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

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What is a pharmacophore?

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

• the portion of drug molecule required for pharmacological activity
Phenanthrene

Heroin

Morphine

Oxycodone
Drug-Targets

• Receptors
• Enzymes
• Membrane Transporters
Fentanyl: Targets

- Pharmacological targets
  - Opioid receptors
    - Members of the GPCR family
      - Mu, delta, and kappa
        » $\text{G}_\alpha_i$ and $\text{G}_\alpha_o$
        » 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

μ-receptors:
- Gi coupled
- decrease release glutamate substance P
Fentanyl: Pharmacology

Adenylate cyclase (-)

Vesicular release (-)

- GIRK (+)
- Delayed rectifier (+)
- Big K (+)
- Ih (+)
- Voltage sensitive Ca^{2+} channels (-)
Fentanyl: Pharmacology
Amino Acids

Aspartic Acid

Glutamic Acid

Arginine

Lysine

Histidine
Drug-Receptor Binding

- Hydrogen bonds
  HBD and HBA

- Ionic bonds

\[ \text{Na} \quad \text{Cl} \]
Fentanyl: Pharmacology

Kaserer et al., 2016
Common HBD and HBA

- Aldehyde
- Ketone
- Alcohol
- Ether
- Carboxylic Acid
- Acid Chloride
- Ester
- Anhydride
- Amine
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
Phenanthrene  
Heroin  
Morphine  
Oxycodone
The Pharmacophore Rule

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.
Application of Pharmacophores to the Synthetic Cannabinoids
\[ \Delta^9-\text{THC} \]

\[ \text{JWH-018} \]

Source: Aung et al., 2000
The Cannabinoid Receptors

CB1R

CB2R

extracellular

intracellular
## 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>

Chemical Scaffold
2. Alkyl or Aryl Side Chain
3. Carbonyl or ester
4. Cyclohexane
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.
Common Scaffolds

Indole  Indoline  Indazole  Benzimidazole

4-Azaindole  7-Azaindole  Benzofuran  Benzothiophene
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.
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.
Common HBD and HBA

Aldehyde        Ketone       Alcohol          Ether        Carboxylic Acid

Acid Chloride       Ester                 Anhydride                 Amine
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).
Steric Substitutions

Cyclohexane

Naphthalene

Carbazole

Tetramethylcyclopropyl

Quinoline

3-methyl-2-(methylamino) butanamide
Application of Pharmacophores to the Synthetic Cathinones
Cathinone Pharmacaphore

4F-α-PVP
Methylnone

Butylone

Pentylone

MDPPP

alpha-PVP

MDPV
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-Micovic 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;
Fentanyl: Legal Updates

• Expansion of the “pharmacophore rule”

2. A second Nitrogen attached to the ring structure
Fentanyl: Legal Updates

• Expansion of the “pharmacophore rule”

3. A polar group attached to the chemical scaffold
Fentanyl: Legal Updates

• Expansion of the “pharmacophore rule”

4. An alkyl or aryl substitution attached to the chemical scaffold
Cyclopropyl fentanyl
Ocentanyl
para-Fluorobutyryl fentanyl
Furanyl fentanyl
FOR IMMEDIATE RELEASE

February 7, 2018
Contact: DEA Public Affairs
(202) 307-7977

Press Release

U.S. Drug Enforcement Administration emergency schedules all illicit fentanyls in an effort to reduce overdose deaths
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, alkoxy, hydroxy, halo, haloalkyl, amino or nitro groups
DEA Requirements

C. Substitution in or on the piperidine ring with alkyl, alkenyl, alkoxy, ester, ether, hydroxyl, halo, haloalkyl, amino, or nitro groups;

D. Replacement of the aniline ring with any aromatic monocycle whether or not further substituted in or on the aromatic monocycle; and/or

E. Replacement of the N-propionyl group by another acyl group
General References


