A major facet of lead optimization involves the replacement of one functional group with a new functional group. The newly prepared analogue is then tested to determine the effect of the structural change. Over time, after many different analogues have been synthesized and tested, certain **structure-activity relationships (SARs)** of the lead become apparent. An SAR is a link between a chemical structure and its physiological activity. Understanding the SAR of a molecule is a foundation of medicinal chemistry. Keep in mind that “activity” is not limited to target binding but also applies to pharmacokinetics.

A very simple scheme showing a preliminary SAR study is shown below. Compound 1, a hypothetical lead, contains a monosubstituted benzene ring. A medicinal chemist would likely take compound 1 and “do some SAR” around the benzene ring. A simple change would be to place a CH$_3$ group on the 4-position of the ring to form analogue 2. If compound 2 were more active than 1, then a reasonable interpretation may be that the methyl group is filling a hydrophobic pocket in the target binding site. If one carbon is good, then maybe two carbons are better. Analogues 3 and 4 would perhaps be prepared to test the hypothesis of a hydrophobic binding pocket by either lengthening the carbon chain (3) or adding yet another methyl group (4). If compound 2 were less active than 1, then a reasonable interpretation may be that the binding site has no room for additional substitution at the 4-position. Analogues 5 and 6 might test this idea. Analogue 5 replaces a ring C-H with a N, a hydrogen-bond acceptor, so the potential for a hydrogen bond with the target becomes a possibility. Analogue 6 replaces a hydrogen with a fluorine. Fluorine has an atomic radius of 1.5 Å compared to hydrogen's radius of 1.2 Å. While not identical, they are very similar. Fluorine, a very electronegative atom, can be introduced into a molecule to test electronic effects without adding steric bulk to the molecule.

Changes of this type represent the logic that medicinal chemists use to explore and optimize the activity of a lead compound.