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Computational Assessment of a Series of Twenty Cannabinoid-Based Compounds Targeting the Androgen Receptor and 5α-Reductase Enzyme

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ABSTRACT

Several studies have reported that certain cannabinoid derivatives may affect prostate cancer progression. However, their specific actions on the androgen receptor and the 5α-reductase enzyme remain ambiguous, likely due to the structural variability among cannabinoid compounds. This computational investigation aimed to explore the theoretical interactions of 20 distinct cannabinoid derivatives (identified as compounds 1 through 20) with the androgen receptor and the 5α-reductase enzyme, using the protein models 3L3X and 7BW1, respectively. In addition, reference ligands such as testosterone, dihydrotestosterone, flutamide, finasteride, and dutasteride were incorporated as standard molecular tools in the analysis. The findings showed that derivatives 6, 13, 16, and 20 demonstrated superior binding affinity to the androgen receptor in comparison to testosterone, dihydrotestosterone, and flutamide. In addition, the data also indicated that compounds 1, 3, 14, and 18 showed a stronger theoretical interaction with 5α-reductase than dutasteride and finasteride. These results suggest that compounds 6, 13, 16, and 20 may act as potential androgen receptor inhibitors, while derivatives 1, 3, 14, and 18 may act as inhibitors of the 5α-reductase enzyme. These interactions highlight the therapeutic promise of these cannabinoid analogs in the context of prostate cancer management.

Keywords: 5α-reductase, Prostate cancer, Androgen receptor, Cannabinoid

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Introduction

Prostate cancer mortality has shown an upward trend in recent years across the globe [1, 2]. Numerous contributing factors are implicated in the onset and progression of this disease, including genetic predisposition [3], obesity [4], the aging process [5], and alcohol consumption [6]. Furthermore, scientific findings have pointed to a potential link between androgens, their receptors, and the pathophysiology of prostate cancer [7, 8]. At present, a range of pharmacological agents is employed in managing this condition, such as flutamide [9], nilutamide [10], bicalutamide [11], enzalutamide [12], apalutamide [13], finasteride [14], and dutasteride [15]. Despite their clinical efficacy, many of these treatments are associated with undesirable side effects, including hot flashes [16], elevated blood pressure [17], liver toxicity [18], and erectile dysfunction [19].

Given these limitations, there is a growing interest in the exploration of alternative therapeutic agents. For example, research has demonstrated the synthesis of dimethylcurcumin through the reaction of curcumin with diazomethane, which exhibited biological interaction with the androgen receptor in DU145 and PC-3 prostate cancer cell lines [20, 21]. In another study, the formation of a fluorobenzamide analog via the condensation of

aminobenzamide with cyanohydrin was reported to show anticancer potential in LNCaP cells [22, 23]. Additional evidence supports the therapeutic potential of JNJ-63576253 for patients exhibiting resistance to both enzalutamide and apalutamide [24, 25]. Another compound, a phenoxybenzoylphenyl acetic acid analog, has been investigated for its inhibitory activity on the 5α-reductase enzyme using both rat and human prostate homogenates [26]. More recently, theoretical models have been employed to study the interaction of certain dibenzo-based molecules with both androgen receptor and 5α-reductase enzyme [27].

In parallel, research has started to highlight the potential of cannabinoid derivatives in reducing prostate cancer cell proliferation [28, 29]. For instance, it was reported that WIN-55,212-2, a cannabinoid analog, suppressed the growth of LNCaP cells, which are androgen-sensitive prostate cancer cells [30]. Similarly, chromenopyrazoldione, another cannabinoid-related compound, was found to inhibit the proliferation of LNCaP cells [31]. Further investigations revealed that (R)-methanandamide, a cannabinoid derivative, could influence androgen receptor expression in androgen-dependent cell lines, thereby affecting cellular proliferation [32]. Another study demonstrated that both (R)-methanandamide and WH-015 act via the CB2 cannabinoid receptor to inhibit the growth of PC-3 human prostate cells [33].

While these findings underscore the therapeutic potential of cannabinoid derivatives in prostate cancer, their precise mechanisms—particularly concerning their interactions with the androgen receptor and 5α-reductase enzyme—remain poorly understood, likely due to variations in molecular structure. To address this uncertainty, the present theoretical study was designed to examine how a set of twenty cannabinoid derivatives might interact with either the androgen receptor or the 5α-reductase enzyme. This analysis employed docking simulations, incorporating reference compounds such as testosterone, dihydrotestosterone, flutamide, dutasteride, and finasteride as comparative molecular models.

Materials and Methods

A set of 20 cannabinoid derivatives **(Figure 1)** was selected for use in this theoretical investigation to explore their potential binding interactions with the androgen receptor and the 5α-reductase enzyme through the following approach:

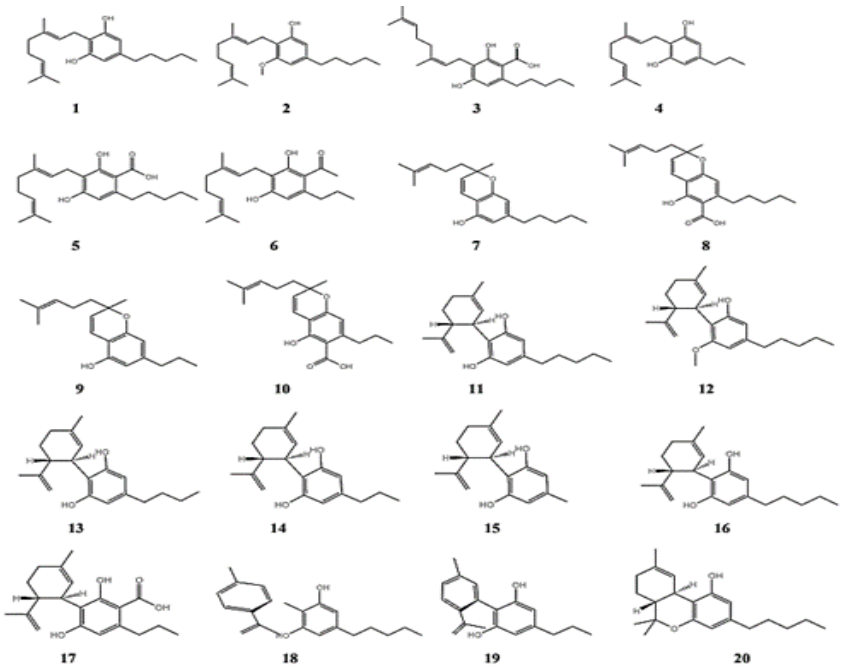

Figure 1. Chemical structure of cannabinoid derivatives (1-27) (source: ChemPub, https://pubchem.ncbi.nlm.nih.gov/);1 = cannabigerol, 2 = cannabigerol monomethyl ether, 3 = cannabinerolic acid, 4 = cannabigerovarin, 5 = cannabigerolic acid, 6 = cannabigerovarinic acid, 7 = cannabichromene, 8 = cannabichromenic acid, 9 = cannabivarichromene, 10 = cannabichromevarinic acid, 11 = cannabidiol CBD-C5, 12 = cannabidiol monomethyl ether, 13 = cannabidiol, 14 = cannabidivarin, 15 =

cannabidiorcol, 16 = cannabidiolic acid, 17 = cannabidivarinic acid, 18 = cannabinodiol, 19 = cannabinodivarin, 20 = dronabinol

Ligand–protein interaction modeling

The theoretical affinity of opioid derivatives for either the androgen receptor or the 5α-reductase enzyme was investigated using protein structures 3L3X (PDB DOI: 10.2210/pdb3L3X/pdb) [34] and 7BW1 (PDB DOI: 10.2210/pdb7BW1/pdb) [35] as molecular targets. To explore the energetic profile of ligand binding and the nature of their molecular interactions, docking simulations were conducted using DockingServer software [36].

Pharmacokinetic predictions

To assess the pharmacokinetic properties inherent in the structural framework of selected cannabinoid derivatives (specifically compounds 1, 3, 6, 13, 16, 18, and 20), SwissADME software was employed [37].

Toxicological evaluation

A computational toxicity screening of cannabinoid derivatives 1, 3, 6, 13, 14, 16, 18, and 20 was carried out through GUSAR software, to estimate their theoretical toxic effects [38].

Results and Discussion

Protein-ligand interaction assessment

Various computational tools, including Gold [39], Glide [40], Autodock [41], and DockingServer [42], have been developed to predict how ligands interact with the androgen receptor. It is known that the hormone-binding pocket of this receptor constitutes a hydrophobic domain that facilitates interaction with androgens through hydrophobic forces involving their steroidal framework [43]. Moreover, specific amino acid residues such as Asn705 and Thr877 are implicated in hydrogen bonding with the 17-hydroxy group of testosterone, while Gln711 and Arg752 interact with its 3-keto group [44]. Emerging theoretical data also support the notion that cannabinoids like tetrahydrocannabinol and cannabidiol could impact androgen receptor activity, potentially contributing to the inhibition of prostate cancer progression [45]. Considering these insights, and in light of findings that cannabinoids may influence prostate cancer biology [28, 30–33], this study conducted docking simulations with twenty cannabinoid derivatives using the androgen receptor model 3L3X. The results, summarized in **Table 1**, suggest that these compounds may engage distinct amino acid residues on the 3L3X protein surface compared to conventional ligands such as testosterone, dihydrotestosterone, and flutamide.

Table 1. Aminoacid residues involved in the coupling cannabinoids derivatives (compounds 1-20) with 3L3X protein surface

Compound	Aminoacid residues
Flutamide	Leu_{701}; Leu_{704}; Leu_{707}; Gln_{711}; Met_{742}; Met_{745}; Val_{746}; Met_{749}; Arg_{752}; Phe_{764}; Met_{787}; Leu_{873}; Thr_{877}
Testosterone	Leu_{701}; Leu_{704}; Asn_{705}; Gln_{711}; Trp_{741}; Met_{742}; Met_{745}; Val_{746}; Met_{749}; Arg_{752}; Phe_{764}; Met_{780}; Met_{787}; Leu_{873}; Thr_{877}; Met_{895}
DHT	Leu_{701}; Leu_{704}; Asn_{705}; Gln_{711}; Met_{742}; Met_{745}; Met_{749}; Arg_{752}; Phe_{764}; Met_{780}; Leu_{873}; Phe_{876}; Thr_{877}; Leu_{880}; Met_{895}
1	Leu_{701}; Leu_{704}; Asn_{705}; Leu_{707}; Gln_{711}; Trp_{741}; Met_{742}; Met_{745}; Val_{746}; Met_{749}; Arg_{752}; Phe_{764}; Met_{780}; Met_{787}; Leu_{873}; Thr_{877}; Met_{895}
2	Leu_{701}; Leu_{704}; Asn_{705}; Leu_{707}; Gln_{711}; Trp_{741}; Met_{742}; Met_{745}; Val_{746}; Met_{749}; Arg_{752}; Phe_{764}; Met_{780}; Met_{787}; Leu_{873}; Thr_{877}
3	Leu_{701}; Leu_{704}; Asn_{705}; Leu_{707}; Gln_{711}; Trp_{741}; Met_{742}; Met_{745}; Val_{746}; Met_{749}; Arg_{752}; Phe_{764}; Met_{780}; Met_{787}; Leu_{873}; Phe_{876}; Thr_{877}; Met_{895}
4	Leu_{701}; Leu_{707}; Gln_{711}; Trp_{741}; Met_{742}; Met_{745}; Val_{746}; Phe_{764}; Met_{780}; Met_{787}; Leu_{873}; Phe_{876}; Thr_{877}; Met_{895}
5	Leu_{701}; Leu_{704}; Asn_{705}; Leu_{707}; Gln_{711}; Trp_{741}; Met_{742}; Met_{745}; Val_{746}; Met_{749}; Arg_{752}; Phe_{764}; Met_{780}; Leu_{873}; Thr_{877}; Met_{895}
6	Leu_{701}; Leu_{704}; Asn_{705}; Leu_{707}; Gln_{711}; Trp_{741}; Met_{742}; Met_{745}; Val_{746}; Phe_{764}; Met_{780}; Met_{787}; Leu_{873}; Phe_{876}; Thr_{877}; Met_{895}
7	Leu_{704}; Leu_{707}; Gln_{711}; Met_{742}; Met_{745}; Val_{746}; Met_{749}; Arg_{752}; Phe_{764}; Met_{780}; Leu_{873}; Phe_{876}; Thr_{877}; Met_{895}

8	Leu_{701}; Leu_{704}; Asn_{705}; Leu_{707}; Gln_{711}; Trp_{741}; Met_{742}; Met_{745}; Val_{746}; Met_{749}; Phe_{764}; Met_{780}; Met_{787}; Thr_{877}; Met_{895}
9	Leu_{704}; Asn_{705}; Trp_{741}; Met_{742}; Met_{745}; Val_{746}; Met_{749}; Phe_{764}; Met_{787}; Leu_{873}; Thr_{877}; Met_{895}
10	Leu_{701}; Leu_{704}; Asn_{705}; Leu_{707}; Gln_{711}; Trp_{741}; Met_{742}; Met_{745}; Val_{746}; Met_{749}; Arg_{752}; Phe_{764}; Met_{780}; Met_{787}; Leu_{873}; Thr_{877}; Met_{895}
11	Leu_{701}; Leu_{704}; Leu_{707}; Gln_{711}; Trp_{741}; Met_{742}; Met_{745}; Val_{746}; Met_{749}; Phe_{764}; Met_{780}; Met_{787}; Leu_{873}; Phe_{876}; Thr_{877}
12	Leu_{701}; Leu_{704}; Asn_{705}; Leu_{707}; Gln_{711}; Trp_{741}; Met_{742}; Met_{745}; Val_{746}; Met_{749}; Arg_{752}; Phe_{764}; Met_{780}; Thr_{877}; Met_{895}; Ile_{899}
13	Leu_{701}; Leu_{704}; Asn_{705}; Leu_{707}; Gln_{711}; Met_{745}; Val_{746}; Met_{749}; Phe_{764}; Met_{780}; Met_{787}; Leu_{873}; Phe_{876}; Thr_{877}; Met_{895}
14	Leu_{701}; Leu_{704}; Leu_{707}; Gln_{711}; Met_{742}; Met_{745}; Val_{746}; Met_{749}; Phe_{764}; Met_{780}; Met_{787}; Leu_{873}; Phe_{876}; Thr_{877}
15	Leu_{701}; Leu_{704}; Asn_{705}; Leu_{707}; Trp_{741}; Met_{742}; Met_{745}; Val_{746}; Phe_{764}; Leu_{873}; Phe_{876}; Thr_{877}; Met_{895}
16	Leu_{701}; Leu_{704}; Asn_{705}; Leu_{707}; Gln_{711}; Trp_{741}; Met_{742}; Met_{745}; Val_{746}; Met_{749}; Phe_{764}; Met_{780}; Met_{787}; Leu_{873}; Phe_{876}; Thr_{877}
17	Leu_{701}; Leu_{704}; Asn_{705}; Leu_{707}; Gln_{711}; Trp_{741}; Met_{742}; Met_{745}; Val_{746}; Met_{749}; Phe_{764}; Met_{780}; Met_{787}; Leu_{873}; Phe_{876}; Thr_{877}; Met_{895}
18	Leu_{704}; Asn_{705}; Leu_{707}; Gln_{711}; Met_{749}; Phe_{764}; Met_{780}; Leu_{873}; Met_{895}
19	Leu_{704}; Asn_{705}; Leu_{707}; Gln_{711}; Trp_{741}; Met_{742}; Met_{745}; Val_{746}; Met_{749}; Arg_{752}; Phe_{764}; Met_{780}; Met_{787}; Leu_{873}; Phe_{876}; Thr_{877}; Met_{895}
20	Leu_{704}; Leu_{707}; Gln_{711}; Trp_{741}; Met_{745}; Val_{746}; Met_{749}; Arg_{752}; Phe_{764}; Met_{780}; Met_{787}; Leu_{873}; Phe_{876}; Thr_{877}; Met_{895}

Nonetheless, it is noteworthy that thermodynamic aspects have been reported to influence the binding of testosterone and its structural analogs with the androgen receptor, as indicated in prior research [46]. In light of this, the present investigation involved a computational analysis of multiple energy-related descriptors—summarized in **Table 2**—for a series of cannabinoid derivatives alongside testosterone, dihydrotestosterone, and flutamide, utilizing the DockingServer platform for molecular modeling.

Table 2. Thermodynamic parameters involved in the interaction of cannabinoid derivates with the 3L3X-protein surface

Comp	I	II	II	IV	V	VI
Flu	-7.3	3.9	-8.5	0.0	-8.5	456.0
Test	-7.7	26.3	-10.4	-0.1	-10.6	499.3
DHT	-10.7	13.3	-10.9	-0.1	-11.0	490.5
1	-7.2	4.6	-10.0	0.0	-10.0	552.3
2	-5.8	50.5	-8.6	0.0	-8.5	553.4
3	-5.5	91.3	-7.8	-0.1	-7.9	599.1
4	-6.7	12.3	-8.6	0.0	-8.6	523.5
5	-7.3	4.4	-9.9	0.0	-10.0	550.1
6	-7.9	1.5	-9.8	0.0	-9.8	531.6
7	-8.4	657.1	-10.2	0.0	-10.3	560.0
8	-5.9	40.6	-6.8	-0.2	-7.0	550.9
9	-7.1	5.5	-8.4	0.0	-8.4	502.0
10	-8.8	312.9	-9.1	-0.4	-9.5	515.6
11	-6.5	16.2	-9.2	0.0	-9.2	566.0
12	-7.0	6.4	-9.2	0.0	-9.2	567.3

13	-7.9	1.4	-9.9	0.0	-10.0	561.6
14	-7.2	4.9	-9.1	0.0	-9.1	538.7
15	-7.2	4.7	-8.4	0.0	-8.4	506.2
16	-7.7	1.9	-9.7	0.0	-9.8	567.6
17	-7.2	5.3	-8.4	0.0	-8.4	573.7
18	-5.1	180.1	-6.6	0.0	-6.7	434.6
19	-6.7	10.7	-8.7	0.0	-8.7	538.7
20	-7.6	2.6	-8.7	0.0	-8.7	554.5

Flu = flutamide, test = Testosterone, DHT = dihydrotestosterone, I = free energy of binding (kcal/mol), II = inhibition constant, Ki (mM), III = Vander waals forces + H-bond + desolv energy (kcal/mol), IV = electrostatic energy (kcal/mol), V = total intermolecular energy (kcal/mol), and VI = interaction surface.

The analysis revealed notable variations in bonding energy among cannabinoid derivatives when compared with testosterone, dihydrotestosterone, and flutamide. Moreover, cannabinoid derivatives 6, 13, 16, and 20 exhibited significantly lower inhibition constants (Ki), implying a stronger binding affinity to the androgen receptor than that observed for testosterone, dihydrotestosterone, or flutamide. These findings point to the potential role of these specific cannabinoid analogs as inhibitors of the androgen receptor, which may contribute to suppressing prostate cancer progression. Despite this, it is essential to acknowledge that the pathogenesis of prostate cancer involves additional biological pathways. For instance, various reports have highlighted that pharmacological agents such as dutasteride and finasteride—recognized inhibitors of the 5α-reductase enzyme—are capable of reducing prostate cancer risk [14, 47]. Building upon these insights, this study also aimed to examine the theoretical interactions of a panel of cannabinoid derivatives (compounds 1 through 20) with the 5α-reductase enzyme, employing the 7BW1 protein structure along with dutasteride and finasteride as reference models for comparison **(Table 3)**.

Table 3. Aminoacid residues involved in the coupling cannabinoids derivatives (compounds 1-20) with 7BW1 protein surface

Compound	Aminoacid residues
Flut	Ile_{202}; Ala_{205}; Leu_{206}; Trp_{209}; Leu_{211}; Leu_{214}; Ala_{217}; Phe_{218}
Test	Tyr_{129}; Ala_{134}; Glu_{135}; Tyr_{136}; Thr_{208}; Trp_{209}; $Ser_{210;}$ Leu_{211}
1	Ile_{202}; Ala_{205}; Leu_{206}; Trp_{209}; Leu_{211}; Leu_{214}
2	Ile_{202}; Ala_{205}; Leu_{206}; Trp_{209}; Leu_{214}
3	Leu_{206}; Trp_{209}; Leu_{214}
4	Tyr_{129}; Ile_{202}; Ala_{205}; Trp_{209}; Leu_{211}; Leu_{214}
5	Tyr_{129}; Ala_{205}; Leu_{206}; Trp_{209}; $Leu_{211;}$ Leu_{214}
6	Ile_{202}; Leu_{206}; Trp_{209}; Leu_{214}; $Phe_{218;}$ Leu_{221}
7	Tyr_{129}; Ile_{202}; Ala_{205}; Prt_{209}; Leu_{211}; Leu_{214}
8	Ile_{202}; Ala_{205}; Leu_{206}; Trp_{209}; Leu_{214}
9	Ile_{144}; Arg_{145}; Leu_{148}; Ile_{202}; Ala_{205}; $Leu_{206;}$ $Trp_{209;}$ Leu_{214}
10	Tyr_{129}; Ala_{205}; Trp_{209}; Ser_{210}; $Leu_{211;}$ Leu_{214}
11	Ile_{202}; Ala_{205}; Leu_{206}; Trp_{209}; Leu_{214}
12	Ile_{202}; Ala_{205};Trp_{209}; Leu_{211}; Leu_{214}; Ala_{217}
13	Ile_{202}; Ala_{205}; Leu_{206}; Trp_{209}; $Leu_{211;}$ Leu_{214}
14	Tyr_{129}; Ala_{205}; Leu_{206}; Trp_{209};$Leu_{211;}$ Leu_{214}
15	Ile_{202}; Ala_{205}; Leu_{206}; Trp_{209}; Leu_{214}

16	Ala_{205}; Leu_{206}; Trp_{209}; Leu_{211}; Leu_{214}
17	Ile_{202}; Ala_{205}; Leu_{206}; Leu_{214}; Ala_{217}; $Phe_{218;}$ Leu_{221}
18	Ala_{205}; Leu_{206}; Trp_{209}; Leu_{211}; Leu_{214}
19	Ile_{202}; Ala_{205}; Leu_{206}; Leu_{214}; Ala_{217}
20	Ile_{202}; Ala_{205}; Leu_{206}; Trp_{209}; Leu_{214}; $Ala_{217;}$ Ala_{218}

Flu = flutamide, and Test = testosterone.

The findings revealed notable variations in the specific amino acid residues involved in the binding of cannabinoid derivatives compared to those engaged by dutasteride and finasteride. Moreover, the inhibition constants (Ki) for cannabinoid compounds 1, 3, 14, and 18 were found to be lower than those of dutasteride and finasteride **(Table 4)**, indicating a potentially stronger interaction. These observations point to the possibility that these particular cannabinoid derivatives may function as 5α-reductase enzyme inhibitors, thereby contributing to the reduction of prostate cancer progression.

Table 4. Thermodynamic parameters involved in the interaction of cannabinoid derivates with the 7BW1-protein surface.

Comp	I	II	II	IV	V	VI
Dut	-8.8	326.1	-9.3	0.0	-9.3	683.7
Finast	-6.7	12.3	-6.8	0.0	-6.8	619.7
1	-3.8	1.4	-6.7	0.0	-6.7	669.1
2	-4.9	229.5	-7.6	0.0	-7.7	651.2
3	-3.7	1.6	-5.8	-0.1	-5.9	628.5
4	-4.6	421.6	-7.2	0.0	-7.3	655.4
5	-5.03	205.92	-7.55	-0.16	-7.70	694.37
6	-4.3	699.1	-6.2	0.0	-6.3	570.1
7	-4.6	382.7	-5.8	0.0	-5.8	538.7
8	-5.8	51.2	-7.3	0.1	-7.4	715.9
9	-5.4	109.5	-7.0	0.0	-7.0	640.9
10	-5.3	114.5	-6.7	0.0	-6.7	617.1
11	-4.8	263.5	-7.1	0.0	-7.1	642.4
12	-4.8	269.8	-7.1	+0.0	-7.1	619.2
13	-4.8	277.1	-6.7	0.0	-6.8	576.2
14	-4.0	1.0	-5.8	0.0	-5.8	582.7
15	-4.7	312.9	-5.9	0.0	-5.9	529.1
16	-4.5	484.7	-6.6	0.0	-6.6	644.3
17	-5.7	61.7	-6.8	-0.1	-6.9	566.0
18	-3.7	1.9	-5.3	0.0	-5.3	496.4
19	-4.2	823.8	-5.9	0.0	-5.9	572.3
20	-5.2	132.2	-6.6	0.0	-6.66	626.9

Com = compound, Dut = dutasteride, Finast = finasteride, I = free energy of binding (kcal/mol), II = inhibition constant, Ki (mM), III = Van der Waals forces + H-bond + desolv Energy (kcal/mol), IV = electrostatic energy (kcal/mol), V = total intermolecular energy (kcal/mol), and VI = interaction surface.

Pharmacokinetic analysis

Pharmacokinetics plays a pivotal role in quantitative assessments of anticancer therapeutics [48]. A variety of computational platforms—such as PKQuest [49], PharmPK [50], and SwissADME [51]—have been employed to estimate key pharmacokinetic properties. Based on this background, the present study utilized the SwissADME tool to assess the pharmacokinetic features of cannabinoid derivatives 1, 3, 6, 13, 14, 16, 18, and 20. The in silico results **(Table 5)** revealed notable variability in gastrointestinal uptake and metabolic interactions, particularly with cytochrome P450 enzymes. These disparities are likely influenced by differences in molecular structure and lipophilicity among the cannabinoid analogs.

Table 5. Pharmacokinetic parameters for cannabinoid derivatives

Com	i	ii	iii	iv	v	vi	vii	viii
Flu	High	Yes	No	Yes	Yes	No	No	No
Test	High	Yes	Yes	No	No	No	No	No
DHT	High	Yes	No	No	No	No	No	No
Dut	Low	Yes	No	No	No	No	No	Yes
Finast	High	Yes	Yes	No	No	No	No	No
1	High	No	No	Yes	Yes	No	Yes	No
3	High	No	No	Yes	No	Yes	No	No
6	High	Yes	No	Yes	No	Yes	No	Yes
13	High	Yes	No	No	Yes	Yes	No	Yes
14	High	Yes	No	No	Yes	Yes	No	Yes
16	High	Yes	No	No	Yes	Yes	Yes	Yes
18	High	No	Yes	Yes	Yes	Yes	Yes	No
20	High	No	No	No	No	No	No	No

Com = compound, Flu = flutamide, Test = testosterone, DHT = dihydrotestosterone, Dut = dutasteride, Finast = finasteride, i = GI absorption, ii = BBB permeant, iii = P-GP substrate, iv = CYP1A2 inhibitor, v = CYP2C19 inhibitor, vi = CYP2C9 inhibitor, vii = CYP2D6 inhibitor, viii = CYP3A4 inhibitor, and ix = Consensus Log PO/W.

Toxicity evaluation

Various methods have been developed to predict the toxicity of compounds, including ADME/Tox [52], eToxPred [53], and GUSSAR [54]. In this study, the GUSSAR software was used to assess the potential toxic effects of cannabinoid derivatives 1, 3, 6, 13, 14, 16, 18, and 20. The findings **(Table 6)** indicate that lower doses of these cannabinoid derivatives are required to induce toxicity when administered orally, in comparison to testosterone and dihydrotestosterone. Additionally, the analysis suggests that compounds 13, 14, 16, and 20 exhibit a higher toxicity at lower doses than dutasteride and finasteride.

Table 6. Pharmacokinetic parameters for cannabinoid derivatives

Com	**IP LD50 (mg/kg)**	**IV LD50 (mg/kg)**	**Oral LD50 (mg/kg)**	**SC LD50 (mg/kg)**
Test	1163.00	24.99	2244.00	2324.00
DHT	1221.00	34.50	2642.00	2069.00
Flut	479.70	156.70	387,10	430.70
Dut	254.10	37.36	946.70	1360.00
Finast	947.80	30.75	1816.00	2268.00
1	582.50	91.93	2813.00	1108.00
3	400.90	142.60	1530.00	561.50
6	469.00	206.30	2346.00	664.10
13	343.300	38.530	799.20	17450

14	365.10	40.55	710,500,	99,420
16	296.30	63.87	786.40	174.60
18	698.70	53.30	1985.00	607.90
20	395.90	39.85	745.50	50.41

Com = compound, Flu = flutamide, Test = testosterone, DHT = dihydrotestosterone, Dut = dutasteride, Finast = finasteride, IP = intraperitoneal, IV = intravenous, Oral = oral, and SC = subcutaneous.

Conclusion

This study investigated the theoretical interactions of 20 cannabinoid derivatives with the androgen receptor and the 5α-reductase enzyme. The results indicated that cannabinoid derivatives 6, 13, 16, and 20 displayed a stronger binding affinity to the androgen receptor compared to testosterone, dihydrotestosterone, and flutamide. On the other hand, derivatives 1, 3, 14, and 18 were found to bind more effectively to the 5α-reductase enzyme than dutasteride and finasteride. These findings suggest that cannabinoid derivatives 6, 13, 16, and 20 might function as inhibitors of the androgen receptor, while derivatives 1, 3, 14, and 18 could serve as inhibitors of the 5α-reductase enzyme. This opens up the possibility of using these derivatives in breast cancer therapy.

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