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Review

Microbiological Aspects of Unique, Rare, and Unusual Fatty Acids Derived from Natural Amides and Their Pharmacological Profile

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Abstract: In the proposed review, the pharmacological profile of unique, rare, and unusual fatty acids derived from natural amides is considered. These amides are produced by various microorganisms, lichens, and fungi. The biological activity of some natural fatty acid amides has been determined by their isolation from natural sources, but the biological activity of fatty acids has not been practically studied. According to QSAR data, the biological activity of fatty acids is shown, which demonstrated strong antifungal, antibacterial, antiviral, antineoplastic, anti-inflammatory activities. Moreover, some fatty acids have shown rare activities such as antidiabetic, anti-infective, anti-eczematic, antimutagenic, and anti-psoriatic activities. For some fatty acids that have pronounced biological properties, 3D graphs are shown that show a graphical representation of unique activities. These data are undoubtedly of both theoretical and practical interest for chemists, pharmacologists, as well as for the pharmaceutical industry, which is engaged in the synthesis of biologically active drugs.

Keywords: fatty acids; bacteria; fungal endophytes; fungi; lichens; amides

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1. Introduction

The amide bond is one of the most prevalent and widespread linkages in nature [1]. Natural fatty acid amides (R-COO-NR_1R_2) have many potential pharmacological uses because they have different biological activities or enzyme inhibitors [2–4]. Fatty acid amides are a diverse family of underappreciated biologically active lipids [1–6].

This article is a review of rare and unusual fatty acids (FA) derived from naturally occurring amides that are produced by fungal endophytes, lichenized ascomycetes, basidiomycetes, actinomycetes, and related microorganisms. The natural compounds presented in this review are of great scientific interest, and many of them demonstrate a wide range of biological activities and have strong antimicrobial, antifungal, phototoxic, HIV-inhibiting, antitumor, immunosuppressive, and other pharmacologically useful properties [7–13], which is of great interest, especially for medicinal chemistry, pharmacology, and the pharmaceutical industry [14–17]. This review is devoted to the biological activity of fatty acids included in amides.

2. Fatty Acids Derived from Microorganisms and Fungi

Two polycyclopropane FA amides—U-106305 and FR-900848 (1, structure **FA** see Figure 1)—were isolated from microbiological sources. Thus, antibiotic U-106305 was produced by Actinomycete *Streptomyces* sp. [18], and *Streptoverticillium fervens* (syn: *Streptomyces fervens*) produced antibiotic, FR-900848, which has strong antifungal activity against filamentous fungi: *Aspergillus niger*, *Mucor rouxianus*, *Aureobasidium pullulans*, *Penicillium chrysogenum*, *Trichophyton metagrophytes*, *T. astervides*, *T. rubrum*, *Fusarium oxysporum*, and *Sclerotinia arachidis* [19].

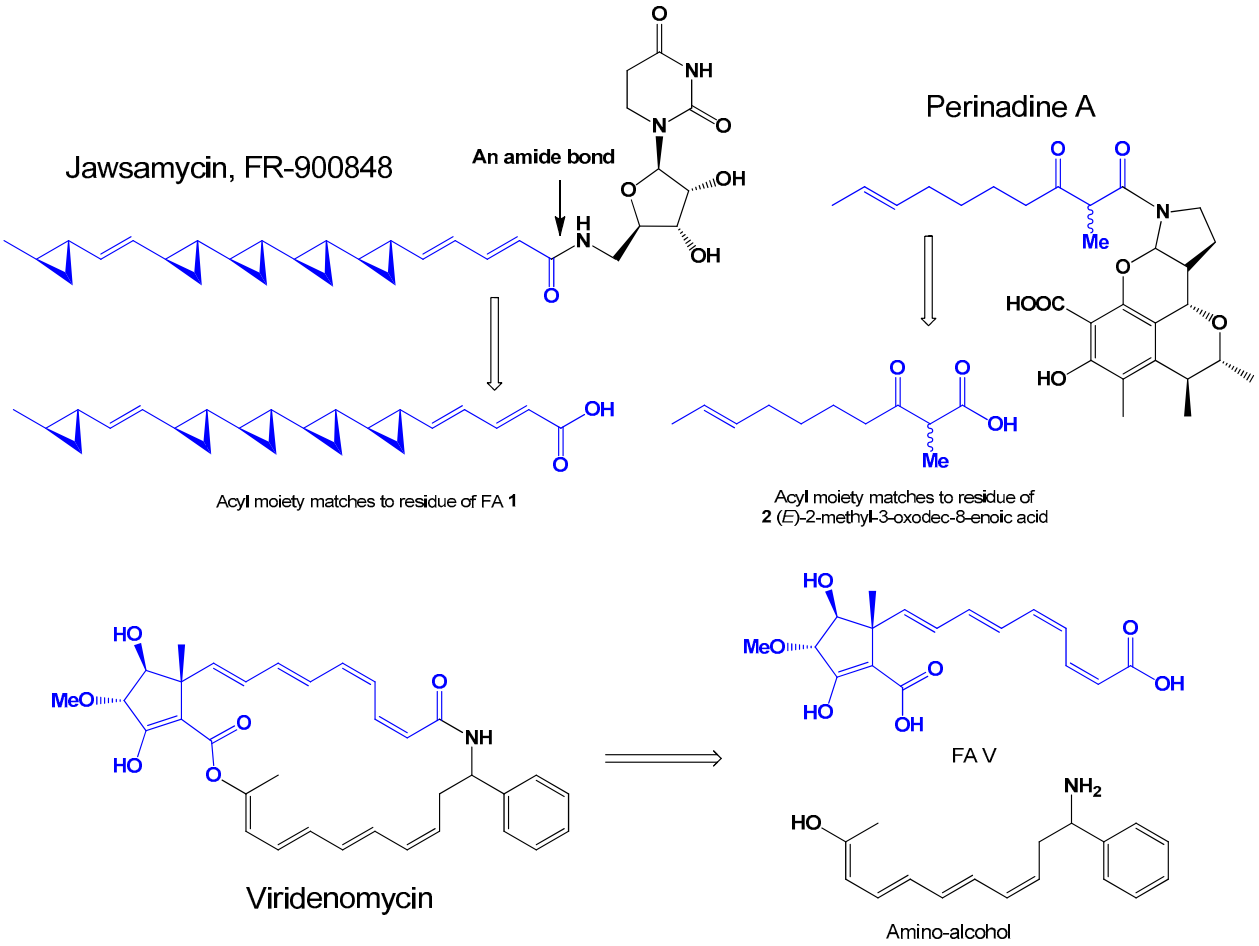


Figure 1. Examples of FA amides derived from Actinomycetes: *Streptomyces* and *Penicillium*.

Perinadine A (for structure, see Figure 1), a tetracyclic alkaloid isolated from from marine-derived fungus *Penicillium citrinum* (see Figure 2), contains FA (2). Perinadine A demonstrated insignificant cytotoxicity against murine leukemia L1210 cells, and antibacterial activity against *Micrococcus luteus* and *Bacilius subtilis* [20]. The 3D graph that shows the predicted and calculated antifungal, antiviral, and antineoplastic activity of FR-900848 and FA (**1**) is shown in Figure 3. FA (**2**) was found in scalusamide A, and scalusamide B and C contain a simlly FA (**3**, for structure see Figure 4) and (**4**), respectively. The fungus *Penicillium citrinum* produces scalusamides that have been isolated from the broth during mycelium cultivation [21]. Two epimeric alkaloids, namely tumonoic acids K (with (*S*,*E*)-2-methyl-3-oxodec-8-enoic acid (5) and L (with (*R*,*E*)-2-methyl-3-oxodec-8-enoic acid (6), were isolated from the marine-derived fungus *Penicillium citrinum* and showed cytotoxic activity against A-375 cell lines [22].

Antibiotic viridenomycin (for structure, see Figure 1) with fatty acid (**FA V**) was isolated from the culture broth of *Streptomyces viridochromogenes* strain No T-24146 and shows strong activity against *Trichomonas vaginalis* and gram-positive bacteria [23].

Figure 1 shows samples of natural FA amides isolated from actinomycetes *Streptomyces* and *Penicillium* and shows fatty acid amide bonds. Table 1 demonstrates the biological activity of both whole molecules of FA amides.

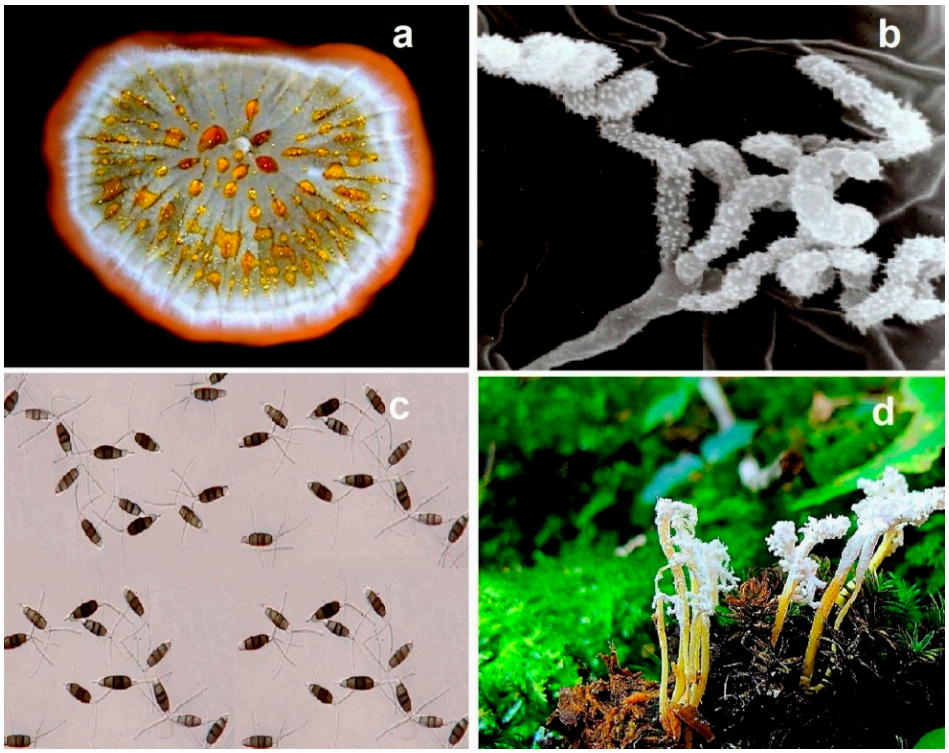


Figure 2. Examples of some fungal endophytes and fungi that synthesize the FA amides presented in this article. See text for details on their metabolites. In the pictures: (**a**)—*Penicillium citrinum*, (**b**)—*Streptomyces viridochromogenes*, (**c**)—*Pestalotiopsis theae*, and (**d**)—*Isaria tenuipes*. Pictures of fungal endophytes, lichenized ascomycetes, and fungi are from sites that allow the use of pictures for non-commercial use. In addition, all pictures are adapted by the author.

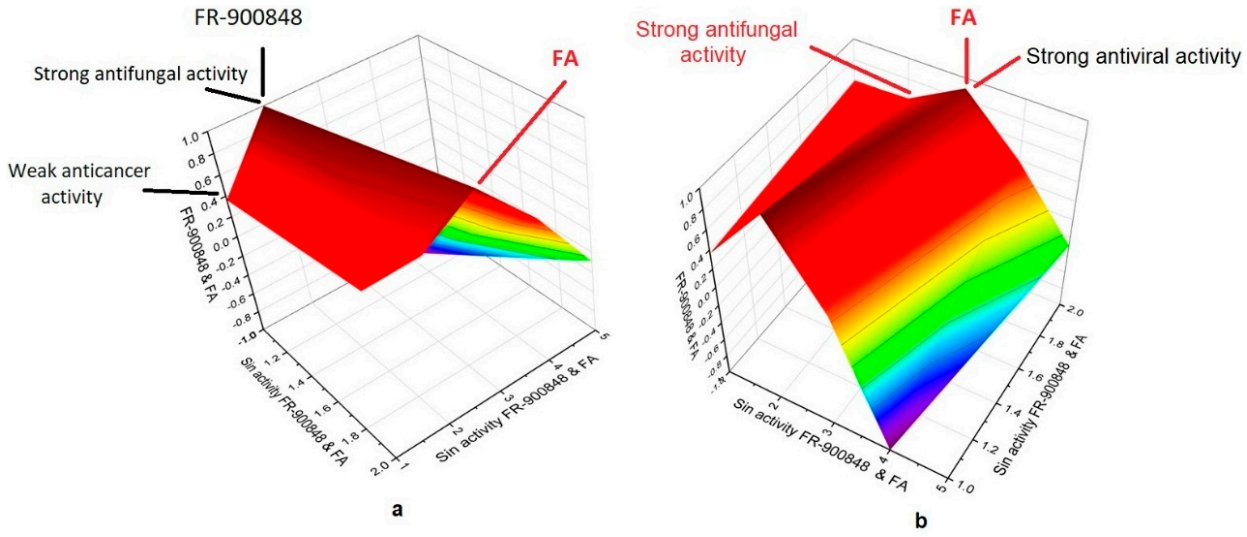


Figure 3. The 3D graph ((**a**), X and (**b**), Y views) shows the predicted and calculated antifungal, antiviral, and antineoplastic activities of FR-900848 and FA (**1**) showing the highest degree of confidence. The presented 3D graph demonstrates the comparative characteristics of the biological activities and the pharmacological profile of the individual fragments of the pseudopeptide referred to as FR-900848. In particular, the red zone of the 3D graph indicates the strong biological properties of both FR-900848 and its fatty acid. To build 3D graphs of the biological activity of fatty acids from natural amides, a proprietary computer program OriginPro 2021 was used, into which data were entered from another computer program PASS, which calculates the degree of reliability of biological activity.

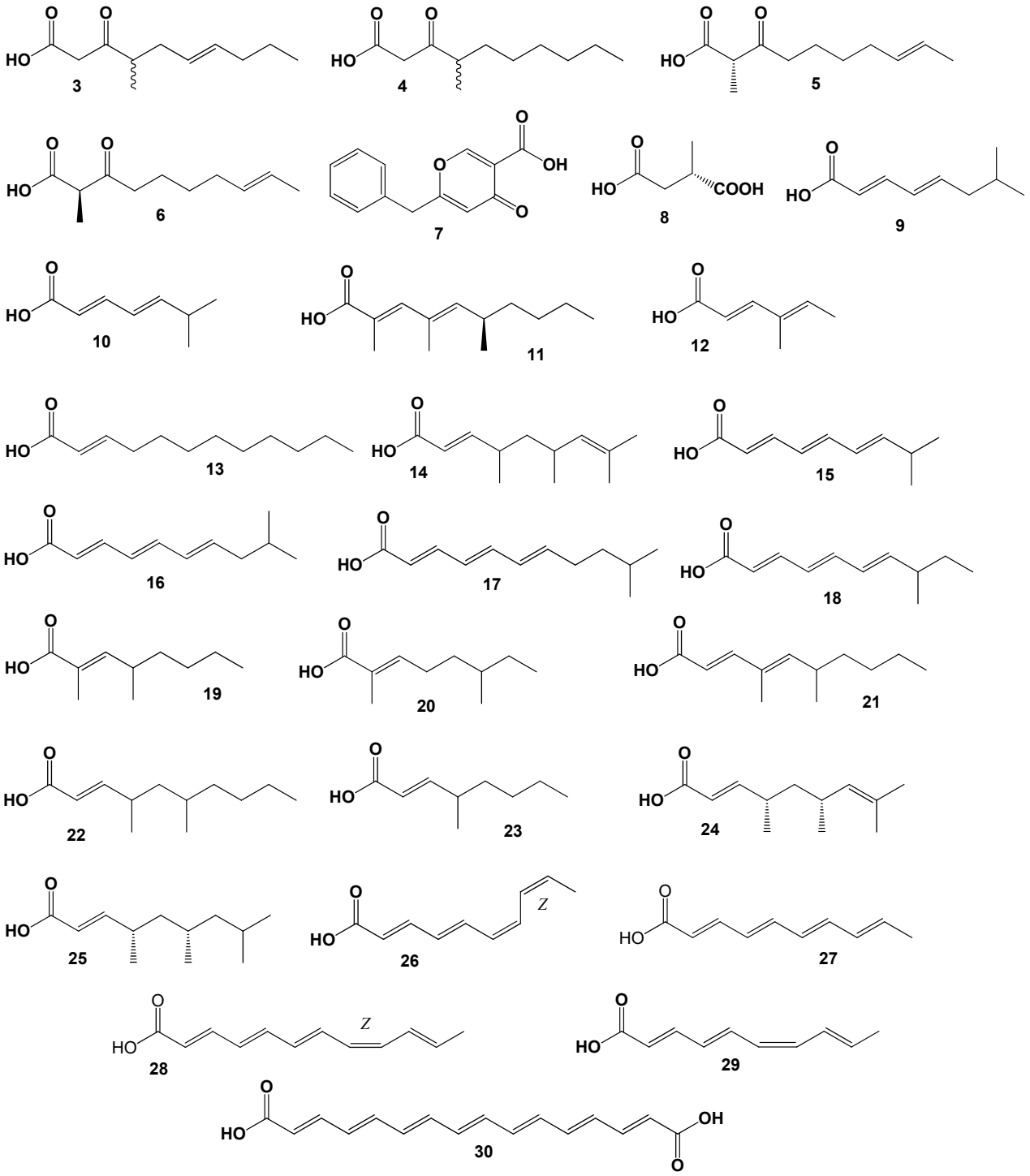


Figure 4. Rare and unusual FA derived from marine and soil microorganisms.

A unique nucleoside polycyclopropane antibiotic named FR-900848 is known to exhibit strong antifungal activity as shown in numerous experimental studies [24–26]. The software PASS has also shown that this antibiotic exhibits strong antifungal activity with 92% confidence (see Table 1). Another interesting property of this antibiotic is the anticancer activity, which was also found in experimental work [27–29], and PASS confirms these data. However, unique (2*E*,4*E*)-5-((1*R*,1′*R*,1″*R*,1‴*R*,2*S*,2′*R*,2″*R*,2‴*S*)-2‴-((*E*)-2-((1*R*,2*R*)-2-methylcyclopropyl)vinyl)-[1,1′:2′,1″:2″,1‴-quartercyclopropan]-2-yl)penta-2,4-dienoic acid (1) exhibits antiviral, antifungal, and anti-inflammatory properties to a greater extent.

Table 1. Pharmacological profile of some amides and their FA derived from microorganisms.

Amides and Their FA	**Predicted Biological Activity, Pa ***
FR-900848	Antifungal (0.924); Antineoplastic (0.831); Antibacterial (0.782) Antineoplastic (lymphocytic leukemia) (0.677)
1 FA	Antiviral (Arbovirus) (0.874); Anti-inflammatory (0.857); Antifungal (0.836) Antiviral (Picornavirus) (0.735); Alzheimer's disease treatment (0.726)
Perinadine A	Antineoplastic (0.926); Antifungal (0.709); Antibacterial (0.626)
2 FA	Preneoplastic conditions treatment (0.898); Antiviral (Arbovirus) (0.706); Antifungal (0.702); Antineoplastic (0.685); Antibacterial (0.568)
Viridenomycin	Antineoplastic (0.872); Antineoplastic (sarcoma) (0.766); Antibacterial (0.733) Prostate disorders treatment (0.672); Antifungal (0.528)
FA V	Antineoplastic (0.859); Antiviral (Arbovirus) (0.774); Cytoprotectant (0.744) Antiparasitic (0.724); Antibacterial (0.655); Antiviral (Picornavirus) (0.636) Antifungal (0.635); Preneoplastic conditions treatment (0.532)
Amino-alcohol	Antiviral (Arbovirus) (0.875); Leukopoiesis stimulant (0.648); Anti-inflammatory (0.574) Cytoprotectant (0.526); Preneoplastic conditions treatment (0.522)

* Only activities with Pa > 0.5 are shown.

Another pseudopeptide named perinadine A, which is synthesized by marine-derived fungus *Penicillium citrinum* (see Figure 2), showed strong cytotoxicity against murine leukemia L1210 cells, and these data are confirmed by PASS. The (*E*)-2-methyl-3-oxodec-8-enoic acid (2) of this pseudopeptide also shows antineoplastic activity.

Viridenomycin, which also belongs to the class of amides, is represented by an acid (FA V) and an amino alcohol, demonstrates antineoplastic activity against sarcoma as well as its FA, although the amino alcohol shows antiviral activity against *Arbovirus* (data are shown in Table 1).

The phytopathogenic fungus *Pestalotiopsis theae*, which was isolated from branches of Camellia sinensis, afforded amides, pestalaminde A, which contain unusual 6-benzyl-4-oxo-4H-pyran-3-carboxylic acid (7), and both pestalamindes, A and B contain (*S*)-2-methylsuccinic acid (8) [30]. Pestalaminde B inhibited HIV-1 replication in C8166 cells and exhibited potent antifungal activity against *A. fumigatus*.

A marine-derived *Streptomyces* sp. CNQ-085 produces antitumor antibiotics designated as daryamides A, B, and C [31]. Both daryamides contain (2*E*,4*E*)-7-methylocta-2,4-dienoic acid (9), and daryamide C contains (2*E*,4*E*)-6-methylhepta-2,4-dienoic acid (10).

The chlorine containing manumycin derivatives named chinikomycins A and B have been found in extracts of *Streptomyces* sp. M045, which is obtained from sediment (Jiaozhou Bay, China). Both compounds displayed anti-tumour activity against several human cancer cell lines, and these metabolites contain (*R*,2*E*,4*E*)-2,4,6-trimethyldeca-2,4-dienoic acid (**11**) [32].

Jomthonic acids A, B, and C were found in the culture fluid of actinomycetes of the genus *Streptomyces*, and only jomthonic acid A induced the differentiation of preadipocytes into mature adipocytes [33]. (2*E*,4*E*)-4-methylhexa-2,4-dienoic acid (**12**) was found in jomthonic acid A and C.

Spirocyclic and bicyclic hemiacetals such as isariotins E, F, and TK-57-164A were detected in lipid extracts in the entomopathogenic fungus *Isaria tenuipes* BCC 12625. It is known from published sources that isariotin F exhibited activity against the malaria parasite *Plasmodium falciparum* K1, and cytotoxic activities against cancer cell lines (KB, BC, and NCI-H187) and non-malignant (Vero) cells. All isolated compounds contain (*E*)-dodec-2-enoic acid (**13**) [34].

Manumycin A contain (*R*,2*E*,4*E*)-2,4,6-trimethyldeca-2,4-dienoic acid (**11**), which was found in chinikomycin A and B. Antibiotic U-56407 was isolated from fermentations of

Streptomyces hagronensis (strain 360) with (*E*)-4,6,8-trimethyl-nona-2,7-dienoic acid (**14**) was active in vitro against gram-positive bacteria [35].

Asukamycins A-II, B-II, C-II, D-II, and E-II are polyketides that are members of the manumycin family of antibiotics and exhibit potent antineoplastic, antifungal, and antibacterial activities that have been found and identified from lipid extracts of the actinomycete bacterium *Streptomyces nodosus* subsp. *asukaensis* [36]. Asukamycin B and asukamycin B-II contain (2*E*,4*E*,6*E*)-8-methylnona-2,4,6-trienoic acid (**15**). Asukamycin C and asukamycin C-II contain (2*E*,4*E*,6*E*)-9-methyldeca-2,4,6-trienoic acid (**16**). Asukamycin D and asukamycin D-II contain (2*E*,4*E*,6*E*)-8-methyldeca-2,4,6-trienoic acid (**17**), and asukamycin E and asukamycin E-II contain (2*E*,4*E*,6*E*)-10-methylundeca-2,4,6-trienoic acid (**18**).

Antitumor antibiotics named TMC-1 A, B, C, and D were obtained from a fermentation broth of *Streptomyces* sp. A-230. These antibiotics showed strong cytotoxic activities against various tumor cell lines in vitro: HCT-1 16 (human colon carcinoma), SW480 (human colon adenocarcinoma), Saos-2 (humanosteogenic sarcoma), WiDr (human colon adenocarcinoma), OVCAR-3 (human ovarian adenocarcinoma), HL-60 (human promyelocytic leukemia), HeLa S3 (human epitheloid carcinoma), and P388D1 (murine lymphoid neoplasm), and manumycin A exhibited antibacterial activity against gram-positive bacteria: *Staphylococcus aureus, Enterococcus faecalis, Bacillus subtilis* [37]. (*E*)-2,4-dimethyloct-2-enoic acid (18) TMC-1A, (*E*)-2,6-dimethyloct-2-enoic acid (**19**) TMC-1B, (2*E*,4*E*)-4,6-dimethyldeca-2,4-dienoic acid (**20**) TMC-1C, and (*E*)-4,6-dimethyldec-2-enoic acid (**21**) TMC-1D.

It is known that inhibitors of the enzyme, EI-1511-3, -5, EI-1625-2, U-56, 407, manumycins A, B, and G, converting interleukin-1β were found in the culture broths of *Streptomyces* sp. selectively inhibited the activity of recombinant human ICE [38]. EI-1511-5 contains FA (**15**), EI-1625-3 contains (2*E*,4*E*)-7-methylocta-2,4-dienoic acid (**9**), and (*E*)-4-methyloct-2-enoic acid (**23**) was found in EI-1625-2.

A halophilic strain of *Streptomyces* isolated from a salt pan on Shinui Island (Korea) is a producer of salternamides A–D. Salternamide A, which is the first chlorinated compound in the manumycin family, is an inhibitor of a human colon cancer cell line (HCT116) and a gastric cancer cell line (SNU638). Salternamides A and D have been found to be inhibitors of Na+/K+ ATPase [39]. Salternamides A and C contain (4*S*,6*R*,*E*)-4,6,8-trimethylnona-2,7-dienoic acid (**24**), and salternamide E contains (4*S*,6*S*,*E*)-4,6,8-trimethylnon-2-enoic acid (**25**).

Colabomycin A and D [40] were isolated from *Streptomyces griseoflavus* TU 2880 [41,42], and antimicrobial antibiotic U-62162 was found in *Streptomyces verdensis* UC-8157 [43]. Colabomycin A and D consist of (2*E*,4*E*,6*Z*,8*E*)-deca-2,4,6,8-tetraenoic acid (**26**) and (2*E*,4*E*,6*E*,8*E*)-deca-2,4,6,8-tetraenoic acid (**27**), respectively. It is known that colabomycin E inhibited IL-1β release from THP-1 cells and might thus potentially act as an anti-inflammatory agent [44], and it is produced by a strain of *Streptomyces aureus* (see Figure 5). Several FA with different properties has been found in isolated antibiotics. Thus, colabomycin E has a (2*E*,4*E*,6*E*,8*Z*,10*E*)-dodeca-2,4,6,8,10-pentaenoic acid (**28**), colabomycin F has an FA (**14**), colabomycin G—FA (**15**), dinocolabomycin E has an FA (**15**), and dinocolabomycin A has an FA (**29**), respectively.

From the culture solution of *Streptomyces limosus* was obtained a yellow crystalline, nitrogenous dye stuff that limocrocin was isolated [45]. Rare polyenoic (2*E*,4*E*,6*E*,8*E*,10*E*,12*E*,14*E*)-hexadeca-2,4,6,8,10,12,14-heptaenedioic acid (**30**) is present in limocrocin. Figure 6 demonstrates in a 3D graph the predicted and calculated antiviral activity of a rare FA (**30**), and activity is presented in Table 2.

Antimycin is a mixture of closely related antibiotics produced by *Streptomyces* sp. [46,47]. Many known antibiotics belonging to the antimycin A family are produced by *Streptomyces* species [48–51], and these compounds have significant antifungal activity and act by blocking the electron transport chain through inhibition of the cytochrome bc1 complex [48,49]. Several FA were contain in antimycin derivatives: (*S*)-2-((1*S*,2*R*)-1,2-dihydroxypropyl)octanoic acid (**31**, 3D graph see Figure 6, right side) in A1a, A1b, A2a, A2b, A15, and A16 (*S*)-2-((1*S*,2*R*)-1,2-dihydroxypropyl)hexanoic acid A3a, A3b, A4a, A4b,

A9, A11, A13 (**32**), (2*S*,3*S*,4*R*)-2-ethyl-3,4-dihydroxypentanoic acid in A5, A6 (**33**), and (2*S*,3*S*,4*R*)-3,4-dihydroxy-2-isobutylpentanoic acid has been found in A7a, A7b, A8, A12, and A14 (**34**).

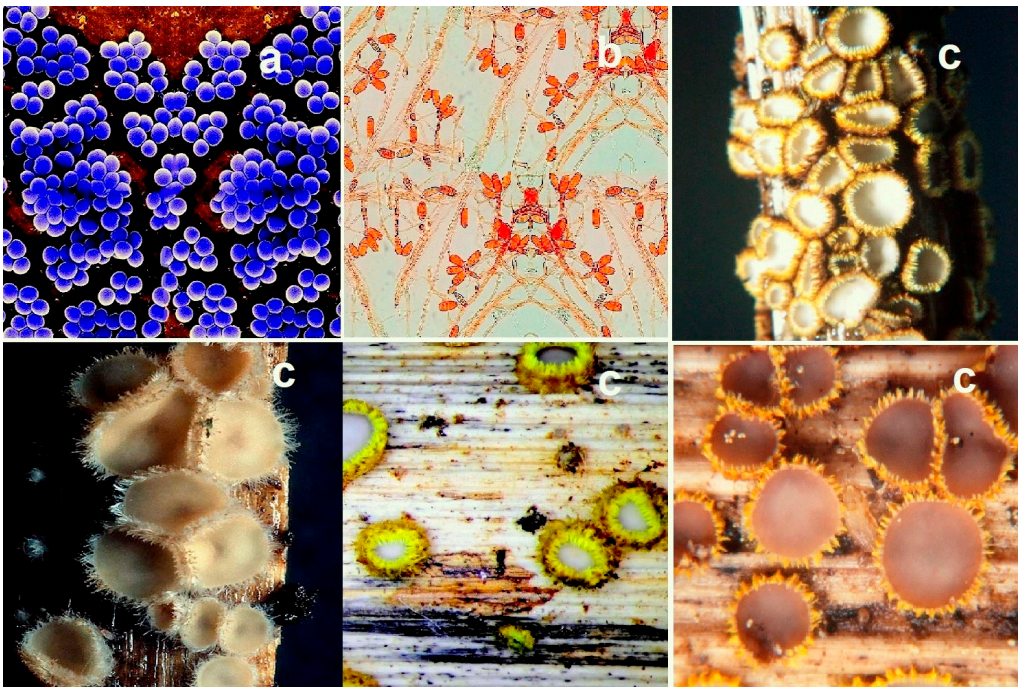
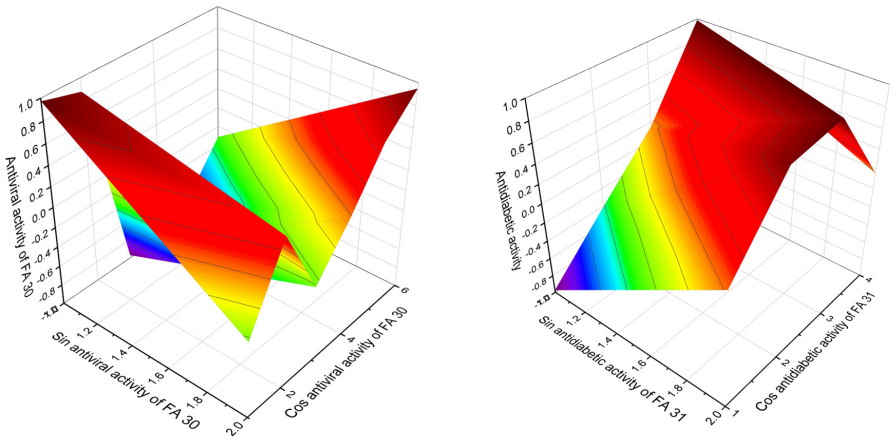


Figure 5. Examples of fungal endophyte, *Streptomyces aureus* (**a**), pathogenic fungus *Bipolaris* spp (**b**), and discomycete *Trichopeziza mollissima* (**c**), which produce bioactive FA amides. Among the microbial species cited, of great interest are Discomycetes, which include cup fungi, spongy fungi, and brain fungi, as well as some club-shaped fungi. In recent years, interest in these fungi has grown as they are a source of biologically active metabolites, including amides. Among the Discomycetes, saprobionts predominate, which grow in conditions of high soil moisture, humus, and on dead wood. They are typical cups or discs, but other forms such as sponges, saddles, tongues, and bells are not uncommon. The pictures (**c**) show varieties of *Trichopeziza mollissima*.



(**a**) (**b**)

Figure 6. The 3D graph shows the predicted and calculated antiviral activity of FA (**30**, **a**). Limocrocin with this rare polyenoic FA, which contains seven conjugated carbon-carbon double bonds shows maximum UV absorption at 260, 420, and 440 nm, and exhibits strong antiviral activity against *Arbovirus*, and it is also a reverse transcriptase inhibitor. The 3D graph shows the predicted and calculated antidiabetic activity of FA (**31**, **b**). Complex molecules of antimycin and closely related antibiotics that contain (*S*)-2-((1*S*,2*R*)-1,2-dihydroxypropyl)-octanoic acid (**31**) exhibit antidiabetic properties.

Table 2. Pharmacological profile of FA derived from microorganisms.

No.	Predicted Biological Activity, Pa *
3	Preneoplastic conditions treatment (0.747); Antiviral (Arbovirus) (0.742); Antineoplastic (0.687)
4	Preneoplastic conditions treatment (0.794); Antiviral (Arbovirus) (0.692); Antineoplastic (0.642)
5	Preneoplastic conditions treatment (0.762); Antiviral (Arbovirus) (0.706); Antifungal (0.702) Antineoplastic (0.685); Cytoprotectant (0.647); Antibacterial (0.568)
6	Preneoplastic conditions treatment (0.762); Antifungal (0.702); Antineoplastic (0.685)
7	Antifungal (0.891); Antibacterial (0.761); Lipid metabolism regulator (0.578)
8	Lipid metabolism regulator (0.808); Antiviral (Arbovirus) (0.699)
9	Antiviral (Arbovirus) (0.853); Antiviral (Picornavirus) (0.760); Antineoplastic (0.722)
10	Antiviral (Arbovirus) (0.819); Apoptosis agonist (0.810); Antineoplastic (0.805)
11	Antineoplastic (0.871); Apoptosis agonist (0.837); Preneoplastic conditions treatment (0.706)
12	Apoptosis agonist (0.879); Antineoplastic (0.878); Preneoplastic conditions treatment (0.618)
13	Antiviral (Arbovirus) (0.944); Preneoplastic conditions treatment (0.768)
14	Antineoplastic (0.835); Antiviral (Arbovirus) (0.801); Antiviral (Picornavirus) (0.743)
15	Antiviral (Arbovirus) (0.819); Apoptosis agonist (0.810); Antineoplastic (0.805) Antiviral (Picornavirus) (0.780); Preneoplastic conditions treatment (0.713)
16	Antiviral (Arbovirus) (0.853); Antiviral (Picornavirus) (0.760); Antineoplastic (0.722)
17	Antiviral (Arbovirus) (0.873); Antiviral (Picornavirus) (0.735); Antineoplastic (0.718)
18	Antiviral (Arbovirus) (0.821); Antineoplastic (0.792); Antiviral (Picornavirus) (0.761)
19	Antineoplastic (0.789); Preneoplastic conditions treatment (0.757); Cytoprotectant (0.553)
20	Lipid metabolism regulator (0.932); Hypolipemic (0.805); Anti-hypercholesterolemic (0.774) Antineoplastic (0.714); Preneoplastic conditions treatment (0.670)
21	Lipid metabolism regulator (0.859); Antineoplastic (0.854); Apoptosis agonist (0.799)
22	Anti-hypercholesterolemic (0.769); Antineoplastic (0.741);
23	Antiviral (Arbovirus) (0.853); Antiviral (Picornavirus) (0.760); Apoptosis agonist (0.731)
24	Antineoplastic (0.835); Apoptosis agonist (0.713); Preneoplastic conditions treatment (0.658)
25	Antineoplastic (0.746); Preneoplastic conditions treatment (0.685); Cytoprotectant (0.607)
26	Antiviral (Arbovirus) (0.861); Antineoplastic (0.791); Antiviral (Picornavirus) (0.776)
27	Antiviral (Arbovirus) (0.861); Antineoplastic (0.791); Antiviral (Picornavirus) (0.776)
28	Antiviral (Arbovirus) (0.861); Antineoplastic (0.791); Antiviral (Picornavirus) (0.776)
29	Anti-inflammatory (0.902); Antiviral (Picornavirus) (0.776); Antifungal (0.774)
30	Antiviral (Arbovirus) (0.938); Antiviral (Picornavirus) (0.887); Anti-inflammatory (0.815) Antineoplastic (0.784); Preneoplastic conditions treatment (0.728); Antimutagenic (0.628)

* Only activities with Pa > 0.5 are shown.

All antibiotics belonging to the antimycin family were active against *Caenorhabditis elegans* and *Artemia salina*. Antimycin A9 demonstrated antimicrobial activity against *Aspergillus niger* KF 103, *Bacillus subtilis* ATCC 6633, *Candida albicans* KF1, *Escherichia coli* NIHJ, *Mucor racemosus* IFO 4581, *Penicillium chrysogenum* KF 270, *Pseudomonas aeruginosa* IFO3080, *Saccharomyces cerevisiae* KF26, *Shizosaccharomyces pombe* IFO 0347, *Staphylococcus aureus* ATCC 6538P, and *Trichophyton mentagrophytes* KF 331 [52,53]. Moreover, antimycins A1, A2, A3, A4, A10, A11, A12, A13, A14, A15, and A16 were obtained from the fermentation broth of strains of *Streptomyces* spp. SPA-10191 and SPA-8893 [53]. These compounds exhibited antifungal activity against *Candida utilis* [54]. (2*S*)-2-((1*S*,2*R*)-1,2-dihydroxypropyl)-6-methyloctanoic acid (**35**) was present in antimycin antibiotics A10a and A10b. Kitamycins A and B acted as plant growth inhibitors produced by *Streptomyces*

sp. K385 [55]. Urauchimycins A and B were isolated from a fermentation broth of a *Streptomyces* sp. Ni-80, which was detected in an unidentified sponge [56]. These antibiotics contain (**32**) acid, and (*S*)-2-((1*R*,2*R*)-1,2-dihydroxypropyl)-6-methylheptanoic acid (**36**), and kitamycin B contains fatty acid (**36**).

Antibiotics named splenocins A–J which are the cytokine inhibitors have been found in extracts of marine-derived *Streptomyces* sp., and another strain of *Streptomyces* CNQ431. Studies of these amides have shown that splenocin B is a potent inhibitor of the pro-inflammatory cytokine, splenocins A–I display suppression of cytokine production by OVA stimulated splenocytes at low nanomolar concentrations, and splenocin J exhibits low micromolar activity in the splenocyte assay [52,54,57–59]. Splenocins A, B, C, I, and J contain in molecules: (2*S*,3*R*,4*R*)-2-benzyl-3,4-dihydroxypentanoic acid (**37**), splenocin D, (2*S*,3*R*,4*R*)-2-ethyl-3,4-dihydroxypentanoic acid (**38**), splenocin E, (*S*)-2-((1*R*,2*R*)-1,2-dihydroxy-propyl)hexanoic acid (**39**), splenocin F, (*S*)-2-((1*R*,2*R*)-1,2-dihydroxy-propyl)-heptanoic acid (**40**), splenocin G, (*S*)-2-((1*R*,2*R*)-1,2-dihydro-xypropyl)-octanoic acid (**41**), splenocin H, (2*S*)-2-((1*R*,2*R*)-1,2-dihydroxypropyl)-4-methyloctanoic acid (**42**, for structure see Figure 7, and for activity see Table 3).

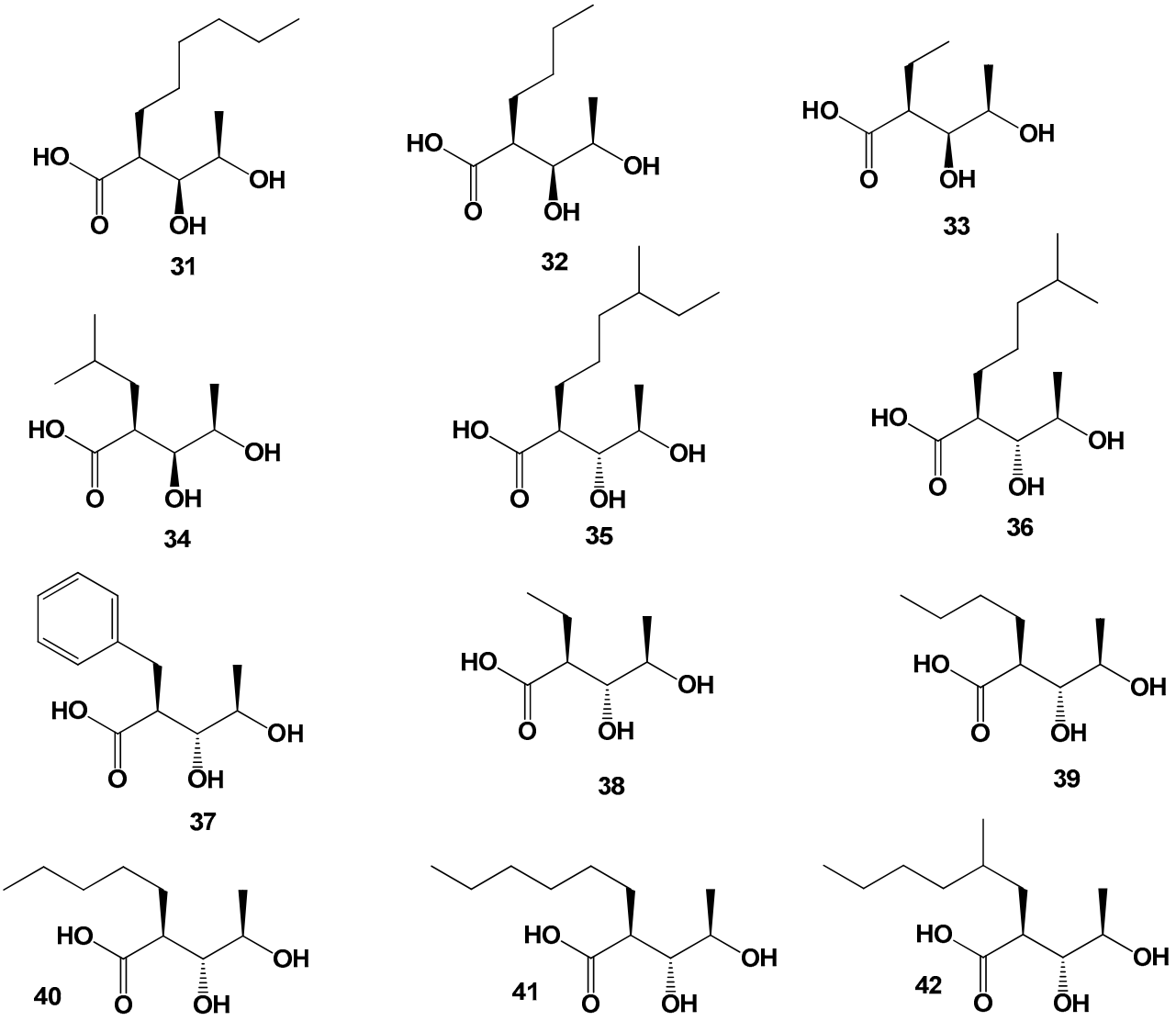


Figure 7. Rare FA derived from marine and soil fungal endophytes.

Table 3. Pharmacological profile of FA derived from microorganisms.

No.	Predicted Biological Activity, Pa *
31	Antidiabetic symptomatic (0.916); Anti-infective (0.741); Antidiabetic (0.729); Antifungal (0.680)
32	Antiviral (Arbovirus) (0.761); Anti-inflammatory (0.758); Antidiabetic symptomatic (0.756)
33	Anti-inflammatory (0.752); Antiviral (Arbovirus) (0.750); Antiviral (HIV) (0.735)
34	Anti-inflammatory (0.754); Antidiabetic symptomatic (0.735); Antiviral (Arbovirus) (0.666) Antifungal (0.647); Lipid metabolism regulator (0.634); Antiviral (HIV) (0.606)
35	Lipid metabolism regulator (0.774); Anti-inflammatory (0.752); Antidiabetic symptomatic (0.733) Anti-infective (0.673); Antiviral (Arbovirus) (0.672); Antifungal (0.625)
36	Anti-inflammatory (0.742); Antidiabetic symptomatic (0.736); Antiviral (Arbovirus) (0.684) Anti-infective (0.669); Antifungal (0.563)
37	Anti-hypoxic (0.711); Antiviral (Arbovirus) (0.688); Antiviral (HIV) (0.610)
38	Antidiabetic symptomatic (0.736); Antiviral (Arbovirus) (0.730); Antiviral (HIV) (0.535)
39	Antiviral (Arbovirus) (0.761); Anti-inflammatory (0.758); Antidiabetic symptomatic (0.756) Anti-infective (0.741); Antidiabetic (0.629); Antiviral (Picornavirus) (0.623)
40	Antiviral (Arbovirus) (0.761); Anti-inflammatory (0.758); Anti-infective (0.741) Antifungal (0.680); Antiviral (Picornavirus) (0.623)
41	Antiviral (Arbovirus) (0.761); Anti-inflammatory (0.758); Anti-infective (0.741) Antifungal (0.680); Antiviral (Picornavirus) (0.623)

* Only activities with Pa > 0.5 are shown.

Carbapenem compounds, to which the OA-6129 group of antibiotics belong, had a relatively strong antimicrobial activity against gram-positive and gram-negative bacteria [60,61]. Antibiotic OA 6129A, B1, B2, and C contains (*R*)-2,4-dihydroxy-3,3-dimethylbutanoic acid (**42**, for structure see Figure 8, and for activity see Table 4).

An endophytic *Streptomyces* sp. isolated from the mangrove tree *Bruguiera gymnorrhiza* is the source of biologically active compounds named divergolides A–D, which were active against *B. subtilis* and *Mycobacterium vaccae* [62,63]. Divergolides A and B contains (*Z*)-2-methylpent-2-enedioic acid (**43**).

Metabolites produced by endophytic fungus *Bipolaris* sp. MU34 from Thai medicinal plants, bipolamides A and B, and pathogenic fungus *Pestalotiopsis oenotherae* isolated from leaves, *Rhizophora mucronata*, (Hainan Is., China) yielded pestalotiopamide E and D with (*E*)-5-acetoxy-3-methylpent-2-enoic acid (**44**) [64]. Pestalotiopen A showed moderate antimicrobial activity against *Enterococcus faecalis* [65]. The plant pathogen endophytic fungus *Pestalotiopsis* sp. was obtained from the leaves of the Chinese mangrove *Rhizophora mucronata* yielded bioactive compounds named pestalotiopamide E and D with FA (**44**) [64].

The fungus *Gymnascella dankaliensis* found in soil in the vicinity of the Giza pyramids (Egypt) produced bioactive compounds that exhibit cytotoxicity against the murine lymphoma cell line L5178Y [66]. 11′-Carboxy-gymnastatin N contains (*R*,2*E*,4*E*)-4,6-dimethyldodeca-2,4-dienedioic acid (**45**), 12′-hydroxy-gymnastatin N, and dankamide—(*R*,2*E*,4*E*)-12-hydroxy-4,6-dimethyldodeca-2,4-dienoic acid (**46**), gymnastatin S—(*R*,2*E*,4*E*)-4,6-dimethylocta-2,4-dienedioic acid (**47**), gymnastatin A, B, and N, aranorosinol A, aranorosin, aranorosin-2-methylether, and other metabolites contain (*R*,2*E*,4*E*)-4,6-dimethyldodeca-2,4-dienoic acid (**48**).

Metabolites produced by endophytic fungus *Bipolaris* sp. MU34 from Thai medicinal plants bipolamides A and B were discovered. Bipolamide B showed antifungal activity against *Aspergillus niger* ATCC 6275, *Cladosporium cladosporioides* FERMS-9, *C. cucumerinum* NBRC 6370, *Rhisopus oryzae* ATCC 10404, and *Saccharomyces cerevisiae* ATCC 9804 [67]. (2*E*,4*E*,6*E*)-6,8-dimethyldeca-2,4,6-trienoic acid (**49**) was present in both metabolites.

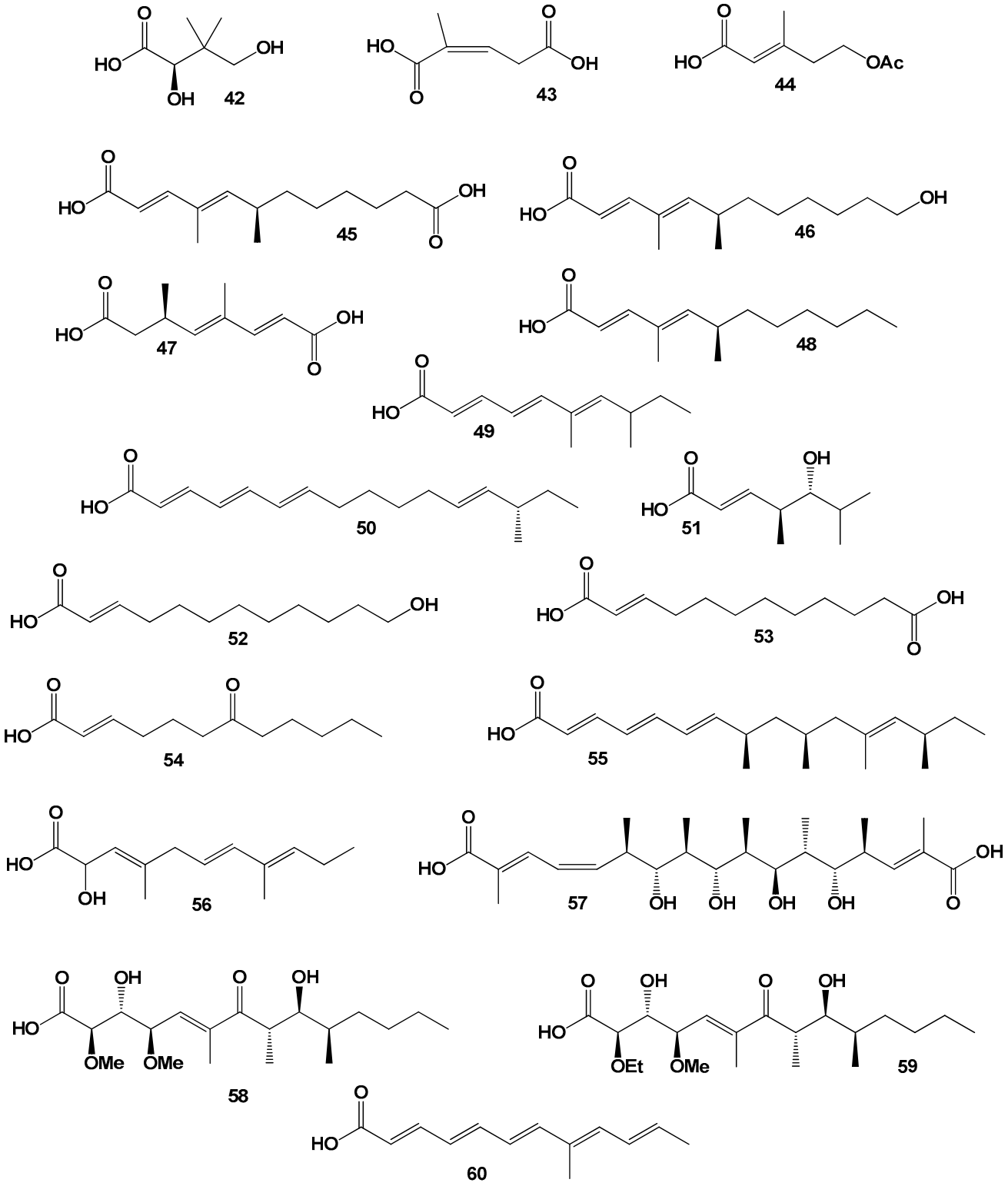


Figure 8. Unusual FA derived from fungal endophytes, and soil fungi.

The fungus *Penicillium variabile* HXQ-H-1 cultivated with the DNA methyltransferase inhibitor 5-azacytidine is a producer of the antibiotic varitatin A. This compound with (*S*,2*E*,4*E*,6*E*,12*E*)-14-methylhexadeca-2,4,6,12-tetraenoic acid (**50**) demonstrated cytotoxicity against HCT-116 cells and inhibition of protein tyrosine kinase [68].

The soil fungus *Streptomyces ostreogriseus* is a producer of the cyclopeptide antibiotic ostreogrycin A with (4*S*,5*R*,*E*)-5-hydroxy-4,6-dimethylhept-2-enoic acid (**51**) and is highly active against gram-positive bacteria, especially methicillin-resistant *S. aureus* [69].

Fungi belonging to the genus *Isaria* are known to be pathogenic for insects belonging to Homoptera, Lepidoptera, and Coleoptera and are producers of unique compounds called isariotins A–D, which possess a unique bicyclo [3.3.1]nonane ring. These amides were found in lipid extracts of the insect pathogenic fungus *Isaria tenuipes* BCC 7831 [70]. Three FA, (*E*)-12-hydroxydodec-2-enoic (**52**), (*E*)-dodec-2-enedioic (**53**), and (*E*)-7-oxododec-2-enoic (**54**, 3D graph see Figure 9) were found in isariotins A, B, and C, respectively.

Table 4. Pharmacological profile of FA derived from microorganisms.

No.	Predicted Biological Activity, Pa *
42	Lipid metabolism regulator (0.936); Hematinic (0.923); Multiple sclerosis treatment (0.918) Autoimmune disorders treatment (0.857); Neurodegenerative diseases treatment (0.816) Hypolipemic (0.783); Anti-hypercholesterolemic (0.632); Atherosclerosis treatment (0.589)
43	Lipid metabolism regulator (0.812); Hypolipemic (0.787); Atherosclerosis treatment (0.638)
44	Lipid metabolism regulator (0.941); Acute neurologic disorders treatment (0.748) Anti-hypercholesterolemic (0.735); Hypolipemic (0.699); Immunosuppressant (0.646)
45	Antineoplastic (0.904); Apoptosis agonist (0.854); Preneoplastic conditions treatment (0.676)
46	Antineoplastic (0.845); Preneoplastic conditions treatment (0.643); DNA synthesis inhibitor (0.527)
47	Antineoplastic (0.865); Apoptosis agonist (0.763); Preneoplastic conditions treatment (0.629)
48	Antineoplastic (0,854); Apoptosis agonist (0.799); Preneoplastic conditions treatment (0.706)
49	Antineoplastic (0.881); Antifungal (0.798); Preneoplastic conditions treatment (0.641)
50	Lipid metabolism regulator (0.913); Hypolipemic (0.855); Anti-hypercholesterolemic (0.786) Apoptosis agonist (0.717); Preneoplastic conditions treatment (0.687)
51	Antibacterial (0.842); Antiviral (Arbovirus) (0.790); Antiviral (Picornavirus) (0.659)
52	Antiviral (Arbovirus) (0.902); Antimutagenic (0.782); Antiviral (Picornavirus) (0.726)
53	Anti-eczematic (0.956); Antiviral (Arbovirus) (0.893); Antimutagenic (0.838) Anti-psoriatic (0.753); Antifungal (0.739); Antiparasitic (0.744)
54	Anti-eczematic (0.920); Antiviral (Arbovirus) (0.903); Antimutagenic (0.818) Anti-psoriatic (0.730); Antiviral (Picornavirus) (0.680); Antifungal (0.657)
55	Hypolipemic (0.915); Lipid metabolism regulator (0.795); Apoptosis agonist (0.795)
56	Lipid metabolism regulator (0.949); Apoptosis agonist (0.861); Hypolipemic (0.791) Anti-hypercholesterolemic (0.629); Atherosclerosis treatment (0.627)
57	Antineoplastic (0.939); Apoptosis agonist (0.910); Antimitotic (0.826) Lipid metabolism regulator (0.783); Antifungal (0.763); Antiparasitic (0.675)
58	Antineoplastic (0.906); Antifungal (0.812); Apoptosis agonist (0.720); Antiparasitic (0.646)
59	Antineoplastic (0.883); Antifungal (0.807); Antiparasitic (0.681); Apoptosis agonist (0.665)
60	Lipid metabolism regulator (0.921); Antifungal (0.818); Antibacterial (0.761)

* Only activities with Pa > 0.5 are shown.

Scyphostatin, a neutral sphingomyelinase inhibitor, with (2*E*,4*E*,6*E*,8*R*,10*S*,12*E*,14*R*)-8,10,12,14-tetramethylhexadeca-2,4,6,12-tetraenoic acid (**55**) was obtained from a discomycete, *Trichopeziza mollissima* SANK 13,892 exhibited potent inhibitory activity [71].

Bioactive compound JBIR-66 with (3*E*,6*E*,8*E*)-2-hydroxy-4,8-dimethylundeca-3,6,8-trienoic acid (**56**) was obtained from the culture broth of the tunicate-derived fungus *Saccharopolyspora* sp. SS081219JE-28 [72]. Two β-hydroxy acetamides, BE-52211, BE-52211 B, and BE-52211 C, as structural analogues of JBIR-66, were obtained from *Streptomyces* sp. They inhibited cell division of starfish embryos at a concentration of 2.5 μg/mL and contain acid (**56**) [73,74].

Antibiotic streptovaricin U with FA (**57**) produced by *Streptontvices spectabilis* [75], and chondrochlorens A and B were obtained from *Chondromyces crocatus* Cmc5 [76] with FA (**58**) and (**59**), respectively.

A microbial metabolite Sch 725,424 with (2*E*,4*E*,6*E*,8*E*,10*E*)-8-methyldodeca-2,4,6,8,10-pentaenoic acid (**60**) was detected in the culture of *Kitasatospora* sp., and it demonstrated inhibitory activity against *Staphylococcus aureus* and *Saccharomyces cerevisiae* [77].

An actinomycete *Streptomyces cavourensis* YY01-17 from the Antarctic area is a producer of pseudopeptide with (*E*)-3-hydroxy-2,4-dimethylhept-4-enoic acid (**61**, for structure see Figure 10, and activity in Table 5) [78]. *Streptomyces versipellis* 4083-SVS6 is a producer of JBIR-07 and JBIR-08 with (6*E*,8*Z*)-3-hydroxy-8-(hydroxymethyl)-2,6-dimethyldeca-6,8-dienoic acid (**62**), and (6*Z*,8*E*)-3-hydroxy-6-(hydroxymethyl)-2,8-dimethyldeca-6,8-dienoic acid (**63**) [79].

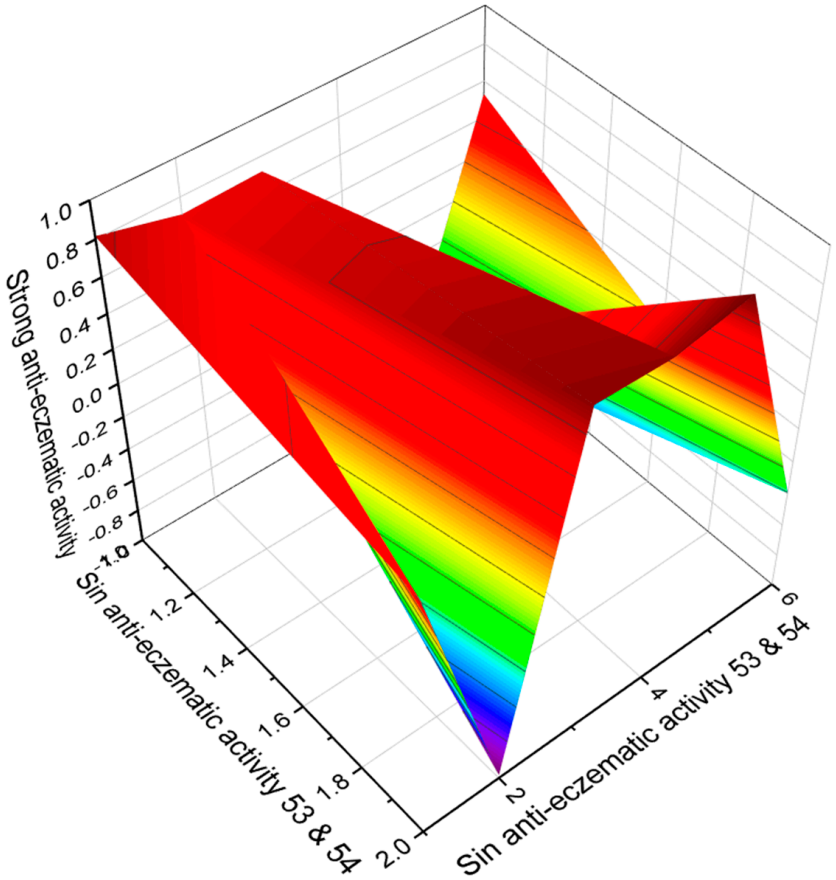


Figure 9. The 3D graph shows the predicted and calculated anti-eczematic activity of FA (**53** and **54**). Both acids have been found in the insect pathogenic fungus *Isaria tenuipes*. It is known that this fungus is one of the potent species of the *Isaria* genus, which is known to have many biologically active substances of therapeutic value. In addition, the crude methanol extract showed potent antioxidant and antiproliferative activity, which is indicative of natural antioxidant and antiproliferative agents.

An entomopathogenic fungus *Metarhizium acridum* is a producer of 17-membered macrocycles named metacridamides A and B. Metacridamide A showed cytotoxicity to three cancer lines against Caco-2 (epithelial colorectal adenocarcinoma), MCF-7 (breast cancer), and HepG2/C3A (hepatoma) cell lines, and metacridamide B was active against HepG2/C3A [80]. Both compounds related to FA (**64**) and (**65**), respectively.

Unusual (8*E*,14*E*)-7,13-dihydroxy-4,10,14-trimethyl-3-oxoheptadeca-8,14,16-trienoic acid (**66**) was detected in macrolide antibiotic angiolam A, which was produced by *Angiococcus disciformis* [81].

An endophytic fungus *Sporormiella minimoides* (Sporormiaceae) isolated from bark *Hintonia latiflora* is a producer of an antibiotic with (2*E*,4*E*,6*E*)-3-methyloctadeca-2,4,6-trienoic acid (**67**) that had antifungal properties [82].

Neutrophic agent named as farinosone C with (2*E*,4*E*)-4,6-dimethylocta-2,4-dienedioic acid (**68**) produced by *Paecilomyces farinosus* RCEF 0101 [83]. The fungus *Gymnasella dankaliensis* from the sponge *Halichondria japonica* has supplied the several gymnastatins A-H, most of which are halogenated compounds. All isolated pseudo-dipeptides contain the (*R*,2*E*,4*E*)-5,7-dimethyltrideca-2,4-dienoic acid (**69**). The same FA was detected in aranochlors A and B [84].

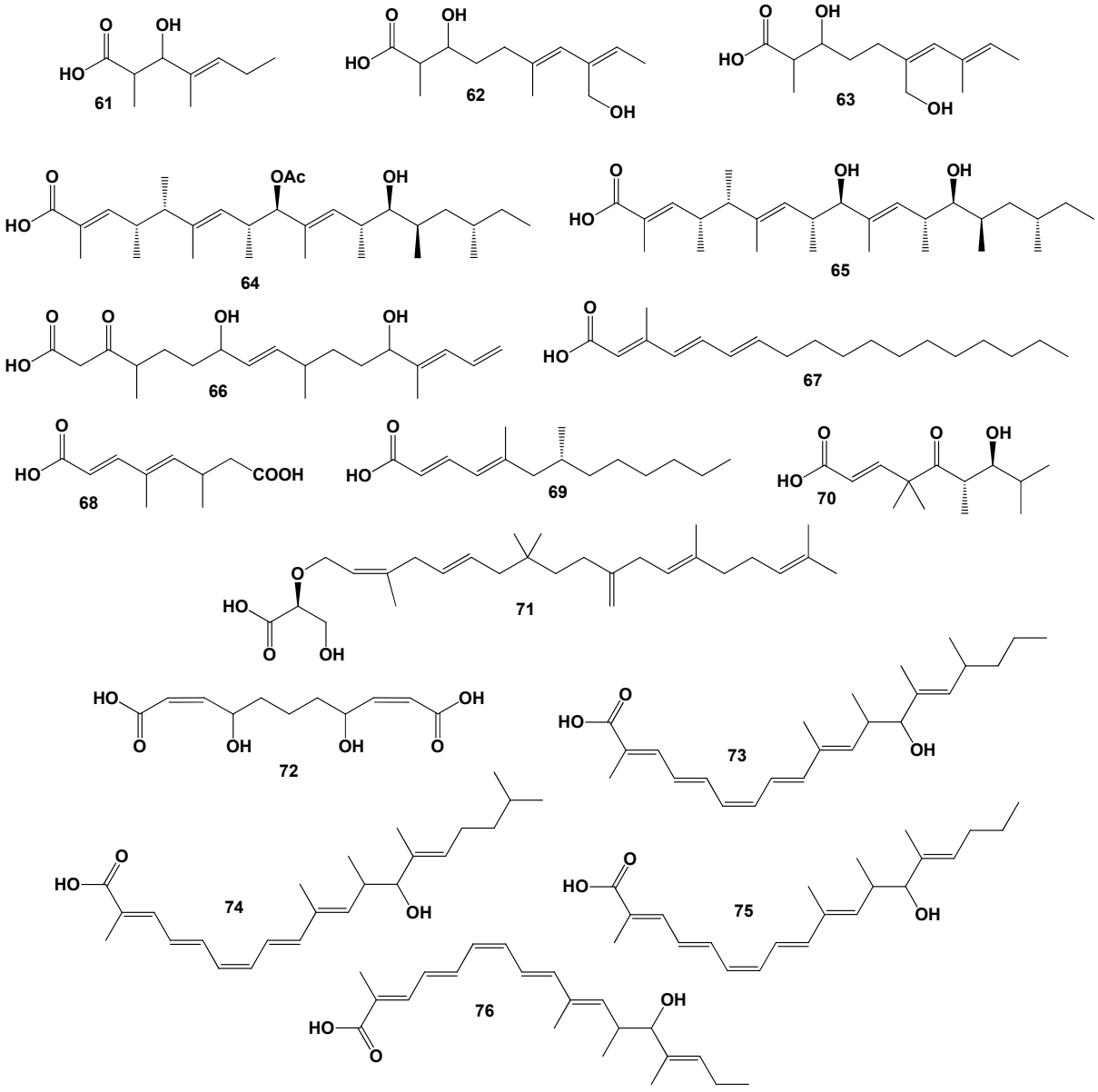


Figure 10. Unusual and rare FA-derived from marine and parasitic fungal endophytes.

A highly unsaturated macrolide lactam named mirabilin with (6*S*,7*S*,*E*)-7-hydroxy-4,4,6,8-tetramethyl-5-oxonon-2-enoic acid (**70**) was found in an unidentified fungus extract that was associated with the marine sponge *Siliquariaspongia mirabilis*. An isolated compound inhibits the growth of the tumor cell line HCT-116 [85].

Streptomyces sp. K04-0144 is a producer of nosokomycins A, B, C, and D, which belong to the moenomycin family, consisting of an oligosaccharide moiety, a 2,3-dihydroxypropionic

acid, and an unusual sesterterpenoid moiety. All isolated nosokomycins contain FA (**71**) [86]. The marine actinomycete B-1758 from collection of the Alfred Wegener Institute for Polar and Marine Research in Bremerhafen (Germany) was isolated diamide, which contains (2*Z*,9*Z*)-4,8-dihydroxyundeca-2,9-dienedioic acid (**72**) [87].

Table 5. Pharmacological profile of FA derived from microorganisms.

No.	Predicted Biological Activity, Pa *
61	Acute neurologic disorders treatment (0.892); Antineoplastic (0.758) Preneoplastic conditions treatment (0.612); Antiviral (Picornavirus) (0.547)
62	Anti-asthmatic (0.908); Acute neurologic disorders treatment (0.731); Antifungal (0.700) Anti-inflammatory (0.697); Antibacterial (0.617); Spasmolytic (0.537)
63	Antineoplastic (0.806); Anti-inflammatory (0.801); Apoptosis agonist (0.764) Acute neurologic disorders treatment (0.763); Antibacterial (0.657)
64	Hypolipemic (0.908); Antineoplastic (0.901); Apoptosis agonist (0.852); Antifungal (0.820)
65	Antineoplastic (0.916); Hypolipemic (0.905); Apoptosis agonist (0.864); Antifungal (0.797)
66	Antineoplastic (0.854); Antifungal (0.826); Hypolipemic (0.793); Apoptosis agonist (0.709)
67	Lipid metabolism regulator (0.962); Antiviral (Arbovirus) (0.917); Antineoplastic (0.867)
68	Antineoplastic (0.865); Apoptosis agonist (0.763); Preneoplastic conditions treatment (0.629)
69	Lipid metabolism regulator (0.931); Hypolipemic (0.853); Anti-hypercholesterolemic (0.748) Atherosclerosis treatment (0.659); Antibacterial (0.595)
70	Antineoplastic (0.813); Antiviral (Arbovirus) (0.748); Antiviral (Picornavirus) (0.585)
71	Lipid metabolism regulator (0.961); Hypolipemic (0.915); Lipoprotein disorders treatment (0.707) Anti-hypercholesterolemic (0.669); Antihypertriglyceridemic (0.532)
72	Antiviral (Arbovirus) (0.870); Anti-inflammatory (0.859); Antiviral (Picornavirus) (0.691)
73	Antineoplastic (0.912); Apoptosis agonist (0.833); Antiviral (Arbovirus) (0.686)
74	Antineoplastic (0.909); Apoptosis agonist (0.873); Lipid metabolism regulator (0.863)
75	Antineoplastic (0,907); Lipid metabolism regulator (0.898); Apoptosis agonist (0.871)
76	Antineoplastic (0.916); Lipid metabolism regulator (0.890); Apoptosis agonist (0.883)

* Only activities with Pa > 0.5 are shown.

The culture supernatant extract of the strain *Myxococcus xanthus* Mx X12 contained the polyene antibiotic compounds named myxalamid A, B, C, and D [88]. Isolated antibiotics contained FA (**73**), (**74**), (**75**), and (**76**, 3D graph, see Figure 11), respectively.

The polyene antifungal antibiotics, 6*E*,2′-O-methylmyxalamide D, 6*E*,10*Z*-2′-O-methylmyxalamide D, 2′-O-methyl-myxalamide D, and acetate derivative of (**77**) have been obtained from myxobacterium *Cystobacter fuscus* AJ-13278, contained FA (**78**), (**79**), and (**80**), respectively [89]. All compounds showed antifungal activities of against the phythopathogenic fungus *Phythopthora capsici*.

Eliamid with (6*E*,10*E*)-2,4,6,8,10-pentamethyl-9-oxododeca-6,10-dienoic acid (**81**) is a secondary metabolite isolated from *Sorangium cellulosum* (see Figure 12) [90]. An actinomycete *Saccharothrix longispora* DSM 43,749 (T) from a Saharan soil in Ghardaïa (Algeria) is a producer of D-(-)-threo chloramphenicol with 2,2-dichloroacetic acid (**82**, for structure see Figure 13, and activity see Table 6) [91].

Microsphaerone A with FA (**83**) is γ-pyrone derivative derived from the sponge-derived fungus *Microsphaeropsis* sp. [92], and a ubiquitin-activating enzyme inhibitor named himeic acid A with FA (**84**) was detected in a culture of marine-derived fungus *Aspergillus* sp. [93].

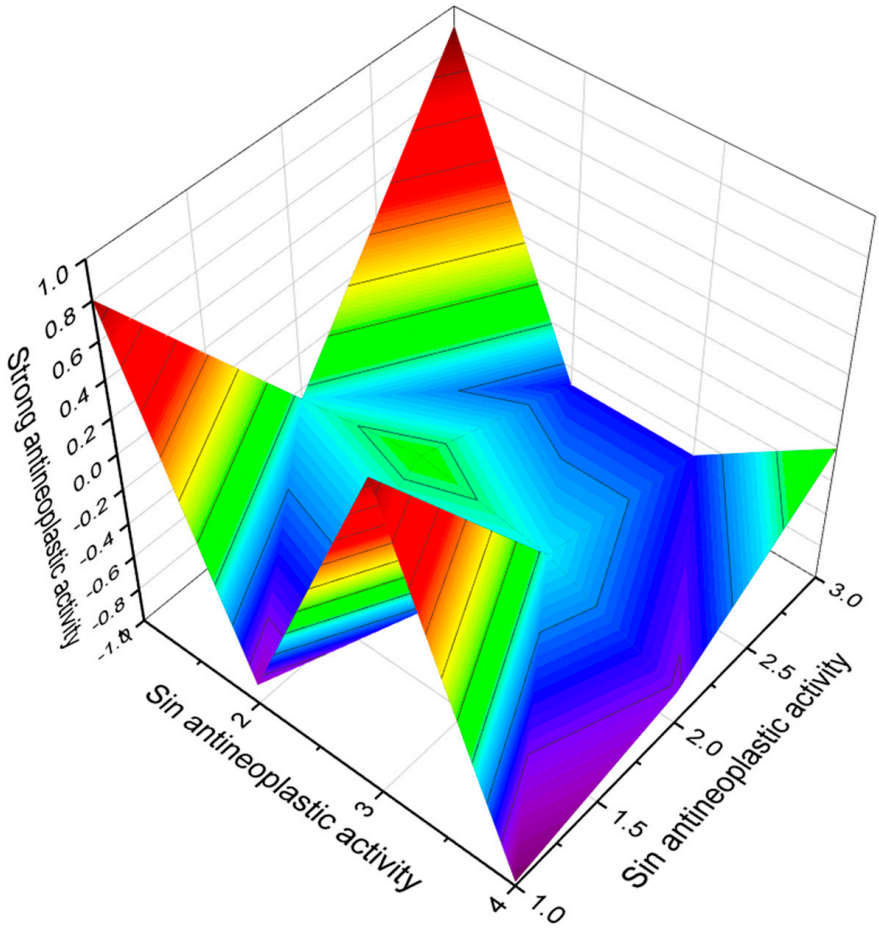


Figure 11. The 3D graph shows the predicted and calculated antineoplastic activity of FA (**73**, **74**, **75**, and **76**). These FA contain amides that are synthesized by the gram-negative rod-shaped myxobacteria, *Myxococcus xanthus*. With an excess of nutrition in cultivated conditions, this bacterium exists in the form of a predatory, saprophytic single-species biofilm called a swarm.

Liquid culture broth of *Pseudomonas* sp. MF381-IODS yielded two antimicrobial agents named pseudotrienic acids A and B with (3*E*,5*E*)-7-hydroxy-4-methylhexadeca-3,5-dienoic (**85**) and (3*E*,5*E*)-7-hydroxy-4-methyltetradeca-3,5-dienoic (**86**) acids, respectively. Both compounds are growth inhibitors of *Staphylococcus aureus* and *Pseudomonas syringae* pv. *syringae* [94]. Citrate-hydroxamate siderophores named nannochelins A, B, and C with 3-hydroxypentane-1,3,5-tricarboxylic acid (**87**) has been obtained from the *Nannocystis exedens* strain Na e485 [95].

An antibiotic named korormicin with (3*R*,4*Z*,6*E*,9*S*,10*R*)-10-bromo-9-hydroxy-3-methyldodeca-4,6-dienoic acid (**88**) was obtained from an extract of the marine actinomycete *Pseudoalteromonas* sp. F-420 and had a specific inhibitory activity against marine gram-negative bacteria [96].

A plant growth regulator, amidenin with (2*E*,4*Z*)-deca-2,4-dienoic acid (**89**) was obtained from an extract of the fermentation broth of an *Amycolatopsis* sp. [97]. In addition, actinonin with 2-pentylsuccinic acid (**90**) has been shown to be an inhibitor of CD13/aminopeptidase and is cytotoxic to some tumor cell lines in vitro [98].

Two aromatic compounds named citrinamides A and B were found and isolated from the culture broth of *Penicillium* sp. FKI-1938. Both citrinamides A and B containing 2,2-dimethylbut-3-enoic acid (**91**) showed moderate potentiation of miconazole activity against *Candida albicans* [99].

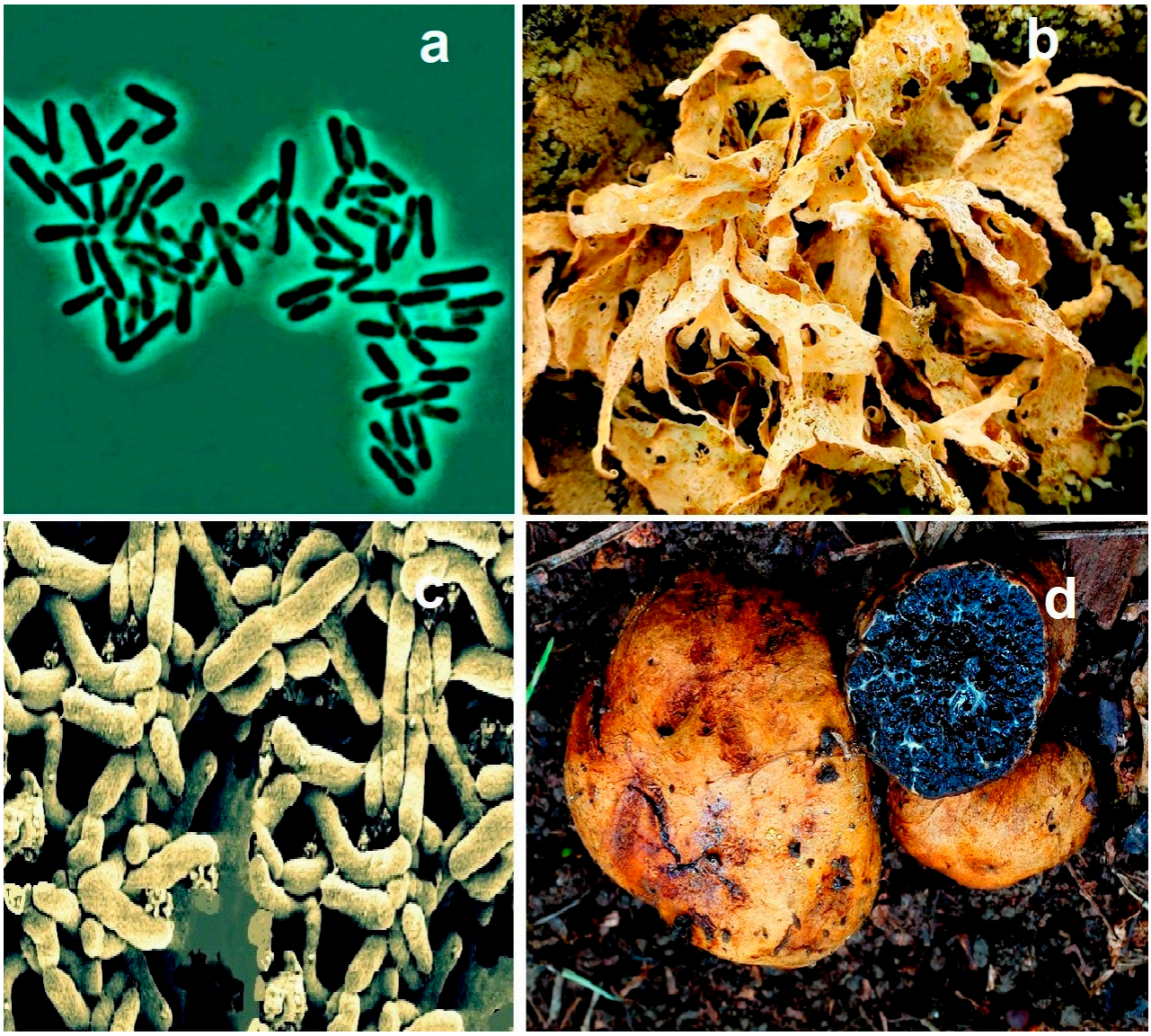


Figure 12. Examples of myxobacteria *Sorangium cellulosum* (**a**), lichenized ascomycete *Ramalina terebarata* (**b**), marine bacteria *Pseudoalteromonas* sp. (**c**), and the subterranean fungus *Melanogaster broomeianus* (**d**) whose extracts contain bioactive FA amides.

Bacillus laterosporus isolate PNG 276 was a producer of compounds named basiliskamide A and B with (2*Z*,4*E*,7*R*,8*R*,9*S*,10*R*)-7,9-dihydroxy-8,10-dimethyldodeca-2,4-dienoic acid (**92**). Both compounds show potent in vitro anti-Candida activity [100]. The sub-acute toxicity of an antimicrobial metabolite with (*Z*)-5-oxoundec-7-enoic acid (**93**) was isolated from a *Streptomyces* sp. [101].

An endophytic fungus *Aspergillus niger* EN-13 isolated from the brown seaweed *Colpomenia sinuosa* was the source of asperamides A and B. Asperamide A displayed moderate activity against *Candida albicans* [102], and asperamide B contained (*R*,3*E*,5*E*,7*E*,9*E*)-2-hydroxytrideca-3,5,7,9-tetraenoic acid (**94**).

Gliding bacterium *Polyangium brachysporum* sp. nov. no. K481-B101 is a producer of antitumor antibiotics named glidobactins A, B, and C, and glidobactin B contained (2*E*,4*E*)-dodeca-2,4-dienoic acid (**95**, 3D graph see Figure 14) [103].

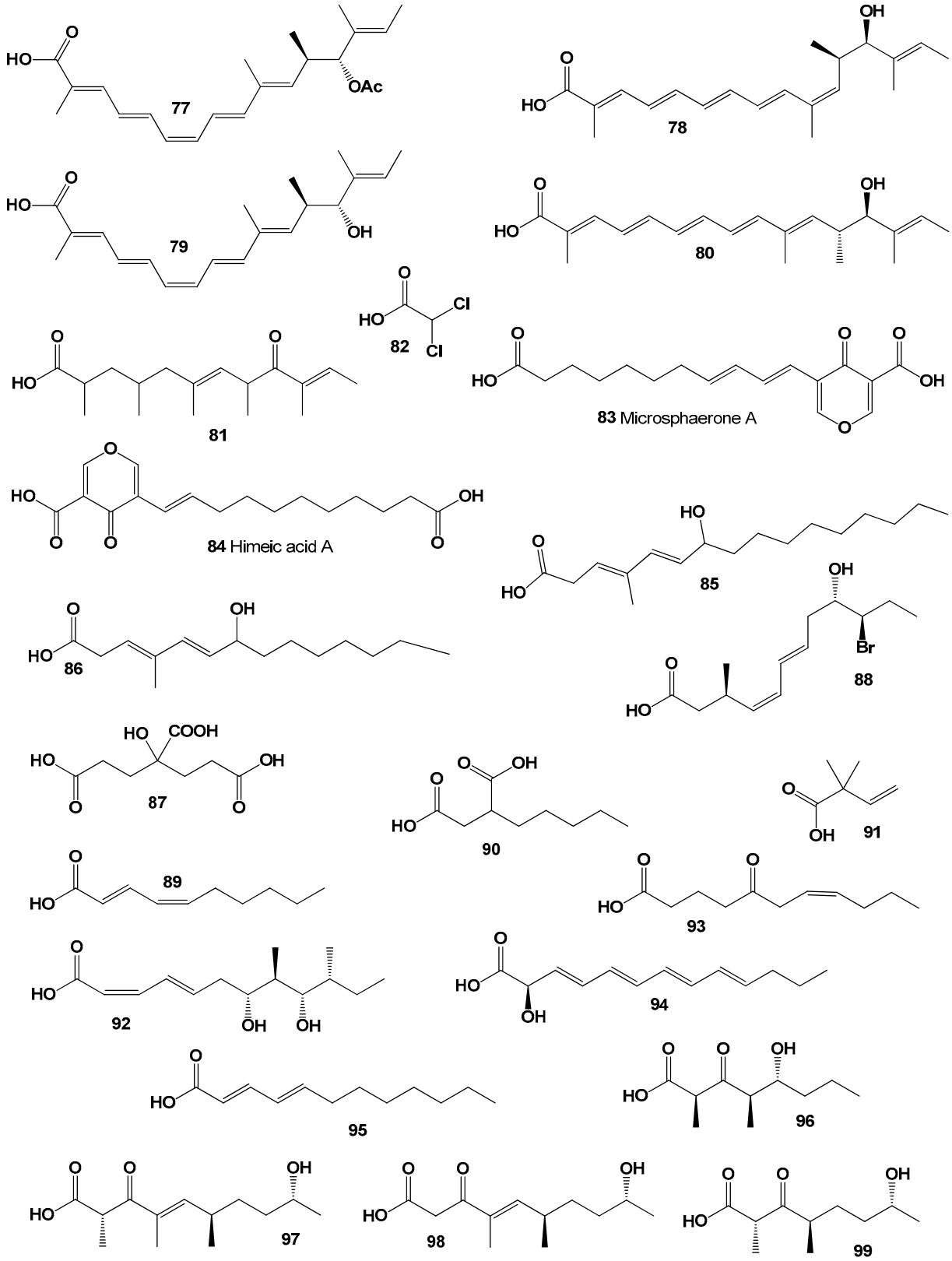


Figure 13. Unusual and rare FA derived from marine and soil microorganisms.

Table 6. Pharmacological profile of FA derived from microorganisms.

No.	Predicted Biological Activity, Pa *
77	Antineoplastic (0.917); Apoptosis agonist (0.870); Lipid metabolism regulator (0.858) Hypolipemic (0.855); Antifungal (0.808); Anti-inflammatory (0.768); Antibacterial (0.665)
78	Antineoplastic (0.929); Apoptosis agonist (0.883); Hypolipemic (0.835); Antifungal (0.788)
79	Antineoplastic (0.929); Apoptosis agonist (0.883); Hypolipemic (0.835); Antifungal (0.788)
80	Antineoplastic (0.929); Apoptosis agonist (0.883); Hypolipemic (0.835); Antifungal (0.788)
81	Antineoplastic (0.914); Hypolipemic (0.829); Apoptosis agonist (0.809); Antifungal (0.791)
82	Apoptosis agonist (0.970); Antineoplastic (0.788); Mucositis treatment (0.705)
83	Lipid metabolism regulator (0.907); Antineoplastic (0.869); Apoptosis agonist (0.843)
84	Lipid metabolism regulator (0.964); Hypolipemic (0.873); Atherosclerosis treatment (0.689)
85	Lipid metabolism regulator (0.937); Hypolipemic (0.866); Atherosclerosis treatment (0.653)
86	Lipid metabolism regulator (0.937); Hypolipemic (0.866); Atherosclerosis treatment (0.653)
87	Lipoprotein disorders treatment (0.912); Atherosclerosis treatment (0.910); Hypolipemic (0.903) Lipid metabolism regulator (0.776); Anti-hypercholesterolemic (0.673)
88	Antifungal (0.728); Antibacterial (0.680); Antiviral (Arbovirus) (0.675)
89	Antiviral (Arbovirus) (0.952); Anti-inflammatory (0.808); Antiviral (Picornavirus) (0.790)
90	Sclerosant (0.906); Anesthetic general (0.881); Anticonvulsant (0.854) Neuroprotector (0.835); Acute neurologic disorders treatment (0.746); Mucositis treatment (0.717)
91	Lipid metabolism regulator (0.868); Hypolipemic (0.680); Anti-hypercholesterolemic (0.641)
92	Antiviral (Arbovirus) (0.814); Antifungal (0.769); Antibacterial (0.626)
93	Anti-eczematic (0.939); Antimutagenic (0.832); Mucositis treatment (0.781)
94	Anti-eczematic (0.912); Lipid metabolism regulator (0.911); Anti-infective (0.876)
95	Anti-eczematic (0.957); Antiviral (Arbovirus) (0.952); Antiviral (Picornavirus) (0.790)
96	Sclerosant (0.834); Antifungal (0.698); Antiviral (Arbovirus) (0.693)
97	Antifungal (0.771); Apoptosis agonist (0.719); Antibacterial (0.632)
98	Antineoplastic (0.857); Apoptosis agonist (0.746); Lipid metabolism regulator (0.629)
99	Anti-ischemic, cerebral (0.835); Acute neurologic disorders treatment (0.783)

* Only activities with Pa > 0.5 are shown.

Stereocalpin A with (2*R*,4*R*,5*R*)-5-hydroxy-2,4-dimethyl-3-oxooctanoic acid (**96**) was found in the Antarctic lichens *Stereocaulon alpinum* (see Figure 15) and *Ramalina terebarata* [104].

The FA amides named calcaripeptides A, B, and C were obtained from MeOH/$CHCl_3$ extracts of the fungus *Calcarisporium* sp. KF525, which found in sediments of the German Wadden Sea [105]. All compounds contained (2*S*,6*R*,9*R*,*E*)-9-hydroxy-2,4,6-trimethyl-3-oxodec-4-enoic (**97**), (6*R*,9*R*,*E*)-9-hydroxy-4,6-dimethyl-3-oxodec-4-enoic (**98**) and (2*S*,4*R*,7*R*)-7-hydroxy-2,4-dimethyl-3-oxooctanoic (**99**) acids, respectively [105].

Streptovaricins are a group of structurally related macrolide antibiotics. They belong to the larger class of antibiotics known as ansamycins. Streptovaricin U is acyclic antibiotic with FA (**100**) [106].

Fusaridione A acid form containing (4*E*,6*E*,8*E*,10*E*,12*E*,14*E*)-2,6,12,14-tetramethyl-3-oxohexadeca-4,6,8,10,12,14-hexaenoic acid (**101**) [107] was produced by the filamentous fungus *Fusarium heterosporum* ATCC 74349. Two polyene pigments, boletocrocin A and B with common (2*E*,4*E*,6*E*,8*E*,10*E*,12*E*,14*E*)-hexadeca-2,4,6,8,10,12,14-heptaenedioic acid (**102**, 3D graph see Figure 16), were isolated from the fruiting bodies of the Japanese mushroom *Boletus laetissimus* [108]. The same compound named calostomal was detected in the gasteromycete *Calostoma cinnabarinum* [109].

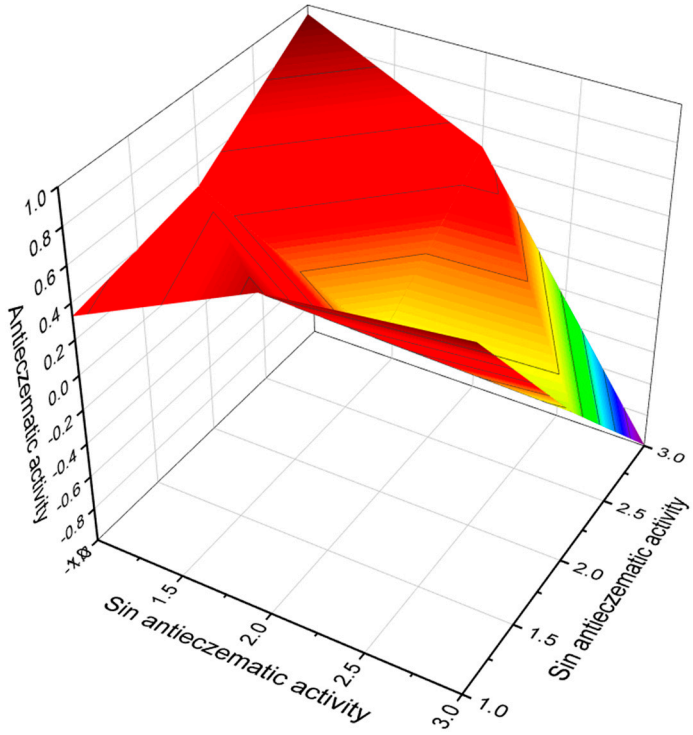


Figure 14. The 3D graph shows the predicted and calculated anti-eczematic activity of FA (**93**, **94**, and **95**). These FA are produced by endophytic microorganisms, *Streptomyces* sp. (**93**), *Aspergillus niger* (**94**), and a gliding bacterium, *Polyangium brachysporum* (**95**), respectively.

A polyene pigment named melanocrocin with FA (**103**) was obtained from lipid extracts of fruit bodies and mycelial cultures of the subterranean fungus *Melanogaster broomeianus*. Melanocrocin is the N-acyl derivative of L-phenylalanine methyl ester with a polyolefinic carboxylic acid [110]. Three glycosphingolipids with a *cis*-17-fatty acyl moiety (**104**, for structure see Figure 17, and activity see Table 7)), namely, catacerebrosides A-C, were obtained from the mushroom *Catathelasma ventricosum* [111].

Streptomyces nodosus NPS007994 found in marine sediment near Scripps Canyon (La Jolla, California) is a producer of the lajollamycin family, a nitro-tetraene spiro-β-lactone-γ-lactam antibiotics. Lajollamycin A contains FA (**105**), and B and C contained (**106**) and D (**107**), and it has shown antimicrobial activity against gram-positive bacteria [112].

Unusual peptide-polyketide hybrid compounds containing a unique spiro-linked β-lactone/γ-lactam, a 5-substituted oxazole ring named oxazolomycins, which exhibits a wide range of biological activities, including antitumor and antibacterial activity, and activity against human immunodeficiency virus [113–115].

Oxazolomycins B and C demonstrated potent inhibitory activity against crown gall formation [116]. 16-Methyl-oxazolomycin showed antibacterial and antialgal activities against *Bacillus subtilis* 1069 (MIC, 5.0/μg/mL) and *Chlorella vulgaris* IFO 15,941 (MIC, 10 μg/mL), respectively, and cytotoxicities (IC_{50} = 0.23 μg/mL against P388 leukemia cells; 4.6 μg/mL against A-549 human lung adenocarcinoma cells) [117]. Oxazolomycin A and 16-methyloxazolomycin contain FA (**108**), B (**109**), C (**110**), and curromycin A and B contain a fatty acid (**111**). Antibiotic curromycin A produced by *Streptomyces hygroscopicus* and *Streptomyces* sp. [118,119]. Both curromycins have shown an inhibitory effect on human immunodeficiency virus replication [120]. Antibioics triedimycins A and B, which are closely related to curromycin, have been found in the culture of *Streptomyces* sp. MJ213-62F4 resembling *Streptomyces melanosporofaciens*. Both triedimycins contain FA (**112**) and exhibited weak antimicrobial activity against *Micrococcus luteus* FDA16 (MIC, 25 μg/mL) and *Pseudomonas aeruginosa* A3 (50 μg/mL) and had potent cytotoxicity to murine leukemia P388 cells (IC_{50} 0.06 and 0.19 μg/mL) [121].

Figure 15. Examples of Japanese mushroom *Boletus laetissimus* (**a**), mushroom *Catathelasma ventricosum* (**b**), Antarctic lichen *Stereocaulon alpinum* (**c**), and a mesophilic proteobacterium *Chondromyces* sp. (**d**) which contain bioactive FA amides.

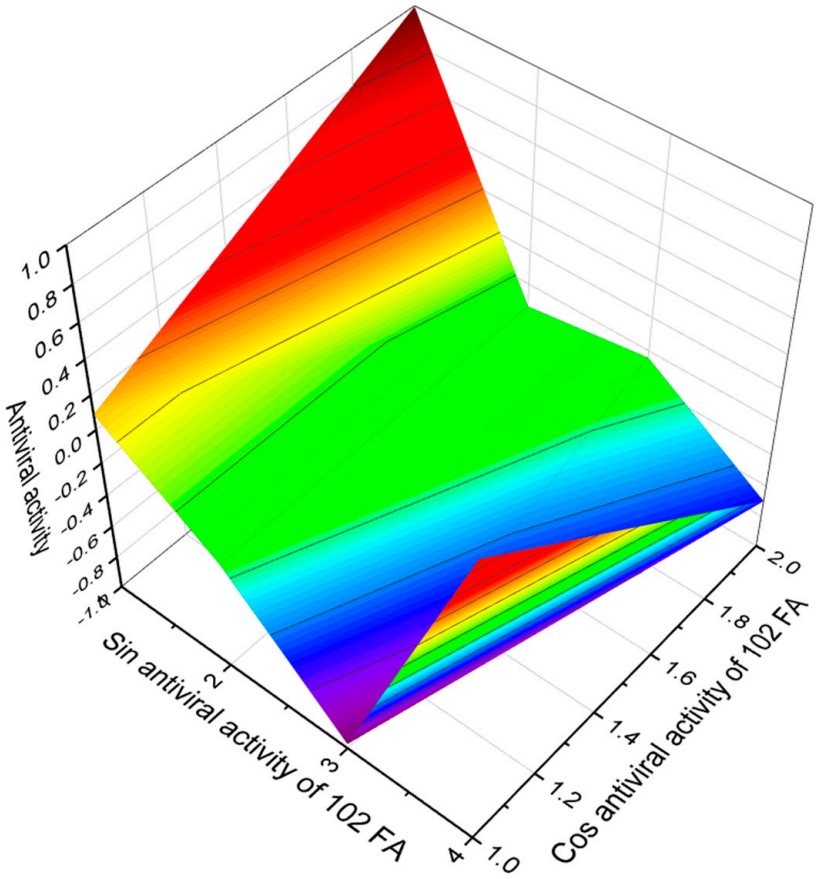


Figure 16. The 3D graph shows the predicted and calculated antiviral activity of FA (**102**). Interestingly, this FA is synthesized in various FA amides by the fruiting bodies of the Japanese mushroom *Boletus laetissimus* or the gasteroid fungus *Calostoma cinnabarinum*.

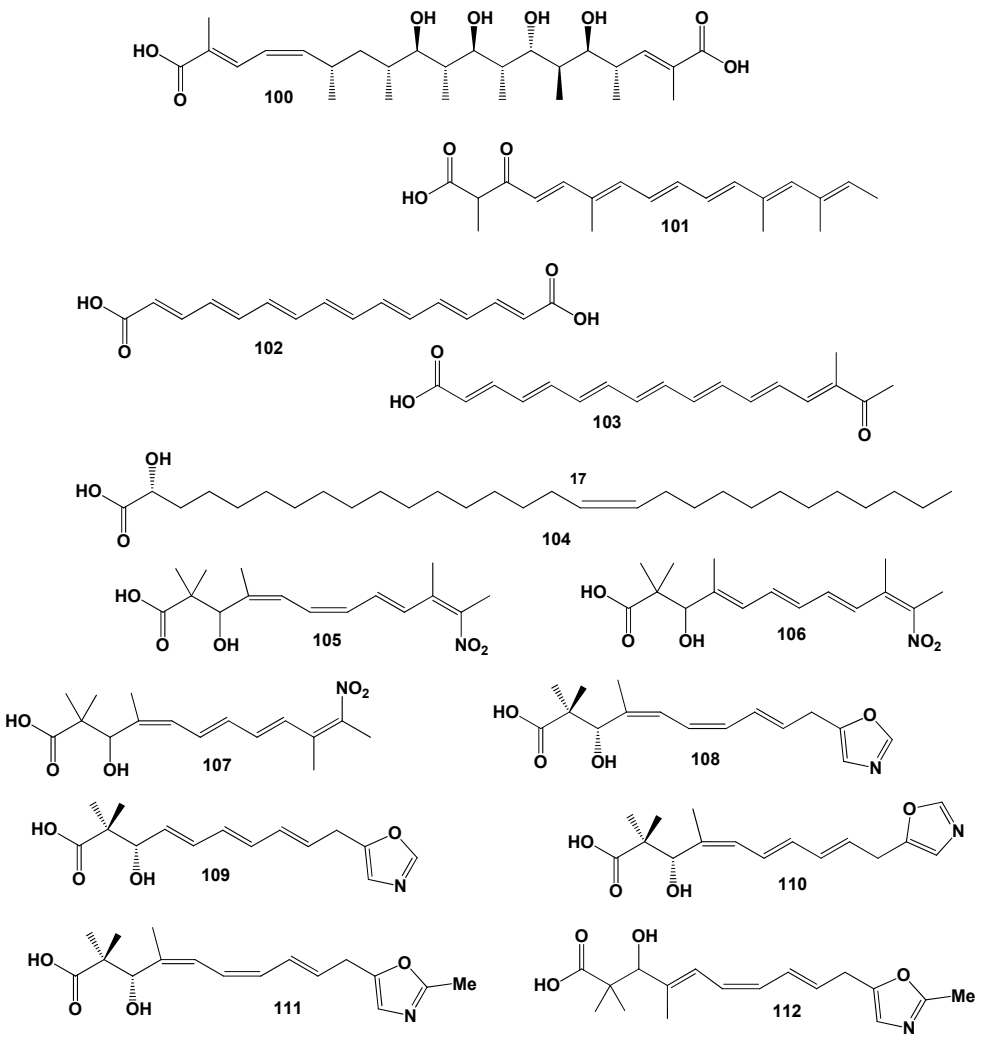


Figure 17. Unique, rare, and unusual FA derived from microorganisms.

Table 7. Pharmacological profile of FA derived from microorganisms.

No.	Predicted Biological Activity, Pa *
100	Antineoplastic (0.945); Apoptosis agonist (0.884); Antifungal (0.809)
101	Antineoplastic (0.892); Antifungal (0.755); Antibacterial (0.640)
102	Antiviral (Arbovirus) (0.930); Antiviral (Picornavirus) (0.917); Anti-inflammatory (0.815)
103	Apoptosis agonist (0.949); Angiogenesis inhibitor (0.892); Antineoplastic (0.881)
104	Lipid metabolism regulator (0.947); Antiviral (Arbovirus) (0.903); Anti-inflammatory (0.715)
105	Antineoplastic (0.987); Apoptosis agonist (0.858)
106	Lipid metabolism regulator (0.800); Antineoplastic (0.789); Hypolipemic (0.705)
107	Anti-inflammatory (0.844); Antineoplastic (0.802); Apoptosis agonist (0.793)
108	Lipid metabolism regulator (0.935); Hypolipemic (0.917); Anti-hypercholesterolemic (0.893)
109	Cell adhesion molecule inhibitor (0.889); Antileukemic (0.840); Antihypertensive (0.765)
110	Antineoplastic (0.864); Apoptosis agonist (0.800); Preneoplastic conditions treatment (0.676)
111	Antineoplastic (0.946); Apoptosis agonist (0.898); Allergic conjunctivitis treatment (0.537)
112	Antineoplastic (0.946); Apoptosis agonist (0.898); Allergic conjunctivitis treatment (0.537)

* Only activities with Pa > 0.5 are shown.

Submerged cultures of the thermophilc fungus *Talaromyces thermophilus* YM cultivated at 45 °C, yielding macrocyclic amides named thermolides A (**113**) and D (**114**, for structure see Figure 18, and activity see Table 8). Thermolide A exhibited strong nematicidal activities against *Meloidogyne incognita*, *Bursaphelenchus xylophilus*, and *Panagrellus redivivus* [122,123].

Le Goff and co-workers [124,125] reported the structural characterization of two alkylhydrazides produced by the bacterial strain *Streptomyces* sp. LMA-545. Geralcins A, B, and D contain 3-(2-oxo-2,5-dihydrofuran-3-yl)-propanoic acid (**115**), and geralcin C contains (*Z*)-2-(1-carboxy-2-hydroxyethyl)-1-hexyldiazene oxide (**116**) [126].

(2*E*,4*E*)-5-Cyclohexylpenta-2,4-dienoic acid (**117**) was found in alisamycin and nisamycin, which was detected in lipid extracts of the culture broth of *Streptomyces* sp. K106 [127]. Nisamycin showed cytotoxic activity, as well as antibacterial and antifungal activities against gram-positive bacteria and fungi [128,129]. Antibiotic asukamycin was obtained from of *Streptomyces nodosus* subsp. *asukaensis*. This antibiotic showed activity against the growth of gram-positive bacteria including *Nocardia asteroides* [130]. (2*E*,4*E*,6*E*)-7-cyclohexylhepta-2,4,6-trienoic acid (**118**) was found in asukamycin and asukamycin A-II.

Neoantimycin and analogues with a rare and unusual ring-extended member was produced by a *Streptomyces* species (*Streptoverticillium orinoci*, *Streptomyces* sp. MST-AS4461) [131–133], and all compounds contained (3*S*,4*S*)-3,4-dihydroxy-2,2-dimethyl-5-phenyl-pentanoic acid (**119**). *Streptomyces violaceoniger* 4521-SVS3 is a producer of prunustatin A with (*R*)-4-hydroxy-2,2-dimethyl-3-oxo-5-phenylpentanoic acid (**120**), and this compound exhibits inhibitory activity against GRP78 expression [134]. Unantimycin A, a neoantimycin analog, contains FA (**120**) [135].

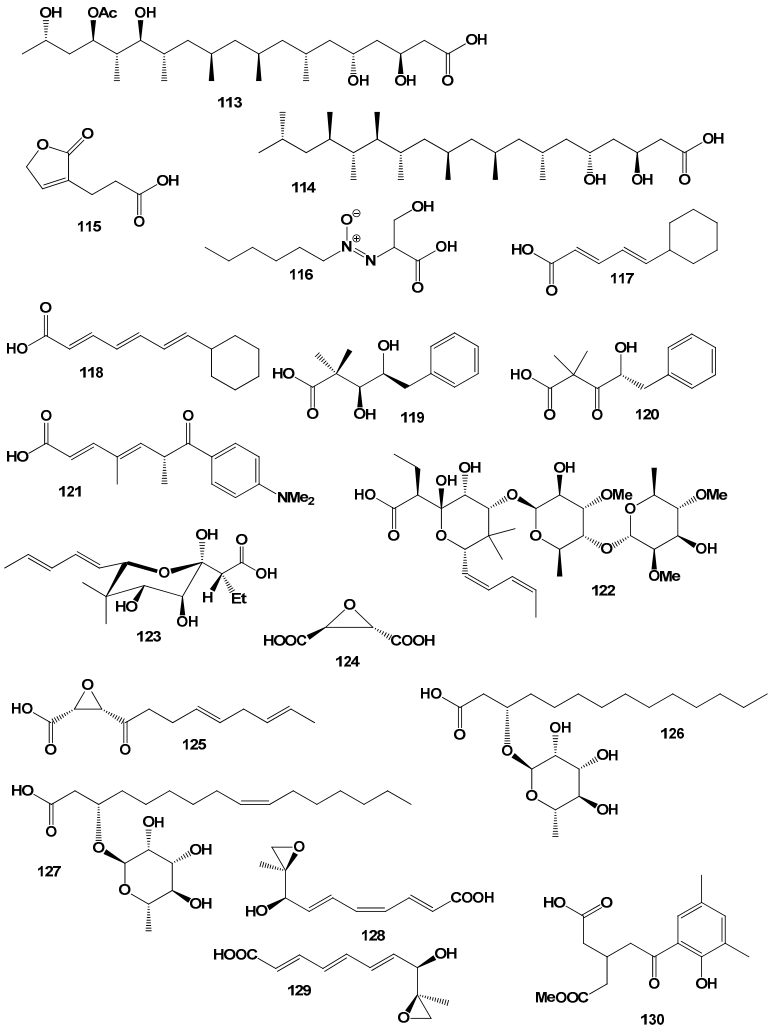


Figure 18. Unique, rare, and unusual FA derived from fungi and bacteria.

Table 8. Pharmacological profile of FA derived from microorganisms.

No.	Predicted Biological Activity, Pa *
113	Antifungal (0.876); Anti-inflammatory (0.776); Antimutagenic (0.674)
114	Antifungal (0.898); Anti-inflammatory (0.823); Antimutagenic (0.672)
115	Hepatic disorders treatment (0.793); Cytoprotectant (0.661)
116	Anti-inflammatory (0.905); Antiviral (Arbovirus) (0.755); Antiviral (Picornavirus) (0.747)
117	Anti-eczematic (0.920); Anti-psoriatic (0.822); Antiviral (Arbovirus) (0.812)
118	Anti-eczematic (0.920); Anti-psoriatic (0.822); Antiviral (Arbovirus) (0.812)
119	Anti-psoriatic (0.929); Dermatologic (0.923); Anti-eczematic (0.695)
120	Lipid metabolism regulator (0.765); Anti-hypercholesterolemic (0.660); Hypolipemic (0.625)
121	Apoptosis agonist (0.834); Antineoplastic (0.817); Proliferative diseases treatment (0.737)
122	Growth stimulant (0.899); Antibacterial (0.897); Antifungal (0.889)
123	Growth stimulant (0.937); Anti-helmintic (0.866); Antiprotozoal (Coccidial) (0.806)
124	Myasthenia Gravis treatment (0.962); Anti-osteoporotic (0.866); Antiarthritic (0.831)
125	Anti-eczematic (0.933); Myasthenia Gravis treatment (0.794); Anti-osteoporotic (0.578)
126	Anti-infective (0.961); Antifungal (0.892); Anti-inflammatory (0.754)
127	Anti-infective (0.966); Antineoplastic (0.842); Antifungal (0.819)
128	Antiviral (Arbovirus) (0.858); Anti-inflammatory (0.785); Antiviral (Picornavirus) (0.723)
129	Antiviral (Arbovirus) (0.858); Anti-inflammatory (0.785); Antiviral (Picornavirus) (0.723)
130	Anti-hypercholesterolemic (0.881); Atherosclerosis treatment (0.859)

* Only activities with Pa > 0.5 are shown.

The marine sponge-derived *Streptomyces* sp. strain RM72 is a producer of trichostatin analogues such as JBIR-109, JBIR-110, and JBIR-111 [136]. All components contain an unusual acid (*R*,2*E*,4*E*)-7-(4-(dimethylamino)-phenyl)-4,6-dimethyl-7-oxohepta-2,4-dienoic acid (**121**).

Efrotomycin including 6-deoxy-4-*O*-(6-deoxy-2,4-di-*O*-methyl-α-L-mannopyranosyl)-3-*O*-methyl-β-D-allopyranose have been detected in the culture of *Nocardia lactamdurans* [137,138]. This antibiotic contains FA (**122**), and aurodox (syn. antibiotic X 5108; goldinodox; goldinomycin; NSC 233989) isolated from *Streptomyces* sp. K06-0806 and contains FA (**123**). The antibiotic aurodox was first described by Berger and co-authors [139,140], and it was produced by *Streptomyces goldiniensis* ATCC 21386. The antibiotic is mainly active against gram-positive bacteria and is an effective poultry growth promotant.

An anamorph, mesophilic fungus *Penicillium citrinum* is a producer of cysteine protease inhibitors, which have been named cathestatin A–C [74]. Cathestatins A–C and estatins A and B have also been found in *Aspergilus terricola* and fungus *Microascus longirostris*, isolated from sponge [141]. All metabolites contain (2*S*,3*S*)-oxirane-2,3-dicarboxylic acid (**124**, 3D graph, see Figure 19).

Cerulenin, with (2*R*,3*S*)-3-((4*E*,7*E*)-nona-4,7-dienoyl)-oxirane-2-carboxylic acid (**125**) was isolated from lipid extracts of an endophytic fungus *Phomopsis* sp. This compound is an inhibitor of FA and polyketide synthase [142,143].

Unusual bicyclic enol-carbamates named brabantamides A–C, although formally known as SB-253514, SB-253517, and SB-253518 were first isolated from the culture extracts of *Pseudomonas fluorescens* [144,145]. Brabantamides A and B contains FA (**126**) and (**127**), respectively.

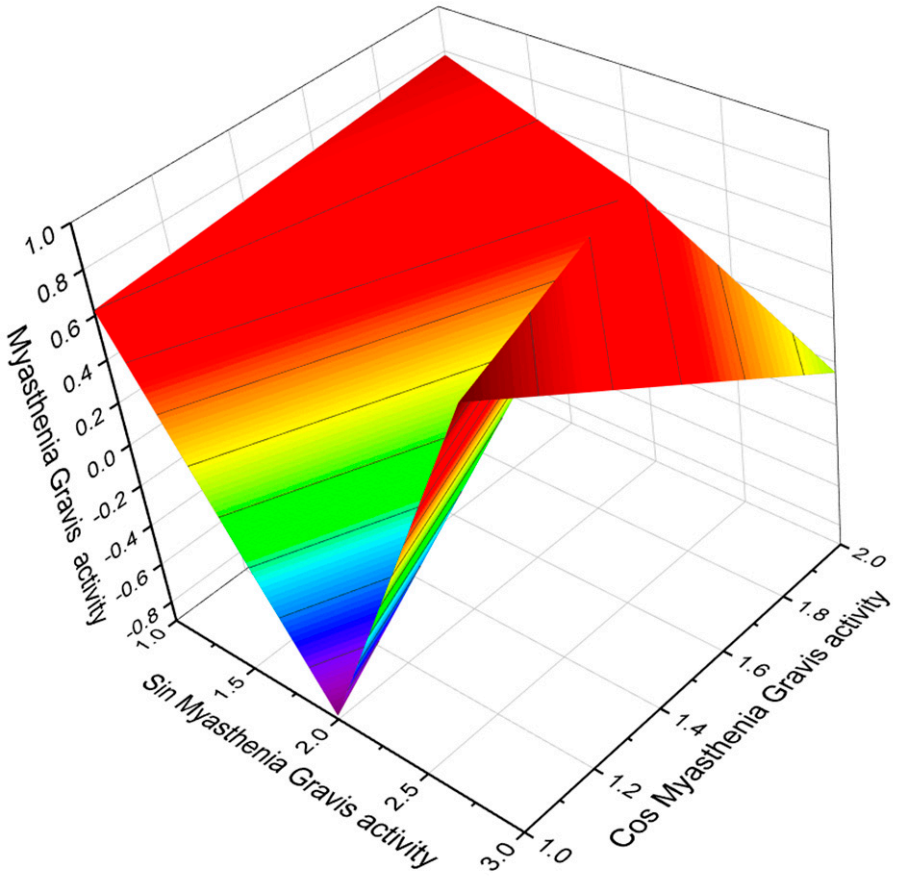


Figure 19. The 3D graph shows the predicted and calculated Myasthenia Gravis activity of FA (**124**). An unusual dicarboxylic acid was found in the FA amides of extracts of two fungi, *Aspergilus terricola* and *Microascus longirostris*.

The filamentous fungus *Alternaria alternata*, which produce various toxins and cause disease in various plants such as Japanese pear, strawberry, and mandarin produced AK-toxin, AF-toxin, and ACT-toxin, respectively, and contained (*R*,2*E*,4*Z*,6*E*)-8-hydroxy-8-((*R*)-2-methyloxiran-2-yl)-octa-2,4,6-trienoic acid (**128**) and (*R*,2*E*,4*E*,6*E*)-8-hydroxy-8-((*R*)-2-methyloxiran-2-yl)-octa-2,4,6-trienoic acid (**129**) [146–148]. Methyl phenatate A with FA (**130**) was detected in the organic extract of a fermentation culture of *Streptomyces* sp. H7372 [149].

Crocacins A–D were produced by *Chondromyces pediculatus* strain Cm p17. Crocacin A showed activity, an MIC of 0.625 µg/mL, against both *Ustilago maydis* and *Saccharomyces cerevisiae*, while crocacin D was more potent against *Saccharomyces cerevisiae*, showing an MIC of 1.4 ng/mL [150]. All compounds having (2*E*,4*E*,6*S*,7*S*,8*R*,9*S*,10*E*)-7,9-dimethoxy-3,6,8-trimethyl-11-phenylundeca-2,4,10-trienoic acid (**131**). A marine actinomycete (strain MST-MA190), which was detected and isolated from a sample of beach sand collected near Lorne on the southwest coast of Victoria (Australia) contained aromatic amides, lorneamide A and lorneamide B [151]. Both compounds contained (*Z*)-4-(2-((*E*)-3-hydroxyhex-1-en-1-yl)-4-methylphenyl)-but-3-enoic acid (**132**) and (*Z*)-4-(4-methyl-2-(3-oxohexyl)phenyl)-but-3-enoic acid (**133**), respectively. The antibiotic meroparamycin with 4-(3-oxo-6-propylnonyl)-benzoic acid (**134**) was produced in the free culture system of *Streptomyces* sp. strain MAR01 [152]. *Streptomyces* sp. MJ995-OF5 is a producer of epostatin which has property as an inhibitor dipeptidyl peptidase II (DPP-II, EC 3.4.14.2) with FA (**135**) [153].

The cultivated strain of *Streptomyces* LZ35 produces cuevaenes A and C, cuevaenes D and E, and cuevaene B. Cuevaenes A–C displayed moderate activity against *Bacillus subtilis* and against fungi *Fusarium verticillioides*, and *Rhizoctonia solani* [154]. Cuevaenes A, C and cuevaene B contained unusual FA (**136–138**), respectively.

Ansamycins designated thiazinotrienomycins A–D were obtained from culture broth of *Streptomyces* sp. MJ672-m3 [155], and contained FA (**139**), and FA (**140**). Cytotrienins A–D with FA (**139** and **140**) are also found in *Streptomyces* sp. RK95-74.12 [156].

A cytotoxic (human A375-S2 and HELA cell lines) isocoumarin with acid (**141**), named Sg17-1-4 were obtained from a marine fungus *Alternaria tenuis* Sg17-1 isolated from an alga (Zhoushan Island, China). The cytotoxicities of these compounds were evaluated in vitro [157].

TPU-0031-A and B antibiotics have been detected in the culture broth of *Streptomyces* sp. TP-A0556 [158]. TPU-0031-A, B and novobiocin contained 4-hydroxy-3-(3-methylbut-2-en-1-yl)-benzoic acid (**142**, for structure see Figure 20, and activity see Table 9).

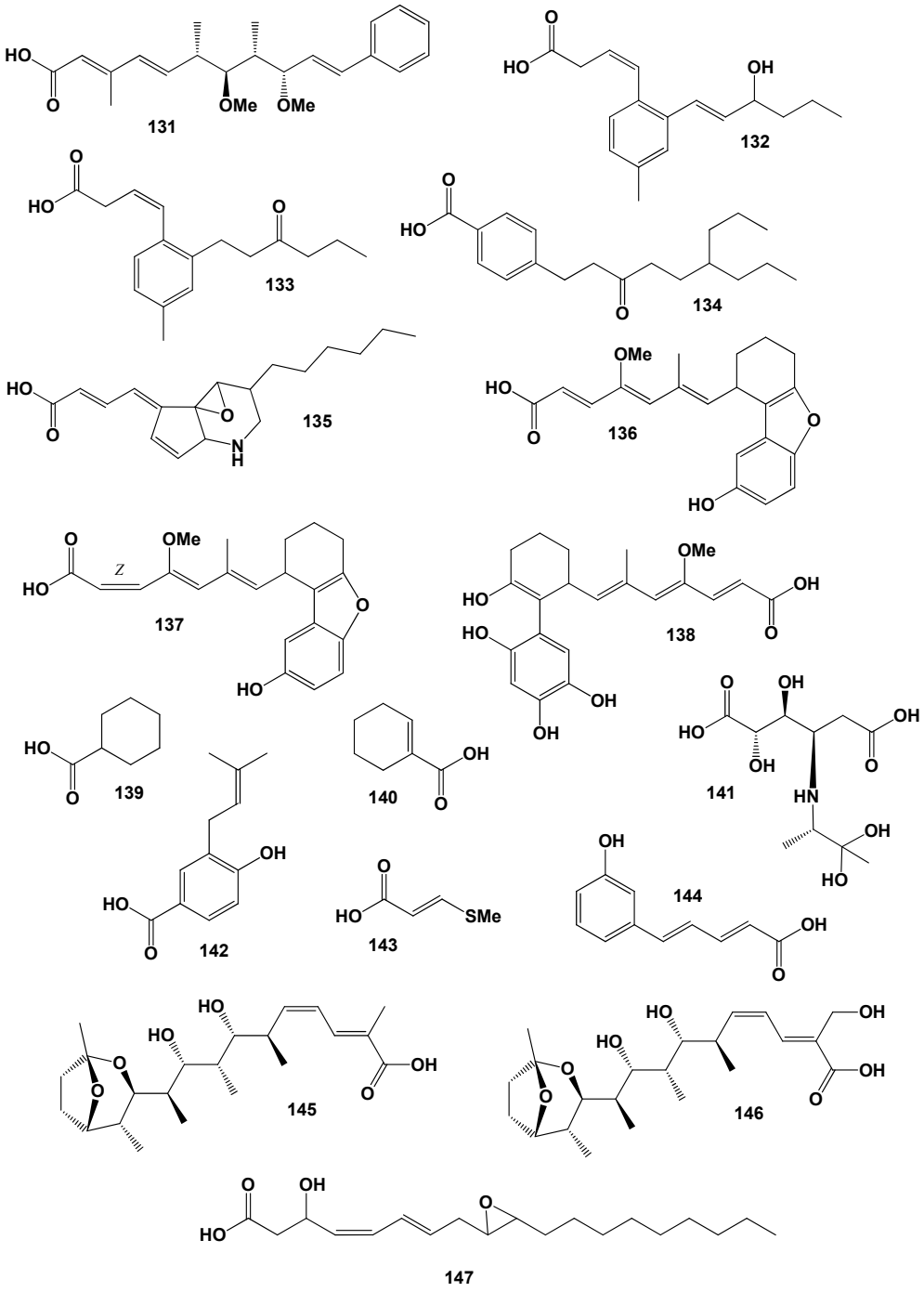


Figure 20. Unique and unusual FA derived from fungal endophytes.

Table 9. Pharmacological profile of FA derived from microorganisms.

No.	Predicted Biological Activity, Pa *
131	Antineoplastic (0.892); Lipid metabolism regulator (0.862); Antifungal (0.777)
132	Anti-inflammatory, intestinal (0.833); Antiviral (Arbovirus) (0.724); Antifungal (0.522)
133	Anti-inflammatory (0.741); Antiviral (Arbovirus) (0.683)
134	Preneoplastic conditions treatment (0.819); Acute neurologic disorders treatment (0.646)
135	Autoimmune disorders treatment (0.977); Antiarthritic (0.968) Systemic lupus erythematosus treatment (0.880); Antiviral (Arbovirus) (0.741)
136	Antineoplastic (0.763); Apoptosis agonist (0.740); Antifungal (0.710)
137	Antineoplastic (0.763); Apoptosis agonist (0.740); Antifungal (0.710)
138	Antineoplastic (0.782); Apoptosis agonist (0.700); Antifungal (0.673)
139	Antiviral (Arbovirus) (0.723); Antiviral (Picornavirus) (0.673); Anti-inflammatory (0.570)
140	Antiviral (Arbovirus) (0.710); Anti-inflammatory (0.680); Antiviral (Picornavirus) (0.594)
141	Antineoplastic (0.813); Antiviral (Arbovirus) (0.748); Antiviral (Picornavirus) (0.585)
142	Anti-infective (0.780); Antiviral (Arbovirus) (0.728); Anti-inflammatory (0.716) Antiviral (Picornavirus) (0.633); Antifungal (0.542); Antibacterial (0.533)
143	Anti-Helicobacter pylori (0.744); Antiviral (Arbovirus) (0.715); Antiviral (Picornavirus) (0.547)
144	Preneoplastic conditions treatment (0.833); Antimutagenic (0.829); Antineoplastic (0.767)
145	Antineoplastic (0.921); Apoptosis agonist (0.798); Chemoprotective (0.590)
146	Antineoplastic (0.922); Antifungal (0.860); Antibacterial (0.824); Apoptosis agonist (0.751)
147	Lipid metabolism regulator (0.956); Vasodilator (0.928); Hypolipemic (0.814)

* Only activities with Pa > 0.5 are shown.

Nucleoside antibiotics, named streptcytosines A–E, have been detected in a culture broth of *Streptomyces* sp. TPU1236A (Okinawa, Japan) [159]. Streptcytosine B and D have contained (*E*)-3-(methylthio)-acrylic (**143**) and 3-methylbut-2-enoic (**81**) acids, respectively.

An endophytic *Streptomyces* sp. YIM65484 isolated from the vine used in traditional Chinese medicine (*Tripterygium wilfordii*) is a producer of the antimicrobial compound with (2E,4E)-5-(3-hydroxyphenyl)-penta-2,4-dienoic acid (**144**) [160].

The cultured broth of the marine actinomycete *Salinispora arenicola* contained a rifamycin antibiotic called salinisporamycin [161], and saliniketals A and B, bicyclic polyketides, were from the same *S. arenicola* [162]. Salinisporamycin and saliniketal A contained FA (**145**), and saliniketal B—FA (**146**, 3D graph, see Figure 21). Korormicin with (4*Z*,6*E*)-3-hydroxy-8-(3-nonyloxiran-2-yl)-octa-4,6-dienoic acid (**147**) had specific inhibitory activity against marine gram-negative bacteria [95].

Myxalamide PI, related to phenalamides, containing FA (**148**, for structure see Figure 22, and activity see Table 10) was isolated from actinomycete *Cystobacter velutus* [163]. Actinomycete *Myxococcus stipitatus* (AJ-12587) from a soil sample from Izu Peninsula, Japan produced antibiotic stipiamide (phenalamide A1) with FA (**149**) [164]. Phenalamide A1 was found to suppress HIV-1 replication in cell cultures and has been detected in *Polyangium* sp. and *Myxococcus stipitatus.* Phenalamide A1 could prevent the HIV-1 infection of MT-4 cells even at concentrations of 1.02 nM, and thiangazole at 4.7 pM [164].

In 1992, Trowitzsch-Kienast and co-workers [165] reported the isolation and characterisation of five new compounds, phenalamides A1, B, A2, A3, and C from *Myxococcus stipitatus* Mx s40. Phenalamide A1 proved to be the same compound as the previously isolated stipiamide. Phenalamide B is a methylated variant of stipiamide, and phenalamide A3 has one less double bond. Phenalamide A2 possesses a cis-alkene, and phenalamide C is an epoxidized derivative. Phenalamides A1, B, A2, and A3 contained (**149**), (**150**), (**151**), (**152**), and (**153**, 3D graph, see Figure 23), respectively.

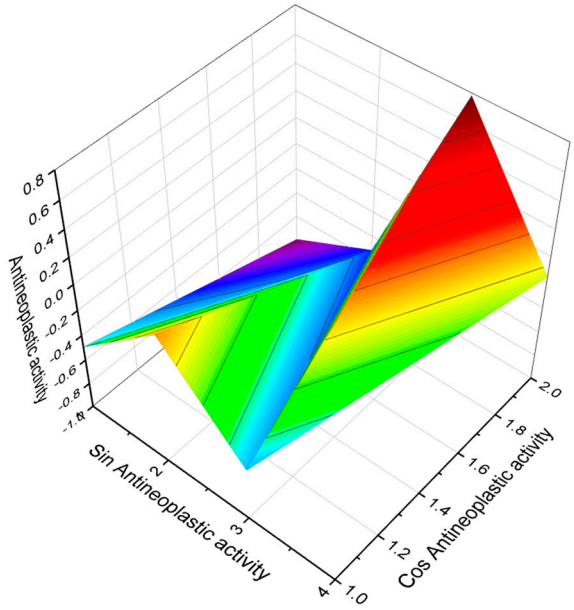


Figure 21. The 3D graph shows the predicted and calculated antineoplastic activity of FA (**145** and **146**). Both FA in the amides is produced by the marine actinomycete *Salinispora arenicola*, and these acids demonstrate anticancer activity with more than 90% confidence.

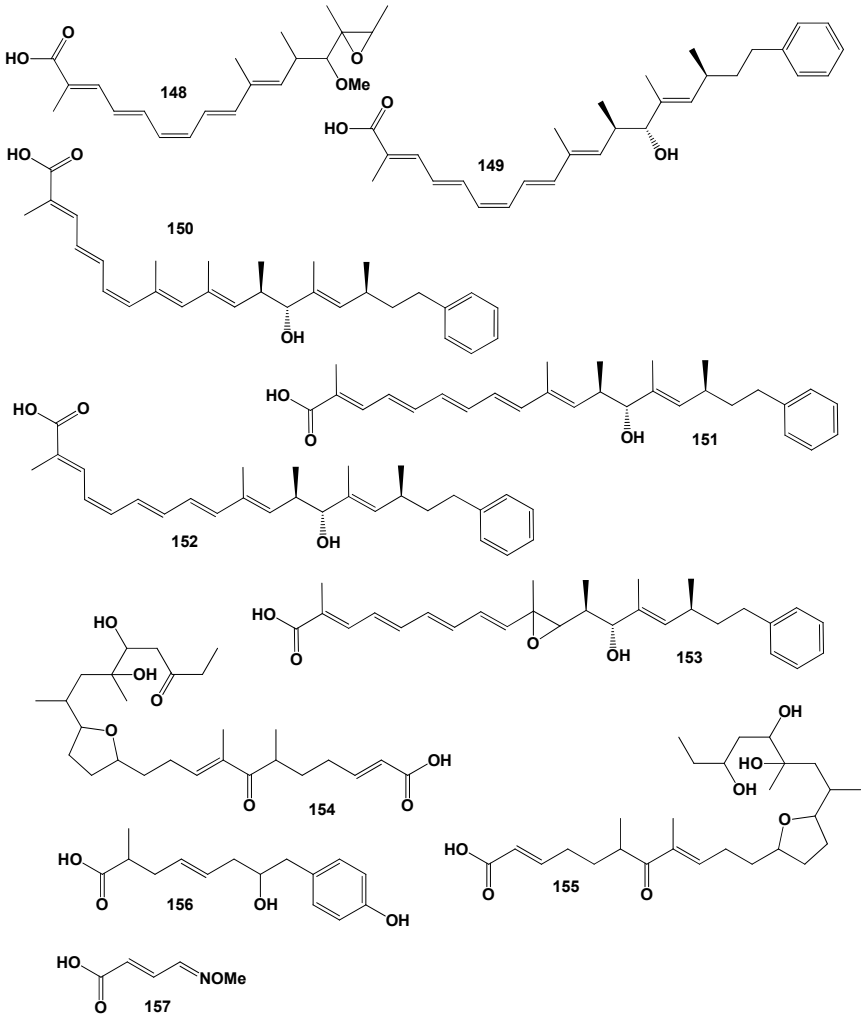


Figure 22. Unusual FA derived from marine actinomycetes.

Table 10. Pharmacological profile of FA derived from microorganisms.

No.	Predicted Biological Activity, Pa *
148	Antineoplastic (0.875); Apoptosis agonist (0.818); Antifungal (0.727); Antiparasitic (0.584)
149	Antineoplastic (0.887); Apoptosis agonist (0.784); Antifungal (0.775); Antibacterial (0.621)
150	Antineoplastic (0.906); Apoptosis agonist (0.834); Antifungal (0.792); Antibacterial (0.645)
151	Antineoplastic (0.887); Apoptosis agonist (0.784); Antifungal (0.775); Antibacterial (0.621)
152	Antineoplastic (0.887); Apoptosis agonist (0.784); Antifungal (0.775); Antibacterial (0.621)
153	Antineoplastic (0.944); Apoptosis agonist (0.823); Antifungal (0.814); Antibacterial (0.652)
154	Lipid metabolism regulator (0.937); Hypolipemic (0.866); Radioprotector (0.850)
155	Lipoprotein disorders treatment (0.912); Atherosclerosis treatment (0.910); Hypolipemic (0.903)
156	Lipid metabolism regulator (0.730); Acute neurologic disorders treatment (0.729) Hypolipemic (0.720); Anti-hypercholesterolemic (0.706); Atherosclerosis treatment (0.566)
157	Antiviral (Arbovirus) (0.761); Antiallergic (0.622); Antifungal (0.541); Antibacterial (0.505)
158	Immunosuppressant (0.933); Antibacterial (0.904); Antineoplastic (0.874); Antifungal (0.867)
159	Immunosuppressant (0.916); Antibacterial (0.893); Antineoplastic (0.880); Antifungal (0.828)
160	Antifungal (0.896); Antibacterial (0.803); Anti-inflammatory (0.747)
161	Antifungal (0.918); Antineoplastic (0.897); Antibacterial (0.849); Apoptosis agonist (0.773)
162	Antifungal (0.906); Antineoplastic (0.871); Antibacterial (0.828); Apoptosis agonist (0.659)
163	Antineoplastic (0.879); Antifungal (0.863); Antibacterial (0.757)
164	Antifungal (0.896); Antineoplastic (0.895); Antibacterial (0.826); Apoptosis agonist (0.739)
165	Antineoplastic (0.905); Antifungal (0.864); Apoptosis agonist (0.837); Antibacterial (0.753)

* Only activities with Pa > 0.5 are shown.

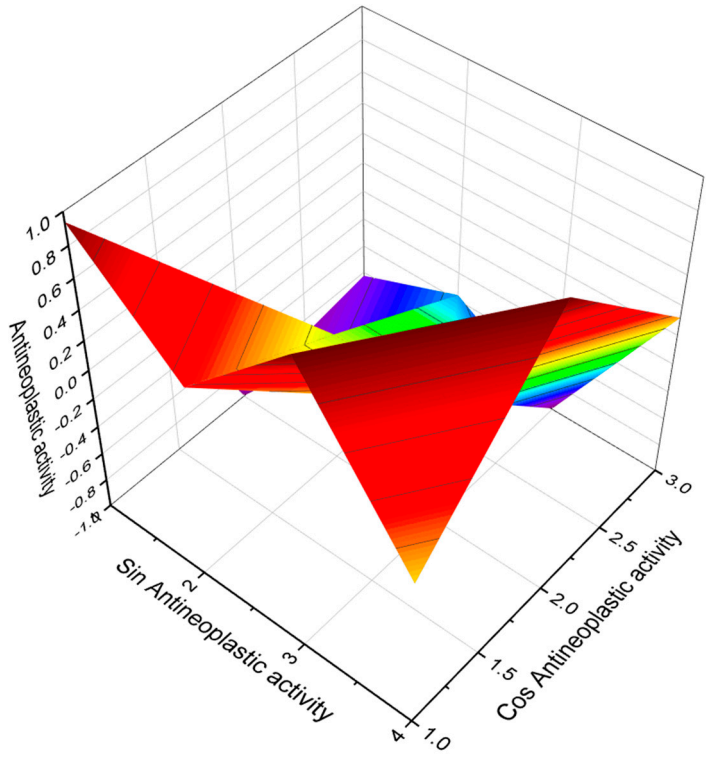


Figure 23. The 3D graph shows the predicted and calculated antineoplastic activity of FA (**150** and **153**). Both FA have been found in amide that is synthesized by a mesophilic Proteobacterium *Myxococcus stipitatus*.

A marine-derived actinomycete *Nocardiopsis* sp. CMB-M0232 obtained from a sediment sample near Brisbane, Australia is a producer of nocardiopsins A–D [166,167]. Nocardiopsins A and C contained FA (**154**), and nocardiopsins B and D contained FA (**155**). Two polyketide metabolites, thailandamide A and thailandamide lactone with (E)-7-hydroxy-8-(4-hydroxyphenyl)-2-methyloct-4-enoic acid (**156**) have been isolated from gram-negative bacillus *Burkholderia thailandensis* [168,169].

Antitumor antibiotics named oximidines I and II were obtained from *Pseudomonas* sp. Q52002. Oximidines I, II and III with (2*E*)-4-(methoxyimino)-but-2-enoic acid (**157**) selectively inhibited the growth of rat 3Y1 cells [170]. Oximidine III, an antitumor antibiotic was isolated from *Pseudomonas* sp. QN05727 [171].

Streptomyces tsukubaenis fermentation broth no. 9993 contained an immunosuppressant, FK-506 [172], and the marine *Streptomyces* sp. CNH189 and *Streptomyces* sp. KCTC 11604BP produced of unnatural 36-methyl-FK506 [173]. Both compounds contained fatty acid (**158**, for structure see Figure 24, activity see Table 10, and 3D graph see Figure 25) and (**159**), respectively.

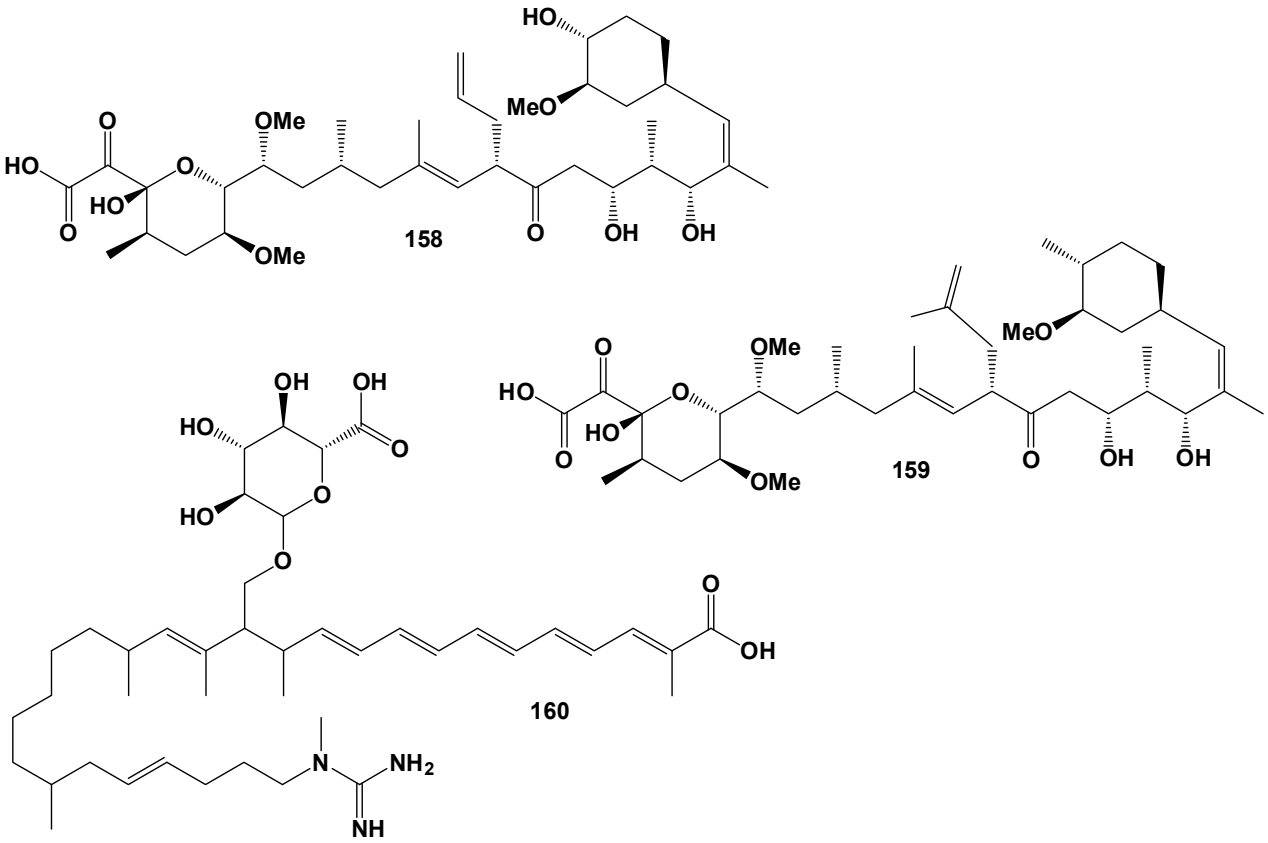


Figure 24. Unusual FA derived from marine fungal endophytes.

Actinomycete *Amycolatopsis orientalis* (see Figure 26), deposited as a vancomycin producer, produced, a glycosidic polyketide ECO-0501, which contained fatty acid (**160**) [174]. *Streptomyces aizunensis* NRRL B-11277 is producer of a unique compound, ECO-02301, with antifungal activity contained amino acid, (**161**, for structure see Figure 27, and for 3D graph see Figure 28) [175]. The fermentation broth of the actinomycete strain *Streptomyces hygroscopicus* TP-A0623 contained clethramycin with FA (**162**) and demonstrated in vitro antifungal activity against *Candida albicans* and *C. glabrata* [176–179].

Streptomyces sp. are producers of zwitterionic polyketides with FA (**163**) and their biosynthesis is well described [180]. Three polyene antibiotics, mediomycins A (**164**), B (**165**), and clethramycin (**163**), were detected in extracts of *Streptomyces mediocidicus* ATCC23936 [181,182].

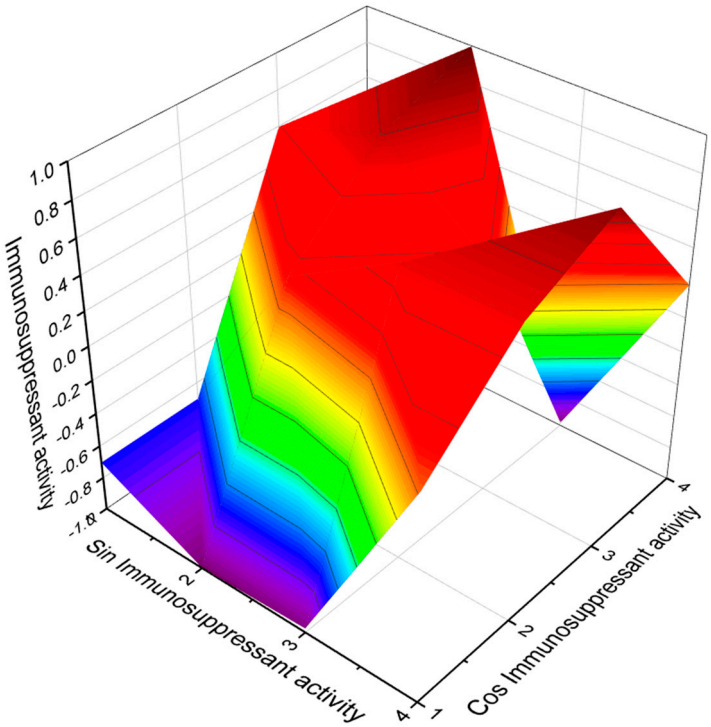


Figure 25. The 3D graph shows the predicted and calculated immunosuppressant activity of FA (**158** and **159**). Both fatty acids were found in a pseudopeptide synthesized by marine fungal endophytes with rare biological properties.

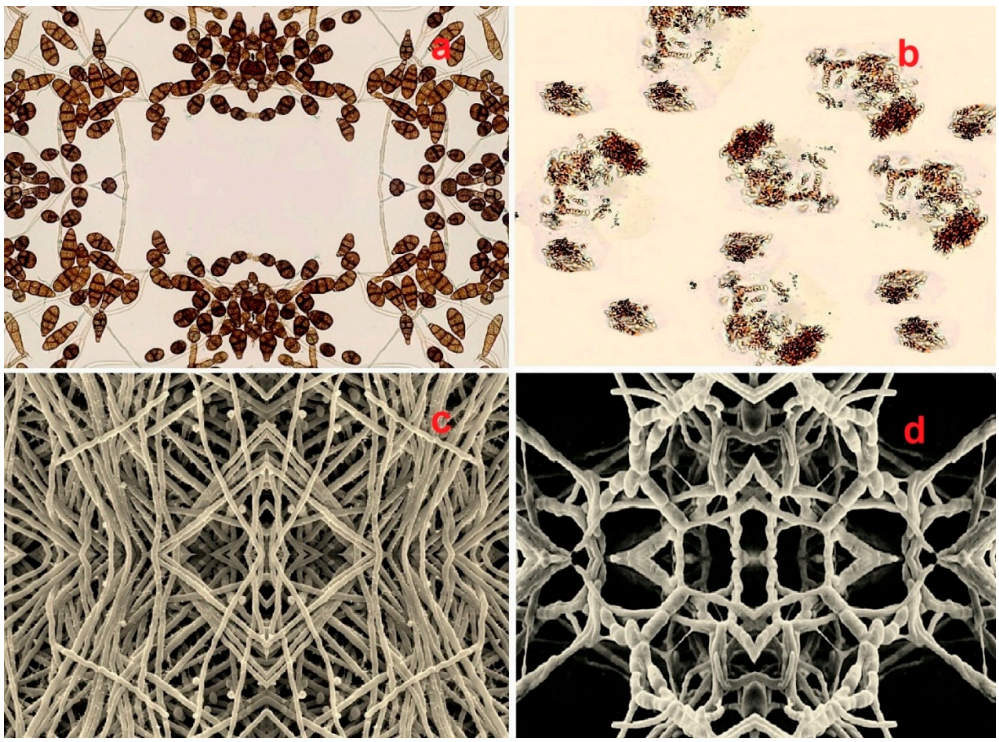


Figure 26. Examples of fungus *Alternaria alternata* (**a**), fungus *Microsphaeropsis* sp. (**b**), actinomycete *Amycolatopsis orientalis* (previously known as *Streptomyces orientalis*) (**c**), and bacteria *Nocardiopsis* sp. (**d**), which are sources of bioactive amides. Pictures adapted by author.

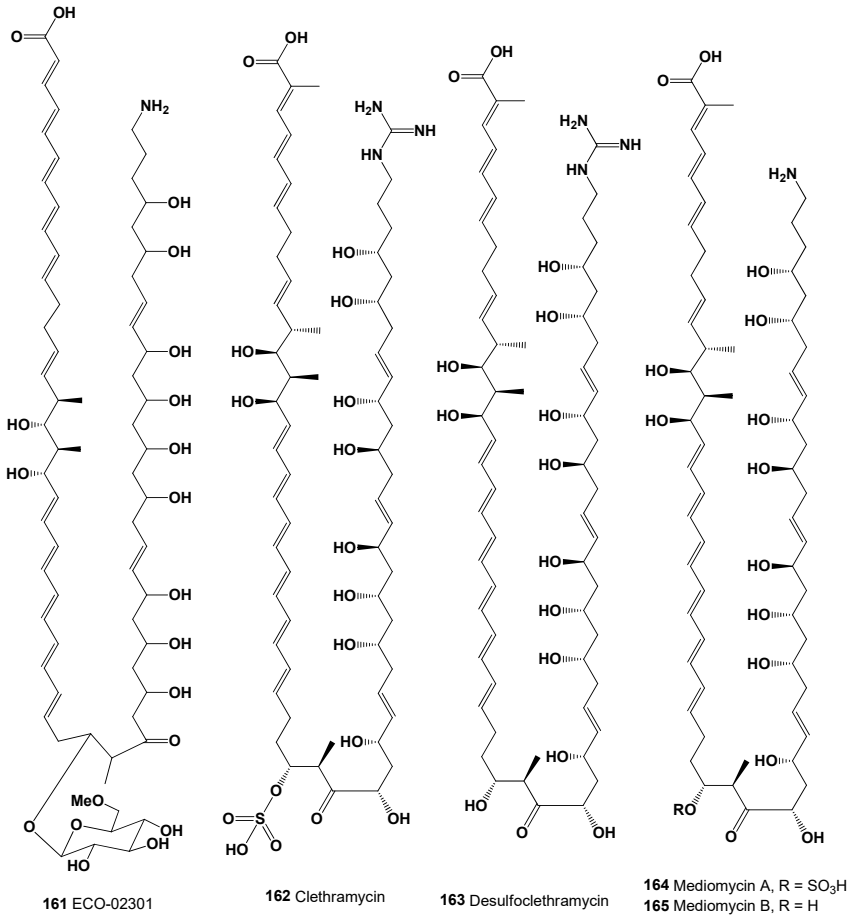


Figure 27. Unique and unusual FA derived from actinomycetes.

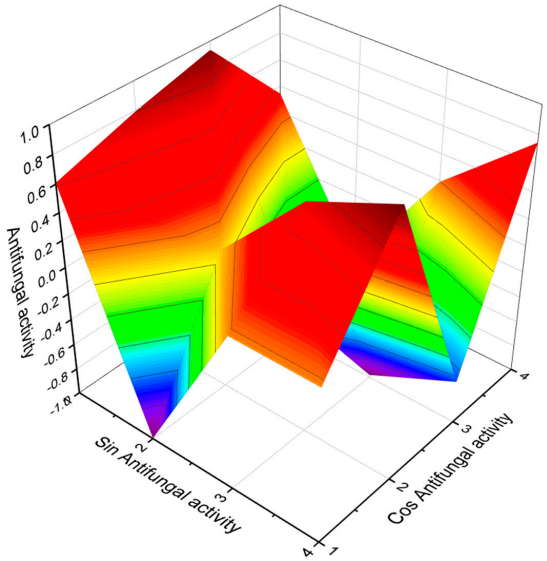


Figure 28. The 3D graph shows the predicted and calculated antifungal activity of FA (**161** and **162**). Both FA were found in the pseudopeptide that synthesizes actinomycete Streptomyces, and both acids show antifungal activity with more than 90% confidence.

3. Structure–Activity Relationships and Biological Activities of Natural FA Amides

Numerous works in the field of pharmacology have shown that the chemical structure of natural chemical molecules predetermines their biological activity, and their mutual relationships can be described as the structure-activity relationships (SAR). Historical studies

have shown that the idea of dependence of activity on the structure of a chemical molecule was first proposed by Brown and Fraser more than 150 years ago, in 1868 [183]. However, according to other data, this was done by Kross in 1863, who established a relationship between the toxicity of primary aliphatic alcohols and their solubility in water [184]. It was established by historians that more than 30 years later Richet in 1893 [185], Meyer in 1899 [186], and Overton in 1901 [187] independently discovered a linear correlation between lipophilicity and biological effects. Additionally, in 1935, Hammett [188,189] described a method for considering the influence of substituents on reaction mechanisms using an equation in which two parameters were considered, namely, the substituent constant and the reaction constant. Moreover, in 1956, Taft made an addition to the Hammett model and proposed an approach to separating the polar, steric, and resonant effects of substituents in aliphatic compounds [190]. Hansch and Fujita, developing these ideas, combined all previous developments and laid the mechanistic basis for the development of the QSAR method [191], and the Hansch linear equation and Hammett electronic constants are described in detail in the book by Hansch and Leo, published in 1995 [192].

At present, well-known computer programs make it possible to evaluate the pharmacological activity of chemical molecules with respect to various biological models with a certain degree of certainty [193–196]. It is known that classical SAR methods are based on the analysis of (quantitative) structure–activity relationships for one or more types of biological activity using organic compounds belonging to the same chemical series as the training set [196].

The software called PASS used to calculate biological activity has been constantly updated and improved over the past thirty years [197] and is based on the analysis of a heterogeneous training set that includes information on more than 1.3 million known biologically active compounds with data on approx. 10,000 types of biological activity [197–199]. Chemical descriptors implemented in PASS, reflecting the features of the ligand-target interaction and the original implementation of the Bayesian approach to elucidation of structure–activity relationships, provide an average accuracy and predictability for several thousand biological activities, equal to approximately 96% [198].

Several comparative studies have shown that PASS is more predictive than some other recently developed methods for assessing biological activity profiles [197,198], although this program is not sufficiently effective for complex molecules or optical isomers. To calculate the pharmacological potential profile of natural substances, we have successfully used PASS for the past fifteen years [200–205].

4. Conclusions

The biological activity of natural FA amides has attracted the attention of pharmacologists for a long time. It is known that this class of compounds is found in many living organisms, including plants, algae, and marine and freshwater invertebrates, but microorganisms attract the greatest interest. This is because various bacteria or fungal endophytes can be isolated from natural sources and cultivated to produce bioactive drugs that are increasingly being used in medicine to fight various diseases. The review offered to the reader covers a small number of natural amides as an example for their further study. This review presents natural FA amides found in extracts from the marine-derived fungi, as well as bacteria isolated from various natural sources. Some fatty acids demonstrated strong antifungal, antibacterial, antiviral, antineoplastic, and anti-inflammatory activities, and other fatty acids have shown rare activities such as antidiabetic, anti-infective, anti-eczematic, antimutagenic, and anti-psoriatic activities. As a rule, the indicated biological activities of fatty acids have a certainty of more than 90%. These data are undoubtedly of interest to chemists and pharmacologists, both from a theoretical and practical point of view.

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