CHAPTER 16

Hepatitis C Virus—Progress Toward Inhibiting the Nonenzymatic Viral Proteins

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Contents

1. INTRODUCTION

The molecular characterization of the hepatitis C virus by Michael Houghton and colleagues in 1991 catalyzed a significant effort to identity and develop potent and selective virus inhibitors suitable for clinical application [1]. The HCV NS3 protease and NS5B RNA-dependent RNA polymerase were inevitably the initial targets of focus because these enzymes were readily recapitulated functionally using biochemical assays, an effort considerably facilitated by the solving of X-ray

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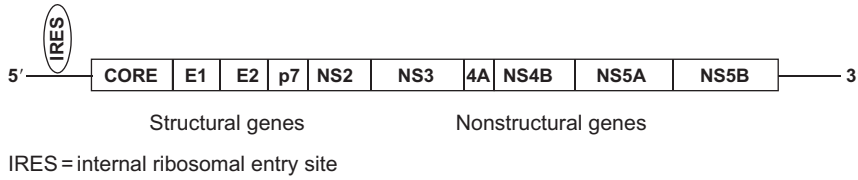


Figure 1 Genomic arrangement of HCV.

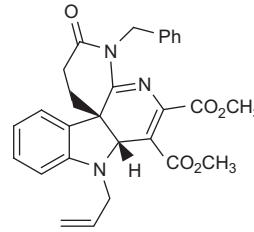
crystallographic structures that informed structure-based drug design campaigns [2,3]. In 2011, boceprevir and telaprevir, the first NS3 protease inhibitors to be submitted for marketing authorization, were approved as adjuncts to the current optimal therapy, comprising a combination of pegylated interferon-α and ribavirin, neither of which are specific antiviral agents. While the addition of these agents to current therapy leads to improved sustained viral response rates and/or shorter drug dosing regimens, it is well recognized that additional direct-acting antiviral agents will be needed to be used in conjunction with interferons and ribavirin or in small molecule combinations, if the opportunity to eradicate HCV within 40 years of its discovery is to be realized [4–6]. The advent of subgenomic replicons in 1999 followed in 2005 by replicating virus provided critical tools to identify and assess inhibitors with novel modes of action that may not be amenable to a simple biochemical assay [7,8]. Combined with the maturing clinical portfolio of NS3 and NS5B inhibitors, the advent of these assays stimulated the identification of a number of molecules targeting interesting and effective viral targets beyond the known enzymes [9]. In this chapter, we summarize the key developments that have occurred in this field over the past several years.

The genomic arrangement of HCV is depicted in Figure 1. The viral genome is translated as a single polyprotein that is cleaved by a combination of host cell proteases and the viral proteases NS2 and NS3. All viral proteins are plausible targets, and since many play multiple roles in replication, temporal selectivity based on unique protein function at different stages of the virus life cycle may be possible.

2. HCV CORE (CAPSID) PROTEIN INHIBITORS

The core or capsid protein is essential to virion assembly and structure, interacts with several host cell proteins, and is the most conserved of all of the viral proteins across the six major genotypes [10]. The core protein oligomerizes during the process of viral assembly, and a screen evaluating dimerization, a process mediated by the N-terminal domain, identified small-molecule inhibitors from a library of indoline derivatives

[11–13]. After library expansion, the racemic hexahydroindolo[2,3-*d*][1,8] naphthyridine **1** was identified as the most potent inhibitor of core protein dimerization ($IC_{50} = 1.4$ μM) that also inhibited genotype 2a virus replication with an $EC_{50} = 2.3$ μM [10,11]. However, the precise mode by which **1** exerts its antiviral effect remains to be established. More recently, dimeric forms of these compounds tethered *via* the indoline N atom have shown improved potency [13].



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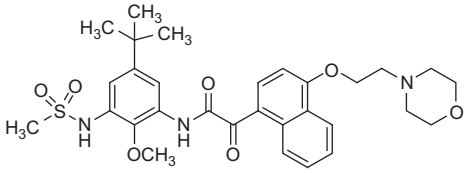
3. HCV ENTRY INHIBITORS

The E1 and E2 proteins are expressed on the surface of the viral membrane and associate into heterodimers in the native state, primed to mediate virus attachment and fusion that allows the virus to enter the host cell cytosol. The precise roles and function of E1 and E2 in the entry process and the choreography associated with the complex series of events as HCV engages several host cell proteins to enter hepatocytes have not been elucidated in detail [14–16]. However, association with highly sulfated heparan sulfate is thought to be an important first step in the binding process, with an ensuing interaction between E2 and the large extracellular loop of the tetraspanin CD81 [17]. Several other host proteins have been shown to be important contributors to the entry process including the tight junction protein claudin-1, the scavenger receptor, class B, type I (SR-BI), and occludin, which may play a role in post-binding events [16,18–22]. Endocytosis of the virus into clathrin-coated pits leads to internalization, with the ensuing fusion of viral and host cell membranes occurring in a process dependent on the low pH environment [23,24].

Screening for inhibitors of HCV entry has been mechanistically agnostic, relying upon the use of either pseudoparticles or infectious virus to identify lead compounds, although the determination of a role for SR-BI in virus entry focused interest on compounds known to interfere with the function of this host cell protein [25–27]. ITX-5061 (**2**) has been advanced into clinical trials where it increased HDL levels by 20% in a cohort of

hypertriglyceridemic subjects. **2** inhibits soluble HCV E2 binding to hepatoma cells and blocks infection of primary hepatocytes by HCV pseudoparticles expressing envelope proteins from all major genotypes [26]. The EC_{50} for inhibition of a pseudoparticle displaying genotype 1b proteins is ~1 nM, and **2** also inhibits infection by a chimeric genotype 2a virus (EC_{50} = 0.1 nM). However, **2** also demonstrates detectable inhibition of p38 mitogen-activated kinase (p38 MAPK) and UDP glucuronosyltransferase 1, polypeptide A1 (UGT1A1), leading to a focus on ITX-7650 (structure not disclosed), which shows enhanced specificity while retaining the antiviral activity, (EC_{50} = 0.25 nM) toward the chimeric genotype 2a virus [26].



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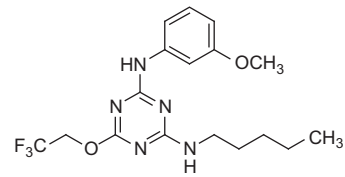

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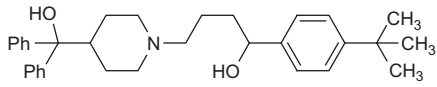
A series of triazine-based inhibitors of HCV entry discovered by broad screening have been described with **3** exhibiting EC_{50}s of 95 and 54 nM toward HCV pseudoparticles expressing genotype 1a and 1b envelopes, respectively [28–30]. A closely related compound demonstrated potent inhibition of cell culture-adapted infectious HCV, with time-of-addition experiments consistent with an entry inhibiting mechanism. Resistance to this chemotype, which afforded a >50-fold shift in the EC_{50}, mapped to a V719P or V719G substitution in the carboxy terminus region of the E2 protein [30].

The antihistamine terfenadine (**4**) and the broad spectrum antiviral agent arbidol (**5**) have been shown to interfere with HCV entry, with the former identified based on inhibition of the CD-81 large extracellular loop interacting with E2, while the latter associates with phospholipid in membranes and also appears to interact with tryptophan residues in lipopeptides [31–33]. A broad range of fused tricyclic derivatives have been claimed as HCV entry inhibitors, while the lectin cyanovirin-N appears to inhibit HCV entry at low nanomolar concentrations by binding to glycans on the viral envelope proteins [34–36].



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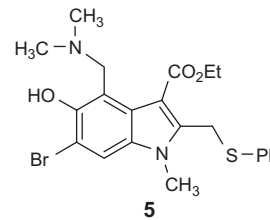

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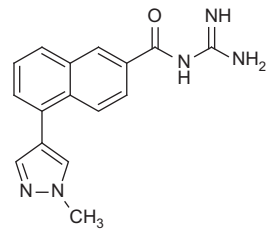
4. HCV P7 INHIBITORS

The HCV p7 protein is a 63 amino acid, short hydrophobic peptide with two membrane-spanning α-helical domains separated by a loop that faces the cytosol [37–39]. This protein plays an important role in virion assembly and release but not replication, since functional subgenomic replicons do not express p7 [40]. The HCV p7 protein is a member of the viroporin family that includes the influenza M2 and HIV Vpu channels, all of which oligomerize to form hydrophilic cation transporters [37–39]. The functional analogy between p7 and the influenza M2 channel, which extends to p7 being able to substitute for M2 in cell-based assays, led to the observation that amantadine and rimantadine also block p7 ion channel activity and, ultimately, to clinical studies with the two drugs in HCV-infected subjects [38,41,42]. Although amantadine exerts no significant effect on viral load as monotherapy, meta-analyses of early clinical studies suggested increased sustained virological response (SVR) rates when added to a regimen of interferon-α and ribavirin. However, subsequent studies have been less compelling, giving rise to considerable ambiguity with respect to the potential of this compound as adjunct therapy [38,43–45]. The p7 inhibitor BIT-225 (**6**) inhibits the JFH-2a infectious virus *in vitro* and reduced viremia by a modest but significant 0.5 $\log_{10}$ following dosing at 200 mg for 7 days to HCV-infected subjects when compared to placebo [46]. However, **6** is also an inhibitor of the related pestivirus bovine viral diarrhea virus (BVDV), $EC_{50} = 314$ nM, and HIV-1 in cell culture, $EC_{50} = 2.25$ μM, with inhibition occurring post-integration and consistent with inhibition of the accessory protein Vpu which plays a role in virus assembly [47,48].



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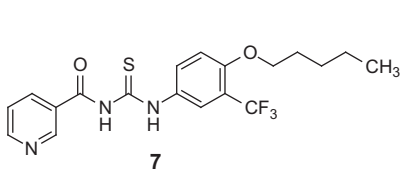
5. HCV NS4A INHIBITORS

The HCV NS4A protein is a critical cofactor that associates with the NS3 protease immediately after its proteolytic release, in essence rendering subsequent NS3-mediated polyprotein processing a pseudo-intramolecular

event. The thiourea ACH-806 (**7**, GS-9132) is a potent genotype 1b inhibitor ($EC_{50} = 14$ nM) that is thought to bind to the NS4A protein and interfere with assembly of the replication complex [49,50]. **7** interacts in a synergistic fashion with HCV NS3 and NS5B inhibitors *in vitro* and resistance maps to changes at C16S and A39V. In clinical studies, 5 days of monotherapy with **7** reduced viral load by a mean of 0.91 $\log_{10}$ at 300 mg BID. However, kidney toxicity was observed, and more recent patent applications have focused on thiazole derivatives, such as **8**, which presumably gave rise to the second advanced compound ACH-1095 [51–53].



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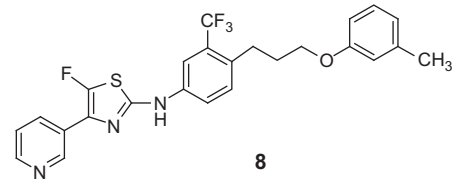

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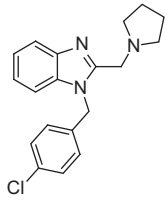
6. HCV NS4B INHIBITORS

HCV NS4B is a 261 residue hydrophobic protein with at least four domains predicted to be membrane spanning and which is released from the viral polyprotein by the NS3 protease [54–56]. The first 27 residues of the amino terminus contain an amphipathic helix that functions as a membrane anchoring element and associates with the endoplasmic reticulum membrane while oligomerization of NS4B is dependent on N-terminus residues and a second amphipathic helix at residues 43–65, a process facilitated by palmitoylation of the C-terminus [54–57]. While the precise role of NS4B is not well understood, the protein is critical for virus replication, inducing membrane vesicle formation and facilitating the formation of a membranous web that acts as a scaffold for the replication complex. NS4B has been shown to bind RNA and is also reported to possess NTPase activity consistent with the presence of a nucleotide binding domain at residues 129–135. NS4B binds and hydrolyzes both ATP and GTP although this aspect of the function of the protein is not well characterized and remains somewhat controversial [58].

The antihistamine clemizole (**9**) was discovered as an inhibitor of the binding of NS4B to the 3′-end of the negative strand of viral RNA, a potent association with a $K_d = 3.4$ nM, using a high-throughput microfluidic affinity analysis screen designed to overcome issues associated with the fragility of NS4B and preserve the natural folding of the protein [59]. **9** inhibits the NS4B/RNA interaction with an $IC_{50} = 24$ nM and abrogates HCV replication in a cell-based transient assay, $EC_{50} \sim 8$ μM. Resistance mapped to

W55R and R214Q substitutions in HCV NS4B, with the W55R mutant NS4B binding to the 3′-end of the viral RNA with fourfold increased affinity, $K_d = 0.75$ nM. **9** interacted synergistically with telaprevir or boceprevir in a luciferase-based reporter assay and additively with interferon, ribavirin, the nucleoside analog NM-283, or the allosteric NS5B inhibitor HCV-796 [60]. Deuterated derivatives of **9** that demonstrate increased metabolic stability in human liver microsomes have been described [61]. **9** has been evaluated clinically for its effect on viremia in HCV-infected patients, but the results have not been published.

Optimization of **9** has focused on improving the inhibitory potency of the compound toward a genotype 1b replicon and reducing the potential for hERG inhibition [62–64]. The benzimidazole **10** and the indazole **11** were the most potent representatives of their respective chemotypes demonstrating EC_{50}s of 1.1 and 3.3 μM, respectively, although both compounds inhibited the hERG channel with similar potency.



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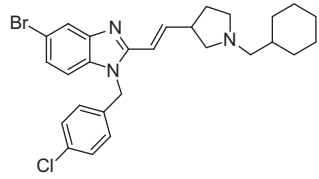

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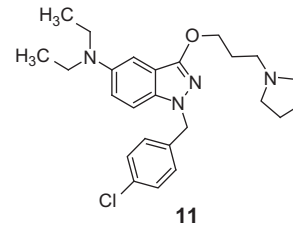

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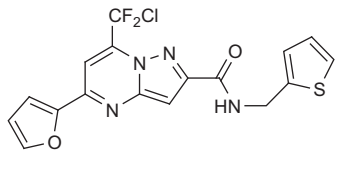
The discovery of a second amphipathic helix in NS4B comprising residues 43–65, designated 4BAH2 to distinguish it from the amphipathic helix in the amino terminus, enabled characterization of this motif as a mediator of protein oligomerization and lipid vesicle aggregation. Using a 384-well assay that monitored the induction of aggregation of fluorescently labeled lipid vesicles upon the addition of the 4BAH2 peptide, several inhibitors were identified, including anguizole (**12**) and the pyrazine **13** [57]. In a transient genotype 1b assay, **12** inhibited replication with an $EC_{50} = 300$ nM but was inactive toward genotype 2a replication, in contrast to **13** which inhibited both viral strains with EC_{50}s = 2.5 and 3.7 μM, respectively. Resistance to **12** mapped to an H94R mutation in NS4B, which exhibited a 37-fold shift in the EC_{50} [65].



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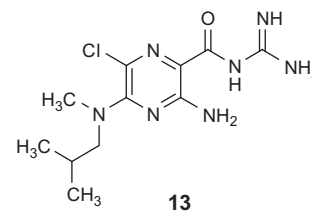

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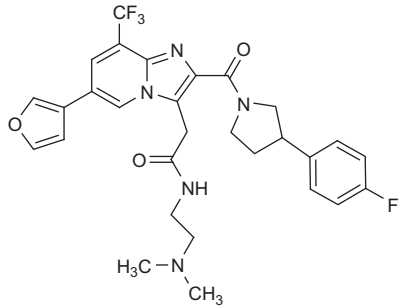
Several patent applications have claimed analogues of **12** including **14**, which completely inhibited HCV replication in a subgenomic replicon at a concentration of 10 μM, while **15** exhibited an $EC_{50} = 7$ nM, and **16** demonstrated balanced inhibition of subgenomic genotype 1a and 1b replicons with EC_{50}s = 10 nM [66–69]. AP-80978 (**17**) inhibited HCV replication *in vitro* with EC_{50}s = 0.9–1.8 μM (genotype 1b) and 7.8 μM (genotype 1a), while a genotype 2a replicon was insensitive, and the enantiomer was essentially inactive, $EC_{50} > 25$ μM [69].



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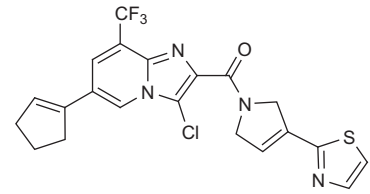

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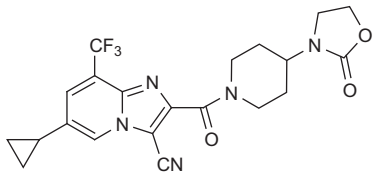

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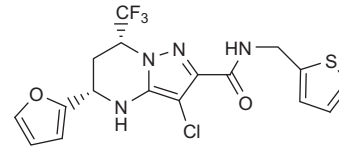

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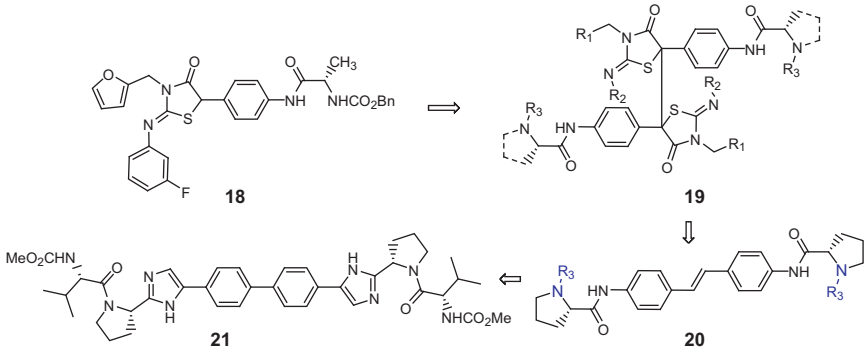
7. HCV NS5A INHIBITORS

NS5A is a multifunctional protein that plays key roles in viral genome replication, particle assembly, and virus–host interactions. The elucidation of the mechanisms by which NS5A is able to orchestrate such a diverse set of functions in the viral life cycle is an active area of considerable interest and investigation. Despite the lack of a complete understanding of the structure and function of the NS5A protein, considerable progress has been made in identifying molecules that selectively disrupt its function and demonstrate antiviral effects in HCV-infected subjects [9,70].

BMS-790052 (**21**) is a highly potent, first-in-class inhibitor that provided proof-of-concept for the clinical efficacy of NS5A inhibitors when a single 100 mg dose of **21** produced a mean viral load decline of 3.3 $\log_{10}$ at 24 h post-dose in genotype 1-infected subjects [71]. The effort that culminated in

its identification began from the screening hit **18** and involved a chemotype evolution based on the discovery of dimeric species **19** that demonstrated potent antiviral activity, leading to the elucidation of the simplified stilbene **20**. Further optimization resulted in **21**, which inhibits HCV genotypes 1–5 with EC_{50}s ranging from 9 to 146 pM [71–74].

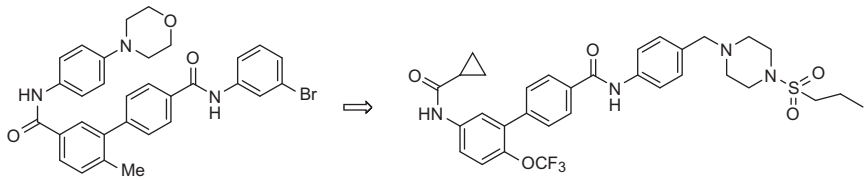


Since monotherapy with **21** leads to the emergence of resistance, Phase-IIa studies have focused on combinations with other agents [75–77]. In a clinical trial of 48 weeks, therapy with **21** (3–60 mg QD) administered with pegylated interferon-α-2a and ribavirin (PEG-IFN/RBV), 92% of the 10 mg group and 83% of the 60 mg group maintained undetectable HCV RNA levels 12 weeks after the end of treatment compared to 25% for the PEG-IFN/RBV control group [77]. In a 24-week study, in which **21** (60 mg QD) was dosed in combination with the NS3 protease inhibitor BMS-650032 (600 mg BID) to null responders with and without PEG-IFN/RBV, a >5 $\log_{10}$ median reduction in viral titer was observed initially in both groups [78]. However, viral breakthrough occurred in some members of the group taking only the direct-acting antiviral agents, but many of these subjects responded to the addition of PEG-IFN/RBV to the dosing regimen. All of the subjects that received the 24 weeks of quadruple therapy had undetectable viral RNA 12 weeks after the end of treatment [78,79].

BMS-824393 (structure not disclosed) is an NS5A inhibitor that, when dosed QD for 3 days, effected a median RNA decline of 2.5–3.9 $\log_{10}$ and 3.2–3.9 $\log_{10}$ in genotype 1a (1–100 mg) and 1b (10–100 mg) infected subjects, respectively [80].

AZD7295 (**23**, A-689), an NS5A inhibitor resulting from optimization of the biarylamide **22**, exhibited EC_{50}s of 1.24 and 0.007 μM toward genotype 1a and 1b replicons, respectively [81,82]. In a 5-day MAD clinical study, **23** at doses of 90 mg TID, 350 mg BID, and 233 mg TID was associated with a 1.2, 1.3, and 2.1 $\log_{10}$ mean reduction in viral load in genotype 1b-infected subjects, respectively, at day 6. However, one-third of the 1b-infected subjects and all subjects infected with genotype 1a or 3 showed no significant reduction in viremia [81,82]. Although **23** and **21** belong to distinct

chemotypes, they exhibit partially overlapping resistance profiles that suggest some similarity in their mode of interaction with the NS5A protein.



22 **23**

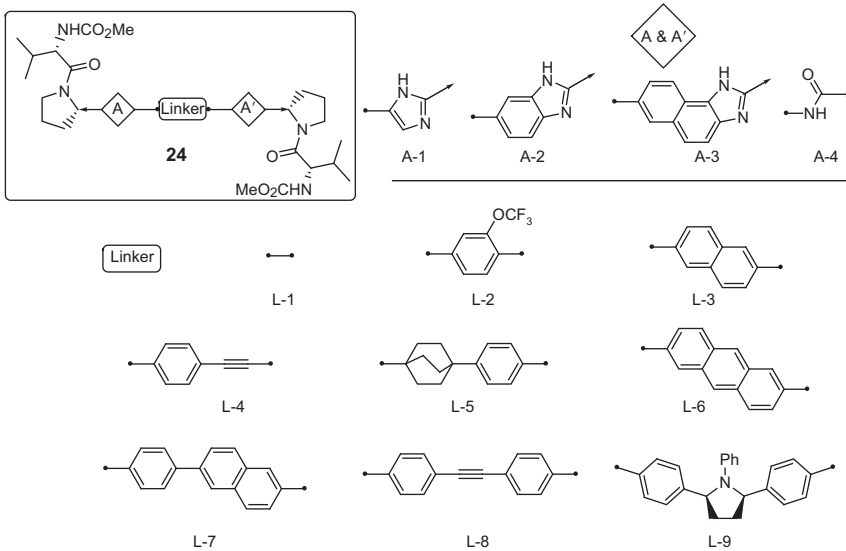
PPI-461 (structure not disclosed) is a potent pan-genotypic HCV inhibitor with EC_{50}s ranging from 0.01 to 9.3 nM that has advanced into Phase 1 clinical studies [83]. In normal healthy volunteers, PPI-461 exhibited a $T_{1/2}$ of 7.9–10.3 h and all subjects receiving doses of 50 mg or higher achieved a C_{24h} concentration greater than the EC_{50} for the least sensitive genotype 3a strain of HCV. A Phase 1b clinical study with PPI-461 has reportedly been initiated [84]. GS-5885 (structure not disclosed) is another potent HCV NS5A inhibitor, EC_{50}s = 0.005–10 nM, that exhibited a dose-proportional increase in C_{max} and AUC and had a long mean $T_{1/2}$ (37–45 h) in normal healthy volunteers [85]. At doses ranging from 3 to 100 mg, GS-5885 achieved C_{24h} plasma concentrations 9- to 366-fold above the genotype 1a protein binding-adjusted EC_{50}. In a MAD study at doses of 1–30 mg administered QD for 3 days conducted in genotype 1-infected subjects, a 3.1–3.3 $\log_{10}$ reduction in median viral load was reported [86]. Finally, the NS5A inhibitor ABT-267 (structure not disclosed) has been reported to exhibit PK and safety profiles in healthy volunteers supportive of further development [87].

The disclosure of clinical efficacy associated with **21** stimulated considerable interest in NS5A inhibitors, reflected in patent filings and discussion of advanced preclinical leads, the structures of which have not been disclosed. ITMN-10050 exhibits *in vitro* potency and preclinical PK properties similar to that of **21**; EDP-239 is two- to fourfold more potent than **21** against genotype 1a and 1b replicons and several 1b-resistant mutants; ACH-2928 exhibited EC_{50}s of <103 pM toward a broad range of HCV genotypes, including some with NS5A derived from clinical isolates, and is 20–40% orally bioavailable in the rat and dog; and GSK-2336805 has EC_{50}s of 44, 8, and 54 pM toward genotype 1a, 1b replicons and 2a-JFH virus, respectively [88–93]. PPI-437, PPI-668, and PPI-833 exhibited promising oral bioavailabilities and acceptable animal toxicology profiles in preclinical species, while IDX210 exhibited EC_{50}s of 6–175 pM toward a range of HCV genotypes and a monkey PK profile similar to that of **21** [94,95]. A common structural thread in the majority of the patent applications published to date and, particularly, in the more recent documents, is a dimeric pharmacophore, not necessarily

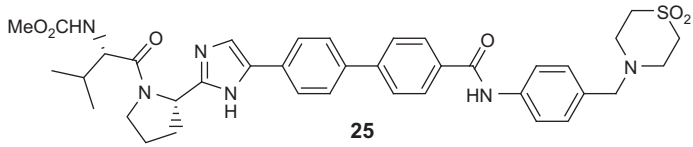
symmetrical, in which variation is focused on a core scaffold that projects two pyrrolidine moieties (see **24**), although some structural variation of the pyrroldine and valine elements has also been described [96–109]. A representative sampling of the chemical diversity that has been surveyed in these patent applications is highlighted below, with the biological data for a selected set of compounds compiled in Table 1.

Finally, a class of NS5A inhibitors exemplified by **25** has been reported that essentially integrates pharmacophoric elements derived from chemotypes that had previously afforded clinical candidates [110].

Table 1 Structure and biological data for select NS5A inhibitors



Compound	A	Linker	A′	Genotypes and EC_{50} (nM)	Reference
24a	A-1	L-9	A-1	1b < 0.1	[96]
24b	A-2	L-1	A-3	1b < 4.6	[98]
24c	A-1	L-3	A-2	1b = 0.0067	[101]
24d	A-1	L-6	A-1	1a/1b = 0.001/0.0007	[103]
24e	A-2	L-2	A-2	1a/1b = 0.05/0.003	[104]
24f	A-1	L-4	A-2	1a/1b = 0.3/0.016	[105]
24g	A-1	L-7	A-1	1a/1b = 0.022/0.0024	[106]
24h	A-1	L-4	A-3	1b < 1	[107]



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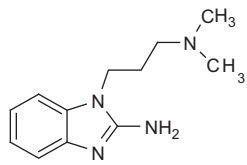
1a/1b EC_{50} = 6.5/0.34 nM

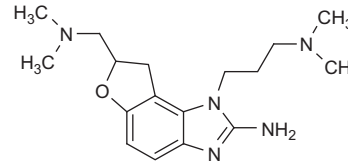
8. HCV IRES INHIBITORS

HCV uses a highly structured element of the 5 -non-translated region spanning residues 40–372 of the genomic RNA as an internal ribosomal entry site (IRES) to initiate translation [111–113]. The IRES contains two major domains, designated II and III, that contain all of the structural elements that recognize initiation factors and the 40S ribosome with the AUG start codon located in domain IV at residues 342–344. Initial approaches to inhibiting the HCV IRES focused on the application of antisense oligonucleotide (ASO) technology, but small-molecule inhibitors have been described more recently. ISIS-14803 is a 20 unit phosphorothiorate ASO that targets nucleotides 330–349 of the 5′-noncoding region, a stem-loop structure in domain 4 of the IRES that encompasses the AUG start codon [114,115]. ISIS-14803 was evaluated clinically in 24 HCV-infected subjects who were administered doses of 0.5, 1.0, 2.0, or 3.0 mg/kg for 4 weeks, with a modest clinical effect observed. Only two patients receiving 2.0 mg/kg experienced a >1.0 $\log_{10}$ reduction, while viremia in nine additional patients declined by <1.0 $\log_{10}$, an effect difficult to distinguish from natural variation in the assay or patient. However, no clear evidence of the emergence of resistant virus was observed in this study, an observation that encourages optimization and further study of ASOs for the treatment of HCV [114,115].

Using a 20-mer construct derived from domain IIa of the HCV IRES (a region known to be critical to virus translation and replication) to probe for association with small molecules from an HTS library, the benzimidazole **26** was identified as a weak binder by mass spectrometry ($K_D = 100$ μM) that bound poorly to a control 33-mer structured RNA construct [116]. SAR by MS established that the dimethylaminopropyl moiety was critical for recognition, with systematic studies leading to the identification of ISIS-11 (**27**) with a K_D of 1.7 μM for a refined 40mer RNA construct adopted based on an NMR structure of domain II. In a subgenomic replicon assay, ISIS-11 exhibited an EC_{50} of 1.5 μM with no overt cytotoxicity observed at a concentration of 100 μM.



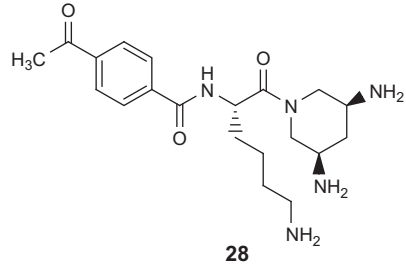
26



27

Detailed NMR studies confirmed that ISIS-11 bound to the lower bulge region of domain IIa, effecting a significant structural reorganization that led to extrusion of the 5′-residues from the bulge while establishing new stacking interactions on the 3′-side of the bulge that ultimately shifts the apical loop of domain II away from the site where eIF5 binds to the 40S subunit, providing a potential explanation for the antiviral activity [116–119].

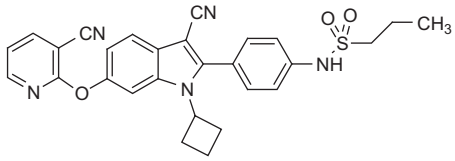
Using a similar RNA binding screen, a series of lysine derivatives incorporating additional basic amines were discovered that offer a binding mode distinct to that of the benzimidazole derivatives with **28** characterized in some detail [120]. This class of compound associates with domain IIa with micromolar affinity and appears to compete with Mg^{2+} binding to the RNA structure, with no evidence of a compound-induced conformational change detected by a FRET assay designed to monitor the intrahelical angle between the base-paired stems. Domain IIa incorporates two binding sites for divalent metal ions in both the crystal state and in solution that contribute to the architectural integrity of the RNA by stabilizing a right-angled bend at the intersection of the two helices and providing the correct conformation association with the 40S ribosomal subunit. In a cell-based replicon assay, **28** dose-dependently inhibited HCV IRES-mediated translation of a luciferase reporter at micromolar concentrations [120].



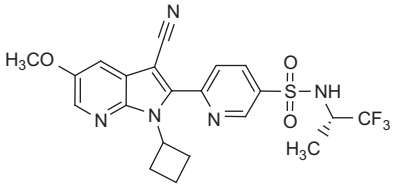
28

A broad range of indole- and azaindole-based HCV IRES inhibitors identified by gene expression modulation by small-molecules (GEMS) technology have been disclosed in a series of patent applications [121–131]. PS-102283 (**29**, SCH-1385145) is one of three compounds

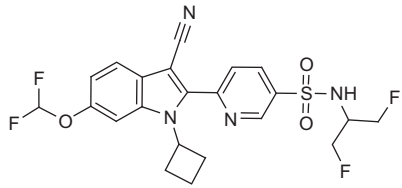
specifically identified as valuable in combination with boceprevir. More recently, the azaindole **30** and indole **31** have been shown to interact synergistically with boceprevir.



29



30



31

9. CONCLUSION

There has been considerable progress made toward the identification of potent and effective inhibitors of HCV that do not target the key enzymes NS3 protease and NS5B polymerase. At this juncture, inhibitors of HCV NS5A are the most clinically advanced and appear to offer promise both as adjunct therapy and in combination with mechanistically complementary direct-acting antiviral agents. Inhibitors of the other nonenzyme targets discussed above remain to be validated clinically, but lead inhibitors have been identified for many of these that have the potential to support drug discovery campaigns.

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