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ADMET profiles of selected anabolic steroid derivatives

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Abstract: There is control over steroids use and marketing, but also new compounds that mimic their effects, steroid derivatives, are being synthesized. They are frequently produced as dietary supplements intended to improve physical activity, and usually no information is provided regarding their composition, dosages, and efficacy or safety. In this study, a computational approach was used to evaluate the absorption, distribution, metabolism, excretion and toxicity (ADMET) profiles of several steroid derivatives: methasterone, methyl-1-testosterone, 4-hydroxytestosterone, methyldienolone, methyltrienolone and 19-nor-5-androstenedione. The following computational prediction tools were applied: admetSAR2.0, ADMETLab2.0, Endocrine Disruptome, PredSkin3.0. All investigated compounds showed good human intestinal absorption, are not able to penetrate the blood-brain barrier and inhibit cytochrome P450 enzymes involved in the metabolism of xenobiotics. These compounds have potential for skin sensitisation, induce reproductive toxicity and endocrine disruption, and have a low potential for hepatotoxicity and respiratory toxicity. It is important that the results of the study are known by those exposed at workplaces where these compounds are produced and packed as well as by consumers. These predictions can also guide the experimental evaluation of the possible toxicity of the investigated compounds, the results of which can be further used for purposes of regulating the use of these steroid derivatives.

Keywords: dietary supplements; steroid derivatives; skin sensitization; hepatotoxicity; reproductive toxicity.

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INTRODUCTION

Some athletes, but also amateurs and even teenagers, interested in improving performance or body appearance, consume specific drugs that are usually represented by a form of steroids, as these drugs are intended to increase their muscle mass and strength. Synthetic anabolic androgenic steroids (AAS) are testosterone-derived compounds produced by pharmaceutical manufacturers and may be used by prescription for some related diseases. Even though the use of these compounds is controlled in many countries, they can be obtained through the Internet and there are also veterinary steroids often used by people to increase their physical performance.[1]

Due to the control of the use and marketing of steroids, new compounds that mimic their effects have been synthesized by similarity to androgenic steroids. These new compounds are known as steroid derivatives (SDs) or designer steroids. They are produced as dietary supplements by less reputable suppliers and are sold on the Internet or in fitness stores.[2] These supplements are designed as pharmaceutical compounds, but information on ingredients, dosages, companies, manufacturers is usually not provided.[3] Data from the literature show that dietary supplements are often contaminated with steroid derivatives or designer steroids.[4]

Published data have revealed numerous effects of AAS. They can help build muscle tissue, increase body mass and improve performance.[5] As toxicological effects of AAS are mentioned: carcinogenic, cardiovascular, cerebrovascular, dermal, endocrine, genito-urinary, genotoxic, hematological, hepatic, immunological, renal and reproductive effects.[6–8]

A concerning feature of the use of these compounds is that data on their efficacy and/or safety are usually not available. In this study, a computational approach is used to evaluate the toxicity of several SDs that are not approved for human use or are considered experimental drugs under certain circumstances: methasterone, methyl-1-testosterone, 4-hydroxytestosterone, methyldienolone, methyltrienolone and 19- nor-5-androstenedione.[9] These compounds were selected because they can be easily purchased on the Internet, and the online Drug Bank database (https://go.drugbank.com/, accessed in October 2023) does not contain information on their ADMET profiles. It was not possible to identify studies that strictly examine Internet sales of the investigated SDs. Information on the internet market for AAS is also scarce, but few recently published articles point out that AAS with controlled use are readily available for purchase, without a valid prescription, on the online market.[10,11] Websites only advertise the aesthetic and ergogenic benefits of use of these compounds and do not inform about the potential complications and adverse effects.[10] Moreover, social media platforms facilitate the supply of AAS and increase the accessibility of these compounds, which especially affect young people and less informed people.[12] In addition, literature data is limited in information regarding the toxicological

effects of the investigated SDs on humans. To our knowledge, this is the first computational study evaluating toxicokinetics of these compounds in humans.

METHOD

The SDs used in this study are presented in Table I. This table also contains, for each compound, the IUPAC (International Union of Pure and Applied Chemistry) name which was extracted from the PubChem database (www.pubchem.org, accessed January 2023),[13] the accession number in Drug Bank online (https://go.drugbank.com/, accessed January 2023) and known toxicological effects. As a control, this study considers oxymetholone, a synthetic AAS that is also a clinical drug used under controlled conditions since 1960.[14]

TABLE I. The compounds that are used in the present study: their common name, IUPAC name, accession number in Drug Bank online (when available), known toxicological effects

Common name	IUPAC name	Drug Bank accession number / status	Toxicological effects listed in Drug Bank
Methasterone	(2*R*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*,17*S*)-17--Hydroxy-2,10,13,17-tetramethyl--2,4,5,6,7,8,9,11,12,14,15,16-dodecahydro-1*H*-cyclopenta[*a*]phenanthren-3-one	Not found in Drug Bank	Not available
Methyl-1-testosterone	(5S,8*R*,9*S*,10*R*,13*S*,14*S*,17*S*)-17--Hydroxy-10,13,17-trimethyl--5,6,7,8,9,11,12,14,15,16-decahydro--4*H*-cyclopenta[*a*]phenanthren-3-one	DB01572 / prohibited doping compound	Not available
4-Hydroxytestosterone	(8*R*,9*S*,10*R*,13*S*,14*S*,17*S*)-4,17-dihydroxy-10,13-dimethyl--1,2,6,7,8,9,11,12,14,15,16,17-dodecahydrocyclopenta[*a*]phenanthren--3-one	DB01485 / experimental/ illicit	Hepatic metabolism, renal excretion
Methyldienolone	(8*S*,13*S*,14*S*,17*S*)-17-Hydroxy-13,17--dimethyl-1,2,6,7,8,11,12,14,15,16--decahydrocyclopenta[*a*]phenanthren-3-one	not found in Drug Bank	not available
Methyltrienolone	(8*S*,13*S*,14*S*,17*S*)-17-Hydroxy-13,17--dimethyl-1,2,6,7,8,14,15,16-octahydrocyclopenta[*a*]phenanthren-3--one	DB02998 / experimental	Not available
19-Nor-5-androstenedione	(8*R*,9*S*,10*R*,13*S*,14*S*)-13-methyl--1,2,4,7,8,9,10,11,12,14,15,16-dodecahydrocyclopenta[*a*]phenanthrene-3,17-dione	DB01443 / Experimental / Illicit	Not available
Oxymetholone	(2*Z*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*,17*S*)-17--hydroxy-2-(hydroxymethylidene)--10,13,17-trimethyl--1,4,5,6,7,8,9,11,12,14,15,16-dodecahydrocyclopenta[*a*]phenanthren-3-one	DB06412 Approved / Illicit	Carcinogenic, cardiotoxicity

In order to obtain the possible toxicity of these compounds on human organs, several computational tools have been used: admetSAR2.0,[15] ADMETLab2.0,[16] Endocrine Disruptome,[17] and Pred-Skin3.0.[18] These computational facilities were used because they are freely available and have been developed by recognized chemiformatics groups. In addition, they are based on models with a large amount of training data, are continuously updated, are robust, and the accuracy of predictions is at least 70 %. These computational facilities were developed to study drug candidates, but they have also been successfully used to predict the human and environmental toxicity of many types of compounds: chito-oligomers[19,20] and some of their water-soluble derivatives,[21] cosmetics,[22] phthalates,[23] oligomers of hydroxyalkanoates[24] and of lactic acid,[25] intensive sweeteners,[26] pesticides,[27-29] acyclic monoterpenes[30] and other steroids.[8] A brief description of each instrument used is presented in Table II.

TABLE II. Online tools used for predicting the absorption, distribution, excretion, metabolism and toxicity of the investigated designer steroids: SMILES – Simplified Molecular Input Line Entry System, CYPs – human cytochromes, NR – nuclear receptors

Online prediction tool	Predicted activity and the accuracy of prediction
ADMETSAR2.0: offers 22 qualitative classification models and 5 quantitative regression models that allow the user to compute the probability of an activity to be present (positive values) or absent (negative values); uses the SMILES formulas of investigated steroids as input data and outputs the probabilities of the predicted pharmacokinetics and toxicological effects.[15]	Gastrointestinal absorption (GI) (96.5 %); Blood brain barrier permeation (BBBP) (90.7 %); Plasma protein binding (PPB) (66.8 %); Substrate/inhibition of the P-glycoprotein (Pgps/Pgpi) (80.2 % / 86.1 %); Substrates (77.9 %) or inhibitors (85.5 %) of the human cytochromes (cyps); Carcinogenicity (89.6 %); Eye corrosion and/or irritation (94.9 %/96.3 %); Hepatotoxicity (83.3 %) Human Ether-a-go-go-Related Gene (herg) inhibition (80.4 %); Mutagenicity by Ames test (84.3 %).[15]
ADMETlab2.0 uses as entry data the SMILES formulas of the investigated steroids; outputs ADMET profiles of the investigated compound. The accuracy of the classification models is of minimum 80 % and most of the regression models have R^2>0.72.[16]	Intestinal absorption, Plasma protein binding, Volume of distribution, Clearance are predicted, P-glycoprotein binding, Blood brain barrier permeation, Binding to the human cyps, Cardiotoxicity, Hepatotoxicity, Mutagenicity, Carcinogenicity Nephrotoxicity, Skin sensitization.[16]
Endocrine Disruptome evaluates the interactions between the investigated steroids and 12 human NR; uses SMILES formulas as input data; delivers computed sensitivity coefficients associated to colour codes: green cells for compounds that do not affect the NR, yellow cells with low probability of affecting NR, orange cells for compounds with mean probability of affecting NR and red cells for compounds revealing a high probability of affecting NR. The accuracy of prediction is at least 78 %.[17]	Interactions with the following nuclear receptors: Androgen receptor (AR) (both agonistic and antagonistic interactions) Oestrogen receptors (ER) α and β Glucocorticoid receptor (GR) (both agonistic and antagonistic interactions) Liver X receptors (LXR) α and β Peroxisome proliferator activated receptors (PPAR) α, β/δ and γ Retinoid X receptor (RR) α Thyroid receptors (TR) α and β.[17]

TABLE II. Continued

Online prediction tool	Predicted activity and the accuracy of prediction
Pred-Skin 3.0 predicts the skin sensitization potential of chemicals; uses the SMILES formulas as input data; outputs the probability of compounds to illustrate or not skin sensitization potential; products a probability map allowing the illustration of the contribution of predicted fragment toward skin sensitization.[18]	Predictions based on five sensitization assays: *In vitro* (keratinosens and human Cell Line Activation Test, H-CLAT, accuracy 80 to 86 %) *In vivo* (murine local lymph node assay, LLNA, accuracy 70 to 84 %) *In chemico* (Direct Peptide Reactivity Assay, DPRA, accuracy 73 to 76 %) Human repeated insult patch (HRIPT) test (accuracy 70 %) Human maximization test (HMT, accuracy 84 %).[18]

RESULTS AND DISCUSSION

The physicochemical and structural properties of query compounds are typically used as descriptors by computational tools that predict chemical ADMET profiles. These properties and the 2D formulas of the investigated steroids were extracted from PubChem database[13] and are shown in Table III. This table also contains the 2D formula and physicochemical properties of oxymetholone, the AAS used as a control in this study.

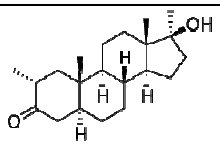
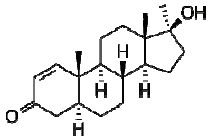
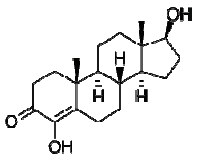
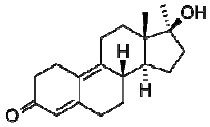
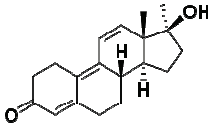
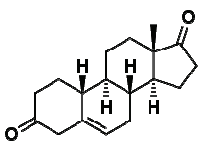
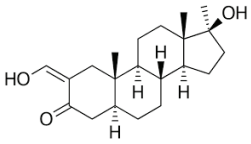
The data presented in Table III show that all investigated SDs have quite similar physicochemical properties to those of oxymetholone: low molecular weights, low numbers of hydrogen bond donors and acceptors and reveal low hydrophobicity. These properties fulfil Lipinski's rule of five[31] and are common to orally administered drugs. This is confirmed by the ADMETLab2.0 tool results illustrating that these compounds satisfy Lipinski's rule (Table S-I of the Supplementary material to this paper). Methasterone and methyl-1-testosterone are considered potentially toxic because they do not meet Pfizer's rule.[32]

It should be noted that the major limiting point of the results of prediction tools based on classification models is the reliability of the predictions because computational models have limited domains of applicability. An applicability domain (AD) is defined as the area of physicochemical and/or structural space in which the model is expected to be exploitable, such as the predictions to be assumed to be reliable.[33] The admetSAR2.0 and ADMETLab2.0 prediction tools allow estimation of the prediction accuracy for each compound individually and specify whether the compound characteristics fall within the AD of the model (illustration in Fig. S-1 of the Supplementary material for 19-nor-5-androstenedione). In the cases of the investigated steroids, the predictions were within the range of applicability.

The absorption, distribution and excretion profiles of the investigated SDs obtained with the admetSAR2.0 and ADMETLab2.0 prediction tools are revealed in Table IV. The data presented in this table bring up quite similar values

obtained for the probabilities related to absorbtion, distribution and excretion profiles of the investigated SDs compared to the those obtained for the control, oxymetholone.

TABLE III. Steroids used in the present study, 2D formulas and their main physicochemical properties extracted from PubChem database;[13] *MW* – molecular weight, log *P* – partition coefficient, *HBD* – hydrogen bonds donors, *HBA* – hydrogen bonds acceptors, *tPSA* – topological polar surface area

Common name	2D formula	*MW* g mol^{-1}	log *P*	*HBD*	*HBA*	*tPSA* Å^2
Methasterone		318.5	4.5	1	2	37.3
Methyl-1-testosterone		302.5	4.1	1	2	37.3
4-Hydroxytestosterone		304.4	3.2	2	3	57.5
Methyldienolone		286.4	2.0	1	2	37.3
Methyltrienolone		284.4	2.1	1	2	37.3
19-Nor-5-androstene-dione		272.4	2.1	0	2	34.1
Oxymetholone		332.5	4.4	1	3	37.5

Predictions obtained using both admetSAR2.0 and ADMETLab2.0 reveal, for all SDs investigated, good human intestinal absorption. This result is in good

correlation with published data disclosing good intestinal absorption of oral steroids[27] in general and of oxymetholone in particular.[14]

Predictions obtained using admetSAR2.0 and ADMETLab2.0 also regarding the ability of SDs to be P-glycoprotein inhibitors are inconsistent, Table IV. ADMETLab2.0 predictions exhibit high probabilities for SDs to be inhibitors of this protein, while admetSAR2.0 predicts that SDs are not inhibitors of P-glycoprotein. This inconsistency may be due to the different models used by the two prediction tools to evaluate this effect. Testosterone is known to be an endogenous substrate of P-glycoprotein[34] and it is expected that its derivatives may also interact with this protein. Further experimental investigations are needed to evaluate the ability of the investigated compounds to inhibit P-glycoprotein.

TABLE IV. Absorption, distribution and excretion profiles of the investigated steroids obtained using admetSAR2.0 and ADMETLab2.0 prediction tools; the data represent the probabilities that the analysed compounds are involved in the following processes: *HIA* – human intestinal absorption, *BBBP* – blood brain barrier penetration, *P-gpi* – inhibitor of the P-glycoprotein, *P-gps* – substrate of the P-glycoprotein, *PPB* – plasma protein binding, *CL* – clearance

Steroid	admetSAR2.0				ADMETLab2.0					
	HIA	*P-gpi*	*P-gps*	*BBBP*	*HIA*	*P-gpi*	*P-gps*	*BBBP*	*PPB* %	*CL* / mL min^{-1} kg^{-1}
Methasterone	0.985	–0.662	–0.823	–0.271	0.982	0.600	0.000	–0.924	95.89	21.338
Methyl-1-testosterone	0.989	–0.732	–0.795	–0.350	0.995	0.974	0.000	–0.419	95.31	18.841
4-Hydroxytestosterone	0.986	–0.581	–0.925	–0.310	0.988	0.971	0.000	–0.484	90.74	18.459
Methyldienolone	0.993	–0.760	–0.819	–0.735	0.978	0.945	0.005	–0.050	87.92	7.716
Methyltrienolone	0.989	–0.845	–0.801	–0.735	0.927	0.997	0.022	–0.127	90.05	5.957
19-Nor-5-androstenedione	0.990	–0.718	–0.841	–0.262	0.992	0.939	0.001	–0.348	88.71	14.532
Oxymetholone	0.771	–0.754	–0.842	0.700	0.986	0.295	0.000	–0.152	66.54	19.616

The investigated SDs are not considered as being able to penetrate the blood brain barrier (BBB) through passive diffusion. This prediction seems to be in contradiction with expected ability of the AAS, due to their low molecular weight and lipophilic character, to penetrate the BBB through passive diffusion. However, even if AAS are known to strongly influence the central nervous system (CNS), the modality how they enter the CNS through the BBB is still poorly understood.[35]

All investigated SDs are able to bind to plasma proteins, but methasterone and methyl-1-testosterone emphasize high levels of plasma protein binding (more than 90 %). This limits their distribution from the blood to the tissues to be meta-

bolized and prolongs their half-life. The binding of several other steroids to plasma proteins has also been studied, and it has been observed that steroids, including oxymetholone, are transported in the blood by their binding to human serum albumin, sex hormone-binding globulin, and corticosteroid-binding globulin.[36]

Regarding metabolism, both prediction tools reveal that none of the SDs investigated in this study, nor the control oxymetholone, are considered cytochrome (CYP) inhibitors involved in xenobiotic metabolism (Tables S-II and S-III of the Supplementary material). Data obtained through *in vitro* experiments show that oxymetholone is able to bind weakly to CYP enzymes, but these interactions have no clinical significance, oxymetholone is not considered an inhibitor of CYPs, nor is it metabolized by these enzymes.[14] It means that investigated SDs do not interfere with drugs or endogenous compounds that are metabolized by these enzymes and do not cause unanticipated adverse reactions or therapeutic failures. Methasterone and methyl-1-testosterone reveal high probabilities of being substrates for CYP2C19, and there are reasonable probabilities for the other SDs to be substrates for CYP3A4. The predictions of the interactions of the investigated SDs with human CYPs are in good correlation with the known data revealing that testosterone is considered as one of the CYP3A4 substrates.[37] An experimental study highlighted that 17 steroids demonstrated strong interactions with CYP3A4 and moderate interactions with CYP2C9, CYP1A2 and CYP2D6.[38] Other steroids showed the ability to interact with CYP2C9 in a computational study.[8]

The prediction of some of the toxicological effects of the investigated SDs are revealed in Fig. 1 and Table S-IV of the Supplementary material.

Fig. 1 highlights that none of the investigated SDs can produce nephrotoxicity, cardiotoxicity through potassium channel inhibition (h-ERG), and the probabilities of producing hepatotoxic effects are usually low. Regarding the cardiotoxicity of AAS through potassium channel inhibition, there is a good correlation of the obtained predictions with the published information revealing the protective effect of steroids on the potassium channel.[39] Predictions regarding nephrotoxicity are not well correlated with literature data revealing that some AAS have been observed to induce or worsen acute and chronic kidney disease and glomerular toxicity.[40] Regarding hepatotoxicity, published data reveal that AAS may lead to hepatomegaly, liver adenomas, cholestatic hepatitis and hepatocellular carcinoma.[8] The high probability revealed by the ADMETLab2.0 tool that oxymetholone induces hepatotoxicity is in agreement with the known information that high doses of oxymetholone have resulted in hepatotoxicity.[14]

The data obtained show that it is possible that the investigated SDs have an impact on the respiratory system and may induce respiratory toxicity (respiratory sensitization, respiratory allergy, rhinitis, asthma).[41] This prediction is in good

correlation with published data revealing that ASA produced acute dyspnea and pulmonary haemorrhage.[42]

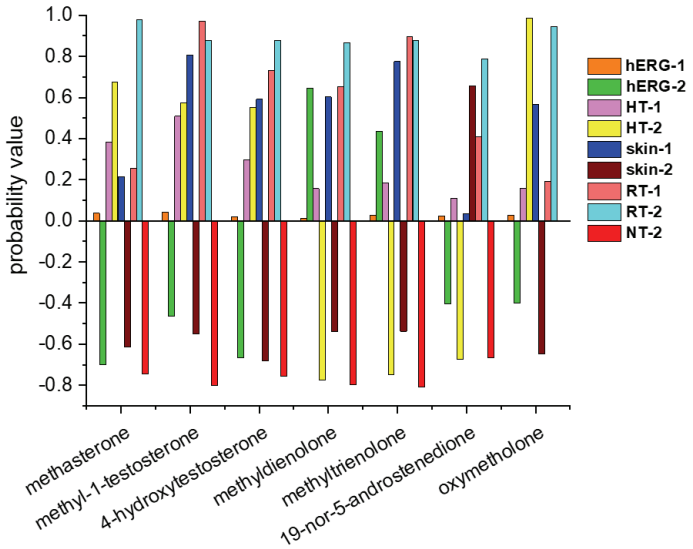


Fig. 1. Predictions regarding the cardiotoxicity (h-ERG), hepatotoxicity (HT), skin sensitization potential (skin), respiratory toxicity (RT) and nephrotoxicity (NT) obtained using ADMETLab2.0 (1) and admetSAR2.0 (2) tools. ADMETLab2.0 does not output information regarding nephrotoxicity.

There is an inconsistency in the predictions regarding the skin sensitization potential of these molecules: ADMETALab2.0 usually predict skin sensitization potential, but admetSAR2.0 predict non skin sensitization potential, with the exception of 19-nor-5-androstenedione that exposes a reasonable probability to produce skin sensitization. Due to this inconsistency, the ability of the investigated SD to produce skin sensitization is also investigated by using PredSkin3.0 prediction tool (see further).

The outcomes of the admetSAR2.0 tool indicate reproductive toxicity of all investigated SDs and high values for the probabilities of these compounds to affect the nuclear receptors (Fig. 2).

All investigated SDs reveal high probabilities to produce reproductive toxicity and to affect the nuclear receptors, excepting the peroxisome proliferators-activated protein (PPAR) gamma. Predictions obtained using ADMETLab2.0 tool also reveal probabilities with reasonable values that the SDs under consideration affect the binding domain of several nuclear receptors (Table S-V of the Supplementary material), excepting PPAR gamma. This result is in good correlation with published data reflecting that numerous synthetic steroids, are able to interact with the nuclear receptors.[42] A molecular docking study revealed that the

synthetic anabolic steroids methandrostenolone, oxandrolone, oxymetholone and stanozolol were able to bind to the human androgen receptor, oestrogen receptor alpha and thyroid receptor.[8]

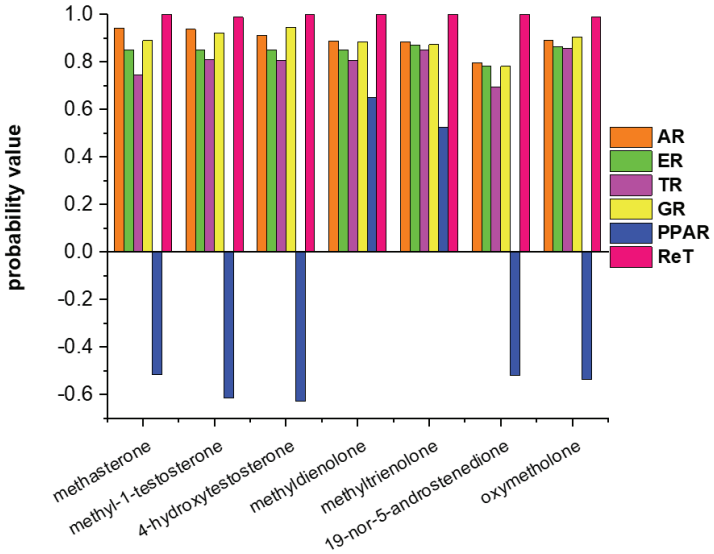


Fig. 2. Predicted values for the probabilities of the investigated steroids to produce reproductive toxicity (ReT) and to affect the nuclear receptors: AR – androgen receptor, ER – oestrogen receptor alpha, TR – thyroid receptor, GR – glucocorticoid receptor, PPAR– peroxisome proliferator-activated receptor gamma.

The Endocrine Disruptome computational tool was also used to obtain predictions regarding the interactions of the investigated SDs with the nuclear receptor, the results being revealed in Fig. 3.

All investigated SDs exhibit the potential for endocrine disruption. The most affected are androgen, oestrogen and thyroid receptors. Peroxisome proliferator-activated α, β and γ receptors are not affected or the possible effect is low. These predictions are in good correlation with those obtained using both ADMETLab2.0 and admetSAR2.0 tools. This result is also in line with literature data revealing the reproductive toxicity and endocrine-disrupting potential of numerous steroids, including oxymetholone.[6,8,42] It should be noted that AAS are expected to bind mainly to the androgen receptor, but their non-specific binding to the other nuclear receptors may be due to the fact that the nuclear receptors share a common spatial structure with a well-conserved ligand-binding domain.[43]

Predictions of the skin sensitization potential of the investigated SDs obtained using the PredSkin3.0 tool are revealed in Table V. Visualization of probability maps illustrating the contribution of different fragments to skin sen-

sitization, which was constructed based on human repeat insult patch and human maximization (HRIPT/HMT) models is revealed in Fig. 4.

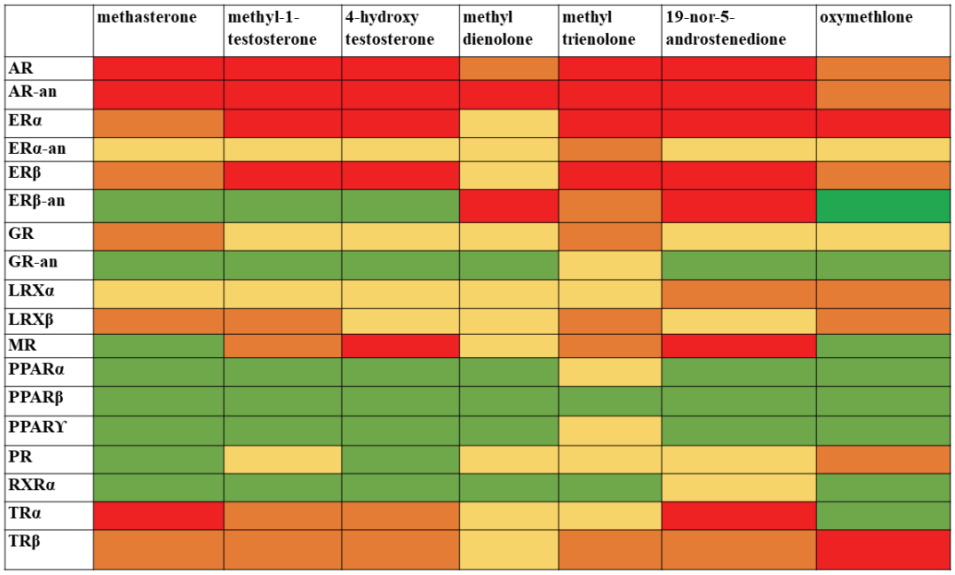


Fig. 3. Endocrine Disruptome predictions of steroid derivatives binding to nuclear receptors: androgen receptor (AR) both agonistic and antagonistic (an) interactions, oestrogen receptors (ER) α and β, glucocorticoid receptor (GR) both agonistic and antagonistic interactions (an), progesterone receptor (PR), liver X receptors (LXR) α and β, peroxisome proliferator activated receptors (PPAR) α, β and γ, retinoid X receptor (RXR) α, and thyroid receptors (TR) α and β. Red cells reveal high effect, orange grey cells reveal mean effect, yellow cells reveal low effect and green cells reveal no effect of the steroids derivatives on the nuclear receptors.

TABLE V. Predictions of the skin sensitization potential of the investigated steroid derivatives based on the following models: DPRA – direct peptide reactive assay, HRIPT/HMT human repeat insult patch and human maximization, KeratinoSens – activation of a cytoprotective pathway in keratinocytes, h-CLAT – human cell line activation test, LLNA – local lymph node assay. The sign ”+” indicates skin sensitization potential and the sign ”–” indicates the absence of skin sensitization potential

Steroid	DPRA	HRIPT/HMT	KerationoSens	h-CLAT	LLNA	Bayesian outcome
Methasterone	+	+	–	+	–	+
Methyl-1-testosterone	+	+	+	+	+	+
4-Hydroxytestosterone	+	+	–	+	–	+
Methyldienolone	+	+	–	+	–	+
Methyltrienolone	+	+	+	+	–	+
19-Nor-5-androstenedione	+	+	–	+	+	+
Oxymetholone	+	+	+	+	–	+

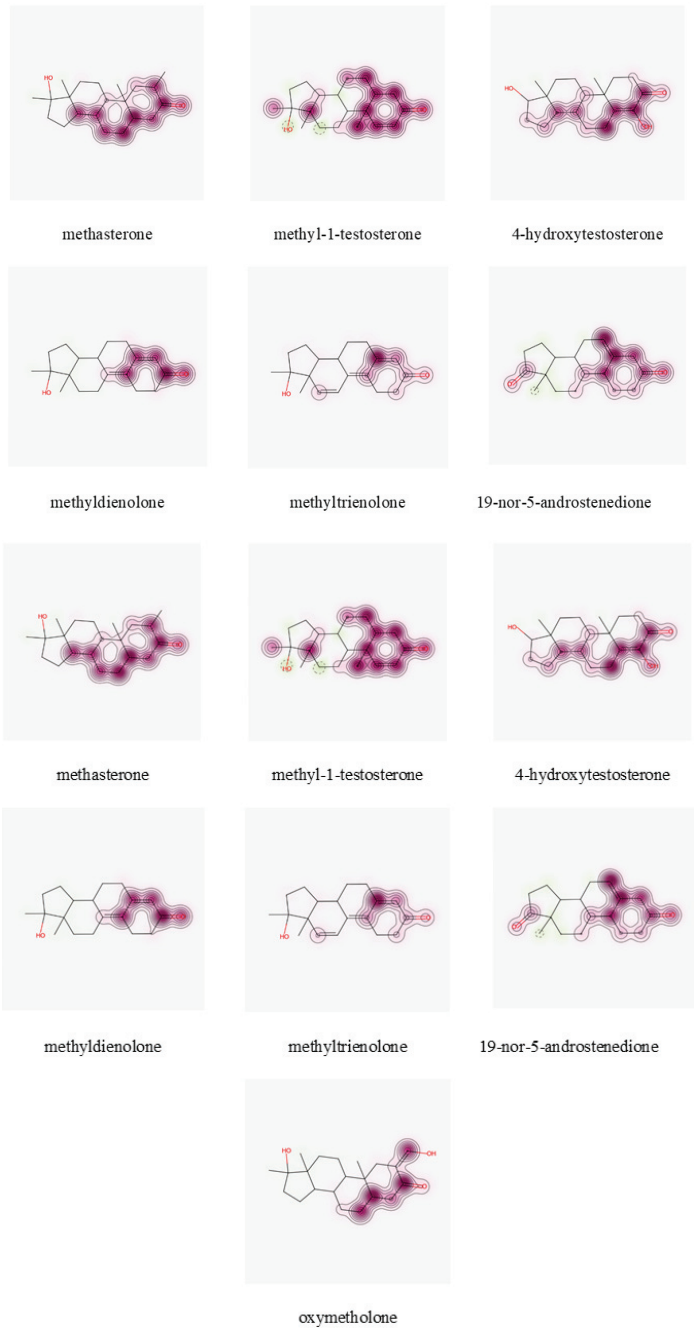


Fig. 4. Visualization of the probability maps illustrating the contribution of various fragment (magenta regions) toward skin sensitization, build based on the human repeated insult patch and human maximization (HRIPT/HMT) models for the investigated steroids derivatives.

The data presented in Table V and Fig. 4 highlight that all investigated SDs have skin sensitization potential. This prediction is in good correlation with the literature data that emphasize several skin effects of AAS use: acne, epidermoid cysts, folliculitis, furunculosis, oily skin and hair, seborrheic dermatitis, *etc*.[44]

Predictions obtained in this study for the SDs do not always correlate with literature data that were obtained for numerous AAS. A possible reason of the mismatch is the fact that the obtained predictions do not take into account the amount of the chemical compound that was ingested (this being a common week point of the *in silico* prediction tools), whereas many of the published papers, highlighting the toxicological effects, mention the high doses of AAS. However, both predictions and published data emphasize the need to implement clinical studies on the potential of the SDs, investigated in this study, to produce toxicological effects before they are approved for human use.

CONCLUSION

The investigated SDs reveal good human intestinal absorption, the inability to penetrate the blood–brain barrier by passive diffusion, and the ability to bind to cytochromes involved in xenobiotic metabolism as substrates or inhibitors. Methasterone and methyl-1-testosterone show high levels of plasma protein binding and moderate clearance. The toxicity evaluation reveals that the investigated SDs can be harmful to human health, causing a diversity of side effects: respiratory toxicity, endocrine disruption, reproductive toxicity, and skin sensitization.

These findings are important for both practitioners and consumers of dietary supplements, especially for the supplements that are intended to enhance physical activity. Potential toxicity should be considered, as many dietary supplements contain designer steroids, which are sometimes not labelled as ingredients and are easily bought on the Internet without any controls. Considering all these adverse effects, consumers should be warned about using either steroid derivatives or dietary supplements that may contain them.

SUPPLEMENTARY MATERIAL

Additional data and information are available electronically at the pages of journal website: https://www.shd-pub.org.rs/index.php/JSCS/article/view/12525, or from the corresponding author on request.

ИЗВОД

ADMET ПРОФИЛИ ОДАБРАНИХ ДЕРИВАТА АНАБОЛИЧКИХ СТЕРОИДА

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Постоји контрола употребе и трговања стероидима, али такође су синтетисани нови стероидни деривати, једињења која опонашају њихов ефекат. Они се често производе као дијетески суплементи који треба да поправе физичку активност, а обично се не дају информације у погледу састојака, дозе, и ефикасности или безбедности. У овој студији се користи рачунарски приступ да би се проценили ADMET профили неколико стероидних деривата: метастерона, метил-1-тестостерона, 4-хидрокситестостерона, метилдиенолона, метилтриенолона, 19-нор-5-андростендиона. Примењена су следећа оруђа за рачунарско предвиђање: admetSAR2.0, ADMETLab2.0, Endocrine Disruptome, PredSkin3.0. Сва истраживана једињења су показала добру апсорпцију у људској утроби, не могу да прођу баријеру између крви и мозга, и инхибирају ензиме цитохрома P450 који су укључени у метаболизам ксенобиотика. Ова једињења имају потенцијал за сензибилизацију коже, да индукују токсичност у репродукцији и ендокрине поремећаје, те имају низак потенцијал за тровање крви и дисајних органа. Резултати ове студије треба да буду познати онима који су изложени на радним местима где се ова једињења праве и пакују, те потрошачима. Ова предвиђања могу такође усмеравати експериментално процењивање могуће токсичноости испитиваних једињења, чији резултати се могу даље користити у сврху регулисања ових стероидних деривата.

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