Drugs of the Future 2012, 37(4): 247-254

CCC: 0377-8282/2012
DOI: 10.1358/dof.2012.37.4.1789350

MONOGRAPH

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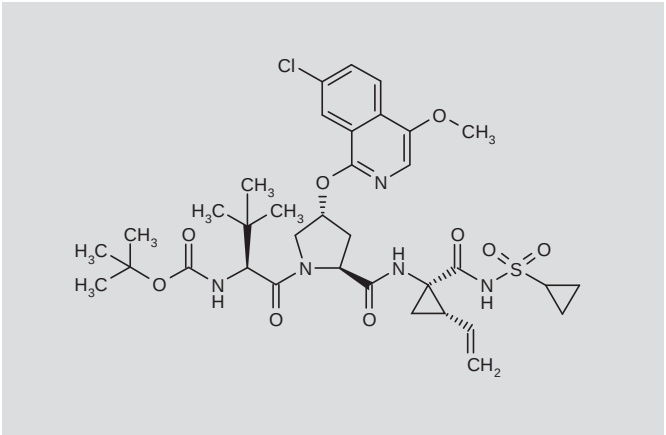
HCV Serine Protease NS3 Inhibitor
Treatment of Hepatitis C Virus

BMS-650032

N-(*tert*-Butoxycarbonyl)-3-methyl-L-valyl-4(*R*)-(7-chloro-4-methoxyisoquinolin-1-yloxy)-*N*-[1(*R*)-[*N*-(cyclopropylsulfonyl)carbamoyl]-2(*S*)-vinylcyclopropyl]-L-prolinamide

InChI: 1S/C35H46ClN5O9S/c1-9-19-16-35(19,31(44)40-51(46,47)22-11-12-22)39-28(42)25-15-21(49-29-24-14-20(36)10-13-23(24)26(48-8)17-37-29)18-41(25)30(43)27(33(2,3)4)38-32(45)50-34(5,6)7/h9-10,13-14,17,19,21-22,25,27H,1,11-12,15-16,18H2,2-8H3,(H,38,45)(H,39,42)(H,40,44)/t19-,21-,25+,27-,35-/m1/s1



$C_{35}H_{46}ClN_5O_9S$
Mol wt: 748.286
CAS: 630420-16-5
EN: 470344

SUMMARY

Hepatitis C virus (HCV) currently affects more than 170 million people worldwide. Over 80% of the infected individuals develop chronic hepatitis, which leads to other complications, such as cirrhosis, fibrosis or liver carcinoma. The current standard of care (SOC), which combines pegylated interferon alfa (pegIFN-α) and ribavirin, has limited efficacy in providing a sustained virological response, especially in HCV genotype 1-infected individuals. Moreover, the lengthy treatment with SOC is frequently associated with undesirable side effects that may be extremely debilitating. There is therefore an urgent medical need to develop anti-HCV therapies that are safer and more effective. Asunaprevir (BMS-650032) is an investigational, oral, selective serine protease NS3 inhibitor with pharmacokinetic parameters that suggest once- or twice-daily administration. Its promising safety profile, in addition to the encouraging clinical proof-of-concept results, make asunaprevir attractive for use in drug combination studies with other HCV therapeutic agents, even in interferon-free regimens and for difficult-to-treat patient populations.

Key words: Serine protease NS3 inhibitor – Hepatitis C virus – Asunaprevir – BMS-650032

SYNTHESIS*

Condensation of ethyl glycinate hydrochloride (I) with benzaldehyde in the presence of Na_2SO_4 and Et_3N in *tert*-butyl methyl ether gives ethyl *N*-benzylideneglycinate (II), which is then cyclocondensed with *trans*-1,4-dibromo-2-butene (III) by means of *t*-BuOLi in toluene to yield ethyl 1-amino-2-vinylcyclopropanecarboxylate (IV). Alternatively, condensation of ethyl *N*-(diphenylmethylene)glycinate (V) also with *trans*-1,4-dibromo-2-butene (III) by means of *t*-BuOK in THF affords cyclopropanecarboxylate (IV), which is then *N*-protected with Boc_2O at reflux to generate *N*-Boc derivative (VI). Enzymatic resolution of the racemate (VI) by means of acalase or savinase (proteases from *Bacillus clausii*) or esperase (protease from *Bacillus halodurans*) in DMSO at 40 °C leads to the desired ethyl (1*R*,2*S*)-*N*-Boc-cyclopropanecarboxylate diastereomer (VII). Hydrolysis of ethyl ester (VII) with LiOH in THF/MeOH leads to the carboxylic acid (VIII), which is then coupled with cyclopropanesulfonamide (IX) using CDI and DBU in THF to provide the sulfonamide (X). *N*-Deprotection of this compound by means of TFA in CH_2Cl_2 followed by treatment with HCl in Et_2O gives amine hydrochloride (XI) (1). Scheme 1.

Cyclopropanesulfonamide (IX) is prepared by amination of 3-chloropropane-1-sulfonyl chloride (XII) with *t*-$BuNH_2$ in THF to provide *N*-*tert*-butyl-3-chloropropane-1-sulfonamide (XIII), which is then cyclocondensed in the presence of BuLi in THF to yield *N*-*tert*-butylcyclopropanesulfonamide (XIV). Finally, the *tert*-butyl group of intermediate (XIV) is removed with TFA, affording cyclopropanesulfonamide (IX), which can also be prepared by direct amination of cyclopropanesulfonyl chloride (XV) with NH_3 in THF (1). Scheme 1.

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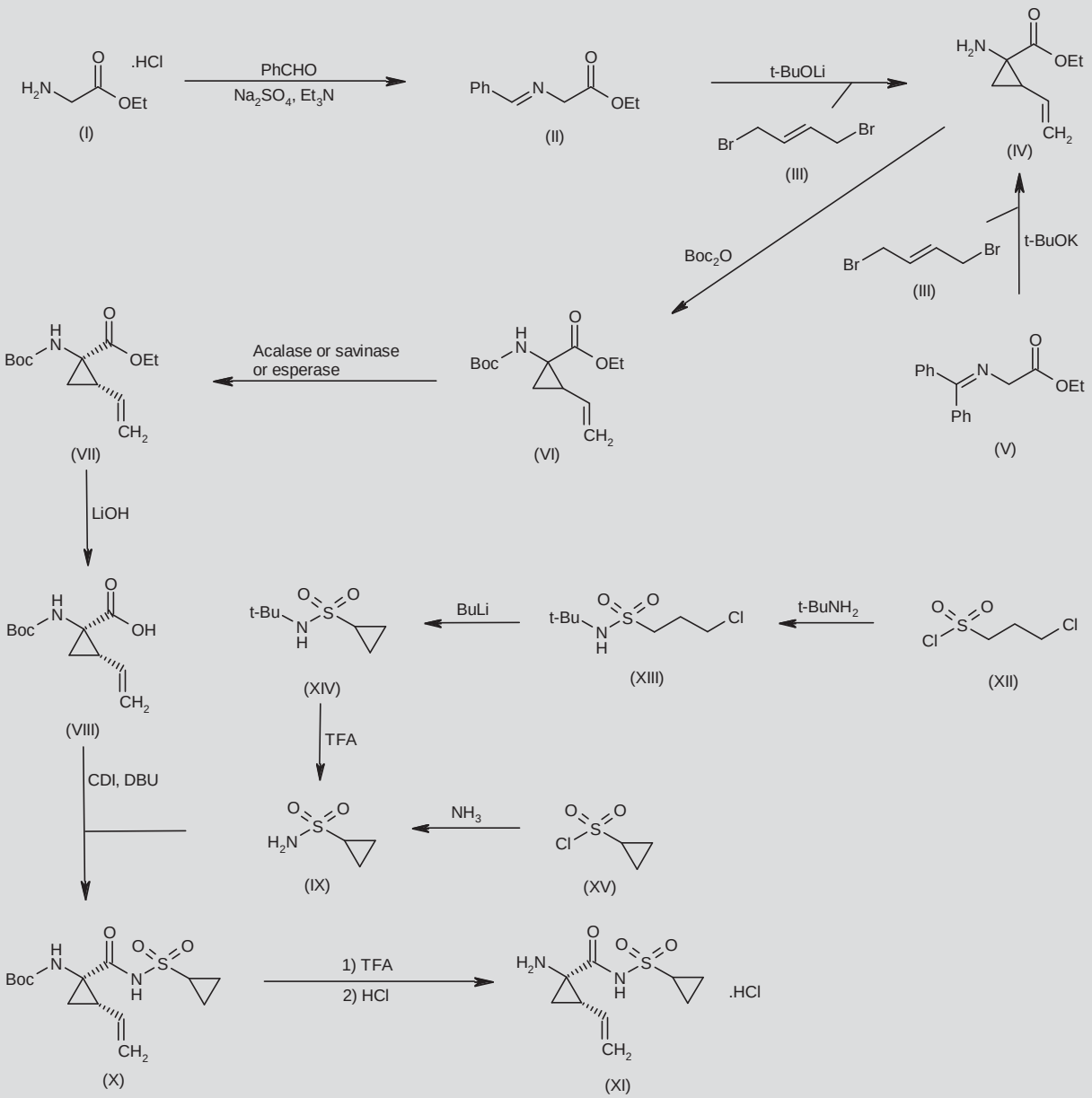
*Synthesis prepared by C. Estivill, J. Bolòs, R. Castañer. Thomson Reuters, Provença 398, 08025 Barcelona, Spain.

Scheme 1. Synthesis of Amine Hydrochloride

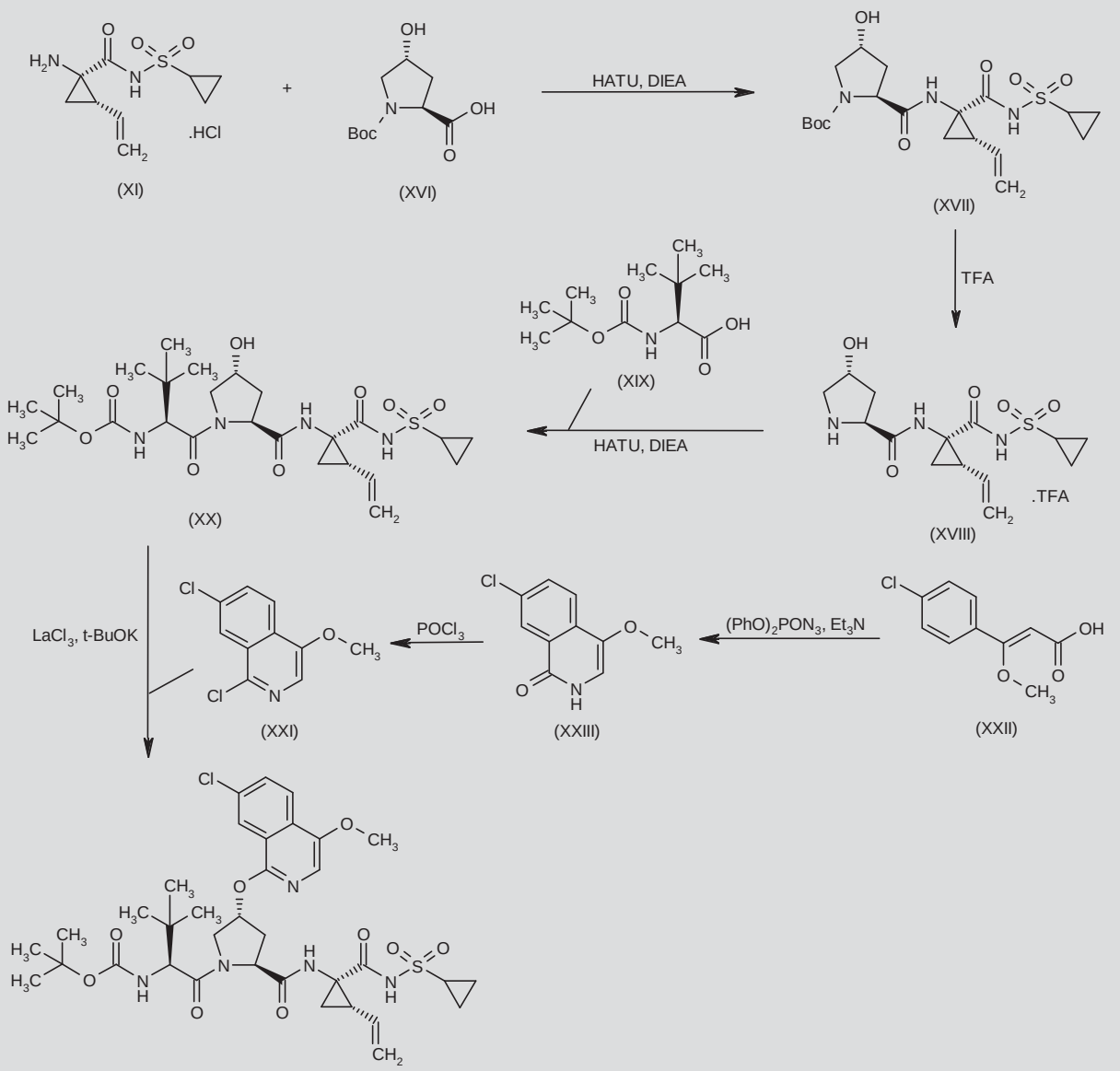


Coupling of primary amine (XI) with 1-(*tert*-butoxycarbonyl)-4(*R*)-hydroxy-L-proline (XVI) by means of HATU and DIEA in CH_2Cl_2 gives dipeptide (XVII), which is treated with TFA in CH_2Cl_2 to provide the deprotected dipeptide (XVIII). Condensation of peptide (XVIII) with *N*-(*tert*-butoxycarbonyl)-3-methyl-L-valine (XIX) using HATU and DIEA in CH_2Cl_2 affords tripeptide (XX), which is finally condensed with 1,7-dichloro-4-methoxyisoquinoline (XXI) in the presence of $LaCl_3$ and *t*-BuOK in DMF (1). Scheme 2.

1,7-Dichloro-4-methoxyisoquinoline (XXI) is obtained by cyclization of 3-(4-chlorophenyl)-3-methoxyacrylic acid (XXII) with $(PhO)_2PON_3$ by means of of Et_3N in benzene, resulting in 7-chloro-4-methoxyisoquinolin-1(2*H*)-one (XXIII), which is then chlorinated with $POCl_3$ in refluxing DMF (1). Scheme 2.

Alternatively, condensation of 1,7-dichloro-4-methoxyisoquinoline (XXI) with 1-(*tert*-butoxycarbonyl)-4(*R*)-hydroxy-L-proline (XVI) in the presence of *t*-BuOK in DMSO gives 1-(*tert*-butoxycarbonyl)-4(*R*)-[(7-

Scheme 2. Synthesis of Asunaprevir

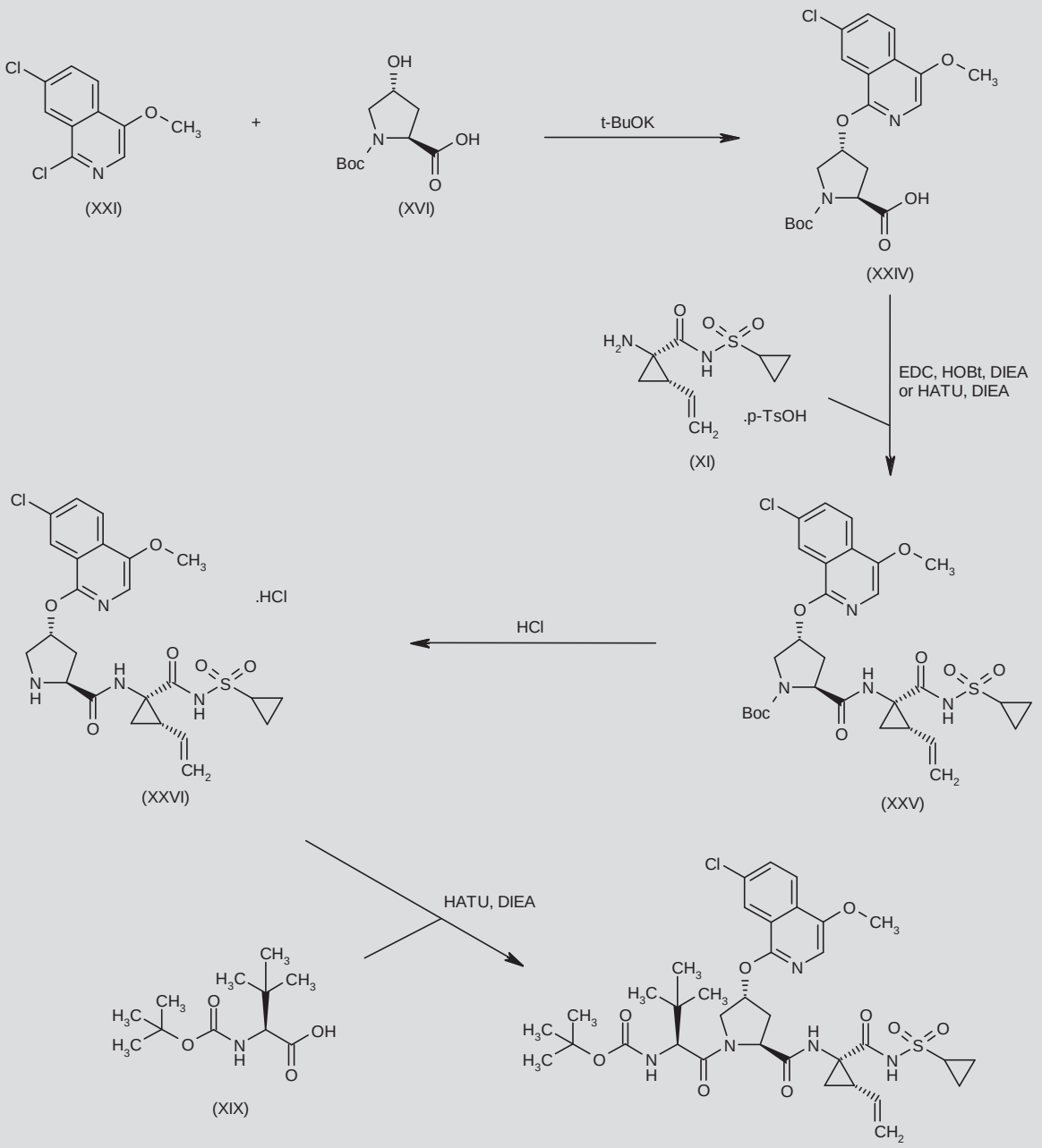


chloro-4-methoxyisoquinolin-1-yl)oxy]-L-proline (XXIV), which is then coupled with 1(*R*)-amino-2(*S*)-vinylcyclopropanecarboxamide (XI) (2, 3) by means of EDC, HOBt and DIEA (1), or HATU and DIEA in CH_2Cl_2 (2), to yield the corresponding dipeptide derivative (XXV). *N*-Boc cleavage by means of HCl in *i*-PrOH (1) or refluxing MeOH (2) provides amine hydrochloride (XXVI), which is finally condensed with *N*-(*tert*-butoxycarbonyl)-3-methyl-L-valine (XIX) using HATU and DIEA in (2, 3). Scheme 3.

BACKGROUND

An estimated 170 million people worldwide are infected with hepatitis C, with genotype 1 being the most prevalent. According to the World Health Organization (WHO), about 40% of those exposed to hepatitis C will clear the virus, making a full recovery, but the remainder, whether they have symptoms or not, become chronic carriers. Approximately 20% of people with chronic hepatitis C will develop cirrhosis, and of those, up to 25% may progress to liver can-

Scheme 3. Synthesis of Asunaprevir



cer. However, although there is no vaccine to prevent hepatitis C, it is a potentially curable disease (4, 5).

Hepatitis C virus (HCV) is an enveloped, plus-strand RNA virus classified as a separate genus (*Hepacivirus*) within the *Flaviviridae* family (6). Its genome is highly mutable and has a long open reading frame that encodes for a large polyprotein, which is ultimately cleaved by cellular and viral proteases into individual smaller proteins (6, 7). The *N*-terminal quarter of the genome encodes the core and structural proteins (core, E1 and E2 [NS1]), components of the viral particle. The rest of the genome encodes protease NS2-3, serine protease

NS3 and non-structural proteins NS4A, NS4B and NS5A. NS2-3, NS3 and NS4A proteins interact to mediate the processing of the presumed NS region of the polyprotein. NS3 is both a proteolytic cleavage enzyme and a helicase, to facilitate unwinding of the viral genome for replication. NS5B is the RNA-directed RNA polymerase needed for viral replication (7, 8).

HCV is highly heterogeneous. Eleven HCV genotypes with several distinct subtypes have been identified throughout the world (9). The current standard therapy for HCV requires the combination of two drugs, i.e., weekly subcutaneous injections of pegIFN-α and twice-daily oral ribavirin (RBV). Treatment can last for 24-72 weeks depending on genotype and the level of viremia. However, this therapy is only moderately effective and is associated with a range of adverse events that can be of sufficient severity to cause discontinuation of treatment (10, 11). Moreover, its effectiveness is highly genotype-dependent (10-12). In fact, for genotypes 1a and 1b, accounting for approximately 60% of global infections, long-term efficacy or a sustained virological response is only achieved in around 50% of chronically infected individuals (13). Therefore, there is an unmet medical need to develop HCV-specific antiviral agents.

Over the last years, an increasing number of small-molecule inhibitors targeting specific viral proteins have entered late-stage clinical development (14, 15).

Currently, four major classes of direct-acting HCV antiviral drug candidates (direct-acting antiviral agents, DAAs) are being investigated in phase II or III clinical trials: serine protease NS3 inhibitors, non-structural protein 4A (NS4A) inhibitors, non-structural protein 5A (NS5A) inhibitors and RNA-directed RNA polymerase (NS5B) inhibitors (16-19). Although these compounds are currently being developed as add-on therapy to the current standard of care (SOC) and have demonstrated potent antiviral activity, trials have also revealed the rapid emergence of resistant viral variants, especially when used alone (20, 21). Therefore, combination therapies may be the answer to suppress resistant viral variants (22).

Asunaprevir (BMS-650032) is a novel, potent and selective HCV serine protease NS3 inhibitor with improvement over the former candidate BMS-605339 (3, 23, 24). In fact, a key element in the identification of asunaprevir was to mitigate the cardiovascular effects seen with BMS-605339 (25).

Asunaprevir has picomolar potency versus NS3/4A complexes in genotype 1a/1b and has favorable safety and tolerability. Its promising antiviral activity in non-responders and treatment-naive patients has been proven in different studies, alone or in combination with SOC and/or with other DAAs (26-28). However, given the high degree of genetic variability within infected individuals, it is unlikely that asunaprevir or any other DAA alone will be successful as a monotherapeutic agent for HCV infection (14). Nevertheless, the latest clinical results suggest that asunaprevir may have interesting antiviral potential in combination with other DAAs such as BMS-790052, even in a pegIFN-α-free treatment regimen, where the most promising results indicate that HCV could be successfully eradicated in chronically infected patients with the combination of these two DAAs (27, 28).

PRECLINICAL PHARMACOLOGY

In vitro, asunaprevir has shown synergistic or additive effects with IFN-α and other HCV inhibitors. It has broad genotype coverage, with EC_{50} values of 4 and 1 nM, respectively, against genotype 1a and 1b replicons, and it exhibited excellent selectivity against the highly homologous GB virus B (GB-V) NS3/4A complex.

The emergence of asunaprevir-resistant signature substitutions was suppressed when HCV replicons were exposed to double and triple drug combinations. It has also shown time-dependent inhibition of cytochrome P450 2D6 and 3A4, with IC_{50} values of 5.7 and 5.4 μM, respectively. It also inhibited P-glycoprotein with an IC_{50} of 11 mM (23).

PHARMACOKINETICS AND METABOLISM

In pharmacokinetic studies across species, asunaprevir was livertropic, plasma exposures increased in a non-linear manner with dose escalation, and it supported once- or twice-daily dosing (23).

Following single administration (single-ascending-dose study) in genotype 1-infected patients, asunaprevir was readily absorbed and its exposure (C_{max}) increased in a dose-related manner, as previously observed in healthy subjects. The t_{max} was reached at about 2.5-4 hours post-dose, with a terminal elimination half-life of 15-22 hours. High mean oral clearance findings support extensive tissue distribution. The pharmacokinetic profile supported a regimen of twice-daily administration (26, 29).

Similarly, t_{max} was reached at about 2.5 hours post-dose, with a $t_{1/2}$ of 17.3-23.4 hours in a multiple-ascending-dose study in healthy subjects. Low plasma exposure and a mean oral clearance that was even higher than that detected in a single-ascending-dose study were reported, consistent with preferential hepatic distribution (30).

SAFETY

Asunaprevir has generally been found to be safe and well tolerated in all studies so far.

In a study combining SOC with asunaprevir, the majority of adverse events (AEs) were consistent with pegIFN-α and RBV, with fatigue being the most common (31).

There were no deaths or discontinuations due to AEs and all AEs were mild to moderate in a single-ascending-dose/multiple-ascending-dose study among chronically infected adults. There was no clinically relevant effect on physical exams, ECGs or laboratory tests in either study (26, 29). Similarly, healthy subjects in both single-ascending-dose and multiple-ascending-dose studies receiving doses of 10-1200 mg asunaprevir for 2 weeks reported mild to moderate AEs that did not differ substantially from those observed in placebo recipients. Headache and diarrhea were the most common AEs. Among the HCV chronically infected patients included in this study, analogous results were observed. No deaths, serious AEs or discontinuations, no clinically relevant trends in laboratory abnormalities, vital signs or physical examinations, and no dose-related variations were noticeable in the analysis of different heart parameters (32).

Asunaprevir does not increase the evidence of either rash or anemia with short-term monotherapy (32). Asunaprevir was safe and well tolerated either alone or coadministered with the probe substrates caffeine (*CYP1A2*), omeprazole (*CYP2C19*), losartan (*CYP2C9*), mida-

zolam (*CYP3A4*), dextromethorphan (*CYP2D6*) and/or digoxin (P-glycoprotein) (33). Most AEs were mild to moderate when asunaprevir was administered in combination with BMS-790052, with or without SOC (27, 28, 34-36), although some AEs led to dose reduction of pegIFN-α or ribavirin (34). There were no relevant changes in ECG findings. High levels of alanine aminotransferase were observed, but there was no evidence of an association between this and the response to therapy or viral breakthrough. All levels stabilized and no interruptions were required (36).

CLINICAL STUDIES

In a single-ascending-dose study in HCV-infected patients there was a 2.9-log decline in HCV RNA after a single dose of 600 mg (22).

In a randomized, placebo-controlled, single-ascending-dose study in treatment-naive patients, 200 mg of asunaprevir twice daily plus SOC for 12 weeks resulted in increased antiviral activity, no viral breakthrough and no discontinuations compared to other doses and/or regimens (31).

In a single-ascending-dose study including chronic HCV genotype 1-infected patients, subjects were randomized to receive doses of 10-1200 mg or placebo for 14 days. In parallel, in a multiple-ascending-dose study, HCV chronically infected subjects received asunaprevir in dose groups of 200-600 mg twice daily, or placebo, for 3 days. Asunaprevir administration resulted in a prompt and clinically relevant antiviral effect after single- and multiple-dose administration (32). In fact, asunaprevir at doses of 200-600 mg elicited rapid mean reductions in HCV RNA, with ranges within those reported for other DAAs (37-39).

In a similar study, no viral breakthrough was observed on 3-day monotherapy or in combination with SOC, and no emergence of resistant variants was detected (40).

Therapy with BMS-790052, asunaprevir and the current SOC for 24 weeks provided a high rate of sustained virological response (SVR) in patients with HCV genotype 1 infection who had not had a previous response to therapy with SOC. In addition, an SVR can be achieved without pegIFN-α and RBV therapy, although the response was low in patients with genotype 1a infection. No viral breakthrough occurred in patients receiving the quadruple therapy, in contrast to the dual DAA therapy (36). Interestingly, quadruple therapy suppressed the emergence of resistance in prior null responders (41).

Due to the side effect profile of pegIFN-α, an interferon-free treatment regimen has become a major issue in drug development for chronic hepatitis C (42). The results of a proof-of-concept study for SVR with a pegIFN-α-free treatment regimen in HCV patients were recently reported. Four of 11 genotype 1 patients who were non-responders to SOC achieved an SVR after 24 weeks of treatment with the combination of the NS5A inhibitor BMS-790052 and asunaprevir, with only one relapse in this cohort (27). Similar results were found in a 12-week therapy study in genotype 1-null responders, although elevated viral breakthrough was also observed when the two drugs were administered alone (34).

High cure rates are possible with dual DAA therapy, especially in patients with genotype 1b, and no viral breakthrough was observed over a 24-week study (28, 35). The antiviral potency of the two DAAs may be sufficient to suppress the emergence of DAA resistance in this difficult-to-treat population (41).

A phase III clinical study combining BMS-790052 and asunaprevir in HCV genotype 1b-infected Japanese subjects who are null responders is now recruiting volunteers (43).

DRUG INTERACTIONS

Asunaprevir has not shown any clinically relevant effect on the pharmacokinetics of the CYP substrate probes caffeine (*CYP1A2*), omeprazole (*CYP2C19*) and losartan (*CYP2C9*) in healthy subjects, while weak to moderate effects on the inhibition or induction of *CYP3A4* (midazolam), *CYP2D6* (dextromethorphan) and P-glycoprotein (digoxin) have been reported (33).

Combinations of two or more DAAs are expected to be part of future HCV therapy, and combination of BMS-790051 and asunaprevir yielded additive to synergistic activity in the replicon system. Asunaprevir has been coadministered with BMS-790052 in healthy subjects, with no clinically meaningful pharmacokinetic interaction reported, as the results were comparable with those of historical data at similar doses for each compound administered alone (44).

SOURCE

Bristol-Myers Squibb Co. (US).

DISCLOSURES

The author states no conflicts of interest.

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