Analogue-based Drug Discovery

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Preface

The International Union of Pure and Applied Chemistry (IUPAC) is the global civil organization of chemists. The Union is organized into Divisions, with Division VII being devoted to Chemistry and Human Health. The latter incorporates the Subcommittee for Medicinal Chemistry and Drug Development which has projects in various stages of completion. One of these projects, which is devoted to "Analogue-Based Drug Discovery", was initiated in 2003.

The goal of the project is to study the role of analogue drugs for medicinal chemistry, and in this respect two interesting points have come to light:

1. Statistically, every second drug is an analogue.
2. The market value of analogue drugs amounts to approximately two-thirds of that for all small-molecule drugs.

Clearly, in order to have reached this level of importance, analogue drugs must have special value.

Today, it is not too difficult to identify analogues among the most frequently prescribed drugs, on the basis of their similarities in structure and biological properties. In the present book, analogue drugs have, for the first time, been collected systematically on the basis of two sources:

- by using actual data from the Anatomical-Therapeutic Chemical (ATC) System of the World Health Organization (WHO); and
- by using the most recently available data of IMS (the former Intercontinental Marketing Services) Health.

In this way, among the Top 500 most frequently used drugs, 67 analogue classes and 306 analogue drugs have been identified.

This book focuses on both structural and pharmacological analogues – that is, those analogues which have similar chemical and biological properties – although some examples are also included where the analogue is derived purely on a similar chemical or a similar biological basis (but not both).

Within the book, it is shown how analogues play an important role in medicinal chemistry and, more importantly, how they optimize drug therapies. Hence, it was for this reason that we sought to select diverse fields of drug research and medicinal chemistry.

The aim of the book was not to provide a comprehensive review, but rather to describe selected analogue classes in a more detailed manner. In support of this aim, we should point out that nine of the authors have played key roles as co-inventors in the discovery of some of the very important drugs detailed in the book.

This book should serve as a useful reference for experts in medicinal chemistry and also for students of this field. Moreover, it will also be of interest to a wide range of scientists, including organic chemists, biochemists, pharmacologists and clinicians, who are interested in drug research.

We extend our sincere thanks to many people involved in the book's preparation. For data collection, we thank our co-workers at Richter Ltd. (Budapest, Hungary): Ildikó Balló, Andrea Donát, Péter Erdélyi, Dr. Tamás Fodor, Sándor Lévai, György Szabó, Dr. Attila Szemző, Katalin Szőke, and Krisztina Vukics.

We are also very much obliged to all project members of the IUPAC Medicinal Chemistry Subcommittee: Prof. Eli Breuer, Prof. Giovanni Gaviraghi, Prof. Per Lindberg, Dr. John Proudfoot, Prof. Jörg Senn-Bilfinger, Prof. Henk Timmerman, and Prof. Camille G. Wermuth, each of whom has contributed chapters. We are also grateful to Prof. Paul W. Erhardt who, as President of the Division of Chemistry and Human Health of the IUPAC, helped in the development of the book, not only in several committee discussions but also as an author. Our thanks are also extended to all co-author experts.

Special thanks are due to Dr. Tom Perun of the IUPAC Medicinal Chemistry Subcommittee, Dr. Hanns Wurziger (Merck KGaA, Darmstadt), Dr. Derek Buckle (DRB Associates), and Dr. Stefan Jaroch (Schering AG, Berlin) for their help in the final preparation and review of the manuscript.

We also received outstanding help from Prof. Sándor Kerpel-Fronius who, as a clinical pharmacologist, helped to create a bridge between medicinal chemistry and clinical pharmacology.

We hope that this book will be a useful reading for all experts participating in drug discovery, both in the industry and in academia.

And last – but not least – we welcome comments from readers, and assure them that these will be taken on board if we are fortunate enough to run to a second edition!

János Fischer and C. Robin Ganellin
Budapest and London
May 2005

Introduction

János Fischer and C. Robin Ganellin

The discovery and development of new drugs to provide medicines for treating diseases is the main role of the pharmaceutical industry. The impact of this process on the well-being of society is considerable, but it is a difficult and costly procedure to conduct. Biological organisms – and especially human beings – are extraordinarily complex, and our understanding of how they function at the molecular level remains rudimentary, although considerable advances in knowledge have been made in recent decades. Whilst an advanced industrial society was able to plan and deliver a man to the moon following a 10-year program, almost 40 years on we are still only able to treat about 60% of cancer patients effectively, and do not understand how to correct most mental diseases.

In order to treat a disease, an attempt must be made to put right something that has gone wrong. However, because of our limited understanding of normal state functions at the molecular level, we must work empirically and in doing so resort to much trial and error. In general, the same situation applies to new drug discovery, with the sources of new drugs falling into three main categories:

- Existing drugs
- Screening against a physiological target
- Structure-based drug design

Existing Drugs

The most fruitful basis to discover a new drug is to start with an old drug, and this has been the most common and reliable route to new products. Thus, existing drugs may need to be improved, for example to develop a better dosage form, to improve drug absorption or duration, to increase potency and reduce the daily dose, or to avoid certain side effects. On occasion, the existing drug is a natural product, but more often than not it is a synthetic compound, and many such examples are provided later in this book.

Natural Products

Historically, natural products have formed the oldest basis for new medicines, and natural selection during evolution and competition between the species has produced powerful, biologically active natural products. These can serve as chemical leads, to be refined by the chemist by creating analogues that will provide a more specifically acting drug, or perhaps avoid a delivery problem or an unwanted adverse side effect.

For example, molds and bacteria produce substances that prevent other organisms from growing in their vicinity. The famous *Penicillium* mold led, via the pharmaceutical industry, to penicillin. However, penicillin was not stable in the acidic environment of the stomach, and so compounds were synthesized by chemists to produce a range of useful semisynthetic penicillin analogues. An example of the use of analogues to develop new antibacterial antibiotics is provided in Chapter II-14, on the development of moxifloxacin.

Another fruitful means of identifying pharmacologically active natural products has been that of folk law remedies, many of which are plant products. Typical examples include alkaloids, such as atropine (from plants of the Solanaceae family, known to the ancient Greeks) and reserpine (from *Rauwolfia serpentina*, the snakeroot), which is popular in India as a herbal remedy for use as a tranquilizer or antihypertensive. Other chapters in the book relate to stigmines (based on physostigmine, an anticholinesterase alkaloid from the Calabar bean in West Africa) that are used to treat Alzheimer's disease (Chapter II-12), and opioid receptor ligands (based on morphine, the most important alkaloid of the opium poppy) for pain relief and as antitussives (Chapter II-11).

Synthetic Drugs

A very important type of synthetic drug is one that opens up a new therapeutic treatment, and this is referred to as a *pioneer drug* because it is used to pioneer a new type of therapy, or to make a marked improvement over what was previously possible. Such a drug is often referred to as "First in class", and might arise through the observation of a side effect of a drug that is already in use but can then be exploited by making an analogue. The side effect may be the result of an astute observation made during pharmacological studies in animals, or from clinical investigations in patients. An example is the discovery of sulfonamide diuretics during the 1950s following the observation that the antibacterial drug sulfanilamide made the urine alkaline by inhibiting the enzyme, carbonic anhydrase. This rendered the then-used toxic organomercurials obsolete, and so constituted a considerable improvement in therapy.

Another example is the discovery made during the use of the antihistamine promethazine to treat surgical shock. In order to improve potency, a chlorine atom was incorporated into the drug molecule. Subsequently, when the patients seemed to be unconcerned about undergoing surgery, chlorpromazine – the first

phenothiazine antipsychotic drug – was born, thereby opening up a new era in the treatment of mental disease.

A more recent example is that of sildenafil which, as a result of observations made during Phase I studies in male volunteers, is now used to treat erectile dysfunction. Sildefanil had originally been designed as an analogue of zaprinast, and a more selective phosphodiesterase inhibitor (PDE5) for use as a cardiovascular agent (see Chapter I-1).

Although such drugs have not been "designed" for their newly observed action, they usually trigger the start of an analogue program to improve upon their activity.

Physiological Targets

Pioneer drugs may also arise more deliberately as a result of ligand design, for example, to block an enzyme, or to block a biogenic amine receptor. Examples are the first inhibitor of the angiotensin-converting enzyme (ACE), captopril, the first H_1-receptor antihistamine, phenbenzamine, the first β-blocker, pronethalol, and the first histamine H_2-receptor antagonist, cimetidine. These have all given rise to analogue programs described later in the book (Chapters II-6, II-18, II-8 and II-1 respectively).

More recently, as a result of the considerable explosion in scientific knowledge of cellular biochemistry and cell biology, a large number of physiological targets have been considered for drug action. A major problem however in this regard is to relate the isolated target to the physiology of the whole animal. Furthermore, it is never clear at the outset of a research program that the particular target will determine the outcome of a disease, as Nature rarely issues monopolies to the putative transmitters. Another problem is that physiological targets may not have a known specific messenger substance, and so there may not be a chemically based lead. Hence, attempts must be made to identify a lead through the high-throughput screen (HTS) of a chemical library.

Structure-Based Drug Design

On occasion – although still rather rarely – sufficient molecular information is known about the physiological target (e.g., it may be the crystal structure of an enzyme showing the precise geometry of the active site) that an attempt can be made to design directly a drug molecule to fit. Although this situation is rather rare, it is clearly intellectually satisfying if success is achieved. In reality, this situation should perhaps be termed "structure-assisted drug design", and examples to date have occurred in the anti-HIV field of drug research and recently in discovery of a promising renin inhibitor (aliskerin).

The foregoing discussion should have provided the reader with the impression that new drug discovery is a very difficult and risky business, and indeed, there are very few industries prepared to invest in research programs where the likeli-

hood of success is so low, especially if the intended outcome is a pioneer drug. Typically, the time scale is likely to be 10–20 years, and there is no guarantee that the product will have an adequate impact on the disease process, or be sufficiently safe and free of unwanted side effects.

Analogue-Based Drug Design

The development of a pioneer drug is extraordinarily uncertain because its therapeutic use has not yet been validated clinically. On the other hand, preparing an analogue of an established drug has the considerable advantage that the predicted therapeutic use of the analogue has already been proved. This removes a major uncertainty from the overall risk of success. Nonetheless, there are still many hurdles to overcome, notably with regard to pharmacokinetic behavior and safety. It is important, however, to identify at the outset of the research program the expected clinical advantage of the analogue over the established drug which is being used as a lead. The aim must be to provide an improvement in the use as a medicine.

Very often, a pioneer drug which demonstrates its success will stimulate many companies to seek an improved analogue. Since the identification of success will be a clinical publication or annual report of sales, companies tend to start their research programs at about the same time. Many different new potential analogue drugs may therefore appear within a year or two of each other, and all must undergo extensive preclinical laboratory studies for safety, as well as clinical trials to prove their advantage over the lead medicine. Eventually, the potential new drug must be marketed in order to gain access to a sufficiently wide patient population and to reveal its advantages and confirm its safety and lack of adverse side effects.

Thus, companies have exchanged the uncertainty of having to determine the clinical use of a pioneer product for the uncertainty which arises through competition with other companies to demonstrate a clinical advantage for their analogue product. The latter is usually a lesser uncertainty and, indeed, there is always the likelihood that a competitive product may run into difficulties – for example, unexpected side effects, a poorer clinical performance than initially predicted, or inadequate marketing. Thus, there are powerful reasons for continuing to develop new analogue compounds, and this leads to an apparent proliferation of new products which, for some time, may lead to confusion about which is the most suitable drug treatment.

From an outsider's view of the pharmaceutical industry, this proliferation of products may be seen as an example of rampant commercialization. The analogue products are often regarded as “me-too” compounds – a term used pejoratively, notably by those who indulge in attacking the pharmaceutical industry, to suggest that because a pioneer medicine has proved to be commercially valuable, other companies want to share in the commercial success. Of course, companies must be commercially successful to stay in existence, as with any other business enterprise, but this cannot be the only basis for a new drug. As has been explained

above, the new drug must demonstrate an advantage if it is to succeed. In effect, the application of new analogue products is the historical means by which a particular drug therapy becomes optimized, and this is clearly demonstrated by the many examples provided in the present book.

Defining Analogues

The term "analogue" is used in its chemical sense and is defined in the IUPAC medicinal chemistry glossary as "... a drug whose structure is related to that of another drug but whose chemical and biological properties may be quite different."

It is useful for present purposes to have a broader definition of analogues, where not only the chemical relationships, but also the pharmacological properties are considered.

In the present context, we consider an analogue drug to be one that has a chemical and/or pharmacological relationship to another drug. We have used a classification of analogue drugs according to three categories in which we have defined chemistry in terms of chemical structure.

Structural and Pharmacological Analogues

Structural and pharmacological analogues are drugs which have similar chemical structures, and a similar main pharmacological activity. One special class of these is considered to be *direct analogues* if they have identical pharmacophores – that is, they can be described by a general structure which includes most of the chemical skeleton. Many analogues, however, share only a small part of the skeleton, and in this case they are not direct analogues.

It is sometimes difficult to discern any true chemical similarity, but the development of an analogue may have started with the lead structure and passed through a series of iterative structure–activity relationships (SARs). Where there is such a historical development, the analogues are still considered to have a structural and pharmacological relationship.

The histamine H_2 antagonist anti-ulcer drugs (see Chapter II-1) illustrate the difference between the definitions. Thus, burimamide provided proof of principle, while metiamide, a *direct analogue*, went into clinic trials and validated the target by demonstrating the therapeutic use. However, metiamide had an unacceptable side effect (granulocytopenia), and so another *direct analogue*, cimetidine, became the *pioneer drug*. With ranitidine came a change in the ring structure (imidazole replaced by dimethylaminomethyl-furan); this does not have the same SAR pattern and so must be considered to be a *structural and pharmacological analogue* (i.e., not a *direct analogue*). Nizatidine appears as a *direct analogue* of ranitidine (thiazole replaces furan). Famotidine has several major changes in structure, but still retains the $CH_2SCH_2CH_2$ chain and the heterocycle and polar "end group"; thus, it is also a *structural and pharmacological analogue*. Roxatidine has many dif-

ferences in its structure and might be considered as a *pharmacological analogue*; however, its SAR development can be directly traced to other analogues with a general structure that fits all of the above compounds, so it must be considered to be a *structural and pharmacological analogue*.

Structural Analogues

Structural analogues are drugs which have a similar chemical structure but have quite different pharmacological properties. These drugs are usually prepared with the intention of being a structural and pharmacological analogue but then, unexpectedly, another pharmacological activity appears. An example is in the case of opiate agonists and antagonists (see Chapter II-11) where morphine, as a prototype opiate agonist, has an N-methyl substituent. The *N*-allyl-normorphine, nalorphine, is used as a morphine antagonist.

In some cases, the simple modification of a drug structure can essentially modify the biological activity profile, whilst preserving some part of the original activity. Drospirenone (see Chapter II-17), an orally active progestin contraceptive with antimineralcorticoid properties, is an example of an analogue-based drug discovery process that started from the diuretic spironolactone.

Pharmacological Analogues

Pharmacological analogues are drugs which have a similar pharmacological activity without having any discernible chemical or structural relationship. This means that different pharmacophores exist to explain the same pharmacological activity of structurally different drugs. Leads for such compounds can arise through screening and/or computer modeling. These analogues are beyond the scope of this book. An example is provided by the three compounds nifedipine, verapamil, and diltiazem, all of which are L-class voltage-gated calcium-channel blockers (see Chapter II-7).

The Content of the Book

This book presents the role of analogues in medicinal chemistry and their contribution to new drug discovery. In Part I, the various chemical approaches to making analogues are reviewed and the general aspects of analogue-based drug discovery (ABDD) are summarized, whilst in Part II are described 19 examples of analogue classes, together with relevant case studies. A table of structural and pharmacological analogues of the most frequently used drugs is provided in Part III.

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