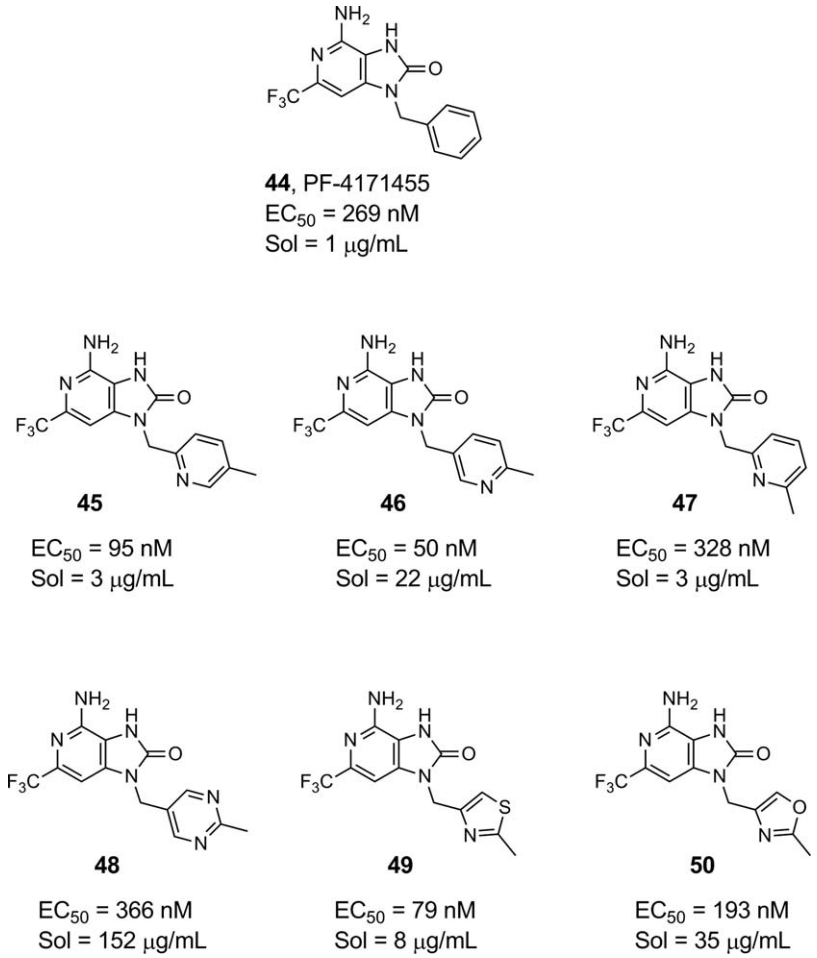

Figure 10.14 Replacement of the 8-oxodeazapurine benzyl group with more polar groups.

these properties. Introducing additional heteroatoms into the ring, as in pyrimidine **48**, led to increased solubility, but potency was negatively affected. Five-membered heterocycle replacements for the phenyl group, exemplified by **49** and **50**, were generally inferior to pyridines in either solubility, potency or both.

Rat pharmacokinetics studies of **46** demonstrated that it had high oral absorption (100%) and bioavailability (78%), but the *in vivo* half-life of 0.5 h was low relative to predictions due to metabolism of the pyridine ring by aldehyde oxidase.

To improve solubility and potency further and potentially address the aldehyde oxidase liability, the C2 position was investigated (Figure 10.15). The propensity for oxidation by aldehyde oxidase was determined by measuring the compound half-life in rat cytosol as a surrogate assay. A short