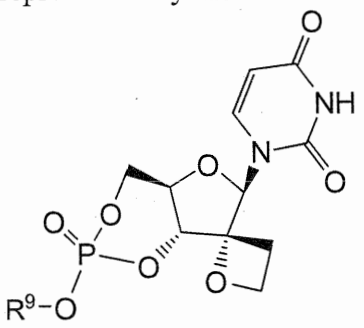
There is a need for HCV inhibitors that may overcome at least one of the disadvantages of current HCV therapy such as side effects, limited efficacy, the emerging of resistance, and compliance failures, or improve the sustained viral response.

The present invention concerns a group of HCV-inhibiting uracyl spirooxetane derivatives with useful properties regarding one or more of the following parameters: antiviral efficacy towards at least one of the following genotypes 1a, 1b, 2a, 2b, 3,4 and 6, favorable profile of resistance development, lack of toxicity and genotoxicity, favorable pharmacokinetics and pharmacodynamics and ease of formulation and administration.

Description ~~of the Invention~~

In one aspect the present ~~invention~~ disclosure provides compounds that can be represented by the formula I:



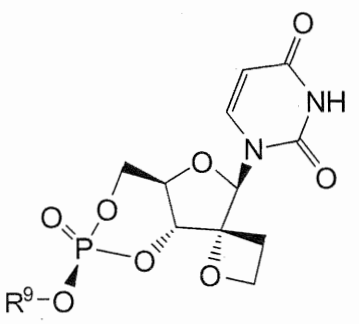
(I)

including any possible stereoisomer thereof, wherein:

R^9 is C_1-C_6alkyl, phenyl, C_3-C_7cycloalkyl or C_1-C_3alkyl substituted with 1, 2 or 3 substituents each independently selected from phenyl, naphtyl, C_3-C_6cycloalkyl, hydroxy, or C_1-C_6alkoxy;

or a pharmaceutically acceptable salt or solvate thereof.

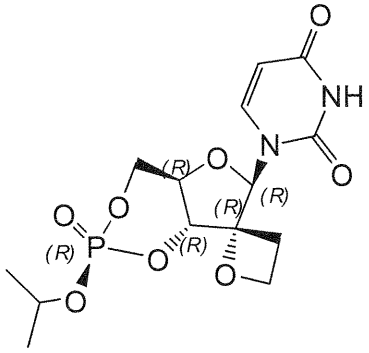
Of particular interest are compounds of formula I or subgroups thereof as defined herein, that have a structure according to formula Ia:



(Ia)

In one embodiment of the present ~~invention~~disclosure, R^9 is C_1-C_6alkyl, phenyl, C_3-C_7cycloalkyl or C_1-C_3alkyl substituted with 1 substituent selected from phenyl, C_3-C_6cycloalkyl, hydroxy, or C_1-C_6alkoxy. In another embodiment of the present disclosure~~invention~~, R^9 in Formula I or Ia is C_1-C_6alkyl or C_1-C_2alkyl substituted with phenyl C_1-C_2alkoxy or C_3-C_6cycloalkyl. In a more preferred embodiment, R^9 is C_2-C_4alkyl and in a most preferred embodiment, R^9 is *i*-propyl.

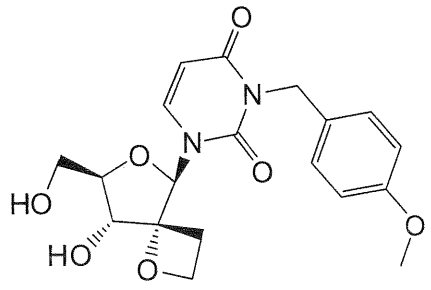
A preferred embodiment according to the disclosure~~invention~~ is a compound according to formula Ib:



(Ib)

including any pharmaceutically acceptable salt or solvate thereof and the use of compound (V) in the synthesis of a compound according to Formula I, Ia or Ib.

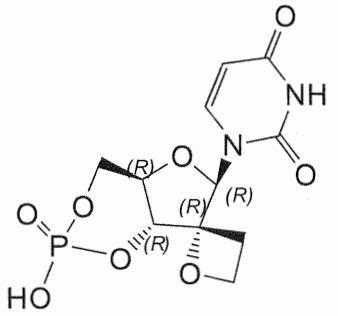
In a second aspect, the disclosure ~~The invention~~ further relates to a compound of formula V:



(V)

including any pharmaceutically acceptable salt or solvate thereof. In a third aspect, the disclosure relates to ~~and~~ the use of compound (V) in the synthesis of a compound according to Formula I, Ia or Ib.

In a fourth aspect ~~addition~~, the disclosure~~invention~~ relates to a compound of formula VI:



(VI)

including any stereochemical form and/or pharmaceutically acceptable salt or solvate thereof.

In a fifth aspect~~Additionally~~, the disclosure ~~invention~~ relates to a pharmaceutical composition comprising a compound according to Formula I, Ia or Ib, and a pharmaceutically acceptable carrier. The disclosure~~invention~~ also relates to a product containing (a) a compound of formula I, Ia or Ib a, and (b) another HCV inhibitor, as a combined preparation for simultaneous, separate or sequential use in the treatment of HCV infections

In a sixth aspect, the disclosure ~~Yet another aspect of the invention~~ relates to a compound according to Formula I, Ia or Ib or a pharmaceutical composition according to the present disclosure~~invention~~ for use as a medicament. In a seventh aspect, the disclosure relates to a compound according to Formula I, Ia or Ib, or a pharmaceutical composition according to the present disclosure, ~~preferably~~ for use in the prevention or treatment of an HCV infection in a mammal.

~~In a further aspect, t~~The disclosure also ~~invention~~ provides a compound of formula I, Ia or Ib or a pharmaceutically acceptable salt, hydrate, or solvate thereof, for use in the treatment or prophylaxis (or the manufacture of a medicament for the treatment or prophylaxis) of HCV infection. Representative HCV genotypes in the context of treatment or prophylaxis in accordance with the invention include genotype 1b (prevalent in Europe) or 1a (prevalent in North America). The disclosure~~invention~~ also provides a method for the treatment or prophylaxis of HCV infection, in particular of the genotype 1a or 1b.

In an eighth aspect, the disclosure relates to a product containing (a) a compound according to Formula I, Ia, Ib or VI, and (b) another HCV inhibitor, as a combined preparation for simultaneous, separate or sequential use in the treatment of HCV infections.

Of particular interest is compound **8a** mentioned in the section "Examples" as well as the pharmaceutically acceptable acid addition salts of this compound.

The compounds of formula I have several centers of chirality, in particular at the carbon atoms 1', 2', 3', and 4'. Although the stereochemistry at these carbon atoms is fixed, the compounds may display at least 75%, preferably at least 90%, such as in excess of 95%, or of 98%, enantiomeric purity at each of the chiral centers.