Outline

- Brief review of isomer nomenclature
- THC numbering systems
- THC isomers
- Conversion of CBD to THC
Isomers:
Molecules with Same Molecular Formula but Differ Structurally

Isomers Come in Many Forms

- Constitutional (structural) isomers
- Stereoisomers (spatial isomers)
  - Diastereomers
  - Enantiomers
  - Cis-trans isomers
  - Conformers
  - Rotamers
A molecule containing a carbon atom with four different groups form a “chiral” molecule

- Optically active, rotates polarized light (d-, l-)

A molecule with a single chiral carbon can exist as two mirror images that can’t be superimposed

- Enantiomers have identical physical properties
Importance of Chirality

**Biological importance -**

Active Molecule  Inactive Molecule

1. **(a)** Molecule fits receptor site, leading to a response
2. **(b)** Molecule does not fit receptor site; no response
Tetrahydrocannabinol Numbering System Can Be Confusing

- Current literature generally uses “Dibenzopyran” system
- Older literature used “Monoterpenoid” system

Δ9-THC
Dibenzopyran System

Δ1-THC
Monoterpenoid System
Tetrahydrocannabinol Isomers

- Δ9-THC has a total of 4 stereoisomers at C6a and C10a (cis and trans)
- Seven double-bond isomers (six in addition to Δ9-THC)
- Only the R, R form of Δ9-THC and Δ8-THC at C6a and C10a occur naturally
- Thirty stereoisomers
Double-Bond Isomers of THC
Double-Bond Isomers of THC

- \( \Delta 6a(7) \)-THC
- \( \Delta 6a(10a) \)-THC
- \( \Delta 10 \)-THC
Δ9-THC

- Δ9-THC is a naturally occurring cannabinoid
- Two stereogenic centers; four stereoisomers (R/S-isomers)
  - The natural active isomer is the R,R-isomer
- R,R-isomer tested extensively in humans
Δ8-THC

- Δ8-THC is a naturally occurring minor cannabinoid
- Two stereogenic centers; 4 stereoisomers (R/S-isomers)
  - Natural active isomer is R, R-isomer
- Tested in humans by oral and IV route (Hollister et al., 1973, Clin Pharmacol Ther)
  - Δ8-THC produced similar effects as Δ9-THC
  - Was approximately 75% as potent as Δ9-THC
- Tested in humans by smoked route (Karniol & Carlini, 1973, Pharmacol)
  - Δ8-THC produced similar effects as Δ9-THC
  - Was approximately 50% as potent as Δ9-THC
Δ6a(10a)-THC

- Δ6a(10a)-THC is not a naturally occurring cannabinoid
- One stereogenic center; two stereoisomers (R/S-isomers)
- R- and S-Δ 6a(10a)-THC tested in humans by IV route (Hollister et al., 1987, Psychopharmacol)
  - S-isomer produced psychic effects similar to Δ9-THC and was 1:3 to 1:6 less potent
  - R-isomer was inactive at 8 mg
- Δ 6a(10a)-THC tested in humans by smoked route (Isbell et al., 1967, Psychopharmacologia [Berl.])
  - Inactive
- Can be synthesized by a condensation reaction between olivetol and pulegone
Δ7-THC

- Δ7-THC is not a naturally occurring cannabinoid
- Three stereogenic centers; eight stereoisomers (R/S-isomers)
- Activity of C9 R/S-epimers (Huffman, et al., Tetrahedron, 1995)
  - Molecular modeling studies predict activity in range of Δ9-THC for the C9S-epimer
  - Cannabinoid receptor binding studies show activity for C9S-epimer (Ki=71.5nM) compared to Δ9-THC (Ki=41nM). C9R was less active (Ki=304nM)
- Can be synthesized by condensation of olivetol with p-menth-4-en-3,8-diol in toluene-p-sulphonic acid (WHO, 2018)
Δ6a(7)-THC

- Δ6a(7)-THC is not a naturally occurring cannabinoid
- Two stereogenic centers; four stereoisomers (R/S-isomers)
- Arnone et al. reported synthesis in 1975 (Tetrahedron, 31, 3093-3096) but did not test for biological activity
- Can be synthesized by condensation of olivetol with p-menth-4-en-3,8-diol in toluene-p-sulphonic acid (WHO, 2018)
Δ10-THC

- Δ10-THC is not a naturally occurring cannabinoid
- Two stereogenic centers; four stereoisomers (R/S-isomers)
- Did not produce Δ9-THC-like effects in pigeons (Jarbe et al., Eur. J. Pharmacol. 1988)
- Can be synthesized by base catalyzed isomerization of Δ9-THC (Srebnik, et al. 1984, J Chem Soc Perkin Trans)
Δ9(11)-THC

- Δ9(11)-THC is not a naturally occurring cannabinoid
- Two stereogenic centers; four stereoisomers (R/S-isomers)
- Δ9(11)-THC produces Δ9-THC-like effects in mice (iv)\(^1\), rhesus monkeys (im)\(^2,3\), and rats (ip).\(^2,4\) Can be synthesized by addition of HCl followed by a dichlorination procedure


\(^4\) 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.
Number of Stereoisomers of THC

<table>
<thead>
<tr>
<th>Isomer</th>
<th>#Optical Centers</th>
<th>#Stereoisomers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ9-THC</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Δ10-THC</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Δ6a(10a)-THC</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Δ6a(7)-THC</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Δ7-THC</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Δ8-THC</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Δ9(11)-THC</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>
# Tabulation of Human Potencies of Cannabinoids

<table>
<thead>
<tr>
<th>Cannabinoid</th>
<th>%Potency (Relative to Δ9-THC)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ9-THC</td>
<td>100</td>
<td>(1)</td>
</tr>
<tr>
<td>Δ10-THC</td>
<td>Not Tested</td>
<td></td>
</tr>
<tr>
<td>Δ6a(10a)-THC</td>
<td>30, 0</td>
<td>(1,2)</td>
</tr>
<tr>
<td>Δ6a(7)-THC</td>
<td>Not Tested</td>
<td></td>
</tr>
<tr>
<td>Δ7-THC</td>
<td>Not Tested</td>
<td></td>
</tr>
<tr>
<td>Δ8-THC</td>
<td>75, 50</td>
<td>(1,3)</td>
</tr>
<tr>
<td>Δ9(11)-THC</td>
<td>Not Tested</td>
<td></td>
</tr>
<tr>
<td>11-OH-Δ9-THC</td>
<td>120</td>
<td>(1)</td>
</tr>
<tr>
<td>11-OH-Δ8-THC</td>
<td>90</td>
<td>(1)</td>
</tr>
<tr>
<td>8-Alpha-OH-Δ9-THC</td>
<td>25</td>
<td>(1)</td>
</tr>
<tr>
<td>8-Beta-OH-Δ9-THC</td>
<td>20</td>
<td>(1)</td>
</tr>
<tr>
<td>Parahexyl (Synhexyl)</td>
<td>30</td>
<td>(1)</td>
</tr>
<tr>
<td>Δ9-THCV</td>
<td>25</td>
<td>(1)</td>
</tr>
<tr>
<td>CBD</td>
<td>0</td>
<td>(1)</td>
</tr>
<tr>
<td>CBN</td>
<td>0</td>
<td>(1)</td>
</tr>
</tbody>
</table>


WHO Expert Committee on Drug Dependence, 40th Report, 2018

- The WHO Technical Report Series makes available the findings of various international groups of experts that provide WHO with the latest scientific and technical advice on a broad range of medical and public health subjects.

- After reviewing the chemistry, pharmacology and toxicology of the seven isomers of THC, the committee concluded that
  - “aside from Δ-9THC, there is no evidence that any of these listed isomers are being abused or are likely to be abused so as to constitute a public health or social problem.”

C&EN Concerns About Safety and Purity of Δ8-THC

- C&EN article (August 30, 2021) warns that Δ8-THC products are not safe or pure

“The conversion of CBD into Δ8-THC also produces small amounts of Δ9-THC and Δ10-THC”
Delta 8 THC: Legal or Not

by Bruce Hovland in CBD News August 3, 2020

Delta-8 THC: Legal or Not
Backed by many scientific studies along with anecdotal proof, Delta 8 THC is enjoying the spotlight for being an amazing ingredient for medicinal and therapeutic benefits. The product is available in numerous forms, including Delta 8 THC vape cartridges, gummies, oral tinctures, and even restaurant delicacies.

However, most people are still confused regarding the legal status of Delta 8 THC. So, the question is, is Delta 8 THC legal?

Is hemp illegal in the US
The short answer to the question is that a substance that matches the definition of “hemp” is legal under the federal controlled substances laws. Delta 8 THC is measured federally legal if it is extracted from hemp containing below 0.3% delta-9-THC, according to the Agriculture Improvement Act of 2018.

So, the answer is, YES, if it is hemp-derived Delta 8. However, Delta 8 legal status can vary state to state as each state has its individual regulations regarding the hemp plant.

D8 Fruit Slice 75mg each “Max Strength” 5 per bag. 30 Bags FREE SHIPPING: $489.99
Internet Article by Justin Cooke “What is Delta 10 THC?”

Characteristics of Delta 10 THC
- Δ10 is roughly half as potent as Δ9 THC
- Δ10 is more stimulating & nootropic
- Δ10 is better than Δ9 for promoting flow states, creativity, euphoria, & focus
- Δ10 appears to have less side effects than Δ9

“These effects are likely going to make delta 10 THC a staple in the cannabis industry over the next couple of years.”
“Delta 8, 9, and 10 THC are essentially different flavors of the THC molecule.”

Comparing The Effects of THC Isomers

Relaxing
- Relaxing
- Sedating
- Muscle-Relaxant
- Increased Hunger

Stimulating
- Stimulating
- Euphoric
- Increased Hunger
- Creativity

Delta 8 THC

Delta 9 THC

Delta 10 THC
CBD is a Structural Isomer of Δ9-THC

- Same molecular formula
- Same stereochemical configuration

CBD
\[ \text{C}_{21}\text{H}_{30}\text{O}_2 \]

Δ9-THC
\[ \text{C}_{21}\text{H}_{30}\text{O}_2 \]
CBD Conversion to THC

CBD → Δ9-THC

CBD → Δ8-THC
Conditions for CBD Conversion to THC

- Feasible under acidic conditions
  - Formation of $\Delta_8$- or $\Delta_9$-THC can be in low or high yield in the presence of acid (Golombek, et al. 2020, Toxics)
  - Incubation with simulated gastric fluid (Merrick et al., 2016, Cannabis and Cannabinoid Research; Watanabe et al., 2007, Forensic Toxicol)
  - Possibly, when CBD is stored under acidic conditions (Golombek, et al. 2020, Toxics)

- Pyrolysis of CBD at e-cigarette (250-400°C) and higher temperature (500°C) produced $\Delta_9$- and $\Delta_8$-THC (Czegeny et al. 2021, Scientific Reports)

- Recent studies of low temperature vaping and oral ingestion found no conversion (Spindle et al. 2019, JAT)
Take Home Message

- Keep your eyes and minds open for the potential appearance of more cannabinoid isomers!