

compounds exist within a limited portion of chemical space. This concept will be discussed in greater detail in Chapter 5, but for the purposes of this discussion, Lipinski's rules suggest that "druglike" compounds will have (1) a molecular weight lower than 500, (2) a logP below 5, (3) less than 5 hydrogen bond donors, (4) less than 10 hydrogen bond acceptors, and (5) less than 10 rotatable bonds. While there are exceptions to these rules (most notably in the natural products arena), their application to chemical space can be useful in that it provides a framework for further movement towards a manageable number of compounds for consideration.

However, these limitations still leave an enormous expanse of chemical space that could be mined in an effort to identify compounds that interact with a biological target of interest. This issue is further complicated by the fact that drugs interacting at the same target may have very little structural overlap. There are, for example, clear similarities between the HMG-CoA reductase inhibitors Lipitor® (Atorvastatin),²⁸ Lescol® (Fluvastatin),⁶⁷ and Crestor® (Rosuvastatin)⁶⁸ (Figure 1.12). They each contain a para-fluorobenzene

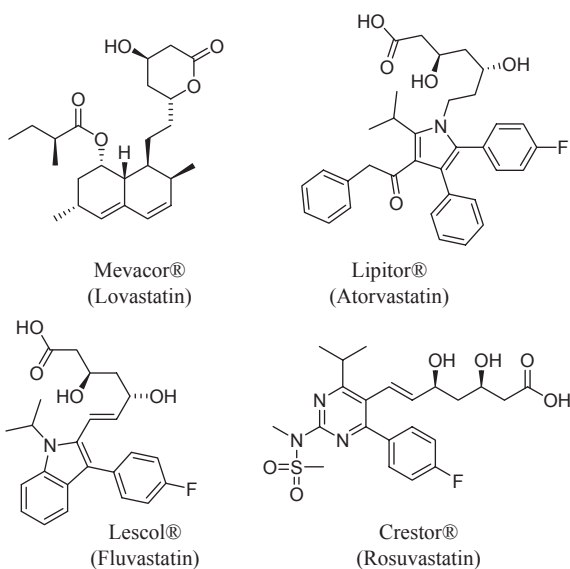


FIGURE 1.12 The HMG-CoA reductase inhibitors Mevacor® (lovastatin), Lipitor® (atorvastatin), Lescol® (Fluvastatin), and Crestor® (rosuvastatin) have some structural similarities, but there are a number of differences that make each unique.

ring and 1,3-diol-carboxylic acid side chain displayed in a similar orientation, but the remainder of the three compounds are substantially different from each other. Mevacor® (Lovastatin, Figure 1.12),⁶⁶ which also inhibits HMG-CoA reductase, is from an entirely separate structural class, and it is not clear to the naked eye how this compound is related to the previously mentioned drugs. Similarly, Viagra® (Sildenafil)⁶⁹ and Cialis®