seroepidemiological investigation in China showed that the ratio of a person having anti-HCV antibodies in a general population was 3.2%.

HBV and HCV belong to different viral genera respectively, although they both belong to the hepatitis virus and have a similar route of infection. HBV belongs to the hepadnaviridae family and is made of a partially double-stranded circular DNA, while HCV belongs to the flaviviridae family and is a positive-sense single-strand RNA virus. At present, clinical anti-HBV drugs are mainly nucleoside drugs, such as lamivudine, famciclovir, lobucavir, adefovir dipivoxiil, FTC (2',3'-dideoxy-5-fluoro-3'-thiacytidine)、FMAU (1-(2-fluoro-5- methyl-beta,L-arabinofuranosyl)uracil), FDDC (5-fluoro-2',3'-dideoxycytidine) 、 BMS 200475 (9-[4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]guanine), and enticavir ~~and the like~~. Since HBV and HCV belong to different viral genera, the existing anti-HBV drugs can not be used for treating Hepatitis C. So far, no effective small molecule drugs for HCV can be used in clinic. Presently, the most effective therapeutic regimen for HCV is the combined administration of interferon and broad-spectrum antiviral agent, such as interferon and ribavirin. But such combined administration only has a sustainable curative effect of less than 40% with serious adverse effect.

Therefore, as , it is always a focus for domestic and foreign pharmaceutical scientists to explore and develop a drug for treatment of viral hepatitides.

International application No. PCT/CN2007/001861 (International Publication No. WO 2007/147336), which is a previous international patent application of the present applicant, discloses a class of heterocyclic non-nucleoside compounds and the anti-HBV bioactivity thereof, and the compounds are useful for treating viral hepatitis B. However, the subsequent research reveals that some of the compounds exhibit poor pharmacokinetic parameters, especially bioavailability. For example, the oral bioavailability of Compound W28F in male rats (10mg/kg) is only 2.80%. Thereby, there is an urgent demand to further modify the compounds so as to improve their bioavailability while maintaining their strong antiviral activity.

The present applicant incorporated a hydroxyl, a halogen atom or a double bond into the side chain at 5-site of thiazole ring of the 2',2-bisthiazole non-nucleoside compounds among the above compounds based on the original structure. The obtained compounds not only retain the same anti-HBV bioactivity as the original ones, but also show effectively improved bioavailability. Extensive research reveals that, besides the anti-HBV bioactivity, such novel 2',2-bisthiazole non-nucleoside compounds have an anti-HCV bioactivity.

through hydrolyzation into a corresponding acid, which reacts with a halogenated benzylamine in the presence of a condensing agent such as EDCI (1-ethyl-(3-dimethylaminopropyl) carbodiimide hydrochloride) to produce the class of 2',2-bisthiazole heterocyclic compounds of the present disclosure.

The novel class of 2',2-bisthiazole non-nucleoside heterocyclic compound provided by the present disclosure exhibits activities against both HBV and HCV, and thus can be used in treatment of hepatitis B and hepatitis C. Pharmacokinetic tests reveal that those compounds have good bioavailability and thus can be used to prepare drugs for treating hepatitis B and/or hepatitis C

The present disclosure provides a method for treating hepatitis B or hepatitis C, comprising administrating a therapeutically effective amount of the 2',2-bisthiazole non-nucleoside compound of the present disclosure to a subject suffering from hepatitis B or hepatitis C.

The present discloser further provides a pharmaceutical composition against viral hepatitis B and/or viral hepatitis C, which comprises a therapeutically effective amount of one or more of the 2',2-bisthiazole non-nucleoside compounds of the present disclosure as an active component, and may further comprise pharmaceutically acceptable adjuvants, such as a dispersant, an excipient, a disintegrant, an antioxidant, a sweetening agent, or a coating agent~~, etc~~. The composition can be prepared by a conventional method in the field of pharmacy, and can be formulated into various routine dosage forms, such as tablet, coating tablet, capsule, or powder~~, etc~~.

Advantageous Effect

The present invention designs and synthesizes a novel class of 2',2-bisthiazole non-nucleoside compounds, which can effectively inhibit the replication of HBV and HCV and thus can be used in treatment of viral hepatitis B and/or viral hepatitis C. Compared with the similar compounds disclosed previously in International Application No. PCT/CN2007/001861 (International Publication No. WO 2007/147336) by the present inventors, the novel 2',2-bisthiazole non-nucleoside compound of the present disclosure exhibits an anti-HCV activity while maintaining the anti-HBV activity, and overcomes the defect of low bioavailability of the previous compounds due to the incorporation of a polar group, such as double bond, hydroxyl, alkoxyl, or halogen atom~~, etc.~~, on the side chain, and thus possesses a good prospect of development.

Best Mode for Carrying Out the Invention

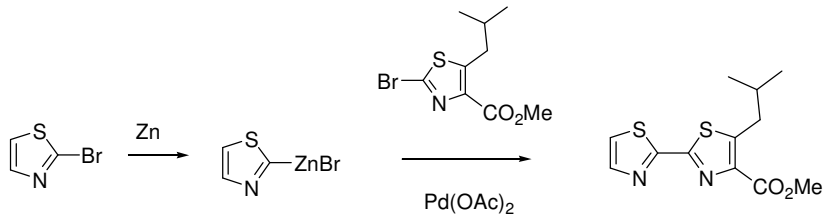
The invention will be described in detail in connection with the specific examples. However, the present invention is not limited to these examples.

Preparation Examples

In the following examples, NMR spectra were obtained on a Mercury-Vx 300M spectrometer from Varian. NMR calibration: **δ H 7.26 ppm ($CDCl_3$).** Mass spectra were obtained on a Agilent 1200 Quadrupole LC/MS instrument. Most reagents were provided by Shanghai Chemical Company. The silica gel plate (Model: HSGF 254) for thin-layer chromatography were produced by Huiyou silica development company, Yantai, Shandong. The silica gel (Model: zcx-11, 200-300 mesh) used in the normal phase column chromatography for purifying the compounds was produced by branch of Qingdao haiyang chemical plant.

Preparation Example 1 Synthesis of intermediate methyl 2',2-bisthiazole-4-carboxylates

(1) Methyl 5-isobutyl-2',2-bisthiazole-4-carboxylate



An activated Zn powder (84 g) was added into a 2L three-necked bottle, and a fresh THF (600ml) was added thereinto. When the mixture was heated to a inside temperature of about 60 °C, a solution of 2-bromothiazole (200 g) in anhydrous THF (60ml) was dropwise added over about 3- 4 hours. The reaction was continued under reflux. The resultant zinc reagent was transferred into a solution of methyl 2-bromo-5-isobutylthiazole-4-carboxylate (233 g), palladium acetate (9.4 g) and triphenylphosphine (22 g) in anhydrous toluene solution (1.2 L), and heated to 80-85 °C and kept at this temperature for 1-1.5 hours. After cooling to room temperature, a 5% HCl aqueous solution (2L) was added into the reaction mixture to separate the organic phase, and the aqueous phase was extracted with ethyl acetate. The combined organic phase was washed with a 5% HCl aqueous solution, and concentrated to obtain a brown-black oil, which was recrystallized in methanol to obtain methyl 5-isobutyl-2',2-bisthiazole-4-carboxylate as a yellowish solid (162 g). Molar yield: 69%.

^{1}HNMR($CDCl_3$): δ 1.00(s, 3H), 1.02(s, 3H), 2.03(m, 1H), 3.17-3.19(d, *J* = 7.2Hz, 2H), 3.96(s, 3H), 7.46-7.47(d, *J* = 3.3Hz, 1H), 7.87-7.88(d, *J* = 3.3Hz, 1H).

ESI-MS (*m/z*): 305.1 $(M+Na)^+$ (Calculated for $C_{12}H_{14}N_2NaO_2S_2$: 305.04).