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Drug Discovery & Development

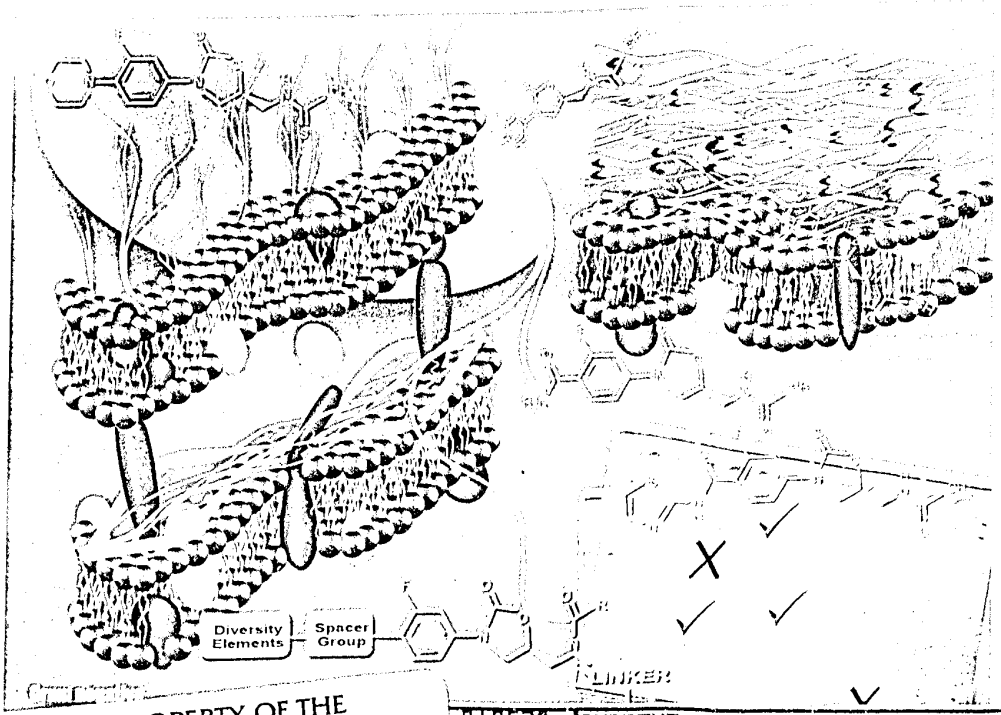
James A Bristol, Simon F Campbell & Paul J Reider EDITORS

In this issue

The Chemistry of Drug Design and Lead Optimization

Edited by William J Greenlee and Manoj C Desai

Authoritative reviews covering aspects of combinatorial chemistry, high-throughput techniques and target validation in drug design and lead optimization



Current Opinion in Drug Discovery & Development

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Aims and organization

The *Current Opinion* journals were developed out of the recognition that specialists have increasing difficulty keeping up to date with the expanding volume of information published in their subject. In ***Current Opinion in* Drug Discovery & Development**, we aim to help the reader by providing in a systematic manner:

- the views of experts on current advances in drug discovery and development in a clear and readable form;
- selection of the most interesting papers from the great wealth of original publications, annotated by experts.

Division of the subject into sections
The subject of drug discovery and development is divided into six major sections, each of which is reviewed once a year.

Selection of topics to be reviewed
Section Editors, who are major authorities in the field, are appointed by the Editors of the journal. They divide their section into a number of topics, ensuring that the field is comprehensively covered and that all issues of current importance are emphasized. Section Editors commission reviews from authorities on each topic that they have selected.

Reviews
Authors write short reviews in which they present recent developments in their subject, emphasizing the aspects that, in their opinion, are most important. In addition, they provide short annotations to the papers that they consider to be the most interesting from all those published in their topic over the previous year. Papers chosen by a reviewer as being 'of special interest' or 'of outstanding interest' are clearly identified in the reference list at the end of each review.

Editorial overview
Section Editors write a short overview at the beginning of the section to introduce the reviews and to draw the readers attention to any particularly interesting developments.

Web alert
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In the last issue of each volume, cumulative indexes of contents, subjects and authors are provided.

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The use of bioisosteric groups in lead optimization

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It is now half a century since Friedman introduced the term bioisosterism for the similar biological activity of structurally related compounds. Since then, the concept has been used extensively and successfully in the optimization of lead compounds in drug discovery. The number of chemical lead compounds has expanded enormously in recent years due to the expression of an increasing number of recombinant proteins, and the screening of these new protein targets against a large number of compounds in high-throughput screens. For the fine-tuning of lead compounds to obtain candidates suitable for clinical trials, which is in most circumstances still a tedious process, the use of bioisosteric replacement can be of significant value. This is especially the case in optimizing for selectivity for a specific target and in improving the pharmacokinetic properties of lead compounds. The use of bioisosteres in lead optimization is illustrated by some recent examples from the literature.

Keywords Bioisosteres, bioisosteric replacement, bioisosteric transformation, bioisosterism, lead optimization

Introduction

With the recent publication of the human genome, it is now clear that the gene-to-protein relationship must be one-to-many, and it is obvious that pharmaceutical companies will select a number of these proteins as possible new therapeutic targets. In the last decade, medicinal chemistry has already been challenged by the expression of an increasing number of recombinant protein targets derived by molecular biology, of which several are suitable targets for research projects. The challenge of finding new chemical lead compounds for these targets has been met by high-throughput screening (HTS) of compound libraries derived from combinatorial chemistry or screening of historical compound libraries, comprising of compounds derived from old research projects. This procedure has now been implemented as standard in most pharmaceutical companies and normally generates a number of leads, which to some extent can be further optimized by parallel synthesis to give compounds with the desired potency and pharmacology.

The lead compounds discovered by this methodology can be very useful in the initial validation of a therapeutic target for a new research project. The identification of a compound which can be immediately used as a clinical candidate, however, is exceedingly rare and a process of optimization generally has to be initiated with the aim of maintaining the activity of the lead compound while improving the physicochemical properties, such as water solubility, logP, pK_a, etc, along with *in vitro* and *in vivo* properties, such as potency, selectivity and ADME (absorption, distribution, metabolism and excretion) profiles [1•].

The final optimization of a lead compound to a drug candidate is therefore, in most circumstances, still a matter of a rational approach to the design and synthesis of single compounds or compound libraries consisting of a very limited number of compounds. QSAR and computational methodology, structure-based design and other technological approaches may be helpful in this process, but the optimization process is frequently supplemented with more intuitive approaches based on, for example, bioisosteric transformations of functionalities within the lead compound to improve its drug-like properties. Finally, the lack of patentability of the lead compound is often a rationale to use bioisosteric replacements for the transformation of a lead compound into a new class of compounds without prior art.

The following review will focus on some recent examples from the literature in which a bioisosteric replacement strategy has been used to improve selectivity for a specific target or the pharmacokinetic properties of a lead compound.

The use of bioisosteric replacement has been recently reviewed by several authors [2••,3•,4•]. For a more detailed discussion on this topic with a number of relevant examples, the reader is directed to these reviews. The use of bioisosteres has traditionally been divided into classical (as given by Burger's definition [5••]) and non-classical bioisosteres. In the examples given, the term has been used broadly for a similar biological activity of structurally related compounds and no discrimination has been made between classical and non-classical bioisosteres. A systematic overview has been attempted by dividing the examples into four different categories:

(i) Ring-to-ring transformation
(ii) Chain-to-ring transformation
(iii) Ring-to-chain transformation
(iv) Chain-to-chain transformation

Ring-to-ring transformations

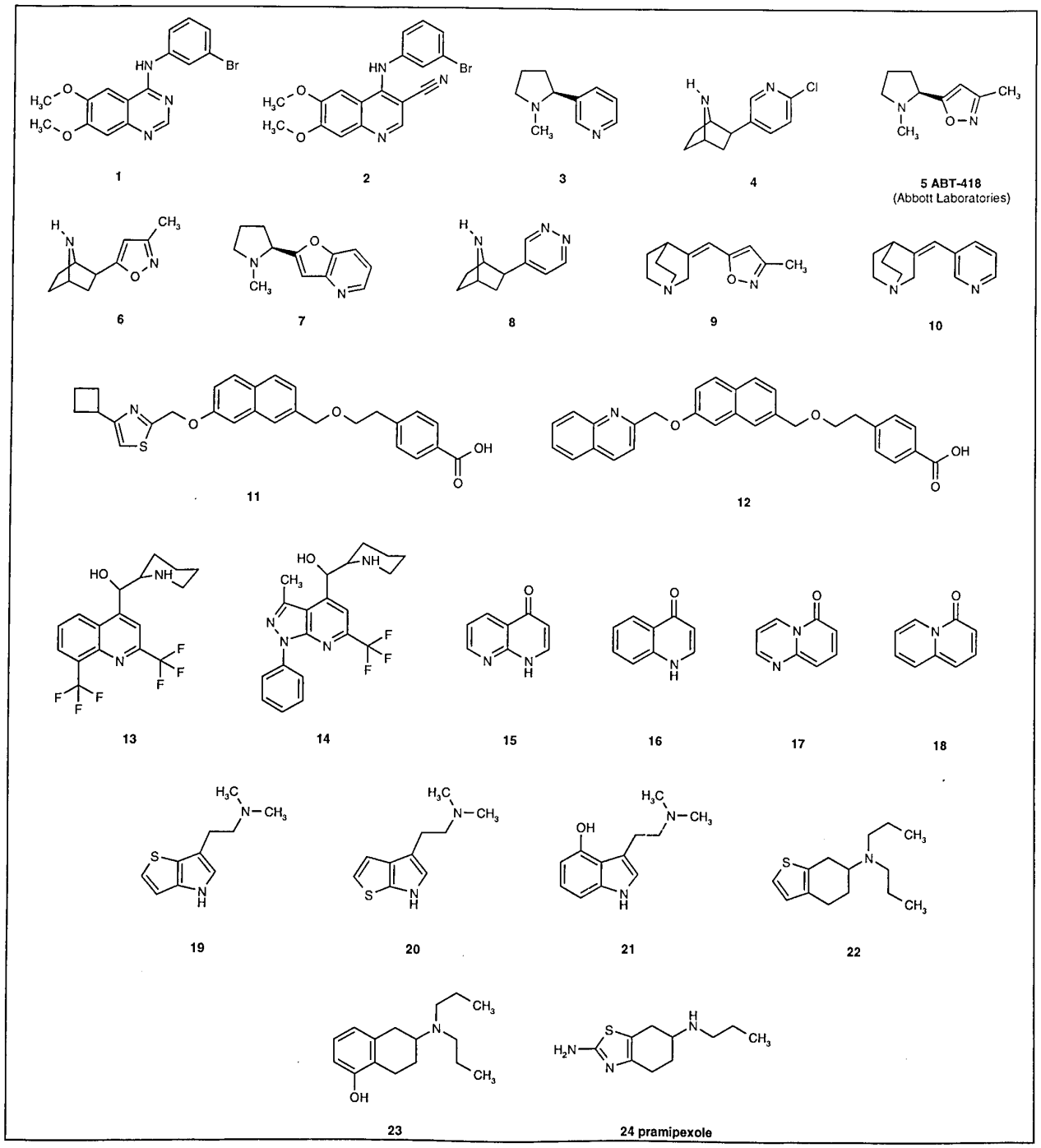
The replacement of a heterocyclic or carbocylic ring with another heterocyclic ring is probably the most widespread method for a bioisosteric transformation used by medicinal chemists. Some of these transformations, such as the substitution of a phenyl carbocycle with a thiophene heterocycle, have been and are still used extensively. Hundreds of examples of ring-to-ring transformation exist, and have been reviewed by several authors [2•,3•,5••].

Of special significance is the proposal that a carbon atom bearing a cyano group can sometimes be bioisosteric with an azomethine group that is hydrogen-bonded to a water molecule [6••]. A new homology model for epidermal growth factor receptor (EGFR) kinase suggests that with the

quinazoline-based inhibitor **1** (Figure 1), the N(3) atom is hydrogen-bonded to a water molecule that, in turn, interacts with Thr[830] in the kinase. It is proposed that quinoline-3-carbonitrile **2** (Figure 1) binds in a similar manner, where the cyano group, which interacts with the same Thr residue, displaces the water molecule. The co-crystallization of lead compounds and the use of macromolecular crystallography for structure determination in drug discovery have become a rapid process that is currently widely used [7]. With the increasing insight into the molecular mechanism for the interaction of ligands with target molecules, this type of replacement may have utility in other areas of drug design and will probably also be extended to other heterocyclic ring systems.

The synthesis of nicotinergic agonists has received much attention over the last couple of years because of their potential use in the treatment of Alzheimer's disease. The putative pharmacophoric elements common to all potent nicotinergic α4β2 ligands include a basic or quaternized

Figure 1. Ring-to-ring transformations.



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