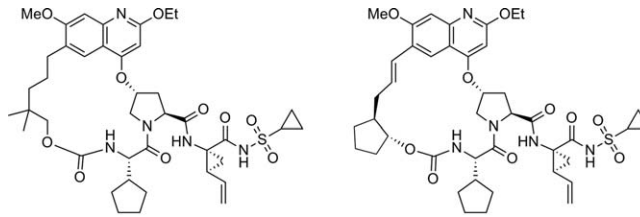

Figure 7.15 2-Ethoxyquinolinecarbamate constrained linkers.

and gt3 inhibitor, which lost a good deal of potency against the gt1 A156T mutant. During the SAR development, which led to the identification of **157**, the effect of alternative carbamates on the P2–P4 scaffold was also examined,[118] given the P4 structural diversity seen in the literature for P1–P3 macrocyclic and non-macrocyclic cores.[119] Introduction of a cyclopentylcarbamate related to that present in BILN-2061 led to **158** (Figure 7.15). While **158** lost about half of the gt3a potency, the activity against gt1b A156T improved >40-fold relative to **157** while still maintaining reasonable rat liver exposure (Table 7.25). The tight SAR around gt1b A156T potency is demonstrated *via* introduction of a methyl group beta to the carbamate oxygen in **158** leading to **159**. Whereas **159** maintains similar gt3a activity, gt1b A156T potency is decreased >40-fold.

Further contraction of cyclic constraints to 1,2- and 1,3-cyclobutane (**160**, **161**) leads to different profiles (Table 7.25). 1,2-Cyclobutane **160** loses potency versus gt3a and gt1b A156T, whereas the 1,3-linked isomer **161** has moderate gt3a activity, but good potency *versus* A156 mutants, including only about a threefold shift on going from A156T to A156V. Moving the fused ring constraint adjacent to the P2 heterocycle led to a compound with the most balanced overall profile within this sub-series. Cyclopropyl analog **162** possesses excellent gt3a ($K_i = 1$ nM) potency, gt1b replicon activity ($IC_{50} = 11$ nM) and rat liver exposure (27 000 nM at 4 h, 5 mg kg^{-1}). In terms of gt1b mutant activity, **162** displays <15 nM K_i against both A156T (2.8 nM) and A156V (14 nM), while maintaining subnanomolar activity against gt1b R155K.

Within the context of the P2 2-quinoline series related to **149**, the introduction of cyclic constraints on the linker was also very effective at improving activity *versus* key gt1 mutant enzymes (Table 7.26). Given the altered orientation of the P2 group, the number of atoms connecting the linker ring to the P2 group was generally increased by two atoms. While introduction of two of the better carbamate linkers from the P2 ethoxyquinoline series (**163**, **164**) led to only moderate gt3a and gt1b A156T/V potency, introduction of an alkoxypyrrolidineurea (**165**, **166**) gave compounds with good overall profiles in terms of potency and rat liver exposure. Compound **165** ($K_i = 3$ nM) is twice as potent as **166** against gt3a ($K_i = 5.9$ nM), but is less potent against gt1b A156 mutants.

A comparison across gt1–3 enzymes and gt1 mutants is shown in Table 7.27 for two different linker-constrained compounds compared with a compound