At times during the lead optimization process, a lead may be found to have drug-like binding to the target but suboptimal pharmacokinetics. Problems in pharmacokinetics can be linked to any of the four aspects of ADME – absorption, distribution, metabolism, and excretion. Some functional group replacements have been found to preserve target binding and yet affect pharmacokinetics. These functional groups are known as isosteres. Isosteres are replacement groups, and one specific group is replaced with another specific group. Isosteres are often divided into two different categories, classical isosteres and non-classical isosteres.

Classical isosteres emphasize the preservation of steric effects within a molecule. Classical isosteres, therefore, are groups that tend to have approximately the same size. A methyl group and a chlorine atom are similarly sized and are isosteres of one another. A number of classical isosteres are included in the web content associated with this subsection.

A simple example of using an isostere in drug discovery is shown below. Compound 1 is a lead with excellent activity on the intended target, but its half-life is shorter than desired. The main metabolite of 1 is carboxylic acid 2, which arises from \( \omega \)-oxidation of the methyl group followed by oxidation of the resulting alcohol. In order to minimize the rate of clearance of 1 from the plasma by metabolism, one might replace the methyl group with a chlorine atom to make analogue 3. Since both the methyl and chlorine are similar in size, binding should be minimally affected, but the half-life of the compound should be lengthened.

Non-classical isosteres, often called bioisosteres, are isosteres that preserve electronic and hydrogen bonding properties of groups. One example is a tetrazole ring (6), which can be used in place of a carboxylic acid (5). Carboxylic acids in drugs provide a site for conjugation reactions. Tetrazoles, however, do not undergo conjugation in the body. While avoiding metabolism, tetrazoles have a very similar \( pK_a \) to carboxylic acids – 4.5 for a carboxylic acid and 4.8 for tetrazole. The tetrazole ring therefore preserves any electronic interactions of the acid while avoiding metabolism issues.