



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

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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 Glorizova 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

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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 (Bezhenstev 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.  $\beta$ -

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  $\beta$ -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  $\beta$ -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  $\beta$ -lactones, 4 $\alpha$ -(3,5-dihydroxy hexyl)-3 $\alpha$ -methyl-2-oxetanone (12), 4 $\alpha$ -(3-methyl-4-formyloxy-hexyl)-3 $\alpha$ -methyl-2-oxetanone (13), 4 $\alpha$ -(3,5-dihydroxy-heptyl)-3 $\alpha$ -methyl-2-oxetanone (14), and 4 $\alpha$ -(3-methyl-4-formyloxy-heptyl)-3 $\alpha$ -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<sub>50</sub> values of 29 and 0.14 ng/mL, respectively. It can also inhibit fatty acid synthase with an IC<sub>50</sub> value of 0.3  $\mu$ M and demonstrates selective toxicity

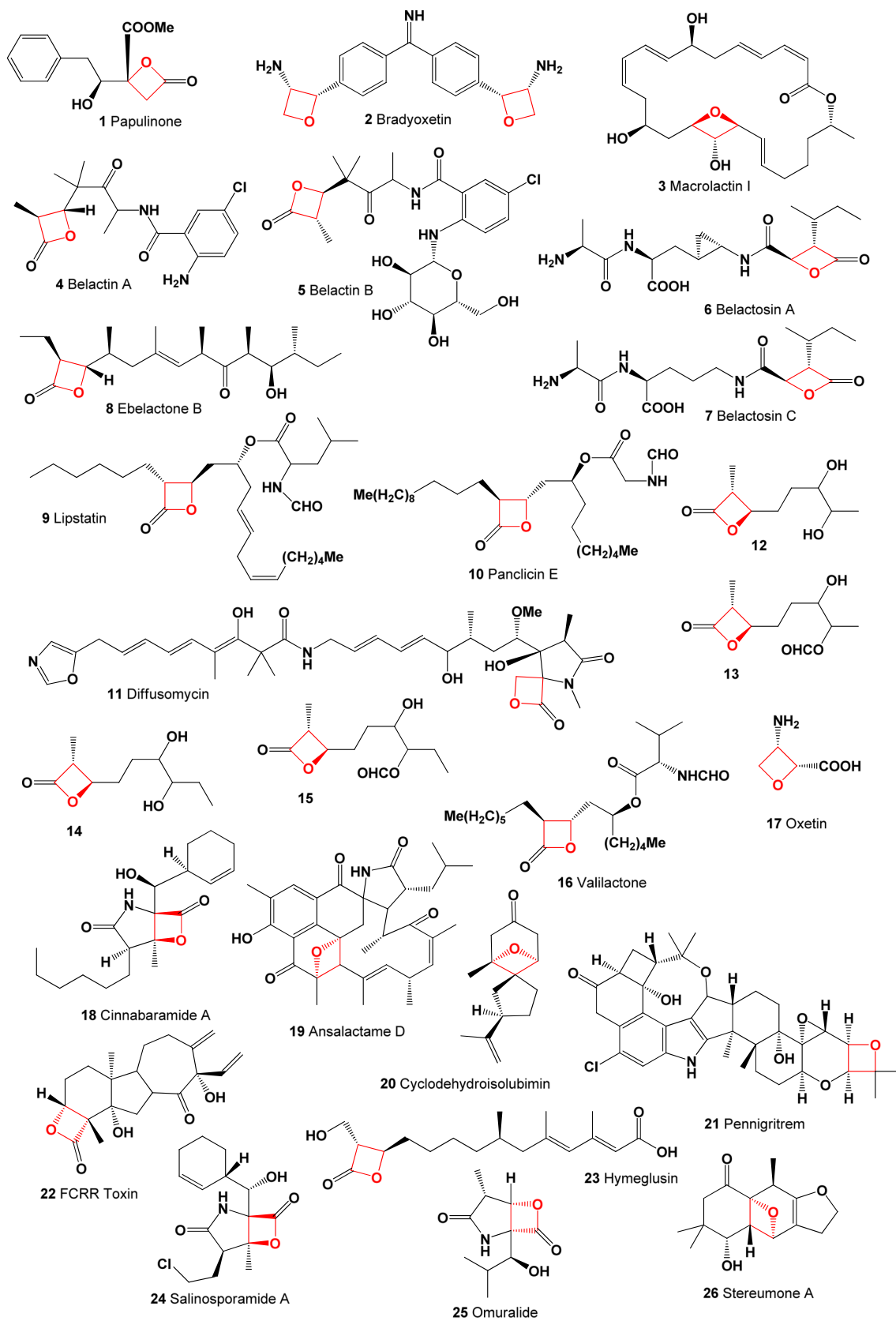


Fig. 1 Oxetane-containing compounds derived from microorganisms

**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)  
Antieczemacic (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); antieczemacic (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); antieczemacic (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); antieczemacic (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); antieczemacic (0.738)  
Lipid metabolism regulator (0.737); immunosuppressant (0.731); apoptosis agonist (0.695); antihelminthic (0.681); antiinflammatory (0.579)
- 9 Antieczemacic (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); antieczemacic (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 Antieczemacic (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); antihelminthic (0.604); antiinflammatory (0.582); antihypertensive (0.565); antipruritic, allergic (0.557)
- 13 Antieczemacic (0.729); antihypertensive (0.716); antineoplastic (0.659); antibacterial (0.617); genital warts treatment (0.531)  
Antiviral (*arbovirus*) (0.510); hypolipemic (0.507)
- 14 Antieczemacic (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); antieczemacic (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); antieczemacic (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); antieczemacic  
(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); antieczemacic (0.589); radiosensitizer (0.509)
- 19 Antineoplastic (0.850); antiinflammatory (0.753); antileukemic (0.643); antibacterial (0.641); antieczemacic (0.518)
- 20 Antipsoriatic (0.885); antineoplastic (0.828); apoptosis agonist (0.797); immunosuppressant (0.741); antieczemacic (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); antihelminthic (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)<br>Neuroprotector (0.955); antineoplastic (0.932); antiasthmatic (0.929); antiinflammatory (0.923); angiogenesis inhibitor (0.918)<br>Rheumatoid arthritis treatment (0.902); antipsoriatic (0.862); stroke treatment (0.843); antiviral ( <i>arbovirus</i> ) (0.584); cardiovascular analeptic (0.572)   |
| 26 | Antidyskinetic (0.780); antineoplastic (0.744); genital warts treatment (0.660); allergic conjunctivitis treatment (0.641); antieczemetic (0.639)<br>Antiviral ( <i>arbovirus</i> ) (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 ( <i>arbovirus</i> ) (0.743); cardiovascular analeptic (0.734)<br>Antibacterial (0.654); antieczemetic (0.625); hypolipemic (0.593); cytostatic (0.592); antimetastatic (0.587); immunosuppressant (0.586)<br>Antiviral ( <i>picornavirus</i> ) (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 ( <i>arbovirus</i> ) (0.649); immunosuppressant (0.640); antiinflammatory (0.622); respiratory analeptic (0.610); antiparasitic (0.601); antihelmintic (0.597)<br>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)<br>Hypolipemic (0.661); antibacterial (0.652); antiviral ( <i>arbovirus</i> ) (0.651); antihelmintic (0.637); antifungal (0.619); antileukemic (0.609)<br>Cytostatic (0.608); antieczemetic (0.589); neuroprotector (0.585); cardiovascular analeptic (0.583)  |
| 30 | Antieczemetic (0.844); antineoplastic (0.839); genital warts treatment (0.743); antiinflammatory (0.727); apoptosis agonist (0.720); antileukemic (0.636)<br>Antiprotozoal (0.612); antinephrotoxic (0.591); antimitotic (0.548); antiviral ( <i>arbovirus</i> ) (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)<br>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 ( <i>Arbovirus</i> ) (0.749)<br>Antiinflammatory (0.749); antiparasitic (0.733); antihelmintic (0.730); immunosuppressant (0.671); cytostatic (0.670); antieczemetic (0.669)<br>Hypolipemic (0.655); antibacterial (0.643); antileukemic (0.627); antifungal (0.615); antiviral ( <i>picornavirus</i> ) (0.602); neuroprotector (0.592) |
| 33 | Respiratory analeptic (0.997); cytostatic (0.985); antimitotic (0.981); anticarcinogenic (0.960); proliferative diseases treatment (0.946)<br>Vasodilator (0.940); antineoplastic (0.911); radiosensitizer (0.736); chemosensitizer (0.639); antileukemic (0.623); prostate cancer treatment (0.610)   |

\*Only activities with Pa &gt; 0.5 are shown

toward MDA-MB-231 breast cancer cells with an IC<sub>50</sub> 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 pennigrin (21) was isolated from *Penicillium nigricans* (Penn et al. 1992).

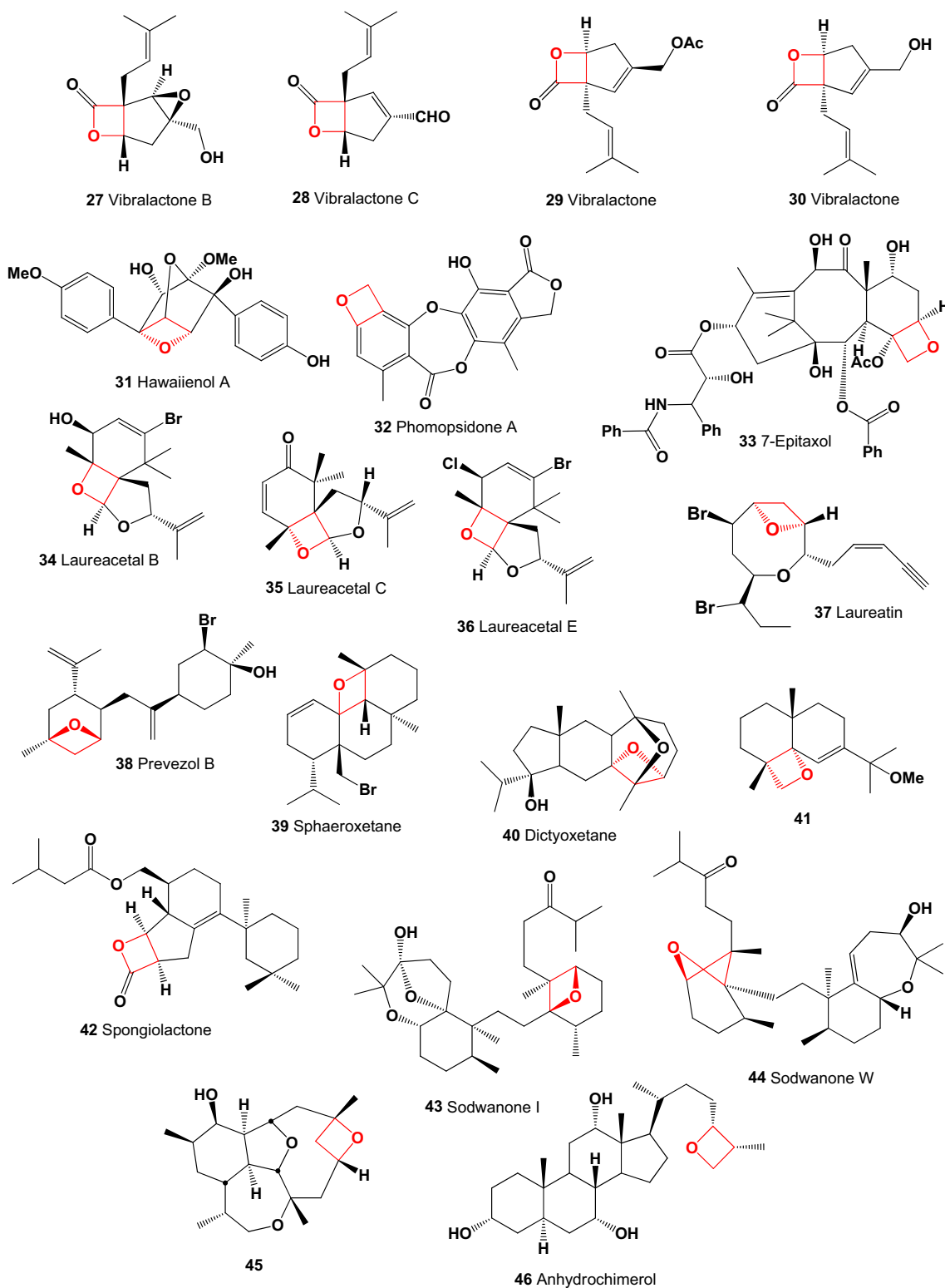
A phytotoxin, FCRR-Toxin (22), was isolated from the culture filtrate of *Fusarium oxysporum* f. sp. *radicis-lycopersici* (Hirota et al. 1994). Fungal β-lactone hymeglusin (23, also known as antibiotic F 244) produced by *Fusarium* sp. It inhibited HMG-CoA synthase (IC<sub>50</sub> = 0.12 μM) by covalently 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 vibrallactone skeleton, vibrallactone B (27, structure shown in Fig. 2 and activity shown in Table 2), vibrallactone C (28), and acetylated vibrallactone (29) have been isolated from cultures of the basidiomycete *Boreostereum vibrans* (Jiang et al. 2008). Vibrallactone (30) has been isolated from cultures of *B. vibrans* (Duan et al. 2018).

Highly oxygenated *p*-terphenyl, hawaiiol 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[3.2.1.0<sup>3,6</sup>]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 ( <i>Plasmodium</i> ) (0.706); antieczemetic (0.701); antiinflammatory (0.684); stroke treatment (0.673)<br>Immunosuppressant (0.671); apoptosis agonist (0.656); respiratory analeptic (0.648); antipsoriatic (0.644); antimitotic (0.586)   |
| 35  | Antiprotozoal ( <i>Plasmodium</i> ) (0.875); antineoplastic (0.838); apoptosis agonist (0.787); respiratory analeptic (0.779); antiinflammatory (0.744)<br>Antieczemetic (0.707); antipsoriatic (0.653); antimetastatic (0.647); immunosuppressant (0.640); antifungal (0.575)  |
| 36  | Respiratory analeptic (0.875); antineoplastic (0.834); antiprotozoal ( <i>Plasmodium</i> ) (0.779); antiinflammatory (0.777); autoimmune disorders<br>treatment (0.742); apoptosis agonist (0.730); antipsoriatic (0.690); immunosuppressant (0.688); rheumatoid arthritis treatment (0.638);<br>antiparasitic (0.601)<br>Antieczemetic (0.587); antifungal (0.548); antihelminthic (0.546); inflammatory bowel disease treatment (0.544); antiasthmatic (0.516)  |
| 37  | Antiprotozoal ( <i>Plasmodium</i> ) (0.906); antineoplastic (0.843); apoptosis agonist (0.676); respiratory analeptic (0.632)   |
| 38  | Apoptosis agonist (0.898); antineoplastic (0.742); antiprotozoal ( <i>Plasmodium</i> ) (0.629); antifungal (0.587); antibacterial (0.576)<br>Chemoprotective (0.568); antiemetic (0.549); antimetastatic (0.524)  |
| 39  | Antineoplastic (0.874); apoptosis agonist (0.819); antieczemetic (0.747); antiprotozoal ( <i>Plasmodium</i> ) (0.645); hypolipemic (0.635)<br>Antileukemic (0.633); antipsoriatic (0.626); postmenopausal disorders treatment (0.610); prostate cancer treatment (0.584); antimetastatic (0.559)<br>Antifungal (0.550); antiinflammatory (0.549)  |
| 40  | Antineoplastic (0.960); angiogenesis inhibitor (0.891); antiinflammatory (0.799); immunosuppressant (0.741); autoimmune disorders treatment<br>(0.694)<br>Prostate cancer treatment (0.662); antimetastatic (0.614); antiarthritic (0.594); apoptosis agonist (0.584); antifungal (0.557); antipsoriatic (0.555)<br>Signal transduction pathways inhibitor (0.546); antieczemetic (0.527); antiallergic (0.526)   |
| 41  | Antineoplastic (0.960); angiogenesis inhibitor (0.891); antiinflammatory (0.799); immunosuppressant (0.741); autoimmune disorders treatment<br>(0.694)<br>Prostate cancer treatment (0.662); antimetastatic (0.614); antiarthritic (0.594); apoptosis agonist (0.584); antifungal (0.557); antipsoriatic (0.555)<br>Signal transduction pathways inhibitor (0.546); antieczemetic (0.527); antiallergic (0.526)   |
| 42  | Antineoplastic (0.789); genital warts treatment (0.772); antiinflammatory (0.733); immunosuppressant (0.682); antiinfertility, female (0.674)<br>Apoptosis agonist (0.657); antieczemetic (0.634); antipruritic (0.613); prostate disorders treatment (0.581); neuroprotector (0.595)<br>Antiosteoporotic (0.548); hypolipemic (0.537)  |
| 43  | Antineoplastic (0.793); antieczemetic (0.684); immunosuppressant (0.623); antimitotic (0.578); antibacterial (0.567); antimetastatic (0.566)<br>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 ( <i>Plasmodium</i> ) (0.690)<br>Antifungal (0.687); antibacterial (0.686); immunosuppressant (0.625); antileukemic (0.604); cytostatic (0.548); antiparasitic (0.541)<br>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); antieczemetic (0.824); antineoplastic<br>(0.815)<br>Hypolipemic (0.810); antipruritic (0.787); antifungal (0.743); hepatoprotectant (0.729); immunosuppressant (0.726); antiinflammatory (0.717)<br>Antipsoriatic (0.651); prostate disorders treatment (0.649); antiosteoporotic (0.623); antiprotozoal ( <i>Plasmodium</i> ) (0.621); antibacterial (0.620)<br>Cholesterol synthesis inhibitor (0.612); atherosclerosis treatment (0.602); dementia treatment (0.569) |

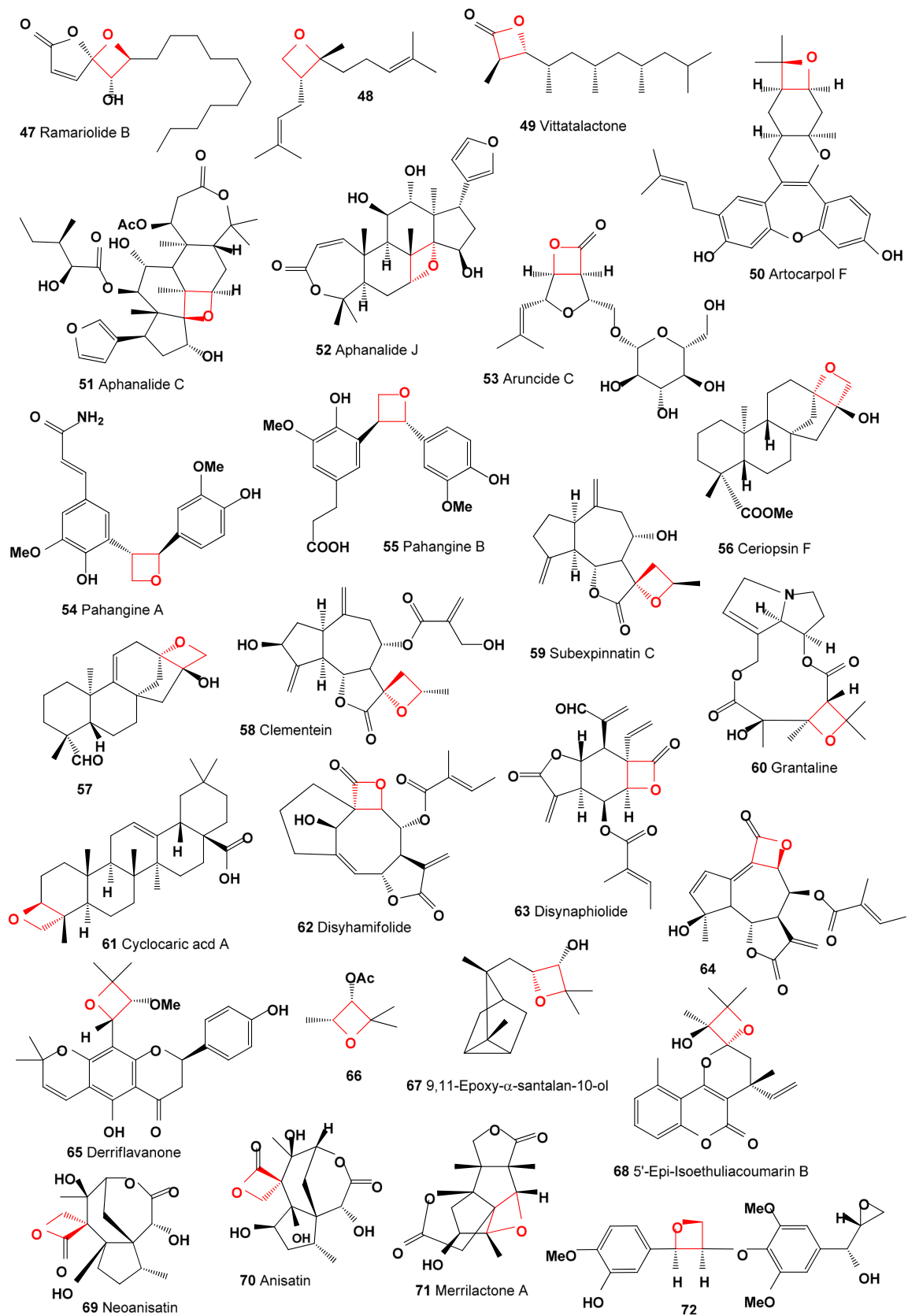
\*Only activities with Pa > 0.5 are shown

## Oxetane-containing compounds derived from marine sources

Several secohamigranes 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); antieczemetic (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); antieczemetic (0.700); cardiovascular analeptic (0.685)  
Antioxidant (0.656); antiulcerative (0.613); antifungal (0.607); antithrombotic (0.606); spasmolytic (0.565)
- 49 Antieczemetic (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); antimetabolic (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); cardiogenic (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); antimetabolic (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); antieczemetic (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); antieczemetic (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); antieczemetic (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 Antieczemetic (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); antieczemetic (0.619); antifungal (0.616)  
Atherosclerosis treatment (0.512)
- 62 Antineoplastic (0.950); apoptosis agonist (0.909); cytostatic (0.871); antiinflammatory (0.848); antieczemetic (0.842); antimetabolic (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); antieczemetic (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)  
Antieczemetic (0.842); antimetabolic (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)<br>Antiulcerative (0.609); immunosuppressant (0.567); antileukemic (0.563); cytostatic (0.552)   |
| 66 | Antineoplastic (0.869); cardiogenic (0.856); antiseborrheic (0.830); antihypertensive (0.774); spasmolytic, urinary (0.744); leukopoiesis inhibitor (0.738); neuroprotector (0.735); antiviral ( <i>arbovirus</i> ) (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); cardiogenic (0.638); antiviral ( <i>arbovirus</i> ) (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)<br>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)<br>Immunosuppressant (0.674); antinephrotoxic (0.645); antileukemic (0.590); apoptosis agonist (0.553); cytostatic (0.546)<br>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)<br>Antimetastatic (0.612); antimetabolic (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); antimetabolic (0.727); antiprotozoal (0.717)<br>Antiarticular (0.639); antipsoriatic (0.615); respiratory analeptic (0.612); immunosuppressant (0.610); antipruritic (0.550); antimetastatic (0.548)<br>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)<br>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)<br>Antifungal (0.669); antibacterial (0.660); antileukemic (0.631); immunosuppressant (0.626); antihelminthic (0.588); hepatoprotectant (0.572)  |

\*Only activities with Pa &gt; 0.5 are shown

24,26-Epoxy-5 $\beta$ -cholestane-3 $\alpha$ ,7 $\alpha$ ,12 $\alpha$ -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  $\beta$ -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- $\beta$ -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. *rhyngopetala* (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

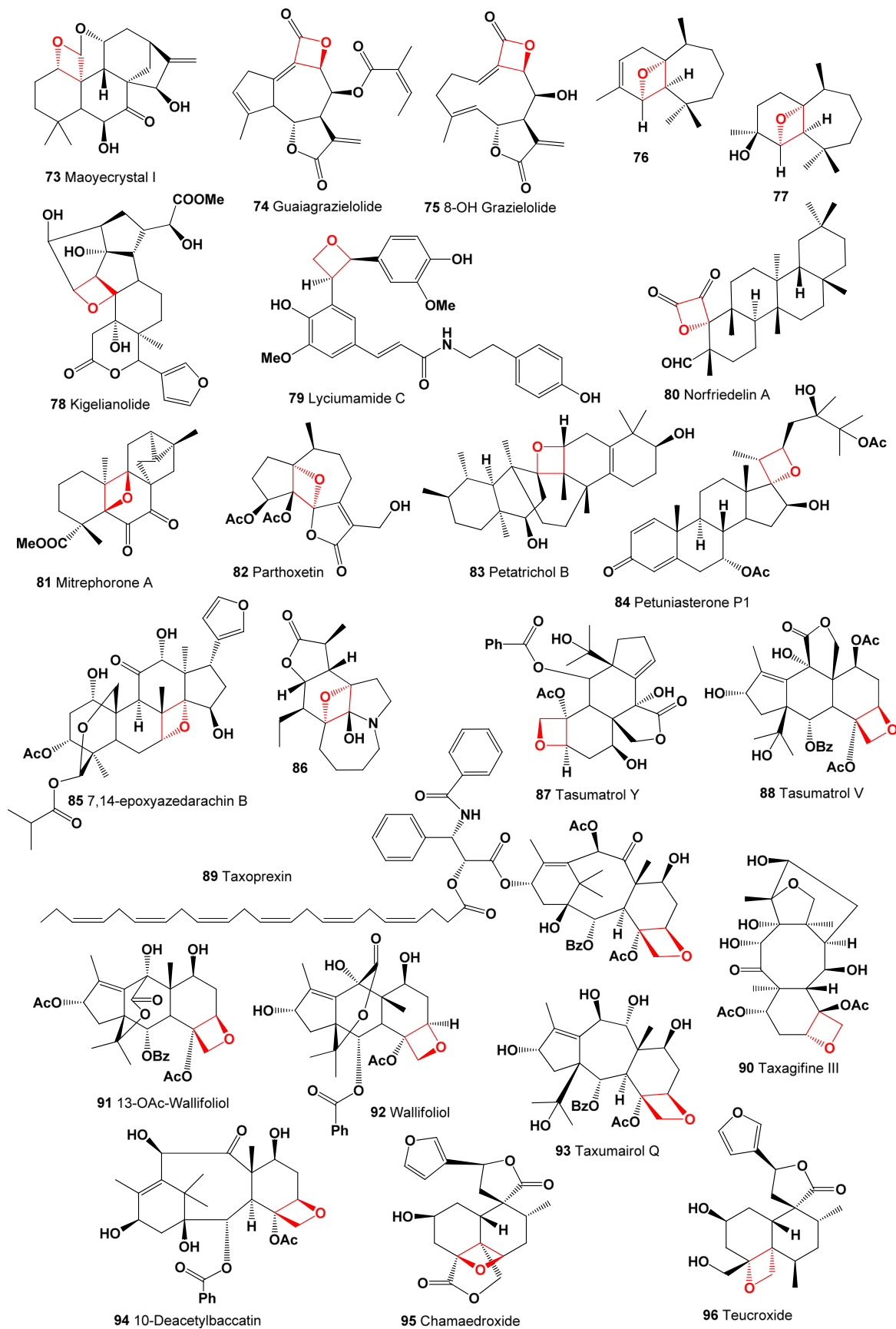


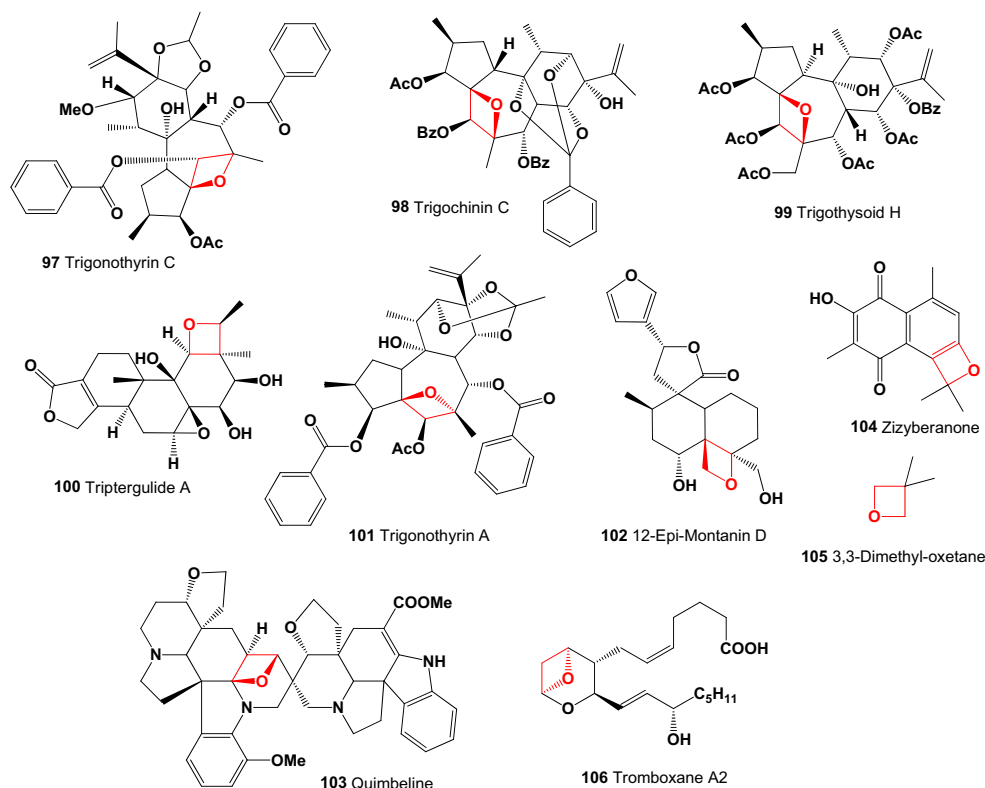
Fig. 4 Oxetane-containing compounds derived from plants

**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); antieczemetic (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); antieczemetic (0.644); antinephrotoxic (0.620); antiviral (arbovirus) (0.615); ovulation inhibitor (0.586) Autoimmune disorders treatment (0.585); antipruritic, allergic (0.576); antiviral ( <i>picornavirus</i> ) (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); antieczemetic (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 ( <i>influenza</i> ) (0.500)  |
| 81 | Antineoplastic enhancer (0.982); antineoplastic (0.902); renin release stimulant (0.843); neurotrophic factor (0.751); antieczemetic (0.507)   |
| 82 | Antieczemetic (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 ( <i>picornavirus</i> ) (0.576); antipruritic, allergic (0.566) Antiprotozoal ( <i>Plasmodium</i> ) (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); antieczemetic (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); antieczemetic (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); antieczemetic (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); antieczemetic (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); antieczemetic (0.763); radiosensitizer (0.728); cancer associated disorders treatment (0.704) Chemosensitizer (0.638); antileukemic (0.611); antiprotozoal ( <i>Leishmania</i> ) (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); antieczemetic (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); antieczemetic (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); antieczemetic (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 &gt; 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, disynamifolide (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 (+)- $\alpha$ -santalol-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  $\gamma$ -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 *Isodon 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  $\beta$ -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, 2 $\alpha$ ,6 $\alpha$ -epoxy-3-himachalene (76, structures shown in Fig. 4 and activity shown in Table 4) and 2 $\alpha$ ,6 $\alpha$ -epoxyhimachalan-3 $\beta$ -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); antieczemetic (0.604); apoptosis agonist (0.586); hepatic disorders treatment (0.565); antileukemic (0.554)<br>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)<br>Antidiabetic symptomatic (0.542)   |
| 99  | Antineoplastic (0.829); apoptosis agonist (0.652); antieczemetic (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); cardiogenic (0.708)<br>Autoimmune disorders treatment (0.623); respiratory analeptic (0.610); hepatoprotectant (0.595); antieczemetic (0.578); antiarthritic (0.573)<br>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); antieczemetic (0.666)<br>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)<br>Spasmodic, 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); antieczemetic (0.656); antipsoriatic (0.654); antinephrotoxic (0.626); respiratory analeptic (0.592)   |
| 106 | Vasoprotector (0.897); antieczemetic (0.895); antithrombotic (0.891); vasodilator, peripheral (0.861); antiulcerative (0.844); antiinflammatory (0.834)<br>Antineoplastic (0.794); antifungal (0.758); immunosuppressant (0.753); apoptosis agonist (0.728); antiglaucomic (0.722); antiasthmatic (0.712)<br>Antiallergic (0.697); antipruritic (0.688); fibrinolytic (0.631); hypolipemic (0.628); antiviral ( <i>arbovirus</i> ) (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  $\alpha$ -oxo- $\beta$ -lactone group (80) and showed acetylcholinesterase inhibitory effects with the IC<sub>50</sub> value of 10.3  $\mu$ M 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 petatrachel 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-9 $\alpha$ -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-deacetylbaecatin (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<sub>50</sub> 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<sub>50</sub> 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 thyrsoidium* (Cheng et al. 2013), the compound demonstrated potent anti-HIV-1 activity, with EC<sub>50</sub> 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 thyrsoidium* (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 chalongana* (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 A<sub>2</sub> (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.

**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors.

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## References

- Abe M (2008) Recent progress regarding regio-, site-, and stereoselective formation of oxetanes in Paterno-Buchi reactions. *J Chin Chem Soc* 55:479–486
- Alabugin IV (2016) Stereoelectronic effects: the Bridge between structure and reactivity. John Wiley & Sons Ltd, Hoboken
- Alabugin IV, Bresch S, Gomes GP (2015) Orbital hybridization: a key electronic factor in control of structure and reactivity. *J Phys Org Chem* 28:147–162
- Alcaide B, Almendros P (2011) Four-membered ring systems. In: Gribble GW, Joule JA (eds) *Progress in heterocyclic chemistry* Vol. 22, Chp 4, 85–107. Elsevier, Oxford, UK
- Anjaneyulu AS, Rao VL (2003) Ceriopsins F and G, diterpenoids from *Ceriops decandra*. *Phytochemistry* 62(8):1207–1211
- Appendino G (1995) The phytochemistry of the yew tree. *Nat Prod Rep* 12:349–360
- Asai A, Hasegawa A, Ochiai K, Yamashit Y (2000) Belactosin A, a novel antitumor antibiotic acting on cyclin/CDK mediated cell cycle regulation, produced by *Streptomyces* sp. *J Antibiot* 53(1):81–83
- Bao S, Deng Z, Fu H, Proksch P, Lin W (2005) Diterpenes and disulfides from the marine mangrove plant *Bruguiera sexangula* var. *rhynchopetala*. *Helv Chim Acta* 88:2757–2763
- Barlow RB (1979) Structure-activity relationships. *Trends Pharmacol Sci* 1(1):109–111
- Bezhtentsev VM, Druzhilovskiy DS, Ivanov SM, Filimonov DA, Sastry GN, Poroikov VV (2017) Web resources for discovery and development of new medicines. *Pharm Chem J* 51(2):91–99

- Bohlmann F, Dhar AK, Jakupovic J, King RM, Robinson H (1981a) Two sesquiterpene lactones with an additional propiolactone ring from *Disynaphia halimifolia*. *Phytochemistry* 20:1077–1080
- Bohlmann F, Zdero C, King RM, Robinson H (1981b) Germacranolides, a guaianolide with a  $\beta$ -lactone ring and further constituents from *Grazielia* species. *Phytochemistry* 20:1069–1075
- Bombardelli E, Bonati A, Danieli B, Gabetta B, Martinelli EM, Mustich G (1975) The structure of quimbeline, a new bisindole alkaloid from *Voacanga chlotiana*. *Experientia* 31(2):139–140
- Brandi A, Cicchi S, Cordero FM (2008) Novel syntheses of azetidines and azetidinones. *Chem Rev* 108:3988–4035
- Bull JA, Croft RA, Davis OA, Doran R, Morgan KF (2016) Oxetanes: recent advances in synthesis, reactivity, and medicinal chemistry. *Chem Rev* 116(19):12150–12233
- Burkhard JA, Wuitschik G, Rogers-Evans M, Müller K, Carreira EM (2010) Oxetanes as versatile elements in drug discovery and synthesis. *Angew Chem Int Ed* 49:9052–9067
- Chagas FO, Pupo MT (2018) Chemical interaction of endophytic fungi and actinobacteria from *Lychnophora ericoides* in co-cultures. *Microbiol Res* 212–213:10–16
- Carreira EM, Fessard TC (2014) Four-membered ring-containing spirocycles: synthetic strategies and opportunities. *Chem Rev* 114:8257–8322
- Centko RM, Ramón-García S, Taylor T, Patrick BO, Thompson CJ, Miao VP, Andersen RJ (2012) Ramariolides A–D, antimycobacterial butenolides isolated from the mushroom *Ramaria cystidiophora*. *J Nat Prod* 75(12):2178–2182
- Chen HD, Yang SP, He XF, Ai J, Liu ZK, Liu HB, Geng MY, Yue JM (2010) Trigochinins A–C: three new daphnane-type diterpenes from *Trigonostemon chinensis*. *Org Lett* 12(6):1168–1171
- Cheng SY, Wang SK, Wen ZH, Dai CF, Duh CY (2009) Three new eudesmanoids from the Formosan soft coral *Nephtea erecta*. *J Asian Nat Prod Res* 11(11):967–973
- Cheng YY, Chen H, He HP, Zhang Y, Li SF, Tang GH, Guo LL, Yang W, Zhu F, Zheng YT, Li SL, Hao XJ (2013) Anti-HIV active daphnane diterpenoids from *Trigonostemon thyrsoideum*. *Phytochemistry* 96:360–369
- Collado IG, Macias FA, Massanet GM, Molinillo JMG, Rodriguez-Luis F (1987) Terpene synthesis. 1. Chemical transformation of deacylsubexpinnatin into the natural oxetane lactone subexpinnatin C. *J Organomet Chem* 52(15):3323–3326
- Coxon DT, Price KR, Stothers JB, Stoessl A (1979) Cyclodehydroisolibimin: a new tricyclic sesquiterpene from potato tubers inoculated with *Phytophthora infestans*. *J Chem Soc Chem Commun* 1:348–349
- Croteau R, Ketchum REB, Long RM, Kaspera R, Wildung MR (2006) Taxol biosynthesis and molecular genetics. *Phytochem Rev* 5(1):75–97
- Da Machado FLS, Kaiser CR, Costa SS, Gestinari LM, Soares AR (2010) Biological activity of the secondary metabolite from marine algae of the genus *Laurencia*. *Rev Bras Pharm* 20(3): 441–452
- Dai J, Fishback JA, Zhou YD, Nagle DG (2006) Sodwanone and yardenone triterpenes from a South African species of the marine sponge *Axinella* inhibit hypoxia-inducible factor-1 (HIF-1) activation in both breast and prostate tumor cells. *J Nat Prod* 69(12):1715–1720
- Das B, Rao SP (1996) Naturally occurring oxetane-type taxoids. *Indian J Chem* 35B:883–888
- Davis OA, Bull JA (2015) Recent advances in the synthesis of 2-substituted oxetanes. *Synthesis* 26:1–6
- De Gutierrez AN, Bardon A, Catalan CAN, Gedris TB, Herz W (2001) Sesquiterpene lactones and other constituents of *Disynaphia multicrenulata* from Argentina. *Biochem Syst Ecol* 29:633–647
- De La Torre MC, Pascual C, Franco BR, Savona PG, Perales A (1986) Neo-clerodane diterpenoids from *Teucrium salviastrum*. *Phytochemistry* 25:1397–1403
- Dembitsky VM (2008) Bioactive cyclobutane-containing alkaloids. *J Nat Med (Tokyo)* 62(1):1–33
- Dembitsky VM (2014) Naturally occurring bioactive cyclobutane-containing (CBC) alkaloids in fungi, fungal endophytes, and plants. *Phytomedicine* 21(12):1559–1581
- Dembitsky VM, Glorizova TA (2017) Naturally occurring boron containing compounds: structures and biological activities. *J Nat Prod Res* 3(2):147–152
- Dembitsky VM, Glorizova TA, VV Poroikov VV (2007) Natural peroxy anticancer agents. *Mini-Rev Med Chem* 7(6):571–589
- Dembitsky VM, Al Quntar AAA, Srebnik M (2011) Natural and synthetic small boron-containing molecules as potential inhibitors of bacterial and fungal quorum sensing. *Chem Rev* 111(1):209–237
- Dembitsky VM, Savidov N, Glorizova TA (2018) Sulphur containing steroids: Structures and biological activities. *Vietnam J Chem* 56(5): 582–540
- De Rosa S, De Stefano S, Scarpelli P, Zavodnik N (1988) Terpenes from the red alga *Sphaerococcus coronopifolius* of the North Adriatic Sea. *Phytochemistry* 27: 1875–1878
- Dimick PS, Hoskin JC (1983) Review of apple flavor - state of the art. *Crit Rev Food Sci Nutr* 18(4):387–409
- Dookran D, Maharaj D, Mootoo BS, Ramsewak R, Tinto WF (1994) Briarane and asbestinane diterpenes from *Briareum asbestinum*. *Tetrahedron* 50:1983–1992
- Duan KT, Li ZHYX, Yuan QX, Wang WX, Li J, Ping H, Feng CT, Liu JK (2018) Vibrallactone derivatives containing  $\gamma,\delta,\epsilon$ -lactone cores from cultures of the basidiomycete *Boreostereum vibrans*. *Fitoterapia* 128:7–11
- Du Toit A (2016) A fungal quorum-sensing system. *Nat Rev Microbiol* 14:404–405
- Eguren L, Perales A, Fayos J, Rodriguez B, Savona G, Piozzi F (1982) New neoclerodane diterpenoid containing an oxetane ring isolated from *Teucrium chamaedrys*. X-ray structure determination. *J Organomet Chem* 47(21):4157–4160
- Elliger CA, Benson M, Haddon WF, Lundin RE, Waiss AC Jr, Wong RY (1989) Petuniasterones. Part 2. Novel ergostane-type steroids from *Petunia hybridavilm.* (solanaceae). *J Chem Soc, Perkin Trans 1* 1: 143–149
- Elliger CA, Benson M, Haddon WF, Lundin RE, Waiss AC Jr, Wong RY (1988) Three new types of ergostanoids with unusual functionalities were isolated from leaves and stems of *Petunia hybrids*. *J Chem Soc, Perkin Trans 1* 1:711–717
- Evidente A, Iacobellis NS, Scopa A, Surico G (1990) Isolation of  $\beta$ -phenyllactic acid related compounds from *Pseudomonas syringae*. *Phytochemistry* 29(5):1491–1499
- Fan YY, Gao XH, Yue JM (2016) Attractive natural products with strained cyclopropane and/or cyclobutane ring systems. *Sci China Chem* 59(9):1126–1141
- Filimonov DA, Druzhilovskiy DS, Lagunin AA, Glorizova TA, Rudik AV, Dmitriev AV, Pogodin PV, Poroikov VV (2018) Computer-aided prediction of biological activity spectra for chemical compounds: opportunities and limitations. *Biom Chem Res Method* 1(1):e00004
- Filimonov DA, Lagunin AA, Glorizova TA, Rudik AV, Druzhilovskiy DS, Pogodin PV, Poroikov VV (2014) Prediction of the biological activity spectra of organic compounds using the PASS online web resource. *Chem Heterocycl Compd* 50(3):444–457
- Fukuyama Y, Nakaoka M, Yamamoto T, Takahashi H, Minami H (2006) Degraded and oxetane-bearing limonoids from the roots of *Melia azedarach*. *Chem Pharm Bull (Tokyo)* 54(8):1219–1222
- Gao K, Ma DW, Cheng Y, Tian XR, Lu YY, Du XY, Tang HF, Chen JZ (2015) Three new dimers and two monomers of phenolic amides from the fruits of *Lycium barbarum* and their antioxidant activities. *J Agric Food Chem* 63:1067–1075
- Georgopoulou K, Smirlis D, Bisti S, Xingi E, Skaltsounis L, Soteriadou K (2007) In vitro activity of 10-deacetylbaicatin III against



- Leishmania donovani* promastigotes and intracellular amastigotes. *Planta Med* 73(10):1081–1088
- Grafe U, Fleck WF, Mblmann U, Schade W, Tonew E, Wiesner J (1988) Diffusomycin, a new macrocyclic polyene lactame antibiotic from *Streptomyces albus* inhibiting bacterial growth only partly. *Int Symp Chem Nat Prod PA* 167:245
- Greenspan MD, Yudkovitz JB, Lo CYL (1987) Inhibition of hydroxymethylglutaryl-coenzyme A synthase by L-659,699. *Proceed Natl Acad Sci USA* 84:7488–7492
- Gryglewski RJ, Dembinska-Kieć A, Korbut R (1978) A possible role of thromboxane A<sub>2</sub> (TXA<sub>2</sub>) and prostacyclin (PGI<sub>2</sub>) in circulation. *Acta Biol Med Ger* 37(5-6):715–723
- Guo S, Tang YP, Duan JA, Su SL, Ding AW (2009) Two new terpenoids from fruits of *Ziziphus jujuba*. *Chin Chem Lett* 20(2):197–200
- Hamberg M, Svensson J, Samuelsson B (1975) Thromboxanes: a new group of biologically active compounds derived from prostaglandin endoperoxides. *Proc Natl Acad Sci U S A* 72(8):2994–2998
- Han Q, Zhang J, Lu Y, Wu Y, Zheng Q, Sun H (2004) A novel cytotoxic oxetane ent-kauranoid from *Isodon japonicus*. *Planta Med* 70(6):581–584
- Hirota A, Ando Y, Monma S, Hirota H (1994) FCRR-toxin, a novel phytotoxin from *Fusarium oxysporum* f. sp. *radicis-lycopersici*. *Biosci Biotechnol Biochem* 58(10):1931–1932
- Howat S, Park B, Oh S, Jin YW, Lee EK, Loake GJ (2014) Paclitaxel: biosynthesis, production and future prospects. *New Biotechnol* 31(3):242–245
- Huang JM, Yokoyama R, Yang CS, Fukuyama Y (2000) Merrillactone A, a novel neurotrophic sesquiterpene dilactone from *Illicium merrillianum*. *Tetrahedron Lett* 41:6111–6114
- Irie T, Izawa M, Kurosawa E (1970) Laureatin and isolaureatin, constituents of *Laurencia nipponica* Yamada. *Tetrahedron* 26:851–870
- Jabeen B, Riaz N, Saleem M, Naveed MA, Ahmed M, Tahir MN, Pescitelli G, Ashraf M, Ejaz SA, Ahmed I, Jabbar A (2013) Isolation and characterization of limonoids from *Kigelia africana*. *Z Naturforsch* 68B:1041–1048
- Jeong SY, Jun do Y, Kim YH, Min BS, Min BK, Woo MH (2011) Monoterpenoids from the aerial parts of *Aruncus dioicus* var. *kamtschaticus* and their antioxidant and cytotoxic activities. *Bioorg Med Chem Lett* 21(11):3252–3256
- Ji NY, Wang BG (2014) Nonhalogenated organic molecules from *Laurencia* algae. *Phytochem Rev* 13:653–670
- Jiang MY, Wang F, Yang XL, Fang LZ, Dong ZJ, Zhu HJ, Liu JK (2008) Derivatives of vibrallactone from cultures of the Basidiomycete *Boreostereum vibrans*. *Chem Pharm Bull* 56(9): 1286–1288
- Jones RJ, Hawkins RE, Eatock MM, Ferry DR, Eskens FA, Wilke H, Evans TR (2008) A phase II open-label study of DHA-paclitaxel (Taxoprexin) by 2-h intravenous infusion in previously untreated patients with locally advanced or metastatic gastric or oesophageal adenocarcinoma. *Cancer Chemother Pharmacol* 61(3):435–441
- Kingston DGI, Jagtap PG, Yuan H, Samala L (2002) The chemistry of taxol and related taxoids. In: Herz W, Falk H, Kirby GW (eds) *Prog Chem Org Nat Prod*, vol 84. Springer, Vienna
- Kitahara M, Asano M, Naganawa H, Maeda K, Hamada M, Aoyagi T, Umezawa H, Iitaka Y, Nakamura H (1987) Valilactone, an inhibitor of esterase, produced by actinomycetes. *J Antibiot (Tokyo)* 40(11): 1647–1650
- Ko HH, Yang SZ, Lin CN (2001) Artocarpol F, a phenolic compound with a novel skeleton, isolated from *Artocarpus rigida*. *Tetrahedron Lett* 42:5269–5270
- Kokh DB, Amaral M, Bomke J, Grädler U, Musil D, Buchstaller HP, Dreyer MK, Frech N, Lowinski M, Vallee F, Bianciotto M, Rak A, Wade RC (2018) Estimation of drug-target residence times by  $\tau$ -random acceleration molecular dynamics simulations. *J Chem Theory Comput* 14(7):3859–3869
- Kurata K, Suzuki T, Suzuki M, Kurosawa E (1983) Laureacetal C, an unusual secohamigrane sesquiterpene from the red alga *Laurencia nipponica* Yamada. *Chem Lett* 12:29–32
- Lagunin AA, Goel RK, Gawande DY, Priynka P, Glorizova TA, Dmitriev AV, Ivanov SM, Rudik AV, Konova VI, Pogodin PV, Druzhilovsky DS, Poroikov VV (2014) Chemo- and bioinformatics resources for in silico drug discovery from medicinal plants beyond their traditional use: a critical review. *Nat Prod Rep* 31(11):1585–1611
- Le TC, Yang I, Yoon YJ, Nam SJ, Fenical W (2016) Ansalactams B–D illustrate further biosynthetic plasticity within the ansamycin pathway. *Org Lett* 18(9):2256–2259
- Leelananda SP, Lindert S (2016) Computational methods in drug discovery. *Beilstein J Org Chem* 12:2694–2718
- Lentini R, Martín NM, Forlin M, Belmonte L, Fontana J, Cornella M, Martini L, Tamburini S, Bentley WE, Jousson O, Mansy SS (2017) Two-way chemical communication between artificial and natural cells. *ACS Cent Sci* 3(2):117–123
- Leśniak S, Lewkowski J, Kudelska W, Zając A (2008) Thietanes and thietes: monocyclic. *Comprehen Heterocycl Chem III* 7:389–428
- Li C, Lee D, Graf TN, Phifer SS, Nakanishi Y, Burgess JP, Riswan S, Setyowati FM, Saribi AM, Soejarto DD, Farnsworth NR, Falkinham JO 3rd, Kroll DJ, Kinghorn AD, Wani MC, Oberlies NH (2005) A hexacyclic ent-trachylobane diterpenoid possessing an oxetane ring from *Mitrephora glabra*. *Org Lett* 7(25):5709–5712
- Li GH, Li L, Duan M, Zhang KQ (2006) The chemical constituents of the fungus *Stereum* sp. *Chem Biodivers* 3(2):210–216
- Liu JQ, Peng XR, Li XY, Li TZ, Zhang WM, Shi L, Han J, Qiu MH (2013) Norfriedelins A–C with acetylcholinesterase inhibitory activity from acerola tree (*Malpighia emarginata*). *Org Lett* 15(7):1580–1583
- Loh J, Carlson RW, York WS, Stacey G (2002) Bradyoxetin, a unique chemical signal involved in symbiotic gene regulation. *Proc Natl Acad Sci U S A* 99(22):14446–1444651
- Mahmoud AA, Ahmed AA, Iinuma M, Tanaka T (1998) Further monoterpene 5-methyl-coumarins and an acetophenone derivative from *Ethulia conyzoides*. *Phytochemistry* 48(3):543–546
- Malakov PY, Papanov GY, Mollov NM (1978) Montanin-D, a new furanoid diterpene of clerodane type from *Teucrium montanum* L. *Z Naturforsch* 33B:1142–1144
- Manam RR, Macherla VR, Tsueng G, Dring CW, Weiss J, Neuteboom STC, Lam KS, Potts BC (2009) Antiprotealide is a natural product. *J Nat Prod* 72(2):295–297
- Massanet GM, Collado IG, Macías FA, Bohlmann F, Jakupovic J (1983) Structural determination of clementein, a new guaianolide isolated from *Centaurea clementei*. *Tetrahedron Lett* 24(15):1641–1642
- Mayol L, Piccialli V, Sica D (1987) Spongiolactone, an unusual  $\beta$ -lactone diterpene isovalerate based on a new rearranged spongiane skeleton from *Spongionella gracilis*. *Tetrahedron Lett* 28(31):3601–3604
- Meng S, Tang GL, Pan HX (2018) Enzymatic formation of oxygen-containing heterocycles in natural product biosynthesis. *Chem Bio Chem* 19(19):2002–2022
- Mondol MAM, Tareq FS, Kim JH, Lee MA, Lee HS, Lee YJ, Lee JS, Shin HJ (2011) Cyclic ether-containing macrolactins, antimicrobial 24-membered isomeric macrolactones from a marine *Bacillus* sp. *J Nat Prod* 74(12):2582–2587
- Morris BD, Smyth RR, Foster SP, Hoffmann MP, Roelofs WL, Franke S, Francke W (2005) Vittatalactone, a  $\beta$ -lactone from the striped cucumber beetle, *Acalymma vittatum*. *J Nat Prod* 68(1):26–30
- Mutoh M, Nakada N, Matsukuma S, Ohshima S, Yoshinari K, Watanabe J, Arisawa M (1994) Panlicins, novel pancreatic lipase inhibitors. I. Taxonomy, fermentation, isolation and biological activity. *J Antibiot (Tokyo)* 47(12):1369–1375
- Murakami S, Harada S, Kojima F, Kinoshita N, Takahashi Y, Hamada M, Takeuchi T, Aoyagi T (1995a) Belactins A and B, new serine carboxypeptidase inhibitors produced by Actinomycete. I. Taxonomy,

- production, isolation and biological activities. *J Enzym Inhib* 9: 8755–5093
- Murakami S, Takahashi Y, Naganawa H, Takeuchi T, Aoyagi T (1995b) Belactins A and B, new serine carboxypeptidase inhibitors produced by *Actinomycete*. II. Physico-chemical properties, structure determinations and enzymatic inhibitory activities compared with other  $\beta$ -lactone containing inhibitors. *J Enzym Inhib* 9(4):277–284
- Nadia S, Azeana S, Liew S, Litaudon M, Issam AM, Wahab HA, Awang K (2018) Pahangine A and B, two new oxetane containing neolignans from the barks of *Beilschmiedia glabra* Kosterm (Lauraceae). *Phytochem Lett* 25:22–26
- Ni L, Ma J, Li CJ, Li L, Guo JM, Yuan SP, Hou Q, Guo Y, Zhang DM (2015) Novel rearranged and highly oxygenated abietane diterpenoids from the leaves of *Tripterygium wilfordii*. *Tetrahedron Lett* 56(10):1239–1243
- Nonaka Y, Ohtaki H, Ohtsuka E, Kocha T, Fukuda T, Takeuchi T (1995) Effects of ebelactone B, a lipase inhibitor, on intestinal fat absorption in the rat. *J Enzym Inhib* 10:57–63
- Okada K, Enomoto S, Morimoto K, Kazuno T (1962) The isolation of a new bile sterol,  $3\alpha,7\alpha,12\alpha$ -trihydroxy-24,27-epoxycoprostance, from Sting-ray bile. *J Biochem (Tokyo)* 51(6):441–442
- Omura S, Murata M, Imamura N, Iwai Y, Tanaka H, Furusaki A, Matsumoto H (1984) Oxetin, a new antimetabolite from an actinomycete. Fermentation, isolation, structure and biological activity. *J Antibiot (Tokyo)* 37(11):1324–1332
- Ostrowska H, Kalinowska J, Chabielska E, Stankiewicz A, Kruszewski K, Buczek W (2005) Ebelactone B, an inhibitor of extracellular cathepsin A-type enzyme, suppresses platelet aggregation ex vivo in renovascular hypertensive rats. *J Cardiovasc Pharmacol* 45(4): 348–353
- Otani T, Yoshida KI, Kubota H, Kawai S, Ito S, Hori H, Ishiyama T, Oki T (2000) Novel triene- $\beta$ -lactone antibiotics, oxazolomycin derivative and its isomer, produced by *Streptomyces* sp. KSM-2690. *J Antibiot (Tokyo)* 53(12):1397–1400
- Pereira NFG, Walmir Silva Garcez CAC, de Siqueira JM (2003) Novel santalane sesquiterpenoids from the stem bark of *Duguetia glabriuscula* – Annonaceae. *Quim Nova* 26(4): 512–516
- Penn J, Biddle JR, Mantle RG, Bilton JN, Sheppard RN (1992) Pennigritrem, a naturally-occurring penitrem A analogue with novel cyclisation in the diterpenoid moiety. *J Chem Soc, Perkin Trans* 10: 23–26
- Prablek MA (2013) Synthesis and activity of oxetane analogs to molecules in bacterial quorum sensing. In: Princeton University. Senior Theses, USA
- Pullaiah KC, Surapaneni RK, Rao CB, Albizati KF, Sullivan BW, Faulkner DJ, He CH, Clardy J (1985) Dictyoxetane, a novel diterpene from the brown alga *Dictyota dichotoma* from the Indian Ocean. *J Organomet Chem* 50:3665–3666
- Rachid S, Huo L, Herrmann J, Stadler M, Köpcke B, Bitzer J (2011) Müller R. Mining the cinnabaramide biosynthetic pathway to generate novel proteasome inhibitors. *Chembiochem* 12(6):922–931
- Ren F, Chen S, Zhang Y, Zhu S, Xiao J, Liu X, Su R, Che Y (2018) Hawaiianols A–D, highly oxygenated p-terphenyls from an insect-associated fungus, *Paraconiothyrium hawaiiense*. *J Nat Prod* 81(8): 1752–1759
- Savidov N, Glorizova TA, Poroikov VV, Dembitsky VM (2018) Highly oxygenated isoprenoid lipids derived from fungi and fungal endophytes: origin and biological activities. *Steroids* 140:114–124
- Selvamani S, Balamurugan S (2015) Phytochemical screening and GC-MS analysis of acetone leaf extract of *Acalypha indica* (Linn.). *Int J Res Stud Biosci* 3(5):229–232
- Sergeiko A, Poroikov VV, Hanuš LO, Dembitsky VM (2008) Cyclobutane-containing alkaloids: origin, synthesis, and biological activities. *The Open Med Chem J* 2:26–31
- Shen YC, Hsu SM, Lin YS, Cheng KC, Chien CT, Chou CH, Cheng YB (2005) New bicyclic taxane diterpenoids from *Taxus sumatrana*. *Chem Pharm Bull* 53(7):808–810
- Shen YC, Wang SS, Chien CT, Khalil AT (2008) Tasumatrols U–Z, taxane diterpene esters from *Taxus sumatrana*. *J Nat Prod* 71(4): 576–800
- Shen YC, Wang SS, Pan YL, Lo KL, Chakraborty R, Chien CT, Kuo YH, Lin YC (2002) New taxane diterpenoids from the leaves and twigs of *Taxus sumatrana*. *J Nat Prod* 65(12):1848–1852
- Shiu LL, Chen WC, Kuo YH (1999) Five new cis-himachalane-type sesquiterpenes from the heartwood of *Juniperus chinensis* var. *tsukusiensis*. *Chem Pharm Bull* 47(4):557–560
- Sliwoski G, Kothiwale S, Meiler J, Lowe EW Jr (2014) Computational methods in drug discovery. *Pharmacol Rev* 66(1):334–395
- Smith LW, Culvenor CCJ (1984) Grantianine and grantaline, alkaloids of *Crotalaria virgulata* subsp. *grantiana*. *Phytochemistry* 23:473–474
- Smoum R, Rubinstein A, Dembitsky VM, Srebnik M (2012) Boron containing compounds as protease inhibitors. *Chem Rev* 112(7):4156–4220
- Subban S, Singh S, Subramani R, Johnpaul M, Chelliah J (2017) Fungal 7-epi-10-deacetylaxol produced by an endophytic *Pestalotiopsis microspora* induces apoptosis in human hepatocellular carcinoma cell line (HepG2). *BMC Complem Alternat Med* 17:504–516
- Taga ME, Bassler BL (2003) Chemical communication among bacteria. *Proc Natl Acad Sci U S A* 100(Suppl 2):14549–14554
- Tonew E, Tonew M, Gräfe U, Zöpel P (1992) On the antiviral activity of diffusomycin (oxazolomycin). *Acta Virol* 36(2):166–172
- Terent'ev AO, Platonov MM, Levitsky DO, Dembitsky VM (2011) Organosilicon and organogermanium peroxides: synthesis and reactions. *Russ Chem Rev* 80:807–828
- Terent'ev AO, Borisov DA, Vil' VA, Dembitsky VM (2014) Synthesis of five- and six-membered cyclic organic peroxides: key transformations into peroxide ring-retaining products. *Beilstein J Org Chem* 10:34–114
- Tomoda H, Ohbayashi N, Morikawa Y (2004) Binding site for fungal  $\beta$ -lactone hymeglusins on cytosolic 3-hydroxy-3-methylglutaryl coenzyme A synthase. *Biochim Biophys Acta* 1636:22–28
- Uyeo S, Irie H, Harada H (1967) The structure of stenine, a new alkaloid occurring in *Stemona tuberosa*. *Chem Pharm Bull* 15:768–770
- Vander Velde DG, Georg GI, Gollapudi SR, Jampani HB, Liang XZ, Mitscher LA, Ye QM (1994) Wallifoliol, a taxol congener with a novel carbon skeleton, from Himalayan *Taxus wallichiana*. *J Nat Prod* 57(6):862–867
- Vikram A, Prithiviraj B, Kushalappa AC (2004) Use of volatile metabolite profiles to discriminate fungal diseases of Cortland and Empire Apples. *J Plant Pathol* 86(3):215–225
- Vil VA, Glorizova TA, Poroikov VV, Terent'ev AO, Savidov N, Dembitsky VM (2018) Peroxy steroids derived from plant and fungi and their biological activities. *Appl Microbiol Biotechnol* 102(18): 7657–7667
- Vil VA, Yaremenko IA, Ilovaisky AI, Terent'ev AO (2017) Peroxides with anthelmintic, antiprotozoal, fungicidal and antiviral bioactivity: properties, synthesis and reactions. *Molecules* 22(11):1881 [doi.org/10.3390/molecules22111881](https://doi.org/10.3390/molecules22111881)
- Walker K., Croteau R. (1999) Taxol Biosynthesis. In: Romeo J.T. (eds) *Phytochemicals in human health protection, nutrition, and plant defense. Recent advances in phytochemistry* (proceedings of the Phytochemical Society of North America), vol 33. Springer, Boston, MA
- Wang JS, Zhang Y, Wang X-B, Kong L-Y (2012) Aphanalides A–H, ring A- secolimonoids from the fruits of *Aphanamixis polystachya*. *Tetrahedron* 68(21):3963–3971
- Wang M, Cornett B, Nettles J, Liotta DC, Snyder JP (2000) The oxetane ring in taxol. *J Organomet Chem* 65:1059–1068
- Wang YF, Shi QW, Dong M, Kiyota H, Gu YG, Cong B (2011) Natural taxanes: developments since 1828. *Chem Rev* 111(12):7652–7709



- Wani MC, Taylor HL, Wall ME, Coggon P, McPhail AT (1971) Plant antitumor agents. VI. Isolation and structure of taxol, a novel anti-leukemic and antitumor agent from *Taxus brevifolia*. *J Am Chem Soc* 93(9):2325–2327
- Waters CM, Bassler BL (2005) Quorum sensing: cell-to-cell communication in bacteria. *Annu Rev Cell Dev Biol* 21:319–346
- Weibel EK, Hadvary P, Hochuli E, Kupfer E, Lengsfeld H (1987) Lipstatin, an inhibitor of pancreatic lipase, produced by *Streptomyces toxytricini*. I. Producing organism, fermentation, isolation and biological activity. *J Antibiot (Tokyo)* 40(8):1081–1085
- Willenbring D, Tantillo DJ (2008) Mechanistic possibilities for oxetane formation in the biosynthesis of taxol's D ring. *Russ J Gen Chem* 78(4):723–731
- Wongsuk T, Pumeesat P, Luplertlop N (2016) Fungal quorum sensing molecules: role in fungal morphogenesis and pathogenicity. *J Basic Microbiol* 56(5):440–447
- Wright M, Byrd J, Gao Y, Stubblefield J, Park H, Dunlap N (2014) Isolation and structural clarification of triterpenes from *Cyclocarya paliurus*: cyclocaric acid A and B. *Planta Med* 80:PD19
- Wuitschik G (2008) Oxetanes in drug discovery. In: Dissertation. Zürich, Switzerland
- Wuitschik G, Carreira EM, Wagner B, Fischer H, Parrilla I, Schuler F, Rogers-Evans M, Müller K (2010) Oxetanes in drug discovery: structural and synthetic insights. *J Med Chem* 53(8):3227–3246
- Xie WD, Zhang Q, Li PL, Ji ZJ (2005) Two triterpenoids and other constituents from *Petasites tricholobus*. *Phytochemistry* 66:2340–2345
- Xu JB, Yue JM (2014) Recent studies on the chemical constituents of *Trigonostemon* plants. *Org Chem Front* 1:1225–1252
- Yamada K, Takada S, Nakamura S, Hirata Y (1968) The structures of anisatin and neoanisatin: toxic sesquiterpenes from *Illicium anisatum* L. *Tetrahedron* 24:199–229
- Yuan JX, Zeng Y, Zou C, Zhao PJ (2013) Four new  $\beta$ -lactones from the endophytic *Streptomyces* sp. T1B1. *Phytochem Lett* 6(4):625–628
- Zhao W, Pu JX, Du X (2011) Chemical constituents from the aerial parts of *Isodon coetsa* and their cytotoxicity. *Archiv Pharm Res* 34(12):2007–2014
- Zhang Z, Jia Z (1991) Taxanes from *Taxus chinensis*. *Phytochemistry* 30:2345–2348
- Zhang L, Luo RH, Wang F, Jiang MY, Dong ZJ, Yang LM, Zheng YT, Liu JK (2010) Highly functionalized daphnane diterpenoids from *Trigonostemon thyrsoideum*. *Org Lett* 12(1):152–155
- Zhang W, Xu L, Yang L, Huang Y, Li S, Shen Y (2014) Phomopsidone A, a novel depsidone metabolite from the mangrove endophytic fungus *Phomopsis* sp. A123 *Fitoterapia* 96:146–151
- Zhu PF, Dai Z, Wang B, Wei X, Yu HF, Yan ZR, Zhao XD, Liu YP, Luo XD (2017) The anticancer activities phenolic amides from the stem of *Lycium barbarum*. *Nat Prod Bioprospect* 7(6):421–431