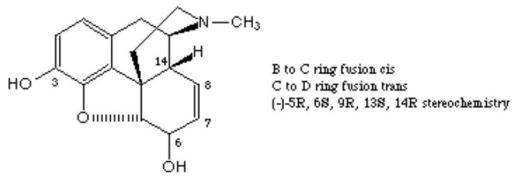
Chemistry of Opioid Analgesics

PHA 4220 - Neurology Pharmacotherapeutics

Required reading assignment: Wilson and Gisvold, pgs. 629-656.

Opioid anagesics are well known for their ability to **reduce the perception of pain without a loss of consciousness**. The original opioids were derived from **opium**, which is a partially dried latex harvested fromt the opium poppy, **papaver somniferum**. Opium contains morphine, codeine, noscapine, papaverine, and thebaine. **Thebaine** is a convulsant drug that produces no analgesia, and as such it is not used clinically. However, it is an important synthetic intermediate in the production of semisynthetic opioids. Opium is a less effective analgesic than pure morphine, because it is slowly absorbed, and has been historically used for its constipating action (paregoric). Morphine itself, which was discovered in 1809, has a variety of effects, among which are an **increase in the tolerance to pain, somnolence, euphoria, an antitussive effect, respiratory depression, constipation and emesis**. In addition, morphine has a **high addiction liability**. Derivatives of morphine have been sought that **retain the anagesic activity** of the parent, but that have **improved oral bioavailability** and a **reduction in addiction liability and other deleterious side effects**.

The structure of morphine is shown below. The rings are lettered **A (aromatic), B (cyclohexane), C (cyclohexene), D (piperidine) and E (tetrahydrofuran)**. All of the derivatives of morphine which possess this basic ring structure have a high addiction liability which is proportional to their analgesic activity.

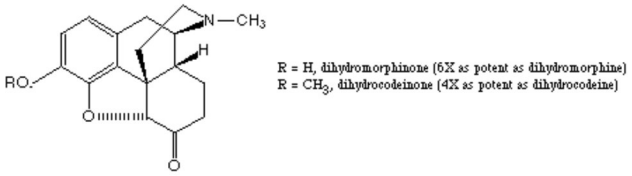


Morphine

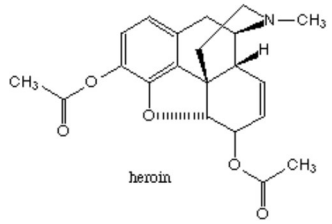
Structure/Activity Relationships of Morphine Analogues

Modifications at the 3- and 6-hydroxyl groups:

- Conversion of the 3-OH to a 3-OCH3, yielding **codeine**, reduces activity to 15% of morphine. Groups larger than a methoxy reduce activity dramatically.
- Conversion of the 6-OH to a 6-OCH3, yielding **heterocodeine**, results in a six-fold increase in activity.
- Oxidation of the 6-OH to a ketone reduces activity when the 7,8-double bond is present (**morphinone** = 37% of morphine). However, as shown below, when the 7,8-double bond is saturated, a 6-keto will increase activity.



- Removal of the 6-OH (**6-desoxymorphine**) increases activity 10-fold in the dihydro series.
- Acetylation of both the 3- and 6-OH produces 3,6-diacetylmorphine, also known as **heroin**. Heroin is 2-3 times more potent than morphine. Most of this increase is due to increased lipid solubility, which leads to enhanced and rapid CNS penetration.
- If the ether linkage is opened up to afford a second OH on the aromatic ring, activity is reduced 90% (see below).



heroin

Modifications at the 7,8-double bond:

- Reduction of the 7,8-double bond results in a slight increase in activity, as in **dihydromorphine and dihydrocodeine**.
- As mentioned above, saturation of the 7,8-double bond has the greates effect when combined with modifications at the 6-position (as in dihydromorphinone).

Modifications of the nitrogen substituent:

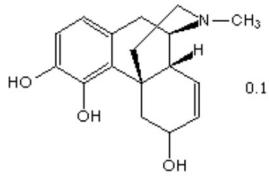
- Methyl is the optimal substituent for agonist activity, and ethyl is passable.
- If the nitrogen substituent is a hydrogen, analgesic effect is reduced 75%, and addicition liability is lowered.

Addition of a phenethyl substituent in place of methyl results in a 14-fold increase in activity over morphine.

- Quaternary ammonium derivatives such as N,N-dimethylmorphine have no analgesic activity, but do have significant curare-like activity.
- If the nitrogen substituent is a bulky alkyl group such as propyl, isobutyl, or especially allyl and cyclopropylmethyl, the compound becomes a narcotic antagonist.

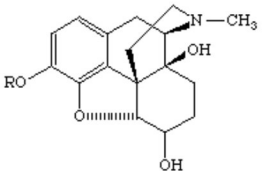
Nuclear (ring) substitutions:

- Opening up the ether linkage (E ring) to form the catechol-type ring system shown below will reduce activity by 90%.

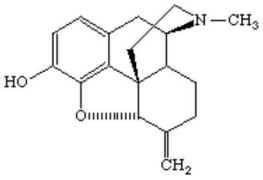


0.1 X the potency of morphine

- Addition of a 14-beta-OH results in a dramatic increase in activity in the dihydromorphinone series, as shown below.



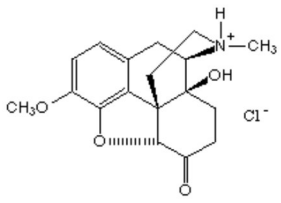
R = H, oxymorphone (10 X morphine)
R = CH3, oxycodone (about equal to morphine)



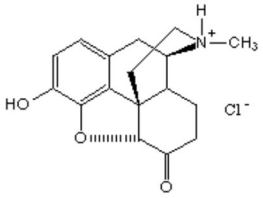
6-methylene-dihydromorphine (80 X morphine)

- If the 6 position is substituted with a methylene substituent, as in the structure above (6-methylene-dihydromorphine), the resulting analogue has 80 times the potency of morphine.

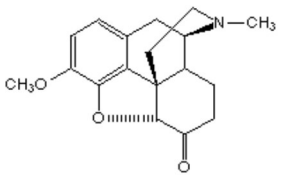
Representative Morphine Analogues



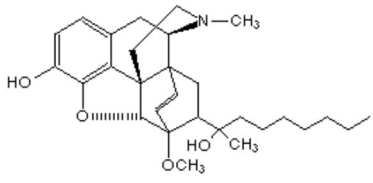
oxycodone HCl (Percodan®, Tylox®)



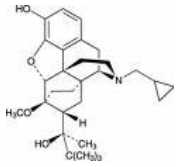
dihydromorphinone HCl (Dilaudid®)



Hydrocodone (Vicodin®)



etorphine (Immobilon®)
an oripavine



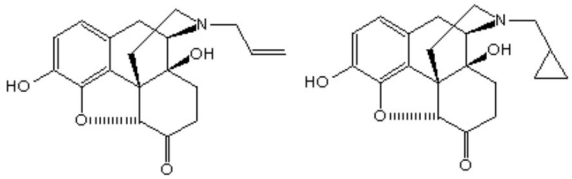
buprenorphine

(Suboxone® = buprenorphine + naloxone sublingual)

(Subutex® = buprenorphine sublingual)

The oripavine derivative etorphine is a representative of a particularly potent class of morphine analogues. Etorphine is approximately 1000 times as potent as morphine, and arguably is too potent to be released for human therapy. It is currently used as a tranquilizer for large animals. A newer, related analogues is **buprenorphine**, which is a potent mu agonist (0.3 mg = 10 mg morphine) that dissociates very slowly from the opiate receptor, giving it a longer duration of action. It also shows antagonist activity in the rat tail flick test. There is some question as to whether naloxone can reverse respiratory depression in patients who have overdosed on buprenorphine. It is used by injection for moderate to severe pain relief. In sublingual form, the products **Suboxone®** and **Subutex®** are used in the treatment of opiate addiction. Subutex contains only buprenorphine, and is used for the initial phase of treatment, followed by Suboxone®, which also contains naloxone.

There are two agents in the morphine class which are marketed as **morphine antagonists**. These agents, naloxone and naltrexone, are shown below. Naloxone is a **pure antagonist**, and is commonly used to treat narcotic overdose. Naltrexone is a similar agent, but does possess **weak agonist activity**, and is used to treat former narcotic addicts.



naloxone (Narcan®) naltrexone (Trexan®)

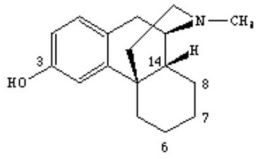
The Morphine Rule

The following structural features are found in most opioid analgesic analogues, and are collectively referred to as the "Morphine Rule". As you will see later, there are some exceptions to this rule.

- 1. A tertiary nitrogen with a small alkyl substituent.
- 2. A quaternary carbon.
- 3. A phenyl group or its isosteric equivalent directly attached to the quaternary carbon.
- 4. A 2 carbon spacer between the quaternary carbon and the tertiary nitrogen.

Structure/Activity Relationships of Morphinans

The **morphinans**, which were first intruduced by Grewe in 1946, are similar in structure to the morphine analogues, but lack the E ring found in the naturally occurring opioids, as well as the 6-OH and the 7,8-double bond. Their general structure is represented by levorphanol, which is shown below.

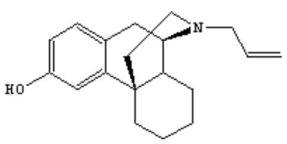


levorphanol (LevoDromeran®)
5 X as active as morphine

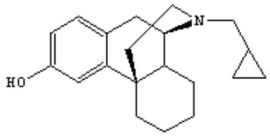
The structure/activity relationships of the morphinans are very similar to those of the morphines:

- A 3-OH is optimal, and a 3-methoxy is less active.
- The nitrogen substituent produces the same activity as in the morphines.
- No other substituents may be added to the A ring.
- The C ring must be unsubstituted.

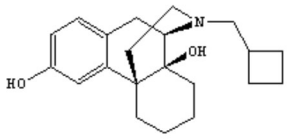
Representative Morphinan Analogues



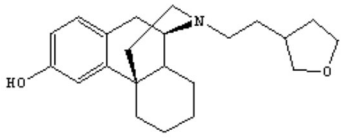
levallorphan (Lorfan®)
antagonist - 5 X nalorphine
weak agonist activity



cyclorphan
narcotic antagonist
agonist 20X morphine
hallucinogenic



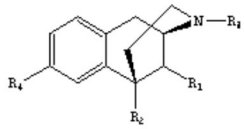
butorphanol (Stadol®)
agonist 4X morphine
weak antagonist
low dependence liability



experimental
30X levorphanol
160X morphine

Structure/Activity Relationships of Benzomorphans

The **benzomorphans**, which were first introduced by May in 1960, are also similar in structure to the morphine analogues, but lack the C and E rings found in the naturally occurring opioids. Their general structure is shown below.

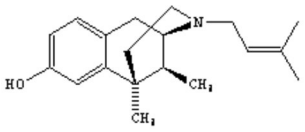


general structure of
the benzomorphans

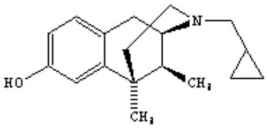
The structure/activity relationships of the follow the same pattern as the morphinans:

- The nitrogen substituent (R3) follows the same rules as the morphinans and morphines. However, antagonist substituents produce analogues with a higher agonist/antagonist ratio.
- R1 and R2 substituents must be present to supply vestiges of the C ring. These are usually methyl, or a similar lower alkyl. R2 must be alpha for the analogue to have agonist activity. R1 can be alpha (cis), producing analogues with activity about equal to morphine, or beta (trans), producing agents 4-30 times as active as morphine. The beta agents will support narcotic addiction, while the alpha series will not.
- R4 must be OH or methoxy.

Representative Benzomorphan Analogues



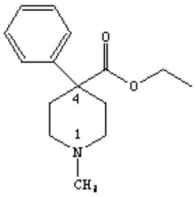
pentazocine (Talwin®)
analgesia 0.5 X morphine
addiction similar to propoxyphene
antagonist - can ppt. withdrawal



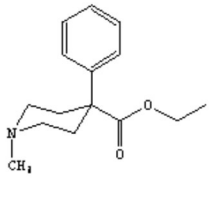
cyclazocine
analgesia 10 X morphine
agonist/antagonist
hallucinogenic - not marketed

Structure/Activity Relationships of the 4-Phenylpiperidines

The representitive 4-phenylpiperidine, meperidine (Demerol, below) was first prepared as an antispasmodic, and in addition to this activity it was found to be **analgesic at about 20% the potency of morphine**. Note that the compound follows the morphine rule.



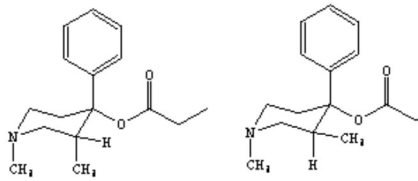
meperidine



active conformation
of meperidine

The structure/activity relationships of 4-phenylpiperidines are fairly simple:

- Both esters and reverse esters at the 4 position are active, as are the simple ketones. propyl is the optimal chain length (excluding the ester oxygen).
- The phenyl ring at the 4 position is necessary for activity, and must be able to assume the axial position, as shown above. Addition of a m-OH group will enhance activity; such analogues are called **bemidones**.
- If a reverse ester is combined with a 3-methyl, the analogues are known as **prodines** (see below). The methyl group may cause enantiomeric recognition by the opioid receptor.

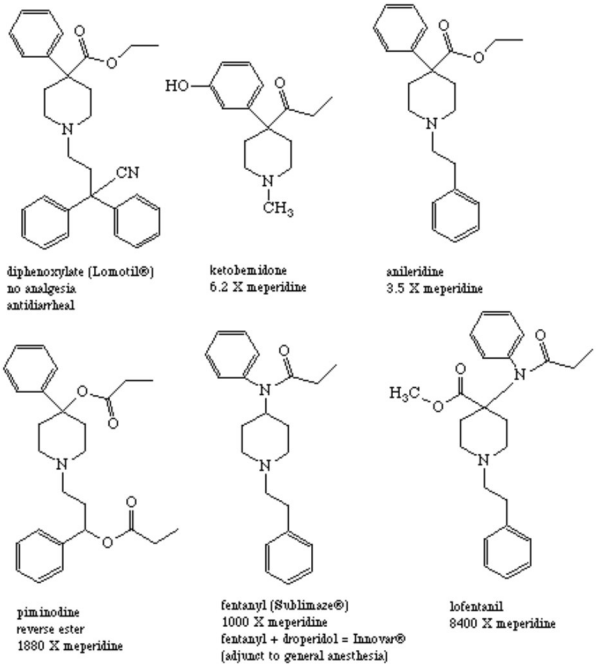


trans = α-prodine
2X morphine
racemate = Nisentil®

cis = β-prodine
9X morphine
racemate
high addiction liability

- The nitrogen substituent is a methyl in most cases. A phenethyl or its equivalent will increase activity. It is not possible to confer antagonist activity with a nitrogen substituent such as allyl.

Representative 4-Phenylpiperidines



diphenoxylate (Lomotil®)
no analgesia
antidiarrheal

ketobemidone
6.2 X meperidine

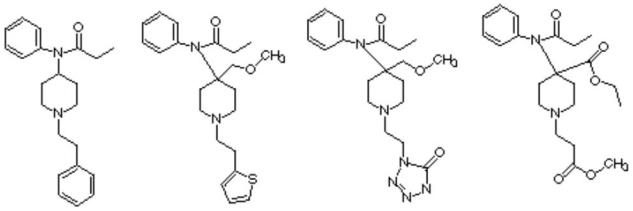
anileridine
3.5 X meperidine

piminodine
reverse ester
1880 X meperidine

fentanyl (Sublimaze®)
1000 X meperidine
fentanyl + droperidol = Innovar®
(adjunct to general anesthesia)

lofentanil
8400 X meperidine

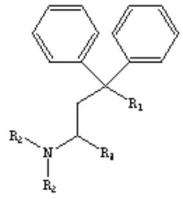
In addition to the 4-phenylpiperadines shown above, the opiate analgesic **fentanyl**, which strictly speaking does not follow the morphine rule, was marketed as a short acting analgesic. Fentanyl, which is 100 times as potent as morphine, is often used for surgical procedures such as endoscopy or colonoscopy.



fentanyl sufentanil alfentanil remifentanyl

Open Chain Opioid Analgesics

Open chain analogues which follow the morphine rule can also have significant analgesic activity. The general structure of these analogues appears below:

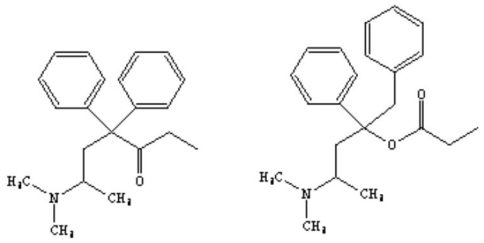


general structure of
open chain opioids

The structure/activity relationships of open chain opioid analgesics is as follows:

- Both phenyl groups must be present.
- The nitrogen substituent R2 can vary, but the nitrogen should be tertiary. It is not possible to produce an antagonist in this class.
- A m-OH reduces activity.
- The (-)-isomers are most potent.
- R1 is usually propionyl.
- R3 is usually methyl, and the total aliphatic chain length is usually 7 carbons.

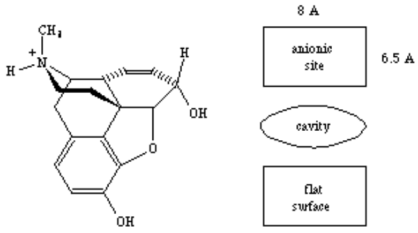
Methadone accumulates in lipid tissue outside of the CNS, and thus has a **slow onset and long duration (24 hours)**. It is used for long term maintenence of addiction. Propoxyphene is a **mild analgesic** with a low addiction liability.



methadone

propoxyphene (Darvon®, Darvocet®)
2S,3R-(+)-isomer is analgesic
(-)-enantiomer is antitussive (Novrad®)

The Opioid Receptor



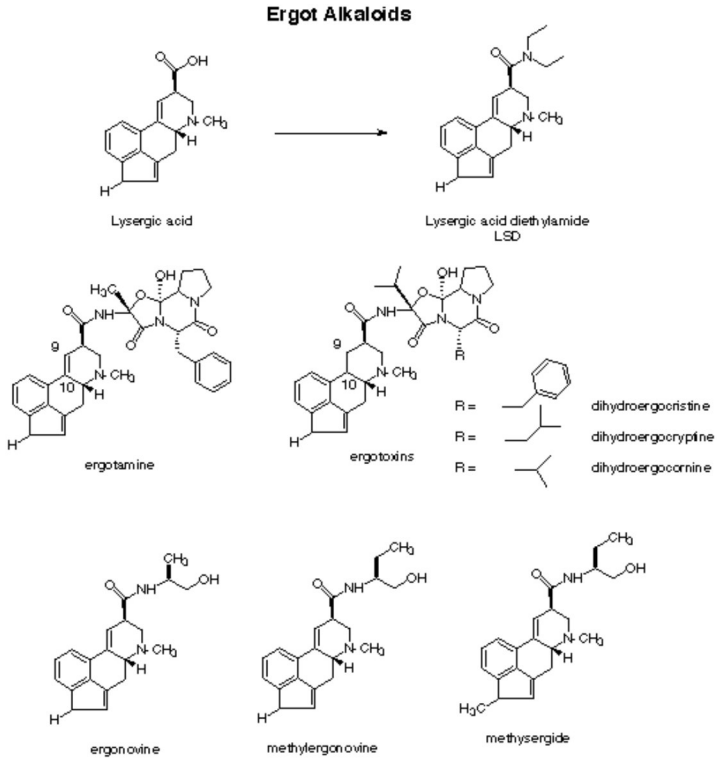
As shown above, the **opioid receptor** is thought to have three main binding areas. There is an **anionic site** (8 by 6.5 angstroms) that bonds to the charged nitrogen of morphine, a **cavity** which accomodates the piperidine ring, and a **flat surface** for binding the aromatic portion of the molecule. All active agonists and antagonists must fit this receptor to some degree. There appear to be four **receptor subtypes**, termed **mu (the morphine receptor), sigma (the phencyclidine receptor), kappa (the ketocyclazocine receptor) and delta (the endorphin/enkephalin receptor)**.

Endorphins and Enkephalins

Endorphins and enkephalins are derived from a 91 amino acid pituitary hormone called **beta-lipotropin**. On release it is cleaved to form three major active products: residue 61-65 is called **met-enkephalin**, residue 61-77 is called **gamma-endorphin**, and residue 61-91 is called **beta-endorphin**. Beta-endorphin is most active, and is about 20 times as potent as morphine. It can produce dependence and tolerance.

Ergot Alkaloids

The ergot alkaloids are a group of indole-containing alkaloids that are produced by the mold *Claviceps purpurea*, a common mold that grows on grains, especially rye. The use of moldy rye in the Middle Ages was responsible for a disease known as St. Anthony's Fire (ergotism), which was characterized by gangrene of the limbs and hallucinations. The cause of the disease was actually due to the lack of blood flow inh the extremities caused by the powerful a-agonist effects of the ergot alkaloids, and their associated CNS stimulatory effects. The structures of some common ergot alkaloids are shown below:

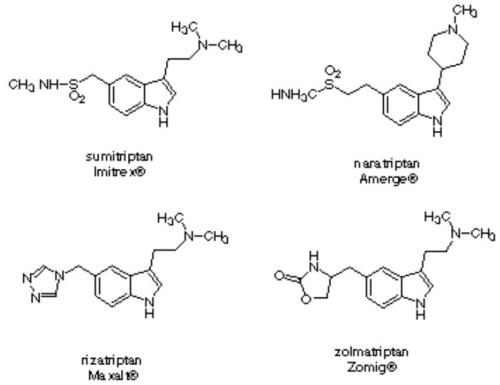


In actuality, crude ergot extract produces a variety of effects, including a-stimulation, a-blockade, CNS stimulation and oxytocic effects. All of the active ergot alkaloids are amides derived from lysergic acid. The best known of these is the powerful hallucinogenic lysergic acid diethylamide (LSD), which produces profound hallucinations through stimulation of the central serotonergic system. **Ergotamine** is a mixed a-agonist/antagonist at central and peripheral adrenoreceptors, and is also a powerful uterine stimulant. Because it is an effective vasoconstrictor, it is used to limit postpartum bleeding, and can also be used to treat migraine headaches. It can be given orally in combination with caffiene (Cafergot®), which potentiates the vasoconstrictive effect. Other more widely used ergot alkaloids used for migraine are **ergonovine** (Ergotrate®), **methylergonovine** (Methergine®) and **methysergide** (Sansert®). In partucular, methysergide has a lower incidence of uterine stimulatory side effects, and thus is more widely used for migraine.

Interestingly, saturation of the 9,10-double bond of ergotamine derivatives afford analogues which are a-blockers, and thus act as vasodilators. Three such synthetic derivatives, **dihydroergocristine, dihydroergocryptine and dihydroergocornine** are marketed in combination as their mesylate salts (ergoloid mesylates, Hydergine®). This preparation is used primarily for peripheral vascular disease.

Other Drugs Used for Pain

In a previous module we discussed the used of aspirin, acetaminophen and the NSAIDS for pain. The reader is invited to review these lectures on the PHA 4110 site at wiz2.pharm.wayne.edu/module/pha413.html.



The **triptans**, shown above, are selective 5-HT1 agonists that are used for the treatment of acute migraine. The hypothesis for their action states that serotonin is a mediator in the development of migraine headache. It is thought that triptans either cause constriction of intracranial blood vessels leading to reduction in pressure, or that they may block the release of proinflammatory neuropeptides from presynaptic nerve terminals. Triptans are used for acute migraine, but not for prophylaxis.

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