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SHORT COMMUNICATION

The mystery behind the apprehensions of the selective cannabinoid receptor type-2 agonist BZO-HEXOXIZID (MDA-19) as a drug of abuse

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Abstract

Purpose MDA-19 or BZO-HEXOXIZID (*N*′-[(3Z)-1-(1-hexyl)-2-oxo-1,2-dihydro-3H-indol-3-ylidene]-benzohydrazide), in a more recent nomenclature, was first synthesized in 2008 as a selective type-2 cannabinoid receptor (CB2) agonist due to its potential to treat neuropathic pain. In Brazil, this substance was identified in a series of 53 apprehensions between September 2021 and February 2022. Nevertheless, what intrigues toxicologists is that BZO-HEXOXIZID does not exert significant type-1 cannabinoid receptor (CB1) agonism—which is responsible for the well-known psychoactivity of Δ-9-tetrahydrocannabinol. Thus, the objective of this work is to report the first apprehension and identification of BZO-HEXOXIZID in Brazil and to discuss pharmacologically the possible reasons why a CB2 agonist has been incorporated to the illicit market.

Methods Suspected seized samples were sent to the Laboratory of the Scientific Police of the State of Sao Paulo. After the screening, samples were confirmed for the presence of BZO-HEXOXIZID using chromatography gas—mass spectrometry, Fourier-transform infrared spectroscopy and nuclear magnetic resonance techniques.

Results Of the 53 samples analyzed, 25 contained only BZO-HEXOXIZID and 28 with mixtures, of which 11 with the CB1 agonist ADB-BUTINACA. Other substances were found in association such as cocaine and caffeine.

Conclusions BZO-HEXOXIZID was detected in a series of seized materials for the first time in Brazil. Nevertheless, there are still unanswered questions regarding the use of this selective CB2 agonist as a drug of abuse.

Keywords BZO-HEXOXIZID · New psychoactive substances · Synthetic cannabinoid receptor agonists · Synthetic cannabinoids

Introduction

First synthesized in 2008 by Diaz and colleagues as a selective type-2 cannabinoid receptor (CB2), MDA-19 (*N*′-[(3-Z)-1-(1-hexyl)-2-oxo-1,2-dihydro-3H-indol-3-ylidene]-benzohydrazide), or BZO-HEXOXIZID, in a more recent nomenclature, was targeted as a potential treatment for neuropathic pain [1]. Thereafter, several researches have been conducted and promising results were published evidencing the therapeutic potential of this compound in different clinical conditions, such as melanoma, osteosarcoma, neurodegenerative disorders, and hepatocellular carcinoma [2–5]. Notwithstanding this potential as a medicine, BZO-HEXOXIZID was unexpectedly apprehended by law enforcement in Spain and Germany a few years later, in 2016 [6, 7]. Furthermore, this substance was prohibited in China in July 2021, while this compound was seized by police officers for the first time more recently in the United States [8].

The emergence of BZO-HEXOXIZID in the illicit drug market is not an isolated event. This approach of exploring new molecules as recreational drugs has been a trend since the early 2000s with the rise of the new psychoactive

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substances (NPS). Several other compounds with a range of psychoactive effects, such as benzodiazepines, opioids, amphetamines, cannabinoids, and piperazines, were designed for therapeutic applications or research purposes in the past, but now their use has followed this same unfortunate fate [9]. An example is HU-210, first synthesized in 1988 to investigate its activity on the type-1 cannabinoid receptor (CB1) with the intent of developing new therapeutics to cardiovascular, neurodegenerative, and intestinal disorders, among others [9, 10].

Up to date, 1124 NPS have been reported to the United Nations Office on Drugs and Crime (UNODC) until December 2021, thus posing a serious threat to law enforcement and healthcare professionals [11]. These new drugs are classified into different groups and one of the most popular is the so-called synthetic cannabinoid receptor agonists (SCRAs) or simply synthetic cannabinoids. In contrast to classic cannabinoids or phytocannabinoids—as those are naturally found in *Cannabis* sp. plants, mainly Δ^9-tetrahydrocannabinol (THC)—SCRAs have more extensive and severe toxicities, e.g., arrhythmia, seizures, hyperthermia, excited delirium syndrome, and even death, which has never been associated with the isolated use of THC [12]. Furthermore, an increase in reports of cannabis adulterated with synthetic cannabinoids—6500 of the 18,700 seizures in the European Union Member States in 2019, and 200 of the 900 kg seized—have been concerning legal authorities given the potency and percentage of deaths related to these adulterations [13].

Considering the massive number of SCRAs reported so far and the variety within these molecules, they are divided into main classes according to their chemical structures and subclasses due to slight changes in these established chemical backbones. The overall agonists of CB1 and CB2 can be divided as such: classic cannabinoids, non-classical cannabinoids, hybrid cannabinoids, aminoalkylindoles, and aminoalkylindazoles. Furthermore, aminoalkylindoles can be further divided into naphthoylindoles, phenylacetylindoles, benzoylindoles, naphthylmethylindoles, cyclopropoylindoles, adamantoylindoles, indole carboxamides, and indole carboxylates; on the other hand, aminoalkylindazoles are divided into naphthoylindazoles and indazole carboxamides [14]. Figure 1 illustrates the main classification of SCRAs groups. Curiously, BZO-HEXOXIZID does not fit into either of these previously established subclasses due to its chemical particularities. In contrast to other synthetic cannabinoids, BZO-HEXOXIZID has a core/linker region

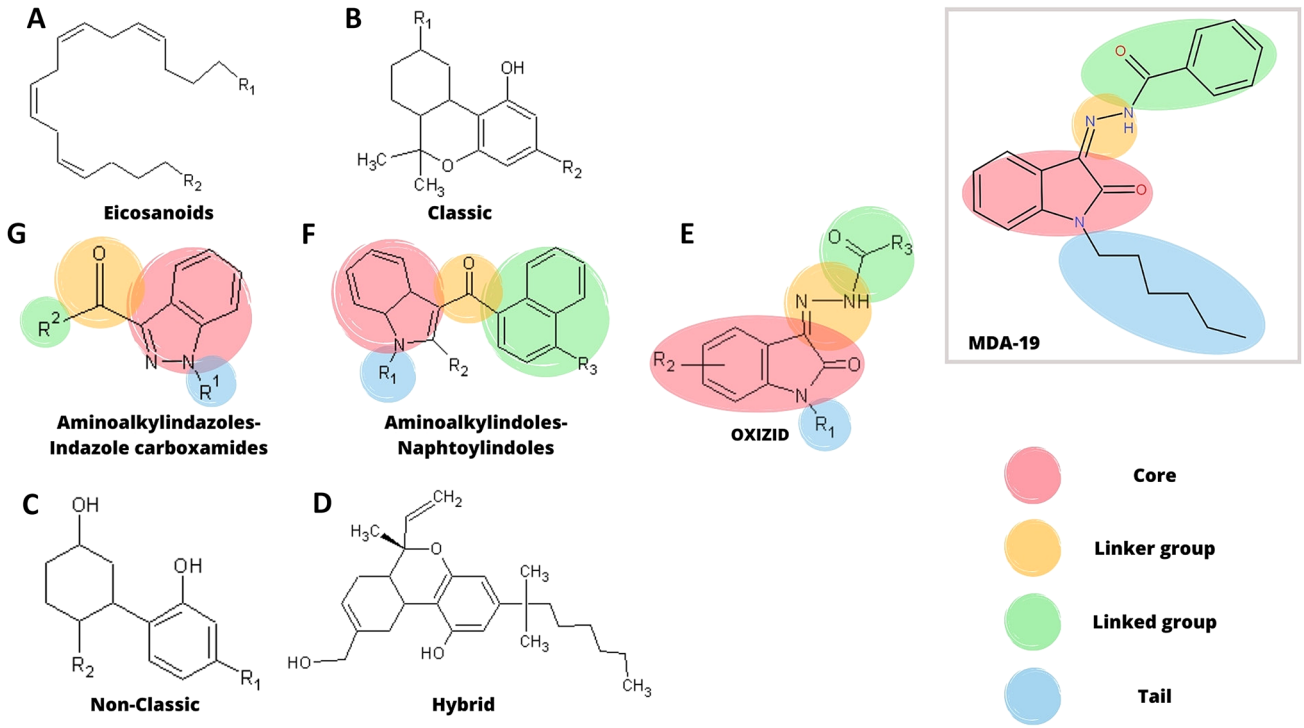


Fig. 1 Illustration of the basic chemical backbone of endocannabinoids, phytocannabinoids, and synthetic cannabinoids. Eicosanoids are the major group of endocannabinoids (**A**). Those SCRAs closely related to the structure of THC, the main phytocannabinoid, are named classic cannabinoids (**B**). Non-classic cannabinoids are referred to those molecules that still possess major similarity to THC, however, considerable modifications are present (**C**). Hybrid cannabinoids have combinations of structural features of both classical and non-classical cannabinoids in their chemical structure (**D**). OXIZIDIs are a new class with an unusual core and activity in CB_2R (**E**). Aminoalkylindoles can be further divided into up to eight subgroups [14] (**F**). Aminoalkylindazoles is another class that can be further divided into subgroups according to Tettey, Justice NA, and colleagues (**G**)

named OXIZID; this type of core is unusual in other synthetic cannabinoids; nonetheless, the tail and a head moiety of the molecule are quite similar to others SCRAs illustrated in Fig. 1 [15]. With that in mind, a major impact of this chemical particularity of BZO-HEXOXIZID in comparison to other SCRAs is that it circumvents legislations–one of the main goals of NPS. Thus, the creation and proper classification of a new subclass of SCRAs are required to encompass these new designer drugs as well as pave the way allowing legal countermeasures to be established.

Recently, the Center for Forensic Science Research and Education (CFSRE) has proposed a new nomenclature for this compound due to misleading interpretations, as the 'MDA' abbreviation is also used for methylenedioxyamphetamine. This classification was stipulated regarding the chemical backbone, being defined as OXIZID. Hence, under this novel nomenclature, this substance would be classified as (Z)-*N*′-(1-hexyl-2-oxoindolin-3-ylidene)benzohydrazide (BZO-HEXOXIZID) and no more as MDA-19 [15]. Considering the history of BZO-HEXOXIZID as a promising candidate for therapeutic applications that ended up being introduced into the illicit drug market, we herein describe the first series of apprehensions of this compound in cellulose paper fragments and herbal materials in Brazil followed by its identification and characterization by the Scientific Police of the State of Sao Paulo. Also, based on these apprehensions and correlating with previous ones in different countries, we will address the intriguing matter of why a selective CB2 agonist with almost no effect on CB1 would be explored as a drug of abuse.

Materials and methods

Fifty-three samples (blotter papers and herbal fragments) were seized by the Sao Paulo State Police, between September 2021 and February 2022, and analyzed by the Seized Drugs Analysis Laboratory of the Scientific Police of the State of Sao Paulo. Cases were first screened using a validated thin-layer chromatography (TLC), a method commonly employed for the provisional finding of cannabis in plant samples in our lab, which consists of using toluene:chloroform (7:3) as mobile phase, Macherey–nagel pre-coated TLC sheets ALIGRAM Xtra SIL G, layer 0.20 mm silica gel 60 and it is revealed through the spraying of a fast blue solution; for further confirmation, liquid chromatography–mass spectrometry (LC–MS/MS) and attenuated total reflection–Fourier-transform infrared spectroscopy (ATR-FTIR), it is used according to laboratories standard operational procedures and the Scientific Working Group for the Analysis of Seized Drugs (SWGDRUG) recommendations.

Preparation of BZO-HEXOXIZID extracts

BZO-HEXOXIZID extracts were obtained from the yellow powders of seized blotter paper samples. An aliquot of approximately 0.010 g the matrix was added into 15 mL conical centrifuge tubes (Falcon tubes) together with 3.00 ± 0.01 mL of HPLC-grade methanol (Merck KGaA, Darmstadt). This solution was vortexed in an Eppendorf Thermomixer under constant stirring at 76 g at room temperature for 15 min. After this time, the solution was centrifuged at 2150 g for 1 min.

LC–MS/MS analysis

Analyses of electrospray ionization mass spectrometry (ESI–MS) were performed on a Nexera 40D XS ultra-high-performance liquid chromatography system coupled to an LCMS8045 triple quadrupole mass spectrometer (MS) (Shimadzu, Kyoto, Japan). The mobile phase A consisted of ultrapure water and B of HPLC-grade methanol, both containing formic acid (0.002%, v/v) and ammonium formate (2 mmol/L), with flow rate of 0.3 mL/min in isocratic mode (50:50, v/v). The ESI–MS operated in positive mode and with interface temperature set at 300 °C, desolvation temperature at 526 °C, heat block temperature at 400 °C, drying gas (N_2) flow at 10 L/min, heating gas flow (air) at 10 L/min, nebulizing gas (N_2) flow at 2 L/min, and collision gas (Ar) was set to 230 kPa. The MS was set to acquire full scan spectra (from *m/z* 150–500) and product ion scan (from *m/z* 40–500) of the precursor ion 350.4 [$(M + H)^+$] with collision energy ranging from 10 to 35 V. One microliter of diluted sample extract was injected into the system.

Attenuated total reflectance–Fourier-transform infrared spectroscopy

The ATR-FTIR spectrum was acquired in Drug Analysis Laboratory of the Scientific Police of the State of Sao Paulo using an Agilent Cary 630, Palo Alto, CA, USA, in absorbance mode, with spectral range from 4000 to 650 cm^{-1}, 2000 scans per sample, resolution 8 cm^{-1}, Happ-Genzel Apodization function and Zero Fill Factor of 2, with Micro-Lab Expert v.1.0.0.7 (Agilent) software Technologies, Inc.

In total, 53 samples were analyzed. Those that could not be analyzed directly through FTIR and/or nuclear magnetic resonance (^{1}H NMR, ^{13}C NMR, ^{1}H -^{13}C HSQC) were confirmed later, using the retention time and electron impact mass spectra obtained from the purified blotter paper samples.

Results

Out of the 53 samples analyzed in the present study, three were blotter papers and fifty were a mixture of herbal fragments; 25 (47.2%) contained only BZO-HEXOXIZID, whereas 28 (52.8%) were associated with other illicit substances. N-[(1S)-1-(aminocarbonyl)-2,2-dimethylpropyl]-1-butyl-1H-indazole-3-carboxamide (ADB-BUTINACA), caffeine, and cocaine were found associated with BZO-HEXOXIZID in 8 (36.4%), 5 (22.7%), and 9 (40.9%) of these samples, respectively, representing 22 cases. Cases containing two or more substances were also found, 6 in total: 2 (33.3%) were BZO-HEXOXIZID, cocaine and caffeine, and in one of each (16.6%), BZO-HEXOXIZID was associated with cocaine and sildenafil; ADB-BUTINACA, caffeine, and lidocaine; THC and ADB-BUTINACA; and THC, ADB-BUTINACA, and cocaine. A detailed information about the 53 apprehensions—other detected compounds, form of presentation and local of the apprehensions (cities)—is presented in Table 1.

Regarding the distribution of the drug in the State, of the total number of cases analyzed (53), the percentage seized in the Metropolitan Region of Sao Paulo represented 77.4% of the cases, while the coastal area 22.6%

LC–MS/MS analysis shows a base peak ion of *m/z* 350.3 (Fig. 2A). As for MS/MS spectra, the most representative spectrum was obtained in 35 V (Fig. 2B). Hence, as shown in Fig. 2, BZO-HEXOXIZID is characterized by $[M+H]^+$ *m/z* 350.4, and the main product ions generated are *m/z* 77.1 and 105.0.

To observe the vibrational modes of the functional groups, a Fourier-transform infrared spectrum was acquired and it is shown in Fig. 3. The wavenumbers, the vibrational modes, and the corresponding functional groups are available in supplementary material (Table S1).

Discussion

After BZO-HEXOXIZID was first detected in Brazil by the Seized Drugs Analysis Laboratory of the Scientific Police of the State of Sao Paulo, the agency responsible for monitoring and legislating on illicit activities for psychoactive substances was notified and the compound, along with 5C-MDA-19 (BZO-POXIZID) and 5F-MDA-19 (5F-BZO-POXIZID) is currently banned in the F2 list of the National Health Surveillance Agency (ANVISA) ordinance 344/98 [16]. Furthermore, a useful countermeasure to NPS used in Brazil is the generic approach—a substance is considered illegal when it fits a generic chemical backbone. This strategy has been particularly effective to deal with NPS; nevertheless, the chemical particularities of BZO-HEXOXIZID circumvent it from such legal measures, as it differs from the pre-established structures that are already controlled, which made it necessary to directly include the substance nominally in the legislation.

The reasons why BZO-HEXOXIZID was found both isolated and mixed with other SCRAs, especially CB1 agonists, remains unclear considering studies that demonstrate CB2 activation does not exert psychoactive effects, unlike the stimulation of CB1 [17]. In fact, BZO-HEXOXIZID was designed and synthesized by Diaz and colleagues as a selective CB2 agonist to be used in clinical models in which this receptor is involved, such as neurodegenerative and immune disorders [1]. Furthermore, it was observed that CB2 is expressed at low levels in healthy physiological conditions; however, in some disorders, such as neuropathic pain, stroke, neurodegenerative diseases, or drug addiction, this receptor can be quickly up-regulated and become widely expressed in the brain [18]. Moreover, functional CB2 is constitutively expressed in dopaminergic neurons of the ventral tegmental area (VTA) that play important roles in the reward system [19]. In this context, Chen et al. showed that the activation of CB2 in VTA of mice reduces neuronal excitability and drug-seeking behavior, however, no reports of antagonism or decreased effects of cocaine were found. In addition, CB2 activation leads to inhibition of postsynaptic neurons of other pathways in the brain, suggesting modulation of a variety of dopamine-associated behaviors, such as food intake, body weight, depression, anxiety, drug craving, and schizophrenia-like states [18]. Altogether, these findings show antagonistic effects between CB1 and CB2 signaling, intriguing toxicologists as to why a potent CB2 agonist, such as BZO-HEXOXIZID, with low CB1 activity would be explored as a drug of abuse. To aid that understanding, we have reviewed pharmacological studies carried out with BZO-HEXOXIZID.

Briefly, BZO-HEXOXIZID has emerged in a 2008 study of a new series of isatins where it was one of several compounds synthesized; however, it differs from the others due to its high potency toward CB2 and almost insignificant potency to CB1 [1]. Interestingly, these properties also differ BZO-HEXOXIZID from other known CB2 agonists, such as 4-[4-(1,1-dimethylheptyl)-2,6-dimethoxyphenyl]-6,6-dimethyl-bicyclo[3.1.1]hept-2-ene-2-methanol (HU-308), (2-iodo-5-nitrophenyl)-(1-(1-methylpiperidin-2-ylmethyl)-1H-indol-3-yl)methanone (AM1241), (1-pentyl-1H-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)-methanone (UR-144), and 3-(1,1-dimethylbutyl)-6aR,7,10,10aR-tetrahydro-6,6,9-trimethyl-6H-dibenzo[b,d]pyran (JWH-133), that even though producing significative agonistic effects, also have moderate potency toward CB1. Furthermore, studies show that the main SCRAs abused as drugs present inhibitory constant (Ki) values—a pharmacological parameter that

Table 1 Detailed information of the 53 apprehensions in which it was detected BZO-HEXOXIZID

Apprehensions	City	Form of presentation	Other detected substances
1	Barueri	Herbal fragments	–
2	Barueri	Herbal fragments	Cocaine
3	Barueri	Herbal fragments	Caffeine
4	Santo André	Herbal fragments	–
5	Barueri	Herbal fragments	Caffeine
6	Santos	Herbal fragments	Cocaine
7	Barueri	Herbal fragments	–
8	Santo André	Herbal fragments	Caffeine
9	Cubatão	Herbal fragments	Caffeine
10	São Vicente	Herbal fragments	–
11	Santo André	Herbal fragments	–
12	Mongaguá	Herbal fragments	Cocaine
13	Praia Grande	Herbal fragments	Cocaine
14	Praia Grande	Herbal fragments	Cocaine
15	Praia Grande	Herbal fragments	Cocaine
16	São Vicente	Herbal fragments	Cocaine and Sildenafil
17	Santos	Herbal fragments	Cocaine and caffeine
18	Cubatão	Herbal fragments	Cocaine and caffeine
19	Praia Grande	Herbal fragments	–
20	Praia Grande	Herbal fragments	ADB-BUTINACA, caffeine and lidocaine
21	São Paulo	Herbal fragments	–
22	São Paulo	Herbal fragments	ADB-BUTINACA
23	São Paulo	Herbal fragments	–
24	São Paulo	Herbal fragments	–
25	São Paulo	Herbal fragments	Caffeine
26	São Paulo	Herbal fragments	–
27	São Paulo	Herbal fragments	Cocaine
28	Franco da rocha	Blotter papers	–
29	Guarulhos	Blotter papers	–
30	São Paulo	Herbal fragments	–
31	Franco da Rocha	Blotter papers	ADB-BUTINACA
32	São Paulo	Herbal fragments	–
33	São Paulo	Herbal fragments	–
34	São Paulo	Herbal fragments	–
35	São Paulo	Herbal fragments	–
36	São Paulo	Herbal fragments	THC and ADB-BUTINACA
37	São Paulo	Herbal fragments	THC, Cocaine and ADB-BUTINACA
38	Cajamar	Herbal fragments	–
39	Cajamar	Herbal fragments	ADB-BUTINACA
40	Cajamar	Herbal fragments	–
41	Cajamar	Herbal fragments	–
42	Cajamar	Herbal fragments	–
43	Cajamar	Herbal fragments	ADB-BUTINACA
44	Cajamar	Herbal fragments	–
45	Cajamar	Herbal fragments	
46	Cajamar	Herbal fragments	ADB-BUTINACA
47	Cajamar	Herbal fragments	Cocaine
48	Cajamar	Herbal fragments	–
49	Cajamar	Herbal fragments	–
50	Cajamar	Herbal fragments	Cocaine

Table 1 (continued)

Apprehensions	City	Form of presentation	Other detected substances
51	Cajamar	Herbal fragments	ADB-BUTINACA
52	Cajamar	Herbal fragments	ADB-BUTINACA
53	Cajamar	Herbal fragments	ADB-BUTINACA

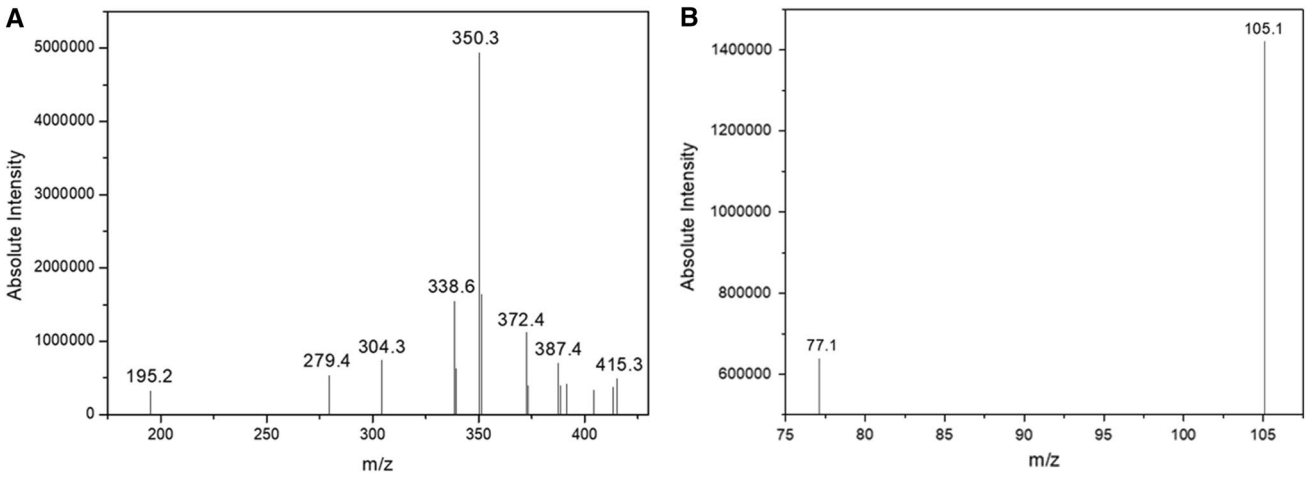
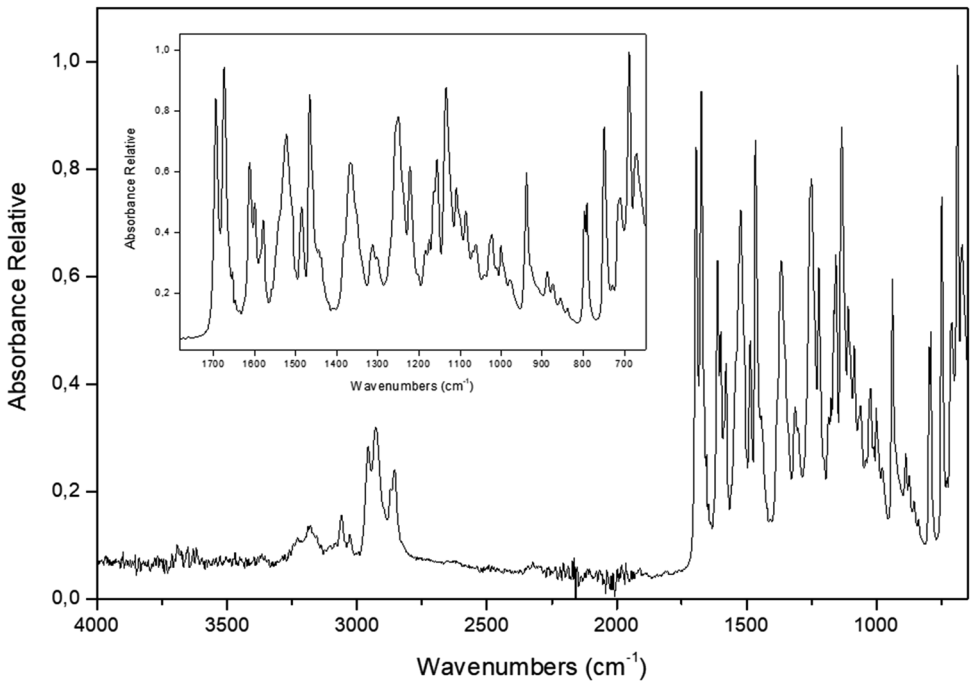


Fig. 2 Full scan acquisition in positive ESI–MS mode showing the base peak of BZO-HEXOXIZID as *m/z* 350.4 (**A**). MS/MS analysis of BZO-HEXOXIZID shows *m/z* 77.1 and 105.0 as the product ions (**B**)

Fig. 3 FTIR spectrum of BZO-HEXOXIZID



indicates the binding affinity of a compound to a receptor—in the range of 1 to 10 nM and 10–100 nM for both CB1 and CB2, parametes that which was used as a comparison in (Table 2) between UR-144, JWH-015, ADB-BUTINACA, BZO-HEXOXIZID and THC [12, 20, 21]. For example, JWH-015 and UR-144 are both potent CB2 agonists with low CB1 activity (Ki > 10 nM) [12, 22]. With that in mind, when comparing with data of in vitro studies published by

Table 2 Comparison between of the pharmacological parameters of some SCRAs and THC

Substance	Ki (CB1)/nM	Ki (CB2)/nM	EC50 CB1 (nM)	EC50 CB2 (nM)	Emax CB_1R (%)	Emax CB_2R (%)	Reference
UR-144	29.0	4.50	98.0	334	–	–	[12, 25]
JWH-015	336	13.8	1100	46.0	94.0	96.0	[12, 22]
BZO-HEXOXIZID[a]	162	43.3	922	83.0	64.5	65.4	[23]
ADB-BUTINACA	0.30[b]	0.91[b]	0.67[c]	4.10[c]	113[c]	101[c]	[26]
THC	41.0	36.0	77.5	12.3	126	52.0	[27, 28]

CB1 cannabinoid receptor type-1, *CB2* cannabinoid receptor type-2, *EC50* 50% effective concentration, *Emax* maximum effect, *Ki* inhibitory constant, *THC* Δ-9-tetrahydrocannabinol

[a]In vitro assay comparing BZO-HEXOXIZID to SR141716A and CP55,940 marked with ^3H

[b]Competitive radio binding assay using radiolabeled CP55,940 and human CB1 and CB2 membrane preparations of HEK293 cells

[c]Cannabinoid functional activity was determined using a fluorescence-based membrane potential assay in transfected AtT20 cells expressing CB_1R or CB_2R with receptors activation normalized to 1 μM CP55,940

Xu and colleagues, BZO-HEXOXIZID showed Ki values of 162 nM and 43.3 nM for CB1 and CB2, respectively; thus, JWH-015 is considerably more selective toward CB2 over CB1 than BZO-HEXOXIZID [23]. Moreover, comparing the 50.0% effective concentration (EC50) and maximum effect (Emax)—two other pharmacological parameters—of both these SCRA allows further speculations. For instance, JWH-015 has the EC50 and Emax for CB2 of 46 nM and 96.0%, respectively, while those of BZO-HEXOXIZID are of 83.0 nM and 65.4%, respectively [23, 24]. On the other hand, as for CB1, these values are of 1100 nM and 94.0% for JWH-015 and 922 nM, and 64.5% for BZO-HEXOXIZID [23, 24]. Hence, these data altogether show that both these synthetic cannabinoids have similar pharmacological properties, albeit JWH-015 is more potent (46.0 vs. 83.0 nM) and exerts a higher maximum effect (96.0 vs. 65.4%) than BZO-HEXOXIZID.

Taking into consideration the available pharmacological data about these SCRAs, the question of why substances that do not exert relevant CB1 stimulation, albeit strongly affect CB2, would be used as SCRAs is missing. However, a plausible hypothesis that could aid the understanding is the attempt to mimic the overall effects achieved with the use of cannabis, which is caused by THC and other phytocannabinoids. It is known that cannabis consumption causes a mix of CB1 and CB2 pharmacological effects due to the presence of agonist and antagonist phytocannabinoids to both these receptors [29]. In that regard, THC, the main psychoactive phytocannabinoid, has Ki values of 41 nM for CB1 and 36.0 nM for CB2; EC50 of 77.5 ± 30.4 nM for CB1 and 12.3 ± 6.80 nM for CB2; and Emax of 126% for CB1 and 52.0% for CB2 [27, 28]. Thus, comparing these values with those of BZO-HEXOXIZID, it is evident that these are compounds that exert very distinct pharmacodynamics—especially regarding the main psychoactive effect caused by stimulation of CB1 by THC. In this context, the association of BZO-HEXOXIZID with other SCRAs to experience similar sensations yielded by cannabis intake would be reasonable. Indeed, ADB-BUTINACA, a potent CB1 and CB2 agonist, has been found associated with BZO-HEXOXIZID in 20.3% of those materials seized in Brazil (Table 1 and Table 2) [30]. Although a low percentage of the overall apprehensions, this CB1 agonist added to these mixtures could be for that purpose. Furthermore, one quarter of the herbal samples also contained cocaine, a phenomenon that has been on the rise in the State of Sao Paulo [31]. In addition, considering BZO-HEXOXIZID has an unusual core to other SCRAs, it is plausible that there are other relevant pharmacological pathways involved in its mechanism of action (with proteins, transporters, receptors, etc.). Thus, such interactions could result in different pharmacological effects additional to its known role with cannabinoid receptors as BZO-HEXOXIZID was found both isolated and in mixtures with ADB-BUTINACA–which is a potent agonist of both CB1 and CB2.

Finally, another role of CB2 agonists that could partially explain the use of BZO-HEXOXIZID as a drug of abuse is the induction of analgesia, as some antinociceptive effects of cannabinoids involve activation of the opioid system [32]. In this regard, some studies have demonstrated that the activation of CB2 stimulates the release of endorphins from keratinocytes inhibiting the nociception by binding to local neuronal μ-opioid receptors [32, 33]. Considering BZO-HEXOXIZID was found isolated in almost half of the apprehensions (47.2%), the effect resulting from the opioid system could be the reason for that. Furthermore, although this role of selective CB2 agonists is most likely only partially responsible for their use as means of obtaining numb sensations, it might also explain the apprehensions of BZO-HEXOXIZID associated with other SCRAs that exert significant CB1 agonistic effects—this strategy would attempt to mimic the effects achieved by marijuana consumption, as discussed earlier [34].

Conclusion

We herein have described the first apprehension followed by identification and characterization of BZO-HEXOXIZID in Brazil by the Scientific Police of the State of Sao Paulo. Different methodologies were employed to perform the structural elucidation of BZO-HEXOXIZID, the fragmentation spectra and exact mass by LC–MS/MS and data obtained by ATR-FTIR. We have also carried out a discussion to better understand the reasons why such a potent agonist of the CB2, which theoretically does not induce any psychoactive effect, would be used as a drug of abuse. Speculations go from its isolated use to induce analgesia states via interaction with opioid receptors or achieve any reward sensation by stimulation of the mesolimbic pathway to the associated use with other SCRAs that significantly stimulate the CB1 resulting in a cannabis-like effect. Anyhow, this new class of synthetic cannabinoids shows that NPS can still surprise skilled toxicologists, while the mystery behind selective CB2 agonists being explored in the illicit drug market has yet to be fully understood.

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Declarations

Conflict of interest The authors have no conflict of interest to declare.

Ethical approval This article does not contain any studies with human participants or animal performed by any of the authors.

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