Chapter 1

Constituents of *Cannabis Sativa*

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1.1 Introduction

Cannabis is a widely distributed plant, found in a variety of habitats and altitudes (Merlin 2003). Its use by humans goes back for over 5000 years (Farnsworth 1969) and it is one of the oldest plant sources of food and textile fiber (Kriese 2004). The cultivation of *Cannabis sativa* (*C. sativa* L.) for textile fiber originated in Western Asia and Egypt, subsequently extended to Europe, and in 1606 hemp cultivation was introduced to North America (Port Royal, Canada) (Small and Marcus 2002). Under current federal laws, it is prohibited to cultivate cannabis in the United States.

Cannabis has been indicated for the treatment of pain, glaucoma, nausea, depression, and neuralgia (Guindon and Hohmann 2009; Jarvinen et al. 2002; Liang et al. 2004; Slatkin 2007; Viveros and Marco 2007). The therapeutic value of the phytocannabinoids has also been reported for HIV/AIDS symptom management and multiple sclerosis treatment (Abrams et al. 2007; Pryce and Baker 2005).

1.2 Constituents of *Cannabis sativa* L.

The total number of natural compounds identified or isolated from *C. sativa* L. has continued to increase over the last few decades. In 1980, 423 compounds were reported in cannabis (Turner et al. 1980). This number increased in 1995 to 483 (Ross and ElSohly 1995). Between 1995 and 2005 eight compounds were added (ElSohly and Slade 2005). The main focus of this chapter is to provide a chemical account of a total of 104 cannabinoids (isolated or reported to date) as well as of the 22 noncannabinoid constituents (isolated between 2005 and 2012) (Table 1.1). This brings the total number of constituents identified in cannabis to 545 compounds.

1.2.1 Cannabinoids (104)

Today, the term "cannabinoids" refers to not only the chemical substances isolated from *C. sativa* L. exhibiting the typical C_{21} terpenophenolic skeleton, but also to their derivatives and transformation products, with the term "phytocannabinoids" coined for those originating from the plant. A total of 104 phytocannabinoids have been isolated to date (Table 1.1), classified into 11 types, namely: (–)-delta-9-*trans*-tetrahydrocannabinol (Δ^9-THC), (–)-delta-8-*trans*-tetrahydrocannabinol (Δ^8-THC), cannabigerol (CBG), cannabichromene (CBC), cannabidiol (CBD), cannabinodiol (CBND), cannabielsoin (CBE), cannabicyclol (CBL), cannabinol (CBN), cannabitriol (CBT), and miscellaneous-type cannabinoids.

Table 1.1 Constituents of *C. sativa* L. by chemical class as of the end of 2012

Chemical class	Number of compounds
Δ^9-THC type	18
Δ^8-THC type	2
CBG type	17
CBC type	8
CBD type	8
CBND type	2
CBE type	5
CBL type	3
CBN type	10
CBT type	9
Misc type	22
Total cannabinoids	**104**
Total noncannabinoids	**441**
Total	**545**

1.2.1.1 (–)-Delta-9-*trans*-tetrahydrocannabinol (Δ^9-THC) type

The structure of Δ^9-THC (*1*) was first reported by Gaoni and Mechoulam (1964a) who not only determined its absolute configuration as *trans*-(6a*R*,10a*R*), but also discussed psychotropic properties of Δ^9-THC (Δ^1-THC according to the terpenoid numbering system). A hexane extract of hashish was chromatographed on florisil to yield an active fraction which was re-chromatographed on alumina to produce Δ^9-THC. Crystalline 3,5-dinitrophenyl urethane of Δ^9-THC was prepared and mild basic hydrolysis yielded pure Δ^9-THC. Archer et al. (1970) reported the detailed conformation of Δ^9-THC using X-ray and proton magnetic resonance analysis. Δ^9-Tetrahydrocannabinol carboxylic acid A (Δ^9-THC acid A, *2*) was first isolated by Korte et al. (1965a) from a hashish extract. Pure Δ^9-THC-acid A is sensitive to light and was not capable of crystallization. Mechoulam et al. (1969) isolated a second Δ^9-THC acid present in hashish (Δ^9-THC-acid B, *3*). Hashish sole (a flat form of illicit hashish that might be rectangular- or oval-shaped) was chromatographed on silicic acid by eluting with a 1:1 ether/petroleum ether solution. Δ^9-THC-acid B was shown to be more polar than Δ^9-THC-acid A on thin layer chromatography (TLC). Hashish soles that contained Δ^9-THC-acid B had little or no Δ^9-THC-acid A which could be caused by biochemical variation. The crystal structure of Δ^9-THC-acid B was determined by Rosenqvist and Ottersen (1975). Gill (1971) isolated Δ^9-tetrahydrocannabivarin (Δ^9-THCV, *4*) from hashish by eluting with 4:1 light petroleum/ether on a column containing deactivated alumina. Countercurrent distribution was used to separate the material after obtaining an orange oil from concentrating the column fractions. The distribution resulted in three fractions in which the second fraction went through another cycle to purify Δ^9-THCV. Fetterman and Turner (1972) reported spectral evidence for Δ^9-*trans*-tetrahydrocannabivarinic acid (Δ^9-THCVA, *5*) followed by mass spectral data (Turner et al. 1973). This report on C_3 homologs of cannabinoids was based on the evaluation of 51 samples from different geographical locations. Vree et al. (1972a) identified

Δ^9-tetrahydrocannabiorcol (*6*) from an extract of Brazilian cannabis as a homologue of Δ^9-THC that contained a methyl side chain. Electron voltage-mass fragment intensity graphs from gas chromatography/mass spectrometry (GCMS) provided a mass of 258 which was the only possible isomer of Δ^9-THC that contained 56 less mass units. The Δ^9-tetrahydrocannabiorcol concentration in hashish samples was very low and, therefore, was not expected to contribute much to the biological activity of the drug. Harvey (1976) discovered Δ^9-tetrahydrocannabinol-C_4 (*7*) and detected delta-9-*trans*-tetrahydrocannabinolic acid-C_4 (Δ^9-*trans*-THCA-C_4, *8*) by GCMS in samples of cannabis. He also detected Δ^9-*trans*-tetrahydrocannabiorcolic acid (*9*). Eight new tetrahydrocannabinol type compounds namely β-fenchyl-Δ^9-tetrahydrocannabinolate (*10*), α-fenchyl-Δ^9-tetrahydrocannabinolate (*11*), *epi*-bornyl-Δ^9-tetrahydrocannabinolate (*12*), bornyl-Δ^9-tetrahydrocannabinolate (*13*), α-terpenyl-Δ^9-tetrahydrocannabinolate (*14*), 4-terpenyl-Δ^9-tetrahydrocannabinolate (*15*), α-cadinyl-Δ^9-tetrahydrocannabinolate (*16*), and γ-eudesmyl-Δ^9-tetrahydrocannabinolate (*17*) were isolated by Ahmed et al. (2008a). Their structures (Fig. 1.1) were established on the basis of nuclear magnetic resonance (NMR) spectroscopic analysis and GCMS as mono- or sesquiterpenoid esters of Δ^9-tetrahydrocannabinolic acid A, the precursor of Δ^9-THC. Under the high temperature conditions of the GCMS analysis, these compounds fragment into their two components to yield Δ^9-THC and the mono- or sesquiterpene. These cannabinoid esters were isolated from a high-potency *C. sativa* variety using multiple chromatographic techniques, including vacuum liquid chromatography (VLC), C_{18} semipreparative high-performance liquid chromatography (HPLC), and semipreparative chiral HPLC (Ahmed et al. 2008a). Cannabisol (*18*, Fig. 1.1), a dimeric cannabinoid, was isolated employing flash silica gel column chromatography from a group of illicit cannabis samples with high CBG content (Zulfiqar et al. 2012).

1.2.1.2 (–)-Delta-8-*trans*-tetrahydrocannabinol (Δ^8-THC) type

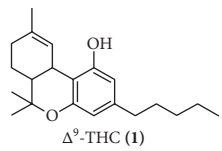
There are only two Δ^8-THC–type cannabinoids in cannabis, namely delta-8-*trans*-tetrahydrocannabinol (Δ^8-THC, *19*) and delta-8-*trans*-tetrahydrocannabinolic acid A (Δ^8-THC acid, *20*, Fig. 1.2) (Hanuŝ and Krejčí 1975; Hively et al. 1966).

Hively et al. (1966) isolated Δ^8-THC (Δ^6-THC following the terpenoid numbering system) from a petroleum ether extract of the leaves and flowering tops of marijuana grown in Maryland. In 1970, Archer et al. (1970) published detailed NMR and X-ray data on Δ^8-THC.

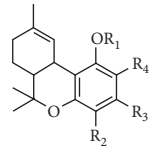
Δ^8-THC acid was isolated from *Cannabis sativa* of Czechoslovakian origin (Hanuŝ and Krejčí 1975).

1.2.1.3 Cannabigerol (CBG) type

The first compound isolated from cannabis resin in a pure form was cannabigerol (CBG-C_5, *21*) (Fig. 1.3). Gaoni and Mechoulam (1964b) were the first to isolate CBG, and reported that it is produced by the condensation of geranyl pyrophosphate with olivetol. They also found cannabigerolic acid (CBGA, *22*), identified as its methyl ester from the acidic fraction of a hashish sole extract, being the most polar acid compound (Mechoulam and Gaoni 1965). Yamauchi et al. (1968) isolated cannabigerol monomethyl ether (CBGM, *23*) by heating the acid fraction of the benzene percolate of the leaves of Minamioshihara No. 1 variety (M-1) for 7 h to obtain a phenolic mixture. Using benzene to elute the compound by column chromatography, a pale yellow substance was obtained and purified by TLC. Mass spectra confirmed that this fraction was CBG monomethyl ether with a molecular weight of 330. Shoyama et al. (1970) isolated cannabigerolic acid monomethyl ether (CBGAM, *24*) by passing M-1 percolate (free of chlorophyll) through a silica gel column with 5:1 hexane/ethyl acetate. CBGAM eluted along with Δ^9-THC-acid. This

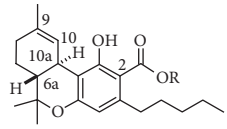


Δ^9-THC **(1)**



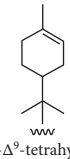
Δ^9-THC acid A
Δ^9-THC acid B
Δ^9-THCV
Δ^9-THCVA
Δ^9-tetrahydrocannabiorcol
Δ^9-tetrahydrocannbinol-C_4
Δ^9-trans-THCA-C_4
Δ^9-tetrahydrocannabiorcolic acid

(2) R_1 = H, R_2 = H, R_3 = C_5H_{11}, R_4 = COOH
(3) R_1 = H, R_2 = COOH, R_3 = C_5H_{11}, R_4 = H
(4) R_1 = H, R_2 = H, R_3 = C_3H_7, R_4 = H
(5) R_1 = H, R_2 = H, R_3 = C_3H_7, R_4 = COOH
(6) R_1 = H, R_2 = H, R_3 = CH_3, R_4 = H
(7) R_1 = H, R_2 = H, R_3 = C_4H_9, R_4 = H
(8) R_1 = H, R_2 = COOH or H, R_3 = C_4H_9, R_4 = COOH or H
(9) R_1 = H, R_2 = COOH or H, R_3 = CH_3, R_4 = COOH or H



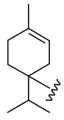
R =

β-fenchyl-Δ^9-tetrahydrocannabinolate **(10)**

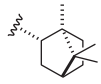


α-terpenyl-Δ^9-tetrahydrocannabinolate **(14)**

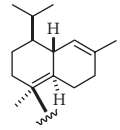
α-fenchyl-Δ^9-tetrahydrocannabinolate **(11)**



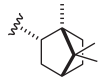
4-terpenyl-Δ^9-tetrahydrocannabinolate **(15)**



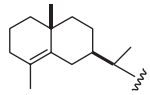
epi-bornyl-Δ^9-tetrahydrocannabinolate **(12)**



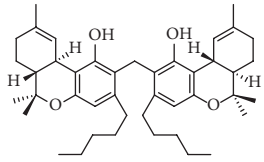
α-cadinyl-Δ^9-tetrahydrocannabinolate **(16)**



bornyl-Δ^9-tetrahydrocannabinolate **(13)**

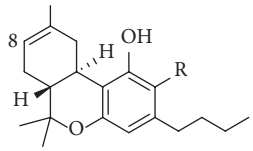


γ-eudesmyl-Δ^9-tetrahydrocannabinolate **(17)**



cannabisol **(18)**

Fig. 1.1 (–)-Δ^9-*trans*-tetrahydrocannabinol (Δ^9-THC) type cannabinoids.



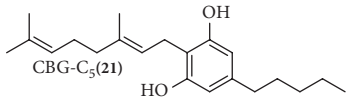
Δ^8-THC (**19**) R = H
Δ^8-THC acid (**20**) R = COOH

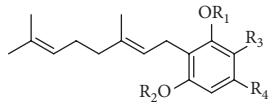
Fig. 1.2 (–)-Δ^8-*trans*-tetrahydrocannabinol (Δ^8-THC) type cannabinoids.

mixture was purified on a second column filled with silver nitrate-silica gel which resulted in pure CBGAM. Cannabigerovarin (CBGV, *25*) was also isolated by Shoyama et al. (1975) by heating the benzene extract of cannabis at 160°C for 20 min to achieve decarboxylation. Neutral cannabinoid fractions were then eluted with benzene and a mixture of (20:10:1) benzene/hexane/diethyl amine from a silica gel column. CBGV was identified by comparison with synthetic CBGV prepared by Mechoulam and Yagen (1969). Cannabigerovarinic acid (CBGVA, *26*) was isolated by Shoyama et al. as a minor component of an extract of dried leaves of Thai *Cannabis* (Shoyama et al. 1977). The acid fraction from the dried leaves was purified by column chromatography on silica gel and eluted with a hexane/ethyl acetate mixture along with a 5:1 benzene-acetone mixture. The product appeared as clear needles after recrystallization from a hexane/chloroform solution. The spectral data showed that CBGVA is the major acid of CBGV and its structure was confirmed by comparison with synthetic CBGVA. Taura et al. (1995) isolated cannabinerolic acid (*27*) from a Mexican strain of *C. sativa* by extracting the air-dried leaves with benzene and evaporating to dryness. After dissolving the residue in Me_2CO and ridding of insoluble particles, the solution was dried and loaded on a silica gel column which was eluted with a 9:1 benzene/Me_2CO mixture. The fraction containing cannabigerolic acid was chromatographed again and eluted with 3:1 hexane/ethyl acetate to give pure cannabigerolic acid.

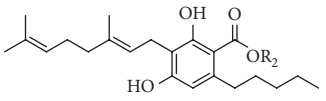
Ahmed et al. (2008a) isolated two cannabigerolic acid esters, γ-eudesmyl cannabigerolate (*28*) and α-cadinyl cannabigerolate (*29*), from *C. sativa* of high potency. The hexane extract of cannabis was purified on flash silica gel using VLC. Fractions that were shown to have compounds with higher retention factor (R_f) than that of Δ^9-THC were mixed together and chromatographed on Sephadex® LH-20 and flash silica gel. Semipreparative reversed-phase (RP) and chiral HPLC were both used for further purification from which the two esters were isolated. The spectroscopic data of γ-eudesmyl cannabigerolate and α-cadinyl cannabigerolate proved that both compounds were esters of CBGA (Radwan et al. 2008a).

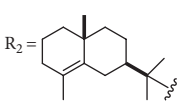
Radwan et al. (2008a, 2009) isolated six compounds (*30*–*35*), 5-acetyl-4-hydroxycannabigerol (*30*), 4-acetoxy-2-geranyl-5-hydroxy-3-*n*-pentylphenol (*31*) (±)-6,7-*trans*-epoxycannabigerolic acid (*32*), (±)-6,7-*cis*-epoxycannabigerolic acid (*33*), (±)-6,7-*cis*-epoxycannabigerol (*34*) and (±)-6,7-*trans*-epxoycannabigerol (*35*), from high-potency *C. sativa* (Fig. 1.3). Hexane extract was chromatographed on flash silica gel. Fractions close to the R_f of Δ^9-THC were combined and purified by flash silica chromatography and Sephadex® LH-20, followed by preparative C_{18} HPLC (Radwan et al. 2009). In their procedures, Appendino et al. (2008) fractionated cannabis extract on a RP C_{18} silica gel column which was followed by silica gel column chromatography and subsequent use of normal phase (NP) HPLC to isolate a novel, polar dihydroxy cannabigerol derivative (carmagerol, *36*). Pollastro et al. (2011) isolated a lipophilic analogue of cannabigerol, sesquicannabigerol (*37*), from the waxy fraction of the variety Carma of fiber hemp. Methanolic KOH was used for the hydrolysis of the wax and purification was performed by gravity silica gel column chromatography which was followed by flash chromatography over neutral alumina.

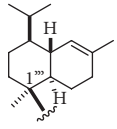




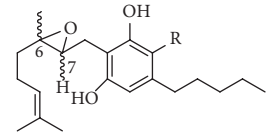
CBGA **(22)** $R_1 = H, R_2 = H, R_3 = COOH, R_4 = C_5H_{11}$
CBGM **(23)** $R_1 = CH_3, R_2 = H, R_3 = H, R_4 = C_5H_{11}$
CBGAM **(24)** $R_1 = H, R_2 = CH_3, R_3 = COOH, R_4 = C_5H_{11}$
CBGV **(25)** $R_1 = H, R_2 = H, R_3 = H, R_4 = C_3H_7$
CBGVA **(26)** $R_1 = H, R_2 = H, R_3 = COOH, R_4 = C_3H_7$
cannabinerolic acid **(27)** $R_1 = H, R_2 = H, R_3 = COOH, R_4 = C_5H_{11}$

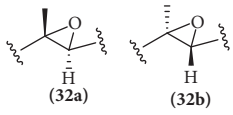






γ-eudesmyl cannabigerolate **(28)** α-cadinyl cannabigerolate **(29)**

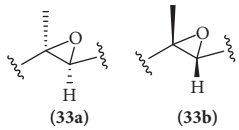




(32a) **(32b)**

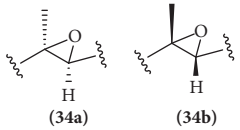
(±)-6,7-trans-epoxycannabigerolic acid

R = COOH



(33a) **(33b)**

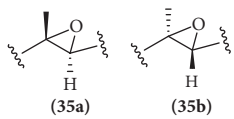
(±)-6,7-cis-epoxycannabigerolic acid



(34a) **(34b)**

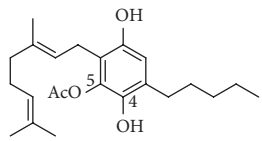
(±)-6,7-cis-epoxycannabigerol

R = H

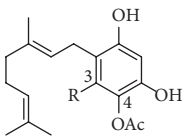


(35a) **(35b)**

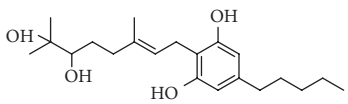
(±)-6,7-trans-epoxycannabigerol



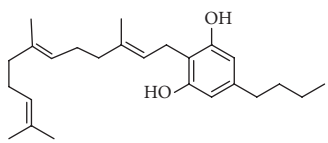
5-acetyl-4-hydroxycannabigerol **(30)**



4-acetoxy-2-geranyl-5-hydroxy-3-n-pentylphenol **(31)R=**



carmagerol **(36)**



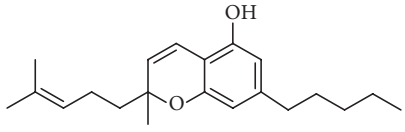
sesquicannabigerol **(37)**

Fig. 1.3 Cannabigerol (CBG) type cannabinoids.

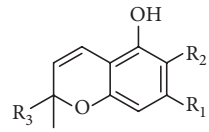
1.2.1.4 Cannabichromene (CBC) type

The research groups of Claussen et al. (1966) and Gaoni and Mechoulam (1966) independently disclosed cannabichromene (CBC-C_5, *38*). Gaoni and Mechoulam (1966) performed isolation from a hexane extract on Florisil that yielded 1.5% of CBC-C_5. Shoyama et al. (1968) isolated cannabichromenic acid (CBCA, *39*) from the benzene percolate of hemp via a procedure described by Shultz et al. (1960). A solvent system of 1:1 hexane/ethyl acetate yielded CBCA which was confirmed by NMR spectroscopy. The infrared (IR) spectra of CBCA displayed intermolecular hydrogen bonding between the carboxyl and hydroxyl groups and the structure showed similarities to that of THCA according to the location of the carboxyl group. Cannabichromevarin (CBCV, *40*) was isolated by Shoyama et al. (1975) as a brownish red cannabinoid by repeatedly passing the neutral cannabinoids from the benzene percolate of the leaves of Thai *Cannabis* through a silica gel column and eluting with benzene and 20:10:1 benzene-hexane-diethyl. Shoyama et al. (1977) also isolated cannabichromevarinic acid (CBCVA, *41*) as a minor fraction from young cannabis. The structure of natural CBCVA was confirmed by synthesis. A CBC-C_3 type compound with a 4-methyl-2-pentenyl side chain at C_2 (*42*) was separated and identified by Morita and Ando (1984).

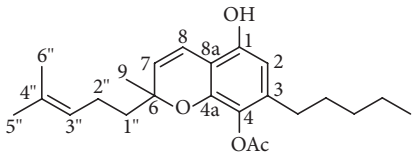
Radwan et al. (2009) reported the isolation of three new cannabichromene type cannabinoids, namely (±)-4-acetoxycannabichromene (*43*), (±)-3″-hydroxy-$\Delta^{4''}$-cannabichromene (*44*), and (–)-7-hydroxycannabichromane (*45*) from high-potency *C. sativa* by applying silica gel VLC, Si HPLC and C_{18} HPLC (Fig. 1.4).



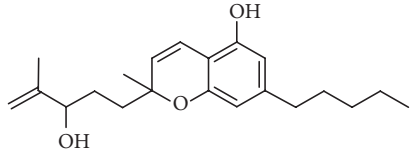
CBC-C_5 **(38)**



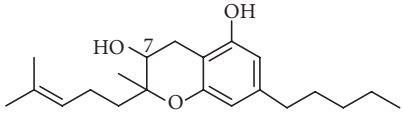
CBCA **(39)** $R_1 = C_5H_{11}$, $R_2 = COOH$, $R_3 = (CH_2)_2CH = C(CH_3)_2$
CBCV **(40)** $R_1 = C_3H_7$, $R_2 = H$, $R_3 = (CH_2)_2CH = C(CH_3)_2$
CBCVA **(41)** $R_1 = C_3H_7$, $R_2 = COOH$, $R_3 = (CH_2)_2CH = C(CH_3)_2$
CBC-C_3 **(42)** $R_1 = C_3H_7$, $R_2 = H$, $R_3 = CH_2CH = CHCH(CH_3)_2$



(±)-4-acetoxycannabichromene **(43)**



(±)-3"-hydroxy-$\Delta^{4"}$-cannabichromene **(44)**



(–)-7-hydroxycannabichromane **(45)**

Fig. 1.4 Cannabichromene (CBC) type cannabinoids.

1.2.1.5 Cannabidiol (CBD) type

Cannabidiol (CBD, *46*) and cannabidiolic acid (CBDA, *47*) are the major metabolites of the nonpsychotropic (fiber-type) varieties of *C. sativa* (Fig. 1.5). Adams et al. (1940a) isolated cannabidiol (CBD) and after allowing the oily CBD to stand for several weeks CBD was crystallized, while, Petrzilka et al. (1969) reported its synthesis and absolute configuration as (−)-*trans*-(1*R*,6*R*). Krejčí and Šantavý (1955) isolated CBDA. Vollner et al. (1969) isolated cannabidivarin (CBDV, *48*) when ligroin extract of hashish was chromatographed on silica gel. Shoyama et al. (1972a) isolated cannabidiol monomethyl ether (CBDM, *49*) by obtaining neutral cannabinoids from the ethanol extract of the leaves from Minamioshihara No. 1 variety (M-1). The cannabinoids were then chromatographed on Florisil and eluted with benzene. The eluted fraction was rechromatographed on silica gel and eluted with 3:1 hexane/benzene to obtain CBDM. Cannabidiorcol (CBD-C_1, *50*) was detected by Vree et al. (1972a) in an n-hexane extract of Lebanese hashish. In a similar extract of Brazilian marijuana, no cannabidiorcol was found. Harvey reported cannabidiol-C_4 (CBD-C_4, *51*) in 1976. Crushed cannabis resin and leaves were percolated with ethyl acetate which upon filtration and concentration gave a residue. This residue was derivatized and analyzed on GCMS. Cannabidiol-C_4 was identified by its mass and methylene unit. From a benzene extract of Thailand cannabis, cannabidivarinic acid (CBDVA, *52*) was isolated by Shoyama et al. (1977). Taglialatela-Scafati et al. (2010) recently isolated cannabimovone (*53*) as a polar cannabinoid from an acetone extract of *Cannabis sativa L.* that is nonpsychotropic.

1.2.1.6 Cannabinodiol (CBND) type

CBND-type cannabinoids are the aromatized derivatives of CBD. Cannabinodiol (CBND-C_5, *54*) and cannabinodivarin (CBND-C_3, *55*) (Fig. 1.6) are the only two compounds from this subclass that have been characterized from *C. sativa* (ElSohly and Slade 2005; Turner et al. 1980). Cannabinodiol was isolated from a hexane-ether extract of Lebanese hashish by Lousberg et al. (1977). The propyl homolog of cannabinodiol, cannabinodivarin, was detected by GCMS (Turner et al. 1980).

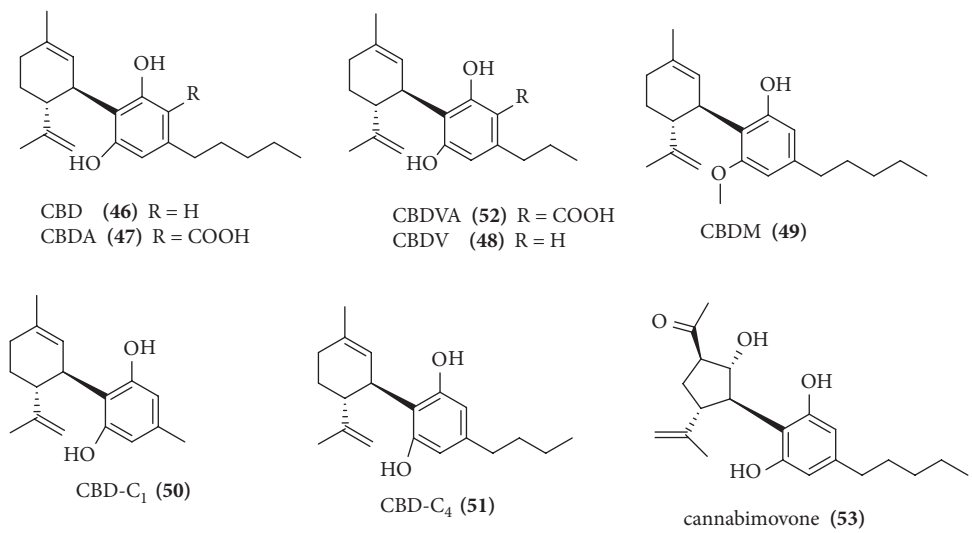
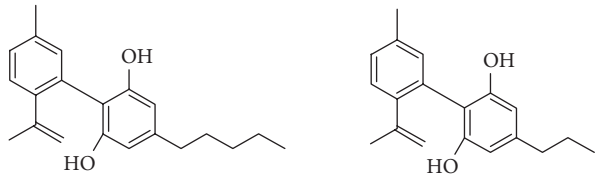


Fig. 1.5 Cannabidiol (CBD) type cannabinoids.



CBND-C_5 **(54)** CBND-C_3 **(55)**

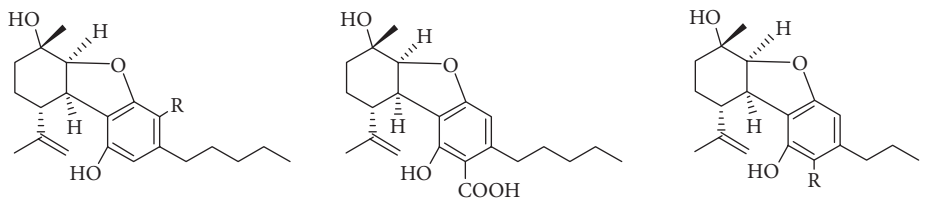
Fig. 1.6 Cannabinodiol (CBND) type cannabinoids.

1.2.1.7 Cannabielsoin (CBE) type

Five cannabielsoin-type cannabinoids named as cannabielsoin (CBE-C_5, *56*), cannabielsoic acid A (CBEA-C_5 A, *57*), cannabielsoic acid B (CBEA-C_5 B, *58*), cannabielsoin-C_3 (CBE-C_3, *59*), and cannabielsoic-C_3 acid B (CBEA-C_3 B, *60*) make up the cannabielsoin-type cannabinoids found in cannabis (Fig. 1.7). These cannabielsoin-type cannabinoids can be produced by photo-oxidation from naturally occurring CBD and CBD acids (Shani and Mechoulam 1974). Cannabielsion (CBE) was detected by Bercht et al. (1973) from an ethanolic extract of Lebanese hashish. This ethanolic extract was subjected to a 130-step counter current distribution. Uliss et al. (1974) established its structure by synthesis starting from cannabidiol diacetate. CBEA-C_5 A and CBEA-C_5 B were isolated from a benzene extract of Lebanese hashish (Shani and Mechoulam 1974). Furthermore, CBE-C_5 was also identified as a mammalian metabolite of CBD (Yamamoto et al. 1991).

1.2.1.8 Cannabicyclol (CBL) type

Cannabicyclol (CBL), cannabicyclolic acid (CBLA), and cannabicyclovarin (CBL-C_3) (Fig. 1.8) are the only compounds isolated from this subclass (Claussen et al., 1968; Korte and Sieper 1964; Mechoulam and Gaoni 1967; Shoyama et al. 1972b, 1981).

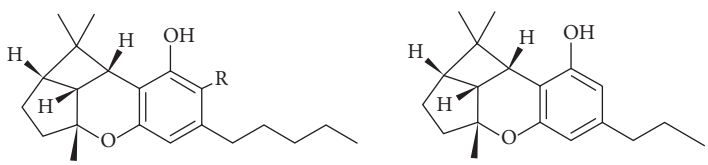


CBE-C_5 **(56)** R = H
CBEA-C_5 A **(57)** R = COOH

CBEA-C_5 B **(58)**

CBE-C_3 **(59)** R = H
CBEA-C_3 B **(60)** R = COOH

Fig. 1.7 Cannabielsoin (CBE) type cannabinoids.



CBL **(61)** R = H
CBLA **(62)** R = COOH

CBL-C_3 **(63)**

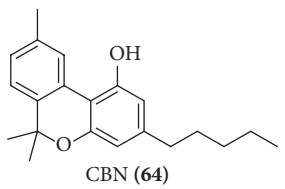
Fig. 1.8 Cannabicyclol (CBL) type cannabinoids.

CBL (*61*) was first detected by Korte and Sieper in 1964. Korte et al. (1965b) isolated CBL by TLC of various hashish and cannabis samples.

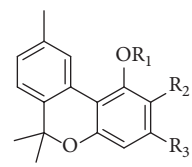
Cannabicyclolic acid (CBLA, *62*) was isolated from benzene extract of dried leaves of cannabis on a polyamide column (Shoyama et al. (1972b). Cannabicyclovarin (CBL-C_3, *63*) was identified in an ether extract of Congo marihuana by comparison of the electron voltage versus mass fragment graph for cannabicyclol and cannabicyclol-C_3 (Korte et al. 1965b).

1.2.1.9 Cannabinol (CBN) type

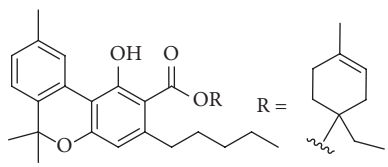
Cannabinol (CBN, *64*), was first named by Wood et al. in 1896. CBN was prepared as oil from exuded resin of Indian hemp. Later, Wood et al. (1899) acetylated this oil and obtained pure CBN as its acetate. Adams et al. (1940b) determined the correct structure of CBN. Cannabinolic acid A (CBNA, *65*) was isolated from a crude acidic fraction of hashish, which was esterified with dioazomethane and purified as its methyl ester on an acid-washed alumina column (Mechoulam and Gaoni 1965). Merkus isolated cannabivarin (CBN-C_3, *66*) from Nepalese hashish and confirmed the structure by mass spectral data (Merkus 1971a, 1971b). Cannabiorcol (*67*) was identified in the *n*-hexane extract of Brazilian marihuana and the structure was confirmed by electron voltage mass fragment intensity graphs (Vree et al. (1972a). Bercht et al. (1973) detected cannabinol methyl ether (*68*) from an ethanolic extract of Lebanese hashish. Cannabinol-C_4 (CBN-C_4, *69*) was detected by GCMS from an ethyl acetate extract of cannabis (Harvey 1976). Cannabinol-C_2 (CBN-C_2, *70*) was identified by Harvey from ethanolic extract of cannabis (Harvey 1985). Ahmed et al. (2008a) isolated 4-terpenyl cannabinolate (*71*, Fig. 1.9) from a high-potency variety of *C. sativa* through a semipreparative chiral HPLC method. When this compound was analyzed on GCMS, compound 71 fragmented to CBN and a monoterpenol. From the same variety of cannabis,



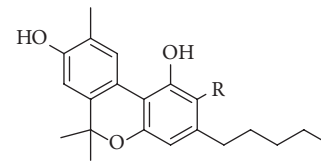
CBN (**64**)



CBNA	(**65**) $R_1 = H, R_2 = COOH, R_3 = C_5H_{11}$
CBN-C_3	(**66**) $R_1 = H, R_2 = H, R_3 = C_3H_7$
cannabiorcol	(**67**) $R_1 = H, R_2 = H, R_3 = CH_3$
cannabinol methyl ether	(**68**) $R_1 = CH_3, R_2 = H, R_3 = C_5H_{11}$
CBN-C_4	(**69**) $R_1 = H, R_2 = H, R_3 = C_4H_9$
CBN-C_2	(**70**) $R_1 = H, R_2 = H, R_3 = C_2H_5$



4-terpenyl cannabinolate (**71**)



8-OH-CBN (**72**) R = H
8-OH-CBNA (**73**) R = COOH

Fig. 1.9 Cannabinol (CBN) type cannabinoids.

8-hydroxycannabinol (8-OH-CBN, *72*) and 8-hydroxy cannabinolic acid A (8-OH-CBNA, *73*) (Fig. 1.9) were isolated (Radwan et al. 2009). Compound 72, was isolated for the first time from a natural source using C_{18} solid phase extraction (SPE) although it was prepared earlier synthetically (Novak and Salemink 1983).

1.2.1.10 Cannabitriol (CBT) type

Obata and Ishikawa (1966) reported cannabitriol, but its chemical structure was elucidated by Chan et al. (1976) while its stereochemistry was determined by X-ray analysis (McPhail et al. 1984). A total of nine CBT-type cannabinoids, (−)-*trans*-cannabitriol ((−)-*trans*-CBT-C_5, *74*), (+)-*trans*-cannabitriol ((+)-*trans*-CBT-C_5, *75*), *cis*-cannabitriol ((±)-*cis*-CBT-C_5, *76*), (−)-*trans*-10-ethoxy-9-hydroxy-$\Delta^{6a(10a)}$-tetrahydrocannabinol ((−)-*trans*-CBT-OEt-C_5, *77*), *trans*-cannabitriol-C_3 ((±)-*trans*-CBT-C_3, *78*), CBT-C_3-homologue (*79*), *trans*-10-ethoxy-9-hydroxy-$\Delta^{6a(10a)}$-tetrahydrocannabivarin-C_3 ((−)-*trans*-CBT-OEt-C_3 *80*), 8,9-dihydroxy-$\Delta^{6a(10a)}$-tetrahydrocannabinol (8-OH-CBT-C_5, *81*), and cannabidiolic acid tetrahydrocannabitriol ester (CBDA-C_5 9-O-CBT-C_5 ester, *82*) (Fig. 1.10), were reported in cannabis (Ross and ElSohly 1995). Compounds 75 and 77 were isolated from an ethanolic extract of cannabis by ElSohly et al. in 1977. The ethanolic extract was chromatographed on silica gel 60 followed by TLC grade silica gel rechromatography. Chan et al. (1976) reported specific rotation of −107° for (−)-*trans*-CBT-C_5. (+)-*Trans*-CBT-C_5 had a rotation of +7° which indicated that the isolated (+)-*trans*-CBT-C_5 was a partially racemized mixture. Compounds 76 and 81 were obtained from a hexane extract of an Indian variant by silica gel chromatography (ElSohly et al. 1978). CBDA-C_5 9-O-CBT-C_5 ester (*82*) was isolated by Von Spulak et al. (1968) from a petroleum ether extract of hashish. As ethanol was used in the isolation of the two ethoxy cannabitriols (*77* and *80*), they are most likely artifacts (ElSohly et al. 1978; Harvey 1985), possibly resulting from the reaction of ethanol with the corresponding 9,10-epoxy-derivative.

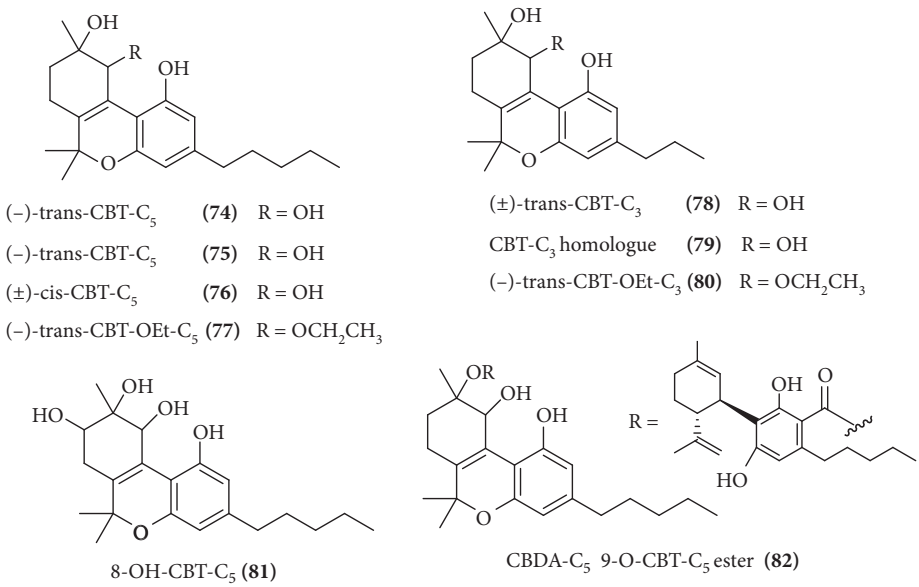
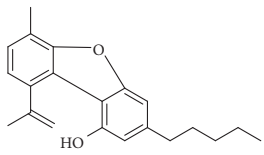
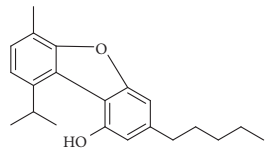


Fig. 1.10 Cannabitriol (CBT) type cannabinoids.



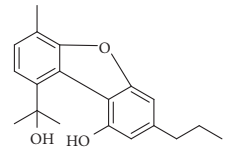
dehydrocannabifuran (DCBF-C_5)

(83)



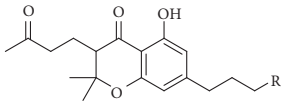
cannabifuran (CBF-C_5)

(84)

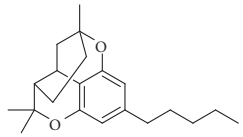


8-hydroxy-isohexahydrocannabivirin (OH-iso-HHCV-C_3)

(85)

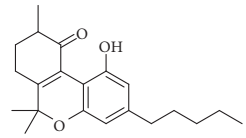


cannabichromanone-C_5 (CBCN-C5), **(86)** R = CH_2CH_3
cannabichromanone-C_3 (CBCN-C_3), **(87)** R = H



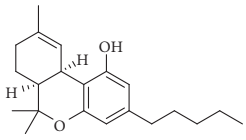
cannabicitran (CBR-C_5)

(88)

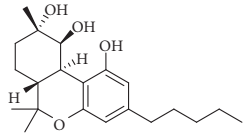


10-OXO-$\Delta^{6a(10a)}$-tetrahydrocannabinol (OTHC)

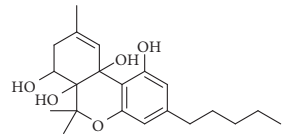
(89)



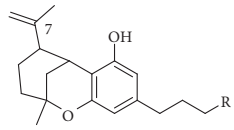
(–)-Δ^9-cis-(6aS, 10aR)-tetrahydrocannabinol (cis-Δ^9-THC) **(90)**



cannabiripsol (CBR) **(91)**



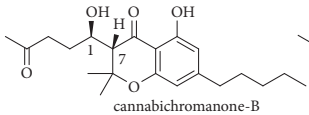
cannabitetrol (CBTT) **(92)**



(±)-Δ^7-cis-isotetrahydrocannabivarin-C_3 (Cis-iso-Δ^7-THCV), **(93)** R = H

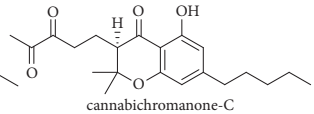
(–)-Δ^7-trans-(1R, 3R, 6R)-isotetrahydrocannabivarin-C_3 (trans-iso-7-THCV), **(94)** R = H

(–)-Δ^7-trans-(1R, 3R, 6R)-isotetrahydrocannabinol-C_5 (trans-iso-Δ^7-THCV), **(95)** R = CH_2CH_3



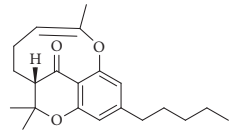
cannabichromanone-B

(96)



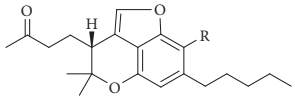
cannabichromanone-C

(97)

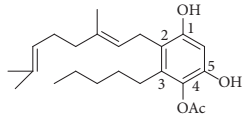


cannabichromanone-D

(98)

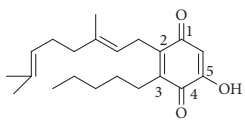


(–)-7R-cannabicourmarone, **(99)** R = H
(–)-7R-cannabicourmaronic acid, **(100)** R = COOH

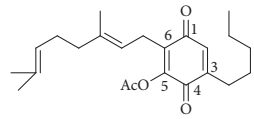


4-acetoxy-2-geranyl-5-hydroxy-3-n-pentylphenol **(101)**

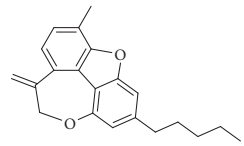
Fig. 1.11 Miscellaneous-type cannabinoids.



2-geranyl-5-hydroxy-3-n-pentyl-1,4-benzoquinone **(102)**



5-acetoxy-6-geranyl-3-n-pentyl-1,4-benzoquinone **(103)**



cannabioxepane (CBX) **(104)**

Fig. 1.11 (continued)

1.2.1.11 Miscellaneous-type cannabinoids

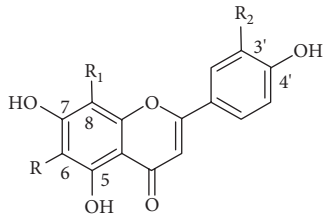
Miscellaneous-type cannabinoids discovered up to 2005 have been represented in a review by ElSohly and Slade (2005). These compounds are of diverse chemical structures. Fig. 1.11 shows the structure of these compounds as well as of additional compounds discovered after the ElSohly and Slade review (Ahmed et al. 2008b; Appendino et al. 2011; Pagani et al. 2011; Radwan et al. (2008b, 2009). Cannabichromanone-B (*96*), -C (*97*), and -D (*98*) were isolated by Ahmed et al. (2008b) from a high-potency cannabis variety, using C_{18} semipreparative HPLC. The absolute configuration was assigned on the basis of Mosher ester analysis and inspection of their circular dichroism spectra. (−)-7*R*-Cannabicoumarononic acid (*100*), 4-actoxy-2-geranyl-5-hydroxy-3-*n*-pentylphenol (*101*), and 2-geranyl-5-hydroxy-3-*n*-pentyl-1,4-benzoquinone (*102*) have been isolated from buds and leaves of the same variety of cannabis by application of several chromatographic techniques, including VLC over silica gel, solid phase extraction columns (C_{18} SPE) and NP HPLC (Radwan et al. 2009). The circular dichroism (CD) spectrum of 100 showed a positive cotton effect (CE) at 246 nm and negative CE at 295 nm, indicating a 7*R* absolute configuration. In addition, 5-acetoxy-6-geranyl-3-*n*-pentyl-1,4-benzoquinone (*103*) was isolated by employing silica gel column chromatography followed by NP HPLC (Radwan et al. 2008b). A tetracyclic cannabinoid (cannabioxepane, CBX, *104*) was recently isolated from *C. sativa*, variety carmagnole (Pagani et al. 2011).

1.2.2 Noncannabinoid constituents

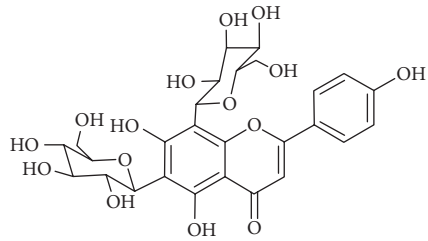
Hundreds of noncannabinoid constituents belonging to a highly diverse chemical class have been identified in/isolated from cannabis (ElSohly and Slade 2005; Ross and ElSohly 1995; Turner et al. 1980). Twenty-two noncannabinoids (*105*–*126*) belonging to eight different chemical classes have been reported since 2005. These new constituents and their chemical classes are described in the following sections (sections 1.2.2.1–1.2.2.8).

1.2.2.1 Flavonoids

Since 2005, a total of four new flavonoids (*105*–*108*) have been reported (Fig. 1.12). Radwan et al. (2008b) isolated canflavin C (*105*), chrysoeriol (*106*), and 6-prenylapigenin (*107*) from a high-potency variety of cannabis using combinations of NP and RP chromatography. The flavonoid glycoside apigenin-6,8-di-C-β-D-glucopyranoside (*108*) was isolated from the *n*-butanol fraction of the methanol extract of hemp leaves and branches (Cheng et al. 2008).



canflavin C **(105)** R= H, R1= R_2 = OMe
chrysoeriol **(106)** R= R1 = H, R_2 = OMe
6-prenylapigenin **(107)** R= $R_1 = R_2 = H$



apigenin-6,8-di-C-β-D-glucopyranoside **(108)**

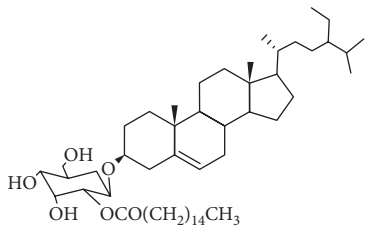
Fig. 1.12 Flavonoids.

1.2.2.2 Steroids

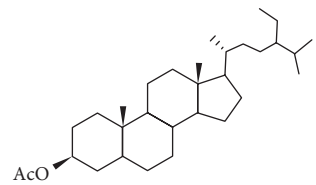
A total of four new steroids (*109–112*) have been reported since 2005 (Fig. 1.13). β-sitosteryl-3-*O*-β-D-glucopyranoside-2′-*O*-palmitate (*109*) was isolated from a high-potency variety of cannabis (Radwan et al. 2008b) using NP and RP chromatographic techniques. Cheng et al. (2008) isolated acetyl stigmasterol (*110*) and α-spinosterol (*111*) from the petroleum ether fraction of the methanol extract of the leaves and branches of hemp, while daucosterol (*112*) was isolated from the fruits of cannabis (Qian et al. 2009). Purification of the latter was carried out using silica gel column and Sephadex® LH-20 chromatography.

1.2.2.3 Phenanthrenes

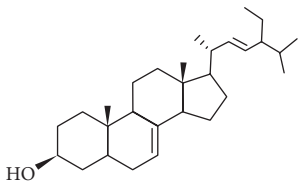
Four phenanthrene derivatives (*113–116*) have been reported since 2005 (Fig. 1.14). Radwan et al. (2008b) isolated 4,5-dihydroxy-2,3,6-trimethoxy-9,10-dihydrophenanthrene (*113*), 4-hydroxy-2,3,6,7-tetramethoxy-9,10-dihydrophenanthrene (*114*) and 4,7-dimethoxy-1,2,5-trihydroxyphenanthrene (*115*) from the ethanolic extract of a high-potency cannabis variety



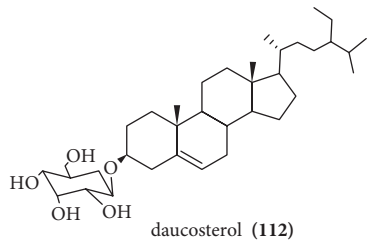
β-sitosteryl-3-O-β-D-glucopyranoside-2′-O-palamite **(109)**



acetyl stigmasterol **(110)**

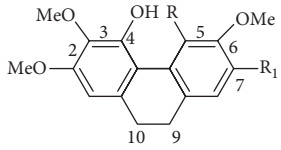


α-spinasterol **(111)**



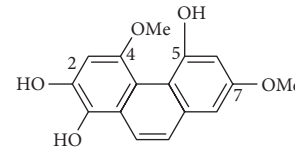
daucosterol **(112)**

Fig. 1.13 Steroids.

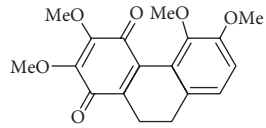


4,5-dihydroxy-2,3,6-trimethoxy-9,10-dihydroxy-phenanthrene **(113)** R=OH, R_1=H

4-hydroxy-2,3,6,7-tetramethoxy-9,10-dihydrophenanthrene **(114)** R=H, R_1=OMe



4,7-dimethoxy-1,2,5-trihydroxyphenanthrene **(115)**



9,10-dihydro-2,3,5,6-tetramethoxyphenanthrene-1,4-dione **(116)**

Fig. 1.14 Phenanthrenes.

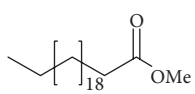
using combination of NP and RP chromatographic techniques. On the other hand, Cheng et al. (2010) isolated 9,10-dihydro-2,3,5,6-tetramethoxyphenanthrene-1,4-dione (*116*) from the leaves and branches of *C. sativa* L. by silica gel and Sephadex® LH-20 chromatography, followed by semi-preparative liquid chromatography.

1.2.2.4 Fatty acids

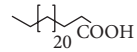
Four fatty acids were reported in cannabis since 2005 (*117–120*) (Fig. 1.15). Docosanoic acid methyl ester (*117*) was isolated from the petroleum ether fraction of the methanol extract of hemp leaves and branches (Cheng et al. 2008) and isoselachoceric acid (*118*) was isolated from the fruits of cannabis and purified by silica gel chromatography (Qian et al. 2009). In addition, two polyunsaturated hydroxyl-C18 fatty acids (*119–120*) were reported from a fiber cultivar of cannabis (variety carmagnola) and purified by RP C_{18} flash chromatography and NP HPLC (Pagani et al. 2011).

1.2.2.5 Spiroindans

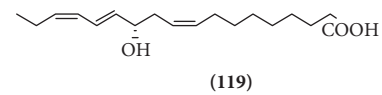
Two spiroindans (*121*, *122*) were isolated since 2005 (Fig. 1.16). Radwan et al. (2008a) isolated 7-methoxy-cannabispirone from the extract of a high-potency cannabis variety using NP chromatography followed by C_{18} HPLC, while Pagani (2011) isolated isocannabispiradienone (*122*) from the extract of a fiber cultivar.



docosanoic acid methyl ester **(117)**

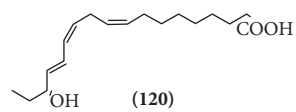


isoselachoceric acid **(118)**



(119)

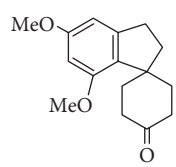
polyunsaturated hydroxy fatty acid



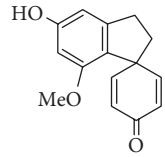
(120)

polyunsaturated hydroxy fatty acid

Fig. 1.15 Fatty acids.



7-methoxy-cannabispirone **(121)**



Isocannabispiradienone **(122)**

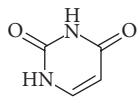
Fig. 1.16 Spiroindans.

1.2.2.6 Nitrogenous compounds

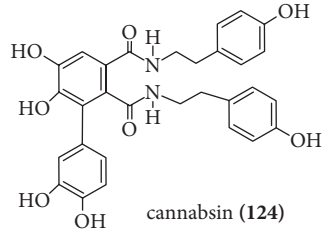
The two nitrogenous compounds isolated from cannabis since 2005 are uracil (*123*) and cannabsin (*124*) (Fig. 1.17). Uracil (*123*) was isolated from the *n*-butanol fraction of the methanolic extract of hemp leaves and branches (Cheng et al. 2008), while cannabsin (*124*) was isolated from the fruits of *C. sativa* and purified by silica gel column and Sephadex® LH-20 chromatography (Qian et al. 2009).

1.2.2.7 Xanthones

Only one xanthone derivative, 1,3,6,7-tetrahydroxy-2-C-β-D-gluco-pyranosylxanthone (*125*), was reported since 2005 (Fig. 1.18). The compound was isolated from the *n*-butanol fraction of a methanolic extract of hemp leaves and branches (Cheng et al. 2008).

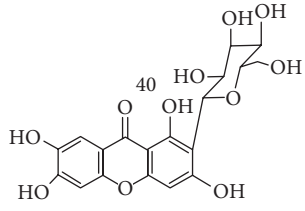


uracil **(123)**



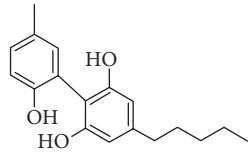
cannabsin **(124)**

Fig. 1.17 Nitrogenous compounds.



1,3,6,7-tetrahydroxy-2-C-β-D-glucopyranosyl xanthone **(125)**

Fig. 1.18 Xanthones.



5'-methyl-4-pentylbiphenyl-2,6,2'-triol **(126)**

Fig. 1.19 Biphenyls.

1.2.2.8 Biphenyls

The only biphenyl derivative reported in cannabis since 2005 is 5′-methyl-4-pentyl-2,6,2′-trihydroxybiphenyl (*126*) (Fig. 1.19), which was isolated from a high-potency cannabis variety and purified by a combination of NP chromatography and C_{18} HPLC (Radwan et al. 2008a).

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