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Cannabinoids: an exploratory review

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Abstract
Since 2000, the synthetic cannabinoids drug market is in a continuous expansion and development. Unfortunately, addictive trends include not only the adult population but also adolescents. The new synthetic cannabinoids compounds have similar effects as the *Cannabis* plant, but are more potent and present a higher risk for consumers. Globally, the fight against drug production, distribution and use involves several directions, including the development of new analytical tools able to identify these new illicit substances. The aim of this paper is to present a systematic review regarding the class of cannabinoids in terms of their physico-chemical properties and biological effects.

Keywords: cannabinoids, natural and synthetic drugs, WIN 55212-2, CP 55940.

1. INTRODUCTION

Adolescent addictions, usually start from the recreational use of nicotine, alcohol and / or caffeine during parties or leisure time spent with friends. *Cannabis* and its alternatives (natural and synthetic cannabinoids) are the most attractive because of their controversial features: legal vs. illegal, safe vs. risky, etc.

Initially, these compounds were designed for medical purposes. However, most of them soon became controlled substances, due to their negative psychoactive effect. Various toxicological and clinical studies have shown that they have a high toxicity and generate addiction. Nevertheless, the illicit laboratories keep producing new synthetic cannabinoids with increased psychoactive potency, some of them having a potency almost two hundred times more than Δ^9THC, i.e. the primary natural psychoactive substance identified in *Cannabis*. Therefore, it is necessary to identify and detect new hallucinogens based on their properties by using different methods such as spectral ones. In this regard, the aim of this paper is to summarize information about the cannabinoids types, as well as their physico-chemical properties and biological effects.

2. MATERIALS AND METHODS

Cannabis refers to psychoactive compounds obtained from *Cannabis sativa* or *Cannabis indica*. These drugs are found under the names of *marijuana* or *hashish* and are extracted from *Cannabis* leaves or resin.

Natural cannabinoids are terpenphenolic compounds extracted from *Cannabis* flowers and leaves resins. Until now, over one hundred phytocannabinoids have been documented, the most psychoactive being Δ^9 THC [1].

Synthetic cannabinoids have similar psychoactive effects as their natural counterparts. The cannabinoids effects on human body are probably due to stimulation of a protein membrane named receptor. So far, two receptors, i.e. CB1 and CB2, were discovered and entirely characterized [2]. The stimulation of the CB1 receptor, which is located in the cells of the central nervous system, affects memory, perception and mobility [2]. The stimulation of CB2, located in the cells of the immune system, explains the immunosuppressive effects [2].

The synthetic cannabinoids are divided into seven main groups, as illustrated in Table 1.

Table 1. Groups of synthetic cannabinoids [3]

Crt. No.	**Group**	**Examples of individual cannabinoids**
1.	naphthoylindoles	JWH-018 JWH-073 JWH-398 JWH -081 AM-1221
2.	naphthoylpyrroles	JWH-030, JWH-147 JWH-370
3.	phenylacetylindoles	JWH-250
4.	naphthylmethylindoles	JWH-184
5.	naphthylmethylindenes	AM-2201
6.	cyclohexylphenols	CP-47,497 Homologues CP-47–498 CP 55940
7.	classical cannabioids	HU -210

The molecular structure of synthetic cannabinoids is different from that of the natural ones. They are insoluble in water, highly lipophilic and highly volatile. They are soluble in solvents such as acetone, ethanol or aliphatic alcohols [4].

One of the first synthetic cannabinoids sold on the black market were CP-47, CP-497 and JWH-018. Later, cannabinoids from a wider group, aminoalkylindoles [4], were seized. They are sold as an white or yellowish crystalline powder that has no smell [4].

In order to analyze some physical and chemical properties, five cannabinoid compounds were compared with THC. Relevant data about the molecular structure and properties were obtained by accessing online chemical databases, such as PubChem and Chemspider. The molecular structures for THC and five synthetic cannabinoids were downloaded from the PubCheme database. Figure 1 shows the 3D structures of the selected compounds that were drawn and optimized with the *ACD/ Chem Sketch* software.

The comparison between molecular descriptors was made by using the *alvaMolecule*, *admetSAR* and *PROTOX* software applications. The results are presented in the following figures and tables.

3. RESULTS AND DISCUSSION

First, the targeted compounds have been characterized by computing their total molecular weight with the help of the *alvaMolecule* software. The results, presented in Figure 2, indicate that the synthetic cannabinoids have all a higher total molecular weight than their natural counterpart (THC).

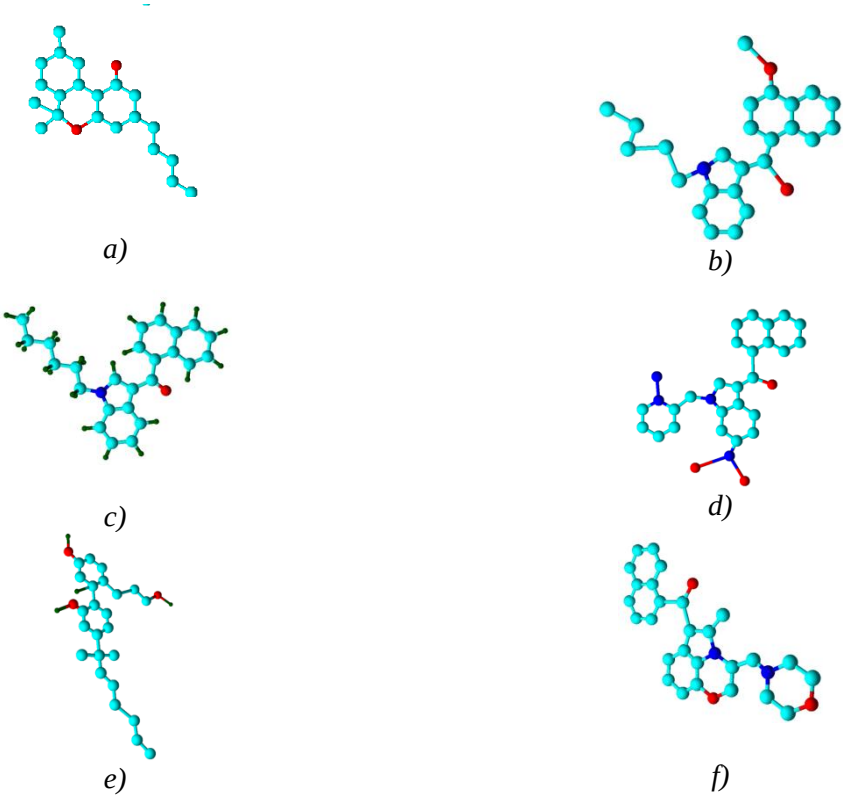


Fig. 1. 3D molecular structure of: a) THC; b) JWH-081; c) JWH-019; d) JWH-307; e) CP-55940; f) WIN 55212-2

Fig. 2. Total molecular weight of selected synthetic cannabinoids, as determined by using the alvaMolecule software

Another important property of the synthetic cannabinoids indicates how well they may be absorbed by the human body. This property may be evaluated by assessing their hydrophilicity with the logP parameter, which was determined for the targeted cannabinoids with the *ACD/ChemSketch* software. The logP parameter is inversely proportional to permeability or absorption, meaning that high values of logP correspond to low absorption [3]. The Moriguchi octanol-water partition coefficient (MlogP) for the same compounds were also determined with the *alvaMolecule* software, while the values of LogP were computed by using the *PROTOX* software. The results are displayed in Table 2. The data computed shows that two compounds, WIN 55212-2 and CP-55940, have lower values for logP than THC, so they have a better absorption than THC - the natural cannabinoid.

Table 2. MlogP and LogP values of selected synthetic cannabinoids.

LogP DESCRIPTORS			
Crt. No.	**Compound identifier**	**MLogP**	**LogP**
01	THC	4.5	5.74
02	JWH-081	4.7	6.22
03	JWH-019	5.26	6.61
04	JWH-307	5.64	6.87
05	CP-55940	4.13	5.66
06	WIN 55212-2	3.11	4.54

Another physico-chemical property linked to hydrophilicity is the solubility in water or aqueous solubility. We have determined these data, presented in Table 3, by using the *admetSAR* application, which is a free online tool predicting drug properties. The results indicate that only WIN 55212-2 has a better aqueous solubility than the natural cannabinoid, the rest of the analyzed compounds having comparable values of approximately -4.

Table 3. Aqueous solubility (LogS), Caco-2 permeability (LogPapp, [cm/s]) and Blood-Brain Barrier (BBB+) values of selected synthetic cannabinoids.

AQUEOUS SOLUBILITY (LOGS) AND CACO-2 PERMEABILITY (LOGPAPP, [CM/S])				
Crt. No.	**Compound identifier**	**Aqueous solubility**	**CACO-2 permeability**	**BBB+ (Probability)**
01	THC	-4.3219	1.7903	0.9685
02	JWH-081	-3.6207	1.3397	0.9968
03	JWH-019	-3.7983	1.1806	0.9932
04	JWH-307	-4.1299	1.2113	0.9864
05	CP-55940	-4.4033	1.2401	0.6874
06	WIN 55212-2	-2.8910	1.1618	0.9592

Another descriptor is CACO-2, a descriptor based on the LogPapp value that models how human intestine absorbs the drugs. Table 3 shows that the largest CACO-2 value is obtained for the natural compound THC.

BBB+ is a descriptor that indicates the probability with which the drug may pass through Blood-Brain Barrier. The larger this probability, the more toxic for the brain the compound is. In our case, the larger values were obtained for the JWH- cannabinoids, followed by WIN 55212-2. The smallest BBB+ value was recorded for the CP 55940 synthetic cannabinoid.

To evaluate the gastrointestinal absorption and the BBB+ based on the position of the molecules, we have used the *Boiled Egg* method developed by A. Daina and V. Zoete [5]. The results, obtained with the *SwissADME* free software [5], are displayed in Figure 3. The yellow area (yolk) corresponds to a high probability of passing through brain barrier and the white area to a high probability to be passively absorbed by the gastrointestinal system [5]. The JWH-307 and JWH-019 synthetic cannabinoids are outside the *Boiled Egg* (grey area). In the same time, THC and the WIN 55212-2 synthetic cannabinoid have a high probability of passing the brain barrier.

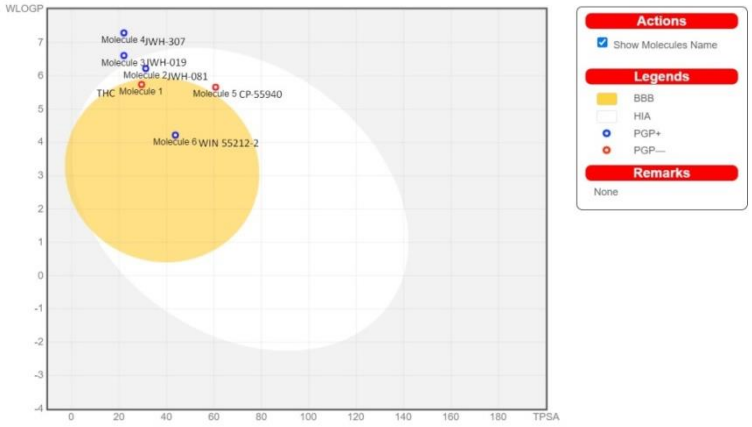
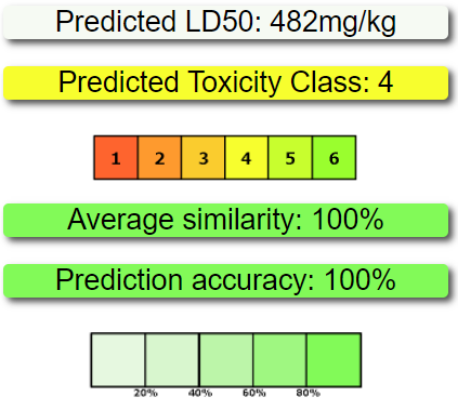


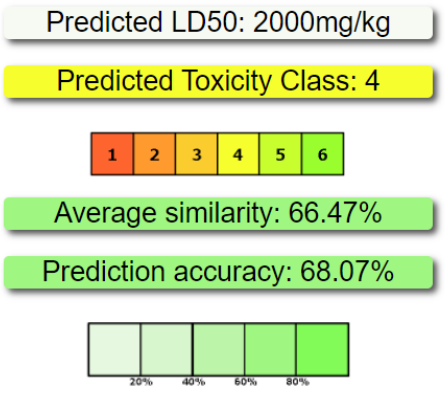
Fig. 3. BOILED Egg diagram evaluating the gastrointestinal absorption and the BBB penetration of selected synthetic cannabinoids

The oral toxicity was predicted for all five synthetic compounds and THC by using the *PROTOX* computer application (see Figure 4). This software, linked to the *PubChem* database, performs the calculations according to the compound name or the canonical SMILE.



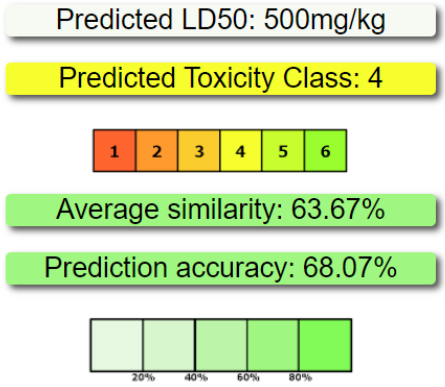
Name	THC
Molweight	314.46
Number of hydrogen bond acceptors	32
Number of hydrogen bond donors	1
Number of atoms	53
Number of bonds	55
Number of rotable bonds	4
Molecular refractivity	97.91
Topological Polar Surface Area	29.46
octanol/water partition coefficient(logP)	5.74

a)



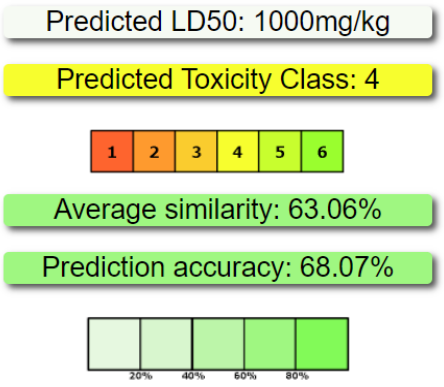
Name	JWH-081
Molweight	371.47
Number of hydrogen bond acceptors	27
Number of hydrogen bond donors	0
Number of atoms	53
Number of bonds	56
Number of rotable bonds	7
Molecular refractivity	116.3
Topological Polar Surface Area	31.23
octanol/water partition coefficient(logP)	6.22

b)



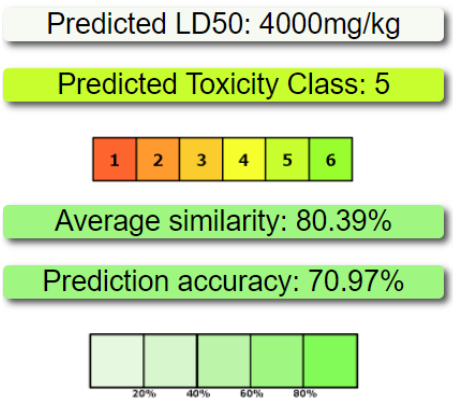
Name	JWH-019
Molweight	355.47
Number of hydrogen bond acceptors	26
Number of hydrogen bond donors	0
Number of atoms	52
Number of bonds	55
Number of rotable bonds	7
Molecular refractivity	114.62
Topological Polar Surface Area	22
octanol/water partition coefficient(logP)	6.61

c)



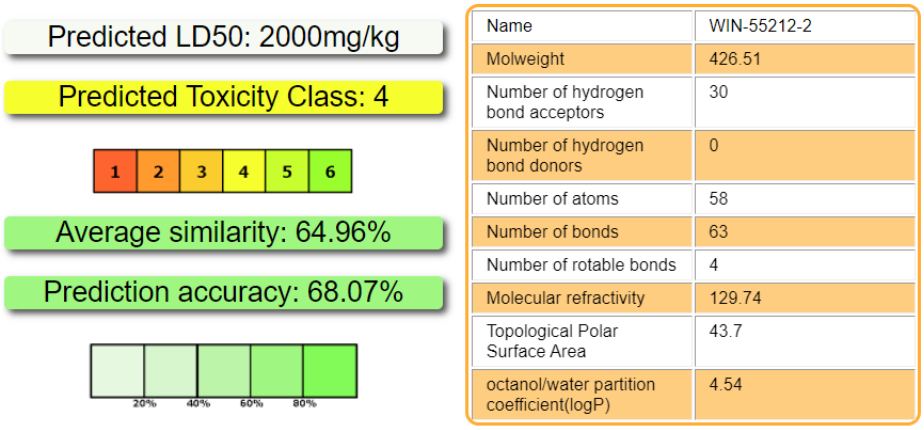
Name	JWH-307
Molweight	385.47
Number of hydrogen bond acceptors	25
Number of hydrogen bond donors	0
Number of atoms	53
Number of bonds	56
Number of rotable bonds	7
Molecular refractivity	117.7
Topological Polar Surface Area	22
octanol/water partition coefficient(logP)	6.87

d)



Name	CP 55940
Molweight	376.57
Number of hydrogen bond acceptors	43
Number of hydrogen bond donors	3
Number of atoms	67
Number of bonds	68
Number of rotable bonds	10
Molecular refractivity	115.4
Topological Polar Surface Area	60.69
octanol/water partition coefficient(logP)	5.66

e)



f)

Fig. 4. Oral toxicity prediction for: a) THC; b) JWH-081; c) JWH-019; d) JWH-307; e) CP-55940; f) WIN 55212-2

As pointed out by the results displayed in Figure 4, all the analyzed compounds belong to the toxicity class 4, with the exception of CP 55940, which belongs to the toxicity class 5. The nearest LD 50 (parameter that measures rat acute toxicity) to the THC was obtained for JWH-019.

Supplementary predictions for the toxicity of these compounds was obtained running the PROTOX computer application. The results regarding the status of active or inactive in terms of the immunotoxicity, mutagenicity, cytotoxicity of the targeted controlled substances are illustrated in Table 4.

Table 4. Predicted toxicity in terms of the immunotoxicity, mutagenicity, cytotoxicity of the targeted controlled substances

PREDICTION FOR TOXICITY				
Crt. No.	**Compound identifier**	**Immunotoxicity**	**Mutagenicity**	**Cytotoxicity**
01	THC	Active	Inactive	Inactive
02	JWH-081	Active	Active	Inactive
03	JWH-019	Active	Active	Inactive
04	JWH-307	Active	Active	Inactive
05	CP-55940	Active	Inactive	Inactive
06	WIN 55212-2	Inactive	Inactive	Inactive

The best absorption of THC is done by the respiratory system of human body. The compound is slowly eliminated, due to a lower liposolubility [2]. The potency, dose and chemical compositions of the cannabinoids may influence the psychoactive and physiological effects on a consumer. The consumer may experience hallucinations, distorted perception of objects or negative emotions, such as fear, suspicion [6]. The side effects of long-term use of psychoactive substances are: psychotic disorders similar to schizophrenia, memory disorders, lung diseases, immune system disorder, endocrine system disorder and new-born malformations [2].

4. CONCLUSIONS

Quantitative indicators of the absorption and toxicity of the five synthetic cannabinoids were computed and compared with those corresponding to THC. The results confirm that the synthetic cannabinoids compounds have effects similar to the extract of the *Cannabis* plant, but are more potent

and present higher risks for consumers. All the analyzed compounds have an important affinity for the CB1 receptor, except for WIN 55212-2, which has affinity for the CB2 receptor. The data obtained suggest an increased toxicity, as indicated by the human intestinal absorption and the probability of passing through the brain protective barrier [7].

The toxicity information determined in this paper will be further used for building quantitative structure-activity relationships (QSAR) and multivariate correlations with spectral data obtained with the methods recommended for characterizing these controlled substances, i.e. GC-IR, GC-FTIR, ATR-FTIR or RAMAN spectroscopy [8].

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