Development of a Library of Novel Anticancer Electrophilic Compounds via the Complexity-to-Diversity Approach

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Over the past decade, the intentional development of bioactive compounds that operate via a covalent mechanism of action has yielded multiple drugs approved by the FDA for the treatment of various cancers. These compounds are comprised of the scaffold that enables a high degree of target selectivity and a mildly reactive electrophilic warhead that engages its target through the formation of a covalent bond. However, despite this renaissance in the pursuit of anticancer electrophilic compounds, such drugs have mainly been restricted to planar, sp^2-rich structures. In order to engage a wider variety of conformationally and stereochemically rich targets, the "Complexity-to-Diversity" approach has been applied to the assembly of a library of novel three-dimensionally complex electrophilic compounds derived from natural products. 101 electrophilic compounds have been synthesized, stemming from 35 scaffolds that originate from 9 parent natural products. To discover new potent and selective anticancer compounds, this library will be screened against a representative and diverse panel of cancer cell lines using the semi-autonomous CELLerator platform.