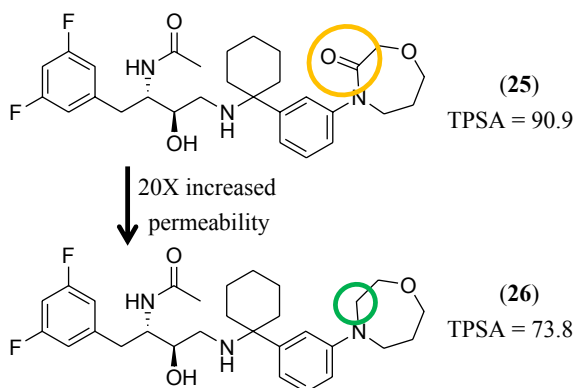


**FIGURE 6.14** The permeability of a series of Beta-secretase (BACE) inhibitors is increased by a factor of 16 by decreasing cLogP. Modification of the *t*-butyl group (22), first by addition of a cyano (23) and then by removal of the flanking methyls (24) lowers the cLogP from 5.5 to 3.86.



**FIGURE 6.15** Removal of a carbonyl in a series of BACE-1 inhibitors leads to a 20 fold increase in permeability.

inhibitors, for example, the presence (25) or absence (26) of a carbonyl produces a 20-fold change in permeability (Figure 6.15).<sup>23</sup>

Although modifying polarity, lipophilicity, and TPSA across a series of compounds can lead to significant changes in permeability, there are additional modifications that can be applied to increase permeability.