Preface

In a rational drug discovery approach, it is necessary to identify the cause of the disease and its mechanism at the molecular level. Protein molecules that are the basic cause of the disease are identified first. Altering or modifying the protein–protein interaction could lead to therapeutic agents. The state-of-the-art methodology in drug discovery demands rational drug design, which will lower side effects and enhance therapeutic effects. Research in the pharmaceutical sciences and medicinal chemistry has taken an important new direction in the past two decades with a focus on large molecules, especially peptides and proteins, and DNA therapeutics. Protein and peptide drugs are currently the most rapidly expanding class of drugs. At present, more than 130 different proteins or peptides have been approved for clinical use. Whether it is peptide/protein-based drugs or organic molecules, the process of drug discovery involves several steps. The first is target identification and lead optimization. In the former process, molecules that bind a drug target and modulate the biological activity are identified using an in vitro assay, while in the latter potential drug molecules are optimized with respect to in vitro potency and other important parameters reflecting bioavailability and pharmacokinetic or toxicological properties. When a therapeutic target has been identified and validated, the next stage in drug discovery is to conduct high-throughput screening based on target binding or cellular assay to identify a lead compound. Once a lead compound is identified, the compound is modified chemically for higher activity and less toxicity. This involves the synthesis of a large number of analogs of the lead compound and testing them for biological activity. With several hundred protein targets available, screening thousands of compounds for biological activity and toxicity is a tedious and time-consuming process. In recent years, there has been an interest in disrupting protein–protein interactions using small molecules and peptides. With this interest in protein–protein interactions for targeting drugs, the number of drug targets will increase from hundreds to thousands. Once the drug-like molecule enters preclinical and clinical trials, it becomes an extremely expensive task to study each target. Hence, several methods have been discovered to screen compounds that may have drug-like properties. These methods involve computational, spectroscopic, analytical, and purification methods, cellular assays, and molecular biology methods. In this particular volume of Methods in Molecular Biology, we present 16 chapters related to drug discovery and screening. It is impossible to cover all the methods related to drug discovery in a single volume. Our intent is to give an in-depth view of some protocols that are commonly used in drug discovery laboratories. Some of these techniques may be old and some are relatively new. They include computational docking, quantitative structure–activity relationship (QSAR), peptide synthesis, labeling of peptides and proteins with fluorescent labels, DNA-microarray, zebrafish model for drug screening, and other analytical screening and biological assays that are routinely used during the drug discovery process. With the availability of three-dimensional structures of protein/DNA target molecules, computational methods have played a key role in designing and screening thousands of compounds as possible candidates for druggable molecules. Hence, we have covered computational methods in
detail. Cellular and whole body imaging using fluorescently labeled molecules have gained popularity compared to procedures using radioactively labeled compounds. The method of fluorescent labeling of peptides and proteins is covered in detail in one chapter. Overall, this volume will serve as a laboratory reference for pharmaceutical chemists, medicinal chemists, and pharmacologists as well as for molecular biologists.

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