

NARCOTIC ANALGESICS: MORPHINE AND “PERIPHERALLY MODIFIED” MORPHINE ANALOGS

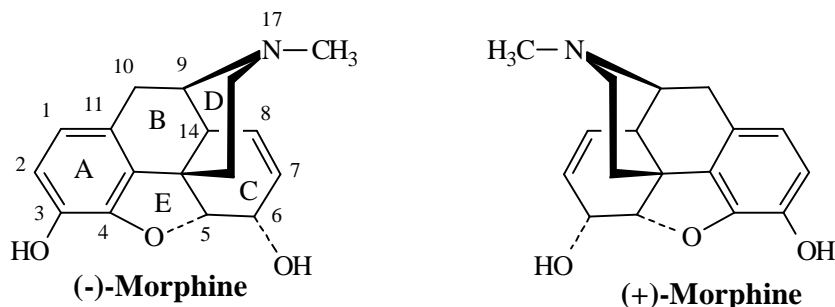
I. Classification of Narcotic Ligands

- Narcotic agonists include natural opium alkaloids (eg, morphine, codeine), semisynthetic analogs (eg, hydromorphone, oxycodone, oxycodone), and synthetic compounds (eg, meperidine, levorphanol, methadone, sufentanil, alfentanil, fentanyl, remifentanyl, and levomethadyl).
- Mixed agonist-antagonist drugs (eg, nalbuphine, pentazocine) have agonist activity at some receptors and antagonist activity at other receptors; also included are the partial agonists (eg, butorphanol, buprenorphine).
- Narcotic antagonists: Narcotic antagonists (eg, naloxone) do not have agonist activity at any of the opioid receptor sites. Antagonists block the opiate receptor, inhibit pharmacological activity of the agonist, and precipitate withdrawal in dependent patients.

II. Morphine

A. Morphine Structure and Chemistry

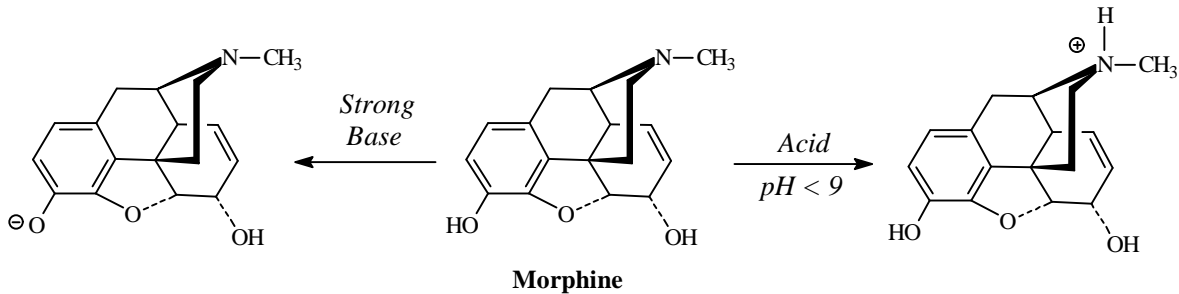
The prototypic narcotic analgesic is (-)-morphine, the principal alkaloid obtained from the opium poppy (*Papaver somniferum*). Because of its natural source, morphine and morphine derivatives are referred to as opiates. Narcotic analgesics will be classified on the basis of their structural derivation from morphine.



Examination of the morphine molecule reveals the following structural features important to its pharmacological profile:

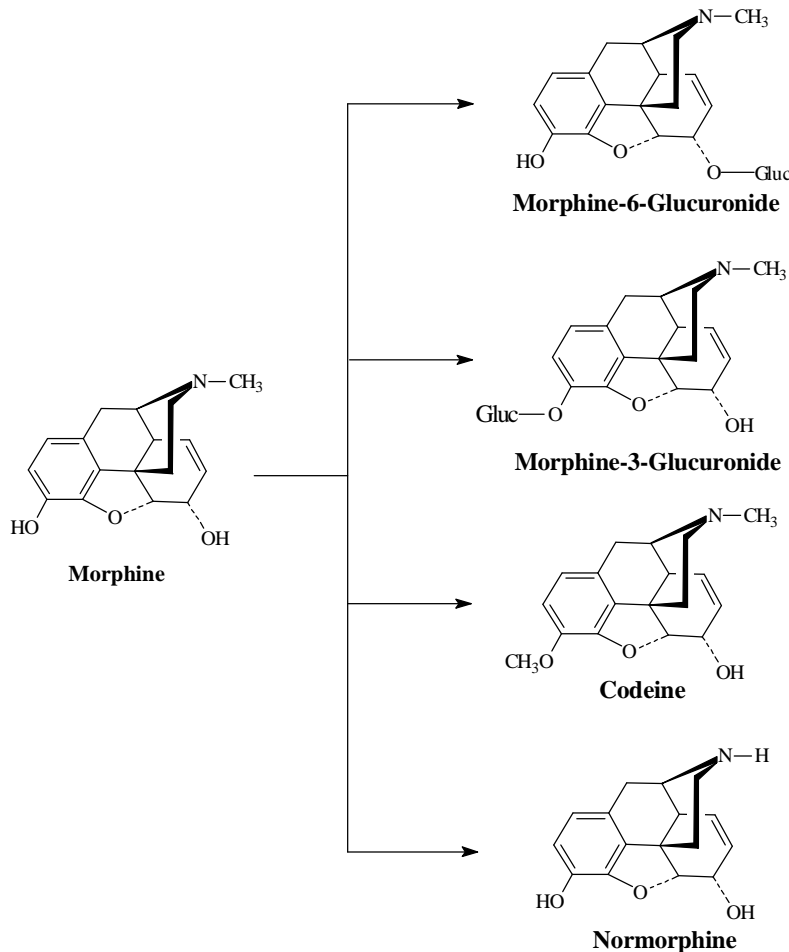
1. A rigid pentacyclic structure consisting of a benzene ring (A), two partially unsaturated cyclohexane rings (B and C), a piperidine ring (D) and a dihydrofuran ring (E). Rings A, B and C are the phenanthrene ring system. This ring system has little conformational flexibility (the importance of this will be addressed later).
2. Two hydroxyl functional groups, a C3-phenolic OH (pKa 9.9) and a C6-allylic OH
3. An ether linkage between C4 and C5,
4. Unsaturation between C7 and C8,
5. A basic, 3°-amine function at position 17,
6. 5 centers of chirality (C5, C6, C9, C13 and C14) with morphine exhibiting a high degree of stereoselectivity of analgesic action. **Only (-)-morphine is active!**

Morphine contains both an acidic phenolic group and a basic tertiary amine functions. However, since the amine functions is significantly more basic than phenol group is acidic, thus, morphine **as well as a majority of narcotic analgesics** are functionally basic compounds both pharmaceutically (dosage forms) and physiologically. Hence, morphine exists as a cation at physiologic pH, and readily forms salts with appropriate acids (commercial products are sulfate and HCl):



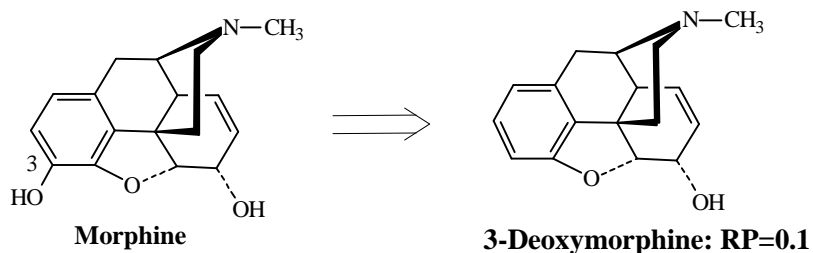
Morphine Biodisposition/Metabolism

- Limited oral bioavailability due to extensive first pass metabolism (see below)
- Lipophilic, but less so than other opioids (i.e. heroin)
- Half-life: 2-3 hrs: Metabolism
- Elimination: Primarily in urine as the glucuronide
- Metabolism: 3- and 6-O-glucuronides, OND and O-methylation to codeine (minor)

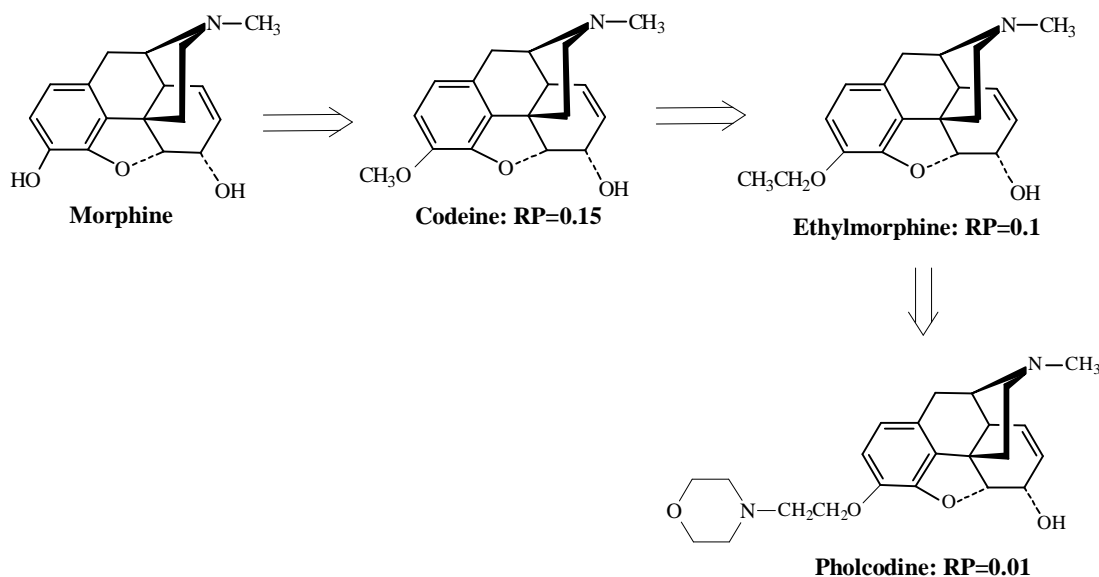


III. "Peripherally Modified Morphines": Ring A Analogues

Ring A and its 3-hydroxyl group is an important structural feature for analgesic activity. Removal of the 3-OH group reduces analgesic activity 10-fold:

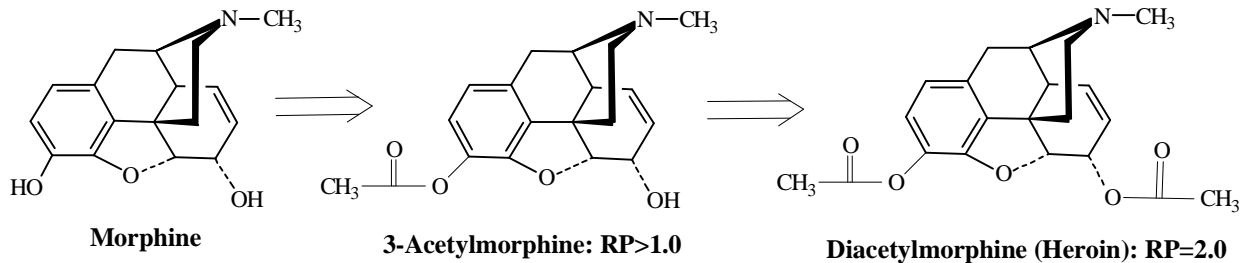


Altering the C-3 OH by etherification as shown by the derivatives below reduces narcotic analgesic activity, the larger the ether group, the lower the analgesic activity. While less active as analgesics, compounds such as codeine possess very useful antitussive activity.



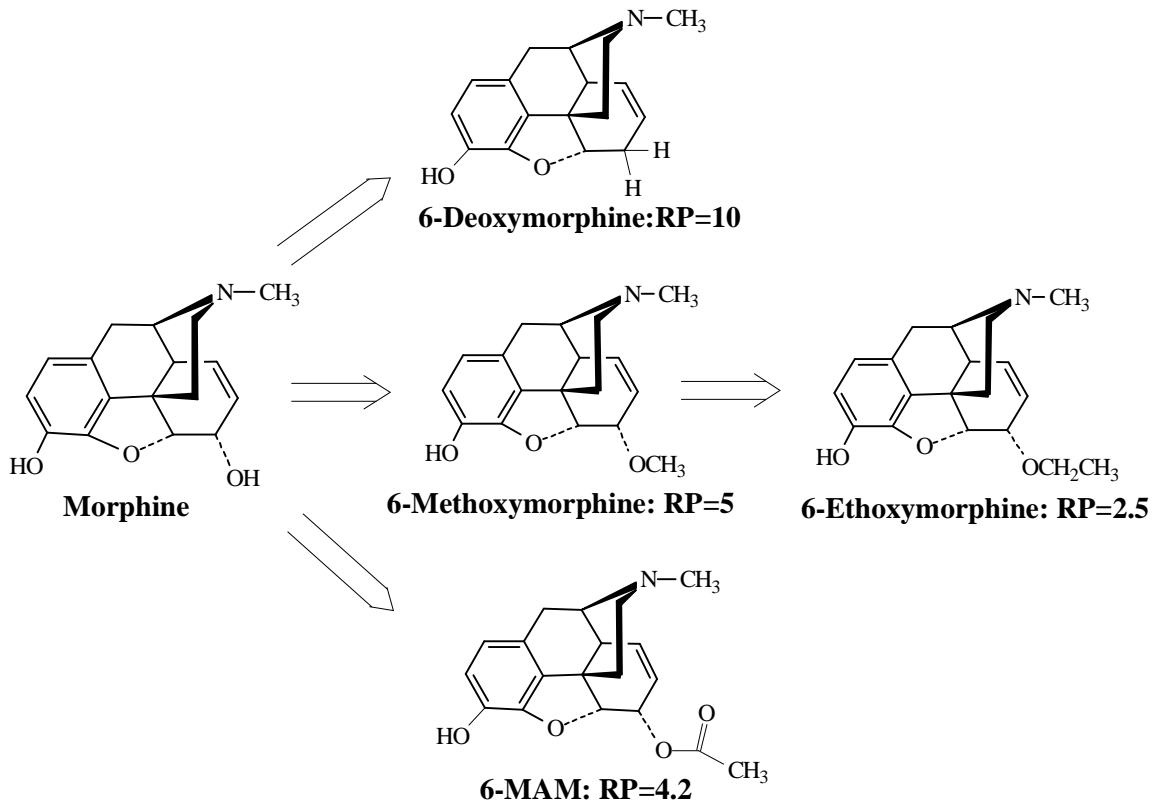
Codeine is available as a sulfate and phosphate salt and also as the free base and as tablets, elixir and solution for injection. The 3-methoxy group protects the 3-position from glucuronide as occurs with morphine. Codeine is used as an analgesic and antitussive. It is metabolized by cytochrome-mediated OOD to morphine (10% of dose), by cytochrome-mediated OND to norcodeine (11% activity of codeine), and conjugation to 6-O-glucuronide. The morphine formed may be further metabolized to by the pathways described above to yield normorphine, conjugates, etc. Some hydromorphone also is reported to form (see structure below)

Derivatization of the C-3 OH by esterification generally only modestly increases activity. Esterification (acetylation) of both the 3- and 6-OH groups yields heroin, a compound which is both more lipophilic and more potent. The primary factor involved in increased analgesic potency is the increased lipophilicity and distribution to the CNS. Heroin is metabolized primarily by hydrolysis of the C-3-O-acetyl moiety to 6-monoacetylmorphine (6-MAM). 6-MAM may be further hydrolyzed to morphine which is conjugated with glucuronic acid at C-3-OH (and converted to the other minor morphine metabolites) and eliminated renally.

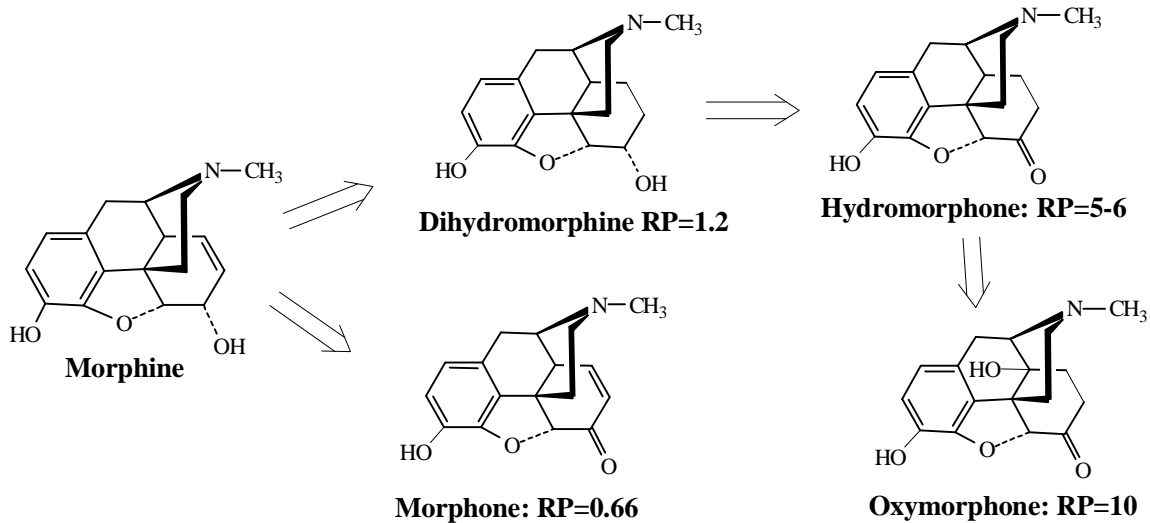


IV. "Peripherally Modified Morphines": Ring C Analogues

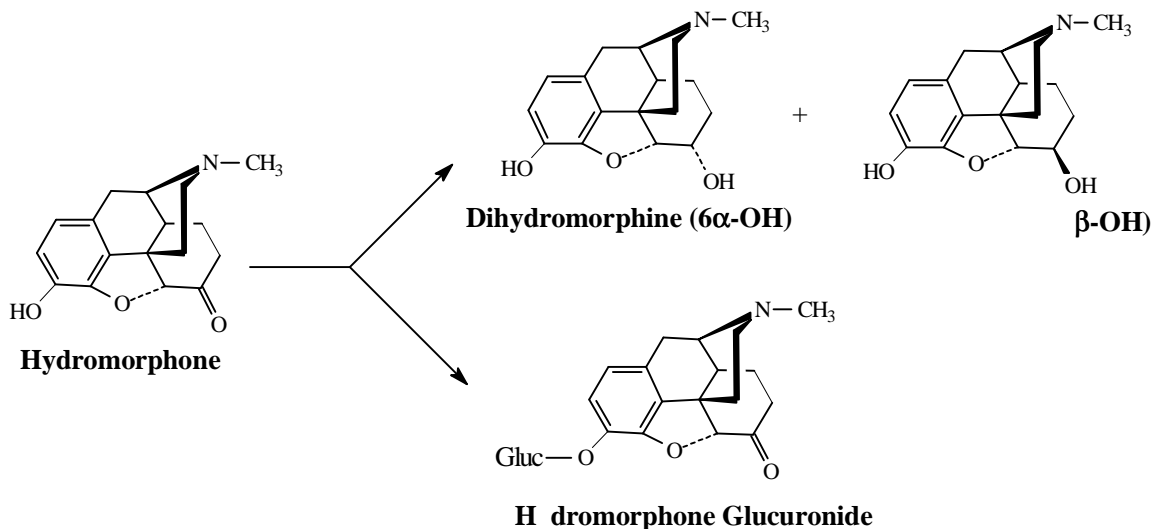
The 6-OH of morphine are not required for analgesic activity as indicated by the relative potencies of the following morphine analogues. Elimination of the 6-OH actually enhances activity. Etherification of this group with relatively small alkyl group also increases activity. Esterification of the 6-OH as in the main hydrolysis metabolite of heroin, 6-MAM, also increases analgesic activity. This increased activity appears to result largely from the enhanced lipophilicity of these compounds and their increased ability to penetrate the CNS.



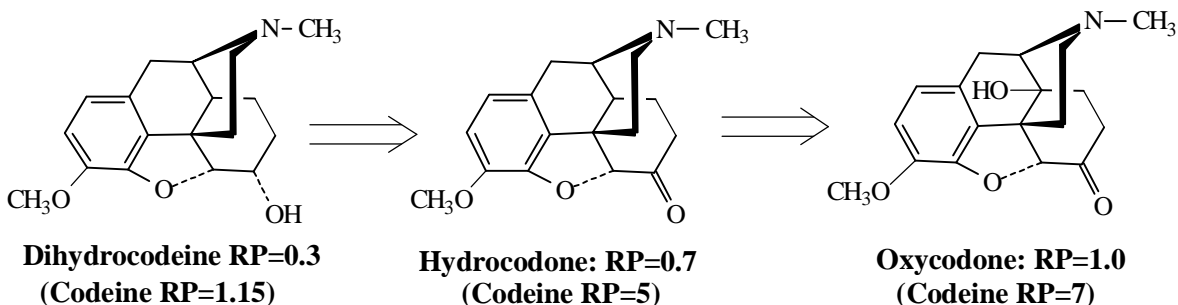
The 7,8-double bond of morphine also is not required for analgesic activity as indicated by the relative analgesic potency of dihydromorphine. Also, oxidation of the 6-OH of dihydromorphine to yield hydromorphone further increases activity. And substitution of a 14-OH group on the hydromorphone structure as in oxymorphone produces a further increase in analgesic activity (RP = 10). Oxidation of the 6-OH of morphine directly as in morphine (without reduction of the 7,8-double bond) does not significantly alter analgesic activity.



Hydromorphone is available as the HCl salt in tablets, liquid, suppository and injectable. It is metabolized to by ketone reduction to the epimeric 6-alcohols (6-OHs) dihydromorphine and dihydroisomorphine. It also undergoes conjugation (glucuronidation) at the 3-OH group. Oxymorphone is available as the HCl salt in a suppository and as an injectable. The primary metabolite formed from oxymorphone is 3-conjugates (glucuronide).



Similar structure activity data is obtained by modification of the codeine structure. Reduction of codeine's 7,8-double bond as in dihydrocodeine increases activity relative to codeine (next page). Oxidation of the 6-OH of dihydrocodeine as in hydrocodone results in a further increase in activity, and 14-OH substitution produces a further increase in analgesic activity.

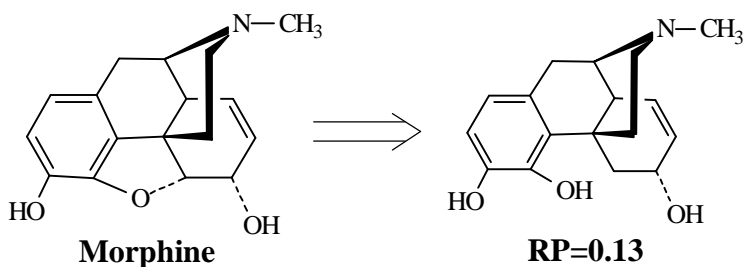


Hydrocodone is available as the bitartrate salt in tablets and syrups. It has analgesic and antitussive activity. Hydrocodone is metabolized by OOD to hydromorphone (active), by OND to norcodeine (less active) and reduction of the 6-keto group to the two epimeric hydrocodols - 6-beta-hydrocodol and 6-alpha-hydrocodol. The epimeric 6-alcohols can undergo OOD to yield the epimeric hydromorphols - 6-beta-hydromorphol and 6-alpha-hydromorphol. Each of the four 6-OH metabolites have pharmacologic activity equal to or greater than the parent compound, with the exception of 6-alpha-hydrocodol which is one sixth as potent. The structures of these metabolites can be derived from the analogous metabolic reactions described above

Oxycodone is available as the HCl salt in tablets and capsules. It has analgesic and antitussive activity. The primary metabolite formed from oxycodone is 3-conjugates (glucuronide).

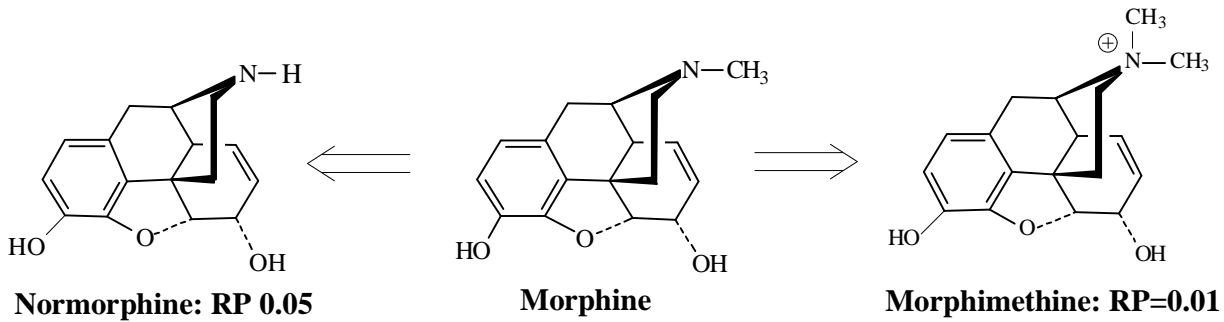
V. "Peripherally Modified Morphines": Ring E Analogues

Simple ring-opened analogues of morphine such as the compound below are less active. However, a number of morphine analogues in which this ring and its functionality are completely removed retain high analgesic activity. These analogues are described in the next chapter.

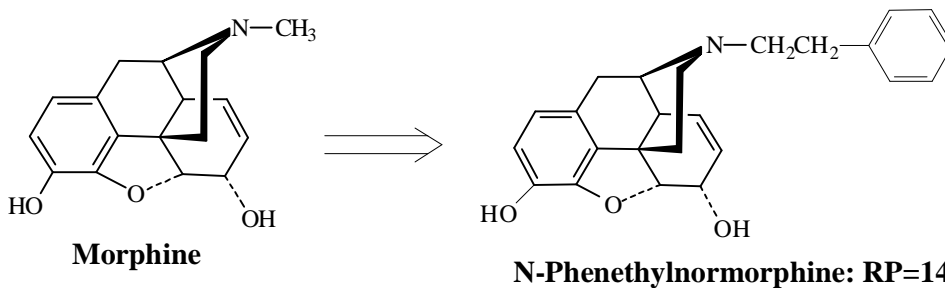


VI. "Peripherally Modified Morphines": Ring D Analogues and the Tertiary Amine Function

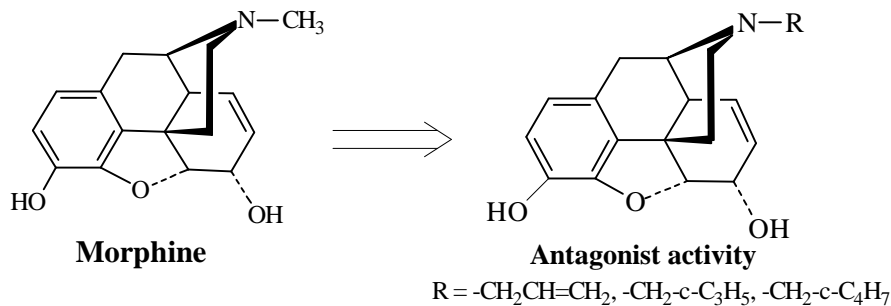
Replacement of morphine's N-methyl group by a hydrogen atom as in normorphine reduces analgesic activity to 1/8th that of morphine. Much of this decrease is due to increased polarity resulting in reduced BBB translocation to the CNS. The quaternary methiodide analogue of morphine is inactive when administered peripherally (by injection) but equi-active when administered directly into the CNS. The activity of this compound demonstrates the importance of cationic structure of morphine for morphine, and the role of structure in CNS penetration.



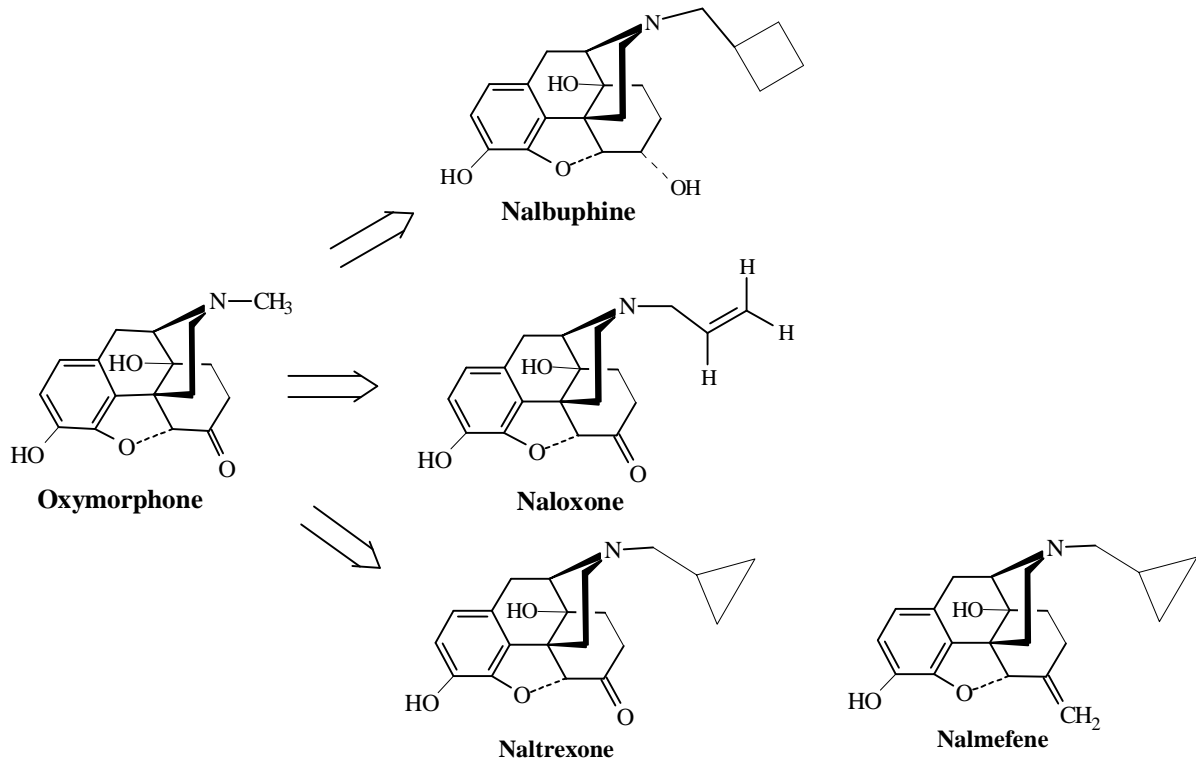
Replacement of morphine's N-methyl group with larger alkyl groups reduces activity. However, substitution with aralkyl groups significantly increases analgesic activity as illustrated by N-phenethylnormorphine:



Replacement of morphine's N-methyl group with an allyl group (-CH₂-CH=CH₂), a methylcyclopropyl group or a methylcyclobutyl group results in the emergence of opiate receptor **antagonist** activity:



Replacement of the potent narcotic agonist oxymorphone's N-methyl group with an allyl group (-CH₂-CH=CH₂), a methylcyclopropyl group or a methylcyclobutyl group also results in the emergence of opiate receptor **antagonist** activity (see structures on the next page). Three of these compounds - naloxone HCl (Narcan) naltrexone HCl (Trexan) and nalmefene (Revox) - are pure opiate antagonists (at mu, kappa and delta receptors) and are used for the reversal of the narcotic/respiratory depression induced by opiate agonists, as well as psychotomimetic actions. These compounds are also used as adjuncts to the maintenance of an opiate-free state in detoxified, formerly opiate-dependent patients.



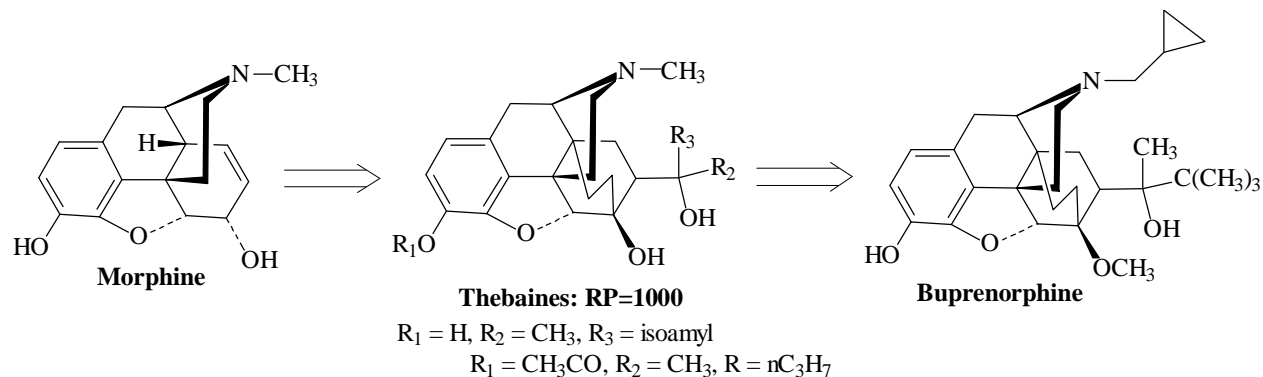
Naloxone is administered IV or IM (low oral bioavailability and slow actino) has a relatively short half-life (1 hour). Naltrexone is used orally and has a substantially longer half-life (10 hours) and duration (24-48 hours) of action. Naltrexone is adminisitered by injection. It also has a longer half-life (10 hours) and duration than naloxone.

Nalbuphine HCl (Nubain) is a mixed opiate agonist/antagonist. It functions as a potent antagonist at μ -receptors, and an agonist equipotent with morphine at κ_1 and κ_3 receptors. The antagonist actions of the drug accounts for a ceiling effect on respiratory depression and a low abuse potential. Nalbuphine is available as a solution for IM injection. It has the same time of onset and duration of action.

The metabolism of the narcotic antgaonists/mixed agonists or antagonistst has not been extensively studied. Nalmefene is known to undergo 3-O-glucuronidation and, to a lesser extent, N-dealkylation. The other compounds are presumed to be metabolized similarly.

VII. “Peripherally Modified Morphines”: The Thebaines

Annelation – adding a sixth ring across carbons 6 and 14 of the C ring of morphine - yields thebaine compounds such as etorphine which are extremely potent analgesics. These compounds are typically used to immobilize large animals (elephants).



Replacement of the N-methyl group of the thebaines with a methylcyclopropyl group yields compounds with mixed agonist/antagonist or partial agonist activity. For example, buprenorphine HCl (Buprenex) is a partial opiate agonist at μ -receptors and an antagonist at κ_1 receptors. As an agonist it is 25-50 times more potent than morphine and slightly longer acting. It is available for IM and sublingual administration and has a half-life of about 5 hours. The metabolic pathways for buprenorphine are not known. Its respiratory depressant activity reaches a ceiling. It has moderate abuse potential. Because of its high affinity and slow dissociation from opiate receptors, larger doses of antagonists such as naloxone are required to produce reversal.

Table of Receptor Activities for the Narcotic Analgesics

Opioid	μ	δ	κ	σ
Leu-enkephalin	+	+++		
Met-enkephalin	++	+++		
Morphine	+++	+	++	
Codeine	+	+	+	
Etorphine	+++	+++	+++	
Fentanyl	+++	+		
Sufentanil	+++	+		
Penatnocine	-	+	(++)	+
Nalbuphine	-	+	(++)	+
Nalorphine	--	(++)	(++)	+
Buprenorphine	(+++)			
Antagonists				
Naloxone	---	--	--	
Naltrexone	---	--	--	

+ agonist, - antagonist, (+) partial agonist