Lichen Depsidones as Potential Novel Pharmacologically Active Compounds

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Abstract: For centuries, lichens have been used in traditional medicine and their use persists to the present day in some parts of the world. Depsidones are one of the classes of secondary metabolites which are mostly produced in lichens. Lichen depsidones have been reported to possess many biological activities, such as antitumor and antimicrobial activities. In order to point out the pharmacological potential of this class of compounds, the present article reviews the structure and biological properties of the known lichen depsidones**.** The biosynthesis of depsidones and the relationship between their chemical structure and biological activity is also discussed.

Keywords: Biological activity, biosynthesis, depsidones, lichen, structure-activity relationship.

1. INTRODUCTION

Natural products are an important source and inspiration for new drugs. Among them, lichen metabolites play an important role because they are unique with respect to those of higher plants and exhibit manifold bioactivities including antimicrobial, antiviral, antiinflammatory, analgesic, antipyretic, antiproliferative and cytotoxic effects [1]. Lichens, as probably the earliest colonizers of terrestrial habitats on the earth [2], have been used in traditional medicines for centuries and still hold considerable interest as alternative treatments in various parts of the world [3-5]. Despite that, their therapeutic potential remains pharmaceutically unexploited.

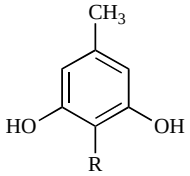
From a chemical point of view, the following compound classes were identified in lichens: mononuclear phenolic compounds (e.g. orcinol and *β*-orcinol derivatives), aliphatic acids (e.g. protolichesterinic acid), hydroxybenzoic acid derivatives (e.g. methylparaben), dibenzofurans (e.g. usnic acid), depsides (e.g. barbatic acid), depsones (e.g. picrol ichenic acid), quinones (e.g. emodin), pulvinic acid derivatives (e.g. vulpinic acid) and epidithiopiperazinediones (e.g. scabrosin) [6]. Over 1000 lichen metabolites have been identified [7].

Several reviews about lichen constituents and their biological activities have been published [1, 3, 6, 8-15]. Due to difficulties involved in isolating pure constituents from crude extracts of lichens, which are complex mixtures of various compound classes, most of the manuscripts reported only the biological activity of crude extracts [16-24].

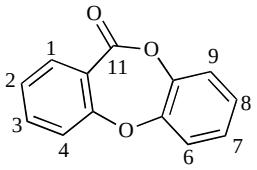
Depsidones are one of the classes of secondary metabolites which are mostly produced in lichens. They have been reported to possess many biological activities, such as antitumor and antimicrobial activities. The aim of this mini review is to summarize the data on biologically active lichen depsidones. It will first focus on the chemical structure and biosynthesis of lichen depsidones. Due to its importance, a detailed summary of biological activities of the lichen depsidones will be given. Finally, the relationship between the chemical structure and biological activity as well as future perspectives will be discussed. To the best of our knowledge, this is the first review of lichen depsidones.

2. THE STRUCTURE OF DEPSIDONES

All depsidones contain a rigid 11H-dibenzo[b,e][1,4]dioxepin-11-one ring (Fig. **1**) that is substituted in different positions with various substituents. Explored by SciFinder Chemical Substructure Registry, 806 substances were found with the given substructure.



orcinol: R=H
β-orcinol: R=CH_3



11*H*-dibenzo[*b*,*e*][1,4]dioxepin-11-one

Fig. (1). Structures of orcinol, β-orcinol and 11H-dibenzo[b,e] [1,4]dioxepin-11-one.

Commonly, depsidones consist of orcinol or β-orcinol units (Fig. **1**) connected by an ether and ester bond.

Some bioactive depsidones have been found in fungi and higher plants. Folipastatin, inhibitor of phospholipase A2 was isolated from *Aspergillus unguis* [25]. Mutagenic mollicellins A, B, C, D, E, F, G, and H were found in *Chaetomium mollicellum* [26], cytotoxic botryorhodine A, B were found in *Botryosphaeria rhodina* [27], corynesidones A, B, inhibitors of aromatase were found in *Corynespora cassiicola L36* [28].

In the case of plant depsidones, atrovirisidone B [29], garcidepsidones A-D [30], brevipsidones A-D [31], and garcinisidones B-F [32] were isolated from *Garcinia* sp. plants. All the abovementioned plant depsidones show cytotoxic activity [29-32].

3. THE BIOSYNTHESIS OF DEPSIDONES

The biosynthesis of depsidones was first explained by the hypothesis that they involved the oxidative coupling of *para*-depsides. Sala and Sargent postulated that benzophenone may lead to the formation of a depsidone through a grisadienedione intermediate (Scheme **1**, route (**a**)). This theory is supported by a chemical synthesis in which oxidative coupling of corresponding benzophenones readily yielded grisadienediones, which rearranged to depsidones under basic, acidic and thermal conditions [33]. Elix and his collaborators proposed a theory for biosynthesis of lichen depsidones via a *meta*-depside intermediate (Scheme **1**, route (**b**)), which is supported by the chemical synthesis where two depsidones, divaronic acid and stenosporonic acid, were prepared by a biomimetic-type approach that involved a Smiles rearrangement of a precursor *meta*-depside in the key step [34]. The most recent hypothesis has suggested that depsidones biosynthesis involves neither oxidative coupling of *para*-depsides nor oxidation followed by Smiles rearangement, but most likely oxidation of *para*-depsides by dioxygenase, followed by the cyclisation of the dihydroxydihydrobenzene intermediate (Scheme **1**, route (**c**)) [7].

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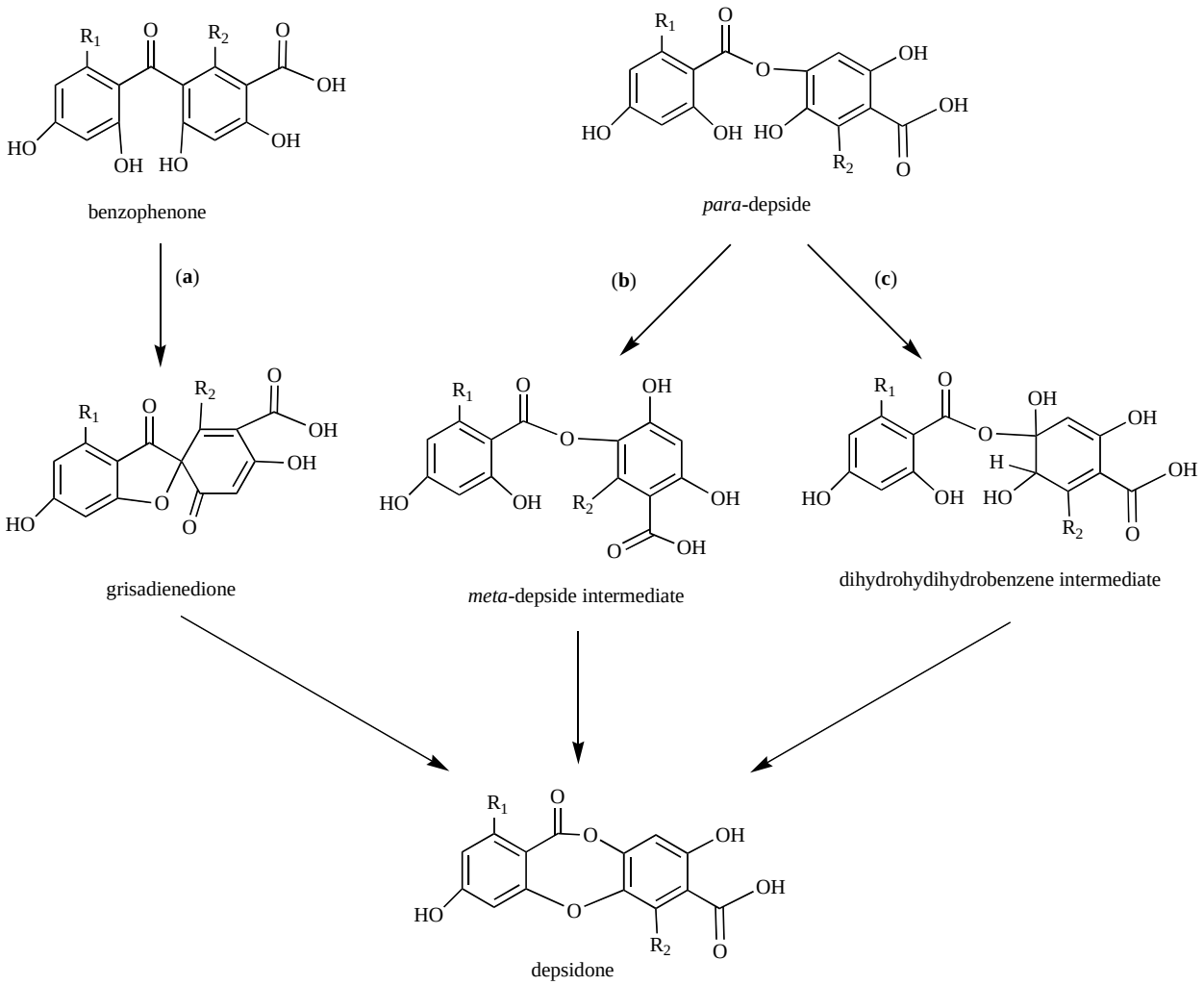


Scheme 1. Proposed biosynthetic pathways of the lichen depsidones (route (**a**) is based on [33], route (**b**) is based on [34], route (**c**) is based on [7]).

4. BIOLOGICAL ACTIVITY

Chemical structures of bioactive lichen depsidones are given in Fig. (**2**). Their common names, chemical names, species from which they were isolated and published activity are presented in Table **1**.

4.1. Cytotoxic Activity

Most of the biological assays were related to cytotoxicity [35-42]. Correche *et al.* [36] tested nine depsidones, four depsides and tridepside gyrophoric acid in the cell culture of lymphocytes. They found that, in general, depsidones displayed stronger cytotoxic activities than depsides. Among them, more active are the structures with an aldehyde group and an adjacent hydroxyl group. Thus, the strong hydrogen bond displayed between the aldehyde and hydroxyl groups could play a key role for the biological response. The observed lower cytotoxic activity of stictic acid in comparison with salazinic acid activity is in agreement with these observations. Namely, the principal structural difference between these acids is that the OH group at C10 is methylated in stictic acid, and therefore hydrogen bond interactions cannot take place in this molecule.

Ogmundsdóttir *et al*. [35] reported that lobaric acid caused a significant reduction of DNA synthesis on three malignant cell-lines (from erythro-leukaemia). Haralsdottir *et al.* [37] published anti-proliferative effects of lobaric acid on 10 other human cancer cell lines (Capan-1, Capan-2 and PANC-1 (all originating from the pancreas), T47-D (the breast), PC-3 (prostate), NCI-H1417 (small lung cells), NIH:OVCAR-3 (the ovaries), AGS (stomach), WiDr (colorectal area), HL-60, K-562 and JURKAT (acute promyelocytic, erythro- and T-cell leukemia, respectively).

Millot *et al.* [39] isolated variolaric acid and α-alectoronic acid from the lichen *Ochrolechia parella*, and evaluated the cytotoxic activity of this compounds against B16 murine melanoma cells, with IC_{50} values of 38.7 μM and 10.3 μM, respectively. Salazinic acid and its di-*O*-alkyl derivatives (alkyl = propyl, butyl, pentyl and hexyl) were tested on tumor cell lines (HCT-8, SF-295 and MDA / MB - 435). Elongation of the alkyl chain causes an increase in the cytotoxic activity of these derivatives [41].

Diploicin was isolated from the lichen *Diploicia canescens* and showed cytotoxic activities against the B16 murine melanoma and HaCaT human keratinocyte cell lines [42]. Pannarin inhibits the growth of human prostate carcinoma DU-145 cells [38] and human melanoma cells (M14 cell line) [40].

4.2. Enzyme Inhibitory Activity

Some depsidones have been found to posses significant enzyme inhibitory activities [43-46]. Neamati *et al.* [43] examined enzyme inhibitory activity of seventeen lichen acids comprising depsides, depsidones, and their synthetic derivatives. It was found that depsidones were active against HIV-1 integrase, while depsides were not, implying the importance of a rigid polycyclic system for activity. Virensic acid, its methyl ester granulatine, stictic acid and chlo-

Table 1. Common Names, Chemical Names, Lichen Species from which Bioactive Depsidones were Isolated and their Biological Activities

Depsidone		Lichen Species	Activity
Common Name	**Chemical Name**		
α-Alectoronic acid	3,8-dihydroxy-11-oxo-1,6-bis(2-oxoheptyl)-11*H*-dibenzo[*b*,*e*][1,4] dioxepine-7-carboxylic acid	*Ochrolechia parella*	Cytotoxic [39][a]
Chloropannarin (*syn*. Argopsin)	2,7-dichloro-3-hydroxy-8-methoxy-1,6,9-trimethyl-11-oxo-11*H*-dibenzo[*b*,*e*][1,4]dioxepine-4-carbaldehyde	*Erioderma chilense*	Cytotoxic [36][a] Antimicrobial [47][a] UV protection [53][a]
Diploicin (*syn*. Diploicine)	2,4,7,9-tetrachloro-3-hydroxy-8-methoxy-1,6-dimethyl-11*H*-dibenzo[*b*,*e*][1,4] dioxepin-11-one	*Diploicia canescens*	Cytotoxic [39][a]
Fumarprotocetraric acid	(*E*)-9-((3-carboxyacryloyloxy) methyl)-4-formyl-3,8-dihydroxy-1,6-dimethyl-11-oxo-11*H*-dibenzo [*b*,*e*][1,4]dioxepin-7-carboxylic acid	*Cladonia furcata*	Cytotoxic [36][a] Antimicrobial [51][a]
Granulatine	methyl 4-formyl-3,8-dihydroxy-1,6,9-trimethyl-11-oxo-11*H*-dibenzo [*b*,*e*][1,4] dioxepine-7-carboxylate	*Pseudocyphellaria granulata* and *P. faveolata*	Inhibition of HIV-1 integrase [43][a]
Lobaric acid (*syn*. Usnetic acid)	8-hydroxy-3-methoxy-11-oxo-1-pentanoyl-6-pentyl-11*H*-dibenzo [*b*,*e*][1,4]dioxepine-7-carboxylic acid	*Stereocaulon* sp.	Cytotoxic [35-37][a] Antimicrobial [48][a] Enzymes inhibition [44-46][a]
Neuropogonine A	2-hydroxy-7,9-bis(hydroxymethyl)-1,6-dimethyl-11-oxo-11*H*-dibenzo [*b*,*e*][1,4]dioxepine-4-carbaldehyde	*Neuropogon* sp.	Antimicrobial [49][a]
Neuropogonine B	4-formyl-3-hydroxy-9-(hydroxymethyl)- 8-methoxy-1,6-dimethyl-11-oxo-11*H*-dibenzo [*b*,*e*][1,4]dioxepine-7-carboxylic acid		
Neuropogonine C	4-formyl-3-hydroxy-9-(hydroxymethyl)-1,6-dimethyl-11-oxo-11*H*-dibenzo[*b*,*e*][1,4]dioxepine-7-carboxylic acid		
Norlobaric acid	3,8-dihydroxy-11-oxo-1-pentanoyl-6-pentyl-11*H*-dibenzo [*b*,*e*] [1,4] dioxepine-7-carboxylic acid	*Stereocaulon* sp.	Inhibition of HIV-1 integrase [43][a]
Pannarin	2-chloro-6-hydroxy-3-methoxy-1 ,4,8-trimethyl-11-oxo-11*H*-dibenzo [*b*,*e*] [1,4] dioxepine-7-carbaldehyde	*Psoroma* sp.	Cytotoxic [36, 38, 40][a] Antimicrobial [47][a] Antioxidant [40][a] UV protection [52][a]
Physodic acid	3,8-dihydroxy-11-oxo-1-(2-oxoheptyl)-6-pentyl-11*H*-dibenzo [*b*,*e*] [1,4] di-oxepine-7- carboxylic acid	*Hypogimnia physodes*	Inhibition of HIV-1 integrase [43][a] Antimicrobial [50][a]
Protocetraric acid	4-formyl-3,8-dihydroxy-9-(hydroxymethyl)-1,6-dimethyl-11-oxo-11*H*-dibenzo[*b*,*e*][1,4]dioxepine-7-carboxylic acid	*Parmelia caperata*	Antimicrobial [51][a]
Psoromic acid (*syn*. Parrelic acid)	4-formyl-3-hydroxy-8-methoxy-1,9-dimethyl-11-oxo-11*H*-dibenzo[*b*,*e*][1,4]dioxepine-6-carboxylic acid	*Psoroma sp.*	Cytotoxic [36][a] Inhibition of HIV-1 integrase [43][a]
Salazinic acid	1,4,10-trihydroxy-5-(hydroxymethyl)-8-methyl-3,7-dioxo-3,7-dihydro-1*H*-benzo[*e*]isobenzofuro[5,4-*b*][1,4] dioxepine-11-carbaldehyde	*Parmotrema lichexanthonicum*	Cytotoxic [36, 41][a] Antimicrobial [41][a] Inhibition of HIV-1 integrase [43][a]
Stictic acid	1,4-dihydroxy-10-methoxy- 5,8-dimethyl -3,7-dioxo- 3,7-dihydro- 1*H*-benzo[*e*]isobenzofuro[5,4-*b*][1,4] dioxepin-11-carbaldehyde	*Parmelia conspresa*	Cytotoxic [36][a] Inhibition of HIV-1 integrase [49][a] Antimicrobial [51][a]
Variolaric acid	4,7-dihydroxy-9-methyl-1*H*-benzo[*e*]isobenzofuro [5,6-*b*][1,4] benzodioxepin-3,10-dione	*Ochrolechia parella*	Cytotoxic [36, 39][a]
Vicanicin	2,7-dichloro-3-hydroxy-8-methoxy-1,4,6,9-tetramethyl-11*H*-dibenzo [*b*,*e*][1,4]dioxepin-11-one	*Erioderma chilense*	Cytotoxic [36][a]
Virensic acid	4-formyl-3,8-dihydroxy-1,6,9-trimethyl-11-oxo-11*H*-dibenzo [*b*,*e*] [1,4] benzodioxepine-2-carboxylic acid	*Alectoria tortuosa*	Inhibition of HIV-1 integrase [43][a]

[a] – reference number in the text

roparellic acid all have IC_{50} of approximately 3 μM. The IC_{50} for parellic, salazinic, physodic and norlobaric acids were 5.3, 12.6, 30.9 and 39.2 μM, respectively. Among the above mentioned lichen acids tested for anti-HIV-1 activity against CEM cells, only the virensic acid and granulatine showed moderate activity. Virensic acid exhibited lower potency than its methyl ester granulatine perhaps due to a decreased cellular uptake [43].

Lobaric acid, a constituent of the lichen *Stereocaulon alpinum*, inhibited contractile activity of the guinea pig taenia coli at 5.8 μM and the formation of cysteinyl-leukotrienes at 5.5μM [44]. This lichen acid also inhibits arachidonate 5-lipoxygenase (IC_{50} = 7.3 μM) [45], and protein tyrosine phosphatase 1B (PTP1B) (IC50 = 0.87 μM) [46]. Kinetic analyses of protein tyrosine phosphatase 1B inhibition by lobaric acid suggested that this compound inhibited

protein tyrosine phosphatase 1B activity in a non-competitive manner [46].

4.3. Antimicrobial Activity

Lichens produce antibiotic secondary metabolites that protect them from pathogens in nature [3]. Lichen depsidones have been shown to be quite effective against a wide variety of microorganisms including fungi, algae, yeast and both Gram-positive and Gram-negative bacteria [41, 47-51].

Ranković and Mišić [51] tested the antimicrobial activity of fumarprotocetraric acid, protocetraric acid and stictic acid against six bacteria and ten fungi. The bacterias showed a higher sensitivity relative to fungi. The lowest MIC value (0.031 mg/mL) was measured for the fumarprotocetraric acid related to the *Klebsiella pneumoniae* species. Stictic acid exhibited the weakest antimicrobial activity against most of the tested microorganisms. Physodic acid demonstrated the weakest antimicrobial activity compared to the activity of usnic acid (dibenzofurane) and depsides antranorin and gyrophoric acid [50]. Lobaric acid from *S. alpinum* and salazinic acid from *Parmelia saxatilis* (L.) Ach. were screened for activity against *Mycobacterium aurum*, a non-pathogenic organism with a similar sensitivity profile to *M. tuberculosis. In vitro* susceptibility was 125 mg/ml for lobaric acid and 250 mg/ml for salazinic acid [48]. Pannarine and 1'-chloropannarine exhibited activity at 50 μg/ml against promastigote forms of three strains of *Leishmania* sp. [47].

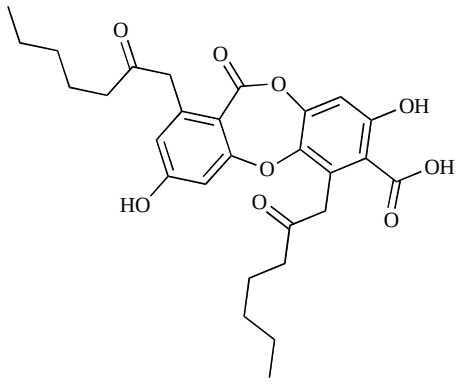
Neuropogonines A, B and C from Antarctic lichen *Neuropogon* sp. exhibited moderate activity against *Mycobacterium vaccae* 10670 (MIC 50 μg/mL) [49]. Salazinic acid and its di-*O*-alkyl derivatives (alkyl = propyl, butyl, pentyl and hexyl) were tested against the bacteria *Escherichia coli* and *Staphylococcus aureus*. Salazinic acid showed activity only in regards to *E. coli.* Its derivatives were active against both bacteria but the exhibited activity was lower than the activity of standard antibiotic amikacin. It seems that elongation of the alkyl chain of salazinic acid does not significantly affect antibacterial activity [41].

4.4. Other Activities

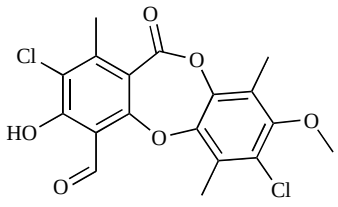
Lichen depsidones have also demonstrated antioxidant activity [41] and possess photoprotector ability [52, 53]. Pannarin is able to reduce NO-induced DNA damage, acting as a NO trapper agent, and it showed a dose-dependent superoxide scavenging effect [40]. Lichen substances strongly absorb UV light and protect phycobionts from dangerous irradiation [3]. Pannarin and 1'-chloropannarin, at a concentration of 10 mM and irradiated at 360 nm, inhibited photobinding to human serum albumin by 40.4% and 31.7%, respectively [52]. Rancan *et al.* [53] tested 1-chloropannarin as possible UV-light filter. The UV light-filtering power of this compound is comparable to that of the commercial substances, such as Nivea sun Spray LSF 5.

5. CONCLUDING REMARKS AND FUTURE PERSPECTIVES

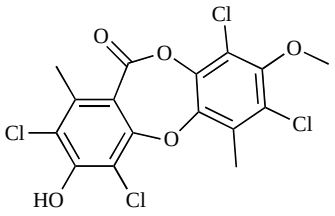
The presented data show that lichen depsidones are diverse in their structures (Fig. **2**) and biological activity (Table **1**). Pharmacological investigations of lichen depsidones has revealed that many compounds are highly bioactive and that some of them may be used as active components of drugs, cosmetics or food supplements. Based on current results, it seems that pannarin, lobaric acid, stictic acid, salazinic acid and psoromic acid possess a promising potential for use as antitumor drugs. Since all the listed compounds are commercially available, it provides opportunities for any further study of their therapeutic use. The inhibitory activity of granulatine, virensic acid, stictic acid and chloroparellic acid against HIV-1 integrase is not negligible. According to the MIC values of tested lichen depsidones which are many times higher than MIC values of standard antibiotics [44, 50-54], their potential as antibiotics is not so great. Pannarin and chloropannarin may be useful as new filters in the preparation of sun-screen products. However, the application of lichen depsidones in the cosmetics industry should be performed with caution because some of them cause contact allergy [57].



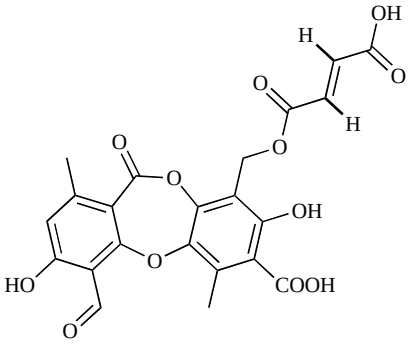
α-Alectoronic acid



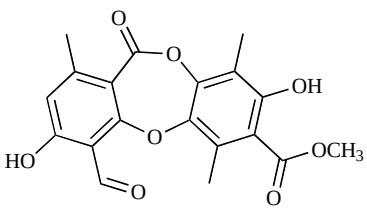
Chloropannarin



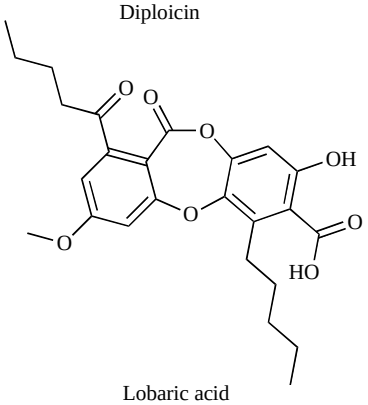
Diploicin



Fumarprotocetraric acid



Granulatine



Lobaric acid

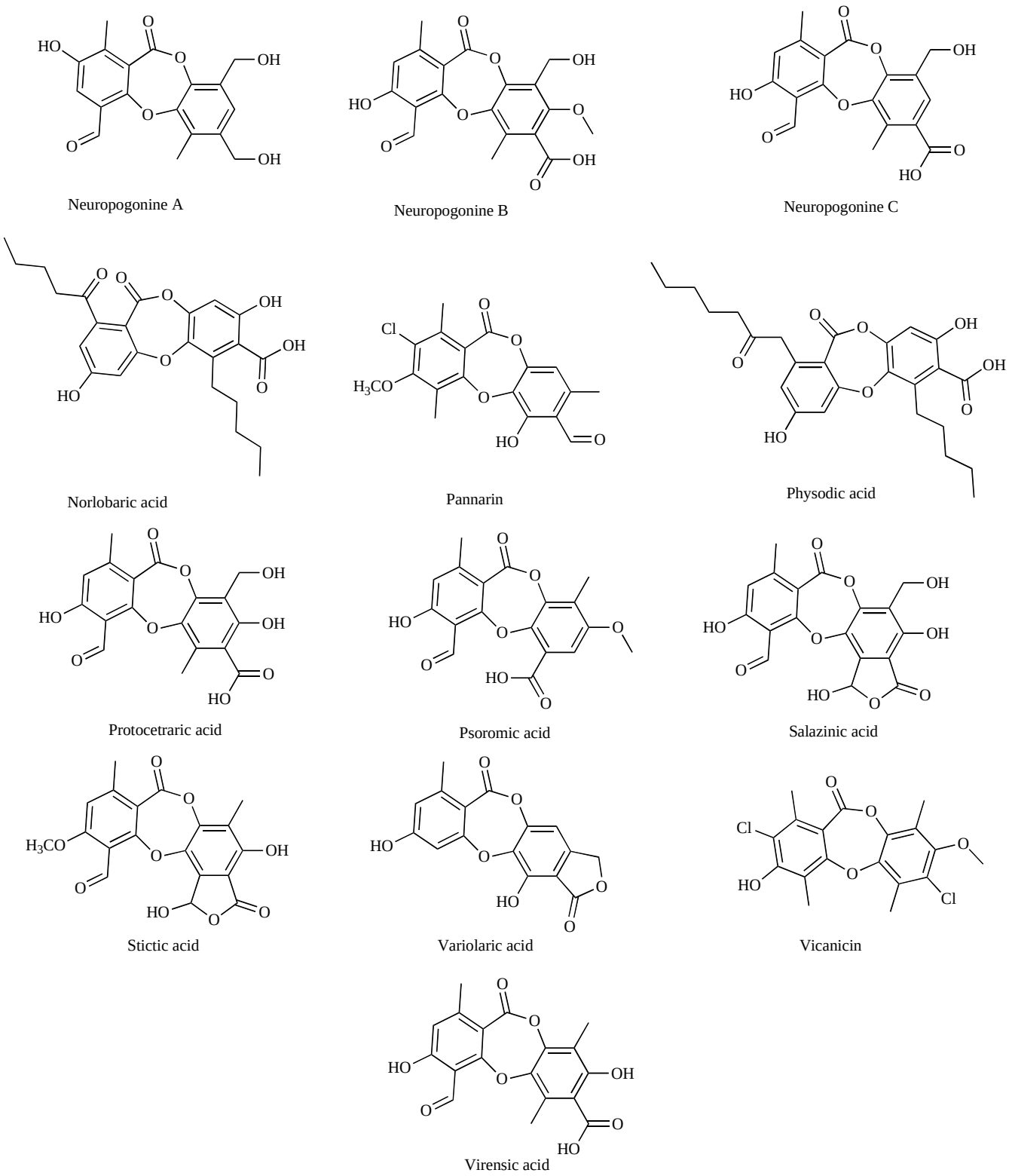


Fig. (2). Structures of bioactive lichen depsidones.

In the future, the application of modern hyphenated methods such as LC-NMR and LC-MS will enable detection and structure determination of new lichen depsidones. The basic requirement for the application of compounds in the pharmaceutical industry is their availability in sufficient quantity. Lichens grow very slowly and need to be collected in large amounts, which are necessary for isolating sufficient quantities of bioactive compounds, which in turn can endanger their survival. Therefore, beside chemical and biological studies, biotechnological studies for obtaining depsidones should be intensified. Another possibility for production of the most active depsidones is chemical synthesis or chemical modification of natural depsidones. Computer drug design may help development of new synthetic depsidone analogues with enhanced pharmacological potency.

ACKNOWLEDGEMENT

This work was financially supported by Ministry of Science and Technological Development of Serbia (Project 172047).

CONFLICT OF INTEREST

None declared.

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Received: April 18, 2011 Revised: June 28, 2011 Accepted: July 12, 2011