Cannabinoids: Big Pharma's Black Sheep

**Historical Timeline**

- **~2600 BCE**: Ancient Chinese medicinal texts mention hemp for cramps and pain.
- **1000 CE**: Cannabis spreads through the Arab world due to Persian influence.
- **1300 CE**: Cannabis spreads across Africa. Soudoun Sheikouni prohibits hashish.
- **1500 CE**: Spaniards bring industrial hemp to S. America for cultivation.
- **1619 CE**: Virginia passes act requiring hemp growers to grow both English and Indian Hemp.
- **1700 CE**: Bonaparte’s invasion in Egypt leads to regulars consuming hashish in the alcoh-prohibited region.
- **1798 CE**: William O’Shaughnessy studies cannabis’ medicinal properties for stimulating appetite, inflammatory pain, and infant seizures.
- **1843 CE**: The Hasheesh Eater by Fitz Hugh Ludlow is published.
- **1896 CE**: CBD is determined to not be the active constituent.
- **1930’s CE**: Reefer Madness is produced (youtu.be/zhQlCMHhFzw).
- **1936 CE**: Manhuana Tax Act bans hemp production.
- **1940 CE**: R. Adams Synthesizes CBD.
- **1842 CE**: THC extracted successfully, but not identified.
- **1863-7 CE**: Mechoulam & Gaoni characterize THC interaction.
- **1984 CE**: Allyn Howlett finds GPCR/Δ9.
- **1985 CE**: Nabilone, first synthetic cannabinoid gains FDA approval.
- **1991 CE**: CB1 is cloned.
- **1992 CE**: Mechoulam discovers Anandamide.
- **1993 CE**: CB2 is cloned.
- **1996 CE**: John W. Huffman publishes alkyl-naphthyl pyroles.
- **1996 CE**: CA. Legalizes medical MJ.
- **2004 CE**: FDA approves Dronabinol (THC).
- **2006-8 CE**: Rimonabant approved in EU, then pulled from market.
- **2012 CE**: CO & WA legalize Cannabis.
- **2016 CE**: CB1 Crystal is published.
- **2018 CE**: Farm Bill legalizes CBD, FDA approves Epidiolex (CBD).
- **2019 CE**: CB2 Crystal published.

**Selected Scientific Champions of the Cannabinoids**

- **Jacques-Joseph Moreau**: First Physician to publish research on hashish’s effects on the CNS.
- **William O’Shaughnessy**: Published a number of therapeutic applications of cannabis in India including spasticity reduction, anti-inflammatory, anti-convulsive.
- **Allyn Howlett**: Professor at Wakeforest who is credited with discovering the first evidence for a cannabinoid receptor in the human body.
- **John W. Huffman**: Discovered >200 research molecules that have furthered cannabinoid understanding.
- **Raphael Mechoulam**: Discovery/Synthesis of THC. Discovery of anandamide.

**Cannabis Sativa**
- Tall Stalk
- Narrow leaf
- High THC content
- More equal THC/CBD ratio

**Cannabis Indica**
- Shrubby plant
- Wide leaf
- Low cannabinoid content
- Auto-flowering

Botanists disagree on the taxonomic classification of Cannabis, some believe that *sativa* and *indica* are the same species. They recommend calling them *Cannabis Sativa* subspecies *sativa* or *indica* respectively.

For Mechoulam’s Story See: youtu.be/qwFC5ye2UBk
Endocannabinoids: Identity, Biosynthesis and Related Systems

Anandamide (N-arachidonoylethanolamine aka AEA)
- Isolated from pig’s brains by Raphael Mechoulam and coworkers (1992)
- ananda (Sanskrit for joy, bliss, delight) + amide
- Member of the eicosanoid family
- Binds to CB1 and CB2 as a full agonist
- Many of the observed biological effects of the phytocannabinoids are similar to AEA’s
- Involved in processes like memory impairment, appetite stimulation, inflammation, immune response, cell proliferation, reward and pain systems.

2-Arachidonoylglycerol (2-AG)
- CB1 and CB2 receptor agonist, less potent than AEA but found in higher conc.
- As research continues, 2-AG grows in its relevance as an endocannabinoid
- Considered the primary endogenous ligand for CB2
- Synthesized by PLC and DAGL. It’s synthesis is Ca^{2+} dependent.
- Hydrolyzed by MAGL and FAAH

Virodhamine
- CB1 antagonist and CB2 agonist.
- Found in the hippocampus but largely concentrated in the peripheral tissue
- Modulates body temperature
- Can be produced non-enzymatically. Biosynthesis unknown.

Paracetamol (Acetaminophen) is a cannabinoid? NO!
- Acetaminophen has been used to relieve inflammatory pain for over a century.
- It loses activity in CB1 knockout mice, despite looking nothing like AEA or 2-AG.
- Furthermore, Acetaminophen is largely devoid of anti-inflammatory activity itself.

Anandamide Biosynthesis and degradation by FAAH
- N-acyltransferase (NAT)
- phosphatidylyethanolamine (PE)
- acylphosphatidylyethanolamine phospholipase D (NAPE-PLD)
- Fatty Acid Amide Hydrolase (FAAH)
- Overview:
  - Prostaglandins & other Lipid Mediators. 2009, 89, 112–119

Related Eicosanoid signaling molecules
- homo-γ-linolenoylethanolamide
- virodhamine
- arachidonoyldopamine
- noladin ether
- docosatetraenoylethanolamide
- oleamide

- AM404 was identified as an endogenous cannabinoid reuptake inhibitor that inhibits FAAH.
- AM404 was also found to act as a COX-1 and -2 inhibitor and TRPV agonist, preventing prostaglandin synthesis.
- Recent evidence also suggests that AM404 interacts directly with CB1.


Cannabinoids: Big Pharma's Black Sheep

Stephen Harwood

Baran Group Meeting
7/18/2020

The Cannabinoid Receptors

- Originally, phytoannabinoid activity was thought to be lipid membrane related.
- First evidence of a receptor was found by Prof. Allyn Howlett (Wakeforest).
- CB1 and CB2 are members of the rhodopsin-like GPCR family, largest family.
- In neurons, they are involved retrograde signaling (post-synaptic communication to pre-synaptic neurons).
- Although only two receptors have been called cannabinoid receptors, much debate exists about the total number of endocannabinoid receptors with some evidence suggesting the existence of more.
- CB1 and CB2 have been the target of dozens of R&D programs.
- Involved in memory, appetite, inflammation, thermoregulation immune response, cell proliferation & differentiation, reward and pain systems.

CB1 (aka CB1R) Cannabinoid Receptor 1

- Cloned in 1990 for the first time. Interacts with Gi, Gs and Go proteins.
- Responsible for Δ9-THC's psychotropic effects.
- Ubiquitous throughout the brain and CNS.
- Activation leads to a cAMP cascade in addition to Ca2+ and K+ channel inhibition affecting neural plasticity and slowing repolarization.
- Receptors located in the basal ganglia and cerebellum are associated with THC's effects on gait.
- Receptors in the cerebral cortex and hippocampus are responsible for THC's impact on cognition and memory (loss).
- It is also located in the spleen, tonsils, GI tract, uterus, prostate, cascular smooth muscles and adrenal glands peripherally, leading to numerous pharma campaigns on IBS and GI conditions.

CB2 (aka CB2R) Cannabinoid Receptor 2

- Cloned in 1993 for the first time. Interacts only with Gi.
- Responsible for Δ9-THC's anti-inflammatory effects.
- CB2 is present in the CNS, but not highly expressed like CB1.
- CB2 is highly expressed in the spleen and immune cells.
- CB2's expression is often upregulated in neuroinflammatory diseases like Huntington's, and Alzheimer's making it a target as a diagnostic and for therapy.
- CB2 has been shown to be involved in cell differentiation and proliferation pathways, consistent with cannabinoids effects on dev.
- CB2 is localized on microglial cells, neutrophils, macrophages, monocytes, and lymphocytes.
- In recent years multiple approaches to selective CB2 agonists have been tried by Pharma for various inflammatory conditions and for pain management.
Cannabinoids: Big Pharma's Black Sheep

The Cannabinoid Pathway

1. A stimulus leads to the synthesis of anandamide (and other endocannabinoids) as demonstrated above. Anandamide enters the synaptic cleft through not fully elucidated mechanisms (possibly involving cholesterol concentration in the lipid membrane).

2. Next, the endocannabinoid binds to the GPCR CB1 or CB2 causing a G-protein mediated signal transduction. With CB1 three events are possible: cAMP production will be downregulated, potassium ions will be imported, and calcium will be exported.

3. The movement of ions in this way decreases the neuron's ability to reach an action potential and will block future neurotransmitter release. This is how the cannabinoid system modulates neuronal plasticity.

4. Through not fully understood mechanisms, the endocannabinoid retrograde signaling molecule will be hydrolyzed. This hydrolysis can occur in the post-synaptic cell where the endocannabinoid originated from by FAAH. Hydrolysis can also occur in the pre-synaptic cell through MAGL.

Although ubiquitous in the brain, regions that have particularly high expression of FAAH are the regions primarily responsible for endocannabinoid signaling. For reasons not fully understood endocannabinoid signaling and FAAH expression are strongly related. A similar mechanism is at play with neuronally expressed CB2, although only cAMP synthesis is affected.

Key Points: Anandamide is synthesized immediately following signal transduction. It acts in retrograde. Activation of CB1 leads to short- and long-term inhibition of plasticity. Anandamide is destroyed after signaling through hydrolysis.

Cannabinoid Receptors' Role in Reward and Addiction Systems

- Physiochemical differences exist in subject populations taking cannabinoid receptor modulators while taking addictive substances compared to control groups.
- Behavioral differences in those two groups have also been observed.
- CB1 knockout mice developed less conditioned place preference while administering ethanol, nicotine or opiates. Similar behavior was observed in a mouse population taking a CB1 antagonist.
- These mice were also less likely to self-administer ethanol, nicotine, or opiates.
- When mice were given a CB1 agonist, the behavior reversed and mice were more likely to self administer alcohol, nicotine, or opiates and develop conditioned place preference.
- Mice consuming stimulants displayed more complex behavior, opposite of the other populations.
- Complex behavior was observed when administration of drugs was forced, indicating CB1 in the reward mechanism of drug consumption.

Phytocannabinoids: Biosynthesis & Bioactivity

This biosynthesis proposal is based on other citran-type natural products not on direct literature precedence.

*J. Org. Chem.* 2020, 85, 2103-2117

Phytocannabinoids: Biosynthesis & Bioactivity (cont.)

Δ9-Tetrahydrocannabinol (THC)
- CB1 and CB2 partial agonist and active constituent in cannabis.
- Metabolized in the liver by p450's to 11-OH-THC, also psychoactive.
- Highly pure samples are used as medicines for neuropathic pain and as an appetite stimulant for AIDS and chemo patients
- Approved brands are: Sativex and Dronabinol.
- It has also been credited with anti-convulsant and anti-inflammatory and anxiolytic properties.
- Beyond CB1 and CB2 THC has shown to inhibit 5HT (serotonin) receptors and have agonistic effects on TRPV (2,3,4) channels.
- Its isomer Δ8-THC is also a psychoactive CB1 and CB2 partial agonist

Cannabinol (CBN)
- Weakly psychoactive oxidized THC metabolite.
- Demonstrates higher affinity for CB2 over CB1 although its role as a modulator is still controversial.
- Has shown to be a TRPA1 agonist and TPRM4 antagonist, although behavioral or physiological effects have not been demonstrated

Cannabinol (CBD)-- What's the truth?
- CBD is NOT psychoactive.
- CBD does NOT bind to CB1 or CB2, although it may indirectly have antagonistic effects.
- CBD seems to bind as an antagonist to GPR55, a potential cannabinoid receptor.
- CBD does NOT mobilize Ca2+, nor does it influence β-arrestin recruitment.
- CBD DOES act as a mild 5HT1A agonist which could be significant if demonstrated in vivo.
- A counterbalancing anxiolytic property of CBD is observed when subjects consume THC.
- CBD is not acutely toxic, subjects have taken > 1g quantities for consecutive days without harm.
- Research suggests that CBD may prevent the degredation of anandamide.
- CBD appears to influence extinction and reconsolidation memory systems by preventing degredation of anandamide, an effect that is reversed when given a CB1 antagonist.
- Effects on hippocampal neurogenesis have been observed, and inhibited in CB1 knockout studies, again suggesting an indirect influence of CBD on CB1 receptors.
- Beyond attenuating THC’s psychosis inducing effects, CBD does not have clear anti-psychotic effects.
- CBD has shown some potential as an anti-inflammatory for collagen induced arthritis diseases, although this has not been well established.
- Several Studies have observed an "inverted U" dose response curve, further contributing to confusion in the data. This may be due to competing pathways being influenced by CBD.
- In 2018 Epidiolex (CBD) was approved by the FDA for treatment of Dravet and Lennox-Gastaut syndromes in epileptic patients 2 years and older.

Unusual Cannabinoids— >120 Cannabinoids Have been isolated to date.

Useful Pharmacology Refs:
- Br J Pharmacol 2012 165 2620
- Phil. Trans. R. Soc. B 2012 367, 3364–3378
Total Synthesis of Canabinoid Natural Products

The First Racemic Total Synthesis of $\Delta^8$-THC (Mechoulan & Gaoni, JACS 1965 3273)

The First Enantioselective Total Synthesis of $\Delta^9$-THC (Mechoulan & Gaoni, JACS 1967 4552)


Other Chiral Pool Approaches to Cannabinoids (for a review on Chiral Pool Synthesis see: Chem. Rev. 2017, 11753)

Razdan, JACS 1974, 5860

trans-$\beta$-terpineol

(1 step from trans-Limonene oxide)

Cycloaddition Approaches to Cannabinoids

(5)-citronellal

Avery, T.L. 2004 1689

machaeriol B displays some antimalarial activity and represents a unique class of hexahydrodibenzopyrans

(+)-machaeriol B

For Topical Synthesis Reviews See:
Progress in the Chemistry of Organic Natural Products
Volume 103. Phyto cannabinoids Unraveling the Complex Chemistry and Pharmacology of Cannabis sativa. Chapter 2 p. 37
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Total Synthesis of Canabinoid Natural Products (Cont.)

**Mech?**
**Name?**
LDA, TBSCI, HMPA

60%

(-)-perrottetinene
unusual cis 6,6- junction


1. POCl₃, DMF; OH; H⁺
2. NaClO₂, DMSO
3. TMSCH₂CH₂OH, DEAD, PPh₃

Structure Activity Relationship of THC

Δ⁹-THC - all remain potent.
Where R=Me or OH the
R- epimer is significantly more potent than S-
R=O is potent (Nabilone)
R=CH₂OH, the main metabolite of THC in the body,
remains psychotropic.
R=CO₂H is another metabolite, but in inactive

Removing H-bond donor increases CB₂ Selectivity

ent-THC loses
all potency.
cis-THC needs
further study.

substitution close
to aryl ring
increases CB₁ selectivity

longer alkyl chain
increases potency. Ideal: 5-9 Carbons

• When conformationally restricted, the alkyl chain pointing away
  from the phenol is more potent.
• Derivatives not containing an ether linkage (CBD-like) lose CB₁/₂
  potency.

Perspectives in Medicinal Chemistry 2018 17–39 doi:10.4137/PMC.S32171
Molecules 2018, 1526; doi:10.3390/molecules23071526
J. Med. Chem. 2017, 9913
Chem. Rev. 2016, 519

**Org. Lett. 2019, 1212**
Angew. Chem. 2016, 16370

**ACIEE 2016 7121**
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Cannabinoids in the Pharmaceutical Industry

- oxoquinolines
- naphthyridones
- coumarins
- indoles & indazoles
- imidazopyridine/pyrazine
- purines
- benzoimidazoles

Initial research began on CB₁ agonists and antagonists, however, due to the psychoactive nature of that receptor its modulation is associated with many psychological side effects.

Recently, several highly selective CB₂ scaffolds have been developed and have been tested for applications in neuroinflammatory diseases, neurodegenerative diseases, and inflammatory pain.

CB₂ is a more attractive candidate because it lacks psychotropic activity and is highly expressed in disease models.

Several clinical failures of CB₂ agonists have given rise to hopeful inverse agonists capable of binding and inactivating CB₂. Only time will tell if these molecules will prove clinically useful.

**FDA Approved Therapeutics**

<table>
<thead>
<tr>
<th>Marinol (THC) 2004</th>
<th>Nabilone (synthetic) 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Perscribed as appetite stimulant, anti-emetic</td>
<td>• Perscribed as anti-emetic</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Nabiximols (THC: CBD 1:1) 2018</th>
<th>Epidiolex (CBD) 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Perscribed for spasticity in patients with MS</td>
<td>• Perscribed for treatment of two rare epilepsy disorders</td>
</tr>
</tbody>
</table>

**Clinical Failures**

**Rimonabant (Approved 2006 by EU, withdrawn 2008)**

- CB₁ inverse agonist/antagonist.
- Designed as an anorectic antiobesity drug.
- Failed FDA NDA. See also NESS-0327.
- Withdrawn after 10% of subjects experienced mood alterations and 1% experienced suicidal ideation.
- Other common side effects were nausea, anxiety, and insomnia.

**GW-842,166X**

- CB₂ selective agonist designed by GSK.
- Brought into 4 Clinical trials, two for pain, two for drug distribution in the body.
- All trials were either withdrawn or completed without posted result.
  NCT00554762, NCT00444769, NCT00536497, NCT00511524

**SAB378 (CB-13)**

- Peripherally located CB₁ and CB₂ agonist.
- Designed to inhibit GI Tract transit, no effect found in clinic.
- Also looked at for HIV associated neuropathy.

**Clinical Failures (cont.)**

**Otenabant**

- CB₁ antagonist discontinued by Pfizer after Rimonabant.
- Designed as an anorectic antiobesity drug.
- Similar clinical side effects to Rimonabant.

**Drinabant**

- CB₂ antagonist discontinued after phase Iib trial for obesity.
- Also evaluated for schizophrenia, Alzheimers, Parkinsons, and nicotine dependence.
- Severe psychiatric effects.
- Licensed by Opiant in 2018 for acute cannabidiol overdose.

**V158866**

- FAAH inhibitor spinal cord injury induced neuropathic pain.
- No substantial effect on primary endpoint after Phase II.
- Was found to successfully elevate endocannabinoid levels in the body.
- Has since been transferred to Neuritek Thera for PTSD research.
  NCT01748695

**PF-04457845**

- FAAH inhibitor for osteoarthritic pain.
- No substantial effect on primary endpoint after Phase II.
- Was found to increase endocannabinoid levels in the body.

**Synthesis: WO 2009/1092224 A1**

**Olenabtant**

- CB₂ antagonist discontinued by Pfizer after Rimonabant.
- Designed as an anorectic antiobesity drug.
- Similar clinical side effects to Rimonabant.

**Drinabant**

- CB₂ antagonist discontinued after phase Iib trial for obesity.
- Also evaluated for schizophrenia, Alzheimers, Parkinsons, and nicotine dependence.
- Severe psychiatric effects.
- Licensed by Opiant in 2018 for acute cannabidiol overdose.

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- FAAH inhibitor for osteoarthritic pain.
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- Was found to increase endocannabinoid levels in the body.

**Pain, 2012, 1837; NCT00981357**
**Clinical Failures (cont.)**

LY2828360
- CB₂ agonist developed by Lilly & Co. for knee pain
- No substantial effect on primary endpoint after Phase II
- Currently being evaluated for neuropathic pain and reduction of opioid dependence development

Mol Pharmacol 2018, 49, 62,

PF-06818883
- MAGL inhibitor pulled from Phase I for safety reasons.
- Evaluated for cerebral hemorrhage

BIA-10-2474
- FAAH inhibitor developed by Bial-Portela & Ca. SA
- For anxiety, Parkinson's, chronic pain, hypertension, cancer
- Phase II halted after highest dose subjects experienced severe permanent neuronal damage and death.
- Caused Janssen to halt development of JNJ-42165279
- Later determined that data of lung damage in dogs and death of monkey models (high dose) were omitted.
- Exact mechanism of toxicity unknown, although, the inhibitor is irreversible not reversible as claimed by Bial.
- Injured subjects had deep hemorrhagic and necrotic lesions, particularly in the hippocampus and pons.

**Ongoing and Unknown Status (Cont.)**

Namacizumab
- First in class negative allosteric modulating antibody (NAMA) acting to stabilize CB₂ in an inactive form
- Phase I cleared primary endpoints
- Phase II planned for non-alcoholic fatty liver disease

Olorinab (APD371)
- CB₂ agonist for abdominal pain in Chron's disease.
- Successful Phase IIa, currently recruiting for Iib
- Peripherally selective.

URB597
- FAAH inhibitor developed by Kadmus Pharmaceuticals
- Developed for Schizophrenia symptoms
- Listed to start Phase I in 2020, not currently recruiting.

NCT00916201

JNJ-42165279
- FAAH inhibitor developed by Janssen and paused after Bial clinical trial deaths.
- Phase II completed 2019, results not yet released.
- Targeted for anxiety, major depressive disorders

MK-4409
- FAAH inhibitor developed by Merck
- Inflammatory and Neuropathic Pain
- Clinical trial results not released.


ABX-1431
- MAGL Inhibitor developed by Abide Thera.
- Tourette Syndrome, chronic motor tic disorder
- Phase I promising, currently in Phase II

NCT03625453

**Useful Reviews on Cannabinoid Based Research Chemicals**

New approaches and challenges to targeting the endocannabinoid system. Nature Reviews Drug Discovery. 2018 623


Perspectives of Cannabinoid Type 2 Receptor (CB₂-R) Ligands in Neurodegenerative Disorders: Structure–Affinity Relationship (SAR) and Structure–Activity Relationship (SAR) Studies. J. Med. Chem. 2017 9913

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Stephen Harwood

7/18/2020

Illicit Synthetic Cannabinoids
- Although their names may seem comical such as "Funky Monkey, Ion Lab, Barely Legal, Moon Spice, Mr. Nice Guy, Sweet Leaf, XLR-11, and AK47 24 karat Gold" Synthetic Cannabinoids are no laughing matter.
- Known most widely as "Spice" or "K2", illicit synthetic cannabinoids are frequently derived from failed CB1 and CB2 clinical candidates or research models.
- As full CB1 and CB2 agonists or antagonists, these molecules are HIGHLY potent and provide a very different high than THC and cannabis.
- Side effects are usually severe (can result in death) such has migraines, nausea, catatonia, anxiety, seizures, paranoia, suicide ideation, confusion and tachycardia.
- Acute and long term toxicology of these compounds are often unknown, and products change their chemical composition and active compounds to avoid detection and legal trouble.
- The 2000's saw a large increase in the usage of these products leading to a series of deaths.
- The illicit use of compounds discovered by Pharma has been a black mark on their record to society with some researchers such as JWH being forced to live in hiding.

The Classes of Synthetic Cannabinoids
- There are roughly 7 classes of compounds that are frequently found in Spice products.
- New active compounds are being identified by forensic chemists every day.
- Nearly all of these scaffolds have been discovered through research of the endocannabinoid system.

Naphthyli(lindoies, methylindoles, pyroles, methylindenes)

1. Mg; CO2
2. SOCl2
1. npentylBr
Base

Naphthyli(lindoies, methylindoles, pyroles, methylindenes)

1. Mg; CO2
2. SOCl2
1. npentylBr
Base

Tetramethylcyclopropylindoles
- Derived from Abbott research chemical UR-144, although the alky fluoride was never identified. Installation of the fluoride confers a 2-5 fold increase in potency in vitro although it is unclear if this is conferred in vivo.
- Named after the first liquid-propelled rocket engine developed in the US.
- Associated with acute kidney injury and cerebral ischemia.

Phenylacetylindoles
- RCS-8 is a derivative of JWH-250, although it has never been published academically. Its widespread use recreationally has led to it being specifically listed in the 2011 Controlled substances act.

Adamantoylindoles
- Much stronger CB1 and CB2 agonist than THC but slightly weaker than JWH-018.

Indazole Carboxamides
- Developed by Pfizer in 2009.
  - EXTREMELY potent CB1/CB2 agonist
  - Linked to hundreds of hospitalizations, some deaths.

Cyclohexylphenols
1. MeBr
2. DIBAL; H+
3. Wittig
4. Pd/C, H2
5. Br2
6. BnBr

Quinolinyl esters
- Identified in synthetic cannabis products in Japan in 2013.
  - EXTREMELY potent CB1/CB2 agonist
  - Origins unclear, might be entirely derived from SAR understanding.

J. Med. Chem. 1984, 67


Reviews on SC’s:
- Hijacking of Basic Research: The Case of Synthetic Cannabinoids. 10.3788/tipress.2011.op.0007.1111.
"Whoever battles monsters should see to it that in the process he does not become a monster himself. And when you look long into the abyss, the abyss also looks into you"

*Beyond Good and Evil*, #146

-- Nietzsche