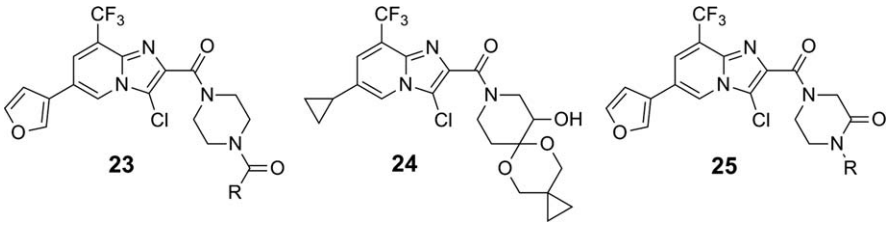

Figure 5.9 A series of analogs (**23**–**25**) designed to maintain the key hydrogen-bond acceptor (C=O or C–OH) in the tail region of the molecule.

synthesized and found to possess antiviral activity (Figure 5.9). For the piperazine carboxamide derivatives **23**, the plethora of commercially available carboxylic acid reagents permitted the preparation of hundreds of analogs. The SARs revealed that replicon activity was highly dependent on the electronic nature of the side chain (R), as replacing the carboxamide group with isosteric urea or carbamate moieties negatively impacted replicon potency. Within the carboxamide series, relatively small steric modifications in the R group produced significant changes in potency. For example, substitution of the amide (R) with Me and Et resulted in poor activity (EC_{50} of 4 and 1 μM, respectively), while addition of small cycloalkyl substituents proved beneficial. More specifically, increasing the size of the ring from cyclopropyl to cyclobutyl to cyclopentyl led to a progressive improvement in potency against the genotype 1a replicon (EC_{50}s of 88, 12 and 5.0 nM, respectively). There were limitations to size of the apparent binding pocket as further ring expansion to the cyclohexyl decreased activity (EC_{50} of 340 nM). Consistent with this finding, substitutions on the cycloalkyl rings (*e.g.* R = cyclobutyl) of **23** were restricted to sterically small groups (*e.g.* methyl, fluoro, hydroxyl). Unfortunately, the *in vivo* rat clearance was uniformly high for this compound class and further efforts were discontinued.

Molecular modeling of **17** suggested that the key carboxamide H-bond acceptor (C=O) could potentially make similar interactions if transposed to the neighboring ring. This element was incorporated into the design of two distinct series, a hydroxyl spirocyclic ketal **24** and the piperazinone **25** (Figure 5.9). The racemic spirocycle **24** exhibited low nanomolar potency against both genotypes 1a and 1b (EC_{50}s of 14 and 6.3 nM, respectively) and possessed a cLog*P* (2.7) in the aspirational range (<3). In addition, the ketal was stable under physiologically relevant conditions and was, therefore, explored in combination with other core scaffolds aimed at replacing the imidazopyridine core (see below).

The piperazinone series (**25**) also afforded highly active HCV replication inhibitors.[33] The initial SARs associated with piperazinone substitution (R) reflected the observations made in the piperazine carboxamide series (**23**), with the H and Me analogs inactive and small cycloalkyl groups imparting replicon potency. In the piperazinone series (**25**), the cyclopropyl compound was weakly active (EC_{50} > 2 μM) while the cyclobutyl, cyclopentyl and cyclohexyl analogs potently inhibited 1a and 1b genotypes (EC_{50}s < 20 nM). As seen previously,