ANTIVIRAL COMPOUNDS WITH A DIBENZOOXAHETEROCYCLE MOIETY

FIELD OF THE INVENTION

The present invention relates to antiviral compounds, their tautomeric forms, their stereoisomers, and their pharmaceutically acceptable salts, pharmaceutical compositions comprising one or more such compounds, and methods of treating viral infection.

CROSS-REFERENCE TO A RELATED APPLICATION

The present application claims the benefit of Indian Provisional Patent Application Nos. 0147/KOL/2012 filed 10th February 2012, and 1017/KOL/2012 filed 4th September 2012~~, the disclosure of which is incorporated herein by reference in its entirety~~.

BACKGROUND OF THE INVENTION

Persistent hepatitis C virus (HCV) infection is a major health problem globally affecting ~3% of the world population and is an important contributor to chronic liver disease culminating with liver cirrhosis, hepatocellular carcinoma and liver failure [Szabo E, Lotz G, et al., *Pathol. Oncol. Res*. 2003, 9, 215-221; Hoofnagle JH., *Hepatology* 1997, 26 15S-20]. An estimated 170 million chronic carriers worldwide are at risk of developing liver disease. In the United States alone ~3 million are chronically infected with HCV and the number of HCV related deaths is increasing significantly over the years [Barnes E., WHO factsheet 2010. Available at: http://www.who.int/vaccine_research/diseases/viral_cancers/en/index2.html].

Clinically, chronic infection is often asymptomatic with latent periods lasting for decades before manifestation by which time extensive liver damage has occurred. HCV is spread primarily by unscreened blood transfusions and use of contaminated needles and syringes; the highest risk groups are intravenous

targeting multiple essential viral functions, in addition to the current viral therapies will be required for effective global control of HCV.

Disclosures describing HCV inhibitors include US 2009/0202478, US 2009/0202483, WO 2009/020828, WO 2009/020825, WO 2009/102318, WO 2009/102325, WO 2009/102694, WO 2008/144380, WO 2008/021927, WO 2008/021928, WO 2008/021936, WO 2006/133326, WO 2004/014852, WO 2008/070447, WO 2009/034390, WO 2006/079833, WO 2007/031791, WO 2007/070556, WO 2007/070600, WO 2008/064218, WO 2008/154601, WO 2007/082554, WO 2008/048589, EP 2121697, US 8008264, US 8008263, US 2011/0217265, US 2011/0217261, US 8012982, US 8012942, US 8012941, US 2011/0223134, WO 2011/106992, WO 2011/106929, US 2011/0237636, US 20110/237579, US 2011/0236348, US 2011/0250176, US 2011/0250172, US 2011/269956, US 2011/274648, EP 2385048, US 2011/0281910, US 2011/0286961, US 2011/0294819, US 2011/0293563, US 2011/300104, WO 2011/156543, WO 2011/153396, WO 2011/151652, WO 2011/151651, US 2012/004196, US 8093243, US 8101643, US 2012/0028978, WO 2012/018534, WO 2012/018325, WO 2012/021704, WO 2012/021591, US 2012/0040977, US 2012/0040962, WO 2012/024363, EP 2086995, EP 2049116, US 8133884, US 2012/0076755, EP 2250163, US 8143414, US 8143301, US 8143288, US 2012/0083483, US 8147818, WO 2012/039717, WO 2012/041227, WO 2012/041014, EP 2146984, US 8188132, and US 8198449~~, the disclosure of which are incorporated by reference~~.

BRIEF SUMMARY OF THE INVENTION

The present invention provides antiviral compounds of the general formula (I):

Renilla-Glo Luciferase Assay kit from Promega as per the manufacturer's instructions. The following equation was used to generate the percent inhibition value for each test concentration.

$$\% \text{ Inhibition} = \frac{\text{Average Control (cells alone +0.5\% DMSO) - Average compound value(cells + drug)}}{\text{Average Control (cells alone+0.5\% DMSO)}} \times 100$$

The IC_{50} value was determined using GraphPad Prism and the following equation:

$$Y = \text{Bottom} + (\text{Top-Bottom})/(1+10\text{^}((\text{Log}IC_{50}\text{-X})*\text{Hill slope}))$$

IC_{50} values/% inhibitions of compounds were determined 2-3 times in the replicon assays.

Compounds of the present invention exhibited IC_{50} values in the range of 1 pM to 100 nM for inhibition of genotype 1b and 2a replicon of HCV, some of the representative results are provided below in table 1

Table 1

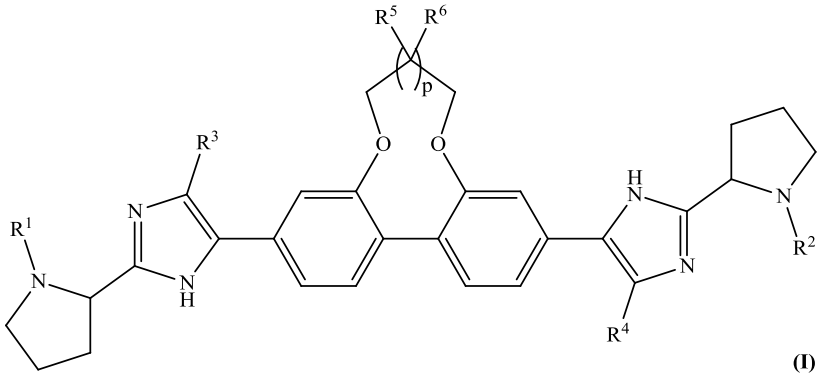
Compound	**Gt1b IC_{50}**	**Gt2a IC_{50}**
Compound 2	51 pM	53 pM
Compound 3	18 pM	37 pM
Compound 6	21 pM	671 pM
Compound 7	4 pM	249 pM

~~All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.~~

The use of the terms "a" and "an" and "the" and "at least one" and similar referents in the context of describing the invention (especially in the context of

CLAIMS

1. A compound of formula (I), its tautomeric forms, its ~~isomers~~stereoisomers, or pharmaceutically acceptable salts thereof,



(I)

wherein,

R^1 and R^2 are each independently selected from hydrogen, substituted- or unsubstituted- alkyl, substituted- or unsubstituted- cycloalkyl, substituted- or unsubstituted- aryl, substituted- or unsubstituted- heteroaryl, substituted- or unsubstituted- heterocyclyl, $R^{7a}C(=O)$-, $R^{7a}S(=O)_2$-, $R^{7a}OC(=O)$-, $(R^8)R^7NC(=O)$-, $R^{7a}OC(=O)N(R^8)CR^b(R^a)C(=O)$-, $R^{7a}OC(=O)N(R^8)CR^b(R^a)C(R^d)(R^c)C(=O)$-, $R^{7a}C(=O)N(R^8)C(R^b)(R^a)C(=O)$-, $R^{7a}C(=O)N(R^8)CR^b(R^a)C(R^d)(R^c)C(=O)$-, $(R^8)R^7NC(=O)N(R^9)C(R^b)(R^a)C(=O)$-, and $R^8(R^7)NC(=O)N(R^9)CR^b(R^a)C(R^d)(R^c)C(=O)$-;

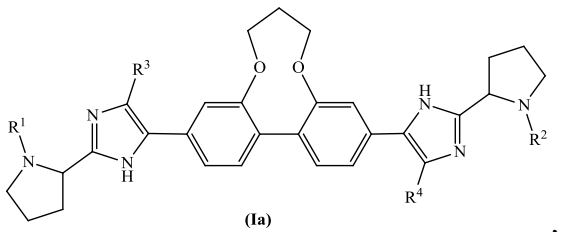
R^3 and R^4 are each independently selected from hydrogen, halogen, substituted- or unsubstituted- alkyl, and substituted- or unsubstituted- cycloalkyl;

R^5 and R^6 are independently selected ~~form~~from hydrogen, substituted- or unsubstituted- alkyl; or

R^5 and R^6 are groups, which together with the carbon atom to which they are attached form a substituted- or unsubstituted- 3 to 6 membered carbocycle or a substituted- or unsubstituted- 5 to 6 membered heterocycle; or R^5 and R^6 are groups, wherein two R^5 groups attached to two different carbon atoms, two R^6 groups attached to two different

R^{10a} is selected from hydrogen, alkyl, perhaloalkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl.

2. The compound of formula (I), its tautomeric form, its ~~isomer~~stereoisomers, or its pharmaceutically acceptable salt, as claimed in claim 1, wherein compound of formula I is selected from



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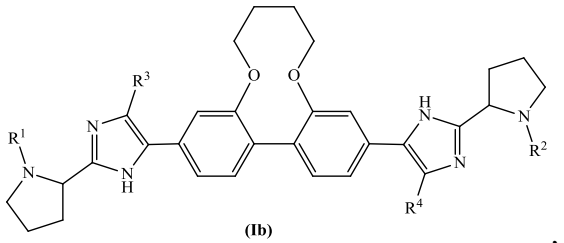
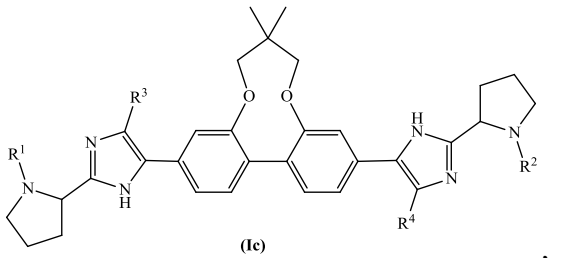


(Ib) ,



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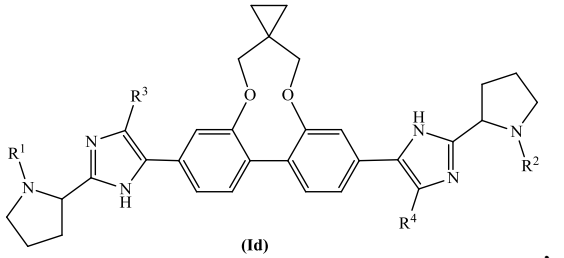

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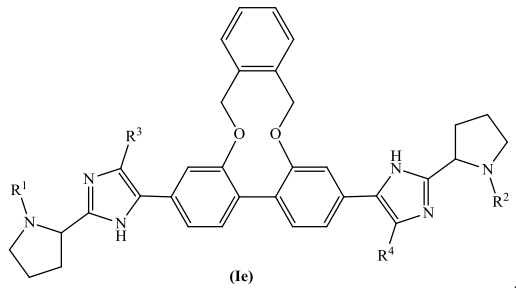

(Ie) and .

3. The compound of formula (I), its tautomeric form, its ~~isomer~~stereoisomers, or its pharmaceutically acceptable salt, as claimed in claim 1 or 2, wherein R^1 and R^2 are selected from $R^{7a}C(=O)$-, $R^{7a}S(=O)_2$-, $R^{7a}OC(=O)$-, $(R^8)R^7NC(=O)$-, $R^{7a}OC(=O)N(R^8)CR^b(R^a)C(=O)$-, $R^{7a}OC(=O)N(R^8)CR^b(R^a)C(R^d)(R^c)C(=O)$-, $R^{7a}C(=O)N(R^8)C(R^b)(R^a)C(=O)$-, $R^{7a}C(=O)N(R^8)CR^b(R^a)C(R^d)(R^c)C(=O)$-, $(R^8)R^7NC(=O)N(R^9)C(R^b)(R^a)C(=O)$-, and $R^8(R^7)NC(=O)N(R^9)CR^b(R^a)C(R^d)(R^c)C(=O)$-.

4. The compound of formula (I), its tautomeric form, its ~~isomer~~stereoisomers, or its pharmaceutically acceptable salt, as claimed in any one of claims 1 to 3, wherein R^1 and R^2 are selected from $R^{7a}OC(=O)N(R^8)CR^b(R^a)C(=O)$-, $R^{7a}OC(=O)N(R^8)CR^b(R^a)C(R^d)(R^c)C(=O)$-, $R^{7a}C(=O)N(R^8)C(R^b)(R^a)C(=O)$-, $R^{7a}C(=O)N(R^8)CR^b(R^a)C(R^d)(R^c)C(=O)$-, $(R^8)R^7NC(=O)N(R^9)C(R^b)(R^a)C(=O)$-, and $R^8(R^7)NC(=O)N(R^9)CR^b(R^a)C(R^d)(R^c)C(=O)$-.

5. The compound of formula (I), its tautomeric form, its ~~isomer~~stereoisomers, or its pharmaceutically acceptable salt, as claimed in any one of claims 1 to 4, wherein R^1 and R^2 both are specifically selected as $R^{7a}OC(=O)N(R^8)CR^b(R^a)C(=O)$-.

6. The compound of formula (I), its tautomeric form, its ~~isomer~~stereoisomers, or its pharmaceutically acceptable salt, as claimed in any one of claims 1 to 5, wherein R^3 and R^4 are selected independently from hydrogen, chloro, ethyl, and cyclopropyl.

7. The compound of formula (I), its tautomeric form, its ~~isomer~~stereoisomers, or its pharmaceutically acceptable salt, as claimed in any one of claims 1 to 6, wherein the compound is selected from

dimethyl ((2*S*,2'*S*)-((2*S*,2'*S*)-2,2'-(5,5'-(7,8-dihydro-6*H*-dibenzo[*f,h*][1,5]dioxonine-3,11-diyl)bis(1*H*-imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl))dicarbamate;

methyl ((*S*)-1-((*S*)-2-(5-(11-(2-((*S*)-1-((*S*)-2-(methoxycarbonyl)amino-3-methylbutanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)-7,8-dihydro-6*H*-