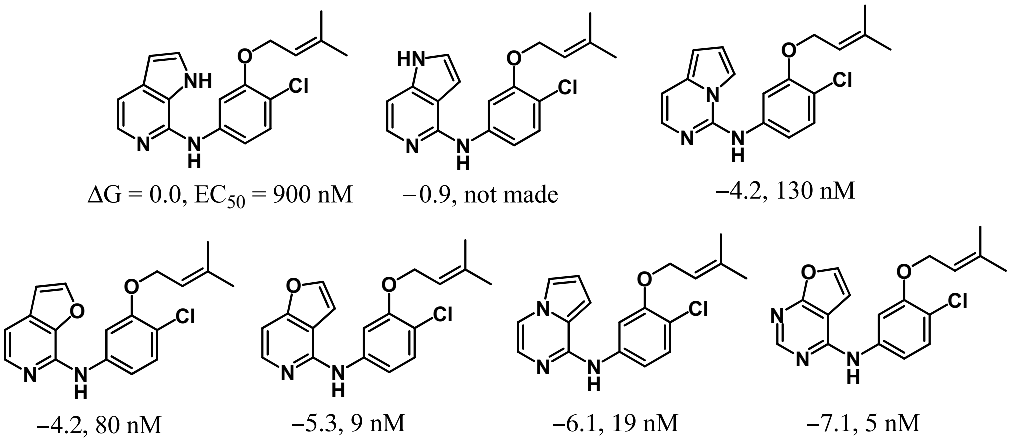
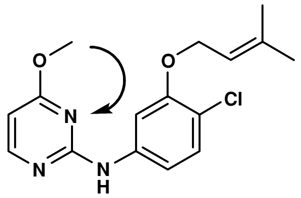


Figure 1.12. FEP results for relative ΔG_b (kcal/mol) and experimental anti-HIV activities (nM).



Scheme 2.

The decision on which analogs to pursue was driven by the prospective FEP results shown in Figure 1.12. Subsequent synthesis and assaying of the series of 6–5 compounds showed close parallel between the predicted and observed activities.[11] The illustrated furanopyrimidine derivative was predicted and observed to be the most potent; it is a highly novel and potent (5 nM) NNRTI. The results highlight the accuracy of the FEP predictions and again the sensitivity of activity to structure. The pyrrolopyrimidine (130 nM) and pyrrolopyrazine (19 nM) pair is particularly striking. After the fact, analyses showed a larger dipole moment for the bound pyrrolopyrazine and more negative charge on the pyrazinyl nitrogen leading to stronger hydrogen bonding with the backbone NH of Lys101.[14]

This procedure can be referred to as a heterocycle scan, which is clearly a powerful lead-optimization strategy.[51] It is also an area where computation is far easier than synthesis, so computational screening to focus the synthetic options is very beneficial. This is particularly true for polycyclic heterocycles, as in Figure 1.12, where there are many options and the synthetic challenges can be great. In this example, heteroaryl halides were needed for reaction with substituted anilines; several were not previously reported and required considerable synthetic effort.[14] Even with the notion of pursuing bicyclic heterocycles, in the absence of the FEP results, the synthetically less accessible ones might have been skipped.

Changing heterocycles in the center of a structure is also often challenging from a synthetic standpoint. For example, synthesis of the oxadiazoles and oxazole in Figure 1.4 requires fundamentally different procedures for the ring construction.[24] This corresponds to a change in chemotype and there can be a significant delay as a viable synthetic route is found for the new target. In the case of this U-5Het-NH-*p*PhX series, FEP calculations were carried out for eleven alternative five-membered-ring heterocycles (5Het) by perturbation from the corresponding thiophene.[24] Remarkably, the only one that was predicted to be more active than the oxadiazole was the 2,5-substituted oxazole. The prediction was confirmed and provided a major step forward for the optimization of this series, as shown in Figure 1.13. It is noted that the approximately eight-fold activity improvement, which corresponds to a $\Delta\Delta G$ of about 1.2 kcal/mol, is less than the computed $\Delta\Delta G$ of 2.5 kcal/mol. This is a common pattern that likely results from the use of a cell-based assay, so the comparison is not with actual binding data (K_d). Moreover, it is also probable that the computed electrostatic interactions in the complexes are not properly damped because of the lack of explicit polarization effects.

In view of the synthetic challenges, only two alternatives were synthesized, the thiadiazole and thiazole analogs,

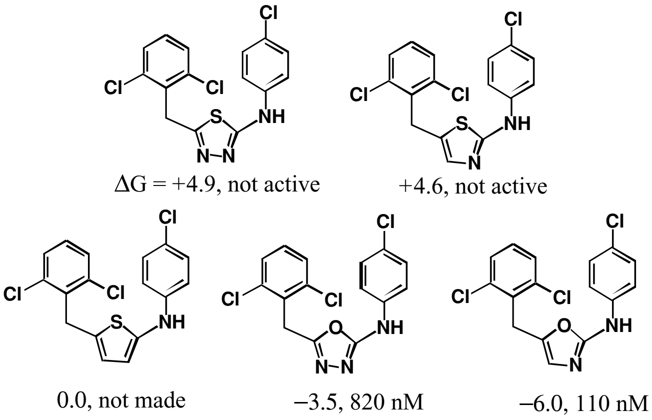


Figure 1.13. Heterocycle scan in the U-5Het-Ph X series; FEP results for ΔG_b (kcal/mol) relative to the thiophene analog and experimental anti-HIV activity (nM).