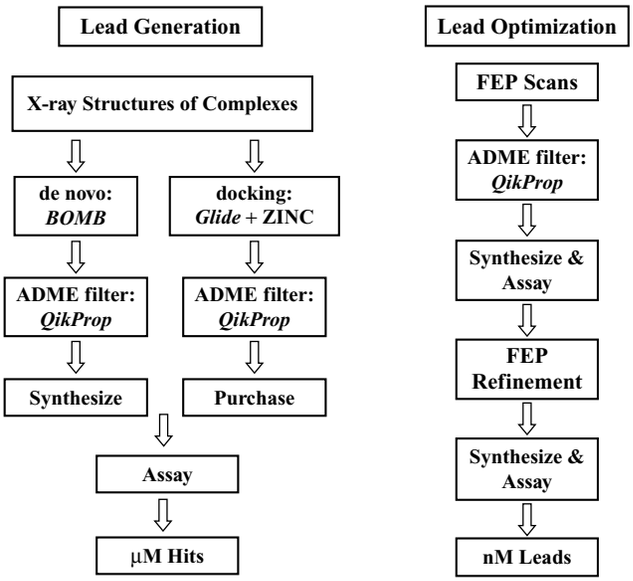

Figure 1.1. Schematic outline for structure-based drug lead discovery and optimization.

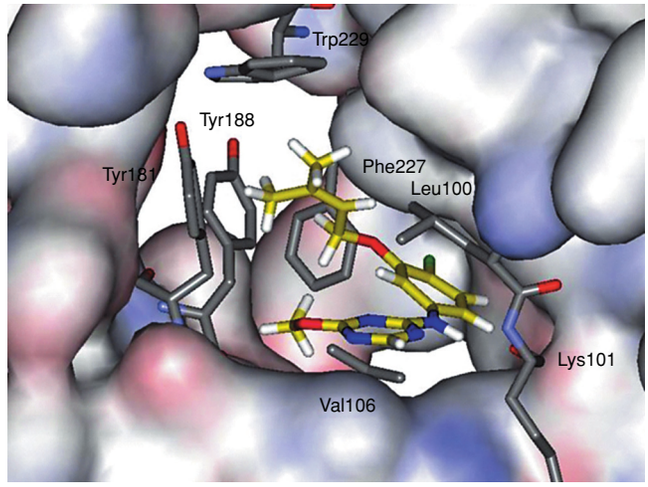

Figure 1.2. An inhibitor built using BOMB in the NNRTI binding site of HIV-RT.

De Novo design with BOMB

BOMB is used to construct complete analogs by adding 0–4 substituents to a core that has been placed in a binding site. A thorough conformational search is performed for each analog, and the position, orientation, and dihedral angles for the analog are optimized using the OPLS-AA force field for the protein and OPLS/CM1A for the analog.[10] The resultant conformer for each analog with the lowest energy is evaluated with a dockinglike scoring function to predict activity. The core may be as simple as, for example, ammonia or benzene, or it may represent a polycyclic framework of a lead series. For the example in Figure 1.2, ammonia was the original core, and it was positioned to form a hydrogen bond with the carbonyl group of Lys101. A library of molecules is then often built using a "template" that has been envisioned by the user to be complementary to the binding site and often to also be amenable to straightforward synthesis. For Figure 1.2, the template was Het-NH-34Ph-U, where Het represents a monocyclic heterocycle, 34Ph is a 3- or 4-substituted phenyl group, and U is an unsaturated hydrophobic group. The template specifies the components that constitute the desired molecules and the topology by which they are linked together.

BOMB includes a library of approximately 700 possible substituents, with code numbers from 1 to about 700, including most common monocyclic and bicyclic heterocycles and about 50 common U groups such as allyl, propargyl, phenyl, phenoxy, and benzyl derivatives. They are provided as groupings by the code numbers or the user can create a custom grouping with desired code numbers. The groupings correspond to template components such as Het, 5Het (just 5-membered ring heterocycles), 6Het, biHet, U, oPhX, mPhX, pPhX, mOPhX, pSPhX, OR, NR, SR, and C = OX. The program then builds all molecules that correspond to the template. In the example, if there were 50 Het and 20 U options, the program would build the 1,000 Het-NH-3-Ph-U and 1,000 Het-NH-4-Ph-U possibilities. This de novo design exercise with HIV-RT as the target resulted in identification of Het = 2-thiazolyl and U = dimethylallyloxy as a promising pair. Subsequent synthesis of the thiazole **1** in Figure 1.3 did provide a 10-μM lead in an MT-2 cell-based assay for anti-HIV activity. As described below, the lead was optimized to multiple highly potent NNRTIs, including the chlorotriazine in Figure 1.2 (31 nM), the corresponding chloropyrimidine (10 nM), and the cyanopyrimidine analog **2** (2 nM).[11–14]

Some additional details should be noted. The host, typically a protein, is rigid in the BOMB optimizations except for variation of terminal dihedral angles for side chains with

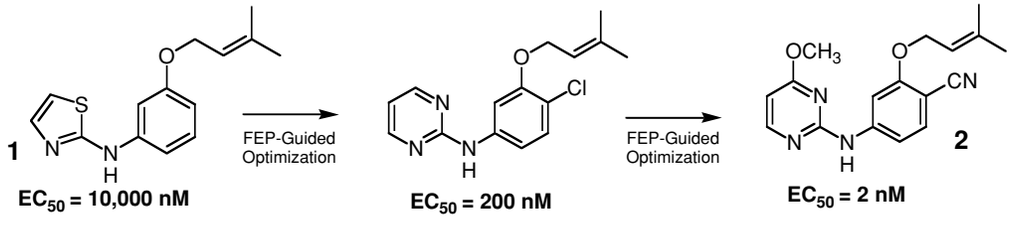

Figure 1.3. Example of a 10-μM lead proposed by BOMB that was optimized to provide numerous potent anti-HIV agents.