

# WHO Expert Committee on Drug Dependence Critical Review

.....

## Isomers of THC



*This report contains the views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization*

© World Health Organization 2018

All rights reserved.

This is an advance copy distributed to the participants of the 41st Expert Committee on Drug Dependence, before it has been formally published by the World Health Organization. The document may not be reviewed, abstracted, quoted, reproduced, transmitted, distributed, translated or adapted, in part or in whole, in any form or by any means without the permission of the World Health Organization.

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

The World Health Organization does not warrant that the information contained in this publication is complete and correct and shall not be liable for any damages incurred as a result of its use.

## Acknowledgments

This report was prepared by the Secretariat of the Expert Committee on Drug Dependence (ECDD) within the Department of Essential Medicines and Health Products (EMP) of the World Health Organization (WHO), Geneva, Switzerland. The WHO staff involved in the production of this document, developed under the overall guidance of Mariângela Simão (Assistant Director General, Access to Medicines, Vaccines, and Pharmaceuticals), Suzanne Hill (Director, Essential Medicines and Health Products), Gilles Forte, (Secretary of the Expert Committee on Drug Dependence) were Dilkushi Poovendran (Technical Officer, WHO Essential Medicines and Health Products) and Wil De Zwart (Technical Officer, WHO Essential Medicines and Health Products).

This report was commissioned as a background document for a preliminary review for the 40<sup>th</sup> Expert Committee on Drug Dependence (ECDD). WHO would like to acknowledge the contributions of the following individuals who authored this report:

### *Chemistry*

Giuseppe Cannazza (University of Modena and Reggio Emilia), Italy  
Cinzia Citti (University of Modena and Reggio Emilia), Italy

### *Pharmacology*

Jenny Wiley (RTI International), USA

### *Epidemiology*

Haya Fernandez (Centre for Addiction and Mental Health), Canada  
Vidhi Thakkar (Centre for Addiction and Mental Health), Canada  
Omer S.M. Hasan (Centre for Addiction and Mental Health), Canada  
Jakob Manthey (Institute for Clinical Psychology and Psychotherapy), Germany  
Jurgen Rehm (Centre for Addiction and Mental Health), Canada  
Astrid Otto (Centre for Addiction and Mental Health), Canada  
Charlotte Probst (Centre for Addiction and Mental Health), Canada  
Julian Sauer (Centre for Addiction and Mental Health), Canada

### *Toxicology*

Jonathon Arnold (University of Sydney), Australia

### *Therapeutic Use*

Kevin P. Hill (Harvard Medical School), USA  
Judith Spahr, (Thomas Jefferson University) USA  
Charles V. Pollack. (Thomas Jefferson University) USA  
Brock Bakewell (Thomas Jefferson University), USA

The Member State questionnaire report was prepared by Jurgen Rehm, Astrid Otto, and Jakob Manthey. Technical editing was provided by Ann Morgan and Susan Kaplan. Administrative support was provided by Afrah Vogel and Christine Berling.

# Isomers of THC

## Section 1: Chemistry

## Contents

<b>1.</b>	<b>delta-6a(10a)-THC.....</b>	<b>6</b>
1.1	Substance identification.....	6
1.1.1	<i>International Nonproprietary Name (INN).....</i>	6
1.1.2	<i>Chemical Abstract Service (CAS) Registry Number.....</i>	6
1.1.3	<i>Other Chemical Names.....</i>	6
1.1.4	<i>Trade names.....</i>	6
1.1.5	<i>Street Names.....</i>	7
1.1.6	<i>Physical Appearance.....</i>	7
1.1.7	<i>WHO Review History.....</i>	7
1.2	Chemistry.....	8
1.2.1	<i>Chemical Name.....</i>	8
1.2.2	<i>Chemical Structure.....</i>	8
1.2.3	<i>Stereoisomers.....</i>	8
1.2.4	<i>Methods and Ease of Illicit Manufacturing.....</i>	9
1.2.5	<i>Chemical Properties.....</i>	10
1.2.6	<i>Solubility.....</i>	10
1.2.7	<i>Identification and Analysis.....</i>	10
1.3	Ease of Convertibility Into Controlled Substances.....	11
<b>2.</b>	<b>delta-6a(7)-THC.....</b>	<b>12</b>
2.1	Substance identification.....	12
	(9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol.....	12
2.1.1	<i>International Nonproprietary Name (INN).....</i>	12
2.1.2	<i>Chemical Abstract Service (CAS) Registry Number.....</i>	12
2.1.3	<i>Other Chemical Names.....</i>	12
2.1.4	<i>Trade names.....</i>	12
2.1.5	<i>Street Names.....</i>	12
2.1.6	<i>Physical Appearance.....</i>	12
2.1.7	<i>WHO Review History.....</i>	12
2.2	Chemistry.....	12

## Section 1: Chemistry

2.2.1	Chemical Name.....	12
2.2.2	Chemical Structure.....	13
2.2.3	Stereoisomers .....	13
2.2.4	Methods and Ease of Illicit Manufacturing .....	13
2.2.5	Chemical Properties .....	13
2.2.6	Identification and Analysis .....	14
2.3	Ease of Convertibility Into Controlled Substances.....	14
<b>3.</b>	<b>delta-7-THC.....</b>	<b>15</b>
3.1	Substance identification .....	15
3.1.1	International Nonproprietary Name (INN).....	15
3.1.2	Chemical Abstract Service (CAS) Registry Number .....	15
3.1.3	Other Chemical Names .....	15
3.1.4	Trade names .....	15
3.1.5	Street Names .....	15
3.1.6	Physical Appearance .....	15
3.1.7	WHO Review History.....	15
3.2	Chemistry .....	15
3.2.1	Chemical Name.....	15
3.2.2	Chemical Structure.....	16
3.2.3	Stereoisomers .....	16
3.3	Methods and Ease of Illicit Manufacturing.....	17
3.4	Chemical Properties .....	17
3.4.1	Melting point .....	17
3.4.2	Boiling point.....	17
3.4.3	Solubility .....	17
3.5	Identification and Analysis.....	17
3.6	Ease of Convertibility Into Controlled Substances.....	17
<b>4.</b>	<b>delta-8-THC.....</b>	<b>19</b>
4.1	Substance identification .....	19
	(6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6Hdibenzo[b,d]pyran-1-ol .....	19
4.1.1	International Nonproprietary Name (INN).....	19

## Section 1: Chemistry

4.1.2	Chemical Abstract Service (CAS) Registry Number .....	19
4.1.3	Other Chemical Names .....	19
4.1.4	Trade names .....	21
4.1.5	Street Names .....	21
4.1.6	Physical Appearance .....	21
4.1.7	WHO Review History .....	21
4.2	Chemistry .....	21
4.2.1	Chemical Name .....	21
4.2.2	Chemical Structure .....	21
4.2.3	Stereoisomers .....	22
4.2.4	Methods and Ease of Illicit Manufacturing .....	25
4.2.5	Other Names .....	25
4.2.6	Other Names .....	26
4.2.7	Methods and Ease of Illicit Manufacturing .....	26
4.2.8	Chemical Properties .....	28
4.2.9	Identification and Analysis .....	29
4.3	Ease of Convertibility Into Controlled Substances .....	30
5.	<b>delta-10-THC.....</b>	<b>31</b>
5.1	Substance identification .....	31
5.1.1	International Nonproprietary Name (INN) .....	31
5.1.2	Chemical Abstract Service (CAS) Registry Number .....	31
5.1.3	Other Chemical Names .....	31
5.1.4	Trade names .....	31
5.1.5	Street Names .....	31
5.1.6	Physical Appearance .....	31
5.1.7	WHO Review History .....	31
5.2	Chemistry .....	32
5.2.1	Chemical Name .....	32
5.2.2	Chemical Structure .....	32
5.2.3	Stereoisomers .....	32
5.2.4	Methods and Ease of Illicit Manufacturing .....	33

## Section 1: Chemistry

5.2.5	<i>Chemical Properties</i> .....	33
5.2.6	<i>Identification and Analysis</i> .....	34
5.3	Ease of Convertibility Into Controlled Substances.....	34
<b>6.</b>	<b>delta-9(11)-THC.....</b>	<b>35</b>
6.1	Substance identification .....	35
6.1.1	<i>International Nonproprietary Name (INN)</i> .....	35
6.1.2	<i>Chemical Abstract Service (CAS) Registry Number</i> .....	35
6.1.3	<i>Other Chemical Names</i> .....	35
6.1.4	<i>Trade names</i> .....	35
6.1.5	<i>Street Names</i> .....	35
6.1.6	<i>Physical Appearance</i> .....	35
6.1.7	<i>WHO Review History</i> .....	36
6.2	Chemistry .....	36
6.2.1	<i>Chemical Name</i> .....	36
6.2.2	<i>Chemical Structure</i> .....	36
6.2.3	<i>Stereoisomers</i> .....	36
6.2.4	<i>Methods and Ease of Illicit Manufacturing</i> .....	37
6.2.5	<i>Chemical Properties</i> .....	37
6.2.6	<i>Identification and Analysis</i> .....	37
6.3	Ease of Convertibility Into Controlled Substances.....	37
<b>7.</b>	<b>REFERENCES.....</b>	<b>38</b>



# 1. delta-6a(10a)-THC

---

## 1.1 Substance identification

7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol

### 1.1.1 International Nonproprietary Name (INN)

N/A

### 1.1.2 Chemical Abstract Service (CAS) Registry Number

7663-50-5

### 1.1.3 Other Chemical Names<sup>1</sup>

- (±)- $\Delta^3$ -Tetrahydrocannabinol<sup>2(B)</sup>
- (±)- $\Delta^{6a,10a}$ -Tetrahydrocannabinol<sup>2(A)</sup>
- Cannabinol,  $\Delta^3$ -tetrahydro-<sup>2(B)</sup>
- EA 1477
- $\Delta^3$ -Tetrahydrocannabinol<sup>2(B)</sup>
- $\Delta^{6a,10a}$ -tetrahydrocannabinol<sup>2(A)</sup>

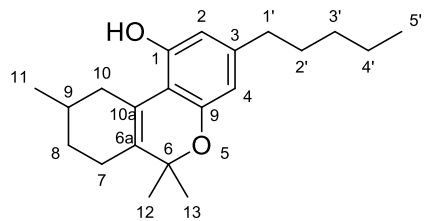
### 1.1.4 Trade names

N/A

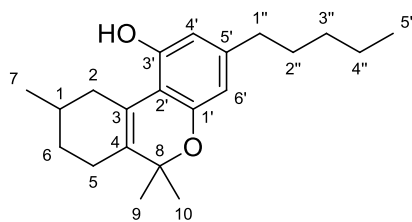
---

<sup>1</sup> Reported by Chemical Abstract Service (CAS).

<sup>2</sup> Alternate numbering systems: (A) "Dybenzopyran"; (B) "Monoterpenoid"



(A)  
Delta-6a(10a)-THC



(B)  
Delta-3-THC

=

## Section 1: Chemistry

### 1.1.5 Street Names

N/A

### 1.1.6 Physical Appearance

The first description of the synthesis of ( $\pm$ )- $\Delta^{6a,10a}$ -THC by Adams et al. in 1947 describes the compound as a viscous oil that solidifies on standing and may be purified by recrystallization from glacial acetic acid forming white crystals [1].

In 1984 Srebnik et al. synthesized each enantiomer of ( $\pm$ )- $\Delta^{6a,10a}$ -THC described as an oil [2].

### 1.1.7 WHO Review History

The following isomers of  $\Delta^9$ -THC and their stereochemical variants:

- 7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol (or  $\Delta^{6a,10a}$ -THC)
- (9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol (or  $\Delta^{6a,7}$ -THC)
- (6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol (or  $\Delta^7$ -THC)
- (6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol (or  $\Delta^8$ -THC)
- 6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol (or  $\Delta^{10}$ -THC)
- (6aR,10aR)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6H-dibenzo[b,d]pyran-1-ol (or  $\Delta^{9,11}$ -THC)

were included in Schedule I of the 1971 Convention on Psychotropic Substances.

These constitutional isomers of delta-9-THC were never subject to a critical review and are still in schedule I of the 1971 Convention.

## Section 1: Chemistry

### 1.2 Chemistry

#### 1.2.1 Chemical Name

IUPAC Name:

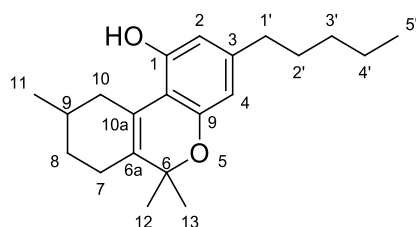
7,8,9,10-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol

CA Index Name:

6H-Dibenzo[b,d]pyran-1-ol, 7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-

#### 1.2.2 Chemical Structure

Free base:



Molecular Formula:

$C_{21}H_{30}O_2$

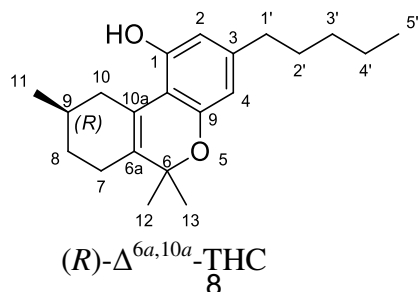
Molecular Weight:

314.46

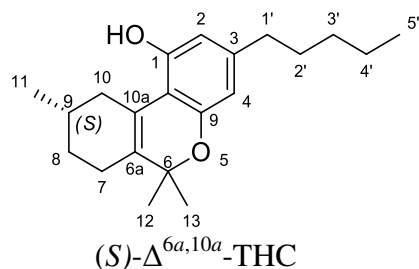
#### 1.2.3 Stereoisomers

The compound has one stereogenic carbon atom and two stereoisomers can be present. Two stereoisomers are known:

- 1) CA Index Name: 6H-Dibenzo[b,d]pyran-1-ol,7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-,(R)- (9CI) [CAS Registry Number: 95720-01-7]



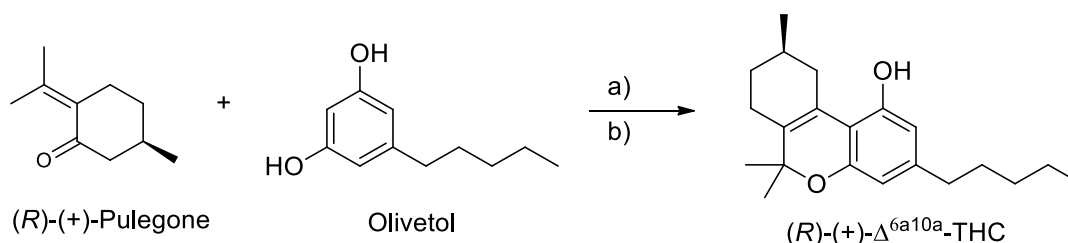
- 2) CA Index Name: 6H-Dibenzo[b,d]pyran-1-ol,7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-,(S)- (9CI) [CAS Registry Number: 95720-02-8]



#### 1.2.4 Methods and Ease of Illicit Manufacturing

$\Delta^{6a,10a}$ -THC is not a naturally occurring cannabinoid and is generally obtained by chemical synthesis. The condensation between olivetol and pulegone under acid catalysis for the preparation of  $\Delta^{6a,10a}$ -THC in its racemic form was investigated in the early 1940s [3-6].

The synthesis and isolation of (R)-(+)- $\Delta^{6a,10a}$ -THC and (S)-(-)- $\Delta^{6a,10a}$ -THC was achieved in 1984 [2]. The method used the single enantiomers of  $\Delta^{10}$ -THC<sup>1</sup>, (9R,6aR)- $\Delta^{10}$ -THC and (9S,6aR)- $\Delta^{10}$ -THC, as starting material that isomerized in toluene-p-sulphonic acid in benzene to lead to (R)-(+)- $\Delta^{6a,10a}$ -THC and (S)-(-)- $\Delta^{6a,10a}$ -THC, respectively. More recently, Rosati et al. developed a one-pot microwave assisted synthesis of (R)-(+)- $\Delta^{6a,10a}$ -THC and (S)-(-)- $\Delta^{6a,10a}$ -THC starting from single enantiomers of pulegone condensed with olivetol (scheme1) under Ytterbium triflate-ascorbic acid catalysis [7].



<sup>1</sup> ( $\pm$ )- $\Delta^{10}$ -THC is in Schedule I of the 1971 Convention.

## Section 1: Chemistry

### Scheme 1

Reagents and conditions: a)  $\text{POCl}_3$  (33 mol %), benzene, reflux, 4h b) Ytterbium triflate-ascorbic acid [YTACA 1:10],  $\text{ClCH}_2\text{CH}_2\text{Cl}$ , 120 min,  $150^\circ\text{C}$

Hollister et al. tested the two enantiomers (R)-(+)- $\Delta^{6a,10a}$ -THC and (S)-(-)- $\Delta^{6a,10a}$ -THC in man for psychoactivity. (S)-(-)- $\Delta^{6a,10a}$ -THC in man had psychic actions similar to those of  $\Delta^9$ -THC but quantitatively less potent (1:3 to 1:6), while the (R)-(+)- $\Delta^{6a,10a}$ -THC was inactive [8].

#### 1.2.5 Chemical Properties

Melting point

About  $72\text{-}73^\circ\text{C}$  [1]

Boiling point

$175\text{-}180^\circ\text{C}$  at 0.02 Torr [1]

#### 1.2.6 Solubility

N/A

#### 1.2.7 Identification and Analysis

Identification of pure enantiomers (R)-(+)- $\Delta^{6a,10a}$ -THC and (S)-(-)- $\Delta^{6a,10a}$ -THC was described by Srebnik et al. reporting optical rotations, UV, IR, NMR and MS spectra [2].

There are few analytical methods for the analysis of  $\Delta^{6a,10a}$ -THC reported in the literature:

1. A gas chromatographic method coupled to mass spectrometry detection (GC-MS) [9]
2. A gas chromatographic (GC) method [10]
3. A micro-analytical determination of  $\Delta^{6a,10a}$ -THC was effected by thin layer chromatography (TLC) (color former: Fast Blue salt B,  $\text{H}_2\text{PtCl}_6\text{-KI}$  or 1%  $\text{KMnO}_4$  solution), GC (3 mm  $\times$  2 m column, silicone SE-30, OV-1, polyethylene glycol 20M,  $130\text{-}270^\circ\text{C}$ ), high performance liquid chromatography (styrene-divinylbenzene polymer, detection at 274 or 258 nm)

## Section 1: Chemistry

(HPLC-UV) and microcrystal test (crystallization from 3% AcOH solution and detection on polarization microscope) [11].

4. Nine different cannabinoids (including  $\Delta^{6a,10a}$ -THC) were converted to their 1-dimethylaminonaphthalene-5-sulfonates. Mixtures of the fluorescent-labeled cannabinoids were separated by TLC and individual spots were detectable at the 0.5 nanogram level. This sensitivity appeared adequate to develop an assay for biotransformation products of cannabinoids in human urine after the smoking of a single cigarette [12].

The methods above are able to distinguish between  $\Delta^{6a,10a}$ -THC and  $\Delta^8$ -THC/  $\Delta^9$ -THC.

### 1.3 Ease of Convertibility Into Controlled Substances

N/A

## 2. delta-6a(7)-THC

---

### 2.1 Substance identification

(9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol

#### 2.1.1 International Nonproprietary Name (INN)

N/A

#### 2.1.2 Chemical Abstract Service (CAS) Registry Number

59042-44-3

#### 2.1.3 Other Chemical Names

N/A

#### 2.1.4 Trade names

N/A

#### 2.1.5 Street Names

N/A

#### 2.1.6 Physical Appearance

Viscous oil [13].

#### 2.1.7 WHO Review History

See data reported for  $\Delta^{6a,10a}$ -THC.

## 2.2 Chemistry

### 2.2.1 Chemical Name

IUPAC Name:

(9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol

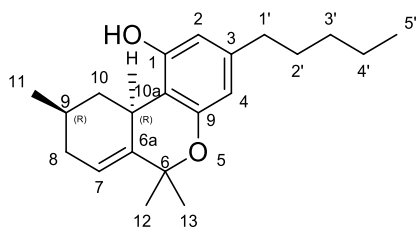
## Section 1: Chemistry

CA Index Name:

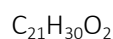
6H-Dibenzo[b,d]pyran-1-ol, 8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, (9R-trans)- (9CI)

### 2.2.2 Chemical Structure

Free base:



Molecular Formula:



Molecular Weight:

314.46

### 2.2.3 Stereoisomers

The compound has two stereogenic carbon atoms and four stereoisomers can be present.

Only the (9R,10aR)- 8,9,10,10a-tetrahydro-6,6,9-trimethyl-1-pentyl-6H-Dibenzo[b,d]pyran-3-ol was described in the literature [13].

### 2.2.4 Methods and Ease of Illicit Manufacturing

Arnone et al reported the synthesis of (9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol by condensation of olivetol with p-menth-4-en-3,8-diol in toluene-p-sulphonic acid at room temperature for two days [13].

### 2.2.5 Chemical Properties

Melting point

N/A



## Section 1: Chemistry

Boiling point

N/A

Solubility

N/A

### **2.2.6 Identification and Analysis**

(9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol was characterized for its UV, NMR, optical rotatory power and MS properties [13]. The analyses were carried out on the pure compound: neither sample pre-treatment nor chromatographic method were set up or developed [13].

### **2.3 Ease of Convertibility Into Controlled Substances**

N/A

### 3. delta-7-THC

---

#### 3.1 Substance identification

(6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6Hdibenzo[b,d]pyran-1-ol

##### 3.1.1 International Nonproprietary Name (INN)

N/A

##### 3.1.2 Chemical Abstract Service (CAS) Registry Number

42793-13-5

##### 3.1.3 Other Chemical Names

N/A

##### 3.1.4 Trade names

N/A

##### 3.1.5 Street Names

N/A

##### 3.1.6 Physical Appearance

Pale yellow oil [14, 15].

##### 3.1.7 WHO Review History

See data reported for  $\Delta^{6a,10a}$ -THC.

#### 3.2 Chemistry

##### 3.2.1 Chemical Name

IUPAC Name:

(6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6Hdibenzo[b,d]pyran-1-ol

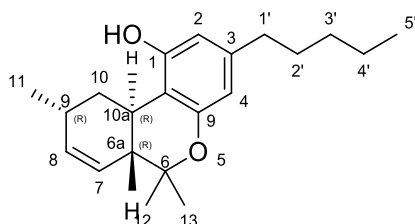
## Section 1: Chemistry

CA Index Name:

6H-Dibenzo[b,d]pyran-1-ol, 6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, [6aR-(6a $\alpha$ , 9 $\beta$ ,10a $\beta$ )]- (9CI)

### 3.2.2 Chemical Structure

Free base:



Molecular Formula:

$C_{21}H_{30}O_2$

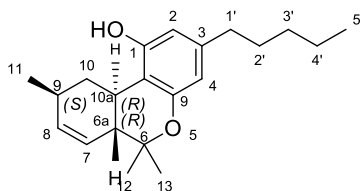
Molecular Weight:

314.46

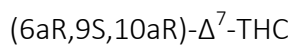
### 3.2.3 Stereoisomers

The compound has three stereogenic carbon atoms and eight stereoisomers can be present. The (6aR,9S,10aR)-  $\Delta^7$ -THC epimer is known:

- 1) CA Index Name: 6H-Dibenzo[b,d]pyran-1-ol, 6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, [6aR-(6a $\alpha$ ,9 $\alpha$ ,10a $\beta$ )]- (9CI) [CAS Registry Number: 162678-94-6]



## Section 1: Chemistry



A stereoselective synthesis was described to obtain the two epimers. Only the (6aR,9S,10aR)- $\Delta^7$ -THC epimer was only slightly less active than delta-9-THC in vitro and in vivo [15].

### 3.3 Methods and Ease of Illicit Manufacturing

N/A

### 3.4 Chemical Properties

#### 3.4.1 *Melting point*

N/A

#### 3.4.2 *Boiling point*

N/A

#### 3.4.3 *Solubility*

N/A

### 3.5 Identification and Analysis

N/A

### 3.6 Ease of Convertibility Into Controlled Substances

N/A

## 4. delta-8-THC

---

### 4.1 Substance identification

(6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6Hdibenzo[b,d]pyran-1-ol

#### 4.1.1 International Nonproprietary Name (INN)

N/A

#### 4.1.2 Chemical Abstract Service (CAS) Registry Number

5957-75-5

#### 4.1.3 Other Chemical Names<sup>1</sup>

- 6H-Dibenzo[b,d]pyran-1-ol, 6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6aR-trans)-<sup>2(A)</sup>
- 6H-Dibenzo[b,d]pyran-1-ol, 6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, trans-(-)- (8CI) <sup>2(A)</sup>
- (6aR,10aR)-6a,7,10,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol<sup>2(A)</sup>
- (-)-trans- $\Delta^8$ -Tetrahydrocannabinol<sup>2(A)</sup>
- (-)- $\Delta^8$ -6a,10a-trans-Tetrahydrocannabinol<sup>2(A)</sup>
- (-)- $\Delta^8$ -THC<sup>2(A)</sup>
- (-)- $\Delta^8$ -Tetrahydrocannabinol<sup>2(A)</sup>
- (-)- $\Delta^8$ -trans-Tetrahydrocannabinol<sup>2(A)</sup>
- $\Delta^8$ -trans-Tetrahydrocannabinol<sup>2(A)</sup>
- $\Delta^8$ -THC<sup>2(A)</sup>
- $\Delta^8$ -Tetrahydrocannabinol<sup>2(A)</sup>
- $\Delta^8$ -l-Tetrahydrocannabinol<sup>2(A)</sup>
- D8-THC<sup>2(A)</sup>
- Delta-8-Tetrahydrocannabinol<sup>2(A)</sup>

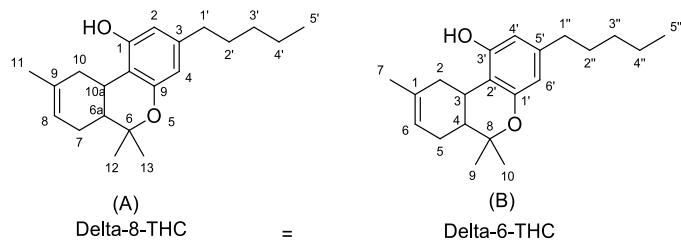
---

<sup>1</sup> Reported by Chemical Abstract Service (CAS).

## Section 1: Chemistry

- l- $\Delta^8$ -Tetrahydrocannabinol<sup>2(A)</sup>
- trans- $\Delta^8$ -Tetrahydrocannabinol<sup>2(A)</sup>
- Cannabinol,  $\Delta^1(6)$ -tetrahydro-<sup>2(B)</sup>
- $\Delta^1(6)$ -Tetrahydrocannabinol<sup>2(B)</sup>
- $\Delta^1(6)$ -trans-Tetrahydrocannabinol<sup>2(B)</sup>
- $\Delta^6$ -Tetrahydrocannabinol<sup>2(B)</sup>
- (-)- $\Delta^6$ -Tetrahydrocannabinol<sup>2(B)</sup>
- NSC 134453

<sup>2</sup> Alternate numbering systems: (A) "Dybenzopyran"; (B) "Monoterpenoid"



## Section 1: Chemistry

### 4.1.4 Trade names

N/A

### 4.1.5 Street Names

N/A

### 4.1.6 Physical Appearance

Gaoni et al. described the compound as an oil with an optical rotation value  $[\alpha]_D^{25} -245$  (CHCl<sub>3</sub>) [16].

Ballerini et al. described the compound as a colorless oil with an  $[\alpha]_D^{25} -245$  (c. 0.78, CHCl<sub>3</sub>) [17].

Rosenkrantz et al. described the pure compound (98-99 % purity by gas chromatography (GC)) as “highly viscous oils, virtually of a glue nature at room temperature” with an “optical rotation values from –254 to –268” [18].

### 4.1.7 WHO Review History

See data reported for  $\Delta^{6a,10a}$ -THC.

## 4.2 Chemistry

### 4.2.1 Chemical Name

#### 4.2.1.1 IUPAC Name:

(6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6Hdibenzo[b,d]pyran-1-ol

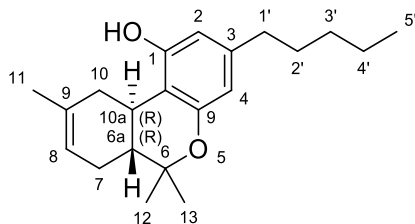
#### 4.2.1.2 CA Index Name:

6H-Dibenzo[b,d]pyran-1-ol, 6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6aR, 10aR)-

### 4.2.2 Chemical Structure

Free base:

## Section 1: Chemistry



Molecular Formula:



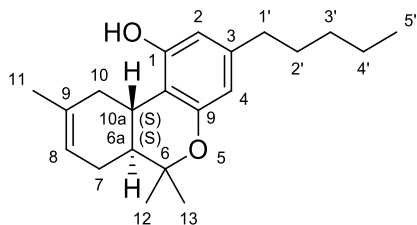
Molecular Weight:

314.46

### 4.2.3 Stereoisomers

The compound has two stereogenic carbon atoms and four stereoisomers can be present. The following stereoisomers are reported in the literature:

- 1) CA Index Name: 6H-Dibenzo[b,d]pyran-1-ol,6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-,(6aS,10aS)- [CAS Registry Number: 33029-18-4]



#### 4.2.3.1 Other Names<sup>1</sup>

- 6H-Dibenzo[b,d]pyran-1-ol, 6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-,(6aS-trans)<sup>2(A)</sup>
- 6H-Dibenzo[b,d]pyran-1-ol, 6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-,(6aS-trans)-<sup>2(A)</sup>

---

<sup>1</sup> Reported by Chemical Abstract Service (CAS).

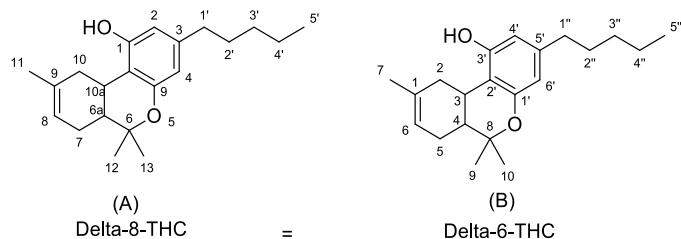


## Section 1: Chemistry

- 6H-Dibenzo[b,d]pyran-1-ol, 6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-,trans-(+)- (8Cl)<sup>2(A)</sup>
- (6aS,10aS)-6a,7,10,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol<sup>2(A)</sup>
- (+)- $\Delta^6$ -Tetrahydrocannabinol<sup>2(B)</sup>
- (+)- $\Delta^8$ -THC<sup>2(A)</sup>
- (+)- $\Delta^8$ -Tetrahydrocannabinol<sup>2(A)</sup>
- d- $\Delta^8$ -Tetrahydrocannabinol<sup>2(A)</sup>

---

<sup>2</sup> Alternate numbering systems: (A) "Dybenzopyran"; (B) "Monoterpenoid"



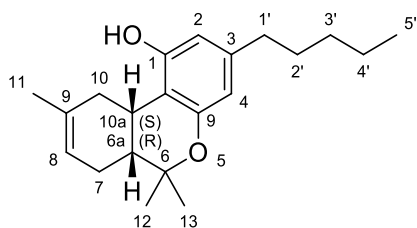


#### 4.2.4 Methods and Ease of Illicit Manufacturing

In the literature are described few syntheses of (+)-trans- $\Delta^8$ -THC [17, 19-21].

The most feasible preparation is that reported in 1967 by Mechoulam et al. [19], where (+)-trans- $\Delta^8$ -THC was obtained from the condensation of a pinane derivative, verbenol, with olivetol in the presence of acid catalysts. Hence, in the presence of toluene-p-sulphonic acid in methylene chloride, (+)-trans-verbenol condensed with olivetol to give 4-trans-(2-olivetyl)pinene that, after chromatographic purification, gave (+)-trans- $\Delta^8$ -THC (80% yield) upon treatment with boron trifluoride etherate in methylene chloride at room temperature.

- 2) CA Index Name: 6H-Dibenzo[b,d]pyran-1-ol, 6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6aR,10aS)- [CAS Registry Number: 65634-24-4]



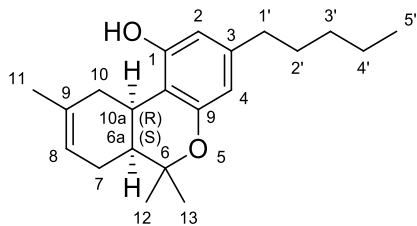
#### 4.2.5 Other Names<sup>1</sup>

- 6H-Dibenzo[b,d]pyran-1-ol, 6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6aR-cis)-
- (6aR,10aS)-6a,7,10,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol

- 3) CA Index Name: 6H-Dibenzo[b,d]pyran-1-ol, 6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6aS,10aR)- [CAS Registry Number: 185752-04-9]

---

<sup>1</sup> Reported by Chemical Abstract Service (CAS).



#### 4.2.6 Other Names<sup>1</sup>

- 6H-Dibenzo[b,d]pyran-1-ol, 6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6aS-cis)-
- (6aS,10aR)-6a,7,10,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol

#### 4.2.7 Methods and Ease of Illicit Manufacturing

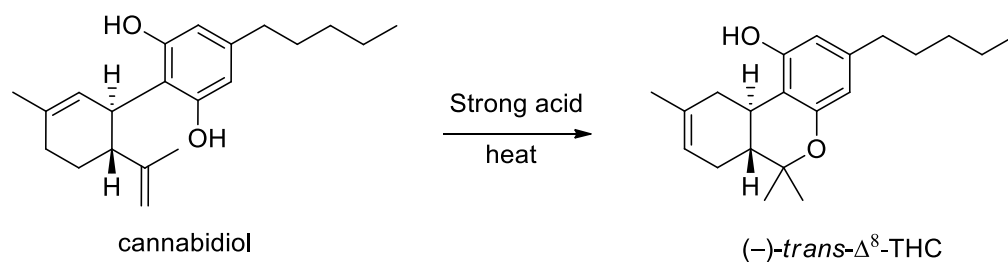
(-)-trans- $\Delta^8$ -THC isomer is a minor active compound in cannabis occurring only in trace amounts, if at all (reported range of the ratio of (-)-trans- $\Delta^9$ -THC to (-)-trans- $\Delta^8$ -THC varied from 99.9:0.1 to 98.6:1.2) [22], although (-)-trans- $\Delta^8$ -THC isomer is notably more stable than its isomer (-)-trans- $\Delta^9$ -THC and persists in old material since it has even been found in a burial tomb dating from the fourth century B.C. [23, 24]. Concerns have been raised about the real natural origin of (-)-trans- $\Delta^8$ -THC suggesting that it should be artifacts resulting from (-)-trans- $\Delta^9$ -THC by acid- or oxidatively promoted shift of the endocyclic double bond [24].

Since (-)-trans- $\Delta^8$ -THC occurs in cannabis only in traces, it is generally obtained by chemical synthesis. Several synthetic methods to obtain (-)-trans- $\Delta^8$ -THC have been reported until now and they are well reviewed by Schafroth and Carreira [25].

The most feasible methods involve the electrophilic cyclization under acidic conditions of cannabidiol (CBD) and the condensation of olivetol with an optically pure monoterpene. The electrophilic cyclization of CBD affords the  $\Delta^8$ -THC isomer upon treatment with a strong acid, while the  $\Delta^9$ -THC isomer is obtained with mild acids [26-32].

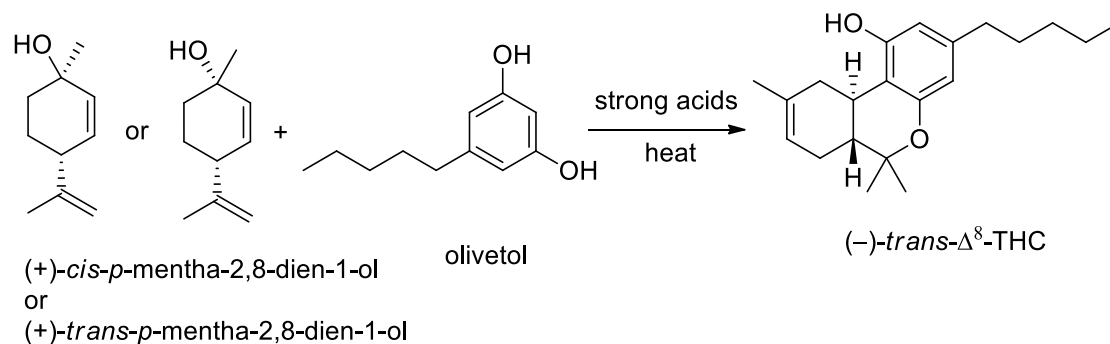
---

<sup>1</sup> Reported by Chemical Abstract Service (CAS).

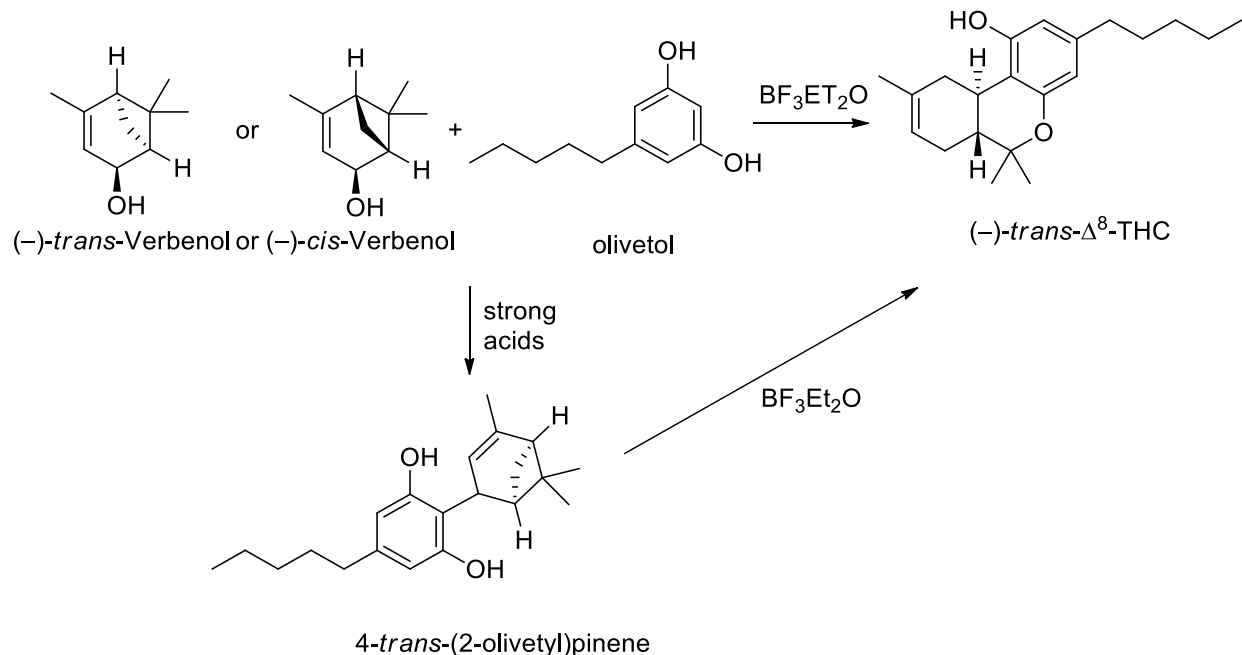


The most common strategy for the synthesis of (-)-trans- $\Delta^8$ -THC is based on the condensation of olivetol with an optically pure monoterpene [33-36].

Condensation of olivetol with readily available (+)-cis/trans-p-mentha-2,8-dien-1-ol in strong acids (e.g. toluene-p-sulphonic acid or hydrochloride acid) led to (-)-trans- $\Delta^8$ -THC in 53% yield [37-39].



In 1967 Mechoulam et al. [19] described a synthesis of (-)-trans- $\Delta^8$ -THC from a pinane derivative, verbenol, and olivetol in the presence of acid catalysts. Thus, in the presence of toluene-p-sulphonic acid in methylene chloride, (-)-cis- or (-)-trans-verbenol condensed with olivetol to give 4-trans-(2-olivetyl)pinene that after chromatographic purification, gave (-)-trans- $\Delta^8$ -THC (80% yield) upon treatment with boron trifluoride etherate in methylene chloride at room temperature.



## 4.2.8 Chemical Properties

### 4.2.8.1 Melting point

N/A

### 4.2.8.2 Boiling point

175-178 °C at atmospheric pressure (760 mmHg) [40, 41].

### 4.2.8.3 Solubility

n-Octanol/water partition coefficients (Po/w)

Brian et al. calculated n-octanol/water partition coefficients (Po/w) of (-)-*trans*- $\Delta^9$ -THC and (-)-*trans*- $\Delta^8$ -THC by two procedures: reverse-phase high performance liquid chromatography (HPLC) and computer calculation. As expected, the position of the double bond in either position 8 or 9 had only a poor effect on the Po/w. Based on the molecular structure, the log Po/w obtained for (-)-*trans*- $\Delta^8$ -THC by computer calculation was 7.18, which is in close agreement with the log Po/w of 7.41 as determined by HPLC. This very high value of log Po/w indicated an extreme lipophilicity [42].

Solvent solubility

Rosenkrantz et al. conducted solubility studies of (–)-trans- $\Delta^9$ -THC, (–)-trans- $\Delta^8$ -THC and pure cannabis extract in several solvents like ethanol, acetone, dimethyl sulfoxide (DMSO), chloroform, benzyl alcohol and sesame oil to obtain suitable oral and parenteral formulations of cannabinoids. Similar solubility values were obtained for (–)-trans- $\Delta^9$ -THC, (–)-trans- $\Delta^8$ -THC and crude cannabis extract in polar solvents. The solubility of (–)-trans- $\Delta^8$ -THC was in ethanol and acetone greater than 1 g/mL, 0.91 g/mL in benzyl alcohol, 0.30 g/mL in sesame oil, 0.62 g/mL in DMSO, 0.89 g/mL in propylene glycol, 0.38 g/mL in glycerol and 0.22 g/mL in polyoxyethylene monooleate (Tween 80) [18].

#### **4.2.9 Identification and Analysis**

Synthetic (–)-trans- $\Delta^8$ -THC was characterized and  $^1\text{H}$  NMR properties [43-46],  $^{13}\text{C}$  NMR properties [43, 44, 47], hetero NMR properties [46], IR properties [43], mass spectrometry properties [43, 48] and UV and visible properties are reported [48, 49].

Several analytical methods are reported regarding (–)-trans- $\Delta^8$ -THC qualitative and quantitative determination in different matrices such as cannabis inflorescence, cannabis extracts and biological fluid. Chromatographic methods are the most employed coupled to several detection modes such as ultraviolet and mass spectrometry [50]. They can be divided into:

##### *4.2.9.1 Thin-layer chromatography (TLC)*

It is quite difficult separate (–)-trans- $\Delta^8$ -THC from (–)-trans- $\Delta^9$ -THC employing a normal- and polar- stationary phase [48]. A two dimensional thin-layer chromatographic (2D TLC) method has been developed with the advantage to obtain a better resolution between the two isomers [51].

##### *4.2.9.2 Gas chromatographic method with mass spectrometry or flame ionization detection (GC-MS or GC-FID)*

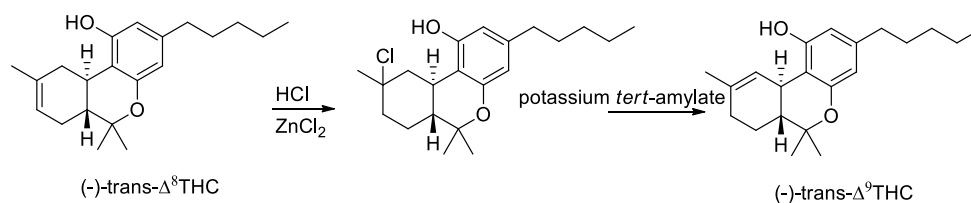
These methods are wide employed in several laboratories and permits to analyse (–)-trans- $\Delta^8$ -THC with or without previous derivatization needed for plant matrices [48, 52].

#### 4.2.9.3 Liquid chromatography (LC)

LC methods are generally coupled to ultraviolet and/or mass spectrometry detection. They offer the advantage of a very high sensitivity without derivatization step [53-57].

### 4.3 Ease of Convertibility Into Controlled Substances

It is possible to convert (-)-trans- $\Delta^8$ -THC into (-)-trans- $\Delta^9$ -THC. Gaseous hydrochloric acid can be added in a quantitative yield to the double bond of (-)-trans- $\Delta^8$ -THC at low temperature with zinc chloride as catalyst. The unstable tertiary chloride obtained can be subsequently dehydrochlorinated by the use of potassium *tert*-amylate, which led to a quantitative formation of (-)-trans- $\Delta^9$ -THC [19, 38].





## 5. delta-10-THC

---

### 5.1 Substance identification

6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol

#### 5.1.1 International Nonproprietary Name (INN)

N/A

#### 5.1.2 Chemical Abstract Service (CAS) Registry Number

7663-51-6

#### 5.1.3 Other Chemical Names<sup>1</sup>

6a,7,8,9-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol

$\Delta^{10}$ -Tetrahydrocannabinol

#### 5.1.4 Trade names

N/A

#### 5.1.5 Street Names

N/A

#### 5.1.6 Physical Appearance

N/A

#### 5.1.7 WHO Review History

See data reported for  $\Delta^{6a(10a)}$ -THC.

---

<sup>1</sup> Reported by Chemical Abstract Service (CAS).

## 5.2 Chemistry

### 5.2.1 Chemical Name

IUPAC Name:

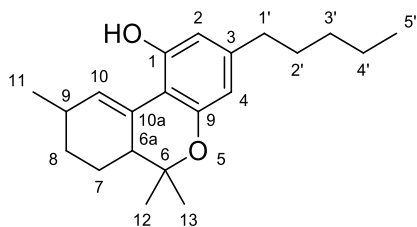
6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol

CA Index Name:

6H-Dibenzo[b,d]pyran-1-ol, 6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-

### 5.2.2 Chemical Structure

Free base:



Molecular Formula:

$C_{21}H_{30}O_2$

Molecular Weight:

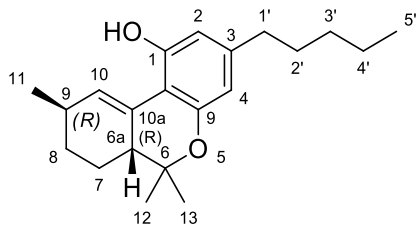
314.46

### 5.2.3 Stereoisomers

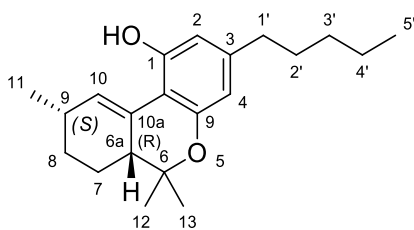
The compound has two stereogenic carbon atoms and four stereoisomers can be present.

Two stereoisomers are reported in the literature:

- 1) CA Index Name: 6H-Dibenzo[b,d]pyran-1-ol, 6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6aR-cis)- (9Cl) [CAS Registry Number: 95543-62-7]



2) CA Index Name: 6H-Dibenzo[b,d]pyran-1-ol, 6a,7,8,9-tetrahydro-6,6,9- trimethyl-3-pentyl-, (6aR-trans)- (9CI) [CAS Registry Number: 95588-87-7]



#### 5.2.4 Methods and Ease of Illicit Manufacturing

In the literature is reported a synthesis of the two stereoisomers obtained by base catalyzed isomerization of (–)-trans- $\Delta^9$ -THC by Srebnik in 1984 [2]. Treatment of (–)-trans- $\Delta^9$ -THC with base gave a mixture of (6aR-trans)- $\Delta^{10}$ -THC (m.p. 153-154 °C;  $\alpha$  –133°) and (6aR-cis)- $\Delta^{10}$ -THC (m.p. 54-55 °C;  $\alpha$  –70°), that are further separated by chromatography [2].

#### 5.2.5 Chemical Properties

##### 5.2.5.1 Melting point

N/A

##### 5.2.5.2 Boiling point

N/A

**5.2.5.3 Solubility**

N/A

**5.2.6 Identification and Analysis**

N/A

**5.3 Ease of Convertibility Into Controlled Substances**

N/A

## 6. delta-9(11)-THC

---

### 6.1 Substance identification

(6aR,10aR)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6H-dibenzo[b,d]pyran-1-ol

#### 6.1.1 International Nonproprietary Name (INN)

N/A

#### 6.1.2 Chemical Abstract Service (CAS) Registry Number

27179-28-8

#### 6.1.3 Other Chemical Names<sup>1</sup>

- 6H-Dibenzo[b,d]pyran-1-ol, 6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-3-pentyl-, (6aR-trans)- (8CI)
- (6aR,10aR)-6a,7,8,9,10,10a-Hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
- (-)- $\Delta^{9,11}$ -THC
- $\Delta^{11}$ -THC
- $\Delta^{11}$ -Tetrahydrocannabinol

#### 6.1.4 Trade names

N/A

#### 6.1.5 Street Names

N/A

#### 6.1.6 Physical Appearance

N/A

---

<sup>1</sup> Reported by Chemical Abstract Service (CAS).

### 6.1.7 WHO Review History

See data reported for  $\Delta^{6a,10a}$ -THC.

## 6.2 Chemistry

### 6.2.1 Chemical Name

IUPAC Name:

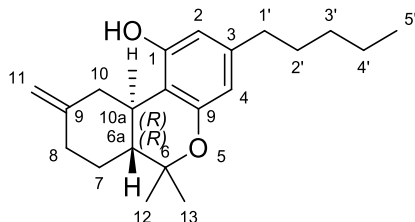
(6aR,10aR)-6a,7,8,9,10,10a-Hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6H-dibenzo[b,d]pyran-1-ol

CA Index Name:

6H-Dibenzo[b,d]pyran-1-ol, 6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-3-pentyl-, (6aR,10aR)-

### 6.2.2 Chemical Structure

Free base:



Molecular Formula:

$C_{21}H_{30}O_2$

Molecular Weight:

314.46

### 6.2.3 Stereoisomers

The compound has two stereogenic carbon atoms and four stereoisomers can be present. No stereoisomers are reported in the literature.

#### **6.2.4 *Methods and Ease of Illicit Manufacturing***

Few methods of preparation are reported in the literature [59]. A method for the preparation of this compound involves ultraviolet irradiation of the corresponding (–)-trans- $\Delta^8$ -THC (yield 30%) [60]. Another commonly used method involves the addition of hydrogen chloride gas to (–)-trans- $\Delta^8$ -THC followed by treatment with potassium tert-amylate under anhydrous conditions [59, 61, 62].

#### **6.2.5 *Chemical Properties***

Melting point

N/A

Boiling point

N/A

Solubility

N/A

#### **6.2.6 *Identification and Analysis***

N/A

#### **6.3 *Ease of Convertibility Into Controlled Substances***

N/A

## 7. REFERENCES

---

- [1] R. Adams, Marijuana active compounds, US patent US2419935A, 1947.
- [2] M. Srebnik, N. Lander, A. Breuer, R. Mechoulam, Base-catalysed double-bond isomerizations of cannabinoids: structural and stereochemical aspects, *Journal of the Chemical Society, Perkin Transactions 1* (1984) 2881-2886.
- [3] R. Ghosh, A.R. Todd, D.C. Wright, 31. *Cannabis indica*. Part VI. The condensation of pulegone with alkyl resorcinols. A new synthesis of cannabinol and of a product with hashish activity, *Journal of the Chemical Society* (1941) 137-140.
- [4] G. Leaf, A.R. Todd, S. Wilkinson, 31. *Cannabis indica*. Part IX. The isolation of 3': 4': 5': 6'-tetrahydrodibenzopyran derivatives from pulegone-orcinol and pulegone-olivetol condensation products. Synthesis of d-tetrahydrocannabinol, *Journal of the Chemical Society* (1942) 185-188.
- [5] R. Adams, S. Loewe, C.M. Smith, W.D. McPhee, Tetrahydrocannabinol homologs and analogs with marijuana activity. XIII, *Journal of the American Chemical Society* 64(3) (1942) 694-697.
- [6] U. Claussen, P. Mummenhoff, F. Korte, Haschisch-XVIII: Zur tetrahydrocannabinol-synthese aus olivetol und pulegon, *Tetrahedron* 24(7) (1968) 2897-2898.
- [7] O. Rosati, F. Messina, A. Pelosi, M. Curini, V. Petrucci, J. Gertsch, A. Chicca, One-pot heterogeneous synthesis of delta(3)-tetrahydrocannabinol analogues and xanthenes showing differential binding to CB(1) and CB(2) receptors, *European Journal of Medicinal Chemistry* 85 (2014) 77-86.
- [8] L.E. Hollister, H.K. Gillespie, R. Mechoulam, M. Srebnik, Human pharmacology of 1S and 1R enantiomers of delta-3-tetrahydrocannabinol, *Psychopharmacology* 92(4) (1987) 505-507.
- [9] H. He, C. Wang, J. Guo, W. Han, Analysis of cannabinoids in Xinjiang cannabis resin by GC/MS, *Chinese Journal of Analysis Laboratory* 22(3) (2003) 34-37.
- [10] A. Stowell, L. Wilson, A simple approach to the interlaboratory transfer of drug retention indices determined by temperature programmed capillary gas chromatography, *Journal of Forensic Sciences* 32(5) (1987) 1214-1220.
- [11] M. Shimamine, K. Takahashi, M. Ono, Identification of psychotropic drugs. II, *Eisei Shikenjo hokoku* (Bulletin of National Institute of Hygienic Sciences) 97 (1979) 82-88.
- [12] I.S. Forrest, S.D. Rose, G.C. Skinner, D.M. Torres, Fluorescent-labelled cannabinoids, *Research Communications in Chemical Pathology and Pharmacology* 2(6) (1971) 787-792.
- [13] A. Arnone, L. Merlini, S. Servi, Hashish: Synthesis of (+)- $\Delta^4$ -tetrahydrocannabinol, *Tetrahedron* 31(24) (1975) 3093-3096.
- [14] R. Mechoulam, Z. Ben-Zvi, H. Varconi, Y. Samuelov, Cannabinoid rearrangements: Synthesis of  $\Delta^5$ -tetrahydrocannabinol, *Tetrahedron* 29(11) (1973) 1615-1619.
- [15] J.W. Huffman, W. Kenneth Banner, G.K. Zoorob, H. Howard Joyner, P.H. Reggio, B.R. Martin, D.R. Compton, Stereoselective synthesis of the epimeric  $\Delta^7$ -tetrahydrocannabinols, *Tetrahedron* 51(4) (1995) 1017-1032.
- [16] R. Mechoulam, P. Braun, Y. Gaoni, Stereospecific synthesis of (-)-delta-1- and (-)-delta-1(6)-tetrahydrocannabinols, *Journal of the American Chemical Society* 89(17) (1967) 4552-4554.
- [17] E. Ballerini, L. Minuti, O. Piermatti, F. Pizzo, High pressure Diels-Alder approach to hydroxy-substituted 6a-cyano-tetrahydro-6H-benzo[c]chromen-6-ones: A route to  $\Delta^6$ -cis-cannabidiol, *Journal of Organic Chemistry* 74(11) (2009) 4311-4317.
- [18] H. Rosenkrantz, G.R. Thompson, M.C. Braude, Oral and parenteral formulations of marijuana constituents, *Journal of Pharmaceutical Science* 61(7) (1972) 1106-12.
- [19] R. Mechoulam, P. Braun, Y. Gaoni, Syntheses of delta-1-tetrahydrocannabinol and related cannabinoids, *Journal of the American Chemical Society* 94(17) (1972) 6159-6165.

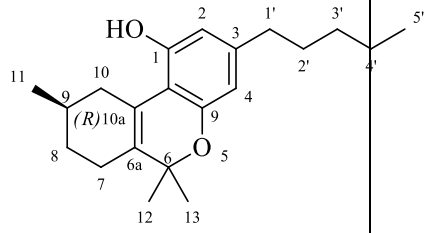
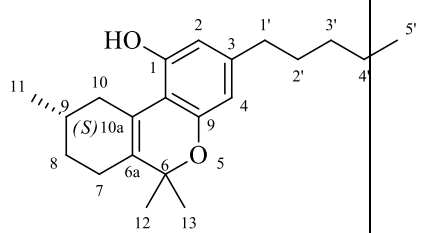


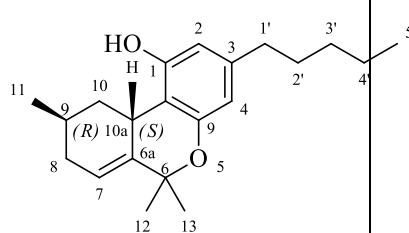
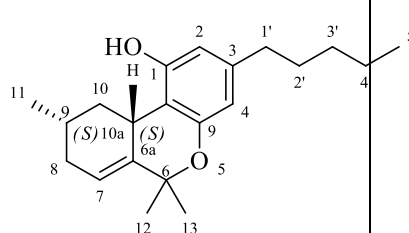
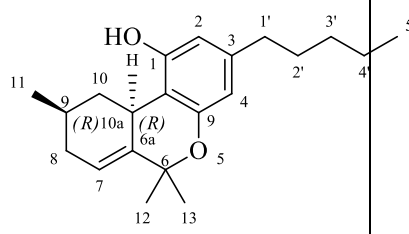
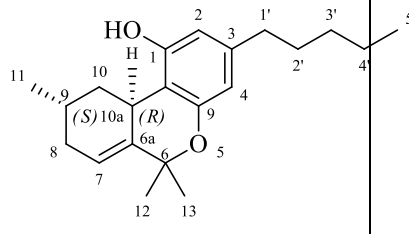
- [20] F. Klotter, A. Studer, Short and divergent total synthesis of (+)-machaeriol B, (+)-machaeriol D, (+)- $\Delta^8$ -THC, and analogues, *Angewandte Chemie International Edition* 54(29) (2015) 8547-8550.
- [21] D.H. Dethe, R.D. Erande, S. Mahapatra, S. Das, V. Kumar B., Protecting group free enantiospecific total syntheses of structurally diverse natural products of the tetrahydrocannabinoid family, *Chemical Communications* 51(14) (2015) 2871-2873.
- [22] R. Mechoulam, Marijuana chemistry, *Science* 168(3936) (1970) 1159-66.
- [23] J. Zias, H. Stark, J. Sellgman, R. Levy, E. Werker, A. Breuer, R. Mechoulam, Early medical use of cannabis, *Nature* 363(6426) (1993) 215.
- [24] L.O. Hanus, S.M. Meyer, E. Munoz, O. Tagliatela-Scafati, G. Appendino, Phytocannabinoids: a unified critical inventory, *Natural Product Report* 33(12) (2016) 1357-1392.
- [25] M.A. Schafroth, E.M. Carreira, Synthesis of Phytocannabinoids, in *Phytocannabinoids. Progress in the Chemistry of Organic Natural Products*, A. Kinghorn, H. Falk, S. Gibbons, J. Kobayashi ed., Springer International Publishing, Switzerland, 2017, p. 37.
- [26] R. Adams, Marijuana: Harvey Lecture, February 19, 1942, *Bulletin of the New York Academy of Medicine* 18(11) (1942) 705-730.
- [27] R. Adams, D.C. Pease, C.K. Cain, J.H. Clark, Structure of cannabidiol. VI. Isomerization of cannabidiol to tetrahydrocannabinol, a physiologically active product. Conversion of cannabidiol to cannabinol, *Journal of the American Chemical Society* 62(9) (1940) 2402-2405.
- [28] R. Adams, B.R. Baker, Structure of cannabidiol. VII. A method of synthesis of a tetrahydrocannabinol which possesses marijuana activity, *Journal of the American Chemical Society* 62(9) (1940) 2405-2408.
- [29] R. Adams, S. Loewe, D.C. Pease, C.K. Cain, R.B. Wearn, R.B. Baker, H. Wolff, Structure of cannabidiol. VIII. Position of the double bonds in cannabidiol. marijuana activity of tetrahydrocannabinols, *Journal of the American Chemical Society* 62(9) (1940) 2566-2567.
- [30] Y. Gaoni, R. Mechoulam, Isolation, structure, and partial synthesis of an active constituent of hashish, *Journal of the American Chemical Society* 86(8) (1964) 1646-1647.
- [31] Y. Gaoni, R. Mechoulam, Hashish-VII: The isomerization of cannabidiol to tetrahydrocannabinols, *Tetrahedron* 22(4) (1966) 1481-1488.
- [32] D. Gold, *Cannabis alchemy: The Art of Modern Hashmaking*, Ronin Publishing, Berkeley, CA, 1989.
- [33] R. Mechoulam, *Cannabinoid Chemistry, Marijuana Chemistry, Pharmacology, Metabolism and Clinical Effects*, Academic Press, New York, 1973, p. 2.
- [34] R. Mechoulam, N.K. McCallum, S. Burstein, Recent advances in the chemistry and biochemistry of cannabis, *Chemical Reviews* 76(1) (1976) 75-112.
- [35] R.K. Razdan, *The total synthesis of natural products*, Wiley-Interscience, New York, 1981, p. 185.
- [36] M.A. Tius, Stereospecific cannabinoid synthesis: the application of new techniques to a classical problem, in *Studies in natural product chemistry, Structure and Chemistry (Part E)*, vol.19, Atta-ur-Rahman ed., Elsevier, Amsterdam, 1996, p. 185.
- [37] T. Petrzilka, W. Haefliger, C. Sikemeier, G. Ohloff, A. Eschenmoser, Synthese und chiralität des (-)-cannabidiols vorläufige mitteilung, *Helvetica Chimica Acta* 50(2) (1967) 719-723.
- [38] T. Petrzilka, C. Sikemeier, Über inhaltsstoffe des haschisch. 3., vorläufige mitteilung. Umwandlung von (-)- $\Delta^{6,1}$ -3,4-trans-tetrahydrocannabinol in (-)- $\Delta^{1,2}$ -3,4-trans tetrahydrocannabinol, *Helvetica Chimica Acta* 50(7) (1967) 2111-2113.
- [39] T. Petrzilka, W. Haefliger, C. Sikemeier, Synthese von haschisch-inhaltsstoffen. 4. Mitteilung, *Helvetica Chimica Acta* 52(4) (1969) 1102-1134.
- [40] J.M. McPartland, E.B. Russo, Cannabis and cannabis extracts, *Journal of Cannabis Therapeutics* 1(3-4) (2001) 103-132.
- [41] E. Russo, *Cannabis therapeutics in HIV/AIDS*, The Haworth Integrative Healing Press, New York, 2001.

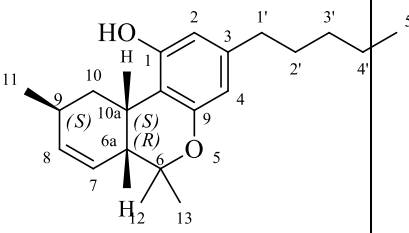
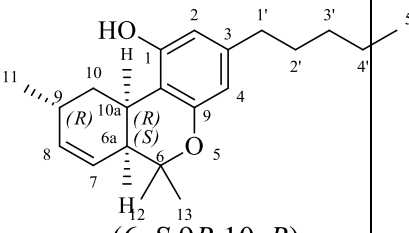
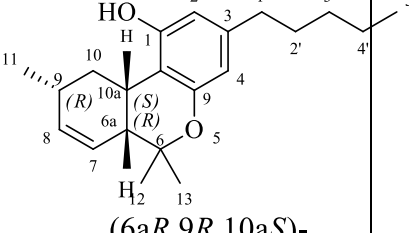
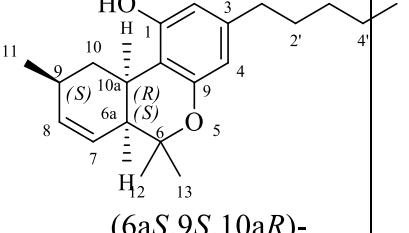
- [42] B.F. Thomas, D.R. Compton, B.R. Martin, Characterization of the lipophilicity of natural and synthetic analogs of delta 9-tetrahydrocannabinol and its relationship to pharmacological potency, *Journal of Pharmacology and Experimental Therapeutics* 255(2) (1990) 624-30.
- [43] Q. Huang, B. Ma, X.a. Li, X. Pan, X. She, Total synthesis of (-)- $\Delta^8$ -trans-tetrahydrocannabinol, *Synthesis* 2010(11) (2010) 1766-1770.
- [44] Y.H. Choi, A. Hazekamp, A.M.G. Peltenburg-Looman, M. Frédérich, C. Erkelens, A.W.M. Lefeber, R. Verpoorte, NMR assignments of the major cannabinoids and cannabiflavonoids isolated from flowers of *Cannabis sativa*, *Phytochemical Analysis* 15(6) (2004) 345-354.
- [45] L. Crombie, W.M.L. Crombie, S.V. Jamieson, C.J. Palmer, Acid-catalysed terpenylations of olivetol in the synthesis of cannabinoids, *Journal of the Chemical Society, Perkin Transactions 1* (5) (1988) 1243-1250.
- [46] J. Guo, S. Pavlopoulos, X. Tian, D. Lu, S.P. Nikas, D.-P. Yang, A. Makriyannis, Conformational study of lipophilic ligands in phospholipid model membrane systems by solution NMR, *Journal of Medicinal Chemistry* 46(23) (2003) 4838-4846.
- [47] R.A. Archer, D.W. Johnson, E.W. Hagaman, L.N. Moreno, E. Wenkert, Carbon-13 nuclear magnetic resonance spectroscopy of naturally occurring substances. 47. Cannabinoid compounds, *The Journal of Organic Chemistry* 42(3) (1977) 490-495.
- [48] A. Hazekamp, A. Peltenburg, R. Verpoorte, C. Giroud, Chromatographic and spectroscopic data of cannabinoids from *Cannabis sativa* L., *Journal of Liquid Chromatography & Related Technologies* 28(15) (2005) 2361-2382.
- [49] B. De Backer, B. Debrus, P. Lebrun, L. Theunis, N. Dubois, L. Decock, A. Verstraete, P. Hubert, C. Charlier, Innovative development and validation of an HPLC/DAD method for the qualitative and quantitative determination of major cannabinoids in cannabis plant material, *Journal of Chromatography B, Analytical Technologies in the Biomedical Life Sciences* 877(32) (2009) 4115-24.
- [50] C. Citti, D. Braghiroli, M.A. Vandelli, G. Cannazza, Pharmaceutical and biomedical analysis of cannabinoids: A critical review, *Journal of Pharmaceutical and Biomedical Analysis* 147 (2018) 565-579.
- [51] S.N. Tewari, J.D. Sharma, Two dimensional thin-layer chromatography of ganja (*Cannabis sativa* L.), *Bulletin on narcotics* 35(1) (1983) 63-7.
- [52] A. Leghissa, Z.L. Hildenbrand, F.W. Foss, K.A. Schug, Determination of cannabinoids from a surrogate hops matrix using multiple reaction monitoring gas chromatography with triple quadrupole mass spectrometry, *Journal of Separation Science* 41(2) (2018) 459-468.
- [53] W. Gul, S.W. Gul, M.M. Radwan, A.S. Wanas, Z. Mehmedic, I.I. Khan, M.H. Sharaf, M.A. ElSohly, Determination of 11 cannabinoids in biomass and extracts of different varieties of cannabis using high-performance liquid chromatography, *Journal of AOAC International* 98(6) (2015) 1523-1528.
- [54] T. Van der Linden, P. Silverans, A.G. Verstraete, Comparison between self-report of cannabis use and toxicological detection of THC/THCCOOH in blood and THC in oral fluid in drivers in a roadside survey, *Drug Test and Analysis* 6(1-2) (2014) 137-142.
- [55] D. Andersen, B. Rasmussen, K. Linnet, Validation of a fully automated robotic setup for preparation of whole blood samples for LC-MS toxicology analysis, *Journal Analytical Toxicology* 36(4) (2012) 280-287.
- [56] A. Petroczi, E.V. Aidman, I. Hussain, N. Deshmukh, T. Nepusz, M. Uvacsek, M. Toth, J. Barker, D.P. Naughton, Virtue or pretense? Looking behind self-declared innocence in doping, *PLoS One* 5(5) (2010) e10457.
- [57] S. Valiveti, D.C. Hammell, D.C. Earles, A.L. Stinchcomb, LC-MS method for the estimation of  $\Delta^8$ -THC and 11-nor- $\Delta^8$ -THC-9-COOH in plasma, *Journal of Pharmaceutical and Biomedical Analysis* 38(1) (2005) 112-118.
- [58] T. Jarbe, A. Hiltunen, R. Mechoulam, M. Srebnik, A. Breuer, Separation of the discriminative stimulus effects of stereoisomers of  $\Delta^2$ - and  $\Delta^3$ -tetrahydrocannabinols in pigeons, *European Journal of Pharmacology* 156(3) (1988) 361-366.

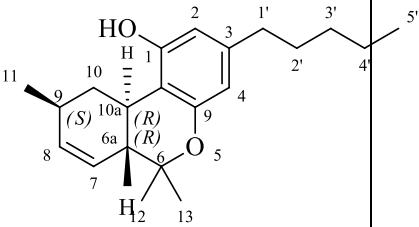
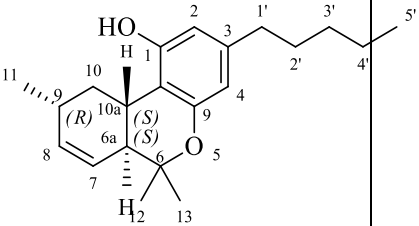
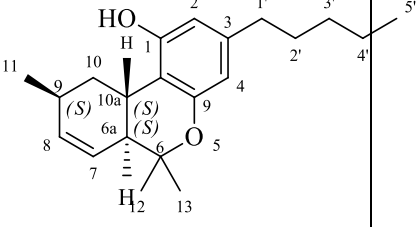
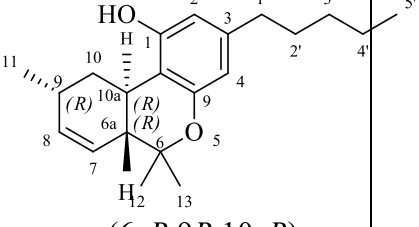
- [59] A.R. Banijamali, C.J. Van Der Schyf, A. Makriyannis, Addition and elimination of HCl to tetrahydrocannabinol isomers. A method for the preparation of stereospecifically  $^2\text{H}$ -labeled cannabinoids, *Journal of Labelled Compounds and Radiopharmaceuticals* 41(2) (1998) 121-130.
- [60] M. Binder, H. Ebery, G. Porath,  $\Delta^7$ -Tetrahydrocannabinol, a non-psychotropic cannabinoid: structure-activity considerations, in *Marihuana Biological Effects*, G.G. Nahas and W.D.M. Paton ed., Pergamon Press Ltd. Published by Elsevier, Amsterdam, 1979, p. 71.
- [61] A.R. Banijamali, A. Makriyannis, Novel synthesis of (-)-trans- $\Delta^{9,11}$ -tetrahydrocannabinol, *Journal of Heterocyclic Chemistry* 25(3) (1988) 823-825.
- [62] C.G. Pitt, J.W. Wildes, N.H. Martin, M.E. Wall, Synthesis of (-)-delta-9(11)-trans-tetrahydrocannabinol, *The Journal of Organic Chemistry* 36(5) (1971) 721-723.

**Annex 1: Isomers of THC**

7 double bond isomers and their 30 stereoisomers						
Formal numbering			Number of stereoisomers	Natural occurrence	CAS Registry Number	Structure
Short name	Chiral centers	Full name				
$\Delta^{6a,10a}$ -THC	C9	7,8,9,10-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol	2	No	95720-01-7	 <p style="text-align: center;">(R)-</p>
				No	95720-02-8	 <p style="text-align: center;">(S)-</p>

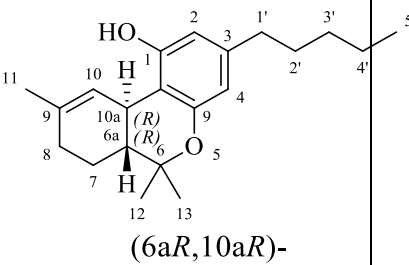
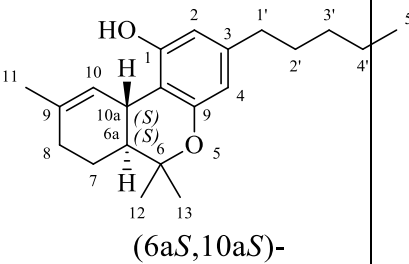
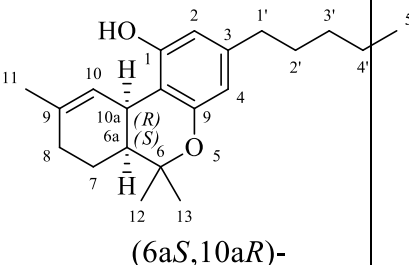
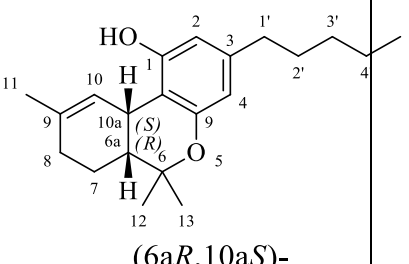
$\Delta^{6a,7}$ - THC	C9 and C10a	8,9,10,10a- tetrahydro-6,6,9- trimethyl-3- pentyl-6H- dibenzo[b,d]pyra- n-1-ol	4	No	unkno wn	 <p>(9<i>R</i>,10<i>aS</i>)-</p>
				No	unkno wn	 <p>(9<i>S</i>,10<i>aS</i>)-</p>
				No	59042- 44-3	 <p>(9<i>R</i>,10<i>aR</i>)-</p>
				No	unkno wn	 <p>(9<i>S</i>,10<i>aR</i>)-</p>

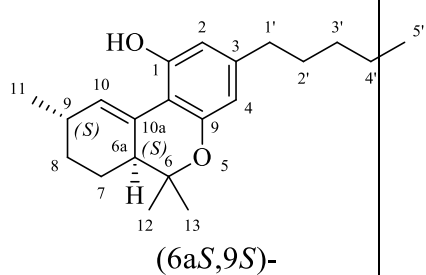
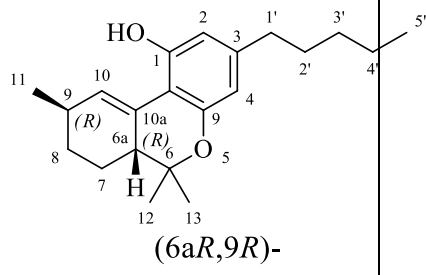
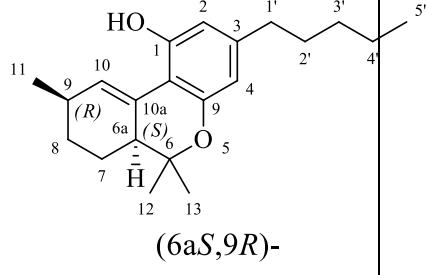
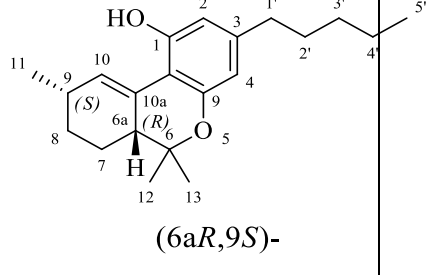
$\Delta^7$ - THC	C6a, C9 and C10a	6a,9,10,10a- tetrahydro-6,6,9- trimethyl-3- pentyl- 6Hdibenzo[b,d]p yran-1-ol	8	No	unkno wn	 <p>(6aR,9S,10aS)-</p>
				No	unkno wn	 <p>(6aS,9R,10aR)-</p>
				No	unkno wn	 <p>(6aR,9R,10aS)-</p>
				No	unkno wn	 <p>(6aS,9S,10aR)-</p>

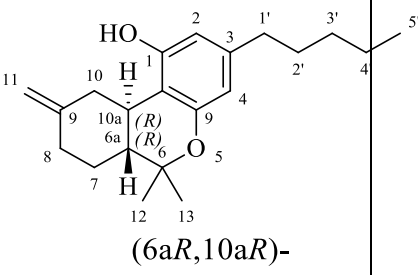
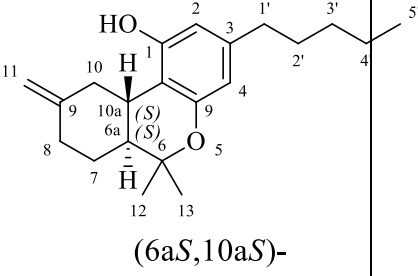
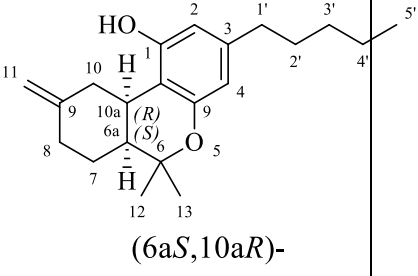
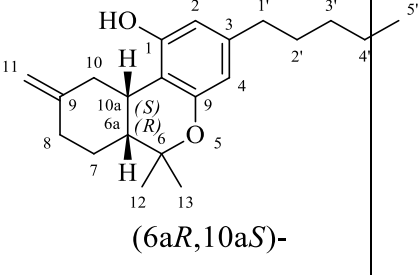
				No	16267 8-94-6	 <p>(6a<i>R</i>,9<i>S</i>,10a<i>R</i>)-</p>
				No	unkno wn	 <p>(6a<i>S</i>,9<i>R</i>,10a<i>S</i>)-</p>
				No	unkno wn	 <p>(6a<i>S</i>,9<i>S</i>,10a<i>S</i>)-</p>
				No	42793- 13-5	 <p>(6a<i>R</i>,9<i>R</i>,10a<i>R</i>)-</p>

$\Delta^8$ - THC	C6a and C10a	6a,7,10,10a- tetrahydro-6,6,9- trimethyl-3- pentyl- 6Hdibenzo[b,d]p yran-1-ol	4	Yes	5957- 75-5	<p>(6aR,10aR)-</p>
				No	33029- 18-4	<p>(6aS,10aS)-</p>
				No	18575 2-04-9	<p>(6aS,10aR)-</p>
				No	65634- 24-4	<p>(6aR,10aS)-</p>



$\Delta^9$ - THC	C6a and C10a	6a,7,8,10a- Tetrahydro- 6,6,9-trimethyl- 3-pentyl-6H- dibenzo[b,d]pyra- n-1-ol	4	Yes	1972- 08-3	 <p>(6a<i>R</i>,10a<i>R</i>)-</p>
				No	17766- 02-8	 <p>(6a<i>S</i>,10a<i>S</i>)-</p>
				No	43009- 38-7	 <p>(6a<i>S</i>,10a<i>R</i>)-</p>
				No	69855- 10-3	 <p>(6a<i>R</i>,10a<i>S</i>)-</p>

$\Delta^{10}$ - THC	C6a and C9	6a,7,8,9- tetrahydro-6,6,9- trimethyl-3- pentyl-6H- dibenzo[b,d]pyra n-1-ol	4	No	unkno wn	 <p>(6aS,9S)-</p>
				No	95543- 62-7	 <p>(6aR,9R)-</p>
				No	unkno wn	 <p>(6aS,9R)-</p>
				No	95588- 87-7	 <p>(6aR,9S)-</p>

$\Delta^{9,11}$ - THC	C6a and C10a		4	No	27179-28-8	 <p>(6a<i>R</i>,10a<i>R</i>)-</p>
				No	unkno wn	 <p>(6a<i>S</i>,10a<i>S</i>)-</p>
				No	unkno wn	 <p>(6a<i>S</i>,10a<i>R</i>)-</p>
				No	unkno wn	 <p>(6a<i>R</i>,10a<i>S</i>)-</p>

# Isomers of THC

## Section 2: Pharmacology

## Contents

<b>1.</b>	<b>General Pharmacology</b> .....	<b>3</b>
1.1	Routes of administration and dosage .....	3
1.2	Pharmacokinetics.....	4
1.3	Pharmacodynamics.....	4
<b>2.</b>	<b>Dependence Potential</b> .....	<b>6</b>
2.1	Animal Studies .....	6
2.2	Human Studies.....	6
<b>3.</b>	<b>Abuse Potential</b> .....	<b>7</b>
3.1	Animal Studies .....	7
3.2	Human Studies.....	8
<b>4.</b>	<b>References</b> .....	<b>9</b>

---

## 1. General Pharmacology

---

Tetrahydrocannabinol (THC) isomers included in the pharmacology pre-review are listed below, along with their more common names in bold type. For ease of presentation, the common name specified below has been used in each pharmacology section.

- 7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol [ $\Delta^{6a(10a)}$ -THC]
- (9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol [ $\Delta^{6a(7)}$ -THC]
- (6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl- 6H-dibenzo[b,d]pyran-1-ol [ $\Delta^7$ -THC]
- (6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol [ $\Delta^8$ -THC]
- 6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol [ $\Delta^{10}$ -THC]
- (6aR,10aR)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6Hdibenzo[b,d]pyran-1-ol [ $\Delta^{9(11)}$ -THC]

### 1.1 Routes of administration and dosage

While several isomers were administered to humans in the context of early experimental studies on cannabis and its constituents, none of the six THC isomers are regularly administered to humans currently. However, tetrahydrocannabinol isomers are lipophilic and would be expected to be readily absorbed and distributed to the brain and other organs following many routes of administration, including intraperitoneal (i.p.), oral (p.o.), intramuscular (i.m.), intravenous (i.v.), and inhalation. The limited direct information available on THC isomers suggests that  $\Delta^8$ -THC,  $\Delta^{9(11)}$ -THC, and  $\Delta^{6a(10a)}$ -THC are absorbed and distributed to the brain after systemic administration, as indicated by their ability to induce cannabimimetic behavioral effects. Based upon the extant research,  $\Delta^8$ -THC and  $\Delta^{9(11)}$ -THC each produced overt  $\Delta^9$ -THC-like pharmacological effects following i.v. administration (mice),<sup>1</sup> i.m. injection (rhesus monkeys),<sup>2, 3</sup> and i.p. injection (rats)<sup>2,4</sup> whereas  $\Delta^{10}$ -THC (i.m.) did not produce cannabimimetic effects (pigeons).<sup>5</sup> In humans,  $\Delta^8$ -THC was active orally, following i.v. injection,<sup>6</sup> and when inhaled via smoking.<sup>7</sup>  $\Delta^{6a(10a)}$ -THC also produced  $\Delta^9$ -THC-like effects when smoked.<sup>8</sup> None of the other isomers have been tested in humans. Additional details of the study designs and endpoints are provided in Section 8 of this pre-review.

### 1.2 Pharmacokinetics

Data on the specific pharmacokinetic profile of the six listed isomers are sparse (except  $\Delta^8$ -THC metabolism); however, the core tetrahydrocannabinol structure present in these isomers suggests

## Section 2: Pharmacology

common biotransformational processes. Initial metabolism of the tetrahydrocannabinols following parenteral injection or oral administration occurs primarily in the liver and is catalyzed by cytochrome P-450 (CYP) enzymes.<sup>9</sup> Tetrahydrocannabinols are extensively metabolized, resulting in numerous metabolites.<sup>9</sup> Because the profile of these enzymes varies across species and among individuals, variations in the ratio of these metabolites have been noted.<sup>10</sup>

The isomer that has received the greatest amount of research attention is  $\Delta^8$ -THC. Hydroxylation of the C-11 site to form 11-hydroxy- $\Delta^8$ -tetrahydrocannabinol (11-OH- $\Delta^8$ -THC) is the initial step of biotransformation of  $\Delta^8$ -THC in most species, including humans.<sup>10, 11</sup> This major metabolite is psychoactive and exhibits stereoselectivity resembling that of the parent compound: whereas (-)-11-OH- $\Delta^8$ -THC (i.m.) fully substitutes for  $\Delta^9$ -THC in pigeons trained to discriminate  $\Delta^9$ -THC from vehicle, (+)-11-OH- $\Delta^8$ -THC failed to do so.<sup>12</sup> In an earlier human study, 11-OH- $\Delta^8$ -THC (i.v.) was also reported to produce psychological and physiological effects resembling those of  $\Delta^9$ -THC in a small sample of men.<sup>7</sup> Although hydroxylation of  $\Delta^8$ -THC at C-11 to form 11-OH- $\Delta^8$ -THC is most common, hydroxylation may also occur at C-7 in rodents<sup>10</sup> and in human hepatic microsomes.<sup>13</sup> The primary CYP isoenzymes that catalyze the hydroxylation reaction are CYP2C9 and CYP3A4.<sup>13</sup> A secondary metabolite, 11-nor-9-carboxy- $\Delta^8$ -tetrahydrocannabinol (11-COOH- $\Delta^8$ -THC or  $\Delta^8$ -THC-COOH), is formed through oxidation of 11-OH- $\Delta^8$ -THC.<sup>14</sup>  $\Delta^8$ -THC-COOH lacks cannabimimetic effect in mice.<sup>14</sup>

Specific data are also available on a second isomer,  $\Delta^{9(11)}$ -THC. Because of its double bond at the C-11 site,  $\Delta^{9(11)}$ -THC has a more diverse profile of metabolites than  $\Delta^9$ - and  $\Delta^8$ -THC.<sup>10</sup>

### 1.3 Pharmacodynamics

Exogenously administered cannabinoids produce their characteristic effects through interaction with an endogenous cannabinoid system that serves to maintain physiological homeostasis as one of its primary functions.<sup>15</sup> Within this endocannabinoid system, two cannabinoid receptors, CB<sub>1</sub> and CB<sub>2</sub>, have been identified.<sup>16, 17</sup> While CB<sub>1</sub> receptors are widespread and abundant in the brain and periphery, CB<sub>2</sub> receptors are confined primarily to the periphery,<sup>18</sup> although recent evidence suggests that CB<sub>2</sub> receptors may be present in the brain under certain conditions.<sup>19</sup> Psychoactive cannabinoids bind to and activate CB<sub>1</sub> receptors in the brain in a manner resembling activation by their endogenous ligands (e.g., anandamide and 2-arachidonoylglycerol). For example, research has shown that the discriminative stimulus effects of  $\Delta^9$ -THC in animals were reversed by pre-injection with rimonabant, a selective CB<sub>1</sub> receptor antagonist, but not by injection with SR144528, selective CB<sub>2</sub> receptor antagonist.<sup>20</sup> Antagonists of other major neurotransmitter systems (e.g., dopamine, acetylcholine, norepinephrine, mu opioid) also did not alter the

## Section 2: Pharmacology

discriminative stimulus effects of  $\Delta^9$ -THC in rats.<sup>21</sup> In humans, rimonabant attenuated the acute psychological and physiological effects of a smoked marijuana cigarette containing 2.64%  $\Delta^9$ -THC,<sup>22</sup> suggesting that the antagonism results from preclinical  $\Delta^9$ -THC discrimination experiments are translational.

Most studies with the six listed isomers were completed in animals and humans prior to 1990 (see Section 8 of this report). Discovery of the endocannabinoid system did not occur until 1992<sup>23</sup> and synthesis of the first selective CB<sub>1</sub> receptor antagonist (SR141716A, rimonabant) was not reported until 1994.<sup>24</sup> Hence, effective tools for determination of the most probable mechanism underlying any abuse- or dependence-related pharmacological effects of the six listed THC isomers were not available until after publication of the studies in which these effects were reported. Non-cannabinoid mechanisms have not been explored.



## **2. Dependence Potential**

---

### **2.1 Animal Studies**

None of the THC isomers have been assessed for dependence potential in animals.

### **2.2 Human Studies**

None of the THC isomers have been assessed for dependence potential in humans.

### 3. Abuse Potential

---

#### 3.1 Animal Studies

Only a limited number of studies have reported successful acquisition of cannabinoid i.v. self-administration in rats, with WIN55,212-2 (a synthetic aminoalkylindole cannabinoid) being the predominant training drug.<sup>25-27</sup> To date, successful acquisition of reliable i.v.  $\Delta^9$ -THC self-administration has been reported in squirrel monkeys only in a single lab.<sup>28, 29</sup> None of the six THC isomers were evaluated in this model. Hence, preclinical assessment of abuse liability of these isomers has concentrated on determination of their pharmacological similarity to  $\Delta^9$ -THC, particularly substitution for  $\Delta^9$ -THC in animals trained to discriminate this drug from vehicle.

Of the six THC isomers reviewed here, three have been tested for substitution in  $\Delta^9$ -THC-trained animals.  $\Delta^{9(11)}$ -THC produced full dose-dependent substitution for  $\Delta^9$ -THC in male rats trained to discriminate 3 mg/kg  $\Delta^9$ -THC (i.p.) from vehicle, with approximately 3-fold less potency than  $\Delta^9$ -THC ( $ED_{50} = 3.2$  mg/kg i.p. for  $\Delta^{9(11)}$ -THC vs. 1 mg/kg i.p. for  $\Delta^9$ -THC).<sup>2</sup> Similar results were reported with  $\Delta^{9(11)}$ -THC when it was tested earlier in a  $\Delta^9$ -THC discrimination procedure using a water maze apparatus.<sup>30</sup>  $\Delta^{9(11)}$ -THC (i.m.) also fully substituted with less potency than  $\Delta^9$ -THC in male rhesus monkeys trained in  $\Delta^9$ -THC discrimination,<sup>2</sup> albeit it was less efficacious in this species at producing typical high dose cannabinoid effects such as ptosis, sedation and ataxia.<sup>31</sup> In contrast, an earlier study reported that  $\Delta^{9(11)}$ -THC did not substitute for  $\Delta^9$ -THC in rats up to a dose of 30 mg/kg.<sup>1</sup> In male mice,  $\Delta^{9(11)}$ -THC (i.v.) effected a tetrad of characteristic  $\Delta^9$ -THC-like effects, including suppression of locomotor activity, hypothermia, antinociception, and ring immobility.<sup>1, 31</sup> Again, in this species, it was several-fold less potent than  $\Delta^9$ -THC for each dependent measure.

A second isomer that has been tested in  $\Delta^9$ -THC discrimination is  $\Delta^8$ -THC. In male mice,  $\Delta^8$ -THC (i.v.) showed pharmacological similarity to  $\Delta^9$ -THC by inducing the characteristic tetrad of cannabinoid effects.<sup>1</sup>  $\Delta^8$ -THC also produced full substitution for  $\Delta^9$ -THC in male rats (i.p.)<sup>4, 30</sup> and rhesus monkeys (i.m.)<sup>3</sup> trained to discriminate  $\Delta^9$ -THC from vehicle. In rats,  $\Delta^8$ -THC was trained as a discriminative stimulus in a t-maze discrimination procedure where it and  $\Delta^9$ -THC cross-substituted with each other.<sup>4, 32</sup> In all studies cited above,  $\Delta^8$ -THC showed less potency than  $\Delta^9$ -THC. Further, the  $\Delta^9$ -THC-like discriminative stimulus effects of  $\Delta^8$ -THC were stereoselective, as (+) $\Delta^8$ -THC (i.p.) failed to substitute for  $\Delta^9$ -THC in male rats.<sup>33</sup>

In contrast with  $\Delta^8$ -THC and  $\Delta^{9(11)}$ -THC,  $\Delta^{10}$ -THC (i.m.) failed to substitute for  $\Delta^9$ -THC in male pigeons.<sup>5</sup> Reports of evaluation of the other 3 isomers ( $\Delta^{6a(10a)}$ -THC,  $\Delta^7$ -THC, and  $\Delta^{6a(7)}$ -THC) in drug discrimination assays were not found, although the 1R and 1S stereoisomers of an acetate analog of  $\Delta^{6a(10a)}$ -THC (i.m.) fully and dose-dependently substituted for  $\Delta^9$ -THC in pigeons with less potency than  $\Delta^9$ -THC.<sup>5</sup> While Mechoulam

## Section 2: Pharmacology

et al.<sup>34</sup> reported that  $\Delta^7$ -THC is inactive in animals, a later study showed that its C-9 epimers are stereoselective with the quasi-axial methyl epimer acting as a weakly active cannabinoid in the tetrad tests in mice and the quasi-equatorial methyl epimer showing only slightly diminished activity in these tests as compared with  $\Delta^9$ -THC.<sup>35</sup>

### 3.2 Human Studies

Systematic investigation of THC isomers in humans has not been undertaken. The scant available knowledge of the abuse potential of THC isomers rests primarily on early observational studies in which their subjective or physiological effects in human volunteers were compared to those reported following  $\Delta^9$ -THC administration. Of the six THC isomers included in this pre-review,  $\Delta^8$ -THC and  $\Delta^{6a(10a)}$ -THC have been assessed in humans. Both isomers produced similar subjective effects in humans when administered orally, i.v., and/or when smoked.<sup>6-8, 36</sup>

## 4. References

---

1. Compton DR, Prescott WR, Jr., Martin BR, Siegel C, Gordon PM, Razdan RK. Synthesis and pharmacological evaluation of ether and related analogues of delta 8-, delta 9-, and delta 9,11-tetrahydrocannabinol. *Journal of Medicinal Chemistry*. 1991;34(11):3310-6.
2. Wiley JL, Barrett RL, Britt DT, Balster RL, Martin BR. Discriminative stimulus effects of delta 9-tetrahydrocannabinol and delta 9-11-tetrahydrocannabinol in rats and rhesus monkeys. *Neuropharmacology*. 1993;32(4):359-65.
3. Wiley JL, Huffman JW, Balster RL, Martin BR. Pharmacological specificity of the discriminative stimulus effects of delta 9-tetrahydrocannabinol in rhesus monkeys. *Drug and Alcohol Dependence*. 1995;40(1):81-6.
4. Järbe TU, Henriksson BG. Discriminative response control produced with hashish, tetrahydrocannabinols (delta 8-THC and delta 9-THC), and other drugs. *Psychopharmacologia*. 1974;40(1):1-16.
5. Järbe TU, Hiltunen AJ, Mechoulam R, Srebnik M, Breuer A. Separation of the discriminative stimulus effects of stereoisomers of delta 2- and delta 3-tetrahydrocannabinols in pigeons. *European Journal of Pharmacology*. 1988;156(3):361-6.
6. Hollister LE, Gillespie HK. Delta-8- and delta-9-tetrahydrocannabinol comparison in man by oral and intravenous administration. *Clinical Pharmacology and Therapeutics*. 1973;14(3):353-7.
7. Hollister LE. Structure-activity relationships in man of cannabis constituents, and homologs and metabolites of delta9-tetrahydrocannabinol. *Pharmacology*. 1974;11(1):3-11.
8. Hollister LE. Tetrahydrocannabinol isomers and homologues: contrasted effects of smoking. *Nature*. 1970;227(5261):968-9.
9. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clinical Pharmacokinetics*. 2003;42(4):327-60.
10. Harvey DJ, Brown NK. Comparative in vitro metabolism of the cannabinoids. *Pharmacology, Biochemistry, and Behavior*. 1991;40(3):533-40.
11. Yamamoto I, Narimatsu S, Watanabe K, Shimonishi T, Yoshimura H, Nagano T. Human liver microsomal oxidation of delta 8-tetrahydrocannabinol. *Chemical and Pharmaceutical Bulletin*. 1983;31(5):1784-7.
12. Järbe TU, Mechoulam R, Zahalka J. Discriminative stimulus- and open-field effects of the enantiomers of 11-hydroxy-delta-8-tetrahydrocannabinol in pigeons and gerbils. *Pharmacology, Biochemistry, and Behavior*. 1994;47(1):113-9.
13. Watanabe K, Yamaori S, Funahashi T, Kimura T, Yamamoto I. Cytochrome P450 enzymes involved in the metabolism of tetrahydrocannabinols and cannabinol by human hepatic microsomes. *Life Sciences*. 2007;80(15):1415-9.
14. Watanabe K, Yamamoto I, Oguri K, Yoshimura H. Comparison in mice of pharmacological effects of delta 8-tetrahydrocannabinol and its metabolites oxidized at 11-position. *European Journal of Pharmacology*. 1980;63(1):1-6.
15. Di Marzo V, Petrosino S. Endocannabinoids and the regulation of their levels in health and disease. *Current Opinion in Lipidology*. 2007;18(2):129-40.
16. Devane WA, Dysarz FA, Johnson MR, Melvin LS, Howlett AC. Determination and characterization of a cannabinoid receptor in rat brain. *Molecular Pharmacology*. 1988;34:605-13.
17. Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. *Nature*. 1993;365(September 2):61-4.
18. Galiègue S, Mary S, Marchand J, Dussosoy D, Carriere D, Carayon P, et al. Expression of central and peripheral cannabinoid receptors in human immune tissues and leukocyte subpopulations. *European Journal of Biochemistry*. 1995;232:54-61.

## Section 2: Pharmacology

19. Atwood BK, Mackie K. CB2: a cannabinoid receptor with an identity crisis. *British Journal of Pharmacology*. 2010;160(3):467-79.
20. Wiley JL, Jefferson RG, Griffin G, Liddle J, Yu S, Huffman JW, et al. Paradoxical pharmacological effects of deoxy-tetrahydrocannabinol analogs lacking high CB1 receptor affinity. *Pharmacology*. 2002;66(2):89-99.
21. Browne RG, Weissman A. Discriminative stimulus properties of  $\Delta^9$ -THC : mechanistic studies. *Journal of Clinical Pharmacology*. 1981;21:227s - 34s.
22. Huestis MA, Gorelick DA, Heishman SJ, Preston KL, Nelson RA, Moolchan ET, et al. Blockade of effects of smoked marijuana by the CB1-selective cannabinoid receptor antagonist SR141716. *Archives of General Psychiatry*. 2001;58(4):322-8.
23. Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science*. 1992;258(18 December):1946-9.
24. Rinaldi-Carmona M, Barth F, Héaulme M, Shire D, Calandra B, Congy C, et al. SR141716A, a potent and selective antagonist of the brain cannabinoid receptor. *Federation of European Biochemical Societies Letters*. 1994;350:240-4.
25. Fattore L, Cossu G, Martellotta CM, Fratta W. Intravenous self-administration of the cannabinoid CB1 receptor agonist WIN 55,212-2 in rats. *Psychopharmacology*. 2001;156(4):410-6.
26. Fattore L, Spano MS, Altea S, Angius F, Fadda P, Fratta W. Cannabinoid self-administration in rats: sex differences and the influence of ovarian function. *British Journal of Pharmacology*. 2007;152(5):795-804.
27. Lefever TW, Marusich JA, Antonazzo KR, Wiley JL. Evaluation of WIN 55,212-2 self-administration in rats as a potential cannabinoid abuse liability model. *Pharmacology, Biochemistry, and Behavior*. 2014;118:30-5.
28. Justinova Z, Tanda G, Redhi GH, Goldberg SR. Self-administration of delta9-tetrahydrocannabinol (THC) by drug naive squirrel monkeys. *Psychopharmacology*. 2003;169(2):135-40.
29. Justinova Z, Goldberg SR, Heishman SJ, Tanda G. Self-administration of cannabinoids by experimental animals and human marijuana smokers. *Pharmacology, Biochemistry, and Behavior*. 2005;81(2):285-99.
30. Semjonow A, Binder M. Generalization of the discriminative stimulus properties of delta 9-THC to delta 9(11)-THC in rats. *Psychopharmacology*. 1985;85(2):178-83.
31. Beardsley PM, Scimeca JA, Martin BR. Studies on the agonistic activity of delta 9-11-tetrahydrocannabinol in mice, dogs and rhesus monkeys and its interactions with delta 9-tetrahydrocannabinol. *Journal of Pharmacology and Experimental Therapeutics*. 1987;241(2):521-6.
32. Järbe TU, Johansson JO, Henriksson BG. Characteristics of tetrahydrocannabinol (THC)-produced discrimination in rats. *Psychopharmacology*. 1976;48(2):181-7.
33. Järbe TU, Swedberg MD, Mechoulam R. A repeated test procedure to assess onset and duration of the cue properties of (-) delta 9-THC, (-) delta 8-THC-DMH and (+) delta 8-THC. *Psychopharmacology*. 1981;75(2):152-7.
34. Mechoulam R, Lander N, Srebnik M, Breuer A, Segal M, Feigenbaum JJ, et al. Stereochemical requirements for cannabimimetic activity. *NIDA Research Monograph*. 1987;79:15-30.
35. Huffman J, Banner WK, Zoorob G, Joyner H, Reggio P, Martin B, et al. Stereoselective synthesis of the epimeric D7-tetrahydrocannabinols. *Tetrahedron*. 1995;51(4):1017-32.
36. Karniol IG, Carlini EA. Comparative studies in man and in laboratory animals on 8 - and 9 -trans-tetrahydrocannabinol. *Pharmacology*. 1973;9(2):115-26.

# Isomers of THC

## Section 3: Toxicology

## Contents

<b>1.</b>	<b>Toxicology .....</b>	<b>3</b>
1.1	$\Delta$ 8-THC.....	3
1.2	$\Delta$ 6a,10a-THC.....	4
1.3	$\Delta^{9,11}$ -THC .....	4
1.4	The remaining isomers.....	5
<b>2.</b>	<b>Adverse reactions in humans .....</b>	<b>6</b>
<b>3.</b>	<b>References .....</b>	<b>7</b>

---

## Section 3: Toxicology

### 1. Toxicology

---

Very little information exists on the isomers of THC listed in Schedule 1 of the 1971 Convention on Psychotropic Substances, other than  $\Delta^8$ -THC which is found in the plant [1]. The other THC isomers do not have a botanical origin and were synthesised by medicinal chemists. As a general statement, toxicity of these isomers is very low. However, there is limited preclinical toxicity data on these isomers and they have not been administered to humans for extended periods of time.

#### 1.1 $\Delta^8$ -THC

(6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol is commonly known as  $\Delta^8$ -THC (dibenzopyran numbering,  $\Delta^6$ -THC in monoterpene numbering).  $\Delta^8$ -THC binds the cannabinoid CB1 receptor and CB2 receptor with lower and higher affinity than  $\Delta^9$ -THC respectively [2]. It has considerably lower potency than  $\Delta^9$ -THC in the mouse tetrad test and unlike  $\Delta^9$ -THC,  $\Delta^8$ -THC did not induce catalepsy or analgesic effects up to 20 mg/kg i.p. [2].

The oral LD<sub>50</sub> for  $\Delta^8$ -THC in rats is 2000 mg/kg [3, 4], which is higher than that found for  $\Delta^9$ -THC (800 mg/kg) [5]. In dogs the LD<sub>50</sub> of  $\Delta^8$ -THC is greater than 3000 mg/kg [6].

Following oral administration or smoking,  $\Delta^8$ -THC has approximately 50-75% the psychotropic potency of  $\Delta^9$ -THC [7-9].  $\Delta^8$ -THC slightly and transiently increases heart rate. Substantial subjective highs were noted at 20 - 40 mg oral doses, smoking doses of 5 - 20 mg and at i.v. doses of 1- 9 mg.

Repeated  $\Delta^8$ -THC dosing prior to conception or during gestation did not have teratogenic effects in rats (up to 40 mg/kg s.c.) [4]. There were no abnormalities in the F2 and F3 generations, although fertility may have been negatively impacted.

While limited data are available,  $\Delta^8$ -THC does not appear to be mutagenic. Blood incubated with  $\Delta^8$ -THC displayed decreased mitosis, although there were no histological abnormalities in the cells examined.  $\Delta^8$ -THC did not cause any abnormalities in chromosome morphology or number - there were no breaks, gaps, lesions or aneuploidy observed [4, 10].  $\Delta^8$ -THC reduces the growth and proliferation of cancer cells in culture (Lewis lung carcinoma and leukaemia cells) [4].  $\Delta^8$ -THC has also been shown to reduce the



### Section 3: Toxicology

proliferation of T and B lymphocytes and induce apoptosis, however this may bear little relevance to human plasma  $\Delta^8$ -THC concentrations attained following cannabis consumption [11].

#### 1.2 $\Delta^{6a,10a}$ -THC

- *7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol* is also commonly referred to as  $\Delta^{6a,10a}$ -THC (dibenzopyran numbering,  $\Delta^3$ -THC in monoterpene numbering).  $\Delta^{6a,10a}$ -THC has low toxicity as it did not promote mortality following a dose of 200 mg/kg i.v. in mice [12].

$\Delta^{6a,10a}$ -THC has much less pharmacological activity than  $\Delta^9$ -THC. An early pharmacological screen of cannabinoid activity was based on the ability of  $\Delta^9$ -THC to induce seizures in a subset of rabbits due to autosomal recessive mutation (THC-SS rabbits). Based on this screen it was shown that  $\Delta^{6a,10a}$ -THC was 15 times less potent than  $\Delta^9$ -THC [13]. In another study, the minimum effective dose of  $\Delta^{6a,10a}$ -THC required to reduce muricidal behaviour, an early model of CNS activity, was double that required with  $\Delta^9$ -THC [14].  $\Delta^{6a,10a}$ -THC was inactive in reducing locomotor activity in mice, unlike  $\Delta^9$ -THC which promoted locomotor suppression.

$\Delta^{6a,10a}$ -THC has been safely administered to humans via smoking, where it had much lower psychoactivity than  $\Delta^9$ -THC [15, 16]. The effects of smoking 15 mg  $\Delta^{6a,10a}$ -THC were less marked and shorter in duration than a 12 mg  $\Delta^9$ -THC dose. The participants experienced light-headedness, numbness and tingling in their extremities and face, fatigue, cold perspiration, drowsiness and a feeling of relaxation. Impairment in thinking and the perception of time were less pronounced than with  $\Delta^9$ -THC. Only 3 of the 6 participants displayed reddened conjunctivae. Although, other studies reported no effects of higher smoked doses of  $\Delta^{6a,10a}$ -THC [15, 16].

#### 1.3 $\Delta^{9,11}$ -THC

(*6aR,10aR*)-*6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6H-dibenzo[b,d]pyran-1-ol* is also more commonly known as  $\Delta^{9,11}$ -THC (dibenzopyran numbering,  $\Delta^{1,7}$ -THC in monoterpene numbering).  $\Delta^{9,11}$ -THC has low toxicity with an i.v. LD<sub>50</sub> of 93 mg/kg in mice which is double that found for  $\Delta^9$ -THC [17]. It has considerably less pharmacological activity than  $\Delta^9$ -THC. Cannabinoid-like effects were observed with  $\Delta^{9,11}$ -THC in the tetrad test in mice, however much higher ED<sub>50</sub> doses were required to reduce locomotor activity and tail-flick latency, and to induce hypothermia and catalepsy -  $\Delta^{9,11}$ -THC was

### Section 3: Toxicology

between 4 and 40 times less potent than  $\Delta^9$ -THC [18].  $\Delta^{9,11}$ -THC displaced CP 55,940 (a synthetic cannabinoid receptor agonist) from rat brain homogenates, indicating it binds cannabinoid receptors, albeit at a higher  $IC_{50}$  than  $\Delta^9$ -THC (ie 334 versus 218 nM).  $\Delta^{9,11}$ -THC however did not display  $\Delta^9$ -THC-like discriminative stimulus effects.  $\Delta^{9,11}$ -THC has been administered i.v. to rhesus monkeys where unlike  $\Delta^9$ -THC it did not promote ptosis, ataxia or sedation [17]. It hasn't been tested in humans, and high doses would be required to produce  $\Delta^9$ -THC-like intoxication [18].

#### 1.4 The remaining isomers

*(9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol* ( $\Delta^{6a,7}$ -THC or  $\Delta^4$ -THC), *(6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol* ( $\Delta^7$ -THC or  $\Delta^5$ -THC) or *6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol* ( $\Delta^{10}$ -THC or  $\Delta^2$ -THC) have not been assessed in any detail for their toxicity.  $\Delta^7$ -THC doesn't appear to have activity in animal models [19]. The others may not have been tested for pharmacological activity.

### Section 3: Toxicology

## 2. Adverse reactions in humans

---

Only  $\Delta^8$ -THC and  $\Delta^{6a,10a}$ -THC have been tested in humans in pure form. As described above the acute intoxicating effects of these molecules was similar in quality but less potent than acute doses of  $\Delta^9$ -THC. These molecules are not available as recreational or therapeutic drugs, so we do not have a good understanding of their adverse effects in humans.

### 3. References

---

1. Patel, B., D. Wene, and Z.T. Fan, *Qualitative and quantitative measurement of cannabinoids in cannabis using modified HPLC/DAD method*. J Pharm Biomed Anal, 2017. **146**: p. 15-23.
2. Radwan, M.M., et al., *Isolation and Pharmacological Evaluation of Minor Cannabinoids from High-Potency Cannabis sativa*. J Nat Prod, 2015. **78**(6): p. 1271-6.
3. Dewey, W.L., L.S. Harris, and J.S. Kennedy, *Some pharmacological and toxicological effects of 1-trans-8 and 1-trans-9 -tetrahydrocannabinol in laboratory rodents*. Arch Int Pharmacodyn Ther, 1972. **196**(1): p. 133-45.
4. Kettenes-van den Bosch, J.J., et al., *Biological activity of the tetrahydrocannabinols*. J Ethnopharmacol, 1980. **2**(3): p. 197-231.
5. Rosenkrantz, H., I.A. Heyman, and M.C. Braude, *Inhalation, parenteral and oral LD50 values of delta 9-tetrahydrocannabinol in Fischer rats*. Toxicol Appl Pharmacol, 1974. **28**(1): p. 18-27.
6. Thompson, G.R., et al., *Comparison of acute oral toxicity of cannabinoids in rats, dogs and monkeys*. Toxicol Appl Pharmacol, 1973. **25**(3): p. 363-72.
7. Hollister, L.E., *Structure-activity relationships in man of cannabis constituents, and homologs and metabolites of delta9-tetrahydrocannabinol*. Pharmacology, 1974. **11**(1): p. 3-11.
8. Hollister, L.E. and H.K. Gillespie, *Delta-8- and delta-9-tetrahydrocannabinol comparison in man by oral and intravenous administration*. Clin Pharmacol Ther, 1973. **14**(3): p. 353-7.
9. Karniol, I.G. and E.A. Carlini, *Comparative studies in man and in laboratory animals on 8 - and 9 - trans-tetrahydrocannabinol*. Pharmacology, 1973. **9**(2): p. 115-26.
10. Neu, R.L., et al., *Delta8- and Delta9-tetrahydrocannabinol: effects on cultured human leucocytes*. J Clin Pharmacol J New Drugs, 1970. **10**(4): p. 228-30.
11. Schwarz, H., F.J. Blanco, and M. Lotz, *Anadamide, an endogenous cannabinoid receptor agonist inhibits lymphocyte proliferation and induces apoptosis*. J Neuroimmunol, 1994. **55**(1): p. 107-15.
12. Avison, A.W.D., A.L. Morrison, and M.W. Parkes, *Tetrahydrodibenzopyran derivatives isomeric with tetrahydrocannabinols*. Journal of the Chemical Society, 1949: p. 952 - 955.
13. Consroe, P., A.R. Martin, and B.S. Fish, *Use of a potential rabbit model for structure--behavioral activity studies of cannabinoids*. J Med Chem, 1982. **25**(5): p. 596-9.
14. Matsumoto, K., P. Stark, and R.G. Meister, *Cannabinoids. 1. 1-Amino- and 1-mercapto-7,8,9,10-tetrahydro-6H-dibenzo [b,d]pyrans*. J Med Chem, 1977. **20**(1): p. 17-24.

### Section 3: Toxicology

15. Consroe, P. and B.S. Fish, *Rabbit behavioral model of marijuana psychoactivity in humans*. Med Hypotheses, 1981. **7**(8): p. 1079-90.
16. Hollister, L.E., *Tetrahydrocannabinol isomers and homologues: contrasted effects of smoking*. Nature, 1970. **227**(5261): p. 968-9.
17. Beardsley, P.M., J.A. Scimeca, and B.R. Martin, *Studies on the agonistic activity of delta 9-11-tetrahydrocannabinol in mice, dogs and rhesus monkeys and its interactions with delta 9-tetrahydrocannabinol*. J Pharmacol Exp Ther, 1987. **241**(2): p. 521-6.
18. Compton, D.R., et al., *Synthesis and pharmacological evaluation of ether and related analogues of delta 8-, delta 9-, and delta 9,11-tetrahydrocannabinol*. J Med Chem, 1991. **34**(11): p. 3310-6.
19. Rapak, R.S. and A. Makriyannis, *Structure-Activity Relationships of the Cannabinoids*, R. S., Editor. 1987, National Institute of Drug Abuse

# **Isomers of THC**

## **Section 4: Therapeutic use**

## Contents

1.	Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use.....	3
2.	Listing on the WHO Model List of Essential Medicines .....	3
3.	Marketing Authorizations (as a Medicinal Product).....	3

## **1. Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use**

---

No information available

## **2. Listing on the WHO Model List of Essential Medicines**

---

Not listed on the WHO Model List of Essential Medicines

## **3. Marketing Authorizations (as a Medicinal Product)**

---

No known marketing authorizations



# Isomers of THC

## Section 5: Epidemiology

## Contents

1.	Epidemiology.....	3
2.	Industrial use .....	3
3.	Therapeutic use .....	3
4.	Non-medicinal use, abuse, dependence .....	3
5.	Nature and magnitude of the public health problems related to misuse, abuse, and dependence 3	
6.	Licit production, consumption, and international trade .....	3
7.	Illicit manufacture and traffic .....	3
8.	References .....	4

## 1. Epidemiology

---

Of the 95 studies relevant to THC, one study analyzed changes in potency of cannabis in the United States between 1995 and 2014 by both  $\Delta^9$ -THC and  $\Delta^8$ -THC content (8). Prior to 2009,  $\Delta^8$ -THC was not detected in cannabis seizures in the United States; a gradual increase in  $\Delta^8$ -THC was observed from 0.01% to 0.07% in 2014 (8). Compared to  $\Delta^9$ -THC,  $\Delta^8$ -THC content was lower by a factor of 10 and increasing potency of  $\Delta^8$ -THC did not appear to impact  $\Delta^9$ -THC concentrations (8)

## 2. Industrial use

---

No data available

## 3. Therapeutic use

---

No data available

## 4. Non-medicinal use, abuse, dependence

---

No data available

## 5. Nature and magnitude of the public health problems related to misuse, abuse, and dependence

---

No data available

## 6. Licit production, consumption, and international trade

---

No data available

## 7. Illicit manufacture and traffic

---

No data available

## 8. References

---

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (5th edition). Philadelphia, USA: American Psychiatric Association; 2013.
2. World Health Organization. The ICD-10 classification of mental and behavioural disorders: Diagnostic criteria for research. Geneva: 1993.
3. ElSohly MA, Slade D. Chemical constituents of marijuana: The complex mixture of natural cannabinoids. Life Sciences. 2005;78(5):539-48.
4. PRISMA. Prism Flow Diagram 2015 [Accessed: 04/04/2018]. Available from: <http://prisma-statement.org/prismastatement/flowdiagram.aspx>.
5. International Narcotics Control Board. List of Psychotropic Substances under International Control. Green List. 2016 [04/04/2018]. Available from: [https://www.swissmedic.ch/dam/swissmedic/en/dokumente/bewilligungen/btm/conversion\\_factorspsychotropics.pdf.download.pdf/conversion\\_factorspsychotropics.pdf](https://www.swissmedic.ch/dam/swissmedic/en/dokumente/bewilligungen/btm/conversion_factorspsychotropics.pdf.download.pdf/conversion_factorspsychotropics.pdf).
6. Hollister LE. Tetrahydrocannabinol isomers and homologues: contrasted effects of smoking. Nature. 1970;227(5261):968-9.
7. Huffman JW, Duncan Jr SG, Wiley JL, Martin BR. Synthesis and pharmacology of the 1',2'-dimethylheptyl-DELTA<sup>8</sup>-THC isomers: Exceptionally potent cannabinoids. Bioorganic and Medicinal Chemistry Letters. 1997;7(21):2799-804.
8. ElSohly MA, Mehmedic Z, Foster S, Gon C, Chandra S, Church JC. Changes in Cannabis Potency Over the Last 2 Decades (1995-2014): Analysis of Current Data in the United States. Biol Psychiatry. 2016;79(7):613-9.

## Section 5: Epidemiology

### Appendix 1: Search Strategy for isomers of THC

Following databases were searched using OVID on March 8, 2018:

1. Embase
2. Medline
3. PsycINFO

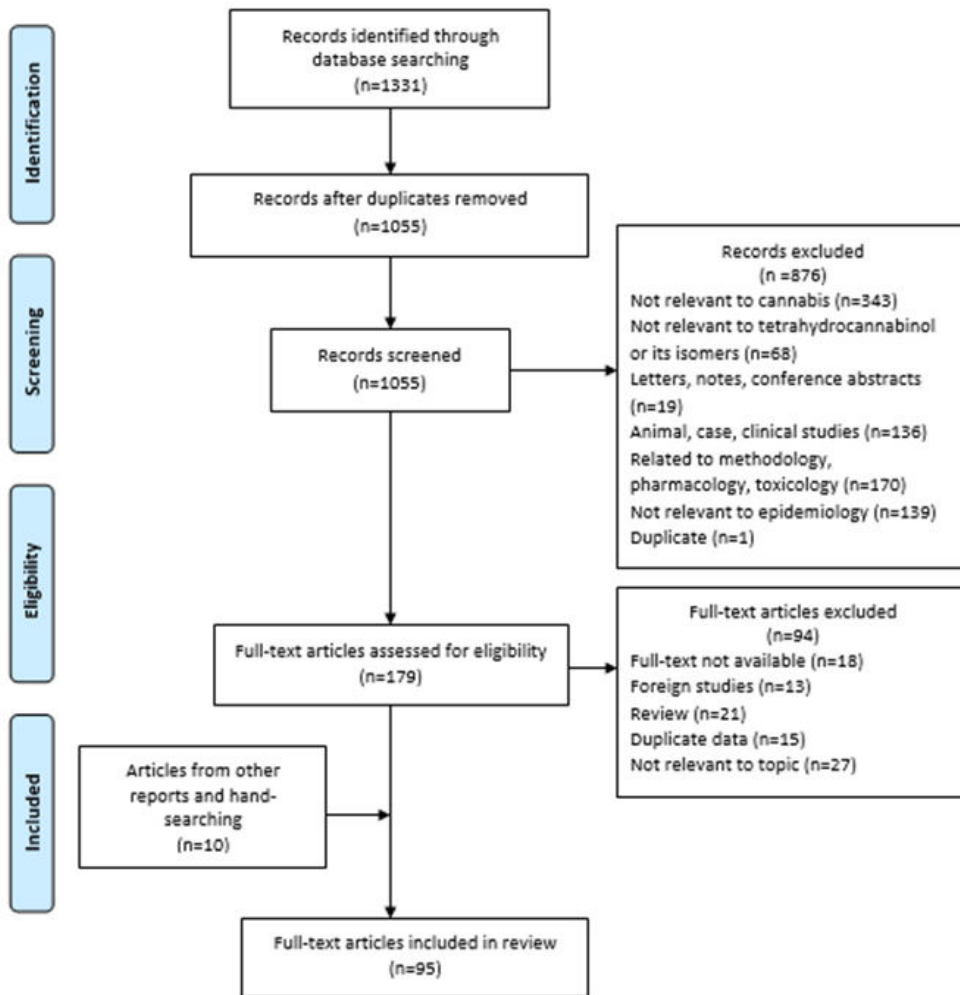
The search strategy (Table 1) was the same as for report 3, but for report 4, we further selected all articles which contained specific information on isomers (for a list of isomers see Table 2).

#### 8.1.1 Table 1: Search strategy for Reports 3 and 4

No.	Searches	Results
1	Human/ or humans/	36244807
2	limit 1 to yr="2000 -Current"	21066974
3	(bibliography or case reports or clinical conference or conference abstract or conference paper or conference proceeding or "conference review" or comment or editorial or in vitro or letter).pt.	8530671
4	2 not 3	16300231
5	epidemiology or exp epidemiology/	3693795
6	prevalence or exp prevalence/	1580556
7	incidence or exp incidence/	1888341
8	population or exp population/	3537733
9	5 or 6 or 7 or 8	8094152
10	delta-9-tetrahydrocannabinol	6047
11	tetrahydrocannabinol or THC	25380
12	dronabinol or exp dronabinol/	13589
13	10 or 11 or 12	29610
14	4 and 9 and 13	1331
15	remove duplicates from 14	1055

Section 5: Epidemiology

8.1.2 Figure 1: PRISMA Diagram for Reports 3 and 4 (4)



## Section 5: Epidemiology

### 8.1.3 Table 2: IUPAC and trivial names of THC isomers

IUPAC name	Trivial name
7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol	$\Delta$ -6a, 10a-tetrahydrocannabinol
(9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol	$\Delta$ -6a(7)-tetrahydrocannabinol
(6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol	$\Delta$ -7-tetrahydrocannabinol
(6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol	$\Delta$ -8-tetrahydrocannabinol
6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol	$\Delta$ 10-Tetrahydrocannabinol
(6aR,10aR)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6Hdibenzo[b,d]pyran1-ol	$\Delta$ -9(11)-tetrahydrocannabinol

Trivial names from: (5)

Of 1055 studies retrieved from the search, 179 were included after screening of title and abstract (see Appendix 1 for Reports 3 and 4 for details). After full-text screening, 95 studies were ultimately included as relevant to THC.

Few articles focused on isomers of THC. The majority of articles retrieved in this search relevant to THC isomers were pharmacological and animal studies.

One study explored the different effects of smoking THC isomers and homologues, but only reported on  $\Delta^9$ -THC and  $\Delta^3$ -THC; the latter is not relevant to this report (6). Another study found the different structures of THC isomers to affect potency;  $\Delta^8$ -THC is reportedly extremely potent as defined by its affinity for the cannabinoid receptor measured by a competitive binding assay (7). Strictly relevant for epidemiology was only one study on increasing and  $\Delta^8$ -THC concentrations (8).

# Isomers of tetrahydrocannabinol (THC)

## Annex 1: Member State Questionnaire



## Annex 1: WHO ECDD Member State Questionnaire

### 1. Introduction

---

Definition for the questionnaires used as the basis of this report:

Isomers and stereochemical variants of tetrahydrocannabinol as listed in Schedule 1 of the 1971 Convention on Psychotropic Substances.

Examples:

- 7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
- (9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
- (6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl- 6H-dibenzo[b,d]pyran-1-ol
- (6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
- 6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
- (6aR,10aR)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6Hdibenzo[b,d]pyran-1-ol

#### a. Overview of Responses

##### i. Q2

**Q2:** Please indicate your country.

Representatives of 75 countries answered the questionnaire:

Algeria, Armenia, Australia, Austria, Bahrain, Barbados, Belarus, Belgium, Benin, Bhutan, Brazil, Brunei Darussalam, Bulgaria, Cabo Verde, Canada, China, Colombia, Cote d'Ivoire, Cyprus, Czech Republic, Congo, Denmark, Ecuador, Egypt, El Salvador, Eritrea, Ethiopia, Fiji, Finland, France, Gabon, Georgia, Germany, Greece, Guatemala, Honduras, Hungary, India, Indonesia, Ireland, Italy, Jamaica, Kenya, Lebanon, Lithuania, Luxembourg, Malaysia, Malta, Mauritius, Mexico, Monaco, Montenegro, Mozambique, Nauru, Netherlands, New Zealand, Nicaragua, Palau, Poland, Portugal, Republic of Korea, Republic of Moldova, Russian Federation, Saint Lucia, Senegal, Serbia, Spain, Sri Lanka, Sweden, Switzerland, Thailand, Trinidad and Tobago, United Kingdom of Great Britain and Northern Ireland (the), United Republic of Tanzania, United States of America.

##### ii. Q4

**Q4:** Do you have any information about the use of **stereoisomers of THC** for any purpose (including medical or non-medical use) in your country?

21 (29%) answered yes, 51 (71%) answered no.

## 2. Results: Approved medical use

---

a. Medical use

i. Q5

1. Description of countries that have approved medical uses

**Q5:** At national level, are any **stereoisomers of THC** legally approved for **medical use** in your country? (including free text):

Countries with approved medical uses:

Colombia, Georgia, Portugal, Sweden, Switzerland.

i. Q6-Q16

**Q6:** Please indicate any approved therapeutic indications for the medical use of **stereoisomers of THC** in your country:

One country mentioned arthritis and dystonia as therapeutic indications, while another country listed multiple sclerosis as an indication (both are European countries). No other country listed any indications. One Latin American country indicated that generally this would depend on the specific product (without mentioning any product).

**Q7:** Please indicate any symptoms that **stereoisomers of THC** are approved to treat.

No specific symptoms were mentioned.

**Q8.** Please indicate whether there are any permitted marketed products of **stereoisomers of THC**:

None mentioned (one country mentioned Sativex, which is not an isomer; but is a mixture of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD)).

**Q9:** Are there any ongoing **approved clinical trials** in your country that are developing **stereoisomers of THC** for medical use?

No approved clinical trials.

## Annex 1: WHO ECDD Member State Questionnaire

**Q10:** Please indicate product name/ trial number/ study phase of any ongoing trials that are developing products of **stereoisomers of THC** for medical use.

No trials listed

**Q11:** Do individuals require a prescription to obtain **stereoisomers of THC**?

The three countries answering positively on Q6 specified yes. However, as indicated above, it is not clear what medications based on isomers they refer to.

**Q12.** What types of professionals are allowed to prescribe **stereoisomers of THC**?

Four countries answering positively listed medical doctors/psychiatrists but this seems to be just a general statement about prescription (see above).

**Q13.** What kinds of settings are approved to legally dispense **stereoisomers of THC** in your country?

The same three countries answered positively on Q6 and they listed just the usual dispensation sites in these countries.

**Q14:** If patients use medical **stereoisomers of THC** on prescription or recommendation of a health professional, will they be **reimbursed** for the costs of their medication?

None

**Q15:** Are any clinical guidelines used in your country for the prescribing of medical **stereoisomers of THC**?

None.

**Q16.** Is there a regulatory agency in your country that monitors **stereoisomers of THC** for medical use?

Three countries (referred to above) reported having regulatory agencies monitoring the use of medical stereoisomers of THC.

## Annex 1: WHO ECDD Member State Questionnaire

- b. National legislation
  - i. Q17-21

**Q17:** How would you describe the trend in the number of users of **stereoisomers of THC** for medical use over the last 3 years?

No information given.

**Q18:** In the past 3 years, has your country changed its national legislation around access to cannabis-related substances for **medical use**?

Two countries have changed their laws regarding to cannabis-related substances for medical use, but it is not clear how this affects isomers/stereochemical variants of THC. Exact implementation is still pending.

**Q19:** If yes, what types of legislative changes has your country made for medical use of **stereoisomers of THC**?

Legislative change	Number of countries	%
Change to the legal status of medical cannabis	2	100
Changes to the supply of medical cannabis (e.g. changes in licensing, import – or export of products)	1	50
Changes to access to medical cannabis (e.g., variety in products, therapeutic indications, etc.)	1	50
Other	1	50

Both countries are in the Americas.

## Annex 1: WHO ECDD Member State Questionnaire

**Q20:** Is your country currently considering changes to its national legislation around access to cannabis and cannabis-related substances for medical use?

Legislative changes prepared for medical use of isomers/stereochemical variants of THC	Number of countries	%
No	16	80
Yes	4	20
Total	20	100

Legislative changes are currently mainly prepared in one European, one Asian, one American and one Australasian country.

**Q21:** In your opinion, how do you feel the changed legislation around access to stereoisomers of THC for medical use would impact / has impacted public health in your country?

Many of the countries who answered indicated not to know the impact of changed availability on public health (5 of 10 for decreased availability: 50%; 5 of 14 for increased availability: 36%).

As for potentially decreased availability of medical use of isomers/stereochemical variants of THC, 3 out of 10 countries (30%) saw a substantial or slightly negative impact, and 2 (20%) expected no impact.

As for increased availability, 4 out of 14 countries (29%) saw either a slightly or substantially positive impact, 2 (14%) expected no impact, and 3 (21%) a slightly or substantially negative effect.

There were no distinct regional patterns.

### 3. Results: Prevalence of non-medical use

---

- a. Non-Medical use (Countries with approved non-medical use can be named)
  - i. Q22

**Q22:** On a **national level**, are **stereoisomers of THC** *legally* available for non-medical use in your country?

Only 4 out of 26 (15%) countries, all European, indicated legal availability of isomers/stereochemical variants of THC for non-medical use, one explicitly for scientific use.

- ii. Q23

**Q23:** Are **stereoisomers of THC** used for cultural, ceremonial, or religious purposes in your country?

None of the 21 countries who answered indicated cultural, ceremonial or religious use.

- b. Public health impact of use
  - i. Prevalence data
    - 1. Adults:

**Q24:** Does your country collect prevalence data around the use of **stereoisomers of THC**?

Four out of 21 countries who answered this question indicated that they collect prevalence data on non-medical use of isomers/stereochemical variants of THC: one African country, two European and one country in the western Pacific region.

**Q25.** Prevalence of use of **stereoisomers of THC** amongst adults (over 18 years of age)?

Only one country indicated data, but from the level of prevalence and the near impossibility of identifying isomers/stereochemical variants of THC, these data most likely referred to cannabis plant and resin use, or use of cannabis general.

- 2. Youth:

**Q26:** Prevalence of use of **stereoisomers of THC** for non-medical use amongst **young people** (below 18 years of age).

See answer Q25

## Annex 1: WHO ECDD Member State Questionnaire

### 3. General Trends:

**Q27:** How would you describe the number of users of **stereoisomers of THC** for non-medical use over the last 3 years in your country?

All 3 countries that answered reported no change.

#### ii. Primary care presentations

##### **Q28-29**

**Q28:** Does your country collect data about presentations to **primary care settings** due to the use of **stereoisomers of THC**?

Of the 20 countries that responded, only two (10%) European countries indicated such a collection of data.

**Q29:** Number of primary care presentations relating to **stereoisomers of THC**:

No country presented data.

#### iii. Emergency presentations

##### **Q30-32**

**Q30:** Does your country collect data about presentations to **emergency care settings** due to the use of **stereoisomers of THC**?

Of the 20 countries that responded to this question, three (15%) indicated such a collection of data: . However, no country presented data

**Q31:** Number of individuals in the past year presenting to emergency settings relating to the use of **stereoisomers of THC**:

No country presented data.

**Q32:** Please list the adverse effects presented for **stereoisomers of THC** at the emergency room/department.

Two countries commented on reasons for presentations: injuries, cannabis use disorders/withdrawal, and psychiatric comorbidity were each mentioned once.

## Annex 1: WHO ECDD Member State Questionnaire

### iv. Drug treatment presentations Q33-34

**Q33:** Does your country collect data about presentations to substance misuse treatment settings due to the use of **stereoisomers of THC**?

Drug treatment for isomers/stereochemical variants of THC	Number of countries	%
No	13	68
Unsure	3	16
Yes	3	16
Total	19	100

*It is not sure, if these data do not pertain to cannabis in some of the countries answering (see general comments to the questionnaire in Question 43)*

**Q34:** Number of individuals in the past year presenting to **substance misuse treatment** due to **stereoisomers of THC**:

None.

### v. Poison Centres Q35-Q36

**Q35:** Does your country collect data about calls to **poison control centres** due to the use of **stereoisomers of THC**?

Poison centre visits due to isomers/stereochemical variants of THC	Number of countries	%
No	13	65
Unsure	5	25
Yes	2	10
Total	20	100

*While THC is measured the origin of the THC is not clear. Mostly this would be due to consumption of cannabis in other forms than isomers/stereochemical variants of THC*

**Q36:** Number of calls to **poison control centres** due to the use of **stereoisomers of THC**.

No relevant answer.

### vi. Cases of impaired driving

**Q37:** Does your country collect data about cases of impaired driving due to the use of **stereoisomers of THC**?



## Annex 1: WHO ECDD Member State Questionnaire

Impaired driving for isomers/stereochemical variants of THC	Number of countries	%
No	12	63
Unsure	4	21
Yes	3	16
Total	19	100

*While THC is measured in the impaired driving tests, the origin of the THC is not clear. Mostly this would be due to consumption of cannabis in other forms than isomers/stereochemical variants of THC (comments on Q36 and general comments to the questionnaire in Q43)*

**Q38:** Number of cases of **impaired driving** due to **stereoisomers of THC**:

No relevant answer.

### c. National legislation

**Q39:** In the past 3 years, has your country changed its national legislation around access to **stereoisomers of THC** for **non-medical use**?

While only one of 21 countries claimed to have changed the law, detailed answers to questions 39 and 40 would indicate that these changes may not concern use of isomers/stereochemical variants of THC for non-medical use.

**Q40:** If yes, what types of legislative changes has your country made for **non-medical use** of **stereoisomers of THC**?

No relevant answers (see also Q39).

**Q41:** Is your country currently considering changes to its national legislation around access **stereoisomers of THC** for **non-medical use**?

Only one out of 20 countries indicated such potential changes; however, it is unclear if these changes actually pertain to isomers/stereochemical variants of THC.

**Q42:** In your opinion, how do you feel the **changed legislation around access** to **stereoisomers of THC** for non-medical use would impact / has already impacted public health in your country?

Potential impact on public health for these few countries with implemented and planned legislative changes cannot be ascertained.

#### **4. Comments from countries**

---

Most of the comments were about general legislation and discussion of cannabis policy in general with few specific comments to isomers/stereochemical variants of THC. Also, several countries specified that isomers/stereochemical variants of THC were playing no role in medicinal cannabis in their countries. Otherwise, there were no specific comments on the medical use of isomers/stereochemical variants of THC. Finally, several countries highlighted that many of their answers referred to THC in general.

## 5. Conclusions

---

Overall, to our knowledge, no country has approved isomers/stereochemical variants of THC for medical use, and answers indicating such approval were based on erroneous perceptions of existing medications such as Sativex or Nabilone being based on isomers/stereochemical variants of THC.

Answers to the questionnaire on prevalence and potential complications of isomers/stereochemical variants of THC are not conclusive and have to be taken very cautiously, as the comments of many countries indicated they had been unclear about what information the questions were asking for, and/or that they had confounded medical or non-medical cannabis use in general with specific uses of isomers/stereochemical variants of THC. Also, some countries explicitly specified in the general comments that they were not answering specifically for isomers/stereochemical variants of THC.

Overall, isomers/stereochemical variants of THC do not seem to play a role either for medical or for non-medical use, except for some scientific experimental use.