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MINI-REVIEW

Oxetane-containing metabolites: origin, structures, and biological activities

Vera Vil[1] · Alexander O. Terent'ev[1] · Abed Al Aziz Al Quntar[2] · Tatyana A. Gloriozova[3] · Nick Savidov[4] · Valery M. Dembitsky[1,4,5]

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Abstract

Cyclobutanes containing one oxygen atom in a molecule are called oxetane-containing compounds (OCC). More than 600 different OCC are found in nature; they are produced by microorganisms, and also found in marine invertebrates and algae. The greatest number of them is found in plants belonging to the genus *Taxus*. Oxetanes are high-energy oxygen-containing non-aromatic heterocycles that are of great interest as new potential pharmacophores with a significant spectrum of biological activities. The biological activity of OCC that is produced by bacteria and Actinomycetes demonstrates antineoplastic, antiviral (*arbovirus*), and antifungal activity with confidence an angiogenesis stimulator, respiratory analeptic, and antiallergic activity dominate with confidence from 81 to 99%.

Keywords Oxetane · Cyclobutane · Microorganisms · Fungi · Algae · Invertebrates · Plant · Activities

Introduction

Cyclobutane-containing metabolites are widely distributed in nature and reported in the scientific literature (Fan et al. 2016; Dembitsky 2008, 2014; Sergeiko et al. 2008). Heterocyclobutanes containing atoms of oxygen (*oxetanes*), nitrogen (*azetidines*), or sulfur (*thietanes*) are also found in nature, but to a much lesser extent (Kingston et al. 2002; Brandi et al. 2008; Leśniak et al. 2008; Alcaide and Almendros 2011; Abe 2008).

At present, high-energy oxygen-containing non-aromatic heterocycles are of great interest as novel pharmacophores with diverse biological activities, and such compounds include endoperoxides and oxetanes (Vil et al. 2017, 2018; Terent'ev et al. 2011, 2014; Dembitsky et al. 2007; Davis and Bull 2015). Currently, both natural and synthetic oxetanes are attracting the attention of pharmacologists, physicians, and chemists as important motives for discovering new drugs because of their interesting physicochemical properties of these compounds (Carreira and Fessard 2014; Prablek 2013; Wuitschik 2008; Wang et al. 2000).

If one looks at oxetanes from the point of view of chemical communication between bacteria and/or fungal endophytes, one can explain the limited presence of oxetane ring in various classes of natural compounds, an including isoprenoid lipids (Chagas and Pupo 2018; Savidov et al. 2018; Du Toit 2016; Wongsuk et al. 2016; Dembitsky et al. 2011). Bacterial and fungal quorum sensing is an interesting research direction in the field of medical chemistry and pharmacology and involves the discovery of the chemical language of information exchange between bacteria or/and fungi (Taga and Bassler 2003; Waters and Bassler 2005; Lentini et al. 2017; Smoum et al. 2012; Dembitsky and Gloriozova 2017).

The synthesis of the OCC is widely described in the scientific literature (Appendino 1995; Kingston et al. 2002; Burkhard et al. 2010; Wuitschik et al. 2010; Bull et al. 2016). Methods for the synthesis of some natural OCC are also described; however, there are practically no reviews

✉ Valery M. Dembitsky
valeryde@imb.dvo.ru

[1] N.D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky Prospect 47, Moscow, Russia 119991

[2] Department of Material Engineering, Faculty of Engineering, Al Quds University, Abu Dies, Palestinian Authority Jerusalem, Israel

[3] Institute of Biomedical Chemistry, Moscow, Russia 119121

[4] Centre for Applied Research and Innovation, Lethbridge College, 3000 College Drive South, Lethbridge, AB T1K 1L6, Canada

[5] Biochemical Lab, National Scientific Center of Marine Biology, 17 Palchevsky Str, Vladivostok, Russia 690041

devoted to natural oxetane-containing compounds (OCC) (Wang et al. 2011; Appendino 1995). According to some authors, the presence in molecule of the oxetane group gives it a definite activity against many pathogens (Kingston et al. 2002). More than 600 different OCC are found in nature; they are produced by microorganisms, and also found in marine invertebrates and algae. The greatest number of them is found in plants belonging to the genus *Taxus* (Wang et al. 2000, 2011; Kingston et al. 2002; Das and Rao 1996; Appendino 1995).

The biosynthesis of the oxetane ring in the taxol molecule has been thoroughly studied and described in many reviews, and different groups of scientists have made chemically based mechanistic suggestions for the biosynthesis of oxetane-containing taxol and its derivatives (Willenbring and Tantillo 2008; Walker and Croteau 1999; Croteau et al. 2006). However, today, the question of the biosynthesis of the oxetane ring remains open and is quite intensively discussed in the scientific literature (Meng et al. 2018; Howat et al. 2014).

Pharmacologists are known to claim that the biological activity of both natural and synthetic compounds is related to the chemical structure (Barlow 1979). As shown by numerous studies in recent years, the stereo-electronic effects of organic molecules demonstrate a link between reactivity and biological activity. In addition, stereo-electronic effects are like a bridge between the structure and the reactivity of the molecules. These effects have wide practical application in asymmetric catalysis, photochemical processes, bioorganic chemistry, biochemistry, inorganic and organometallic reactivity, and supramolecular chemistry (Alabugin 2016; Alabugin et al. 2015).

Currently, a number of computer programs are known that, with a certain degree of probability (Sliwoski et al. 2014; Leelananda and Lindert 2016; Kokh et al. 2018), estimate the activity of drug-like organic compounds (Bezhentsev et al. 2017; Lagunin et al. 2014). The PASS program contains information about one million chemical compounds and more than 9000 biological activities (Filimonov et al. 2014). The algorithm for practical use of PASS has been described in detail in several publications (Vil et al. 2018; Filimonov et al. 2018, Dembitsky et al. 2018). We used this program to help us determine the biological activity of the OCC presented in this article. The biological activity of many of these compounds has not been studied previously.

The mini review presented by us is the first successful analysis of the description of the chemical structures of natural OCC and their biological activity.

Oxetane-containing compounds produced by microorganisms

The OCC are produced by both bacteria and various strains of Actinomycetes, moreover mainly *Streptomyces* strain. β-Lactone called papulinone ((1), structure shown in Fig. 1 and activity shown in Table 1) is weakly phytotoxic on apple and bean leaves, has been isolated from a rod-shaped, Gram-negative bacterium *Pseudomonas syringae* (Evidente et al. 1990). Bradyoxetin (2) is a unique chemical component that participates in symbiotic regulation of genes. This metabolite produces a symbiotic bacterium *Bradyrhizobium japonicum* (Loh et al. 2002). The ethyl acetate extract of a marine bacteria *Bacillus* sp. from sediments (Ieodo, South Korea) yielded 24-membered antibacterial macrolactone called macrolactin I (3) (Mojid Mondol et al. 2011).

Belactins A (4) as a serine carboxypeptidase inhibitor was discovered in the fermentation broth of *Saccharopolyspora* sp. MK19-42F6 (known as *Streptomyces erythraeus*) (Murakami et al. 1995a, b). An inhibitor of serine carboxypeptidase called belactins B (5) was discovered in the fermentation broth of *Saccharopolyspora* sp. MK19-42F6 (Murakami et al. 1995a, b).

Two antitumor peptide antibiotics, belactosin A (6) and C (7), acting on cyclin/CDK mediated cell cycle regulation produced by soil *Streptomyces* sp. KYI 1780 from Kanagawa prefecture, Japan (Asai et al. 2000). Ebelactone B (8) is a β-lactone potent inhibitor of pancreatic lipase produced by *Streptomyces aburaviensis* (Nonaka et al. 1995; Ostrowska et al. 2005). The potent inhibitor of pancreatic lipase called lipstatin (9) was obtained from the fermentation broth of *Streptomyces toxytricini* (Weibel et al. 1987).

A series of pancreatic lipase inhibitors with an oxetane ring called panclicins A, B, C, D, and E are produced by *Streptomyces* sp. NR0619 (Mutoh et al. 1994). The structure of one of them panclicin E (10) is shown in Fig. 1. Antibacterial the β-lactone antibiotics called diffusomycin (11) derived from *Streptomyces albus* (Grafe et al. 1988), and the same compound called oxazolomycin (11) produced by *Streptomyces* sp. KBFP-2025 (Otani et al. 2000). Tonew and co-authors (1992) showed that diffusomycin (oxazolomycin) demonstrated also the antiviral activity (Tonew et al. 1992).

Four β-lactones, 4α-(3,5-dihydroxy hexyl)-3α-methyl-2-oxetanone (12), 4α-(3-methyl-4-formyloxy-hexyl)-3α-methyl-2-oxetanone (13), 4α-(3,5-dihydroxy-heptyl)-3α-methyl-2-oxetanone (14), and 4α-(3-methyl-4-formyloxy-heptyl)-3α-methyl-2-oxetanone (15), were obtained from the endophytic *Streptomyces* sp. T1B1 which was identified from the old bast tissue of *Taxus yunnanensis* (Yuan et al. 2013). Actinomycete *Streptomyces albolongus* MG147-CF2 was isolated from a soil sample collected in Shirane Mountain, Gunma Prefecture, contains antibiotic valilactone (16). The isolated compound inhibited hog liver esterase and hog pancreas lipase with IC_{50} values of 29 and 0.14 ng/mL, respectively. It can also inhibit fatty acid synthase with an IC_{50} value of 0.3 μM and demonstrates selective toxicity

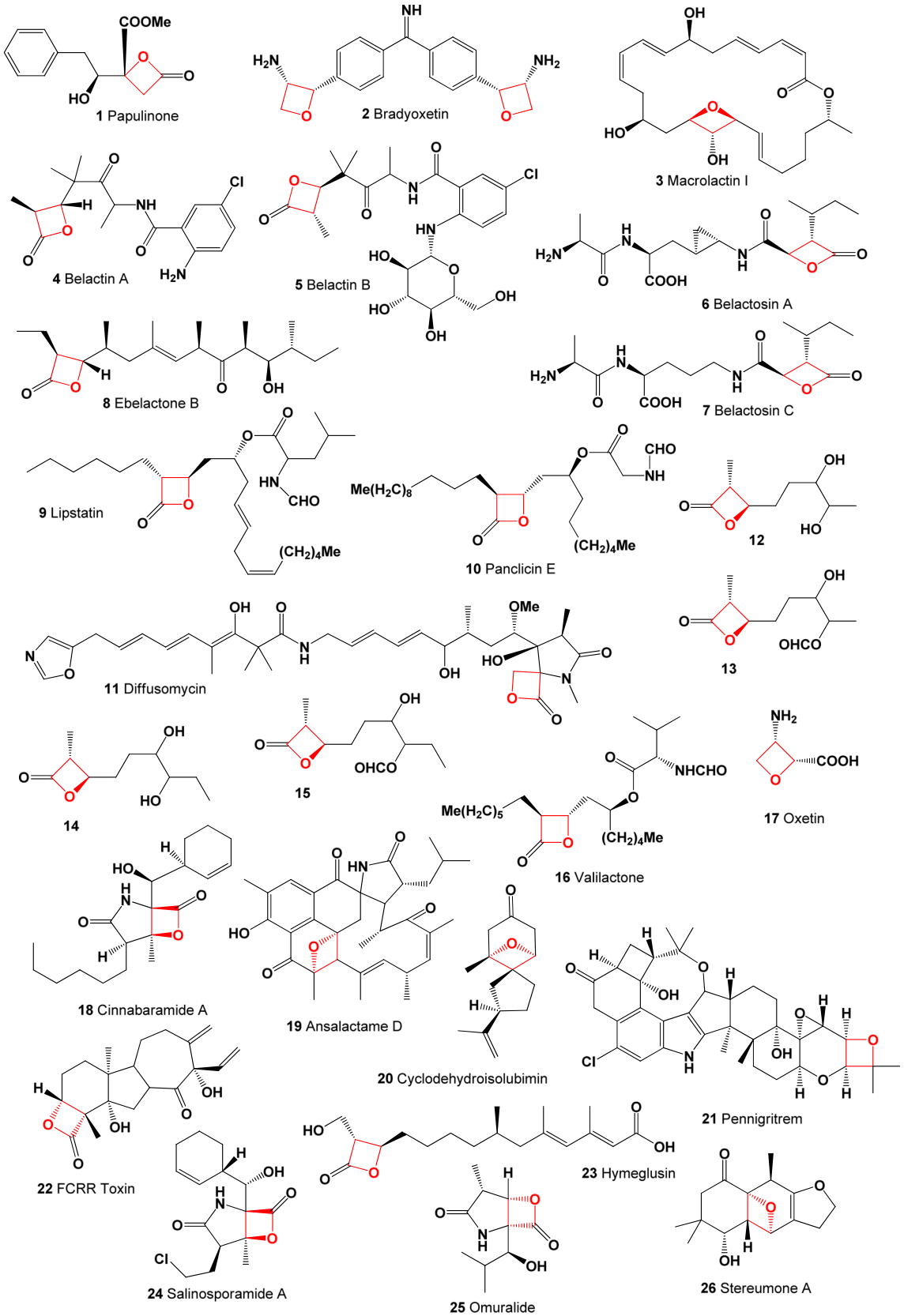

Fig. 1 Oxetane-containing compounds derived from microorganisms

Table 1 Biological activities oxetane-containing compounds produced by microorganisms

No.	Predicted biological activities of oxetane-containing compounds (Pa)*
1	Antineoplastic (0.790); antiviral (*arbovirus*) (0.670); fibrinolytic (0.652); phobic disorders treatment (0.624); genital warts treatment (0.552) Antieczematic (0.530); lipid metabolism regulator (0.502)
2	Phobic disorders treatment (0.709); antidiabetic (0.624); psychotropic (0.592); genital warts treatment (0.589); antidyskinetic (0.560) Antiviral (*picornavirus*) (0.528); antiviral (*arbovirus*) (0.504)
3	Antineoplastic (0.906); antifungal (0.813); antibacterial (0.799); antiparasitic (0.770); immunosuppressant (0.757); cytostatic (0.702) Antimetastatic (0.692); apoptosis agonist (0.679); antieczematic (0.671); genital warts treatment (0.671); respiratory analeptic (0.619)
4	Antihypertensive (0.972); general pump inhibitor (0.849); diuretic (0.630); antidyskinetic (0.618); antiviral (*arbovirus*) (0.601)
5	Antihypertensive (0.924); genital warts treatment (0.806); general pump inhibitor (0.797); antineoplastic (0.665); antihemorrhagic (0.595) Antidiabetic (0.579); immunosuppressant (0.567)
6	Mucositis treatment (0.660); antieczematic (0.629); allergic conjunctivitis treatment (0.617); immunosuppressant (0.591); antineoplastic (0.578) Antibiotic glycopeptide-like (0.572)
7	Mucositis treatment (0.890); antineoplastic (0.690); natural killer cell stimulant (0.673); antieczematic (0.646); psychostimulant (0.614) Radioprotector (0.610); antiviral (*arbovirus*) (0.602); antifungal (0.568); neuroprotector (0.546); biliary tract disorders treatment (0.532)
8	Antineoplastic (0.932); antifungal (0.861); hypolipemic (0.829); antibacterial (0.796); antiparasitic (0.775); antieczematic (0.738) Lipid metabolism regulator (0.737); immunosuppressant (0.731); apoptosis agonist (0.695); antihelmintic (0.681); antiinflammatory (0.579)
9	Antieczematic (0.879); antidiabetic symptomatic (0.779); antineoplastic (0.749); antifungal (0.706); antibacterial (0.674); antiinflammatory (0.638) Immunosuppressant (0.634); hypolipemic (0.588); antithrombotic (0.574); apoptosis agonist (0.556); antileukemic (0.546); antiulcerative (0.534)
10	Antidiabetic symptomatic (0.807); antineoplastic (0.692); antieczematic (0.679); antifungal (0.634); antibacterial (0.591); hypolipemic (0.576) Chemoprotective (0.573); antithrombotic (0.547); lipase inhibitor (0.529); antiulcerative (0.520)
11	Antineoplastic (0.926); alkylator (0.747); antibacterial (0.591); antineoplastic antibiotic (0.564); genital warts treatment (0.516)
12	Antieczematic (0.810); antineoplastic (0.739); lipid metabolism regulator (0.700); hypolipemic (0.698); antiinfective (0.692); antiparasitic (0.684) Antiviral (*arbovirus*) (0.681); antifungal (0.673); antiischemic, cerebral (0.644); vasoprotector (0.626); antidiabetic (0.621); immunosuppressant (0.617) Antinephrotoxic (0.611); antihelmintic (0.604); antiinflammatory (0.582); antihypertensive (0.565); antipruritic, allergic (0.557)
13	Antieczematic (0.729); antihypertensive (0.716); antineoplastic (0.659); antibacterial (0.617); genital warts treatment (0.531) Antiviral (arbovirus) (0.510); hypolipemic (0.507)
14	Antieczematic (0.829); hypolipemic (0.742); vasoprotector (0.719); antiviral (arbovirus) (0.719); lipid metabolism regulator (0.697) Antifungal (0.681); antineoplastic (0.672); immunosuppressant (0.654); antinephrotoxic (0.631); kidney function stimulant (0.607) Antiinflammatory (0.596); antiparasitic (0.588); antihypertensive (0.587); antidiabetic (0.577); antipruritic, allergic (0.573); leukopoiesis stimulant (0.561)
15	General pump inhibitor (0.956); protein synthesis inhibitor (0.766); antieczematic (0.740); antibacterial (0.629); antineoplastic (0.595) Antihypertensive (0.590); antiviral (*arbovirus*) (0.534); hypolipemic (0.524)
16	Antidiabetic symptomatic (0.792); antineoplastic (0.732); antifungal (0.664); antibacterial (0.639); antieczematic (0.619); immunosuppressant (0.571) Antileukemic (0.561); cytostatic (0.541); hypolipemic (0.538); antithrombotic (0.509)
17	Antibiotic glycopeptide-like (0.965); phobic disorders treatment (0.837); genital warts treatment (0.787); antiinflammatory (0.722) Antiviral (arbovirus) (0.704); antiarthritic (0.689); antiviral (picornavirus) (0.667); antinephrotoxic (0.643); antibacterial (0.582); antieczematic (0.580)
18	Antineoplastic (multiple myeloma) (0.981); apoptosis agonist (0.946); autoimmune disorders treatment (0.900); antineoplastic (0.894) Proteasome inhibitor (0.855); rheumatoid arthritis treatment (0.846); angiogenesis inhibitor (0.838); antiasthmatic (0.796); antibacterial (0.685) Antiarthritic (0.654); multiple sclerosis treatment (0.619); antiischemic, cerebral (0.591); antieczematic (0.589); radiosensitizer (0.509)
19	Antineoplastic (0.850); antiinflammatory (0.753); antileukemic (0.643); antibacterial (0.641); antieczematic (0.518)
20	Antipsoriatic (0.885); antineoplastic (0.828); apoptosis agonist (0.797); immunosuppressant (0.741); antieczematic (0.719); antiacne (0.678) Antiinflammatory (0.678); chemopreventive (0.668); antifungal (0.624); respiratory analeptic (0.527); antileukemic (0.512); antiviral (HIV) (0.505)
21	Antineoplastic (0.869); potassium channel blocker (0.827); chloride channel blocker (0.811); hypolipemic (0.799); antihypertensive (0.709) Interleukin antagonist (0.676); apoptosis agonist (0.613); antiarthritic (0.551)
22	Genital warts treatment (0.930); angiogenesis inhibitor (0.918); antineoplastic (0.918); vasoprotector (0.861); antifungal (0.827); antiparasitic (0.819) Hepatoprotectant (0.789); antihypercholesterolemic (0.781); antihelmintic (0.780); antiinflammatory (0.769); neuroprotector (0.753); antibacterial (0.744) Antihypoxic (0.739); antidiabetic (0.721); antithrombotic (0.710); cytostatic (0.692); radioprotector (0.686); apoptosis agonist (0.675)
23	Antineoplastic (0.836); antifungal (0.762); antiinflammatory (0.752); chemopreventive (0.725); skin whitener (0.703); antiprotozoal (0.626) Apoptosis agonist (0.617); antibacterial (0.613); cytostatic (0.562)
24	Antineoplastic (multiple myeloma) (0.990); apoptosis agonist (0.964); antineoplastic (0.947); autoimmune disorders treatment (0.937)

Table 1 (continued)

No.	Predicted biological activities of oxetane-containing compounds (Pa)*
	Angiogenesis inhibitor (0.925); rheumatoid arthritis treatment (0.922); antiarthritic (0.718); antiasthmatic (0.697); antibacterial (0.684)
25	Autoimmune disorders treatment (0.995); antiischemic, cerebral (0.994); multiple sclerosis treatment (0.994); transplant rejection treatment (0.983) Neuroprotector (0.955); antineoplastic (0.932); antiasthmatic (0.929); antiinflammatory (0.923); angiogenesis inhibitor (0.918) Rheumatoid arthritis treatment (0.902); antipsoriatic (0.862); stroke treatment (0.843); antiviral (*arbovirus*) (0.584); cardiovascular analeptic (0.572)
26	Antidyskinetic (0.780); antineoplastic (0.744); genital warts treatment (0.660); allergic conjunctivitis treatment (0.641); antieczematic (0.639) Antiviral (*arbovirus*) (0.592); antinephrotoxic (0.579); dementia treatment (0.574); antiinflammatory (0.557); ovulation inhibitor (0.529)
27	Antineoplastic (0.871); apoptosis agonist (0.842); antiinflammatory (0.760); antiviral (*arbovirus*) (0.743); cardiovascular analeptic (0.734) Antibacterial (0.654); antieczematic (0.625); hypolipemic (0.593); cytostatic (0.592); antimetastatic (0.587); immunosuppressant (0.586) Antiviral (*picornavirus*) (0.573); antifungal (0.558); antileukemic (0.551); antiallergic (0.542); antiparasitic (0.537); antiulcerative (0.528)
28	Apoptosis agonist (0.949); antineoplastic (0.897); antiulcerative (0.737); cardiovascular analeptic (0.688); antibacterial (0.651); antiviral (*arbovirus*) (0.649); immunosuppressant (0.640); antiinflammatory (0.622); respiratory analeptic (0.610); antiparasitic (0.601); antihelmintic (0.597) Antifungal (0.574); hypolipemic (0.567); antileukemic (0.555); cytostatic (0.541)
29	Apoptosis agonist (0.939); antineoplastic (0.877); antiinflammatory (0.783); antiulcerative (0.780); immunosuppressant (0.688); antiparasitic (0.686) Hypolipemic (0.661); antibacterial (0.652); antiviral (*arbovirus*) (0.651); antihelmintic (0.637); antifungal (0.619); antileukemic (0.609) Cytostatic (0.608); antieczematic (0.589); neuroprotector (0.585); cardiovascular analeptic (0.583)
30	Antieczematic (0.844); antineoplastic (0.839); genital warts treatment (0.743); antiinflammatory (0.727); apoptosis agonist (0.720); antileukemic (0.636) Antiprotozoal (0.612); antinephrotoxic (0.591); antimitotic (0.548); antiviral (arbovirus) (0.541); immunosuppressant (0.505)
31	Antineoplastic (0.790); genital warts treatment (0.751); apoptosis agonist (0.748); antiinflammatory (0.736); antiischemic, cerebral (0.700) Antiallergic (0.640); antiasthmatic (0.572); myasthenia gravis treatment (0.563); kidney function stimulant (0.540); antifungal (0.524)
32	Apoptosis agonist (0.937); antineoplastic (0.875); cardiovascular analeptic (0.781); antiulcerative (0.778); antiviral (Arbovirus) (0.749) Antiinflammatory (0.749); antiparasitic (0.733); antihelmintic (0.730); immunosuppressant (0.671); cytostatic (0.670); antieczematic (0.669) Hypolipemic (0.655); antibacterial (0.643); antileukemic (0.627); antifungal (0.615); antiviral (*picornavirus*) (0.602); neuroprotector (0.592)
33	Respiratory analeptic (0.997); cytostatic (0.985); antimitotic (0.981); anticarcinogenic (0.960); proliferative diseases treatment (0.946) Vasodilator (0.940); antineoplastic (0.911); radiosensitizer (0.736); chemosensitizer (0.639); antileukemic (0.623); prostate cancer treatment (0.610)

*Only activities with Pa > 0.5 are shown

toward MDA-MB-231 breast cancer cells with an IC_{50} value of 10 μM (Kitahara et al. 1987). (2*R*,3*S*)-3-Amino-2-oxetane carboxylic acid called oxetin (17) was isolated from a fermentation broth of a *Streptomyces* sp. OM-2317 (Omura et al. 1984). Cinnabaramide A (18) as a proteasome inhibitor was detected in fermentation broth of *Streptomyces* sp. JS360 (Rachid et al. 2011). A marine-derived *Streptomyces* sp. has led to the isolation of ansalactam D (19) (Le et al. 2016).

Tricyclic sesquiterpene called cyclodehydroisolubimin (20) has been isolated from potato tubers inoculated with an oomycete *Phytophthora infestans* (Coxon et al. 1979). A fungal indol-diterpenoid with oxetane ring called pennigritrem (21) was isolated from *Penicillium nigricans* (Penn et al. 1992).

A phytotoxin, FCRR-Toxin (22), was isolated from the culture filtrate of *Fusarium oxysporum* f. sp. *radicis-lycopersici* (Hirota et al. 1994). Fungal β-lactone hymeglusin (23, also known as antibiotic F 244) produced by *Fusarium* sp. It inhibited HMG-CoA synthase (IC_{50} = 0.12 μM) by covalently modifying the active Cys129 residue of the enzyme (Greenspan et al. 1987; Tomoda et al. 2004).

The marine *Salinispora tropica* produced antibiotics, salinosporamide A (24), and omuralide (25) (Manam et al. 2009). Sesquiterpene called stereumone A (26) was isolated from a culture broth of the fungus *Stereum* sp. (Li et al. 2006) which showed nematicidal activity against nematode *Panagrellus redivivus*.

A few natural products possessing vibralactone skeleton, vibralactone B (27, structure shown in Fig. 2 and activity shown in Table 2), vibralactone C (28), and acetylated vibralactone (29) have been isolated from cultures of the basidiomycete *Boreostereum vibrans* (Jiang et al. 2008). Vibralactone (30) has been isolated from cultures of *B. vibrans* (Duan et al. 2018).

Highly oxygenated *p*-terphenyl, hawaiienol A (31), has been isolated from cultures of *Paraconiothyrium hawaiiense*, a fungus associated with the *Septobasidium*-infected insect *Diaspidiotus* sp. The compound (31) with 4,7-dioxatricyclo[3.2.1.03,6]octane unit in its *p*-terphenyl skeleton and showed cytotoxicity toward six human tumor cell lines (Ren et al. 2018). Pentacyclic depsidone containing an oxetane unit, phomopsidone A (32), was isolated

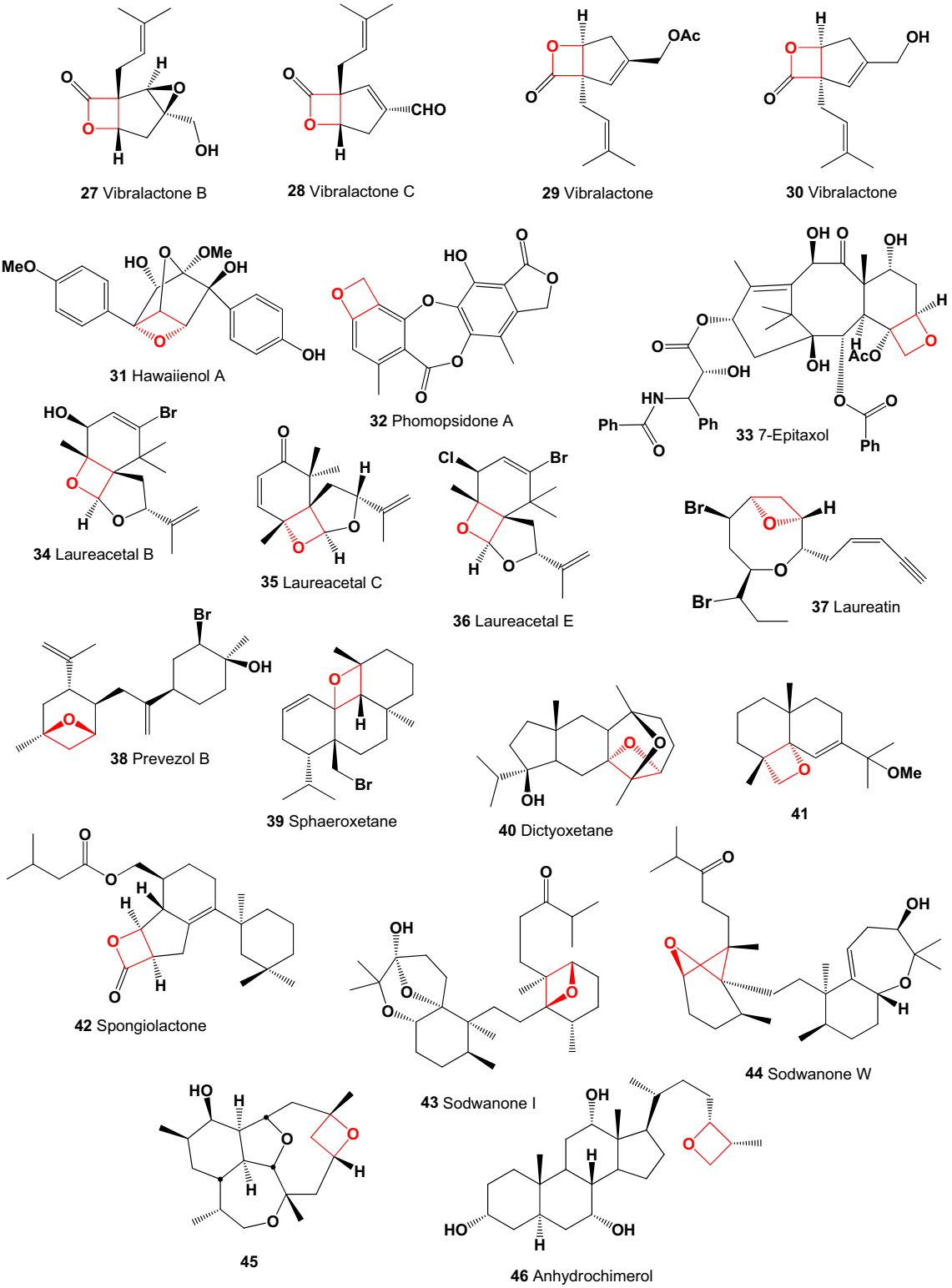

Fig. 2 Oxetane-containing compounds derived from microorganisms and marine sources

from the mangrove endophytic fungus *Phomopsis* sp. A123. The bioactivity assays showed that this compound possesses cytotoxic, antioxidant, and antifungal activities (Zhang et al. 2014).

A taxol derivative named 7-epi-10-deacetyltaxol (33) was detected in the culture of an endophytic fungus *Pestalotiopsis microspora* which isolated from the bark of *Taxodium mucronatum* (Subban et al. 2017).

Table 2 Biological activities oxetane-containing compounds produced by microorganisms

No.	Predicted biological activities of oxetane-containing compounds (Pa)*
34	Antineoplastic (0.859); antiprotozoal (*Plasmodium*) (0.706); antieczematic (0.701); antiinflammatory (0.684); stroke treatment (0.673) Immunosuppressant (0.671); apoptosis agonist (0.656); respiratory analeptic (0.648); antipsoriatic (0.644); antimitotic (0.586)
35	Antiprotozoal (*Plasmodium*) (0.875); antineoplastic (0.838); apoptosis agonist (0.787); respiratory analeptic (0.779); antiinflammatory (0.744) Antieczematic (0.707); antipsoriatic (0.653); antimetastatic (0.647); immunosuppressant (0.640); antifungal (0.575)
36	Respiratory analeptic (0.875); antineoplastic (0.834); antiprotozoal (*Plasmodium*) (0.779); antiinflammatory (0.777); autoimmune disorders treatment (0.742); apoptosis agonist (0.730); antipsoriatic (0.690); immunosuppressant (0.688); rheumatoid arthritis treatment (0.638); antiparasitic (0.601) Antieczematic (0.587); antifungal (0.548); antihelmintic (0.546); inflammatory bowel disease treatment (0.544); antiasthmatic (0.516)
37	Antiprotozoal (*Plasmodium*) (0.906); antineoplastic (0.843); apoptosis agonist (0.676); respiratory analeptic (0.632)
38	Apoptosis agonist (0.898); antineoplastic (0.742); antiprotozoal (*Plasmodium*) (0.629); antifungal (0.587); antibacterial (0.576) Chemoprotective (0.568); antiemetic (0.549); antimetastatic (0.524)
39	Antineoplastic (0.874); apoptosis agonist (0.819); antieczematic (0.747); antiprotozoal (*Plasmodium*) (0.645); hypolipemic (0.635) Antileukemic (0.633); antipsoriatic (0.626); postmenopausal disorders treatment (0.610); prostate cancer treatment (0.584); antimetastatic (0.559) Antifungal (0.550); antiinflammatory (0.549)
40	Antineoplastic (0.960); angiogenesis inhibitor (0.891); antiinflammatory (0.799); immunosuppressant (0.741); autoimmune disorders treatment (0.694) Prostate cancer treatment (0.662); antimetastatic (0.614); antiarthritic (0.594); apoptosis agonist (0.584); antifungal (0.557); antipsoriatic (0.555) Signal transduction pathways inhibitor (0.546); antieczematic (0.527); antiallergic (0.526)
41	Antineoplastic (0.960); angiogenesis inhibitor (0.891); antiinflammatory (0.799); immunosuppressant (0.741); autoimmune disorders treatment (0.694) Prostate cancer treatment (0.662); antimetastatic (0.614); antiarthritic (0.594); apoptosis agonist (0.584); antifungal (0.557); antipsoriatic (0.555) Signal transduction pathways inhibitor (0.546); antieczematic (0.527); antiallergic (0.526)
42	Antineoplastic (0.789); genital warts treatment (0.772); antiinflammatory (0.733); immunosuppressant (0.682); antiinfertility, female (0.674) Apoptosis agonist (0.657); antieczematic (0.634); antipruritic (0.613); prostate disorders treatment (0.581); neuroprotector (0.595) Antiosteoporotic (0.548); hypolipemic (0.537)
43	Antineoplastic (0.793); antieczematic (0.684); immunosuppressant (0.623); antimitotic (0.578); antibacterial (0.567); antimetastatic (0.566) Antineoplastic (renal cancer) (0.537)
44	Antineoplastic (0.812); antiviral (0.626); antibacterial (0.599); immunosuppressant (0.579); genital warts treatment (0.558); antimetastatic (0.525)
45	Antineoplastic (0.904); angiogenesis inhibitor (0.822); antimitotic (0.762); antimetastatic (0.691); antiprotozoal (*Plasmodium*) (0.690) Antifungal (0.687); antibacterial (0.686); immunosuppressant (0.625); antileukemic (0.604); cytostatic (0.548); antiparasitic (0.541) Apoptosis agonist (0.516); antinephrotoxic (0.513); Alzheimer's disease treatment (0.501)
46	Respiratory analeptic (0.845); antihypercholesterolemic (0.828); biliary tract disorders treatment (0.827); antieczematic (0.824); antineoplastic (0.815) Hypolipemic (0.810); antipruritic (0.787); antifungal (0.743); hepatoprotectant (0.729); immunosuppressant (0.726); antiinflammatory (0.717) Antipsoriatic (0.651); prostate disorders treatment (0.649); antiosteoporotic (0.623); antiprotozoal (*Plasmodium*) (0.621); antibacterial (0.620) Cholesterol synthesis inhibitor (0.612); atherosclerosis treatment (0.602); dementia treatment (0.569)

*Only activities with Pa > 0.5 are shown

Oxetane-containing compounds derived from marine sources

Several secochamigranes called laureacetal B (34, structure shown in Fig. 2 and activity shown in Table 2), C (35), and E (36) were identified from Japanese red algae *Laurencia nipponica* (Kurata et al. 1983; Ji and Wang 2014). The bromo compound, laureatin (37), was also isolated from *L. nipponica* (Irie et al. 1970). Diterpene with anticancer activity known as prevezol B (38) was found in the red algae *Laurencia rigida* (Machado et al. 2010). Diterpenoid sphaeroxetane (39) was detected in the red alga *Sphaerococcus coronopifolius* collected in the North Adriatic Sea (De Rosa et al. 1988). The diterpene having the 2,7-dioxa-tricyclo[4.2.1.0]nonane ring subunit called dictyoxetane (40) was isolated from the brown alga *Dictyota dichotoma* collected from the Indian Ocean (Pullaiah et al. 1985).

The organic extract of the Formosan soft coral *Nephthea erecta* led to the isolation of sesquiterpene (41) (Cheng et al. 2009). Diterpene isovalerate, spongiolactone (42), was isolated from the Mediterranean sponge *Spongionella gracilis* (Mayol et al. 1987). A South African marine sponge *Axinella* sp. yielded a series of anticancers of sodwanone triterpenoids, including sodwanone I (43) and sodwanone W (44) (Dai et al. 2006). Unusual asbestinane diterpene (45) has been isolated from octocoral *Briareum asbestinum* collected off the coast of Tobago, West Indies (Dookran et al. 1994).

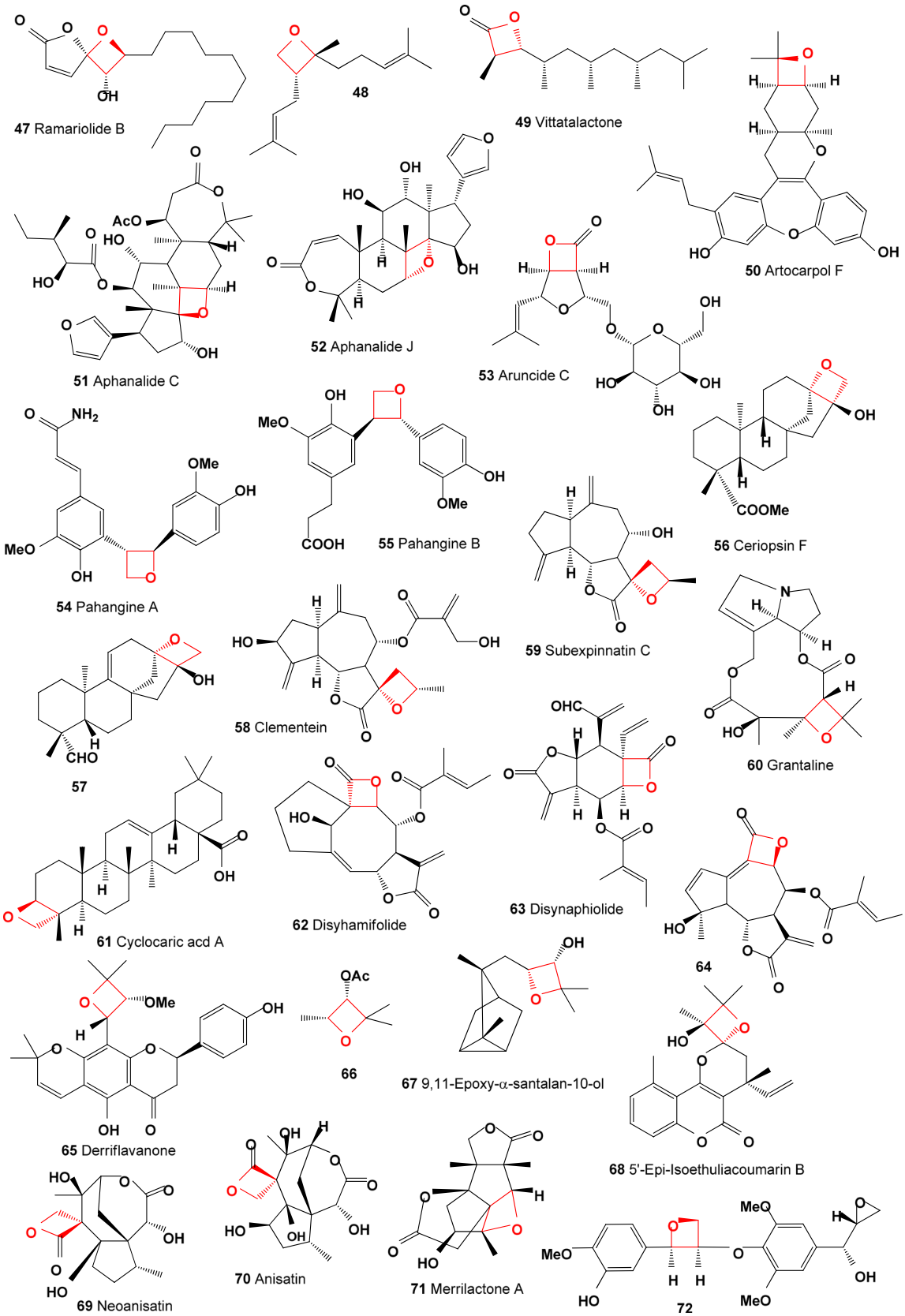

Fig. 3 Oxetane-containing compounds derived from fungi and plants

Table 3 Biological activities oxetane-containing compounds derived from fungi and plants

No.	Predicted biological activities of oxetane-containing compounds (Pa)*
47	Angiogenesis stimulant (0.993); apoptosis agonist (0.967); antineoplastic (0.909); antieczematic (0.811); antifungal (0.732); antiparasitic (0.702) Antihelmintic (0.681); lipid metabolism regulator (0.676); antiviral (*arbovirus*) (0.632); antibacterial (0.631); spasmolytic, urinary (0.629) Vasoprotector (0.621); immunosuppressant (0.620); antipruritic (0.589); cardiovascular analeptic (0.588); mucositis treatment (0.551) Antiulcerative (0.545); antipsoriatic (0.544); platelet aggregation inhibitor (0.538)
48	Antiarthritic (0.959); antiallergic (0.942); apoptosis agonist (0.822); antiinflammatory (0.766); antiviral (*arbovirus*) (0.732); hypolipemic (0.725) Antineoplastic (0.712); cell adhesion molecule inhibitor (0.706); thrombolytic (0.704); antieczematic (0.700); cardiovascular analeptic (0.685) Antioxidant (0.656); antiulcerative (0.613); antifungal (0.607); antithrombotic (0.606); spasmolytic (0.565)
49	Antieczematic (0.834); antiparasitic (0.774); phobic disorders treatment (0.767); hypolipemic (0.743); antifungal (0.715); antihelmintic (0.695) Antiinflammatory (0.684); antineoplastic (0.660); Alzheimer's disease treatment (0.657); antiarthritic (0.652); immunosuppressant (0.651) Lipid metabolism regulator (0.628); antinephrotoxic (0.605); antibacterial (0.596); angiogenesis stimulant (0.593)
50	Respiratory analeptic (0.836); antineoplastic (0.789); apoptosis agonist (0.764); skin whitener (0.746); antiparasitic (0.735); neuroprotector (0.642) Spasmolytic (0.633); antiinflammatory (0.626); immunosuppressant (0.623); antibacterial (0.609); cytostatic (0.602); antifungal (0.601) Hepatoprotectant (0.586); antiischemic, cerebral (0.583); antihelmintic (0.574); antioxidant (0.564)
51	Antineoplastic (0.841); respiratory analeptic (0.813); chemopreventive (0.772); immunosuppressant (0.772); antifungal (0.755) Apoptosis agonist (0.726); hepatoprotectant (0.700); antibacterial (0.662); antimitotic (0.627); hypolipemic (0.592); cytostatic (0.574)
52	Antineoplastic (0.795); immunosuppressant (0.767); apoptosis agonist (0.766); respiratory analeptic (0.721); chemopreventive (0.715) Antiinflammatory (0.657); hepatoprotectant (0.653); antifungal (0.622); cardiotonic (0.608); antibacterial (0.546); prostate disorders treatment (0.517)
53	Genital warts treatment (0.930); angiogenesis inhibitor (0.918); antineoplastic (0.918); vasoprotector (0.861); antifungal (0.827); antiparasitic (0.819) Hepatoprotectant (0.789); antihypercholesterolemic (0.781); antihelmintic (0.780); antiinflammatory (0.769); neuroprotector (0.753); antibacterial (0.744) Antihypoxic (0.739); antidiabetic (0.721); antithrombotic (0.710); cytostatic (0.692); radioprotector (0.686); apoptosis agonist (0.675)
54	Genital warts treatment (0.803); antineoplastic (0.718); apoptosis agonist (0.681); antimitotic (0.564); fibrinolytic (0.562); chemopreventive (0.560) Antiinflammatory (0.535); preneoplastic conditions treatment (0.530); mucositis treatment (0.519); antifungal (0.506)
55	Genital warts treatment (0.807); antihypercholesterolemic (0.801); neuroprotector (0.684); antineoplastic (0.678); antieczematic (0.675) Fibrinolytic (0.652); apoptosis agonist (0.618); antimutagenic (0.602); antiasthmatic (0.587); antiinflammatory (0.568) Preneoplastic conditions treatment (0.567); hepatoprotectant (0.560); acute neurologic disorders treatment (0.538); vasodilator, coronary (0.534) Antipyretic (0.527); antiallergic (0.519)
56	Antineoplastic (0.738); chemopreventive (0.731); antiinflammatory (0.716); antiarthritic (0.663); antieczematic (0.663); hepatic disorders treatment (0.634); immunosuppressant (0.630); antidiabetic (0.626); apoptosis agonist (0.611); antiviral (influenza) (0.608); antinephrotoxic (0.604) Acute neurologic disorders treatment (0.593); antipruritic (0.533); antipsoriatic (0.524); hypolipemic (0.514); dementia treatment (0.505)
57	Antineoplastic (0.813); apoptosis agonist (0.760); chemopreventive (0.565); respiratory analeptic (0.533); ovulation inhibitor (0.510) Prostate disorders treatment (0.501)
58	Antineoplastic (0.931); antieczematic (0.914); apoptosis agonist (0.894); antifungal (0.775); antiinflammatory (0.748); antipsoriatic (0.735) Immunosuppressant (0.730); antibacterial (0.682); genital warts treatment (0.600); antileukemic (0.563); chemopreventive (0.550); spasmolytic (0.541) Cytostatic (0.530); antiosteoporotic (0.521)
59	Antieczematic (0.919); antineoplastic (0.916); apoptosis agonist (0.840); antiinflammatory (0.820); immunosuppressant (0.747); antipsoriatic (0.738) Antifungal (0.694); antibacterial (0.653); analeptic (0.652); antimetastatic (0.646); Alzheimer's disease treatment (0.598); antiulcerative (0.578) Antiosteoporotic (0.574); cytostatic (0.561); antileukemic (0.559)
60	Expectorant (0.884); genital warts treatment (0.854); antineoplastic (0.849); antitussive (0.766); antidyskinetic (0.707); apoptosis agonist (0.665) Antineoplastic (myeloid leukemia) (0.580); spasmolytic (0.517); cardiovascular analeptic (0.515); antiinflammatory (0.513)
61	Wound healing agent (0.940); apoptosis agonist (0.871); hepatoprotectant (0.829); diuretic (0.810); antipruritic (0.789); antineoplastic (0.789) Antiinflammatory (0.784); antiulcerative (0.783); lipid metabolism regulator (0.746); vasodilator, peripheral (0.729); antiviral (influenza) (0.695) Immunosuppressant (0.682); prostate disorders treatment (0.649); antipsoriatic (0.620); antieczematic (0.619); antifungal (0.616) Atherosclerosis treatment (0.512)
62	Antineoplastic (0.950); apoptosis agonist (0.909); cytostatic (0.871); antiinflammatory (0.848); antieczematic (0.842); antimitotic (0.811) Antifungal (0.701); antiparasitic (0.691); antibacterial (0.667); antileukemic (0.653); spasmolytic (0.561); hepatoprotectant (0.531)
63	Antineoplastic (0.949); apoptosis agonist (0.942); antineoplastic (myeloid leukemia) (0.842); antieczematic (0.825); antiinflammatory (0.776) Antiparasitic (0.769); antifungal (0.750); antibacterial (0.687); antileukemic (0.656); hepatoprotectant (0.569); antihelmintic (0.529)
64	Antineoplastic (0.950); apoptosis agonist (0.909); antineoplastic (myeloid leukemia) (0.874); cytostatic (0.871); antiinflammatory (0.848) Antieczematic (0.842); antimitotic (0.811); antifungal (0.701); antiparasitic (0.691); antibacterial (0.667); antileukemic (0.653) Genital warts treatment (0.595); spasmolytic (0.561); hepatoprotectant (0.531)

Table 3 (continued)

No.	Predicted biological activities of oxetane-containing compounds (Pa)*
65	Antineoplastic (0.854); chemopreventive (0.767); neuroprotector (0.740); skin whitener (0.737); anticarcinogenic (0.727); hepatic disorders treatment (0.709); vasodilator (0.702); antiobesity (0.697); apoptosis agonist (0.668); antioxidant (0.661); antifungal (0.617); spasmolytic, urinary (0.611) Antiulcerative (0.609); immunosuppressant (0.567); antileukemic (0.563); cytostatic (0.552)
66	Antineoplastic (0.869); cardiotonic (0.856); antiseborrheic (0.830); antihypertensive (0.774); spasmolytic, urinary (0.744); leukopoiesis inhibitor (0.738); neuroprotector (0.735); antiviral (*arbovirus*) (0.734); respiratory analeptic (0.734); antinephrotoxic (0.727); antiinflammatory (0.725); antiarrhythmic (0.699); antianginal (0.697); apoptosis agonist (0.692); antiviral (picornavirus) (0.661); vasoprotector (0.654); fibrinolytic (0.651); antihypoxic (0.639); immunosuppressant (0.637); antiparasitic (0.627); hypolipemic (0.620); antifungal (0.603)
67	Genital warts treatment (0.726); vasoprotector (0.725); antineoplastic (0.706); antieczematic (0.684); antiseborrheic (0.682); cardiotonic (0.638); antiviral (*arbovirus*) (0.632); respiratory analeptic (0.629); spasmolytic, urinary (0.627); antinephrotoxic (0.608); kidney function stimulant (0.605); dementia treatment (0.588); erythropoiesis stimulant (0.586); antibacterial (0.578); alopecia treatment (0.562); antipruritic (0.551); ovulation inhibitor (0.547)
68	Antineoplastic (0.699); apoptosis agonist (0.647); histidine kinase inhibitor (0.595); antieczematic (0.575); antipsoriatic (0.567)
69	Genital warts treatment (0.782); antineoplastic (0.737); immunosuppressant (0.728); Alzheimer's disease treatment (0.684); antinephrotoxic (0.639) Antiinflammatory (0.632); antileukemic (0.558); antioxidant (0.538); apoptosis agonist (0.533)
70	Genital warts treatment (0.782); antineoplastic (0.765); Alzheimer's disease treatment (0.712); antiinflammatory (0.706); antieczematic (0.679) Immunosuppressant (0.674); antinephrotoxic (0.645); antileukemic (0.590); apoptosis agonist (0.553); cytostatic (0.546) Neurodegenerative diseases treatment (0.540); antioxidant (0.530); antibacterial (0.529)
71	Stroke treatment (0.996); cognition disorders treatment (0.995); apoptosis agonist (0.908); antineoplastic (0.829); genital warts treatment (0.802) Antimetastatic (0.612); antimitotic (0.535)
72	Genital warts treatment (0.731); general pump inhibitor (0.549); membrane integrity agonist (0.539); antineoplastic (0.534); cytoprotectant (0.518)
73	Antineoplastic (0.958); apoptosis agonist (0.902); antiinflammatory (0.811); antieczematic (0.787); antimitotic (0.727); antiprotozoal (0.717) Antiarthritic (0.639); antipsoriatic (0.615); respiratory analeptic (0.612); immunosuppressant (0.610); antipruritic (0.550); antimetastatic (0.548) Autoimmune disorders treatment (0.536); antibacterial (0.534)
74	Antineoplastic (0.931); apoptosis agonist (0.919); cytostatic (0.912); antiinflammatory (0.837); antieczematic (0.830); antiparasitic (0.739) Antifungal (0.718); antileukemic (0.681); antibacterial (0.650); hepatoprotectant (0.638); hemostatic (0.611); spasmolytic (0.530)
75	Antineoplastic (0.935); apoptosis agonist (0.933); cytostatic (0.916); antieczematic (0.912); antiinflammatory (0.819); antiparasitic (0.779) Antifungal (0.669); antibacterial (0.660); antileukemic (0.631); immunosuppressant (0.626); antihelmintic (0.588); hepatoprotectant (0.572)

*Only activities with Pa > 0.5 are shown

24,26-Epoxy-5β-cholestane-3α,7α,12α-triol known as anhydrochimerol (46) was obtained from hydrolysis of bile salts of the rabbit fish *Chimaera monstrosa* (Okada et al. 1962).

Oxetane-containing compounds derived from fungi, plants, and insects

Butenolide, ramariolide B (47, structure shown in Fig. 3 and activity shown in Table 3), has been isolated from the fruiting bodies of the coral mushroom *Ramaria cystidiophora* (Centko et al. 2012).

Acetone extract of the Indian herb *Acalypha indica* leaves from the southern part of India particularly in Tamilnadu contains the compound with oxitane ring (48) (Selvamani and Balamurugan 2015). A β-lactone, vittatalactone (49), was isolated from collections of airborne volatile compounds from feeding male striped cucumber beetles, *Acalymma vittatum* (Morris et al. 2005).

Artocarpol F (50) is a phenolic compound containing an oxepine ring was isolated from the root bark of *Artocarpus rigida* (Ko et al. 2001). Two ring A-secolimonoids, aphanalide C (51) and limonoid with an unusual oxetane ring between C-7 and C-14 called aphanalide J (52), were isolated from the fruits of *Aphanamixis polystachya* (Wang et al. 2012). The aerial parts of *Aruncus dioicus* var. *kamtschaticus* afforded monoterpenoid-O-β-D-glucopyranoside called aruncide C (53) (Jeong et al. 2011). Two oxetane-containing neolignans, called pahangine A (54) and B (55), were found in extract of the barks of *Beilschmiedia glabra* (Nadia et al. 2018).

Methanol-chloroform extract of the roots of *Ceriops decandra* collected from Kauvery estuary resulted in the isolation of diterpenoid, ceriopsin F (56) (Anjaneyulu and Rao 2003), and 17-hydroxy-16-oxobeyer-9(11)-en-19-al (57) was found in the stems of *Bruguiera sexangula* var. *rhynchopetala* (Bao et al. 2005). Clementein (58), a guaianolide isolated from *Centaurea clementei* (Massanet et al. 1983). An oxetane lactone subexpinnatin C (59) is a secondary metabolite was isolated from *Centaurea canarienses* (Collado et al. 1987). The

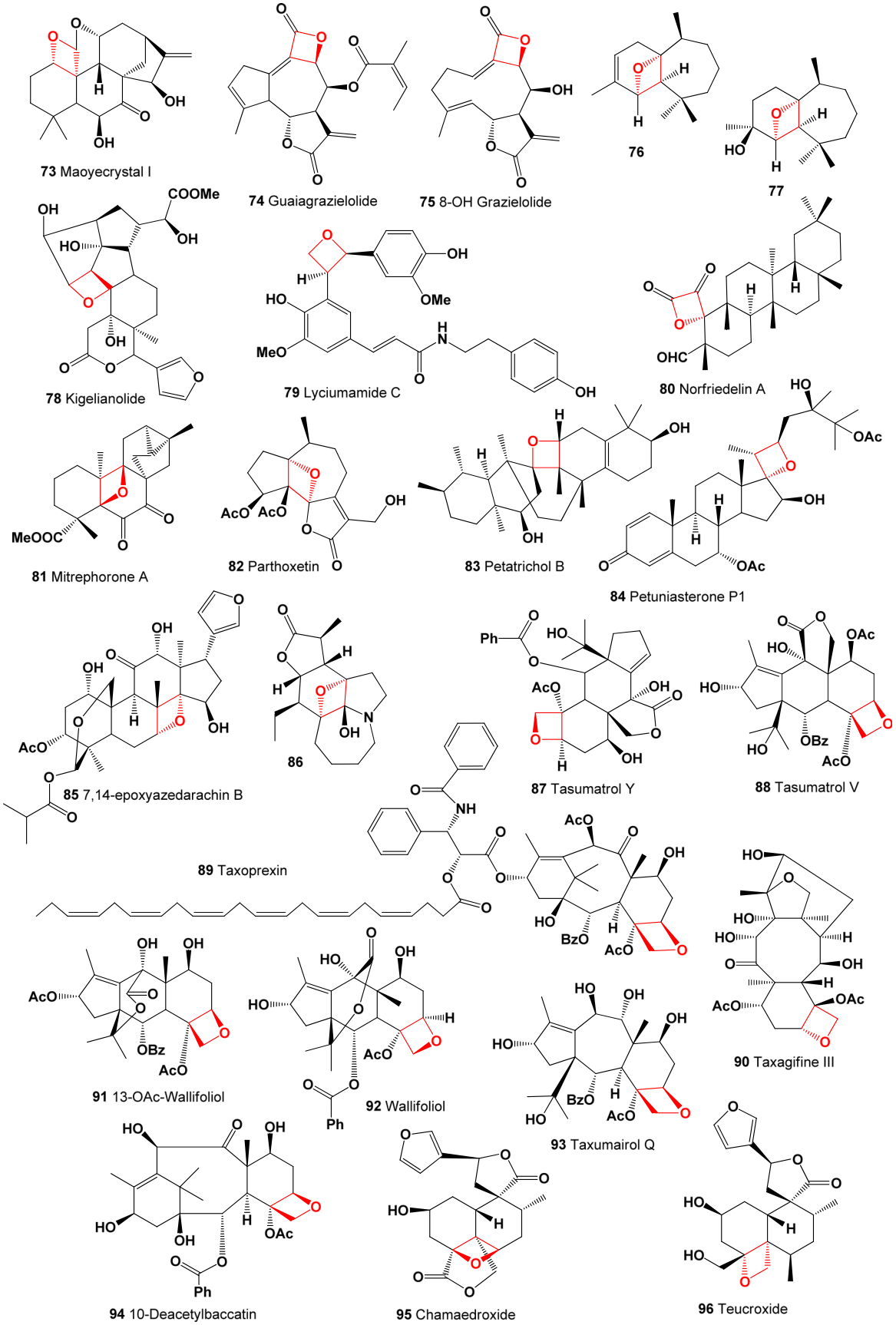

Fig. 4 Oxetane-containing compounds derived from plants

Table 4 Biological activities oxetane-containing compounds derived from plants

No.	Predicted biological activities of oxetane-containing compounds (Pa)*
76	Antineoplastic (0.818); antidyskinetic (0.790); cardiovascular analeptic (0.685); analgesic (0.663); antieczematic (0.660); antinephrotoxic (0.604) Immunosuppressant (0.540); kidney function stimulant (0.539); antifungal (0.510)
77	Cardiovascular analeptic (0.845); antineoplastic (0.801); hypolipemic (0.781); antiinflammatory (0.752); antiprotozoal (0.674); antifungal (0.663) Antiseborrheic (0.653); antieczematic (0.644); antinephrotoxic (0.620); antiviral (arbovirus) (0.615); ovulation inhibitor (0.586) Autoimmune disorders treatment (0.585); antipruritic, allergic (0.576); antiviral (*picornavirus*) (0.566); menopausal disorders treatment (0.542)
78	Renin release stimulant (0.885); antineoplastic (0.760); bilirubin oxidase inhibitor (0.693); phosphatase inhibitor (0.641); analgesic (0.619) Calcium regulator (0.554)
79	Genital warts treatment (0.721); cytoprotectant (0.680); apoptosis agonist (0.627); antineoplastic (0.627); free radical scavenger (0.577) Chemopreventive (0.567)
80	Apoptosis agonist (0.862); antineoplastic (0.841); respiratory analeptic (0.823); antiinflammatory (0.804); hepatic disorders treatment (0.735) Antiarthritic (0.663); lipid metabolism regulator (0.618); antieczematic (0.617); diuretic (0.603); prostate disorders treatment (0.591) Antidiabetic (0.587); immunosuppressant (0.575); antipruritic (0.561); antipsoriatic (0.555); antiulcerative (0.549); antiviral (*influenza*) (0.500)
81	Antineoplastic enhancer (0.982); antineoplastic (0.902); renin release stimulant (0.843); neurotrophic factor (0.751); antieczematic (0.507)
82	Antieczematic (0.772); antineoplastic (0.709); antinephrotoxic (0.668); immunosuppressant (0.656); antiinflammatory (0.644); antiallergic (0.632) Antiasthmatic (0.597); antifungal (0.589); antiviral (arbovirus) (0.582); antiviral (*picornavirus*) (0.576); antipruritic, allergic (0.566) Antiprotozoal (*Plasmodium*) (0.547); antipsoriatic (0.540); antiseborrheic (0.537); lipid metabolism regulator (0.531); antibacterial (0.524)
83	Apoptosis agonist (0.895); antineoplastic (0.872); hypolipemic (0.774); antiinflammatory (0.758); antieczematic (0.707) Immunosuppressant (0.673); hepatic disorders treatment (0.639); prostate cancer treatment (0.570); antifungal (0.557); antiosteoporotic (0.547) Dementia treatment (0.541); contraceptive (0.539); antileukemic (0.514)
84	Antineoplastic (0.892); antiinflammatory (0.838); immunosuppressant (0.804); antipruritic (0.790); apoptosis agonist (0.746) Antihypercholesterolemic (0.725); antiallergic (0.684); lipid metabolism regulator (0.651); neuroprotector (0.633); prostate disorders treatment (0.618) Menopausal disorders treatment (0.617); hypolipemic (0.609); ovulation inhibitor (0.603); respiratory analeptic (0.602); hepatoprotectant (0.601) Antifungal (0.598); antiprotozoal (0.597); antipsoriatic (0.583); antiosteoporotic (0.565); autoimmune disorders treatment (0.562)
85	Antineoplastic (0.908); antiinflammatory (0.845); analgesic (0.783); antieczematic (0.712); diuretic (0.644); antiseborrheic (0.521)
86	Antineoplastic (0.807); analgesic (0.783); cardiovascular analeptic (0.758); antitussive (0.689); antidyskinetic (0.624); antieczematic (0.612) Antinephrotoxic (0.568); antibacterial (0.539); antileukemic (0.520)
87	Respiratory analeptic (0.893); antineoplastic (0.885); antimitotic (0.861); cytostatic (0.858); genital warts treatment (0.736) Proliferative diseases treatment (0.642); chemopreventive (0.641); antiinflammatory (0.615); anticarcinogenic (0.610); antifungal (0.594) Antileukemic (0.566); radiosensitizer (0.561); apoptosis agonist (0.546)
88	Respiratory analeptic (0.973); antineoplastic (0.899); antimitotic (0.866); cytostatic (0.840); antieczematic (0.765); antiinflammatory (0.759) Anticarcinogenic (0.755); immunosuppressant (0.748); genital warts treatment (0.718); proliferative diseases treatment (0.700); antipsoriatic (0.640) Analgesic (0.608); radiosensitizer (0.603); antileukemic (0.579); antifungal (0.571)
89	Respiratory analeptic (0.997); anticarcinogenic (0.980); proliferative diseases treatment (0.971); cytostatic (0.957); antimitotic (0.949) Vasodilator (0.921); antineoplastic (0.908); antieczematic (0.763); radiosensitizer (0.728); cancer associated disorders treatment (0.704) Chemosensitizer (0.638); antileukemic (0.611); antiprotozoal (*Leishmania*) (0.610); prostate cancer treatment (0.574)
90	Respiratory analeptic (0.966); antineoplastic (0.911); antimitotic (0.897); cytostatic (0.864); anticarcinogenic (0.677); radiosensitizer (0.675) Proliferative diseases treatment (0.645); prostate cancer treatment (0.632); antifungal (0.616); antileukemic (0.603); vasodilator (0.601) Chemosensitizer (0.588); T cell inhibitor (0.587); antiinflammatory (0.565); antinephrotoxic (0.537)
91	Respiratory analeptic (0.975); antimitotic (0.871); antineoplastic (0.858); cytostatic (0.840); anticarcinogenic (0.702); antihypertensive (0.669) Proliferative diseases treatment (0.652); radiosensitizer (0.649); antileukemic (0.611); vasodilator (0.607); cancer associated disorders treatment (0.533)
92	Respiratory analeptic (0.972); antineoplastic (0.864); antimitotic (0.862); antieczematic (0.781); cytostatic (0.722); antihypertensive (0.671) Anticarcinogenic (0.660); proliferative diseases treatment (0.635); radiosensitizer (0.622); antileukemic (0.616); antipsoriatic (0.599)
93	Respiratory analeptic (0.982); antineoplastic (0.922); antimitotic (0.873); antieczematic (0.773); cytostatic (0.727); anticarcinogenic (0.698) Proliferative diseases treatment (0.690); immunosuppressant (0.629); antiinflammatory (0.622); radiosensitizer (0.616); antipsoriatic (0.600)
94	Respiratory analeptic (0.997); cytostatic (0.953); anticarcinogenic (0.950); proliferative diseases treatment (0.947); antineoplastic (0.934) Vasodilator (0.915); antieczematic (0.779); radiosensitizer (0.740); chemosensitizer (0.676); prostate cancer treatment (0.665); antileukemic (0.646) Antipsoriatic (0.639); antineoplastic enhancer (0.612); rheumatoid arthritis treatment (0.520)
95	Antineoplastic (0.861); apoptosis agonist (0.821); genital warts treatment (0.738); antiinflammatory (0.720); immunosuppressant (0.677) Chemopreventive (0.641); antioxidant (0.554); Alzheimer's disease treatment (0.554); neurodegenerative diseases treatment (0.521)
96	Antineoplastic (0.866); antiinflammatory (0.778); genital warts treatment (0.707); apoptosis agonist (0.703); antifungal (0.642) Antibacterial (0.633); immunosuppressant (0.568); antipruritic (0.557); chemopreventive (0.508)

*Only activities with Pa > 0.5 are shown

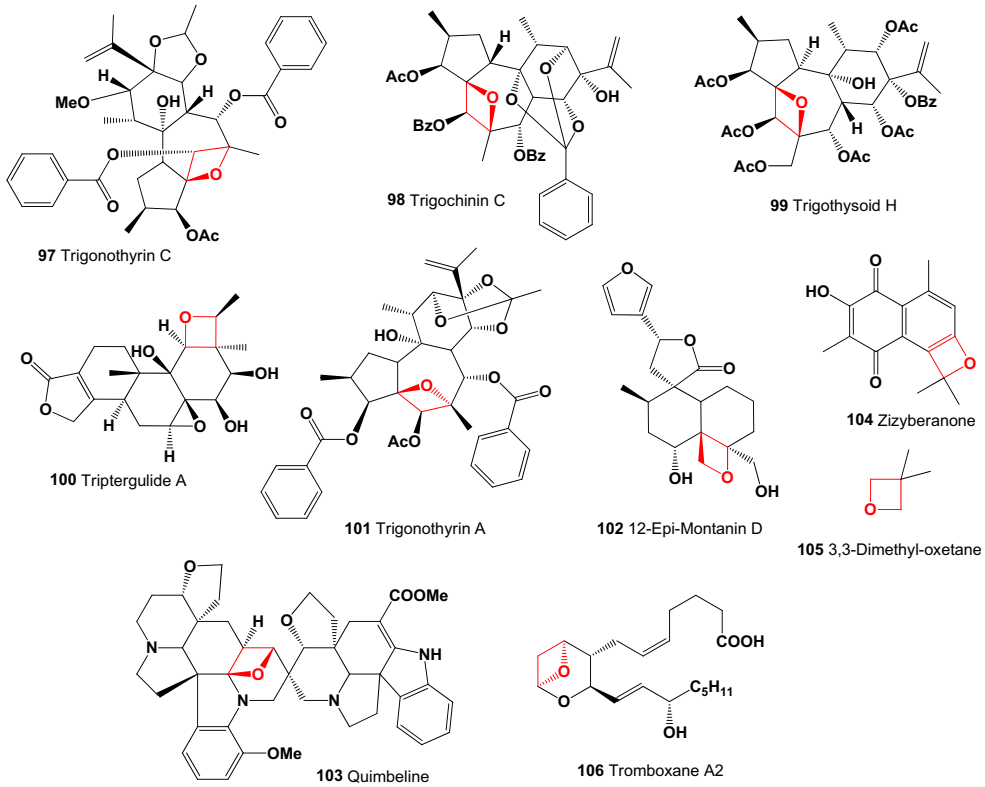

Fig. 5 Oxetane-containing compounds derived from plants and insects

plant growing in Australia *Crotalaria virgulata* subsp. *grantiana* contains alkaloid grantaline (60) (Smith et al. 1984). Cyclocaric acid A (61) was detected in the ethanol extract of *Cyclocarya paliurus* (Wright et al. 2014).

The South American flowering plant *Disynaphia halimifolia* afforded sesquiterpene lactones, disyhamifolide (62) and disynaphiolide (63) (Bohlmann et al. 1981a, b), and flowers and leaves of *Disynaphia multicrenulata* from Argentina contained sesquiterpene dilactone (64) (De Gutierrez et al. 2001).

Flavonoid called derriflavanone (65) was discovered from Chinese lianas *Derris laxiflora*. The stem bark of *Duguetia glabriuscula* collected in the municipality of Jardim, Brazil, contains two oxetane-containing metabolites, (66) and (+)-α-santalan-9,11-epoxy-10-ol (67) (Gomes Pereira et al. 2003).

The aerial parts of *Ethulia conyzoides* from Egypt afforded monoterpene 5-methyl-coumarin, called 5′-epi-isoethuliacoumarin B (68) (Mahmoud et al. 1998). Toxic metabolites, neoanisatin (69) and anisatin (70), were isolated from Japanese star anise *Illicium anisatum* (Yamada et al. 1968). A unique sesquiterpene bearing two γ-lactones and an oxetane ring called merrilactone A (71) was isolated from the pericarps of *Illicium merrillianum*, shows an intriguing neurotrophic activity in the cultures of fetal rat cortical neurons (Huang et al. 2000). Neolignan (72) was detected in the aerial parts of *Isodon coetsa* (Zhao et al. 2011).

Unusual metabolite called maoyecrystal I (structure shown in Fig. 3 and activity shown in Table 3, 73) with a 11,20:1,20-diepoxy-ent-kaurane skeleton showed cytotoxic activity against K562 cells was found in the extract of *Isodan japonicus* (Han et al. 2004). The author believes that the presence of the oxetane group in the molecule maoyecrystal I determines its biological activity.

Guaiagrazielolide (74), a guaianolide with a β-lactone ring and an oxetane ring, has been obtained from leaves of the South American flowering plant *Grazielia* sp. (Bohlmann et al. 1981a, b) as well as the compound called 8-hydroxygrazielolide (75). *cis*-Himachalane-type sesquiterpenes, 2α,6α-epoxy-3-himachalene (76, structures shown in Fig. 4 and activity shown in Table 4) and 2α,6α-epoxyhimachalan-3β-ol (77), were isolated from the heartwood of *Juniperus chinensis* var. *tsukusiensis* (Shiu et al. 1999).

Limonoid, kigelianolide (78), was isolated from the ethyl acetate-soluble fraction of the methanolic extract of an African plant *Kigelia africana*. The obtained compound showed weak inhibitory activities against the enzymes acetylcholinesterase, butyrylcholinesterase, and lipoxygenase (Jabeen et al. 2013).

Table 5 Biological activities oxetane-containing compounds derived from plants

No.	Predicted biological activities of oxetane-containing compounds (Pa)*
97	Antineoplastic (0.913); antieczematic (0.604); apoptosis agonist (0.586); hepatic disorders treatment (0.565); antileukemic (0.554)
	Antiinflammatory (0.517); antimitotic (0.513); antimetastatic (0.501)
98	Antineoplastic (0.824); hepatic disorders treatment (0.576); apoptosis agonist (0.558); antineoplastic (genitourinary cancer) (0.552)
	Antidiabetic symptomatic (0.542)
99	Antineoplastic (0.829); apoptosis agonist (0.652); antieczematic (0.634); immunosuppressant (0.585); antineoplastic (genitourinary cancer) (0.533)
100	Apoptosis agonist (0.916); antineoplastic (0.895); antiinflammatory (0.843); immunosuppressant (0.801); antileukemic (0.754); cardiotonic (0.708)
	Autoimmune disorders treatment (0.623); respiratory analeptic (0.610); hepatoprotectant (0.595); antieczematic (0.578); antiarthritic (0.573)
	Cytostatic (0.568); antifungal (0.564); antinephrotoxic (0.550); dementia treatment (0.525)
102	Antineoplastic (0.863); antiinflammatory (0.731); genital warts treatment (0.698); antifungal (0.676); apoptosis agonist (0.674); antieczematic (0.666)
	Antibacterial (0.603); antipruritic (0.582); antileukemic (0.570); immunosuppressant (0.548); Alzheimer's disease treatment (0.509)
103	Polarization stimulant (0.604); antineoplastic (0.587)
104	Apoptosis agonist (0.794); antineoplastic (0.794); antiinflammatory (0.747); antiseborrheic (0.616); antifungal (0.605); neuroprotector (0.601)
	Spasmolytic, urinary (0.551); hemostatic (0.542); antioxidant (0.529); antipsoriatic (0.519); antiparasitic (0.518); ovulation inhibitor (0.513)
105	Antiarthritic (0.923); phobic disorders treatment (0.895); antiasthmatic (0.882); antiallergic (0.872); cardiovascular analeptic (0.855); hypolipemic (0.790); vasoprotector (0.750); antineurotic (0.706); rheumatoid arthritis treatment (0.696); autoimmune disorders treatment (0.681); leukopoiesis stimulant (0.679); antiviral (arbovirus) (0.676); antieczematic (0.656); antipsoriatic (0.654); antinephrotoxic (0.626); respiratory analeptic (0.592)
106	Vasoprotector (0.897); antieczematic (0.895); antithrombotic (0.891); vasodilator, peripheral (0.861); antiulcerative (0.844); antiinflammatory (0.834)
	Antineoplastic (0.794); antifungal (0.758); immunosuppressant (0.753); apoptosis agonist (0.728); antiglaucomic (0.722); antiasthmatic (0.712)
	Antiallergic (0.697); antipruritic (0.688); fibrinolytic (0.631); hypolipemic (0.628); antiviral (*arbovirus)* (0.601); antibacterial (0.597)

*Only activities with Pa > 0.5 are shown

Phenolic amide, lyciumamide C (79), was identified from the stem of *Lycium barbarum*, and exhibited moderate anticancer activity against human glioma stem cell lines (Gao et al. 2015; Zhu et al. 2017).

Norfriedelane A possessing an α-oxo-β-lactone group (80) and showed acetylcholinesterase inhibitory effects with the IC_{50} value of 10.3 μM was isolated from the branches and roots of *Malpighia emarginata* (Liu et al. 2013). *ent*-Trachylobane diterpenoid, mitrephorone A (81), possesses a hexacyclic ring system with adjacent ketone moieties and an oxetane ring was detected in the stem bark of *Mitrephora glabra* (Li et al. 2005).

Parthoxetin (82) was detected in a flowering plant *Parthenium fruticosum* (Chrysanthemum family). Triterpenoid carbon framework, named petatrichol B (83), was isolated from the rhizome of *Petasites tricholobus*. The isolated compound exhibited significant antibacterial activity against *Bacillus subtilis* (Xie et al. 2005). A series of ergostane-type steroids, including petuniasterone P1 (84), were isolated from leaves and stems of *Petunia hybrida* (Elliger et al. 1988, 1989). Limonoid, 7,14-epoxy-azedarachin B (85), was detected in a methanol extract of the roots of *Melia azedarach* (Fukuyama et al. 2006). An alkaloid 1,9-epoxy-9α-hydroxystenine (86) has been isolated from the roots of *Stemona tuberosa* (Uyeo et al. 1967).

The genus *Taxus* contains more than 450 taxane diterpenes, including tasumatrols A-W many of which contained oxetane ring (Shen et al. 2005). Thus, an acetone extract of the leaves and twigs of *Taxus sumatrana* has resulted in the isolation of bicyclic taxoid tasumatrol Y (87) and tasumatrol V (88) (Shen et al. 2008). Anticancer agent taxoprexin (89) was first isolated from the bark of *Taxus brevifolia* (Wani et al. 1971; Jones et al. 2008). Taxane diterpene taxagifine III (90) was isolated from the leaves and stems of *Taxus chinensis* (Zhang and Jia

1991). A taxoid, 13-O-acetyl wallifoliol (91), has been isolated from extracts of the needles of Himalayan *Taxus wallichiana* (Velde et al. 1994). Diterpene with the 5/6/6/6/4 ring system called wallifoliol (92) has been isolated from extracts of the needles of Himalayan *Taxus wallichiana* (Vander Velde et al. 1994). Taxumairol Q (93) has been isolated from the leaves and twigs of *Taxus sumatrana*. Both compounds exhibited significant cytotoxicities against both Hepa 59 T/VGH (human liver carcinoma) and KB (human oral epidermoid carcinoma) tumor cells (Shen et al. 2002). Anti *Leishmania donovani* agent called 10-deacetylbaccatin (94) and a series of closely related natural organic compounds have been isolated from the yew tree *Taxus* sp. (Georgopoulou et al. 2007). Neo-clerodane diterpenoid, chamaedroxide (95), containing an oxetane ring has been found in *Teucrium chamaedrys* (Eguren et al. 1982), and the aerial parts of *Teucrium salviastrum* contain diterpene teucroxide (96) (De La Torre et al. 1986).

Highly oxygenated diterpene, trigochinin C (97, structures shown in Fig. 5 and activity shown in Table 5), was isolated from *Trigonostemon chinensis*. The isolated compound showed significant inhibition against MET tyrosine kinase activity with at IC_{50} value of 2 μM (Chen et al. 2010). Highly oxygenated diterpene, trigonothyrin C (98), was isolated from *Trigonostemon chinensis*. Obtained diterpene showed significant inhibition against MET tyrosine kinase activity with at IC_{50} value of 2 μM (Chen et al. 2010). Daphnane diterpenoid, trigothysoid H (99), was isolated from the methanol extract of the twigs and leaves of *Trigonostemon thyrsoideum* (Cheng et al. 2013), the compound demonstrated potent anti-HIV-1 activity, with EC_{50} value of 0.001 nM and TI value of 1618 (Xu and Yue (2014).

Abietane diterpene, triptergulide A (100) containing a fused 5/6/6/3/6/4 hexacyclic system, was isolated from the leaves of *Tripterygium wilfordii* (Ni et al. 2015). Highly functionalized daphnane diterpenoid, namely trigonothyrin A (101), was found in extract of the stems of *Trigonostemon thyrsoideum* (Zhang et al. 2010). A furanoid diterpene of clerodane type, 12-epi-montanin D (102), was isolated from the bitter fraction of the areal parts of the Mediterranean tree, *Teucrium montanum* (syn. *Chamaedrys montana*) (Malakov et al. 1978).

Bisindole alkaloid namely quimbeline (103) has been found in the root bark of *Voacanga chalotiana* (Bombardelli et al. 1975). Sesquiterpene called zizyberanone (104) was isolated from the fruits of a thorny rhamnaceous plant *Ziziphus jujuba* (Rhamnaceae) (Guo et al. 2009).

About 300 compounds including 3,3-dimethyl-oxetane (105) contributing to apple flavor and aroma from different cultivars Cortland and Empire have been reviewed earlier (Dimick and Hoskin 1983; Vikram et al. 2004). Hormone thromboxane A2 (106) has been discovered in the blood platelets (Hamberg et al. 1975; Gryglewski et al. 1978).

Conclusion

In conclusion, we would like to say that this review presents more than 100 different types of natural metabolites that contain an oxetane ring. Oxetane-containing compounds are produced by many microorganisms found in marine organisms, but their highest content was found in plants, especially in the family of Taxaceae. Oxetane-containing compounds exhibit various biological activities, but antineoplastic, antiviral, and antifungal activities are dominant. Many taxol derivatives show anticancer activity. Our proposed article is the first and most comprehensive review of the biological activities of rare natural oxetane-containing compounds.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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