Applying Pharmacy Scientific Principles to the Laws Associated with Synthetic Drug of Abuse

What is a pharmacophore?
• the portion of drug molecule required for pharmacological activity

Phenanthrene
Heroin

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Drug-Targets
• Receptors
• Enzymes
• Membrane Transporters
Fentanyl: **Targets**

- Pharmacological targets
  - Opioid receptors
    - Members of the GPCR family
      - Mu, delta, and kappa
        - $G_{o}$ and $G_{i}$
        - Inhibition AC, voltage-gated Ca$^{2+}$ channels
        - Activation of MAPK, inwardly rectifying K$^{+}$ (GIRK) channels
  - Results in decreased neurotransmitter release and inhibition of neuronal firing

Fentanyl: **Pharmacology**

- $\mu$-receptors:
  - $G_{i}$ coupled
  - Decrease release glutamate substance P

**Amino Acids**

- Aspartic Acid
- Glutamic Acid
- Arginine
- Lysine
- Histidine

**Drug-Receptor Binding**

- Hydrogen bonds HBD and HBA
- Ionic bonds

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Fentanyl: Pharmacology

Common HBD and HBA

Functional Groups

- In a chemical sense, a drug can be described as a core scaffold decorated by functional groups
- Functional groups provide HBD, HBA and may increase lipophilicity

The Pharmacophore Rule

Application of Pharmacophores to the Synthetic Cannabinoids

The Pharmacophore Rule was written so chemists would be able to identify the basic structural elements required for a compound to bind to the cannabinoid structure.
Receptor Binding

<table>
<thead>
<tr>
<th>Chemical Analog</th>
<th>CB1 Ki (nM)</th>
<th>CB2 Ki (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>JWH-018</td>
<td>9.0 (least potent)</td>
<td>2.9</td>
</tr>
<tr>
<td>AM2201</td>
<td>1.0</td>
<td>2.6</td>
</tr>
<tr>
<td>JWH-081</td>
<td>1.2</td>
<td>12.4 (least potent)</td>
</tr>
<tr>
<td>JWH-122</td>
<td>0.69</td>
<td>1.2</td>
</tr>
<tr>
<td>JWH-210</td>
<td>0.46 (most potent)</td>
<td>0.69 (most potent)</td>
</tr>
</tbody>
</table>


**Common Scaffolds**

- **Indole**
- **Indoline**
- **Indazole**
- **Benzimidazole**
- **4-Azaindole**
- **7-Azaindole**
- **Benzo furan**
- **Benzothiophene**

**Chemical Scaffold**

A chemical scaffold consists of substituted or nonsubstituted ring structures that facilitate binding of required elements (such as indole compounds, indazoles, benzimidazole, or other ring types).

**Why is this important?**

The indole ring structure provides the scaffold for the molecule. The scaffold is where the functional groups are added to the compound.
2. **Alkyl or Aryl Side Chain**

An Alkyl or Aryl side chain off the chemical scaffold provides hydrophobic interaction with the CB1 and CB2 receptors.

**Why is this important?**
The side chain in this photo shows a total of five carbons. For optimal binding to CB1 and CB2 receptors, at least four to six carbons must be present.

3. **Carbonyl or ester**

A Carbonyl, ester, or equivalent is present for hydrogen bonding.

**Why is this important?**
Hydrogen bond donors (HBD) and acceptors (HBA) allow for drugs to bind to the amino acids of the receptor.

4. **Cyclohexane**

A Cyclohexane, naphthalene ring, substituted butanamide, or equivalent is present for steric requirements for CB1 and CB2 receptor binding.

**Why is this important?**
Mains rigidity to the molecule for binding to the CB1 and CB2 receptors (proper orientation).

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**Common HBD and HBA**

- Aldehyde
- Ketone
- Alcohol
- Ether
- Carboxylic Acid
- Acid Chloride
- Ester
- Anhydride
- Amine

**Steric Substitutions**

- Cyclohexane
- Naphthalene
- Carbazole
- Tetramethylcyclopropyl
- Quinoline
- 3-methyl-2-(methylamino)butanamide

**Application of Pharmacophores to the Synthetic Cathinones**
Chemistry

Cathinone Pharmacophore

4F-α-PVP

Methylone
Butylone
Pentylone

Fentanyl: Legal Updates
• Expansion of the “pharmacophore rule”
Ohio Administrative Code 4729-11-02

Fentanyl: Opioid Pharmacophore
• Highlighted structure present in µ-receptor binders:

Fentanyl: Opioid Pharmacophore
• Binding to the mu receptor requires the following:
  1. protonated amine nitrogen
  2. polar function for hydrogen bonding
  3. one aromatic ring for lipophilic interaction
  4. another aromatic ring for electron transfer

Dosen-Misovic et al., 1996
**Fentanyl: Legal Updates**

- Expansion of the “pharmacophore rule”

- Required structural components:
  1. Chemical scaffold consisting of a Nitrogen containing 5, 6 or 7 member ring and;
     
     ![Chemical structure 1](image1)

  2. A second Nitrogen attached to the ring structure
     
     ![Chemical structure 2](image2)

  3. A polar group attached to the chemical scaffold
     
     ![Chemical structure 3](image3)

  4. An alkyl or aryl substitution attached to the chemical scaffold
     
     ![Chemical structure 4](image4)

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**Cyclopropyl fentanyl**

![Chemical structure 5](image5)

**Ocentanyl**

![Chemical structure 6](image6)
**DEA Requirements**

- **A.** Replacement of the phenyl portion of the phenethyl group by any monocycle, whether or not further substituted in or on the monocycle;
- **B.** Substitution in or on the phenethyl group with alkyl, alkenyl, alkoxyl, hydroxyl, halo, haloalkyl, amino or nitro groups;

**General References**