Original Article

Theoretical Evaluation of Twenty-Cannabinoid Derivatives on Either Androgen Receptor or 5α-Reductase Enzyme

Abstract

There are studies which suggest that some cannabinoids derivatives can produce effects on prostate cancer; however, the effect exerted on androgen receptor and 5α-reductase is very confusing; perhaps, this phenomenon is due to differences in the chemical structure of cannabinoids. The aim of this theoretical research was to evaluate the possible interaction of twenty-cannabinoids derivatives (compounds 1 to 20) with either androgen receptor or 5α-reductase enzyme using either 3L3X or 7BW1 proteins as the theoretical models. Besides, testosterone, dihydrotestosterone, dutasteride, finasteride and flutamide drugs were used as theoretical tools. The results showed higher affinity of cannabinoid derivatives 6, 13, 16 and 20 for the androgen receptor surface compared to testosterone, dihydrotestosterone and flutamide. In addition, other data indicate that cannabinoid derivatives 1, 3, 14 and 18 could have higher affinity by 5α-reductase enzyme compared with dutasteride and finasteride. All these data suggest that cannabinoid derivatives 6, 13, 16 and 20 could act as androgen receptor inhibitors. In addition, the cannabinoid analogs 1, 3, 14 and 18 could exert their biological activity as 5α-reductase enzyme inhibitors. This phenomenon could be translated as good candidates for the treatment of prostate cancer.

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

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Introduction

Several Mortality rate from prostate cancer has increased in recent years worldwide.[1, 2] It is important to mention that there are several factors involved in the development of this clinical pathology such as genetics,[3] obesity,[4] aging,[5] alcohol.[6] Additionally, some studies indicate that androgens and their receptors may be associated with prostate cancer.[7, 8] It is noteworthy that currently several drugs are used to treat patients with prostate cancer, such as flutamide[9] nilutamide[10] bicalutamide[11] enzalutamide[12] and apalutamide[13] finasteride[14] and dutasteride.[15] However, some drugs can produce some secondary effects, such as hot flashes[16] hypertension[17] hepatotoxicity[18] and erectile dysfunction.[19] In the search for new alternative therapeutics for treating prostate cancer, some compounds have been prepared; for example, a study showed the synthesis of dimethylcurcumin from curcumin and diazomethane with biological activity on the androgen receptor using DU145 and PC-3 human prostate cancer cell lines.[20, 21] Besides, a report displayed the reaction of an aminobenzamide analog with cyanohydrin to form a fluorobenzamide derivative as anticancer agent using LNCaP cells line.[22, 23] Other data indicate that JNJ-63576253 drug could be a therapeutic alternative for the treatment of patients with prostate cancer who do not respond to enzalutamide and apalutamide.[24, 25] In addition, a phenoxybenzoylphenyl acetic acid derivative was prepared as 5α-reductase enzyme inhibitor using either rat prostate homogenates or human prostate homogenate.[26] Recently, a study showed the interaction of some dibenzo derivatives on both androgen receptor and 5α-reductase enzyme using a theoretical model.[27]

On the other hand, some studies suggest that cannabinoid derivatives may reduce prostate cancer.[28, 29] For example, one study showed that a cannabinoid derivative WIN-55,212-2) produces decreased growth of LNCaP cells (androgen-sensitive human prostate cells).[30] In addition, one study indicates that the cannabinoid derivative chromenopyrazoldione may decrease the LNCaP cells growth.[31]

Other data showed that (R)-methanandamide drug (a cannabinoid

How to cite this article: Lopez-Ramos M, Figueroa-Valverde L, Diaz-Cedillo F, Rosas-Nexticapa M, Alvarez-Ramirez M. Theoretical Evaluation of Twenty-Cannabinoid Derivatives on Either Androgen Receptor or 5α-Reductase Enzyme. Clin Cancer Investig J. 2023;12(2):27-32. https://doi.org/10.51847/5MYimTzeXf

Access this article online

Website: www.ccij-online.org

DOI: 10.51847/5MYimTzeXf

Quick Response Code:

derivative) could modify the expression of the androgen receptor in an androgen-dependent cell line, resulting in the regulation of prostate cell growth.[32] However, a study displayed that both (R)-methanandamide and WH-015 drug decreasing prostate cancer though CB2 cannabinoid-receptor using a PC-3 cell line (human prostate epithelial cells).[33] All this data suggests that some cannabinoid derivatives can produce effects on prostate cancer; however, the possible effect exerted on either androgen receptor, or 5-α reductase enzyme is very confusing; perhaps, this phenomenon is due to differences in the chemical structure of cannabinoids. Analyzing this hypothesis. The aim of this theoretical study was to evaluate the possible interaction of twenty-cannabinoids derivatives on either androgen receptor or 5α-reductase enzyme using testosterone, dihydrotestosterone, flutamide, dutasteride, and finasteride drugs as theoretical tools in a Docking model.

Materials and Methods

Twenty-cannabinoid derivatives were used as theoretical tools **(Figure 1)** to evaluate their possible interaction with either androgen receptor or 5α-reductase enzyme as follows:

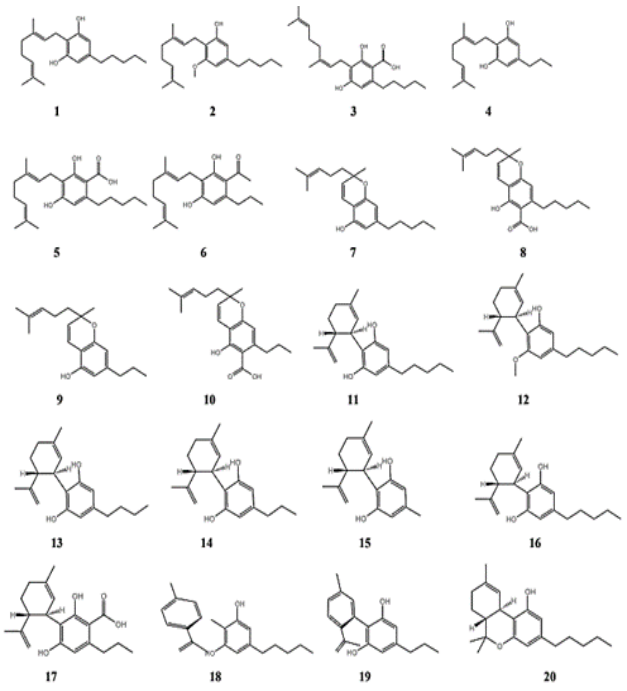

Figure 1. Chemical structure of cannabinoid derivatives (1-27). Source: ChemPub (https://pubchem.ncbi.nlm.nih.gov/).

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-C_5
12 = Cannabidiol monomethyl ether
13 = Cannabidiol
14 = Cannabidivarin
15 = Cannabidiorcol
16 = Cannabidiolic acid
17 = Cannabidivarinic acid
18 = Cannabinodiol
19 = Cannabinodivarin
20 = Dronabinol

Ligand-protein complex

The interaction of opioid derivatives with either androgen receptor or 5α-reductase enzyme surface was evaluated using either 3L3X **(**PDB DOI: 10.2210/pdb3L3X/pdb)[34] or 7BW1 **(**PDB DOI: 10.2210/pdb7BW1/pdb)[35] proteins as theoretical models. Besides, to evaluate the different types of binding energy involved in opioid derivative-protein complex formation, the DockingServer program was used.[36]

Pharmacokinetics parameter

Some Pharmacokinetic involved in the chemical structure of cannabinoid derivatives (1, 3, 6, 13, 16, 18 and 20) were determined using the SwissADME software.[37]

Toxicity analysis

Theorethical toxicity produced by either cannabinoid derivatives (1, 3, 6, 13, 14, 16, 18 and 20) was determined using GUSAR software.[38]

Results and Discussion

Protein-ligand analysis

Several methods to predict the interaction of several drugs with androgen receptor such as Gold,[39] Glide,[40] Autodock,[41] and DockigServer[42] have reported. For example, a theoretical study indicates that hormone-binding site which is well-characterized as a hydrophobic cavity that forms strong hydrophobic interactions with a steroidal core of androgens.[43] Another report showed that amino acid residues such as Asn705 and Thr877 may involve hydrogen bond interactions with the 17-hydroxy group of testosterone and Gln711 and Arg752 with the 3-keto group of this androgen.[44] In addition, a theoretical study suggests that some cannabinoids such as tetrahydrocannabinol and cannabidiol may have biological activity on androgen receptor translated as an inhibition of prostate cancer progression.[45] Analyzing these data, and other studies which suggest that cannabinoids may reduce prostate cancer;[28, 30-33] in this investigation twenty cannabinoid derivatives were used to evaluate their interaction with androgen receptor using at 3L3X protein as theoretical model. The results **(Table 1)** showed that interaction of cannabinoid derivatives with 3L3X protein surface could possibly involve some different aminoacid-residues compared to testosterone, dihydrotestosterone and flutamide.

Table 1. Aminoacid residues involved in the coupling cannabinoides 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}

However, it is important to mention that a study showed that some thermodynamic parameters are involved in the interaction of testosterone and its analogues on the androgen receptor.[46] For this reason, in this study several energy parameters **(Table 2)** for cannabinoid derivatives, testosterone, dihydrotestosterone and flutamide were evaluated using DockingServer program.

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)
VI = Interaction Surface

The results showed differences in bond-energy levels for cannabinoid derivatives, testosterone, dihydrotestosterone and flutamide. Besides, the inhibition constant (Ki) was lower for cannabinoid derivatives 6, 13, 16 and 20 compared to testosterone dihydrotestosterone and flutamide; these data

suggest that these cannabinoid analogues could act as androgen receptor inhibitors, resulting in a decrease in prostate cancer. However, it is noteworthy that other molecular mechanisms are involved in the development of prostate cancer; for example, several studies indicate that some drugs such as dutasteride and finasteride (5α-reductase enzyme inhibitors)[14, 47] can decrease prostate cancer. Analyzing these data, the aim of this research was to evaluate the theoretical interaction of cannabinoid derivatives (Compound 1 to 20) on 5α-reductase enzyme using at 7BW1 protein, dutasteride and finasteride as theoretical tools **(Table 3)**.

Table 3. Aminoacid residues involved in the coupling cannabinoides 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
Test = testosterone

The results showed differences in some aminoacid residues for cannabinoid derivatives compared with dutasteride and finasteride. Besides, the Ki for cannabinoid analogs such as 1, 3, 14 and 18 was lower compared with dutasteride and finasteride **(Table 4)**; These data suggest that these cannabinoid derivatives could act as 5α-reductase enzyme inhibitors, producing a decrease in prostate cancer.

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 = Vander Waals forces + H-bond + desolv Energy (kcal/mol)
IV = Electrostatic Energy (kcal/mol)
V = Total Intermolecular Energy (kcal/mol)
VI = Interaction Surface

Pharmacokinetic analysis

Pharmacokinetic characteristics is an area which have been focused on quantitative pharmacological studies for anticancer drugs.[48] It is important to mention that several theoretical methods have been used to predict some pharmacokinetic parameters, such as PKQuest[49] PharmPK,[50] and SwissADME.[51] Analyzing these data, in this investigation, some pharmacokinetic parameters for cannabinoid derivatives 1, 3, 6, 13, 14, 16, 18 and 20 were evaluated using the SwissADME program. Theoretical results **(Table 5)** show differences in gastrointestinal absorption and metabolism involving some cytochrome P450 systems; this phenomenon could depend on the chemical structure of the cannabinoid derivatives and their degree of lipophilicity.

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
ix = Consensus Log $P_{O/W}$

Toxicity analysis

Some methods have been used to predict the degree of toxicity of various compounds such as ADME/Tox,[52] eToxPred,[53] GUSSAR.[54] Analyzing these data, the aim of this study was to evaluate the possible toxic effect produced by cannabinoid derivatives 1, 3, 6, 13, 14, 16, 18 and 20 using the GUSSAR software. The results **(Table 6)** suggest that lower doses of cannabinoid derivatives are needed (via oral) to produce toxicity compared to testosterone and dihydrotestosterone. Besides, other data indicate that compounds 13, 14, 16 and 20 require low doses to induce toxicity compared with 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.
SC = Subcutaneous.

Conclusion

In this investigation, the theoretical interaction of twenty cannabinoid derivatives with the androgen receptor or 5α-reductase enzyme was determined. Theoretical interaction showed higher affinity of cannabinoid derivatives 6, 13, 16 and 20 for the androgen receptor surface compared to testosterone, dihydrotestosterone and flutamide. Besides, other results suggest that cannabinoid derivatives 1, 3, 14 and 18 could have higher affinity by 5α-reductase enzyme compared with dutasteride and finasteride. All these data suggest that cannabinoid derivatives 6, 13, 16 and 20 could act as androgen receptor inhibitors. In addition, the cannabinoid analogs 1, 3, 14 and 18 could exert their biological activity as 5α-reductase enzyme inhibitors. This phenomenon could be translated as good candidates for the treatment of breast cancer.

Acknowledgments

None.

Conflict of interest

None.

Financial support

None.

Ethics statement

None.

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