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Review Article

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Natural Occurring Thiirane Containing Compounds: Origin, Chemistry, and their Pharmacological Activities

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Abstract This mini review describes research on rare and unusual natural and/or semi-synthetic thiirane-containing compounds isolated from plant, fungi, bacteria, and invertebrates. About 40 biologically active epithio metabolites demonstrate confirmed pharmacological activity, including antitumor, antimicrobial, and antibacterial effects. The structures, origin, and biological activities of epithio metabolites are reviewed. Utilizing the computer program PASS, some structure–activity relationship new activities are also predicted, pointing toward possible new applications of these compounds. This article emphasizes the role of natural and/or semi-synthetic thiirane-containing compounds as an important source of drug prototypes and leads for drug discovery.

Keywords Epithio, thiirane, plant, SAR, pharmacology, activity, metabolites, anticancer

1. Introduction

The chemistry of thiirane-containing compounds has played a considerable role in the development of modern organic, bioorganic chemistry and biochemistry [1-5]. The chemistry of the saturated three-membered rings containing sulphur (e.g., thiiranes) has been relatively well established for some time, the analogous unsaturated compounds have been known more than 50 years [5-9]. Thiirane derivatives have been reported to possess variety of cytotoxic activities, and showed other anticipated biological activities. Epithio compounds are widely used as anticancer agents [5, 8-11]. Also, thiiranes which demonstrated confirmed activity as inhibitors of the peptidase, carboxypeptidase A, gelatinase, aromatase and metalloproteinases. The thiirane moiety is an important substance and shows some important biological activities [10-14].

Recently, much attention has been focused on thiirane-containing compounds for their scarcity of their pharmacological activities [15-16]. At present, there is no reliable data on the biological activity of epithio containing metabolites. We used an algorithm by which we calculated the biological activity of natural thiirane-containing containing metabolites. Computer program PASS, which we tested on chemical compounds, which belong to a different class of compounds and are described earlier [17-22]. PASS program contains more than one million chemical compounds that are related to biologically active compounds, and are associated with more than 8,000 biological activities. The algorithm of practical use of PASS is described in detail in several publications [23-25]. Thus, the values of Pa and Pi are calculated for each activity, which can be interpreted either as the probability of a molecule belonging to classes of active and inactive compounds, respectively, or as probabilities of the first and second kind of errors in forecasting. Computer analysis of the predicted spectra of biological activity showed that 278 species of biological activity are predicted with Pa> 70% and 91 with Pa> 50%. Although most of the known biological activities for the corresponding epithio compounds are linked to the lipid exchange regulator and antineoplastic properties, their amount is more than 70% of the predicted focal activity.

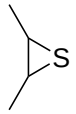
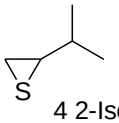
All presented natural thiirane-containing components are divided into four groups. The first group includes natural thiirane-containing hydrocarbons. The second group includes nitrogen- and thiirane containing metabolites, and cyclic and acyclic alcohols. The third group includes natural and semi-synthetic epithio fatty acids and thiirane containing carboxylic acids. The fourth group includes natural and/or semi-synthetic steroids, peptides, and polyethers. Current mini review devoted to the chemistry, biology and pharmacological activities of natural thiirane-containing compounds.

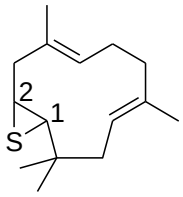
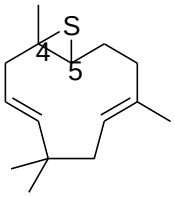
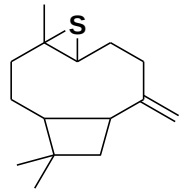
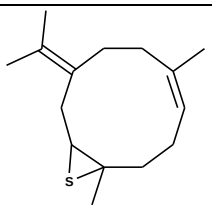
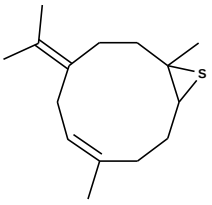
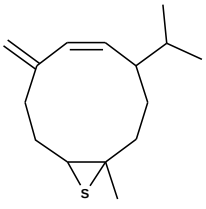
2. Natural Thiirane-containing Metabolites

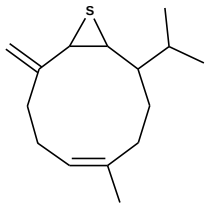
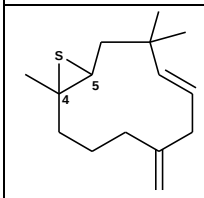
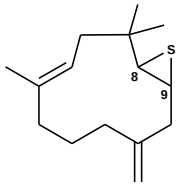
A simple thiirane (**1**), methyl thiirane (**2**), 2,3-dimethylthiirane (**3**) and 2-isopropylthiirane (**4**) have been detected by GC-MS in oils of some plants [15,16]. Thus, it was found in garlic *Allium sativum* and *Allium cepa* [15,16, 26-31]. Thiirane was isolated from red algae *Gelidium arbuscula* [32]. In addition methyl thiirane was found in *Allium pekinense* (bulbs), *A. cepa* (bulbs), and *A. fistulosum* (whole plant) [33], leaves and roots of *Allium schoenoprasum* (Alliaceae) [34], and Chinese toon (*Toona sinensis*), and 2,3-dimethyl-*thiirane* (3) was isolated from roots, leaves and inflorescence of flowering plant *Petiveria alliacea* [35,36]. (1-methylethyl)-thiirane (**4**) was also detected in beer with an onion-like off-flavour [37].

Several sesquiterpene episulphides are known in nature. Thus, 1,2- (**5**), 4,5-epithio-humulene (**6**) and 4,5-epithiocaryophyllene (**7**) have been isolated from hops [38]. Thus, hop oils may contain low levels of for example 1,2- (**8**) and 7,8-epithiogermacrene B (**9**), 1,2- (**10**) and 6,7-epithiogermacrene-D (**11**), 4,5-epithio-β-humulene (**12**) and 8,9-epithio-β-humulene (**13**, structures and activities shown in Table 1) in addition to those episulphides described previously [38-41]. For the group epithio hydrocarbons, antineoplastic and antieczematic activities are characteristic, and some components are stimulants renin release and RNA-directed RNA polymerase (Table 1).

Table 1: Confirmed and predicted pharmacological activities of thiirane-containing hydrocarbons (**1**-**13**)

Thiirane-containing hydrocarbons	**Activity reviewed**	**Activities confirmed (Pa)**	**Additional predicted activities (Pa)***
 1 Thiirane	Antifungal	Not predicted: Carbons: 2 < 3	Not predicted: Carbons: 2 < 3
 2 Me-thiirane	Antifungal	Macrophage colony stimulating factor agonist (0,585), Membranepermeabilityinhibitor (0,569),	Renin release stimulant (0,882) Transferase stimulant (0,841) Growth hormone agonist (0,802) Phobic disorders treatment (0,750) Antiseborrheic (0,714) Leukopoiesis stimulant (0,666) Kidney function stimulant (0,655) Antineoplastic (sarcoma) (0,602)
 3 2,3-DiMe-thiirane	Not studied		Renin release stimulant (0,918) Transferase stimulant (0,873) Aspulvinonedimethylallyltransferase inhibitor (0,872) Testosterone 17-β-dehydrogenase (NADP+) inhibitor (0,866) Phobic disorders treatment (0,829) Antiseborrheic (0,768) Antipsoriatic (0,754) Kidney function stimulant (0,685)
 4 2-Isopropylthiirane	Not studied		Renin release stimulant (0,872) Acylcarnitine hydrolase inhibitor (0,852) Alkylacetylglycerophosphatase inhibitor (0,846) Phobic disorders treatment (0,770) Carminative (0,701) Antiseborrheic (0,688)

			Antineoplastic (sarcoma) (0,639) Antidiabetic (0,629)
 5 1,2-Epithiohumulene	Not studied		Antineoplastic (0,887) RNA-directed RNA polymerase stimulant (0,868) Renin release stimulant (0,845) Antieczematic (0,844) Antiinflammatory (0,784) Apoptosis agonist (0,698) Antipsoriatic (0,682)
 6 4,5-Epithiohumulene	Not studied		Cardiotonic (0,996) Antineoplastic (0,972) Antieczematic (0,831 Apoptosis agonist (0,821) Antiinflammatory (0,792) Renin release stimulant (0,717) Analgesic (0,663) Antidiabetic (0,618)
 **7** 4,5-Epithiocaryophyllene	Not studied		Cardiotonic (0,996) Antineoplastic (0,969) Antieczematic (0,893) Renin release stimulant (0,725) Apoptosis agonist (0,695) Antiinflammatory (0,676) Antipsoriatic (0,642) Dermatologic (0,628) Antiarthritic (0,611)
 **8** 1,2-epithiogermacrene B	Not studied		Cardiotonic (0,996) Antineoplastic (0,965) Antieczematic (0,869) Dopamine D4 antagonist (0,722) Renin release stimulant (0,733) Chemoprotective (0,570)
 **9** 7,8-epithiogermacrene B	Not studied		Cardiotonic (0,996) Antineoplastic (0,960) Antieczematic (0,857) Dopamine D4 antagonist (0,804) Renin release stimulant (0,699) Antiasthmatic (0,619)
 **10** 1,2-epithiogermacrene D	Not studied		Cardiotonic (0,995) Antineoplastic (0,963) Antieczematic (0,903) Carminative (0,652) Calcium regulator (0,650) Antipsoriatic (0,593)

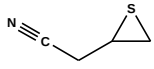
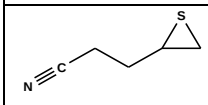
 **11** 6,7-epithiogermacrene D	Not studied		Antieczematic (0,933) Platelet aggregation inhibitor (0,866) Carminative (0,846) Renin release stimulant (0,780) Antiinflammatory (0,770) Antineoplastic (0,772) Antipsoriatic (0,733) Apoptosis agonist (0,684)
 **12** 4,5-Epithio-β-humulene	Not studied		Cardiotonic (0,996) Antineoplastic (0,986) Antieczematic (0,896) Apoptosis agonist (0,843) Antiarthritic (0,757) Antipsoriatic (0,657) Antileukemic (0,632)
 **13** 8,9-Epithio-β-humulene	Not studied		Antieczematic (0,930) Antineoplastic (0,931) Apoptosis agonist (0,868) Antiischemic, cerebral (0,853) Antipsoriatic (0,825) Antiinflammatory (0,784) Dermatologic (0,739) Antileukemic (0,633)

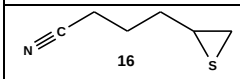
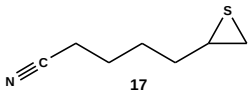
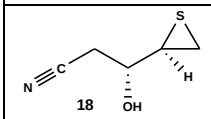
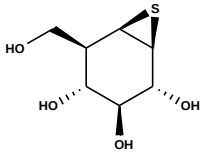
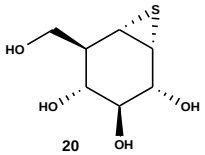
* Only activities with Pa > 0.5 are shown

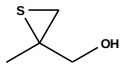
The second group includes nitrogen- and thiirane containing metabolites, and cyclic and acyclic alcohols (structures, **14-21**, Table 2). Epithionitriles (**14-18**) have been isolated from crude extracts of *Brassica*, *Sinapis* and *Raphanus* species when glucosinolates were separated [42-48]. Several recent publications showed that isothiocyanates and epithionitriles demonstrated anticancer and other pharmacological activities [49-52]. Cyclophellitol was isolated from fungus *Phellinus* sp., and it is a potent and specific mechanism-based inhibitor of retaining β-glucosidases [53]. This compound is a close structural mimic of β-glucopyranose that fits well in the active pocket of retaining β-glucosidases. β-Thiiranecyclophellitol (**19**) and its epimer (**20**) have been obtained from natural cyclophellitol and showed activity as inhibitor for human β-glucosidases [54]. For both compounds, inhibitory activity against glucan 1,4-β-glucosidase and prunasinβ-glucosidase was confirmed. In addition, the compounds demonstrate inhibition of platelet aggregation, and show antineoplastic (sarcoma) activity.

(*2*-Methyl-thiiranyl)-methanol (**21**) was found in *Maranta arundinacea* commonly known as arrowroot is a starch rich tuberous plant [55]. This natural metabolite is a stimulant of transferase, renin and leukopoiesis, and also demonstrates anti-eczematic, anti-seborrheic and antidiabetic activities (Table 2).

Table 2: Confirmed and predicted pharmacological activities of thiirane-containing compounds **(14-21)**

Thiirane-containing compounds	**Activity reviewed**	**Activities confirmed (Pa)**	**Additional predicted activities (Pa)***
 **14** 3,4-Epithiobutanenitrile	Antifungal	Macrophage colony stimulating factor agonist (0,537), Membrane permeability inhibitor (0,553)	Renin release stimulant (0,807) Protein phosphatase inhibitor (0,724) Phobic disorders treatment (0,652) Inflammatory Bowel disease treatment (0,646) Pediculicide (0,558) Kidney function stimulant (0,574)
 **15** 4,5-Epithiovaleronitrile	Antifungal	Macrophage colony stimulating factor agonist (0,498),	Protein-tyrosine phosphatase F inhibitor (0,954) Growth stimulant (0,750)

		Membrane permeability inhibitor (0,445)	Antiischemic, cerebral (0,630) Antineoplastic (sarcoma) (0,595) Septic shock treatment (0,540)
 **16**	Antifungal, Dehydrogenase inhibitor	Macrophage colony stimulating factor agonist (0,524)	Protein-tyrosine phosphatase F inhibitor (0,950) Growth stimulant (0,730) Antiischemic, cerebral (0,637) Antineoplastic (sarcoma) (0,583)
 **17**	Antifungal	Macrophage colony stimulating factor agonist (0,546), Membrane permeability inhibitor (0,407)	Protein-tyrosine phosphatase F inhibitor (0,947) Growth stimulant (0,708) Antiischemic, cerebral (0,638) Antineoplastic (sarcoma) (0,592)
 **18**	Antifungal	Mitochondrial electron transport inhibitor (0,694), Macrophage colony stimulating factor agonist (0,526), Membrane permeability inhibitor (0,561)	Renin release stimulant (0,856) Antiischemic, cerebral (0,617) Antiviral (Picornavirus) (0,594) Growth stimulant (0,570) Radioprotector (0,552)
 **19** Cyclophellitol thiirane	β-Glucosidases inhibitor	Glucan endo-1,6-β-glucosidase inhibitor (0,849) Glucan 1,4-β-glucosidase inhibitor (0,543) Prunasinβ-glucosidase inhibitor (0,430) Glucan 1,3-β-glucosidase inhibitor (0,413)	Platelet aggregation inhibitor (0,900) Antidiabetic (0,860) Genital warts treatment (0,859) Antineoplastic (0,762) Antineoplastic (sarcoma) (0,761) Natural killer cell stimulant (0,685) Cardiotonic (0,625) Antimetastatic (0,615)
 **20**	β-Glucosidases inhibitor	Glucan endo-1,6-β-glucosidase inhibitor (0,849) Glucan 1,4-β-glucosidase inhibitor (0,543) Prunasinβ-glucosidase inhibitor (0,430) Glucan 1,3-β-glucosidase inhibitor (0,413)	Platelet aggregation inhibitor (0,900) Antidiabetic (0,860) Genital warts treatment (0,859) Antineoplastic (0,762) Antineoplastic (sarcoma) (0,761) Natural killer cell stimulant (0,685) Cardiotonic (0,625) Antimetastatic (0,615)

 **21** (2-Methyl-thiiranyl)-methanol	Not studied		Transferase stimulant (0,914) Antieczematic (0,901) Renin release stimulant (0,866) Antiischemic, cerebral (0,842) Leukopoiesis stimulant (0,781) Phobic disorders treatment (0,759) Antiseborrheic (0,727) Antidiabetic (0,706)

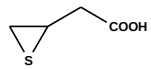
* Only activities with Pa > 0.5 are shown

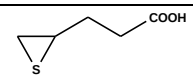
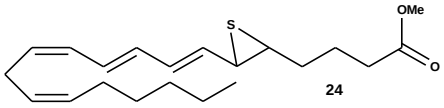
The third group includes natural and semi-synthetic epithio fatty acids and thiirane containing carboxylic acids (Table 3). Thiirane-containing carboxylic acids (**22** and **23**) have been isolated from Cottonseed oil of various plant species, mainly *Gossypium hirsutum* and *G. herbaceum* [56-57]. Also these carboxylic acids (**22** and **23**) were isolated from Crambeabyssinica seed flour [58-59].

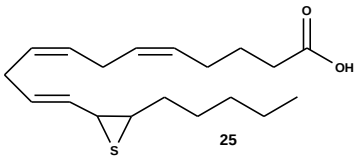
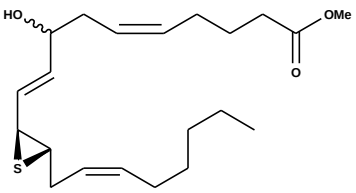
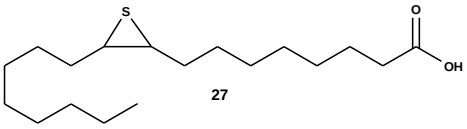
Unusual unsaturated thiirane-containing fatty acids (**24**-**26**) were obtained from naturally occurring unsaturated fatty acids and they showed antibacterial properties. An analogue of hepoxilin A3 was synthesized in which the 11,12-epoxide group has been altered to a thiirano group. Synthesized thiirano-hepoxilin A3 raises intracellular calcium concentrations in intact human neutrophils [60].

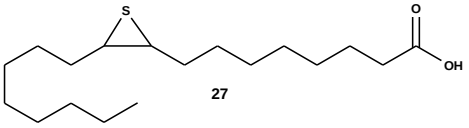
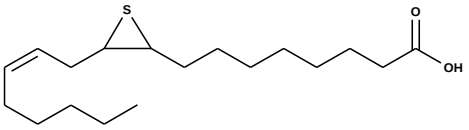
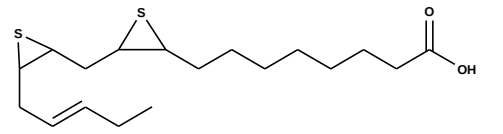
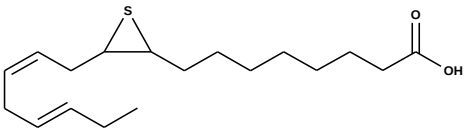
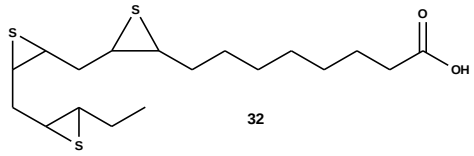
Thiirane-, dithiirane and trithiirane-containing fatty acids (**27**-**32**, structures and activities shown in Table 3) have been obtained from soya bean oil and other vegetable oils [61], and also from individual fatty acids: myristoleic, palmitoleic, oleic, ricinoleic, linoleic, and linolenic acids [62]. For this group of lipids, the characteristic properties are the radioprotector and the vasoprotector, in addition, these fatty acids are regulators of lipid metabolism.

Table 3: Confirmed and predicted activities of thiirane-containing fatty (carbocylic) acids (**22**-**32**)

Thiirane-containing fatty (carbocylic) acids	**Activity reviewed**	**Activities confirmed (Pa)**	**Additional predicted activities (Pa)***
 **22** 3,4-Epithiobutanoic acid	Not studied		Phobic disorders treatment (0,808) Kidney function stimulant (0,684) Lipotropic (0,676) Leukopoiesis stimulant (0,668) Acute neurologic disorders treatment (0,628) Antiviral (Arbovirus) (0,625) Antidiabetic (0,610) Mucositis treatment (0,609) Allergic conjunctivitis treatment (0,601) Antiviral (Picornavirus) (0,594) Alopecia treatment (0,592) Antiischemic, cerebral (0,599) Antineoplastic (sarcoma) (0,582) Erythropoiesis stimulant (0,566) Hypolipemic (0,532) Lipid metabolism regulator (0,530)
	Not studied		Phobic disorders treatment (0,839) Acute neurologic disorders treatment (0,769) Leukopoiesis stimulant (0,701)

 **23** 3,4-Epithiopentanoic acid			Antineoplastic (sarcoma) (0,688) Growth stimulant (0,672) Kidney function stimulant (0,671) Radioprotector (0,653) Erythropoiesis stimulant (0,646) Antidiabetic (0,636) Antiviral (Arbovirus) (0,605) Antitoxic (0,602) Mucositis treatment (0,596) Neuroprotector (0,581) Hepatic disorders treatment (0,568) Cytoprotectant (0,579) Antiviral (Picornavirus) (0,560) Stroke treatment (0,544) Chemoprotective (0,538) Inflammatory Bowel disease treatment (0,535) Alopecia treatment (0,535)
 **24** Methyl 4-(3-((1*E*,3*E*,5*Z*,8*Z*)-tetradeca-1,3,5,8-tetraen-1-yl)thiiran-2-yl)butanoate	Not studied		Lipid metabolism regulator (0,824) Angiogenesis stimulant (0,767) Radioprotector (0,758) Neuroprotector (0,761) Antiinflammatory (0,718) Hypolipemic (0,707) Antiviral (Arbovirus) (0,703) Cytoprotectant (0,682) Antiulcerative (0,651) Antitoxic (0,627) Dermatologic (0,616) Hepatic disorders treatment (0,609) Vasoprotector (0,611) Antifungal (0,599) Mucositis treatment (0,590) Antithrombotic (0,588) Antipruritic (0,583) Chemoprotective (0,571) Acute neurologic disorders treatment (0,568) Antimutagenic (0,552) Antisecretoric (0,549) Apoptosis agonist (0,540) Antiparasitic (0,534)
	Not studied		Angiogenesis stimulant (0,780) Lipid metabolism regulator (0,779) Hypolipemic (0,718) Antisecretoric (0,708) Radioprotector (0,704)

 **25** (5*Z*,8*Z*,11*E*)- 12-(3-pentylthiiran-2-yl)dodeca-5,8,11-trienoic acid			Neuroprotector (0,706) Vasoprotector (0,681) Antitoxic (0,670) Mucositis treatment (0,680) Antiviral (Arbovirus) (0,678) Cytoprotectant (0,668) Antiinflammatory (0,659) Antithrombotic (0,645) Hepatic disorders treatment (0,642) Antiulcerative (0,632) Antimutagenic (0,619) Phobic disorders treatment (0,598) Antifungal (0,567) Ophthalmic drug (0,566) Acute neurologic disorders treatment (0,562) Antipruritic (0,545) Dermatologic (0,541) Preneoplastic conditions treatment (0,536)
 **26** 11,12-thiirane hepoxilin A3	*hepoxilin* A3 hydrolase inhibitor	Lipid metabolism regulator (0,804)	Lipid metabolism regulator (0,804) Hypolipemic (0,733) Ophthalmic drug (0,732) Antithrombotic (0,732) Vasoprotector (0,702) Antisecretoric (0,698) Antiulcerative (0,688) Angiogenesis stimulant (0,681) Cytoprotectant (0,669) Vasodilator (0,627) Antiviral (Arbovirus) (0,615) Antifungal (0,603) Antiinflammatory (0,573) Apoptosis agonist (0,549) Preneoplastic conditions treatment (0,547)
 **27** 8-(3-octylthiiran-2-yl)octanoic acid	Not studied		Antieczematic (0,873) Phobic disorders treatment (0,854) Lipotropic (0,773) Mucositis treatment (0,761) Vasoprotector (0,756) Radioprotector (0,749) Lipid metabolism regulator (0,733) Hypolipemic (0,729) Leukopoiesis stimulant (0,728)
	Not studied		Antieczematic (0,823) Vasoprotector (0,809)

 **27** 8-(3-octylthiiran-2-yl)octanoic acid			Radioprotector (0,790) Hypolipemic (0,743) Leukopoiesis stimulant (0,733) Lipid metabolism regulator (0,719) Antiischemic, cerebral (0,716) Fibrinolytic (0,714) Lipotropic (0,700) Antiviral (Arbovirus) (0,693)
 **29** (*Z*)-8-(3-(oct-2-en-1-yl)thiiran-2-yl)octanoic acid	Not studied		Antieczematic (0,917) Vasoprotector (0,818) Angiogenesis stimulant (0,790) Lipid metabolism regulator (0,757) Antiviral (Arbovirus) (0,719) Neuroprotector (0,707) Antisecretoric (0,706) Hypolipemic (0,699) Radioprotector (0,696)
 **30** (*E*)-8-(3-((3-(pent-2-en-1-yl)thiiran-2-yl)methyl)thiiran-2-yl)octanoic acid	Not studied		Antieczematic (0,877) Vasoprotector (0,751) Lipid metabolism regulator (0,740) Phobic disorders treatment (0,726) Angiogenesis stimulant (0,716) Hypolipemic (0,698) Antiinflammatory (0,678) Allergic conjunctivitis treatment (0,670) Hepatic disorders treatment (0,663)
 **31** 8-(3-((2*Z*,5*E*)-octa-2,5-dien-1-yl)thiiran-2-yl)octanoic acid	Not studied		Antieczematic (0,935) Angiogenesis stimulant (0,810) Lipid metabolism regulator (0,796) Antiinflammatory (0,753) Hypolipemic (0,740) Phobic disorders treatment (0,726) Hepatic disorders treatment (0,725) Ophthalmic drug (0,692) Vasoprotector (0,689) Hepatoprotectant (0,653)
 **32** 8-(3-((3-((3-ethylthiiran-2-yl)methyl)thiiran-2-yl)methyl)thiiran-2-yl)octanoic acid	Not studied		Antieczematic (0,845) Phobic disorders treatment (0,834) Lipotropic (0,753) Fibrinolytic (0,684) Inflammatory Bowel disease treatment (0,668) Antiischemic, cerebral (0,668) Hypolipemic (0,660)

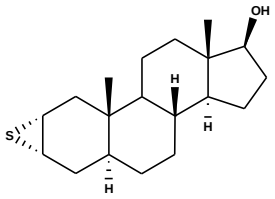
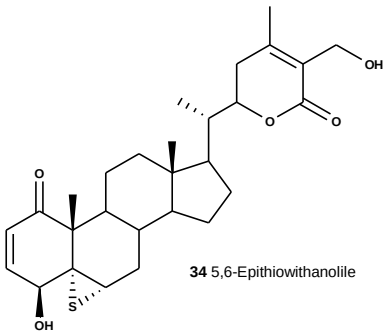
* Only activities with Pa > 0.5 are shown

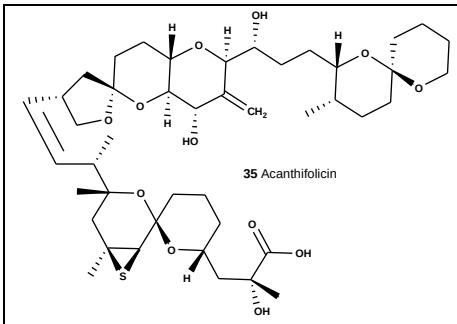
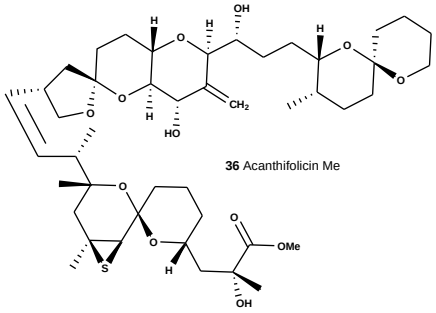
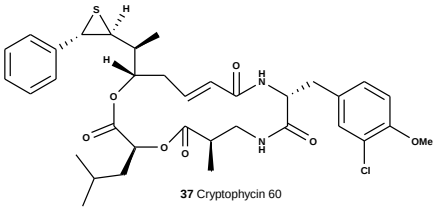
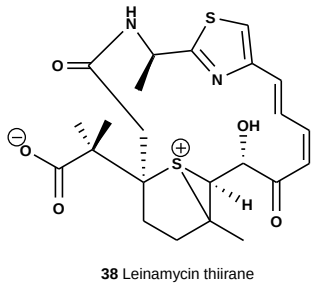
An antineoplastic agent for the treatment of breast cancer, epitiostanol (**33**) also known as epithio-androstanol or 2α,3α-epithio-5α-androstan-17-β-ol is anabolic steroid, was described for the first time in 1965*[63,64]*.This

anticancer agent (**33**), in addition to its major function, also demonstrates anti-inflammatory and immunosuppressant properties (Table 4).

Anticancer agent withanolide A, (4β,5β,6β,22R)-4,27-dihydroxy-5,6,-22,26-diepoxyergosta-2,24-diene-1,26-di one, belonging to group of C28 steroidal lactones was isolated from leaves of *Withania somnifera* (Ashwagandha) [65-67]. 5,6-Epithiowithanolile A (**34**) was obtained from withanolide A by transformation epoxy group to thiirane group [68]. Withanolides A, also acts as a hepatoprotection and immunosuppressant, and can be used for the treatment of Alzheimer's disease (Table 4).

Table 4: Confirmed and predicted activities of thiirane-containing compounds (**33-38**)

Thiirane-containing compounds	**Activity reviewed**	**Activities confirmed (Pa)**	**Additional predicted activities (Pa)***
 **33** Epitiostanol	Anticancer, Gynecomastia inhibitor, Antibreast cancer	Antineoplastic (0,964) Antineoplastic (breast cancer) (0,598)	Antineoplastic (0,964) Antisecretoric (0,948) Alopecia treatment (0,806) Cytostatic (0,798) Erythropoiesis stimulant (0,760) Cardiotonic (0,729) Prostate disorders treatment (0,709) Neuroprotector (0,723) Bone diseases treatment (0,693) Immunosuppressant (0,679) Antiinflammatory (0,658) Dermatologic (0,655) Cytoprotectant (0,654) Dementia treatment (0,630) Anabolic (0,598) Apoptosis agonist (0,563) Hepatic disorders treatment (0,556) Hypolipemic (0,530)
 **34** 5,6-Epithiowithanolile	Prostate and liver cell lines inhibitor	Antineoplastic (0,874) Prostate disorders treatment (0,572)	Hepatoprotectant (0,940) Antieczematic (0,939) Hepatic disorders treatment (0,935) Cytostatic (0,934) Macular degeneration treatment (0,930) Immunosuppressant (0,822) Antifungal (0,795) Apoptosis agonist (0,753) Alzheimer's disease treatment (0,743) Antibacterial (0,726) Dermatologic (0,715) Angiogenesis inhibitor (0,711) Antipsoriatic (0,684)
	Inhibitorof ProteinPhosphatases	Protein phosphatase PP1 inhibitor (0,753)	Angiogenesis stimulant (0,977) Cardiotonic (0,977) Lipid metabolism regulator (0,966) Antineoplastic (0,957)

 **35** Acanthifolicin		Protein phosphatase inhibitor (0,417)	Apoptosis agonist (0,915) Antifungal (0,760) Antibacterial (0,704) Hypolipemic (0,535) Antimitotic (0,533)
 **36** Acanthifolicin Me	Inhibitorof Protein Phosphatases	Protein phosphatase PP1 inhibitor (0,744)	Angiogenesis stimulant (0,975) Cardiotonic (0,971) Lipid metabolism regulator (0,961) Antineoplastic (0,953) Apoptosis agonist (0,910) Antieczematic (0,769) Antifungal (0,737) Antibacterial (0,679)
 **37** Cryptophycin 60	Anticancer	Antineoplastic (0,696)	Antifungal (0,827) Antineoplastic (0,696) Antimitotic (0,651) Apoptosis agonist (0,545)
 **38** Leinamycin thiirane	Anticancer	Antineoplastic (0,891)	Antineoplastic (0,891) Antibiotic Glycopeptide-like (0,658) Antibacterial (0,555)

* Only activities with Pa > 0.5 are shown

More than 35 years ago, unusual an episulfide-containing polyether carboxylic acid, called acanthifolicin (**35**), has been isolated from extracts of the marine sponge *Pandaros acanthifolium* [69]. Acanthifolicin showed activity against of protein phosphatases-1 and 2A [70-73]. Acanthifolicin methyl ester (**36**) has been obtained fromacanthifolicin and showed same activity as compound (**35**). Acanthifolicin activity against protein phosphatase (more than 74%) was confirmed, antineoplastic activity was also noted, and apoptosis agonist, too.

Cyanobacteria *Nostoc* sp. produced a lot of bioactive metabolites [74-77], including cryptophycin 60 (**37**) [78]. Isolated anticancer cryptophycins showed to inhibit the proliferation of hyper-proliferative cells with drug resistant

phenotypes, and to treat pathological conditions, such as neoplasia [78-80]. Cryptophycin 60 (**37**), in addition to anticancer activity, also showed high reliability of antifungal and antimitotic activities.

Leinamycin is an 18-membered macrolactam produced by several species of *Streptomyces atroolivaceus* [81]. This macrolactam has been shown to exhibit antitumor properties as well as antimicrobial properties against Gram-positive and Gram-negative bacteria. Derivative of leinamycin with thiirane group (**38**, structures and activities shown in Table 4) also showed anticancer and antibacterial activities [81,82].

Conclusion Remarks

Natural and/or semi-synthetic thiirane-containing compounds possess mainly antimicrobial and cytotoxic activities, although the predicted biological activity showed a broad spectrum of activities. The most characteristic activity, which have been found are: antineoplastic, anti-secretoric, antiviral, antidiabetic, anti-ischemic, phobic disorders treatment, lipid metabolism regulator, and also others. The biological profile of these new generations of epithio metabolites presents much progress with regards to the old compounds.

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Conflicts of Interest

The authors declare no conflict of interest

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