Breaking bud: the effect of direct chemical modifications of phytocannabinoids on their bioavailability, physiological effects, and therapeutic potential.

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Abstract

Tetrahydrocannabinol (THC) and cannabidiol (CBD) are the two "major cannabinoids". However, their incorporation into clinical and nutraceutical preparations is challenging, owing to their limited bioavailability, low water solubility, and variable pharmacokinetic profiles. Understanding the organic chemistry of the major cannabinoids provides us with potential avenues to overcome these issues through derivatization. The resulting labile pro-drugs offer ready cannabinoid release *in vivo*, have augmented bioavailability, or demonstrate interesting pharmacological properties in their own right. This review identifies, tabulates, and discusses a subset of these advanced derivatization strategies for the major cannabinoids, where the starting material is the pure phytocannabinoid itself, and the final product either a cannabinoid pro-drug, or a novel pharmacoactive material.

Introduction

The cannabis plant produces cannabinoid-enriched buds valued for their psychoactive and medicinal properties[1] and has been historically consumed ceremonially, recreationally, and medicinally.[2] After approximately a century of restriction, the 21^{st} century has witnessed the emergence of a more research- and evidence-based approach to cannabis policy. As the therapeutic benefits of cannabis become increasingly accepted, the use of nutraceutical and recreational cannabis products have been decriminalized in countries including Argentina, Belgium, Canada, Georgia, Uruguay, South Africa, and certain states of the USA.[3]

Cannabis extract is a highly complex matrix, containing well over 150 closely related major and minor cannabinoids alongside other phytochemicals such as terpenes and flavonoids.[4,5] Cannabinoid pharmacology has focused around their molecular interactions with their putative G-protein coupled receptor (GPCR) targets, cannabinoid receptor 1 (CB_1) and cannabinoid receptor 2 (CB_2),[6] although their activity is broader and more complex.[7] Δ^9- tetrahydrocannabinol (THC) and cannabidiol (CBD) are by far the most abundant phytocannabinoids, and are considered the "major cannabinoids" (Figure 1). As of 2020, over 150 minor cannabinoids, collectively constituting less than 1% of the total dry mass of the cannabis bud, have been identified; however, very little is known about their pharmacological effects; for the purposes of this review, we will consider only the major cannabinoids, THC and CBD.[8] For the sake of convenience, THC here onwards implies Δ^9-THC; other isomers such as Δ^8-THC will be explicitly indicated.

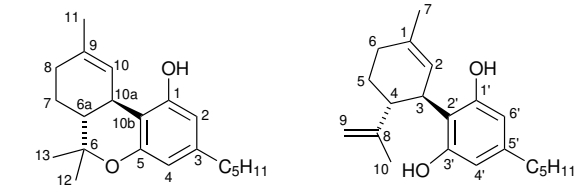

Figure 1: The major cannabinoids with numbering schemes. Note: THC typically uses the dibenzopyran numbering convention, whereas CBD uses the monoterpenoid scheme.

THC and CBD have demonstrated neuroprotective, immunomodulatory, and anti-inflammatory effects, leading to their exploration as adjunctive treatments for nausea,[9] Parkinson's disease,[10] Alzheimer's disease,[11] multiple sclerosis,[12] neuropathic pain,[13] and childhood seizure disorders.[14] Building on extant anecdotal evidence, clinical trials are being conducted to examine the therapeutic potential of the major cannabinoids for conditions including, but not limited to, generalized anxiety disorder,[15] cancer-related breakout pain,[16] schizophrenia,[17] opiate addiction,[18] post-traumatic stress disorder,[17] graft-versus-host disease,[19] and inflammatory bowel disease.[20] In 1985, Dronabinol (gelatin capsules containing (-)-*trans*-Δ^9–THC dissolved in sesame oil) became the first FDA-approved cannabinoid medication – for appetite stimulation, countering emesis, and for chronic pain relief.[21] Epidiolex/Epidyolex® – formulated, pure CBD – has been approved by regulatory bodies in the US and Europe; it is typically prescribed as an adjunctive therapy for seizures associated with Lennox Gastaut syndrome (LGS) or Dravet syndrome (DS).[22] Sativex® is another cannabis-based pharmaceutical product – an oromucosal spray approved over a decade ago in the United Kingdom intended to alleviate neuropathic pain, spasticity, overactive bladder, and other symptoms of multiple sclerosis.[23] It is considered to be a combination drug, containing both major cannabinoids in a 1:1 ratio, albeit standardized in composition, formulation, and dose., with each spray of Sativex® delivering 2.7 mg THC and 2.5 mg CBD.[24] This drug has also been approved by Health Canada for the treatment of MS spasticity, as well as for the symptomatic relief of neuropathic pain in MS and cancer-related breakout pain.[25]

Despite their pharmacological promise, cannabinoids are typically highly hydrophobic; their solubility in aqueous media such as serum is extremely limited. The standard measure for chemical solubility is the partition coefficient between water and octanol ($\log(c_{octanol}/c_{water})$, calculated lipophilicity, **C.logP**).[26] Hardman and colleagues recorded the **C.logP** values of Δ^9-THC (7.2) and CBD (6.6); CBD has two hydroxyl groups (at C_2' and C_6') to THC's one, which presumably explains the difference in their **C.logP** values.[27] In terms of solubility in water, CBD is an order of magnitude more soluble in water than THC (saturation concentra-

tions from ALOGP algorithms: $[\mathrm{THC}]_{water} = 2.8\ \mu\mathrm{g/L}$; $[\mathrm{CBD}]_{water} = 12.6\ \mu\mathrm{g/L}$).[28,29] This lack of ready solubility, and consequent low bioavailability upon oral consumption, is why smoking has been the traditional method to introduce cannabinoids. While scattered cultural traditions consumed cannabis orally, it is only recently that mass-produced oral preparations of cannabis have emerged as viable alternatives to inhalation as an administration route for people unwilling or unable to smoke the "laser lettuce". Inhalation has health risks, including small particulate matter, and is not an ideal way to consume cannabis; similarly, it is difficult to ensure a specific dose through smoking cannabis, oral formulations could provide better control.[30] However, apart from the limited water solubility of the cannabinoids, oral cannabis formulations must overcome several hurdles to deliver an experience comparable to inhalation.[31]

1. orally administered cannabis has delayed onset times for effect, as well as longer retention time in the human body;

2. the onset and retention times of orally administered cannabis depend on the ingestion matrix and the physiology of the person ingesting the preparation;

3. orally administered cannabis shows reduced bioavailability compared to inhaled cannabis; and,

4. incomplete absorption of cannabinoids by the gastrointestinal tract and/or first pass metabolism by liver enzymes reduces the effect of ingested cannabis.

It was reported, for instance, that THC showed only 6% bioavailability (measured by plasma THC concentration values) following the oral ingestion of a cookie containing 20 mg of THC.[32] Dissolution of THC in long chain triglycerides (oils) typically leads to improved bioavailability (rising to between 10 and 20%), potentially owing to the formation of chylomicrons.[33] Chylomicrons are lipoprotein particles that transport dietary lipids from the intestines to other locations in the body, and serve as "trojan horses", carrying THC

and CBD through the epithelial layer to the intestinal lymphatic system, bypassing hepatic first-pass metabolism. This results in higher bioavailability of lipid-solubilized cannabis compared to lipid-free cannabis extracts. Since the ingestion of undiluted lipids loaded with cannabis extract is typically a highly unpleasant organoleptic experience, various strategies have been developed to generate water-soluble cannabis-loaded lipid systems for pharmaceutical and nutraceutical applications.[34] These include nanoemulsions, microemulsions, solid lipid nanoparticles, nanostructured lipid carriers, lipid based self-(nano)emulsifying drug delivery systems, liposomes, filled microgels, as well as their solid analogues, in the form of capsules, chewables, and spray-dried powders. Physical strategies for formulating cannabis beverages and edibles have been reviewed multiple times in the recent past.[35–37]

There is, however, a different approach to solving oral bioavailability: breaking bud, or chemically derivatizing the materials to improve solubility. Pro-drugs are a well established strategy in pharmacology. These can be harnessed to create water-soluble, bioavailable cannabinoid preparations without involving multiple surfactants, adjuvants, carrier lipids, *etc.*[38] A pro-drug is a medication which, after ingestion, is metabolized within the patient's body into a pharmacologically active molecule, often *via* an enzymatically catalyzed transformation.[39] They are designed to improve the bioavailability of a drug which in itself is poorly absorbed from the GI tract. Many traditional herbal and botanical remedies actually contain glycosides of the pharmacologically active ingredient; upon intake, the sugar moiety is cleaved in the GI tract by enzymes to release the bioactive aglycone. A familiar example of this phenomenon is salicin, an alcoholic β-glucoside found in willow bark, which, upon cleavage by esterases, releases the analgesic salicylic acid.[40] A rather more potent analgesic, benzhydrocodone, is the benzoic ester of hydrocodone; benzhydrocodone is pharmacologically inactive, but releases hydrocodone upon cleavage of the benzoate by intestinal enzymes.[41] Approximately 10% of all marketed drugs are pro-drug formulations.[42]

The focus of this review is on advances in the chemical derivatization of THC and CBD, to enhance uptake or aqueous solubility and bioavailability. Relatively minor changes in

the chemical structure of phytocannabinoids can lead to enormous changes in their biological effects owing to novel receptor-ligand interactions – for instance, the methyl ether of Δ^9-THC was found to be 100 times weaker than its parent cannabinoid in mice.[43] Oral, topical, oromucosal, transdermal, sublingual, buccal, ocular and other delivery routes will be considered as viable entry points for derivatized phytocannabinoids. We will also consider derivatized cannabinoids which **do not** behave as pro-drugs, but can play important roles in biological systems for the treatment of a variety of conditions, without the need for any prior metabolism. However, synthetic agonists and antagonists of the human endocannabinoid receptors, which are typically not obtained by direct chemical modifications of the phytocannabinoids, and are, instead, designed and synthesized using a *de novo* approach, lie outside the scope of this review. Similarly, we are not reviewing the semi-synthesis of minor cannabinoids from major cannabinoids, although this is also a very important and rapidly growing area of focus.

Post-ingestion fate of cannabinoids

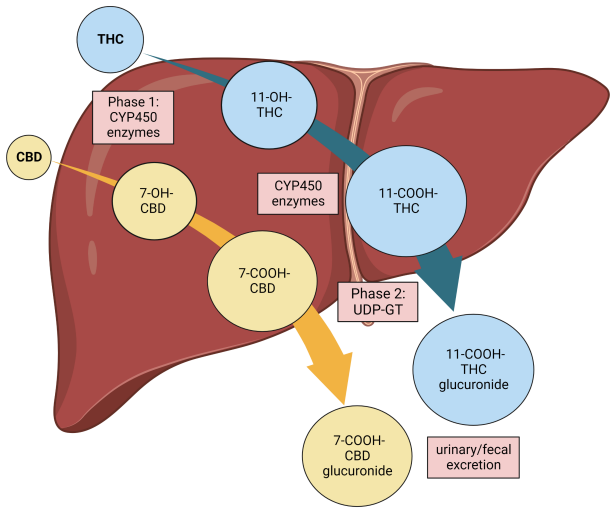

Figure 2: Metabolism of THC and CBD after ingestion.

Cannabis edibles introduce cannabinoids to the body through the GI tract, where they are

absorbed into the bloodstream *via* the hepatic portal vein (Figure 2).[44] The systemic absorption of cannabinoids after oral ingestion of cannabis-enriched food or beverages is relatively slow compared to that from inhaled cannabis.[45] Maximum Δ^9-THC plasma concentrations are typically attained within a few hours rather than the few minutes from inhalation. Extensive liver metabolism reduces the oral bioavailability of Δ^9-THC by ∼4-12%. Approximately 90% of Δ^9-THC in blood is circulated in plasma, and the rest in red blood corpuscles. Following entry into the bloodstream, Δ^9-THC is rapidly transported to adipose tissue, as well as to highly vascularized tissues, such as the brain.[46] This tissue penetration is then followed by its slow return from adipose tissue back into the bloodstream. The cannabinoids are then metabolized in the liver.[47] THC and CBD are subjected to two phases of metabolism once inside the liver (Figure 2). Phase 1 is conducted by the cytochrome P450 system - a superfamily of enzymes that function as monooxygenases. Phase 2 involves the glucuronidation of phase 1 metabolites, which facilitates fecal and urinary excretion from the kidneys. The main metabolite of interest of Δ^9-THC is **11-OH**-THC; A psychoactive metabolite more potent than THC that is also able to cross the blood-brain barrier. **11-OH**-THC has been observed to have higher blood concentration levels when Δ^9-THC is ingested rather than inhaled, suggesting that it could be responsible for the stronger and longer-lasting 'high' typically experienced when consuming cannabis infused edibles.[48]

CBD also metabolizes into various hydroxylated and decarbonylated forms, with the most abundant being **7-OH**-CBD which further oxidases to **7-COOH**-CBD (Note: because THC and CBD follow different numbering schemes it may not be obvious that **11-OH**-THC and **7-OH**-CBD have been oxidised at the equivalent allylic methyl groups). These metabolites are excreted in feces and urine, both neat, and as their glucuronide conjugates.[49] Similar to THC, this process follows the same two-phase structure, with the first phase being oxidation, first by the CYP2C19 and CYP3A4 enzyme subfamilies, then subsequently by the CYP1A1, CYP1A2, CYP2C9, and CYP2D6 subfamilies. Then, phase two uses UDP-GT to enzymatically form the glucuronide conjugates. Two other processes involve glucuronyl

transferases and sulfotransferases; however, the CYP450 family of enzymes remains the only one thoroughly studied in humans. These CBD metabolites have been synthesized and studied for therapeutic pharmacological effects - for instance, Tchilibon and Mechoulam reported an eight-step synthesis of **7-OH**-CBD starting from CBD itself in 2020.[50]

Chemical modifications of Δ^9-THC, Δ^8-THC, and their analogues

O-acyl derivatives

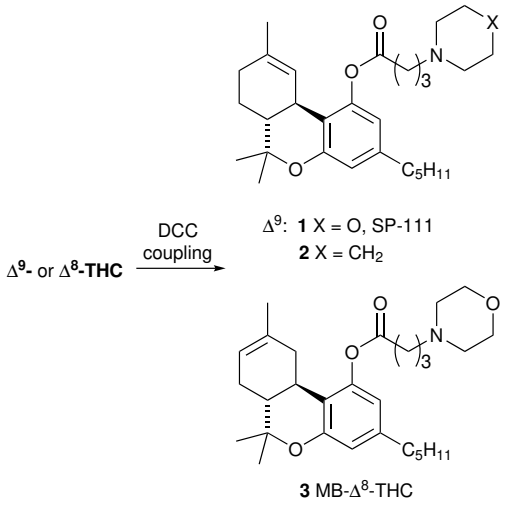

Figure 3: Conversion of Δ^9-THC and Δ^8-THC to their γ-morpholinobutyric acid esters.

One of the earliest examples of THC functionalization for augmenting water-solubility for improved oral uptake was reported by Zitko and colleagues in 1972, only 8 years after the isolation and characterization of THC from phytocannabinoid distillates. The derivatives in question were nitrogen-bearing esters of the phenolic -OH on THC.[51] Dicylohexylcarbodiimide (DCC) was used to obtain γ-morpholinobutyrate **1**, SP-111, and β-piperidinopropionate **2** esters of THC, the latter ester in smaller yields than the former (Figure 3). Ester **1** is a solid, freely soluble in water; *in vitro* hydrolysis of the side chain in the presence of

microsomal liver preparations quickly generates free THC. In animal studies, the derivative demonstrated both dose dependent ataxia and a time-to-onset-of-action comparable to underivatized THC. The authors briefly mentioned the diethylaminobutyrate class of water-soluble esters of THC which also produced ataxia in unanesthetized animals, but the onset of action was considerably delayed and the effective dosage was five to ten times higher, indicating reduced bioavailability. SP-111 was subsequently studied by many other groups as a model water-soluble Δ^9-THCpro-drug. The corresponding Δ^8-THC ester **3** has also been prepared.[52,53]

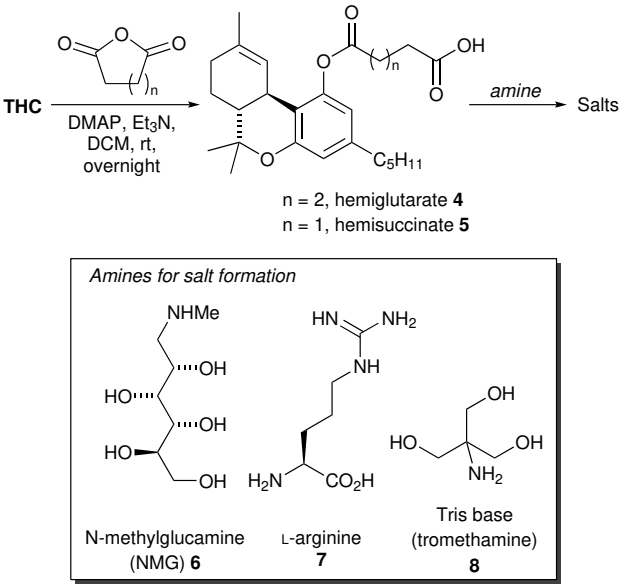

Figure 4: Δ^9-THC hemisuccinate and hemiglutarate ester salts as prospective glaucoma therapeutics.

ElSohly and colleagues have published a number of protocols for generating water-soluble derivatives of Δ^9- and Δ^8-THC over the years. In one preformulation study they synthesized the hemiglutarate prodrug **4** by the reaction of THC with a slight excess of glutaric anhydride in dichloromethane at room temperature in the presence of triethylamine and catalytic DMAP; this derivative was then incorporated within poly(ethylene oxide)/PEG matrices using a hot-melt method.[54] A similar reaction with succinic anhydride led to the hemisuccinate ester **5**. They reported the synthesis of N-methylglucamine (NMG, **6**) salts of the hemisuc-

cinate esters and hydrochloride salts of the alaninate esters of Δ^9- and Δ^8-THC. The NMG salt was prepared by combining equimolar amounts of **5** with **6** in ethanol, followed by evaporation of the solvent. These THC derivatives retained the therapeutic value of THC against glaucoma by lowering intraocular pressure (IOP) in test animals upon topical application in aqueous formulations; Δ^9-THCderivatives showed greater IOP reduction in comparison to Δ^8-THC. In another study, aimed at improving the *in vitro* transcorneal permeability characteristics of THC through prodrug derivatization, hemiglutarate and hemisuccinate derivatives of THC were created, and an ion-pair complex with a hydrophilic counter ion (L-arginine **7**/tromethamine **8**) was then generated to improve the solubility of the drug.[55] Formation of these ion-pair complexes led to a 7-fold increase in the solubility of the THC pro-drug compared to unfunctionalized THC (Figure 4). The same group also formulated suppositories laced with **5**, as well as its NMG salt. In both cases, animal studies revealed excellent bio-availability of THC from these derivatives, comparable to that of Δ^9-THCfrom oral administration in a sesame seed oil mixture. In the control animals treated with unmodified THC suppositories, no THC could be detected in the blood plasma. Apparently one needs to break the bud to potentiate it *in ano*.

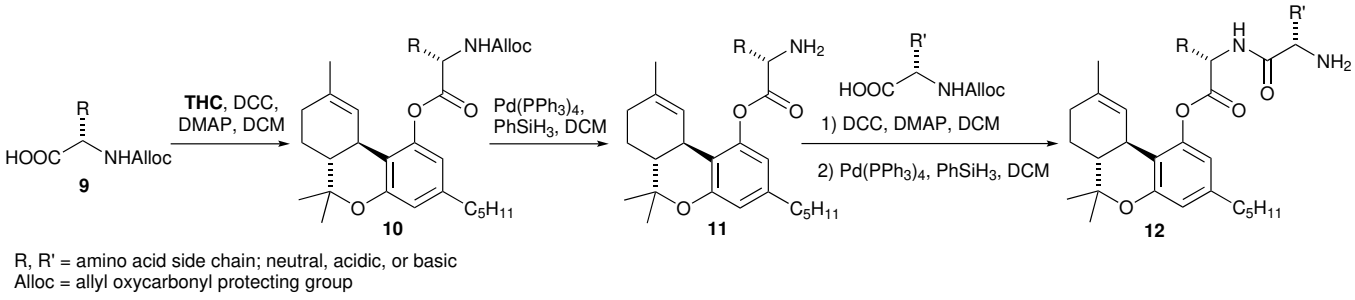

Figure 5: Attachment of multiple amino acids to the phenolic -OH of Δ^9-THC.

In a 2014 patent, ElSohly *et al.* described in detail a protocol for obtaining amino acid-THC derivatives for ophthalmic use.[56] The use of Boc or Fmoc protected amino acids for this reaction were problematic: in the case of Boc, deprotection under various conditions always resulted in conversion of the Δ^9-THC, at least in part, to Δ^8-THC; deprotection of Fmoc resulted in reversion to Δ^9-THC. In order to circumvent this obstacle, Alloc protected

amino acids **9** were used. DCC coupling attached the protected amino acids to the Δ^9-THCcore, yielding ester **10**; the Alloc group was then removed using palladium catalysis to provide **11**. These steps could then be used iteratively to produce dipeptides **12**; up to three amino acids could be attached to Δ^9-THCby this approach (Figure 5).[57] A similar patent by Stinchcomb *et al.* dealt with THC prodrugs containing hydrophilic functional groups (such as phosphonates, carbonates, esters, and variations thereof) conjugated to the phenolic -OH of THC; these were supposed to be used as transdermally applied cannabinoid prodrugs with augmented bioavailability, meant to treat a variety of conditions.[58]

An example of Δ^9-THC conjugated to an opioid was prepared by Dhooper *et al.*, who linked codeine **13** and Δ^9-THC using a carbonate linker **15** (Figure 6). Several attempts were made to vary the base as well as other reaction conditions, and a MALDI spectrum showed evidence for formation of a conjugate, but the reaction never went to completion, and presumably no conjugate was actually isolated. A microwave-mediated reaction did not improve the situation. However, in a third reaction, the coupling of the *p*-nitrophenol carbonate of codeine **14** with Δ^9-THC was successful. In this reaction, Δ^9-THC was treated first with NaH at a low temperature, followed by drop-wise addition of **14**, leading to a 43% yield of the conjugate drug. The co-drug generated a stronger and longer amelioration of neuropathic pain in mice, when compared with either of the constituent pharmacophores alone.[59]

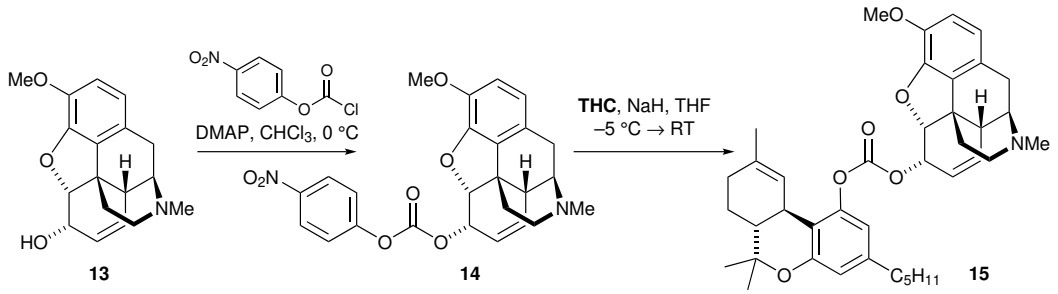

Figure 6: Synthesis of a Δ^9-THC-codeine co-drug for enhanced pain relief.

Acylation of the phenolic -OH in Δ^9-THC does not always lead to increased bioavailability, water-solubility, or novel receptor responses. Little *et al.* concluded in 1987 that

1-N,N-*bis*-(dichloroethyl)carbamate-Δ^9-THC, a nitrogen mustard analog of Δ^9-THC, lacked cannabinoid activity following peripheral administration. However, intravenous administration in test animals produced weak cannabimimetic effects. The nitrogen mustard analog of Δ^9-THC was as effective as Δ^9-THC in reducing rectal temperature, but 5 times less active than Δ^9-THC in decreasing spontaneous activity of mice.[60] However, acetylation of the phenolic -OH of Δ^9-THC with acetic anhydride produced the corresponding acetate which was claimed to be twice as potent as THC, with a slight delay of onset times.[61]

O-alkyl derivatives

Ether derivatives of Δ^8-THC and Δ^9-THC mostly fall outside the scope of this review because the ones presented in literature do not tend to have augmented hydrophilicity or bioavailability in comparison to the unmodified phytocannabinoids, nor are they designed to be hydrolysed *in vivo* to the parent compound and so are not pro-drugs *per se*. However, some ether analogues of the cannabinoid drug class are interesting because they demonstrate novel agonist and antagonist pharmacological properties (Figure 7). In 1991, Compton *et al.* synthesized a variety of ether biphenyl, phthalimide, alkyl, and aminoalkyl derivatives of Δ^8-THC and $\Delta^{9,11}$-THC, and evaluated them for their agonist/antagonist activities in animal models. While the methyl ethers of Δ^8-THC and Δ^9-THC showed limited activity in mice, their effects differed from each other. $\Delta^{9,11}$-THC showed weak pharmacological activity at large doses. However, the weakly active ether analogues of THC did not demonstrate mixed agonist/antagonist properties.[62] Similarly, novel oxepin derivatives of Δ^9-THC, synthesized by Jorapur and co-workers, proved that the incorporation of a seven-membered oxepin in the Δ^9-THC structure eliminated cannabinoid activity altogether.[63]

The use of cannabinoid-based entities in theranostics (combining diagnosis and therapy) is in its infancy; however, in 2019 Bryant *et al.* created a complex conjugate containing a cannabinoid cyclam **16** and a radionuclide label (such as ^{99m}Tc, ^{211}At, ^{111}In, and many others) as a novel theranostic agent **18** (Figure 8). The cannabinoid was developed as an

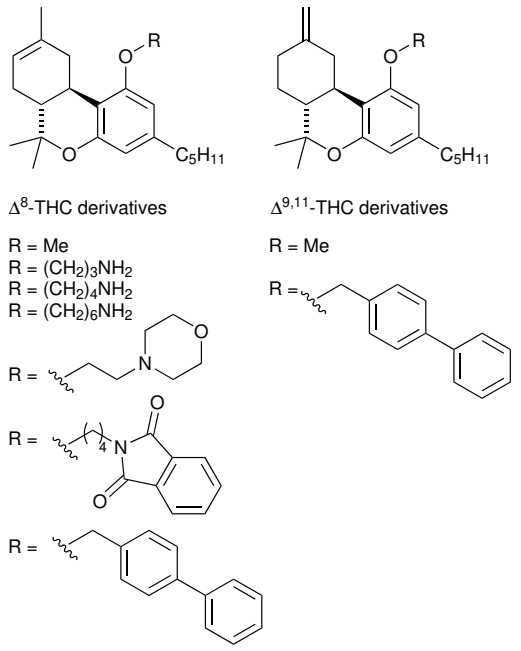

Figure 7: Some representative ether derivatives of Δ^8-THC and $\Delta^{9,11}$-THC.

immune check point cannabinoid receptor agonist. In some embodiments of this invention, a chemotherapeutic agent such as ibrutininb or tumorex were also involved. As Figure 8 shows, this protocol could also be applied to CBD in order to create the corresponding conjugate species **17** prior to the chelation of the radionuclide. The potential theranostic applications cited for these conjugate systems are too numerous for a brief mention; the interested reader is referred to the patent for further information.[64]

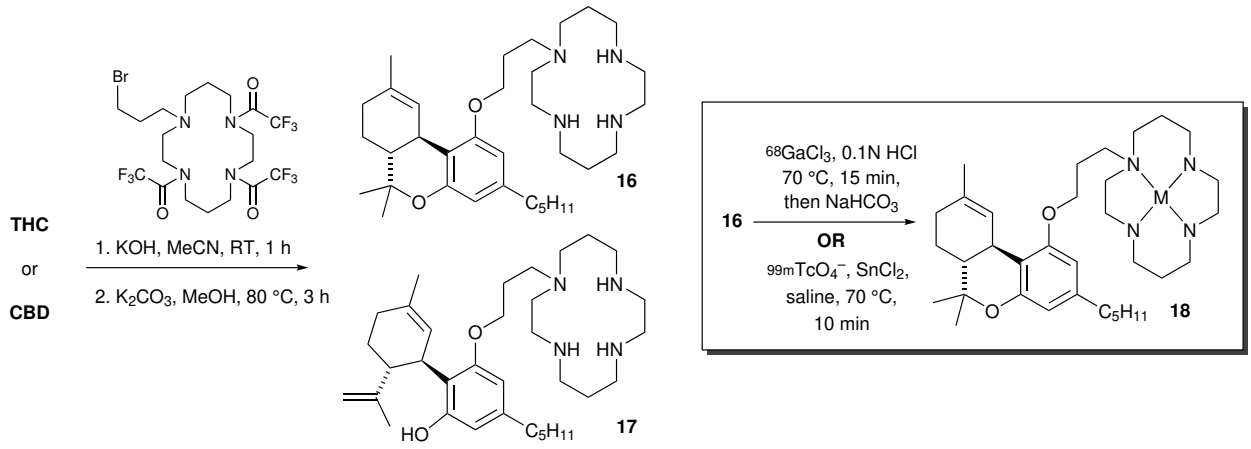

Figure 8: Creation of a cannabinoid/chelator/radionuclide theranostic system.

Numerous (less active) O-alkyl substituted derivatives of Δ^9-THC were synthesized by Rehman and coworkers. Upon treatment with different electrophiles in the presence of sodium hydride and DMF, THC furnished O-substituted derivatives which were seen to inhibit the enzyme butylcholinesterase, with IC_{50} values between 60 and 112 μM, compared to approx. 49 μM for unmodified THC.[65]

In 1990, Reggio and colleagues synthesized a pair of rotationally restricted tetrahydrocannabinol (THC) ethers, supposedly to test the concept that the psychopharmacological activity of cannabinoids show a dependence on the orientation of the lone pairs of electrons of the phenolic hydroxyl oxygen. Through annulations leading to cyclic ether formations, these new derivatives locked the orientation of the lone pairs of electrons towards and away from the cyclohexene ring, respectively. No biological testing was, however, carried out by the authors in that study.[62]

Miscellaneous derivatives

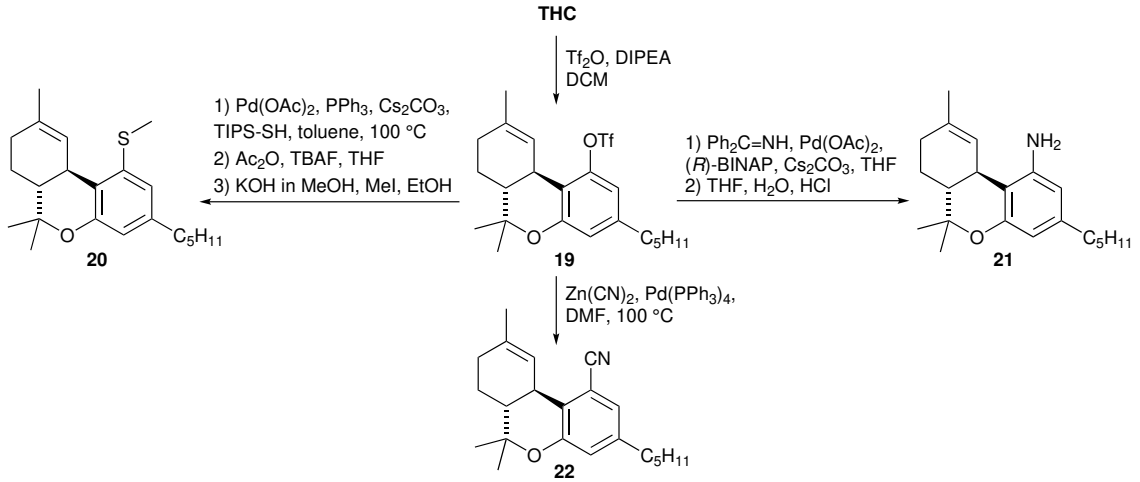

Figure 9: Conversion of Δ^9-THC to derivatives *via* a triflate ester intermediate.

In 2009, Burdick *et al.* prepared a series of novel Δ^9-THC analogues in order to evaluate their cannabinoid receptor modulatory activities (Figure 9). In an initial step, Δ^9-THC was converted to its triflate ester **19**; from this, a variety of derivatives were generated by

palladium-catalyzed reactions. The derivatives were evaluated in *in vitro* binding assays; three of the derivatives (thiomethyl ether **20**, amine **21**, and nitrile **22**) showed CB_2 binding affinities in the 200-500 nM region, and were considered 'hits'. A two-fold selectivity for CB_2 over CB_1 was observed for thioether **20**, while 3-4-fold selectivity for CB_2 over CB_1 was recorded for **21** and **22**.[66]

Conversely, novel mercapto and thioacetyl-decorated derivatives **23-26** of Δ^8-THC synthesized by Compton *et al.* were broadly pharmacologically inactive except for the production of hypothermia in mice by **23**, though by a significantly lesser extent than the parent Δ^8-THC. This was particularly surprising, as the substitution of alcohol **22** for the more lipophilic thiol was expected to increase its potency, indicating the need for the conservation of specific cannabinoid structural features to retain *in vivo* cannabimimetic activity (Figure 10).[67] The 11-substituted derivatives **22-24** were all prepared by selenium dioxide oxidation on acetyated Δ^8-THC; the sulfur was then introduced through a Mitsunobu reaction with thioacetic acid. The same conditions were also used to prepare thioacetate **26** from **25**, which was itself prepared from CBD (*vide infra*), although in lower yield; the authors considered this an expected consequence of the greater reactivity of the allylic alcohol in **22** *vs* the neopentyl alcohol in **25**.

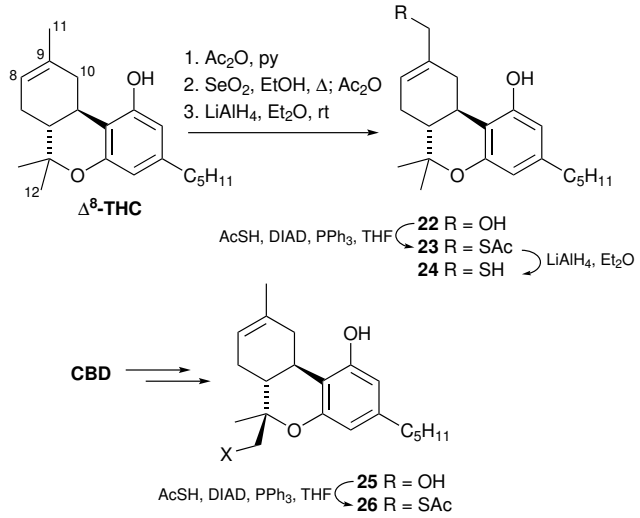

Figure 10: Mercapto and thioacetyl derivatives of Δ^8-THC.

Glycosides of small molecules can be transported across the blood brain barrier (BBB) by glucose transporter GLUT1; their use in pro-drugs is becoming increasingly common. Zipp *et al.* used glycosyltransferase-mediated glycosylation of cannabinoid molecules to form cannabinoid glycoside prodrugs.[27] For re-conversion of the pro-drug back to THC or CBD, they noted that the glucose residues of glycosides are hydrolyzed in the stomach at acidic pHs, or are cleaved by glycosidase enzymes in tissues having increased expression of glycosidases. The hydrophobic aglycone cannabinoid moiety is then released into the targeted tissue or organ. This new class of cannabinoid-glycosides were called *cannabosides* by the authors, and they were found to have excellent serum solubility, making them suitable for oral administration. This was followed by a 2018 patent which described the use of cannabinoids as antimicrobials, with the cannabinoid glycosides behaving as as prodrugs.[68] A 2020 patent with new related compounds, structures, and functional improvements, and yet another on the reactor system for production of the glycosides was published.[69]

It is to be noted that there are many synthetic cannabinoids with gross structural similarities to Δ^8-THC and Δ^9-THC; a common example is the 1,1-dimethylheptyl analogue of Δ^9-THC and its many derivatives, which typically demonstrate bioactivities and cannabinoid receptor binding affinities an order of magnitude higher than their parent. However, these are typically not synthesized from the phytocannabinoid; rather, they are prepared *de novo*. The interested reader is directed to other excellent accounts of synthetic cannabinoids and their bio-activity profiles.[70,71]

Chemical modifications of CBD and its analogues

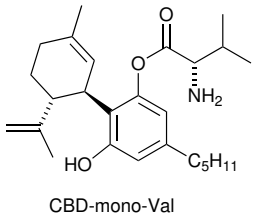

Figure 11: Monovalinated CBD.

A search of the relevant literature seems to indicate that chemical modifications of CBD have been attempted more frequently than that of THC; this could potentially be explained by the non-psychotropic nature of CBD, a more diverse benefits "portfolio", and a structure that is more flexible and offers more functionalization sites. In this section, therefore, we will focus only on CBD derivatives that have shown some novel biological properties. In a previous review on the delivery protocols for CBD, Millar *et al.* have summarized some of the CBD formulations under development by pharmaceutical companies with information in the public domain.[72] Of these, the ones that are significant for the purposes of this review include CBD conjugated with naproxen (oral; for acute and chronic pain relief); CBD conjugated with codeine (synergistic effectiveness and prolonged pain management in comparison to the parent drugs); water-soluble bisulfate derivative of CBD (oral; for ulcerative colitis); a novel aerosolized formulation of the biphosphate derivative of CBD (intra-tracheal; for adult respiratory distress syndrome); and a L-valine ester of CBD (topical; for chronic inflammatory skin disease; Figure 11). The reader is directed to this earlier review for detailed accounts of these CBD derivatives.[72]

CBD bears an ^{n}pentyl group at its C_5' position. While there are several natural and synthetic cannabinoids bearing different C_5' terminal groups (mostly,[73] though not always,[74] alkyl groups with different chain lengths) tethered to a core CBD structure, none of them have been generated directly from CBD, and are, therefore, outside the scope of this review.

O-acyl derivatives

Many acylated CBD derivatives have proved to be hydrophilic prodrugs, releasing CBD *in vivo* upon displacement of a biolabile linker. The rate and extent of the absorption and metabolism of the drug molecule, however, was influenced by the choice of substituent. Recently, a patent disclosed the synthesis of two CBD derivatives, HU-435 **28** and HU-436 **29** (the maleate salt of HU-435), Figure 12. These molecules use the same solubilising side chain as was used previously in the THC derivative SP-111 (**1**), *vide supra*. HU-435 was obtained from the esterification of mono-methoxy CBD **27** and 3-morpholinopropionic acid using DCC and catalytic 4-pyrrolidinopyridine in DCM. HU-436 was then obtained by treatment of **28** with maleic acid in *iso*-propanol. These molecules were evaluated as potential drug candidates; they inhibited the formation of reactive oxygen species in cells, and in murine models, suppressed TNFα by 46%. These CBD derivatives also suppressed the appetites of the mouse subjects.[75] We note in passing that there are many more such patents extant in the relevant literature; however, their claim to novelty lie in the nature of the substituent rather than strategy.

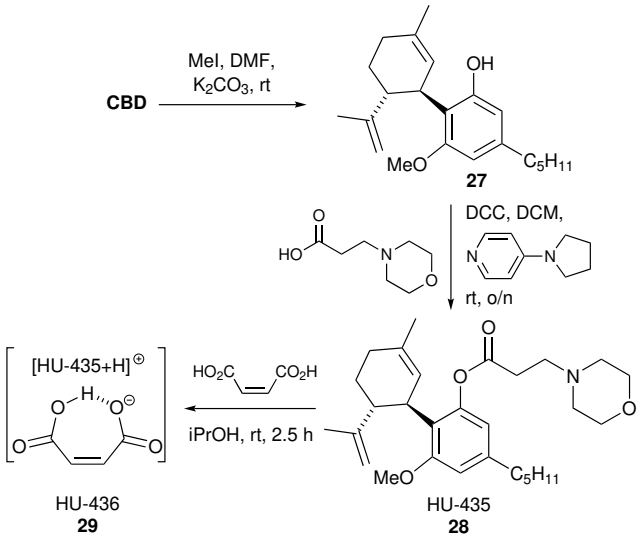

Figure 12: Preparation of water-soluble HU-435 and its salt HU-436.

A variety of CBD pro-drugs were patented in 2011 by Stinchcomb *et al.* for application

on microneedle-treated skin for the alleviation of pain. These pro-drugs were water-soluble owing to the presence of quaternary ammonium groups; while this type of functionalization approach has been used in the past, the novelty of some of the CBD "dimer"-type pro-drugs such as cation **30** and zwitterion **31** (Figure 13) deserves mention. The total CBD flux from a tested pro-drug on microneedle-treated Yucatan pig-skin was approximately 12 times higher than a control formulation of unmodified CBD gel.[76]

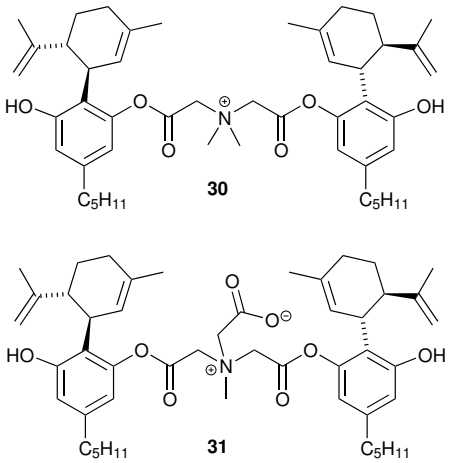

Figure 13: Quaternary ammonium functionalized CBD "dimer" prodrugs.

The creation of an inclusion complex between functionalised cyclodextrins and CBD has been mentioned in the literature in the past.[29] A recent patent improved on this idea by coupling amino-functionalized cyclodextrins to carboxylic acid modified CBD (using standard amide coupling conditions such as DCC or HATU) to form a CBD-cyclodextrin covalent conjugate rather than an inclusion complex. The complex conjugate thus produced linked the CBD to the water-soluble cyclodextrin through covalent bonds, leading to superior water solubility and enhanced bioavailability of CBD in comparison to emulsified CBD.[77] The carboxylic acid modifications used in this study were analogous to those previously mentioned for THC, *i.e.* a phenol group was acylated with a cyclic anhydride (succinic or glutaric) in the presence of catalytic DMAP to generate the corresponding semisuccinate or semiglutarate (*c.f.* Figure 4).

O-alkyl derivatives

There have been many reports on attempted functionalizations of the phenolic -OH groups in CBD, and it remains one of the easiest sites to modify in order to create water-soluble derivatives of CBD. Mechoulam *et al.* have published several studies and patents on CBD derivatives with functional groups (such as -CH_2CH_2OH, -CH_2CH_2NHBoc, and -CH_2CN) replacing one of the phenolic protons on the benzene ring. These were generated from CBD in 2-3 steps by simple chemical transformations.[78,79]

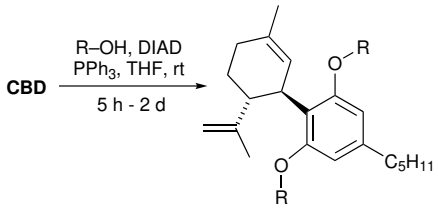

Figure 14: Mitsunobu protocol for the preparation of O-alkylated CBD derivatives.

Whilst most alkylated phenol derivatives are prepared under basic conditions with an alkyl halide (or equivalent), a Mitsunobu protocol for modification of CBD was reported by Ziegler and Cosky in 2021 (Figure 14). CBD, upon reaction with primary alcohols, produced the corresponding *bis*-alkylated cannabidiols. No such reaction, however, was seen in the case of Δ^9-THC. When ester groups were present on the alkyl chain, highly water-soluble potassium salts could be obtained by saponification using KOH.[80]

There are numerous examples of CBD conjugated to drug molecules, such as multi-functional conjugates of CBD linked to β-lactam antibiotics; reactive oxygen species such as hydroxyl radicals (whose formation may be promoted by CBD) are supposed to trigger bacterial annihilation on top of the bacteriostatic or bacteriocidal activity of the antibacterial drug (Figure 15). The drug conjugate binds to penicillin binding protein (PBP); nucleophilic attack by the protein on the β-lactam moiety then releases the cannabinoid for its secondary therapeutic action.[81]

Among studies that leverage the lability of the phenolic proton in derivatizing CBD, one that deserves a brief mention incorporates long PEG chains with azide termini **32** (Figure

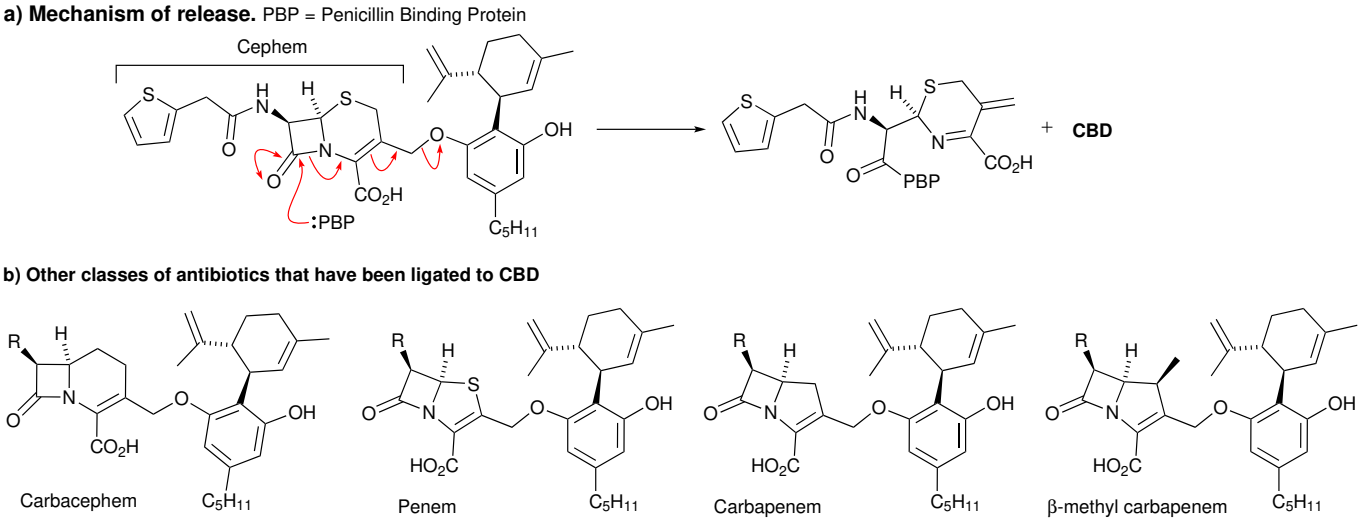

Figure 15: CBD-β-lactam conjugates: a) CBD release mechanism; b) selected antibiotic classes.

16). These can then undergo a copper(I)-catalysed azide-alkyne cycloaddition reaction with alkyne-containing pharmacophores to provide drug conjugates **33** with enhanced water solubility, imparted by the PEG domain. Some of these CBD ethers had low hepatic extraction ratios and were believed to be less susceptible to metabolic degradation and elimination by the liver during the initial pass. Nor were they susceptible to conversion to Δ^9-THC *in vivo*. The patent went on to describe a veritable cornucopia of medications to be developed from these functionalized CBD oligo-ethers, for treatment of conditions related to epilepsy and other neuronal disorders.[82]

Miscellaneous derivatives

The resorcinol ring in CBD is very electron rich, and thus can be quite reactive towards electrophiles or oxidants. As a result, such chemistry is often performed on the diacetate **34**, first reported in 1976 by Agurell *et al.*, and prepared from CBD by using acetic anhydride in pyridine.[83] The electron-withdrawing acetate protecting groups reduce the electron density in the resorcinol moiety, and thus is an ideal protecting group for oxidation chemistry. For example, **34** undergoes oxidation on the aliphatic ring when treated with sodium chromate

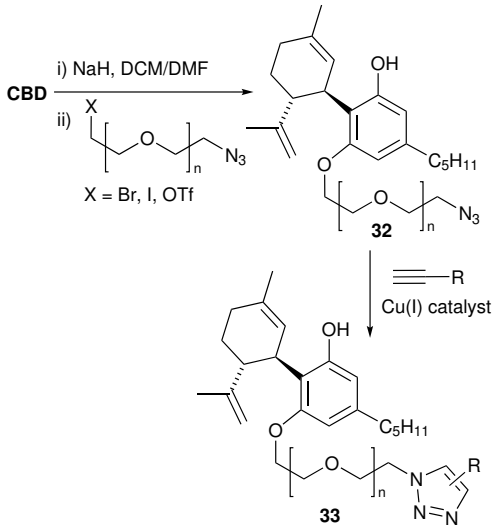

Figure 16: Pharmacophore ligation using CuAAC click chemistry.

to provide 6-oxo-CBD diacetate **35** in moderate yield. Conversely, treatment of **27** with selenium dioxide regioselectively hydroxylated C_{10}; acetate protection of the primary alcohol provided triacetate **29** in low yields, with the major product of this reaction sequence being the over-oxidised aldehyde **30** (Figure 17).

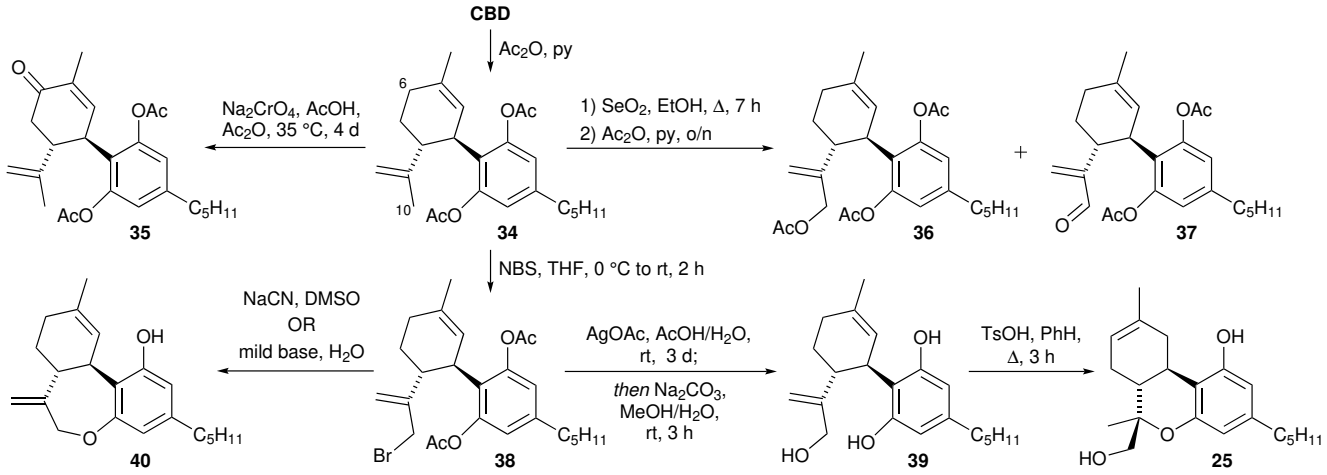

Figure 17: Acetylation of CBD and use as a protecting group in the synthesis of oxidized derivatives.

An improved approach to 10-HO-CBD **39** proceeded through bromide **38**, which was prepared regioselectively by the reaction between diacetate **34** and NBS under ionic conditions (*i.e.* in the dark) in good yield (81%). Initial attempts to displace the bromide

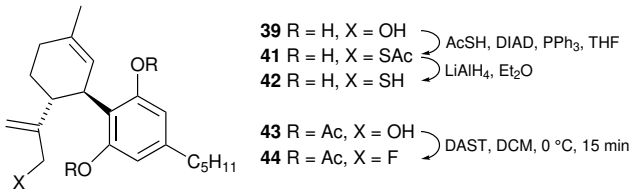

Figure 18: Exocyclic C_{10} modification of CBD.

using cyanide or mildly alkaline conditions resulted in the formation of oxepin **40**; conversely, treatment of **38** with various amines resulted in the corresponding 10-amino-CBD derivatives. It was finally determined that the use of silver acetate and subsequent hydrolysis of the crude reaction mixture could provide **39** in 86% yield.[84] When **39** was treated with p-toluenesulfonic acid in refluxing benzene one of the phenol groups cyclised onto the isopropenyl moiety with concomittant isomerisation of the endocyclic alkene, yielding 12β-HO-Δ^8-THC **25** (*vide supra*). The origin of the stereoselectivity in the cyclisation was not determined. The authors had previously isolated 12β-HO-Δ^9-THC as a minor side product (¡10% yield) during their studies on the epoxidation of CBD, which was found to have comparable bioactivity to Δ^9-THC itself.[85] As a Δ^8-THC derivative, **25** was expected to have reduced bioactivity than the Δ^9-THC analogue; this was borne out by experiments in mice.

The exocyclic alcohol in **39** could be converted to the corresponding thiol **42** using a Mitsunobu reaction to first produce thioacetate **41**; the acetyl was removed reductively using $LiAlH_4$ (Figure 18).[67] These derivatives showed little-to-no cannabimimetic activity in murine studies. Fluoride **44**, prepared by the treatment of diacetate **43** with nucleophilic fluorinating agent diethylaminosulfur trifluoride (DAST), was likewise found to be inactive in multiple assays.[86]

A natural metabolite of CBD, 7-HO-CBD **48**, was synthesized in the laboratory by Tchilibon and Mechoulam in 2000 in an eight-step synthesis.[50] Its pharmacology has not been exhaustively studied since, although patents indicate that it has anti-convulsant properties, and can lower blood triglyceride levels.[87] A subsequent publication from the same group extended this synthesis to another CBD metabolite, 7-COOH-CBD **49**. As mentioned

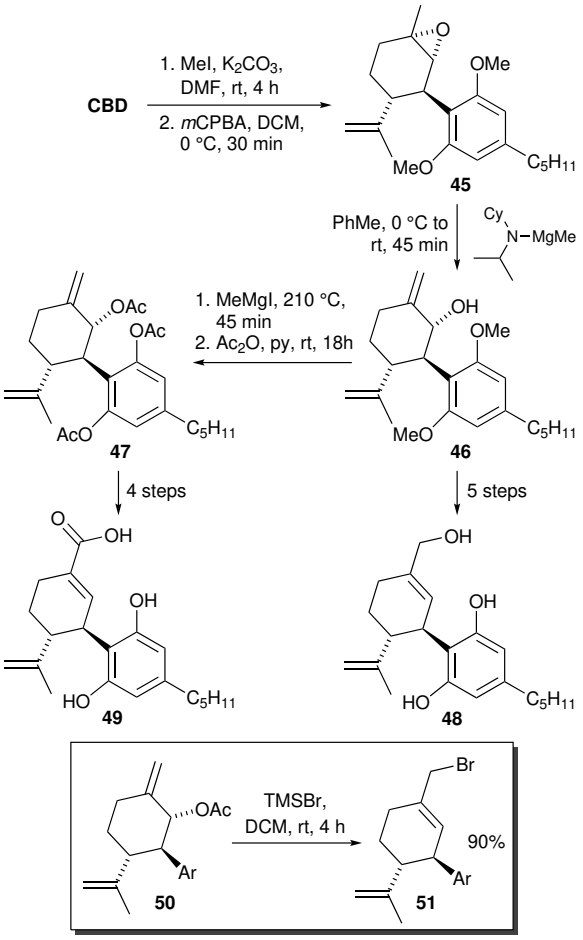

Figure 19: Mechoulam *et al.*'s approach to 7-OH-CBD and 7-COOH-CBD from CBD; the key allylic transposition step is highlighted.

previously, bromination and hydroxylation reactions performed on CBD result in functionalisation at C_{10}; thus functionalisation at C_7 required a more circuitous approach. Both **48** and **49** were obtained from the same intermediate **46**: after protection of the phenol groups, epoxide **45** was obtained in a regio- and stereoselective fashion; subsequent elimination using a strong, hindered base then gave allylic alcohol **46**. The synthesis of **49** involved a change in protecting group on the phenol oxygen atoms to acetyl in intermediate **47**. Presumably the more electron-withdrawing protecting group was required to attenuate the electron density of the aromatic ring, which may have been susceptible to the increased oxidising conditions (K_2CrO_4 in HMPA followed by Pinnick oxidation) required to obtain the acid in **49**. The key functional group transposition from C_2 to C_7 was enacted in both cases by treatment of the C-2 acetate **50** with TMSBr, providing the corresponding allylic bromide **51** in high yield. The derivatives of both natural (-) and unnatural (+) enantiomers of CBD were synthesized in this study. Surprisingly, the (-)-CBD derivatives were inactive upon binding to cannabinoid receptors, whereas the (+)-CBD-derived series showed enhanced activity upon binding (Figure 19).[88]

Recently, Appendino and colleagues published an extensive account of CBD oxidation on the aromatic ring to the respective quinone **52** (CBDQ, originally reported by Mechoulam as HU-331) by a variety of oxidants including base-catalyzed aerobic oxidation, oxidation with metals, and oxidation with hypervalent iodine reagents (Figure 20, a).[89] Oxidation of the resorcinol moiety of CBD using 5% KOH in ethanol with ambient oxygen generated hydroxyquinone **52** in low yields (approx. 20% at 0 °C); however, the yield was significantly improved (to ¿60%) by using stabilized 2-iodoxybenzoic acid (SIBX). This compound displayed enhanced cytotoxicity towards human colon carcinoma HT-29 cells, and the quinone moiety was found to be essential for the anti-proliferative activity against diverse cancer cell lines. It should be noted that this oxidation protocol has also been used to prepare the corresponding hydroxy- and alkoxy-quinones of some other phytocannabinoids, such as cannabigerol (CBG, **54**), cannabichromene (CBC, **55**) and cannabinol (CBN, **55**), Figure 20, b. These cannabi-

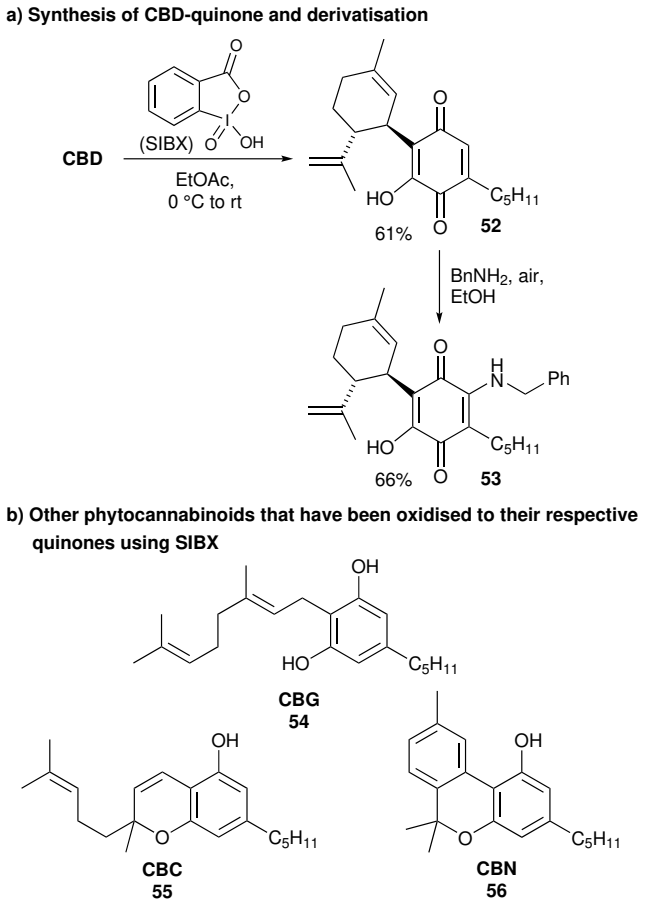

Figure 20: Conversion of the resornicol moiety of phytocannabinoids to quinone structures by oxidation.

noquinoids showed different degrees of modulation of the peroxisome proliferator-activated receptor gamma (PPAR-γ) activity, outperforming the parent compounds in terms of potency.[89,90]

The quinones offer a novel route for functionalisation of phytocannabinoids. For example, reaction of **52** with primary amines in the presence of air led to aminoquinone derivatives of CBD.[91] The benzylamine-derived aminoquinone **53** was found to have potential neuroprotective activity and was subsequently investigated as an experimental treatment for scleroderma.[92]

Hydrogenation of CBD using Adam's catalyst takes place selectively at the exocyclic $\Delta^{8,9}$ double bond to yield H_2-CBD **57**, but overreduction (to H_4-CBD, **58**) is possible with

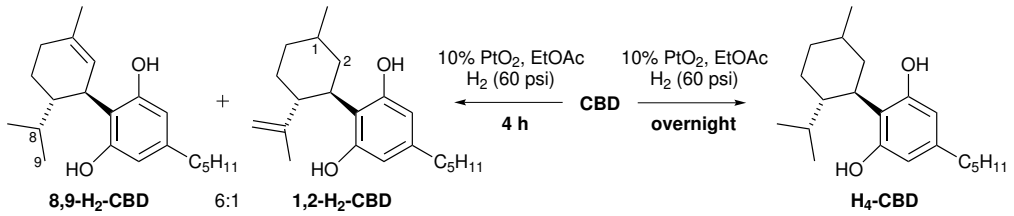

Figure 21: Hydrogenation of the *endo* and the *exo* C=C bonds in the limonene moiety of CBD.

extended reaction times and and greater pressures of hydrogen.[93] The regioselectivity was found to be 6:1 ($\Delta^{8,9}$:$\Delta^{1,2}$) in the initial report, but improved conditions provide **57** in essentially quantitative yield (Figure 21, a);[94] like the parent CBD molecule, **57** has anticonvulsant properties. H_2-CBD can also inhibit cytochrome P450, diminish the production of reactive oxygen intermediates, nitric oxide, and TNFα in murine macrophages.[93,95,96] Furthermore, since it cannot convert *in vivo* to THC (unlike CBD itself) its psychotropic effects are minimal. The loss of the (typically) more reactive $\Delta^{8,9}$ double bond thus allows for functionalisation at and around the $\Delta^{1,2}$ double bond. For example, after protection of **57** as the diacetate, oxidation with SeO_2 yielded an inseparable mixture of the C_6 and (desired) C_7 allylic alcohols. After deprotection of the acetyl groups by $NaBH_4$ these isomers could be separated, providing the desired triol **60** (30%) and its isomer **59** (60%). **60** and it's (entirely) synthetic enantiomer were also seen to be capable of decreasing the activation of Encephalitogenic T cells.[94] Subsequent reaction of **60** with DAST provided the corresponding fluoride **61**, which was found to have some activity in antidepressant and anxiolytic assays (Figure 21, b).[86]

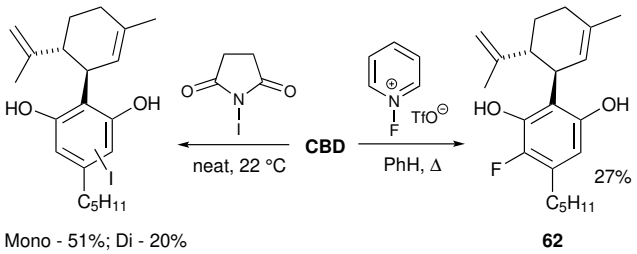

Figure 22: Ring halogenated derivatives of CBD.

Ring-halogenated (Cl, Br, I) analogs of CBD were obtained by Usami *et al.*, either by the use of N-iodosuccinimide at room temperature, or by refluxing CBD with N-halopyridinium triflates in benzene (Figure 22). Often, these conversions led to a mixture of mono- and di-halogenated derivatives of CBD, thereby limiting their scope and utility.[97] Selective monofluorination could, however, be achieved using N-fluoropyridinium triflate; the resultant derivative **62** showed enhanced anxiolytic, antidepressant and antipsychotic effects in mouse models compared to both CBD itself and fluoride **61** (Note: **61** showed no activity in the antipsychotic assay).[86]

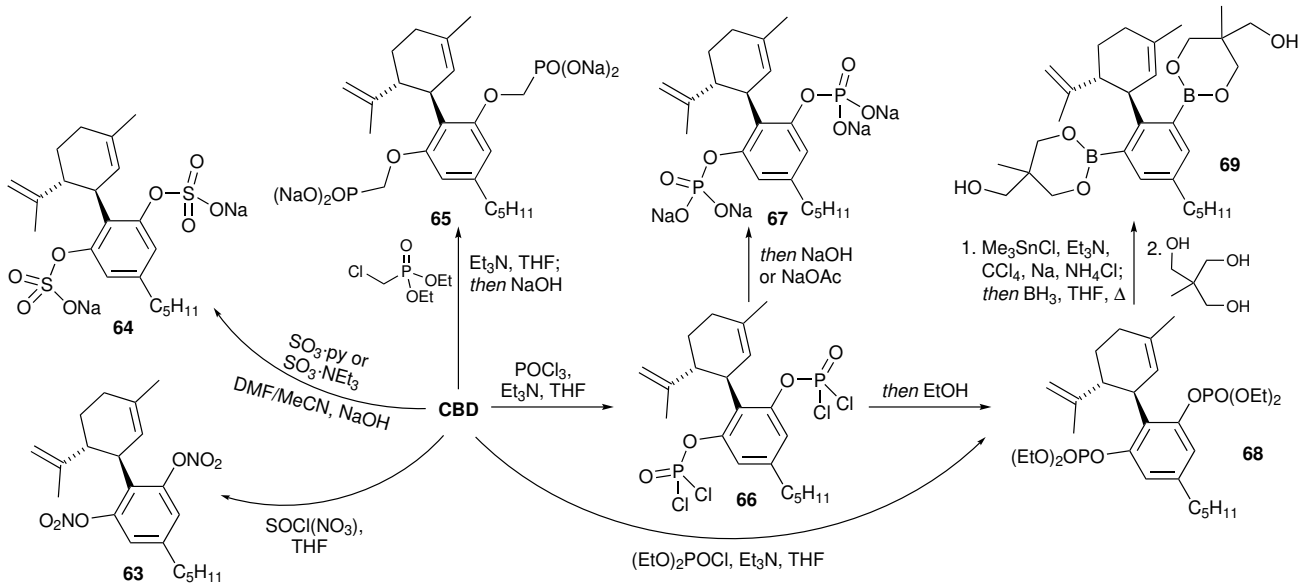

Figure 23: Functional group conversions of the phenol groups in CBD.

In 2018, Salzman and co-workers reported a series of CBD pro-drugs with heteroatom-bearing functionalities on one or both of the phenol groups.[98] The phenol groups were converted into, among others: the nitrate **63** ($ArO{-}NO_2$), sulphate **64** ($ArO{-}SO_3Na$), phosphonate **65** ($ArO{-}CH_2PO(ONa)_2$) and phosphate **67** ($ArO{-}PO(ONa)_2$). **67** was prepared by reaction of CBD with $POCl_3$ to give intermediate dichlorophosphate **44**; basic hydrolysis yielded **67**, but quenching with ethanol gave the useful phosphate ester **46** (which could also be prepared directly from CBD using $(EtO)_2POCl$). The phosphate esters in **68** could be used as leaving groups in coupling reactions, and were used to prepare an unusual diboron

derivative **69** (Figure 23). These compounds were potentially useful in the treatment of diseases affecting the bone, given CBD's role in increased collagen cross-linking and better outcomes in bone fracture healing upon the administration of CBD.[99]

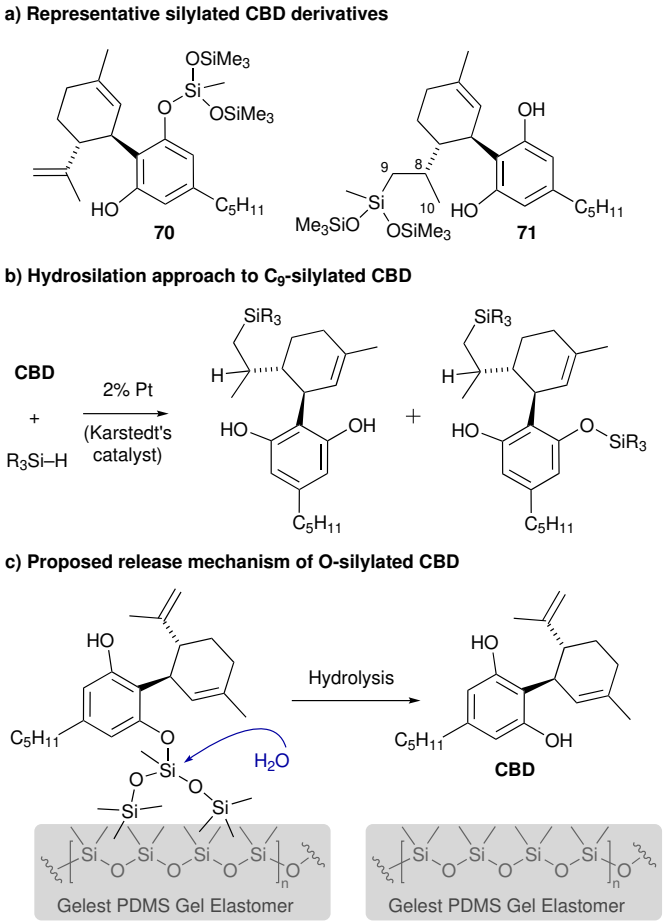

Figure 24: Silylated CBD derivatives: synthesis and CBD release through hydrolysis.

Silicon-containing CBD derivatives have been prepared recently by Arkles and colleagues as a potential active ingredient in topical formulations for amelioration of pruritus and localized pain.[100] Derivatives with silicon groups on both a phenol oxygen (*e.g.* **70**) or on the limonene C_9 (*e.g.* **71**). The C–Si derivatives were prepared by hydrosilation of CBD using Karstedt's catalyst, occurring selectively at the $\Delta^{8,9}$ alkene (Figure 24, b). The silylated derivatives were insoluble in water but soluble in both oils and silicones, especially upon slight heating. The inventors propose that CBD is released by hydrolysis of the silyl group, as shown in Figure 24, c. However, no animal studies were reported in the patent

application to demonstrate the efficacy of these formulations.

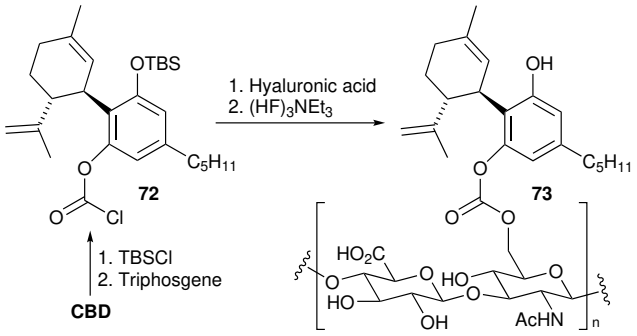

Figure 25: Preparation of a CBD-hyaluronic acid conjugate.

Another CBD prodrug for topical use was featured in a patent application in 2009 by Stinchcomb and colleagues. This was CBD-hyaluronic acid conjugate **73**, with a carbonate linker connecting the two moieties (Figure 25). Hyaluronic acid is a polymeric, anionic, nonsulfated glycosaminoglycan that occurs naturally in organisms, and it was indicated that most of the primary alcohol groups of this polymer would be involved in forming linkages with CBD. The conjugate was formed between hyaluronic acid and ^{t}butyldimethylsilyl (TBS) protected chloroformate **72**; the use of an additional spacer such as glycine is also possible, although this would result in a carbamate rather than carbonate linkage to the polymer. The TBS group was subsequently removed using $(HF)_3NEt_3$. This preparation was meant to be suitable for transdermal application, and is metabolized to release CBD.[101]

Finally, while this review has primarily focused on modulating the reactivity of the major cannabinoids, it should be noted that there are many minor cannabinoids which may be of pharmaceutical significance; these structures are also known to co-exist with THC and CBD in cannabis plant biomass, but in such small amounts that their isolation is expensive and difficult which has hindered the investigation of their bioactivity. In 2022, Dennis *et al.* described the semi-synthesis of several minor cannabinoids from CBD, which is, by comparison, readily available and relatively inexpensive. The synthesis of representative examples from two subtypes, the cannabifuran (**76**) series and the cannabimovone (**81**) is shown in Figure 26.

Both synthetic routes begin from CBD diacetate **34**. Epoxide **74** was prepared by chemo- and stereo-selective epoxidation of **34**; the heterocyclic core of cannabielsoin **75** was then obtained by closure of the deprotected phenolate to the less hindered end of the epoxide. Cannabifuran **76** was then obtained by dehydration of the alcohol and several RedOx steps. The cyclopentane ring of the cannabimovone series was obtained by selective oxidative cleavage of the endocyclic alkene followed by acid-catalysed aldol condensation to provide α,β-unsaturated ketone **79**. Attempts to introduce the cyclopentane 3′-hydroxyl group by intermolecular oxa-Michael reactions were unsuccessful (acetate deprotection and *intra*molecular conjugate addition were observed instead), and so a borylation/oxidation sequence was used. Gratifyingly, the platinum-catalysed borylation gave the correct stereochemistry at the 2′ position, but unexpectedly gave the wrong 3′-epimer **80**; this was readily epimerised to the desired *anti* diastereomer under acidic conditions before oxidation/deprotection using sodium perborate.

Several of the compounds prepared following these synthetic routes - cannabielsoin, dehydrocannabielsoin, cannabimovone, and 3′-epicannabimovone, in particular - showed some promise as anti-inflammatory agents. These CBD derivatives could reduce inflammation in a BV2 mouse microglial cell culture model, as evidenced by suppression of prototypical pro-inflammatory biomarkers.[102]

Conclusions

The discovery of pharmacologically active compounds from natural sources is enjoying a comeback in recent years, with cannabinoids and psychedelics/entheogens becoming the poster children in this trend of revisiting biological molecules previously ignored owing to social stigma associated with their consumption. However, the transition of these pharmacologically promising molecules from plant extracts to prescription-ready medication is neither linear nor straight-forward. The present review discusses advances in the functionalization

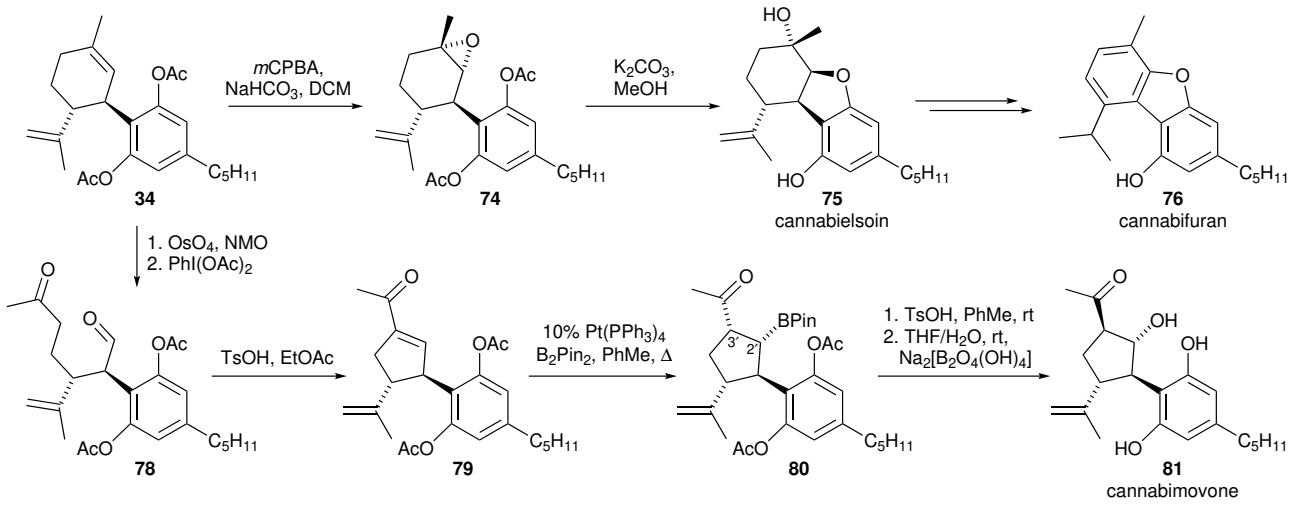

Figure 26: Synthesis of several minor cannabinoids from CBD.

of the major phytocannabinoids with potential applications in biomedicine. While we explore a wide variety of THC and CBD derivatives during the course of this review, including cannabinoids tethered to other drug molecules, our primary interest remains in "breaking bud", *i.e.*, functionalizing the major cannabinoids to create molecules of interest with well-defined therapeutic properties. We have noted that the high lipophilicity and high sensitivity to first pass metabolism of cannabinoids make their oral delivery a challenge; much of the research presented in this review, therefore, focuses on enhancing the solubility, absorption, and bioavailability of the major phytocannabinoids by suitable chemical modifications.

Functionalization of phytocannabinoids, however, has consequences far beyond simple enhancement of bioavailability or hydrophilicity. While some functionalized THC or CBD derivatives serve merely as pro-drugs, undergoing spontaneous conversion to the native phytocannabinoids under biological conditions (such as upon being exposed to enzymes or stomach acids), there are numerous other derivatives whose biological activities differ profoundly from the parent cannabinoid. For example, γ-morpholinobutyric acid and β-piperidinopropionic acid esters of THC (**1** and **2**, Figure 3) undergo rapid hydrolysis *in vivo* to generate free THC. In contrast, 1-N,N-*bis*-(dichloroethyl)carbamate-Δ^9-THC (a nitrogen mustard analog of Δ^9-THC) demonstrated a lack of cannabinoid activity following peripheral

administration, only showing weak cannabimimetic activity upon intravenous administration in test animals. Meanwhile, CBD conjugated to β-lactam antibiotics by bio-labile linkages serve merely as an adjunct to the main antibacterial component, whereas H_2-CBD **57** can inhibit cytochrome P450 and diminish the production of reactive oxygen intermediates, nitric oxide, and tumor necrosis factor in murine macrophage[93,95,96] without conversion to psychotropic THC *in vivo*.

What is clear from conducting this review is that the study of derivatized cannabinoids remains in its infancy. In the cases where the biological activity (beyond simple bioavailability studies) was determined, the mechanism of that activity, if it differs from the parent cannabinoid, was not examined. The metabolites besides the parent cannabinoids have not been determined, and the potential of these for providing the observed effects cannot be discounted. This is not a criticism of the fine work done to date; these efforts are always scaffolded in science, but it does highlight that there is not only room for developing and delivering novel chemically-modified cannabinoids, but that there is a need to understand the mode of action of already discovered prodrugs. We also made the editorial choice not to discuss prodrugs or derivatives of minor cannabinoids; as these materials may be responsible for some of the biological activity observed and could prove a rich mine for bioprospecting, we expect that a future review will centre upon these molecules; however, at this point, their limited availability has made those studies extremely preliminary. This is changing fast, partially through their semi-synthesis from major cannabinoids. As always, more research is needed on these questions, but in this case, that research is likely to be conducted as it has direct economic and commercial implications.

Of course, the primary limitation to cannabinoid functionalization is regulatory and economic rather than scientific. Many of the molecules discussed here are better versions of the major cannabinoids and better suited to beverage and food products. However, they are new chemical entities. This raises significant regulatory challenges as they need to be approved individually and determined safe through appropriate studies. Physical formulation, which

sidesteps this issue, has been a "good enough" solution to date. This is especially true in the consumer market where the benefits of innovation are often outweighed by the need to get product to market as quickly as possible. However, should the cannabinoids, potentially the minor cannabinoids not discussed in this review, be shown to be medically relevant for specific indications, we can expect significant incentives for both intellectual property and efficacy reasons, to see a rationale for the clinical development of cannabinoid prodrugs. Until that time, the contributions of the community will continue to improve our understanding of the possible.

Drug functionalization and delivery studies have already revolutionized the way we discover, modify, re-purpose and administer drugs in biological systems. We can now add major cannabinoids to that ever-burgeoning class of molecules of pharmaceutical interest whose derivatives may, in the long run, prove to be even more versatile than the parent molecules (here, THC and CBD) in wide-ranging therapeutic applications. This will continue to be relevant as long as cannabinoid derivatives are anticipated to remain molecules of interest in preclinical research and in the lab-to-pharmacy pipeline. For the foreseeable future, cannabinoids and their derivatives will be intensely pursued for their potential to offer novel solutions to longstanding healthcare challenges.

Author Contributions

Conceptualization: ARB, JJH, JFT; Funding acquisition: JFT; Supervision: Unsupervised play; Writing original draft: ARB, JJH; Writing-review and editing: All authors.

Conflicts of interest

There are no conflicts to declare.

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