DISCIPLINARUM SCIENTIA *Disciplinarum Scientia.* **Série: Naturais e Tecnológicas**
Santa Maria, v. 25, n. 3, p. 145-160, 2024
Recebido em: 22.11.2024. Aprovado em: 03.01.2025.
ISSN 2176-462X | DOI: doi.org/10.37779/nt.v25i3.5179

MOLECULAR MODELING OF CANNABINOID BINDING TO THE CB1 RECEPTOR: COMPARING *CANNABIS SATIVA* AND SYNTHETIC CANNABINOIDS

MODELAGEM MOLECULAR DA LIGAÇÃO DE CANABINOIDES AO RECEPTOR CB1: COMPARANDO O THC E CANABINOIDES SINTÉTICOS

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ABSTRACT

This study conducted a comparative theorical molecular modeling analysis of tetrahydrocannabinol (THC), the primary active compound in *Cannabis sativa*, and synthetic cannabinoids (SCs) reported by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) from 2008 to 2022 between 2009 and 2022. The study aims to analyze the interactions of these compounds with the type 1 cannabinoid receptor (CB1), which is responsible for many of the psychoactive effects of cannabis and its synthetic analogues. Using computer simulations, we sought to identify the differences and similarities in binding affinity and molecular conformations, contributing to a better understanding of the clinical and toxicological impacts of synthetic cannabinoids compared to THC. In this research, we carried out molecular docking simulations to investigate the interactions between THC and the CB1 cannabinoid receptor, as well as synthetic cannabinoids. We selected compounds described between 2008 and 2022, excluding those unavailable on PubChem. We used the crystallized three-dimensional structure of the Cannabinoid Receptor type 1 (CB1), using the code 5TGZ obtained from the Protein Data Bank (PDB). The structural files of the ligands were extracted from PubChem. The simulations were performed using AutoDock 4 software, targeting the active site of CB1 with a 21 Å grid box centered at coordinates (43.60, 27.40, 318.50. The molecular docking results indicate that several compounds have a stronger binding affinity for the CB1 receptor compared to THC (control compound), with EG-018, BB-22, JWH-307 and APINACA standing out. EG-018 exhibited the highest binding affinity, highlighting its potential as a highly potent CB1 ligand. Compounds such as APINACA and BB-22 also exhibited high binding efficiency. The constant spread of synthetic cannabinoids poses a significant challenge due to the unpredictability of their side effects. The results of this study suggest that many SCs have a higher binding affinity for CB1 compared to THC, which may result in more intense and unpredictable clinical and toxicological effects. A detailed understanding of the molecular interactions of SCs is fundamental to mitigating their risks and developing safer and more effective therapeutic strategies.

Keywords: Drugs synthetic; Computer simulation; Theorical studies; Bioinformatics.

RESUMO

Este estudo realizou uma análise teórica comparativa de modelagem molecular do tetrahidrocanabinol (THC), o principal composto ativo da Cannabis sativa, e dos canabinoides sintéticos (SCs) relatados pelo Observatório Europeu da Droga e da Toxicodependência (OEDT) de 2008 a 2022 entre 2009 e 2022. O estudo tem como objetivo analisar as interações desses compostos com o receptor canabinoide tipo 1 (CB1), que é responsável por muitos dos efeitos psicoativos da cannabis e de seus análogos sintéticos.

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Usando simulações de computador, procuramos identificar as diferenças e semelhanças na afinidade de ligação e nas conformações moleculares, contribuindo para uma melhor compreensão dos impactos clínicos e toxicológicos dos canabinoides sintéticos em comparação com o THC. Nesta pesquisa, realizamos simulações de acoplamento molecular para investigar as interações entre o THC e o receptor canabinoide CB1, bem como os canabinoides sintéticos. Selecionamos compostos descritos entre 2008 e 2022, excluindo os que não estavam disponíveis no PubChem. Usamos a estrutura tridimensional cristalizada do receptor canabinoide tipo 1 (CB1), usando o código 5TGZ obtido do Protein Data Bank (PDB). Os arquivos estruturais dos ligantes foram extraídos do PubChem. As simulações foram realizadas com o software AutoDock 4, visando o local ativo do CB1 com uma caixa de grade de 21 Å centrada nas coordenadas (43,60, 27,40, 318,50). Os resultados do acoplamento molecular indicam que vários compostos têm uma afinidade de ligação mais forte para o receptor CB1 em comparação com o THC (composto de controle), com destaque para o EG-018, BB-22, JWH-307 e APINACA. O ligante EG-018 apresentou a maior afinidade de ligação, destacando seu potencial como um ligante CB1 altamente potente. Compostos como o APINACA e o BB-22 também apresentaram alta eficiência de ligação. A constante disseminação de canabinoides sintéticos representa um desafio significativo devido à imprevisibilidade de seus efeitos colaterais. Os resultados deste estudo sugerem que muitos SCs têm uma afinidade de ligação maior para CB1 em comparação com o THC, o que pode resultar em efeitos clínicos e toxicológicos mais intensos e imprevisíveis. Uma compreensão detalhada das interações moleculares dos CSs é fundamental para mitigar seus riscos e desenvolver estratégias terapêuticas mais seguras e eficazes.

Palavras-chave: *Drogas sintéticas; Interações moleculares; Simulação computacional.*

INTRODUCTION

THE HISTORY AND USE OF CANNABIS SATIVA

Cannabis sativa is one of humanity's oldest cultivated plants, with a rich and diverse history. Used for a variety of purposes, including textiles, medicine, and recreation, its domestication began in East Asia during the Neolithic period. This process led to the development of distinct hemp and drug cultivars, all originating from a common ancestral gene pool (Ren *et al*., 2021).

Throughout millennia, cannabis has been recognized for its pharmacological properties. Compounds like phytocannabinoids and terpenes have demonstrated efficacy in treating diseases such as epilepsy, pain, and nausea (Stasilowicz *et al*., 2021). Psychoactive preparations of the plant, like marijuana, have been used for centuries, although their safety and efficacy remain the subject of debate (Carranza, 2012).

Cannabis sativa has been utilized for over 4,000 years in medicinal, religious, and recreational contexts. Since the 1960s, recreational use of the plant has increased significantly, becoming a global health concern (Carranza, 2012)."

CANNABINOID RECEPTORS TYPE 1 (CB1) AND TYPE 2 (CB2)

The endocannabinoid system (ECS) is pivotal in regulating various physiological processes through the action of its primary receptors, CB1 and CB2. These G protein-coupled receptors mediate the effects of endogenous cannabinoids such as anandamide and 2-arachidonoylglycerol. Synthesized on demand, these compounds primarily exert their functions at presynaptic receptors (Laere, 2007).

CB1 receptors are predominantly found in the central nervous system (CNS) where they play a crucial role in neurotransmitter release, pain modulation, and neuroprotection (Laere, 2007; Graham, 2009). In contrast, CB2 receptors are primarily expressed in the immune system, regulating inflammation and immune cell function (Haugh *et al*., 2016).

These receptors are considered promising targets for treating various conditions, including anxiety, pain, and neurodegenerative diseases. However, challenges such as adverse effects and the development of tolerance remain to be overcome (Leo and Abood, 2021; Makriyannis *et al*., 2006). THC, for instance, exhibits high affinity for CB1, similar to endogenous cannabinoids like anandamide (Reggio, 2005).

When THC binds to the CB1 receptor, it activates the receptor, inhibiting adenylyl cyclase activity, resulting in reduced levels of cyclic adenosine monophosphate (cAMP) in neurons. Additionally, THC activates G protein-coupled cannabinoid receptors, inhibiting adenylyl cyclase and increasing potassium conductance, altering neuronal excitability and mediating various neurobiological effects (Childers et al., 1993). CB1 activation by THC also stimulates the c-Jun N-terminal kinase (JNK) pathway, contributing to neurotoxic effects such as apoptosis in cortical neurons (Downer, Fogarty, and Campbell, 2003).

Both Δ9-THC and synthetic cannabinoids bind to CB1 and CB2 receptors, activating signal transduction pathways and mimicking the effects of endogenous cannabinoids like anandamide (Van der Stelt & Di Marzo, 2005). These compounds exhibit analgesic, antiemetic, and anticonvulsant properties, with affinities that vary according to structural modifications (Palmer, Khanolkar, & Makriyannis, 2000).

SYNTHETIC CANNABINOIDS

Since the mid-2000s, there have been online reports about the existence of “herbal smoking blends” marketed as “legal highs,” capable of producing intense effects similar to cannabis. However, it was only in 2008 that forensic investigators in Germany and Austria first detected the synthetic cannabinoid JWH-018 in a product marketed under the brand “Spice.” Typical examples of these products include Spice Gold, Spice Silver, and Yucatan Fire, although many others have emerged subsequently. Many of the cannabinoids found in these products were initially developed by scientists

studying how cannabinoids affect the body, with the aim of determining their potential in treating diseases and symptoms, such as neurodegenerative diseases, chemical dependency, pain disorders, and cancer. However, thus far, it has been difficult to separate the desired therapeutic properties from the unwanted psychoactive effects (European Monitoring Centre for Drugs and Drug Addiction, 2017).

Synthetic cannabinoids play a significant role in the rapidly evolving illicit market of "legal highs," a generic term used to describe new, unregulated psychoactive substances that generally mimic the effects of controlled drugs and are sold on the open market. There is limited data on their consumption, and the associated risks and harms are largely unknown, causing great concern due to the potency of these drugs. Smoking blends containing synthetic cannabinoids, for example, can show considerable variations from batch to batch or even within the same batch, both in terms of the substances present and their concentrations (European Monitoring Centre for Drugs and Drug Addiction, 2017).

In 2021, for the first time since 2016, there was an increase in the first identifications of new synthetic cannabinoids (SCs) in Europe, with 15 new substances being detected.

It is important to note that these new compounds, observed since mid-2021, are structurally very diverse and include new or rarely seen cores, tails, and/or linking groups. Among them are four OXIZID compounds and some substituted indazole cores (including five indazole compounds with bromine substitution at position 5). SCs with new or rarely seen naphthalene cores (A-PONASA) and quinoline cores (ADB-FUBHQUCA) were also reported. In terms of tails, two new properties, cyclohexyl sulfonyl and 10-carbon decyl, were observed in three SCs reported in the first half of 2022. It is noteworthy that four reported compounds (ADB-5Br-INACA, ADB-IACA, MDMB-5Br-INACA, and CUMYL-INACA) in 2022 do not have a tail group. The impact of the absence of the tail on the pharmacological activity of SCs has not yet been evaluated. Finally, with regard to linking groups, acetamides (ATA) were identified for the first time (for example, in ADB-FUBIATA formally reported by the EMCDDA in December 2021) (Andrews *et al*., 2022).

SCs represent the largest category of new psychoactive substance (NPS) monitored by the EMCDDA, with 224 different substances identified in Europe by December 2021, plus 13 more detected between January and July 2022. Although they have similar pharmacological profiles, their chemical structures are quite varied (Andrews *et al*., 2022).

The variation in building blocks seems to be influenced by three main factors: ease of synthesis, the search for more potent compounds, and the attempt to avoid existing and anticipated legal controls. Until 2021, structural variations generally focused on the introduction of different tails and/or groups linked to the molecules, allowing new substances to be classified into "series" or "generations." Although the properties of the resulting compounds were often unknown, there was a certain degree of predictability in the changes, which allowed forensic and toxicology laboratories to prepare for the new derivatives (Andrews *et al*., 2022).

NEGATIVE HEALTH IMPACTS OF SYNTHETIC CANNABINOIDS

Many cases of non-fatal intoxications and a smaller number of deaths associated with the consumption of these compounds have been reported. Considering the high potency of some of them, the probability of toxic effects is elevated. These risks can be exacerbated by the manufacturing process, which can result in an uneven distribution of substances in the plant material. This can cause some products to contain parts with high concentrations of cannabinoids, resulting in doses higher than expected and increasing the risk of severe adverse effects. It is also likely that some of these adverse effects are caused by mechanisms other than interaction with cannabinoid receptors, such as interference with other physiological functions of the body (European Monitoring Centre for Drugs and Drug Addiction, 2017).

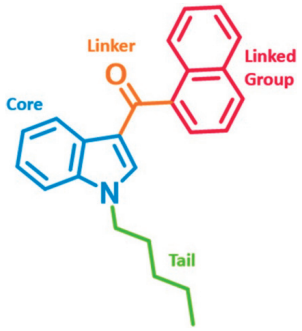
The most common symptoms of intoxication include agitation, nausea, and rapid heart rate, while other serious adverse events, such as strokes, seizures, heart attacks, muscle failure, kidney damage, psychoses, and severe or prolonged vomiting, in addition to associated deaths, are less frequent. Symptoms suggestive of dependence and withdrawal have also been reported. In general, it is difficult to calculate the frequency of these adverse effects because, among other factors, the total number of people exposed to the drugs is unknown (European Monitoring Centre for Drugs and Drug Addiction, 2017).

CHEMICAL STRUCTURE AND NOMENCLATURE OF SYNTHETIC CANNABINOIDS

Many synthetic cannabinoids monitored by the EMCDDA have code names that reflect their origins. Some names are based on the initials of the scientists who synthesized them, such as “JWH” for John W. Huffman and “AM” for Alexandros Makriyannis. Other names are derived from the institutions where they were created, such as the “HU” series from the Hebrew University of Jerusalem and “CP” from Carl Pfizer. Some names are chosen for marketing purposes, such as “AKB-48” and “2NE1,” which are names of popular bands in Japan and South Korea, respectively. The cannabinoid “XLR-11” was named in reference to a US liquid-fueled rocket (European Monitoring Centre for Drugs and Drug Addiction, 2017).

Currently, many synthetic cannabinoids are given code names based on their long chemical names, such as APICA and APINACA. The EMCDDA has developed a method for applying to new emerging substances, showing how their constituent parts can be combined. The structures of these cannabinoids can be divided into four components: tail, core, link, and attached group (European Monitoring Centre for Drugs and Drug Addiction, 2017), as shown in Figure 1.

Figure 1 - Chemical structure of the first synthetic cannabinoid reported to the European Monitoring Centre for Drugs and Drug Addiction: JWH-018.



Source: Andrews *et al*., 2022.

Given the increasing use of synthetic cannabinoids and growing concerns about their adverse health impacts, this article aims to explore their origins, structural characteristics, and molecular interactions with the CB1 receptors. To achieve this, molecular docking simulations will be conducted, investigating the interactions between THC, selected synthetic cannabinoids, and the CB1 receptor, with the intention of understanding the mechanisms of action and contributing to the development of safer and more effective therapeutic strategies.

METHODOLOGY

This section describes the preparation and execution process of the molecular docking simulations conducted to investigate the interactions between THC and CB1, as well as the interactions of the mentioned synthetic cannabinoids. The selection of compounds included substances described between 2008 and 2022, as illustrated in Figure 2. However, some compounds were excluded from the research due to their unavailability in PubChem.

It is worth noting that 15 monitored compounds that do not fit the existing four-part structure model were classified as “others.” These compounds are CP 47.497, CP 47,497-C6 homolog, CP 47,497-C8 homolog, CP 47,497-C9 homologs, HU-210, CP 47,497 (C8, C2), Org 27569, Org 27759, Org 29647, HU-331, trans-CP 47,497-C8, URB-754, URB-754, URB (Andrews *et al*., 2022).

Figure 2 presents a timeline of the main structural changes of SCs introduced in the European market. Generally, as expected, the structural variety of SCs increased dramatically between 2011 and 2015, with the increase of new substances introduced into the market. However, this variation did not decrease in the following years, despite the lower number of identifications of new SCs in Europe (Andrews *et al*., 2022).

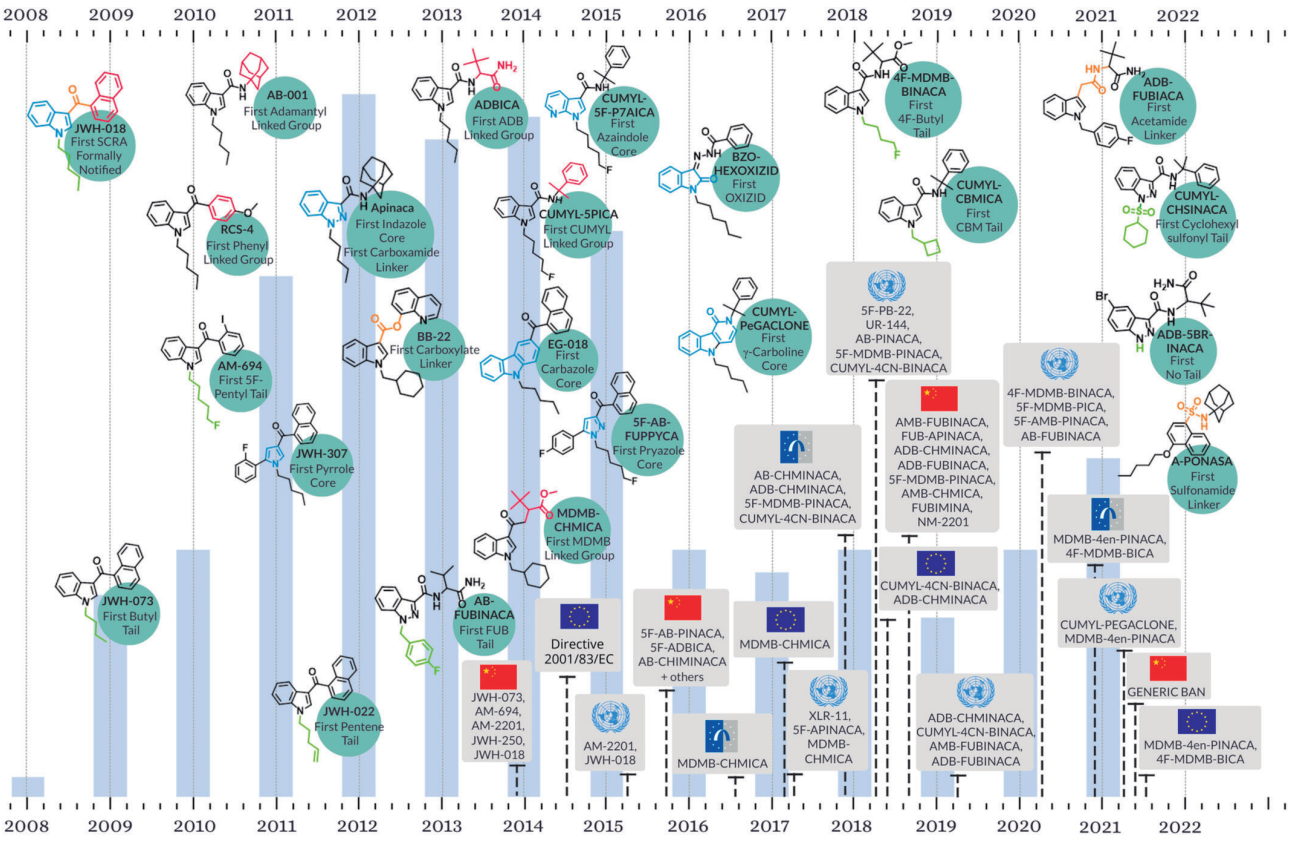
The three-dimensional structure of CB1 was obtained from the Protein Data Bank (PDB), a database maintained by the Research Collaboratory for Structural Bioinformatics (RCSB) in collaboration with the Worldwide Protein Data Bank (wwPDB). This platform brings together 3D structures of proteins and nucleic acids, widely used in structural bioinformatics studies. For this analysis, the PDB code 5TGZ, referring to CB1, was used, as described by Hua *et al*. (2016).

The structural files of the THC ligand and the other synthetic cannabinoids were extracted from PubChem, a public database managed by the National Center for Biotechnology Information (NCBI). This repository provides detailed information on molecular compounds, including their chemical and physical properties, biological activities, safety and toxicity data, as well as details about their structures.

The interaction simulations were conducted using the AutoDock 4 software, which allows the modeling of interactions between molecules, such as ligands and proteins. The search space was delimited around the active site of the CB1 receptor, using a grid box with dimensions of 21 Å, centered at coordinates 43.60, 27.40, and 318.50, as described in the article on the CB1 binding site (5TGZ) (Hua *et al*., 2016).

Molecular docking is an in silico technique that simulates the interaction between small molecules (ligands) and macromolecules (receptors), aiming to predict binding affinity and orientation. This method evaluates molecular interactions based on spatial conformations and binding energies, simulating the docking of a ligand to the active site of a receptor. In the context of this study, this technique is essential to elucidate the molecular interactions between THC and SCs with the CB1 receptor, providing valuable insights for the comparative analysis of these interactions and their potential effects on the human organism (Pinzi and Rastelli, 2019).

Figure 2 - Synthetic cannabinoids monitored by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA).



Source: Andrews *et al*., 2022.

RESULTS AND DISCUSSION

Table 1 presents the molecular docking results for the CB1 receptor, named "CB1_LIMPO_h" in the simulations. Compounds were evaluated based on binding affinity (in kcal/mol), inhibition constant (estimated Ki) and ligand efficiency. The compound named "thc_original", which corresponds to Tetrahydrocannabinol (THC), was used as a control.

The molecular docking results indicate that several compounds have a stronger binding affinity to the CB1 receptor compared to THC (control). Compounds such as EG-018, BB-22, JWH-307, and APINACA stood out with binding affinities greater than -11 kcal/mol, suggesting a more potent interaction with the CB1 receptor.

It is important to note that binding affinity values are considered in absolute terms, meaning that more negative values (in absolute terms) indicate a stronger binding.

The analysis of the results suggests that the compound EG-018 has the highest binding affinity, indicating its potential as a highly effective ligand for the CB1 receptor. The high ligand efficiency observed in compounds APINACA and BB-22 is also noteworthy, suggesting that these compounds may be promising candidates for future CB1 receptor affinity studies.

Comparing the results with the control (THC), we observed that most of the evaluated compounds showed a stronger binding affinity. With the exception of 4F-MDMB-BINACA, the compounds exhibited significantly more negative affinity values than THC, indicating a potential for greater efficacy in activating the CB1 receptor.

The ligand efficiency varied between -0.31 and -0.42, with APINACA and AB-001 showing higher values, suggesting a more efficient interaction with the CB1 receptor. These results provide a solid basis for the selection of candidates for future pharmacological and clinical studies.

In Figures 3 to 7, it is possible to observe the amino acids of the CB1 receptor interacting with different ligands. The four synthetic compounds (SCs) with the strongest binding affinity to the target receptor, as demonstrated in Table 1, were chosen, along with THC for comparison. It can be observed that various types of interactions occur between the ligands and the CB1 amino acids, including conventional hydrogen bonds, pi-pi stacking, pi-sigma, and pi-alkyl interactions.

These interactions are essential for understanding the affinity and specificity of each ligand in relation to the CB1 receptor. For example, the conventional hydrogen bonds indicated in green are fundamental for the stabilization of the complexes, while the pi-pi stacking and pi-alkyl interactions contribute to molecular recognition and binding affinity. (FONTE)

A detailed analysis of these interactions provides valuable insights into how these ligands behave in a biological environment, which can guide the design of new compounds with therapeutic potential for modulating the CB1 receptor.

In Figures 8 to 12, we can observe the energy donor and acceptor regions in hydrogen bonds between the type 1 cannabinoid receptor (CB1) and the ligand molecules with the highest binding affinity identified in this study. The energy donor areas, indicated in purple, show where the CB1 donates energy to form hydrogen bonds with the ligands. The acceptor areas, indicated in green, represent the sites where the ligands receive this energy APRESENTADAS NA FIGURAS 8 A 12. Such molecular interactions are essential for stabilizing the complexes and provide critical insights into the affinity and specificity of ligands for CB1. A detailed analysis of these interactions helps guide the development of new compounds with therapeutic potential to modulate the CB1 receptor effectively.

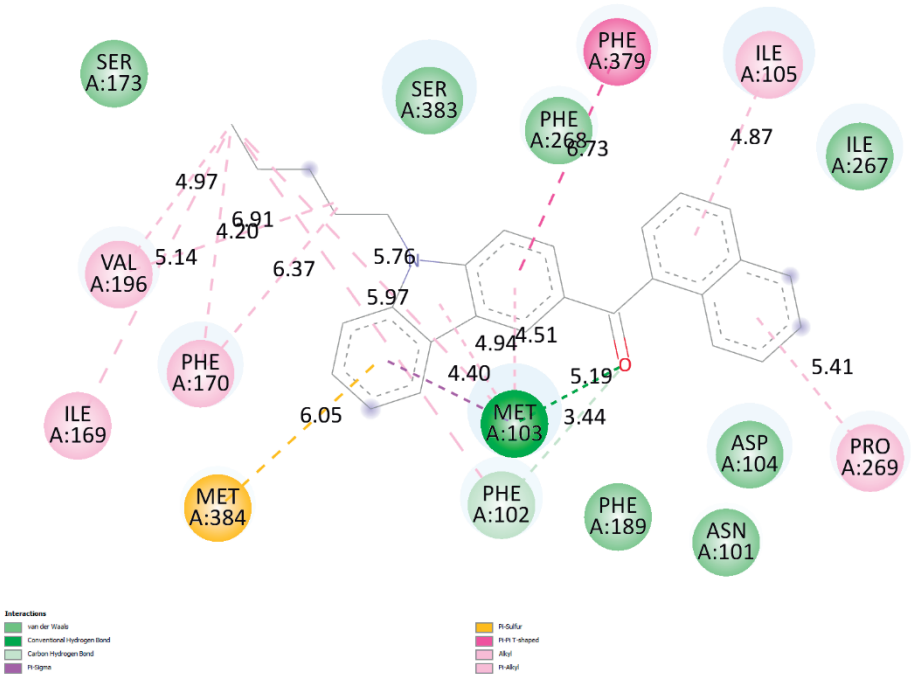
Table 1 - Results of molecular docking simulations.

RESULT FOR TARGET: CB1_LIMPO_h

POSES	AFFINITY (KCAL/MOL)	ESTIMATED Ki	Ki UNITS	LIGAND EFFICIENCY
THC	-7.9	1.62	uM	-0.34
ADBICA	-8.76	379.21	nM	-0.35
ADB-FUBIACA	-10.15	36.31	nM	-0.35
AB-FUBINACA	-9.32	147.37	nM	-0.35
4F-MDMB-BINACA	-7.96	1.46	uM	-0.31
APINACA	-11.4	4.40	nM	-0.42
BB-22	-11.86	2.03	nM	-0.41
CUMYL-5F-P7AICA	-8.92	289.47	nM	-0.33
CUMYL-CBMICA	-10.18	34.52	nM	-0.39
CUMYL-PEGACLONE	-10.5	20.11	nM	-0.38
EG-018	-12.38	0.84	nM	-0.41
JWH-022	-10.36	25.47	nM	-0.40
RCS-4	-9.17	189.82	nM	-0.38
MDMB-CHMICA	-9.89	56.31	nM	-0.35
AB-001	-10.81	11.92	nM	-0.42
AM-694	-9.48	112.49	nM	-0.40
JWH-018	-10.43	22.63	nM	-0.40
JWH-307	-11.22	5.97	nM	-0.39
JWH-073	-10.01	45.99	nM	-0.40

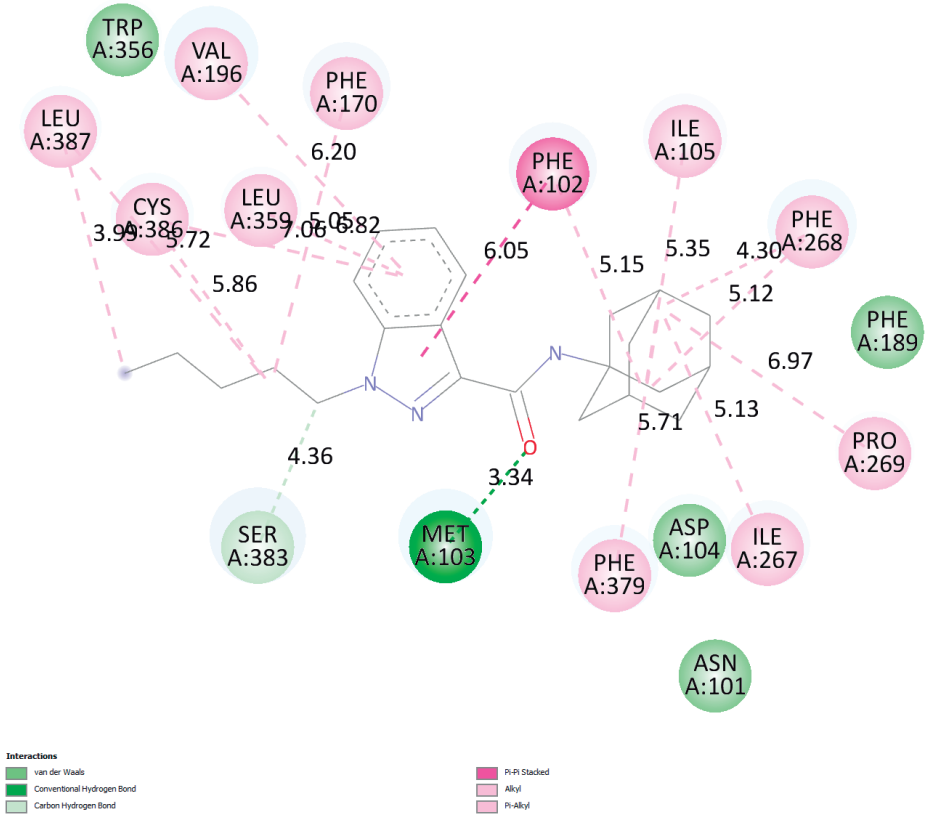
Source: Developed by the authors, 2024.

Figure 3 - Interactions between CB1 amino acids and the EG-018 molecule.



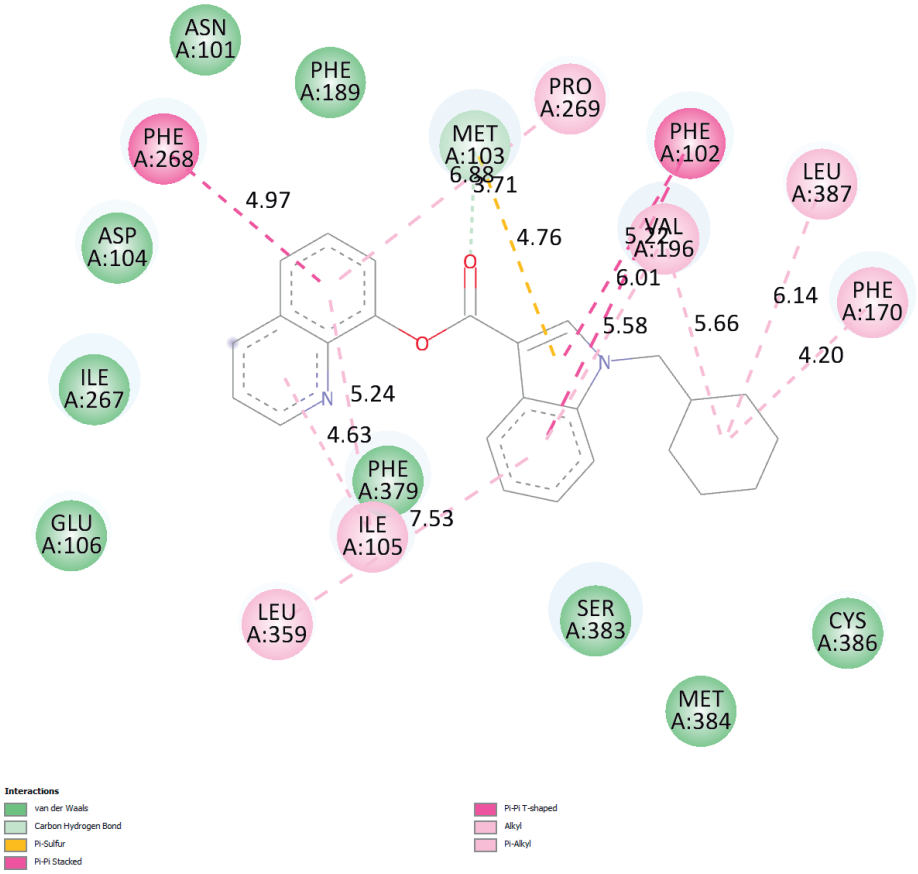
Source: Developed by the authors, 2024.

Figure 4 - Interactions between CB1 amino acids and the APINACA molecule.



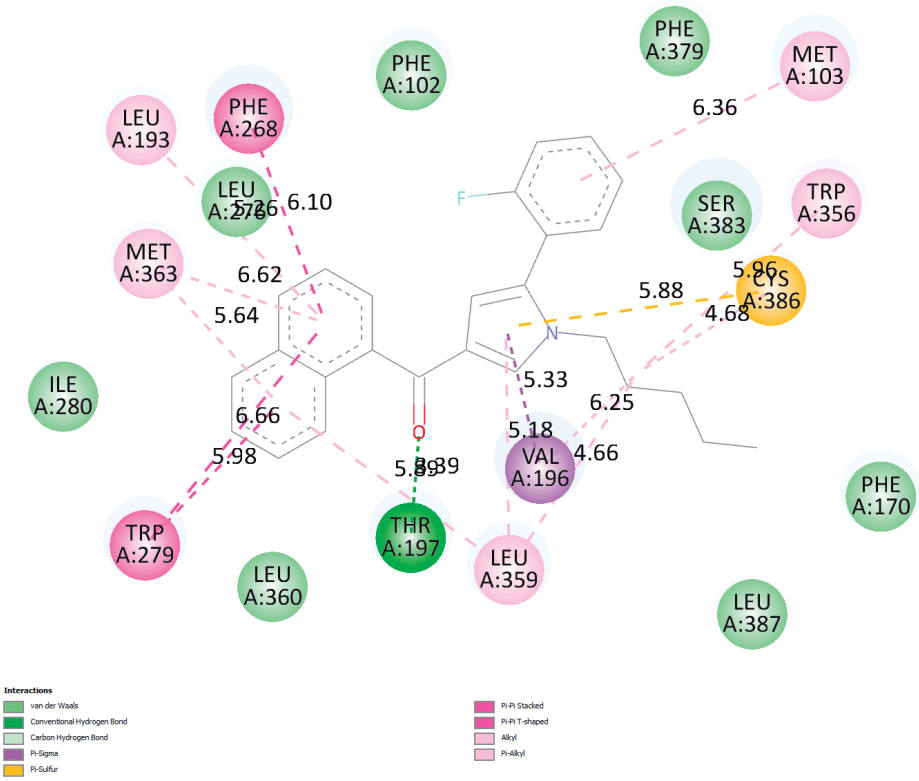
Source: Developed by the authors, 2024.

Figure 5 - Interactions between CB1 amino acids and the BB-22 molecule.



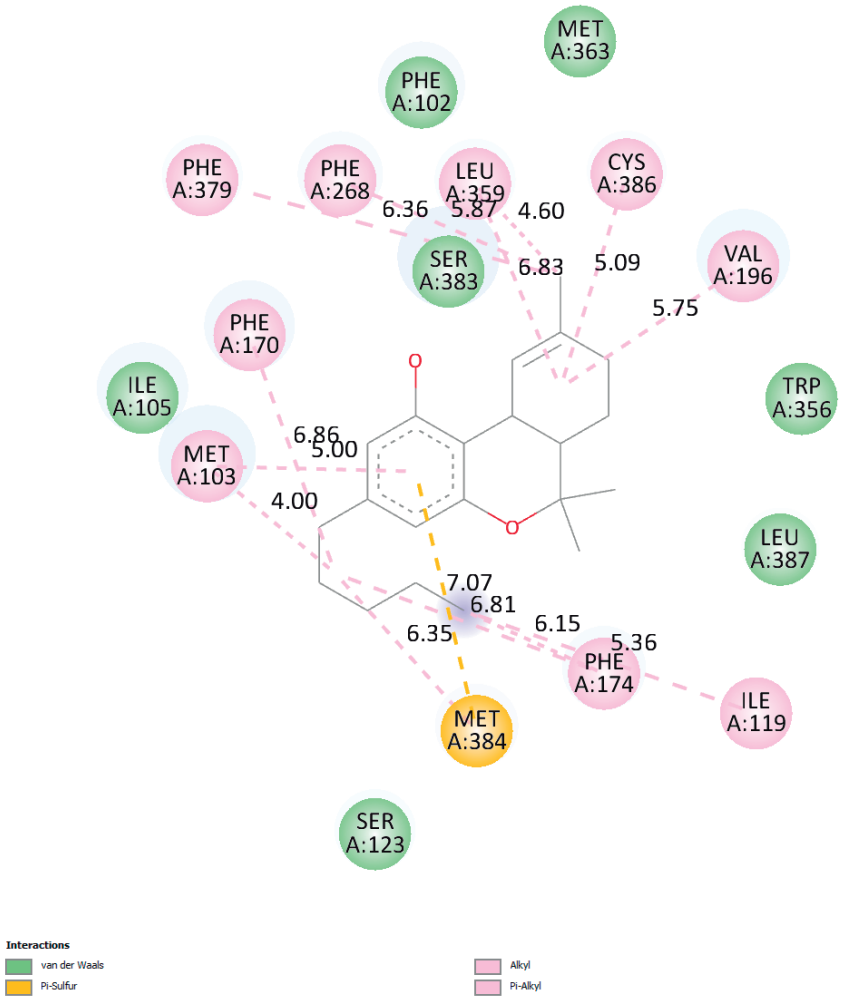
Source: Developed by the authors, 2024.

Figure 6 - Interactions between CB1 amino acids and the JWH-307 molecule.



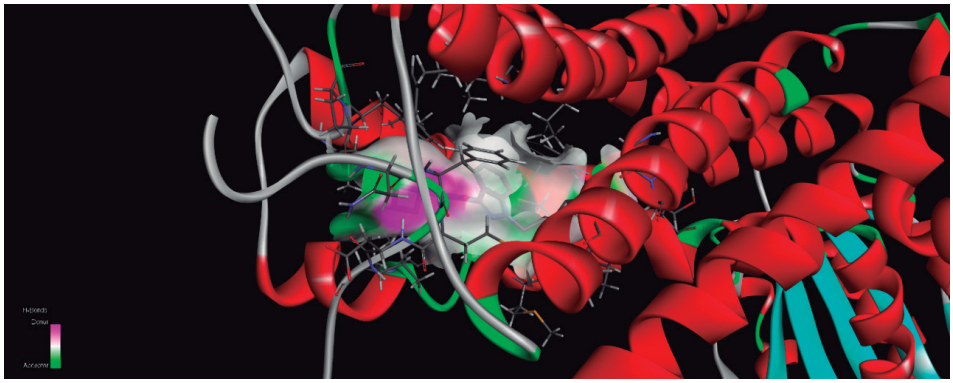
Source: Developed by the authors, 2024.

Figure 7 - Interactions between CB1 amino acids and the THC molecule.



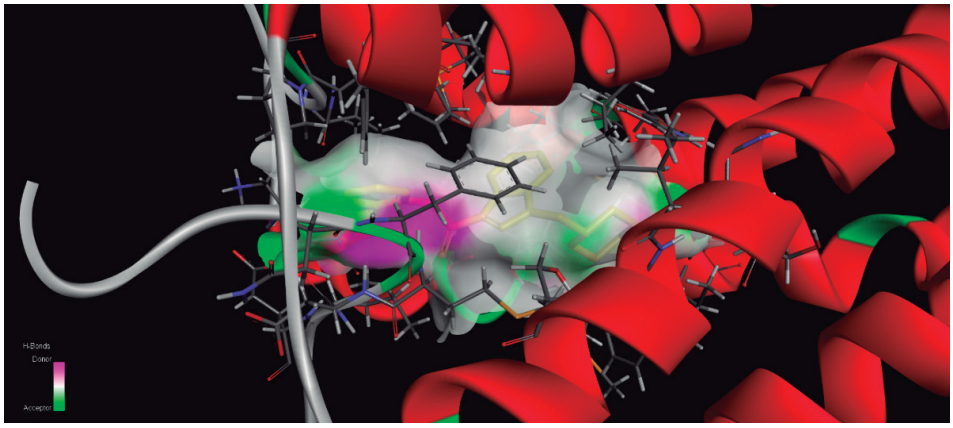
Source: Developed by the authors, 2024.

Figure 8 - Interaction between the CB1 receptor and APINACA, highlighting energy donor (purple) and acceptor (green) regions in hydrogen bonds.



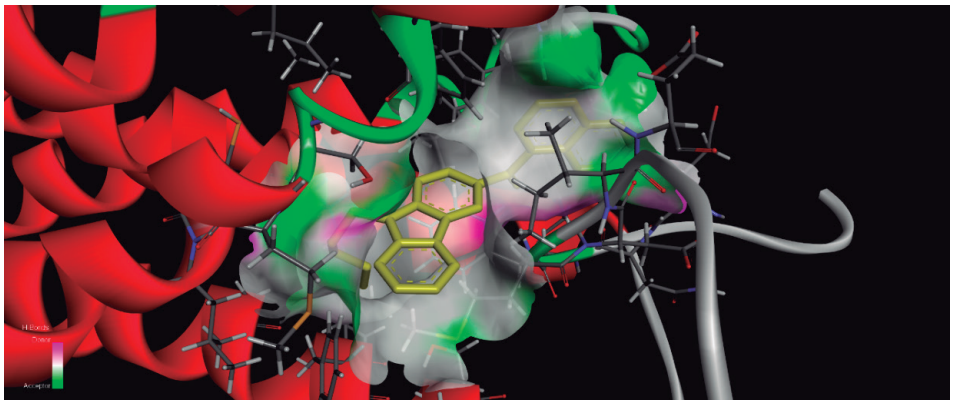
Source: Developed by the authors, 2024.

Figure 9 - Interaction between the CB1 receptor and BB-22, highlighting energy donor (purple) and acceptor (green) regions in hydrogen bonds.



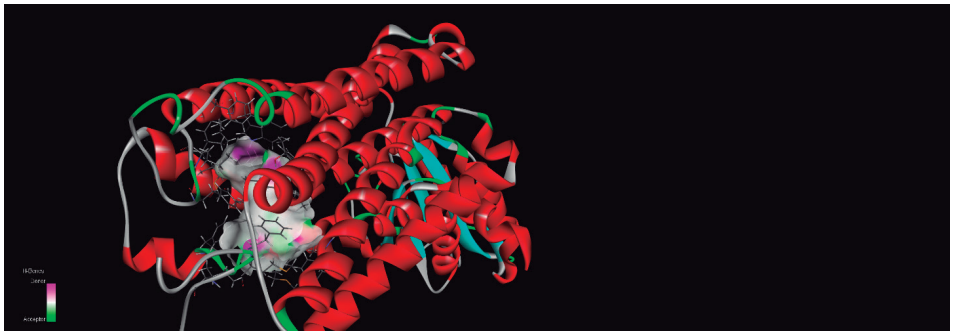
Source: Developed by the authors, 2024.

Figure 10 - Interaction between the CB1 receptor and EG-018, highlighting energy donor (purple) and acceptor (green) regions in hydrogen bonds.



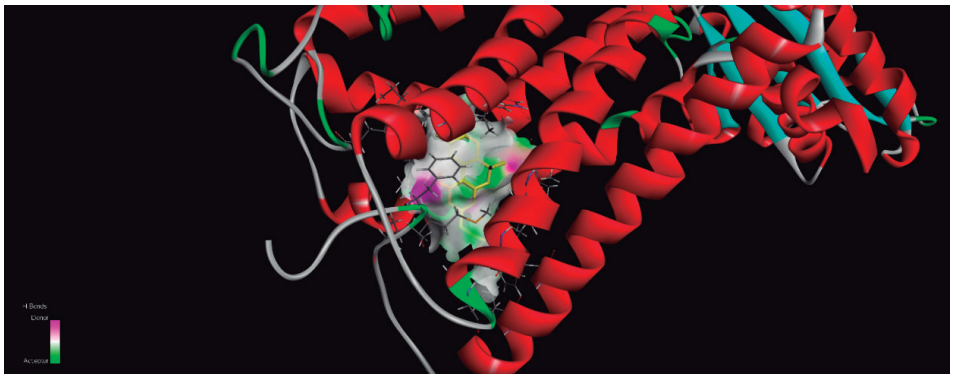
Source: Developed by the authors, 2024.

Figure 11 - Interaction between the CB1 receptor and JWH-307, highlighting energy donor (purple) and acceptor (green) regions in hydrogen bonds.



Source: Developed by the authors, 2024.

Figure 12 - Interaction between the CB1 receptor and THC, highlighting energy donor (purple) and acceptor (green) regions in hydrogen bonds.



Source: Developed by the authors, 2024.

CONCLUSION

The constant dissemination of SCs represents a significant challenge due to the unpredictability of their side effects, which can be potentially deleterious and even fatal. The results of this study indicate that many SCs have a higher binding affinity to the CB1 receptor compared to THC, suggesting their potential to cause more intense and unpredictable damage.

The comparative analysis conducted in this work revealed crucial differences in the molecular interactions between EG-018 showed and SCs with the CB1 receptor, providing valuable information about the mechanisms that may underlie the clinical and toxicological effects of these compounds. This knowledge is essential not only to understand the risks associated with SC consumption but also to explore their potential in the development of new therapies targeting the CB1 receptor.

It is suggested that further studies be conducted on the interpretation of the results found in this work. Based on the values obtained in molecular docking, it is possible to construct systems for evaluation by molecular dynamics between the molecules, as well as subsequent *in vitro* analysis of the interactions predicted by the software used in this work.

These elements could not be fully explored due to the time constraints involved in the construction of this article, as it is part of an undergraduate thesis.

We conclude that the detailed characterization of the molecular interactions of SCs is a fundamental step to mitigate their risks and enhance advances in safer and more effective therapeutic strategies. This work contributes to the advancement of understanding the impact of SCs on public health and reinforces the need for continuous monitoring of these substances in a global context.

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