# The Organic Chemistry of Drug Design and Drug Action

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CHAPTER 2

# Drug Discovery, Design, and Development



## I. Drug Discovery

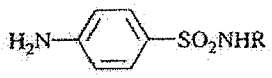
In general, clinically used drugs are not discovered. What is more likely discovered is known as a *lead* compound. The lead is a prototype compound that has the desired biological or pharmacological activity, but may have many other undesirable characteristics, for example, high toxicity, other biological activities, insolubility, or metabolism problems. The structure of the lead compound is then modified by synthesis to amplify the desired activity and to minimize or eliminate the unwanted properties. Prior to an elaboration of approaches to lead discovery and lead modification, two of the rare drugs discovered without a lead are discussed.

## A. Drug Discovery without a Lead

### 1. Penicillins

In 1928 Alexander Fleming noticed a green mold growing in a culture of *Staphylococcus aureus*, and where the two had converged, the bacteria were lysed.[1] This led to the discovery of penicillin, which was produced by the mold. It may be thought that this observation was made by other scientists who just ignored it, and, therefore, Fleming was unique for following up on it. However, this is not the case. Fleming tried many times to rediscover this phenomenon without success; it was his colleague, Dr. Ronald Hare,[2,3] who was able to reproduce the observation. It only occurred the first time because a combination of unlikely events all took place simultaneously. Hare found that very special conditions were required to produce the phenomenon initially observed by Fleming. The culture dish inoculated by Fleming must have become accidentally and simultaneously contaminated with the mold spore. Instead of placing the dish in the refrigerator or incubator when he went on vacation as is normally done, Fleming inadvertently left it on his lab bench. When he returned the following month, he noticed the lysed bacteria. Ordinarily, penicillin does not lyse these bacteria; it prevents them from developing, but it has no effect if added after the bacteria have developed. However, while Fleming was on vacation (July to August) the weather was unseasonably cold, and this provided the particular temperature required for the mold and the staphylococci to grow slowly and produce the lysis. Another extraordinary circumstance was that the particular strain of the mold on Fleming's culture was a relatively good penicillin producer, although most strains of that mold (*Penicillium*) produce no penicillin at all. The mold presumably came from the laboratory just below Fleming's where research on molds was going on at the time.

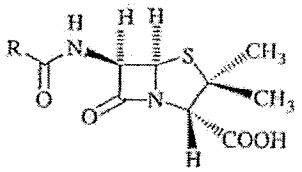
Although Fleming suggested that penicillin could be useful as a topical antiseptic, he was not successful in producing penicillin in a form suitable to treat infections. Nothing more was done until Sir Howard Florey at Oxford University reinvestigated the possibility of producing penicillin in a useful form. In 1940 he succeeded in producing penicillin that could be administered topically and systemically,[4] but the full extent of the value of penicillin was not revealed until the late 1940s.[5] Two reasons for the delay in the universal utilization of penicillin were the emergence of the sulfonamide antibacterials (sulfa drugs, **2.1**; see Chapter 5, Section IV,B,1) in 1935 and the outbreak of World War II. The pharmacology, production, and clinical application of penicillin were not revealed until after the war so that this wonder drug would




**2.1**

not be used by the Germans. A team of Allied scientists who were interrogating German scientists involved in chemotherapeutic research were told that the Germans thought the initial report of penicillin was made just for commercial reasons to compete with the sulfa drugs. They did not take the report seriously.

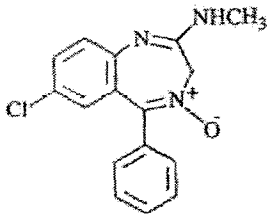
The original mold was *Penicillium notatum*, a strain that gave a relatively low yield of penicillin. It was replaced by *Penicillium chrysogenum*,[6] which had been cultured from a mold growing on a grapefruit in a market in Peoria, Illinois! The correct structure of penicillin (**2.2**) was elucidated in 1943 by Sir Robert Robinson (Oxford) and Karl Folkers (Merck). Several different penicillin analogs (R group varied) were isolated early on; only two of these (**2.2**, R = $PhOCH_2$, penicillin V, and **2.2**, R = $CH_2Ph$, penicillin G) are still in use today.



**2.2**

## 2. Librium

The first benzodiazepine tranquilizer drug, Librium [7-chloro-2-(methylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide, **2.3**], was discovered serendipitously.[7] Dr. Leo Sternbach at Roche was involved in a program to synthesize a new class of tranquilizer drugs. He originally set out to prepare a series of benzheptoxdiazines (**2.4**), but when $R^1$ was $CH_2NR_2$ and $R^2$ was $C_6H_5$, it was found that the actual structure was that of a quinazoline 3-oxide (**2.5**). However, none of these compounds gave any interesting pharmacological results. The program was abandoned in 1955 in order for Sternbach to work on a different project. In 1957 during a general laboratory cleanup a vial containing what was thought to be **2.5** (X = 7-Cl, $R^1 = CH_2NHCH_3$, $R^2 = C_6H_5$) was found and, as a last effort, was submitted for pharmacological testing. Unlike all the other compounds submitted, this one gave very promising results in six different tests used for preliminary screening of tranquilizers.



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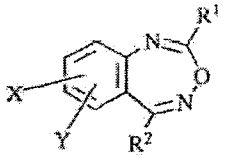

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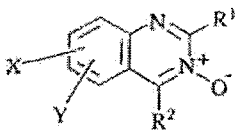

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