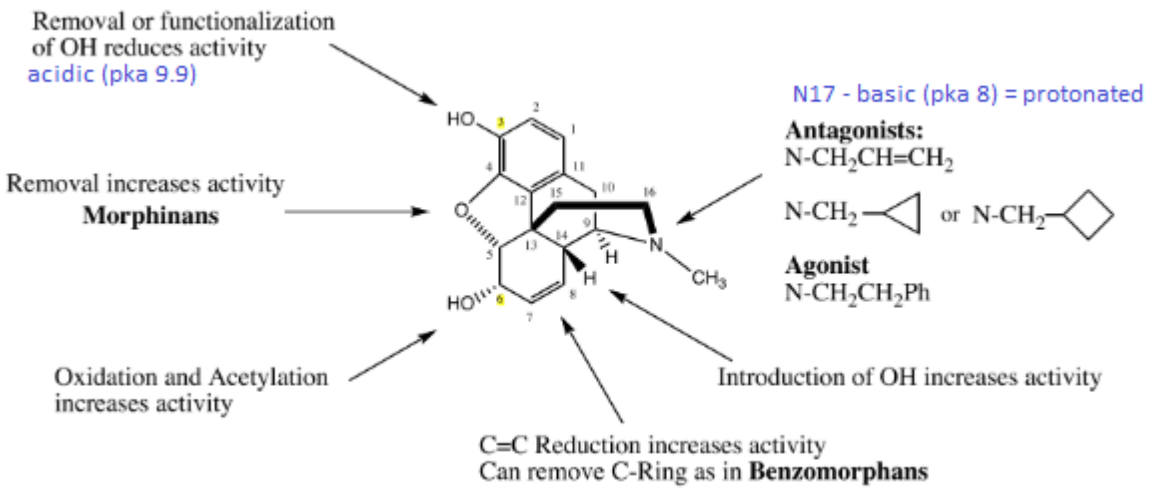
Summary of structure-activity relationships



Relationship between morphine and encephalin: structural simplification → minimum structure for its activity = TYROSINE MIMIC

GPCR

7-transmembrane helix (TMH) receptors
- Periplasmic N-terminal domain
- Cytoplasmic C-terminal domain
- 7 transmembrane helices
- 3 extracellular loops
- 3 intracellular loops

Opioid receptors
- μ-OR couples predominantly to G protein Gi (Gi/o)
- opioid agonists reduce neuronal excitability by:
  - inhibiting calcium entry
  - enhancing outward movement of K via GIRKs
  - inhibiting adenylate cyclase

Toggle switch: agonist binding to inactive conformer of opioid receptor promotes movements → active
- Two key interactions between morphine and μ-opioid receptor
  - Tertiary N in morphine & Asp 147 in TM-3 = salt-bridge type interaction
  - C-3 (phenolic OH group) & HIst 297 in Tm-6
- Binding of morphine in μ receptor breaks Asp147 – Tyr 326 H-bond
  - This triggers signal transduction through movement of the TMs

Message-Address
- Message: binding interactions deep in receptor site between <<Tyr>> like component in ligand and the conserved Asp, Tyr & His residues in the receptor → receptor activation
- Address: complementary interactions involving other structural elements in the ligand with key (non-conserved) amino acid residues in the surface/extracellular side of TM6 and TM7 and the extracellular loops EL2 and EL3 → selective binding to mu, kappa, or delta receptor