



## **Biological Activities of Nitro 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 the biological activities of synthetic nitro steroids. More than fifty biologically active nitro steroids showed an analeptic, antineoplastic, anesthetic, neuroprotector, immunosuppressant, dermatologic properties, and also show other biological activities. The structures and activities of a selection of nitro steroids are reported. Also, some new and additional activities are predicted with the computer program PASS, based on structure–activity relationships (SAR), which point toward new possible applications of these lipid compounds. This review emphasizes the role of the nitro steroids, as an important source of leads for drug discovery.

**Keywords:** Nitro group; steroids; lipids; pharmacology; activities; analeptic; antineoplastic; SAR; PASS.

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## 1. INTRODUCTION

Nitro-containing compounds are natural or synthetic compounds containing a nitro group linked to a basic molecule by a C-N bond. The vast majority of nitro aliphatic and aromatic compounds are synthetic, although biologically produced nitro-containing metabolites have been identified [1-4]. Nitro group-containing compounds are widely distributed in nature [5-8]. The most famous group of nitro-containing natural compounds is the aristolochic acid and its derivatives, which are found in the *Aristolochia* species (family Aristolochiaceae) [9-11]. It is also known that *Streptomyces* and *Penicillium* members produce a wide range of antibiotics, including simple nitroaromatic metabolites, as well as more complex ones, such as siderophores or cyclic heptapeptides [5,12-15]. According to the *Dictionary of Natural Compounds*, about 900 natural compounds containing one or more nitro group(s) are known today [16].

Nitro group is found in aliphatic and aromatic hydrocarbons, fatty and carboxylic acids, terpenoids, as well as in heterocyclic compounds and peptides [10-15]. Nitro group not only provides a charge of the molecule, but also imparts unique properties that make the nitro group an important functional group in chemical synthesis. The nitro group is an excellent electron acceptor. Nitro group is used in many organic reactions, and its easy transformation into various functional groups aggravates the importance of nitro compounds in the synthesis of complex molecules [1-4,17,18].

In recent years, numerous review articles have examined the toxicity and mutagenicity of nitro containing compounds, the biosynthesis and the biodegradation of these compounds [19-22].

We selected fifty steroids in which the nitro group is in different positions of the steroid skeleton. 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 52 nitro steroids. This is the first time to study the biological activity of nitro steroids widely and qualitatively.

## 2. BIOLOGICAL ACTIVITIES OF NITRO STEROIDS

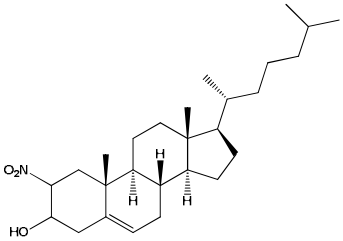
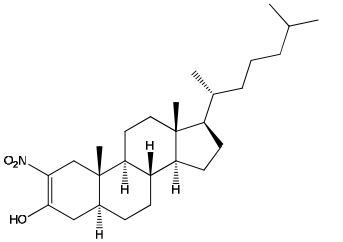
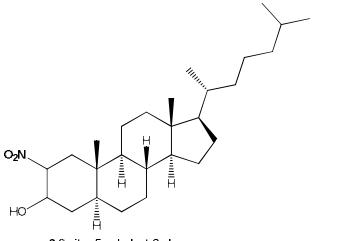
Surprisingly, but in nature has not been found so far, steroids containing a nitro group. Currently, about 300 nitro synthetic steroids are known [1-4,23-25]. Many of these compounds exhibit antitumor, antibacterial, antifungal and other activities [26].

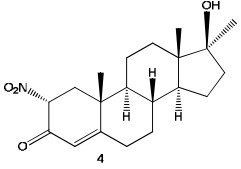
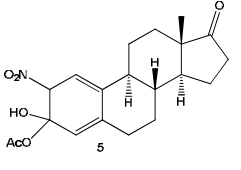
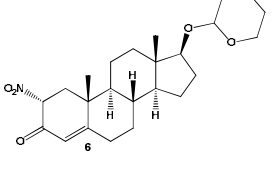
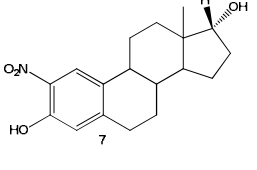
All nitro steroids that are selected for the study are divided into six groups. The first group includes steroids that contain a nitro group in the second position (**1-10**, Table 1). The second group includes anabolic steroids containing a nitro group in the third position (**11-20**, Table 2). The third group includes steroids containing the nitro group in the fourth position (**21-30**, Table 3). The fourth group includes steroids containing the nitro group in the sixth position (**31-39**, Table 4). The fifth group includes steroids containing the nitro group in the seventh position (**40-43**, Table 5). And the last group that includes the nitro group at positions 11, 16, 17, 20, and 21 in the skeleton of steroids (**44-52**, Table 6).

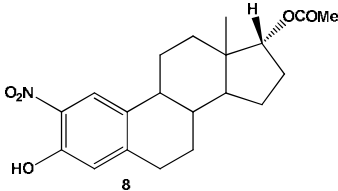
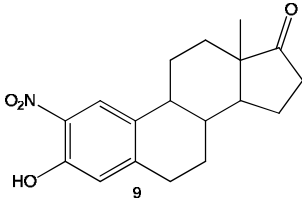
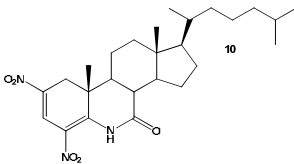
2-Nitro-3-oxo steroids (**4**) showed significant activity and inhibited the growth of communicable pathogen fungi *Trichophyton mentogrophytes* and *Microsporzzm gypseuin* [27]. 2-Nitro-3-oxo steroids are widely used as fungicides against dermatophytosis, a superficial fungal skin disease. 2-Nitro-cholestan-3-one, 2-nitro-cholestan-3 $\beta$ -ol, 2-nitro-cholestene and 2-nitro-cholestane have been synthesized [28]. Synthetic 2-nitro steroids (**7-9**) showed antitumor activity, which confirmed by us using PASS program [26]. 2- and 4-Nitro-steroids (**10**) showed a wide range of biological activities [29]. Synthesis of other 2-nitro steroids has also been described [17,26,30,31]. The dominant activities that are characteristic of 2-nitro steroids are: antineoplastic, immunosuppressant, bone diseases inhibitor, analeptic, dermatologic and many others properties (Table 1).

It should be noted some of the special properties of 2-Nitro steroids, except those that relate to the basic properties. Thus, some steroids from this class of compounds exhibit anesthetic, analeptic and antipruritic properties. In addition, some steroids can be used as dermatologic agents for the treatment of skin, nail or hair diseases. Contraceptive properties are also characteristic of some 2-Nitro steroids (see Table 1).

**Table 1. Confirmed and predicted pharmacological activities of 2-nitro steroids (1-10)**

2-Nitro steroids	Activity reviewed	Activities confirmed (Pa)*	Additional predicted activities (Pa)*
 <p data-bbox="305 674 456 695">1,2-nitro-cholest-5-en-3-ol</p>	Not studied		Respiratory analeptic (0,951) Anesthetic general (0,929) Antihypercholesterolemic (0,908) Analeptic (0,847) Anesthetic (0,815) Antieczematic (0,810) Antipruritic (0,799) Neuroprotector (0,785) Antineoplastic (0,784) Immunosuppressant (0,782) Dermatologic (0,747) Chemopreventive (0,733) Hepatoprotectant (0,713) Prostate disorders treatment (0,712) Bone diseases treatment (0,712) Proliferative diseases treatment (0,706) Antiosteoporotic (0,703)
 <p data-bbox="305 1304 456 1325">2,2-nitro-5,7-cholest-2-en-3-ol</p>	Not studied		Respiratory analeptic (0,962) Anesthetic general (0,917) Analeptic (0,873) Antihypercholesterolemic (0,845) Antieczematic (0,819) Antineoplastic (0,798) Dermatologic (0,758) Choleric (0,745) Antiosteoporotic (0,716) Bone diseases treatment (0,714) Prostate disorders treatment (0,708)
 <p data-bbox="305 1703 456 1724">3,2-nitro-5,7-cholest-3-ol</p>	Not studied		Respiratory analeptic (0,953) Anesthetic general (0,951) Analeptic (0,865) Antihypercholesterolemic (0,839) Antieczematic (0,835) Antipruritic (0,806) Immunosuppressant (0,763) Antineoplastic (0,762) Hepatoprotectant (0,742) Dermatologic (0,740) Antiosteoporotic (0,715) Bone diseases treatment (0,713) Antifungal (0,710)

2-Nitro steroids	Activity reviewed	Activities confirmed (Pa)*	Additional predicted activities (Pa)*
 <p>4</p>	Fungicide		Antiseborrheic (0,893) Respiratory analeptic (0,867) Ovulation inhibitor (0,841) Muscular dystrophy treatment (0,813) Antineoplastic (0,808) Antisecretoric (0,798) Antiinflammatory (0,751) Analeptic (0,741) Antipruritic (0,733) Prostate disorders treatment (0,719) Prostatic (benign) hyperplasia treatment (0,707)
 <p>5</p>	Not studied		Antiseborrheic (0,909) Ovulation inhibitor (0,872) Antineoplastic (0,818) Respiratory analeptic (0,809) Neuroprotector (0,787) Analeptic (0,769) Alopecia treatment (0,746) Acute neurologic disorders treatment (0,705) Menopausal disorders treatment (0,689) Prostate disorders treatment (0,660)
 <p>6</p>	Not studied		Antineoplastic (0,870) Immunosuppressant (0,723) Prostate disorders treatment (0,716) Contraceptive (0,695) Dermatologic (0,656) Prostatic (benign) hyperplasia treatment (0,651) Ovulation inhibitor (0,646) Respiratory analeptic (0,636) Anesthetic general (0,606) Antiinflammatory (0,618)
 <p>7</p>	Anticancer	Antineoplastic (0,792) Bone diseases treatment (0,734) Prostate disorders treatment (0,695)	Alopecia treatment (0,924) Antiseborrheic (0,925) Anesthetic general (0,882) Neuroprotector (0,815) Antisecretoric (0,793) Antineoplastic (0,792) Ovulation inhibitor (0,772) Acute neurologic disorders treatment (0,761) Respiratory analeptic (0,744) Bone diseases treatment (0,734)

2-Nitro steroids	Activity reviewed	Activities confirmed (Pa)*	Additional predicted activities (Pa)*
			Antiosteoporotic (0,734) Prostate disorders treatment (0,695)
 8	Anticancer	Antineoplastic (0,784)	Antiseborrheic (0,962) Alopecia treatment (0,850) Antisecretoric (0,851) Neuroprotector (0,810) Acute neurologic disorders treatment (0,791) Respiratory analeptic (0,789) Antineoplastic (0,784) Anesthetic general (0,753) Analeptic (0,753) Contraceptive (0,711) Antipruritic (0,700) Menopausal disorders treatment (0,676)
 9	Anticancer	Antineoplastic (0,797)	Antiseborrheic (0,899) Ovulation inhibitor (0,885) Alopecia treatment (0,839) Neuroprotector (0,806) Antineoplastic (0,797) Anesthetic general (0,750) Respiratory analeptic (0,749) Male reproductive dysfunction treatment (0,741) Acute neurologic disorders treatment (0,718) Prostate disorders treatment (0,703)
 10	Not studied		Antieczematic (0,789) Prostate disorders treatment (0,784) Dermatologic (0,716) Prostatic (benign) hyperplasia treatment (0,675) Antineoplastic (0,672) Bone diseases treatment (0,591) Antiosteoporotic (0,581)

\* Only activities with Pa > 0.5 are shown

A series of unsaturated steroids (**11-15**) having a nitro group at 3 position (**11-20**) were synthesized and shown *in vitro* as inhibitors of human and rat prostatic steroid 5 $\alpha$ -reductase [24,32,33]. Another series of 5 $\alpha$ -steroids with 3 $\beta$ -, 3 $\alpha$ -, 4 $\beta$ -, 4 $\alpha$ -, 6 $\beta$ -, 6 $\alpha$ -, 7 $\beta$ -, 7 $\alpha$ -, and 17 $\beta$ -nitro groups and of 4 $\beta$ - and 4 $\alpha$ -nitro-5 $\beta$ -cholestane, as well as of some related compounds have been synthesized and their properties studied and

reported [26,31,34,35]. The dominant activities that are characteristic of 3-nitro steroids are: analeptic, anti-seborrheic, neuroprotector, antineoplastic, bone diseases treatment properties and others biological activities presented in Table 2.

The 3-nitro steroids also have some special properties. So, some steroids can be used as

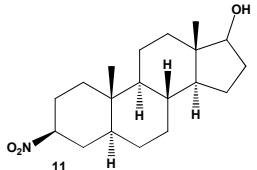
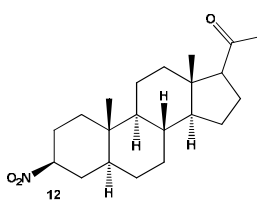
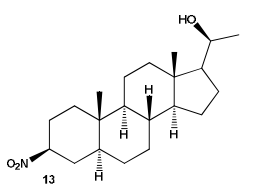
preventive agents for prostate disorders, prostatic (benign) hyperplasia, and bone diseases treatments, respectively (Table 2).

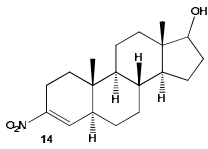
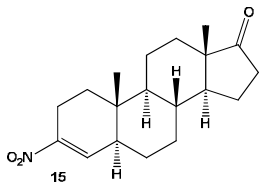
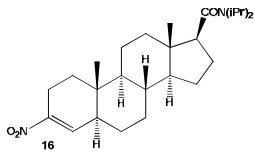
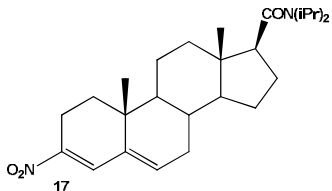
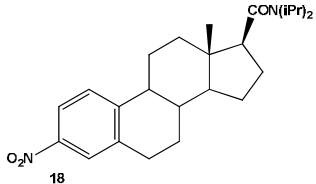
The 4-substituted estrones as well as series of 6 $\alpha$ - and 6 $\beta$ -substituted estrones are an aromatase inhibitors [36]. Two 4-nitro steroids (**21-30**), 17 $\beta$ -cyclopropyloxy-4-nitroandrost-4-en-3-one (**29**) and 20,21-dihydroxy-4-nitropregn-4-en-3-one are aromatase inhibitors, steroid C<sub>17-20</sub> lyase and 5 $\alpha$ -reductase inhibitors [37]. Three 4-nitro steroids (**27-29**) were synthesized and

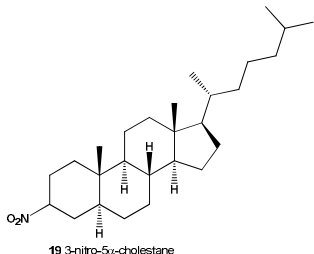
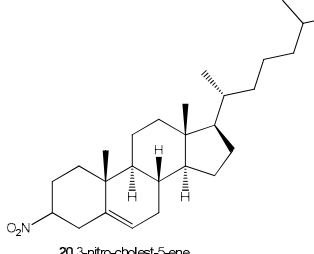
identified as potential inhibitors of 4-methyl sterol oxidase [38]. The main activities that are characteristic of 4-nitro steroids are anti-eczematic, anti-hypercholesterolemic, anti-fungal, antineoplastic, and anti-osteoporotic properties. Other activities of 4-nitro steroids are presented in the Table 3.

Some special properties for 4-nitro steroids are also noted, of which anti-hypercholesterolemic and anti-psoriatic properties should be distinguished (Table 3).

**Table 2. Confirmed and predicted pharmacological activities of 3-Nitro steroids (11-20)**

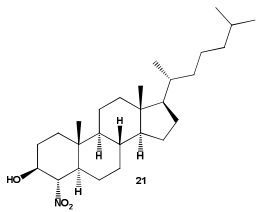
3-Nitro steroids	Activity reviewed	Activities confirmed (Pa)*	Additional predicted activities (Pa)*
	Inhibitor 5 $\alpha$ -reductase	Prostate disorders treatment (0,708)	Respiratory analeptic (0,882) Antiseborrheic (0,860) Alopecia treatment (0,827) Antisecretoric (0,819) Neuroprotector (0,805) Antineoplastic (0,790) Analeptic (0,768) Erythropoiesis stimulant (0,740) Anesthetic general (0,740) Male reproductive dysfunction treatment (0,713) Prostate disorders treatment (0,708)
	Inhibitor 5 $\alpha$ -reductase	Prostate disorders treatment (0,750) Prostatic (benign) hyperplasia treatment (0,665)	Anesthetic general (0,865) Erythropoiesis stimulant (0,805) Prostate disorders treatment (0,750) Respiratory analeptic (0,739) Neuroprotector (0,726) Dermatologic (0,691) Antinociceptive (0,682) Prostatic (benign) hyperplasia treatment (0,665) Anesthetic (0,642) Anticonvulsant (0,636)
	Inhibitor 5 $\alpha$ -reductase	Prostatic (benign) hyperplasia treatment (0,646) Prostatic (benign) hyperplasia treatment (0,646)	Respiratory analeptic (0,964) Analeptic (0,884) Prostate disorders treatment (0,735) Dermatologic (0,711) Anesthetic (0,690) Neuroprotector (0,709) Spasmolytic, Papaverin-like (0,667) Erythropoiesis stimulant (0,663) Prostatic (benign) hyperplasia treatment (0,646) Antieczematic (0,672) Immunosuppressant (0,641)

<b>3-Nitro steroids</b>	<b>Activity reviewed</b>	<b>Activities confirmed (Pa)*</b>	<b>Additional predicted activities (Pa)*</b>
 <p>14</p>	Inhibitor 5 $\alpha$ - reductase	Prostate disorders treatment (0,920) Prostatic (benign) hyperplasia treatment (0,714)	Prostate disorders treatment (0,920) Anesthetic general (0,843) Alopecia treatment (0,837) Antiseborrheic (0,841) Antineoplastic (0,764) Respiratory analeptic (0,752) Prostatic (benign) hyperplasia treatment (0,714) Erythropoiesis stimulant (0,704) Neuroprotector (0,719)
 <p>15</p>	Inhibitor 5 $\alpha$ - reductase	Prostate disorders treatment (0,959)	Prostate disorders treatment (0,959) Male reproductive dysfunction treatment (0,759) Prostatic (benign) hyperplasia treatment (0,755) Antineoplastic (0,764) Antiseborrheic (0,716) Respiratory analeptic (0,703) Ovulation inhibitor (0,689) Alopecia treatment (0,668) Analeptic (0,664) Dermatologic (0,650) Neuroprotector (0,673)
 <p>16</p>	Inhibitor 5 $\alpha$ - reductase	Prostate disorders treatment (0,976)	Prostate disorders treatment (0,976) Prostatic (benign) hyperplasia treatment (0,895) Dermatologic (0,785) Antiacne (0,654) Antineoplastic (0,599) Erythropoiesis stimulant (0,588) Antiosteoporotic (0,555) Bone diseases treatment (0,552)
 <p>17</p>	Inhibitor 5 $\alpha$ - reductase	Prostate disorders treatment (0,946)	Prostate disorders treatment (0,946) Prostatic (benign) hyperplasia treatment (0,883) Dermatologic (0,795) Antiacne (0,678) Antineoplastic (0,687) Ovulation inhibitor (0,640) Bone diseases treatment (0,584) Antiosteoporotic (0,577)
 <p>18</p>	Inhibitor 5 $\alpha$ - reductase	Prostate disorders treatment (0,815) Prostatic (benign) hyperplasia treatment	Prostate disorders treatment (0,815) Dermatologic (0,766) Prostatic (benign) hyperplasia treatment (0,753) Alopecia treatment (0,701) Antineoplastic (0,688) Antiosteoporotic (0,654)

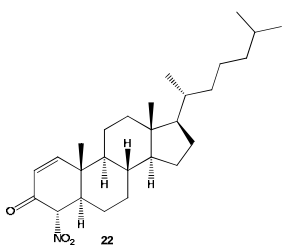
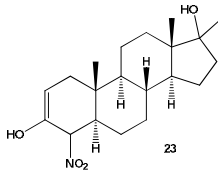
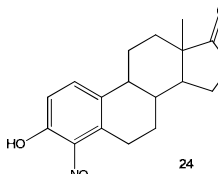
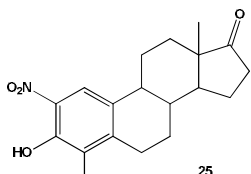
3-Nitro steroids	Activity reviewed	Activities confirmed (Pa)* (0,753)	Additional predicted activities (Pa)*
 <p>19 3-nitro-5<math>\alpha</math>-cholestane</p>	Not studied		Antiseborrheic (0,646) Bone diseases treatment (0,631) Antiacne (0,619)
	Not studied		Respiratory analeptic (0,918) Anesthetic general (0,839) Antieczematic (0,820) Antipruritic (0,781) Dermatologic (0,741) Prostate disorders treatment (0,714) Bone diseases treatment (0,708) Antineoplastic (0,705) Antiosteoporotic (0,695) Biliary tract disorders treatment (0,693) Antihypercholesterolemic (0,691) Immunosuppressant (0,690) Antipsoriatic (0,652)
 <p>20 3-nitro-cholest-5-ene</p>	Not studied		Respiratory analeptic (0,880) Anesthetic general (0,812) Antihypercholesterolemic (0,808) Antieczematic (0,791) Antipruritic (0,773) Dermatologic (0,753) Analeptic (0,755) Prostate disorders treatment (0,729) Immunosuppressant (0,724) Antineoplastic (0,738) Bone diseases treatment (0,714) Antiosteoporotic (0,696)
	Not studied		

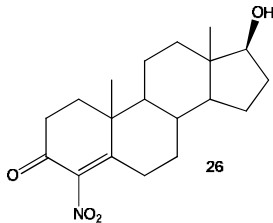
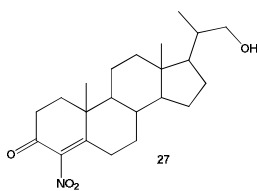
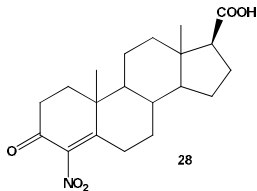
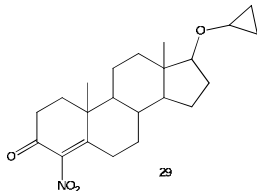
\* Only activities with Pa &gt; 0.5 are shown

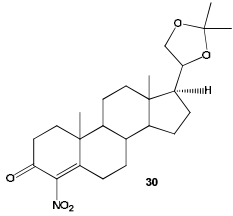
**Table 3. Confirmed and predicted pharmacological activities of 4-Nitro steroids (21-30)**

4-Nitro steroids	Activity reviewed	Activities confirmed (Pa)*	Additional predicted activities (Pa)*
 <p>21</p>	Not studied		Respiratory analeptic (0,929) Anesthetic general (0,919) Antieczematic (0,857) Analeptic (0,833) Antihypercholesterolemic (0,819) Antipruritic (0,799) Immunosuppressant (0,773) Antifungal (0,758) Antineoplastic (0,752) Bone diseases treatment (0,734) Antiosteoporotic (0,729) Dermatologic (0,726) Hepatoprotectant (0,719)
	Not studied		



4-Nitro steroids	Activity reviewed	Activities confirmed (Pa)*	Additional predicted activities (Pa)*
	Not studied		Antieczematic (0,814) Antipruritic (0,769) Respiratory analeptic (0,760) Dermatologic (0,736) Immunosuppressant (0,722) Antineoplastic (0,709) Prostate disorders treatment (0,708) Antiosteoporotic (0,706) Bone diseases treatment (0,701) Prostatic (benign) hyperplasia treatment (0,687) Anesthetic general (0,679) Antifungal (0,671)
	Not studied		Antiseborrheic (0,872) Antineoplastic (0,799) Respiratory analeptic (0,748) Prostate disorders treatment (0,715) Antiallergic (0,681) Antisecretoric (0,677) Ovulation inhibitor (0,671) Antiosteoporotic (0,667) Prostatic (benign) hyperplasia treatment (0,645) Dermatologic (0,646) Muscular dystrophy treatment (0,631) Antiinflammatory (0,649)
	Not studied		Antiseborrheic (0,895) Alopecia treatment (0,820) Ovulation inhibitor (0,819) Neuroprotector (0,807) Antineoplastic (0,797) Respiratory analeptic (0,741) Male reproductive dysfunction treatment (0,720) Acute neurologic disorders treatment (0,727) Analeptic (0,706) Prostate disorders treatment (0,689) Cardiovascular analeptic (0,666) Antiosteoporotic (0,652)
	Not studied		Antiseborrheic (0,859) Ovulation inhibitor (0,811) Alopecia treatment (0,774) Antineoplastic (0,785) Neuroprotector (0,774) Prostate disorders treatment (0,689) Male reproductive dysfunction treatment (0,688) Respiratory analeptic (0,642)

4-Nitro steroids	Activity reviewed	Activities confirmed (Pa)*	Additional predicted activities (Pa)*
			Acute neurologic disorders treatment (0,644) Analeptic (0,622)
	Not studied		Antineoplastic (0,906) Prostate disorders treatment (0,883) Alopecia treatment (0,864) Antiseborrheic (0,863) Respiratory analeptic (0,860) Male reproductive disfunction treatment (0,858) Anesthetic general (0,837) Neuroprotector (0,800) Dermatologic (0,765) Prostatic (benign) hyperplasia treatment (0,736) Analeptic (0,726)
	4-methyl sterol oxidase		Prostate disorders treatment (0,887) Antineoplastic (0,870) Dermatologic (0,839) Respiratory analeptic (0,841) Antieczematic (0,834) Anesthetic general (0,826) Prostatic (benign) hyperplasia treatment (0,768) Antiacne (0,689) Neuroprotector (0,708) Immunosuppressant (0,648) Hair growth stimulant (0,627)
	4-methyl sterol oxidase	Male reproductive disfunction treatment (0,684)	Prostate disorders treatment (0,890) Antineoplastic (0,834) Respiratory analeptic (0,818) Prostatic (benign) hyperplasia treatment (0,793) Dermatologic (0,786) Antieczematic (0,764) Antiseborrheic (0,727) Neuroprotector (0,730) Erythropoiesis stimulant (0,701) Male reproductive disfunction treatment (0,684)
	4-methyl sterol oxidase	Male reproductive disfunction treatment (0,684)	Prostate disorders treatment (0,976) Antineoplastic (0,922) Prostatic (benign) hyperplasia treatment (0,862) Dermatologic (0,808) Antiseborrheic (0,803) Male reproductive disfunction treatment (0,798) Respiratory analeptic (0,796) Antiacne (0,728)

4-Nitro steroids	Activity reviewed	Activities confirmed (Pa)*	Additional predicted activities (Pa)*
 30	Not studied		Alopecia treatment (0,725)
			Antisecretoric (0,711)
			Antineoplastic (0,890)
			Prostate disorders treatment (0,809)
			Antiinflammatory (0,755)
			Respiratory analeptic (0,751)
			Dermatologic (0,726)
			Prostatic (benign) hyperplasia treatment (0,675)
			Antipruritic (0,661)
			Immunosuppressant (0,661)
			Apoptosis agonist (0,659)

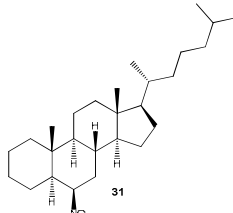
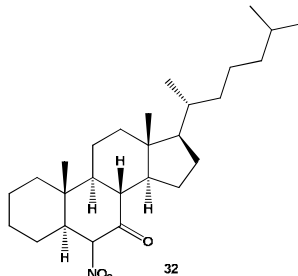
\* Only activities with Pa > 0.5 are shown

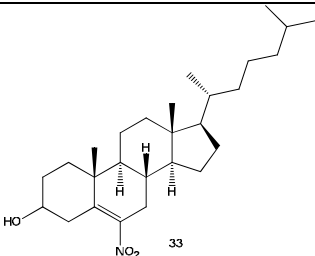
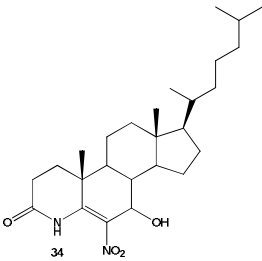
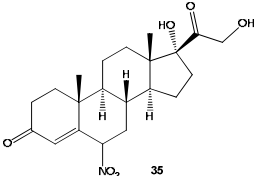
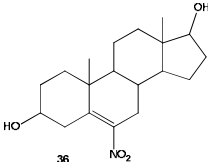
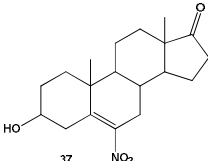
Ringold and co-authors [39] synthesized a series of 6-nitro steroids, and showed that many of these compounds showed anti-inflammatory activity. For 6-nitro steroids (**31-39**), characteristic activities are an antineoplastic, neuro-protector, ovulation inhibitor, prostate disorders treatment, muscular dystrophy treatment and other activities as shown in Table 4. The activity

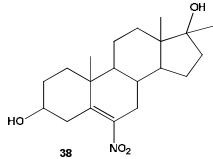
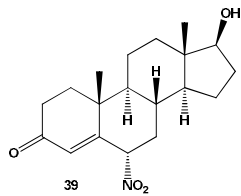
of 6-nitro steroids (**31-39**) presented in Table 4 was not previously studied.

The 6-nitro steroids also have some special properties, such as respiratory analeptic, muscular dystrophy treatment, ovulation inhibitor and hypogonadism treatment (Table 4).

**Table 4. Predicted pharmacological activities of 6-Nitro steroids (31-39)**

6-Nitro steroids	Additional predicted activities (Pa)*
 31	Respiratory analeptic (0,883)
	Antieczematic (0,831)
	Anesthetic general (0,782)
	Antipruritic (0,772)
	Analeptic (0,769)
	Dermatologic (0,731)
	Bone diseases treatment (0,702)
	Prostate disorders treatment (0,698)
	Antiosteoporotic (0,690)
	Antineoplastic (0,669)
Antipsoriatic (0,645)	
 32	Antieczematic (0,834)
	Respiratory analeptic (0,829)
	Antipruritic (0,746)
	Anesthetic general (0,740)
	Dermatologic (0,713)
	Analeptic (0,712)
	Prostate disorders treatment (0,693)
	Immunosuppressant (0,680)
	Antiosteoporotic (0,661)
	Antifungal (0,623)
	Respiratory analeptic (0,966)
	Anesthetic general (0,934)
	Antihypercholesterolemic (0,894)
	Analeptic (0,873)
	Antineoplastic (0,849)

6-Nitro steroids	Additional predicted activities (Pa)*
 <p>33</p>	Prostate disorders treatment (0,812) Antipruritic (0,800) Dermatologic (0,793) Immunosuppressant (0,761) Neuroprotector (0,756) Hepatoprotectant (0,752) Antiosteoporotic (0,734)
 <p>34</p>	Anesthetic general (0,905) Respiratory analeptic (0,905) Analeptic (0,838) Antieczematic (0,836) Neuroprotector (0,793) Antihypercholesterolemic (0,777) Antipruritic (0,761) Dermatologic (0,756) Antineoplastic (0,739) Prostate disorders treatment (0,703) Biliary tract disorders treatment (0,697)
 <p>35</p>	Respiratory analeptic (0,976) Analeptic (0,900) Antineoplastic (0,898) Antisecretoric (0,880) Antiinflammatory (0,870) Antipruritic (0,818) Antiseborrheic (0,791) Muscular dystrophy treatment (0,762) Antiallergic (0,759) Immunosuppressant (0,739)
 <p>36</p>	Antineoplastic (0,903) Respiratory analeptic (0,881) Male reproductive dysfunction treatment (0,871) Neuroprotector (0,869) Prostate disorders treatment (0,868) Antiseborrheic (0,834) Anesthetic general (0,827) Dermatologic (0,773) Analeptic (0,752) Bone diseases treatment (0,738) Antiosteoporotic (0,731) Prostatic (benign) hyperplasia treatment (0,726) Ovulation inhibitor (0,721) Erythropoiesis stimulant (0,716)
 <p>37</p>	Respiratory analeptic (0,928) Neuroprotector (0,916) Antineoplastic (0,904) Male reproductive dysfunction treatment (0,889) Muscular dystrophy treatment (0,882) Ovulation inhibitor (0,866) Analeptic (0,864) Prostate disorders treatment (0,848) Anesthetic general (0,774) Antiseborrheic (0,782) Alopecia treatment (0,753) Dermatologic (0,746)

6-Nitro steroids	Additional predicted activities (Pa)*
 38	Erythropoiesis stimulant (0,713)
	Prostatic (benign) hyperplasia treatment (0,711)
	Respiratory analeptic (0,941)
	Muscular dystrophy treatment (0,920)
	Antineoplastic (0,909)
	Prostate disorders treatment (0,863)
	Antiseborrheic (0,859)
	Analeptic (0,831)
	Ovulation inhibitor (0,812)
	Antisecretoric (0,778)
	Dermatologic (0,774)
	Antihypercholesterolemic (0,768)
Antiinflammatory (0,760)	
Hypogonadism treatment (0,746)	
 39	Antineoplastic (0,905)
	Respiratory analeptic (0,886)
	Alopecia treatment (0,851)
	Antiseborrheic (0,830)
	Neuroprotector (0,823)
	Antisecretoric (0,814)
	Anesthetic general (0,772)
	Analeptic (0,765)
	Ovulation inhibitor (0,749)
	Prostate disorders treatment (0,702)

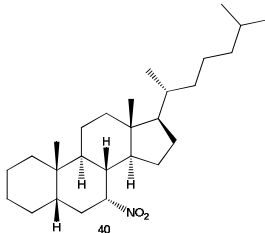
\* Only activities with Pa > 0.5 are shown

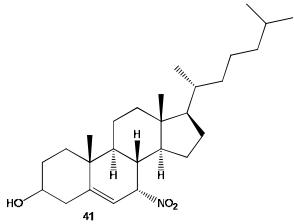
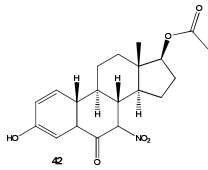
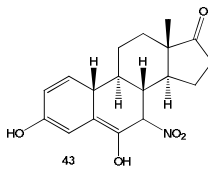
Some 7-nitro steroids (**40-43**) were prepared and showed that to inhibited gonatropin and ovulation [40]. The dominant activities that are an anti-neoplastic, ovulation inhibitor, anti-seborrheic, cardiovascular analeptic, and antipruritic, and other activities of 7-nitro steroids are presented in the Table 5.

The last miscellaneous group (Table 6) includes steroids in which the nitro group is in different positions. Various nitro steroids were synthesized and their activity was partially

studied [22,24,40-52]. So for 11-nitro steroids antineoplastic and anesthetic activity is characteristic; for 16-nitro steroids – anti-inflammatory and anesthetic activities; for 17-nitro steroids – anti-inflammatory and anti-secretoric activities; for 20-nitro steroids - respiratory analeptic and prostate disorders activities; and for 21-nitro steroids – anti-allergic and ovulation inhibitor activities. The activity of nitro steroids (**44-52**) presented in Table 6 was not previously studied.

**Table 5. Confirmed and predicted pharmacological activities of 7-Nitro steroids (40-43)**

7-Nitro steroids	Activity reviewed	Activities confirmed (Pa)*	Additional predicted activities (Pa)*
 40	Not studied		Respiratory analeptic (0,891)
			Antieczematic (0,831)
			Anesthetic general (0,788)
			Analeptic (0,780)
			Antipruritic (0,764)
			Dermatologic (0,709)
			Biliary tract disorders treatment (0,690)
			Prostate disorders treatment (0,679)
			Immunosuppressant (0,662)
			Antipsoriatic (0,647)

7-Nitro steroids	Activity reviewed	Activities confirmed (Pa)*	Additional predicted activities (Pa)*
	Not studied		Respiratory analeptic (0,953) Anesthetic general (0,919) Antihypercholesterolemic (0,892) Analeptic (0,858) Antieczematic (0,834) Antipruritic (0,798) Immunosuppressant (0,769) Antineoplastic (0,766) Antifungal (0,731) Neuroprotector (0,742)
	Inhibitor of gonatropin and ovulation		Antiseborrheic (0,932) Antineoplastic (0,810) Antisecretoric (0,784) Analeptic (0,745) Alopecia treatment (0,735) Respiratory analeptic (0,731) Immunosuppressant (0,690) Hepatoprotectant (0,671) Prostate disorders treatment (0,650) Antibacterial (0,629)
	Inhibitor of gonatropin and ovulation	Ovulation inhibitor (0,733)	Antiseborrheic (0,851) Neuroprotector (0,811) Male reproductive dysfunction treatment (0,792) Alopecia treatment (0,763) Antineoplastic (0,773) Respiratory analeptic (0,755) Analeptic (0,745) Ovulation inhibitor (0,733) Cardiovascular analeptic (0,731) Acute neurologic disorders treatment (0,724) Prostate disorders treatment (0,669)

\* Only activities with Pa > 0.5 are shown

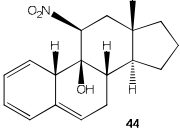
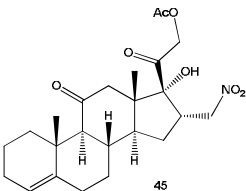
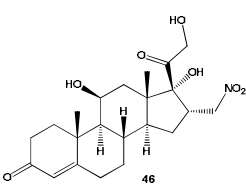
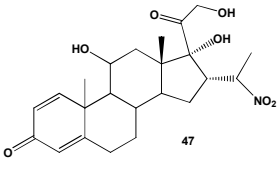
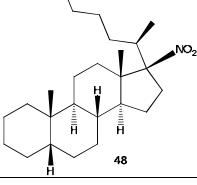
### 3. STRUCTURE ACTIVITY RELATIONSHIP OF NITRO STEROIDS

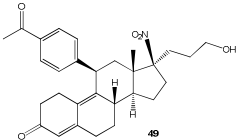
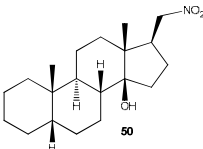
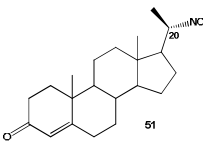
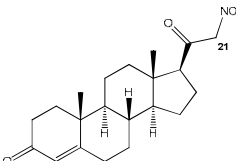
Through the use of the structure–activity relationships (SAR) approach realized in the computer program PASS, some additional activities were predicted; indicating new possible applications for these compounds. The data presented below on the biological activity of nitro steroids, characterized only a small part of the possible biological potential in these molecules. The synthetic nitro steroids and their structures and some detected activities are published previously [53,54]. The biological activity spectra were estimated using the computer prediction.

For this purpose the computer program PASS [55,56] was used. PASS predictions are based on SAR analysis of the training set, which consisted of about 1 million drugs and more than 8,000 pharmacological activities. Algorithm of the PASS practical utilization is described in detail in several publications [57–61]. The user may get a list of probable biological activities for any drug-like molecule as an output, using MOL or SD files as an input for PASS program. Pa and Pi values are calculated for each activity, 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 316 types of biological activity are predicted with  $P_a > 70\%$  and 92 with  $P_a > 50\%$ . In a biological activity spectrum estimated by PASS, the activity predicted with the highest probability is called the focal activity.

**Table 6. Predicted pharmacological activities of 11-, 16-, 17-, 20-, and 21-Nitro steroids (44-52)**

Nitro steroids	Additional predicted activities ( $P_a$ )*
 <p>44</p>	Anesthetic general (0,707) Antineoplastic (0,718) Neuroprotector (0,699) Prostate disorders treatment (0,651) Ovulation inhibitor (0,635) Alopecia treatment (0,635) Dermatologic (0,635) Antinociceptive (0,609) Antiseborrheic (0,630)
 <p>45</p>	Antiinflammatory (0,891) Anesthetic general (0,826) Antipruritic (0,817) Analgesic (0,805) Respiratory analeptic (0,791) Immunosuppressant (0,769) Antineoplastic (0,747) Muscular dystrophy treatment (0,724) Antiallergic (0,682)
 <p>46</p>	Respiratory analeptic (0,980) Antisecretoric (0,937) Antiinflammatory (0,930) Analeptic (0,912) Antipruritic (0,846) Antiallergic (0,827) Antineoplastic (0,809) Immunosuppressant (0,792) Analgesic (0,766) Proliferative diseases treatment (0,723) Prostate disorders treatment (0,697) Antiasthmatic (0,693)
 <p>47</p>	Antiinflammatory (0,951) Antisecretoric (0,939) Muscular dystrophy treatment (0,926) Respiratory analeptic (0,920) Antiallergic (0,898) Antipruritic (0,854) Antiasthmatic (0,833) Analeptic (0,821) Antineoplastic (0,815) Immunosuppressant (0,805) Antiarthritic (0,785) Autoimmune disorders treatment (0,776)
 <p>48</p>	Anesthetic general (0,905) Respiratory analeptic (0,782) Antipruritic (0,684) Prostate disorders treatment (0,669) Neuroprotector (0,686) Antineoplastic (0,686) Analeptic (0,666)

Nitro steroids	Additional predicted activities (Pa)*
	Dermatologic (0,644) Antiinflammatory (0,649)
	Neuroprotector (0,713) Contraceptive (0,696) Antineoplastic (0,683) Acute neurologic disorders treatment (0,601) Menopausal disorders treatment (0,592) Antiinflammatory (0,562) Gynecological disorders treatment (0,540) Radiosensitizer (0,540) Prostate disorders treatment (0,535)
	Cardiotonic (0,890) Anesthetic general (0,707) Respiratory analeptic (0,676) Spasmolytic, urinary (0,675) Prostate disorders treatment (0,641) Erythropoiesis stimulant (0,616) Immunosuppressant (0,559) Dementia treatment (0,543) Menopausal disorders treatment (0,522)
	Respiratory analeptic (0,868) Prostate disorders treatment (0,782) Anesthetic general (0,780) Ovulation inhibitor (0,769) Analeptic (0,759) Antineoplastic (0,757) Dermatologic (0,736) Antiseborrheic (0,736) Prostatic (benign) hyperplasia treatment (0,684) Alopecia treatment (0,669) Antiosteoporotic (0,641)
	Anesthetic general (0,863) Respiratory analeptic (0,863) Prostate disorders treatment (0,769) Antiallergic (0,762) Ovulation inhibitor (0,744) Analeptic (0,735) Dermatologic (0,718) Antipruritic (0,718) Antineoplastic (0,710) Menopausal disorders treatment (0,650) Antiseborrheic (0,672)

\* Only activities with Pa > 0.5 are shown

#### 4. CONCLUSION

Nitro steroids are organic compounds that are inherently classed as lipids, which have a high biological activity. Steroid hormones, including nitro steroids, are involved in the regulation of the metabolism and certain physiological functions of the human body. A number of synthetic hormones, by action on the body, surpass natural analogues. A number of anabolic hormones are known, including nitro steroid, which are potent anti-cancer, antibacterial

agents, or show properties that are characteristic only of these compounds. The data given by us for nitro steroids are of great interest, primarily for academic science and pharmaceutical companies that work in the market for the production of anabolic steroids.

For each individual group, Nitro steroids also feature characteristic features that may not be found for other steroids groups. Based on the data obtained for the biological activities of 2-, 3-, 4-, 6-, 7-, 11-, 16-, 17-, 20-, and 21-Nitro



steroids, we believe that the results presented will stimulate scientists, who working in the field of medical chemistry, to give preference to the synthesis of a particular group of Nitro steroids.

## 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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