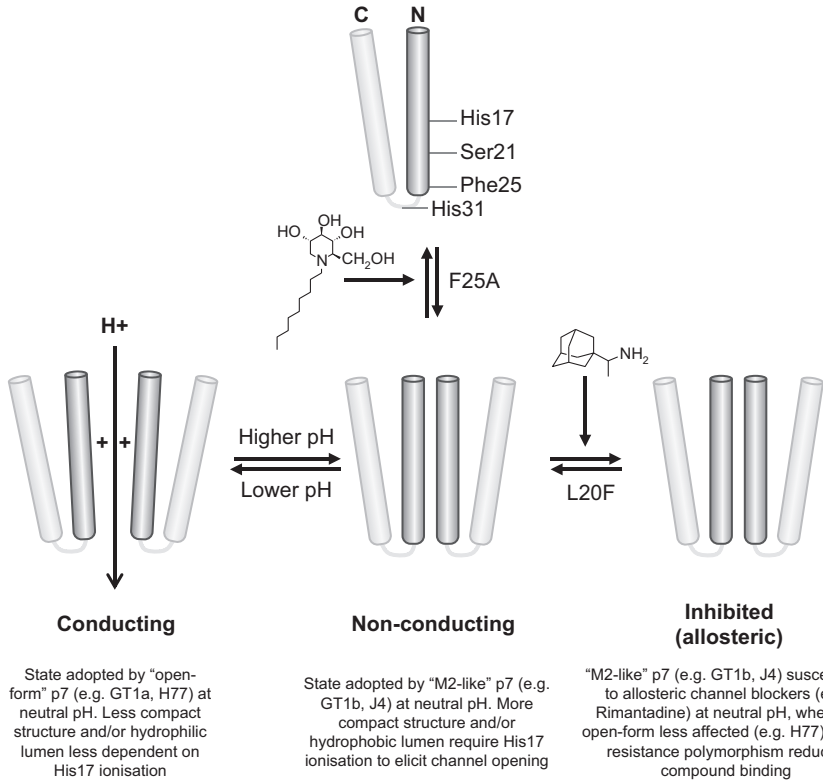

Figure 9.3 Model for p7 channel activity and drug inhibition. Based on *in vitro* studies of p7 channel gating and drug susceptibility, channels originating from certain HCV genotypes (*e.g.* 1b) behave similarly to M2, where reduced external pH enhances channel opening in a unidirectional fashion, whereas others (*e.g.* 1a) behave in more of an 'open-form' fashion, allowing protons to pass through according to electrochemical gradients in either direction (see Section 9.2.3.3). One explanation is that M2-like channels form more compact structures with hydrophobic constrictions within their lumens, which therefore require energy from side-chain ionisation to open efficiently. This is not so for open-form channels, in which the channel equilibrium is shifted towards the open state independent of pH. M2-like channels are therefore more likely to be inhibited by compounds targeting the allosteric site on the channel periphery, such as rimantadine, whereas both channel types are equally likely to be susceptible to alkylated imino sugars. However, amino acid changes within the respective binding sites also dictate the resistance/susceptibility of individual channels, including L20F for rimantadine and F25A for imino sugars (Section 9.2.3.4).

recently demonstrated, whereby genotype 1a channels, which possess a non-essential His17,[249] displayed substantially altered activity in liposomes upon alteration of external buffer pH.[253] Unlike genotype 1b channels, where lowering the external pH, thereby increasing the electrochemical gradient