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## Synthetic medicinal compounds for the treatment of hepatitis C

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### ABSTRACT

Hepatitis C has become a major clinical and public health problem worldwide. Accordingly, pharmaceutical research companies are making efforts to develop new synthetic medicinal compounds along with biologics, drug combinations and new dosage forms. The approval of two new synthetic medicinal compounds in late 2013 namely sofosbuvir and simeprevir by the U.S. Food and Drug Administration (U.S. FDA) for the treatment of hepatitis C is the result of the efforts made by these pharmaceutical research companies. The U.S. FDA approved synthetic medicinal compounds have opened the door for the oral regimens as the future standard of treatment for hepatitis C. This review article provides preliminary information about recently approved synthetic medicinal compounds as well as some important synthetic medicinal compounds in the pipeline for the treatment of hepatitis C.

**Keywords:** Clinical Trial, U.S. FDA, Hepatitis C, Synthetic Medicinal Compounds.

### INTRODUCTION

Hepatitis C is a liver disease caused by the infection with hepatitis C virus (HCV) which was identified in 1989 [1]. It is a blood born infection that is spread through any activity in which blood is transferred from one person to another, for example, frequent sharing of injection needles contaminated with HCV among different users allows for frequent transmission of the virus. The infection with HCV causes many severe liver disorders including hepatocellular carcinoma, liver cirrhosis, end stage liver disease, hepatic steatosis and various metabolic disorders [1, 2].

According to World Health Organization's Media Centre report on Hepatitis C (<http://www.who.int/mediacentre/factsheets/fs164/en/> accessed on May 21, 2014), 130 to 150 million people globally have chronic hepatitis C infection; a significant number of those who are chronically infected will develop liver cirrhosis or liver cancer and 350000 to 500000 people die each year from hepatitis C related liver diseases. Recently, it is reported that the global burden of this disease has increased from an estimated 2.3% to 2.8%. According to the reported data the highest reported prevalence of chronic HCV is in Asia and the Middle East, wherein Egypt has the highest prevalence of HCV with up to 15% of the population positive for anti-HCV antibody, and an estimated 10% with chronic HCV infection. One study mentions that the incidence of new infections worldwide is approximately 7 subjects per 1000 patients per year, i.e. there are about 500000 new infections per year [3, 4]. According to another report HCV related deaths will double between 2010 and 2019, and the projected financial burden for treating HCV related diseases during this interval will be about \$6.5 and \$13.6 billion [5].

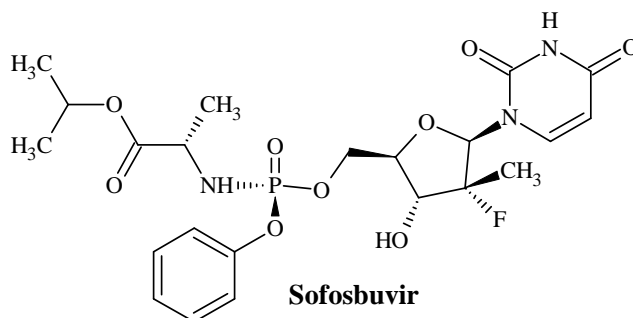
Further report states that most peoples born between 1945 and 1965 are unaware of their diagnosis for Hepatitis C. If these peoples are screened for HCV, it is expected that a large number of persons may be found to be infected with the HCV virus [6].

Today, chronic HCV infection or hepatitis C has become a major clinical and public health problem. Accordingly, pharmaceutical research companies are making efforts to develop biologics, drug combinations, new dosage forms as well as new synthetic medicinal compounds for the treatment of hepatitis C. These efforts are mainly to develop direct acting antivirals for hepatitis C in the form of NS3 protease inhibitors, NS4B inhibitors, NS5A inhibitors, NS5B nucleoside inhibitors, NS5B Non-nucleoside inhibitors, inhibitors of host targets, MIR122 inhibitors and Entry inhibitors [5]. Some review articles that provide information on the epidemiology of HCV and their genomic organization [1]; the natural history of chronic hepatitis C infection [2]; Management of hepatitis C virus infection [3, 4] and therapies for HCV infection [5, 6] have been published. This review article provides preliminary information about recently approved synthetic medicinal compounds as well as some important synthetic medicinal compounds in the pipeline for the treatment of hepatitis C.

## RECENT SYNTHETIC MEDICINAL COMPOUNDS APPROVED BY U.S. FOOD AND DRUG ADMINISTRATION (U.S. FDA) FOR THE TREATMENT OF HEPATITIS C

### 1. Sofosbuvir (Proprietary Name: Sovaldi)

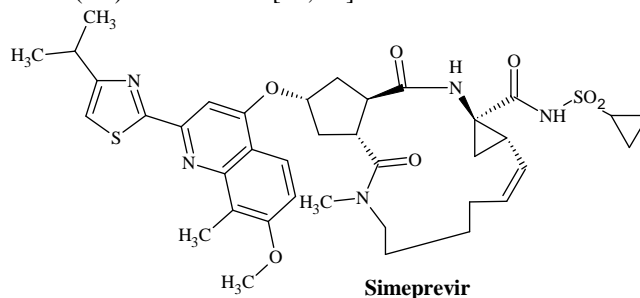
Sofosbuvir is a nucleotide analog inhibitor of HCV NS5B polymerase and is a prodrug of 2'-deoxy-2'-fluoro-2'-C-methyluridine monophosphate that is converted within hepatocytes to its active uridine triphosphate form [7]. The chemical name for sofosbuvir is (S)-Isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)-(phenoxy)phosphorylamino)propanoate [8, 9].



The tablet of sofosbuvir of 400 mg strength for oral administration has been approved by U.S. FDA on December 6, 2013. This drug developed by Gilead Sciences Inc. ([www.gilead.com](http://www.gilead.com)) has been approved by U.S. FDA for the treatment of chronic hepatitis C infection as a component of a combination antiviral treatment regimen [9].

### 2. Simeprevir (Proprietary Name: Olysio)

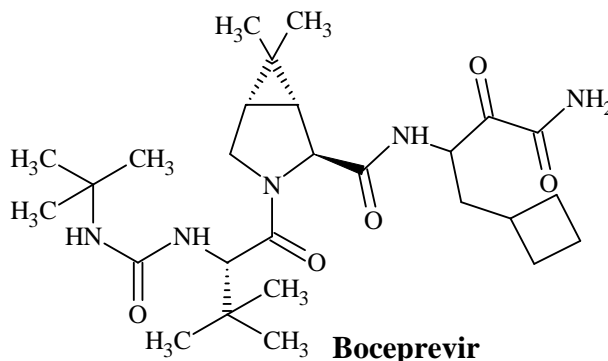
Simeprevir is an inhibitor of the HCV NS3/4A protease [10]. The chemical name for simeprevir is (2R,3aR,10Z,11aS,12aR,14aR)-N-(cyclopropylsulfonyl)-2-[[2-(4-isopropyl-1,3-thiazol-2-yl)-7-methoxy-8-methyl-4-quinolinyl]oxy]-5-methyl-4,14-dioxo-2,3,3a,4,5,6,7,8,9,11a,12,13,14,14a-tetradecahydrocyclopenta[c]cyclopropa[g][1,6]diazacyclotetradecine-12a(1H)-carboxamide [11, 12].



The capsule containing 154.4 mg of simeprevir sodium salt, which is equivalent to 150 mg of simeprevir, for oral administration has been approved by U.S. FDA on November 22, 2013. This drug developed by Janssen Research and Development (<http://www.janssenrnd.com>) has been approved by U.S. FDA for the treatment of chronic hepatitis C infection as a component of a combination antiviral treatment regimen [12].

### 3. Boceprevir (Proprietary Name: Victrelis)

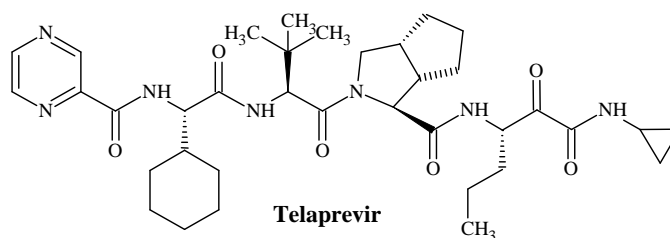
Boceprevir is an inhibitor of the hepatitis C virus (HCV) non-structural protein 3 (NS3) serine protease [13]. Its chemical name is (1R,5S)-N-[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(S)-[[[(1,1-dimethylethyl)amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-2(S)-carboxamide [14, 15, 16].



The capsule of boceprevir of strength 200 mg for oral administration has been approved by U.S. FDA on May 13, 2011. This drug developed by Merck Sharp Dohme (<http://www.merck.com>) has been approved by U.S. FDA for the treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy, including prior null responders, partial responders, and relapsers [16].

### 4. Telaprevir (Proprietary Name: Incivek)

Telaprevir is an inhibitor of the HCV NS3/4A protease [17]. Its chemical name is (1S,3aR,6aS)-2-[(2S)-2-((2S)-2-cyclohexyl-2-[(pyrazin-2-ylcarbonyl)amino]acetyl)amino]-3,3-dimethylbutanoyl]-N-[(3S)-1-(cyclopropylamino)-1,2-dioxohexan-3-yl]-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrole-1-carboxamide [18, 19].

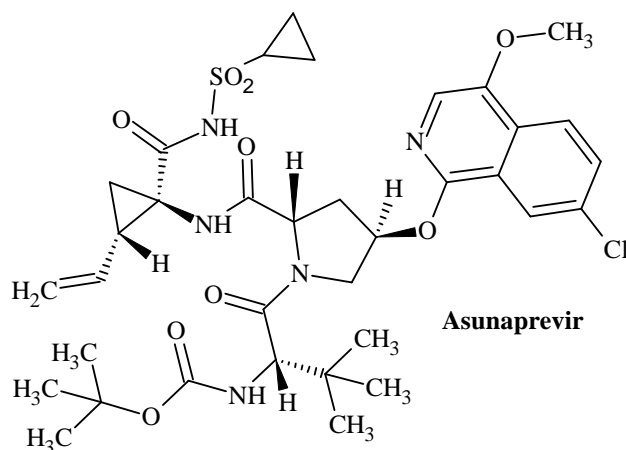


The tablet of telaprevir of 375 mg strength for oral administration has been approved by U.S. FDA on May 23, 2011. This drug developed by Vertex Pharmaceuticals (<https://www.vrtx.com>) has been approved by U.S. FDA, in combination with peginterferon alfa and ribavirin, for the treatment of genotype 1 chronic hepatitis C (CHC) in adult patients with compensated liver disease, including cirrhosis, who are treatment-naïve or who have been previously treated with interferon-based treatment, including prior null responders, partial responders, and relapsers [19].

## SYNTHETIC MEDICINAL COMPOUNDS IN PHASE III OF CLINICAL TRIAL

### 1. Asunaprevir

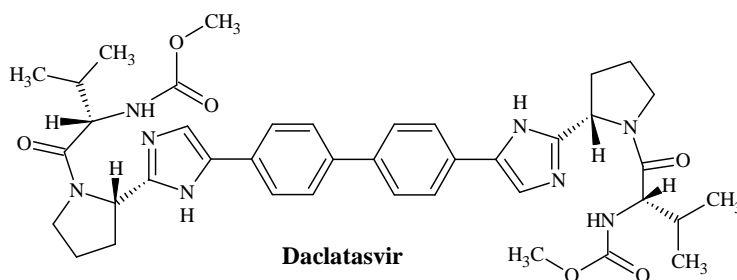
Asunaprevir (BMS-650032) chemically is 1,1-dimethylethyl [(1S)-1-[[[(2S,4R)-4-(7-chloro-4-methoxyisoquinolin-1-yloxy)-2-((1R,2S)-1-[(cyclopropylsulfonyl)carbamoyl]-2-ethenylcyclopropyl)carbamoyl]pyrrolidin-1-yl]carbonyl]-2,2-dimethylpropyl]carbamate [20, 21].



This hepatitis C virus (HCV) non-structural protein protease inhibitor currently in Phase III clinical trial has been developed by Bristol-Myers Squibb (<http://www.bms.com>) for the treatment of HCV infection [20-23].

## 2. Daclatasvir

Daclatasvir chemically is dimethyl N,N'-(biphenyl-4,4'-diylbis{1H-imidazole-5,2-diyl}[(2S)-pyrrolidine-2,1-diyl][(1S)-1-(1-methylethyl)-2-oxoethane-2,1-diyl]})dicarbamate [24-26].



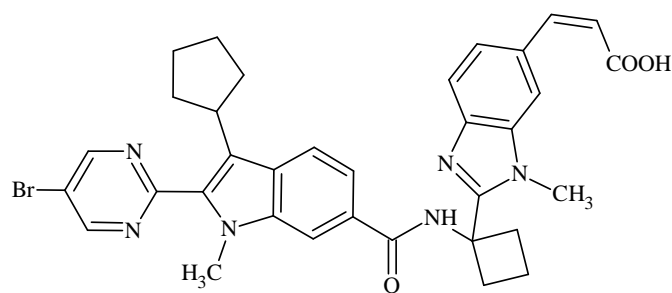
This Hepatitis C Virus NS5A replication complex inhibitor currently in Phase III clinical trial has been developed by Bristol-Myers Squibb (<http://www.bms.com>) for the treatment of HCV infection [25, 26].

## 3. Alisporivir (DEB025)

Alisporivir chemically is Cyclo[L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl-(2S,3R,4R,6E)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoyl-(2S)-2-aminobutanoyl-N-methyl-D-alanyl-N-ethyl-L-valyl-L-valyl-N-methyl-L-leucyl] or [8-(N-methyl-D-alanine),9-(N-ethyl-L-valine)]cyclosporine [27-29]. This cyclophilin inhibitor of HCV currently in Phase III clinical trial has been developed by Novartis ([www.novartis.com](http://www.novartis.com)) for the treatment of HCV infection [28, 29].

## 4. Deleobuvir

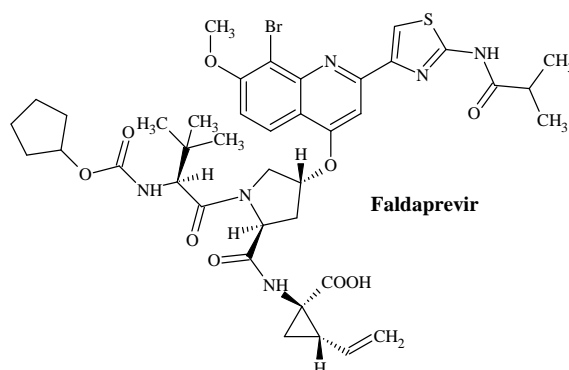
Deleobuvir chemically is (2E)-3-{2-[1-({2-(5-bromopyrimidin-2-yl)-3-cyclopentyl-1-methyl-1H-indol-6-yl}carbonyl)amino]cyclobutyl}-1-methyl-1H-benzimidazol-6-yl}prop-2-enoic acid [30].

**Deleobuvir**

This non-nucleoside inhibitor of the HCV polymerase, that inhibits HCV genotype-1 replication and which, when combined with faldaprevir and other direct acting antivirals for HCV infection, has the potential to produce sustained clearance of detectable HCV in patients with HCV genotype-1 infection without the use of interferon. Deleobuvir has been developed by Boehringer Ingelheim Pharmaceuticals ([www.boehringer-ingelheim.com](http://www.boehringer-ingelheim.com)) for the treatment of HCV infection [31].

### 5. Faldaprevir

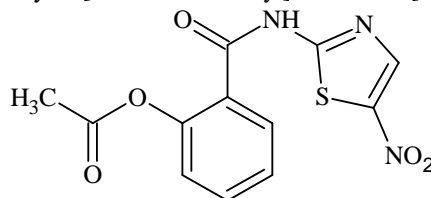
Faldaprevir chemically is (1R,2S)-1-[[[(2S,4R)-4-[[8-bromo-7-methoxy-2-[2-(2-methylpropanamido)-1,3-thiazol-4-yl]quinolin-4-yl]oxy]-1-[(2S)-2-[[cyclopentyl]oxy]carbonyl]amino]-3,3-dimethylbutanoyl]pyrrolidine-2-carboxamido]-2-ethenylcyclopropane-1-carboxylic acid [32].

**Faldaprevir**

Faldaprevir is an oral protease inhibitor that targets viral replication in the liver. This compound has been developed by Boehringer Ingelheim Pharmaceuticals ([www.boehringer-ingelheim.com](http://www.boehringer-ingelheim.com)) for the treatment of HCV infection [33].

### 6. Nitazoxanide (NT-675)

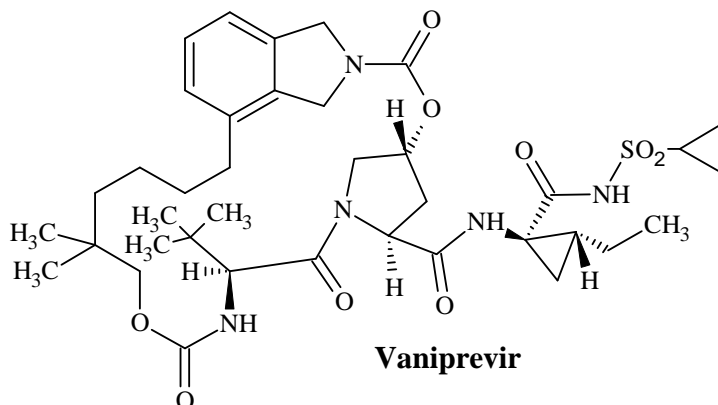
Nitazoxanide chemically is 2-acetyloxy-N-[5-nitro-2-thiazolyl]benzamide [34].

**Nitazoxanide**

Nitazoxanide, a thiazide, modulates cell signaling pathways involved in the host cell's innate defense against viruses. This drug developed by Romark Laboratories ([www.romark.com](http://www.romark.com)) is currently in Phase 2b-3 for the treatment of hepatitis C [35].

**7. Vaniprevir (MK-7009)**

Vaniprevir chemically is (5R,7S,10S)-N-[(1R,2R)-1-[(cyclopropylsulfonyl)carbamoyl]-2-ethylcyclopropyl]-10-(1,1-dimethylethyl)-15,15-dimethyl-3,9,12-trioxo-6,7,9,10,11,12,14,15,16,17,18,19-dodecahydro-1H,3H,5H-2,23:5,8-dimethano-4,13,2,8,11-benzodioxatriazacyclohenicosine-7-carboxamide [36, 37].



Vaniprevir is a macrocyclic Hepatitis C virus (HCV) NS3/4a protease inhibitor. This drug developed by Merck ([www.merck.com](http://www.merck.com)) is in phase III of its clinical trial for the treatment of hepatitis C [38].

There are many other synthetic medicinal compounds which are either in their clinical trial phase II or lesser clinical trial phase. The authors believe that all of these compounds may not become drugs for the treatment of hepatitis as their drug candidature is still subjected to their phase III clinical trial as well as the marketing approval by the drug approval authorities worldwide. Accordingly, the authors are only mentioning the name of few synthetic medicinal compounds which are either in their clinical trial phase II or lesser clinical trial phase. These include Danoprevir [39], Lomibuvir [40], Mericitabine [41], Setrobuvir [42], Vedroprevir [43] and Neceprevir [44].

**CONCLUSION**

The approval of sofosbuvir and simeprevir by the U.S. FDA has opened the door for the oral regimens as the future standard of treatment for hepatitis C, potentially avoiding interferon and its harsh side effects. As on date, these synthetic medicinal compounds are expensive and this may create a potential barrier for many patients. However, these therapies may still be considered as cost effective in terms of decreased risk of advanced liver diseases and its complications in patients infected with HCV. To combat this problem, many synthetic medicinal compounds developed by pharmaceutical industries are in the pipeline for the treatment of hepatitis C. As more orally active synthetic medicinal compounds become available for the treatment of HCV infection, the cost of HCV infection therapy will also decrease. It will make the treatment of HCV infection simpler, safer and more effective. It would be interesting to see how many new synthetic medicinal compounds for the treatment of HCV infection would be approved by the U.S. FDA and would be available in the market in future.

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