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Thiirane-containing carboxylic (fatty) acids and their biological activities: A brief review

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Abstract
The present review describes the biological activities of synthetic thiirane-containing (TC) carboxylic (fatty) acids. More than 30 biologically active TC fatty acids are lipid metabolism regulators, radioprotectors, or hypolipidemic agents, and they also show other pharmacological activities. The structures and predicted activities of a selection of TC fatty (carboxylic) acids are reported. Also, some additional activities are predicted with the computer program PASS, based on structure–activity relationships (SAR), which point toward new possible applications of these lipids. This article emphasizes the role of the TC carboxylic (fatty) acids, as an important source of leads for drug discovery.

Keywords: thiirane-containing fatty (carboxylic) acids; pharmacological activities; SAR, PASS

1. Introduction

Heterocyclic systems are structural fragments of some of the most important natural metabolites, and form the basis of many drugs, vitamins, pigments, and dyes [1-5]. The three-membered heterocyclic compounds containing sulfur, known as ethylene sulfides or thiiranes, are extremely reactive compounds due to the structural features of their cycle. They react in various ways following the opening of the cycle, which can lead to the syntheses of various substances, whose preparation can be difficult or impossible by other methods [6-10]. The uses of thiiranes are diverse. They include the syntheses of thiosugars, thioalcohols, and other heterocyclic compounds, the creation of drugs and physiologically active substances, and the production of polymers with valuable properties.

The chemistry of thiirane-containing compounds has played a significant role in the development of modern organic, bioorganic and medicinal chemistry. The compounds have demonstrated confirmed activities as the inhibitors of peptidase, carboxypeptidase A, gelatinase, aromatase, and metalloproteinases [11-16].

As already proved by numerous works, there is a relationship between structure and activity, and this principle is called SAR (Structure-Activity-Relationship). We used the computer program PASS, containing about one million chemical compounds and more than 8,000 biological activities, and calculated the biological activity of different natural and/or synthetic compounds [17-19]. PASS predictions are based on SAR analysis of the training set consisting of more than one million drugs, drug candidates and lead compounds. The algorithm of PASS practical utilization is described in detail in several publications [20-22].

This review is devoted to an interesting topic, i.e., TC fatty (carboxylic) acids and their biological activities.

Biological Activities of Thiirane-containing Carboxylic (Fatty) Acids

All synthetic TC fatty (carboxylic) acids were divided into four groups. The first group includes TC fatty (carboxylic) acids (1-7, see Table 1); the second group comprises esters of TC fatty (carboxylic) acids (8-18, Table 2); the third group consists of TC carboxylic acid derivatives (19-22, Table 3); the fourth group comprises TC fatty (carboxylic) acid amides (23-29, Table 4); and the fifth group includes the adamantine TC carboxylic acid derivatives (30-33, Table 5).

As shown by the analysis of the chemical structures of TC carboxylic acids (1-5), the dominant activities for these compounds are: treatment of phobic disorders, kidney function stimulation, treatment of acute neurologic disorders, and as hypolipidemic agents (Table 1). For (5*Z*,8*Z*,11*Z*)-12-(3-pentylthiiran-2-yl)dodeca-5,8,11-trienoic acid (6), more than 20 different activities with Pa > 50% have been determined.

Thiirane-2,3-dicarboxylic acid (**7**) belongs to the class of dicarboxylic acids (or dioic acids), which are products of the oxidation of fatty acids [23,24]. Dioic acids and their derivatives exhibited antitumor, as well as other activities [25,26]. These acids are produced by various microorganisms [27-29]. These acids are also found in plants, mammals, and foods [30-32]. The dominant applications of thiirane-2,3-dicarboxylic acid are as an antiviral, hypolipidemic, treatment of phobic disorders, and as a kidney function stimulant (Table 1).

For the two carboxylic acids, (*R*)-methyl-thiirane-2-carboxylate (8) and (*R*)-methyl-3-(thiiran-2-yl) propanoate (9), the dominant activity is in the treatment of phobic disorders (Table 2). (*E*)-7-(thiiran-2-yl)hept-6-enoic acid, in the form of its ethyl (10) and isopropyl (11) esters has a common activity as a lipid metabolism regulator. 9-(thiiran-2-yl) nonanoic acid has four ester derivatives, such as isopropyl (12), butyl (13), isobutyl (14), and isooctyl (15). For all these

derivatives (12-15) of 9-(thiiran-2-yl) nonanoic acid, that have common biological activities, these two agents are radioprotectors and antineoplastics (sarcoma). For the methyl ester of 4-(3-((1*E*,3*E*,5*Z*,8*Z*)-tetradeca-1,3,5,8-tetraen-1-yl)thiiran-2-yl)butanoic acid (16) containing an epithio group in position 5 and 6, the main activity is as a lipid metabolism regulator [33].

Both of the isomers (*S*,5*Z*,9*E*)-8-hydroxy-10-((2*S*,3*S*)-3-((*Z*)-oct-2-en-1-yl)thiiran-2-yl)deca-5,9-dienoic acid, (17) and (*R*,5*Z*,9*E*)-8-hydroxy-10-((2*S*,3*S*)-3-((*Z*)-oct-2-en-1-yl)thiiran-2-yl)deca-5,9-dienoic acid, (18) have the common name 11,12-epithio-hepoxilin A3, and both are hydrolase inhibitors. It is known that hepoxilin A3 and other hepoxilins constitute a group of 12*S*-hydroperoxyeicosatetraenoic acid (12*S*-HpETE)-derived epoxy-hydroxy fatty acids, that have been detected in various cell types and tissues [34, 35].

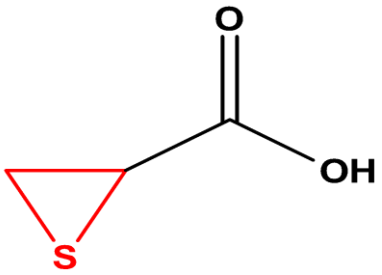
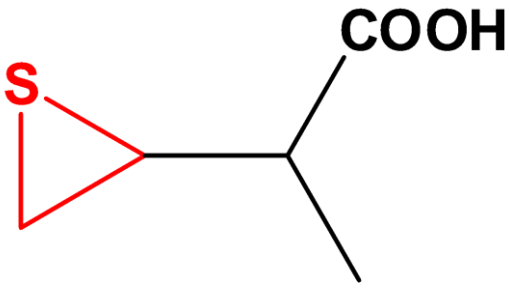
Hepoxilin A3 inhibited biosynthesis of hormones involved in inflammation [36-38]. Both isomers 11,12-epithio-hepoxilin A3 (17 and 18) have common biological activities, such as lipid metabolism regulators, hypolipemics, anti-thrombotics, and vasoprotectors (Table 2).

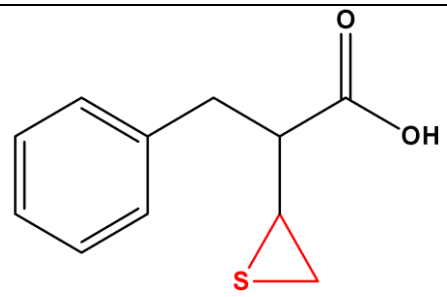
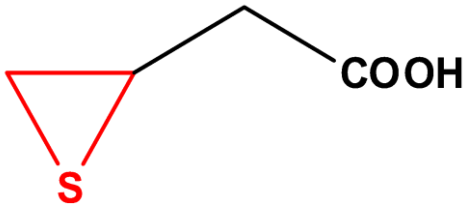
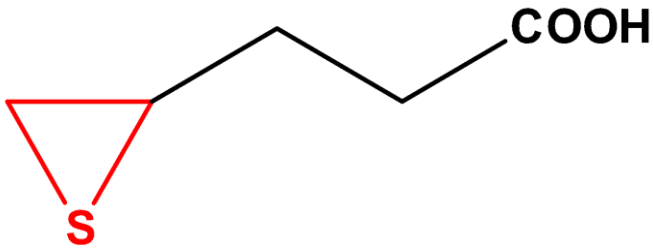
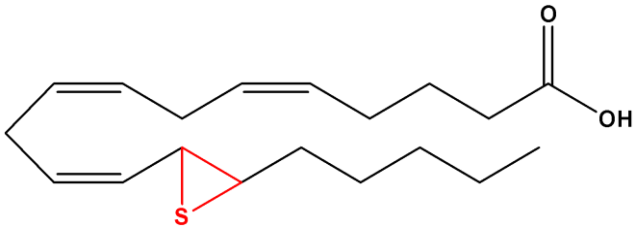
One of the activities for the compounds, thiiran-2-yl-methyl acetate (19) and (*S*)-thiiran-2-yl-methyl methacrylate (20), is in treatment of phobic disorders. The compound 3-(thiiran-2-yl) propyl methacrylate (21) shows antineoplastic (sarcoma), antieczematic, and pediculicide activities (Table 3). Compound (22) also shows antiulcerative and antiallergic activities.

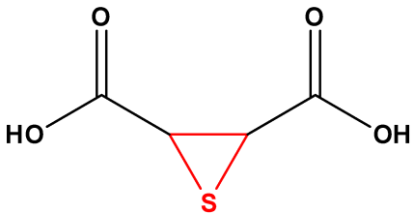
Table 4 shows the predicted activities of amides of carboxylic acids (23-28). The dominant activities are: anti-ischemic, treatment of phobic disorders, antineoplastic (sarcoma), antiobesity, antidiabetic, antiviral, and spasmolytic. The amide of fatty acid (29, N-(2-hydroxyethyl)-2-tetradecylthiirane-2-carboxamide) shown antiviral, phobic treatment and leukopoiesis stimulant activities.

Adamantine TC carboxylic acid derivatives (30-33), whose structures are shown in Table 5, are interesting compounds, and have predominantly antiviral, kidney function stimulant, and phobic treatment activities.

Table 1: Predicted activities of TC fatty (carboxylic) acids (1-8)

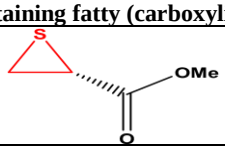
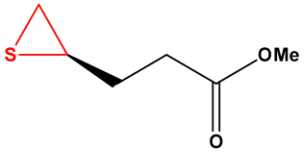
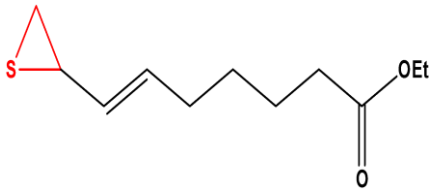
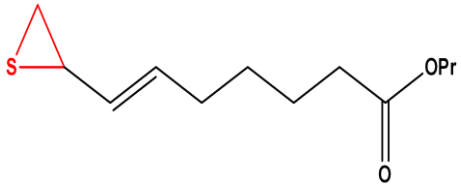
No.	Thiirane-containing fatty (carboxylic) acids	Predicted activities (Pa)*
1		Phobic disorders treatment (0,762)
		Kidney function stimulant (0,706)
		Leukopoiesis stimulant (0,640)
		Hypolipidemic (0,624)
		Antiviral (Arbovirus) (0,628)
		Lipotropic (0,589)
		Antidiabetic (0,595)
		Erythropoiesis stimulant (0,589)
		Antiviral (Picornavirus) (0,589)
		Acute neurologic disorders treatment (0,607)
		Mucositis treatment (0,589)
		Antineoplastic (sarcoma) (0,579)
		Alopecia treatment (0,553)
		Antiischemic, cerebral (0,570)
2		Phobic disorders treatment (0,813)
		Antiseborrheic (0,784)
		Antieczematic (0,769)
		Fibrinolytic (0,731)
		Leukopoiesis stimulant (0,675)
		Kidney function stimulant (0,666)
		Antiinflammatory (0,667)
		Mucositis treatment (0,656)
		Lipid metabolism regulator (0,642)
		Lipotropic (0,603)
		Antineoplastic (sarcoma) (0,613)
		Inflammatory Bowel disease treatment (0,508)
		Radioprotector (0,591)
		Acute neurologic disorders treatment (0,606)
		Antiviral (Arbovirus) (0,612)
		Alopecia treatment (0,580)
		Antiviral (Picornavirus) (0,573)
		Hypolipemic (0,540)
		Erythropoiesis stimulant (0,536)
		Antinephrotoxic (0,534)
3		Phobic disorders treatment (0,794)
		Acute neurologic disorders treatment (0,687)
		Kidney function stimulant (0,629)
		Mucositis treatment (0,609)

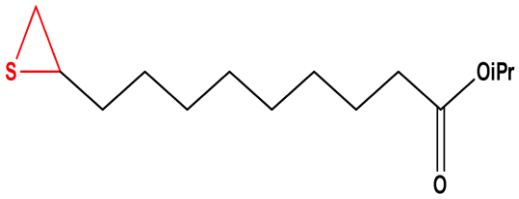
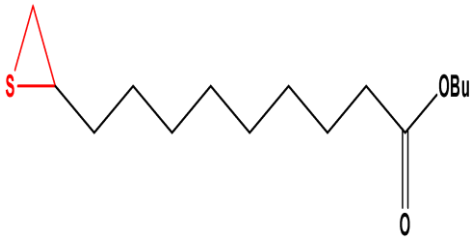
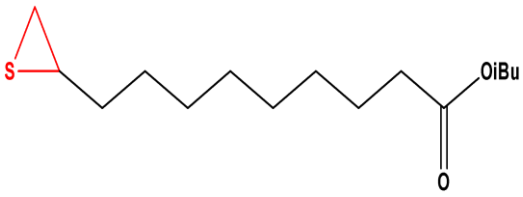
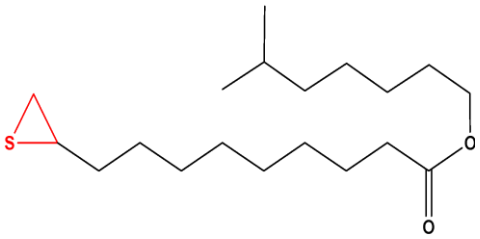
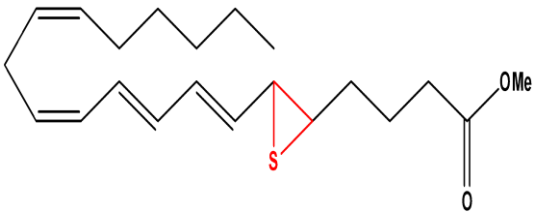
		Lipid metabolism regulator (0,589) Leukopoiesis stimulant (0,579) Antiviral (Arbovirus) (0,607) Antiviral (Picornavirus) (0,575) Antiinflammatory (0,588) Alopecia treatment (0,566) Inflammatory Bowel disease treatment (0,554) Antidiabetic (0,548) Antineoplastic (sarcoma) (0,563) Antiarthritic (0,536) Radioprotector (0,529)
4		Phobic disorders treatment (0,808) Kidney function stimulant (0,684) Lipotropic (0,676) Leukopoiesis stimulant (0,668) Antidiabetic (0,610) Acute neurologic disorders treatment (0,628) Antiviral (Arbovirus) (0,625) Mucositis treatment (0,609) Allergic conjunctivitis treatment (0,601) Antiviral (Picornavirus) (0,594) Alopecia treatment (0,592) Antiischemic, cerebral (0,599) Erythropoiesis stimulant (0,566) Antineoplastic (sarcoma) (0,582) Hypolipemic (0,532) Lipid metabolism regulator (0,530)
5		Phobic disorders treatment (0,839) Acute neurologic disorders treatment (0,769) Leukopoiesis stimulant (0,701) 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)
6		Angiogenesis stimulant (0,780) Lipid metabolism regulator (0,779) Hypolipidemic (0,718) Antisecretoric (0,708) Radioprotector (0,704) Neuroprotector (0,706) Vasoprotector (0,681) Antitoxic (0,670) Mucositis treatment (0,680) Cytoprotectant (0,668) Antiviral (Arbovirus) (0,678) Antithrombotic (0,645) Hepatic disorders treatment (0,642) Antiinflammatory (0,659) Antiulcerative (0,632) Antimutagenic (0,619)

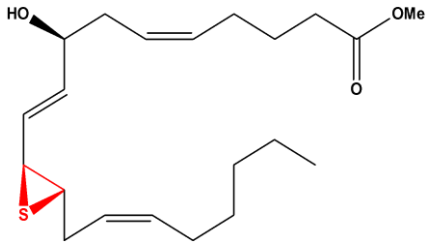
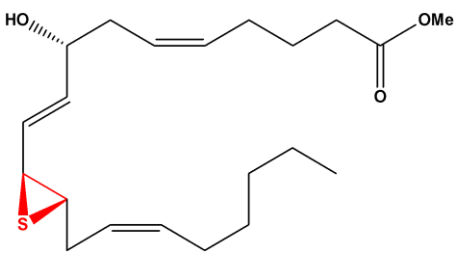
		Ophthalmic drug (0,566)
		Antifungal (0,567)
		Antipruritic (0,545)
		Dermatologic (0,541)
		Acute neurologic disorders treatment (0,562)
		Preneoplastic conditions treatment (0,536)
		Phobic disorders treatment (0,598)
7		Hypolipidemic (0,866)
		Kidney function stimulant (0,731)
		Phobic disorders treatment (0,837)
		Antiviral (Arbovirus) (0,628)
		Erythropoiesis stimulant (0,663)
		Antiviral (Picornavirus) (0,651)
		Antidiabetic (0,651)
		Leukopoiesis stimulant (0,629)
		Mucositis treatment (0,631)
		Preneoplastic conditions treatment (0,609)
		Alopecia treatment (0,591)
		Lipotropic (0,566)
		Antimyopathies (0,556)
		Dermatologic (0,532)

* Only activities with Pa > 0.5 are shown

Table 2: Predicted activities of TC fatty (carboxylic) acid esters (8-18)

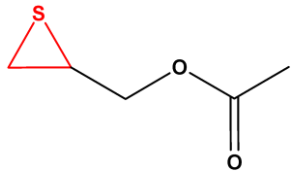
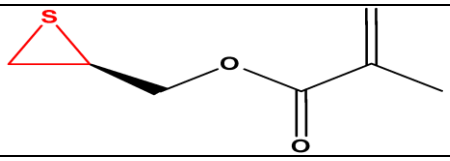
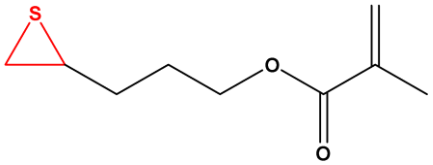
No.	Thiirane-containing fatty (carboxylic) acid esters	Predicted activities (Pa)*
8		Phobic disorders treatment (0,774)
		Fibrinolytic (0,596)
		Kidney function stimulant (0,559)
		Leukopoiesis stimulant (0,533)
9		Phobic disorders treatment (0,758)
		Antiischemic, cerebral (0,690)
		Acute neurologic disorders treatment (0,633)
		Antineoplastic (sarcoma) (0,614)
		Preneoplastic conditions treatment (0,603)
		Mucositis treatment (0,606)
10		Antieczematic (0,873)
		Pediculicide (0,770)
		Antiulcerative (0,745)
		Lipid metabolism regulator (0,728)
		Cytoprotectant (0,662)
		Antisecretoric (0,660)
		Antiviral (Arbovirus) (0,665)
		Leukopoiesis stimulant (0,644)
		Acute neurologic disorders treatment (0,641)
		Antithrombotic (0,591)
		Mucositis treatment (0,598)
		Preneoplastic conditions treatment (0,567)
		Radioprotector (0,545)
11		Lipid metabolism regulator (0,653)
		Preneoplastic conditions treatment (0,637)
		Leukopoiesis stimulant (0,620)
		Cytoprotectant (0,619)
		Antithrombotic (0,607)
		Acute neurologic disorders treatment (0,641)
		Vasodilator, peripheral (0,607)
		Mucositis treatment (0,613)
		Acute neurologic disorders treatment (0,614)
		Phobic disorders treatment (0,656)
		Angiogenesis stimulant0,557
		Antiviral (Picornavirus) (0,560)
		Antipruritic (0,556)
		Antianginal (0,546)

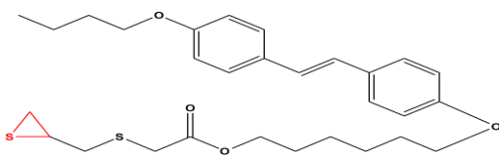
12		Pediculicide (0,779) Acute neurologic disorders treatment (0,715) Hepatic disorders treatment (0,672) Lipid metabolism regulator (0,666) Neuroprotector (0,678) Antineoplastic (sarcoma) (0,637) Antianginal (0,611) Ophthalmic drug (0,572) Hypolipemic (0,549)
13		Antieczematic (0,751) Leukopoiesis stimulant (0,725) Phobic disorders treatment (0,731) Antiischemic, cerebral (0,697) Radioprotector (0,686) Preneoplastic conditions treatment (0,675) Pediculicide (0,664) Acute neurologic disorders treatment (0,663) Lipid metabolism regulator (0,647) Antineoplastic (sarcoma) (0,633) Antiviral (Arbovirus) (0,624) Neuroprotector (0,633) Antiulcerative (0,598) Mucositis treatment (0,595) Cytoprotectant (0,588) Antisecretoric (0,567) Antiviral (Picornavirus) (0,562)
14		Phobic disorders treatment (0,742) Radioprotector (0,701) Acute neurologic disorders treatment (0,706) Antieczematic (0,657) Antianginal (0,622) Antineoplastic (sarcoma) (0,619) Lipid metabolism regulator (0,597) Pediculicide (0,569) Preneoplastic conditions treatment (0,575) Leukopoiesis stimulant (0,502)
15		Phobic disorders treatment (0,840) Leukopoiesis stimulant (0,563) Acute neurologic disorders treatment (0,727) Radioprotector (0,701) Neuroprotector (0,658) Preneoplastic conditions treatment (0,629) Antiulcerative (0,625) Antineoplastic (sarcoma) (0,629) Sclerosant (0,590) Lipid metabolism regulator (0,598) Antisecretoric (0,574) Leukopoiesis stimulant (0,563) Immunostimulant (0,543)
16		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)

		Antithrombotic (0,588)
		Antipruritic (0,583)
		Chemoprotective (0,571)
		Mucositis treatment (0,590)
		Antimutagenic (0,552)
		Antisecretoric (0,549)
		Acute neurologic disorders treatment (0,568)
		Antiparasitic (0,534)
		Apoptosis agonist (0,540)
17		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)
		Antifungal (0,603)
		Antiviral (Arbovirus) (0,615)
		Antiinflammatory (0,573)
		Apoptosis agonist (0,549)
		Preneoplastic conditions treatment (0,547)
18		Lipid metabolism regulator (0,789)
		Hypolipidemic (0,776)
		Ophthalmic drug (0,715)
		Antithrombotic (0,705)
		Vasoprotector (0,695)
		Angiogenesis stimulant (0,688)
		Antisecretoric (0,678)
		Antiulcerative (0,657)
		Cytoprotectant (0,647)
		Vasodilator (0,613)
		Antifungal (0,597)
		Antiviral (Arbovirus) (0,585)
		Antiinflammatory (0,573)
		Apoptosis agonist (0,538)

* Only activities with Pa > 0.5 are shown

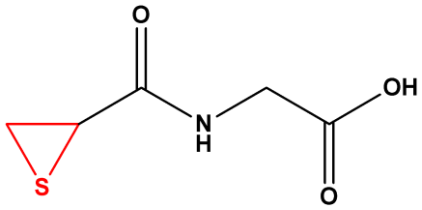
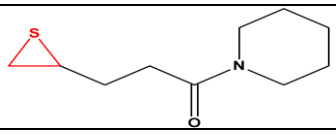
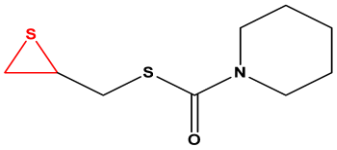
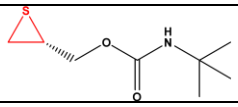
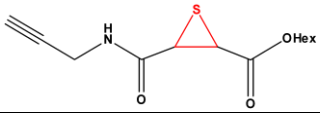
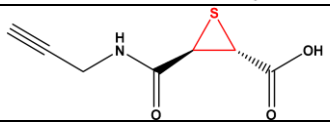
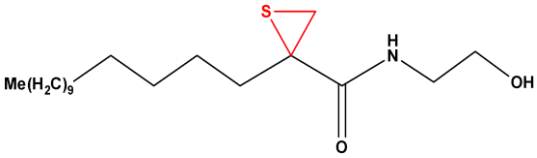
Table 3: Predicted activities of TC carboxylic acid derivatives (19-22)

No.	Thiirane-containing carboxylic acid derivatives	Predicted activities (Pa)*
19		Phobic disorders treatment (0,703)
		Leukopoiesis stimulant (0,613)
		Fibrinolytic (0,601)
		Lipotropic (0,532)
		Antineoplastic (sarcoma) (0,563)
		Pediculicide (0,509)
		Antiviral (0,504)
		Kidney function stimulant (0,529)
20		Pediculicide (0,571)
		Phobic disorders treatment (0,514)
21		Pediculicide (0,556)
		Antieczematic (0,604)
		Antineoplastic (sarcoma) (0,539)
		Leukopoiesis stimulant (0,512)
		Acute neurologic disorders treatment (0,523)
		Phobic disorders treatment (0,572)
		Antiinflammatory (0,501)

22		Antiulcerative (0,641) Antiallergic (0,638) Acute neurologic disorders treatment (0,600) Antiasthmatic (0,565) Radioprotector (0,557) Antieczematic (0,578) Lipid metabolism regulator (0,529) Antiseborrheic (0,519)

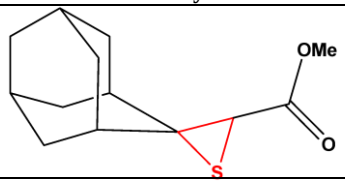
* Only activities with Pa > 0.5 are shown

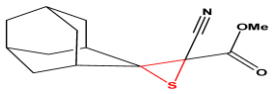
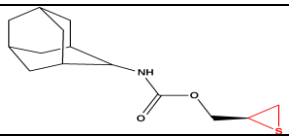
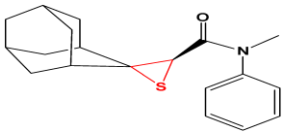
Table 4: Predicted activities of TC fatty (carboxylic) acid amides (23-29)

No.	Thiirane-containing fatty (carboxylic) acids	Predicted activities (Pa)*
23		Antiischemic, cerebral (0,855) Phobic disorders treatment (0,857) Kidney function stimulant (0,639) Leukopoiesis stimulant (0,605) Hepatic disorders treatment (0,580) Antianginal (0,569) Antiviral (Picornavirus) (0,540) Acute neurologic disorders treatment (0,562) Antineoplastic (sarcoma) (0,557) Antiviral (Arbovirus) (0,570)
24		Antiischemic, cerebral (0,633) Antineoplastic (sarcoma) (0,576) Kidney function stimulant (0,504)
25		Antiobesity (0,941) Antidiabetic (0,834) Antiinfertility, female (0,828) Antiallergic (0,704) Inflammatory Bowel disease treatment (0,694) Antiasthmatic (0,615)
26		Antiviral (0,619) Antineoplastic (sarcoma) (0,548) Spasmolytic, urinary (0,514)
27		Phobic disorders treatment (0,763) Spasmolytic, urinary (0,640) Psychostimulant (0,522) Neuroprotector (0,569)
28		Phobic disorders treatment (0,717) Spasmolytic, urinary (0,638) Muscular dystrophy treatment (0,511) Kidney function stimulant (0,544)
29		Phobic disorders treatment (0,778) Antiviral (Arbovirus) (0,697) Leukopoiesis stimulant (0,677) Antieczematic (0,643) Antiischemic, cerebral (0,607) Lipotropic (0,566) Mucositis treatment (0,571) Kidney function stimulant (0,550)

* Only activities with Pa > 0.5 are shown

Table 5: Predicted activities of adamantine TC carboxylic acid derivatives (30-33)

No.	Adamantine TC carboxylic acid derivatives	Predicted activities (Pa)*
30		Phobic disorders treatment (0,810) Cognition disorders treatment (0,783) Kidney function stimulant (0,684) Antiviral (Picornavirus) (0,621) Antiviral (Arbovirus) (0,624) Antinephrotoxic (0,573)

		Fibrinolytic (0,597)
31		Antihypertensive (0,827) Phobic disorders treatment (0,785) Kidney function stimulant (0,663) Antinephrotoxic (0,549) Antieczematic (0,575) Antiviral (0,505)
32		Antidiabetic (0,536) Phobic disorders treatment (0,501)
33		Cognition disorders treatment (0,728) Antiviral (Arbovirus) (0,690) Kidney function stimulant (0,663) Phobic disorders treatment (0,708) Antiviral (Picornavirus) (0,629)

* Only activities with Pa > 0.5 are shown

Concluding Remarks

Synthetic thiirane-containing fatty (carboxylic) acids, steroids and other lipophilic compounds are of great interest to pharmacologists, owing to their diverse biological activities. For example, some thiirane-containing steroids are anabolic hormones. The predicted activities of more than 30 fatty and carboxylic acids were analysed, using the computer program PASS. Thiirane-containing acids show the dominant pharmacological activities of being lipid metabolism regulators, radioprotectors, or hypolipidemic agents - in addition to other less frequent activities.

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Conflict of interest

All authors declare that they have no conflicts of interest.

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