Analgesics

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CHAPTER OVERVIEW

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.

Analgesics can be broadly categorized, according to their therapeutic use, into several drug classes: (a) the opioids (or narcotic analgesics), which play a major role in the relief of acute pain and in the management of moderate to severe chronic pain; (b) the NSAIDs and acetaminophen, which are the most widely used analgesic drugs for relieving mild to moderate pain and reducing fever; (c) the triptans (the antimigraine medications), which are specifically designed and targeted for acute and abortive treatment of migraine and cluster headaches; and (d) a new emerging class of analgesics known as analgesic adjuvants that include tricyclic antidepressants such as amitriptyline, anticonvulsants such as gabapentin and pregabalin, and topical analgesics such as lidocaine patches that can be used to treat neuropathic pains.

In this chapter, only the first three classes of pain medications are covered. The main objectives of this chapter will be focusing on their mechanism of action, structure–activity relationships (SARs), pharmacokinetic properties, and their clinical applications for pain management. Readers should consult other chapters under anticonvulsants, antidepressants, and local anesthetics for a detailed discussion of drugs used for treating neuropathic and other incidental pains associated with minor cuts, burns, and insect bites.

PAIN AND PAIN MANAGEMENT

Pain, one of the most common complaints for which patients seek medical attention, is also the hardest to manage despite the availability of many analgesic medications as well as other nonpharmacologic treatment options. Pain management, especially the use of opioids in patients with chronic pains, is one of the most troublesome public health issues for patients, doctors, and other healthcare providers.[1,2] As early as the 1970s, the National Institutes of Health formed a committee, at the request of the president, to investigate therapies for rare diseases, but the initial focus was on pain management. The committee found that the problem associated with the use of the opioid analgesics was a lack of training of physicians in pain management and misinformation among healthcare providers because of fear of psychological dependence (commonly referred to as addiction), disciplinary action, or adverse effects such as tolerance and physical dependence of the pain medications.[2,3] As a result, many patients with moderate to severe pain are often undertreated or untreated.[3–5] Another possible reason for treatment failure is the fact that pain perception may also vary among individuals especially across racial and ethnic origins.[6]

Origin of Pain

Pain differs in its underlying causes, symptoms, and neurobiological mechanisms and has been classified into three major types: physiological (nociceptive), inflammatory, and neuropathic.[7,8] Physiological pain is the most common and is often caused by an injury to body organs or tissues. It is further categorized, according to the source of the pain, into cutaneous pains (skin and surface tissues), somatic pains (ligaments, tendons, bones, blood vessels), and visceral pains (body organs and internal cavities). 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.[9] Neuropathic pain may originate from limb amputation, spinal surgery, viral infections such as shingles, or worsening of disease states associated with diabetes, acquired immunodeficiency syndrome (AIDS), or multiple sclerosis. The pharmacological interventions are very complex and often require the use of other analgesic adjuvants not covered in this chapter. Readers should consult a recent review for a practical guide to the current clinical management of neuropathic pain.[10]

Acute and Chronic Pain

Pain may be acute or chronic.[11] Acute pain is often severe but usually lasts only until the removal of the source that triggered the pain. Acute pain includes nociceptive, somatic, or visceral pain, postoperative and posttraumatic pain, burn pain, acute pain during childbirth, acute headache, etc. Acute and postoperative pains are most often treated with the opioid analgesics.

Chronic pain, on the other hand, is defined as a pain lasting longer than 6 months that persists even when the initial cause has been resolved through appropriate medical intervention. Chronic pain can be further divided into chronic malignant pain (e.g., cancer, human immunodeficiency virus [HIV]/AIDS, amyotrophic lateral sclerosis, multiple sclerosis, end-stage organ failure) and chronic nonmalignant pain (e.g., lower-back pain, chronic degenerative

arthritis, osteoarthritis (OA), rheumatoid arthritis (RA), migraine and chronic headache, and bond pain). Pain therapy in patients with chronic pain only provides transient pain relief but does not resolve the underlying pathological process.[7] Chronic pain is also often associated with behavior and psychological components that make effective pain management quite subjective and difficult to resolve.[10,12,13] Chronic pain is also the leading cause of disability among the elderly; the prevalence of pain may be as high as 80%.[3]

Significant advances in understanding the pathophysiology and neurobiology of pain have occurred in the past 10 years.[5,13–17] However, a full discussion of complex pain-signaling mechanisms and the etiology of pain is beyond the scope of this chapter.

Approaches to Pain Management

The World Health Organization (WHO), through its *Access to Controlled Medications Programme*, has brought together an international, multidisciplinary group of experts to discuss and formulate a series of WHO guidelines, including the "three-step analgesic ladder" on pain management.[11,18] The use of the WHO three-step analgesic ladder has allowed physicians to select the most appropriate drug treatment regimen and has resulted in adequate analgesia for their patients, according to a 10-year prospective study published in 1995.[18] This guideline has now been adapted for treating other noncancer pains.[19] According to this analgesic ladder model (see Fig. 24.1), the choice of analgesic therapy is based on assessment of pain intensity. Thus, nonopioid analgesics such as acetaminophen and NSAIDs are the drugs of choice for mild pain. The patients should continue on this regimen for as long as they are receiving adequate pain control, although an analgesic adjuvant may be added to help relieve the side effects associated with pain medications. 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.[11]

OPIOIDS

Opioid Receptor Discovery and Endogenous Ligands

There was no direct evidence for the existence of specific opioid receptors until the 1970s when Goldstein et al.[20] found that radiolabeled levorphanol bound stereospecifically to certain mouse brain fractions. They hypothesized that this compound bound to an "opiate receptor." This prediction gained credence in 1973 when additional studies showed that opioid agonists and opioid antagonists compete for the same binding site. Building on these studies, Pert[21] was able to show that the pharmacologic potencies of the opioid drugs were proportional to their ability to compete with the antagonist for opioid receptor binding.

As it seemed unlikely that these receptors evolved in response to a plant alkaloid, the search for endogenous ligands was intense. The discovery and identification of endogenous substrates for the opioid receptor by Hughes[22,23] in 1975 further confirmed the existence of an opioid receptor and intensified the SAR studies of the analgesic opioids. The endogenous peptide ligands for the opioid receptors were originally isolated from pig brains but have been found in every mammal studied. The first
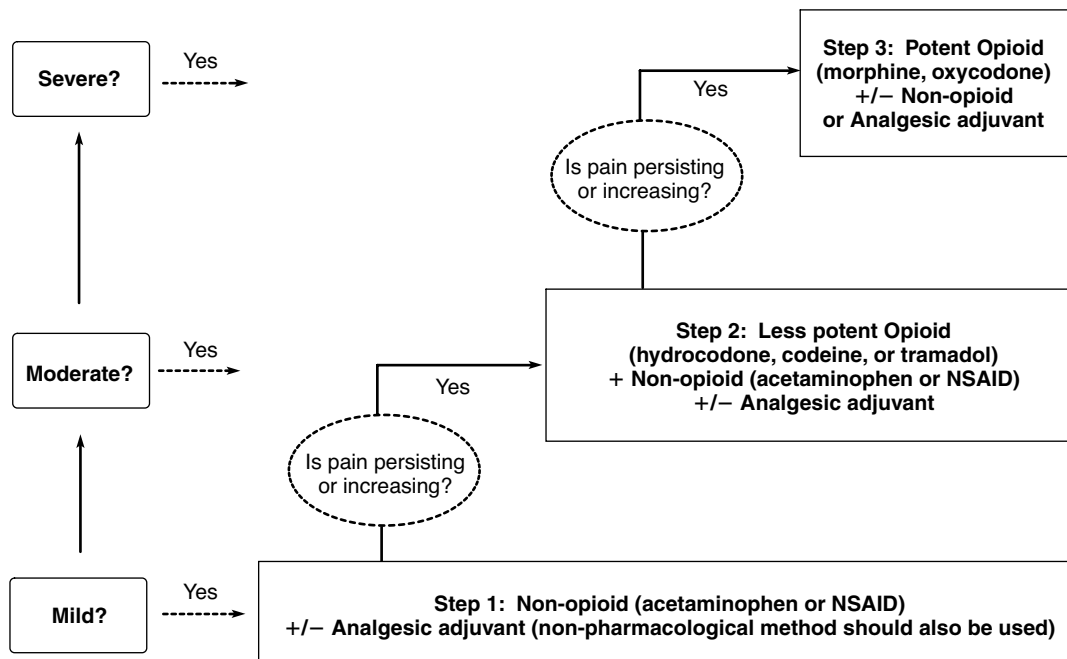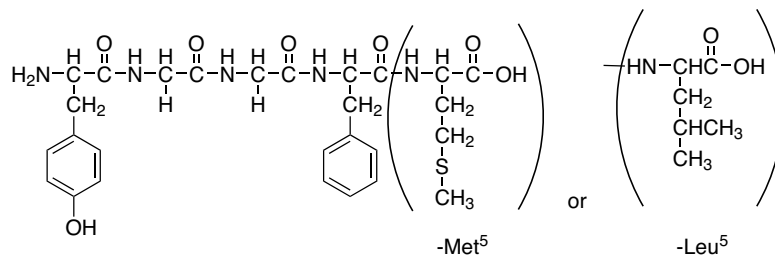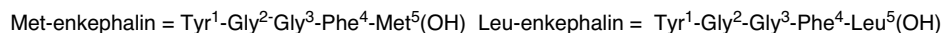
WHO 3-Step Analgesic Ladder - Is the pain...

Figure 24.1 ● Algorithm for pain management based on the WHO three-Step Analgesic Ladder. (Source: http://www.who.int/cancer/palliative/painladder/en/.)

Met-enkephalin = Tyr^1-Gly^2-Gly^3-Phe^4-Met^5(OH)   Leu-enkephalin = Tyr^1-Gly^2-Gly^3-Phe^4-Leu^5(OH)

endogenous peptide was termed *enkephalin*, which was found to be a mixture of the two pentapeptides that only differ in their terminal amino acid.

Both methionine-enkephalin (Met-enkephalin) and leucine-enkephalin (Leu-enkephalin) were shown to inhibit the contraction of electrically stimulated guinea pig ileum (GPI) and mouse vas deferens (MVD). These two tests are still used as screening methods for opioid activity. Naloxone completely reversed the inhibitory effects of enkephalin, which led Hughes to infer that the peptides were acting on an opioid receptor.[22] The central administration of enkephalins in rats produced short analgesic activity. The transient nature of the enkephalins' actions correlated with the rapid degradation of the enkephalin Tyr-Gly bond by aminopeptidases. Much synthetic work has been done in an attempt to increase the duration of action of the opioid peptides and maintain their analgesic effect.

SARs of Enkephalins

TYR^1

The first amino acid of the pentapeptide shows a distinct preference for tyrosine. Most changes to this amino acid, either by substituting with other amino acids or masking the phenolic hydroxyl (OH) or amino function, produce an inactive or weakly active peptide.

GLY^2

Replacing the naturally occurring L-Gly with various D-amino acids produces a peptide that is resistant to peptide cleavage by aminopeptidases. Replacement with D-Ser is the most effective replacement, and all L-amino acid analogs had low activities. Substituting D-amino acids for L-amino acids produces stable peptides, and the stereochemical change may give the peptide access to additional binding sites on the receptors; both of these actions may explain their increased potencies. Replacing the Gly^2 with D-Ala^2 while simultaneously replacing the L-Leu^5 with D-Leu^5 produces the peptide known as D-Ala^2, D-Leu^5 enkephalin (DADLE), which is commonly used as a selective δ-agonist.

GLY^3

Almost all changes to this amino acid result in a drop in potency, unless they are also accompanied by another change such as replacing the Gly^2 with D-Ala^2 as described above.

PHE^4

The aromatic nature of the fourth residue is required for high activity. When combined with the D-Ala^2 replacement, the addition of an electron withdrawing, lipophilic substituent (e.g., NO_2, Cl, and Br) in the para position of Phe^4 greatly increases activity. Para substitutions with electron donating, hydrophilic functional groups (e.g., NH_2 and OH) abolish activity.

MET^5/LEU^5

Position 5 appears to tolerate more residue changes than the other positions. Many amino acid substitutions at this position maintain activity (e.g., Ala, Gly, Phe, Pro). Even the loss of the fifth residue to yield the tetrapeptide Tyr^1-Gly^2-Gly^3-Phe^4 maintains weak activity in both the GPI and MVD assays. The protected peptide, Tyr^1-D-Ala^2-Gly^3-$MePhe^4$-Gly-ol^5, known as DAMGO is highly selective for the μ-receptor.

The pituitary gland, hypothalamus, and the adrenal medulla all produce various opioid peptides. Many of these materials were found to be fragments of β-lipotropin (β-LPT) a 91 amino acid peptide. β-LPT has no opioid activity itself. The fraction containing amino acids 61–91 is designated β-endorphin (a word derived from combining *endo*genous and m*orphin*e). It is much more potent than the enkephalins in both in vivo and in vitro tests. The search for opioid peptides continued, and additional precursor proteins were discovered. Many additional precursor proteins synthesized in the pituitary, adrenal glands, and brain nerve terminals were found to contain sequences of amino acids that were enkephalins or other active opioid peptides. It appears that naturally occurring peptides may serve roles as both short-acting analgesics and long-term neuronal or endocrine modulators. Acupuncture, running, or other physical activity may induce the release of neuropeptides although studies exist that both confirm and refute these claims.[24,25] A complete discussion on the neuropeptides is beyond the scope of this chapter. Some examples of opioid peptides are given in Figure 24.2.[26–29]

Opioid Receptors

The discovery of the endogenous opioid peptides paralleled the development of radiolabeling techniques. During the 1970s, researchers were able to label opioid receptors with reversible radioactive ligands that allowed pharmacological actions of specific receptors and their locations to be identified. These techniques allowed for the identification of opioid receptor locations in the brain. Additional pharmacological advances in gene expression studies led to the identification of peripheral opioid receptor locations.[30] Opioid receptors are distributed throughout the brain, spinal cord, and peripheral tissues. The distribution of specific opioid receptor subtypes (μ, δ, and κ) usually overlaps. In rats, high concentrations of all three genes for the μ-, δ-, and κ-receptors were found in the hypothalamus and cerebral

Endogenous Precursor Proteins
Pro-opimelanocortin ⟶ ACTH + β LPH ⟶ γ-LPH + β endorphin
Pro-enkephalin A[263] ⟶ 4Met-enkephalin + Leu-enkephalin
Pro-enkephalin B[256] ⟶ β neo-endorphin[175-183] + dynorphin[209-225] + Leu-enkephalin[228-232]

Endogenous Opioid Peptide sequences
β Endorphin = Tyr-Gly-Gly-Phe-Met[5]-Thr-Ser-Glu-Lys-Ser[10]-Gln-Thr-Pro-Leu-Val[15]-Thr-Leu-Phe-Lys-Asn[20]-Ala-Ile-Ile-Lys-Asn[25]-Ala-Tyr-Lys-Lys-Gly-Glu[31] = δ and μ opioid receptor ligand
Endomorphin-1 = Tyr-Pro-Trp-Phe-NH$_2$ = μ receptor agonist
Endomorphin-2 = Tyr-Pro-Phe-Phe-NH$_2$ = μ receptor agonist

Dynorphin = Tyr-Gly-Gly-Phe-Leu[5]-Arg-Arg-Ile-Arg-Pro[10]-Lys-Leu-Lys[13] = κ opioid selectivity
α-Neoendorphin = Tyr-Gly-Gly-Phe-Leu[5]-Arg-Lys-Tyr-Pro-Lys[10]
β-Neoendorphin = Tyr-Gly-Gly-Phe-Leu[5]-Arg-Lys-Tyr-Pro[9]

Nociceptin = Phe-Gly-Gly-Thr-Gly[5]-Ala-Arg-Lys-Ser-Ala[10]-Lys-Ala-Asn-Gln[14] = orphanin receptor
Orphanin FQ = Phe-Gly-Gly-Phe-Thr[5]-Gly-Ala-Arg-Lys-Ser[10]-Ala-Arg-Lys-Leu-Ala-Asn-Gln[17]

Exogenous Opioid Peptide sequences "Exorphins"
DADLE = Tyr-D-Ala-Gly-Phe-D-Leu = δ selective agonist
DPDPE = Tyr-D-Pen-Gly-Phe-D-Pen = δ selective agonist
DSLET = Tyr-D-Ser-Gly-Phe-Leu-Thr = δ selective agonist
Casomorphin (cow's milk μ opioid receptor agonist) = Tyr-Pro-Phe-Pro-Gly-Pro-Ile[7]
Dermorphin (South American frog skin μ opioid receptor agonist) = Tyr-D-Ala-Phe-Gly-Tyr-Pro-Ser[7]-NH$_2$
Gluten exorphins (multiple peptides from wheat having opioid agonist and antagonist activity)

Figure 24.2 ● Endogenous and exogenous opioid peptides.

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. The gene for the μ-opioid receptor was not found in the stomach, heart, endothelium, or synovium of the rat.[30] Opioid receptors are also found on the peripheral terminals of sensory neurons in inflamed rat paws.[31] Thus, the central and peripheral distribution of opioid receptors is complex. This complicates the interpretation of pharmacological data of individual drugs that may have overlapping binding at multiple opioid receptor subtypes. In addition, opioid receptors form homodimers and heterodimers with opioid receptors and nonopioid receptors such as the α_{2a}-adrenergic receptors resulting in different pharmacologic actions and altered coupling to second messengers.[32]

Genes for the four major opioid receptor subtypes have been cloned; the MOP = μ-receptor (mu for morphine), the KOP = κ-receptor (kappa for ketocyclazocine), the DOP = δ-receptor (delta for deferens because it was originally discovered in the MVD), and the NOP = nociception/orphanin FQ receptor (named as an orphan receptor because the endogenous/exogenous ligand was unknown at its time of discovery).[33] The opioid receptor subtypes share extensive residue homology in their transmembrane (TM) domains with most of the variation found in the extracellular loops (Fig. 24.3).[33] All of the opioid receptors belong to the G-protein–coupled receptor class and as such, they are composed of seven TM domains. When the receptor is activated, a portion of the G protein diffuses within the membrane and causes an inhibition of adenylate cyclase activity. The decreased enzyme activity results in a decrease in cyclic adenosine monophosphate (cAMP) formation, which regulates numerous cellular processes. One process that is inhibited is the opening of voltage-gated calcium influx channels on nociceptive C-fibers. This results in the hyperpolarazation of the nerve cell and decreased firing and release of pain neurotransmitters such as glutamate and substance P.[34]

OPIOID LIGAND BINDING SITE

There are no x-ray crystal structures reported for any opioid receptor, and most modeling work has been based on the crystal structure of rhodopsin. Many groups have attempted to find the specific binding site through homology modeling, molecular dynamics, site-directed mutagenesis, chimeric receptors, truncated receptors, and SAR studies. As of yet, no definitive model of the ligand-binding site is available. The opioid-binding site for all four opioid receptors is believed to be an inner cavity formed by conserved residues on TM helices TM3, TM4, TM5, TM6, and TM7.[33,35] Not all groups agree that the binding pocket is formed via TM domains; some evidence suggest that the amino terminus is an important determinant of ligand binding affinity as well.[36] The ligand specificity that each receptor shows may be a result of differences in the extracellular loops that form lids on the binding cavities or differences in amino acids within the binding cavity. Within the cavity, agonists are thought to bind toward the bottom of the cavity via interactions with a conserved Asp from TM3 and a His from TM6. Molecular modeling calculations show that the phenolic OH of the Tyr[1] opioid peptide, or the ring A OH of nonpeptide opioids, forms a hydrogen bond with the conserved His on TM6. The Tyr[1]-charged nitrogen, or the N$^+$ of the nonpeptide agonist, forms an ionic bond with the conserved Asp of TM3. Antagonist ligands are thought to bind deeper in the binding pocket but retain the ionic bond with the Asp of TM3. The bulky substituent on the charged nitrogen of antagonists is believed to insert itself between TM3 and TM6, preventing the shifts required for activation. Thus, antagonists prevent the necessary movement of TM3 and TM6 resulting in functional antagonism.[33,35]

THE μ-RECEPTOR

Mu receptors are found primarily in the brainstem and medial thalamus.[34] Endogenous peptides for the μ-receptor include endomorphin-1, endomorphin-2, and β-endorphin
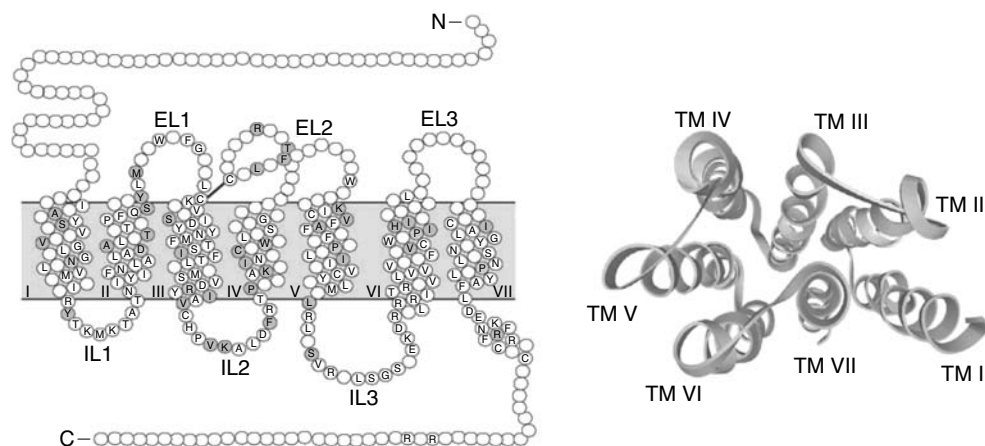
Figure 24.3 ● Structure of opioid receptors. (*Left*) Serpentine model of the opioid receptor. Each transmembrane helix is labeled with a roman number. The white empty circles represent nonconserved amino acids among the MOP, DOP, KOP, and NOP receptors. White circles with a letter represent identical amino acids among all four opioid receptors. Violet circles represent further identity between the MOP-R, DOP-R, and KOP-R. Green circles highlight the highly conserved fingerprint residues of family A receptors, Asn I:18 in TM1, AspII:10 in TM2, CysIII:01 in TM3, TrpIV:10 in TM4, ProV:16 in TM5, ProVI:15 in TM6, and ProVII:17 TM7. Yellow circles depict the two conserved cystines in EL loops 1 and 2, likely forming a disulfide bridge. (IL, intracellular loop, and EL, extracellular loop.) (*Right*) Proposed arrangement of the seven transmembrane helices of opioid receptors as viewed from the top (extracellular side). The seven transmembrane helices are arranged sequentially in a counterclockwise manner. Each transmembrane helix is labeled with a roman number. (Reprinted with permission from the *Annual Review of Biochemistry*, Volume 73 © 2004 by Annual Reviews.)

(Fig. 24.2). Exogenous agonists for the μ-receptor include drugs from the five structural classes discussed later in this chapter (4,5-epoxymorphinan, morphinan, benzomorphan, 4-phenyl/4-anilido piperidines, and the diphenylheptanes) and exogenous peptides such as dermorphin isolated from the skin of South American frogs. Recently, human neuroblastoma cells have been shown to be capable of synthesizing morphine via biosynthesis from radiolabeled tyramine. The synthetic route involves at least 19 steps and is similar, but not exact, to the synthetic route used by the poppy plant.[37] The exact role of endogenous morphine is unknown at this time. In general, agonists at the μ-receptor produce analgesia, respiratory depression, decreased gastrointestinal (GI) motility, euphoria, feeding, and the release of hormones. 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 described previously, Met and Leu enkephalin, as well as some synthetic peptides such as DADLE, DSLET, and DPDPE (see Fig. 24.2 for amino acid sequences). These peptides have high affinity for the receptor but low bioavailability and thus limited clinical usefulness. They are used in animal in vitro studies as probes for δ-receptor location and function.

In an attempt to distinguish the amino acids responsible for δ-receptor ligand specificity, point mutations of the δ-receptor, and μ/δ-receptor chimeras were constructed.[38] The altered receptors had a decreased ability to bind to δ-receptor selective peptide and nonpeptide ligands, when amino acids in the extracellular top of TM6 and TM7 and the extracellular loop (EC loop 3) that connected them were mutated.

Specifically, amino acids Try^{284}, Val^{296}, and Val^{297} were crucial to selective δ-ligand binding. These amino acids may provide recognition sites on the receptor that the ligand would have to pass through to reach the putative binding site deeper in the TM cavity. Befort et al.[39] also used site-directed point mutant receptors along with molecular modeling to identify Tyr^{129} in TM3 as the most crucial amino acid for ligand binding. In addition, they found a role for amino acid Tyr^{308} (TM7) in ligand binding.

Nonpeptide agonists and antagonists have been designed to further study the function of the δ-receptor. The first nonpeptide lead compound selective for the δ-receptor came from screening. Modifications to the lead compound led to the identification of SNC-80 as a potent agonist specific for the δ-receptor (Fig. 24.4). This compound has weak antinociceptive effects in monkeys, an effect that can be reversed with the δ-antagonist naltrindole (NTI) (Fig. 24.4).[40] A series of SNC-80 analog, prepared by multiple groups, found that the amide nitrogen appears to be the most sensitive to modifications and may play an important role in δ-receptor selectivity.[41] Portoghese designed 7-spiroindanyloxymorphone (SIOM) (Fig. 24.4) based on the idea that the indole of NTI is acting as an "address" mimic of the Phe^4 phenyl group of enkephalin. The "address–message" concept proposes that one part of the molecule may act as an "address," essentially directing the chemical to the correct receptor by binding specifically to that receptor, and another part of the molecule acts as the "message," which gives the compound the biological action. The indole of NTI was replaced with a spiroindane functional group equivalent address in SIOM. The *N*-methyl group of SIOM confers an agonist message as opposed to the antagonist message of the NTI cyclopropyl methyl.[42] Additional agonists for the δ-receptor have been
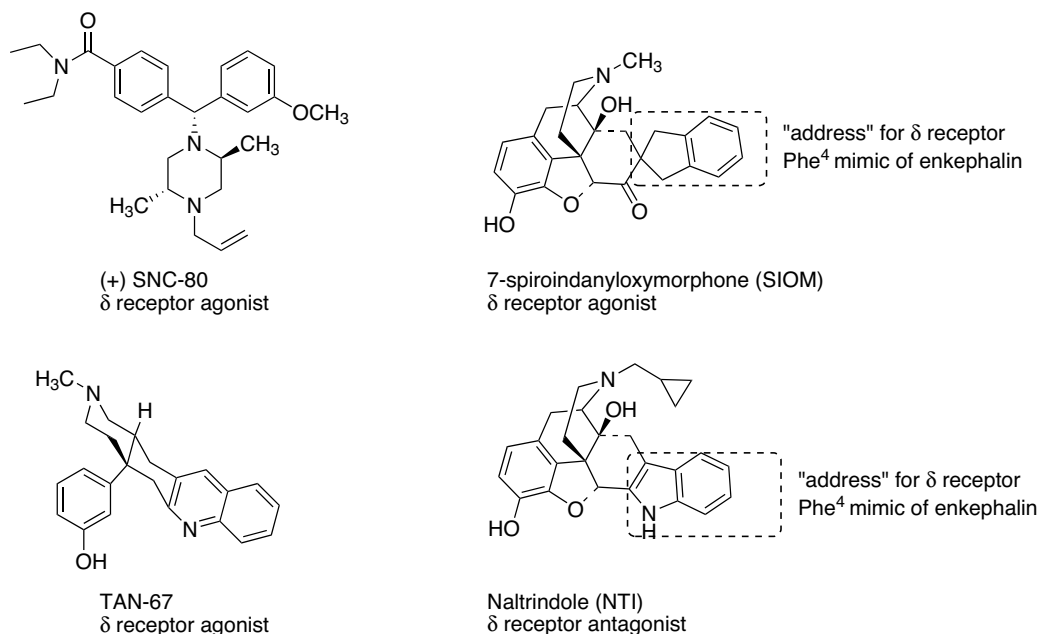
Figure 24.4 ● Selective δ-receptor ligands.

developed based on the octahydroisoquinoline structure with five-membered ring spacers being δ-receptor antagonists and six-membered ring spacers, agonists. TAN-67 is the most extensively studied in this class (Fig. 24.4).[41] The δ-receptor tolerates multiple chemical structures, and no pharmacophore has been identified that can accommodate all of the diverse structures.[38,43]

Transgenic mice lacking the δ-receptor have been generated and found to display increased levels of anxiety. In addition, δ-receptor agonist show antidepressant activity in rat models.[32,44] These results suggest that ligands targeting this receptor may represent new leads for the treatment of schizophrenia, bipolar disorders, and depression. There are few clinical reports of selective δ-receptor agonist use in humans, although they are reported to have proconvulsive activity that may limit their use.[44]

THE κ-RECEPTOR

Kappa receptors are primarily found in the limbic, brain stem, and spinal cord.[34] The κ-receptor shows less structural homology to the μ-receptor than the δ-receptor does. (Fig. 24.3) Unlike the μ- and δ-receptors that bind the (enkephalin) peptide sequence Tyr-Gly-Gly-Phe-(Leu/Met), the κ-receptor does not. The κ-receptor shows a clear preference for binding peptides with an arginine in position 6 as seen in the dynorphin peptides (Fig. 24.2).[45]

The structure of some κ-agonists and an antagonist can be seen in Figure 24.5.[46,47] TRK-820 is a κ-agonist displaying approximately 15 times selectivity toward κ-receptors versus μ-receptors.[46] The 4,5-epoxymorphinan structure of TRK-820 is proposed to mimic the tyrosine–glycine moiety of endogenous opioid peptides, in effect the agonist message. The additional 6β-substituent constitutes the address directing the compound to the κ-receptor. Spiradoline was one of the earliest compounds to show improved κ-receptor selectivity (125 times over μ-receptors). SARs on this class of compounds revealed that methyl-substituted nitrogen amides, a methylene spacer between the amide and

the aromatic ring and the (−) isomer were all required for κ-activity. The dichlorophenyl ring could be replaced with a 4-benzothiophene or a 4-benzofuran for increased potency and κ-receptor selectivity.[41] Salvinorin A (Fig. 24.5) a nonnitrogen-containing natural compound found in the herb sage is a potent agonist at the κ-receptor.[48] The hallucinogenic properties of *salvia divinorum* (sage) have been known for hundreds of years but recently, these properties have been exploited by online groups attempting to sell legal hallucinogenic compounds. The κ-antagonist nor-binaltorphimine (nor-BNI) was made by incorporating a rigid pyrrole spacer linking two κ-pharmacophores. Nor-BNI is used in the laboratory to determine if κ-receptors are involved in an observed activity.[41] The second pharmacophore of nor-BNI is not required for κ-antagonism, and compounds that are missing the second aromatic ring have been found to be even more selective and potent antagonists at the κ-receptor.

In clinical trials, most κ-agonists produce dysphoria and thus may be less psychologically addicting but also less acceptable to patients. Some compounds with κ-agonist activity (e.g., pentazocine, nalbuphine) are available, but the clinical development of pure κ-agonists has been limited by the centrally mediated side effects. Spiradoline was developed under the premise that a selective κ-agonist would be an analgesic without the μ-opioid–mediated problems associated with addiction and respiratory depression. Clinical trials in humans found that spiradoline did not produce analgesic effects within a dose range that did not also cause dysphoria, diuresis, and sedation.[47] The selective κ-agonist TRK-820 shows some promise for the treatment of uremic pruritus, the itch associated with dialysis.[49]

THE ORPHANIN RECEPTOR/FQ/NOP₁

The traditional opioid peptides do not elicit any biological effect at the orphanin receptor. An endogenous peptide for the orphanin receptor has been found and termed orphanin FQ or *nociceptin* (Fig. 24.2). This 17 amino acid peptide can reverse the analgesic effects of morphine thus is antiopioid
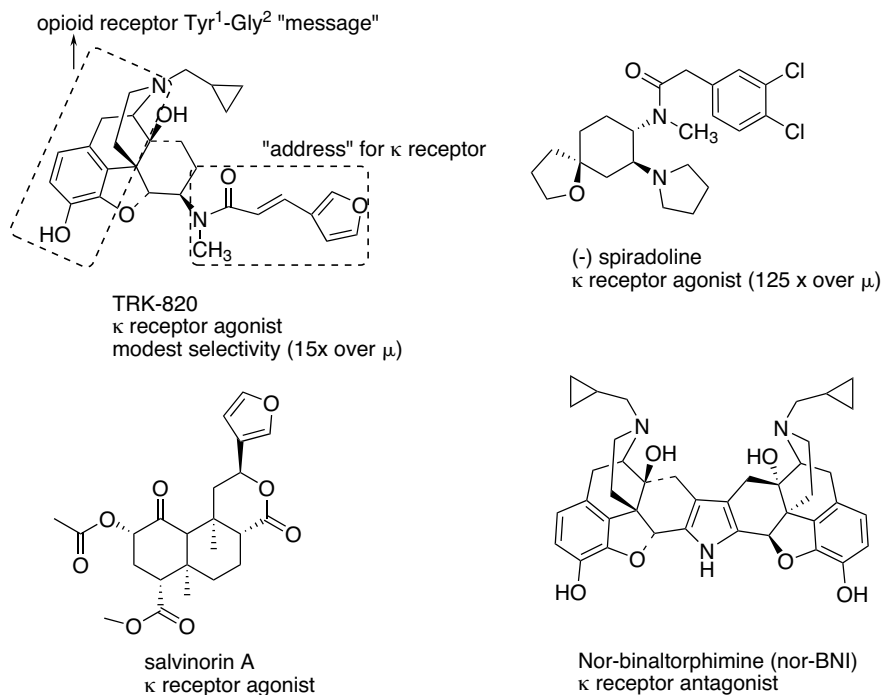
Figure 24.5 ● Selective κ-receptor ligands.

in some situations.[50] The carboxy-terminal half of the receptor may serve as the portion that excludes binding to the μ-, δ-, and κ-opioid ligands. The functional role of the receptor is still being investigated, but selective agonists have been shown to delay gastric emptying and decrease gastric secretory functions in rats.[51] In addition, this receptor is found on airway nerves, and agonists decrease bronchospasms in guinea pigs and cats. This receptor is a target for the design of novel peripherally acting antitussive agents, although no compounds are on the market at present.

STRUCTURE–ACTIVITY RELATIONSHIPS

Relating the structure of the chemical ligand to the physiologic activity it induces can only be accomplished by looking at each receptor type individually. The chemically diverse nature of agonists and antagonists found for the μ-, δ-, and κ-receptors is testimony to the adaptability of the

receptors to multiple chemical backbones and tolerance for divergent functional groups. The reader is referred to reviews of the κ- and δ-receptor for detailed SARs for ligands at those receptors.[41] A summary review of the SARs of the μ-receptor compounds is included in the drug monograph section below. For the purpose of this chapter, the drug classes covered will be 4,5-epoxymorphinans, morphinans, benzomorphans, 4-phenylpiperidines/4-anilidopiperidines, diphenylheptanes, and the miscellaneous category.

⬡ DRUG MONOGRAPHS

4,5-Epoxymorphinans

A summary of the SARs of the 4,5-epoxymorphinan structure can be seen in Figure 24.6, and these are discussed in the succeeding individual drug monographs.
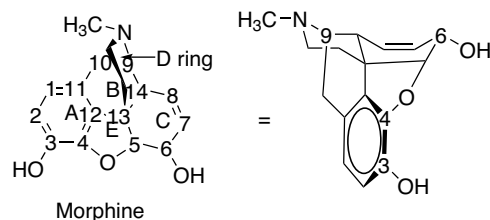
Changes on Morphine that increase analgesic activity
C6 - OH to OAc
C3 and C6 - OH to OAc
C6 - OH to O-Sulfate or O-glucuronide
C6 - OH to =O and C7-C8 single bond
C6 - OH to H and C7-C8 single bond
C14 - H to βOH
N - CH_3 to CH_2CH_2Ph
N - CH_3 to CH_2CH_2furan
N - CH_3 to CH_2C=OPh
Removal of C4-C5 ether link

Changes on Morphine that produce antagonists
N - CH_3 to CH_2CH=CH_2
N - CH_3 to CH_2—▷

Figure 24.6 ● Summary of functional group changes on morphine structure.

MORPHINE

The prototype ligand for the μ-receptor is morphine. The numbering and ring lettering (A, B, C. . .) can be seen in Figure 24.6. 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). The x-ray determined conformation of morphine is a "T" shape with the A, B, and E rings forming the vertical portion, and the C and D ring forming the top (Fig. 24.6).[41]

Morphine was isolated from opium in 1806 by a German pharmacist, Seturner. He named the compound "morphine" after the Greek god of dreams "Morpheus." The first mention of the opium poppy was found in Iraq on clay tablets inscribed in cuneiform script in about 3000 BC.[52] Opium has been used throughout history and is found in ancient Egyptian, Greek, Roman, Arabic, Indian, and Chinese writing. Opium is isolated from the opium poppy, *Papaver somniferum*, by lancing the unripe pod and collecting and drying the latex that seeps from the incision. Opium contains over 40 different alkaloids with most alkaloids represented in the following five structures: morphine (8%–17%), codeine (0.7%–5%), thebaine (0.1%–2.5%), papaverine (0.5%–1.5%), and noscapine (1%–10%).[52]

Although the total synthesis of morphine has been accomplished by various chemical processes, it is still produced from the poppy latex.[53] Thus far, no synthetic pathway is efficient enough to make it competitive with the preparation of morphine from either isolation or semisynthesis from a precursor compound from the poppy plant. The endogenous synthesis of morphine in human neuroblastoma cells has been elegantly described.[37] The function of endogenous morphine is unknown at this time, but the genes and enzymes involved in morphine biosynthesis may become targets for novel drugs used to treat pain.

Morphine is the prototype μ-receptor agonist; it is the drug to which all other μ-agonists are compared. The pharmacological properties of morphine are well documented and include analgesia, its primary use. For equivalent analgesic effect, the oral dose must be 3 times the intravenous (IV) dose to account for the morphine lost to first-pass hepatic metabolism. The equianalgesic dose of morphine congeners can be seen in Figure 24.7.

Morphine is extensively metabolized via phase II conjugation to morphine-3-glucuronide ($\sim$60%), morphine-6-glucuronide ($\sim$9%), and, to a lesser extent, the *N*-demethylated metabolite ($\sim$3%)[54] (Fig. 24.8). Much controversy exists on the contribution of the metabolites of both codeine-6-glucuronide and morphine-6-glucuronide to their analgesic effect. In some studies, the 6-glucuronide metabolite of both drugs contributes significantly to their potency.[55–57] In other studies, the 6-glucuronide metabolites of morphine and codeine produces very little analgesic effect.[58,59]

Morphine, or another potent opioid drug, is introduced in the WHO stepladder when pain is severe and no relief is obtained from NSAIDs or a combination of NSAIDs and a less potent opioid. Morphine is a monoacidic base and readily forms water-soluble salts with most acids. Because morphine itself is poorly soluble in water (1 g/5,000 mL at 25°C), the
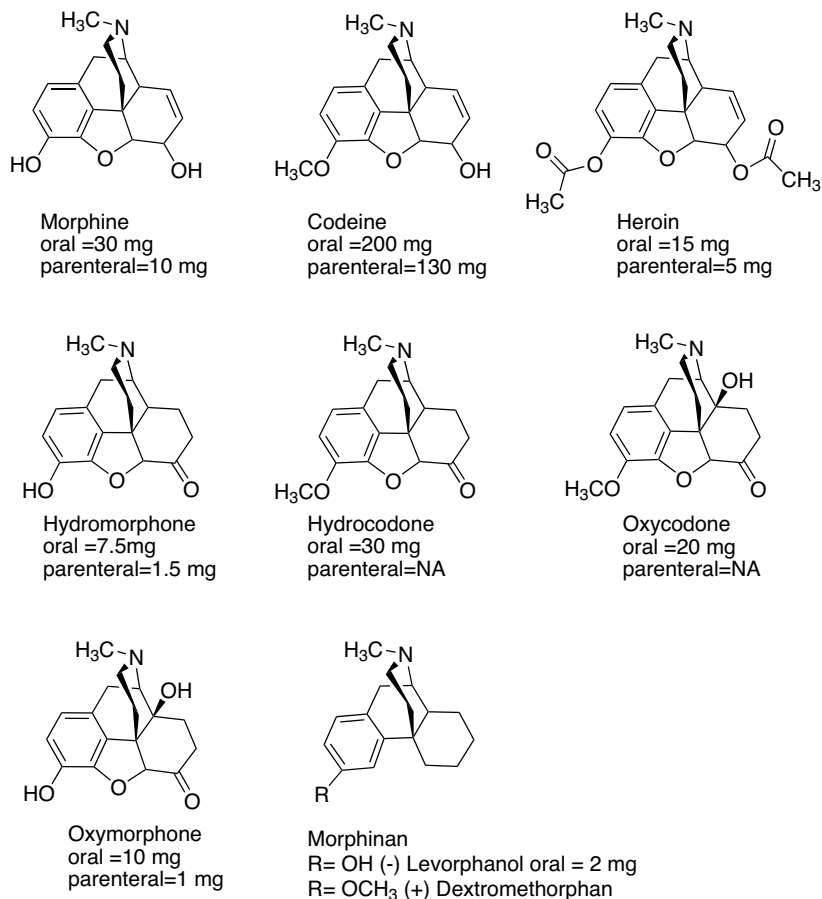

Morphine
oral =30 mg
parenteral=10 mg

Codeine
oral =200 mg
parenteral=130 mg

Heroin
oral =15 mg
parenteral=5 mg

Hydromorphone
oral =7.5mg
parenteral=1.5 mg

Hydrocodone
oral =30 mg
parenteral=NA

Oxycodone
oral =20 mg
parenteral=NA

Oxymorphone
oral =10 mg
parenteral=1 mg

Morphinan
R= OH (-) Levorphanol oral = 2 mg
R= OCH₃ (+) Dextromethorphan

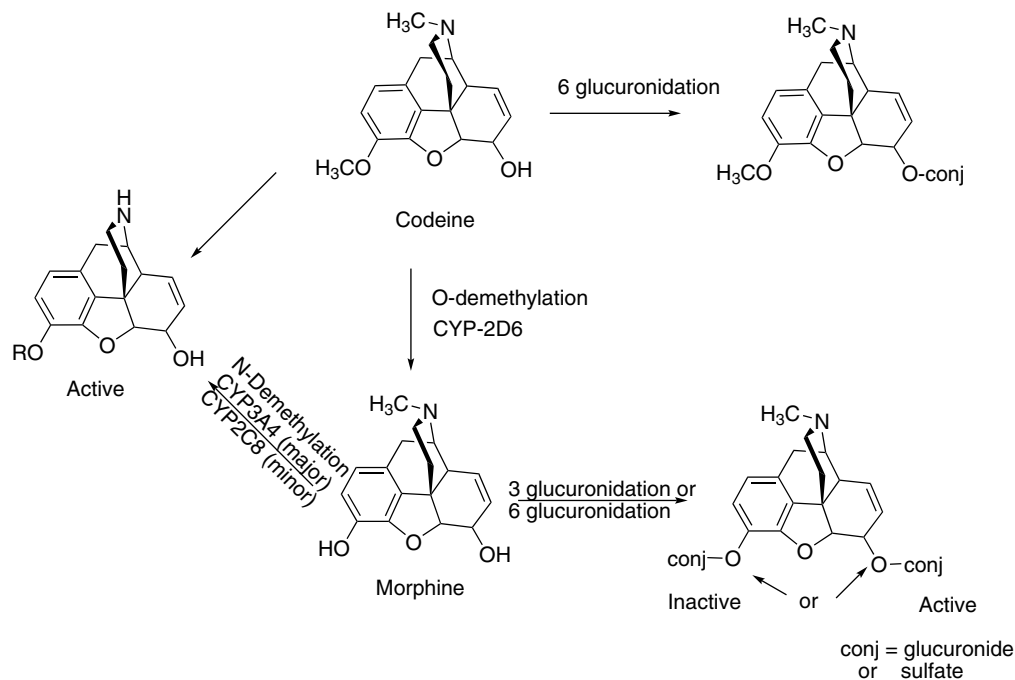**Figure 24.7** ● 4,5-Epoxymorphinans and morphinans.

Figure 24.8 ● Metabolism of morphine and codeine.

sulfate salt is formed for both oral, IV, and suppository use. The usual starting parenteral dose of morphine in adults is 2.5 to 5 mg q 4 hours. Morphine is available for oral use both as an immediate release and sustained release formulation. The immediate release preparations are dosed q 4 hours, and the sustained release formulations are dosed q 12 to q 24 hours depending on the formulation.

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. It occurs as levorotatory, colorless, efflorescent crystals, or as a white crystalline powder. It is light sensitive. Codeine is a monoacidic base and readily forms salts with acids, with the most important being the sulfate and the phosphate. The acetate and methylbromide derivatives have been used to a limited extent in cough preparations.

The general pharmacological action of codeine is similar to that of morphine, but it does not possess the same analgesic potency. The equianalgesic dose of parenteral morphine 3 to 5 mg q 4 hours is codeine 30 to 65 mg q 4 hours. The equianalgesic dose of oral morphine 10 mg q 4 hours is codeine 60 mg q 4 hours. The decreased potency also leads to a lower addiction potential compared with morphine. Side effects include respiratory depression, mioisis, constipation, nausea, itching, dry mouth, and drowsiness. Approximately 5% of codeine is metabolized to morphine via *O*-demethylation. (Fig. 24.8) The enzyme responsible for the *O*-demethylation of codeine is cytochrome P450 (CYP) 2D6. This enzyme exhibits genetic polymorphism with an estimated 7% to 10% of Caucasians designated as poor metabolizers, and thus only able to form traces of morphine after codeine is administered.[60] The analgesic component of codeine has long been assumed to

be the *O*-demethylated metabolite, morphine. If codeine has no analgesic potency itself, then patients who lack this enzyme should have no analgesic effect to administered codeine. This has been shown not to be the case, so codeine itself may posses analgesic activity, or codeine-6-glucuronide may be the active analgesic.[56,57]

Codeine's role as an effective antitussive agent has been questioned. A Cochrane evidence-based review of the literature shows that codeine is no more effective than placebo for acute cough in children or adults.[61] Codeine is available in several combination products with either aspirin, ibuprofen, or acetaminophen for the treatment of moderate pain.

HEROIN

Heroin, was first commercially synthesized in 1898 by Bayer company in Germany as an alternate analgesic to morphine. Heroin is the 3,6 diacetylated form of morphine (Fig. 24.7). The laboratory researchers, which also used the acetylation process to convert salicylic acid into acetyl salicylic acid (aspirin), believed that heroin would be an effective analgesic with no addictive properties. This was unfortunately not the case. They named the product "heroin" because it made the test subjects, including some of the chemists, feel "heroic." 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.[62]

Heroin is not available as a prescription product in the United States, although it is available in some countries to treat pain associated with cancer and myocardial infarctions. It remains one of the most widely used narcotics for illicit purposes and places major economic burdens on society.

HYDROMORPHONE

Hydromorphone, (Dilaudid) is a synthetic derivative of morphine prepared by the catalytic hydrogenation and dehydrogenation of morphine under acidic conditions, using a large excess of platinum or palladium.[63] Oxidation of the 6-OH of morphine resulted in a compound with decreased potency. Reducing the 7,8 double bond of morphine increased the flexibility of the molecule and resulted in a compound with slightly enhanced binding. Making both of these structural changes to morphine-produced hydromorphone, a compound approximately 5 times as potent as morphine. Hydromorphone was introduced in 1926 and is available as an immediate release tablet, a liquid, and a suppository. A sustained release form is available in some countries but not in the United States. The sustained release form was removed from the U.S. market in 2005 when studies showed that drinking 8 oz of alcohol (40%) could cause the drug to be released from the capsule immediately and lead to concentrations that were 5.5 times higher than in patients that did not drink alcohol. This potentially lethal combination prompted the Food and Drug Administration (FDA) to remove it from the market.

HYDROCODONE

Hydrocodone is the 3 methoxy version of hydromorphone. The loss of the 3-OH group yields a compound that is approximately 4 to 5 times less potent than hydromorphone, thus about equal to morphine. Unlike codeine, the agonist activity of hydrocodone does not require 3-*O*-demethylation, although it does occur via CYP2D6 representing 4.6% of total clearance.[64] The protected 3-position has better brain penetration, and the 7,8-dihydro-6-keto C ring contributes to the increased binding of the compound to the μ-receptor.

There are no pure hydrocodone products available on the U.S. market. All FDA-approved products containing hydrocodone are combination products. Like codeine, hydrocodone is marketed as an antitussive agent. It is available combined with the anticholinergic agent homatropine as a syrup and a tablet. The addition of the anticholinergic agent is to discourage abuse. It is also available in a delayed release suspension form (Tussionex). This formulation uses a sulfonated styrene divinylbenzene copolymer complexed with hydromorphone and chlorpheniramine that acts as a cation-exchange resin slowly releasing the drugs over a 12-hour period. Hydrocodone is also marketed in combination with acetaminophen (Vicodin, Lortab) or aspirin (Lortab ASA) for the treatment of pain. The dose of acetaminophen consumed by the patient must be closely monitored, and prescriptions that allow for greater than 4 grams of acetaminophen per 24-hour period should not be dispensed.

OXYCODONE

Oxycodone is synthesized from the natural opium alkaloid thebaine. Oxycodone is the 14 beta-hydroxyl version of hydrocodone. This additional functional group gives oxycodone greater potency (1.5 times orally) than hydrocodone presumably by increasing receptor affinity. The oral bioavailability of oxycodone is 65% to 87%.[65] The metabolism of oxycodone follows the similar pattern of opioid metabolism with *N*-demethylation, *O*-demethylation, and their glucuronides all identified. Per the manufacturer, the analgesic effect of oxycodone correlates well with oxycodone plasma concentrations, not the minimal amount of oxymorphone formed, thus

oxycodone is not assumed to be a prodrug. There are no large-scale studies of oxycodone used for analgesia in CYP2D6 poor metabolizers that can confirm this.

Oxycodone is marketed in combination with acetaminophen (Percocet), aspirin (Percodan), and ibuprofen (Combunox). It has been available for over 50 years as an immediate-release tablet, and in 1995 an extended-release tablet was approved by the FDA (OxyContin). OxyContin is manufactured in eight strengths from 10 to 160 mg, and the high-dose preparations quickly became attractive to drug abusers. The extended-release tablets are crushed and then injected or snorted to give an immediate high. The Drug Abuse Warning Network (DAWN) is a public health surveillance system that monitors drug-related emergency room visits and drug-related deaths. In 1995, they estimated that 598,542 emergency room visits involved the nonmedical use of a pharmaceutical (e.g., antidepressant, anxiolytic, stimulant). Of these ER visits, 160,363 visits were attributed to opiates with an estimated 42,810 involving oxycodone or an oxycodone combination. Methadone and hydrocodone/combinations were estimated to be similar to oxycodone.[66]

OXYMORPHONE

Oxymorphone is the 14 beta-hydroxyl version of hydromorphone, analogous to the hydrocodone, oxycodone pair discussed above. Although the addition of the 14 beta-hydroxyl group to hydrocodone (30 mg) yielded oxycodone (20 mg), a more potent drug, the opposite is true for the conversion of hydromorphone (7.5 mg) to oxymorphone (10 mg). The reason for this is that the oral bioavailability of oxymorphone (10%) is lower than that of hydromorphone (35%) because of decreased absorption and increased first-pass metabolism. Presumably, the addition of the OH group does increase its binding affinity at the receptor as the injectable form of oxymorphone (1 mg) is more potent than injectable hydromorphone (1.5 mg).

Oxymorphone is available as a suppository (5 mg), an injection (1 mg/mL), an immediate-release tablet (5 mg, 10 mg), and in 2003 the FDA approved a sustained release formulation (Opana ER 5 mg, 10 mg, 20 mg, and 40 mg). The 12-hour coverage of the extended release tablet provides another option for those patients suffering from chronic pain. The side effect profile of the extended release formulations of morphine, oxycodone, and oxymorphone are similar, and there appears to be no clear advantage of one over the other.

Morphinans

The morphinans were made by removing the E ring of morphine, the 4,5-ether bridge, in an attempt to simplify the structure (Fig. 24.7).

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. The plasma half-life of levorphanol is about 6 to 8 hours but displays great interperson variability and may increase upon repeated dosing. The excretion of levorphanol is dependent on the kidneys, so caution must be used in renally compromised patients.[67]

The analgesic effect of levorphanol may not match the long plasma half-life, and patients must be closely monitored for drug accumulation and respiratory depression. Levorphanol has strong agonist activity at the μ-, κ-, and δ-opioid receptors and has also been shown to be a noncompetitive *N*-methyl-D-aspartate (NMDA)-receptor antagonist.[68] The pharmacodynamic properties of levorphanol are sufficiently different to make it an attractive alternate for patients that receive inadequate pain relief from morphine. Levorphanol is available as a 2-mg oral tablet (Levo-Dromoran), and a 2-mg/mL solution for injection.

DEXTROMETHORPHAN

Dextromethorphan is the dextrorotatory form of levorphanol with a methoxy group on the 3-position (Fig. 24.7). It is available in more than 140 over-the-counter (OTC) cough and cold formulations.[69] Evidence-based reviews have been unable to conclude that it is more effective than placebo in reducing cough.[61,70] Like (+) and (−) levorphanol, (+) dextromethorphan is a potent NMDA antagonist and, in higher than recommended doses, has the potential for causing dissociative anesthetic effects similar to ketamine or phencyclidine (PCP). The OTC status and availability of pure dextromethorphan powder online has contributed greatly to its abuse in recent years. DAWN reports that in 2004, there were approximately 12,500 emergency room visits involving dextromethorphan with 44% of those involving abuse of the drug.[71] The *2006 National Survey on Drug Abuse* report shows that nearly 1 million persons aged 12 to 25 years (1.7%) misused OTC cough and cold medications in the past year.[69]

Dextromethorphan's ability to antagonize the NMDA receptor has led to its use to treat phantom pain, diabetic neuropathy, and postoperative acute pain.[72,73]

Benzomorphans

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*.
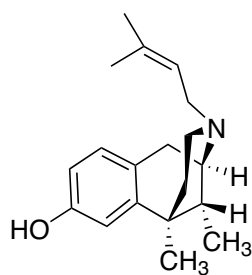
Pentazocine

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 (carbons 9, 13, and 14 of morphine). The only benzomorphan in clinical use is pentazocine, which is prepared as the 2(R), 6(R), 11(R) enantiomer (*Chemical Abstracts* numbering).[74] 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.

According to the manufacturer, a 50-mg dose of pentazocine has about the same analgesic potency as 60 mg of codeine and about 1/50th the antagonistic activity of nalorphine.[74] Pentazocine is also an agonist at the κ-receptor, and this may be responsible for the higher percentage of patients that experience dysphoria with pentazocine versus morphine.[75] Some evidence also exists that women respond better to κ-agonists than men.[76,77] Pentazocine is available in a 50-mg tablet along with a low dose of the antagonist naloxone 0.5 mg (Talwin NX). Naloxone 0.5 mg orally is expected to have no pharmacological effect but is included to dissuade IV drug abusers from dissolving and injecting Talwin NX.

4-Phenylpiperidines and 4-Anilidopiperidines

Further structural simplification of the benzomorphan ring system, via 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. Much SAR work has been conducted on theses compounds, and the reader is referred to Casy's book for a detailed review.[62]

MEPERIDINE

Meperidine (Demerol) (Fig. 24.9) was discovered in 1939 during a serendipitous screening of compounds being studied for antispasmodic activity. Mice given meperidine were noted to carry their tails in an erect position (the Straub tail reaction), which was indicative of narcotic analgesia. This led to the study of meperidine and derivatives as analgesic agents. 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.[41] Meperidine is an agonist at the μ-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.

The 4-ethyl ester was found to be the optimal length for analgesic potency. Increasing or decreasing the chain length decreased activity.[41] Structural changes that increase the potency of meperidine include the introduction of an m-hydroxyl on the phenyl ring, substituting the methyl on the N for a phenylethyl or a *p*-aminophenylethyl.[41] Replacing the *N*-methyl with an *N*-allyl or *N*-cyclopropylmethyl group does not generate an antagonist, unlike the similar substitution of the morphine congeners. Meperidine quickly penetrates the blood-brain barrier and thus has a quick onset of activity and a high abuse potential. Meperidine is metabolized to normeperidine (Fig. 24.10) by the liver enzymes CYP3A4 and CYP2C18 and in the brain by CYP2B6. Meperidine and normeperidine are also metabolized by liver carboxylesterases.[78,79] The metabolism to normeperidine has clinical consequences. The duration of analgesia of meperidine may be shorter than the 3- to 4-hour half-life of the drug. This may necessitate frequent dosing to relieve pain, and thus the excessive formation of normeperidine. Normeperidine has been shown to cause central nervous system (CNS) excitation that presents clinically as tremors, twitches, "shaky feelings," and multifocal myoclonus potentially followed by grand mal seizures.[80] Patients at the greatest risk of developing normeperidine toxicity are those that are on high doses, long durations (greater than 3 days), have
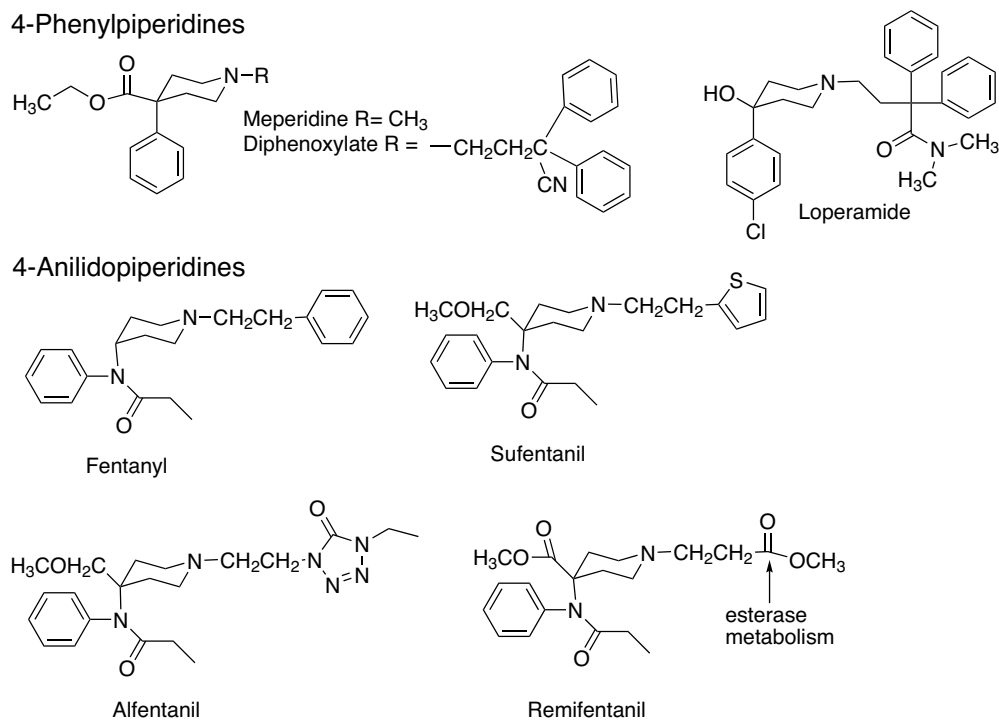
4-Phenylpiperidines

Meperidine R= CH₃
Diphenoxylate R = —CH₂CH₂C

Loperamide

4-Anilidopiperidines

Fentanyl

Sufentanil

Alfentanil

Remifentanil

esterase metabolism

Figure 24.9 ◆ 4-Phenylpiperidines and 4-anilidopiperidines.

renal dysfunction, thus cannot eliminate the normeperidine, and those on CYP inducers.[81]

In addition to the CNS toxicity of normeperidine, meperidine has also been found to be a weak serotonin reuptake inhibitor and has been involved in serotonin toxicity reactions when used with monoamine oxidase inhibitors or serotonin reuptake inhibitors.[82] Meperidine is available in tablet, liquid, and injectable forms. The use of meperidine should be limited to those patients that have true allergies to the morphine-type opioids, and patients should be monitored for toxicity.

DIPHENOXYLATE

Diphenoxylate (Fig. 24.9) is a weak opioid agonist and is available combined with atropine (Lomotil) for use as an antidiarrheal agent. At low doses, the opioid effect is minimal,

and the atropine is added to dissuade abuse. One study found both codeine and loperamide to be superior to diphenoxylate for treating chronic diarrhea.[83] The manufacturer has strict dosing guidelines for pediatric use because opioid intoxication and deaths from diphenoxylate have been reported.[84]

LOPERAMIDE

Loperamide (Imodium) is a 4-phenylypiperidine with a methadone-like structure attached to the piperidine nitrogen (Fig. 24.9). It acts as an antidiarrheal by directly binding to the opiate receptors in the gut wall. Loperamide inhibits acetylcholine and prostaglandin release, decreasing peristalsis and fluid secretion thus increasing the GI transit time and reducing the volume of fecal matter.[85,86] Loperamide is
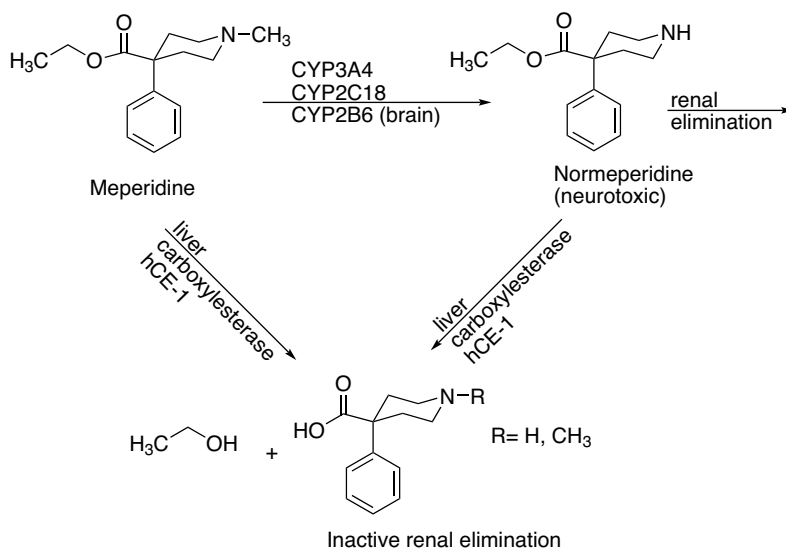

Figure 24.10 ◆ Metabolism of meperidine.

sufficiently lipophilic to cross the blood-brain barrier, yet it displays no CNS-opioid effects. The reason for this is that it is actively pumped out of the brain via the P-glycoprotein pump (MDR1).[87] Knockout mice with the P-glycoprotein pump genetically removed were given radiolabeled loperamide and sacrificed 4 hours later. The [3H]loperamide concentrations were measured and compared with wild-type mice. A 13.5-fold increase in loperamide concentration was found in the brain of the knockouts. In addition, the mice lacking the P-glycoprotein pump displayed pronounced signs of central opiate agonism.[87] Loperamide is available as 2-mg capsules for treatment of acute and chronic diarrhea. Recommended dosage is 4 mg initially, with 2 mg after each loose stool for a maximum of 16 mg/d.

FENTANYL

When the 4-phenyl substituent of meperidine was replaced with a 4-aniline with a nitrogen connection, the potency increased. This led to the development of the 4-anilidopiperidine series of compounds seen in Figure 24.9. Fentanyl (Sublimaze) was the first compound marketed and was found to be almost 500 times more potent than meperidine. 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 (Duragesic). 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. Patches are replaced every 72 hours, and serum concentrations of fentanyl can be maintained relatively constant. A transmucosal lollipop form (Actiq) for breakthrough pain only in opioid tolerant cancer patients is also available.

The SAR studies of the 4-phenylpiperidine analgesics found that the propionamide is the optimal chain length. Adding polar groups to the 4-piperidine carbon (CH_2OCH_3 in sufentanil and alfentanil, $COOCH_3$ in remifentanil) increases potency. The piperidine nitrogen of fentanyl contains a phenethyl substituent that appears to be the correct chain length for optimal potency. Molecular docking studies speculate that the phenethyl group of fentanyl binds to a crevice between TM2 and TM3 of the μ-opioid receptor. This model also aligns the cationic nitrogen of fentanyl with the conserved Asp but leaves the aromatic pocket of the ring unoccupied.[88] Substituting the *N*-phenethyl group with bioisosteres led to the development of fentanyl congeners alfentanil, sufentanil, and remifentanil.

ALFENTANIL

The addition of a methoxy methyl on the 4-piperidine and the substitution of the phenethyl ring for an ethyl-substituted tetrazole-one yielded a compound with about one fourth to one third the potency of fentanyl (Fig. 24.9). Although less potent, it has a quicker onset of action, a shorter duration of action, and thus a better, safety profile for use as an anesthetic adjunct. The piperidine amine has a pK_a of 6.5 compared with fentanyl's pK_a of 8.4. This results in a higher proportion of unionized drug for alfentanil leading to quicker penetration through the blood-brain barrier and thus onset of action.[41] Alfentanil (Alfenta) is available as an IV injection for use as an analgesic adjunct for induction of general anesthesia and to maintain analgesia during general surgical procedures.

SUFENTANIL

Sufentanil (Sufenta) contains the same 4 methoxy methyl substituent as alfentanil along with an isosteric replacement of the phenyl of the phenethyl group with a thiophene ring (Fig. 24.9). The resulting compound is about 7 times more potent than fentanyl with an immediate onset of action and a similar recovery time compared with fentanyl. Sufentanil is only available in an injectable formulation and is also used as an anesthetic adjunct.

REMIFENTANIL

Remifentanil (Ultiva) was designed as a "soft drug." Soft drugs are designed to undergo metabolism quickly and thus have ultrashort durations of action. In place of the ethyl aromatic ring seen on the other piperidine opioids, remifentanil has an ester group (Fig. 24.9). 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).[89] The n-octanol/water partition coefficient of remifentanil is 17.9. The pK_a 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). The ester hydrolysis leads to a quick recovery (5–10 minutes) independent of duration of drug administration, renal, or liver function. The favorable pharmacodynamics of remifentanil have led to its use for induction and maintenance of surgical anesthesia.

Diphenylheptanes

METHADONE

Methadone (Dolophine) (Fig. 24.11) is a synthetic opioid approved for analgesic therapy and for the maintenance and treatment of opioid addiction. Methadone is marketed as the
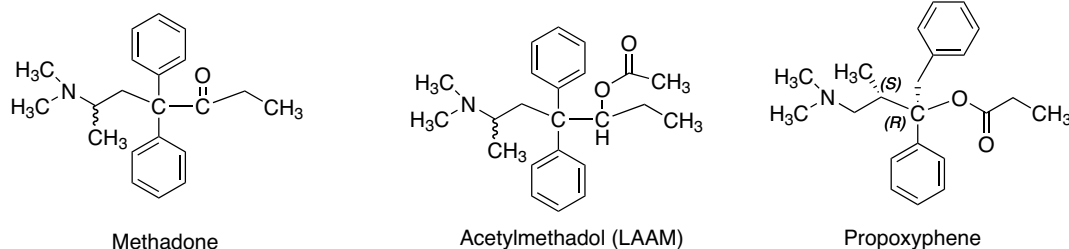

Figure 24.11 ● Diphenylheptanes.

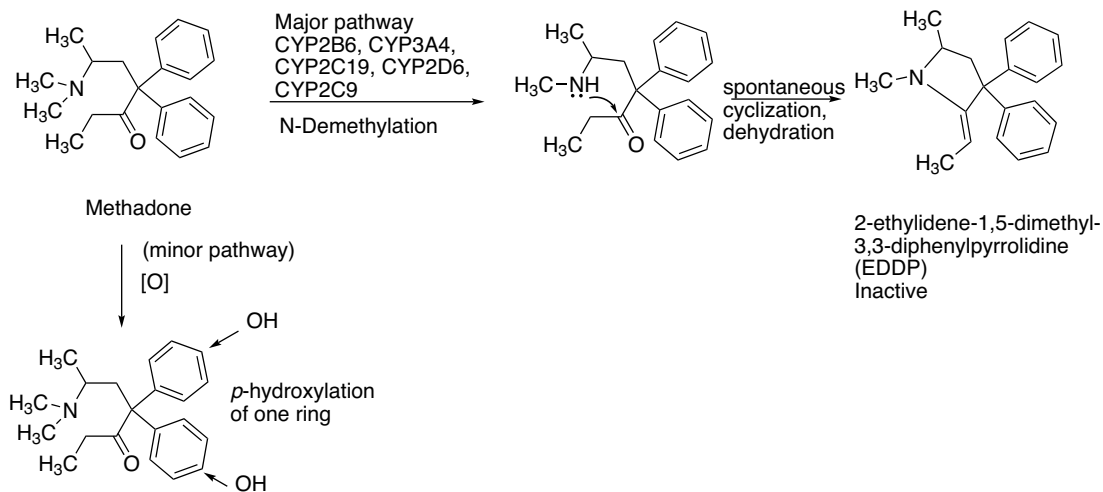Methadone   Acetylmethadol (LAAM)   Propoxyphene

Figure 24.12 ● Metabolism of methadone.

racemate, although the opioid activity resides in the R-enantiomer (7–50 times more potent than the S-enantiomer). Methadone may only be dispensed for the treatment of opioid addiction by a program certified by the Federal Substance Abuse and Mental Health Services Administration. Methadone is a μ-receptor agonist with complex and highly variable pharmacokinetic parameters. Bioavailability following oral administration ranges from 36% to 100%. Steady-state volume of distribution ranges between 1.0 to 8.0 L/kg. Methadone is highly bound to plasma α_1-acid glycoprotein (85%–90%), and $t_{1/2}$ elimination ranged between 8 and 59 hours. The wide range in parameters leads to difficulty when trying to switch from one opioid to methadone for either treatment of pain or substance abuse. Methadone doses and administration schedules need to be individualized and closely monitored. The metabolism and elimination of methadone also lead to much interpatient variability and can be effected by genetic CYP levels, drug–drug interactions, and the pH of the urine (Fig. 24.12).[90] The major metabolic pathway of methadone metabolism is via *N*-demethylation to an unstable product that spontaneously cyclizes to form the inactive 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP). Initial reports concluded that CYP3A4 was the major isoform responsible for this pathway, but more recent reports indicate that CYP2B6 is primarily responsible for the *N*-demethylation.[91–95]

Adverse effects of methadone include all of the standard opioid effects including constricted pupils, respiratory depression, physical dependence, extreme somnolence, coma, cardiac arrest, and death. In addition, QT interval prolongation and torsades de pointes have been reported. The QT interval prolongation reported for methadone was also observed in another diphenylheptane, levomethadyl, or levo-α-acetylmethadol (LAAM) (Orlaam) that was also used to treat opioid addiction. The severe cardiac-related adverse events resulted in the removal of LAAM from the U.S. market in 2003.

PROPOXYPHENE

Most of the structural changes to the methadone skeleton resulted in compounds with decreased opioid potencies, thus most of these compounds, with the exception of LAAM were not developed. Propoxyphene is a derivative of methadone marketed in 1957 as the enantiomerically pure (2S, 3R)-4-(Dimethylamino)-3-methyl-1,2,-diphenyl-2-butanol propionate (ester). It is only about 1/10th as potent as morphine as an analgesic yet retains all the same opioid adverse effects. One propoxyphene 65-mg capsule has the same analgesic effect of 650 mg of aspirin or 1,000 mg of acetaminophen, thus overdoses of propoxyphene can occur if patients do not follow the prescribed dose. Between 1981 and 1999, 2,110 accidental deaths were reported because of propoxyphene. Propoxyphene and all propoxyphene combination products are listed using the Beers criteria as medications to avoid in patients older than 65 years of age.[96] The metabolism of propoxyphene also contributes to the potential dangers of the drug. Propoxyphene is metabolized via *N*-demethylation to form norpropoxyphene. Norpropoxyphene has been shown to build up in cardiac tissues and result in naloxone-insensitive cardiotoxicity.[97] The weak analgesic action and potential risk to the patient have some health practitioners advocating to remove all drugs containing propoxyphene from the market.[98] The hydrochloride salt is marketed as Darvon, the napsylate salt as Darvon-N, both salts are also available combined with acetaminophen (Darvocet, Darvocet-N) and a propoxyphene, aspirin, caffeine product is also available.

Miscellaneous
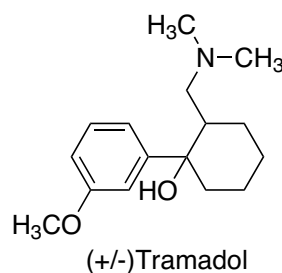
(+/-)Tramadol

TRAMADOL

Tramadol (Ultram) is an analgesic agent with multiple mechanisms of action. It is a weak μ-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 with

the B, D, and E ring removed. The manufacturer states that patients allergic to codeine should not receive tramadol, because they may be at increased risk for anaphylactic reactions.[99] Tramadol is synthesized and marketed as the racemic mixture of two (the [2S, 3S] [-] and the [2R, 3R] [+]) of the four possible enantiomers.[100] The (+) enantiomer is about 30 times more potent than the (−) enantiomer; however, racemic tramadol shows improved tolerability.[101,102] Neurotransmitter reuptake inhibition is also responsible for some of the analgesic activity with the (−) enantiomer primarily responsible for norepinephrine reuptake and the (+) enantiomer responsible for inhibiting serotonin reuptake.[101,103] Like codeine, tramadol is *O*-demethylated via CYP2D6 to a more potent opioid agonist having 200-fold higher affinity for the opioid receptor than the parent compound. Tramadol was initially marketed as nonaddictive, and a 3-year follow up study showed that the abuse potential is very low, but not zero. Most abusers of tramadol have abused opioid drugs in the past.[104] Both enantiomers of tramadol and the major *O*-demethylated metabolite are proconvulsive, and tramadol should not be used in patients with a low-seizure threshold including patients with epilepsy.[101]

Mixed Agonist/Antagonist
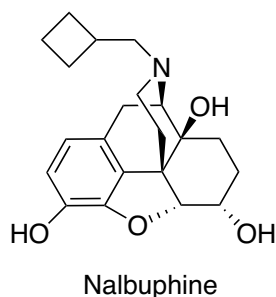
Nalbuphine

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. Although the abuse potential of nalbuphine is low, it is not zero, and increasing reports of diversion and abuse can be found in the literature and the Internet.[105] 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. However, escalating doses above 30 mg does not produce further respiratory depression.[106] The oral bioavailability of nalbuphine is only 12%, and the drug is only marketed as an injectable.[107] Patents have been filed for an oral extended-release formulation, and it is presently in phase II testing.[108] The pharmacologic profile of nalbuphine in animal studies includes agonist activity at the κ-receptor and antagonist activity at the μ-receptor.[109] Clinical studies have shown that nalbuphine, and κ-agonists in general, may have better analgesic activity in female patients compared with male patients.[77] 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.[110] Nalbuphine also may have a role in

treating opioid-induced pruritus, because it can reverse the pruritus without reversing the analgesic effect when used in low doses. Nalbuphine is marketed as an injectable (10 and 20 mg/mL). The usual dose is 10 mg administered subcutaneously, intramuscularly, or intravenously at 3- to 6-hour intervals, with a maximal daily dose of 160 mg.
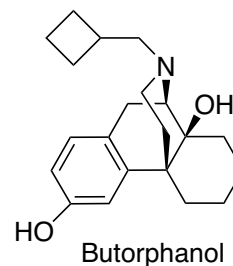
Butorphanol

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 κ-receptor but at the μ-receptor butorphanol is both a partial agonist and an antagonist.[111] The affinity for opioid receptors in vitro is 1:4:25 for the μ-, δ-, and κ-receptors respectively.[111] The high affinity for the κ-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, and administration to humans maintained on high-potency μ-agonists such as morphine may precipitate withdrawal. Butorphanol was found to produce convulsions in morphine-deprived, morphine-dependent monkeys.[112]

The parenteral injection is used for moderate to severe pain associated with orthopedic procedures, obstetric surgery, and burns. The recommended dose is 1 mg IV or 2 mg intramuscular (IM) every 3 to 4 hours as needed. Early studies proposed a "ceiling effect" for butorphanol's antinociception and respiratory depressant effect. More recently, the WHO Expert Committee on Drug Dependence performed a critical review of butorphanol and found no ceiling effect to the respiratory depressant effect of parenteral butorphanol in monkeys and humans.[112] The nasal preparation (Stadol NS) is an effective analgesic for the relief of moderate to severe pain such as migraine attacks, dental, or other surgical pain where an opioid is appropriate. The nasal spray is administered 1 mg (1 spray in one nostril) with an additional spray 60 to 90 minutes later if adequate pain relief is not achieved. Respiratory depression is not an issue with normal doses of the nasal preparation, but CNS side effects are the same as parenteral butorphanol. Increased reports of abuse and addiction of the nasal spray led the FDA to change the product to a Schedule IV drug in 1997.
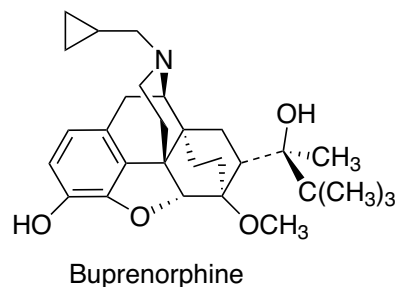
Buprenorphine

BUPRENORPHINE

Buprenorphine is a semisynthetic, highly lipophilic opiate derived from thebaine. Pharmacologically, it is classified as a mixed μ-agonist/antagonist (a partial agonist) and a weak κ-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).[113] 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.[114] 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.[113] 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. In a human study designed to precipitate withdrawal from buprenorphine, a naloxone dose (mean = 35 mg) 100 times the dose usually needed to precipitate withdrawal in methadone-dependent subjects was used. For comparison, approximately 0.3 mg, 4 mg, 4 mg, and 10 mg of naloxone would be required to precipitate withdrawal from heroin, butorphanol, nalbuphine, or pentazocine respectively.[115]

The unique pharmacologic and pharmacokinetic profile of buprenorphine made it a drug of interest for the treatment of opioid dependence. The first study of buprenorphine for this purpose was published in 1978 and confirmed that buprenorphine was an acceptable alternative to methadone for addicts and that it blocked the effects of large single doses of morphine for at least 24 hours.[116] Early clinical studies showed that the oral bioavailability of buprenorphine was low because of intestinal and liver metabolism. Therefore, a sublingual (SL) formulation (Subutex) was developed that would bypass this metabolism. The SL tablet has a bioavailability of 55% but varies widely among individuals.[116] SL buprenorphine is also available combined with naloxone (Suboxone) in sufficient quantity (25% of the buprenorphine dose) to discourage crushing and injecting the SL tablet. SL naloxone is 0% to 10% bioavailable, and it does not change the absorption or action of the SL buprenorphine. Abrupt withdrawal of chronically administered buprenorphine produces mild to moderate opioid withdrawal symptoms peaking between 3 and 5 days following the last buprenorphine dose. These symptoms require no therapeutic intervention. Suboxone and Subutex are the first medications approved for office-based treatment of opioid dependence under the Drug Addiction Treatment Act of 2000. U.S. pharmacists may only dispense these medications when prescribed by physicians that meet special training criteria and are registered with the Center for Substance Abuse Treatment, a component of the Substance Abuse and Mental Health Services Administration. A transdermal buprenorphine patch is available outside the United States for use in chronic pain.[117] This product is currently undergoing phase III clinical trials in the United States.

Buprenorphine is oxidatively metabolized by *N*-dealkylation by hepatic CYP3A4 and to a lesser extent CYP2C8 to the active metabolite norbuprenorphine. Both the parent and major metabolite undergo glucuronidation at the phenolic-3 position. Minor metabolites include hydroxylation of the aromatic ring of buprenorphine and norbuprenorphine at an unspecified site.[118]

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.[119] Currently, Vivitrol is only indicated for the treatment of alcohol dependence. A Cochrane review found insufficient evidence from randomized controlled trials to evaluate its effectiveness for treating opioid dependence.[120] Currently, phase II and phase III clinical trials of an implantable pellet form of naltrexone are being conducted for treating opioid dependence.

The CYP450 system is not involved in naltrexone metabolism. Naltrexone is reduced to the active antagonist 6-β-naltrexol by dihydrodiol dehydrogenase, a cytosolic enzyme. Naltrexone has a black box warning, because it has the potential to cause hepatocellular injury when given in excessive doses.[119]

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
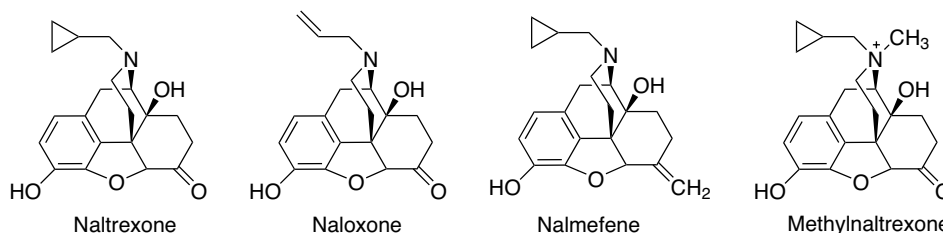

Figure 24.13 ● Opioid antagonists.

Naltrexone   Naloxone   Nalmefene   Methylnaltrexone

retains high binding affinity to the receptor, but no intrinsic activity. It is used to reverse the respiratory depressant effects of opioid overdoses.

Naloxone is administered intravenously with an onset of action within 2 minutes. Because it is competing with the opioid for the receptor sites, the dose and frequency of administration will depend on the amount and type of narcotic being antagonized. Overdoses of long-acting opioids (methadone) may require multiple IV doses of naloxone or continuous infusions. Neonates born to opioid-exposed mothers may be given IV naloxone at birth to reverse the effects of opiates.

Very few metabolism studies on naloxone have been conducted, although the major metabolite found in the urine is naloxone-3-glucuronide.[121,122]

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 but otherwise has a similar pharmacodynamic and metabolic (3-glucuronidation) profile. Nalmefene has higher oral bioavailability (approximately 40%)[123] than naloxone or naltrexone and is currently being investigated as an oral treatment for pathological gambling[124] and alcohol abuse.[125]

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. Relistor was approved in April 2008 to treat opioid-induced constipation in patients receiving palliative care. It is administered as a SC injection once every other day.

⬡ NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

NSAIDs including aspirin and acetaminophen, two of the oldest pain medications, are among the most widely prescribed drugs worldwide for the treatment of rheumatic arthritis and other degenerative inflammatory joint diseases.[126,127] Although NSAIDs are very effective in relieving mild to moderate pains and inflammation, their use is also often associated with many undesirable side effects, including GI irritation and bleeding, platelet dysfunction, kidney damage, and bronchospasm.[126–129]

With the exception of acetaminophen (Tylenol) and the newer "coxibs" drugs, the conventional NSAIDs (also commonly referred to as the *aspirin-like drugs*), share very similar therapeutic and side effect profiles. The conventional NSAIDs exert their therapeutic action by inhibiting two isoforms of cyclooxygenase (COX-1, the constitutive isozyme and COX-2, the inducible isozyme), which is the rate-limiting enzyme responsible for the biosynthesis of the proinflammatory prostaglandins (PGs) such as the PGD_2, PGE_2,

$PGF_{2\alpha}$, and PGI_2 and thereby modulating pain transmission, attenuating inflammation, and reducing fever.[127,128] They also produce their undesirable side effects such as GI bleeding, ulcerations, or renal impairments by blocking the same cyclooxygenases responsible for synthesizing PGs that modulate platelet activity (TXA_2 and PGI_2), gastric acid secretion and cytoprotection (PGE_2 and PGI_2), and renal blood flow (PGE_2).[128–132]

In early 1990, Vane et al.[133,134] hypothesized that the undesirable side effects of the conventional NSAIDs are a result of inhibition of the COX-1 isozyme, whereas the therapeutic effects are related mainly to their inhibitory action on the inducible COX-2 isozyme. This hypothesis has stimulated extensive drug development and hasty market introductions of many selective COX-2 inhibitors, or coxibs drugs.[130,135] However, all of the marketed coxibs drugs except celecoxib (Celebrex), the first FDA-approved COX-2 drug in 1998, have been withdrawn from the market because of the potential risk of a cardiovascular event, including heart attack or stroke, especially in cardiac patients.[136] Recent clinical trials have placed all NSAIDs under surveillance for their potential cardiovascular risk, thus the indiscriminate use of any NSAIDs including naproxen in cardiac patients should be avoided.[135–137]

Mechanism of Action and NSAID-Induced Side Effects

For aspirin and many of the conventional NSAIDs, despite their worldwide use as pain medications for over a century, their mechanism of action was not completely known until 1971 when Vane first identified the cyclooxygenases as their molecular targets.[128] Cyclooxygenase (also known as prostaglandin endoperoxide synthase or PGH synthase) is the rate-limiting enzyme responsible for the biosynthesis of PGs.

PGs are short-lived, lipidlike molecules that play a vital role in modulating many important physiological and pathophysiological functions including pain, inflammation, gastric acid secretion, wound healing, and renal function. They are biosynthesized via a tissue-specific cyclooxygenase pathway (COX-1 or COX-2) either on an as-needed basis (mostly via the COX-1 isozyme) or via the induced and overexpressed COX-2 isozyme because of an injury, inflammation, or infection.[126,129] Some of the salient features of the cyclooxygenase pathway involved in the biosynthesis of these PGs from arachidonic acid (AA) (5,8,11,14-eicosatetraenoic acid), a polyunsaturated fatty acid released from membrane phospholipids by the action of phospholipase A_2, are depicted in Figure 24.14.

As stated earlier, all classes of NSAIDs strongly inhibit prostaglandin synthesis in various tissues, especially at the site of the tissue damage or inflammation. This inhibition occurs at the stage of oxidative cyclization of AA, catalyzed by the rate-limiting enzyme, cyclooxygenase (or PGH synthase), to the hydroperoxy-endoperoxide (prostaglandin G_2, PGG_2) and its subsequent reduction to key intermediate, prostaglandin H_2 (PGH_2) needed for all prostaglandin biosynthesis.[138]

Blockade of PGH_2 production, thus prevents its further conversion, by tissue-specific terminal prostaglandin synthases or isomerases, into different biologically active PGs
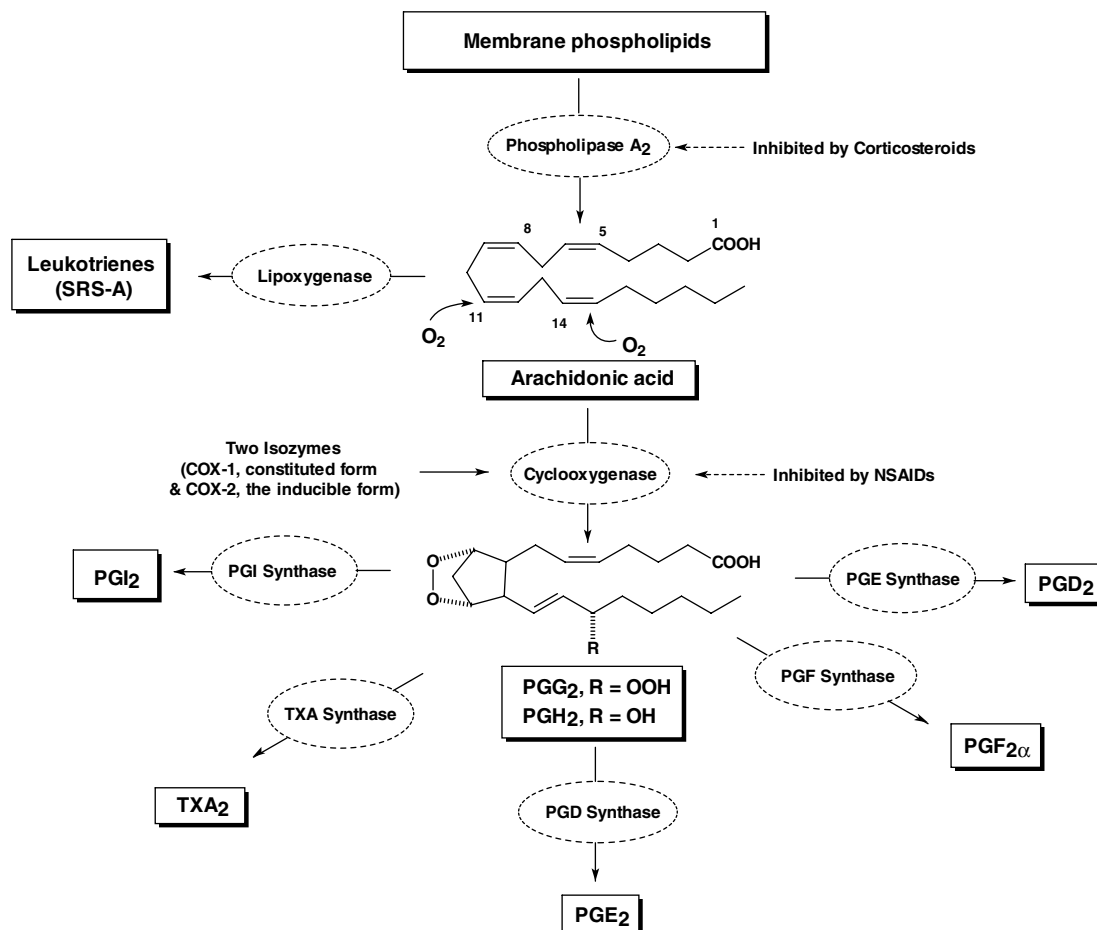
Figure 24.14 ● Conversion of arachidonic acid to prostaglandins.

including PGE_2, PGD_2, $PGF_{2\alpha}$, PGI_2 (prostacyclin), and thromboxane A_2 (TXA_2) (Fig. 24.14).[138,139]

Among the PGs synthesized by the action of either COX-1 or COX-2 isozymes, PGI_2 and PGE_2 made at the site of injury (via COX-2 isozyme in the inflammatory cells such as monocytes and macrophages) and also in the brain, are known to play a dominant role in mediating inflammation and inducing hyperanalgesia.[132] However, their synthesis in the GI tract (via COX-1 isozyme) and in the renal tubules (via COX-1 and COX-2 isozymes), is essential to provide cytoprotective action for restoring the integrity of the stomach lining and maintaining renal functions in an otherwise compromised kidney as a result of constant insult.[132,138] Thus, inhibition of PGE_2 synthesis by the conventional NSAIDs in the parietal cells removes its ability to modulate histamine-mediated release of gastric acid from the parietal cells, whereas blockade of PGI_2 and PGE_2 synthesis in the epithelial cells in the stomach linings also prevents their action on the biosynthesis and release of bicarbonate and mucous gel desperately needed to repair damage resulting from erosion caused by gastric acid and other aggressive factors.[127,129,132] Thus, it should not be surprising to note that NSAID-induced gastric ulcers can only be prevented clinically with coadministration of misoprostol, a stable PGE analog, but not with either the histamine H_2-antagonists, sucralfate, or any proton pump inhibitors such as omeprazole.[127] Furthermore, maintenance of kidney function,

especially in patients with congestive heart failure, liver cirrhosis, or renal insufficiency, is reliant on the action of PGI_2 and PGE_2 to restore normal renal blood flow. Thus, NSAID use (both COX-1 and COX-2 inhibitors) will increase the risk of renal ischemia and therefore is contraindicated in these patients.[129]

The readers should consult Chapter 26 of this text on "Prostanglandins, Leukotrienes, and Other Eicosanoids" for a detailed discussion of PGs, their physiological and pathophysiological functions, and their corresponding PG receptors.

Structure–Activity Relationships of NSAIDs

It is well established that the therapeutic potency of the conventional NSAIDs are highly correlated with their ability to induce upper GI toxicity.[127] But, are all NSAIDs other than coxibs really equally effective in the treatment of pain and inflammation? Some insight might be found by exploring how these chemically diverse classes of drugs bind to their molecular targets (i.e., their selectivity for COX-2 relative to COX-1).[140] Thus, the benefit/risk profile of individual NSAIDs, as reflected by their COX selectivity, may be more clinically relevant for predicting the risk of GI complications. Table 24.1 summarizes a few representative drugs from different NSAID classes with their recommended daily

TABLE 24.1 Comparison of Relative Risk of NSAID-Induced Gastrointestinal Complication

Drug	Trade Name	Dosing Range (Total Daily Dose)	Relative Risk for GI complication	COX-2/COX-1 Selectivity Ratio
Not on NSAIDs or Aspirin			1.0	—
Celecoxib	Celebrex	100–200 mg BID[a] (200–400 mg)	—	0.7
Meloxicam	Mobic	7.5–15 mg daily	—	0.37
Ibuprofen	Advil, Motrin	200–600 mg TID[b] (0.6–1.8 g)	2.9 (1.7–5.0)	0.9
Sulindac	Clinoril	150–200 mg BID (300–600 mg)	2.9 (1.5–5.6)	29 (on active sulfide)
Aspirin	—	325–650 mg QID[c] (1.3–2.6 g)	3,1 (2.0–4.8)	>100
Naproxen	Aleve, Naprosyn	125–500 mg BID (0.5–1.0 g)	3.1 (1.7–5.9)	3.0
Diclofenac	Voltaren	25–50 mg TID (75–150 mg)	3.9 (2.3–6.5)	0.5
Ketoprofen	Orudis	50–100 mg TID (150–300 mg)	5.4 (2.6–11.3)	61
Indomethacin	Indocin	25–50 mg TID (75–150 mg)	6.3 (3.3–12.2)	80
Piroxicam	Feldene	10–20 mg daily	18.0 (8.2–39.6)	3.3

[a]BID, bis in die (twice a day).
[b]TID, ter in die (3 times a day).
[c]QID, quater in die (4 times a day).

dosages and their relative risks of bleeding peptic ulcer complications.[130,141,142]

ENZYMATIC STRUCTURE OF CYCLOOXYGENASES

Cyclooxygenases (COX-1 and COX-2) are heme-containing, membrane-bound proteins that share a high degree of sequence identity and also have very similar active site topography.[138,143–145] Note that the homologous residues of the COX-2 isozyme are numbered in parallel with the similar amino acid residues found at the active site of COX-1 isozyme for easier comparison of their structural differences in the following discussion (i.e., the actual Arg-106 of human COX-2 [hCOX-2] is numbered as Arg-120).[143] The actual hCOX-2 assignments for these residues are provided in parentheses.

Thus, despite their similarity, the active site for hCOX-2 is approximately 20% larger than the COX-1 binding site because of the replacement of Ile-523 in COX-1 with a smaller Val-523 in hCOX-2 (Val-509).[138,144,145] There are a total of 24 amino acid residues lining the largely hydrophobic AA binding site with only one difference between the isozymes (i.e., Ile-523 in COX-1 and Val-509 in hCOX-2). The hCOX-2 isozyme has an additional hydrophilic side pocket accessible for drug binding, extended from the main binding pocket.[143] The size and nature of this hydrophilic side pocket for binding in hCOX-2 is a result of further substitutions Ile-434 and His-513 in COX-1 with a smaller Val-434 (Val 420 in hCOX-2) and a more basic Arg-513 (Arg-499 in hCOX-2).[146] Thus, it is not surprising that this basic amino acid residue in hCOX-2 (Arg-499) may provide an additional binding interaction for selective COX-2 inhibitors such as celecoxib.[144] Although there is only a very limited amount of published data showing how the substrate, AA, binds to cyclooxygenases, the relative positioning of the double bonds in AA at the active site, proposed by Gund and Shen based on the conformational analysis of indomethacin and other conventional NSAIDs, is still currently valid.[147]

Interestingly, Arg-120 (Arg-104 in hCOX-2) is the only positively charged amino acid residue in the COX active site, on one end of the active site as depicted by Luong[144,148] and is responsible for binding, via an ionic interaction, with the carboxylate anion of the substrate (AA) or the conventional NSAIDs. The amino acid residue Tyr-385 (Tyr-371 in hCOX-2) is located on the opposite end of the COX active site and is believed to serve as the catalytic residue for activating molecular oxygen and its initial addition to the Δ^{11}-double bond of the substrate to form PGG_2.[143–148] Furthermore, the presence of an amino acid residue, Ser-530 (Ser-516 in hCOX-2) is believed to be involved only in the irreversible inactivation by aspirin and NSAID action but not contributing to any substrate binding.[143]

BINDING OF NSAID TO CYCLOOXYGENASE

Most NSAIDs possess a free carboxylic acid (COOH) for an ionic interaction with the positively charged arginine residue at the active site of the cyclooxygenases (i.e., Arg-120 in COX-1 or Arg-106 in COX-2 isozymes). This acidic moiety is further linked to an aromatic (or heteroaromatic) ring for binding to either the Δ^5-double-bond or Δ^8-double-bond binding regions, and an additional center of lipophilicity in the form of an alkyl chain (e.g., ibuprofen) or an additional aromatic ring (e.g., indomethacin) for binding to the Δ^{11}-double-bond binding region.

A hypothetical binding model for indomethacin and related analogs to the COX-1 isozyme is shown in Figure 24. 15-A, based on the crystallographic and SAR data found in the literature.[146,149] The suggested orientation and placement of the *N*-*p*-chlorobenzoyl group to the Δ^{11}-double-bond binding region and the indole ring to the Δ^5- and Δ^8-double-bond binding regions is made from assuming that a preferred, lower-energy conformation of indomethacin is essential for its binding to COX isozymes[147], and the fact that this orientation also allows correct positioning of the amide carbonyl oxygen for possible binding interactions to Ser-530 and the 5-methoxy group to Ser-355 at the active site of the enzymes.[146]

Additional support for this model can be obtained from the observation that the (*Z*)-isomer of sulindac, an indene isosteric analog of indomethacin, is much more potent than the corresponding (*E*)-isomer and the fact that replacement of the 5-methoxy group with a fluorine atom on the indole ring further enhances its analgesic action.[145,149] Furthermore, because there is limited space available for

binding around either Leu-384 or Ile-523 (i.e., both around the Δ^{11}-double-bond binding region), it is not surprising to see a facile conversion of the indomethacin from a nonselective COX inhibitor into a potent and highly selective COX-2 inhibitor with just a simple substitution of the *p*-chlorine with a larger bromine atom or by addition of two chlorine atoms to the *o,o'* positions of the *N-p*-chlorobenzoyl group reported by Kalgutkar et al.[150] This observation can explain why a lower risk for GI complications was reported with sulindac than indomethacin, because it requires metabolic activation, via reduction of its bulky sulfoxide moiety into a much smaller methyl sulfide for binding into the Leu-384 pocket. The fact that kidneys possess a high level of the flavin-containing monooxygenases for deactivating the active metabolite of sulindac back into its inactive sulfoxide or sulfone, further provided evidence for this binding model.[149,151]

With this binding model, it is also possible to see why the relative therapeutic potency of the conventional NSAIDs and their ability to induce GI complication is in the order: indomethacin >ketoprofen ~diclofenac >naproxen >ibuprofen. Ibuprofen is the least potent because it can only bind to the Δ^5-double-bond region with additional weak van der Waals interactions to the Δ^{11}-double-bond region. Naproxen is slightly more active than ibuprofen, because its naphthalene ring, isosteric to the indole ring, can interact with both the Δ^5- and Δ^8-double-bond regions. Ketoprofen and diclofenac are slightly less potent than indomethacin because of the absence of an additional ring for binding to either the Δ^5- or the Δ^8-double-bond regions.

BINDING OF CELECOXIB TO COX-2 ISOZYME

The hypothetical binding model for binding of celecoxib, the only selective "coxibs" type COX-2 inhibitor shown on Figure 24.15B, is purely speculative, based only on the crystallographic binding data reported for SC-558 (the *p*-bromophenyl analog of celecoxib) with the murine COX-2 isozyme.[146] However, the celecoxib selectivity toward the COX-2 isozyme is most likely a result of the extension of the sulfonamide moiety into the extra hydrophilic-binding pocket, surrounded by His-90 (His-76 in hCOX-2) and Arg-513 (Arg-499 in hCOX-2). The opening of this additional pocket for binding is the result of the replacement of Ile-523

in the COX-1 with a smaller valine residue (Val 509 in hCOX-2). It should be pointed out that a similar hydrophilic pocket does exist in the COX-1 isozyme, but it is inaccessible because of the bulkier Ile-523 residue that guards the entrance to this side pocket of the COX-1 isozyme (see Fig. 24.15-A).

The COX-2/COX-1 selectivity ratios, estimated by different research groups, can be quite different (e.g., the reported selectivity ratio for celecoxib ranges any where from 0.003–0.7; for piroxicam, the range is 3.3–600). Thus, the selectivity ratios included in Table 24.1, obtained from one such study, is only valid for comparing their differences among these NSAIDs. Furthermore, recent reviews comparing the SAR among different structural classes of COX-2 inhibitors have indicated that there is little or no common pharmacophore required for their COX-2 selectivity, but minor changes within the structure type, in terms of molecular shape, lipophilicity, electronic density, flexibility, polarity, and hydrogen-bonding properties, can all have drastic effects in its COX selectivity.[152,153]

PIROXICAM AND MELOXICAM: THE DIFFERENCE IN THEIR COX SELECTIVITY

Piroxicam and meloxicam have nearly identical structural features but also have at least a ninefold difference in selectivity for meloxicam to COX-2 isozyme and an even larger difference in their relative risks for GI complications (i.e., piroxicam has the highest risk among NSAIDs, whereas meloxicam has very little or no such side effects) (Table 24.1). A closer comparison of their structure (Fig. 24.16), however, reveals no apparent reason for these differences, either in size, lipophilicity, or electronic properties, between the 2-pyridyl group (in piroxicam) and the 5-methyl-2-thiazoyl group (meloxicam) that may alter their ability to bind COX isozymes. It is unlikely that these drastic differences in their COX selectivity, especially the drug-induced GI toxicity, could be due solely to the binding of the parent molecules with such minor changes in their structures. Thus, could the observed differences, especially the differences in drug-induced GI side effects, be attributed to the involvement of an active metabolite of piroxicam and/or meloxicam?

The metabolism of piroxicam to its major active metabolite, 5'-hydroxypiroxicam and meloxicam to its
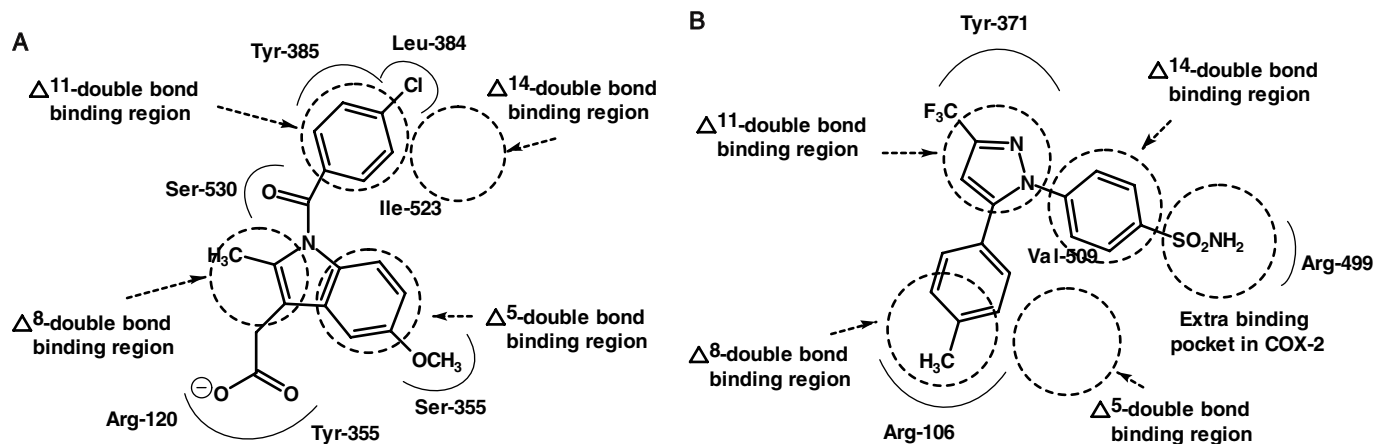

Figure 24.15 ● Hypothetical binding models of indomethacin to COX-1 and Celecoxib to COX-2. **A.** Binding of the conventional NSAID, indomethacin, to the active site of COX-1; **B.** Binding of celecoxib, a selective COX-2 inhibitor to the active site of COX-2 with crystallographic maps suggested by Luong et al. (Flexibility of the NSAID binding site in the structure of human cyclooxygenase-2. Nat. Struct. Biol. 1996;3:927–933)
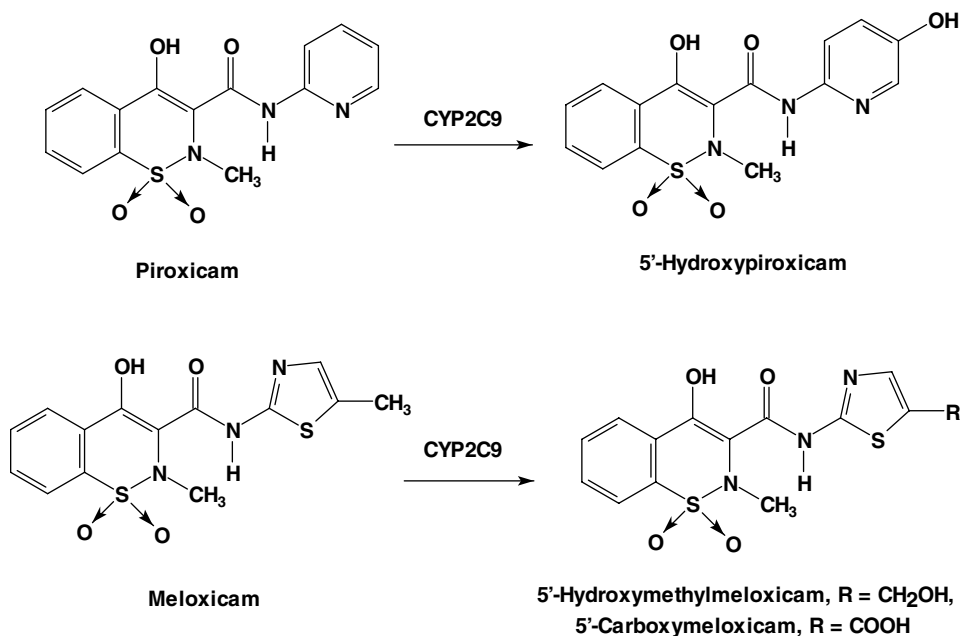
Figure 24.16 ● Metabolism of piroxicam and meloxicam.

5′-hydroxy-methylmeloxicam and 5′-carboxymeloxicam metabolites are shown in Figure 24.16.[154–156] Thus, with the proposed binding interaction of indomethacin described earlier (Fig. 24.15), it is reasonable to assume that the pyridyl group of the piroxicam or the 5′-hydroxy-pyridyl group of its active metabolite will be directed to bind to the Δ^{11}-double-bond binding region (especially the active metabolite caused by an additional H-bonding to the Tyr-385 residue), in a similar manner as the *N-p*-chlorobenzoyl group of the indomethacin. This would also allow the OH group of the acidic enol carboxamide moiety of the piroxicam or its active metabolite to position itself for binding to the Ser-530 residue of the COX-1 isozyme. However, a similar binding interaction of the active metabolites of meloxicam, especially the 5′carboxy metabolite, to the active site of the COX-1 isozyme may not be possible, because it will reorient itself for a stronger ionic interaction with the Arg-120 of the COX-1 isozyme. Thus, they can fit only into the active site of the COX-2 isozyme because the binding of an acidic moiety to Arg-106 in the active site of the COX-2 isozyme is believed to play a lesser role in the inhibitory action of the COX-2 selective inhibitors like celecoxib[152] (i.e., the most acidic moiety, sulfonamide is extended into the side pocket instead of binding to Arg-106).

ASPIRIN AND ITS COX-1 SELECTIVITY

Aspirin covalently modifies COX-1 and hCOX-2 isozymes by acetylating the OH group of Ser-530 in COX-1 and Ser-516 in hCOX-2 isozymes. This is made possible by an ionic attraction between the carboxylate anion of aspirin and the arginine cation of Arg-120 in COX-1 (or Arg-106 in hCOX-2), thereby positioning the acetyl group of aspirin for acetylating the COX isozymes. Even though both COX isozymes are irreversibly acetylated by aspirin, acetylation of Ser-530 totally blocks the accessibility of substrate AA from entering into the active site, whereas an acetylated hCOX-2 is still able to form a significant amount of PGG_2.[143] Thus, aspirin, among all conventional NSAIDs,

exhibits the highest selectivity toward the COX-1 isozyme, especially the COX-1 isozyme present in the platelets.

Aspirin and Salicylic Acid Derivatives

Aspirin and the salicylates were among the first group of NSAIDs introduced into medicine for their use as analgesics to relieve pain and as antipyretics to reduce fever.[157] As early as 1763, the Reverend Edward Stone of Chipping Norton in Oxfordshire, England reported the use of dried willow bark to parishioners suffering from rheumatic fever.[129,158] The active ingredient of willow bark was isolated by Leroux, in 1827 and named salicin, which is a salicylic acid containing glycoside. After these discoveries, Cahours (1844) obtained salicylic acid from oil of wintergreen (methyl salicylate), and Kolbe and Lautermann (1860) prepared it synthetically from phenol. Sodium salicylate was introduced in 1875 by Buss, followed by the introduction of phenyl salicylate by Nencki in 1886. Aspirin, or acetylsalicylic acid, was first prepared in 1853 by Gerhardt but remained obscure until Felix Hoffmann from Bayer discovered its pharmacological activities in 1899. It was tested and introduced into medicine by Dreser (1899), who named it *aspirin* by taking the *a* from acetyl and *spirin*, an old name for salicylic or spiric acid, derived from its natural source of spirea plants.

Most of the salicylic acid drugs (commonly referred to as the salicylates) are either marketed as salts of salicylic acid (sodium, magnesium, bismuth, choline, or triethanolamine) or as ester or amide derivatives (aspirin, salsalate, salicylamide). (Fig. 24.17) Children, between the ages of 3 and 12, who are recovering from flu or chicken pox, should not be taking aspirin or any salicylates because of the perceived risks of a rare disease known as Reye syndrome.[159]

MECHANISM OF ACTION OF SALICYLATES

Salicylates, in general, exert their antipyretic action in febrile patients by increasing heat elimination of the body via the mobilization of water and consequent dilution of
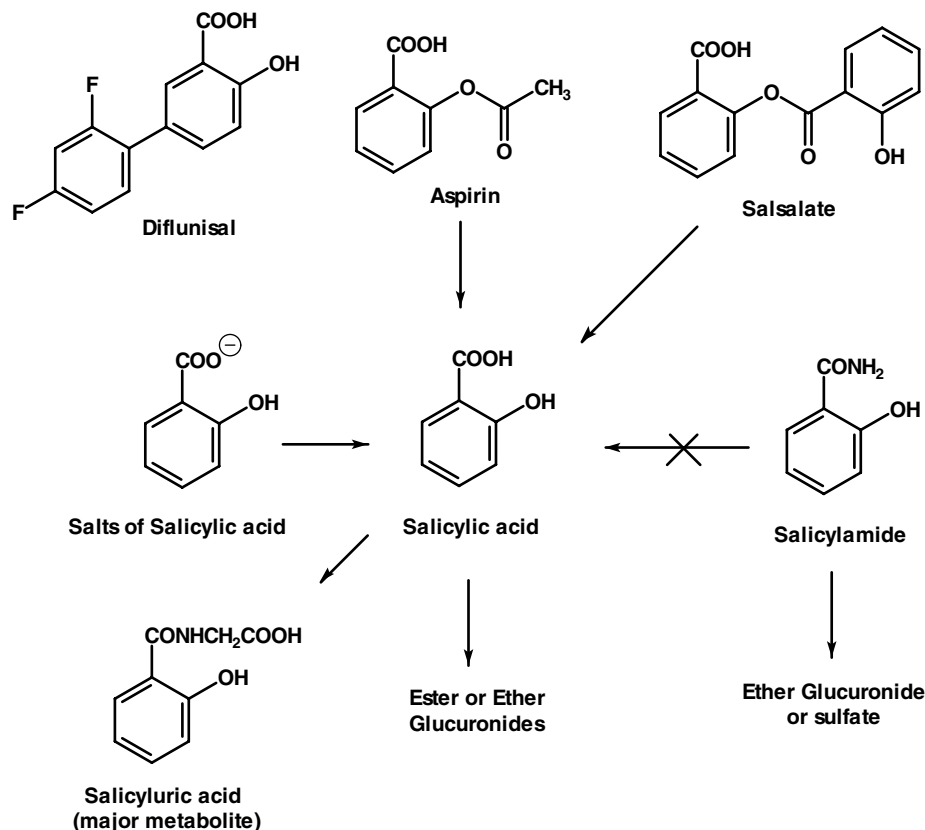
Figure 24.17 ● Salicylates and their metabolism.

the blood. This brings about perspiration, causing cutaneous dilatation. This does not occur with normal temperatures. The antipyretic and analgesic actions are believed to work by inhibiting cyclooxygenase and reducing the levels of PGE_2, a proximal mediator of the febrile response, in the hypothalamic area of the brain that regulates body temperature.[157]

It is well established that a low daily dose of aspirin (75–100 mg or one tablet of baby aspirin) is sufficient to completely block platelet TXA_2 production and its ability to induce platelet aggregation after only 1 week of dosing, thereby preventing the risk of a cardiovascular event, including myocardial infarction and ischemic stroke.[160,161] This antiplatelet action of aspirin is because COX-2 is not expressed in platelets; therefore, aspirin can selectively and irreversibly inhibit platelet TXA_2 production for 8 to 10 days (i.e., until new platelets are formed) at such a low dose (i.e., via the irreversible acetylation of Ser-530 of the COX-1 isozymes discussed earlier). However, the analgesic, antipyretic, and anti-inflammatory action of aspirin is more complex and may involve other mechanisms of action than simply based on its ability to irreversibly inhibit the COX isozymes.[157,162,163] Furthermore, it is worth noting that up to 50% of the oral analgesic dose of aspirin is rapidly deacetylated before it reaches general circulation, and its major active metabolite, salicylic acid, is found to have comparable in vivo antipyretic and anti-inflammatory properties to aspirin but is a very weak inhibitor of cyclooxygenases (i.e., in vitro binding studies).[164] Several possible mechanisms of action have recently been suggested for aspirin and especially the salicylates including blocking the induction of the COX-2 isozyme at the genetic levels,[165] turning off the

nuclear factor-κB-mediated polymorphonuclear leukocyte apoptosis signaling[166,167] or blocking the activation of the mitogen-activated kinase, Erk signaling associated with inflammatory responses.[168]

PHARMACOKINETICS OF SALICYLATES

The salicylates, being acidic in nature, are readily absorbed from the stomach and the small intestine. However, their absorption depends strongly on the pH of the environment, thus coadministration of an antacid or other buffering agents should be avoided because it greatly hinders their absorption and reduces their bioavailability and onset of action. They are also highly bound to plasma proteins, a major source of potential drug interactions with other medications.

Salicylic acid undergoes extensive phase-II metabolism (see Fig. 24.17) and is excreted via the kidneys as the water-soluble glycine conjugate, salicyluric acid, the major metabolite ($>75\%$) or as the corresponding acyl glucuronides (i.e., the ester type, via the COOH) or *O*-glucuronides (i.e., the ether type, via the phenolic OH) ($\sim15\%$). Alkalinization of the urine increases the rate of excretion of the free salicylates.

Aspirin

Aspirin, acetylsalicylic acid (Aspro, Empirin), was introduced into medicine by Dreser in 1899.

Aspirin occurs as white crystals or as a white crystalline powder and must be kept under dry conditions. It is not advisable to keep aspirin products in the kitchen or bathroom cabinets, because aspirin is slowly decomposed into acetic and salicylic acids in the presence of heat and moisture. Several proprietaries (e.g., Bufferin) use compounds such as

sodium bicarbonate, aluminum glycinate, sodium citrate, aluminum hydroxide, or magnesium trisilicate to counteract aspirin's acidic property. One of the better antacids is dihydroxyaluminum aminoacetate. Aspirin is unusually effective when prescribed with calcium glutamate. The more stable, nonirritant calcium acetylsalicylate is formed, and the glutamate portion (glutamic acid) maintains a pH of 3.5 to 5. Practically all salts of aspirin, except those of aluminum and calcium, are unstable for pharmaceutical use. These salts appear to have fewer undesirable side effects and induce analgesia faster than aspirin. A timed release preparation of aspirin is available. It does not appear to offer any advantages over aspirin, except for bedtime dosage.

Aspirin is used as an analgesic for minor aches and pains and as an antipyretic to reduce fever. Although higher doses of aspirin can also be used to treat inflammation, its use is often associated with many unwanted side effects including ulcers, stomach bleeding, and tinnitus. A low dosage form of aspirin, 81 mg, equivalent to the dose recommended for infants (the "baby aspirin"), is recommended as a daily dose for individuals who are at even a low cardiovascular risk. Several large studies have found that this low dose of aspirin reduces the number of heart attacks and thrombotic strokes.[160,161] Other salicylates and NSAIDs have not shown similar effects. In fact, a recent report indicated using ibuprofen can interfere with aspirin's cardiovascular benefits, and they should not be taken within 12 hours of each other.[169]

Aspirin and other potent NSAIDs (except salicylates) are also known to precipitate asthma attacks and other hypersensitivity reactions in up to 10% of the patients who have any type of respiratory problems.[170] This hypersensitivity reaction is believed to occur as a result of shifting the substrate, AA from the inhibited cyclooxygenase pathway to the lipoxygenase pathway (see Fig. 24.14), therefore resulting in overproduction of anaphylactic leukotrienes because of the blockade of the cyclooxygenase pathway by aspirin and other potent NSAIDs.[171]

Salsalate

Salsalate, salicylsalicylic acid (Amigesic, Disalcid, Salflex), is the ester formed between two salicylic acid molecules. It is rapidly hydrolyzed to salicylic acid following its absorption. It reportedly causes less gastric irritation than aspirin, because it is relatively insoluble in the stomach and is not absorbed until it reaches the small intestine.

Diflunisal

Diflunisal (Dolobid), is a longer acting and more potent drug than aspirin because of its hydrophobic, 2,4-difluorophenyl group attached to the 5-position of the salicyclic acid. In a large-scale comparative study with aspirin, it was also better tolerated with less GI complications than aspirin.[172] It is marketed in tablet form for treating mild to moderate postoperative pain as well as RA and OA.

Diflunisal is highly protein bound. Its metabolism is subject to a dose-dependent, saturable, and capacity-limited glucuronide formation.[173] This unusual pharmacokinetic profile is a result of an enterohepatic circulation and the reabsorption of 65% of the drug and its glucuronides, followed by cleavage of its unstable, acyl glucuronide back to the active drug. Thus, diflunisal usage in patients with renal impairment should be closely monitored.

Sodium Salicylate

Sodium salicylate may be prepared by the reaction, in aqueous solution, by adding equal molar ratio of salicylic acid and sodium bicarbonate; evaporating to dryness yields the white salt. In solution, particularly in the presence of sodium bicarbonate, the salt will darken on standing. This is the salt of choice for salicylate medication and usually is administered with sodium bicarbonate to lessen gastric distress, or it is administered in enteric coated tablets. However, the use of sodium bicarbonate is ill advised, because it decreases the plasma levels of salicylate and increases the excretion of free salicylate in the urine.

Sodium salicylate, even though not as potent as aspirin for pain relief, also has less GI irritation and is useful for patients who are hypersensitive to aspirin.

OTHER SALTS OF SALICYLIC ACID

Sodium thiosalicylate (Rexolate) is the sulfur or thio analog of sodium salicylate. It is more soluble and better absorbed, thus allowing lower dosages. It is recommended for gout, rheumatic fever, and muscular pains, but it is available only for injection.

Magnesium salicylate (Mobidin, Magan) is a sodium-free salicylate preparation for use when sodium intake is restricted. It is claimed to produce less GI irritation.

Choline salicylate (Arthropan) is extremely soluble in water and is available as a flavored liquid. It is claimed to be absorbed more rapidly than aspirin, giving faster peak blood levels. It is used when salicylates are indicated. It is also available in combination with magnesium salicylate (Trilisate, Tricosal, Trisalcid, CMT) for the relief of minor to moderate pains and fever associated with arthritis, bursitis, tendinitis, menstrual cramps, and others.

Salicylamide

Salicylamide, o-hydroxybenzamide, is a derivative of salicylic acid that is fairly stable to heat, light, and moisture. It reportedly exerts a moderately quicker and deeper analgesic effect than aspirin because of quicker CNS penetration. Its metabolism differs from aspirin, because it is not metabolized to salicylic acid but rather excreted exclusively as the ether glucuronide or sulfate.[174] Thus, as a result of lack of contribution from salicylic acid, it has a lower analgesic and antipyretic efficacy than that of aspirin. However, it can be used in place of salicylates for patients with a demonstrated sensitivity to salicylates. It is also excreted much more rapidly than other salicylates, which accounts for its lower toxicity. It is available in several nonprescription products, in combination with acetaminophen and phenyltoloxamine (e.g., Rid-A Pain compound, Cetazone T, Dolorex, Ed-Flex, Lobac) or with aspirin, acetaminophen, and caffeine (e.g., Saleto, BC Powder).

The Conventional Nonselective Cyclooxygenase Inhibitors

With the removal of rofecoxib (Vioxx) from the market and the concern of cardiovascular risk associated with celecoxib (Celebrex), the conventional NSAIDs, being more potent than aspirin and related salicylates, once again become the drug of choice for the treatment of RA and other inflammatory diseases.[130] The conventional NSAIDs vary considerably in terms of their selective inhibitory action for COX-2 relative to COX-1 isozymes and also their relative

drug-induced toxicities discussed earlier in this text. Although several drugs in this class are available OTC, they are no safer than prescription medications with regard to their drug-induced GI liability.[127] The conventional NSAIDs, as a group, are highly protein bound and exhibit both pharmacokinetic as well as pharmacodynamic interactions with many drugs, especially anticoagulants, diuretics, lithium, and other arthritis medications.

For the purpose of comparing their SAR, toxicity, and metabolic biotransformations, the conventional NSAIDs are further divided into several chemical classes.

ARYL- AND HETEROARYLACETIC ACIDS

This group of NSAIDs has received the most intensive attention for new clinical candidates. As a group, they show high analgesic potency in addition to their potent anti-inflammatory activity, needed for treating inflammatory diseases. Among the members of this class shown in Figure 24.18, ketorolac, indomethacin, and tolmetin have the highest risk of GI complications because of their higher affinity for the COX-1 isozymes, whereas etodolac has the lowest risk because of its COX-2 selective inhibitory action. Both sulindac and nabumetone are prodrugs that require activation, and therefore have lower risk of causing GI irritation than indomethacin.[130]

Indomethacin
From the time of its introduction in 1965, indomethacin (Indocin) has been widely used as an analgesic to relieve inflammatory pain associated with RA, OA and ankylosing spondylitis, and, to a lesser extent, in gout. Although both its analgesic and anti-inflammatory activities are well established, its use is often limited because of frequent GI distress and potential drug interactions, especially with warfarin furosemide, and lithium (i.e., it elevates blood levels of lithium as a result of reducing renal blood flow and therefore increases lithium toxicities).

Following oral administration, indomethacin is rapidly absorbed and is 90% protein bound at therapeutic plasma concentrations.[175] The drug has a biological half-life of about 5 to 10 hours and a plasma clearance of 1 to 2.5 ml/kg per minute. It is metabolized to its inactive, *O*-desmethyl, *N*-deschlorobenzoyl-, and *O*-desmethyl, *N*-deschlorobenzoylindomethacin metabolites.[175]

Sulindac
Sulindac, (*Z*)-5-fluoro-2-methyl-1-([*p*-(methylsulfinyl)phenyl]methylene)-1*H*-indene-3-acetic acid (Clinoril), is an NSAID prodrug that contains a chiral sulfoxide moiety but is marketed as the racemate because it undergoes in vivo reduction by the hepatic enzymes into its achiral, active metabolite, methyl sulfide that exhibits potent and nonselective COX inhibition similar to indomethacin.[151]

The parent sulfoxide has a plasma half-life of 8 hours, and the active methyl sulfide metabolite is 16.4 hours. The more polar and inactive sulfoxide is virtually the only form excreted into the renal tubules, thus sulindac is believed to have minimal nephrotoxicity associated with indomethacin.[176] The long half-life of sulindac is caused by the extensive enterohepatic circulation and reactivation of the inactive sulfoxide excreted. Coadministration of aspirin is contraindicated because it considerably reduces the sulfide blood levels. Careful monitoring of patients with a history of ulcers is recommended. Gastric bleeding, nausea, diarrhea, dizziness, and other adverse effects have been noted with sulindac, but with a lower frequency than with aspirin. Sulindac is recommended for RA, OA, and ankylosing spondylitis.

Tolmetin
Tolmetin sodium (Tolectin), is an arylacetic acid derivative with a pyrrole as the aryl group. This drug is well absorbed

Tolmetin, R$_1$=CH$_3$, R$_2$=H
Zomipirac, R$_1$=Cl, R$_2$=CH$_3$

Indomethacin   **Sulindac**   **Ketorolac**

Etodolac

Bromfenac, R$_1$=OH, R$_2$=Br
Amfenac,   R$_1$=OH, R$_2$=H
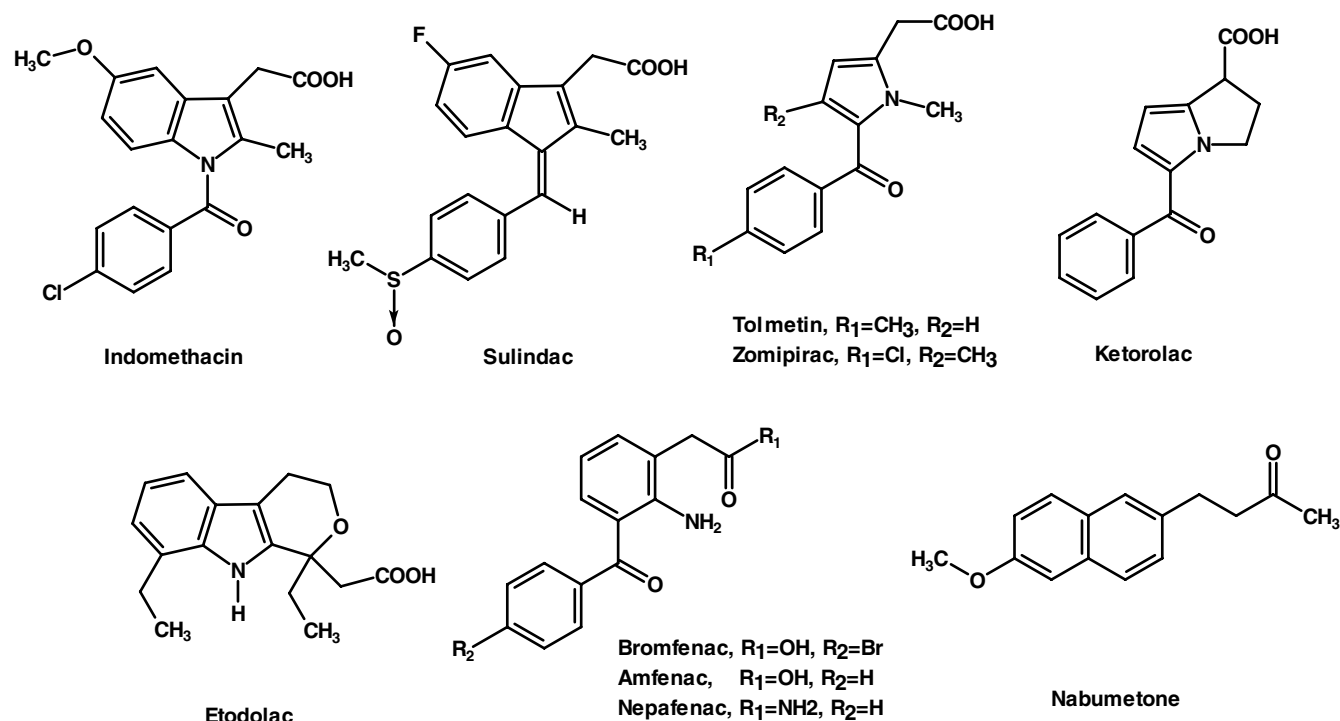**Nepafenac, R$_1$=NH2, R$_2$=H**

Nabumetone

Figure 24.18 ● Aryl- and heteroarylacetic acid derivatives.

and has a relatively short plasma half-life (1 hour). It is recommended for use in the management of acute and chronic RA. Its efficacy is similar to aspirin and indomethacin, but with less frequency of the adverse effects and tinnitus associated with aspirin. It does not potentiate coumarin-like drugs nor alter the blood levels of sulfonylureas or insulin. However, tolmetin, and especially its closely related drug, zomepirac (i.e., with a *p*-chlorobenzoyl group and an additional methyl group on the pyrrole ring), can produce a rare but fatal anaphylactic reaction because of irreversible binding of their unstable acyl glucuronides.[177] Zomepirac was withdrawn from market because it is eliminated only via the ester-type, acyl glucuronide.[178] It is possible that tolmetin is less toxic in this regard because it undergoes additional hepatic benzylic hydroxylation via its *p*-methyl group and is excreted as its stable ether glucuronide.

Ketorolac
Ketorolac tromethamine (Toradol), marketed as a mixture of (R)- and (S)-ketorolac enantiomers, is a potent NSAID analgesic indicated for the treatment of moderately severe, acute pain. It should be noted that the pharmacokinetic disposition of ketorolac in humans is subject to marked enantioselectivity. Thus, it is important to monitor the individual blood levels so an accurate assessment of its therapeutic action can be made correctly.[179] However, it should be noted that, being one of the conventional NSAIDs with highest risk of GI complications, its administration should not exceed 5 days.

Nabumetone
Nabumetone (Relafen), a nonacidic NSAID prodrug, is classified as an arylacetic acid, because it undergoes rapid hepatic metabolism to its active metabolite, 6-methoxy-2-naphthylacetic acid.[180] Similar to the other arylacetic acid drugs, it is used in short- or long-term management of RA and OA. Being nonacidic, it does not produce significant primary insult to the GI mucosa lining and also has no effect on prostaglandin synthesis in gastric mucosa, thus producing minimum secondary GI damage when compared with other conventional NSAIDs.

Etodolac
Etodolac (Lodine, Ultradol), a chiral, COX-2 selective NSAID drug that is marketed as a racemate, possesses an indole ring as the aryl portion of this group of NSAID drugs. It shares many similar properties of this group and is indicated for short- and long-term management of pain and OA.

Similar to ketorolac, etodolac exhibits several unique enantioselective pharmacokinetic properties.[181] For example, the "inactive" (R)-enantiomer has approximately a 10-fold higher plasma concentration than the active (S)-enantiomer. Furthermore, the active (S)-enantiomer is less protein bound than its (R)-enantiomer and therefore has a very large volume of distribution. It is well absorbed with an elimination half-life of 6 to 8 hours. Etodolac is extensively metabolized into three major inactive metabolites, 6-hydroxy etodolac (via aromatic hydroxylation), 7-hydroxy-etodolac (via aromatic hydroxylation), and 8-(1′-hydroxylethyl) etodolac (via benzylic hydroxylation), which are eliminated as the corresponding ether glucuronides.[182] Its unstable, acyl glucuronide, however, is subject to enterohepatic circulation and reactivation to the parent drug, similar to other NSAIDS in this class.

In a recent study comparing its gastric safety profile with those of meloxicam, diclofenac, and indomethacin, etodolac

was found to have the highest safety index among these NSAIDs in arthritic rats.[183] Thus, etodolac is an example of a COX-2 selective drug with a much better safety profile among the first generation of NSAIDs developed through the traditional route of using only animal model studies. Its selective COX-2 inhibitory action, which was not realized until much later, explains its much lower risk of the GI side effects among first-generation NSAIDs.

Amfenac, Bromfenac, and Nepafenac
Amfenac (Fenazox), its amide prodrug, nepafenac (Nevanac), and the related analog, bromofenac, are amphoteric because of the presence of an additional aromatic amine group. They are less likely to be absorbed into the general circulation. They are approved for use as topical ocular anti-inflammatory agents for the treatment of postoperative ocular pain, inflammation, and posterior segment edema.[184] The only observed side effects of these drugs are all related to tissues around the eye including abnormal ocular sensation, eye redness and irritation, burning and stinging, and conjunctival or cornea edema.

ARYL- AND HETEROARYLPROPANOIC ACIDS

These are perhaps the most widely used drugs worldwide because three members of this class, ibuprofen, naproxen, and ketoprofen, are now available without a prescription (Fig. 24.19). Their indiscriminate use, however, by the general public without a doctor's prescription, has resulted in an increased incidence of complications in adolescents, including acute and chronic renal failure.[185]

All of the members of this class (except oxaprozin) contain a chiral carbon in the α-position of the acetic acid side chain. Even though most are marketed as racemates, only the (S)-enantiomer was found to have any inhibitory activity against the COX isozymes. Thus, the (S)-enantiomer is believed to be solely responsible for the observed therapeutic action as well as the drug-induced GI side effects and nephrotoxicity. Furthermore, in most cases, the inactive (R)-enantiomer is epimerized in vivo, via the 2-arylpropionyl coenzyme-A epimerase to its active (S)-enantiomer.[186]

Ibuprofen
Ibuprofen, 2-(4-isobutylphenyl)propionic acid (Motrin, Advil, Nuprin), was introduced into clinical practice following extensive clinical trials. It appears to have comparable efficacy to aspirin in the treatment of RA, but with a lower incidence of side effects. It has also been approved for use in the treatment of primary dysmenorrhea, which is thought to be caused by an excessive concentration of PGs and endoperoxides.[187] However, a recent study indicates that concurrent use of ibuprofen and aspirin may actually interfere with the cardioprotective effects of aspirin, at least in patients with established cardiovascular disease.[169] This is because ibuprofen can reversibly bind to the platelet COX-1 isozymes, thereby blocking aspirin's ability to inhibit TXA_2 synthesis in platelets.

Naproxen
Naproxen (Naprosyn, Anaprox), marketed as the (S)-enantiomer, is well absorbed after oral administration, giving peak plasma levels in 2 to 4 hours and a half-life of 13 hours. Naproxen is highly protein bound and displaces most protein-bound drugs. It is recommended for use in RA, OA,
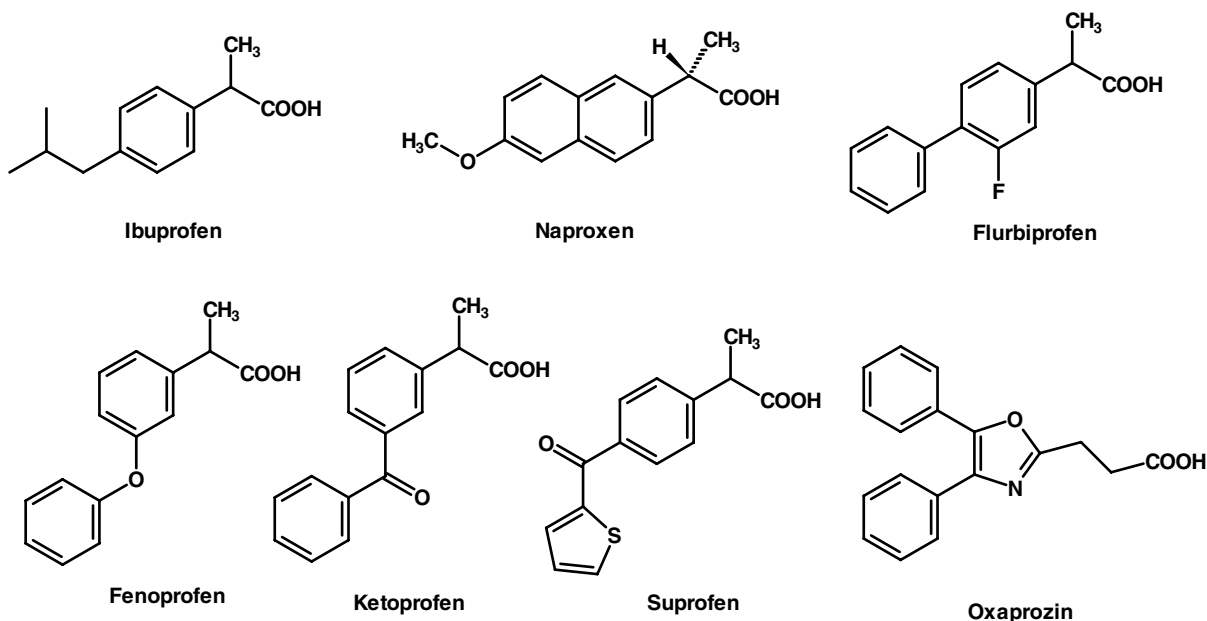
Figure 24.19 ● Aryl- and heteroarylpropionic acids.

acute gouty inflammation, and in primary dysmenorrhea. It shows good analgesic activity (i.e., 400 mg is comparable to 75–150 mg of oral meperidine and superior to 65 mg of propoxyphene and 325 mg of aspirin plus 30 mg of codeine). It is also available OTC as 200-mg tablets (Aleve).

Fenoprofen
Fenoprofen (Nalfon), is rapidly absorbed orally, reaches peak plasma levels within 2 hours, and has a short plasma half-life (3 hours). It is highly protein bound, just like the other NSAIDs, thus caution is needed when it is used concurrently with other medications including hydantoins, sulfonamides, and sulfonylureas. It is recommended for RA and OA, at an oral dose of 300 to 600 mg for 3 or 4 times per day, but not exceeding 3 g/d to avoid any serious side effects. It should be noted that in a comparison study of all NSAIDs, fenoprofen is the one that has been most closely associated with a rare acute interstitial nephritis.[188] For mild to moderate pain relief, the recommended dosage is 200 mg given every 4 to 6 hours, as needed.

Ketoprofen and Suprofen
Ketoprofen (Orudis, Rhodis) and suprofen (Profenal) are closely related to fenoprofen in their structures, properties, and indications. Even though ketoprofen has been approved for OTC use (Orudis KT, Actron), its GI side effects are similar to indomethacin (Table 24.1), and therefore its use should be closely monitored, especially in patients with GI or renal problems.

Flurbiprofen
Flurbiprofen (Ansaid, Ocufen, Froben), is another drug in this class indicated for both acute and long-term management of RA and OA but with a more complex mechanism of action. Unlike the other drugs in this class, it does not undergo chiral inversion (i.e., the conversion of the "inactive" [R]-enantiomer to the active, [S]-enantiomer). Similar to aspirin and other salicylates, both flurbiprofen enantiomers block COX-2 induction as well as inhibiting the nuclear factor-κB-mediated polymorphonuclear leukocyte apoptosis

signaling[189]; therefore, both enantiomers are believed to contribute equally to its overall anti-inflammatory action.

(R)-flurbiprofen is actually a strong clinical candidate for the treatment of Alzheimer disease, because it has been shown to reduce Aβ42 production by human cells.[190]

Oxaprozin
Oxaprozin, 4,5-diphenyl-2-oxazolepropionic acid (Daypro), differs from the other members of this group in being an arylpropionic acid derivative. It shares the same properties and side effects of other members in this group. It is indicated for the short- and long-term management of OA and RA, administered as a once-daily dose of 600- to 1,200-mg dose because of its long duration of action.[191]

N-ARYLANTHRANILIC ACIDS (FENAMATES) AND STRUCTURALLY RELATED ANALOGS

This class of NSAIDs shares one common structural feature that is not present in the other classes discussed earlier. Unlike other classes discussed earlier, the second aromatic ring in this class is connected to the main aromatic carboxylic acid containing ring through a secondary amine linkage (rather than carbonyl group or other nonbasic linker) and at the ortho position rather than at the meta or para position (see their structures in Fig. 24.20). As a result of this structural feature, this class of NSAIDs appears to have a lower risk of causing GI irritation. Recent crystallographic evidence suggests that diclofenac binds to COX isozymes in an inverted conformation with its carboxylate group hydrogen-bonded to Tyr-385 and Ser-530.[192] This finding provides a reason why diclofenac and especially its related analog, lumicoxib, have much greater selectivity toward COX-2 isozymes.

Mefenamic Acid
Mefenamic acid (Ponstel, Ponstan) is one of the oldest NSAIDs, introduced into the market in 1967 for mild to moderate pain and for primary dysmenorrhea. It is rapidly
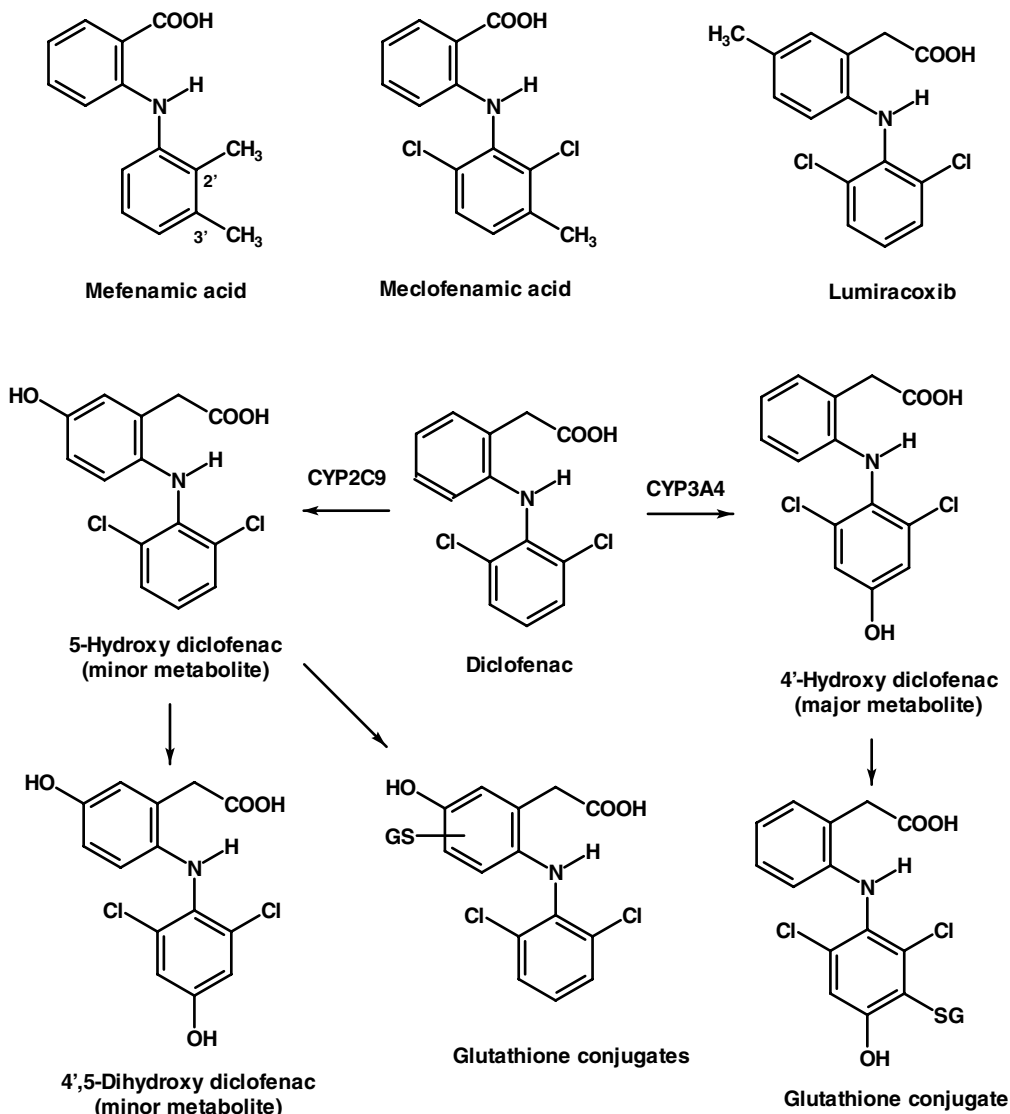
Figure 24.20 ● Fenamates and metabolism of diclofenac.

absorbed with peak plasma levels occurring 2 to 4 hours after oral administration. It undergoes hepatic benzylic hydroxylation of its 3′methyl group regioselectively into two inactive metabolites, 3′-hydroxymethylmefenamic acid and the 3′carboxylate metabolite (via further oxidation of the benzylic alcohol group). The parent drugs and these metabolites are conjugated with glucuronic acid and excreted primarily in the urine. Thus, although patients with known liver deficiency may be given lower doses, it is contraindicated in patients with preexisting renal dysfunction.

Common side effects associated with its use include diarrhea, drowsiness, and headache. The possibility of blood disorders has also prompted limitation of its administration to 7 days. It is not recommended for children or during pregnancy.

Meclofenamate

Meclofenamate sodium (Meclomen) is available for use in the treatment of acute and chronic RA, OA, and primary dysmenorrhea. It is metabolized in a similar manner to mefenamic acid discussed above, thus a similar restriction is also applied to meclofenamate. The most significant side effects are GI, including diarrhea.

Diclofenac and Lumiracoxib

Diclofenac sodium (Voltaren), is indicated for short- and long-term treatment of RA, OA, and ankylosing spondylitis. The potassium salt (Cataflam), which is faster acting, is indicated for the management of acute pain and primary dysmenorrhea. Diclofenac was first marketed in Japan in 1974 but was not approved for its use in the United States until 1989, perhaps because of concerns about its hepatotoxicity. Diclofenac is also available in combination with misoprostol (Arthrotec).

Unlike the other NSAIDs, diclofenac appears to be more hepatotoxic and, in rare cases, can cause severe liver damage. This idiosyncratic hepatotoxicity has been attributed to the formation of reactive benzoquinone imines, similar to acetaminophen, which will be discussed later.[193] Diclofenac undergoes hepatic CYP2C9/3A4 catalyzed aromatic hydroxylations to give 4′-Hydroxy-diclofenac as its major inactive metabolite (~30%) and 5-hydroxy- and 4′5-dihydroxy-diclofenac as its minor metabolites (Fig. 24.20). These hydroxylated metabolites are excreted, normally, such as their glucuronides. Similar to that of acetaminophen, both the 4′ and 5-hydroxylated metabolites can be further activated to their reactive quinone imines (not shown in the

Figure), which are normally deactivated by glutathione, the host defensive mechanism, to its inactive glutathione conjugates shown in Figure 24.20. Thus, it is reasonable to assume that patients with low levels of glutathione are more susceptible to diclofenac toxicity, and their use in these patients should be avoided.

Lumiracoxib (Prexige), one of the most COX-2 selective inhibitors marketed in Australia (2004), the United Kingdom (2005), and the United States (2007), was the mainstay of therapy for OA, RA, and acute pain. It differs from diclofenac with an additional methyl substituted onto the 5-position of phenylacetic acid ring. It is extensively metabolized by CYP2C9, just like diclofenac, into three major inactive metabolites, 5-carboxy, 4′-hydroxy, and 4′-hydroxy-5-carboxy derivative, through the oxidation of the 5-methyl group and hydroxylation of the dichloroaromatic ring.[194] Although no evidence of formation of potentially reactive metabolites was reported, the 4′-hydroxy derivatives are the major inactive metabolites eliminated (as the glucuronides), so it is not surprising to learn that lumiracoxib was withdrawn from market in October, 2007 because of several cases of serious adverse liver reactions to the drug, including two deaths and two liver transplants. Thus, patients with low glutathione levels or glucuronyl transferase activity as a result of drug interactions or aging are susceptible for forming reactive metabolites that are not found with healthy individuals, the subjects used in the original metabolic study.[194]

OXICAMS

Oxicams, are first-generation NSAIDs that lack a free carboxylic acid side chain but with an acidic enolic 1,2-benzothiazine carboxamide ring (see Fig. 24.16). Only two members of this class, piroxicam and meloxicam, are available in the United States for the management of inflammatory arthritis. Tenoxicam (Mobiflex), a close isosteric analog of piroxicam (i.e., with a 1,2-thiazole ring replacing the benzene ring fused to the thiazine ring), is available in Canada but with a pharmacodynamic and pharmacokinetic profile similar to piroxicam. As discussed earlier, piroxicam and meloxicam have very different affinities for the COX isozymes, and therefore exhibit very different risks for GI complications.

Piroxicam
Piroxicam (Feldene) is the most widely used oxicam because of its once-daily dosing schedule. It is well absorbed after oral administration and has a plasma half-life of 50 hours, thus requiring a dose of only 20 to 30 mg once daily.[195] It undergoes extensive hepatic metabolism, catalyzed by CYP2C9 to give 5-hydroxypiroxicam as its major metabolite (See Fig. 24.16).[154] Several piroxicam prodrugs have been synthesized via derivatization of the enol alcohol group (amipiroxicam, droxicam, and pivoxicam) to reduce piroxicam-induced GI irritation.[195]

Meloxicam
Meloxicam (Mobic) is a selective COX-2 inhibitor among oxicams indicated for use in RA and OA. It also has a relatively long half-life of 15 to 20 hours and has a much lower rate of serious GI side effects and a lower than average risk of nephropathy when compared with other conventional NSAIDs.[196] The recommended dose is 7.5 mg once daily with a maximum of 15 mg/d. Meloxicam is metabolized in humans mainly by CYP2C9 (with a minor contribution via

CYP3A4) to 5′-hydroxymethylmeloxicam and 5′carboxymeloxicam (see Fig. 24.16).[156]

In large-scale comparative trials, meloxicam was found to be at least as effective as most conventional NSAIDs in the treatment of rheumatic disease or postoperative pain, but has demonstrated a more favorable GI tolerability profile.[158]

The Selective COX-2 Inhibitors

As stated earlier, the development and hasty market introduction of the first selective coxibs drugs, celecoxib (Celebrex), and rofecoxib (Vioxx) in 1999, was based on Vane's[133,134] hypothesis that blocking an inducible COX-2 isozyme retains all of the therapeutic effects but none of the side effects of the conventional NSAIDs. Shortly after their market introduction, the results of a preliminary Vioxx gastrointestinal outcomes research (VIGOR) trial was reported in 2000 that raised concern and much debate on the cardiovascular safety of all selective COX-2 inhibitors.[135–137,197] Several additional coxibs drugs including valdecoxib (Bextra), etoricoxib (Arcoxia), and parecoxib sodium (Dynastat), were introduced into the worldwide market during 2002. The potential cardiovascular risk was not taken seriously until late 2004 when rofecoxib (Vioxx) was voluntary withdrawn from the worldwide market, based on an additional risk assessment from a 3-year randomized, placebo-controlled, double-blind clinical trial.[197] To date, all but the least potent of COX-2 drugs, celecoxib (Celebrex), have been removed from the worldwide market, therefore depriving an otherwise, rational choice of pain medications, especially for arthritic patients who are at higher risk of serious GI complications.[137]

An overexpression of COX-2 was found in multiple cancer types, especially in colorectal cancer,[198,199] thus future roles of the selective COX-2 inhibitors may be realized in the chemoprevention of cancers and other inflammatory degenerative diseases. The reader should consult several excellent reviews on these latest developments.[200–202]

CELECOXIB

Celecoxib (Celebrex) was the first selective COX-2 inhibitor drug introduced into the market in 1998 for use in the treatment of RA, OA, acute pain, and menstrual pain. The real benefit is that it has caused fewer GI complications when compared with other conventional NSAIDs. It has also been approved for reducing the number of adenomatous colorectal polyps in familial adenomatous polyposis (FAP).

Celecoxib is well absorbed and undergoes rapid oxidative metabolism via CYP2C9 to give its inactive metabolites (Fig. 24.21).[203] Thus, a potential drug interaction exists between celecoxib and warfarin because the active isomer of warfarin is primarily degraded by CYP2C9.

The Analgesic Antipyretics: Acetaminophen (Paracetamol) and Related Analogs

From a historical perspective, acetaminophen (paracetamol) and the related analgesic antipyretic drugs such as acetanilide, antipyrine, and dipyrone were introduced into the market about the same time as aspirin and the other salicylates (i.e., acetanilide, 1886; phenacetin, 1887; and acetaminophen, 1893).[204] They were once the most widely used analgesic
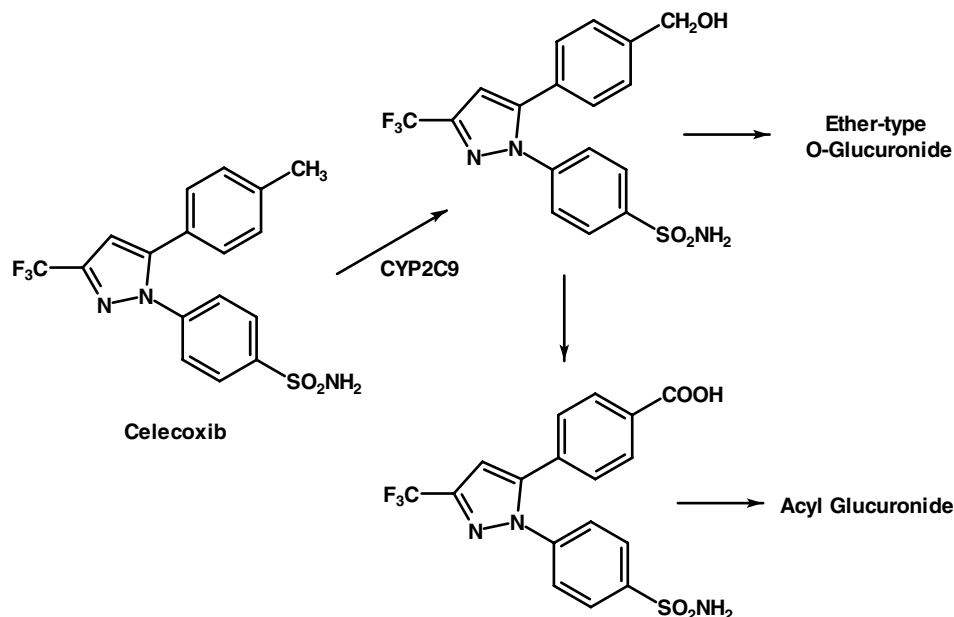
Figure 24.21 ● Metabolic biotransformation of celecoxib.

antipyretics for relieving pain and reducing fever because, unlike aspirin and salicylates, they do not cause ulceration or increase bleeding time.[204] Among these agents, phenacetin was once a very popular analgesic antipyretic drug, more so than acetaminophen, because it was perceived to be safer than acetaminophen toward the stomach (i.e., less acidic in nature). Its use was continued until the late 1970s, even though Brodie and Axelrod had already reported in 1949 that acetaminophen was the active metabolite of acetanilide and phenacetin.[205] In their elegant studies, acetanilide was found to undergo hepatic metabolism (i.e., via an aromatic hydroxylation) to acetaminophen, whereas only a small amount of the drug was hydrolyzed to give aniline, which can be further *N*-hydroxylated to phenylhydroxylamine, the compound believed to be responsible for acetanilide toxicity because of methemoglobin formation. Phenacetin, on the other hand, was found to undergo mostly *O*-dealkylation to acetaminophen, whereas a small amount was converted by deacetylation to *p*-phenetidine, also responsible for methemoglobin formation.

Phenacetin only fell out of favor around 1980 when it was found to cause renal and urinary tract tumors in experimental animal models.[206] Because of the toxicity described above, both acetanilide and phenacetin are now no longer available, thus acetaminophen is the only drug in this class that is still widely used worldwide because it is a safer and better tolerated pain medication.

MECHANISM OF ACTION: ACETAMINOPHEN AND THE COX-3 PUZZLE

Acetaminophen and other analgesic antipyretics have similar analgesic and antipyretic efficacies to the conventional NSAIDs such as aspirin, ibuprofen, or diclofenac. However, unlike the conventional NSAIDs, they lack the antiplatelet effects of aspirin or the GI side effects associated with NSAIDs. Acetaminophen also has little or no anti-inflammatory properties.[207–209] Although it has been in use for nearly a century, the mechanism of action of acetaminophen and related analgesic antipyretics remains unknown, but it is generally assumed that they work centrally by blocking a brain-specific enzyme, perhaps a COX-3 isozyme, responsible for the biosynthesis of prostaglandin.[210]

In 2002, Simmons et al.,[211] through cloning studies, identified a distinct variant of the canine COX-1 isozyme found only in the canine brain, which was designated as the COX-3 isozyme and hypothesized this isozyme as the target for acetaminophen and related analgesic-antipyretic drugs because this isozyme was selectively inhibited by acetaminophen, phenacetin, antipyrine, and dipyrone. This hypothesis was further supported by the findings that acetaminophen produces analgesia and induces hypothermia centrally and that both of these actions are accompanied by a dose-dependent reduction of brain PGE_2 levels that is not observed with diclofenac, a conventional NSAID.[209] In addition, the peripheral levels of PGE_2/PGI_2 levels were reduced only by diclofenac but not by acetaminophen.[210] Moreover, acetaminophen-induced hypothermia was reduced in COX-1 but not COX-2 gene-deleted animal studies.[209,212] These observations appear to provide additional support for hypothesis that the analgesia and hypothermia of acetaminophen are indeed mediated by inhibition of a distinct COX isozyme present only in the brain. However, most of the recent studies focusing on finding this elusive human COX-3 isozyme have not been successful.[207,213,214] Moreover, a similar COX-1 variant identified and expressed in humans (this isozyme was designated as COX-1b) was not inhibited by acetaminophen even though it is active in catalyzing PGH_2 synthesis in the brain. Thus, although the COX-3 isozyme may indeed be the molecular target responsible for acetaminophen action in canines, its role in humans is still unproven.[213,214]

In a recent commentary, Aronoff et al.[208] suggested an alternative target (mechanism) by which acetaminophen (APAP) blocks the cyclooxygenase action. Their hypothesis is based on the fact that acetaminophen acts as a reducing co-substrate, thus actively competing with PGG_2 for its conversion to PGH_2, catalyzed by the peroxidase (POX) action of COX enzymes. Figure 24.22 summarizes some of the key mechanism of COX's action suggested by Aronoff et al.[208] and includes the additional hypothesis suggested by Gram and Scott[215] that acetaminophen acts by depleting the stores
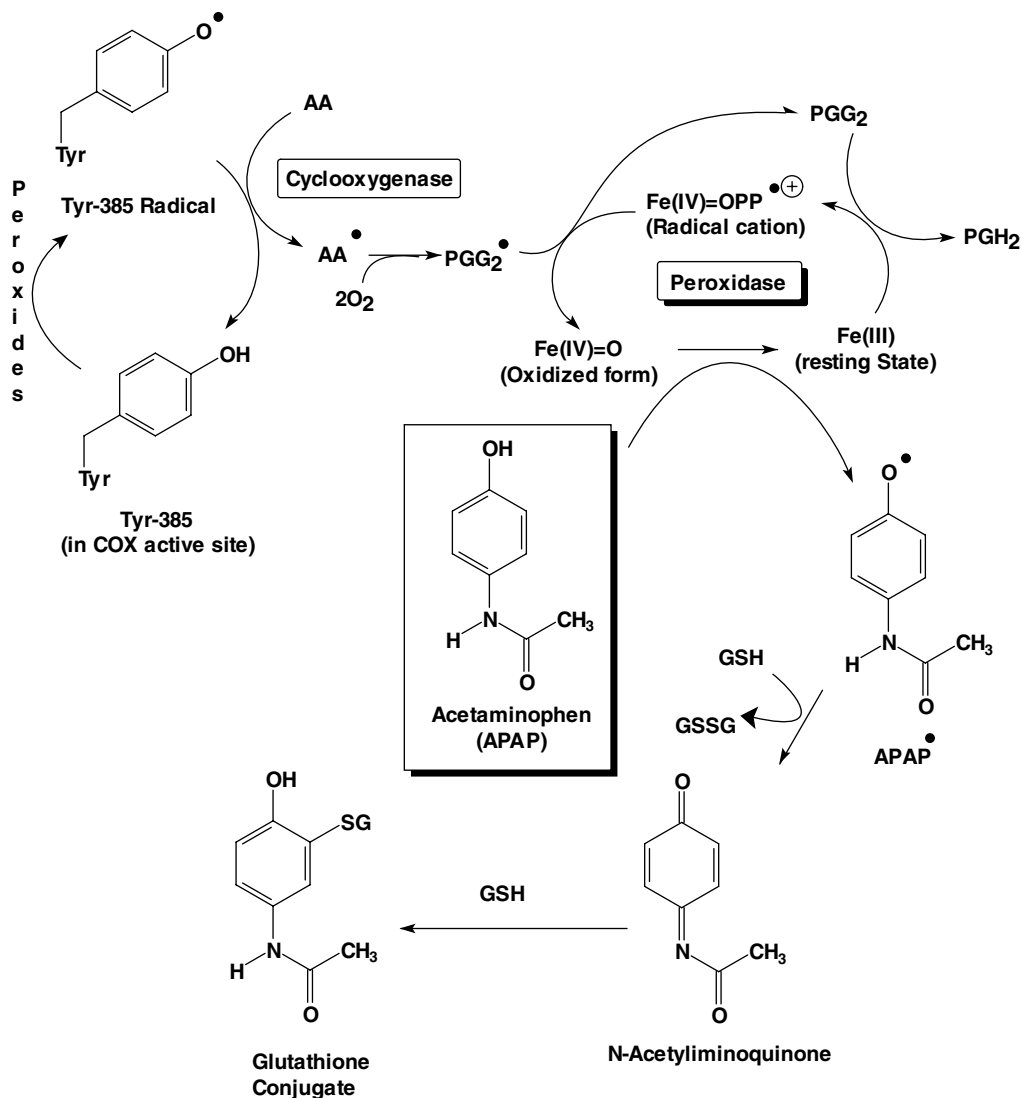
Figure 24.22 ● Mechanism of action of acetaminophen on PGH_2 synthesis.

of glutathione (GSH), which is a known cofactor for PGE synthase. Thus, with this illustration, it is now possible to see why acetaminophen's action depends on the level of peroxide generated in solution (i.e., PGG_2 and other lipid peroxides, generated by the lipoxygenase pathway), and its effectiveness varies with COX activity.[207] At low peroxide concentrations, acetaminophen can compete effectively with the electron transfer mechanism between the Tyr-385 residue and the heme radical, which generates the tyrosine radical in the active site of COX enzymes for the production of PGG_2, it also prevents the regeneration of Fe (IV) (APAP causes the formation of Fe (III), thus ↓ activity of POX), a process that is essential for starting a new POX cycle as shown in Fig. 24.22. However, acetaminophen is ineffective during inflammation because the higher concentration of PGG_2 or other peroxides, produced in the inflamed cells as a consequence of induction of the COX-2 isozyme and lipoxygenase, can overcome the acetaminophen inhibition by degrading acetaminophen in the synovial fluids as depicted in Figure 24.22 (i.e., conversion of APAP to its inactive glutathione conjugate shown).

This mechanism would also explain the recent findings that acetaminophen, unlike NSAIDs, cannot inhibit COX activity in broken cells, and the observation that only the inhibitory effects of acetaminophen, not indomethacin or diclofenac, were abolished by increasing intracellular oxidation conditions with the addition of cell-permeable hydroperoxide, t-butyl-OOH.[216] This hypothesis would also provide an additional reason why depletion of glutathione is the main cause of acetaminophen toxicity discussed under the next section. In summary, APAP does not compete with AA for the binding site on the COX enzyme. Its mechanism of action is via inhibiting the peroxidase activity of the COX enzyme.

TOXICITY IN ACETAMINOPHEN AND PHENACETIN

Acetaminophen and phenacetin can be metabolized to reactive hepatotoxic and renal toxic metabolites by various mechanisms.[217] Readers should consult a more detailed discussion in the drug metabolism chapter of this text. Figure 24.23 summarizes only the salient features for the purpose of discussing phenacetin/acetaminophen-induced liver and renal toxicities.

Acetanilide and phenacetin are hydroxylated or *O*-dealkylated, respectively via CYP1A2 to their active metabolite, acetaminophen.[206] In healthy individuals, acetaminophen is primarily eliminated as its *O*-sulfates and *O*-glucuronides, with only a small amount of the
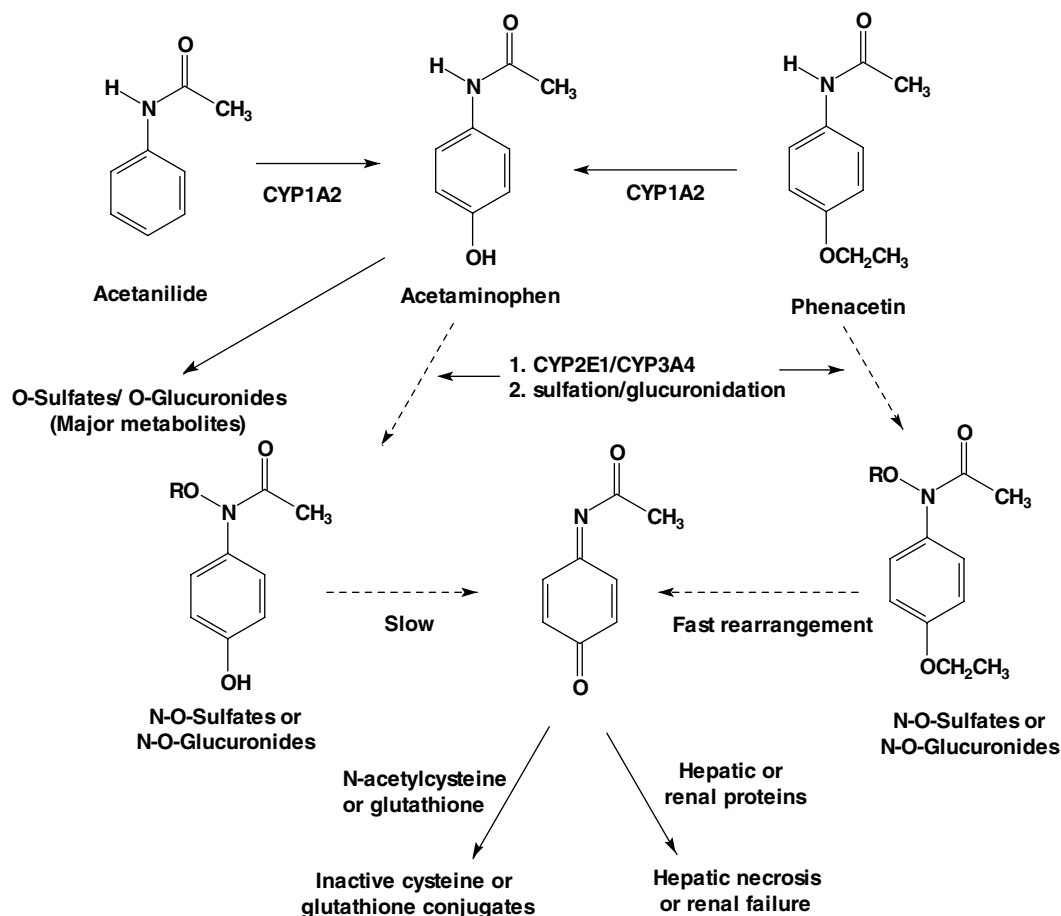
Figure 24.23 ● Metabolic activation of acetaminophen and phenacetin.

N-hydroxylated metabolite (via CYP2E1/CYP3A4 isozymes), which can be sulfated or glucuronidated.[217,218] Small amounts of these *O*-sulfates, if accumulated in liver or renal tubules, can slowly rearrange to form the reactive *N*-acetyliminoquinone metabolites, shown in Figure 24.23. However, these reactive metabolites, once formed, are immediately deactivated by glutathione, the body's defense mechanism for detoxifying reactive metabolites.

In contrast, a similar *N*-*O*-sulfate of phenacetin will immediately rearrange to this reactive metabolite, *N*-acetyliminoquinone, whereas the corresponding *N*-*O*-glucuronide can also be slowly converted to this reactive metabolite.[217] Thus, it is not surprising that acetaminophen is a much safer drug than phenacetin with regard to their relative toxicities (i.e., with occasional use, most of acetaminophen is eliminated as its *O*-sulfates and *O*-glucuronides). However, it should be pointed out that acetaminophen-induced toxicity can be greatly increased by concurrent use of alcoholic beverages, especially in alcoholic individuals. This is because both CYP2E1 and CYP3A4 isozymes are induced by alcohol consumption.[218] Moreover, heavy caffeine use, together with alcohol, would further increase the risk of alcohol-mediated acetaminophen hepatotoxicity.[219] *N*-acetylcysteine is typically given as an antidote to treat possible acetaminophen poisoning even before plasma levels of acetaminophen are determined. Similar to glutathione, it deactivates the *N*-acetyliminoquinone metabolite before it changes to covalently bind cellular proteins (Fig. 24.23).

ACETAMINOPHEN

Acetaminophen (also known as paracetamol, APAP), a well established analgesic/antipyretic drug, is frequently used by itself OTC (Panado, Tempra, Tylenol) or in combination with codeine (Tylenol 3), hydrocodone (Vicodin), or oxycodone (Percocet) for the treatment of mild to moderate pain and to reduce fever. It is available in several nonprescription forms and is also marketed in combination with aspirin and caffeine (Excedrin, Vanquish).

Unlike aspirin or ibuprofen, acetaminophen is well tolerated with a low incidence of GI side effects. It also has good oral bioavailability, a fast onset and a plasma half-life of approximately 2 hours after dosing. Although it is a relatively safe pain medication, several precautions should be recognized, including not exceeding the recommended maximum dosage of 4 g/d. A lower daily dose of less than 2 g/d is required in patients who are chronic alcoholics or have renal complications.[220]

DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

RA is one of the most common chronic, inflammatory autoimmune diseases, affecting approximately 1% of the world's adult population.[221] It is characterized by persistent inflammation of the synovial lining of the joints that causes

pain, swelling, and stiffness of the upper and lower extremities. RA, if left untreated, can lead to permanent joint cartilage and bone damage that eventually results in disability and a significant impairment of quality of life.[221,222] A typical treatment of RA may involve a combination of physical and drug therapy including aspirin, other NSAIDs, or glucocorticoids initially to provide symptomatic relief of pain and swelling, and one or more of the disease-modifying antirheumatic drugs (DMARDs) to slow down the underlying disease progression and to limit further joint damage.[223,224]

DMARDs, sometime also referred to as the "slow-acting antirheumatic drugs," include a diverse class of synthetic drugs such as methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, azathioprine, organic gold compounds, or immunobiologicals useful for treating the persistent inflammatory conditions associated with RA. DMARDs have very different mechanisms of action that allow physicians to individualize treatment strategies to slow down the clinical and radiographic progression of RA,

even though it takes between 6 weeks to 6 months to fully realize any of their therapeutic effects.[222,224–226]

In this chapter, only a few of the commonly used synthetic DMARDs are covered to exemplify different treatment strategies. Readers interested in more detailed information regarding the structure–activity and mechanism of actions of these DMARDs and related analogs should consult other chapters in antimalarials (chloroquine and hydroxychloroquine), anti-infectives (sulfasalazine), and antineoplastic agents (methotrexate, azathioprine, leflunomide). Recent advances in new disease-modifying anti-tumor necrosis factor agents such as etanercept, adalimumab, and infliximab are covered in a separate chapter entitled "Immunobiologicals" in this text as well as in several recent reviews.[221,222,225–227]

Synthetic Disease-Modifying Antirheumatic Drugs

Figure 24.24 contains the chemical structures of the DMARDs and their metabolites mentioned in this section.
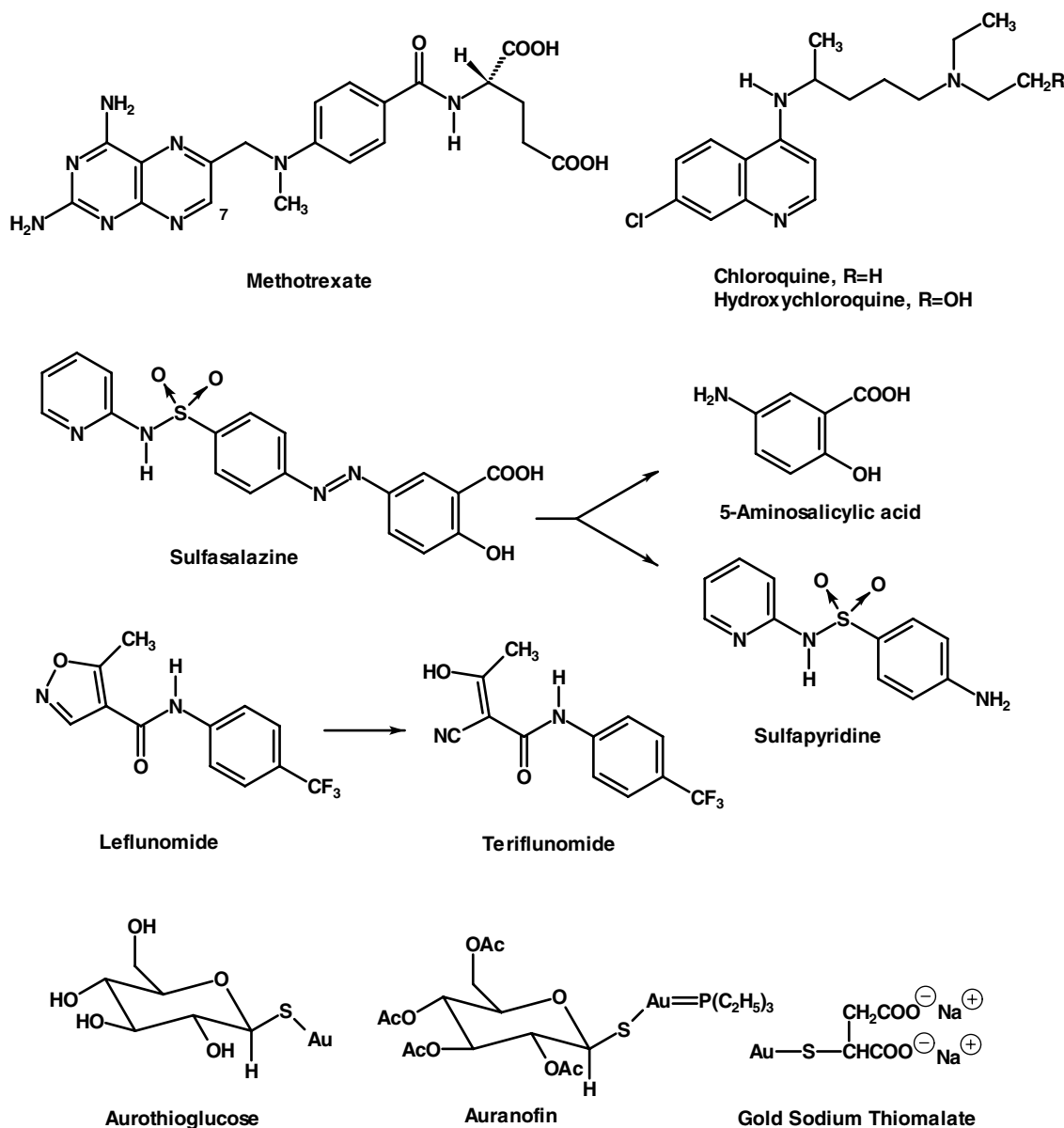

Figure 24.24 ● Disease-modifying antirheumatic drugs.

Readers should consult other chapters in this text for additional information regarding these drugs.

METHOTREXATE

Methotrexate (MTX, Rheumatrex), an antifolate drug used in cancer treatment, has also been used in the disease management of RA since the 1950s. Because of its quicker therapeutic onset among all DMARDs and its demonstrated efficacy, tolerability, and low cost, MTX has been the first-line therapy for RA patients who are not responsive to NSAIDs alone.[224,226,227] Recent findings have indicated that other DMARDs should only be used for patients who are refractory to MTX.[224,226]

At least four anti-inflammatory mechanisms of action have been suggested for MTX's ability to slow down RA disease progression.[222,228] First, MTX, being a folate antagonist, prevents antigen-dependent T-cell proliferation by blocking de novo pyrimidine biosynthesis, via a reversible inhibition of dihydrofolate reductase.[228] It also inhibits folate-mediated production of spermine and spermidine in synovial tissue. These polyamines are believed to be the toxic compounds responsible for causing tissue injury in RA. MTX can also reduce intracellular glutathione concentration, thereby altering the cellular redox state that suppresses the formation of reactive oxygen radicals in synovial tissue. Lastly, MTX, similar to sulfasalazine, infliximab, and IL-4, can also inhibit osteoclastogenesis (i.e., bone erosion) in patients with RA, by modulating the interaction of the receptor activator of nuclear factor κB, its ligand, and osteoprotegrin.[229]

Methotrexate is usually administered in a once-weekly dose in the range of 15 to 17.5 mg. Although it has good oral bioavailability ($\sim$70%), it is more efficacious via IM or SC routes, because its uptake from the GI tract is mediated by a saturable transporter, known as the reduced folate carrier-1.[225,228] Most of the administered dose of methotrexate is eliminated in the urine via its 7-hydroxymethotrexate metabolite.

Common side effects of MTX include nausea, anemia, and GI mucosa ulcerations. The use of folinic acid supplement to reduce MTX-mediated toxicities, however, is not recommended for RA patients, because high dosages of folinic acid will compete with MTX for the same transporter for absorption from the GI tract and for cellular uptake. Thus, it may also reverse MTX's anti-inflammatory effects in RA patients.[228] Moreover, MTX can cause birth defects in unborn children, thus it is contraindicated for women during pregnancy.

HYDROXYCHLOROQUINE AND CHLOROQUINE

Hydroxychloroquine (Plaquenil, Quineprox) is an older drug used to treat malaria that is used more often in the treatment of RA and lupus erythematosus. Although its mechanism of action is not known, its ability to interfere with lipopolysaccharide-induced TNF-α gene expression, thereby preventing TNF-α release from mononuclear phagocytes has been suggested.[230] It is usually taken orally with food or milk to prevent stomach irritation and is preferred over chloroquine because of a lower incidence of ocular toxicity. However, long-term use of this medication requires periodic retinal examinations because of rare but potentially preventable retinopathy associated with its use, especially at a daily dose over 6.5 mg/kg.[231]

SULFASALAZINE

Sulfasalazine (Azufidine) is an azo prodrug that is reduced by the bacterium present in the lower intestine to its active metabolites, sulfapyridine and 5-aminosalicylic acid (5-ASA or mesalamine). It has been used for the treatment of RA or ankylosing spondylitis, and inflammatory bowel diseases (IBDs) such as ulcerative colitis and Crohn disease.

It is generally agreed that the therapeutic effects of sulfasalazine in treating IBDs are due mainly through its active metabolite, 5-ASA. 5-ASA is believed to work, via similar mechanisms of action to the salicylates discussed earlier, by blocking prostaglandin synthesis in the lower intestine.[165–168] On the other hand, because 5-ASA is completely ionized and very little of this metabolite can enter into systemic circulation, the antirheumatic effects of sulfasalazine have been attributed to its other active metabolite, sulfapyridine.[232] In a more recent study, sulfasalazine and sulfapyridine were found to inhibit 5-aminoimidazole-4-carboxamide ribonucleotide transformylase, an enzyme involved in de novo purine biosynthesis.[233] Sulfasalazine also inhibits neutrophil function, reduces immunoglobulin levels, and interferes with T-cell function via suppression of NF-κB activation.[233] Furthermore, like methotrexate, sulfasalazine has also been shown to inhibit osteoclastogenesis, thereby preventing bone erosion in arthritic patients.[229,234]

It should be pointed out that approximately one third of the patients treated long term with sulfasalazine discontinued the drug because of dose-related adverse effects including nausea, dyspepsia, vomiting, headache, rash, gastric distress, especially in patients on a daily dosage of greater than 4 g (or a serum sulfapyridine levels above 50 mg/mL).

LEFLUNOMIDE

Leflunomide (Arava), an isoxazole prodrug, is an orally active DMARD marketed in 1998 for the treatment of RA. It is well absorbed and extensively metabolized in vivo to its active metabolite, 2-cyano-3-hydroxy-2-buteneamide (teriflunomide), resulting from a reductive ring opening of the isoxazole ring (see Fig. 24.24). Unlike MTX, teriflunomide blocks T-cell proliferation by inhibiting dihydroorotate dehydrogenase, the rate-limiting enzyme in the de novo biosynthesis of pyrimidine that is believed to be responsible for the immunosuppressive properties of leflunomide.[235,236] For this reason, it is not surprising that leflunomide has a very comparable therapeutic efficacy to the first-line DMARD, MTX as shown in several extended open clinical trials.[237] However, even though leflunomide is well tolerated like MTX, several cases of toxic neuropathy have been observed during its use, thus careful monitoring of the patient's neurological status during treatment is mandatory.[237] Like MTX, leflunomide is contraindicated in pregnancy or in women considering pregnancy.

THE GOLD COMPOUNDS

The gold salts, gold sodium thiomalate (Aurolate), aurothioglucose (Solganal), and auranofin (Ridaura) have been known to be effective in the treatment of RA for more than 60 years.[225] Recent findings have suggested that, auranofin, an orally active gold salt, inhibits Nuclear factor κB (NF-κB) activation TLR4-mediated activation of the signaling pathway that leads to the blocking of the formation of

inflammatory gene product such as cytokines and COX-2.[238] Because zinc is a necessary component of NF-κB, a transcription factor that is critical for its DNA binding, Yang et al.[239] suggested that auranofin works by oxidizing the zinc containing thiolate anions of NF-κB into a disulfide, thus abolishing the DNA binding requirement for gene expression. However, few patients take gold salt therapy for longer than 5 years because of their toxicities including mucocutaneous reactions, proteinuria, and cytopenias.[222]

OTHER DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

Other DMARDs that can be used in the treatment of RA include penicillamine (Cuprimine), a metabolite of penicillin, or the cytotoxic anticancer drugs such as chlorambucil (Leukeran), Azathioprine (Imuran) and cycophosphamide (Cytoxan), or the other immunosuppressants such as cyclosporine (Sandimmune) and mycophenolate mofetil (MMF). However, most of these drugs are less commonly used because of their toxicities.

◆ DRUGS USED IN THE MANAGEMENT OF GOUT AND HYPERURICEMIA

In contrast to RA discussed earlier, gout is somewhat unique, in that its cause is well known, therefore gouty inflammation can be effectively controlled and treated with medications.[240,241] Gout is one of the most common causes of acute inflammatory arthritis in men older than 40 years old, characterized by the deposition of monosodium urate crystals in the joints and cartilage.[242] Phagocytosis of urate crystals by human neutrophils (and macrophage) induces the synthesis and release of a glycoprotein, the crystal-induced chemotactic factor (CCF), which is believed to be the initial stimulus in the development of acute gouty attacks.[243] Gouty arthritis is also more prevalent in men than in women by a ratio of approximately 6 to 1.

Hyperuricemia

Hyperuricemia is defined as having serum uric acid levels of greater than 7.0 mg/dL in men or more than 6.0 mg/dL in women. Although recurrent attacks of gouty arthritis in a patient are typically associated with hyperuricemia, most people with high serum urate levels are asymptomatic and may never develop gout.[241,244] Uric acid is a normal metabolic end product of purine nucleotide catabolism (i.e., adenine and guanine), but unlike other mammals, humans lack a critical enzyme, urate oxidase (uricase), needed to further break down uric acid into more water-soluble allantoin (Fig. 24.25).[241,245,246]

Risk Factors

In addition to hyperuricemia, other factors that may also increase the risk of development of gout include hypertension, renal insufficiency, obesity, and the use of thiazides or loop
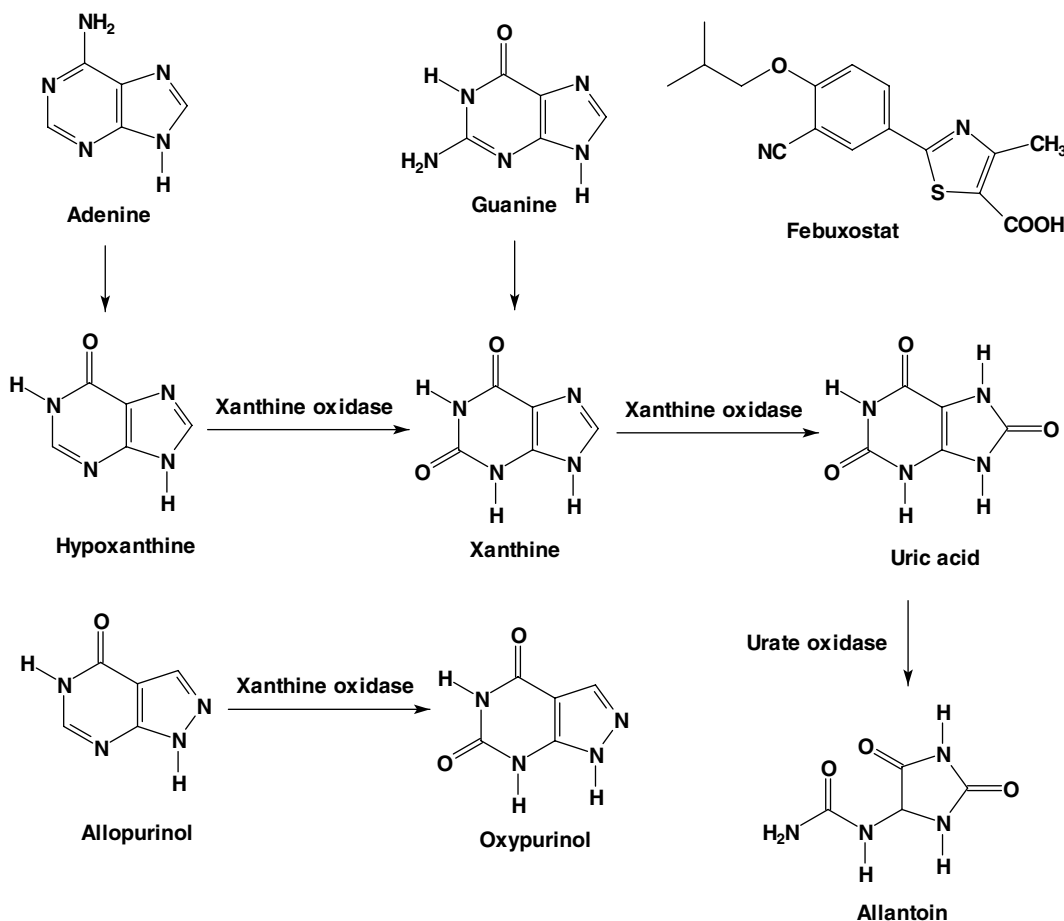

Figure 24.25 ● Catabolism of purine nucleotides and xanthine oxidase inhibitors.
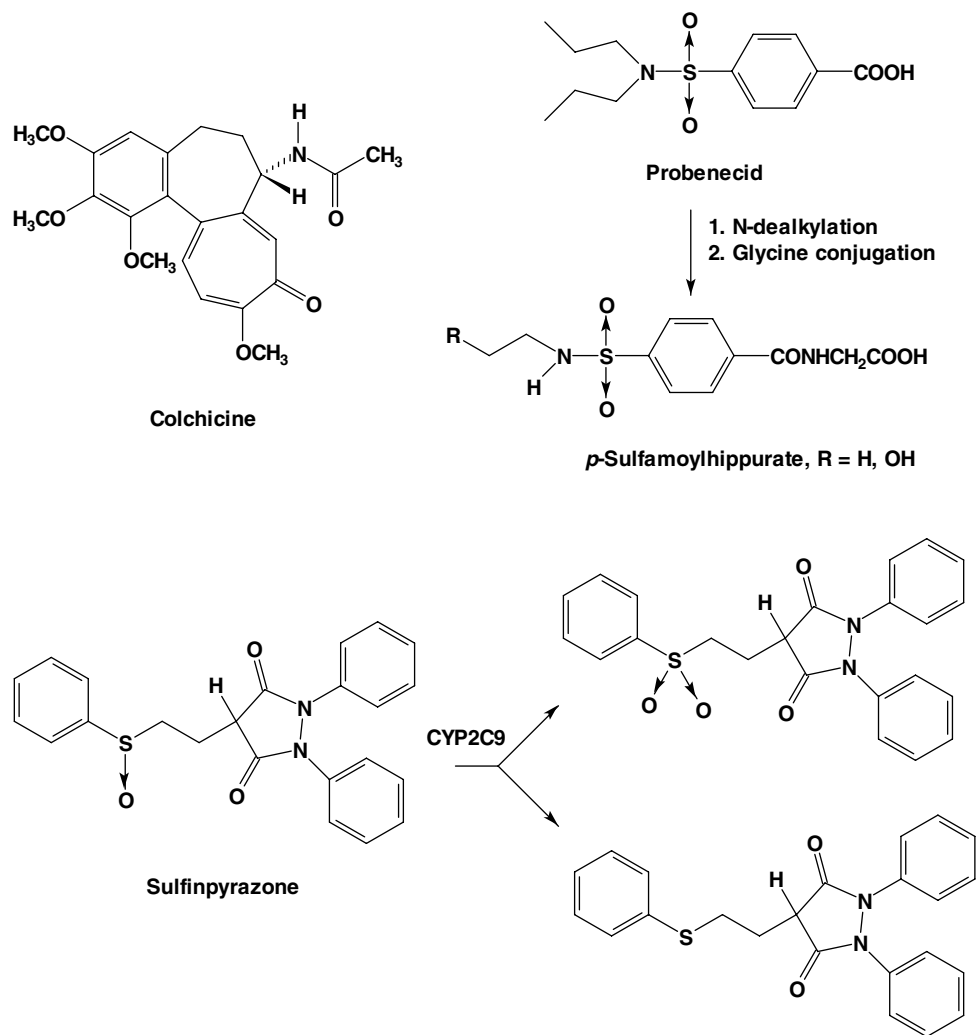
Figure 24.26 ● Colchicine and uricosuric acids.

diuretics, or high intake of alcoholic beverages and purine-rich foods such as meats, liver, bacon, fish, and beans.[241,242] The prevalence of gout also increases in organ-transplant patients who are treated with cyclosporine. Furthermore, early onset of gout (between 20 and 30 years of age) is most likely a result of hereditary disorders of purine metabolism, especially in those who have a hypoxanthine-guanine phosphoribosyltransferase deficiency, thus it should be evaluated before proper treatment is given.[245,247]

Treatment of Acute Gouty Arthritis

The main goal of the pharmacotherapy of acute gouty arthritis is a rapid resolution of pain and debility. The treatment of choice in the United States is the use of NSAIDs for patients with an established diagnosis of uncomplicated gout (i.e., those with heart failure, renal insufficiency, or GI disease).[241,248] For patients who have active peptic ulcers or renal impairment, the choice is either an IM dose of *corticotropin* (ACTH) or an intra-articular injection of glucocorticoids. The chemical aspects of corticosteroids and their therapeutic uses are covered in a separate chapter in this text. Colchicine is generally reserved for prophylaxis of recurrent, acute flare-ups of gouty arthritis or in patients in whom the diagnosis of gout is not yet confirmed.[245,248]

COLCHICINE

Colchicine is an alkaloid isolated from the dried corns and seeds of *Colchicum autumnale L.*, commonly known as autumn crocus or meadow saffron, (see Fig. 24.26 for structure). It is specifically indicated for acute treatment of gouty arthritis because of its ability to block the production and release of the CCF that mediates the inflammatory response because of urate crystals, a mechanism different from colchicine's antimitotic action, which is being investigated for its anticancer properties.[243] It is often quite effective in aborting an acute gouty attack if given within the first 10 to 12 hours after the onset of arthritis.[248,249]

Colchicine can be administered orally or intravenously. A low oral dose of 0.6 mg is taken every 1 to 2 hours, until either the resolution of gouty symptoms or the occurrence of GI toxicities such as increased peristalsis, abdominal discomfort, nausea and vomiting, and diarrhea.[248] Most of the severe systemic toxicity associated with IV administration of colchicine has been linked to an inappropriate use of the drug.[250] Several recent findings comparing the safety and efficacy of colchicine to that of NSAIDs and corticosteroids, have provided strong evidence for eliminating the IV use of colchicine in the treatment of acute gouty arthritis because improper IV dosing can cause severe bone marrow

suppression, renal failure, and death.[251,252] Moreover, oral colchicine is also recommended only as a second-line therapy for acute gout treatment when NSAIDs or corticosteroids are contraindicated or ineffective.[252] Concomitant use of oral colchicine with any of the cholesterol-lowering statins including pravastatin (Pravachol) should also be avoided because of increased risk of axonal neuromyopathy that can progress to rhabdomyolysis with renal failure.[253] This is because most of the statins and colchicine are metabolized in liver primarily by the hepatic CYP3A4 isozymes. Colchicine can also induce acute myopathy in patients when used with pravastatin even though it is not metabolized by CYP3A4, because they share the same P-glycoprotein efflux transporter system.[253]

Control of Hyperuricemia

In general, if a patient who has hyperuricemia and the recurrence of gouty arthritis attacks (i.e., less than two attacks/year), their gout can usually be controlled by maintaining serum urate levels below the limit of solubility (i.e., at 6 mg/dL or lower) with drugs that block uric acid synthesis by inhibiting xanthine oxidase or with uricosuric drugs that promote uric acid elimination from the renal tubules.[244,245,248]

XANTHINE OXIDASE INHIBITORS: ALLOPURINOL, OXYPURINOL, FEBUXOSTAT

Allopurinol (Zyloprim, Progout) is the only xanthine oxidase inhibitor available in this class. It is rapidly metabolized to its active isomer oxypurinol (Oxyprim), an experimental drug currently in phase III trials, that has a half-life of approximately 15 hours but was found to exhibit a similar side effect profile to that of allopurinol (i.e., 40% of those allergic to allopurinol have similar cross-reactivity to this drug).[240] Allopurinol and its active metabolite, oxypurinol, works by effectively competing with the substrate hypoxanthine and xanthine, respectively, because of their structural similarity to xanthine, for xanthine oxidase, thus blocking uric acid formation from purine nucleosides, adenine, and guanine as shown in Figure 24.25. Similarly, allopurinol (or oxypurinol) may also exhibit potential drug interactions with other medications such as didanosine (antiviral agent), azathioprine and mercaptopurine (anticancer drugs), and theophylline (asthma drug). For example, if a patient is given a prescription for allopurinol and azathioprine (Imuran), then the dose of azathioprine should be reduced by at least 50% to avoid the risk of myelosuppression by azathioprine.[254]

Febuxostat is a novel and selective, nonpurine inhibitor of xanthine oxidase currently awaiting FDA approval for treatment of chronic gout. It is more effective, at a daily dose of 80 or 120 mg, than allopurinol at the commonly recommended daily dose of 300 mg in lowering serum urate levels.[255,256] Unlike allopurinol, it has minimal effects on other enzymes involved in purine and pyrimidine metabolisms.

URICOSURIC AGENTS: PROBENECID AND SULFINPYRAZONE

Probenecid (Benemid) and sulfinpyrazone (Anturane) are uricosuric agents that work by preventing uric acid reab-

sorption from the renal proximal tubules (see Fig. 24.26 for structures).[257] They are only effective in patients with normal renal function who are not taking any medications such as the thiazide diuretics that compete for uric acid excretion via the organic anion transporter system (OATS) at the renal proximal tubules. In addition, patients who are using probenecid should also be counseled to avoid using any salicylates at doses greater than 81 mg/d or sulfonamide-containing diuretics such as furosemide, because concomitant use of any salicylates or diuretics can negate its uricosuric activity.[242]

Probenecid
Probenecid (Benemid) is the most widely used uricosuric agent in the United States. It is selectively excreted into the renal tubules by OATS. It is extensively metabolized via *N*-dealkylation or ω-oxidation, followed by phase II conjugation into the active metabolite, *p*-sulfamyl hippurate, which exhibits a high affinity, similar to *p*-aminohippurate, for binding to OATS, thereby preventing uric acid reabsorption from the renal proximal tubules (Fig. 24.26) [257]

Sulfinpyrazone
Sulfinpyrazone (Anturane) produces its uricosuric action in a similar manner to that of probenecid and is indicated for the treatment of chronic and recurrent gouty arthritis. It is well absorbed with approximately 50% of the administered dose excreted as unchanged drug into the renal tubules. The rest of the drug is primarily metabolized via CYP2C9 into the corresponding sulfide and sulfone metabolites, thus it can potentiate the anticoagulant effect of warfarin.[258]

⬡ TRIPTANS

Triptans are safe and effective drugs for abortive, but not for prophylactic, treatment of moderate to severe migraine and cluster headaches.[259] Because of their higher affinity and selectivity for the serotonin 5-HT$_{1B/1D}$ receptors at the trigeminal nerve fibers and dural vasculature, they are able to induce vasoconstrictions at these sites, thereby relieving pain from cranial vasodilatation and reducing neurogenic inflammation associated with these disorders.[259,260] However, triptans are often contraindicated in patients with uncontrolled hypertension, especially those with coronary vascular diseases, even though there are far fewer 5-HT$_{1B}$ receptors found in coronary blood vessels and in the peripheral vasculatures than in the cranial blood vessels.[261] Thus, special attention should also be given to assess the safety and tolerability profile of the triptans when choosing among available drugs because of their pharmacokinetic differences.[261,262]

Pathophysiology of Migraine

Migraine, a recurrent and debilitating headache disorder, affects about 12% of the worldwide population with a higher prevalence in women (~18%) than in men (~6%).[259] In the most recent classification and diagnostic criteria for headache disorders published by the Headache Classification Committee of the International Headache Society, the terms, *common* and *classical* migraines have been replaced with *migraine without aura* and *migraine with aura*, respectively.[263] The patients often describe their migraine attack as having an intense pulsating and

throbbing headache lasting from 4 hours to 3 days, if not properly treated.[259,260] In addition to this excruciating pain, migraine patients often have other symptoms like nausea, vomiting, sensitivity to light (photophobia), sound (phonophobia), or movements that can also severely impact their quality of life.

Although the etiology of migraines remains poorly understood, activation of the meningeal nociceptors at the intracranial trigeminovascular system (TGVS, also referred to as the trigeminal pain pathway) is believed to play a key role in promoting headache and other symptoms associated with migraines.[264–266] Several theories have been suggested to explain the underlying causes for the symptoms associated with migraines.[259] Only two of the most prominent theories are briefly discussed under this section.

THE VASCULAR THEORY OF MIGRAINES

According to the vascular theory, the vasodilatation of cranial carotid arteriovenous anastomoses (sites of many 5-$HT_{1B/1D}$ receptors) and meningeal, dural, cerebral, or pial vessels (primary sites of 5-HT_{1B} receptors) plays an important role in the pathogenesis of migraines and is responsible for the pain associated with migraine headaches.[259,261] The fact that sumatriptan-induced cranial vasoconstriction is selectively blocked by a selective 5-HT_{1B} antagonist, and not by a 5-HT_{1D} antagonist, lends further support to this vascular theory of migraines.[267]

THE NEUROGENIC INFLAMMATION THEORY OF MIGRAINES

This theory suggests that migraine headaches occur as a result of an abnormal firing of meningeal nociceptors at the TGVS. Activation of trigeminal neurons releases vasoactive peptides including calcitonin gene-related peptide (CGRP, a vasodilator peptide), substance P, and neurokinin A (both play an important role in pain transmission as well as activation of immune responses and neurogenic inflammation) onto dural tissue where these peptides produce a local response known as neurogenic inflammation.[259] These peptides induce cranial vasodilatation, especially at the dural membranes surrounding the brain (mainly a result of CGRP), thus producing the pain associated with migraine attacks. Further evidence supporting this theory as the underlying cause of migraines can be found from a recent study linking the dural mast cell degranulation to the prolonged activation of the trigeminal pain pathway and neurogenic inflammation.[268]

The discovery of these vasoactive peptides provides new targets for the future design of nonvasoconstrictors, nontriptan drugs such as CGRP antagonists for the acute and preventive treatment of migraine and cluster headaches.[259,269]

Structure–Activity Relationship

All clinically available triptans possess comparable pharmacodynamic properties. They all bind and stimulate serotonin 5-$HT_{1B/1D}$ with affinity in the low nanomolar ranges, thus they are equally effective for the acute treatment of migraine.[262,270] However, they all have different pharmacokinetic properties and side effect profiles that vary in type and severity.[261] Thus, they are not equally efficacious in preventing migraine recurrence because of the differences in their elimination half-lives.[262] They also differ in their potential to induce drug-related CNS side effects, especially somnolence and paresthesia that may lead to a patient's noncompliance of an otherwise effective migraine treatment.[270]

Table 24.2 summarizes the pharmacokinetic properties of clinically available triptans that contributes to their efficacy, safety, and tolerability.[259,262,270–274] A quick glance at their chemical structures (see Fig. 24.27) reveals two general structural types, which might provide insights for assessing some of these differences.

The 3-alkylaminoethyl containing triptans (sumatriptan, zolmitriptan, rizatriptan, and almotriptan) are substrates for the hepatic monoamine oxidase type A (MAO-A) because

TABLE 24.2 Pharmacokinetic Properties of the Triptans[a]

Drug	Trade Name	Bioavailability Oral (%)	Onset Time (min)	Plasma Half-life (h)	Metabolizing Enzyme[a,b]	Drug Interactions	% CNS Side Effects
Sumitriptan	Imitrex Imigrain	14	10–15 (iv) 15–30 (nasal) 30–90 (PO)	2	MAO-A	MAOIs especially MAO-A inhibitors	1.7–6.3
Zolmitriptan	Zomig, Zomig-ZMT	40–48	10–15 (nasal) 45–60 (PO)	3	CYP1A2 MAO-A	MAOIs, SSRIs, Cimethidine	9.9–11.5
Naratriptan	Amerge Naramig	63 (men) 74 (women)	60–180 (PO)	5–6.3	Renal/CYP isozymes		1.9
Rizatriptan	Maxalt Maxalt-MLT	45	30–120 (PO)	2–3	MAO-A	MAOIs especially MAO-A inhibitors, Propranolol	6.1–9.4
Almotriptan	Axert	70–80	60–180 (PO)	3.3	MAO-A CYP3A4		1.5
Frovatriptan	Prova	60	120–180 (PO)	26	CYP1A2	Fluvoxamine, ciprofloxacin, mexiletine	6.0
Eletriptan	Relpax	50	30–60 (PO)	3.6–5.5	CYP3A4	Ketoconazole and other CYP3A4 inhibitors	2.6–14.6

[a]Compiled from data reported in the following references (1, 4, 12, and 13).
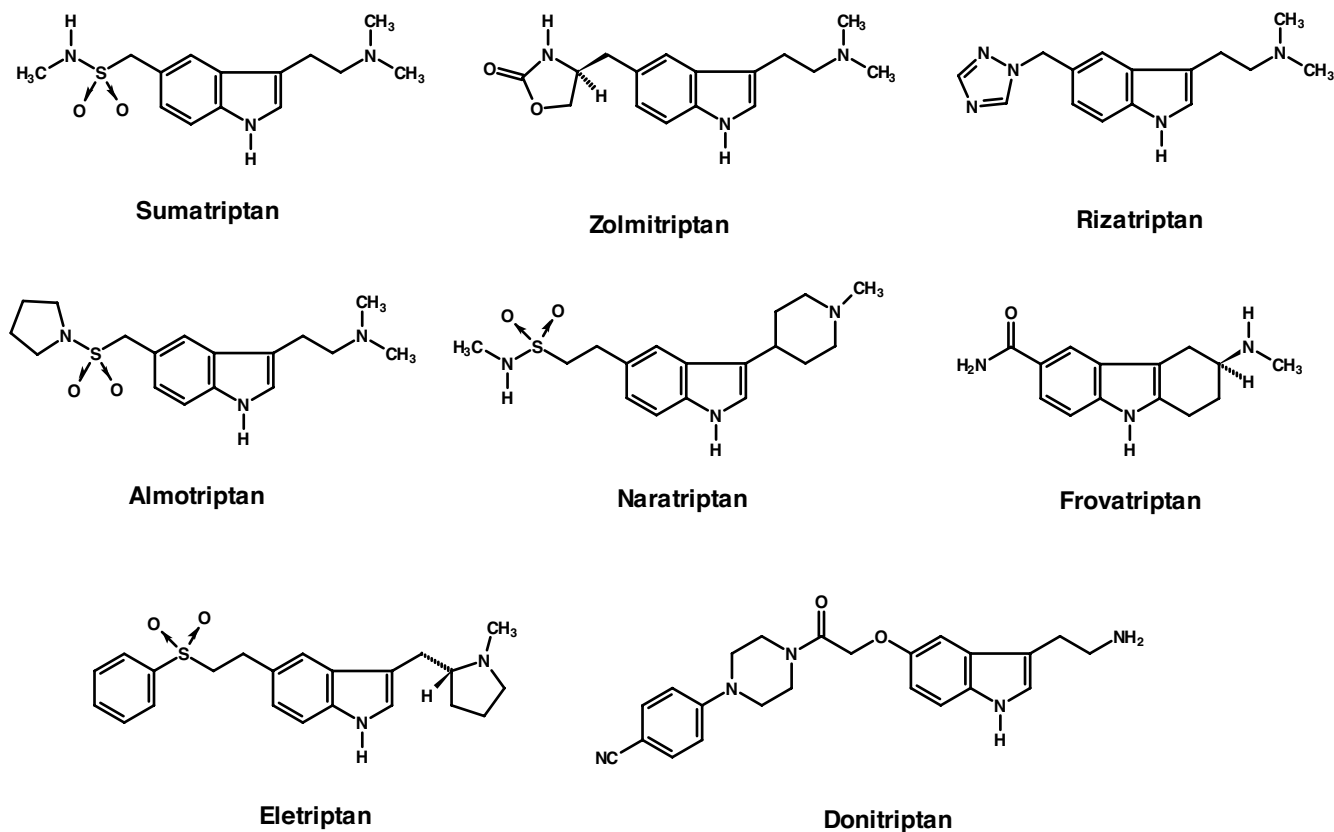[b]Primary mode of metabolism listed first.

Figure 24.27 ● Triptans.

of their structural resemblance to 5-HT, the preferred substrate for MAO-A. They all have a relatively short duration of action (i.e., 2–3 hours) because of first-pass metabolic inactivation by the MAO-A into an indole acetic acid metabolite that is rapidly eliminated as their corresponding glucuronides. Thus, the use of these triptans requires repeat dosing to prevent the recurrence of migraine attack. They are also contraindicated with concomitant use of any MAO inhibitors, especially inhibitors of MAO-A such as the antidepressant drug, moclobemide (Aurorix, Mauerix).[261,273]

Eletriptan, frovatriptan, and naratriptan, on the other hand, with their 3-alkylamino side chain fused into a carbocyclic ring structure, all have much longer elimination half-lives and lower incidence of headache recurrence reported.[273] This is because they are not a substrate for MAO-A (amphetamine is not a substrate for MAO because it has an additional methyl group α to the terminal amine function). These triptans are mainly degraded by the hepatic CYP isozymes (CYP1A2, 2D6, 3A4), but their bioavailability may be altered with a drug that inhibits or induces these CYP isozymes.[275] For example, eletriptan is primarily metabolized by CYP3A4 isozyme, thus it is not advisable to use eletriptan with a CYP3A4 inhibitor such as ketoconazole, or nefazodone without appropriately adjusting their dosages.[275]

The highest reported incidences of drug-induced CNS toxicities were found with eletriptan (14% at 80-mg dose), zolmitriptan (11.5% at 5-mg dose) and rizatriptan (9.4% at 10-mg dose). They all have *N*-demethylated, active metabolites that can easily gain entry into the brain because of their high lipophilicity.[270] Thus, the presence of this active metabolite in the brain and the high lipophilicity of the parent triptan have been suggested as a factor for contributing to the observed CNS side effects of the triptans.[270] This hypothesis is further supported by the fact that frovatriptan has a much lower CNS toxicity because of the greater water solubility of its *N*-demethylated active metabolite that prevents it from entering the brain, whereas sumatriptan, almotriptan, and naratriptan all have a very low reported incidence of CNS side effects because they have no clinically significant active metabolites.[270,276]

Donitriptan, a unique high-efficacy and high-selectivity 5-HT$_{1B/1D}$ agonist (i.e., with high-intrinsic activity approaching that of the endogenous agonist 5-HT) currently in late-stage clinical trials, is a novel arylpiperazole derivative with much better consistency of pain relief and a lower incidence of migraine recurrence.[277] Furthermore, unlike sumatriptan, it can also block capsaicin-sensitive trigeminal sensory nerves from releasing CGRP, resulting in selective cranial vasodilatation and central nociception.[278]

Mechanism of Action

Triptans are specifically designed to bind to the 5-HT$_{1B/1D}$ receptors based on the findings that 5-HT$_{1B}$ receptors are present in the cranial blood vessels[279,280] and 5-HT$_{1B/1D}$ receptors are found in the trigeminal pain pathway.[280,281] Three distinct mechanisms have been suggested to explain the actions of triptans: (a) Triptans abort migraine headache by its agonist action at the 5-HT$_{1B}$ receptors,

thereby inducing vasoconstriction of the meningeal, dural, or pial blood vessels.[279] (b) Triptans also inhibit neurogenic inflammation via its presynaptic stimulation of 5-HT$_{1D}$ receptors and/or through its additional action at the 5-HT$_{1B/1D}$ receptors.[281] (c) Triptans relieve migraine pain transmission most likely because of its inhibitory action at the trigeminal pain pathway mediated via 5-HT$_{1B/1D/1F}$ receptors.[259,279,280]

Antimigraine Drugs Acting on 5-HT$_{1B/1D}$ Receptors

SUMATRIPTAN (IMITREX)

Sumatriptan was the first triptan approved (1991) for the acute treatment of migraine headaches. It has the lowest oral bioavailability among all triptans because of its low lipophilicity. The availability of many different dosage forms (i.e., an oral tablet, a SC injection, a nasal spray formulation, and a suppository) allows the flexibility of tailoring therapy to the needs of the individual patients, thus making sumatriptans a very useful drug for an acute treatment of migraine headaches.[262,282] It also has a very fast onset of action via SC injection or nasal spray administration. However, sumatriptan is contraindicated with monoamine oxidase inhibitors because it is primarily degraded by hepatic MAO-A. Thus, it may require frequent dosing as a result of its short duration of action to prevent migraine recurrence.[262,282]

ZOLMITRIPTAN (ZOMIG, ZOMIG-ZMT)

Zolmitriptan, the second triptan marketed (approved in 1997), has a much better bioavailability (40%–48%) than sumatriptan. It is rapidly absorbed after oral or nasal spray administration. It also has an orally disintegrating tablet formulation (Zomig ZMT), which can be taken without water. Zolmitriptan undergoes rapid *N*-demethylation via CYP1A2 to a more potent, active metabolite, *N*-desmethylzolmitriptan, which is 2 to 6 times more potent than the parent drug.[262,283] This active metabolite was detected 5 minutes after dosing and accounts for about two thirds of the plasma concentration of the administered dose of the parent drug.[284] Thus, it is reasonable to assume that the therapeutic effects and especially the CNS side effects of zolmitriptan must be in part attributed to the plasma levels of this active metabolite, at least until it is further degraded by hepatic MAO-A to its inactive indole acetic acid derivatives.[262,283]

NARATRIPTAN (AMERGE, NARAMIG)

Naratriptan, the third triptan approved in 1998, is one of the most lipophilic triptans marketed to date. It has a much improved bioavailability (63% in men and 74% in women), a greater affinity for 5-HT$_{1B/1D}$ receptors (3–6 times), and a lower recurrence rate than sumatriptan because of its much longer elimination half-life.[262,285] Naratritan also has a favorable CNS side effect profile when compared with sumatriptan or zolmitriptan because of its metabolic stability, thereby lacking a *N*-demethylated active metabolite and a significant renal excretion (>70% of naratriptan is excreted unchanged and the rest of the administered dose is degraded via several CYP isozymes).[262,270,286]

RIZATRIPTAN (MAXALT)

Rizatriptan, approved in 1998, is a fast-acting triptan because of its moderate lipophilicity yet has a very short elimination half-life similar to sumatriptan (i.e., like sumatriptan, it is mainly metabolized by MAO-A). The only advantages of this drug when compared with sumatriptan are that it has a slightly faster onset and that it has an orally disintegrating tablet formulation which can be taken without water.[262]

ALMOTRIPTAN (AXERT)

Almotriptan, marketed in 2000, has the highest oral bioavailability among all triptans (see Table 24.2). It is metabolized by both MAO-A and CYP3A4, thus has a more favorable side effects profile when compared with sumatriptan. However, it is only available in a 12.5 mg tablet form.

FROVATRIPTAN (FROVA)

Frovatriptan is a newer triptan introduced into the market in 2001. With the incorporation of a 3-alkylamino side chain into a carbazole ring structure, it is not a substrate for MAO-A or CYP3A4. Thus, unlike the other clinically available triptans, it possesses a much longer duration of action with fewer drug–drug interactions with MAO inhibitors or with drugs metabolized by the CYP3A4 isozymes.[274,276] It is primarily metabolized by CYP1A2 to give its active metabolite, *N*-desmethyl-frovatriptan, which has about one third of the binding affinity for 5-HT$_{1D/1B}$ receptors but with three times longer plasma half-life of the parent drug.[276,287]

Frovatriptan also has the highest affinity for brain 5-HT$_{1B}$ receptors and the longest elimination half-life among all triptans.[273,288] The only disadvantage of this drug is its slower onset of action because of its greater water solubility. However, it is a drug of choice for patients with long-lasting migraines or if recurrence is a problem.[273]

ELETRIPTAN (RELPAX)

Eletriptan, introduced into the market in 2002, is the newest triptan with highest affinity for 5-HT$_{1B}$, 5-HT$_{1D}$, and 5-HT$_{1F}$ receptors. It is one of the most lipophilic triptans marketed to date and is well tolerated and safe across its dosing range of 20 to 80 mg.[275] However, it is metabolized primarily (>90%) by CYP3A4 isozyme to its active metabolite, the *N*-desmethyleletriptan, which accounts for approximately 10% to 20% of the plasma concentration of that observed for parent drug.[289] Thus, coadministration of eletriptan with potent CYP3A4 inhibitors such as ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, and nelfinavir may require dose reduction and closer monitoring for CNS side effects.[262,275] Furthermore, because eletriptan and its active metabolite, *N*-desmethyleletriptan, are also substrates for the P-glycoprotein efflux pumps that are responsible for their removal from the brain, coadministration of eletriptan with a known P-glycoprotein inhibitor and/or inducer such as digoxin, diltiazem, verapamil, or St. John's Worth would result in higher brain levels of its active metabolite, and thus a higher rate of the CNS side effects reported for this drug.[290]

◆ R E V I E W   Q U E S T I O N S ◆

1. A patient is brought to the emergency room via ambulance. He is unresponsive to questions, has a respiratory rate of 4 breaths per minute, and an arterial oxygen saturation (SpO_2) of 82% measured by finger pulse oximetry. On physical exam, multiple injection (track) marks are identified on his forearms, and the patient also displays a cutaneous rash over his trunk. The suspected diagnosis is a heroin overdose. The nurse calls the pharmacy for 50 mg of diphenhydramine to treat the cutaneous rash. You do not dispense it, why?

2. A new mom comes to your pharmacy to refill her codeine prescription, prescribed for episiotomy pain. She is concerned because her 2-week-old breastfed baby is extremely lethargic, sleeps all day, and seems unresponsive to stimulus. You recommend that she bring the baby to the emergency room immediately. What genetic polymorphism do you suspect the mom has? What danger does this pose to her breastfed infant?

3. A patient presents to your pharmacy with a prescription for Vicodin ES; 2 tablets q 6 hours around the clock; #240; refills = zero. You do not dispense it, why?

4. A 72-year-old man who has been taking the antiarrythmic drug quinidine for 4 years self treats his diarrhea with Imodium (loperamide). His son calls your pharmacy to report that his father is very sleepy, his pupils are pinpoints, and he is acting "very strange." You suspect that loperamide is having CNS effects. What is the pharmacological reason behind the quinidine-loperamide drug–drug interaction?

5. Diflunisal is a potent, long acting nonselective COX inhibitor. Explain how this drug binds to the COX-1 enzyme, and how it is eliminated from the body.

6. Provide a biochemical reason why acetaminophen, unlike aspirin and other NSAIDS, is a centrally acting analgesic/antipyretic drug that has no anti-inflammatory activity.

7. Provide a possible rationale for why CYP3A4 inducers can increase the clearance of diclofenac, yet CYP3A4 inhibitors have little or no effect on its pharmacokinetic profile.

8. Sulindac, a potent nonselective COX inhibitor, is said to have a lower risk of stomach bleeding and nephrotoxicity than other aspirin-like NSAIDs such as indomethacin. Explain.

9. Provide a possible chemical/biochemical rationale why frovatriptan has a much lower CNS toxicity than eletriptan.

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