

FIGURE 6.27 (a) Human monoamine oxidase B (MAO-B) in complex with rosiglitazone, RCSB file 4A7A. (b) Close up image of binding site of MAO-B in complex with rosiglitazone, RCSB file 4A7A. (c) Structure of flavin adenine dinucleotide.

dinucleotide (Figure 6.27)⁴⁸ which serves as a carrier for oxygen that is delivered to FMO substrates. To date, five FMOs, designated FMO1–5 have been identified, and much like the CYP450s, their catalytic sites are designed to accommodate a wide range of structural diversity, which leads to lower substrate conversion rates (decreased enzyme velocity). Additional enzymes that play a role in phase 1 metabolism include aldehyde oxidase (AO),⁴⁹ alcohol dehydrogenase (ADH),⁵⁰ monoamine oxidases (MAOs),⁵¹ and nitroreductases.⁵² Some common phase 1 processes are shown in Figure 6.28. All of these enzyme-mediated reactions can be employed by the body to eliminate potential drug molecules.

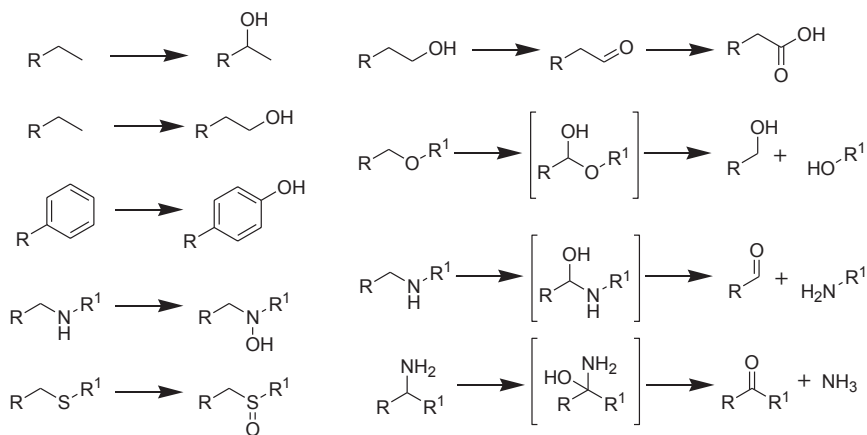


FIGURE 6.28 Typical phase 1 metabolic processes.

Hydroxylation of an aliphatic or aromatic carbon is the most commonly observed metabolic product. If further oxidation to an aldehyde, ketone, or carboxylic acid is possible, then additional phase 1 oxidative metabolism may occur. Heteroatoms such as nitrogen and sulfur can also