

Fragment-based Drug Design

Another approach to improve productivity of drug discovery programs is “fragment-based” drug design (FBDD). At the root of this strategy is the observation that “lead” compounds are not always as “drug-like” as the final FDA-approved drug that they precede. Specifically, as initial hits are being optimized, they tend to lead to compounds of higher molecular weight and higher lipophilicity.

Whatever virtues Lipinski’s Rule of 5 brings to the drug-discovery process, thinking outside of the box engenders the possibility of starting with compounds that are smaller and more hydrophilic than the Rule of 5 would suggest. The fragment approach is an iterative process that evolves drugs rather than trying to screen only compounds that are already drug-like.

Intuitively, the chance of screening a compound that is a perfect match for the intended target (typically a receptor or enzyme) binding site is remotely small. Indeed, the probability of any complex molecule recognizing a complex complement is tiny because so many interactions (in three dimensions!) are involved. At the other end of this spectrum are simpler molecules (fragments) with fewer necessary interactions and thus a much better chance of orienting with the target in a favorable manner, albeit the interaction is liable to be weak.

Although higher substrate concentrations are typically used, the screening methods which have been employed to detect fragment binding include nuclear magnetic resonance (NMR), X-ray crystallography, surface plasmon resonance (SPR) and mass spectrometry. NMR and X-ray crystallography provide additional advantages in that they serve as a guide to the binding site and binding mode of the fragment, paving the way for fragment elaboration or fusion.

At ChemDiv, we can assist you in the rational selection and design of scaffolds and the synthesis of some small series (5-10 molecules) of lead-like fragments around them. The main principle of scaffold selection consists in the use of a knowledge database of known target (GPCR, ion-channel, enzyme, etc.) ligands as the prototypes. The single lead compound is a source for the generation of several fragment series. The compounds chosen for synthesis possess lead-like properties related to the following rules:

Number of non-H atoms	≤ 20	H-Bond donors	≤ 5
Molecular weight	≤ 300	H-Bond acceptors	≤ 3
ClogP	≤ 3.0	Number of rotatable bonds	≤ 3
Polar surface area	≤ 80	Number of rings	> 0

The fragments selected contain only C, H, N, O, S, P, F, Cl, and Br atoms. Fragments with undesirable properties are eliminated by applying our special medicinal chemistry filters. The fragments selected possess good water solubility (Clog SW > -3.0) required for HCS. Overall, fragments satisfy key features such as diversity, reduced structural complexity, drug-/lead likeness and possess a great potential for “fragment evolution” and “fragment linking”.

The current version of fragment-based library includes:

number of compounds	number of unique heterocycles	diversity coefficient	number of screens	Property range
4987	615	0.856	5970	<ul style="list-style-type: none"> · 96 < MW < 301; 245 on average · 0 < H-bond acceptors < 6; 3 on average · 0 < H-bond donors < 5; 1 on average · 0 < rotatable bonds < 3; 2 on average · -8.0 < logD (pH 7.4) < 5.17; 1.6 on average · -5.1 < log of solubility in water (pH 7.4) < 6.8; -2.2 on average