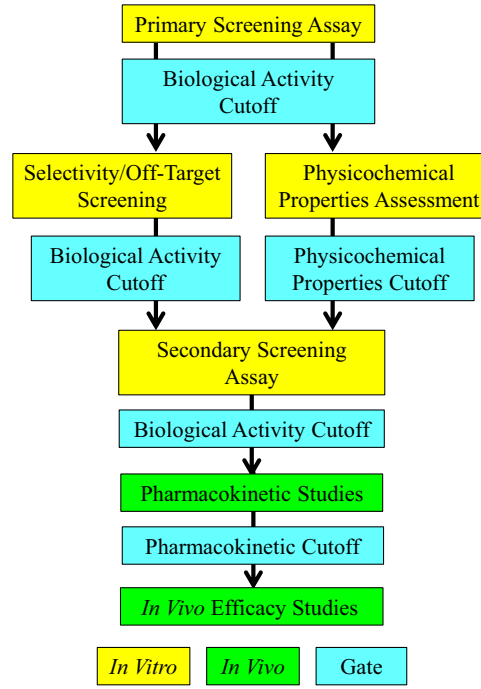

FIGURE 1.18 A screening tree is designed to identify lead compounds by establishing a series of qualifications or "gates" that a compound must surpass in order to advance through the process.

compounds examined at each level in order to ensure that compounds with flaws are removed as early as possible. The cascade, also referred to as a screening tree, begins with *in vitro* profiling and then transitions into *in vivo* studies designed to determine a compound's pharmacokinetic profile and demonstrate efficacy in an appropriate animal model.

At the top of the cascade, compounds are screened for activity against the biological target and a threshold of interest is generally set to determine if compounds are active enough to warrant further investigation. Potency is, of course, an important issue, as dosing requirements are lower for compounds that are more potent. All other things being equal, compounds with higher potency can be dosed at lower levels, decreasing the likelihood of side effects. A compound with target potency of 5 nM in theory could be provided to a patient at a significantly lower dose than a compound serving the same function but with a potency of 5 μM.

Once a compound has satisfied the potency criteria, selectivity and physicochemical properties criteria are typically examined. Nature has developed exquisite systems to accomplish very specific tasks with highly selective systems, but many of these systems overlap structurally, and this can have a significant impact on the biological properties of a given test compound. Thus, the next biological screening step in a typical screening cascade is often an assessment of a compound's potency at biological