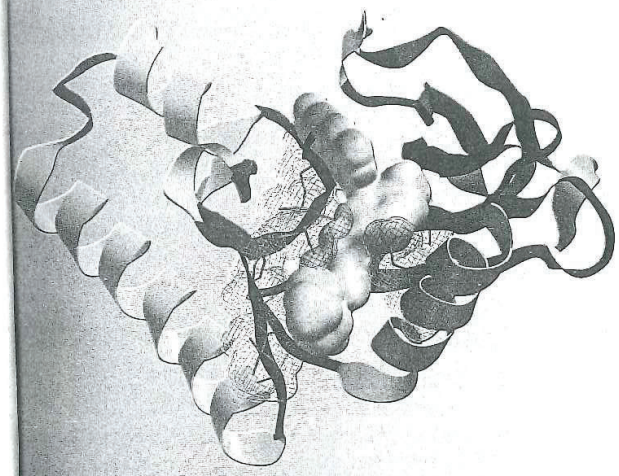

FOYE'S Principles of Medicinal Chemistry

SIXTH EDITION

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Cover image courtesy of Wavefunction, Inc. The ribbon display (green and red) is tyrosine kinase. The "active site" for tyrosine kinase is shown as tube display with a mesh-style electrostatic potential map (a charge distribution map), with the drug imatinib shown in the "active site" with a solid-color style electrostatic potential map (where the colors toward red depict negative potential; colors toward blue depict positive potentials; and colors such as yellow, orange, green, and violet depict intermediate values). Imatinib (a 2-phenyl amino pyrimidine derivative, a.k.a. CGP57148B, STI571 or Gleevec®) is a selective inhibitor of several tyrosine kinases that binds to the ATP-binding pocket of tyrosine kinase and blocks the activities of Abl, c-kit, and PDGFR. It is used for treating chronic myelogenous leukemia (CML), gastrointestinal stromal tumors (GISTs), and a number of other malignancies.

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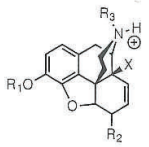
Table 24.3. Marketed Drugs that are Derivatives of Morphine



Generic nam e	R_1	R_2	R_3	X	Other
(-)-Morphine	H	OH	$-CH_3$	H	None
(-)-Codeine	CH_3	OH	$-CH_3$	H	None
(-)-Hydromorphone	H	Keto	$-CH_3$	H	No 7,8-double bond
(-)-Oxymorphone	H	Keto	$-CH_3$	OH	No 7,8-double bond
(-)-Hydrocodone	CH_3	Keto	$-CH_3$	H	No 7,8-double bond
(-)-Oxycodone	CH_3	Keto	$-CH_3$	OH	No 7,8-double bond
(-)-Nalbuphine	H	OH	$-H_2C-cBu$	H	No 7,8-double bond
(-)-Naloxone	H	Keto	$-CH_2-CH=CH_2$	OH	No 7,8-double bond
(-)-Naltrexone	H	Keto	$-H_2C-cPr$	OH	No 7,8-double bond

dose of morphine is usually 60 mg, followed by maintenance doses of 20 to 30 mg every 4 hours. Addiction to clinically used morphine by the oral route generally is not a problem.

Overdoses of morphine, as well as all μ agonists in this section, can be effectively reversed with naloxone.

(−)-Codeine Phosphate

Codeine is used extensively to treat moderate to mild pain. Codeine is a weak μ agonist, but approximately 10% of an oral dose (30–60 mg) is metabolized to morphine (see the section on metabolism in this chapter), which contributes significantly to its analgesic effect. The plasma half-life of codeine after oral dose is 3.5 hours. The dose of codeine needed to produce analgesia after parenteral dose causes releases of histamine sufficient to produce hypotension, pruritus, and other allergic responses. Thus, administration of codeine by parenteral route is not recommended.

(−)-Hydromorphone Hydrochloride (Dilaudid)

Hydromorphone is a potent μ agonist (eight times greater than morphine) that is used to treat severe pain. It is available in intramuscular, intravenous, subcutaneous, oral, and rectal dosage forms. Like all strong μ agonists, hydromorphone is addicting and is a Schedule II drug. Hydromorphone has an oral:parenteral potency ratio of 5:1. The plasma half-lives after parenteral and oral dosage are 2.5 and 4 hours, respectively.

(−)-Oxymorphone Hydrochloride (Numorphan)

Oxymorphone is a potent μ agonist (10 times greater than morphine) that is used to treat severe pain. It is used by intramuscular, subcutaneous, intravenous, and rectal routes of administration. The intramuscular dose of oxymorphone (1 mg) has a half-life of 3 to 4 hours. It is a Schedule II drug. Oxymorphone, because of its 1 hydroxy group, has low antitussive activity.

(−)-Levorphanol Bitartrate (Levo-Dromoran)

Levorphanol is a potent μ agonist (approximately sixfold greater than morphine), and its uses, side effects, and physical dependence liability are like those of oxymorphone or hydromorphone. Levorphanol is available in oral, subcutaneous, and intravenous dosage forms. The oral dose of levorphanol is approximately twice the parenteral dose. This drug is unique among the μ agonists in that its analgesic duration of action is 4 to 6 hours, whereas its clearance half-life is 11.4 hours. Thus, effective analgesic doses of this agent can lead to a buildup of the drug in the body and result in excessive sedation.

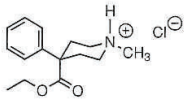
(−)-Hydrocodone Bitartrate (Lortab, Vicodin in Combinations with Acetaminophen)

Hydrocodone is a Schedule III drug that is used to treat moderate pain. It is used mostly by the oral route (5-mg tablets and solutions) in combination with acetaminophen. The compound has good oral bioavailability and is metabolized in a manner similar to codeine.

(−)-Oxycodone Hydrochloride (Roxicodone, Oxycontin Sustained Release; and Percocet, Percodan, Tylox; in Combinations)

Oxycodone is about equipotent with morphine, but because of the 3-OCH group, it has a much lower oral:parenteral dose ratio. Thus, oxycodone is used orally to treat severe to moderate pain. It is a Schedule II drug as a single agent and when combined in strong analgesic mixtures. Oxycodone has a plasma half-life of approximately 4 hours and requires dosing every 4 to 6 hours. Metabolism of this agent is comparable to that of codeine.

Meperidine Hydrochloride (Demerol)



Meperidine is a μ agonist with approximately one-tenth the potency of morphine after intramuscular dose. Meperidine produces the analgesia, respiratory depression, and euphoria caused by other μ opioid agonists, but it causes less constipation and does not inhibit cough. When given orally, meperidine has 40 to 60% bioavailability because of significant first-pass metabolism. Because of the limited bioavailability, it is one-third as potent after an oral dose compared to a parenteral dose.

Meperidine has received extensive use in obstetrics because of its rapid onset and short duration of action. When it is given intravenously in small (25-mg) doses during delivery, the respiratory depression in the newborn child is minimized. Meperidine is used as an anal-