Methods and Principles in Medicinal Chemistry

Edited by Nathan Brown

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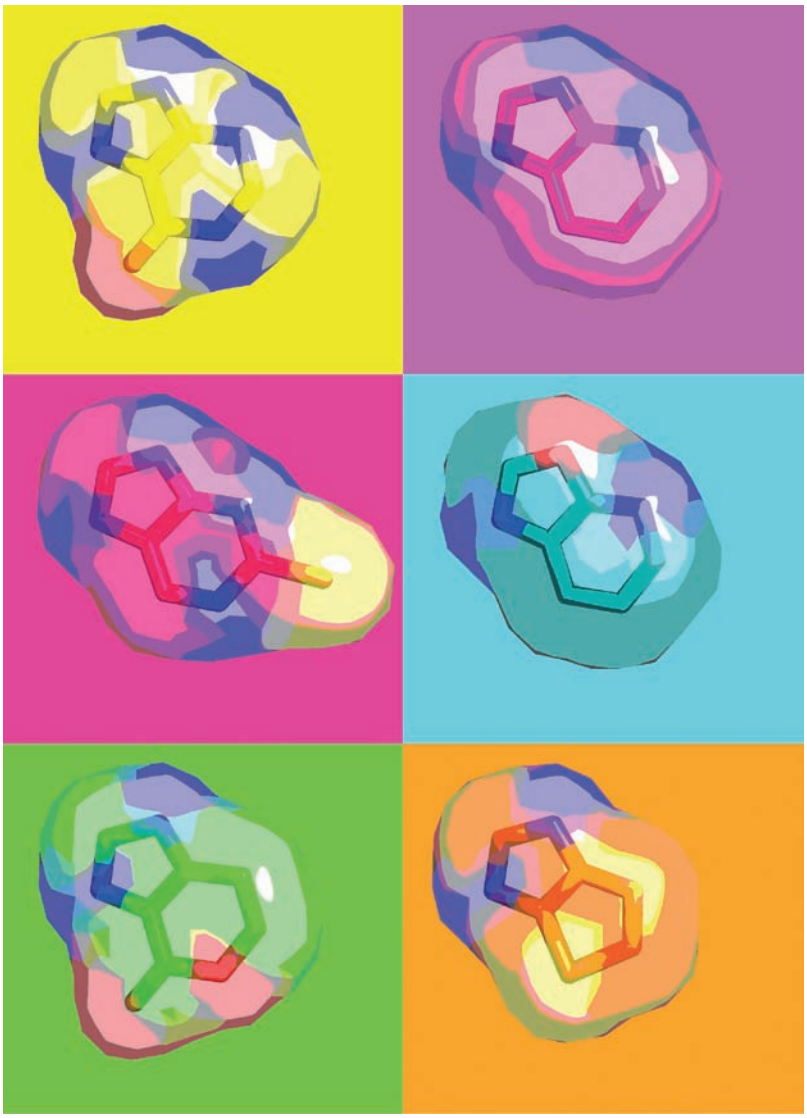
Bioisosteres in Medicinal Chemistry



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Preface

Bioisosteric replacement of substituents, ring atoms, linkers, and other groups aims to generate chemical substitutes with related biological properties, in the hope that the new analogues may have somewhat better properties. Such replacements are the toolbox of medicinal chemists to optimize their lead structures with respect to lipophilicity, solubility, activity, selectivity, absorption, metabolism, and lack of toxic and other side effects. Whenever an analogue with some improved properties is observed, the new compound is taken as the starting point for further modification. In this evolutionary procedure, either a preclinical or a clinical candidate results or the project has to be terminated, without success. Whereas the whole process quite often follows a trial and error procedure, certain empirical rules developed in medicinal chemistry. Very simple ones are, for example, the replacement of a hydrogen atom in the *para*-position of a benzene ring, to avoid rapid metabolic degradation, or, on the other hand, the introduction of an aromatic methyl group instead of a chlorine atom, to avoid too long biological half-life. More sophisticated rules exist for modification of the ligands of certain targets, for example, proteases or kinases.

The organization of this book follows a logical sequence, starting with Part One on the principles of bioisosterism, including an introductory chapter, and chapters on classical bioisosteres in medicinal chemistry and the logical but often surprising consequences of bioisosteric replacement. Part Two presents a database on bioisosteres and bioanalogues and discusses the search for bioisosteres, using the Cambridge Structure Database of 3D structures of small molecules, as well as the mining of bioisosteric pairs. Part Three presents methods to identify bioisosteres under the aspect of physicochemical properties, molecular topology, molecular shape, and protein 3D structures. Part Four describes a computer program for drug design, using medicinal chemistry rules, discusses the bioisosteric modification of a receptor antagonist, and ends with a concluding chapter on perspectives from medicinal chemistry.

Whereas some reviews on bioisosteres are found in the literature, as well as chapters in medicinal chemistry books, no dedicated monograph on bioisosteres has been published so far. Thus, we are very grateful to Nathan Brown for editing such a book, which will help novices in the field as well as experienced scientists to manage lead structure optimization in an even more rational manner. In addition, we are

very much indebted to Frank Weinreich and Heike Nöthe, both at Wiley-VCH. Their support and ongoing engagement, not only for this book but also for the whole series "Methods and Principles in Medicinal Chemistry," adds to the success of this excellent collection of monographs on various topics, all related to drug research.

March 2012
Düsseldorf
Weisenheim am Sand
Zürich

Raimund Mannhold
Hugo Kubinyi
Gerd Folkers

A Personal Foreword

"Hamlet: Do you see yonder cloud that's almost in shape of a camel?
Polonius: By th' Mass, and 'tis like a camel, indeed.
Hamlet: Methinks it is like a weasel.
Polonius: It is backed like a weasel.
Hamlet: Or like a whale.
Polonius: Very like a whale."

Hamlet, Act III, Scene II
William Shakespeare

The essence of design is the identification of appropriate constituents and their careful arrangement in sympathy with the requirements of the desired object. The same principles apply in drug design, where the components are elements and elemental groups, and their arrangement is achieved through the synthetic organic chemistry that is undertaken. The ultimate requirement in the design of new drugs is an entity that summons a physiological response of benefit to the patient.

In this book, we cover the key aspects of drug design through the identification and replacement of bioisosteric groups within the context of the drug design ethic. Bioisosterism is a phenomenon where molecular groups are functionally similar, that is, they have a similar biological effect, while modulating other properties. This is the first book to provide a general overview of the field of bioisosterism at a time when its application has become a formal process. There are now many information sources and design tools available to assist the medicinal chemist in the identification of relevant bioisosteres.

The first part of this book covers the historical aspects of bioisosterism, from its founding principles of isosterism from Langmuir through defined sets of classical isosteres and bioisosteres, to the potential consequences of bioisosteric replacement in context.

A considerable amount of knowledge has been collated in recent years, in large molecular databases with metadata that can be analyzed and brought to bear in bioisosteric replacement. Knowledge-based methods form the second part, covering experimentally determined bioisosteric replacements from the medicinal chemistry

literature; small-molecule crystal identification of bioisosteres; and mining unknown bioisosteres from these databases through the application of recently developed methods for their identification.

One can describe a molecule in many ways and the same applies to bioisosteres. Molecular descriptor methods are covered in the third part by the application of different representations. A number of computational approaches to bioisosteric replacement are covered in chapters on physicochemical properties, molecular topology, molecular shape, and the use of protein structure information. Each chapter covers many common methods and overviews of when best to apply these methods, and where they have been successfully applied.

This book concludes with two case studies of where bioisosteric replacement strategies have been applied in drug discovery, to provide demonstrable evidence of their utility. Finally, a few leading scientists in this field have kindly provided personal perspectives on bioisosterism and its relevance to drug discovery.

My sincere wish is that you enjoy reading this book as much as I did working with the very talented team of scientists who contributed chapters. I would also like to thank the publishing team and the series editors for their help in bringing this book together.

London, 2012 *Nathan Brown*

Part one
Principles

Bioisosteres in Medicinal Chemistry, First Edition. Edited by Nathan Brown

1
Bioisosterism in Medicinal Chemistry

Nathan Brown

1.1
Introduction

One of the key challenges for the medicinal chemist today is the modulation and mediation of the potency of a small-molecule therapeutic against its biological target. In addition, it is essential to ensure that the molecule reaches its target effectively while also ensuring that it satisfies necessary safety requirements. One of the most significant approaches to assist in efficiently navigating the available chemistry space is that of bioisosteric replacement.

This book, the first dedicated solely to the subject of bioisosterism, covers the field from the very beginning to its development as a reliable and well-used approach to assist in drug design. This book is split into four parts. The first part covers the principles and theory behind isosterism and bioisosterism. The second part investigates methods that apply knowledge bases of experimental data from a variety of sources to assist in decision making. The third part reports on the four main computational approaches to bioisosteric identification and replacement using molecular properties, topology, shape, and protein structure. This book concludes with real-world examples of bioisosterism in application and a collection of reflections and perspectives on bioisosteric identification and replacement from many of the current leaders in the field.

This chapter provides an overview of the history of bioisosterism from its beginning in the early twentieth century to the present day. We also provide an overview of the importance of judicious bioisosteric replacement in lead optimization to assist in the path toward a viable clinical candidate and, ultimately, a drug.

1.2
Isosterism

James Moir [1] first considered isosterism in all but name, in 1909. It was not until 1919 that the term isosterism was given to this phenomenon by Irving Langmuir [2] in his landmark paper "Isomorphism, isosterism and covalence." The focus of this

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Table 1.1 Experimental data from Landolt–Börnstein's tables and Abegg's handbook for nitrous oxide (N_2O) and carbon dioxide (CO_2).

Property	N_2O	CO_2
Critical pressure (atm)	75	77
Critical temperature (°C)	35.4	31.9
Viscosity at 20 °C	148×10^{-6}	148×10^{-6}
Heat conductivity at 100 °C	0.0506	0.0506
Density of liquid at −20 °C	0.996	1.031
Density of liquid at + 10 °C	0.856	0.858
Refractive index of liquid, D line, 16 °C	1.193	1.190
Dielectric constant of liquid at 0 °C	1.598	1.582
Magnetic susceptibility of gas at 40 atm, 16 °C	0.12×10^{-6}	0.12×10^{-6}
Solubility in water at 0 °C	1.305	1.780
Solubility in alcohol at 15 °C	3.25	3.13

early isosterism work was on the electronic configuration of atoms. Langmuir used experiment to identify the correspondence between the physical properties of different substances. Langmuir, in accordance with the octet rule where atoms will often combine to have eight electrons in their valence shells, compared the number and arrangement of electrons between nitrogen, carbon monoxide, and the cyanogen ion and identified that these would be the same. This relationship was demonstrated to be true between nitrogen and carbon monoxide in terms of their physical properties. The same similarities were also reported between nitrous oxide and carbon dioxide when taking experimental data from Landolt–Börnstein's tables and Abegg's handbook (Table 1.1).

However, Langmuir identified one distinct property that is substantially different between nitrous oxide and carbon dioxide, the freezing point: −102 and −56 °C, respectively. Evidence for this was assumed to be due to the freezing point being "abnormally sensitive to even slight differences in structure."

With this observation of the correlation between the structure and arrangement of electrons with physical properties, Langmuir defined the neologism calling them isosteres, or isosteric compounds. Langmuir defined isosterism as follows:

> "Comolecules are thus isosteric if they contain the same number and arrangement of electrons. The comolecules of isosteres must, therefore, contain the same number of atoms. The essential differences between isosteres are confined to the charges on the nuclei of the constituent atoms. Thus in carbon dioxide the charges on the nuclei of the carbon and oxygen atoms are 6 and 8, respectively, and there are $2 \times 8 + 6 = 22$ electrons in the molecule. In nitrous oxide the number of charges on the nitrogen nuclei is 7, but the total number of electrons in the molecule is again $2 \times 7 + 8 = 22$. The remarkable similarity of the physical properties of these two substances proves that their electrons are arranged in the same manner."

Table 1.2 List of isosteres defined by Langmuir in 1919.

Type	Isosteres
1	H^-, He, Li^+
2	O^{2-}, F^-, Ne, Na^+, Mg^{2+}, Al^{3+}
3	S^{2-}, Cl^-, A, K^+, Ca^{2+}
4	Cu^+, Zn^{2+}
5	Br^-, Kr, Rb^+, Sr^{2+}
6	Ag^+, Cd^{2+}
7	I^-, Xe, Cs^+, Ba^{2+}
8	N_2, CO, CN^-
9	CH_4, NH_4^+
10	CO_2, N_2O, N_3^-, CNO^-
11	NO_3^-, CO_3^{2-}
12	NO_2^-, O_3
13	HF, OH^-
14	ClO_4^-, SO_4^{2-}, PO_4^{3-}
15	ClO_3^-, SO_4^{2-}, PO_4^{3-}
16	SO_3, PO_3^-
17	$S_2O_6^{2-}$, $P_2O_6^{4-}$
18	$S_2O_7^{2-}$, $P_2O_7^{4-}$
19	SiH_4, PH_4^+
20	MnO_4^-, CrO_4^{2-}
21	SeO_4^{2-}, AsO_4^{3-}

The list of isosteres that Langmuir described in 1919 is given in Table 1.2. Langmuir extended his concept of isosterism to predicting likely crystal forms using sodium and fluorine ions as exemplars, these having been solved by William Henry Bragg and William Lawrence Bragg – father and son who were together awarded the Nobel Prize for Physics in 1915. Since the magnesium and oxygen ions are isosteric with the sodium and fluorine ions, it follows that magnesium oxide will have a crystal structure that is identical to that of sodium fluoride.

In 1925, H.G. Grimm [3] extended the concept of isosterism, introduced by Langmuir, with Grimm's hydride displacement law:

> "Atoms anywhere up to four places in the periodic system before an inert gas change their properties by uniting with one to four hydrogen atoms, in such a manner that the resulting combinations behave like pseudoatoms, which are similar to elements in the groups one to four places, respectively, to their right."

Therefore, according to this law, the addition of hydrogen to an atom will result in a *pseudoatom* with similar properties to the atom of the next highest atomic number. So, CH is isosteric with N and NH is isosteric with O and so on.

Beginning in 1932, Friedrich Erlenmeyer [4, 5] extended the concepts from Grimm further and the first applications of isosterism to biological systems. Erlenmeyer redefined isosteres as:

> "...elements, molecules or ions in which the peripheral layers of electrons may be considered identical."

In addition, Erlenmeyer also proposed the following three additions to the concept of isosteres:

1) All elements within the same group in the periodic table are isosteres of each other. Therefore, silicon and carbon are isosteres of each other, as are oxygen and sulfur.
2) Pseudoatoms are included to characterize groups that appear superficially different but are actually very similar in physical properties. Pseudohalogens are an instance of this class, where Cl $\approx$ CN $\approx$ SCN, and so on.
3) Finally, ring equivalences are included to permit isosteric matches between different ring systems. One example is the isosteric properties between benzene and thiophene, where $-CH{=}CH- \approx -S-$.

It was with Erlenmeyer that the concept of bioisosterism was introduced to differentiate from classical isosteres, ensuring its relevance to medicinal chemistry. The introduction of ring equivalences is significant. This was the formalization of what we consider to be a bioisosteric comparison and is the first definition of most relevance to medicinal chemistry.

1.3 Bioisosterism

Classical isosteres are traditionally categorized into the following distinct groupings [6]:

1) Monovalent atoms or groups.
2) Divalent atoms or groups.
3) Trivalent atoms or groups.
4) Tetrasubstituted atoms.
5) Ring equivalents.

A number of classical bioisosteric examples are provided in Table 1.3 that illustrate typical replacements possible in each of these five groups.

However, more recent definitions of isosterism, and more specifically bioisosterism, relax these constraints and permit bioisosteric pairings between moieties that do not necessarily contain the same number of atoms. Specifically, nonclassical bioisosteres include the addition of the following two groups:

1) Rings versus acyclic structures.
2) Exchangeable groups.