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Review of the Grazoprevir Patent Landscape:

A scoping report

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This report was prepared by Andrew Brown and Amel Garbi (Pharmathen) with input from Karin Timmermans (UNITAID).

World Health Organization

CONTENTS

Abbreviations

API	active pharmaceutical ingredient
AUC	area under the (plasma concentration/time) curve
DAA	direct-acting antiviral
HCV	hepatitis C virus
HIV	human immunodeficiency virus
PCT	Patent Cooperation Treaty
RNA	ribonucleic acid

1. INTRODUCTION

Hepatitis C virus (HCV) is a major global health problem. With 80 – 150 million people worldwide chronically infected with the virus, the prevalence of HCV is higher than that of the human immunodeficiency virus (HIV). It is estimated that, worldwide, 4 – 5 million people are coinfected with HIV and HCV. Each year, 500 000 – 700 000 people die of HCV-related liver disease, and evidence indicates that the HCV burden is increasing.[1,2] While the HCV epidemic is global in scope, the HCV burden varies considerably between countries.

The virus has six primary genotypes. Genotypes 1 and 3 are the most prevalent, accounting respectively for 46% and 30% of HCV cases worldwide. Together, genotypes 2, 4 and 6 represent around 23% of HCV cases, while genotype 5 accounts for less than 1%.[3]

Efforts to treat HCV have historically been hampered by suboptimal and inadequate treatments. However, the development of direct-acting antivirals (DAAs) has dramatically improved HCV treatment prospects and has altered the standard of care. Several new DAAs that do not require pegylated interferon were launched in late 2013 and in 2014, and a number of other DAAs are in development.

These DAAs generate cure rates that approach or exceed 90%. Some combination regimens may have pangenotypic efficacy, which would simplify treatment and monitoring.

UNITAID's Hepatitis C Medicines Technology and Market Landscape, published in February 2015, identified Merck's investigational compound MK-5172 – grazoprevir – as being of interest. The combination grazoprevir/elbasvir has breakthrough therapy designation in the United States for treatment of certain patients with chronic HCV infection.

In view of grazoprevir's potential role in future treatment, this report explores the patent landscape of grazoprevir.

1 Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095–128.

2 GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;385(117–71).

3 Messina JP, Humphreys I, Flaxman A, Brown A, Cooke GS, Pybus OG et al. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology. 2014;61(1):77–87.

II. METHODOLOGY

Relevant patents and patent applications were identified by searching patent and non-patent databases, namely: PatBase, TotalPatent, SciFinder and Google patent. Searches were carried out using keywords, semantic searches and structure searches.

For each of the most relevant patents or applications, the equivalents were identified (INPADOC family) and the legal status of each of the equivalents was checked on the websites of the relevant patent offices. The countries listed in Annex 1 represent those for which INPADOC data is available.

Data for Thailand and Viet Nam were checked by local patent attorneys at the local patent office. In Pakistan, the local patent office provided a search for equivalents to help prepare this report.

The searches were carried out in January 2015. The analysis of the identified patents and patent applications was undertaken on the basis of the European patent/application unless otherwise indicated.

Caveat: It is important to note that the patent status of a given product in a given country may change and that data may therefore become outdated. It is advisable always to check with the relevant national or regional patent office for the most up-to-date information on the status of a given patent or patent application.

This report was prepared by Andrew Brown and Amel Garbi (Pharmathen), with input from Karin Timmermans (UNITAID). The patent searches were conducted by Amel Garbi (Pharmathen).

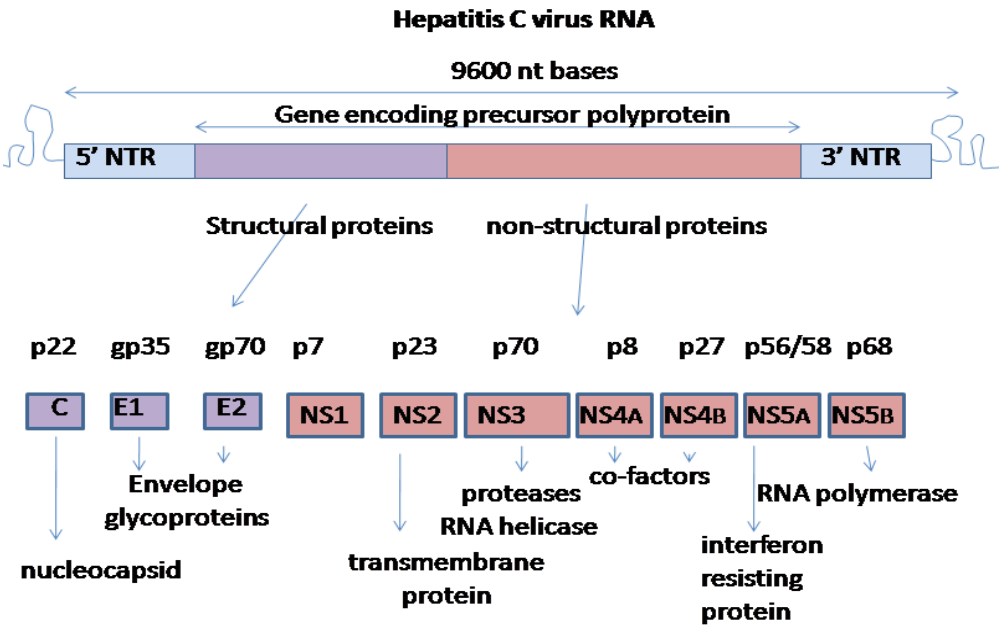
The following reviewers provided valuable input, comments and suggestions on all or part of a draft version of this report: Peter Beyer, Esteban Burrone, Yao Cheng, Ellen ‘t Hoen, Yuanqiong Hu and Leena Menghaney.

III. BACKGROUND

Hepatitis C virus

The hepatitis C virus is a small (55 – 65 nm), enveloped, positive-sense single-stranded RNA virus of the *Flaviviridae* family. The virus consists of three structural proteins (core, E1 and E2), the ion channel protein p7, and six non-structural (NS) proteins (NS2, NS3, NS4A, NS4B, NS5A and NS5B) (see Figure 1). Each of these proteins plays a role in HCV entry, infection, replication or maturation and is therefore a potential target for medicines.

Figure 1. Hepatitis C virus RNA



Source: Graham Colm.

DAAs block viral production by directly inhibiting one or more steps of the HCV replication cycle. DAAs can be divided into categories – notably NS3/NS4A serine protease inhibitors, NS5A complex inhibitors and NS5B RNA polymerase inhibitors (both nucleoside and non-nucleoside).

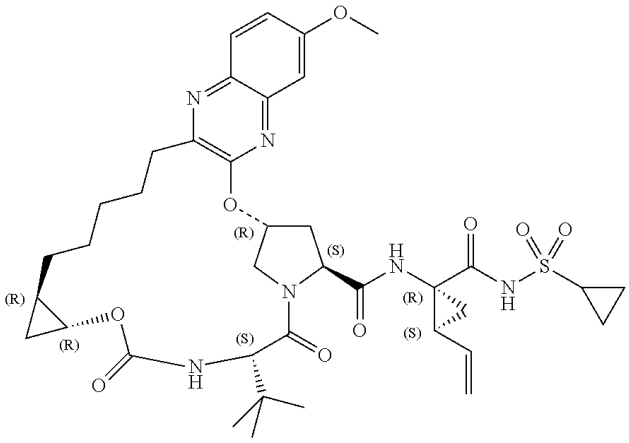
Grazoprevir is an NS3/NS4A protease inhibitor that is currently in phase III clinical trials.

In April 2015, Merck announced that the United States Food and Drug Administration (FDA) had granted breakthrough therapy designations to grazoprevir/elbasvir for treatment of certain patients with chronic HCV infection (genotypes 1 and 4).[4] Breakthrough therapy designation is intended to expedite the development and review of a candidate that is planned for use, alone or in combination, to treat a serious or life-threatening disease or condition when preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints.

Grazoprevir

Grazoprevir (MK-5172) is a novel P2-P4 quinoxaline macrocyclic HCV NS3/4A protease inhibitor. The structure of grazoprevir is shown in Figure 2.

Figure 2. Structure of grazoprevir



Chemical name: (1aR,5S,8S,10R,22aR)-5-tert-butyl-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-14-methoxy-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.

Molecular formula: $C_{38}H_{50}N_6O_9S$

Molecular weight: 766.9034 g/mol

CAS registry numbers:

1350462-55-3 for the hydrate form; and

1350514-68-9 for the anhydrous form.

4 Grazoprevir/Elbasvir, Merck's Investigational Chronic Hepatitis C Therapy, Granted FDA Breakthrough Therapy Designations; New Phase 2 and 3 Data in Multiple HCV Patient Types to be Presented at The International Liver Congress™ 2015. Business Wire, 8 April 2015.

IV. OVERVIEW OF GRAZOPREVIR PATENTS

Nine patents and/or patent applications related to grazoprevir (MK-5172) have been identified as appearing to be the most relevant. These nine patents/applications, and a divisional patent/application, include the patent/application covering the compound per se, as well as processes for preparing it and formulations and combinations that include it.

Patent 1 and patent 2 are the main patents; they cover the compound grazoprevir and would likely block the production, import, marketing and use of generic versions of grazoprevir in countries where one or both patents are in force.

Patents 3 to 9 can also hamper the production, import, marketing and use of generic versions of grazoprevir in countries where they are granted, but they are not as absolute a barrier to generic production, import and use as patents 1 and 2.

Patents 3, 7 and 8 relate to combinations that include grazoprevir. Patent 3 claims the combination grazoprevir/elbasvir. Patent 7 claims combinations of grazoprevir with several other HCV medicines, but not the combination with elbasvir. Patent 8 claims combinations of ombitasvir with other HCV medicines, including the combination of ombitasvir with grazoprevir for use with or without ribavirin.

Patent 4 covers certain crystalline forms of grazoprevir.

Patents 5, 6 and 9 relate to synthetic routes that can be used to produce grazoprevir.

A brief overview of the nine most relevant patents and/or applications can be found in Table 1. More extensive information is provided in section V and Annex 1.

Table 1. Overview of key patents on grazoprevir

	Application/patent number	Applicants	Filing date	Comments
1.	EP2086982A WO2008057209A	Merck (USA) MSD Italia (IT)	23.10.2007	Broad compound patent (Markush formula). Likely to block generic market entry where it is in force.
2.	EP2310095B WO2010011566A	Merck (USA) MSD Italia (IT)	17.07.2009	Basic compound patent; claims the API. Likely to block generic market entry where it is in force.
	EP2540349B EP2540350B	Divisional Divisional		Divisionals to the basic compound patent (patent 2).
3.	EP2621501A WO2012050850A	Merck (USA)	28.09.2011	Combination grazoprevir/ elbasvir and its use.
4.	EP2744507A WO2013028465A	Merck (USA & UK)	16.08.2012	Several different crystal forms of grazoprevir.
5.	EP2744331A WO2013028471A	Merck (USA & UK)	16.08.2012	Intermediates and processes for the production of grazoprevir.
6.	EP2744336A WO2013028470A	Merck (USA & UK)	16.08.2012	Intermediates and processes for the production of grazoprevir.
7.	EP2773342A WO2013066753A	Merck (USA) MSD Italia (IT)	26.10.2012	Combination of grazoprevir and certain other HCV inhibitors (but not grazoprevir/ elbasvir).
8.	EP2797594A WO2013101552A	AbbVie (USA)	18.12.2012	Combination of ombitasvir with certain other HCV inhibitors, including ombitasvir/ grazoprevir.
9.	EP2802595A WO2013106631A	AbbVie (USA)	11.01.2013	Intermediates and processes for the production of grazoprevir.

Patent 1 was published before the main grazoprevir compound patent – patent 2 – was filed. Therefore, patent 1 can be cited for novelty and inventive step against the main compound patent (patent 2). On the basis of evidence submitted by the applicant (in the application for patent 2), showing a benefit of grazoprevir over the compounds of patent 1, compound patent 2 falls within the scope of the earlier published patent 1. In other words, patent 1 would be relevant prior art for patent 2.

Patents 5, 6 and 9 describe synthetic routes that can be used to produce grazoprevir (the API). These routes can be used in countries where the respective patents are not in force or after they expire (which would be *after* the expiry of patents 1 and 2). Patents 1 and 2 also describe synthetic routes that can be used to make grazoprevir. As these synthetic routes are disclosed but not claimed, the chemical processes to synthesize grazoprevir described in patents 1 and 2 could be used to manufacture grazoprevir before patents 1 and 2 expire.

V. ANALYSIS OF GRAZOPREVIR PATENTS/APPLICATIONS

Patent 1

Title: HCV NS3 protease inhibitors.

WO2008057209 (*Merck (US) and MSD Italia (IT), filed 23.10.2007*); **EP2086982A**

Summary

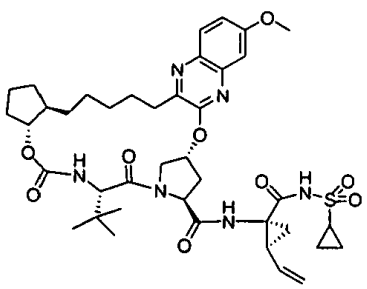
This is a broad compound patent that claims compounds of Markush formula (I), including grazoprevir.

This patent would likely block generic market entry in the countries where it is in force.

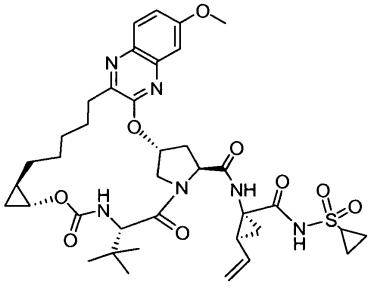
Description

Grazoprevir (MK-5172), Merck's investigational NS3/4A protease inhibitor, has a chemical structure that is very close to the claimed compounds (I) and thus this application is considered as closest prior art.

The compound of example 118 is structurally the closest compound to grazoprevir. The difference between the two compounds is the presence of a cyclopentyl group for compound 118 instead of a cyclopropyl group for grazoprevir (see the chemical structures below).



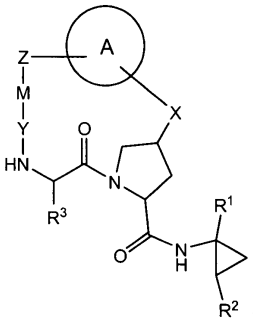
compound 118



.grazoprevir

Synthetic schemes disclosed in the present application and procedures detailed in the illustrative examples can be applied to the preparation of grazoprevir.

The compounds disclosed and claimed in this patent/application are of Markush formula (I) wherein all substituents are defined in the description and claims.



formula (I)

This application relates to macrocyclic compounds (I) and/or to pharmaceutically acceptable salts or hydrates thereof that are useful as inhibitors of the HCV NS3 protease in the prevention or treatment of one or more of the symptoms of HCV infection, either as compounds or as pharmaceutical composition ingredients.

As pharmaceutical composition ingredients, these compounds, their salts and hydrates may be the primary active therapeutic agent and, when appropriate, may be combined with other therapeutic agents, including but not limited to other HCV antivirals, anti-infectives and immunomodulators.

The application also claims pharmaceutical compositions comprising an effective amount of the compound according to any one of claims 1 – 15 and a pharmaceutically acceptable carrier and its use.

The application discloses, but does not claim, processes for the preparation of compounds claimed and their key intermediates. By using appropriate intermediates (A1, B27 and C17), the compound of example 118 was prepared according to the procedures of example 94 in the patent application (see Annex 2).

Observations

Patent 1 was published before patent 2 and is citable for novelty and inventive step against the main compound patent 2 (i.e. patent 1 would be relevant prior art for patent 2).

In countries where compound patent 2 has not been filed or has not been granted, patent 1 will likely constrain the production, import and use of generic versions of grazoprevir (when granted).

Patent 2

Title: Macrocyclic quinoxaline compounds as HCV NS3 protease inhibitors.

WO2010011566 (*Merck & Inst Di Ricerche Di Biologia Molecolare P. Angeletti, filed 17.07.2009*); **EP2310095B**

Summary

This is the basic compound patent covering grazoprevir. The patent claims grazoprevir (the API) as well as pharmaceutical compositions comprising it, its use and its combination with other HCV agents.

This patent would likely block generic market entry in the countries where it is in force.

Description

This patent claims a macrocyclic quinoxaline compound – grazoprevir – and pharmaceutically acceptable salts thereof, as well as its use as an inhibitor of HCV NS3 protease and its use in treating or preventing HCV infections.

The patent also claims compositions comprising an effective amount of grazoprevir and methods of use, its administration and form/route of administration, and its use in combination treatments involving one or more additional therapeutic agents.

Grazoprevir is a selection compound from compounds disclosed and claimed in PCT application WO2008057209 (patent 1). In patent 2, the patentee has put forward advantageous properties of grazoprevir over the compounds of patent 1 (notably the compounds of examples 110 and 118 of patent 1) in order to overcome the inventive step concerns raised in the EPO prosecution and to obtain the grant of the patent.

Grazoprevir was compared to the compounds of examples 110 and 118 of patent 1. The results of this comparison, as provided by the applicant, are given in Table 1 and Table 2 below; they show the advantage of grazoprevir over the compounds of patent 1.

Grazoprevir, when compared to the compound of example 110 of patent 1, showed advantageous properties for its formulation and administration. This is due mainly to the lack of salt disproportionation which enabled enhanced dissolution in water. The patentee states that the lack of this behaviour provides an unexpected advantage in its formulation for pharmaceutical administration and results in improved pharmacokinetic properties (see plasma AUC and liver exposure for rat and dog) as reported in Table 1.

Additionally, compared to example 110 of patent 1, grazoprevir showed:

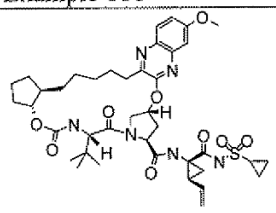
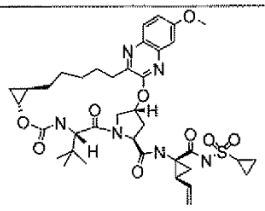
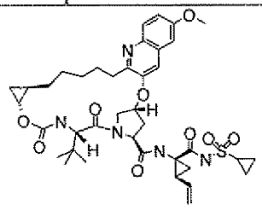
- low in-vivo covalent binding; and
- high plasma and liver exposure.

Grazoprevir showed undetectable binding to plasma proteins following oral administration of a single 20 mg/kg dose to rats. Under the same conditions, the compounds of examples 96, 103, 108 and 118 of patent 1 showed detectable binding to rat liver proteins.

The resistance profile of grazoprevir, when compared with the compound of example 118 of patent 1, showed an improved enzyme affinity (Ki) against different mutant enzymes that are known to confer resistance to HCV NS3 protease inhibitors, as shown in Table 2.

Table 3 below provides additional in-vivo covalent binding data.

Table 1. Comparison of grazoprevir with compounds of WO2008057209 (patent 1)

	WO 2008/057209 Example 118	Example 1	WO 2008/057209 Example 110
Structure			
NS 3/4A Inhibitory Activity[1] (Ki) 1b	< 0.016 nM	< 0.016 nM	< 0.016 nM
Replicon Activity[2] EC_{50} gt1b	3 nM	2 nM	5 nM
Rat Plasma AUC @ 25mpk per os[3]	38.5μM.h	20.6 μM.h	5.8 μM.h
Rat Liver Concentration @ 24h (25 mpk per os)[3]	18.4 μM	27.9 μM	8.5 μM
Dog Plasma AUC @ 5mpk per os[3]	10.9 μM.h	48.6 μM.h	1.0 μM.h
Dog Liver Concentration @ 24h (5mpk per os)[3]	Not Available	120 μM	3.3 μM
Covalent Protein Binding In Vivo[4]	Rat @ 6h plasma = BLQ , liver=30±3pmol/mg protein	Rat @ 6h plasma = LOQ , liver = LOQ	Rat @ 6h plasma = BLQ, liver = BLQ
Physical properties[5]	Potassium salt does not disproportionate in solution.	Potassium salt does not disproportionate in solution.	Potassium salt disproportionates to crystalline neutral form in solution

Ki: Inhibition constant; reference to < 0.016 nM indicates that the observed activity is less than 0.016 nM, the exact amount less than 0.016 nM was not determined by the assay.

EC_{50}: Effective concentration achieving 50% viral replication suppression.

Gt: Genotype.

AUC: Area under the plasma concentration/time curve.

LOQ: Limit of quantitation (3 pmol/mg).

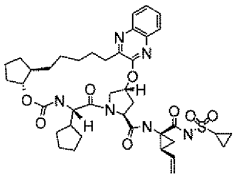
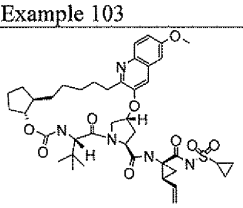
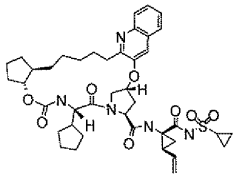
BLQ: Below limit of quantitation.

Table 2. Ki values[1] vs. 1bmutant enzyme (nM)

1b SHIFT	D168T	D168A	D168E	D168G	D168V	D168Y	D168Q
Example 1	0.18	0.43	0.04	0.08	0.14	0.22	0.12
cmp 118	0.78	0.86	0.12	0.45	0.65	1.5	0.42
1b SHIFT	A156S	A156T	A156V	R155K	R155Q	R155G	R155N
Example 1	0.05	5.2	11	0.07	0.43	0.63	0.13
cmp 118	0.10	3.4	15	0.08	1.9	2.3	0.56

[1]Comparative data collected in the same run of the enzyme assays

Table 3.

	WO 2008/057209 Example 108	WO 2008/057209 Example 103	WO 2008/057209 Example 96
Structure			
Covalent Protein Binding In Vivo[4]	Rat @ 6h plasma = 15 pmol eq./mg liver = 38 pmol eq./mg	Rat @ 6h plasma = 6 pmol eq./mg liver = 24 pmol eq./mg	Rat @ 6h plasma = 6 pmol eq./mg liver = 63 pmol eq./mg

Observations

Patent 2 also discloses, without claiming them, processes for making grazoprevir, including processes for making the key intermediates (see Annex 2). These processes may represent opportunities to produce grazoprevir while avoiding the later patented processes (though the latter may be more efficient).

PATENT 2 - DIVISIONALS

At the European Patent Office, two divisional patent applications have been filed (EP2540349 and EP2540350).

PATENT 2b

Title: Pharmaceutical compositions comprising a macrocyclic quinoxaline compound which is an HCV NS3 protease inhibitor.

EP2540349B (divisional to EP-B-2310095 (patent 2)).

Description

This patent, divisional to EP'095 (patent 2), claims a pharmaceutical composition that comprises grazoprevir or a pharmaceutically acceptable salt thereof (more specifically the potassium salt) and a pharmaceutically acceptable carrier. The said composition is in solid form and is suitable for oral administration (e.g. capsule or tablet).

Observations

It is likely that the '349 patent (patent 2b) would constrain generic market entry in the countries where it is in force.

PATENT 2c

Title: Combinations of a macrocyclic quinoxaline compound which is an HCV NS3 protease inhibitor with other HCV agents.

EP2540350B (divisional to EP-B-2310095 (patent 2)).

Description

This patent is another divisional patent to EP'095 (patent 2). This divisional claims the combination of grazoprevir or a pharmaceutically acceptable salt thereof (more specifically the potassium salt) and one or more additional therapeutic agents.

This patent claims, in a dependent claim, the specific combination: grazoprevir + pegylated interferon-α + ribavirin.

Observations

Where granted, the '350 patent (patent 2c) would likely constrain generic market entry of formulations containing grazoprevir plus certain other active ingredients.

PATENT 3

Title: Polycyclic heterocycle derivatives and methods of use thereof for the treatment of viral diseases.

WO2012050850 (*Merck Sharp & Dohme, filed 28.09.2011*); **EP2621501A**

Summary

This application claims the combination grazoprevir/elbasvir. The combination may further comprise a third therapeutic agent selected from an HCV protease inhibitor, an interferon and an HCV polymerase inhibitor.

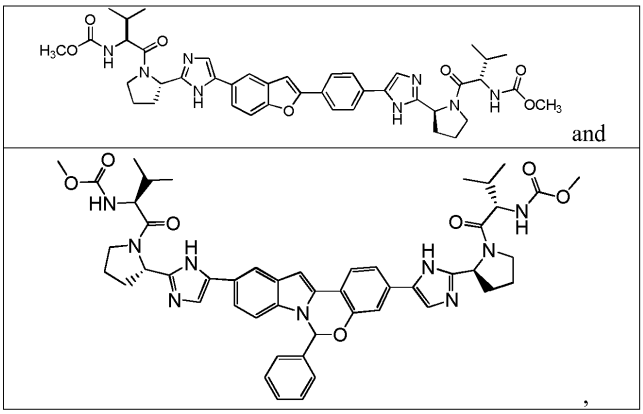
Description

The PCT application claims compositions comprising a polycyclic heterocycle compound selected from 14 compounds in Table 1 of the patent application (elbasvir is compound 8) or a pharmaceutically acceptable salt thereof, together with an additional therapeutic agent that is selected from compounds F1 – F28 (grazoprevir is compound F5) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, with the said composition being effective in treating HCV infection. The application also claims the pharmaceutical composition described above in combination with a second additional therapeutic agent (pegylated interferon, ribavirin). Finally, the use of the compositions for inhibiting HCV NS5A activity or for preventing and/or treating infection by HCV is claimed.

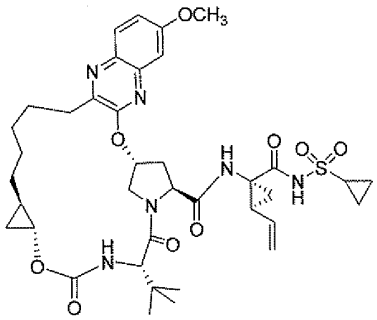
In the European phase, the claims were found to be novel but not inventive, in view of WO2010011566A (patent 2) or US20080299075A. Additionally, in view of the number of alternative compound combinations falling within the scope of the claims as originally filed, the European examiner expressed doubts that all of them possess the type and level of activity claimed; experimental evidence was provided only for the specific combination of compound 2 of Table 1 + F5/F7. The other combinations have been tested neither for their activity nor for synergism.

To overcome the objections of the European examiner, the applicants have submitted amendments (08.10.2014), limiting the scope of the claims. The revised European application provides a composition for the treatment of HCV which comprises one of the compounds of Table 1 + F5/F7.

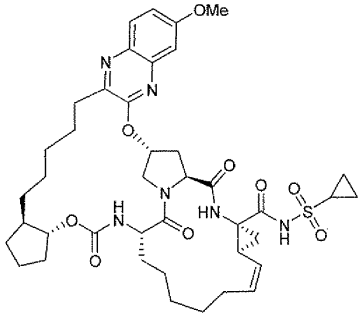
The compounds of Table 1 (after amendment):



First additional therapeutic agents (after amendment):



F5



F7

Observations

This application is under examination in several countries (see Annex 1). As a result of the European examiner's observations, the applicants have restricted the scope of the claims of the European application and have provided experimental evidence for the specific combination of compound 2 of Table 1 (elbasvir) with F5 (grazoprevir) or F7. The other combinations have been tested neither for their activity nor for their synergism in any data submitted by the patentee so far.

PATENT 4

Title: Crystal forms of a HCV protease inhibitor.

WO2013028465 (*Merck Sharp & Dohme, filed 16.08.2012*); **EP2744507A**

Summary

This application claims certain crystalline forms of grazoprevir. It also claims a crystalline sodium salt and a crystalline potassium salt of grazoprevir.

Description

This application discloses and claims six different crystalline hydrate forms of grazoprevir. They are characterized by given 2Θ values of the X-ray powder diffraction pattern obtained using copper Kα radiation or by given peaks (ppm) of the solid-state carbon-13 CPMAS NMR. The application identifies hydrate III as being the most stable hydrate form.

The application also discloses and claims a crystalline sodium salt of grazoprevir and a crystalline potassium salt characterized by given X-ray powder diffraction patterns obtained using copper Kα radiation.

Another embodiment of the invention is directed to a method of making hydrate III from crude grazoprevir (hydrate-II) using acetone/water and drying.

Finally, the application also claims a pharmaceutical composition comprising an effective amount of the claimed form of grazoprevir with or without a second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators and anti-infective agents.

Observations

The application is under examination by the European Patent Office:

- The claimed sodium salt and hydrate forms are not disclosed in prior art.
- The claimed potassium salt is disclosed in the basic API patent WO2010011566 (patent 2).
- According to the European examiner, the applicant has to show that the claimed crystalline sodium salt and hydrates have an unexpected effect (such as stability, bio-availability etc.) over WO'566 (patent 2) in order to be considered inventive.

Provided that generic manufacturers use a different form of grazoprevir, this patent will not constrain generic market entry.

PATENT 5

Title: Methods and intermediates for preparing macrolactams.

WO2013/028471 (*Merck Sharp & Dohme, filed 16.08.2012*); **EP2744331A**

Summary

This application claims intermediates and processes for the preparation of grazoprevir.

Description

This application discloses and claims intermediates and processes for the preparation of macrolactam compounds that are able to inhibit HCV NS3 protease activity. An example described in the application is grazoprevir (compound A). The application also discloses and claims processes for the preparation of these intermediates (see Annex 2).

Observations

The application is under examination by the European Patent Office and the United States Patent and Trademark Office.

According to the European patent examiner, all compounds and processes claimed are novel. However, while claims 1, 8 and 9 do involve an inventive step, claims 2 – 7 lack an inventive step vis-à-vis WO2010011566 (patent 2) and in view of WO2008057209 (patent 1).

Provided that API suppliers manufacture grazoprevir by different processes and using different intermediates, this patent would not constrain generic market entry.

PATENT 6

Title: Process and intermediates for preparing macrolactams.

WO2013028470 (*Merck Sharp & Dohme, filed 16.08.2012*); **EP2744336A**

Summary

This application claims intermediates and processes for the preparation of grazoprevir.

Description

This application discloses and claims compounds that are useful as intermediates in the preparation of macrolactams – in particular macrolactam compounds inhibiting HCV NS3 protease activity and, more particularly, grazoprevir. The application also discloses and claims processes for the preparation of these intermediates, as well as processes for the preparation of the macrolactams (see Annex 2).

Observations

The application is under examination; according to the European patent examiner:

- Claims 1, 4 and 5 lack novelty as being anticipated by WO2010011566 (patent 2).
- Claims 1 – 6 and 13 lack an inventive step as being obvious over WO2010011566 (patent 2) in combination with other prior art, as detailed in the European search report.
- Claims 7 – 10 are both novel and inventive.

Provided that API suppliers manufacture grazoprevir by different processes and using different intermediates, this patent would not constrain generic market entry.

PATENT 7

Title: Compositions useful for the treatment of viral diseases.

WO2013066753 (*Merck Sharp & Dohme and Instituto di Ricerche di Biologia Molecolare P. Angeletti, filed 26.10.2012*); **EP277342A**

Summary

This application concerns the combination of grazoprevir with another HCV inhibitor other than elbasvir and other compounds listed in the disclaimer.

Description

This application claims compositions comprising inhibitors of HCV protease and one or more additional therapeutically effective agents – effective combinations for the treatment of HCV infection and inhibition of HCV viral replication.

The claimed pharmaceutical composition comprises: (i) a pharmaceutically acceptable carrier; (ii) a compound selected from Table 1 (*grazoprevir is compound 5*), or a pharmaceutically acceptable salt thereof; and (iii) one or more primary additional therapeutic agents, or a pharmaceutically acceptable salt thereof selected from HCV protease inhibitors, HCV polymerase inhibitors, HCV NS4A inhibitors and HCV NS5A inhibitors. The claim has a disclaimer – a list of compounds which cannot be primary additional therapeutic agents; elbasvir, compound 8, is one of them. Thus, this application does not pertain to the combination of grazoprevir with elbasvir.

PATENT 8

Title: Methods for treating HCV.

WO2013101552 (*AbbVie, filed 18.12.2012*); **EP2797594A**

Summary

This application claims combinations of ombitasvir with another anti-HCV agent, including the combination of ombitasvir with grazoprevir. Each treatment regimen claimed is interferon-free, with or without administering ribavirin.

Description

This application claims combinations of Compound I (ombitasvir), an HCV NS5A inhibitor marketed by AbbVie and described, for example, in US 2010/0317568 with another anti-HCV agent.

The application contains a table that lists 80 non-limiting examples of treatment regimens claimed in the patent application. In each treatment regimen, Compound I (ombitasvir) or a pharmaceutically acceptable salt thereof, and the other anti-HCV agent, are administered daily to an HCV patient. Example 49 refers to the combination of ombitasvir with grazoprevir.

Each claimed treatment regimen claimed is interferon-free, with or without ribavirin.

Observations

This application is under examination by the European Patent Office.

This patent application attempts to claim any therapy that uses ombitasvir in combination with other anti-HCV medicines (including grazoprevir) as defined in the patent filing but wherein interferon is not used.

PATENT 9

Title: Processes for making HCV protease inhibitors.

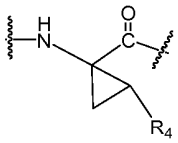
WO2013106631 (*AbbVie, filed 11.01.2013*); **EP2802595A**

Summary

This application claims intermediates and processes for the preparation of HCV protease inhibitors, including grazoprevir.

Description

This application discloses and claims processes for making HCV protease inhibitors, most of them containing the moiety shown below. These processes permit the incorporation of this moiety, or an equivalent one, into precursors of HCV protease inhibitors.



Observations

The application is under examination in several countries (see Annex 1). The European search report is not yet available and no amendments have been filed as yet. To date, only the written opinion of the International Searching Authority (ISA) has been published, considering the subject matter of claims 1 – 15 to be novel over the prior art and involving an inventive step.

Provided that the API suppliers manufacture grazoprevir using intermediates that are different from the claimed ones, this patent would not constrain generic market entry.

ANNEX 1. Grazoprevir patent situation in countries

The INPADOC patent family members for each of the nine patents/applications are listed in the tables below.

Anticipated expiry dates of patents 1 and 2 have been provided. Differences between countries are due to differences in patent term or because the patent application was filed – on a different date – directly at the concerned office (instead of through the PCT route). The indicated expiry dates therefore must be checked in countries that offer patent term extension/restoration (such as European Union countries, Japan and the USA). If grazoprevir is approved for use, it is likely that the innovator will apply for patent term extension/restoration.

	Patent 1	**Patent 2**	**Patent 3**	**Patent 4**
	WO2008057209A1 **PCT/US2007/022460**	**WO2010011566A1** **PCT/US2009/050915**	**WO2012050850A** **PCT/US2011/053562**	**WO2013028465A** **PCT/US2012/051168**
Applicants	**Merck & Co (USA)** **MSD Italia (IT)**	**Merck & Co (USA)** **MSD Italia (IT)**	**Merck Sharp & Dohme (USA)**	**Merck Sharp & Dohme (USA & UK)**
Filing date	**23.10.2007**	**17.07.2009**	**28.09.2011**	**16.08.2012**
Title	**HCV NS3 protease inhibitors.**	**Macrocyclic quinoxaline compounds as HCV NS3 protease inhibitors.**	**Polycyclic heterocycle derivatives and methods of use thereof for the treatment of viral diseases.**	**Crystal forms of a HCV protease inhibitor.**
Subject matter	**Broad compound patent – likely constraining for generic medicines where granted.**	**Basic compound patent – likely constraining for generic medicines where granted.**	**Grazoprevir/elbasvir combination with or without a third therapeutic agent.**	**Six different crystalline hydrate forms of grazoprevir.** **Process for making hydrate-III from hydrate-II.**
Priority data	**US 60/854,912 – 27.10.2006** **US 60/997,434 – 03.10.2007**	**US 61/135,559 – 22.07.2008**	**US 61/387,825 – 29.09.2010**	**US 61/525,462 – 19.08.2011** **US 61/533,439 – 12.09.2011** **US 61/533,915 – 13.09.2011** **US 61/539,540 – 27.09.2011**
African Regional Intellectual Property Organization*				
Argentina		Appl. N°: 2009P102779 Publ. N°: 072588A1 Status not available.		
Australia	2007318165B Granted Expiry: 23.10.2027	2009274190B2 Granted Expiry: 17.07.2029	2011314170A1 Under examination	2012299218A1 Under examination
Brazil	PI0718161A Under examination			
Canada	2667031C Granted Expiry: 23.10.2027	2731177C Granted Expiry: 17.07.2029	2811752A1 Under examination	2844386A Under examination
China	Appl. N°: 200780048666 Publ. N°: 101611039A Under examination	Appl. N°: 200980137118 Publ. N°: 102159285B Granted Expiry: 17.07.2029		Appl. N°: 201280050382 Publ. N°: 103889439A Under examination
China, Hong Kong SAR		Appl. N°: 20130100580 Publ. N°: 1173402A		
		Appl. N°: 20130100581 Publ. N°: 1173403A Status not available.		

	Patent 1	Patent 2	Patent 3	Patent 4
Colombia	Appl. N°: 20090042384 Publ. N°: 6180506A Granted Expiry: 27.04.2029	Appl. N°: 20110005448 Publ. N°: 6351757A2 Granted Expiry: 19.01.2031		
Costa Rica	10776A Status not available	2011-0089A Status not available.		
Croatia		P2012-0866B P2014-0693B EP designated.		
Dominican Republic		P2011-0023A Status not available.		
Ecuador	Appl. N°: 2009SP09288 Publ. N°: 099288A Status not available	SP11010777A Status not available.		
Egypt	2009040576A Status not available	2011010126A Status not available.		
El Salvador	2009003239A Status not available	2011003813A Status not available		
Eurasian Patent Office*		Appl. N°: 20110070241 Publ. N°: 019327B1 Status not available.		
European Patent Office*	Appl. N°: 07839746 Publ. N°: 2086982A Under examination	2310095B 2540349B 2540350B Granted Expiry: 17.07.2029	Appl. N°: 11833019 Publ. N°: 2621501A Under examination	Appl. N°: 12825540 Publ. N°: 2744507A Under examination
Guatemala	200900097A Status not available			
Honduras	2009000792A Status not available	2011000209A Status not available.		
India	3304/DELNP/2009 Under examination	328/DELNP/2011 Under examination	2234/CHENP/2013 Deemed withdrawn	
Israel	198401A Granted Expiry: 23.10.2027	210580A Granted Expiry: 11.01.2031		
Japan	Appl. N°: 2009534619 Publ. N°: 2010507661A Patent N°: 5268927B Granted Expiry: 23.10.2027	Appl. N°: 20110520110 Publ. N°: 2011528713A Patent N°: 4920797B2 Granted Expiry: 17.07.2029	Appl. N°: 2013531744 Publ. N°: 2013544232A Withdrawn	Appl. N°: 2014526215 Publ. N°: 2014524442A Under examination
Malaysia		Appl. N°: 2011PI00310 Publ. N°: 152070A		
Mexico	2009004556A Under examination	2011000826A Under examination	2013003634A Under examination	2014001944A Under examination
Morocco	Appl. N°: 31877 Publ. N°: 30893B Status not available	Appl. N°: 33556 Publ. N°: 32502B1 Status not available		
New Zealand	Appl. N°: 20070576345 Patent N°: 576345A Granted Expiry: 23.10.2027	Appl. N°: 20090590638 Patent N°: 590638A Granted Expiry: 17.07.2029		

	Patent 1	Patent 2	Patent 3	Patent 4
Norway	20092053L Under examination			
Pakistan+		671/2009 Under examination 412/2012 Granted (filed 26.06.2012)		
Peru		Appl. N°: 20110006720 Publ. N°: 02122011A Granted Expiry: 17.07.2029		
Philippines	12009500765B Granted Expiry: 21.04.2029	12011500151A		
Republic of Korea	Appl. N°: 1020097010912 Publ. N°: 1020090075874A Refused	Appl. N°: 1020117003982 Publ. N°: 1020110036627A Publ. N°: 10201313675B Granted Expiry: 17.07.2029	Appl. N°: 1020137010752 Publ. N°: 1020130120469A Unexamined	Appl. N°: 1020147006888 Publ. N°: 1020140059236A Unexamined
Russia	Publ. N°: 2009120056A Patent N°: 2468029C Granted Expiry: 23.10.2027			
Serbia		Appl. N°: P-2012/0463 Publ. N°: 52534B Equivalent to EP2310095		
		Appl. N°: P-2014/0375 Publ. N°: 53420B Equivalent to EP2540350 EP designated		
South Africa	200902475A Lapsed			
Thailand+		124148A (0901003251A) Under examination		
Ukraine	Appl. N°: 20090005267 Publ. N°: 95990C2 Granted? Status not available	Appl. N°: a201102068 Patent N°: 100436C Granted Expiry: 17.07.2029		
USA	Appl. N°: 12/447,342 Publ. N°: 20100099695A Under examination	Appl. N°: 12/504,955 Publ. N°: 20100029666A Patent N°: 7973040B2	Appl. N°: 13/876,908 Publ. N°: 20130280214A Under examination	Appl. N°: 14/239,389 Publ. N°: 20140206605A Under examination
		Appl. N°: 13/112,281 Publ. N°: 2011/0224134A Patent N°: 8080654B2 Expiry: 17.07.2029		
Viet Nam+	1-2009-01058 Under examination	1-2011-00289 Under examination		

	Patent 5	Patent 6	Patent 7	Patent 8	Patent 9
	WO2013028471A1 PCT/US2012/051182	WO2013028470A1 PCT/US2012/051177	WO2013066753A1 PCT/US2012/062145	WO2013101552A1 PCT/US2012/070356	WO2013106631A1 PCT/US2013/021118
Applicants	Merck Sharp & Dohme (USA & UK)	Merck Sharp & Dohme (USA)	Merck Sharp & Dohme (USA) MSD Italia (IT)	AbbVie Inc. (USA)	AbbVie Inc. (USA)
Filing date	16.08.2012	16.08.2012	26.10.2012	18.12.2012	11.01.2013
Title	Methods and intermediates for preparing macrolactams.	Process and intermediates for preparing macrolactams.	Compositions useful for the treatment of viral diseases.	Methods for treating HCV.	Processes for making HCV protease inhibitors.
Subject matter	Intermediates and processes for their preparation	Intermediates, processes for their preparation and processes for preparation of macrolactams (grazoprevir)	Compositions comprising grazoprevir with another HCV inhibitor other than elbasvir	Treatment regimen comprising AbbVie HCV NS5A inhibitor + another anti-HCV agent (e.g grazoprevir) with or without ribavirin but interferon-free	Processes for making HCV protease inhibitors precursors
Priority data	US 61/525,462 – 19.08.2011 US 61/533,439 – 12.09.2011 US 61/533,915 – 13.09.2011 US 61/539,540 – 27.09.2011	US 61/525,462 – 19.08.2011 US 61/533,439 – 12.09.2011 US 61/533,915 – 13.09.2011 US 61/539,540 – 27.09.2011	US 61/553,677 – 31.10.2011	US 61/580,871 – 28.12.2011	US 61/585,280 – 11.01.2012
African Regional Intellectual Property Organization*					
Argentina					
Australia		2012299223A1 Under examination	2012332832A8 Under examination		
Brazil					
Canada		2844388A1 Under examination	2854129A1 Under examination		2863002A Under examination
China		Appl. N°: 201280050361 Publ. N°: 103874414A Under examination	Appl. N°: 201280053013 Publ. N°: 104220067A Under examination		Appl. N°: 201380005393 Publ. N°: 104136453A Under examination
China, Hong Kong SAR					
Colombia					
Costa Rica					
Dominican Republic					
Ecuador					
Egypt					
El Salvador					

	Patent 5	Patent 6	Patent 7	Patent 8	Patent 9
Eurasian Patent Office*					
European Patent Office*	Appl. N°: 12825726 Publ. N°: 2744331A Under examination	Appl. N°: 12826404 Publ. N°: 2744336A Under examination	Appl. N°: 12846336 Publ. N°: 2773342A Under examination	Appl. N°: 12806852 Publ. N°: 2797594A Under examination	Appl. N°: 13700966 Publ. N°: 2802595A Under examination
Guatemala					
Honduras					
Croatia					
India					
Israel					
Japan		Appl. N°: 2014526217 Publ. N°: 2014521750A Unexamined	Appl. N°: 2014539050 Publ. N°: 2015513520A Unexamined		Appl. N°: 2014552315 Publ. N°: 2015508413A Unexamined
Malaysia					
Mexico		2014001945A Status not available	2014005210A Under examination		2014008516A Under examination
Morocco					
New Zealand					
Norway					
Pakistan+					
Peru					
Philippines					
Republic of Korea		Appl. N°: 1020147006858 Publ. N°: 1020140053330A Unexamined	Appl. N°: 1020147014362 Publ. N°: 1020140098759A Under examination		
Russia			Appl. N°: 2014122154		
Serbia					
South Africa					
Thailand					
Ukraine					
USA	Appl. N°: 14/239,391 Publ. N°: 20140243519A Under examination	Appl. N°: 14/239,393 Publ. N°: 20140200343A Under examination	Appl. N°: 14/355,363 Publ. N°: 20140328799A Under examination	Appl. N°: 13/718,167 Publ. N°: 20130172240A Abandoned	Appl. N°: 13/739,174 Publ. N°: 20130178630A1 Under examination
Viet Nam					

Notes:
Cells in grey colour indicate that no patent or patent application has been found in the INPADOC database or – in the cases of Pakistan, Thailand and Viet Nam – during the check at the National Patent Office. This may mean that no patent application was filed, that the application has not been found (e.g. in the case of clerical error), or the application had not been published at the time of the search. Information in this Annex should therefore always been checked at the relevant patent office.

***African Regional Intellectual Property Organization (ARIPO):** Botswana, Gambia, Ghana, Kenya, Lesotho, Liberia, Malawi, Mozambique, Namibia, Rwanda, São Tomé and Príncipe, Sierra Leone, Somalia, Sudan, Swaziland, Uganda, United Republic of Tanzania, Zambia, Zimbabwe.

*** European Patent Office (EPO):** ***designated contracting states*****:** Austria, Belgium, Bulgaria, Switzerland, Cyprus, Czech Republic, Germany, Denmark, Estonia, Spain, Finland, France, United Kingdom, Greece, Hungary, Ireland, Iceland, Italy, Liechtenstein, Lithuania, Luxembourg, Latvia, Monaco, Malta, Netherlands, Poland, Portugal, Romania, Sweden, Slovenia, Slovakia, San Marino, Turkey; ***Extension states*****:** Albania, Bosnia & Herzegovina, Croatia, Montenegro, Macedonia (former Yugoslav Republic of Macedonia), Serbia.

*** Eurasian Patent Organization (EA):** Armenia, Azerbaijan, Belarus, Kazakhstan, Kyrgyz Republic, Moldova, Russian Federation, Tajikistan and Turkmenistan.

[+] Confirmed in checks at the local patent office.

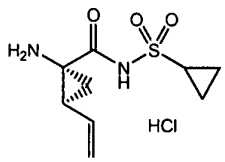
ANNEX 2. Process chemistry extracted from grazoprevir patents/applications

PATENT 1

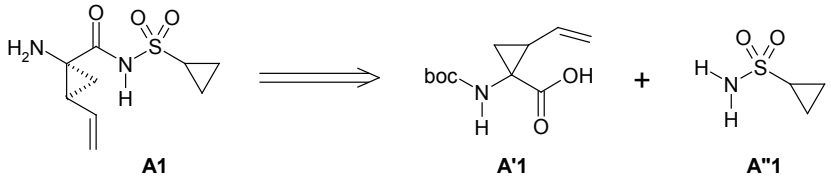
This patent/application discloses but does not claim processes for the preparation of the claimed compounds and their key intermediates.

By using the appropriate intermediates (numbered A1, B27 and C17 in the patent application), the compound of example 118 (which has a structure that is very similar to grazoprevir) was prepared according to the procedures of example 94 in the application.

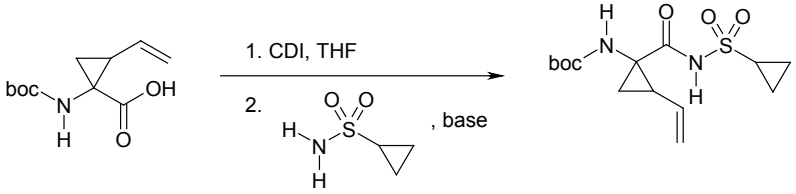
❖ Intermediate A1

A1		(1*R*,2*S*)-1-Amino-*N*-(cyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide hydrochloride	US 6,995,174

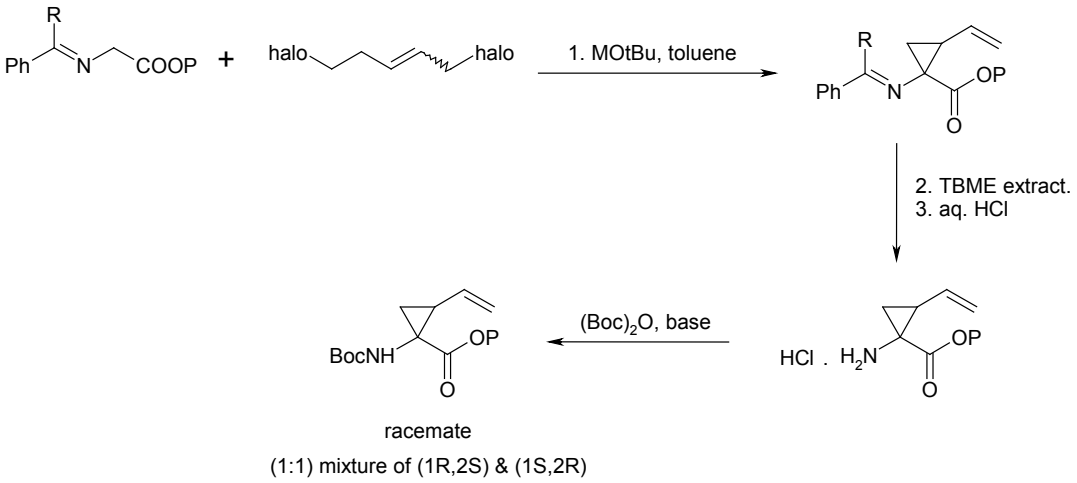
The process for the preparation of intermediate A1 is depicted below:



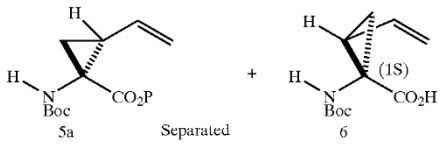
Intermediate A1 is prepared by coupling compound A'1 with compound A"1 according to the following scheme:



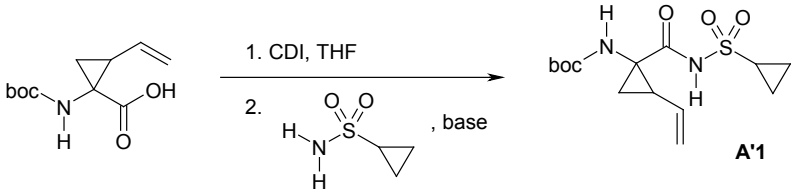
Intermediate A'1 can be prepared according to the process depicted below:



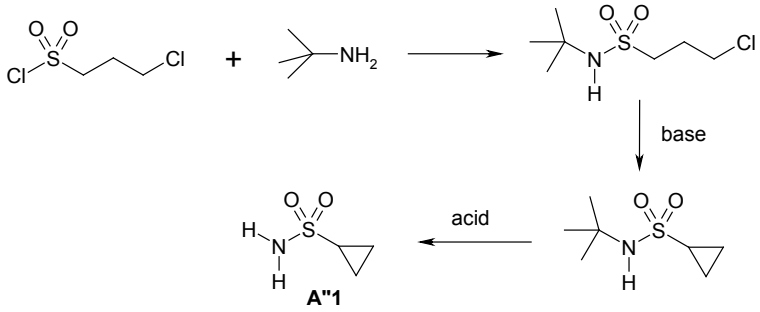
The racemate obtained is resolved by a stereoselective enzymatic process. In the presence of an enzyme, the undesired (1S,2R) enantiomer undergoes ester cleavage leading to the corresponding carboxylic acid while the desired (1R,2S) enantiomer does not undergo ester cleavage. Upon completion, the ester 5a is separated from the acid 6 by known methods.



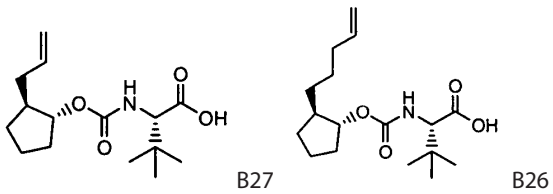
The Boc protected ester is hydrolyzed into the corresponding acid, and the product obtained is then coupled with cyclopropyl sulfonamide according to the scheme below:



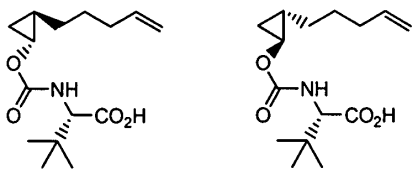
The cyclopropyl sulfonamide A"1 used can be prepared according to the process depicted below:



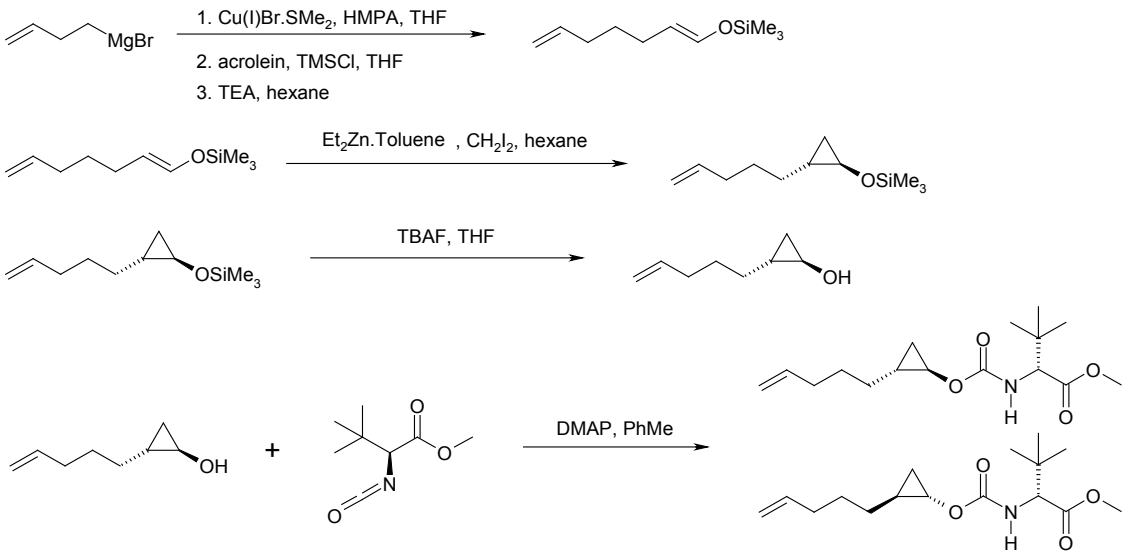
❖ Intermediate B27



A process for the preparation of intermediate B27 is disclosed; however, intermediate B25 (B25a and B25b) would be the intermediates of use for the preparation of grazoprevir.

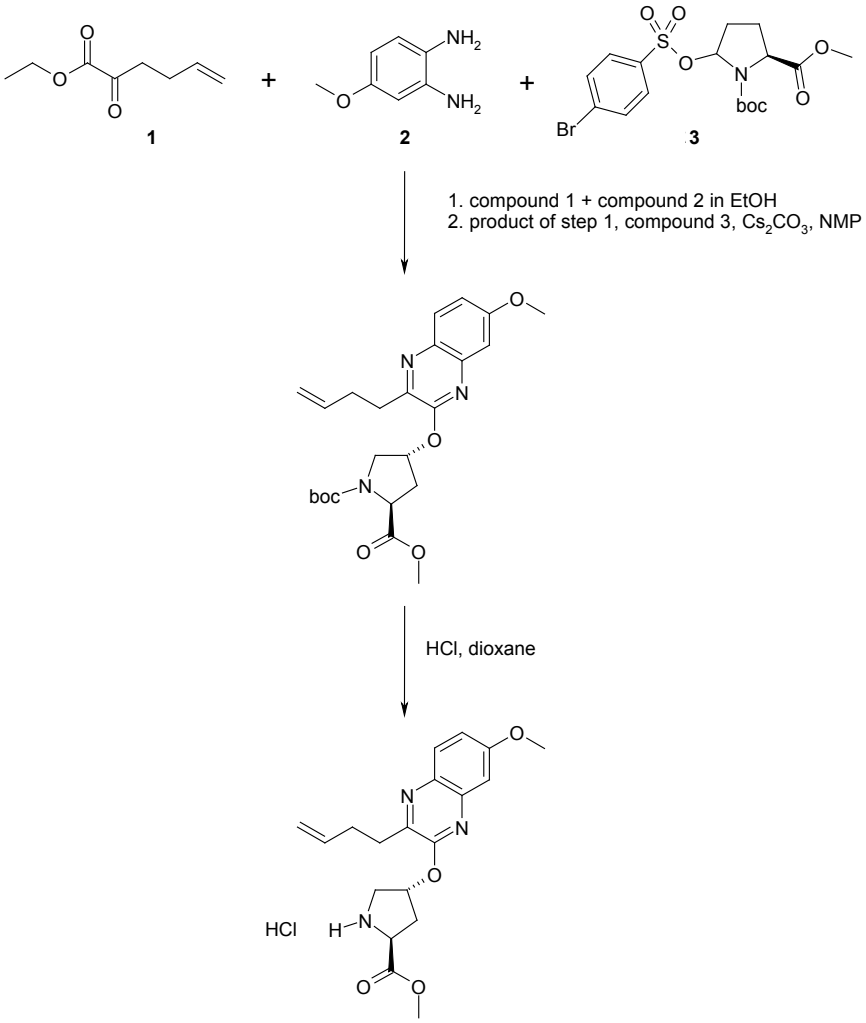


Similarly to the process for the preparation of intermediate B27 described in the above-mentioned patent application, intermediates B25a & B25b useful for the preparation of grazoprevir can be prepared according to the following scheme:

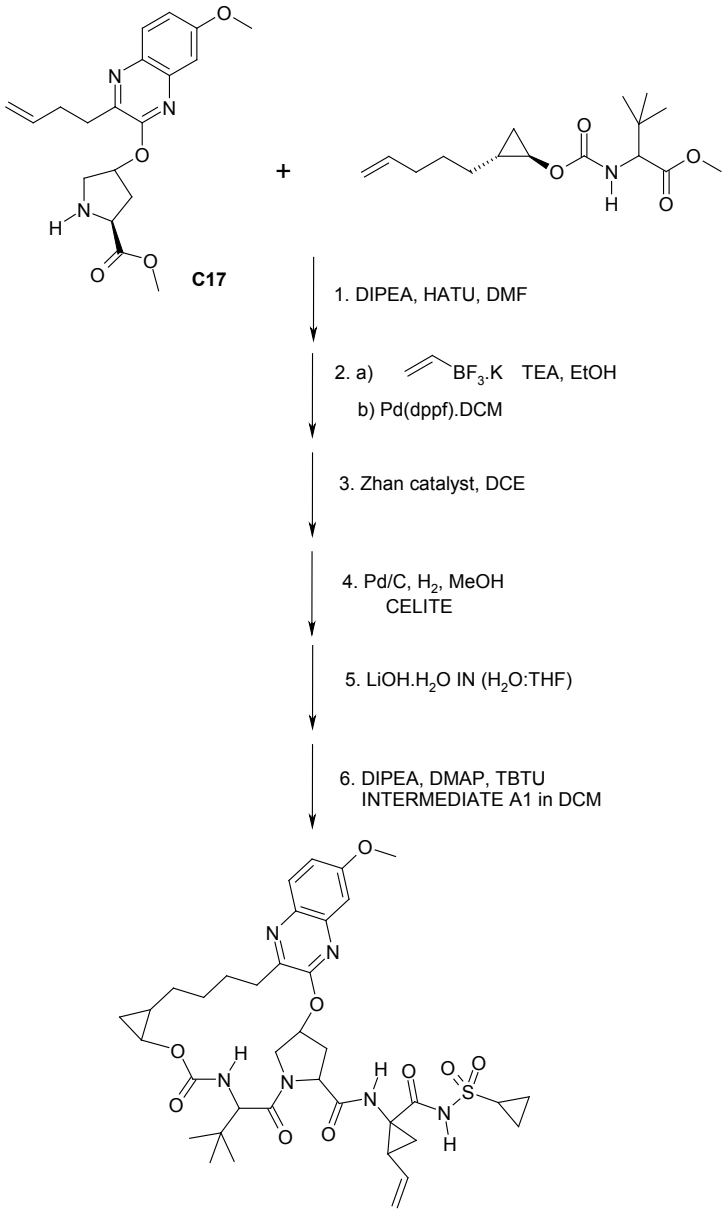


❖ Intermediate C17

Intermediate C17 can be prepared according to the process depicted below:



Finally, grazoprevir could be prepared following the process depicted in the scheme below:



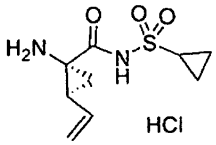
PATENT 2

The patent discloses, without claiming them, processes for making grazoprevir, including processes for making the key intermediates. These processes are summarized below.

The processes may represent opportunities to make grazoprevir while avoiding the later patented processes (though the latter may be more efficient).

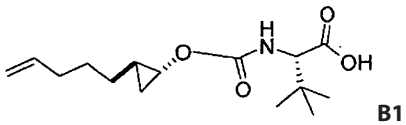
Synthesis of intermediates

❖ Intermediates A

Intermediate #	Structure	Name	Lit. Reference
A1		(1*R*,2*S*)-1-Amino-*N*-(cyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide hydrochloride	Wang et al, US 6,995,174

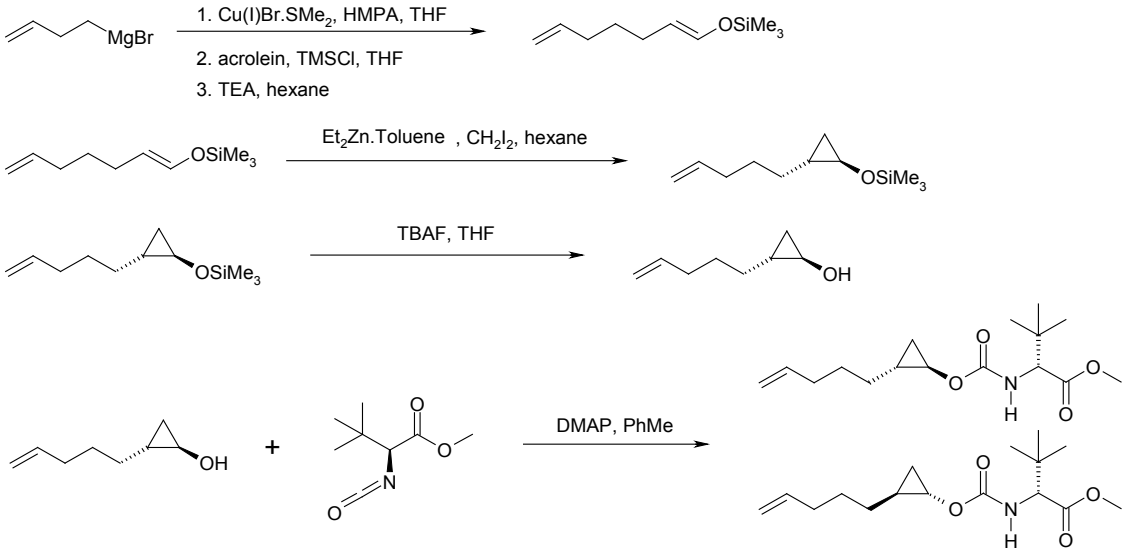
The process for the preparation of intermediate A1 has been detailed earlier in the section on intermediates for compounds (I) of WO2008057209 (patent 1). Please refer to that section.

❖ Intermediate B1: 3-methyl-N-({[(1R,2R)-2-pent-4-en-1-yl cyclopropyl]oxy}carbonyl)-L-valine



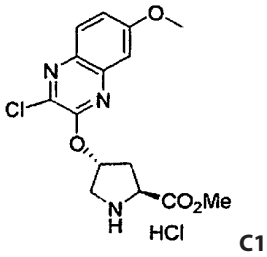
B1

The process for the preparation of intermediate B1 is depicted below.



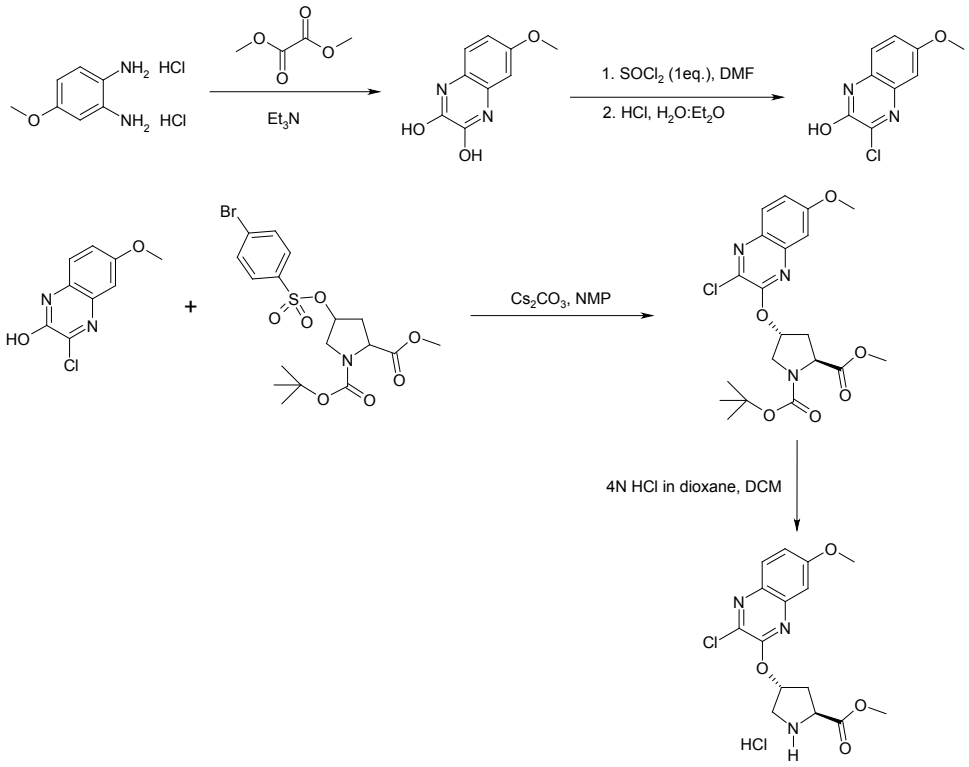
The (1R,2R) enantiomer was separated from the (1S,2S) enantiomer by flash chromatography.

❖ **Intermediates C1: methyl (4R)-[(3-chloro-7-methoxyquinoxalin-2-yl)oxy]-L-prolinate HCl.**

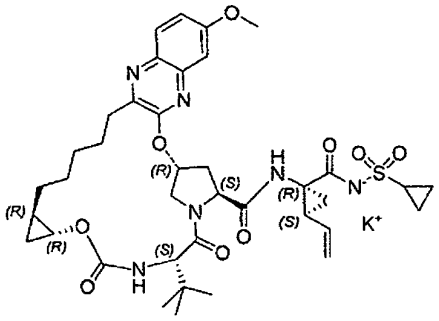


C1

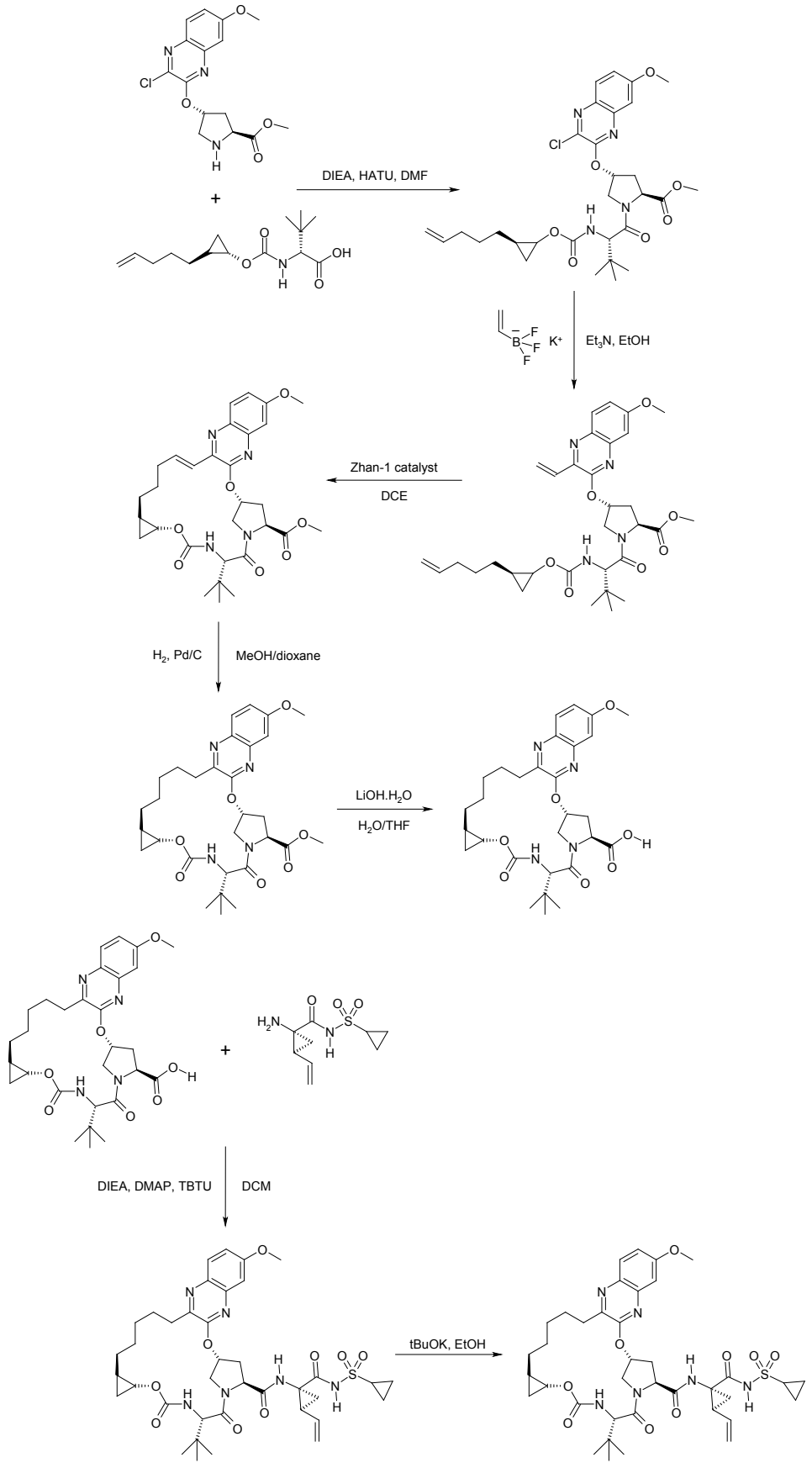
The process for the preparation of intermediate C1 is depicted in the scheme below.



Example 1: Potassium {[(1R,2S)-1-({ [(1aR,5S,8S.10R,22aR)-5-tert-butyl-14-methoxy-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6] dioxadiazacyclononadecino[11,12-b]quinoxalin-8-yl]carbonyl}amino)-2-vinylcyclopropyl]carbonyl} (cyclopropylsulfonvl)azanide



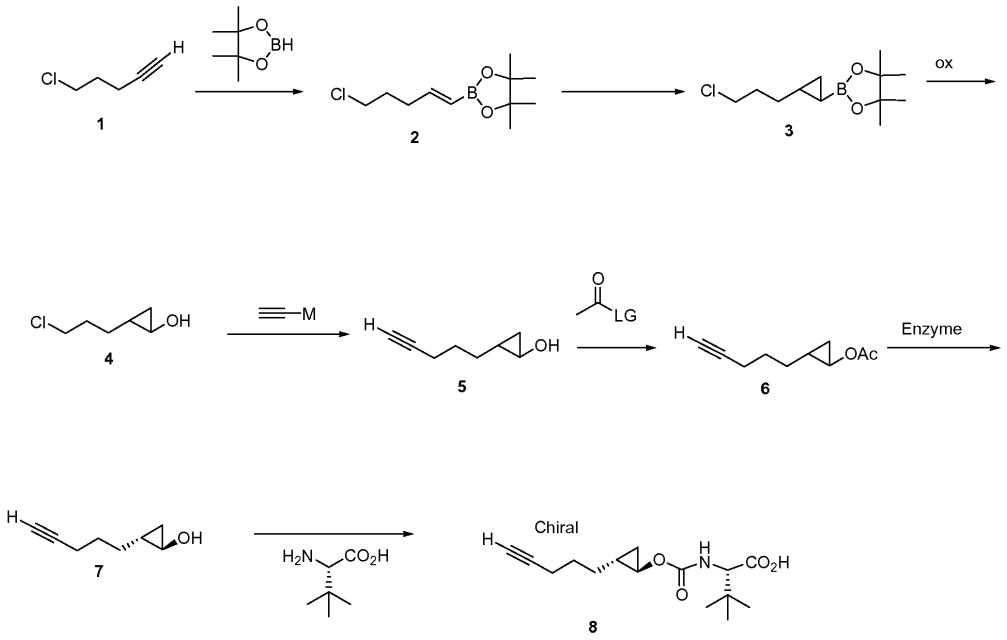
The process for the preparation of grazoprevir potassium salt is given in the scheme below.



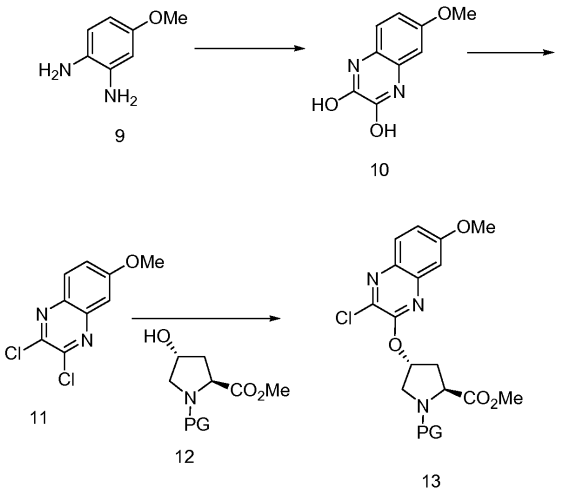
PATENT 5

Overall processes for producing grazoprevir and several key intermediates are depicted below.

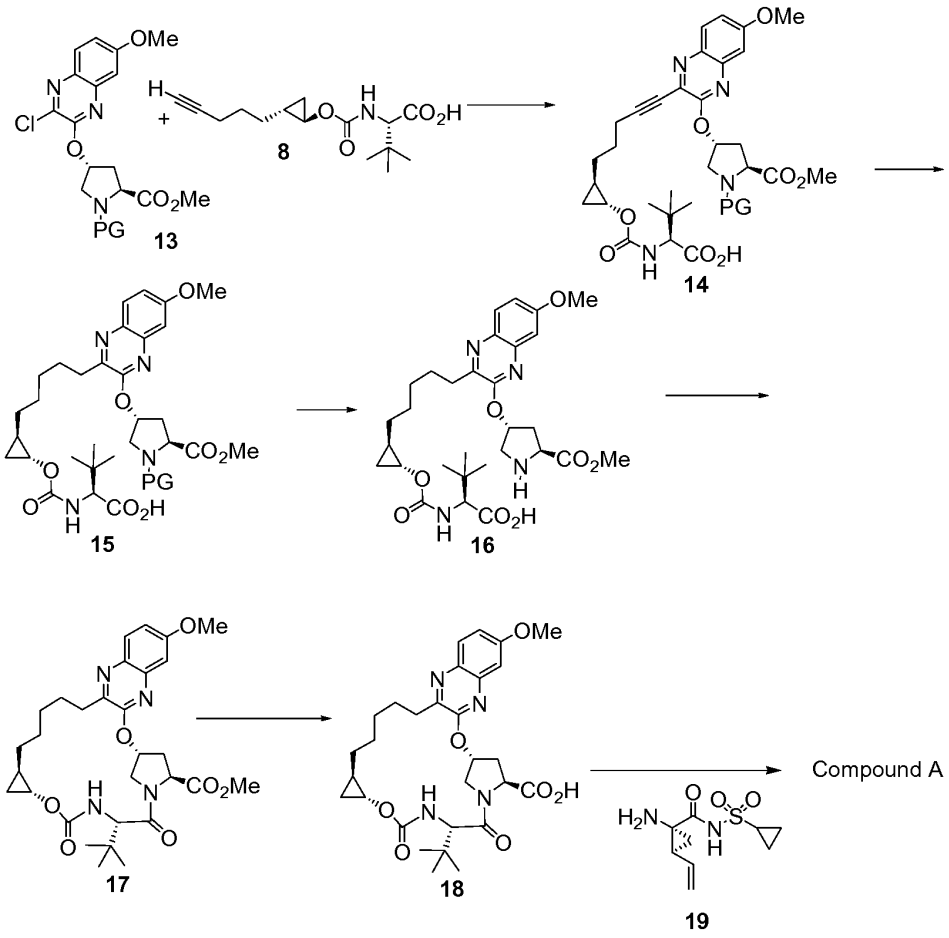
❖ The process for the preparation of intermediate compound 8



❖ The process for the production of quinoloxine compound 11 and its coupling with hydroxyproline compound 12 to produce compound 13



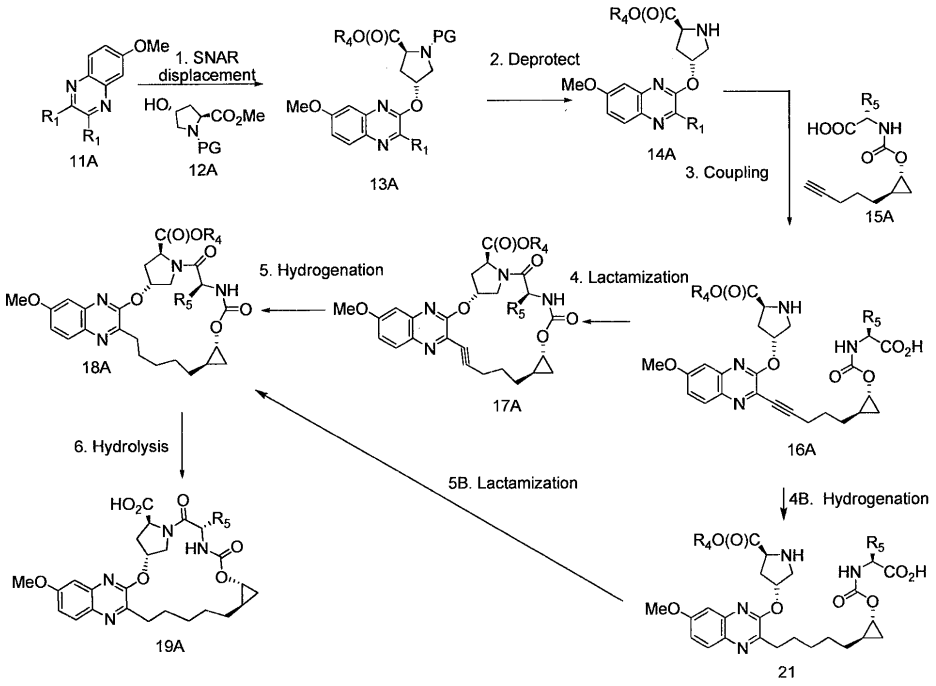
❖ **Process for the preparation of compound A (grazoprevir)**



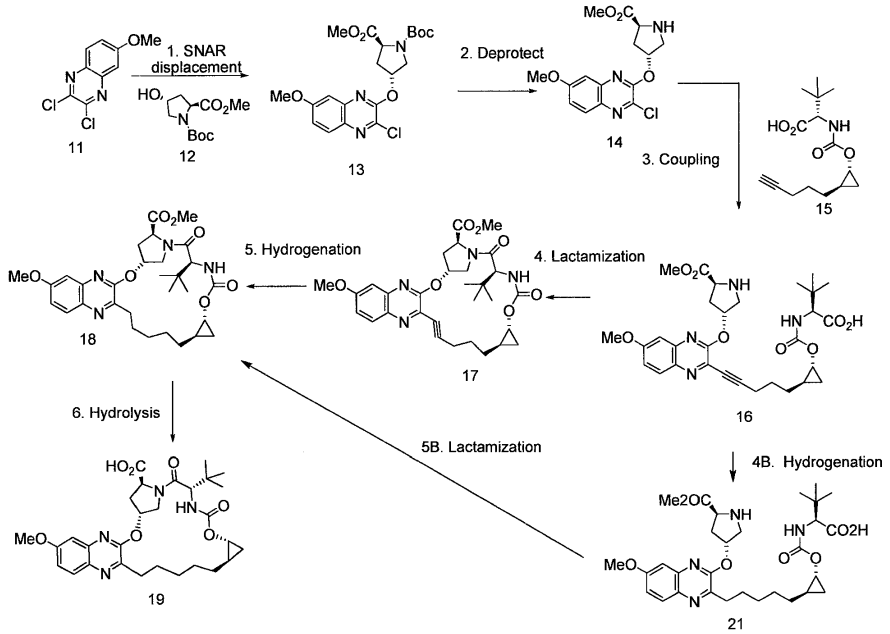
PATENT 6

Processes for producing grazoprevir and key intermediates disclosed and claimed is depicted below.

Overall synthetic scheme

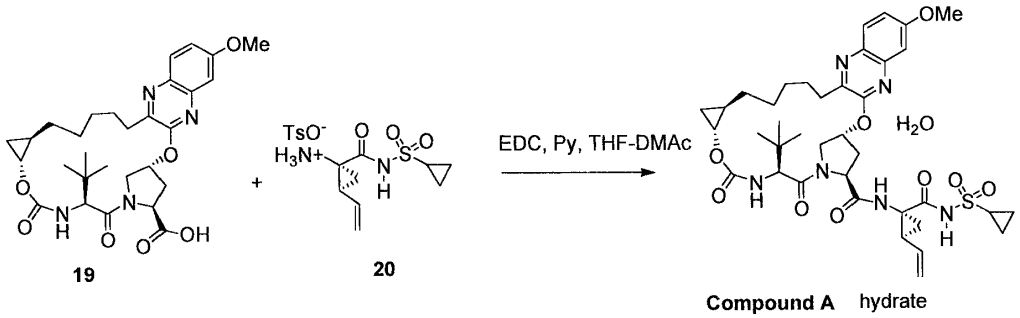


Prefered overall scheme

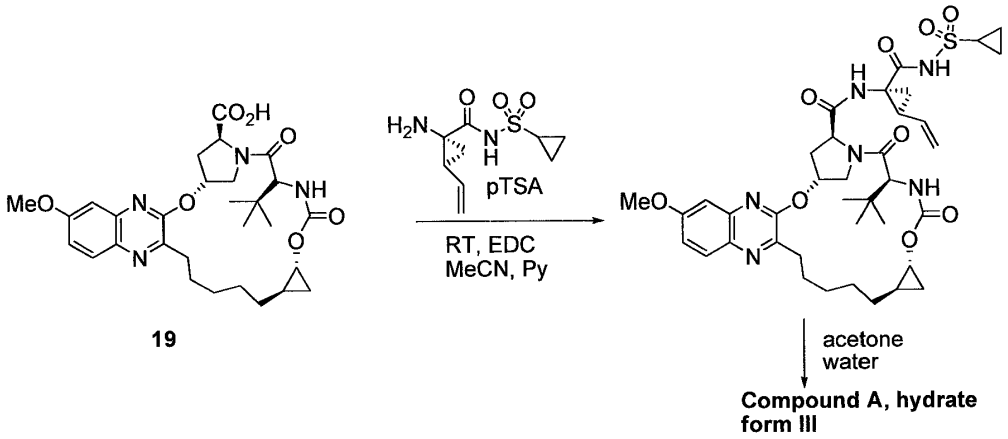


The application claims compounds of general formula (I) – in particular compounds 14, 16, 16A and 17 or salt thereof; and a method of making compounds 16A, 16 and 17. It also claims a method for making compounds 18 and 14, and a method for making compound A (grazoprevir).

Preparation of compound A (grazoprevir)



Preparation of compound A (grazoprevir) – alternative procedure

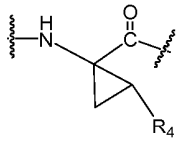


Processes for the preparation of compounds 3, 4, rac-5, rac-6, 7, 8, 10 and 11 are as disclosed in WO2013028471 (patent 5).

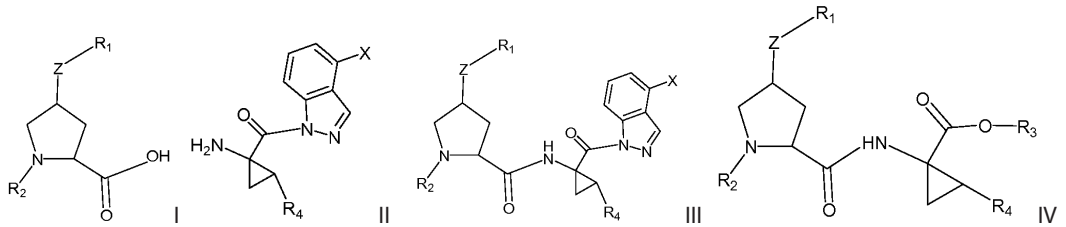
Finally, it claims an MeCN solvate of a compound 14 methylsulfonic acid salt where the solvate is characterized by an X-ray powder diffraction pattern obtained using copper Kα radiation, and a compound 19 hydrate-I characterized either by an X-ray diffraction pattern obtained using copper Kα radiation or by a solid-state carbon-13 CPMAS NMR spectrum.

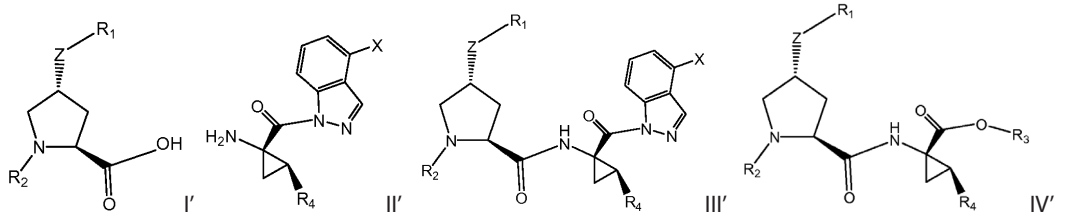
PATENT 9

This application discloses and claims processes that permit the incorporation of the moiety below, or an equivalent one, into precursors of HCV protease inhibitors.

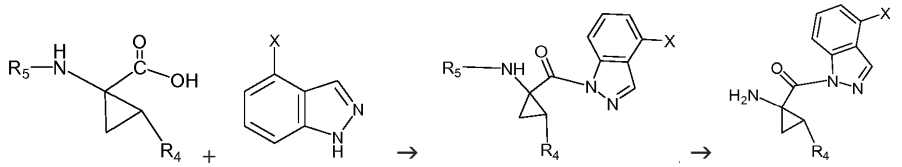


In one aspect, the processes comprises reacting compound I with compound II to form compound III; and further reacting compound III with R_3-OH to form compound IV.

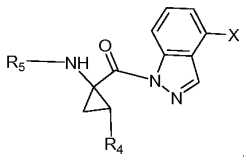




The application also discloses processes for making compound II, as depicted in the scheme below:



Finally, the application claims compounds of general formula, as depicted below:



Illustrative example: