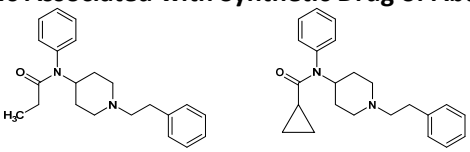
OHIO ATTORNEY GENERAL'S CENTER for the FUTURE of FORENSIC SCIENCE AT BOWLING GREEN STATE UNIVERSITY

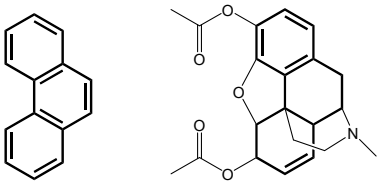
Applying Pharmacy Scientific Principles to the Laws Associated with Synthetic Drug of Abuse



Jon E. Sprague, RPh, PhD

What is a pharmacophore?

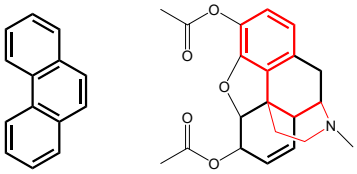
- the portion of drug molecule required for pharmacological activity



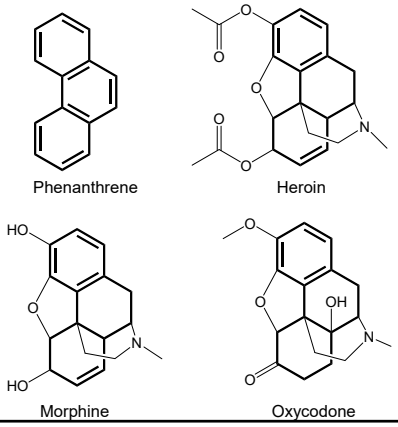
Phenanthrene Heroin

What is a pharmacophore?

- the portion of drug molecule required for pharmacological activity



Phenanthrene Heroin



Phenanthrene Heroin

Morphine Oxycodone

Drug-Targets

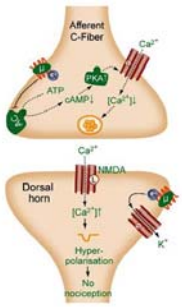
- Receptors
- Enzymes
- Membrane Transporters

Fentanyl: Targets

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

7

Fentanyl: Pharmacology

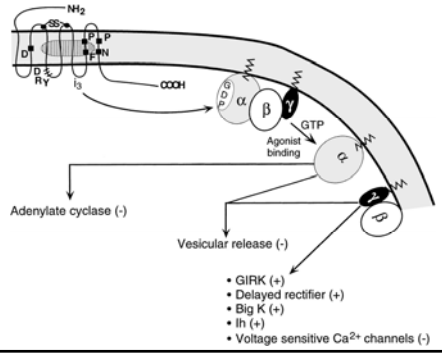


μ-receptors:

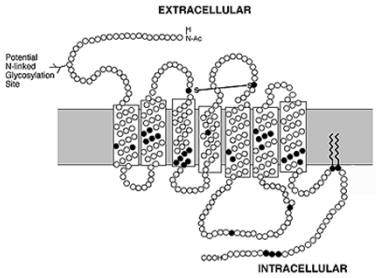
- Gi coupled

-decrease release
glutamate
substance P

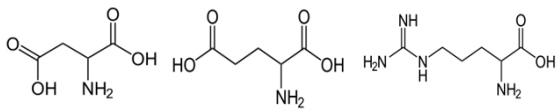
Fentanyl: Pharmacology



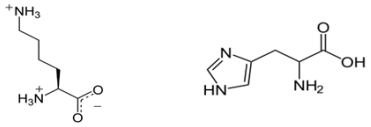
Fentanyl: Pharmacology



Amino Acids



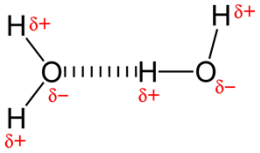
Aspartic Acid Glutamic Acid Arginine



Lysine Histidine

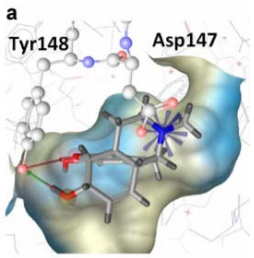
Drug-Receptor Binding

- Hydrogen bonds
  HBD and HBA



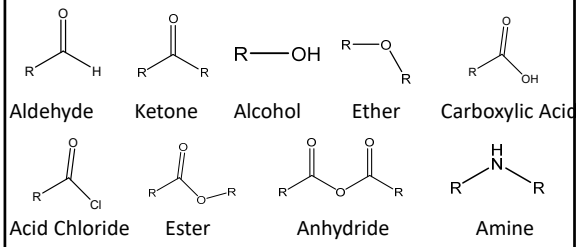
- Ionic bonds

Fentanyl: Pharmacology



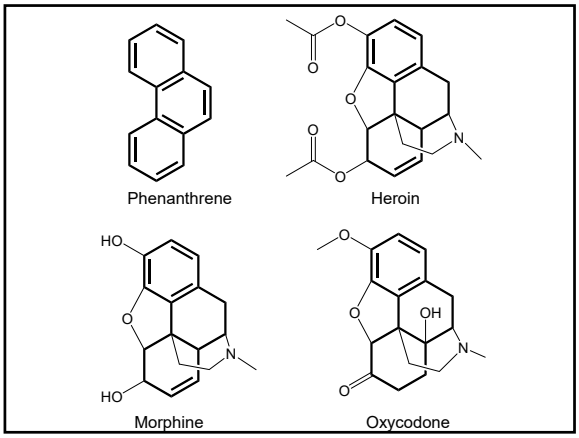
Kaserer et al., 2016

Common HBD and HBA



Functional Groups

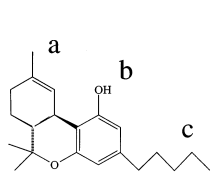
- ***In a chemical sense, a drug can be described as a core scaffold decorated by functional groups***
- Functional groups provide HBD, HBA and may increase lipophilicity



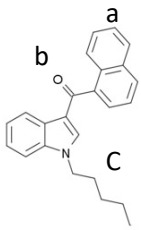
The Pharmacophore Rule

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



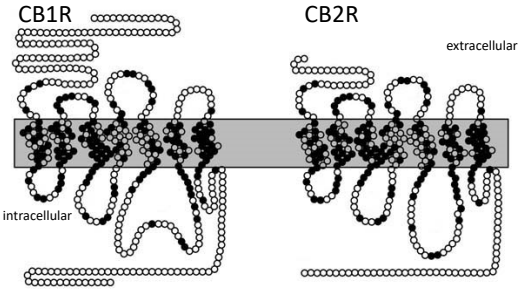
Δ^9-THC



JWH-018

Source: Aung et al., 2000

The Cannabinoid Receptors



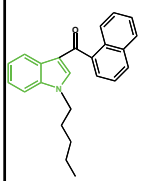
Receptor Binding

Chemical Analog	CB1 Ki (nM)	CB2 Ki (nM)
JWH-018	9.0 (least potent)	2.9
AM2201	1.0	2.6
JWH-081	1.2	12.4 (least potent)
JWH-122	0.69	1.2
JWH-210	0.46 (most potent)	0.69 (most potent)

Aung, M.M. et al., Drug and Alcohol Dependence, 2000. 60(2): p. 133-140.
Huffman, J. W., et al. Bioorganic & medicinal chemistry, 2005. 13(1), 89-112.
Makriyannis A. and Deng H. Patent: Cannabimimetic Indole Derivatives (2008)

1. Chemical Scaffold
2. Alkyl or Aryl Side
3. Carbonyl or ester
4. Cyclohexane

1 Chemical Scaffold

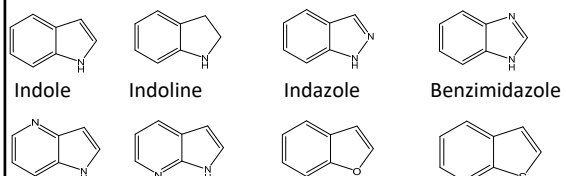


A chemical scaffold consists of substituted or nonsubstituted ring structures that facilitate binding of required elements (such as indole compounds, indazoles, benzimidazole, or other ring types.

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.

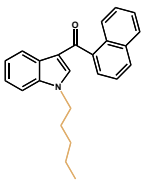
Common Scaffolds



Indole | Indoline | Indazole | Benzimidazole

4-Azaindole | 7-Azaindole | Benzofuran | Benzothiophene

2 Alkyl or Aryl Side Chain

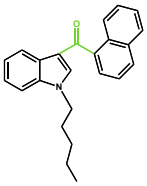


An Alkyl or Aryl side chain off the chemical scaffold provides hydrophobic interaction with the CB1 and CB2 receptors.

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

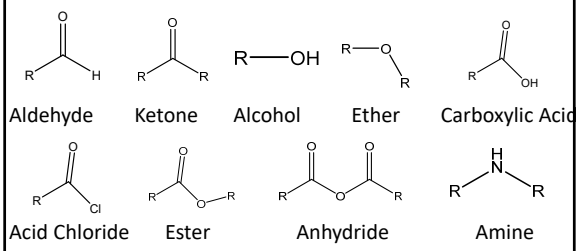


A Carbonyl, ester, or equivalent is present for hydrogen bonding

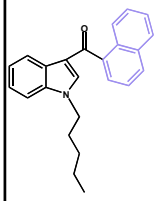
Why is this important?

Hydrogen bond donors (HBD) and acceptors (HBA) allow for drugs to bind to the amino acids of the receptor.

Common HBD and HBA



4 Cyclohexane

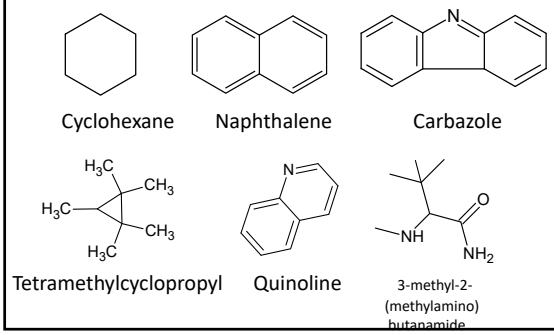


A Cyclohexane, naphthalene ring, substituted butanamide, or equivalent is present for steric requirements for CB1 and CB2 receptor binding.

Why is this important?

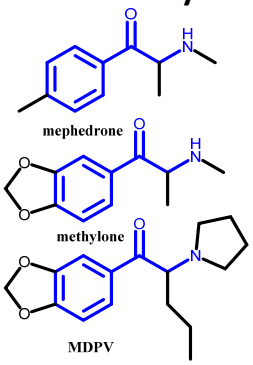
Mains rigidity to the molecule for binding to the CB1 and CB2 receptors (proper orientation).

Steric Substitutions

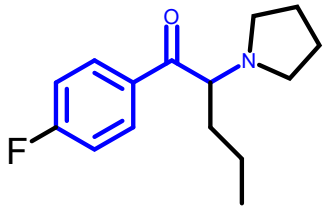


Application of Pharmacophores to the Synthetic Cathinones

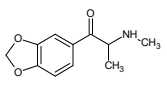
Chemistry



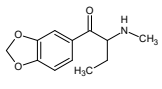
Cathinone Pharmacophore



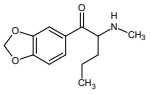
4F-α-PVP



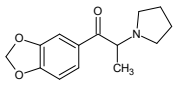
Methylone



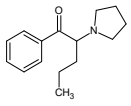
Butylone



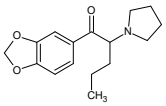
Pentylone



MDPPP



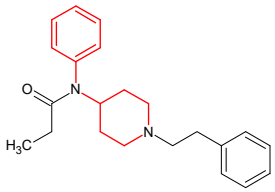
alpha-PVP



MDPV

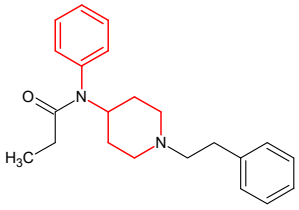
Fentanyl: Legal Updates

- Expansion of the "pharmacophore rule" Ohio Administrative Code 4729-11-02



Fentanyl: Opioid Pharmacophore

- Highlighted structure present in μ-receptor binders:



Fentanyl: Opioid Pharmacophore

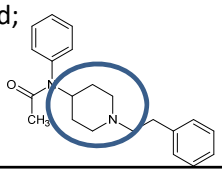
- Binding to the mu receptor requires the following:
  1. protonated amine nitrogen
  2. polar function for hydrogen bonding
  3. one aromatic ring for lipophilic interaction
  4. another aromatic ring for electron transfer

Dosen-Micovic et al., 1996

Fentanyl: Legal Updates

- Expansion of the "pharmacophore rule"
- Required structural components:

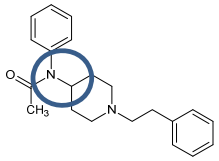
1. Chemical scaffold consisting of a Nitrogen containing 5, 6 or 7 member ring and;



Fentanyl: Legal Updates

- Expansion of the "pharmacophore rule"

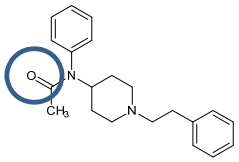
2. A second Nitrogen attached to the ring structure



Fentanyl: Legal Updates

- Expansion of the "pharmacophore rule"

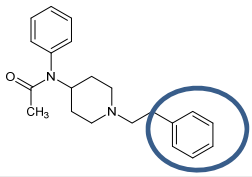
3. A polar group attached to the chemical scaffold



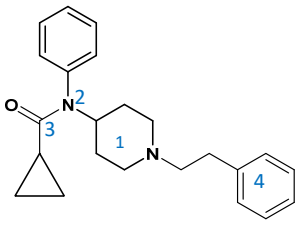
Fentanyl: Legal Updates

- Expansion of the "pharmacophore rule"

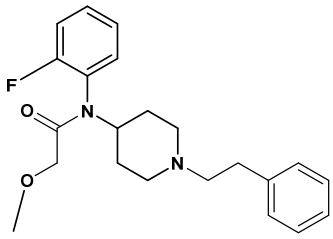
4. An alkyl or aryl substitution attached to the chemical scaffold



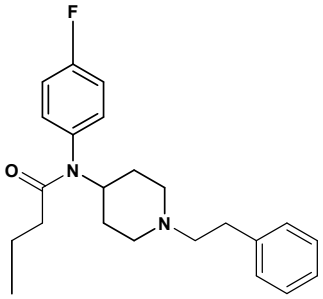
Cyclopropyl fentanyl



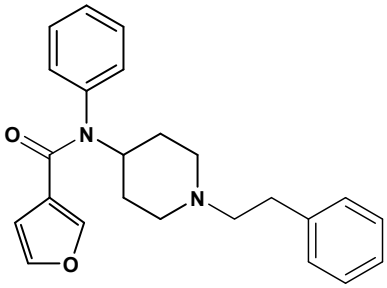
Ocentanyl



para-Fluorobutyryl fentanyl



Furanyl fentanyl



U.S. Drug Enforcement Administration

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, alkoxyl, hydroxyl, 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

1. Alexandros Makriyannis and Hongfeng Deng. Patent: Cannabimimetic Indole Derivatives (2008).

2. Aung, M.M., G. Griffin, J.W. Huffman, M.J. Wu, C. Keel, B. Yang, V.M. Showalter, M.E. Abood, and B.R. Martin, Influence of the N-1 alkyl chain length of cannabimimetic indoles upon CB1 and CB2 receptor binding. Drug and Alcohol Dependence, 2000. 60(2): p. 133-140.

3. Dosen-Micovic, I. Roglic, G., Micovic, V., Ivanovic, M. Conformational study of fentanyl and its analogs 1. Conformational space of the N-phenethyl substituent. Elec J Theoretical Chem. 199-210; 1996.

4. Huffman, J. W., Zengin, G., Wu, M., Lu, J., Hynd, G., Bushell, K., et al. (2005). Structure-activity relationships for 1-alkyl-3-(1-naphthoyl)indoles at the cannabinoid CB(1) and CB(2) receptors: steric and electronic effects of naphthoyl substituents. New highly selective CB(2) receptor agonists. Bioorganic & medicinal chemistry, 13(1), 89-112. doi: 10.1016/j.bmc.2004.09.050.

5. Jordon, A. M.; Roughley, S.D. Drug discovery chemistry: a primer for the non-specialist. Drug Discovery Today. 14:731-744; 2009.

6. Kaserer, T., Lantero, A., Schmidhammer, H., Spetea, M., Schuster, D. μ Opioid receptor: novel antagonists and structural modeling. Scientific Rep. 1-15; 2016.

7. Worst TJ, Sprague JE. The "pharmacophore rule" and the spices. Forensic Toxicol. 33(1):170-173; 2015.

8. Federal Register. Vol. 83(25): 5188-5192; 2018.