Trop J Nat Prod Res, September 2017; 1(3):95-96

TROPICAL JOURNAL OF NATURAL PRODUCT RESEARCH TJNPR

EDITORIAL

Natural Product Synthesis and Drug Discovery: Shortcomings and Successes

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Natural products have evolved over the years and several of them have been found to interact with biological macromolecules in intact organisms. Their structural complexity often makes it difficult to produce natural drug molecules via chemical synthesis. This limitation can hinder their further development as drugs. Modification of a natural product's structure by chemical synthesis to address issues of unwanted side effects can also be very difficult. As an alternative to chemical synthesis, the natural products are isolated in commercial quantities from their sources. This however, poses other challenges such as the need to obtain enough raw material in an environmentally sustainable fashion to ensure an adequate supply of the drug. There is also variability in how some substances produce often trace amounts of potential drugs. In the pharmaceutical industry, such drawbacks have led to the deprioritization of natural products as drug leads, or even in the total elimination of natural product-based drug discovery efforts, in favor of studying and developing smaller, lower molecular weight molecules, substances that are more easily synthesized and modified. The shift away from natural products as leads is perhaps unfortunate, given their impressive track record as effective drugs, particularly in the fields of cancer therapy and the treatment of infectious diseases.[1]

The structural complexity, including stereochemistry, of natural products is one significant drawback of producing natural products by chemical synthesis during early drug discovery. Advancing a natural product lead may require an investment of years of experimentation and the optimization of multi-step routes to provide sufficient materials for biological evaluation. A second drawback is that often the natural product itself is not ideally suited for animal use due to poor pharmacokinetics, toxicity, stability, etc. Thus, a structural analogue might be preferred. It may, however, be nearly impossible to synthesize enough analogues of such complex molecules, with each analogue requiring a significant investment in time and resources, to find one with the ideal balance of properties that are essential for successful drug development. Even if the natural product or analogue can be synthesized in sufficient quantity for preclinical evaluation, most total syntheses are not amenable to large-scale production of the active compound.

Despite these challenges, significant progress has been made in the synthesis of natural products for drug development. One example to consider is Discodermolide, a natural product isolated from a deep-sea sponge.[1] While its activity against several multidrug resistant cancer cell lines was impressive, it could not be isolated in sufficient quantities to permit clinical studies. Multiple research groups published total syntheses of Discodermolide. Though no single route seemed fully viable for production, a combination of two synthetic strategies, by the Smith and Paterson groups, allowed Novartis Pharmaceuticals to develop a multigram synthesis of Discodermolide for clinical studies.[2] Unfortunately, Discodermolide was unsuccessful in clinical trials.[1]

Though natural product drugs can be commercially produced by total synthesis, often natural product isolation can be combined with late-stage chemical modification, a strategy termed semi-synthesis. Modification of naturally-obtained core structures can provide analogues with enhanced properties, help in determination of the mechanism of action, and identify the pharmacophore, i.e., the essential structural elements responsible for its useful biological properties. In some cases, however, it is difficult to obtain a core structure by isolation. The producing organism may be seasonal, may be impossible to culture, or may produce the compound in very small or variable quantities. In such instances, total synthesis may be the only way to access the compounds for modification and ultimately for clinical studies. As an example, the natural product Halichondrin B showed, in preclinical studies, highly potent activity against an otherwise poorly-treatable aggressive tumor.[3] It was not available on scale by isolation, thus it was necessary to synthesize this very complex natural product for further development. Multi-year total synthesis efforts and collaborative studies led to the identification of the pharmacophore and simplification of the structure to a smaller fragment, termed Eribulin mesylate (Halaven®), which retained the potency of the natural material. The synthetic efforts paid off with the approval of Eribulin in various countries for the treatment of cancer. This natural product-derived drug is commercially produced by total synthesis through a lengthy (but viable) synthetic route.

Semi-synthesis is quite often effective for advancing natural product-like drug leads. Paclitaxel (Taxol®) was isolated from the bark of the Pacific yew tree and was found to possess significant antitumor activities.[1] Early clinical trials progressed using bark-derived material, which was in exceedingly short supply. Thus, the large-scale production of Taxol® from tree bark was ecologically unsustainable. Fortunately, a late-stage precursor, 10-Deacetylbaccatin III, is accessible from the *needles* of a *Taxus* species. These needles can be harvested sustainably and used for the semi-synthesis of Taxol® on a commercial scale.

Another prominent example of industrial semi-synthesis is Trabectedin (Yondelis®), which is produced from a bacterial product, Safracin B, that can be cultured efficiently.[3] Bacteria have been a high yielding source of drugs. Recently the study of how, at a genetic level, microbes produce natural products has also led to their bioengineering to efficiently produce

substantial quantities of desired natural products for use as drugs or drug precursors. Complementing such biotechnological advances are advances in synthetic chemistry methodology, which can greatly shorten and economize natural product modification or total synthesis.

Given the high failure rate of drugs progressing through preclinical and clinical studies, a diversity of strategies, including the pursuit of natural products, is needed to ensure success. The issues of speed of development and cost-effectiveness must be reconsidered by pharmaceutical companies as they support a program through the discovery phase and then through clinical trials. Though the commercial synthesis of natural products is hampered by their structural complexity, long timelines for development, and difficulty of structural modification, success in this area has been achieved including the development of natural products derivatives and analogues, and drugs with structures that have been inspired by natural products. Natural product synthesis and semi-synthesis are likely to continue to be important means of providing chemical probes, drug leads, and marketed drugs.

References and Notes:

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https://doi.org/10.26538/tjnpr/v1i3.1