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Pharmacological Activities of Epithio Steroids

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

The present review describes biological activities of semi- and synthetic epithio steroids. About fifty biologically active compounds have shown confirmed antitumor, immunosuppressant, or aromatase inhibition and other activities. More than a quarter of all studied steroids belong to the group of anabolic steroids, and they showed many new and additional activities. Epithio steroids possess mainly cytotoxic activities, although the predicted biological activity showed a broad spectrum of activities. As we found, the position of the epithio group in the core of steroids can significantly change the activity of steroids. The structures, as well as reported and predicted activities of a selection of epithio steroids, are reported. With the computer program PASS based on structure–activity relationships (SAR), some additional activities are also predicted, which point toward new possible applications of these lipids. This review emphasizes the role of epithio steroids as an important source of leads for drug discovery, and they are of great interest to chemists, physicians, biologists, pharmacologists and the pharmaceutical industry.

Keywords: Anabolic; steroids; ethylene sulphides; thiirane; epithio; lipidomics; activities.

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1. INTRODUCTION

The chemistry of thiirane-containing compounds, including lipophilic molecules as steroids, has played a considerable role in the development and use of synthetic materials in the field of medicine, modern organic, bioorganic, medicinal chemistry and the pharmaceutical industry [1-12].

Anabolic steroids are pharmacological drugs that mimic the effect of the male sex hormone testosterone and its derivatives [13-15]. Anabolic steroids accelerate the synthesis of protein within cells, which leads to a pronounced hypertrophy of the muscle tissue, as a result of which they have found wide application in sports medicine and bodybuilding [16-19].

The use of anabolic steroids began in the middle of the 19th century. In 1849, A. Berthold suggested that in the extract from the seminal glands are very active substances. Of course, then their structure remained unsettled. Forty years later, the 72-year-old Professor Brown-Séquard at a meeting of the Paris Biological Society reported on the results of the experiments on himself. He injected himself with the extracts of the guinea pigs and dogs gonads and received a rejuvenating effect [20]. Brown-Séquard extract from testes is called the '*Elixir of Youth*'. According to the author, the extract caused cheerfulness, increased efficiency, muscle strength and sexual activity [21].

The beginning of research in the field of chemistry and pharmacology of hormones belongs to the 20s of the 20th century. In 1935, Ernst Laqueur isolated a male hormone from the testicles of a bull, in the same year the German chemist Adolf Friedrich Johann Butenandt received and described the structure of testosterone, and a week later the Yugoslav chemist Leopold Ruzicka carried out his partial synthesis of cholesterol [22]. In 1939, Ruzicka and Butenandt received the Nobel Prize for the discovery of a method for the synthesis of testosterone from cholesterol.

Semi- and/or synthetic epithio steroids represent a rare group of bioactive lipids since they are hydrophobic molecules insoluble in water, which were not found in nature. Epithio steroids have been reported to possess a variety of cytotoxic activities, and they are widely used as anticancer agents. The thiirane group is an important substance and shows some promising biological activities. Steroids containing an epithio group in positions 2 and 3 belong to anabolic steroids and are widely known and used in sports medicine and are of great interest for the pharmacology of sports and other aspects of medicine [23-26]. The most widely known are such epithio steroids that are used in sports pharmacology and medicine: *epistane* (2α,3α-epithio-17α-methyl-5α-androstan-17β-ol), *epitiostanol* (2α,3α-epithio-5α-androstan-17β-ol, a known potent anti-estrogenic and antitumor agent), *hemapolin* (2α,3α-epithio-17α-methyl-5α-androstan-17β-ol), *mepitiostane* (epitiostanol 17β-methoxy-cyclopentyl ether), *epivol* (2α,3α-epithio-17α-methyletioallocholanol), *epivol black* (2,3α-epithio-17α-methyl-5α-androstan-17β-ol), and *straight epi* (2,3α-Epithio-17α-methyl-etioallo-cholane-17β-ol) [23-30].

Thiirane-containing compounds demonstrated confirmed activity as inhibitors of the peptidase, carboxypeptidase A, gelatinase, aromatase and metalloproteinases [31-36].

Recently, much attention has been focused on epithio steroids for the scarcity of their pharmacological activities. Current review devoted to pharmacological activities of epithio steroids that were estimated using the computer program PASS.

2. STRUCTURE ACTIVITY RELATIONSHIP FOR EPITHIO STEROIDS

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 epithio steroids [37-40]. 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 [41-45].

Semi- and synthetic epithio steroids were used to calculate their pharmacological activity [46-53]. Using MOL or SD files as an input for PASS program, the user may get a list of probable biological activities for any drug-like molecule as an output. For each activity, Pa and Pi values are calculated, which can be interpreted either as the probabilities of a molecule belonging to the classes of active and inactive compounds, respectively, or as the probabilities of the first

and second kind of errors in prediction. A computer analysis of the predicted biological activity spectra showed that 87 types of biological activity are predicted with Pa>70% and 289 with Pa>50%. In a biological activity spectrum estimated by PASS, the activity predicted with the highest probability is called the focal activity. Although the majority of the known biological activities for respective epithio steroids are associated with antineoplastic action, their number is less than 60% among the predicted focal activities.

3. PHAMACOLOGICAL ACTIVITIES OF EPITHIO STEROIDS

Stable oily of epithio steroids useful as a pharmaceutical or veterinary medicine in their strong anti-progestational, anti-estrogenic myogenic, anti-lipeamic, androgenic, anticancer, and other hormonal activities were synthesized and reported during 60-70s [54-71]. Androstane, pregnane, estrane, cholane, cholestane and other similar steroids having an epithio group at the positions 1 and 2; 2 and 3; 3 and 4; 4 and 5; 5 and 6; 6 and 7; 11 and 12; 14 and 15; 15 and 16 or 16 and 17 of the steroid nucleus [54,64-66]. At present, more than 300 synthetic epithio steroids are known [2,4,7,8,46-71]. We selected fifty epithio steroids, which represent all varieties of synthetic epithio steroids, and they are of interest to academic science and the pharmaceutical industry.

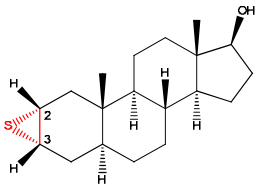
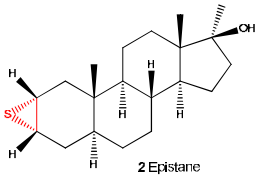
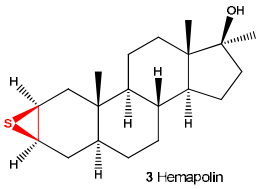
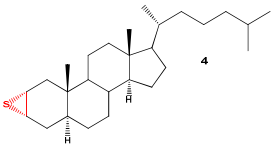
2,3-epithio steroids (**1**-**13**) belong to a large group of anabolic steroids and are of the greatest interest to pharmacologists and lipidomic networks. Two known 2,3-epithio steroids, such as epitiostanol (2α,3α-epithio-5α-androstan-17α-ol) and epistane (17α-methyl-2α,3α-epithio-5α-androstan-17β-ol) methylated prohormone, were both synthesized in the 1960's and used as a treatment for breast cancer, and second steroid used to increase lean muscle mass as well as cutting fat [55-58]. The 2,3-epithio steroids have exhibited other specific physiological activities.

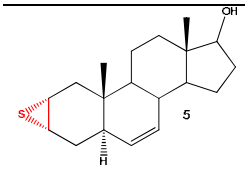
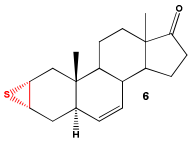
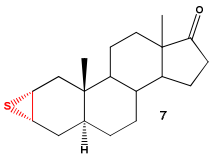
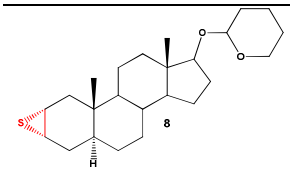
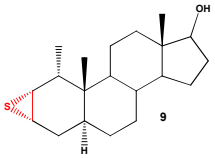
For instance, 2β,3β-epithio-5α-androstan-17β-ol 17-acetate showed inhibition of gonadotropin secretion, and 2α,3α-epithio-5α-androstan-17β-ol 17-acetate showed inhibition of gonadotropin hypersecretion in mice. Both steroids also block ova-implantation and showed myotropic and androgenic activities. The other 2,3-epithio-steroids, 2α,3α-epithio-5α-cholestane, 2β,3β-epithio-5α-cholestane, 2β,3β-epithio-5α-androstan-17β-ol 17-acetate, 2α,3α-epithio-5α-pregnan-20-one, 2β,3β-epithio-5α-pregnan-11β, 17α,21-triol-20-one, 2β,3β-epithio-5α-pregnane-11β-ol-20-one, 2α,3α-epithio-5α-estran-17β-ol, 2α,3α-epithio-5α-estran-17β-ol 17-acetate, 2α, 3α-epithio-5α-estran-17β-ol 17-propionate, 2β, 3β-epithio-5α-androstan-17-one, 2α,3α-epithio-5α-androstan-17-one, 2β,3β-epithio-5α-androstan-17β-ol 17-acetate, 2α,3α-epithio-5α-androstan-17β-ol 17-propionate, 2α,3α-epithio-5α-androstan-17β-ol 17-caprylate, 2α,3α-epithio-5β-androstane-11,17-dione, 2β,3β-epithio-5α-androstane-11,l7-dione, 2α,3α-epithio-17α-methyl-5α-androstan-17β-ol, 2α,3α-epithio-17α-ethyl-5α-androstan-17β-ol, 2α,3α-epithio-17α-vinyl-5α-androstan-17β-ol, 2α,3α-epithio-17α-ethynyl-5α-androstan-17β-ol, 2β,3β-epithio-5α-pregnan-20-one, 2α,3α-epithio-5α-pregnan-20-one, 2α,3α-epithio-5α-pregnane-11,20-dione, 2α,3α-epithio-17α,21-dihydroxy-5α-pregnane-11,20-dione, also showed similar pharmacological activities [55-59,68,69,72].

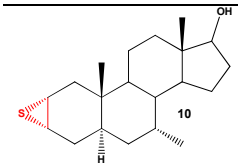
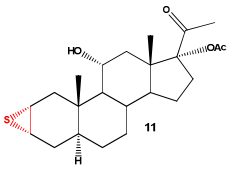
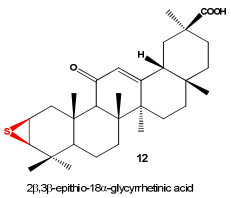
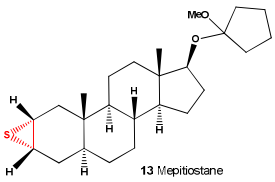
Glycyrrhetinic acid (or glycyrrhetic acid) was isolated from the herb liquorice (*Glycyrrhiza uralensis*) in the 1930s [73,74]. Other physiological activities of glycyrrhetinic acid have also been reported in some reviews [75,76]. Recently, the anticancer agent 2β,3β-epithio-18β-glycyrrhetinic acid (**12**) has been prepared from a natural sample of glycyrrhetinic acid by Kang and co-workers [77]. More other biological activities for compound (**12**) are shown in Table 1.

The 2α,3α-epithio-5α-steroids have a hormonal activity, e.g. myogenic, antiestrogenic, androgenic, anti-lipemic, uterotropic activity, etc. Such useful products include 2α,3α-epithio-5α-androstan-17β-ol, including its esters and ethers, 2α,3α-epithio-5α-androst-6-en-17β-ol, 2β-methyl-2α,3α-epithio-5α-androstan-17β-ol, 3β-methyl-2α,3α-epithio-5α-androstan-17β-ol, 7α-methyl-2α,3α-epithio-5α-andrstan-17β-ol, 17α-methyl-2α,3α-epithio-5α-androstan-17β-ol, 2α,3α-epithio-5α-pregn-20-one, 17α,21-dihydroxy-2α, 3α-epithio-5α-pregnane-11,20-dione, and 2α,3α-epithio-5α-cholestane [60]. Pharmacological confirmed and predicted activities of 2,3-epithio steroids (**1**-**13**) are shown in Table 1.

Table 1. Confirmed and predicted pharmacological activities of anabolic 2,3-epithio steroids (1-13)

2,3-Epithio steroids	Activity reviewed	Activities confirmed (Pa)*	Additional predicted activities (Pa)*
 1 Epitiostanol	Anti-breast cancer, Estrogen receptor antagonist	Antineoplastic (0,964) Antineoplastic (breast cancer) (0,598) Estrogen antagonist (0,860)	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) Dermatologic (0,655) Cytoprotectant (0,654) Antiinflammatory (0,658) Dementia treatment (0,630) Anabolic (0,598)
 2 Epistane	Anti-estrogenic	Antineoplastic (0,966) Estrogen antagonist (0,832)	Antineoplastic (0,966) Antisecretoric (0,952) Antiinflammatory (0,754) Prostate disorders treatment (0,736) Cytostatic (0,681) Prostatic (benign) hyperplasia treatment (0,673) Dermatologic (0,676) Immunosuppressant (0,678) Bone diseases treatment (0,663) Anabolic (0,648) Muscular dystrophy treatment (0,640)
 3 Hemapolin	Anabolic	Antineoplastic (0,966) Estrogen antagonist (0,832) Anabolic (0,648)	Antineoplastic (0,966) Antisecretoric (0,952) Antiinflammatory (0,754) Prostate disorders treatment (0,736) Cytostatic (0,681) Prostatic (benign) hyperplasia treatment (0,673) Dermatologic (0,676) Immunosuppressant (0,678) Bone diseases treatment (0,663) Anabolic (0,648) Muscular dystrophy treatment (0,640)
 4	Anabolic	Antineoplastic (0,932) Bone diseases treatment (0,729) Estrogen antagonist (0,660)	Antineoplastic (0,932) Antisecretoric (0,863) Antieczematic (0,840) Antihypercholesterolemic (0,759) Dermatologic (0,747) Anesthetic general (0,738) Antipruritic (0,732) Bone diseases treatment (0,729) Immunosuppressant (0,732) Antiosteoporotic (0,727) Respiratory analeptic (0,725) Prostate disorders treatment (0,715) Antiinfertility, female (0,709) Biliary tract disorders treatment (0,692) Hypolipemic (0,676) Antipsoriatic (0,659) Cytoprotectant (0,663) Estrogen antagonist (0,660)
	Anabolic	Antineoplastic	Antineoplastic (0,955)

2,3-Epithio steroids	Activity reviewed	Activities confirmed (Pa)*	Additional predicted activities (Pa)*
		(0,955) Anabolic (0,665)	Antisecretoric (0,938) Antiseborrheic (0,814) Estrogen antagonist (0,807) Alopecia treatment (0,750) Prostate disorders treatment (0,716) Cytostatic (0,676) Anabolic (0,665) Immunosuppressant (0,677) Erythropoiesis stimulant (0,643) Dermatologic (0,639)
	Anabolic	Antineoplastic (0,962) Anabolic (0,404)	Antineoplastic (0,962) Antisecretoric (0,841) Male reproductive disfunction treatment (0,800) Prostate disorders treatment (0,735) Estrogen antagonist (0,692) Ovulation inhibitor (0,651) Prostatic (benign) hyperplasia treatment (0,644) Anabolic (0,404)
	Anabolic	Antineoplastic (0,971)	Antineoplastic (0,971) Antisecretoric (0,861) Antiseborrheic (0,830) Male reproductive disfunction treatment (0,808) Estrogen antagonist (0,761) Prostate disorders treatment (0,730) Ovulation inhibitor (0,714) Cardiotonic (0,701) Antineoplastic (breast cancer) (0,671)
	Anabolic	Antineoplastic (0,970) Estrogen antagonist (0,686)	Antineoplastic (0,970) Prostate disorders treatment (0,729) Immunosuppressant (0,729) Estrogen antagonist (0,686) Antisecretoric (0,677) Cardiotonic (0,672) Dermatologic (0,649)
	Anticancer	Antineoplastic (0,883) Cytostatic (0,661) Anabolic (0,467)	Antiseborrheic (0,926) Antisecretoric (0,906) Antineoplastic (0,883) Male reproductive disfunction treatment (0,811) Platelet aggregation inhibitor (0,768) Alopecia treatment (0,763) Estrogen antagonist (0,750) Dermatologic (0,743) Cardiotonic (0,730) Erythropoiesis stimulant (0,705) Immunosuppressant (0,704) Antieczematic (0,711) Prostate disorders treatment (0,684) Neuroprotector (0,694) Cytostatic (0,661) Antiosteoporotic (0,648) Anabolic (0,467)
	Anticancer	Antineoplastic (0,960) Anabolic (0,857)	Antisecretoric (0,965) Antineoplastic (0,960) Estrogen antagonist (0,915) Anabolic (0,857) Antiseborrheic (0,848)

2,3-Epithio steroids	Activity reviewed	Activities confirmed (Pa)*	Additional predicted activities (Pa)*
			Antiosteoporotic (0,729) Cytostatic (0,724) Bone diseases treatment (0,716) Prostate disorders treatment (0,710) Neuroprotector (0,726)
	Anabolic	Antineoplastic (0,939) Anabolic (0,823)	Antisecretoric (0,967) Estrogen antagonist (0,946) Antineoplastic (0,939) Antiinflammatory (0,929) Antiseborrheic (0,849) Anabolic (0,823) Antipruritic (0,812) Immunosuppressant (0,795) Cytostatic (0,787)
	Anticancer	Antineoplastic (0,924) Apoptosis agonist (0,869)	Antisecretoric (0,970) Lipid metabolism regulator (0,954) Antineoplastic (0,924) Antiinflammatory (0,877) Apoptosis agonist (0,869) Hepatoprotectant (0,852) Antiulcerative (0,849) Hepatic disorders treatment (0,808) Diuretic inhibitor (0,798) Antitussive (0,777) Estrogen antagonist (0,495)
	Anti-estrogen, Anti-neoplastic	Antineoplastic (0,974) Estrogen antagonist (0,870)	Antineoplastic (0,974) Estrogen antagonist (0,870) Antisecretoric (0,827) Prostate disorders treatment (0,722) Antiseborrheic (0,710) Immunosuppressant (0,690) Antiprotozoal (Plasmodium) (0,642) Anabolic (0,616) Dermatologic (0,598) Prostatic (benign) hyperplasia treatment (0,583)

** Only activities with Pa > 0.5 are shown*

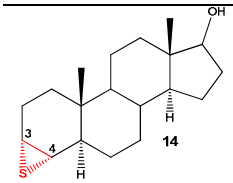
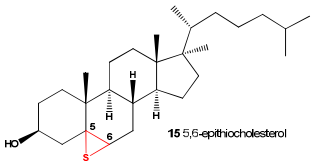
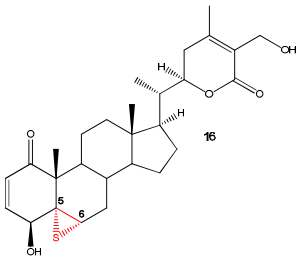
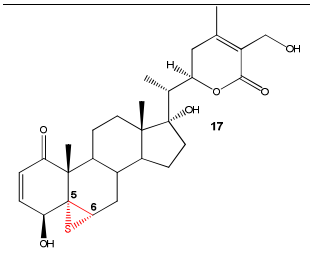
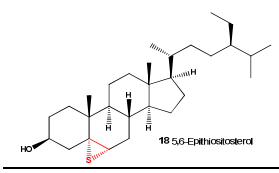
3,4-epithio-5α-androstan-17β-ol and 17-acelate have shown pharmacological activity, i.e. pituitary gonadotrophin inhibiting activity [56]. Several 3,4-epithio steroids, 3β,4β-epithio-5α-androstan-17β-ol, 3α,4α-epithio-5α-androstan-17β-ol, 3α,4α-epithio-5β-androstan-17β-ol 17-acetate, 3α,4α-epithio-5β-androstan-17β-ol, and 3β,4β-epithio-5α-androstan-17β-ol have also shown gonadotrophin activity [57]. Compound (**14**) has shown more than ten pharmacological activities with dominated cardiotonic activity (Table 2).

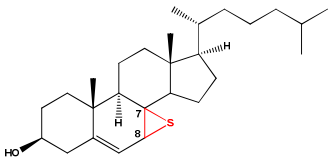
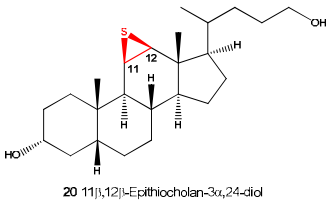
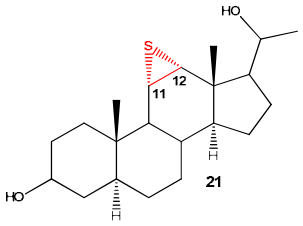
Cholesterol, 7-dehydrocholesterol, lanosterol, dihydrolanosterol, agnosterol, dihydroagnosterol, sitosterol, stigmasterol, and ergosterol having a double bond at the 5 and 6 position in the nucleus of the molecule form an epithio group at the same position. 7-Dehydrocholesterol, lanosterol, dihydrolanosterol, dihydroagnosterol, ergosterol contain a double bond in the 7:8 position and also form an epithio group at the same position. Lanosterol contains a double bond in the 24:25 position in the molecule form epithio group at the same position. Agnosterol occurs in wool fat. It contains three double bonds which are in the 7:8, 9:11, and 24:25 positions in its molecule, and forms an epithio group at the same positions. These sulfurized sterols possess antiseptic, germicidal and fungicidal characteristics which render them especially valuable for use as, or in, skin compounds for the prevention of occupational dermatitis and for the protection of the skin in other ways [78].

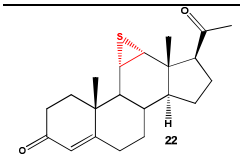
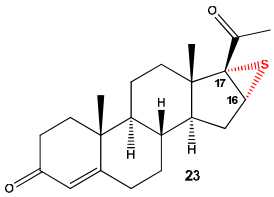
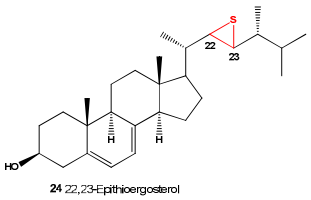
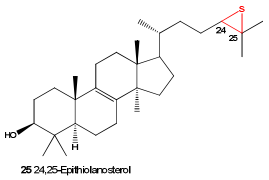
5,6-epithio steroids (**15**-**18**) having more than ten biological activities with a maximum for:

(**15**) - antieczematic, for (**16** and **17**) – anticancer and for compound (**18**) - cholesterol antagonist activities. 7,8-epithio steroid (**19**) showing respiratory analeptic, cholesterol antagonist and anti-hypercholesterolemic activities (Table 2).

Table 2. Confirmed and predicted pharmacological activities of epithio steroids (14-25)

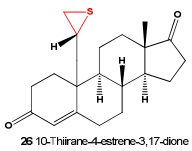
Epithio steroids	Activity reviewed	Activities confirmed (Pa)*	Additional predicted activities (Pa)*
 **14**	Gonadotrophin inhibitor	Antineoplastic (0,868)	Cardiotonic (0,925) Antiseborrheic (0,869) Antineoplastic (0,868) Antiarrhythmic (0,858) Antisecretoric (0,854) Alopecia treatment (0,806) Atherosclerosis treatment (0,798) Antiinflammatory (0,733) Erythropoiesis stimulant (0,720) Prostate disorders treatment (0,688) Estrogen antagonist (0,615)
 **15** 5,6-epithiocholesterol	Antiseptic, Germicidal Fungicidal	Antineoplastic (0,780) Immunosuppressant (0,751)	Anesthetic general (0,847) Antisecretoric (0,804) Antieczematic (0,811) Antipruritic (0,768) Antineoplastic (0,780) Hepatoprotectant (0,763) Immunosuppressant (0,751) Antiinflammatory (0,739) Respiratory analeptic (0,718) Antihypercholesterolemic (0,715) Estrogen antagonist (0,410)
 **16**	Anticancer	Antineoplastic (0,874)	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) Angiogenesis inhibitor (0,711) Prostate disorders treatment (0,572)
 **17**	Anticancer	Antineoplastic (0,872) Antineoplastic (breast cancer) (0,449)	Antieczematic (0,929) Cytostatic (0,926) Hepatoprotectant (0,923) Macular degeneration treatment (0,824) Immunosuppressant (0,819) Hepatic disorders treatment (0,816) Apoptosis agonist (0,790) Prostate disorders treatment (0,565)
 **18** 5,6-Epithiositosterol	Antiseptic, Germicidal, Fungicidal	Hepatoprotectant (0,850) Hepatic disorders treatment (0,761)	Cholesterol antagonist (0,933) Antihypercholesterolemic (0,929) Respiratory analeptic (0,892) Antieczematic (0,884) Hepatoprotectant (0,850) Anesthetic general (0,850) Hypolipemic (0,818)

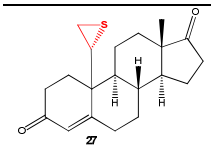
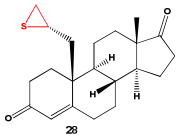
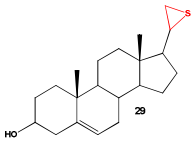
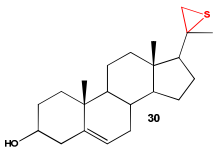
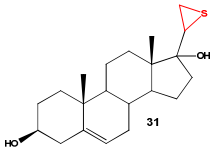
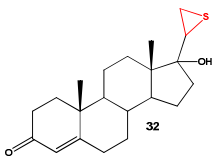
Epithio steroids	Activity reviewed	Activities confirmed (Pa)*	Additional predicted activities (Pa)*
			Antineoplastic (0,804) Antiosteoporotic (0,793) Bone diseases treatment (0,793) Immunosuppressant (0,770) Analeptic (0,764) Hepatic disorders treatment (0,761) Apoptosis agonist (0,763) Estrogen antagonist (0,443)
 **19** 7,8-Epithio-7-dehydrocholesterol	Antiseptic, Germicidal, Fungicidal	Hepatoprotectant (0,808)	Respiratory analeptic (0,963) Cholesterol antagonist (0,946) Antihypercholesterolemic (0,930) Anesthetic general (0,913) Antieczematic (0,891) Analeptic (0,876) Hepatoprotectant (0,808) Antipruritic (0,798) Immunosuppressant (0,781) Hypolipemic (0,781) Neuroprotector (0,777) Antineoplastic (0,779) Bone diseases treatment (0,754) Apoptosis agonist (0,707) Estrogen antagonist (0,465)
 **20** 11β,12β-Epithiocholan-3α,24-diol	DOCA inhibitor	Cardiotonic (0,886) Antineoplastic (0,775)	Cholesterol antagonist (0,932) Anesthetic general (0,923) Respiratory analeptic (0,919) Antihypercholesterolemic (0,900) Cardiotonic (0,886) Choleretic (0,871) Analeptic (0,872) Hepatoprotectant (0,853) Cytoprotectant (0,848) Atherosclerosis treatment (0,838) Antieczematic (0,829) Antisecretoric (0,813) Antipruritic (0,810) Antiarrhythmic (0,772) Immunosuppressant (0,768) Antineoplastic (0,775) Hypolipemic (0,746) Estrogen antagonist (0,611)
 **21**	DOCA inhibitor	Cardiotonic (0,941) Antineoplastic (0,745)	Respiratory analeptic (0,959) Cardiotonic (0,941) Analeptic (0,877) Antiarrhythmic (0,844) Atherosclerosis treatment (0,805) Erythropoiesis stimulant (0,801) Antiseborrheic (0,795) Anesthetic general (0,778) Antisecretoric (0,754) Neuroprotector (0,762) Anesthetic (0,744) Choleretic (0,742) Immunosuppressant (0,740) Antineoplastic (0,745) Estrogen antagonist (0,441)
	DOCA inhibitor	Cardiotonic (0,883) Antineoplastic (0,766)	Anesthetic general (0,897) Cardiotonic (0,883) Antiarrhythmic (0,806) Antisecretoric (0,805)

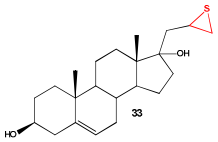
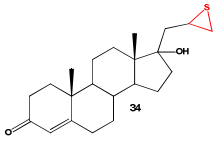
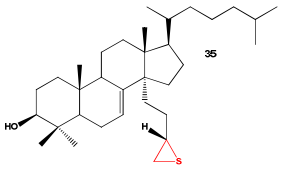
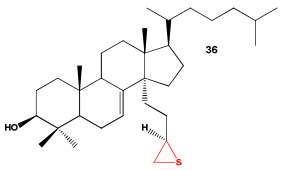
Epithio steroids	Activity reviewed	Activities confirmed (Pa)*	Additional predicted activities (Pa)*
 11α,12α-epithioprogesterone			Atherosclerosis treatment (0,774) Antiinflammatory (0,776) Ovulation inhibitor (0,761) Neuroprotector (0,771) Antineoplastic (0,766) Estrogen antagonist (0,636)
 16α,17α-epithioprogesterone	DOCA inhibitor	Cardiotonic (0,936) Antineoplastic (0,912)	Cardiotonic (0,936) Antineoplastic (0,912) Antisecretoric (0,857) Ovulation inhibitor (0,810) Antiseborrheic (0,815) Respiratory analeptic (0,781) Anesthetic general (0,746) Prostate disorders treatment (0,717) Antipruritic (0,707) Cholesterol antagonist (0,690) Estrogen antagonist (0,556)
 24 22,23-Epithioergosterol	Cholesterol antagonist	Cholesterol antagonist (0,858)	Antihypercholesterolemic (0,865) Cholesterol antagonist (0,858) Hepatic disorders treatment (0,792) Antieczematic (0,788) Hepatoprotectant (0,762) Anesthetic general (0,759) Dermatologic (0,748) Antineoplastic (0,756) Antipsoriatic (0,731)
 25 24,25-Epithiolanosterol	Cholesterol antagonist	Cholesterol antagonist (0,754)	Antieczematic (0,901) Antiinfertility, female (0,841) Hepatoprotectant (0,834) Antineoplastic (0,828) Hypolipemic (0,805) Hepatic disorders treatment (0,791) Apoptosis agonist (0,785) Antiinflammatory (0,783) Cholesterol antagonist (0,754) Atherosclerosis treatment (0,657)

** Only activities with Pa > 0.5 are shown*

Table 3. Confirmed and predicted pharmacological activities of thiiranyl steroids (26-36)

Thiiranyl-containing steroids	Activity reviewed	Activities confirmed (Pa)*	Additional predicted activities (Pa)*
 26 10-Thiirane-4-estrene-3,17-dione	Estrogen synthetase inhibitor (aromatase inhibitor)	Aromatase inhibitor (0,884) Antineoplastic (0,806)	Male reproductive disfunction treatment (0,896) Antineoplastic (0,806) Neuroprotector (0,690) Prostate disorders treatment (0,656) Dermatologic (0,642) Antiosteoporotic (0,618) Alopecia treatment (0,607) Bone diseases treatment (0,605) Prostatic (benign) hyperplasia treatment (0,541) Anti-ischemic, cerebral (0,574) Immunosuppressant (0,528)
	Aromatase	Aromatase	Male reproductive disfunction treatment

Thiiranyl-containing steroids	Activity reviewed	Activities confirmed (Pa)*	Additional predicted activities (Pa)*
	inhibitor	inhibitor (0,884) Antineoplastic (0,806)	(0,896) Aromatase inhibitor (0,884) Antineoplastic (0,806) Neuroprotector (0,690) Prostate disorders treatment (0,656) Dermatologic (0,642) Alopecia treatment (0,607) Bone diseases treatment (0,605) Prostatic (benign) hyperplasia treatment (0,541) Anti-ischemic, cerebral (0,574) Immunosuppressant (0,528)
	Aromatase inhibitor	Aromatase inhibitor (0,854) Antineoplastic (0,746)	Aromatase inhibitor (0,854) Ovulation inhibitor (0,750) Antineoplastic (0,746) Male reproductive disfunction treatment (0,720) Antiseborrheic (0,722) Antiobesity (0,684) Prostate disorders treatment (0,677) Antineoplastic (breast cancer) (0,672) Antidiabetic (0,636)
	Not studied		Neuroprotector (0,866) Cholesterol antagonist (0,839) Ovulation inhibitor (0,776) Antineoplastic (0,758) Respiratory analeptic (0,744) Antisecretoric (0,737) Antihypercholesterolemic (0,737) Apoptosis agonist (0,730) Estrogen antagonist (0,455)
	Not studied		Cholesterol antagonist (0,916) Respiratory analeptic (0,903) Anesthetic general (0,858) Ovulation inhibitor (0,855) Antisecretoric (0,853) Antihypercholesterolemic (0,836) Antiseborrheic (0,828) Hypolipemic (0,801) Neuroprotector (0,797) Antineoplastic (0,798) Hepatoprotectant (0,731)
	Not studied		Neuroprotector (0,916) Cholesterol antagonist (0,893) Respiratory analeptic (0,832) Antineoplastic (0,819) Apoptosis agonist (0,810) Ovulation inhibitor (0,794) Cardiotonic (0,788) Antiinflammatory (0,779) Antihypercholesterolemic (0,771) Hepatoprotectant (0,731) Estrogen antagonist (0,604)
	Not studied		Antiseborrheic (0,851) Neuroprotector (0,827) Antineoplastic (0,804) Cholesterol antagonist (0,784) Ovulation inhibitor (0,780) Anesthetic general (0,773) Diuretic (0,770)

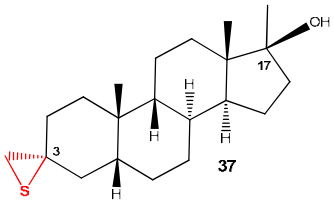
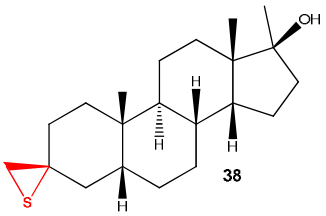
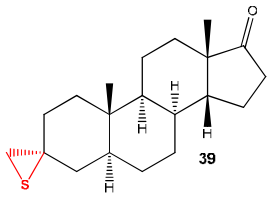
Thiiranyl-containing steroids	Activity reviewed	Activities confirmed (Pa)*	Additional predicted activities (Pa)*
			Respiratory analeptic (0,772) Antiinflammatory (0,764) Antipruritic (0,752) Apoptosis agonist (0,752)
	Not studied		Muscular dystrophy treatment (0,873) Antihypercholesterolemic (0,872) Ovulation inhibitor (0,865) Acute neurologic disorders treatment (0,849) Antiseborrheic (0,835) Antineoplastic (0,822) Cholesterol antagonist (0,817) Antiinflammatory (0,779) Respiratory analeptic (0,775) Antisecretoric (0,743) Hepatoprotectant (0,724)
	Not studied		Antiseborrheic (0,895) Ovulation inhibitor (0,855) Acute neurologic disorders treatment (0,854) Antineoplastic (0,809) Antisecretoric (0,784) Antiinflammatory (0,765) Antipruritic (0,753) Diuretic (0,738) Antihypercholesterolemic (0,718) Cholesterol antagonist (0,701) Estrogen antagonist (0,529)
	Sterol biosynthesis inhibitor	Cholesterol synthesis inhibitor (0,634)	Hepatoprotectant (0,859) Cholesterol antagonist (0,824) Hypolipemic (0,781) Hepatic disorders treatment (0,762) Antineoplastic (0,755) Anti-ulcerative (0,727) Antiinfertility, female (0,724) Chemopreventive (0,716) Apoptosis agonist (0,709) Antifungal (0,668) Antihypercholesterolemic (0,655)
	Sterol biosynthesis inhibitor	Cholesterol synthesis inhibitor (0,634)	Hepatoprotectant (0,859) Cholesterol antagonist (0,824) Hypolipemic (0,781) Hepatic disorders treatment (0,762) Antineoplastic (0,755) Anti-ulcerative (0,727) Antiinfertility, female (0,724) Chemopreventive (0,716) Apoptosis agonist (0,709) Antifungal (0,668) Antihypercholesterolemic (0,655)

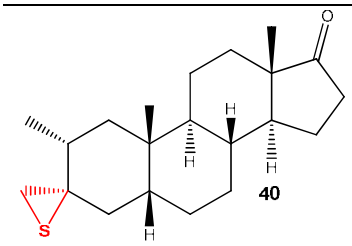
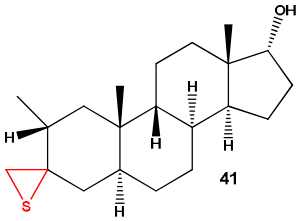
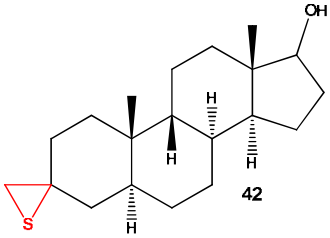
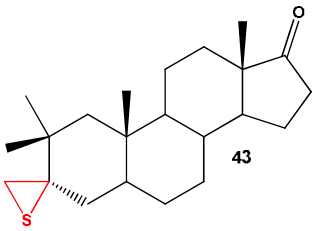
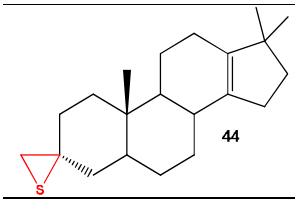
** Only activities with Pa > 0.5 are shown*

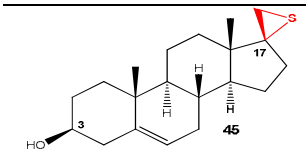
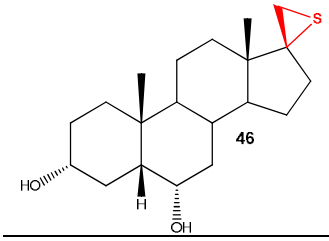
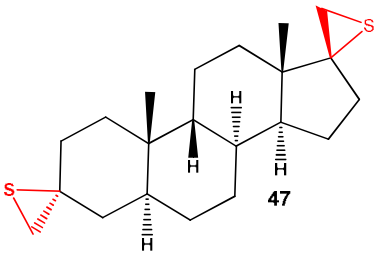
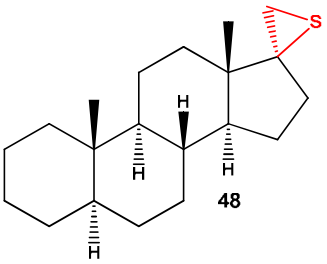
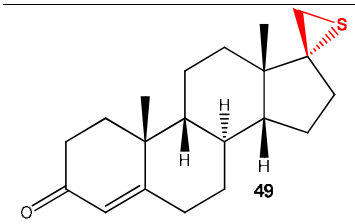
Withanolides, steroidal lactones, showed antimicrobial, anticancer, antiproliferative, anti-inflammatory and antiarthritic activities have been isolated from the Indian plant *Withania somnifera* and related species [79-81]. Anticancer agents, thiirane withanolide derivatives, were prepared (**16** and **17**), and their activity was reported [82].

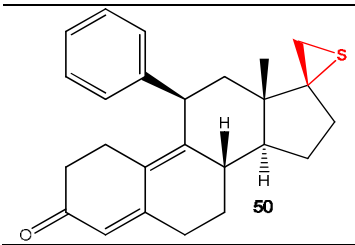
All prepared of 11,12-epithiopregnanes (11α,12α-epithio-5α-pregnane, 11β,12β-epithio-5α-pregnane, 3α-hydroxy-11α,12α-epithio-5β-pregnane, 3β-hydroxy-11α,12α-epithio-5α-pregnane, 3β,20β-dihydroxy-11α,12α-epithio-5α-pregnane, 3β,20β-diacetyloxyl-1α,12α-epithio-5α-pregnane, 3β,20β-diacetyloxy-11α,12α-epithio-5α-pregnane, 3,20-dioxo-11α, 12α-epithio-5α-pregnane, 3,20-dioxo-11α, 12α-epithio-5α-pregnane, 3,20-dioxo-11α,12α-epithio-4-pregnene, 3,3-ethylenedioxy-11α,12α-epithio-5-pregnene, 3α-hydroxy-11β,12β-epithio-5β-pregnane, 3β-hydroxy-11β,12β-epithio-5α-pregnane, 3β,20β-dihydroxy-11β,12β-epithio-5α-pregnane, 3β,20β-diacetyloxy-11β,12β-epithio-5α-pregnane, 3β,20β,-diacetyloxy-11β,12β-epithio-5β-pregnane, 3,20-dioxo-11β,12β-epithio-5α-pregnane, 3,20-dioxo-11β,12β-epithio-5β-pregnane, 3,20-dioxo-11β,12β-epithio-4-pregnene, and 3,3-ethylenedioxy-11β,12β-epithio-5-pregnene) having pharmacological activities have been synthesized from corresponding 11,12-epoxypregnanes (11α,12α-epoxypregnanes and 11β,12β-epoxy-pregnanes). All obtained 11,12-epithiopregnanes have been characterized by showing anti-DOCA (desoxycorticosterone acetate) activity in general. For instance, 3β,20β-dihydroxy-11β,12β-epithio-5α-pregnane showed the inhibition of the response caused by 10 μg of DOCA. Other 11,12-epithiopregnanes also show a similar activity. Accordingly, they are useful as anti-DOCA agents [56].

Table 4. Predicted pharmacological activities of 3,2'- and 17,2'- thiirane steroids (37-50)

Thiirane-containing steroids	Activities confirmed (Pa)*	Additional predicted activities (Pa)*
 37 3,2'-thiiran-(2'*S*,5*R*,8*S*,9*R*,10*S*,13*S*,14*S*,17*S*)-10,13,17-trimethyl-5β-androstane-17-ol	Not studied	Antisecretoric (0,823) Antineoplastic (0,781) Prostate disorders treatment (0,725) Antitoxic (0,692) Dermatologic (0,691) Prostatic (benign) hyperplasia treatment (0,666) Antiosteoporotic (0,665) Muscular dystrophy treatment (0,636) Analeptic (0,631) Anti-inflammatory (0,633) Bone diseases treatment (0,617)
 38	Not studied	Antisecretoric (0,823) Antineoplastic (0,781) Prostate disorders treatment (0,725) Antitoxic (0,692) Dermatologic (0,691) Prostatic (benign) hyperplasia treatment (0,666) Antiosteoporotic (0,665) Muscular dystrophy treatment (0,636) Analeptic (0,631) Anti-inflammatory (0,633) Bone diseases treatment (0,617)
 39	Not studied	Male reproductive disfunction treatment (0,825) Antineoplastic (0,768) Prostate disorders treatment (0,718) Dermatologic (0,651) Erythropoiesis stimulant (0,647) Alopecia treatment (0,642) Analeptic (0,646) Prostatic (benign) hyperplasia treatment (0,629)
	Not studied	Male reproductive disfunction treatment (0,826) Antineoplastic (0,787) Cholesterol antagonist (0,775)

Thiirane-containing steroids	Activities confirmed (Pa)*	Additional predicted activities (Pa)*
 **40**		Antisecretoric (0,739) Prostate disorders treatment (0,723) Analeptic (0,703) Dermatologic (0,675) Antihypercholesterolemic (0,657) Erythropoiesis stimulant (0,655) Prostatic (benign) hyperplasia treatment (0,647) Antiosteoporotic (0,645) Bone diseases treatment (0,637)
 **41** 3,2'-thiiran-(2*R*,5*S*,8*S*,9*R*,10*S*,13*S*,14*S*,17*R*)-2,10,13-trimethyl-5α-androstane-17-ol	Not studied	Antiseborrheic (0,924) Antisecretoric (0,888) Alopecia treatment (0,799) Antieczematic (0,797) Antihypercholesterolemic (0,775) Antineoplastic (0,786) Anesthetic general (0,770) Respiratory analeptic (0,764) Erythropoiesis stimulant (0,746) Bone diseases treatment (0,747) Antiosteoporotic (0,743) Hepatoprotectant (0,716) Prostate disorders treatment (0,702) Estrogen antagonist (0,470)
 **42**	Not studied	Antiseborrheic (0,905) Alopecia treatment (0,819) Antisecretoric (0,810) Antineoplastic (0,768) Antieczematic (0,763) Erythropoiesis stimulant (0,740) Anesthetic general (0,707) Cholesterol antagonist (0,705) Prostate disorders treatment (0,696) Antiosteoporotic (0,653) Bone diseases treatment (0,646) Antihypercholesterolemic (0,560)
 **43**	Not studied	Antiseborrheic (0,845) Male reproductive disfunction treatment (0,838) Antineoplastic (0,778) Respiratory analeptic (0,762) Cholesterol antagonist (0,745) Analeptic (0,741) Prostate disorders treatment (0,726) Ovulation inhibitor (0,691) Antieczematic (0,710)
 **44**	Not studied	Antieczematic (0,819) Dermatologic (0,769) Antiseborrheic (0,777) Prostate disorders treatment (0,692) Antipsoriatic (0,679) Antineoplastic (0,697) Antiosteoporotic (0,559)
	Not studied	Cholesterol antagonist (0,875) Ovulation inhibitor (0,804) Antineoplastic (0,774) Antisecretoric (0,728) Neuroprotector (0,726) Anti-inflammatory (0,711) Dermatologic (0,685) Muscular dystrophy treatment (0,671)

Thiirane-containing steroids	Activities confirmed (Pa)*	Additional predicted activities (Pa)*
 17,2'-thiiran-(2'*R*,3*S*,8*R*,9*S*,10*R*,13*S*,14*R*)-10,13-dimethyl-androstane-3-ol		Prostate disorders treatment (0,671) Apoptosis agonist (0,656) Antihypercholesterolemic (0,649)
	Not studied	Antiseborrheic (0,846) Cholesterol antagonist (0,809) Respiratory analeptic (0,804) Erythropoiesis stimulant (0,778) Antieczematic (0,763) Hepatic disorders treatment (0,744) Antineoplastic (0,754) Hepatoprotectant (0,735) Alopecia treatment (0,731) Hypolipemic (0,693)
	Not studied	Prostate disorders treatment (0,710) Erythropoiesis stimulant (0,696) Alopecia treatment (0,689) Dermatologic (0,668) Antisecretoric (0,630) Cytoprotectant (0,633) Prostatic (benign) hyperplasia treatment (0,619) Dementia treatment (0,577) Male reproductive disfunction treatment (0,572) Antineoplastic (0,562)
	Not studied	Antieczematic (0,745) Alopecia treatment (0,731) Prostate disorders treatment (0,716) Erythropoiesis stimulant (0,696) Antisecretoric (0,696) Dermatologic (0,683) Cholesterol antagonist (0,679) Cytoprotectant (0,655) Antineoplastic (0,644) Ovulation inhibitor (0,640) Prostatic (benign) hyperplasia treatment (0,628)
	Not studied	Ovulation inhibitor (0,830) Antisecretoric (0,754) Antineoplastic (0,764) Alopecia treatment (0,742) Cholesterol antagonist (0,734) Prostate disorders treatment (0,721) Diuretic (0,718) Antipruritic (0,713) Dermatologic (0,706)
	Not studied	Antineoplastic (0,713) Gynecological disorders treatment (0,676) Alopecia treatment (0,669) Contraceptive (0,661) Psychosexual dysfunction treatment (0,637) Ovulation inhibitor (0,637) Menopausal disorders treatment (0,619) Prostate disorders treatment (0,587) Male reproductive disfunction treatment (0,562)

Thiirane-containing steroids	Activities confirmed (Pa)*	Additional predicted activities (Pa)*
 **50**		Dermatologic (0,561) Antiosteoporotic (0,531)

** Only activities with Pa > 0.5 are shown*

11,12-epithio steroids [20-22] showed more than 10 different activities, with a dominance in [20]: cholesterol antagonist, anesthetic general, respiratory analeptic and anti-hypercholesterolemic activities; in [21] respiratory analeptic and cardiotonic and for steroid [22], 2 equally important activities are characteristic: anesthetic and cardiotonic (Table 3).

Several 16,17-epithioandrostanes, 3α-hydroxy-16β,17β-epithio-5β-androstane, 3β-hydroxy-16β,17β-epithio-5α-androstane, 3-oxo-16β,17β-epithio-5α-androstane, 3-oxo-16β,17β-epithio-5β-androstane, 3-oxo-16β,17β-epithio-4-androstene, 3-oxo-16β,17β-epithio-1,4-androstadiene, 3α, 11β-dihydroxy-16β,17β-epithio-5β-andro-stane, 3β-hydroxy-11-oxo-16β,17β-epithio-5α-andro-stane, 3,11-dioxo-16β,17β-epithio-4-andro-stene, 3,11-dioxo-16β,17β-epithio-1,4-androsta-diene, 16α,17α-epithio-5α-androstane, showed anti-DOCA activity, some from them showed a strong inhibition of DOCA: 3-oxo-16β,17β-epithio-4-androstene, 3-oxo-16β,17β-epithio-1,4-androsta-diene, 3-oxo-16β,17β-epithio-4,6-andro-stadiene and 3β-hydroxy-16β,17β-epithio-5α-androstane [57,58]. 16α,17α-epithio-progesterone (**23**) showed more than ten activities at Pa > 0.5 with dominated antineoplastic and cardiotonic activities (Table 3).

Two types of epithio steroids (**24** and **25**) contain the epithio group at positions 22 and 23 or 24 and 25 in the hydrocarbon tails of cholesterol and lanosterol, respectively. Both steroids showed cholesterol antagonist activity (Table 2). Thiiranyl steroids (**26**-**36**) have been synthesized and have shown biological activities (Table 3) [83,84]. It is known that 10-thiiranyl-4-estrene-3,17-diones (**26** and **27**) are an inhibitor of estrogen synthetase from human placental microsomes [84]. Thiiranyl steroids (**35** and **36**) were synthesized as inhibitors of lanosterol 14α-demethylase ($P450_{14DM}$) and also inhibited cholesterol biosynthesis [83]. Their activity was confirmed using our computer program PASS (Table 3).

An interesting group of thiirane-containing steroids that are derivatives, or analogues of α- and/or β-androstanes (**37**-**50**) are presented in Table 4, including structures and activities. Steroids (**37**-**44**) contain the epithio group in position 3, and steroids (**45**-**50**) contain this group in position 17. Dominated activities for compounds (**37**-**44**) were antiseborrheic, antiseborrheic, antineoplastic, alopecia treatment, dermatologic, cholesterol antagonist, ovulation inhibitor, gynecological disorders treatment, and others activities (see Table 4).

4. CONCLUSION

Semi- and synthetic epithio steroids possess mainly cytotoxic activities, although the predicted biological activity showed a broad spectrum of activities. As we found, the position of the epithio group in the core of steroids can significantly change the activity of steroids. A variety of activities is presented in the table data. The most characteristic activities, which have been found are antineoplastic, anti-secretoric, antiviral, antidiabetic, anti-ischemic, phobic disorders treatment, lipid metabolism regulator and others. The biological profile of these new generations of thiirane-containing metabolites presents much progress with regards to the old compounds. The results obtained are of great interest to sports physicians, chemists, pharmacologists and the pharmaceutical industry.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

ACKNOWLEDGEMENTS

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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