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MONOGRAPH

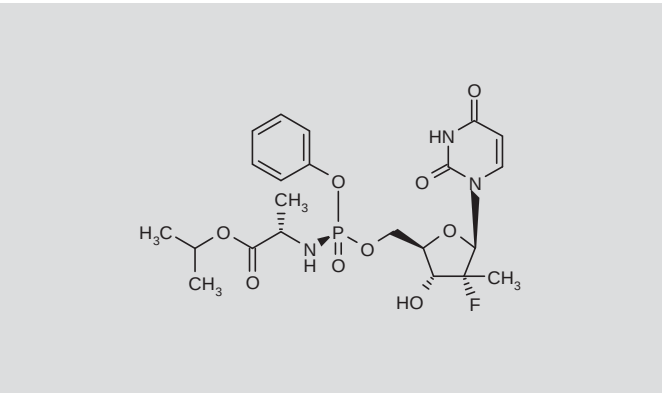
PSI-7977

Treatment of Hepatitis C Virus Infection
RNA-Directed RNA Polymerase (NS5B) Inhibitor

GS-7977

[*P*(*S*)]-2'-Deoxy-2'-fluoro-5'-*O*-[(*O*-isopropyl-L-alanino)(phenoxy)phosphoryl]-2'-methyluridine

InChI: 1S/C22H29FN3O9P/c1-13(2)33-19(29)14(3)25-36(31,35-15-8-6-5-7-9-15)32-12-16-18(28)22(4,23)20(34-16)26-11-10-17(27)24-21(26)30/h5-11,13-14,16,18,20,28H,12H2,1-4H3,(H,25,31)(H,24,27,30)/t14-,16+,18+,20+,22+,36-/m0/s1



$C_{22}H_{29}FN_3O_9P$
Mol wt: 529.453
EN: 685161

SUMMARY

Hepatitis C virus (HCV) infection is a major global health problem that currently affects over 180 million people worldwide. The hallmark of HCV infection is chronicity, resulting in chronic hepatitis, chronic cirrhosis, fibrosis and liver carcinoma. The current standard of care for HCV-infected patients consists of regular injections of PEGylated interferon alfa and oral ribavirin, a poorly tolerated regimen with a high number of debilitating side effects and variable virologic response rates dependent on viral genotypes. Therefore, novel approaches are needed for effective treatment of this disease. PSI-7977 is a chirally pure isomer form of PSI-7851, a uridine nucleotide analogue currently in development for the treatment of chronic hepatitis C. It has shown notable clinical efficacy, and broad genotype coverage in vitro. PSI-7977 is safe and generally well tolerated. With its promising profile, PSI-7977 may have potential as a component in upcoming combination strategies for the treatment of HCV infection.

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Key words: Hepatitis C virus – RNA-directed RNA polymerase inhibitor – PSI-7977 – GS-7977

SYNTHESIS*

PSI-7977 can be synthesized by the following methods:

Benzoylation of 2'-deoxy-2'-fluoro-2'-*C*-methylcytidine (I) with PhCOCl in pyridine gives the tribenzoyl fluorocytidine (II) (1, 2), which by benzamide hydrolysis with AcOH at reflux gives the uridine derivative (III). Ammonolysis of the benzoate esters of protected uridine (III) with NH_3 in MeOH yields the deprotected uridine (IV) (1, 3), which is then coupled with isopropyl *N*-[chloro(phenoxy)phosphoryl]-L-alaninate (V) (1-3), optionally (2, 3) in the presence of 1-methylimidazole in THF (1, 3) or CH_2Cl_2 (2), to provide 2'-deoxy-2'-fluoro-5'-*O*-[(*O*-isopropyl-L-alanino)(phenoxy)phosphoryl]-2'-methyluridine (VI) as a diastereomeric mixture (1-3). Finally, this compound is submitted to fractional crystallization and PSI-7977 is obtained as a single diastereoisomer (2, 3). Scheme 1.

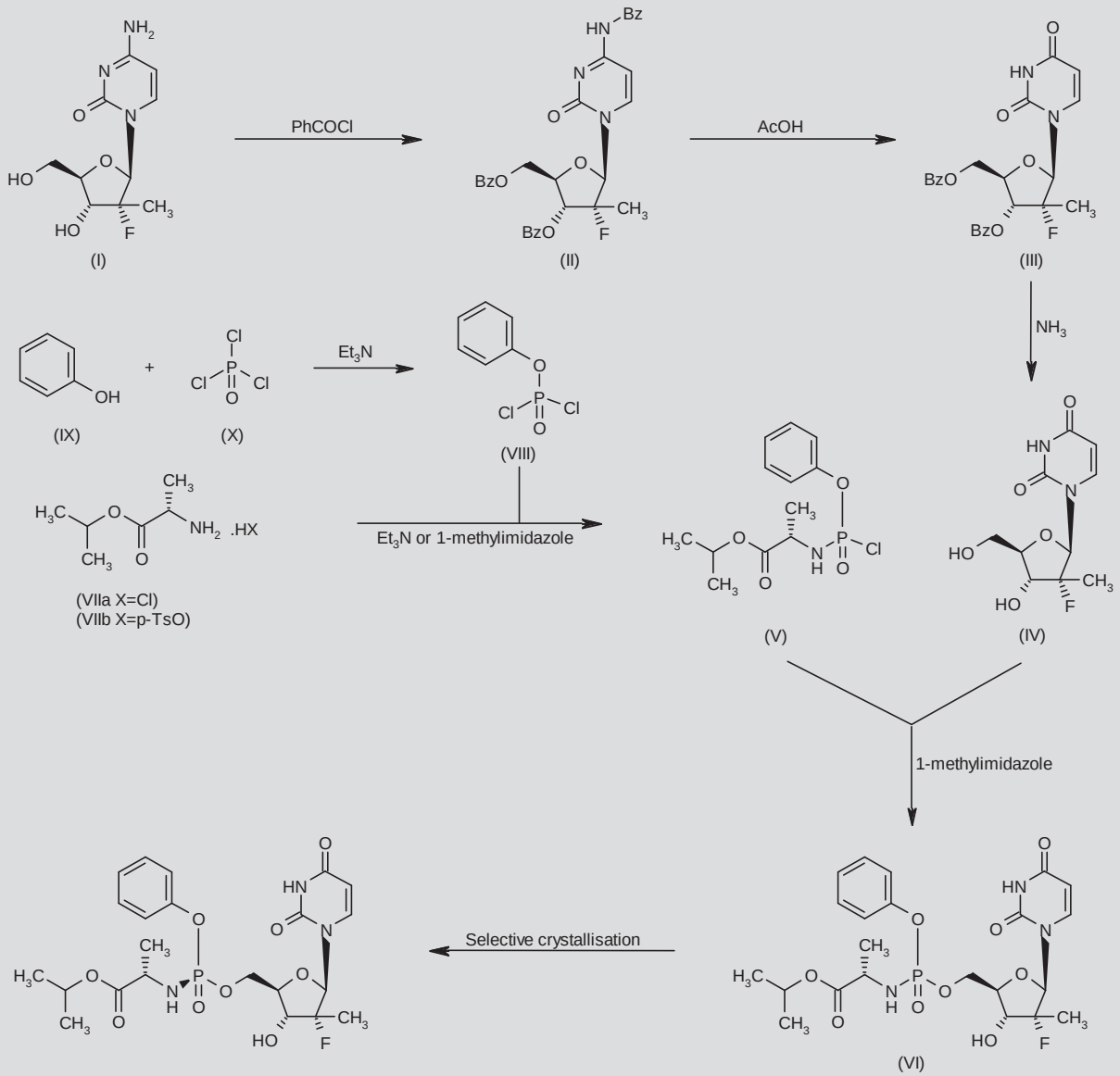
Alaninate intermediate (V) is prepared by condensation of isopropyl L-alaninate hydrochloride (VIIa) (1-3) or tosylate (VIIb) (1) with phenyl dichlorophosphate (VIII) [generated by condensation of phenol (IX) with phosphoryl chloride (X) by means of Et_3N in ether (1)] in the presence of Et_3N (1, 3) or 1-methylimidazole (2, 3) in CH_2Cl_2 (1-3). Scheme 1.

Tribenzoyl fluorocytidine (II) can be synthesized in several ways:

Grignard condensation of carbohydrate (VII) with MeLi in ethyl ether gives the methylated carbohydrate (VIII), which by treatment with DAST in CH_2Cl_2 yields the α-fluoroglycoside (IX). The debenzylation of glycoside (III) by means of Pd/C and cyclohexene, followed by reprotection of the hydroxy groups with benzoyl chloride and pyridine, yields the dibenzoate (X), which is condensed with bis(trimethylsilyl)-*N*-benzoyl cytosine (XI) by means of trimethylsilyl triflate in dichloroethane/toluene to provide the tribenzoylated fluorocytidine (II) (4, 5). Scheme 2.

Reaction of cytidine (XII) with benzoyl anhydride in DMF gives *N*-benzoylcytidine (XIII), which is selectively protected with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane ($TIPDSCl_2$) in pyridine to yield the silylated cytidine (XIV). Oxidation of the remaining OH group of (XIV) by means of DMSO, TFAA and TEA produces the

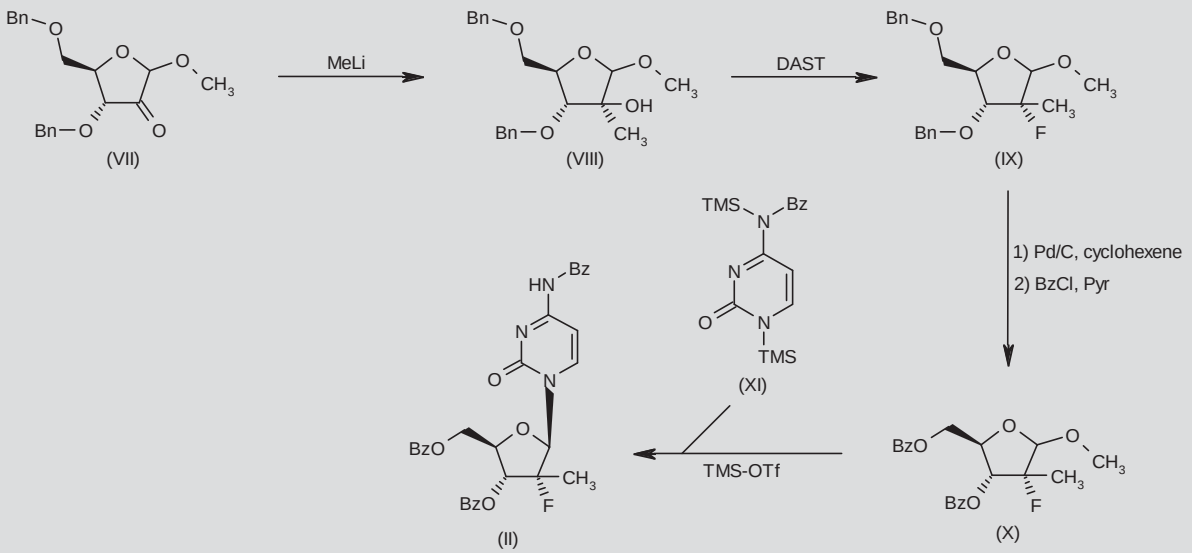
Scheme 1. Synthesis of PSI-7977



ketone (XV), which by a Grignard condensation with MeLi, followed by a desilylation with AcOH provides the tertiary alcohol (XVI). Selective benzoylation of the primary and secondary OH groups of compound (XVI) with benzoyl chloride and pyridine results in tribenzoate (XVII) with a remaining free tertiary OH group. Finally, benzoate (XVII) is fluorinated with DAST to yield the tribenzoylated fluorocytidine (II) (4, 5). Scheme 3.

Oxidation of unsaturated ester (XVIII) with sodium permanganate and $NaHCO_3$ produces dihydroxy ester (XIX), which is converted to the cyclic sulfite (XX) by treatment with $SOCl_2$ in the presence of Et_3N. After oxidation of sulfite (XX) to the corresponding sulfate (XXI) by means of NaOCl, addition of triethylamine trihydrofluoride in triethylamine solution at 85 °C leads the fluorolactone (XXIII) via intermediate (XXII). Subsequent acylation of diol (XXIII) with benzoyl chloride and DMAP, followed by reduction of the resulting dibenzoyloxy lactone (XXIV) with Red-Al in CH_2Cl_2/toluene/trifluoroethanol produces lactol (XXV), which is converted to the furanosyl chloride (XXVI) by addition of sulfuryl chloride and catalytic TBAB. Finally,

Scheme 2. Synthesis of Tribenzoyl Fluorocytidine (II)



silylation of *N*-benzoylcytosine (XXVII) by heating with hexamethyldisilazane and ammonium sulfate, followed by coupling with the glycosyl chloride (XXVII) by means of $SnCl_4$, yields the tribenzoyl fluorocytidine derivative (II) (6). Scheme 4.

BACKGROUND

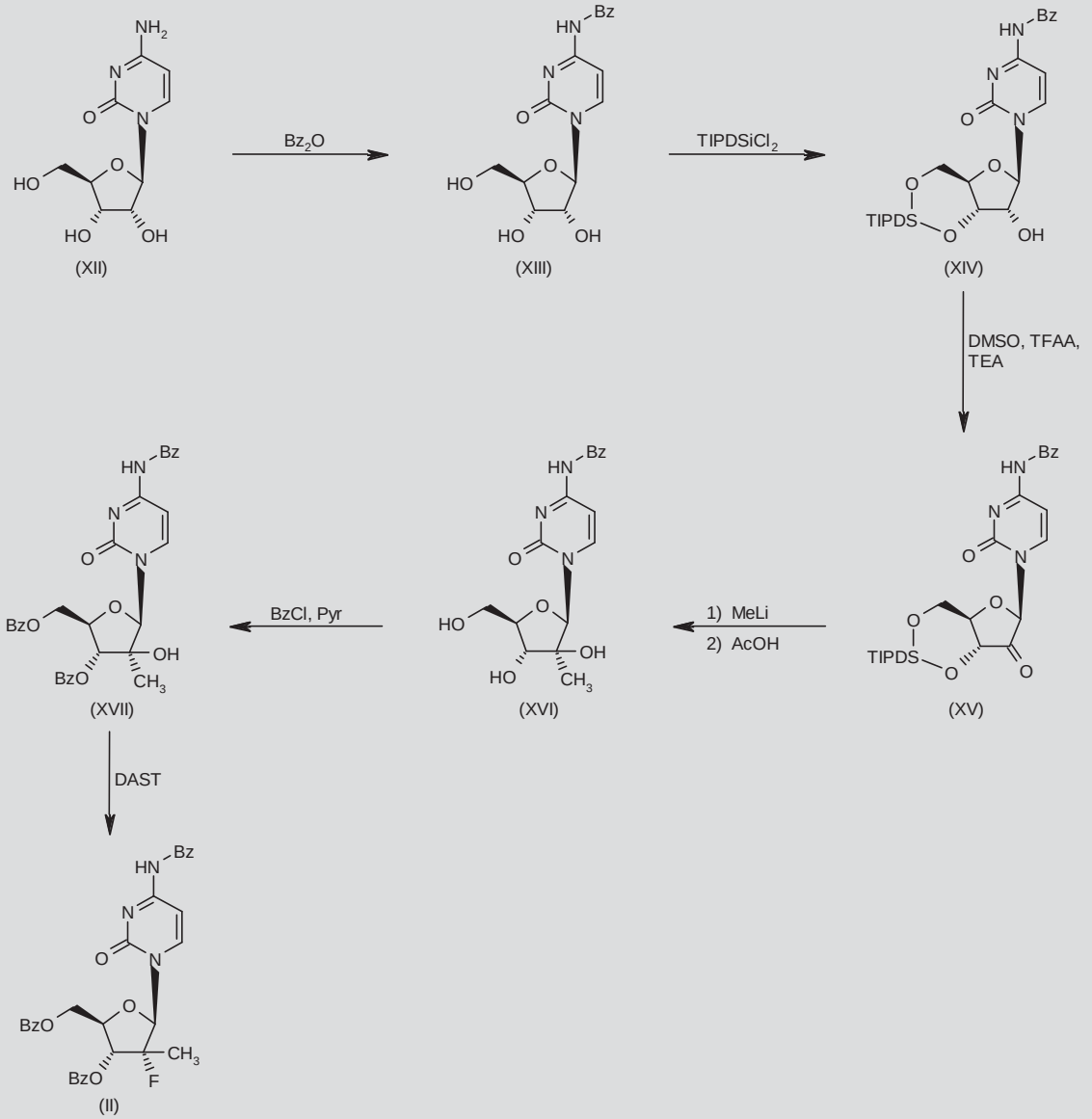
Hepatitis C virus (HCV) infection is a global health problem, with over 180 million individuals affected worldwide, 80% of whom progress to chronic liver disease (7, 8). The initial symptoms of HCV infection include fatigue, abdominal pain, loss of appetite, nausea and vomiting. However, in most cases, these symptoms do not become evident until the infection has become chronic. Individuals with chronic HCV infection are at considerable risk of developing cirrhosis, end-stage liver disease and hepatocellular carcinoma (9, 10).

HCV belongs to the *Flaviviridae* virus family, which is only known to infect humans and chimpanzees. It is an enveloped, plus-strand RNA virus with a 9.6-kb genome encoding a large polyprotein that is ultimately cleaved by cellular and viral proteases into 10 proteins (11, 12). The non-structural proteins serine protease NS3, NS4A, NS4B and RNA-directed RNA polymerase (NS5B) are involved in the replication of the viral genome, whereas the structural proteins (core proteins, envelope glycoproteins E1 and E2) are the components of the viral particle. The remaining proteins, p7 and protease NS2, are dispensable for RNA replication and there is no evidence that they are part of the viral particle (13). HCV mutates rapidly, making the infection extremely difficult to treat (12). It has six major genotypes, each of them with multiple subtypes based on sequence diversity (11, 13).

The standard therapy for HCV infection currently requires PEGylated interferon alfa (PEG-IFN-α) and ribavirin and can last 24-72 weeks depending on the HCV genotype. PEG-IFN-α is administered by weekly subcutaneous injections and ribavirin is orally administered twice daily (7, 14, 15). Currently available treatments for HCV infection are highly dependent on genotype, and are unsuccessful in many patients with HCV genotype 1 (16-18). For genotypes 1a and 1b (constituting approximately 60% of global HCV infections), long-term efficacy or a sustained virologic response is only achieved in around 50% of chronically infected individuals (16, 19). More importantly, the treatment cannot be administered to certain types of patients, while in others it is poorly tolerated and has a significant incidence of side effects (14-18). Therefore, there is an urgent need to develop more effective and safer antiviral drugs for the treatment of HCV infection. In this context, an increasing number of HCV-specific small-molecule inhibitors targeting different viral proteins have recently advanced to clinical trials, and some have shown promising results (17, 18, 20-22). The most advanced direct-acting antiviral agents (DAAs) for HCV infection target the enzymatic activities of the nonstructural HCV proteins NS3, NS5A (a component of the membrane-associated HCV replication complex) and NS5B (20, 22). Although these compounds are currently being developed as add-on therapies to the standard of care and have demonstrated potent antiviral activities, trials have also revealed the rapid emergence of resistant viral variants in some of the cases (20, 23-26).

PSI-7851 is a mixture of two molecules of identical chemical composition, PSI-7976 and PSI-7977, which only differ in the stereo-orien-

Scheme 3. Synthesis of Tribenzoyl Fluorocytidine (II)

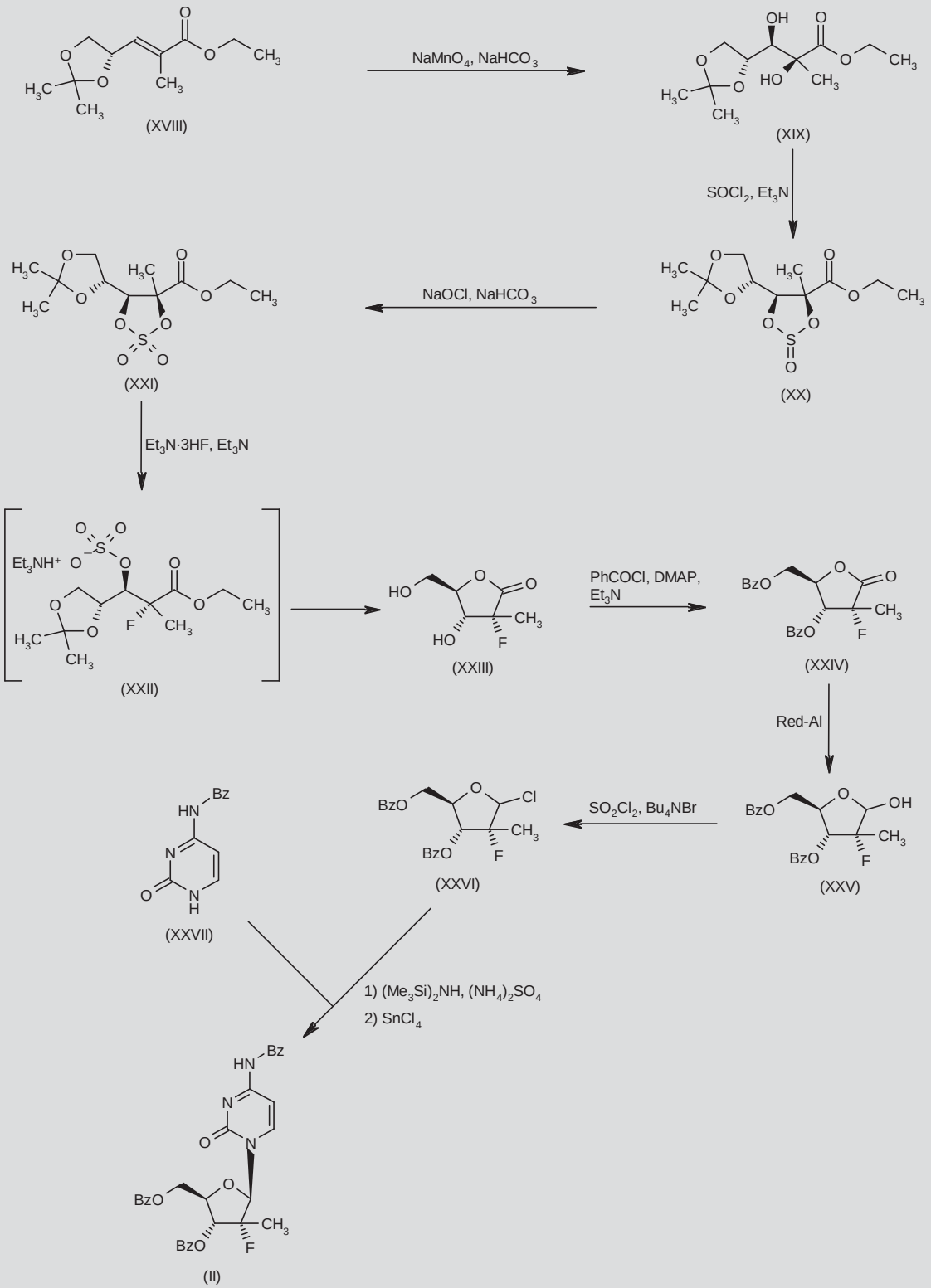


tation of one of the atoms. Once inside a liver cell, both molecules are rapidly converted to the same active triphosphate (27).

PSI-7977 is a potent inhibitor of HCV RNA replication that targets the nonstructural HCV protein NS5B. In fact, several nonstructural proteins are attractive targets for the development of anti-HCV therapies (28, 29). HCV NS5B is part of a membrane-associated replication complex that is composed of other viral proteins, viral RNA and altered cellular membranes. The polymerase is necessary for HCV replication (28, 29).

In combination with the current standard of care, PSI-7977 has exhibited notable antiviral effects in subjects infected with HCV genotypes 1, 2 and 3, and was well tolerated in several phase II studies (24-27). However, given the high degree of genetic variability within infected individuals, it is unlikely that PSI-7977 or any other DAA alone will be successful as a monotherapy for HCV infection (18). In this context, the latest clinical data suggest PSI-7977 may have an interesting antiviral potential in combination with other DAAs and/or PEG-IFN-α/ribavirin (28-32). In fact, there is a new 12-

Scheme 4. Synthesis of Tribenzoyl Fluorocytidine (II)



week trial planned, with once-daily dual regimens combining PSI-7977 with the investigational NS5A inhibitor daclatasvir dihydrochloride (BMS-790052) (33, 34). With the results obtained thus far, PSI-7977 has the potential to dramatically change the treatment paradigm for HCV infection of all genotypes and populations (32).

PRECLINICAL PHARMACOLOGY

While a time-dependent loss of sensitivity was observed with the combination of the protease inhibitor telaprevir (VX-950) and the non-nucleoside NS5B inhibitor nesbuvir (HCV-796, VB-19796), the combination of two nucleotide analogues (PSI-7977 and PSI-352938 [PSI-938]) produced little change in susceptibility in replicon cell assays. After 120 days, the EC_{50} decreased approximately 3-fold, compared with a 20-fold decrease observed at day 56 for the protease/non-nucleoside inhibitor combination (35). In fact, combination therapies using complementary nucleotide NS5B inhibitors could provide a significant barrier to resistance selection that might not be seen with a combination of a protease inhibitor and a non-nucleoside inhibitor (18, 35).

In the clone A replicon assay, PSI-7977 displayed anti-HCV activity with an EC_{90} of 0.42 μM. Cytotoxicity profiles of PSI-7977 and its diastereoisomer PSI-7976 were also studied, and both compounds were essentially devoid of cytotoxicity at 100 μM when assessed against an expanded cell panel. Mitochondrial toxicity (CC_{90}) was also evaluated, and again, neither agent demonstrated measurable mitochondrial toxicity at concentrations up to 100 μM in CEM cells; however, PSI-7977 showed CC_{90} values of 72.1 and 68.6 μM for the inhibition of mitochondrial DNA (mtDNA) and ribosomal DNA (rDNA), respectively, in human hepatocellular carcinoma Hep G2 cells (3). PSI-7977 displayed additive to synergistic effects with PSI-352938; the combination was able to clear wild-type and S282T-mutant NS5B replicons. The combination of PSI-7977 or PSI-352938 with either a benzothiadiazine non-nucleoside polymerase inhibitor or telaprevir was also able to clear wild-type replicons. These in vitro results might be indicative of the potential of PSI-7977 as a candidate for combination therapy with other anti-HCV therapeutic agents to effectively suppress resistant replicons (36).

PHARMACOKINETICS AND METABOLISM

Several phase I studies of PSI-7851 and of the combination of PSI-7977 and PSI-7976 were conducted in 2009. The first was a single-ascending-dose study that assessed the safety, tolerability and pharmacokinetics of PSI-7851 in healthy subjects, and the second one was a corresponding multiple-ascending-dose study in HCV-infected patients. Preliminary and final results were promising; in fact, PSI-7851 resulted in increased liver exposure to the active triphosphate metabolite in laboratory animals (37).

Because PSI-7977 is more easily manufactured, has potentially advantageous in vitro characteristics and is rapidly converted to the same active triphosphate as PSI-7976 once inside a liver cell, PSI-7977 was selected for further clinical development (2, 3). PSI-7977 is rapidly metabolized to the inactive nucleoside PSI-6206, which has an elimination half-life of 9-11 hours. Systemic exposure to this primary metabolite increased relatively dose-proportionally over a range of 100-400 mg PSI-7977 and, relative to the first dose, was approximately 10% higher after 28-day dosing. PSI-6206 exposures were similar after administration of PSI-7977 and PSI-7851 at 100 and 200 mg (38).

SAFETY

PSI-7977 is generally safe and well tolerated at therapeutic (400 mg) and supratherapeutic (1200 mg) doses; in fact, it does not have any meaningful effect on the electrocardiogram corrected QT (QTcF) intervals (28).

No discontinuations or adverse events were observed in a study including treatment-naive patients with noncirrhotic livers infected with HCV genotype 2 or 3 (29, 39). These results were similar to those observed in a phase IIb study assessing the safety and efficacy of PSI-7977 for the first 4 weeks of therapy. No dose-limiting toxicity was detected and both laboratory changes and adverse events were similar to clinical experience with PEG-IFN-α/ribavirin (30). Similarly, no serious adverse events or adverse events leading to treatment discontinuation were reported in a phase IIa study with treatment-naive patients infected with HCV genotype 1 without cirrhosis. All adverse events reported were mild in intensity and similar to those associated with the current standard of care. There were no dose-related changes in safety laboratory assessments, vital signs or electrocardiograms (31). Safety of PSI-7977 was similar to that of standard of care alone, and no safety events related to the study drug were reported in an analogous dose-ranging phase II study including the same type of patients (32, 40). Specifically, there were no reports of deaths, serious adverse effects or discontinuations due to adverse events or clinically relevant adverse effects (28-32).

In a 14-day proof-of-concept study, PSI-938 and PSI-7977 purine and pyrimidine nucleotide analogues alone and in combination demonstrated favorable safety and tolerability, without any serious adverse events or discontinuations. Side effects included mild headache, fatigue, dizziness and non-cardiac-related chest pain (41).

CLINICAL STUDIES

Combination treatments including PSI-7977 plus PEG-IFN-α/ribavirin have demonstrated high rates of on-treatment viral suppression in subjects infected with genotype 1 HCV and 100% sustained virologic response rates 12 weeks after cessation of treatment in subjects infected with genotypes 2 and 3 (28). Similarly, PSI-7977 in combination with standard of care demonstrated potent antiviral activity in treatment-naive patients infected with genotypes 2 or 3 without cirrhosis, with an overall rapid virologic response of 95% and no viral breakthroughs (30).

PROTON, a dose-ranging phase IIb study of PSI-7977 with the current standard of care, demonstrated potent on-treatment antiviral activity in treatment-naive patients with hard-to-treat genotype 1 HCV infection and no cirrhosis. Greater efficacy for the 400- versus the 200-mg dose was demonstrated by three viral breakthroughs and one relapse with the 200-mg dose, compared with no breakthrough or relapse with the 400-mg dose (32, 40). PSI-7977, in addition to the standard of care, demonstrated potent short-term antiviral activity with a rapid virologic response of 88-94% in treatment-naive patients with genotype 1 HCV infection at all doses tested. All patients receiving active PSI-7977 exhibited continuous

declines in HCV RNA, with no viral breakthrough during the 28 days of therapy, with a further decline in HCV RNA after discontinuation of PSI-7977 (31). When stratification by interleukin-28B (IL-28B) status was used to ensure balance across cohorts, significant and consistent antiviral activity was also observed (42).

Compared to the data on PSI-7977 monotherapy and placebo plus standard of care, and assuming additive activity, administration of PSI-7977 and standard of care reduced HCV RNA beyond what was predicted as early as day 1. Maximal HCV RNA suppression was achieved with 400 mg PSI-7977 plus standard of care, showing rates as good as or better than those reported for other DAAs plus standard of care (38).

PSI-7977 with ribavirin brought out rapid declines in HCV RNA when administered with or without PEG-IFN-α in treatment-naive patients infected with HCV genotype 2 or 3 without cirrhosis, showing that the combination of PSI-7977 and ribavirin may be sufficient to treat HCV infection (29, 39).

In interferon-free treatments, PSI-7977 has also been tested, including in combination with the guanine nucleotide analogue PSI-352938 (28), and further studies are planned for this combination therapy (43). PSI-352938 and PSI-7977 demonstrated a robust 14-day antiviral activity alone and in combination against genotype 1 HCV. Significant reductions in HCV RNA were observed, with some participants reaching nondetectable HCV RNA levels in as little as 3 days (41).

In the ongoing phase IIb ATOMIC study, previously untreated patients infected with HCV genotype 1, 4, 5 or 6 will receive once-daily PSI-7977 in combination with standard of care for 12 or 24 weeks (44).

Future clinical trials include a phase II study combining TMC-435 (TMC-435350) and PSI-7977 in patients infected with HCV genotype 1 whose disease did not respond to standard of care (45), a phase III study of PSI-7977 and ribavirin compared to standard of care (46), and a comparison study between PSI-7977 with or without ribavirin (47).

DRUG INTERACTIONS

A substantial number of HCV-infected patients are receiving methadone, a narrow-therapeutic-range drug prescribed for opiate addiction. In this context, steady-state PSI-7977 does not alter methadone pharmacokinetics or pharmacodynamics, so PSI-7977 and methadone may be safely coadministered without any dose readjustment (48). In vitro drug–drug interaction results suggest that it is unlikely that coadministered telaprevir would affect the antiviral activity of PSI-7977 in the liver (27).

SOURCE

Gilead Sciences, Inc. (US).

DISCLOSURES

The author states no conflicts of interest.

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