COMBINATORIAL CHEMISTRY

Synthesis and Application

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CONTENTS

1

INTRODUCTION TO COMBINATORIAL LIBRARIES: CONCEPTS AND TERMS

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In the past few years, combinatorial chemistry has become the popular and often misunderstood "new wave" in drug discovery. In some cases, combinatorial chemistry is presented as being in direct competition with rational, or computer-aided, drug design. Nothing could be further from the truth. Combinatorial chemistry encompasses many strategies and processes for the rapid synthesis of large, organized collections of compounds called libraries. When planned intelligently, combinatorial methods produce collections of molecularly diverse compounds that can be used for rapidly screening for biological activity. Without planning, the GIGO (garbage in–garbage out) principle applies. Whether or not a library has in some way been designed or made more or less at random depends on the reasons for preparing the compounds. Combinatorial chemistry as a laboratory practice cannot replace computer modeling as an exercise in refining our basic understanding of molecular interactions. It is likely that both rational drug design and combinatorial chemistry will be used, in concert when appropriate, or directly applied to the problems best suited to each method.

Combinatorial chemistry includes many research areas—new analytical methods, new computer modeling and database-related challenges, new synthetic approaches, new types of reagents, and new types of assays. Although this chapter will provide current leads into all these fields, the basic groundwork for combinatorial chemistry is still being laid. Many new research areas have yet to be explored.

Combinatorial chemistry has its conceptual roots in the immune system. In the body, when a new antigen comes in contact with the preexisting large collection of antibodies, the antibody that binds best is selected and reproduced in large numbers

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