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RESEARCH PAPER

Computational Assessment of Pharmacokinetics and Biological Effects of Some Anabolic and Androgen Steroids

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ABSTRACT

Purpose The aim of this study is to use computational approaches to predict the ADME-Tox profiles, pharmacokinetics, molecular targets, biological activity spectra and side/toxic effects of 31 anabolic and androgen steroids in humans.

Methods The following computational tools are used: (i) FAFDrugs4, SwissADME and admetSARfor obtaining the ADME-Tox profiles and for predicting pharmacokinetics;(ii) SwissTargetPrediction and PASS online for predicting the molecular targets and biological activities; (iii) PASS online, Toxtree, admetSAR and Endocrine Disruptomefor envisaging the specific toxicities; (iv) SwissDock to assess the interactions of investigated steroids with cytochromes involved in drugs metabolism.

Results Investigated steroids usually reveal a high gastrointestinal absorption and a good oral bioavailability, may inhibit someof the human cytochromes involved in the metabolism of xenobiotics (CYP2C9 being the most affected) and reflect a good capacity for skin penetration. There are predicted numerous side effects of investigated steroids in humans: genotoxic carcinogenicity, hepatotoxicity, cardiovascular, hematotoxic and genitourinary effects, dermal irritations, endocrine disruption and reproductive dysfunction.

Conclusions These results are important to be known as an occupational exposure to anabolic and androgenic steroids at workplaces may occur and because there also is a deliberate human exposure to steroids for their performance enhancement and anti-aging properties.

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KEY WORDS ADME-Tox · molecular docking · pharmacocinetics · steroids · toxicity

ABBREVIATIONS

AAS	Anabolic androgen steroids
ADME-Tox	Absorption, Distribution, Metabolization, Excretion and Toxicity
AR	Agonistic conformation of the androgenic receptor
AR an	Antagonistic conformation of the androgenic receptor
BBBP	Blood brain barrier permeant
ER α	Agonistic conformation of the estrogen receptor alpha
ER α an	Antagonistic conformation of the estrogen receptor
ER β	Estrogen receptor beta
ER β an	Antagonistic conformation of the sstrogen receptor beta
FDA	Food and drug administration
GI	Gastrointestinal absorption
GR	Agonistic conformation of the glucocorticoid receptor
GR an	Antagonistic conformation of the glucocorticoid receptor
hARLBD	Human androgen receptor ligand-binding domain
HSDB	Hazardous substances data bank
IUPAC	International union of pure and applied chemistry
LRX β	Liver X receptor beta
LXR α	Liver X receptor alpha
PASS	Prediction of activity spectra of substances
PDB	Protein data bank
P-gp	P-glycoprotein
PPRA α	Peroxisome proliferator activated receptor alpha

PPRA β	Peroxisome proliferator activated receptor beta
PPRA γ	Peroxisome proliferator activated receptor gamma
QSAR	Quantitative structure-activity relationship
RXR α	Retinoid X receptor alpha
TR α	Thyroid receptor alpha
TR β	Thyroid receptor beta

INTRODUCTION

Anabolic androgen steroids (AAS) are synthetic drugs derived from testosterone that can be used under medical prescription for treating diseases resulting from steroid hormone deficiency or from the loss of muscle mass. They are used to develop the male sexual characteristics (the androgenic effect) or/and to promote skeletal muscle growing (the anabolic effect) and are controlled substances in many countries.

Testosterone is a male sex hormone that is responsible, among the others, for the increased muscle and bone mass. This hormone is fast metabolized in the liver and it conducted to the development of more stable testosterone derivatives known as anabolic and androgen steroids. Also, some testosterone derivatives were produced to enhance the anabolic effect of the steroid. The number of individual AAS is large and grows continuously, especially by development of analogues considered as nutritional supplements (1). However, AAS may be divided in three broad classes (2,3): class A resulting from esterification at17-beta-hydroxy position possessing a better lipid solubility and with intramuscular administration, class B containing testosterone derivatives alkylated at the 17-alpha-hydroxy position having a good oral bioavailability and class C compounds that are alkylated in the A, B, or C rings of the testosterone also resulting in a good oral bioavailability (Fig. 1).

Considering the typical routes of administration of AAS, they may be divided into oral, injectable, gels and skin patches steroids (4). Oral steroids are fat-soluble and they are rapidly absorbed and metabolized and this administration route may conduct to liver damages (5). The injectable steroids are slowly released from the muscles into the rest of the body being better tolerated and are considered more effectively. The local gels and/or skin patches act by delivering a steady dose of AAS through the skin that enters into the bloodstream. Long-term steroid consumers prefer to use injectable steroids (5).

Administration of AAS provided to have dose dependent side effects manifested especially when they were used in high doses and for a long period of time. Specific literature is abundant in research data that were reviewed and revealed the adverse effects of AAS: hepatic, reproductive, cardiovascular, cerebrovascular, haematological, musculoskeletal, endocrine, renal, immunologic, infectious and psychologic effects (3,6–12). The side effects of AAS are typically the results of their nonspecific interactions. It is well known that all AAS are active at the androgenic receptor (AR) (13) as all endogenous androgens, but there are experimental evidences emphasising that some synthetic AAS are also able to interact with glucocorticoid receptor (14), estrogen receptors alpha and beta (ERα, ERβ), progestin receptors, a few enzymes involved in steroids biotransformation and with ion-channels (15), conducting to important biological actions. Crystallographic structure of human androgen receptor ligand-binding domain (hARLBD) solved in complex with various steroids exposed the flexibility of several residues belonging to the ligand-binding region of the protein allowing it to accommodate a range of ligand structures (16). The interactions of steroids with hARLBD provided to be strongly influenced by the structural properties of the ligand, a molecular modelling study emphasized that only minor modifications in the ligand structure may have a great impact on the interactions with hARLBD (16). It is also true for other molecular interactions developed by the AAS and their analogues. These affirmations are sustained by both experimental and molecular modelling data. A quantitative structure–activity relationship (QSAR) prediction reveals that shape, hydrophobicity and the electronic properties of a steroid have a significant role in its molecular interactions (17). A molecular docking study performed by our group revealed the potency of a few oral

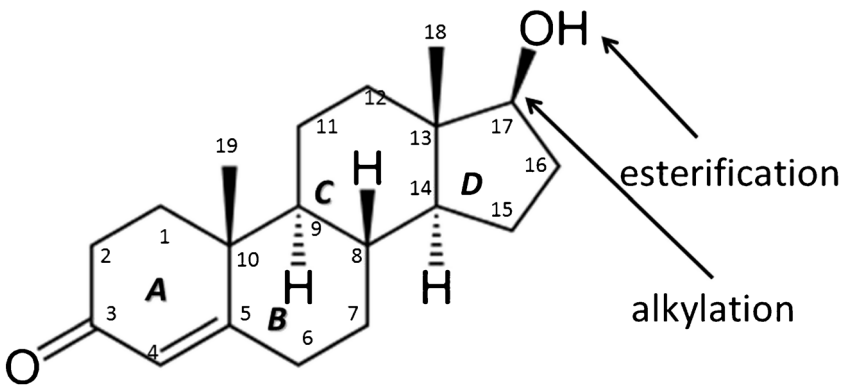

Fig. 1 Testosterone structure illustrating structural modifications conducting to more stable and effective derivatives.

administrable AAS (oxymetholone, oxandrolone, methandrostenolone and stanozolol) to bind to estrogen receptor, nuclear receptor, thyroid receptor and orphan nuclear receptor in humans (18). Our study exposed that methandrostenolone possesses the highest binding affinity to hARLBD and stanozolol revealed the stronger interactions to the nonspecific targets (18). Another molecular docking study revealed that the biological action of ecdysterone, a dietary supplement, is mediated by the ERβ estrogen receptor (19). Furthermore, all the published data concerning experimentally obtained results that we considered when designed this study, demonstrated that the chemical composition of individual AAS was an important factor in determining its biological actions.

To the best of our knowledge, some of the AAS have been tested and approved as drugs used for humans or animals, but other AAS (including designer AAS) are under control/evaluation and their metabolism, effects and side effects are not well understood. More than it, literature data concerning the androgenic, anabolic and side effects of AAS are often discordant, the targets of AAS in the human body are not well known and characterized and molecular mechanisms of AAS actions are also poorly understood. In addition, the administrated doses by both athletes and non-athletes are often higher than those used in controlled studies conducting to unknown or more pronounced side effects than what is reported in scientific literature. Not at last, veterinary drugs are often used by humans to enhance their physical performances.

The aim of this study is to predict the absorption, distribution, metabolization, excretion and toxicity (ADME-Tox) profiles and other pharmacokinetic characteristics, the biological activity spectra, the molecular targets and the toxicological and/or side effects of the most common AAS and some designer AAS, to assess the predicted interactions by molecular docking and to correlate these predictions with available literature data concerning the side effects of synthetic AAS.

MATERIALS AND METHODS

Within this study we have considered the most commonly used AAS with oral and injectable administration (6) and some AAS that are found on the market as nutritional supplements (20). Considered AAS are presented in Table I. This table contains the commercial names for the AAS, their names according to IUPAC nomenclature, the route of administration and their status established by US Food and Drug Administration. We had not find data concerning these compounds on the European Medicine Agency database.

Information concerning these compounds that is needed for the further computational analysis is extracted from PubChem database (21).

There are numerous free available web resources that may be use to predict the ADME-tox profiles, pharmacokinetics and toxic and/or side effects of chemical compounds. We have chosen some of these resources because their accessibility by easy inputs and interpretations, accompanied by sensitivity, specificity and accuracy and taking into account their continuous updating.

In order to estimate the ADME-Tox and pharmacokinetic profiles of considered steroids we have used FAFDrugs4 (22) computational tool. When using FAFDrugs4, distinct filters may be applied for predicting the ADME-Tox profile of a compound, depending on the route of administration and the aim of the study (22). We have used Drug-Like Soft filtering to assess the profiles and pharmacokinetics of steroids. This the Lipinski's rule, Veber's rule, Egan's rule and Bayer Oral Phys Chem score for predicting bioavailability of a compound and on GSK 4/400 rule and Pfizer 3/75 rule for predicting the safety profile of the compound (22). Concerning prediction of the safety profiles of steroids, we also considered the Phospholipidosis Inducer and Lilly Med Chem rules, the applied demerit level being "regular" (22).

When predicting the biological activity of chemical compound, ligand-based and structure-based approaches complements each other and strength the accuracy of computational predictions (23).SwissADME computational tool allows prediction of the following pharmacokinetic characteristics: gastrointestinal absorption (GI), P-glycoprotein (P-gp) substrate, inhibitor of some cytochromes P450 (CYP)known to be regularly involved in the interactions with xenobiotics (CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A423), blood brain barrier permeant (BBBP) and skin permeability with an accuracy of 71% to 89% (24). Skin permeation is appreciated considering the logarithm of the permeability coefficient (logKp), the more negative is the logKp for a compound, less skin permeant is this compound. The same pharmacokinetics characteristics of investigated steroids have been predicted using admetSAR tool, a database providing a broad estimation of biological activity and toxicity profiles for various compounds (25). It also includes models with highly predictive accuracy (between 72.3% and 76.7%) allowing estimation of the biological activity for novel chemicals. We have used this database to obtain/predict the biological activity (GI, P-gp, BBBP, CYP inhibition) of investigated steroids and the result are compared with the predictions made by SwissADME computational tool.

Swiss ADME and admet SAR tools use a ligand-based approach when predicting the cytochromes inhibition by chemicals, structures of both known inactive and active compounds on a specific target being modelled to derive quantitative structure-activity relationships (24).

Molecular docking is a typical computational method that uses the target-based approach when predicting the biological activity of a chemical, the structures of the enzymes being the

Table I Common and IUPAC Names of AAS Considered in this Study, Their Chemical Structures, Typical Route of Administration and Their Status on the Market. (FDA – US Food and Drug Administration, https://www.fda.gov/default.htm)

Common name	IUPAC name	Route of administration	Status
Oxymetholone	(2Z,5S,8R,9S,10S,13S,14S,17S)-17-hydroxy-2-(hydroxymethylidene)-10,13,17-trimethyl-1,4,5,6,7,8,9,11,12,14,15,16-dodecahydrocyclopenta[a]phenanthren-3-on	oral	FDA approved
Oxandrolone	(1S,3aS,3bR,5aS,9aS,9bS,11aS)-1-hydroxy-1,9a,11a–trimethyl-2,3,3a,3b,4,5,5a,6,9,9b,10,11-dodecahydroindeno[4,5-h]isochromen-7-one	oral	FDA approved
Methandrostenolone	(8R,9S,10R,13S,14S,17S)-17-hydroxy-10,13,17-trimethyl-7,8,9,11,12,14,15,16-octahydro-6H-cyclopenta[a]phenanthren-3-one	oral	Controlled Substances Act 2016
Ethylestrenol	(8R,9S,10R,13S,14S,17S)-17-ethyl-13-methyl-2,3,6,7,8,9,10,11,12,14,15,16-dodecahydro-1H-cyclopenta[a]phenanthren-17-ol	oral	FDA approved
Stanozolol	(1S,3aS,3bR,5aS,10aS,10bS,12aS)-1,10a,12a–Trimethyl-1,2,3,3a,3b,4,5,5a,6,7,10,10a,10b,11,12,12a–hexadecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-ol	oral and injectable	FDA approved
Fluoxymesterone	(8S,9R,10S,11S,13S,14S,17S)-9-fluoro-11,17-dihydroxy-10,13,17-trimethyl-1,2,6,7,8,11,12,14,15,16-decahydrocyclopenta[a]phenanthren-3-one	oral	FDA approved
Norethandrolone	(8R,9S,10R,13S,14S,17S)-17-ethyl-17-hydroxy-13-methyl-1,2,6,7,8,9,10,11,12,14,15,16-dodecahydrocyclopenta[a]phenanthren-3-one	oral	Controlled Substances Act 2016
Methenolone acetate	[(5S,8R,9S,10S,13S,14S,17S)-1,10,13-trimethyl-3-oxo-4,5,6,7,8,9,11,12,14,15,16,17-dodecahydrocyclopenta[a]phenanthren-17-yl] acetate	oral	Not approved in US
Mesterolone	(1S,5S,8R,9S,10S,13S,14S,17S)-17-hydroxy-1,10,13-trimethyl-1,2,4,5,6,7,8,9,11,12,14,15,16,17-tetradecahydrocyclopenta[a]phenanthren-3-one	oral	Controlled Substances Act 2016
Testosterone undecanoate	[(8R,9S,10R,13S,14S,17S)-10,13-dimethyl-3-oxo-1,2,6,7,8,9,11,12,14,15,16,17-dodecahydrocyclopenta[a]phenanthren-17-yl] undecanoate	oral	FDA approved
Nandrolonedecanoate	[(8R,9S,10R,13S,14S,17S)-13-methyl-3-oxo-2,6,7,8,9,10,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-17-yl] decanoate	injectable	FDA approved
Nandrolonephenpropionate	[(8R,9S,10R,13S,14S,17S)-13-methyl-3-oxo-2,6,7,8,9,10,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-17-yl] 3-phenylpropanoate	injectable	FDA approved
Testosterone cypionate	[(8R,9S,10R,13S,14S,17S)-10,13-dimethyl-3-oxo-1,2,6,7,8,9,11,12,14,15,16,17-dodecahydrocyclopenta[a]phenanthren-17-yl] 3-cyclopentylpropanoate	injectable	FDA approved
Testosterone enanthate	[(8R,9S,10R,13S,14S,17S)-10,13-dimethyl-3-oxo-1,2,6,7,8,9,11,12,14,15,16,17-dodecahydrocyclopenta[a]phenanthren-17-yl] heptanoate	injectable	FDA approved
Testosterone propionate	[(8R,9S,10R,13S,14S,17S)-10,13-dimethyl-3-oxo-1,2,6,7,8,9,11,12,14,15,16,17-dodecahydrocyclopenta[a]phenanthren-17-yl] propanoate	injectable	FDA approved
Methenoloneenanthate	[(5S,8R,9S,10S,13S,14S,17S)-1,10,13-trimethyl-3-oxo-4,5,6,7,8,9,11,12,14,15,16,17-dodecahydrocyclopenta[a]phenanthren-17-yl] heptanoate	injectable	Not approved in US
Boldenoneundecyclenate	[(8R,9S,10R,13S,14S,17S)-10,13-dimethyl-3-oxo-6,7,8,9,11,12,14,15,16,17-decahydrocyclopenta[a]phenanthren-17-yl] undec-10-enoate	injectable	Not approved for human use, veterinary drug.
Trenbolone acetate	[(8S,13S,14S,17S)-13-methyl-3-oxo-2,6,7,8,14,15,16,17-octahydro-1H-cyclopenta[a]phenanthren-17-yl] acetate	injectable	Veterinary drug
Trenbolone	(8S,13S,14S,17S)-17-hydroxy-13-methyl-2,6,7,8,14,15,16,17-octahydro-1H-cyclopenta[a]phenanthren-3-one	injectable	Veterinary drug
1-Androsterone	(3R,5S,8R,9S,10R,13S,14S)-3-hydroxy-10,13-dimethyl-3,4,5,6,7,8,9,11,12,14,15,16-dodecahydrocyclopenta[a]phenanthren-17-one	oral	Pro-steroid, Controlled Substances Act 2016
4-Hydroxytestosterone		oral	listed in the 'Anabolic Steroid Control Act 2014'

Table I (continued)

Common name	IUPAC name	Route of administration	Status
	(8R,9S,10R,13S,14S,17S)-4,17-dihydroxy-10,13-dimethyl-1,2,6,7,8,9,11,12,14,15,16,17-dodecahydrocyclopenta[a]phenanthren-3-one		
7-Keto-dehydroepiandrosterone	(3S,8R,9S,10R,13S,14S)-3-hydroxy-10,13-dimethyl-2,3,4,8,9,11,12,14,15,16-decahydro-1H-cyclopenta[a]phenanthrene-7,17-dione	oral	Bulk drug substances under evaluation2017
Androst-4-ene-3,11,17-trione	(10R,13S)-10,13-dimethyl-1,7,8,9,10,11,12,13,15,16-decahydro-2H-cyclopenta[alpha]phenanthrene-3,6,17(14H)-trione	oral	Not approved in US.
Androsta-1,4,6-triene-3,17-dione	(8R,9S,10R,13S,14S)-10,13-dimethyl-9,11,12,14,15,16-hexahydro-8H-cyclopenta[a]phenanthrene-3,17-dione	oral	listed in the 'Designer Anabolic Steroid Control Act 2014'
Androsterone acetate	[(3R,5S,8R,9S,10S,13S,14S)-10,13-dimethyl-17-oxo-1,2,3,4,5,6,7,8,9,11,12,14,15,16-tetradecahydrocyclopenta[a]phenanthren-3-yl] acetate	oral	pro-steroid, dietary supplement
Androsta-1,4-diene-3,17-dione	(8R,9S,10R,13S,14S)-10,13-dimethyl-7,8,9,11,12,14,15,16-octahydro-6H-cyclopenta[a]phenanthrene-3,17-dione	oral	listed in the 'Designer Anabolic Steroid Control Act 2014'
Epiandrosterone	(3S,5S,8R,9S,10S,13S,14S)-3-hydroxy-10,13-dimethyl-1,2,3,4,5,6,7,8,9,11,12,14,15,16-tetradecahydrocyclopenta[a]phenanthren-17-one	oral	Veterinary drug
Epietiocholanolone	(3S,5R,8R,9S,10S,13S,14S)-3-hydroxy-10,13-dimethyl-1,2,3,4,5,6,7,8,9,11,12,14,15,16-tetradecahydrocyclopenta[a]phenanthren-17-one	oral	pro-steroid, dietary supplement
Estra-4,9-diene-3,17-dione	13-methyl-1,2,6,7,8,11,12,14,15,16-decahydrocyclopenta[a]phenanthrene-3,17-dione	oral	pro-steroid, dietary supplement
Methasterone	(2R,5S,8R,9S,10S,13S,14S,17S)-17-hydroxy-2,10,13,17-tetramethyl-2,4,5,6,7,8,9,11,12,14,15,16-dodecahydro-1H-cyclopenta[a]phenanthren-3-one	oral	listed in the 'Designer Anabolic Steroid Control Act 2014'
Prostanozol	(1S,2S,10S,13R,14S,17S,18S)-2,18-dimethyl-17-(oxan-2-yloxy)-6,7-diazapentacyclo[11.7.0.0^{2},^{10}.0^{4},^{8}.0^{14},^{18}]icosa-4,7-diene	oral	listed in the 'Designer Anabolic Steroid Control Act 2014'

starting point in finding the active compounds. Consequently molecular docking studies were performed to assess the interactions of considered steroids with cytochromes. The crystallographic structures of the human CYP1A2, CYP2C19, CYP2C9, CYP2D6 and CYP3A4 in complex with inhibitors have been identified in the Protein Data Bank (PDB) (26) and those having the highest resolution have been considered, the codes entry being: 2HI4 for CYP1A2, 4GQS for CYP2C19, 4NZ2 for CYP2C9, 4XRZ for CYP2D6 and 4D6Z for CYP3A4, respectively. For the considered structural files of CYPs, the ligands, excepting heme, have been removed and structures have been prepared for molecular docking using the *DockPrep* utility under Chimera software (27). Molecular docking studies have been performed using SwissDock software (28) that is based on EADock algorithm (29). We have considered blind, accurate and rigid docking. Visualization and analysis of the molecular docking results have been also performed using Chimera.

Endocrine disruptors, hERG blocking potential, carcinogenicity/mutagenicity and teratogenicity are toxicological endpoints that are of the highest concern for human health being the object of FDA regulations. Consequently, within this study we also characterize the possible carcinogenic and mutagenic potential of considered AAS using Toxtree (30) and admetSAR computational tools. Toxtree performs predictions for toxicological endpoints such as carcinogenicity based on the Benigni/Bossa rule (31) and mutagenicity considering the Ames test (32) with an accuracy of 70%. AdmetSAR predicts toxicological endpoints such as carcinogenicity and hERG channel-blocking potential with an overall accuracy of 88.9% (25). The endocrine disruption potential is assessed using Endocrine Disruptome computational tool (33). This tool uses molecular docking to predict interactions between the investigated compounds with 12 distinct human nuclear receptors: (i) steroids receptors such as androgen receptor (AR); estrogen receptors α (ER α) and β (ER β); glucocorticoid receptor (GR); liver X receptors α (LXR α) and β (LRX β) with both agonistic and antagonistic (an) conformations where available; (ii) ligand-dependent nuclear receptors others than steroid receptors: peroxisome proliferator activated receptors α (PPRA α), β/δ (PPRA β), and γ (PPRA γ); retinoid X receptor α (RXR α) and thyroid receptors α (TR α)

and β (TR β). Molecular docking calculations are made using AutoDockVina and starting from validated structures for the considered nuclear receptors. For interpreting the results, the compounds are classified in four classes taking into account the value of the sensitivity (SE) parameter: SE < 0.25 corresponds to the "red" class with high probability of binding, 0.25 < SE < 0.50 to the "orange" class and 0.50 < SE < 0.75 to the "yellow" class, both indicating medium probability of binding and SE > 0.75 to the "green" class corresponding to low probability of binding (33).

For prediction of molecular targets of steroids we have used Swiss Target Prediction computational tool and a probability of interaction higher than 0.7 has been considered (34). This tool combines 2D and 3D similarity measures and it increases significantly the target prediction accuracy.

We have used the PASS online tool (Prediction of Biological Activity Spectra) to envisage the pharmacological effects, biochemical mechanisms of action, specific toxicities and side effects (mutagenicity, teratogenicity, embryotoxicity, carcinogenicity) of the investigated AAS (35). This computational tool predicts with an accuracy of 95% the activity spectrum of a specified chemical compound by calculating in an independent manner two probabilities: a probability to be active (Pa) and a probability to be inactive (Pi) (35). When Pa > Pi and Pa > 0.700, the chance to find experimentally the predicted activity is strongly increased (36). This tool has been used previously to predict, besides the activity spectra of drugs, the biological activity spectra of some cyclic nitrones (36) and of some natural products (37,38). In treating our results obtained using PASS utility, we have considered for every compound only those activities with Pa > Pi and Pa > 0.900.

In order to compare the predictions of the computational tools with known experimental data, we only considered information available from in vivo experiments for human exposure and extracted from PubChem Compound database (https://pubchem.ncbi.nlm.nih.gov/), Hazardous Substances Data Bank (HSDB, https://toxnet.nlm.nih.gov/newtoxnet/hsdb.htm),Drugs.com database (https://www.drugs.com/) and SIDER database (http://sideeffects.embl.de/) (39) that we have accessed between January 2017–January 2018.

RESULTS

ADME-Tox profiles of the steroids considered in this study have been obtained using FAFDrugs4tool and are revealed in Table II. The values of the physicochemical properties considered by Pfizer 3/75 rule are revealed in Table II because this is the main rule that is not respected by considered AAS.

Almost all considered steroids reveal good oral bioavailability. For some of them, especially for those with injectable route of administration, there are one or two violations of the Lipinski's rule. Concerning the safety profiles, all considered AAS do not completely respect Pfizer 3/75 rule and a few steroids also do not respect GKS 4/400 rule. None of considered steroids are predicted to produce phospholipidosis and a few steroids do not respect LillyMedChem rules. There are a few steroids that are rejected when applying the DrugLike filter under FAFDrugs computational tool: stanozolol, nandrolonedecanoate, testosterone undecanoate, testosterone cypionate, testosterone enanthate, methenoloneenanthate and prostanozol.

Predictions concerning the pharmacokinetics of considered steroids have been obtained using SwissADME, admetSAR and SwisDock computational tools and are presented in Tables III and IV.

Except testosterone undecanoate and nandrolonedecanoate, all the other considered steroids are predicted to have a high gastrointestinal absorption and this result is not unexpected taking into consideration that these two steroids have an injectable route of administration. admetSAR computational tool reveals that all steroids are able to penetrate the blood brain barrier and consequently, to affect the central nervous system, this prediction being confirmed by the results obtained using SwissADME tool for numerous steroids. Concerning the interactions with the P-gp protein, admetSAR reflect that, except the androsterone acetate, the other steroids could be substrates for this enzyme, but SwissADME tool predicts that only a limited number of steroids are expected to be substrates of P-gp protein, meaning that their systemic exposure could be reduced.

All considered steroids have the capability to penetrate into the skin and it is important to be known as occupational exposure may occur through dermal contact at workplaces where AAS are produced, packaged or administrated.

Some of considered steroids are foreseen by the SwissADME tool to inhibit the human CYP enzymes that are mainly involved in metabolization of xenobiotics. CYP1A2 is predicted to be inhibited by stanozolol and prostanozol. CYP2C19 may be inhibited by ethylestrenol, trenbolone acetate, androsta-1,4,6-triene-3,17-dione, boldion (androsta-1,4-diene-3,17-dione) and estra-4,9-diene-3,17-dione.Considered steroids are predicted to have the highest inhibitory effects on CYP2C9:oxymetholone, oxandrolone, methandrostenolone, ethylestrenol, methenolone acetate, nandrolonedecanoate, nandrolonephenpropionate, testosterone cypionate, testosterone enanthate, testosterone propionate, methenoloneenanthate, boldenoneundecyclenate, trenbolone acetate, androsta-1,4,6-triene-3,17-dione and androsterone acetate are all expected to inhibit this enzyme. Nandrolonephenpropionate is the only steroid expected to inhibit CYP2D6 and probable inhibitors of CYP3A4 are nandrolonephenpropionate and trenbolone

Table II ADME-Tox Profiles of Considered Steroids Obtained Using FAFDrugs Tool. Green Boxes Illustrate that Corresponding Rules are Respected, Yellow Boxes Denote Rules that are Partially Respected and Red Boxes Illustrate Rules that are Entirely Broken

Steroids name	ADMET Profiling									Status	Observations
	Oral Bioavailability				Drug Safety Profiling						
	Lipinski RO5	Veber Rule	Egan Rule	Bayer Oral Physchem Sc	GSK 4/400 Rule	Pfizer 3/75 Rule		Phospholipidosis Non Inducer	Lilly Med Chem Rules		
						logP	tPSA				
Oxymetholone										Accepted	oral route of administration
Oxandrolone										Accepted	
Methandrostenolone										Accepted	
Ethylestrenol										Accepted	
Stanozolol*										Rejected	
Fluoxymesterone										Accepted	
Norethandrolone										Accepted	
Methenolone acetate										Accepted	
Mesterolone										Accepted	
Testosterone undecanoate										Rejected	
Nandrolonedecanoate										Rejected	injectable route of administration
Nandrolonephenpropionate										Accepted	
Testosterone cypionate										Rejected	
Testosterone enanthate										Rejected	
Testosterone propionate										Accepted	
Methenoloneenanthate										Rejected	
Boldenone										Accepted	
Trenbolone acetate										Accepted	
Trenbolone										Accepted	
1-Androsterone										Accepted	food supplements
4-Hydroxytestosterone										Accepted	
7-Keto-dehydroepiandrosterone										Accepted	
Androst-4-ene-3,11,17-trione										Accepted	
Androsta-1,4,6-triene-3,17-dione										Accepted	
Androsterone acetate										Accepted	
Boldione (Androsta-1,4-diene-3,17-dione)										Accepted	
Epiandrosterone										Accepted	
Epietiocholanolone										Accepted	
Estra-4,9-diene-3,17-dione										Accepted	
Methasterone										Accepted	
Prostanozol										Rejected	

*Stanozolol has two routes of administration, oral and injectable

acetate.admetSAR predictions envisage only a few possible interactions of steroids with cytochromes: CYP1A2 and CYP3A4 could be inhibited by stanozolol and CYP2C19 by testosterone undecanoate, nandrolonephenpropionate, testosterone enanthate, testosterone propionate, methenoloneenanthate, trembolone and prostanozol. Taking into account the quite contradictory predictions made by the two computational tools, in order to better assess the inhibitory effects of steroids on CYP enzymes, we have also performed molecular docking studies using SwissDock

Table III Pharmacokinetics of Considered Steroids Predicted Using SwissADME Computational Tool. GI – Gastrointestinal Absorption, BBBP – Blood-Brain Barrier Permeation

Steroids name/ prediction tool	GI		BBBP		P-gp substrate		Log Kp (cm/s)
	swissADME	admetSAR	swissADME	admetSAR	swissADME	admetSAR	swissADME
Oxymetholone	High	High	Yes	Yes	No	Yes	−5.22
Oxandrolone	High	High	Yes	Yes	No	Yes	−5.51
Methandrostenolone	High	High	Yes	Yes	No	Yes	−5.60
Ethylestrenol	High	High	Yes	Yes	No	Yes	−4.47
Stanozolol	High	High	Yes	Yes	Yes	Yes	−5.14
Fluoxymesterone	High	High	Yes	Yes	Yes	Yes	−6.84
Norethandrolone	High	High	Yes	Yes	No	Yes	−5.65
Methenolone acetate	High	High	Yes	Yes	No	Yes	−5.24
Mesterolone	High	High	Yes	Yes	No	Yes	−5.25
Testosterone undecanoate	Low	High	No	Yes	Yes	Yes	−3.04
Nandrolonedecanoate	Low	High	No	Yes	No	Yes	−3.75
Nandrolonephenpropionate	High	High	Yes	Yes	No	Yes	−5.17
Testosterone cypionate	High	High	No	Yes	No	Yes	−4.29
Testosterone enanthate	High	High	No	Yes	No	Yes	−4.24
Testosterone propionate	High	High	Yes	Yes	No	Yes	−5.31
Methenoloneenanthate	High	High	No	Yes	No	Yes	−3.93
Boldenoneundecyclenate	High	High	Yes	Yes	No	Yes	−5.54
Trenbolone acetate	High	High	Yes	Yes	No	Yes	−6.45
Trenbolone	High	High	Yes	Yes	Yes	Yes	−6.60
1-Androsterone	High	High	Yes	Yes	No	Yes	−5.41
4-Hydroxytestosterone	High	High	Yes	Yes	Yes	Yes	−5.91
7-Keto-dehydroepiandrosterone	High	High	Yes	Yes	Yes	Yes	−6.74
Androst-4-ene-3,11,17-trione	High	High	Yes	Yes	Yes	Yes	−7.02
Androsta-1,4,6-triene-3,17-dione	High	High	Yes	Yes	No	Yes	−5.89
Androsterone acetate	High	High	Yes	Yes	No	No	−5.30
Boldione	High	High	Yes	Yes	No	Yes	−5.93
Epiandrosterone	High	High	Yes	Yes	No	Yes	−5.45
Epietiocholanolone	High	High	Yes	Yes	No	Yes	−5.45
Estra-4,9-diene-3,17-dione	High	High	Yes	Yes	Yes	Yes	−6.91
Methasterone	High	High	Yes	Yes	No	Yes	−5.28
Prostanozol	High	High	Yes	Yes	No	Yes	−4.70

tool.Molecular docking studies have been applied for all the considered steroids against the five cytochromes: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4. The results reveal that all AAS interact with CYPs but some of the AAS are able to bind to the active sites of some of the enzymes. Figure 2 illustrates that neither stanozolol nor prostanazol bind to the active site of CYP1A2. It is also true for some of the other interactions predicted by the two ligand-based investigation tools.

Other predictions concerning the interactions of steroids with cytochromes are confirmed when using molecular docking approach, the AAS binding to the active sites of enzymes. Figure 3 illustrates that androsterone acetate is linked to the active site of CYP2C9.

For the ligand-based predictedinteractions confirmed by using molecular docking approach, a structure-based prediction method, the binding free energies are emphasized in Table IV and confirm that CYP2C9 is the most affected cytochrome by AAS administration.

The differences between the predictions concerning the cytochromes inhibition by steroids obtained using ligand- and structure-based may be interpreted in terms of the limitations of both approaches. None of these approaches allows taking into consideration the thermodynamics of the ligand-target association and the complexity of the way the ligand interacts with the target.

The data obtained using SwissTargetPredictionand PASS online computational toolsare illustrated in Table V. Besides

Table IV Inhibition of the Cytochromes Mainly Involved in the Metabolism of Xenobiotics by Considered Steroids

Steroids name/prediction tool	CYP1A2 inhibitor		CYP2C19 inhibitor		CYP2C9 inhibitor		CYP2D6 inhibitor		CYP3A4 inhibitor		CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor
	SwissADME	admetSAR	SwissADME	admetSAR	SwissADME	admetSAR	SwissADME	admetSAR	SwissADME	admetSAR	SwissDock		
Oxymetholone	No	No	No	No	Yes	No	No	No	No	No	–	−7.55	–
Oxandrolone	No	No	No	No	Yes	No	No	No	No	No	–	−7.71	–
Methandrostenolone	No	No	No	No	Yes	No	No	No	No	No	–	−7.78	–
Ethylestrenol	No	No	Yes	No	Yes	No	No	No	No	No	–	−7.57	–
Stanozolol	Yes	Yes	No	Yes	No	No	No	No	No	Yes	–	–	–
Fluoxymesterone	No	No	No	No	No	No	No	No	No	No	–	–	–
Norethandrolone	No	No	No	No	No	No	No	No	No	No	–	–	–
Methenolone acetate	No	No	No	No	Yes	No	No	No	No	No	–	−7.94	–
Mesterolone	No	No	No	No	No	No	No	No	No	No	–		–
Testosterone undecanoate	No	No	No	Yes	Yes	No	No	No	No	No	–	−9.05	–
Nandrolonedecanoate	No	No	No	No	Yes	No	No	No	No	No	–	−9.41	–
Nandrolonephenpropionate	No	No	No	Yes	Yes	No	Yes	No	Yes	No	–	−8.36	−8.96
Testosterone cypionate	No	No	No	No	Yes	No	No	No	No	No	–	−8.49	–
Testosterone enanthate	No	No	No	Yes	Yes	No	No	No	No	No	–	−8.08	–
Testosterone propionate	No	No	No	Yes	Yes	No	No	No	No	No	–	−8.15	–
Methenoloneenanthate	No	No	No	Yes	Yes	No	No	No	No	No	–	−8.19	–
Boldenoneundecylenate	No	No	No	No	Yes	No	No	No	No	No	–	−7.13	–
Trenbolone acetate	No	No	Yes	No	Yes	No	No	No	Yes	No	−7.51	−7.88	−7.93
Trenbolone	No	No	No	Yes	No	No	No	No	No	No	–	–	–
1-Androsterone	No	No	No	No	No	No	No	No	No	No	–	–	–
4-Hydroxytestosterone	No	No	No	No	No	No	No	No	No	No	–	–	–
7-Keto-dehydroepiandrosterone	No	No	No	No	No	No	No	No	No	No	–	–	–
Androst-4-ene-3,11,17-trione	No	No	No	No	No	No	No	No	No	No	–	–	–
Androsta-1,4,6-triene-3,17-dione	No	No	Yes	No	Yes	No	No	No	No	No	−6.94	−7.50	–
Androsterone acetate	No	No	No	No	Yes	No	No	No	No	No	–	−7.67	–
Boldione	No	No	Yes	No	No	No	No	No	No	No	−7.64	–	–
Epiandrosterone	No	No	No	No	No	No	No	No	No	No	–	–	–
Epietiocholanolone	No	No	No	No	No	No	No	No	No	No	–	–	–
Estra-4,9-diene-3,17-dione	No	No	Yes	No	No	No	No	No	No	No	−7.50	–	–
Methasterone	No	No	No	No	No	No	No	No	No	No	–	–	–
Prostanozol	Yes	No	No	Yes	No	No	No	No	No	No	–	–	–

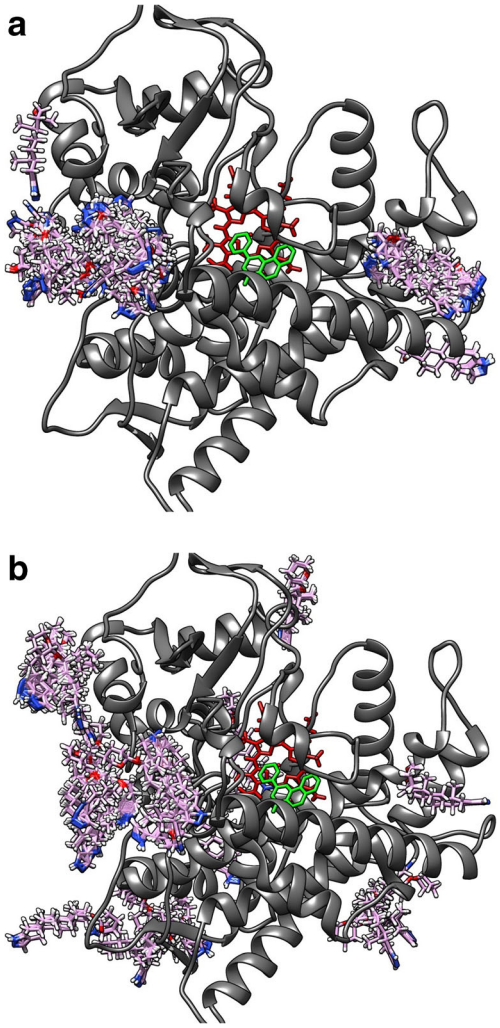

Fig. 2 Interactions of stanozolol (**a**) and prostanazol (**b**) with human cytochrome 2A1. The enzyme is presented in dim grey cartoon, hem group in red sticks, the inhibitor found in the crystallographic structure, alpha-naphthoflavone, is presented in green sticks and stanozolol and prostanozole respectively are presented in sticks colored by atom type: carbons in pink, nitrogen in blue, in oxygen red and hydrogen in white.

the androgen and estrogenreceptors, there are numerous other molecular targets of steroids identified by SwissTargetPrediction tool: many other receptors, cytochromes and microtubule-associated protein *tau*. This broad spectrum of molecular targets may explain both the biological activity spectra and the various side effects manifested by numerous steroids. Between the side effects, cardiotoxicity, hepatotoxicity (hepatic carcinoma), gastrointestinal disruption, behavioural disturbance, endocrine disruption, embryotoxicity and reproductive dysfunction seem to be common side effects for the most of investigated steroids. Table V also contains the experimentally/clinically observed side effects for investigated steroids (when available), this information being extracted from PubChem, HSDB, Drugs.com and SIDER databases.

Predictions concerning thecarcinogenicity/mutagenicity (performed using Toxtree software (31), those concerning the Ames test and inhibition potential of the hERG channel (predicted using admetSAR computational tool (25), and the endocrine disruption potential (computed using Endocrine Disruptome tool (33) of considered AAS are presented in Tables VI and VII, respectively.

None of the investigated compounds reflects non-genotoxic carcinogenicity, but numerous steroids are predicted as structural alerts for genotoxic carcinogenicity. Some of these compounds, testosterone undecanoate, testosterone cypionate, testosterone enanthate, methenoloneenanthate and nandrolonedecanoate are also predicted as structural alerts when using FAFDrugs4 software.admetSAR predictions reveal a weak potential of AAS for inhibiting the hERG channel. This result is in good agreement with information contained in hERGAPDbase (a free data base containing the chemical compounds with known hERG channel-blocking potential from the electrophysiological experimental data (40), none of the considered AAS being listed therein.

Numerous steroids that are designed for veterinary use, under control and listed in the 'Designer Anabolic Steroid

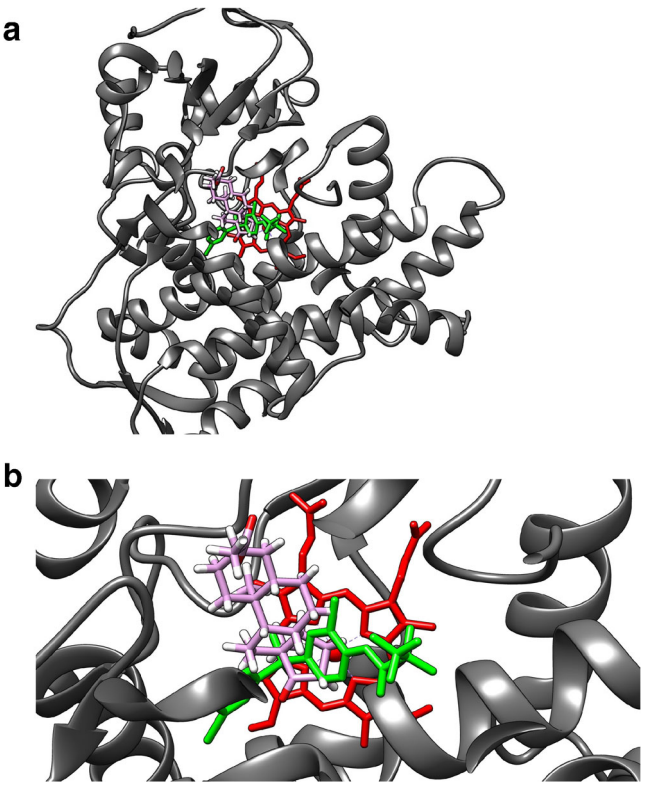

Fig. 3 Molecular docking result concerning interaction of androsterone acetate with CYP2C9.Androsterone acetate (sticks colored by atom type – carbon in pink, hydrogen in white) binds to the active center of CYP2C9 (**a**), with a different orientation that the inhibitor ((2R)-N-{4-[(3-bromophenyl)sulfonyl]-2-chlorophenyl}-3,3,3-trifluoro-2-hydroxy-2-methylpropan amide – green sticks) found in the crystallographic structure of CYP2C9. Hem group is illustrated in red sticks.

Table V Identified Molecular Targets, Predicted Biological Activity Spectra, Predicted Adverse&Toxic Effects and Clinically Observed Side Effects for Considered Steroids. The Probability for Every Prediction is Emphasized

Steroid	Predicted molecular targets ($P > 0.7$)	Prediction of biological activity (Pa > 0.9)	Possible adverse&toxic effects (Pa > 0.9)	Known side effects
Oxymetholone	androgen receptor (1,00), tyrosyl-DNA phosphodiesterase 1(1,00)	anabolic (0.946), androgen agonist (0.907), antiseborrheic (0.907)	excitability (0.988), sleep disturbance (0.981), behavioral disturbance (0.976), teratogen (0.955), embryotoxic (0.953), hepatotoxic (0.954), necrosis (0.948), toxic gastrointestinal (0.945), cholestasis (0.932), emetic (0.929), toxic (0.929), nausea (0.927), carcinogenic group 2B (0.918)	cardiac effects (fluid retention, edema, congestive heart failure),genitourinary effects (oligospermia, decreased ejaculatory volume, libido changes, virilisation in both males and females), gastrointestinal effects (nausea, vomiting, diarrhea), hepatic effects (hepatocellular carcinoma, peliosis hepatitis, liver-cell adenoma and alterations of liver morphology), hematologic effects (alterations in clotting factors II, V, VII and X, prolonged prothrombin time, increased red cell production), endocrine effects (inhibition of endogenous testosterone release), dermatologic effects (allergic reaction, acne, change in colour of skin), psychiatric effects (excitability,insomnia, depression).
Oxandrolone	microtubule-associated protein tau (0.84), m-phase inducer phosphatase 1 (0.82), m-phase inducer phosphatase 2 (0.82)	hepatic disorders treatment (0.958), antihypercholesterolemic (0.945), muscular dystrophy treatment (0.915), antiseborrheic (0.907)	euphoria (0.989), excitability (0.979), behavioral disturbance (0.946), hepatotoxic (0.940), necrosis (0.938)	cardiovascular effects (edema with and without congestive heart failure), genitourinary effects (oligospermia, decreased ejaculatory volume, virilisation in the females), gastrointestinal effects (nausea, vomiting, diarrhoea), hepatic effects (peliosis hepatitis, hepatic neoplasms, hepatocellular carcinomas), hematologic effects (alterations in clotting factors II, V, VII and X, prolonged prothrombin time, increased red cell production), endocrine effects (inhibition of endogenous testosterone release), dermatologic effects (acne, change in colour of skin), psychiatric effects (excitability, insomnia, depression).
Methandrostenolone	microtubule-associated protein tau (0.95), CYP19A1 (0.90), androgen receptor (0.81), glucocorticoid receptor (0.79), mineralocorticoid receptor (0.79), estrogen receptor (0.75), estrogen receptor beta (0.75)	CYP2C19 inhibitor (0.965), CYP2C9 substrate (0.952), testosterone 17beta-dehydrogenase, (NADP+) inhibitor (0.950), indanol dehydrogenase inhibitor (0.947), antiseborrheic (0.938), CYP2C12 substrate (0.937), gonadotropin antagonist (0.933), CYP2B6 substrate (0.925), CYP3A1 substrate (0.919), CYP3A4 substrate (0.907), aldehyde oxidase inhibitor (0.905), prostaglandin-E2 9-reductase inhibitor (0.904), CYP2J substrate (0.903)	euphoria (0.983), excitability (0.983), toxic, respiration (0.973), endocrine disruptor (0.968), hyperglycemic (0.962), consciousness alteration (0.962), behavioral disturbance (0.950), weight loss (0.946), sleep disturbance (0.945), hepatotoxic (0.936), headache (0.934), necrosis (0.929), teratogen (0.928), paralysis (0.928), embryotoxic (0.927), reproductive dysfunction (0.928), pain (0.920), hematotoxic (0.919), nausea (0.916), keratopathy (0.912), ocular toxicity	psychotic episodes, benign liver cell adenoma and heart failure

Table V (continued)

Steroid	Predicted molecular targets ($P > 0.7$)	Prediction of biological activity (Pa > 0.9)	Possible adverse&toxic effects (Pa > 0.9)	Known side effects
			(0.913), dermatitis (0.905), toxic, gastrointestinal (0.908), tachycardia (0.900), sensory disturbance (0.902), dizziness (0.901)	
Ethylestrenol	estrogen receptor (0.95), muscarinic acetylcholine receptor M2 (0.95), muscarinic acetylcholine receptor M4 (0.95), muscarinic acetylcholine receptor M5 (0.95), androgen receptor (0.95), muscarinic acetylcholine receptor M1 (0.95), muscarinic acetylcholine receptor M3 (0.95), acetylcholinesterase (0.95), sodium-dependent noradrenaline transporter (0.95), sodium-dependent serotonin transporter (0.95), CYP2C19 (0.95), sodium- and chloride-dependent glycine transporter 1 (0.95), sodium-dependent dopamine transporter (0.95), estrogen receptor beta (0.95), cholinesterase (0.95)	ovulation inhibitor (0.947), antiseborrheic (0.944), testosterone 17beta-dehydrogenase (NADP+) inhibitor (0.935), lysase inhibitor (0.915), CYP2J substrate (0.900)	reproductive dysfunction (0.927), excitability (0.922), consciousness alteration (0.922), behavioral disturbance (0.918), embryotoxic (0.911), teratogen (0.911), sleep disturbance (0.914)	venous and/or arterial thrombosis, hepatic carcinoma and dysfunction, anaemia, edema, gastric irritation, prostatic carcinoma and prostatic hyperplasia
Stanozolol	estrogen receptor (0.97), androgen receptor (0.97), CYP2D6 (0.97), CYP2C9 (0.97), CYP2C19 (0.97), adenosine receptor A3 (0.97), estrogen receptor beta (0.97), CYP2J2 (0.97), CYP2E1 (0.97), CYP2C8 (0.97), CYP2A6 (0.97), CYP2B6 (0.97), CYP2A7 (0.97), CYP2F1 (0.97), CYP2C18 (0.97)	antisecretoric (0.813)	endocrine disruptor (0.909)	cardiovascular effects (edema with and without congestive heart failure,coronary heart disease), genitourinary effects (testicular atrophy and suppression of spermatogenesis in males, oligospermia, decreased ejaculatory volume, virilisation in the females), gastrointestinal effects (nausea, vomiting), hepatic effects (peliosis hepatitis, hepatic neoplasms, hepatocellular carcinomas), hematologic effects (alterations in clotting factors II, V, VII and X, prolonged prothrombin time, increased red cell production), endocrine effects (inhibition of endogenous testosterone release), renal failure
Fluoxymesterone	androgen receptor (0.92), CYP19A1 (0.80)	androgen agonist (0.992), androgen antagonist (0.984), anabolic (0.983), gonadotropin antagonist (0.978), CYP2C9 substrate (0.975), CYP2C19 substrate (0.956), antiinflammatory (0.955), CYP3A4 substrate (0.948), testosterone 17beta-dehydrogenase (NADP+) inhibitor (0.944), UGT2B substrate (0.919), CYP3A4 inducer (0.914), trans-1,2-dihydrobenzene-1,2-diol dehydrogenase	consciousness alteration (0.992), sleep disturbance (0.990), excitability (0.987), behavioral disturbance (0.988), endocrine disruptor (0.981), hyperglycemic (0.977), headache (0.978), hypertensive (0.978), nausea (0.976), necrosis (0.974), coma (0.973), pain (0.973), embryotoxic (0.972), teratogen (0.970), hematotoxic (0.970), sensory disturbance (0.970), reproductive dysfunction (0.969), toxic,	gastrointestinal effects (nausea), genitourinary effects (oligospermia, azoospermia, or reduced sperm function in males, impairing fertility in both males and females, foetal harm when administered to pregnant women, prostate cancer), hepatic effects (peliosis hepatitis, hepatic neoplasms, hepatic coma), hematologic effects (polycythemia, suppression of clotting factors II, V, VII, and X; bleeding in

Table V (continued)

Steroid	Predicted molecular targets ($P > 0.7$)	Prediction of biological activity (Pa > 0.9)	Possible adverse&toxic effects (Pa > 0.9)	Known side effects
		inhibitor (0.912), steroid-like (0.909), CYP3A5 substrate (0.906), antiallergic (0.908), CYP2C12 substrate (0.907)	gastrointestinal (0.969), toxic, respiration (0.971), dizziness (0.967), dermatitis (0.964), ocular toxicity (0.960), asthma (0.959), keratopathy (0.954), paralysis (0.953), cleft palate (0.949), toxic, vascular (0.947), xerostomia (0.946), hepatotoxic (0.943), toxic (0.942), tachycardiac (0.940), conjunctivitis (0.938), dependence (0.928), emetic (0.930), optic neuropathy (0.913), thrombophlebitis (0.909), inflammation (0.912), euphoria (0.911), optic neuritis (0.903), dyskinesia (0.904), nephrotoxic (0.900)	patients on concomitant anticoagulant therapy), endocrine effects (virilization, gonadotropin secretion inhibition, amenorrhea and other menstrual irregularities in females and gynecomastia, oligospermia, penile erections of excessive frequency and duration in males), dermatologic effects (hirsutism, male pattern baldness, acne), psychiatric effects (decreased libido, anxiety, mental depression and generalized paraesthesia), nervous system effects (headache, generalized paresthesia).
Norethandrolone	androgen receptor (0.93), glucocorticoid receptor (0.93), mineralocorticoid receptor (0.93), steroid 17-alpha-hydroxylase/17,20 lyase (0.93), CYP19A1 (0.92), sex hormone-binding globulin (0.92), microtubule-associated protein tau (0.92), muscleblind-like protein 1 (0.89), muscleblind-like protein 2 (0.89), muscleblind-like protein 3 (0.89), sigma non-opioid intracellular receptor 1 (0.87), progesterone receptor (0.86), sodium-dependent noradrenaline transporter (0.85), sodium-dependent serotonin transporter (0.85), sodium- and chloride-dependent glycine transporter 1 (0.85)	testosterone 17beta-dehydrogenase (NADP+) inhibitor (0.971), antiseborrheic (0.956), gonadotropin antagonist (0.955), ovulation inhibitor (0.953), lysase inhibitor (0.943), CYP2J2 substrate (0.939), prostaglandin-E2 9-reductase inhibitor (0.938), CYP2C12 substrate (0.939), CYP2C9 substrate (0.903), CYP3A4 substrate (0.902)	reproductive dysfunction (0.959), consciousness alteration (0.955), excitability (0.953), weight gain (0.947), depression (0.936), endocrine disruptor (0.935), sleep disturbance (0.937), behavioral disturbance (0.933), teratogen (0.927), embryotoxic (0.925), euphoria (0.919), asthma (0.903)	NA
Methenolone acetate	steroid 17-alpha-hydroxylase/17,20 lyase (0.93), androgen receptor (0.90), microtubule-associated protein tau (0.89), glucocorticoid receptor (0.85), progesterone receptor (0.85), mineralocorticoid receptor (0.85), CYP19A1 (0.84), corticosteroid 11-beta-dehydrogenase isozyme 1 (0.83), hydroxysteroid 11-beta-dehydrogenase 1-like protein (0.83), estradiol 17-beta-dehydrogenase 2 (0.81), corticosteroid 11-beta-dehydrogenase isozyme 2 (0.81), CYP2C9 (0.81), CYP2C19 (0.81), CYP2E1 (0.81), CYP2C8 (0.81)	antiseborrheic (0.958), testosterone 17beta-dehydrogenase (NADP+) inhibitor (0.943), CYP2C12 substrate (0.933), CYP2J2 substrate (0.911)	embryotoxic (0.924), teratogen (0.924), reproductive dysfunction (0.902)	NA
Mesterolone	androgen receptor (0.94), CYP19A1 (0.93), glucose-6-phosphate 1-dehydrogenase (0.93), testosterone 17-beta-	antiseborrheic (0.976), testosterone 17beta-dehydrogenase (NADP+) inhibitor (0.970), CYP2C12 substrate (0.942),	excitability (0.923), reproductive dysfunction (0.919)	NA

Table V (continued)

Steroid	Predicted molecular targets ($P > 0.7$)	Prediction of biological activity (Pa > 0.9)	Possible adverse&toxic effects (Pa > 0.9)	Known side effects
	dehydrogenase 3 (0.92), estradiol 17-beta-dehydrogenase 12 (0.92), muscleblind-like protein 1 (0.82), muscleblind-like protein 2 (0.82), muscleblind-like protein 3 (0.82), microtubule-associated protein tau (0.76), m-phase inducer phosphatase 1 (0.75), m-phase inducer phosphatase 2 (0.75)	CYP2J substrate (0.940), alkenylglycerophosphocholine hydrolase inhibitor (0.937), CYP2J2 substrate (0.935), alkylacetylglycerophosphatase inhibitor (0.934), acylcarnitine hydrolase inhibitor (0.930)		
Testosterone undecanoate	microtubule-associated protein tau (0.94), androgen receptor (0.84), corticosteroid 11-beta-dehydrogenase isozyme 1 (0.82), hydroxysteroid 11-beta-dehydrogenase 1-like protein (0.82), glucocorticoid receptor (0.76), mineralocorticoid receptor (0.76), progesterone receptor (0.74), steroid 17-alpha-hydroxylase/17,20 lyase (0.72), complex FNTA/FNTB (0.70)	CYP2J2 substrate (0.986), testosterone 17beta-dehydrogenase (NADP+) inhibitor (0.978), CYP2C12 substrate (0.977), CYP2C6 substrate (0.965), prostaglandin-E2 9-reductase inhibitor (0.966), CYP2C11 substrate (0.957), CYP3A1 substrate (0.941), antisecretoric (0.940), HMOX1 expression enhancer (0.935), CYP4B1 substrate (0.925), CYP2A4 substrate (0.923), gonadotropin antagonist (0.916), CYP2A1 substrate (0.914), alkenylglycerophosphocholine (0.910), oxidoreductase inhibitor (0.906), CYP2B6 substrate (0.907), antiseborrheic (0.906), CYP2C9 substrate (0.906), lysase inhibitor (0.905), CYP2A substrate (0.900)	excitability (0.976), reproductive dysfunction (0.967), endocrine disruptor (0.957), teratogen (0.939), conjunctivitis (0.940), embryotoxic (0.936), ocular toxicity (0.931), behavioral disturbance (0.930), porphyria (0.923), hepatotoxic (0.926), dyspnea (0.908), sleep disturbance (0.912)	gastrointestinal effects (nausea diarrhoea), genitourinary effects (growth of the prostate gland, prostate cancer), hepatic effects (hepatic tumours), endocrine effects (penile erections of excessive frequency and duration in males), dermatologic effects (pruritus, acne), psychiatric effects (depression, nervousness), electrolyte changes (sodium, potassium, calcium, inorganic phosphate and water retention)
Nandrolonedecanoate	microtubule-associated protein tau (0.98), androgen receptor (0.84), glucocorticoid receptor (0.83), mineralocorticoid receptor (0.83), corticosteroid 11-beta-dehydrogenase isozyme 1 (0.83), hydroxysteroid 11-beta-dehydrogenase 1-like protein (0.83), CYP2C9 (0.78), CYP2C19 (0.78), CYP2E1 (0.78), CYP2C8 (0.78), CYP2A6 (0.78), CYP2B6 (0.78), CYP2A7 (0.78), CYP2F1 (0.78), CYP2C18 (0.78)	CYP2J2 substrate (0.977), testosterone 17beta-dehydrogenase (NADP+) inhibitor (0.964), gonadotropin antagonist (0.963), CYP2C12 substrate (0.962), prostaglandin-E2 9-reductase inhibitor (0.955), antisecretoric (0.942), CYP2C11 substrate (0.926), lysase inhibitor (0.926), antiseborrheic (0.925), oxidoreductase inhibitor (0.909), CYP2C9 substrate (0.911), alkenylglycerophosphocholine hydrolase inhibitor (0.910)	excitability (0.975), reproductive dysfunction (0.968), endocrine disruptor (0.940), teratogen (0.938), embryotoxic (0.936), behavioral disturbance (0.928), ocular toxicity (0.920), hepatotoxic (0.913), conjunctivitis (0.914), sleep disturbance (0.913)	cardiovascular effects (edema with and without congestive heart failure,coronary heart disease), genitourinary effects (oligospermia, decreased ejaculatory volume, virilisation in the females), gastrointestinal effects (nausea, vomiting, diarrhoea), hepatic effects (peliosis hepatitis, hepatic neoplasms, hepatocellular carcinomas), hematologic effects (alterations in clotting factors II, V, VII and X, prolonged prothrombin time, increased red cell production), endocrine effects (inhibition of endogenous testosterone release), dermatologic effects (acne), psychiatric effects (habituation, excitation, insomnia, depression, libido changes), renal effects (retention of nitrogen, sodium, potassium, chloride, water and phosphorus, decreased urinary excretion of calcium)

Table V (continued)

Steroid	Predicted molecular targets ($P > 0.7$)	Prediction of biological activity (Pa > 0.9)	Possible adverse&toxic effects (Pa > 0.9)	Known side effects
Nandrolonephenpropionate	–	testosterone 17beta-dehydrogenase (NADP+) inhibitor (0.966), CYP2C12 substrate (0.957), CYP2J2 substrate (0.952), gonadotropin antagonist (0.944), lysase inhibitor (0.932), CYP2C substrate (0.930), antiseborrheic (0.917), prostaglandin-E2 9-reductase inhibitor (0.905), oxidoreductase inhibitor (0.902)	excitability (0.964), reproductive dysfunction (0.961), endocrine disruptor (0.912)	NA
Testosterone cypionate	microtubule-associated protein tau (0.88), corticosteroid 11-beta-dehydrogenase isozyme 1 (0.86), hydroxysteroid 11-beta-dehydrogenase 1-like protein (0.86), glucocorticoid receptor (0.84), mineralocorticoid receptor (0.84), steroid 17-alpha-hydroxylase/17,20 lyase (0.81), androgen receptor (0.81), CYP2C9 (0.77), CYP2C19 (0.77), CYP2E1(0.77), CYP2C8 (0.77), CYP2A6 (0.77), CYP2B6 (0.77), CYP2A7(0.77), CYP2F1(0.77)	testosterone 17beta-dehydrogenase (NADP+) inhibitor (0.973), CYP2J2 substrate (0.956), CYP2C12 substrate (0.945), prostaglandin-E2 9-reductase inhibitor (0.933), CYP2C substrate (0.933), CYP2A1 substrate (0.922), CYP2C6 substrate (0.914), oxidoreductase inhibitor (0.910)	reproductive dysfunction (0.964), excitability (0.953), endocrine disruptor (0.944), conjunctivitis (0.915), asthma (0.907), ocular toxicity (0.905)	cardiovascular effects (chest pain or pressure), genitourinary effects (impotence, ejaculation problems, decreased amounts of semen, decrease in testicle size;, painful or difficult urination, virilisation in females), gastrointestinal effects (nausea, vomiting), dermatologic effects (acne, increased facial or body hair growth, male-pattern baldness), psychiatric effects (anxiety), nervous system effects (headache)
Testosterone enanthate	microtubule-associated protein tau (0.89), corticosteroid 11-beta-dehydrogenase isozyme 1 (0.86), hydroxysteroid 11-beta-dehydrogenase 1-like protein (0.86), glucocorticoid receptor (0.83), mineralocorticoid receptor (0.83), CYP 19A1 (0.79), estradiol 17-beta-dehydrogenase 2 (0.77), corticosteroid 11-beta-dehydrogenase isozyme 2 (0.77), progesterone receptor (0.72), CYP2C9 (0.72), CYP2C19 (0.72), CYP2E1 (0.72), CYP2C8 (0.72), CYP2A6 (0.72), CYP2B6 (0.72)	CYP2J2 substrate (0.986), testosterone 17beta-dehydrogenase (NADP+) inhibitor (0.978), CYP2C12 substrate (0.977), CYP2C6 substrate (0.965), prostaglandin-E2 9-reductase inhibitor (0.966), CYP2C11 substrate (0.957), CYP3A1 substrate (0.941), antisecretoric (0.940), HMOX1 expression enhancer (0.935), CYP4B1 substrate (0.925), CYP2A4 substrate (0.923), gonadotropin antagonist (0.916), CYP2A1 substrate (0.914), alkenylglycerophosphocholine hydrolase inhibitor (0.910), oxidoreductase inhibitor (0.906), CYP2B6 substrate (0.907), antiseborrheic (0.906), CYP2C9 substrate (0.906), lysase inhibitor (0.905), CYP2A substrate (0.900)	excitability (0.976), reproductive dysfunction (0.967), endocrine disruptor (0.957), teratogen (0.939), conjunctivitis (0.940), embryotoxic (0.936), ocular toxicity (0.931), behavioral disturbance (0.930), porphyria (0.923), hepatotoxic (0.926), dyspnea (0.908), sleep disturbance (0.912)	cardiovascular effects (high blood pressure, blood clots, a stroke, a heart attack), genitourinary effects (prostate cancer), metabolic effects (higher cholesterol and triglycerides.)
Testosterone propionate	steroid 17-alpha-hydroxylase/17,20 lyase (0.96), androgen receptor (0.96), microtubule-associated protein tau (0.95), progesterone receptor (0.87), glucocorticoid receptor (0.87), mineralocorticoid receptor (0.87), CYP2C9 (0.87), CYP2C19 (0.87), CYP2E1 (0.87), CYP2C8 (0.87), CYP2A6 (0.87),	testosterone 17beta-dehydrogenase (NADP+) inhibitor (0.983), CYP2J2 substrate (0.978), CYP2C12 substrate (0.975), CYP2C6 substrate (0.965), CYP2C11 substrate (0.955), prostaglandin-E2 9-reductase inhibitor (0.947), CYP2A4 substrate (0.940), CYP2A1 substrate (0.928), lysase	excitability (0.975), reproductive dysfunction (0.968), endocrine disruptor (0.939), teratogen (0.936), embryotoxic (0.933), behavioral disturbance (0.930), hepatotoxic (0.929), ocular toxicity (0.927), porphyria (0.921), conjunctivitis (0.926), asthma (0.903), sleep disturbance (0.906)	cardiovascular effects (chest pain or pressure), genitourinary effects (reduction in sperm production, painful and unwanted erections, libido changes), gastrointestinal effects (nausea), dermatologic effects (acne, hirsutism), hepatic effects (liver cancer), psychiatric effects (anxiety,depression, irritability,

Table V (continued)

Steroid	Predicted molecular targets ($P > 0.7$)	Prediction of biological activity (Pa > 0.9)	Possible adverse&toxic effects (Pa > 0.9)	Known side effects
	CYP2B6 (0.87), CYP2A7 (0.87), CYP2F1 (0.87), CYP2C18 (0.87)	inhibitor (0.926), antiseborrheic (0.926), CYP3A1 substrate (0.925), CYP2C9 substrate (0.926), antisecretoric (0.924), gonadotropin antagonist (0.920), CYP2B5 substrate (0.919), CYP2A2 substrate (0.914), CYP2B6 substrate (0.904)		nervousness,), nervous system effects (headache), blood disorder affecting red blood cells, changes in sodium and calcium levels in the blood with fluid retention,excessive sweating, chest pain, dizziness
Methenoloneenanthate	microtubule-associated protein tau (0.89), corticosteroid 11-beta-dehydrogenase isozyme 1 (0.87), hydroxysteroid 11-beta-dehydrogenase 1-like protein (0.87), glucocorticoid receptor (0.81), mineralocorticoid receptor (0.81), steroid 17-alpha-hydroxylase/17,20 lyase (0.77), androgen receptor (0.77), CYP19A1 (0.75), estradiol 17-beta-dehydrogenase 2 (0.74), corticosteroid 11-beta-dehydrogenase isozyme 2 (0.74)	CYP2J2 substrate (0.949), CYP2C12 substrate (0.942), antiseborrheic (0.921), testosterone 17beta-dehydrogenase (NADP+) inhibitor (0.921), alkenylglycerophosphocholine hydrolase inhibitor (0.921)	teratogen (0.937), embryotoxic (0.936), excitability (0.933), reproductive dysfunction (0.926)	NA
Boldenoneundecyclenate	microtubule-associated protein tau (0.92), CYP19A1 (0.91), androgen receptor (0.79), glucocorticoid receptor (0.78), mineralocorticoid receptor (0.78), estrogen receptor (0.76), estrogen receptor beta (0.76)	testosterone 17beta-dehydrogenase (NADP+) inhibitor (0.987), CYP2C12 substrate (0.981), CYP2J2 substrate (0.971), CYP19 inhibitor (0.957), CYP2A4 substrate (0.956), JAK2 expression inhibitor (0.946), prostaglandin-E2 9-reductase inhibitor (0.945), aldehyde oxidase inhibitor (0.937), gonadotropin antagonist (0.931), CYP2B11 substrate (0.929), alkenylglycerophosphocholine hydrolase inhibitor (0.931), CYP2C9 substrate (0.930), antiseborrheic (0.927), UGT1A9 substrate (0.921), CYP3A1 substrate (0.921), CYP2B substrate (0.920), UGT1A6 substrate (0.917), CYP2A2 substrate (0.916),lysase inhibitor (0.916), CYP2A1 substrate (0.913), CYP2B6 substrate (0.911), indanol dehydrogenase inhibitor (0.909), alopecia treatment (0.903), 27-Hydroxycholesterol 7alpha-monooxygenase inhibitor (0.901)	Excitability (0.973), toxic respiration (0.972), endocrine disruptor (0.939), euphoria (0.938), consciousness alteration (0.933), reproductive dysfunction (0.930), behavioral disturbance (0.918), necrosis (0.913), conjunctivitis (0.914), ocular toxicity (0.910), dizziness (0.911), hypertensive (0.908), allergic dermatitis (0.904), sleep disturbance (0.910), paralysis (0.901), sensory disturbance (0.905)	NA
Trenbolone acetate	glucocorticoid receptor (0.75), mineralocorticoid receptor (0.75), androgen receptor (0.75), steroid 17-alpha-hydroxylase/17,20 lyase (0.74)	gonadotropin antagonist (0.963), antiseborrheic (0.940), testosterone 17beta-dehydrogenase (NADP+) inhibitor (0.933), prostaglandin-E2 9-reductase	reproductive dysfunction (0.925), endocrine disruptor (0.923)	reproductive toxicity

Table V (continued)

Steroid	Predicted molecular targets ($P > 0.7$)	Prediction of biological activity (Pa > 0.9)	Possible adverse&toxic effects (Pa > 0.9)	Known side effects
		inhibitor (0.922), lysase inhibitor (0.907), CYP2J2 substrate (0.904)		
Trenbolone	androgen receptor (0.95), sex hormone-binding globulin (0.92), glucocorticoid receptor (0.90), mineralocorticoid receptor (0.90), CYP19A1 (0.85), 3-oxo-5-alpha-steroid 4-dehydrogenase 2 (0.75)	testosterone 17beta-dehydrogenase (NADP+) inhibitor (0.976), CYP2C12 substrate (0.963), CYP2J2 substrate (0.953), prostaglandin-E2 9-reductase inhibitor (0.943), JAK2 expression inhibitor (0.939), lysase inhibitor (0.938), gonadotropin antagonist (0.923), CYP2A4 substrate (0.920), UGT1A6 substrate (0.918), antiseborrheic (0.906)	reproductive dysfunction (0.926), endocrine disruptor (0.907)	reproductive toxicity
Androsterone	CYP19A1 (0.95), glucose-6-phosphate 1-dehydrogenase (0.85), androgen receptor (0.82), glucocorticoid receptor (0.82), mineralocorticoid receptor (0.82), estrogen receptor (0.76), estrogen receptor beta (0.76), 3-oxo-5-alpha-steroid 4-dehydrogenase 2 (0.76), sex hormone-binding globulin (0.70), sigma non-opioid intracellular receptor 1 (0.70)	testosterone 17beta-dehydrogenase (NADP+) inhibitor (0.973), alkenylglycerophosphocholinehydrolase inhibitor (0.969), alkylacetylglycerophosphatase inhibitor (0.967), acylcarnitine hydrolase inhibitor (0.964), 27-hydroxycholesterol 7alpha-monooxygenase inhibitor (0.960), dextranase inhibitor (0.952), CYP2C12 substrate (0.949), CYP2J2 substrate (0.942), morphine 6-dehydrogenase inhibitor (0.937), UGT1A6 substrate (0.932), UGT1A substrate (0.929), glucan endo-1,3-beta-D-glucosidase inhibitor (0.924), cholesterol antagonist (0.921), linoleate diol synthase inhibitor (0.919), CYP4B1 substrate (0.911), cholestanetriol 26-monooxygenase inhibitor (0.911), trans-1,2-dihydrobenzene-1,2-diol dehydrogenase inhibitor (0.910), respiratory analeptic (0.912)3(or 17)alpha-hydroxysteroid dehydrogenase inhibitor (0.907), membrane permeability inhibitor (0.909), UGT1A4 substrate (0.907), UDP-glucuronosyltransferase substrate (0.903), antiseborrheic (0.904), CYP2C substrate (0.901)	Irritation (0.940)	skin and eye irritation, respiratory irritation
4-Hydroxy-testosterone	CYP19A1 (0.88), androgen receptor (0.84), glucocorticoid receptor (0.81), mineralocorticoid receptor (0.81), progesterone receptor (0.79), sodium-dependent noradrenaline transporter (0.79), sodium-dependent serotonin transporter (0.79), sodium-dependent dopamine transporter	testosterone 17beta-dehydrogenase (NADP+) inhibitor (0.987), CYP2C12 substrate (0.980), CYP2J2 substrate (0.972), CYP19 inhibitor (0.958), CYP2A4 substrate (0.945), prostaglandin-E2 9-reductase inhibitor (0.945), lysase inhibitor (0.936), JAK2 expression	reproductive dysfunction (0.918), excitability (0.914)	cholesterol increase, acne, hypertension, liver damage

Table V (continued)

Steroid	Predicted molecular targets ($P > 0.7$)	Prediction of biological activity (Pa > 0.9)	Possible adverse&toxic effects (Pa > 0.9)	Known side effects
	(0.79), sodium- and chloride-dependent glycine transporter 1 (0.79), sodium-dependent proline transporter (0.79), sodium- and chloride-dependent neutral and basic amino acid transporter B(0+) (0.79), sodium- and chloride-dependent glycine transporter 2 (0.79), sex hormone-binding globulin (0.78), steroid 17-alpha-hydroxylase/17,20 lyase (0.78), sigma non-opioid intracellular receptor 1 (0.78)	inhibitor (0.928), alkenylglycerophosphocholine hydrolase inhibitor (0.918), 27-hydroxycholesterol 7alpha-monooxygenase inhibitor (0.915), antiseborrheic (0.916), CYP2B11 substrate (0.908), CYP2A11 substrate (0.907), CYP2A1 substrate (0.906), CYP2A2 substrate (0.904), CYP3A1 substrate (0.905)		
7-Keto-dehydro-epiandrosterone	androgen receptor (0.81), CYP 19A1 (0.81), muscleblind-like protein 1 (0.72), muscleblind-like protein 2 (0.72), muscleblind-like protein 3 (0.72), sodium-dependent noradrenaline transporter (0.72), sodium-dependent serotonin transporter (0.72), sodium-dependent dopamine transporter (0.72), glucocorticoid receptor (0.72), mineralocorticoid receptor (0.72), glucose-6-phosphate 1-dehydrogenase (0.70), microtubule-associated protein tau (0.70)	testosterone 17beta-dehydrogenase (NADP+) inhibitor (0.979), 27-Hydroxycholesterol 7alpha-monooxygenase inhibitor (0.969), CYP2C12 substrate (0.962), CYP2J2 substrate (0.954), ovulation inhibitor (0.923), CYP2A4 substrate (0.916), prostaglandin-E2 9-reductase inhibitor (0.918), CYP2A2 substrate (0.905)	endocrine disruptor (0.867), ocular toxicity (0.855), toxic, vascular (0.845) Reproductive dysfunction (0.840), necrosis (0.838), teratogen (0.831), sensitization (0.822), neurotoxic (0.831), toxic (0.837), optic neuropathy (0.817), embryotoxic (0.819), hypertensive (0.817), optic neuritis (0.802), behavioral disturbance (0.811)	NA
Androst-4-ene-3,11,17-trione	musdeblind-like protein 1 (0.89), muscleblind-like protein 2 (0.89), muscleblind-like protein 3 (0.89), 3-oxo-5-alpha-steroid 4-dehydrogenase 2 (0.83), 3-oxo-5-alpha-steroid 4-dehydrogenase 1 (0.82), CYP19A1 (0.82), microtubule-associated protein tau (0.78), estrogen receptor (0.75), estrogen receptor beta (0.75), glucocorticoid receptor (0.75), mineralocorticoid receptor (0.75), androgen receptor (0.73), testosterone 17-beta-dehydrogenase 3 (0.73), estradiol 17-beta-dehydrogenase 12 (0.73), progesterone receptor (0.72)	testosterone 17beta-dehydrogenase (NADP+) inhibitor (0.978), CYP2B5 substrate (0.973), CYP2C12 substrate (0.960),CYP2J2 substrate (0.951), CYP2A1 substrate (0.940), 27-Hydroxycholesterol 7alpha-monooxygenase inhibitor (0.935), CYP2B substrate (0.934), CYP2A2 substrate (0.922), ovulation inhibitor (0.919), CYP2A4 substrate (0.916),CYP2B11 substrate (0.912), CYP2B6 substrate (0.911), lysase inhibitor (0.908), cholesterol antagonist (0.900)	excitability (0.961)	NA
Androsta-1,4,6-triene-3,17-dione	–	CYP2B5 substrate (0.950), testosterone 17beta-dehydrogenase (NADP+) inhibitor (0.927), gonadotropin antagonist (0.908), CYP2C12 substrate (0.902)	endocrine disruptor (0.909), euphoria (0.907)	NA
Androsterone acetate	microtubule-associated protein tau (0.96), CYP19A1 (0.80), platelet-activating factor receptor (0.78), tyrosine-protein	testosterone 17beta-dehydrogenase (NADP+) inhibitor (0.940), respiratory analeptic (0.938), acylcarnitine hydrolase	irritation (0.905)	NA

Table V (continued)

Steroid	Predicted molecular targets ($P > 0.7$)	Prediction of biological activity (Pa > 0.9)	Possible adverse&toxic effects (Pa > 0.9)	Known side effects
	phosphatase non-receptor type 2 (0.73), tyrosine-protein phosphatase non-receptor type 1 (0.73)	inhibitor (0.935), alkenylglycerophosphocholine hydrolase inhibitor (0.932), dextranase inhibitor (0.928), antiseborrheic (0.922), alkylacetylglycerophosphatase inhibitor (0.921), membrane permeability inhibitor (0.912), CYP2C9 substrate (0.912), CYP2J2 substrate (0.908), 27-hydroxycholesterol 7alpha-monooxygenase inhibitor (0.904), cholesterol antagonist (0.901)		
Boldion (Androsta-1,4-diene-3,17-dione)	CYP19A1 (0.95), androgen receptor (0.78)	CYP2B5 substrate (0.975), testosterone 17beta-dehydrogenase (NADP+) inhibitor (0.968), CYP2C12 substrate (0.952), CYP19 inhibitor (0.944), 27-Hydroxycholesterol 7alpha-monooxygenase inhibitor (0.933), CYP2J2 substrate (0.929), CYP2C substrate (0.927), CYP2A1 substrate (0.921), indanol dehydrogenase inhibitor (0.916), CYP3A1 substrate (0.916), CYP2B11 substrate (0.909), CYP2A2 substrate (0.908), CYP2C9 substrate (0.910) CYP2B substrate (0.902)	euphoria (0.946), excitability (0.943), endocrine disruptor (0.936)	increase in blood pressure
Epiandrosterone	glucose-6-phosphate 1-dehydrogenase (1,00), testosterone 17-beta-dehydrogenase 3 (0.94), estradiol 17-beta-dehydrogenase 12 (0.94), androgen receptor (0.94)CYP 19A1 (0.94), muscleblind-like protein 1 (0.80), muscleblind-like protein 2 (0.80), muscleblind-like protein 3 (0.80), microtubule-associated protein tau (0.80), complex (0.75), m-phase inducer phosphatase 1 (0.75), m-phase inducer phosphatase 2 (0.75), UDP-glucuronosyl-transferase 2B7 (0.70), UDP-glucuronosyl-transferase 2B11 (0.70), UDP-glucuronosyl-transferase 2B17 (0.70)	testosterone 17beta-dehydrogenase (NADP+) inhibitor (0.973), alkenylglycerophosphocholine hydrolase inhibitor (0.969), alkylacetylglycerophosphatase inhibitor (0.967), acylcarnitine hydrolase inhibitor (0.964), 27-Hydroxycholesterol 7alpha-monooxygenase inhibitor (0.960), dextranase inhibitor (0.952), CYP2C12 substrate (0.949),CYP2J2 substrate (0.942), morphine 6-dehydrogenase inhibitor (0.937), UGT1A6 substrate (0.932), UGT1A substrate (0.929), Glucan endo-1,3-beta-D-glucosidase inhibitor (0.924), cholesterol antagonist (0.921), linoleate diol synthase inhibitor (0.919), CYP4B1 substrate (0.911), cholestanetriol 26-monooxygenase inhibitor (0.911), trans-1,2-dihydrobenzene-1,2-diol dehydrogenase inhibitor (0.910), respiratory analeptic (0.912), 3(or 17)alpha-	irritation (0.940)	hair loss, acne

Table V (continued)

Steroid	Predicted molecular targets ($P > 0.7$)	Prediction of biological activity (Pa > 0.9)	Possible adverse&toxic effects (Pa > 0.9)	Known side effects
		hydroxysteroid dehydrogenase inhibitor (0.907), membrane permeability inhibitor (0.909), UGT1A4 substrate (0.907), UDP-glucuronosyltransferase substrate (0.903), antiseborrheic (0.904), CYP2C substrate (0.901)		
Epietiocholanolone	testosterone 17-beta-dehydrogenase 3 (0.95), estradiol 17-beta-dehydrogenase 12 (0.95), glucose-6-phosphate 1-dehydrogenase (0.95), androgen receptor (0.95), CYP 19A1 (0.94), microtubule-associated protein tau (0.83), muscleblind-like protein 1 (0.82), muscleblind-like protein 2 (0.82), muscleblind-like protein 3 (0.82), m-phase inducer phosphatase 1 (0.75), m-phase inducer phosphatase 2 (0.75), complex (0.70), UDP-glucuronosyl-transferase 2B7 (0.70), UDP-glucuronosyl-transferase 2B11 (0.70), UDP-glucuronosyl-transferase 2B17 (0.70)	testosterone 17beta-dehydrogenase (NADP+) inhibitor (0.973), alkenylglycerophosphocholine hydrolase inhibitor (0.969), alkylacetylglycerophosphatase inhibitor (0.967), acylcarnitine hydrolase inhibitor (0.964), 27-hydroxycholesterol 7alpha-monooxygenase inhibitor (0.960), dextranase inhibitor (0.952), CYP2C12 substrate (0.949),CYP2J2 substrate (0.942), morphine 6-dehydrogenase inhibitor (0.937), UGT1A6 substrate (0.932), UGT1A substrate (0.929), glucan endo-1,3-beta-D-glucosidase inhibitor (0.924), cholesterol antagonist (0.921), linoleate diol synthase inhibitor (0.919), CYP4B1 substrate (0.911), cholestanetriol 26-monooxygenase inhibitor (0.911), trans-1,2-dihydrobenzene-1,2-diol dehydrogenase inhibitor (0.910), respiratory analeptic (0.912), 3(or 17)alpha-hydroxysteroid dehydrogenase inhibitor (0.907), membrane permeability inhibitor (0.909), UGT1A4 substrate (0.907), UDP-glucuronosyltransferase substrate (0.903), antiseborrheic (0.904), CYP2C substrate (0.901)	irritation (0.940)	blood pressure, hepatoxicity, acne, hair loss
Estra-4,9-diene-3,17-dione	androgen receptor (0.93), CYP19A1 (0.92), progesterone receptor (0.86), muscleblind-like protein 1 (0.76), muscleblind-like protein 2 (0.76), muscleblind-like protein 3 (0.76), 3-oxo-5-alpha-steroid 4-dehydrogenase 1 (0.73), 3-oxo-5-alpha-steroid 4-dehydrogenase 2 (0.73), testosterone 17-beta-dehydrogenase 3 (0.73), estradiol 17-beta-dehydrogenase 12 (0.73), glucocorticoid receptor (0.71), mineralocorticoid receptor (0.71)	testosterone 17beta-dehydrogenase (NADP+) inhibitor (0.964), CYP2B5 substrate (0.956), CYP2C12 substrate (0.934),lysase inhibitor (0.924), CYP2J2 substrate (0.920), ovulation inhibitor (0.916), CYP3A1 substrate (0.905)	endocrine disruptor (0.921)	NA

Table V (continued)

Steroid	Predicted molecular targets ($P > 0.7$)	Prediction of biological activity ($Pa > 0.9$)	Possible adverse&toxic effects ($Pa > 0.9$)	Known side effects
Methasterone	androgen receptor (0.92), CYP 19A1 (0.92), glucose-6-phosphate 1-dehydrogenase (0.91), testosterone 17-beta-dehydrogenase 3 (0.90), estradiol 17-beta-dehydrogenase 12 (0.90), muscleblind-like protein 1 (0.82), muscleblind-like protein 2 (0.82), muscleblind-like protein 3 (0.82), m-phase inducer phosphatase 1 (0.77), m-phase inducer phosphatase 2 (0.77), complex (0.77), microtubule-associated protein tau (0.74), tyrosyl-DNA phosphodiesterase 1 (0.70)	antiseborrheic (0.948), antihypercholesterolemic (0.934), antisecretoric (0.924), androgen antagonist (0.901)	excitability (0.973), euphoria (0.954), reproductive dysfunction (0.936), behavioral disturbance (0.935), sleep disturbance (0.933), necrosis (0.923), hepatotoxic (0.925), embryotoxic (0.919), consciousness alteration (0.918), teratogen (0.909)	NA
Prostanozol	estrogen receptor (0.62)	antineoplastic (0.832)	embryotoxic (0.849), teratogen (0.849)	NA

Control Act 2014' reflect high potential as endocrine disruptors, as presented in Table VII.

They usually reflect high binding capacity to the androgen and estrogen receptors in both agonistic and antagonistic conformations and consequently they may produce cancerous tumours, developmental disorders, reproductive dysfunctions, neurologicaland immune effects in humans. The results obtained using Endocrine Disruptome computational facility are in good agreement with published data concerning both experimental and molecular modelling studies revealing the interactions of different steroids with steroids receptors and other nuclear receptors (13–18).

DISCUSSION

There is not a total consensus between the predictions concerning the same characteristics obtained using diverse software. It could be explained by the fact that different authors have used distinctive parameters in their models, different numbers of compounds and/or distinct types of chemical structures for their training and testing data sets. Also, different statistical approaches have been used to describe the goodness of the models used.

However, some of the predicted features of investigated steroids are confirmed by several computational tools. All the specific computational methods that we have used predicted that investigated AAS revealed good oral bioavailability, a good capacity for skin penetration, the ability to penetrate the blood brain barrier and that some of them are substrates for the P-gp protein. Their ability to penetrate the blood brain barrier is also confirmed by the predictions obtained using PASS online, the latter envisaging that euphoria, excitability and behavioural disturbance are common side effects manifested by all investigated steroids. Furthermore, these side effects have been noticed in clinical studies for numerous steroids.

Many of the predictions concerning the interactions of steroids with CYPs that have been obtained using SwissADME tool have been confirmed by the results acquired by means of SwissTargetPrediction and PASS online tools and are confirmed by the molecular docking studies. Our results emphasised that numerous investigated AAS are able to inhibit CYPs involved in the metabolism of endogenous compounds and drugs, especially the cytochrome 2C19, but also CYP1A2 and CYP2C9.

There also is a good correlation between the predictions concerning the interactions of investigated steroids with some of the human nuclear receptors obtained using SwissTargetPrediction, PASS online and Endocrine Disruptome computational facilities. Furthermore, these predictions are in good agreement to other published data

Table VI Assessment of the Toxic Potential of Investigated Steroids

Steroid	Carcinogenicity			Ames toxicity		hERG
	Toxtree prediction		admetSAR prediction	Toxtree prediction	admetSAR prediction	
	Non-genotoxic carcinogenicity	Genotoxic carcinogenicity	Carcinogen			
Oxymetholone	No	Yes	No	Yes	No	Weak
Oxandrolone	No	No	No	No	No	Weak
Methandrostenolone	No	Yes	No	Yes	No	Weak
Ethylestrenol	No	No	No	No	No	Weak
Stanozolol	No	No	No	No	No	Weak
Fluoxymesterone	No	Yes	No	Yes	No	Weak
Norethandrolone	No	Yes	No	Yes	No	Weak
Methenolone acetate	No	Yes	No	Yes	No	Weak
Mesterolone	No	No	No	No	No	Weak
Testosterone undecanoate	No	Yes	No	Yes	No	Weak
Nandrolonedecanoate	No	Yes	No	Yes	No	Weak
Nandrolonephenpropionate	No	Yes	No	Yes	No	Weak
Testosterone cypionate	No	Yes	No	Yes	No	Weak
Testosterone enanthate	No	Yes	No	Yes	No	Weak
Testosterone propionate	No	Yes	No	Yes	No	Weak
Methenoloneenanthate	No	Yes	No	Yes	No	Weak
Boldenoneundecyclenate	No	Yes	No	Yes	No	Weak
Trenbolone acetate	No	Yes	No	Yes	No	Weak
Trenbolone	No	Yes	No	Yes	No	Weak
1-Androsterone	No	No	No	No	No	Weak
4-Hydroxytestosterone	No	Yes	No	Yes	No	Weak
7-Keto-dehydroepiandrosterone	No	Yes	No	Yes	No	Weak
Androst-4-ene-3,11,17-trione	No	Yes	No	Yes	No	Weak
Androsta-1,4,6-triene-3,17-dione	No	Yes	No	Yes	No	Weak
Androsterone acetate	No	No	No	No	No	Weak
Androsta-1,4-diene-3,17-dione	No	Yes	No	Yes	No	Weak
Epiandrosterone	No	No	No	No	No	Weak
Epietiocholanolone	No	No	No	No	No	Weak
Estra-4,9-diene-3,17-dione	No	Yes	No	Yes	No	Weak
Methasterone	No	No	No	No	No	Weak
Prostanozol	No	No	No	No	No	Weak

(13–18) and the clinically observed adverse effectsfor some considered steroids.

Our results emphasize thatAAS reveal different degrees of toxicity and numerous side effects on humans: cardiotoxicity, gastrointestinal toxicity, hepatotoxicity (especially hepatic neoplasms or hepatocellular carcinomas), hematotoxicity, embryotoxicity, dermatological adverse effects, psychiatric effects, endocrine disruption and reproductive dysfunction. Predicted side effects are in very good agreement with experimental/clinical data known for several steroids that are used as drugs. Taking into account that steroids may be used illegally, some of their side effects may also not be reported.

There also are some research limitations. Even if computational methods are widely used to assess the prediction of pharmacokinetics and side/toxic effects of xenobiotics, important false-positive rates may occur. Rule-based, approaches are capable to detect most toxicophores, but predictions taking into account doses of xenobiotics and/or their accumulation remain challenging. Another limitation that must be underlined is that many side effects may be observed not for the whole population but just in some particular persons. There are many factors that may have a critical impact on the occurrence of adverse effects of drugs and other xenobiotics: dose and frequency, age (very

Table VII Evaluation of the Endocrine Disruptor Potential of Investigated Steroids: Green – Low Endocrine Disruption Potential, Light Yellow – Low to Medium Endocrine Disruption Potential, Orange – Medium Endocrine Disruption Potential, Red – High Endocrine Disruption Potential

	AR	AR an	ER α	ER α an	ER β	ER β an	GR	GR an	LXR α	LXR β	PPAR α	PPAR β	PPAR γ	RXR α	TR α	TR β
Oxymetholone																
Oxandrolone																
Methandrostenolone																
Ethylestrenol																
Stanozolol																
Fluoxymesterone																
Norethandrolone																
Methenolone acetate																
Mesterolone																
Testosterone undecanoate																
Nandrolonedecanoate																
Nandrolonephenpropionate																
Testosterone cypionate																
Testosterone enanthate																
Testosterone propionate																
Methenoloneenanthate																
Boldenoneundecyclenate																
Trenbolone acetate																
Trenbolone																
1-Androsterone																
4-Hydroxytestosterone																
7-Keto-dehydroepiandrosterone																
Androst-4-ene-3,11,17-trione																
Androsta-1,4,6-triene-3,17-dione																
Androsterone acetate																
Androsta-1,4-diene-3,17-dione																
Epiandrosterone																
Epietiocholanolone																
Estra-4,9-diene-3,17-dione																
Methasterone																
Prostanozol																

young and very old people being more vulnerable), gender, genetic factors, health status, smoking, alcohol intake, co-administrated medication (41).Computational methods do not take into account any of these factors.

However, computational methods have advantages complementing in vivo toxicity tests and improving toxicity prediction and safety assessment of AAS.

CONCLUSIONS

To the best of our knowledge, this is a first study dealing with predictions of ADME-Tox profiles, pharmacokinetics, molecular targets, biological activity spectra and adverse effects in humans of the steroids that are already approved and used as drugs but also for those that are approved to be used for animals and designer steroids that are under control/evaluation, respectively. The metabolism, effects and side effects of many steroids on humans are not well understood and the outcomes of this study may inform both professionals and population about the health issues that may be associated with their use.

Steroids considered in this study usually reveal a high gastrointestinal absorption and consequently a good oral bioavailability and they reflect a good capacity for skin penetration. Investigated steroids may inhibit many of the human cytochromes involved in the metabolism of numerous xenobiotics, CYP2C9 being the most affected, and consequently their use may impair the efficiency of other medication.

There are predicted various side effects of these anabolic and androgenic steroids in humans, such as cardiotoxicity, gastrointestinal toxicity, genitourinary effects, dermal irritations, hepatotoxicity, psychiatric disorders, endocrine disruptions and reproductive dysfunction. Many of these side effects are confirmed by case studies reported in specific literature and it enhances the accuracy of predictions.

The outcomes of this study concerning the inhibition of the cytochromes by steroids are important to be known to avoid co-administration of steroids with some drugs. Identification of the molecular targets and of the possible side and/or toxic effects of investigated steroids also has practical implications for the awareness of those who use them deliberately for their performance enhancement and anti-aging properties and for people that are professionally exposed.

These data expose that computational predictions have a good degree of accuracy and must be taken into consideration when designing new compounds with biological activity.

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