and Development

I. Drug Discovery

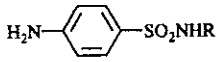
In general, clinically used drugs are not discovered. What is more likely discovered is known as a *lead* compound. The lead is a prototype compound that has the desired biological or pharmacological activity, but may have many other undesirable characteristics, for example, high toxicity, other biological 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.

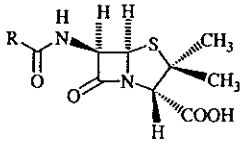
Although Fleming suggested that penicillin could be useful as a topical antiseptic, he was not successful in producing penicillin in a form suitable to treat infections. Nothing more was done until Sir Howard Florey at Oxford University reinvestigated the possibility of producing penicillin in a useful 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.

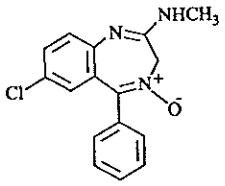
The original mold was *Penicillium notatum*, a strain that gave a relatively low yield of penicillin. It was replaced by *Penicillium chrysogenum*,[6] which had been cultured from a mold growing on a grapefruit in a market in Peoria, Illinois! The correct structure of penicillin (**2.2**) was elucidated 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.



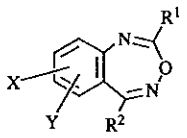
2.2

2. Librium

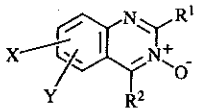
The first benzodiazepine tranquilizer drug, Librium [7-chloro-2-(methylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide, **2.3**], was discovered serendipitously.[7] Dr. Leo Sternbach at Roche was involved in a program to synthesize a new class of tranquilizer drugs. He originally set out to prepare a 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.



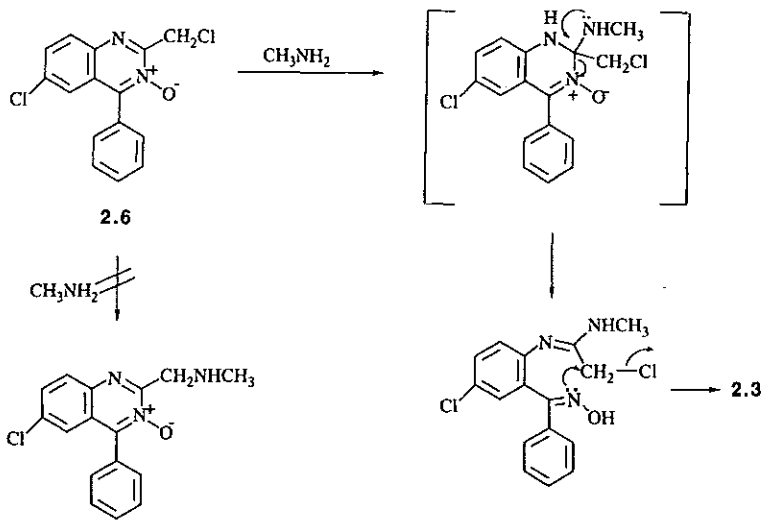
2.3



2.4



2.5



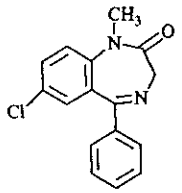
Scheme 2.1. Mechanism for formation of Librium.

Further investigation revealed that the compound was not a quinazoline 3-oxide but, rather, was the benzodiazepine 4-oxide (**2.3**), presumably produced in an unexpected reaction of the corresponding chloromethyl quinazoline 3-oxide (**2.6**) with methylamine (Scheme 2.1). If this compound had not been found in the laboratory cleanup, all of the negative pharmacological results would have been reported for the quinazoline 3-oxide class of compounds, and benzodiazepine 4-oxides may not have been discovered for many years to come.

The examples of drug discovery without a lead are quite few in number. The typical occurrence is that a lead compound is identified and its structure is modified to give, eventually, the drug that goes to the clinic.

B. Lead Discovery

Penicillin V and Librium are, indeed, two important drugs that were discovered without a lead. Once they were identified, however, they then became lead compounds for future analogs. There are now a myriad of penicillin-derived antibacterials that have been synthesized as the result of the structure elucidation of the earliest penicillins. Valium (diazepam, **2.7**) was synthesized at Roche even before Librium was introduced on to the market; this drug was derived from the lead compound Librium and is almost 10 times more potent than the lead.



2.7

In general, the difficulty arises in the discovery of the lead compound. There are several approaches that can be taken to identify a lead. The first requirement for all of the approaches is to have a means to assay compounds for a particular biological activity, so that it will be known when a compound is active. A *bioassay* (or *screen*) is a means of determining in a biological system, relative to a control compound, whether a compound has the desired activity and, if so, what the relative potency of the compound is. Note the distinction between the terms activity and potency. *Activity* is the particular biological or pharmacological effect (e.g., antibacterial activity or anticonvulsant activity); *potency* is the strength of that effect. Some bioassays (or screens) begin as *in vitro* tests, for example, the inhibition of an enzyme or antagonism of a receptor; others are *in vivo* tests, for example, the ability of the compound to prevent an induced seizure in a mouse. In general, the *in vitro* tests are quicker and less expensive. Once the bioassay is developed, there are a variety of approaches to identify a lead.

1. Random Screening

Random screening involves no intellectualization; all compounds are tested in the bioassay without regard to their structures. Prior to 1935 (the discovery of sulfa drugs), random screening was essentially the only approach; today this method is used to a lesser degree. However, random screening programs are still very important in order to discover drugs or leads that have unexpected and unusual structures for various targets.

The two major classes of materials screened are synthetic chemicals and natural products (microbial, plant, and marine). An example of a random screen of synthetic and natural compounds is the "war on cancer" declared by Congress and the National Cancer Institute in the early 1970s. Any new compound submitted was screened in a mouse tumor bioassay. Few new anticancer drugs resulted from that screen, but many known anticancer drugs also did not show activity in the screen used. As a result of that observation, multiple bioassay systems are now utilized. In the 1940s and 1950s a random screen by various pharmaceutical companies of soil samples in search of new antibiotics was undertaken. In this case, however, not only were numerous leads uncovered, but two important antibiotics, streptomycin and the tetracyclines, were found.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.