



ISSN (E): 2277- 7695  
ISSN (P): 2349-8242  
NAAS Rating 2017: 5.03  
TPI 2017; 6(11): 84-92  
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www.thepharmajournal.com  
Received: 14-08-2017  
Accepted: 15-09-2017

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## Synthetic steroids containing a tertiary butyl group and their biological activities

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### Abstract

The present review article describes biological activities of synthetic steroids containing a tertiary butyl group. More than 25 biological active steroids have shown confirmed antitumor, antiviral, or apoptosis, and other activities. The structures, reported and predicted activities of a selection of describes 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 article emphasizes the role of steroids containing a tertiary butyl group as an important source of leads for drug discovery.

**Keywords:** steroids, tertiary butyl group, lipids, activities

### 1. Introduction

Biologically active compounds containing a tertiary butyl group(s) [or tert-butyl unit(s)] are rather rare metabolites that have been found in nature <sup>[1, 2]</sup>. These compounds were found in bacteria, the leaves of plants, fungi and marine invertebrates and algae <sup>[1, 2]</sup>.

A tertiary butyl group (tert-butyl, t-Bu, or -CMe<sub>3</sub>) is commonly used in organic chemistry; <sup>[3, 4, 5, 6, 7]</sup> however, in lipid chemistry or as is currently called lipidomics, such a group (or unit) has a very specific name, a neo group (or neo unit), which occurs in the composition of hydrocarbons (alkanes and alkenes) and fatty (carboxylic) acids <sup>[1, 2, 6, 7]</sup>.

As already proved by numerous works, there is a relationship between structure and activity, and this principle is called SAR (Structure-Activity-Relationship) <sup>[8, 9]</sup>. We used the computer program PASS, containing about one million chemical compounds and more than 8,000 biological activities, and calculated the biological activity of different natural and/or synthetic compounds <sup>[10, 11]</sup>. 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 <sup>[12-14]</sup>. 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 158 types of biological activity are predicted with Pa>70% and 67 with Pa>50%. In a biological activity spectrum estimated by PASS, the activity predicted with the highest probability is called the focal activity.

This mini review is devoted to synthetic steroids containing a tertiary butyl group and their biological activities.

### 2. Biological activities of synthetic steroids

A series of steroids containing a tertiary butyl group were synthesized and the activity of many of them was determined. We chose different types of steroids in which a tertiary butyl group was incorporated into the different positions of the steroid core (1-21).

Morisaki and colleagues synthesized cholesterol analogues, including an antibacterial agent, cholesterol containing a tertiary butyl group, and 25-methyl-cholest-5-en-3 $\beta$ -ol (1) in the tail of the steroid <sup>[15]</sup>. The inhibition of 3-hydroxy-3-methyl-glutaryl coenzyme A reductase, which is called 25-methyl-5 $\alpha$ -cholestane-3 $\beta$ , 22S-diol (2), was synthesized by Chorvat <sup>[16]</sup>. The steroids (3) showed anti-vitamin D activity and intestinal calcium transport inhibitor has been synthesized by De Luca and co-workers <sup>[17]</sup>. Compounds (4 and 5) were synthesized as inhibitors of acyl-coenzyme A: cholesterol acyltransferases <sup>[16]</sup>.

The 17 $\alpha$ -benzyl-t-Bu oestradiol derivative (73) was synthesized as an inhibitor of steroid

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sulfatase [17, 18]. Neo 7-ketocholesterol (74) has been synthesized by Dygos and Desai [19] as an inhibitor of  $\beta$ -hydroxy- $\beta$ -methylglutaryl Co A reductase.

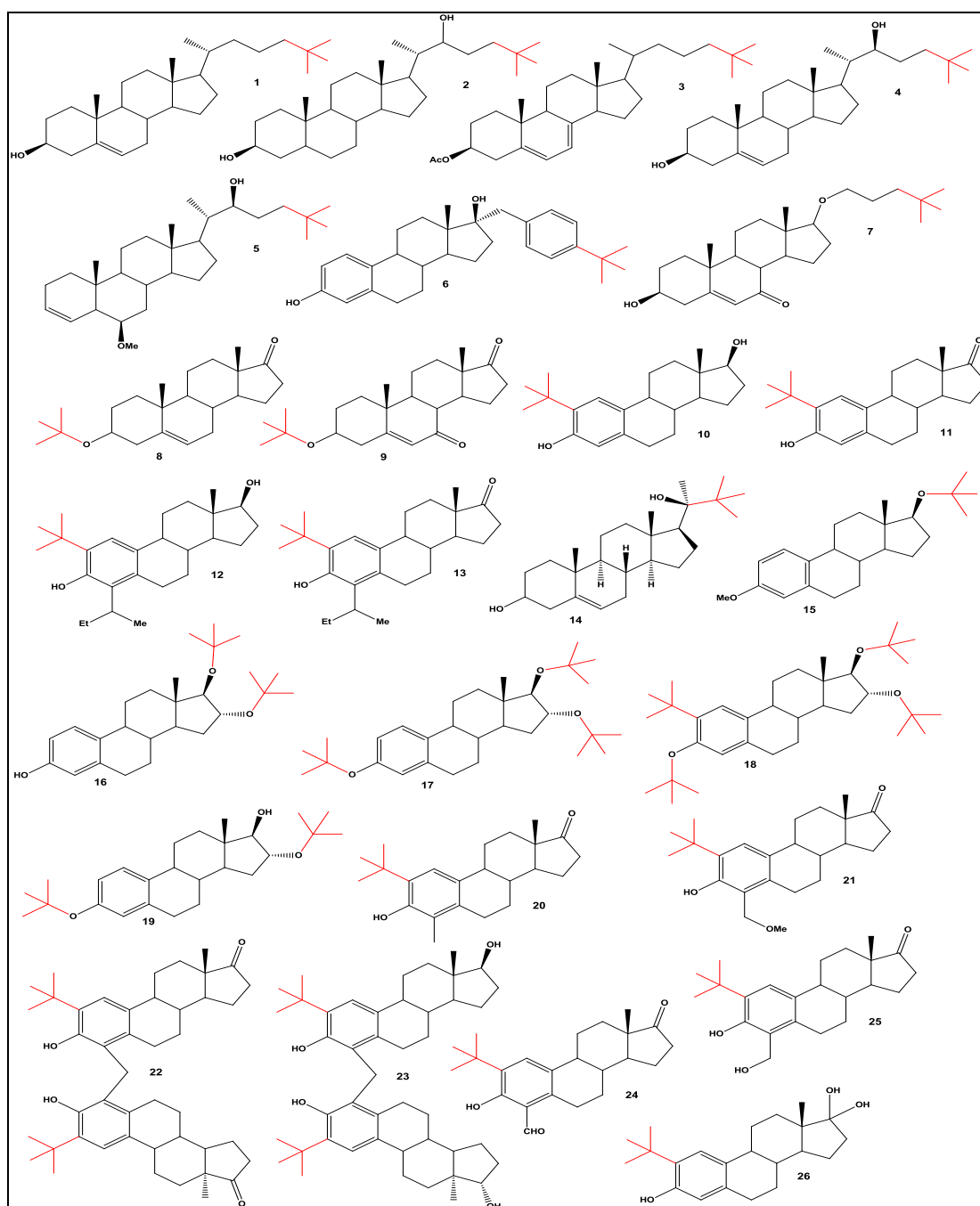
$3\beta$ -tert-Butoxyandrost-5-en-17-one (6) and analogue (9) showed potential activity for the treatment of prostate cancer [20]. Several tert-butyl-substituted aromatic steroids (10-12) with cytoprotective activity have been synthesized and their activities reported [21]. Also, the authors claim that synthesized steroids can be used to prevent or treat diseases such as chronic neurodegenerative diseases including Alzheimer's disease, peripheral neuropathy, multiple sclerosis, amyotrophic lateral sclerosis, Huntington's disease and Parkinson's disease, Creutzfeldt-Jakob disease and AIDs dementia.

Steroid, (20*R*)-20-t-Bu-5-pregnene-3 $\beta$ , 20-diol (13) has been synthesized and used as bioactive hormonal precursor [22, 23]. Estrogens represent the group of the female sex steroid hormones that play an important role in the reproductive cycle

in women, and also inhibit the growth of mammary cancer, and regulate women's menopause and pregnancy. Several bioactive steroids with a tertiary butyl group (14-19) were synthesized by modification of natural estrogens [24]. Liu [25] synthesized a series of tert-butyl-containing aromatic steroids (20-26) as inhibitors of steroid sulfatase.

### 3. Conclusion

It can be concluded that synthetic steroids containing a tertiary butyl group possess mainly cytotoxic activities, although the predicted biological activity showed a broad spectrum of activities. As we found, the position of a tertiary butyl group in the core of steroids can significantly change the activity of steroids. A variety of activities is presented in the table data. The results obtained are of great interest to sports physicians, chemists, pharmacologists and the pharmaceutical industry.



**Fig 1:** Selected of bioactive synthetic steroids containing a tertiary butyl group

**Table 1:** Confirmed and new pharmacological activities of synthetic steroids (1-26)

| No. | Activity reviewed   | Activities confirmed (Pa)  | Additional predicted activities (Pa)*   |
|-----|---|--|---|
| 1   | Antibacterial   | Antibacterial (0,475)<br>Immunostimulant (0,597)<br>Membrane permeability enhancer (0,519) | Respiratory analeptic (0,977)<br>Antihypercholesterolemic (0,966)<br>Anesthetic general (0,905)<br>Antihyperlipoproteinemic (0,888)<br>Antieczematic (0,872)<br>Hypolipemic (0,857)<br>Hepatoprotectant (0,837)<br>Antineoplastic (0,821)<br>Hair growth stimulant (0,809)<br>Antipruritic (0,808)<br>Antiosteoporotic (0,798)<br>Antiinflammatory (0,785)<br>Ovulation inhibitor (0,782)<br>Antipsoriatic (0,772)<br>Cytoprotectant (0,757)<br>Antiinfertility, female (0,756)<br>Prostate disorders treatment (0,747) |
| 2   | 3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor | Hydroxymethylglutaryl-CoA reductase inhibitor (0,483)                                      | Respiratory analeptic (0,965)<br>Antihypercholesterolemic (0,909)<br>Anesthetic general (0,897)<br>Hepatoprotectant (0,888)<br>Antineoplastic (0,873)<br>Antieczematic (0,869)<br>Antiinfertility, female (0,851)<br>Apoptosis agonist (0,846)<br>Antiseborrheic (0,816)<br>Cytoprotectant (0,811)<br>Erythropoiesis stimulant (0,806)<br>Hypolipemic (0,802)<br>Antipruritic (0,794)<br>Antiinflammatory (0,778)<br>Antipsoriatic (0,755)<br>Antiosteoporotic (0,722)<br>Prostate disorders treatment (0,712)          |
| 3   | calcium transport inhibitor                               | Calcium regulator (0,613)  | Respiratory analeptic (0,972)<br>Antihypercholesterolemic (0,953)<br>Antieczematic (0,861)<br>Hypolipemic (0,847)<br>Antineoplastic (0,795)<br>Antipruritic (0,788)<br>Apoptosis agonist (0,769)<br>Antiosteoporotic (0,740)<br>Antiseborrheic (0,740)<br>Antipsoriatic (0,735)<br>Antiinflammatory (0,734)<br>Antiinfertility, female (0,721)<br>Chemopreventive (0,717)<br>Cytoprotectant (0,699)<br>Prostate disorders treatment (0,696)   |
| 4   | Inhibitor cholesterol acyltransferases                    | Antihypercholesterolemic (0,937)   | Respiratory analeptic (0,964)<br>Antihypercholesterolemic (0,937)<br>Antineoplastic (0,878)<br>Hepatoprotectant (0,871)<br>Antieczematic (0,847)<br>Apoptosis agonist (0,841)<br>Antiinflammatory (0,819)<br>Anesthetic general (0,794)<br>Hypolipemic (0,793)<br>Antipruritic (0,784)<br>Radioprotector (0,745)<br>Antipsoriatic (0,742)<br>Prostate disorders treatment (0,728)<br>Oxytocic (0,714)<br>Antiosteoporotic (0,709)   |
| 5   | Inhibitor cholesterol acyltransferases                    | Antihypercholesterolemic (0,937)   | Respiratory analeptic (0,883)<br>Antieczematic (0,851)<br>Antineoplastic (0,851)<br>Apoptosis agonist (0,813)<br>Antiinfertility, female (0,794)  |

|    |                                |   |   |
|----|--------------------------------|---|---|
|    |                                |   | Hepatoprotectant (0,779)<br>Anesthetic general (0,774)<br>Antihypercholesterolemic (0,756)<br>Hypolipemic (0,748)<br>Antipruritic (0,733)<br>Antiinflammatory (0,729)<br>Cytoprotectant (0,714)<br>Antifungal (0,696)<br>Antipsoriatic (0,683)<br>Prostate disorders treatment (0,664)<br>Atherosclerosis treatment (0,654)   |
| 6  | Inhibitor of steroid sulfatase | Antineoplastic (0,817)  | Antiseborrheic (0,926)<br>Antihypercholesterolemic (0,896)<br>Neuroprotector (0,859)<br>Antineoplastic (0,817)<br>Antiinflammatory (0,752)<br>Antisecretoric (0,732)<br>Hepatoprotectant (0,721)<br>Respiratory analeptic (0,718)<br>Hypolipemic (0,710)<br>Antiosteoporotic (0,708)<br>Vasoprotector (0,705)<br>Prostate disorders treatment (0,700)<br>Menopausal disorders treatment (0,693)<br>Ovulation inhibitor (0,693)<br>Contraceptive (0,632)       |
| 7  | Inhibitor Co A reductase       | Hypolipemic (0,710)<br>Antiosteoporotic (0,708)   | Antiseborrheic (0,926)<br>Antihypercholesterolemic (0,896)<br>Neuroprotector (0,859)<br>Antineoplastic (0,817)<br>Antiinflammatory (0,752)<br>Antisecretoric (0,732)<br>Hepatoprotectant (0,721)<br>Respiratory analeptic (0,718)<br>Hypolipemic (0,710)<br>Antiosteoporotic (0,708)<br>Vasoprotector (0,705)<br>Prostate disorders treatment (0,700)<br>Menopausal disorders treatment (0,693)<br>Ovulation inhibitor (0,693)<br>Cytoprotectant (0,679)      |
| 8  | Anticancer                     | Antineoplastic (0,849)<br>Antineoplastic (breast cancer) (0,695)<br>Prostate cancer treatment (0,652)<br>Anticarcinogenic (0,552)<br>Antineoplastic (sarcoma) (0,547)   | Ovulation inhibitor (0,933)<br>Antihypercholesterolemic (0,915)<br>Respiratory analeptic (0,891)<br>Neuroprotector (0,885)<br>Male reproductive dysfunction treatment (0,815)<br>Antiseborrheic (0,805)<br>Menopausal disorders treatment (0,791)<br>Antianorexic (0,786)<br>Antisecretoric (0,756)<br>Lipid metabolism regulator (0,746)<br>Prostate disorders treatment (0,745)<br>Antiinflammatory (0,737)<br>Antiosteoporotic (0,712)<br>Oxytocic (0,666) |
| 9  | anticancer                     | Antineoplastic (0,850)<br>Antineoplastic (breast cancer) (0,698)<br>Prostate cancer treatment (0,613)<br>Anticarcinogenic (0,565)<br>Antineoplastic (pancreatic cancer) (0,547)<br>Antineoplastic (sarcoma) (0,534) | Neuroprotector (0,914)<br>Ovulation inhibitor (0,876)<br>Male reproductive dysfunction treatment (0,848)<br>Antihypercholesterolemic (0,788)<br>Antiseborrheic (0,785)<br>Respiratory analeptic (0,749)<br>Menopausal disorders treatment (0,735)<br>Antiinflammatory (0,723)<br>Prostate disorders treatment (0,722)<br>Antisecretoric (0,694)<br>Antiosteoporotic (0,693)<br>Lipid metabolism regulator (0,676)<br>Diuretic (0,663)                         |
| 10 | cytoprotective activity        | Cytoprotectant (0,639)  | Antiseborrheic (0,946)  |

|    |                                |  |  |
|----|--------------------------------|--|--|
|    |                                |  | <p>Alopecia treatment (0,929)<br/>         Antihypercholesterolemic (0,911)<br/>         Anesthetic general (0,910)<br/>         Neuroprotector (0,899)<br/>         Acute neurologic disorders treatment (0,834)<br/>         Antineoplastic (0,827)<br/>         Antisecretoric (0,812)<br/>         Ovulation inhibitor (0,810)<br/>         Antiinflammatory (0,788)<br/>         Antiosteoporotic (0,787)<br/>         Menopausal disorders treatment (0,759)<br/>         Vasoprotector (0,718)<br/>         Contraceptive (0,716)</p>   |
| 11 | cytoprotective activity        | Cytoprotectant (0,565)   | <p>Antiseborrheic (0,928)<br/>         Ovulation inhibitor (0,906)<br/>         Antihypercholesterolemic (0,899)<br/>         Neuroprotector (0,893)<br/>         Alopecia treatment (0,850)<br/>         Antineoplastic (0,832)<br/>         Anesthetic general (0,821)<br/>         Acute neurologic disorders treatment (0,794)<br/>         Male reproductive dysfunction treatment (0,787)<br/>         Lipid metabolism regulator (0,772)<br/>         Antiinflammatory (0,752)<br/>         Menopausal disorders treatment (0,735)<br/>         Antiosteoporotic (0,732)<br/>         Cardiovascular analeptic (0,718)<br/>         Diuretic (0,710)<br/>         Contraceptive (0,709)<br/>         Prostate disorders treatment (0,708)</p> |
| 12 | cytoprotective activity        | Cytoprotectant (0,526)   | <p>Anesthetic general (0,943)<br/>         Antihypercholesterolemic (0,932)<br/>         Antiseborrheic (0,890)<br/>         Neuroprotector (0,867)<br/>         Antineoplastic (0,815)<br/>         Alopecia treatment (0,799)<br/>         Acute neurologic disorders treatment (0,795)<br/>         Antiinflammatory (0,782)<br/>         Antiosteoporotic (0,745)<br/>         Contraceptive (0,714)<br/>         Antieczematic (0,710)<br/>         Apoptosis agonist (0,690)<br/>         Hypolipemic (0,686)<br/>         Prostate disorders treatment (0,678)<br/>         Ovulation inhibitor (0,639)</p>   |
| 13 | cytoprotective activity        | Cytoprotectant (0,405)   | <p>Antihypercholesterolemic (0,923)<br/>         Anesthetic general (0,913)<br/>         Neuroprotector (0,860)<br/>         Antiseborrheic 90,850)<br/>         Antineoplastic (0,820)<br/>         Acute neurologic disorders treatment (0,751)<br/>         Antiinflammatory (0,750)<br/>         Ovulation inhibitor (0,742)<br/>         Male reproductive dysfunction treatment (0,725)<br/>         Contraceptive (0,707)<br/>         Prostate disorders treatment (0,686)<br/>         Antiosteoporotic (0,684)<br/>         Lipid metabolism regulator (0,654)</p>   |
| 14 | Inhibitor biosynthesis hormone | <p>Gestagen antagonist (0,688)<br/>         Androgen antagonist (0,683)<br/>         Steroid synthesis inhibitor (0,595)</p> | <p>Respiratory analeptic (0,945)<br/>         Antihypercholesterolemic (0,908)<br/>         Analgesic (0,904)<br/>         Anesthetic (0,901)<br/>         Antiinflammatory (0,892)<br/>         Ovulation inhibitor (0,816)<br/>         Antineoplastic (0,805)</p>   |

|    |            |   |  |
|----|------------|---|--|
|    |            |   | Antiseborrheic (0,801)<br>Antieczematic (0,760)<br>Prostate disorders treatment (0,752)<br>Antiosteoporotic (0,743)<br>Neuroprotector (0,742)<br>Hypolipemic (0,735)<br>Antipruritic (0,720)<br>Erythropoiesis stimulant (0,717)<br>Hepatoprotectant (0,717)<br>Contraceptive (0,708)<br>Menopausal disorders treatment (0,704)  |
| 15 | Anticancer | Antineoplastic (0,756)<br>Antineoplastic (breast cancer) (0,629)<br>Prostatic (benign) hyperplasia treatment (0,565)<br>Antineoplastic (renal cancer) (0,549)                                     | Antiseborrheic (0,958)<br>Ovulation inhibitor (0,842)<br>Antihypercholesterolemic (0,806)<br>Antisecretoric (0,804)<br>Alopecia treatment (0,803)<br>Antiosteoporotic (0,762)<br>Menopausal disorders treatment (0,739)<br>Genital warts treatment (0,695)<br>Prostate disorders treatment (0,692)<br>Male reproductive dysfunction treatment (0,662)<br>Anesthetic general (0,649)<br>Neuroprotector (0,626)<br>Contraceptive (0,621)<br>Cytoprotectant (0,613)<br>Dementia treatment (0,592) |
| 16 | Anticancer | Antineoplastic (0,807)<br>Antineoplastic (breast cancer) (0,656)<br>Antineoplastic (sarcoma) (0,620)<br>Antineoplastic (renal cancer) (0,602)<br>Prostate cancer treatment (0,516)                | Antiseborrheic (0,958)<br>Alopecia treatment (0,878)<br>Anesthetic general (0,782)<br>Antiosteoporotic (0,779)<br>Antihypercholesterolemic (0,772)<br>Ovulation inhibitor (0,766)<br>Menopausal disorders treatment (0,759)<br>Neuroprotector (0,735)<br>Antipruritic (0,724)<br>Antisecretoric (0,708)<br>Antieczematic (0,701)<br>Genital warts treatment (0,682)<br>Prostate disorders treatment (0,671)<br>Cytoprotectant (0,642)<br>Apoptosis agonist (0,637)                             |
| 17 | Anticancer | Antineoplastic (0,786)<br>Antineoplastic (breast cancer) (0,623)<br>Antineoplastic (sarcoma) (0,611)<br>Antineoplastic (renal cancer) (0,583)<br>Prostatic (benign) hyperplasia treatment (0,557) | Antiseborrheic (0,932)<br>Alopecia treatment (0,805)<br>Ovulation inhibitor (0,758)<br>Antiosteoporotic (0,748)<br>Antihypercholesterolemic (0,732)<br>Neuroprotector (0,697)<br>Prostate disorders treatment (0,672)<br>Antieczematic (0,676)<br>Menopausal disorders treatment (0,667)<br>Antipruritic (0,660)<br>Lipid metabolism regulator (0,617)<br>Male reproductive dysfunction treatment (0,610)<br>Antiinflammatory (0,608)  |
| 18 | Anticancer | Antineoplastic (0,772)<br>Antineoplastic (breast cancer) (0,592)<br>Antineoplastic (sarcoma) (0,563)<br>Antineoplastic (renal cancer) (0,535)<br>Prostatic (benign) hyperplasia treatment (0,531) | Antiseborrheic (0,861)<br>Antihypercholesterolemic (0,774)<br>Neuroprotector (0,739)<br>Antiosteoporotic (0,728)<br>Antiinflammatory (0,719)<br>Alopecia treatment (0,707)<br>Hypolipemic (0,649)<br>Prostate disorders treatment (0,647)<br>Lipid metabolism regulator (0,642)<br>Atherosclerosis treatment (0,641)<br>Ovulation inhibitor (0,640)<br>Menopausal disorders treatment (0,573)<br>Contraceptive (0,545)   |
| 19 | Anticancer | Antineoplastic (0,795)<br>Antineoplastic (breast cancer) (0,650)  | Antiseborrheic (0,939)<br>Alopecia treatment (0,839)   |

|    |                             |   |  |
|----|-----------------------------|---|--|
|    |                             | Antineoplastic (sarcoma) (0,627)<br>Antineoplastic (renal cancer) (0,593)<br>Prostatic (benign) hyperplasia treatment (0,528) | Antihypercholesterolemic (0,817)<br>Ovulation inhibitor (0,781)<br>Menopausal disorders treatment (0,780)<br>Antiosteoporotic (0,777)<br>Neuroprotector (0,743)<br>Genital warts treatment (0,733)<br>Anesthetic general (0,730)<br>Antieczematic (0,722)<br>Lipid metabolism regulator (0,688)<br>Acute neurologic disorders treatment (0,669)<br>Prostate disorders treatment (0,654)<br>Antiinflammatory (0,642)<br>Contraceptive (0,634)   |
| 20 | Inhibitor steroid sulfatase | Antineoplastic (0,831)  | Neuroprotector (0,932)<br>Antihypercholesterolemic (0,922)<br>Antiseborrheic (0,900)<br>Acute neurologic disorders treatment (0,880)<br>Antineoplastic (0,831)<br>Male reproductive dysfunction treatment (0,824)<br>Ovulation inhibitor (0,821)<br>Antiinflammatory (0,788)<br>Antiischemic, cerebral (0,783)<br>Alopecia treatment (0,765)<br>Diuretic (0,740)<br>Antipruritic (0,720)<br>Antiosteoporotic (0,709)<br>Contraceptive (0,669)<br>Menopausal disorders treatment (0,657)<br>Prostate cancer treatment (0,593)               |
| 21 | Inhibitor steroid sulfatase | Antineoplastic (0,830)  | Antiseborrheic (0,878)<br>Ovulation inhibitor (0,877)<br>Antihypercholesterolemic (0,833)<br>Antineoplastic (0,830)<br>Neuroprotector (0,799)<br>Male reproductive dysfunction treatment (0,765)<br>Acute neurologic disorders treatment (0,712)<br>Cardiovascular analeptic (0,708)<br>Antiinflammatory (0,697)<br>Antipruritic (0,695)<br>Prostate disorders treatment (0,688)<br>Respiratory analeptic (0,669)<br>Alopecia treatment (0,663)<br>Lipid metabolism regulator (0,659)<br>Contraceptive (0,653)<br>Antiosteoporotic (0,648) |
| 22 | Inhibitor steroid sulfatase | Antineoplastic (0,820)  | Antihypercholesterolemic (0,910)<br>Neuroprotector (0,894)<br>Antiseborrheic (0,873)<br>Acute neurologic disorders treatment (0,822)<br>Antineoplastic (0,820)<br>Ovulation inhibitor (0,794)<br>Antiinflammatory (0,777)<br>Male reproductive dysfunction treatment (0,747)<br>Alopecia treatment (0,741)<br>Anesthetic general (0,729)<br>Antiallergic (0,714)<br>Lipid metabolism regulator (0,701)<br>Antiischemic, cerebral (0,695)<br>Prostate disorders treatment (0,687)<br>Antiosteoporotic (0,687)<br>Contraceptive (0,605)      |
| 23 | Inhibitor steroid sulfatase | Antineoplastic (0,815)  | Antihypercholesterolemic (0,920)<br>Antiseborrheic (0,906)<br>Neuroprotector (0,900)   |

|    |                             |                                    |   |
|----|-----------------------------|------------------------------------|---|
|    |                             |                                    | Anesthetic general (0,871)<br>Alopecia treatment (0,870)<br>Acute neurologic disorders treatment (0,852)<br>Antineoplastic (0,815)<br>Antiinflammatory (0,807)<br>Antiosteoporotic (0,752)<br>Antiallergic (0,736)<br>Genital warts treatment (0,698)<br>Ovulation inhibitor (0,680)<br>Prostate disorders treatment (0,678)<br>Diuretic (0,656)<br>Hypolipemic (0,651)<br>Antiasthmatic (0,626)<br>Contraceptive (0,618)   |
| 24 | Inhibitor steroid sulfatase | Lipid metabolism regulator (0,660) | Antihypercholesterolemic (0,886)<br>Neuroprotector (0,859)<br>Antineoplastic (0,845)<br>Ovulation inhibitor (0,817)<br>Antiseborrheic (0,812)<br>Antiinflammatory (0,752)<br>Acute neurologic disorders treatment (0,726)<br>Contraceptive (0,698)<br>Prostate disorders treatment (0,692)<br>Male reproductive dysfunction treatment (0,669)<br>Antiosteoporotic (0,663)<br>Alopecia treatment (0,663)<br>Lipid metabolism regulator (0,660)<br>Erythropoiesis stimulant (0,654)<br>Menopausal disorders treatment (0,591) |
| 25 | Inhibitor steroid sulfatase | Lipid metabolism regulator (0,775) | Antihypercholesterolemic (0,930)<br>Neuroprotector (0,914)<br>Antiseborrheic (0,857)<br>Acute neurologic disorders treatment (0,827)<br>Antineoplastic (0,802)<br>Lipid metabolism regulator (0,775)<br>Antiinflammatory (0,747)<br>Ovulation inhibitor (0,728)<br>Anesthetic general (0,728)<br>Male reproductive dysfunction treatment (0,725)<br>Alopecia treatment (0,700)<br>Antiosteoporotic (0,681)<br>Prostate disorders treatment (0,674)<br>Antischismic, cerebral (0,659)<br>Diuretic (0,622)                    |
| 26 | Not studied                 |                                    | Antiseborrheic (0,922)<br>Alopecia treatment (0,832)<br>Antineoplastic (0,783)<br>Antiinflammatory (0,766)<br>Antihypercholesterolemic (0,763)<br>Ovulation inhibitor (0,759)<br>Neuroprotector (0,747)<br>Antiosteoporotic (0,707)<br>Anesthetic general (0,699)<br>Antiprotozoal (Plasmodium) (0,684)<br>Prostate disorders treatment (0,664)<br>Menopausal disorders treatment (0,595)<br>Contraceptive (0,561)  |

\* Only activities with  $P_a > 0.5$  are shown

#### 4. Acknowledgements

The work was supported in the framework of the Russian State Academies of Sciences Fundamental Research Program for 2013-2020.

#### 5. Competing Interests

Authors have declared that no competing interests exist.

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