Natural products have been an excellent and abundant source of therapeutics for many decades. To expand on their success, and explore areas of chemical space not covered by biosynthesis, the synthesis of natural product-inspired compound collections has emerged as a viable strategy. Herein we describe the principles behind biology-oriented synthesis and related approaches, the requirements for development of novel chemistry and how phenotypic screens are a very fruitful way to explore the bioactivity of compounds made using these approaches. Finally, we summarize state-of-the-art techniques to identify the biological targets of any hits identified.