as the identity of the matched site pharmacophore(s) was known for each compound, target site-based diversity of binding modes could be explored in the design process. An optimized selection of reactants was possible, and the value to the design of reactants with different chain lengths could be evaluated.

6 CONCLUSIONS AND FUTURE DIRECTIONS

Similarity and diversity metrics have been successfully used for a variety of tasks, including virtual screening, subset selection, and combinatorial library design. Databases of virtual compounds (e.g., from validated combinatorial chemistry protocols and reactants) can be used for both virtual screening and library design (virtual screening on virtual libraries with additional combinatorial constraints). The ability to exploit rapidly large virtual libraries of compounds that could be made by validated combinatorial chemistry protocols provides very powerful virtual screening and library design approaches. Future directions for library design will involve the application of such approaches in a fully integrated fashion (e.g., the ADEPT tool described in Section 4.10) and further enhancements to the constraints necessary to achieve druglike compounds (e.g., 80% compliance to the Rule of 5, predictive models for metabolism- and toxicity-related issues). Where the goal is lead generation (e.g., to enrich the compound screening file for high throughput screening), a focus will be on target classes (gene families) of interest, and the generation of compounds with leadlike properties, such as a lower molecular weight. The move away from combinatorial libraries to sparse arrays and noncombinatorial (cherry-picked) libraries (90) will continue, enabling more effective designs with control of associated properties. However, as more property constraints are applied to the library designs for leadlike/druglike properties, the need to include positive design elements to ensure good biological activity is emphasized. The goal for drug discovery is thus to identify targets and to generate compounds that are at the intersection of chemical, biological, and druglike property (e.g., absorption, toxicophores) space. Different targets and different expected routes of administration will require different constraints, and an element of diversity (with constraints toward a drug-occupied chemical space) will remain important, to enable the most effective use of combinatorial library chemistry and to discover new leads for both established and new targets.

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