space transforming densely functionalized compounds. Diversification can then be implemented either by allowing a limited repertoire of reactions to decorate a pluripotent scaffold or by altering reaction conditions on a simple skeleton (Burke and Schreiber 2004). Finally, any route taken during DOS results in a compound selection being smaller in size compared to traditional libraries, but structurally more complex in particular with respect to higher stereochemical variability. An attractive approach by Tan and coworkers using DOS in synthesis of a library of macrocycles via oxidative ring expansion highlights many aspects of this chapter (Kopp et al. 2012).

7 Target-Oriented Synthesis and Lead Optimization

While most high-throughput synthesis approaches presented thus far were predominantly focused on driving the library to maximal diversity, target-oriented synthesis (TOS) narrows down the diversity with respect to a defined target protein structure (Schreiber 2000). Thereby, TOS resembles more traditional synthesis efforts in pharmaceutical industry. There are many excellent examples that utilize a targeted approach exploring the binding site of a defined target, but at the same time implementing sophisticated high-throughput chemistry. One such example comes from Morgan and coworkers and utilizes an affinity-based screening technique. A library of 800-million DNA-encoded small molecules on the basis of a previously explored pharmacophore of Aurora A kinase and p38 MAPK was screened (Clark et al. 2009). This is the first report of DNA-encoded libraries (DEL) being utilized for identification of enzyme inhibitors (Fig. 6).

8 Conclusion

There is an emerging discrepancy between the augmented identification of potential drug targets and the lack of novel chemical entities being successful in drug design campaigns. High-throughput chemistry is a major motor to fill the gap by opening new doors to innovative libraries and lead optimization schemes. In that, a paradigm change has occurred, setting up new measures for the success of such a high-throughput synthesis. Sheer numbers of compounds as a sole measure for potential success are not applicable anymore. More than ever, innovative organic synthesis is the key feature that opens new avenues in drug discovery. Many approaches have diverged from the original thought of combinatorial chemistry or entered the field from various facets of chemistry, and none has proven to give the simple answer the field is looking for. Therefore, current strategies have to prove useful or will remain mere academic exercises.