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Preface

HIGH-THROUGHPUT SCREENING IN COMBINATORIAL CHEMISTRY FOR DRUG DISCOVERY

In spite of the recent advances in molecular biology and genomic research, which have helped to elucidate new pathways and have uncovered new targets for pharmacological action, the discovery of drugs has not been as productive as expected. This is due, in part, to the time needed for the synthesis and evaluation of candidate molecules one at a time, and in part to the increasingly complex, costly and long drug development in a heavily reglemented world-wide environment. Because of the recent changes in the health care systems, pharmaceutical industry has been looking for alternative schemes for increasing productivity in a shorter period of time.

The birth of combinatorial chemistry, more than three decades ago, has brought an attractive alternative to serial compound conventional synthesis. Since then, combinatorial synthesis of small molecular mass compounds has become a key component of contemporary drug discovery programmes. Parallel synthesis based on solid or liquid phase systems generates great molecular diversity. Although the underlying principles are the same, the approach is dramatically different. Instead of producing a single compound of previously specified structure, thousands to millions of compounds are synthesised under automated instrumental control within a single operation, i.e. interconnection of a set or sets of small reactive molecules, calling building blocks, resulting in 'chemical libraries' which give rise to hits, leads and candidate drug molecules. These libraries are constructed either as 'primary' for random screening or 'focussed' on a structure with a biological activity. Library congeners should satisfy a certain number of criteria, such as minimum purity and optimized physico-chemical properties (molecular mass, pKa, log D, etc.).

These populations of molecules are screened for particular activity by appropriate high-throughput miniaturised techniques (affinity chromatography and electrophoresis, scintillation proximity assays, interfacial optical assays, immobilisation of target macromolecules, ultrafiltration methods, immunoassays, phage displays, etc.) to obtain pharmacological lead structures.

Characterisation and fingerprinting of library congeners has necessitated the use of rapid, sensitive and highly informative analytical techniques, such as MALDI-TOF mass spectrometry, MAS-NMR, LC-API/MS, LC-NMR, capillary electrophoresis, Fourier transform ion cyclotron resonance, etc.

In order to cope with the large number of compounds to analyse, these techniques necessitate automation and computerisation data management systems.

It is hoped that these innovative approaches will provide new possibilities to pharmaceutical research at the dawn of the new millennium.

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