Table 4.1. Property ranges used to define druglike compounds, leadlike compounds, fragments, and scaffolds

	Druglike (rule-of-five) properties[4]	Leadlike properties[6]	Fragment-like (rule-of-three) properties[9]	Scaffold-like properties[10]
Molecular weight	≤500	≤450	<300	≤350
Clog*P*	≤5	−3.5 to 4.5	≤3	≤2.2
Hydrogen bond donors (e.g., NH, OH)	≤5	≤5	≤3	≤3
Hydrogen bond acceptors (e.g., N, O)	≤10	≤8	≤3	≤8
Rotatable bonds	(Not defined)	≤9	≤3	≤6

Table 4.1, many other factors are considered when selecting fragments for screening, including solubility (a critical factor due to the high concentrations necessary to detect weak binding), chemical stability, low reactivity, commercial availability of compounds and analogs, synthetic accessibility, and the presence of preferred binding motifs.

The three principles of FBLD: Efficiency, efficiency, and efficiency

Conventional methods for lead discovery using phenotypic or biochemically based assays have produced many success stories. So why use fragment-based methods? Along with the successes of conventional methods, there have been many cases where leads could not be found or could not be developed into drugs because of inadequate potency; rapid metabolism or excretion; toxicity or off-target effects; difficulties with synthesis or formulation; and poor solubility, oral availability, or cell permeability.

Fragment-based lead discovery produces more choices, and potentially better choices, for lead optimization than conventional methods alone. FBLD is a complementary approach that generates independent sets of leads from which medicinal chemists may choose, and the pursuit of multiple chemically distinct lead classes for any given program increases the likelihood that at least one will succeed. Furthermore, by starting from leads that have lower molecular weights and bind more efficiently than typical high-throughput screening (HTS) hits, it is more likely that the final, optimized compounds will have desirable physicochemical (and hence ADME) properties. It has been argued that fragment-derived drug candidates, in addition to having lower molecular weights, tend to be more polar and water soluble. For example, the mean Clog*P* value for fragment-derived molecules patented by Astex in 2006 was 2.4, compared to a range of 3.5 to 4.2 for conventionally derived compounds from four major pharmaceutical companies.[16,17]

The key advantage of FBLD lies in its efficiency, as embodied by three principles, each of which will be discussed in detail in the following sections:

Chemical efficiency: Fragments sample chemical space more effectively than large molecules.

Searching efficiency: Fragments probe protein binding sites more efficiently and produce higher hit rates than large molecules.

Binding efficiency: By starting from fragments that bind very efficiently, it is possible to construct highly efficient lead molecules and thus better drug candidates.

The chemical efficiency of fragments

The number of possible druglike compounds containing up to thirty C, N, O, and S atoms is enormous and has been estimated to comprise around 10^{63} molecules.[18] It is impossible to effectively sample such a vast and diverse "chemistry space" with a screening library (to begin with, there is not enough matter on Earth to make that many molecules). Furthermore, maximizing chemistry diversity alone is an inherently inefficient strategy for library design. If biologically active molecules were uniformly distributed throughout chemistry space, then it has been estimated that at least 10^{14} compounds would have to be screened to find a single hit.[19] The fact that libraries of 10^5 to 10^6 molecules routinely produce multiple hits simply reflects the well-known empirical observation that biologically active molecules are actually clustered within small regions of chemistry space.

The number of possible fragments is, however, many orders of magnitude smaller than the number of possible druglike compounds. For example, a virtual library of all 26.4 million possible molecules containing up to eleven C, N, O, and F atoms has been computationally enumerated, and approximately half of the molecules conform to the rule-of-three.[20] It is therefore possible to sample more of the available chemistry space with much smaller libraries of compounds by screening fragments instead of larger molecules. Furthermore, fragments can be combined to make larger compounds, vastly expanding the represented chemical space. For example, if a receptor contains two binding sites that are close together, then rather than screen large molecules containing two components intended to bind to both sites simultaneously, fragments capable of binding to one or the other site individually can be screened and any hits subsequently linked together. Assuming that the binding modes of the individual fragments mimic that of a linked molecule, a 1,000-fragment library with several possible synthetic linkers could represent the chemistry space of a multimillion-member combinatorial library.