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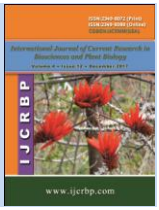

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Halogenated (F, Cl, Br, I) Anabolic Steroids and their Biological Activities

Anna Kilimnik[1], Tatyana A. Gloriozova[2] and Valery M. Dembitsky[3]*

[1]*National Institute of Water and Atmospheric Research, Private Bag 14-901, Wellington 6241, New Zealand*
[2] *Institute of Biomedical Chemistry, Moscow, Russia 119 121*
[3] *Biochemistry Laboratory, National Scientific Center of Marine Biology, 17 Palchevsky Str., Vladivostok, Russia 690 041*

Corresponding author.

Abstract

The present review describes the biological activities of synthetic anabolic halogenated (F, Cl, Br and I) steroids. About sixty biologically active halogenated steroids have shown confirmed anti-inflammatory, estrogenic, anabolic, gynecological disorders, anti-arthritic, antineoplastic, and other activities. The structures and reported and predicted activities of halogenated steroids are available. With the computer programme PASS and based on structure–activity relationships (SAR), some additional activities are also predicted, which point towards new possible applications of these lipids. This review emphasizes the role of halogenated steroids as an important source and potential leads for drug discovery and they are of great interest to chemists, physicians, biologists, pharmacologists and the pharmaceutical industry.

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Introduction

The topic of halogenated natural metabolites, which has been actively popularized for more than four decades by Gordon W. Gribble (Gribble, 1996, 1998, 1999, 2010, 2015), is increasingly of interest at the present time. More than 5,000 natural halogenated compounds have been isolated from microorganisms, fungi, plants, marine organisms, and they are found in the animal kingdom (Dembitsky et al., 2017; Gribble, 2015; Dembitsky and Tolstikov, 2003; Cabrita et al., 2010; Dembitsky, 2006; Dembitsky and Srebnik, 2002; Wagner et al., 2009).

Haloperoxidases, enzymes that incorporate halogen atoms (F, Cl, Br, and I) into molecules of both natural and synthetic compounds are found in microorganisms, fungi, and some marine invertebrates (Agarwal et al., 2017; Wang et al., 2014; Dembitsky, 2003; Butler and Walker, 1993; Butler, 1998).

Synthesis of halogenated compounds, and above all of steroids, is both of academic interest and of interest to the pharmaceutical industry (Neumann et al., 2008; Blasiak and Drennan, 2009; Vaillancourt et al., 2006; Dembitsky et al., 2002). At present, more and more attention is paid to synthetic anabolic hormones, which are used in sports medicine and are of great commercial interest (Dembitsky et al., 2017a,b; Agarwal et al., 2017; Chung and Vanderwal, 2016).

As already proved by numerous works, there is a relationship between structure and activity, and this principle is called SAR (Structure-Activity-Relationship). We used the computer program PASS, containing about one million chemical compounds and more than 8,000 biological activities, and calculated the biological activity of different natural and/or synthetic compounds (Dembitsky et al., 20017a-e). 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 (Filz, Poroikov, 2012; Lagunin et al., 2010, 2011; Goel et al., 2011).

This review is devoted to synthetic halogenated (F, Cl, Br, I) steroids and their biological activity.

Halogenated (F, Cl, Br, and I) Steroids

The halogenated steroids presented in the review are divided into four groups. The first group includes steroids containing a fluorine atom, which is incorporated into the composition of the molecule of steroids. Structures of the fluorine containing steroids are presented in Fig. 1, and their biological activity is shown in Table 1. The second group includes steroids containing a chlorine atom in the molecule. The structures of chlorine-containing sterols are shown in Fig. 2, and the biological activity is shown in Table 2.The third group contains information on bromine containing steroids, which is presented in Figure 3 and Table 3, respectively. The fourth group is devoted to iodine containing steroids, and structures and biological activity are presented in Fig. 4 and Table 4, respectively.

Table 1. Biological activities of fluorinated steroids (**1-15**).

No.	Activity reviewed	Activities confirmed (Pa)	Predicted activities (Pa)*
1	Anti breast cancer inhibitor of 11β-hydroxysteroid dehydrogenase	Anabolic (0.983) Antineoplastic (0.855) Ovulation inhibitor (0.794) Menopausal disorders treatment (0.718)	Anabolic (0.983) Antiinflammatory (0.967) Antiallergic (0.959) Antiasthmatic (0.946) Antiarthritic (0.931) Antineoplastic (0.855) Antipruritic (0.837) Antiseborrheic (0.832) Autoimmune disorders treatment (0.814) Immunosuppressant (0.803) Ovulation inhibitor (0.794) Inflammatory Bowel disease treatment (0.779) Respiratory analeptic (0.776) Antisecretoric (0.768) Diuretic (0.766) Menopausal disorders treatment (0.718) Prostate disorders treatment (0.689) Antiosteoporotic (0.659)
2	Gonadotropin Inhibitor	Ovulation inhibitor (0.678) Endometrios treatment (0.668) Gynecological disorders treatment (0.597) Male reproductive disfunction treatment (0.883)	Antineoplastic (0.961) Male reproductive disfunction treatment (0.883) Antiseborrheic (0.821) Prostate disorders treatment (0.746) Antipruritic (0.744) Prostate cancer treatment (0.717) Antiosteoporotic (0.700) Ovulation inhibitor (0.678) Endometrios treatment (0.668) Immunosuppressant (0.663) Contraceptive (0.617) Gynecological disorders treatment (0.597)

No.	Activity reviewed	Activities confirmed (Pa)	Predicted activities (Pa)*
3	Not studied		Prostate disorders treatment (0.780) Dermatologic (0.768) Antineoplastic (0.762) Anesthetic general (0.754) Antiinflammatory (0.751) Antiinfertility, female (0.750) Antipruritic (0.733) Erythropoiesis stimulant (0.700) Prostatic (benign) hyperplasia treatment (0.692) Immunosuppressant (0.645) Menopausal disorders treatment (0.631) Ovulation inhibitor (0.631) Contraceptive (0.622) Antiosteoporotic (0.597)
4	Not studied		Antiallergic (0.849) Anesthetic general (0.842) Antineoplastic (0.834) Erythropoiesis stimulant (0.816) Prostate disorders treatment (0.780) Antipruritic (0.753) Antiasthmatic (0.738) Antieczematic (0.691) Antiinflammatory (0.690) Prostatic (benign) hyperplasia treatment (0.686) Choleretic (0.682) Immunosuppressant (0.668) Contraceptive (0.627) Menopausal disorders treatment (0.626) Antiosteoporotic (0.623)
5	Not studied		Antiinflammatory (0.988) Antiallergic (0.980) Antiasthmatic (0.962) Antiarthritic (0.956) Antipruritic (0.902) Autoimmune disorders treatment (0.887) Immunosuppressant (0.839) Antipsoriatic (0.822) Antineoplastic (0.816) Inflammatory Bowel disease treatment (0.752) Allergic rhinitis treatment (0.749) Rheumatoid arthritis treatment (0.721) Chronic obstructive pulmonary disease treatment (0.693) Prostate disorders treatment (0.634)
6	Not studied		Anesthetic general (0.900) Antineoplastic (0.805) Contraceptive (0.765) Antipruritic (0.757) Cardiotonic (0.746) Immunosuppressant (0.719) Antiinflammatory (0.682) Neuroprotector (0.668)

No.	Activity reviewed	Activities confirmed (Pa)	Predicted activities (Pa)*
			Menopausal disorders treatment (0.664) Prostate disorders treatment (0.648) Ovulation inhibitor (0.596) Antiosteoporotic (0.522) Prostate cancer treatment (0.507)
7	menopause disorders perimenopause disorders	Gynecological disorders treatment (0.962) Antineoplastic (0.916) Prostatic (benign) hyperplasia treatment (0.899) Ovulation inhibitor (0.821) Menopausal disorders treatment (0.662) Male reproductive disfunction treatment (0.600)	Prostate disorders treatment (0.992) Gynecological disorders treatment (0.962) Antiacne (0.949) Antineoplastic (0.916) Prostatic (benign) hyperplasia treatment (0.899) Anesthetic general (0.824) Ovulation inhibitor (0.821) Antiseborrheic (0.805) Antipruritic (0.769) Antiinflammatory (0.768) Alopecia treatment (0.694) Respiratory analeptic (0.689) Menopausal disorders treatment (0.662) Immunosuppressant (0.627) Male reproductive disfunction treatment (0.600) Antiosteoporotic (0.589)
8	Not studied		Prostate disorders treatment (0.992) Gynecological disorders treatment (0.951) Antiacne (0.932) Antineoplastic (0.930) Prostatic (benign) hyperplasia treatment (0.873) Antipruritic (0.784) Ovulation inhibitor (0.734) Antiinflammatory (0.724) Antiseborrheic (0.662) Analgesic (0.622) Alopecia treatment (0.617) Neuroprotector (0.597) Menopausal disorders treatment (0.576) Antiosteoporotic (0.567) Diuretic (0.542)
9	Not studied		Respiratory analeptic (0.950) Antiinflammatory (0.922) Antineoplastic (0.905) Antisecretoric (0.875) Antipruritic (0.854) Ovulation inhibitor (0.819) Diuretic (0.816) Antiallergic (0.808) Antiseborrheic (0.807) Contraceptive (0.788) Immunosuppressant (0.770) Acute neurologic disorders treatment (0.767) Prostate disorders treatment (0.724) Antiarthritic (0.658) Antiosteoporotic (0.639)

No.	Activity reviewed	Activities confirmed (Pa)	Predicted activities (Pa)*
10	Not studied		Antiinflammatory (0.925) Antiallergic (0.902) Antiasthmatic (0.823) Antineoplastic (0.820) Antipruritic (0.807) Immunosuppressant (0.756) Antiarthritic (0.738) 6Prostate disorders treatment (0.720) Diuretic (0.656) Contraceptive (0.654) Anesthetic general (0.647) Antipsoriatic (0.645) Antiosteoporotic (0.639) Erythropoiesis stimulant (0.623) Menopausal disorders treatment (0.608)
11	Not studied		Antineoplastic (0.914) Antiseborrheic (0.852) Alopecia treatment (0.827) Prostate disorders treatment (0.710) Antiosteoporotic (0.700) Neuroprotector (0.679) Anesthetic general (0.666) Ovulation inhibitor (0.663) Erythropoiesis stimulant (0.652) Menopausal disorders treatment (0.625) Vasoprotector (0.601) Prostate cancer treatment (0.589) Male reproductive disfunction treatment (0.583) Contraceptive (0.570)
12	Not studied		Antiallergic (0.961) Antiasthmatic (0.955) Antiinflammatory (0.937) Antiarthritic (0.915) Male reproductive disfunction treatment (0.903) Antineoplastic (0.902) Inflammatory Bowel disease treatment (0.824) Ovulation inhibitor (0.820) Antipruritic (0.818) Antipsoriatic (0.760) Immunosuppressant (0.758) Prostate disorders treatment (0.743) Antiseborrheic (0.742) Prostate cancer treatment (0.677) Antiosteoporotic (0.666)
13	Not studied		Antineoplastic (0.888) Anesthetic general (0.865) Antihypercholesterolemic (0.840) Antieczematic (0.824) Respiratory analeptic (0.807) Antipruritic (0.794) Antiosteoporotic (0.755) Immunosuppressant (0.701)

No.	Activity reviewed	Activities confirmed (Pa)	Predicted activities (Pa)*
			Prostatic (benign) hyperplasia treatment (0.663) Antipsoriatic (0.656) Hypolipemic (0.653) Antiinflammatory (0.629) Antiacne (0.553)
14	Not studied		Dermatologic (0.917) Antiinflammatory (0.916) Antiallergic (0.902) Antiasthmatic (0.883) Antiarthritic (0.880) Antisecretoric (0.858) Antipruritic (0.854) Antineoplastic (0.840) Hepatoprotectant (0.818) Male reproductive disfunction treatment (0.805) Immunosuppressant (0.803) Antipsoriatic (0.800) Antieczematic (0.799) Antiosteoporotic (0.746) Respiratory analeptic (0.721) Prostatic (benign) hyperplasia treatment (0.675) Autoimmune disorders treatment (0.660)
15	Not studied		Anesthetic general (0.865) Antineoplastic (0.865) Antieczematic (0.827) Prostatic (benign) hyperplasia treatment (0.825) Antihypercholesterolemic (0.821) Respiratory analeptic (0.821) Antipruritic (0.774) Antiosteoporotic (0.718) Immunosuppressant (0.688) Hypolipemic (0.661) Biliary tract disorders treatment (0.655) Antipsoriatic (0.655) Antiseborrheic (0.650) Prostate cancer treatment (0.505)
16	Not studied		Anesthetic general (0.928) Antineoplastic (0.903) Prostatic (benign) hyperplasia treatment (0.871) Respiratory analeptic (0.862) Antieczematic (0.855) Antihypercholesterolemic (0.853) Antipruritic (0.792) Antiosteoporotic (0.785) Immunosuppressant (0.745) Antipsoriatic (0.711) Hypolipemic (0.700) Antiinflammatory (0.669) Biliary tract disorders treatment (0.655) Hepatic disorders treatment (0.642) Prostate cancer treatment (0.538)

* Only activities with Pa > 0.5 are shown.

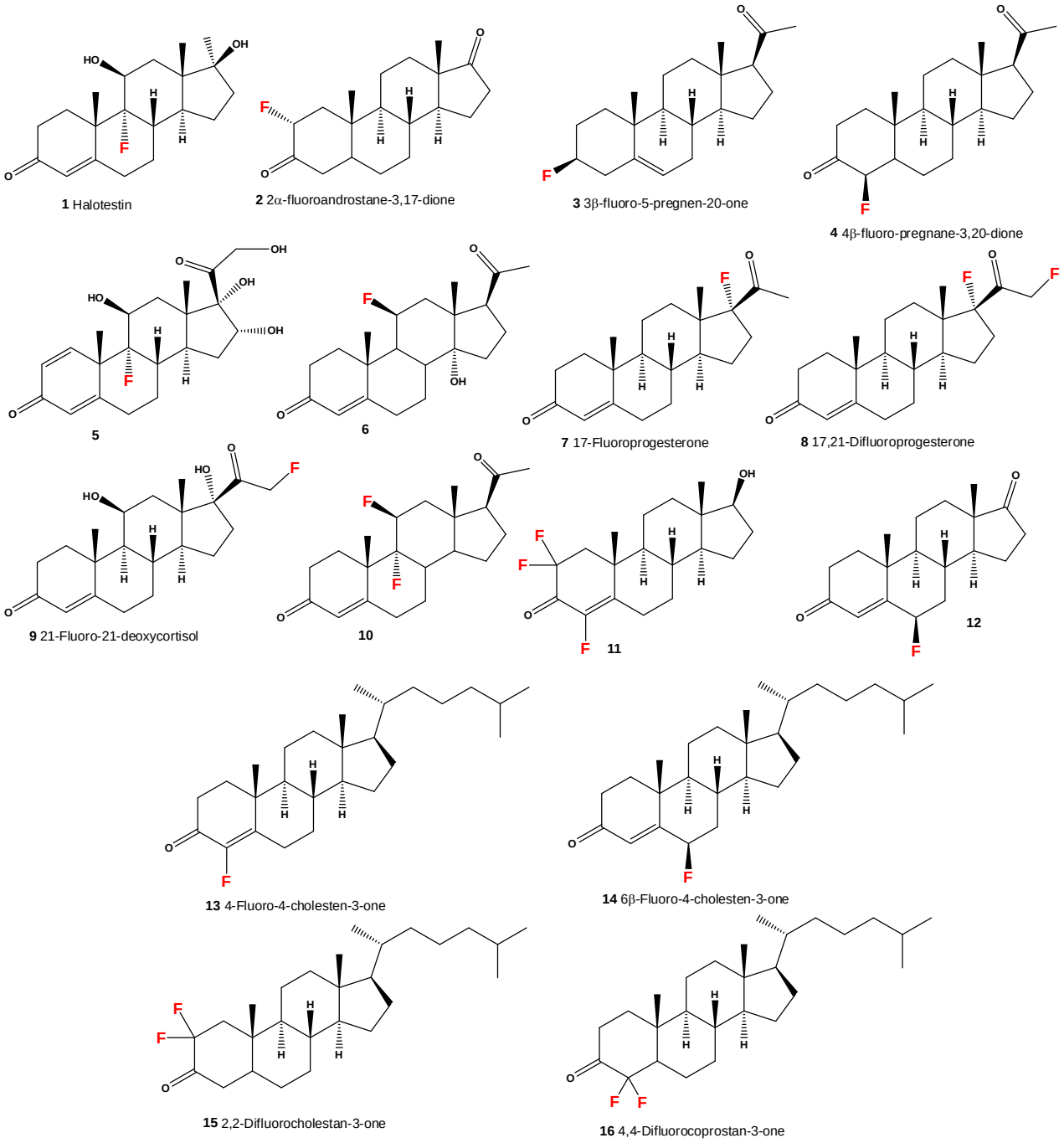

Fig. 1: Bioactive anabolic fluorinated steroids (**1-15**).

Fluorinated steroids

Fluorine containing metabolites is a small group of natural compounds that are isolated from plants (Ward et al., 1964; O'Hagan and Harper, 1999; Dembitsky and Srebnik, 2002). All fluoride containing steroids, for today, are synthetic (Wettstein, 1971, 1972; Al Jasema et al., 2016). Many of these lipid compounds belong to the class of anabolic steroids and are used in sports medicine and bodybuilding (Wettstein 1971; Kourounakis et al., 1976; Reyes-Moreno et al., 2009).

One of the most famous fluorinated steroids is halotestin (**1**), which is a 17α-alkylated derivative of testosterone, belongs to the class of active anabolic-androgenic hormones. Halotestin was synthesized in the late 50s of the 20th century (Mayer and Rosen, 1975; Loebell 1955). One of the most known is fluorinated steroids is

halotestin (**1**), which is a 17α-alkylated derivative of testosterone, belongs to the class of active anabolic-androgenic hormones. Halotestin was synthesized in the late 50s of the 20th century. Halotestin is also a significant inhibitor of 11β-hydroxysteroid dehydrogenase type 2, and also showed anticancer activity to breast cancer (Kennedy, 1958; Kicman, 2008).

The 2-Fluoro-5α-androstane-3,17-diones series, including (**2**), was synthesized by Allinger and co-workers (1963), and the configuration and conformation of synthesized steroids was determined, but without determining their biological activity. Another series of 2-fluoro androstanes were synthesized as inhibitors of gonadotropin in pregnancy and menstrual disorders (Hogg and Nathan, 1968).

3β-Fluoro-5-pregnen-20-one (**3**) and other steroids (**4**), (**5**), (**6**), (**8**), (**9**), (**10**) and (**12**) were synthesized in order to find an efficient method for the synthesis of these compounds. The activity of synthesized steroids has not been studied (Ayer, 1962; Wettstein, 1971, 1972; Thomas, 1980).

17-Fluoroprogesterone (**7**) was synthesized as a hormone for the treatment of menopause or perimenopause, without complications in the uterus of warm-blooded animals (Bouali et al., 2003). Synthesis of rare 2,2,4-trifluoro-steroid (**11**) has been described more than forty years ago, but their activity has not been studied (Nakanishi and Jensen, 1977).

A series of fluorinated cholesterol and its derivatives including fluorine containing steroids (**13**, **14**, **15**, and **16**) has been described by many authors, but the activity of many of them has not been published (Gabbard and Jensen, 1958; Cross et al., 1964; Thomas et al., 1999).

If we sum up the data given in Table 1, which is devoted to the biological activity of fluorinated steroids, then these compounds refer to anabolic steroids, and in general they exhibit anti-inflammatory, anti-allergic, anti-asthmatic, gynecological disorders, anti-arthritic, and antineoplastic activities (structures given in Fig. 1).

Chlorinated steroids

Chlorine containing steroids are the most famous group of natural compounds (Gribble, 2015; Dembitsky and Tolstikov, 2003). These chlorinated lipid metabolites are found predominantly in plants, and also found in marine invertebrates. More details can be found in the recently published reviews (Dembitsky et al., 2017; Wang et al., 2013; Misico et al., 2011).

Among the synthetic chlorinated steroids, the most popular among athletes are anabolic hormones such as 4-chlorotestosterone (known as clostebol, **17**), norclostebol (**18**), oral turinabol (**19**), and oxyguno (**20**, structure see in Fig. 2). It is known that clostebol has anabolic effects and is used in sports to improve physical performance, prohibited by the International Olympic Committee (Debruyckere et al., 1992). Norclostebol (known as lentabol, **18**) is a derivative of testosterone. It is 6.6 times more than anabolic, and 40% more androgenic than testosterone. It is a powerful anabolic compound with a minimal tendency to side effects (Le Bizec et al., 2006).

4-chlorodehydromethyltestosterone (known as oral turinabol, **19**) is a potent and unique anabolic steroid that was synthesized in 1962 in East Germany. Steroid has a very high safety rating for many decades, both among men, women and even children. Increases body weight without side effects (Hinkel, 1966; Petzold et al., 1969). 4-chloro-17α-methyl-etioallochol-4-ene-17β-ol-3,11-dione (known as oxyguno, **20**) is an anabolic steroid that has only seven percent of the androgenic testosterone effect and at least 850 percent of the anabolic testosterone effect. This hormone was synthesized in East Germany in the 60s of the 20th century, and was used by GDR (German Democratic Republic) sportsmen (Wong et al., 2015; Akram et al., 2011).

6-Chloro-androst-4-ene-3-one-17β-ol (hexadrone, **21**) is a new generation of legal androgens that increases muscle mass (up to 8-12 pounds) and increases the strength of the athlete. It is very powerful, prohormone, does not retain water in the body, and has a strong anabolic and androgenic ratio of 300:1 (Joseph and Parr, 2015).

6 β -Chloro-androst-4-en-17 β-ol-3-one (**22**) is an epimer of hexadrone, and has milder properties than hexadrone. 3-Chloro-17-methylandrostenediol (promagnon, **23**) is a methylated derivative of the anabolic steroid testosterone, which is designed to stimulate and build muscle mass, as well as improve muscle density, vascularity and hardness (Lootens et al., 2011). Additional biological activity for anabolic chlorinated hormones (**17**-**23**) is shown in Table 2.

Table 2. Biological activities of chlorinated steroids (**17**-**30**).

No.	Activity reviewed	Activities confirmed (Pa)	Predicted activities (Pa)*
17	Anabolic effects Bodybuilding Effect	Antiseborrheic (0.926) Growth stimulant (0.903) Endometrios treatment (0.770) Neuroprotector (0.770)	Antiseborrheic (0.926) Growth stimulant (0.903) Antineoplastic (0.882) Alopecia treatment (0.861) Respiratory analeptic (0.796) Antihypercholesterolemic (0.793) Antisecretoric (0.786) Endometrios treatment (0.770) Neuroprotector (0.770) Ovulation inhibitor (0.754) Antiosteoporotic (0.738) Menopausal disorders treatment (0.703) Erythropoiesis stimulant (0.698) Prostate cancer treatment (0.570)
18	Anabolic effects Bodybuilding Effect	Antiseborrheic (0.936) Growth stimulant (0.900)	Antiseborrheic (0.936) Growth stimulant (0.900) Antineoplastic (0.888) Antihypercholesterolemic (0.830) Respiratory analeptic (0.828) Ovulation inhibitor (0.824) Antisecretoric (0.801) Endometrios treatment (0.796) Contraceptive (0.761) Antiinflammatory (0.751) Antiosteoporotic (0.746) Lipid metabolism regulator (0.735) Menopausal disorders treatment (0.733) Prostate cancer treatment (0.629)
19	Anabolic effects Bodybuilding Effect	Antiseborrheic (0.941) Growth stimulant (0.873) Antiinflammatory (0.868) Antisecretoric (0.802)	Antiseborrheic (0.941) Antineoplastic (0.893) Growth stimulant (0.873) Antiinflammatory (0.868) Antisecretoric (0.802) Antipruritic (0.777) Antiosteoporotic (0.743) Ovulation inhibitor (0.726) Contraceptive (0.713) Immunosuppressant (0.713) Antihypercholesterolemic (0.687) Menopausal disorders treatment (0.685) Antiallergic (0.668) Diuretic (0.662) Endometrios treatment (0.648) Prostate cancer treatment (0.578)
20	Anabolic effects Bodybuilding effect	Antiseborrheic (0.909) Growth stimulant (0.886) Antiinflammatory (0.806) Immunosuppressant (0.703)	Antiseborrheic (0.909) Antineoplastic (0.888) Growth stimulant (0.886) Antiinflammatory (0.806) Endometrios treatment (0.771) Male reproductive disfunction treatment (0.763) Ovulation inhibitor (0.744) Contraceptive (0.734)

No.	Activity reviewed	Activities confirmed (Pa)	Predicted activities (Pa)*
			Immunosuppressant (0.703) Antiacne (0.691) Antipruritic (0.687) Antiosteoporotic (0.680) Antihypercholesterolemic (0.673) Menopausal disorders treatment (0.658) Prostate cancer treatment (0.649)
21	Anabolic effects Bodybuilding effect	Antiseborrheic (0.919) Antihypercholesterolemic (0.914)	Respiratory analeptic (0.925) Antiseborrheic (0.919) Antihypercholesterolemic (0.914) Antineoplastic(0.900) Antiinflammatory (0.871) Antipruritic (0.769) Antisecretoric (0.763) Ovulation inhibitor (0.755) Antiallergic (0.747) Hepatoprotectant (0.722) Immunosuppressant (0.716) Contraceptive (0.692) Alopecia treatment (0.667) Antiosteoporotic (0.641) Prostatic (benign) hyperplasia treatment (0.582) Antifungal (0.579)
22	Anabolic effects Bodybuilding effect	Antiseborrheic (0.919) Antihypercholesterolemic (0.914)	Respiratory analeptic (0.925) Antiseborrheic (0.919) Antihypercholesterolemic (0.914) Antineoplastic(0.900) Antiinflammatory (0.871) Antipruritic (0.769) Antisecretoric (0.763) Ovulation inhibitor (0.755) Antiallergic (0.747) Hepatoprotectant (0.722) Immunosuppressant (0.716) Contraceptive (0.692) Alopecia treatment (0.667) Antiosteoporotic (0.641) Prostatic (benign) hyperplasia treatment (0.582) Antifungal (0.579)
23	Anabolic effects Bodybuilding effect	Gynecological disorders treatment (0.959) Antiseborrheic (0.944) Antihypercholesterolemic (0.887)	Gynecological disorders treatment (0.959) Antineoplastic (0.947) Antiseborrheic (0.944) Antihypercholesterolemic (0.887) Respiratory analeptic (0.880) Growth stimulant (0.848) Antidepressant (0.833) Ovulation inhibitor (0.828) Lipid metabolism regulator (0.828) Antiinflammatory (0.774) Antipruritic (0.759) Antiosteoporotic (0.740) Contraceptive (0.709) Alopecia treatment (0.709) Psychotropic (0.712)

No.	Activity reviewed	Activities confirmed (Pa)	Predicted activities (Pa)*
			Prostate cancer treatment (0.628) Dementia treatment (0.585) 0.951
24	Anabolic effects Bodybuilding effect	Antipruritic (0.797) Antiseborrheic (0.785) Male reproductive disfunction treatment (0.779)	Anesthetic general (0.951) Antiinflammatory (0.863) Antineoplastic (0.821) Antipruritic (0.797) Antiseborrheic (0.785) Male reproductive disfunction treatment (0.779) Respiratory analeptic (0.764) Immunosuppressant (0.736) Antiallergic (0.734) Ovulation inhibitor (0. 679) Antisecretoric (0.679) Neuroprotector (0.650) Erythropoiesis stimulant (0.649) Menopausal disorders treatment (0.606) Prostate cancer treatment (0.565)
25	Anti-inflammatory activity	Antiinflammatory (0.888)	Antiinflammatory (0.888) Antiseborrheic (0.887) Antiasthmatic (0.847) Ovulation inhibitor (0.844) Antiallergic (0.832) Antineoplastic (0.825) Antipruritic (0.798) Male reproductive disfunction treatment (0.786) Alopecia treatment (0.771) Immunosuppressant (0.712) Cardiovascular analeptic (0.701) Neuroprotector (0.705) Menopausal disorders treatment (0.614) Vasoprotector (0.613) Erythropoiesis stimulant (0.590) Antiosteoporotic (0.573) Prostate cancer treatment (0.519)
26	Not studied		Antiseborrheic (0.937) Antineoplastic (0.818) Alopecia treatment (0.805) Anesthetic general (0.769) Antiosteoporotic (0.761) Immunosuppressant (0.713) Acute neurologic disorders treatment (0.702) Menopausal disorders treatment (0.696) Genital warts treatment (0.692) Antiinflammatory (0.652) Ovulation inhibitor (0.638) Male reproductive disfunction treatment (0.633) Prostatic (benign) hyperplasia treatment (0.629)
27	Estrogenic activity	Antiasthmatic (0.957) Antiarthritic (0.926) Antiallergic (0.907) Immunosuppressant (0.838)	Antiinflammatory (0.979) Antiasthmatic (0.957) Antiarthritic (0.926) Antiallergic (0.907) Immunosuppressant (0.838)

No.	Activity reviewed	Activities confirmed (Pa)	Predicted activities (Pa)*
			Antipruritic, allergic (0.832) Respiratory analeptic (0.809) Antineoplastic (0.741) Antiseborrheic (0.681) Autoimmune disorders treatment (0.679) Antipsoriatic (0.647) Contraceptive (0.640) Rheumatoid arthritis treatment (0.607) Prostate disorders treatment (0.607)
28	Not studied		Antihypercholesterolemic (0.926) Anesthetic general (0.913) Respiratory analeptic (0.897) Neuroprotector (0.872) Antiseborrheic (0.862) Ovulation inhibitor (0.822) Antieczematic (0.822) Erythropoiesis stimulant (0.817) Menopausal disorders treatment (0.795) Antiinflammatory (0.779) Antineoplastic (0.770) Immunosuppressant (0.755) Alopecia treatment (0.725) Hepatoprotectant (0.719) Antiosteoporotic (0.655) Prostate cancer treatment (0.526)
29	Not studied		Antiinflammatory (0.956) Antineoplastic (0.906) Antiallergic (0.904) Respiratory analeptic (0.816) Immunosuppressant (0.803) Antipruritic, allergic (0.741) Antipsoriatic (0.723) Antihypercholesterolemic (0.640) Menopausal disorders treatment (0.596) Antifungal (0.588) Contraceptive (0.572) Ovulation inhibitor (0.551) Prostatic (benign) hyperplasia treatment (0.543) Antiosteoporotic (0.527)
30	Not studied		Antiinflammatory (0.955) Antiallergic (0.920) Male reproductive disfunction treatment (0.872) Antineoplastic (0.854) Antipruritic (0.819) Immunosuppressant (0.812) Antiasthmatic (0.795) Antiarthritic (0.743) Antiseborrheic (0.709) Antipsoriatic (0.647) Prostate cancer treatment (0.633) Contraceptive (0.626) Rheumatoid arthritis treatment (0.612) Antiosteoporotic (0.544)

* Only activities with Pa > 0.5 are shown.

Table 3. Biological activities of brominated steroids (**31**-**42**).

No.	Activity reviewed	Activities confirmed (Pa)	Predicted activities (Pa)*
31	Progestational activity	Menopausal disorders treatment (0.782) Antipruritic (0.776) Ovulation inhibitor (0.757) Immunosuppressant (0.704) Contraceptive (0.640)	Antineoplastic (0.886) Antiseborrheic (0.833) Antiinflammatory (0.819) Menopausal disorders treatment (0.782) Antipruritic (0.776) Ovulation inhibitor (0.757) Immunosuppressant (0.704) Contraceptive (0.640) Antisecretoric (0.632) Endometrios treatment (0.624) Male reproductive disfunction treatment (0.606) Prostate cancer treatment (0.574) Antiosteoporotic (0.537)
32	Progestational activity	Ovulation inhibitor (0.696) Growth stimulant (0.673)	Antineoplastic (0.902) Male reproductive disfunction treatment (0.829) Antiseborrheic (0.715) Antiinflammatory (0.710) Ovulation inhibitor (0.696) Allergic conjunctivitis treatment (0.690) Growth stimulant (0.673) Prostatic (benign) hyperplasia treatment (0.673) Alopecia treatment (0.623) Antipruritic (0.582) Cystic fibrosis treatment (0.555) Menopausal disorders treatment (0.553) Immunosuppressant (0.531) Antiosteoporotic (0.518)
33	Not studied		Antiseborrheic (0.915) Ovulation inhibitor (0.887) Alopecia treatment (0.836) Antineoplastic (0.833) Male reproductive disfunction treatment (0.779) Menopausal disorders treatment (0.728) Neuroprotector (0.707) Antiosteoporotic (0.680) Contraceptive (0.609) Diuretic (0.606) Endometrios treatment (0.600) Respiratory analeptic (0.595) Prostate cancer treatment (0.594) Lipid metabolism regulator (0.562) Dementia treatment (0.556)
34	Not studied		Antiseborrheic (0.911) Ovulation inhibitor (0.859) Antineoplastic (0.848) Alopecia treatment (0.817) Male reproductive disfunction treatment (0.742) Cardiovascular analeptic (0.740) Antiosteoporotic (0.701) Menopausal disorders treatment (0.691) Neuroprotector (0.627) Endometrios treatment (0.620) Prostate cancer treatment (0.561)

No.	Activity reviewed	Activities confirmed (Pa)	Predicted activities (Pa)*
			Antihypercholesterolemic (0.543) Dementia treatment (0.517)
35	Not studied		Antiinflammatory (0.895) Respiratory analeptic (0.875) Antisecretoric (0.855) Antiseborrheic (0.841) Antipruritic (0.815) Ovulation inhibitor (0.801) Antineoplastic (0.800) Immunosuppressant (0.777) Menopausal disorders treatment (0.765) Contraceptive (0.745) Antiallergic (0.720) Endometrios treatment (0.549) Antiosteoporotic (0.543) Prostate cancer treatment (0.508)
36	Not studied		Antiinflammatory (0.879) Antineoplastic (0.816) Antiseborrheic (0.787) Ovulation inhibitor (0.783) Antipruritic (0.770) Immunosuppressant (0.741) Antiallergic (0.730) Alopecia treatment (0.720) Neuroprotector (0.685) Male reproductive disfunction treatment (0.679) Menopausal disorders treatment (0.655) Contraceptive (0.643) Growth stimulant (0.629) Antiasthmatic (0.604) Prostatic (benign) hyperplasia treatment (0.586) Antiosteoporotic (0.588)
37	Anticancer	Apoptosis agonist (0.752) Antineoplastic (0.751)	Antieczematic (0.776) Apoptosis agonist (0.752) Antineoplastic (0.751) Antinociceptive (0.734) Antipruritic (0.693) Cytoprotectant (0.682) Antifungal (0.668) Hepatoprotectant (0.635) Antipsoriatic (0.621) Cystic fibrosis treatment (0.580) Antiviral (Influenza) (0.578) Erythropoiesis stimulant (0.572) Prostate disorders treatment (0.567) Antiinflammatory (0.566) Antibacterial (0.553)
38	Anticancer	Angiogenesis inhibitor (0.945) Antineoplastic (0.891) Apoptosis agonist (0.785)	Angiogenesis inhibitor (0.945) Antineoplastic (0.891) Apoptosis agonist (0.785) Cytoprotectant (0.647) Antiinflammatory (0.645) Antieczematic (0.639)

No.	Activity reviewed	Activities confirmed (Pa)	Predicted activities (Pa)*
			Prostate disorders treatment (0.568) Antiviral (Influenza) (0.567) Antipsoriatic (0.509) Hepatoprotectant (0.503)
39	Anticancer	Antiviral (Influenza) (0.818) Apoptosis agonist (0.775) Antineoplastic (0.757)	Antiviral (Influenza) (0.818) Apoptosis agonist (0.775) Antineoplastic (0.757) Antiinflammatory (0.712) Cytoprotectant (0.681) Antieczematic (0.676) Immunosuppressant (0.622) Hepatoprotectant (0.593) Prostate disorders treatment (0.590) Antinociceptive (0.580)
40	Glucocorticoid activity	Antineoplastic (0.751) Cystic fibrosis treatment (0.740) Alopecia treatment (0.695)	Antiseborrheic (0.886) Ovulation inhibitor (0.793) Antineoplastic (0.751) Cystic fibrosis treatment (0.740) Alopecia treatment (0.695) Genital warts treatment (0.583) Menopausal disorders treatment (0.579) Prostatic (benign) hyperplasia treatment (0.539) Male reproductive disfunction treatment (0.526) Radiosensitizer (0.506)
41	Glucocorticoid activity	Alopecia treatment (0.785) Antineoplastic (0.785) Genital warts treatment (0.759)	Antiseborrheic (0.916) Alopecia treatment (0.785) Antineoplastic (0.785) Genital warts treatment (0.759) Ovulation inhibitor (0.742) Menopausal disorders treatment (0.618) Dementia treatment (0.571) Antiosteoporotic (0.560) Radiosensitizer (0.528) Antisecretoric (0.521) Prostatic (benign) hyperplasia treatment (0.515)
42	Glucocorticoid activity	Apoptosis agonist (0.869)	Apoptosis agonist (0.869) Antiinflammatory (0.853) Antiseborrheic (0.853) Antineoplastic (0.852) Respiratory analeptic (0.760) Antipruritic (0.740) Immunosuppressant (0.718) Male reproductive disfunction treatment (0.714) Anesthetic general (0.686) Antiallergic (0.665) Erythropoiesis stimulant (0.645) Menopausal disorders treatment (0.563) Prostate cancer treatment (0.562) Antipsoriatic (0.555) Cytostatic (0.532)

* Only activities with Pa > 0.5 are shown.

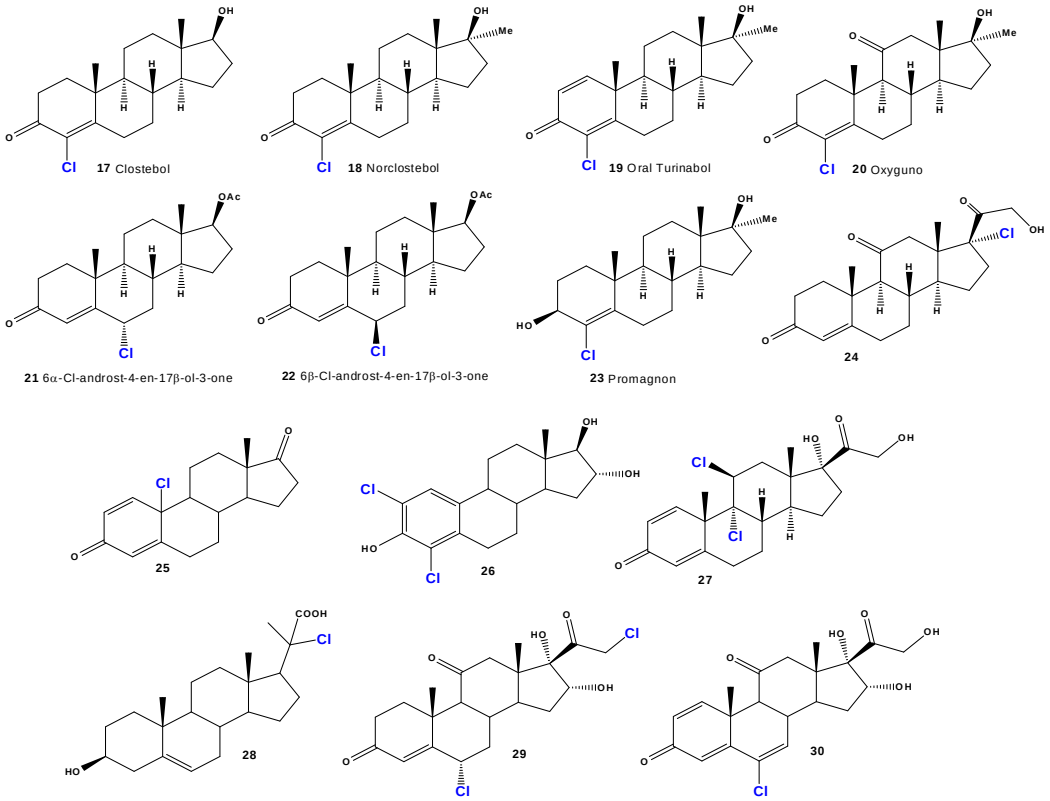

Fig. 2: Bioactive anabolic chlorinated steroids (**17**-**30**).

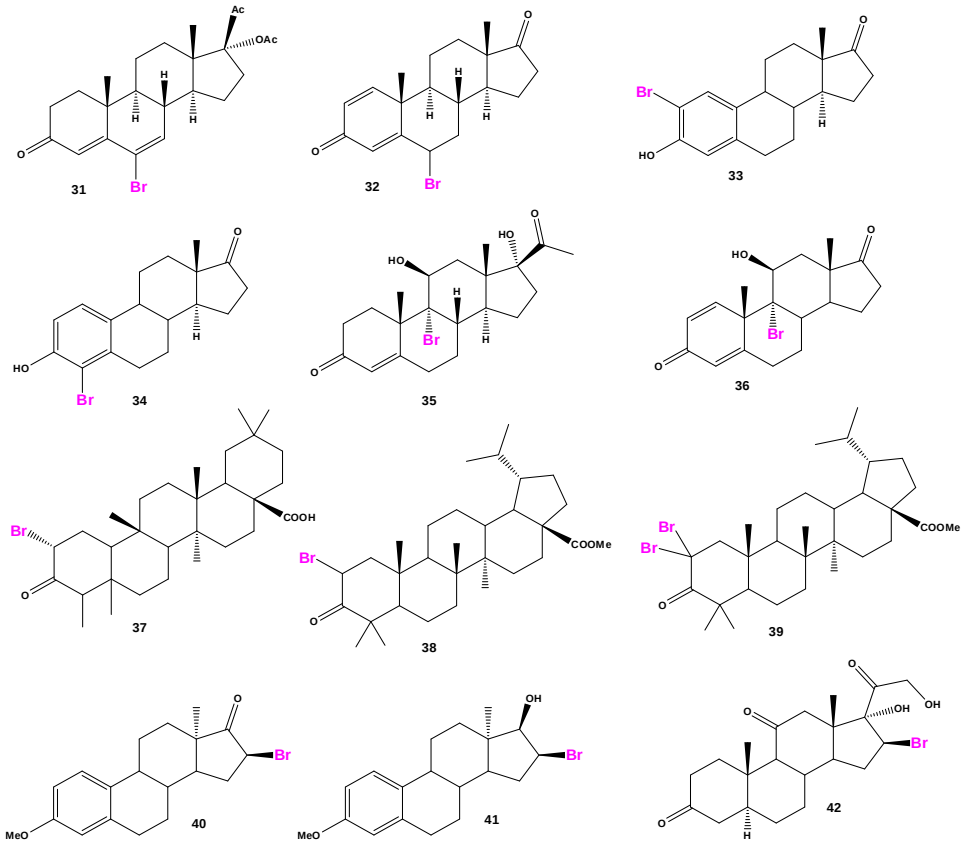

Fig. 3: Bioactive anabolic brominated steroids (**31**-**42**).

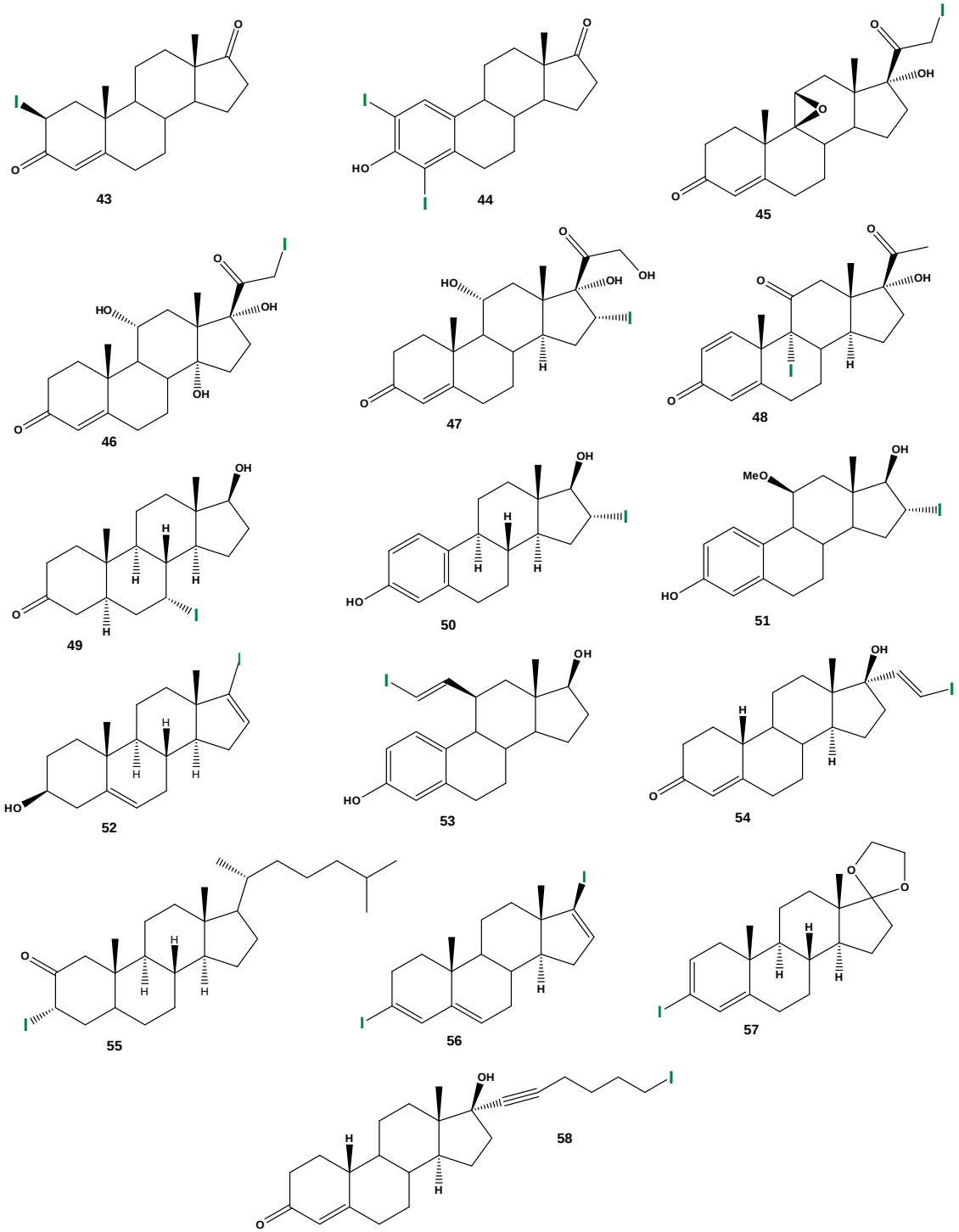

Fig. 4: Bioactive anabolic iodinated steroids (**43**-**58**).

The 17-chloro steroids series was synthesized as an anti-influenza drug, one of them (**24**) had the most pronounced anti-inflammatory activity (Laurent et al., 1973). The 10-chloro-19-norcardiosteroid (**25**) was synthesized, but their activity was not determined (Makarevich et al., 2009). Nakamura and co-workers (2006) synthesized a number of chloro- and bromo-estrogens, including 2,4-dichloro-estriol (**26**), which showed estrogenic activity.Chlorine containing steroids (**27**-**30**) were synthesized by different authors, but their activity was not determined (Berkoz 1972; Herz and Josef, 1959; Allan and Ringol, 1961; Engel et al., 1960).

Table 4. Biological activities of iodinated steroids (**43**-**58**).

No.	Activity reviewed	Activities confirmed (Pa)	Predicted activities (Pa)*
43	Not studied		Antineoplastic (0.906) Ovulation inhibitor (0.840) Antiseborrheic (0.760) Male reproductive disfunction treatment (0.757) Prostate cancer treatment (0.712) Alopecia treatment (0.673) Menopausal disorders treatment (0.599) Antileukemic (0.586) Neuroprotector (0.569) Antiosteoporotic (0.564) Antipruritic (0.538) Endometrios treatment (0.530) Erythropoiesis stimulant (0.511) Growth stimulant (0.508)
44	Not studied		Antiseborrheic (0.882) Antihypercholesterolemic (0.877) Antineoplastic (0.823) Ovulation inhibitor (0.814) Alopecia treatment (0.770) Male reproductive disfunction treatment (0.754) Antisecretoric (0.749) Diuretic (0.738) Respiratory analeptic (0.698) Growth stimulant (0.609) Menopausal disorders treatment (0.604) Antiosteoporotic (0.597) Prostate cancer treatment (0.567) Neuroprotector (0.562) Endometrios treatment (0.559) Antiinflammatory (0.539)
45	Not studied		Respiratory analeptic (0.947) Antineoplastic (0.855) Diuretic (0.813) Apoptosis agonist (0.780) Antiinflammatory (0.756) Contraceptive (0.736) Antiseborrheic (0.735) Cardiotonic (0.733) Antipruritic (0.710) Antiarthritic (0.691) Autoimmune disorders treatment (0.688) Ovulation inhibitor (0.683) Immunosuppressant (0.615) Renal disease treatment (0.601) Antihypertensive (0.593) Prostate disorders treatment (0.590) Antiosteoporotic (0.573)
46	Not studied		Respiratory analeptic (0.895) Antiinflammatory (0.848) Antineoplastic (0.820) Contraceptive (0.796)

No.	Activity reviewed	Activities confirmed (Pa)	Predicted activities (Pa)*
			Antipruritic (0.795) Immunosuppressant (0.726) Cardiotonic (0.716) Antisecretoric (0.714) Diuretic (0.701) Ovulation inhibitor (0.651) Antidiabetic (0.650) Anesthetic general (0.645) Antiallergic (0.631) Prostate disorders treatment (0.609) Menopausal disorders treatment (0.602)
47	Anti-inflammatory	Antiinflammatory (0.924)	Respiratory analeptic (0.980) Antisecretoric (0.932) Antiinflammatory (0.924) Antineoplastic (0.915) Antipruritic (0.835) Antiallergic (0.815) Diuretic (0.777) Immunosuppressant (0.769) Antiseborrheic (0.753) Contraceptive (0.742) Ovulation inhibitor (0.703) Prostate cancer treatment (0.640) Antiosteoporotic (0.586) Antipsoriatic (0.579)
48	Anticancer	Antineoplastic (0.840)	Antiinflammatory (0.910) Antiseborrheic (0.880) Antineoplastic (0.840) Antisecretoric (0.828) Antipruritic (0.817) Antiallergic (0.809) Ovulation inhibitor (0.724) Immunosuppressant (0.723) Menopausal disorders treatment (0.678) Contraceptive (0.656) Growth stimulant (0.647) Antiasthmatic (0.632) Antiarthritic (0.624) Autoimmune disorders treatment (0.623) Respiratory analeptic (0.620) Antiosteoporotic (0.566) Prostate cancer treatment (0.529)
49	Androgenic activity	Antineoplastic (0.924) Antiseborrheic (0.915)	Antineoplastic (0.924) Antiseborrheic (0.915) Alopecia treatment (0.792) Respiratory analeptic (0.791) Erythropoiesis stimulant (0.738) Male reproductive disfunction treatment (0.711) Prostate cancer treatment (0.710) Antihypercholesterolemic (0.685) Neuroprotector (0.680) Antiosteoporotic (0.659)

No.	Activity reviewed	Activities confirmed (Pa)	Predicted activities (Pa)*
			Antieczematic (0.654) Menopausal disorders treatment (0.653) Antileukemic (0.652) Ovulation inhibitor (0.624) Dementia treatment (0.558)
50	Estrogenic activity	Antiseborrheic (0.940) Antineoplastic (0.905)	Antiseborrheic (0.940) Antineoplastic (0.905) Alopecia treatment (0.903) Genital warts treatment (0.729) Ovulation inhibitor (0.726) Antiosteoporotic (0.696) Menopausal disorders treatment (0.643) Antisecretoric (0.638) Prostate cancer treatment (0.608) Antileukemic (0.595) Cytostatic (0.585) Antihypercholesterolemic (0.576)
51	Estrogenic activity	Antineoplastic (0.883)	Antiseborrheic (0.897) Antineoplastic (0.883) Genital warts treatment (0.724) Alopecia treatment (0.723) Antileukemic (0.599) Allergic conjunctivitis treatment (0.589) Ovulation inhibitor (0.587) Prostate disorders treatment (0.575) Cytostatic (0.565) Menopausal disorders treatment (0.561) Antiosteoporotic (0.551)
52	Not studied		Respiratory analeptic (0.952) Antihypercholesterolemic (0.927) Ovulation inhibitor (0.913) Neuroprotector (0.889) Antineoplastic (0.856) Antiseborrheic (0.848) Anesthetic (0.834) Antiinflammatory (0.811) Alopecia treatment (0.775) Erythropoiesis stimulant (0.753) Apoptosis agonist (0.740) Menopausal disorders treatment (0.721) Hypolipemic (0.705) Antiosteoporotic (0.703) Immunosuppressant (0.699) Prostate cancer treatment (0.640) Dementia treatment (0.592)
53	Not studied		Antiseborrheic (0.903) Alopecia treatment (0.864) Antineoplastic (0.847) Antiosteoporotic (0.793) Contraceptive (0.771) Antisecretoric (0.729)

No.	Activity reviewed	Activities confirmed (Pa)	Predicted activities (Pa)*
			Genital warts treatment (0.692) Ovulation inhibitor (0.680) Antihypercholesterolemic (0.643) Menopausal disorders treatment (0.619) Antiinflammatory (0.612) Prostate disorders treatment (0.604) Apoptosis agonist (0.538)
54	Not studied		Contraceptive (0.908) Antiseborrheic (0.906) Ovulation inhibitor (0.885) Antineoplastic (0.883) Antiosteoporotic (0.770) Prostate disorders treatment (0.712) Menopausal disorders treatment (0.677) Alopecia treatment (0.646) Growth stimulant (0.645) Endometrios treatment (0.638) Antipruritic (0.617) Antiinflammatory (0.615) Apoptosis agonist (0.606) Respiratory analeptic (0.599) Prostate cancer treatment (0.590) Diuretic (0.533)
55	Not studied		Antineoplastic (0.846) Antieczematic (0.817) Anesthetic general (0.757) Antipruritic (0.741) Antihypercholesterolemic (0.741) Respiratory analeptic (0.677) Antiosteoporotic (0.658) Biliary tract disorders treatment (0.638) Choleretic (0.624) Antipsoriatic (0.621) Antileukemic (0.615) Hepatic disorders treatment (0.595) Hypolipemic (0.582) Prostate cancer treatment (0.575) Erythropoiesis stimulant (0.572)
56	Not studied		Ovulation inhibitor (0.833) Antiseborrheic (0.826) Antineoplastic (0.812) Respiratory analeptic (0.803) Antisecretoric (0.794) Antihypercholesterolemic (0.750) Antiinflammatory (0.720) Alopecia treatment (0.712) Apoptosis agonist (0.647) Erythropoiesis stimulant (0.643) Antiosteoporotic (0.606) Antiacne (0.596) Prostate cancer treatment (0.590) Diuretic (0.580)

No.	Activity reviewed	Activities confirmed (Pa)	Predicted activities (Pa)*
57	Not studied		Antineoplastic (0.827) Prostate cancer treatment (0.775) Cardiotonic (0.723) Autoimmune disorders treatment (0.708) Antiinflammatory (0.658) Dermatologic (0.613) Ovulation inhibitor (0.608) Apoptosis agonist (0.603) Antiarrhythmic (0.568) Antiarthritic (0.536) Allergic conjunctivitis treatment (0.522) Antipruritic, allergic (0.506)
58	Not studied		Ovulation inhibitor (0.903) Antineoplastic (0.860) Antiseborrheic (0.850) Contraceptive (0.835) Antiosteoporotic (0.758) Hair growth stimulant (0.753) Antiinflammatory (0.725) Antipruritic (0.720) Prostate disorders treatment (0.704) Menopausal disorders treatment (0.692) Endometrios treatment (0.651) Antiacne (0.622) Psychosexual dysfunction treatment (0.575) Prostate cancer treatment (0.519)

* Only activities with Pa > 0.5 are shown.

Brominated steroids

Brominated natural compounds are widely synthesized in marine invertebrates and algae (Gribble, 2015; Dembitsky and Tolstikov, 2003; Cabrita et al., 2010). They are also found in the Acorospora lichen(Řezanka and Guschina, 1999; Rezanka and Dembitsky, 1999, 2001), and are not found in plants.Brominated steroids are very rare natural lipids, and are found only in marine sponges. Thus, two related C-nor-D-homosteroids, nakiterpiosinone and nakiterpiosin, were isolated from the sponge *Terpios hoshinota*. Both compounds may be useful as an anticancer agent in tumours resistant to existing antimitotic agents and dependent on Hedgehog pathway responses for growth (Teruya et al., 2004; Gao et al., 2010).

A series of 6-bromo compounds (**31** and **32**) was synthesized more than 55 years ago as therapeutic agents that demonstrate progestational activity (Ringold et al., 1962; George et al., 1963). 2-Bromo- (**33**) and 4-bromoestrones (**34**) and the corresponding derivatives were synthesized by Suzuki-Miyaura cross-coupling method, but no activity was published (Burmester et al., 2013). Farrar (1955) reported the synthesis of 9-bromo-11β-hydroxy steroids (**35** and **36**), the resulting steroids were not studied for their biological activity.

Brominated triterpenoids (**37**, **38** and **39**) were synthesized from betulinic acid, which was isolated from *Bischofia javanica*. The obtained compounds showed strong activity against Topoisomerase IIa, and also demonstrated activity against HeLa cells (Gosh et al., 2017).

A series of 16-bromo steroids (**40**, **41**, and **42**) that demonstrated a significant anti-inflammatory and glucocorticoid activity and to a lesser extent, arthritic, allergic and asthmatic activities were synthesized (Fajkoš 1959; Ayer 1965; Schonecker et al., 2000; Saikia et al., 2016).

Iodinated steroids

Iodinated natural metabolites are synthesized exclusively by marine organisms and algae (Gribble 2015; Dembitsky and Tolstikov, 2003). They come with the composition of lipids, fatty acids, peptides, and other

complex compounds (Dembitsky, 2002, 2006; Dembitsky and Srebnik, 2002; Wagner, et al., 2009; Cabrita et al., 2010). Iodinated steroids have not been found in nature, although more than 100 iodine-containing synthetic steroids are known today.

The biological activity of iodine-containing steroids has been studied much worse than, for example, their analogs, which contain fluorine, chlorine or bromine. Thus, Freied (1957), investigating the effect of 9α-halo (F, Cl, Br, I)-11-hydroxyprogesterones on the inhibition of glycogen biosynthesis in rat liver, showed that the activity of halogenated steroids increases from 9 α-iodo-11-hydroxy-(0.1) to 9β-fluoro-11-hydroxy-progesterones (0.85), and adrenocortical activity increases from 0.1 (iodine), 0.3 (bromine), 4.7 (chlorine) to 10.7 (fluorine)for the same compounds.

2-Iodo-androst-4-ene-3,17-dione (**43**) and a series of similar 2-iodo-steroids have been synthesized without determining the activity of these compounds (Westermann et al., 1991). 2,4-Diiodoestrones (**44**) was synthesized by Suzuki-Miyaura cross-coupling method, but no activity was published (Burmester et al., 2013). To develop methods for the synthesis of iodine-containing steroids, 21-iodo-20-keto-pregnanes (**45** and **46**) were obtained by various methods, and in both cases the activity of the steroids was not studied (Heinrich 1951; Stork et al., 1959).

The 16-iodo steroids (**47**, **50** and **51**) have a different biological activity. Thus, steroids (**47** and **51**) exhibit significant anti-inflammatory and glucocorticoid activities (Ayer, 1965), and 16α-estradiol, or 16α-Iodo-E2 (**50**) has a significant estrogenic activity and is used to study the estrogen receptor (Hochberg et al., 1086), and also regulates cell growth with the help of estrogen signals and potential targets for thyroid cancer (Chen et al., 2008). As mentioned above, 9-iodo steroids inhibit glycogen biosynthesis in rat liver, but to a lesser degree than its fluoride-containing analog (Freied, 1957), it also applies to the steroid (**48**).

7α-iodo-5α-dihydrotestosterone (**49**) shows high androgenic activity, and is an excellent receptor-mediated diagnostic imaging agent (Labaree et al., 1999). The synthesis of the iodinated steroids series (**52-58**) has been described, but biological activity has not been determined (Kiss 2015; Skoda-Földes et al., 1995, 2003; Acs et al., 2009).

Conclusion

Biological activity of halogenated (F, Cl, Br and I) steroids is presented in this paper. Sixty biologically active halogenated steroids have shown confirmed and predictedanti-inflammatory, estrogenic, anabolic, gynecological disorders, anti-arthritic, antineoplastic, and other activities.This work is of great interest for pharmacologists, physicians, biochemists, as well as for the farming industry.

Conflict of interest statement

Authors declare that they have no conflict of interest.

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