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Structure-Activity Relationships in Cannabinoids*

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I. Introduction

MARIJUANA is a plant product which has numerous chemical constituents, but it is the active constitutent (−)-Δ^9-6a,10a-*trans*-tetrahydrocannabinol (THC), generally referred to as Δ^9-THC, which is responsible for the main pharmacological effect. The class of compounds is called cannabinoids, and this term is used for the typical C_{21} groups of compounds present in *Cannabis sativa* L. and includes their analogs and transformation products. The following two different numbering systems, dibenzopyran and monoterpenoid, are generally used for naming the cannabinoids (figure 1).

Based on the monoterpenoid numbering system, Δ^9-THC is also known as Δ^1-THC. The other physiologically active isomer, Δ^8-THC (alternate name Δ^6-THC), is found only in a few varieties of the plant. The other two isomers with a 6a,10a-*cis* ring junction are *cis*-Δ^9-THC and *cis*-Δ^8-THC, both of which have been synthesized and are relatively physiologically inactive, but so far only the former has been found in the plant. As expected, the *trans* compounds are more thermodynamically stable than the *cis* compounds. In the *trans* series, however, the Δ^8-THC is more stable than Δ^9-THC, since the latter is easily isomerized to Δ^8-THC on treatment with acids. The main pharmacological interest centers around the thermodynamically less stable Δ^9-THC and its various derivatives and metabolites. This has posed many synthetic problems, because during chemical reactions the more stable derivatives of *trans*-Δ^8-THC are mostly formed. In addition, the chemistry of cannabinoids is much more complex than the structure of Δ^9-THC would indicate. The reactions are capricious and sensitive to reaction conditions, and they form complex mixtures which are difficult to separate. This makes development in this field difficult and slow.

Δ^9-THC is an optically active resinous material which is very lipid soluble and water insoluble. In general, most of the cannabinoids display similar properties which makes their pharmacological testing difficult. The compounds have to be administered in various solvents such as polyethylene glycol, Tween, Triton, emulphor, or alcohol, which are not without pharmacological activity. However, the clinical effects produced by ingesting marijuana or Δ^9-THC are unique (see, e.g., refs. 47, 24, and 104). The gross effects produced in man or animals cannot be classified pharmacologically as being primarily due to a stimulant, sedative, tranquilizer, or a hallucinogen, although they share some properties with each of these. In general, the effects produced by this drug are dose dependent. Thus, in small doses, it produces stimulation followed by sedation. In high doses, it produces subjective effects more typical of a hallucinogen and somewhat resembling those of a small dose of lysergic acid diethylamide (LSD). However, unlike the latter, it produces sedative effects, with no significant sympathomimetic actions, and there is no cross-tolerance to LSD. In addition, it is not a narcotic, and compared to many drugs such as the opiates, barbiturates, etc., it does not produce physical dependence. Interestingly, the user may

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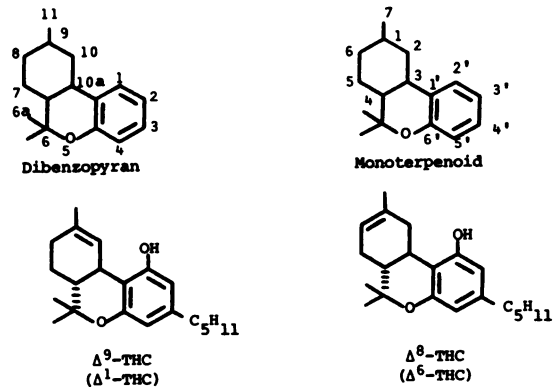


FIG. 1. Dibenzopyran and monoterpenoid numbering systems generally used for naming cannabinoids.

be in a high state of intoxication, but to an observer, he may appear to be in a near normal state. Mild states of intoxication are generally undetected, and the mood may vary from being happy and gregarious to quiet and introspective. With high doses, notable signs are minimal, but the most reproducible signs include an increase in pulse rate and bloodshot eyes. Dryness of the mouth and throat and an increased appetite are common. In some cases, there may also be slurring of the speech. With moderate dosages, the user can perform simple physical and mental tasks, but the performance of more complicated physical and psychological tasks may be impaired. The most common subjective effect appears to be time distortion with other effects varying from pleasant relaxation to acute anxiety, loss of contact with reality, hallucinations, and panic. These latter effects are generally associated with large dosages. As with other psychoactive drugs, the effects vary greatly and are mostly dictated by the psychological makeup of the individual and the setting under which the drug is used.

In various animals (see, e.g., refs. 24 and 103), the cannabinoids show predominantly central nervous system (CNS) depression and ataxia which lasts from several hours to days, depending on the dose administered. The characteristic effect of cannabinoids, which distinguishes them from all other psychoactive drugs, is a postural arrest phenomenon with relaxed staring and is accompanied by hypersensitivity to external stimuli. The animals are not anesthetized, as they can always be aroused through adequate sensory stimulation. The dog is particularly sensitive to this class of compounds which produces a characteristic pattern of ataxia. Cataleptic effects are observed in nearly all species. In the mouse, motor excitement can be observed after very small doses, and the animals show hyperexcitability or the "popcorn" effect when subjected to auditory and tactile stimuli.

From the above, it is quite clear that the task of clinical evaluation and determination of therapeutic utility of this class of drugs is complex. This is borne out by the fact that, in spite of extensive pharmacological and biochemical studies in the marijuana field, the two most promising therapeutic areas for the cannabinoids, antiemetic and antiglaucoma activities, were discovered serendipitously without any preclinical pharmacology. The role of Δ^9-THC as an antinauseant in patients undergoing cancer chemotherapy is now well established. This is mainly because Δ^9-THC is more effective in controlling nausea than some of the presently available drugs. Besides Δ^9-THC, a synthetic analog Nabilone has recently been marketed as an antiemetic, and the potential of cannabinoids as therapeutic agents is now beginning to emerge. In the antiglaucoma field, the utility of Δ^9-THC as a novel agent has been established, and several synthetic analogs are presently in the developmental stage. Other areas of potential therapeutic use of cannabinoids include anticonvulsants, analgesics, antiasthmatics, antianxiety, appetite stimulant, and treatment of anorexia nervosa, etc. This aspect has been discussed in depth previously (117).

II. Drug Development: An Overview

Since structure-activity relationships (SAR) studies are helpful in the designing and development of therapeutic agents, an overview of cannabinoids from the drug development point of view is presented below.

Marijuana itself, being a plant material and thus a complex mixture of compounds, is unlikely to be used as a marketable drug. However, the active constitutent of marijuana, Δ^9-THC, has just been approved for marketing in the USA as an antinauseant in cancer chemotherapy treatment. Even before the structure of Δ^9-THC was firmly established, several synthetic analogs in the $\Delta^{6a,10a}$ series had been prepared by R. Adams and A. R. Todd in the early 1940s and were shown to have similar activity to marijuana. This was followed in the 1960s by an intense interest in structural modification of Δ^9-THC and other carbocyclic analogs. In addition, a large variety of heterocyclic analogs were prepared. All these modifications have resulted in a series of novel THC derivatives and analogs which show a wide variety of enhanced activities such as antiglaucoma, antinausea, analgesic, tranquilizer, anticonvulsant, antihypertensive, etc.

The future development of clinically useful drugs from this field will undoubtedly depend on the success achieved by synthesis in introducing structural changes in the THC molecule, which will lead to selectivity of pharmacological action. This presupposes the availability of reliable animal models for screening this class of drugs. The shortcomings in this area of pharmacological evaluation make the development of drugs from this field exceptionally difficult.

There is the difficulty of initial screening, i.e., the selection of compounds prior to the more expensive and more sophisticated behavioral tests in dogs and monkeys. Generally, the activity cage, roto rod, hypothermia, and the popcorn tests in mice and rats are used for initial screening. What relevance these tests have in identifying potential therapeutic candidates is presently not clear.

Primarily, these tests only give an indication that the compound is "cannabis-like" and will show a similar profile. There is need for the development of other rodent models, which will provide better criteria than presently available for identifying potential therapeutic candidates from this field.

For more advanced screening, the presently available pharmacological models for cannabinoids, such as the dog ataxia and the monkey behavioral tests, do provide a good indication of the psychoactive component of these compounds, since there is a good correlation in extrapolating from animal data to humans. But the problem arises in quantifying the extent of separation of psychoactive and other CNS side effects from therapeutic effects.

Unless progress is made in this direction, one would be left with no recourse but to rely on the importance of early studies in humans. The extent of separation of undesirable CNS side effects from clinically useful effects could only be meaningfully gauged in human studies. This point is well illustrated by the results obtained in the clinical evaluation of analgesics. Nabitan and Levonantradol, two synthetic nitrogen analogs of THC, were both developed as analgesics on the basis of animal experiments. Both were found to be clinically effective as analgesics in cancer and postoperative pain, respectively, but the incidence of side effects was higher than the animal data indicated (117).

In drug development from this field, the above clinical experience highlights the point that, so far, very few cannabinoids have been studied in the clinic, and the base line data generated are not sufficient to provide proper guidelines for extrapolation of animal data to humans in terms of dosages and side effect to therapeutic ratios. When more compounds have been clinically evaluated, the interpretation of animal data will become more meaningful.

It appears that further modifications in the structures of Nabitan and Levonantradol will be necessary to develop useful analgesics from this field. It should be emphasized that the potential exists for development of novel analgesics from this field, as cannabinoids act at different receptors than the opiates (analgesic action is not antagonized by naloxone), do not have the physical dependence liability and respiratory depression properties of the strong opiates, and are orally active with a long duration of action.

Anticonvulsants are one area where animal studies have provided a good indication for a clinical candidate from this field (ref. 117 and references cited therein). Of all the natural constituents of marijuana studied for antiepileptic activity, cannabidiol (CBD) was proposed as the agent of choice. This is primarily because in animal screens it was found to be devoid of marijuana-like CNS effects, a finding that was confirmed in humans. In the only clincial study, CBD was reported to be effective. This bears out the animal model data. Further confirmation of these results and more clinical studies will no doubt be required before CBD's place in the treatment of epilepsy can be judged.

There are a few other instances (e.g., refs. 1 and 45) where animal models have indicated a clear separation or dissociation of cannabinoid (psychotropic effects) from other therapeutic effects. However, it remains to be seen if they can be substantiated in the clinic.

Progress is being made. Several novel behavioral and drug discrimination tests have been designed and introduced to test these compounds, and it is hoped that in the near future more meaningful data will be forthcoming from these tests. The rate of development of therapeutic agents should then accelerate.

In summary, the concept of drug development from THCs and cannabinoids is based on very sound foundations, since Δ^9-THC has remarkably low toxicity in animals and humans. In addition, it has practically no respiratory-depressant activity and no or very low physical dependence liability, and, finally, it has a unique pharmacological profile compared to other psychoactive drugs.

III. Assessment of Biological Activity

In the early 1940s, Roger Adams reported the first systematic study of SAR of cannabinoids (2). It was based on the characteristic dog ataxia test, as developed and quantitated with estimates of error by Loewe (81). At about the same period, Todd and others (130, 5) used the Gayer areflexia test (37) for suppression of rabbit corneal reflex to determine the potency of various extracts of cannabis and synthetic cannabinoids. They also reported SAR of cannabinoids based on this test. Both groups assumed that the activity in these tests was a quantitative measure of the behavioral or psychotropic activity of marijuana in man, although no controlled experiments to support this assumption were reported. Since that time, a number of natural and synthetic cannabinoids have been evaluated clinically, and there appears to be a good correlation between the relative potency in the dog ataxia test and the psychoactive component of these compounds in man. The usefulness of the rabbit areflexia test has, however, been controversial. In this test, Loewe (79) found a large variation among individual animals and noticed the development of tolerance. Similarly, Grlic (39) and Miras (98) found it to be unsatisfactory as it is difficult to quantitate the results. Others (80, 62, 75) have found the test unreliable. On the other hand, some workers have found the areflexia test to be satisfactory (10, 136, 14), but its usefulness is very limited, and today it is not in general use for screening cannabinoids.

In the 1960s when pure Δ^9-THC and other cannabinoids became available, several other tests in different animals were reported to qualitatively determine the "cannabis-like" activity of various compounds, for example, cataleptic reaction in mice, effects on motor ac-

tivity and gross behavior in mice and rats, digging activity of gerbils, suppression of aggressiveness in isolated mice, operant conditioning techniques in various animals, ichthyotoxicity, etc. All these are well documented and will not be discussed here.

In 1968, Scheckel *et al.* (124) reported the first study on the effects of cannabinoids in monkeys. Since then, largely due to the efforts of Grunfeld, Edery, and Mechoulam (40, 93, 26, 27), the monkey behavioral test procedures have been standardized, and the SAR of cannabinoids have been developed. This test, which provides good correlation between potencies of various cannabinoids in monkeys and man, complements the dog ataxia test. Loewe's procedure for the dog ataxia test has been further refined and standardized. The SAR based on both of these tests are very similar and provide a good foundation for the SAR of cannabinoids. However, it should be emphasized that these SAR are mainly reflective of the behavioral activity, rather than the other pharmacological properties, of the cannabinoids. From time to time, attempts have been made to introduce newer models for the bioassay of cannabinoids. These include the mouse ring immobility assay, the genetically unique tetrahydrocannabinol-seizure susceptible (THC-SS) rabbit, and spontaneous activity and body temperature in mice. Recently, the drug discrimination procedure has been used to study cannabinoids in rats and pigeons. With this background, we will examine in detail the various procedures which have been used to develop the SAR of cannabinoids.

A. Dog Ataxia Test

In 1938, Walton and his colleagues (138) described the dog ataxia test for cannabinoids. They performed the test by defining six degrees of ataxia but did not establish a dose-response curve for the standard marijuana extract. As a result, their test could not be quantitated. Loewe (81) rectified this and developed a method of successive approximation for the unknown compound by comparing it to a standard preparation. From the results obtained, he reported a ±5–15% range of deviation for his assays. He described his procedure with a detailed example in which he adapted his data to an ordinary probit analysis and obtained a SE of ±2.54 for a potency ratio of 35 from 57 experiments. As pointed out by Paton and Pertwee (103), a plot of Loewe's data shows that the responses in the dog appear to be normally distributed with arithmetic increases in dose, but the dose-response curve is somewhat flat, which makes precise assay difficult.

With the availability of pure Δ^9-THC and other cannabinoids, Grunfeld and Edery in 1969 (40) reexamined the behavioral effects in various animals and repeated the dog ataxia test in mongrel dogs. The motor disturbances were rated according to a scale similar to that of Walton *et al.* (138), and they reported that Δ^9- and Δ^8-THCs were active at 0.25 mg/kg and 0.5 mg/kg (i.v.), respectively. These authors, however, preferred the rhesus monkey model (see below).

The dog ataxia test was further refined and modified by Martin *et al.* (84, 85), and at present, this procedure is generally used. The quantification of cannabinoid behavioral effects was examined in mongrel dogs of either sex (8–12 kg). Prior to drug administration, the animals were observed for their degree of spontaneous activity: gait; tail-tuck; etc. The animals were then given injections i.v. of the drug or vehicle (1 ml/5 kg of body weight), observed for the occurrence of the signs described in table 1, and rated according to the scale. Most of the signs were present for any given score. The animals were rated at 5-min intervals by three observers who were blind with regard to treatment. The maximum scores (which usually occurred at 30 min) were averaged for each dog. A typical test session consisted of five animals that received either vehicle: Δ^9-THC (0.2 mg/kg) or the unknown cannabinoid treatments. All drugs were prepared for pharmacological testing by dissolving 100 mg in 1 ml of a 1:1 mixture of emulphor (GAF Corp., Linden, NJ) and ethanol with the aid of a sonicator. Appropriate dilutions were made with saline to give a final concentration of emulphor:ethanol:saline (1:1:18) (table 1).

Using this procedure, Δ^9-THC was found to be active at 0.1 mg/kg (i.v.), giving a score of 1. At 0.2 mg/kg, a score of 3 was obtained. Similarly, Δ^8-THC was found to be active at 0.25 mg/kg (i.v.).

B. Monkey Behavioral Test

As mentioned earlier, this test was standardized by Edery *et al.* (27, 40, 93, 26) and is primarily based on the changes noted in behavior patterns of rhesus monkeys under the influence of cannabinoids. It appears to be a suitable model, as most of the symptoms observed in man with Δ^9-THC (i.e., redness of the conjunctiva, pseu-

TABLE 1
Quantification of cannabinoid behavioral effects in dogs

Score	Depression*	Static ataxia†	Prancing‡	Hyperreflexia§	Tail-tucked‖
0					
1	+	3–5 min	−	−	−
2	+	2–3 min	+/−	+/−	+/−
3	+	1–2 min	+	+	+
4	++	1 min	+	++	+
5	++	30 s	+	++	+
6	+++	Prostate	NA¶	++	+

* +, slight decrease in spontaneous activity; ++, moderate depression; +++, severe depression.

† Animal sways forward and backward and/or side to side after standing in one position for the indicated time.

‡ Careful placement of forepaws with a high step action.

§ Exaggerated reflex to an object thrust in the direction of their face. −, absent; +, slight; ++, severe.

‖ Tail which was lifted on swaying during control period is between hind legs, often against abdomen.

¶ NA, not applicable.

doptosis, loss of aggressiveness, and indifference to the environment) were also observed in monkeys. The doses at which effects of the Δ^9-THC could be observed in monkeys were smaller than those needed to produce similar effects in other species of animals and were comparable with those needed in man. Typically, two to six adult animals of both sexes were used for each dose level. Two independent observers, blind with regard to the treatment, scored in accordance to the severity of the behavioral and somatic changes in the monkey, spread over the 0.5 h before and 5 h after the injection. More than one compound was often tested in the same animal, but injections were given at least 1 wk apart. Δ^8-THC was used as the standard to compare the potencies of various cannabinoids (table 2).

Solvents such as propylene glycol (e.g., for Δ^9-THC), polyethylene glycol (e.g., for Δ^8-THC), mixtures of propylene glycol and ethanol (1:10), and dimethyl formamide were used as vehicles for injection purposes. Injections were made into one of the saphenous veins at a maximum volume of 0.1 ml/kg. The vehicle did not cause any noticeable changes in control animals. It was also observed that rhesus monkeys of the active, alert, and aggressive type were found most suitable for cannabinoid testing.

Δ^9-THC was active at 0.05 mg/kg (i.v.) and Δ^8-THC at 0.1–0.25 mg/kg in this test (27).

C. Mouse Ring Immobility Assay

This assay procedure is based on observation by Loewe (80) that mice, after treatment with cannabinoids, show a cataleptic effect and can be placed in a prone position supported only by their thighs and jaws until aroused. By using a 5.5-cm-diameter horizontal ring and determining the percentage of time a mouse can stay immobile during a 5-min period, Pertwee (109) screened several compounds and developed an assay procedure. The data collected suggest that Δ^9-THC produces a dose-related graded effect and that the threshold doses vary with route of administration. This test can be used to assess cannabis-like activity and, with suitably designed experiments, can provide estimates of error. As expected, cannabidiol is inactive in this test, and Δ^9-THC was found to be 10–20 times more active than marijuana extract. It is noteworthy that this characteristic cataleptic behavior on the ring is also shown by chlorpromazine, but not by barbiturates.

TABLE 2

Notations and symptoms in the monkey using Δ^8-THC as the standard

Notation	Dose (mg/kg)	Symptoms in the monkey
–		No change
±	0.1	Tranquility
+	0.25	Drowsiness, decreased motor activity, occasional partial ptosis, occasional head drop
++	(0.5–0.9)	Stupor, ataxia, suppression of motor activity, full ptosis, typical crouched posture ("thinker position") lasted for up to 3 h. The animal could, however, regain normal behavior for short periods of time if external sensorial stimuli (pinching, noise) were applied
+++	(1.0–2.0)	Severe stupor and ataxia, full ptosis, immobility, crouched posture lasting for more than 3 h and absence of reaction to external stimuli

D. Tetrahydrocannabinol-Seizure Susceptible (THC-SS) Rabbit Model

Recently Consroe *et al.* (refs. 19 and 20 and references cited therein) described a new (THC-SS) rabbit model which correlates very well with the psychoactivity of various cannabinoids in man, as well as the behavioral test in rhesus monkeys and the dog ataxia test. They found that, because of a homozygous expression of a single autosomal gene (*thc*) in their rabbit colony (Uaz:NZW-*thc*), THC-SS rabbits exhibited nonfatal behavioral convulsions when given injections of Δ^9-THC. These seizures were not observed in rabbits without this genetic background. Besides the psychoactivity of various cannabinoids, good correlations were also obtained between other cannabinoid-induced behavioral effects in man and THC-SS rabbits. These include Δ^9-THC dose-effect relationships, comparability of minimally effective doses of Δ^9-THC to elicit the behaviors, reversible tolerance development with chronic Δ^9-THC administration, electroencephalogram (EEG) correlates with Δ^9-THC, and the ability of the nonpsychoactive cannabidiol to block the Δ^9-THC-produced behaviors.

In this procedure, the cannabinoid, prepared in a vehicle of 10% polysorbate 80 and 90% physiological saline solution, was injected i.v. to adult THC-SS rabbits of both sexes (2–4 kg), and the presence or absence of behavioral convulsion was recorded within a 20-min period. Essential criteria for convulsion included the presence of limb extension, clorus, and thrashing, since all cannabinoid convulsions are composed of these end points. In addition, the convulsions consist of head tuck, extreme mydriasis, and nystagmus. Generally, four rabbits were used for each dose level, and more than one compound and/or dose was tested in the same animal, these treatments being given at least 7 days apart. The rabbits were given treatment randomly, but all received 0.05 mg of Δ^9-THC per kg at least once (all adult THC-SS rabbits convulse to this dose of Δ^9-THC). The potencies of the various cannabinoids were determined relative to the lowest dose of Δ^9-THC that produced convulsions in 100% of the THC-SS rabbits, i.e., 0.05 mg/kg. This was set at 100%. Relative potencies were then calculated

by the following formula:

$$\text{Relative potency} = \frac{\text{lowest affective dose of } \Delta^9\text{-THC (0.05 mg/kg)}}{\text{lowest effective dose of cannabinoid}} \times \%\text{ of rabbits convulsed}$$

Based on this test the relative potencies of some of the important cannabinoids are shown in table 3. This model appears to be reliable for assessing the psychoactive potential of cannabis-like compounds in structure-behavioral activity studies. The only drawback at the present time is that these THC-SS rabbits are bred exclusively in the University of Arizona laboratory and are not generally available to other workers.

E. Spontaneous Activity and Body Temperature in Mice

A decrease in locomotor activity and a fall in body temperature in rodents is a very well-known effect of cannabinoids. As early as 1928, Gayer (37) reported a fall in spontaneous activity in mice, an effect since noted by several other investigators (103). The fall in spontaneous activity was measured by several investigators using photocell activity chambers (36, 23, 14). A more detailed examination of this effect has shown it to be biphasic and dose dependent (36, 14, 22, 3, 30). There are also reports to indicate that tolerance develops to this effect (22, 3).

Hypothermia was reported by Miras (98) and Garattini (35) after an i.p. injection of cannabis resin into rats. Temperature falls of 2–3° were observed with a slow onset, and the effect lasted for several hours. Similar results were observed in mice (38, 52) and confirmed by other investigators. Greater falls in temperature were noted with higher doses (38). Hypothermia was also reported in dogs and monkeys (43). The mechanism of hypothermia is not clear, but it appears that it is caused by a primary effect on thermoregulatory centers, since it was found that cannabis injected into the cerebral ventricles of mice or rats is more effective than when injected either i.v. or i.p. (35, 38). In causing hypothermia, the cannabinoids resemble the phenothiazines, but they are less potent in that respect.

The evaluation of cannabinoids for their ability to alter spontaneous activity and body temperature in mice has served mainly as a primary screen. The procedure has been standardized by Martin *et al.*; it uses small amounts of material and provides useful data in further characterization and study of the SAR of cannabinoids (85, 86, 42, 123). Briefly, the procedure is as follows. Male ICR mice (22–30 g) were housed in the laboratory for 24 h before treatment. The ambient temperature of the laboratory, which varies from 21–34°C from day to day, was recorded at the beginning and end of each experiment. Rectal temperature was determined by a thermistor probe (inserted 25 mm) and a telethermometer (Yellow Springs Instrument Co., Yellow Springs, OH) just prior to vehicle or drug administration. Following the initial temperature determinations, mice were given injections i.v. of either vehicle or drug (0.1 mg/10 g of body weight) and immediately placed in photocell activity chambers (mice were not habituated to the apparatus). After the animals were placed in the chambers, interruptions of the photocell beams were recorded for 10 min. The results were expressed as the percentage of vehicle-treated mice, and the 50% effective doses (ED_{50}s) and their confidence limits were determined by the method of Litchfield and Wilcoxon (76). The mice were removed from the activity chambers, and rectal temperatures were measured immediately and at 10-min intervals up to 60 min after drug administration. The difference between pre- and postinjection temperatures was calculated for each animal. These experiments were always carried out between 8 a.m. and 11 a.m. The data for Δ^9-THC, Δ^8-THCs, and CBD in this test are shown in table 4.

TABLE 3

Relative potency of Δ^8-THC and other cannabinoids in the THC-SS rabbit model (20)

Cannabinoid	Dose(s) (mg/kg, i.v.)	No. of rabbits convulsed/no. tested	Relative potency
11-OH-Δ^9-THC	0.01, 0.05, 0.1	3/4, 4/4, 4/4	375
11-OH-Δ^8-THC	0.01, 0.04, 0.25	2/4, 4/4, 1/1	250
3′-OH-Δ^9-THC	0.01, 0.05	2/4, 4/4	250
Δ^9-THC	0.01, 0.05, 0.1	0/4, 14/14, 10/10	100
Δ^8-THC	0.05, 0.1, 0.5	2/4, 4/4, 7/7	50
$\Delta^{6a(10a)}$-THC	0.1, 0.5, 0.9	0/2, 2/3, 4/4	6.7
8β-OH-Δ^9-THC	0.1, 0.9, 5.0	0/2, 0/1, 2/2	1
Cannabinol	10.0, 15.0	4/6, 10/10	0.3
8α-OH-Δ^9-THC	0.1, 0.9, 20	0/1, 0/1, 0/2	0
Cannabidiol	15.0, 20.0	0/7, 0/6	0

F. Drug Discrimination Procedure

It is well known that, in drug discrimination procedures, the animals are trained to discriminate between the effects induced by the training drug and the drug vehicle in a two-choice discrimination paradigm. The response of animals is the same when the training drug is substituted by another drug which has a similar pharmacological profile. The response is thus specific to a particular class of drugs, and in view of this, such drug discrimination studies have gained importance in recent years in behavioral pharmacology. The correlation between animal models and humans has been excellent in a wide variety of substances from other pharmacological classes, i.e., other behavioral drugs. Δ^9-THC has been established as a discriminative stimulus in several species such as pigeons, gerbils, rats, and monkeys, and the response is selective, since animals do not generalize this behavior when tested with compounds belonging to other pharmacological classes. Thus, the use of THC-vehicle discriminations in animals as a test for drugs with marijuana-like intoxicating effects in humans has been pro-

TABLE 4

Effects of Δ^9- and Δ^8-THCs and CBD on spontaneous activity and rectal temperature in mice (85)

Compound	Spontaneous activity [ED_{50} (mg/kg)]	Hypothermia	
		Dose (mg/kg)	Δ°C
Δ^9-THC	3.2 (1.7–6.2)*	2.5	3.4
		5.0	4.4
		7.5	4.6
		10.0	5.0
Δ^8-THC	7.1 (4.5–11.2)	5.0	0.2
		10.0	0.7
		20.0	2.7
CBD	40.0 (25.0–65.0)	50.0	0.5
		75.0	2.2
		100.0	2.6

* Numbers in parentheses, confidence limits.

posed by several investigators (59, 68, 143, 6, 60, 61, 32, 86, 11).

The procedures used for drug discrimination studies in rats are well described (see, for example refs. 86 and 32). Generally, male rats (Sprague-Dawley or Holtzman) with no previous experimental history are used. The training and testing are carried out in a standard two-level operant chamber with an arrangement for a dipper located between the two levers which provides sweetened milk reinforcement (0.01 ml) subsequent to correct responding. During training, 30 min before each daily 15-min session, rats were given injections i.p. of either Δ^9-THC (3 mg/kg) or the Δ^9-THC vehicle (1 ml/kg). On any given day, half of the subjects were pretreated with the drug, and other half were pretreated with the vehicle. For half of the rats, responding on the left lever was reinforced when Δ^9-THC was given before the session, and responding on the right lever was reinforced when the pretreatment was a vehicle injection. The opposite reinforced lever-drug pretreatment association existed for the other half of the rats. All rats were required to elicit a total of 32 responses on the correct level (FR-32) before reinforcement was delivered. Drug treatments were alternated in a counterbalanced sequence across days (i.e., THC, THC vehicle, vehicle, or vehicle, vehicle, THC, THC).

Generalization testing was conducted after all rats reached a drug-lever response minimum criterion of 80% when Δ^9-THC was given presession, and 20% when the vehicle was given presession. Testing of novel compounds occurred when rats were given injections 30 min presession and placed in operant chambers for 2.5 min with no reinforcement delivered during testing. Both responses/s and the percentage of drug-lever response were calculated for each rat for each session. Once testing was completed for all animals at a given test dose, the mean ± SE of the session data was calculated for all of the rats. Test doses were given in a randomized sequence.

In this procedure, Δ^9-THC has been shown to function in a dose-related manner as a discriminative stimulus. The metabolite 11-OH-Δ^9-THC was found to be more potent than Δ^9-THC, since at one-third the THC training dose, it produced Δ^9-THC-like discriminative stimulus effects and markedly decreased the mean response rate. Similarly, other cannabinoids, such as Δ^8-THC, 11-OH-Δ^8-THC, and Nabilone, which are known to produce marijuana-like effects in humans, generalized to Δ^9-THC. On the other hand, cannabinoids such as cannabidiol and the 8-OH and 8,11-dihydroxy metabolites of Δ^9-THC, which are essentially inactive in humans, did not generalize to Δ^9-THC. It appears that this procedure could be utilized as a sensitive and specific method for demonstrating THC-like behavioral effects in drugs. It is important to note that other hallucinogens, such as LSD, mescaline, and phencyclidine, are not generalized to THC and vice versa, thus pointing to the specificity of this procedure.

As mentioned before, pigeons and other animals have been used in drug discrimination studies. Although the discriminative performance of pigeons was as efficient and, in most respects, similar to that of rats (60), rats should be the animals of choice in this test, primarily because much more is known about the effect of cannabinoids and other drugs in rats.

G. Conclusions

In conclusion, various quantitative procedures, such as the dog ataxia, monkey behavior, THC-SS rabbit model, and rat discriminative tests, are now available for assessing the psychoactive component of cannabinoids. In addition, the mouse ring mobility assay and the spontaneous activity and hypothermia in mice provide a quantitative measure of some of the other aspects of cannabis pharmacology. But on the basis of these tests, it is presently not possible to quantify the extent of separation of psychoactive and other side effects from therapeutic effects. In other words, if a compound is equiactive with Δ^9-THC in the dog ataxia or the rat discriminative tests and is 5 times more active than Δ^9-THC in the analgesic tests, it is difficult to predict if the same ratios of analgesic to psychoactive properties will be maintained in humans. Furthermore, there is a need to develop other assays to delineate different aspects of cannabis pharmacology to ascertain the therapeutic potential of these compounds. Only with the development of such new assays will it be possible to expect a rapid advance in this field. It is to be expected that, when more cannabinoids have been tested in the clinic, a better understanding of toxic:therapeutic ratios in humans will emerge. The extrapolation of animal data to humans will then become more meaningful.

It is important to point out that the SAR of cannabinoids is presently based on their psychoactive component of cannabis-like effect.

IV. Structure Activity Relationships (SAR)

The development of the SAR in cannabinoids has been discussed earlier in this article (see "Assessment of Biological Activity"). Mechoulam and Edery (90) discussed the SAR of cannabinoids in detail, and this was extended by Pars *et al.* (102). Since then, several metabolites of Δ^9- and Δ^8-THCs and analogs of THCs have been tested in the clinic, and it is therefore important to consider the SAR of cannabinoids in man before discussing in detail the general SAR of cannabinoids, which is mainly developed on the basis of animal pharmacological data (i.e., cannabis-like effects).

A. SAR in Man

The various cannabinoids which have been evaluated clinically are summarized in Table 5. In this table, the dose corresponds to total dose (mg) in man, and in some instances, where the values given in the literature are in μg/kg, these have been converted to mg/75-kg man. The relative potencies of various compounds are at best very rough estimates. Hollister (49) has estimated the potency of Δ^9- and Δ^8-THCs and their metabolites and some other homologs and analogs which are included in this table. For other cannabinoids in this table, the relative potencies have been estimated on the basis of subjective effects described in the literature using a total dose of 20 mg (p.o.) or 2 mg (i.v.) of Δ^9-THC as standard (i.e., 100).

On the basis of comparative data, Δ^9-THC by smoking is considered to be 2.6–3 times more potent, and i.v.-administered Δ^9-THC is about 10 times more potent than Δ^9-THC ingested p.o. (57, 50). By either smoking or i.v., the effects of Δ^9-THC appear within seconds or minutes, whereas with p.o. doses, the onset of symptoms is delayed from 30 min–2 h. The clinical syndrome, however, is very similar in all cases. Hollister (46) reported definite marijuana-like effects, although the potency was much less with $\Delta^{6a,10a}$-THC by smoking, but Isbell and coworkers (57) failed to find any activity with this compound at a dose of 400 μg/kg (30-mg total dose) by the same route of administration. This discrepancy may be due to the fact that the source of material used by Isbell's group was different, and in addition, the technique of smoking used may have resulted in more than the usual amount of pyrolysis of the THC. A similar difference in activity was found with 8α-hydroxy-Δ^9-THC when given i.v. Hollister reported it active (49), and Perez-Rayes *et al.* (107) found it to be inactive. This inactivity in man is surprising in view of its reported activity, albeit slight, in various animals (ref. 107 and refs. cited therein) (figure 2).

An examination of Table 5 suggests the following SAR in man.

1. It appears that a benzopyran ring is a definite requirement for activity, since the ring-opened compound cannabidiol is inactive. However, the benzopyran by itself does not confer activity, since cannabichromene is inactive. Moreover, the oxygen in the benzopyran ring can be substituted by a nitrogen without loss of activity, as in Levonantradol.

2. Attachment of a *nonplanar* alicyclic ring (i.e., ring C) to the benzopyran ring in the 3,4-position is important for activity. However, a planar ring attachment as in cannabinol reduces activity (nearly inactive).

3. In place of a nonplanar ring attachment, a bulky substituent in the 4-position of the benzopyran ring can also confer activity to the molecule as in BRL-4664 (Nonabine).

4. A variety of substituents can be introduced in the alicyclic ring C without loss of activity. Thus, the methyl in 9-position as present in Δ^9-THC is not essential and can be replaced by a hydroxyl (Levonantradol), a hydroxymethyl (11-hydroxy-Δ^9-THC), or a ketone (Nabilone) without loss of activity. Even the presence of two different substituents in the alicyclic ring, such as a methyl group at 9-position and a double bond in the ring (e.g., Δ^9, Δ^8, Δ^{6a}-THCs), or a hydroxyl in a 8-position (8-hydroxy-THCs) retains activity. In the double bond isomers, the position of the double bond at 9-position appears optimum for activity (Δ^9- > Δ^8- > Δ^{6a}-THCs).

5. The alicyclic ring attachment to the benzopyran ring can be substituted by a heterocyclic ring (i.e., tetrahydropyridine ring as in SP-1, Nabitan, and Abbott-41988) without loss of activity.

6. In the aromatic ring, esterification of the phenolic group retains activity (Naboctate and Levonantradol).

7. The length of the aromatic side chain can be varied without loss of activity, but a three-carbon chain seems minimal for activity, and branching of the chain increases potency. Attachment of the side chain to the aromatic ring can also be via an oxygen atom (i.e., an ether as in Levonantradol) without loss of activity.

It is noteworthy that, within the structural constraints as present in the THC ring system, changing the position of the double bond in the alicyclic ring, the length and branching of the side-chain, or producing hydroxy metabolites at the 11- or 8-positions *does not alter qualitatively the THC effects but may strongly affect potency.* Changing the double bond from Δ^9- to Δ^8- or Δ^{6a}- reduces

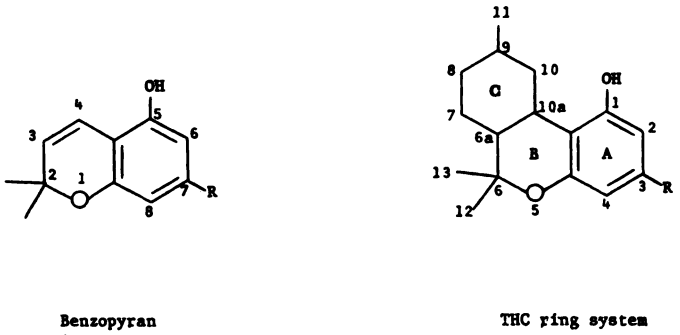


FIG. 2. Comparison of the structures of the benzopyran and THC ring systems.

potency. Decreasing the length of the side chain by two carbons reduces potency by 75%. Increasing the length of the side chain with branching enhances potency severalfold. Substitution of a hydroxyl group in the 11-position retains potency, while hydroxylation in the 8-position reduces potency by 80%.

From the examination of table 5, it is also apparent that, in various structurally modified THCs, there is an indication of separation of pharmacological activities which could be taken advantage of in therapeutics. Apparently this is the primary basis for the use of Δ^9-THC and Nabilone as antinauseants for cancer chemotherapy treatment, the development of Levonantradol and Nabitan as analgesics, and the development of Naboctate as an antiglaucoma agent.

In summary, although 21 compounds have been clinically evaluated, most of them have been tested solely for their ability to produce marijuana-like "highs," and only a few compounds (eight or nine) have been tested for their therapeutic utility. Except for Δ^9-THC and Nabilone, the therapeutic utility of the remaining compounds has been examined only cursorily, primarily in Phase II clinical trials. In other words, very little is known, and much more detailed clinical work is required to develop their therapeutic potential.

B. SAR in Animals

The various THCs have been tabulated in table 6 with Δ^9-THC and its derivatives followed by Δ^8-THC, CBD, cannabinol (CBN), cannabichromene, other related natural constituents of the plant, and miscellaneous compounds including hexahydrocannabinols (HHCs) and their derivatives. The behavioral effects observed in monkeys, activity in the dog ataxia test, and mouse activity cage ED_{50}s are summarized in this table. In all these tests, the dosages are in mg/kg given i.v., so the figures given are comparable and show the effects in different species. To provide comparative data between man and animals, the mg/kg i.v. data for man from table 5 have been included. In addition, the relative potency in the THC-SS rabbit model (19, 20) using Δ^9-THC = 100 as the standard has been included to provide a comparison of this model with the monkey and dog ataxia tests.

A separate table, table 7, was compiled for the large number of THCs with a double bond in the $\Delta^{6a,10a}$-position. It is important because the initial SAR in THCs was developed on the basis of these compounds, using mainly the old dog ataxia test as used by Loewe (81) and the rabbit corneal areflexia test (37). The figures in the dog ataxia test indicate the relative potencies of various THCs compared to (±)-$\Delta^{6a,10a}$-THC (compound no. 1) = 1.0 as the standard. Relative potencies of some of the compounds as found in the rat are also included. These are based on synhexyl (compound no. 15) = 1.0 as the standard. Some significant differences were observed between the SAR in the dog and the rat. These have been discussed previously (102, 77).

Miscellaneous THC analogs are shown in table 8. A distinction is made from the miscellaneous THCs listed in table 7, as compounds listed in table 8 have a different side chain (nonalkyl, e.g., compound no. 2 or difference in position, e.g., compound nos. 6–10), or one of the rings in THCs is different or missing.

Table 9 lists the heterocyclic analogs of THCs. These are compounds which have a heteroatom in one of the rings of THCs. A detailed discussion of the SAR of heterocyclic analogs of THCs has been reported previously by Pars *et al.* (102).

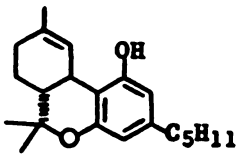
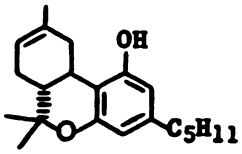
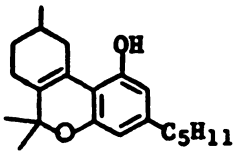
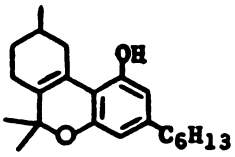
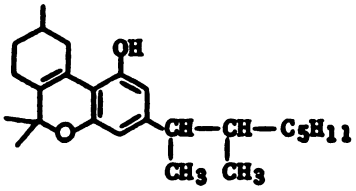
It should be pointed out that, in these tables, an attempt has been made to include a large number of diverse cannabinoids whose biological activity has been recorded, and only important references useful from the point of view of the SAR have been included. The list of compounds and their biological activities are by no means exhaustive. These tables may provide a readily available reference point for examining the CNS activity of various types of cannabinoids.

On the basis of recent data available from animal studies (tables 6–9), the following conclusions are drawn regarding the SAR in cannabinoids. It should be emphasized that the SAR is developed on the basis of cannabis-like effects in animals, especially in the monkey and the dog (see "Assessment of Biological Activity").

1. Essentially a benzopyran structure with an aromatic hydroxyl group at C-1 position and an alkyl or alkoxyl group at C-3 position is a requirement for activity. In general, changing the above substitution pattern leads to a major loss of potency (5, 77), but the exception is the dimethylheptyl analog (table 7, compound no. 98), which was found to be 10 times more potent than synhexyl in the rat. Unfortunately, no tests in the dog or monkey have been reported for this compound. Although a benzopyran ring is a definite requirement for activity, the benzopyran by itself does not confer activity. This is based on the observation that the ring-opened compound CBD (table 6, compound no. 86) is inactive in both the monkey and the dog and did not generalize to Δ^9-THC in the drug discrimination test in the rat. Similarly, cannabichromene (table 6, compound no. 107) and steroidal analogs (table 7, compound nos. 117–119), which have an intact benzopyran ring, are inactive. However, it is interesting to note that, although cannabis-like effects may be absent, other CNS effects may be retained. This is exemplified by several ring-opened compounds which have shown potent analgesic effects (table 8, compound nos. 17–24) and several pyran ring-expanded compounds which have retained CNS-depressant properties (table 7, compound nos. 108–111; table 8, compound no. 1). This separation of CNS activities may point the way to the development of therapeutically useful compounds.

2. The position and the environment around the aromatic hydroxyl group are very important for activity,

TABLE 5
Cannabinoids in man

Compound	Structure	Dose (mg)	Route of administration	Estimated relative potency	Comments	Ref.
1. Δ^9-THC		~4–15*	Smoking	100	Marijuana "high"; 2.6–3 times more potent by smoking than p.o.	57
		9–36*	p.o.	100		
		30–70	p.o.		Clinical syndrome identical that obtained by eating hashish	51
		20	p.o.	100	Cannabis-like effects were quantitated and compared by both routes of administration (i.v. in ethanol); 10 times more potent by i.v. than p.o.	49–51
		1–6	i.v.	~100		
		35	p.o.		Tested in different vehicles; the speed and degree of absorption are greatly influenced by vehicle	105
		~3–4*	i.v.		Administered Δ^9-THC as a microsuspension in human serum albumin	108, 106
2. Δ^8-THC		20	p.o.	75	Marijuana "high"; the potency ratio was the same by both routes of administration	50, 49
		40				
		1–9	i.v.	75		
3. $\Delta^{6a,10a}$-THC		15	Smoking	15–30	Marijuana "high" but much less potent	49, 46
		~30*	Smoking	0	No "high" was observed; the source of the material was different which may account for the lack of activity	57
4. Synhexyl (pyrahexal)		50–200	p.o.	30	Marijuana "high" but much less potent; slow onset but longer duration	51, 49, 46
		15	Smoking	15–30		
5. DMHP (racemic mixture)		0.2	i.v.	~1000	Marijuana "high" questionable; mainly postural hypotension, tachycardia, drowsiness, etc.; (i.v. in ethanol)	73
		0.3–0.6*	i.v.		Cluster of symptoms similar to Δ^9-THC; the individual iso-	126, 111
		0.5–4.0	p.o.			

* Total dose calculated by converting μg/kg mean values to mg/75-kg man.

TABLE 5—Continued

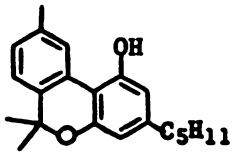
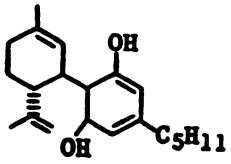
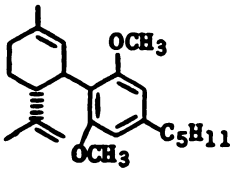
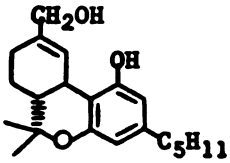
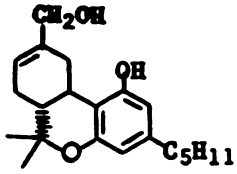
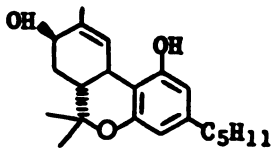
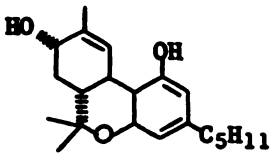
Compound	Structure	Dose (mg)	Route of administration	Estimated relative potency	Comments	Ref.
					mers 2 and 4 were 4 times more potent; (i.v. in propylene glycol); the acetate was equipotent	
6. Cannabinol		400	p.o.	0	No effect	49, 48
		13–15	i.v.	<10	Very mild "high" (i.v. as a microsuspension in serum albumin)	106
7. Cannabidiol		100	p.o.	0	Inactive; no "high"; shows anticonvulsant properties at p.o. doses at 200–300 mg and hypnotic properties at 160 mg	49, 48
		30	i.v.	0		106
		18–20	i.v.	0		12
8. Cannabidiol dimethyl ethers		188*	p.o.	0	Inactive	57
9. 11-Hydroxy-Δ^9-THC		3.5–5	i.v.	120	Marijuana "high" but less intense and shorter duration of action than Δ^9-THC; (i.v. in ethanol)	49
		2.5	i.v.	100	(i.v. as a microsuspension in serum albumin)	108, 106
		1.0	i.v.		More potent than Δ^9-THC (i.v. in ethanol with dextrose-water infusion)	72
10. 11-Hydroxy-Δ^8-THC		1–8	i.v.	90	Marijuana "high" but more intense and longer duration of action than Δ^8-THC; (i.v. in ethanol)	49
11. 8β-Hydroxy-Δ^9-THC		1–20	i.v.	20	Marijuana "high"; (i.v. in ethanol)	49
		~13–15*	i.v.		Less potent than Δ^9-THC; (i.v. as a microsuspension in serum albumin)	107
12. 8α-Hydroxy-Δ^9-THC		2–14	i.v.	25	Marijuana "high" but mild; (i.v. in ethanol)	49
		~15*	i.v.	0	Inactive; no increase in heart rate was ob-	107

TABLE 5—Continued

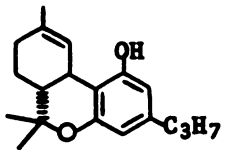
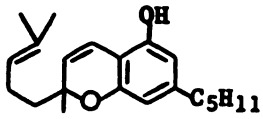
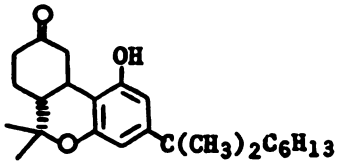
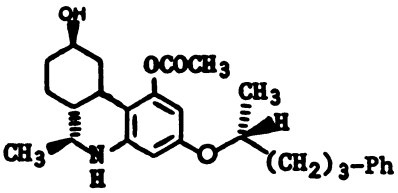
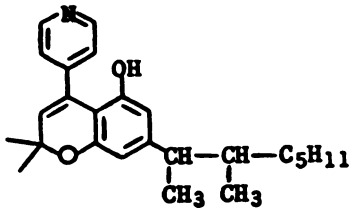
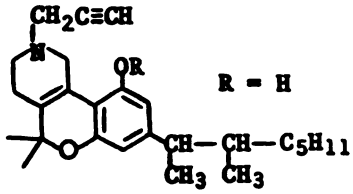
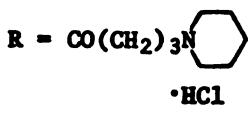
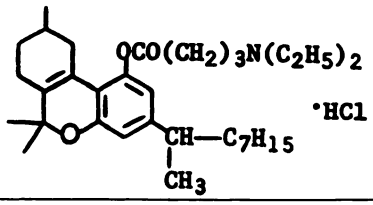
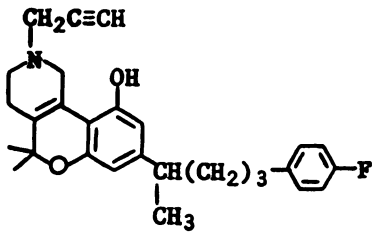
Compound	Structure	Dose (mg)	Route of administration	Estimated relative potency	Comments	Ref.
					served; (i.v. as a microsuspension in serum albumin)	
13. Tetrahydrocannabivarin		7	i.v.	25	Marijuana "high" but moderate to mild; (i.v. in ethanol)	49
14. Cannabichromene		188*	p.o.	0	Inactive	57
15. Nabilone		1–5	p.o.	~400–800	At 2.5 mg, ⅓ felt "high"; at 5 mg, ⅔ felt high; effective antinauseant at 2-mg p.o. dose	74, 29
16. Levonantradol		0.5–2.0	p.o.	~400–800	Somnolence and "high" feelings; effective antinauseant at 2-mg p.o. dose	69
		0.5–2.0	i.m.		Effective antinauseant (i.m. in 75% propylene glycol); has analgesic properties	69, 58
17. BRL-4664 (Nonabine)		Up to 10	p.o.	~200–300	Marijuana-like "high"; effective antinauseant at 10–15 mg p.o. dose	127, 102
18. SP-1 (Abbott 40174)		1–9	p.o.	~300	Marijuana-like "high" at 6–7 mg dose	112
19. Nabitan (SP-106; Abbott 40656)		5–20	p.o.	~130–200	Lightheaded at 10 mg; "high" at 15-mg dose; has analgesic, antinauseant, and antiglaucoma properties	141, 53, 56, 129
20. Naboctate		1–5	p.o.	~300–400	Very mild "high" at 5-mg dose; reduces intraocular pressure	142

TABLE 5—Continued

Compound	Structure	Dose (mg)	Route of administration	Estimated relative potency	Comments	Ref.
21. Abbott 41988 (BW 29Y)		2–10	p.o.	~350–500	Relaxed feeling at 2-, 4-, and 6-mg dose; no decrease in intraocular pressure	41, 129

viz., (*a*) the OH at position C-1 is in itself necessary for activity. Thus, the abnormal compounds where the hydroxyl and the side chain have been interchanged (i.e., side chain at C-1 and OH at C-3) are all inactive (table 8, compounds 6–11). Similarly, removal of OH at C-1 eliminates activity (table 7, compound nos. 100–101). (*b*) Esterification of the OH at C-1 retains activity and, in some carbocyclic and heterocyclic analogs, can lead to greater selectivity of action; e.g., in the carbocyclic series (table 7, compound no. 37), the morpholine butyrate is a potent analgesic, whereas the homopiperidino butyrate series shows potent anticonvulsant properties; similarly in the heterocyclic series (table 9, compound no. 8) various esters show selectivity of action in animal tests (122, 102). Etherification of the OH at C-1 eliminates activity, as is clear from the methyl ethers of both Δ^9- and Δ^8-THCs (table 6, compound nos. 6 and 36; see also table 7, compound no. 6). The glucoronide and the sulfate of Δ^8-THC are also inactive (table 6, compound nos. 34 and 35), and the phosphate (table 6, compound no. 33) has only one-tenth the activity of Δ^8-THC. Replacement of the OH by NH_2 retains activity (table 7, compound nos. 103–107); replacement by SH eliminates activity (table 7, compound no. 102). (*c*) Since C-10 in the alicyclic ring C is in close proximity to the OH group, a methyl substituent at C-10 significantly alters the activity in the case of a planar five-membered C-ring (115).

3. Substitution in the aromatic ring by electronegative groups like carboxyl, carbomethoxyl, and acetyl groups eliminates activity, whereas alkyl or hydroxyl groups at C-2 position retain, and in C-4 position reduce, activity. The exception is compound nos. 7 and 8 (table 7), which are reported to produce general CNS depression. It is not clear if they are cannabis-like (33).

4. A minimum length of the aromatic side chain is necessary to elicit activity, and the branching of the alkyl side chain increases potency. Thus, 1′,2-dimethylheptyl or 1′,1′-dimethlyheptyl gives the most potent compounds. Similarly, *p*-fluorophenyl alkyl and side chains as shown retain good activity: —O—$CH(CH_3)(CH_2)_3Ph$, —CH_2—CH=CH—C—C_5H_{11}, and —$CH_2CH_2CHC_2H_5$.

O OH

5. On ring B, the gem dimethyl group at C-6 is optimum for activity (table 7, compare compound nos. 1, 64, and 66). Replacement of one of the geminal methyl groups at C-6 by a hydroxymethyl group retains activity (table 6; compound no. 20 is as active as Δ^9-THC). Replacement of pyran O by N (table 9, compound no. 2) and ring expansion of ring B by one carbon (table 8, compound no. 1; table 7, compound no. 108) can retain activity.

6. In the alicyclic ring C, compounds with the double bond in Δ^9-, Δ^8, or $\Delta^{6a,10a}$-position are active. It is noteworthy that compounds with a double bond in the $\Delta^{10,10a}$-position are also active (table 6, compound nos. 127 and 128), but only a few examples are available at present. A 6a,10a-*trans* junction increases, and a *cis* junction decreases, activity (table 6, compare Δ^9-THC with compound no. 120, (+)-*cis*-Δ^9-THC). The natural THCs are active in the 10a R and 6a R series only. A methyl at C-9 increases and is optimum for activity (table 6, compare compound no. 85 with Δ^8-THC and the latter with compound nos. 73–78), but metabolism to the 11-hydroxymethyl is not as prerequisite for THC activity, since 9-nor-Δ^8-THC (table 6, compound 85) is active.

Compounds are active even when no double bonds are present in the ring, e.g., the HHCs. In these compounds, an equatorial group at C-9 increases activity, and an axial group decreases activity (table 6, compare compound nos. 129 and 131 versus 130 and 132). Furthermore, the activity is retained even when diverse groups are present such as an epoxide, a ketone, or an alcohol (table 6, compound nos. 144, 159, and 158; see also compound no. 136).

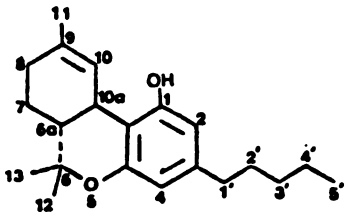
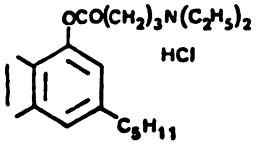
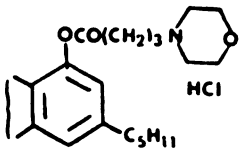
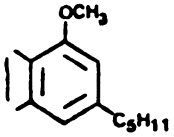
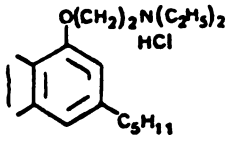
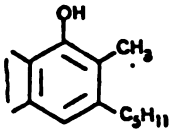
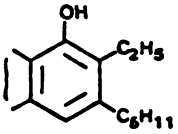
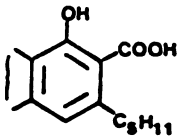
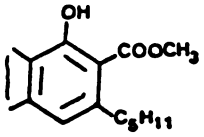
7. The C-ring can be substituted by a variety of nitrogen- and sulfur-containing rings without loss of activity. With the nitrogen and sulfur analogs, the most active CNS agents are obtained when the heteroatom is in a phenethyl orientation, e.g., inserted in place of C-7 or C-9. A detailed discussion of the SAR of heterocyclic analogs of THCs has been reported previously (102).

8. Planarity of the C-ring is not a necessary criterion for activity. See, e.g., the quinuclidine analog (table 9, compound no. 3) and benzoxocine compounds (table 8, compound nos. 27–30).

9. In both carbocyclic and heterocyclic analogs, opening the pyran ring generally decreases activity. An exception is compound 115 (table 7), which is approximately

TABLE 6

Natural and synthetic THC and their pharmacological effects

Compound	Structure	Man (mg/kg i.v.)	Monkey* mg/kg i.v.	Monkey* Effect
Δ⁹-THCs				
1. (−)-Δ⁹-THC		0.027 (50) 0.040 (108)	0.05 0.10	+ (27) ++
2. (+)-Δ⁹-THC			0.5 1.0	− (26, 90) −
3. Δ⁹-THC acetate			0.2 0.5	± (27) +
4. Diethylaminobutyric acid ester of Δ⁹-THC				
5. Morpholinobutyric acid ester of Δ⁹-THC (SP-111)				
6. Δ⁹-THC methyl ether			10.0	− (27)
7. Diethylaminoethyl ether of Δ⁹-THC				
8. 2-Methyl-Δ⁹-THC			0.1 0.5	± (27) ++
9. 2-Ethyl-Δ⁹-THC			0.2 0.5	± (27) ++
10. 2-Carboxy-Δ⁹-THC			5.0	± (27)
11. 2-Carbomethoxy-Δ⁹-THC			5.0	− (27)

* For notations and symptoms in the monkey using Δ⁹-THC as the standard, see table 2.

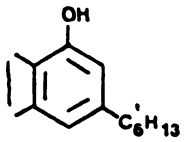
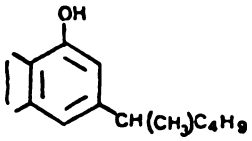
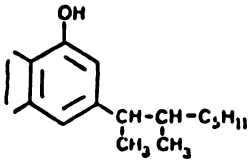
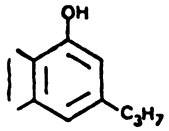
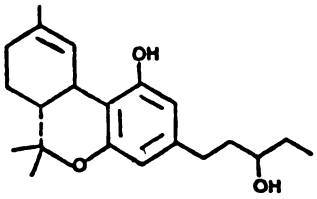
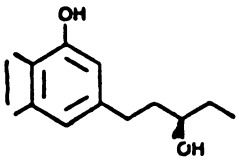
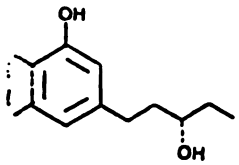
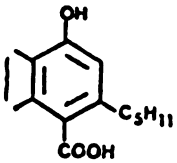
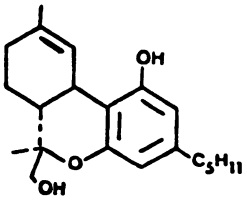
† For quantifications of cannabinoid behavioral effects in dogs, see table 1; realtive potency is given using Δ⁹-THC as 1.0.

‡ Relative potency is given using Δ⁹-THC as 100; see reference 20.

§ Dog ataxia test as carried out by Loewe (81).

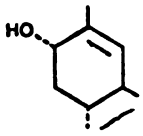
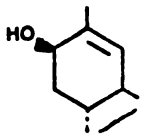
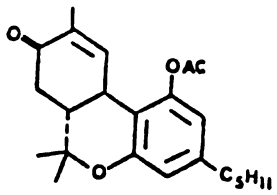
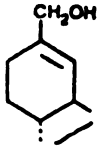
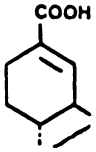
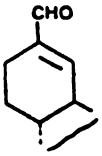
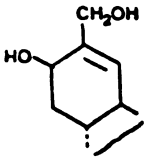
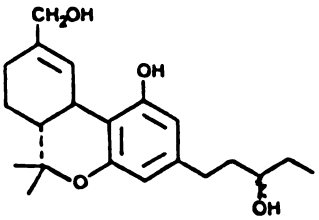
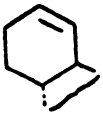
Dog ataxia†		Mouse (activity cage ED_{50}: mg/kg i.v.)	THC-SS rabbit relative potency (20)‡	Comments
mg/kg i.v.	Relative potency			
0.1–0.2 0.25–0.50	1.0 (84, 85) (40, 27)	3.2 (85) 2.6 (83)	100	Drug discrimination in rats: ED_{50} 1.5 mg/kg (86); 0.88 mg/kg (11)
	Minimal effects at 0.2–2.0, <0.1 (83)	14.6 (83)		Dog ataxia: at 5.0 mg/kg, dog prostrate; effects not cannabinoid like (83). In mouse ring test, 1/12 as active as Δ^9-THC (65)
	Caused characteristic ataxia; much less active than Δ^9-THC (116)	ED_{50} = 18.0 mg/kg i.p. (116)		Dog ataxia: test carried out under nonstandard conditions (116)
1.0	0.2 (151)	ED_{50} = 8.2 mg/kg i.p. (151)	7.5	
	0.04 (85)			
	Inactive at 10 mg/kg i.v. (116)	ED_{50} = 12.0 mg/kg i.p. (116)		Much more toxic than Δ^9-THC in mice (116)

TABLE 6—Continued

Compound	Structure	Man (mg/kg i.v.)	Monkey* mg/kg i.v.	Monkey* Effect
12. Hexyl homolog of Δ^9-THC			0.05 0.1	– (27) +
13. 1′-Methyl-Δ^9-THC			0.5 1.0	– (27) ++
14. 1′,2′-Dimethylheptyl homolog of Δ^9-THC			0.05 0.1	± (27) +
15. Tetrahydrocannabivarin (propyl analog of Δ^9-THC)		0.093 (49)		
16. (*R*/*S*)-3′-OH-Δ^9-THC				
17. *R*-3′-OH-Δ^9-THC				
18. *S*-3′-OH-Δ^9-THC				
19. 4-Carboxy-Δ^9-THC			5.0 10.0	– (27) ±
20. 12β-Hydroxy-Δ^9-THC				

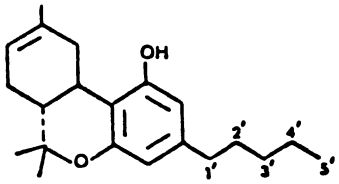
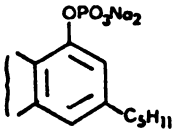
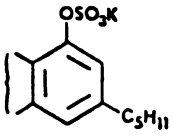
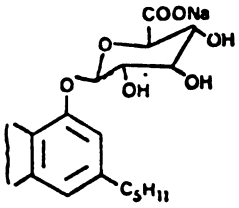
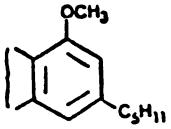
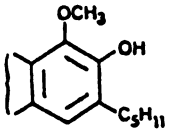
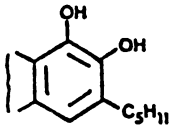
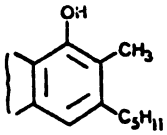
Dog ataxia†		Mouse (activity cage ED_{50}; mg/kg i.v.)	THC-SS rabbit relative potency (20)‡	Comments
mg/kg i.v.	Relative potency			
0.01 0.04	No effect (27) Ataxia, etc.			It is approximately equiactive with Δ^9-THC in the monkey but is 10 times more active in the dog (27)
		Produces catalepsy in mice; ⅕th as active as Δ^9-THC (38)		Man; marijuana "high" but much less active than Δ^9-THC (49)
0.05–0.2	(86, 42)	0.85 (86)	250	Dog ataxia: more potent than Δ^9-THC (86, 42). Drug discrimination in rats: ED_{50}, 0.31 mg/kg (86)
0.2–5.0	(86)	2.48 (86)		Dog ataxia: ⅕th as active as *S*-isomer at 0.2 mg/kg i.v. (86). Drug discrimination in rats: ED_{50}, 1.67 mg/kg (86)
0.1–0.2	(86)	0.34 (86)		Dog ataxia: slightly more active than *R*/*S*-isomer at 0.2 mg/kg i.v. (86). Drug discrimination in rats: ED_{50}, 0.25 mg/kg (86)
0.1–0.2	1.0 (85, 118)	8.0 (112) Reduced activity by ~37% at 10 mg/kg i.p. compared to 42% by Δ^9-THC (118)		Active; equipotent with Δ^9-THC

TABLE 6—Continued

Compound	Structure	Man (mg/kg i.v.)	Monkey* mg/kg i.v.	Monkey* Effect
21. 8α-Hydroxy-Δ⁹-THC		0.027–0.187 (49) 0.187 (No effect) (107)	0.5 1.0 2.0	– (90, 8) + ++
22. 8β-Hydroxy-Δ⁹-THC		0.013–0.027 (49) 0.173–0.2 (107)	1.0 2.0	+ (8) ++
23. 8-oxo-Δ⁹-THC acetate			5.0	– (90, 94)
24. 11-Hydroxy-Δ⁹-THC		0.047–0.067 (49) 0.033 (108, 106) 0.014 (72)		
25. 11-Carboxy-Δ⁹-THC				
26. 11-oxo-Δ⁹-THC				
27. 8,11-Dihydroxy-Δ⁹-THC				
28. (±)-3′,11-Dihydroxy-Δ⁹-THC				
29. 9-Nor-Δ⁹-THC				

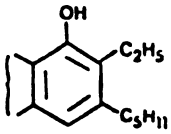
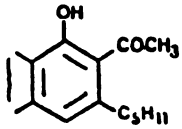
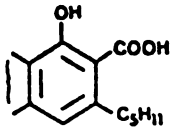
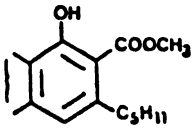
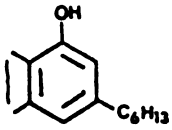
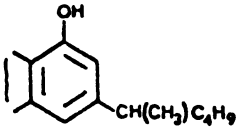
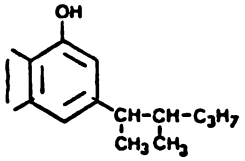
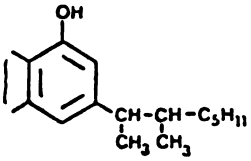
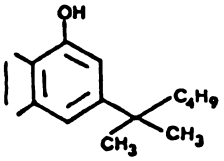
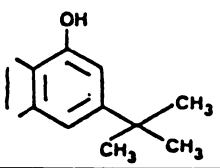
Dog ataxia†		Mouse (activity cage ED_{50}; mg/kg i.v.)	THC-SS rabbit relative potency (20)‡	Comments
mg/kg i.v.	Relative potency			
				Man: marijuana "high" but mild (49). Also reported to be inactive up to 0.187 mg/kg i.v. (107)
				Man: marijuana "high" ⅓th as potent as Δ^9-THC (49). Less potent than Δ^9-THC (107)
0.01–0.10	4.0 (85, 145)	Decreased activity; twice as potent as Δ^9-THC i.v. (17)	375	Man: marijuana "high"; more potent than Δ^9-THC (49, 72); drug discrimination in rats: ED_{50}, 0.22 mg/kg (11)
				Stated to be inactive but no data were given (110)
				Mice: active when given i.v.; effects like Δ^9-THC (112)
		Inactive in mice at 10 mg/kg i.v. (137)		
0.2–0.5	0.4 (85, 42)	8.7 (85, 42)		
	~1.0 (84)			As active as Δ^9-THC; similar pharmacological profile in mice and dogs (84)

TABLE 6—Continued

Compound	Structure	Man (mg/kg i.v.)	Monkey* mg/kg i.v.	Monkey* Effect
Δ⁸-THCs				
30. (−)-Δ⁸-THC		0.034 (50)	0.10 0.25 0.5–0.9	± (27) + ++
31. (+)-Δ⁸-THC			1.0	− (26, 90)
32. Δ⁸-THC acetate			0.2 0.5 1.0	− (27) + ++
33. Δ⁸-THC phosphate ester (disodium salt)				
34. Δ⁸-THC sulfate (potassium salt)				
35. Δ⁸-THC glucuronide (sodium salt)				
36. Δ⁸-THC methyl ether			10.0	− (27)
37. 2-Hydroxy-Δ⁸-THC methyl ether				
38. 2-Hydroxy-Δ⁸-THC				
39. 2-Methyl-Δ⁸-THC			1.0 5.0	+ (27) +++

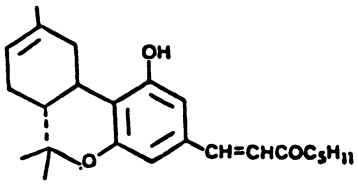
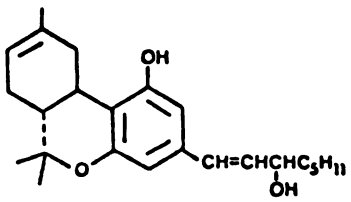
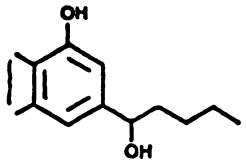
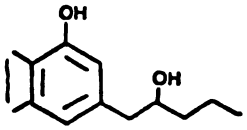
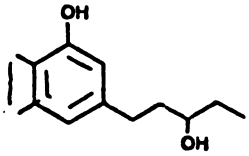
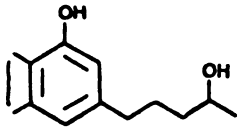
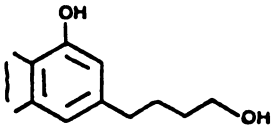
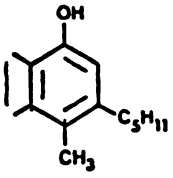
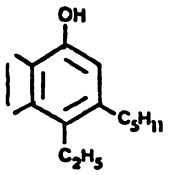
Dog ataxia†		Mouse (activity cage ED_{50}; mg/kg i.v.)	THC-SS rabbit relative potency (20)‡	Comments
mg/kg i.v.	Relative potency			
0.25	0.4 (84, 85)	7.1 (85, 123)	50	Drug discrimination in rats: 2.02 mg/kg (11). Cataleptogenic effect in mice; ED_{50}, 3.30 mg/kg i.v. (140, 100)
	Minimal effects at 1.0, <0.25 (83)		0.5	Dog ataxia: at 4.0 mg/kg, dog prostrate; effect not cannabinoid like (83)
				⅒th potency of Δ^8-THC for producing catalepsy but equipotent for producing hypothermia in mice (149)
				Inactive; does not produce catalepsy in mice. High acute toxicity (139)
				Inactive; does not produce catalepsy in mice (139)
				Inactive
		40.0 (85)		
		10.0 (85)		Nearly as active as Δ^8-THC but did not produce hypothermia in mice (85)
				Active

TABLE 6—Continued

Compound	Structure	Man (mg/kg i.v.)	Monkey*	
			mg/kg i.v.	Effect
40. 2-Ethyl-Δ^8-THC			1.5	++ (27)
41. 2-Acetyl-Δ^8-THC			1.0 5.0	− (27) ±
42. 2-Carboxy-Δ^8-THC			5.0	− (27)
43. 2-Carbomethoxy-Δ^8-THC			10.0	− (27)
44. Hexyl homolog of Δ^8-THC			0.05 0.1	+ (27) ++
45. 1′-Methyl-Δ^8-THC			0.1 0.2 1.0	− (27) + +++
46. 1′,2′-Dimethyl-Δ^8-THC			0.025 0.05 1.0	− (27) ++ +++
47. 1′,2′-Dimethylheptyl homolog of Δ^8-THC			0.025 0.05 1.0	− (27) ++ +++
48. 1′,1′-Dimethyl-Δ^8-THC				
49.				

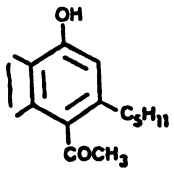
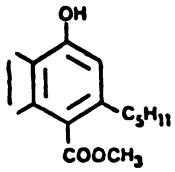
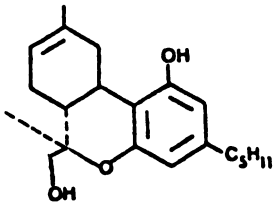
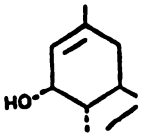
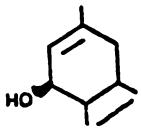
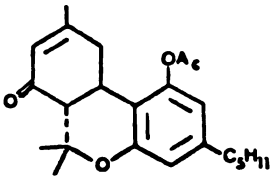
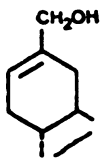
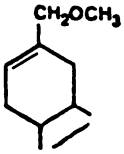
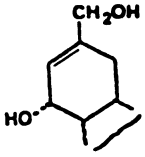
Dog ataxia†		Mouse (activity cage ED_{50}; mg/kg i.v.)	THC-SS rabbit relative potency (20)‡	Comments
mg/kg i.v.	Relative potency			
				Active
				Inactive
				Inactive
				Inactive
				More potent than the corresponding compound in the Δ^9-series
		Decreased activity at 50 mg/kg i.p. (34)		More potent than the corresponding compound in the Δ^9-series. Mice: decreased motor coordination at 25 mg/kg i.p. (34)
				At 1.0 mg, activity lasts ~30 h
				At 1.0 mg, activity lasts 48 h; more potent than the corresponding compound in the Δ^9-series
		Decreased activity at 50 mg/kg i.p. (34)		Mice: decreased motor coordination at 25 mg/kg i.p. (34)
		Decreased activity at 50 mg/kg i.p. (34)		Mice: decreased motor coordination at 25 mg/kg i.p. (34)

TABLE 6—Continued

Compound	Structure	Man (mg/kg i.v.)	Monkey* mg/kg i.v.	Monkey* Effect
50.				
51.				
52. 1′-Hydroxy-Δ^8-THC			1.0 5.0–7.0	– (99) +
53. 2′-Hydroxy-Δ^8-THC			1.0 2.0	+ (99) ++
54. 3′-Hydroxy-Δ^8-THC			0.05–0.1 0.2	– (99) ++
55. 4′-Hydroxy-Δ^8-THC			0.1 0.25–0.5	– (99) ++
56. 5′-Hydroxy-Δ^8-THC			0.25 0.5	– (99) ++
57. 4-Methyl-Δ^8-THC			5.0 10.0	– (27) –
58. 4-Ethyl-Δ^8-THC			10.0	– (27)

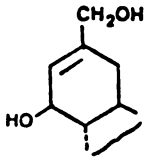
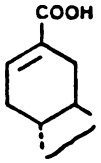
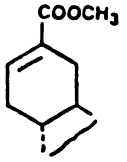
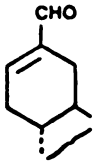
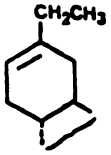
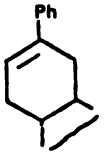
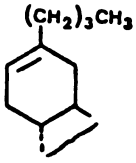
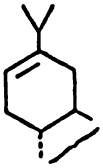
Dog ataxia†		Mouse (activity cage ED_{50}; mg/kg i.v.)	THC-SS rabbit relative potency (20)‡	Comments
mg/kg i.v.	Relative potency			
				Mice: ataxia and hyperexcitability ED_{50}, <0.1 mg/kg i.v.; much more potent than Δ^9-THC (114)
				Mice: ataxia and hyperexcitability ED_{50}, 1.0 mg/kg i.v.; less potent than Δ^9-THC (114)
				Much less potent than Δ^8-THC; produces catalepsy in mice (100)
				Produces catalepsy in mice (100)
				Slightly more potent than Δ^8-THC. Produces catalepsy in mice (100)
				Slightly more potent than Δ^8-THC. Produces catalepsy in mice (100)
				Equipotent to Δ^8-THC; produces catalepsy in mice (100)
				Inactive
				Inactive

TABLE 6—Continued

Compound	Structure	Man (mg/kg i.v.)	Monkey* mg/kg i.v.	Monkey* Effect
59. 4-Acetyl-Δ^8-THC			10.0	– (27)
60. 4-Carbomethoxy-Δ^8-THC			5.0	– (27)
61. 12β-Hydroxy-Δ^8-THC				
62. 7α-Hydroxy-Δ^8-THC			0.25 0.50	± (90, 94) ++
63. 7β-Hydroxy-Δ^8-THC			1.0 2.0	– (94) +
64. 7-oxo-Δ^8-THC acetate			0.5 1.0	+ (90, 94) ++
65. 11-Hydroxy-Δ^8-THC		0.027 (49)	0.10 0.25 0.5–0.9	± (90, 7) + ++
66. 11-Methoxy-Δ^8-THC				
67. 7α,11-Dihydroxy-Δ^8-THC				

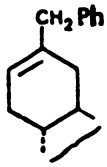
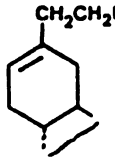
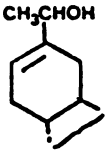
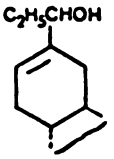
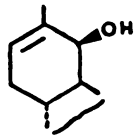
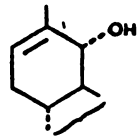
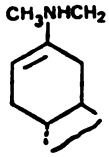
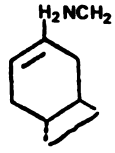
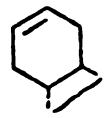
Dog ataxia†		Mouse (activity cage ED_{50}; mg/kg i.v.)	THC-SS rabbit relative potency (20)‡	Comments
mg/kg i.v.	Relative potency			
				Inactive
				Inactive
		23.0 (112)		Active but much less potent than Δ^8-THC
				6–8 times less active than the 7α-isomer (94)
		Decreased activity; twice as potent as Δ^9-THC i.v. (17)	250	Man: marijuana "high"; more potent than Δ^8-THC (49). Drug discrimination in rats: generalized to Δ^9-THC at 3 mg/kg i.m. (60). Cataleptogenic effects in mice: ED_{50}, 0.66 mg/kg i.v. (100, 140)
2.0	0.1 (29, 110)			
		1/8th as active as Δ^9-THC i.v. (17)		

TABLE 6—Continued

Compound	Structure	Man (mg/kg i.v.)	Monkey[a] mg/kg i.v.	Monkey[a] Effect
68. 7β,11-Dihydroxy-Δ⁸-THC				
69. 11-Carboxy-Δ⁸-THC			10.0	− (89)
70. 11-Carbomethoxy-Δ⁸-THC acetate			10.0	− (89)
71. 11-oxo-Δ⁸-THC acetate			1.0	+ (90, 89)
72. 11-oxo-Δ⁸-THC				
73. 11-Methyl-Δ⁸-THC				
74. 9-Nor-9-phenyl-Δ⁸-THC				
75. 9-Nor-9*n*-butyl-Δ⁸-THC				
76. 9-Nor-9-isopropyl-Δ⁸-THC				

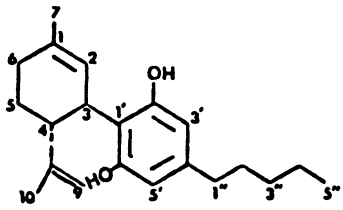
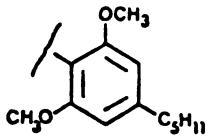
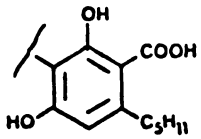
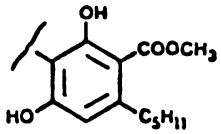
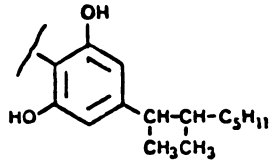
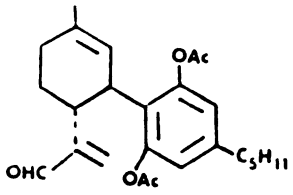
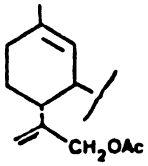
Dog ataxia†		Mouse (activity cage ED_{50}; mg/kg i.v.)	THC-SS rabbit relative potency (20)‡	Comments
mg/kg i.v.	Relative potency			
		1/17th as active as Δ^9-THC i.v. (17)		
				Inactive; produced no cataleptogenic effects in mice at 150 mg/kg i.v. (140)
				Inactive
				Less potent than Δ^8-THC
			100	Mice: produced cataleptogenic effects in mice; ED_{50}, 2.25 mg/kg i.v., more potent than Δ^8-THC (140)
1.0–2.0	0.1 (144)			Mice: no analgesic activity (144)
		67.0 (123)		
		32.0 (123)		
		26.0 (123)		

TABLE 6—Continued

Compound	Structure	Man (mg/kg i.v.)	Monkey[a] mg/kg i.v.	Monkey[a] Effect
77. 9-Nor-9-benzyl-Δ^8-THC				
78. 9-Nor-9-phenethyl-Δ^8-THC				
79. 9-Nor-9-(1-hydroxyethyl)-Δ^8-THC				
80. 9-Nor-9-(1-hydroxypropyl)-Δ^8-THC				
81. 10β-Hydroxy-Δ^8-THC			1.0 2.0	− (90) +
82. 10α-Hydroxy-Δ^8-THC			0.1 0.2	+ (90) ++
83. 11-(*N*-Methyl)amino-Δ^8-THC				
84. 11-Amino-Δ^8-THC				
85. 9-Nor-Δ^8-THC				

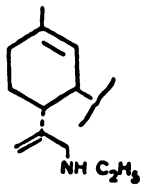
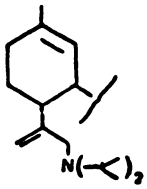
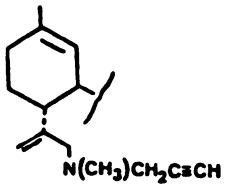
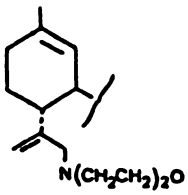
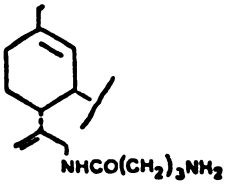
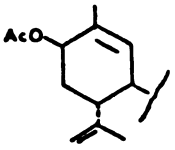
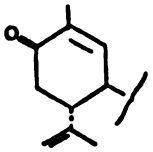
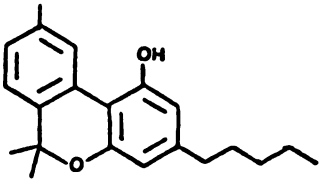
Dog ataxia†		Mouse (activity cage ED_{50}; mg/kg i.v.)	THC-SS rabbit relative potency (20)‡	Comments
mg/kg i.v.	Relative potency			
		32.0 (123)		
		43.0 (123)		
		27.0 (123)		Less potent than 11-hydroxy-Δ^8-THC in analgesic tests (123)
		39.0 (123)		
				Much less active than 10α-hydroxy-Δ^8-THC isomer
				As active as Δ^8-THC
		11.0 (85)		Active
2.0	<0.1 (144)			Mice: no analgesic activity (144)
0.2–0.4	0.4 (84)			As active as Δ^8-THC; similar pharmacological profile in mice and dogs (84)

TABLE 6—Continued

Compound	Structure	Man (mg/kg i.v.)	Monkey*	
			mg/kg i.v.	Effect
Cannabidiols				
86. (−)-Cannabidiol (CBD)		Inactive up to 30 mg i.v. and 100 mg p.o. (49, 106, 48)		Inactive (93, 90)
87. (+)-CBD				
88. CBD dimethyl ethers		Inactive, 188 mg, p.o. (57)		
89. Cannabidiolic acid (CBDA)				Inactive (93, 90)
90. 3′-Carbomethoxy-CBD			5.0	− (27)
91. (−)-1″,2″-Dimethylheptyl homolog of CBD				
92. (+)-1″,2″-Dimethylheptyl homolog of CBD				
93. 10-oxo-CBD diacetate				
94. 10-Acetoxy-CBD diacetate				

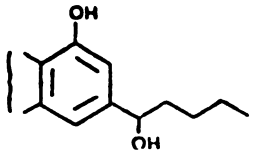
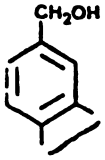
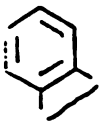
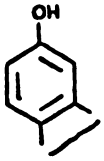
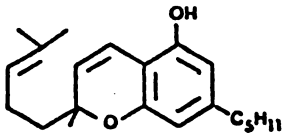
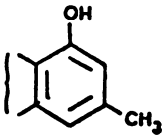
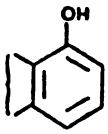
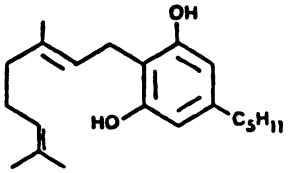
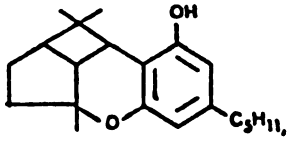
Dog ataxia†		Mouse (activity cage ED_{50}: mg/kg i.v.)	THC-SS rabbit relative potency (20)‡	Comments
mg/kg i.v.	Relative potency			
	Inactive (93, 82)	40.0 (85, 66)	0	Man: shows anticonvulsant properties at p.o. doses of 200–300 mg and hypnotic properties at 160 mg (12). Drug discrimination in rats: did not generalize to Δ^9-THC up to 100 mg/kg i.p. (32)
				Mice: anticonvulsant properties and potentiates pentobarbitone sleeping time, equiactive with (−)-CBD (71)
				Inactive
				Inactive
				Mice: anticonvulsant properties and potentiates pentobarbitone sleeping time (71)
				Mice: anticonvulsant properties and potentiates pentobarbitone sleeping time (71); more potent anticonvulsant than the (−)-isomer (71)
				Mice: anticonvulsant properties and potentiates pentobarbital sleeping time; high toxicity (13)
		Decreased motor activity at 12.5 and 25 mg/kg i.p. (13)		Mice: anticonvulsant properties and potentiates pentobarbital sleeping time; high toxicity (13)

TABLE 6—Continued

Compound	Structure	Man (mg/kg i.v.)	Monkey* mg/kg i.v.	Monkey* Effect
95. 10-(*N*-ethyl)amino CBD				
96. 10-(*N*,*N*-diisopropyl)amino-CBD diacetate				
97. 10-(*N*-methyl-*N*-propargyl)amino-CBD diacetate				
98. 10-Morpholino-CBD diacetate				
99. 10-(*N*-4-aminobutyroyl)amino-CBD				
100. 6-Acetoxy-CBD diacetate				
101. 6-oxo-CBD diacetate				
Cannabinols				
102. Cannabinol (CBN)		Inactive p.o. up to 400 mg (49, 48) Very mild effect at 13–15 mg i.v. (106)		Inactive (93, 90)

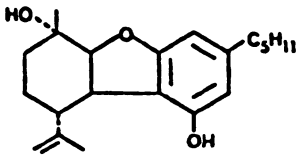
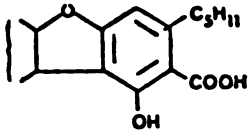
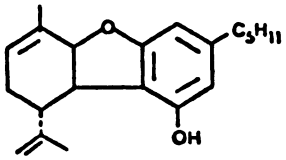
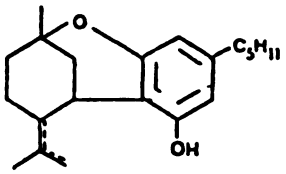
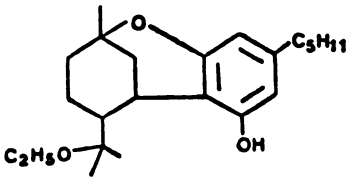
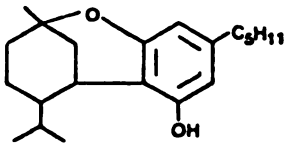
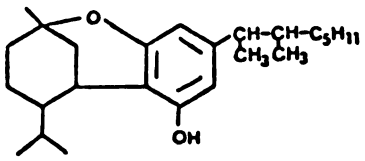
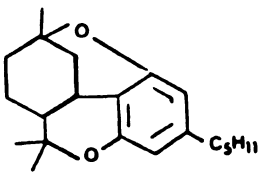
Dog ataxia†		Mouse (activity cage ED_{50}; mg/kg i.v.)	THC-SS rabbit relative potency (20)‡	Comments
mg/kg i.v.	Relative potency			
		4.0 (85, 66)		As active as Δ^9-THC; high toxicity; blocks Δ^8-THC's antinociceptive activity (66)
		Inactive (66)		Partially blocks Δ^8-THC antinociceptive activity (66)
		13.0 (66)		Partially blocks Δ^8-THC antinociceptive activity (66)
		16.0 (66)		
		30.0 (85, 66)		Partially blocks Δ^8-THC antinociceptive activity (66)
				Mice: anticonvulsant properties and potentiates pentobarbital sleeping time (13)
				Mice: anticonvulsant properties and potentiates pentobarbital sleeping time (13)
	Decreased activity, ~0.2 (85) No ataxia (79, 82)	1/33 as active as Δ^9-THC i.v. (17)	0.3	Dog ataxia: severe CNS depression after 5.0 mg/kg (85). Mice: potentiated barbiturate sleeping time at 50 mg/kg (67). Drug discrimination in rats: 6.77 mg/kg (11)

TABLE 6—Continued

Compound	Structure	Man (mg/kg i.v.)	Monkey*	
			mg/kg i.v.	Effect
103. 1′-Hydroxy-CBN				
104. 11-Hydroxy-CBN				⅓₀th as active as Δ^8-THC (92)
105. 9-Nor-CBN				
106. 9-Nor-9-hydroxy-CBN				
107. Cannabichromene (CBC)		Inactive, 188 mg, p.o. (57)		Inactive (93, 90)
108. Cannabichromene-C_1				
109. Cannabichromene-C_0				
110. Cannabigerol				Inactive (40, 93, 90)
111. Cannabicyclol				Inactive (93, 90)

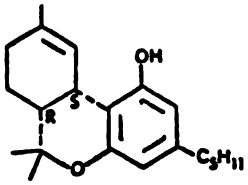
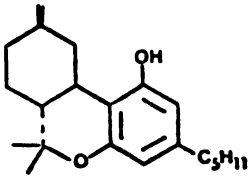
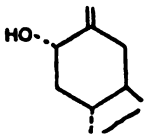
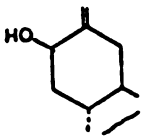
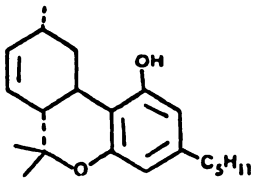
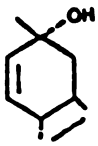
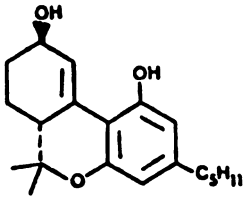
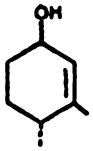
Dog ataxia†		Mouse (activity cage ED_{50}; mg/kg i.v.)	THC-SS rabbit relative potency (20)‡	Comments
mg/kg i.v.	Relative potency			
			0	
	~0.5 (85)		1	Dog ataxia: variable response. All of the typical cannabinoid signs were seen at 1.0 mg/kg before the animal became prostrate (85)
	0.2 (85)			
	Decreased activity (85)			Dog ataxia: not cannabinoid like; severe CNS depression after 10 mg/kg (85, 146)
	Inactive (40)		0.1	Mice: passive, slight loss of neuromuscular coordination at 10 mg/kg s.c. Cyanosis, urination increased at 15–30 mg/kg s.c. (119). Rat: antiinflammatory activity (131)
				Rat: antiinflammatory activity (131)
				Rat: antiinflammatory activity (131)
	Inactive (40)			
				Mice: irritable when touched; piloerection, increased respiration, flushed at 10 mg/kg i.v. (119)

TABLE 6—Continued

Compound	Structure	Man (mg/kg i.v.)	Monkey*	
			mg/kg i.v.	Effect
112. Cannabielsoin				
113. Cannabielsoic acid				Inactive (90)
114. Dehydrocannabielsoin			10.0	Inactive (92) –
Iso-THCs				
115. Iso-THC				
116. Ethoxy-Iso-THC			5.0	– (40)
117. Dihydro-Iso-THC				
118.				
119. Cannabicitran (tetracyclic ether)				

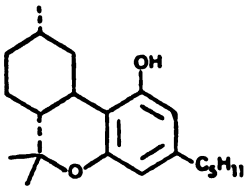
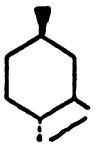
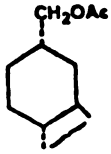
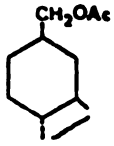
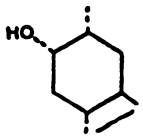
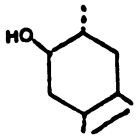
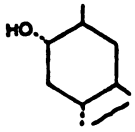
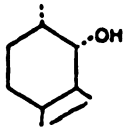
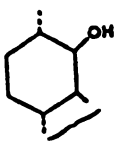
Dog ataxia†		Mouse (activity cage ED_{50}: mg/kg i.v.)	THC-SS rabbit relative potency (20)‡	Comments
mg/kg i.v.	Relative potency			
				Mice: inactive up to 10 mg/kg i.v. (134)
				Inactive
				Inactive
				Mice: aggressive, increased reactivity at 10 mg/kg i.v. (119). Inactive (90)
	Inactive up to 7.0 mg/kg (40)			Inactive
				Rat: decreased motor activity, ptosis, cataleptic, etc at 10-25 mg/kg p.o. (54, 55)
				Rat: decreased motor activity, ptosis, cataleptic, etc at 10-25 mg/kg p.o. (54, 55)
				Mice: suggestion of depression at 100 mg/kg i.v. (119)

TABLE 6—Continued

Compound	Structure	Man (mg/kg i.v.)	Monkey[a] mg/kg i.v.	Monkey[a] Effect
Miscellaneous THCs				
120. (+)-*cis*-Δ^9-THC				
121. (±)-*cis*-Δ^9-THC			1.0 1.5	− (90) −
122. (−)-$\Delta^{9,11}$-THC			5.0	− (9)
123. 8α-Hydroxy-$\Delta^{9,11}$-THC			5.0 10.0	− (90) +
124. 8β-Hydroxy-$\Delta^{9,11}$-THC			5.0 10.0	+ (90) +
125. (−)-Δ^7-THC			5.0 10.0	− (90) −
126. 9α-Hydroxy-Δ^7-THC				
127. (±)-9-Nor-9β-hydroxy-Δ^{10}-THC				
128. (±)-9-Nor-9-hydroxy-Δ^{10}-THC				

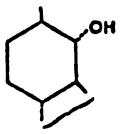
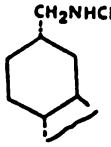
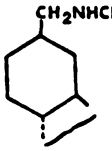
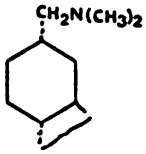
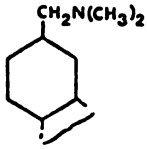
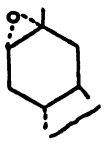
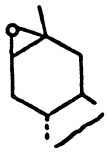
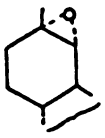
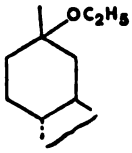
Dog ataxia†		Mouse (activity cage ED_{50}; mg/kg i.v.)	THC-SS rabbit relative potency (20)‡	Comments
mg/kg i.v.	Relative potency			
	Minimal effects at 0.2–1.25, <0.1 (83)			Effects not cannabinoid like (83)
		Decreased activity by 25% at 100 mg/kg i.p. (132)		Mice: ataxia and excitability observed at 10 mg/kg i.v. (132)
		½₀th as active as Δ^9-THC (17)		Monkey: the (±)-compound was inactive (90)
				½₀₀th as active as Δ^9-THC
				Inactive
		Inactive (34)		Mice: has some analgesic activity (34)
1.0–2.0	0.4 (85, 146)			
	0.2 (85)			

TABLE 6—Continued

Compound	Structure	Man (mg/kg i.v.)	Monkey*	
			mg/kg i.v.	Effect
129. 11α-Hexahydrocannabinol (HHC)			1.0 2.0	− (90, 91) +
130. 11β-HHC			0.1 0.5	± (90, 91) ++
131. 11α-Acetoxy-HHC			1.0 5.0	− (91) −
132. 11β-Acetoxy-HHC			0.5 1.0	+ (91) ++
133. 8α-Hydroxy-11α-HHC			0.5 1.0	+ (91) ++
134. 8β-Hydroxy-11α-HHC			1.0 2.0	− (91) −
135. 8α-Hydroxy-11β-HHC			2.0 5.0	− (91) −
136. 10α-Hydroxy-11α-HHC			0.5 1.0 2.0	+ (91) ++ ++
137. 10β-Hydroxy-11α-HHC			1.0 5.0	− (91) −

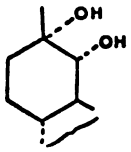
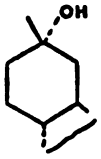
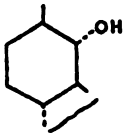
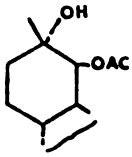
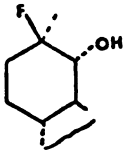
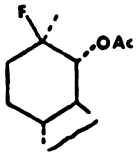
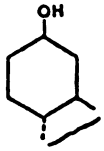
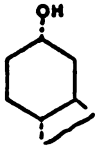
Dog ataxia†		Mouse (activity cage ED_{50}; mg/kg i.v.)	THC-SS rabbit relative potency (20)‡	Comments
mg/kg i.v.	Relative potency			
				C-11 methyl group is axial
				C-11 methyl group is equatorial; more potent than axial isomer
				Acetoxymethyl group is axial
				Acetoxymethyl group is equatorial; more potent than axial isomer
				8α-Hydroxy group is equatorial; more active than the axial isomer
				8β-Hydroxy group is axial
				Inactive; 11-methyl group and 8-hydroxy group are equatorial
				10α-Hydroxy group is equatorial; more active than axial isomer
				10α-Hydroxy group is axial

TABLE 6—Continued

Compound	Structure	Man (mg/kg i.v.)	Monkey*	
			mg/kg i.v.	Effect
138. 10α-Hydroxy-11β-HHC			2.0 5.0	– (91) +
139. 11α-(*N*-methyl)amino-HHC			*In baboons* 5.0 10.0	 – (28) ±
140. 11β-(*N*-methyl)amino-HHC			*In baboons* 2.0 5.0	 – (28) ±
141. 11α-(*N*-dimethyl)amino-HHC			*In baboons* 5.0 10.0	 – (28) –
142. 11β-(*N*-dimethyl)amino-HHC			*In baboons* 2.0 4.0	 – (28) –
143. 8α,9α-Epoxy-HHC				
144. 8β,9β-Epoxy-HHC				
145. 9α,10α-Epoxy-HHC			0.1 0.5	– (90) ++
146. 9-Ethoxy-HHC			5.0	– (40)

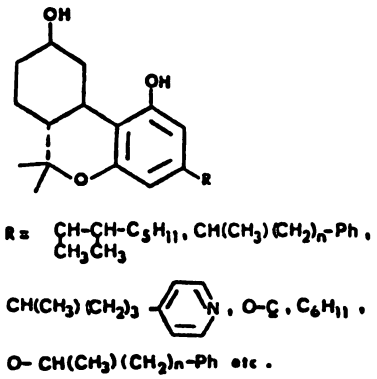
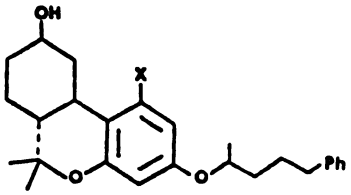
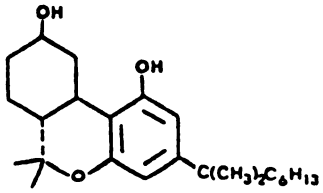
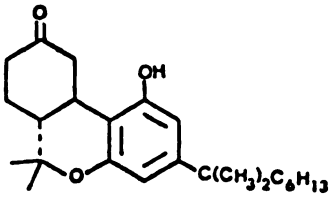
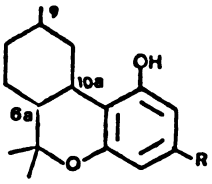
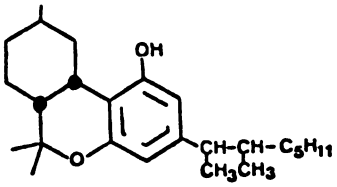
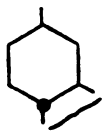
Dog ataxia†		Mouse (activity cage ED_{50}; mg/kg i.v.)	THC-SS rabbit relative potency (20)‡	Comments
mg/kg i.v.	Relative potency			
				11-Methyl group and 10-hydroxy group are equatorial
				Effects in baboons were similar to those in monkeys. Yawning and scratching was present (28)
				Yawning and scratching was absent (28)
				Yawning and scratching was present (28)
				Yawning and scratching was absent (28)
				Mice: produced catalepsy, hypothermia, etc.; less potent than Δ^8-THC (148)
				Mice: same as the 8α,9α-isomer but more potent than Δ^8-THC (148)
				Mice: produces cataleptic effects similar to Δ^8-THC at 2.1 mg/kg i.v.; more potent than Δ^8-THC (100)
	Inactive up to 7.0 mg/kg (40)			Inactive

TABLE 6—Continued

Compound	Structure	Man (mg/kg i.v.)	Monkey*	
			mg/kg i.v.	Effect
147. 9α,10α-Dihydroxy-HHC			5.0 10.0	– (90) –
148. 9α-Hydroxy-HHC				
149. 10α-Hydroxy-HHC				
150. 9α-Hydroxy-10β-acetoxy-HHC				
151. 9β-Fluoro-10α-hydroxy-HHC				
152. 9β-Fluoro-10α-acetoxy-HHC				
153. (−)-9-Nor-9β-hydroxy-HHC				
154. (±)-9-Nor-9β-hydroxy-HHC				
155. (±)-9-Nor-9α-hydroxy-HHC				

Dog ataxia†		Mouse (activity cage ED_{50}; mg/kg i.v.)	THC-SS rabbit relative potency (20)‡	Comments
mg/kg i.v.	Relative potency			
				Inactive
		Increased activity at 50 mg/kg i.p. (34)		Mice: decreased motor coordination at 25 mg/kg i.p. (34)
		Inactive (34)		Mice: decreased motor coordination at 25 mg/kg i.p. (34)
		Inactive (34)		Mice: decreased motor coordination at 25 mg/kg i.p. (34)
		Inactive (34)		Mice: decreased motor coordination at 25 mg/kg i.p. (34)
		Decreased activity at 50 mg/kg i.p. (34)		Mice: decreased motor coordination at 25 mg/kg i.p. (34)
0.05–0.10	3.0 (145)	Decreased activity (145)		Drug discrimination in rats: ED_{50}, 0.65 mg/kg (11); dog ataxia: more potent than Δ^9-THC; hydroxyl group equatorial. Mice: potent analgesic (145)
	3.0 (145)	Decreased activity (145)		Drug discrimination in rats: ED_{50}, 0.65 mg/kg (11); dog ataxia: more potent than Δ^9-THC; hydroxyl group equatorial. Mice: potent analgesic (145)
0.5	~0.6 (145)	Decreased activity (145)		Less active than Δ^9-THC; hydroxyl group axial; no analgesic activity (145)

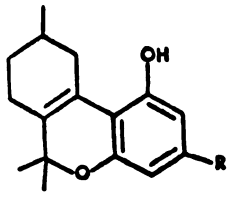
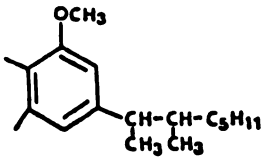
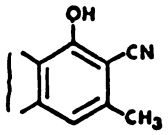
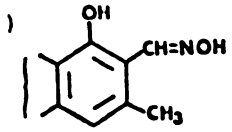
TABLE 6—Continued

Compound	Structure	Man (mg/kg i.v.)	Monkey*	
			mg/kg i.v.	Effect
156.	 R = CH-CH-C_5H_{11}, $CH(CH_3)(CH_2)_n$-Ph, CH_3 CH_3; $CH(CH_3)(CH_2)_3$-, O-C, C_6H_{11}, O-$CH(CH_3)(CH_2)_n$-Ph etc.			
157.	 X = H, CH_3, CH_2OH, COOH, NH_2, SH, Cl, etc			
158. Canbisol				
159. Nabilone		1–5 p.o. (74, 29)		
160. Miscellaneous HHC's stereochemistry at C-9, C-6a, C-10a not known *R* = C_3H_7, C_4H_9, C_6H_{13}, C_7H_{15}				
161. *cis*-Dihydro-$\Delta^{6a,10a}$-DMHP				
162. *trans*-Dihydro-$\Delta^{6a,10a}$-DMHP				

Dog ataxia†		Mouse (activity cage ED_{50}; mg/kg i.v.)	THC-SS rabbit relative potency (20)‡	Comments
mg/kg i.v.	Relative potency			
				Mice: potent analgesics PBQ test, MPE_{50}, 0.06–10.0 mg/kg, s.c. (64)
				Mice: some analgesic properties; potency decreases dramatically (64)
0.004 (0.062 = Δ^9-THC)	15.0 (128)	Decreased activity at 2.5–10.0 mg p.o. (128)		Dog ataxia: much more potent than Δ^9-THC. Potent analgesic in mice (64)
0.032 (0.062 = Δ^9-THC)	2.0 (128)	Decreased activity at 5–10 mg p.o. (128)	750	Drug discrimination in rats: ED_{50}, 0.36 mg/kg (11); effective antinauseant in man at 2-mg p.o. dose (74, 29)
	Potency varies from 0.24–1.86 based on relative potency of $\Delta^{6a,10a}$-THC = 1 (90)§			Rabbit: corneal areflexia at 5 mg/kg (90)
				Rat: relative potency is 1 compared to synhexyl = 1 (77)
				Rat: relative potency is 20 compared to synhexyl = 1 (77)

TABLE 7

Synthetic $\Delta^{6a,10a}$-THCs and their pharmacological effects

Compound	Biological test*	Comments
1. 		
(±)-$\Delta^{6a,10a}$-THC ($R = C_6H_{11}$)	Man: see table 5	
	Monkey: *Dose (mg/kg)* 0.5 *Effect* –	
	1.0 + (90)	
	5.0 ++	
	Dog: relative potency, 1.0 (79, 82)	Reference standard in the dog ataxia test
	Rabbit: corneal areflexia [1.0 mg/kg (90), 4.6 mg/kg (14, 90)]; ½sth as active as Δ^9-THC in THC-SS rabbit test (20)	
	Rat: relative potency (synhexyl), 0.5 (77)	Relative potency compared to synhexyl, 1
2. (−)-$\Delta^{6a,10a}$-THC ($R = C_6H_{11}$)	Dog: relative potency, 1.66 (90)	
	Rabbit: corneal areflexia 11–15 times more active than (+)-form (90)	
3. (+)-$\Delta^{6a,10a}$-THC ($R = C_6H_{11}$)	Dog: relative potency, 0.38 (90)	
	Rabbit: corneal areflexia; 6–8 mg/kg (90)	
4. (±)-$\Delta^{6a,10a}$-THC acetate ($R = C_6H_{11}$)	Rabbit: corneal areflexia; as active as THC; slow onset but prolonged (90)	
5. (±)-$\Delta^{6a,10a}$-THC, disodium phosphate ($R = C_6H_{11}$)	Rabbit: corneal areflexia; inactive (90)	
6. 	Rat: relative potency (synhexyl), <0.4 (77)	
7. 	General CNS depression; analgesic activity (33)	
8. 	General CNS depression; analgesic activity (33)	

* For notations and symptoms in the monkey, see table 2; the relative potency in the dog refers to the dog ataxia test as carried out by Loewe (81) using (±)-$\Delta^{6a,10a}$-THC as the reference standard expressed as 1.0; the relative potency in the rat is expressed using synhexyl as 1.0; ED_{50} of corneal areflexia in the rabbit is given in mg/kg.

TABLE 7—Continued

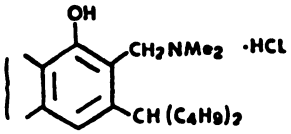
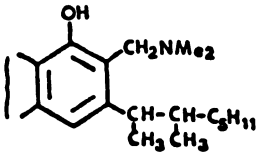
Compound	Biological test*	Comments
9. 	Rat: relative potency (synhexyl), <0.4 (77)	
10. 	Rat: relative potency (synhexyl), 1 (77)	
11. $R = CH_3$	Dog: relative potency, 0.16 (90)	
	Rabbit: corneal areflexia; inactive at 20 mg/kg (90)	
12. $R = C_2H_5$	Rabbit: corneal areflexia; inactive 15 mg/kg (90)	
13. $R = C_3H_7$	Dog: relative potency, 0.4 (90)	
	Rabbit: corneal areflexia; inactive at 20 mg/kg (90)	
14. $R = C_4H_9$	Dog: relative potency, 0.37 (90)	
	Rabbit: corneal areflexia; 1 mg/kg (90)	
15. Synhexyl ($R = C_6H_{13}$)	Man: see table 5	
	Dog: relative potency, 1.82 (90)	
	Rabbit: corneal areflexia; 0.1 mg/kg (90) and 0.03 mg/kg	
	Rat: relative potency (synhexyl), 1.0 (77)	Rat: reference standard
16. $R = C_7H_{15}$	Dog: relative potency, 1.05 (90)	
	Rabbit: corneal areflexia: 0.1 mg/kg (90)	
17. $R = C_8H_{17}$	Dog: relative potency, 0.66 (90)	
	Rabbit: corneal areflexia; 1 mg/kg (90)	
18. $R = C_9H_{19}$	Rat: relative potency (synhexyl), 4 (77)	
19. $R = CH(CH_3)C_3H_7$	Dog: relative potency, 1.84 (90)	
20. $R = CH(C_2H_5)C_3H_7$	Dog: relative potency, 1.67 (90)	
21. $R = CH(CH_3)_2C_3H_7$	Dog: relative potency, 4.18 (90)	
23. $R = CH(CH_3)C_4H_9$	Dog: relative potency, 3.65; 3.17 (90)	
	Rabbit: corneal areflexia; 0.3 mg/kg (90)	
24. $R = CH(C_3H_7)C_4H_9$	Dog: relative potency, 3.17 (90)	
25. $R = CH(CH_3)C_5H_{11}$	Dog: relative potency, 4.85 (90)	
	Rat: relative potency (synhexyl), 20 (77)	

TABLE 7—Continued

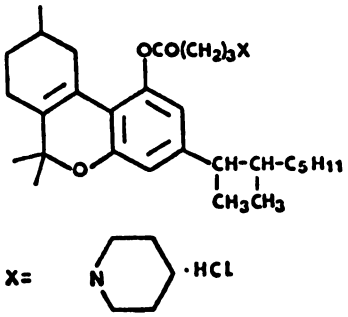
Compound	Biological test*	Comments
26. $R = CH(CH_3)C_6H_{13}$	Dog: relative potency, 16.4 (90)	
	Rabbit: corneal areflexia; 0.0025 mg/kg (90)	Relative potency much more in the rat than in the dog (77)
	Rat: relative potency (synhexyl), 100 (77)	
27. $R = CH(C_2H_5)C_6H_{13}$	Rat: relative potency (synhexyl), 100 (77)	
28. $R = C(CH_3)_2C_6H_{13}$	Dog: relative potency, 21.8 (90)	Relative potency much more in the rat than in the dog (77)
	Rat: relative potency (synhexyl), 1000 (77)	
29. $R = CH(CH_3)C_7H_{15}$	Dog: relative potency, 32.6 (90)	
	Rat: relative potency (synhexyl), 50 (77)	
30. $R = CH(CH_3)C_8H_{17}$	Dog: relative potency, 2.08 (90)	
31. $R = CH_2CH(CH_3)C_2H_7$	Dog: relative potency, 1.58 (90)	
32. $R = CH_2CH(CH_3)C_6H_{11}$	Rat: relative potency (synhexyl), 2 (77)	
33. $R = CH(CH_3)CH(CH_3)C_2H_5$	Dog: relative potency, 3.80 (90)	
34. $R = CH(CH_3)CH(CH_3)C_4H_9$	Dog: relative potency, 39 (90)	Relative potency much more in the rat than in the dog (77)
	Rat: relative potency (synhexyl), 100 (77)	
35. DMHP ($R = CH(CH_3)—CH(CH_3)—C_5H_{11}$;-racemic mixture)	Man: see table 5	
	Dog: relative potency, 512 (90)	
	Rat: relative potency (synhexyl), 500 (77); potent CNS activity in rodent screens and in dogs (115)	
36. DMHP acetate	Man: see table 5	
	Rat: relative potency (synhexyl), >20 (77)	
37. DMHP water-soluble derivatives		
	Potent to moderate CNS activity in rodent screens and in the dog p.o. (122, 102)	

TABLE 7—Continued

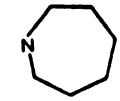
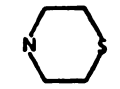
Compound	Biological test*	Comments
X=  ·HCl	Potent to moderate CNS activity in rodent screens and in the dog p.o. (122, 102)	Potent analgesic activity (122, 102)
X=  ·HCl	Potent to moderate CNS activity in rodent screens and in the dog p.o. (122, 102)	Potent anticonvulsant activity (122, 102)
X=  ·HCl	Potent to moderate CNS activity in rodent screens and in the dog p.o. (122, 102)	
38. $R = CH(CH_3)CH(CH_3)C_6H_{13}$	Dog: relative potency, 19 (90) Rat: relative potency (synhexyl), 100 (77)	Relative potency much more in the rat than in the dog (77)
39. $R = CH(CH_3)CH(CH_3)CH_2CH(CH_3)C_2H_5$	Dog: relative potency, 39 (90)	
40. $R = CH(C_2H_5)CH(CH_3)CH_3$	Dog: relative potency, 3.40 (90)	
41. $R = CH(C_4H_9)_2$	Rat: relative potency (synhexyl), <0.6 (77)	
42. $R = C_2H_4CH(CH_3)C_2H_5$	Dog: relative potency, 1.26 (90)	
43. $R = C_3H_6CH(CH_3)_2$	Dog: relative potency, 1.14 (90)	
44. $R = CH(CH_3)(CH_2)_2$  F	Potent to moderate CNS activity in rodent screens, dogs, and monkeys (147)	
45. $R = CH(CH_3)(CH_2)_3$  F	Potent to moderate CNS activity in rodent screens, dogs, and monkeys (147)	As potent as DMHP
46. $R = CH(CH_3)(CH_2)_4$  F	Potent to moderate CNS activity in rodent screens, dogs, and monkeys (147)	
47. $R = CH(CH_3)(CH_2)_3$ 	Potent to moderate CNS activity in rodent screens, dogs, and monkeys (147)	
48. $R = CH(CH_3)(CH_2)_3$  CH_3	Potent to moderate CNS activity in rodent screens, dogs, and monkeys (147)	
49. $R = CH(CH_3)CH(CH_3)\text{-}CH_2$  F	Potent to moderate CNS activity in rodent screens, dogs, and monkeys (147)	
50. $R = CH(CH_3)CH(CH_3)(CH_2)_2$  F	Potent to moderate CNS activity in rodent screens, dogs, and monkeys (147)	
51. $R = CH(CH_3)CH(CH_3)(CH_2)_3$  F	Potent to moderate CNS activity in rodent screens, dogs, and monkeys (147)	
52. $R = (CH_2)_6$  F	Potent to moderate CNS activity in rodent screens, dogs, and monkeys (147)	
53. $R = CH(CH_3)CH(CH_3)(CH_2)_2$  N	Potent to moderate CNS activity in rodent screens, dogs, and monkeys (147)	
54. $R = CH(CH_3)(CH_2)_3\ N(CH_3)_2$	Potent to moderate CNS activity in rodent screens, dogs, and monkeys (147)	
55. $R = (CH_2)_2\ N(CH_3)_2$	CNS active in mice (102, 119)	
56. $R = CH(CH_3) = C(CH_3)C_5H_{11}$	Rat: relative potency (synhexyl), 500 (77)	

TABLE 7—Continued

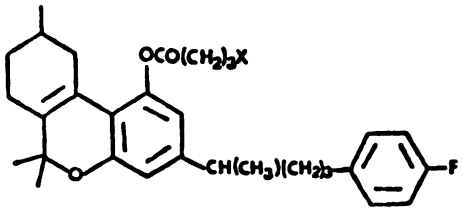
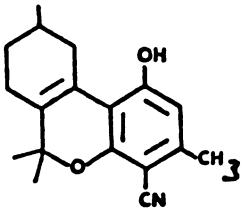
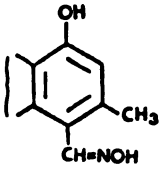
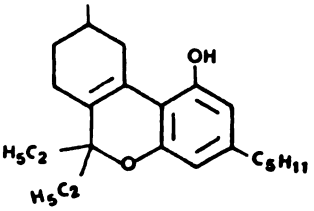
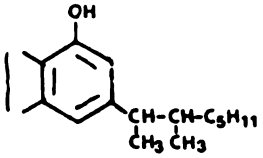
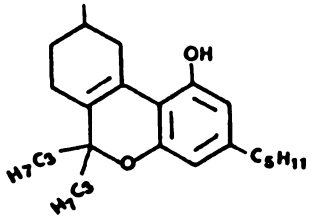
Compound	Biological test*	Comments
57. R = OH	Rabbit: corneal areflexia; inactive at 15 mg/kg (90)	
58. R = O-C_4H_9	Rabbit: corneal areflexia; inactive (90)	
59. R = O-C_7H_{15}	Rabbit: corneal areflexia; inactive (90)	
60. R = $OCH(CH_3)C_8H_{11}$	Rat: relative potency (synhexyl), 10 (77)	
61. 	Potent CNS activity in rodent screens, dogs, and monkeys (147)	
X = 	Potent CNS activity in rodent screens, dogs, and monkeys (147)	
= 	Potent CNS activity in rodent screens, dogs, and monkeys (147)	
62. 	Inactive (33)	
63. 	Inactive (33)	
64. 	Dog: relative potency, 0.12 (90) Rabbit: corneal areflexia; inactive at 20 mg/kg (90)	
65. 	Rat: relative potency (synhexyl), 2 (77)	
Acetate	Rat: relative potency (synhexyl), 0.5 (77)	
66. 	Dog: relative potency, 0.04 (90)	

TABLE 7—Continued

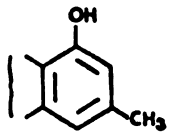
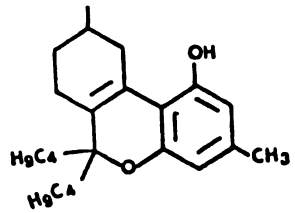
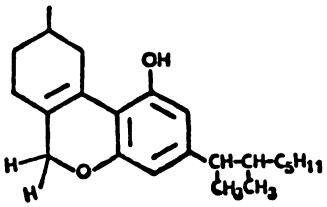
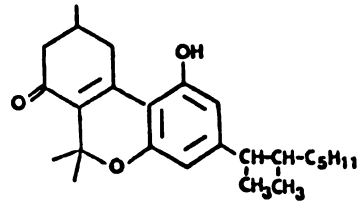
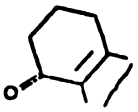
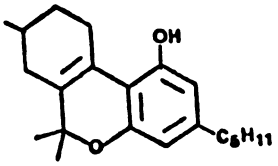
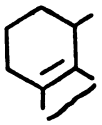
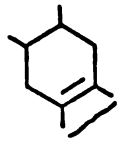
Compound	Biological test*	Comments
67. 	Rabbit: corneal areflexia; inactive at 15 mg/kg (90)	
68. 	Rabbit: corneal areflexia; inactive at 20 mg/kg (90)	
69. 	Rat: relative potency (synhexyl), 5 (78)	
70. 	Analgesic activity (hot plate) ED_{50}, 9.0 mg/kg p.o. (113)	
71. 	General CNS mouse screen; active at 2.0 mg/kg i.v. (113)	
72. 	Dog: relative potency, 0.137 (90) Rabbit: corneal areflexia; inactive at 20 mg/kg (90) Rat: relative potency (synhexyl), 1 (77)	
73. 	Dog: relative potency, 0.25 (90) Rabbit: corneal areflexia; 1 mg/kg (90); potent CNS activity in rodent screens and in dogs (115)	
74. 	Dog: relative potency, 0.75 (90)	
75. 	Dog: relative potency, 0.11 (90)	

TABLE 7—Continued

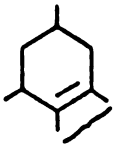
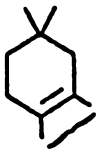
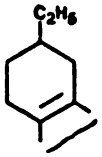
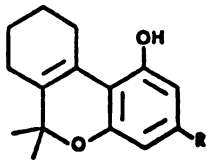
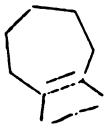
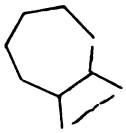
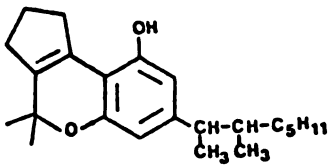
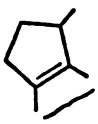
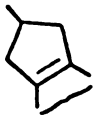
Compound	Biological test*	Comments
76. 	Rat: relative potency (synhexyl), 50 (77)	
77. 	Dog: relative potency, 0.10 (90)	
78. 	Dog: relative potency, 0.22 (90) Rat: relative potency (synhexyl), 20 (77)	
79. 		
$R = C_6H_{11}$	Dog: relative potency, 0.13 (90) Rabbit: 1/1000th as active as Δ^9-THC in THC-SS rabbit test (20) Rat: relative potency (synhexyl), 10 (77)	
$R = CH(CH_3)-CH(CH_3)-C_5H_{11}$	Rat: relative potency (synhexyl), >2 (77)	Tested as the acetate
$R = OH$	Anticonvulsant properties (102)	
80. 	Dog: relative potency, 0.2 (90)	
81. 	Dog: relative potency, 0.2 (90)	
82. 	Rabbit: corneal areflexia; not active at 30 mg/kg (90)	
83. 	Potent to moderate CNS activity in rodent screens and in dogs (115)	
84. 	Potent to moderate CNS activity in rodent screens and in dogs (115)	
85. 	Potent to moderate CNS activity in rodent screens and in dogs (115)	

TABLE 7—Continued

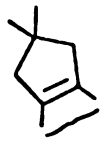
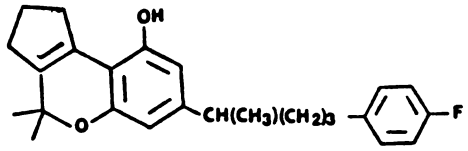
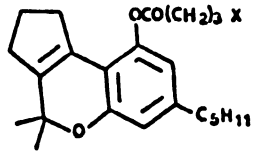
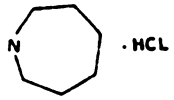
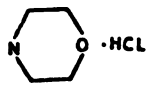
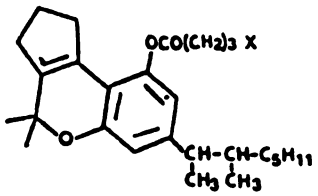
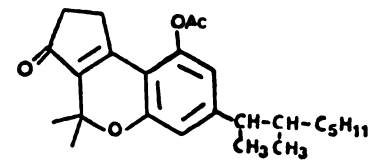
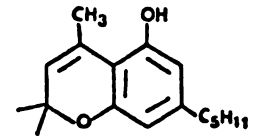
Compound	Biological test*	Comments
86. 	Potent to moderate CNS activity in rodent screens and in dogs (115)	
87. 	Potent to moderate CNS activity in rodent screens and in dogs (147)	
88. 		
X= 	Some CNS activity in rodent screens (102–122)	
= 	Some CNS activity in rodent screens (102, 122)	
= 	Some CNS activity in rodent screens (1023, 122)	
89. 		
X= 	Potent to moderate CNS activity in rodent screens and in dogs (102, 122)	
= 	Potent to moderate CNS activity in rodent screens and in dogs (102, 122)	
= 	Potent to moderate CNS activity in rodent screens and in dogs (102, 122)	
= 	Potent to moderate CNS activity in rodent screens and in dogs (102, 122)	As potent as DMHP
= 	Potent to moderate CNS activity in rodent screens and in dogs (102, 122)	
90. 	General CNS mouse screen, active at 5 mg/kg i.v. (113)	
91. 	Dog: relative potency, 0.03 (90) Rabbit: corneal areflexia; inactive at 15 mg/kg (90)	

TABLE 7—Continued

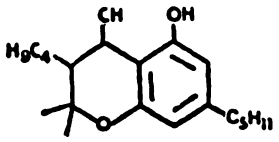
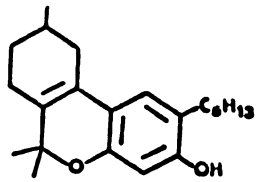
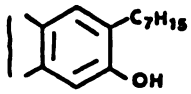
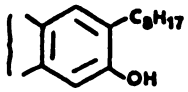
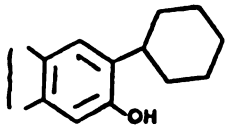
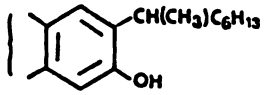
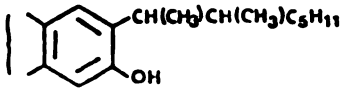
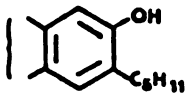
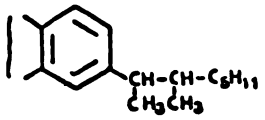
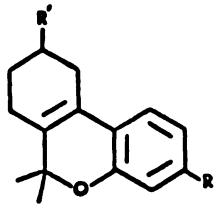
Compound	Biological test*	Comments
92. 	Dog: relative potency, 0.04 (90) Rabbit: corneal areflexia; inactive at 10 mg/kg (90)	
93. 	Rabbit: corneal areflexia; inactive 1.25 mg/kg (5)	Active in the Gayer test but not considered as potent as THCs (5)
94. 	Rabbit: corneal areflexia; 0.06 mg/kg (5)	Active in the Gayer test but not considered as potent as THCs (5)
95. 	Rabbit: corneal areflexia; 0.044 mg/kg (5)	Active in the Gayer test but not considered as potent as THCs (5)
96. 	Rabbit: corneal areflexia; 0.04 mg/kg (5)	Active in the Gayer test but not considered as potent as THCs (5)
97. 	Rabbit: corneal areflexia; 0.07 mg/kg (5)	Active in the Gayer test but not considered as potent as THCs (5)
98. 	Inactive (90) Rat: relative potency (synhexyl), 10 (77)	
99. 	Rabbit: corneal areflexia; inactive at 20 mg/kg (90)	
100. 	Rat: relative potency (synhexyl), 1 (77)	
101.  R' = H or CH_3 R = CH_3, C_5H_{11} = OH, OAc, $OCOC_3H_7$ = OC_2H_5, OC_4H_9	Dog: relative potency, inactive (90) Rabbit: corneal areflexia; inactive (90)	

TABLE 7—Continued

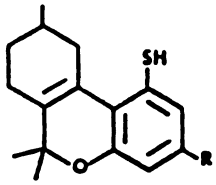
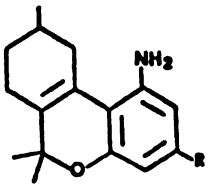
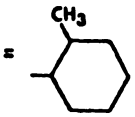
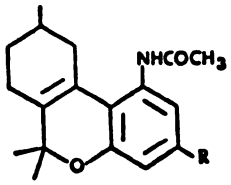
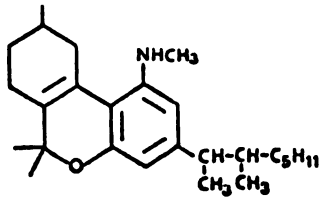
Compound	Biological test*	Comments
102. 		
$R = C_5H_{11}$	Inactive at 10–20 mg/kg p.o. in mice and rats (87)	
$= CH\text{-}CH\text{-}C_5H_{11}$ (CH$_3$, CH$_3$)	Inactive at 10–20 mg/kg p.o. in mice and rats (87)	
103. 		
$R = C_5H_{11}$	Inactive at 10–20 mg/kg p.o. in mice and rats (87)	
$= CH\text{-}CH\text{-}C_5H_{11}$ (CH$_3$, CH$_3$)	Active in muricidal, septal-lesioned rat tests and mouse activity test (87)	
$= C(CH_3)_2C_5H_{13}$	Active in muricidal and mouse activity test only (87)	The *d*- and *l*- compounds were also tested (87)
= 	Active in mouse activity test only (87)	
104. 		
$R = C_5H_{11}$	Inactive (87)	
$= CH—CH—C_5H_{11}$ (CH$_3$, CH$_3$)	Active in muricidal test only (87)	
105. 	Active in mouse activity test only (87)	

TABLE 7—Continued

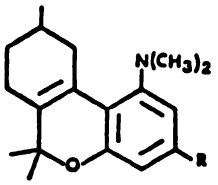
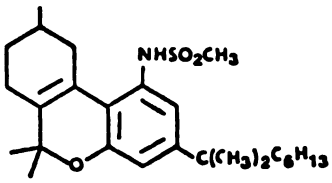
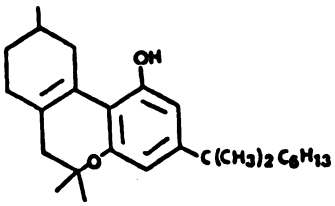
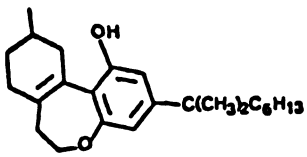
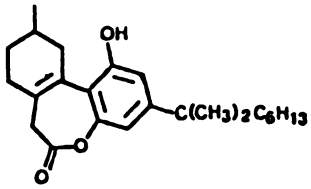
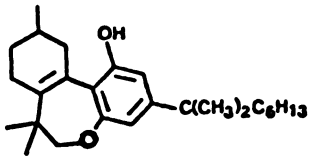
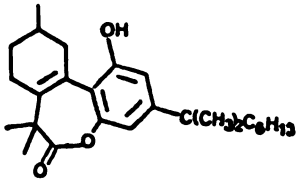
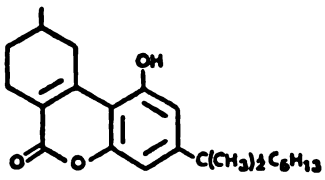
Compound	Biological test*	Comments
106. 		
$R = C_8H_{11}$	Inactive (87)	
$= CH—CH—C_5H_{11}$ (CH₃ CH₃)	Active in mouse activity test only (87)	
107. 	Active in mouse activity test only (87)	
108. 	Active in muricidal and mouse activity tests (88)	
109. 	Active in muricidal, septal-lesioned rat tests and mouse activity test (88)	
110. 	Active in muricidal and mouse activity tests only (88)	
111. 	Active in mouse activity test only (88)	
112. 	Inactive (88)	
113. 	Inactive (88)	

TABLE 7—Continued

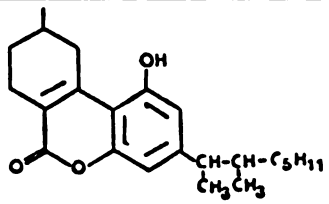
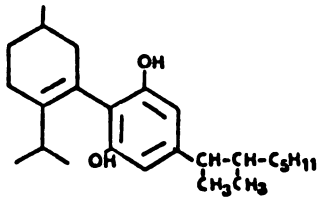
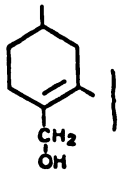
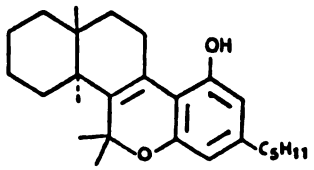
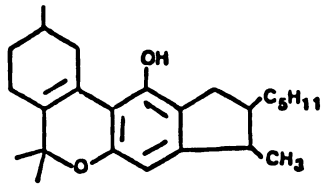
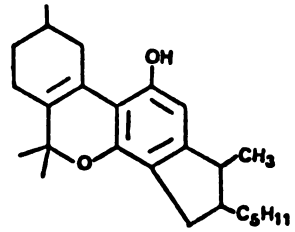
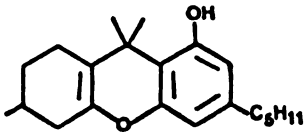
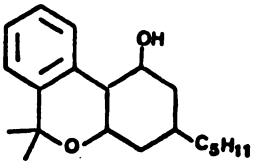
Compound	Biological test*	Comments
114. 	Rat: relative potency (synhexyl), <0.1 (77)	
115. 	General CNS mouse screen; active at 0.1 mg/kg i.v. (102)	Mice: profile similar to DMHP
116. 	Rat: relative potency (synhexyl), <1 (77)	
117. 	Inactive at 10 mg/kg i.v. (120)	Steroidal analog of THC
118. 	Inactive (112a)	Cyclic analog of DMHP
119. 	Inactive (112a)	Cyclic analog of DMHP
120. 	Inactive in mice and rabbits (14, 90)	
121. 	Inactive in mice and rabbits (14, 90)	

TABLE 8

Miscellaneous THCs and their pharmacological effects

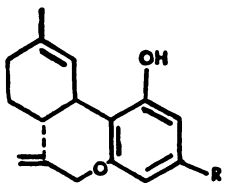
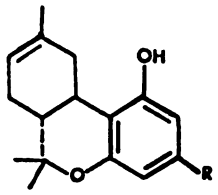
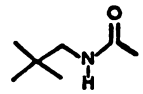
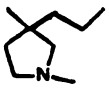
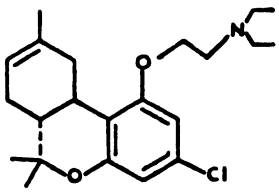
Compound	Biological test*	Comments
1. 		
$R = C_6H_{11}$	Dog ataxia: inactive at 5.0 mg/kg i.v. (85, 66)	Inactive
	Mice: decreased activity; ED_{50}, >100 mg/kg i.v. (85, 66)	
$R = CH(CH_3)—CH(CH_3)—C_5H_{11}$	Dog ataxia: inactive at 0.5 mg/kg i.v. (85, 66)	Active in mice but inactive in the dog
	Mice: decreased activity, ED_{50}, 4.2 mg/kg i.v. (85, 66)	
2. 	Mice: decreased activity at 50 mg/kg i.p.; decreased motor coordination at 25 mg/kg i.p. (34)	
R = 	Mice: decreased activity at 50 mg/kg i.p.; decreased motor coordination at 25 mg/kg i.p. (34)	
= 	Mice: decreased activity at 50 mg/kg i.p.; decreased motor coordination at 25 mg/kg i.p. (34)	
= 	Mice: decreased activity at 50 mg/kg i.p.; decreased motor coordination at 25 mg/kg i.p. (34)	
= 	Mice: decreased activity at 50 mg/kg i.p.; decreased motor coordination at 25 mg/kg i.p. (34)	
= Cl	Mice: decreased motor coordination at 25 mg/kg i.p. (34)	
3. 	Mice: decreased motor coordination at 25 mg/kg i.p. (34)	

TABLE 8—Continued

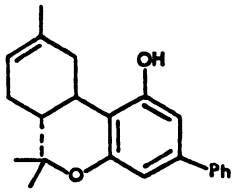
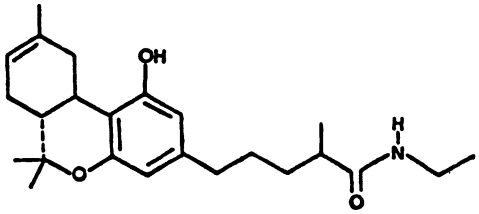
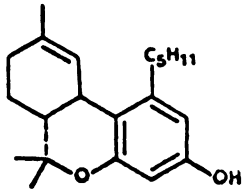
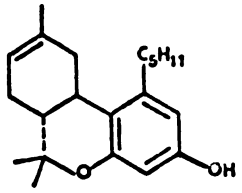
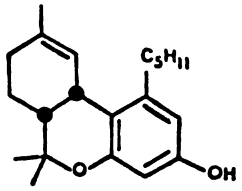
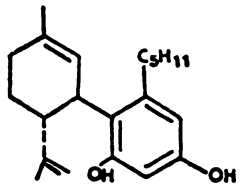
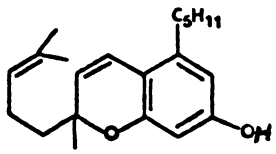
Compound	Biological test[a]	Comments
4. 	Mice: CNS active; potency ½ as active as Δ^9-THC (135)	Active
5. 	Rat: drug discrimination: generalized to Δ^9-THC but ⅕th less potent (125)	THC-like but less potent
6. (−)-Abnormal-Δ^9-THC 	Mice: inactive at 100 mg/kg i.p. (132)	Inactive
7. (−)-Abnormal-Δ^8-THC 	Mice: inactive at 100 mg/kg i.p. (132)	Inactive
8. (±)-Abnormal-*cis*-Δ-THC 	Mice: inactive at 100 mg/kg i.p. (132)	
9. (−)-Abnormal-CBD 	Dog: antihypertensive (1) Mice: inactive (132)	Antihypertensive in dogs, but no behavioral effects (1, 132)
10. 	Rat: Antiflammatory activity (131)	

TABLE 8—Continued

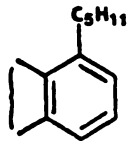
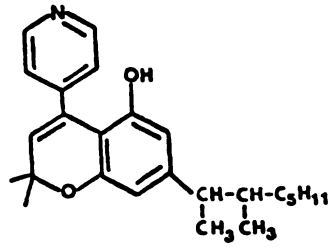
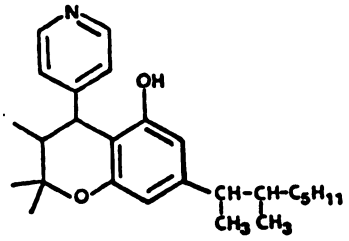
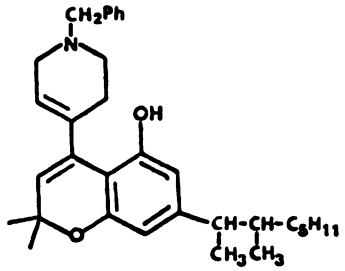
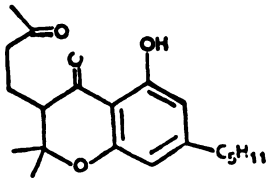
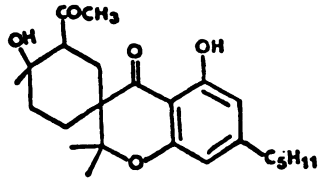
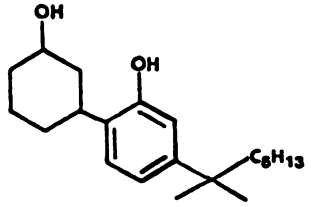
Compound	Biological test*	Comments
11. 	Rat: Antiflammatory activity (131)	
12. BRL-4664 (Nonabine) 	Man: see table 5 Baboons: tranquilizing activity (102) Mice: CNS active at 0.1 mg/kg i.v. (102); decreased activity (102, 44, 18)	Effective antinauseant in man at 10–15 mg dose p.o. (127)
13. 	Mice: CNS active at 0.2 mg/kg i.v. (56); decreased activity, tranquilizing activity (102, 44, 18)	Active
14. BRL-6155 	Rat: antihypertensive with minimal CNS effects (102, 31)	Antihypertensive activity
15. 	Inactive in unspecified CNS tests (16)	Inactive
16. 	Inactive in unspecified CNS tests (16)	Inactive
17. 	Mice: potent analgesic (95)	Potent analgesic

TABLE 8—Continued

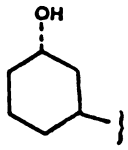
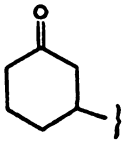
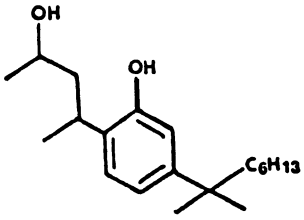
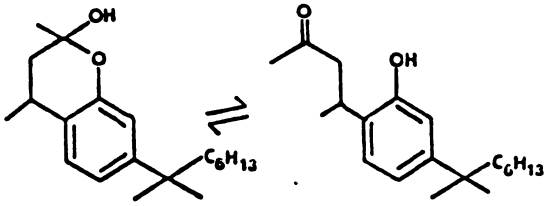
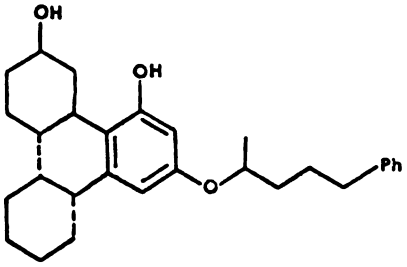
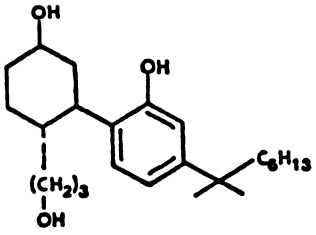
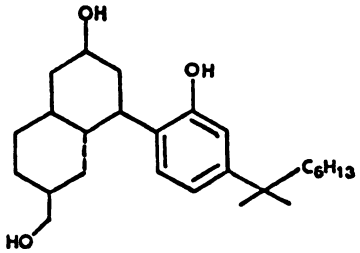
Compound	Biological test*	Comments
18. 	Mice: analgesic but less potent than the β-hydroxy isomer (95)	Analgesic
19. 	Mice: analgesic but less potent than the β-hydroxy isomer (95)	Analgesic
20. 	Mice: Some analgesic activity (95)	
21. 	Mice: inactive (95)	Inactive
22. 	Potent analgesic in animal tests (63)	3–10-fold potency of morphine (63)
23. CP-55940 	Potent analgesic in animal tests (96)	8–25-fold potency of morphine (96)
24. CP-55244 	Potent analgesic in animal tests (97)	60–190-fold potency of morphine (97)

TABLE 8—Continued

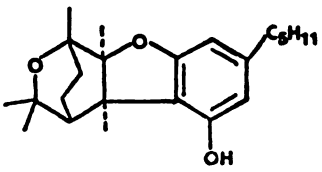
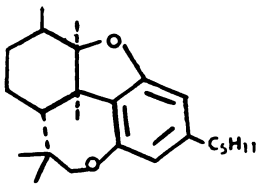
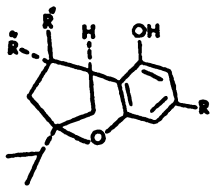
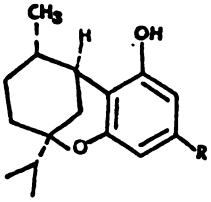
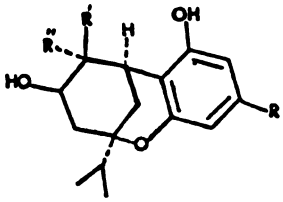
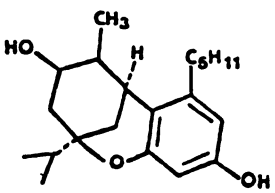
Compound	Biological test*	Comments
25. 	Mice: mild catatonia at 10 mg/kg i.v. (133)	
26. 	Mice: inactive at 10 mg/kg i.v. (134)	Inactive
27.  R= C_5H_{11}, CH(CH$_3$)-CH(CH$_3$)-C_5H_{11}; R'= H, CH_3; R''= H, CH_3	Rat: ptosis and catalepsy, etc.; decreased motor activity at 10–200 mg/kg p.o. (54)	Active
28.  R= C_5H_{11}, CH(CH$_3$)-CH(CH$_3$)-C_5H_{11}	Rat: ptosis and catalepsy, etc.; decreased motor activity at 1–10 mg/kg p.o. (54)	Active
29.  R= C_5H_{11}, CH(CH$_3$)-CH(CH$_3$)-C_5H_{11}; R'= H, CH_3; R''= H, CH_3	Rat: ptosis and catalepsy, etc.; decreased motor activity at 1–50 mg/kg p.o. (54)	Active
30. 	Rat: ptosis and catalepsy, etc.; decreased motor activity at 50 mg/kg p.o. (54)	Active

TABLE 9

Heterocyclic analogs of THCs and their pharmacological effects

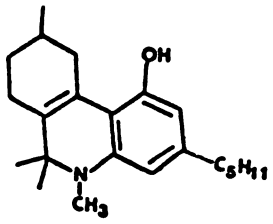
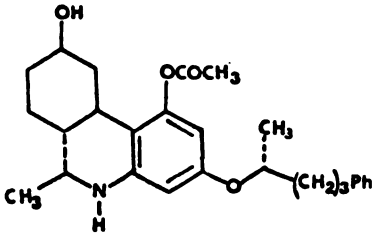
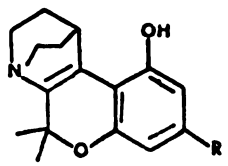
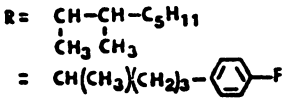
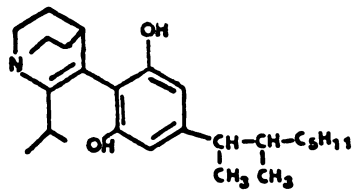
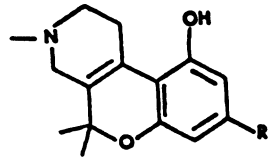
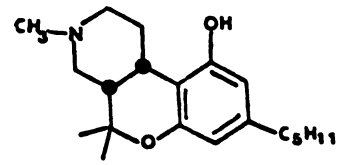
Compound	Biological test[a]	Comments
1. 	Inactive, test not specified (90)	
2. Levonantradol 	Man: see table 5	Effective antinauseant and analgesic in man (69, 58)
	Rabbit: 7.5-fold more potent than Δ^9-THC in THC-SS rabbit test (20)	
	Rat: drug discrimination ED_{50}, 0.02 mg/kg (11)	
	Mice: potent analgesic (64)	
Dextro- and epiisomers	Mice: potent analgesic (64)	
3. 		
R = 	Potent CNS activity in mice (101, 102)	
	Potent CNS activity in rodent screen and in dogs, monkeys (147)	
4. 	CNS active in mice (102)	
5. 		
$R = C_5H_{11}$	No analgesic activity (4)	
R = 	CNS active in mice (101, 102)	
6. 	No analgesic activity (4)	

TABLE 9—Continued

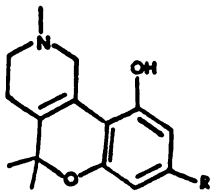
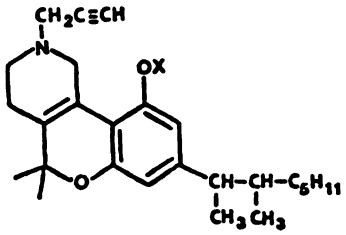
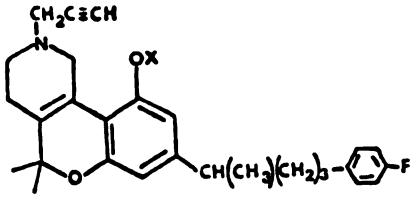
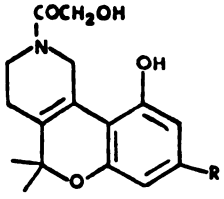
Compound	Biological test*	Comments
7. 		
R = CH_3, C_5H_{11}, C_7H_{15}, C_9H_{19}, $CH(CH_3)C_5H_{11}$, $CH(CH_3)C_6H_{11}$, $CH(CH_3)C_{12}H_{25}$;	CNS activity in mice (101)	
= $CH_3-CH(CH_3)-CH-C_5H_{11}$	Potent CNS activity in mice (101, 102)	Parallels THC activity (101, 102)
8. 		
X= H (SP-1; ABBOTT 40174)	Man: see table 5; CNS profile in monkey, dog, cats, and rodents (101, 23)	THC-like properties in man (112)
= $CO(CH_2)_3N$  . HCl (Nabilan, SP-106, ABBOTT, 40656)	Man: see table 5; CNS profile in monkey, dog, cat, and rodents (122)	Has analgesic, antinauseant, and antiglaucoma properties in man (53, 56, 129)
= Various other ester groups	Potent to moderate CNS activity in rodent screens and in dogs (102, 122)	
9. 		
X= $CO(CH_2)_3N$	Potent CNS activity in rodent screens and in dogs and monkeys (147)	
= Various other ester groups	Potent CNS activity in rodent screens and in dogs and monkeys (147)	
10. 		
R= $CH_3-CH(CH_3)-CH-C_5H_{11}$; $CH(CH_3)(CH_2)_3$ 		
and other related compounds	Potent antihypertensive activity in rats (150)	

TABLE 9—Continued

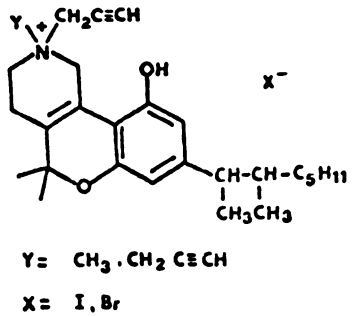
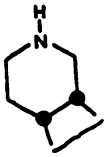
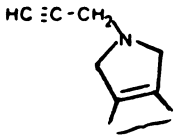
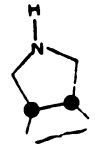
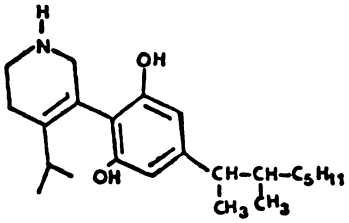
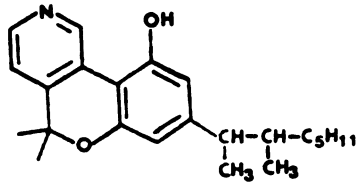
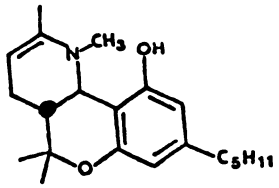
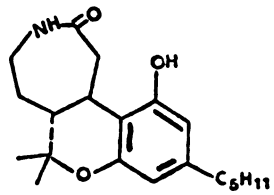
Compound	Biological test*	Comments
11.  Y= CH_3 . CH_2 C≡CH X= I, Br	CNS activity in mice (101, 102)	Much less active in mice
12. 	CNS active in mice (101, 102)	
13. 	Very little CNS activity in rodent screens (112)	
14. 	Some CNS activity in mice (101, 102)	
15. 	Some CNS activity in mice (102)	
16.  and other related compounds	Potent to moderate CNS activity in rodent screens and in dogs (70)	
17. 	CNS active; antidepressant and anticonvulsant activity (21)	
18. 	Dog ataxia: relative potency, 0.5 compared to Δ^9-THC (85)	THC-like activity in the dog (85)

TABLE 9—Continued

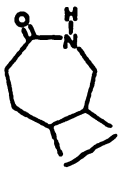
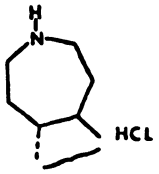
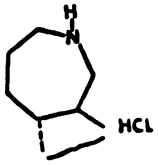
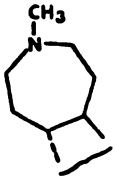
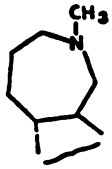
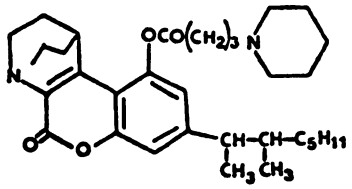
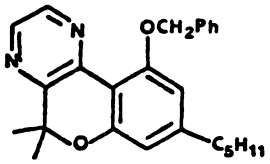
Compound	Biological test*	Comments
19. 	Dog ataxia: not cannabinoid like up to 8 mg/kg i.v. (85)	Inactive
20. 	Dog ataxia: marked CNS depression at 8 mg/kg i.v. (85)	Active but few cannabinoid-like signs (85)
21. 	Dog ataxia; marked CNS depression at 8 mg/kg i.v. (85)	Active but few cannabinoid-like signs (85)
22. 	Dog ataxia: relative potency, 0.1 compared to Δ^9-THC (85)	THC-like (85)
23. 	Dog ataxia: slight CNS depression at 8 mg/kg (85)	Active, but few cannabinoid-like signs (85)
24. 	Inactive in CNS tests in dogs, rats, and mice (25) Rabbits: reduces intraocular pressure topically (25)	Reduces intaocular pressure in rabbits topically (25)
25. 	Inactive in unspecified CNS tests (15)	Inactive
26. 	Inactive in unspecified CNS tests (15)	Inactive
27. 	Inactive in unspecified CNS tests (15)	Inactive

TABLE 9—Continued

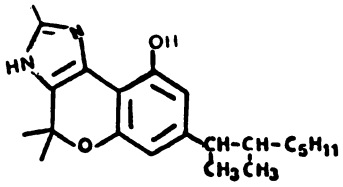
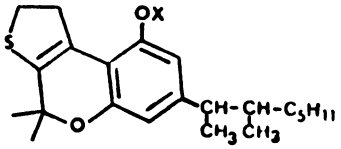
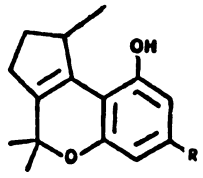
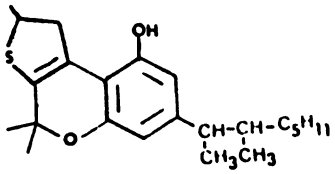
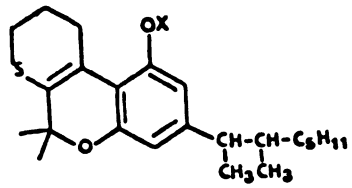
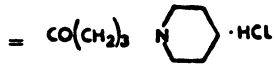
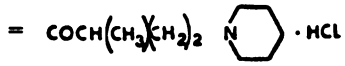
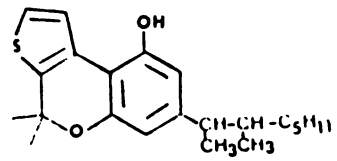
Compound	Biological test*	Comments
28. 	Very little CNS activity in rodent screen (112)	Very slightly active
29. 		
X = H	Potent activity in the dog and other CNS rodent screens (23, 121, 102)	THC-like activity in the dog (23)
= $CO(CH_2)_3N$⬡·HCl	Moderate CNS activity (121, 102)	
= $CO(CH_2)_3N$⬡O·HCl	Moderate CNS activity (121, 102)	
30. 		
R = $CH(CH_3)CH(CH_3)C_5H_{11}$	Potent activity in the dog and other CNS rodent screens (115, 102)	Potent analgesic activity (115)
= $CH(CH_3)(CH_2)_3$⬡F	Potent activity in the dog and other CNS rodent screens (147, 102)	
31. 	Potency in various CNS tests decreases (115, 102)	
32. 	Potency in various CNS tests decreases (115, 102)	
33. 	Potency in various CNS tests decreases (121, 102)	
34. 	Potency in various CNS tests decreases (121, 102)	

TABLE 9—Continued

Compound	Biological test*	Comments
35. 		
X = H	Potent activity in the dog and in other CNS rodent screens (121, 102)	Good analgesic activity (121)
= 	Potency decreases (121, 102)	
= 	Potency decreases (121, 102)	
36. 	Some CNS activity (121, 102)	

equiactive with Adams' DMHP (table 7, compound no. 35) in the mouse screen (102).

V. Conclusion

Despite the extensive knowledge about the pharmacological actions of cannabinoids, the two most promising therapeutic areas of Δ^9-THC, i.e., antiemetic and antiglaucoma activities, were discovered serendipitously without any preclinical pharmacology. This emphasizes the importance of early studies in humans and the difficulties encountered in correlating animal activity with activity in man for this class of compounds.

The role of cannabinoids as antinauseants to patients undergoing cancer chemotherapy is now well established. Δ^9-THC has recently been approved by the Food and Drug Administration (FDA) for marketing in the USA, and a synthetic analog, Nabilone, is already marketed in Europe. In the antiglaucoma field, the utility of Δ^9-THC as a novel agent has been established, and several synthetic analogs are presently in the developmental stage.

From pharmacological screening of cannabinoids, a separation of several specific pharmacological actions has been noted in different derivatives, but the relevance of these to humans is not presently clear. Hopefully, with the introduction of more sophisticated pharmacological screens and with the extended clinical usage of Δ^9-THC and Nabilone, there will be a resurgence of interest in this field. Other areas of therapeutic use will become evident, and the potential of this class of novel drugs will begin to emerge.

A parallel can be drawn between the opioid and the cannabinoids, since morphine and Δ^9-THC both are drugs of abuse. To use the opioid work as a guide, the cannabinoids are at present in their early stages of development, comparable to morphine before the discovery of nalorphine. However, it should be emphasized that the concept of drug development from THCs and cannabinoids is based on very sound foundations, since, unlike morphine, Δ^9-THC has a remarkably low toxicity in animals and humans. In addition, it has practically no respiratory-depressant activity, none or very low physical dependence liability, and, finally, a unique pharmacological profile compared to other psychoactive drugs.

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