CHEMISTRY 4000

Topic #0: Drug Discovery and Design

Spring 2022

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How Do We Get From an Idea to a Drug?

- It takes a lot of people to develop a pharmaceutical:
  - Someone needs to come up with the initial idea (**target molecule**)
    - It may be a computational chemist building computer models of active sites within the body using software similar to HyperChem. By studying those active sites, they can suggest what types of molecules might fit into them, binding strongly enough to have the desired **biological activity** (trigger production of a given biomolecule, prevent production of a biomolecule, prevent binding of a biomolecule to the active site, etc.)
    - It may be a biologist screening large numbers of different natural products to see which ones have biological activity.
    - It may be a chemist, biochemist or biologist who has worked with similar compounds OR worked with that compound in a different context.
      - Viagra started off as a target against angina, but didn't treat the condition as anticipated. Interesting side effects were observed, and the drug's intended purpose changed.

How Do We Get From an Idea to a Drug?

- Someone needs to make enough of the target molecule to run preliminary tests on it *(assuming that it is not already widely available – in which case, it's probably not patentable though it may be of interest to nonprofit organizations).*
  - A medicinal chemist develops a synthetic route to the target molecule. Typically, whole families of molecules are prepared for preliminary testing so it is ideal if the synthesis can cope with substantial variation in substituents. After all, a drug may go from useless to perfect just by changing one or two atoms. At this stage, only very small amounts of the target are necessary.

- Someone needs to run these preliminary tests.
  - A biologist runs tests to confirm which of the family of target molecules bind to the active site with the right strength. (Too much binding can be just as bad as too little.)

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- Someone needs to develop a synthesis that will give the successful targets in multigram amounts.
  - A medicinal chemist may have to develop a completely new synthesis of the targets that performed well in preliminary testing. (If they're lucky, their preliminary synthesis can be scaled up, but that's not always possible.)

- Someone needs to run further tests.
  - A biologist runs tests to confirm the specificity of the target molecules. Do they just bind to the site of interest, or do they bind more generally? If they bind too generally, side effects are likely to be bad. At this stage, properties like the halflife of the targets as well as maximum safe dose can be investigated. These tests are typically performed *in vivo* using animals. (*In vitro* alternatives are preferred but not always practical.)

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- Someone needs to develop a synthesis that can truly be performed on a large scale – generating kilos or even tons of perfectly pure material per batch.
  - A process chemist is faced with limitations that the medicinal chemist is not. The best process chemists are very creative.
    - They cannot use highly toxic solvents and must avoid metal catalysts in the last 4-5 steps of the synthesis so that the target will not have any trace metal contaminants.
    - They cannot use overly expensive starting materials as the target could not then be made in a cost effective fashion.
    - They cannot use many of the common separation methods like chromatography.
    - They do, however, get to use GINORMOUS glassware! *(The image at the left shows some of the smaller glassware a process chemist might use.)*
    - Meanwhile, other chemists are designing the method of delivery for the potential drug.



Image from http://www.scynexis.com/images/leftgalley/process_chemistry.jpg

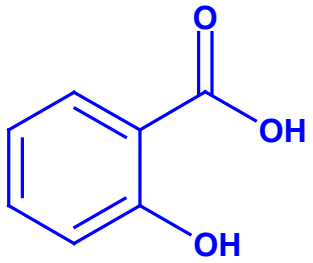
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- Someone needs to run clinical trials to determine the safeness and efficacy of the target in humans.
  - In Phase 1, the target is administered to a small group of people in doses much smaller than the maximum safe dose found for animals. The person is carefully monitored for side effects, and their fluids are analyzed to see how long the target persists. If side effects are minimal, a higher dose is administered to the next group until a maximum tolerated dose is determined.
  - In Phase 2, the target is administered to a larger group of people, primarily those suffering from the condition the target is intended to treat, so it is possible to determine how well it works. Side effects are, again, monitored. If the target works well and has minimal/tolerable side effects, it proceeds to Phase 3.
  - In Phase 3, the target is administered to much larger groups of patients to further evaluate safety and efficacy. For a drug to be sold, it often requires multiple successful Phase 3 trials.
  - Phase 4 occurs after the drug is available to the public. These are ongoing studies looking for longterm side effects.

A Tale of Two Pain Relievers

- Most targets "fail" somewhere along the way. For every successful pharmaceutical, thousands of targets failed. While the success stories are inspiring, some of the failures are more interesting…

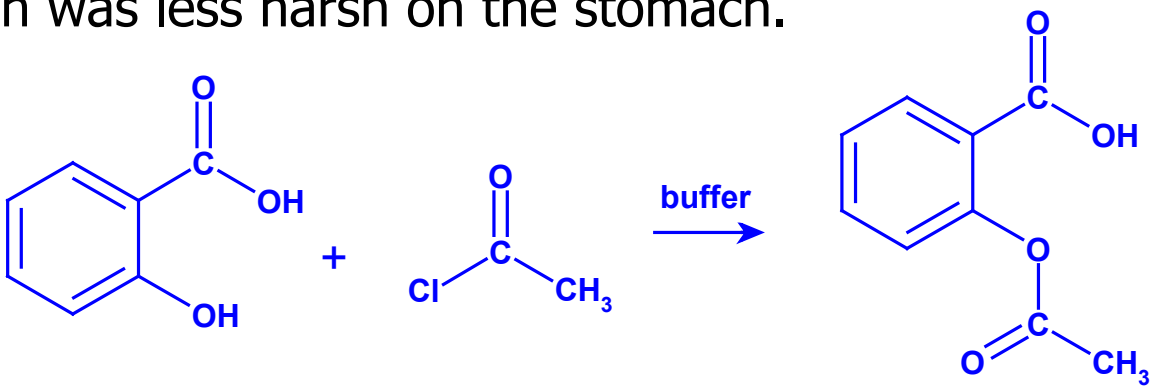
- Thousands of years ago, it was discovered that willow bark contained something that helped relieve pain. The exact compound responsible for this activity was discovered in the early 1800s to be salicylic acid:



While an effective pain reliever, salicylic acid had one major drawback – it tended to be tough on stomachs. This was likely due to the acidity that has led its use as a wart remover today!

A Tale of Two Pain Relievers

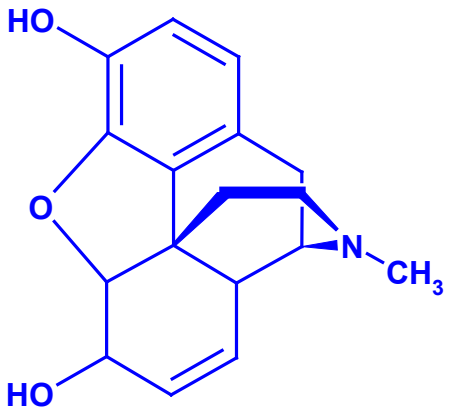
- In 1853, a French chemist named Charles Frederic Gerhardt converted salicylic acid into acetylsalicylic acid *(see below),* which was less harsh on the stomach.



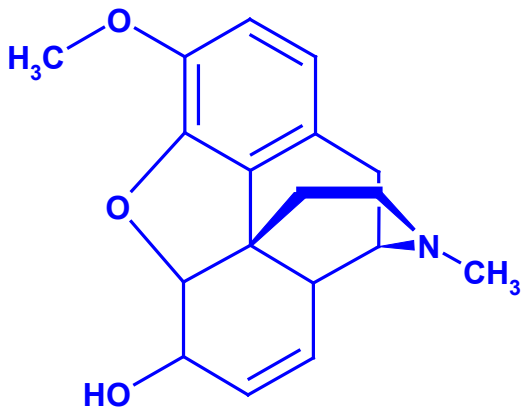
- Not having much interest in business, Gerhardt didn't pursue this discovery. It was about forty years later when Felix Hoffmann, a chemist working at a German dye manufacturer called Bayer and Company, repeated Gerhardt's reaction and used the product to treat his father. Hoffman convinced Bayer that it should market this drug and, in 1900, Aspirin was patented. It was first sold as a powder; the tablets we know didn't become available until 1915. Definitely a success story.

A Tale of Two Pain Relievers

- Inspired by the success of aspirin, Hoffman decided to take a similar approach to a problem that sounded similar. In this case, the problematic medication was morphine:



morphine

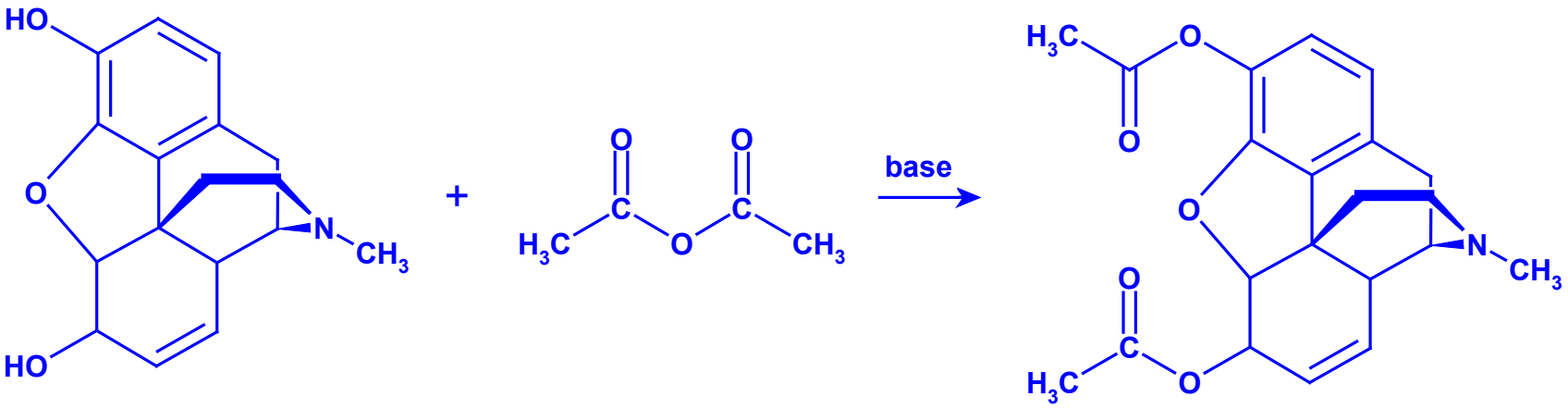


codeine

- Morphine is an effective pain reliever but quite addictive. Codeine was also an effective pain reliever and less addictive. Why not treat morphine with acetic anhydride? Essentially the same thing as was done to convert salicylic acid to Aspirin…

A Tale of Two Pain Relievers

- Hoffman went ahead and performed this reaction:



- Tests by Heinrich Dreser showed that the product was an even better pain reliever than morphine, so it could be administered in even smaller doses. Because of the smaller doses, the more common side effects of morphine (nausea, constipation, etc.) weren't observed. It was presumed that the side effect of addiction would also be avoided, and the new drug diacetylmorphine was referred to as a "hero".

A Tale of Two Pain Relievers

- That "hero" designation even appeared in the drug's patented name – Heroin. Clearly, the side effect of addiction was NOT, in fact, avoided by acetylation. The lower doses were possible only because the heroin was more readily transported across the blood-brain barrier where the two acetyl groups were removed, regenerating morphine. This same rapid transport was the reason why heroin is actually MORE addictive than morphine.

- Heroin was sold legally from 1898 until 1923! First as a cough suppressant (until 1911) then as a pain reliever. A study published in the *Journal of the American Medical Association* in 1912 warned that this must stop.

- Since then, Bayer has distanced themselves from heroin. When generic versions of aspirin appeared, Bayer sued for copyright violation over the name. While the term heroin is widely used, Bayer has never sued for copyright violation over this term…