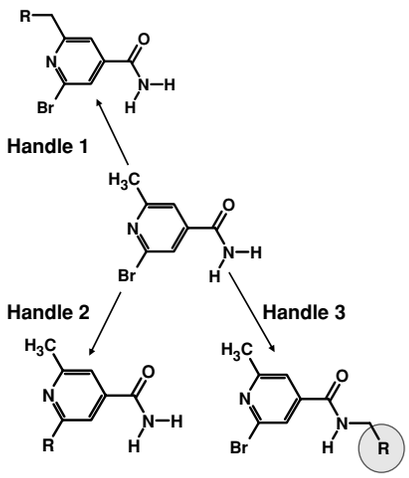

Figure 3.1. A typical member of the SGX core fragment library showing three chemical handles that support rapid R group elaboration.

screening library selection criteria that focus on yet smaller, simpler molecules. Hann and Oprea[10] proposed a "reduced complexity" screening set, with the following properties: MW $\leq$ 350, Clog $P \leq 2.2$, freely rotatable bonds ≤ 6, heavy atoms $\leq$ 22, hydrogen-bond donors $\leq$ 3, and hydrogen-bond acceptors $\leq$ 3. Congreve et al.[18] proposed a similar "rule-of-three": MW < 300, Clog $P < 3$, hydrogen-bond donors < 3, and freely rotatable bonds < 3. General conclusions from these studies provided guidance for the initial design and ongoing refinement of the SGX core fragment library, which follows a "rule-of-two" (Figure 3.1).

We have exploited two other important considerations in the design and ongoing refinement of the SGX core fragment library. First, hits from HTS and literature sources are not infrequently incompatible with efficient follow-on syntheses and may require substantial custom, labor-intensive chemistry for optimization. In practice, the probability of optimizing a hit increases with the synthetic amenability of the hit to follow-up elaboration. We, therefore, enriched the SGX core fragment screening library with compounds that support rapid, forty-eight- or ninety-six-at-a-time, automated parallel synthesis using liquid handling robotics and well-established synthetic routes. Second, aromatic bromine is a particularly useful substituent for an x-ray crystallographic approach to fragment discovery and optimization. The anomalous dispersion signal from one or more bromine atoms enhances the utility of fragment x-ray screening if the x-ray energy can be tuned to the bromine absorption edge. In addition, a bromide can act as a leaving group during carbon-carbon bond formation via Suzuki coupling and related reactions.

Enabling the target, fragment screening, initial SAR optimization, and the end game

Our FAST (Fragments of Active STructures) fragment-based structure-guided drug discovery process encompasses the following steps: (1) target enablement; (2) screening of the core fragment library and selected fragments derived from other sources; (3) structural guided selection of fragments for SAR exploration; (4) SAR exploration design/prioritization; (5) initial chemical elaboration of selected fragments; (6) analysis of the results of initial fragment elaboration with x-ray crystallography and in vitro biochemical assays of potency; (7) subsequent rounds of fragment elaboration/evaluation, now including cellular potency assays, selectivity profiling, in vitro and in vivo pharmacokinetic studies, and in vivo efficacy studies; and (8) further focused optimization of development candidates versus the target product profile, now including rat toxicology studies.

Properties of the deliverable

Recently published studies[19,20] have documented that the likelihood of success in clinical trials depends critically on compound molecular weight. Specifically, clinical candidates with MW $\leq$ 400 have a 50% greater probability of obtaining approval as compared to those with MW >400. Paolini et al. extended these analyses to a second dimension by analyzing both MW and Clog P for approved orally administered compounds.[21] Their work identified a "sweet spot" for oral drugs, falling within the following MW and Clog P ranges: $300 <$ MW < 400 and $2.5 <$ Clog $P < 4.5$. Insights from these studies provided general guidance for the prosecution of the SGX fragment-based structure-guided drug discovery process against all of our targets.

SGX FAST FRAGMENT-BASED STRUCTURE-GUIDED DRUG DISCOVERY PROCESS

Properties of the SGX core fragment library

A diverse screening library of ~1,500 leadlike compound fragments has been assembled over the past five years in various stages. Most library members possess two to three built-in synthetic handles to aid rapid elaboration of structurally validated fragment hits (Figure 3.1). Approximately one-third of library members contain one or more bromine atoms to facilitate detection and routine synthetic elaboration of crystallographic screening hits. The bulk of the library was assembled with no bias toward particular targets or target classes. During the most recent stage of library expansion, however, ~100 unrewarding fragments were removed and ~500 fragments biased toward protein kinases were added. Figure 3.2 illustrates five histograms summarizing various properties of the SGX core fragment library. (See Blaney et al. for a detailed account of library inclusion criteria.[22])

The current size of our core library reflects the balance struck among potential chemical diversity, the time required to screen the library using x-ray crystallography, and target screening hit rates. At present, screening can be completed in two to three days of x-ray beam time by dividing the ~1,500-compound core fragment library