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Mini-review

Recent progress in potential anti-hepatitis B virus agents: Structural and pharmacological perspectives

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ABSTRACT

Hepatitis B virus (HBV) infections affect about 240 million patients worldwide and increase the risk of liver cirrhosis and hepatocellular carcinoma. It is estimated that about 686 thousand people died annually of liver damage resulted from HBV infections. At present, two classes of antiviral drugs have been approved by the Food and Drug Administration (FDA) for the treatment of hepatitis B, immunomodulators (interferon [IFN]-a and pegylated-interferon [PEG-IFN]-a) and nucleos(t)ide analogs (lamivudine, telbivudine, adefovir, tenofovir [TDF], and entecavir [ETV]). However, it still remains a daunting challenge for curing HBV, because of the low sustained response rates (20–30%) and many side effects of IFN and peg-IFN. Although nucleoside analogues are well tolerated and exhibit an early and potent antiviral effect, the selection of resistant mutants and nephrotoxicity during long-term therapy limit their use. Here, we focus on summarizing the currently approved *anti*-HBV drugs and characterization of novel HBV inhibitors and analysing their structures, targets, *anti*-HBV effects and mechanisms of action, which may shed new light on the discovery of small compounds as potential *anti*-HBV drugs for treatment of HBV.

1. Introduction

Hepatitis B virus (HBV), the most well-known member of the Hepadnaviridae family, is a small, circular, enveloped, and partially double-stranded DNA virus harboring only four overlapping reading frames that encode for precore/core, polymerase, envelop and X proteins [1,2]. Chronic HBV reinfection remains a common public health issue worldwidely, which is strongly associated with hepatitis, cirrhosis, and hepatocellular carcinomas [3,4]. Indeed, approximately 240 million people around the world are chronically infected and it contributes to 686,000 deaths annually [5,6].

At present, there are several nucleos(t)ide analogues that have been approved by the Food and Drug Administration (FDA) for the treatment of hepatitis B, including lamivudine, telbivudine, adefovir, tenofovir, and entecavir [4]. A major limitation of nucleos(t)ide analogues treatments for HBV infection is the rapid development of resistant variants. The emerging of a reversal of viral suppression and histological improvement will exacerbate HBV-related diseases [7]. Both lamivudine and telbivudine belong to L-nucleosides, resulting in chain termination and prevention of viral replication. Entecavir's mechanism is that it inhibits three functions of the HBV DNA polymerase: promoting the HBV DNA polymerase, synthesizing the positive strand HBV DNA and reversing transcription of the negative strand [8,9]. Viral mutations limit the use of currently approved *anti*-HBV drugs [10,11]. Thus, it is of great interest to discover *anti*-HBV agents which are effective against drug-resistant HBV mutants.

Considering the extensive pathways of HBV, in this review, we

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Table 1
Potential agents for chronic hepatitis B therapy.

NO.	Compound name	Mechanisms	Experimental model	Clinical trial	References
1	Cyclosporin A	Inhibiting HBV entry by targeting a specific binding receptor (NTCP)	HepG2 cells	–	[48]
2	SCY446	Inhibiting HBV entry by targeting a specific binding receptor (NTCP)	HepG2 cells	–	[48]
3	SCY450	Inhibiting HBV entry by targeting a specific binding receptor (NTCP)	HepG2 cells	–	[48]
4	SCYX618806	Inhibiting HBV entry by targeting a specific binding receptor (NTCP)	HepaRG, HepAD38, PHHs cells	–	[51]
5	SCYX1774198	Inhibiting HBV entry by targeting a specific binding receptor (NTCP)	HepaRG, HepAD38, PHHs cells	–	[51]
6	SCYX827830	Inhibiting HBV entry by targeting a specific binding receptor (NTCP)	HepaRG, HepAD38, PHHs cells	–	[51]
7	SCYX1454139	Inhibiting HBV entry by targeting a specific binding receptor (NTCP)	HepaRG, HepAD38, PHHs cells	–	[51]
8	Ezetimibe	Inhibiting HBV entry by targeting a specific binding receptor (NTCP)	Huh7 cells	–	[43,44]
9	NTI007	Inhibiting HBV entry by targeting a specific binding receptor (NTCP)	HepG2.2.15 cells	–	[52]
10	Vanitaracin A	Inhibiting HBV entry by targeting a specific binding receptor (NTCP)	HepG2-hNTCP-C4, Hep38.7-Tet, Huh-7.5.1 cells	–	[53]
11	Azelastine hydrochloride (N4)	Inhibiting HBV entry by targeting a specific binding receptor (NTCP)	HepG2.2.15 cells	–	[54]
12	Irbesartan	Inhibiting HBV entry by targeting a specific binding receptor (NTCP)	HepG2 cells	–	[55]
13	Epigallocatechin-3-gallate (EGCG)	Inhibiting HBV entry by targeting a specific binding receptor (NTCP)	HepG2.2.15 cells	–	[56]
14	Ginkgolic acid (13:0)	Inhibiting HBV entry by targeting a specific binding receptor (NTCP)	HepG2.2.15 cells	–	[57]
15	Ginkgolic acid (15:1)	Inhibiting HBV entry by targeting a specific binding receptor (NTCP)	HepG2.2.15 cells	–	[57]
16	OHBF-C	Inhibiting HBV entry by targeting a specific binding receptor (NTCP)	HepG2 cells	–	[55]
17	Ritonavir	Inhibiting HBV entry by targeting a specific binding receptor (NTCP)	HepG2.2.15 cells	–	[58]
18	Myrcludex-B	Inhibiting HBV entry by targeting a specific binding receptor (NTCP)	HepG2.2.15 or HepAd38 cells	phase IIa	[40]
19	Bay41-4109	Blocking the normal formation of nucleocapsids	HBV-transgenic mice	–	[61,62]
20	Bay 38-7690	Blocking the normal formation of nucleocapsids	HBV-transgenic mice	–	[61,62]
21	Bay 39-5493	Blocking the normal formation of nucleocapsids	HBV-transgenic mice	–	[61,62]
22	SBA-R01	Blocking the normal formation of nucleocapsids	HepG2.2.15 cells	–	[67]
23	BA-26019	Blocking the normal formation of nucleocapsids	HepG2, AML12 cells	–	[68]
24	BA-38017	Blocking the normal formation of nucleocapsids	HepG2, AML12 cells	–	[68]
25	JNJ-632	Blocking the normal formation of nucleocapsids	HepG2.2.15 cells	–	[69]
26	HAP18	Blocking the normal formation of nucleocapsids	*Escherichia coli* cells	–	[70]
27	HAP1	Blocking the normal formation of nucleocapsids	*Escherichia coli* cells	–	[70]
28	34a	Blocking the normal formation of nucleocapsids	HepDE19 cells	–	[71]
29	GLS4	Blocking the normal formation of nucleocapsids	HepAD38, HepG2.2.15 cells	–	[72–75]
30	Pyridazinone Derivative compound 3711	Blocking the normal formation of nucleocapsids	HepG2.2.15, Huh7 cells	–	[76]
31	AT-61	Preventing the encapsidation of viral pregenomic RNA into nucleocapsid	HepG2 cells	–	[64–66]
32	AT-130	Preventing the encapsidation of viral pregenomic RNA into nucleocapsid	HepG2 cells	–	[64–66]
33	TAF	Inhibiting potent polymerase	HepG2.2.15 cells	Approved	[78–84]
34	LB80380	Inhibiting potent polymerase	HepG2.2.15 cells	approved in South Korea	[84–85]
35	Clevudine	Inhibiting potent polymerase	HepG2.2.15 cells	–	[86]
36	B-L-Hyd4C	Inhibiting potent polymerase	HepG2.2.15 cells	–	[87]
37	B-L-MetCdR	Inhibiting potent polymerase	HepG2.2.15 cells	–	[87]
38	CCC0975	Inhibiting relax-circular DNA to cccDNA conversion	HepG2.2.15, HepDE19, HepDES19 cells	–	[91]
39	CCC0346	Inhibiting relax-circular DNA to cccDNA conversion	HepG2.2.15, HepDE19, HepDES19 cells	–	[91]
40	FIT039	Reduce cccDNA	HepG2.2.15, Hep38.7-Tet cells	–	[92]
41	Punicalagin	Preventing cccDNA format and promot cccDNA decay	HepG2.2.15, HepG2.117, HepDES19 cells	–	[93]
42	Punicalin	Preventing cccDNA format and promot cccDNA decay	HepG2.2.15, HepG2.117, HepDES19 cells	–	[93]
43	Geraniin	Preventing cccDNA format and promot cccDNA decay	HepG2.2.15, HepG2.117, HepDES19 cells	–	[93]
44	MH	Inhibiting cccDNA format	HepG2.2.15 cells	–	[95]
45	Helioxanthin	Inhibiting HBV DNA, RNA and protein expression	HepG2.2.15 cells	–	[96]
46	Helioxanthin analogue	Inhibiting HBV DNA, RNA and protein expression	HepG2.2.15 cells	–	[97]
47	Sulfonamide derivative I	Site-specific cleavage of DNA	HepG2.2.15 cells	–	[98]