



An Overview on Medicinal Chemistry of Synthetic and Natural Derivatives of Cannabidiol

Paula Morales¹, Patricia H. Reggio¹ and Nadine Jagerovic^{2*}

¹ Department of Chemistry and Biochemistry, University of North Carolina Greensboro, Greensboro, NC, United States,

² Instituto de Química Médica, Consejo Superior de Investigaciones Científicas, Unidad Asociada I+D+i al Instituto de Química Médica/Universidad Rey Juan Carlos, Madrid, Spain

OPEN ACCESS

Edited by:

Saoirse Elizabeth O'Sullivan,
University of Nottingham,
United Kingdom

Reviewed by:

Rajendra Karki,
St. Jude Children's Research
Hospital, United States
Andrea Vernall,
School of Pharmacy, University
of Otago, New Zealand

*Correspondence:

Nadine Jagerovic
nadine@iqm.csic.es

Specialty section:

This article was submitted to
Ethnopharmacology,
a section of the journal
Frontiers in Pharmacology

Received: 18 October 2016

Accepted: 14 June 2017

Published: 28 June 2017

Citation:

Morales P, Reggio PH and
Jagerovic N (2017) An Overview on
Medicinal Chemistry of Synthetic
and Natural Derivatives
of Cannabidiol.
Front. Pharmacol. 8:422.
doi: 10.3389/fphar.2017.00422

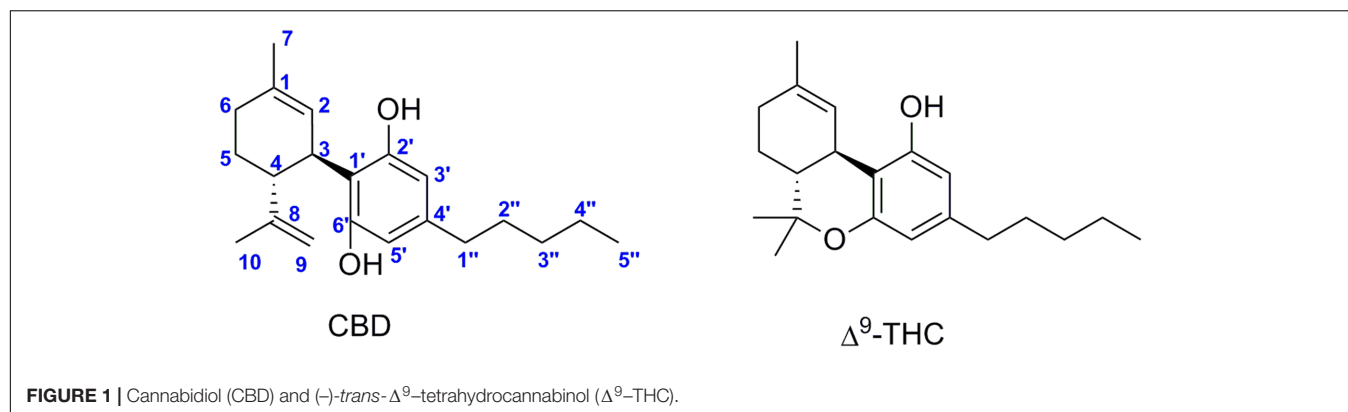
Cannabidiol (CBD) has been traditionally used in *Cannabis*-based preparation, however historically, it has received far less interest as a single drug than the other components of *Cannabis*. Currently, CBD generates considerable interest due to its beneficial neuroprotective, antiepileptic, anxiolytic, antipsychotic, and anti-inflammatory properties. Therefore, the CBD scaffold becomes of increasing interest for medicinal chemists. This review provides an overview of the chemical structure of natural and synthetic CBD derivatives including the molecular targets associated with these compounds. A clear identification of their biological targets has been shown to be still very challenging.

Keywords: cannabidiol, cannabidiol derivative, cannabinoid receptor, molecular target, therapeutic application

INTRODUCTION

In the mid-seventies, major efforts were focused on the identification of new natural cannabinoids isolated from preparations of *Cannabis sativa* and of other subspecies and varieties, such as *Cannabis indica* and *Cannabis ruderalis*. The two most abundant and most therapeutically relevant components of the plants are (-)-*trans*- Δ^9 -tetrahydrocannabinol (Δ^9 -THC) and (-)-cannabidiol (CBD) (**Figure 1**). Over these last two decades, the endocannabinoid system (ECS) related to the effects of *Cannabis sativa* has been emerging as target of pharmacotherapy showing very considerable physiological significance (Mechoulam et al., 2014). This system includes two cannabinoid receptors (CB₁ and CB₂) and endogenous ligands named endocannabinoids (Matsuda et al., 1990; Munro et al., 1993). CB₁ receptor is abundant in the brain, but to a less extent in peripheral tissues. CB₂ receptor is mainly expressed in immune cells.

Δ^9 -THC is responsible for the psychoactive effects of *Cannabis sativa* mediated by the activation of CB₁ receptor in the brain, whereas CBD is considered non-psychoactive. Currently, CBD is clinically used in association with Δ^9 -THC in a cannabis-based preparation (Sativex®) that contains equimolar content of both for managing neuropathic symptoms associated with multiple sclerosis (Fernandez, 2016). CBD as a single drug is currently generating considerable interest due to its beneficial neuroprotective (Fernandez-Ruiz et al., 2013; Scuderi et al., 2014; Ibeas Bih et al., 2015), antiepileptic (Devinsky et al., 2015; Wright et al., 2015), hypoxia-ischemia (Lafuente et al., 2011; Mori et al., 2017), anxiolytic (Massi et al., 2013; Schier et al., 2014), antipsychotic (Bhattacharyya et al., 2010), analgesic (Maione et al., 2011), anti-inflammatory (Ruiz-Valdepeñas et al., 2011; Burstein, 2015), anti-asthmatic (Ribeiro et al., 2015; Vuolo et al., 2015), and antitumor properties (McAllister et al., 2011; Massi et al., 2013) among others



(Mechoulam et al., 2007; Zhornitsky and Potvin, 2012; Renard et al., 2017; Watt and Karl, 2017). In 2016, GW pharmaceuticals reported the first positive results of CBD (Epidiolex[®]) in phase III clinical trials for treatment-resistant seizure disorders, including Lennox–Gastaut and Dravet syndromes. An overview of regulatory approvals and clinical trials of CBD has been recently published (Fasinu et al., 2016).

The molecular targets involved in the diverse therapeutic properties produced by CBD are still not very well-understood (Morales et al., 2017). Unlike Δ^9 -THC, CBD does not bind to the orthosteric binding site of the CB₁ and CB₂ cannabinoid receptors (McPartland et al., 2007). Despite this lack of orthosteric affinity, CBD has been shown to antagonize the effects of the CB₁/CB₂ agonists CP-55,940 and WIN55212 at the mouse CB₁ and at the human CB₂ receptors (Pertwee et al., 2002; Thomas et al., 2007). Therefore, allosteric activity of CBD at these receptors has been hypothesized. In a recent report, CBD was shown to be a negative allosteric modulator of Δ^9 -THC and the endogenous cannabinoid 2-AG providing a possible explanation for some *in vivo* CBD effects (Laprairie et al., 2015; Morales et al., 2016). CBD has also been shown to modulate endocannabinoid tone by inhibiting the cellular uptake of the endocannabinoid anandamide (Leweke et al., 2012). This effect has been attributed to the fact that CBD competes with anandamide for binding to fatty acid-binding proteins (FABPs) which are intracellular proteins involved in the transport of anandamide to its metabolic enzyme fatty acid amide hydrolase (FAAH) (Elmes et al., 2015). Other possible molecular targets of CBD have been explored. Modulation of the GPR55 receptor by CBD has been evaluated in different signaling pathway assays. CBD acts as an antagonist preventing [³⁵S]GTP γ S binding and Rho activation (Ryberg et al., 2007; Whyte et al., 2009; Ford et al., 2010), modulating Ca²⁺ mobilization (Lauckner et al., 2008) and β -arrestin recruitment (Yin et al., 2009). CBD has also been proposed as an antagonist of the GPR18 cannabinoid receptor (McHugh et al., 2012, 2014). Certain actions of CBD such as anti-inflammatory and immunosuppressive effects appear to be partially mediated through the serotonin and adenosine receptors that are not considered part of the ECS. For instance, CBD acts as a full 5-HT_{1A} agonist, 5-HT_{2A} weak partial agonist and a non-competitive 5HT_{3A} antagonist (Russo et al., 2005; Yang et al., 2010; Rock et al., 2012). The ability of CBD to activate

the A_{1A} adenosine receptor has also been proposed (Gonca and Darıcı, 2014). Other molecular targets have also been studied, among them, the PPAR γ nuclear receptors (O'Sullivan et al., 2009; Esposito et al., 2011; Scuderi et al., 2014), glycine receptors (Ahrens et al., 2009; Xiong et al., 2012), GABA_A receptors (Bakas et al., 2016), and transient receptor potential (TRP) channels (De Petrocellis et al., 2011, 2012). Studies focused on the possible epigenetic regulation of skin differentiation genes by CBD revealed that CBD is a transcriptional repressor that can control cell proliferation and differentiation through DNA methylation (Pucci et al., 2013). Despite all of this data, the mechanistic bases for the effects of CBD remain complex.

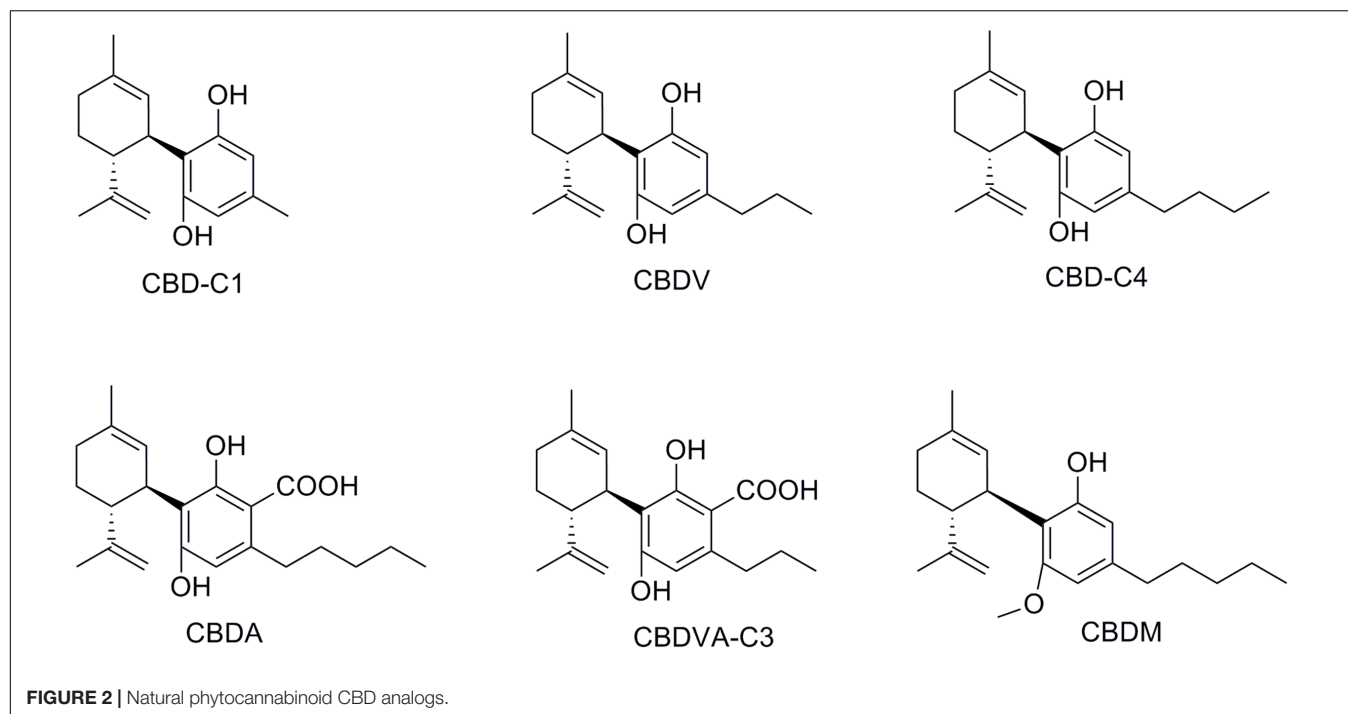
Cannabidiol constitutes one of the most important components of therapeutic interest from *Cannabis sativa*. However, unlike the numerous synthesized cannabimimetics generated to provide a synthetic alternative to THC, CBD derivatives have only been superficially explored. The purpose of this review is to provide a structural overlook at natural and synthetic CBD derivatives. Due to the fact that diverse molecular targets are involved in the therapeutic properties produced by CBD, we associated CBD structures to their biological targets. Thus, this review is intended to be a useful tool especially for medicinal chemists.

The basic structure of the CBD derivatives described in this review consists of 5-alkyl resorcinols substituted in position 2 by a propenylcyclohexene. Structural modifications on the alkyl side-chain, on the propenylcyclohexene, and substitution of the phenolic hydroxyl groups are concerned. Quinone CBD analogs are also included in this classification as far as their structures are closely related to CBD.

NATURAL CANNABIDIOL DERIVATIVES

In a recently published review dedicated to the diversity of cannabis phytocannabinoids, the authors updated the inventory of naturally occurring CBD derivatives (Hanuš et al., 2016). Herein, we are associating these structures to their possible molecular targets.

Of the over 100 natural cannabinoids identified in *Cannabis Sativa*, seven have been classified as CBD-type compounds including CBD (Figure 2) (ElSohly and Slade, 2005; ElSohly and



Gul, 2014; Aizpurua-Olaizola et al., 2016). All of them have the same absolute configuration than CBD; they are 5'-methyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-dioles retaining the *trans*-(1*R*,6*R*) configuration. Cannabidiolic acid (CBDA) and cannabidivarinic acid (CBDVA-C3) are C3'-carboxylic derivatives, whereas cannabidiol (CBD-C1), cannabidiol-C4 also named as *nor*-cannabidiol (CBD-C4), and cannabidivarin (CBDV) differ from CBD by the length of their C4'-side chain. Cannabidiol monomethyl ether (CBDM), the C6'-methoxy CBD analog, was also isolated from the plant. Despite the potential therapeutic interest of these naturally occurring CBD derivatives, only a few related pharmacological studies have been reported (Table 1). Like most non-steroidal anti-inflammatory drugs, CBDA is characterized by a carboxylic group resulting in a selective inhibition of cyclooxygenase-2 (Takeda et al., 2008). CBDA does not have effect on anandamide inactivation in FAAH assays (Inhibition of [¹⁴C]-anandamide uptake: IC₅₀ > 50 μM) contrary to CBD (IC₅₀ = 28 μM) (Bisogno et al., 2001; Ligresti, 2006). Other molecular targets proposed for CBDA include GPR55 (Anavi-Goffer et al., 2012) and TRPA1 with moderate activity (De Petrocellis et al., 2011). CBDA has been shown to be an inhibitor of cell migration in the highly aggressive human breast cancer MDA-MB-231 by alteration of Rho GTPase activity (Takeda et al., 2012). CBDV, the C4'-propyl analog of CBD, displays very weak affinity for CB₁ and CB₂ receptors (Hill et al., 2013; Rosenthaler et al., 2014), whereas it has been reported to inhibit the activity of the putative endogenous ligand LPI in *h*GPR55-HEK293 cells (Anavi-Goffer et al., 2012). CBDV also targets the human TRPA1 channel (De Petrocellis et al., 2011, 2012). In several animal seizures models, CBDV exerted notable anticonvulsant effects

without affecting normal motor function (Hill et al., 2012). The mechanisms through which CBDV exerts its antiepileptic effects are uncertain (Jones and Whalley, 2015). CBDV is currently in Phase II clinical trials as an antiepileptic drug under the name GWP42006.¹

Two aromatic analogs of CBD have been isolated from Lebanese hashish (ElSohly and Slade, 2005): cannabiniol (CBND-C5), and cannabidivarin (CBND-C3) (Figure 3) whose structural elucidation required their total synthesis (Robert et al., 1977). CBND-C₅ found in the plant's flowers in low concentration, is considered a product of CBD photochemical conversion.

The conversion of CBD into human metabolites has been the subject of a recent interesting review (Ujváry and Hanuš, 2016). CBD biotransformation shows considerable species variability. The main biotransformation, including hydroxylation and oxidation, involves the CYP450 enzyme family. While 7-hydroxy-CBD (7-OH-CBD) derivatives are found in low concentration, the most abundant metabolites are hydroxylated 7-carboxylic acid derivatives of CBD (7-COOH-CBD, Figure 4). Glucuronidation of CBD seems to frequently occur at the phenolic oxygen (Figure 4). Another cannabinoid metabolite, the so called cannabielsoin (CBE), has been identified in plants as a product of photo-oxidation from CBD and CBDA (Shani and Mechoulam, 1974; Ujváry and Hanuš, 2016), or by biotransformation using tissue cultures under normal growth conditions (Hartsel et al., 1983; Yamamoto et al., 1991). CBE was also identified as a metabolite in guinea pigs, mice, rabbits, and rats (Yamamoto et al., 1991). Despite the fact that CBD

¹ClinicalTrials.gov. A Study of GWP42006 in People With Focal Seizures. <https://clinicaltrials.gov/ct2/show/NCT02369471> (accessed September 22, 2016).

metabolites have been the subject of many studies, few *in vivo* studies have been published. Therefore, their therapeutic benefits remain to be established.

Beyond the *Cannabis* plant, other naturally occurring products have been reported to interact with the ECS (Gertsch et al., 2010). However, only few of them are CBD-based compounds. Isolation and characterization of (+)-*trans*-hexahydrodibenzopyrans from the stem bark of the Amazonian liana *Machaerium multiflorum* Spruce led to the identification of the CBD related structures machaeridiols A, B, and C (Figure 5) (Muhammad et al., 2003).

The total synthesis of these compounds via an efficient highly regio- and stereoselective approach has also been described (Huang et al., 2007). Although their activity at the CB₁ and CB₂ cannabinoid receptors has not been reported, these compounds displayed antimicrobial, antifungal, and antiparasitic activity in diverse *in vitro* assays (Muhammad et al., 2003). Machaeridiol B stands out as the most potent inhibitor against *Plasmodium falciparum* [chloroquine-sensitive (D6) and chloroquine-resistant (W2) clones] and *Leishmania donovani* with IC₅₀ values in the low micromolar range (Table 1).

TABLE 1 | CB₁/CB₂ cannabinoid receptor binding, molecular targets and therapeutic potential of CBD derivatives.

Compounds	CB ₁ R K _i [nM]	CB ₂ R K _i [nM]	Reference	Other targets	Therapeutic potential	Reference
(-)-CBD	> 10000	> 10000	Bisogno et al., 2001	NAM-CB ₁ ; FABPs; GPR55; GPR18; 5-HT _{1A} ; 5-HT _{2A} ; 5-HT _{3A} ; GlyR A _{1A} ; PPAR _γ ; GABA _A , TRPs	Neuroprotection; epilepsy; anxiety; psychosis; inflammation	Fasinu et al., 2016; Morales et al., 2017
(-)-CBDA				COX-2; TRPA1; DAGL _α	Inflammation; cancer; bacteria	Appendino et al., 2008; Takeda et al., 2008, 2012; De Petrocellis et al., 2011
(-)-CBDV	14711 ± 5734	574.2 ± 146	Rosenthaler et al., 2014	GPR55; TRPA1; CYP1A1	Convulsion; epilepsy	De Petrocellis et al., 2011; Anavi-Goffer et al., 2012; Hill et al., 2012, 2013; Yamaori et al., 2013; Rosenthaler et al., 2014; Jones and Whalley, 2015
Machaeridiol B	–	–		–	<i>Plasmodium falciparum</i> ; <i>Leishmania donovani</i>	Muhammad et al., 2003
Ferruginene C	NR	Weak	Seephonkai et al., 2011	TRPA1	Cancer	Seephonkai et al., 2011
(-)-7-OH-CBD	> 10000	> 10000	Bisogno et al., 2001	–	–	
(+)-7-OH-CBD	5.3 ± 0.5	101.0 ± 5.1	Fride et al., 2004	–	–	
(-)-7-COOH-CBD	> 10000	> 10000	Bisogno et al., 2001	–	–	
(+)-7-COOH-CBD	13.2 ± 0.4	312.8 ± 15.8	Fride et al., 2004	–	–	
CBE	–	–		CYP1A1	–	Yamaori et al., 2013
(+)-CBD	842 ± 36	203 ± 16	Bisogno et al., 2001	–	–	
H ₂ -CBD	> 1000	–	Ben-Shabat et al., 2006	–	Inflammation	Ben-Shabat et al., 2006
H ₄ -CBD	145	–	Ben-Shabat et al., 2006	–	Inflammation	Ben-Shabat et al., 2006
HU-444	> 10000	> 10000	Haj et al., 2015	–	Inflammation	Haj et al., 2015
HU-446	~1000	> 10000	Kozela et al., 2015	–	Inflammation	Haj et al., 2015
HU-465	76.7 ± 58	12.1 ± 2.3	Kozela et al., 2015	–	Inflammation	Haj et al., 2015
(-)-DMH-CBD	> 10000	> 1000	Bisogno et al., 2001	–	Anxiety; pain; inflammation; cancer	Burstein, 2015; Juknat et al., 2016
(+)-DMH-CBD	17.4 ± 1.8	211 ± 23	Bisogno et al., 2001	–	–	
(-)-7-OH-DMH-CBD	> 4000	671 ± 12	Bisogno et al., 2001	TRPV1, opioid, α ₂ -AR	–	Fride et al., 2005; Pertwee et al., 2005

(Continued)

TABLE 1 | Continued

Compounds	CB ₁ R K _i [nM]	CB ₂ R K _i [nM]	Reference	Other targets	Therapeutic potential	Reference
(+)-7-OH-DMH-CBD	2.5 ± 0.03	44.0 ± 3.1	Bisogno et al., 2001	–	–	
(-)-7-COOH-DMH-CBD (HU-320)	> 1000	>4000	Bisogno et al., 2001	–	Inflammation, immunosuppression	Sumariwalla et al., 2004
(+)-7-COOH-DMH-CBD	5.8 ± 0.7	155.5 ± 5.3	Fride et al., 2004	–	–	
H ₂ -DMH-CBD	124	–	Ben-Shabat et al., 2006	–	–	
H ₄ -DMH-CBD	17	–	Ben-Shabat et al., 2006	–	–	
HU-308	>10000	22.7 ± 3.9	Hanus et al., 1999	–	Inflammation; hepatic ischemia; osteoporosis; pain	Ofek et al., 2006; Rajesh et al., 2007a,b; Burstein, 2015
(-)-CBDD	>10000	>10000	Hanus et al., 2005	15-LOX	Atherosclerosis, body weight regulation	Takeda et al., 2009, 2011, 2015
(+)-CBDD	>10000	>10000	Hanus et al., 2005	–	–	
(-)-DMH-CBDD	>10000	>10000	Hanus et al., 2005	–	–	
(+)-DMH-CBDD	>10000	<10000	Hanus et al., 2005	–	–	
KLS-13019	–	–			Neuroprotection	Kinney et al., 2016
HUF-101	–	–			Anxiety; depression, psychosis; convulsion	Breuer et al., 2016
CBD-aldehyde-diacetate	–	–			Convulsion	Carlini et al., 1975
6-Oxo-CBD-diacetate	–	–			Convulsion	Carlini et al., 1975
6-OH-CBD-triacetate	–	–			Convulsion	Carlini et al., 1975
9-OH-CBD-triacetate	–	–			Convulsion	Carlini et al., 1975
HU-331	NR	NR	Kogan et al., 2004	Topoisomerase II α ; Caspases; ROS; PARP	Cancer	Kogan et al., 2004, 2007; Petronzi et al., 2013; Regal et al., 2014
CBD-Q (V)	–	–		PPAR γ	Neuroprotection	Appendino et al., 2015
CBD-Q (VIII)	–	–		PPAR γ	Neuroprotection	Appendino et al., 2015
Abn-CBD	–	–		GPR55; GPR18	Vasodilatation; bacteria; diabetes; colitis	Johns et al., 2007; Ryberg et al., 2007; Appendino et al., 2008; Console-Bram et al., 2014; Krohn et al., 2016; McKillop et al., 2016
O-1602	NR	NR		GPR55; GPR18	Central nervous system; metabolism	Johns et al., 2007; Romero-Zerbo et al., 2011; Ashton, 2012; Console-Bram et al., 2014
CBG	897 ± 596	153 ± 42	Rosenthaler et al., 2014	α_2 -AR; TRP; COX-1; COX-2; 5-HT _{1A}	Bacteria; bowel inflammation; depression	Appendino et al., 2008; Cascio et al., 2010; El-Alfy et al., 2010; De Petrocellis et al., 2011; Ruhaak et al., 2011; Borrelli et al., 2013; Rosenthaler et al., 2014
Cannabimovone	>10000	>10000	Tagliatalata-Scafati et al., 2010	TPRV1	–	Tagliatalata-Scafati et al., 2010

NR, no response.

Ferruginene C, a methylpentanol derivative of CBD (Figure 5), was recently isolated from the leaves of *Rhododendron ferrugineum* L. as a mixture of diastereoisomers (Seephonkai et al., 2011). Ferruginene C has been shown to be cytotoxic in the

HL-60 cancer cell-line (IC₅₀ 13.7 μ M) with selectivity toward non-cancerous cell-line. It binds weakly to CB₂ and TPRV1 receptors, but it did not show significant affinity for CB₁ and 5-HT_{1A} receptors (Table 1).

in inflammatory and autoimmune diseases models. However, only the (+)-enantiomer (HU-465) displays affinity for the cannabinoid CB₁ and CB₂ receptors (Table 1).

1',1'-Dimethylheptyl-CBD Derivatives

Taking into account that substitution of the pentyl chain of Δ^9 -THC by a 1', 1'-dimethylheptyl (DMH) lipophilic alkyl chain resulted in more active compounds than natural Δ^9 -THC (Mechoulam et al., 1988), a similar approach was performed for the CBD scaffold (Mechoulam et al., 1990; Hanus et al., 2005) (Table 1). Thus, the synthesis of DMH-CBD derivatives, such as DMH-CBD, HU-320, DMH-CBDD, and 7-OH-DMH-CBD (Figure 7) have been reported by Mechoulam and coworkers (Leite et al., 1982; Hanus et al., 2005). Introduction of the DMH alkyl chain in the (-)-DMH-CBD series did not change the lack of CB₁ and CB₂ receptor affinity except for (-)-7-OH-DMH-CBD that moderately binds to CB₂ (Table 1) (Bisogno et al., 2001). However, in the case of the (+)-DMH-CBD series, the presence of the DMH alkyl chain improved both CB₁ receptor affinity compared to (+)-CBD (Table 1). (-)-DMH-CBD analogs have displayed anxiolytic, analgesic, anti-inflammatory, or antiproliferative effects in diverse assays (Burstein, 2015). For instance, (-)-DMH-CBD has shown anti-inflammatory and antiproliferative properties in human acute myeloid leukemia, microglial or encephalitogenic T cells (Juknat et al., 2016). The carboxylic acid HU-320 produced strong anti-inflammatory and immunosuppressive effects in an *in vivo* model of collagen-induced arthritis (Sumariwalla et al., 2004). Interestingly, (-)-7-OH-DMH-CBD exhibited potent inhibition of electrically evoked contractions of the mouse vas deferens that was not mediated through CB₁, CB₂, TRPV1, opioid, or α_2 -adrenergic receptors (Fride et al., 2005; Pertwee et al., 2005).

As previously mentioned for the pentyl CBD derivatives, hydrogenation of DMH-CBD has been studied (Ben-Shabat et al., 2006). Partial hydrogenation gave H₂-DMH-CBD (Figure 7) as the major epimer (hydrogenation at C8) with small amounts of the hydrogenated C1 epimer being obtained. Full hydrogenation allowed the formation of H₄-DMH-CBD (Figure 7). These hydrogenated compounds, which bind to the CB₁ receptor with affinity constants in the nanomolar range, displayed weak anti-inflammatory effects when compared to CBD or DMH-CBD.

The pinene dimethoxy-DMH-CBD derivative HU-308 (Figure 7) was identified decades ago as a potent peripheral CB₂-selective agonist (Mechoulam et al., 1990; Hanus et al., 1999). HU-308 has shown very interesting properties such as anti-inflammatory, analgesic, neuroprotective or antitumor effects, and has been used as a pharmacological tool in numerous cannabinoid studies contributing to the progress in this field (e.g., Hanus et al., 1999; Ofek et al., 2006; Rajesh et al., 2007a,b; Burstein, 2015). More recently, the efficacy of HU-308 and HU-433, two enantiomers, has been tested in ovariectomy-induced bone loss and ear inflammation (Smoum et al., 2015) showing an inverse relationship between binding affinity and biological potency.

Other Modifications on the C4'-Alkyl Chain

In order to improve oral bioavailability and solubility issues, a novel series of CBD analogs have recently been synthesized (Kinney et al., 2016) (Figure 8). Structural modifications at the pharmacophoric lipophilic chain allowed fine-tuning the “drug-likeness” of this scaffold by variation of different physicochemical parameters such as the number of hydrogen bond donors, acceptors, and polar surface area. Among these new derivatives depicted in Figure 8, KLS-13019 stands out as being 50-fold more potent and more than 400-fold safer than CBD preventing damage to hippocampal neurons induced by ammonium acetate and ethanol with improved oral bioavailability compared to CBD (Kinney et al., 2016).

Halogenated CBD Derivatives

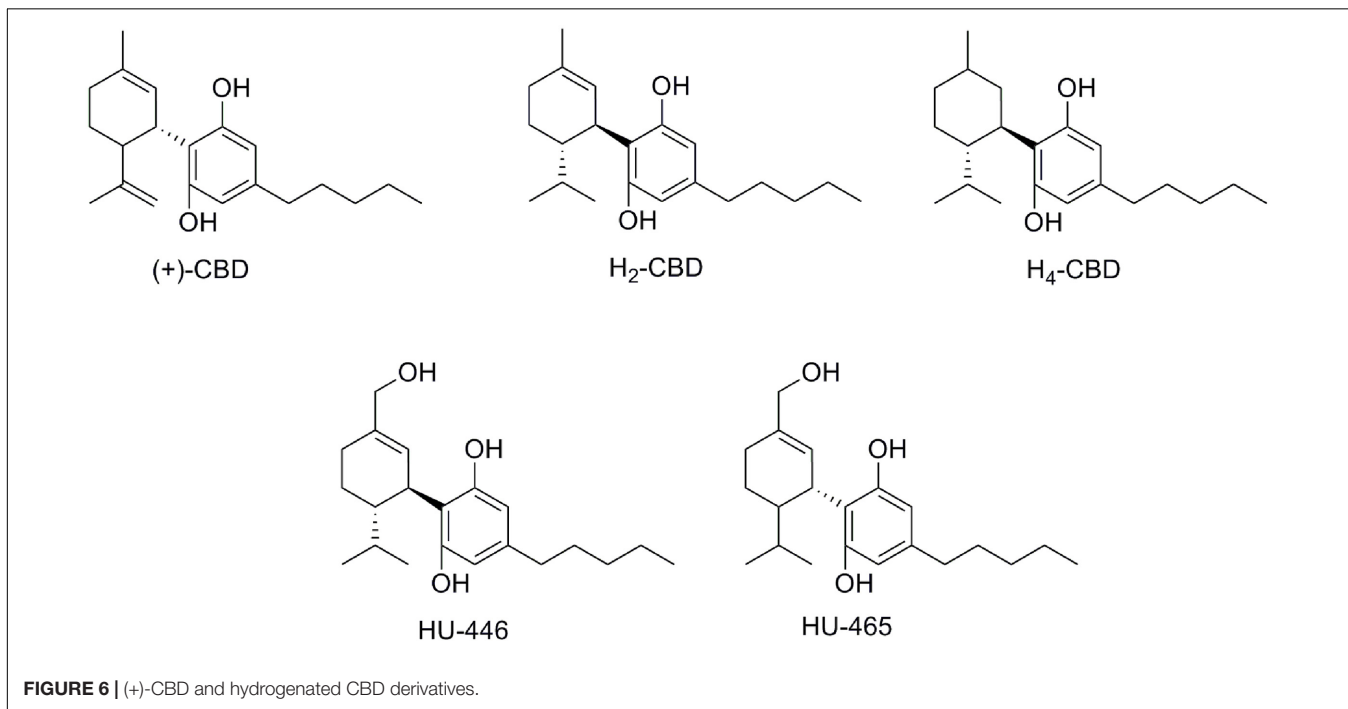
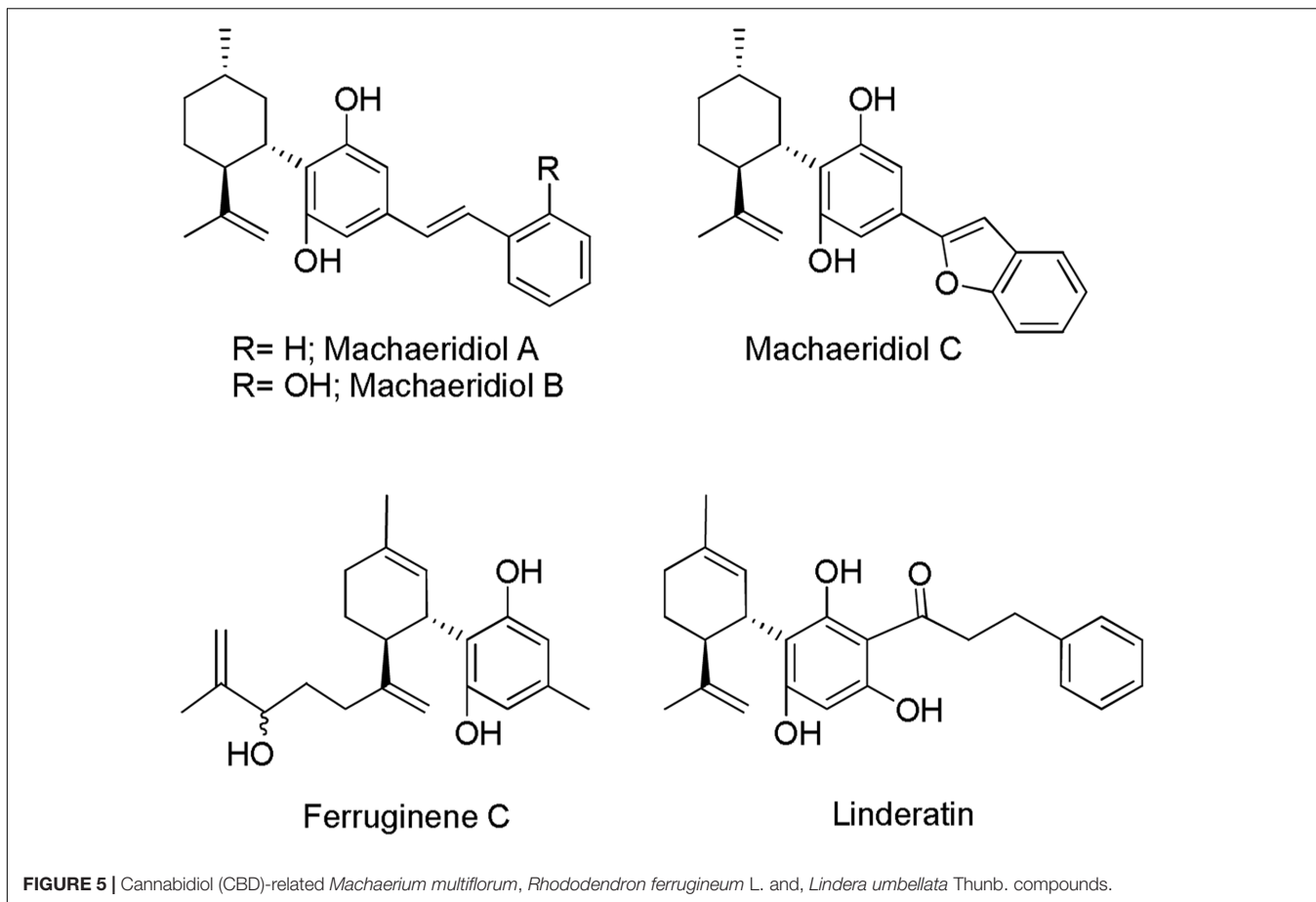
Structural modifications of CBD include halogenated substituents on the phenol ring. The first reported halogenations occurred at the 3' and/or 5' positions by chlorine, bromine or iodine substitution, allowing the preparation of 3'-Cl-CBD, 3',5'-diCl-CBD, 3'-Br-CBD, 3',5'-diBr-CBD, 3'-I-CBD, and 3',5'-diI-CBD (Figure 9) (Usami et al., 1999). These halogenated compounds were evaluated in murine models of barbiturate-induced sleep prolongation, electroshock-induced seizures and locomotor activity resulting in activity similar to CBD for the monohalogenated analogs, whereas the dihalogenated derivatives displayed lower activity (Table 1).

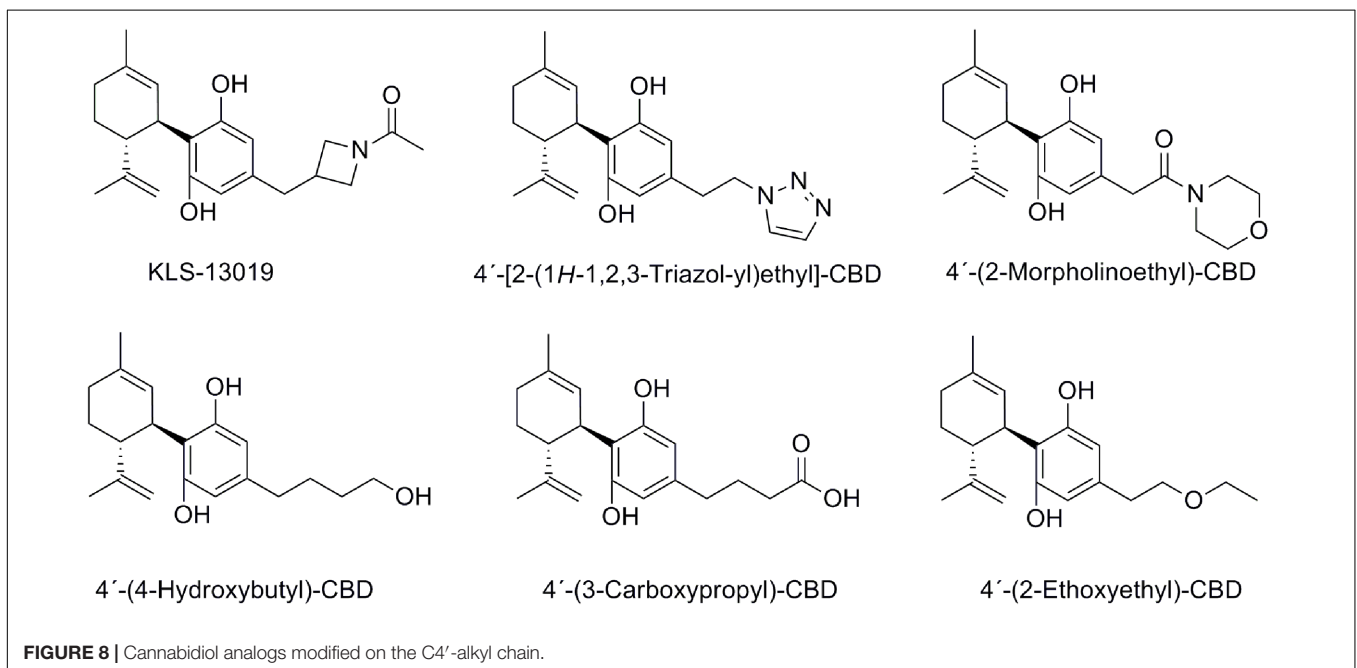
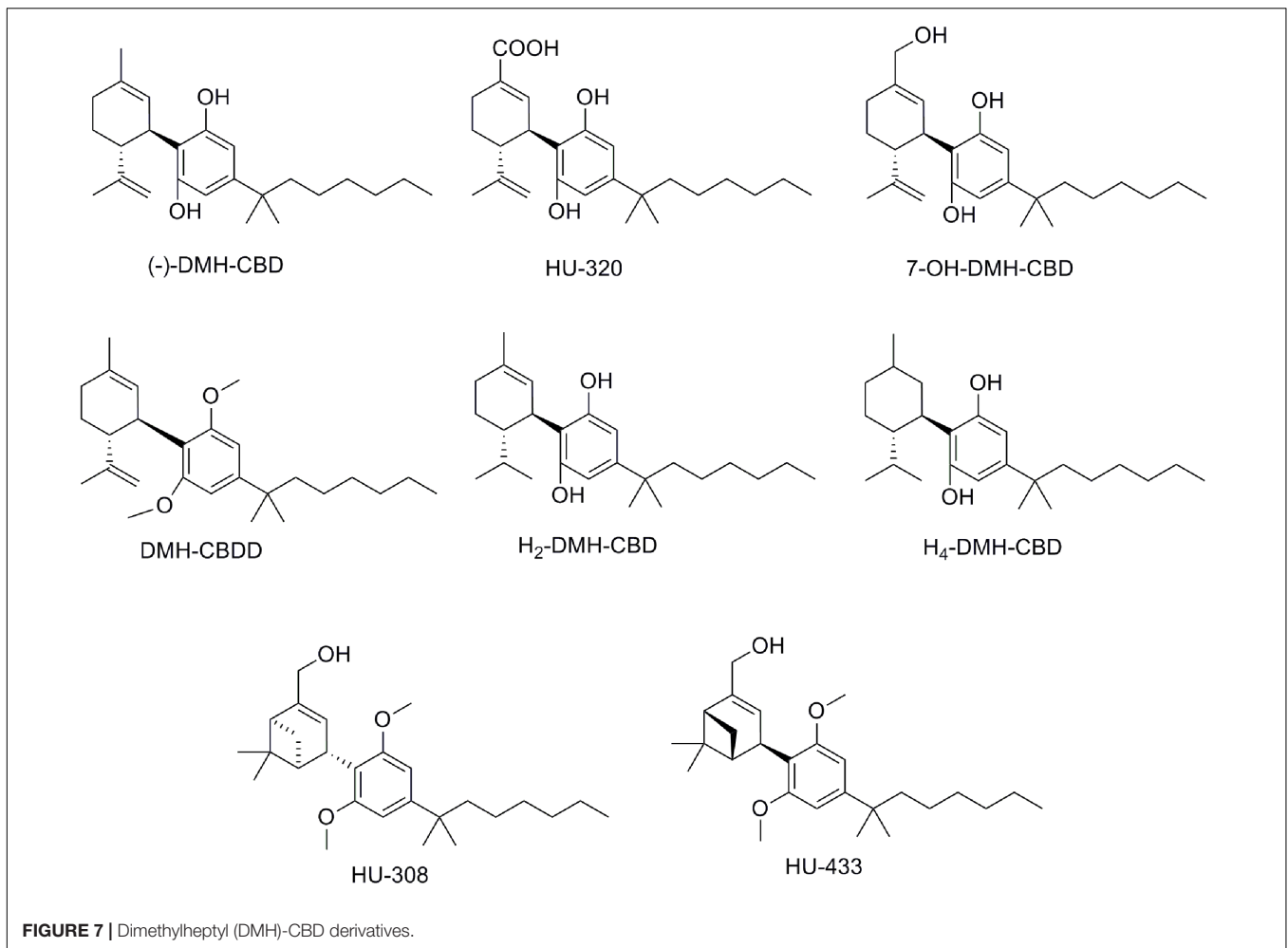
The synthesis and pharmacological evaluation of three new fluorine halogenated CBD derivatives have been reported (Breuer et al., 2016). Two of these were fluorinated at the cyclohexenyl ring substituent (Figure 10: HUF-102 and HUF-103), and the third one was fluorinated at the phenol ring (HUF-101). HUF-101 displayed the most promising results in four mice behavioral assays (elevated plus-maze, forced swimming test, prepulse inhibition, and marble burying test) that target anxiolytic, antidepressant, antipsychotic and anticomulsive activity respectively. HUF-101 may be an interesting prototype for further development since it showed higher potency than CBD in the animal assays cited above. In these tests, HUF-102 did not show activity at the doses tested (1–10 mg/kg), whereas HUF-103 showed moderate to low activity compared to HUF-101.

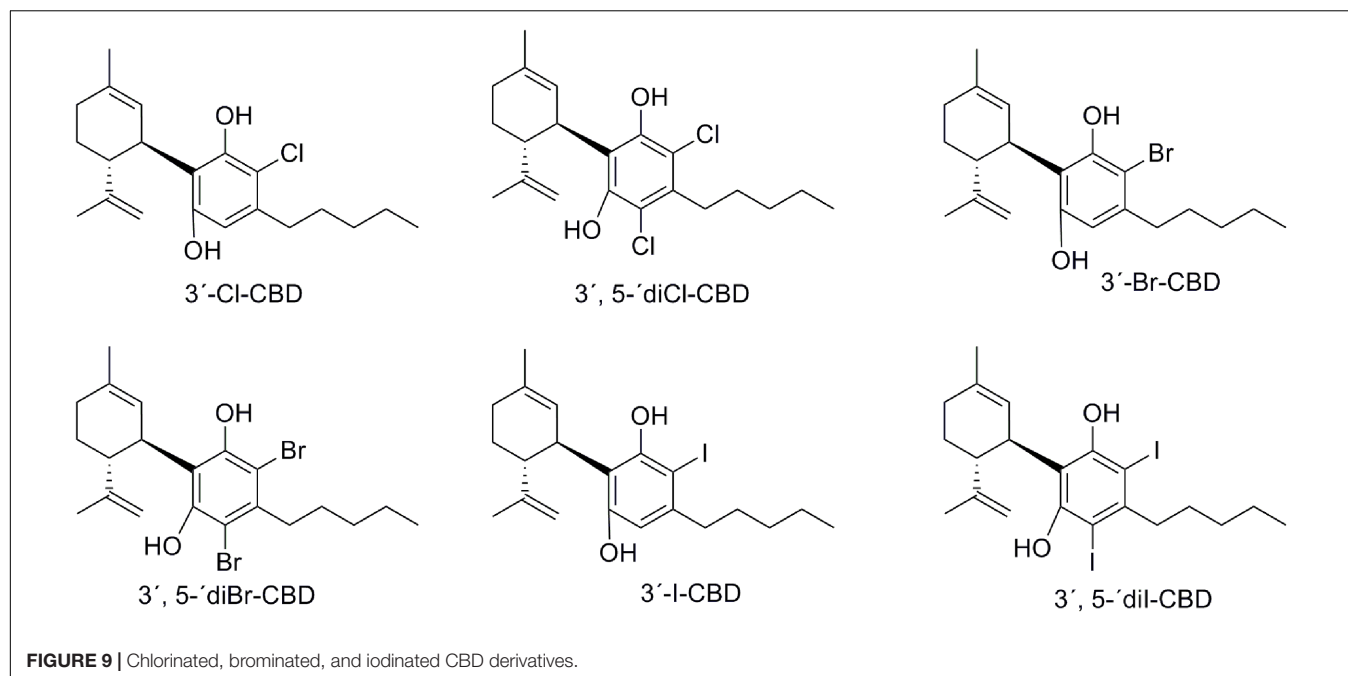
Modifications on the Hydroxyl Groups

Modifications on the resorcinol hydroxyl groups have been explored. Computational studies suggested that the removal of one of the CBD hydroxyl groups may enable the ligand to reach the CB₁ binding site (Reggio et al., 1995). Thus, desoxy-CBD represented in Figure 11 was synthesized and evaluated. Pharmacological data for desoxy-CBD corroborated the computational studies showing CB₁ partial agonism in the mouse vas deferens assay.

Different research groups have developed acetylations and alkylations at one or both phenolic hydroxyls. For instance, the dimethylated CBD derivative named CBDD (Figure 11), as well as the monomethylated derivative (CBD-2'-monomethylether o







O-methylcannabidiol) revealed higher potency and selectivity as 15-lipoxygenase inhibitors compared to CBD (Takeda et al., 2009, 2011). Consequently, the resorcinol moiety seems to be a determinant for the activity in this target. Further studies performed with CBDD suggest that this compound is not only a potential prototype for atherosclerosis treatment, but also a pharmacological tool to study the mechanisms of body weight regulation (Takeda et al., 2015). Other alkylations on the phenolic hydroxyl group have been reported such as *O*-propyl- and *O*-pentylcannabidiol that have been structurally characterized but no pharmacological data have been described so far (Hendricks et al., 1978).

Cannabidiol derivatives bearing one or both hydroxyl substitutions have been reported in the patent literature to be active as anti-inflammatory agents (Mechoulam et al., 2008). Selected examples disclosed in this patent (HU-410, HU-427, and HU-432) are depicted in **Figure 11**. It is interesting to highlight that some of these compounds present improved solubility, stability and bioavailability parameters when compared with CBD. Likewise, the non-CB₁, non-CB₂ ligand HU-444 has shown anti-inflammatory properties *in vitro* and *in vivo* in a murine model of collagen-induced arthritis (Haj et al., 2015).

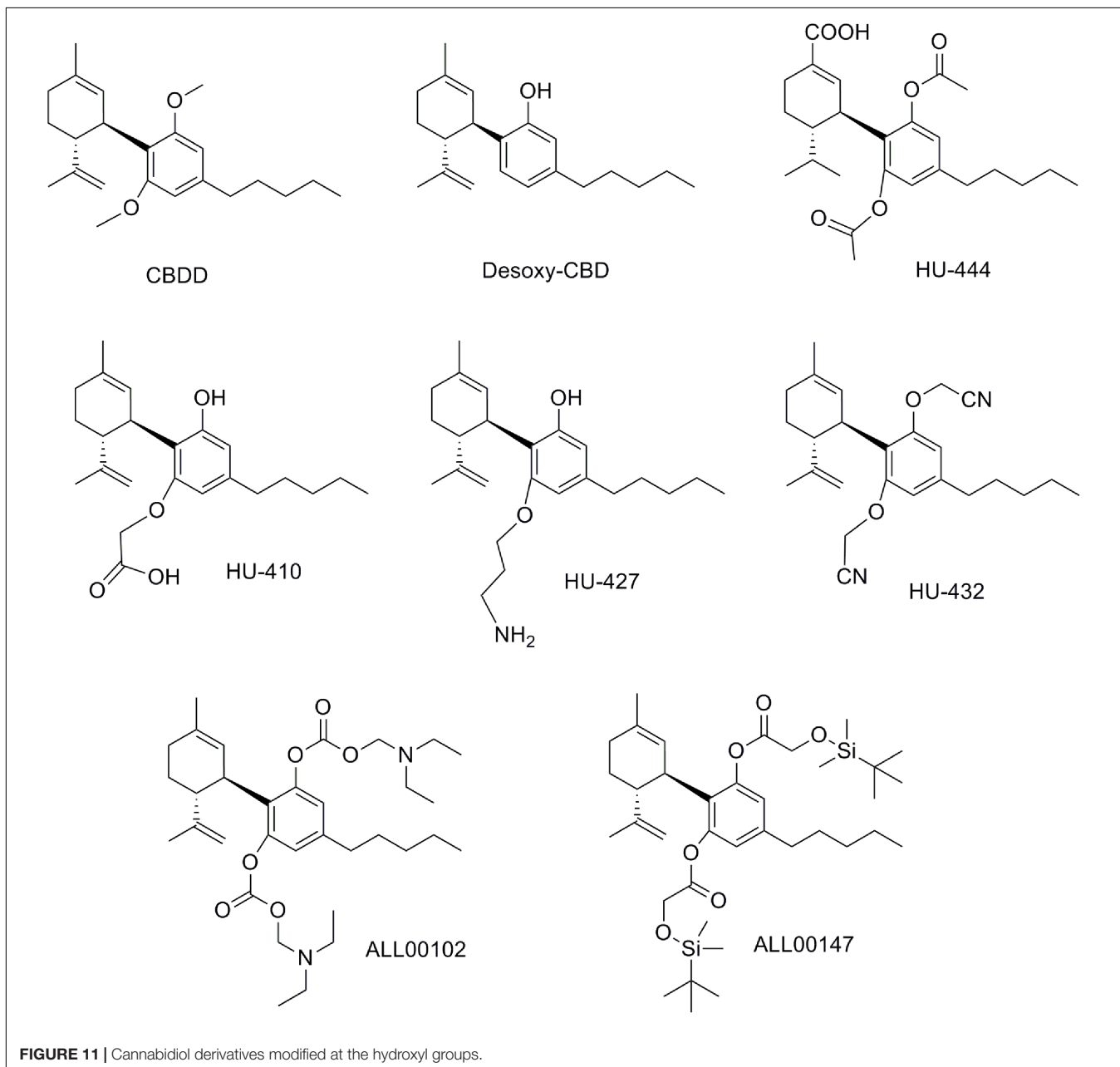
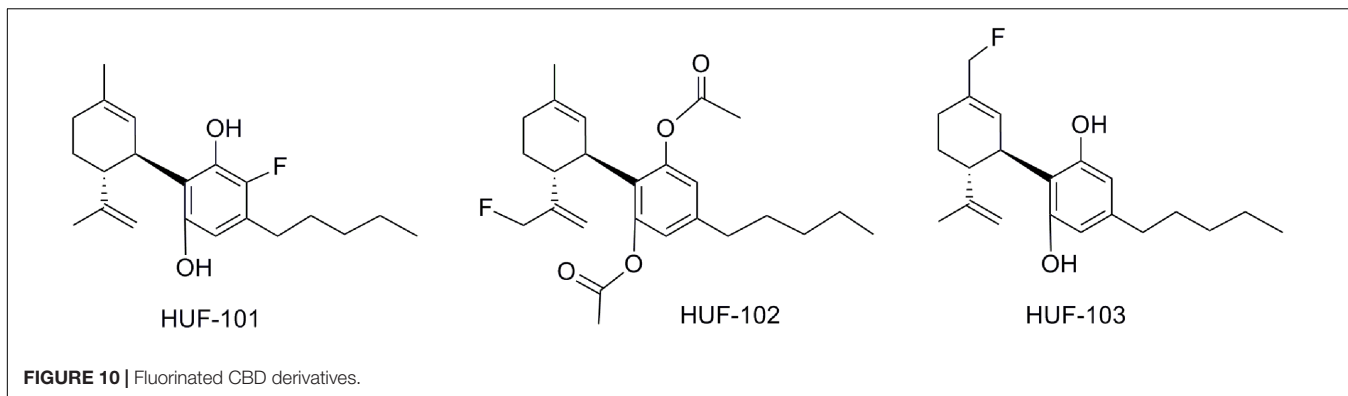
In addition, the *in vivo* anticonvulsant activity of four diacetylated-CBD analogs (CBD-aldehyde-diacetate, 6-oxo-CBD-diacetate, 6-hydroxy-CBD-triacetate, and 9-hydroxy-CBD-triacetate, **Figure 12**) was demonstrated in a mouse model (Carlini et al., 1975). Their effects against maximal electroshock convulsions, potentiation of pentobarbital sleeping-time and reduction of spontaneous motor activity were evaluated obtaining significant anticonvulsant effects at high doses. It is noteworthy that the safety, efficiency, and potency of these four compounds were lower than that of CBD in the same assays.

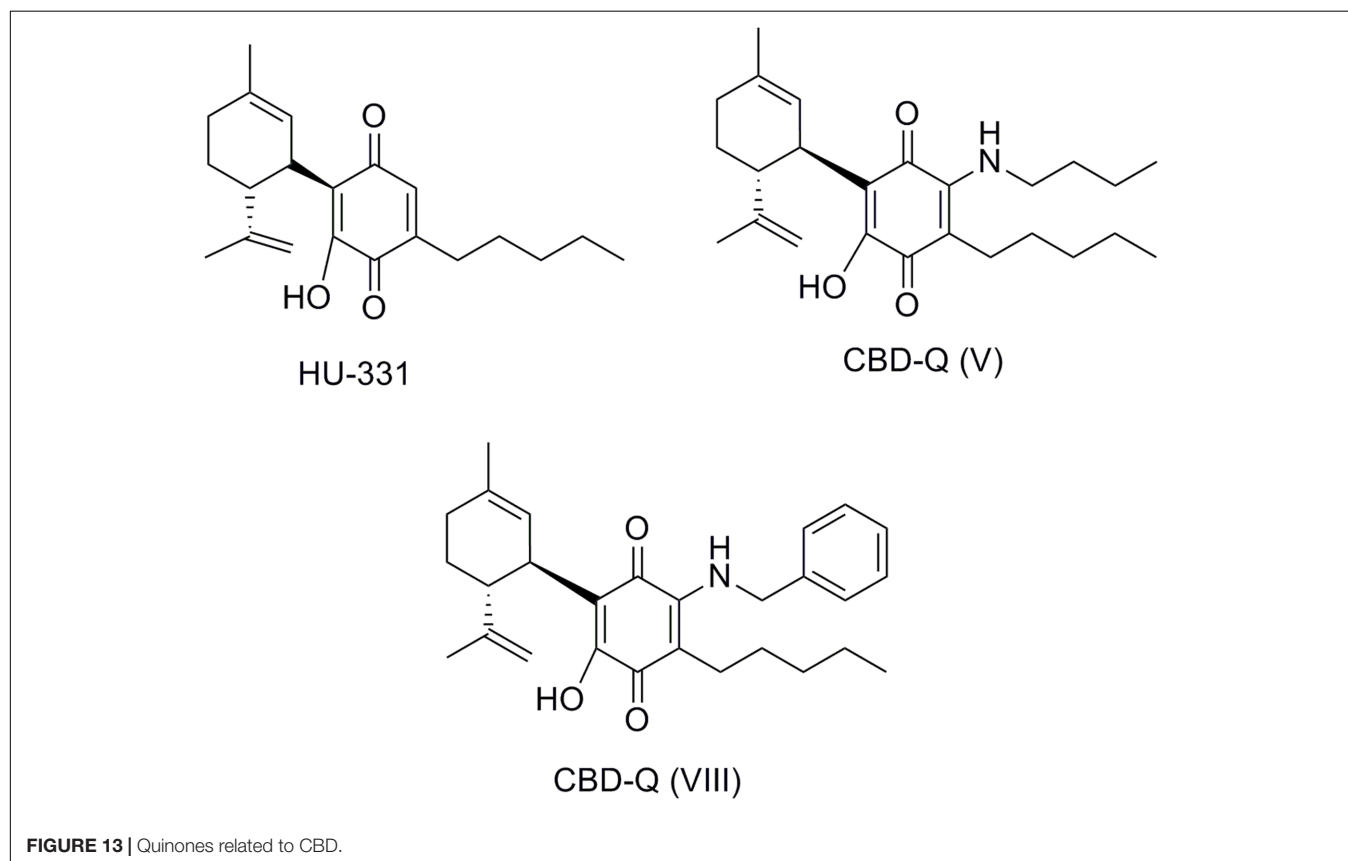
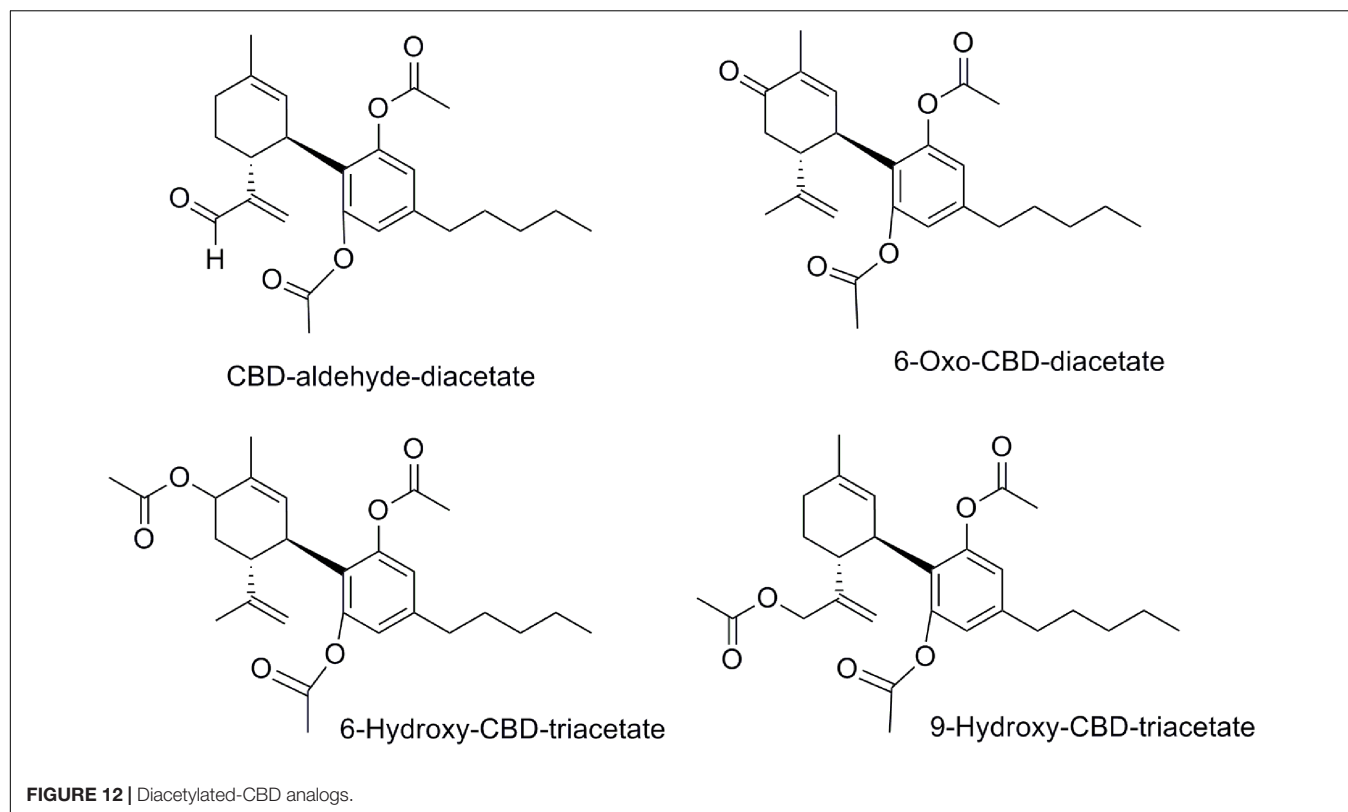
At that point it is interesting to mention that these diacetate CBD derivatives could have been considered as prodrugs. Considering that CBD is rapidly distributed in adipose tissues and it undergoes a CYP3A- and CYP2C- dependent first-pass metabolism to give 7-hydroxy-CBD (Fasinu et al., 2016), a prodrug concept could be very useful. Therefore, the phenyl acetate groups could be deacetylated to give CBD. The pharmaceutical company, AllTranz, now called Zyberba Pharmaceuticals, developed transdermal solutions of CBD-esters and -carbonates among others. The dicarbonate All00102 and the diglycolate AL00147 shown in **Figure 11** are two examples disclosed in a AllTranz's patent (Stinchcomb et al., 2009). Another company, Kalytera Therapeutics is currently undertaking the preclinical stage of K-1012, a bi-phosphate derivative of CBD designed as a prodrug indicated for acute respiratory distress syndrome.²

Quinone Derivatives of CBD

The quinone derivative of CBD, HU331, was first synthesized in Mechoulam et al. (1968) by oxidation of CBD. HU331 has been suggested to be a CBD metabolite having inhibitory effect on cytochrome P450 (Bornheim and Grillo, 1998). It was not until Kogan et al. (2004) that the antineoplastic activity of HU-331 was reported. HU-331 was very effective in reducing growth of human colon carcinoma HT-29 cells in nude mice. The mechanism by which HU-331 acts as an antitumor agent is independent of the CB₁ and CB₂ cannabinoid receptors. HU-331 does not promote cell death via cell cycle arrest, cell apoptosis, or caspase activation. Extensive studies have shown that HU-331 anticancer properties were due to selective inhibition of the ATPase function of human topoisomerase II α (Kogan et al.,

²<https://kalytera.co/programs/preclinical/> (accessed June 8, 2017).





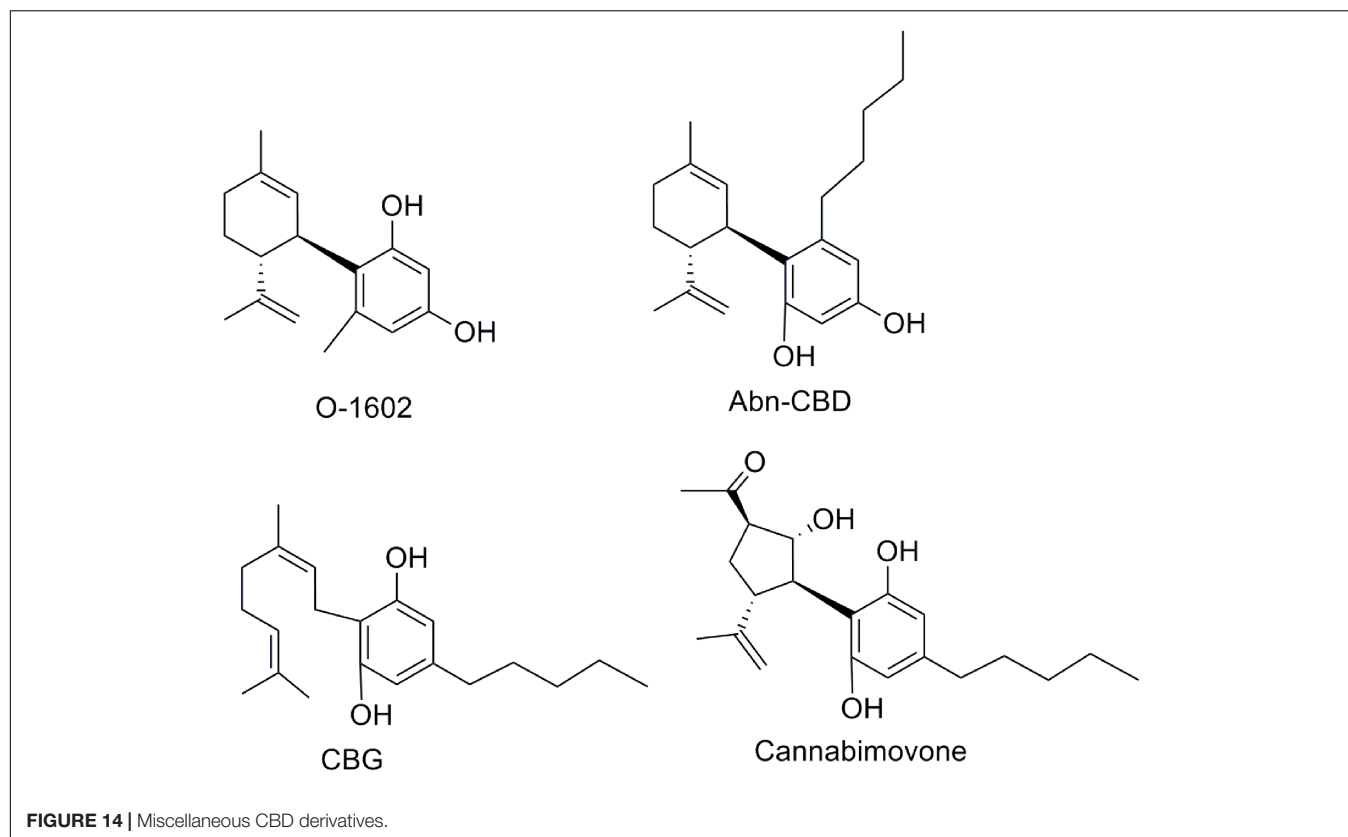


FIGURE 14 | Miscellaneous CBD derivatives.

2007; Peters and Kogan, 2007; Regal et al., 2014). Thus, HU-331 with a selective topoisomerase inhibition is expected to have less off-target toxicity than doxorubicin which antitumor activity is mediated through numerous mechanisms, such as apoptosis, abrogation of the cell cycle, activation of caspases, generation of ROS, and inhibition of both topoisomerases among others.

Structural modifications realized on the substituents of HU-331 led to the benzoquinones having anti-proliferative activity against diverse cancer cell lines (Petronzi et al., 2013). Unlike HU-331, benzoquinone mechanism of action involves caspase activation, poly-(ADP-ribose)-polymerase (PARP) protein cleavage, and reactive oxygen species (ROS) production. These data show the influence of CBD structure compared to the quinone core on the processes producing anticancer effects.

A recent patent from VivaCell Technology discloses HU-331 analogs which act as PPAR γ agonists showing a neuroprotective profile in different models (Appendino et al., 2015). The disclosed quinones are substituted in position 3' by different amines or carboxylates that were synthesized by amination of CBD or esterification of CBDA respectively. Compounds CBD-Q (V) and CBD-Q (VIII) illustrated in **Figure 13** are representative of the HU-331 analogs.

Miscellaneous CBD Derivatives

Abnormal cannabidiol (Abn-CBD) (Razdan et al., 1974), a non-psychoactive synthetic regioisomer of CBD (**Figure 14**), has been the subject of numerous studies that have shown Abn-CBD therapeutic potential as a vasodilator (Johns et al., 2007),

antibacterial (Appendino et al., 2008), antidiabetic (McKillop et al., 2016), or anti-colitis agent (Krohn et al., 2016). Recently, two molecular targets, GPR55 and GPR18, have been identified for Abn-CBD (Johns et al., 2007; Ryberg et al., 2007; Console-Bram et al., 2014). Abn-CBD stimulated [35 S]GTP γ S binding at GPR55 (Oka et al., 2007) and increased calcium mobilization and ERK1/2 phosphorylation at GPR18 (Console-Bram et al., 2014).

The synthetic cannabinoid O-1602 that does not bind significantly to CB $_1$ or CB $_2$ receptors, stimulates GTP γ S activation in membranes from human recombinant GPR55-expressing cells (EC $_{50}$ = 1.4 nM) (Johns et al., 2007; Console-Bram et al., 2014). *In vivo*, O-1602 showed anti-inflammatory activity in mice with cerulein-induced acute pancreatitis characterized by an increased expression of GPR55 receptor (Li et al., 2013). O-1602 has also been shown to increase levels of GPR18-mediated MAPK activity and calcium mobilization, but not β -arrestin signaling, thus supporting that O-1602 acts as a biased-agonist at GPR18 (Console-Bram et al., 2014). Data have been reported suggesting the therapeutic potential of O-1602 for diseases related to the central nervous system (Ashton, 2012), or to metabolic diseases (Romero-Zerbo et al., 2011).

Another minor component of *Cannabis sativa* is cannabigerol (CBG) (Gaoni and Mechoulam, 1971). Structurally, CBG can be considered the cyclohexenyl-opened analog of CBD. Different therapeutic applications have been proposed for CBG, more recently CBG has been shown to have antibacterial action (Appendino et al., 2008), antidepressant-like action

(El-Alfy et al., 2010), and anti-inflammatory properties for bowel disease (Borrelli et al., 2013). Molecular targets of CBG include the α_2 adrenergic receptor, TRP channels, cyclooxygenase (COX-1 and COX-2) enzymes, as well as the 5-HT_{1A} and cannabinoid receptors (Cascio et al., 2010; De Petrocellis et al., 2011; Ruhaak et al., 2011). Cannabimovone is one of the latest natural phytocannabinoids that has been extracted from a cultivar of hemp rich in CBD (Tagliatalata-Scafati et al., 2010). The terpenoid structure of cannabimovone replaces the cyclohexenyl ring of CBD by a functionalized cyclopentane including four contiguous stereocenters. Its total synthesis has been reported very recently (Carreras et al., 2016). Cannabimovone is devoid of CB₁ and CB₂ activity, whereas it is a weak TPRV1 agonist.

CONCLUSION

A significant amount of preclinical data has shown the high therapeutic potential of CBD especially in inflammatory mouse models. According to ClinicalTrials.gov records, CBD is currently tested in clinical phases for different inflammatory diseases. The results of the first clinical study of CBD for the treatment of inflammatory bowel have been published very recently. Unfortunately, the effects of CBD on Crohn's disease were ineffective in a randomized placebo-controlled trial on 20 patients probably due to low used doses (Naftali et al., 2017). The potential antiepileptic effects of CBD in patients suffering seizures associated with Lennox-Gastaut syndrome and in children and young patients with Dravet syndrome are currently on-going. The research has tended to focus on CBD therapeutic applications. Less attention has been paid to the therapeutic utility of CBD derivatives.

Despite the identifications of CBD metabolites and naturally occurring CBD analogs, in general, their pharmacological properties have not been extensively studied. In what concerns synthetic CBD-based compounds, several of them have shown interesting pharmacological properties but none has been introduced into clinical trials yet. In a pharmacological point of view, whereas CBD does not have affinity for both classical CB₁

and CB₂ cannabinoid receptors, most of (+)-CBD derivatives do bind to CB₁ and/or CB₂ receptors. Others, such as Abn-CBD, O-1602, CBG, cannabimovone, ferruginene C, (–)-CBDV, and (–)-CBDA, have shown activity at other receptors including TPRV1, GPR35 and/or GPR18 receptors, or enzymes such as COX-2. A limitation of the development of CBD synthetic derivatives probably resides in the lack of a unique common molecular target.

In future therapeutic development of CBD derivatives, it will be prudent to take into account some structural considerations around the CBD scaffold. One of them is the possible atropisomerism around the phenyl-hexenyl bond. Ortho-substitution on the phenyl ring could have stereochemical consequences generating hindered rotation of the phenyl-hexenyl bond due to steric or electronic constraints, generating two isolable conformers in the case of slow interconversion (Berber et al., 2014; Flos et al., 2016). Thus, it is necessary to consider the implication of a possible atropisomerism for new CBD analogs discovery (Clayden et al., 2009).

The complexity of the pharmacological processes of CBD and CBD analogs suggest that a better understanding of their mechanism of action is required to devise successful synthetic CBD-based drug therapies.

AUTHOR CONTRIBUTIONS

PM, PHR, and NJ substantially contributed to the redaction of the manuscript. Then, they all approved the manuscript to be published.

FUNDING

Financial support was provided by Spanish Grants from Ministerio de Economía y Competitividad SAF2015-68580-C2-2-R (MINECO/FEDER) (NJ) and NIH grants RO1 DA003934 and KO5 DA021358 (PR).

REFERENCES

- Ahrens, J., Demir, R., Leuwer, M., De La Roche, J., Krampfl, K., Foadi, N., et al. (2009). The nonpsychotropic cannabinoid cannabidiol modulates and directly activates alpha-1 and alpha-1-beta glycine receptor function. *Pharmacology* 83, 217–222. doi: 10.1159/000201556
- Aizpurua-Olaizola, O., Soydaner, U., Öztürk, E., Schibano, D., Simsir, Y., Navarro, P., et al. (2016). Evolution of the cannabinoid and terpene content during the growth of cannabis sativa plants from different chemotypes. *J. Nat. Prod.* 79, 324–331. doi: 10.1021/acs.jnatprod.5b00949
- Anavi-Goffer, S., Baillie, G., Irving, A. J., Gertsch, J., Greig, I. R., Pertwee, R. G., et al. (2012). Modulation of L- α -lysophosphatidylinositol/GPR55 mitogen-activated protein kinase (MAPK) signaling by cannabinoids. *J. Biol. Chem.* 287, 91–104. doi: 10.1074/jbc.M111.296020
- Appendino, G., Cabello de Alba, M. L. B., and Munoz Blanco, E. (2015). Preparation of novel cannabidiol quinone derivatives as PPAR γ agonists. International Patent No WO2015/158381. Washington, DC.
- Appendino, G., Gibbons, S., Giana, A., Pagani, A., Grassi, G., Stavri, M., et al. (2008). Antibacterial Cannabinoids from *Cannabis sativa*: a structure-activity study. *J. Nat. Prod.* 71, 1427–1430. doi: 10.1021/np8002673
- Ashton, J. C. (2012). The atypical cannabinoid O-1602: targets, actions, and the central nervous system. *Cent. Nerv. Syst. Agents Med. Chem.* 12, 233–239. doi: 10.2174/187152412802430156
- Bakas, T., Devenish, S., Van Nieuwenhuizen, P., Arnold, J., McGregor, I., and Collins, M. (2016). "The actions of cannabidiol and 2-arachidonyl glycerol on GABA-A receptors," in *Proceedings of the 26th Annual Symposium on the Cannabinoids, International Cannabinoid Research Society*, Bukovina, 28.
- Ben-Shabat, S., Hanuš, L. O., Katzavian, G., and Gallily, R. (2006). New cannabidiol derivatives: synthesis, binding to cannabinoid receptor, and evaluation of their antiinflammatory activity. *J. Med. Chem.* 49, 1113–1117. doi: 10.1021/jm050709m
- Berber, H., Lameiras, P., Denhez, C., Antheaume, C., and Clayden, J. (2014). Atropisomerism about aryl-csp³ bonds: the electronic and steric influence of ortho-substituents on conformational exchange in cannabidiol and linderatin derivatives. *J. Org. Chem.* 79, 6015–6027. doi: 10.1021/jo5006069
- Bhattacharyya, S., Morrison, P. D., Fusar-Poli, P., Martin-Santos, R., Borgwardt, S., Winton-Brown, T., et al. (2010). Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. *Neuropsychopharmacology* 35, 764–774. doi: 10.1038/npp.2009.184

- Bisogno, T., Hanus, L., De Petrocellis, L., Tchilibon, S., Ponde, D. E., Brandi, L., et al. (2001). Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. *Br. J. Pharmacol.* 134, 845–852. doi: 10.1038/sj.bjp.0704327
- Bornheim, L. M., and Grillo, M. P. (1998). Characterization of cytochrome P450 3A inactivation by cannabidiol-hydroxyquinone as a P450 inactivator. *Chem. Res. Toxicol.* 11, 1209–1216. doi: 10.1021/tx9800598
- Borrelli, F., Fasolino, I., Romano, B., Capasso, R., Maiello, F., Coppola, D., et al. (2013). Beneficial effect of the non-psychotropic plant cannabinoid cannabigerol on experimental inflammatory bowel disease. *Biochem. Pharmacol.* 85, 1306–1316. doi: 10.1016/j.bcp.2013.01.017
- Breuer, A., Haj, C. G., Fogaça, M. V., Gomes, F. V., Silva, N. R., Pedrazzi, J. F., et al. (2016). Fluorinated cannabidiol derivatives: enhancement of activity in mice models predictive of anxiolytic, antidepressant and antipsychotic effects. *PLoS ONE* 11:e0158779. doi: 10.1371/journal.pone.0158779
- Burstein, S. (2015). Cannabidiol (CBD) and its analogs: a review of their effects on inflammation. *Bioorgan. Med. Chem.* 23, 1377–1385. doi: 10.1016/j.bmc.2015.01.059
- Carlini, E. A., Mechoulam, R., and Lander, N. (1975). Anticonvulsant activity of four oxygenated cannabidiol derivatives. *Res. Commun. Chem. Pathol. Pharmacol.* 12, 1–15.
- Carreras, J., Kirillova, M. S., and Echavarren, A. M. (2016). Synthesis of (-)-cannabimovone and structural reassignment of anhydrocannabimovone through gold(I)-catalyzed cycloisomerization. *Angew. Chemie - Int. Ed.* 55, 7121–7125. doi: 10.1002/anie.201601834
- Cascio, M. G., Gauson, L. A., Stevenson, L. A., Ross, R. A., and Pertwee, R. G. (2010). Evidence that the plant cannabinoid cannabigerol is a highly potent α 2-adrenoceptor agonist and moderately potent 5HT 1A receptor antagonist. *Br. J. Pharmacol.* 159, 129–141. doi: 10.1111/j.1476-5381.2009.00515.x
- Clayden, J., Moran, W. J., Edwards, P. J., and Laplante, S. R. (2009). The challenge of atropisomerism in drug discovery. *Angew. Chemie - Int. Ed.* 48, 6398–6401. doi: 10.1002/anie.200901719
- Console-Bram, L., Brailoiu, E., Brailoiu, G. C., Sharir, H., and Abood, M. E. (2014). Activation of GPR18 by cannabinoid compounds: a tale of biased agonism. *Br. J. Pharmacol.* 171, 3908–3917. doi: 10.1111/bph.12746
- De Petrocellis, L., Ligresti, A., Moriello, A. S., Allarà, M., Bisogno, T., Petrosino, S., et al. (2011). Effects of cannabinoids and cannabinoid-enriched *Cannabis* extracts on TRP channels and endocannabinoid metabolic enzymes. *Br. J. Pharmacol.* 163, 1479–1494. doi: 10.1111/bph.2011.163.issue-7
- De Petrocellis, L., Orlando, P., Moriello, A. S., Aviello, G., Stott, C., Izzo, A. A., et al. (2012). Cannabinoid actions at TRPV channels: effects on TRPV3 and TRPV4 and their potential relevance to gastrointestinal inflammation. *Acta Physiol.* 204, 255–266. doi: 10.1111/j.1748-1716.2011.02338.x
- Devinsky, O., Marsh, E., Friedman, D., Thiele, E., Laux, L., Sullivan, J., et al. (2015). Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. *Lancet Neurol.* 15, 270–278. doi: 10.1016/S1474-4422(15)00379-8
- El-Alfy, A. T., Ivey, K., Robinson, K., Safwat, A., Radwan, M., Slade, D., et al. (2010). Antidepressant-like effect of Δ 9-tetrahydrocannabinol and other cannabinoids isolated from *Cannabis sativa* L. *Pharmacol. Biochem. Behav.* 95, 434–442. doi: 10.1016/j.pestbp.2011.02.012. Investigations
- Elmes, M. W., Kaczocha, M., Berger, W. T., Leung, K., Ralph, B. P., Wang, L., et al. (2015). Fatty acid-binding proteins (FABPs) are intracellular carriers for Δ 9-tetrahydrocannabinol (THC) and cannabidiol (CBD). *J. Biol. Chem.* 290, 8711–8721. doi: 10.1074/jbc.M114.618447
- ElSohly, M. A., and Gul, W. (2014). “Constituents of *cannabis sativa*,” in *Handbook of Cannabis*, ed. R. G. Pertwee (Oxford: Oxford University Press), 3–22. doi: 10.1093/acprof
- ElSohly, M. A., and Slade, D. (2005). Chemical constituents of marijuana: the complex mixture of natural cannabinoids. *Life Sci.* 78, 539–548. doi: 10.1016/j.lfs.2005.09.011
- Esposito, G., Scuderi, C., Valenza, M., Tognà, G. I., Latina, V., de Filippis, D., et al. (2011). Cannabidiol reduces A β -induced neuroinflammation and promotes hippocampal neurogenesis through PPAR γ involvement. *PLoS ONE* 6:e28668. doi: 10.1371/journal.pone.0028668
- Fasinu, P. S., Phillips, S., Elsohly, M. A., and Walker, L. A. (2016). Current status and prospects for cannabidiol preparations as new therapeutic agents. *Pharmacotherapy* 36, 781–796. doi: 10.1111/j.1875-9114.2016.01780.x
- Fernandez, O. (2016). THC:CBD in daily practice: available data from UK, Germany and Spain. *Eur. Neurol.* 75, 1–3. doi: 10.1159/000444234
- Fernandez-Ruiz, J., Sagredo, O., Pazos, M. R., Garcia, C., Pertwee, R., Mechoulam, R., et al. (2013). Cannabidiol for neurodegenerative disorders: important new clinical applications for this phytocannabinoid? *Br. J. Clin. Pharmacol.* 75, 323–333. doi: 10.1111/j.1365-2125.2012.04341.x
- Flos, M., Lameiras, P., Denhez, C., Mirand, C., and Berber, H. (2016). Atropisomerism about Aryl-C(sp 3) Bonds: conformational behavior of substituted phenylcyclohexanes in solution. *J. Org. Chem.* 81, 2372–2382. doi: 10.1021/acs.joc.5b02856
- Ford, L. A., Roelofs, A. J., Anavi-Goffer, S., Mowat, L., Simpson, D. G., Irving, A. J., et al. (2010). A role for L-alpha-lysophosphatidylinositol and GPR55 in the modulation of migration, orientation and polarization of human breast cancer cells. *Br. J. Pharmacol.* 160, 762–771. doi: 10.1111/j.1476-5381.2010.00743.x
- Fride, E., Feigin, C., Ponde, D. E., Breuer, A., Hanuš, L., Arshavsky, N., et al. (2004). (+)-Cannabidiol analogues which bind cannabinoid receptors but exert peripheral activity only. *Eur. J. Pharmacol.* 506, 179–188. doi: 10.1016/j.ejphar.2004.10.049
- Fride, E., Ponde, D., Breuer, A., and Hanuš, L. (2005). Peripheral, but not central effects of cannabidiol derivatives: mediation by CB1 and unidentified receptors. *Neuropharmacology* 48, 1117–1129. doi: 10.1016/j.neuropharm.2005.01.023
- Gaoni, Y., and Mechoulam, R. (1971). The isolation and structure of delta-1-tetrahydrocannabinol and other neutral cannabinoids from hashish. *J. Am. Chem. Soc.* 93, 217–224. doi: 10.1021/ja00730a036
- Gertsch, J., Pertwee, R. G., and Di Marzo, V. (2010). Phytocannabinoids beyond the cannabis plant - do they exist? *Br. J. Pharmacol.* 160, 523–529. doi: 10.1111/j.1476-5381.2010.00745.x
- Gonca, E., and Darıcı, F. (2014). The effect of cannabidiol on ischemia/reperfusion-induced ventricular arrhythmias: the role of adenosine A1 receptors. *J. Cardiovasc. Pharmacol. Ther.* 1:76. doi: 10.1177/1074248414532013
- Haj, C. G., Sumariwalla, P. F., Hanuš, L., Kogan, N. M., Yektin, Z., Mechoulam, R., et al. (2015). HU-444, a novel, potent anti-inflammatory, nonpsychotropic cannabinoid. *J. Pharmacol. Exp. Ther.* 355, 66–75. doi: 10.1124/jpet.115.226100
- Hanus, L., Breuer, A., Shiloah, S., Tchilibon, S., Gollenberg, D., Horowitz, M., et al. (1999). HU-308: a specific agonist for CB(2), a peripheral cannabinoid receptor. *Proc. Natl. Acad. Sci. U.S.A.* 96, 14228–14233. doi: 10.1073/pnas.96.25.14228
- Hanus, L. O., Meyer, S. M., Muñoz, E., Tagliatalata-Scafati, O., and Appendino, G. (2016). Phytocannabinoids: a unified critical inventory. *Nat. Prod. Rep.* 33, 1357–1392. doi: 10.1039/c6np00074f
- Hanus, L. O., Tchilibon, S., Ponde, D. E., Breuer, A., Frider, E., and Mechoulam, R. (2005). Enantiomeric cannabidiol derivatives: synthesis and binding to cannabinoid receptors. *Org. Biomol. Chem.* 3, 1116–1123. doi: 10.1039/b416943c
- Hartsel, S. C., Loh, W. H., and Robertson, L. W. (1983). Biotransformation of cannabidiol to cannabielsoin by suspension cultures of *Cannabis sativa* and *Saccharum officinarum*. *Planta Med.* 48, 17–19. doi: 10.1055/s-2007-969870
- Hendricks, H., Malingré, T. M., Batterman, S., and Bos, R. (1978). The essential oil of *Cannabis sativa*. *Pharm. Weekbl.* 113, 413–424.
- Hill, A. J., Mercier, M. S., Hill, T. D. M., Glyn, S. E., Jones, N. A., Yamasaki, Y., et al. (2012). Cannabidivarin is anticonvulsant in mouse and rat. *Br. J. Pharmacol.* 167, 1629–1642. doi: 10.1111/j.1476-5381.2012.02207.x
- Hill, T. D. M., Cascio, M. G., Romano, B., Duncan, M., Pertwee, R. G., Williams, C. M., et al. (2013). Cannabidivarin-rich cannabis extracts are anticonvulsant in mouse and rat via a CB1 receptor-independent mechanism. *Br. J. Pharmacol.* 170, 679–692. doi: 10.1111/bph.12321
- Huang, Q., Wang, Q., Zheng, J., Zhang, J., Pan, X., and She, X. (2007). A general route to 5,6-seco-hexahydrodibenzopyrans and analogues: first total synthesis of (+)-Machaeridiol B and (+)-Machaeriol B. *Tetrahedron* 63, 1014–1021. doi: 10.1016/j.tet.2006.10.067
- Ibeas Bih, C., Chen, T., Nunn, A. V. W., Bazélot, M., Dallas, M., and Whalley, B. J. (2015). Molecular targets of cannabidiol in neurological disorders. *Neurotherapeutics* 12, 699–730. doi: 10.1007/s13311-015-0377-3
- Johns, D. G., Behm, D. J., Walker, D. J., Ao, Z., Shapland, E. M., Daniels, D. A., et al. (2007). The novel endocannabinoid receptor GPR55 is activated by atypical

- cannabinoids but does not mediate their vasodilator effects. *Br. J. Pharmacol.* 152, 825–831. doi: 10.1038/sj.bjp.0707419
- Jones, N. A., and Whalley, B. J. (2015). Progress report on new antiepileptic drugs: a summary of the Twelfth Eilat Conference (EILAT XII). *Epilepsy Res.* 111, 113–114. doi: 10.1016/j.eplepsyres.2015.01.001
- Juknat, A., Kozela, E., Kaushansky, N., Mechoulam, R., and Vogel, Z. (2016). Anti-inflammatory effects of the cannabidiol derivative dimethylheptyl-cannabidiol – studies in BV-2 microglia and encephalitogenic T cells. *J. Basic Clin. Physiol. Pharmacol.* 27, 289–296. doi: 10.1515/jbcp-2015-0071
- Kinney, W. A., McDonnell, M. E., Zhong, H. M., Liu, C., Yang, L., Ling, W., et al. (2016). Discovery of KLS-13019, a cannabidiol-derived neuroprotective agent, with improved potency, safety, and permeability. *ACS Med. Chem. Lett.* 7, 424–428. doi: 10.1021/acsmchemlett.6b00009
- Kogan, N. M., Rabinowitz, R., Levi, P., Gibson, D., Sandor, P., Schlesinger, M., et al. (2004). Synthesis and antitumor activity of quinonoid derivatives of cannabinoids. *J. Med. Chem.* 47, 3800–3806. doi: 10.1021/jm040042o
- Kogan, N. M., Schlesinger, M., Priel, E., Rabinowitz, R., Berenshtein, E., Chevion, M., et al. (2007). HU-331, a novel cannabinoid-based anticancer topoisomerase II inhibitor. *Mol. Cancer Ther.* 6, 173–183. doi: 10.1158/1535-7163.MCT-06-0039
- Kozela, E., Haj, C., Hanuš, L., Chourasia, M., Shurki, A., Juknat, A., et al. (2015). HU-446 and HU-465, derivatives of the non-psychoactive cannabinoid cannabidiol, decrease the activation of encephalitogenic T cells. *Chem. Biol. Drug Des.* 87, 143–153. doi: 10.1111/cbdd.12637
- Krohn, R. M., Parsons, S. A., Fichna, J., Patel, K. D., Yates, R. M., Sharkey, K. A., et al. (2016). Abnormal cannabidiol attenuates experimental colitis in mice, promotes wound healing and inhibits neutrophil recruitment. *J. Inflamm.* 13:21. doi: 10.1186/s12950-016-0129-0
- Lafuente, H., Alvarez, F. J., Pazos, M. R., Alvarez, A., Rey-Santano, M. C., Mielgo, V., et al. (2011). Cannabidiol reduces brain damage and improves functional recovery after acute hypoxia-ischemia in newborn pigs. *Pediatr. Res.* 70, 272–277. doi: 10.1203/PDR.0b013e3182276b11
- Laprairie, R. B., Bagher, A. M., Kelly, M. E. M., and Denovan-Wright, E. M. (2015). Cannabidiol is a negative allosteric modulator of the type 1 cannabinoid receptor. *Br. J. Pharmacol.* 172, 4790–4805. doi: 10.1111/bph.13250
- Lauckner, J. E., Jensen, J. B., Chen, H.-Y., Lu, H.-C., Hille, B., and Mackie, K. (2008). GPR55 is a cannabinoid receptor that increases intracellular calcium and inhibits M current. *Proc. Natl. Acad. Sci. U.S.A.* 105, 2699–2704. doi: 10.1073/pnas.0711278105
- Leite, J. R., Carlini, E. A., Lander, N., and Mechoulam, R. (1982). Anticonvulsant effects of the (-) and (+)isomers of cannabidiol and their dimethylheptyl homologs. *Pharmacology* 24, 141–146. doi: 10.1159/000137588
- Leweke, F. M., Piomelli, D., Pahlisch, F., Muhl, D., Gerth, C. W., Hoyer, C., et al. (2012). Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Transl. Psychiatry* 2:e94. doi: 10.1038/tp.2012.15
- Li, K., Feng, J., Li, Y., Yucee, B., Lin, X., Yu, L., et al. (2013). Anti-inflammatory role of cannabidiol and O-1602 in cerulein-induced acute pancreatitis in mice. *Pancreas* 42, 123–129. doi: 10.1097/MPA.0b013e318259f6f0
- Ligresti, A. (2006). Antitumor activity of plant cannabinoids with emphasis on the effect of cannabidiol on human breast carcinoma. *J. Pharmacol. Exp. Ther.* 318, 1375–1387. doi: 10.1124/jpet.106.105247
- Maione, S., Piscitelli, F., Gatta, L., Vita, D., De Petrocellis, L., Palazzo, E., et al. (2011). Non-psychoactive cannabinoids modulate the descending pathway of antinociception in anesthetized rats through several mechanisms of action. *Br. J. Pharmacol.* 162, 584–596. doi: 10.1111/j.1476-5381.2010.01063.x
- Massi, P., Solinas, M., Cinquina, V., and Parolaro, D. (2013). Cannabidiol as potential anticancer drug. *Br. J. Clin. Pharmacol.* 75, 303–312. doi: 10.1111/j.1365-2125.2012.04298.x
- Matsuda, L. A., Lolait, S. J., Brownstein, M. J., Young, A. C., and Bonner, T. I. (1990). Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature* 346, 561–564. doi: 10.1038/346561a0
- McAllister, S. D., Murase, R., Christian, R. T., Lau, D., Zielinski, A. J., Allison, J., et al. (2011). Pathways mediating the effects of cannabidiol on the reduction of breast cancer cell proliferation, invasion, and metastasis. *Breast Cancer Res. Treat.* 129, 37–47. doi: 10.1007/s10549-010-1177-4
- McHugh, D., Page, J., Dunn, E., and Bradshaw, H. B. (2012). Δ9-Tetrahydrocannabinol and N-arachidonyl glycine are full agonists at GPR18 receptors and induce migration in human endometrial HEC-1B cells. *Br. J. Pharmacol.* 165, 2414–2424. doi: 10.1111/j.1476-5381.2011.01497.x
- McHugh, D., Roskowski, D., Xie, S., and Bradshaw, H. B. (2014). Δ9-THC and N-arachidonyl glycine regulate BV-2 microglial morphology and cytokine release plasticity: implications for signaling at GPR18. *Front. Pharmacol.* 4:162. doi: 10.3389/fphar.2013.00162
- McKillop, A. M., Moran, B. M., Abdel-Wahab, Y. H. A., Gormley, N. M., and Flatt, P. R. (2016). Metabolic effects of orally administered small-molecule agonists of GPR55 and GPR119 in multiple low-dose streptozotocin-induced diabetic and incretin-receptor-knockout mice. *Diabetologia* 59, 2674–2685. doi: 10.1007/s00125-016-4108-z
- McPartland, J. M., Glass, M., and Pertwee, R. G. (2007). Meta-analysis of cannabinoid ligand binding affinity and receptor distribution: interspecies differences. *Br. J. Pharmacol.* 152, 583–593. doi: 10.1038/sj.bjp.0707399
- Mechoulam, R., Ben-Zvi, Z., and Gaoni, Y. (1968). Hashish-XIII. On the nature of the beam test. *Tetrahedron* 24, 5615–5624. doi: 10.1016/0040-4020(68)88159-1
- Mechoulam, R., Feigenbaum, J. J., Lander, N., Segal, M., Hiltunen, T. U. C., and Consroe, P. (1988). Enantiomeric cannabinoids: stereospecificity of psychotropic activity. *Experientia* 44, 762–764. doi: 10.1007/BF01959156
- Mechoulam, R., and Hanuš, L. (2002). Cannabidiol: an overview of some chemical and pharmacological aspects, Part I: Chemical aspects. *Chem. Phys. Lipids* 121, 35–43. doi: 10.1016/S0009-3084(02)00144-5
- Mechoulam, R., Hanuš, L. O., Pertwee, R., and Howlett, A. C. (2014). Early phytocannabinoid chemistry to endocannabinoids and beyond. *Nat. Rev. Neurosci.* 15, 757–764. doi: 10.1038/nrn3811
- Mechoulam, R., Kogan, N. M., Gallily, R., and Breuer, A. (2008). Novel Cannabidiol Derivatives and their use as anti-inflammatory agents. International Patent No WO2008/107879. Washington, DC.
- Mechoulam, R., Lander, N., Breuer, A., and Zahalka, J. (1990). Synthesis of the individual, pharmacologically distinct enantiomers of a tetrahydrocannabinol derivative. *Tetrahedron Asymmetry* 1, 315–318. doi: 10.1016/S0957-4166(00)86322-3
- Mechoulam, R., Peters, M., Murillo-Rodríguez, E., and Hanus, L. O. (2007). Cannabidiol—recent advances. *Chem. Biodivers.* 4, 1678–1692. doi: 10.1002/cbdv.200790147
- Morales, P., Goya, P., Jagerovic, N., and Hernandez-Folgado, L. (2016). Allosteric modulators of the CB1 cannabinoid receptor: a structural update review. *Cannabinoid Res.* 1, 22–30. doi: 10.1089/can.2015.0005
- Morales, P., Hurst, D. P., and Reggio, P. H. (2017). “Molecular targets of the phytocannabinoids: a complex picture,” in *Progress in the Chemistry of Organic Natural Products: Phytocannabinoids, Unravelling the Complex Chemistry and Pharmacology of Cannabis sativa*, eds A. D. Kinghorn, H. Falk, S. Gibbons, and J. Kobayashi (Berlin: Springer), doi: 10.1007/978-3-319-45541-9_4
- Mori, M. A., Meyer, E., Soares, L. M., Milani, H., Guimarães, F. S., and de Oliveira, R. M. W. (2017). Cannabidiol reduces neuroinflammation and promotes neuroplasticity and functional recovery after brain ischemia. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 75, 94–105. doi: 10.1016/j.pnpbp.2016.11.005
- Muhammad, I., Li, X.-C., Jacob, M. R., Tekwani, B. L., Dunbar, D. C., and Ferreira, D. (2003). Antimicrobial and antiparasitic (+)- trans - hexahydrodibenzopyrans and analogues from *Machaerium multiflorum*. *J. Nat. Prod.* 66, 804–809. doi: 10.1021/np030045o
- Munro, S., Thomas, K. L., and Abu-Shaar, M. (1993). Molecular characterization of a peripheral receptor for cannabinoids. *Nature* 365, 61–65. doi: 10.1038/365061a0
- Naftali, T., Mechulam, R., Marii, A., Gabay, G., Stein, A., Bronshtain, M., et al. (2017). Low-dose cannabidiol is safe but not effective in the treatment for Crohn’s disease, a randomized controlled trial. *Dig. Dis. Sci.* 62, 1–6. doi: 10.1007/s10620-017-4540-z
- Ofek, O., Karsak, M., Leclerc, N., Fogel, M., Frenkel, B., Wright, K., et al. (2006). Peripheral cannabinoid receptor, CB2, regulates bone mass. *Proc. Natl. Acad. Sci. U.S.A.* 103, 696–701. doi: 10.1021/jm4005626
- Oka, S., Nakajima, K., Yamashita, A., Kishimoto, S., and Sugiura, T. (2007). Identification of GPR55 as a lysophosphatidylinositol receptor. *Biochem. Biophys. Res. Commun.* 362, 928–934. doi: 10.1016/j.bbrc.2007.08.078
- O’Sullivan, S. E., Sun, Y., Bennett, A. J., Randall, M. D., and Kendall, D. A. (2009). Time-dependent vascular actions of cannabidiol in the rat aorta. *Eur. J. Pharmacol.* 612, 61–68. doi: 10.1016/j.ejphar.2009.03.010

- Pertwee, R. G., Ross, R. A., Craib, S. J., and Thomas, A. (2002). (-)-Cannabidiol antagonizes cannabinoid receptor agonists and noradrenaline in the mouse vas deferens. *Eur. J. Pharmacol.* 456, 99–106. doi: 10.1016/S0014-2999(02)02624-9
- Pertwee, R. G., Thomas, A., Stevenson, L. A., Maor, Y., and Mechoulam, R. (2005). Evidence that (-)-7-hydroxy-4'-dimethylheptyl-cannabidiol activates a non-CB1, non-CB2, non-TRPV1 target in the mouse vas deferens. *Neuropharmacology* 48, 1139–1146. doi: 10.1016/j.neuropharm.2005.01.010
- Peters, M., and Kogan, N. M. (2007). HU-331: a cannabinoid quinone, with uncommon cytotoxic properties and low toxicity. *Expert Opin. Investig. Drugs* 16, 1405–1413. doi: 10.1517/13543784.16.9.1405
- Petronzi, C., Festa, M., Peduto, A., Castellano, M., Marinello, J., Massa, A., et al. (2013). Cyclohexa-2,5-diene-1,4-dione-based antiproliferative agents?: design, synthesis, and cytotoxic evaluation. *J. Exp. Clin. Cancer Res.* 32:24. doi: 10.1186/1756-9966-32-24
- Pucci, M., Rapino, C., Di Francesco, A., Dainese, E., D'Addario, C., and Maccarrone, M. (2013). Epigenetic control of skin differentiation genes by phytocannabinoids. *Br. J. Pharmacol.* 170, 581–591. doi: 10.1111/bph.12309
- Rajesh, M., Mukhopadhyay, P., Batakai, S., Hasko, G., Liaudet, L., Huffman, J. W., et al. (2007a). CB2-receptor stimulation attenuates TNF-alpha-induced human endothelial cell activation, transendothelial migration of monocytes, and monocyte-endothelial adhesion. *Am. J. Physiol. Heart Circ. Physiol.* 293, H2210–H2218. doi: 10.1152/ajpheart.00688.2007
- Rajesh, M., Pan, H., Mukhopadhyay, P., Batakai, S., Osei-Hyiaman, D., Haskó, G., et al. (2007b). Cannabinoid-2 receptor agonist HU-308 protects against hepatic ischemia/reperfusion injury by attenuating oxidative stress, inflammatory response, and apoptosis. *J. Leukoc. Biol.* 82, 1382–1389. doi: 10.1189/jlb.0307180
- Razdan, R. K., Dalzell, H. C., and Handrick, G. R. (1974). Hashish: a simple one-step synthesis of (-)-delta1-tetrahydrocannabinol (THC) from p-mentha-2,8-dien-1-ol and olivetol. *J. Am. Chem. Soc.* 96, 5860–5865. doi: 10.1021/ja00825a026
- Regal, K. M., Mercer, S. L., and Dewese, J. E. (2014). HU-331 is a catalytic inhibitor of topoisomerase II α . *Chem. Res. Toxicol.* 27, 2044–2051. doi: 10.1021/tx500245m
- Reggio, P. H., Bramblett, R. D., Yuknavich, H., Seltzman, H. H., Fleming, D. N., Fernando, S. R., et al. (1995). The design, synthesis and testing of desoxy-CBD: further evidence for a region of steric interference at the cannabinoid receptor. *Life Sci.* 56, 2025–2032. doi: 10.1016/0024-3205(95)00185-9
- Renard, J., Norris, C., Rushlow, W., and Laviolette, S. R. (2017). Neuronal and molecular effects of cannabidiol on the mesolimbic dopamine system: implications for novel schizophrenia treatments. *Neurosci. Biobehav. Rev.* 75, 157–165. doi: 10.1016/j.neubiorev.2017.02.006
- Ribeiro, A., Almeida, V. I., Costola-de-Souza, C., Ferraz-de-Paula, V., Pinheiro, M. L., Vitoretti, L. B., et al. (2015). Cannabidiol improves lung function and inflammation in mice submitted to LPS-induced acute lung injury. *Immunopharmacol. Immunotoxicol.* 37, 35–41. doi: 10.3109/08923973.2014.976794
- Robert, J. J., Ch, L., Ludwig Bercht, C. A., van Ooyen, R., and Spronck, H. J. W. (1977). Cannabinodiol: conclusive identification and synthesis of a new cannabinoid from *Cannabis sativa*. *Phytochemistry* 16, 595–597. doi: 10.1016/0031-9422(77)80023-X
- Rock, E. M., Bolognini, D., Limebeer, C. L., Cascio, M. G., Anavi-Goffer, S., Fletcher, P. J., et al. (2012). Cannabidiol, a nonpsychotropic component of cannabis, attenuates vomiting and nausea-like behaviour via indirect agonism of 5-HT 1A somatodendritic autoreceptors in the dorsal raphe nucleus. *Br. J. Pharmacol.* 165, 2620–2634. doi: 10.1111/j.1476-5381.2011.01621.x
- Romero-Zerbo, S. Y., Rafacho, A., Díaz-Arteaga, A., Suárez, J., Quesada, I., Imbernon, M., et al. (2011). Role for the putative cannabinoid receptor GPR55 in the islets of Langerhans. *J. Endocrinol.* 211, 177–185. doi: 10.1530/JOE-11-0166
- Rosenthaler, S., Pöhn, B., Kolmanz, C., Nguyen Huu, C., Krewenka, C., Huber, A., et al. (2014). Differences in receptor binding affinity of several phytocannabinoids do not explain their effects on neural cell cultures. *Neurotoxicol. Teratol.* 46, 49–56. doi: 10.1016/j.nt.2014.09.003
- Ruhaak, L. R., Felth, J., Karlsson, P. C., Rafta, J. J., Verpoorte, R., and Bohlin, L. (2011). Evaluation of the cyclooxygenase inhibiting effects of six major cannabinoids isolated from *Cannabis sativa*. *Biol. Pharm. Bull.* 34, 774–778. doi: 10.1248/bpb.34.774
- Ruiz-Valdepeñas, L., Martínez-Orgado, J. A., Benito, C., Millán, A., Tolón, R. M., and Romero, J. (2011). Cannabidiol reduces lipopolysaccharide-induced vascular changes and inflammation in the mouse brain: an intravital microscopy study. *J. Neuroinflammation* 8:5. doi: 10.1186/1742-2094-8-5
- Russo, E. B., Burnett, A., Hall, B., and Parker, K. K. (2005). Agonistic properties of cannabidiol at 5-HT1a receptors. *Neurochem. Res.* 30, 1037–1043. doi: 10.1007/s11064-005-6978-1
- Ryberg, E., Larsson, N., Sjögren, S., Hjorth, S., Hermansson, N.-O., Leonova, J., et al. (2007). The orphan receptor GPR55 is a novel cannabinoid receptor. *Br. J. Pharmacol.* 152, 1092–1101. doi: 10.1038/sj.bjp.0707460
- Schier, A., Ribeiro, N., Coutinho, D., Machado, S., Arias-Carrion, O., Crippa, J., et al. (2014). Antidepressant-like and anxiolytic-like effects of cannabidiol: a chemical compound of *Cannabis sativa*. *CNS Neurol. Disord. - Drug Targets* 13, 953–960. doi: 10.2174/1871527313666140612114838
- Scuderi, C., Steardo, L., and Esposito, G. (2014). Cannabidiol promotes amyloid precursor protein ubiquitination and reduction of beta amyloid expression in SHSY5YAPP+ cells through PPAR γ involvement. *Phyther. Res.* 28, 1007–1013. doi: 10.1002/ptr.5095
- Seephonkai, P., Popescu, R., Zehl, M., Krupitza, G., Urban, E., and Kopp, B. (2011). Ferruginenes A-C from rhododendron ferrugineum and their cytotoxic evaluation. *J. Nat. Prod.* 74, 712–717. doi: 10.1021/np100778k
- Shani, A., and Mechoulam, R. (1974). Cannabielsoic acids: isolation and synthesis by a novel oxidative cyclization. *Tetrahedron* 30, 2437–2446. doi: 10.1016/S0040-4020(01)97114-5
- Smoum, R., Baraghithy, S., Chourasia, M., Breuer, A., Mussai, N., Attar-Namdar, M., et al. (2015). CB2 cannabinoid receptor agonist enantiomers HU-433 and HU-308: an inverse relationship between binding affinity and biological potency. *Proc. Natl. Acad. Sci. U.S.A.* 112, 8774–8779. doi: 10.1073/pnas.1503395112
- Stinchcomb, A. L., Golinski, M. J., Hammell, D. C., Howard, J. L., and Banks, S. L. (2009). Prodrugs of cannabidiol, compositions comprising prodrugs of cannabidiol, and methods of using the same. Patent No US2009036523A1. Washington, DC.
- Sumariwalla, P. F., Gallily, R., Tchilibon, S., Fride, E., and Mechoulam, R. (2004). A novel synthetic, nonpsychoactive cannabinoid acid (HU-320) with antiinflammatory properties in murine collagen-induced arthritis. *Arthritis Rheum* 50, 985–998. doi: 10.1002/art.20050
- Taghialatela-Scafati, O., Pagani, A., Scala, F., De Petrocellis, L., Di Marzo, V., Grassi, G., et al. (2010). Cannabimovone, a cannabinoid with a rearranged terpenoid skeleton from hemp. *Eur. J. Org. Chem* 2067–2072. doi: 10.1002/ejoc.200901464
- Takeda, S., Hirayama, A., Urata, S., Mano, N., and Aramaki, H. (2011). Cannabidiol-2',6'-dimethyl ether as an effective protector of 15-lipoxygenase-mediated low-density lipoprotein oxidation in vitro. *Biol. Pharm. Bull.* 34, 1252–1256. doi: 10.1016/j.drudis.2011.09.009
- Takeda, S., Hirota, R., Teradaira, S., and Takeda-imoto, M. (2015). Cannabidiol-2',6'-dimethyl ether stimulates body weight gain in apolipoprotein E-deficient BALB/c, KOR/Stm. *J. Toxicol. Sci.* 40, 739–743. doi: 10.2131/jts.40.739
- Takeda, S., Misawa, K., Yamamoto, I., and Watanabe, K. (2008). Cannabidiolic acid as a selective cyclooxygenase-2 inhibitory component in cannabis. *Drug Metab. Dispos.* 36, 1917–1921. doi: 10.1124/dmd.108.020909
- Takeda, S., Okajima, S., Miyoshi, H., Yoshida, K., Okamoto, Y., Okada, T., et al. (2012). Cannabidiolic acid, a major cannabinoid in fiber-type cannabis, is an inhibitor of MDA-MB-231 breast cancer cell migration. *Toxicol. Lett.* 214, 314–319. doi: 10.1016/j.toxlet.2012.08.029
- Takeda, S., Usami, N., Yamamoto, I., and Watanabe, K. (2009). Cannabidiol-2',6'-dimethyl ether, a cannabidiol derivative, is a highly potent and selective 15-lipoxygenase inhibitor. *Drug Metab. Dispos.* 37, 1733–1737. doi: 10.1124/dmd.109.026930
- Tanaka, H., Ichino, K., and Ito, K. (1984). A novel dihydrochalcone, linderatin from *Lidera Umbellata* Var. *Lancea*. *Chem. Pharm. Bull. (Tokyo)* 32, 3747–3750. doi: 10.1248/cpb.32.3747
- Tchilibon, S., and Mechoulam, R. (2000). Synthesis of a primary metabolite of cannabidiol. *Org. Lett.* 2, 3301–3303. doi: 10.1021/ol006369a
- Thomas, A., Baillie, G. L., Phillips, A. M., Razdan, R. K., Ross, R. A., and Pertwee, R. G. (2007). Cannabidiol displays unexpectedly high potency as an antagonist

- of CB1 and CB2 receptor agonists in vitro. *Br. J. Pharmacol.* 150, 613–623. doi: 10.1038/sj.bjp.0707133
- Ujváry, I., and Hanuš, L. (2016). Human metabolites of cannabidiol: a review on their formation, biological activity, and relevance in therapy. *Cannabis Cannabinoid Res.* 1, 90–101. doi: 10.1089/can.2015.0012
- Usami, N., Okuda, T., Yoshida, H., Kimura, T., Watanabe, K., Yoshimura, H., et al. (1999). Synthesis and pharmacological evaluation in mice of halogenated cannabidiol derivatives. *Chem. Pharm. Bull.* 47, 1641–1645. doi: 10.1248/cpb.47.1641
- Vuolo, F., Petronilho, F., Sonai, B., Ritter, C., Hallak, J. E. C., Zuardi, A. W., et al. (2015). Evaluation of serum cytokines levels and the role of cannabidiol treatment in animal model of asthma. *Mediators Inflamm.* 2015:538670. doi: 10.1155/2015/538670
- Watt, G., and Karl, T. (2017). In vivo evidence for therapeutic properties of cannabidiol (CBD) for alzheimer's disease. *Front. Pharmacol.* 8:20. doi: 10.3389/fphar.2017.00020
- Whyte, L. S., Ryberg, E., Sims, N. A., Ridge, S. A., Mackie, K., Greasley, P. J., et al. (2009). The putative cannabinoid receptor GPR55 affects osteoclast function in vitro and bone mass in vivo. *Proc. Natl. Acad. Sci. U.S.A.* 106, 16511–16516. doi: 10.1073/pnas.0902743106
- Wright, S., Sommerville, K., Jones, N. A., and Whalley, B. J. (2015). Progress report on new antiepileptic drugs : a summary of the twelfth eilat conference (EILAT XII). *Epilepsy Res.* 111, 111–113. doi: 10.1016/j.eplepsyres.2015.01.001
- Xiong, W., Cui, T., Cheng, K., Yang, F., Chen, S. R., Willenbring, D., et al. (2012). Cannabinoids suppress inflammatory and neuropathic pain by targeting alpha3 glycine receptors. *J. Exp. Med.* 209, 1121–1134. doi: 10.1084/jem.20120242
- Yamamoto, I., Gohda, H., Narimatsu, S., Watanabe, K., and Yoshimura, H. (1991). Cannabielsoin as a new metabolite of cannabidiol in mammals. *Pharmacol. Biochem. Behav.* 40, 541–546. doi: 10.1016/0091-3057(91)90360-E
- Yamaori, S., Okushima, Y., Masuda, K., Kushihara, M., Katsu, T., Narimatsu, S., et al. (2013). Structural requirements for potent direct inhibition of human cytochrome P450 1A1 by cannabidiol: role of pentylresorcinol moiety. *Biol. Pharm. Bull.* 36, 1197–1203. doi: 10.1248/bpb.b13-00183
- Yang, K.-H., Galadari, S., Isaev, D., Petroianu, G., Shippenberg, T. S., and Oz, M. (2010). The nonpsychoactive cannabinoid cannabidiol inhibits 5-hydroxytryptamine3A receptor-mediated currents in *Xenopus laevis* oocytes. *J. Pharmacol. Exp. Ther.* 333, 547–554. doi: 10.1124/jpet.109.162594
- Yin, H., Chu, A., Li, W., Wang, B., Shelton, F., Otero, F., et al. (2009). Lipid G protein-coupled receptor ligand identification using beta-arrestin Path Hunter assay. *J. Biol. Chem.* 284, 12328–12338. doi: 10.1074/jbc.M806516200
- Zhornitsky, S., and Potvin, S. (2012). Cannabidiol in humans—the quest for therapeutic targets. *Pharmaceuticals* 5, 529–552. doi: 10.3390/ph5050529

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2017 Morales, Reggio and Jagerovic. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.