Function-Oriented Synthesis: Overcoming the Supply Challenges for Bryostatin

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Despite the historical impact of natural products on drug discovery\(^1\), the last decade has seen a reduced interest in these compounds from the pharmaceutical industry\(^2\). One of the main reasons for this trend is the difficulty in obtaining a reliable supply of the lead compound from either a natural source or a synthetic approach. A second reason is that natural products are not designed to be optimized therapeutic agents. As such many natural products suffer from numerous drawbacks such as side effects, poor bioavailability, and difficulties in formulation\(^3\). A recent approach pioneered by Paul Wender at Stanford is that of function-oriented synthesis (FOS)\(^5\). This approach aims to reduce the structural complexity of the natural lead while maintaining or increasing the potency (function) of the compound. Ideally, this results in making the analogs more amenable to large scale synthesis while also modifying the structure to limit side effects and increase the therapeutic value of the target compounds\(^5\). The FOS approach will be demonstrated by using the bryostatins, a series of marine natural products with promising anticancer properties\(^6\). Despite currently being in clinical trials, the structural complexity and low natural abundance of the bryostatins have combined to result in a severe supply problem which has limited the work that can be done to advance these compounds further in a drug discovery setting\(^5\). Through the FOS approach researchers have generated numerous analogs that are synthetically accessible and in many cases match or exceed the potency of the parent lead compounds\(^5\). The synthetic studies have also revealed the likely pharmacophore of the bryostatins, thereby allowing further tuning of the analog series with the goal of making a suitable therapeutic agent\(^7,8\).

References: