TOTAL SYNTHESIS AND BIOLOGICAL ACTIVITY OF "SUPERNATURAL" PRODUCTS

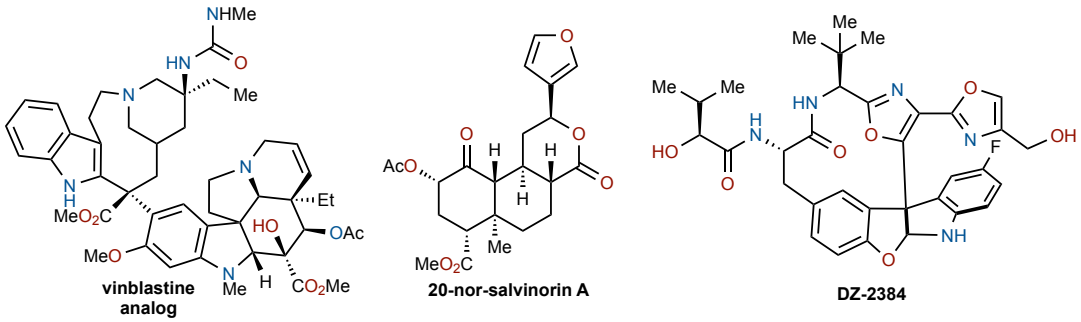
Reported by Emma Simmons October 19, 2023

INTRODUCTION

Natural products possess unrivaled structural diversity, function, and complexity. The application of these molecules in biology and medicine has become more frequent as techniques to investigate and understand mechanism of action and biological target have advanced. Historically, there have been successes in directly implementing natural products into humans for medicinal treatment. However, challenges arise in that the compounds meticulously evolved for a specific purpose in nature do not always translate readily to treatment in human biological systems. Poor pharmacokinetic properties, low bioavailability, low potency, low natural abundance, and lack of reliable synthetic access are a few of the numerous challenges faced when implementing natural products directly for medical use. Thus, classical medicinal chemistry approaches, SAR campaigns, and extensive analysis of analogs are not typically thought of as readily translatable to complex natural products.

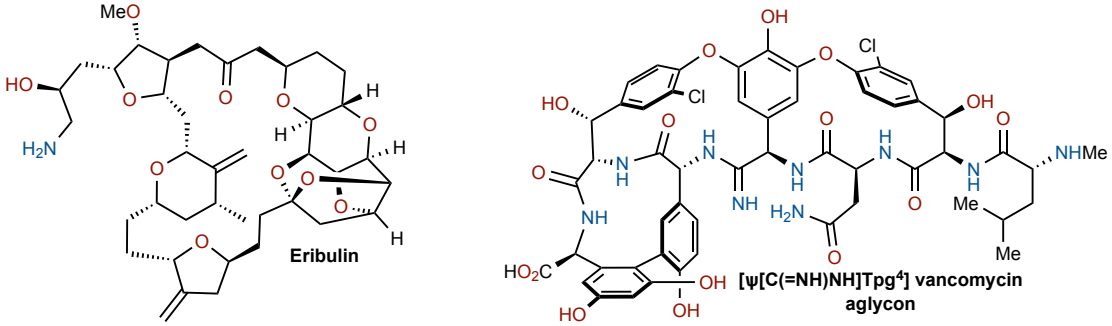
SUPERNATURAL PRODUCTS

The term "supernatural" products was first coined by Shenvi in 2016 pertaining to the total synthesis of asmarine alkaloid natural products.[1] A total synthesis approach to "supernatural" products presents a complementary approach to traditional medicinal chemistry while allowing access to molecules that in many ways behave superiorly to the parent natural product. Additionally, total synthesis provides analogs that are inaccessible by biosynthetic or semisynthetic derivatizations. In a recent review, Boger and coworkers detail nearly two dozen stories of supernatural products over the last twenty years.[2] Five natural products have been selected to highlight the variety of medicinal, chemical, and biological problems that total synthesis has the capacity to address. Supernatural products, when taken through extensive iterations of analogs can be significantly more potent than the parent, as in vinblastine (**Scheme**



Scheme 1. Derivatives of vinblastine, salvinorin A, and diazonamide

1).[3] Salvinorin A suffers from conformational instability that limits analog development; Shenvi and coworkers made a seemingly simple one-atom substitution that drastically altered the conformational flexibility.[4,5] Efforts toward diazonamide A demonstrate how the simplification of the synthesis, in this case through development of a powerful method, allows for discovery of valuable analogs.[6] Eribulin, derived from the scaffold of halichondrin B, illustrates the power of simplifying the structure of a natural product with high bioactivity, but extremely low natural abundance (**Scheme 2**).[7] Boger and coworkers' strategy in the total synthesis of vancomycin, a potent antibiotic against gram-positive bacteria, affected a deep-seated structural change that overcomes the mechanism of resistance.[8]



Scheme 2. Derivatives of halichondrin B and vancomycin

CONCLUSION AND OUTLOOK

The improvements made in supernatural products are not mutually exclusive: elements such as potency, stability, simplified structure, scalable synthesis, pharmacokinetic properties, and mechanism of action all interplay. Total synthesis enables discovery of analogs that would not be feasible via bio- or semi-synthetic approaches. Although the biological advances are noteworthy, this approach has as much to offer to the field of organic chemistry as it does to medicinal chemistry. The challenges faced in the endeavors to access supernatural products have led to novel synthetic methods, new strategies toward complex scaffolds, and creative solutions to access modified core structures of the parent natural products.

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