Toward Drugs Derived from Cannabis

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Recent work aimed at the introduction of natural and synthetic cannabinoids as drugs is reviewed. Δ^1-Tetrahydrocannabinol (Δ^1-THC) is mainly investigated as a potential drug against glaucoma and asthma, and as an antiemetic agent in cancer chemotherapy. Cannabidiol is being tried in the clinic against epilepsy and as a hypnotic. Numerous synthetic cannabinoids are currently being investigated as analgetics and as sedative-relaxants.

Ibn al-Badri, in a treatise on hashish written around 1464 (preserved in Paris in manuscript form) tells that the poet Ali ben Makki visited the epileptic Zahir-ad-din Muhammed, the son of the Chamberlain of the Caliphate Council in Baghdad, and gave the reluctant Zahir-ad-din hashish as medication. It cured him completely but he could not be without the drug ever after [1].

Cannabis has been used as a therapeutic agent since ancient times. The above, recently discovered evidence from the 15th century, is another link in the uneven, somewhat broken, chain of documented use starting in ancient times. A Chinese treatise about 2000 years old records the use of *Cannabis* as anesthetic in surgery [2]. In Ayurvedic (Hindu) medicine it was (and probably still is) used as hypnotic, analgetic and spasmolytic, in mental conditions and to increase body resistance to severe physical stress.

Walton [3] and more recently Mikurya [4] have summarized the medical use of *Cannabis* in Europe during the 19th and early 20th centuries. Hashish, as well as the local medical (and not-so-medical) knowledge of its use and effects, was brought from Egypt by Napoleon's army and from India by British physicians. O'Shoughnessy in 1842 [5] experimentally showed in India that *Cannabis* considerably helped to relieve pain and to relax muscles that were in spasm. Some fifty years later, Reynolds [6] reviewed the experience accumulated in England and concluded that *Cannabis* was useful for epilepsy, neuralgia, migraine, and psychosomatic disorders, but not for neuritis, arthritis, and other rheumatic conditions. Yet, around the turn of the century, its use slowly declined. There are two major reasons for this:

1. The constituents of *Cannabis* had not been isolated in a pure form. Hence, crude plant preparations or extracts had to be used. *Cannabis* is notorious for its chemical variability and its easy deterioration. Therefore, reproducible clinical effects were not always obtained.
2. Legally, in many countries, *Cannabis* was linked to the opiates. The use of these drugs was officially controlled and frequently made difficult. However, the opiates due to their medical indispensibility continued to be widely employed; *Cannabis* use declined. Today there is virtually no official medical use of *Cannabis* in the Western world.

Interest in *Cannabis* was renewed between 1940–1950 as a result of the chemical research of Adams and the pharmacologic research of Loewe [7]. However, as the major constituents were still not isolated in pure form and their structures were only generally known, and as they were not available for biological research, interest soon declined.

In 1964 the major psychotropically active constituent, Δ^1-tetrahydrocannabinol (Δ^1-THC), was isolated in a pure form and its structure was elucidated [8]. It was shown that it could be easily obtained from the psychotropically inactive, crystalline major constituent, cannabidiol. Many new constituents were identified and today they number more than 40. Numerous total syntheses of THC and other natural cannabinoids were achieved [7]. Δ^1-THC and several other components became readily available. Since 1964 about 2000 papers on the chemistry, pharmacology, metabolism, and clinical effects of Δ^1-THC have appeared.

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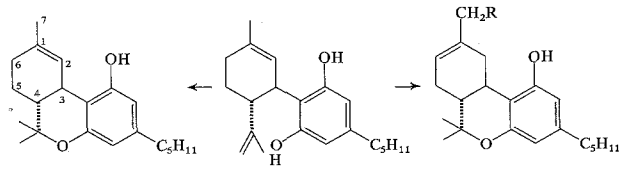
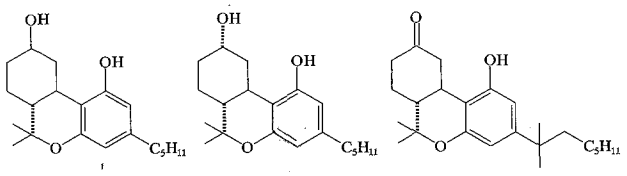
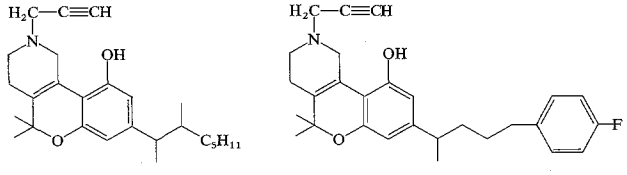


Δ^1-THC Cannabidiol R=H: Δ^6-THC R=OH: 7-OH-Δ^6-THC



1β-OH-7-nor-hexahydrocannabinol 1α-OH-7-nor-hexahydrocannabinol Nabilone



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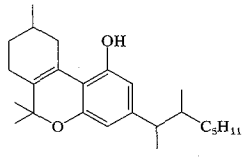

Dimethylheptyl homolog of Δ^8-THC (DMHP)

The chemistry and pharmacology of *Cannabis* have been reviewed [7, 9]. We would like to point out several properties highly relevant to the present discussion. The cannabinoids are very lipid-soluble materials and remain in the lipid stores of the body over a considerable length of time. Although the cannabinoids possess a phenolic group, which has to be free (or potentially free, as in a hydrolyzable ester) and which is a prerequisite for activity, this class of compounds is not acidic. Cannabinoids are not extractable by base, but are very soluble in nonpolar solvents.

The mode of action of cannabinoids is not yet known. Recent data are consistent with the picture of reduced sympathetic and enhanced parasympathetic activity [10]. Toxicity is very low.

In man, the common effect of moderate *Cannabis* use (5–20 mg THC) is characterized by benign CNS effects such as easy laughing, elation, heightened awareness, deterioration of time-estimation and time-producing tasks, mild aberration of fine motor coordination, and some distortion of activities and interactions with others. In American slang these effects are called a 'high.' At doses above 30–35 mg (but sometimes even at lower doses) there may be anxiety, depersonalization, and paranoid-like states. The most consistent cardiovascular effect in man is tachycardia. Some hypotension may be observed and mild lowering of the body temperature is frequently noted.

Δ^1-THC

The detailed investigations on Δ^1-THC and other cannabinoids have to some extent clarified the problem of their possible therapeutic potential. The proceedings of a symposium and a review on the subject have been published [11].

Δ^1-THC in Glaucoma

In 1971, Hepler and Frank [12] found that marihuana smokers had reduced intraocular pressure. Following this chance discovery, a double-blind study on volunteers was undertaken. These volunteers were kept in a hospital for over 3 months. They were given either marihuana (by smoking) or Δ^1-THC (orally) and the previous observations were confirmed. Hepler and Petrus [13] then gave Δ^1-THC to glaucoma patients. Glaucoma is a serious eye disease that can lead to blindness. Not all glaucoma cases are sufficiently helped by existing drugs. When THC was given orally in doses up to 20 mg, the intraocular pressure in most cases dropped from 30–40 mm to the normal 15 mm Hg, and stayed low for about 4 h. The intraocular pressure-reducing effects appeared to add to the effects of conventional glaucoma medications, hence providing a basis for continued interest in the possible therapeutic effects of *Cannabis* in the treatment of chronic simple glaucoma. Cannabinoids, other than Δ^1-THC, have also been found to reduce intraocular pressure [14, 15], but a clear-cut separation of psychotropic activity and high antiglaucoma activity is still to be achieved. Although, in a well-publisized case, the US legal and health authorities have allowed a glaucoma patient to grow and use *Cannabis*, the problem of introducing a new medicament for glaucoma, based on a cannabinoid structure, is not yet solved.

Δ^1-THC in Asthma

Studies in the past several years have established a bronchodilator action for smoked marihuana in

normal and asthmatic subjects [16–18]. Recently, Tashkin's group [19] succeeded in preparing an aerosol of Δ^1-THC that was directly administered (at a dose of 5–20 mg) by inhalation to asthmatic patients and to healthy volunteers, and its action was compared to that of an aerosol of isoproterenol, a standard antiasthma agent at the therapeutic dose of 1.25 mg. While during the first 15 min THC was only equal to isoproterenol, later it caused considerably greater bronchodilation, which lasted 5–6 h. In some patients, however, local irritating effects on the airways were observed that might preclude the therapeutic use of Δ^1-THC. Surprisingly, in one case at least, even orally administered Δ^1-THC was found to cause bronchoconstriction [20]. Obviously Δ^1-THC will not be the drug of choice in asthma, but other cannabinoids might show a better therapeutic ratio of beneficial effect to psychotropic effects and occasional bronchoconstriction.

Δ^1-THC as an Antiemetic Agent in Cancer Chemotherapy

Repeated vomiting is a serious side effect of drug or radiation cancer therapy. This condition is not always improved by existing antiemetic drugs. For the last 10 years young people in the US undergoing such treatments have claimed that marihuana smoking is quite beneficial in alleviating or totally preventing such emesis. A research group at the Harvard Medical School has now confirmed this finding [21]. Oral administration of 15–20 mg Δ^1-THC, up to three times a day, in a double-blind experiment was highly effective in preventing or significantly reducing emesis. No patient vomited while experiencing a subjective 'high feeling.' Some of the patients who did not feel 'high' had emesis. This lack of THC effect (both 'high' and antiemesis) might have been due to failure of absorption.
The antiemetic effect of Δ^1-THC is presently being evaluated in several clinics and quite possibly will become a standard treatment in the near future.

Δ^1-THC in Hypertension

As mentioned above, Δ^1-THC may cause some lowering of the blood pressure. Can Δ^1-THC be used as a new antihypertensive drug? The answer is still equivocal. Benowitz and Jones [22] administered Δ^1-THC to healthy volunteers in oral doses gradually reaching 210 mg/day. The volunteers were kept in a hospital under carefully controlled conditions for 20 days. During the first days the CNS effects and the tachycardia were predominant; the blood pressure was not significantly reduced. However, tolerance gradually developed, first to the tachycardia and then to the CNS effects; the blood pressure slowly decreased and became stabilized at ca. 95/65 on standing. A comparable study with hypertensive patients has not been reported yet.

Other Potentially Therapeutic Effects of Δ^1-THC

Sofia has found that Δ^1-THC has anti-inflammatory [23] effects in animals. The results were negative in other tests [24]. Δ^1-THC has also been reported, again only in animal studies, to have antitussive [25] and antifertility activity [26] and to potentiate the action of anesthetics [27]. A clinical study [28] has shown that Δ^1-THC significantly decreases the time it takes physically healthy insomniacs to fall asleep.

Will Δ^1-THC Become a Clinically Useful Drug?

We believe that, except as an antiemetic agent in cancer chemotherapy, the results so far are not encouraging. The CNS effects and the tachycardia will not be acceptable in treatment of most disease states. In addition, several groups have found potentially dangerous cellular, immunological, and enzymatic effects [29–31]. While most of these are observed in in-vitro or in specialized conditions, and their clinical significance is uncertain [32], one should have to keep these potential danger signals in mind. It seems to us that the positive results obtained with Δ^1-THC can be used as leads for further pharmacologic and clinical research, which should be undertaken with nonpsychotropic cannabinoids or with cannabinoids in which a more significant separation of side effects from desired effects has been achieved. Some work along these lines has already been published.

Cannabidiol (CBD) in Epilepsy and as an Hypnotic Drug

In 1973 two studies from Brazilian investigators showed that CBD (which is not hallucinogenic) was active in reducing or blocking convulsions produced in experimental animals by a variety of procedures [33, 34]. Other laboratories confirmed these findings and showed that the CBD effects were comparable to those of diphenylhydantoin and other drugs clinically effective in major seizures [35]. These findings supported old reports ascribing an antiepileptic effect of marihuana preparations in humans [1, 5, 6] and

encouraged us to test CBD in humans. We expected CBD to possess considerably fewer side effects than THC. This assumption proved to be correct. Cunha et al. [36] administered 200 mg daily of CBD to 8 healthy volunteers and placebo to another 8, over 30 days, in a double-blind procedure. Clinical (including ECG), neurologic (including EEG), psychiatric, blood, and urine examinations, performed at weekly intervals, revealed that CBD induced no toxic effects in any of the volunteers.

The lack of toxicity in healthy volunteers led to a clinical trial with 9 epileptic patients, suffering from uncontrolled secondary generalyzed epilepsy with temporal focuses, who were refractory to several antiepileptic drugs. In a double-blind procedure the patients received either 200 mg CBD daily (4 patients) or placebo (5 patients) for a 3-month period, in addition to their habitual medication. Two of the epileptics under CBD showed a remarkable improvement: they had no convulsions during the entire 3-month period. The third patient had a partial improvement, while no improvement was observed in the fourth patient. No toxic effects were observed. None of the placebo patients showed any improvement. This work is now continuing with more patients. If these preliminary results are confirmed, it will remain to be seen whether CBD was effective *per se* or potentiated the effects of the other drugs (diphenylhydantoin, phenobarbital) that the patients continued taking during the CBD treatment.

Another potential use of CBD appeared to be as an hypnotic drug. To test this, rats with chronically implanted electrodes were injected with the drug and the sleep-wakefulness cycle was recorded. CBD-treated animals showed a decrease in latency to the appearance of the first episode of slow-wave sleep (SWS), and a decrease of total time of wakefulness with a concomitant increase in total time of SWS (Monti, in preparation). Based on these animal experiments, a pilot study with 15 healthy insomniac volunteers was carried out. Placebo, 5 mg nitrazepam and 40, 80, and 160 mg of CBD were given, in a double-blind cross-over design, at weekly intervals. The volunteers under 160 mg of CBD slept significantly more than when they were under placebo, and with all 3 doses of CBD they reported fewer dreams (Carlini, Masur, and Magalhaes, to be published). It is premature to accept these preliminary results as evidence for a significant hypnotic effect of CBD but, if confirmed later by other laboratories, it would be pertinent to recall Fronmuller's observations of 1860 [37]:

"Dr. Fronmuller, after a large number of experiments, draws the following resume of the value of this drug. Of all anaesthetics ever proposed, Indian hemp is the one which produced a narcotism most closely resembling the natural sleep without causing any extraordinary excitement of the vessels, or any particular suspension of secretions, or without fear of a dangerous reaction, and consecutive paralysis. It acts neither as violently nor as surely as opium. It can be given in all acute inflammatory diseases as well as typhoid affections. It is well adapted as an alternate with opium in case this ceases to act. Its best mode of administration consists in pills of the alcoholic extract and powdered seed."

Other Cannabinoids

Cannabinoids as New Analgetic Agents

Shortly after the identification of Δ^1-THC as the major psychotropic constituent of hashish, it was shown that the long-recognized analgetic properties of *Cannabis* were due to this same component [38]. This was unfortunate as the use of THC as an analgetic is obviously not practical. Recently, a group at the US National Institute of Health showed [39] that in certain animal tests 7-hydroxy-Δ^6-THC, a metabolite of Δ^6-THC [40], was as analgetic as morphine, while Δ^6-THC was ca. 7 times less active, i.e., it was as active as codeine. These compounds are known to be psychotropically almost equally active both in animals and in man [40, 41], which indicates that, at least on the basis of the particular analgetic test used, a certain separation of effects might have been achieved. The same group later found [42] that in animal tests 1β-hydroxy-7-nor-hexahydrocannabinol was analgetically a very potent substance [43]. The isomeric 1α-hydroxy-7-nor-hexahydrocannabinol, which is as psychotropic as the 1β isomer, is not analgetic, which again points out that the two effects can be disassociated.

If a complete separation between psychotropic and analgetic effects is achieved, the field may be wide open for the possible development of nonaddicting potent analgetics. It is well known that cannabinoids do not cause physical addiction: even after prolonged use the sudden interruption of *Cannabis* consumption causes only minor withdrawal effects. One can expect the development of some psychologic dependence to cannabinoid drugs which, however, should not be severe.

Synthetic Cannabinoids

The obvious therapeutic potential of *Cannabis* has led several pharmaceutical companies to initiate pro-

grams aimed at cannabinoid drugs devoid of the undesirable CNS effects.

Research at the US company Ely Lilly has led to a synthetic cannabinoid named Nabilone [44], which is presently tested in the clinic. Preliminary results indicate that a considerable separation was achieved (at an oral dose of 2 mg) between the undesirable effects (both psychologic and cardiovascular) and the desirable sedation and relaxation. At a dose of ca. 5 mg, the side effects (euphoria and postural hypotension) were significant though tachycardia was not observed. On chronic treatment (1 or 2 mg twice daily) tolerance developed to the side effects, while the sedative-relaxant effect was apparently still significant. This last point needs further clarification.

The joint research of the US firms Abbott and SISA has led to the development of nitrogen-containing cannabinoids such as Abbott 40174 and Abbott 41988. In animal tests [45, 46] these compounds, as well as several related ones, were shown to possess: tranquilizer properties, comparable in certain tests, to those of diazepam and chlorpromazine; analgetic potency, higher (in the mouse writhing and other tests) than that of codeine; sedative-hypnotic activity; and intraocular pressure-lowering activity. Although no clinical data has yet been released, it seems that in view of their pharmacologic similarity [46] to the dimethylheptyl homolog of Δ^3-THC (DMHP), which has been tested in man [47], the side effects may be considerable.

Why Do Cannabinoids Act on so Many Biological Functions?

The catholic range of activity of the cannabinoids, which in many clinical effects resemble the benzodiazepines, poses a basic question. Are we dealing with a nonspecific group of compounds that act mainly on the lipid-rich cell membranes, by virtue of their high lipid solubility? In our view the answer is negative. We believe that cannabinoids act on specific receptors. The fact that the unnatural (+)-isomer of Δ^1-THC is almost devoid of activity [48] supports our contention.

The reason for the wide range of activity of cannabinoids might be more subtle. One can postulate that organisms have developed a tendency of, what may be termed, *maximal structural economy*, i.e., the organism will tend to synthesize its structural elements in the most efficient way possible. In this respect one can compare organisms to an ideally organized chemical plant in which as many products as possible, for economic reasons, are synthesized by the same routes, or through common intermediates. Large savings in unit synthetic processess and in energy are achieved in this manner. Organisms are known to do the same. For example, various cells produce steroids for a multiplicity of unrelated biological reactions: cortisone, testosterone, progesterone, estrone, etc. aim at different receptors, yet they are very closely related biogenetically. Although the structure of biological receptors is not yet known, we can assume that organisms have applied to them the same principle of maximal structural economy, i.e., the structure of many of these receptors may be related. These receptors are built for the organisms' own endogeneous chemical transmitters and modulators, which are designed to be specific. Exogeneous compounds are not necessarily so. Hence, frequently when a new biologically active synthetic structure is discovered, its activity is not confined to a single type of effect. Such compounds possibly fit several structurally related (but not functionally related) receptors. By structural modification it is possible to increase one type of activity while decreasing another. This is the basis for the intensive research on structure-activity relationships in medicinal chemistry. Cannabinoids seem to be one such class of compounds. They apparently 'fit' several active sites. By changing the structure of THC, cannabidiol, and other cannabinoids, one may expect to better the 'fit' to certain receptors, thus increasing specificity and reducing side effects.

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