ANALGESICS

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Analgesics

The terms analgesics and analgetic drugs are often used interchangeably to describe a diverse group of pain medications such as opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and triptans, each with very different mechanisms of action for relieving pains of a wide array of causes.

Origin of Pain

Pain differs in its underlying causes, symptoms, and neurobiological mechanisms and has been classified into three major types:

Physiological pain is the most common and is often caused by an injury to body organs or tissues.

Inflammatory pain originates from an infection or inflammation as a result of the initial tissue or organ damage.

Neuropathic pain is a very complex, chronic pain, resulting from injury of the nervous systems.

Approaches to Pain Management

the choice of analgesic therapy is based on assessment of pain intensity. Thus, non-opioid analgesics such as acetaminophen and NSAIDs are the drugs of choice for mild pain.

For moderate pain, a combination of an NSAID (or acetaminophen) and a weak opioid such as codeine should be used.

Morphine, fentanyl, and other potent opioids are reserved only for severe pain, especially in patients who are terminally ill, to control pain and to improve their quality of life.

Opioid Receptors

Opioid receptors are distributed throughout the brain, spinal cord, and peripheral tissues. The distribution of specific opioid receptor subtypes (μ, K and δ)

In rats, high concentrations of all three genes for the μ -, K -, and δ -receptors were found in the hypothalamus and cerebral cortex.

Intermediate concentrations were found in the small intestine, adrenal gland, testes, ovary, and uterus.

Low concentrations of all the three gene transcripts were found in the lung and kidney

All of the opioid receptors belong to the G-protein–coupled receptor class and as such, they are composed of seven TM domains

THE μ-RECEPTOR

Mu receptors are found primarily in the brainstem and medial thalamus. Endogenous peptides for the μ -receptor include endomorphin-1, endomorphin-2, and β-endorphin .Exogenous agonists for the μ -receptor include drugs from the five structural classes (4,5-epoxymorphinan, morphinan, benzomorphan, 4-phenyl/4-anilido piperidines, and the diphenylheptanes).

Agonists at the μ -receptor produce analgesia, respiratory depression, decreased gastrointestinal (GI) motility, and euphoria. Agonists are also responsible for the addictive effects of the opioid analgesics. Most clinically used opioid drugs bind to the μ -opioid receptor.

THE δ-RECEPTOR

Opioid peptides for the δ -receptor include the endogenous peptides Met and Leu enkephalin. These peptides have high affinity for the receptor but low bioavailability and thus limited clinical usefulness.

THE K -RECEPTOR

Kappa receptors are primarily found in the limbic, brain stem, and spinal cord. The K -receptor shows less structural homology to the μ-receptor than the δ-receptor does. Unlike the μ - and δ -receptors that bind the (enkephalin) peptide sequence Tyr-Gly-Gly-Phe-(Leu/Met), the K -receptor does not.

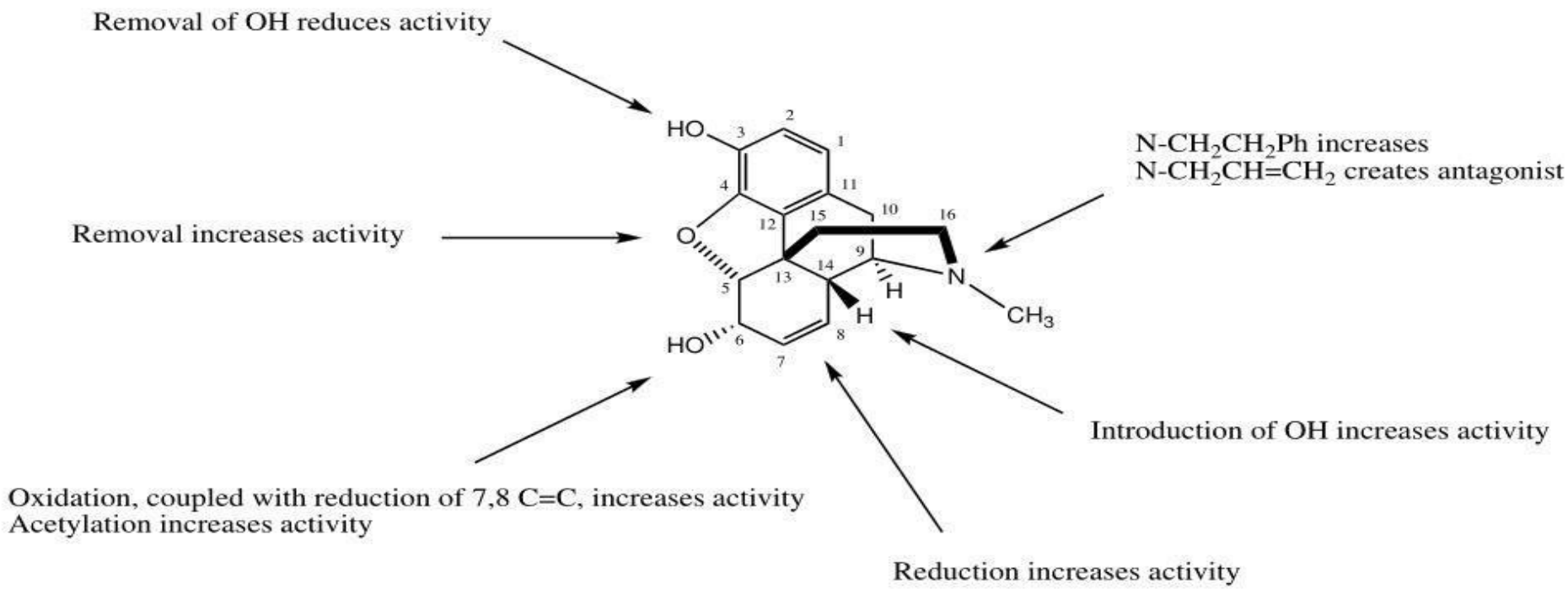
The K -receptor shows a clear preference for binding peptides with an arginine in position 6 as seen in the dynorphin peptides .

Drugs monographs

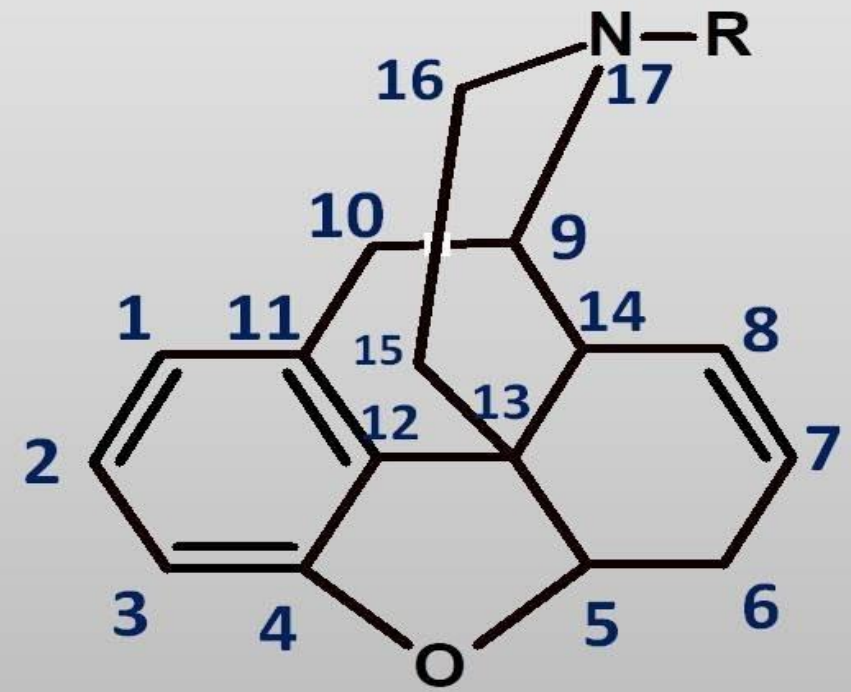
4,5-Epoxymorphinans

MORPHINE The prototype ligand for the μ-receptor is morphine. Morphine contains 5 chiral centers and has 16 optical isomers (not 32 because of the restriction of C-9 to C-13 ethanamino bridge). The naturally occurring, active form of morphine is the levorotatory enantiomorph with the stereochemistry 5(R), 6(S), 9(R), 13(S), and 14 (R).

Summary of structure-activity relationships (SAR's)



SAR of OPIOIDS

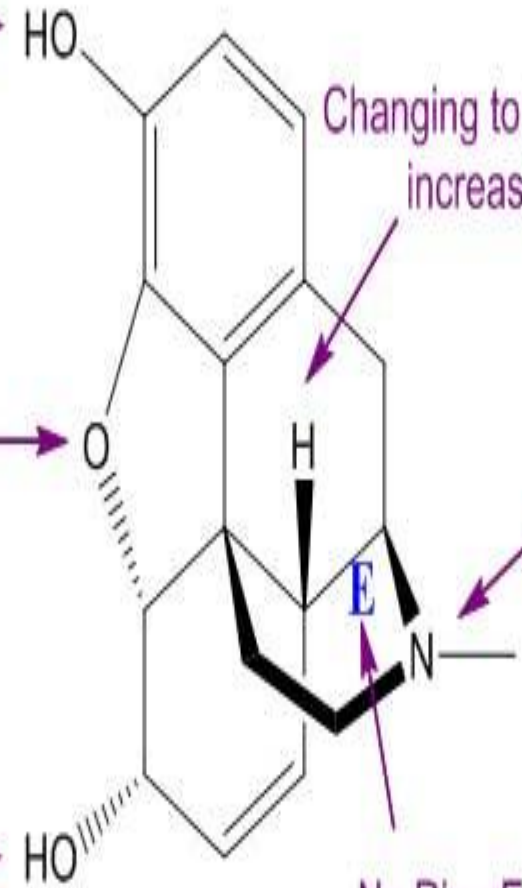


Chain length of R

< 3	→	Agonist
3-5	→	Antagonist
> 5	→	Agonist with potency

Summary

- Removal = reduced activity.
- Can be masked as another functional group (i.e. prodrugs)



Changing to hydroxyl (-OH) increases activity

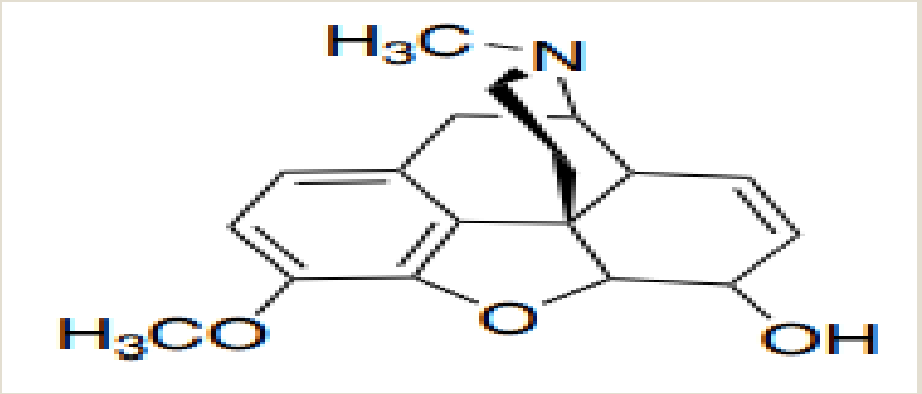
Removal:
- Enhances biological activity.
- Makes chemical synthesis relatively easier.

R = phenethyl -} enhances activity
R = cyclopropylmethyl or allyl -} confers antagonistic properties

Can be masked as another functional group (i.e. prodrugs)

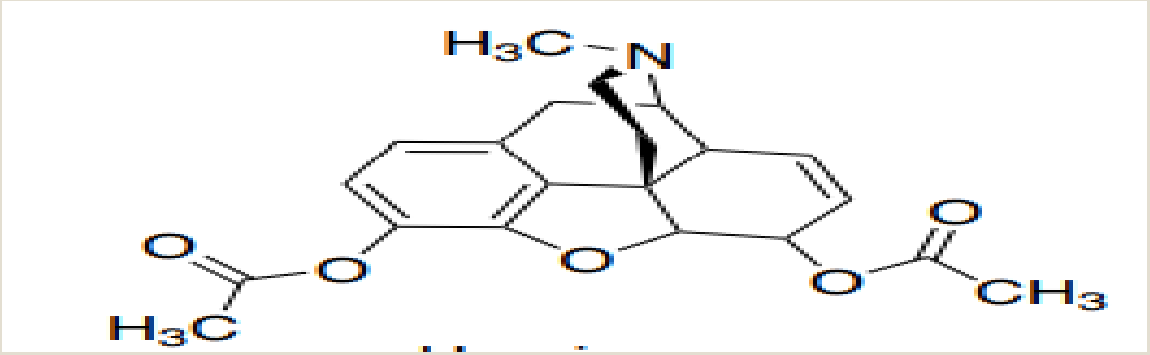
No Ring E = No Activity

CODEINE



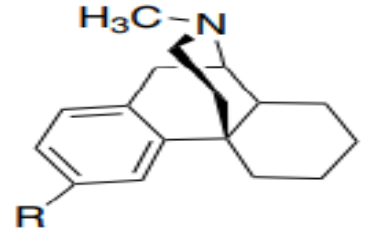
Codeine is an alkaloid that occurs naturally in opium, but the amount present is usually too small to be of commercial importance. Consequently, most commercial codeine is prepared from morphine by methylating the phenolic OH group. Approximately 5% of codeine is metabolized to morphine via O-demethylation. The general pharmacological action of codeine is similar to that of morphine, but it does not possess the same analgesic potency Codeine's role as an effective antitussive agent has been questioned.

HEROIN



Heroin, was first commercially synthesized as an alternate analgesic to morphine. Heroin is the 3,6 diacetylated form of morphine . believed that heroin would be an effective analgesic with no addictive properties. With both OH groups protected as an ester, heroin can pass through the blood-brain barrier quicker than morphine and lead to the euphoric “rush” that becomes so addictive to addicts, especially after IV injection. Once heroin is in the brain, it is quickly metabolized to 3-acetylmorphine, which has low to zero activity at the μ-receptor and 6-acetylmorphine, which is 2 to 3 times more potent at the μ-receptor than morphine.

Morphinans



Morphinan
R= OH (-) Levorphanol oral = 2 mg
R= OCH_3 (+) Dextromethorphan

The morphinans were made by removing the E ring of morphine, the 4,5-ether bridge,in an attempt to simplify the structure.

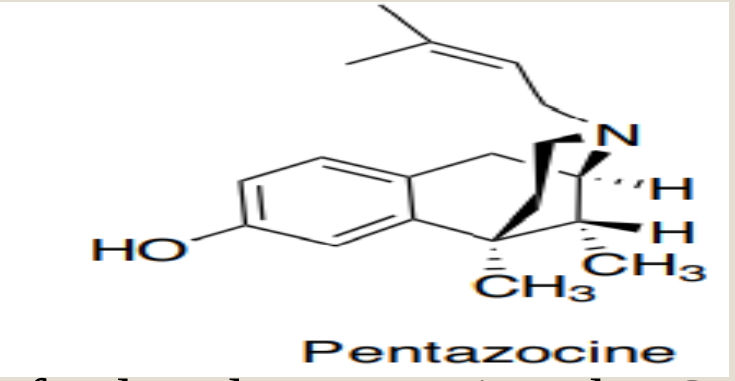
LEVORPHANOL

Levorphanol tartrate is the levorotatory form of methorphan and is approximately 7.5 times more potent than morphine orally. The loss of the 4,5-epoxide and the 7,8-double bond allows levorphanol greater flexibility and presumable leads to the increased binding affinity at all opioid receptor subtypes compared with morphine.

DEXTROMETHORPHAN

Dextromethorphan is the dextrorotatory form of levorphanol with a methoxy group on the 3-position . It is available in more than 140 over-the-counter (OTC) cough and cold formulations.

Benzomorphans



Pentazocine

Structural simplification of the morphine ring system further, by removing the C ring of the morphinan structure, yields the benzomorphans also referred to as the benzazocines

PENTAZOCINE

The benzomorphans are prepared synthetically and thus result in several stereoisomers. The active benzomorphans are those that have the equivalent bridgehead carbons in the same absolute configuration of morphine. The only benzomorphan in clinical use is pentazocine.

Pentazocine is a mixed agonist/antagonist displaying differing intrinsic activity at the opioid receptor subtypes. At the μ-receptor, pentazocine is a partial agonist and a weak antagonist.

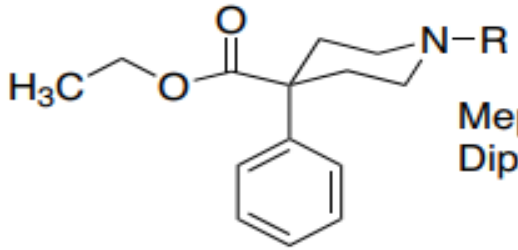
4-Phenylpiperidines and 4-Anilidopiperidines

Removal of the B ring of the benzomorphans yields the 4-substituted piperidines. The resultant structures are flexible and, without the B ring locking the A ring in an axial position relative to the piperidine (D) ring, the A ring can exist in either an axial or an equatorial position.

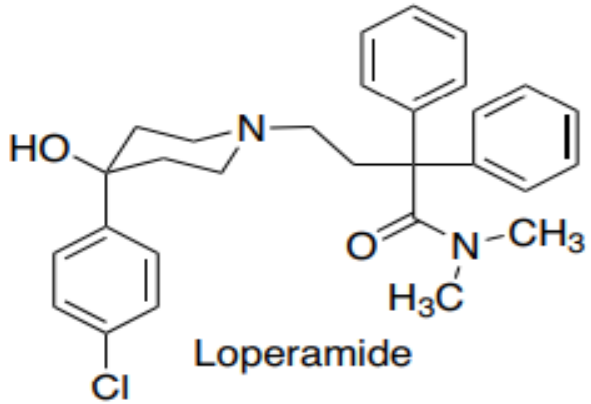
MEPERIDINE

Meperidine was found to have low potency at the receptor compared with morphine (0.2%) but much higher penetration into the brain resulting in a compound with about 10% of the potency of morphine. Meperidine is an agonist at the -receptor and a 300-mg oral or 75-mg IV dose is reported to be equianalgesic with morphine 30-mg oral or 10-mg IV dose.

4-Phenylpiperidines

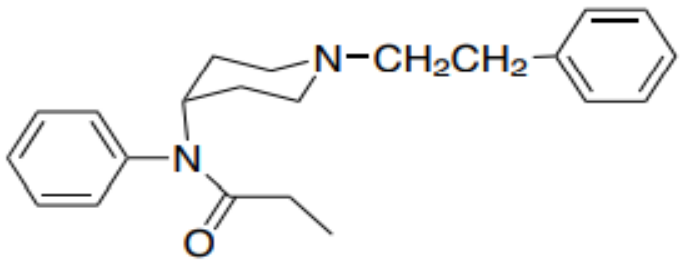


Meperidine R= CH_3
Diphenoxylate R = $—CH_2CH_2C(CN)$

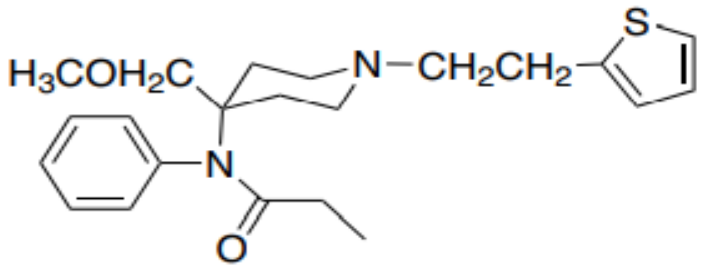


Loperamide

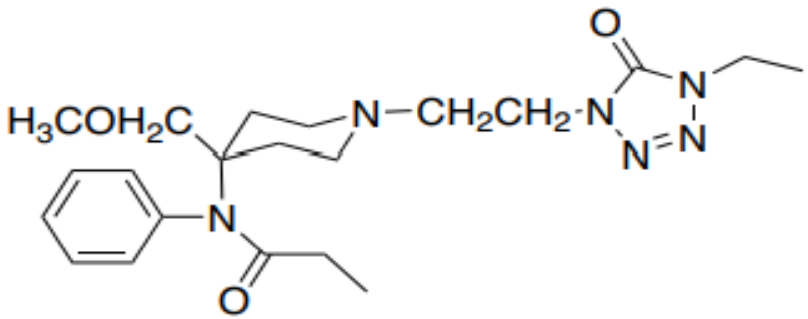
4-Anilidopiperidines



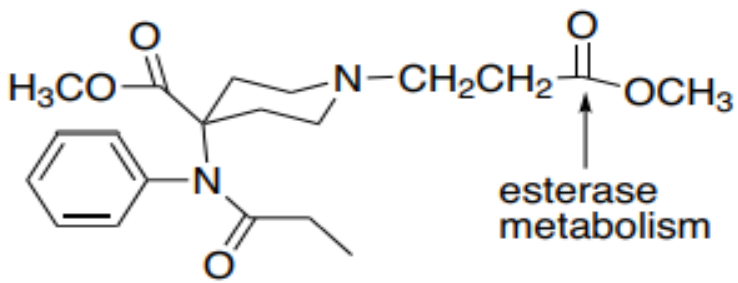
Fentanyl



Sufentanil



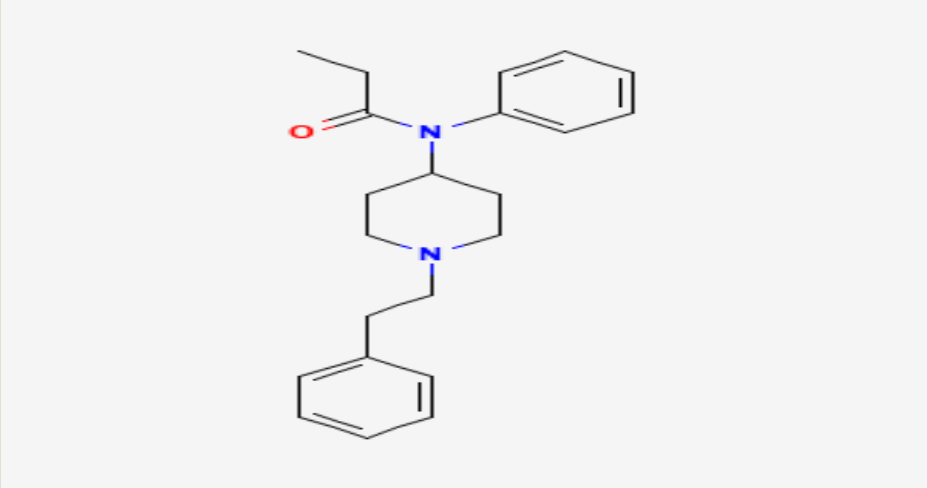
Alfentanil



Remifentanil

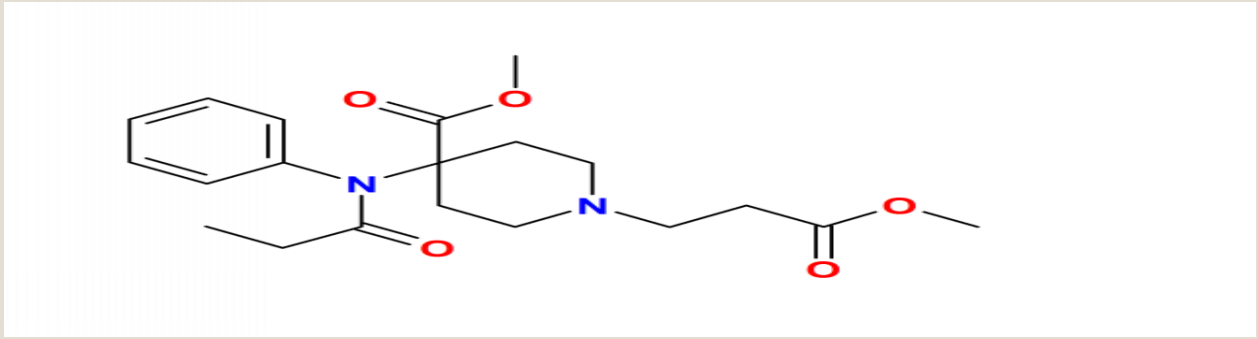
Figure 24.9 ● 4-Phenylpiperidines and 4-anilidopiperidines.

FENTANYL



The high lipophilicity of fentanyl gave it a quick onset, and the quick metabolism led to a short duration of action. The combination of potency, quick onset, and quick recovery led to the use of fentanyl as an adjunct anesthetic. In addition to the injectable formulation, fentanyl is available in a unique transdermal system . This formulation is beneficial to many chronic pain sufferers unable to take oral medication. The transdermal system releases fentanyl from the drug reservoir patch into the skin, forming a depot layer. The fentanyl is then absorbed into the systemic circulation.

REMIFENTANIL

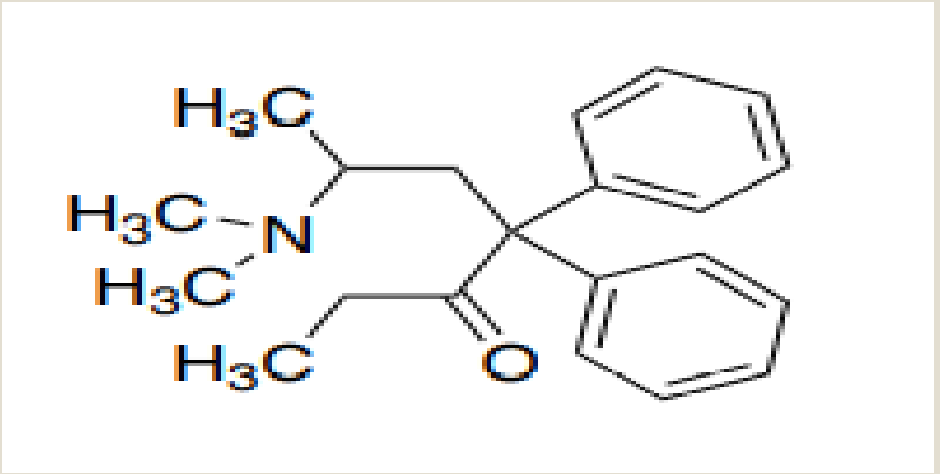


Remifentanil was designed as a “soft drug.” Soft drugs are designed to undergo metabolism quickly and thus have ultra short durations of action. In place of the ethyl aromatic ring seen on the other piperidine opioids, remifentanil has an ester group . This ester group is metabolized by esterases in the blood and tissue to a weakly active metabolite (1:300–1:1,000 the potency of remifentanil).

The n-octanol/water partition coefficient of remifentanil is 17.9. The pKa of remifentanil is 7.07, thus it is predominately unionized at physiological pH. Both of these properties account for its rapid distribution across the blood-brain barrier (1 minute).

Diphenylheptanes

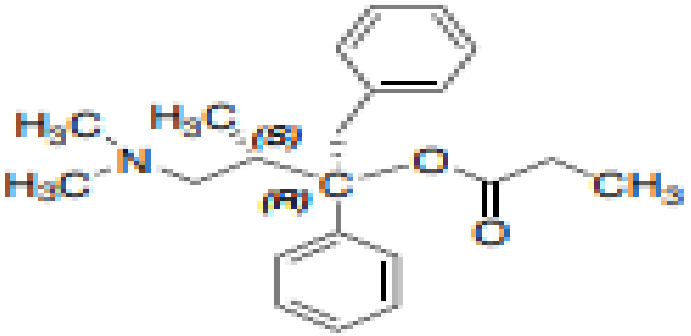
METHADONE



Methadone is a synthetic opioid approved for analgesic therapy and for the maintenance and treatment of opioid addiction.

although the opioid activity resides in the R-enantiomer (7–50 times more potent than the S-enantiomer). Methadone is a μ-receptor agonist with complex and highly variable pharmacokinetic parameters. Bioavailability following oral administration ranges from 36% to 100%.

PROPOXYPHENE

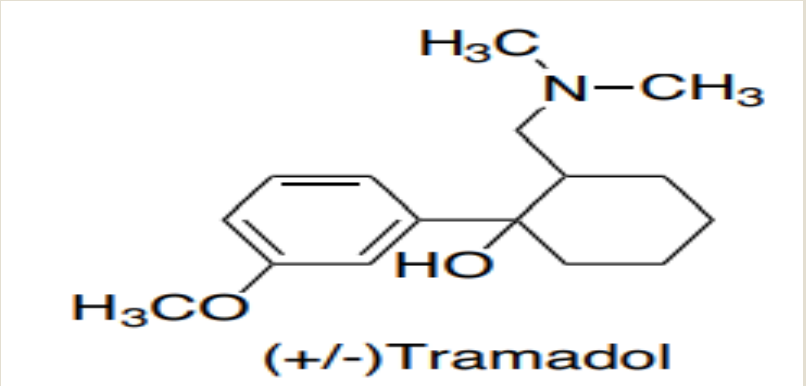


Propoxyphene

Most of the structural changes to the methadone skeleton resulted in compounds with decreased opioid potencies, Propoxyphene is a derivative of methadone marketed in 1957 as the enantiomerically pure (2S, 3R). It is only about 1/10th as potent as morphine as an analgesic yet retains all the same opioid adverse effects.

Miscellaneous

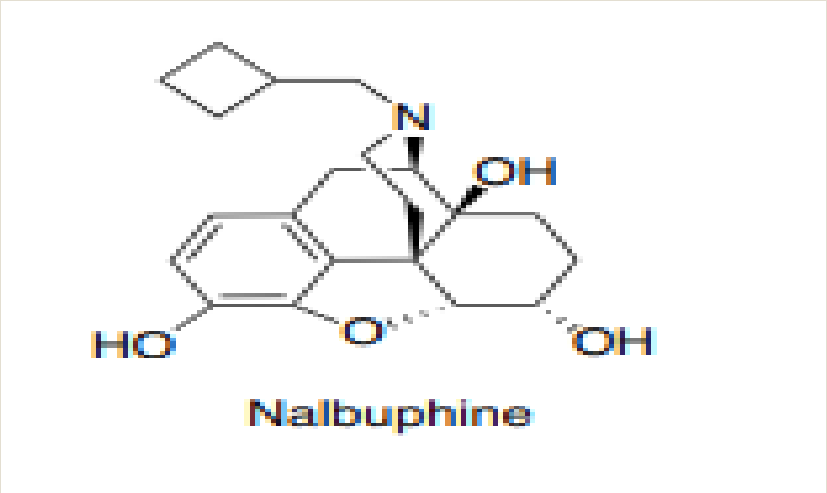
TRAMADOL



Tramadol is an analgesic agent with multiple mechanisms of action. It is a weak -agonist with approximately 30% of the analgesic effect antagonized by the opioid antagonist naloxone. Used at recommended doses, it has minimal effects on respiratory rate, heart rate, blood pressure, or GI transit times. Structurally, tramadol resembles codeine .

Mixed Agonist/Antagonist

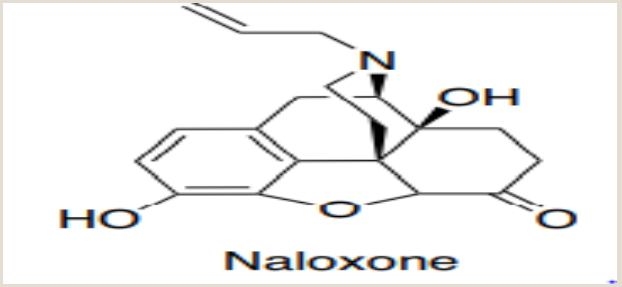
NALBUPHINE



it has an analgesic potency approximately two thirds that of morphine, and it has a similar degree of respiratory depression. The oral bioavailability of nalbuphine is only 12%, and the drug is only marketed as an injectable.

Opioid antagonist

NALOXONE



Naloxone is a pure antagonist at all opioid receptor subtypes. Structurally, it resembles oxymorphone except that the methyl group on the nitrogen is replaced by an allyl group. This minor structural change retains high binding affinity to the receptor, but no intrinsic activity. It is used to reverse the respiratory depressant effects of opioid overdoses.

THANK YOU