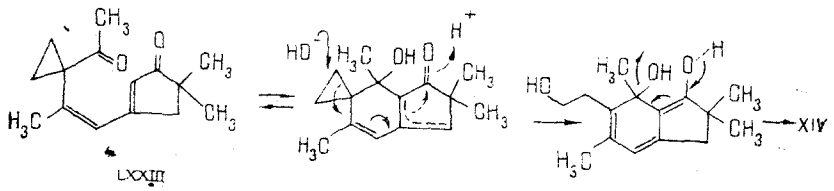
BIOSYNTHESIS

The natural indanones belong to the class of sesquiterpene compounds. It has been shown that biosynthetically they arise from mevalonate via farnesyl pyrophosphate (LXX). There are two hypotheses on the concrete pathways leading from (LXX) to the pterosins. According to the first [27], the direct precursor of the pterosin skeleton is formed from the humulene (LXXI) through the cation (LXXII). Subsequent glycosylation, oxidation, and aromatization lead to pterosin Z (XV).



LXX LXXI LXXII XIV

According to the second hypothesis, the precursor of the pterosins is the seco-illudoid hypacrone (LXXIII), which has been found in the fern *Hypolepis punctata* Mett. [28]. Hypacrone is readily converted into pterosin Z (XIV) on treatment with sulfuric acid. It is assumed that the same transformation takes place in the biosynthesis of the pterosins [28-30].



The biogenetic pathways leading to the pterosins are common, in their main stages, with the pathways of the biosynthesis of the illudins, the coriolins, and the marasmic and hirsutic, and some other, terpenoid structures that are characteristic for low forms of life [31]. So far as concerns higher plants, here, as well, this type of biosynthesis has so far been detected only in the phylogenetically earliest representatives of the vegetable kingdom — ferns and horsetails.

BIOLOGICAL PROPERTIES

Some species of ferns on being eaten by animals cause toxicoses and the induction of malignant neoplasms [32, 33]. It has been shown [34, 35] that the toxic and carcinogenic factors of ferns also exhibit mutagenic properties and the nature of their action resembles radiation damage. Attempts to identify these biologically active factors chemically led to the isolation of natural indanone derivatives. However, an investigation of pure pterosin B and pteroside B did not reveal carcinogenic properties in them, although leaves and extracts from *Pteridium aquilinum* Khun var. *latiusculum* were strong tumor-inducing agents [32, 36]. At the same time, it has been found that some of the pterosins, particularly pterosins Z and E, are moderately toxic for HeLa cells. Individual indanones that were studied [36] exhibited none of the other toxic properties characteristic for the ferns from which they were isolated, either.

Antimicrobial properties have been detected in pterosins B and O [14]. However, the bacteriostatic action of crude extracts of *Pteris inaequalis* Bak. is stronger than that of the pure substances.

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