# Opioids: Natural and Synthetic

## Historical Timeline

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>3400 BCE</td>
<td>Sumerian records show cultivation of <em>huil gil</em> (Plant of Joy)</td>
</tr>
<tr>
<td>150 CE</td>
<td>Religious Crusaders bring opium home</td>
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<tr>
<td>1100 CE</td>
<td>Ancient Greek physician Galen administers opium as treatment of pain, asthma and heart failure</td>
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<tr>
<td>1400 CE</td>
<td>Recreational use begins in China</td>
</tr>
<tr>
<td>1729 CE</td>
<td>Opium Use Banned in China</td>
</tr>
<tr>
<td>1764 CE</td>
<td>Morphine isolated by Sertürner (and Derosne); named after Morphoeus</td>
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<tr>
<td>1803-6 CE</td>
<td>William Gregory invents isolation process</td>
</tr>
<tr>
<td>1827 CE</td>
<td>Lin Zexu destroys 20K chests of opium, sparking the Opium Wars</td>
</tr>
<tr>
<td>1831 CE</td>
<td>Hypodermic Syringe is invented.</td>
</tr>
<tr>
<td>1850 CE</td>
<td>Morphine used as medicine in US Civil War. Creates widespread addiction in veterans</td>
</tr>
<tr>
<td>1860s CE</td>
<td>Heroin, synthesized in 1874, is marketed by Bayer as non-addictive</td>
</tr>
<tr>
<td>1897 CE</td>
<td>Weijard and Erikson discover first opioid antagonist, nalorphine</td>
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<tr>
<td>1925 CE</td>
<td>Robinson proposes correct structure of Morphine</td>
</tr>
<tr>
<td>1942 CE</td>
<td>Gates completes first total synthesis of Morphine; validating structure</td>
</tr>
<tr>
<td>1946 CE</td>
<td>Methadone is synthesized</td>
</tr>
<tr>
<td>1952 CE</td>
<td>Janssen makes Fentanyl</td>
</tr>
<tr>
<td>1959 CE</td>
<td>Dr. Bentley's thebaine analogs</td>
</tr>
<tr>
<td>1960's CE</td>
<td>Pert and Snyder, Simon, Terenius find stereospecific opiate binding sites in CNS</td>
</tr>
<tr>
<td>2001 CE</td>
<td>Afghanistan's opium production begins rising after being down 94%</td>
</tr>
</tbody>
</table>

Opium Latex containing ~12% morphine is obtained through the labor intensive scoring of the immature opium seed pods by hand. These cuts release the latex which is then collected by hand after drying.

In the illicit trade, extraction and acylation of morphine from the latex leads to an 88% reduction in volume with a compound twice as potent as morphine. Making it easier to smuggle and more valuable.

### T & H Smith Process (1878)
- A modified procedure of the Robinson-Gregory Process that improves yield and avoids the slow filtration of Gregory’s Salts.

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**Helpful Resources on the History of Opium**
- The Isolation of Morphine: First Principles in Science and Ethics *Molecular Interventions 2001* 189-191
- The manufacture of medicinal alkaloids from the opium poppy- a review of a traditional biotechnology *Chemistry and Industry 1988* 146-153

**Molecules That Changed the World** chapter 10, 67-78

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**Not Discussed:**
- Policy Decisions
- Rewriting History, a Response to the 2008 World Drug Report
- Transnational Institute 2008
- Opioid Epidemic in the United States
- Physician 2012 E9-ES38
- Chemical Interventions for the Opioid Crisis: Key Advances and Remaining Challenges *JACS 2019* 1788-1806
Pharmacology and Biology

Opioid Receptors
- Belong to the 7TM GPCR Superfamily (Barton, 2019)
- Activated by endogenous and exogenous opioids
  - opioid peptides interact with highly divergent extracellular loops providing selectivity
  and allowing discrimination of the different receptors.
  - Small molecule opioids interact predominantly with conserved residues in the bottom of the binding pocket.
- 4 receptor subtypes with native ligands
  - \(\mu\)-Opioid Receptor (MOR)
  - \(\delta\)-Opioid Receptor (DOR)
  - \(\kappa\)-Opioid Receptor (KOR)
  - N-Opioid Receptor (NOR/ORL-1)
- Existence proposed in 1950’s. Discovered in mammalian brain tissue in 1973
- Diversification through posttranslational modifications, alternative mRNA splicing, Homo and Hetero-dimerization.

\(\mu\)-Opioid Receptor (MOR, MOP or MOP-R)
- Mu- for morphine, the ligand that was found to bind this receptor when discovered.
- most expressed receptor in amygdala (processing of emotions), thalamus (motor function, sleep and alertness), and mesencephalon (midbrain—motor control, sleep/wake)
- Plays a critical role in mediating natural rewards. Agonists produce positive reinforcement
- Associated with analgesia, hyperlocomotion, respiratory depression, immunosuppression

\(\delta\)-Opioid Receptor (DOR, DOP or DOP-R)
- delta- for vas deferens (brain region where they were discovered in mice)
- most expressed receptor in olfactory tract, neocortex (perception, cognition), and striatum (motor and reward systems)
- Agonists produce positive reinforcement

\(\kappa\)-Opioid Receptor (KOR, KOP or KOP-R)
- kappa- for ketocyclazocine, the ligand that was found to bind this receptor when discovered.
  Found only in stress axis regions of brain.
- most expressed receptor in basal anterior forebrain (acetylcholine production, learning), hypothalamus (temperature, hunger), and pituitary (growth, blood pressure, sex organs)
- Agonists produce aversion, hallucinations, malaise (opposite of MOR agonists)

N-Opioid Receptor (NOR, NOP-R, or ORL-1)
- Discovered before its principal ligand (very rare)
- Lacks conserved binding sites of other receptors, therefore, many opioids do not bind here.
- Involved in pain and reward circuitry but does not have positive reinforcing effects.
- Activation of this receptor can cause dissapearance of conditioned place preference.

Self-Check: Do you understand the Biology?
How would eating behavior change if a MOR/DOR agonist was injected into the hippocampus?
medical hypotheses 1995 491-497
Salvinorin A is a selective KOR agonist, what effects would it have if ingested?
Front. Pharmacol. 2015 article 190
Could a MOR antagonist cause hyperalgesia (increased pain sensitivity)?
Life Sci. 1983 2139-46

MOR Knockout Mice Studies
- These mice lose motivation to eat and have diminished foot anticipatory behavior.
- Reduced Maternal attachment.
- Knockout experimentation suggests MOR is responsible for reward properties of drug use.
- Withdrawal symptoms in these mice are reduced.

DOR Knockout Mice Studies
- Evidence suggests DOR is somewhat responsible for reward properties of drug use.
- Knockouts do not develop morphine tolerance to the same degree as wild type mice.
- These knockouts display higher levels of anxiety, implicating the receptor in schizophrenia, bipolar disorder, anxiety and depression.
- DOR knockouts increased self-administration of alcohol.
- Knockouts demonstrate increased motor impulsivity, suggests DOR activity on inhibitory controls.

KOR Knockout Mice Studies
- These mice do not show altered basal nociceptive thermal or mechanical sensitivity
- Visceral pain sensitivity increased
- Knockouts do not display place aversion or dysphoria when treated with KOR agonists.
- Experiments suggest KOR plays a role in stress-induced emotional responses and learning in stressful situations (learned helplessness, aversion, Pavlovian fear conditioning etc.)

Mechanism of Action

- Ligand-induced conformational change in GPRC
- Interactions between agonist and G protein

- GPCR-mediated effects include:
  - Inhibition of effector signaling through feedback loops
  - Activation of second messengers by effectors
  - GPCR phosphorylation by G protein kinase

- Binding of \(\delta\)-amino laevulinate to phospholipid bilayer
- N-association of heterotrimeric G proteins

- Interaction of G protein subunits with effectors


- https://www.youtube.com/watch?v=qB62xhNiAow
- https://www.youtube.com/watch?v=4wq7NGhwv0
Pharmacology and Biology (Cond.)

Other Receptors

\( \alpha \)-receptor
- Most likely a splice variant, posttranslationally modified, or dimer of known receptors
- Several drugs selectively hit this receptor
- \( \epsilon \)-receptor selective drugs lose activity in triple knockout (MOR,DOR,KOR) mice.

\( \delta \)-receptor
- Once thought to be opioid receptors, now it is clear they are not opioid receptors
- Some opioids have effects on the \( \delta \)-receptor
- Exogenous agonists include: PCP, cocaine, morphine, methanphetamine

Regulation of the Opioid Receptors

Desensitization
- Mechanistically Complicated. Typically through phosphorylation by GRK's followed by \( \beta \)-arrestin recruitment.

Endocytosis
- Takes place quickly after phosphorylation, fast mechanism ideal for neurotransmitters;
- Receptors can then be recycled back into the cellular membrane (resensitization) or they can be degraded.

Downregulation
- Slowing in the rate of receptor synthesis, folding, or secretion

Anti-Opioid System

cAMP Superactivation
- Chronic morphine use leads to cellular upregulation of cAMP so basal conc. is high.
- Effectively drowns opioid signal in noise, leading to decreased responsiveness.

Cholecystokinin (CCK)
- Highly potent antagonists of opioid system. CCK knockout mice have high opioid concentrations in the brain.
- Also a gastrointestinal hormone involved in digestion of fats and proteins.

NMDA Receptors
- Chronic morphine exposure leads to upregulation of NR2A and NR1 subunits.
- Thought to play a role in tolerance development.
- Inhibition of NMDA with antagonists can inhibit the induction of tolerance.
- Once tolerance is established, it cannot be attenuated through NMDA antagonists.

Evidence of the Opioid Receptors

On Right: Chromosome containing a unireceptor similar to ORL (and rhodopsin)

 Experienced a duplication event to produce two opioid receptors (ORL/KOR and DOR/MOR).

 Asymmetric divergence ensued and the DOR/KOR partner evolved faster than the ORL/KOR partner chromosome. This ancestral chromsome pair then experienced a duplication event to give the 4 opioid receptor types today. Asymmetric divergence led to KOR and MOR evolving faster than ORL and DOR

Evidence: DOR and MOR are most identical to each other in sequence. Similarly, KOR and NOR are most identical in sequence. Additionally, ligand overlap between MOR-DOR and KOR-NOR suggest relationships within these pairs.

Conclusion: A duplication event of two ancestral genes to produce MOR and DOR as well as NOR and KOR took place

Evidence: The Genetic record shows that a 2R event took place (2R hypothesis)

Conclusion: All four receptor types originated from a single ancestral receptor.

Evidence: hMOR was one of only 9 genes controlling brain size/bevavior that showed an increase rate of protein evolution. Likewise, NOR protein is most analogous to rhodopsin.

Conclusion: MOR and KOR were the fast evolving members of the asymmetrical diverging pairs.

Evidence: Higher mammals show increased divergence in homology of the 4 receptor types, however, comparisons between mammals show convergence between analogous receptors.

Conclusion: Asymmetric divergence facilitated adaptive evolution and different species convergently evolved a more selective and sensitive receptor (both MOR and KOR) as a result of molecular level selection pressure.

On Right: Phylogenetic analysis of MOR, DOR, KOR, and ORL in 6 vertebrates. Notice that MOR and KOR exhibit higher degrees of divergence between vertebrates. Also, notice that ORL most closely resembles rhodopsin and displays the most divergence of all the receptors.

Helpful Resources on Opioid Receptor Biology:

Reward processing by the opioid system in the brain.
Physiol. Rev. 2009 1379-1412

Opioid Receptors. Annu. Rev. Biochem. 2004 953-990

Opioid receptors: distinct roles in mood disorders.
Trends Neurosci 2013 195-206

The delta opioid receptor: an evolving target for the treatment of brain disorders.
Trends Pharmacol Sci 2011 581-590

15 years of genetic approaches in vivo for addiction research:
opioid receptor and peptide gene knockout in mouse models of drug abuse.
Neuropsychopharmacology 2014 204-217

Other helpful resources:

Frontiers in Bioscience 2009 1247-1269,

Page-Turning review:
The evolution of vertebrate opioid receptors
Frontiers in Bioscience 2009 1247-1269,

PNAS 2008 15487-15492
vitamins and hormones 2015 57-94
Opioids: Natural and Synthetic

**Natural Opioid Peptides**

**Endogenous Opioid Peptides**
- Nearly every opioid peptide is derived from the degradation of one of four larger proteins

**Pro-opiomelanocortin (POMC)**
- 241 amino acid residues
- Degradation produces several important hormones
- Opioids produced: Endorphins, Enkephalins, Lipotropins
- β-endorphin containing neurons are long projecting systems
- Typically located in medial hypothalamus, diencephalon and pons

**Proenkephalin (PENK)**
- 267 amino acid residues
- Contains 4 copies of met-enkephalin and 1 copy of leu-enkephalin
- Neurons containing PENK are more widespread in the brain than POMC containing neurons
- Found in short projection neurons

**Prodynorphin (proenkephalin B)**
- Contains dynorphin A, dynorphin B, α-neoendorphin and β-neoendorphin
- Incomplete processing leads to "big dynorphin", a peptide of dynorphin A and B
- Found in generally distributed central and peripheral neurons

**Prepronociceptin (Orphanin FQ)**
- Precursor protein of nociceptin and nocistatin
- Nocistatin is the NOP/ORL-1 agonist
- Nocistatin is the NOP/ORL-1 antagonist
- NOP is generally distributed in the CNS so its effectors also are widespread

**Helpful Reviews:**
- Progress in Brain Research 2007 227-293
- Hormones, Brain and Behavior 2009, Part V, 2541-2599

For some factors, the purification of nanograms of active peptide required hundreds of thousands of brains.

Helpful Reviews:
- Progress in Brain Research 2007 227-293
- Hormones, Brain and Behavior 2009, Part V, 2541-2599

**α-endorphin (16 AA)**
- Sequence: Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr
- Blue region is conserved among nearly every endogenous opioid peptide
- Red region Tyrosine is analogous to morphine backbone and is responsible for potency

**β-endorphin (31 AA)**
- Sequence: Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu-Phe-Lys-Asn-Ala-Ile-Ile-Lys-Asn-Ala-Tyr-Lys-Lys-Gly-Glu
- Endogenous MOR ligand, extremely high affinity and prolonged agonistic effect on MOR
- Associated with hunger, thrill, pain, maternal care, sexual behavior, and reward cognition
- Exercise releases β-endorphin and β-lipotropin, this release is known as "runners high"

**γ-endorphin (17 AA)**
- Sequence: Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu
- Exact function unknown. Structure is identical to α-endorphin with an extra leucine

**Enkephalins**

**Leu-enkephalin (5 AA)**
- Sequence: Tyr-Gly-Gly-Phe-Leu
- Analgesic properties as a MOR and DOR agonist

**Met-enkephalin (5 AA)**
- Sequence: Tyr-Gly-Gly-Phe-Met
- Primary endogenous ligand for DOR
- Endogenous ligand for Opioid Growth
- Factor Receptor (sometimes called η-opioid receptor)

**Metorphamide (8 AA)**
- Sequence: Tyr-Gly-Gly-Phe-Met-Arg-Arg-Val-NH₂
- Balanced MOR/KOR agonist
- Little affinity for DOR
- Analgesic and respiratory depressive

**Peptide E (25 AA)**
- Clevage produces Bovine Adrenal Medulla 18 (BAM-18, Red) and Leu-enkephalin (Blue)

**Dynorphins**
- Responsible for maintaining homeostasis. These opioid peptides regulate functions like appetite, circadian rythms, body temperature.
- Dynorphins play a role in addiction, dysphoria, place aversion, stress and depression, and learned helplessness.
- Act primarily on KOR

**Big Dynorphin (32 AA)**
- Principal Endogenous agonist for human KOR
- NOciceptive and anxiolytic properties and effects memory in mice.
Opioids: Natural and Synthetic

Natural Opioid Peptides (cont.)

Dynorphins (cont.)

Dynorphin A (17 AA)
Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys
• Truncated version Dynorphin A₁₋₃ displays agonistic activity at MOR; DOR high affinity for KOR

Leumorphin (29 AA)
Tyr-Gly-Gly-Phe-Leu-Arg-Gln-Phe-Lys-Val-Val-Thr-Arg-Ser-Gln-Glu-Asp-Pro-Asn-Ala-Tyr-Tyr-Glu-Glu-Leu-Phe-Asp-Val
• also known as Dynorphin B₁₋₁₉
• Potent, selective KOR agonist.

Dynorphin B (13 AA)
Tyr-Gly-Gly-Phe-Leu-Arg-Gln-Phe-Lys-Val-Val-Thr
• also known as Rimorphin
• Cleavage product of Leumorphin

Neoendorphins
α- Tyr-Gly-Gly-Phe-Leu-Arg-Lys-Tyr-Pro-Lys
β- Tyr-Gly-Gly-Phe-Leu-Arg-Lys-Tyr-Pro
• KOR ligands.

Future Medicinal Chemistry 2012. 205-226

Nociceptin (17 AA)
• Principal endogenous ligand for NOR/ORL₁.
• Potent anti-algesic, counters effect of pain relievers
• High levels of nociception are marked with hyperalgesia
• When administered to CNS, exhibits classical opioid behavior with lower tolerance development and risk of addiction.
• Has been evaluated as therapeutic for drug abuse.

Peptides 2011 15-30-1535;
Current Topics in Med. Chem. 2011 1151-1156

Endomorphins (4 AA)

• EM₁: Tyr-Pro-Trp-Phe-NH₂
• EM₁ produces conditioned place preference
• High affinity MOR agonist, equipotent to morphine
• Produces conditioned place preference

• EM₂: Tyr-Pro-Phe-NH₂
• Produces conditioned place aversion
• MOR agonist, produces analgesia, prevalent in CNS
• Induces release of dynorphin A, a KOR agonist.
• EM₂ is arrestin biased agonist of MOR. Induces phosphorylation of GPCR and recruitment of arrestin to signal endocytosis after signal transduction. Potential mechanism of action less prone to dependence/tolerance. Oliceridine (TVA-130) attempted this, was pulled by FDA out of concern. See CYT 2012. 178-188
• Genes encoding EM₁ and EM₂ have not been identified, potentially synthesized by NRPS

Enkephalinase Inhibitors

• Opiorphin (Gln-Arg-Phe-Ser-Arg)
  • First isolated from human saliva. Has pankilling effect great than morphine. Prevents degradation of enkephalins in the spinal cord
  • Spinorphin (Leu-Val-Val-Tyr-Pro-Trp-Thr)
  • Prevents degradation of enkephalins by inhibiting peptidase enzymes.

Hemorphins (hemoglobin derived opioid peptides)

• Valorphin (Val-Tyr-Pro-Trp-Thr-Gln)
  • Produced via cleavage of AA 33-39 of hemoglobin.
  • Hemorphin-4 (Tyr-Pro-Trp-Thr)
  • MOR, DOR, KOR ligand also possessing inhibitory effects on angiotensin-converting enzyme (ACE) indicating a role in blood pressure regulation. FEBS 1991 39-41

Endogenous Opioid Peptides Summary Table

• Principal agonists in blue

<table>
<thead>
<tr>
<th>Receptor</th>
<th>MOR</th>
<th>DOR</th>
<th>KOR</th>
<th>NOR</th>
<th>Protease Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ligands</td>
<td></td>
<td></td>
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<tr>
<td>β-endorphin</td>
<td>α-endorphin</td>
<td>α/β-Enkephalin</td>
<td>Metorphamide B₅-₈</td>
<td>DYNorphin A₁₋₃</td>
<td>Endorphin 1/2</td>
</tr>
<tr>
<td>Leu/Met-Enkephalin</td>
<td>DYNorphin A₁₋₃</td>
<td>Hemorphin-4</td>
<td>Metorphamide</td>
<td>Peptide E</td>
<td>DYNorphin A₁₋₃</td>
</tr>
<tr>
<td>Nociceptin</td>
<td>Opiorphin</td>
<td>Spinorphin</td>
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</tr>
</tbody>
</table>

Exogenous Opioid Peptides

From food sources:

• Casomorphin (breakdown of casen in milk)
• Gluten exorphins (digestion of gluten)
• Gliadorphin/ Glutemorphin (digestion of gluten)
• Soymanorphin-5 (degredation of soybean β-cyglicinin)
• Rubiscolin (degredation of rubisco in spinach leaves)

Anphibian Opioid Peptides

• Endogenous to frogs of the Phylomedusa genus
• Produced in their skin and secreted
• One of the highest affinity natural opioid peptides for DOR
• Very potent, very selective.
• These proteins contain D-amino acids which are a post-translational modification via an isomerase enzyme.

Deltorphin A (Tyr-D-Met-Phe-His-Leu-Met-Asp)
Deltorphin I (Tyr-D-Ala-Phe-Asp-Val-Gly)
Dermorphin (Tyr-D-Ala-Phe-Gly-Tyr-Pro-Ser) MOR-agonist
Deltorphin II

Phylomedusa sauvagii (waxy tree frog) on right:

Kambo Frog Ceremony

• A burning stick is placed against the skin to make a small wound. The waxy secretion on the frog’s skin is collected and placed onto the wound. This induces a phisiological response similar to morphine. Nausea, hot flashes, hallucinations, respiratory suppression and drowsiness all occur. Symptoms subside after several hours. Used as a "medical" treatment to cleanse the body of negative spirits.
Opioids: Natural and Synthetic

**Biosynthesis**
- Opioids are primarily derived from the Benzylisoquinoline alkaloids (BIA)
- 2,500 elucidated structures
- Morphine, Codeine, papaverine and sanguinarine are notable family members
- Naturally occuring in the *papaver somniferum* (opium poppy), *Eschscholtzia californiam*, *Thalictrum* species, and *Coptis japonica*.

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**Additional Support:**
- (S)-Reticuline becomes Morphine (inversion event)
- CD$_3$-N-thebaine becomes CD$_3$-N-Morphine

**Conclusion:**
- human cells possess all the enzymatic machinery to convert tyrosine to morphine

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**Human cells produce morphine at the nanomolar range (packed cell volume)**

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**Tyrusine decarboxylase (TYDC)**

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**Tyrosine decarboxylase** (TYDC) is a key enzyme in the biosynthesis of opioids.

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**NCS:** norcoclaurine synthase

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**OMT:** oripavine 6-Methyltransferase

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**CNMT:** thebaine 6-O-methyltransferase

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**CDOM:** codeine O-demethylase

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**Nature Chemical Biology 2010 251–252**
Opioids: Natural and Synthetic

Selected Total Syntheses/ Semi-Syntheses (cont.)

Rice, 1980 JOC 1980 3135-3137 (Morphine, 14 steps, 29%)

- Still the highest overall yield to date
- Biomimetic approach
- Developed scalable conditions for the conversion of codeine to morphine


[Formal Synthesis Endpoint]

Rice. Heterocycles 1977 1157-1165

Magnus JACS 2009 16045-16047 (rac- Codeine, 13 steps, 20%)

- Combination of modern methodology and lessons from Rice’s Synthesis
- Used dibromohyantoin derivative to epoxidize on more hindered face

Divergent synthesis to access large amounts of galanthamine via narwedine reduction
Opioids: Natural and Synthetic

Selected Total Syntheses/ Semi-Syntheses (cont.)
Trost JACS 2002 14542 (Codeine, 15 steps, 6.8%)

Synthesis Quick Hits

Parker JACS 1992 9688

Ogasawara, Org. Lett. 2002 4515

Nagase, Tetrahedron 2009 4808–4813

See also: Chemistry of Opioids Topics Curr. Chem. vol 299 DOI: 10.1007/978-3-642-18107-8

Great review of opioid total synthesis from 2005-2011
DOI: 10.1007/978-3-642-25529-8
See also: The Way of Synthesis, chapter 4.7 pg 727
Opioids: Natural and Synthetic

Stephen Harwood

Salvinorin A: The First (and only known) non-nitrogenous KOP receptor ligand (agonist)
- Neoclerodane diterpene with 7 contiguous stereocenters
- Active component of *Salvia divinorum*
- Potent hallucinogen-- 200 to 1000μg is enough when smoked
- First Completed total synthesis: Evans JACS **2007** 8968-8969 (29-33 steps, 0.8-4.5% overall)
- For a recent analog synthesis of Salvinorin A see: Shenvi, *ACS Cent. Sci.* **2017**, 1329-1336

Evans, 2007

**Bis-Michael** (stepwise)  

**TBAF**  
-78 to 5 °C  
99%, >95:5dr

**exo-Diels-Alder** (concerted)

Baran Group Meeting  
5/11/19


Perlmutter *JOC* **2009**, 2589-2591

Hagiwara *Org. Lett.* **2008** 1365-1368  
(20 steps, 0.95% overall)

For a comprehensive overview of the synthesis, derivitization, and biology of Salvinorin A see: Chemistry of Opioids *Topics Curr. Chem.* vol 299 DOI: 10.1007/978-3-642-18107-8

"The remarkable narcotic power of one such derivative was revealed when someone unknown made the coffee for the lab workers with a contaminated conical flask. Within minutes, half dozen bodies, including Professor Bentley were lying unconscious on the lab floor. Fortunately they came around quickly, although not before the quick thinking company doctor had carried out an impromptu assessment of the clinical effects of this remarkable drug. A close analogue, M₉₉, was subsequently dubbed Etorphine and is still in use as a powerful narcotic sedative for veterinary work."

Robert Bryant, The manufacture of medicinal alkaloids from the opium poppy - a review of a traditional biotechnology.

*Chemistry and Industry* 1988 pages 146-153

**Scaffolds in Current Pharmaceuticals** (Medicinal Research Reviews 2004 182-212)

**Examples of Current Pharmaceuticals**

- Oripavine Skeleton
- Morphine Skeleton
- Morphanan Skeleton
- Benzomorphan Skeleton
- Phenylpiperidine Skeleton
- 4-anilino-Phenylpiperidine Skeleton
- N-benzylpiperazines Phenylpiperidine Skeleton
- Methadone Skeleton

- Diprenorphine
- Oxycodone
- Levorphanol
- Pentazocine
- Meperidine
- Fentanyl (MDMA alternative)
- Methadone
Some Known Opioids and Their Properties

**MOR Agonists**

- **Morphine**
  - RP 1
  - Although old, remains one of the most highly used in medicine today.
  - 333 tons (2006)
  - SN: White Lady, Salt and Sugar Miss Emma, M

- **Acetaminophen**
  - RP-2 X Morphine
  - Developed by Merck
  - Marketed as nonaddictive
  - Used on children
  - Street Names (SN): Dope, Smack, H, Junk, Skag Snow, Horse, China White, Beast

- **Codeine**
  - RP 0.15
  - Antitussive (cough suppression)
  - More potent, less addictive, still dangerous
  - SN: Captain Cody, little C, school boy, lean, purple drank, Texas tea

- **Oxycodone**
  - RP 1.5
  - OxyContin (slow release formula)
  - SN: Hilairy heroin, Blues, Kickers, OC, OXY

- **Hydrocodone**
  - RP 1
  - Top Prescribed Drug
  - US consumes 95% world supply
  - SN: Vikes, Viko, Norco, Hydro

- **Hydromorphone**
  - RP 4
  - 3.9 Million prescriptions (2012)
  - Legal supply increased from 3,340Kg (2009) to 6,980Kg (2013)
  - SN: Dust, Juice, Smack, D, Footballs

- **Oxymorphone**
  - RP 3
  - $400 mil. in 2011
  - 3,070Kg (2011) to 6,880Kg (2013)
  - Extremely addictive!
  - SN: Blue Heaven, Mrs. O Octagons, Orgasmas, Pink Lady, Stop Signs, The O Bomb

- **Oripavine**
  - Useful as synthetic intermediate
  - Bad Tox. Not clinically useful
  - Not from Opium Poppy
  - Comes from *papaver orientale*
  - and the *papaver bracteatum*

- **Alazocine**
  - Benzomorphon Derivative
  - (-) enantiomer non-selective
  - High affinity agonist
  - of MOR, KOR, DOR
  - (+) enantiomer selective α receptor agonist
  - With little opioid receptor affinity
  - Led to discovery of α-receptors

- **Meperidine**
  - Easily synthesized
  - Really Bad Tox.
  - Metabolizes to normeperidine
  - Which is toxic, accumulates, has hallucinogenic and convulsant effects
  - Illicit use declined as Fentanyl use increased.

- **Tianeptine**
  - Antidepressant
  - Although MOR agonist, little sedative properties
  - High doses can produce euphoria, creating concerns over abuse

- **Tramadol**
  - RP: 0.10
  - 19 million prescriptions (2016)
  - Also blocks uptake of norepinephrine and serotonin
  - Naltroxone only partially reverses its effects
  - Typically used for mild to moderate pain
  - SN: trammles, Chill Pills, Ultras

- **Levorphanol**
  - RP: 11
  - Sometimes referred to as "forgotten" or "underutilized"
  - Active at all 4 opioid receptors
  - Its enantiomer dextrophan is a potent dissociative hallucinogen
  - Racemate called racemorphan

- **CYT-1010**
  - Mechanism based on Endomorphin-1
  - Gained Phase 2 approval Feb 2019
  - 29,000 overdose deaths in US (2017)
  - Most widely used synthetic opioid in 2017
  - LD₅₀ ~ 2mg in humans
  - SN: Apache, China Girl, Dance Fever, Jackpot, Goodfellas, Murder 8, Tango & Cash

- **Fentanyl (SN: Grey Death)**
  - RP: 100
  - Can be absorbed through skin
  - 1600Kg produced globally (2015)
  - Most widely used synthetic opioid in 2017
  - LD₅₀ ~ 2mg in humans
  - SN: Apache, China Girl, Dance Fever, Jackpot, Goodfellas, Murder 8, Tango & Cash

- **Carfentanil (SN: Grey Death)**
  - RP: 10,000
  - Short acting, fast onset.
  - Has a wide therapeutic window.
  - Lethal dose is equal to Fentanyl.
  - Used in tranquilizer darts for large animals
  - Last 20 years have seen influx of illicit carfentanil into US
  - Used in Russian hostage crisis, 125 of the 800 hostages died from OD
  - 39th ECDD (2017) Agenda Item 4.8

- **Dihydroetorphine**
  - RP: 1000-12,000
  - Relative of etorphine
  - Used in China like US
  - Uses buprenorphine
  - Banned under Controlled Substance Act of 1970

- **Oliceridine**
  - Less β-arrestin recruitment than morphine (See also PZM21)
  - Showed great promise in Phase 1 & 2 but ultimately voted against by FDA advisory board after depression of respiratory drive led to safety concerns
Opioids: Natural and Synthetic

Some Known Opioids and Their Properties
MOR Partial Agonists and Antagonists

Pentazocine
- MOR antagonist, KOR agonist
- hallucinogenic, delusion inducing
- mixed with naloxone to prevent misuse
SN, T's and B's
(Produced by Talwin, Blue pill)

Naloxone
- non-selective antagonist
- standard of care for opioid OD
- often mixed with other opioids to prevent their misuse
- Available over the counter
- one of WHO's essential medicines

Butorphanol
- partial agonist and antagonist
- used as migraine therapy
- KOR agonist that reduces post-operative shivering
- ubiquitous in veterinary med.

Diprenorphine
- high affinity, weak partial agonist of MOR, KOR, DOR
- veterinary medicine used to reverse effects of super-potent analgesics like carfentanil
- not currently used in humans

Thebaine
- name from ancient city of Thebes
- Stimulant, not sedative
- high doses cause convulsions similar to strychnine poisoning
- not used clinically
- essential semi-synthesis material
- (+)-isomer is active, (-)-natural isomer is not

Nalmefene
- silent MOR antagonist
- weak partial agonist of KOR
- treatment for alcohol dependence
- has been investigated for pathological gambling addiction

Protease Inhibitors

Naldeine
- MOR antagonist
- Discovered 1915, but never marketed
- First opioid antagonist to be discovered
- Also an agonist of KOR

Samidorphan
- MOR antagonist currently under development by Alkemines for Major Depressive Disorder
- Potential for combination therapy with buprenorphine (KOR antagonist, MOR agonist) anti-depression, no euphoria or dependence

Naltrexone
- MOR antagonist
- the opioid you take when you are dependent on opioids (or alcohol)
- significant side effects.

Racecadotril
- Enkephalinase inhibitor
- reduces secretion of water and electrolytes into intestine.

Ubenimex (bestatin)
- reversible protease inhibitor
- inhibits degradation of oxytocin, vasopressin and enkephalins

RB-101 (see also RB-120 & RB-3007)
- Enkephalinase inhibitor used in research
- prodrug disulfide is cleaved in brain
- cleavage produces two inhibitors which block metallopeptidases from breaking down endogenous opioids
- similar effects to MOP agonism but resistant to dependence due to decreased potential for overstimulation

KOR Agonists and Antagonists

Naltorafine
- Selective KOR agonist
- Anti-pruritic (anti-itch)
- First KOR agonist approved for clinical use.
- dubiously referred to as the first non-narcotic opioid drug in history

Dilelifekalin
- peripherally specific KOR agonist
- a.k.a. CR845, FE-202845
- under development by Cara Therapeutics for post-op pain.
- lacks sedation, dysphoria, hallucinogenic side effects as a result of peripheral mechanism
- Completed Phase 2 with success

Zyklophine
- Selective KOR antagonist
- blocks stress induced restatement of cocaine-seeking in animals
- currently under investigation as a potential therapeutic

CERC-501
- Selective KOR agonist
- Originally developed by Lilly
- currently being pursued by Janssen as treatment for Major Depressive Disorder and substance abuse

PF-4455242
- Selective Short acting KOR antagonist
- Pursued by Pfizer in 2009
- long term animal toxicology to halting phase 1

BU09059
- potent, short acting
- KOR agonist
- intended for psychiatric disorders
- highly KOR selective over MOR, DOR
Some Known Opioids and Their Properties

**Peripheral acting/ anti-diarrheals**
- Methylnaltrexone
  - Newer MOP antagonist
  - Cannot cross BBB
  - Reverses opioid side effects like constipation without affecting analgesia

- Ioperamide (Imodium)
  - MOP agonist, cannot cross BBB
  - Anti-diarrheal, IBS treatment
  - One of WHO’s Essential Medicines
  - 1 mlll prescriptions in US (2016)
  - One of WHO’s essential medicines
  - “Poor man’s methadone”

- Naloxegol
  - Peripherally selective antagonist
  - Treatment for opioid induced constipation (OIC)
  - PEG prevents BBB crossing
  - Developed by AstraZeneca

- Alvimopan
  - Peripheral MOP antagonist
  - Limited BBB crossing
  - Only FDA approved treatment for post-op ileus

- Nalmédeme
  - Peripheral MOR antagonist
  - Treatment for OIC
  - Currently under investigation

- Brenopran
  - aka CB-5945, ALD-5945, MK-2402, OPRA III
  - Peripheral MOR, DOR antagonist
  - Developed by Cubist Pharma, for OIC
  - Discontinued in Phase III

**Eluxadoline**
- MOR, KOR agonist
- DOR antagonist
- Approved for use as anti-diarrheal and for abdominal pain in individuals with diarrhea-predominant IBS
- WO200609960A2

**Difenoxin**
- Anti-diarrheal
- Crosses BBB causing euphoria and other opioid side effects, including addiction
- Schedule 1 by itself

**Future Directions?**
- Can we genetically engineer better opioid receptors with less addictive associations?
- Will Synthetic Chemists achieve a truly preparative synthesis of Morphine?
- When will we have a full grasp of addiction and its causes?
- Discovery of a low abuse liability painkiller, or Aldous Huxley’s Brave New World?

**Opioid Vaccines**

- J-113,397
  - Selective NOR antagonist
  - Prevents morphine tolerance
  - Prevents hyperalgesia
  - Stimulates dopamine release and increases rewarding effects of cocaine

- SB-612,111
  - Selective NOR antagonist
  - More potent than J-113,397
  - Prevents hyperalgesia
  - Shows anti-depressant effects

- Hapten: small molecule which, when bound to a protein can elicit production of antibodies which bind to it

Great Perspective: Janda, JACS 2019, 1798-1806