



Astonishing diversity of carbon-bridged steroids and their biological activities: A brief review

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Abstract

The present review describes the biological activities of carbon-bridged steroids. More than fifty biologically active compounds have shown confirmed antiviral, anti-tumour, antibacterial, and other activities. The structures and reported and predicted activities of synthetic carbon-bridged 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 carbon-bridged 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.

Keywords: carbon-bridged steroids, lipids, anabolic, activities, SAR, PASS

1. Introduction

Carbon-bridged steroids (CBS) are a rare group of synthetic lipids that are interesting, both in the beauty of the chemical structure and in their biological activity. Steroids of this type are found in nature, and are a rare group of compounds containing the cyclopropane ring in the tail of the common steroid core or cycloartenol core ^[1, 5]. Steroids of this type are found in plants, fungi, and marine invertebrates ^[2, 8]. Currently, more than 500 carbon-bridged steroids are known, which have been synthesized and the activity of some of them has been investigated.

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 ^[9, 11]. 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 ^[12, 15].

This review is the first attempt to combine available data on carbon-bridged steroids and summarize what biological activities are characteristic of the steroids of this group of lipids.

2. Biological activities of carbon-bridged steroids

We selected more than 50 steroids that contain carbon-bridges in various steroid core positions from more than 500 steroids of this type that have been synthesized in more than 50 years. Typically, chemists were only interested in the synthesis process and chemical structure of carbon-bridged steroids, therefore, in most cases, biological activity has not been studied.

Synthesis of rare 1 β , 4 β -methano-bridged steroids (1-4) was conducted more than 30 years ago in the Lash Miller laboratory in Toronto ^[16, 17]. Series of 2, 5-carbon-bridged steroids (5-10) have been obtained by introduction of the bridge into a steroid precursor via an ene reaction ^[18, 19, 20]. The biological activity of synthesized steroids (1-10) has not been studied.

2, 19-methylene- (11), 2, 19-ethylene-bridged (12), and 2, 19-methano- (13) androstenediones ^[21, 24], as well as 3,19- (14), 4,19- (22), 6,19-bridged (23), (25) and (26) androstenedione derivatives were synthesized as potential aromatase inhibitors can thus regulate or inhibit androgen to estrogen conversion ^[25].

A series of 3, 5- (15-18) and 3,10- (19) carbon-bridged steroids, including B-norsteroid having *cis*-bicyclo [3,2,1] octane ring system (15) ^[26], 6 β -hydroxy-3 α ,5-cyclo-5 α -androstane-17-one (16), and others (17, 18 and 37) were synthesized as steroidal blood pressure-lowering hormones ^[27, 28].

Cyclosteroids (19, 20, 21 and 22), which show an anabolic effect, were synthesized from 19-nor steroids, and would be of great interest for sports medicine as representatives of anabolic steroids ^[29, 30]. The biological activity of other cyclosteroids (24, 27, 28, 29 and 30) has not been studied ^[19, 31, 35].

A series of 6, 19-carbon-bridged steroids (31-36) has been synthesized by various authors ^[36, 38]. Many of them show biological activity. 6 β , 19-Bridged androstenedione analogs (31 and 32) are known aromatase inhibitors ^[36], and cyclosteroids (33-36) demonstrate antiherpes virus and cytotoxicity activities ^[37, 38].

A series of cyclopropane (37-42, 47, 53), cyclobutane (44-47), cyclopentane (48, 54, 55), and cyclohexane (49, 50, 51, 52, 53) containing steroids also belonging to the group of carbon-bridged steroids, representing interesting chemical structures

were synthesized without determining their biological activity [27, 28, 39, 49].

Table 1: Biological activities of CBS steroids (1-55)

No.	Activity reviewed	Activities confirmed (Pa)*	Additional predicted activities (Pa)*
1	Not studied		Anesthetic general (0,901) Respiratory analeptic (0,884) Antieczematic (0,879) Antihypercholesterolemic (0,829) Antiosteoporotic (0,791) Antipruritic (0,788) Hypolipemic (0,756) Prostate disorders treatment (0,755) Antiseborrheic (0,753) Antineoplastic (0,741) Biliary tract disorders treatment (0,740) Antipsoriatic (0,734) Immunosuppressant (0,712) Prostatic (benign) hyperplasia treatment (0,683) Hepatic disorders treatment (0,680) Atherosclerosis treatment (0,632) Male reproductive dysfunction treatment (0,631) Antifungal (0,628) Hair growth stimulant (0,619)
2	Not studied		Antiseborrheic (0,851) Antineoplastic (0,830) Antiprotozoal (0,781) Respiratory analeptic (0,777) Cardiotonic (0,773) Cardiovascular analeptic (0,738) Anesthetic general (0,687) Prostate disorders treatment (0,671) Spasmolytic, urinary (0,666) Diuretic (0,656) Erythropoiesis stimulant (0,640) Ovulation inhibitor (0,640) Antipruritic (0,638) Male reproductive dysfunction treatment (0,635) Menopausal disorders treatment (0,589) Prostatic (benign) hyperplasia treatment (0,532)
3	Not studied		Cardiovascular analeptic (0,913) Male reproductive dysfunction treatment (0,889) Antiseborrheic (0,862) Antineoplastic (0,820) Prostate disorders treatment (0,784) Neuroprotector (0,726) Ovulation inhibitor (0,724) Diuretic (0,718) Respiratory analeptic (0,699) Erythropoiesis stimulant (0,695) Prostatic (benign) hyperplasia treatment (0,684) Alopecia treatment (0,653) Prostate cancer treatment (0,627) Cytoprotectant (0,625) Vasoprotector (0,609) Antiosteoporotic (0,592)
4	Not studied		Antineoplastic (0,910) Cardiovascular analeptic (0,888) Male reproductive dysfunction treatment (0,861) Antiseborrheic (0,845) Apoptosis agonist (0,765) Antiinfertility, female (0,703) Hepatic disorders treatment (0,677) Alopecia treatment (0,628) Ovulation inhibitor (0,617) Diuretic (0,602) Cytoprotectant (0,593) Immunosuppressant (0,588) Prostate cancer treatment (0,538)
5	Not studied		Antieczematic (0,862) Antiosteoporotic (0,826) Antihypercholesterolemic (0,824) Antipruritic (0,783) Antineoplastic (0,765) Antipsoriatic (0,752)

			<p>Immunosuppressant (0,718) Anesthetic general (0,712) Hypolipemic (0,686) Prostatic (benign) hyperplasia treatment (0,653) Cytoprotectant (0,641) Atherosclerosis treatment (0,629) Antiparkinsonian, rigidity relieving (0,625) Biliary tract disorders treatment (0,621) Hepatic disorders treatment (0,584) Diabetic neuropathy treatment (0,576) Antiviral (Influenza) (0,576) Antiacne (0,575)</p>
6	Not studied		<p>Antiosteoporotic (0,972) Antipsoriatic (0,884) Male reproductive dysfunction treatment (0,816) Antineoplastic (0,803) Antiseborrheic (0,791) Alzheimer's disease treatment (0,778) Ovulation inhibitor (0,747) Cardiovascular analeptic (0,711) Neurodegenerative diseases treatment (0,642) Erythropoiesis stimulant (0,632) Prostatic (benign) hyperplasia treatment (0,617) Alopecia treatment (0,595) Menopausal disorders treatment (0,561) Contraceptive (0,553) Antiparkinsonian (0,533) Endometriosis treatment (0,522) Prostate cancer treatment (0,518)</p>
7	Not studied		<p>Antiosteoporotic (0,965) Antiseborrheic (0,891) Antipsoriatic (0,864) Alopecia treatment (0,812) Antineoplastic (0,797) Alzheimer's disease treatment (0,750) Erythropoiesis stimulant (0,745) Antieczematic (0,713) Prostate disorders treatment (0,680) Ovulation inhibitor (0,667) Vasoprotector (0,658) Neurodegenerative diseases treatment (0,648) Immunosuppressant (0,639) Male reproductive dysfunction treatment (0,629) Contraceptive (0,622) Anesthetic general (0,613) Menopausal disorders treatment (0,612) Dementia treatment (0,589) Prostatic (benign) hyperplasia treatment (0,551)</p>
8	Not studied		<p>Antieczematic (0,846) Antiosteoporotic (0,787) Anesthetic general (0,787) Male reproductive dysfunction treatment (0,780) Antineoplastic (0,775) Antihypercholesterolemic (0,772) Antipruritic (0,734) Immunosuppressant (0,708) Prostate disorders treatment (0,706) Antipsoriatic (0,700) Cytoprotectant (0,638) Prostatic (benign) hyperplasia treatment (0,624) Apoptosis agonist (0,620) Hypolipemic (0,617) Antiinflammatory (0,587) Biliary tract disorders treatment (0,569) Hepatoprotectant (0,565)</p>
9	Not studied		<p>Antihypercholesterolemic (0,866) Antieczematic (0,840) Antiosteoporotic (0,792) Anesthetic general (0,785) Antipruritic (0,779) Antineoplastic (0,777) Immunosuppressant (0,747) Respiratory analeptic (0,710) Hypolipemic (0,705)</p>

			<p>Cytoprotectant (0,689) Hepatoprotectant (0,686) Antipsoriatic (0,684) Prostate disorders treatment (0,677) Antiinflammatory (0,662) Biliary tract disorders treatment (0,620) Antifungal (0,598) Male reproductive disfunction treatment (0,597) Cholesterol synthesis inhibitor (0,588) Prostatic (benign) hyperplasia treatment (0,581)</p>
10	Not studied		<p>Antineoplastic (0,911) Antieczematic (0,907) Apoptosis agonist (0,894) Antiosteoporotic (0,884) Antipsoriatic (0,764) Antipruritic (0,764) Antiinflammatory (0,760) Prostate disorders treatment (0,699) Respiratory analeptic (0,691) Immunosuppressant (0,687) Antihypercholesterolemic (0,674) Hypolipemic (0,622) Prostatic (benign) hyperplasia treatment (0,597) Cytoprotectant (0,597) Contraceptive (0,583) Hepatoprotectant (0,573)</p>
11	Aromatase inhibitor	Aromatase inhibitor (0,896)	<p>Male reproductive disfunction treatment (0,940) Antineoplastic (0,913) Antiseborrheic (0,820) Ovulation inhibitor (0,789) Neuroprotector (0,734) Alopecia treatment (0,725) Prostate disorders treatment (0,705) Contraceptive (0,700) Antiosteoporotic (0,668) Immunosuppressant (0,650) Diuretic (0,638) Antiinflammatory (0,608) Prostatic (benign) hyperplasia treatment (0,601) Menopausal disorders treatment (0,600) Apoptosis agonist (0,596) Antipruritic (0,580) Cardiovascular analeptic (0,576)</p>
12	Aromatase inhibitor	Aromatase inhibitor (0,903)	<p>Male reproductive disfunction treatment (0,938) Antineoplastic (0,907) Ovulation inhibitor (0,798) Antiseborrheic (0,793) Alopecia treatment (0,741) Neuroprotector (0,735) Contraceptive (0,702) Prostate disorders treatment (0,697) Antiosteoporotic (0,662) Immunosuppressant (0,654) Diuretic (0,645) Cardiovascular analeptic (0,615) Menopausal disorders treatment (0,604) Antiinflammatory (0,598) Prostatic (benign) hyperplasia treatment (0,591) Antipruritic (0,583) Vasoprotector (0,576)</p>
13	Aromatase inhibitor	Aromatase inhibitor (0,717)	<p>Male reproductive disfunction treatment (0,923) Antineoplastic (0,891) Antiseborrheic (0,844) Cardiovascular analeptic (0,812) Ovulation inhibitor (0,748) Prostate disorders treatment (0,736) Diuretic (0,701) Antiosteoporotic (0,700) Anesthetic (0,691) Alopecia treatment (0,679) Erythropoiesis stimulant (0,672) Prostatic (benign) hyperplasia treatment (0,656) Contraceptive (0,588) Cardiotonic (0,587)</p>

			<p>Immunosuppressant (0,571) Prostate cancer treatment (0,564) Antipruritic (0,560) Muscular dystrophy treatment (0,556) Menopausal disorders treatment (0,542)</p>
14	Aromatase inhibitor	Aromatase inhibitor (0,578)	<p>Male reproductive dysfunction treatment (0,897) Cardiovascular analeptic (0,854) Antineoplastic (0,842) Antiseborrheic (0,822) Ovulation inhibitor (0,774) Prostate disorders treatment (0,740) Diuretic (0,738) Antiosteoporotic (0,724) Alopecia treatment (0,706) Anesthetic (0,698) Neuroprotector (0,680) Prostatic (benign) hyperplasia treatment (0,662) Erythropoiesis stimulant (0,649) Immunosuppressant (0,613) Cardiotonic (0,605) Contraceptive (0,604) Antipruritic (0,603) Vasoprotector (0,586) Menopausal disorders treatment (0,577) Prostate cancer treatment (0,569)</p>
15	Blood pressure-lowering	<p>Atrial natriuretic peptide agonist (0,552) Kidney function stimulant (0,528) Diuretic (0,509)</p>	<p>Antiosteoporotic (0,972) Antineoplastic (0,892) Antieczematic (0,881) Antipsoriatic (0,880) Antiseborrheic (0,726) Apoptosis agonist (0,710) Antiinflammatory (0,707) Erythropoiesis stimulant (0,700) Ovulation inhibitor (0,667) Prostate disorders treatment (0,662) Alopecia treatment (0,660) Immunosuppressant (0,635) Menopausal disorders treatment (0,614) Contraceptive (0,611) Hepatoprotectant (0,590) Antibacterial (0,572) Prostatic (benign) hyperplasia treatment (0,541)</p>
16	Blood pressure-lowering	<p>Kidney function stimulant (0,636) Diuretic (0,625)</p>	<p>Antidepressant (0,954) Psychotropic (0,919) Antineoplastic (0,891) Antiseborrheic (0,848) Male reproductive dysfunction treatment (0,805) Ovulation inhibitor (0,793) Alopecia treatment (0,772) Erythropoiesis stimulant (0,760) Antiosteoporotic (0,737) Respiratory analeptic (0,719) Antipruritic (0,715) Cardiovascular analeptic (0,707) Neuroprotector (0,697) Prostate disorders treatment (0,696) Vasoprotector (0,671) Apoptosis agonist (0,665)</p>
17	Blood pressure-lowering	<p>Kidney function stimulant (0,664) Diuretic (0,520)</p>	<p>Antidepressant (0,961) Psychotropic (0,953) Antineoplastic (0,871) Antiseborrheic (0,827) Apoptosis agonist (0,814) Erythropoiesis stimulant (0,781) Antiosteoporotic (0,768) Alopecia treatment (0,742) Antiinflammatory (0,736) Antipruritic (0,703) Prostate disorders treatment (0,699) Antipsoriatic (0,676) Ovulation inhibitor (0,675) Anesthetic general (0,673) Cytoprotectant (0,670) Dementia treatment (0,652)</p>

18	Blood pressure-lowering	Kidney function stimulant (0,642)	Antiseborrheic (0,846) Antineoplastic (0,845) Cardiovascular analeptic (0,828) Ovulation inhibitor (0,793) Hepatic disorders treatment (0,791) Vasoprotector (0,760) Antipruritic (0,728) Antieczematic (0,726) Neuroprotector (0,721) Male reproductive disfunction treatment (0,713) Alopecia treatment (0,699) Erythropoiesis stimulant (0,684) Antiosteoporotic (0,662) Prostate disorders treatment (0,639) Cytoprotectant (0,625) Contraceptive (0,607) Menopausal disorders treatment (0,602) Atherosclerosis treatment (0,600) Antiviral (Influenza) (0,555)
19	Blood pressure-lowering Anabolic	Diuretic (0,605) Muscular dystrophy treatment (0,611) Erythropoiesis stimulant (0,557)	Antiseborrheic (0,914) Antineoplastic (0,899) Male reproductive disfunction treatment (0,861) Antiosteoporotic (0,782) Antiinflammatory (0,763) Respiratory analeptic (0,756) Ovulation inhibitor (0,755) Antipruritic (0,727) Contraceptive (0,716) Menopausal disorders treatment (0,699) Antihypercholesterolemic (0,696) Immunosuppressant (0,672) Prostatic (benign) hyperplasia treatment (0,663) Alopecia treatment (0,651) Lipid metabolism regulator (0,604) Prostate cancer treatment (0,570)
20	Anabolic	Erythropoiesis stimulant (0,796) Muscular dystrophy treatment (0,583) Androgen agonist (0,450)	Antiseborrheic (0,905) Alopecia treatment (0,879) Male reproductive disfunction treatment (0,878) Anesthetic general (0,850) Antineoplastic (0,827) Antiosteoporotic (0,782) Vasoprotector (0,736) Ovulation inhibitor (0,734) Neuroprotector (0,730) Prostate disorders treatment (0,723) Antieczematic (0,723) Antiinflammatory (0,718) Diuretic (0,684) Immunosuppressant (0,680) Radioprotector (0,679) Respiratory analeptic (0,666) Contraceptive (0,656) Hepatoprotectant (0,649) Menopausal disorders treatment (0,643) Antihypercholesterolemic (0,642) Prostatic (benign) hyperplasia treatment (0,619)
21	Anabolic	Erythropoiesis stimulant (0,677) Muscular dystrophy treatment (0,596)	Antineoplastic (0,877) Male reproductive disfunction treatment (0,864) Antiseborrheic (0,849) Vasoprotector (0,759) Antiinflammatory (0,757) Ovulation inhibitor (0,741) Alopecia treatment (0,725) Neuroprotector (0,712) Cardiovascular analeptic (0,707) Immunosuppressant (0,707) Prostate disorders treatment (0,682) Anesthetic (0,679) Antieczematic (0,665) Antipruritic (0,651) Antiosteoporotic (0,620) Apoptosis agonist (0,611) Respiratory analeptic (0,610) Menopausal disorders treatment (0,607)

			Antiallergic (0,607)
22	Aromatase inhibitor Anabolic	Muscular dystrophy treatment (0,512) Erythropoiesis stimulant (0,731) Androgen agonist (0,502)	Antiseborrheic (0,863) Antineoplastic (0,810) Antieczematic (0,809) Male reproductive dysfunction treatment (0,769) Immunosuppressant (0,764) Neuroprotector (0,749) Antiinflammatory (0,748) Prostate disorders treatment (0,726) Antipruritic (0,720) Ovulation inhibitor (0,716) Antihypercholesterolemic (0,705) Contraceptive (0,681) Alopecia treatment (0,675) Cytoprotectant (0,656) Respiratory analeptic (0,655) Prostatic (benign) hyperplasia treatment (0,647) Antiosteoporotic (0,645) Dementia treatment (0,623)
23	Aromatase inhibitor		Antineoplastic (0,754) Postmenopausal disorders treatment (0,694) Immunosuppressant (0,665) Ovulation inhibitor (0,654) Antiprotozoal (Plasmodium) (0,648) Diuretic (0,646) Antieczematic (0,643) Prostate disorders treatment (0,632) Antiseborrheic (0,622) Antiinflammatory (0,613) Contraceptive (0,603) Antifungal (0,587) Erythropoiesis stimulant (0,577) Dementia treatment (0,575) Menopausal disorders treatment (0,550) Antinephrotoxic (0,545) Antiosteoporotic (0,531)
24	Not studied		Antieczematic (0,838) Antineoplastic (0,774) Hypolipemic (0,766) Antiosteoporotic (0,721) Antipruritic (0,716) Respiratory analeptic (0,715) Antifungal (0,714) Immunosuppressant (0,713) Anesthetic (0,662) Antipsoriatic (0,653) Antihypercholesterolemic (0,652) Cytoprotectant (0,633) Antiinflammatory (0,623) Cholesterol synthesis inhibitor (0,615) Hepatoprotectant (0,615) Prostate disorders treatment (0,572)
25	Aromatase inhibitor		Antineoplastic (0,854) Hypolipemic (0,832) Antieczematic (0,814) Antifungal (0,760) Antipruritic (0,696) Immunosuppressant (0,690) Antiosteoporotic (0,657) Respiratory analeptic (0,651) Antihypercholesterolemic (0,635) Antipsoriatic (0,633) Cholesterol synthesis inhibitor (0,612) Apoptosis agonist (0,590) Proliferative diseases treatment (0,588) Hepatoprotectant (0,586) Cytoprotectant (0,574) Antimetastatic (0,552) Prostate disorders treatment (0,543) Anesthetic (0,540)
26	Aromatase inhibitor		Antineoplastic (0,858) Hypolipemic (0,838) Antieczematic (0,805) Antifungal (0,748)

			<p>Antipruritic (0,741) Immunosuppressant (0,695) Antiosteoporotic (0,657) Respiratory analeptic (0,647) Antipsoriatic (0,640) Hepatoprotectant (0,630) Antihypercholesterolemic (0,611) Proliferative diseases treatment (0,604) Cholesterol synthesis inhibitor (0,601) Apoptosis agonist (0,583) Cytoprotectant (0,561) Antimetastatic (0,549) Prostate disorders treatment (0,535) Anesthetic (0,533)</p>
27	Not studied		<p>Male reproductive disfunction treatment (0,896) Antineoplastic (0,864) Antiseborrheic (0,844) Ovulation inhibitor (0,748) Antiinflammatory (0,739) Prostate disorders treatment (0,731) Cardiovascular analeptic (0,702) Alopecia treatment (0,679) Immunosuppressant (0,665) Prostatic (benign) hyperplasia treatment (0,652) Antiosteoporotic (0,649) Erythropoiesis stimulant (0,625) Neuroprotector (0,607) Menopausal disorders treatment (0,572) Prostate cancer treatment (0,564) Contraceptive (0,549) Endometriosis treatment (0,524)</p>
28	Not studied		<p>Antineoplastic (0,905) Male reproductive disfunction treatment (0,897) Antiosteoporotic (0,866) Antiseborrheic (0,823) Antiinfertility, female (0,792) Cardiovascular analeptic (0,756) Prostate disorders treatment (0,742) Ovulation inhibitor (0,724) Alopecia treatment (0,653) Contraceptive (0,652) Prostatic (benign) hyperplasia treatment (0,621) Erythropoiesis stimulant (0,601) Immunosuppressant (0,599) Diuretic (0,577) Antimitotic (0,559) Menopausal disorders treatment (0,557)</p>
29	Not studied		<p>Antihypercholesterolemic (0,881) Antieczematic (0,850) Respiratory analeptic (0,846) Antiosteoporotic (0,811) Antipruritic (0,808) Antineoplastic (0,791) Hepatoprotectant (0,767) Hypolipemic (0,735) Immunosuppressant (0,732) Antifungal (0,714) Cytoprotectant (0,713) Biliary tract disorders treatment (0,704) Antipsoriatic (0,704) Antibacterial (0,678) Proliferative diseases treatment (0,662) Cholesterol synthesis inhibitor (0,641) Prostate disorders treatment (0,641)</p>
30	Not studied		<p>Respiratory analeptic (0,898) Antihypercholesterolemic (0,873) Anesthetic general (0,848) Antieczematic (0,847) Antipruritic (0,808) Hypolipemic (0,789) Antineoplastic (0,744) Immunosuppressant (0,720) Antiosteoporotic (0,705) Hepatoprotectant (0,684)</p>

			Prostate disorders treatment (0,677) Antipsoriatic (0,664) Cytoprotectant (0,653) Cholesterol synthesis inhibitor (0,619) Antifungal (0,614) Male reproductive disfunction treatment (0,595) Prostatic (benign) hyperplasia treatment (0,589)
31	Not studied		Antiseborrheic (0,783) Antieczematic (0,776) Diuretic (0,742) Antineoplastic (0,742) Neuroprotector (0,734) Prostate disorders treatment (0,726) Erythropoiesis stimulant (0,718) Immunosuppressant (0,705) Antipruritic (0,697) Male reproductive disfunction treatment (0,690) Contraceptive (0,682) Prostatic (benign) hyperplasia treatment (0,662) Respiratory analeptic (0,644) Antiosteoporotic (0,638) Antihypercholesterolemic (0,622) Ovulation inhibitor (0,612) Antiinflammatory (0,610) Anticonvulsant (0,579) Antiviral (Influenza) (0,543)
32	Aromatase inhibitor	Aromatase inhibitor (0,417)	Anesthetic general (0,877) Diuretic (0,784) Antineoplastic (0,769) Erythropoiesis stimulant (0,755) Prostate disorders treatment (0,753) Male reproductive disfunction treatment (0,745) Anticonvulsant (0,733) Neuroprotector (0,727) Contraceptive (0,719) Immunosuppressant (0,674) Antiseborrheic (0,664) Prostatic (benign) hyperplasia treatment (0,663) Antieczematic (0,662) Menopausal disorders treatment (0,657) Antiosteoporotic (0,651) Antipruritic (0,648) Ovulation inhibitor (0,640) Antiinflammatory (0,633) Antiacne (0,550)
33	Cytotoxicity	Antineoplastic (0,669)	Immunosuppressant (0,727) Prostate disorders treatment (0,715) Antiinflammatory (0,666) Antineoplastic (0,669) Antipsoriatic (0,645) Antieczematic (0,617) Antiseborrheic (0,615) Prostatic (benign) hyperplasia treatment (0,587) Antipruritic, allergic (0,533) Keratolytic (0,527) Respiratory analeptic (0,513) Antiosteoporotic (0,510) Postmenopausal disorders treatment (0,507) Male reproductive disfunction treatment (0,507) Anesthetic (0,507) Antiacne (0,503)
34	Cytotoxicity	Antineoplastic (0,707)	Immunosuppressant (0,761) Antineoplastic (0,707) Antiinflammatory (0,706) Prostate disorders treatment (0,686) Antieczematic (0,657) Antipsoriatic (0,644) Respiratory analeptic (0,628) Cytoprotectant (0,609) Antipruritic, allergic (0,575) Antiosteoporotic (0,560) Antiseborrheic (0,554) Prostatic (benign) hyperplasia treatment (0,536) Male reproductive disfunction treatment (0,517)

35	Cytotoxicity	Antineoplastic (0,860)	Male reproductive disfunction treatment (0,902) Antineoplastic (0,860) Postmenopausal disorders treatment (0,845) Ovulation inhibitor (0,794) Antiseborrheic (0,779) Diuretic (0,766) Prostate disorders treatment (0,717) Neuroprotector (0,716) Contraceptive (0,699) Antiosteoporotic (0,685) Immunosuppressant (0,682) Alopecia treatment (0,681) Cardiovascular analeptic (0,680) Antipruritic (0,651) Prostatic (benign) hyperplasia treatment (0,621) Menopausal disorders treatment (0,591) Erythropoiesis stimulant (0,564) Endometriosis treatment (0,548)
36	Cytotoxicity	Antineoplastic (0,792)	Anesthetic general (0,906) Diuretic (0,863) Antineoplastic (0,792) Antipruritic (0,776) Antiinflammatory (0,775) Immunosuppressant (0,757) Contraceptive (0,750) Anticonvulsant (0,739) Prostate disorders treatment (0,724) Neuroprotector (0,720) Postmenopausal disorders treatment (0,701) Male reproductive disfunction treatment (0,688) Antieczematic (0,657) Erythropoiesis stimulant (0,622) Prostatic (benign) hyperplasia treatment (0,608) Antiosteoporotic (0,602) Respiratory analeptic (0,596) Menopausal disorders treatment (0,589)
37	Blood pressure-lowering	Antihypertensive (0,802) Diuretic (0,973) Mineralocorticoid antagonist (0,956) Aldosterone antagonist (0,842)	Postmenopausal disorders treatment (0,891) Contraceptive (0,888) Antineoplastic (0,851) Antihyperaldosteronism (0,842) Respiratory analeptic (0,826) Cerebrovascular disorders treatment (0,798) Ovulation inhibitor (0,777) Vascular (periferal) disease treatment (0,772) Renal disease treatment (0,770) Heart failure treatment (0,745) Cardiotonic (0,731) Antiseborrheic (0,698) Antiinflammatory (0,665) Apoptosis agonist (0,634) Antiosteoporotic (0,622) Prostate cancer treatment (0,613) Prostatic (benign) hyperplasia treatment (0,592)
38	Not studied		Antiseborrheic (0,892) Male reproductive disfunction treatment (0,868) Anesthetic (0,855) Antineoplastic (0,841) Diuretic (0,755) Prostate disorders treatment (0,733) Antiosteoporotic (0,717) Erythropoiesis stimulant (0,693) Antiviral (Influenza) (0,686) Alopecia treatment (0,652) Contraceptive (0,649) Respiratory analeptic (0,648) Cardiovascular analeptic (0,638) Ovulation inhibitor (0,637) Prostatic (benign) hyperplasia treatment (0,636) Antiinflammatory (0,621) Cytoprotectant (0,620)
39	Not studied		Respiratory analeptic (0,863) Erythropoiesis stimulant (0,784) Anesthetic (0,746) Antineoplastic (0,714)

			<p>Cytoprotectant (0,710) Antiseborrheic (0,705) Antieczematic (0,690) Hypolipemic (0,689) Neuroprotector (0,688) Antiinflammatory (0,674) Immunosuppressant (0,660) Antipruritic (0,653) Hepatic disorders treatment (0,637) Antihypercholesterolemic (0,625) Prostate disorders treatment (0,619) Antifungal (0,614) Male reproductive dysfunction treatment (0,609) Menopausal disorders treatment (0,591) Dementia treatment (0,590)</p>
40	Not studied		<p>Menopausal disorders treatment (0,865) Antiseborrheic (0,860) Antineoplastic (0,849) Erythropoiesis stimulant (0,816) Ovulation inhibitor (0,810) Male reproductive dysfunction treatment (0,802) Diuretic (0,774) Neuroprotector (0,760) Contraceptive (0,754) Antiosteoporotic (0,754) Prostate disorders treatment (0,733) Anesthetic general (0,733) Antipruritic (0,726) Respiratory analeptic (0,724) Immunosuppressant (0,690) Alopecia treatment (0,669) Antihypercholesterolemic (0,666) Cardiotonic (0,657) Prostatic (benign) hyperplasia treatment (0,665)</p>
41	Not studied		<p>Antiseborrheic (0,837) Respiratory analeptic (0,765) Antineoplastic (0,749) Cardiovascular analeptic (0,745) Antiosteoporotic (0,740) Prostate disorders treatment (0,737) Male reproductive dysfunction treatment (0,732) Erythropoiesis stimulant (0,711) Alopecia treatment (0,696) Neuroprotector (0,693) Anesthetic general (0,692) Immunosuppressant (0,686) Diuretic (0,679) Vasoprotector (0,640) Antipruritic (0,631) Antiviral (Influenza) (0,605) Prostatic (benign) hyperplasia treatment (0,603) Ovulation inhibitor (0,587) Antihypercholesterolemic (0,580) Dementia treatment (0,571)</p>
42	Not studied		<p>Antihypercholesterolemic (0,909) Respiratory analeptic (0,818) Antineoplastic (0,792) Neuroprotector (0,788) Antieczematic (0,775) Ovulation inhibitor (0,771) Immunosuppressant (0,764) Antipruritic (0,747) Prostate disorders treatment (0,742) Menopausal disorders treatment (0,701) Hepatoprotectant (0,696) Antipsoriatic (0,692) Antiinflammatory (0,684) Anesthetic general (0,682) Erythropoiesis stimulant (0,681) Prostatic (benign) hyperplasia treatment (0,657) Hypolipemic (0,602) Antiosteoporotic (0,599)</p>
43	Not studied		<p>Antihypercholesterolemic (0,964) Respiratory analeptic (0,964)</p>

			<p>Anesthetic general (0,898) Antieczematic (0,869) Hypolipemic (0,849) Antineoplastic (0,849) Hepatoprotectant (0,831) Antipruritic (0,818) Immunosuppressant (0,792) Antiinflammatory (0,792) Neuroprotector (0,792) Ovulation inhibitor (0,790) Antiosteoporotic (0,782) Apoptosis agonist (0,750) Prostate disorders treatment (0,744) Antipsoriatic (0,740) Antifungal (0,724) Cytoprotectant (0,717) Atherosclerosis treatment (0,610) Prostate cancer treatment (0,601)</p>
44	Not studied		<p>Respiratory analeptic (0,871) Antiinflammatory (0,837) Antineoplastic (0,805) Ovulation inhibitor (0,794) Antiseborrheic (0,781) Immunosuppressant (0,760) Antipruritic (0,754) Diuretic (0,744) Prostate disorders treatment (0,707) Antiosteoporotic (0,675) Male reproductive dysfunction treatment (0,666) Contraceptive (0,662) Menopausal disorders treatment (0,651) Muscular dystrophy treatment (0,639) Alopecia treatment (0,639) Antihypertensive (0,626) Hepatic disorders treatment (0,601) Prostatic (benign) hyperplasia treatment (0,591) Antihypercholesterolemic (0,589)</p>
45	Not studied		<p>Antiseborrheic (0,915) Alopecia treatment (0,893) Antiosteoporotic (0,791) Vasoprotector (0,752) Contraceptive (0,742) Acute neurologic disorders treatment (0,740) Antineoplastic (0,736) Ovulation inhibitor (0,704) Neuroprotector (0,687) Menopausal disorders treatment (0,660) Male reproductive dysfunction treatment (0,639) Anesthetic general (0,608) Diuretic (0,599) Kidney function stimulant (0,590) Prostate disorders treatment (0,589) Antihypercholesterolemic (0,582) Antioxidant (0,552) Atherosclerosis treatment (0,534)</p>
46	Not studied		<p>Antiseborrheic (0,917) Antiosteoporotic (0,904) Alopecia treatment (0,800) Antineoplastic (0,750) Prostate disorders treatment (0,713) Contraceptive (0,712) Ovulation inhibitor (0,693) Menopausal disorders treatment (0,620) Genital warts treatment (0,595) Spasmolytic, urinary (0,586) Cardiovascular analeptic (0,576) Vasoprotector (0,554) Cardiotonic (0,542) Neuroprotector (0,539) Antipruritic (0,536) Acute neurologic disorders treatment (0,520) Prostatic (benign) hyperplasia treatment (0,501)</p>
47	Not studied		<p>Antiseborrheic (0,924) Alopecia treatment (0,879)</p>

			<p>Antineoplastic (0,786) Antiosteoporotic (0,752) Genital warts treatment (0,749) Ovulation inhibitor (0,727) Contraceptive (0,700) Antipruritic (0,613) Menopausal disorders treatment (0,608) Prostate disorders treatment (0,596) Cytoprotectant (0,590) Vasoprotector (0,588) Male reproductive dysfunction treatment (0,585) Apoptosis agonist (0,567) Kidney function stimulant (0,561) Neuroprotector (0,561)</p>
48	Not studied		<p>Antiseborrheic (0,928) Alopecia treatment (0,855) Ovulation inhibitor (0,715) Antiosteoporotic (0,703) Vasoprotector (0,694) Antineoplastic (0,694) Cardiovascular analeptic (0,674) Prostate disorders treatment (0,621) Menopausal disorders treatment (0,580) Antineoplastic (breast cancer) (0,572) Genital warts treatment (0,616) Contraceptive (0,546) Male reproductive dysfunction treatment (0,507)</p>
49	Not studied		<p>Postmenopausal disorders treatment (0,879) Antiseborrheic (0,873) Diuretic (0,855) Antineoplastic (0,854) Alopecia treatment (0,852) Ovulation inhibitor (0,840) Antiosteoporotic (0,814) Respiratory analeptic (0,789) Antisecretoric (0,783) Neuroprotector (0,756) Contraceptive (0,748) Acute neurologic disorders treatment (0,741) Prostate disorders treatment (0,739) Menopausal disorders treatment (0,736) Antihypercholesterolemic (0,682) Anesthetic general (0,681) Erythropoiesis stimulant (0,668) Male reproductive dysfunction treatment (0,656) Prostatic (benign) hyperplasia treatment (0,621)</p>
50	Not studied		<p>Cardiotonic (0,917) Antineoplastic (0,845) Antiarrhythmic (0,809) Antiseborrheic (0,787) Prostate disorders treatment (0,673) Apoptosis agonist (0,654) Antiinflammatory (0,648) Immunosuppressant (0,626) Analgesic (0,619) Contraceptive (0,616) Prostatic (benign) hyperplasia treatment (0,585) Antifungal (0,583) Menopausal disorders treatment (0,577) Hypolipemic (0,548) Ovulation inhibitor (0,536) Antipruritic (0,517)</p>
51	Not studied		<p>Anesthetic general (0,841) Antineoplastic (0,823) Ovulation inhibitor (0,822) Antiseborrheic (0,806) Male reproductive dysfunction treatment (0,783) Prostate disorders treatment (0,746) Antipruritic (0,743) Antiosteoporotic (0,742) Antiinflammatory (0,741) Contraceptive (0,719) Alopecia treatment (0,695) Respiratory analeptic (0,695)</p>

			<p>Neuroprotector (0,691) Diuretic (0,676) Menopausal disorders treatment (0,647) Immunosuppressant (0,643) Erythropoiesis stimulant (0,625) Prostatic (benign) hyperplasia treatment (0,623)</p>
52	Not studied		<p>Antiosteoporotic (0,819) Antineoplastic (0,715) Anesthetic general (0,712) Prostate disorders treatment (0,701) Antiinflammatory (0,696) Respiratory analeptic (0,676) Ovulation inhibitor (0,642) Immunosuppressant (0,637) Male reproductive dysfunction treatment (0,625) Prostatic (benign) hyperplasia treatment (0,619) Diuretic (0,618) Menopausal disorders treatment (0,608) Antipruritic (0,597) Contraceptive (0,569) Spasmolytic, urinary (0,517)</p>
53	Not studied		<p>Ovulation inhibitor (0,850) Antineoplastic (0,834) Respiratory analeptic (0,824) Anesthetic general (0,805) Antihypercholesterolemic (0,794) Antiseborrheic (0,772) Neuroprotector (0,756) Erythropoiesis stimulant (0,746) Antiinflammatory (0,744) Antipruritic (0,735) Contraceptive (0,733) Immunosuppressant (0,726) Prostate disorders treatment (0,720) Antiosteoporotic (0,720) Menopausal disorders treatment (0,716) Alopecia treatment (0,682) Muscular dystrophy treatment (0,678) Male reproductive dysfunction treatment (0,678) Radioprotector (0,673)</p>
54	Not studied		<p>Antiosteoporotic (0,934) Antiseborrheic (0,918) Alopecia treatment (0,848) Antineoplastic (0,796) Genital warts treatment (0,729) Apoptosis agonist (0,723) Vasoprotector (0,717) Ovulation inhibitor (0,713) Contraceptive (0,711) Prostate disorders treatment (0,676) Menopausal disorders treatment (0,668) Neuroprotector (0,656) Antiinflammatory (0,635) Antipruritic (0,617) Spasmolytic, urinary (0,571) Anesthetic general (0,552) Antihypercholesterolemic (0,527) Dementia treatment (0,522)</p>
55	Not studied		<p>Spasmolytic, urinary (0,961) Respiratory analeptic (0,891) Antiosteoporotic (0,881) Anesthetic (0,782) Antineoplastic (0,757) Hepatic disorders treatment (0,733) Immunosuppressant (0,719) Neuroprotector (0,704) Ovulation inhibitor (0,659) Prostate disorders treatment (0,658) Antiinflammatory (0,619) Menopausal disorders treatment (0,585) Antisecretoric (0,554) Apoptosis agonist (0,550) Antiseborrheic (0,532) Prostatic (benign) hyperplasia treatment (0,503)</p>

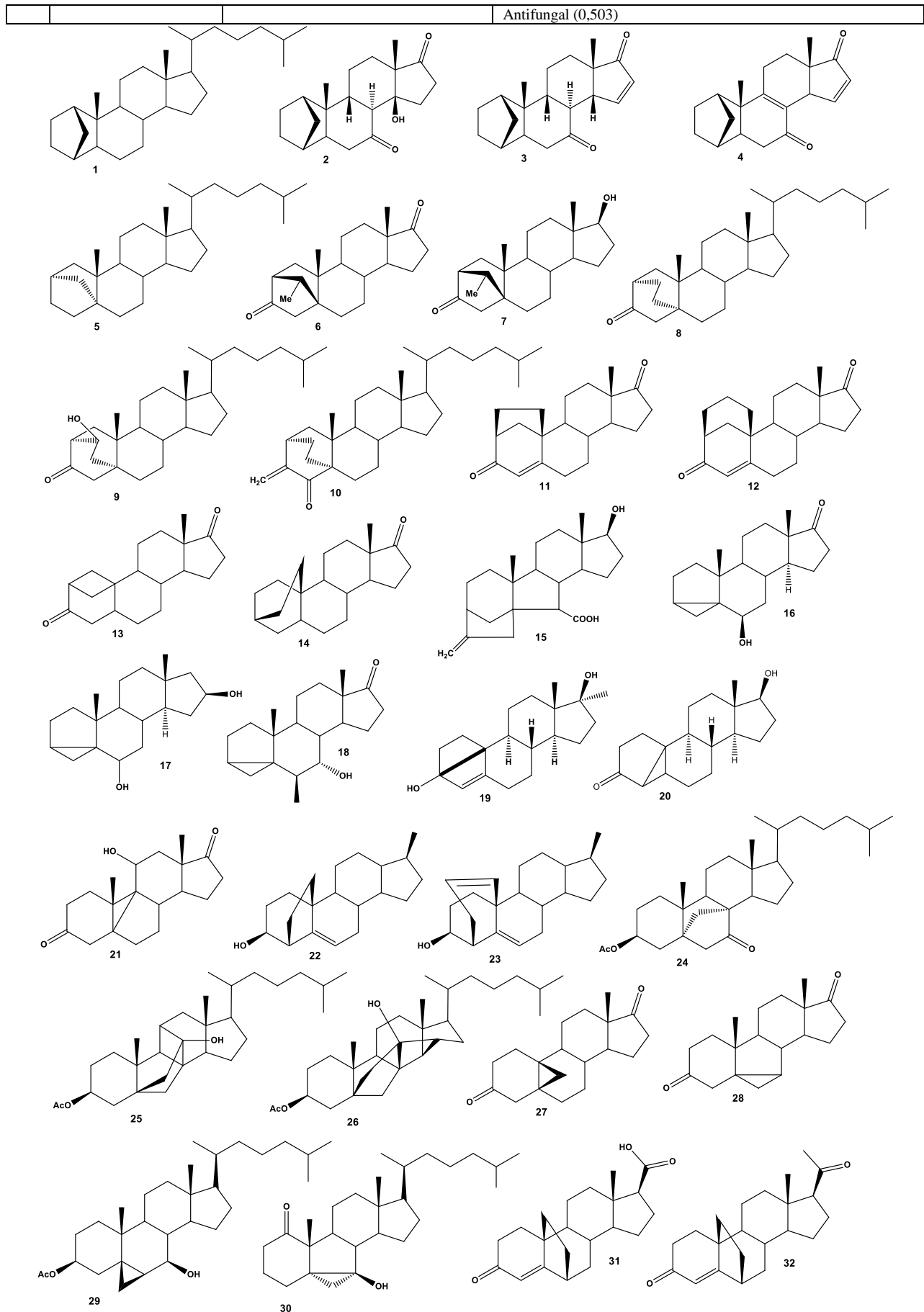


Fig 1: Biological active carbon-bridged steroids (1-32)

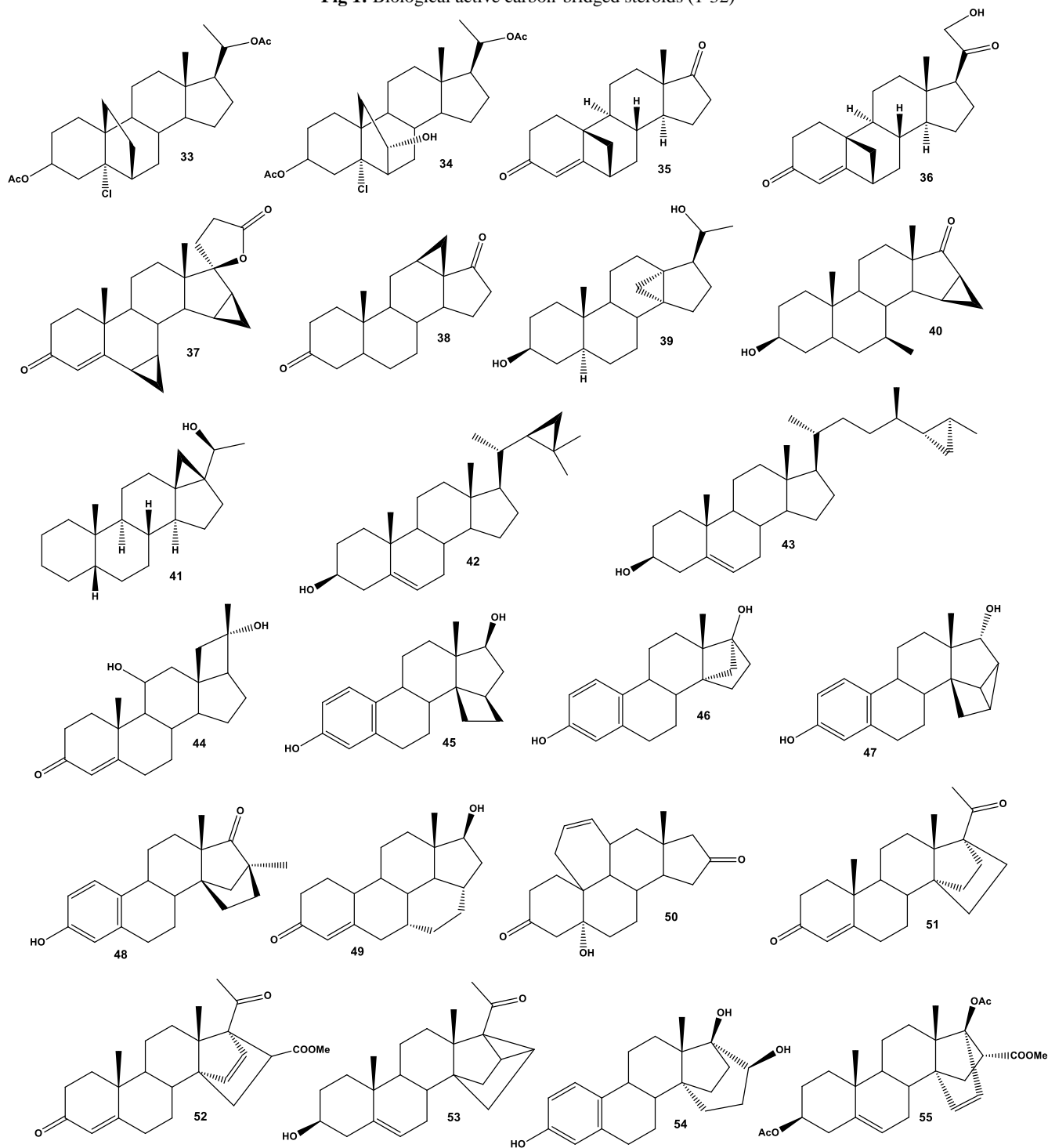


Fig 2: Biological active carbon-bridged steroids (33-55)

3. Competing Interests

Authors have declared that no competing interests exist.

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