Natural Peroxy Anticancer Agents

Valery M. Dembitsky[1,*], Tatyana A. Gloriozova[2] and Vladimir V. Poroikov[2]

[1]*Department of Medicinal Chemistry and Natural Products, School of Pharmacy, P.O. Box 12065, Hebrew University, Jerusalem 91120, Israel;* [2]*Institute of Biomedical Chemistry, Russian Academy of the Medical Sciences, Moscow 119121, Russia*

Abstract: Present review describes research on novel natural anticancer agents isolated from terrestrial and marine sources. More than 120 cytotoxic anticancer compounds have shown confirmed activity *in vitro* tumor cell lines bioassay and are of current interest to Natural Cancer Institute for further *in vivo* evaluation. Intensive searches for new classes of pharmacologically potent agents produced by terrestrial and marine organisms have resulted in the discovery of dozens of compounds possessing high cytotoxic activities. However, only a limited number of them have been tested in pre-clinical and clinical trials. One of the reasons is a limited supply of the active ingradients from the natural sources. However, the pre-clinical and clinical development of many terrestrial and/or marine-derived natural products into pharmaceuticals is often hampered by a limited supply from the natural source. Total synthesis is of vital importance in these situations, allowing for the production of useful quantities of the target compound for further biological evaluation. With computer program PASS some additional biological activities are also predicted, which point toward new possible applications of these compounds. This review emphasizes the role of terrestrial and marine peroxides as an important source of leads for drug discovery.

Key Words: Peroxides, anticancer, antibacterial, reviewed, predicted, activities, plant, marine, fatty acids, lipids.

1. FATTY ACID PEROXIDES AND THEIR REPORTED ACTIVITIES

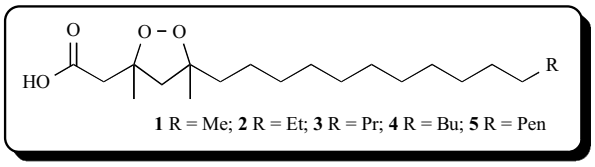
More than 600 peroxides have been isolated and structurally characterized from natural sources, mainly as constituents of family Compositae and occur randomly in about ten other plant families, they also were found in marine invertebrates, particular in sponge species, and other organisms [1-6]. Among peroxides studied, fatty acid derivatives, sesquiterpene endoperoxide, quinghaosu, has already been clinical applied as a new antimalarial drug [7-9].

Some synthesized peroxides as well as natural compounds are shown many biological activities [10-13]. The preparation of chiral compounds in non-racemic form is a goal of great interest in organic synthesis, due to the large application that these compounds have in several fields, such as in medicinal chemistry [14]. Interest in this field has been directed towards the use of biocatalysis for regio- and stereoselective discrimination of alcohol functions, so as to achieve polyhydroxylated compounds in enantiopure form [15,16]. The enantioselective direct introduction of oxygen onto olefins with biocatalysis by haloperoxidases, in oxygenase-type reactions, is very useful and effective for this purpose [17,18].

Among naturally occurring peroxides fatty acid derivatives represented a large group compounds which are shown cytotoxic and anticancer activities.

The first of natural peroxide to be reported was antibiotic plakortin, a six membered ring cycloperoxide found in 1978 by Higgs and Faulkner [19] in the marine sponge *Plakortis halicondrioides.* Natural fatty acid peroxides that have potent biological activities with novel diverse structures are reviewed with classification as secondary metabolites such as 1,2-dioxolane carboxylates (five-membered ring cyclic peroxides), 1,2-dioxane carboxylates (six-membered ring cyclic peroxides), cyclic peroxides with ring sizes greater than six, and their analogues and derivatives.

Saturated fatty acids **1**-**5**, which contain 1,2-dioxolane ring were isolated from *Halichondriidae* marine sponges [20], are antitumor, antibacterial and antifungal agents. Dioxolane-3-acetic acids **4** and **5** at 0.5, and 10 μg/mL inhibited the growth of P388 mouse leukemia cells and HCT-8 human colon cells by 90-100% of control growth, respectively.



1 R = Me; **2** R = Et; **3** R = Pr; **4** R = Bu; **5** R = Pen

Four new metabolites containing five-membered peroxide rings, plakinic acid C **6**, D **8**, and epiplakinic acids C **10**, and D **12**, and their methyl esters **7**,**9**,**11**,**13** have been isolated from a *Plakortis* sponge collected near the Fiji Islands [21]. These substances and their Me esters exhibited cytotoxicity towards human epidermoid carcinoma (KB) cells, human colorectal adenocarcinoma (LoVo) cells, and L1210 murine leukemia. A shorter saturated chain analog, methyl ester of epiplakinic acid E **14**, was isolated from *Plakinastrella onkodes*, and it was showed cytotoxic activity (Table **1**) [22].

*Address correspondence to this author at the Department of Medicinal, Chemistry and Natural Products, School of Pharmacy, P.O. Box 12065, Hebrew University, Jerusalem 91120, Israel; Tel.: 972-2-675-8042; Fax: 972-2-590-2947; E-mail: dvalery@cc.huji.ac.il

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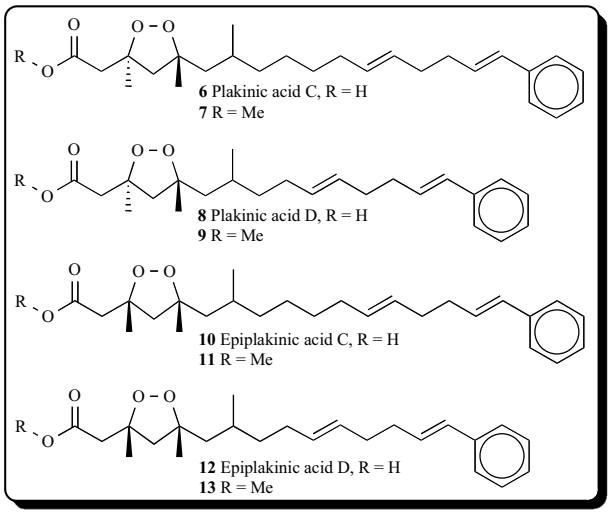
Table 1. Cytotoxic Activity Peroxides Plakinic and Epiplakinic Acids and their Methyl Esters (6-9) Against some Tumor Cell Lines

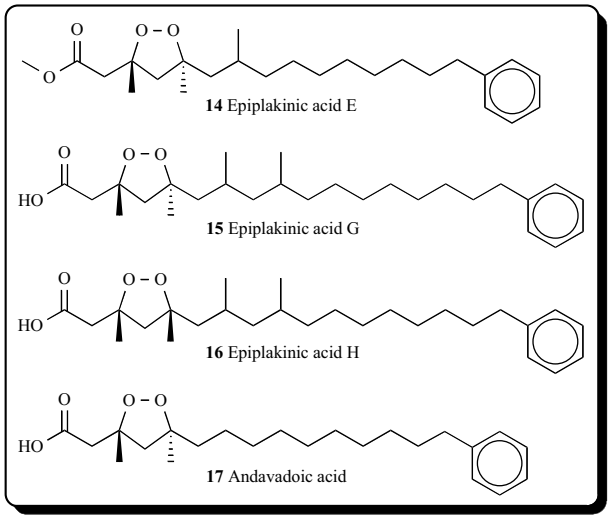
Compound	L1210[a]	KB[b]	LoVo[b]
6	0.017	0.01	0.1
7	0.013	1.0	1.0
8	0.026	0.001	0.001
9	0.0043	1.0	0.1
10	0.052	0.01	1.0
11	0.29	0.1	0.1
12	0.017	0.1	1.0
13	0.003	0.1	0.1

[a]IC_{50} = μg/mL; [b]MIC μg/mL

Two cyclic peroxides, epiplakinic acids G **15** and H **16**, were isolated from the deep-water sponge *Plakortis nigra* from Palau [23]. Isolated metabolites inhibited the HCT-116 human colon tumor cell line [23]. New 1,2-dioxolane, designated andavadoic acid **17**, have been isolated the sponge *Plakortis aff simplex*, collected in Madagascar, was found to be cytotoxic to a series of human tumor cells [24]. Andavadoic acid is **17** showed significant activity against 13 tumor cells with GI_{50} values in the submicromolar range.

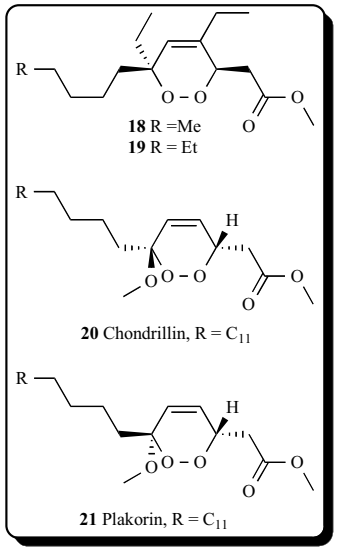


Two new cyclic peroxides, **18** and **19**, were isolated from the Norwegian sponge *Plakortis simplex* [25]. Compound **19** exhibited moderate *in vitro* activity against six solid human tumor cell lines with IC_{50} values in the range 7-15 μg/mL. Chondrillin **20** for first time was isolated from marine sponge belonging to the genus *Chondrilla* by Wells in 1976 [26], and more recently, it was found in extract of Taiwanese marine sponge *Plakortis simplex* [27]. Compounds **20**, and **22-25** were identified from *Plakortis lita* [28]. Both chondrillin **20** and **24** demonstrated cytotoxic activity against P388 cells, ED_{50} > 10 μg/mL. The epimer of chondrillin **20**, plakorin **21**, was identified from *Plakortis* sp. [29]. Plakorin is a potent activator of sarcoplasmic reticulum Ca^{2+} - ATP-ase, and also exhibited activity *in vitro* against murine lymphoma L1210 cells (IC_{50} = 0.85 μg/mL), and human epidermoid carcinoma KB cells (IC_{50} = 1.8 μg/mL) [30]. Compounds **26-29** also were identified from sponge *P.lita*, and these peroxy metabolites having shorter fatty chain-sides than plakorin [31]. Xestin A **30** and B **31** produced by sponge *Xestospongia* sp. [32], and both peroxides were showed cytotoxic activity against P388 cells, IC_{50} = 0.3 and 3.0 μg/mL, respectively.



Other simpler types of peroxides were isolated from the Okinawan sponge *Plakortis lita* [33]. Haterumadioxin A **32** and B **33** were evaluated against a human cancer cell line panel to show significant cytotoxicity against P833 cells, with IC_{50} values of 11 and 5.5 ng/mL, respectively. The cyclic peroxides peroxidessethyl plakortide Z **34**, ethyl didehydroplakortide Z **35**, and methyl didehydro-plakortide Z **36** were identified from the sponge *Plakortis lita* from (Papua New Guinea). Compound **34** was equally active *in vitro* against solid tumor and L1210 leukemia cell lines, and other compounds were less active [34].

Two new cyclic peroxides, **37** and **38**, were isolated from the sponge *Plakortis simplex* [25]. Compound **38** exhibited moderate *in vitro* activity against six solid human tumor cell lines with IC_{50} values in the range 7-15μg/mL (Table **2**) [35]. From the sponge *Plakortis* sp. collected at Jamaica, four new cyclic peroxides, plakortolide I(M) **39**, J(N) **40**, K **41**, and L **42** were isolated [36]. Plakortolide I(M) is the first report of a polyketide-derived peroxide with an α,β-unsaturated ketone moiety in the side chain and exhibits significant antimalarial activity against the W2 clone of *Plasmodium falciparum* with an IC_{50} value of 0.57μg/mL. Two new cyclic peroxides, **43** and **44**, were isolated from sponge *Plakortis* sp. collected at Discovery Bay, Jamaica. Both **43** and **44** exhibited significant antimicrobial activity against pathogenic bacteria and fungi with IC_{50} values of 0.9-5.0 μg/mL and 0.7-8.0 μg/mL, respectively [37].

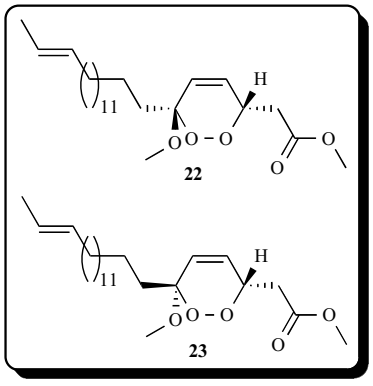


The cytotoxic cyclic peroxides, methyl capucinoate A **45**, **46** and **47** were identified from the Dominican marine sponges *Plakinastrella onkodes* by cytotoxicity-guided fractionation [38]. The cyclic peroxides **45** (B16F1: IC_{50}, 12 ng/mL), and **46** (B16F1: IC_{50}, 12 ng/mL) **47** (P388: IC_{50}, 55 ng/mL), all showed *in vitro* cytotoxicity, but none of them showed *in vivo* activity against murine leukemia P388.

Table 2. Antitumor Activity for Compounds 37 and 38*

Tumor cell line	37	38
GXF 251L	>10	8.3
LXF 529L	>10	7.7
MAXF 401NL	>10	14.9[a]
MEXF 642NL	>10	7.2
RXF 486L	>10	14.4[a]
UXF 1138L	>10	14.1[a]

[a] Value extrapolated; *IC_{50} μg/mL

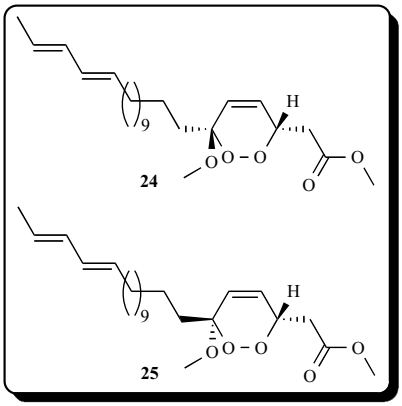


Three new peroxylactones, plakortolides B **48**, C **50**, and D **49**, and a new peroxy ester, epiplakinic acid E Me ester, were isolated and characterized from a previously unstudied marine sponge, Plakinastrella onkodes. A mixture of steroidal peroxides was also found in this organism. Plakortolides B and D, and epiplakinic acid E Me ester, were evaluated for biological activity and found to showed cytotoxicity against the A549 human lung carcinoma and P388 murine leukemia cell lines, and to effect adhesion in an assay employing the EL-4.IL-2 cell line, which correlates with signal transduction activity (Table **3**) [39].

Table 3. Antitumor Activities for Some Peroxy Metabolites*

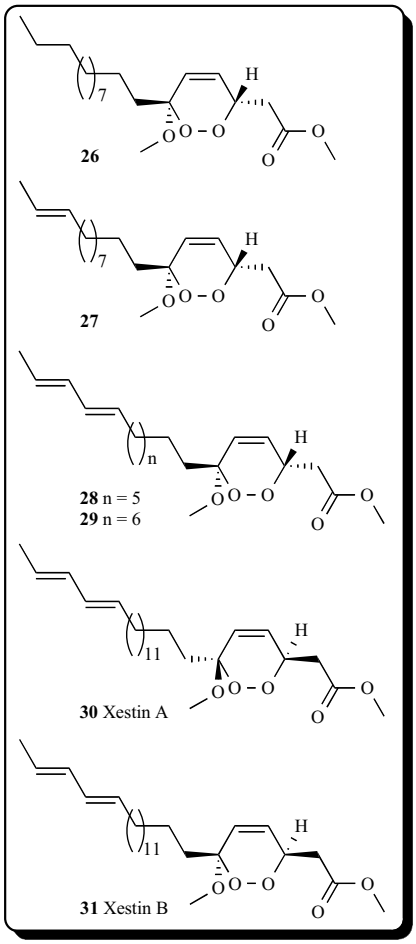
Compound	A549	P388	EL-4
10	2.0	2.5	4.6
20	0.3	2.4	0.4
48	1.3	0.4	4.4
49	3.8	0.8	15.8

*IC_{50}, μg/mL

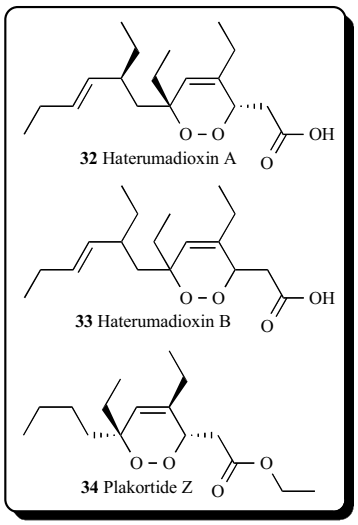


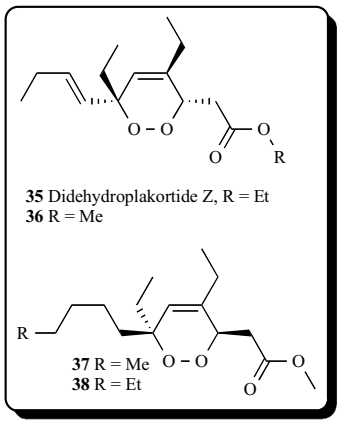
Plakortolide B **48** induced cell adhesion in the EL-4.E-2 cell line, which corresponded to very modest agonistic activity against a suite of protein kinase C isoenzymes [40,41] (activity at 50 pg/mL: alpha - 19%, beta I - 13%, beta II - 27%, delta -9%, epsilon - 38%, and gamma -9%). In contrast, chondrillin **20** induced cell adhesion in the EL-4.E-2 cell line but expressed modest antagonistic activity against the PKC isoenzymes (IC_{50} values (μg/mL): α- +36, β-I +49, β-II +49, δ- +23, ε- + 30, γ- > 150, and ζ- +43). A cytotoxic cyclic peroxide-containing metabolite plakortolides A **51** has been identified from a *Plakortis* sponge [42].

Bioactive compounds from the MeOH-EtOAc extract of the sponge *Plakortis aff simplex*, collected in Madagascar, was found to be cytotoxic to a series of human tumor cells. From this sponge, three new compounds and one known one, two new 1,2-dioxane peroxylactones named plakortolides H (**52**) and I (**53**), and one new 1,2-dioxolane, designated andavadoic acid **13**, have been isolated and their structures elucidated [43]. Andavadoic acid (**13**) is showed significant activity against 13 tumor cells with GI_{50} values in the submicromolar range.

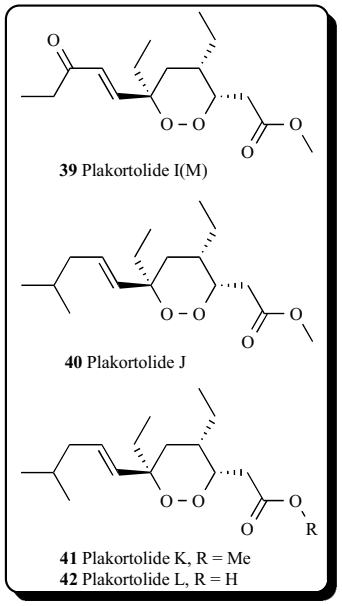


Cyclic peroxide-containing polyketide C16 acids and their Me esters **54**-**57** have been isolated from the Indo-Pacific marine sponge *Plakortis* aff. *simplex* [44]. Compounds **54,55** are proposed to contain a single 1,2-dioxene ring, while **56**,**57** incorporate two 1,2-dioxene rings. The Me esters were found to be active against cultured P-388 murine leukemia cells.



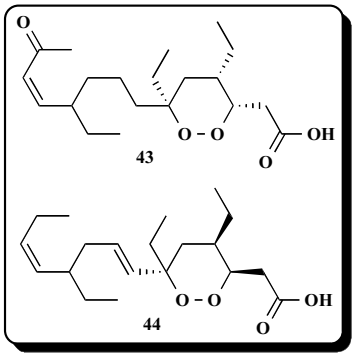


Two antifungal and cytotoxic cyclic-peroxide-containing acids, **58** and **59**, were isolated from a marine sponge, *Plakortis angulospiculatus*, which was collected by scuba off the coast of Venezuela. The acids are potent cytotoxic and antifungal agents although their esters are only cytotoxic [45].



Manadic acid A **60** and B **61** were recovered from extracts of Indonizean *Plakortis* sp. sponge [46]. Both peroxides were shown against tumor cell lines. Two short branched-chain acids, **62** and **63**, were isolated from a sponge collected in New Guinea, a *Callyspongia* sp. [47]. These metabolites inhibited leukemia cell growth with ED_{50} values of 5.5 and 2.6 μg/mL for **52** and **53**, respectively.

Two 3,6-epidioxy-7,10-tetrahydrofurano C26 unsaturated fatty acids, stolonic acids A **64** and B **65**, were isolated from a previously undescribed ascidian species, *Stolonica* sp. collected off the Maldive Islands in the Indian Ocean. Both compounds exhibited antiproliferative activity against selected human melanoma and ovarian tumor cell lines, with IC_{50} values of approximately 0.05-0.1 μg/mL [48].



Stolonoxide A **66** (as Na salt **67**, and methyl ester **68**), a novel peroxide possessing an unprecedented mol. arrangement, has been isolated as its Me ester from the marine Mediterranean tunicate *Stolonica socialis* [49]. A series of stolonoxide A related compounds (**69-75**) was independently isolated by bioassay guided screening from researchers of the University of Cadiz (Spain) [50]. A strong cytotoxicity (IC_{50} 0.1 μg/mL) against several mammalian tumor cell lines for purified and for a crude mixture of (**66-75**) has been found and showed in Table **4** [50-52].

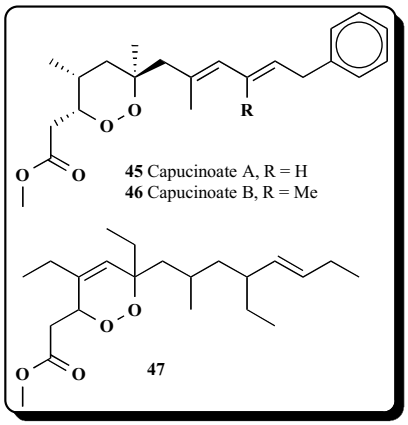


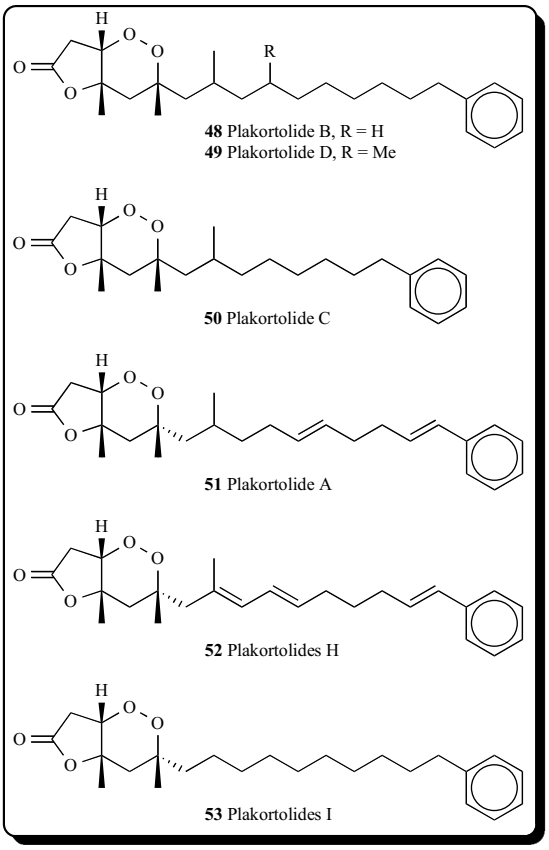
Table 4. Cytotoxic Activity of Stolonoxides Against Tumor Cell Lines*

Compound	P388	A549	HT29	MEL28	DU145
66	0.01	0.10	0.10	0.10	0.10
67	0.01	0.10	0.10	0.10	0.10
68	0.05	0.10	0.10	0.10	0.10
69	0.05	0.10	0.10	0.10	0.10
70	0.10	0.10	0.10	-	0.10
71	0.50	0.10	0.10	0.50	0.10
72	0.50	0.10	0.05	0.50	0.10
73	0.50	0.10	0.05	0.10	0.10
74	0.01	0.01	0.05	0.10	0.10
75	0.01	0.01	0.05	0.10	0.10
Doxorubicin	0.02	0.002	0.05	0.02	-

*IC_{50} μg/mL

2. PREDICTED ACTIVITIES FOR FATTY ACID PEROXY DERIVATIVES

Probable additional biological activities of peroxides obtained from living organisms were evaluated by computer prediction. For this purpose we used the computer program PASSπ [53-60], which predicts about 2,500 pharmacological effects, mechanisms of action, mutagenicity, carcinogenicity, teratogenicity and embryotoxicity on the basis of structural formulae of compounds. PASS predictions are based on structure-activity relationship (SAR) analysis of the training set consisting of about 60,000 drugs, drug-candidates and lead compounds. The algorithm of PASS prediction is described in detail in several publications [53-60]. Using MOL or SD files as an input for the PASS program, a user may get a list of probable biological activities for any drug-like molecule as an output. An explanation of predicted biological activities for some natural metabolites also was published recently [61].



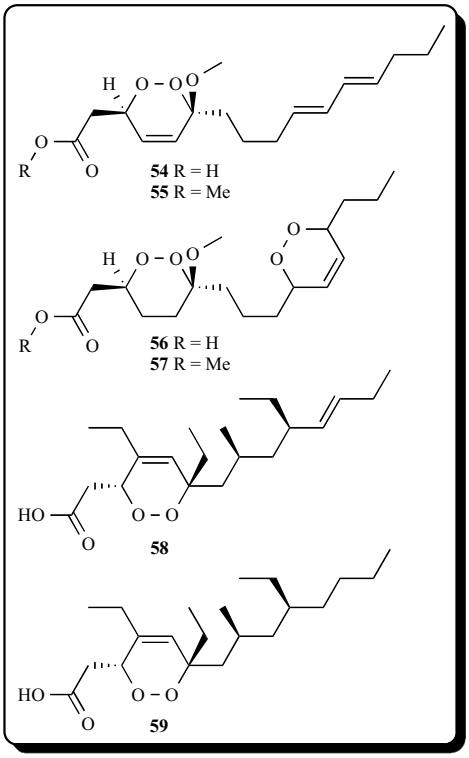
For each activity, P_a and P_i values are calculated, which can be interpreted either as the probabilities of a molecule belonging to the classes of active and inactive compounds, respectively, or as the probabilities of the first and second types of errors in prediction.

Interpretation of the predicted results and selection of the most promising compounds are based on flexible criteria, which depend on the purpose of a particular investigation. If the user chooses a rather high value of P_a as a threshold for

Table 5. Prediction of Biological Activity for (1-6) Fatty Acid Peroxides

No.	Drug-Likeness	Activity Reported	Focal Activity and Activities Confirmed
1	0.977	Antineoplastic Antibacterial Antifungal	**0.688 0.007 Antifungal**
2	0.977	Antineoplastic Antibacterial Antifungal	**0.688 0.007 Antifungal**
3	0.977	Antineoplastic Antibacterial Antifungal	**0.688 0.007 Antifungal**
4	0.977	Antineoplastic Antibacterial Antifungal	**0.688 0.007 Antifungal**
5	0.977	Antineoplastic Antibacterial Antifungal	**0.688 0.007 Antifungal**
6	0.961	Antineoplastic Cytotoxic	**0.899 0.014 Antiseborrheic** 0.264 0.203 Antineoplastic (multiple myeloma) 0.122 0.120 Antineoplastic antibiotic 0.238 0.038 Cytotoxic

selection of probable activities, the chance to confirm the predicted activities by the experiment is also high , but many existing activities will be lost.



Typically, there are several dozen biological activities in the predicted biological activity spectra; activity that is predicted with the highest probability is called "focal". Focal biological activities for natural peroxides isolated from different organisms are shown in the Tables **5-14**, **16-19**, **21**, **22**, and **24**.

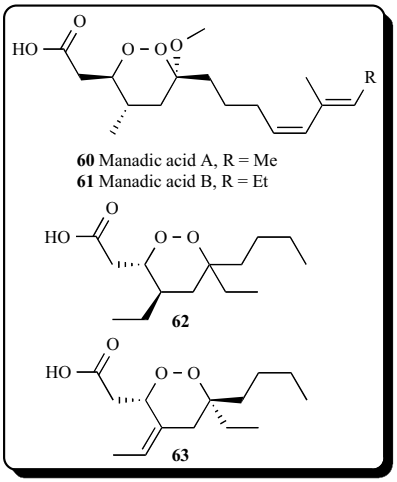


Table 6. Prediction of Biological Activity for (7-18) Fatty Acid Peroxides

No.	Drug-Likeness	Activity Reported	Focal Activity and Activities Confirmed
7	0.928	Antineoplastic Cytotoxic	**0.885 0.020 Antiseborrheic** 0.299 0.132 Antineoplastic (multiple myeloma) 0.145 0.102 Antineoplastic antibiotic 0.257 0.033 Cytotoxic
8	0.962	Antineoplastic Cytotoxic	**0.899 0.014 Antiseborrheic** 0.272 0.186 Antineoplastic (multiple myeloma) 0.125 0.117 Antineoplastic antibiotic 0.243 0.037 Cytotoxic
9	0.928	Antineoplastic Cytotoxic	**0.885 0.020 Antiseborrheic** 0.307 0.119 Antineoplastic (multiple myeloma) 0.149 0.099 Antineoplastic antibiotic 0.261 0.031 Cytotoxic
10	0.961	Antineoplastic Cytotoxic	**0.899 0.014 Antiseborrheic** 0.264 0.203 Antineoplastic (multiple myeloma) 0.122 0.120 Antineoplastic antibiotic 0.238 0.038 Cytotoxic
11	0.928	Antineoplastic Cytotoxic	**0.885 0.020 Antiseborrheic** 0.299 0.132 Antineoplastic (multiple myeloma) 0.145 0.102 Antineoplastic antibiotic 0.257 0.033 Cytotoxic

(Table 6. Contd….)

No.	Drug-Likeness	Activity Reported	Focal Activity and Activities Confirmed
12	0.962	Antineoplastic Cytotoxic	**0.899 0.014 Antiseborrheic** 0.272 0.186 Antineoplastic (multiple myeloma) 0.125 0.117 Antineoplastic antibiotic 0.243 0.037 Cytotoxic
13	0.928	Antineoplastic Cytotoxic	**0.885 0.020 Antiseborrheic** 0.307 0.119 Antineoplastic (multiple myeloma) 0.149 0.099 Antineoplastic antibiotic 0.261 0.031 Cytotoxic
14	0.910	Antineoplastic Cytotoxic	**0.905 0.011 Antiseborrheic** 0.316 0.103 Antineoplastic (multiple myeloma) 0.248 0.036 Cytotoxic
15	0.968	Antineoplastic Cytotoxic	**0.908 0.010 Antiseborrheic** 0.263 0.206 Antineoplastic (multiple myeloma) 0.213 0.047 Cytotoxic
16	0.968	Antineoplastic Cytotoxic	**0.908 0.010 Antiseborrheic** 0.263 0.206 Antineoplastic (multiple myeloma) 0.213 0.047 Cytotoxic
17	0.955	Antineoplastic Cytotoxic	**0.724 0.078 Phosphatase inhibitor**
18	0.897	Antineoplastic Cytotoxic	**0.984 0.003 Antimetabolite** 0.873 0.007 Antineoplastic 0.326 0.088 Antineoplastic (multiple myeloma) 0.139 0.106 Antineoplastic antibiotic 0.249 0.035 Cytotoxic

Table 7. Prediction of Biological Activity for (19-26) Fatty Acid Peroxides

No.	Drug-Likeness	Activity Reported	Focal Activity and Activities Confirmed
19	0.897	Antineoplastic Cytotoxic	**0.984 0.003 Antimetabolite** 0.873 0.007 Antineoplastic 0.326 0.088 Antineoplastic (multiple myeloma) 0.139 0.106 Antineoplastic antibiotic 0.249 0.035 Cytotoxic
20	0.942	Antineoplastic Cytotoxic	**0.775 0.003 Antiprotozoal (Plasmodium)** 0.491 0.064 Antineoplastic 0.390 0.008 Antineoplastic antibiotic 0.320 0.096 Antineoplastic (multiple myeloma) 0.159 0.078 Cytotoxic

(Table 7. Contd….)

No.	Drug-Likeness	Activity Reported	Focal Activity and Activities Confirmed
21	0.942	Antineoplastic Cytotoxic	**0.775 0.003 Antiprotozoal (Plasmodium)** 0.491 0.064 Antineoplastic 0.390 0.008 Antineoplastic antibiotic 0.320 0.096 Antineoplastic (multiple myeloma) 0.159 0.078 Cytotoxic
22	0.975	Antineoplastic Cytotoxic	**0.763 0.003 Antiprotozoal (Plasmodium)** 0.529 0.052 Antineoplastic 0.417 0.007 Antineoplastic antibiotic 0.298 0.134 Antineoplastic (multiple myeloma) 0.233 0.040 Cytotoxic
23	0.975	Antineoplastic Cytotoxic	**0.763 0.003 Antiprotozoal (Plasmodium)** 0.529 0.052 Antineoplastic 0.417 0.007 Antineoplastic antibiotic 0.298 0.134 Antineoplastic (multiple myeloma) 0.233 0.040 Cytotoxic
24	0.979	Antineoplastic Cytotoxic	**0.757 0.003 Antiprotozoal (Plasmodium)** 0.573 0.040 Antineoplastic 0.433 0.007 Antineoplastic antibiotic 0.289 0.151 Antineoplastic (multiple myeloma) 0.249 0.035 Cytotoxic
25	0.979	Antineoplastic Cytotoxic	**0.757 0.003 Antiprotozoal (Plasmodium)** 0.573 0.040 Antineoplastic 0.433 0.007 Antineoplastic antibiotic 0.289 0.151 Antineoplastic (multiple myeloma) 0.249 0.035 Cytotoxic
26	0.942	Antineoplastic Cytotoxic	**0.775 0.003 Antiprotozoal (Plasmodium)** 0.491 0.064 Antineoplastic 0.390 0.008 Antineoplastic antibiotic 0.320 0.096 Antineoplastic (multiple myeloma) 0.159 0.078 Cytotoxic

Table 8. Prediction of Biological Activity for (27-35) Fatty Acid Peroxides

No.	Drug-Likeness	Activity Reported	Focal Activity and Activities Confirmed
27	0.975	Antineoplastic Cytotoxic	**0.763 0.003 Antiprotozoal (Plasmodium)** 0.529 0.052 Antineoplastic 0.417 0.007 Antineoplastic antibiotic 0.298 0.134 Antineoplastic (multiple myeloma) 0.233 0.040 Cytotoxic

(Table 8. Contd….)

No.	Drug-Likeness	Activity Reported	Focal Activity and Activities Confirmed
28	0.979	Antineoplastic Cytotoxic	**0.757 0.003 Antiprotozoal (Plasmodium)** 0.573 0.040 Antineoplastic 0.433 0.007 Antineoplastic antibiotic 0.289 0.151 Antineoplastic (multiple myeloma) 0.249 0.035 Cytotoxic
29	0.979	Antineoplastic Cytotoxic	**0.757 0.003 Antiprotozoal (Plasmodium)** 0.573 0.040 Antineoplastic 0.433 0.007 Antineoplastic antibiotic 0.289 0.151 Antineoplastic (multiple myeloma) 0.249 0.035 Cytotoxic
30	0.979	Antineoplastic Cytotoxic	**0.757 0.003 Antiprotozoal (Plasmodium)** 0.573 0.040 Antineoplastic 0.433 0.007 Antineoplastic antibiotic 0.289 0.151 Antineoplastic (multiple myeloma) 0.249 0.035 Cytotoxic
31	0.979	Antineoplastic Cytotoxic	**0.757 0.003 Antiprotozoal (Plasmodium)** 0.573 0.040 Antineoplastic 0.433 0.007 Antineoplastic antibiotic 0.289 0.151 Antineoplastic (multiple myeloma) 0.249 0.035 Cytotoxic
32	0.950	Antineoplastic Cytotoxic	**0.732 0.004 Antiprotozoal (Plasmodium)** 0.334 0.078 Antineoplastic (multiple myeloma) 0.273 0.035 Antineoplastic antibiotic 0.426 0.007 Cytotoxic
33	0.950	Antineoplastic Cytotoxic	**0.732 0.004 Antiprotozoal (Plasmodium)** 0.334 0.078 Antineoplastic (multiple myeloma) 0.274 0.035 Antineoplastic antibiotic 0.426 0.007 Cytotoxic
34	0.883	Antineoplastic Cytotoxic	**0.985 0.003 Antimetabolite** 0.853 0.007 Antineoplastic 0.271 0.187 Antineoplastic (multiple myeloma) 0.241 0.037 Cytotoxic
35	0.908	Antineoplastic Cytotoxic	**0.899 0.004 Antimetabolite** 0.764 0.011 Antineoplastic 0.204 0.067 Antineoplastic antibiotic 0.281 0.167 Antineoplastic (multiple myeloma) 0.243 0.037 Cytotoxic

3. TERPENOIDS AND THEIR REPORTED ACTIVITIES

Some identified terpenoids from marine and terrestrial showed cytotoxic activities against tumor cell lines. Tasnemoxides A-C (**76-78**), three new cytotoxic cyclic nors-

Table 9. Prediction of Biological Activity for (36-43) Fatty Acid Peroxides

No.	Drug-Likeness	Activity Reported	Focal Activity and Activities Confirmed
36	0.920	Antineoplastic Cytotoxic	**0.906 0.004 Antimetabolite** 0.804 0.008 Antineoplastic 0.343 0.068 Antineoplastic (multiple myeloma) 0.241 0.047 Antineoplastic antibiotic 0.255 0.033 Cytotoxic
37	0.897	Antineoplastic Cytotoxic	**0.984 0.003 Antimetabolite** 0.873 0.007 Antineoplastic 0.326 0.088 Antineoplastic (multiple myeloma) 0.139 0.106 Antineoplastic antibiotic 0.249 0.035 Cytotoxic
38	0.897	Antineoplastic Cytotoxic	**0.984 0.003 Antimetabolite** 0.873 0.007 Antineoplastic 0.326 0.088 Antineoplastic (multiple myeloma) 0.139 0.106 Antineoplastic antibiotic 0.249 0.035 Cytotoxic
39	0.970	Antiprotozoal (Plasmodium)	**0.715 0.010 Leukotriene C4 antagonist** 0.380 0.010 Antineoplastic antibiotic 0.447 0.082 Antineoplastic 0.323 0.092 Antineoplastic (multiple myeloma) 0.134 0.105 Cytotoxic
40	0.984		**0.708 0.004 Antiprotozoal (Plasmodium)** 0.578 0.039 Antineoplastic 0.440 0.007 Antineoplastic antibiotic 0.367 0.045 Antineoplastic (multiple myeloma) 0.147 0.088 Cytotoxic
41	0.984		**0.708 0.004 Antiprotozoal (Plasmodium)** 0.578 0.039 Antineoplastic 0.440 0.007 Antineoplastic antibiotic 0.367 0.045 Antineoplastic (multiple myeloma) 0.147 0.088 Cytotoxic
42	0.991		**0.712 0.020 Oxidoreductase inhibitor** 0.581 0.038 Antineoplastic 0.426 0.007 Antineoplastic antibiotic 0.337 0.075 Antineoplastic (multiple myeloma) 0.127 0.115 Cytotoxic
43	0.991	Antibiotic	**0.788 0.028 Aminocarboxymuconate-semialdehyde decarboxylase inhibitor** 0.415 0.097 Antineoplastic 0.329 0.018 Antineoplastic antibiotic 0.317 0.101 Antineoplastic (multiple myeloma) 0.285 0.024 Cytotoxic 0.140 0.061 Antibiotic Glycopeptide-like

Table 10. Prediction of Biological Activity for (44-52) Fatty Acid Peroxides

No.	Drug-Likeness	Activity Reported	Focal Activity and Activities Confirmed
44	0.993	Antibiotic	**0.722 0.004 Antiprotozoal (Plasmodium)** 0.535 0.050 Antineoplastic 0.418 0.007 Antineoplastic antibiotic 0.261 0.212 Antineoplastic (multiple myeloma) 0.278 0.026 Cytotoxic
45	0.979	Antineoplastic Cytotoxic	**0.765 0.011 Antineoplastic** 0.311 0.023 Antineoplastic antibiotic 0.316 0.103 Antineoplastic (multiple myeloma) 0.209 0.049 Cytotoxic
46	0.987	Antineoplastic Cytotoxic	**0.795 0.009 Antineoplastic** 0.340 0.016 Antineoplastic antibiotic 0.316 0.103 Antineoplastic (multiple myeloma) 0.222 0.044 Cytotoxic
47	0.965	Antineoplastic Cytotoxic	**0.966 0.003 Antimetabolite** 0.831 0.008 Antineoplastic 0.341 0.068 Antineoplastic (multiple myeloma) 0.237 0.049 Antineoplastic antibiotic 0.387 0.008 Cytotoxic
48	0.984	Antineoplastic Cytotoxic Protein kinase C stimulant	**0.885 0.020 Antiseborrheic** 0.571 0.040 Antineoplastic 0.334 0.078 Antineoplastic (multiple myeloma) 0.163 0.090 Antineoplastic antibiotic 0.615 0.004 Cytotoxic 0.077 0.075 Protein kinase stimulant
49	0.989	Antineoplastic Cytotoxic	**0.874 0.026 Antiseborrheic** 0.553 0.045 Antineoplastic 0.318 0.100 Antineoplastic (multiple myeloma) 0.157 0.094 Antineoplastic antibiotic 0.596 0.005 Cytotoxic
50	0.984	Antineoplastic Cytotoxic	**0.885 0.020 Antiseborrheic** 0.571 0.040 Antineoplastic 0.334 0.078 Antineoplastic (multiple myeloma) 0.163 0.090 Antineoplastic antibiotic 0.615 0.004 Cytotoxic
51	0.986	Antineoplastic Cytotoxic	**0.861 0.033 Antiseborrheic** 0.620 0.030 Antineoplastic 0.324 0.091 Antineoplastic (multiple myeloma) 0.201 0.068 Antineoplastic antibiotic 0.603 0.005 Cytotoxic
52	0.990	Antineoplastic Cytotoxic	**0.822 0.008 Antineoplastic** 0.288 0.152 Antineoplastic (multiple myeloma) 0.169 0.086 Antineoplastic antibiotic 0.550 0.005 Cytotoxic

Table 11. Prediction of Biological Activity for (53-60) Fatty Acid Peroxides

No.	Drug-Likeness	Activity Reported	Focal Activity and Activities Confirmed
53	0.987	Antineoplastic Cytotoxic	**0.770 0.057 Phosphatase inhibitor** 0.612 0.031 Antineoplastic 0.299 0.133 Antineoplastic (multiple myeloma) 0.594 0.005 Cytotoxic
54	0.981	Antineoplastic Cytotoxic	**0.745 0.004 Antiprotozoal (Plasmodium)** 0.532 0.050 Antineoplastic 0.385 0.009 Antineoplastic antibiotic 0.292 0.145 Antineoplastic (multiple myeloma) 0.183 0.062 Cytotoxic
55	0.966	Antineoplastic Cytotoxic	**0.762 0.003 Antiprotozoal (Plasmodium)** 0.542 0.048 Antineoplastic 0.407 0.008 Antineoplastic antibiotic 0.308 0.114 Antineoplastic (multiple myeloma) 0.312 0.235 Antineoplastic (solid tumors) 0.205 0.051 Cytotoxic
56	0.970	Antineoplastic Cytotoxic	**0.766 0.003 Antiprotozoal (Plasmodium)** 0.522 0.054 Antineoplastic 0.391 0.008 Antineoplastic antibiotic 0.302 0.127 Antineoplastic (multiple myeloma) 0.156 0.080 Cytotoxic
57	0.946	Antineoplastic Cytotoxic	**0.779 0.003 Antiprotozoal (Plasmodium)** 0.530 0.051 Antineoplastic 0.417 0.007 Antineoplastic antibiotic 0.319 0.096 Antineoplastic (multiple myeloma) 0.181 0.063 Cytotoxic
58	0.983	Antineoplastic Cytotoxic Antifungal	**0.975 0.003 Antimetabolite** 0.835 0.008 Antineoplastic 0.467 0.029 Antifungal 0.313 0.107 Antineoplastic (multiple myeloma) 0.221 0.057 Antineoplastic antibiotic 0.378 0.008 Cytotoxic
59	0.972	Antineoplastic Cytotoxic Antifungal	**0.976 0.003 Antimetabolite** 0.839 0.008 Antineoplastic 0.424 0.041 Antifungal 0.306 0.119 Antineoplastic (multiple myeloma) 0.170 0.085 Antineoplastic antibiotic 0.319 0.015 Cytotoxic
60	0.992	Antineoplastic Cytotoxic	**0.737 0.004 Antiprotozoal (Plasmodium)** 0.723 0.015 Antineoplastic 0.560 0.005 Antineoplastic antibiotic 0..318 0.099 Antineoplastic (multiple myeloma) 0.171 0.069 Cytotoxic

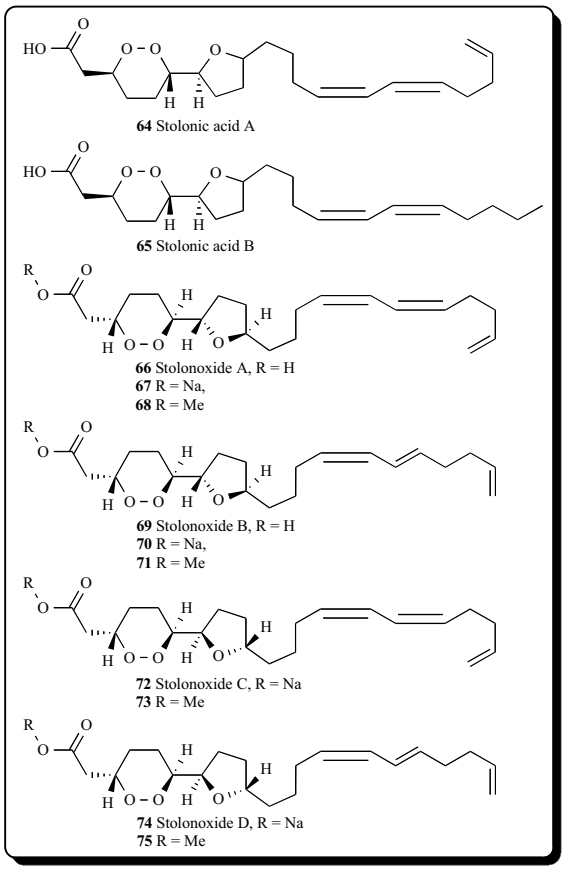


Table 12. Prediction of Biological Activity for (61-62) Fatty Acid Peroxides

No.	Drug-Likeness	Activity Reported	Focal Activity and Activities Confirmed
61	0.991	Antineoplastic Cytotoxic	**0.820 0.059 (-)-4S)-limonene synthase inhibitor** 0.320 0.098 Antineoplastic (multiple myeloma) 0.213 0.062 Antineoplastic antibiotic 0.204 0.051 Cytotoxic
62	0.991	Antineoplastic Cytotoxic	**0.732 0.014 Oxidoreductase inhibitor** 0.556 0.044 Antineoplastic 0.388 0.009 Antineoplastic antibiotic 0.277 0.175 Antineoplastic (multiple myeloma) 0.181 0.063 Cytotoxic

Table 13. Prediction of Biological Activity for (63-72) Fatty Acid Peroxides

No.	Drug-Likeness	Activity Reported	Focal Activity and Activities Confirmed
63	0.980	Antineoplastic Cytotoxic	**0.724 0.004 Antiprotozoal (Plasmodium)** 0.712 0.016 Antineoplastic 0.195 0.071 Antineoplastic antibiotic 0.251 0.237 Antineoplastic (multiple myeloma) 0.154 0.081 Cytotoxic

(Table 13. Contd….)

No.	Drug-Likeness	Activity Reported	Focal Activity and Activities Confirmed
64	0.990	Antimitotic	**0.914 0.007 Phosphatase inhibitor** 0.416 0.096 Antineoplastic 0.300 0.026 Antineoplastic antibiotic 0.283 0.025 Cytotoxic 0.138 0.043 Antimitotic
65	0.990	Antimitotic	**0.918 0.007 Phosphatase inhibitor** 0.417 0.095 Antineoplastic 0.298 0.027 Antineoplastic antibiotic 0.282 0.025 Cytotoxic 0.116 0.059 Antimitotic
66	0.990	Antineoplastic Cytotoxic	**0.914 0.007 Phosphatase inhibitor** 0.416 0.096 Antineoplastic 0.299 0.026 Antineoplastic antibiotic 0.283 0.025 Cytotoxic
67	0.990	Antineoplastic Cytotoxic	**0.919 0.007 Phosphatase inhibitor** 0.307 0.024 Antineoplastic antibiotic 0.367 0.121 Antineoplastic 0.296 0.021 Cytotoxic
68	0.976	Antineoplastic Cytotoxic	**0.900 0.008 Phosphatase inhibitor** 0.419 0.094 Antineoplastic 0.314 0.021 Antineoplastic antibiotic 0.294 0.021 Cytotoxic
69	0.990	Antineoplastic Cytotoxic	**0.914 0.007 Phosphatase inhibitor** 0.416 0.096 Antineoplastic 0.300 0.026 Antineoplastic antibiotic 0.283 0.025 Cytotoxic
70	0.990	Antineoplastic Cytotoxic	**0.920 0.007 Phosphatase inhibitor** 0.308 0.024 Antineoplastic antibiotic 0.367 0.121 Antineoplastic 0.296 0.021 Cytotoxic
71	0.976	Antineoplastic Cytotoxic	**0.901 0.008 Phosphatase inhibitor** 0.420 0.094 Antineoplastic 0.315 0.021 Antineoplastic antibiotic 0.294 0.021 Cytotoxic
72	0.990	Antineoplastic Cytotoxic	**0.921 0.007 Phosphatase inhibitor** 0.307 0.024 Antineoplastic antibiotic 0.367 0.121 Antineoplastic 0.296 0.021 Cytotoxic

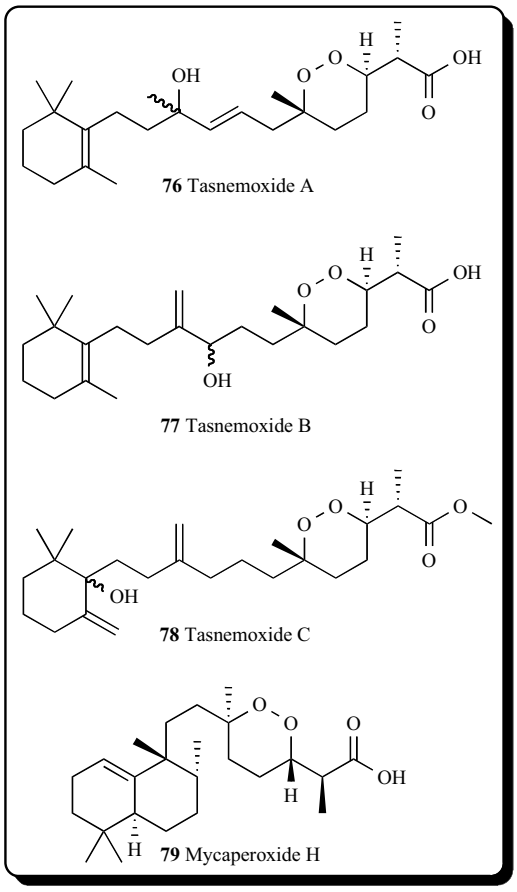
Table 14. Prediction of Biological Activity for (73-75) Fatty Acid Peroxides

No.	Drug-Likeness	Activity Reported	Focal Activity and Activities Confirmed
73	0.976	Antineoplastic Cytotoxic	**0.900 0.008 Phosphatase inhibitor** 0.421 0.094 Antineoplastic 0.316 0.021 Antineoplastic antibiotic 0.294 0.021 Cytotoxic

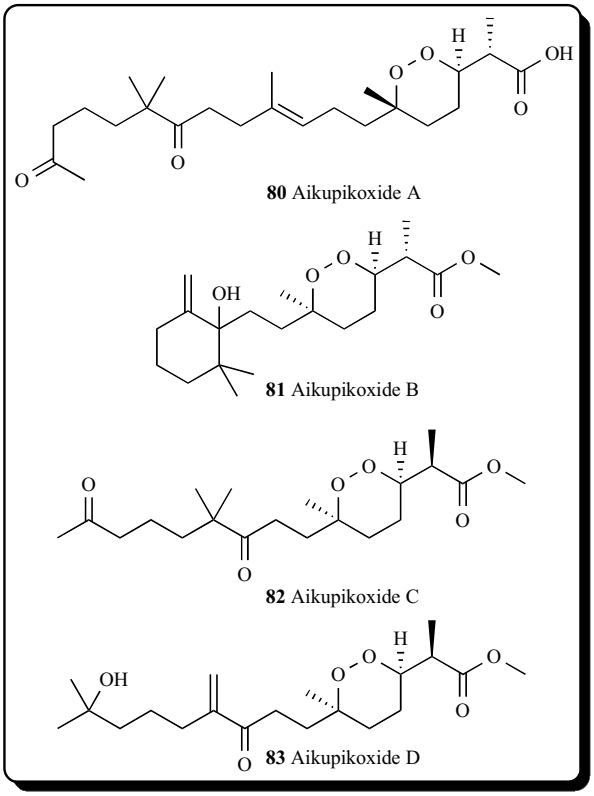
(Table 14. Contd….)

No.	Drug-Likeness	Activity Reported	Focal Activity and Activities Confirmed
74	0.990	Antineoplastic Cytotoxic	**0.920 0.007 Phosphatase inhibitor** 0.307 0.024 Antineoplastic antibiotic 0.367 0.121 Antineoplastic 0.296 0.021 Cytotoxic
75	0.976	Antineoplastic Cytotoxic	**0.901 0.008 Phosphatase inhibitor** 0.420 0.094 Antineoplastic 0.315 0.021 Antineoplastic antibiotic 0.294 0.021 Cytotoxic

estertepene peroxides were isolated from the Red Sea sponge *Diacarnus erythraenus*, together with the known compound sigmosceptrellin B. Isolated metabolites **76-78** are shown cytotoxicity (IC_{50} > 1 μg/mL) against the three types of cells, including murine leukemia (P-388; ATCC: CCL 46), human lung carcinoma (A-549; ATCC: CCL 8), and human colon carcinoma (HT-29; ATCC: HTB 38) [62]. Mycaperoxide H (**79**), a new cyclic norsesterterpene peroxide, was isolated from a Thai marine sponge *Mycale* sp. Mycaperoxide H was cytotoxic against HeLa cells with an IC_{50} value of 0.8 μg/mL [63].



The lipophilic extract of the Red Sea sponge *Diacarnus erythraenus* contain cyclic peroxide, aikupikoxide A **80**, B **81**, C **82**, and D **83**, as well as the known norterpene peroxides muqubilin **84**, and nuapapuin A Me ester **85**. Isolated metabolites **80-83** are showed cytotoxicity (IC_{50} > 1 μg/mL) against the three types of cells, including murine leukemia (P-388; ATCC: CCL 46), human lung carcinoma (A-549; ATCC: CCL 8), and human colon carcinoma (HT-29; ATCC: HTB 38) [64].



The marine sponge *Diacarnus* cf. *spinopoculum* has provided a series of norterpenes, including eight peroxides **86-93** [65]. Eight of these compounds represent additional examples of the muqubilin/sigmosceptrellin classes (norsesterterpene peroxides) or the nuapapuin class (norditerpene peroxides). Also isolated were dinorditerpenones which are biosynthetically related to the muqubilin/sigmosceptrellin structure classes. In all eleven compounds were evaluated for their cytotoxic properties using a soft agar assay system and the NCI's 60 cell-line screen (Table **15**). Overall, the norsesterterpene peroxides were less selective as cytotoxins than norditerpene peroxide analogs. Two compounds, nuapapuin A Me ester and nuapapuin B, which were somewhat selective in their cytotoxic behavior, were selected for further *in vivo* evaluation.

A cytotoxic norsesterterpenoid, mycaleperoxide **94**, was isolated from sponge *Mycale izuensis* collected in Thailand [66]. Cytotoxic a hydroperoxy sesquiterpene lactone peroxyferolide **95** was isolated from *Liriodendron tulipifera* [67]. It possesses activity against KB cells with an ED_{50}, 0.29 μg/mL New hydroperoxy lepidozenes **96–98** were recovered from extracts of marine anemone *Anthopleura pacifica* [68].

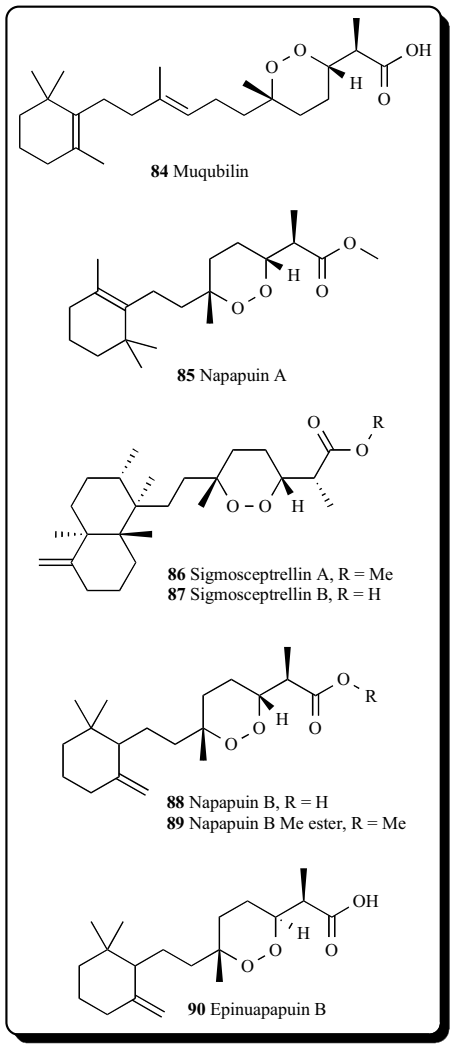
Table 15. ***In Vivo*** **Growth Inhibition (GI_{50} μM) from NCT's 60 Cell Lines**

No.	HL60	MOLT4	A549	KM12	LOX	IGRO	7860	BT549
86	0.14	0.98	1.45	0.94		0.12	0.61	0.96
87	0.14	0.84	0.94	0.95	0.16	0.10	0.50	0.96
88	1.63	2.16	3.05	4.82	0.25	0.63	0.94	1.05
89	1.60	>5.0	0.64	0.40	0.47	0.50	0.27	4.95
90	2.06	>5.0	>5.0	>5.0		1.73	>5.0	>5.0
91	>5.0	>5.0	>5.0	>5.0	>5.0	>5.0	>5.0	>5.0
92	>5.0	>5.0	>5.0	>5.0		>5.0	>5.0	>5.0
93	>5.0	>5.0	>5.0	>5.0	>5.0	2.42	>5.0	

Cell-lines: HL-60 (TB)/MOLT-4, leukemia; A549/ATCC, nonsmall cell lung cancer; KM12, colon cancer; LOX IMVI, melanoma; IGROV1, ovarian cancer; 786-0, renal cancer; BT-549, breast cancer.

Isolated sesquiterpenoids (**96-98**) exhibit the following cytotoxicity against murine melanoma cells (IC_{50} μg/mL): **96,** 0.7; **97,** 2.3; and **98,** 0.9. Nardosinone **99** for the first time was identifird from *Nardostachys chinensis* (Valerianaceae), in 1965 [69]. More recently, it has been detected in the same plant [70,71]. Nardosinone is shown cytotoxic activity against P-388 cells. Planaxool **100**, a cytotoxic cembranoid from the mollusk *Planaxis sulcatus* [72]. Planaxool are showed cytotoxicity (IC_{100}) against L1210 (mouse murine leukemia) cell line at a level of 2.4 μg/mL.

New diterpenoid, **101** having a dolabellane skeleton were isolated from the Okinawan soft coral of the genus *Clavularia*. This diterpenoid showed cytotoxic activity against tumor cells [73]. Sesquiterpene, majapolenes A **102** was isolated from a Philippine collection of *Laurencia majuscule* [74]. Compound **102** represents the major and only active component of the *L. mjuscula* extract. It displayed modest mean response parameter values for all NCI 60-cell lines of 0.4 μM for GI_{50} (50% net growth inhibition, relative to controls), 0.9 μM for TGI (net total growth inhibition) and 2.8 μM for LC_{50} (50% net cell death). Oxygenated sesquiterpenoid, peroxygibberol **103**, was isolated from a Formosan soft coral, *Sinularia gibberosa*. The sesquiterpene **103** exhibited moderate cytotoxicity against the growth of the Hepa59T/VGH cell line (ED_{50} 8.2 μg/mL) [75]. Cytotoxic dolabellane-type diterpene **104** with highest cytotoxicity was identified from extract of the Formosan soft coral *Clavularia inflata.* Reviewed activities for **104** against tumor cell lines: A549 (ED_{50} = 0.57 μg/mL), HT-29 = ED_{50} = 0.31 μg/mL, and P-388 (0.052 μg/mL) [76].

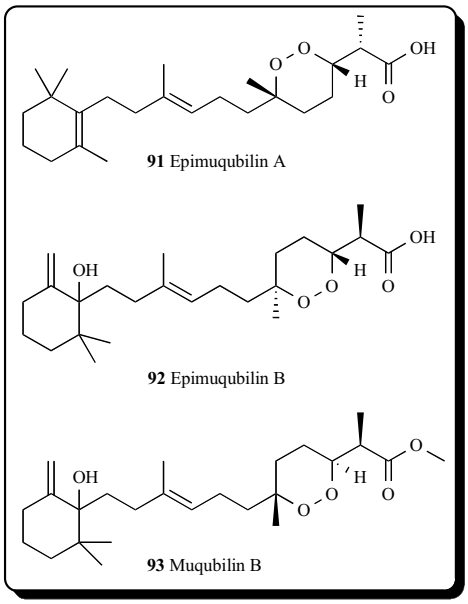


4. TERPENOIDS AND THEIR PREDICTED ACTIVITIES

Additional predicted as well as reported activities for natural peroxy terpenoids are shown in Tables **16-19**.

5. STEROIDAL PEROXIDES AND THEIR REPORTED ACTIVITIES

Many steroids containing hydroperoxy groups of have been identified in marine and terrestrial organisms [2,4]. 24-Hydroperoxy-24-vinylcholesterol **105**, a highly cytotoxic compound, was recovered from the brown alga *Turbinaria*



conoids [77], and more recently from the methanolic extract of the red alga *Ceratodictyon spongiosum* and symbiotic sponge *Sigmadocia symbiotica* [78].

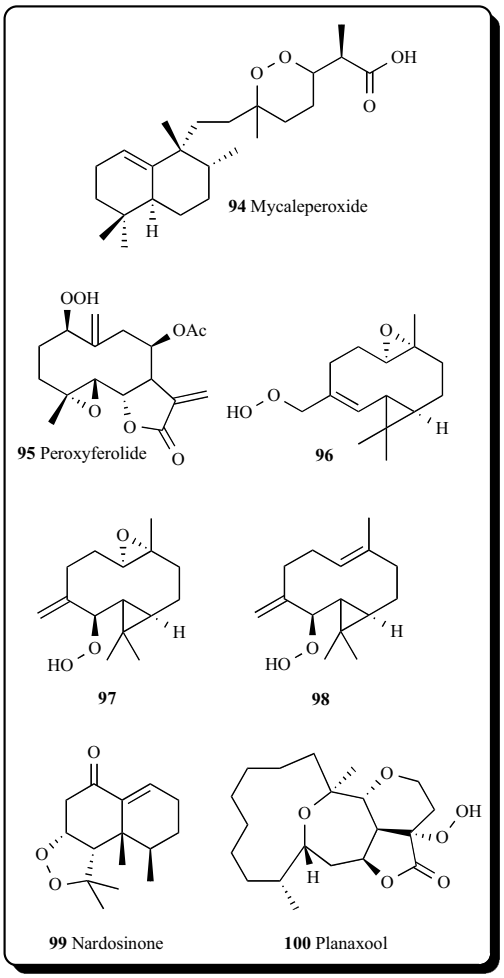


Table 16. Prediction of Biological Activity for Natural Peroxy Compounds (76-87)

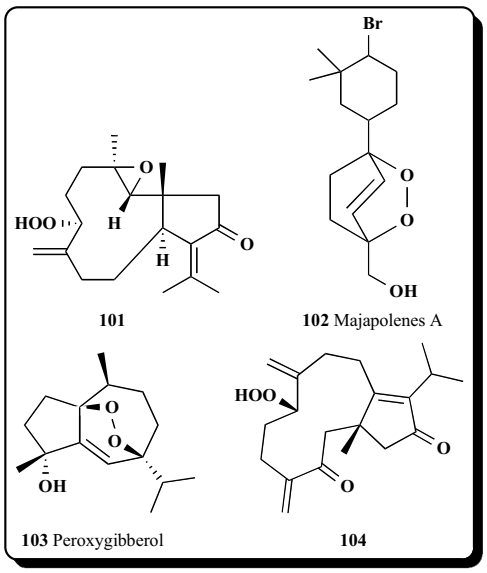
No.	Drug-Likeness	Activity Reported	Focal Activity and Activities Confirmed
76	0.988	Antineoplastic Cytotoxic	**0.763 0.042 Beta-adrenergic-receptor kinase inhibitor** 0.599 0.034 Antineoplastic 0.277 0.174 Antineoplastic (multiple myeloma)
77	0.992	Antineoplastic Cytotoxic	**0.782 0.002 Retinoic acid receptor antagonist** 0.641 0.026 Antineoplastic 0.232 0.040 Cytotoxic
78	0.991	Antineoplastic Cytotoxic	**0.698 0.018 Antineoplastic** 0.263 0.207 Antineoplastic (multiple myeloma) 0.123 0.119 Antineoplastic antibiotic 0.229 0.041 Cytotoxic
79	0.993	Antineoplastic Cytotoxic	**0.722 0.015 Antineoplastic** 0.268 0.195 Antineoplastic (multiple myeloma) 0.152 0.083 Cytotoxic
80	0.978	Antineoplastic Cytotoxic	**0.871 0.021 Mucomembranous protector** 0.347 0.132 Antineoplastic 0.308 0.117 Antineoplastic (multiple myeloma) 0.171 0.069 Cytotoxic
81	0.983	Antineoplastic Cytotoxic	**0.775 0.010 Antineoplastic** 0.298 0.133 Antineoplastic (multiple myeloma) 0.181 0.063 Cytotoxic
82	0.939	Antineoplastic Cytotoxic	**0.711 0.037 Cholesterol synthesis inhibitor** 0.330 0.083 Antineoplastic (multiple myeloma) 0.301 0.163 Antineoplastic 0.132 0.107 Cytotoxic
83	0.973	Antineoplastic Cytotoxic	**0.771 0.020 Cholesterol synthesis inhibitor** 0.479 0.068 Antineoplastic 0.317 0.100 Antineoplastic (multiple myeloma) 0.123 0.123 Cytotoxic
84	0.988		**0.831 0.001 Retinoic acid receptor antagonist** 0.712 0.016 Antineoplastic 0.297 0.136 Antineoplastic (multiple myeloma) 0.180 0.063 Cytotoxic
85	0.968		**0.808 0.002 Retinoic acid receptor antagonist** 0.755 0.012 Antineoplastic 0.293 0.142 Antineoplastic (multiple myeloma) 0.125 0.120 Cytotoxic

(Table 16. Contd….)

No.	Drug-Likeness	Activity Reported	Focal Activity and Activities Confirmed
86	0.991	Antineoplastic Cytotoxic	**0.852 0.000 Transforming growth factor beta 1 agonist** 0.709 0.017 Antineoplastic 0.286 0.156 Antineoplastic (multiple myeloma) 0.165 0.073 Cytotoxic
87	0.992	Antineoplastic Cytotoxic	**0.858 0.000 Transforming growth factor beta 1 agonist** 0.698 0.018 Antineoplastic 0.257 0.222 Antineoplastic (multiple myeloma)

Table 17. Prediction of Biological Activity for Natural Peroxy Compounds (88-91)

No.	Drug-Likeness	Activity Reported	Focal Activity and Activities Confirmed
88	0.993	Antineoplastic Cytotoxic	**0.774 0.010 Antineoplastic** 0.150 0.098 Antineoplastic antibiotic 0.227 0.042 Cytotoxic
89	0.992	Antineoplastic Cytotoxic	**0.783 0.009 Antineoplastic** 0.268 0.194 Antineoplastic (multiple myeloma) 0.235 0.039 Cytotoxic
90	0.993	Antineoplastic Cytotoxic	**0.774 0.010 Antineoplastic** 0.150 0.098 Antineoplastic antibiotic 0.227 0.042 Cytotoxic
91	0.991	Antineoplastic Cytotoxic	**0.845 0.001 Retinoic acid receptor antagonist** 0.699 0.018 Antineoplastic 0.268 0.195 Antineoplastic (multiple myeloma) 0.172 0.068 Cytotoxic



101 **102** Majapolenes A

103 Peroxygibberol **104**

Table 18. Prediction of Biological Activity for Natural Peroxy Compounds (92-98)

No.	Drug-Likeness	Activity Reported	Focal Activity and Activities Confirmed
92	0.993	Antineoplastic Cytotoxic	**0.750 0.013 Antineoplastic** 0.268 0.194 Antineoplastic (multiple myeloma) 0.248 0.035 Cytotoxic
93	0.992	Antineoplastic Cytotoxic	**0.851 0.045 (-)-(4S)-limonene synthase inhibitor** 0.748 0.013 Antineoplastic 0.299 0.129 Antineoplastic (multiple myeloma) 0.250 0.035 Cytotoxic
94	0.993	Antineoplastic Cytotoxic	**0.722 0.015 Antineoplastic** 0.268 0.195 Antineoplastic (multiple myeloma) 0.152 0.083 Cytotoxic
95	0.993	Antineoplastic Cytotoxic	**0.930 0.007 Antineoplastic** 0.425 0.017 Antineoplastic (multiple myeloma) 0.205 0.065 Antineoplastic antibiotic 0.134 0.019 Antineoplastic, alkylator 0.602 0.005 Cytotoxic
96	0.976	Antineoplastic Cytotoxic	**0.942 0.004 4-Methoxybenzoate monooxygenase (O-demethylating) inhibitor** 0.608 0.032 Antineoplastic 0.325 0.090 Antineoplastic (multiple myeloma) 0.317 0.015 Cytotoxic
97	0.991	Antineoplastic Cytotoxic	**0.885 0.012 Phosphatase inhibitor** 0.829 0.008 Antineoplastic 0.135 0.019 Antineoplastic, alkylator 0.464 0.006 Cytotoxic

Table 19. Prediction of Biological Activity for Natural Peroxy Compounds (98-104)

No.	Drug-Likeness	Activity Reported	Focal Activity and Activities Confirmed
98	0.972	Antineoplastic Cytotoxic	**0.883 0.005 4-Methoxybenzoate monooxygenase (O-demethylating) inhibitor** 0.695 0.019 Antineoplastic 0.167 0.015 Antineoplastic, alkylator 0.348 0.011 Cytotoxic
99	0.982	Antineoplastic Cytotoxic	**0.866 0.030 Antiseborrheic** 0.550 0.006 Antineoplastic (multiple myeloma) 0.463 0.075 Antineoplastic 0.315 0.019 Antineoplastic (breast cancer) 0.266 0.030 Cytotoxic

(Table 19. Contd….)

No.	Drug-Likeness	Activity Reported	Focal Activity and Activities Confirmed
100	0.993	Antineoplastic Cytotoxic	**0.941 0.005 Phosphatase inhibitor** 0.830 0.008 Antineoplastic 0.379 0.037 Antineoplastic (multiple myeloma) 0.300 0.026 Antineoplastic antibiotic 0.145 0.017 Antineoplastic, alkylator 0.350 0.010 Cytotoxic
101	0.987	Antineoplastic Cytotoxic	**0.940 0.006 Urologic disorders treatment** 0.874 0.007 Antineoplastic 0.498 0.007 Antineoplastic (multiple myeloma) 0.124 0.022 Antineoplastic, alkylator 0.367 0.009 Cytotoxic
102	0.964	Antineoplastic Cytotoxic	**0.814 0.008 Antineoplastic** 0.244 0.046 Antineoplastic antibiotic
103	0.992	Antineoplastic Cytotoxic	**0.926 0.006 Phosphatase inhibitor** 0.326 0.087 Antineoplastic (multiple myeloma) 0.184 0.061 Cytotoxic
104	0.979	Antineoplastic Cytotoxic	**0.821 0.007 4-Methoxybenzoate monooxygenase (O-demethylating) inhibitor** 0.725 0.015 Antineoplastic 0.422 0.017 Antineoplastic (multiple myeloma) 0.286 0.024 Cytotoxic

The ubiquitous ergosterol peroxide **106** was isolated from number of sources, marine as well as terrestrial. In addition, a glucosylated derivative of ergosterol peroxide **107** has been obtained from *Hericum erinacens* [79]. Ergosterol peroxide **106** is showed potent cytotoxicity against mouse lymphemia L-1210/v/c *in vitro*, but exhibited no significant antitumor

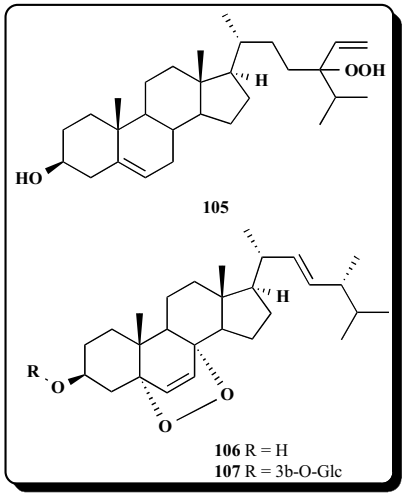


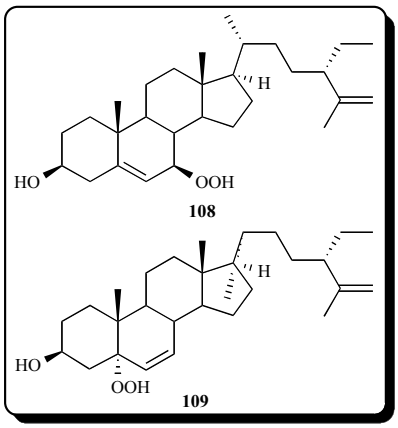
Table 20. Cytotoxicity Peroxy Sterols from Marine Alga *Codium arabicum* *

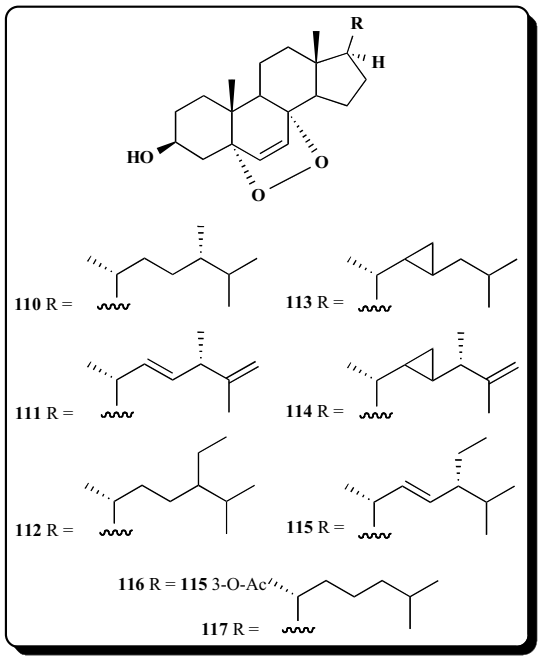
Compound	P-388	KB	A-549	HY-29
108	0.5	1.0	1.1	0.9
109	0.4	1.1	0.5	0.6

*ED_{50} μg/mL

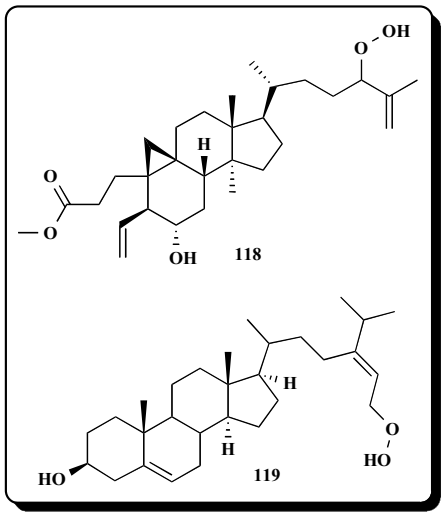
activity against either leukemia P-388 in CDF1 mouse or sarcoma 180 in mouse [80]. It displayed potent antitumor activity against Walker 256 carcinosarcoma and MCF-7 breast cancer cell lines [81]. Ergosterol peroxide was found to be a greater inhibitor to the proliferation of K562, Jurkat, WM-1341, HL-60 and RPM1-8226 tumor cell lines by 10 to 40% at 10 μg/mL [82]. Ergosterol peroxide from the marine sponge *Spirastrella abata* showed cytotoxicity against 5 human solid tumor cell lines including A549, SK-OV-3, SK-MEL-2, XF498, and HCT15 [83], and also against human gastric tumor cell line (SNU-1), human hepatoma cell line (SNU-354), human colorectal tumor cell line (SNU-C4) and murine sarcoma-180 were 18.7, 158.2, 84.6 and 74.1 μM (IC_{50}), respectively [84]. Ergosterol peroxide was isolated from the fruiting bodies of *Ganoderma applanatum*, and it was found to exhibit potent of rat lens aldose reductase inhibition, with IC_{50} value being 15.4 μ/mL [85]. Ergosterol peroxide was isolated for the first time in *Oryza sativa*. This is the first report of potential allelopathic activity of steroids on weeds based on their phytotoxicity on barnyardgrass (Echinochloa crus-galli) as target species [86]. Among the lipophilic extracts of seven traditional edible mushrooms, the acetone extract of *Sarcodon aspratus* markedly inhibited the growth of HL60 human leukemia cells and induced apoptosis after 24 h incubation. The major active component was identified as ergosterol peroxide [87]. It is completely inhibited growth and induced apoptosis of HL60 cells at a concentration of 25 μM.

The two hydroperoxy clerosterols, (24S)-24-ethyl-7-oxocholesta-5,25-dien-3β-ol **108**, and (24S)-24-ethyl-cholesta-5,25-dien-3β,7α-diol **109**, were isolated from the marine green alga *Codium arabicum*. Isolated peroxides are showed significant cytotoxicity toward various cancer cell lines (Table **20**) [88].





A number of other steroidal endoperoxides (**110**-**117**) have been reported which differ in the nature of the side-chain. These peroxides have been identified from marine and terrestrial sources [2,4]. Among isolated compounds **115** was found to be an inhibitor of induced inflammation and tumor promotion in mouse studies [89].



Two (6S)-hydroxy-29-nor-3,4-seco-cycloart-4(30),24-dien-3-oic acid **118** was isolated from the aerial parts of *Antirhea acutata* [90]. Compound **118** is shown moderate inhibitory activities in cyclooxygenase-1 and -2 assays (IC_{50} 43.7 and 4.7 μM, respectively.).

A series of the cytotoxic components of the marine sponge *Spirastrella abata*, 5α,8α-epidioxy Δ6 sterols and 5α,8α-epidioxy Δ6,9(11) sterols (**110**,**111**,**112**,**115**, and **117**) were isolated. These compounds were showed cytotoxicity against 5 human solid tumor cell lines including A549, SK-OV-3, SK-MEL-2, XF498, and HCT15 [83].

The glycosylated form of ergosterol peroxide **107** from *Cordyceps sinensis* was found to be a greater inhibitor to the proliferation of K562, Jurkat, WM-1341, HL-60 and RPM1-8226 tumor cell lines by 10 to 40% at 10 μg/mL than its previously identified aglycon, 5α,8α-epidioxy-24(R)-methyl-cholesta-6,22-dien-3β-ol [90]. The cytotoxic steroid **119** obtained from *Ciona intestinalis* was prepared by photooxidation of fucosterol in the presence of eosin; small amounts of **119**. Compound **119** and intermediates are showed cytotoxicity against L1210 leukemia cells [91].

6. PREDICTED ACTIVITIES FOR STEROIDAL PEROXIDES

Additional predicted as well as reported activities for natural steroidal peroxides are shown in Tables **21** and **22**.

Table 21. Prediction of Biological Activity for Steroidal Peroxides (105-107)

No	Drug-Likeness	Activity Reported	Focal Activity and Activities Confirmed
105	0.973	Antineoplastic Cytotoxic	**0.872 0.016 Prostaglandin-E2 9-reductase inhibitor** 0.510 0.007 Antineoplastic (multiple myeloma) 0.423 0.093 Antineoplastic 0.318 0.020 Antineoplastic (breast cancer) 0.105 0.033 Antineoplastic, alkylator
106	0.981	Antineoplastic Cytotoxic	**0.902 0.003 Alcohol O-acetyltransferase inhibitor** 0.436 0.087 Antineoplastic 0.363 0.048 Antineoplastic (multiple myeloma) 0.193 0.057 Cytotoxic
107	0.991		**0.822 0.005 Alcohol O-acetyltransferase inhibitor** 0.479 0.068 Antineoplastic 0.284 0.161 (multiple myeloma) 0.161 0.076 Cytotoxic

Table 22. Prediction of Biological Activity for Steroidal Peroxides (108-119)

No.	Drug-Likeness	Activity Reported	Focal Activity and Activities Confirmed
108	0.962	Antineoplastic Cytotoxic	**0.873 0.016 Prostaglandin-E2 9-reductase inhibitor** 0.462 0.075 Antineoplastic 0.292 0.144 Antineoplastic (multiple myeloma) 0.157 0.015 Antineoplastic, alkylator 0.218 0.151 Antineoplastic (breast cancer) 0.145 0.090 Cytotoxic

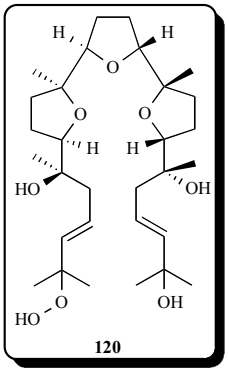
(Table 22. Contd….)

No.	Drug-Likeness	Activity Reported	Focal Activity and Activities Confirmed
109	0.953	Antineoplastic Cytotoxic	**0.793 0.015 Cholesterol synthesis inhibitor** 0.420 0.094 Antineoplastic 0.299 0.132 Antineoplastic (multiple myeloma) 0.123 0.022 Antineoplastic, alkylator 0.133 0.106 Cytotoxic
110	0.975	Antineoplastic Cytotoxic	**0.889 0.011 Phosphatase inhibitor** 0.359 0.052 Antineoplastic (multiple myeloma) 0.327 0.144 Antineoplastic 0.131 0.109 Cytotoxic
111	0.980	Antineoplastic Cytotoxic	**0.862 0.018 Phosphatase inhibitor** 0.463 0.075 Antineoplastic 0.234 0.039 Cytotoxic
112	0.981	Antineoplastic Cytotoxic	**0.896 0.010 Phosphatase inhibitor** 0.351 0.059 Antineoplastic (multiple myeloma) 0.370 0.120 Antineoplastic 0.137 0.100 Cytotoxic
113	0.991		**0.886 0.012 Phosphatase inhibitor** 0.381 0.035 Antineoplastic (multiple myeloma) 0.359 0.125 Antineoplastic
114	0.985		**0.867 0.016 Phosphatase inhibitor** 0.299 0.132 Antineoplastic (multiple myeloma) 0.241 0.213 Antineoplastic 0.136 0.101 Cytotoxic
115	0.981	Antineoplastic Cytotoxic	**0.884 0.006 Cholesterol antagonist** 0.408 0.100 Antineoplastic 0.356 0.054 Antineoplastic (multiple myeloma) 0.196 0.055 Cytotoxic
116	0.967		**0.877 0.014 Phosphatase inhibitor** 0.405 0.023 Antineoplastic (multiple myeloma) 0.380 0.114 Antineoplastic 0.192 0.057 Cytotoxic
117	0.976	Antineoplastic Cytotoxic	**0.893 0.010 Phosphatase inhibitor** 0.378 0.038 Antineoplastic (multiple myeloma) 0.368 0.120 Antineoplastic 0.146 0.089 Cytotoxic
118	0.971	Cyclooxygenase 1 inhibitor Cyclooxygenase 2 inhibitor	**0.745 0.008 4-Methoxybenzoate monooxygenase (O-demethylating) inhibitor** 0.292 0.145 Antineoplastic (multiple myeloma) 0.134 0.104 Cytotoxic
119	0.972	Antineoplastic Cytotoxic	**0.882 0.014 Prostaglandin-E2 9-reductase inhibitor** 0.426 0.016 Antineoplastic (multiple myeloma) 0.392 0.109 Antineoplastic 0.262 0.062 Antineoplastic (breast cancer)

Table 23. Cytotoxicity of Polycyclic Hydroquinones

Compound	PC-3	HERP3B
121	56	5
122	35	5
Taxol (0.1 μg/mL)	80	85

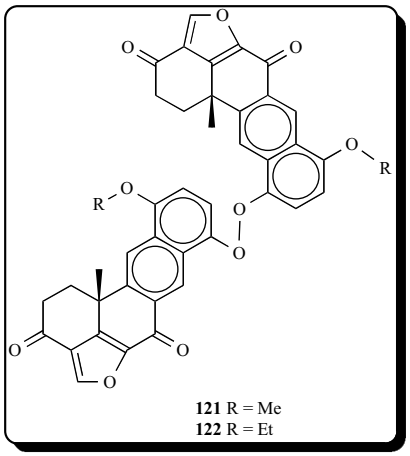
PC-3, human prostate cancer cells;
Herp3b, human hapatoma cancer cells



120

7. OTHER METABOLITES AND THEIR REPORTED AND PREDICTED ACTIVITIES

Longilene peroxide **120**, from *Eurycoma longifolia*, represents a new qualene-type triterpene. The compound exhibits cytotoxic activity against KB cells, IC_{50} 5.3 μg/mL [92, 93]. Two novel pentacyclic polyketide dimers, dihalenaquinolides A **121** and B **122**, have been isolated from the marine sponge *Petrosia elastica* collected in Nan-wan, Taiwan [94]. The cytotoxic activity of the isolated pentacyclic hydroquinones and quinones were tested *in vitro* against human prostate (PC-3) and hepatoma (Hep3B) tumor cell lines, and results are shown in Table **23**, and predicted biological activity for natural peroxy compounds are shown in Table **24**.



121 R = Me
122 R = Et

Table 24. Prediction of Biological Activity for Natural Peroxy Compounds

No.	Drug-Likeness	Activity Reported	Focal Activity and Activities Confirmed
120	0.993	Antineoplastic Cytotoxic	**0.943 0.003 4-Methoxybenzoate monooxygenase (O-demethylating) inhibitor** 0.587 0.037 Antineoplastic 0.261 0.212 Antineoplastic (multiple myeloma) 0.301 0.019 Cytotoxic
121	0.951	Antineoplastic Cytotoxic	**0.902 0.004 Kinase inhibitor** 0.619 0.030 Antineoplastic 0.318 0.018 Antineoplastic (breast cancer) 0.323 0.093 Antineoplastic (multiple myeloma) 0.134 0.103 Cytotoxic
122	0.938	Antineoplastic Cytotoxic	**0.878 0.004 Kinase inhibitor** 0.519 0.054 Antineoplastic 0.289 0.035 Antineoplastic (breast cancer)

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