1
Serendipitous Target-Based Drug Discoveries

János Fischer and David P. Rotella

1.1
Introduction

Breakthrough drug discoveries – based on a molecular biological target – can significantly improve therapy for disease. For example, captopril (discovered in 1976) is a pioneer angiotensin-converting enzyme (ACE)-inhibitor used for treatment of essential hypertension. Subsequent compounds acting on the same target (e.g., enalapril, lisinopril, and perindopril) are used for the same purpose. An alternative and complementary treatment for hypertension involves use of angiotension II receptor antagonists. Losartan (discovered in 1986) was the first compound in this class and was followed by several additional molecules (e.g., valsartan, telmisartan, and irbesartan). Treatment of hypertension by these mechanisms provided physicians with additional options to consider as a part of combination therapy or when other possibilities such as diuretics and/or β-blockers are unsatisfactory. For the treatment of obstructive airway diseases several short and long-acting β-2-adrenoreceptor agonists (e.g., salbutamol, formoterol, and salmeterol) that act directly on lung tissue to improve airway function have been discovered. Antimuscarinics selective for M1 and M3 receptors such as tiotropium bromide (discovered in 1989) were found to be effective for treatment of chronic obstructive pulmonary disease (COPD). These distinct mechanisms of action can be used in combination to treat COPD and other complex airway disorders. Imatinib (discovered in 1992) is a BCR-Abl tyrosine kinase inhibitor for the treatment of chronic myeloid leukemia (CML) that demonstrated the concept of targeted chemotherapy substantially improving survival in this difficult to treat disease. In the field of metabolic diseases, sitagliptin (discovered in 2001) was the first dipeptidyl peptidase-IV (DPP-IV) inhibitor for the treatment of type 2 diabetes. The recognition that inhibition of this enzyme could prolong the serum half life of glucagon-like peptide-1 (GLP-1), a peptide hormone that helps tightly regulate blood sugar without substantial risk of hypoglycemia, provided physicians, and patients with another effective mechanistic option for treatment of type 2 diabetes.

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1.2 Recent Examples of Target-Based Drug Discovery

In contemporary drug discovery, a key feature to help maximize the chance for success (i.e., marketing approval) is a clear understanding of the molecular target and mechanism of action for a drug candidate. Contributions to this volume describe the rationale for target selection, association(s) with the disease, and in some cases clinical biomarkers that provide critical information on target engagement as well as the correlation between dose and effect pharmacokinetic/pharmacodynamic (PK/PD) effects. This approach allows the discovery team to test a hypothesis for a first-in-class drug candidate. For a follow-on program where previous experience provides the necessary background, it may prove necessary to investigate aspects such as selectivity or adverse events that were not appreciated or were incompletely understood with the initial molecule.

For example, the discovery of dapagliflozin, the first sodium-glucose transporter type 2 (SGLT2) inhibitor approved for use in the treatment of type 2 diabetes, had a clear mechanism and target. By preventing reabsorption of glucose in the kidney, lower blood sugar could result. Approximately 90% of glucose reabsorption occurs in the kidney, and by promoting glucose excretion, lowered blood sugar should result. Lowering blood glucose is an indicator of target engagement that is also a clinically relevant biomarker for efficacy. This mechanism of action has a low risk of hypoglycemia because it is independent of insulin secretion, providing clinicians with a useful option to use in combination with metformin or insulin. Clinical trials revealed that SGLT2 inhibition could also lead to weight loss and improved plasma lipid profiles. Each of these unanticipated (based on the mechanism of action) effects are welcome benefits in type 2 diabetic patients because of other comorbidities including obesity, atherosclerosis, and hyperlipidemia. Combination studies of SGLT2 inhibitors with other diabetes treatments are underway, including use with DPP4 inhibitors. Given the complexity of type 2 diabetes, addition of another validated mechanism to treat the disease, especially one that can be used effectively in combination with others, is a true advance in the treatment of a serious and widespread disease.

The introduction of trastuzumab emtansine for treatment of metastatic breast cancer represents a particularly interesting example of a combination of a small molecule cytotoxic agent DM1 and the antibody trastuzumab that recognizes the human epidermal growth factor receptor 2 (HER2) receptor specifically expressed in breast cancer cells. In spite of the utility of the antibody alone for treatment of the disease, not all HER2 positive tumors respond, and some patients become refractive. While trastuzumab exerts its effect via more than one mechanism, the appeal of targeted delivery of a potent cytotoxic agent has potential advantages for therapeutic efficacy. Selective delivery only to cancer cells continues to be one of the limitations associated with use of cytotoxic agents in oncology that is most difficult to overcome. DM1 is a microtubule binding agent that is 3–10 times more potent in vitro compared to the well studied derivative maytansine, and up to 500 times more potent compared to the widely used taxanes. High potency for the

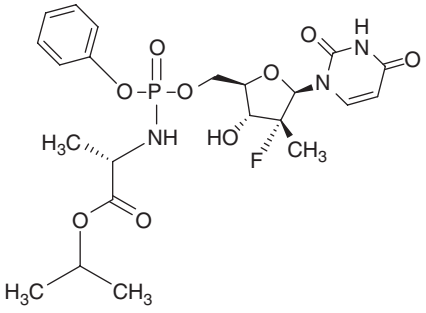

Figure 1.1 Sofosbuvir (Sovaldi).

small molecule target was recognized to be an important goal because of dose limiting toxicities. This antibody–drug conjugate employs two distinct and complementary mechanisms to achieve these goals, providing patients and clinicians facing metastatic breast cancer with a potentially useful option.

The approval of sofosbuvir (Sovaldi®) (Figure 1.1) in 2013, a viral ribonucleic acid (RNA) polymerase inhibitor used in combination with ribavarin represents the first all oral therapy for treatment of hepatitis C viral (HCV) infection. This chronic disease was initially treated with a combination of injectable interferon and ribavarin and was associated with significant adverse events, and it was also inconvenient for patients because one of the drugs had to be injected and the extended therapeutic course had to be an extended one (~52 weeks) to achieve maximal efficacy. Against this therapeutic backdrop for a disease that affects over 150 million people worldwide, a number of alternative approaches with specific molecular targets associated with the virus are being investigated. Foremost among these are two proteases, NS3A/NS4A, along with viral RNA polymerase. Polymerase approaches for viral diseases are being very actively investigated; however, they frequently suffer from low potency because the molecule must be converted to a triphosphate derivative in cells. The first step in this process is slow and rate limiting, which results in reduced efficacy. Sofosbuvir is a monophosphate prodrug of a modified nucleoside that can bypass the slow initial phosphorylation step. The molecule is rapidly converted to a triphosphate derivative, which is a potent inhibitor of the viral enzyme. Clinical studies with sofosbuvir revealed that a sustained viral response could be achieved rapidly (in as short as 24 weeks) in combination with ribavarin. This substantially reduces the time course of therapy, is associated with fewer adverse events, and can be more easily administered because it is an all-oral regimen.

Treatment of rheumatoid arthritis is dominated by a number of biologics that require periodic injections. These therapies, while beneficial and effective, are recognized to be less convenient compared to oral administration of a small molecule. A number of approaches have been investigated to identify suitable molecular targets and small molecules for this purpose. In 2012, the approval of tofacitinib (Figure 1.2) represented the first small molecule since methotrexate to be approved for treatment of this crippling progressive disorder. Tofacitinib inhibits Janus kinase 3 (JAK3), an intracellular tyrosine kinase that plays a role

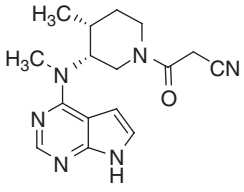

Figure 1.2 Tofacitinib (Xeljanz).

in signal transduction associated with a number of proinflammatory cytokines. JAK3 is localized in lymphocytes; analysis of plasma in rheumatoid arthritis patients showed that high levels of the kinase were present in the synovial fluid. This link between pathology and the site of action (i.e., the joint) provided reasonable assurance that inhibition of the enzyme represented a mechanistically reasonable approach for treatment of this disease. Kinase selectivity was a key objective to address because inhibition of JAK1 and/or JAK2 was undesirable because of potential toxicity. Clinical studies revealed that the molecule was effective as monotherapy and had an acceptable safety profile. More recently, Phase 2 and 3 combination studies with methotrexate showed efficacy in patients who did not respond to other anti-TNF (tumor necrosis factor) therapies such as adalimumab.

In early 2014, a novel small molecule was approved for treatment of psoriatic arthritis. Apremilast (Figure 1.3) is an inhibitor of phosphodiesterase 4 (PDE4), a well known enzyme that has been studied for a number of years. It was well known that inhibition of this cyclic nucleotide hydrolase elevated local concentration of cyclic AMP, an important second messenger that reduced circulating levels of inflammatory cytokines. These proteins are well known to be elevated in a number of types of arthritis. A number of PDE4 inhibitors were evaluated clinically and failed for both safety and efficacy reasons. Apremilast demonstrated potential disease modifying effects in patients with psoriatic arthritis, and is continuing to undergo clinical evaluation for osteoarthritis and rheumatoid arthritis.

These examples illustrate the strong connection between a target, mechanistic hypothesis, and measurable pharmacologic effects. While this approach to drug discovery represents a proven approach that can be successful, it does not guarantee success from a preclinical/discovery perspective or in the clinic. For example, inhibition of cyclooxygenase 2 (COX2), while efficacious for treatment of inflammatory disorders, also had undesirable cardiovascular effects. As outlined in the following paragraphs, serendipity and unexpected results play a

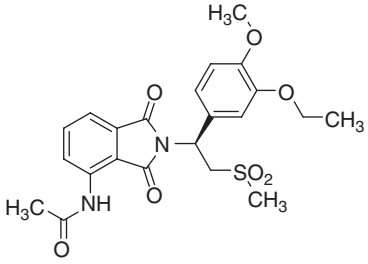

Figure 1.3 Apremilast (Otezla).

role in the discovery of novel therapeutic agents. Given the complexity of the undertaking, it is perhaps not surprising, however, that as a scientist one must be prepared to recognize and take advantage of these opportunities, using them to advance a project into and through the clinic to benefit patients.

1.3
Serendipitous Target-Based Drug Discoveries

As described in the introduction, target-based discoveries have an important role to play in new drugs. In some special cases, however, the initial drug target only helps to find a lead molecule, but the final product has a different mechanism of action, that is, a different target. These serendipitous target-based drug discoveries are discussed in this chapter using the following drug discoveries as examples in alphabetic order: drospirenone, escitalopram, ezetimibe, lamotrigine, and omeprazole.

1.4
Drospirenone (Contraceptive with Anti-aldosterone Activity)

Aldosterone (Figure 1.4) is the most potent natural mineralocorticoid hormone. It has an important role in the regulation of fluid and electrolyte balance and blood pressure. Spironolactone (Figure 1.5) is the first successful aldosterone antagonist that has been used since 1959 as a diuretic agent for the treatment of edema, liver cirrhosis, and as an antihypertensive drug.

Spironolactone causes hormone-related side effects such as menstrual irregularity, gynecomastia, and impotence due to its low receptor selectivity. Between the mid-1970s and the mid-1980s, a new search started for novel aldosterone antagonists with a primary goal to identify structures free from the unwanted effects seen with spironolactone.

Wiechert and coworkers synthesized more than 600 steroid derivatives [1] and investigated their anti-aldosterone activity. Compounds with fused cyclopropane rings displayed remarkable activity, and spirorenone (Figure 1.6) was selected as a clinical candidate.

The chemical name of spirorenone is: (6β,7β); 15β,16β-dimethylen-3-oxo-17α-pregna-1,4-dien-21,17-carbolactone. Spirorenone differs from spironolactone in

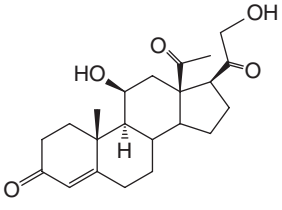

Figure 1.4 Aldosterone.

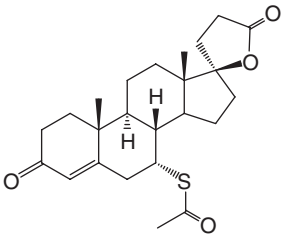

Figure 1.5 Spironolactone.

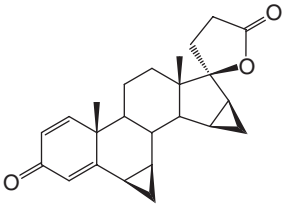

Figure 1.6 Spirorenone.

that an additional double bond at C-1 in ring A and two cyclopropane rings fused to rings B and D are present while the 7-acetylthio-substituent is missing.

Spirorenone proved to have five times higher anti-aldosterone activity compared to spironolactone, and its hormonal side effects were much lower. It was serendipitously found that low doses of spirorenone resulted in reduction of the testosterone level in men. This unexpected effect derived from the metabolic transformation of spirorenone to 1,2-dihydrospirorenone (drospirenone) (Figure 1.7), which was found to be an orally active progestin with anti-androgen properties. Unlike other species, spirorenone is metabolized to drospirenone in humans and in monkeys by the action of the enzyme Δ^1-hydrase. Drospirenone is used as a successful contraceptive.

1.4.1 Summary of Drospirenone Discovery

The initial step in the target-based drug discovery of drospirenone afforded the rather active lead molecule, spirorenone, as a potent aldosterone antagonist. The clinical studies of spirorenone led to the discovery of drospirenone, which was also identified as a metabolite of spirorenone. Drospirenone is an orally active

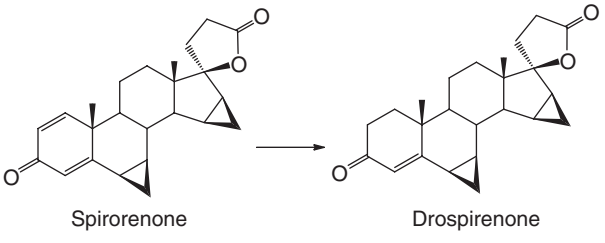

Figure 1.7 Formation of drospirenone from spirorenone.

progestin with notable anti-androgen and anti-mineralocorticoid properties, and has been developed as a contraceptive.

1.5
Escitalopram (Selective Serotonin Reuptake Inhibitor Antidepressant)

Researchers at Lundbeck [2] wanted to prepare a trifluoromethyl-substituted derivative of the tricyclic antidepressant melitracen. Instead of the expected analog a novel phthalane derivative was formed (Figure 1.8).

Melitracen acted as a norepinephrine (NE) reuptake inhibitor (unselective, due to action on various postsynaptic receptor sites), and serendipitously, it was found that the structurally different phthalane derivative also had this mechanism of action. Analog design revealed that the unsubstituted N-des-methyl analog, talopram (Figure 1.9), was – in contrast to melitracene – a highly selective and very potent NE uptake inhibitor.

The clinical trial of talopram was halted in Phase II because of its psychomotor side effects. On the recommendation of Professor Arvid Carlsson, a new research

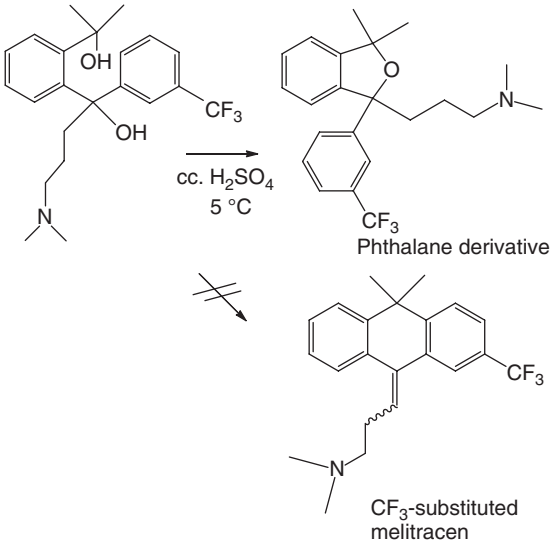

Figure 1.8 Unexpected formation of a phthalane derivative.

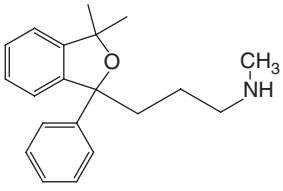

Figure 1.9 Talopram.

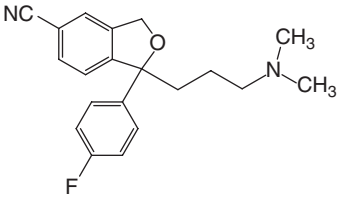

Figure 1.10 Citalopram.

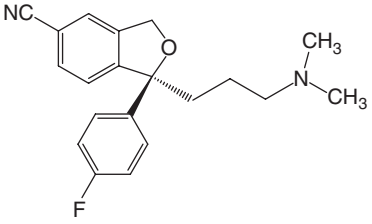

Figure 1.11 Escitalopram.

program started at Lundbeck in 1971. The research was aimed at finding selective 5-hydroxytryptamine (5-HT) uptake inhibitors, and it was assumed that these drugs would not have the above activating profile.

It seems paradoxical that talopram, a highly selective NE uptake inhibitor was used as a lead for the design of selective serotonin reuptake inhibitors (SSRIs), but some analogs of talopram from the Lundbeck compound collection had dual 5-HT/NE inhibition. This research afforded citalopram (Figure 1.10) which has a 5-cyano group on the isobenzofuran ring and is unsubstituted in the 3-position, has a 4-fluoro substituent at the phenyl group, and a dimethylamino group in its side chain. Citalopram became a successful antidepressant as a selective serotonin reuptake inhibitor.

Pure enantiomers of citalopram became available in 1988. The biological activity of racemic citalopram resides in the *S*-citalopram, which has a primary (inhibitory) (S1) site at the serotonin transporter (SERT) protein and a secondary allosteric binding site (S2) that modulates the binding properties at the primary site. *R*-citalopram is not a neutral component in racemic citalopram, and it counteracts the effects of escitalopram (Figure 1.11). The precise mechanism is not clear, but *R*-citalopram counteracts the association of escitalopram with the S1 site, perhaps, through its interaction with the SERT allosteric S2 site.

Retrospectively, it is interesting to analyze the structure–activity relationships of the direct analogs of citalopram. A compound deriving from the citalopram synthesis as an impurity (Figure 1.12) had one of the highest affinities at the S1 site, whereas it was inactive at the allosteric site (S2). It was a fortunate step to select citalopram for development and not a derivative (such as this by-product) which has no allosteric activity.

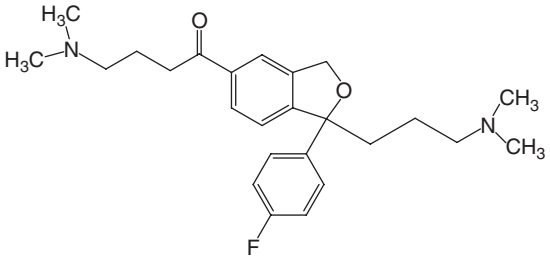

Figure 1.12 Synthesis byproduct of citalopram.

1.5.1
Summary of the Escitalopram Discovery

It was serendipitous that citalopram, a selective serotonin inhibitor was discovered from the selective NE uptake inhibitor talopram. It was fruitful that citalopram was selected for the development, because *S*-citalopram is also active as an allosteric modulator at SERT, whereas more potent compounds later proved to be inactive at this receptor site. When the selection was made there was no knowledge of the allosteric site of SERT.

1.6
Ezetimibe (Inhibitor of Cholesterol Absorption)

Cholesterol in the serum has two major sources: it is either endogenously synthesized or it has a dietary origin. The statins are excellent cholesterol-lowering drugs and they decrease cholesterol levels by inhibiting cholesterol biosynthesis. Ezetimibe is the only successful drug which inhibits the absorption of dietary cholesterol. Two recently published books describe the discovery of ezetimibe. It is described as a standalone drug [3] and as an example of small-molecule drug discovery [4]. In this chapter we discuss the role of the targets in its discovery.

Research at Schering-Plough (now Merck) focused on inhibitors of the enzyme acyl-Coenzyme A cholesterol acyltransferase (ACAT). This protein is located in the endoplasmic reticulum and forms cholesteryl esters from cholesterol, that is, the enzyme has two substrates: acyl-CoA and cholesterol and the enzyme-catalyzed reaction affords CoA and cholesteryl ester. The esterification of cholesterol mediated by ACAT is important for the absorption of cholesterol. Inhibition of this enzyme blocks the absorption of intestinal cholesterol.

The ACAT inhibitors SA 58035 (Sandoz) and CI 976 (Parke-Davis) were used as lead molecules (Figure 1.13).

The two known ACAT inhibitors are rather different and have only one common feature, open-chain amides. Researchers at Schering–Plough synthesized 2-azetidinone derivatives (compounds A and B) as the simplest ring-closure derivatives (Figure 1.14).

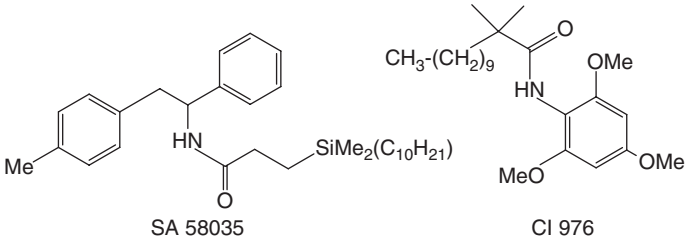

Figure 1.13 ACAT inhibitor lead molecules.

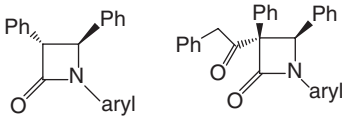

Figure 1.14 Structures of compounds A and B.

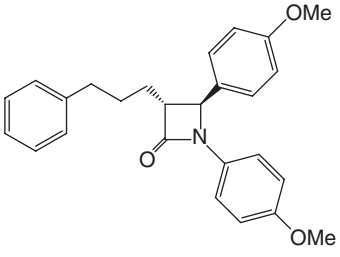

Figure 1.15 SCH 48461.

Compound A was inactive but compound B showed activity in hamsters. Several derivatives were synthesized and investigated *in vitro* (ACAT assay: inhibition of the esterification of cholesterol by oleic acid) and *in vivo* (inhibition of plasma cholesterol and accumulation of cholesteryl ester in 7 day cholesterol-fed hamsters).

The *in vitro* and *in vivo* activities showed a poor correlation; therefore, only the *in vivo* results were followed and SCH 48461 (Figure 1.15) was shown to reduce the serum cholesterol in clinical trials.

SCH 48461 was found to be rapidly and completely metabolized in animals and the metabolite mixture had a higher activity of cholesterol absorption than did the clinical candidate. The most probable metabolites were synthesized and tested *in vivo* to identify the most potent metabolite of SCH 48461 (Figure 1.16). Further optimization of this compound by introducing two fluorine atoms to block metabolism afforded ezetimibe. (Figure 1.17) which was 50 times more potent than SCH 48461 in the cholesterol-fed hamster assay. Following successful clinical trials ezetimibe was introduced in the market in 2002. It was only in 2004 that Schering-Plough researchers discovered its mechanism of action. The molecular target of ezetimibe is the NPC1L1 (Niemann-Pick C1-like1) protein, which is a critical mediator of cholesterol absorption.

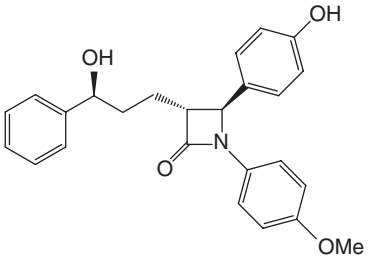

Figure 1.16 Potent metabolite of SCH 48461.

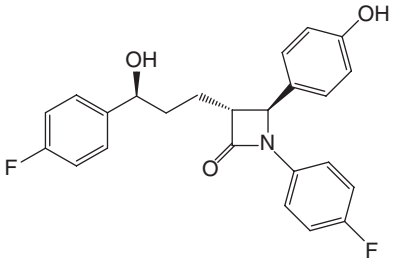

Figure 1.17 Ezetimibe.

1.6.1
Summary of Ezetimibe Discovery

A research program into cholesterol absorption inhibitors started with inhibitors of ACAT enzyme. Poor correlation between *in vitro* and *in vivo* assays led to the abandonment of the *in vitro* studies, and the initial azetidinone derivatives were optimized in animal tests to give a clinical candidate. It was further optimized following analysis of metabolites and direct analogs to afford ezetimibe whose mechanism of action was elucidated years after its introduction.

1.7
Lamotrigine (Discovery of a Standalone Drug for the Treatment of Epilepsy)

The discovery of lamotrigine as a standalone drug was recently described in a book chapter [3].

The discovery process was partly serendipitous, based on the observation that folic acid produces epileptogenic foci and that antiepileptic drugs (Figure 1.18) such as phenytoin, phenobarbital, and carbamazepine have antifolate properties. Thus, a correlation between antiepileptic and antifolate properties was assumed.

In 1973, Burroughs Wellcome (now GSK) researchers examined the anticonvulsant activity of their investigational antifolate drugs [5]. Pyrimethamine was developed in 1950 for both the treatment and prevention of malaria. It was found to have some anticonvulsant and antifolate activity, and it was increased in the analog BW 99U (Figure 1.19).

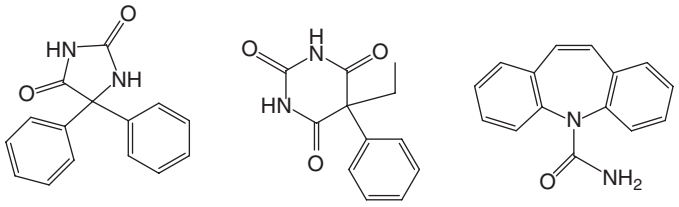

Figure 1.18 Antiepileptic drugs: phenytoin, phenobarbital, and carbamazepine.

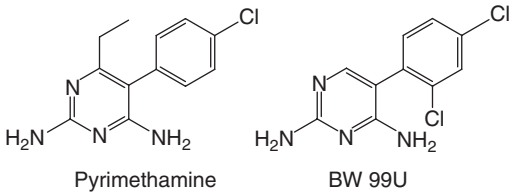

Figure 1.19 Pyrimethamine and BW 99U.

A series of structurally analogous phenyltriazines were synthesized in order to enhance anticonvulsant activity. One of these, BW 288U, had good anticonvulsant activity, although it was a mediocre antifolate. Further optimization afforded the most active analog, lamotrigine, which had a very weak antifolate activity. Lamotrigine (Figure 1.20) was at least as potent as phenytoin and long-acting. It was introduced in 1990 for the treatment of partial and secondary generalized seizures.

Lamotrigine is the first medication besides topiramate used in the treatment of seizures associated with the Lennox–Gastaut syndrome, a severe form of epilepsy. It was noticed that patients reported a higher level of happiness and mastery, or perceived internal locus of control, independent of seizure control. It received approval in 2003 for the treatment of bipolar I disorder, the first drug to do so since lithium.

In vitro studies demonstrated that lamotrigine primarily acts as a blocker of voltage sensitive sodium ion channels.

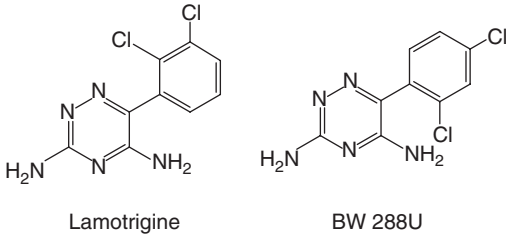

Figure 1.20 Lamotrigine and BW 288U.

1.7.1
Summary of Lamotrigine Discovery

An erroneous working hypothesis, namely the hypothetical correlation between antiepileptic drugs and antifolate acidity serendipitously helped to select pyrimethamine, an antimalaria drug, as a lead molecule to search for new anticonvulsive agents among its analogs. This research work afforded the successful antiepileptic lamotrigine, which has a different mechanism of action.

1.8
Omeprazole (Proton Pump Inhibitor Acid-Suppressive Agent)

The discovery of proton-pump inhibitors has been described in a chapter of a book in 2006 [6].

The treatment of gastroesophageal reflux disease (GERD) and peptic ulcers had a breakthrough during the late 1970s with cimetidine and other analogous H_2 receptor antagonists. The second breakthrough was the introduction of proton-pump inhibitors at the end of 1980 and in the 1990s. Proton-pump inhibitors have a higher efficacy and a longer duration of action.

The success story of proton pump inhibitors goes back to antigastrin research which started in the 1960s. The peptide hormone, gastrin, is produced in the lower stomach and it stimulates the production of hydrochloric acid in the parietal cells. After the structure elucidation of gastrin (1964), ICI researchers synthesized about a thousand substances similar to the gastrin molecule but none could be developed. Servier and Searle also synthesized the gastrin analogs CMN 131 and SC-15396 (antigastrin) (Figure 1.21).

The molecules of Servier and Searle had weak antisecretory effects in animals, but because of toxicity they were not developed. Researchers at Hässle used CMN 131 as the lead molecule, and derivatives, which had no thioamide moiety, were designed in order to avoid its toxic effects. A new animal model, the conscious gastric fistula dog, was a very important tool in the successful research to give timoprazole (Figure 1.22).

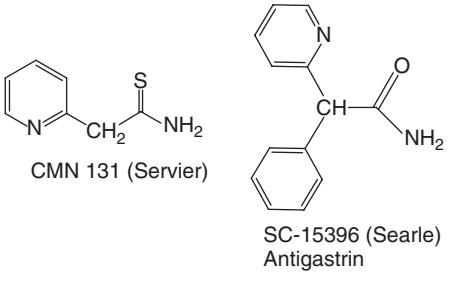

Figure 1.21 Gastrin receptor blockers.

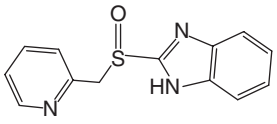

Figure 1.22 Structure of timoprazole.

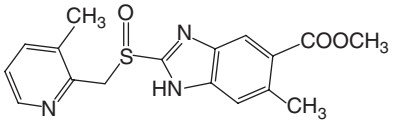

Figure 1.23 Structure of picoprazole.

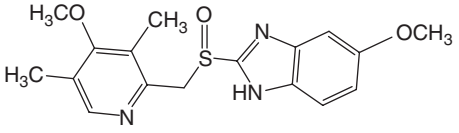

Figure 1.24 Structure of omeprazole.

Timoprazole caused enlargement of the thyroid gland and research continued to study substituted derivatives of timoprazole. Picoprazole (Figure 1.23) was the most potent antisecretory compound in this series without thyroid effects and it was a clinical candidate in 1976.

Picoprazole, however, caused necrotizing vasculitis in beagle dogs, but this side effect was observed only in dogs treated with a particular antiparasitic drug.

At the end of 1970s the proton pump (an H^+, K^+-ATP-ase) was discovered which regulates acid secretion in parietal cells and in 1983 substituted benzimidazoles, such as timoprazole were found to inhibit the proton pump.

Optimization continued using *in vitro* techniques and a great number of new substituted benzimidazoles were studied. The product of this research was omeprazole (Figure 1.24) synthesized in 1979. Following a long development process omeprazole was introduced in the market in 1988.

1.8.1 Summary of Omeprazole Discovery

Antigastrin projects started in 1967 and the discovery process lasted 4 years to give a lead compound of thioamide structure (CMN 131). The lead compound, however, was too toxic and heterocyclic compounds, where no thioamide moiety was present, were designed. The new molecules were tested in conscious gastric fistula dogs to give picoprazole, and its further optimization with the help of *in vitro* studies of proton pump inhibition afforded the successful pioneer drug, omeprazole.

1.9 Outlook

In this short survey we have discussed five very important drug discoveries where the starting targets helped the discovery process, but the drug product had a different mechanism of action.

The following general remarks can be made for target-based drug discovery research:

1) In target-based drug discovery, it is very useful to start phenotypic screening as early as possible, and if there are insufficient correlations between the two approaches, then phenotypic screening should be preferred.
2) The above very successful drug discoveries demonstrate that even an inappropriate target can be very useful to generate an important lead molecule.
3) It can happen that the mechanism of action of a drug will be discovered in a late phase of the drug research, or only after the introduction of the drug.

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List of Abbreviations

ACAT	acyl-coenzyme a Cholesterol acyltransferase
ACE	angiotensin-converting enzyme
COPD	chronic obstructive pulmonary disease
COX	cyclooxygenase
DM1	mertansine, a derivative of maytansine, cytotoxic agent
DPP	dipeptidyl peptidase
GLP-1	glucagon-like peptide-1
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
5-HT	5-hydroxytryptamine (serotonin)
JAK	Janus kinase
NE	norepinephrine
NPC1L1	Niemann-Pick C1-like1
PDE	phosphodiesterase
RNA	ribonucleic acid
SERT	serotonin transporter
SGLT-2	sodium-glucose transporter type 2
SSRI	serotonin reuptake inhibitor
TNF	tumor necrosis factor

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