Parallel and Miniaturized Combinatorial Synthesis and Subsequent Analysis of Small Molecules using Droplet Microarrays

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High-throughput screening (HTS) is an often-used method in drug discovery, which allows researchers to quickly identify novel biological active agents from various libraries of natural products or synthetic compounds. However, the costly libraries and the unaffordable automatic equipment required for the screening are big concerns to most researchers. Discovery of new drugs often takes more than 20 years of work producing costs of over 2 billion dollars per drug.

The droplet-microarray (DMA) offers an excellent platform to combine high-throughput synthesis, analysis and HTS of potential biological active compounds. Using different combinatorial synthesis approaches the fabrication of large libraries can be achieved in a very short time, with low solvent volumes and small used masses of reagents. Subsequent on-chip analysis and HTS of the libraries saves again a lot of time and resources.

In this project we utilized on-chip solid phase synthesis to combine the four component Ugi reaction and the three-component disulfide-thiolactone reaction in order to synthesize 10000 compounds in parallel by only using 40 different starting materials. UV-labile linker was used to enable cleavage of compounds after the synthesis and purification into individual nanoliter droplets. Another strategy used was to employ palladium catalysed reactions. We synthesized an array of 800 carboxylic

acid or amide containing biphenyls via Suzuki-Miyaura reaction. The palladium precatalyst was also prepared on-chip prior to the synthesis, thus minimizing the usage of precious palladium or laborious pre-synthesis.

Via formation of the droplet microarray on a conductive ITO surface, on-chip MALDI-TOF analysis could be used for determination of synthetic success in addition to standard LC-MS measurements.