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(54) **Title**: HEPATITIS B ANTIVIRAL AGENTS

(57) **Abstract**: The present invention discloses compounds of Formula (I), or pharmaceutically acceptable salts, esters, or prodrugs thereof: X-A_1-Y-A_2-Z-L-R (I) which inhibit the protein(s) encoded by hepatitis B virus (HBV) or interfere with the function of the HBV life cycle of the hepatitis B virus and are also useful as antiviral agents. The present invention further relates to pharmaceutical compositions comprising the aforementioned compounds for administration to a subject suffering from HBV infection. The invention also relates to methods of treating an HBV infection in a subject by administering a pharmaceutical composition comprising the compounds of the present invention.

HEPATITIS B ANTIVIRAL AGENTS

RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 62/195,674, filed on July 22, 2015. The entire teachings of the above application are incorporated herein by reference.

TECHNICAL FIELD

The present invention relates generally to novel antiviral agents. Specifically, the present invention relates to compounds which can inhibit the protein(s) encoded by hepatitis B virus (HBV) or interfere with the function of the HBV life cycle, compositions comprising such compounds, methods for inhibiting HBV viral replication, methods for treating or preventing HBV infection, and processes for making the compounds.

BACKGROUND OF THE INVENTION

HBV infection remains a major public health problem, affecting approximately 2 billion people worldwide. Among them, 350 million people worldwide and 1.4 million in the US develop a chronic infection, which can lead to chronic persistent hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC). Every year 500,000 to 1 million people die from the end stage of liver diseases caused by HBV infection.

Despite the availability of a prophylactic HBV vaccine, the burden of chronic HBV infection continues to be a significant unmet worldwide medical problem, due to suboptimal treatment options and sustained rates of new infections in most parts of the developing world. Current treatments do not provide a cure and are limited to only two classes of agents (interferon and nucleoside analogues/inhibitors of the viral polymerase); drug resistance, low efficacy, and tolerability issues limit their impact. The low cure rates of HBV are attributed at least in part to the presence and persistence of covalently closed circular DNA (cccDNA) in the nucleus of infected hepatocytes. However, persistent suppression of HBV DNA slows liver disease progression and helps to prevent HCC. Current therapy goals for HBV-infected patients are directed to reducing serum HBV DNA to low or undetectable levels, and to ultimately reducing or preventing the development of cirrhosis and HCC.

The HBV is an enveloped, partially double-stranded DNA (dsDNA) virus of the hepadnavirus family *(Hepadnaviridae)*. HBV capsid protein (CP) plays essential roles in

HBV replication. The predominant biological function of capsid protein is to act as a structural protein to encapsidate pre-genomic RNA and form immature capsid particles, which spontaneously self-assemble from many copies of core dimers in the cytoplasm. Capsid protein also regulates viral DNA synthesis through different phosphorylation status of its C-terminal phosphorylation sites. Also, capsid protein might facilitate the nuclear translocation of viral relaxed circular genome by means of the nuclear localization signals located in the Arginine-rich domain of the C-terminal region of capsid protein. In the nucleus, as a component of viral cccDNA minichromosome, capsid protein could play a structural and regulatory role in the functionality of cccDNA minichromosomes. Capsid protein also interacts with viral large envelope protein in endoplasmic reticulum (ER) and triggers the release of intact viral particles from hepatocytes.

Capsid related anti-HBV inhibitors have been reported. For example, phenylpropen-amide derivatives, including compounds named AT-61 and AT-130 (Feld J. et al. Antiviral Res. 2007, 76, 168), and a class of thiazolidin-4-ones from Valeant (W02006/033995), have been shown to inhibit pregenomic RNA (pgRNA) packaging. Heteroaryldihydropyrimidines or HAPs were discovered in a tissue culture-based screening (Weber et al., Antiviral Res. 2002, 54, 69). These HAP analogs act as synthetic allosteric activators and are able to induce aberrant capsid formation that leads to degradation of the core protein. A subclass of sulphamoyl-arylamides also shows activity against HBV (WO2013/006394, WO2013/ 096744, and WO 2014/184365). It was also shown that the small molecule bis-ANS acts as a molecular 'wedge' and interferes with normal capsid-protein geometry and capsid formation (Zlotnick A. et al. J. Virol. 2002, 4848).

There is a need in the art for novel therapeutic agents that treat, ameliorate or prevent HBV infection. Administration of these therapeutic agents to an HBV infected patient, either as monotherapy or in combination with other HBV treatments or ancillary treatments, will lead to significantly improved prognosis, diminished progression of the disease, and enhanced seroconversion rates.

SUMMARY OF THE INVENTION

The present invention relates to novel antiviral compounds, pharmaceutical compositions comprising such compounds, as well as methods to treat or prevent viral (particularly HBV) infection in a subject in need of such therapy with said compounds. Compounds of the present invention inhibit the protein(s) encoded by hepatitis B virus

(HBV) or interfere with the life cycle of HBV and are also useful as antiviral agents. In addition, the present invention includes the process for the preparation of the said compounds.

In its principal aspect, the present invention provides a compound of Formula (**I**):

$$X-A_1-Y-A_2-Z-L-R \quad (I)$$

or a pharmaceutically acceptable salt thereof, wherein:

X is an optionally substituted aryl or optionally substituted heteroaryl; preferably X is an optionally substituted phenyl;

A_1 is absent, or selected from the group consisting of –NH–, –NHC(O)–, –NHC(O)NR_3–, and optionally substituted azolyl;

Y is an optionally substituted aryl or optionally substituted heteroaryl; preferably Y is an optionally substituted phenyl, optionally substituted thiophenyl, or optionally substituted azolyl;

A_2 is absent or –NR_4-;

Z is –CR^aR^b-; wherein R^a and R^b are each independently selected from the group consisting of hydrogen, OH, OMe, halogen, and methyl optionally substitituted with 1 to 3 substituents selected from the group consisting of fluoro, chloro, OH, and OMe; wherein at least one of R^a and R^b is not hydrogen; preferably, Z is –CF_2-, –$C(CH_2F)_2$-, or –$CH(CF_3)$-;

Alternatively, R^a, R^b, and the carbon atom to which they are attached to form an oxetanyl, 5- to 6-membered cyclic ketal, or -C(=CF_2)-;

L is –NR_1-, O or -CR_1R_2-; and

R, R_1, R_2, R_3 and R_4 at each occurrence are independently selected from the group consisting of hydrogen, optionally substituted –C_1-C_8 alkyl, optionally substituted –C_2-C_8 alkenyl, optionally substituted –C_2-C_8 alkynyl, optionally substituted –C_3-C_8 cycloalkyl, optionally substituted 3- to 8-membered heterocyclic, optionally substituted aryl and optionally substituted heteroaryl; alternatively, R_1 and R_2 or R_1 and R are taken together with the atom to which they are attached to form an optionally substituted C_3-C_8 cycloalkyl or an optionally substituted 3- to 8-membered heterocyclic. Preferably R is terminally substituted C_1-C_4-alkyl, more preferably terminally substituted C_2-alkyl.

Each preferred group stated above can be taken in combination with one, any or all other preferred groups.

DETAILED DESCRIPTION OF THE INVENTION

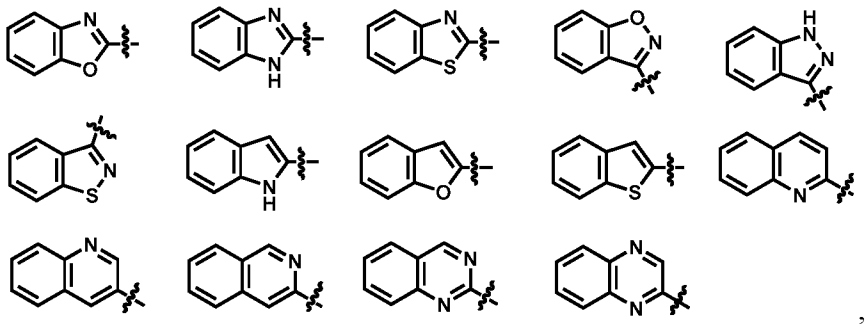
In one embodiment of the present invention is a compound of Formula (**I**) as described above, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts thereof, wherein X is optionally substituted phenyl. In one embodiment, X is a phenyl optionally substituted with one or more substituents selected from halo, CN, OH, OMe, Me, -CO_2Me, and cyclopropyl. In another embodiment, X is a fluoro- or cyano-substituted phenyl. In yet another embodiment, X is 3,4,5-trifluorophenyl.

In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts thereof, wherein X is optionally substituted monocyclic heteroaryl. In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts thereof, wherein X is optionally substituted bicyclic heteroaryl.

In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts thereof, wherein X is benzimidazolyl, benzothiazolyl, benzoxazolyl, indazolyl, quinolyl, isoquinolyl or quinazolyl; each optionally substituted.

In another embodiment, the present invention relates to compounds of Formula (**I**), or a pharmaceutically acceptable salt thereof, wherein X is a bicyclic heteroaryl group derived from the groups set forth below:



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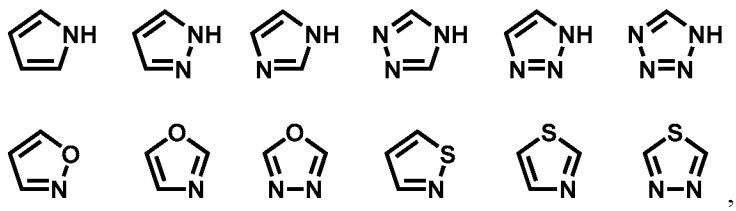
wherein each of the above shown groups is optionally substituted when possible.

In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts thereof, wherein A_1 is absent. In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts thereof, wherein A_1 is –NHC(O)–. In certain embodiments, the present invention relates to compounds of Formula (**I**), and

pharmaceutically acceptable salts thereof, wherein A_1 is –NH–. In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts thereof, wherein A_1 is –NHC(O)NR_3–. In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts thereof, wherein A_1 is an optionally substituted azolyl.

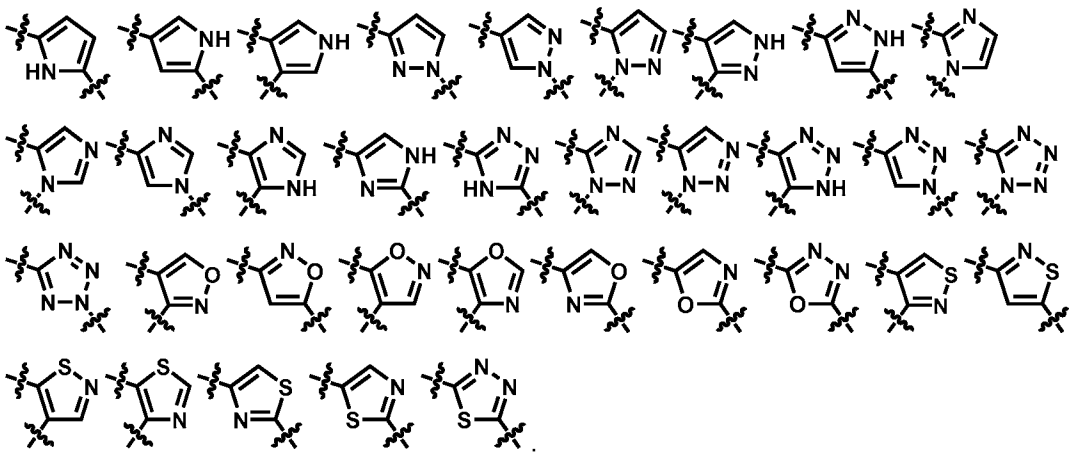
In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts thereof, wherein A_1 is an optionally substituted imidazolyl, optionally substituted pyrazolyl, or optionally substituted triazolyl.

In another embodiment, the present invention relates to compounds of Formula (**I**), or a pharmaceutically acceptable salt thereof, wherein A_1 is an azolyl group derived from one of the following, or a tautomer thereof, by removal of two hydrogen atoms:



wherein each of the above shown azole groups is optionally substituted when possible and it may be connected to groups X and Y through either carbon or, when possible, nitrogen.

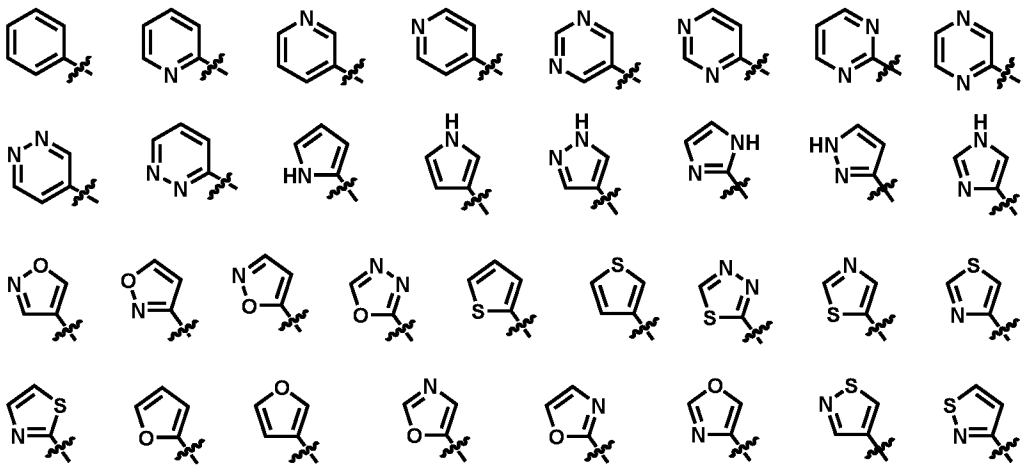
In certain embodiments, A_1 is selected from the groups set forth below, and can optionally be substituted when possible:



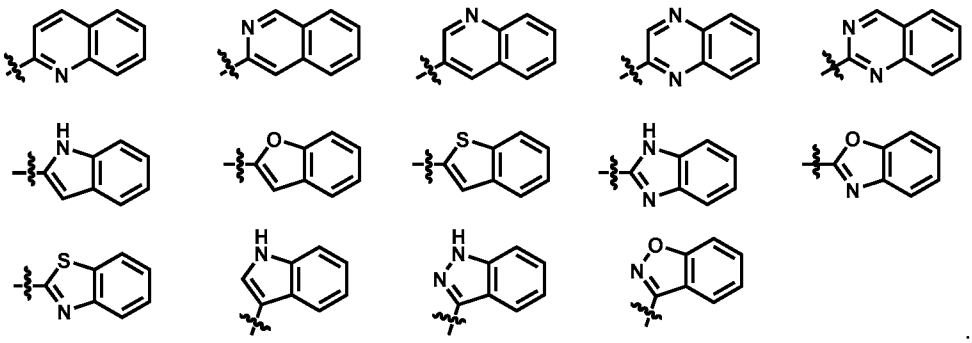
In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts thereof, wherein A_1 is an optionally substituted azolyl and is connected to groups X and Y in a relative 1,3-*meta*-substitution position pattern.

In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salt thereof, wherein Y is optionally substituted phenyl. In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts thereof, wherein Y is optionally substituted monocyclic heteroaryl. In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts thereof, wherein Y is optionally substituted bicyclic heteroaryl. In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts thereof, wherein Y is optionally substituted azolyl.

In certain embodiments, Y is preferably selected from the groups set forth below, which can be optionally substituted; wherein the second connection point of Y can be at any available carbon atom of a phenyl ring or any available carbon or nitrogen atom of a heteroaryl ring:



In certain embodiments, Y is preferably selected from the groups set forth below, which can be optionally substituted; wherein the second connection point of Y is preferably at any available carbon atom of the fused benzo ring:



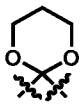
In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts thereof, wherein X is optionally substituted phenyl; and Y is optionally substituted phenyl or optionally substituted monocyclic heteroaryl.

In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts thereof, wherein X is optionally substituted monocyclic heteroaryl; and Y is optionally substituted phenyl.

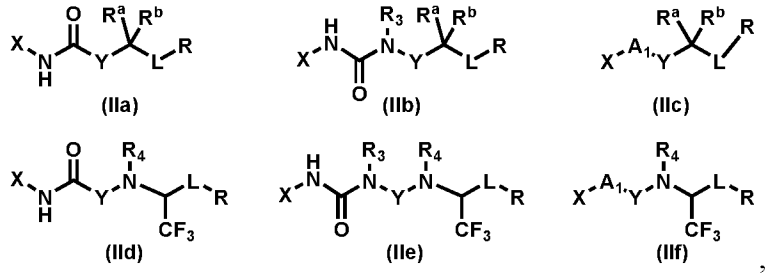
In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts thereof, wherein X and Y are each independently phenyl optionally substituted with one to more substituents selected from the group consisting of halo, CN, and optionally substituted methyl.

In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts thereof, wherein X is optionally substituted phenyl; Y is optionally substituted phenyl or optionally substituted azolyl; and A_1 is –NHC(O)- or –NHC(O)NR_1-.

In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts thereof, wherein X is optionally substituted phenyl; Y is optionally substituted phenyl or optionally substituted azolyl; and A_1 is independently an optionally substituted azolyl.

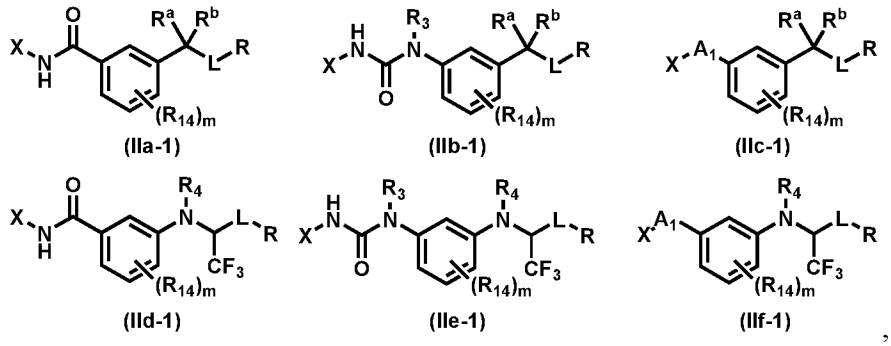
In certain embodiments, the present invention relates to compounds of Formula (**I**), or a pharmaceutically acceptable salt thereof, wherein Z is –CF_2-. In certain embodiments, the present invention relates to compounds of Formula (**I**), or a pharmaceutically acceptable salt thereof, wherein Z is –CClF-. In certain embodiments, the present invention relates to compounds of Formula (**I**), or a pharmaceutically acceptable salt thereof, wherein Z is –CCl_2-. In certain embodiments, the present invention relates to compounds of Formula (**I**), or a pharmaceutically acceptable salt thereof, wherein Z is –CH(CF_3)-. In certain embodiments, the present invention relates to compounds of Formula (**I**), or a pharmaceutically acceptable salt thereof, wherein Z is –C(=CF_2)-. In certain embodiments, the present invention relates to compounds of Formula (**I**), or a pharmaceutically acceptable salt thereof, wherein Z is  ,  , or  .

In another embodiment, the compound of Formula (**I**) is represented by Formula (**IIa**), (**IIb**), (**IIc**), (**IId**), (**IIe**), or (**IIf**), or a pharmaceutically acceptable salt thereof:



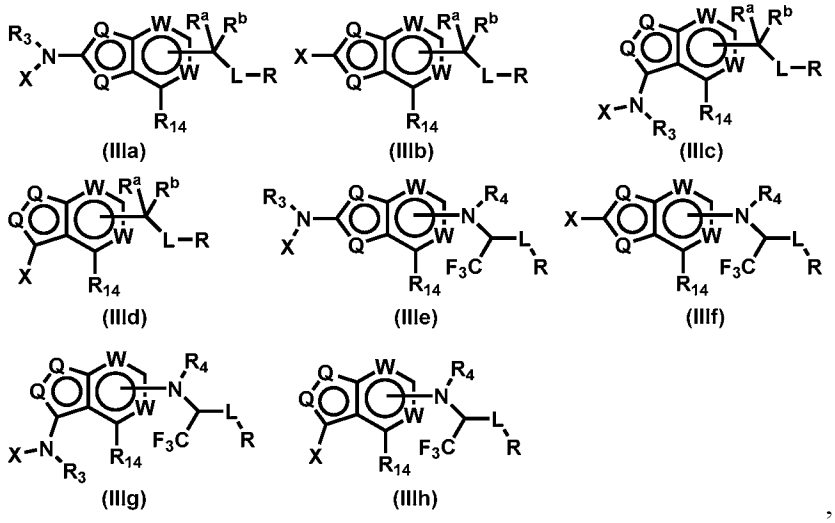
wherein A_1 is an optionally substituted azolyl, and is preferably carbon-connected to groups X and Y; and X, Y, L, R_3, R_4, R, R^a, and R^b are as previously defined.

In another embodiment, the compound of Formula (**I**) is represented by Formula (**IIa-1**), (**IIb-1**), (**IIc-1**), (**IId-1**), (**IIe-1**), or (**IIf-1**), or a pharmaceutically acceptable salt thereof:



wherein R_{14} at each occurrence is independently selected from the group consisting of hydrogen, OH, protected OH, halo, -CN, $-NO_2$, amino, protected amino, optionally substituted $-C_1$-C_6 alkyl, optionally substituted $-C_2$-C_8 alkenyl, optionally substituted $-C_2$-C_8 alkynyl, optionally substituted $-C_3$-C_8 cycloalkyl, optionally substituted 3- to 8-membered heterocyclic, optionally substituted $-C_1$-C_6 alkoxy, $-C(O)-O-C_1$-C_6 alkyl, $-C(O)NH-C_1$-C_6 alkyl, and $-C(O)-C_1$-C_6 alkyl; m at each occurrence is each independently 0, 1, 2, 3 or 4; A_1 is optionally substituted azolyl; and X, L, R, R_3, R_4, R^a, and R^b are as previously defined.

In another embodiment, the compound of Formula (**I**) is represented by Formula (**IIIa**), (**IIIb**), (**IIIc**), (**IIId**), (**IIIe**), (**IIIf**), (**IIIg**), or (**IIIh**), or a pharmaceutically acceptable salt thereof:



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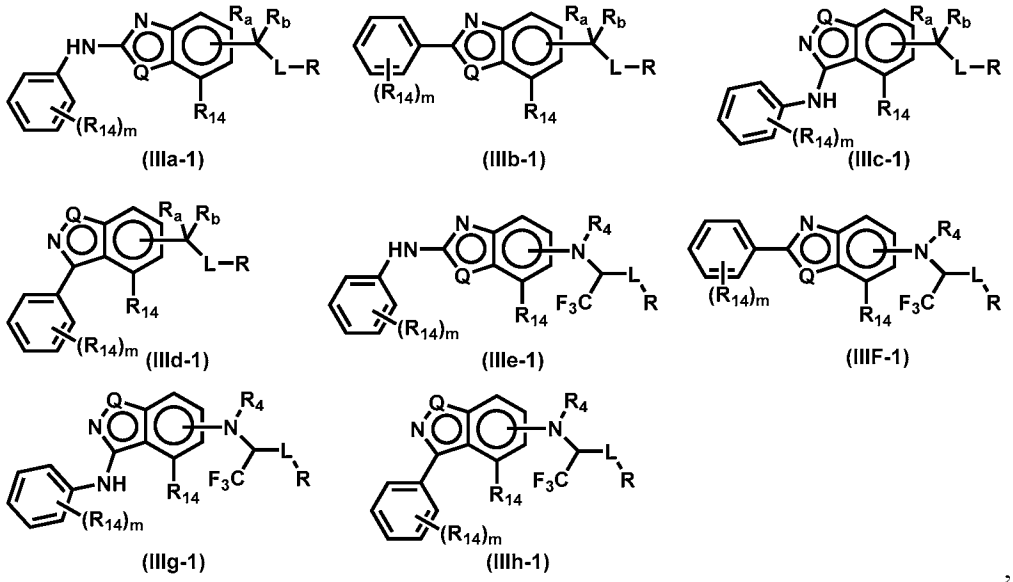
wherein W at each occurrence is independently selected from N or CR_{14}; each Q is independently N, NR_{11}, CR_{12}, O or S, preferably one Q is N or CR_{12} and the other Q is O, S, or NR_{11}; R_{11} at each occurrence is each independently selected from the groups consisting of hydrogen, optionally substituted -C_1-C_6 alkyl and optionally substituted –C_3-C_8 cycloalkyl; R_{12} at each occurrence is independently selected from the groups consisting of hydrogen, halo, -CN, -NO_2, optionally substituted -C_1-C_6 alkyl, optionally substituted -C_1-C_6 alkoxy and optionally substituted –C_3-C_8 cycloalkyl; and X, L, R, R^a, R^b, R_3, R_4, and R_{14} are as previously defined.

In another embodiment, the compound of Formula (**I**) is represented by Formula (**IIIa-1**), (**IIIb-1**), (**IIIc-1**), (**IIId-1**), (**IIIe-1**), (**IIIf-1**), (**IIIg-1**), or (**IIIh-1**), or a pharmaceutically acceptable salt thereof:



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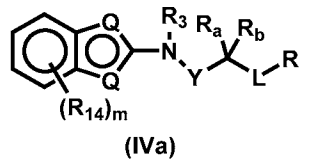
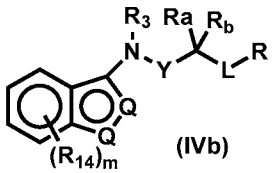
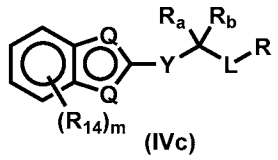
wherein Q is NR_{11}, O, S or CR_{12}, provided that when Q is CR_{12}, N in the five-membered ring represents NR_{11}; m, L, R, R^a, R^b, R_{11}, R_{12}, and R_{14} are as previously defined. It is to be understood that the positions of Q and N in the ring in each formula can be switched.

In another embodiment, the compound of Formula (**I**) is represented by Formula (**IVa**), (**IVb**), (**IVc**), (**IVd**), (**IVe**), (**IVf**), (**IVg**), or (**IVh**), or a pharmaceutically acceptable salt thereof:


(IVa)


(IVb)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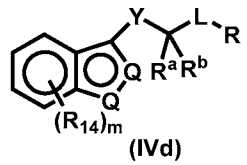
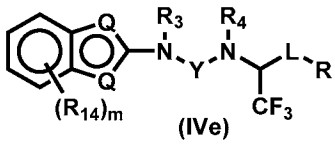
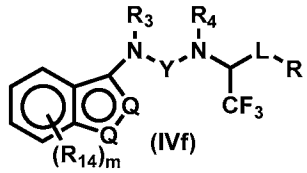
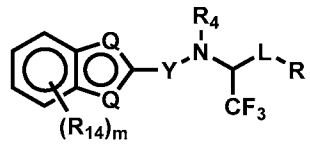
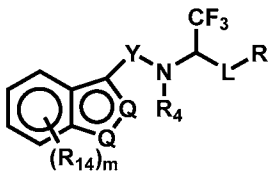

(IVd)


(IVe)


(IVf)


(IVg)


(IVh)

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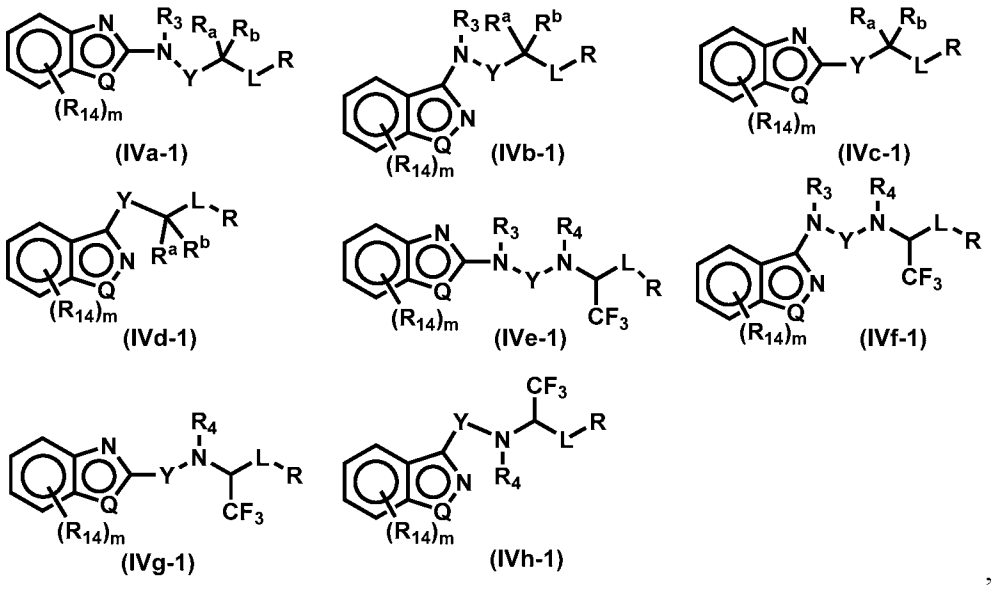
wherein each Q is independently N, NR_{11}, O, S or CR_{12}; m, Y, L, R, R^a, R^b, R_3, R_4, R_{11}, R_{12} and R_{14} are as previously defined. Preferably, one Q is N or CR_{12} and the other Q is NR_{11}, O or S.

In another embodiment, the compound of Formula (**I**) is represented by Formula (**IVa-1**), (**IVb-1**), (**IVc-1**), (**IVd-1**), (**IVe-1**), (**IVf-1**), (**IVg-1**), or (**IVh-1**), or a pharmaceutically acceptable salt thereof:



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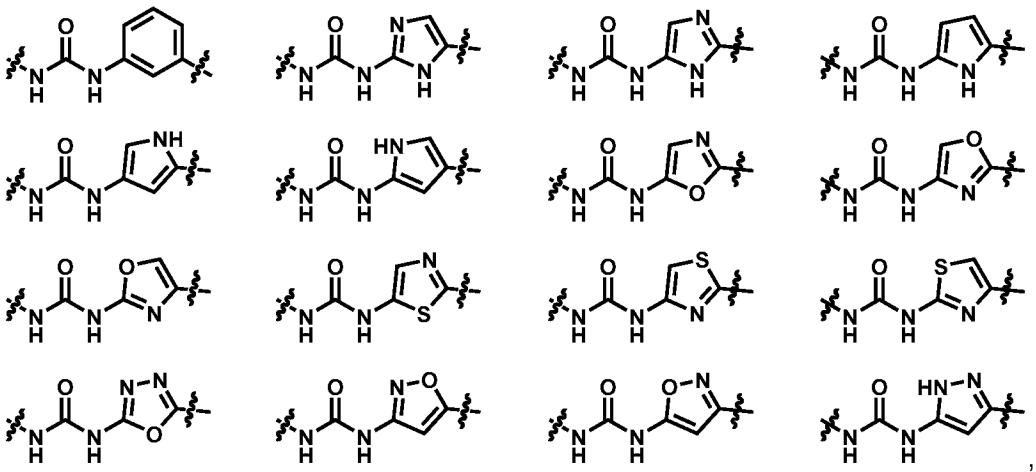
wherein Q is NR_{11}, O, S or CR_{12},, provided that when Q is CR_{12}, N in the five-membered ring represents NR_{11}; m, L, R, R^a, R^b, R_1, R_3, R_4, R_{11}, R_{12} and R_{14} are as previously defined. It is to be understood that the positions of Q and N in the ring in each formula can be switched. In still another embodiment, the invention relates to compounds of Formula (**I**) and pharmaceutically acceptable salts thereof, wherein A_1-Y are taken together to represent a system selected from the following:



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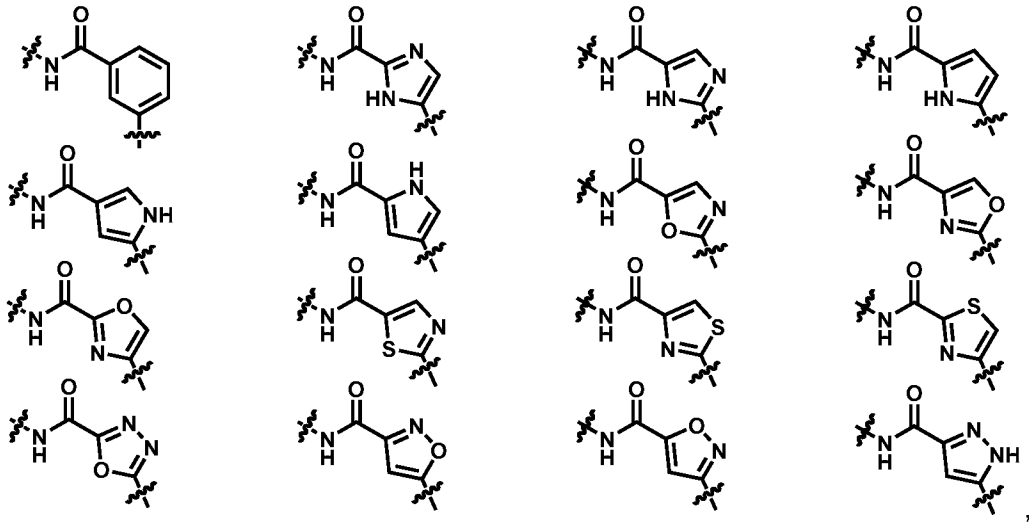
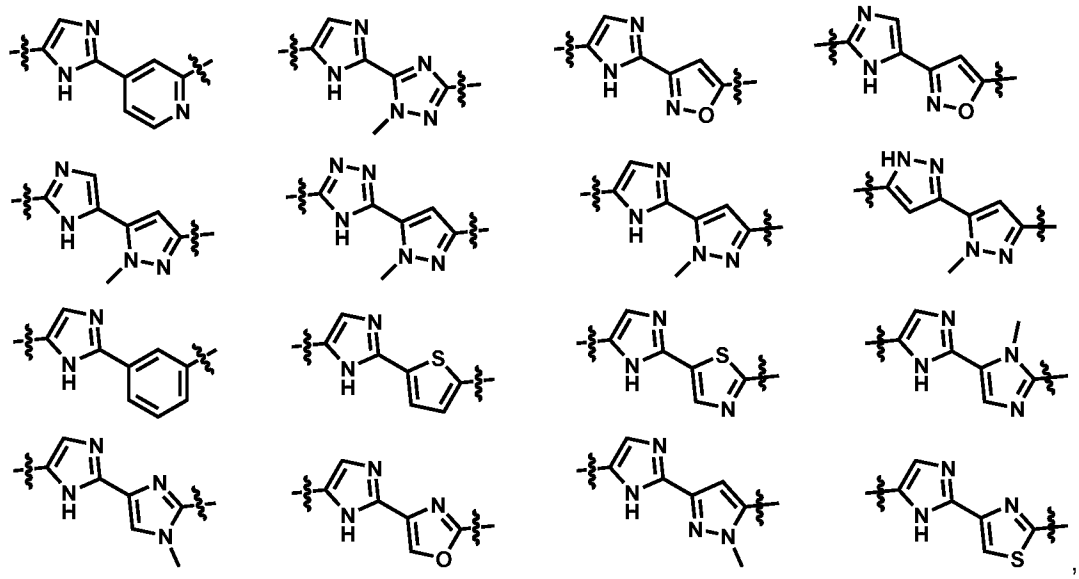
wherein each of the above shown core groups is optionally substituted and each CH in each phenyl or heteroaryl ring can be independently replaced with an N if possible.

In still another embodiment, the invention relates to compounds of Formula (**I**) and pharmaceutically acceptable salts thereof, wherein A_1-Y are taken together to represent a system selected from the following:



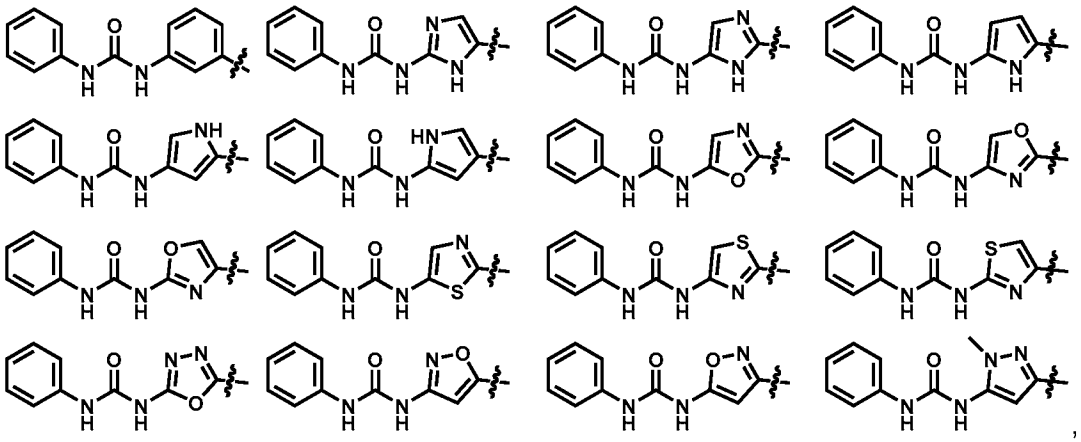
wherein each of the above shown core groups is optionally substituted and each CH in each phenyl or heteroaryl ring can be independently replaced with an N if possible.

In still another embodiment, the invention relates to compounds of Formula (**I**) and pharmaceutically acceptable salts thereof, wherein A_1-Y are taken together to represent a polycyclic system selected from the following:



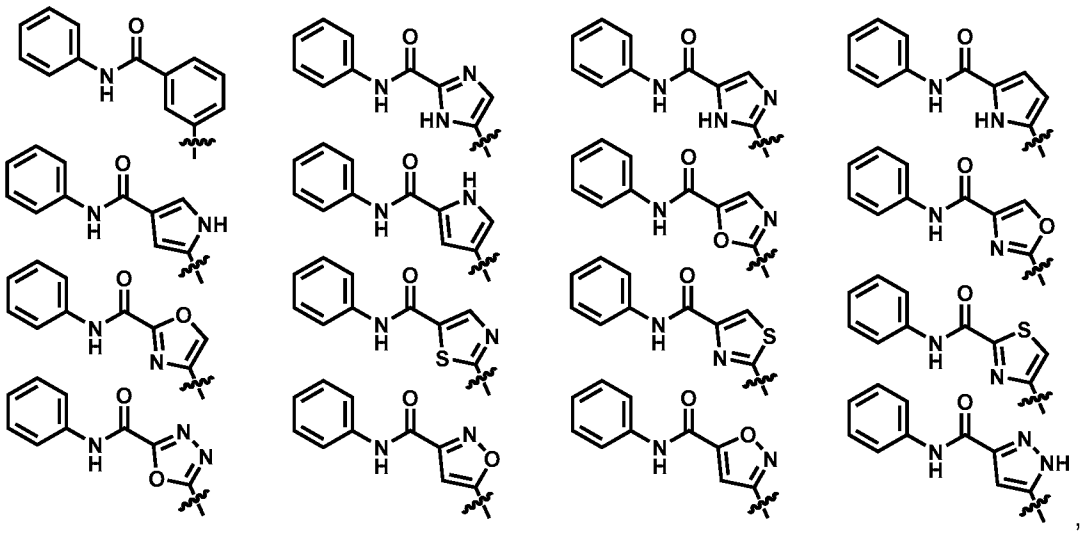
wherein each of the above shown core groups is optionally substituted and each CH in each phenyl or heteroaryl ring can be independently replaced with an N if possible.

In still another embodiment, the invention relates to compounds of Formula (**I**) and pharmaceutically acceptable salts thereof, wherein X-A_1-Y are taken together to form a polycyclic system selected from the following:



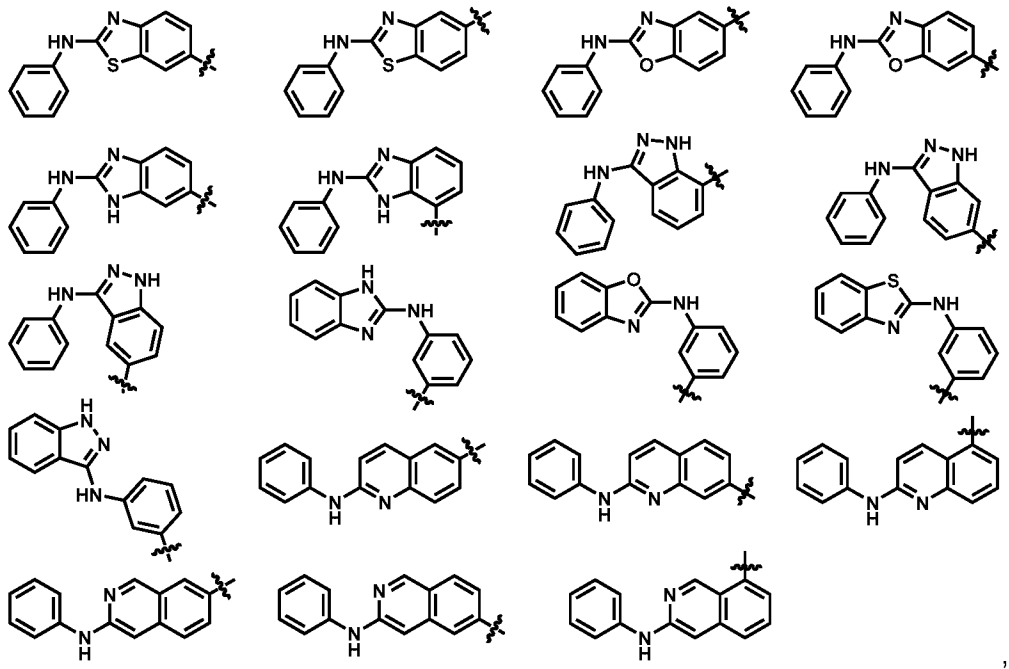
wherein each of the above shown core groups is optionally substituted and up to three CHs in each phenyl or heteroaryl ring can be independently replaced with an N if possible.

In still another embodiment, the invention relates to compounds of Formula (**I**) and pharmaceutically acceptable salts thereof, wherein X-A_1-Y are taken together to form a polycyclic system selected from the following:



wherein each of the above shown core groups is optionally substituted and up to three CHs in each phenyl or heteroaryl ring can be replaced with an N if possible.

In still another embodiment, the invention relates to compounds of Formula (**I**) and pharmaceutically acceptable salts thereof, wherein X-A_1-Y are taken together to form a polycyclic system selected from the following:



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wherein each of the above shown core group is optionally substituted and up to three CHs in each phenyl or heteroaryl ring can be replaced with a N if possible.

In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts thereof, wherein L is $-NR_1$, wherein R_1 is as previously defined.

In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts thereof, wherein L is O.

In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts thereof, wherein L is $-NR_1$, wherein R_1 is $-C_1$-C_8 alkyl, $-C_3$-C_8 cycloalkyl, or 3- to 8-membered heterocyclic, each optionally substituted with one, two or three groups independently selected from hydroxy, protected hydroxy, halo, -CN, amino, protected amino, optionally substituted -C_1-C_6 alkyl, optionally substituted $-C_3$-C_8 cycloalkyl, optionally substituted -C_1-C_3 alkoxy, -$C(O)_2$-C_1-C_6 alkyl, -C(O)NH-C_1-C_6 alkyl, and -C(O)-C_1-C_6 alkyl.

In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts thereof, wherein R is $-C_1$-C_8 alkyl, $-C_2$-C_8 alkenyl, $-C_2$-C_8 alkynyl, $-C_3$-C_8 cycloalkyl, or 3- to 8-membered heterocyclic, each optionally substituted with one, two or three groups independently selected from hydroxy, protected hydroxy, halo, -CN, amino, protected amino, optionally substituted -C_1-C_6 alkyl, optionally substituted $-C_3$-C_8 cycloalkyl, optionally substituted -C_1-C_3 alkoxy, -C(O)OR_{15},

-OC(O)NH- R_{15}, -C(O)NH- R_{15}, and -C(O)- R_{15}. In certain embodiments, R is optionally substituted C_1-C_4-alkyl, for example, optionally substituted C_2-alkyl. In certain embodiments, R is 2-substituted ethyl. R_{15} is optionally substituted –C_1-C_8 alkyl, optionally substituted –C_2-C_8 alkenyl, optionally substituted –C_2-C_8 alkynyl, optionally substituted –C_3-C_8 cycloalkyl, optionally substituted 3- to 8-membered heterocyclic, optionally substituted aryl or optionally substituted heteroaryl.

In certain embodiments, the present invention relates to compounds of Formula (**I**), or a pharmaceutically acceptable salt thereof, wherein R is optionally substituted -C_1-C_6 alkyl. In certain embodiments, the present invention relates to compounds of Formula (**I**), or a pharmaceutically acceptable salt thereof, wherein R is -C_1-C_6 alkyl optionally substituted with -C(O)OC_1-C_6 alkyl, -OC(O)NH-C_1-C_6 alkyl, -C(O)NH-C_1-C_6 alkyl, and -C(O)-C_1-C_6 alkyl, wherein said -C_1-C_6 alkyl is optionally substituted. In certain embodiments, the present invention relates to compounds of Formula (**I**), or a pharmaceutically acceptable salt thereof, wherein R is -C_1-C_6 alkyl optionally substituted with aryl or heteroaryl, wherein said aryl or heteroaryl is optionally substituted.

In another embodiment, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts thereof, wherein L is –NH or -CH_2.

In another embodiment, the present invention relates to compounds of Formula (**I**), or a pharmaceutically acceptable salt thereof, wherein L is –NH; R is optionally substituted arylalkyl or optionally substituted heteroarylalkyl.

In another embodiment, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts thereof, wherein L is –NH; R is arylalkyl or heteroarylalkyl, each optionally substituted with one, two or three groups independently selected from hydroxy, protected hydroxy, halo, -CN, amino, protected amino, optionally substituted -C_1-C_6 alkyl, optionally substituted –C_3-C_8 cycloalkyl, optionally substituted -C_1-C_3 alkoxy, -C(O)$_2$-C_1-C_6 alkyl, -C(O)NH-C_1-C_6 alkyl, and -C(O)-C_1-C_6 alkyl.

In another embodiment, the present invention relates to compounds of Formula (**I**), or a pharmaceutically acceptable salt thereof, wherein L is –NR_1 and R_1 is optionally substituted arylalkyl or optionally substituted heteroarylalkyl.

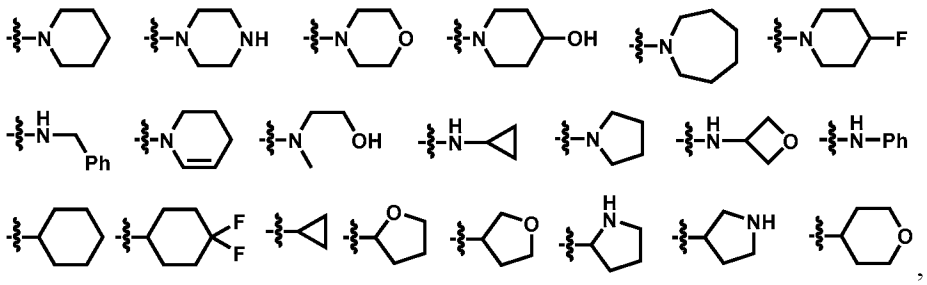
In another embodiment, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts thereof, wherein L is –NR_1, and R_1 is arylalkyl or heteroarylalkyl, each optionally substituted with one, two or three groups independently selected from hydroxy, protected hydroxy, halo, -CN, amino, protected amino, optionally

substituted -C_1-C_6 alkyl, optionally substituted –C_3-C_8 cycloalkyl, optionally substituted -C_1-C_3 alkoxy, -$C(O)_2$-C_1-C_6 alkyl, -C(O)NH-C_1-C_6 alkyl, and -C(O)-C_1-C_6 alkyl.

In another embodiment, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts thereof, wherein -L-R taken together represents a C_3-C_8 cycloalkyl or optionally substituted 3- to 8-membered heterocyclic.

In another embodiment, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts thereof, wherein -L-R taken together represents a C_3-C_8 cycloalkyl or 3- to 8-membered heterocyclic containing one or two heteroatoms selected from N, O and S; each optionally substituted with one, two or three groups independently selected from hydroxy, protected hydroxy, halo, -CN, amino, protected amino, optionally substituted -C_1-C_6 alkyl, optionally substituted –C_3-C_8 cycloalkyl, optionally substituted -C_1-C_3 alkoxy, -$C(O)_2$-C_1-C_6 alkyl, -C(O)NH-C_1-C_6 alkyl, and -C(O)-C_1-C_6 alkyl.

In another particular embodiment, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts thereof, wherein -L-R is selected from the following:



wherein each of these groups is optionally substituted.

It will be appreciated that the description of the present invention herein should be construed in congruity with the laws and principles of chemical bonding. In some instances it may be necessary to remove a hydrogen atom in order to accommodate a substituent at any given location.

It is intended that the definition of any substituent or variable (e.g. R, R_1, R_2, etc.) at a particular location in a molecule is independent of its definitions elsewhere in that molecule.

It will be yet appreciated that the compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic, diastereoisomeric, and optically active forms. It will still be appreciated that certain compounds of the present

invention may exist in different tautomeric forms. All tautomers are contemplated to be within the scope of the present invention.

In one aspect, the compounds of the invention are useful in HBV treatment by disrupting, accelerating, reducing, delaying and/or inhibiting normal viral capsid assembly and/or disassembly of immature or mature particles, thereby inducing aberrant capsid morphology and leading to antiviral effects such as disruption of virion assembly and/or disassembly, virion maturation, and/or virus egress. In one embodiment, a disruptor of capsid assembly interacts with mature or immature viral capsid to perturb the stability of the capsid, thus affecting assembly and/or disassembly. In another embodiment, a disruptor of capsid assembly perturbs protein folding and/or salt bridges required for stability, function and/or normal morphology of the viral capsid, thereby disrupting and/or accelerating capsid assembly and/or disassembly. In yet another embodiment, the compounds of the invention bind capsid and alter metabolism of cellular polyproteins and precursors, leading to abnormal accumulation of protein monomers and/or oligomers and/or abnormal particles, which causes cellular toxicity and death of infected cells. In another embodiment, the compounds of the invention cause failure of the formation of capsid of optimal stability, affecting efficient uncoating and/or disassembly of viruses (e.g., during infectivity).

In one embodiment, the compounds of the invention disrupt and/or accelerate capsid assembly and/or disassembly when the capsid protein is immature. In another embodiment, the compounds of the invention disrupt and/or accelerate capsid assembly and/or disassembly when the capsid protein is mature. In yet another embodiment, the compounds of the invention disrupt and/or accelerate capsid assembly and/or disassembly during vial infectivity. In yet another embodiment, the disruption and/or acceleration of capsid assembly and/or disassembly attenuates HBV viral infectivity and/or reduces viral load. In yet another embodiment, disruption, acceleration, inhibition, delay and/or reduction of capsid assembly and/or disassembly eradicates the virus from the host organism. In yet another embodiment, eradication of the HBV from a host advantageously obviates the need for chronic long-term therapy and/or reduces the duration of long-term therapy.

In one embodiment, the compounds of the invention disrupt, reduce, delay and/or inhibit viral DNA synthesis, viral relaxed circular genome translocation, and/or viral cccDNA stability or transcription.

In one embodiment, the compounds described herein are suitable for monotherapy and are effective against natural or native HBV strains and against HBV strains resistant to currently known drugs. In another embodiment, the compounds described herein are suitable for use in combination therapy.

In another embodiment, the compounds of the invention can be used in methods of modulating (e.g., inhibit, disrupt or accelerate) the activity of HBV cccDNA. In yet another embodiment, the compounds of the invention can be used in methods of diminishing or preventing the formation of HBV cccDNA. In another embodiment, the additional therapeutic agent is selected from immune modulator or immune stimulator therapies, which includes T-cell response activator AIC649 and biological agents belonging to the interferon class, such as interferon alpha 2a or 2b or modified interferons such as pegylated interferon, alpha 2a, alpha 2b, lamda; or TLR modulators such as TLR-7 agonists or TLR-9 agonists; or therapeutic vaccines to stimulate an HBV-specific immune response such as virus-like particles composed of HBcAg and HBsAg, immune complexes of HBsAg and HBsAb, or recombinant proteins comprising HBx, HBsAg and HBcAg in the context of a yeast vector; or immunity activator such as SB-9200 of certain cellular viral RNA sensors such as RIG-I, NOD2, and MDA5 protein, or RNA interence (RNAi) or small interfering RNA (siRNA) such as ARC-520, ARC-521, ARB-1467, and ALN-HBV RNAi, or antiviral agents that block viral entry or maturation or target the HBV polymerase such as nucleoside or nucleotide or non-nucleos(t)ide polymerase inhibitors, and agents of distinct or unknown mechanism including agents that disrupt the function of other essential viral protein(s) or host proteins required for HBV replication or persistence such as REP 2139. In an embodiment of the combination therapy, the reverse transcriptase inhibitor is at least one of Zidovudine, Didanosine, Zalcitabine, ddA, Stavudine, Lamivudine, Abacavir, Emtricitabine, Entecavir, Apricitabine, Atevirapine, ribavirin, acyclovir, famciclovir, valacyclovir, ganciclovir, valganciclovir, Tenofovir, Adefovir, PMPA, cidofovir, Efavirenz, Nevirapine, Delavirdine, or Etravirine.

In another embodiment of the combination therapy, the TLR-7 agonist is selected from the group consisting of SM360320 (9-benzyl-8-hydroxy-2-(2-methoxy-ethoxy)adenine), AZD 8848 (methyl [3-({ [3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9H-purin-9-yl)propyl][3-(4-morpholinyl) propyl] amino Imethyl)phenyl] acetate), GS-9620 (4-Amino-2-butoxy-8-[3-(1-pyrrolidinylmethyl)benzyl]-7,8-dihydro-6(5H)-pteridinone), and RO6864018.

In another embodiment, the additional therapeutic agent is a modulator of viral capsid protein and/or its assembly. In one embodiment of the combination therapy, the capsid modulator is selected from the group consisting of NVR3-778, AB-423, GLS4, ABI-H0731, ABI-H0808, ABI-H0986, GLP-26, Bay 41-4109, and AT-130.

In an embodiment of these combination therapies, the compound and the additional therapeutic agent are co-formulated. In another embodiment, the compound and the additional therapeutic agent are co-administered.

In another embodiment of the combination therapy, administering the compound of the invention allows for administering of the additional therapeutic agent at a lower dose or frequency as compared to the administering of the at least one additional therapeutic agent alone that is required to achieve similar results in prophylactically treating an HBV infection in an individual in need thereof.

In another embodiment of the combination therapy, before administering the therapeuticly effective amount of the compound of the invention, the individual is known to be refractory to a compound selected from the group consisting of a HBV polymerase inhibitor, interferon, viral entry inhibitor, viral maturation inhibitor, distinct capsid assembly modulator, antiviral compounds of distinct or unknown mechanism, and combination thereof.

In still another embodiment of the method, administering the compound of the invention reduces viral load in the individual to a greater extent compared to the administering of a compound selected from the group consisting of a HBV polymerase inhibitor, interferon, viral entry inhibitor, viral maturation inhibitor, distinct capsid assembly modulator, antiviral compounds of distinct or unknown mechanism, and combination thereof.

In another embodiment, administering of the compound of the invention causes a lower incidence of viral mutation and/or viral resistance than the administering of a compound selected from the group consisting of a HBV polymerase inhibitor, interferon, viral entry inhibitor, viral maturation inhibitor, distinct capsid assembly modulator, antiviral compounds of distinct or unknown mechanism, and combination thereof.

DEFINITIONS

Listed below are definitions of various terms used to describe this invention. These definitions apply to the terms as they are used throughout this specification and claims,

unless otherwise limited in specific instances, either individually or as part of a larger group.

The term "aryl," as used herein, refers to a mono- or polycyclic carbocyclic ring system comprising at least one aromatic ring, including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, and indenyl. A polycyclic aryl is a polycyclic ring system that comprises at least one aromatic ring. Polycyclic aryls can comprise fused rings, covalently attached rings or a combination thereof.

The term "heteroaryl," as used herein, refers to a mono- or polycyclic aromatic radical having one or more ring atom selected from S, O and N; and the remaining ring atoms are carbon, wherein any N or S contained within the ring may be optionally oxidized. Heteroaryl includes, but is not limited to, pyridinyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzoxazolyl, quinoxalinyl. A polycyclic heteroaryl can comprise fused rings, covalently attached rings or a combination thereof.

In accordance with the invention, aromatic groups can be substituted or unsubstituted.

The term “bicyclic aryl” or “bicyclic heteroaryl” refers to a ring system consisting of two rings wherein at least one ring is aromatic; and the two rings can be fused or covalently attached.

The term "azole group," as used herein, refers to 5-membered heteroaromatic ring containing at least one nitrogen atom. Preferred azole groups contain a nitrogen atom and at least one additional heteroatom, preferably a nitrogen, oxygen or sulfur atom. Azole groups include, but are not limited to pyrazole, imidazole, thiazole, oxazole, isoxazole, 1,2,3-triazole, 1,2,4- triazole, tetrazole. An azole group is termed “ortho” substituted in reference to two substituents which are on adjacent ring atoms. An azole group is termed “meta” substituted in reference to two substituents which are not on adjacent ring positions. An “azolyl” group is a univalent or bivalent group derived from an azole group by removal of one or two hydrogen atoms. Azolyl groups include, but are not limited to, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, 1,2,3-triazolyl, 1,2,4- triazolyl, tetrazolyl.

The term “bicyclic azole” or “bicyclic azole group” refers to an aromatic ring system consisting of two rings wherein at least one ring is azole group; and the two rings can be fused or covalently attached. Preferred bicyclic azole groups are those in which an

azole ring is fused to a six-membered aromatic or heteroaromatic ring. Such groups include, but are not limited to, benzimidazole, benzopyrazole, benzotriazole, benzoxazole, benzisoxazole benzothiazole, imidazolopyridine, pyrazolopyridine, thiazolopyridine, oxazolopyridine, isoxazolopyridine, triazolopyridine, and tetrazolopyridine. A bicyclic azolyl group is a univalent or bivalent group derived from a biclyclic azole group by removal of one or two hydrogen atoms. Such groups include, but are not limited to, benzimidazolyl, benzopyrazolyl, benzotriazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, imidazolopyridyl, pyrazolopyridyl, thiazolopyridyl, oxazolopyridyl, isoxazolopyridyl, triazolopyridyl, and tetrazolopyridyl. A univalent bicyclic azolyl group can be derived from the corresponding bicyclic azole group by removal of a hydrogen atom from either ring. A bivalent bicyclic azolyl group can be derived from the corresponding bicyclic azole group by removal of two hydrogen atoms from the same ring or one hydrogen atom from each ring.

The term “alkyl” as used herein, refers to saturated, straight- or branched-chain hydrocarbon radicals. "C_1-C_4 alkyl," "C_1-C_6 alkyl," “C_1-C_8 alkyl," "C_2-C_4 alkyl," or "C_3-C_6 alkyl," refer to alkyl groups containing from one to four, one to six, one to eight carbon atoms, 2 to 4 and 3 to 6 carbon atoms respectively. Examples of C_1-C_8 alkyl radicals include, but are not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *tert*-butyl, neopentyl, n-hexyl, heptyl and octyl radicals.

The term “alkenyl” as used herein, refers to straight- or branched-chain hydrocarbon radicals having at least one carbon-carbon double bond by the removal of a single hydrogen atom. “C_2-C_8 alkenyl,” “C_2-C_4 alkenyl,” “C_3-C_4 alkenyl,” or “C_3-C_6 alkenyl,” refer to alkenyl groups containing from two to eight, two to four, three to four or three to six carbon atoms respectively. Alkenyl groups include, but are not limited to, for example, ethenyl, propenyl, butenyl, 1-methyl-2-buten-1-yl, heptenyl, octenyl, and the like.

The term “alkynyl” as used herein, refers to straight- or branched-chain hydrocarbon radicals having at least one carbon-carbon double bond by the removal of a single hydrogen atom. “C_2-C_8 alkynyl,” “C_2-C_4 alkynyl,” “C_3-C_4 alkynyl,” or “C_3-C_6 alkynyl,” refer to alkynyl groups containing from two to eight, two to four, three to four or three to six carbon atoms respectively. Representative alkynyl groups include, but are not limited to, for example, ethynyl, 1-propynyl, 1-butynyl, heptynyl, octynyl, and the like.

The term “cycloalkyl”, as used herein, refers to a monocyclic or polycyclic saturated carbocyclic ring compound, and the carbon atoms may be optionally oxo-

substituted. Preferred cycloalkyl groups include C_3-C_8 cycloalkyl and C_4-C_7 cycloalkyl. Examples of C_3-C_8 cycloalkyl include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentyl and cyclooctyl; and examples of C_4-C_7 cycloalkyl include, but are not limited to, cyclopentyl, cyclohexyl, bicyclo [2.2.1] heptyl, and the like.

The term "cycloalkenyl", as used herein, refers to monocyclic or polycyclic carbocyclic ring compound having at least one carbon-carbon double bond and the carbon atoms may be optionally oxo-substituted. Preferred cycloalkenyl groups include C_3-C_8 cycloalkenyl or C_5-C_7 cycloalkenyl groups. Examples of C_3-C_8 cycloalkenyl include, but not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, and the like; and examples of C_5-C_7 cycloalkenyl include, but not limited to, cyclopentenyl, cyclohexenyl, cycloheptenyl, and the like.

As used herein, the term "arylalkyl" means a functional group wherein an alkylene chain is attached to an aryl group, e.g., -CH_2CH_2-phenyl. The term "substituted arylalkyl" means an arylalkyl functional group in which the aryl group is substituted. Similarly, the term "heteroarylalkyl" means a functional group wherein an alkylene chain is attached to a heteroaryl group. The term "substituted heteroarylalkyl" means a heteroarylalkyl functional group in which the heteroaryl group is substituted.

As used herein, the term "alkoxy" employed alone or in combination with other terms means, unless otherwise stated, an alkyl group having the designated number of carbon atoms connected to the rest of the molecule via an oxygen atom, such as, for example, methoxy, ethoxy, 1-propoxy, 2-propoxy (isopropoxy) and the higher homologs and isomers. Preferred alkoxy are (C_1-C_3) alkoxy.

It is understood that any alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclic and cycloalkenyl moiety described herein can also be an aliphatic group or an alicyclic group.

An "aliphatic" group is a non-aromatic moiety comprised of any combination of carbon atoms, hydrogen atoms, halogen atoms, oxygen, nitrogen or other atoms, and optionally contains one or more units of unsaturation, e.g., double and/or triple bonds. Examples of aliphatic groups are functional groups, such as alkyl, alkenyl, alkynyl, O, OH, NH, NH_2, C(O), $S(O)_2$, C(O)O, C(O)NH, OC(O)O, OC(O)NH, $OC(O)NH_2$, $S(O)_2NH$, $S(O)_2NH_2$, $NHC(O)NH_2$, NHC(O)C(O)NH, $NHS(O)_2NH$, $NHS(O)_2NH_2$, $C(O)NHS(O)_2$, $C(O)NHS(O)_2NH$ or $C(O)NHS(O)_2NH_2$, and the like, groups comprising one or more functional groups, non-aromatic hydrocarbons (optionally substituted), and groups wherein one or more carbons of a non-aromatic hydrocarbon (optionally substituted) is replaced by a functional group. Carbon atoms of an aliphatic group can be

optionally oxo-substituted. An aliphatic group may be straight chained, branched, cyclic, or a combination thereof and preferably contains between about 1 and about 24 carbon atoms, more typically between about 1 and about 12 carbon atoms. In addition to aliphatic hydrocarbon groups, as used herein, aliphatic groups expressly include, for example, alkoxyalkyls, polyalkoxyalkyls, such as polyalkylene glycols, polyamines, and polyimines, for example. Aliphatic groups may be optionally substituted.

The terms "heterocyclic" or "heterocycloalkyl" can be used interchangeably and referred to a non-aromatic ring or a bi- or tri-cyclic group fused or bridged system, where (i) each ring system contains at least one heteroatom independently selected from oxygen, sulfur and nitrogen, (ii) each ring system can be saturated or unsaturated (iii) the nitrogen and sulfur heteroatoms may optionally be oxidized, (iv) the nitrogen heteroatom may optionally be quaternized, (v) any of the above rings may be fused to an aromatic ring, and (vi) the remaining ring atoms are carbon atoms which may be optionally oxo-substituted. Representative heterocycloalkyl groups include, but are not limited to, 1,3-dioxolane, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, 2-azabicyclo[2.2.1]heptyl, and tetrahydrofuryl. Such heterocyclic groups may be further substituted. Heteroaryl or heterocyclic groups can be C-attached or N-attached (where possible).

It is understood that any alkyl, alkenyl, alkynyl, alicyclic, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclic, aliphatic moiety or the like, described herein can also be a divalent or multivalent group when used as a linkage to connect two or more groups or substituents, which can be at the same or different atom(s). One of skill in the art can readily determine the valence of any such group from the context in which it occurs.

The term "substituted" refers to substitution by independent replacement of one, two, or three or more of the hydrogen atoms with substituents including, but not limited to, -F, -Cl, -Br, -I, -OH, C_1-C_{12}-alkyl; C_2-C_{12}-alkenyl, C_2-C_{12}-alkynyl, protected hydroxy, -NO_2, -N_3, -CN, -NH_2, protected amino, oxo, thioxo, -NH-C_1-C_{12}-alkyl, -NH-C_2-C_8-alkenyl, -NH-C_2-C_8-alkynyl, -NH-C_3-C_{12}-cycloalkyl, -NH-aryl, -NH-heteroaryl, -NH-heterocycloalkyl, -dialkylamino, -diarylamino, -diheteroarylamino, -O-C_1-C_{12}-alkyl, -O-C_2-C_8-alkenyl, -O-C_2-C_8-alkynyl, -O-C_3-C_{12}-cycloalkyl, -O-aryl, -O-heteroaryl, -O-heterocycloalkyl, -C(O)-C_1-C_{12}-alkyl, -C(O)-C_2-C_8-alkenyl, -C(O)-C_2-C_8-alkynyl, -C(O)-C_3-C_{12}-cycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocycloalkyl, -$CONH_2$, -CONH-C_1-C_{12}-alkyl, -CONH-C_2-C_8-alkenyl, -CONH-C_2-C_8-alkynyl, -CONH-C_3-C_{12}-

cycloalkyl, -CONH-aryl, -CONH-heteroaryl, -CONH-heterocycloalkyl, -OCO_2-C_1-C_{12}-alkyl, -OCO_2-C_2-C_8-alkenyl, -OCO_2-C_2-C_8-alkynyl, -OCO_2-C_3-C_{12}-cycloalkyl, -OCO_2-aryl, -OCO_2-heteroaryl, -OCO_2-heterocycloalkyl, -CO_2-C_1-C_{12} alkyl, -CO_2-C_2-C_8 alkenyl, -CO_2-C_2-C_8 alkynyl, CO_2-C_3-C_{12}-cycloalkyl, -CO_2- aryl, CO_2-heteroaryl, CO_2-heterocyloalkyl, -$OCONH_2$, -OCONH-C_1-C_{12}-alkyl, -OCONH-C_2-C_8-alkenyl, -OCONH-C_2-C_8-alkynyl, -OCONH-C_3-C_{12}-cycloalkyl, -OCONH-aryl, -OCONH-heteroaryl, -OCONH- heterocyclo-alkyl, -NHC(O)H, -NHC(O)-C_1-C_{12}-alkyl, -NHC(O)-C_2-C_8-alkenyl, -NHC(O)-C_2-C_8-alkynyl, -NHC(O)-C_3-C_{12}-cycloalkyl, -NHC(O)-aryl, -NHC(O)-heteroaryl, -NHC(O)-heterocyclo-alkyl, -$NHCO_2$-C_1-C_{12}-alkyl, -$NHCO_2$-C_2-C_8-alkenyl, -$NHCO_2$- C_2-C_8-alkynyl, -$NHCO_2$-C_3-C_{12}-cycloalkyl, -$NHCO_2$-aryl, -$NHCO_2$-heteroaryl, -$NHCO_2$- heterocycloalkyl, -NHC(O)NH_2, -NHC(O)NH-C_1-C_{12}-alkyl, -NHC(O)NH-C_2-C_8-alkenyl, -NHC(O)NH-C_2-C_8-alkynyl, -NHC(O)NH-C_3-C_{12}-cycloalkyl, -NHC(O)NH-aryl, -NHC(O)NH-heteroaryl, -NHC(O)NH-heterocycloalkyl, NHC(S)NH_2, -NHC(S)NH-C_1-C_{12}-alkyl, -NHC(S)NH-C_2-C_8-alkenyl, -NHC(S)NH-C_2-C_8-alkynyl, -NHC(S)NH-C_3-C_{12}-cycloalkyl, -NHC(S)NH-aryl, -NHC(S)NH-heteroaryl, -NHC(S)NH-heterocycloalkyl, -NHC(NH)NH_2, -NHC(NH)NH-C_1-C_{12}-alkyl, -NHC(NH)NH-C_2-C_8-alkenyl, -NHC(NH)NH-C_2-C_8-alkynyl, -NHC(NH)NH-C_3-C_{12}-cycloalkyl, -NHC(NH)NH-aryl, -NHC(NH)NH-heteroaryl, -NHC(NH)NH-heterocycloalkyl, -NHC(NH)-C_1-C_{12}-alkyl, -NHC(NH)-C_2-C_8-alkenyl, -NHC(NH)-C_2-C_8-alkynyl, -NHC(NH)-C_3-C_{12}-cycloalkyl, -NHC(NH)-aryl, -NHC(NH)-heteroaryl, -NHC(NH)-heterocycloalkyl, -C(NH)NH-C_1-C_{12}-alkyl, -C(NH)NH-C_2-C_8-alkenyl, -C(NH)NH-C_2-C_8-alkynyl, -C(NH)NH-C_3-C_{12}-cycloalkyl, -C(NH)NH-aryl, -C(NH)NH-heteroaryl, -C(NH)NH-heterocycloalkyl, -S(O)-C_1-C_{12}-alkyl, -S(O)-C_2-C_8-alkenyl, - S(O)-C_2-C_8-alkynyl, -S(O)-C_3-C_{12}-cycloalkyl, -S(O)-aryl, -S(O)-heteroaryl, -S(O)-heterocycloalkyl, -SO_2NH_2, -SO_2NH-C_1-C_{12}-alkyl, -SO_2NH-C_2-C_8-alkenyl, -SO_2NH- C_2-C_8-alkynyl, -SO_2NH-C_3-C_{12}-cycloalkyl, -SO_2NH-aryl, -SO_2NH-heteroaryl, -SO_2NH- heterocycloalkyl, -$NHSO_2$-C_1-C_{12}-alkyl, -$NHSO_2$-C_2-C_8-alkenyl, - $NHSO_2$-C_2-C_8-alkynyl, -$NHSO_2$-C_3-C_{12}-cycloalkyl, -$NHSO_2$-aryl, -$NHSO_2$-heteroaryl, -$NHSO_2$-heterocycloalkyl, -CH_2NH_2, -$CH_2SO_2CH_3$, -aryl, -arylalkyl, -heteroaryl, -heteroarylalkyl, -heterocycloalkyl, -C_3-C_{12}-cycloalkyl, polyalkoxyalkyl, polyalkoxy, -methoxymethoxy, -methoxyethoxy, -SH, -S-C_1-C_{12}-alkyl, -S-C_2-C_8-alkenyl, -S-C_2-C_8-alkynyl, -S-C_3-C_{12}-cycloalkyl, -S-aryl, -S-heteroaryl, -S-heterocycloalkyl, or methylthio-methyl. It is understood that the aryls, heteroaryls, alkyls, cycloalkyls and the like can be further substituted.

The term "halo" or "halogen" alone or as part of another substituent, as used herein, refers to a fluorine, chlorine, bromine, or iodine atom.

The term "optionally substituted", as used herein, means that the referenced group may be substituted or unsubstituted. In one embodiment, the referenced group is optionally substituted with zero substituents, i.e., the referenced group is unsubstituted. In another embodiment, the referenced group is optionally substituted with one or more additional group(s) individually and independently selected from groups described herein.

The term "hydrogen" includes hydrogen and deuterium. In addition, the recitation of an atom includes other isotopes of that atom so long as the resulting compound is pharmaceutically acceptable.

The term "hydroxy activating group," as used herein, refers to a labile chemical moiety which is known in the art to activate a hydroxyl group so that it will depart during synthetic procedures such as in a substitution or an elimination reaction. Examples of hydroxyl activating group include, but not limited to, mesylate, tosylate, triflate, *p*-nitrobenzoate, phosphonate and the like.

The term "activated hydroxyl," as used herein, refers to a hydroxy group activated with a hydroxyl activating group, as defined above, including mesylate, tosylate, triflate, p-nitrobenzoate, phosphonate groups, for example.

The term "hydroxy protecting group," as used herein, refers to a labile chemical moiety which is known in the art to protect a hydroxyl group against undesired reactions during synthetic procedures. After said synthetic procedure(s) the hydroxy protecting group as described herein may be selectively removed. Hydroxy protecting groups as known in the art are described generally in T.H. Greene and P.G. M. Wuts, Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons, New York (1999). Examples of hydroxyl protecting groups include benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, tert-butoxy-carbonyl, isopropoxycarbonyl, diphenylmethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, allyloxycarbonyl, acetyl, formyl, chloroacetyl, trifluoroacetyl, methoxyacetyl, phenoxyacetyl, benzoyl, methyl, t-butyl, 2,2,2-trichloroethyl, 2-trimethylsilyl ethyl, allyl, benzyl, triphenyl-methyl (trityl), methoxymethyl, methylthiomethyl, benzyloxymethyl, 2-(trimethylsilyl)-ethoxymethyl, methanesulfonyl, trimethylsilyl, triisopropylsilyl, and the like.

The term "protected hydroxy," as used herein, refers to a hydroxy group protected with a hydroxy protecting group, as defined above, including benzoyl, acetyl, trimethylsilyl, triethylsilyl, methoxymethyl groups, for example.

The term "hydroxy prodrug group," as used herein, refers to a promoiety group which is known in the art to change the physicochemical, and hence the biological properties of a parent drug in a transient manner by covering or masking the hydroxy group. After said synthetic procedure(s), the hydroxy prodrug group as described herein must be capable of reverting back to hydroxy group *in vivo*. Hydroxy prodrug groups as known in the art are described generally in Kenneth B. Sloan, Prodrugs, Topical and Ocular Drug Delivery, (Drugs and the Pharmaceutical Sciences; Volume 53), Marcel Dekker, Inc., New York (1992).

The term "amino protecting group," as used herein, refers to a labile chemical moiety which is known in the art to protect an amino group against undesired reactions during synthetic procedures. After said synthetic procedure(s) the amino protecting group as described herein may be selectively removed. Amino protecting groups as known in the art are described generally in T.H. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons, New York (1999). Examples of amino protecting groups include, but are not limited to, methoxycarbonyl, t-butoxycarbonyl, 9-fluorenyl-methoxycarbonyl, benzyloxycarbonyl, and the like.

The term "protected amino," as used herein, refers to an amino group protected with an amino protecting group as defined above.

The term "leaving group" means a functional group or atom which can be displaced by another functional group or atom in a substitution reaction, such as a nucleophilic substitution reaction. By way of example, representative leaving groups include chloro, bromo and iodo groups; sulfonic ester groups, such as mesylate, tosylate, brosylate, nosylate and the like; and acyloxy groups, such as acetoxy, trifluoroacetoxy and the like.

The term "aprotic solvent," as used herein, refers to a solvent that is relatively inert to proton activity, i.e., not acting as a proton-donor. Examples include, but are not limited to, hydrocarbons, such as hexane and toluene, for example, halogenated hydrocarbons, such as, for example, methylene chloride, ethylene chloride, chloroform, and the like, heterocyclic compounds, such as, for example, tetrahydrofuran and N-methylpyrrolidinone, and ethers such as diethyl ether, bis-methoxymethyl ether. Such compounds are well known to those skilled in the art, and it will be obvious to those skilled in the art that individual solvents or mixtures thereof may be preferred for specific compounds and reaction conditions, depending upon such factors as the solubility of reagents, reactivity of reagents and preferred temperature ranges, for example. Further

discussions of aprotic solvents may be found in organic chemistry textbooks or in specialized monographs, for example: Organic Solvents Physical Properties and Methods of Purification, 4th ed., edited by John A. Riddick *et al.*, Vol. II, in the Techniques of Chemistry Series, John Wiley & Sons, NY, 1986.

The term "protic solvent," as used herein, refers to a solvent that tends to provide protons, such as an alcohol, for example, methanol, ethanol, propanol, isopropanol, butanol, t-butanol, and the like. Such solvents are well known to those skilled in the art, and it will be obvious to those skilled in the art that individual solvents or mixtures thereof may be preferred for specific compounds and reaction conditions, depending upon such factors as the solubility of reagents, reactivity of reagents and preferred temperature ranges, for example. Further discussions of protogenic solvents may be found in organic chemistry textbooks or in specialized monographs, for example: Organic Solvents Physical Properties and Methods of Purification, 4th ed., edited by John A. Riddick *et al.*, Vol. II, in the Techniques of Chemistry Series, John Wiley & Sons, NY, 1986.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable," as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., therapeutic or prophylactic administration to a subject).

The synthesized compounds can be separated from a reaction mixture and further purified by a method such as column chromatography, high pressure liquid chromatography, or recrystallization. As can be appreciated by the skilled artisan, further methods of synthesizing the compounds of the Formula herein will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the compounds described herein are known in the art and include, for example, those such as described in R. Larock, Comprehensive Organic Transformations, 2nd Ed. Wiley-VCH (1999); T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley and Sons (1999); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); and L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995), and subsequent editions thereof.

The term "subject," as used herein, refers to an animal. Preferably, the animal is a mammal. More preferably, the mammal is a human. A subject also refers to, for example, dogs, cats, horses, cows, pigs, guinea pigs, fish, birds and the like.

The compounds of this invention may be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and may include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

The compounds described herein contain one or more asymmetric centers and thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)-, or as (D)- or (L)- for amino acids. The present invention is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optical isomers may be prepared from their respective optically active precursors by the procedures described above, or by resolving the racemic mixtures. The resolution can be carried out in the presence of a resolving agent, by chromatography or by repeated crystallization or by some combination of these techniques which are known to those skilled in the art. Further details regarding resolutions can be found in Jacques, *et al.*, Enantiomers, Racemates, and Resolutions (John Wiley & Sons, 1981). When the compounds described herein contain olefinic double bonds, other unsaturation, or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both *E* and *Z* geometric isomers or cis- and trans-isomers. Likewise, all tautomeric forms are also intended to be included. Tautomers may be in cyclic or acyclic. The configuration of any carbon-carbon double bond appearing herein is selected for convenience only and is not intended to designate a particular configuration unless the text so states; thus a carbon-carbon double bond or carbon-heteroatom double bond depicted arbitrarily herein as *trans* may be *cis*, *trans*, or a mixture of the two in any proportion.

Certain compounds of the present invention may also exist in different stable conformational forms which may be separable. Torsional asymmetry due to restricted rotation about an asymmetric single bond, for example because of steric hindrance or ring strain, may permit separation of different conformers. The present invention includes each conformational isomer of these compounds and mixtures thereof.

As used herein, the term "pharmaceutically acceptable salt," refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, *et al.* describes pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 66: 1-19 (1977). The salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or separately by reacting the free base function with a suitable organic acid. Examples of pharmaceutically acceptable salts include, but are not limited to, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include, but are not limited to, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentane-propionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, *p*-toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, alkyl having from 1 to 6 carbon atoms, sulfonate and aryl sulfonate.

As used herein, the term "pharmaceutically acceptable ester" refers to esters which hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Examples of particular esters include, but are not limited.

PHARMACEUTICAL COMPOSITIONS

The pharmaceutical compositions of the present invention comprise a therapeutically effective amount of a compound of the present invention formulated together with one or more pharmaceutically acceptable carriers or excipients.

As used herein, the term "pharmaceutically acceptable carrier or excipient" means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols such as propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir, preferably by oral administration or administration by injection. The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compound or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intra-arterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol,

benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions, may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectable.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions that are compatible with body tissues.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or: a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be

required. Ophthalmic formulation, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to the compounds of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

For pulmonary delivery, a therapeutic composition of the invention is formulated and administered to the patient in solid or liquid particulate form by direct administration e.g., inhalation into the respiratory system. Solid or liquid particulate forms of the active compound prepared for practicing the present invention include particles of respirable size: that is, particles of a size sufficiently small to pass through the mouth and larynx upon inhalation and into the bronchi and alveoli of the lungs. Delivery of aerosolized therapeutics, particularly aerosolized antibiotics, is known in the art (see, for example U.S. Pat. No. 5,767,068 to Van Devanter *et al.*, U.S. Pat. No. 5,508,269 to Smith *et al.*, and WO 98/43650 by Montgomery, all of which are incorporated herein by reference).

ANTIVIRAL ACTIVITY

An inhibitory amount or dose of the compounds of the present invention may range from about 0.01 mg/Kg to about 500 mg/Kg, alternatively from about 1 to about 50 mg/Kg. Inhibitory amounts or doses will also vary depending on route of administration, as well as the possibility of co-usage with other agents.

According to the methods of treatment of the present invention, viral infections, conditions are treated or prevented in a patient such as a human or another animal by administering to the patient a therapeutically effective amount of a compound of the invention, in such amounts and for such time as is necessary to achieve the desired result.

By a "therapeutically effective amount" of a compound of the invention is meant an amount of the compound which confers a therapeutic effect on the treated subject, at a reasonable benefit/risk ratio applicable to any medical treatment. The therapeutic effect may be objective (i.e., measurable by some test or marker) or subjective (i.e., subject gives an indication of or feels an effect). An effective amount of the compound described above may range from about 0.1 mg/Kg to about 500 mg/Kg, preferably from about 1 to about 50 mg/Kg. Effective doses will also vary depending on route of administration, as well as the possibility of co-usage with other agents. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or contemporaneously with the specific compound employed; and like factors well known in the medical arts.

The total daily dose of the compounds of this invention administered to a human or other animal in single or in divided doses can be in amounts, for example, from 0.01 to 50 mg/kg body weight or more usually from 0.1 to 25 mg/kg body weight. Single dose compositions may contain such amounts or submultiples thereof to make up the daily dose. In general, treatment regimens according to the present invention comprise administration to a patient in need of such treatment from about 10 mg to about 1000 mg of the compound(s) of this invention per day in single or multiple doses.

The compounds of the present invention described herein can, for example, be administered by injection, intravenously, intra-arterial, subdermally, intraperitoneally, intramuscularly, or subcutaneously; or orally, buccally, nasally, transmucosally, topically, in an ophthalmic preparation, or by inhalation, with a dosage ranging from about 0.1 to about 500 mg/kg of body weight, alternatively dosages between 1 mg and 1000 mg/dose, every 4 to 120 hours, or according to the requirements of the particular drug. The methods herein contemplate administration of an effective amount of compound or compound composition to achieve the desired or stated effect. Typically, the pharmaceutical compositions of this invention will be administered from about 1 to about 6 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or

acute therapy. The amount of active ingredient that may be combined with pharmaceutically excipients or carriers to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Alternatively, such preparations may contain from about 20% to about 80% active compound.

Lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, condition or symptoms, the patient's disposition to the disease, condition or symptoms, and the judgment of the treating physician.

Upon improvement of a patient's condition, a maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

When the compositions of this invention comprise a combination of a compound of the Formula described herein and one or more additional therapeutic or prophylactic agents, both the compound and the additional agent should be present at dosage levels of between about 1 to 100%, and more preferably between about 5 to 95% of the dosage normally administered in a monotherapy regimen. The additional agents may be administered separately, as part of a multiple dose regimen, from the compounds of this invention. Alternatively, those agents may be part of a single dosage form, mixed together with the compounds of this invention in a single composition.

The said "additional therapeutic or prophylactic agents" includes but not limited to, immune therapies (eg. interferon), therapeutic vaccines, antifibrotic agents, anti-inflammatory agents such as corticosteroids or NSAIDs, bronchodilators such as beta-2 adrenergic agonists and xanthines (e.g. theophylline), mucolytic agents, anti-muscarinics, anti-leukotrienes, inhibitors of cell adhesion (e.g. ICAM antagonists), anti-oxidants (eg N-acetylcysteine), cytokine agonists, cytokine antagonists, lung surfactants and/or antimicrobial and anti-viral agents (e.g. ribavirin and amantidine). The compositions

according to the invention may also be used in combination with gene replacement therapy.

Combination and Alternation Therapy for HBV

It has been recognized that drug-resistant variants of HIV, HBV and HCV can emerge after prolonged treatment with an antiviral agent. Drug resistance most typically occurs by mutation of a gene that encodes for a protein such as an enzyme used in viral replication, and most typically in the case of HIV, reverse transcriptase, protease, or DNA polymerase, and in the case of HBV, DNA polymerase, or in the case of HCV, RNA polymerase, protease, or helicase. Recently, it has been demonstrated that the efficacy of a drug against HIV infection can be prolonged, augmented, or restored by administering the compound in combination or alternation with a second, and perhaps third, antiviral compound that induces a different mutation from that caused by the principle drug. The compounds can be used for combination are selected from the group consisting of a HBV polymerase inhibitor, interferon, TLR modulators such as TLR-7 agonists or TLR-9 agonists, therapeutic vaccines, immune activator of certain cellular viral RNA sensors, viral entry inhibitor, viral maturation inhibitor, distinct capsid assembly modulator, antiviral compounds of distinct or unknown mechanism, and combination thereof. Alternatively, the pharmacokinetics, biodistribution, or other parameter of the drug can be altered by such combination or alternation therapy. In general, combination therapy is typically preferred over alternation therapy because it induces multiple simultaneous stresses on the virus.

Preferred compounds for combination or alternation therapy for the treatment of HBV include 3TC, FTC, L-FMAU, interferon, adefovir dipivoxil, entecavir, telbivudine (L-dT), valtorcitabine (3'-valinyl L-dC), β-D-dioxolanyl-guanine (DXG), β-D-dioxolanyl-2,6-diaminopurine (DAPD), and β-D-dioxolanyl-6-chloropurine (ACP), famciclovir, penciclovir, lobucavir, ganciclovir, and ribavirin.

Although the invention has been described with respect to various preferred embodiments, it is not intended to be limited thereto, but rather those skilled in the art will recognize that variations and modifications may be made therein which are within the spirit of the invention and the scope of the appended claims.

Abbreviations

Abbreviations which may be used in the descriptions of the scheme and the examples that follow are: Ac for acetyl; AcOH for acetic acid; AIBN for azobisisobutyronitrile; BINAP for 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl; Boc_2O for di-*tert*-butyl-dicarbonate; Boc for *t*-butoxycarbonyl; Bpoc for 1-methyl-1-(4-biphenylyl)ethyl carbonyl; Bz for benzoyl; Bn for benzyl; BocNHOH for *tert*-butyl N-hydroxycarbamate; t-BuOK for potassium *tert*-butoxide; Bu_3SnH for tributyltin hydride; BOP for (benzotriazol-1-yloxy)tris(dimethylamino)phospho-nium Hexafluorophosphate; Brine for sodium chloride solution in water; BSA for N,O-bis(trimethylsilyl)acetamide; CDI for carbonyldiimidazole; CH_2Cl_2 for dichloromethane; CH_3 for methyl; CH_3CN for acetonitrile; Cs_2CO_3 for cesium carbonate; CuCl for copper (I) chloride; CuI for copper (I) iodide; dba for dibenzylidene acetone; dppb for diphenylphos-phinobutane; DBU for 1,8-diazabicyclo[5.4.0]-undec-7-ene; DCC for N,N'-dicyclohexyl-carbodiimide; DEAD for diethylazodicarboxylate; DIAD for diisopropyl azodicarboxylate; DIPEA or $(i\text{-}Pr)_2EtN$ for N,N,-diisopropylethyl amine; Dess-Martin periodinane for 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one; DMAP for 4-dimethylamino-pyridine; DME for 1,2-dimethoxyethane; DMF for N,N-dimethylformamide; DMSO for dimethyl sulfoxide; DMT for di(*p*-methoxyphenyl)-phenylmethyl or dimethoxytrityl; DPPA for diphenylphosphoryl azide; EDC for N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide; EDC HCl for N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride; EtOAc for ethyl acetate; EtOH for ethanol; Et_2O for diethyl ether; HATU for O-(7-azabenzotriazol-1-yl)-N,N,N',N',-tetramethyluronium Hexafluoro-phosphate; HCl for hydrogen chloride; HOBT for 1-hydroxybenzotriazole; K_2CO_3 for potassium carbonate; *n*-BuLi for *n*-butyl lithium; *i*-BuLi for *i*-butyl lithium; *t*-BuLi for *t*-butyl lithium; PhLi for phenyl lithium; LDA for lithium diisopropylamide; LiTMP for lithium 2,2,6,6-tetramethyl-piperidinate; MeOH for methanol; Mg for magnesium; MOM for methoxymethyl; Ms for mesyl or $-SO_2-CH_3$; Ms_2O for methanesulfonic anhydride or mesyl-anhydride; MTBE for t-butyl methyl ether; $NaN(TMS)_2$ for sodium bis(trimethylsilyl)amide; NaCl for sodium chloride; NaH for sodium hydride; $NaHCO_3$ for sodium bicarbonate or sodium hydrogen carbonate; Na_2CO_3 for sodium carbonate; NaOH for sodium hydroxide; Na_2SO_4 for sodium sulfate; $NaHSO_3$ for sodium bisulfite or sodium hydrogen sulfite; $Na_2S_2O_3$ for sodium thiosulfate; NH_2NH_2 for hydrazine; NH_4HCO_3 for ammonium bicarbonate; NH_4Cl for ammonium chloride; NMO for N-methylmorpholine N-oxide; $NaIO_4$ for sodium periodate; Ni for

nickel; OH for hydroxyl; OsO_4 for osmium tetroxide; PTSA for *p*-toluenesulfonic acid; PPTS for pyridinium *p*-toluenesulfonate; TBAF for tetrabutylammonium fluoride; TEA or Et_3N for triethylamine; TES for triethylsilyl; TESCl for triethylsilyl chloride; TESOTf for triethylsilyl trifluoromethanesulfonate; TFA for trifluoroacetic acid; THF for tetrahydrofuran; TMEDA for N,N,N',N'-tetramethylethylene-diamine; TPP or PPh_3 for triphenyl-phosphine; Troc for 2,2,2-trichloroethyl carbonyl; Ts for tosyl or $-SO_2-C_6H_4CH_3$; Ts_2O for tolylsulfonic anhydride or tosyl-anhydride; TsOH for p-tolylsulfonic acid; Pd for palladium; Ph for phenyl; POPd for dihydrogen dichlorobis(di-tert-butylphosphinito-κP)palladate(II); $Pd_2(dba)_3$ for tris(dibenzylideneacetone) dipalladium (0); $Pd(PPh_3)_4$ for tetrakis(triphenylphosphine)palladium (0); $PdCl_2(PPh_3)_2$ for trans-dichlorobis-(triphenylphosphine)palladium (II); Pt for platinum; Rh for rhodium; rt for room temperature; Ru for ruthenium; TBS for *tert*-butyl dimethylsilyl; TMS for trimethylsilyl; or TMSCl for trimethylsilyl chloride.

SYNTHETIC METHODS

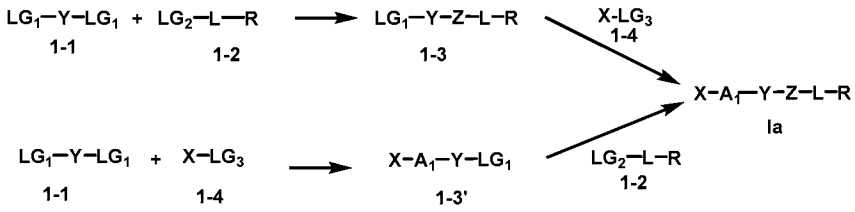
The compounds and processes of the present invention will be better understood in connection with the following synthetic schemes that illustrate the methods by which the compounds of the invention may be prepared. These schemes are of illustrative purpose, and are not meant to limit the scope of the invention. Equivalent, similar, or suitable solvents, reagents or reaction conditions may be substituted for those particular solvents, reagents, or reaction conditions described herein without departing from the general scope of the method of synthesis.

The compounds of the present invention may be prepared via several different synthetic strategies and routes from a variety of phenyl, 5- and 6-membered heteroaryl or fused bicyclic aryl or heteroaryl precursors using the reactions that are known to those skilled in the art. In a general strategy, specific aryl or heteroaryl moieties in the target molecules are connected together via suitable reactions from properly functionalized aryl or heteroaryl precursors. These reactions include, but not limited to, organometallics catalyzed cross-coupling, amino nucleophilic displacement reaction, carbodiimide (DCC, EDC) mediated amide formation, Curtius rearrangement, *et al.* More specifically, two general strategies could be envisioned; in the first scenario, A_2 is absent and Y is connected with Z directly. Y is firstly connected with L through a linker, which is transformed into Z through proper functional group manipulation. In the other scenario, A_2

is –NH-. The A_2 amino group is installed on Y or Z at first, and then couples with Z or Y through coupling conditions or substitution.

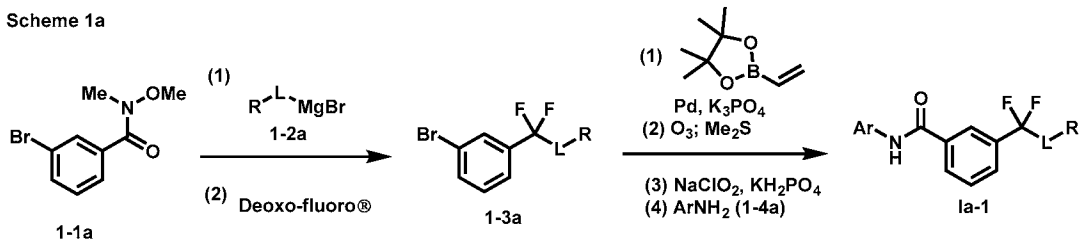
As illustrated in Scheme 1, wherein X, A_1, Y, Z, L, R are as defined previously for formula (I); LG_1 is independently selected from carboxyl acid, ester, amide, nitrile, halogen, triflate and acyl halide; LG_2 is independently selected from lithium, magnesium bromide, halogen, triflate and mesylate; LG_3 is amino, halo. An optionally substituted aryl or heteroaryl **1-1** reacts with **1-2** to give an intermediate **1-3** in which Y is connected with L through a linker. In most cases, this linker is a carbonyl, which could be transformed into Z through functional group manipulation. This intermediate **1-3** directly would couple with **1-4** to give a compound with general formula **Ia**. Additionally, when A_1 is azole, an optionally substituted aryl or heteroaryl **1-1** would react with **1-4** to give an intermediate **1-3'**. This intermediate **1-3'** would be coupled with **1-2** through a linker, which would be transformed into Z by functional group manipulation to give a compound with general formula **Ia**.

Scheme 1



As a specific example shown in Scheme 1a, amide compound **1-1a** would be treated with Grignard compound **1-2a** to afford a ketone intermediate which would be sequentially transformed to give difluoro product **1-3a**. The bromide on **1-3a** would be transformed into a carboxyl acid, through a sequence of Suzuki coupling, ozonolysis and Pinnick oxidation, which could react with an arylamino compound **1-4a** in the present of a suitable dehydrating reagent such as EDC, HATU and an organic base (TEA, DIPEA) in proper organic solvent (CH_2Cl_2, CH_3CN, DMF) to give a compound with general formula **Ia-1**.

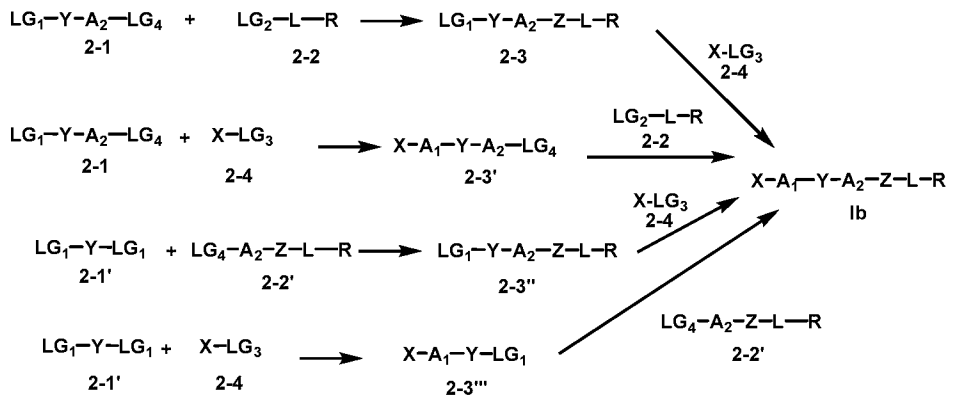
Scheme 1a



As illustrated in Scheme 2, wherein X, A_1, Y, L, R, LG_1, LG_2 and LG_3 are as defined previously, A_2 is –NH- and LG_4 is hydrogen or amino protecting group, an

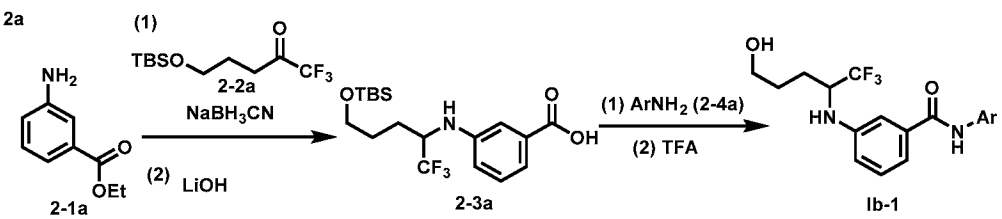
optionally substituted **2-1** reacts with an optionally substituted **2-2** to give the advanced intermediate **2-3.** The proper reaction employed here includes, but not limited to, reductive amination and substitution. Following similar procedure as in Scheme 1, a compound with general Formula **Ib** would be obtained. Alternatively, the starting material **2-1** could react with **2-4** to give the advanced intermediate **2-3'.** Follow similar procedure as in Scheme 1, a compound with the general formula **Ib** also would be obtained. Another alternative option is starting with **2-2'**. The C-N bond formation by the coupling between **2-1'** and **2-2'** could give the intermediate **2-3''**, which could be coupled with **2-4** to give the general Formula **Ib**. Another alternative option is coupling **2-1'** and **2-4** at first. The resulting intermediate **2-3'''** would be coupled with **2-2'** to give the compound of the general Formula **Ib**. It should be appreciated that the chemistry just described above may be variable to switch the coupling partners at certain steps to afford the same or isomeric target molecule.

Scheme 2



A specific example is shown in Scheme 2a. An aniline **2-1a** may react with trifluoromethyl ketone **2-2a** to give an amine intermediate **2-3a** from a reductive animation. When this intermediate **2-3a** was hydrolyzed, the resulting carboxylic acid could couple with aniline **2-4a**. The final deprotection could give the compound with general formula **Ib-1**.

Scheme 2a



It will be appreciated that, with appropriate manipulation and protection of any chemical functionality, synthesis of compounds of Formula (I) is accomplished by

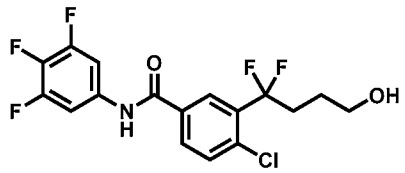
methods analogous to those above and to those described in the Experimental section. Suitable protecting groups can be found, but are not restricted to, those found in T W Greene and P G M Wuts "Protective Groups in Organic Synthesis", 3rd Ed (1999), J Wiley and Sons.

All references cited herein, whether in print, electronic, computer readable storage media or other form, are expressly incorporated by reference in their entirety, including but not limited to, abstracts, articles, journals, publications, texts, treatises, internet web sites, databases, patents, and patent publications.

EXAMPLES

The compounds and processes of the present invention will be better understood in connection with the following examples, which are intended as an illustration only and not limiting of the scope of the invention.

Example 1



Step 1a. To a solution of 5-bromo-2-chlorobenzoic acid (2.894 g, 12.29 mmol) in DMF (62 mL) was added HN(OMe)Me•HCl (1.199 g, 12.29 mmol), DIPEA (3.177 g, 24.58 mmol) and HATU (4.673 g, 24.8 mmol). Then the resulting solution was stirred at rt for 14 hours. The solution was partitioned (EtOAc-brine). The organic was dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed (silica, ethyl acetate/hexanes) to give the desired compound as a white solid (2.878 g, 84%). ESIMS m/z = 277.96 $[M+H]^+$.

Step 1b. To a solution of the compound from Step 1a (2.3710 g, 8.513 mmol) in THF (21.3 mL) at 0 °C was added a solution of 0.5 M 3-butenylmagnesium bromide in THF (25.54 mL, 12.77 mmol). Then the solution was stirred at 0 °C for 2 hours, then warmed up to rt and kept for 14 hours. The solution was partitioned (EtOAc-NH_4Cl aq. solution). The organic was dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed (silica, ethyl acetate/hexanes) to give the desired compound as colorless oil (1.687 g, 73%). 1H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 2.2 Hz, 1H), 7.50 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.34 – 7.21 (d, *J* = 8.4, Hz 1H), 5.86 (dq, *J* = 16.8, 7.3 Hz, 1H), 5.08 (d, *J*

= 17.1 Hz, 1H), 5.03 (d, *J* = 10.3 Hz, 1H), 3.04 (td, *J* = 7.3, 2.0 Hz, 2H), 2.47 (q, *J* = 7.2 Hz, 2H).

Step 1c. To a solution of the compound from Step 1b (1.061 g, 3.878 mmol) in DCM (4.0 mL) at rt was added ethanol (179 mg, 3.878 mmol) and DEOXO-FLUORO® (5.147 g, 23.27 mmol). Then the resulting solution was stirred at rt for 5 days. The solution was diluted with DCM (30 mL), then slowly poured into an Erlenmeyer Flask with 150 ml saturated $NaHCO_3$ aq. solution. $NaHCO_3$ solid was added into the mixture to neutralize excess DEOXO-FLUORO®. The solution was partitioned (EtOAc-brine). The organic was dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed (silica, ethyl acetate/hexanes) to give the desired compound as a yellow oil (923 mg, 81%). 1H NMR (500 MHz, $CDCl_3$)

δ 7.72 (d, *J* = 2.2 Hz, 1H), 7.49 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.31 (d, *J* = 8.5 Hz, 1H), 5.87 – 5.72 (m, 1H), 5.04 (d, *J* = 17.6 Hz, 1H), 5.00 (d, *J* = 10.8 Hz, 1H), 2.42 (m, 2H), 2.20 (q, *J* = 7.5 Hz, 2H).

Step 1d. To a solution of the compound from Step 1c (225 mg, 0.761 mmol) in DCM (7.6 mL) at -78 °C was induced ozone until the solution changed into pale blue. Then O_2 was induced until the blue color disappeared. The solution was warmed to 0 °C and $NaBH_4$ (57.6 mg, 1.52 mmol) was added. The mixture was kept at 0 °C for 2 hours. The solution was partitioned (EtOAc-brine). The organic was dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed (silica, ethyl acetate/hexanes) to give the desired compound as colorless oil (103.2 mg, 46%). 1H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 2.1 Hz, 1H), 7.48 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 3.69 (t, *J* = 6.5 Hz, 2H), 2.43 (tdd, *J* = 16.3, 8.8, 6.4 Hz, 2H), 1.83 – 1.67 (m, 2H).

Step 1e. To a solution of the compound from Step 1d (103.2 mg, 0.3445 mmol) in DCM (3.4 mL) at 0 °C was added 2,6-lutidine (107.2 mg, 1.034 mmol) and TBSOTf (133.6 mg, 0.5168 mmol). Then the resulting solution was stirred at 0 °C for 4 hours. The solution was partitioned (EtOAc-brine). The organic was dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed (silica, ethyl acetate/hexanes) to give the desired compound as colorless oil (102.7 mg, 72%). 1H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 2.3 Hz, 1H), 7.44 (d, *J* = 8.5 Hz, 1H), 7.27 (dd, *J* = 8.4, 2.1 Hz, 1H), 2.37 (tdd, *J* = 17.7, 7.9, 3.7 Hz, 2H), 1.69 – 1.53 (m, 2H), 0.85 (s, 9H), 0.19(s, 3H), -0.09 (s, 3H).

Step 1f. To a solution of 1.0M K_3PO_4 solution (1.165 mL, 1.165 mmol) was added vinylboronic acid pinacol ester (53.9 mg, 0.350 mmol) and toluene (6.0 mL), then the

mixture was stirred at rt for 10 minutes. The resulting mixture was transferred into another solution of the compound from Step 1e (96.6 mg, 0.233 mmol) in toluene (4.0 mL). Then PPh_3 (61.1 mg, 0.233 mmol) and $Pd(OAc)_2$ (10.5 mg, 0.0466 mmol) were added into the mixture. The reaction mixture was degased by bubbling N_2 for 5 minutes. The mixture was then heated to 95 °C and kept for 14 hours. The mixture was partitioned (EtOAc-brine). The organic was dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed (silica, ethyl acetate/hexanes) to give the desired compound as colorless oil (83.6 mg, 99%).

1H NMR (500 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.35 (s, 1H), 6.66 (ddd, J = 17.6, 10.8, 1.9 Hz, 1H), 5.75 (dd, J = 17.6, 1.9 Hz, 1H), 5.31 (dd, J = 11.0, 1.9 Hz, 1H), 3.59 (dt, J = 6.5, 3.8 Hz, 2H), 2.39 (dq, J = 23.5, 8.5, 7.7 Hz, 2H), 1.61 (dq, J = 11.8, 6.5 Hz, 2H), 0.85 (s, 9H), -0.00 (s, 3H), -0.02 (s, 3H).

Step 1g. To a solution of the compound from Step 1f (83.6 mg, 0.232 mmol) in DCM (5.0 mL) mL) at -78 °C was induced ozone until the solution changed into pale blue. Then O_2 was induced until the blue color disappeared. Me_2S (0.2 mL) was added. The mixture was warmed to rt and kept for 14 hours. The solution was concentrated and the residue was chromatographed (silica, ethyl acetate/hexanes) to give the desired compound as colorless oil (51.5 mg, 62%).1H NMR (500 MHz, $CDCl_3$) δ 10.00 (d, J = 1.7 Hz, 1H), 8.07 (t, J = 1.9 Hz, 1H), 7.86 (dt, J = 8.4, 1.9 Hz, 1H), 7.59 (d, J = 8.1 Hz, 1H), 3.61 (t, J = 6.1 Hz, 2H), 2.42 (dt, J = 16.8, 7.9 Hz, 2H), 1.75 – 1.50 (m, 2H), 0.85 (s, 9H), -0.00 (s, 6H).

Step 1h. To a solution of the compound from Step 1g (51.5 mg, 0.142 mmol) in a mixture of 2-methyl-2-butene (2.0 mL) and *t*-BuOH (2.0 mL) at 0 °C was added a solution of 1.25 M KH_2PO_4 solution (0.5 mL) and $NaClO_2$ (80%, 160 mg, 1.42 mmol). Then the resulting mixture was stirred at 0 °C for 3 hours. The solution was partitioned (EtOAc-brine). The organic was dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed (silica, ethyl acetate/hexanes) to give the desired compound as colorless oil (43.3 mg, 81%).

1H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, J = 2.1 Hz, 1H), 8.05 (d, J = 7.9 Hz, 1H), 7.53 (d, J = 8.3 Hz, 1H), 3.61 (t, J = 6.3 Hz, 2H), 2.41 (tt, J = 16.6, 6.6 Hz, 2H), 1.62 (dq, J = 13.6, 6.3 Hz, 2H), 0.84 (s, 9H), -0.00 (s, 6H).

Step 1i. To a solution of the compound from Step 1h (34.2 mg, 0.0903 mmol) in DMF (3.0 mL) was added 3,4,5-trifluoroaniline (13,3 mg, 0.0903 mmol), DIPEA (23.3 mg, 0.181 mmol) and HATU (34.3 mg, 0.0903 mmol). Then the resulting solution was stirred

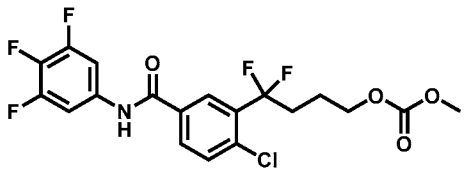
at rt for 14 hours. The solution was partitioned (EtOAc-brine). The organic was dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed (silica, ethyl acetate/hexanes) to give the desired compound as colorless oil (16.4 mg, 36%).

1H NMR (500 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.87 (s, 1H), 7.85 – 7.79 (m, 1H), 7.54 (d, *J* = 8.3 Hz, 1H), 7.36 (dd, *J* = 8.9, 6.1 Hz, 1H), 3.60 (t, *J* = 5.7 Hz, 2H), 2.41 (tt, *J* = 16.9, 7.9 Hz, 2H), 1.60 (q, *J* = 7.5, 6.2 Hz, 2H), 0.91 (s, 9H), -0.06 (s, 6H).

Step 1j. To a solution of the compound from Step 1i (16.4 mg, 0.0323 mmol) in THF (3.2 mL) at 0 °C was added a solution of 1.0 M TBAF (96.9 μL, 0.0969 mmol). Then the resulting solution was stirred at 0°C for 6 hours. The solution was partitioned (EtOAc-brine). The organic was dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed (silica, ethyl acetate/hexanes) to give the title compound as white powder (10.8 mg, 85%).

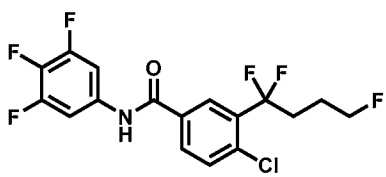
1H NMR (500 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.91 (s, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 8.3 Hz, 1H), 7.30 (dd, *J* = 8.9, 6.2 Hz, 1H), 3.61 (t, *J* = 6.4 Hz, 2H), 2.35 (dq, *J* = 23.6, 8.5, 7.9 Hz, 2H), 1.63 (m, 2H).

Example 2



Step 2a. A mixture of the title compound 1 (11.2 mg, 0.028), pyridine (258 mg, 2.84 mmol) and methyl chloroformate (4.0 mg, 0.043 mmol) in CH2Cl2 (1.4 mL) was stirred at rt for overnight. The mixture was concentrated and the residue was chromatographed (silice gel, EtOAc/hexanes) to give the title compound (10.8 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.04 (d, *J* = 2.2 Hz, 1H), 7.94 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.61 (d, *J* = 8.3 Hz, 1H), 7.55 – 7.42 (m, 2H), 4.23 (t, *J* = 7.2 Hz, 2H), 3.78 (s, 3H), 2.51 (tt, *J* = 16.7, 7.3 Hz, 2H), 1.82 (p, *J* = 7.2 Hz, 2H).

Example 3

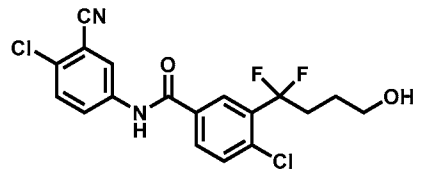


Step 3a. To a solution of the compound from Step 1d (146 mg, 0.49 mmol) in DCM (4.0 mL) at 0°C was added DAST (0.10 mL, 0.75 mmol) and the resulting solution was stirred

at rt overnight. Aqueous Sat. $NaHCO_3$ was added to the mixture and it was partitioned (EtOAc-brine). The organic was dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed (silica, ethyl acetate/hexanes) to give the desired compound as colorless oil (100 mg, 68%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.74 (d, *J* = 2.7 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 1H), 7.33 (d, *J* = 8.5 Hz, 1H), 4.51 (dt, *J* = 47.1, 6.1 Hz, 2H), 2.48 (tdd, *J* = 17.0, 9.2, 6.6 Hz, 2H), 1.98 – 1.83 (m, 2H).

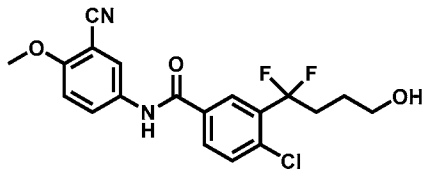
Step 3b-e. The title compound was prepared by a procedure similar to that described in step 1f-i. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.04 (s, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.83 (s, 1H), 7.61 (d, *J* = 8.3 Hz, 1H), 7.40 (dd, *J* = 8.9, 6.1 Hz, 2H), 4.52 (t, dt, *J* = 47.1, 6.1 Hz, 2H), 2.52 (tdd, *J* = 17.0, 9.2, 6.6, 2H), 1.93 (ddt, *J* = 31.8, 11.8, 5.8 Hz, 2H).

Example 4



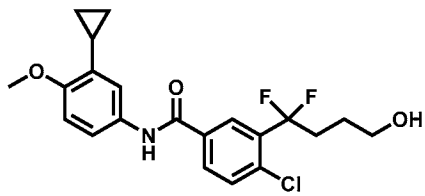
The title compound was prepared by a procedure similar to that described in example 1. MS $(M+H)^+$ 399.05, 401.05.

Example 5



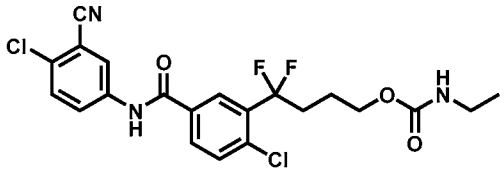
The title compound was prepared by a procedure similar to that described in example 1. MS $(M+H)^+$ 395.10, 397.10.

Example 6



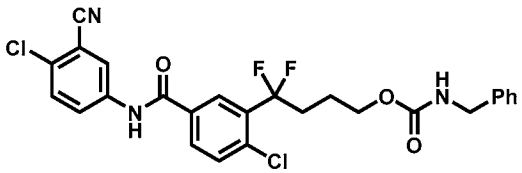
The title compound was prepared by procedure similar to that described in example 1. MS $(M+H)^+$ 410.14, 412.14.

Example 7



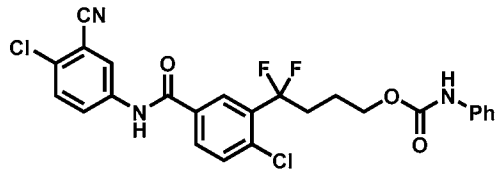
Step 7. To a solution of the title compound 4 (20 mg, 0.050 mmol) in DCM (0.4 mL) and DMF (0.1 mL) was added DIPEA (18 µL, 0.100 mmol) and ethyl isocyanate (8 µL, 0.100 mmol). The resulting solution was stirred at rt for 18 hours. The solution was partitioned (EtOAc-brine). The organic was dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed (silica, ethyl acetate/hexanes) to give the title compound as white solid (10 mg, 42%). MS ESI (M+NH4)+ 487.24, 488.27, 489.27, 490.25.

Example 8



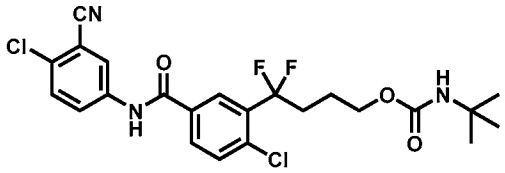
Step 8. To a solution of the title compound 4 (20 mg, 0.050 mmol) in DCM (0.4 mL) and DMF (0.1 mL) was added DIPEA (18 µL, 0.100 mmol) and benzyl isocyanate (12 µL, 0.100 mmol). The resulting solution was stirred at rt for 18 hours. The solution was partitioned (EtOAc-brine). The organic was dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed (silica, ethyl acetate/hexanes) to give the title compound as white solid (13 mg, 49%). MS ESI (M+H)+ 532.11, 534.10.

Example 9



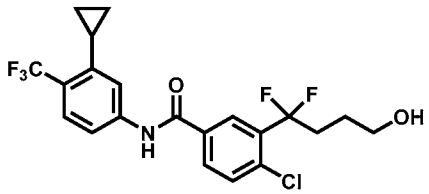
Step 9. To a solution of the title compound 4 (23 mg, 0.058 mmol) in DCM (0.45 mL) and DMF (0.12 mL) was added DIPEA (50 µL, 0.288 mmol) and phenyl isocyanate (31 µL, 0.288 mmol). The resulting solution was stirred at rt for 18 hours. The solution was partitioned (EtOAc-brine). The organic was dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed (silica, ethyl acetate/hexanes) to give the title compound as white solid (22 mg, 74%). MS ESI (M+NH4)+ 534.18, 535.18, 536.18, 537.18.

Example 10



Step 10. To a solution of the title compound 4 (24 mg, 0.050 mmol) in DCM (0.48 mL) and DMF (0.12 mL) was added DIPEA (53 μL, 0.300 mmol) and *tert*-butyl isocyanate (34 μL, 0.300 mmol). The resulting solution was stirred at rt for 18 hours. The solution was partitioned (EtOAc-brine). The organic was dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed (silica, ethyl acetate/hexanes) to give the title compound as white solid (3 mg, 5%). MS ESI (M+H)+ 498.12, 500.12.

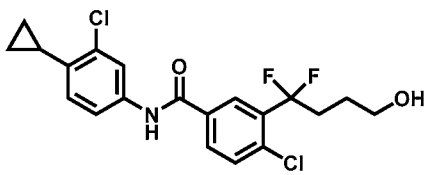
Example 11



Step 11a. To a solution of the compound from Step 1h (50 mg, 0.132 mmol) in acetonitrile (1 mL) was added 3-cyclopropyl-4-(trifluoromethyl)aniline (40 mg, 0.198 mmol), DMAP (4 mg, 0.033 mmol) and EDC (51 mg, 0.264 mmol). The resulting solution was stirred at rt for 18 hours. The solution was partitioned (EtOAc-brine). The organic was dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed (silica, ethyl acetate/hexanes) to give the desired compound as colorless oil (32 mg, 43%).

Step 11b. To a solution of the compound from Step 11a (32 mg, 0.057 mmol) in MeOH (2 mL) was added conc. HCl (50 μL, 1.65 mmol). The resulting solution was stirred at rt for 1 hour. The reaction mixture was concentrated. The residue was chromatographed (silica, methanol:dichloromethane) to give the title compound as white solid (22 mg, 86%). MS ESI (M-H)- 446.13, 448.11.

Example 12

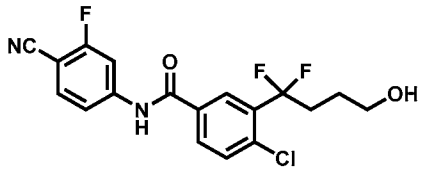


Step 12a. To a solution of the compound from Step 1h (50 mg, 0.132 mmol) in acetonitrile (1 mL) was added 3-chloro-4-cyclopropylaniline (33 mg, 0.198 mmol),

DMAP (4 mg, 0.033 mmol) and EDC (51 mg, 0.264 mmol). The resulting solution was stirred at rt for 18 hours. The solution was partitioned (EtOAc-brine). The organic was dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed (silica, ethyl acetate/hexanes) to give the desired compound as colorless oil (43 mg, 62%).

Step 12b. To a solution of the compound from Step 12a (43 mg, 0.081 mmol) in MeOH (2 mL) was added conc. HCl (50 μL, 1.65 mmol). The resulting solution was stirred at rt for 1 hour. The reaction mixture was concentrated. The residue was chromatographed (silica, methanol:dichloromethane) to give the title compound as white solid (33 mg, 98%). MS ESI (M-H)- 412.08, 414.06.

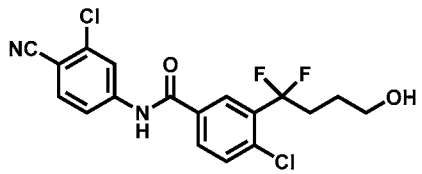
Example 13



Step 13a. To a solution of the compound from Step 1h (50 mg, 0.132 mmol) in acetonitrile (1 mL) was added 4-amino-2-fluorobenzonitrile (27 mg, 0.198 mmol), DMAP (4 mg, 0.033 mmol) and EDC (51 mg, 0.264 mmol). The resulting solution was stirred at rt for 18 hours. The solution was partitioned (EtOAc-brine). The organic was dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed (silica, ethyl acetate/hexanes) to give the desired compound as yellow oil (17 mg, 26%).

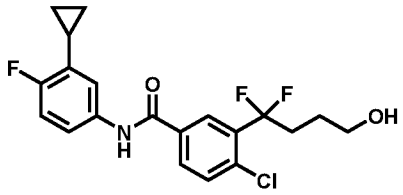
Step 13b. To a solution of the compound from Step 13a (17 mg, 0.034 mmol) in MeOH (2 mL) was added conc. HCl (50 μL, 1.65 mmol). The resulting solution was stirred at rt for 1 hour. The reaction mixture was concentrated. The residue was chromatographed (silica, methanol:dichloromethane) to give the title compound as white solid (11 mg, 84%). MS ESI (M-H)- 381.09, 383.07.

Example 14



The title compound was prepared by a procedure similar to that described in example 1. MS $(M-H)^-$ 397.03, 399.03.

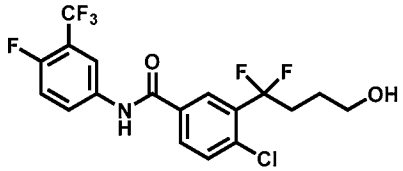
Example 15



The title compound was prepared by a procedure similar to that described in example 1.

MS $(M+H)^{+-}$ 398.12, 400.12.

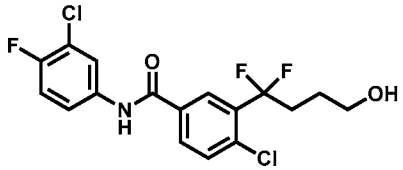
Example 16



The title compound was prepared by a procedure similar to that described in example 1.

MS $(M-H)^{-}$ 424.05, 426.05.

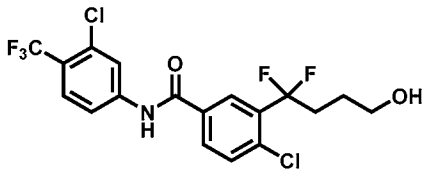
Example 17



The title compound was prepared by a procedure similar to that described in example 1.

MS $(M-H)^{-}$ 390.02, 392.02.

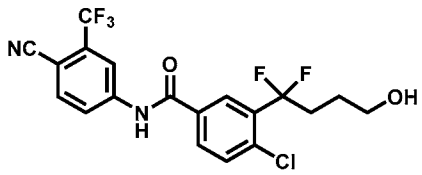
Example 18



The title compound was prepared by a procedure similar to that described in example 1.

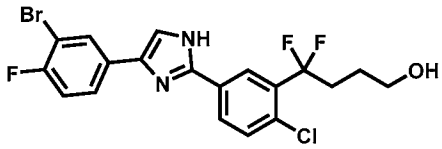
MS $(M-H)^{-}$ 440.02, 442.

Example 19



The title compound was prepared by a procedure similar to that described in example 1. MS $(M-H)^-$ 431.06, 433.06.

Example 20



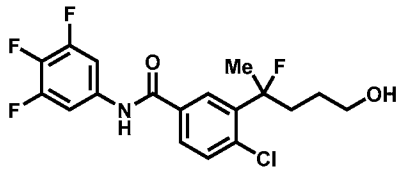
Step 20a: To a stirred solution of compound from step 1h (60 mg, 0.158 mmol) and 2-bromo-1-(3-bromo-4-fluorophenyl)ethan-1-one (70.3 mg, 0.238 mmol) in acetonitrile (1.0 ml) and DMF (1.0 ml) was addedsodium bicarbonate (39.9 mg, 0.475 mmol) at 0 °C. The resulting mixture was slowly warmed up to rt and stirred at rt overnight. The reaction mixture was then diluted with ethyl acetate (20 ml) and washed with brine (10 mL x 2). The organic layer was dried with Na_2SO_4, filtered and concentrated to provide a crude product, which was purified by ISCO silica gel chromatography (eluent: 0→60% ethyl acetate in hexane) to provide the desired compound (89 mg, 95%). ESI-MS m/z =591.06, 593.07 $[M-H]^-$.

Step 20b: A stirred mixture of 2-(3-bromo-4-fluorophenyl)-2-oxoethyl 3-(4-((tert-butyl-dimethylsilyl)oxy)-1,1-difluorobutyl)-4-chlorobenzoate (50 mg, 0.084 mmol), ammonium acetate (97 mg, 1.263 mmol) in toluene (2.0 ml) in a sealed heating tube was heated at 120 °C for 2h. The reaction mixture was diluted by DCM (20 mL), and washed with aq. $NaHCO_3$ solution (10mL). The organic layer was dried and concentrated to provide a crude product, which was purified by ISCO silica gel chromatography (eluent: 0→8% MeOH in DCM) to provide the desired compound (16 mg, 33%). ESI-MS m/z =573.11, 575.10 $[M+H]^+$.

Step 20c: To a stirred solution of 4-(3-bromo-4-fluorophenyl)-2-(3-(4-((tert-butyldimethyl-silyl)oxy)-1,1-difluorobutyl)-4-chlorophenyl)-1H-imidazole (5 mg, 8.71 µmol) in MeOH (2.0 ml) was added concentrated HCl (0.073 ml, 0.871 mmol) at 0 °C. The reaction was stirred at rt for 30min.The mixture was then concentrated under reduced pressure. The residue was re-dissovled in DCM (30 mL) and was washed with aq.

NaHCO3 solution (10 mL x 2). The organic layer was seperated, dried and concentrated to give a crude residue, which was purified by ISCO silica gel chromatography (eluent: 0→8% MeOH in DCM) to provide the title compound (2.3 mg, 57%). ^{1}H NMR (400 MHz, Methanol-*d*4) δ 8.22 (d, *J* = 2.2 Hz, 1H), 8.08 (dd, *J* = 6.7, 2.2 Hz, 1H), 7.99(dd, *J* = 8.5, 2.2 Hz, 1H), 7.78 (ddd, *J* = 8.8, 4.6, 2.2 Hz, 1H), 7.68 – 7.50 (m, 2H), 7.24 (t, *J* = 8.6Hz, 1H), 3.58 (t, *J* = 6.4 Hz, 2H), 2.48 (dp, *J* = 16.7, 7.9 Hz, 2H), 1.77 – 1.55 (m, 2H). ESI-MS m/z =459.05, 461.05 $[M+H]^+$.

Example 21



Step 21a. To a solution of the compound from Step 1b (1.265 g, 4.62 mmol) in THF (23 mL) at 0 °C was added methylmagnesium bromide (2.31 mL, 6.94 mmol, 3M in Et_2O). The resulting solution was stirred at rt for 18 hours. The solution was partitioned (EtOAc-NH_4Cl). The organic was dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed (silica, ethyl acetate/hexanes) to give the desired compound as colorless oil (1.225 g, 91%).

Step 21b. To a solution of the compound from Step 21a (600 mg, 2.07 mmol) in DCM (2.1 mL) was added DEOXO-FLUORO® (1.91 mL, 5.18 mmol). The resulting solution was stirred at rt for 1.5 hours. The solution was partitioned (DCM-$NaHCO_3$). The organic was dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed (silica, ethyl acetate/hexanes) to give the desired compound as colorless oil (450 mg, 75%).

Step 21c. To a solution of the compound from Step 21b (450 mg, 1.54 mmol) in DCM (15 mL) at -78 °C was induced ozone until the solution changed into pale blue. Then O_2 was induced until the blue color disappeared. Me_2S (1.14 mL, 15.4 mmol) was added. The solution was warmed to rt and kept 1h. Methanol (1.5 mL) and $NaBH_4$ (117 mg, 3.09 mmol) was added. The mixture was kept at rt for 3 hours. The solution was partitioned (EtOAc-brine). The organic was dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed (silica, ethyl acetate/hexanes) to give the desired compound as colorless oil (144 mg, 32%).

Step 21d. To a solution of the compound from Step 21c (144 mg, 0.487 mmol) in DCM (2.4 mL) at 0 °C was added 2,6-lutidine (170 μL, 1.46 mmol) and TBSOTf (157 μL, 0.974 mmol). Then the resulting solution was stirred at 0 °C for 30 minutes. The solution was

partitioned (EtOAc-brine). The organic was dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed (silica, ethyl acetate/hexanes) to give the desired compound as colorless oil (157 mg, 79%).

Step 21e. To a solution of 1.0M K_3PO_4 solution (2.68 mL, 2.68 mmol) was added vinylboronic acid pinacol ester (97 μL, 0.575 mmol) and toluene (7.0 mL), then the mixture was stirred at rt for 10 minutes. The resulting mixture was transferred into another solution of the compound from Step 21d (157 mg, 0.383 mmol) in toluene (5.0 mL). Then PPh_3 (100 mg, 0.383 mmol) and $Pd(OAc)_2$ (17.2 mg, 0.0766 mmol) were added into the mixture. The reaction mixture was degased by bubbling N_2 for 5 minutes. The mixture was then heated to 95 °C and kept for 14 hours. The mixture was partitioned (EtOAc-brine). The organic was dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed (silica, ethyl acetate/hexanes) to give the desired compound as colorless oil (87 mg, 64%).

Step 21f. To a solution of the compound from Step 21e (87 mg, 0.245 mmol) in DCM (5.0 mL) mL) at -78 °C was induced ozone until the solution changed into pale blue. Then O_2 was induced until the blue color disappeared. Me_2S (1 mL) was added. The mixture was warmed to rt and kept for 14 hours. The mixture was partitioned (EtOAc-brine). The organic was dried (Na_2SO_4), filtered and concentrated. The residue was used as crude (93 mg).

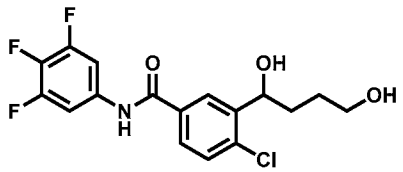
Step 21g. To a solution of the compound from Step 21f (93 mg, 0.245 mmol) in a mixture of 2-methyl-2-butene (2.0 mL) and *t*-BuOH (2.0 mL) at 0 °C was added a solution of 1.25 M KH_2PO_4 solution (0.5 mL) and $NaClO_2$ (80%, 160 mg, 1.42 mmol). Then the resulting mixture was stirred at 0 °C for 3 hours. The solution was partitioned (EtOAc-brine). The organic was dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed (silica, ethyl acetate/hexanes) to give the desired compound as colorless oil (85 mg, 87%).

Step 21h. To a solution of the compound from Step 21g (85 mg, 0.227 mmol) in DMF (1.1 mL) was added 3,4,5-trifluoroaniline (34 mg, 0.227 mmol), DIPEA (79 μL, 0.453 mmol) and HATU (86 mg, 0.227 mmol). Then the resulting solution was stirred at rt for 14 hours. The solution was partitioned (EtOAc-brine). The organic was dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed (silica, ethyl acetate/hexanes) to give the desired compound as colorless oil (105 mg, 92%).

Step 21i. To a solution of the compound from Step 21h (105 mg, 0.208 mmol) in MeOH (2 mL) at rt was conc. HCl (50 μL, 1.65 mmol). The resulting solution was stirred at rt for

1 hour. The reaction mixture was concentrated. The residue was chromatographed (silica, ethyl acetate:hexanes) to give the title compound as white solid (24 mg, 30%). MS ESI (M-H)- 388.151, 390.153.

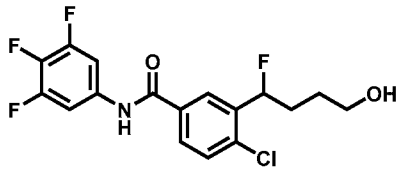
Example 22



Step 22a. To a solution of the compound from Step 1b (500 mg, 1.83 mmol) in MeOH (23 mL) at 0 °C was added $NaBH_4$ (84 mg, 2.19 mmol. The resulting solution was stirred at 0 °C for 1 hour. The solution was partitioned (EtOAc-brine). The organic was dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed (silica, ethyl acetate/hexanes) to give the desired compound as colorless oil (500 mg, 100%).

Step 22b-h. The title compound was prepared by a procedure similar to that described in example 21. MS ESI (M-H)- 372.080, 374.136.

Example 23



Step 23a. To a solution of the compound from Step 22a (250 mg, 1.83 mmol) in DCM (2.1 mL) was added DEOXO-FLUORO® (0.64 mL, 1.73 mmol). The resulting solution was stirred at rt for 1.5 hours. The solution was partitioned (DCM-$NaHCO_3$). The organic was dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed (silica, ethyl acetate/hexanes) to give the desired compound as colorless oil (185 mg, 77%).

Step 22b-h. The title compound was prepared by a procedure similar to that described in example 21. MS ESI (M-H)- 374.187, 376.081

BIOLOGICAL ACTIVITY

Methods: HepAD38 cells are maintained as previously reported (Ladner *et al*, *Antimicrob. Agents Chemother.* 1997, 4, 1715). Briefly, cells are passaged upon attaining confluency in DMEM/F12 media in the presence of 10% FBS, Penn/Strep, 250 μg/mL

G418, and 1 ug/ml tetracycline. Novel compounds are screened by first washing cells three times with PBS to remove tetracycline, and plating in 96 well plates at 35,000 cells/well. Compounds dissolved in DMSO are then diluted 1:200 into wells containing cells. Five days after compound addition, material is harvested for analysis. For an extended 8 day analysis, cells are plated and treated as described above, but media and compound are refreshed on d2 and d5 post initial treatment.

On harvest day, virion DNA is obtained by lysing with Sidestep Lysis and Stabilization Buffer and then quantified via quantitative real time PCR. Commercially available ELISA kits are used to quantitate the viral proteins HBsAg (Alpco) or HbeAg (US Biological) by following the manufacturer's recommended protocol after diluting samples to match the linear range of their respective assays. Irrespective of readout, compound concentrations that reduce viral product accumulation in the cell lysates or supernatants by 50% relative to no drug controls (EC_{50}) are reported; EC_{50} ranges are as follows: A < 1μM; B 1-10μM; C > 10μM.

Additionally, on day of harvest, compound toxicity is evaluated by treating cells with ATPlite 1Step according to the manufacturer's protocol. Compound concentrations that reduce total ATP levels in wells by 50% relative to no drug controls (CC_{50}) are reported; CC_{50} ranges are as follows: A > 30μM; B 10-30μM; C < 10μM.

Table 1 Summary of Activities

Compound Number	HepAD38 EC_{50} (μM)	CC_{50} (μM) ATPlite	CompoundNumber	HepAD38 EC_{50} (μM)	CC_{50} (μM) ATPlite
1	A	C	13	C	
2	B	B	14	C	
3	A	C	15	C	
4	C		16	C	
5	C		17	C	
6	B		18	C	
7	C		19	C	
8	C		20	C	
9	C		21	C	A
10	C		22	C	

11	C		23	C	
12	C				

.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

What is claimed:

1. A compound represented by Formula (I):

$$X-A_1-Y-A_2-Z-L-R \quad (I),$$

or a pharmaceutically acceptable salt thereof, wherein:

X is an optionally substituted aryl or optionally substituted heteroaryl;

A_1 is absent, or selected from the group consisting of –NH–, –NHC(O)–, –NHC(O)N(R_3)–, and optionally substituted azolyl;

Y is an optionally substituted aryl or optionally substituted heteroaryl;

A_2 is absent or –N(R_4)-;

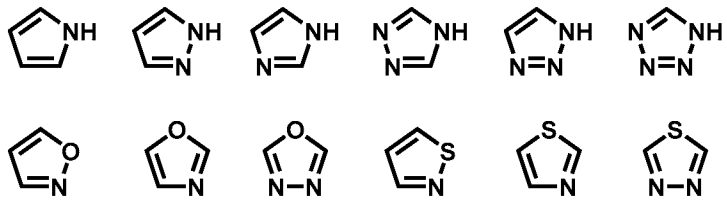
Z is –CR^aR^b–; wherein R^a and R^b are each independently selected from the group consisting of hydrogen, OH, OMe, halogen, and methyl optionally substitituted with 1 to 3 substituents selected from the group consisting of fluoro, chloro, OH, and OMe; wherein at least one of R^a and R^b is not hydrogen;

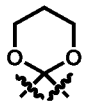
alternatively, R^a, R^b, and the carbon atom to which they are attached form an oxetanyl, 5- to 6-membered cyclic ketal, or -C(=CF_2)-;

L is –NR_1-, O or -CR_1R_2-; and

R, R_1, R_2, R_3 and R_4 at each occurrence are independently selected from the group consisting of hydrogen, optionally substituted –C_1-C_8 alkyl, optionally substituted –C_2-C_8 alkenyl, optionally substituted –C_2-C_8 alkynyl, optionally substituted –C_3-C_8 cycloalkyl, optionally substituted 3- to 8-membered heterocyclic, optionally substituted aryl and optionally substituted heteroaryl; alternatively, R_1 and R_2 or R_1 and R are taken together with the atom to which they are attached to form an optionally substituted C_3-C_8 cycloalkyl or an optionally substituted 3- to 8-membered heterocyclic.

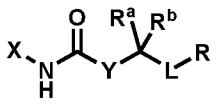
2. A compound of claim 1, wherein A_1 is –NHC(O)–, or –NHC(O)N(R_3)–, or an optionally substituted when possible azolyl group derived from one of the following, or a tautomer thereof, by removal of two hydrogen atoms:

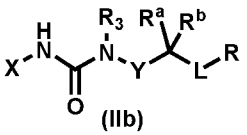


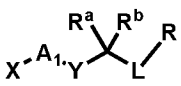
3. A compound of claim 1, wherein Z is selected from the group consisting of $-CF_2-$, $-CClF-$, $-CCl_2-$, $-CH(CF_3)-$, $-C(=CF_2)-$, $-CMe_2-$,  ,  , and  .

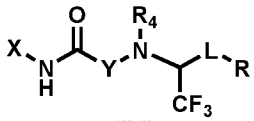
4. A compound of claim 1, wherein R is $-C_1$-C_8 alkyl, $-C_2$-C_8 alkenyl, $-C_2$-C_8 alkynyl , $-C_3$-C_8 cycloalkyl, or 3- to 8-membered heterocyclic, each optionally substituted with one, two or three groups independently selected from hydroxy, protected hydroxy, halo, -CN, amino, protected amino, optionally substituted -C_1-C_6 alkyl, optionally substituted –C_3-C_8 cycloalkyl, optionally substituted -C_1-C_3 alkoxy, -C(O)OR_{15}, -OC(O)NH- R_{15}, -C(O)NH- R_{15}, and -C(O)- R_{15}, wherein R_{15} is optionally substituted $-C_1$-C_8 alkyl, optionally substituted $-C_2$-C_8 alkenyl, optionally substituted $-C_2$-C_8 alkynyl, optionally substituted $-C_3$-C_8 cycloalkyl, optionally substituted 3- to 8-membered heterocyclic, optionally substituted aryl or optionally substituted heteroaryl.

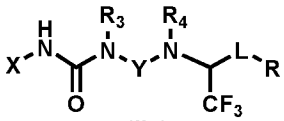
5. A compound of claim 1, represented by Formula (**IIa**), (**IIb**), (**IIc**), (**IId**), (**IIe**), or (**IIf**):

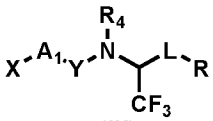

(IIa)


(IIb)


(IIc)


(IId)

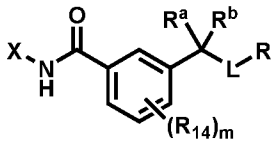

(IIe)

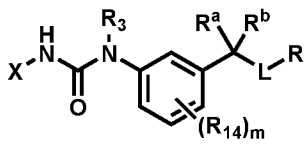

(IIf)

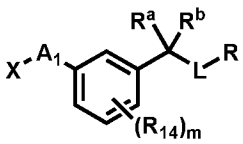
or a pharmaceutically acceptable salt thereof, wherein:

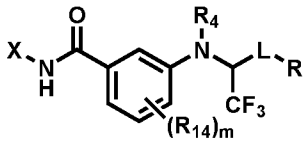
A_1 is an optionally substituted azole group; and X, Y, L, R_3, R_4, R, R^a, R^b are as defined in claim 1.

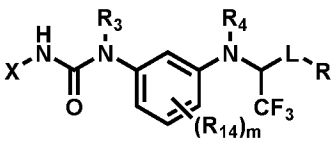
6. A compound of claim 1, represented by Formula (**IIa-1**), (**IIb-1**), (**IIc-1**), (**IId-1**), (**IIe-1**), or (**IIf-1**):

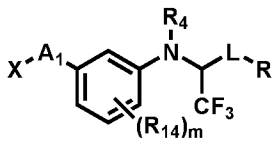

(IIa-1)


(IIb-1)


(IIc-1)


(IId-1)

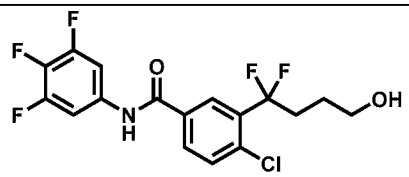
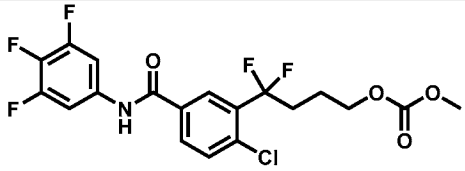
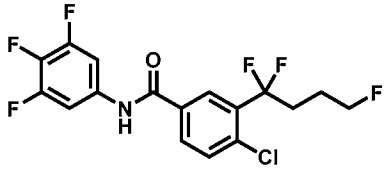

(IIe-1)

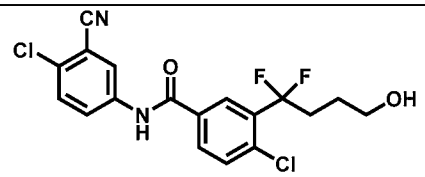
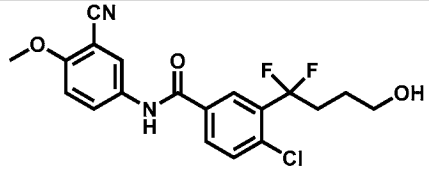
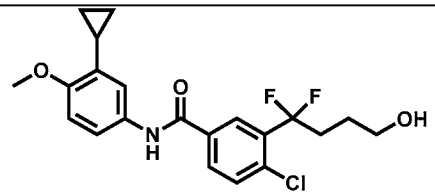
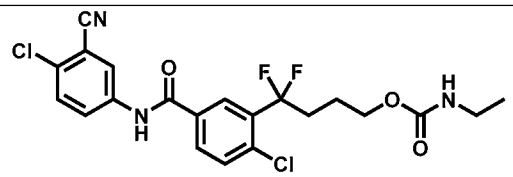
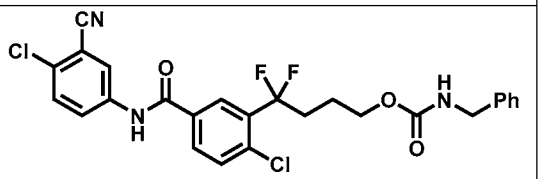
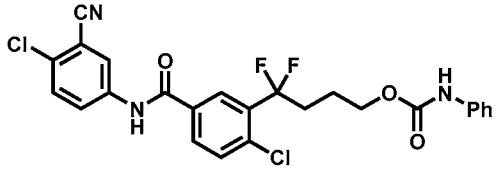
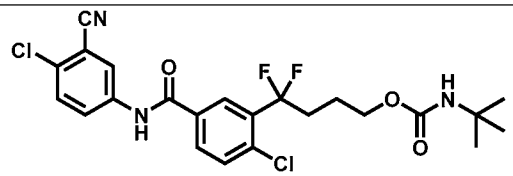
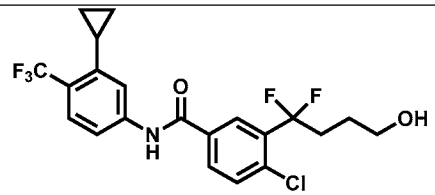
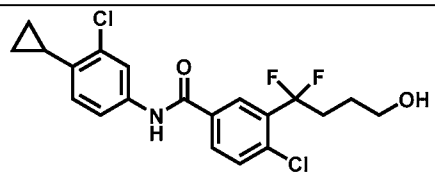

(IIf-1)

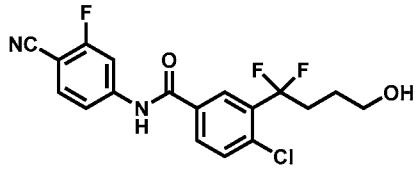
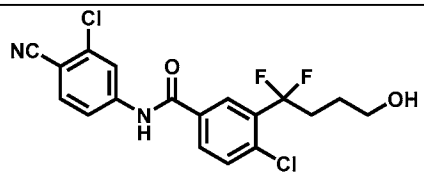
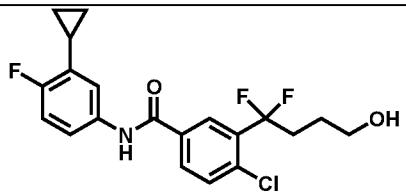
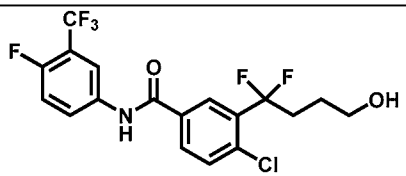
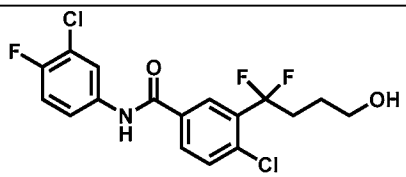
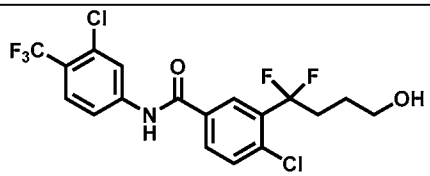
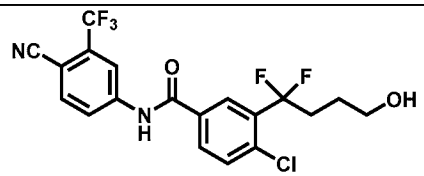
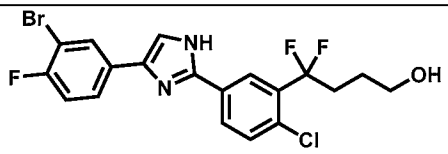
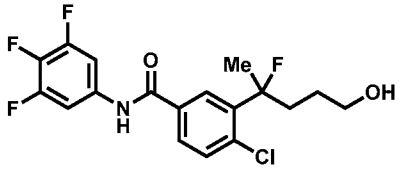
or a pharmaceutically acceptable salt thereof, wherein:

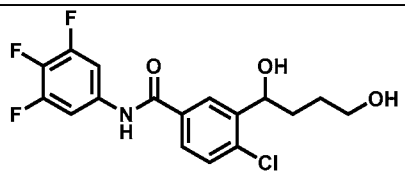
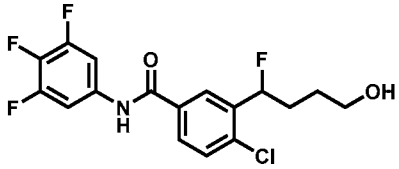
R_{14} at each occurrence is each independently selected from the groups consisting of hydrogen, hydroxy, protected hydroxy, halo, -CN, -NO_2, amino, protected amino, optionally substituted -C_1-C_6 alkyl, optionally substituted –C_2-C_8 alkenyl, optionally substituted –C_2-C_8 alkynyl, optionally substituted –C_3-C_8 cycloalkyl, optionally substituted 3- to 8-membered heterocyclic, optionally substituted -C_1-C_6 alkoxy, -$C(O)_2$-C_1-C_6 alkyl, -C(O)NH-C_1-C_6 alkyl, and -C(O)-C_1-C_6 alkyl; m is 0, 1, 2, 3 or 4; A_1 is an optionally substituted azole group; and X, L, R_3, R_4, R, R^a, R^b are as defined in claim 1.

7. The compound of claim 1, selected from the compounds set forth below or a pharmaceutically acceptable salt thereof:

Compound	Structure
1	
2	
3	

4	
5	
6	
7	
8	
9	
10	
11	
12	

13	
14	
15	
16	
17	
18	
19	
20	
21	

22	
23	

8. A pharmaceutical composition, comprising a compound or a combination of compounds according to any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier or excipient.

9. A method of treating or preventing an HBV infection in an individual in need thereof, comprising administering the subject a therapeutically effective amount of a compound or a combination of compounds of any one of claims 1 to 7.

10. The method of claim 9, further comprising administering to the individual at least one additional therapeutic agent selected from the group consisting of a HBV polymerase inhibitor, interferon, viral entry inhibitor, viral maturation inhibitor, literature-described capsid assembly modulator, reverse transcriptase inhibitor, TLR-agonist, inducer of cellular viral RNA sensor, therapeutic vaccine, and agents of distinct or unknown mechanism, and a combination thereof.

11. The method of claim 10, wherein the compound and the at least one additional therapeutic agent are co-formulated.

12. The method of claim 10, wherein the compound and the at least one additional therapeutic agent are co-administered.

13. The method of claim 10, wherein administering the compound allows for administering of the at least one additional therapeutic agent at a lower dose or frequency as compared to the administering of the at least one additional therapeutic agent alone that

is required to achieve similar results in prophylactically treating an HBV infection in an individual in need thereof.

14. The method of claim 9, wherein before administering the therapeutically effective amount of the compound of Formula (I), the individual is known to be refractory to a compound selected from the group consisting of a HBV polymerase inhibitor, interferon, viral entry inhibitor, viral maturation inhibitor, distinct capsid assembly modulator, inducer of cellular viral RNA sensor, therapeutic vaccine, antiviral compounds of distinct or unknown mechanism, and combination thereof.

15. The method of claim 9, wherein the administering of the compound reduces viral load in the individual to a greater extent compared to the administering of a compound selected from the group consisting of a HBV polymerase inhibitor, interferon, viral entry inhibitor, viral maturation inhibitor, distinct capsid assembly modulator, inducer of cellular viral RNA sensor, therapeutic vaccine, antiviral compounds of distinct or unknown mechanism, and combination thereof.

16. The method of claim 9, wherein the administering of the compound causes a lower incidence of viral mutation and/or viral resistance than the administering of a compound selected from the group consisting of a HBV polymerase inhibitor, interferon, viral entry inhibitor, viral maturation inhibitor, distinct capsid assembly modulator, inducer of cellular viral RNA sensor, therapeutic vaccine, antiviral compounds of distinct or unknown mechanism, and combination thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/43324

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07C 233/12; A61K 31/167; A61P 31/12 (2016.01)
CPC - C07C233/12; C07C233/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): C07C 233/12; A61K 31/167; A61P 31/12 (2016.01)
CPC: C07C233/12; C07C233/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 564/179; 564/168; 564/184

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Scholar, PubWEST, SureChem, Pubchem
Hepatitis B, HBV, infection, treat, benzanilide, benzamide, difluorobutyl, trifluorobutyl, Deoxo-fluor

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2011/0281950 A1 (BAIOCCHI et al.) 17 November 2011 (17.11.2011) para [0032]-[0033], [0048]-[0049], [0059]	1-3, 5-6, 8/(1-3,5-6)
Y		4, 8/4, 9-16
A		7, (8-16)/7
Y	US 7,741,494 B2 (BRESSI et al.) 22 June 2010 (22.06.2010) col 23, ln 5-31; col 168	4, (8-16)/4
A		7, (8-16)/7
Y	WO 2013/181584 A2 (GUO) 05 December 2013 (05.12.2013) para [0064], [0068]-[0069], [0084]	9-16
A	PUBCHEM-CID 63186259 Create Date: 22 October 2012 (22.10.2012) pg 3, Fig	7, (8-16)/7
A	US 2007/0225373 A1 (CHEN et al.) 27 September 2007 (27.09.2007) Fig 7	7, (8-16)/7

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
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Date of the actual completion of the international search	Date of mailing of the international search report
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