Drug discovery is a complex, expensive, and time-consuming endeavor. The rewards of successfully bringing an NCE to the market, however, can translate to extended or improved quality of life for members of the public, increased knowledge for the scientific community at large, and continued business growth for investors. Sources of lead compounds in drug discovery programs at pharmaceutical and biotech companies vary, but over the last decade have primarily come from combinatorial chemistry efforts. Despite this large investment, however, the number of NCEs are steadily declining while cost-to-market is on the rise. Alternatively, marine natural products offer a different type of lead compound than typical HTS libraries provide. Atypical synthetic methodology, such as high energy cold-plasma reactions, may also be a route to new chemical leads. Yet another avenue for improved success can be innovative drug delivery platforms that allow medicinal chemists to explore physicochemical space not accessed using conventional drug delivery. This discussion will focus on specific examples of these “periphery” aspects of drug discovery.