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Phytochemistry 66 (2005) 747–769

PHYTOCHEMISTRY

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Review

Secondary metabolites of slime molds (myxomycetes)

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Received 18 January 2005; received in revised form 14 February 2005

Abstract

The compounds reported from the slime molds (myxomycetes) species are described. Almost 100 natural compounds including their chemical structures and biological activities are described in this review article. Only metabolites with a well-defined structure are included.

Keywords: Slime molds; Myxomycetes; Metabolites; Lipids; Fatty acids; Alkaloids; Pigments; Terpenoids; Glycosides

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Contents

1. Introduction

The myxomycetes (plasmodial slime molds) are a group of fungus-like organisms usually present and sometimes abundant in terrestrial ecosystems. The myxomycete life cycle involves two very different trophic (feeding) stages, one consisting of uninucleate amoebae, with or without flagella, and the other consisting of a distinctive multinucleate structure, the plasmodium. Myxomycete plasmodia typically occur in cool, moist, shady places such as within crevices of decaying wood, beneath the partially decayed bark of logs and stumps

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doi:10.1016/j.phytochem.2005.02.017

or other organic matter retaining abundant moisture, and in leaf litter on the forest floor. Under favorable conditions, the plasmodium gives rise to one or more fruiting bodies containing spores. The spores of myxomycetes are for most species apparently wind-dispersed and complete the life cycle by germinating to produce the uninucleate amoeboflagellate cells. The myxomycetes are actually just one of three groups of organisms to which the name "slime mold" has been applied, and they also include other slime molds: Dictyostelids and Protostelids (Alexopoulos and Mims, 1979; Stephenson and Stempen, 1994). Members of both groups are so small that they are virtually impossible to observe directly in the field. Instead, surveys for Dictyostelids and Protostelids are carried out in the laboratory by culturing these organisms from various types of organic material brought in from the field. Slime molds feed on decaying organic matter, bacteria, protozoa, and other minute organism, which they engulf and digest (Stephenson and Stempen, 1994).

Although presently classified as protozoans (kingdom Protista), slime molds were once thought to be fungi (kingdom Mycetae) because they produce spores that are borne in sporangia, a characteristic common to some

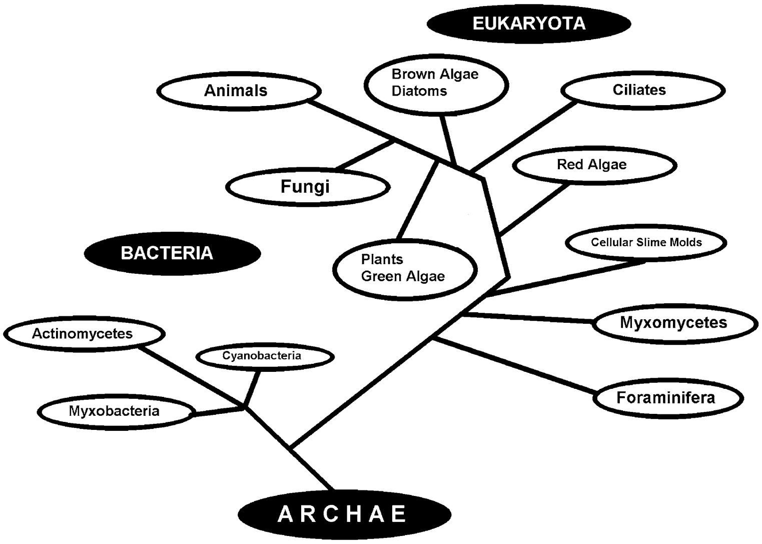


Fig. 1. Position of myxomycetes on the phylogenic tree.

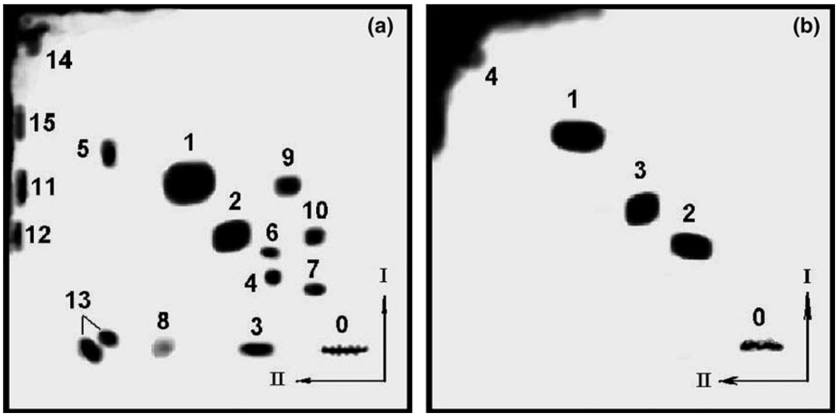


Fig. 2. Separation of polar lipids by 2-D TLC isolated from the *Physarum polycephalum*. Lipids were separated on pre-coated silica gel plates 10 × 10 cm (Merck 5715). Chromatogram A: the 1st dimension, chloroform–methanol–28% ammonia (130:70:10, v/v); the 2nd dimension, chloroform–acetone–methanol–acetic acid–water (50:20:10:10:1, v/v). After 1st dimension, the plate was developed by 4 M HCl in methanol for hydrolyzed plasmalogenic lipids. Spots developed with spray reagent, 5% sulfuric acid in methanol. For separation of alkylacyl, alkenylacyl, and diacyl lipids by micro-TLC method, see Dembitsky (1988). Abbreviations: 0, origin; 1, summary of 1,2-diacyl- and 1-alkyl-2-acyl-PE; 2, summary of 1,2-diacyl- and 1-alkyl-2-acyl-PC; 3, PS; 4, PI; 5, CL; 6, LPE; 7, LPC; 8, PA; 9, 1-lyso-2-acyl-PE obtained after hydrolyzed plasmalogen-containing PPE; 10, 1-lyso-2-acyl-PC obtained after hydrolyzed plasmalogen-containing PC; 11, fatty aldehydes released after hydrolyzed PE; 12, fatty aldehydes released after hydrolyzed PC; 13, pigments; 14, neutral lipids; 15, free fatty acids. Chromatogram B: 1st dimension, chloroform–methanol–*n*-propanol–25% ammonia (40:30:20:10, v/v); the 2nd dimension, chloroform–acetone–formic acid–methanol–*n*-propanol–water (60:30:20:20:10:5, v/v). Abbreviations: 0, origin; 1, 1-alkyl-2-lyso-PE; 2, 1-alkyl-2-lyso-PC; 3, sphingomyelin (internal standard); 4, products of saponification.

taxa of fungi. However, the assimilative stage in slime molds is morphologically similar to that of an amoeba. This assimilative stage has been designated a myxamoeba. The myxamoeba, as is the case of the amoeba, is a uninucleate, haploid cell which is not enclosed in a rigid cell wall, and ingests its food by means of phagocytosis. The slime molds at this time were thought to be a monophyletic group, based on the amoeba stage that germinated from spore and consumed nourishment via phagocytosis. However, that these organisms were related to the fungi was finally laid to rest. Most mycologists had not recognized slime molds as being related to fungi for quite some time. The amoebae feed on bacterial cells, their DNA persists throughout the life cycle of the slime molds, making it impossible to obtain pure genomic samples of slime molds. According to DNA and RNA analyses (Baldauf, 1999, 2003; Baldauf and Doolittle, 1997; Horton and Landweber, 2000), the phylogenetic tree was created as shown in Fig. 1.

Chemical studies on the secondary metabolites of the myxomycetes have so far been limited. Early explorative studies were reviewed by Steglich (1989), and demonstrated that myxomycetes have developed rather unique secondary metabolites. Almost 100 natural compounds including their chemical structures and biological activities are described in this invited review

Table 1
Composition of polar lipids of some slime mold species

Classes of lipids[a]	*Arcyria* sp.	*Fuligo septica*	*Physarum polycephalum*	*Trichia varia*
1,2-Diacyl-phosphatidylethanolamine (PE)	4.8	8.5	7.3	10.1
1-Alk-1′-enyl-2-acyl-PE (plasmalogen, PPE)	20.1	12.5	14.1	18.8
1-Alkyl-2-acyl-PE (APE)	16.9	23.9	20.4	12.1
Lysophosphatidylethanolamine (LPE)	0.8	1.6	2.8	1.1
Phosphatidylserine (PS)	7.2	6.1	5.1	8.6
Total amino lipids	**49.8**	**52.6**	**49.7**	**50.7**
1.2-Diacyl-phosphatidylcholine (PC)	6.1	4.2	6.9	3.9
1-Alk-1′-enyl-2-acyl-PC (plasmalogen, PPC)	9.6	12.5	11.2	15.1
1-Alkyl-2-acyl-PC (APC)	20.4	17.3	16.7	17.8
Lysophosphatidylcholine (LPC)	1.7	2.1	3.4	0.5
Total choline lipids	**37.5**	**36.1**	**38.2**	**37.3**
Phosphatidylinositol (PI)	3.8	3.7	4.2	3.3
Cardiolipin (CL)	7.8	5.4	6.2	4.9
Phosphatidic acid (PA)	0.8	2.2	1.7	3.8

[a] Percentage of total polar lipids.

Table 2
Saturated fatty acids of slime molds

Fatty acid	*A. c.*[a]	*A. d.*	*A. n.*	*F. s.*	*L. e.*	*L. f.*	*P.* sp.	*T. f.*	*T. v.*
i-13:0	0.07	0.14	0.07	0.00	0.07	0.14	0.00	0.08	0.09
ai-13:0	0.00	0.00	0.00	0.15	0.00	0.00	0.18	0.00	0.00
13:0	0.22	0.14	0.21	0.20	0.29	0.22	0.09	0.17	0.28
i-14:0	0.07	0.14	0.14	0.00	0.14	0.08	0.00	0.17	0.09
14:0	0.51	0.35	0.42	0.39	0.29	0.37	0.41	0.17	0.36
i-15:0	0.15	0.14	0.21	0.00	0.14	0.08	0.00	0.17	0.09
ai-15:0	0.00	0.00	0.00	0.34	0.00	0.00	0.23	0.00	0.00
15:0	0.59	0.42	0.56	0.30	0.65	0.74	0.55	0.73	0.64
i-16:0	0.59	0.64	0.84	0.00	0.57	0.82	0.00	0.40	0.64
16:0	5.73	4.55	5.66	6.66	5.62	5.10	8.17	9.08	9.29
i-17:0	0.44	0.57	0.62	0.00	0.36	0.44	0.00	0.49	0.64
ai-17:0	0.00	0.00	0.07	0.44	0.00	0.00	0.41	0.00	0.00
17:0	0.51	0.57	0.49	0.59	0.29	0.44	0.59	0.40	0.55
i-18:0	0.22	0.14	0.21	0.00	0.22	0.22	0.00	0.17	0.28
18:0	1.32	1.42	1.46	2.17	1.37	1.63	2.53	2.51	2.67
i-19:0	0.07	0.07	0.14	0.00	0.14	0.14	0.00	0.17	0.28
ai-19:0	0.00	0.00	0.00	0.15	0.00	0.00	0.23	0.00	0.00
19:0	0.15	0.07	0.14	0.05	0.14	0.08	0.05	0.08	0.19
20:0	0.36	0.49	0.56	0.79	0.36	0.44	0.64	0.49	0.74
22:0	0.22	0.21	0.28	0.59	0.22	0.14	0.45	0.32	0.46
24:0	0.15	0.07	0.14	0.39	0.14	0.00	0.27	0.17	0.28
Saturated	11.37	10.13	12.22	13.21	11.01	11.08	14.80	15.77	17.57

[a] *A. c.*, *Arcyria cinerea*; *A. d.*, *A. denudata*; *A. n.*, *A. nutans*; *F. s.*, *Fuligo septica*; *L. e.*, *Lycogala epidendrum*; *L. f.*, *L. flavoscum*; *P.* sp., *Physarium species*; *T. f.*, *Trichia favogiena*; *T. v.*, *T. varia*.

Table 3
Monoenoic fatty acids of slime molds

Fatty acid	*A. c.*[a]	*A. d.*	*A. n.*	*F. s.*	*L. e.*	*L. f.*	*P.* sp.	*T. f.*	*T. v.*
14:1*n* − 7	0.07	0.14	0.21	0.25	0.00	0.08	0.18	0.17	0.19
14:1*n* − 5	0.15	0.21	0.21	0.30	0.14	0.22	0.14	0.24	0.36
16:1*n* − 9	0.15	0.14	0.14	0.10	0.22	0.30	0.14	0.08	0.19
16:1*n* − 7	1.61	2.34	1.88	1.72	1.58	1.78	1.85	1.46	1.48
16:1*n* − 5	0.22	0.14	0.21	0.39	0.22	0.30	0.23	0.17	0.28
17:1*n* − 8	0.22	0.35	0.28	0.44	0.22	0.14	0.36	0.32	0.36
18:1*n* − 13	0.36	0.42	0.49	0.54	0.65	0.60	0.59	0.49	0.64
18:1*n* − 11	0.22	0.14	0.35	0.44	0.51	0.52	0.23	0.40	0.55
18:1*n* − 9	25.72	24.32	25.15	18.74	20.91	22.18	28.17	15.72	15.22
18:1*n* − 7	0.59	0.49	0.42	0.25	0.43	0.37	0.23	0.57	0.74
18:1*n* − 5	0.15	0.07	0.28	0.34	0.36	0.52	0.32	0.24	0.55
19:1*n* − 10	0.00	0.00	0.00	0.05	0.00	0.08	0.09	0.00	0.00
19:1*n* − 8	0.22	0.14	0.21	0.25	0.14	0.14	0.27	0.17	0.28
20:1*n* − 15	0.07	0.00	0.00	0.05	0.00	0.00	0.05	0.00	0.00
20:1*n* − 13	0.07	0.07	0.14	0.44	0.57	0.37	0.32	0.49	0.46
20:1*n* − 11	0.15	0.21	0.14	0.34	0.29	0.14	0.23	0.32	0.46
20:1*n* − 9	0.96	1.21	0.98	1.13	0.94	1.26	0.95	0.97	1.48
20:1*n* − 7	0.36	0.28	0.42	0.25	0.22	0.22	0.14	0.24	0.19
21:1*n* − 9	0.22	0.21	0.28	0.34	0.29	0.14	0.09	0.17	0.09
22:1*n* − 15	0.00	0.00	0.00	0.05	0.00	0.00	0.05	0.00	0.00
22:1*n* − 13	0.00	0.00	0.00	0.15	0.00	0.00	0.09	0.00	0.00
22:1*n* − 11	0.15	0.07	0.14	0.30	0.14	0.08	0.23	0.17	0.09
22:1*n* − 9	0.44	0.35	0.35	0.44	0.29	0.37	0.45	0.24	0.36
22:1*n* − 7	0.15	0.14	0.07	0.20	0.00	0.08	0.23	0.00	0.09
23:1*n* − 9	0.00	0.00	0.00	0.05	0.00	0.00	0.05	0.00	0.00
24:1*n* − 9	0.00	0.07	0.07	0.20	0.00	0.08	0.09	0.00	0.00
Monoenoic	32.25	31.51	32.42	27.75	28.12	29.97	35.77	22.63	24.06

[a] *A. c.*, *Arcyria cinerea*; *A. d.*, *A. denudata*; *A. n.*, *A. nutans*; *F. s.*, *Fuligo septica*; *L. e.*, *Lycogala epidendrum*; *L. f.*, *L. flavoscum*; *P.* sp., *Physarium species*; *T. f.*, *Trichia favogiena*; *T. v.*, *T. varia*.

article. Only metabolites with a well-defined structure are included.

2. Lipids

The first report on fatty acids in myxomycetes has been published more than 40 years ago by Davidoff and Korn (1963a,b, 1964). Authors studied distribution of fatty acids in the cellular slime mold, *Dictyostelium discoideum*, and found it to contain a high percentage of unsaturated fatty acids (Davidoff and Korn, 1963a). Several of these are unique dienoic acids that do not contain the methylene-interrupted double bonds usually present in most natural polyenoic fatty acids. For reasons that will be developed later, the major fatty acids of this organism may be divided into three metabolic groups: (a) palmitic acid, 16:0 (5%), palmitoleic acid, 9–16:1 (3%), and a diunsaturated acid, 5,9–16:2 (8%); (b) *cis*-vaccenic acid, 9–18:1 (29%), and an 18 carbon diunsaturated acid, 5,11–18:2 (19%), and (c) stearic acid, 18:0, oleic acid, 18:1, and a diunsaturated acid, 5,9–18:2 (32%). Some minor acids were also found: 17:0, 5–17:1, 5,9–17:2, 19:1, and 20:0. Biosynthesis of these fatty acids has also been studied (Davidoff and Korn, 1963b, 1964). The molecular species of fatty acids in α- and β-positions in phosphatidylethanolamine (PE) and phosphatidylcholine (PC) were studied. Major acids in α-position of PE were: 16:0 (23.0%), 18:1 (20.6%), and 20:0 (32.8%); in β-position – 18:1 (23.3%), 18:2 (47.3%), and 19:1 (11%). PC contain in α-position: 16:2 (30.4%), 18:2 (50.0%), and 18:1 (9.9%); the same acids are present in β-position: 16:2 (12.7%), 18:2 (49.5%), and 18:1 (15.4%).

Fatty acids of a wild-type strain of *D. discoideum* grown on *Aerobacter aerogenes* have been studied (Long and Coe, 1977). Fatty acid composition of lipid fractions and of total lipids obtained from vegetative amoebae and mature sorocarps were compared. Fatty acids isolated from vegetative cells were found to include large quantities of 17- and 19-carbon cyclopropane fatty acids, while straight-chain, saturated fatty acids represented only 10% of total fatty acids. These cyclopropane fatty acids appear to be derived from ingested bacteria and are preferentially incorporated into neutral lipids of the slime mold. Development of amoebae to mature sorocarps was accompanied by a substantial decrease in cyclopropane fatty acid content and a concomitant increase in unsaturated fatty acids, mostly as octadeca-5,11-dienoic acid. The Δ^{22} stigmastenyl ester fraction is the richest source of this acid, where 65% of the fatty acids in this fraction are the octadecadienoates (Long and Coe, 1977). Among neutral lipids in *D. discoideum* were found di- and triglycerides, sterols, and esters of

Table 4
Dienoic and polyenoic fatty acids of slime molds

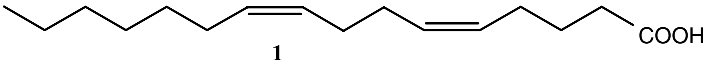
Fatty acid	*A. c.*[a]	*A. d.*	*A. n.*	*F. s.*	*L. e.*	*L. f.*	*P.* sp.	*T. f.*	*T. v.*
5,9–16:2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.12	0.15
16:2$n-4$	1.47	1.07	1.19	1.58	1.16	1.26	1.99	1.70	1.45
5,9–18:2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.37	0.41
5,11–18:2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.05	0.08
18:2$n-9$	1.99	2.49	2.17	2.17	1.30	1.70	2.71	2.03	1.34
18:2$n-6$	35.63	36.54	33.64	34.97	39.14	38.29	24.02	47.15	43.49
5,11–20:2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.32	0.55
5,13–20:2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.17	0.28
20:2$n-9$	0.59	0.64	0.49	0.59	0.65	0.82	0.95	0.24	0.74
20:2$n-6$	1.18	1.00	0.91	1.33	0.87	0.66	1.76	1.38	1.65
7,13–22:2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.32	0.19
7,15–22:2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.24	0.09
dienoic	0.86	41.74	38.40	40.64	43.12	42.73	31.43	54.09	50.42
18:3$n-6$	2.50	2.56	2.03	5.00	5.83	6.81	4.43	0.52	0.31
18:3$n-3$	3.96	4.48	4.96	6.66	1.95	2.59	5.92	4.37	4.51
18:4$n-3$	0.36	0.49	0.42	0.59	0.36	0.52	0.64	0.49	0.64
20:3$n-9$	0.36	0.49	0.42	0.15	0.57	0.74	0.55	0.17	0.09
20:3[b]	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.57	0.46
20:3$n-6$	0.66	0.86	0.98	0.84	0.79	0.66	0.59	0.00	0.00
20:4$n-6$	4.77	5.15	5.36	2.11	4.18	0.34	4.09	0.40	0.28
20:3$n-3$	1.67	1.35	1.46	1.72	1.95	2.27	0.81	0.17	0.36
20:4[c]	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.14	1.03
20:4$n-3$	0.36	0.49	0.56	0.59	1.01	1.11	0.36	0.24	0.19
22:3$n-9$	0.22	0.14	0.07	0.20	0.22	0.30	0.29	0.00	0.00
22:3$n-6$	0.15	0.14	0.14	0.25	0.29	0.37	0.09	0.00	0.00
22:4$n-6$	0.36	0.35	0.49	0.15	0.51	0.44	0.23	0.00	0.00
24:4$n-6$	0.15	0.02	0.07	0.14	0.09	0.07	0.00	0.15	0.08
polyenoic	15.52	16.52	16.96	18.40	17.75	16.22	18.00	8.22	7.95

Rare types fatty acids 5,9–16:2 **1**.

[a] *A. c.*, *Arcyria cinerea*; *A. d.*, *A. denudata*; *A. n.*, *A. nutans*; *F. s.*, *Fuligo septica*; *L. e.*, *Lycogala epidendrum*; *L. f.*, *L. flavoscum*; *P.* sp., *Physarium species*; *T. f.*, *Trichia favogiena*; *T. v.*, *T. varia.*

[b] 5,11,14–20:3.

[c] 5,11,14,17–20:4.



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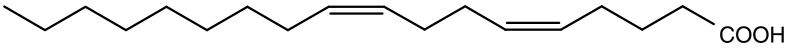

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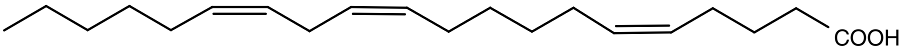

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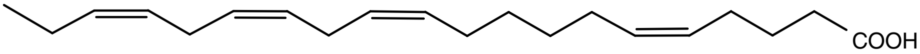

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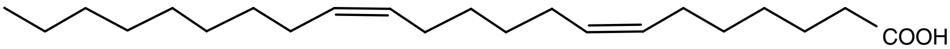

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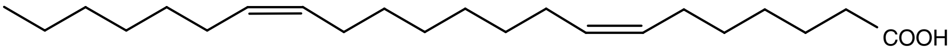

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Fig. 3. Fatty acids.

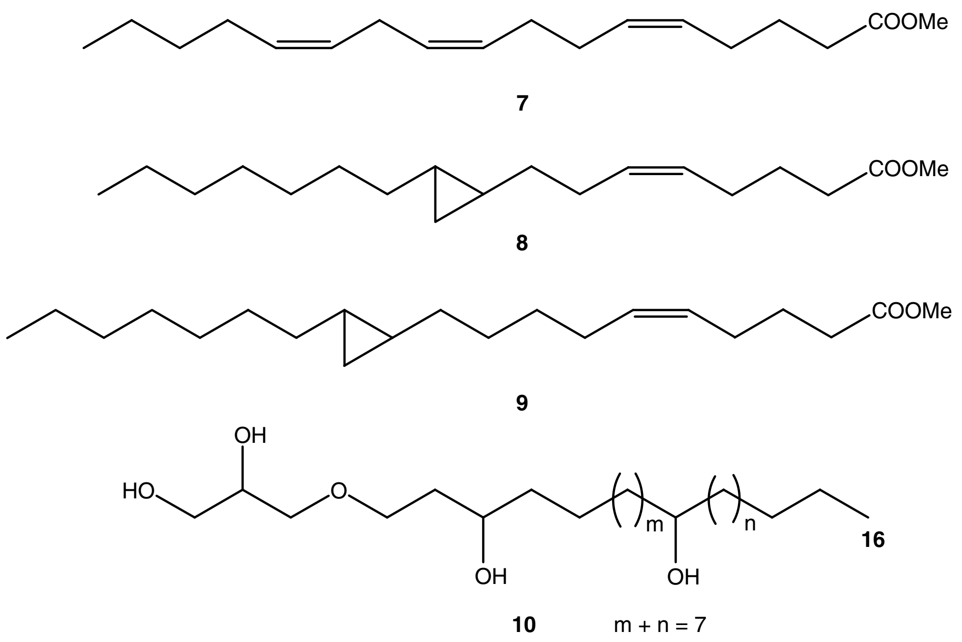
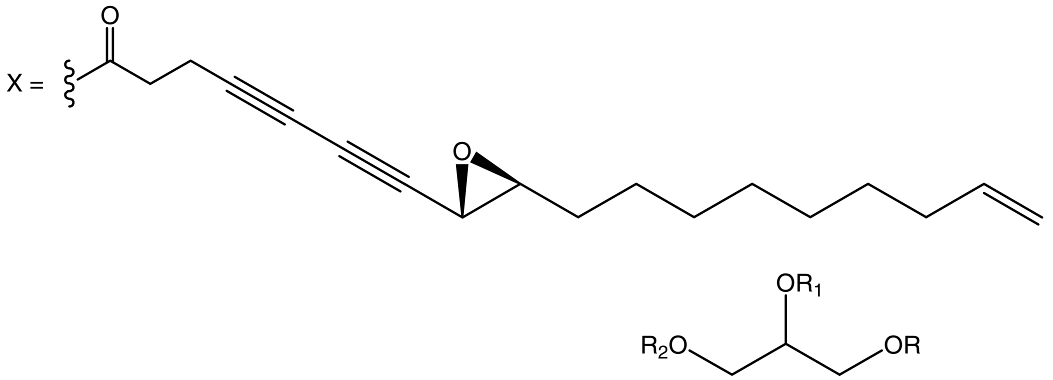
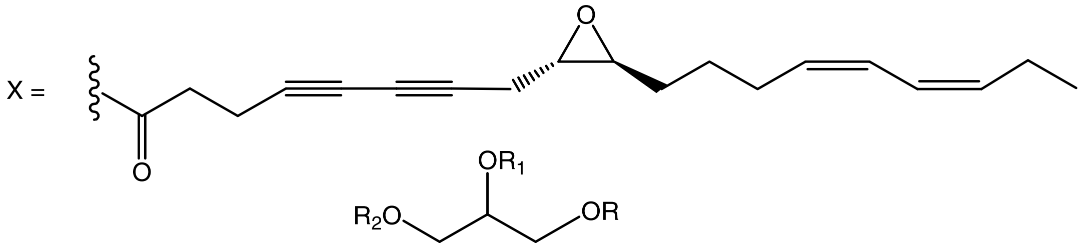


Fig. 4. Lipids.



11 $R = R_1 = R_2 = X$
12 $R = R_1 = X$, $R_2 = (CH_2)_nMe$, $n = 14\text{-}20$
13 $R = X$, $R_1 = R_2 = (CH_2)_nMe$, $n = 14\text{-}20$



14 $R = R_1 = R_2 = X$
15 $R = R_1 = X$, R_2 = C15-C20 saturated and unsaturated fatty acids
16 $R = R_1 = X$, $R_2 = H$
17 $R = R_2 = X$, $R_1 = H$

Fig. 5. Lycogarides A–G.

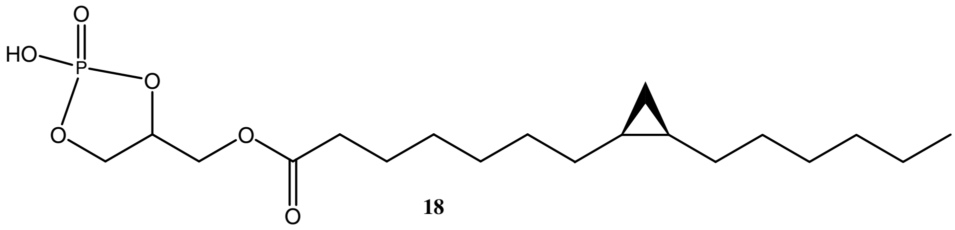


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Fig. 6. Cyclic phosphatidic acid.

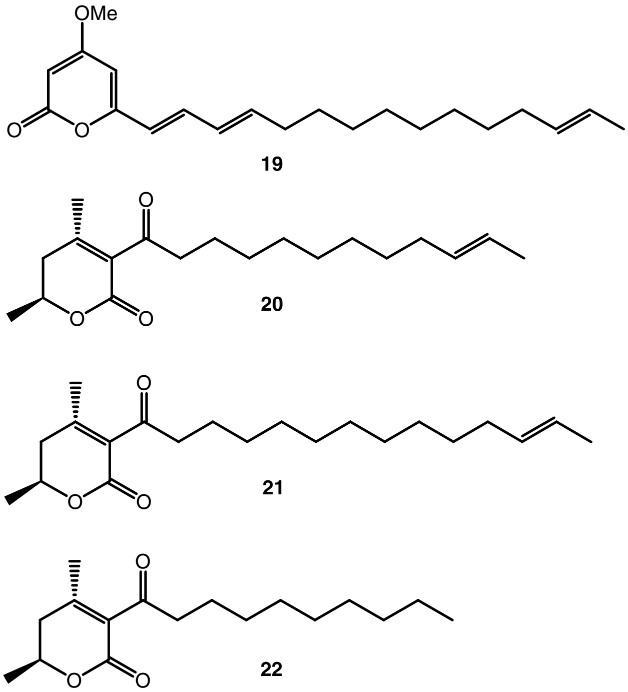

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Fig. 7. Lipid's lactones.

sterols (Long and Coe, 1974). The major sterol of *D. discoideum* has been identified as stigmast-22-en-3β-ol (Heftmann et al., 1959).

Korn et al. (1965) later studied fatty acids from neutral fractions, phospholipids, and also total lipids of *Physarum polycephalum*. The fatty acid composition of this slime mold is of particular interest in comparison to the fatty acids of the cellular slime mold *D. discoideum* (Davidoff and Korn, 1963a), and the soil amoeba *Acanthamoeba* sp. *P. polycephalum* has qualitatively the same pattern of unsaturated fatty acids as *Acanthamoeba* sp. (major fatty acids of total lipids were found as: 9–18:1 (45.4%), 16:0 (9.4%), 9,12–18:2 (5.3%), 11–20:1 (1.5%), 11,14–20:2 (5.7%), 8,11,14–20:3 (5.6%), and 5,8,11,14–20:4 (7.6%); which indicates the presence of 11–20:1 (1.8% in phospholipid fraction, 1.2% in neutral fraction, and 1.3% in total lipids, respectively), 11,14–20:2 (3.4%, 1.9%, and 2.5%), 8,11,14–20:3 (1.4%, 1.2%, and 1.0%), and 5,8,11,14–20:4 (3.1%, 4.2%, and 2.5%), and the absence of 9,12,15–18:3 acid and its metabolic derivatives. Major fatty acids in *P. polycephalum* were found to be 9–18:1 (37.3%, 21.5%, and 35%), 9,12–18:2 (36.2%, 27.2%, and 34.2%), and 16:0 (5.7%, 31.0%, and 7.8%). *P. polycephalum* does not contain the unique dienoic fatty acids 5,9–16:2, 5,9–18:2, and 5,11–18:2 characteristic of *D. discoideum*. According to the obtained data, the authors concluded that the fatty acid composition supports the view that the true slime mold is protozoal, closely related to the soil amoebae, rather than fungal, as has also been suggested because of certain morphological characteristics.

The sterols of an axenic strain of *P. polycephalum* M$_3$c have been studied and six components, namely stigmasterol, β-sitosterol, stigmastanol, campesterol, campestanol, and cholesterol, have been identified (Lenfant et al., 1970). Lanosterol and 24-methylene dihydrolanosterol were found in the triterpene fraction of this organism. The phospholipid composition of the *P. polycephalum* was reported (Comes and Kleinig, 1973), see also Fig. 2. The main components were PC (50%), PE (40%), and phosphatidylinositol (7%). Unusually high amounts of alk-1-enylacyl and alkyl-acyl derivatives were present in the phospholipid fractions. Oleic acid, linoleic acid, and a 20:2 acid were the main fatty acid moieties of phospholipids. Nearly no differences in the acid patterns of individual lipids were observed (Comes and Kleinig, 1973). Phospholipid composition of some slime mold species has been also reviewed by one of the co-authors (Dembitsky, 1996).

Content of plasmalogen (alk-1′-enyl-acyl-), alkyl-acyl and diacyl forms, in the main classes of glycerophospholipids was established by means of the micro-TLC method (Dembitsky, 1988). The main components are amino phospholipids; their content in the total lipid extract varies from 49% to 52%. Alkyl forms dominate in both major phospholipids classes, e.g. PE and PC (Table 1). The content of alkylacyl glycerophospholipids in myxomycete species can be compared with that of Protozoa, particularly Ciliophora species such as *Tetrahymena* (Nozava and Thompson, 1971; Kulikov and Muzya, 1997) and *Paramecium* (Kaneshiro et al., 1987). As Kaneshiro (1987) states in his review, Ciliophora type contains a large quantity of alkylacyl forms of glycerophospholipids practically in all phospholipid classes: PE, PC, PS, and PI. The similarity of lipid composition in lower marine invertebrates, e.g. marine (Dembitsky et al., 1989) or freshwater sponges (Dembitsky et al., 1991, 2003), and Ciliophora type seems to be regular because the slime molds are evolutionarily related with Protozoa and/or sponges and have the same precursors. Myxomycetes, Ciliophora, and Porifera represent a dead end branch of the evolution; therefore, they retain relict alkylglycerophospholipids (Dembitsky, 1996; Kaneshiro, 1987). It should be noted that archaebacteria are one of the most ancient branches of the live organic world and are characterized exclusively by di- and tetraether lipids (Jahn et al., 2004; Kamekura and Kates, 1999) which form unique biomembranes, thus ensuring their existence for at least 3.5 billion years at temperatures over 100 °C and at high pressure (Konings et al., 2002).

Fatty acids of nine different slime molds have been studied by Řezanka (1993). In addition to the common fatty acids, polyunsaturated and methylene non-interrupted dienoic fatty acids, further acids with 5,9- and/or 5,11-double bonds, were identified by GC–mass spectrometry as their corresponding oxazolines. The above-mentioned compounds have been identified in only one slime mold and, therefore, their presence offers a new concept of biosynthesis of these compounds and chemotaxonomy of the slime molds. Among 21 saturated fatty acids we found some methyl branched acids such as, *iso*- and *anteiso*-acids, and major saturated fatty acids were 16:0 (from 4.55% to 9.29%) (Table 2). Most of the fatty acids identified in slime molds were monoenes ranging from 7–14:1 to 9–24:1 (Table 3). C18 acids were represented by five isomers, 5–, 7–, 9–, 11–, and 13–18:1. C20 acids were also represented by five isomers, 7–, 9–, 11–, 13–, and 15–20:1. Interesting structures were also found among isomers of docosaenoic acid (22:1).

Dienoic acids formed a large portion of the total fatty acids and varied from 31.43% in *Physarum* sp. to 54.09% in *Trichia favogiena*, being represented by four major isomers of 18:2 and trace isomers of 20:2 (Table 4). The total polyenoic acids varied widely, from 8.22% in *T. favogiena* to 18.4% in *Fuligo septica*, and were represented by tri- and tetraenoic acids only, with 9,12,15–18:3 (varied from 1.95% to 6.66%), and 5,8,11,14–20:4 (from 0.28% to 5.36%) acids most abundant.

Rare fatty acids all-*cis* 5,9–16:2 (**1**), 5,9–18:2 (**2**), 5,11,14–20:3 (**3**), 5,11,14,17–20:4 (**4**), 7,13–22:2 (**5**), and 7,15–22:2 (**6**) (Fig. 3) have been identified in two slime

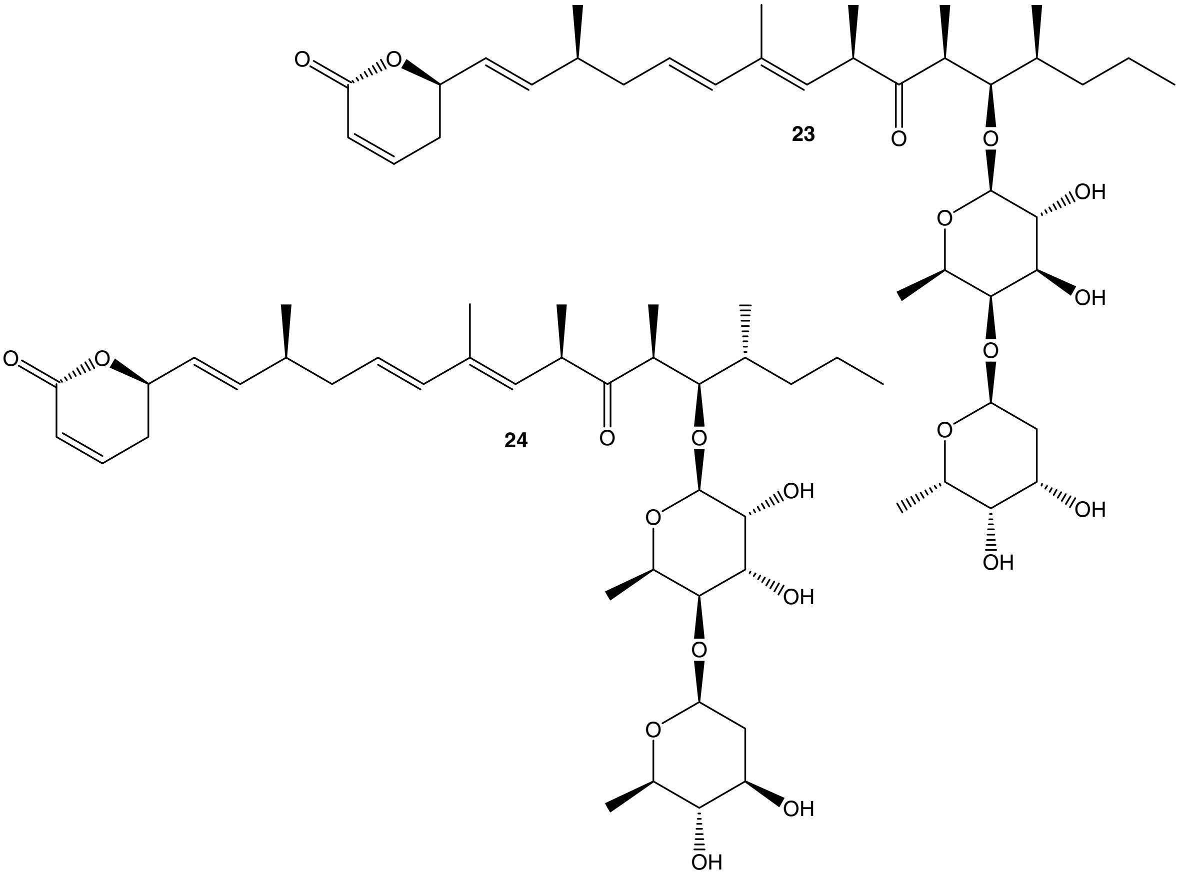

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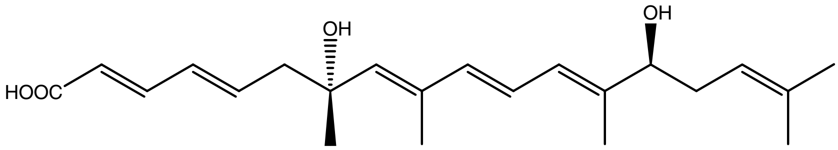
Fig. 8. Lipid's glycosides.



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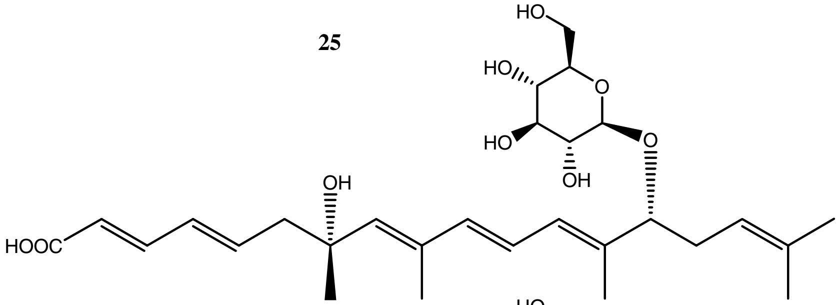

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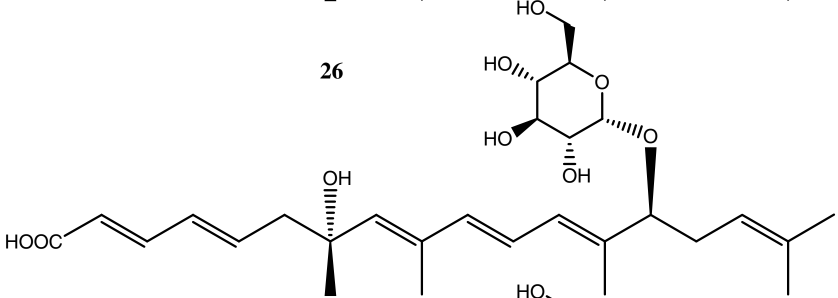

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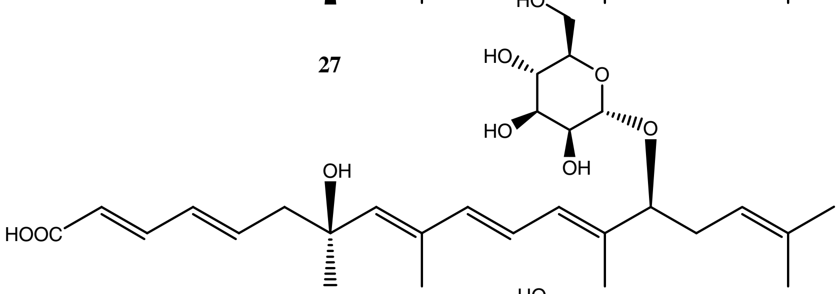

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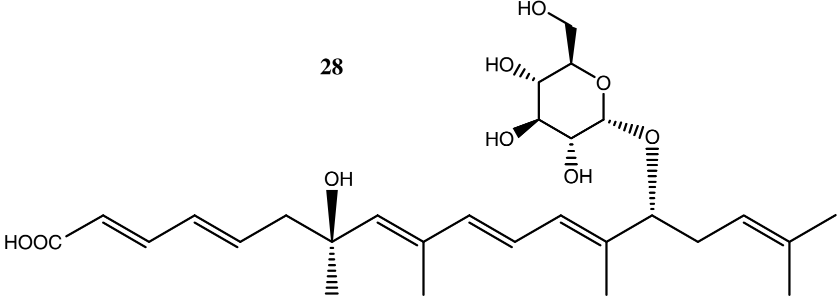

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Fig. 9. Multibranched polyunsaturated acids and their glycosides.

molds *T. favogiena* and *Trichia varia* only. Fatty acids with $\Delta^{5,9}$-position of two double bonds are mostly present in marine sponges (Carballeira and Shalabi, 1990; Carballeira and Maldonado, 1986), and in some marine invertebrates, e.g. sea anemone *Stoichactis helianthus* (Carballeira and Medina, 1994), or sea rod *Eunicea succinea* (Carballeira et al., 1997) but in myxomycetes they were identified for the first time. The antimicrobial activity of some $\Delta^{5,9}$-acids was also described (Carballeira et al., 1997).

A novel all-*cis*-5,9,12-heptadecatrienoic acid (**7**) (Fig. 4) was identified in the cellular slime mold *Polysphondylium pallidum* (Saito and Ochiai, 1996). This cellular slime mold was grown on *Escherichia coli*, and the fatty acid composition of total lipids obtained from vegetative amoebae and aggregation-competent cells was compared (Saito and Ochiai, 1998). Cyclopropane fatty acids isolated from vegetative cells included 17:0 (20.8%), 5–17:1 (**8**) (4.5%), 19:0 (17.7%), and 5–19:1 (**9**) (2.9%) acids and also straight-chain saturated (12:0, 14:0, 16:0, and 17:0) fatty acids. The cyclopropane fatty acids were derived from the ingested bacteria. Development of amoebae to aggregation-competent cells was accompanied by a substantial decrease in saturated cyclopropane fatty acids and a concomitant increase in unsaturated fatty acids and unsaturated cyclopropane fatty acids, mostly 5,9,12–18:3 (25.8%). The occurrence of Δ^5 desaturated cyclopropane fatty acids, namely, 9,10-methylene-5-hexadecenoic acid and 11,12-methylene-5-octadecenoic acid was reported. These fatty acids have not been reported previously in the related species *D. discoideum*, which also feeds on *E. coli* and contains Δ^5 desaturation moiety (Saito and Ochiai, 1998).

Bahiensol (**10**), a new monoalkyl-glycerol with antimicrobial activity against *Bacillus subtilis*, has been isolated from a cultured plasmodium of the myxomycete *Didymium bahiense* var. *bahiense* (Misono et al., 2003a). Two secondary hydroxyl groups were included in the C16 aliphatic chain, and one of the two secondary hydroxyl groups was shown to be located in C-3 position and the position of the other secondary hydroxyl group was implied to be between C-6 and C-13.

Three novel polyacetylene triglycerides, named lycogarides A–C (**11**–**13**) (Fig. 5), were isolated from the myxomycete *Lycogala epidendrum* (Hashimoto et al., 1994). Four other unusual new acylglycerols, lycogarides D–G (**14**–**17**), have also been isolated from the same slime mold (Buchanan et al., 1996).

A novel bioactive lipid, cyclic phosphatidic acid (**18**) (CPA, Fig. 6), was isolated from a true slime mold, *P. polycephalum*, and has now been detected in a wide range of organisms from slime molds to humans. It has a cyclic phosphate at the sn-2 and sn-3 positions of the glycerol carbons, which structure is absolutely necessary for its activities (Kobayashi et al., 2002). This substance showed specific biological functions, including antimitogenic regulation of the cell cycle, regulation of actin stress fiber formation and rearrangement, inhibition of cancer cell invasion and metastasis, regulation of differentiation and viability of neuronal cells, and mobilization of intracellular calcium. Although the structure of CPA is similar to that of lysophosphatidic acid (LPA), its biological activities are apparently distinct from those of LPA. The enzymatic formation of CPA, the antimitogenic regulation of the cell cycle, the

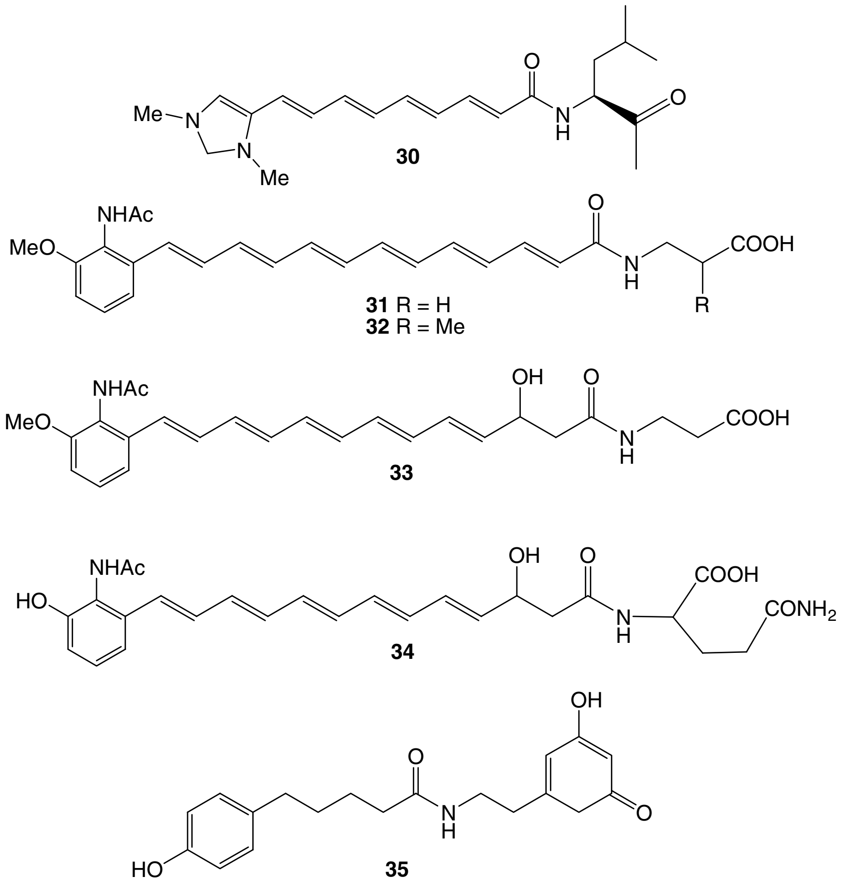


Fig. 10. Amides.

inhibition of cancer cell invasion and metastasis, and the neurotrophic effect of CPA have been reported (Kobayashi et al., 2002).

A natural pigment with a pyrone ring, ceratiopyrone (**19**) (Fig. 7), was found in plasmodia of *Ceratiomyxa fruticulosa* (Steglich, 1989). From the methanol extract of fruit bodies of three species of slime molds, three novel compounds, dictyopyrone A (**20**) and B (**21**) from *D. discoideum* and *D. rhizoposium* and dictyopyrone C (**22**) from *D. longosporum*, were isolated (Takaya et al., 2000). They possess a unique *R*-pyrone moiety with a side chain at the C-3 position. Their relative structures were elucidated by spectral analysis, and the absolute configuration was confirmed by asymmetric synthesis of **20**. Since these compounds were obtained from different species of *Dictyostelium* slime molds, they may be representative compounds common to this genus.

Recently, we found two novel polypropionate lactone glycosides, lycogalinosides A (**23**) and B (**24**) (Fig. 8), from the slime mold *L. epidendrum* (Řezanka and Dvořáková, 2003). Compounds **23** and **24** are unique in structure containing a 2-deoxy-α-L-fucopyranosyl-(1 $\rightarrow$ 4)-6-deoxy-β-D-gulopyranosyl unit and a β-D-olivopyranosyl-(1 $\rightarrow$ 4)-β-D-fucopyranosyl unit, respectively, and exhibit growth inhibitory activities against Gram-positive bacteria.

Chemical structures of five novel compounds, i.e. one multibranched polyunsaturated fatty acid (2*E*,4*E*,7*S*,8*E*,10*E*,12*E*,14*S*)-7,9,13,17-tetramethyl-7,14-dihydroxy-2,4,8,10,12,16-octadecahexaenoic acid, **25**) and its four glycosides **26**–**29** (Fig. 9) from seven different myxomycetes were described (Řezanka, 2002). The absolute configuration of both hydroxyl groups was determined. The glycosides contain glucose, mannose, and rhamnose. Three of them were identified in *Arcyria cinerea*, two in *Arcyria denudata*, and *Arcyria nutans*. *F. septica*, *L. epidendrum*, *P. polycephalum*, and *T. varia* contained one of the identified glycosides each.

3. Fatty acid amides and derivatives

Fatty acid amides were isolated from some slime mold species. They belong to the group of natural pigments and exhibit absorption in UV-A and UV-B areas.

A yellow optically active pigment, chrysophysarin A (**30**) (Fig. 10), was isolated from microplasmodia of

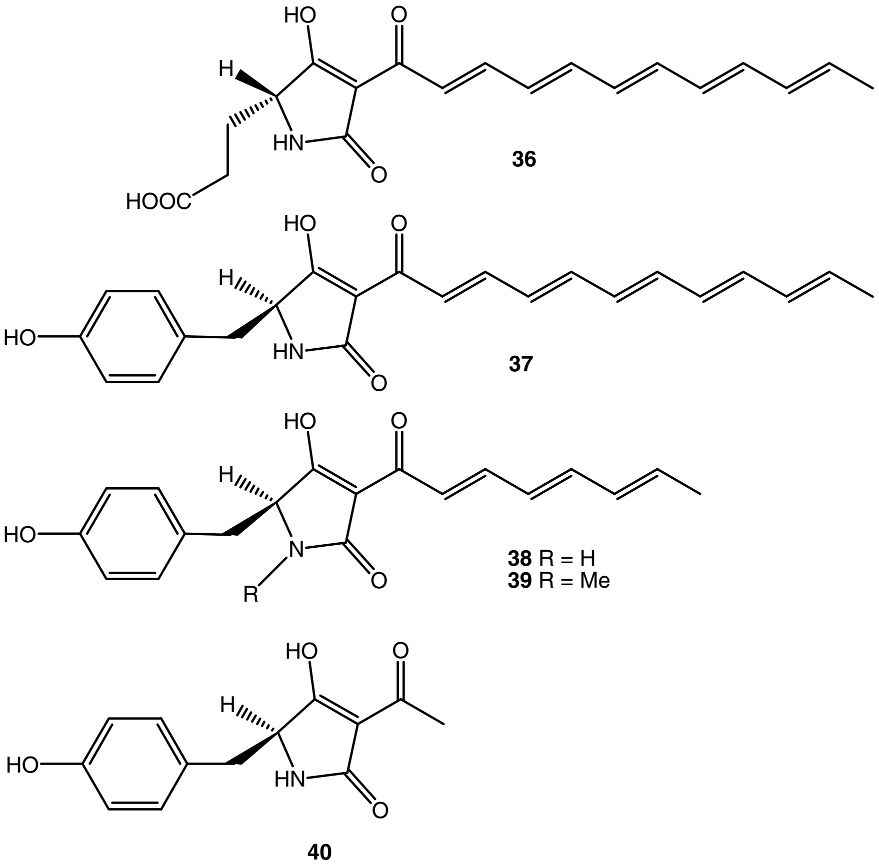


Fig. 11. Pyrrolinones.

the slime mold *P. polycephalum* (Eisenbarth and Steffan, 2000). The absolute configuration was assigned by the synthesis of *N*-(3,3-dimethylacryloyl) derivatives of (*S*)- and (*R*)-leucine and by comparison of the corresponding CD spectra. In the UV spectrum, the pigment exhibits absorption maxima (MeOH) at $\lambda_{max} = 262$ and 355 nm. The biosynthesis of the compound was elucidated by feeding labeled acetate to the plasmodia. The incorporation rate of 4.6% into carbon C-21, not only by feeding [$^{13}C_2$-2-D_3]Na acetate but also by feeding [2-^{13}C]Na acetate, shows that the methyl group C-21 originates from a fragmented acetate unit, whose carboxy group was presumably lost by decarboxylation. A similar procedure, but without fragmentation, is used to elongate the carbon chain by insertion of histidine for the formation of the polyene system: histidine is transformed into the corresponding α,β-unsaturated acid and connected by means of its carboxy group to three acetate units. Therefore, L-leucine, acetate, and histidine are proposed as biosynthetic building blocks for the biosynthesis of chrysophysarine A (**30**).

Physarigins A–C (**31–33**), three new yellow pigments, were been isolated from a cultured plasmodium of the myxomycete *Physarum rigidum* (Misono et al., 2003b). Physarigin A (**31**) and B (**32**) showed the same absorption at λ_{max} (MeOH) 403 and 426 nm, indicating the presence of a conjugated system. Physarigin C (**33**), a yellow amorphous solid, has absorption at λ_{max} (MeOH) 351, 368, and 390 nm.

A yellow pigment physarochrome A (**34**) was isolated from plasmodia of the slime mold *P. polycephalum* (Steffan et al., 1987). Its structure has been established as all-*trans*-*N*-[11-(2-acetylamino-3-hydroxyphenyl)-2,4,6,8, 10-undecapentaenoyl]-*S*-glutamine (**34**) on the basis of spectroscopic evidence and hydrogenation to a decahydro derivative. An unusual amid derivative with a pyrone ring, fuligopyrone (**35**), was found in plasmodia of *Fuligo septica* (Steglich, 1989).

A series of natural pigments with butenolide structure (**36–40**) (Fig. 11), were discovered in some myxomycete species. A yellow pigment fuligorubin A (**36**), exhibiting absorption maximum at 450 nm, was isolated from slime mold *F. septica* (Casser et al., 1987); and synthesis of this metabolite also was reported (Ley et al., 1988, 1992). Compounds **37–40** were isolated from the orange-yellow pigment of plasmodia *Leocarpus fragilis* (Steglich, 1989).

Physarorubinic acids A (**41**) and B (**42**) (Fig. 12), and also unusual tetramic acids, polycephalin B (**43**) and C (**44**) (all compounds with a strong absorption in the UV–visible spectra) were isolated from plasmodia of the slime mold *P. polycephalum* (Nowak and Steffan, 1998). The absolute configuration (Blumenthal et al., 2002), and the total synthesis of the polyenoyltetramic acid polycephalin C (**44**), was described (Longbottom et al., 2003).

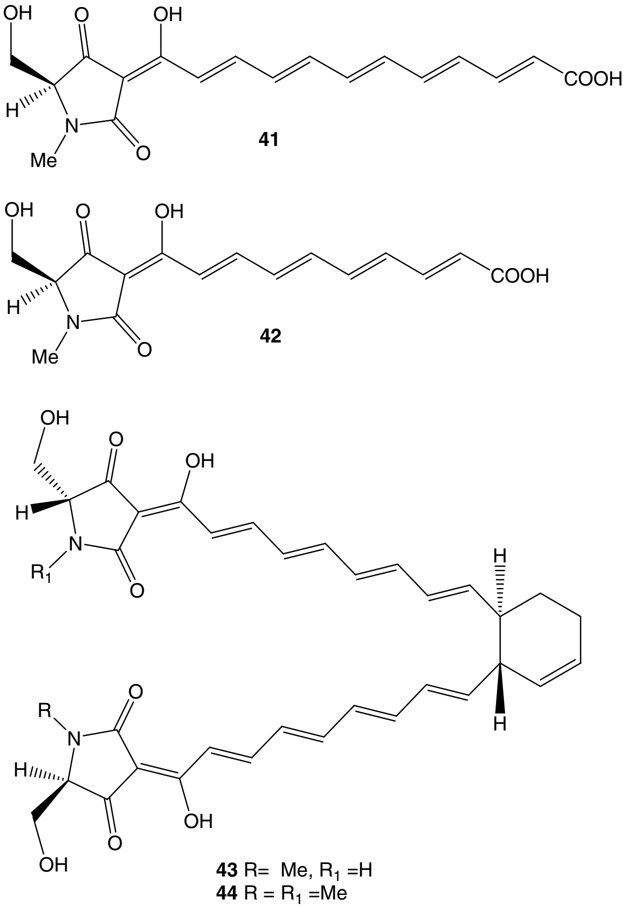
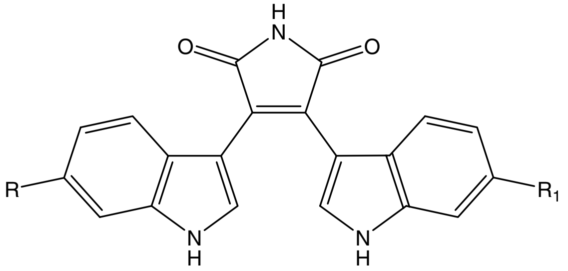


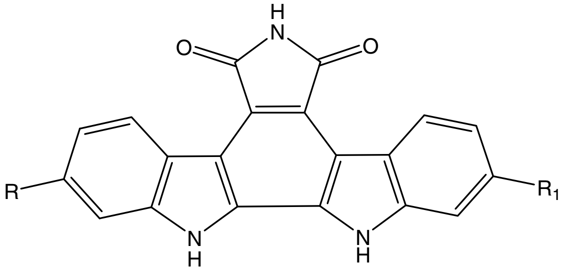
Fig. 12. Polyenoic derivatives of pyrrolidinediones.

4. Alkaloids

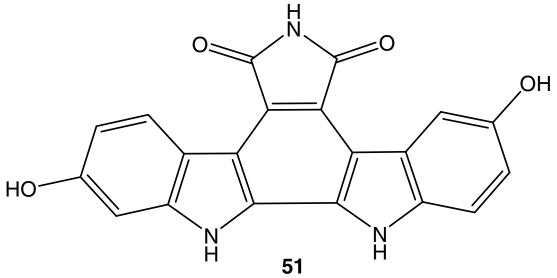
Red colored sporophores of *A. denudata* contain major pigments, named arcyriarubins A–C (**45–47**), respectively, and arcyriaflavins A–C (**48–50**), and D (**51**) (Fig. 13) (Steglich et al., 1980). The indole[2,3-*a*]carbazole alkaloid ring system is present in several biologically active molecules, such as the arcyriaflavins and related compounds (Steglich, 1989). This structurally rare class of compounds represents, together with the closely related arcyriarubins (**45–47**), new lead structures for the synthesis of biologically active substances. For example, arcyriaflavin derivatives have antimicrobial activity against *Bacillus cereus* (Pereira et al., 1996), antitumor activity against P388 leukemia cells (Pereira et al., 1996), and inhibit protein kinase A (PKA), protein kinase C (PKC) (Pereira et al., 1996; Trinks et al., 1994; Sancelme et al., 1994), topoisomerases I and II (Pereira et al., 1996) as well as tyrosine and serine kinases (Trinks et al., 1994). Arcyriaflavin analogues are currently being evaluated in human clinical trials as anticancer drugs (Sancelme et al., 1994). Arcyriarubins (**45–47**), isolated



45 R = R_1 = H
46 R = OH, R_1 = H
47 R = R_1 = OH



48 R = R_1 = H
49 R = OH, R_1 = H
50 R = R_1 = OH



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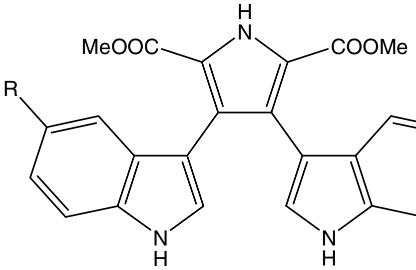
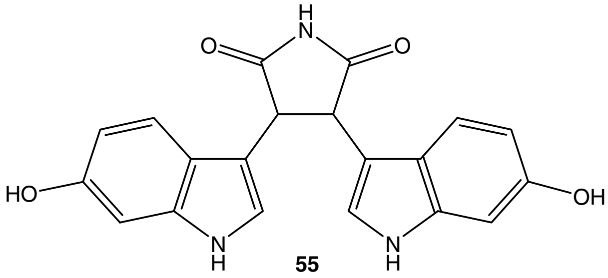


52 R = R_1 = H
53 R = OH, R_1 = H
54 R = R_1 = OH

Fig. 13. Indole alkaloids I.



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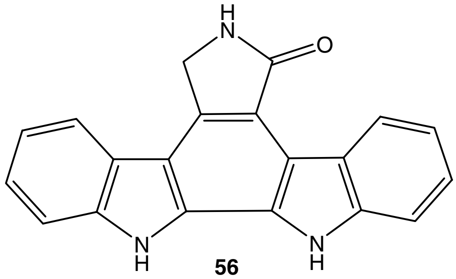

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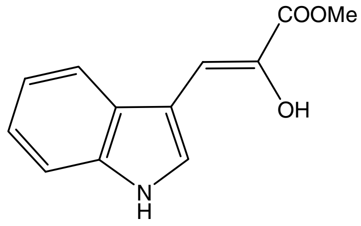

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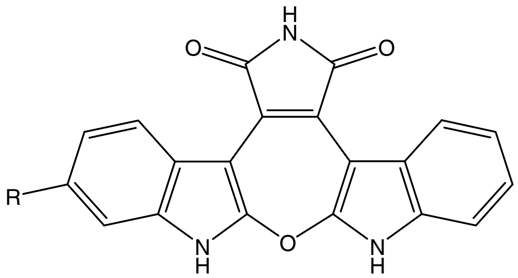
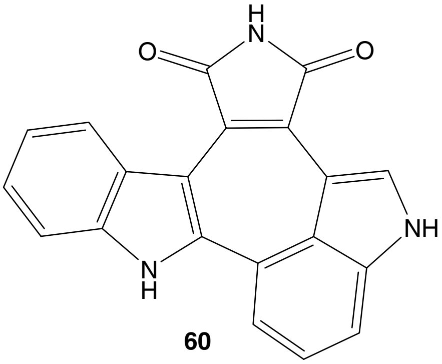


58 R = H
59 R = OH

Fig. 14. Indole alkaloids II.

from the fruiting bodies of the slime mold *A. denundata* (Steglich et al., 1980; Davis et al., 1992a,b; Toullec et al., 1991; Huang et al., 2003), and related compounds also show highly potent biological effects. Inhibition of protein kinases A and C and of protein tyrosine kinase (PTK) has been described (Steglich, 1989; Toullec et al., 1991; Lakatosh et al., 2002). These bisindolylimides and their derivatives are, in contrast to indolo[2,3-*a*] carbazoles, not bridged at their indole-2-positions and show different biological activies (Routier et al., 2002; Caballero et al., 2003; Lobo and Prabhakar, 2002; Slater et al., 2001). Therefore, they are also named secoindolocarbazoles (Link et al., 1995).

The 3,4-bis(indol-3-yl)pyrrole-2,5-dicarboxylic acid and derivatives **52** and **53** were isolated from *L. epidendrum* (Buchanan et al., 1996; Fröde et al., 1994). From the myxomycete *Arcyria ferruginea*, dihydroarcyriarubin C (**55**) (Fig. 14), a new bisindole alkaloid, was together with two known bisindoles, arcyriarubin C (**47**) and arcyriaflavin C (**50**). Compound **50** was also isolated from *Tubifera casparyi* together with arcyriaflavin B (**49**). Arcyriaflavin C (**50**) exhibited cell cycle inhibition effect at G1 and G2/M stage at 10 and 100 ng/ml, respectively (Nakatani et al., 2003). Arcyriaflavin C (**50**) also was found in *Metatrichia vesparium* (Kopanski et al., 1982).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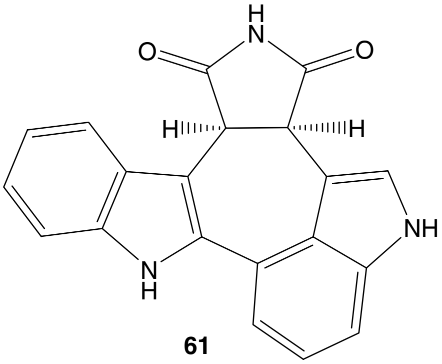
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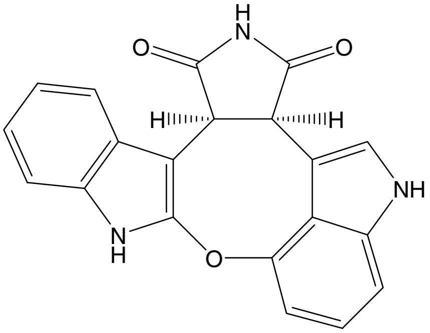
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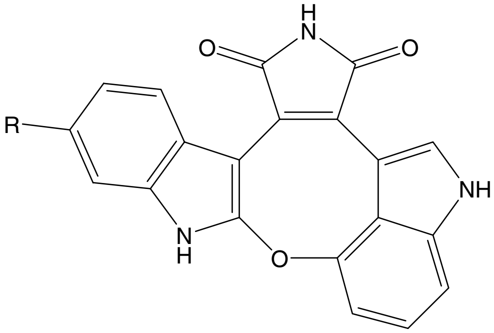
63 R = H
64 R = OH

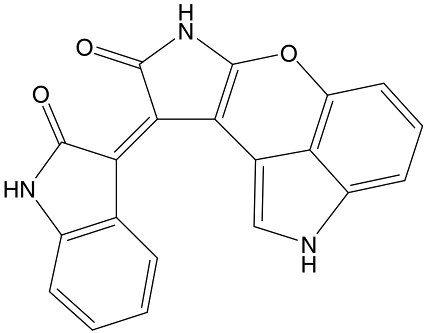
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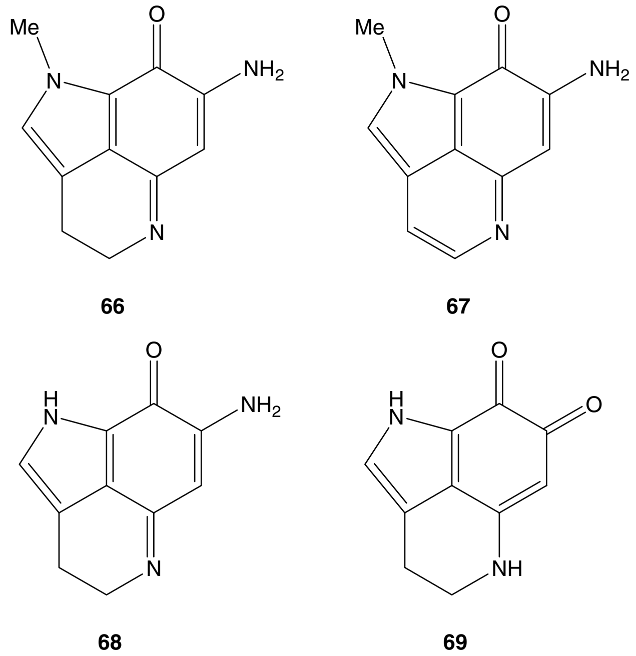
Fig. 15. Indole alkaloids III.

Staurosporinone (also known as K-252) (**56**) (Fig. 14) and (*Z*)-methyl-2-hydroxy-3-(1*H*-indol-3-yl)acrylate (**57**) were isolated from *L. epidendrum* (Fröde et al., 1994). K-252 was previously found in a *Nocardiopsis* strain (Nakanishi et al., 1986). The red pigments arcyroxepins A (**58**) and B (**59**) were produced by *A. denudata* (Steglich, 1989).

A series of alkaloid-like pigments, arcyriacyanin A (**60**), dihydroarcyriacyanin A (**61**), dihydroarcyrioxocin A (**62**), arcyroxocins A (**63**) and B (**64**), and arcyroxindole A **65** (Fig. 15), were isolated from the red plasmodia of *A. denudata* (Steglich, 1989). Synthesis of **63** was reported by Mayer et al. (1996).

Pyrroloiminoquinone alkaloids based on 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*] quinoline ring have attracted considerable attention due to their unique structures and potentially valuable biological activities (Ding et al., 1999). Makaluvamines exhibit in vitro cytotoxicity against the human colon tumor cell-line HCT 116, show differential toxicity against the topoisomerase II sensitive CHO cell-line xrs, and inhibit topoisomerase II in vitro (Radisky et al., 1993; Barrows et al., 1993). Makaluvamine A and C exhibit in vivo antitumor activity against the human ovarian carcinoma Ovcar 3 implanted in athymic mice (Radisky et al., 1993; Barrows et al., 1993; Matsumoto et al., 1999).

Two pyrroloiminoquinone pigments, named makaluvamine A (**66**) and B (**67**) (Fig. 16), were isolated from the fruiting bodies of *D. bahiense* (Ishibashi et al., 2001) and from the marine sponge *Zyzzya* (Radisky et al., 1993), respectively. A green pigment, makaluvamine I (**68**), and also damirone C (**69**) were produced by slime mold *Didymium iridis* (Nakatani et al., 2005b). Isolation of makaluvamine I (**68**) and damirone C (**69**) has previously been reported from a marine sponge *Zyzzya fuliginosa* or *Histodermella* sp. (Schmidt et al., 1995; Carney and Scheuer, 1993). Other related pyrroloiminoquinone pigments, makaluvamines A–N and damirones A–B, were also isolated from marine sponges (Radisky et al., 1993; Venables et al., 1997; Izawa et al., 1994). Total syntheses of makaluvamines A, B, C, and D have been reported by Izawa et al. (1994).



66 **67** **68** **69**

Fig. 16. Pyrroloiminoquinones.

Cycloanthranilylproline (**70**) and its derivatives **71**–**74** (Fig. 17) were isolated from field-collected fruit-bodies of a myxomycete *Fuligo candida*. Compound **73**, contained in the aqueous fraction of this myxomycete, was unstable and quite susceptible to decarboxylation to yield compound **71**, which was a major constituent of the EtOAc-soluble fraction of this extract (Nakatani et al., 2004).

5. Amino acids and peptides

Amino acid composition of three slime mold species, *Physarum flavicomun* variety 1, *P. polycephalum*, and *P. rigidum* has been studied (Table 5) (Simon and Henney, 1970). Organisms were grown on a synthetic liquid medium containing protein hydrolysate. The carbohydrate portions composed of the neutral sugar – galactose, and the proteins contained similar proportions of common amino acids.

The changes in the free amino acid levels were determined during spore germination in *D. discoideum* and cyst germination in *P. pallidum* (Ennis, 1981). Spores and cysts contained high levels of alanine, aspartic acid, glutamic acid, glycine, lysine, serine, and threonine, but their concentrations decreased greatly during germination. The same changes were observed in a mutant of *D. discoideum* which is defective in germination and in the wild type in which protein synthesis was inhibited. Spores and cysts do not contain free tryptophane and cystine.

Melleumin A (**75**), a novel peptide lactone, and its *seco* acid methyl ester, melleumin B (**76**) (Fig. 18), were isolated from the cultured plasmodium of the myxomycete *Physarum melleum* (Nakatani et al., 2005a). Melleumin A (**75**) consisted of four residues (*p*-methoxybenzoic acid, L-threonine, glycine, and an unusual amino acid, a tyrosine-attached acetic acid).

6. Naphthoquinone pigments

Natural naphthoquinone derivatives are encountered in some microorganisms, fungi, and in the

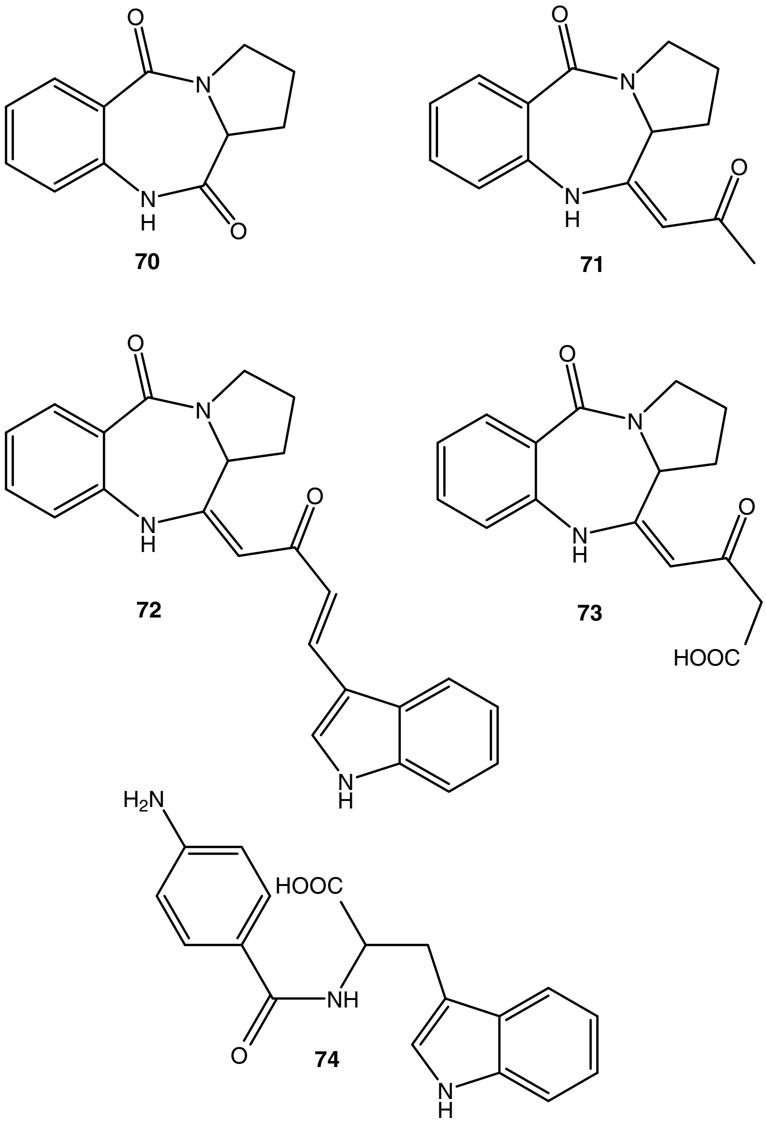


Fig. 17. Alkaloids.

leaves, seeds, and wood of higher plants. They can be recovered as yellow, orange, red, or purple crystals. Color is due to the 1,4-naphthoquinone chromogen and shifted by introduction of further amino and hydroxyl groups into the quinonoid ring (i.e. positions 2 and 3), into the benzenoid ring (more particularly positions 5 and 8), or into both rings (Grolig and Wagner, 2002).

Several naphthoquinone pigments have been found in myxomycete species. The sporophores of *Trichia* species, *Metatrichia floriformis*, and *M. vesparium* produced trichione (**77**) and homotrichione (**78**) (Fig. 19) (Kopanski et al., 1982, 1987). The lindbladione (**79**) and lindbladiapyrone (**80**) were isolated from plasmodia of *Lindbladia tubulina* after treatment with mineral acids (Steglich, 1989). Three new naphthoquinone pigments, 6,7-dimethoxydihydrolindbladione (**81**), dihydrolindbladione (**82**), and 6-methoxydihydro-lindbladione (**83**), were isolated from a myxomycete *L. tubulina* (Ishikawa et al., 2002; Misono et al., 2003c). and their structures were elucidated by spectrometry. Compound **83** exhibited a reversal effect on multidrug resistance. Lindbladione (**79**), the major pigment of this myxomycete, was also isolated from *Cribraria intricata*. Cribrarione A (**84**), a new dihydrofuranonaphthoquinone pigment with antimicrobial activity against *B. subtilis*, was isolated from the myxomycete *Cribraria purpurea* (Naoe et al., 2003). Vesparione (**85**) was isolated from *M. vesparium* (Steffan et al., 1987), a more complex pigment TF-1 (**86**), and simple 2,3,5-trihydroxynaphthoquinone (**87**) were isolated from *Trichia floriformis* (Steglich, 1989).

Table 5
Amino acid composition of some slime mold from *P. flavicomum*, *P. polycephalum* and *P. rigidum*

AA	Mol/100 mol of AA
D	10.2
T	7.0
S	6.9
E	8.0
P	5.1
G	8.4
A	7.8
C	2.3
V	6.1
M	1.7
I	5.2
L	7.6
Y	3.2
F	4.6
K	7.2
H	3.8
R	4.9

7. Aromatic compounds

Two novel aromatic compounds named dictyomedin A (**88**) and B (**89**) (Fig. 20) were isolated from the methanol extract of fruit body of *Dictyostelium medium* (Takaya et al., 2001). Fulicineroside (**90**), glycosidic dibenzofuran metabolite, was isolated from the slime mold *Fuligo cinerea* collected in the Czech Republic (Řezanka et al., 2005). The compound was highly active against Gram-positive bacteria and crown gall tumors.

8. Carbohydrate compounds

Two novel acylated amino sugars, dictyoglucosamine A **91** from *Dictyostelium purpureum* and dictyoglucosamine B (**92**) (Fig. 21) from *D. discoideum*, were isolated (Kikuchi et al., 2002). Biological evaluation of **91** and **92** showed that they induce neuronal differentiation of rat pheochromocytoma (PC-12) cells. Also two novel amino sugar analogues, furanodictine A (**93**) and B (**94**), were found in *D. discoideum* (Kikuchi et al., 2001). They are the first 3,6-anhydrosugars isolated from natural sources. These furanodictines potently induce neuronal differentiation of rat pheochromocytoma (PC-12) cells. Their relative structures were elucidated by spectral analysis, and their absolute configurations were confirmed by asymmetric syntheses. A novel and efficient strategy was described for the asymmetric synthesis of furanodictine A (**93**) (Yoda et al., 2004).

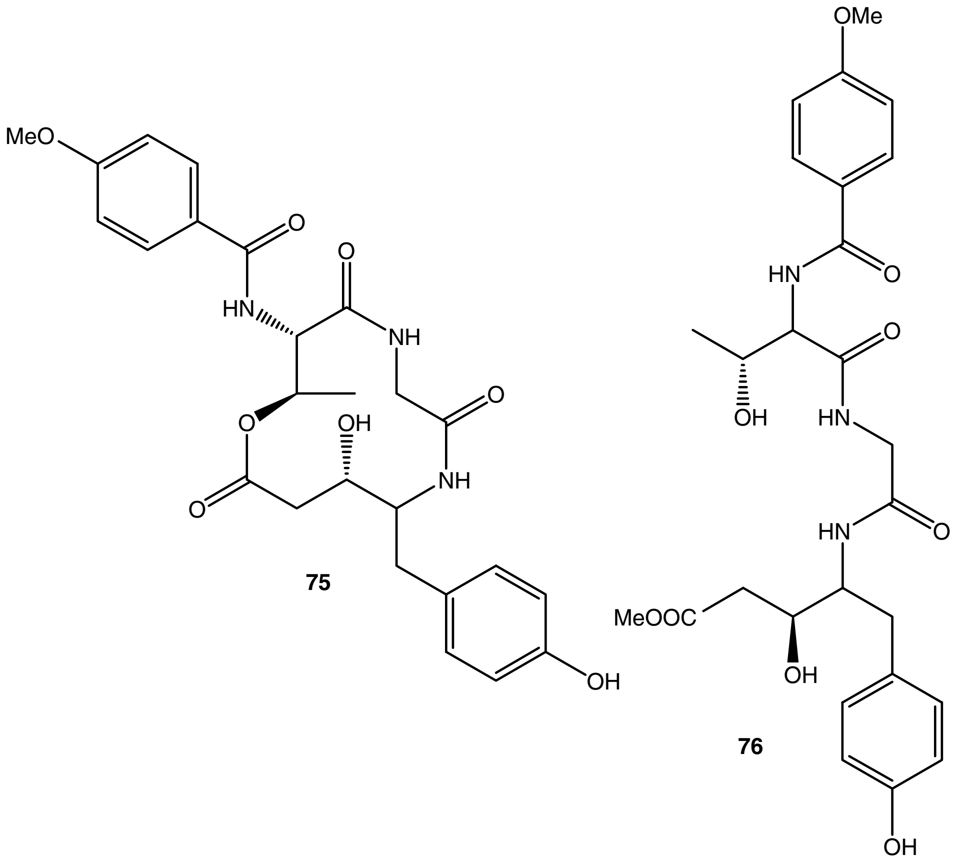


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Fig. 18. Peptides.

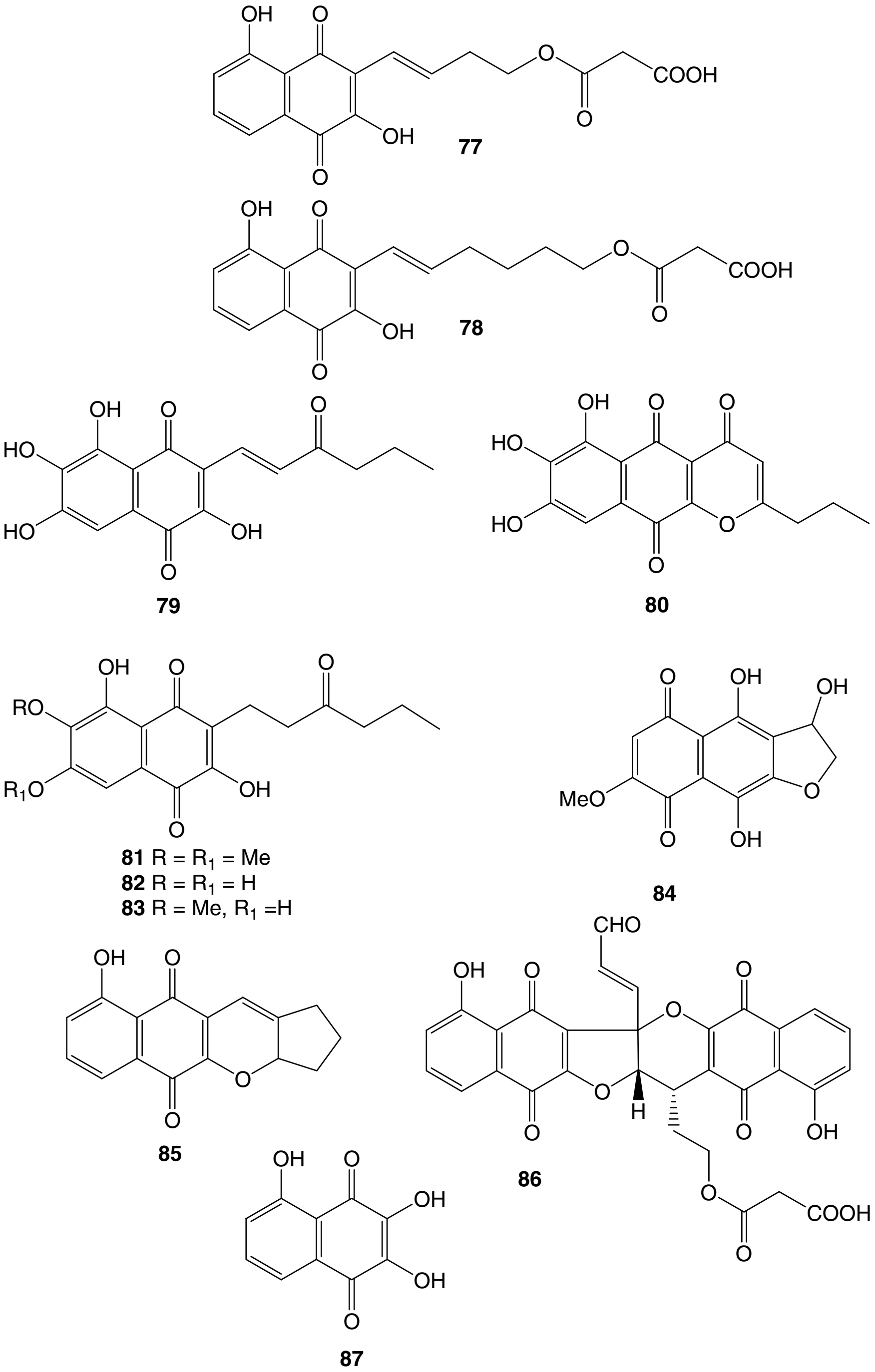
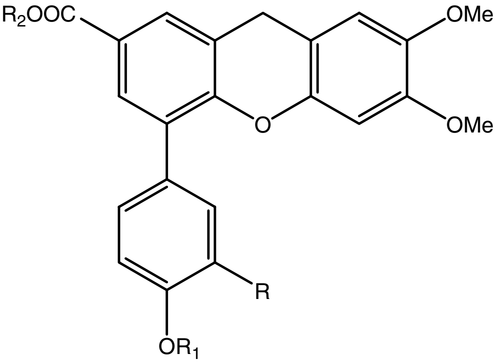


Fig. 19. Naphthoquinone pigments.

A sulfated and phosphorylated β-D-galactan was isolated from the nuclei of the slime mold *P. polycephalum* (Farr and Horisberger, 1978). The polysaccharide was isolated by cesium chloride gradients during the preparation of ribosomal DNA and further purified. The purified galactan contained 89% galactose, 2.5% phosphate, and 9.6% sulfate groups and had an average degree of polymerization of 560. Periodate degradation and permethylation studies indicated the presence of mainly (1 → 4)-, but also of (1 → 3)-, and (1 → 6)-linked galactose units with one branch every 13 units. These results suggested that the intracellular galactan, apart from its higher sulfate content, is similar to the extracellular polysaccharide produced by *P. polycephalum*.

A new hemagglutinin was isolated from the plasmodium of *P. polycephalum* (Yokota and Nitta, 1996). This



88 R = OMe, $R_1 = R_2 = H$
89 $R = R_1 = R_2 = H$

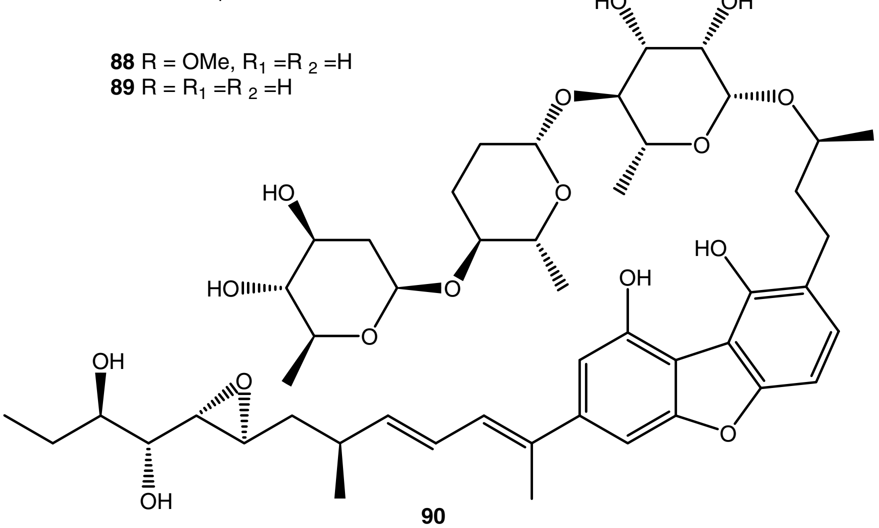


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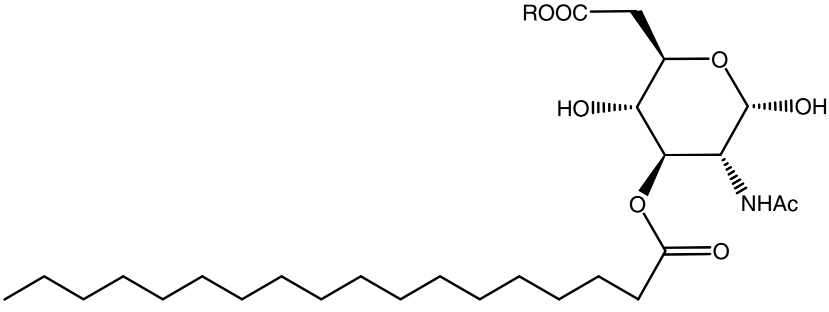
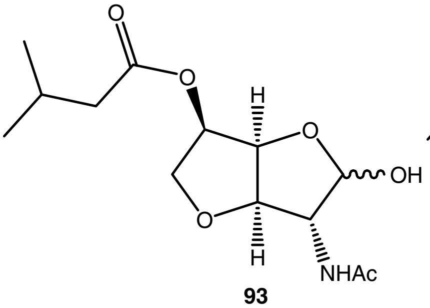
Fig. 20. Aromatic compounds.



91 R = Et
92 R = *t*-Bu



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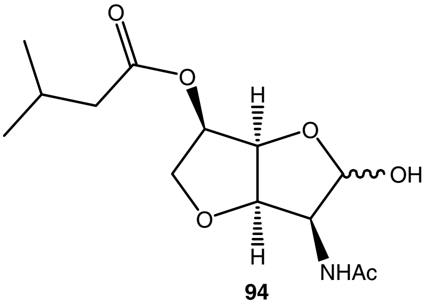

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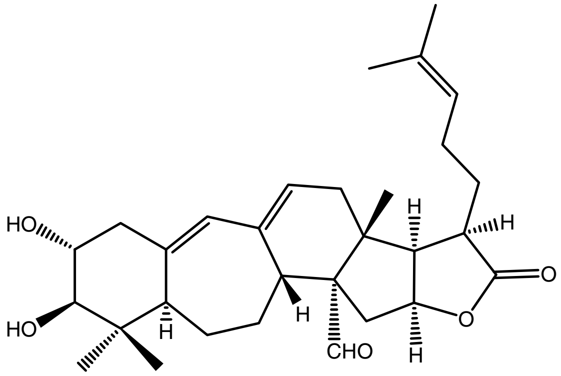
Fig. 21. Carbohydrate compounds.

hemagglutinin, named physarumin, was purified 1000-fold over crude extracts. Physarumin agglutinated rabbit, guinea pig, horse and human erythrocytes. Physarumin-induced hemagglutination was inhibited by fetuin and α-(1)-acid glycoprotein, but not by commercially available mono- and disaccharides. Hemagglutinating activity was blocked by EDTA and was restored by adding Ca^{2+} but not by Mg^{2+}.

9. Terpenoid compounds

Tubiferal A (**95**) (Fig. 22), a novel rearranged triterpenoid lactone, was isolated from field-collected fruit bodies of the myxomycete, *Tubifera dimorphotheca* (Kamata et al., 2004). Tubiferal A possesses a 9,10-secocycloartan-16,21-olide skeleton, and this new compound exhibited a reversal effect of vincristine (VCR) resistance (more than 4-fold) against VCR-resistant KB cell lines. Tubiferal B **96**, corresponding to the *seco* acid of **95,** was also isolated but showed no comparable activity.



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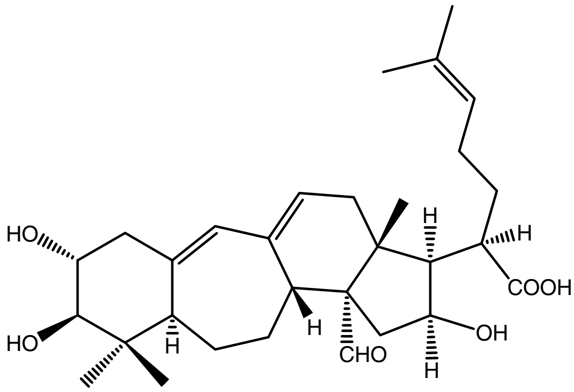

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Fig. 22. Terpenoid compounds.

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