

Natural Product Drug Discovery

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Natural products and their derivatives have long been of interest in the fields of chemistry, biology, and medicine because of their unique structural diversity, numerous biological activity, and medicinal properties. Natural product based drug discovery and development is a highly integrated multidisciplinary approach. A significant fraction of the drugs are either natural products or are derived from natural products. Natural products represent a unique and rich source of therapeutic agents and lead structures for new drug discovery.

The therapeutic potential of these important molecules, as stated by Berkowitz, “if we eliminated natural products from drug discovery in the past, we would not have the top-selling drug class today, the statins; the whole field of angiotensin antagonists and angiotensin-converting-enzyme inhibitors; the whole area of immunosuppressive; nor most of the anticancer and antibacterial drugs. Imagine all of those drugs not being available to physicians or patients today” [1]. According to Danishefsky, “a small collection of smart compounds may be more valuable than a much larger hodgepodge collection mindlessly assembled” [2].

Development of better drugs originating from natural products can be achieved by combining advanced technologies like chemical synthesis, HTS-HCS assays, informatics, omics, such as genomics, proteomics and metabolomics. Emerging technologies combined with high-resolution instrumentation will help in advance the process.

The major inroads made in the field of total synthesis of natural products with a wide variety of biological properties led to the development of new analogs with improved biological properties. Combinatorial chemistry plays a major role in the development of ideal drug molecule from a large number of potential candidates. Also a wide variety of bioorganic methods are emerging on the scientific frontier which is helping in the drug discovery. As stated by Nicolaou et al. “Today, natural product total synthesis is associated with prudent and tasteful selection of challenging and preferably biologically important target molecules; the discovery and invention of new synthetic strategies and technologies; and explorations in chemical biology through molecular design and mechanistic studies. Future strides in the field are likely to be aided by advances in the isolation and characterization of novel molecular targets from Nature, the availability of new reagents and synthetic methods, and information and automation technologies” [3].

Natural products hold a prominent position as potent cytotoxic drugs for antibody-drug conjugates (ADCs). According to Gromek

and Balunas [4] out of 114 ongoing or recently completed clinical trials, cytotoxic payloads utilized in ADCs only seven payload compounds showed diversity. Out of seven compounds, six are from natural product sources. Cytotoxic natural products become an important component in ADC strategy to make successful antibodies [5].

In silico characterization of natural products and pharmacophore modeling is more challenging, particularly for large macrocyclic lactones and peptides due to their conformational flexibility. Also many natural products do not follow Lipinski’s “Rule of Five” and differ from other properties like heteroatom count, stereo centers, aromatic ring count and lipophilicity, but exhibit biological effects. In combination with modern chemical synthesis HTS-HCS screening and the applications of new concepts in cheminformatics [6] will enhance the chemical space, structural activity and diversity.

Even though lengthy and difficult synthetic routes pose challenge for the discovery of drugs from natural products, technical advancements achieved in the field help in enabling of the screening and evaluation of natural products with greater efficiency. Diversity and the lack of side effects during the treatment, make the naturally occurring compounds an attractive target for development of future drugs.

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