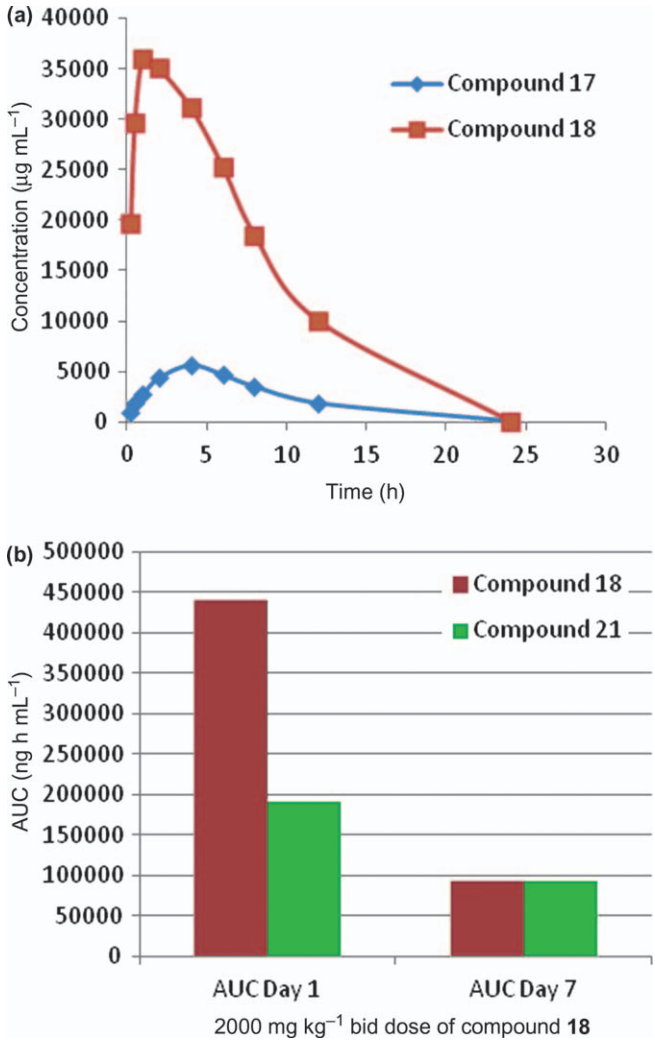

Figure 5.8 (a) Comparison of the drug plasma exposures ($AUC_{0-24\,h}$) in rats for compounds **17** and **18**. (b) The drug plasma exposures ($AUC_{0-24\,h}$) of compound **18** and its active metabolite **21** in rats on day 1 and day 7 upon bid dosing of **18** at 2000 mg kg^{-1}.

in the case of analog **19**, which displayed an EC_{50} of 7.8 nM (genotype 1a) with a cLog*P* of 2.5. Therefore, C5-cyclopropyl was introduced on all subsequent analogs.

The impressive replicon activity achieved by the addition of the oxazolidinone substituent (*e.g.* **17**–**19**) suggested that a hydrogen-bond acceptor in this portion of the molecule might serve as an important pharmacophore. *In silico* modeling guided the design of other amine tail fragments aimed at preserving this structural feature. The structurally diverse analogs **23**–**25** were