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In Silico Screening of DrugBank Compounds as Potential Inhibitors for Human Steroid 5α-Reductase 2 for Androgen-Related Diseases

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Abstract: Steroid 5α-reductase 2 (SRD5A2) is an enzyme that catalyzes the reduction of testosterone to dihydrotestosterone. Due to its influence on steroidogenesis, it has been proposed as an interesting pharmacological target for androgen-related diseases such as benign prostatic hyperplasia, androgenic alopecia, and prostate cancer. Nevertheless, current commercially available drugs lack specificity and cause side effects. This work aims to identify potential new commercially available drugs as SRD5A2 inhibitors. Molecular docking using Glide was performed with SRD5A2 crystal structure and 9213 compounds downloaded from the DrugBank database. Lipinksi, Ghose, and Veber's rules were applied, and energetic and spatial analyses were made. Eleven compounds fulfilled the criteria of being oral drugs and had better binding coupling energy than testosterone. From these, only four were positioned within the SRD5A2 binding site and interacted with its key residues E57 and R114: mestranol, lorcaserin, phenindamine, and stiripentol. However, it was found that only the last one could be a repositioned drug for the SRD5A2 target and, consequently, for androgen-related human diseases. Stiripentol could be a suitable candidate for SRD5A2 inhibition; nevertheless, it did not interact directly with the R114 side chain, and consequently, in vivo trials are required. The other drugs positioned in the SRD5A2 binding site should be studied deeply to evaluate their repositioning potential.

Keywords: steroid 5α-reductase 2 inhibitors; molecular docking; drug repositioning; SRD5A2; DrugBank.
List of Abbreviations: SRD5A2 = Human steroid 5α-reductase 2; T = Testosterone; DHT = Dihydrotestosterone; DTD = Dutasteride; FTD = Finasteride; PDB = Protein Data Bank; RSMD = Root-mean-square deviation of atomic positions; ATC = Anatomical Therapeutic Chemical; DDD = Defined Daily Dose; BCE = Binding Coupling Energy; FDA = Food and Drug Administration.

1. Introduction

Human steroid 5α-reductase isoform 2 (SRD5A2) is a highly expressed protein in the male reproductive system. It catalyzes the reduction of the Δ4 bond of testosterone (T) to synthesize dihydrotestosterone (DHT), the main circulating androgen in humans [1,2]. Among all SRD5A2 isoforms, types 1 and 2 play important roles in DHT biosynthesis. Meanwhile, isoform 3 is implicated in the N-glycosylation of proteins via the formation of dolichol

phosphate [3,4]. Altered expression of steroid 5α-reductases, particularly overexpression of SRD5A2, has been related to the progression of several diseases such as benign prostatic hyperplasia [5-7], alopecia [8-10] and prostate cancer [11,12]. For the latter disease, it has been suggested that treatment with SRD5A2 inhibitors could benefit patients [13,14]. Due to the key role of SRD5A2 in developing serious medical illnesses, it has emerged as an important pharmacological target. Additionally, the scarce efficacy and adverse reactions of the SRD5A2 inhibitors dutasteride (DTD) and finasteride (FTD) have been reported in multiple investigations [15-17]. These two drugs appear to show similar effects on sexual dysfunction.

Adverse effects of FTD may be related to unspecific binding to phenylethanolamine-N-methyltransferase and its action mechanism through SRD5A2 [18]. Because of this, there is a necessity for new selective drugs targeting SRD5A2. Conventionally, developing new drugs represents a costly and time-consuming process [19-21]. As a result, drug repositioning studies have successfully optimized the preclinical process of developing novel drugs [22,23]. The advantage of this scientific strategy is that these drugs have already been approved in clinical trials. Therefore, their side effects are usually known, resulting in reduced time and expense for their adoption in other therapeutic uses [24,25]. This study describes the identification of commercially available drugs as potential inhibitors of SRD5A2, thus suggesting that they could be of interest for the treatment of multiple SRD5A2-related diseases such as benign prostatic hyperplasia, alopecia, and prostate cancer.

2. Materials and Methods

2.1. Protein and drug database preparation.

The crystal structure of the target in complex with NADPH and finasteride was obtained from RCSB Protein Databank [26] (PBD ID: 7BW1 [27]) and prepared as was previously reported [28] in Schrödinger suite [29]. The list of drugs was obtained from Drug Bank [30] containing 9213 molecular structures that were prepared in the Ligprep module [28,29]. The DTD and FDT were taken as endogen ligands references and are commercially available as SRD5A2 inhibitors [31].

2.2. Molecular docking.

The molecular coupling was realized in Schrödinger glide [32] using a protocol previously reported [28], and shortly illustrated in figure 1. Redocking with FTD yielded an RSMD value of 0.998 Å. The 2D and 3D analyses were realized in Maestro [33], BIOVIA Discovery Studio [34], and Pymol [35].

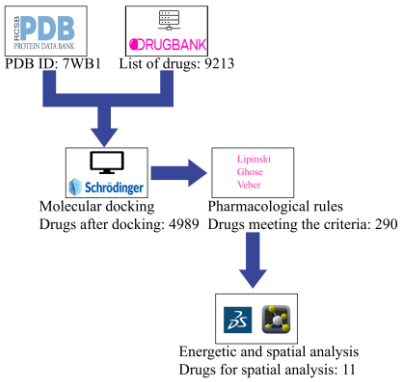

Figure 1. Diagram applied for drug repositioning for SRD5A2 inhibitors.

3. Results and Discussion

3.1. Prediction of drug-similarity and ATC codes.

After molecular docking was performed using Glide, and tautomeric, protonated forms and conformers were filtered, 2310 molecular structures remained. Lipinski, Ghose, and Veber's rules were applied, and structures with one or more violations of any of these rules were discarded for further analysis. Lipinski's rule of five was used to evaluate if a molecule could be orally active, taking into consideration four parameters: [36] (1) molecular weight must be less than 500, (2) octanol/water partition coefficient (log P) must be less than 5, (3) No more than 5 hydrogen bond donors should have a drug, and (4) A limit of 10 hydrogen bond acceptors is suitable. Furthermore, Ghose's rules evaluate drug-likeness considering other descriptors such as: (1) molecular weight range between 180-480, (2) calculated log P between -0.4-5.6, (3) molar refractivity value must be between 40-130, and (4) the total number of atoms must be between 20-70 [37]. After evaluating drugs according to Lipinski, Ghose, and Veber's rules, a total of 290 structures remained. Anatomical Therapeutic Chemical (ATC) Classification System codes were examined in the ATC/DDD index 2022 of the World Health Organization's Collaborative Center for Drug Statistics Methodology [38-40] and shown in Table 1 and the best drug for each group as an example.

Table 1. Percentage of analyzed drugs and meaning of Anatomical Therapeutic Chemical (ATC) codes of analyzed drugs.

Letter	Bioactivity	Analyzed drugs (%)	Example
A	Alimentary tract and metabolism	12 (4)	Ondansetron
B	Blood and blood-forming organs	5 (2)	Menadione
C	Cardiovascular system	14 (5)	Ephedrine
D	Dermatological	14 (5)	Dimetindene
G	Genito-urinary system and sex hormones	18 (6)	Norgestrel
J	Anti-infective for systemic use	4 (1)	Efavirenz
L	Antineoplastic and immune-modulating agent	3 (1)	Abiraterone
M	Musculoskeletal system	4 (1)	Flurbiprofen
N	Nervous system	106 (37)	Donepezil
P	Antiparasitic products, insecticides, and repellents	8 (3)	Chloroquine
R	Respiratory system	33 (11)	Azelastine
S	Sensory organs	4 (1)	Aceclidine
NA	Not Assigned	65 (22)	Mestranol

Thirty-seven percent of structures correlate to classification N, meaning they have expected effects on the central nervous system. The second t-frequent classification was R (eleven percent), corresponding to drugs influencing the respiratory system. Twenty-two percent of the structures had no ATC category, meaning they could be discontinued drugs, tinction agents, or substances used as cosmetics. Only one percent could be classified as antineoplastic and immunomodulating agents. Drug repositioning in the same ATC classification is desired but considering different diseases.

3.2. Molecular docking.

The binding coupling energy (BCE, kcal/mol) of the 288 structures were compared to those of the reference ligands: DTD (-7.338 kcal/mol), FTD (-6.799 kcal/mol), and T (-6.756 kcal/mol). These results are consistent with their reported inhibitor activity as their BCE is

more important than that offered by T, meaning that the ligand-protein complex with inhibitors is thermodynamically more favored than that produced by T.

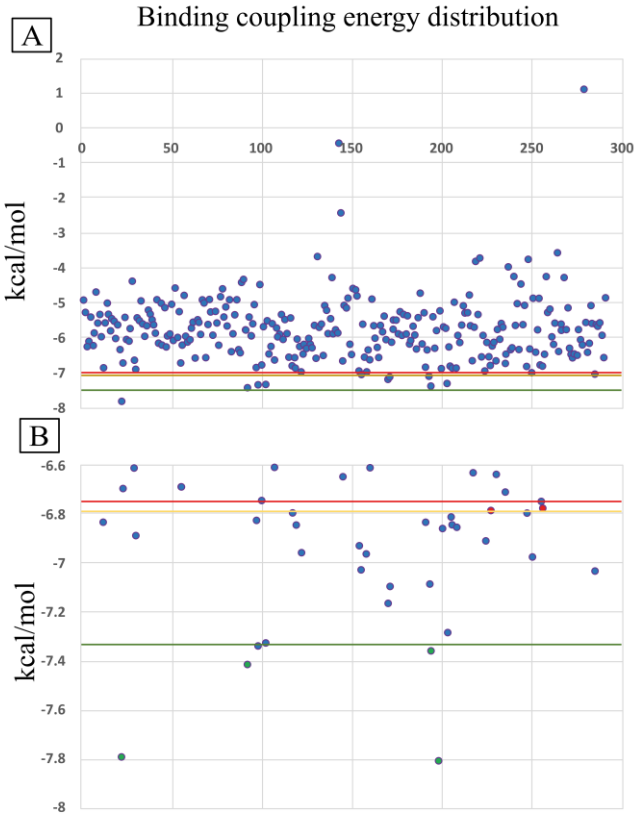

Figure 2. **(A)** BCE distribution. **(B)** Expanded region from -8.0 to -6.6 kcal/mol. Reference ligands: testosterone (red); finasteride (yellow), and dutasteride (green).

Figure 2 shows the BCE dispersion values. According to BCE, the following classification was established:

Structures having higher BCE than T but lower than FTD.

Structures showing higher BCE than FTD but lower than DTD.

Structures with higher BCE than DTD.

For the first group, only progesterone (-6.789 kcal/mol) is selected as an endogenous ligand, but it can also be used as a drug in hormone replacement therapy. The second group includes 22 drugs, described in Table 2. For many therapeutic purposes, oral drugs are desirable since oral administration is non-invasive, painless, easy to apply, and accepted by all patients. From this group, only 18 drugs met these criteria; they are commercially available and do not act as endogenous ligands.

Table 2. Description of drugs in the second group.

Name	BCE (kcal/mol)	Name	BCE (kcal/mol)
Efavirenz	-7.326	Pregnenolone □	-6.913
Pentazocine	-7.283	Brexanolone	-6.890
Mesoridazine	-7.165	Palonosetron ▲	-6.861
Mestranol	-7.096	Phenindamine	-6.857
Norethynodrel	-7.088	Flibanserin	-6.850
Vortioxetine	-7.034	Perphenazine	-6.849
Lorpiprazole	-7.031	Amitriptylinoxide	-6.838
Stiripentol	-6.977	Nomifensive ■	-6.836
Lynestrenol	-6.965	Duloxetine	-6.830
Fluoxetine	-6.960	Pergolide	-6.817
Lorcaserin	-6.930	Rotigotine Δ	-6.801

Endogenous substrates □; intravenous drugs ▲; drugs removed from the market ■ and transdermal drugs Δ.

Finally, group three comprises four structures: ondansetron, norgestrel, donepezil, and azelastine. No further analysis was made for the latter because its pharmaceutical presentation is as a spray. The last step before 2D and 3D analysis was to eliminate those drugs that attack targets related to the central nervous system. Consequently, the remaining structures were ondansetron, norgestrel, efavirenz, pentazocine, mestranol, norethynodrel, stiripentol, lynestrenol, lorcaserin, phenindamine, and flibanserin.

The next step was to analyze the protein-ligand complex interactions since BCE is closely related to these interactions. Figure 3 shows the noncovalent protein-ligand interactions between SRD5A2 and DTD or FTD. In both cases, residues E57 and R114 play an important role in stabilizing protein-ligand complexes by establishing hydrogen bonds and hydrophobic interactions.

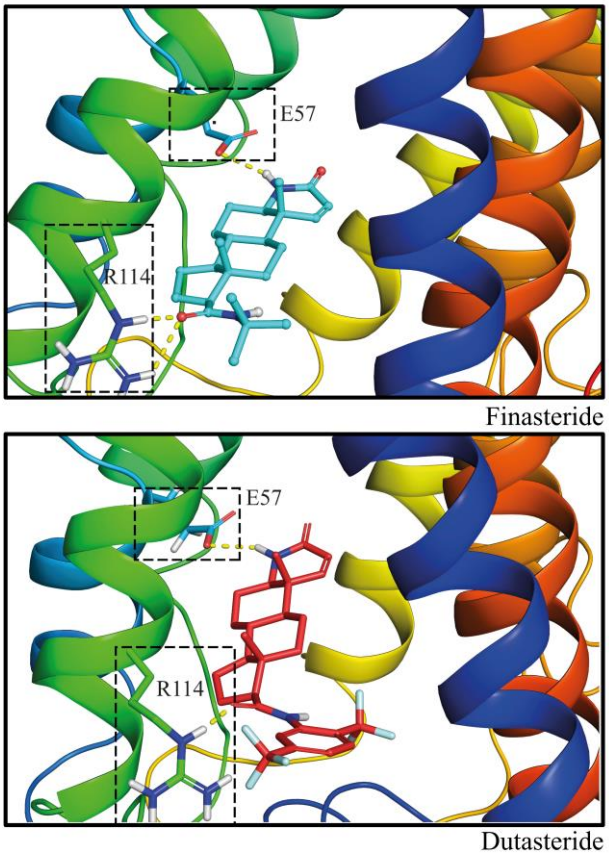

Figure 3. Molecular interactions of FTD and DTD at the SRD5A2 binding site.

The lactam N-H acts in both structures as a hydrogen bond donor showing a hydrogen bond length of 2.2 Å for DTD and 2.3 Å for FTD. According to our results, the carbonyl group of N-tert-butoxycarbonyl moiety of FTD serves twice as a hydrogen bond acceptor with R114; meanwhile, in DTD, this same residue establishes just one hydrogen bond with the amide carbonyl group. It is useful to determine if an SRD5A2 inhibitor is embedded in a hydrophobic pocket in proximity with helices 2, 4, and 5 and interacting with residues W53, F118, L111, and F223 in the case of DTD, and W53, F118, F223, and L111 for FTD. On the other hand, side chains are next to helix 1.

The docking scores are shown in Table 3 for the selected drugs and ranged from -7.807 to -6.850 kcal/mol. All structures fit well at the binding site and share a rigid and flat carbon skeleton containing aromatic rings, a structural feature that seems to be important to facilitate that binding.

Table 3. List of interactions between SRD5A2 and evaluated drugs.

Name	BCE kcal/mol	Interactions
Ondansetron	-7.807	H-bond: E57, S31; Charged (positive): E57; Pi-Pi Stacked: F118; Alkyl, Pi-Alkyl: F118, L20, F219, A24.
Norgestrel	-7.359	H-bond: E57, S31, Y91; Alkyl, Pi-Alkyl: F118, F223, F216, F219, L224.
Efavirenz	-7.326	H-bond: E57, S220, Y91, C119; Alkyl, Pi-Alkyl: F194, W53, L224, F223, L:118, P219; Halogen: E197; Pi-anion: E197.
Pentazocine	-7.283	H-bond: E57, Y91; Pi-cation: F223, F118; Alkyl, Pi-Alkyl: A24, L20, F219, W53, Y33, F118, F223.
Mestranol	-7.096	H-bond: E57, Y91; Pi-Pi stacked: Y33, F223; Alkyl, Pi-Alkyl: R114, L111, W53, C119, F118, L224.
Norethynodrel	-7.088	H-bond: E57, Y:91; Alkyl, Pi-Alkyl: F223, P118, L224, F219, C119, W53.
Stiripentol	-6.977	H-bond: E57, Y91, Q56; Amide-Pi Stacked: R114
Lynestrenol	-6.965	H-bond: E57, Y91; Alkyl, Pi-Alkyl: Y33, L111, F223, L224, F216, F118, C119
Lorcaserin	-6.930	Salt bridge: E57; Alkyl, Pi-Alkyl: L20, F118, F223; Amide-Pi Stacked: R114, F118
Phenindamine	-6.857	Salt bridge: E57; Pi-Alkyl: L20; Amide-Pi Stacked: R114, F118; Pi-Pi T-shaped: F219; Pi-Sigma: F118
Flibanserin	-6.850	H-bond: S31, Y91, E197; Pi-Pi Stacked: F223, W53; Alkyl, Pi-Alkyl: A24, F223, L20, F118, L224
Finasteride	-6.850	H-bond: E57, R114; Alkyl, Pi-Alkyl: L111, F223, F118, W53, R114
Dutasteride	-6.850	H-bond: E57, R114; Alkyl, Pi-Alkyl: L23, F223, A24, L111, F118, W53
Testosterone	-6.756	H-bond: E197, Y91; Alkyl, Pi-Alkyl: F223, F118, F219, Y33

Flibanserin produced an H-bond with E57, like the one established by FDT and DTD. Mestranol, stiripentol, lorcaserin, and phenindamine presented interactions with R114, but no H-bond with this residue was found. In the case of mestranol, as shown in Figure 4a, the hydroxyl group at C-17 serves as both donor and acceptor of hydrogen bonds with Y91 and E57, favoring a ligand-protein complex. The disposition of the aromatic ring A of mestranol in the binding site allows residues P223 and Y33 to be oriented towards a Pi-Pi stacked interaction. As shown in Figures 4b and 4c, mestranol is superimposed with DTD; the steroid nucleus is in the hydrophobic region of the binding site.

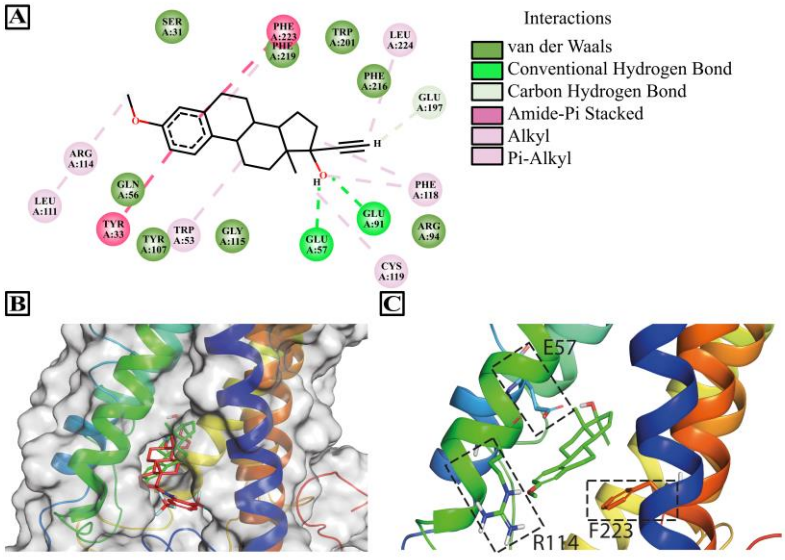

Figure 4. Mestranol drug in the binding site of SRD5A2. **(A)** Interactions with important residues in the binding site; **(B)** Mestranol superimposed with DTD; **(C)** Hydrophobic residues surrounding mestranol drug.

In contrast, the trimethyl moiety of stiripentol is surrounded by hydrophobic residues such as F118, F219, F216, F223, and L224, as shown in Figure 5. The hydroxyl group establishes a hydrogen bond with Y91.

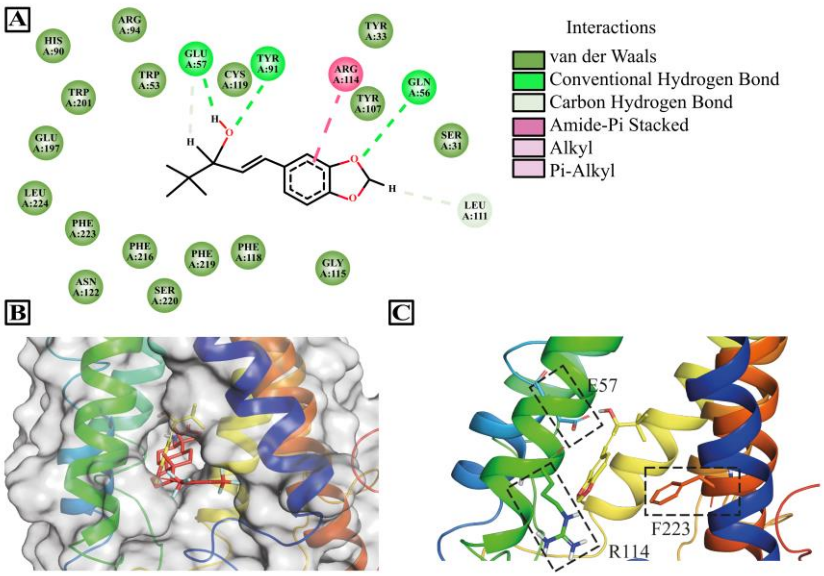

Figure 5. Stiripentol in the binding site of SRD5A2**. (A)** interactions with important residues in the binding site; **(B)** superposition with DTD; **(C)** residues surrounding stiripentol drug.

In Figure 6a, the amide-pi stacked interaction with R114 is not with the guanidine group but with a pi system of the carbonyl group in the peptide bond. This must be considered since direct interaction with the guanidine group seems important to inhibit SRD5A2. Lorcaserin and stiripentol interact with R114 via amide-pi stacked interaction and not with the side chain (Figure 6b). In the binding pocket, the ring system is superimposed with the steroid nucleus of DTD.

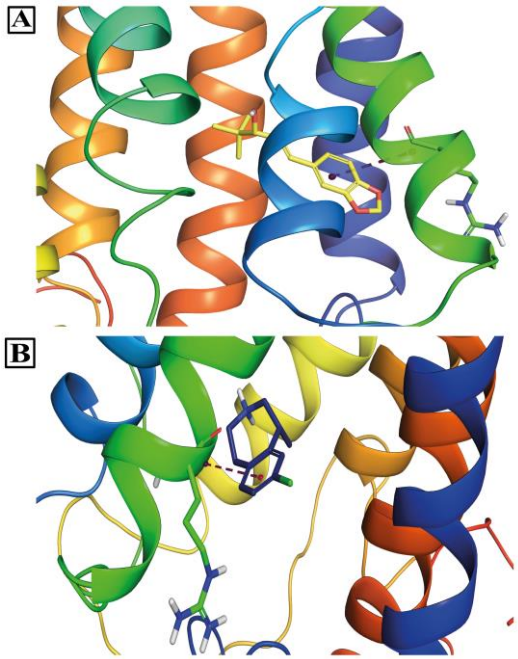

Figure 6. π-electron interactions between residue R114 of SRD5A2, and **(A)** stiripentol**,** and **(B)** lorcaserin**.**

Meanwhile, E57 establishes a salt bridge with the N-H of the seven-membered ring of lorcaserin, as shown in figure 7. In comparison to the previous two drugs, fewer hydrophobic interactions are observed, indicating that these are important to stabilize the ligand-protein complex. The drug with these interactions had the greater BCE.

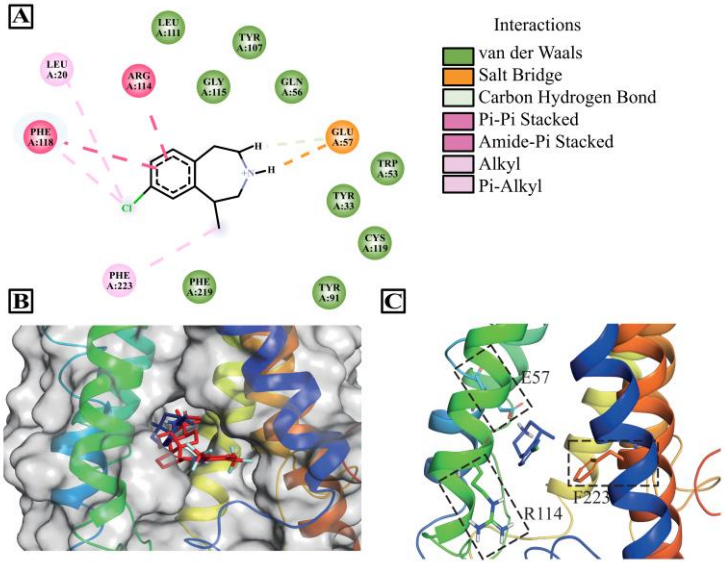

Figure 7. Lorcaserin in the binding site of SRD5A2. **(A)** Interactions with key residues in binding site; **(B)** Overlap of lorcaserin with DTD; **(C)** Residues surrounding lorcaserin drug.

Lastly, phenindamine also interacts with the carbonyl group in the peptide bond of R114. Its former positive charge in the six-membered ring allows interaction with E57 (Figure 8). These interactions are different from those established by DTD and FTD, and no inhibitory activity is expected for this drug. Only mestranol interacts with the R114 side chain and with E57 via H-bond. Nevertheless, stiripentol and lorcaserin should not be discarded since they occupy the binding site and are located near R114 and E57. Therefore, an inhibitory activity could be expected from these drugs, but in vitro assays are necessary.

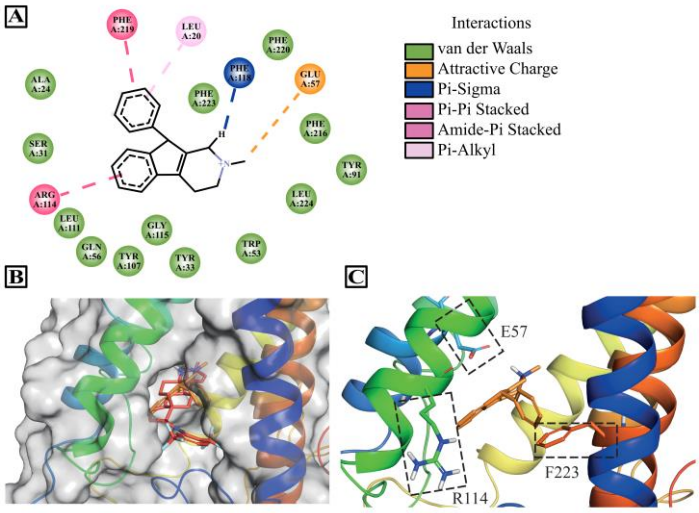

Figure 8. Phenindamine in the binding site of SRD5A2. **(A)** interactions with important residues in the binding site; **(B)** superposition with DTD;**(C)** residues surrounding stiripentol drug.

As shown in Table 4, mestranol is a drug used as an oral contraceptive and for dysmenorrhea, and its use in patients with hormone-dependent cancers has not been recommended yet. On the other hand, in February 2020, the FDA reported a higher incidence of cancer in patients treated with lorcaserin compared with those with no treatment. However, more trials are necessary [41]. Only stiripentol lacks restrictions for use in patients with cancer.

Table 4. Side and adverse effects of mestranol, stiripentol, and lorcaserin.

Name	Current use	Side and adverse effects	References
Mestranol	Contraceptive	Proliferative atypia, hypertension, intrahepatic cholestasis, cerebrovascular occlusion.	[42-45]
Stiripentol	Treating seizures	Bone structure abnormalities, sedation, anorexia, weight loss, unsteadiness and tiredness, somnolence.	[46-49]
Lorcaserin	Treatment of obesity	Hypoglycemia and headache, nausea, vomiting, dizziness, and an increase in heart rate.	[50-53]

Although drugs like ondansetron, norgestrel, efavirenz, and pentazocine did not meet the criteria for interacting with R114, a biological action should not be discarded due to their high BCE towards the enzyme. These drugs could inhibit SRD5A2 by displacing T from the binding site because, according to this in silico analysis, the produced protein-ligand complex is thermodynamically more favorable.

4. Conclusions

This study evaluated 9213 molecular structures from the Drugbank database as inhibitors of SRD5A2. Molecular coupling studies and interactional analysis of the physiological conditions of the ligands and the enzyme allow us to propose 11 candidates for repositioning. Considering the dosage and adverse effects of the candidates, only stiripentol turned out to be a potential drug that could be used to treat benign prostatic hyperplasia, alopecia, and prostate cancer. Stiripentol does not directly interact with the side chain of the enzyme R114 but establishes a hydrogen bond with E57, which is essential for the inhibition of SRD5A2. In addition, it shows the mildest known side effects compared to the other tested drugs. However, to corroborate this *in silico* analysis, *in vivo* tests must be performed.

Funding

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Conflicts of Interest

The authors declare no conflict of interest.

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