Share Your Innovations through JACS Directory

Journal of Natural Products and Resources

Visit Journal at http://www.jacsdirectory.com/jnpr

ISSN: 2455-0299

Naturally Occurring Boron Containing Compounds and Their Biological Activities

V.M. Dembitsky[1,*], T.A. Gloriozova[2]

[1]*National Scientific Center of Marine Biology, Vladivostok, Russia 690041.*
[2]*Institute of Biomedical Chemistry, Moscow, Russia 119121.*

ARTICLE DETAILS

Article history:
Received 11 December 2017
Accepted 22 December 2017
Available online 26 December 2017

Keywords:
Boron
Polyketide Antibiotics
Boronic Lipids

ABSTRACT

Boron containing metabolites are found in plants, algae and microorganisms. Boron forms complexes with fatty acids, such as borophycin, aplasmomycin, and tartrolon, and their derivatives. All these metabolites are polyketide antibiotics and are of great interest for medicine, and the pharmaceutical industry. In this paper, using the PASS computer program, we computed new biological activities for boron compounds. The results obtained show that fifty biologically active boron compounds show anti-cancer, antibacterial, and antifungal activity, with a confidence of 50 to 90 percent.

1. Introduction

Element boron with atomic number 5 was first discovered in 1808 by French chemists Joseph Louis Gay-Lussac and Louis Jacques Thénard [1]. A few months later, British chemist Humphry Davy received pure boron [2]. Boron, an orphan of the periodic table of the elements, is unique not only in its chemical properties but also in its roles in biology [3-6].

After the discovery in 1808 that boron is one of the essential microelements for higher plants, its biological role has been the subject of a number of studies [7-9]. Boron is an important microelement necessary for normal vital activity of plants, fungi and microorganisms. The lack of boron stops their development, causes various diseases in plants [10-12]. Biological and physiological functions for boron-containing compounds are well established, nevertheless, many questions still remain to be answered [13-15]. In addition, synthetic boron compounds exhibit significant pharmacological activity [5, 6, 16-20].

As already proved by numerous works, there is a relationship between structure and activity, and this principle is called SAR (Structure-Activity-Relationship). We used the computer program PASS, containing about one million chemical compounds and more than 8,000 biological activities, and calculated the biological activity of different natural and/or synthetic compounds [21-23]. PASS predictions are based on SAR analysis of the training set consisting of more than one million drugs, drug candidates and lead compounds. The algorithm of PASS practical utilization is described in detail in several publications [24-26].

In this paper, using the PASS computer program, we computed new biological activities for boron compounds. The results obtained show that complex boron compounds show anti-cancer, antibacterial, and antifungal activity, with a confidence of 50 to 90 percent.

2. Natural Boron Polyketide Antibiotics

Ionophoric macrodiolide anticancer antibiotic borophycin (**1**, structures see in Fig. 1) has been isolated from the lipophilic extract of a marine strain of the cyanobacterium *Nostoc linckia* UH isolate GA-5-23. Isolated natural antibiotic was found to display cytotoxic activity against colon human LoVo cells line (MIC = 0.06 μg/mL) and an epidermal carcinoma KB cells line (MIC = 3.3 μg/mL) [27,28].

Second boron containing antibiotic, named as boromycin (**2**), was isolated from a fermentation broth of *Streptomyces* sp. A-3376 [29], although it was previously isolated from an African soil sample containing *Streptomyces antibioticus* [30, 31]. It has showed antiviral activity against HIV-1 and HIV-2 *in vitro* [30-32], and also antibacterial activity against *Mycobacterium tuberculosis* [33]. Two minor antibiotics (**3** and **4**) of the boromycin fermentation, such as N-acetyl boromycin and N-formyl boromycin have been discovered from the mycelia of the boromycin producing *Streptomyces antibioticus* [34]. Boromycin derivative known as desvalinoboromycin or TMC 25B (**5**), with anti-HIV activity was isolated from soil *Streptomyces* sp. [29].

Antibiotic aplasmomycin (**6**) was first isolated from a broth cultivated with a marine isolate from a protozoan parasite *Plasmodium berghei* [35], although it was previously isolated from *Streptomyces griseus* SS-20, found in shallow sea sediment [36]. Two other aplasmomycins such as B (**7**) and C (**8**) are produced by a strain *Streptomyces griseus* NCIB 11371 [37]. *Streptomyces griseus* strain NCIB 11371 is also used to produce aplasmomycin, boromycin, and monoacetyl-aplasmomycin [38].

Tartrolon polyketide antibiotics (**9**-**11**) were isolated from the culture broth of the gliding bacteria, *Sorangium cellulosum* strain source 678 [39-41]. Isolated antibiotics were active against Gram-positive bacteria and mammalian cells [5, 7, 42]. As well as boronated tartrolon antibiotics produced by symbiotic cellulose-degrading bacteria *Teredinibacter turnerae* in shipworm gills [41].

Biological activity of natural boron polyketide antibiotics is shown in Table 1, and the structures of these compounds are given in Fig. 1. In addition, the basic biological activities that are characteristic of compounds of this class are antineoplastic, antifungal, and antimitotic, and exhibit cytotoxic properties.

3. Boron Siderophore Complexes

Low-molecular-weight molecules known as siderophores have a high specificity for chelating or binding several metals: iron, aluminum, boron, cadmium, chromium, copper, gallium, indium, lead, manganese, plutonium, uranium, vanadium, zinc and etc [43, 44, 45]. At present nearly 500 terrestrial siderophores are reported from selected microorganisms, although only few metabolites of marine siderophores were identified [46, 47, 48]. Siderophores have applications in medicine for iron and aluminum overload therapy and antibiotics for improved targeting [49, 50]. In the medicine, siderophore uses the "*Trojan horse strategy*" to form complexes with antibiotics and helps in the selective delivery of antibiotics to the antibiotic-resistant bacteria [51, 52].

*Corresponding Author
Email Address: valeryde@imb.dvo.ru(Valery M. Dembitsky)

Cite this Article as: V.M. Dembitsky, T.A. Gloriozova, Naturally occurring boron containing compounds and their biological activities, J. Nat. Prod. Resour. 3(2) (2017) 147-154.

Boron siderophore complexes for vibrioferrin (**12**), rhizoferrin (**13**), and petrobactin (**14**) have been obtained from the corresponding natural metabolites [53, 54]. Vibrioferrin belonging to the carboxylate class of siderophores have been isolated from *Vibrio parahemolyticus*, and *Gymnodinium catenatum* [55, 56]. Rhizoferrin is a novel carboxylatetype siderophore which has been isolated from *Rhizopus microsporus* and other fungi of the Mucorales (Zygomycetes) [57, 58]. Petrobactin, a bis-catecholate, R-hydroxy acid siderophore produced by the oil-degrading marine bacterium *Marinobacter hydrocarbonoclasticus* [59, 60].

The structures of the boron siderophore complexes are shown in Fig. 2, and the biological activity is shown in Table 2. For these boron compounds, antieczematic, antinephrotoxic, and anti-inflammatory activity are characteristic.

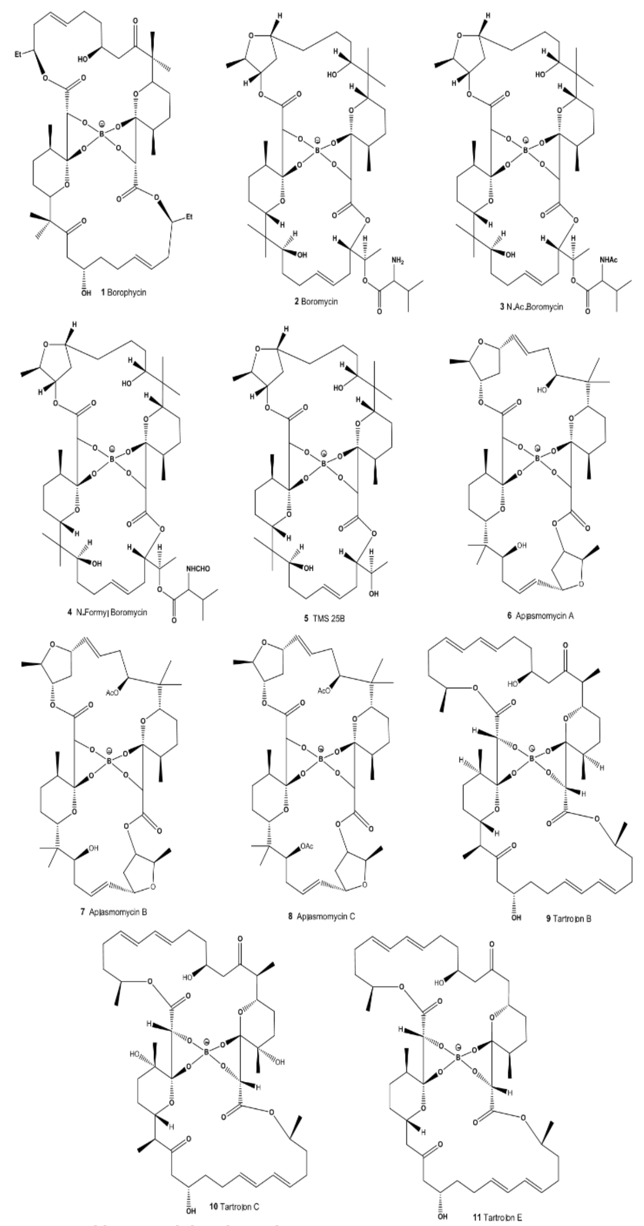

Fig. 1 Natural boron polyketide antibiotics

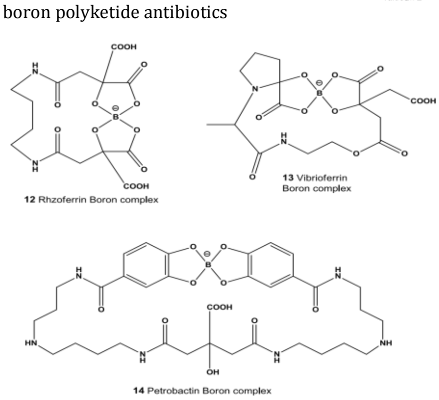

Fig. 2 Bioactive boron siderophore complexes

Table 1 Biological activities of boron polyketide antibiotics (**1-11**)

No.	Activity reviewed	Activities confirmed (Pa)	Additional predicted activities (Pa)*
1	Antibiotic Macrolide-like Antineoplastic antibiotic Cytotoxic	Antineoplastic (0,853) Antibacterial (0,777) Cytotoxic (0,675) Antibiotic (0,537)	Antieczematic (0,914) Antifungal (0,834) Immunosuppressant (0,727) Antiprotozoal (0,697) Antimitotic (0,692)
2	Antibiotic Antiviral (HIV) Antimycobacterial	Antibacterial (0,868) Antibiotic (0,711)	Antineoplastic (0,906) Antifungal (0,890) Antimitotic (0,742) Cytotoxic (0,731) Apoptosis agonist (0,725) Immunosuppressant (0,620) Hypolipemic (0,597)
3	Antibiotic	Antibacterial (0,844) Antibiotic (0,632)	Antineoplastic (0,895) Antifungal (0,840) Cytotoxic (0,770) Antimitotic (0,725) Apoptosis agonist (0,725) Immunosuppressant (0,687) Antiparasitic (0,538)
4	Antibiotic	Antibacterial (0,864) Antibiotic (0,652)	Antineoplastic (0,909) Cytotoxic (0,866) Antifungal (0,866) Antimitotic (0,721) Apoptosis agonist (0,723) Antiparasitic (0,586) Immunosuppressant (0,598) Antithrombotic (0,534)
5	Antiviral (HIV)	Antibiotic (0,684)	Antineoplastic (0,928) Antifungal (0,864) Apoptosis agonist (0,854) Antibacterial (0,848) Cytotoxic (0,810) Antimitotic (0,805) Antiparasitic (0,773) Antibiotic (0,684) Immunosuppressant (0,667) Antiprotozoal (0,568) Antipsoriatic (0,541) Antithrombotic (0,525)
6	Antibiotic	Antibacterial (0,782) Antibiotic (0,550)	Antineoplastic (0,944) Apoptosis agonist (0,842) Antifungal (0,838) Antimitotic (0,801) Antiparasitic (0,786) Cytotoxic (0,741) Antiprotozoal (0,629) Immunosuppressant (0,632)
7	Antibiotic	Antibacterial (0,809) Antibiotic (0,613)	Antineoplastic (0,941) Antifungal (0,867) Apoptosis agonist (0,851) Antimitotic (0,804) Antiparasitic (0,792) Cytotoxic (0,788) Immunosuppressant (0,701) Antieczematic (0,666) Antinephrotoxic (0,605) Hypolipemic (0,585)
8	Antibiotic	Antibacterial (0,780) Antibiotic (0,553)	Antineoplastic (0,941) Antifungal (0,845) Apoptosis agonist (0,846) Antimitotic (0,792) Antiparasitic (0,747) Cytotoxic (0,733) Antiprotozoal (0,689) Immunosuppressant (0,656) Antieczematic (0,630) Antinephrotoxic (0,587) Hypolipemic (0,539) Antipsoriatic (0,533)
9	Antibiotic	Antibacterial (0,804) Antibiotic (0,575)	Antieczematic (0,898) Antineoplastic (0,868) Antifungal (0,850) Antiparasitic (0,824) Apoptosis agonist (0,797)

			Immunosuppressant (0,762) Antihelmintic (0,744) Vasoprotector (0,747) Antiinflammatory (0,706) Antimitotic (0,692) Antinephrotoxic (0,679) Cytotoxic (0,675) Antithrombotic (0,644) Neuroprotector (0,566) Cholesterol antagonist (0,502)
10	Antibiotic	Antibacterial (0,806) Antibiotic (0,597)	Antieczematic (0,873) Antineoplastic (0,867) Antifungal (0,852) Antiparasitic (0,817) Immunosuppressant (0,779) Antiinflammatory (0,754) Cytotoxic (0,734) Apoptosis agonist (0,700) Antimitotic (0,687) Antithrombotic (0,642) Antinephrotoxic (0,622) Antipsoriatic (0,611) Hypolipemic (0,541) Lipid metabolism regulator (0,544)
11	Antibiotic	Antibacterial (0,802) Antibiotic (0,549)	Antifungal (0,869) Antieczematic (0,865) Antineoplastic (0,859) Apoptosis agonist (0,834) Immunosuppressant (0,755) Neuroprotector (0,736) Antimitotic (0,677) Antihelmintic (0,653) Antiinflammatory (0,641) Hypolipemic (0,602) Antileukemic (0,594) Cholesterol antagonist (0,596)

** Only activities with Pa > 0.5 are shown*

Table 2 Biological activities of boron containing siderophores (**12-14**)

No.	Activity reviewed	Activities confirmed (Pa)	Additional predicted activities (Pa)*
12	Antibacterial	(R)-Pantolactone dehydrogenase (flavin) inhibitor (0,704) Membrane integrity antagonist (0,609) Membrane permeability inhibitor (0,608) Membrane permeability enhancer (0,419)	Renin release stimulant (0,903) Antiischemic, cerebral (0,758) Antieczematic (0,728) Antiviral (Arbovirus) (0,707) Antinephrotoxic (0,663) Neuroprotector (0,662) Platelet adhesion inhibitor (0,602) Histamine release inhibitor (0,532)
13	Not studied		Allergic conjunctivitis treatment (0,645) Antieczematic (0,632) Antinephrotoxic (0,586) Antiinflammatory (0,607) Renin release stimulant (0,616) Antiischemic, cerebral (0,537) Antineoplastic (0,524)
14	Not studied		Adrenergic, ophthalmic (0,955) HIV-2 integrase inhibitor (0,833) Antiischemic, cerebral (0,626) Antineoplastic (0,607) Fibrinolytic (0,550)

** Only activities with Pa > 0.5 are shown*

4. Boron Sugar Alcohol Complexes

Since the discovery of the first boron biomolecule, boromycin, several other similar biomolecules are now well-characterized. More recently, it was shown that the boromycin is natural anti-HIV antibiotic which is produced by *Streptomyces* species and *Sorangium cellulosum* [29-40]. Natural boric acid can form borate complexes with organic acids such as malic acid neutral borate complex, monomalic acid borate complex, and the bis(malic acid) borate complex. These boron-containing compounds were found in apple juice and wine [5, 7, 42].

Boron alcohol complexes were discovered more than 40 years ago by Alan Darvill and co-workers, who described one of the most complex carbohydrates found in nature [61]. Rhamnogalacturonan II, or RG-II, is found in plant cell walls [62-64]. Boron alcohol complexes are found in all higher plant [5, 7, 65, 66]. In a normal plant, boron binds to RG-II and forms a bridge that holds everything together. In the mutant, a little bit of the structure of the RGII has been changed, and because of the change in shape, it cannot hold the boron quite as well. Fertilizing mutants with high levels of boron also reversed dwarfing because the high amount of available boron effectively forced RG-II to cross-link [67, 68].

Complexes of boron with sugars or/or sugar alcohols are utilized as nutritional supplements, with the carbohydrate portion being selected to provide a relatively high boron-sugar association constant of at least 250 and preferably 500 or more [5, 7, 42, 69-71]. In one class of preferred embodiments, boron is complexed with a saccharide (**15-29**) having coplanar cis-OH groups capable of forming five- or six-membered rings through ester bonding with boric acid. Such complexes may advantageously comprise fructose, mannose, xylose, or sorbose. In another aspect of the invention, a carbohydrate-boric acid complex may exist charged or neutralized with calcium, magnesium, or other cation(s) in which calcium fructoborate is the preferential form.

Compound (**15**) is the central part of boron containing dimeric polysaccharide complex known as RG-II with missing links. It is present in the cell walls of all higher [5, 7, 13, 42]. Autoinducer-2 (**16**) and common analogous compounds of arabinitol, ribitol, and xylitol boron-sugar complexes (**17-29**) have been isolated from natural sources, and they belonging to family of signaling molecules used in quorum sensing [5,7]. Natural boron sugar alcohol complexes as established having antibacterial and antifungal properties [13, 42]. Predicted activities of these boron carbohydrate complexes showed in Table 3.

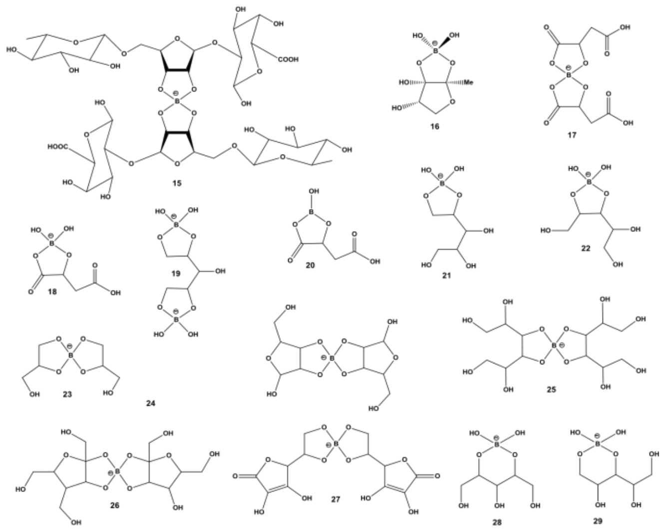

Fig. 3 Boron sugar alcohol complexes (**15-29**)

Table 3 Confirmed and predicted activities of boron sugar alcohol complexes (**15-32**)

No.	Activity reviewed	Activities confirmed (Pa)	Additional predicted activities (Pa)*
15	Antibacterial, antifungal	Antifungal (0,814) Antibacterial (0,797)	Antineoplastic (0,857) Antithrombotic (0,790) Antiinflammatory (0,788) Hepatoprotectant (0,774) Antiparasitic (0,712) Vasoprotector (0,702) Antioxidant (0,651) Neuroprotector (0,676) Apoptosis agonist (0,643) Cytotoxic (0,571) Cholesterol antagonist (0,542) Interleukin antagonist (0,538) Antibiotic (0,537) Antidiabetic (0,511)
16	Antibacterial, antifungal	Antifungal (0,636) Antibacterial (0,616)	Antieczematic (0,875) Antineoplastic (0,869) Antipsoriatic (0,727) Antinephrotoxic (0,684) Antiinflammatory (0,692) Antiprotozoal (Plasmodium) (0,651)

			Radiosensitizer (0,647) Allergic conjunctivitis treatment (0,643) Antiviral (Picornavirus) (0,578) Antiviral (0,552)
17	Antibacterial, antifungal	Antifungal (0,533) Antibacterial (0,447)	Antiischemic, cerebral (0,913) Phobic disorders treatment (0,883) Antieczematic (0,865) Platelet antagonist (0,813) Antiviral (Arbovirus) (0,778) Vasoprotector (0,756) Antidiabetic symptomatic (0,752) Anticoagulant (0,710) Antidiabetic (0,682) Antipsoriatic (0,666) Antiviral (Picornavirus) (0,652) Antiarthritic (0,639)
18	Antibacterial, antifungal	Antifungal (0,585) Antibacterial (0,499)	Antiischemic, cerebral (0,834) Antieczematic (0,825) Antiinflammatory (0,805) Antipsoriatic (0,742) Radiosensitizer (0,707) Antinephrotoxic (0,700) Antineoplastic (0,686) Antiprotozoal (0,644) Antiinfective (0,581) Antiviral (Picornavirus) (0,583)
19	Antibacterial, antifungal	Antifungal (0,443) Antibacterial (0,421)	Multiple sclerosis treatment (0,967) Autoimmune disorders treatment (0,947) Antipsoriatic (0,893) Antiarthritic (0,879) Antineoplastic (0,810) Radiosensitizer (0,721) Antiinflammatory (0,595)
20	Antibacterial, antifungal	Antifungal (0,543)	Adrenergic, ophthalmic (0,999) Antieczematic (0,751) Antinephrotoxic (0,652) Antipsoriatic (0,642) Antiviral (Arbovirus) (0,656) Antiischemic, cerebral (0,612) Antiinflammatory (0,602)
21	Antibacterial, antifungal	Antifungal (0,517) Antibacterial (0,462)	Adrenergic, ophthalmic (0,911) Vasoprotector (0,779) Antiviral (0,758) Neuroprotector (0,761) Antiinfective (0,646) Allergic conjunctivitis treatment (0,623) Antiviral (Influenza B) (0,518)
22	Antibacterial, antifungal	Antifungal (0,545) Antibacterial (0,521)	Adrenergic, ophthalmic (0,918) Antiinflammatory (0,783) Antineoplastic (0,772) Antiviral (Arbovirus) (0,753) Neuroprotector (0,762) Radiosensitizer (0,731) Lipid metabolism regulator (0,681) Antiviral (Picornavirus) (0,677) Antileukemic (0,675) Antithrombotic (0,604) Antiinfective (0,598) Autoimmune disorders treatment (0,588)
23	Antibacterial, antifungal	Antifungal (0,482) Antibacterial (0,429)	Antiischemic, cerebral (0,763) Vasoprotector (0,759) Antineoplastic (0,753) Antiinfective (0,722) Antihypoxic (0,718) Antiviral (0,693) Antiinflammatory (0,686) Antidiabetic (0,667) Dementia treatment (0,614) Vascular dementia treatment (0,519)
24	Antibacterial, antifungal	Antifungal (0,573) Antibacterial (0,552)	Antioxidant (0,959) Antiinflammatory (0,925) Antineoplastic (0,891) Antiinfective (0,776) Vasoprotector (0,776) Antiarthritic (0,742) Antiviral (0,736) Apoptosis agonist (0,674)
25	Antibacterial, antifungal	Antifungal (0,441) Antibacterial (0,436)	Vasoprotector (0,898) Antiviral (Arbovirus) (0,781) Apoptosis agonist (0,771) Antiischemic, cerebral (0,770) Antiinflammatory (0,766) Neuroprotector (0,751) Autoimmune disorders treatment (0,613) Platelet adhesion inhibitor (0,578) Antithrombotic (0,576)
26	Antibacterial, antifungal	Antifungal (0,593) Antibacterial (0,580)	Antineoplastic (0,788) Antiviral (Picornavirus) (0,654) Hypolipemic (0,650) Antileukemic (0,644) Antinephrotoxic (0,600) Dementia treatment (0,587) Antiviral (0,580)
27	Antibacterial, antifungal	Antifungal (0,532) Antibacterial (0,459)	Antineoplastic (0,926) Apoptosis agonist (0,783) Antiarthritic (0,774) Chemoprotective (0,752) Vasoprotector (0,736) Antioxidant (0,717) Antiviral (Arbovirus) (0,623)
28	Antibacterial, antifungal	Antifungal (0,566) Antibacterial (0,508)	Adrenergic, ophthalmic (0,914) Antidiabetic (0,834) Antineoplastic (0,730) Antiviral (Arbovirus) (0,723) Antiinfective (0,720) Vasoprotector (0,705) Antieczematic (0,700) Antipsoriatic (0,688) Antiinflammatory (0,693) Antiviral (0,671)
29	Antibacterial, antifungal	Antibacterial (0,564) Antifungal (0,529)	Vasoprotector (0,879) Antineoplastic (0,799) Antiinflammatory (0,726) Neuroprotector (0,727) Antiinfective (0,681) Apoptosis agonist (0, 653) Antipsoriatic (0,627) Antiviral (Picornavirus) (0,619) Antithrombotic (0,559)

** Only activities with Pa > 0.5 are shown*

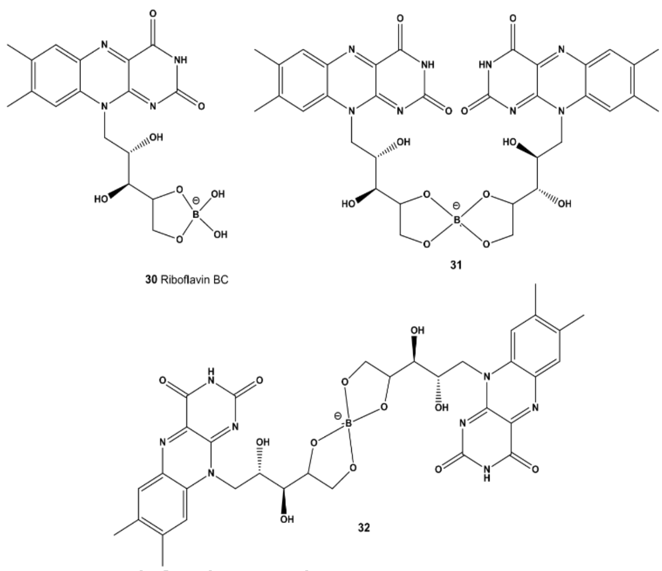

Fig. 4 Bioactive riboflavin boron complexes

5. Riboflavin Boron Complexes

The pigment with yellow-green fluorescence was first found and described by the English chemist Alexander Wynter Blyth in 1872 [72]. Much later, in the 20-30s of the 20th century, vitamin B2, also called riboflavin, was isolated and its structure was established [73-75]. Riboflavin is used for increasing energy levels, boosting immune system function, maintaining healthy hair, skin, mucous membranes, and nails, for slowing aging, canker sores, and for memory loss including Alzheimer's disease [73-77]. It is also used for preventing various types of cancer including cervical, gastric, liver, and lung cancer, eye fatigue, cataracts, and glaucoma [78, 79].

Water-soluble vitamin B2 boron complex was first isolated in 1942 by Douglas Frost [80], later their structures were studied and described [81, 82]. The structures of riboflavin boron complexes (**30-32**) are shown in Fig. 4, and the biological activity of these compounds is shown in Table 4.

Table 4 Biological activities of boron containing (**30-32**)

No.	Activity reviewed	Predicted biological activities (Pa)*
30	Not studied	Trimethylamine-oxide aldolase inhibitor (0,908) (R)-Pantolactone dehydrogenase (flavin) inhibitor (0,906) Isopenicillin-N epimerase inhibitor (0,798) Sulfur dioxygenase inhibitor (0,783) Genital warts treatment (0,577) Antineoplastic (sarcoma) (0,506)
31	Not studied	Trimethylamine-oxide aldolase inhibitor (0,895) (R)-Pantolactone dehydrogenase (flavin) inhibitor (0,891) 4-Hydroxyphenylacetate 3-monooxygenase inhibitor (0,791) Isopenicillin-N epimerase inhibitor (0,768) Sulfur dioxygenase inhibitor (0,765) Protoporphyrinogen oxidase inhibitor (0,744) Bilirubin oxidase inhibitor (0,632) Genital warts treatment (0,565)
32	Not studied	Trimethylamine-oxide aldolase inhibitor (0,895) (R)-Pantolactone dehydrogenase (flavin) inhibitor (0,891) 4-Hydroxyphenylacetate 3-monooxygenase inhibitor (0,791) Isopenicillin-N epimerase inhibitor (0,768) Sulfur dioxygenase inhibitor (0,765) Protoporphyrinogen oxidase inhibitor (0,744) Bilirubin oxidase inhibitor (0,632) Genital warts treatment (0,565)

** Only activities with Pa > 0.5 are shown*

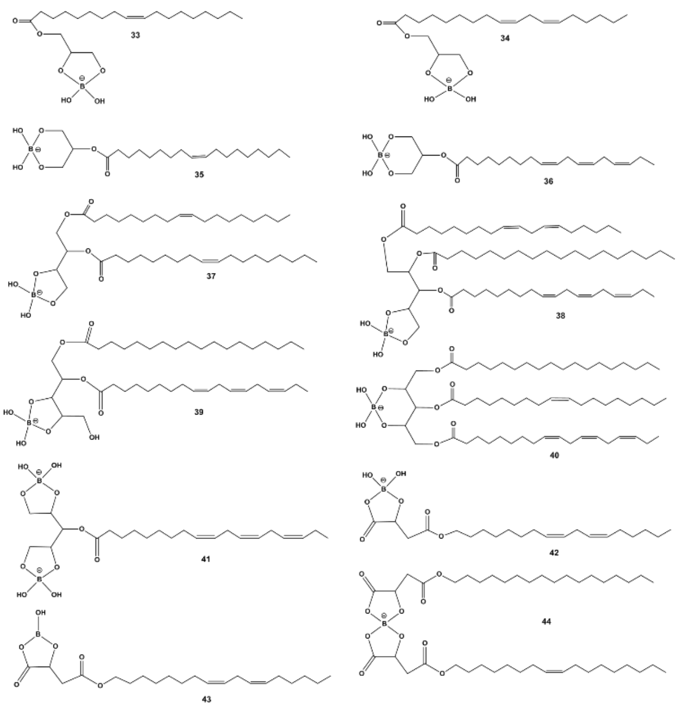

Fig. 5 Boron carbohydrate lipophilic complexes (Boronic lipids)

6. Boron Carbohydrate Lipophilic Complexes (Boronic Lipids)

Boron containing metabolites are widely distributed in nature [5, 7, 13, 42]. Marine algae synthesized many different biological active compounds [5, 7], produced boron containing [42] and also metalloperoxidases [59]. Boron carbohydrate complexes have been isolated from algae, lichens, fungi and microorganisms [5, 42].

Boron carbohydrate lipophilic complexes (**33-44**) were synthesized in 2009-2011; however, the results of these studies were never published [83]. The physiological role of boron carbohydrate lipophilic complexes is not established. Physiological activities of boron carbohydrate lipophilic complexes (**33-45**) were calculated using the PASS program, is presented in Table 5, structures are shown in Fig. 5.

Table 5 Biological activities of boron sugar alcohol lipophilic complexes (**33-44**)

No.	Predicted biological activities (Pa)*
33	Antieczematic (0,912); Vasoprotector (0,786); Antiinfective (0,768); Antiviral (Arbovirus) (0,763); Antiinflammatory (0,756); Neuroprotector (0,743) Antithrombotic (0,682); Antifungal (0,673); Platelet adhesion inhibitor (0,645); Antineoplastic (0,676); Apoptosis agonist (0,619); Immunosuppressant (0,604)
34	Antieczematic (0,948); Antiinflammatory (0,802); Lipid metabolism regulator (0,799); Neuroprotector (0,769); Spasmolytic (0,738); Antithrombotic (0,713) Antiinfective (0,714); Antifungal (0,678); Antipsoriatic (0,659) Antineoplastic (0,680); Hypolipemic (0,603); Antibacterial (0,530)
35	Antieczematic (0,912); Antiviral (Arbovirus) (0,807); Vasoprotector (0,776); Lipid metabolism regulator (0,752); Antiinflammatory (0,736); Spasmolytic (0,723) Antiviral (0,656); Antiinfective (0,651); Antifungal (0,651); Antithrombotic (0,632); Antineoplastic (0,654); Hypolipemic (0,553); Antibacterial (0,520)
36	Antieczematic (0,944); Antiinflammatory (0,842); Lipid metabolism regulator (0,841); Spasmolytic (0,771); Antiviral (Arbovirus) (0,746); Cholesterol antagonist (0,739) Apoptosis agonist (0,717); Antineoplastic (0,701); Antipsoriatic (0,683); Antithrombotic (0,675); Antifungal (0,665); Hypolipemic (0,650)
37	Antiinflammatory (0,916); Spasmolytic (0,890); Vasoprotector (0,855); Antiviral (Arbovirus) (0,781); Lipid metabolism regulator (0,708); Antipsoriatic (0,694) Antithrombotic (0,678); Antineoplastic (0,651); Antifungal (0,648); Autoimmune disorders treatment (0,614)
38	Antiinflammatory (0,938); Lipid metabolism regulator (0,900); Spasmolytic (0,834); Antineoplastic (0,817); Antithrombotic (0,803); Antiviral (Arbovirus) (0,700) Antifungal (0,670); Antipsoriatic (0,656); Neuroprotector (0,634); Antiinfective (0,574); Hepatoprotectant (0,529)
39	Antieczematic (0,939); Antiinflammatory (0,934); Spasmolytic (0,932); Vasoprotector (0,813); Antiviral (Arbovirus) (0,735); Antipsoriatic (0,712); Neuroprotector (0,695); Antineoplastic (0,690); Antifungal (0,675); Radiosensitizer (0,651); Autoimmune disorders treatment (0,633)
40	Antidiabetic (0,860); Antiinflammatory (0,840); Spasmolytic (0,818); Neuroprotector (0,748); Antithrombotic (0,746); Antineoplastic (0,730); Antifungal (0,724); Apoptosis agonist (0,718); Hypolipemic (0,668); Antipruritic (0,660) Immunosuppressant (0,612); Hepatoprotectant (0,601)
41	Antiinflammatory (0,821); Lipid metabolism regulator (0,818); Angiogenesis stimulant (0,795); Spasmolytic (0,732); Antiviral (Arbovirus) (0,708); Antithrombotic (0,706) Antineoplastic (0,696); Apoptosis agonist (0,660); Vasoprotector (0,640); Antifungal (0,616); Antibacterial (0,501)
42	Antieczematic (0,954); Antiinflammatory (0,807); Antiviral (Arbovirus) (0,804); Phobic disorders treatment (0,786); Spasmolytic (0,778); Lipid metabolism regulator (0,723); Antithrombotic (0,703); Vasoprotector (0,701); Hypolipemic (0,656); Antifungal (0,643); Antineoplastic (0,584)
43	Antiviral (Arbovirus) (0,754); Angiogenesis stimulant (0,732); Antiinflammatory (0,726); Antifungal (0,633); Antithrombotic (0,624); Lipid metabolism regulator (0,619); Leukopoiesis stimulant (0,569)
44	Antiviral (Arbovirus) (0,881); Vasoprotector (0,824); Lipid metabolism regulator (0,816); Antiinflammatory (0,769); Leukopoiesis stimulant (0,732); Analeptic (0,708) Neuroprotector (0,699); Antifungal (0,611)

** Only activities with Pa > 0.5 are shown*

7. Borolithochrome Complexes

Red algae - this is the most elegant and beautiful in form and color, a group of algae, and the inhabitants of marine ponds [84, 85]. Fossil remains indicate that this is a very ancient group of plants. Fossil red algae are found in Cretaceous sediments [86, 87]. There is a close connection between red and blue-green algae, which manifests itself in the similarity of pigments, the structure of thylakoids, and the reserve material [85, 88, 89]. Red algae contain unusual fatty acids [90-93], polar lipids [90, 94], polysaccharides [95, 96], halogenated and antifouling compounds [97, 98] and also other biologically active compounds [99, 100].

A group of researchers from the University of Göttingen, and the University of Linz has determined the structure and origin of Jurassic period borolithochromes. Borolithochromes (**45-53**) are organic biomolecules that were from the Jurassic putative red alga *Solenopora jurassica* [101, 102]. These pigments were identified as spiroborates with two pentacyclic sec-butyl-trihydroxy-methyl-benzo[gh]-tetraphen-one ligands and less-substituted derivatives. The borolithochromes are unique spiroborates with two exceptional pentacyclic aromatic ligands. It is the first reported boronated aromatic polyketide, whose structural similarity to modern-day clostrubin A, a secondary metabolite, suggests that borolithochromes may come from ancient bacteria. The borolithochromes are characterized as complicated spiroborates (boric acid esters) with two phenolic moieties as boron ligands, representing a unique class of fossil organic pigments.

The biological activity of isolated boron containing complexes was not determined. Therefore it was interesting, using the computer program PASS, which allowed to clean up possible biological activities. Fig. 6 shows the structures of the viable compounds, and Table 6 shows the biological activities. We can note that virtually all components have dominant activities such as cardiotonic, antiarrhythmic, and antineoplastic, with a confidence of 75 to 90 percent.

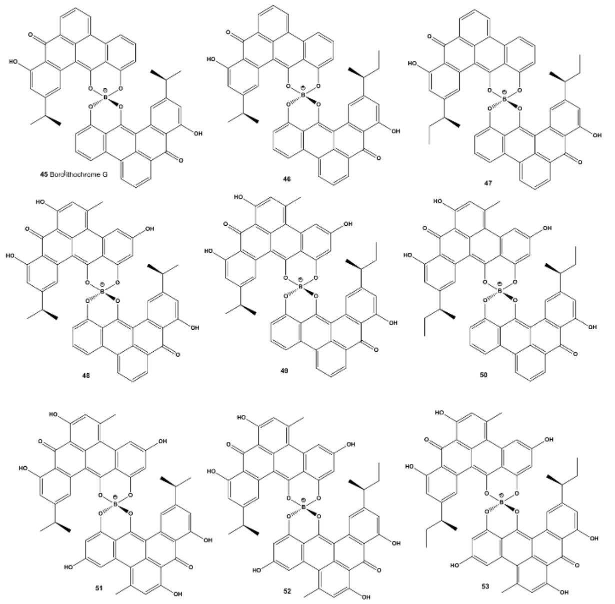

Fig. 6 Bioactive borolithochrome complexes

Table 6 Predicted biological activities for borolithochrome complexes (**45-53**)

No.	Predicted biological activities (Pa)*
45	Cardiotonic (0,901); Antiarrhythmic (0,889); Antineoplastic (0,758) Antiseptic (0,673); Antieczematic (0,663); Psychotropic (0,609) Mucositis treatment (0,607); Apoptosis agonist (0,585); Antiinflammatory (0,570) Antiinfective (0,552); Antifungal (0,547); Fibrinolytic (0,544)
46	Cardiotonic (0,877); Antiarrhythmic (0,860); Antineoplastic (0,741) Antieczematic (0,656); Mucositis treatment (0,583); Antifungal (0,579) Antiinflammatory (0,557); Apoptosis agonist (0,552); Antiseptic (0,543) Psychotropic (0,514)
47	Cardiotonic (0,881); Antiarrhythmic (0,865); Antineoplastic (0,752) Antieczematic (0,678); Antifungal (0,572); Antiinflammatory (0,564) Mucositis treatment (0,555); Apoptosis agonist (0,554); Psychotropic (0,542)
48	Cardiotonic (0,862); Antiarrhythmic (0,842); Antineoplastic (0,756) Antiseptic (0,728); Apoptosis agonist (0,606); Antiinflammatory (0,575) Antifungal (0,540); Antieczematic (0,551); Fibrinolytic (0,507)
49	Cardiotonic (0,843); Antiarrhythmic (0,818); Antineoplastic (0,742) Antiseptic (0,584); Apoptosis agonist (0,575); Antifungal (0,572) Antiinflammatory (0,563); Antieczematic (0,558); Fibrinolytic (0,507)
50	Cardiotonic (0,847); Antiarrhythmic (0,822); Antineoplastic (0,750) Antieczematic (0,582); Apoptosis agonist (0,577); Antiinflammatory (0,568) Antifungal (0,565); Antiseptic (0,529)
51	Cardiotonic (0,886); Antiarrhythmic (0,868); Antineoplastic (0,771) Antiseptic (0,645); Apoptosis agonist (0,620); Antieczematic (0,617) Antiinflammatory (0,590); Fibrinolytic (0,572); Kidney function stimulant (0,543) Antifungal (0,540)
52	Cardiotonic (0,863); Antiarrhythmic (0,843); Antineoplastic (0,756) Antieczematic (0,617); Apoptosis agonist (0,585); Antiinflammatory (0,576) Antifungal (0,571); Antiseptic (0,525); Kidney function stimulant (0,513)
53	Cardiotonic (0,868); Antiarrhythmic (0,846); Antineoplastic (0,764) Antieczematic (0,639); Apoptosis agonist (0,587); Antiinflammatory (0,582) Antifungal (0,564); Kidney function stimulant (0,544); Antimutagenic (0,509)

** Only activities with Pa > 0.5 are shown*

8. Conclusion

For more than 100 years, scientists have been interested in the element of boron, as well as in its natural complexes found in microorganisms and algae. Biological activity of many of them has already been studied, but the discovery of new natural complexes, as well as the synthesis of new boron compounds, will undoubtedly be a breakthrough in the pharmacology of boron compounds. The data given by us on the biological activity of already known boron compounds shows, that these compounds are very interesting and useful both for academic science and for pharmacology and medicine.

References

[1] J.L. Gay Lussac, L.J. Thenard, On the decomposition and recomposition of boracic acid, Annal. Chim. 68 (1808) 169–174.
[2] H. Davy, An account of some new analytical researches on the nature of certain bodies, particularly the alkalies, phosphorus, sulphur, carbonaceous matter, and the acids hitherto undecomposed: with some general observations on chemical theory, Philosoph. Trans. Royal Soc. London 99 (1809) 39–104.
[3] L. Bolaños, K. Lukaszewski, I. Bonilla, D. Blevins, Why boron?, Plant Physiol. Biochem. 42 (2004) 907-912.
[4] W.D. Loomis, R.W. Durst, Chemistry and biology of boron, Biofactors 3 (1992) 229-239.
[5] V.M. Dembitsky, A.A. Quntar, M. Srebnik, Natural and synthetic small boron-containing molecules as potential inhibitors of bacterial and fungal quorum sensing, Chem. Rev. 111 (2011) 209-237.
[6] R. Smoom, O. Rubenstein, V.M. Dembitsky, M. Srebnik, Boron compounds as inhibitors of proteases, Chem. Rev. 112 (2012) 4156–4220.
[7] V.M. Dembitsky, R. Smoum, A.A. Al-Quntar, H. Abu Ali, I. Pergament, M. Srebnik, Natural boron-containing compounds in plants, algae and microorganisms, Curr. Topics Phytochem. 5 (2002) 67-76.
[8] I. Uluisik, H.C. Karakaya, A. Koc, The importance of boron in biological systems. J. Trace Elem. Med. Biol. 45 (2018) 156-162.
[9] M.A. Wimmer, T. Eichert, Review: mechanisms for boron deficiency-mediated changes in plant water relations, Plant Sci. 203-204 (2013) 25-32.
[10] T. Tanada, Boron as a transducer in some physiological processes of plants, J. Plant Nutr. 18 (1995) 1743-1750.
[11] L. Huang, Z. Ye, R.W. Bell, B. Dell, Boron nutrition and chilling tolerance of warm climate crop species, Ann Bot. 96 (2005) 755-767.
[12] K. Miwa, T. Fujiwara, Boron transport in plants: co-ordinated regulation of transporters, Ann Bot. 105 (2010) 1103-1108.
[13] H. Abu Ali, V.M. Dembitsky, M. Srebnik, Contemporary Aspects of Boron: Chemistry and Biological Applications, Elsevier, Amsterdam, 2005, p.618.
[14] A. Yoshinari, J. Takano, Insights into the mechanisms underlying boron homeostasis in plants, Front. Plant Sci. 8 (2017) 1951-1958.
[15] R. Scorei, Is boron a prebiotic element? A mini-review of the essentiality of boron for the appearance of life on earth, Orig. Life Evol. Biosph. 42 (2012) 3-17.
[16] V.M. Dembitsky, M. Srebnik, Synthesis and biological activity of α-aminoboronic acids, amine-carboxyboranes and their derivatives, Tetrahedron 59 (2003) 579-593.
[17] V.M. Dembitsky, H. Abu Ali, M. Srebnik, Recent development in bisdiborane chemistry: B-C-B, B-C-C-B, B-C=C-B, and B-C≡C-B, Appl. Organomet. Chem. 17 (2003) 327-345.
[18] V.M. Dembitsky, A.A. Quntar, M. Srebnik, Recent developments on α-aminoboronic acids, amine-carboxyboranes and derivatives, Mini Rev. Med. Chem. 4 (2004) 1001-1018.
[19] H. Hori, Y. Uto, E. Nakata, Boron tracedrugs challenge for neutron dynamic therapy, Anticancer Res. 32 (2012) 2235-2239.

[20] B.C. Das, P. Thapa, R. Karki, C. Schinke, S. Das, S. Kambhampati, S.K. Banerjee, P. Van Veldhuizen, A. Verma, L.M. Weiss, T. Evans, Boron chemicals in diagnosis and therapeutics, Future Med. Chem. 5 (2013) 653-676.

[21] V.M. Dembitsky, T.A. Gloriozova, V.V. Poroikov, Natural steroids containing a tertiary butyl group and their biological activities, European J. Biomed. Pharm. Sci. 4 (2017) 32-58.

[22] V.M. Dembitsky, T.A. Gloriozova, V.V. Poroikov, Chlorinated plant steroids and their biological activities, Int. J. Cur. Res. Biosci. Plant Biol. 4 (2017) 70-85.

[23] D.V. Kuklev, T.A. Gloriozova, V.V. Poroikov, V.M. Dembitsky, Pharmacological activities of thiirane-containing fatty (carboxylic) acids and their derivatives, Chem. Res. J. 2 (2017) 19-27.

[24] O.A. Filz, V. Poroikov, Design of chemical compounds with desired properties using fragment libraries, Russ. Chem. Rev. 81 (2012) 158-174.

[25] A. Lagunin, A. Zakharov, D. Filimonov, V. Poroikov, QSAR modelling of rat acute toxicity on the basis of PASS prediction, Mol. Inform. 30 (2011) 241-250.

[26] D.O. Levitsky, T.A. Gloriozova, V.V. Poroikov, V.M. Dembitsky, Naturally occurring isocyano/isothiocyanato compounds: Their pharmacological and SAR activities, Mathews J. Pharm. Sci. 1 (2016) 003-018.

[27] T. Hemscheidt, M.P. Puglisi, L.K. Larsen, G.M.L. Patterson, R.E. Moore, J.L. Rios, J. Clardy, Structure and biosynthesis of borophycin, a new boeseken complex of boric acid from a marine strain of the blue-green alga *Nostoc linckia*, J. Org. Chem. 59 (1994) 3467–3471.

[28] R. Banker, S. Carmeli, Tenuecyclamides A-D, cyclic hexapeptides from the cyanobacterium *Nostoc spongiaeforme* var. tenue, J. Nat. Prod. 61 (1998) 1248-1251.

[29] J. Kohno, T. Kawahata, T. Otake, M. Morimoto, H. Mori, N. Ueba, M. Nishio, A. Kinumaki, S. Komatsubara, K. Kawashima, Boromycin, an anti-HIV antibiotic, Biosci. Biotechnol. Biochem. 60 (1996) 1036–1037.

[30] R. Hütter, W. Keller-Schien, F. Knüsel, V. Prelog, G.C. Rodgers Jr., P. Suter, G. Vogel, W. Voser, H. Zähner, Metabolites of microorganisms, 57. Communication, Boromycin, Helv. Chim. Acta. 50 (1967) 1533–1539.

[31] J.D. Dunitz, D.M. Hawley, D. Miklo, D.N.J. White, Yu. Berlin, R. Marui, V. Prelog, Structure of boromycin, Helv. Chim. Acta. 54 (1971) 1709–1713.

[32] T.C. Somers, J.D. White, J.J. Lee, P.J. Keller, C.J. Chang, H.G. Floss, A NMR analysis of boromycin sodium complex and sodium desvalinoboromycinate, J. Org. Chem. 51 (1986) 464–471.

[33] W. Moreira, D.B. Aziz, T. Dick, Boromycin kills mycobacterial persisters without detectable resistance, Front. Microbiol. 7 (2016) 199-205.

[34] J.J. Lee, T.S. Chen, C.J. Chang, C. Fenselau, H.G. Floss, Isolation of two minor components of the boromycin fermentation: N-acetylboromycin and N-formyl-boromycin, J. Antibiot. (Tokyo) 38 (1985) 1444-1446.

[35] Y. Okami, T. Okazaki, T. Kitahara, H. Umezawa, Studies on marine microorganisms. V. A new antibiotic, aplasmomycin, produced by a streptomycete isolated from shallow sea mud, J. Antibiot. (Tokyo) 29 (1976) 1019-1025.

[36] H. Nakamura, Y. Iitaka, T. Kitahara, T. Okazaki, Y. Okami, Structure of aplasmomycin, J. Antibiot. (Tokyo) 30 (1977) 714-719.

[37] K. Sato, T. Okazaki, K. Maeda, Y. Okami, New antibiotics, aplasmomycins B and C, J. Antibiot. (Tokyo) 31 (1978) 632-635.

[38] J. Davies, D. Davies, Origins and evolution of antibiotic resistance, Microbiol. Mol. Biol. Rev. 74 (2010) 417–433.

[39] H. Irschik, D. Schummer, K. Gerth, G. Höfle, H. Reichenbach, The tartrolons, new boron-containing antibiotics from a myxobacterium, *Sorangium cellulosum*, J. Antibiot. (Tokyo) 48 (1995) 26-30.

[40] J. Mulzer, M. Berger, Total synthesis of the boron-containing ion carrier antibiotic macrodiolide tartrolon B, J. Org. Chem. 69 (2004) 891-898.

[41] S.I. Elshahawi, A.E. Trindade-Silva, A. Hanora, A.W. Han, M.S. Flores, Boronated tartrolon antibiotic produced by symbiotic cellulose-degrading bacteria in shipworm gills, Proc. Natl. Acad. Sci. U.S.A. 110 (2013) 295-304.

[42] V.M. Dembitsky, R. Smoum, A.A. Al-Quntar, H. Abu Ali, I. Pergament, M. Srebnik, Natural occurrence of boron-containing compounds in plants, algae and microorganisms, Plant Sci. 163 (2002) 931-942.

[43] S.S. Ali, N.N. Vidhale, Bacterial siderophore and their application: A review, Int. J. Curr. Microbiol. App. Sci. 2 (2013) 303-312.

[44] A. Del Olmo, C. Caramelo, C. San Jose, Fluorescent complex of pyoverdin with aluminium, J. Inorg. Biochem. 97 (2003) 384-387.

[45] I.J. Schalk, M. Hannauer, A. Braud, New roles for bacterial siderophores in metal transport and tolerance, Environ. Microbiol. 13 (2011) 2844-2854.

[46] D. Ferreira, A.M. Seca, C. Gad, A.M. Silva, Targeting human pathogenic bacteria by siderophores: A proteomics review, J. Proteomics 145 (2016) 153-166.

[47] M. Saha, S. Sarkar, B. Sarkar, B.K. Sharma, S. Bhattacharjee, P. Tribedi, Microbial siderophores and their potential applications: a review, Environ. Sci. Pollut. Res. Int. 23 (2016) 3984-3999.

[48] E. Ahmed, S.J. Holmström, Siderophores in environmental research: roles and applications, Microb. Biotechnol. 7 (2014) 196-208.

[49] R.C. Hider, X. Kong, Chemistry and biology of siderophores, Nat. Prod. Rep. 27 (2010) 637-657.

[50] B.R. Wilson, A.R. Bogdan, M. Miyazawa, K. Hashimoto, Y. Tsuji, Siderophores in iron metabolism: from mechanism to therapy potential, Trends Mol. Med. 22 (2016) 1077–1090.

[51] A.E. Fazary, A.S. Al-Shihri, M.Y. Alfaifi, K.A. Saleh, M.A. Alshehri, S.E. Elbehairi, Y.H. Ju, Microbial production of four biodegradable siderophores under submerged fermentation, Int. J. Biol. Macromol. 88 (2016) 527-541.

[52] C. Kurth, H. Kage, M. Nett, Siderophores as molecular tools in medical and environmental applications, Org. Biomol. Chem. 14 (2016) 8212-8227.

[53] W.R. Harris, S.A. Amin, F.C. Küpper, D.H. Green, C.J. Carrano, Borate binding to siderophores: structure and stability, J. Am. Chem. Soc. 129 (2007) 12263-12271.

[54] S.A. Amin, F.C. Küpper, D.H. Green, W.R. Harris, C.J. Carrano. Boron binding by a siderophore isolated from marine bacteria associated with the toxic dinoflagellate *Gymnodinium catenatum*, J. Am. Chem. Soc. 129 (2007) 478–479.

[55] S.A. Amin, D.H. Green, M.C. Hart, F.C. Küpper, W.G. Sunda, C.J. Carrano, Photolysis of iron–siderophore chelates promotes bacterial–algal mutualism, Proceed. Nat. Acad. U.S.A. 106 (2009) 17071–17076.

[56] C.J.S. Bolch, T.A. Subramanian, D.H. Green, The toxic dinoflagellate *Gymnodinium catenatum* (Dinophyceae) requires marine bacteria for growth, J. Phycol. 47 (2011) 1529-1537.

[57] B. Holinsworth, J.D. Martin, Siderophore production by marine-derived fungi, Biometals. 22 (2009) 625-632.

[58] A. Thieken, G. Winkelmann, Rhizoferrin: a complexone type siderophore of the Mucorales and entomophthorales (Zygomycetes), FEMS Microbiol. Lett. 73 (1992) 37-41.

[59] K. Barbeau, G. Zhang, D.H. Live, A. Butler, Petrobactin, a photoreactive siderophore produced by the oil-degrading marine bacterium Marinobacter hydrocarbonoclasticus, J. Am. Chem. Soc. 124 (2002) 378-379.

[60] W.R. Harris, S.A. Amin, F.C. Küpper, D.H. Green, C.J. Carrano, Borate binding to siderophores: structure and stability, J. Am. Chem. Soc. 129 (2007) 12263-12271.

[61] A.G. Darvill, M. McNeil, P. Albersheim, Structure of plant cell walls. VIII. A new pectic polysaccharide, Plant Physiol. 62 (1978) 418–422.

[62] M. McNeil, A.G. Darvill, S.C. Fry, P. Albersheim, Structure and function of the primary cell walls of plants, Annu. Rev. Biochem. 53 (1984) 625-663.

[63] V. Puvanesarajah, A.G. Darvill, P. Albersheim, Structural characterization of two oligosaccharide fragments formed by the selective cleavage of rhamnogalacturonan II: evidence for the anomeric configuration and attachment sites of apiose and 3-deoxy-2-heptulosaric acid, Carbohydr. Res. 218 (1991) 211-222.

[64] A. Heredia, A. Jiménez, R. Guillén, Composition of plant cell walls, Z. Lebensm. Unters. Forsch. 200 (1995) 24-31.

[65] D. Chormova, D.J. Messenger, S.C. Fry, Boron bridging of rhamnogalacturonan-II, monitored by gel electrophoresis, occurs during polysaccharide synthesis and secretion but not post-secretion, Plant J. 77 (2014) 534-546.

[66] M.A. O'Neill, T. Ishii, P. Albersheim, A.G. Darvill, Rhamnogalacturonan II: structure and function of a borate cross-linked cell wall pectic polysaccharide, Annu. Rev. Plant Biol. 55 (2004) 109-139.

[67] P.V. Mikshina, A.A. Petrova, D.A. Faizullin, Y.F. Zuev, T.A. Gorshkova, Tissue-specific rhamnogalacturonan I forms the gel with hyperelastic properties, Biochem. (Mosc) 80 (2015) 915-924.

[68] T.A. Gorshkova, L.V. Kozlova, P.V. Mikshina, Spatial structure of plant cell wall polysaccharides and its functional significance, Biochem. (Mosc) 78 (2013) 836-853.

[69] S.G. Penn, H. Hu, P.H. Brown, C.B. Lebrilla, Direct analysis of sugar alcohol borate complexes in plant extracts by matrix-assisted laser desorption/ionization fourier transform mass spectrometry, Anal. Chem. 69 (1997) 2471-2477.

[70] F. Jiang, W.D. Jeschke, W. Hartung, D.D. Cameron, Mobility of boron-polyol complexes in the hemiparasitic association between Rhinanthus minor and *Hordeum vulgare*: the effects of nitrogen nutrition, Physiol. Plant. 134 (2008) 13-21.

[71] P. Saenz, R.E. Cachau, G. Seoane, M. Kieninger, O.N. Ventura, A new perspective in the Lewis acid catalyzed ring opening of epoxides, Theoretical study of some complexes of methanol, acetic acid, dimethyl ether, diethyl ether, and ethylene oxide with boron trifluoride, J. Phys. Chem. A 110 (2006) 11734-11751.

[72] C.A. Northrop-Clewes, D.I. Thurnham, The discovery and characterization of riboflavin, Ann. Nutr. Metab. 61 (2012) 224-230.

[73] H. Chick, M.H. Roscoe, On the composite nature of the water-soluble B vitamin, Biochem. J. 21 (1927) 698–711.

[74] P. Gyorgy, Investigations on the vitamin B2 complex, The differentiation of lactoflavin and the 'rat antipellagra' factor, Biochem. J. 29 (1935) 741–759.

[75] H. Chick, A.M. Copping, The alcohol-solubility of the anti-dermatitis, more heat-stable vitamin B2 constituent of the vitamin B complex, Biochem. J. 24 (1930) 1744-1749.

[76] J.T. Pinto, R.S. Rivlin, Drugs that promote renal excretion of riboflavin, Drug Nutr. Interact. 5 (1987) 143-151.

[77] I. Hassan, S. Chibber, I. Naseem, Vitamin B_2: a promising adjuvant in cisplatin based chemoradiotherapy by cellular redox management, Food Chem. Toxicol. 59 (2013) 715-723.

[78] I.A. Borzenko, Clinico-pharmacologic aspects of using riboflavin and riboflavin coenzymes, Vrach. Delo. 10 (1983) 4-8.

[79] T.R. Koch, F.C. Finelli, Postoperative metabolic and nutritional complications of bariatric surgery, Gastroenterol. Clin. North Am. 39 (2010) 109-124.

[80] D.V. Frost, The water-soluble riboflavin-boron complex, J. Biol. Chem. 145 (1942) 693-700.

[81] D.H. Kim, K.F. Faull, C.D. Eckhert, Investigating the complex formation between boron and riboflavin using electrospray ionization mass spectrometry and fluorescence spectroscopy, FASEB J. 24 (2010) Supplement, 537.

[82] D.A. Köse, B. Zümreoglu-Karan, T. Hökelek, Boric acid complexes with organic biomolecules: Mono-chelate complexes with salicylic and glucuronic acids, Inorg. Chim. Acta 363 (2010) 4031–4037.

[83] V.M. Dembitsky, M. Srebnik, Boronic lipids, Synthesis of new lipids containing boron, Workshop on Boron Chemistry. Jerusalem, 2011.

[84] H.S. Yoon, K.M. Müller, R.G. Sheath, F.D. Ott, D. Bhattacharya, Defining the major lineages of red algae (Rhodophyta), J. Phycol. 42 (2006) 482–492.

[85] G.W. Saunders, M.H. Hommersand, Assessing red algal supraordinal diversity and taxonomy in the context of contemporary systematic data, Am. J. Bot. 91 (2004) 1494–1507.

[86] H. Tappan, The paleobiology of plant protists, W.H. Freeman, San Francisco, 1980.

[87] S. Bengtson, T. Sallstedt, V. Belivanova, M. Whitehouse, Three-dimensional preservation of cellular and subcellular structures suggests 1.6 billion-year-old crown-group red algae, PLoS Biol. 15 (2017) e2000735.
[88] S.B. Gould, R.F. Waller, G.I. McFadden, Plastid Evolution, Ann. Rev. Plant Biol. 59 (2008) 491–517.
[89] R. Viola, P. Nyvall, M. Pedersén, The unique features of starch metabolism in red algae, Proc. Royal Soc. London B. 268 (2001) 1417–1422.
[90] V.M. Dembitsky, O.A. Rozentsvet, Phospholipid composition of some marine red algae, Phytochem. 29 (1990) 3149-3152.
[91] V.M. Dembitsky, G.A. Tolstikov, Natural halogenated organic compounds, Geo-Science, Novosibirsk, pp. 366, 2003.
[92] V.M. Dembitsky, E.E. Pechenkina-Shubina, O.A. Rozentsvet, Glycolipids and fatty acids of some seaweeds and marine grasses from Black Sea, Phytochem. 30 (1991) 2279-2283.
[93] V.M. Dembitsky, O.A. Rozentsvet, E.E. Pechenkina, Glycolipids, phospholipids and fatty acids of some brown algae species from the Black Sea, Phytochem. 29 (1990) 3417-3421.
[94] B. Kalisch, P. Dörmann, G. Hölzl, DGDG and glycolipids in plants and algae, Subcell. Biochem. 86 (2016) 51-83.
[95] W.K. Lee, Y.Y. Lim, A.T. Leow, P. Namasivayam, J. Ong Abdullah, C.L. Ho, Biosynthesis of agar in red seaweeds: A review, Carbohydr. Polym. 164 (2017) 23-30.
[96] N. Florez, M.J. Gonzalez-Munoz, D. Ribeiro, E. Fernandes, H. Dominguez, M. Freitas, Algae polysaccharides' chemical characterization and their role in the inflammatory Process, Curr. Med. Chem. 24 (2017) 149-175.
[97] V.M. Dembitsky, M. Srebnik, Natural halogenated fatty acids: their analogues and derivatives, Prog. Lipid Res. 41 (2002) 315-367.
[98] H.U. Dahms, S. Dobretsov, Antifouling compounds from marine macroalgae, Mar. Drugs 15 (2017) pii: E265.
[99] J.W. Blunt, B.R. Copp, R.A. Keyzers, M.H.G. Munro, M.R. Prinsep, Marine natural products, Nat. Prod. Rep. 34 (2017) 235-294.
[100] B. Pejin, K.K. Jovanovic, A.G. Savic, New antitumour natural products from marine red algae: covering the period from 2003 to 2012, Mini Rev. Med. Chem. 15 (2015) 720-730.
[101] K. Wolkenstein, J.H. Gross, H. Falk, Boron-containing organic pigments from a Jurassic red alga, Proc. Natl. Acad. Sci. U.S.A. 107 (2010) 19374-19378.
[102] K. Wolkenstein, H. Sun, H. Falk, C. Griesinger, Structure and absolute configuration of Jurassic polyketide-derived spiroborate pigments obtained from microgram quantities, J. Am. Chem. Soc. 137 (2015) 13460-13463.