Cannabinoid chemistry: an overview

Article · January 2005

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Cannabinoid chemistry: an overview

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Introduction

Cannabis sativa probably originates from neolithic China [1]. However the exact period of its domestication is unknown. The first known record of the use of cannabis as a medicine was published in China 5000 years ago in the reign of the Emperor Chen Nung. It was recommended for malaria, constipation, rheumatic pains, absent-mindedness and female disorders. Later its use spread into India and other Asian countries, the Middle East, Asia, South Africa and South America. It was highly valued in medieval Europe. In Western Europe, particularly in England, cannabis was extensively used as a medicine during the 19th century, while in France it was mostly known as a "recreational" drug [2].

Natural cannabinoids

The first successful attempt to identify a typical cannabis constituent was achieved by Wood et al. [3], who isolated cannabinol from the exuded resin of Indian hemp (*charas*), which was analysed as $C_{21}H_{26}O_2$. Another big step was made by Cahn, who advanced the elucidation of the structure of cannabinol [4], leaving as uncertain only the positions of a hydroxyl and a pentyl group. Several years later Todd's group in the UK [5, 6] and independently Adam's group in the USA [7] synthesized several cannabinol isomers and compared them with the natural one. One of the synthetic isomers was identical to the natural product. The correct structure of the first natural cannabinoid, cannabinol, was thus finally elucidated. These two groups assumed that the psychotropically active constituents were tetrahydrocannabinols (THCs), which however they could not isolate in pure form and therefore they could not elucidate their structures.

   A second cannabis constituent, the psychotropically inactive cannabidiol, was also isolated, but its structure was only partially clarified [8]. Synthetic THC derivatives, which showed cannabis-like activity in animal tests, were prepared, but they obviously differed from the active natural product, on the basis of their UV spectrum [9–12].

In a systematic study of the antibacterial substances in hemp Krejčí and Šantavý found that an extract containing carboxylic acids was effective against *Staphylococcus aureus* and other Gram-positive micro-organisms. They isolated cannabidiolic acid and reported a nearly correct structure [13, 14] (Fig. 1).
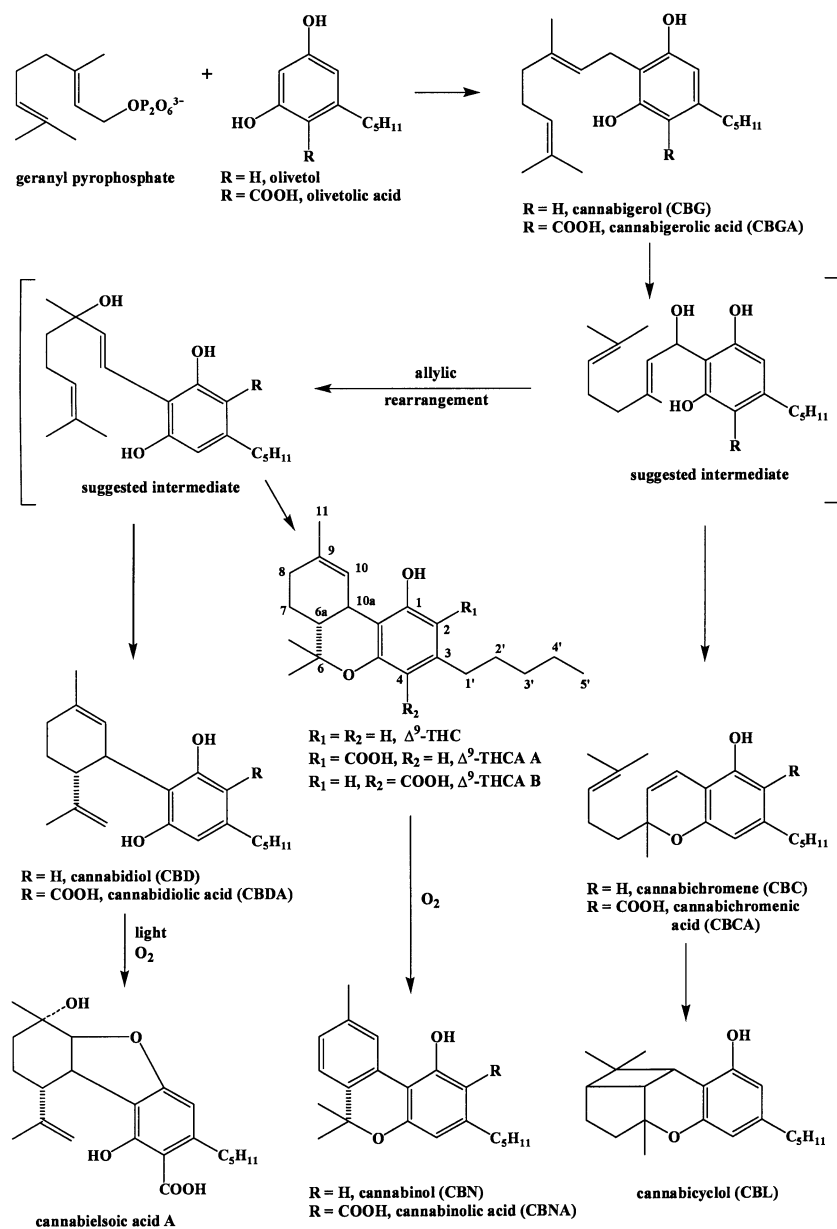

Figure 1. A tentative biogenesis of the plant cannabinoids

Advances in isolation methods made possible a clarification of the chemistry of cannabis. In 1963 our group reisolated cannabidiol and reported its correct structure and stereochemistry [15]. A year later we finally succeeded in isolating pure THC (Δ^9-THC); we elucidated its structure, obtained a crystalline derivative and achieved a partial synthesis from cannabidiol [16]. The absolute configuration of cannabidiol and of THC was established by correlation with known terpenoids [17]. Several years later a minor psychotomimetically active constituent, Δ^8-THC, was isolated from marijuana [18]. Whether this THC isomer is a natural compound, or an artifact formed during the drying of the plant, remains an open problem.

Several additional, non-psychotropic cannabinoids were also identified at that time. The best known are cannabigerol [19], cannabichromene [20, 21] and cannabicyclol [22]. For a better understanding of the biogenesis of a cannabinoids in the plant the isolation and identification of cannabinoid acids turned out to be essential. Alongside cannabidiolic acid, the cannabinolic and cannabigerolic acids were identified [23], followed by two Δ^9-THC acids, A and B [24, 25], as well as Δ^8-THC acid [26, 27] and cannabielsoic acid [28]. The decarboxylated product of cannabielsoic acid, cannabielsoin, is found in mammals as a metabolite of cannabidiol [29]. The syntheses of some of the cannabinoid acids have been reported [30].

A tentative pathway for the biogenesis of cannabinoids in the plant has been published [31–34]. However the only experimental support for Δ^9-THC acid formation from cannabigerolic acid (by direct oxidocyclization and not through cannabidiolic acid as was assumed before) has been reported by Shoyama's group [35]. They showed that the presence of a carboxyl group in the substrate is essential for enzymatic cyclization of the terpene moiety. This finding may explain the presence of THC and THC acids in certain cannabis strains (e.g. South African) that do not contain cannabidiol or its acid [36–38].

In a series of elegant publications Shoyama's group identified an enzyme forming cannabichromenic acid and showed that this acid is formed directly from cannabigerolic acid [39, 40].

It is possible that some of the natural neutral cannabinoids are artifacts formed through decarboxylation, photochemical cyclization (cannabicyclol), oxidation (cannabielsoic acid) or isomerization (Δ^8-THC and Δ^8-THC acid) of other constituents.

Endogenous cannabinoids

The discovery of a high-affinity, stereoselective and pharmacologically distinct cannabinoid receptor in a rat brain tissue [41] led to a search for natural endogenous ligands in the brain, which bind to this cannabinoid receptor. We assumed that the cannabinoid receptor in the brain is not present just to bind a plant constituent, but to be activated by specific endogenous ligands. Our approach involved first the synthesis of a potent labeled agonist (HU-243),

which made possible a sensitive bioassay. This compound is the most active cannabinoid known so far [65]. In a standard bioassay we expected that endogenous compounds with cannabinoid activity would displace tritiated HU-243 bound to the central cannabinoid receptor (CB_1).

Rat brains are too small and hence we started our isolations with porcine brains. After nearly 2 years of tedious work, which involved numerous chromatographic separations, we isolated from brain an endogenous compound that binds to the cannabinoid receptor with about the same potency as Δ^9-THC. This endogenous ligand was named anandamide [42], a name derived from the Sanskrit word for bliss, *ananda*. When administered intraperitoneally to mice it caused reduced activity in an immobility test and in open field tests, and produced hypothermia and analgesia, a tetrad of assays typical of the psychotropic cannabinoids [43]. Later we isolated two additional, apparently minor, endogenous cannabinoids, homo-γ-linoleoylethanolamide and 7,10,13,16-docosatetraenoylethanolamide [44].

The existence of a peripheral cannabinoid receptor (CB_2) led to the search for a ligand to this receptor. We isolated from canine gut another arachidonic acid derivative, 2-arachidonoyl glycerol (2-AG) [45]. At around the same time this compound was detected in brain [46] (see Fig. 2).

Hanuš et al. reported a third, ether-type endocannabinoid, 2-arachidonyl glyceryl ether (noladin ether), isolated from porcine brain [47]. It binds to the CB_1 cannabinoid receptor ($K_i = 21.2 \pm 0.5$ nM) and causes sedation, hypothermia, intestinal immobility and mild antinociception in mice. It binds very weakly to the CB_2 receptor. The presence of this endocannabinoid in brain has been questioned [48]. However as this type of natural glycerol derivative (an ether group on the 2-position) is unusual, we have repeated its isolation with an identical result (unpublished observations).

In the course of the development of a bioanalytical method to assay anandamide in brain and peripheral tissues, a compound with the same molecular weight as anandamide, but with a shorter retention time, was identified as *O*-arachidonoyl ethanolamine (arachidonic acid and ethanolamine joined by an ester linkage). This compound was named virodhamine [49].

On the basis of previous structure–activity relationship studies and on the existence in body tissues of biosynthetic precursors, Huang et al. assumed that *N*-arachidonoyl-dopamine (NADA) may exist as an endogenous "capsaicin-like" cannabinoid in mammalian nervous tissues and may possibly bind to the vanilloid receptor VR1 [50]. They found that NADA is indeed a natural endocannabinoid in nervous tissues, with high concentrations found in the striatum, hippocampus and cerebellum and lower concentrations in the dorsal root ganglion. NADA binds to the cannabinoid receptors with a 40-fold greater selectivity for the CB_1 ($K_i = 250 \pm 130$ nM) than the CB_2 receptor [50–52].

One of the typical endocannabinoid effects is pain suppression. Some endogenous fatty acid derivatives (palmitoylethanolamide, oleamide), which do not bind to CB_1 or CB_2, either enhance this effect (the so-called entourage

anandamide

homo-γ-linolenoylethanolamide

7,10,13,16-docosatetraenoylethanolamide

2-arachidonoyl glycerol

noladin ether
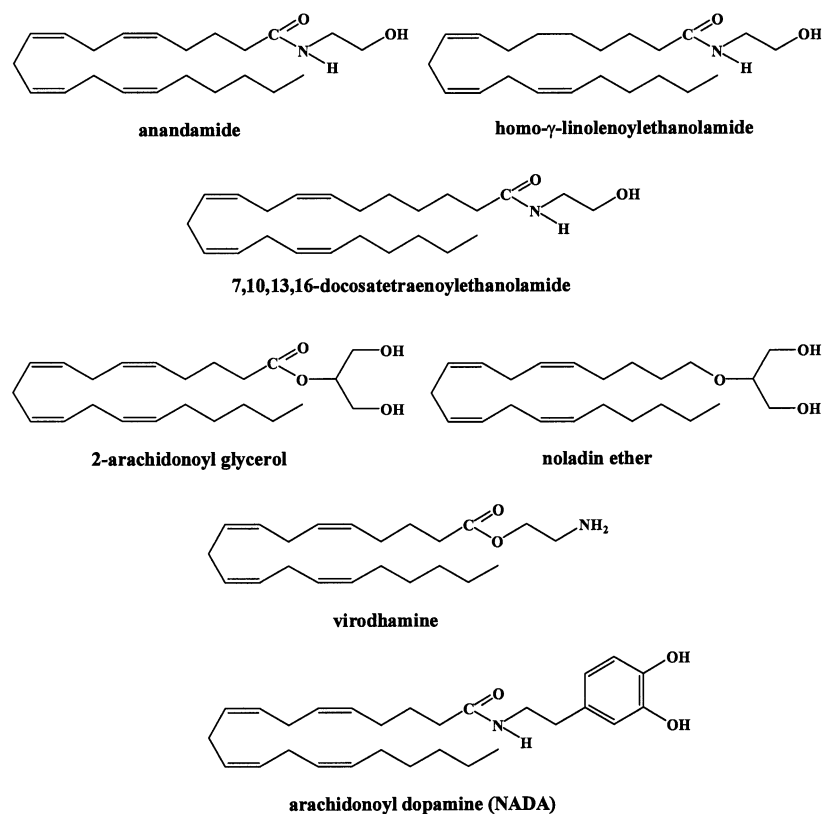
virodhamine

arachidonoyl dopamine (NADA)

Figure 2. The main endocannabinoids

effect) or actually show activity by themselves, presumably by binding to as-yet unidentified cannabinoid receptors [53].

Shortly after the isolation of anandamide, its biosynthesis, metabolism and degradation in the body were studied [54, 55].

Synthetic cannabinoid receptors agonists/antagonists

In the late 1970s Pfizer initiated a cannabinoid project aimed at novel analgesic compounds. Numerous active bicyclic compounds were synthesized. The compound chosen for clinical evaluation was CP-55,940 [56, 57]. This compound is more potent than morphine and is at least 200-fold more potent than its enantiomer [55]. Structural and stereochemical evaluations led to highly active analogs [58]. The cannabinoid-type side effects observed with this group of "non-classical" cannabinoids led to the termination of the project [58]. However, these compounds helped advance the cannabinoid field as they

were the first cannabinoids that were widely used as labeled ligands. Indeed, in 1988 Allyn Howlett's group used tritium-labeled CP-55,940 for the identification of the first cannabinoid receptor [59]. [^{3}H]CP-55,940 is now an important tool in the study of cannabinoid receptors [60].
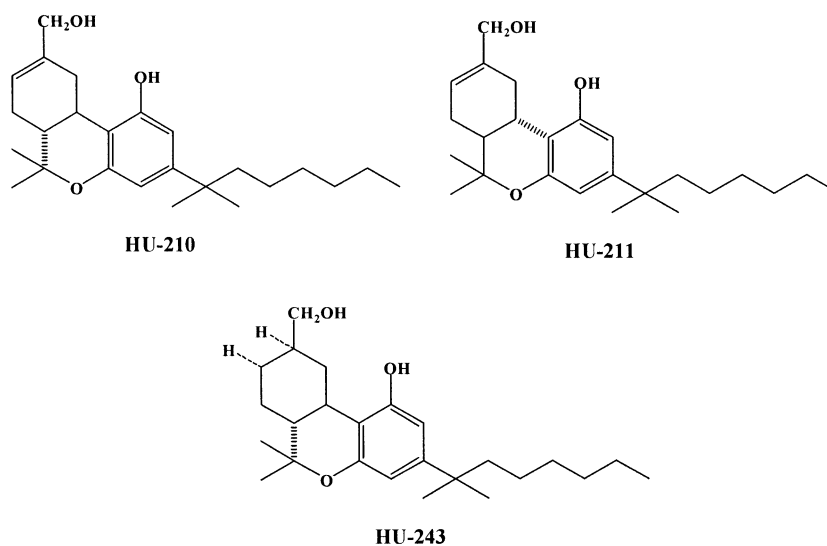
Structure 1
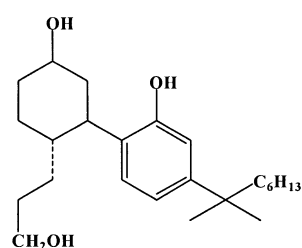
CP-55940

The need for stereospecific cannabinoid ligands led to further syntheses of enantiomers with essentially absolute stereochemical purity. This endevour culminated by the preparation of very potent cannabimimetic compounds [61]. Replacement of the n-pentyl side chain with a 1,1-dimethyl heptyl side chain in one of the major active primary metabolites of Δ^8-THC, 11-hydroxy-Δ^8-THC, led to the highly active ligand 11-hydroxy-Δ^8-THC-dimethylheptyl, or HU-210. The psychotropically inactive enantiomer, HU-211, is however analgesic, antiemetic and is at present being evaluated as an anti-trauma agent. Both compounds were synthesized with very high enantiomeric purity (99.8%) [62]. The high degree of enantioselectivity and potency of HU-210 was demonstrated in mice, dogs and pigeons [63, 64].

The synthetic HU-210 was used to prepare a novel probe for the cannabinoid receptor. Hydrogenation of this compound yielded two epimers of 5'-(1,1-dimethylheptyl)-7-hydroxyhexahydrocannabinol [65]. The equatorial epimer (designated HU-243) binds to the cannabinoid receptor with a K_D value of 45 pM, and is the most potent CB$_1$ agonist described so far. Tritiated HU-243 was used as a novel probe for the cannabinoid receptor.

An effort to find new synthetic cannabinoids with increased therapeutic activity and few adverse side effects led to the preparation of ajulemic acid (HU-239), an analgetic and anti-inflammatory cannabinoid [66, 67]. This compound has anti-tumor effects in mice [68], binds to the peroxisome proliferator-activated receptor γ (PPARγ), a pharmacologically important member of the nuclear receptor superfamily [69], and induces apoptosis in human T lymphocytes [70]. However, it binds to CB$_1$ and has activity at the level of THC in the tetrad assay in mice [71].

A group at the Sterling pharmaceutical company prepared analogs of the anti-inflammatory drug pravadoline, an aminoalkylindole. To their surprise

Structure 2

HU-210

HU-211

HU-243

Structure 3


Ajulemic acid (CT$_3$, HU-239)
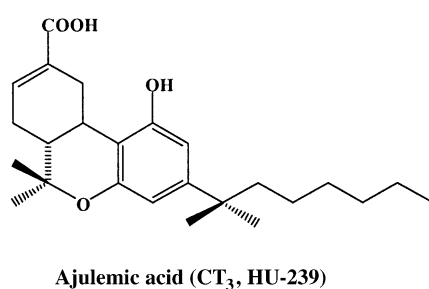
they discovered that these compounds acted not only as cyclooxygenase inhibitors, but also as cannabinoid agonists [72]. *In vitro* structure–activity relationship studies of these compounds led to numerous new compounds with cannabinoid receptor agonist activity [73, 74]. The best-known compound in this series is the conformationally restricted derivative WIN-55212-2 [75]. A binding assay in rat cerebellum membranes has been developed. It makes use of the stereospecific radioligand [^{3}H](R)-(+)-WIN-55212-2.

The first potent and selective antagonist of the central cannabinoid receptor (CB$_1$), SR-141716A, was reported in 1994 by a group at Sanofi [76]. This compound is not active on the peripheral cannabinoid receptor (CB$_2$) and has rapidly become a new tool in the study of cannabinoid receptor mechanisms and in research on new therapeutic agents. Another novel CB$_1$ antagonist, LY320135, which is not as selective as the previous one, was reported soon
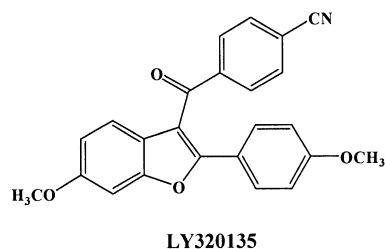
Structure 4

WIN-55212-2

SR-141716A
(rimonabant)
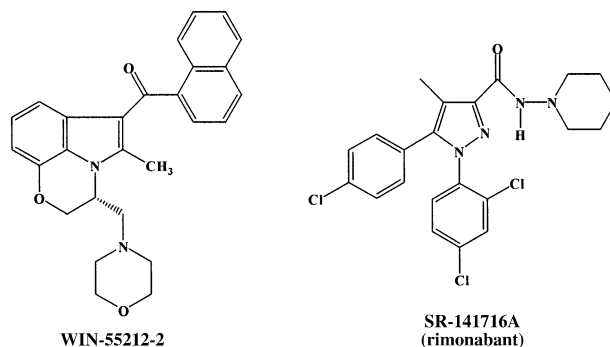
thereafter. This substituted benzofuran reverses anandamide-mediated adeny-
late cyclase inhibition and also blocks WIN-55212-2-mediated inhibition of
N-type calcium channels [77].

Structure 5

LY320135

The Sanofi group also described the first potent and selective antagonist of
the peripheral cannabinoid receptor (CB_2), SR-144528 [78], and like the
above-mentioned CB_1 antagonist, it soon became a major tool in cannabinoid
research [79].

Our group reported the preparation of a CB_2-selective ligand, HU-308 [80],
which is now being investigated as an anti-inflammatory drug by Pharmos, a
pharmaceutical firm. It shows no central nervous system effects due to its
essential lack of affinity for the CB_1 receptor. In HU-308 both phenolic groups
are blocked as methyl ethers. This is in contrast to cannabinoid CB_1 agonists
in which at least one of the phenolic groups has to be free.

Traumatic brain injury is a major cause of mortality and morbidity. There is
no effective drug to treat brain-injured patients. We found that on closed head
injury the amounts of 2-AG produced by the brain are increased 10-fold, and
that this endocannabinoid apparently has a neuroprotective role, as adminis-
tration of 2-AG to mice with head trauma reduces both the neurological dam-
age and the edema [81]. Numerous other groups have recorded work on vari-

Structure 6

SR-144528   HU-308
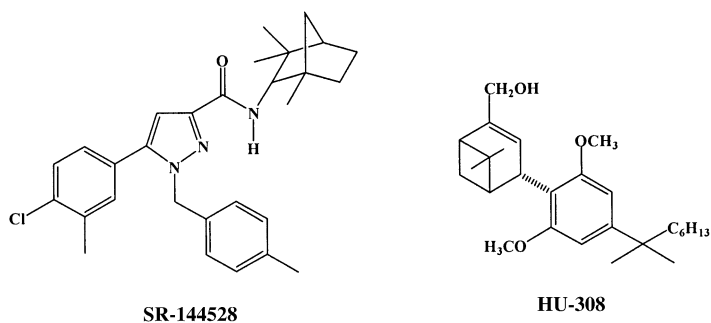
ous aspects of cannabinoids as neuroprotective agents (see Chapter by Fernández-Ruiz et al. in this volume). On this basis a structurally novel, highly potent CB_1/CB_2 cannabinoid receptor agonist, BAY 38-7271, was prepared and shown to have pronounced neuroprotective efficacy in a rat model of traumatic brain injury [82–85].

Structure 7

BAY 38-7271
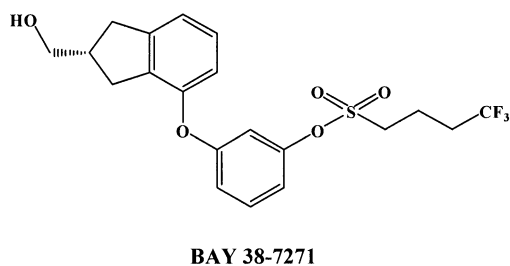
Pharmos have developed a cannabinoid, PRS 211,096, that binds to the peripheral cannabinoid receptor and which is being assayed for treatment of multiple sclerosis [86].

Structure 8

PRS 211,096
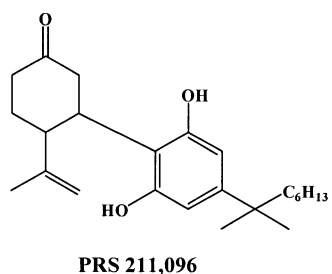
(*R*)-Methanandamide (AM-356) is a chiral analog of the endocannabinoid ligand anandamide, It is more stable than anandamide to hydrolysis by fatty acid amide hydrolase (FAAH), as the methyl group adjacent to the amide moiety apparently interferes with the enzyme. It has a K_i value of 20 ± 1.6 nM for the CB_1 receptor [87]. The K_i value for binding to the CB_2 receptor from mouse spleen is 815 nM [88]. Thus (*R*)-methanandamide has a high selectivity for the CB_1 receptor.

6-Iodo-pravadofine (AM-630), an aminoalkylindole, attenuates the ability of a number of cannabinoids to inhibit electrically evoked twitches of vas deferens isolated from mouse [89]. AM-630 behaves as a competitive antagonist of cannabinoid receptor agonists in the guinea-pig brain [90]. AM-630 also antagonizes the ability of the cannabinoid agonist WIN-55212-2 to stimulate guanosine-5'-*O*-(3-[^{35}S]thio)triphosphate ([^{35}S]GTPγS) binding in mouse brain membrane preparations [91].

Gatley et al. [92] have developed a novel radioligand, [^{123}I]AM-281, structurally related to the CB_1-selective antagonist SR-141716A, that is suitable for *in vivo* studies of the central cannabinoid receptor and for imaging this receptor in the living human brain [92].
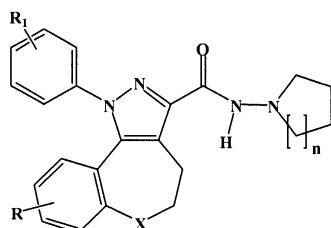
Structure 9

AM-281

AM-630

AM-1241

AM-2233
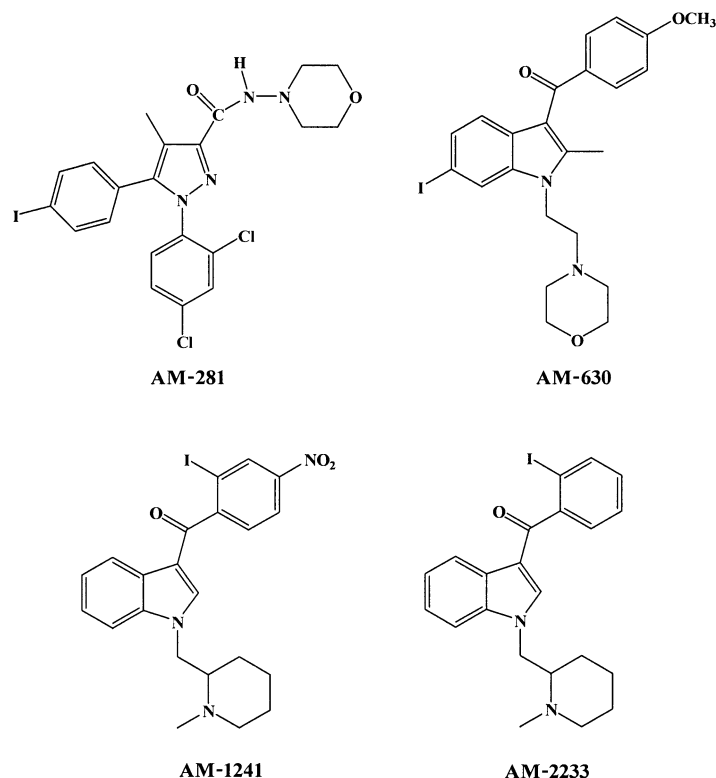
Scientists at the University of Connecticut have synthesized and studied a series of aminoalkylindoles as selective CB_2 agonists. The compounds are stated to be useful for the treatment of pain, glaucoma, multiple sclerosis and other diseases and disorders. Compound AM-1241 has a high affinity for the CB_2 receptor in a mouse spleen preparation ($K_i = 3.4 \pm 0.5$ nM), with good selectivity *versus* the CB_1 receptor in a rat brain preparation ($K_i = 280 \pm 41$ nM). This compound has recently been found to inhibit neuropathic pain in rodents [93].

AM-2233, a novel aminoalkylindole CB_1 agonist, was found to have a greater potency than WIN-55212-2 in assays *in vitro*, but has a similar potency to it in a mouse locomotor assay. It was suggested that its behavioral effects could have been mediated, in part, via an action on another receptor type in addition to the CB_1 receptor. AM-2233 represents the first agonist CB1 receptor ligand ($K_i = 0.4$ nM) with potential as an *in vivo* imaging agent for this receptor [94, 95]. Stoit et al. [96] have reported the syntheses and biological activities of potent pyrazole-based tricyclic CB_1 receptor antagonists. One can find additional information on cannabinoid receptor agonists and antagonists in Barth's review [97].
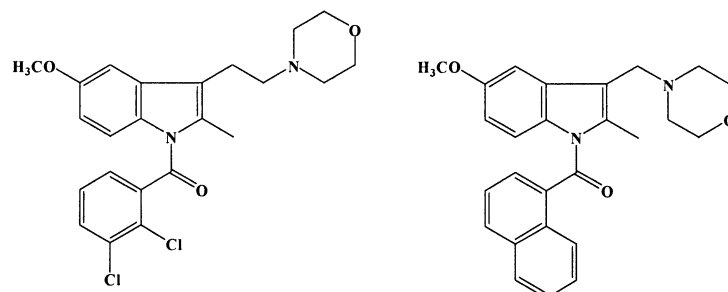
Structure 10

Pyrazole-based tricyclic CB_1 antagonists

Gallant et al. [98] have described two indole-derived compounds (see structures below), with binding potency for the human peripheral cannabinoid receptor (CB_2) in the nanomolar region, They are highly selective.

A new series of rigid 1-aryl-1,4-dihydroindeno[1, 2-c]pyrazole-3-carboxamides was recently designed [99]. Seven of the new compounds displayed very high *in vitro* CB_2-binding affinities. Four compounds showed very high selectivity for the CB_2 receptor.

Cannabinoid structure–activity relationship data have indicated that the cannabinoid side chain and the phenolic hydroxyl are key elements in CB_1 receptor recognition. To test this hypothesis, the 1-deoxy analog, JWH-051, of the very potent cannabinoid 11-hydroxy-Δ^8-THC-dimethylheptyl (HU-210) was prepared and the affinity of this compound for the CB_1 receptor was determined [100]. Contrary to expectations, this 1-deoxy analog still had high affinity for the CB_1 receptor ($K_i = 1.2 \pm 0.1$ nM) and even greater affinity for the

Structure 11

**Indole derivatives**

Structure 12
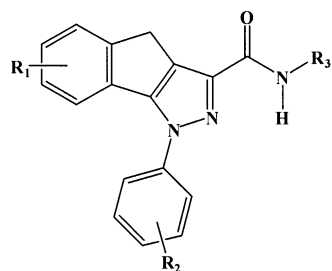
**1,4-Dihydroindeno[1,2-c]pyrazole
derivatives**

CB$_2$ receptor (K_i = 0.032 ± 0.19 nM). On the basis of these data, it is apparent that a phenolic hydroxyl group is not essential for cannabinoid activity.

To obtain selective ligands for the CB$_2$ and to explore the structure–activity relationship of the 1-deoxy-cannabinoids, the same research group described the synthesis and pharmacology of 15 1-deoxy-Δ^8-THC analogues [101]. Five of these analogues had high affinity ($K_i \leq 20$ nM) for the CB$_2$ receptor. Four of them also had low affinity for the CB$_1$ receptor ($K_i \geq 295$ nM). 3-(1',1'-Dimethylbutyl)-1-deoxy-Δ^8-THC (JWH-133) had very high affinity for the CB$_2$ receptor (K_i = 3.4 ± 1.0 nM) and low affinity for the CB$_1$ receptor (K_i = 677 ± 132 nM).

In view of the importance of the CB$_2$ receptor, three series of CB$_2$-selective cannabinoid receptor ligands, 1-methoxy-, 1-deoxy-11-hydroxy- and 11-hydroxy-1-methoxy-Δ^8-THCs, were designed [102]. All of these compounds have greater affinity for the CB$_2$ receptor than for the CB$_1$ receptor; however, only 1-methoxy-3-(1',1'-dimethylhexyl)-Δ^8-THC (JWH-229) had essentially no affinity for the CB$_1$ receptor (K_i = 3134 ± 110 nM) with high affinity for CB$_2$ (K_i = 18 ± 2 nM).

Structure 13

JWH-051   **JWH-133**

JWH-229
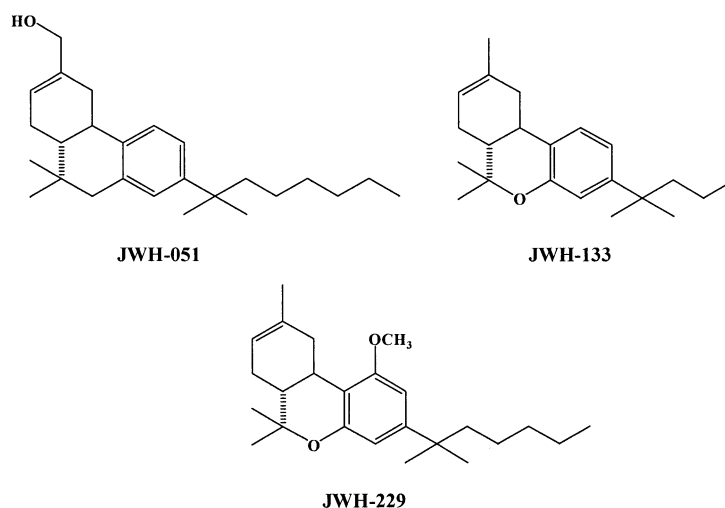
Recently the discovery of a further class of diarylpyrazolines with high potency and selectivity for the CB_1 receptor was described [103]. These compounds were found to be CB_1 antagonists. SLV319 was found to be a potent CB_1 antagonist ($K_i = 7.8$ nM) close to that of the Sanofi compound SR-141716A, with more than 1000-fold selectivity against CB_2.

Structure 14

Diarylpyrazolines   **(−)-Enantiomer**
                               (SLV319)
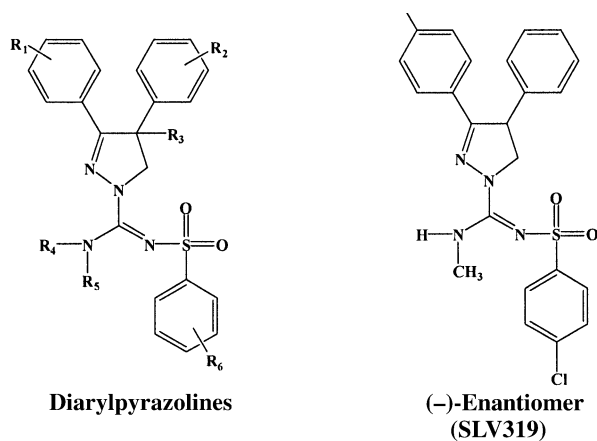
Additional synthetic compounds that bind to the CB_1 and/or CB_2 receptors have been mentioned in patents. These were recently reviewed by Hertzog [104].

Novartis AG has recently filed a patent application on a series of quinazo-lines as cannabinoid agonists useful for the treatment of pain, osteoarthritis, rheumatoid arthritis and glaucoma, among other indications [105]. Compound **1** binds to both CB_1 ($K_i = 34$ nM) and CB_2 ($K_i = 11$ nM). The patent application refers to the compound as having CB_2 agonist activity. Additionally, this compound has been shown to be active in a rodent neuropathic pain model when administered at an oral dose of 0.5 mg/kg.

Structure 15

1
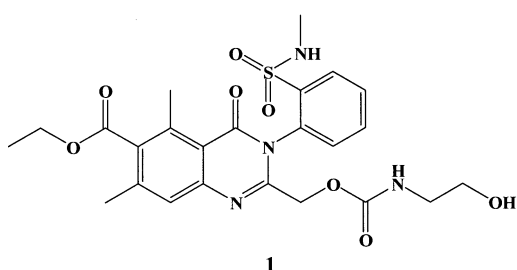
The University of Connecticut has disclosed a series of indazole derivatives that have been found to act as agonists of cannabinoid receptors [106]. The compounds exhibit a range of selectivities for CB_2 over CB_1. Compound **2**, for instance, exhibited K_i values of 2.28 and 0.309 nM for the CB_1 and CB_2 receptors, respectively. This compound produced dose-dependent anti-nociception to thermal stimulus in rats. The compound reduced locomotor activity in rats after intravenous administration, an effect attributed to activation of the CB_1 receptor.

Structure 16

2
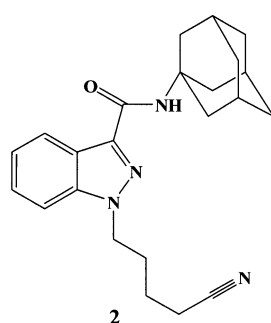
A series of aromatic CB_2 agonists has been disclosed by the Schering-Plough Research Institute [107, 108]. The compounds are reported to have anti-inflam-

matory and immunomodulatory activities, and to be active in cutaneous T cell lymphoma, diabetes mellitus and other indications. Compound **3** is stated to bind to CB_2 with a K_i value in the range 0.1–10 nM.

Structure 17
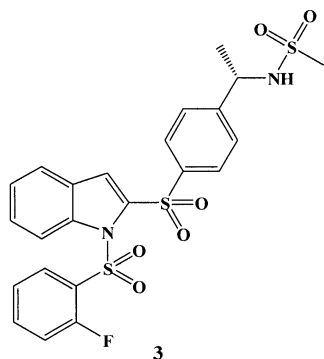
Researchers at AstraZeneca have disclosed a series of benzimidazoles and azabenzimidazoles to be CB_2 agonists [109]. The compounds are described as useful in the treatment of pain, cancer, multiple sclerosis, Parkinson's disease, Huntington's chorea, transplant rejection and Alzheimer's disease. Cannabinoid receptor selectivity data are provided for some of the new compounds. For instance, compound **4** binds to CB_2 ($K_i = 3.1$ nM) with much greater affinity than to CB_1 ($K_i = 2.8$ μM). No *in vivo* data are provided for the compounds.

Structure 18
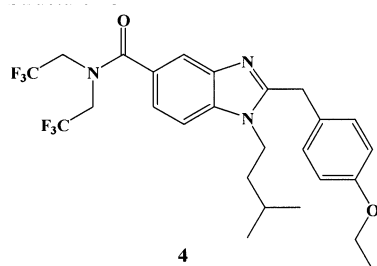
The University of Connecticut has disclosed a series of biphenyls as cannabinoid modulators [110]. These non-classical cannabinoids are described as useful for the treatment of peripheral pain, neuropathy, neurodegenerative diseases and other indications. Several of the compounds were found to bind selectively to the CB_2 receptor. For instance, compound **5** binds to CB_2 with a K_i value of 0.8 nM and to CB_1 with a K_i value of 241 nM.

Structure 19

5
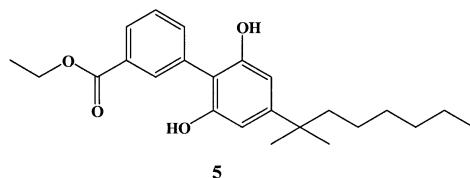
The Virginia Commonwealth University has filed a patent application on a series of resorcinol derivatives as selective CB_2 agonists useful for the treatment of pain, inflammation and autoimmune diseases [111]. Binding data for the compounds to CB_1 and CB_2 are provided, and the compounds were assayed for *in vivo* activity in mouse tail-flick, spontaneous activity and rectal temperature assays. Compound **6** had K_i values of 40 and 0.8 nM, respectively, for the CB_1 and CB_2 receptors. In addition, this compound was assessed by intravenous administration and exhibi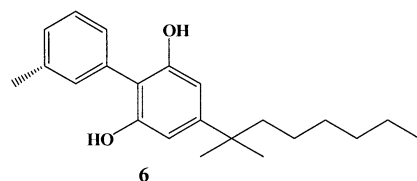ted ED_{50} values of 2.7, 2.4 and 3.6 mg/kg in the spontaneous activity, tail-flick and rectal temperature assays, respectively.

Structure 20

6

The University of Connecticut has disclosed a series of dihydrotetrazines and derivatives as CB_2 agonists [112]. Compound **7** is reported to be a potent CB_2 agonist (K_i = 19 nM) with 88-fold selectivity for the CB_2 over the CB_1 receptor. Such compounds are reported to be useful in the treatment of pain, glaucoma, multiple sclerosis, Parkinson's disease, Alzheimer's disease and other disorders.

Structure 21

7
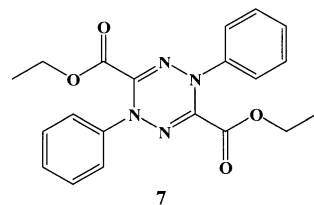
Shionogi has also disclosed two series of thiazine-containing CB_2 agonists, of which compounds **8** and **9** are examples [113, 114]. Selectivity data for several of the compounds with regard to CB_2/CB_1 affinities are described. For

example, compound **8** binds to CB_2 with a K_i value of 0.3 nM and a K_i value of >5000 nM for CB_1. Compound **9** displayed a K_i value of 1.2 nM at the CB_2 receptor and 80 nM at the CB_1 receptor. When dosed orally at 100 mg/kg in a mouse pruritis model, this compound reduced scratching by 98% relative to control animals.

Structure 22

8   **9**
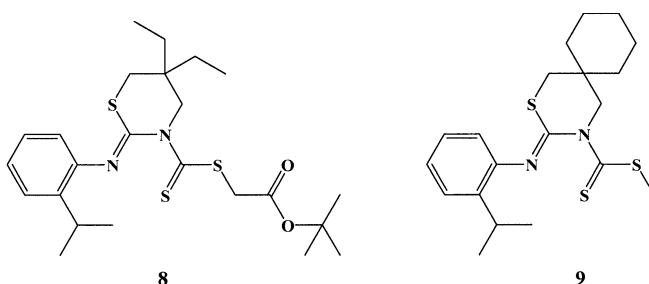
Shionogi has disclosed a series of amide-containing CB_2 modulators stated to be useful in the treatment of inflammation, nephritis, pain, allergies, rheumatoid arthritis, multiple sclerosis, brain tumors and glaucoma [115]. Compound **10** was found to bind to the CB_2 receptor with a K_i value of 4 nM, with very little affinity for CB_1 ($K_i < 5$ μM).

Structure 23

10
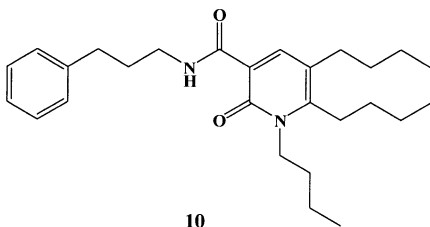
Recently 1,8-naphthyridin-4(1*H*)-on-3-carboxamide derivatives (**11**) were synthesized as new ligands of cannabinoid receptors [116]. Some of these compounds possess a greater affinity for the CB_2 receptor than for the CB_1 receptor. Compound 7-chloro-*N*-cyclohexyl-1-(2-morpholin-4-ylethyl)-1,8-naphthyridin-4(1*H*)-on-3-carboxamide (**12**) revealed a good CB_2 selectivity (CB_1, $K_i = 1$ μM; CB_2, $K_i = 25 \pm 1.8$ nM).

Indole derivatives were prepared and tested for their CB_1 and CB_2 receptor affinities [117]. Three new highly selective CB_2 receptor agonists were identified, namely JWH-120 (CB_1, $K_i = 1054 \pm 31$ nM; CB_2, $K_i = 6.1 \pm 0.7$ nM), JWH-151 (CB_1, $K_i > 10000$ nM; CB_2, $K_i = 30 \pm 1.1$ nM) and JWH-267 (CB_1, $K_i = 381 \pm 16$ nM; CB_2, $K_i = 7.2 \pm 0.14$ nM).

Structure 24

11   **12**

Structure 25

JWH-120

JWH-151   **JWH-267**
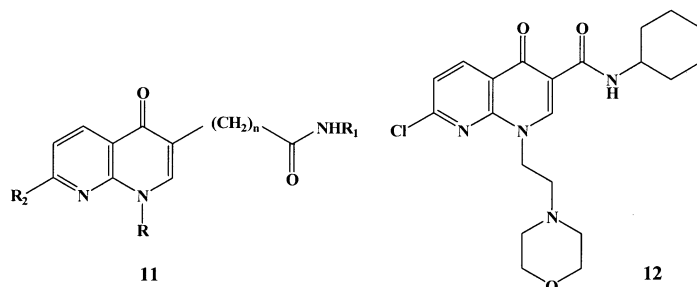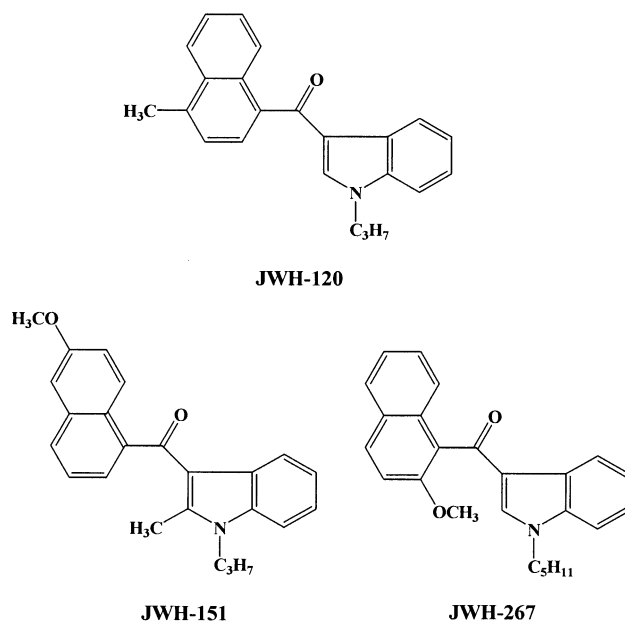
Conclusions

C. sativa L. has been used throughout history not only for its fiber, but also as a medicinal plant. It has been the object of scientific research over the past 150 years. After the isolation of the plant's constituents, biochemical work led to the identification of two receptors and of endogenous cannabinoids. Over the last decade numerous synthetic agonists and antagonists have been prepared. We may be approaching an important goal in cannabinoid research – the use of cannabinoids in medicine – which has been the dream of several generations of scientists.

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