Title: METHOD OF PREVENTING OR TREATING VIRAL INFECTION

Abstract: Disclosed are compounds and pharmaceutical compositions containing compounds that inhibit JMJD2 proteins, including those of the formula (I): wherein \( R^1, R^2, R^3, \) and \( R^4 \) are defined herein or pharmaceutically acceptable salts thereof. Also disclosed is a method of preventing or treating a viral infection of a host, comprising administering to the host an effective amount of an inhibitor of the JMJD2 family of histone demethylases, for example, a compound of the formula (I). The viral infection may be a primary infection, reactivation of a virus after latency in a host, or may be in a mammal that has undergone, is undergoing, or will undergo immunosuppressive therapy.
METHOD OF PREVENTING OR TREATING VIRAL INFECTION

CROSS-REFERENCE TO A RELATED APPLICATION


INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ELECTRONICALLY

[0002] Incorporated by reference in its entirety herein is a computer-readable nucleotide/amino acid sequence listing submitted concurrently herewith and identified as follows: One 1,055 Byte ASCII (Text) file named "708658_ST25.txt" created on July 13, 2011.

BACKGROUND OF THE INVENTION

[0003] Herpes viral infections, including herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) infections, are common infections worldwide. HSV-2 is the cause of most genital herpes and is generally sexually transmitted. In contrast, HSV-1 is usually transmitted via nonsexual contacts. Preexisting HSV-1 antibodies can alleviate clinical manifestations of subsequently acquired HSV-2. Furthermore, HSV-1 has become an important cause of genital herpes in some developed countries. Varicella Zoster virus characteristically produces vesicular pruritic disseminated lesions at varying degrees of maturity. It occurs most frequently in children, with prodromal malaise, pharyngitis and rhinitis, usually with fever and pruritus (chickenpox). Varicella Zoster virus may cause more severe illness in adults, where the lesions are localized and painful, and often involve the trunk (shingles). Additional manifestations of HSV viral infection may include encephalitis and keratitis. Cytomegalovirus is an additional herpesvirus which can cause considerable morbidity in infants and individuals with compromised immune systems.

[0004] Although proposals have been made for a cure for the above diseases, an unmet need continues to exist for methods of preventing or treating a viral infection of a host.

BRIEF SUMMARY OF THE INVENTION

[0005] An embodiment of the invention provides a substance for use in preventing or treating a viral infection of a host, wherein the substance is an inhibitor of a JMJD2 protein.
An embodiment of the invention provides a compound of the formula (I):

\[
\begin{array}{c}
\text{R}^1 \quad \text{R}^2 \\
\text{R}^3 \quad \text{R}^4 \\
\text{R}^5 \\
\end{array}
\]

wherein R\(^1\), R\(^2\), R\(^3\), R\(^4\), and R\(^5\) are as defined herein, as well as a pharmaceutical composition comprising a compound of formula (I), and a method of preventing or treating viral infection.

An embodiment of the invention provides a method of preventing or treating a viral infection of a host, comprising administering to the host an effective amount of an inhibitor of the JMJD2 family of histone demethylases, such as a compound described herein, wherein the administration of the inhibitor prevents or treats the viral infection.

Embodiments of the invention include preventing or treating a viral infection where the viral infection is reactivation of a virus after latency in a host and/or is in a mammal that has undergone, is undergoing, or will undergo immunosuppression or immunosuppressive therapy.

Another embodiment of the invention includes a method of inhibiting a member of the JMJD2 family of histone demethylases in a virus-infected host, comprising administering to the host an effective amount of a compound described herein.

**BRIEF DESCRIPTION OF THE DRAWINGS**

Figure 1 shows histone H3-Lysine 9 demethylases and their respective target specificity. LSD1 can demethylate di- (D) and mono- (M) methyl-lysine to the unmethylated state (U). In contrast, most members of the JMJD2 family convert a tri-methyl-lysine (T) to di-methyl.

Figure 2A is a bar graph, showing herpes simplex virus Immediate Early (IE) gene ICP27 mRNA levels after administration of siRNA directed against JMJD2a (A), JMJD2b (B), JMJD2c (C), JMJD2d (D), and combinations of these. Figure 2B is a bar graph, showing herpes simplex virus Immediate Early gene ICP4 mRNA levels after administration of siRNA directed against A, B, C, and D, and combinations of these. In accordance with embodiments of the invention, the viral IE mRNA levels decrease after administration of siRNA directed against the JMJD2 family of histone demethylases.
[0012] Figure 3 is a bar graph, showing the impact of depletion of members of the JMJD2 family on HSV IE gene expression in MRC5 cells. In accordance with embodiments of the invention, the viral IE mRNA levels decrease after administration of siRNA directed against the JMJD2 family of histone demethylases.

[0013] Figure 4 shows a bar graph of levels of tri-methylated histone H3 or total histone H3 associated with viral IE promoters for ICP27 and ICP4 in the presence of JMJD2 siRNA. In accordance with an embodiment of the invention, Figure 4 shows siRNA depletion of JMJD2 proteins results in accumulation of repressive chromatin on HSV-1 IE promoters. H3 represents total histone H3; K9me3 represents histone H3-lysine 9 trimethylation.

[0014] Figure 5 is a bar graph showing recovery of herpes simplex virus Immediate Early gene ICP4 mRNA levels after administration of control siRNA (Cntrl) or siRNA directed against JMJD2b (B), JMJD2c (C), or JMJD2d (D). Post depletion, cells were transfected with plasmids expressing control LacZ (bars labeled "LZ") or siRNA resistant JMJD2s (bars labeled "R"). In accordance with embodiments of the invention, depletion of JMJD2s decrease viral IE mRNA expression.

[0015] Figure 6 is a line graph, showing herpes simplex virus ICP4 protein levels at increasing concentrations of N-methoxyoxoacetyl-glycine methyl ester (dimethyloxalylglycine, or DMOG). In accordance with an embodiment of the invention, the viral ICP4 protein level decreases as the concentration of DMOG increases.

[0016] Figure 7 shows a line graph of HSV-1 IE mRNA levels in cells infected in the presence of DMOG. In accordance with an embodiment of the invention, the HSV-1 mRNA levels of ICP4 and ICP27 decrease with increasing concentration of DMOG, whereas control mRNA (si 5) does not.

[0017] Figure 8 shows a bar graph of levels of tri-methylated histone H3 or total histone H3 associated with viral IE promoters for ICP0, ICP27, and ICP4 in the presence of DMOG. In accordance with an embodiment of the invention, Figure 8 shows DMOG inhibition of JMJD2 proteins results in accumulation of repressive chromatin on HSV-1 IE promoters. H3 represents total histone H3; K9me3 represents histone H3-lysine 9 trimethylation. DMSO is dimethyl sulfoxide.

[0018] Figure 9 is a line graph of cytomegalovirus (CMV) IE gene expression (IE1 and UL37) and control TBP in the presence of increasing concentrations of DMOG. In accordance with an embodiment of the invention, the CMV mRNA levels of IE1 and UL37
decrease with increasing concentration of DMOG, whereas control niRNA (Tata Binding Protein, TBP) does not.

[0019] Figure 10 shows a line graph of HSV-1 lytic viral yields in the presence of DMOG. In accordance with an embodiment of the invention, viral yields decrease with increasing concentration of DMOG.

[0020] Figure 11 shows a dot plot of viral yield per ganglia in the presence of control vehicle DMSO, DMOG, or tranylcypromine (TCP). In accordance with an embodiment of the invention, the viral yield decreases after administration of DMOG or an inhibitor of the LSD1 protein, TCP.

[0021] Figure 12 shows a bar graph of the relative mRNA levels in HSV-1 latently infected trigeminal ganglia explanted in the presence of either acyclovir (ACV) or DMOG at 7 hours post explant. Total RNA was isolated and subjected to reverse transcription. The resulting cDNAs were analyzed for viral Immediate Early ICP4 and ICP27 mRNAs relative to an infected cell standard by nested or qPCR. In accordance with an embodiment of the invention, DMOG reduces the levels of viral mRNAs in explanted/reactivated ganglia.

DETAILED DESCRIPTION OF THE INVENTION

[0022] An embodiment of the invention provides a substance for use in preventing or treating a viral infection of a host, wherein the substance is an inhibitor of a JMJD2 protein.

[0023] In an embodiment of the invention, the invention provides a compound of the formula (I)

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wherein R¹ and R² are each independently H or C=C₆ alkyl, or together form =CH₂,
=CH-(C₆ alkyl) or =C(d-C₆ alkyl)(C₁-C₆ alkyl) where the C₁-C₆ alkyl groups are the same or different; R³ is H or a group of the formula -Y-L-W, wherein Y is linked to N and is CH₂, C=0, or NH, L is C-C₆ alkylenyl, (CH₂)ₘ-(C₆-C₆ₗaryl)-(CH₂)ₙ, or [(CH₂)₉O]₉CH₂, wherein m and n are each independently 0 to 6, q is 1 to 6, and r is 1 to 3, and W is R⁶, COR⁶, S0₂R⁶, CH=NR⁷, or NHOR⁷, wherein R⁶ is NR⁷R⁷, guanidinyl, a carbamoyl moiety, or OR⁷, and each R⁷ is independently H or CH₃; R⁴ and R⁵ are each independently H,
Ci-C₆ alkyl, C₆-C₂₀ aryl, or C₆-C₂₀ aryl C₁-C₆ alkyl; and X is O, S, or NH; or a pharmaceutically acceptable salt thereof; with the provisos that when R⁴ and R⁵ are each H, X is O, and R¹ and R² are each H or one of R¹ and R² is H and the other of R¹ and R² is C₁-C₆ alkyl, then R³ is not H,

; and

when R⁴ and R⁵ are each C₁-C₆ alkyl, X is O, and R¹ and R² are each H, then R³ is not H or

[0024] In another embodiment of the invention, the compound or salt is as described above, wherein R¹ and R² are each independently H or Ci-C₆ alkyl; R³ is H or a group of the formula -Y-L-W, wherein Y is linked to N and is CH₂, C=0, or NH, L is Ci-C₆ alkylencyl, (CH₂)ₘ-(C₆-C₂₀ aryl)-(CH₂)ₘ, or (CH₂CH₂O)ₙCH₂, wherein m and n are each independently 0 to 6 and q is 1 to 6, and W is R⁶, wherein R⁶ is NR⁷R⁷ or OR⁷, and each R⁷ is independently H or CH₃; R⁴ and R⁵ are each independently H or Ci-C₆ alkyl; and X is O.

[0025] In yet another embodiment, the invention provides a compound as described above, wherein R¹, R², R⁴, and R⁵ are each independently H or CH₃.

[0026] In yet another embodiment, the invention provides a compound as described above, wherein R¹ and R² are both C₁-C₆ alkyl.

[0027] In another embodiment of the invention, the invention provides a method of preventing or treating a viral infection of a host, comprising administering to the host an effective amount of
(a) a compound of the formula (I)

\[
\begin{align*}
R^1 & \quad \text{or} \quad \text{CH}_2, \\
R^2 & \\
R^3 & \\
R^4 & \\
R^5 & \\
R^6 & \\
X & \\
\end{align*}
\]

wherein \(R^1\) and \(R^2\) are each independently H or Ci-C\text{6} alkyl, or together form =CH\text{2}, =CH-(Ci-C\text{6} alkyl) or =C(d-C\text{6} alkyl)(C\text{1}-C\text{6} alkyl) where the C\text{1}-C\text{6} alkyl groups are the same or different; \(R^3\) is H or a group of the formula -Y-L-W, wherein \(Y\) is linked to N and is CH\text{2}, C=0, or NH, \(L\) is C\text{1}-C\text{8} alkylenyl, (CH\text{2})\text{m}-(C\text{6}-C\text{20} aryl)-(CH\text{2})\text{n}, or [(CH\text{2})\text{O}]\text{q}CH\text{2}, wherein \(m\) and \(n\) are each independently 0 to 6, \(q\) is 1 to 6, and \(r\) is 1 to 3, and \(W\) is \(R^6\), COR\text{6}, S0\text{2}R\text{6}, CH=NR\text{7}, or NHOR\text{7}, wherein \(R^6\) is NR\text{7}R\text{7}, guanidinyl, a ureido moiety, a carbamate moiety, or OR\text{7}, and each \(R^7\) is independently H, Ci-C\text{6} alkyl, C\text{6}-C\text{20} aryl, or C\text{6}-C\text{20} aryl C\text{1}-C\text{6} alkyl; and \(X\) is O, S, or NH; or a pharmaceutically acceptable salt thereof; wherein the administration of the compound prevents or treats the viral infection.

(b) a compound of the formula:
(c) a compound of the formula

\[
\text{HO}_2C \xrightarrow{\text{O}} \text{N} \xrightarrow{\text{HO}} \text{O}
\]

wherein \( R^{10} \) is

\[
\text{CH}_2\text{SH}, \text{CH}_2\text{Ph}, \text{methyl}, \text{or CH}_2\text{CH}_2\text{Ph};
\]

(d) a compound of the formula

\[
\text{HO}_2C \xrightarrow{\text{O}} \text{N} \xrightarrow{\text{HO}} \text{O}
\]

(e) a compound of the formula

\[
\text{HO}_2C \xrightarrow{\text{O}} \text{N} \xrightarrow{\text{HO}} \text{O}
\]

wherein \( R^{20} \) is OCH\(_3\) or H and \( X' \) is S or CH\(_2\).
(f) a compound of the formula

\[
\begin{align*}
\text{wherein } R^{30} & \text{ is } \\
\end{align*}
\]

\[
\begin{align*}
\text{wherein } R^{40} & \text{ is } H, \text{2-methyl, 4-phenyl, 3-fluoro, 2,4-difluoro, 2-chloro, 3-methoxy, or 4-cyano,} \\
\text{wherein } R^{50} & \text{ is } H, \text{2-methyl, 4-methyl, 2,4,6-trimethyl, 2-fluoro, 3,4-difluoro, 2-fluoro-3-trifluoromethyl, 4-chloro, 3-methoxy, 3-chloro, 2-nitro, 2-methoxy-5-nitro, 4-methoxycarbonyl, 3-cyano, or 4-(2,3,4-thiadiazolyl),} \\
\text{wherein one, two, three, four, or five groups of } R^{40} \text{ or } R^{50} \text{ can be present on the phenyl ring,}
\end{align*}
\]
wherein $R^{60}$ is

wherein $R^{70}$ is
wherein R^{80} is

[Chemical Structures]

wherein R^{90} is

[Chemical Structures]
(g) a compound of the formula

wherein \( R^1 \) is \( \text{Ci-C}_4 \text{alkyl} \), \( \text{NH(Ci-C}_4 \text{alkyl)} \), \( \text{N(d-C}_4 \text{alkyl)benzyl} \), \( \text{N(C}_-,\text{C}_4 \text{alkyl})(\text{Ci-C}_4 \text{alkyl)} \) where the \( \text{C}_1-\text{C}_4 \text{alkyl} \) groups are the same or different; \( W^1 \) and \( W^2 \) are each independently \( \text{CO} \) or a \( \text{N-C} \) bond; and \( p \) is 0 to 11; or

(h) an siRNA directed against a member of the JMJD2 family of histone demethylases;

or a pharmaceutically acceptable salt thereof;

wherein the administration of the compound prevents or treats the viral infection.

[0028] In a further embodiment, the invention provides a substance as described herein for use in preventing or treating a viral infection of a host.

[0029] In a further embodiment, the invention provides the above method, wherein the compound of formula (I) is such that \( R^1 \) and \( R^2 \) are each independently \( \text{H} \) or \( \text{Ci-C}_6 \text{alkyl} \); \( R^3 \) is \( \text{H} \) or a group of the formula \(-Y-L-W\), wherein \( Y \) is linked to \( N \) and is \( \text{CH}_2 \), \( \text{C}=0 \), or \( \text{NH} \), \( L \) is \( \text{Ci-C}_6 \text{alkylenyl} \), \( \text{(CH}_2\text{)}_{m}(\text{C}_6\text{-C}_2\text{aryl})\text{-}(\text{CH}_2\text{)}_{n} \), or \( \text{(CH}_2\text{CH}_2\text{O})_{q}\text{CH}_2 \), wherein \( m \) and \( n \) are each independently 0 to 6 and \( q \) is 1 to 6, and \( W \) is \( \text{R}^6 \), wherein \( \text{R}^6 \) is \( \text{NR}^7\text{R}^7 \) or \( \text{OR}^7 \), and each \( \text{R}^7 \) is independently \( \text{H} \) or \( \text{CH}_3 \); \( \text{R}^4 \) and \( \text{R}^5 \) are each independently \( \text{H} \) or \( \text{Ci-C}_6 \text{alkyl} \); and \( X \) is \( \text{O} \).

[0030] In a further embodiment, the invention provides the above method, wherein the compound of formula (I) is such that \( R^1 \), \( R^2 \), \( R^4 \), and \( R^5 \) are each independently \( \text{H} \) or \( \text{CH}_3 \).

[0031] In another embodiment, the invention provides the above method, wherein the compound of formula (I) is \( \text{N-oxalylglycine} \), \( \text{dimethyloxalylglycine} \), which has the structure

![Chemical Structure Image]
In another embodiment, the invention provides the above method, wherein the compound is
In yet another embodiment, the invention provides a method of preventing or treating reactivation of a virus after latency in a host, comprising administering to the host an effective amount of any compound as described above.

In yet another embodiment, the invention provides a method of preventing or treating a viral infection in a mammal that has undergone, is undergoing, or will undergo an organ or tissue transplant, comprising administering to the mammal an effective amount of any compound as described above.

In a further embodiment, the invention provides a method of inhibiting a member of the JMJD2 family of histone demethylases in a virus-infected host, comprising administering to the host an effective amount of any compound as described above.

In a further embodiment, the invention provides a substance as described herein for use in inhibiting a member of the JMJD2 family of histone demethylases in a virus-infected host.

A "host" may be considered a single cell, a tissue, an organ, or an individual organism, such as a mammal. The mammal can be any suitable mammal, such as a mammal selected from the group consisting of a mouse, rat, guinea pig, hamster, cat, dog, pig, cow, horse, and primate. In one embodiment, the mammal is a human.
A viral infection is present in a host when a virus replicates itself within the host. A virus contains its own genetic material but uses the machinery of the host to reproduce. The virus may reproduce immediately, whereby the resulting virions destroy a host cell to attack additional cells. This process is the viral lytic cycle. Alternatively, a virus may establish a quiescent infection in a host cell, lying dormant until environmental stimuli trigger re-entry into the lytic replication cycle. Such re-emergence or re-entry into the lytic replication cycle is termed reactivation. In an embodiment of the invention, the host has a viral infection or is at risk for viral infection but is free from cancer.

The viral infection may be due to a nuclear DNA viral infection such as a herpes viral infection. The herpesvirus may be, e.g., herpes simplex virus (HSV) type 1, herpes simplex virus type 2, varicella zoster virus (VZV), or cytomegalovirus (CMV). The herpesvirus may be Epstein-Barr virus (EBV), Kaposi's Sarcoma-Associated herpesvirus, herpes simiae virus, herpes lymphotropic virus, human herpesvirus-7 (HHMV-7), or human herpesvirus-8 (HHMV-8).

Viral infections especially pose a threat to individuals that have suppressed (immunosuppressed) or otherwise compromised (immunocompromised) immune systems. For example, individuals with HIV/AIDS, diabetes, or cancer often have reduced ability to ward off additional and/or opportunistic viral infections due to immune systems that are adversely affected by the underlying, primary infection or condition. Therefore, preventing or treating viral infection or re-activation is especially important for these individuals.

Another embodiment of the invention provides a method of preventing or treating a viral infection in a mammal that has undergone, is undergoing, or will undergo an organ or tissue transplant, comprising administering to the mammal an effective amount of any of the compounds described above, wherein the administration of the inhibitor(s) prevents or treats the viral infection. A non-limiting example would be to administer an effective amount of an inhibitor of the JMJD2 family of histone demethylases and/or a dimethyloxalylglycine or analog thereof to a mammal undergoing immunosuppressive therapy and who is suspected of being infected with virus.

Other inhibitors of the JMJD2 family of histone demethylases can be used. A suitable inhibitor includes a nucleic acid (e.g., RNA), protein, small molecule, or antibody that specifically binds to a JMJD2 histone demethylase, inhibits translation of a JMJD2 histone demethylase, inhibits transcription of a JMJD2 histone demethylase, or otherwise interferes with the biological expression and/or activity of a JMJD2 histone demethylase.
One such inhibitor is an RNA interference (RNAi) inhibitor. The RNAi inhibitor may comprise any RNA sequence that is complementary to the target JMJD2 histone demethylase nucleic acid or a portion thereof, and include small inhibitor RNA (siRNA) directed against any of the members of the JMJD2 family (a, b, c, and/or d). Antibodies and RNAi inhibitors of JMJD2 histone demethylases can be prepared using routine techniques.

Methylation of chromatin, a reversible modification mediated by histone methyltransferases and demethylases, is a significant component of cellular transcriptional regulation. Such chromatin modifications also impact invading viral pathogens that rely upon the host cell transcriptional apparatus. During infection of cells by viruses, the assembly and modification of chromatin on the viral genomes has the potential to determine the progression of lytic infection as well as control recurrent latency-reactivation cycles.

Without intending to be bound by any theory, HCF-1 is a cellular transcriptional coactivator that is required for the expression of the immediate early genes (IE), such as the IE genes of a-herpesviruses HSV-1 and VZV-1, during the initiation of lytic infection. Viruses, such as HSV and VZV, utilize virion-encapsidated transcriptional activators to recruit the HCF-1-Set/MLL1 histone methyl-transferase (HMT) complexes to the viral IE promoters, resulting in histone H3-lysine 4 (H3K4) trimethylation and initiation of IE gene transcription.

Furthermore, depletion of HCF-1 results in an increase in the levels of repressive histone H3-lysine 9 (H3K9) methylation, providing a central role for HCF-1 in modulating chromatin modifications that determine viral gene expression. A description of the role of HCF-1 in reactivation from latency is set forth in Whitlow and Kristie (J. Virol., 2009, 83:9591-5); Kolb and Kristie (J. Virol., 2008, 82:9555-63); and Kristie, Liang, and Vogel (Biochim. Biophys. Acta., 2010, 1799:257-65 (published online Aug. 12, 2009). The JMJD2 family members interact with HCF-1 and have been shown to possess H3K9 demethylase activity which is important for the activation of nuclear hormone receptor-dependent transcription, cell fate determination, and cell cycle progression.

LSD1 (also known as BHC1 10) also interacts with HCF-1 and has been shown to possess H3K9 demethylase activity. LSD1 demethylates lysine residues via a flavin-adenine-dinucleotide-dependent reaction that is inhibited by MAOIs and siRNA (International Patent Application No. PCT/US2009/051557, published as WO 2010/01845, which is incorporated by reference). Inhibition of LSD1 activity not only results in a block to viral IE gene expression in lytic infection but also prevents the reactivation of HSV from latency in a mouse ganglia explant model system, indicating that HCF-1 chromatin modulation
complexes play a role in the viral latency-reactivation cycle. Either the JMJD2 family of histone demethylases or LSD1, or both simultaneously, may be inhibited to achieve inhibition of viral infection or reactivation. Inhibitors of LSD1 include the MAOIs Pargyline, SELEGILINE, and tranylcypromine (TCP).

[0045] As used herein, unless otherwise specified, the term "alkyl" means a saturated straight chain or branched non-cyclic hydrocarbon having an indicated number of carbon atoms (e.g., C1-C20, C1-C6, C1-C4, etc.). Representative saturated straight chain alkyls include -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl, -n-hexyl, -n-heptyl, -n-octyl, -n-nonyl and -n-decyl; while representative saturated branched alkyls include -isopropyl, -sec-butyl, -isobutyl, -tert-butyl, -isopentyl, 2-methylbutyl, 3-methylbutyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 2,3-dimethylbutyl, 2,3-dimethylpentyl, 2,4-dimethylpentyl, 2,3-dimethylhexyl, 2,4-dimethylhexyl, 2,5-dimethylhexyl, 2,2-dimethylpentyl, 2,2-dimethylhexyl, 3,3-dimethylpentyl, 3,3-dimethylhexyl, 4,4-dimethylhexyl, 2-ethylpentyl, 3-ethylpentyl, 2-ethylhexyl, 3-ethylhexyl, 4-ethylhexyl, 2-methyl-2-ethylpentyl, 2-methyl-3-ethylpentyl, 2-methyl-4-ethylpentyl, 2-methyl-2-ethylhexyl, 2-methyl-3-ethylhexyl, 2-methyl-4-ethylhexyl, 2,2-diethylpentyl, 3,3-diethylhexyl, 2,2-diethylhexyl, 3,3-diethylhexyl and the like.

[0046] Whenever a range of the number of atoms in a structure is indicated (e.g., a C1-C8, C1-C6, C1-C4, or C1-C3 alkyl, haloalkyl, alkylamino, alkenyl, etc.), it is specifically contemplated that any sub-range or individual number of carbon atoms falling within the indicated range also can be used. Thus, for instance, the recitation of a range of 1-8 carbon atoms (e.g., C1-C8), 1-6 carbon atoms (e.g., C1-C6), 1-4 carbon atoms (e.g., C1-C4), 1-3 carbon atoms (e.g., C1-C3), or 2-8 carbon atoms (e.g., C2-C8) as used with respect to any chemical group (e.g., alkyl, haloalkyl, alkylamino, alkenyl, etc.) referenced herein encompasses and specifically describes 1, 2, 3, 4, 5, 6, 7, or 8 carbon atoms, as appropriate, as well as any sub-range thereof (e.g., 1-2 carbon atoms, 1-3 carbon atoms, 1-4 carbon atoms, 1-5 carbon atoms, 1-6 carbon atoms, 1-7 carbon atoms, 1-8 carbon atoms, 2-3 carbon atoms, 2-4 carbon atoms, 2-5 carbon atoms, 2-6 carbon atoms, 2-7 carbon atoms, 2-8 carbon atoms, 3-4 carbon atoms, 3-5 carbon atoms, 3-6 carbon atoms, 3-7 carbon atoms, 3-8 carbon atoms, 4-5 carbon atoms, 4-6 carbon atoms, 4-7 carbon atoms, 4-8 carbon atoms, 5-6 carbon atoms, 5-7 carbon atoms, 5-8 carbon atoms, 6-7 carbon atoms, or 6-8 carbon atoms, as appropriate).

[0047] An inhibitor of the JMJD2 family of histone demethylases and/or any compound or RNAi described above can be administered in a composition (e.g., pharmaceutical
composition) that can comprise at least one carrier (e.g., a pharmaceutically acceptable carrier), as well as other therapeutic agents (e.g., other inhibitors of the JMJD2 family of histone demethylases). The composition can be administered by any suitable route, including parenteral, topical, oral, or local administration. One embodiment of the invention is topical administration of an inhibitor of the JMJD2 family of histone demethylases. Such topical administration may be accomplished using a cream or lotion formulation for, e.g., the clearance of cold sores (HSV-1), genital sores (HSV-2), or shingles (VZV).

The pharmaceutically acceptable carrier (or excipient) is preferably one that is chemically inert to the inhibitor of the JMJD2 family of histone demethylases and one that has little or no side effects or toxicity under the conditions of use. Such pharmaceutically acceptable carriers include, but are not limited to, water, saline, Cremophor EL (Sigma Chemical Co., St. Louis, MO), propylene glycol, polyethylene glycol, alcohol, and combinations thereof. The choice of carrier will be determined in part by the particular inhibitor of the JMJD2 family of histone demethylases as well as by the particular method used to administer the composition. Accordingly, there is a wide variety of suitable formulations of the composition.

Preservatives may be used in the pharmaceutical composition. Suitable preservatives may include, for example, methylparaben, propylparaben, sodium benzoate, and benzalkonium chloride. A mixture of two or more preservatives optionally may be used. The preservative or mixtures thereof are typically present in an amount of about 0.0001% to about 2% by weight of the total composition.

Suitable buffering agents may be used in the pharmaceutical composition and may include, for example, citric acid and sodium citrate, phosphoric acid and potassium phosphate, and various other acids and salts. A mixture of two or more buffering agents optionally may be used. The buffering agent or mixtures thereof are typically present in an amount of about 0.001% to about 4% by weight of the total composition.

The following formulations for oral, nasal, parenteral (e.g., subcutaneous, intravenous, intraarterial, intramuscular, intradermal, interperitoneal, and intrathecal), and rectal administration are merely exemplary and are in no way limiting.

Formulations suitable for oral administration can consist of (a) liquid solutions, such as an effective amount of the compound dissolved in diluents, such as water, saline, or orange juice; (b) capsules, sachets, tablets, lozenges, and troches, each containing a predetermined amount of the active ingredient, as solids or granules; (c) powders; (d)
suspensions in an appropriate liquid; and (e) suitable emulsions. Liquid formulations may include diluents, such as water and alcohols, for example, ethanol, benzyl alcohol, and the polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent, or emulsifying agent. Capsule forms can be of the ordinary hard- or soft-shelled gelatin type containing, for example, surfactants, lubricants, and inert fillers, such as lactose, sucrose, calcium phosphate, and cornstarch. Tablet forms can include one or more of lactose, sucrose, mannitol, corn starch, potato starch, alginic acid, microcrystalline cellulose, acacia, gelatin, guar gum, colloidal silicon dioxide, croscamiellose sodium, talc, magnesium stearate, calcium stearate, zinc stearate, stearic acid, and other excipients, colorants, diluents, buffering agents, disintegrating agents, moistening agents, preservatives, flavoring agents, and pharmacologically compatible carriers. Lozenge forms can comprise the active ingredient in a flavor, usually sucrose and acacia or tragacanth, as well as pastilles comprising the active ingredient in an inert base, such as gelatin and glycerin, or sucrose and acacia, emulsions, gels, and the like containing, in addition to the active ingredient, such carriers as are known in the art. A component of the formulation may serve more than one function.

The inhibitors of the JMJD2 family of histone demethylases, alone or in combination with other suitable components, can be made into aerosol formulations to be administered via inhalation. These aerosol formulations can be placed into pressurized acceptable propellants, such as dichlorodifluoromethane, propane, nitrogen, and the like. They also may be formulated as pharmaceuticals for non-pressured preparations, such as in a nebulizer or an atomizer.

Formulations suitable for parenteral administration include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain anti-oxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. The inhibitors of the JMJD2 family of histone demethylases may be administered in a physiologically acceptable diluent in a pharmaceutical carrier, such as a sterile liquid or mixture of liquids, including water, saline, aqueous dextrose and related sugar solutions, an alcohol, such as ethanol, isopropanol, or hexadecyl alcohol, glycols, such as propylene glycol or polyethylene glycol, glycerol ketals, such as 2,2-dimethyl-1,3-dioxolane-4-methanol, ethers, such as poly(ethyleneglycol) 400, an oil, a fatty acid, a fatty acid ester or glyceride, or an acylated
fatty acid glyceride with or without the addition of a pharmaceutically acceptable surfactant, such as a soap or a detergent, suspending agent, such as pectin, caribomers, methylcellulose, hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agents and other pharmaceutical adjuvants.

[0055] Oils, which can be used in parenteral formulations, include petroleum, animal, vegetable, or synthetic oils. Specific examples of oils include peanut, soybean, sesame, cottonseed, corn, olive, petrolatum, and mineral. Suitable fatty acids for use in parenteral formulations include oleic acid, stearic acid, and isostearic acid. Ethyl oleate and isopropyl myristate are examples of suitable fatty acid esters.

[0056] Suitable soaps for use in parenteral formulations may include fatty alkali metal, ammonium, and triethanolamine salts, and suitable detergents include (a) cationic detergents such as, for example, dimethyl dialkyl ammonium halides, and alkyl pyridinium halides, (b) anionic detergents such as, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates, (c) nonionic detergents such as, for example, fatty amine oxides, fatty acid alkanolamides, and polyoxyethylene-polypropylene copolymers, (d) amphoteric detergents such as, for example, alkyl-beta-aminopropionates, and 2-alkyl-imidazoline quaternary ammonium salts, and (3) mixtures thereof.

[0057] The parenteral formulations will typically contain from about 0.5 to about 25% by weight of the active ingredient in solution. Suitable preservatives and buffers can be used in such formulations. In order to minimize or eliminate irritation at the site of injection, such compositions may contain one or more nonionic surfactants having a hydrophilic-lipophilic balance (HLB) of from about 12 to about 17. The quantity of surfactant in such formulations ranges from about 5% to about 15% by weight. Suitable surfactants include polyethylene sorbitan fatty acid esters, such as sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol. The parenteral formulations can be presented in unit-dose or multidose sealed containers, such as ampoules and vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, water, for injections, immediately prior to use. Extemporaneous injection solutions and suspensions can be prepared from sterile powders, granules, and tablets.

[0058] The inhibitors of the JMJD2 family of histone demethylases may be administered as an injectable formulation. The requirements for effective pharmaceutical carriers for injectable compositions are well known to those of ordinary skill in the art. See
Topical formulations, including those that are useful for transdermal drug release, are well known to those of skill in the art and are suitable in the context of embodiments of the invention for application to skin.

The concentration of a compound of embodiments of the invention in the pharmaceutical formulations can vary, e.g., from less than about 1%, usually at or at least about 10%, to as much as 20% to 50% or more by weight, and can be selected primarily by fluid volumes, and viscosities, in accordance with the particular mode of administration selected.

Methods for preparing administrable (e.g., parenterally administrable) compositions are known or apparent to those skilled in the art and are described in more detail in, for example, Remington: The Science and Practice of Pharmacy, Lippincott Williams & Wilkins, 21st ed. (2005).

In addition to the aforementioned pharmaceutical compositions, the inhibitors of the JMJD2 family of histone demethylases can be formulated as inclusion complexes, such as cyclodextrin inclusion complexes, or liposomes. Liposomes can serve to target the inhibitor of the JMJD2 family of histone demethylases to a particular tissue. Liposomes also can be used to increase the half-life of the inhibitor of the JMJD2 family of histone demethylases. Many methods are available for preparing liposomes, as described in, for example, Szoka et al., Ann. Rev. Biophys. Bioeng., 9, 467 (1980) and U.S. Patents 4,235,871, 4,501,728, 4,837,028, and 5,019,369.

When inhibitors of the JMJD2 family of histone demethylases are administered with one or more additional therapeutic agents, including additional inhibitors of the JMJD2 family of histone demethylases or with inhibitors of the LSD1 protein as the additional therapeutic agents, one or more additional therapeutic agents can be coadministered to the mammal. By "coadministering" is meant administering one or more additional therapeutic agents and the inhibitors of the JMJD2 family of histone demethylases sufficiently close in time such that these can enhance the effect of one or more additional therapeutic agents. In this regard, the inhibitors of the JMJD2 family of histone demethylases can be administered first and the one or more additional therapeutic agents can be administered second, or vice versa, to provide for sequential administration. Alternatively, the inhibitors of the JMJD2
family of histone demethylases and the one or more additional therapeutic agents can be administered simultaneously. Inhibitors of the JMJD2 family of histone demethylases and the one or more additional therapeutic agents also can be administered cyclically.

[0064] The delivery systems useful in the context of embodiments of the invention may include time-released, delayed release, and sustained release delivery systems such that the delivery of the inventive composition occurs prior to, and with sufficient time to cause, sensitization of the site to be treated. The inventive composition can be used in conjunction with other therapeutic agents or therapies. Such systems can avoid repeated administrations of the inventive composition, thereby increasing convenience to the subject and the physician, and may be particularly suitable for certain composition embodiments of the invention.

[0065] Many types of release delivery systems are available and known to those of ordinary skill in the art. They include polymer base systems such as poly(lactide-glycolide), copolyoxalates, polycaprolactones, polyesteramides, polyorthoesters, polyhydroxybutyric acid, and polyanhydrides. Microcapsules of the foregoing polymers containing drugs are described in, for example, U.S. Patent 5,075,109. Delivery systems also include non-polymer systems that are lipids including sterols such as cholesterol, cholesterol esters, and fatty acids or neutral fats such as mono-di-and tri-glycerides; hydrogel release systems; sylastic systems; peptide based systems; wax coatings; compressed tablets using conventional binders and excipients; partially fused implants; and the like. Specific examples include, but are not limited to: (a) erosional systems in which the active composition is contained in a form within a matrix such as those described in U.S. Patents 4,452,775, 4,667,014, 4,748,034, and 5,239,660 and (b) diffusional systems in which an active component permeates at a controlled rate from a polymer such as described in U.S. Patents 3,832,253 and 3,854,480. In addition, pump-based hardware delivery systems can be used, some of which are adapted for implantation.

[0066] The terms "treat," "prevent," and "inhibit" as well as words stemming therefrom, as used herein, do not necessarily imply 100% or complete treatment, prevention, or inhibition. Rather, there are varying degrees of treatment, prevention, or inhibition of which one of ordinary skill in the art recognizes as having a potential benefit or therapeutic effect. In this respect, the inventive methods can provide any amount of any level of treatment, prevention, or inhibition of a condition associated with, e.g., JMJD2 histone demethylase activity, such as demethylation of histones, in a host. Furthermore, the treatment, prevention,
or inhibition provided by the inventive methods can include treatment, prevention, or inhibition of one or more conditions or symptoms of the disease being treated, prevented, or inhibited. Also, for purposes herein, "prevention" or "inhibiting" can encompass delaying the onset of the disease or a symptom or condition thereof.

[0067] An "effective amount" refers to a dose that is adequate to prevent, treat, or inhibit a condition associated with, e.g., JMJD2 histone demethylase activity. Amounts effective for a therapeutic or prophylactic use will depend on, for example, the stage and severity of the disease or disorder being treated, the age, weight, and general state of health of the patient, and the judgment of the prescribing physician. The size of the dose will also be determined by the compound selected, method of administration, timing and frequency of administration as well as the existence, nature, and extent of any adverse side-effects that might accompany the administration of a particular compound and the desired physiological effect. For example, the dose of the inhibitor to be administered for treating a condition associated with, e.g., JMJD2 histone demethylase activity, can be about 0.1 mg to about 10 g per day (e.g., 0.5 mg, 1 mg, 5 mg, 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, 1000 mg, 2 g, 3 g, 4 g, 5 g, 6 g, 7 g, 8 g, 9 g, or ranges of any of the values described herein). The dose of the inhibitor to be administered for preventing a condition associated with, e.g., JMJD2 histone demethylase activity, can be less than the dose for treating such a condition, e.g., about 0.001 mg/kg per day to about 1 mg/kg per day (e.g., 0.001 mg/kg, 0.005 mg/kg, 0.01 mg/kg, 0.05 mg/kg, 0.1 mg/kg, 0.5 mg/kg, 1 mg/kg, or ranges of any of the values described herein). Alternatively or in addition, the dose of inhibitor to be administered for prevention or treatment can be 0.001 mg/kg to 200 mg/kg per day (e.g., 0.01 mg/kg, 0.05 mg/kg, 0.1 mg/kg, 0.5 mg/kg, 1 mg/kg, 5 mg/kg, 10 mg/kg, 50 mg/kg, 100 mg/kg, 150 mg/kg, or ranges of any of the values described herein). It will be appreciated by one of skill in the art that various diseases or disorders could require prolonged treatment involving multiple administrations, perhaps using inhibitors of the JMJD2 family of histone demethylases in each or various rounds of administration.

[0068] The following examples further illustrate the invention but, of course, should not be construed as in any way limiting its scope.
EXAMPLE 1

[0069] In accordance with embodiments of the invention, this Example demonstrates the inhibition of members of the JMJD2 family of histone demethylases by siRNA.


[0071] siRNA sequences used were

- JMJD2A: GAACCGACCUCUAAACUUU (SEQ ID NO: 1)
- JMJD2B: GCAGGCACCGUCCACAUUU (SEQ ID NO: 2)
- JMJD2C: GAGAGGACAUCUACUUU (SEQ ID NO: 3)
- JMJD2D: CUGGAAGAACCACAUCUAUAA (SEQ ID NO: 4).

[0072] siRNA depletion of JMJD2 family members reduces HSV-1 IE gene expression. Figures 2A and 2B show herpes simplex virus Immediate Early genes ICP27 and ICP4 mRNA levels after administration of siRNA directed against JMJD2a (A), JMJD2b (B), JMJD2c (C), JMJD2d (D), and combinations of these. Hela cells were transfected with 1 nmol of siRNAs against the indicated JMJD2 histone demethylase or control siRNA for 48 hrs. Cells were subsequently infected with 0.1 PFU/cell HSV-1 for 2 hrs. Total RNA was extracted, reverse-transcribed, and cDNAs were quantitated by qPCR using primers to relevant genes of interest. Figure 3 is a bar graph, showing the impact of depletion of members of the JMJD2 family on HSV IE gene expression in MRC5 cells, using similar methods.

[0073] siRNA depletion of JMJD2 proteins results in accumulation of repressive chromatin on HSV-1 IE promoters (Figure 4). Hela cells were transfected with siRNAs against JMJD2 family demethylases. Forty-eight hours later, cells were infected with 0.1 pfu/cell of HSV-1 for 3 hrs. Standard Chromatin-Immunoprecipitation procedures were preformed (Liang, Vogel, Narayanan, Peng & Kristie, 2009, Nature Med 15:1312-17) to determine the levels of total histone H3 or tri-methylated histone H3 associated with the indicated viral IE promoters.

[0074] Figure 5 shows recovery of HSV-1 IE gene expression by siRNA resistant JMJD2 family members. Herpes simplex virus Immediate Early gene ICP4 mRNA levels were measured after administration of control siRNA or siRNA directed against JMJD2s (sequences provided above). Post depletion, cells were transfected with plasmids expressing control LacZ or siRNA resistant JMJD2s. Plasmids expressing siRNA resistant JMJD2 mRNAs were generated by site-specific mutagenesis according to standard protocols. Cells
were subsequently infected with 0.1 PFU/cell HSV-1 for 2 hrs. Total RNA was extracted, reverse-transcribed, and cDNAs were quantitated by qPCR using primers to viral IE genes.

**EXAMPLE 2**

In accordance with embodiments of the invention, this Example demonstrates the inhibition of the catalytic activity of members of the JMJD2 family of histone demethylases by small molecule inhibitors that block viral immediate early gene expression during lytic infection with HSV-1 and reactivation from latency.

Antibodies and primers used are described in Liang, Vogel, Narayanan & Kristie, Nature Med., 2009, 15:1312-1317.

HSV-1 IE protein levels of ICP4 decrease in cells infected in the presence of DMOG. HeLa cells were infected with HSV-1 at 0.1 PFU/cell for 3 hrs in the presence of increasing concentrations of DMOG. Cells were harvested and the levels of viral IE proteins (ICP4 shown) were determined by quantitative western blot analyses. As the concentration of DMOG is increased, the levels of ICP4 decrease (Figure 6).

HSV-1 IE mRNA levels of ICP4 and ICP27 decrease in cells infected in the presence of DMOG. Human foreskin fibroblast (HFF) cells were infected with HSV-1 at 0.1 PFU/cell for 3 hrs in the presence of increasing concentrations of DMOG. Cells were harvested and the levels of viral IE (ICP4, ICP27) and cell control (si 5) mRNAs were assessed by qRT-PCR. As the concentration of DMOG is increased, the mRNA levels of ICP4 and ICP27 decrease, whereas that of the control mRNA (si 5) does not (Figure 7).

DMOG inhibition of JMJD2 proteins results in accumulation of repressive chromatin on HSV-1 IE promoters (Figure 8). Hela cells were pretreated with 2 mM DMOG for 4 hours prior to infection. Cells were infected with 0.1 pfu/cell of HSV-1 for 3 hrs. Standard Chromatin-Immunoprecipitation procedures were preformed (Liang, Vogel, Narayanan, Peng & Kristie, 2009, Nature Med 15:1312-17) to determine the levels of total histone H3 or tri-methylated histone H3 associated with the indicated viral IE promoters.

CMV IE gene expression (IE1 and UL37) and control TBP (Tata binding Protein) in the presence of increasing concentrations of DMOG were also studied (Figure 9). HFF
were pretreated with the indicated concentration of DMOG for 3.5 hrs and infected with CMV for 4 hrs. Total RNA was extracted, reverse-transcribed, and cDNAs were quantitated by qPCR using primers to viral IE genes or control genes. As the concentration of DMOG is increased, the mRNA levels of IE7 and UL37 decrease, whereas that of the control mRNA (TBP) does not.

HSV-1 lytic viral yields decrease in the presence of DMOG (Figure 10). HFF cells were pretreated with DMSO control or JMJD2 inhibitor DMOG for 5hrs and infected with 0.1 pfu/cell of HSV-1 for 24hrs in the presence of DMSO or DMOG. The yield of infectious virus derived from each treatment were determined by titrating on Vero cells according to standard procedures.

Viral yields decrease from HSV-1 latently infected ganglia explanted in the presence of LSD 1 or JMJD2 inhibitors (Figure 11). Balb/c mice were infected with 5 x 10^6 PFU HSV-1 (strain F) per eye after corneal scarification. Latently infected mice were sacrificed 45 days post clearance of the primary infection and trigeminal ganglia were rapidly explanted into culture in the presence of 2 mM DMOG, 2 mM TCP, or control (DMSO or ACV, acyclovir) for 48 hours. Post explant incubation, the ganglia were homogenized and briefly sonicated. The reactivated viral yield of each ganglia was determined by titrating the clarified supernatant on Vero cells. Statistical comparisons were made using Wilcoxon signed rank test (paired ganglia) with a statistical significance of <0.05. Each data point was the result of a single ganglia divided and treated in the presence and absence of DMSO and DMOG or DMSO and TCP. Therefore, a Wilcoxon signed rank test was used to assess differences between each treated and untreated sample. The significant difference between DMSO control and DMOG was p = 0.0018. This test used an exact p-value for small sample sizes with an a level of 0.05. n=20. Analyses were made using Prism (V5.0a) and are expressed as the mean +/- s.e.m. No viral yields are obtained in the presence of ACV.

IE gene transcription is repressed in explanted latently infected sensory ganglia in the presence of DMOG (Figure 12). Total RNA was extracted from ganglia of latently infected mice explanted in the presence of control ACV or DMOG for 7 hours. Random primed cDNA was produced from total RNA using RNAqueous-4PCR and RETROscript (Ambion, Austin, TX, USA) according to the manufacturer’s recommendations. cDNAs were quantitated by nested PCR or qPCR using primers specific for the HSV-1 ICP4 and ICP27 IE mRNAs.
Given the chemical mechanism by which LSD1 functions, the protein is only capable of removing mono- and dimethylation. As repressive tri-methylated H3-Lys9 is readily detected early in viral infection, an additional histone demethylase(s) with the complementing activity is required in cooperation with LSD1 to effectuate viral replication. Inhibition of JMJD2 activities results in reduced viral IE mRNAs and viral yield during reactivation from latency demonstrating that inhibition of JMJD2 activities blocks viral reactivation from latency.

All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein. The use of the terms "a" and "an" and "the" and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The terms "comprising," "having," "including," and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to," ) unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention. Preferred embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and
equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.
CLAIM(S):

1. A substance for use in preventing or treating a viral infection of a host, wherein the substance is an inhibitor of a JMJD2 protein.

2. The substance of claim 1, wherein the substance is selected from the group consisting of

(a) a compound of the formula (I):

wherein

R\(^1\) and R\(^2\) are each independently H or C\(_1\)-C\(_6\) alkyl, or together form =CH\(_2\), =CH- (C\(_1\)-C\(_6\) alkyl) or =C(C\(_1\)-C\(_6\) alkyl)(C\(_1\)-C\(_6\) alkyl) where the C\(_1\)-C\(_6\) alkyl groups are the same or different;

R\(^3\) is H or a group of the formula: -Y-L-W

wherein Y is linked to N and is CH\(_2\), C=0, or NH,

L is C\(_1\)-C\(_8\) alkyleneyl, (CH\(_2\))\(^m\)-(C\(_6\)-C\(_20\) aryl)-(CH\(_2\))\(^n\), or

[(CH\(_2\))\(^q\)]\(_n\)CH\(_2\), wherein m and n are each independently 0 to 6,

q is 1 to 6, and r is 1 to 3, and

W is R\(^6\), COR\(^6\), S0\(_2\)R\(^6\), CH=NR\(^7\), or NHOR\(^7\),

wherein R\(^6\) is NR\(^7\)R\(^7\), guanidinyl, a ureido moiety, a carbamate moiety, or OR\(^7\), and

each R\(^7\) is independently H or CH\(_3\);

R\(^4\) and R\(^5\) are each independently H, C\(_1\)-C\(_6\) alkyl, C\(_6\)-C\(_20\) aryl, or C\(_6\)-C\(_20\) aryl C\(_1\)-C\(_6\) alkyl; and

X is O, S, or NH;
(b) a compound of the formula

(c) a compound of the formula
wherein $R^{10}$ is

\[
\begin{align*}
\text{CH}_2\text{SH}, & \quad \text{methyl, or CH}_2\text{CH}_2\text{Ph}; \\
\end{align*}
\]

(d) a compound of the formula

\[
\begin{align*}
\text{HO-} & \quad \text{O-} \\
\text{CONH-} & \quad \text{OH} \\
\end{align*}
\]

(e) a compound of the formula

\[
\begin{align*}
\text{HO-} & \quad \text{O-} \\
\text{CONH-} & \quad \text{OH} \\
\end{align*}
\]

wherein $R^M$ is OCH$_3$ or H and $X'$ is S or CH$_2$;

(f) a compound of the formula

\[
\begin{align*}
\text{HO-} & \quad \text{O-} \\
\text{CONH-} & \quad \text{OH} \\
\end{align*}
\]
wherein $R^{30}$ is

- $R^{30} = H$, 2-methyl, 4-phenyl, 3-fluoro, 2,4-difluoro, 2-chloro, 3-methoxy, or 4-cyano,

wherein $R^{50}$ is $H$, 2-methyl, 4-methyl, 2,4,6-trimethyl, 2-fluoro, 3,4-difluoro, 2-fluoro-3-trifluoromethyl, 4-chloro, 3-methoxy, 3-chloro, 2-nitro, 2-methoxy-5-nitro, 4-methoxycarbonyl, 3-cyano, or 4-(2,3,4-thiadiazolyl),

wherein $R^{80}$ is
wherein $R^{70}$ is
wherein $R^{80}$ is

![Chemical structures](image)

or

wherein $R^{90}$ is

![Chemical structures](image)

or
(g) a compound of the formula

\[
\begin{align*}
R^1 & \quad (\_\_\_)_p \quad W^1 \quad N \quad W^2 \quad \text{OH} \\
\end{align*}
\]

wherein \( R^1 \) is \( C_1-C_4 \) alkyl, \( NH(C_1-C_4 \text{ alkyl}) \), \( N(C_1-C_4 \text{ alkyl}) \) benzyl, \( N(d-C_4 \text{ alkyl})(C_1-C_4 \text{ alkyl}) \) where the \( C_1-C_4 \) alkyl groups are the same or different; \( W^1 \) and \( W^2 \) are each independently CO or a N-C bond; and \( p \) is 0 to 11; and

(h) an siRNA directed against a member of the JMJD2 family of histone demethylases;

or a pharmaceutically acceptable salt thereof;

for use in preventing or treating a viral infection of a host.

3. The substance of claim 2, wherein for the compound of formula (I),

\( R^1 \) and \( R^2 \) are each independently \( H \) or \( Ci-C_6 \text{ alkyl} \);

\( R^3 \) is \( H \) or a group of the formula: \(-Y-L-W\)

wherein \( Y \) is linked to \( N \) and is \( CH_2, C=O \), or \( NH \),

\( L \) is \( C_1-C_6 \text{ alkylenyl} \), \( (CH_2)_m-(C_6-C_{20} \text{ aryl})-(CH_2)_n \) or

\( (CH_2CH_20)_q CH_2 \), wherein \( m \) and \( n \) are each independently 0 to 6 and \( q \) is 1 to 6, and

\( W \) is \( R^6 \),

wherein \( R^6 \) is \( NR^7R^7 \) or \( OR^7 \), and each \( R^7 \) is independently \( H \) or \( CH_3 \);

\( R^4 \) and \( R^5 \) are each independently \( H \) or \( Ci-C_6 \text{ alkyl} \); and

\( X \) is \( O \).

4. The substance of claim 3, wherein \( R^1, R^2, R^4, \) and \( R^5 \) are each independently \( H \) or \( CH_3 \).
5. The substance of claim 4, wherein the compound is N-oxalylglycine, dimethyloxalylglycine,

6. The substance of claim 2, wherein the compound is
7. The substance of claim 2, wherein the siRNA is any one of SEQ ID NOS: 1-4.

8. The substance of any one of claims 2-7, wherein the viral infection involves reactivation of a virus after latency in the host.

9. The substance of any one of claims 2-8, wherein the viral infection is due to a herpesvirus.

10. The substance of claim 9, wherein the herpesvirus is herpes simplex virus type 1, herpes simplex virus type 2, varicella zoster virus, cytomegalovirus, Epstein-Barr, or Kaposi's Sarcoma-Associated herpesvirus.

11. The substance of any one of claims 2-10, wherein the host is a mammal.

12. The substance of claim 11, wherein the mammal has undergone, is undergoing, or will undergo immunosuppression.

13. The substance of claim 11, wherein the compound or salt prevents or treats viral-induced encephalitis, viral-induced keratitis, or reduces the severity of infection.
14. The substance of claim 11, wherein the mammal is an immunocompromised mammal.

15. The substance of any one of claims 2-14, for use in combination with an inhibitor of the LSD1 protein.

16. The substance of claim 15, wherein the inhibitor of the LSD1 protein is a monoamine oxidase inhibitor or an RNAi molecule.

17. The substance of claim 16, wherein the monoamine oxidase inhibitor is pargyline or tranylcypromine.

18. A substance selected from the group consisting of
(a) a compound of the formula (I):

![Chemical structure image]

wherein

1. and R² are each independently H or Ci-C₆ alkyl, or together form =CH₂, =CH-(Ci-C₆ alkyl) or =C(Ci-C₆ alkyl)(Ci-C₆ alkyl) where the Ci-C₆ alkyl groups are the same or different;

2. is H or a group of the formula: -Y-L-W

wherein Y is linked to N and is CH₂, C=0, or NH,

L is C,-Cg alkyl, (CH₂)_m(C₆-C₂₀ aryl)-(CH₂)_n, or

[(CH₂)O]ₜCH₂, wherein m and n are each independently 0 to 6,

q is 1 to 6, and r is 1 to 3, and

W is R⁶, COR⁶, S₀₂R⁶, CH=NR⁷, or NHOR⁷,

wherein R⁶ is NR⁷R⁷, guanidinyl, a ureido moiety, a carbamate moiety, or OR⁷, and
each R⁷ is independently H or CH₃;
R^4 and R^5 are each independently H, C_1-C_6 alkyl, C_6-C_20 aryl, or C_6-C_20 aryl C_1-C_6 alkyl; and

X is O, S, or NH;

(b) a compound of the formula

(c) a compound of the formula
wherein $R^{10}$ is

$$\text{CH}_2\text{SH, } \text{CH}_2\text{Ph, methyl, or CH}_2\text{CH}_2\text{Ph;}$$

(d) a compound of the formula

$$\text{HO-} \overset{\text{N}}{\text{CH}} \overset{\text{Me}}{\text{O}} \text{NH} \text{CO} \text{HO}$$

(e) a compound of the formula

[diagram]

wherein $R^{20}$ is OCH$_3$ or H and $X'$ is S or CH$_2$;

(f) a compound of the formula

[diagram]

wherein $R^{30}$ is

[diagram]
wherein $R^{40}$ is H, 2-methyl, 4-phenyl, 3-fluoro, 2,4-difluoro, 2-chloro, 3-methoxy, or 4-cyano,

wherein $R^{50}$ is H, 2-methyl, 4-methyl, 2,4,6-trimethyl, 2-fluoro, 3,4-difluoro, 2-fluoro-3-trifluoromethyl, 4-chloro, 3-methoxy, 3-chloro, 2-nitro, 2-methoxy-5-nitro, 4-methoxycarbonyl, 3-cyano, or 4-(2,3,4-thiadiazolyl),

wherein $R^{60}$ is
wherein $R^{70}$ is

wherein $R^{80}$ is
wherein $R^{90}$ is

![Chemical Structures](image)

(a) a compound of the formula

![Chemical Structures](image)

wherein $R^1$ is C$_{1-4}$ alkyl, NH(C$_{1-4}$ alkyl), N(C$_{1-4}$ alkyl)benzyl, N(C$_{1-4}$ alkyl)(C$_{1-4}$ alkyl) where the C$_{1-4}$ alkyl groups are the same or different; $W^1$ and $W^2$ are each independently CO or a N-C bond; and $p$ is 0 to 11; and

(h) an siRNA directed against a member of the JMJD2 family of histone demethylases;

or a pharmaceutically acceptable salt thereof;

for use in inhibiting a member of the JMJD2 family of histone demethylases in a virus-infected host.

19. The substance of claim 18, wherein for the compound of formula (I), $R^1$ and $R^2$ are each independently H or C$_{1-6}$ alkyl;

$R^3$ is H or a group of the formula: $-Y-L-W$

wherein $Y$ is linked to N and is CH$_2$, C=O, or NH,

L is C$_{1-6}$ alkylenyl, (CH$_2$)$_m$-(C$_{6-20}$ aryl)-(CH$_2$)$_n$ or...
(CH₂CH₂O)ₜCH₂, wherein m and n are each independently 0 to 6 and q is 1 to 6, and

W is R⁶,

wherein R⁶ is NR'R⁷ or OR⁷, and
each R⁷ is independently H or CH₃;

R⁴ and R⁵ are each independently H or Ci-C₆ alkyl; and

X is O.

20. The substance of claim 19, wherein R¹, R², R⁴, and R⁵ are each independently H or CH₃.

21. The substance of claim 20, wherein the compound is N-oxalylglycine, dimethyloxalylglycine,
22. The substance of claim 18, wherein the compound is

23. The substance of claim 18, wherein the siRNA is any one of SEQ ID NOS: 1-4.

24. The substance of any one of claims 18-23, wherein the viral infection involves reactivation of a virus after latency in the host.

25. The substance of any one of claims 18-24, wherein the viral infection is due to a herpesvirus.
26. The substance of claim 25, wherein the herpesvirus is herpes simplex virus type 1, herpes simplex virus type 2, varicella zoster virus, cytomegalovirus, Epstein-Barr, or Kaposi’s Sarcoma-Associated herpesvirus.

27. The substance of any one of claims 18-26, wherein the host is a mammal.

28. The substance of claim 27, wherein the mammal has undergone, is undergoing, or will undergo immunosuppression.

29. The substance of claim 27, wherein the compound or salt prevents or treats viral-induced encephalitis, viral-induced keratitis, or reduces the severity of infection.

30. The substance of claim 27, wherein the mammal is an immunocompromised mammal.

31. The substance of any one of claims 18-30, for use in combination with an inhibitor of the LSD1 protein.

32. The substance of claim 31, wherein the inhibitor of the LSD1 protein is a monoamine oxidase inhibitor or an RNAi molecule.

33. The substance of claim 32, wherein the monoamine oxidase inhibitor is pargyline or tranylcypromine.

34. A compound of the formula (I):

\[
\begin{align*}
&\text{R}^4 - O - N(\text{CH}_{2})_{m} - \text{C}(\text{O}) - O - \text{R}^5 \\
&\text{R}^1 \text{R}^2 \text{R}^3 \text{R}^4 \text{R}^5
\end{align*}
\]

wherein

R^1 and R^2 are each independently H or C_1-C_6 alkyl, or together form =CH, =CH-(C_1-C_6 alkyl) or =C(C_1-C_6 alkyl)(C_1-C_6 alkyl) where the C_1-C_6 alkyl groups are the
same or different;

R³ is H or a group of the formula: \(-Y-L-W\)

wherein Y is linked to N and is CH², O=O, or NH,

L is C₁-C₈ alkylenyl, (CH₂)ᵐ-(C₆-C₂₀ aryl)-(CH₂)ⁿ, or

\([(CH₂)ₐ CH₂,\] wherein m and n are each independently 0 to 6,
q is 1 to 6, and r is 1 to 3, and

W is R⁶, COR⁶, S0₂R⁶, CH=NR⁷, or NHOR⁷,

wherein R⁹ is NR²R⁷, guanidinyl, a ureido moiety, a carbamate moiety, or OR⁷, and
each R⁷ is independently H or C₃⁴;

R⁴ and R⁵ are each independently H, C₁-C₆ alkyl, C₆-C₂₀ aryl, or C₆-C₂₀ aryl Ci-C₆ alkyl; and

X is O, S, or NH;
or a pharmaceutically acceptable salt thereof;

with the provisos that

when R⁴ and R⁵ are each H, X is O, and R¹ and R² are each H or one of R¹ and R² is H
and the other of R¹ and R² is Ci-C₆ alkyl, then R³ is not H,

when R⁴ and R⁵ are each Ci-C₆ alkyl, X is O, and R¹ and R² are each H, then R³ is not H
or

35. The compound or salt of claim 34, wherein both R¹ and R² are Ci-C₆ alkyl.
36. The compound or salt of claim 34 or 35, wherein
R¹ and R² are each independently H or Ci-C₆ alkyl;
R³ is H or a group of the formula: -Y-L-W

wherein Y is linked to N and is CH₂, C=0, or NH,
L is C₇-C₆ alkylenyl, (CH₂)ₘ(C₆-C₂₀ aryl)-(CH₂)ₙ, or
(CH₂CH₂O)ₚCH₂, wherein m and n are each independently 0 to
6 and p is 1 to 6, and
W is R⁶,
wherein R⁶ is NR⁷R⁷ or OR⁷, and
each R⁷ is independently H or C₃₄;
R⁴ and R⁵ are each independently H or Ci-C₆ alkyl; and
X is O.

37. The compound or salt of claim 36, wherein R¹, R², R⁴, and R⁵ are each
independently H or CH₃.

38. A pharmaceutical composition comprising a compound or salt of any one of
claims 34-37 and a pharmaceutically acceptable carrier.
Figure 1
Figure 2A

Figure 2B
Figure 3

jmjd2 depletions in mrc5 cells

mRNA levels in Jmjd2 depleted relative to control siRNA

siRNA  | Jmjd2a | Jmjd2b | Jmjd2c | Jmjd2d
-------|-------|-------|-------|-------
ICP27  |       |       |       |       
ICP4   |       |       |       |       
ICP22  |       |       |       |       

Figure 4

JMJD2 Depletion

Fold relative to control siRNA

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<th>K9me3</th>
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<td>ICP4</td>
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</table>
Figure 5

[Bar chart showing IE mRNA levels relative to control depletion across different siRNA and addback conditions]

siRNA: Cntrl, B, C, D
Addback: LZ, R, LZ, R, LZ, R
Figure 6
Figure 7
Figure 8

JMJD2 Inhibition

Fold DMOG/DMSO

K9me3 H3 K9me3 H3 K9me3 H3
ICP0 ICP27 ICP4
Figure 9

IE mRNA levels
% control DMSO

mM DMOG

TBP
IE1
UL37
Figure 10

Viral Yields vs. DMOG (mM)
Figure 11

$p = .0018$

Viral yield per ganglia

- DMSO
- DMOG
- TCP
Figure 12

[Graph showing relative IE mRNA levels for ACV and DMOG for ICP4 and ICP27]
# INTERNATIONAL SEARCH REPORT

<table>
<thead>
<tr>
<th>A. CLASSIFICATION OF SUBJECT MATTER</th>
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According to International Patent Classification (IPC) and/or both national classification and IPC

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<th>B. FIELDS SEARCHED</th>
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal , BIOSIS, CHEM ABS Data, EMBASE, WPI Data

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<th>C. DOCUMENTS CONSIDERED TO BE RELEVANT</th>
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Further documents are listed in the continuation of Box C. See patent family annex.

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search 26 September 2011

Date of mailing of the international search report 01/12/2011

Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

Authorized officer Schei the, Rupert

Form PCT/ISA/210 (second sheet) (April 2003)
### Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

- see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☑ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

- see annex

**Remark on Protest**

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.
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<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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Form PCT/ISA210 (continuation of second sheet) (April 2005)
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<td>GABRIELA TURK ET AL: &quot;Anti retrovi ral activi ty and cytoto xi city of novel zi dovudi ne (AZT) deri vati ves and the rel ati on to thei r r chemi cal structure&quot;, INTERNATIONAL JOURNAL OF ANTIMICROBIAL AGENTS, vol. 20, no. 4, 1 October 2002 (2002-10-01), pages 282-288, XP055007633, ISSN: 0924-8579, DOI: 10.1016/50924-8579 (02)00191-7 abstract, Fig. 1-3</td>
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<td>FAUCONNIER B: &quot;Inhibitory acti on of succi nic aci d on the multiplicati on of infl uenza virus in embryonated eggs &quot;, COMPTES RENDUS HEBDOMADAI RES DES SEANCES DE L'ACADEMI E DE SCIENTIFI ENCES, GAUTHER-VI LLARS, PARIS, FR, vol. 239, no. 25, 20 December 1954 (1954-12-20), pages 1886-1888, XP008143273, ISSN: 0001-4036 the whole document</td>
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<td>US 2010/015174 AI (FERNANDEZ-POL JOSE ALBERTO [US] ET AL) 21 January 2010 (2010-01-21) [0038], [0055], Table 12, claim 1</td>
<td>1-5, 8-21, 24-33</td>
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This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 3-5, 19-21, 34-38 (completely); 1, 2, 8-18, 24-33 (partially)

A substance for use in preventing or treating a viral infection of a host (claim 1) or for use in inhibiting a member of the JMJD2 family of histone demethylases in a virus infected host (claim 18), wherein the substance is an inhibitor of a JMJD2 protein selected from the group consisting of a compound of the formula a (I), the three oxalyl glycine derivatives in item (b) and a compound of the formulae of items (c)-(f) of claim 2.

A compound of the formula a (I) according to claim 34 or a pharmaceutical composition according to claim 38.

---

2. claims: 1, 2, 8-18, 24-33 (all partially)

A substance for use in preventing or treating a viral infection of a host (claim 1) or for use in inhibiting a member of the JMJD2 family of histone demethylases in a virus infected host (claim 18), wherein the substance is an inhibitor of a JMJD2 protein selected from the five hydroxamic acid derivatives in item (b) of claim 2.

---

3. claims: 1, 2, 8-18, 24-33 (all partially)

A substance for use in preventing or treating a viral infection of a host (claim 1) or for use in inhibiting a member of the JMJD2 family of histone demethylases in a virus infected host (claim 18), wherein the substance is an inhibitor of a JMJD2 protein selected from the four pyridine derivatives in item (b) of claim 2.

---

4. claims: 1, 2, 8-18, 24-33 (all partially)

A substance for use in preventing or treating a viral infection of a host (claim 1) or for use in inhibiting a member of the JMJD2 family of histone demethylases in a virus infected host (claim 18), wherein the substance is an inhibitor of a JMJD2 protein which is the pyrimidine derivatives in item (b) of claim 2.

---

5. claims: 1, 2, 8-18, 24-33 (all partially)

A substance for use in preventing or treating a viral infection of a host (claim 1) or for use in inhibiting a member of the JMJD2 family of histone demethylases in a virus infected host (claim 18), wherein the substance is an inhibitor of a JMJD2 protein selected from succinic acid and
FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

6. Claims: 6, 22 (completely) ; 1, 2, 8-18, 24-33 (partially)

A substance for use in preventing or treating a viral infection of a host (claim 1) or for use in inhibiting a member of the JMJD2 family of histone demethylases in a virus infected host (claim 18), wherein the substance is an inhibitor of a JMJD2 protein selected from a compound of the formula of item (g) of claim 2.

7. Claims: 7, 23 (completely) ; 1, 2, 8-18, 24-33 (partially)

A substance for use in preventing or treating a viral infection of a host (claim 1) or for use in inhibiting a member of the JMJD2 family of histone demethylases in a virus infected host (claim 18), wherein the substance is an inhibitor of a JMJD2 protein which is a siRNA according to item (h) of claim 2.