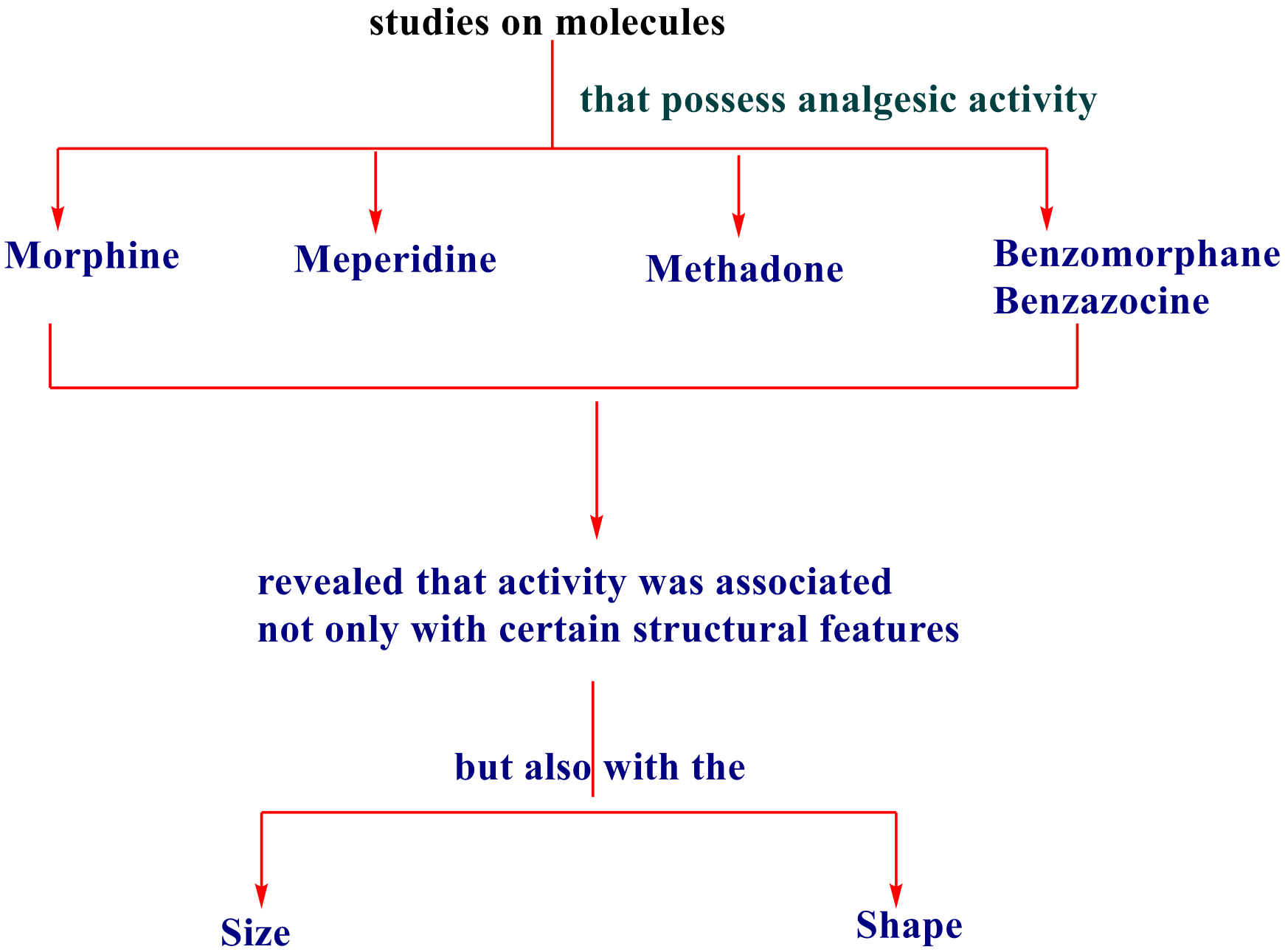
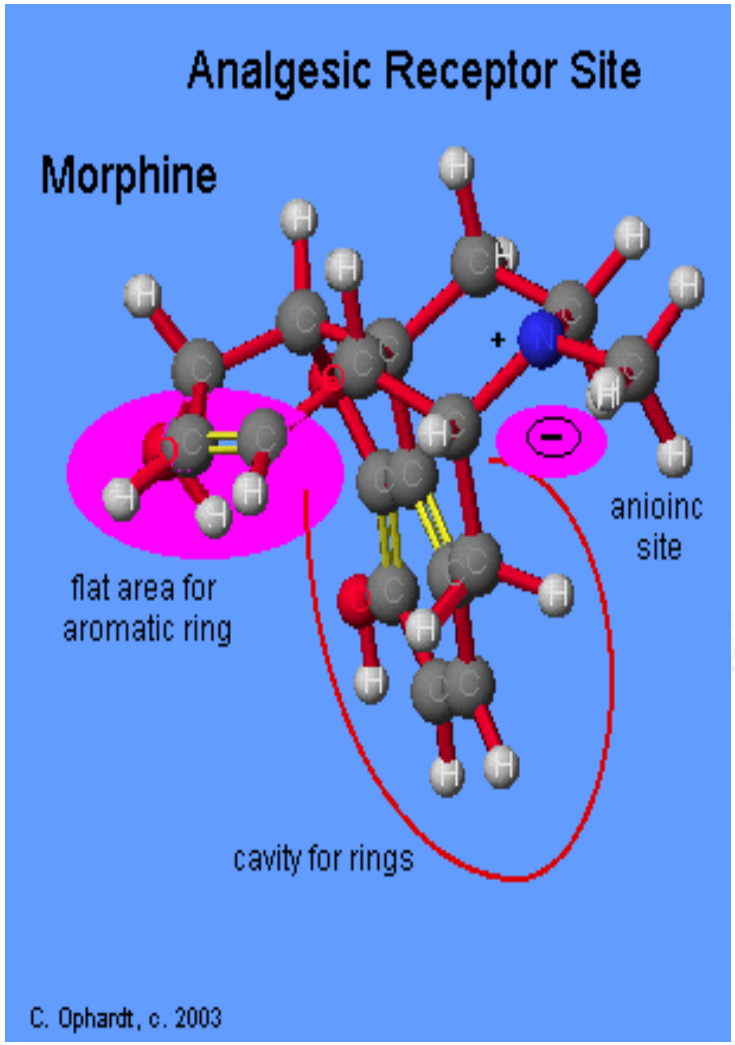
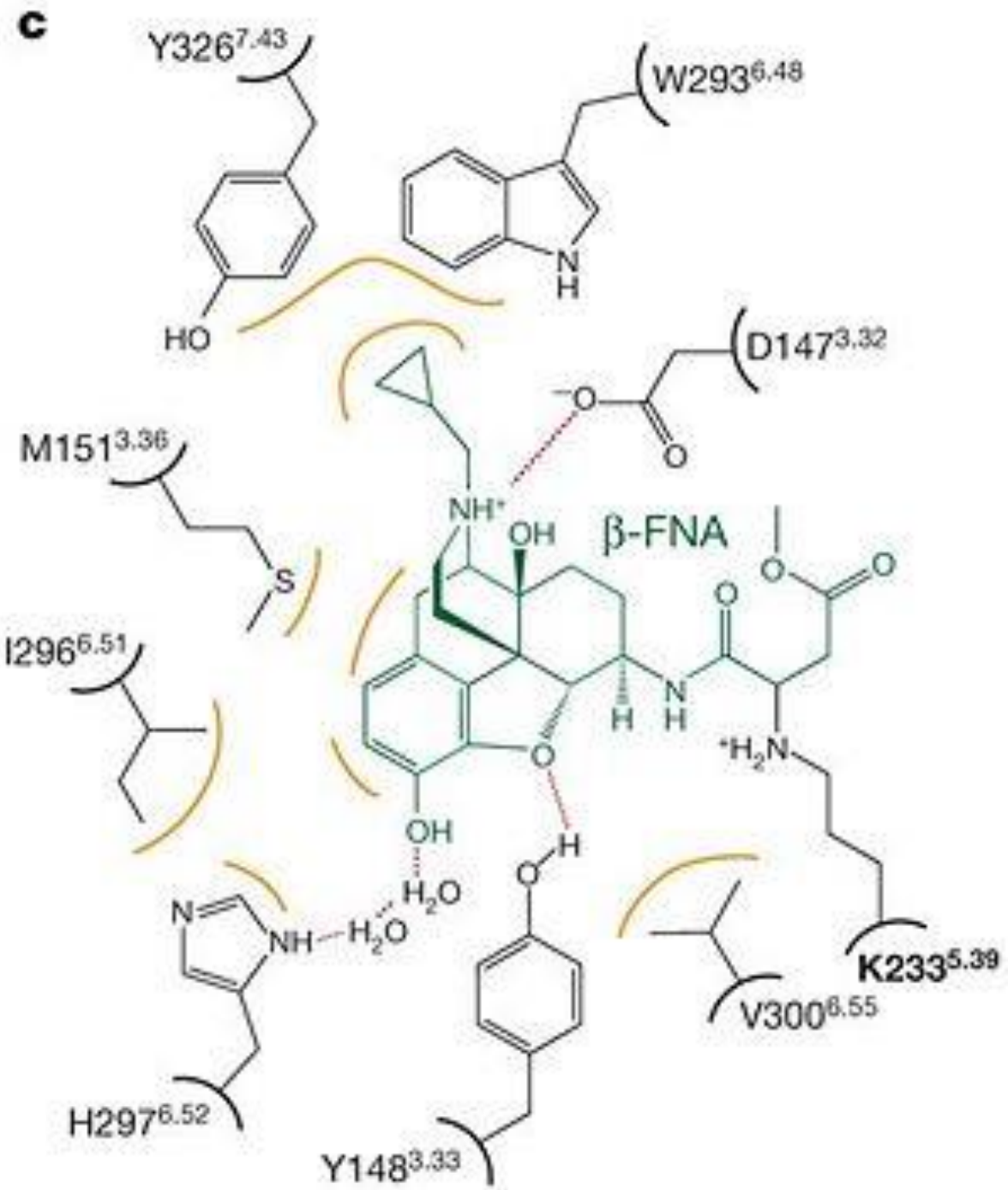
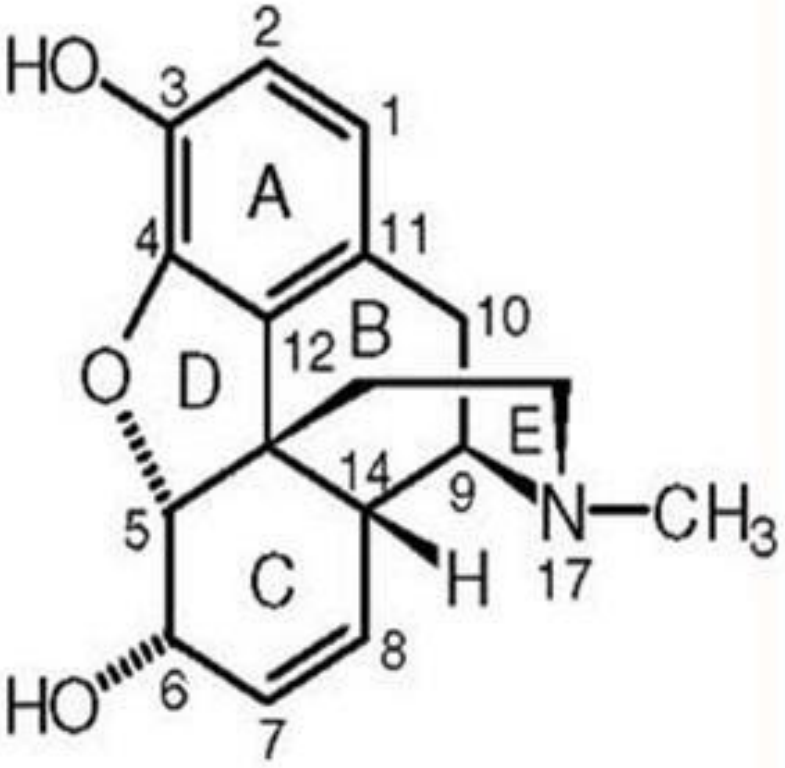
Organic Pharmaceutical Chemistry II

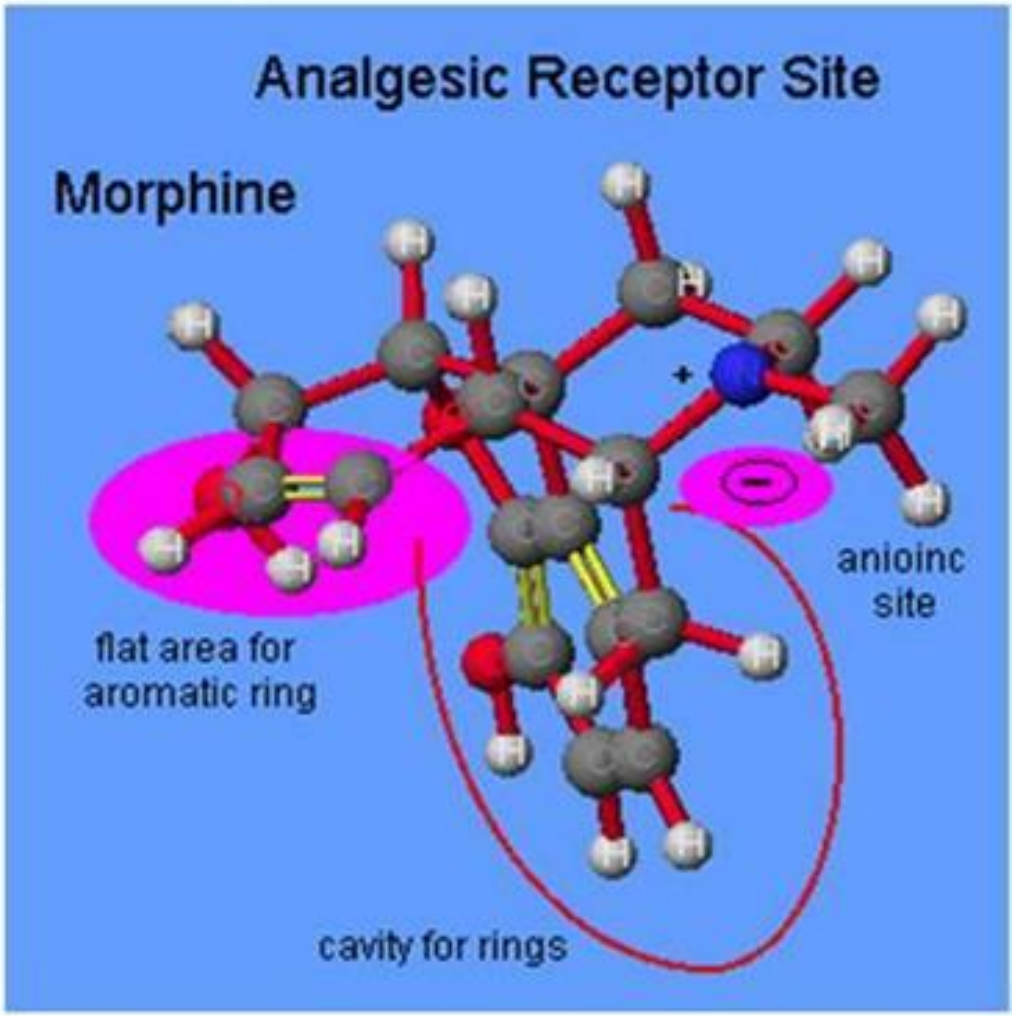

studies on molecules
that possess analgesic activity
Morphine
Meperidine
Methadone
Benzomorphane
Benzazocine
revealed that activity was associated
not only with certain structural features
but also with the
Size
Shape


Analgesic Receptor Site
Morphine
flat area for aromatic ring
anioinc site
cavity for rings
C. Ophardt, c. 2003


c
Y326 7.43
W293 6.48
HO
N H
D147 3.32
M151 3.36
NH+
OH
β-FNA
S
I296 6.51
N H
+H2N
OH
H
H2O
N
NH
H2O
K233 5.39
V300 6.55
H297 6.52
Y148 3.33

SAR OF MORPHINE



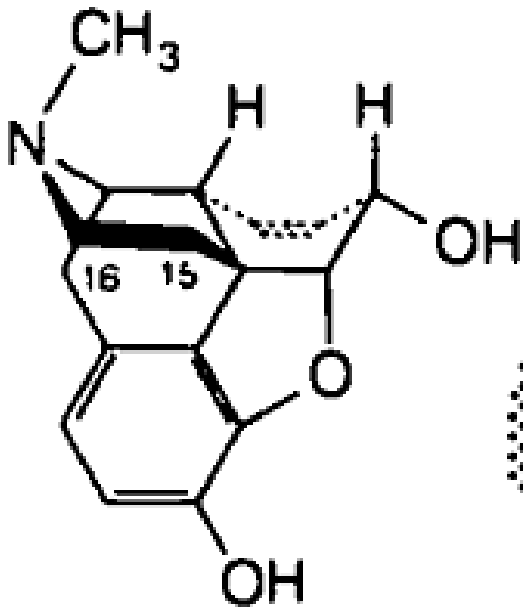


UNIT -V

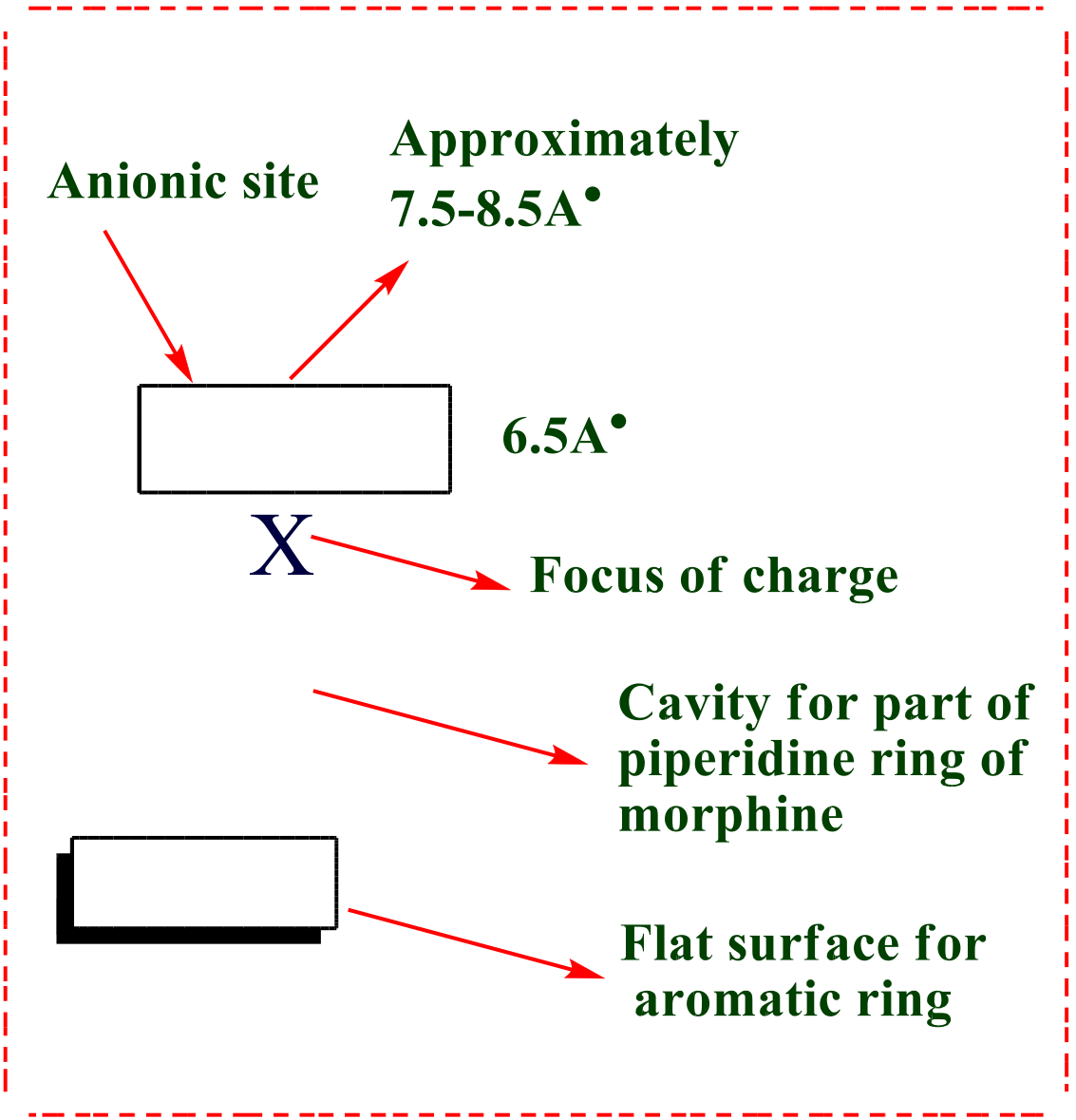
ALKALOIDS

Dr.J.BelsenDavid, MPharm, PhD

Associate Professor



(-) Morphine



Receptor

The essential features for the proper receptor fit are-:

.1 A basic center able to associate with an anionic site on the receptor surface.

.1 A flat aromatic structure, coplanar with the basic center, allowing van der Waals bonding to a flat surface on the receptor site to reinforce the ionic bond.

.1 A suitably positioned projecting hydrocarbon moiety forming a three-dimensional geometric pattern with the basic center and the flat aromatic structure.

Antitussive agents

Cough is a protective, physiological reflex that occurs in health as well as in disease. It is considered as a mild symptom, occurs due to irritation of mucosa exciting the cough center causing bronchoconstriction followed by dilation due to disease and allergy.

Among the agents that used in symptomatic control of cough are those that act by depressing the cough center located in the medulla. The more important and widely used ones are morphine, hydromorphone. Codeine, hydrocodone, Methadone, and levorphanol, which are all narcotic agents.

Many of the cough preparations contain various other ingredients in addition to the primary antitussive agent, like-:

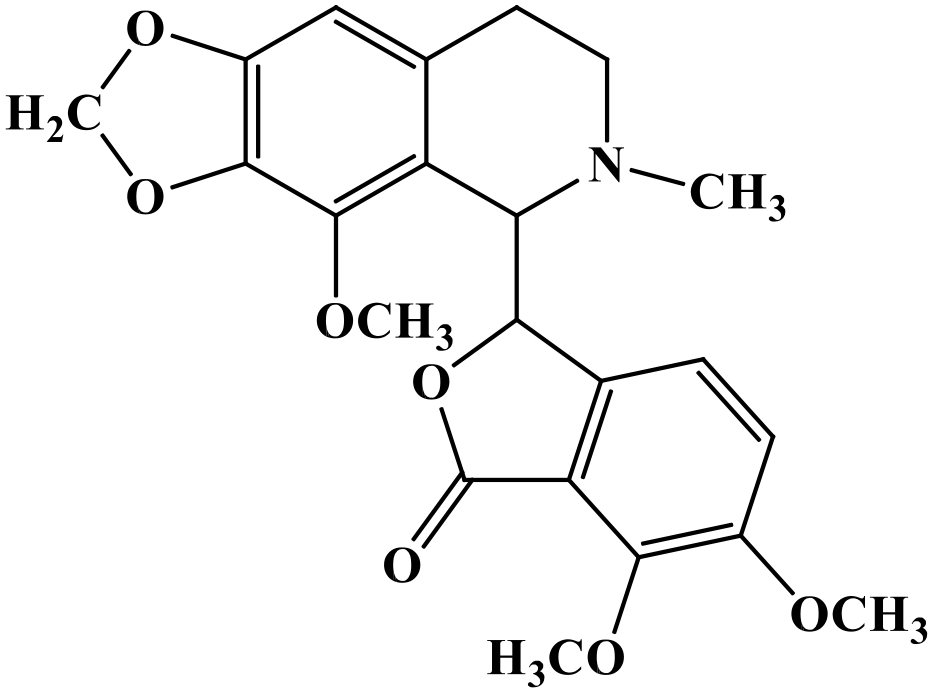
.1 Antihistamines, useful when the cause of the cough is allergic, (e.g., diphenhydramine) which have also central antitussive action.

.1 bronchodilator activity, like ephedrine, methamphetamine. phenylpropanolamine. Isoproterenol, and isooctylamine.

.1 parasympatholytics. which help to dry secretions in the upper respiratory tract.

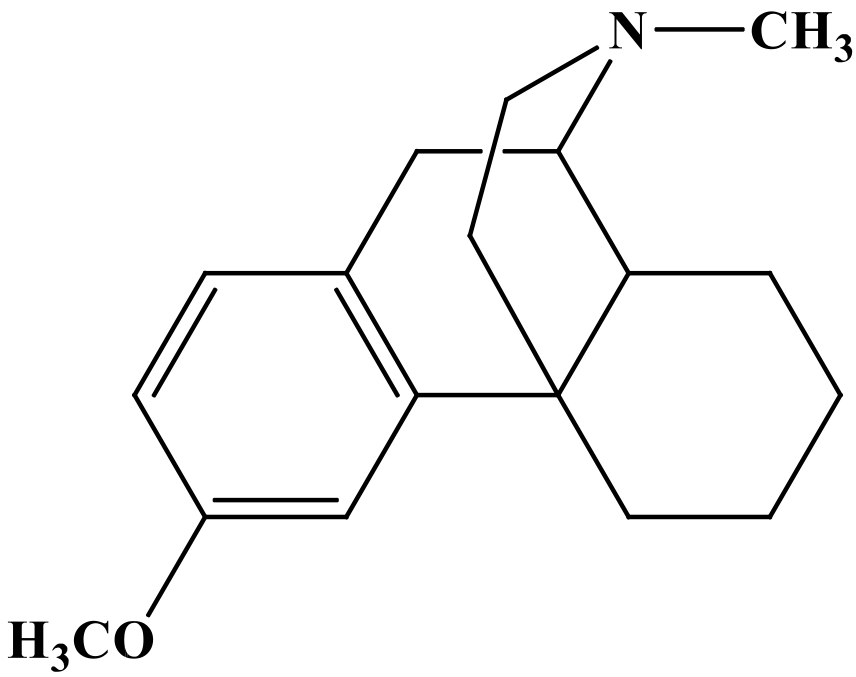
Products

- Noscapine



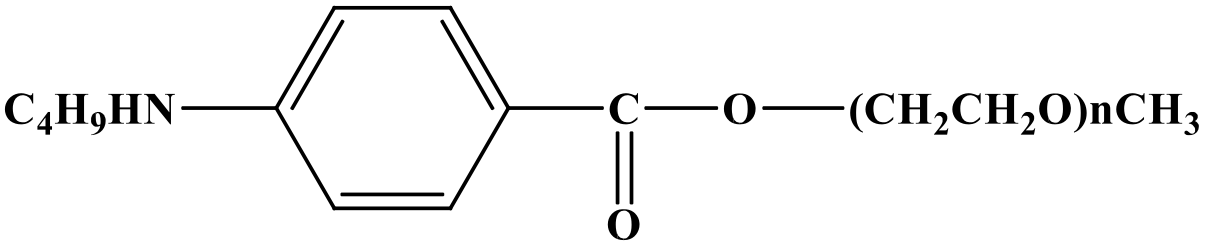
Noscapine [(-)-Narcotine]
central action bronchodilation

Dextromethorphan hydrobromide•



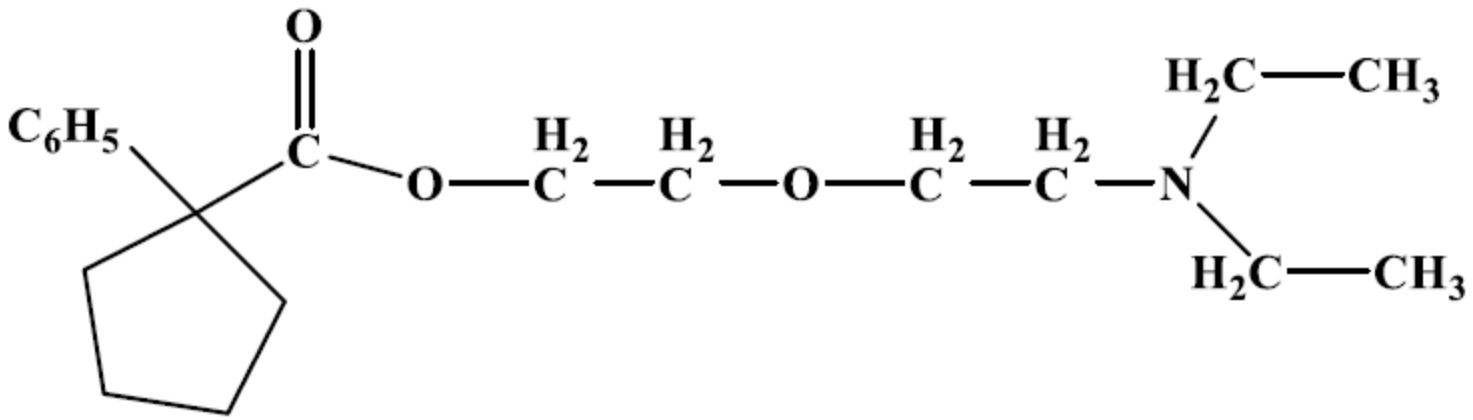
It possesses the antitussive properties of codeine, without the analgesic, addictive, central depressant, and constipating features

Benzonatate



Benzonatate possesses both peripheral and central activity in producing its antitussive effect

Carbetapentane•



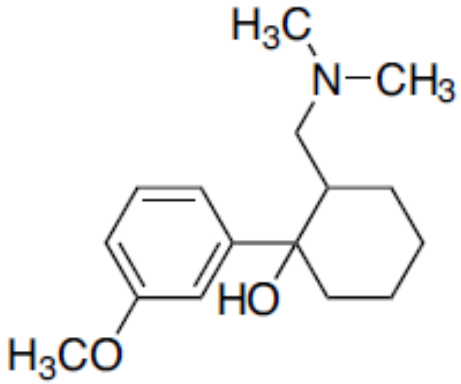
2-[2-(diethylamino)-ethoxy]ethyl -1 -phenylcyclopentanecarboxylate
Equivalent to codeine as antitussive and has low S/E

Miscellaneous

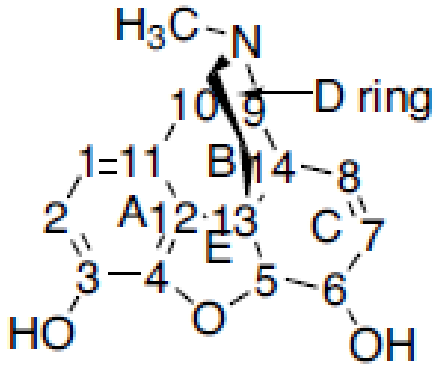
TRAMADOL

Tramadol (Ultram) is an analgesic agent with multiple mechanisms of action. It is a weak – agonist, Used at recommended doses, it has minimal effects on respiratory rate, heart rate, blood pressure, or GI transit times.

Structurally, tramadol resembles codeine with the B, D, and E ring removed. Tramadol is synthesized and marketed as the racemic mixture of two (the [2S, 3S] [-] and the [2R, 3R] []) of the four possible enantiomers. The (+) enantiomer is about 30 times more potent than the (-) enantiomer; however, racemic tramadol shows improved tolerability



(+/-)Tramadol



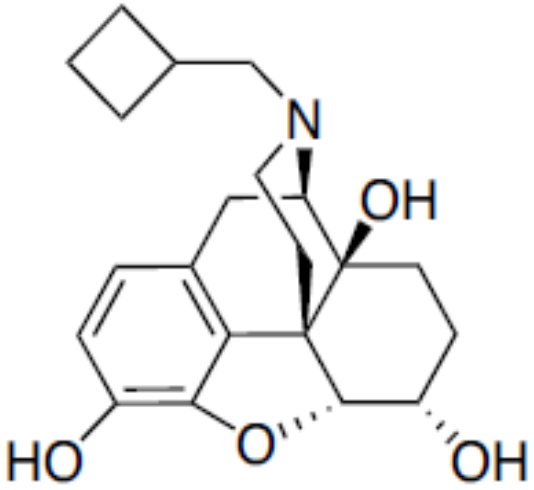
Morphine

Mixed Agonist/Antagonist

NALBUPHINE

Nalbuphine (Nubain) is structurally a member of the phenanthrene class of compounds and resembles oxymorphone with a cyclobutyl methyl group on the nitrogen, equivalent to naloxone's substitution. It was introduced in 1979 as an agonist/antagonist with the hope of becoming an effective pain reliever with little abuse potential.

At low parenteral doses (0.5 mg), it has an analgesic potency approximately two thirds that of morphine, and it has a similar degree of respiratory depression.



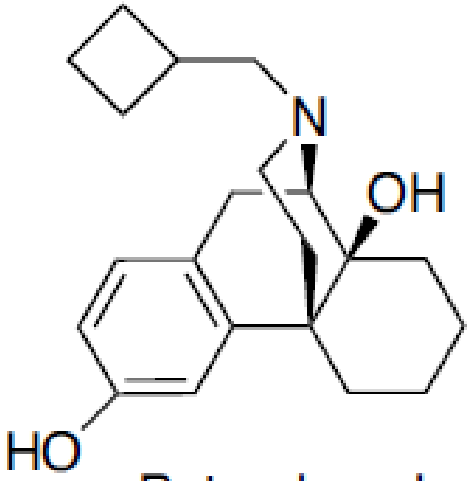
Nalbuphine

The pharmacologic profile of nalbuphine in animal studies includes agonist activity at the k–receptor and antagonist activity at the μ-receptor. Clinical studies have shown that nalbuphine, and k-agonists in general, may have better analgesic activity in female patients compared with male patients

Used as the sole opioid agent, nalbuphine has been used successfully to treat the pain of labor, cesarean section, dental extraction, hip replacement, and hysterectomy surgery

BUTORPHANOL

Structurally, butorphanol is a morphinan and shares the same cyclobutyl methyl group on the nitrogen as nalbuphine. Like nalbuphine, butorphanol is an agonist at the k-receptor but at the μ-receptor butorphanol is both a partial agonist and an antagonist. The affinity for opioid receptors in vitro is 1:4:25 for the μ-, δ-, and k-receptors respectively. The high affinity for the k-receptors is proposed to give butorphanol its analgesic properties and is also responsible for the CNS adverse effects such as hallucinations, psychosis, and paranoid reactions. Butorphanol binds with μ-receptors as a partial agonist, The parenteral injection is used for moderate to severe pain associated with orthopedic procedures, obstetric surgery, and burns.

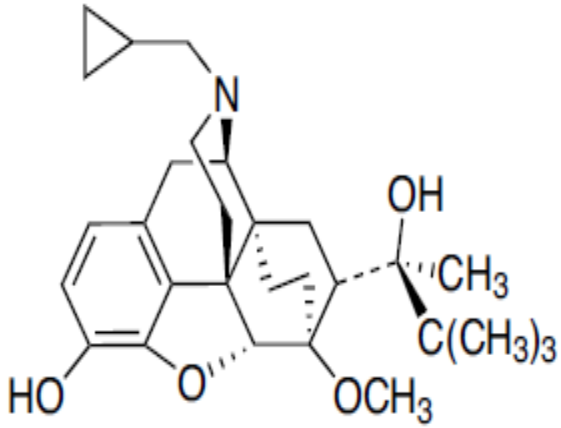


Butorphanol

BUPRENORPHINE

Buprenorphine is a semisynthetic, highly lipophilic opiate derived from the baine. Pharmacologically, it is classified as a mixed μ-agonist/antagonist (a partial agonist) and a weak k- antagonist. It has a high affinity for the μ–receptors (1,000 times greater than morphine) and a slow dissociation rate leading to its long duration of action (6–8 hours). At recommended doses, it acts as an agonist at the μ–receptor with approximately 0.3 mg IV equianalgesic to 10 mg of IV morphine. One study in humans found that buprenorphine displays a ceiling effect to the respiratory depression, but not the analgesic effect over a dose range of 0.05 to 0.6 mg. In practice, this makes buprenorphine a safer opiate (when used alone) than pure μ-agonists. Relatively few deaths from buprenorphine overdose (when used alone) have been reported.

The tight binding of the drug to the receptor also has led to mixed reports on the effectiveness of using naloxone to reverse the respiratory depression. In animal studies, normal doses of the pure antagonist naloxone were unable to remove buprenorphine from the receptor site and precipitate withdrawal.



Buprenorphine

Opioid Antagonists

NALTREXONE

Naltrexone (Fig. 24.13) is a pure opioid antagonist at all opioid receptor subtypes with the highest affinity for the μ-receptor. Naltrexone is orally bioavailable and blocks the effects of opiate agonists for approximately 24 hours after a single dose of 50 mg. It produces no opioid agonist effects and is devoid of any intrinsic actions other than opioid receptor blockade. Theoretically, it should work well to treat opioid dependence but in clinical practice, patients have shown poor compliance and high relapse rates. Naltrexone has also been studied to treat alcohol dependence with mixed results.

To address the compliance issues and effectively remove the "choice" of taking the antagonist, naltrexone was developed into an extended release injectable microsphere formulation for IM injection once a month (Vivitrol). This formulation provides steady-state plasma concentrations of naltrexone threefold to fourfold higher than the 50-mg oral dose 4 times a day. Currently, Vivitrol is only indicated for the treatment of alcohol dependence.

NALOXONE

Naloxone (Narcan) (Fig. 24.13) 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.

NALMEFENE

Nalmefene (Revex) is a pure opioid antagonist that is the 6-methylene analog of naltrexone. It is available as a solution for IV, IM, or subcutaneous (SC) administration to reverse the effects of opioids after general anesthesia and in the treatment of overdose. It is longer acting than naloxone

METHYLNALTREXONE

Methylnaltrexone (Relistor) is the methylated, quaternary form of naltrexone (Fig. 24.13). The permanently charged nitrogen prevents the drug from crossing the blood-brain barrier. Thus, it only acts as an antagonist at peripheral opioid receptors.

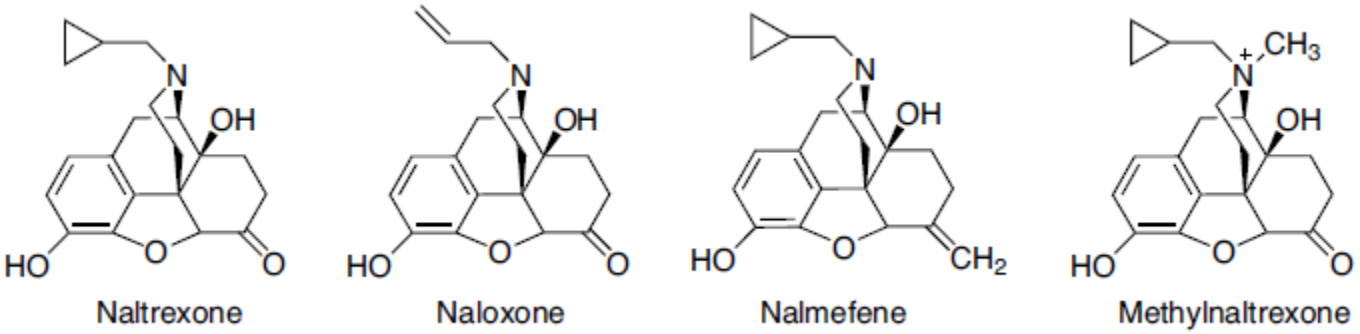


Figure 24.13 ● Opioid antagonists.