UNITAID

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Review of the Elbasvir 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

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Abbreviations

DAA direct acting antiviral

HCV hepatitis C virus

HIV human immunodeficiency virus

PCT Patent Cooperation Treaty

RNA ribonucleic acid

I. 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. Genotypes 2, 4 and 6 together represent around 23% of HCV cases, while genotype 5 accounts for less than 1%.[3] The distribution of HCV genotypes varies between regions.

Efforts to treat HCV have historically been hampered by suboptimal and inadequate treatments. The development of direct-acting antivirals (DAAs) has dramatically improved HCV treatment prospects and altered the standard of care. Several new DAAs that do not require pegylated interferon were launched in late 2013 and in 2014. 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-8742 – elbasvir – 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 elbasvir's potential role in future treatment, this report explores the patent landscape of elbasvir.

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.

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).

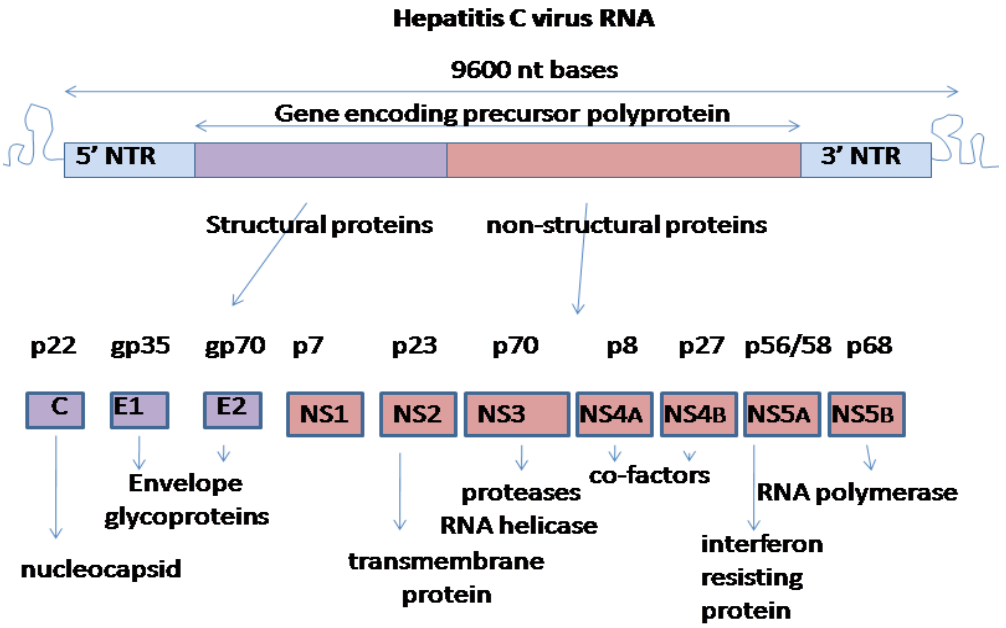
The following reviewers provided valuable input, comments and suggestions on all or part of a draft version of this report: Peter Beyer, Yao Cheng, Carlos Correa, Ellen ‘t Hoen, Yuanqiong Hu, Leena Menghaney and Chan Park.

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 6 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).

NS5A is a 447 amino acid, zinc-binding phosphoprotein that is believed to play a key role in HCV RNA replication. NS5A exists in 2 forms: a hypophosphorylated p56 and a hyperphosphorylated p58 based on electrophoric mobility. NS5A is essential to HCV genome replication.

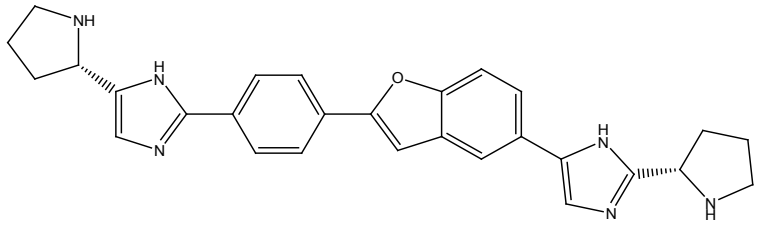
Elbasvir (MK-8742) is an NS5A inhibitor that is currently in phase III clinical trials.

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.

Elbasvir

Merck's early work on NS5A inhibitors led to the discovery of their first clinical candidate: MK-4882 (or [2-((S)-pyrrolidin-2-yl)-5-(2-(4-(5-((S)-pyrrolidin-2-yl)-1H-imidazol-2-yl)phenyl)benzofuran-5-yl)-1H-imidazole]). The structure of MK-4882 is shown in Figure 2.

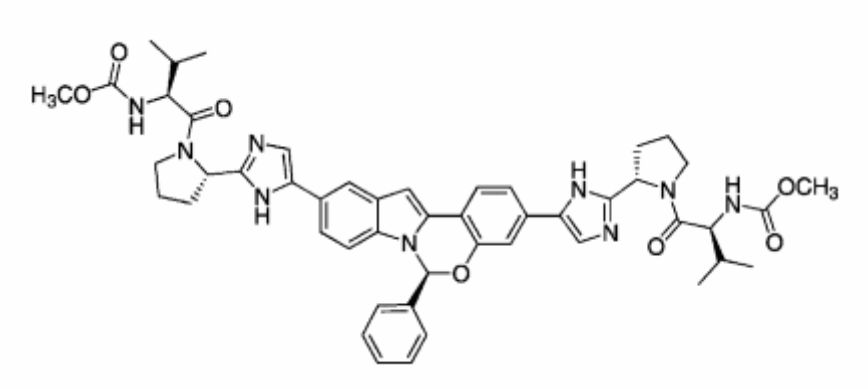
Figure 2. Structure of MK-4882



Mutation of the MK-4882 core by introduction of a cyclic constraint resulted in a series of tetracyclic molecules, some of which reportedly show activity against many HCV genotypes/subtypes.

Among these molecules is MK-8742, or elbasvir, a tetracyclic indole-based NS5A HCV.

Figure 3. Structure of elbasvir



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.

Chemical names:

- Dimethyl ((2S,2'S)-((2S,2'S)-2,2'-(5,5'-((S)-6-phenyl-6H-benzo[5,6][1,3]oxazino[3,4-a]indole-3,10-diyl)bis(1H-imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl) dicarbamate.
- Dimethyl N,N'-(((6S)-6-phenylindolo-(1,2-c)(1,3)benzoxazine-3,10-diyl)bis(1H-imidazole-5,2-diyl-(2S)-pyrroline-2,1-diyl((2S)-3-methyl-1-oxobutane-1,2-diyl)))dicarbamate.

Molecular formula: $C_{49}H_{55}N_9O_7$

Molecular weight: 882.0171 g/mol

CAS registry number: 1370468-36-2

IV. OVERVIEW OF ELBASVIR PATENTS

Five patents and/or patent applications related to elbasvir (MK-8742) have been identified as appearing to be the most relevant. These five patents/applications include the patents/applications covering the compound per se, as well formulations and combinations that include it.

Patent 1 and patent 2 are the main patents. The PCT applications of these patents cover the compound elbasvir. The production, import, marketing and use of generic versions of elbasvir would likely be blocked in countries where one or both patents are in force. Patent 2 is a selection patent from WO2010111483A (patent 1).

Patent 3 claims the combination grazoprevir/elbasvir.

Patent 4 covers certain (crystalline) pseudopolymorphs of elbasvir, amorphous elbasvir, and compositions comprising them.

Patent 5 relates to synthetic routes that can be used to produce elbasvir.

A brief overview of the five most relevant patents and/or applications can be found in Table 1. More extensive information about patents 1, 2 and 3 is provided in section V and Annex 1.

Table 1. Overview of key patents on elbasvir

	Patent/application number	Applicants	Filing date	Comments
1.	EP2410844A WO2010111483A	Merck (USA)	25.03.2010	Broad compound patent. Claims elbasvir through a broad Markush formula and a specific reference to its chemical name. The broad compound claim includes a large number of analogue compounds of elbasvir.
2.	WO2012040923A	Merck (USA)	29.09.2010	Compound patent. Claims elbasvir as well as a large number of analogues of elbasvir.
2b.	EP2621931A WO2012041014A	Merck (USA)	28.09.2011	Hetero aryl derivatives structurally related to elbasvir but not including elbasvir. This patent is in the same patent family as patent 2 but is not relevant.
3.	EP2621501A WO2012050850A	Merck (USA)	28.09.2011	Combination grazoprevir/ elbasvir and its use.
4.	WO2015065817A	Merck (USA)	24.10.2014	(Crystalline) pseudopolymorphs of elbasvir and amorphous elbasvir.
5.	WO2015065821A	Merck (USA)	24.10.2014	Processes for the preparation of elbasvir and intermediates thereof.

V. ANALYSIS OF ELBASVIR PATENTS/APPLICATIONS

Patent 1

Title: Inhibitors of hepatitis C virus replication.

WO2010111483A (*Merck, filed 25.03.2010*); **EP2410844A**

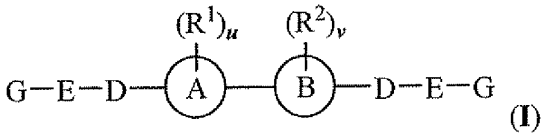
Summary

This is the basic compound patent. It is a broad compound patent that claims compounds of Markush formula (I), including elbasvir. Elbasvir is also specifically claimed (by chemical name).

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

Description

The PCT application relates to compounds of Markush formula (I) and/or pharmaceutically acceptable salts, hydrates, solvates, prodrugs or isomers thereof that are useful as NS5A inhibitors.



(I)

The moieties A, B, D, E, G and substituents are defined in the description and the claims; the patent/application covers many different classes of chemical compounds.

Pharmaceutical compositions comprising an effective amount of compound (I) or a pharmaceutically acceptable salt thereof and a carrier are also claimed, as well as a combination of compound (I) or a salt thereof and a second therapeutic agent selected from HCV antiviral agents, immunomodulators and anti-infective agents. More specifically, a combination of compound (I) or a salt thereof with an HCV protease inhibitor or an HCV NS5B polymerase inhibitor is claimed. Finally, the use of such pharmaceutical compositions for the treatment of HCV is claimed.

The PCT application covers elbasvir through the Markush formula (I), which covers an extremely broad range of compounds, but elbasvir is also specifically claimed by chemical name (in claims 31 and 33 of the PCT application).

Examination at the European Patent Office

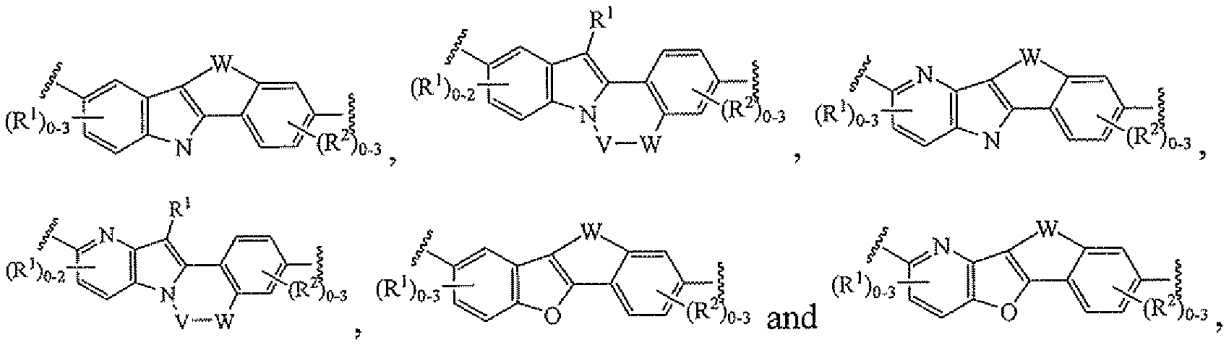
During examination at the European Patent Office, the PCT application, as originally filed, was found to contain multiple independent compound claims (claims 1, 2 and 11), with overlapping scope and was considered to lack clarity and conciseness. Additionally, the scope of these claims was found to be broader than the subject matter supported by the description and/or examples.

Thus, the applicants were invited in the first instance to elect/restrict these claims.

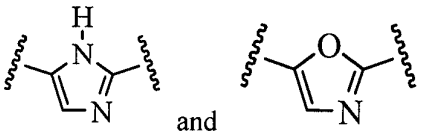
However, even after the applicants had elected only claims 30 – 39, the examiner identified five different inventions. Thus, the applicants were invited to limit the application to only one invention and to file divisional applications for the rest.

Further to the European examiner's objections, the applicants filed amendments (on 13.09.2013) that limited the invention to compounds of formula (I) in which substituents A and B are taken together and form a condensed tetracyclic moiety. To overcome the novelty objections, the subject matter has been further restricted to moiety D being selected from imidazolyl and oxazolyl groups.

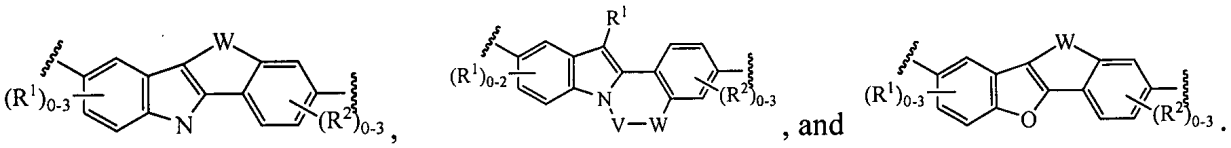
A and B taken together form the following tetracyclic moiety:



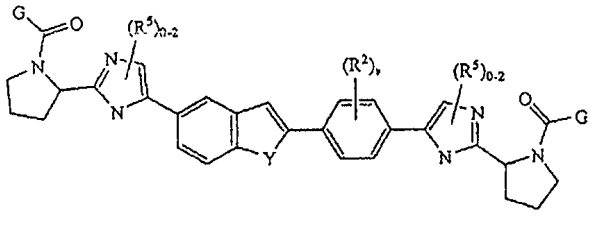
Each D is a group independently chosen from:



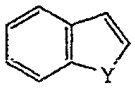
In dependent claim 2, the compounds (I) are preferably compounds in which A and B taken together are represented by:

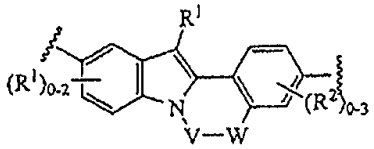


More preferably, compound (I) is a compound of formula (Ib), as shown below (13th embodiment):



(Ib)

or pharmaceutically acceptable salt thereof, and in which  and  taken together are:



Elbasvir is specifically claimed, by its chemical name, in amended claim 14.

During European prosecution, three documents were cited as prior art: US 20060258682A (XTL Biopharmaceuticals, filed 16.05.2005; equivalent to US 7994360B and WO 2006124861A), US 20070049593A and EP1719773A (Japan Tobacco, filed 23.02.2005) and are novelty destroying documents.

The applicants had until the end of February 2015 to file amendments, taking into account the comments and objections of the European examiner. As the applicants failed to do so, the European patent application was deemed withdrawn (31.03.2015). Since the applicants failed to redress this decision within two months, the applicants have lost their rights. Thus, this patent will not be granted by the European Patent Office.

Observations

In the USA, the compound claim has been limited specifically to elbasvir, and the patent has been granted (patent number US8871759B).

The pending or granted claims in other countries will need to be monitored and checked.

The PCT application of patent 1 also discloses, without claiming them, processes for producing elbasvir (see Annex 2 for more details).

Patent 2

Title: Tetracyclic indole derivatives and methods of use thereof for the treatment of viral diseases.

WO2012040923A (*Merck, filed 29.09.2010*)

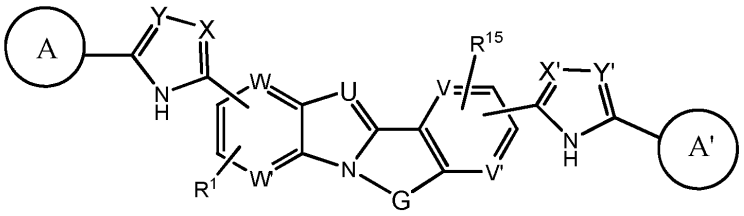
Summary

This application claims elbasvir via a Markush structure (I), covering a much smaller class of compounds than patent 1. It is a selection of WO2010111483 (patent 1).

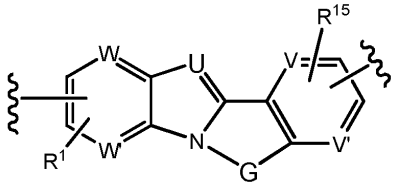
This patent would likely block generic market entry in the countries where it is in force.

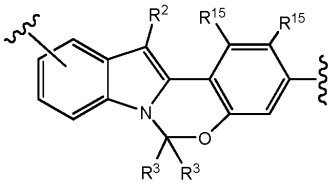
Description

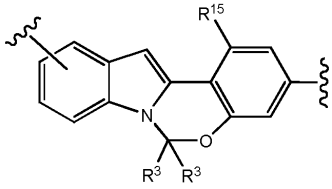
The application relates to tetracyclic indole compounds of formula (I) or pharmaceutically acceptable salts thereof, compositions comprising them and methods of using them for treating or preventing HCV. Also within the scope of the invention are: the hydrates, solvates, prodrugs (e.g. esters) and stereoisomers.



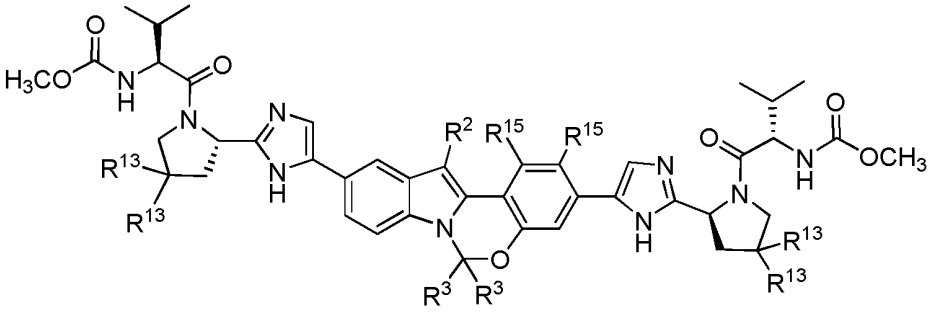
(I) **I**

In one embodiment, the group:  has the following structures:





In another embodiment, the compounds of formula (I) have the formula (Ib):



Ib

in which R^2 is H or F; R^3 is independently H, C_{1-6} alkyl, cycloalkyl, 5- or 6-membered heteroaryl and phenyl, optionally substituted; R^{13} is H or halo; and R^{15} is H or halo.

The application also claims a pharmaceutical composition comprising an effective amount of a compound (I) or pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier; and the said composition, further comprising a second therapeutic agent selected from HCV antiviral agents (HCV protease inhibitors and HCV NS5A polymerase inhibitors), immunomodulators and anti-infective agents; combination with an effective amount of at least one second therapeutic agent.

The applicants provide a list of non-limiting examples at Table-1, p. 42 – 64 of the PCT application (compounds 1 – 246). Most of the compounds are mono-, di or tri-halogenated derivatives of elbasvir, elbasvir and stereoisomers (compounds 124, 212, 213 and 233).

Example 30 presents cell-based HCV replicon assay results of selected compounds, including compound A: elbasvir (see p.132 – 133 of the PCT application).

Observations

Patent/application 2 is a selection patent. However, elbasvir has explicitly been mentioned in the larger, prior Markush disclosure (i.e. WO2010111483A or patent/application 1). WO' 483 (patent 1) was cited in the International Search report as prior art relevant to novelty (category E) as it was filed and claimed priority earlier than the filing date of WO' 923 (patent 2) but was published one day later than the filing date of WO' 923.

The application has not entered into the European phase (06.06.2013).

PATENT 2 - DIVISIONALS

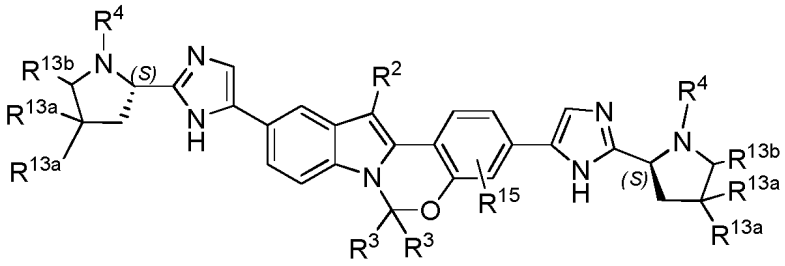
PATENT 2b

Title: Tetracyclic indole derivatives for treating Hepatitis C virus infection.

WO2012041014A (divisional to **WO2012040923A** (patent 2)).

Description

This PCT application (and its equivalents) are listed in the same INPADOC family; however it claims selection compounds (Ib) in which one occurrence of R^3 is H and the other is a 5- or 6-membered monocyclic heteroaryl or 9-membered bicyclic heteroaryl. As a result, this application does not pertain to elbasvir.



(Ib)

Observations

The PCT application does not cover elbasvir. However it would be important to check at the relevant patent office whether any amendments have been filed that would include elbasvir within the scope of this patent/application.

Patent 3

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

WO2012050850A (*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.

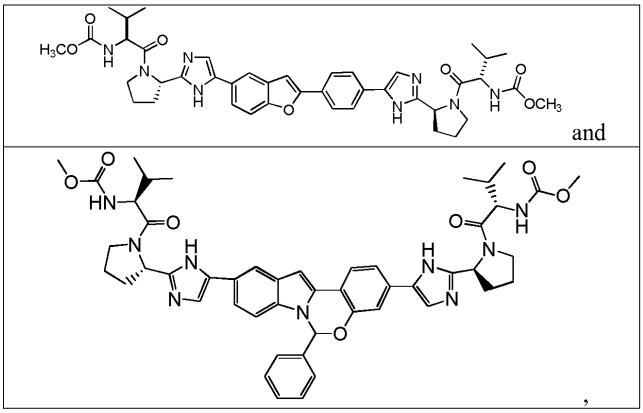
Description

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.

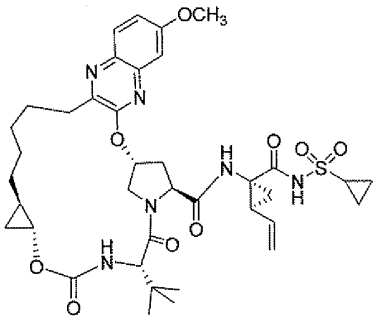
In the European phase, the claims were found to be novel but not inventive, in view of WO2010011566A or US20080299075A. Additionally, in view of the number of alternative compound combinations falling within the scope of the claims as originally filed, the European examiner expressed doubts that all 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.

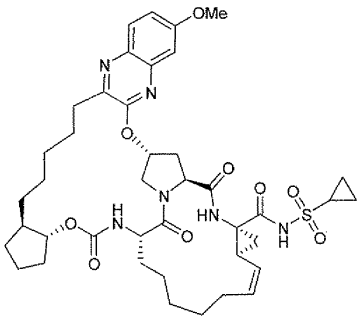
The compounds of Table 1: (after amendments)



First additional therapeutic agents (after amendments):



F5



F7

Observations

This application is under examination. 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.

Assuming that elbasvir is approved for use only in combination with another anti-HCV drug (such as grazoprevir), this patent would likely constrain generic market entry.

Patent 4

Title: Pseudopolymorphs of an HCV NS5A inhibitor and uses thereof.

WO2015065817A (*Merck Sharp & Dohme, filed 24.10.2014*)

Summary

This application claims several pseudopolymorphs of elbasvir (such as hydrate, alcohol solvate, glycol solvate or ketone solvate). The application more specifically claims the pseudopolymorphs in crystalline forms but it also claims amorphous elbasvir. And it claims pharmaceutical compositions comprising these pseudopolymorphs, processes for making such compositions, and their use for inhibiting HCV replication or for treating HCV infection.

Description

This application discloses novel pseudopolymorphs of the compound of formula A (elbasvir).

The pseudopolymorphs are solvates such as hydrate, alcohol solvate (C_{1-4} alcohol solvate), chloroalkane solvate, ester solvate, cycloether solvate, glycol solvate (C_{2-4} glycol solvate) or ketone solvate (C_{1-5} ketone solvate) or mixtures thereof.

The pseudopolymorphs are more specifically Form A (methanolate), Form B (ethanolate), Form C (1-propanolate), Form D (2-propanolate), Form E (acetonate), Form F (1-butanolate), Form G (ethylene glycolate), Form H (propylene glycolate), Form I (methyl isobutyl ketone/propylene glycol mixed solvate), Form J (hydrate) and Form K (1,5-naphthalene disulfonic acid salt methanol solvate).

The pseudopolymorphs are in crystalline forms; tables of the characteristic peaks in the X-ray powder diffraction (XRPD) patterns of two methanolates (example 2), the ethanolate (example 3), the 1-propanolate (example 4), the 2-propanolate (example 5), the acetonate (example 6), the 1-butanolate (example 7), the ethylene glycolate (example 8), the propylene glycolate (example 9), the methyl isobutyl ketone/propylene glycol mixed solvate (example 10), the hydrate (example 11) and the methanol solvate of the 1,5-naphthalene disulfonic acid salt (example 12) are given.

The application also provides, without claiming them, processes for preparing the crystalline pseudopolymorphs. Essentially these consist of:

(1) combining compound A with an organic solvent, or water, or mixtures of water and water miscible organic solvent;

(2) applying any suitable technique to induce crystallization; and

(3) isolating the desired crystalline pseudopolymorphs (refer to the examples mentioned above).

Pharmaceutical compositions comprising an effective amount of the disclosed pseudopolymorphs together with a pharmaceutically acceptable carrier, and optionally with a second therapeutic agent (HCV antiviral agent, immunomodulator and anti-infective agent) and a third therapeutic agent (HCV protease inhibitor, HCV NS5A inhibitor and HCV NS5B polymerase inhibitor) are claimed.

The application also claims a pharmaceutical composition comprising: compound A or a pharmaceutically acceptable salt thereof; a concentration-enhancing polymer, where the polymer increases the bioavailability or enhances the dissolution behavior of compound A, and is water soluble or readily disperses in water; and optionally one or more surfactants. The process for making such composition is also claimed.

The process either involves:

- spray-drying a solution comprising a pseudopolymorph of compound A (or a pharmaceutically acceptable salt thereof), the concentration-enhancing polymer, optionally one or more surfactants, and one or more solvents; or

- hot-melt extrusion of a mixture comprising a pseudopolymorph of compound A (or a pharmaceutically acceptable salt thereof), the concentration-enhancing polymer and, optionally, one or more surfactants.

The composition therefore appears to be directed to an amorphous form of elbasvir, as these processes render the crystalline pseudopolymorphs amorphous. The concentration-enhancing polymer forms an amorphous dispersion with compound A by either dissolving compound A or interacting with compound A in such a way that compound A does not form crystals or crystalline domains in the polymer. As a result, at least a major portion of elbasvir would be present in the amorphous form.

The amorphous forms have benefits relative to other morphological forms, such as a greater solubility and/or a faster dissolution rate. This improves the bioavailability of the compound, facilitates a faster onset of the therapeutic action, reduces the variability of the therapeutic response among subjects and reduces the effect of food.

Observations

This application has been published recently (07.05.2015). To date, only the International Search report has been published.

According to the International Searching Authority, the application comprises multiple inventions.

Patent 5

Title: Process for preparing tetracyclic heterocycle compounds.

WO2015065821A (*Merck Sharp & Dohme, filed 24.10.2014*)

Summary

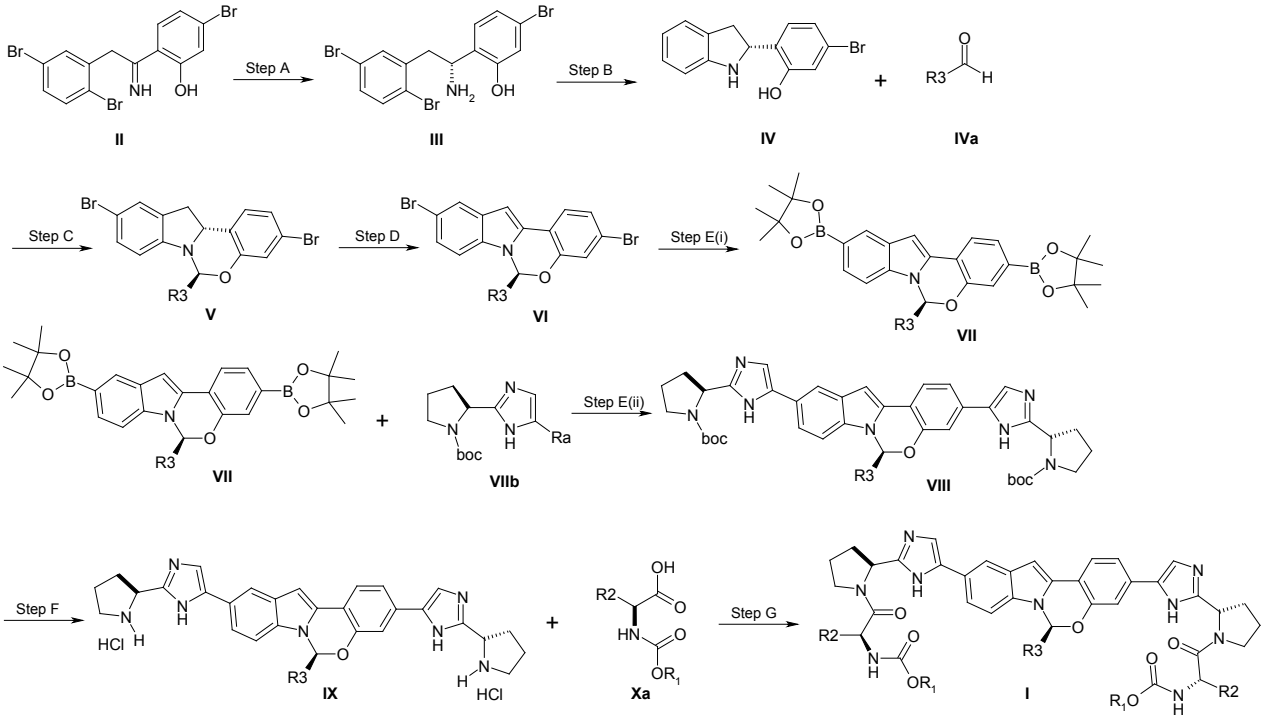
This application claims a process for the preparation of elbasvir, using novel intermediates. The application furthermore claims those novel intermediates and processes for their preparation.

Description

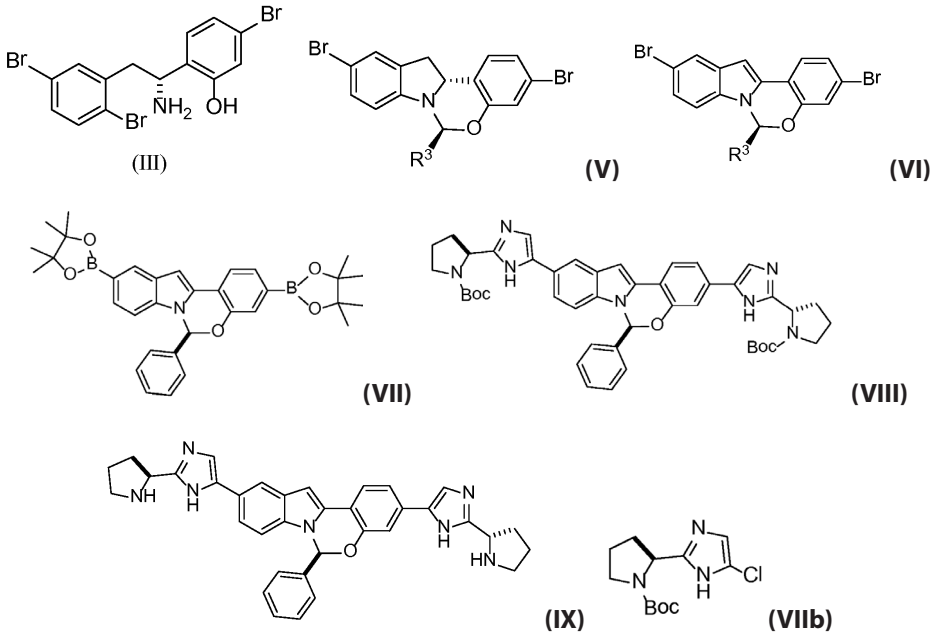
This application relates to an improved process for the preparation of compounds of general formula (I), useful as HCV NS5A inhibitors, and more particularly for the preparation of compound A (elbasvir).

According to the process disclosed, compound (I) – and elbasvir – is prepared in seven steps (see Annex 2 for a short description of those steps).

Overview of the steps in the preparation process:



The application claims novel key intermediates useful for the preparation of elbasvir; notably compound (III), compound (V), compound (VI), compound (VII), compound (VIII), compound (IX) and compound (VIIb). The chemical structures of these compounds are depicted below.



Processes for the preparation of several novel key intermediates are also disclosed and claimed in the PCT application.

Observations

This application has been published recently (07.05.2015). To date, only the International Search report has been published, with a written opinion on patentability based on prior art searches performed by the International Searching Authority (ISA).

According to the International Searching Authority:

- The application comprises multiple inventions. Thus, the applicants will have to limit the application to only one invention (and may file divisional applications covering the other inventions). The International Searching Authority has only provided an opinion regarding the patentability of claims 1-6 (invention 1); these claims were considered both novel and inventive.
- Compounds VII, VIII and IX are already known in the prior art, notably WO2012041014A1 (patent 2b); thus, they are neither novel nor inventive.

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

ANNEX 1 - Elbasvir patent situation in countries

The INPADOC patent family members for patent/application 1, 2 and 3 are listed in the tables below.

Anticipated expiry dates of patents 1 have been provided. Differences between countries, if any, 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 elbasvir is approved for use, it is likely that the innovator will apply for patent term extension/restoration.

	Patent 1	**Patent 2**	**Patent 2b**	**Patent 3**
	WO2010111483A1 **PCT/US2010/028653**	**WO2012040923A1** **PCT/CN2010/077493**	**WO2012041014A1** **PCT/CN2011/001638**	**WO2012050850A1** **PCT/US2011/053562**
Applicants	**Merck Sharp & Dohme (USA)**	**Merck Sharp & Dohme (USA)**	**Merck Sharp & Dohme (USA)**	**Merck Sharp & Dohme (USA)**
Filing date	**25.03.2010**	**29.09.2010**	**28.09.2011**	**28.09.2011**
Title	**Inhibitors of Hepatitis C virus replication.**	**Tetracyclic indole derivatives and methods of use thereof for the treatment of viral diseases.**	**Tetracyclic indole derivatives for treating Hepatitis C virus infection.**	**Polycyclic heterocycle derivatives and methods of use thereof for the treatment of viral diseases.**
Subject matter	**Basic compound patent. Very broad Markush formula covering many compounds, including elbasvir.**	**Broad compound patent; claims elbasvir and a large number of elbasvir analogues.**	**PCT application is not relevant; it covers compounds structurally related to elbasvir but not elbasvir. It is advisable to check the actual claims at national level.**	**Grazoprevir/elbasvir combination in the same formulation with or without a third therapeutic agent**
Priority data	**US 61/163,958 – 27.03.2009** **US 61/247,318 – 30.09.2009**		**PCT/CN2010/077493 – 29.09.2010** **US 61/426,724 – 23.12.2010**	**US 61/387,825 – 29.09.2010**
African Regional Intellectual Property Organization*				
Argentina				
Australia	2010229833B Expiry: 25.03.2030 2014200550A Divisional – Under examination Filing date: 31.01.2014		2011307953B2 Lapsed: 19.11.2014 (non-payment of fees)	2011314170A Under examination
Brazil				
Canada	2756172A Under examination		2811662A Under examination	2811752A Under examination

	Patent 1	Patent 2	Patent 2b	Patent 3
China	Appl. N°: 201080021629 Publ. N°: 102427729B Expiry: 25.03.2030		Appl. N°: 201180057516 Publ. N°: 103459399A Under examination	
	Appl. N°: 201410127412 Publ. N°: 103880862A Divisional – Under examination			
China, Hong Kong SAR				
Colombia	Appl. N°: 20110124967 Publ. N°: 6420390A Expiry: 23.09.2031(?)			
Costa Rica	20110506A Status not available			
Croatia				
Dominican Republic	(P)2011000298A Status not available			
Ecuador	(SP)11011357A Status not available			
El Salvador				
Eurasian Patent Office*	Appl. N°: 201171174A Publ. N°: 020898B1 Expiry: 25.03.2030			
European Patent Office*	Appl. N°: 10756840 Publ. N°: 2410844A Deemed withdrawn (31.03.2015)	Appl. N°: 10857686 Non-entry into EU phase (06.06.2013)	Appl. N°: 11827912 Publ. N°: 2621931A Deemed withdrawn; not relevant	Appl. N°: 11833019 Publ. N°: 2621501A Under examination
Georgia	Publ. N°: 12428A Status not available			
Guatemala				
Honduras				
India	7033/DELNP/2011 Under examination			2234/CHENP/2013 Deemed withdrawn
Israel	215094 A Under examination			
Japan	Appl. N°: 2012-502245 Publ. N°: 2012-522000A Refused (26.03.2014) Amended (26.09.2014)		Appl. N°: 2013530529 Publ. N°: 2013538831A Status not available	Appl. N°: 2013531744 Publ. N°: 2013544232A Withdrawn
	Divisional application: Appl. N°: 2014-195016 Publ. N°: 2015-028055A Under examination			
	Divisional application: Appl. N°: 1020137031213 Publ. N°: 1020130140219A			
Mexico	Publ. N°: 2011010084A Under examination		Publ. N°: 2013003631A Not relevant	Publ. N°: 2013003634A Under examination
Morocco	Appl. N°: 34270 Publ. N°: 33209B1 Status not available			

	Patent 1	Patent 2	Patent 2b	Patent 3
New Zealand	Appl. N°: 20100595410 Patent N°: 595410A Expiry: 25.03.2030			
	Divisional application: Publ. N°: 618322A Under examination			
Peru	Appl. N°: 20110171820 Publ. N°: 000765/2012-OIN Under examination			
Philippines	Appl. N°: 12011501911 Publ. N°: PH/1/2011/501911			
Republic of Korea	Appl. N°: 1020117025316 Publ. N°: 1020110130516A Patent N°: 101387274 B1 Expiry: 25.03.2030		Appl. N°: 1020137010717 Publ. N°: 1020140001879A Unexamined	Appl. N°: 1020137010752 Publ. N°: 1020130120469 A Unexamined
	Divisional application: Appl. N°: 1020137031213 Publ. N°: 1020130140219A			
Russia				
Serbia				
Singapore	Appl. N°: 2011069887 Publ. N°: 174929A Abandoned (14.12.2014)			
	Divisional application: Appl. N°: 10201402969A Under examination			
South Africa				
Thailand+				
Ukraine				
USA	Appl. N°: 13/260,684 Publ. N°: 20120083483A Patent N°: 8871759B Expiry: 25.03.2030 + patent term adjustments: 405 days			Appl. N°: 13/876,908 Publ. N°: 20130280214A Under examination
	Appl. N°: 14/473,117 Publ. N°: 20140371138A Under examination			
Viet Nam+	1-2011-02560A Expiry 25.03.2030 Approved for grant with claim scope same as US8871759			

Notes:
Cells in grey colour indicate that no patent or patent application has been found in the INPADOC database or – in the cases of 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 that the application had not been published at the time of the search. Information in this Annex should therefore always be 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.

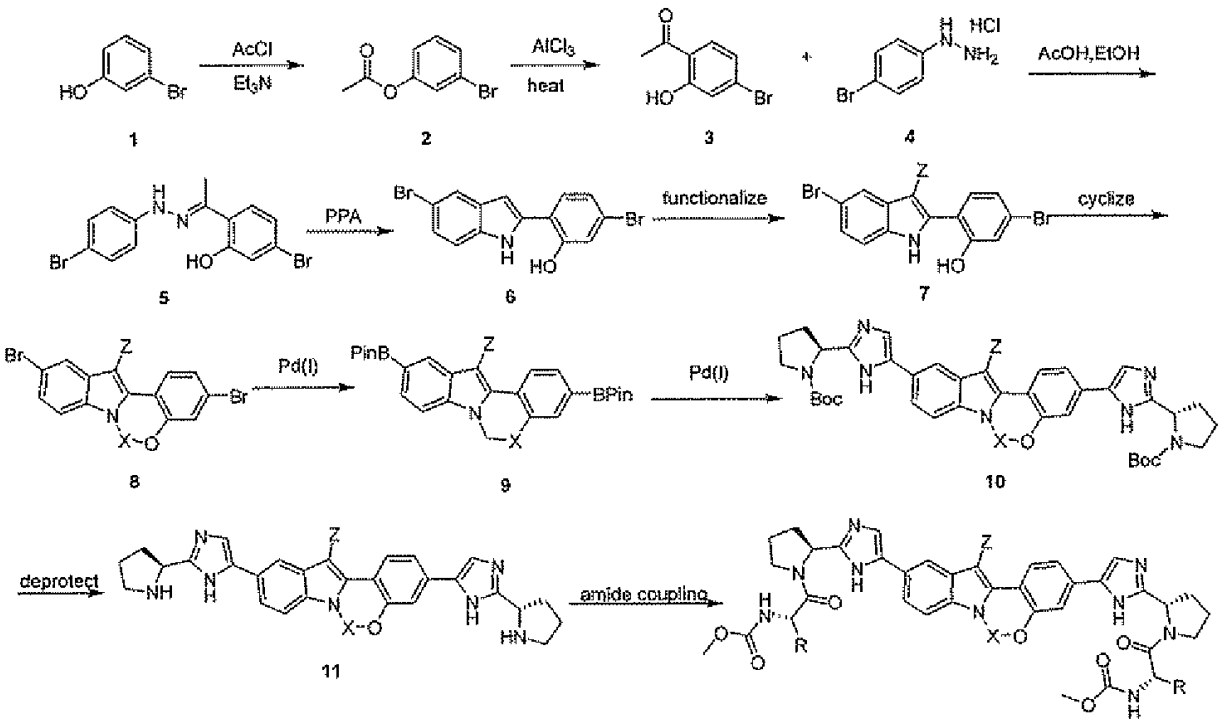
*** Eurasian Patent Organization (EA):** Armenia, Azerbaijan, Belarus, Kazakhstan, Kyrgyz Republic, Moldova, Russian Federation, Tajikistan and Turkmenistan.

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

ANNEX 2 - Process chemistry extracted from elbasvir patents/applications

PATENT 1

Processes for the preparation of claimed compounds (including elbasvir structure) are disclosed in the description of the PCT application, although not claimed. Refer to Scheme T, original PCT application (p. 60):



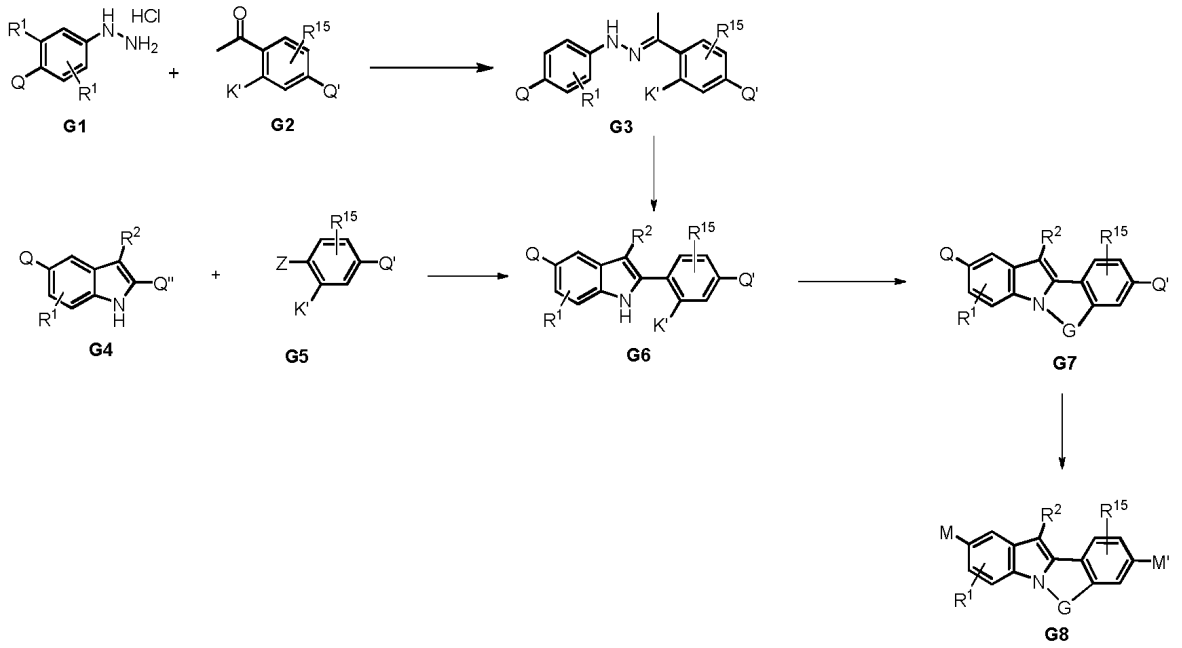
Compounds in Scheme T can be prepared by starting from a suitably substituted phenol 3 and a hydrazine reagent, such as 4, using established Fisher indole conditions. The indole 3 position can then be functionalized or the indole NH can be cyclized onto the C-2 aromatic ring using standard conditions to give tetracycles 8, which can subsequently be converted to the corresponding boronate esters using standard procedures. Intermediates 9 can then be coupled to a heterocyclic halide in the presence of a Pd(II) catalyst to provide compounds 10. Deprotection and coupling with an appropriately substituted carboxylic acid and an amide bond-forming reagent, such as HATU, can provide the targeted compound.

The illustrative example 189b procedure can be followed for the preparation of elbasvir: compound 223 (i.e. methyl [(2S)-1-{(2S)-2-[5-(10-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-6-phenylindolo[1,2-c][1,3]benzoxazin-3-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate) using the appropriate starting materials and intermediates.

PATENT 2

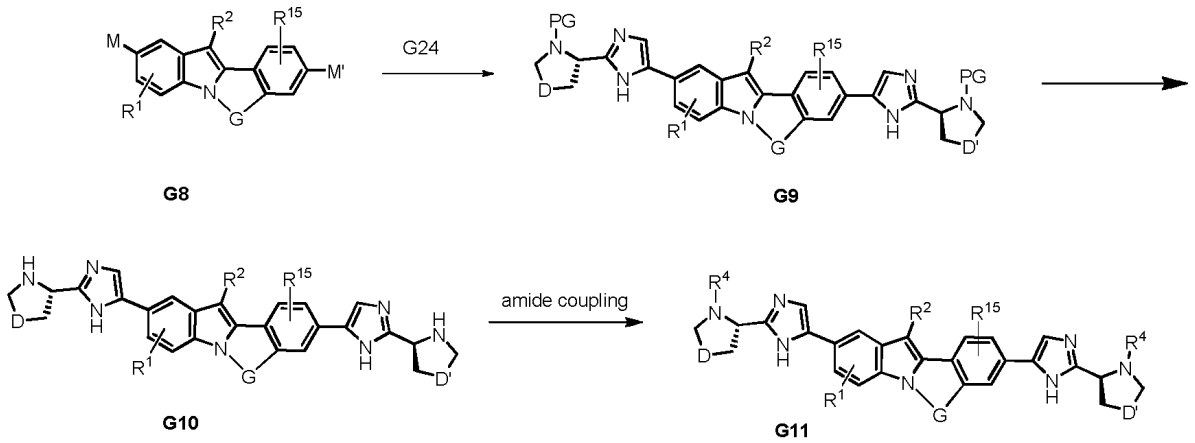
Several processes for the preparation of claimed compounds and their key intermediates are also disclosed (refer to Schemes 1, 2 and 5).

Scheme 2



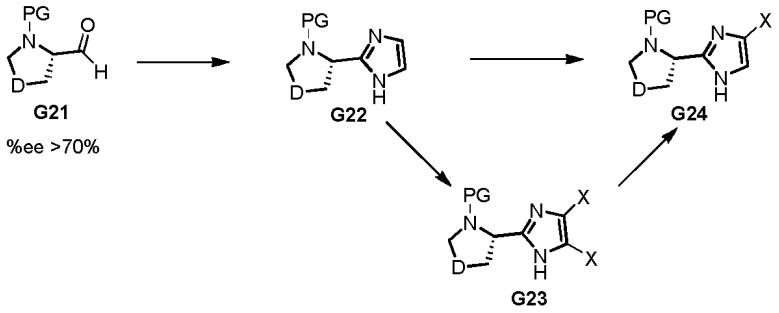
Tetracyclic compounds G8 can be prepared from substituted indole G6 which is then cyclized to provide tetracyclic compound G7. Indoles G6 are either commercially available or can be made via dehydration of hydrazide G1 with a ketone G2 to provide hydrazone G3, which can then be cyclized in the presence of a strong acid such as polyphosphoric acid or a Lewis-acid such as aluminium trichloride to provide compound G4. Compound G4 is then reacted with aldehyde: R^3CHO to provide the cyclized compound G8.

Scheme 2



Compound G8 is coupled with appropriate protected compound G24 to provide compound G9. After deprotection, compound G10 obtained is coupled with appropriate amide to provide compound G11.

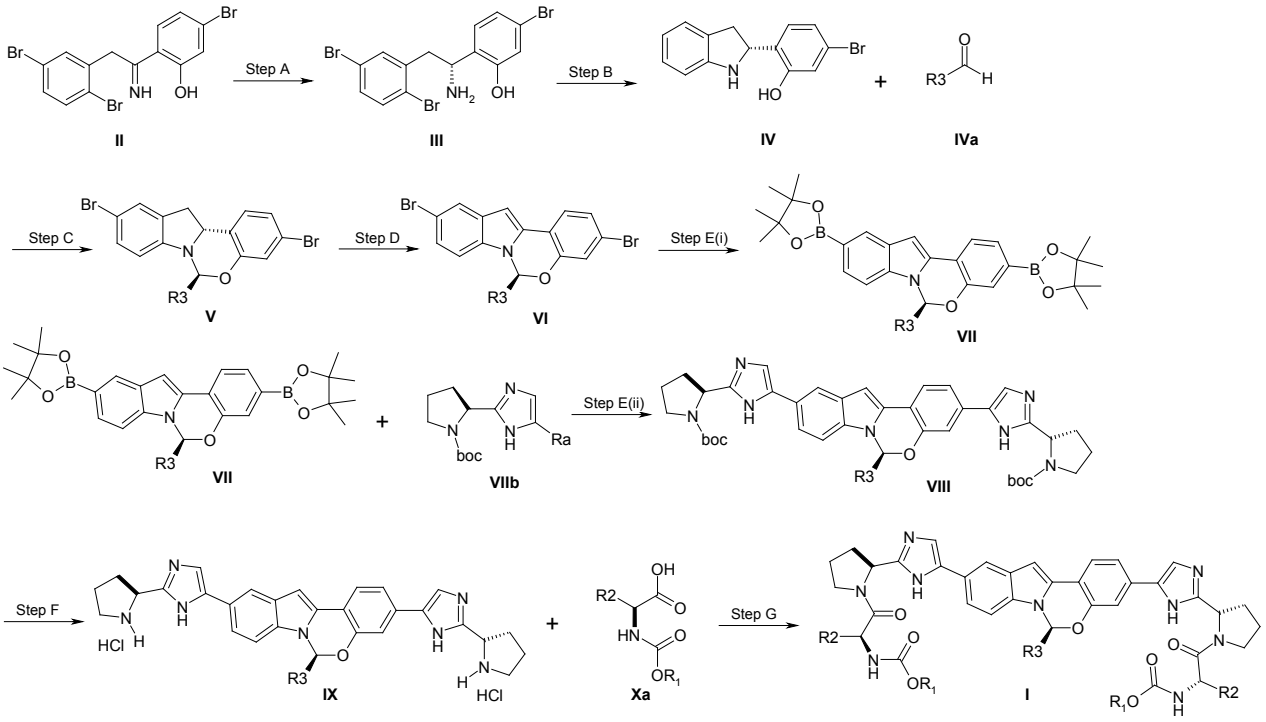
Scheme 5



An appropriately functionalized aldehyde G21 can be reacted with glyoxal and ammonia to provide a substituted imidazole G22; which can be subsequently selectively mono-halogenated to provide mono-halogenated imidazole G24 or, alternatively, compound G22 can be di-halogenated to provide compound G23 which is selectively reduced to provide compound G25.

PATENT 5

The patent discloses a process for the preparation of compound **(I)** – and elbasvir – in seven steps.



- **Step A**
  Contacting compound II with a ruthenium-based catalyst in the presence of one of the following compounds: ammonium formate, ammonium acetate, ammonium benzoate, ammonium salicylate, $H(CH_3)_2SiOSi(CH_3)_2H$ or polymethylhydrosiloxane, in an *organic solvent A* (acetonitrile, methanol, ethanol, isopropanol, tetrahydrofuran, 2-methyl tetrahydrofuran, toluene, chlorobenzene, dichloromethane and dichloroethane) to provide an amine III.

- **Step B**
  Contacting compound III with a carbonate or phosphonate base in the presence of a copper (I) salt in an *organic solvent B* (N,N-dimethylformamide, acetonitrile, dimethylacetamide, N-methyl pyrrolidinone and dimethylsulfoxide) to provide an indoline compound IV.

- **Step C**
  Contacting compound IV with a compound IVa in the presence of an acid in an organic solvent C (acetonitrile, toluene, dichloromethane, tetrahydrofuran, 2-methyl tetrahydrofuran, ethyl acetate and isopropyl acetate) to provide a tetracyclic compound V.

- **Step D**
  Contacting compound V with an oxidizing agent in the presence of an acid, in a mixture of water and *organic solvent D* (tetrahydrofuran, acetone, N,N-dimethylacetamide, dichloromethane and toluene) to provide an indole compound VI.

- **Step E**
  (E)(i): contacting compound VI with bis(pinacoloato)diboron in the presence of an acetate or pivalate base, a transition metal catalyst, and optionally in the presence of a phosphorus ligand source, in an organic solvent E (dimethylacetamide (DMAc), toluene, acetonitrile (ACN), N,N-dimethylformamide (DMF), tetrahydrofuran (THF), 2-methyl tetrahydrofuran, cyclopentyl methyl ether (CPME), isopropanol, ethanol (EtOH), ethyl acetate (EtOAc), isopropyl acetate and dimethoxyethane) to provide an intermediate compound VII.

  E(ii): contacting intermediate compound VII with a compound VIIb in the presence of a carbonate, acetate or pivalate base and a transition metal catalyst, and optionally in presence of a phosphorus ligand, in a mixture of water and organic solvent E' (dimethylacetamide, toluene, acetonitrile, N,N-dimethylformamide, tetrahydrofuran, 2-methyl tetrahydrofuran, CPME, isopropanol, ethanol, ethyl acetate, isopropyl acetate and dimethoxyethane) to provide compound VIII.

- **Step F**
  Contacting the di-*p*-nitrobenzoate salt of compound VIII with an inorganic base in an organic solvent F (methanol, acetonitrile, tetrahydrofuran, 2-methyl tetrahydrofuran, ethanol, isopropanol and toluene) for a time sufficient to remove the Boc protecting groups from compound VIII, then treat deprotected compound obtained with HCl in said organic solvent F to provide compound IX.

- **Step G**
  Contacting compound IX with an additive selected from 2-hydroxypyridine-N-oxide, N-hydroxysuccinimide, HOBt and pyridine, and a non-nucleophilic base in the presence of compound Xa and an amide coupling reagent, in an organic solvent G (tetrahydrofuran, N,N-dimethylformamide, dimethylacetamide, N-methylpyrrolidinone and dimethylsulfoxide) to provide desired compound I.

Preparation of novel intermediates

Processes for the preparation of several novel key intermediates are also disclosed and claimed in the PCT application:

- A process for the preparation of key intermediate (III) which comprises contacting compound (II) with a ruthenium-based catalyst in an organic solvent A selected from acetonitrile, methanol, ethanol, isopropanol, tetrahydrofuran, 2-methyl tetrahydrofuran, toluene, chlorobenzene, dichloromethane and dichloroethane, in the presence of ammonium formate, ammonium acetate, ammonium benzoate, ammonium salicylate or siloxane (PCT claim 7) – corresponding to step-A of the multi-step process for the preparation of elbasvir.
- A process for the preparation of key intermediate (V) which comprises contacting compound (IV) with compound (IVa) in the presence of an acid in an organic solvent C selected from acetonitrile, toluene, dichloromethane, tetrahydrofuran, 2-methyl tetrahydrofuran, ethyl acetate and isopropyl acetate (PCT claim 9) – corresponding to step-C of the multi-step process for the preparation of elbasvir.
- A process for the preparation of compound (VI) which comprises contacting compound (V) with an oxidizing agent in the presence of a carbonate or a phosphonate base, in a mixture of water with an organic solvent D selected from tetrahydrofuran, acetone, dimethylacetamide, dichloromethane and toluene (PCT claim 11) – corresponding to step-D of the multi-step process for the preparation of elbasvir.