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CANNABINOIDS IN PHARMACEUTICAL INDUSTRY

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PRODUCTION OF CANNABINOIDS IN THE PHARMACEUTICAL INDUSTRY

BURAK KUZU
FUAT KARAKUŞ
ZÜBEYDE TANRIVERDİ

The medicinal use of cannabis (*Cannabis* plants) was reported in the Chinese pharmacopeia, Ebers papyrus, Assyrian tablets, and Ancient Greek and Roman sources in the centuries BC. During these periods, various parts of the cannabis plant were used as analgesics and antipyretics. It was also suggested for the treatment of fatigue and mood disorders, rheumatism, malaria, eczema, and psoriasis. In the centuries after Christ, hemp was also used as an antispasmodic, sedative, antiemetic, and hypnotic. It gained a bad reputation since the early 1900s due to its recreational use and worldwide cannabis production restricted (1,2).

Thanks to scientific studies on cannabis, it has been understood that its medicinal or toxic effects are due to the phytocannabinoids, and more than one hundred phytocannabinoids have been identified to date. The most prominent of these are Δ^9 -tetrahydrocannabinol (THC or Δ^9 -THC) and cannabidiol (CBD). Thanks to the isolation of these phytocannabinoids, identification of their structure, and determination of their medicinal uses, cannabis production for medical use has resumed in many countries in recent years, and cannabis extract and phytocannabinoids have begun to be used in the pharmaceutical industry (2).

There is currently one cannabis-derived product on the market (Epidiolex™, which contains CBD extracted from cannabis) and three FDA-approved cannabis-related synthetic drugs [Marinol™ (dronabinol), Syndros™ (dronabinol), and Cesamet™ (nabilone)]. Besides, Sativex™ [Nabiximols (standardized cannabis extract containing THC and CBD)], which has been approved in some countries, is also available on the market as a cannabis-derived drug product.

The synthesis processes of THC, CBD, and some other important synthetic cannabinoids (cannabinoid receptor agonists and antagonists) in the pharmaceutical industry are explained in detail below.

After Mechoulam and his group reported the first isolation and stereospecific synthesis of the natural Δ^9 -THC in 1960, a significant number of cannabinoids were designed and synthesized. This has led to the advancement of biochemical, pharmacological, and clinical research of natural cannabinoids as well as the production of synthetic cannabinoids. While the development of classical cannabinoid derivatives continued over time, non-classical and hybrid cannabinoid derivatives have been developed with the introduction

of non-classical bicyclic cannabinoids by Pfizer. Classical cannabinoids generally provide cannabinergic activity with four pharmacophore groups attached to the tricyclic center containing a benzopyran ring (3). In addition, compounds formed by hybridization of pharmacophore groups in classical cannabinoids with other non-classical cannabinoids (such as diarylpyrazoles) are currently used as precursors (e.g., rimonabant) for pharmacological action (Figure 1).

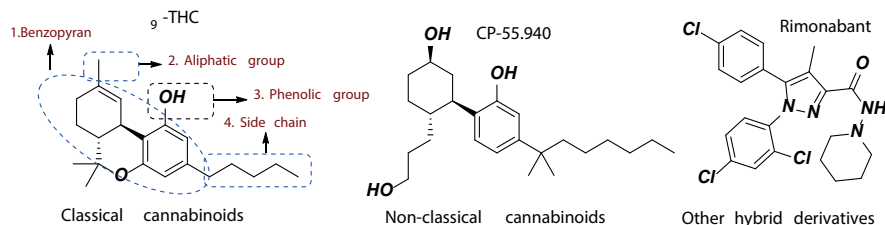
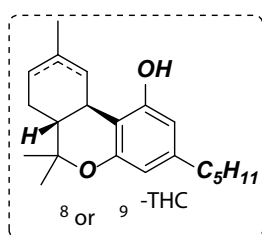


Figure 1. Pharmacophore groups of classical cannabinoids and structural classes of some cannabinoids

Synthesis of Tetrahydrocannabinol (THC or Δ^9 -THC)



The Δ^9 derivative among tetrahydrocannabinols, Δ^9 -THC, is an FDA-approved drug with the generic name Dronabinol (trade name Marinol) used as an appetite stimulant, sleep apnea reliever, and for the prevention of chemotherapy-induced nausea and vomiting. The Δ^8 derivative of THC (Δ^8 -tetrahydrocannabinol; Δ^8 -THC) is an isomer of the Δ^9 -THC and has similar pharmacological activity but is less effective. Apart from the method found thanks to the chemical instability of CBD, which is also a natural cannabinoid derivative, many synthetic methods have been discovered in the synthesis of THC.

In fact, although the biosynthesis of THC was very popular in the early days, the difficulties in isolating pure cannabinoids from the plant and the need to selectively obtain a single pure active substance from among many active substances intensified research in the synthesis of THCs chemically. In addition, cannabinoid production by synthetic methods can provide the targeted active substance with enantiomeric purity and a clear structural characterization.

Mechoulam and his colleagues obtained Δ^8 -THC in a 35% yield for the first time using a two-step reaction of olivetol and verbenol in the chemical synthesis of THC in enantiomeric purity. This structure could then be converted to Δ^9 -THC with a reaction efficiency of 55% in the base and metal-catalyzed medium (Figure 2) (4).

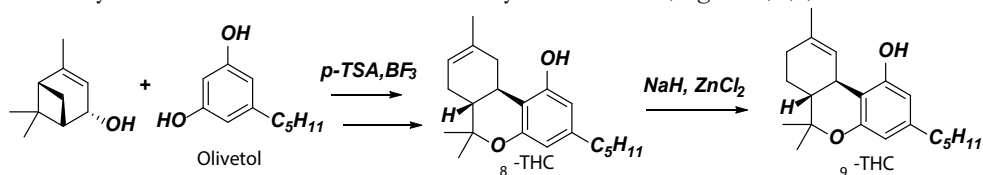


Figure 2. The THC synthesis method was developed by Mechoulam and his group

Similar to the synthetic method of Mechoulam et al., the production of THC₈ and cannabidiol can be achieved using olivetol as a starting compound (Figure 3) (5).

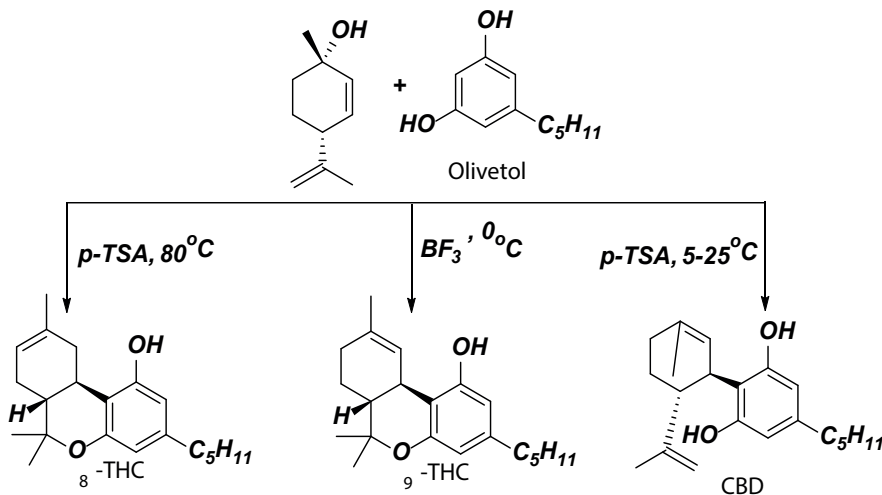


Figure 3. Methods applied in the synthesis of THC₈ and CBD.

This method has produced THC₈ with reaction yields exceeding 50% and has served as the starting point for the production of other synthetic cannabinoids (3). For instance, AM-411 (high affinity for CB1) and AMG-3 (a potential agonist for CB1 and CB2) can be synthesized with high efficiency by derivatization of olivetol with this method (Figure 4).

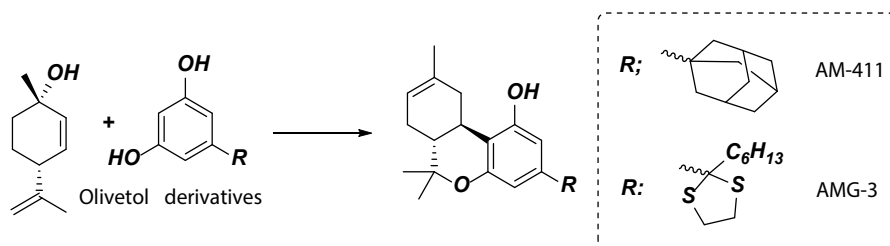


Figure 4. Synthesis method for THC derivatives AM-411 and AMG-3

Many methods have been developed by expanding the starting compounds with chiral structures used in the production of THC₈. These methods are of great importance in terms of synthetically producing natural compounds of enantiomeric purity. However, the difficulties in obtaining the starting compounds and the low reaction yields still remain insufficient to reduce the cost of producing THC₈. Although more advanced approaches in chemical synthesis methods (such as Diels-Alder reaction and Claisen rearrangement) and modern heterocyclic synthesis designs (asymmetric hydrogenation and carbene-catalyzed cyclizations) provide a different synthetic perspective to THC₈ production (6), the new synthesis methods for THC₈ still continue to be investigated (Figure 5).

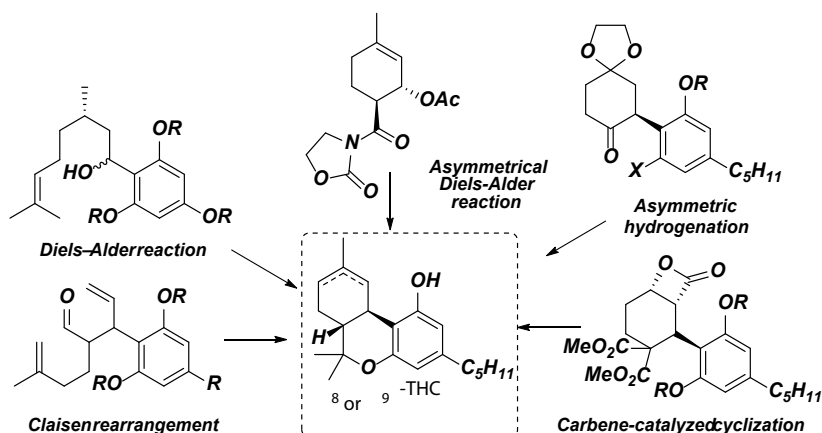
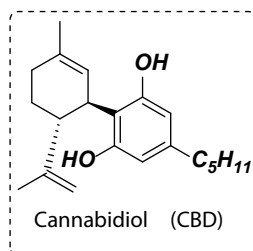


Figure 5. Modern synthesis methods developed so far in the synthesis of THC

Synthesis of Cannabidiol (CBD)



Olivetol, a resorcinol derivative with a pentyl side chain, is used as the first and long-standing traditional method in the production of synthetic CBD. Olivetol, also known as 5-pentyl-1,3-benzenediol, is an organic compound naturally found in certain lichen species and can be easily isolated by extraction and used as a precursor compound in CBD synthesis. The synthetic production of CBD was first made in 1965, and the 1,3-dimethoxy derivative of olivetol was used as the starting material. This method involves cyclization of lithiated olivetol with citral (limonal) with tosyl chloride followed by demethylation with methyl magnesium iodide (Figure 6).

This method involves cyclization of lithiated olivetol with citral (limonal) with tosyl chloride followed by demethylation with methyl magnesium iodide (Figure 6).

However, this method has the disadvantage that CBD is obtained in the form of a racemic mixture ($\pm$ CBD) and with a very low yield (7).

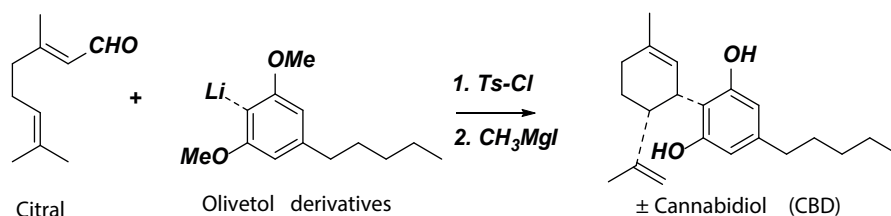


Figure 6. Synthesis of citral-based cannabidiol

The disadvantage in the racemic mixture was eliminated by the reaction of olivetol with (+)-p-metha-2,8-dienol, a method developed in 1969, but the low reaction efficiency still persists. In addition, an undesirable by-product formation was also detected in this method. Later, the use of boron trifluoride (BF_3) as a weak acid in 1974 increased the reaction efficiency, and by-product formation could be prevented with the modification of the method in 1985 (Figure 7) (8).

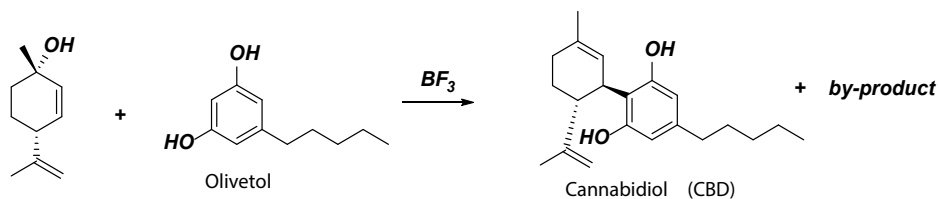


Figure 7. Synthesis of CBD using chiral terpene

However, one of the most important problems in the synthesis of CBD is that the synthesized CBD is unstable and, accordingly, Δ^9 -THC is formed under weakly acidic conditions or Δ^8 -THC under strongly acidic conditions (Figure 8). In fact, these chemical transformations are an important process that provides the synthetic production of Δ^9 -THC.

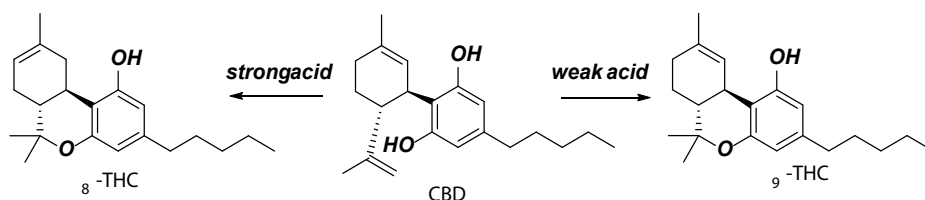
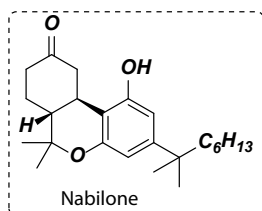


Figure 8. Synthesis of Δ^9 -THC derived from CBD

Synthesis of Nabilone



Nabilone is an FDA-approved synthetic cannabinoid that has dronabinol (Δ^9 -THC)-like pharmacological activity and prevents chemotherapy-induced nausea and vomiting with oral use. The first procedure involving the enantiomeric purity synthesis of Nabilone, also known as the 9-ketocannabinoid, was developed by Archer and his group in 1977. The difficulties in separating the enantiomers from each other were tried to be overcome by using

the β -pinene starting compound in the experiments with the conversion and ketalization of the resorcinol derivative to the coumarin ring. However, a racemate mixture of nabilone could be made again by this method. Finally, when Nopinone was used as the starting compound, the synthesis of enantiomeric purity Nabilone was achieved (Figure 9) (9).

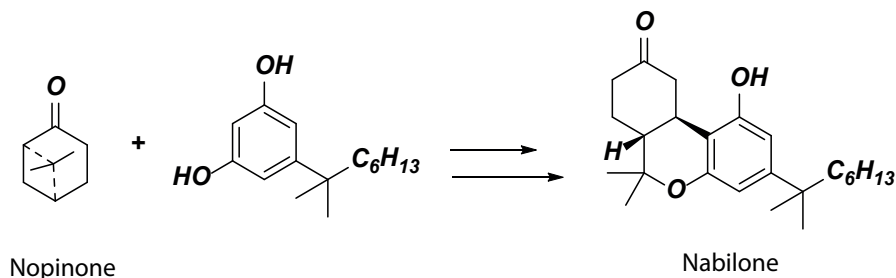


Figure 9. Synthesis of Nabilone derived from Nopinon

Although many different synthesis methods have been designed and applied in the synthesis of nabilone, enantiomeric impurities during the synthesis pose a serious problem. In the method published in 1991, consisting of seven steps and the total reaction efficiency of 14%, the enantiomerically pure Nabilone was obtained by the advanced reaction steps of the Δ^9 -THC carboxylic acid derivative obtained with the bis-ether derivative of apo-verbenone and olivetol (Figure 10). However, the low reaction efficiency in the mentioned method and the problems during the isolation of the target product from the environment made it necessary to search for new synthetic methods (10).

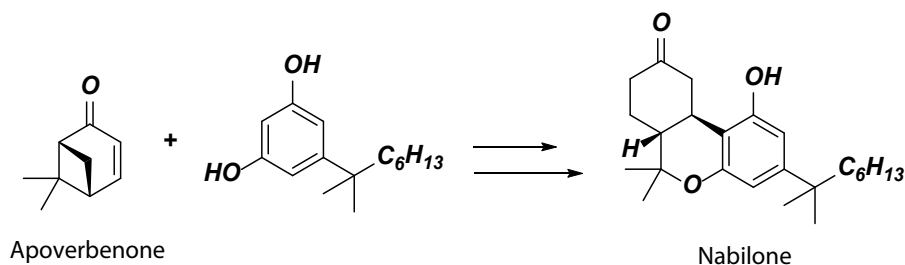
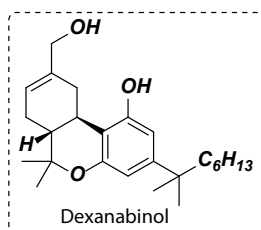


Figure 10. Synthesis of Nabilone derived from Apoverbenone

Synthesis of Dexanabinol



Dexanabinol, also known as HU-211 or ETS2101, is the enantiomer of the unnatural synthetic cannabinoid derivative HU-210. Unlike other cannabinoid derivatives, it does not have an agonist effect on cannabinoid receptors, while it has an antagonist effect on N-demethyl-D-aspartate (NMDA) receptors. Therefore, it does not have cannabis-like effects. In addition to the anticonvulsant and neuroprotective effects of dexanabinol, its applications are currently being studied in the treatment of injury and cancer. Dexanabinol, which was found to be safe in clinical trials, continues to be studied in phase I in brain cancer and advanced solid tumors (11).

In the synthesis of dexanabinol, a path similar to the synthesis method of classical THC is followed. Dexanabinol with high enantiomeric purity can be synthesized with this method. In the synthesis, the starting compound of Myrtenol is first converted into an ester with pivaloyl chloride, and the keto form is obtained by oxidation. Subsequently, dexanabinol is obtained by reduction of the keto group and then the reaction of BF_3 with an olivetol derivative (Figure 11) (12).

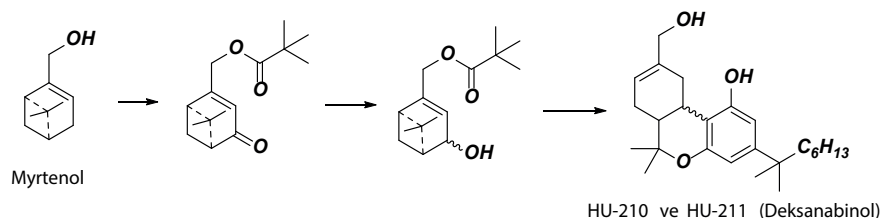
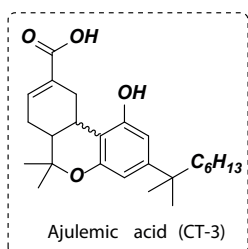


Figure 11. Synthesis of HU-210 and HU-211

Synthesis of Ajulemic acid (CT-3)



Another synthetic cannabinoid derivative, ajulemic acid, is the carboxylic acid derivative of the Δ^8 -THC. Ajulemic acid, also known as CT-3, does not show an anti-emetic effect like its other cannabinoids, but it has been found to have anti-inflammatory activity in preclinical studies. As a first step in the synthesis of ajulemic acid, the -OH group in HU-210 is protected with a silyl ether derivative (TBS) and then oxidized with chromium (III) oxide (CrO₃) to obtain an aldehyde derivative. In the last step, the aldehyde group is converted to carboxylic acid by oxidation, and then the silyl ether protecting group is removed to obtain ajulemic acid (Figure 12) (13).

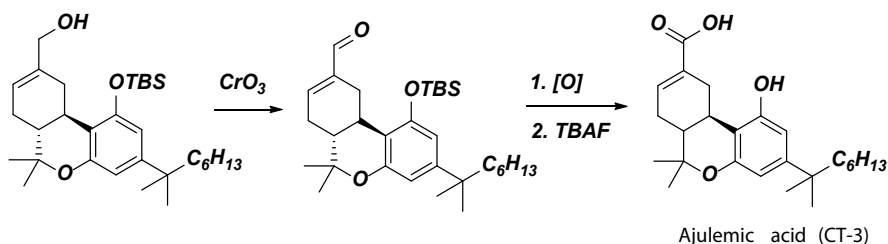


Figure 12. Synthesis of CT-3 derived from HU-210

In another important synthesis method developed as an alternative to this method, the acetate derivative of the -OH group in Δ^8 -THC is used as the starting compound. Firstly, the allylic -OH group was oxidized with selenium dioxide to aldehyde, and then ajulemic acid was obtained by a series of reactions (oxidation of aldehyde to carboxylic acid and hydrolysis of the ester group) (Figure 13) (14).

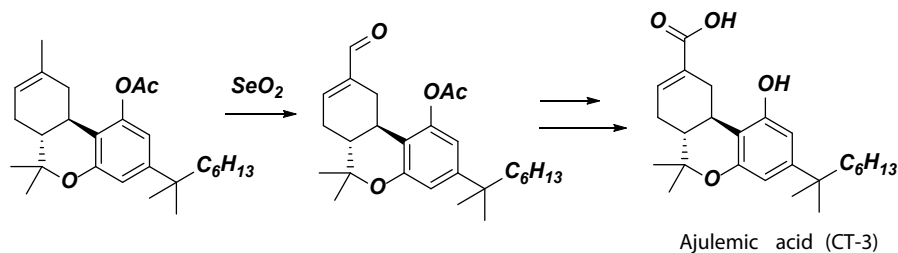
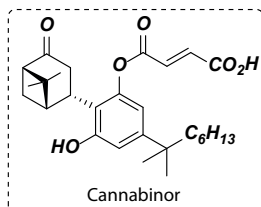


Figure 13. Synthesis of Ajulemic acid derived Δ^8 -THC acetyl

Synthesis of Cannabinor



Cannabinor, which has the chemical structure of CBD and is a selective CB2 receptor agonist, is a non-classical cannabinoid. Even though Cannabinor showed an analgesic effect in *in vivo* animal models, it failed in Phase II trials due to its low efficacy (15). Cannabinor synthesis is carried out by acid-catalyzed condensation of a chiral monoterpene and resercinol, just like in the

synthesis of CBD. In the synthesis, first a condensation product was obtained with the reaction of the diacetate derivative and the appropriate resercinol derivative, and then cannabinor was synthesized by providing the substitution of the -OH group by using fumaryl chloride (Figure 14) (3).

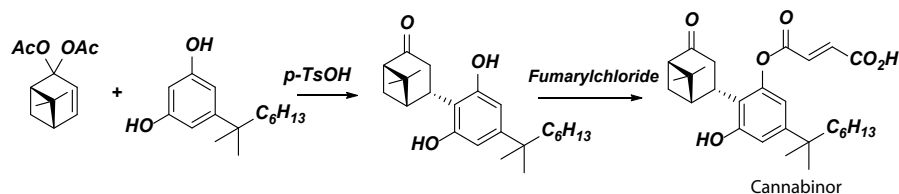
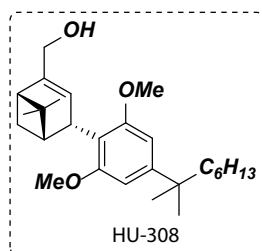


Figure 14. Synthesis of cannabinor from a diacetal starting compound

Synthesis of HU-308



Compound HU-308, also known as Onternabez, it is a CBD-derived compound with 5,000 times higher affinity for CB2 compared to CB1. It is obtained by a condensation reaction similar to cannabinor synthesis. In the synthesis, firstly, condensation of the pivaloyl ester derivative of the 4-hydroxymyrtanyl compound and the appropriate resercinol derivative is provided. Subsequently, the -OH groups attached to the resercinol in the obtained compound are methylated, and the pivaloyl ester group is reduced to obtain HU-308 (Figure 15) (16).

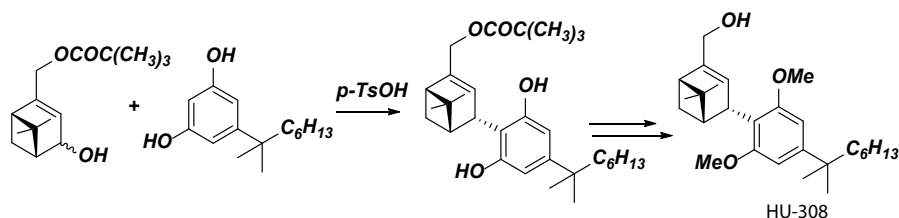
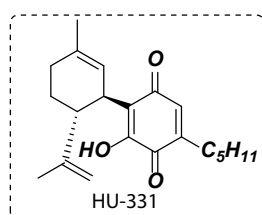


Figure 15. Synthesis of HU-308

Synthesis of HU-331



Another quinone ring-containing cannabinoid derivative, HU-331, is a compound in which the benzene ring in the CBD structure is replaced with quinone. The anticancer activity of quinone derivatives is well known. HU-331 selectively inhibits DNA topoisomerase II compared to the best known anticancer quinone derivatives. HU-331, which can inhibit DNA topoisomerase II even at nanomolar concentrations, is in the class of anticancer drugs

with a quinone structure. HU-331 is synthesized from CBD with the help of oxygen in a basic medium. In addition, HU-336, another anticancer quinone compound, can be produced by the reaction of HU-331 in an acidic medium (Figure 16) (3).

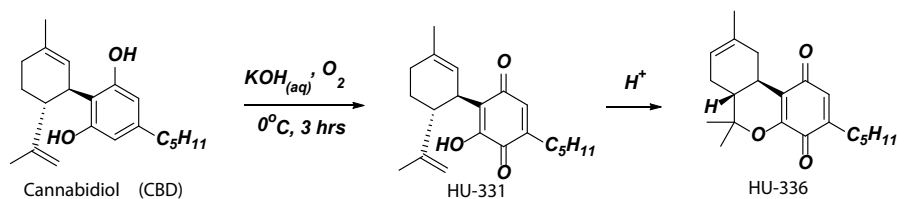
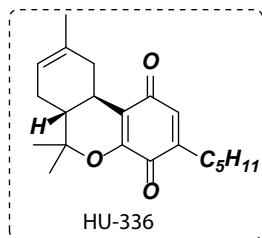


Figure 16. Synthesis of HU-331 and HU-336.

Synthesis of HU-336



HU-336, produced by the exchange of the benzene ring with quinone in classical cannabinoids, has a very strong anti-angiogenic effect. It can inhibit angiogenesis even at < 300 nM by inducing apoptosis in vascular endothelial cells.

Although it is technically obtained by oxidizing the Δ^8 -THC compound, it does not have psychoactive properties. The oxidation of Δ^8 -THC in bis(trifluoroethoxy) iodobenzene yields HU-336 with a medium efficiency (Figure 17) (17).

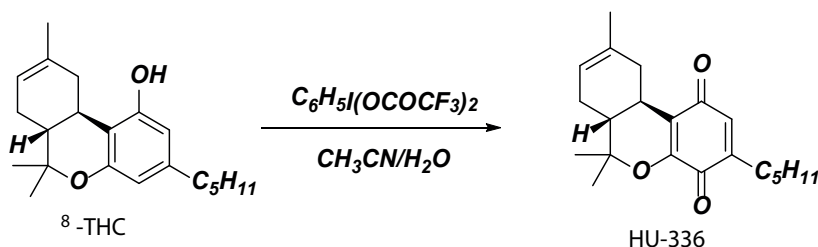


Figure 17. Synthesis of HU-336 from Δ^8 -THC

In the recently developed method, HU-336 was synthesized via singlet oxygen photooxygenation of Δ^8 -THC (Figure 18). It was found that solvent exchange was highly effective in increasing the reaction yield in the synthesis method proceeding in the medium of *meso*-Tetraphenylporphyrin (18).

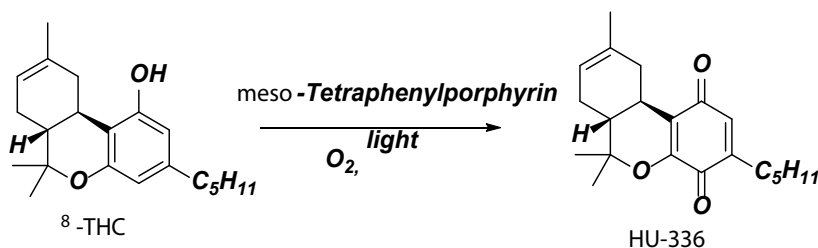
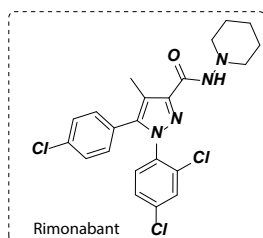


Figure 18. Synthesis of HU-336 by photooxygenation of Δ^8 -THC

Synthesis of Rimonabant



Rimonabant is a fully synthetic heterocyclic compound that does not contain a THC or CBD structure, unlike natural cannabinoids or synthetic derivatives developed later. It acts as a selective antagonist for the CB1 receptor and is used as an anorectic antiobesity drug. Although the use of rimonabant was discontinued in 2008 due to its serious adverse effects, it is currently used as a CB1 receptor inhibitor in research studies.

Extensive studies continue on the synthesis of rimonabant and its various derivatives. The synthesis of rimonabant is generally done in a six-step process from the 4-chloropropiophenone starting reagent. In the synthesis, 4-chloropropiophenones are fused with ethyl oxalate in a cold medium with a base. By adding 2,4-dichlorophenyl hydrazine to the product, first the condensation product is obtained, then the tetrasubstituted pyrazole ring is obtained by cyclization in an acidic medium. The ester group in the third position of the pyrazole ring is hydrolyzed in a basic medium and then converted into acyl chloride with thionyl chloride. In the next step, rimonabant is obtained by converting the acyl group to the hydrazide functional group with 1-aminopiperidine (Figure 19) (19).

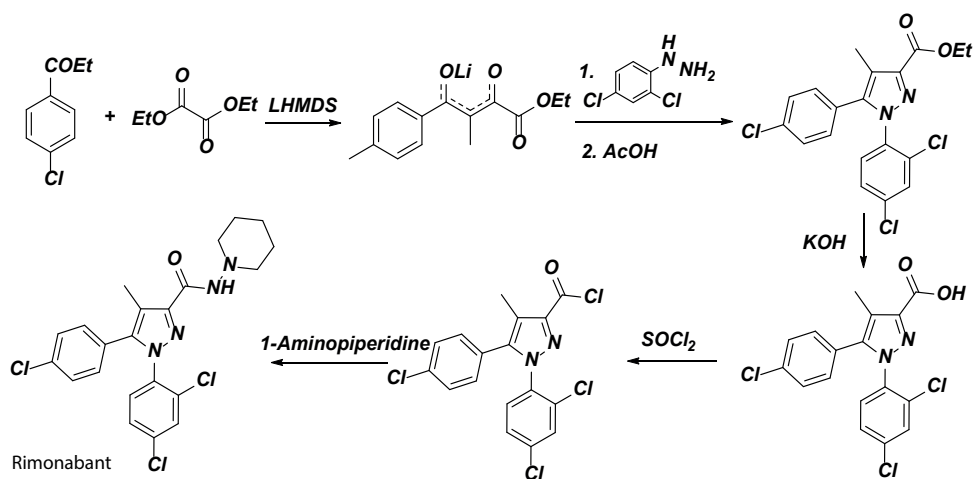
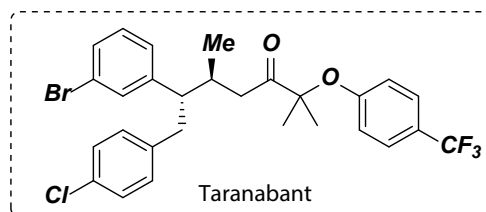


Figure 19. Synthesis of Rimonabant

Synthesis of Taranabant



shown in Figure 20.

With the withdrawal of rimonabant from the market, Taranabant was developed as a CB1 receptor agonist, but it was discontinued in Phase III trials due to its adverse effects, such as depression and anxiety. The synthesis process of Taranabant, developed by the Merck medicinal chemistry group, is

In the synthesis, 3-bromophenyl acetate was first substituted with *p*-chlorobenzyl bromide and the ester group was converted to the acetyl group.

Then, the -OH group in the compound obtained by stereoselective reduction of the carbonyl group was protected by converting it to the -NH group. In the later steps, taranabant was obtained by the conversion of the bromine group in the compound into nitrile and its reaction with the pyridine derivative carrying carboxylic acid. However, after the last step, it should be purified stereoselectively using the chiral HPLC method (20).

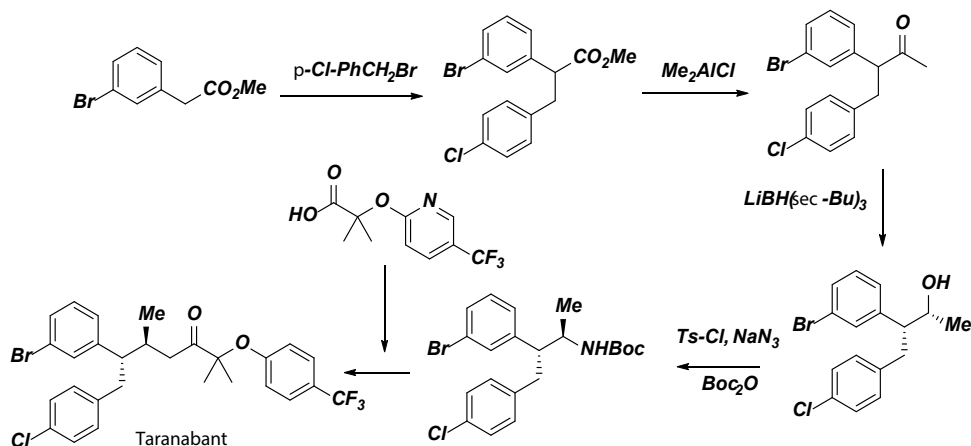


Figure 20. Synthesis of Taranabant

In the last three decades, a variety of classical, nonclassical, and hybrid cannabinoids have been synthesized. Thanks to the very high binding affinity and selectivity of the newly developed hybrid compounds against cannabinoid receptors, it has been possible to produce new drug groups with various pharmacological activities. With the decrease in the synthesis costs of hybrid cannabinoids and the development of new compounds with fewer adverse effects over time, cannabinoid-based active compounds will take an even more important place in the pharmaceutical industry in the future.

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