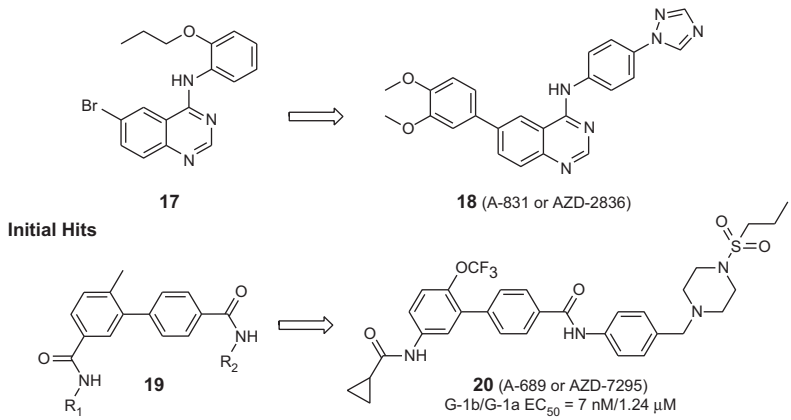

Figure 1.5 AstraZeneca's HCV clinical candidates exhibiting NS5A mutations.

also appeared to target the NS5A protein and which were optimized to the two clinical candidates AZD-2836 (**18**) and AZD-7295 (**20**) (Figure 1.5).[27] Interestingly, although resistance associated with the quinazoline series mapped to the NS5A protein, along with some accompanying mutations in the NS4B and NS5B regions, reverse genetic engineering of the mutations into a G-1b replicon, either alone or in combination, failed to recapitulate the resistant phenotype. On the other hand, the biphenyl carboxamide series afforded mutations in Domain I, the Y93H/C change being the hallmark and in the C-terminal region of the NS5A protein, for which additional details were not provided.

1.4 Highlights of Recent Literature Disclosures

The high *in vitro* inhibitory potency associated with **1** and its clinical validation of NS5A as a target for therapeutic intervention in HCV infection have generated considerable interest in this class of HCV inhibitor. Over the past 4 years, more than 100 patent applications have been published claiming various NS5A inhibitors, the majority of which are based on structural variation of the dimeric pharmacophore element pioneered by **1**.[28] Comprehensive and insightful overviews of the NS5A patent literature that provide distinct perspectives have been published, and in the next section highlights of more recent developments in the field are provided.[27,29,30]

A dimeric pharmacophore that does not necessarily embrace chemical symmetry is a common theme throughout the majority of the published patent applications. Each pharmacophore unit typically contains a spacer element that projects hydrogen bond-donating and -accepting properties attached to a pyrrolidine-like fragment that is derivatized with an amino acid moiety (Figure 1.6). Most of the molecules disclosed maintain some variation of either