nature. This can be accomplished by adding polar groups, increasing the number of hydrogen bond donors and acceptors, or by adding ionizable groups to the compound in question. The addition of even a single hydrogen bond donor or acceptor, for example, can have a significant impact on solubility. Again referring to the series of amino-imidazolidinone Kv1.5 blockers, exchanging a methyl group (**3**) with a methoxy (**4**) more than doubles the observed solubility (Figure 6.5).[3] Increased polarity and the ability

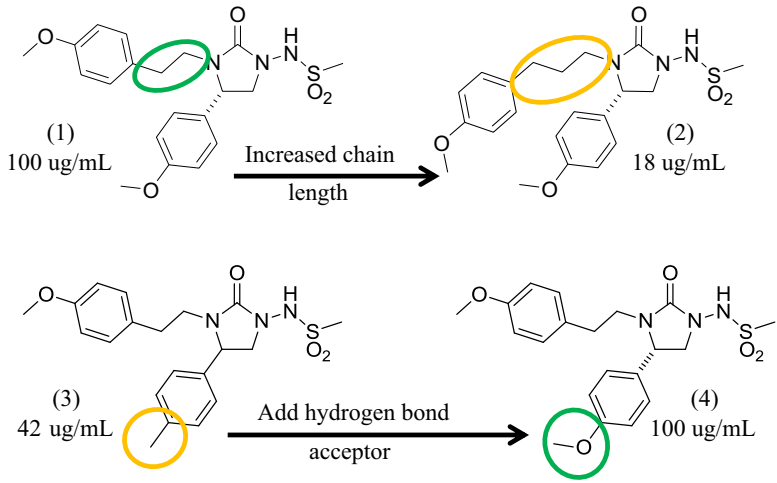

FIGURE 6.5 Increasing the length of the carbon linker by one methylene unit, as seen in (**1**) and (**2**), leads to a 5 fold change in solubility. The addition of a hydrogen bond acceptor (**3** vs **4**) more than double aqueous solubility.

to form additional hydrogen bonds were also factors in improved solubility in the series of benzoimidazol-2-one androgen receptor antagonists (Figure 6.6). Modification of benzoimidazol-2-one (**5**) to include the nitrile as seen in (**6**) increases the overall polarity of the compound and adds an additional hydrogen bond acceptor, which results in a greater than 5 fold increase in solubility. In the same series, modification of (**7**) to incorporate a fluorine atom and an *N*-methyl acetamide (**8**) provides increased polarity and a substituent capable of acting as both a hydrogen bond donor and acceptor. As a result, the aqueous solubility increases by more than 75 fold.[4]

In some cases, dramatic improvements in aqueous solubility can be accomplished with a simple isosteric replacement as seen in the carbon/nitrogen switch in hexahydropyrazinoquinolines (**9**) and (**10**) (Figure 6.7). This simple change had minimal impact on the desired dopamine D_3 binding (5.1 nM vs 9.7 nM), but provided a 50 fold increase in solubility (from 1 mg/mL to 50 mg/mL, **9** vs **10**). In this case, the pyridine nitrogen installed in (**10**) is both capable of hydrogen bonding interaction and can