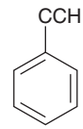
APPLY the skill

This graphic from the cited journal article represents the "plethora of biomedical applications that harbor the potential to be revolutionized by conductive polymers," including tissue engineering, regenerative medicine, optoelectronics, and biosensors.

2.8 Phenylacetylene (shown below) is a building block that can produce long carbon chains called polymers. Scientists are interested in studying poly(phenylacetylene) and related polymers because they have interesting electrical properties. These "conducting polymers" can be used to build molecular electronics with biomedical applications,[3] such as implants that can stimulate the brain to treat Parkinson's disease. Draw a 3D sketch for phenylacetylene. Be sure to draw all C and H atoms (do not use a bond-line drawing).



Phenylacetylene

need more **PRACTICE?** **Try Problems 2.44, 2.74b–d, 2.75b–d**

BioLinks The Opioids: Miraculous and Murderous

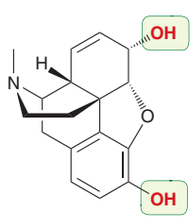
Morpheus, the god of sleep and the namesake of morphine, is often depicted holding poppies.

For thousands of years, humans have used opium for its pain-relieving, sedative and euphoric effects. The natural substance is obtained from the unripe seed pods of the poppy plant, and it is traditionally smoked by users. Dating back to at least 3400 BC in Mesopotamia, opium was widely traded across the world. Its use is documented throughout history, ranging from religious rituals to medieval medical books to opium dens. Poppies can be found adorning Egyptian, Greek and Roman gods in ancient images and statues. The biologically active component of opium is the compound morphine, named after Morpheus, the Greek god of sleep.

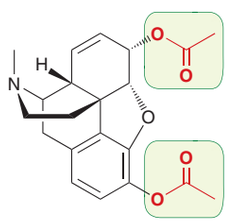
Morphine and similar molecules (such as heroin, codeine, and fentanyl), are members of a drug family called opioids. Molecules in the opioid family bind to opioid receptors in the nervous system and block the transmission of pain signals to the brain. As a result, they are potent analgesics (pain relievers). In addition, opioids are known to act as depressants (causing sedation, constipation, and slower respiratory function), and at high doses they can produce a state of euphoria. Morphine is addictive, so it is primarily used for the short-term treatment of acute pain and for terminally ill patients suffering from extreme pain. Morphine was first isolated from opium in 1803, and by the mid-1800s, it was used heavily to control pain during and after surgical procedures. By the end of the 1800s, the addictive properties of morphine became apparent, which fueled the search for nonaddictive analgesics.

As mentioned in the chapter opener, there are many techniques that scientists employ in the design of new drugs. One such technique is called lead modification, which involves modifying the structure of a compound known to exhibit desirable medicinal properties. The known compound "leads" the way to the development of other similar compounds and is therefore called the lead compound. A story that begins with morphine provides a good example of this process.

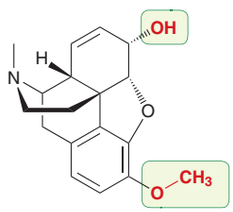
In 1925, the structure of morphine was correctly determined. Functioning as a lead compound, the structure of morphine was modified to produce other compounds with analgesic properties. Early modifications focused on replacing the hydroxyl (OH) groups with other functional groups. Examples include heroin and codeine:



Morphine



Heroin

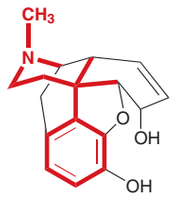


Codeine

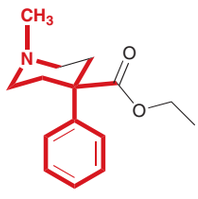
Heroin exhibits stronger activity than morphine and is extremely addictive. Codeine shows less activity than morphine, and it is also less addictive. Codeine is currently used as a pain reliever and cough suppressant.

In 1938, the analgesic properties of meperidine, also known as Demerol, were fortuitously discovered. As the story goes, meperidine was originally prepared to function as an antispasmodic agent (to suppress muscle spasms). When administered to mice, it

curiously caused the tails of the mice to become erect. It was already known that morphine and related compounds produced a similar effect in mice, so meperidine was further tested and found to exhibit pain-relieving properties. This discovery generated much interest by providing new insights in the search for other analgesics. By comparing the structures of morphine, meperidine, and their derivatives, scientists were able to determine which structural features are essential for analgesic activity, shown in red:

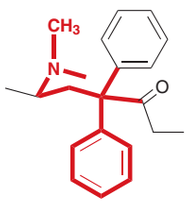


Morphine

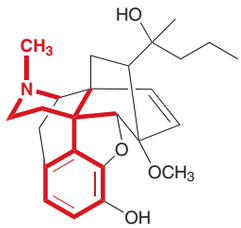


Meperidine

When morphine is drawn to illustrate its 3D shape, its structural similarity to meperidine becomes more apparent. Specifically, the bonds indicated in red represent the portion of each compound responsible for the analgesic activity. This part of the compound is called the *pharmacophore*. If any part of the pharmacophore is removed or changed, the resulting compound will not bind effectively to the appropriate biological receptor, and the compound will not exhibit analgesic properties. Alterations made to the rest of the compound (the bonds shown in black) may or may not affect the strength with which the pharmacophore binds to the receptor, so the compound's analgesic potency may or may not be affected. When designing a new drug based on a lead compound, the regions outside of the pharmacophore are the portions targeted for modification. For example, note that the modified drugs methadone and etorphine share the same pharmacophore as the lead compound morphine. Etorphine is over 3,000 times more potent than morphine and is used exclusively in veterinary medicine to immobilize elephants and other large mammals.



Methadone

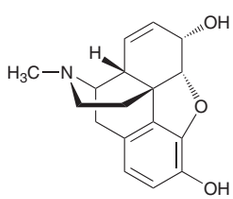


Etorphine

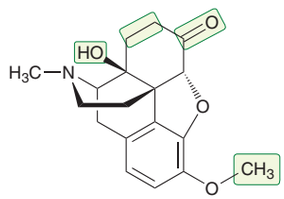
Former organic chemistry student and current veterinarian, Kim De La Peza, is ready to administer etorphine, but only to patients weighing over 1,000 lbs.

Methadone, developed in Germany during World War II, is used to treat heroin addicts suffering from withdrawal symptoms. Methadone binds to the same receptor as heroin, but it has a longer retention time in the body, thereby enabling the body to cope with the decreasing levels of drug that normally cause withdrawal symptoms.

Oxycodone and fentanyl are two additional opioids that have received a lot of media attention in the 21st century, because of the high number of overdose deaths attributed to their use. Oxycodone is made by modifying the structure of morphine as shown (the modifications are highlighted). Oxycodone has nearly twice the potency of morphine. Like morphine, it is approved for treating severe pain that can result from surgery, trauma, or cancer. In 1996, a long-acting form of oxycodone, called OxyContin, was developed by Purdue Pharma. The sustained release often did not provide 12 hours of pain-relief as promised, causing withdrawal symptoms and craving. This made OxyContin a very high risk for addiction and abuse. Seeing the potential for large profits, unethical doctors and pain clinics became "pill mills," specializing in writing and filling prescriptions for OxyContin in huge quantities. Turning a blind eye to the unfolding epidemic, Purdue Pharma continued to aggressively market OxyContin, and overdose deaths from the drug climbed. In 2015, a California doctor became the first physician to be found guilty of second-degree murder, due to her reckless writing of opioid prescriptions. Along with the US Department of Justice, 48 states have filed lawsuits against Purdue and its owners, the Sackler family, resulting in settlements worth billions of dollars. The company filed for bankruptcy in 2019, but the opioid crisis that was fueled by greed has not shown any signs of slowing.



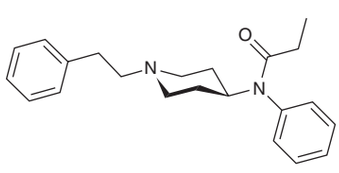
Morphine



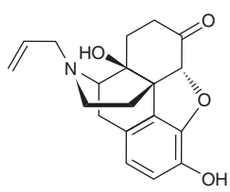
Oxycodone

With a crackdown on pill mills in 2010-2011 came the rise of the street value of OxyContin and the production of counterfeit pills. What started as a crisis of addiction to prescription painkillers began escalating to a much broader problem. Many people who were hopelessly addicted to the painkiller turned to a drug that was cheaper and easier to obtain: heroin. In addition, counterfeit pills are frequently laced with additives that are even more powerful and dangerous, such as fentanyl. The synthetic opioid fentanyl (a painkiller that is 100 times more potent than morphine) has quickly risen to become one of the deadliest drugs in the history of the United States.

As of 2021, there are over 100,000 drug-related deaths annually in the US, with fentanyl contributing to most of them. Like other opioids, fentanyl slows down breathing rates, and overdose deaths are usually the result of breathing stopping entirely. It must be ingested (despite hysterical rumors to the contrary), but as little as 2 mg—barely enough to see—is a potentially lethal dose. Fentanyl is easy and inexpensive to make, and it has been transported into the US in massive quantities, mostly from Mexico and



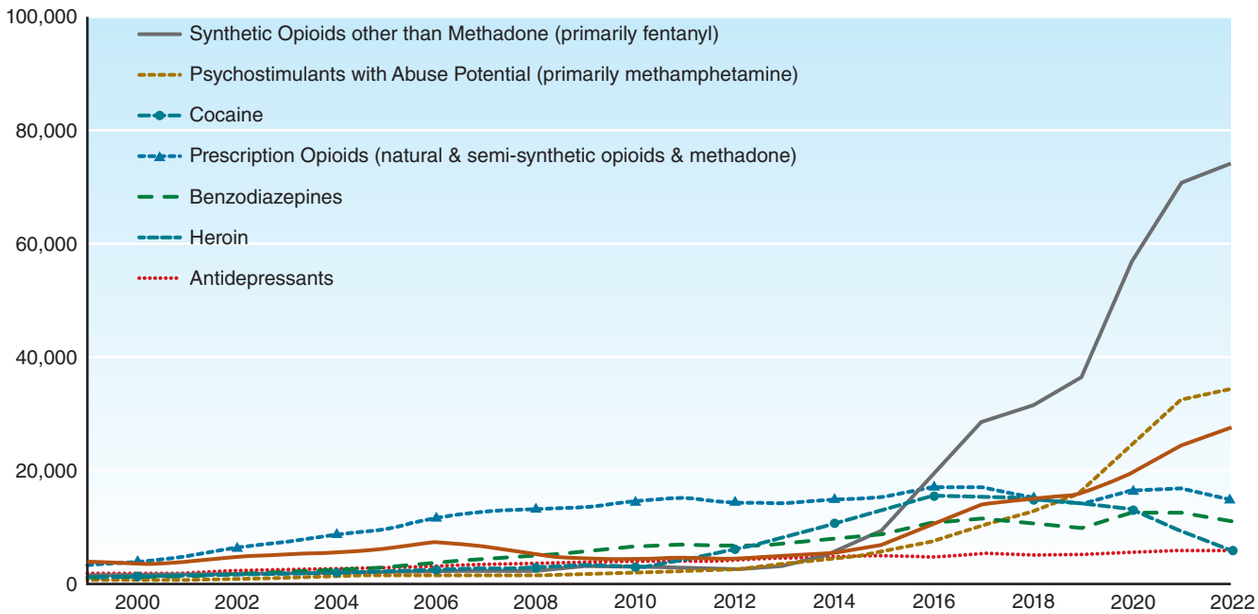
Fentanyl



Naloxone

China. Fifty times stronger than heroin, fentanyl is often added to illicit drugs to increase their euphoric effects. But fentanyl also turns up in apparently legal drugs, such as Adderall or OxyContin, that are purchased on the black market or outside the US. Because accidental fentanyl overdose can happen so easily (and to people who are unaware they are ingesting the drug), many public health officials advise schools to keep the potentially lifesaving antidote Narcan (naloxone) on hand. Administered as a nasal spray, Narcan reverses the effects of opioids, so it can revive someone who has overdosed on fentanyl, heroin, or OxyContin. Naloxone is an opioid *antagonist*, meaning it binds to and blocks opioid receptors in the body.

Drugs like fentanyl play a critical role in the management of severe pain. Synthetic opioids help people recover from surgery, enable those with chronic pain to live normal lives, and bring comfort to those who are terminally ill. The continuing challenge faced by society is how to deal with the recreational use and abuse of these miraculous but deadly drugs.



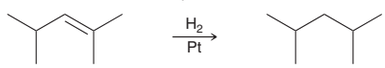
Drug-Involved Overdose Deaths in the US, 1999-2021 (NIH)

2.4 Identifying Functional Groups

Bond-line drawings are the preferred drawing style used by practicing organic chemists. In addition to being more efficient, bond-line drawings are also easier to read. As an example, consider the following reaction:

$$(CH_3)_2CHCHC(CH_3)_2 \xrightarrow[Pt]{H_2} (CH_3)_2CHCH_2CH(CH_3)_2$$

When the reaction is presented in this way, it is difficult to see what is happening. It takes time to digest the information being presented. However, when we redraw the same reaction using bond-line structures, it becomes much easier to identify the transformation taking place:



It is immediately apparent that a double bond is being converted into a single bond. With bond-line drawings, it is easier to identify the functional group and its location. A **functional group** is a characteristic group of atoms/bonds that possess a predictable chemical behavior. In each of the reactions below, the starting material has a carbon-carbon double bond, which is a functional group. Compounds with carbon-carbon double bonds typically react with molecular hydrogen (H_2) in the presence of a catalyst (such as Pt). Both of the starting materials below have a carbon-carbon double bond, and consequently, they exhibit similar chemical behavior.