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(54) Title: N-HYDROXYPYRIMIDINE-2,4-DIONES AS INHIBITORS OF HIV AND HCV

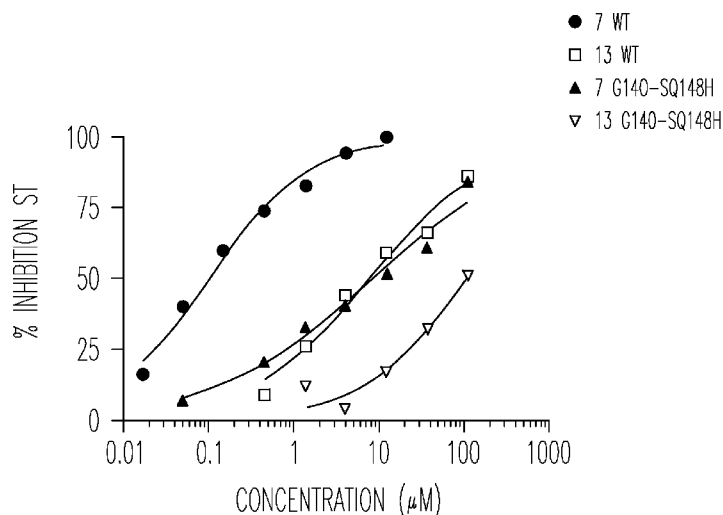


Fig. 1

(57) Abstract: The invention provides antiviral compounds that can be used in therapy against human immunodeficiency virus (HIV) and hepatitis C virus (HCV). Compounds of the invention can be dual targeted inhibitors of HIV, inhibiting both the reverse transcriptase and the integrase enzyme systems, thus increasing the barrier to development of viral resistance in patients. Prodrugs of the inventive antiviral compounds are also provided. Compounds of the invention can be used to treat HCV secondary infections in HIV-afflicted patients, reducing the need for administration of drug cocktails containing multiple, potentially conflicting, medicinal compounds. Methods of synthesis of the compounds and methods of treatment using the compounds are also provided.



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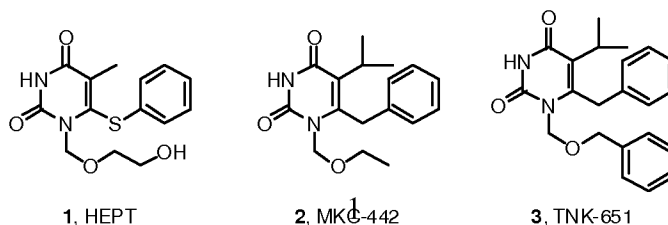
CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the priority of U.S. Ser. No. 61/389,795, filed on October 5, 2010, which is incorporated herein by reference in its entirety.

BACKGROUND

Due to their common routes of transmission, nearly a third of all human immunodeficiency virus (HIV) positive patients in the USA are also infected with hepatitis C virus (HCV).¹ This co-infection has a profound impact on the natural history of both viruses and the clinical management of infected patients. HIV co-infection causes a higher rate of viral persistence, increased viral load, and more rapid disease progression of HCV patients², and the same trend could be expected from HIV patients with HCV co-infection.³ Additionally, co-infection of HCV to HIV-1 patients compromises the highly active antiretroviral therapy (HAART)³, and treatment of HCV in HIV positive patients with the standard of care (SOC) yields substantially lower sustained virological response (SVR) rates than in HCV monoinfected patients⁴. Furthermore, the combined use of HAART and SOC for treating co-infected patients is confronted with markedly increased mitochondrial toxicities.⁵ Given such antagonisms between these two viral infections and their treatment regimens, it is highly desirable to develop antivirals active against both viruses.

HEPT (1)⁶ analogues constitute an important class of HIV non-nucleoside reverse transcriptase inhibitors (NNRTIs)⁷, among which MKC-442 (emivirine, 2)⁸⁻¹⁰ and TNK-651 (3)¹¹ (below) were candidates for clinical development. However, certain pharmaceutical barriers, particularly adverse drug-drug interactions, have limited their clinical efficacy. Simplifying the regimen setting of these drugs by converting them into multi-functional inhibitors would help overcome these barriers. By designing in additional inhibitory activity, these compounds could inhibit HCV as well.



The inventors herein have previously disclosed molecular scaffolds with dually inhibitory activities, particularly against HIV reverse transcriptase (RT) and integrase (IN) enzymes.¹²⁻

¹⁴Dual targeting can create a greater barrier to development of resistance by the viral strain than is normally encountered when only a single viral enzyme system is inhibited by a compound. Also, the use of dual targeting can result in an antiviral therapy in humans that requires less dosing complexity, minimizes drug-drug interactions, and reduces toxicity, all of which can serve to better patient adherence and a higher treatment success rate.

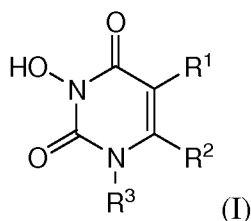
SUMMARY

The present invention is directed to compounds that can inhibit the viral replication of HIV through dual targeting of both the reverse transcriptase and the integrase enzymes of HIV, or can inhibit the viral replication of both HIV and HCV, or both; to methods of preparing the compounds; and to methods of using the compounds such as in the treatment of viral infections in human patients.

In various embodiments of the invention, compounds are provided for dual targeting of the HIV reverse transcriptase and integrase enzymes systems. In various embodiments, the invention provides an antiviral therapy against HIV wherein dual targeting of HIV RT and IN is used, a method of treatment of patients infected with HIV having some or all of the advantages outlined above.

In treating HIV infections, secondary viral infections are often encountered which can be of greater severity due to the immune-compromised status of the HIV-infected patient. The leading opportunistic co-infective agent is hepatitis C virus (HCV), which causes up to 50% of all HIV deaths due to severe liver damage. In various embodiments, the present invention provides compounds that are active against both HIV and HCV, and methods of treatment of HIV-infected patients who suffer from HCV co-infection.

In various embodiments, the invention provides a compound of formula (I)



wherein R^1 is hydrogen, (C₁-C₆)alkyl, (C₃-C₉)cycloalkyl, (C₃-C₉)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₄)aryl, or (C₆-C₁₄)aryl(C₁-C₆)alkyl, wherein any alkyl, cycloalkyl, cycloalkylalkyl, or aralkyl can be mono- or multi-substituted with J;

R^2 is hydrogen, (C₁-C₆)alkyl, (C₆-C₁₄)aryl, (C₆-C₁₄)aryl(C₁-C₆)alkyl, (C₆-C₁₄)aryl(C₁-C₆)alkoxy, (C₆-C₁₄) aroyl, (C₆-C₁₄) aryloxy, or a 5-9 membered mono- or bicyclic heteroaryl or heteroarylalkyl, wherein any alkyl or aryl or aralkyl or aroyl or aryloxy or heteroaryl is substituted with n R^5 groups;

or R^1 and R^2 together with the atoms to which they are bonded form a fused (C₃-C₉) cycloalkyl or (C₆-C₁₀) aryl, wherein the cycloalkyl or aryl is substituted with n R^5 groups;

R^3 is CH(R) R^4 , wherein R^4 is hydrogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₆-C₁₄)aryl, (C₆-C₁₄)aryloxy, (C₆-C₁₀)aryl(C₁-C₆)alkyl, or (C₆-C₁₀)aryl(C₁-C₆)alkoxy, wherein any alkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy is substituted with n_2 R^6 groups;

R is hydrogen or (C₁-C₆)alkyl;

J is halo, nitro, (C₁-C₆)alkoxy, or (C₁-C₆)alkyl;

R^5 is halo, nitro, (C₁-C₆)alkoxy, or (C₁-C₆)alkyl;

R^6 is halo, nitro, (C₁-C₆)alkoxy, or (C₁-C₆)alkyl;

$n = 0, 1, 2$, or 3 ;

$n_2 = 0, 1, 2$, or 3 ;

or a pharmaceutically acceptable salt thereof.

In various embodiments, the invention provides prodrugs of compounds of formula (I), wherein the prodrugs are N-hydroxy esters as described herein, such that the prodrugs have enhanced cellular uptake properties compared to the bioactive compounds of formula (I), resulting in higher intracellular concentrations of the compound of formula (I) following hydrolysis of the N-hydroxy ester *in vivo*.

In various embodiments, the invention provides a method of treating a viral infection, such as an HIV infection in a patient, comprising administering to the patient an effective

amount of a compound of the invention at a frequency and for a duration to provide a beneficial effect to the patient.

In various embodiments, the invention provides a method of treating an HCV infection in a patient, comprising administering to the patient an effective amount of a compound of the invention at a frequency and for a duration to provide a beneficial effect to the patient. In various embodiments, the HCV-infected patient can also be infected with HIV, such that administering the compound of the invention to the patient also provides a treatment for the HIV infection.

In various embodiments, the invention provides the use of a compound of the invention to treat a viral infection in a human subject. The viral infection can be an HIV infection, an HCV infection, or both.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph illustrating variation of percentage inhibition of Strand Transfer with concentration of a compound of the invention;

Figure 2A is a depiction of a molecular model, illustrating mode of binding of compounds of the invention in HIV Non-Nucleoside Reverse Transcriptase Inhibitor binding pocket; and

Figure 2B is a depiction of a molecular model, illustrating a mode of binding of compounds of the invention in HIV-1 Integrase Catalytic Core Domain in complex with Mg^{2+} and DNA.

DETAILED DESCRIPTION

Definitions

As used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise.

The term "about" as used herein, when referring to a numerical value or range, allows for a degree of variability in the value or range, for example, within 10%, or within 5% of a stated value or of a stated limit of a range.

All percent compositions are given as weight-percentages, unless otherwise stated.

All average molecular weights of polymers are weight-average molecular weights, unless otherwise specified.

As used herein, "individual" (as in the subject of the treatment) means both mammals and non-mammals. Mammals include, for example, humans; non-human primates, e.g. apes and monkeys; and non-primates, e.g. dogs, cats, cattle, horses, sheep, and goats. Non-mammals include, for example, fish and birds.

The terms "disease" or "disorder" or "malcondition" are used interchangeably, and are used to refer to diseases or conditions wherein human immunodeficiency virus (HIV), or hepatitis C virus (HCV) plays a role in the biochemical mechanisms involved in the disease or malcondition such that a therapeutically beneficial effect can be achieved by acting on either or both viruses.

The expression "effective amount", when used to describe therapy to an individual suffering from a disorder, refers to the amount of a compound of the invention that is effective to act on the HIV or HCV virus, or both, in the individual's tissues wherein such action occurs to an extent sufficient to produce a beneficial therapeutic effect.

"Substantially" as the term is used herein means completely or almost completely; for example, a composition that is "substantially free" of a component either has none of the component or contains such a trace amount that any relevant functional property of the composition is unaffected by the presence of the trace amount, or a compound is "substantially pure" means that there are only negligible traces of impurities present.

"Treating" or "treatment" within the meaning herein refers to an alleviation of symptoms associated with a disorder or disease, or inhibition of further progression or worsening of those symptoms, or prevention or prophylaxis of the disease or disorder, or curing the disease or disorder. Similarly, as used herein, an "effective amount" or a "therapeutically effective amount" of a compound of the invention refers to an amount of the compound that alleviates, in whole or in part, symptoms associated with the disorder or condition, or halts or slows further progression or worsening of those symptoms, or prevents or provides prophylaxis for the disorder or condition. In particular, a "therapeutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result. A therapeutically effective amount is also one in which any toxic or detrimental effects of compounds of the invention are outweighed by the therapeutically beneficial effects.

An "antiviral compound" within the meaning herein refers to a chemical compound that suppresses viral replication in a living host, or interferes with viral transmission between hosts, or both. An adjuvant compound refers to a chemical compound that merely mitigates the symptoms of a viral infection without interfering with viral replication or transmission, e.g., a febricide. When it is stated that a compound of the invention is substantially the only antiviral compound administered to a patient in treatment of a viral infection, the statement signifies that another compound that suppresses viral replication or interferes with viral transmission is not administered, but that administration of additional compounds treating symptoms of viral infection is not ruled out. Such adjuvant treatments of viral symptoms can include administration of analgesics, febricides, antibacterials, antifungals, and the like.

By "chemically feasible" is meant a bonding arrangement or a compound where the generally understood rules of organic structure are not violated; for example, a structure within a definition of a claim that would contain in certain situations a pentavalent carbon atom that would not exist in nature would be understood to not be within the claim. The structures disclosed herein, in all of their embodiments are intended to include only "chemically feasible" structures, and any recited structures that are not chemically feasible, for example in a structure shown with variable atoms or groups, are not intended to be disclosed or claimed herein.

When a substituent is specified to be an atom or atoms of specified identity, "or a bond", a configuration is referred to when the substituent is "a bond" that the groups that are immediately adjacent to the specified substituent are directly connected to each other in a chemically feasible bonding configuration.

All chiral, diastereomeric, racemic forms of a structure are intended, unless a particular stereochemistry or isomeric form is specifically indicated. Compounds used in the present invention can include enriched or resolved optical isomers at any or all asymmetric atoms as are apparent from the depictions, at any degree of enrichment. Both racemic and diastereomeric mixtures, as well as the individual optical isomers can be isolated or synthesized so as to be substantially free of their enantiomeric or diastereomeric partners, and these are all within the scope of the invention.

In general, "substituted" refers to an organic group as defined herein in which one or more bonds to a hydrogen atom contained therein are replaced by one or more bonds to a non-hydrogen atom such as, but not limited to, a halogen (i.e., F, Cl, Br, and I); an oxygen atom in

groups such as hydroxyl groups, alkoxy groups, aryloxy groups, aralkyloxy groups, oxo(carbonyl) groups, carboxyl groups including carboxylic acids, carboxylates, and carboxylate esters; a sulfur atom in groups such as thiol groups, alkyl and aryl sulfide groups, sulfoxide groups, sulfone groups, sulfonyl groups, and sulfonamide groups; a nitrogen atom in groups such as amines, hydroxylamines, nitriles, nitro groups, N-oxides, hydrazides, azides, and enamines; and other heteroatoms in various other groups. Non-limiting examples of substituents that can be bonded to a substituted carbon (or other) atom include F, Cl, Br, I, OR', OC(O)N(R')₂, CN, NO, NO₂, ONO₂, azido, CF₃, OCF₃, R', O (oxo), S (thiono), C(O), S(O), methylenedioxy, ethylenedioxy, N(R')₂, SR', SOR', SO₂R', SO₂N(R')₂, SO₃R', C(O)R', C(O)C(O)R', C(O)CH₂C(O)R', C(S)R', C(O)OR', OC(O)R', C(O)N(R')₂, OC(O)N(R')₂, C(S)N(R')₂, (CH₂)₀₋₂N(R')C(O)R', (CH₂)₀₋₂N(R')N(R')₂, N(R')N(R')C(O)R', N(R')N(R')C(O)OR', N(R')N(R')CON(R')₂, N(R')SO₂R', N(R')SO₂N(R')₂, N(R')C(O)OR', N(R')C(O)R', N(R')C(S)R', N(R')C(O)N(R')₂, N(R')C(S)N(R')₂, N(COR')COR', N(OR')R', C(=NH)N(R')₂, C(O)N(OR')R', or C(=NOR')R' wherein R' can be hydrogen or a carbon-based moiety, and wherein the carbon-based moiety can itself be further substituted.

When a substituent is monovalent, such as, for example, F or Cl, it is bonded to the atom it is substituting by a single bond. When a substituent is more than monovalent, such as O, which is divalent, it can be bonded to the atom it is substituting by more than one bond, i.e., a divalent substituent is bonded by a double bond; for example, a C substituted with O forms a carbonyl group, C=O, which can also be written as "CO", "C(O)", or "C(=O)", wherein the C and the O are double bonded. When a carbon atom is substituted with a double-bonded oxygen (=O) group, the oxygen substituent is termed an "oxo" group. When a divalent substituent such as NR is double-bonded to a carbon atom, the resulting C(=NR) group is termed an "imino" group. When a divalent substituent such as S is double-bonded to a carbon atom, the results C(=S) group is termed a "thiocarbonyl" group.

Alternatively, a divalent substituent such as O, S, C(O), S(O), or S(O)₂ can be connected by two single bonds to two different carbon atoms. For example, O, a divalent substituent, can be bonded to each of two adjacent carbon atoms to provide an epoxide group, or the O can form a bridging ether group, termed an "oxy" group, between adjacent or non-adjacent carbon atoms, for example bridging the 1,4-carbons of a cyclohexyl group to form a [2.2.1]-oxabicyclo system.

Further, any substituent can be bonded to a carbon or other atom by a linker, such as $(CH_2)_n$ or $(CR'_2)_n$ wherein n is 1, 2, 3, or more, and each R' is independently selected.

$C(O)$ and $S(O)_2$ groups can be bound to one or two heteroatoms, such as nitrogen, rather than to a carbon atom. For example, when a $C(O)$ group is bound to one carbon and one nitrogen atom, the resulting group is called an "amide" or "carboxamide." When a $C(O)$ group is bound to two nitrogen atoms, the functional group is termed a urea. When a $S(O)_2$ group is bound to one carbon and one nitrogen atom, the resulting unit is termed a "sulfonamide." When a $S(O)_2$ group is bound to two nitrogen atoms, the resulting unit is termed a "sulfamate."

Substituted alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl groups as well as other substituted groups also include groups in which one or more bonds to a hydrogen atom are replaced by one or more bonds, including double or triple bonds, to a carbon atom, or to a heteroatom such as, but not limited to, oxygen in carbonyl (oxo), carboxyl, ester, amide, imide, urethane, and urea groups; and nitrogen in imines, hydroxyimines, oximes, hydrazones, amidines, guanidines, and nitriles.

Substituted ring groups such as substituted cycloalkyl, aryl, heterocyclyl and heteroaryl groups also include rings and fused ring systems in which a bond to a hydrogen atom is replaced with a bond to a carbon atom. Therefore, substituted cycloalkyl, aryl, heterocyclyl and heteroaryl groups can also be substituted with alkyl, alkenyl, and alkynyl groups as defined herein.

By a "ring system" as the term is used herein is meant a moiety comprising one, two, three or more rings, which can be substituted with non-ring groups or with other ring systems, or both, which can be fully saturated, partially unsaturated, fully unsaturated, or aromatic, and when the ring system includes more than a single ring, the rings can be fused, bridging, or spirocyclic. By "spirocyclic" is meant the class of structures wherein two rings are fused at a single tetrahedral carbon atom, as is well known in the art.

As to any of the groups described herein, which contain one or more substituents, it is understood, of course, that such groups do not contain any substitution or substitution patterns which are sterically impractical and/or synthetically non-feasible. In addition, the compounds of this disclosed subject matter include all stereochemical isomers arising from the substitution of these compounds.

Selected substituents within the compounds described herein are present to a recursive degree. In this context, “recursive substituent” means that a substituent may recite another instance of itself or of another substituent that itself recites the first substituent. Because of the recursive nature of such substituents, theoretically, a large number may be present in any given claim. One of ordinary skill in the art of medicinal chemistry and organic chemistry understands that the total number of such substituents is reasonably limited by the desired properties of the compound intended. Such properties include, by way of example and not limitation, physical properties such as molecular weight, solubility or log P, application properties such as activity against the intended target, and practical properties such as ease of synthesis.

Recursive substituents are an intended aspect of the disclosed subject matter. One of ordinary skill in the art of medicinal and organic chemistry understands the versatility of such substituents. To the degree that recursive substituents are present in a claim of the disclosed subject matter, the total number should be determined as set forth above.

Alkyl groups include straight chain and branched alkyl groups and cycloalkyl groups having from 1 to about 20 carbon atoms, and typically from 1 to 12 carbons or, in some embodiments, from 1 to 8 carbon atoms. Examples of straight chain alkyl groups include those with from 1 to 8 carbon atoms such as methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, and n-octyl groups. Examples of branched alkyl groups include, but are not limited to, isopropyl, iso-butyl, sec-butyl, t-butyl, neopentyl, isopentyl, and 2,2-dimethylpropyl groups. As used herein, the term “alkyl” encompasses n-alkyl, isoalkyl, and anteisoalkyl groups as well as other branched chain forms of alkyl. Representative substituted alkyl groups can be substituted one or more times with any of the groups listed above, for example, amino, hydroxy, cyano, carboxy, nitro, thio, alkoxy, and halogen groups.

Cycloalkyl groups are cyclic alkyl groups such as, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl groups. In some embodiments, the cycloalkyl group can have 3 to about 8-12 ring members, whereas in other embodiments the number of ring carbon atoms range from 3 to 4, 5, 6, or 7. Cycloalkyl groups further include polycyclic cycloalkyl groups such as, but not limited to, norbornyl, adamantyl, bornyl, camphenyl, isocamphenyl, and carenyl groups, and fused rings such as, but not limited to, decalanyl, and the like. Cycloalkyl groups also include rings that are substituted with straight or branched chain alkyl groups as defined above. Representative substituted cycloalkyl groups can

be mono-substituted or substituted more than once, such as, but not limited to, 2,2-, 2,3-, 2,4-, 2,5- or 2,6-disubstituted cyclohexyl groups or mono-, di- or tri-substituted norbornyl or cycloheptyl groups, which can be substituted with, for example, amino, hydroxy, cyano, carboxy, nitro, thio, alkoxy, and halogen groups. The term "cycloalkenyl" alone or in combination denotes a cyclic alkenyl group.

The terms "carbocyclic," "carbocyclyl," and "carbocycle" denote a ring structure wherein the atoms of the ring are carbon, such as a cycloalkyl group or an aryl group. In some embodiments, the carbocycle has 3 to 8 ring members, whereas in other embodiments the number of ring carbon atoms is 4, 5, 6, or 7. Unless specifically indicated to the contrary, the carbocyclic ring can be substituted with as many as N-1 substituents wherein N is the size of the carbocyclic ring with, for example, alkyl, alkenyl, alkynyl, amino, aryl, hydroxy, cyano, carboxy, heteroaryl, heterocyclyl, nitro, thio, alkoxy, and halogen groups, or other groups as are listed above. A carbocyclyl ring can be a cycloalkyl ring, a cycloalkenyl ring, or an aryl ring. A carbocyclyl can be monocyclic or polycyclic, and if polycyclic each ring can be independently be a cycloalkyl ring, a cycloalkenyl ring, or an aryl ring.

(Cycloalkyl)alkyl groups, also denoted cycloalkylalkyl, are alkyl groups as defined above in which a hydrogen or carbon bond of the alkyl group is replaced with a bond to a cycloalkyl group as defined above.

Alkenyl groups include straight and branched chain and cyclic alkyl groups as defined above, except that at least one double bond exists between two carbon atoms. Thus, alkenyl groups have from 2 to about 20 carbon atoms, and typically from 2 to 12 carbons or, in some embodiments, from 2 to 8 carbon atoms. Examples include, but are not limited to vinyl, $-\text{CH}=\text{CH}(\text{CH}_3)$, $-\text{CH}=\text{C}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)=\text{CH}_2$, $-\text{C}(\text{CH}_3)=\text{CH}(\text{CH}_3)$, $-\text{C}(\text{CH}_2\text{CH}_3)=\text{CH}_2$, cyclohexenyl, cyclopentenyl, cyclohexadienyl, butadienyl, pentadienyl, and hexadienyl among others.

Cycloalkenyl groups include cycloalkyl groups having at least one double bond between 2 carbons. Thus for example, cycloalkenyl groups include but are not limited to cyclohexenyl, cyclopentenyl, and cyclohexadienyl groups. Cycloalkenyl groups can have from 3 to about 8-12 ring members, whereas in other embodiments the number of ring carbon atoms range from 3 to 5, 6, or 7. Cycloalkyl groups further include polycyclic cycloalkyl groups such as, but not limited to, norbornyl, adamantyl, bornyl, camphenyl, isocamphenyl, and carenly groups, and

fused rings such as, but not limited to, decalinyl, and the like, provided they include at least one double bond within a ring. Cycloalkenyl groups also include rings that are substituted with straight or branched chain alkyl groups as defined above.

(Cycloalkenyl)alkyl groups are alkyl groups as defined above in which a hydrogen or carbon bond of the alkyl group is replaced with a bond to a cycloalkenyl group as defined above.

Alkynyl groups include straight and branched chain alkyl groups, except that at least one triple bond exists between two carbon atoms. Thus, alkynyl groups have from 2 to about 20 carbon atoms, and typically from 2 to 12 carbons or, in some embodiments, from 2 to 8 carbon atoms. Examples include, but are not limited to $-\text{C}\equiv\text{CH}$, $-\text{C}\equiv\text{C}(\text{CH}_3)$, $-\text{C}\equiv\text{C}(\text{CH}_2\text{CH}_3)$, $-\text{CH}_2\text{C}\equiv\text{CH}$, $-\text{CH}_2\text{C}\equiv\text{C}(\text{CH}_3)$, and $-\text{CH}_2\text{C}\equiv\text{C}(\text{CH}_2\text{CH}_3)$ among others.

The term "heteroalkyl" by itself or in combination with another term means, unless otherwise stated, a stable straight or branched chain alkyl group consisting of the stated number of carbon atoms and one or two heteroatoms selected from the group consisting of O, N, and S, and wherein the nitrogen and sulfur atoms may be optionally oxidized and the nitrogen heteroatom may be optionally quaternized. The heteroatom(s) may be placed at any position of the heteroalkyl group, including between the rest of the heteroalkyl group and the fragment to which it is attached, as well as attached to the most distal carbon atom in the heteroalkyl group. Examples include: $-\text{O}-\text{CH}_2-\text{CH}_2-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2\text{CH}_2-\text{OH}$, $-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_3$, $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_3$, $-\text{CH}_2\text{CH}_2-\text{S}(=\text{O})-\text{CH}_3$, and $-\text{CH}_2\text{CH}_2-\text{O}-\text{CH}_2\text{CH}_2-\text{O}-\text{CH}_3$. Up to two heteroatoms may be consecutive, such as, for example, $-\text{CH}_2-\text{NH}-\text{OCH}_3$, or $-\text{CH}_2-\text{CH}_2-\text{S}-\text{S}-\text{CH}_3$.

A "cycloheteroalkyl" ring is a cycloalkyl ring containing at least one heteroatom. A cycloheteroalkyl ring can also be termed a "heterocyclyl," described below.

The term "heteroalkenyl" by itself or in combination with another term means, unless otherwise stated, a stable straight or branched chain monounsaturated or di-unsaturated hydrocarbon group consisting of the stated number of carbon atoms and one or two heteroatoms selected from the group consisting of O, N, and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. Up to two heteroatoms may be placed consecutively. Examples include $-\text{CH}=\text{CH}-\text{O}-\text{CH}_3$, $-\text{CH}=\text{CH}-\text{CH}_2-\text{OH}$, $-\text{CH}_2-\text{CH}=\text{N}-\text{OCH}_3$, $-\text{CH}=\text{CH}-\text{N}(\text{CH}_3)-\text{CH}_3$, $-\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_2-\text{SH}$, and $-\text{CH}=\text{CH}-\text{O}-\text{CH}_2\text{CH}_2-\text{O}-\text{CH}_3$.

Aryl groups are cyclic aromatic hydrocarbons that do not contain heteroatoms in the ring. Thus aryl groups include, but are not limited to, phenyl, azulenyl, heptalenyl, biphenyl, indacenyl, fluorenyl, phenanthrenyl, triphenylenyl, pyrenyl, naphthacenyl, chrysenyl, biphenylenyl, anthracenyl, and naphthyl groups. In some embodiments, aryl groups contain about 6 to about 14 carbons in the ring portions of the groups. Aryl groups can be unsubstituted or substituted, as defined above. Representative substituted aryl groups can be mono-substituted or substituted more than once, such as, but not limited to, 2-, 3-, 4-, 5-, or 6-substituted phenyl or 2-8 substituted naphthyl groups, which can be substituted with carbon or non-carbon groups such as those listed above.

Aralkyl groups are alkyl groups as defined above in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to an aryl group as defined above. Representative aralkyl groups include benzyl and phenylethyl groups and fused (cycloalkylaryl)alkyl groups such as 4-ethyl-indanyl. Aralkenyl group are alkenyl groups as defined above in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to an aryl group as defined above.

The term "alkoxy" refers to an oxygen atom connected to an alkyl group, including a cycloalkyl group, as are defined above. Examples of linear alkoxy groups include but are not limited to methoxy, ethoxy, propoxy, butoxy, pentyloxy, hexyloxy, and the like. Examples of branched alkoxy include but are not limited to isopropoxy, sec-butoxy, tert-butoxy, isopentyloxy, isohexyloxy, and the like. Examples of cyclic alkoxy include but are not limited to cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, and the like. An alkoxy group can include one to about 12-20 carbon atoms bonded to the oxygen atom, and can further include double or triple bonds, and can also include heteroatoms. For example, an allyloxy group is an alkoxy group within the meaning herein. A methoxyethoxy group is also an alkoxy group within the meaning herein, as is a methylenedioxy group in a context where two adjacent atoms of a structures are substituted therewith.

The terms "halo" or "halogen" or "halide" by themselves or as part of another substituent mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom, preferably, fluorine, chlorine, or bromine.

A "haloalkyl" group includes mono-halo alkyl groups, poly-halo alkyl groups wherein all halo atoms can be the same or different, and per-halo alkyl groups, wherein all hydrogen atoms are replaced by halogen atoms, such as fluoro. Examples of haloalkyl include trifluoromethyl,

1,1-dichloroethyl, 1,2-dichloroethyl, 1,3-dibromo-3,3-difluoropropyl, perfluorobutyl, and the like.

A "haloalkoxy" group includes mono-halo alkoxy groups, poly-halo alkoxy groups wherein all halo atoms can be the same or different, and per-halo alkoxy groups, wherein all hydrogen atoms are replaced by halogen atoms, such as fluoro. Examples of haloalkoxy include trifluoromethoxy, 1,1-dichloroethoxy, 1,2-dichloroethoxy, 1,3-dibromo-3,3-difluoropropoxy, perfluorobutoxy, and the like.

The term " (C_x-C_y) perfluoroalkyl," wherein $x < y$, means an alkyl group with a minimum of x carbon atoms and a maximum of y carbon atoms, wherein all hydrogen atoms are replaced by fluorine atoms. Preferred is $-(C_1-C_6)$ perfluoroalkyl, more preferred is $-(C_1-C_3)$ perfluoroalkyl, most preferred is $-CF_3$.

The term " (C_x-C_y) perfluoroalkylene," wherein $x < y$, means an alkyl group with a minimum of x carbon atoms and a maximum of y carbon atoms, wherein all hydrogen atoms are replaced by fluorine atoms. Preferred is $-(C_1-C_6)$ perfluoroalkylene, more preferred is $-(C_1-C_3)$ perfluoroalkylene, most preferred is $-CF_2-$.

The terms "aryloxy" and "arylalkoxy" refer to, respectively, an aryl group bonded to an oxygen atom and an aralkyl group bonded to the oxygen atom at the alkyl moiety. Examples include but are not limited to phenoxy, naphthyloxy, and benzyloxy.

An "acyl" group as the term is used herein refers to a group containing a carbonyl moiety wherein the group is bonded via the carbonyl carbon atom. The carbonyl carbon atom is also bonded to another carbon atom, which can be part of an alkyl, aryl, aralkyl cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclalkyl, heteroaryl, heteroarylalkyl group or the like. In the special case wherein the carbonyl carbon atom is bonded to a hydrogen, the group is a "formyl" group, an acyl group as the term is defined herein. An acyl group can include 0 to about 12-20 additional carbon atoms bonded to the carbonyl group. An acyl group can include double or triple bonds within the meaning herein. An acryloyl group is an example of an acyl group. An acyl group can also include heteroatoms within the meaning here. A nicotinoyl group (pyridyl-3-carbonyl) group is an example of an acyl group within the meaning herein. Other examples include acetyl, benzoyl, phenylacetyl, pyridylacetyl, cinnamoyl, and acryloyl groups and the like. When the group containing the carbon atom that is bonded to the carbonyl carbon

atom contains a halogen, the group is termed a "haloacyl" group. An example is a trifluoroacetyl group.

A "salt" as is well known in the art includes an organic compound such as a carboxylic acid, a sulfonic acid, or an amine, in ionic form, in combination with a counterion. For example, acids in their anionic form can form salts with cations such as metal cations, for example sodium, potassium, and the like; with ammonium salts such as NH_4^+ or the cations of various amines, including tetraalkyl ammonium salts such as tetramethylammonium, or other cations such as trimethylsulfonium, and the like. A "pharmaceutically acceptable" or "pharmacologically acceptable" salt is a salt formed from an ion that has been approved for human consumption and is generally non-toxic, such as a chloride salt or a sodium salt. A "zwitterion" is an internal salt such as can be formed in a molecule that has at least two ionizable groups, one forming an anion and the other a cation, which serve to balance each other. For example, amino acids such as glycine can exist in a zwitterionic form. A "zwitterion" is a salt within the meaning herein. The compounds of the present invention may take the form of salts. The term "salts" embraces addition salts of free acids or free bases which are compounds of the invention. Salts can be "pharmaceutically-acceptable salts." The term "pharmaceutically-acceptable salt" refers to salts which possess toxicity profiles within a range that affords utility in pharmaceutical applications. Pharmaceutically unacceptable salts may nonetheless possess properties such as high crystallinity, which have utility in the practice of the present invention, such as for example utility in process of synthesis, purification or formulation of compounds of the invention.

Suitable pharmaceutically-acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid. Examples of inorganic acids include hydrochloric, hydrobromic, hydriodic, nitric, carbonic, sulfuric, and phosphoric acids. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which include formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, trifluoromethanesulfonic, 2-hydroxyethanesulfonic, p-toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, stearic, alginic, β -hydroxybutyric, salicylic, galactaric and

galacturonic acid. Examples of pharmaceutically unacceptable acid addition salts include, for example, perchlorates and tetrafluoroborates.

Suitable pharmaceutically acceptable base addition salts of compounds of the invention include, for example, metallic salts including alkali metal, alkaline earth metal and transition metal salts such as, for example, calcium, magnesium, potassium, sodium and zinc salts. Pharmaceutically acceptable base addition salts also include organic salts made from basic amines such as, for example, *N,N'*-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Examples of pharmaceutically unacceptable base addition salts include lithium salts and cyanate salts. Although pharmaceutically unacceptable salts are not generally useful as medicaments, such salts may be useful, for example as intermediates in the synthesis of Formula (I) compounds, for example in their purification by recrystallization. All of these salts may be prepared by conventional means from the corresponding compound according to Formula (I) by reacting, for example, the appropriate acid or base with the compound according to Formula (I). The term "pharmaceutically acceptable salts" refers to nontoxic inorganic or organic acid and/or base addition salts, see, for example, Lit et al., *Salt Selection for Basic Drugs* (1986), *Int J. Pharm.*, **33**, 201-217, incorporated by reference herein.

In addition, where features or aspects of the invention are described in terms of Markush groups, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group. For example, if X is described as selected from the group consisting of bromine, chlorine, and iodine, claims for X being bromine and claims for X being bromine and chlorine are fully described. Moreover, where features or aspects of the invention are described in terms of Markush groups, those skilled in the art will recognize that the invention is also thereby described in terms of any combination of individual members or subgroups of members of Markush groups. Thus, for example, if X is described as selected from the group consisting of bromine, chlorine, and iodine, and Y is described as selected from the group consisting of methyl, ethyl, and propyl, claims for X being bromine and Y being methyl are fully described.

If a value of a variable that is necessarily an integer, e.g., the number of carbon atoms in an alkyl group or the number of substituents on a ring, is described as a range, e.g., 0-4, what is meant is that the value can be any integer between 0 and 4 inclusive, i.e., 0, 1, 2, 3, or 4.

In various embodiments, the compound or set of compounds, such as are used in the inventive methods, can be any one of any of the combinations and/or sub-combinations of the above-listed embodiments.

In various embodiments, a compound as shown in any of the Examples, or among the exemplary compounds, is provided. Provisos may apply to any of the disclosed categories or embodiments wherein any one or more of the other above disclosed embodiments or species may be excluded from such categories or embodiments.

The present invention further embraces isolated compounds according to formula (I). The expression "isolated compound" refers to a preparation of a compound of formula (I), or a mixture of compounds according to formula (I), wherein the isolated compound has been separated from the reagents used, and/or byproducts formed, in the synthesis of the compound or compounds. "Isolated" does not mean that the preparation is technically pure (homogeneous), but it is sufficiently pure to compound in a form in which it can be used therapeutically. Preferably an "isolated compound" refers to a preparation of a compound of formula (I) or a mixture of compounds according to formula (I), which contains the named compound or mixture of compounds according to formula (I) in an amount of at least 10 percent by weight of the total weight. Preferably the preparation contains the named compound or mixture of compounds in an amount of at least 50 percent by weight of the total weight; more preferably at least 80 percent by weight of the total weight; and most preferably at least 90 percent, at least 95 percent or at least 98 percent by weight of the total weight of the preparation.

The compounds of the invention and intermediates may be isolated from their reaction mixtures and purified by standard techniques such as filtration, liquid-liquid extraction, solid phase extraction, distillation, recrystallization or chromatography, including flash column chromatography, or HPLC.

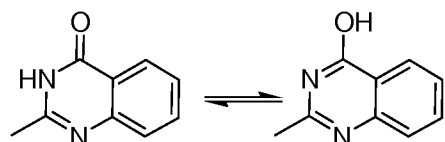
Tautomerism

Within the present invention it is to be understood that a compound of the formula (I) or a salt thereof may exhibit the phenomenon of tautomerism whereby two chemical compounds that are capable of facile interconversion by exchanging a hydrogen atom between two atoms, to either of which it forms a covalent bond. Since the tautomeric compounds exist in mobile equilibrium with each other they may be regarded as different isomeric forms of the same compound. It is to be understood that the formulae drawings within this specification can

represent only one of the possible tautomeric forms. However, it is also to be understood that the invention encompasses any tautomeric form, and is not to be limited merely to any one tautomeric form utilized within the formulae drawings. The formulae drawings within this specification can represent only one of the possible tautomeric forms and it is to be understood that the specification encompasses all possible tautomeric forms of the compounds drawn not just those forms which it has been convenient to show graphically herein. For example, tautomerism may be exhibited by a pyrazolyl group bonded as indicated by the wavy line. While both substituents would be termed a 4-pyrazolyl group, it is evident that a different nitrogen atom bears the hydrogen atom in each structure.



Such tautomerism can also occur with substituted pyrazoles such as 3-methyl, 5-methyl, or 3,5-dimethylpyrazoles, and the like. Another example of tautomerism is amido-imido (lactam-lactim when cyclic) tautomerism, such as is seen in heterocyclic compounds bearing a ring oxygen atom adjacent to a ring nitrogen atom. For example, the equilibrium:



is an example of tautomerism. Accordingly, a structure depicted herein as one tautomer is intended to also include the other tautomer.

Optical Isomerism

It will be understood that when compounds of the present invention contain one or more chiral centers, the compounds may exist in, and may be isolated as pure enantiomeric or diastereomeric forms or as racemic mixtures. The present invention therefore includes any possible enantiomers, diastereomers, racemates or mixtures thereof of the compounds of the invention.

The isomers resulting from the presence of a chiral center comprise a pair of non-superimposable isomers that are called "enantiomers." Single enantiomers of a pure compound are optically active, *i.e.*, they are capable of rotating the plane of plane polarized light. Single enantiomers are designated according to the *Cahn-Ingold-Prelog* system. The priority of substituents is ranked based on atomic weights, a higher atomic weight, as determined by the

systematic procedure, having a higher priority ranking. Once the priority ranking of the four groups is determined, the molecule is oriented so that the lowest ranking group is pointed away from the viewer. Then, if the descending rank order of the other groups proceeds clockwise, the molecule is designated (*R*) and if the descending rank of the other groups proceeds counterclockwise, the molecule is designated (*S*). In the example in Scheme 14, the *Cahn-Ingold-Prelog* ranking is $A > B > C > D$. The lowest ranking atom, D is oriented away from the viewer.



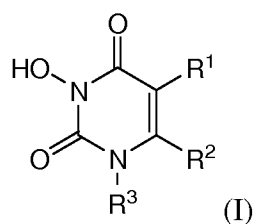
The present invention is meant to encompass diastereomers as well as their racemic and resolved, diastereomerically and enantiomerically pure forms and salts thereof. Diastereomeric pairs may be resolved by known separation techniques including normal and reverse phase chromatography, and crystallization.

“Isolated optical isomer” means a compound which has been substantially purified from the corresponding optical isomer(s) of the same formula. Preferably, the isolated isomer is at least about 80%, more preferably at least 90% pure, even more preferably at least 98% pure, most preferably at least about 99% pure, by weight.

Isolated optical isomers may be purified from racemic mixtures by well-known chiral separation techniques. According to one such method, a racemic mixture of a compound of the invention, or a chiral intermediate thereof, is separated into 99% wt.% pure optical isomers by HPLC using a suitable chiral column, such as a member of the series of DAICEL[®] CHIRALPAK[®] family of columns (Daicel Chemical Industries, Ltd., Tokyo, Japan). The column is operated according to the manufacturer’s instructions.

Compounds of the Invention

In various embodiments, the invention is directed to a compound of formula (I)



wherein R^1 is hydrogen, (C₁-C₆)alkyl, (C₃-C₉)cycloalkyl, (C₃-C₉)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₄)aryl, or (C₆-C₁₄)aryl(C₁-C₆)alkyl, wherein any alkyl, cycloalkyl, cycloalkylalkyl, or aralkyl can be mono- or multi-substituted with halo;

R^2 is hydrogen, (C₁-C₆)alkyl, (C₆-C₁₄)aryl, (C₆-C₁₄)aryl(C₁-C₆)alkyl, (C₆-C₁₄)aryl(C₁-C₆)alkoxy, (C₆-C₁₄) aroyl, (C₆-C₁₄) aryloxy, or a 5-9 membered mono- or bicyclic heteroaryl or heteroarylalkyl, wherein any alkyl or aryl or aralkyl or aroyl or aryloxy or heteroaryl is substituted with $n R^5$ groups;

or R^1 and R^2 together with the atoms to which they are bonded form a fused (C₃-C₉) cycloalkyl or (C₆-C₁₀) aryl, wherein the cycloalkyl or aryl is substituted with $n R^5$ groups;

R^3 is CH(R) R^4 , wherein R^4 is hydrogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₆-C₁₄)aryl, (C₆-C₁₄)aryloxy, (C₆-C₁₀)aryl(C₁-C₆)alkyl, or (C₆-C₁₀)aryl(C₁-C₆)alkoxy, wherein any alkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy is substituted with $n_2 R^6$ groups;

J is halo, nitro, (C₁-C₆)alkoxy, or (C₁-C₆)alkyl;

R is hydrogen or (C₁-C₆)alkyl;

R^5 is halo, nitro, (C₁-C₆)alkoxy, or (C₁-C₆)alkyl;

R^6 is halo, nitro, (C₁-C₆)alkoxy, or (C₁-C₆)alkyl;

$n = 0, 1, 2$, or 3 ;

$n_2 = 0, 1, 2$, or 3 ;

or a pharmaceutically acceptable salt thereof.

For example, any halo can be fluoro or chloro.

For example, R^1 can be methyl, ethyl, isopropyl, benzyl, or p-fluorobenzyl.

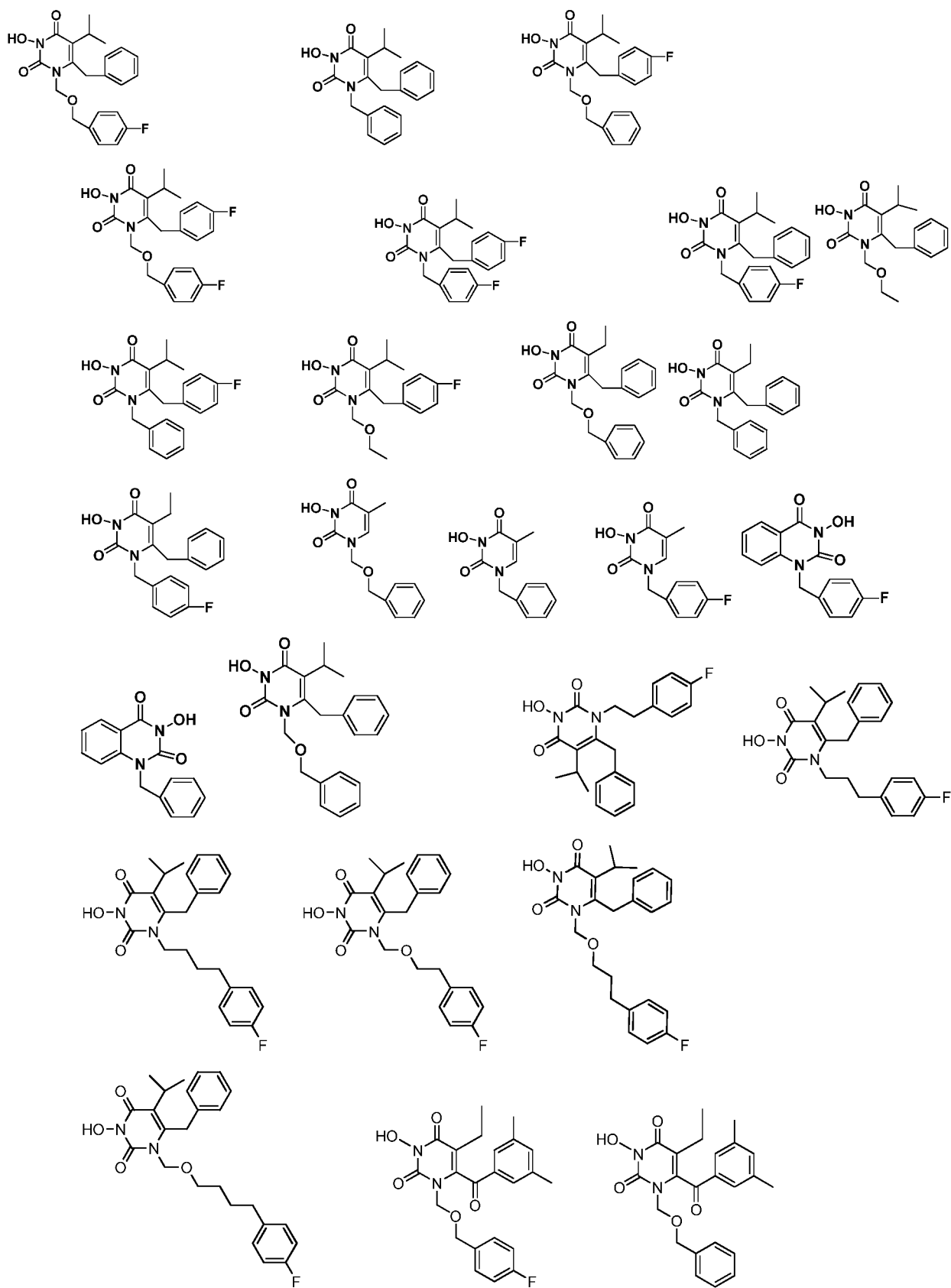
For example, R^2 can be benzyl, p-fluorobenzyl, benzoyl, or 3,5-dimethylbenzoyl; or, R^1 and R^2 can together with the atoms to which they are bonded form a phenyl ring or a fluoro-substituted phenyl ring.

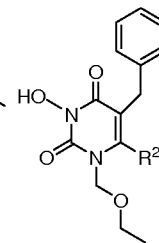
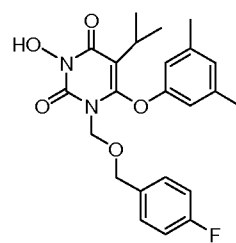
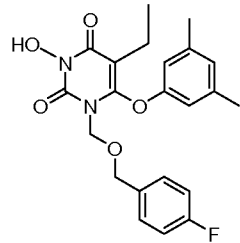
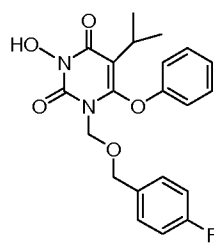
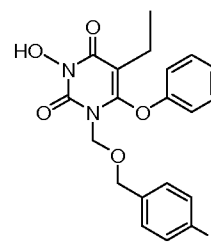
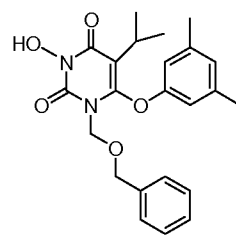
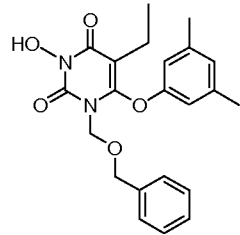
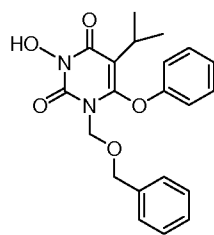
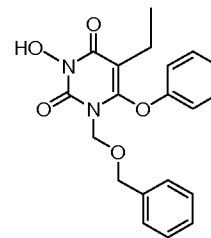
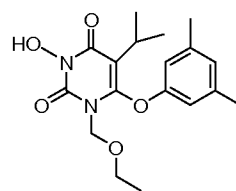
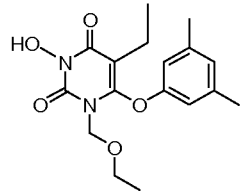
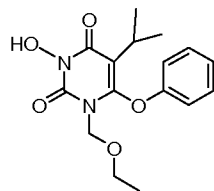
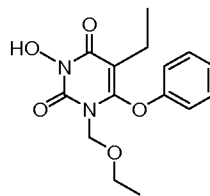
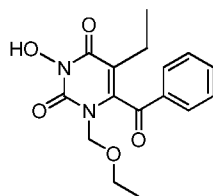
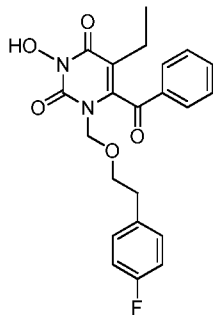
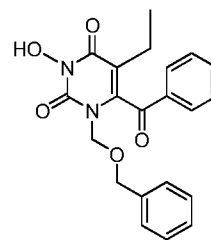
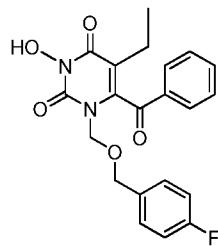
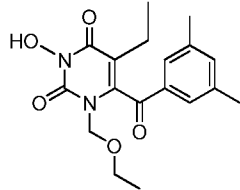
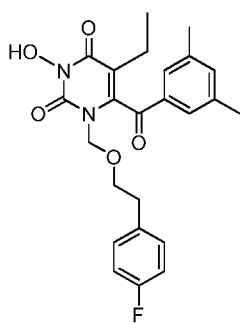
In other embodiments, R^2 can be heteroaryl, such as thienyl or furanyl.

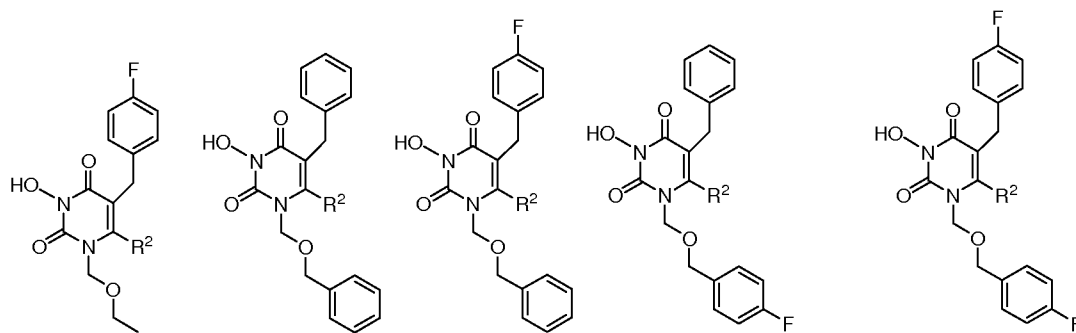
In various embodiments, R can be H. In other embodiments R can be methyl.

In various embodiments, R^4 can be phenyl, p-fluorophenyl, p-fluorobenzyl, p-fluorophenethyl, p-fluorophenyl-n-propyl, ethoxy, benzyloxy, p-fluorobenzyloxy, p-fluorophenethoxy, p-fluorophenyl-n-propoxy, or p-fluorophenyl-n-butoxy.

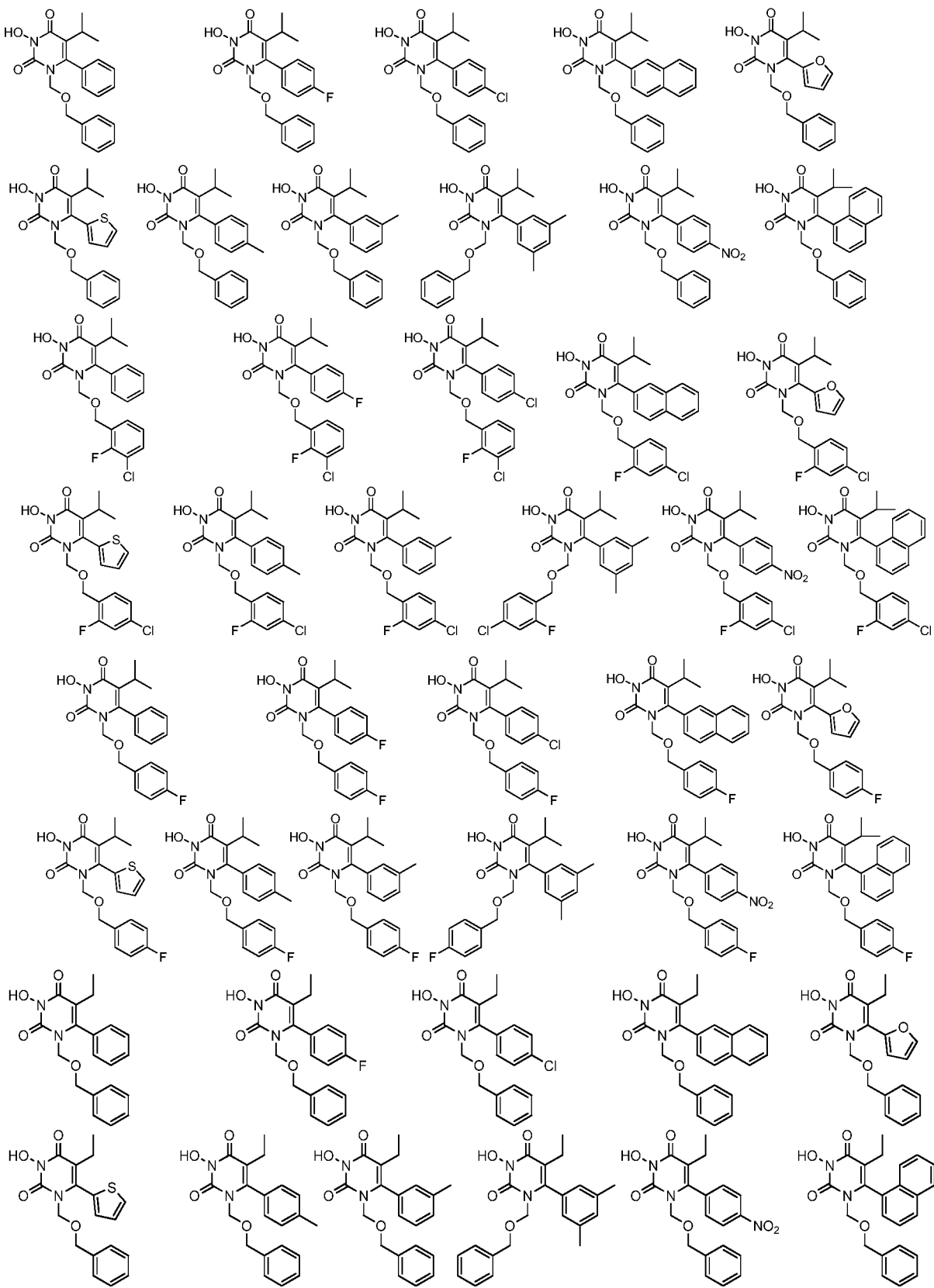
In various embodiments, the compound can be any of the following

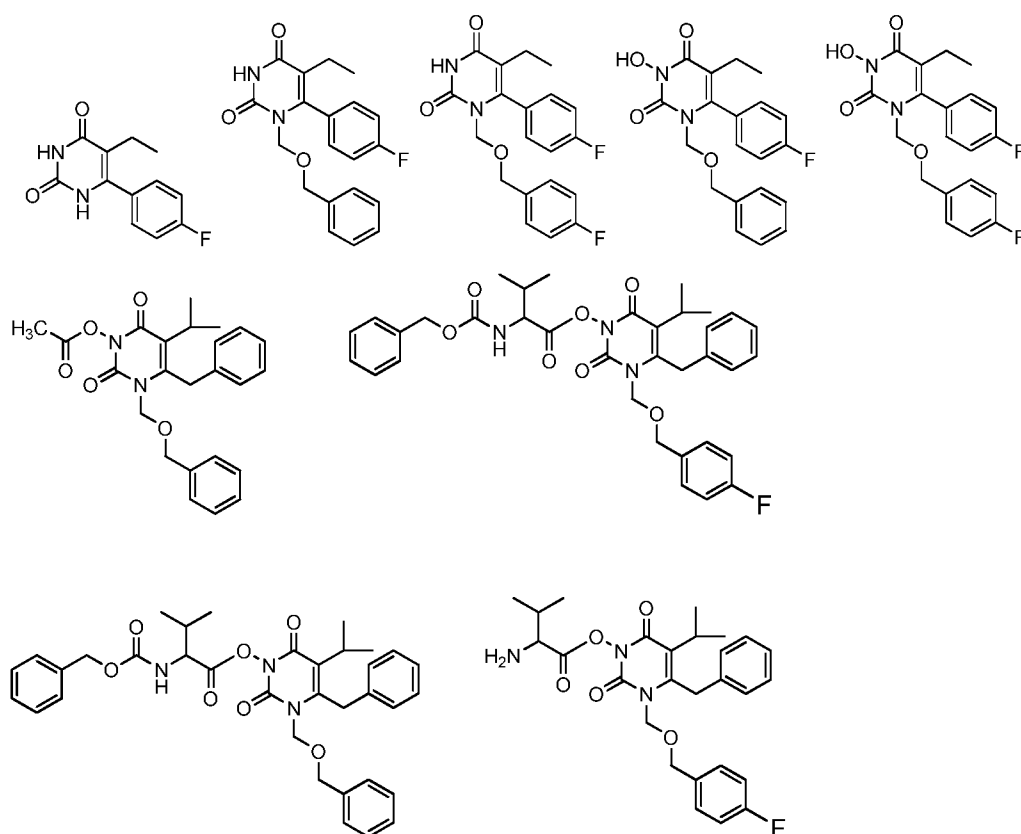






wherein R^2 is methyl, ethyl, or isopropyl;





; or a pharmaceutically acceptable salt thereof.

Prodrugs of Compounds of the Invention

The prodrugs of compounds of the invention chemically modify pharmacologically active agents with a structure that can improve solubility, permeability or stability to overcome pharmacokinetic barriers. The pro-moiety can undergo transformation *in vivo* to release the active drug. Although required by target binding, the 3-N-hydroxyl group in compounds can cause undesired hydrophilicity, which compromises cell permeability and oral absorption. To increase lipophilicity and mask hydrogen bonding groups of the active compound, a carboxylic acid ester moiety can be introduced, which upon administration to a patient afflicted with HIV or HCV, can be hydrolyzed by esterases upon cellular uptake to provide the active antiviral agent. Aromatic (e.g. benzoyl) acid and aliphatic (e.g. pivaloyl) acid esters can be used to improve permeability by passive diffusion. Amino acid or peptide esters (e.g. valinyl) can be used to achieve transporter-mediated permeability. The prodrugs of the compounds of the invention can improve the activity in cell-based assays as well as the animal pharmacokinetics.

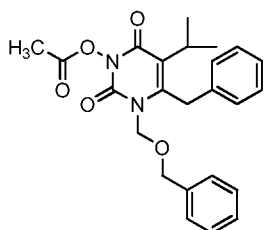
In various embodiments, the invention provides prodrugs of the viral-inhibitory compounds of the invention, comprising an N-hydroxy ester of a compound of the invention.

In various embodiments, the invention provides a prodrug of a viral-inhibitory compounds of any one of claims 1-7, comprising an N-hydroxy ester of the compound of formula (I), wherein the N-hydroxy ester is an alkyl ester or an aryl ester.

For example, the N-hydroxy ester can be a (C₁-C₁₀)acyl ester or a (C₆-C₁₄)aroyl ester of the compound of formula (I). An ester of a compound of formula (I) can have enhanced uptake into virally-infected cells due to, for example, enhanced lipophilicity or solubility, or both, relative to an analogous N-hydroxy compound of formula (I).

In other embodiments, the N-hydroxyester can be an aminoacyl ester or a peptidyl ester of the compound of formula (I). An aminoacid or peptide ester of an N-hydroxy compound of the invention can have enhanced uptake into virally-infected cells due to, for example, enhanced active transport by way of specific transporter mechanisms of the cell that recognize an aminoacide or peptide moiety as a structural determinant for uptake and internalization of the compound into the cell.

For example, an N-hydroxy acetyl ester of formula:

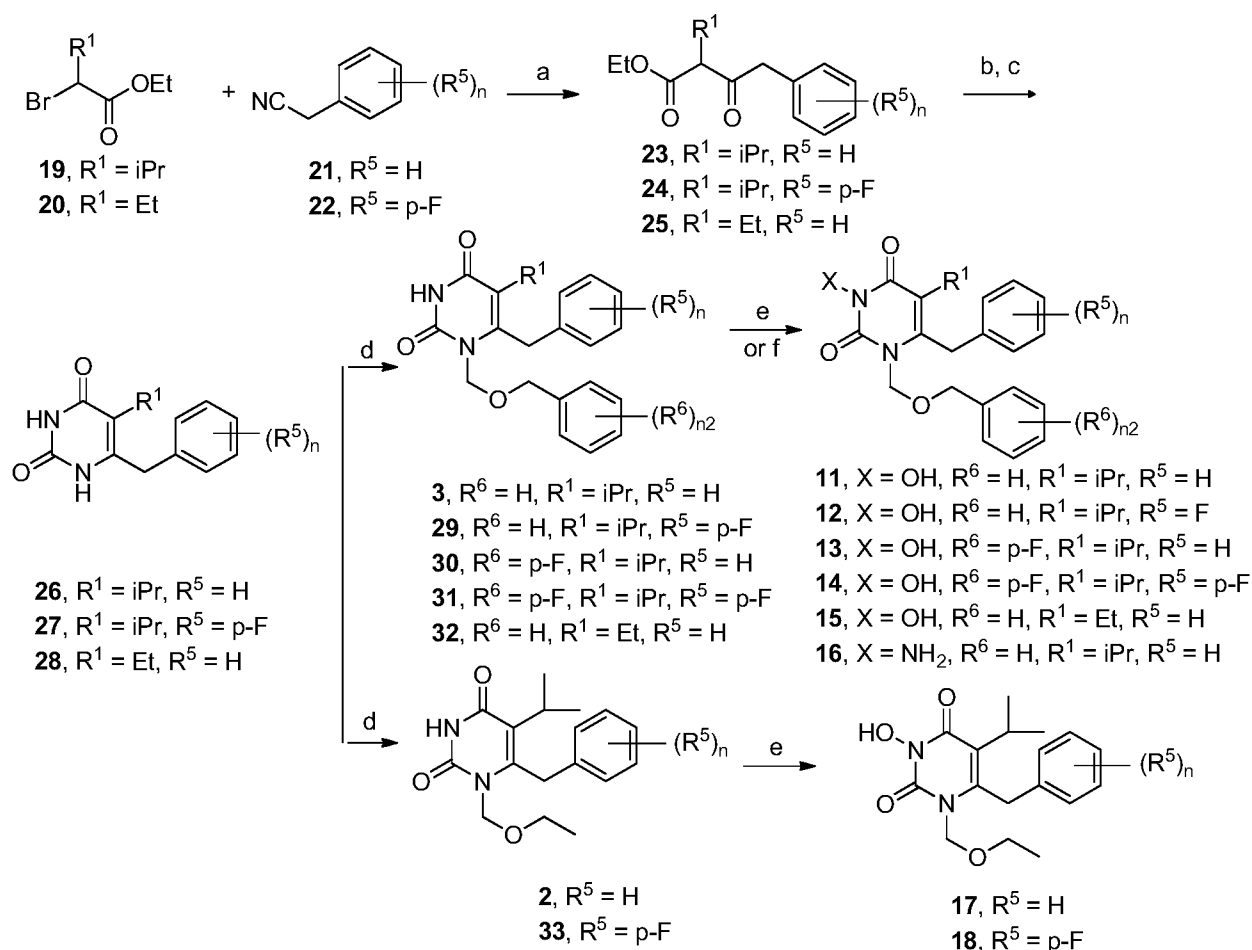


was found to exhibit 74% inhibition against HIV at 10 μ M. While not wishing to be bound by theory, the inventors herein believe that the acetate ester is taken up more readily than the free N-hydroxy compound, then is intracellularly hydrolyzed to provide the free N-hydroxy compound as the viral-inhibitory agent.

Methods of Synthesis

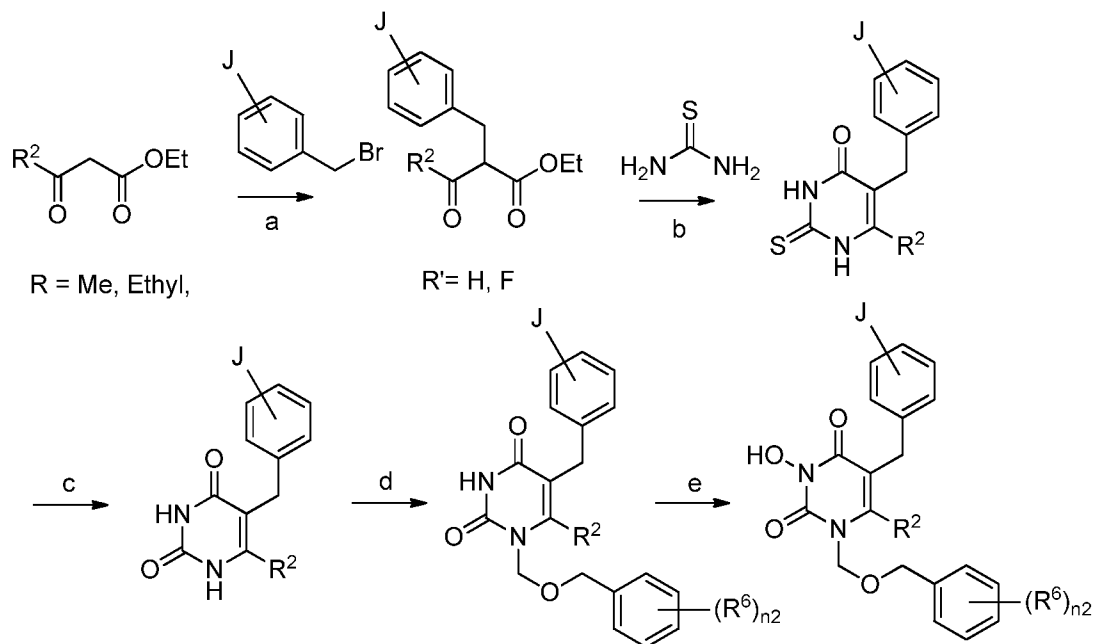
The designed inhibitors can be synthetically accessed through routes as are outlined in Schemes 1, 2, 3 and 4. The synthesis of advanced intermediates **2-3** and **29-33** is well-established in literature²⁴ whereas the key transformation, the N-3 hydroxylation, is rarely known. This transformation was achieved through deprotonation of HEPT intermediates and the

subsequent treatment with an oxidizing agent. After screening a wide array of oxidants, it was found that m-CPBA could effect this N-3 hydroxylation efficiently (Scheme 1). Adaptation of this method also allowed us to successfully prepare an N-3 amino analogue (**16**), wherein mesityl sulfonyl-O-hydroxyl amine (MSH)²⁵ was employed as the aminating agent.

Scheme 1^a

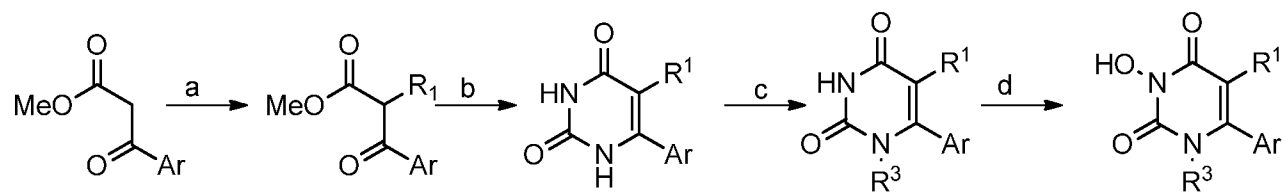
^aReagents and conditions: a) Zn, I₂ (cat.), THF, 89-90%; b) Thiourea, KOtBu, i-PrOH, 40-71%; c) ClCH₂CO₂H, AcOH, H₂O, 38-78%; d) CH₃C(OTMS)=NTMS (BSA), selected chloromethyl ether, TBAI (cat.), CH₂Cl₂, rt, 51-89%; (e) NaH, m-CPBA, THF, rt, 50-73%; f) NaH, MSH, THF, rt, 54%.

Scheme 2



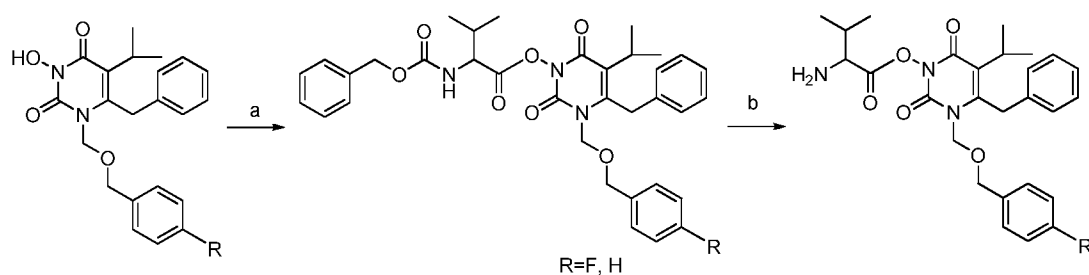
Step (a) can be effected based on a literature procedure (Kurouchi, H.; Sugimoto, H.; Otani, Y.; Ohwada, T. *J. Am. Chem. Soc.* **2010**, 132, 807-815). The rest of the synthesis can follow the same procedures for the preparation of compounds already synthesized.

Scheme 3



Reagents and condition: a) NaOMe, R¹Br, MeOH; b) NaOMe, urea, MeOH, reflux; c) CH₃C(OTMS)=NTMS (BSA), CH₂Cl₂; R²OH, (HCHO)_n, TMSCl, TBAI (cat.); d) NaH / THF, mCPBA.

Scheme 4



Reagents and condition: a) Cbz-Val, PyBOP, DIEA, DCM, rt; b) Pd/C, H₂, MeOH, rt.

Certain details are provided in the Examples, below.

Pharmaceutical Compositions

Another aspect of an embodiment of the invention provides compositions of the compounds of the invention, alone or in combination with another medicament. As set forth herein, compounds of the invention include stereoisomers, tautomers, solvates, prodrugs, pharmaceutically acceptable salts and mixtures thereof. Compositions containing a compound of the invention can be prepared by conventional techniques, e.g. as described in Remington: *The Science and Practice of Pharmacy*, 19th Ed., 1995, or later versions thereof, incorporated by reference herein. The compositions can appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.

Typical compositions include a compound of the invention and a pharmaceutically acceptable excipient, which can be a carrier or a diluent. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier, which can be in the form of an ampoule, capsule, sachet, paper, or other container. When the active compound is mixed with a carrier, or when the carrier serves as a diluent, it can be solid, semi-solid, or liquid material that acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid carrier, for example contained in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatin, lactose, terra alba, sucrose, dextrin, magnesium carbonate, sugar, cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent can include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax.

The formulations can be mixed with auxiliary agents, which do not deleteriously react with the active compounds. Such additives can include wetting agents, emulsifying and suspending agents, salt for influencing osmotic pressure, buffers and/or coloring substances preserving agents, sweetening agents or flavoring agents. The compositions can also be sterilized if desired.

The route of administration can be any route which effectively transports the active compound of the invention to the appropriate or desired site of action, such as oral, nasal, pulmonary, buccal, subdermal, intradermal, transdermal or parenteral, e.g., rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic solution or an ointment, the oral route being preferred.

If a solid carrier is used for oral administration, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge. If a liquid carrier is used, the preparation can be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

Injectable dosage forms generally include aqueous suspensions or oil suspensions which can be prepared using a suitable dispersant or wetting agent and a suspending agent. Injectable forms can be in solution phase or in the form of a suspension, which is prepared with a solvent or diluent. Acceptable solvents or vehicles include sterilized water, Ringer's solution, or an isotonic aqueous saline solution. Alternatively, sterile oils can be employed as solvents or suspending agents. Preferably, the oil or fatty acid is non-volatile, including natural or synthetic oils, fatty acids, mono-, di- or tri-glycerides.

For injection, the formulation can also be a powder suitable for reconstitution with an appropriate solution as described above. Examples of these include, but are not limited to, freeze dried, rotary dried or spray dried powders, amorphous powders, granules, precipitates, or particulates. For injection, the formulations can optionally contain stabilizers, pH modifiers, surfactants, bioavailability modifiers and combinations of these. The compounds can be formulated for parenteral administration by injection such as by bolus injection or continuous infusion. A unit dosage form for injection can be in ampoules or in multi-dose containers.

The formulations of the invention can be designed to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art. Thus, the formulations can also be formulated for controlled release or for slow release.

Compositions contemplated by the present invention can include, for example, micelles or liposomes, or some other encapsulated form, or can be administered in an extended release form to provide a prolonged storage and/or delivery effect. Therefore, the formulations can be compressed into pellets or cylinders and implanted intramuscularly or subcutaneously as depot

injections. Such implants can employ known inert materials such as silicones and biodegradable polymers, e.g., polylactide-polyglycolide. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides).

For nasal administration, the preparation can contain a compound of the invention, dissolved or suspended in a liquid carrier, preferably an aqueous carrier, for aerosol application. The carrier can contain additives such as solubilizing agents, e.g., propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabens.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet that can be prepared by conventional tableting techniques can contain ingredients as shown in Table I.

Table I: Specific Oral Formulation

Core		
	Active compound (as free compound or salt thereof)	250 mg
	Colloidal silicon dioxide (Aerosil)®	1.5 mg
	Cellulose, microcryst. (Avicel)®	70 mg
	Modified cellulose gum (Ac-Di-Sol)®	7.5 mg
	Magnesium stearate	Ad.
<u>Coating:</u>		
	HPMC approx.	9 mg
	*Mywacett 9-40 T approx.	0.9 mg

*Acylated monoglyceride used as plasticizer for film coating.

A typical capsule for oral administration contains compounds of the invention (250 mg), lactose (75 mg) and magnesium stearate (15 mg). The mixture is passed through a 60 mesh sieve and packed into a No. 1 gelatin capsule. A typical injectable preparation is produced by

aseptically placing 250 mg of compounds of the invention into a vial, aseptically freeze-drying and sealing. For use, the contents of the vial are mixed with 2 mL of sterile physiological saline, to produce an injectable preparation.

The compounds of the invention can be administered to a mammal, especially a human in need of such treatment, prevention, elimination, alleviation or amelioration of a malcondition. Such mammals include also animals, both domestic animals, e.g. household pets, farm animals, and non-domestic animals such as wildlife.

The compounds of the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.05 to about 5000 mg, preferably from about 1 to about 2000 mg, and more preferably between about 2 and about 2000 mg per day can be used. A typical dosage is about 10 mg to about 1000 mg per day. In choosing a regimen for patients, it can frequently be necessary to begin with a higher dosage and reduce the dosage when the condition is under control. The exact dosage will depend upon the activity of the compound, mode of administration, on the therapy desired, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

Generally, the compounds of the invention are dispensed in unit dosage form including from about 0.05 mg to about 1000 mg of active ingredient together with a pharmaceutically acceptable carrier per unit dosage.

Usually, dosage forms suitable for oral, nasal, pulmonal or transdermal administration include from about 125 µg to about 1250 mg, preferably from about 250 µg to about 500 mg, and more preferably from about 2.5 mg to about 250 mg, of the compounds admixed with a pharmaceutically acceptable carrier or diluent.

Dosage forms can be administered daily, or more than once a day, such as twice or thrice daily. Alternatively dosage forms can be administered less frequently than daily, such as every other day, or weekly, if found to be advisable by a prescribing physician.

Methods of Treatment

In various embodiments, the invention provides a method of treating a human immunodeficiency viral (HIV) infection in a patient, comprising administering to the patient afflicted with an HIV infection an effective amount of a compound of the invention at a frequency and for a duration to provide a beneficial effect to the patient.

In various embodiments, in carrying out the treatment of the HIV infection, the compound of the invention can be substantially the only antiviral compound administered to a patient in treatment of the HIV infection. As discussed above, what is meant is that the compound of the invention is substantially the only compound administered to the patient that interferes with viral replication *in vivo* in the patient, or interferes with *in vivo* transmission of the virus between living human beings. Compounds that are used merely to treat the symptoms of an HIV infection, e.g., febricides, anti-bacterial agents, fungicides, and the like can also be administered in carrying out a method of the invention.

In various embodiments, the method can further comprise administering an effective amount of a second antiviral compound. Examples of compounds that can be coadministered with a compound of the invention include a protease inhibitor (e.g., indinavir, ritonavir, and the like), a reverse transcriptase inhibitor (e.g., zidovudine, lamivudine, and the like), or an entry inhibitor (e.g., maraviroc, and the like).

An outstanding advantage of a compound of the invention is that dual targeting can be achieved in treatment of HIV, in that a compound of the invention can be effective as an inhibitor both of the reverse transcriptase (RT) enzyme system, and of the integrase (IN) enzyme system of the HIV. By targeting two distinct and substantially unrelated enzyme systems, the development of resistance by the virus is much less likely to occur, as mutations would have to simultaneously take place in the viral genome at two different loci.

In various embodiments, the invention provides a method of treating a hepatitis C viral (HCV) infection in a patient, comprising administering to the patient afflicted with an HCV infection an effective amount of a compound of the invention at a frequency and for a duration to provide a beneficial effect to the patient.

In various embodiments, in carrying out the treatment of the HCV infection, the compound of the invention can be substantially the only antiviral compound administered to a patient in treatment of the HCV infection. As discussed above, what is meant is that the compound of the invention is substantially the only compound administered to the patient that interferes with viral replication *in vivo* in the patient, or interferes with *in vivo* transmission of the virus between living human beings. Compounds that are used merely to treat the symptoms of an HCV infection, e.g., febricides, anti-bacterial agents, fungicides, and the like can also be administered in carrying out a method of the invention.

In various embodiments, the method can further comprise administering an effective amount of a second antiviral compound. Examples of compounds that can be coadministered with a compound of the invention include a protease inhibitor (e.g., indinavir, ritonavir, and the like), a reverse transcriptase inhibitor (e.g., zidovudine, lamivudine, and the like), or an entry inhibitor (e.g., maraviroc, and the like).

In various embodiments, the invention provides a method of simultaneously treating HIV and HCV infections in a patient, wherein an HIV patient is also secondarily infected with HCV. As discussed above, the leading causative agent of secondary infection in HIV patients is hepatitis C virus, and the direct cause of death of HIV patients is often liver failure resulting from a secondary HCV infection.

In various embodiments, in carrying out the treatment of the combined HIV and HCV infection, the compound of the invention can be substantially the only antiviral compound administered to a patient in simultaneous treatment of the two viral infections. As discussed above, what is meant is that the compound of the invention is substantially the only compound administered to the patient that interferes with viral replication *in vivo* in the patient, or interferes with *in vivo* transmission of the virus between living human beings. Compounds that are used merely to treat the symptoms of an HIV or HCV infection, e.g., febricides, anti-bacterial agents, fungicides, and the like can also be administered in carrying out a method of the invention.

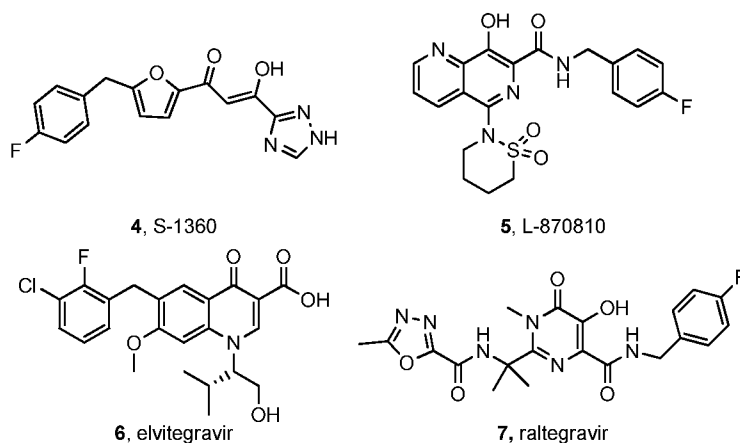
In various embodiments, the method can further comprise administering an effective amount of a second antiviral compound. Examples of compounds that can be coadministered with a compound of the invention include a protease inhibitor (e.g., indinavir, ritonavir, and the like), a reverse transcriptase inhibitor (e.g., zidovudine, lamivudine, and the like), or an entry inhibitor (e.g., maraviroc, and the like).

In various embodiments, the invention provides the use of a compound of the invention in manufacture of a medicament for the treatment of a viral infection. More specifically, the viral infection can comprise an HIV infection, an HCV infection, or both.

In various embodiments, the invention provides the use of a compound of the invention to treat a viral infection in a human subject. The viral infection can be an HIV infection, an HCV infection, or both.

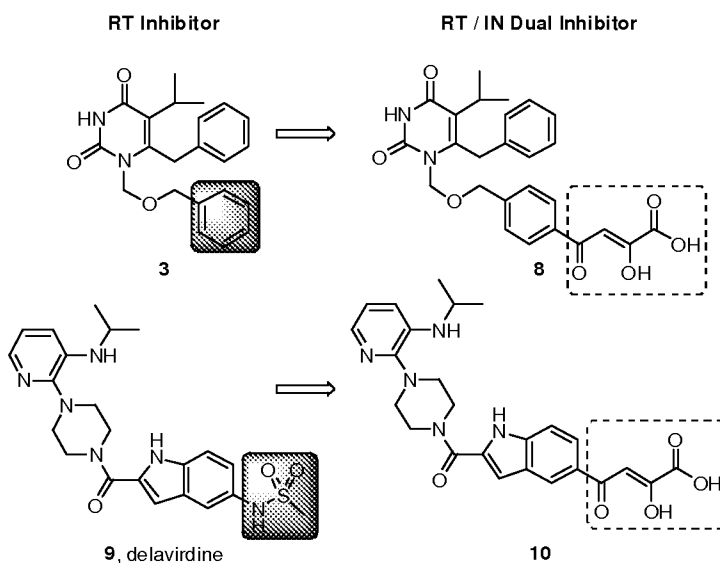
Previous work has demonstrated the viability of constructing RT / IN dual inhibitors based on another structural class of compounds from NNRTIs using a design-in strategy.¹⁵⁻

¹⁷Significantly, IN binding requires minimally a two metal ion chelating functionality and a hydrophobic benzyl group (below). Certain NNRTI scaffolds, including HEPT¹⁸ and BHAP¹⁹ (e.g. delavirdine, **9**), have structural moieties that are sitting on the P236 loop of the NNRTI binding pocket and are not directly involved in RT binding.

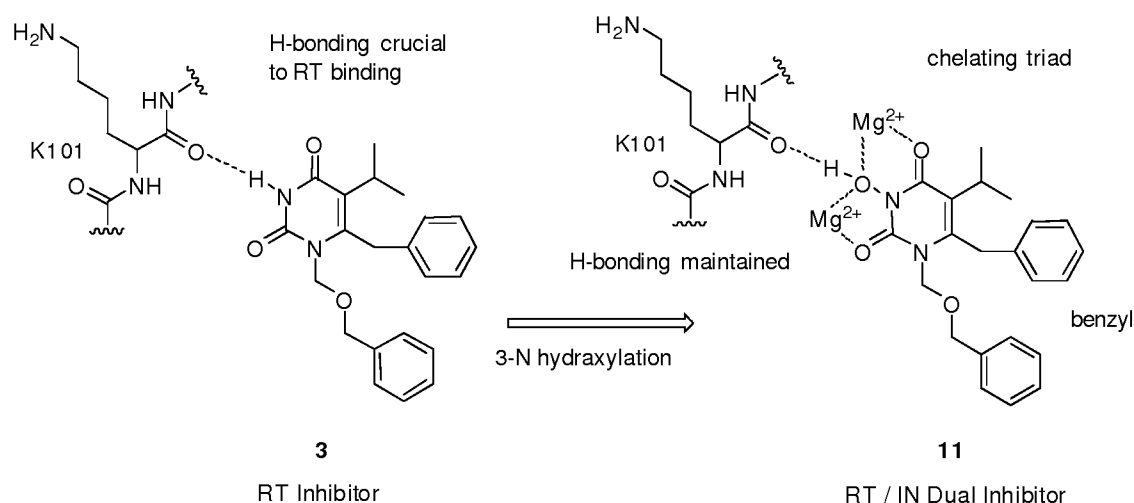


These moieties provide valuable handles (highlighted, below) for incorporating a relatively hydrophilic chelating functionality (boxed) to satisfy binding to the IN (below).^{12,}

¹⁴Most of other NNRTIs are deeply buried in the highly hydrophobic binding pocket, thus are less amenable to hydrophilic modifications. In these cases, designing in structural components for IN binding requires careful considerations of all binding interactions of NNRTIs.



Notably the NNRTI binding pocket is largely hydrophobic and few H-bonds are accommodated. For the HEPT type of NNRTIs, the H-bond between the N(3)H of the inhibitor (e.g. inhibitor **3**, below) and the backbone carbonyl group of K101 represents the major hydrophilic interaction.²⁰ This H-bond contributes to the NNRTI binding affinity, and more importantly, serves as an anchor for the inhibitor to adopt optimized conformation so that hydrophobic interactions can be maximized throughout the binding pocket. Additional water mediated H-bonds may be present, albeit of much less significance.⁹ Therefore, the N(3)H group is generally considered too important to be modified. In our design, we hypothesize that hydroxylation of the N-3 of compound **3** would not significantly compromise its binding affinity to RT. This hypothesis is based on two observations: 1) the newly incorporated OH would retain H-bonding ability; and 2) the NNRTI binding pocket has four consecutive lysine residues (K101-K104) that could potentially H-bond to the newly introduced OH. Since this minimal modification only results in an insertion of an oxygen atom to NH, we expect that the key H-bond can be formed between the OH and one of these lysine residues, and the overall conformation of the inhibitor should be largely preserved. On the other hand, such a simple hydroxylation yields a C(2)O-N(3)OH-C(4)O chelating triad (**11**) capable of chelating two magnesium ions, which along with an existing hydrophobic benzyl group at N-1 or C-6 will essentially provide the minimal pharmacophore for IN binding. Therefore, through a simple N-3 hydroxylation, these HEPT type NNRTIs could be converted into RT / IN dual inhibitors. The H-bond crucial to RT binding is maintained and the conformation of the molecule remains unchanged. The N-3 hydroxylation yields a chelating triad, a critical structural components for IN binding.



This design is verified in silico by molecular modeling. All modeling was carried out using the Schrödinger modeling suite package.²¹ Docking of all compounds was carried out using Glide v2.5 at Standard Precision.²² For docking into HIV-1 IN, both Mg^{2+} ions and the interfacial hydrophobic pocket between the HIV-1 IN and DNA were defined as required constraints. Docking of **3** and **11** reveals their mode of binding in the NNRTI binding pocket almost identically as illustrated in Figure 2A. Both compounds hydrogen bonded to the backbone carbonyl oxygen atom of K101. Interestingly the OH of **11** and NH of **3** are both situated in close proximity of the K101 backbone (1.7 Å and 1.6 Å respectively). Accordingly, the H-bonding allows both inhibitors to adopt a nearly identical conformation in the binding pocket, suggesting that N-3 hydroxylation should not significantly compromise RT binding. Docking of **11** into our recent homology model²³ of HIV-1 IN catalytic core domain (CCD) in complex with Mg^{2+} and DNA indicated the newly designed inhibitor **11** also showed reasonable IN binding as illustrated in Figure 2B. The 3-N hydroxylation of the pyrimidine ring yields a chelating triad for Mg^{2+} binding while allowing the placement of the benzyl group into the protein-DNA interfacial hydrophobic pocket, a crucial pharmacophore requirement for potent HIV-1 ST inhibition.^{24,25} The 3-N hydroxyl group simultaneously chelates to both Mg^{2+} ions while allowing the placement of the benzyl group into the protein-DNA interfacial hydrophobic pocket. The electrostatic potential surface of the binding pocket highlights the hydrophobic regions in both enzymes as illustrated in Figure 2B.

Testing of these compounds against recombinant HIV IN provided the first validation of the design. In this assay both the 3' processing (3'P) and the strand transfer (ST) activities, the two primary functions of IN, were assessed. The inhibitory activities of compounds 11-18 against HIV IN are presented in Table II. It is evident from Table II that all N-3 hydroxylated compounds (**11-15**, **17-18**) selectively inhibit ST over 3'P at low micromolar concentrations, whereas the unmodified compound (**3**) did not show any inhibitory activity against HIV IN. This observation strongly suggests that the N-3 hydroxyl group, partially forming the chelating triad is crucial to IN binding. Interestingly, the N-3 amino compound (**16**) also turned out inactive in IN assay. It is not surprising that the N-3 hydroxylation yields a better chelating triad than the N-3 amination as O tends to have a higher affinity for Mg^{2+} than N. In addition, compounds **17** and **18** demonstrate significantly reduced (ca. 10-fold) inhibition against ST when compared with

compounds **11-15**, indicating that the benzyl group at N-1 side chain is far more important for IN binding than the one at C-6 position of the pyrimidine-2,4-dione ring.

Table II: Inhibitory Concentrations (50%) for Specific Compounds

Compound	3'P IC ₅₀ ^a (μM)	ST IC ₅₀ ^a μM)
11	>333	21
12	>333	7.3
13	>333	3.5
14	>333	5.5
15	>333	8.2
16	>333	>333
17	>333	85
18	>333	105
3	>333	>333

^a Concentration inhibiting enzyme activity by 50%.

To further characterize the mechanism of action of the newly designed compounds, a representative compound **13** was tested head-to-head with raltegravir (**7**) against a recombinant HIV IN containing major resistant mutations G140S and Q148H.^{26, 27} The comparisons were shown in Figure 1. It is clear from Figure 1 that although inhibiting IN at a higher concentration when compared with **7**, compound **13** does show similar resistance profile to **7**, further proving that the inhibitors disclosed in the invention are targeting IN ST.

Having established these new inhibitors as valid HIV IN inhibitors, their ability to inhibit HIV RT was studied. Through a quick biochemical assay using commercial RT assay kit it was found that N-3 hydroxylated compounds (**13**) and aminated compound (**16**) all show inhibitory activity at low or sub-micromolar range as shown in Table III. Anti-RT and Anti-HIV activities of inhibitors **11-18** are presented in Table III. Apparently an N-3 OH or NH₂ allows these compound to virtually maintain the key H-bonding ability as expected, though the unmodified N(3)H group of compound **3** appears to form better H-bonding as compound **3** inhibits RT at a considerably lower concentration. Meanwhile, a dramatic fluorine effect was also observed with

compounds **12**, **14** and **18**, where a fluorine substitution at the para position of the C-6 benzyl completely disables RT binding. By contrast, the para position of the other benzyl group in N-1 side chain appears to be highly tolerant towards fluorine substitution (compound **13**).

Table III: Inhibitory Concentrations (50%) and Anti-HIV Bioactivities of Specific Compounds

Compound	RT IC ₅₀ (μM) ^a	HIV-1		
		EC ₅₀ (μM) ^b	CC ₅₀ (μM) ^c	TI ^d
11	6.2	0.0080	>20	>2500
12	>100	>10	--	--
13	0.17	0.024	>20	>830
14	>100	>10	--	--
15	9.4	1.1	>20	>18
16	1.5	>10	--	--
17	13	4.3	>20	>4.7
18	>100	>10	--	--
3	0.040	0.013	>20	>1500

^a Concentration inhibiting enzyme activity by 50%; ^b Concentration inhibiting virus replication by 50%; ^c Concentration resulting in 50% cell death; ^d Therapeutic index, defined by CC₅₀ / EC₅₀.

Finally, these compounds were tested in cell-based antiviral assay against HIV 1. With the exception of compounds with a terminal fluorine atom on the C-6 benzyl group (**12**, **14** and **18**), and the one with N-3 amino group (**16**), these inhibitors generally show excellent antiviral potency and safety (Table 2). The best compounds in this series, compounds **11** and **13**, demonstrate low nanomolar anti-HIV activity that is comparable to or even better than reference compound **3**.

In summary, through rational design a novel series of anti-HIV compounds were generated that are dually active against IN and RT at low and sub-micromolar concentrations. The design involves a key structural modification on HEPT NNRTI inhibitor scaffold to introduce inhibitory activity against IN. Major structural determinants for IN binding as well as a dramatic fluorine effect for RT binding were identified through preliminary SAR efforts. In the end, two compounds (**11** and **13**) were found to have low nanomolar inhibitory activities against

HIV-1 in cell culture. Anti HIV data and HCV assay results for the compounds of the invention are presented in Table IV and Table V.

Table IV: Anti-HIV Bioactivities of Specific Compounds

Compound	RT IC ₅₀ (μM)	IN IC ₅₀ (μM)		HIV-1	
		ST	3P'	EC ₅₀ (μM)	CC ₅₀ (μM)
I	0.17	3.5	>111	0.024	>20
II	~100	28	>111	ND	ND
III	47	22	>111	6.0	18
IV	13	85	>111	4.3	>20
V	> 100	7.3	>111	ND	ND
VI	> 100	5.5	>111	ND	ND
VII	> 100	32	>111	ND	ND
VIII	> 100	105	>111	ND	ND
IX	> 100	105	>111	ND	ND
X	9.4	8.2	>111	1.1	>20
XI	> 100	>111	>111	N/A	>20
XII	ND	24	>111	18	>20
XIII	> 100	69 / 78	>111	11	>20
XIV	> 100	>111	>111	ND	ND
XV	>100	>111	>111	ND	ND
XVI*	0.04	>111	>111	0.013	>20
XVII	>100	>111	>111	ND	ND
XVIII	>100	>111	>111	ND	ND

XIX	6.2	21	>111	0.008	>20
XX*	1.5	>333	>111	ND	ND
XXI	> 100	46	>111	ND	ND
XXII	8.7	0.44	12.53	ND	ND
XXIII	>100	0.56	17.7	ND	ND
XIV	21	1.6	>111	ND	ND
XV	7.3	3.2	>111	ND	ND
XVI	> 100	4.5	>111	ND	ND
XVII	7.6	20.5	>111	0.36	28
XVIII	1.0	40.5	>111	0.061	33
XXIX	10	7.0	>111	ND	ND
XXX	0.5	>111	>111	0.030	77
XXXI	23	25.5	>111	2.0	>100
XXXII	14	36.5	>111	1.4	>100
XXXIII	ND	4.1	>111	0.34	>100
XXXIV	43	>111	>111	2.3	94
XXXV	ND	2.3	>111	0.95	>100
XXXVI	ND	4.8	>111	2.06	>100
XXXVII	ND	>111	>111	ND	ND
XXXVIII	ND	>111	>111	ND	ND
XXXIX	ND	11.3	ND	ND	ND
XXXX	ND	36	ND	ND	ND

RT: reverse transcriptase; IN: integrase; ST: strand transfer; 3'P: 3' processing; ND: not determined.

*compounds XVI and XX are not compounds of the invention and are included for comparative purposes.

Table V: Anti-HCV Bioactivities of Specific Compounds

Compound	EC ₅₀ (μM)	CC ₅₀ (μM)	TI
I	4.3	>150	>35
XVI*	inactive	ND	--
III	~10	ND	--
IIIa*	inactive	ND	--
V	~ 10	ND	--
Va*	inactive	ND	--
VI	2.8	>150	>54
VIa*	inactive	ND	--
VIII	1.7	>150	>88
VIIIa*	inactive	ND	--
RBV	12	27	2.3

EC₅₀: concentration of compound for 50% inhibition; **CC₅₀**: concentration of compound causing 50% cytotoxicity; **TI**: therapeutic index, defined as CC₅₀ / EC₅₀; **RBV**: ribavirin, an antiviral used in combination with interferon alpha to form the current standard of care for HCV infection; **ND**: not determined.

*compounds XVI, IIIa, Va, VIa, VIIIa and RBV (ribivarin) are not compounds of the invention and are included for comparative purposes.

Evaluations

It is within ordinary skill to evaluate any compound disclosed and claimed herein for effectiveness in inhibition of HIV or HCV viral replication, inhibition of reverse transcriptase and integrase enzymatic activity, and in the various cellular assays using the procedures described above or found in the scientific literature. Accordingly, the person of ordinary skill can prepare and evaluate any of the claimed compounds without undue experimentation.

Any compound found to be an effective inhibitor in any of the above-listed criteria can likewise be tested in animal models and in human clinical studies using the skill and experience of the investigator to guide the selection of dosages and treatment regimens.

Examples

Chemistry Experimental

General Procedures.

All commercial chemicals were used as supplied unless otherwise indicated. Dry solvents (THF, Et₂O, CH₂Cl₂ and DMF) were dispensed under argon from an anhydrous solvent system with two packed columns of neutral alumina or molecular sieves. Flash chromatography was performed on a Teledyne Combiflash RF-200 with RediSep columns (silica) and indicated mobile phase. All reactions were performed under inert atmosphere of ultra-pure argon with oven-dried glassware. ¹H and ¹³C NMR spectra were recorded on a Varian 600 MHz spectrometer. Mass data were acquired on an Agilent TOF II TOS/MS spectrometer capable of ESI and APCI ion sources. Analysis of sample purity was performed on a Varian Prepstar SD-1 HPLC system with a Varian Microsorb-MW 100-5 C18 column (250mm x 4.6 mm).

The following compounds exemplify the methods outlined in Synthetic Schemes 1, 2, 3 and 4:

Ethyl 2-isopropyl-3-oxo-4-phenylbutanoate (23).²⁸

Yield: 90%; ¹HNMR (600 MHz, CDCl₃) δ 7.24 (t, *J* = 7.2 Hz, 2H), 7.20 (m, 1H), 7.14 (d, *J* = 7.8 Hz, 2H), 4.06 (q, *J* = 7.2 Hz, 2H), 3.71 (s, 2H), 3.25 (d, *J* = 9.0 Hz, 1H), 2.35 (m, 1H), 1.17 (t, *J* = 7.2 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.79 (d, *J* = 6.6 Hz, 3H).

Ethyl 4-(4-fluorophenyl)-2-isopropyl-3-oxobutanoate (24).²⁸

Yield: 89%; ^1H NMR (600 MHz, CDCl_3) δ 7.09 (dd, $J = 3.0$ Hz, 8.4 Hz, 2H), 6.94 (t, $J = 8.4$ Hz, 2H), 4.07 (q, $J = 7.2$ Hz, 2H), 3.69 (s, 2H), 3.23 (d, $J = 9.0$ Hz, 1H), 2.41 (m, 1H), 1.17 (t, $J = 7.2$ Hz, 3H), 0.88 (d, $J = 6.6$ Hz, 3H), 0.79 (d, $J = 6.6$ Hz, 3H).

6-Benzyl-5-isopropylpyrimidine-2,4(1H,3H)-dione (26).²⁸

Yield: 38%; ^1H NMR (600 MHz, CDCl_3) 10.32 (br, 1H), 10.18 (br, 1H), 7.28 (m, 2H), 7.22 (t, $J = 7.2$ Hz, 1H), 7.11 (d, $J = 7.2$ Hz, 2H), 3.82 (s, 2H), 2.85 (septet, $J = 7.2$ Hz, 1H), 1.16 (d, $J = 7.2$ Hz, 6H); MS (ESI+) m/z : 245.28 (M+1).

6-Benzyl-5-isopropylpyrimidine-2,4(1H,3H)-dione (27).²⁸

Yield 78%, ^1H NMR (600 MHz, CD_3OD) δ 7.19 (m, 2H), 7.01 (t, $J = 8.4$ Hz, 2H), 3.72 (s, 2H), 2.87 (septet, $J = 7.2$ Hz, 1H), 1.16 (d, $J = 7.2$ Hz, 6H); MS (ESI+) m/z : 263.12 (M+1).

6-Benzyl-1-((4-fluorobenzyloxy)methyl)-5-isopropylpyrimidine-2,4(1H,3H)-dione (30).¹²

Yield 89%, : ^1H NMR (600 MHz, CDCl_3) δ 8.97 (b, 1H), 7.34 (t, $J = 7.2$ Hz, 2H), 7.30 (m, 3H), 7.07 (d, $J = 7.8$ Hz, 2H), 7.03 (m, 2H), 5.20 (s, 2H), 4.61 (s, 2H), 4.16 (s, 2H), 2.88 (septet, $J = 7.2$ Hz, 1H), 1.28 (d, $J = 7.2$ Hz, 6H); MS (ESI+) m/z : 383.18 (M+1).

4-Fluorobenzyl alcohol (0.252 g, 2.0 mmol) was added to a suspension of paraformaldehyde (0.066 g, 2.2 mmol) in TMSCl (1.0 mL) at room temperature. The resulting suspension was stirred until a clear solution was achieved (ca. 45 min). The solution was concentrated under reduced pressure to give compound 4-fluorobenzyl chloromethyl ether as oil, which was taken to the next step without further purification. To the suspension of pyrimidine (0.244 g 1.0 mmol) in 5.0 mL of DCM was added BSA (0.542 mL, 2.2 mmol) at room temperature. The resulting mixture was stirred until a clear solution was achieved (ca. 30 min). To this was then added freshly prepared chloromethyl ether followed by the addition of a catalytic amount of TBAI. The reaction mixture was kept overnight and then quenched by adding a saturated aqueous solution of NaHCO_3 . The aqueous phase was extracted with CH_2Cl_2 (10 mL x 3). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The resultant residue was subjected to combiflash (Hex / EtOAc, 2:1) to afford 0.34 g of compound 30 as a pale yellow solid.

6-Benzyl-1-(benzyloxymethyl)-5-isopropylpyrimidine-2,4(1H,3H)-dione (3).

Yield: 56%; ^1H NMR (600 MHz, CDCl_3) δ 7.28 (m, 6H), 7.20 (m, 2H), 7.00 (d, $J = 7.8$ Hz, 2H), 5.14 (s, 2H), 4.59 (s, 2H), 4.10 (s, 2H), 2.79 (septet, $J = 6.6$ Hz, 1H), 1.21 (d, $J = 6.6$ Hz, 6H); MS (ESI+) m/z : 365.17 (M+1).

This compound was prepared as a white solid following the procedure described for the preparation of **30**.

1-(Benzyloxymethyl)-6-(4-fluorobenzyl)-5-isopropylpyrimidine-2,4(1H,3H)-dione (**29**).

Yield: 51%; ¹H NMR (600 MHz, CDCl₃) δ 9.66 (b, 1H), 7.33 (m, 5H), 7.01 (m, 4H), 5.21 (s, 2H), 4.66 (s, 2H), 4.13 (s, 2H), 2.84 (septet, *J* = 7.2 Hz, 1H), 1.28 (d, *J* = 7.2 Hz, 6H); MS (ESI+) *m/z*: 383.18 (M+1).

This compound was prepared as a white solid following the procedure described for the preparation of **30**.

6-(4-Fluorobenzyl)-1-((4-fluorobenzyloxy)methyl)-5-isopropylpyrimidine-2,4(1H,3H)-dione (**31**).

Yield: 53%; ¹H NMR (600 MHz, CDCl₃) δ 9.80 (b, 1H), 7.30 (dd, *J* = 3.0, 8.4 Hz, 2H), 7.03 (m, 6H), 5.19 (s, 2H), 4.61 (s, 2H), 4.12 (s, 2H), 2.83 (septet, *J* = 7.2 Hz, 1H), 1.26 (d, *J* = 7.2 Hz, 6H); MS (ESI+) *m/z*: 401.17 (M+1).

This compound was prepared as a white solid following the procedure described for the preparation of **30**.

6-Benzyl-1-(benzyloxymethyl)-5-ethylpyrimidine-2,4(1H,3H)-dione (**32**).

Yield: 70%; ¹H NMR (600 MHz, CDCl₃) δ 9.96 (b, 1H), 7.33 (m, 7H), 7.26 (m, 1H), 7.07 (d, *J* = 7.2 Hz, 2H), 5.41 (s, 2H), 4.66 (s, 2H), 4.15 (s, 2H), 2.47 (q, *J* = 7.8 Hz, 2H), 1.07 (t, *J* = 7.8 Hz, 3H); MS (ESI+) *m/z*: 351.17 (M+1).

This compound was prepared as a white solid following the procedure described for the preparation of **30**.

6-Benzyl-1-(ethoxymethyl)-5-isopropylpyrimidine-2,4(1H,3H)-dione (**2**).

Yield: 60%; ¹H NMR (600 MHz, CDCl₃) δ 10.05 (b, 1H), 7.32 (t, *J* = 7.8 Hz, 2H), 7.25 (t, *J* = 7.2 Hz, 2H), 7.10 (d, *J* = 7.2 Hz, 2H), 5.12 (s, 2H), 4.17 (s, 2H), 3.62 (q, *J* = 7.2 Hz, 2H), 2.87 (septet, *J* = 7.2 Hz, 1H), 1.27 (d, *J* = 7.2 Hz, 6H), 1.66 (t, *J* = 7.2 Hz, 3H); MS (ESI+) *m/z*: 303.18 (M+1).

This compound was prepared as a white solid following the procedure described for the preparation of **30**.

1-(ethoxymethyl)-5-ethyl-6-(4-fluorobenzyl)pyrimidine-2,4(1H,3H)-dione (**33**).

Yield: 58%; ^1H NMR (600 MHz, CDCl_3) δ 9.70 (b, 1H), 7.32 (dd, $J = 5.4, 8.4$ Hz, 2H), 7.03 (t, $J = 8.4$ Hz, 2H), 5.12 (s, 2H), 4.13 (s, 2H), 3.62 (q, $J = 7.2$ Hz, 2H), 2.83 (septet, $J = 7.2$ Hz, 1H), 1.26 (d, $J = 7.2$ Hz, 6H), 1.66 (t, $J = 7.2$ Hz, 3H); MS (ESI+) m/z : 321.16 ($M+1$).

This compound was prepared as a white solid following the procedure described for the preparation of **30**.

6-Benzyl-1-((4-fluorobenzyloxy)methyl)-3-hydroxy-5-isopropylpyrimidine-2,4(1H,3H)-dione (13).

Yield 73% based on consumed start material, ^1H NMR (600 MHz, CDCl_3) δ 7.33-7.26 (m, 5H), 7.04-6.99 (m, 4H), 5.03 (s, 2H), 4.64 (s, 2H), 4.19 (s, 2H), 2.90 (septet, $J = 7.2$ Hz, 1H), 1.29 (d, $J = 6.6$ Hz, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.3, 162.4, 161.6, 152.1, 149.8, 148.3, 135.2, 133.1, 129.7, 129.6, 129.2, 127.2, 119.9, 115.4, 115.3, 72.8, 70.9, 33.5, 28.2, 20.4; HRMS (ESI+) calcd. for $\text{C}_{22}\text{H}_{23}\text{FN}_2\text{O}_4$ [$M+H$] $^+$ 399.1715, found 399.1705 ($E = 2.4$ ppm); HPLC: retention time 10.80 min.

To a solution of **30** (0.100 g, 0.26 mmol) in 3 mL of THF was added NaH (0.0314 g, 1.30 mmol) at 0 °C. This reaction mixture was allowed to warm to room temperature over 1h., and then cooled to 0 °C followed by the addition of m-CPBA (0.135 g, 0.79 mmol). After stirring for 0.5 h, this reaction mixture was stirred at room temperature overnight. After the reaction was quenched by adding 10 mL of H_2O , the aqueous phase was acidified with 1N HCl to pH = 7, and then extracted with ethyl acetate (10 mL x 3). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The resultant residue was subjected to combiflash (Hex / EtOAc, 1:1) to give 0.038 g of compound **13** as a white solid.

6-Benzyl-1-(benzyloxymethyl)-3-hydroxy-5-isopropylpyrimidine-2,4(1H,3H)-dione (11).

Yield: 53% based on consumed start material; ^1H NMR (600 MHz, CDCl_3) δ 7.32-7.30 (m, 7H), 7.02 ($J = 7.2$ Hz, 2H), 5.30 (s, 2H), 4.67 (s, 2H), 4.19 (s, 2H), 2.90 (septet, $J = 7.2$ Hz, 1H), 1.28 (d, $J = 6.6$ Hz, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 162.2, 151.9, 148.4, 137.3, 135.3, 129.1, 128.5, 128.0, 127.8, 127.3, 127.2, 119.8, 73.0, 71.8, 33.5, 28.2, 20.4; HRMS (ESI+) calcd. for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_4$ [$M+H$] $^+$ 381.1809, found 381.1803 ($E = 1.5$ ppm); HPLC: retention time 10.79 min.

This compound was prepared as a white solid following the procedure described for the preparation of **13**.

1-(Benzyloxymethyl)-6-(4-fluorobenzyl)-3-hydroxy-5-isopropylpyrimidine-2,4(1H,3H)-dione (12).

Yield: 74% based on consumed start material; ^1H NMR (600 MHz, CDCl_3) δ 7.32-7.27 (m, 5H), 7.00-6.98 (m, 4H), 5.28 (s, 2H), 4.67 (s, 2H), 4.14 (s, 2H), 2.81 (septet, $J = 7.2$ Hz, 1H), 1.27 (d, $J = 6.6$ Hz, 6H); HRMS (ESI+) calcd. for $\text{C}_{22}\text{H}_{23}\text{FN}_2\text{O}_4[\text{M}+\text{H}]^+$ 399.1715, found 399.1706 ($E = 2.1$ ppm); HPLC: retention time 10.63 min.

This compound was prepared as a white solid following the procedure described for the preparation of **13**.

6-(4-Fluorobenzyl)-1-((4-fluorobenzyloxy)methyl)-3-hydroxy-5-isopropylpyrimidine-2,4(1H,3H)-dione (14).

Yield: 72% based on consumed start material; ^1H NMR (600 MHz, CDCl_3) δ 7.28-7.27 (m, 2H), 7.00-6.98 (d, $J = 7.2$ Hz, 6H), 5.24 (s, 2H), 4.61 (s, 2H), 4.12 (s, 2H), 2.83 (septet, $J = 7.2$ Hz, 1H), 1.25 (d, $J = 6.6$ Hz, 6H); HRMS (ESI+) calcd. for $\text{C}_{22}\text{H}_{22}\text{F}_2\text{N}_2\text{O}_4[\text{M}+\text{H}]^+$ 417.1620, found 417.1620 ($E = 0.1$ ppm); HPLC: retention time 10.93 min.

This compound was prepared as a white solid following the procedure described for the preparation of **13**.

6-Benzyl-1-(benzyloxymethyl)-5-ethyl-3-hydroxypyrimidine-2,4(1H,3H)-dione (15).

Yield: 70% based on consumed start material; ^1H NMR (600 MHz, CDCl_3) δ 7.33-7.27 (m, 8H), 7.03 (d, $J = 7.8$ Hz, 2H), 5.26 (s, 2H), 4.65 (s, 2H), 4.15 (s, 2H), 2.51 (q, $J = 7.8$ Hz, 2H), 1.06 (t, $J = 7.2$ Hz, 3H), HRMS (ESI+) calcd. for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_4[\text{M}+\text{H}]^+$ 367.1652, found 367.1641 ($E = 3.1$ ppm); HPLC: retention time 10.79 min.

This compound was prepared as a white solid following the procedure described for the preparation of **13**.

6-Benzyl-1-(ethoxymethyl)-3-hydroxy-5-isopropylpyrimidine-2,4(1H,3H)-dione (17).

Yield: 72% based on consumed start material; ^1H NMR (600 MHz, CDCl_3) δ 7.35-7.32 (t, $J = 7.2$ Hz, 2H), 7.28 (d, $J = 7.8$ Hz, 1H), 7.09 (d, $J = 7.2$ Hz, 2H), 5.22 (s, 2H), 4.21 (s, 2H), 3.65 (q, $J = 7.2$ Hz, 2H), 2.81 (septet, $J = 7.2$ Hz, 1H), 1.30 (d, $J = 6.6$ Hz, 6H), 1.19 (t, $J = 7.2$ Hz, 3H), HRMS (ESI+) calcd. for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_4[\text{M}+\text{H}]^+$ 319.1652, found 319.1637 ($E = 4.8$ ppm); HPLC: retention time 10.88 min.

This compound was prepared as a white solid following the procedure described for the preparation of **13**.

1-(Ethoxymethyl)-6-(4-fluorobenzyl)-3-hydroxy-5-isopropylpyrimidine-2,4(1H,3H)-dione (18).

Yield: 63% based on consumed start material; ¹H NMR (600 MHz, CDCl₃) δ 7.35-7.32 (t, *J* = 7.2 Hz, 2H), 7.28 (d, *J* = 7.8 Hz, 1H), 7.09 (d, *J* = 7.2 Hz, 2H), 5.22 (s, 2H), 4.21 (s, 2H), 3.65 (q, *J* = 7.2 Hz, 2H), 2.81 (septet, *J* = 7.2 Hz, 1H), 1.30 (d, *J* = 6.6 Hz, 6H); 1.19 (t, *J* = 7.2 Hz, 3H), HRMS (ESI+) calcd. for C₁₇H₂₁FN₂O₄[M+H]⁺ 337.1558, found 337.1572 (E = -4.1 ppm); HPLC: retention time 11.12 min.

This compound was prepared as a white solid following the procedure described for the preparation of **13**

3-Amino-6-benzyl-1-(benzyloxymethyl)-5-isopropylpyrimidine-2,4(1H,3H)-dione (16).

Yield 54% based on consumed start material, ¹H NMR (600 MHz, CDCl₃) δ 7.33-7.26 (m, 8H), 7.04-7.03 (d, *J* = 7.2 Hz, 2H), 5.24 (s, 2H), 4.66 (s, 2H), 4.19 (s, 2H), 2.90 (septet, *J* = 7.2 Hz, 1H), 1.29 (d, *J* = 6.6 Hz, 6H); HRMS (ESI+) calcd. for C₂₂H₂₅N₃O₃ [M+H]⁺ 380.1969, found 380.1976 (E = -1.9 ppm); HPLC: retention time 8.31 min.

To a solution of **30** (0.060 g, 0.16 mmol) in 1.0 mL of THF, NaH (0.0314 g, 0.82 mmol) was added at 0 °C. This reaction mixture was allowed to warm to room temperature over 1h., and then cooled to 0 °C followed by the addition of O-(Mesitylsulfonyl) hydroxylamine^[S3] (MSH, 0.066 g, 0.32 mmol). After stirring for 0.5 h, this reaction mixture was stirred at room temperature overnight. The reaction was quenched by adding 10 mL of H₂O, the aqueous phase was then extracted with ethyl acetate (10 mL x 3). The combined organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure. The resultant residue was subjected to combiflash (Hex / EtOAc, 1:1) to give 0.022 g of compound **16** as a white solid.

5-Ethyl-6-(4-fluorophenyl)-3-hydroxypyrimidine-2,4(1H,3H)-dione (34)

Yield 50 %. ¹H NMR (600 MHz, CD₃OD) δ 7.81 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 9.0 Hz, 2H), 4.06 (q, *J* = 6.6 Hz, 2H), 1.33 (t, *J* = 6.6 Hz, 3H); MS (ESI-) *m/z*: 233.09 (M-1).

To a solution of methyl 2-(4-fluorobenzoyl)butanoate (1.0 g, 4.5 mmol) in 15 mL anhydrous MeOH, Urea (0.616 g, 10.3mmol) and the freshly prepared NaOMe (0.529 g, 9.8 mmol) were added. This reaction mixture was heated to reflux for overnight. Then the solvent was removed and the residue was redissolved in 5 mL water and the pH was adjusted to 4 by adding 2N HCl to form the white precipitate. The solution was filtered and washed with water and ether to form 0.525 g of desired product as white sold.

1-(Benzyloxymethyl)-5-ethyl-6-(4-fluorophenyl)pyrimidine-2,4(1H,3H)-dione (35).

Yield: 42 %; ^1H NMR (600 MHz, CDCl_3) δ 8.60 (s, 1H), 7.26-7.21 (m, 5H), 7.15 (d, J = 7.2 Hz, 2H), 7.11 (t, J = 8.4 Hz, 2H), 4.87 (s, 2H), 4.43 (s, 2H), 1.98 (q, J = 7.2 Hz, 2H), 0.85 (t, J = 7.8 Hz, 3H).; MS (ESI-) m/z : 353.37 (M-1).

5-Ethyl-1-((4-fluorobenzyloxy)methyl)-6-(4-fluorophenyl)pyrimidine-2,4(1H,3H)-dione (36).

Yield: 33 %; ^1H NMR (600 MHz, CDCl_3) δ 8.59 (s, 1H), 7.23-7.20 (m, 2H), 7.14-7.09 (m, 4H), 6.95 (t, $J = 8.4$ Hz, 2H), 4.85 (s, 2H), 4.39 (s, 2H), 1.99 (q, $J = 7.2$ Hz, 2H), 0.85 (t, $J = 7.2$ Hz, 3H).; MS (ESI-) m/z : 371.36 (M-1).

1-(Benzyloxymethyl)-5-ethyl-6-(4-fluorophenyl)-3-hydroxypyrimidine-2,4(1H,3H)-dione (37).

Yield: 47 %; ^1H NMR (600 MHz, CDCl_3) δ 7.26-7.23 (t, $J = 7.2$ Hz, 3H), 7.22 (d, $J = 7.2$ Hz, 2H), 7.15 (d, $J = 7.8$ Hz, 2H), 7.11 (t, $J = 8.4$ Hz, 2H), 4.87 (s, 2H), 4.43 (s, 2H), 1.97 (q, $J = 7.8$ Hz, 2H), 0.84 (t, $J = 7.8$ Hz, 3H).; MS (ESI-) m/z : 369.29 (M-1).

5-Ethyl-1-((4-fluorobenzyloxy)methyl)-6-(4-fluorophenyl)-3-hydroxypyrimidine-2,4(1H,3H)-dione (38).

Yield: 55 %; ^1H NMR (600 MHz, CDCl_3) δ 7.15-7.12 (m, 4H), 7.10 (t, $J = 7.8$ Hz, 2H), 6.93 (t, $J = 7.8$ Hz, 2H), 4.92 (s, 2H), 4.44 (s, 2H), 2.02 (q, $J = 7.8$ Hz, 2H), 0.85 (t, $J = 7.8$ Hz, 3H).; MS (ESI-) m/z : 387.11 (M-1).

4-Benzyl-3-(benzyloxymethyl)-5-isopropyl-2,6-dioxo-2,3-dihydropyrimidin-1(6H)-yl acetate (39).

Yield: 94 %; ^1H NMR (600 MHz, CDCl_3) δ 7.27-7.22 (m, 6H), 7.21-7.19 (m, 2H), 7.01 (d, $J = 7.8$ Hz, 2H), 5.17 (s, 2H), 4.61 (dd, $J = 33.0, 12.0$ Hz, 2H), 4.12 (s, 2H), 2.82 (m, $J = 7.2$ Hz, 1H), 2.33 (s, 3H), 1.21 (d, $J = 7.2$ Hz, 6H).; MS (ESI-) m/z : 421.42 (M-1).

To a solution 6-benzyl-1-(benzyloxymethyl)-3-hydroxy-5-isopropylpyrimidine-2,4(1H,3H)-dione (5.0 mg, 0.013 mmol) in 1 mL anhydrous THF, triethylamine (1.1 mg, 0.013 mmol) and acetyl chloride (2.0 mg, 0.026 mmol) were added. The reaction mixture was stirred at room temperature for overnight. The reaction is quenched by adding saturated NaHCO_3 solution and extracted with DCM. The organic phase was collected and dried over Na_2SO_4 . The solvent was removed to afford 5.0 mg of the desired compound.

4-Benzyl-3-((4-fluorobenzyloxy)methyl)-5-isopropyl-2,6-dioxo-2,3-dihydropyrimidin-1(6H)-yl 2-(benzyloxycarbonylamino)-3-methylbutanoate (40).

Yield: 65 %; ^1H NMR (600 MHz, CDCl_3) δ 7.31-7.19 (m, 3H), 7.26 (d, $J = 7.8$ Hz, 3H), 7.21 (m, 4H), 7.00 (d, $J = 6.6$ Hz, 2H), 6.96 (t, $J = 8.4$ Hz, 2H), 5.28 (m, 1H), 5.14 (m, 1H), 5.11 (m, 2H), 4.72 (m, 1H), 4.54 (m, 2H), 4.12 (s, 2H), 2.84 (septet, $J = 6.6$ Hz, 1H), 2.42 (m, 1H), 1.20 (d, $J = 6.6$ Hz, 6H), 1.06 (m, 6H); MS (ESI+) m/z : 632.69 (M+1).

To a solution of A (40 mg, 0.10 mmol) in 1 mL DCM, CbZ-val (28 mg, 0.11 mmol), DIEA (13 mg, 0.11 mmol) and PyBOP (58 mg, 0.11 mmol) were added. The resulted reaction mixture was stirred at room temperature for overnight and quenched by adding water. The aqueous phase was extracted with CH₂Cl₂ (10 mL x 3). The combined organic extracts were washed with water, dried over Na₂SO₄ and concentrated under reduced pressure. The resultant residue was purified to afford desired compound 41 mg.

4-Benzyl-3-(benzyloxymethyl)-5-isopropyl-2,6-dioxo-2,3-dihydropyrimidin-1(6H)-yl 2-(benzyloxycarbonylamino)-3-methylbutanoate (41).

Yield: 60 %. ¹H NMR (600 MHz, CDCl₃) δ 7.31-7.22 (m, 6H), 7.22-7.19 (m, 7H), 6.99 (d, *J* = 7.2 Hz, 2H), 5.26 (m, 1H), 5.15 (m, 1H), 5.11 (m, 2H), 4.72 (m, 1H), 4.59 (m, 1H), 4.55 (m, 1H), 4.11 (s, 2H), 2.83 (septet, *J* = 6.6 Hz, 1H), 2.42 (m, 1H), 1.20 (d, *J* = 6.6 Hz, 6H), 1.06 (m, 6H); MS (ESI+) *m/z*: 614.70 (M+1).

4-Benzyl-3-((4-fluorobenzyloxy)methyl)-5-isopropyl-2,6-dioxo-2,3-dihydropyrimidin-1(6H)-yl 2-amino-3-methylbutanoate (42).

Yield: 81 %; ¹H NMR (600 MHz, CDCl₃) δ 7.27 (m, 3H), 7.22 (m, 3H), 6.98 (d, *J* = 7.8 Hz, 1H), 6.95 (t, *J* = 7.8 Hz, 2H), 5.23 (s, 2H), 4.56 (s, 1H), 4.11 (s, 2H), 3.65 (s, 2H), 3.31 (m, 1H), 2.84 (septet, *J* = 6.6 Hz, 1H), 1.22 (d, *J* = 7.2 Hz, 6H), 0.92 (d, *J* = 7.2 Hz, 3H), 0.86 (d, *J* = 7.2 Hz, 3H); MS (ESI+) *m/z*: 498.55 (M+1).

To a suspension of Pd/C 10% (3 mg) in 1 mL MeOH, 4-Benzyl-3-(benzyloxymethyl)-5-isopropyl-2,6-dioxo-2,3-dihydropyrimidin-1(6H)-yl 2-(benzyloxycarbonylamino)-3-methylbutanoate (25 mg, 0.039 mmol) was added. The reaction mixture was stirred at room temperature for 20 min under H₂ condition. The solution is filtrated and the solvent was removed to form the desired product as white sold 16 mg.

HPLC Analysis of final compounds of the invention is presented in Table VI.

Table VI: HPLC Purity Data for Selected Specific Compounds

Compound	<i>t</i> _{ret} (min)	Purity (%)
11	10.79	98
12	10.63	97
13	10.80	97
14	10.93	96

15	10.79	97
16	8.31	96
17	10.88	98
18	11.12	98

* General conditions: reverse-phase Varian Microsorb-MW 100-5 C18 column with detection at 254 nm; solvent A = H₂O, solvent B = MeCN; flow rate = 1.0 mL/min; Method: linear 30-95% (B) over 25 min.

Biology

RT Assay.

This assay was performed using the Quan-T-RT™ Assay System kit from Perkin Elmer (TRK1022). The Quan-T-RT™ Assay system contains SPA (scintillation proximity assay) beads, assay buffer, stop solution and [3H]-TTP. Experiments were conducted using 0.65 mL sterile snap cap tubes with streptavidin-coated SPA beads, where a short poly(rA) tail and an oligo(dT) primer have been coupled via a biotin linkage to the streptavidin-coated resin bead containing scintillation cocktail. This resin was incubated with the drug compound and [3H]-TTP tracer; the reaction initiated by the addition of the HIV-RT (RT) enzyme from Ambion: the RNA Company (AM2045). The [3H]-TTP was incorporated into the poly(rA) tail by the RT enzyme but in the presence of the drug candidate this incorporation should be inhibited. This reaction was incubated for 3 h at 37°C and quenched by the addition of the stop buffer. These tubes were then transferred to 20 mL scintillation tubes (glass) and counted for 5 minutes per sample using a Beckman Coulter LS 6500 Multi-Purpose Scintillation Counter.

In Vitro Integrase Catalytic Assays.

Expression and purification of the recombinant IN in Escherichia coli were performed as previously reported²⁶ with addition of 10% glycerol to all buffers. Preparation of oligonucleotide substrates has been described.²⁹ Integrase reactions were performed in 10 µL with 400 nM of recombinant IN, 20 nM of 5'-end [32P]-labeled oligonucleotide substrate and inhibitors at various concentrations. Solutions of 10% DMSO without inhibitors were used as controls. Reactions were incubated at 37 °C (60 minutes) in buffer containing 50 mM MOPS, pH 7.2, 7.5 mM MgCl₂, and 14.3 mM 2-mercaptoethanol. Reactions were stopped by addition of 10 µL of loading dye (10 mM EDTA, 98% deionized formamide, 0.025% xylene cyanol and 0.025% bromophenol blue). Reactions were then subjected to electrophoresis in 20% polyacrylamide-7

M urea gels. Gels were dried and reaction products were visualized and quantitated with a Typhoon 8600 (GE Healthcare, Little Chalfont, Buckinghamshire, UK). Densitometric analyses were performed using ImageQuant from Molecular Dynamics Inc. The concentrations at which enzyme activity was reduced by 50% (IC₅₀) were determined using “Prism” software (GraphPad Software, San Diego, CA) for nonlinear regression to fit dose-response data to logistic curve models.

HIV-1 Assay.

The HIV Cytoprotection assay used CEM-SS cells and the IIIB strain of HIV-1. Briefly, virus and cells were mixed in the presence of test compound and incubated for 6 days. The virus was pre-titered such that control wells exhibit 70 to 95% loss of cell viability due to virus replication. Therefore, antiviral effect or cytoprotection was observed when compounds prevent virus replication. Each assay plate contained cell control wells (cells only), virus control wells (cells plus virus), compound toxicity control wells (cells plus compound only), compound colorimetric control wells (compound only) as well as experimental wells (compound plus cells plus virus). Cytoprotection and compound cytotoxicity were assessed by MTS (CellTiter® 96 Reagent, Promega, Madison WI) and the EC₅₀ (concentration inhibiting virus replication by 50%), CC₅₀ (concentration resulting in 50% cell death) and a calculated TI (therapeutic index CC₅₀/EC₅₀) were provided. Each assay included the HIV RT inhibitor AZT as a positive control.

HCV replicon assays.

Huh7 liver cells stably maintaining the HCV pLC609 replicon (genotype 1b) were provided by Dr. Luo (Univ of KY). The replicon contains a renilla luciferase gene thereby allowing the determination of luciferase activity as a surrogate for determining the extent of viral RNA replication. Six thousand cells per well of a 96-well dish were incubated with compound (in DMSO) for three days. The medium (DME, 10% fetal bovine serum, pen/strep, and compound) was removed and replaced by cell culture medium containing ViviRen™ Live Cell substrate (Promega). Renilla luciferase activity was immediately measured using a Molecular Devices SpectraMax M5^e reader. For single concentration experiments, compound was added at 10 μM and each plate also contained replicon cells that received DMSO alone, ribavirin at 10 μM (near our determination of the EC₅₀ for that compound) and 2'-C-methyl adenosine at 0.5 μM (a concentration that results in greater than

a 90% reduction in luciferase activity). The 50% effective concentration (EC₅₀) was defined as the concentration of compound that reduced luciferase activity by 50%. The EC₅₀ was determined by comparing luciferase activity for eight serial dilutions of compound and vehicle treated cells using GraphPad Prism software.

To measure cell proliferation and viability, replicon cells were plated out at 6000 cells per well in a clear 96-well tissue culture plate. The next day, the cells were incubated at 37°C/5% CO₂ in culture medium containing compound (dissolved in DMSO), DMSO alone, or nothing added for three days. CellTiter 96 AQueous One Solution Cell Proliferation reagent (Promega) was added according to manufacturer's instructions and viability measured by spectrometry at 450 nm with a SpectraMax E5 (Molecular Devices). The 50% cytotoxic concentration (CC₅₀) was defined as the concentration of compound that reduced cell proliferation by 50%. The CC₅₀ was determined by comparing absorbance readings from eight serial dilutions of compound and vehicle treated cells using GraphPad Prism software.

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While the invention has been described and exemplified in sufficient detail for those skilled in this art to make and use it, various alternatives, modifications, and improvements will be apparent to those skilled in the art without departing from the spirit and scope of the claims.

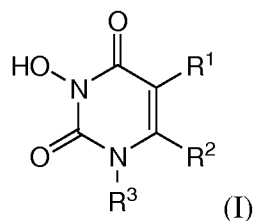
All patents and publications referred to herein are incorporated by reference herein to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference in its entirety.

The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the appended claims.

CLAIMS

What is claimed is:

1. A compound of formula (I)



wherein R¹ is hydrogen, (C₁-C₆)alkyl, (C₃-C₉)cycloalkyl, (C₃-C₉)cycloalkyl(C₁-C₆)alkyl, (C₆-C₁₄)aryl, or (C₆-C₁₄)aryl(C₁-C₆)alkyl, wherein any alkyl, cycloalkyl, cycloalkylalkyl, or aralkyl can be mono- or multi-substituted with J;

R² is hydrogen, (C₁-C₆)alkyl, (C₆-C₁₄)aryl, (C₆-C₁₄)aryl(C₁-C₆)alkyl, (C₆-C₁₄)aryl(C₁-C₆)alkoxy, (C₆-C₁₄) aroyl, (C₆-C₁₄) aryloxy, or a 5-9 membered mono- or bicyclic heteroaryl or heteroarylalkyl, wherein any alkyl or aryl or aralkyl or aroyl or aryloxy or heteroaryl is substituted with n R⁵ groups;

or R¹ and R² together with the atoms to which they are bonded form a fused (C₃-C₉) cycloalkyl or (C₆-C₁₀) aryl, wherein the cycloalkyl or aryl is substituted with n R⁵ groups;

R³ is CH(R)R⁴, wherein R⁴ is hydrogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₆-C₁₄)aryl, (C₆-C₁₄)aryloxy, (C₆-C₁₀)aryl(C₁-C₆)alkyl, or (C₆-C₁₀)aryl(C₁-C₆)alkoxy, wherein any alkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy is substituted with n₂ R⁶ groups;

J is halo, nitro, (C₁-C₆)alkoxy, or (C₁-C₆)alkyl;

R is hydrogen or (C₁-C₆)alkyl;

R⁵ is halo, nitro, (C₁-C₆)alkoxy, or (C₁-C₆)alkyl;

R⁶ is halo, nitro, (C₁-C₆)alkoxy, or (C₁-C₆)alkyl;

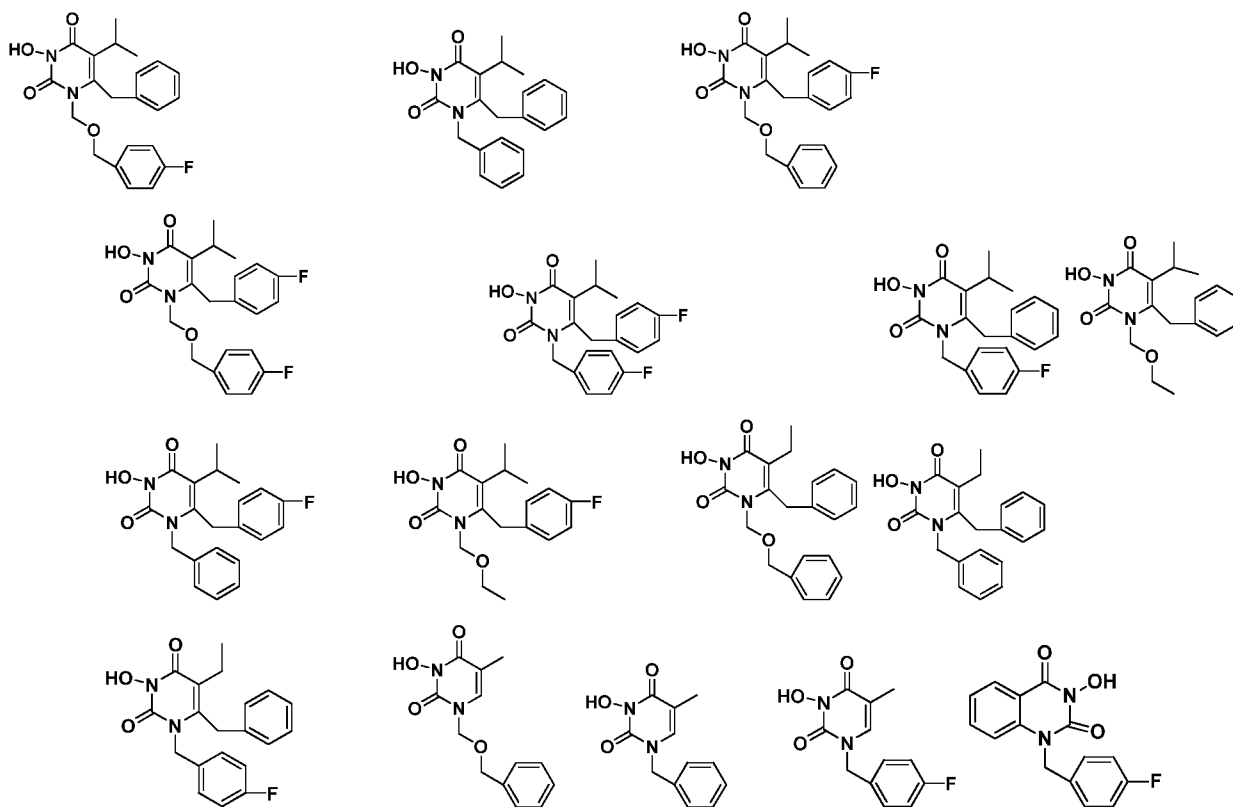
n = 0, 1, 2, or 3;

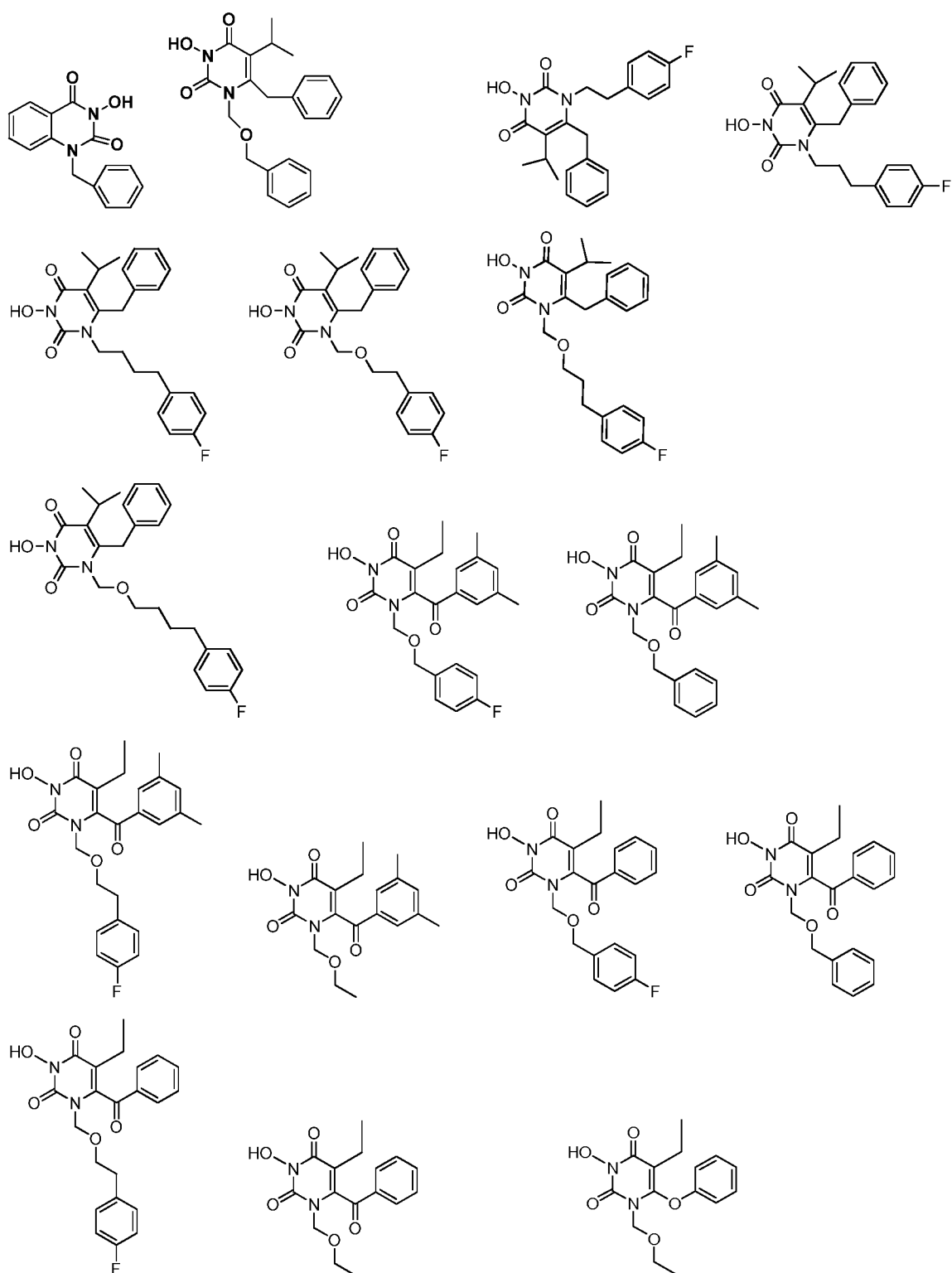
n₂ = 0, 1, 2, or 3;

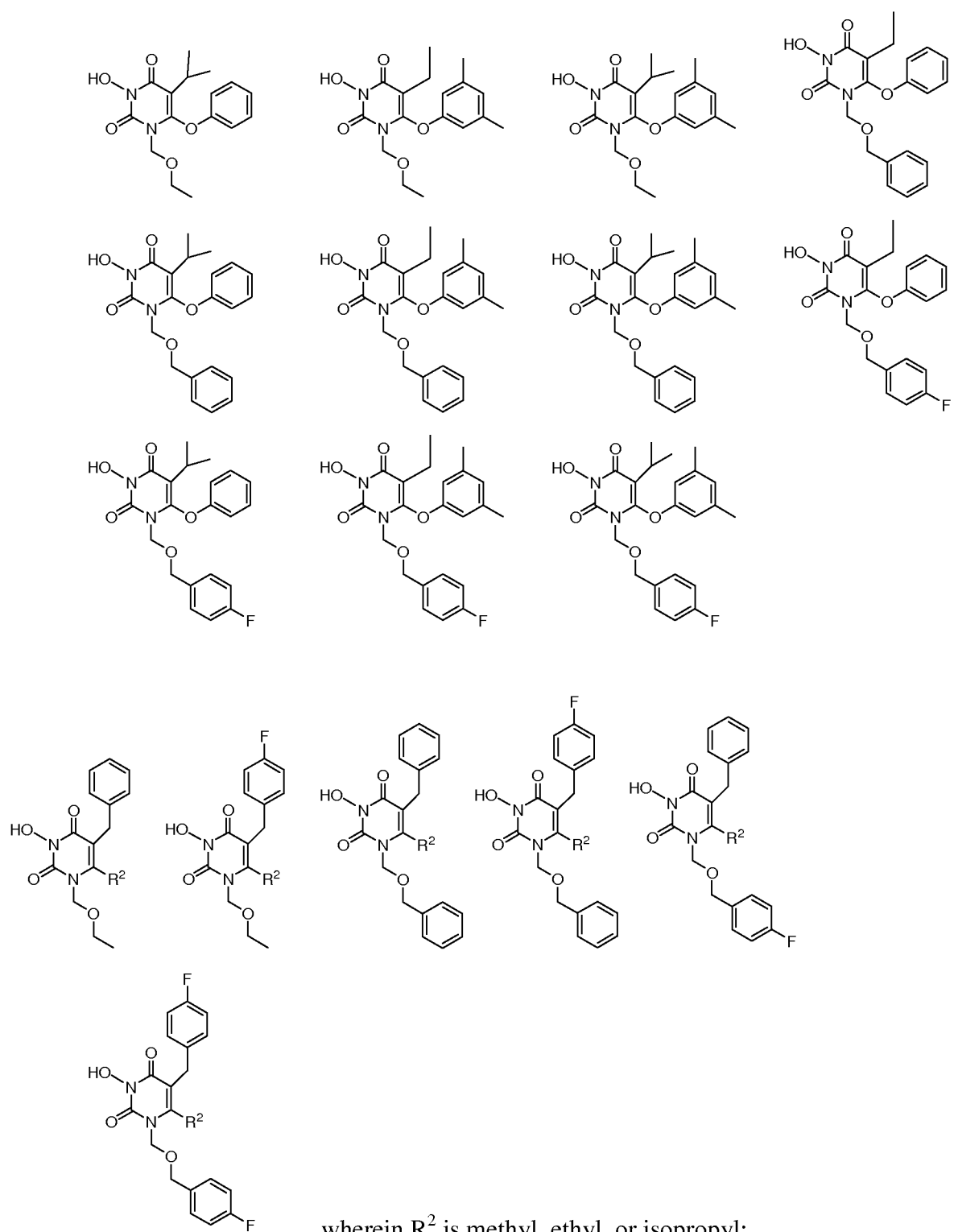
or a pharmaceutically acceptable salt thereof.

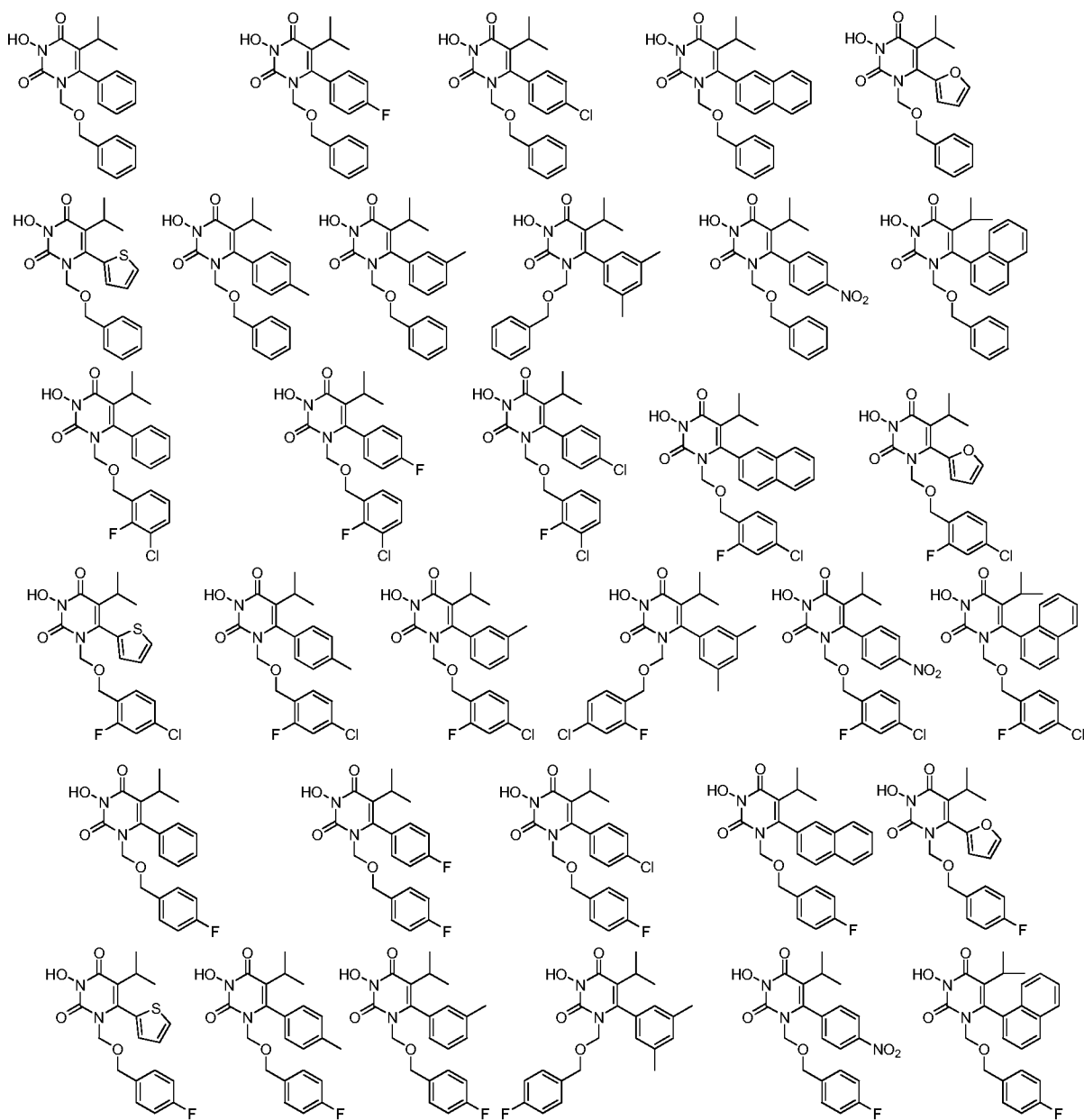
2. The compound of formula (I) of claim 1 wherein any halo is independently selected fluoro or chloro.

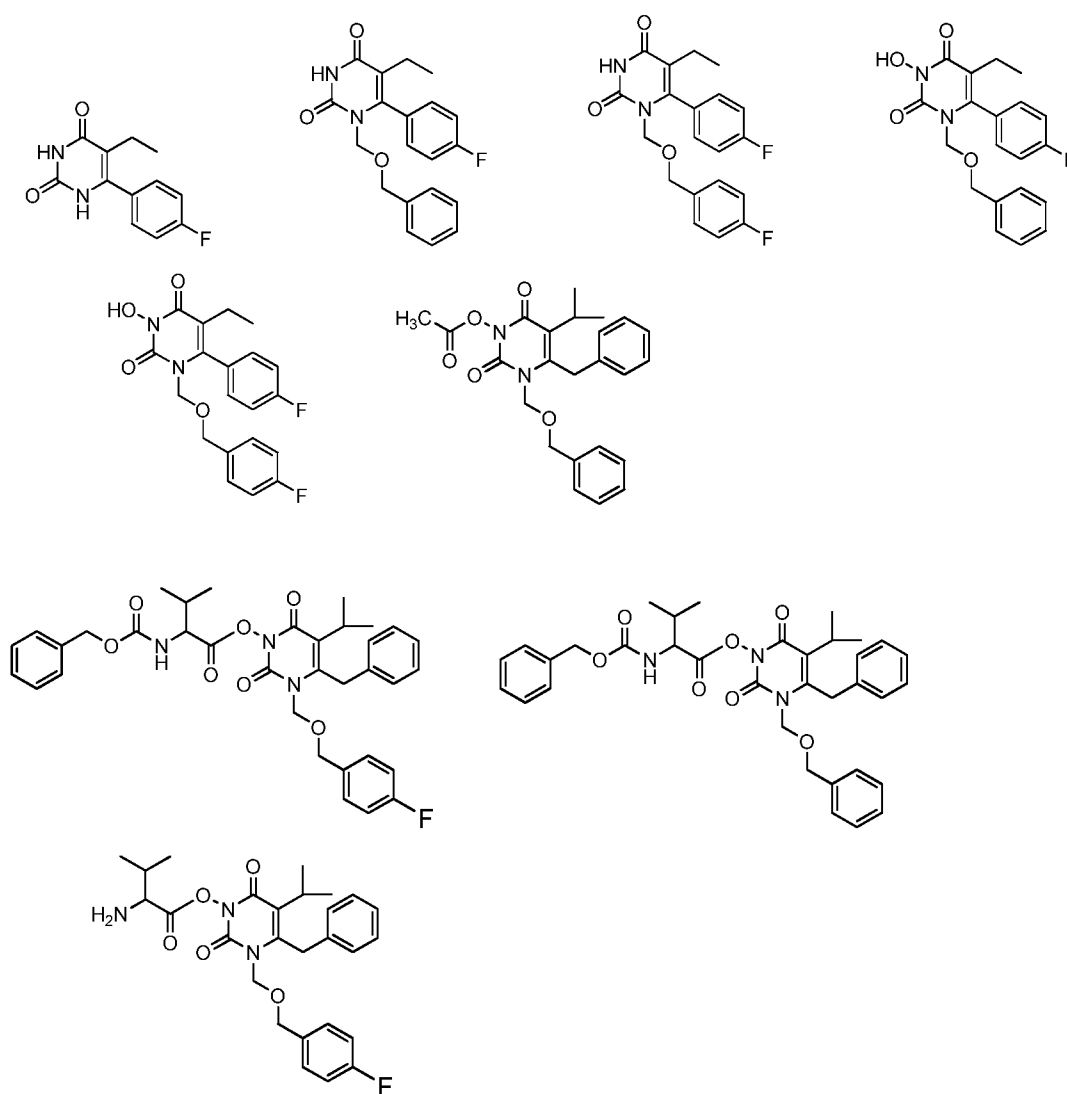
3. The compound of formula (I) of claim 1 wherein R¹ is methyl, ethyl, isopropyl, benzyl, or p-fluorobenzyl.
4. The compound of formula (I) of claim 1 wherein R² is benzyl, p-fluorobenzyl, benzoyl, or 3,5-dimethylbenzoyl.
5. The compound of formula (I) of claim 1 wherein R¹ and R² together with the atoms to which they are bonded form a phenyl ring or a fluoro-substituted phenyl ring.
6. The compound of formula (I) of claim 1 wherein R⁴ is phenyl, p-fluorophenyl, p-fluorobenzyl, p-fluorophenethyl, p-fluorophenyl-n-propyl, ethoxy, benzyloxy, p-fluorobenzyloxy, p-fluorophenethoxy, p-fluorophenyl-n-propoxy, or p-fluorophenyl-n-butoxy.
7. The compound of formula (I) of claim 1 wherein the compound is any of the following











; or a pharmaceutically acceptable salt thereof.

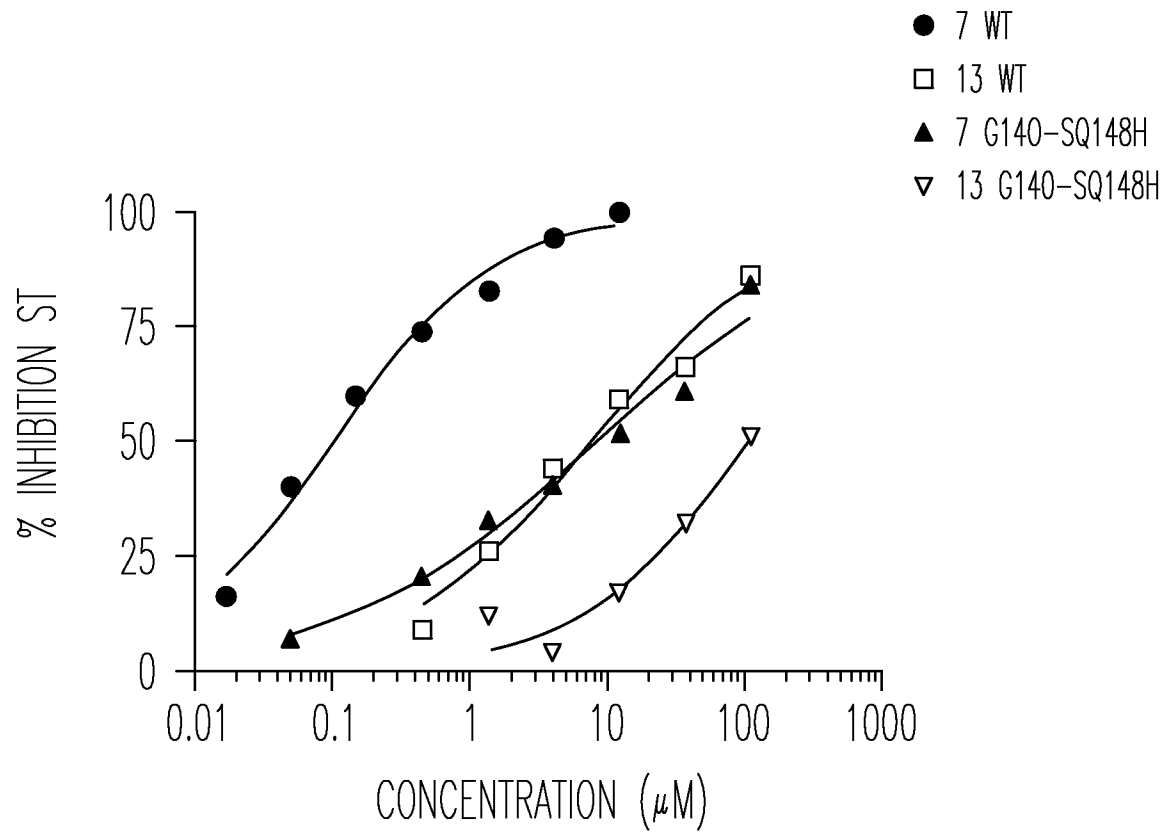
8. A prodrug of a viral-inhibitory compounds of any one of claims 1-7, comprising an N-hydroxy ester of the compound of formula (I), wherein the N-hydroxy ester is an alkyl ester or an aryl ester.

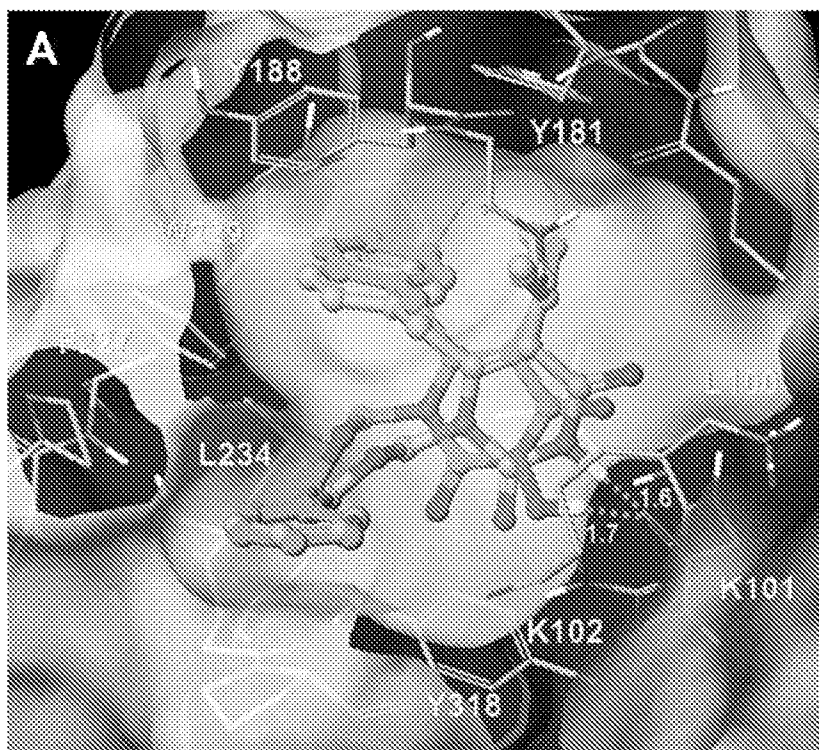
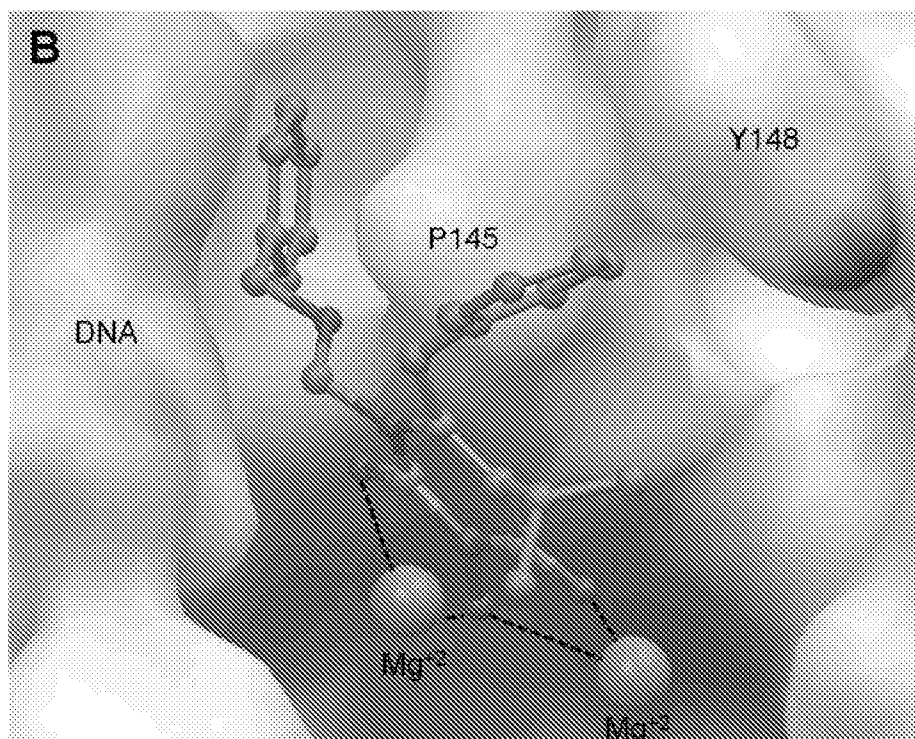
9. The prodrug of claim 8 wherein the N-hydroxy ester is a (C₁-C₁₀)acyl ester or a (C₆-C₁₄)aroyl ester of the compound of any one of claims 1-7.

10. The prodrug of claim 8 wherein the N-hydroxyester is an aminoacyl ester or a peptidyl ester of the compound of any one of claims 1-7.

11. A pharmaceutical composition comprising a compound of any one of claims 1-10 and a pharmaceutically acceptable excipient.
12. A method of treating an HIV infection in a patient, comprising administering to the patient afflicted with an HIV infection an effective amount of a compound of any one of claims 1-10 at a frequency and for a duration to provide a beneficial effect to the patient.
13. The method of claim 12 wherein the compound of any one of claims 1-10 is substantially the only antiviral compound administered to a patient in treatment of the HIV infection.
14. The method of claim 13 further comprising administering an effective amount of a second antiviral compound.
15. A method of treating an HCV infection in a patient, comprising administering to the patient afflicted with an HCV infection an effective amount of a compound of any one of claims 1-10 at a frequency and for a duration to provide a beneficial effect to the patient.
16. The method of claim 15 wherein the compound of any one of claims 1-10 is substantially the only antiviral compound administered to a patient in treatment of the HCV infection.
17. The method of claim 15 further comprising administering an effective amount of a second antiviral compound.
18. The method of claim 16, wherein the patient is also infected with an HIV infection, and administering the compound of the invention to the patient simultaneously provides a treatment for the HIV infection and for the HCV infection.
19. The method of claim 18 wherein the compound of any one of claims 1-10 is substantially the only antiviral compound administered to a patient in treatment of the HCV infection and the HIV infection.

20. The method of claim 18 further comprising administering an effective amount of a second antiviral compound.
21. Use of a compound of any one of claims 1-10 in manufacture of a medicament for the treatment of a viral infection.
22. The use of claim 21 wherein the viral infection comprises an HIV infection, an HCV infection, or both.
23. Use of a compound of any one of claims 1-10 to treat a viral infection in a human subject.
24. Use of a compound of claim of any one of claims 1-10 to treat an HIV infection, an HCV infection, or both, in a human subject.

*Fig. 1*

*Fig. 2A**Fig. 2B*