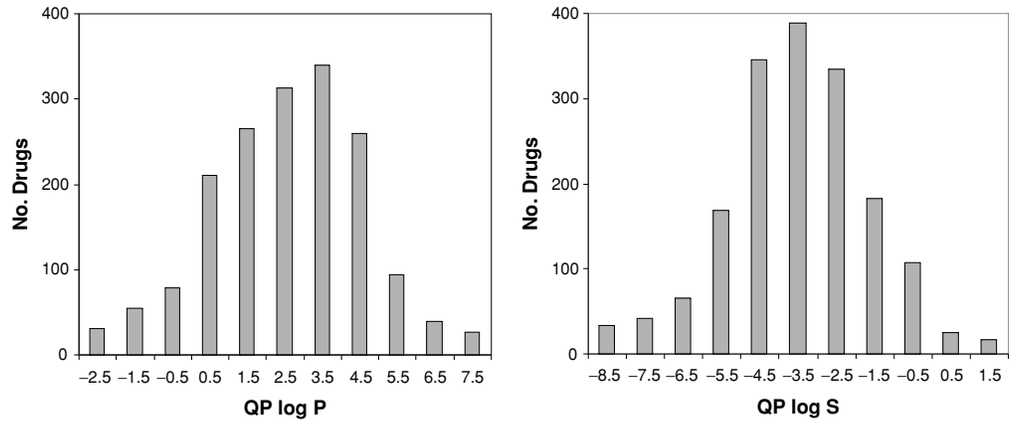
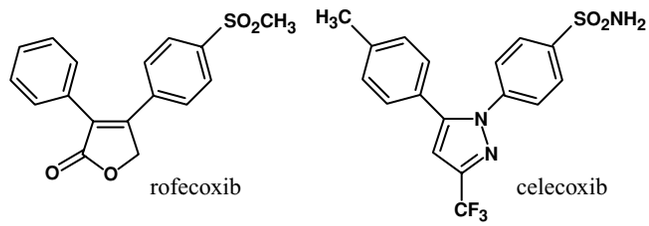


Figure 1.8. QikProp distributions for log $P_{o/w}$ (left) and log S (right) for 1712 oral drugs.

QPlog*P* values below 5.0. However, values below zero are uncommon, presumably because of poor cell permeability, and the "sweet" range for log $P_{o/w}$ appears to be 1–5. For aqueous solubility, 90% of the QPlog*S* values are above −5.7, that is, *S* is greater than 1 μM. QPlogS values less than −6 or greater than −1 are undesirable. The QikProp results also state that 90% of oral drugs have cell permeabilities, P_{Caco}, above 22 nm/s and no more than six primary metabolites. These quantities and limits address important components of bioavailablility, namely, solubility, cell permeability, and metabolism.

For our design purposes (Figure 1.1), a compound is viewed as potentially ADME challenged if it does not satisfy all components of a "rule-of-three": predicted log $S > -6$, $P_{Caco} > 30$ nm/s, and maximum number of primary metabolites of 6. For central nervous system (CNS) activity requiring blood-brain barrier penetration, an addendum is that QPlogBB should be positive. Also, some caution is warranted for a compound with no metabolites because of possible clearance problems.[17] A further note is that QPlog*P* and QPlog*S* are correlated with an r^2 of 0.68, so there would be some redundancy in invoking limits on both. Among reasons for preferring solubility, there are quite a few examples of relatively small drugs that have log $P_{o/w}$ values greater than 5 but have acceptable solubility, for example, meclizine, prozapine, clocinizine, bepridil, denaverine, bopindolol, phenoxybenzamine, and terbinafine. Of course, compounds with reactive functional groups, for example, those that are readily hydrolizable or strongly electrophilic, are flagged by QikProp and normally eliminated from inclusion in a lead structure. For example, in rofecoxib (Vioxx) concern could be expressed for possible nucleophilic attack and ring opening at the furanone carbonyl and for Michael addition to the α,β-double bond; metabolic oxidation at the allylic methylene group is also expected to yield the 5-hydroxy derivative (Scheme 1). For celecoxib (Celebrex), metabolic oxidation to the benzylic alcohol is noted by QikProp, and an "alert" is given that



Scheme 1.

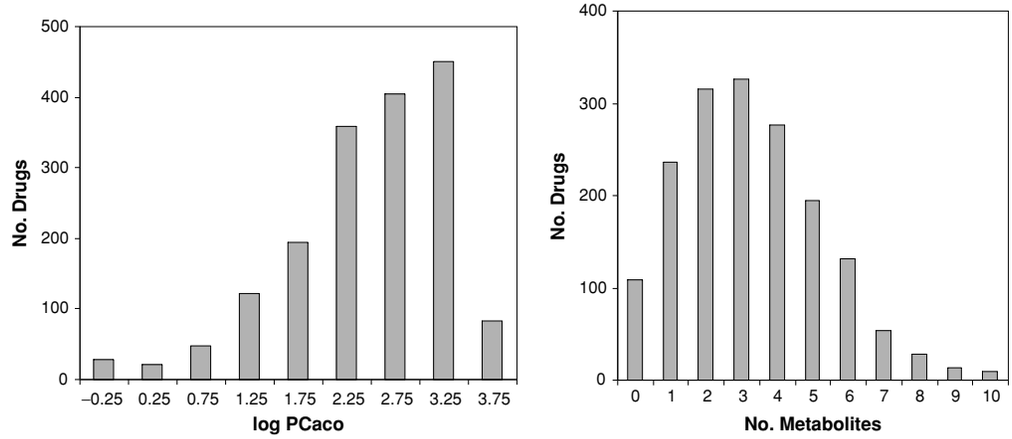


Figure 1.9. QikProp distributions for log P_{Caco} (left) and number of primary metabolites (right) for 1,712 oral drugs. P_{Caco} is the Caco-2 cell permeability in nm/s.