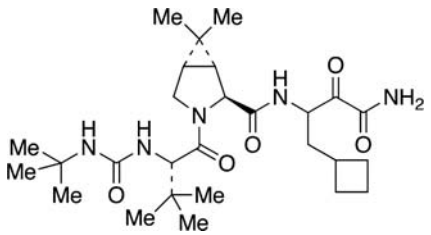
encoded by the host cell, include TIP47 and ADRP. TIP47 binds to one of HCV's proteins, namely, NS5A. TIP47 is required for HCV replication, as demonstrated by experimentally created mutations in TIP47 that prevent binding and that also prevent HCV replication (21).

VI. NS3/4A PROTEASE

NS3/4A protease is described first, because it is the target of the anti-HCV drugs, boceprevir, telaprevir, and simeprevir. The structure of boceprevir is shown below. The molecule is a mimetic of an oligopeptide:



NS3/4A protease is a heterodimer of two subunits, a catalytic subunit (NS3) and an activating cofactor (NS4A). NS3/4A is responsible for cleaving four sites of HCV's polyprotein. NS3 is a 631-amino-acid polypeptide. In the absence of NS4A, the NS3 protease is able to make one of the cleavages, but it is not able to cleave at the three other sites (22).

As is common with many other proteases, NS3 contains a zinc atom. NS3 holds this zinc atom by way of cysteine-97, cysteine-99, cysteine-145, and histidine-149. This information about amino acid residues is useful, since it provides a context for better understanding the naturally occurring mutations in NS3 that cause HCV to become resistant to drugs that inhibit NS3. Naturally occurring mutations in NS3 have been found that provide resistance to telaprevir, boceprevir, and simeprevir. These include mutations resulting in amino acid substitutions at arginine-155 or at alanine-156 (23,24). Footnote (25) provides a list of NS3/4A protease inhibitors (26).

VII. NS5A—HCV'S RECRUITING AND ASSEMBLY PROTEIN

NS5A is the target of the drugs, ledipasvir, daclatasvir, and samatasvir. The structure of ledipasvir is shown below. As is evident from the backbone of benzene rings, ledipasvir is not a peptide mimetic (oligopeptides do not contain a backbone of benzene rings):

[21]Vogt DA, et al. Lipid droplet-binding protein TIP47 regulates hepatitis C virus RNA replication through interaction with the viral NS5A protein. PLoS Pathogens. 2013;9:e1003302 (14 pp).

[22]Lin C. HCV NS3-4A Serine protease. Chapter 6 (Tan SL, editor) Hepatitis C viruses: genome and molecular biology. Norfolk (UK): Horizon Bioscience; 2006. (64 pp).

[23]Paolucci S, Fiorina L, Piralla A, et al. Naturally occurring mutations to HCV protease inhibitors in treatment-naive patients. Virology J. 2012;9:245 (8 p).

[24]Lenz O, Verbinnen T, Lin TI, et al. In vitro resistance profile of the hepatitis C virus NS3/4A protease inhibitor TMC435. Antimicrob. Agents Chemother. 2010;54:1878–87.

[25]ABT-450/r, faldaprevir, asunaprevir, GS-9256, vedroprevir (GS-9451), danoprevir, MK-5172, vaniprevir, sovaprevir, ACH-2684, narlaprevir simeprevir, telaprevir, and boceprevir.

[26]De Clercq E. Current race in the development of DAAs (direct-acting antivirals) against HCV. Biochem. Pharmacol. 2014;89:441–52.