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

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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-Δ⁹-tetrahydrocannabinol (Δ⁹-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 extend in peripheral tissues. CB₂ receptor is mainly expressed in immune cells.

Δ⁹-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-psychotropic. Currently, CBD is clinically used in association with Δ⁹-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
CBD acts as an antagonist preventing 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 Δ⁹-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 anandamide to its metabolic enzyme fatty acid amide hydrolase which are intracellular proteins involved in the transport of anandamide for binding to fatty acid-binding proteins (FABPs)

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The molecular targets involved in the diverse therapeutic properties produced by CBD are still not very well-understood (Morales et al., 2017). Unlike Δ⁹-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 Δ⁹-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 anandamide to its metabolic enzyme fatty acid amide hydrolase which are intracellular proteins involved in the transport of anandamide for binding to fatty acid-binding proteins (FABPs)

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 cannabinoid there are currently being researched, the A₁A adenosine receptor has also been proposed (Gonca and Darici, 2014). Other molecular targets have also been studied, among them, the PPARγ 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 cannabinoids 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 overview 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.
FIGURE 2 | Natural phytocannabinoid CBD analogs.

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-(1R,6R) configuration. Cannabidiolic acid (CBDA) and cannabidivarinic acid (CBDVA-C3) are C3′-carboxylic derivatives, whereas cannabidiorcol (CBD-C1), cannabidiol-C4 also named as nor-cannabidiol (CBD-C4), and cannabidivar (CBD-C4) 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 hGPR55-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): cannabinodiol (CBND-C5), and cannabinodivarin (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      | CB₁ Ki [nM] | CB₂ Ki [nM] | Reference                | Other targets                          | Therapeutic potential              | Reference                |
|----------------|-------------|-------------|--------------------------|----------------------------------------|-------------------------------------|--------------------------|
| (−)-CBD        | > 10000     | > 10000     | Bisogno et al., 2001     | NAM-CB₁; FABPs; 5-HT₂A; 5-HT₂C; 5-HT₃A; GPR18; GPR55; CB₁; GPR11; GlyR A₁α; GABAₐ; TRPs | Neuroprotection; anxiety; psychosis; inflammation | Fasini et al., 2016; Morales et al., 2017 |
| (−)-CBD A      | 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 |             |             |                         |                                        |                                     | Muhammad et al., 2003   |
| Ferruginene C  |             |             | Seephonkai et al., 2011  | TRPA1                                  | Cancer                              | Seephonkai et al., 2011   |
| (−)-7-OH-CBD   | > 10000     | > 10000     | Bisogno et al., 2001     | –                                      |                                     |                         |
| (−)-7-OCOOH-CBD| 13.2 ± 0.4  | 312.8 ± 15.8| Frider et al., 2004      | –                                      |                                     |                         |
| CBE            |             |             | –                        | CYP1A1                                 | Inflammation                        | Ben-Shabat et al., 2006  |
| H₂-CBD         | > 1000      |             | Ben-Shabat et al., 2006  | Inflammation                           |                                     |                         |
| H₄-CBD         | 145         |             | Ben-Shabat et al., 2006  | Inflammation                           |                                     |                         |
| HU-444         | > 10000     | > 10000     | Haj et al., 2015         | –                                      | Inflammation                        | Haj et al., 2015         |
| HU-465         | 12.1 ± 2.3  |            | Kozela et al., 2015      | –                                      | Inflammation                        | Haj et al., 2015         |
| (−)-DMH-CBD    | > 10000     | > 10000     | Bisogno et al., 2001     | –                                      | Anxiety; pain; inflammation; cancer | Burstein, 2015; Juknat et al., 2016 |
| (−)-7-OH-DMH-CBD| 17.4 ± 1.8  | 211 ± 23    | Bisogno et al., 2001     | TRPV1, opioid, a₂-AR                    | –                                    | Fride et al., 2005; Pertwee et al., 2005 |

(Continued)
Ferruginene C, a methypentanol 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 (IC$_{50}$ 13.7 µM) with selectivity toward non-cancerous cell-line. It binds weakly to CB$_2$ and TPRV1 receptors, but it did not show significant affinity for CB$_1$ and 5-HT$_{1A}$ receptors (Table 1).
Even though linderatin (Figure 5), isolated from fresh leaves of Lindera umbellata Thunb. (Tanaka et al., 1984), is not considered a phytocannabinoid (Hanuš et al., 2016), it is interesting to include in the present review since closely related to CBD. No biological data have been reported so far.

SYNTHETIC CBD ANALOGS

Due to the promising therapeutic effects of CBD in a wide variety of diseases, synthetic CBD derivatives have attracted the attention of drug discovery programs in both industry and academia with the aim to improve the potency, efficacy, or pharmacokinetic properties of this interesting phytocannabinoid.

Synthetic approaches for different CBD metabolites such as 7-COOH-CBD or 7-OH-CBD (Figure 4) have been reported (Tchilibon and Mechoulam, 2000; Mechoulam and Hanuš, 2002). Moreover, structural modifications on different pharmacophoric positions such as the lipophilic side chain, the phenolic hydroxyl groups or the C7-methyl have been widely accomplished. In addition to the (−)-CBD enantiomers, the (+)-CBD derivatives [(+)-CBD depicted in Figure 6] have also been synthesized and pharmacologically evaluated (Bisogno et al., 2001; Fride et al., 2004; Hanus et al., 2005). Measurements of the binding affinities of these compounds for the CB₁ and CB₂ cannabinoid receptors yielded unexpected outcomes. Contrary to the naturally occurring (−)-CBD analogs, which showed no orthosteric affinity, most of the compounds in the (+)-CBD series bind to both receptors displaying selectivity toward CB₁ (Table 1).

Hydrogenation of CBD yielded the dihydro- and tetrahydro-cannabidiol derivatives H₂-CBD and H₄-CBD (Figure 6) (Ben-Shabat et al., 2006). Their effects on the production of reactive oxygen intermediates, nitric oxide, and tumor necrosis factor showed their anti-inflammatory capacity. In contrast to CBD, H₂-CBD, and H₄-CBD have affinity for the cannabinoid CB₁ receptor (Table 1). Additionally, the (−)- and (+)-dihydro-7-hydroxy-CBD enantiomers (HU-446 and HU-465, Figure 6) have recently been synthesized and biologically characterized in an inflammatory model of encephalitogenic T cells (Kozela et al., 2015). Both compounds showed anti-inflammatory potential.
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 Δ⁹−THC by a 1′, 1′-dimethylheptyl (DMH) lipophilic alkyl chain resulted in more active compounds than natural Δ⁹−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-inflammatoriy, 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 α₂-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 of 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 anticonvulsive 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
FIGURE 5 | Cannabidiol (CBD)-related Machaerium multiflorum, Rhododendron ferrugineum L. and, Lindera umbellata Thunb. compounds.

FIGURE 6 | (+)-CBD and hydrogenated CBD derivatives.
FIGURE 7 | Dimethylheptyl (DMH)-CBD derivatives.

FIGURE 8 | Cannabidiol analogs modified on the C4′-alkyl chain.
**FIGURE 9** | Chlorinated, brominated, and iodinated CBD derivatives.

O-methylcannabinol) 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-pentylcannabinol that have been structurally characterized but no pharmacological data have been described so far (Hendricks et al., 1978).

Cannabinoid 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 Pharmaceutics, developed transdermal solutions of CBD-esters and -carbonates among others. The dicarbonate All00102 and the diglicolate 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 IIα (Kogan et al.,

²https://kalytera.co/programs/preclinical/ (accessed June 8, 2017).
FIGURE 10 | Fluorinated CBD derivatives.

FIGURE 11 | Cannabidiol derivatives modified at the hydroxyl groups.
**FIGURE 12** | Diacetylated-CBD analogs.

- CBD-aldehyde-diacetate
- 6-Oxo-CBD-diacetate
- 6-Hydroxy-CBD-triacetate
- 9-Hydroxy-CBD-triacetate

**FIGURE 13** | Quinones related to CBD.

- HU-331
- CBD-Q (V)
- CBD-Q (VIII)
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 caspasas, 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 PPARγ 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 [35S]GTPγS 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 CB1 or CB2 receptors, stimulates GTPγS activation in membranes from human recombinant GPR55-expressing cells (EC50 = 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 α2 adrenergic receptor, TRP channels, cyclooxygenase (COX-1 and COX-2) enzymes, as well as the 5-HT1A and cannabinoid receptors (Cascio et al., 2010; De Petrocellis et al., 2011; Ruhaak et al., 2011). Cannabimovone is one of the latest natural phyto cannabinoids that has been extracted from a cultivar of hemp rich in CBD (Taglialatela-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 studies. 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 (−)-CBDVA, 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 atropoisomerism 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 atropoisomerism 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

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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.

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