

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
25 November 2010 (25.11.2010)

PCT

(10) International Publication Number
WO 2010/132992 A1

(51) International Patent Classification:

C07C 251/86 (2006.01) **C07D 239/26** (2006.01)
A61K 31/166 (2006.01) **C07D 257/04** (2006.01)
A61K 31/41 (2006.01) **C12Q 1/70** (2006.01)
A61K 31/44 (2006.01) **G01N 33/571** (2006.01)
A61K 31/505 (2006.01) **G06F 17/50** (2006.01)
A61P 31/22 (2006.01) **G06F 19/00** (2006.01)
C07D 213/53 (2006.01)

(21) International Application Number:

PCT/CA2010/000762

(22) International Filing Date:

19 May 2010 (19.05.2010)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/213,240 20 May 2009 (20.05.2009) US

(71) Applicant (for all designated States except US): **UNIVERSITÉ LAVAL** [CA/CA]; Vice Rectorat à la recherche et à la création, Pavillon des Sciences de l'Éducation, 2320 rue des Bibliothèques, local 1434, Québec, Québec G1V 0A6 (CA).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **BOIVIN, Guy** [CA/CA]; 2531 Montbray, Québec, Québec G1V 1E7 (CA). **LIN, Sheng-Xiang** [CN/CA]; 2931 Chemin St-Louis, Québec, Québec G1W 1P6 (CA). **MARTIN, Mélanie** [CA/CA]; 3600 Avenue des Compagnons, Apt 416, Québec, Québec G1X 3Z4 (CA). **AZZI, Arezki**

[CA/CA]; 880 Grand-Jean Apt 520, Québec, Québec G1X 3Z3 (CA).

(74) Agent: **FASKEN MARTINEAU DuMOULIN LLP**; Stock Exchange Tower, P.O. Box 242, Bureau 3700, 800, Square Victoria, Montreal, Québec H4Z 1E9 (CA).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: COMPOUNDS FOR THE INHIBITION OF HERPESVIRUSES

(57) Abstract: 3D protein modeling and virtual screening of commercially-available compounds were performed to identify new inhibitors of the herpesvirus DNA polymerase, a key enzyme in the viral replication cycle. Two compounds (Nos 2 and 9) were particularly active against HSV-1 and HSV-2 strains and one compound (No 3) inhibited specifically cytomegalovirus (CMV) strains (overall hit rate of 25%). Some of the tested compounds inhibited wild-type viruses and strains resistant to current antiviral agents. New chemical entity derivatives of compound 2 with binding potential to the DNA polymerase retained an excellent activity against HSV-1, HSV-2 and VZV like the parental compound, as well as against strains resistant to current antiviral agents. These non-nucleosidic herpesvirus DNA polymerase inhibitors with in vitro activity against drug-resistant clinical isolates warrant further pre-clinical studies.



WO 2010/132992 A1

TITLE: Compounds for the Inhibition of Herpesviruses**FIELD OF THE INVENTION**

The present invention relates to compounds and their use in impairing the replication of herpesviruses. These compounds are particularly active against the herpes simplex
5 viruses (HSV) types -1 and -2, the cytomegalovirus (CMV) and the varicella-zoster virus (VZV) and may be used to inhibit wild-type viruses or strains resistant to current antiviral agents.

BACKGROUND OF THE INVENTION

Herpesviruses are DNA-containing enveloped viruses belonging to the *Herpesviridae*
10 family. Among these viruses, HSV-1 and HSV -2 are responsible for recurrent orolabial and genital infections, VZV is responsible for chickenpox and shingles and CMV is associated with disseminated infections such as pneumonitis, colitis and retinitis in immunocompromised individuals. All herpesviruses establish lifelong latent infections in humans with periodic symptomatic and asymptomatic
15 reactivations.

Antiviral agents are commonly used to treat frequent HSV reactivations (mainly genital infections) in immunocompetent individuals, VZV reactivation (shingles or zoster) in elderly subjects and severe HSV, VZV and CMV infections in immunocompromised hosts such as HIV-infected patients, transplant recipients and
20 subjects with neoplasia. Active compounds currently available for the treatment of herpesvirus infections include the nucleoside analogues acyclovir (ACV and its prodrug valacyclovir or VACV), penciclovir (PCV and its prodrug famciclovir), and ganciclovir (GCV and its prodrug valganciclovir or VGCV) as well as the nucleotide analogue cidofovir (CDV) and the pyrophosphate analogue foscarnet (FOS). All these
25 compounds interfere with viral DNA synthesis by inhibiting the viral DNA polymerase (pol). The nucleoside and nucleotide analogues must be phosphorylated to exert their antiviral effect whereas the pyrophosphate analogue FOS directly inhibits viral DNA pol. The nucleoside analogues ACV and GCV are considered the first-line drugs against HSV/VZV and CMV diseases, respectively, whereas CDV and FOS are
30 considered second-line drugs due to their important toxicity (nephrotoxicity and electrolyte imbalances) and lack of oral formulations.

The emergence of herpesvirus drug resistance is frequent in immunocompromised subjects and only surpassed by that of HIV resistance [1]. For instance, HSV resistance to ACV, the first-line drug, varies from 4 to 14% among various immunocompromised groups, although it is infrequent in immunocompetent subjects [1]. The rate of CMV resistance to the gold standard GCV is also substantial with 7% resistance after 6 months of treatment in HIV-infected patients [2] and up to 30% in lung transplant recipients [3]. Due to less frequent use, fewer data on CMV resistance to CDV and FOS have been reported. Some CMV studies reported resistance rate to FOS and CDV similar or higher to that observed with GCV [4,5]. Resistance to the nucleoside analogues can be conferred by alterations in the viral activating gene (HSV/VZV thymidine kinase or CMV UL97 protein kinase) or in the target gene, i.e. the viral DNA pol. Resistance to CDV and FOS arises from mutations in the viral DNA pol gene only. Notably, some mutations in the viral DNA pol gene can confer resistance to all currently-available antiviral agents [6,7]. Thus, there is an urgent need to develop other non-toxic and highly effective compounds with different mechanisms of action to inhibit herpesvirus replication.

The aim of this project was to identify compounds with high binding potential to the DNA pol of HSV-1 by using a strategy that combines 3D modeling and virtual screening of a large bank of compounds. The antiviral activity and toxicity of the top leading compounds were examined *in vitro* against HSV-1, HSV-2, VZV and CMV. Recombinant and clinical isolates susceptible and/or resistant to current antivirals prescribed for the treatment of herpesvirus infections were used to determine the antiviral potential of these new compounds.

SUMMARY OF THE INVENTION

The present invention relates to compounds, pharmaceutical compositions comprising these compounds and their use in impairing or inhibiting (e.g., interfering) herpesvirus replication. Some of the compounds of the present are readily available to the public while others are new chemical entities.

The present invention especially contemplates compounds that are new chemical entities. However, both new chemical entities and known compounds may be used in pharmaceutical compositions and in methods of inhibiting herpesvirus replication.

Compounds of formula IA and IB that are described herein may be suitable for impairing herpesvirus replication. Some compounds of formula IA have been found particularly suitable for interfering with the replication of herpes simplex 1 and herpes simplex 2 while some compounds of formula IB have been found particularly suitable for interfering with the replication of cytomegaloviruses. Both compounds of formula IA and IB have also the ability to interfere with the replication of varicella zoster virus.

Some of the compounds described herein may even be used to interfere with the replication of herpesviruses that show resistance to other antivirals including, acyclovir, ganciclovir and/or foscarnet.

The invention also provides chemical intermediates of formula IA¹, IA², IB¹ and IB² that may be used in the manufacture of compounds of formula IA or IB.

Methods for identifying a ligand capable of interacting with a herpesvirus DNA polymerase are also encompassed herewith. The method entails using computer-generated models of a putative ligand and of a HSV-1 DNA polymerase pocket that is located near its active site. Putative compounds that fit into the pocket may be selected according to an estimation of the free energy of ligand binding and hydrogen bonding potential of the ligand with the DNA polymerase.

The pocket of interest is delimited by residues Val715, Asp717, Ser720, Arg785, Lys811, Asn815, Tyr884 and Lys939. Selected compounds may be tested for their ability to interfere with the activity of the DNA polymerase (accession No. CAA32323). For example, the putative ligand may be obtained and tested for *in vitro* inhibition of replication of a herpesvirus using a method described herein. The present invention thus also relates to compounds that are selected by this method and that are capable of inhibiting viral replication.

BRIEF DESCRIPTION OF THE DRAWINGS

In drawings which illustrates non-limitative exemplary embodiments of the present invention,

Figure 1 is a schematic representation of the structure of HSV-1 DNA polymerase

docking cleft used in virtual screening experiments delimited by residues Val715, Asp717, Ser720, Arg785, Lys811, Asn815, Tyr884, Lys939;

Figure 2 is a table representing the high ranking compounds selected from virtual screening of the HSV-1 DNA polymerase active site near Mg^{2+} ;

- 5 **Figure 3** is a table showing the chemical structure of compounds having a high affinity with the viral DNA polymerase active site near Mg^{2+} ;

Figure 4A represents the structure of compound 2 derivatives;

Figure 4B represents the name of compound 2 derivatives;

- 10 **Figure 4C** is a table representing the result of the docking simulation of chemical compounds derived from compound 2 on HSV-1 DNA polymerase. Docking was done with GOLD v.3.2 software and compounds were ranked with ChemScore function;

Figure 5 represents the chemical structure of selected derivatives of compounds 2 and 3;

- 15 **Figure 6** shows histograms describing the toxicity of the most potent compounds 2 and 3 on Vero (A) and HFF (B) cells using a MTS assay.

Figure 7A Screening activity of compounds 1 to 8 against representative HSV-1 (A) and HSV-2 (B) strains;

- 20 **Figure 7B** Screening activity of compounds 1 to 8 against representative VZV (C) and CMV (D) strains;

Figure 8 is a table representing the IC_{50} values for the most potent compounds 2, 3 and 9 against herpesvirus reference strains;

Figure 9 is a table representing the antiviral activity of compound 2 against wild-type and drug-resistant HSV-1 clinical isolates and recombinant viruses;

- 25 **Figure 10** is a table representing the antiviral activity of compound 2 against wild-type and drug-resistant HSV-2 clinical isolates;

Figure 11 is a table representing the antiviral activity of compound 2 against a wild-type VZV strain and a drug-resistant VZV clinical isolate;

Figure 12 is a table representing the antiviral activity of compound 3 against wild-type and drug-resistant CMV clinical isolates;

- 5 **Figure 13** is a table representing the results of Parallel Artificial Membrane Permeability Assays (PAMPA) for compounds 2 and 3;

Figure 14 is a table representing the results of microsomal stability of compounds 2 and 3 using male rat liver microsomes;

- 10 **Figure 15** is a table representing the antiviral activity of compounds 2 and 3 derivatives against herpesvirus strains;

Figure 16 is a table representing the toxicity of compounds 2 and 3 and their derivatives for Vero cells and HFFs;

Figure 17 is a scheme representing the chemical synthesis of compound 2 and derivative compounds C2.05, C2.11, and C2.20, and;

- 15 **Figure 18** is a scheme representing the chemical synthesis of compound 3 and derivative compounds C3-1 and C3-2.

DETAILED DESCRIPTION OF THE INVENTION

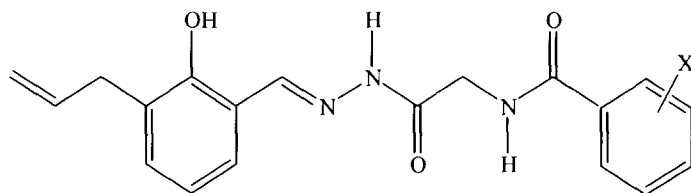
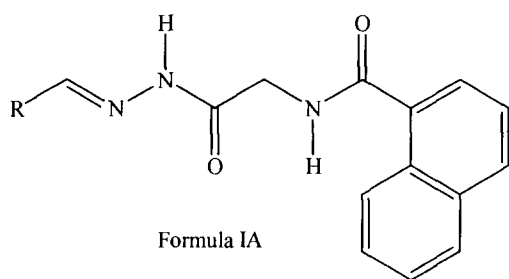
The present invention relates to compounds, pharmaceutical compositions comprising these compounds and their use in impairing or inhibiting herpesvirus replication.

- 20 Some of the compounds of the present are readily available to the public while others are new chemical entities.

- The present invention especially contemplates compounds that are new chemical entities. However, both new chemical entities and known compounds may be used in pharmaceutical compositions and in methods and uses for inhibiting herpesvirus replication.
- 25

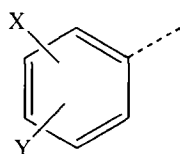
In an aspect, the present invention relates to a compound of formula IA or formula IB or a pharmaceutically acceptable salt thereof as well as pharmaceutical compositions

comprising such compounds and a pharmaceutically acceptable carrier;



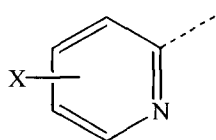
where R may be selected, for example, from the group consisting of :

- 5 **a)** unsubstituted benzyl or a substituted benzyl of formula II

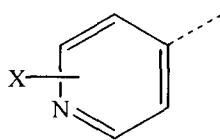


II;

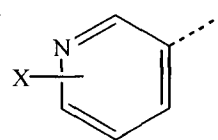
- b)** an unsubstituted pyridine or a substituted pyridine selected from the group consisting of:



,

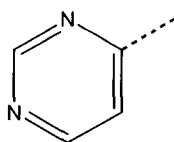


and

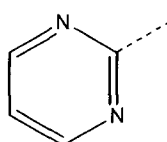


; and

- 10 **c)** a pyrimidine selected from the group consisting of



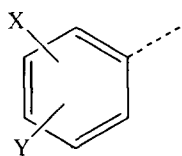
and



X and Y may each independently be selected from the group consisting of H, $-OR_1$, NH_2 , F, Cl, Br, I, an alkyl group of 1 to 3 carbon atoms and an allyl group, and;

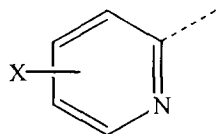
R_1 may be selected from the group consisting of H and an alkyl group of 1 to 3 carbon atoms.

- 5 In accordance with the present invention, the compound may be, for example, a compound of formula IA, wherein R may be selected, for example, from the group consisting of unsubstituted benzyl or a substituted benzyl of formula II:



II; and,

an unsubstituted pyridine or a substituted pyridine of formula:



10

wherein X and Y each may independently be selected from the group consisting of H, $-OR_1$, NH_2 , F, Cl, Br, I, an alkyl group of 1 to 3 carbon atoms and an allyl group and wherein R_1 may be selected from the group consisting of H and an alkyl group of 1 to 3 carbon atoms.

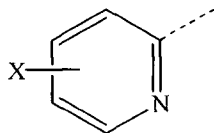
- 15 In accordance with an embodiment of the invention R may be a substituted benzyl of formula II, where X may be OR_1 and Y may be either F, OR_1 or H.

In accordance with a specific embodiment of the invention, X may be OH and Y may be F.

- 20 In accordance with another specific embodiment of the invention, X may be OH and Y may be H.

In accordance with yet another specific embodiment of the invention, X may be OR_1 and Y may be OH. In such instance R_1 may be, for example H or methyl.

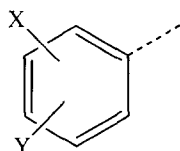
Also in accordance with the present invention, the compound may be, for example, a compound of formula IA, where R may be a substituted pyridine of formula



and where X is OR_1 .

- 5 In accordance with a specific embodiment of the invention, R_1 may be, for example, H.

In an exemplary embodiment, the compound of the present invention may be selected from those of formula IA, wherein R is a substituted benzyl of formula II:

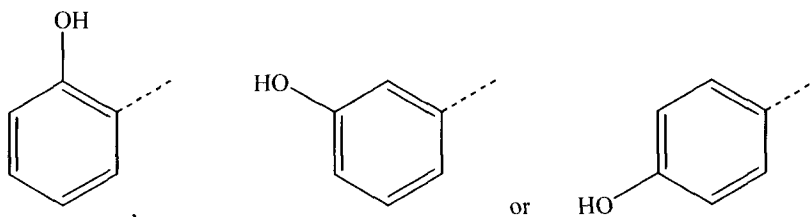


II

- 10 wherein X may be H or OR_1 and wherein Y is OH.

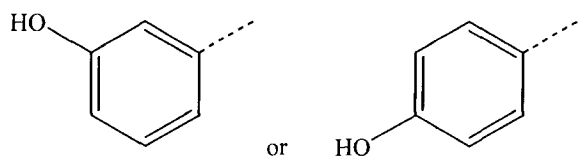
In accordance with a specific embodiment of the invention, X may be OR_1 while Y may be OH. In accordance with another specific embodiment of the invention, X may be H while Y may be OH. In accordance with yet another exemplary embodiment, X may be OMe while Y may be OH.

- 15 In another exemplary embodiment, the compound of the present invention is selected from those of formula IA, wherein R may be for example, a hydroxy-substituted benzyl of formula:

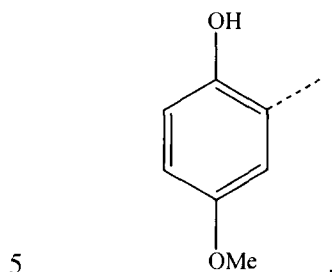


In accordance with a particular embodiment of the invention, R may be for instance, a

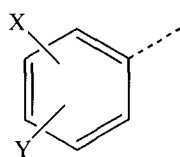
hydroxy-substituted benzyl of formula:



In accordance with another particular embodiment of the invention, R may be for instance a substituted benzyl of formula:



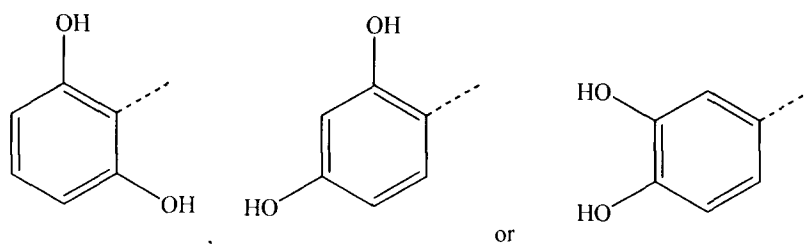
In an exemplary embodiment, the compound of the present invention may be selected from those of formula IA, wherein R is a substituted benzyl of formula II:



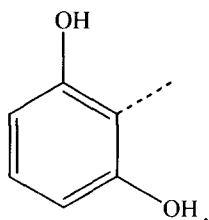
II

and wherein X and Y are both OH.

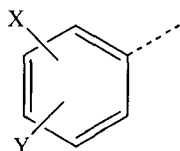
- 10 In accordance with an exemplary embodiment of the invention R may be a hydroxy-substituted benzyl of formula:



In accordance with a specific embodiment of the invention R may be for example, a hydroxy-substituted benzyl of formula,



In a further exemplary embodiment, the compound of the present invention may be selected from those of formula IA, wherein R is a substituted benzyl of formula II:

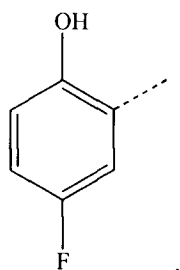


II

- 5 wherein X may be H or OH and wherein Y may be F, Cl, Br or I.

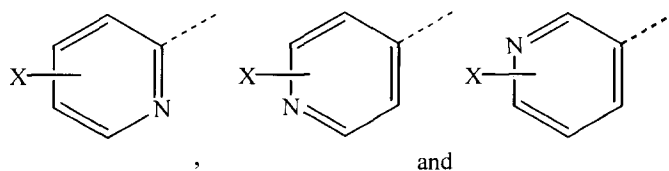
In accordance with a particular embodiment of the invention X may be OH while Y may be F.

In accordance with an exemplary embodiment of the invention R may be, for example a substituted benzyl of formula:



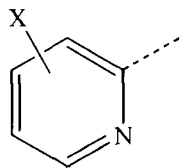
10

In an additional embodiment, the compound of the present invention may be selected from those of formula IA, wherein R is a substituted pyridine selected from the group consisting of:

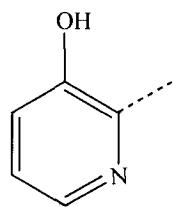


and wherein X is OH.

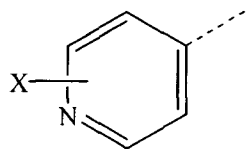
In an exemplary embodiment of the invention, R may be, for example, a substituted pyridine group of formula:



- 5 In accordance with the invention, X may be OH. The substituted pyridine group may thus be, for instance:

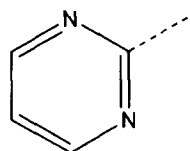


In another exemplary embodiment of the invention, R may be, for example, a substituted or unsubstituted (wherein X is H) pyridine of formula:



10

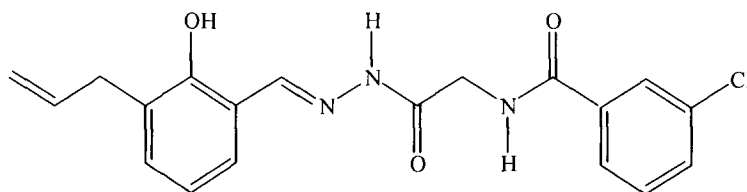
In yet another exemplary embodiment of the invention, R may be, for example, a pyrimidine group of formula:



- 15 In a further embodiment, the compound of the present invention may be selected from those of formula IB wherein X is of H, $-OR_1$, NH_2 , F, Cl, Br, I, an alkyl group of 1 to 3 carbon atoms and an allyl group and; wherein R_1 is selected from the group consisting of H and an alkyl group of 1 to 3 carbon atoms. In a particular

embodiment, X may be, for example, F, Cl, Br or I. In a more specific embodiment X may be Cl.

In accordance with an embodiment of the invention, the compound of formula IB may have the following formula:

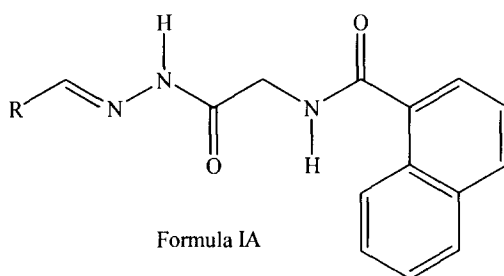


5

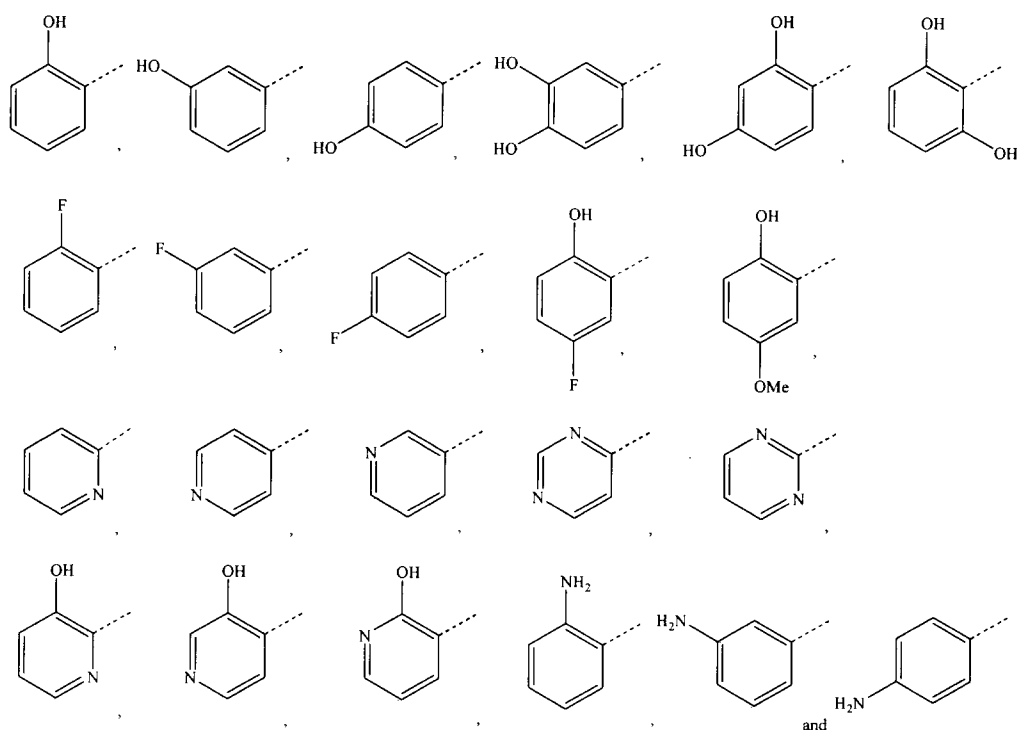
In some aspect of the invention including for example, pharmaceutical compositions, uses and methods, the compounds listed below or listed in Figure 2 may be included, while in other aspects (compounds *per se*) these compounds may, if desired, be excluded from the invention:

- 10 i. N-(2-(2-(2-hydroxybenzylidene) hydrazino)-2- oxoethyl)-1- naphthamide;
- ii. N-(2-(2-(2-hydroxy-5-methoxybenzylidene) hydrazino)-2- oxoethyl)-1- naphthamide, or
- 15 iii. N-(2-(2-(3- allyl -2- hydroxybenzylidene) hydrazino)-2- oxoethyl)-1- naphthamide.

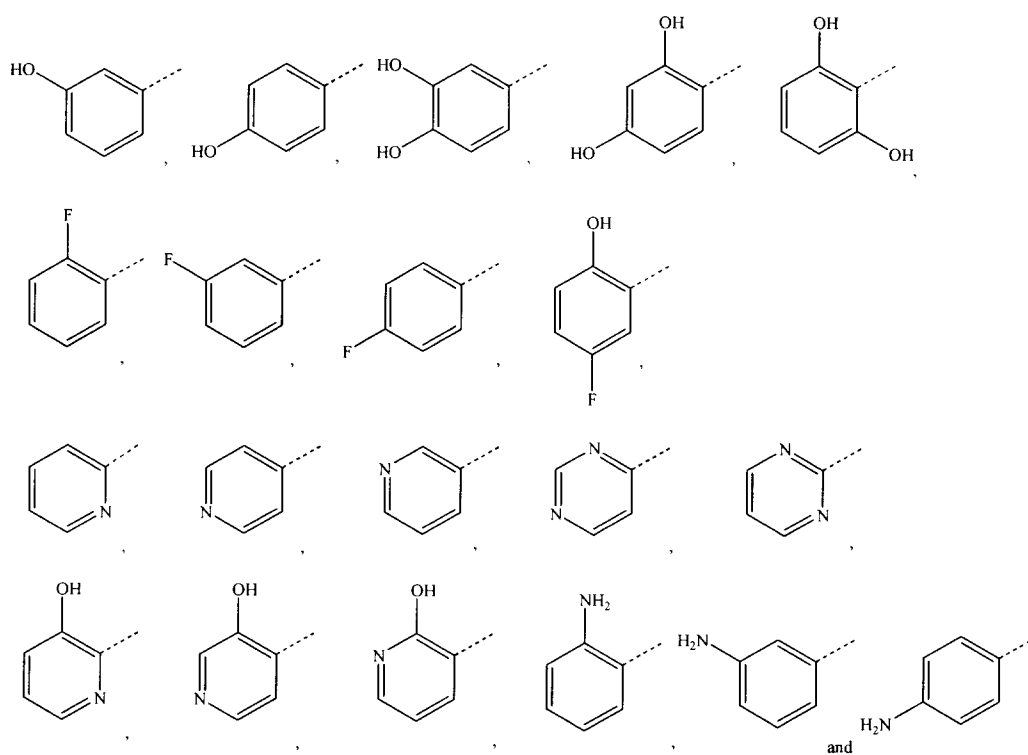
In another aspect the present invention provides a compound of formula IA or a pharmaceutically acceptable salt thereof,



wherein R may be selected, for example, from the group consisting of:

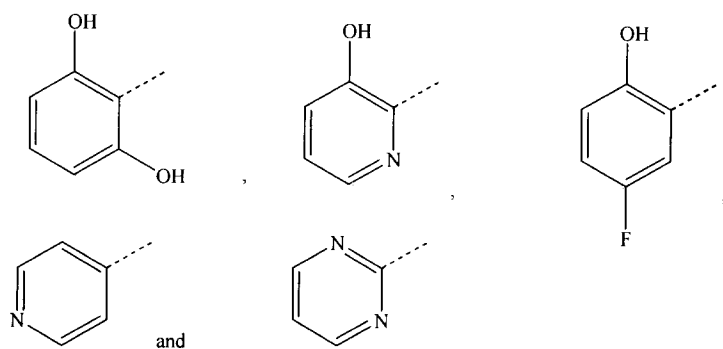


In accordance with an embodiment of the invention, R may be more particularly selected from the group consisting of :

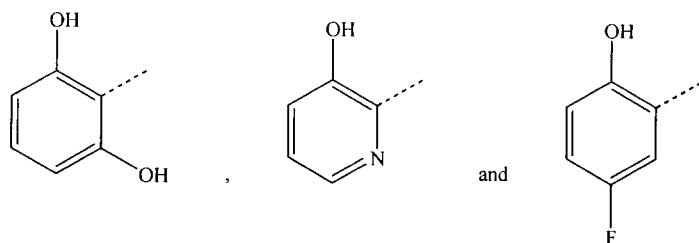


5 In accordance with a specific embodiment of the invention, R may be more

particularly selected from the group consisting of:



In accordance with another specific embodiment of the invention, R may be more particularly selected from the group consisting of:



5

In a further aspect, the present invention relates to the use of the compounds of formula IA and/or formula IB or other compounds as described herein for interfering with (e.g., treating, preventing) a herpesvirus replication. Compounds of the present invention may found particular use in the inhibition of herpesvirus replication, thereby reducing the viral load. The compounds of formula IA and/or IB described herein may be capable of interacting with the DNA polymerase of some herpesviruses and thereby impairing the activity of the DNA polymerase.

Some of the compounds described herein may be suitable for interfering with the replication of herpesvirus such as herpes simplex 1, herpes simplex 2, cytomegalovirus and/or varicella zoster virus.

15

For instance, some compounds of formula IA or pharmaceutically acceptable salts have a better activity against herpes simplex 1 and/or herpes simplex 2 and may thus be particularly suitable to inhibit the replication of these herpesviruses.

Some compounds of formula IA or their pharmaceutically acceptable salts have also been found suitable for inhibiting the replication of herpesviruses that are

20

characterized as being resistant to a nucleoside analogue and/or a pyrophosphate analogue.

- For example, some compounds of formula IA or their pharmaceutically acceptable salts have also been found suitable for inhibiting the replication of herpesviruses that are characterized as being resistant to foscarnet or resistant to a nucleoside analogue acyclovir and/or foscarnet. as well as to foscarnet.

Compounds of formula IB or pharmaceutically acceptable salts have a better activity against cytomegalovirus and may thus be particularly suitable to inhibit the replication of this herpesvirus.

- It has also been found that some compounds of formula IB or their pharmaceutically acceptable salts may be capable of impairing the replication of viruses that are otherwise resistant to a nucleoside analogue and/or a pyrophosphate analogue.

- For example, some compounds of formula IB or their pharmaceutically acceptable salts have been found suitable for inhibiting the replication of herpesviruses that are resistant to ganciclovir and/or foscarnet.

In an additional aspect, the present invention provides a pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt thereof of formula IA or IB or any other compounds described herein and a pharmaceutically acceptable carrier.

- Such pharmaceutical composition may be used for interfering with herpesvirus replication. The herpesviruses that are more specifically targeted are for example, herpes simplex 1, herpes simplex 2, cytomegalovirus and varicella-zoster. However, other herpesviruses may be targeted such as herpesvirus type 6, 7 and 8 as well as Epstein Barr virus.
- Pharmaceutical composition comprising compounds of formula IA may be suitable for impairing the replication of herpes simplex 1 or herpes simplex 2 as well as varicella-zoster virus. Such pharmaceutical composition may also be suitable for impairing the replication of herpesviruses (e.g., HSV-1, HSV-2, VZV) that are characterized as being resistant to acyclovir and/or foscarnet.

Pharmaceutical composition comprising compounds of formula IB may be suitable for impairing the replication of cytomegalovirus. Such pharmaceutical composition may also be suitable for impairing the replication of cytomegaloviruses that are characterized as being resistant to ganciclovir and/or foscarnet.

- 5 In a further aspect, the present invention provides a method of treating or preventing a herpesvirus infection. The method may comprise administering a compound or a pharmaceutically acceptable salt thereof of formula IA or IB or any other compounds described herein to a mammal in need.

10 In accordance with the invention, the mammal in need may be immunocompetent or may be immunocompromised.

For example, immunocompromised individuals who may benefit from such treatment are those who suffer from HIV-infection or neoplasia or transplant recipients.

15 The method of the present invention may be particularly useful for treating or preventing infections in mammals which are infected with herpesviruses including those who suffer from chickenpox or shingles associated with varicella-zoster virus, oro-labial or genital infection associated with HSV-1 or HSV-2 or pneumonitis, colitis or retinitis associated with cytomegalovirus.

20 In accordance with the present invention, the mammal may be infected with or is suffering from an infection caused by herpes simplex 1, herpes simplex 2, cytomegalovirus or varicella-zoster virus.

25 Methods of treatment of the present invention entail administering, for example, a compound of formula IA or a pharmaceutically acceptable salt to a mammal suffering from an infection with herpes simplex 1 or herpes simplex 2. Methods of treatment with compounds of formula IA may be particularly suitable for treating a mammal having a virus that is resistant to treatment with acyclovir or acyclovir prodrug and/or foscarnet.

Other methods of treatment of the present invention entail administering, for example, a compound of formula IB or a pharmaceutically acceptable salt to a mammal suffering from an infection with cytomegalovirus. Methods of treatment with

compounds of formula IB may be particularly suitable for treating a mammal having a virus that is resistant to treatment with ganciclovir or a ganciclovir prodrug and/or foscarnet.

In yet a further aspect, the present invention provides a method for interfering with the replication of a herpesvirus from a cell. The method may comprise contacting a cell
5 infected by the herpesvirus (or susceptible to being infected by the herpesvirus) with a compound of formula IA or IB or a pharmaceutically acceptable salt thereof as defined herein. Again, such method is particularly beneficial for interfering with the replication of herpes simplex 1, herpes simplex 2, cytomegalovirus and varicella
10 zoster virus.

The method may be carried out by contacting a cell infected or susceptible to being infected with herpes simplex 1 or herpes simplex 2, with a compound of formula IA. Such method may be carried out for viruses that are resistant to acyclovir and/or foscarnet.

15 The method may also be carried out by contacting a cell infected or susceptible to being infected with a cytomegalovirus, with a compound of formula IB. Such method may be carried out for viruses that are resistant to ganciclovir and/or foscarnet.

In yet a further aspect, the present invention provides a method for identifying a ligand capable of interfering with the replication of herpesvirus. The method may
20 comprise docking a computer-generated model of a putative ligand onto a computer-generated model of a pocket located near the active site of a HSV-1 DNA polymerase (in a non-replicating state), and selecting compounds according to an estimation of a ChemScore. Ligands with lowest free binding energy and higher hydrogen bonding potential to the DNA polymerase are selected for *in vitro* tests.

25 The pocket is delimited by residues Val715, Asp717, Ser720, Arg785, Lys811, Asn815, Tyr884 and Lys939 and therefore compounds that can fit into this pocket may be identified as putative ligand of the DNA polymerase and may also potentially interfere with the activity of this enzyme.

The putative ligand may be obtained and tested for *in vitro* inhibition of herpesvirus
30 replication using a method described herein.

Other aspects of the invention relates to a ligand obtained by the method described herein. Such ligand may potentially be used for inhibiting herpesvirus replication.

In another aspect, the present invention relates to a pharmaceutical composition comprising a compound selected, for example, from the group consisting of:

- 5 N-(2-(2-(2-hydroxy-5-methoxybenzylidene) hydrazino)-2-oxoethyl)-3-methylbenzamide;
- N-(2-(2-(2-hydroxybenzylidene) hydrazino)-2-oxoethyl)-1-naphthamide;
- N-(2-(2-(3-allyl-2-hydroxybenzylidene) hydrazino)-2-oxoethyl)-3-chlorobenzamide;
- N-[2-(4-methoxyphenyl)ethyl]-2-[(1-phenyl-1H-tetrazol-5-yl)thio]acetamide;
- 10 1-(2-chloro-5-nitrophenyl)iminomethyl)-2-naphthol;
- N-1H-tetrazol-5-yl-4-biphenylcarboxamide;
- 9-anthracenecarbaldehyde 1H-tetrazol-5-ylhydrazone;
- N-[(2-methyl-2H-tetrazol-5-yl) amino]carbonothioyl}-2-thiophenecarboxamide;
- 15 N-(2-(2-(2-hydroxy-5-methoxybenzylidene)hydrazino)-2-oxoethyl)-1-naphthamide;
- N-(2-(2-(3-allyl-2-hydroxybenzylidene) hydrazino)-2-oxoethyl)-2-chlorobenzamide;
- N-(2-(2-(3-allyl-2-hydroxybenzylidene) hydrazino)-2-oxoethyl)-4-chlorobenzamide;
- 20 N-(2-(2-(3-allyl-2-hydroxybenzylidene) hydrazino)-2-oxoethyl)-1-naphthamide;
- (E)-N-(2-(2-(2-hydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- (E)-N-(2-(2-(3-hydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- 25 (E)-N-(2-(2-(4-hydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- (E)-N-(2-(2-(3,4-dihydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- (E)-N-(2-(2-(2,4-dihydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- 30 (E)-N-(2-(2-(2,6-dihydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;

- (E)-N-(2-oxo-2-(2-(pyrimidin-4-ylmethylene)hydrazinyl)ethyl)-1-naphthamide;
- (E)-N-(2-oxo-2-(2-(pyridin-2-ylmethylene)hydrazinyl)ethyl)-1-naphthamide;
- (E)-N-(2-oxo-2-(2-(pyridin-4-ylmethylene)hydrazinyl)ethyl)-1-naphthamide;
- 5 (E)-N-(2-oxo-2-(2-(pyridin-3-ylmethylene)hydrazinyl)ethyl)-1-naphthamide;
- (E)-N-(2-oxo-2-(2-(pyrimidin-2-ylmethylene)hydrazinyl)ethyl)-1-naphthamide;
- (E)-N-(2-(2-((3-hydroxypyridin-2-yl)methylene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- 10 (E)-N-(2-(2-((3-hydroxypyridin-4-yl)methylene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- (E)-N-(2-(2-((2-hydroxypyridin-3-yl)methylene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- (E)-N-(2-(2-(2-aminobenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- 15 (E)-N-(2-(2-(3-aminobenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- (E)-N-(2-(2-(4-aminobenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- (E)-N-(2-(2-(2-fluorobenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- (E)-N-(2-(2-(3-fluorobenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- (E)-N-(2-(2-(4-fluorobenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- 20 (E)-N-(2-(2-(5-fluoro-2-hydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide, and;
- (E)-N-(2-(2-(2-hydroxy-5-methoxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide

and a pharmaceutically acceptable carrier.

- 25 Such pharmaceutical compositions may be used, for example, for interfering with the replication of herpesvirus as described herein.

- In yet another aspect, the present invention relates to the use of a compound of formula IA or IB for interfering with herpesviruses replication or the use of such compound in the manufacture of a medicament for interfering with herpesviruses replication. In exemplary embodiments of the invention, the compound comprises
- 30 formula IA or IB or may be selected, for example, from the group consisting of:

- N-(2-(2-(2-hydroxy-5-methoxybenzylidene) hydrazino)-2-oxoethyl)-3-methylbenzamide;
- N-(2-(2-(2-hydroxybenzylidene) hydrazino)-2-oxoethyl)-1-naphthamide;
- N-(2-(2-(3-allyl-2-hydroxybenzylidene) hydrazino)-2-oxoethyl)-3-chlorobenzamide;
- 5 N-[2-(4-methoxyphenyl)ethyl]-2-[(1-phenyl-1H-tetrazol-5-yl)thio]acetamide;
- 1-(2-chloro-5-nitrophenyliminomethyl)-2-naphthol;
- N-1H-tetrazol-5-yl-4-biphenylcarboxamide;
- 9-anthracenecarbaldehyde 1H-tetrazol-5-ylhydrazone;
- 10 N-[(2-methyl-2H-tetrazol-5-yl) amino]carbonothioyl}-2-thiophenecarboxamide;
- N-(2-(2-(2-hydroxy-5-methoxybenzylidene)hydrazino)-2-oxoethyl)-1-naphthamide;
- N-(2-(2-(3-allyl-2-hydroxybenzylidene) hydrazino)-2-oxoethyl)-2-chlorobenzamide;
- 15 N-(2-(2-(3-allyl-2-hydroxybenzylidene) hydrazino)-2-oxoethyl)-4-chlorobenzamide;
- N-(2-(2-(3-allyl-2-hydroxybenzylidene) hydrazino)-2-oxoethyl)-1-naphthamide;
- (E)-N-(2-(2-(2-hydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- 20 (E)-N-(2-(2-(3-hydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- (E)-N-(2-(2-(4-hydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- (E)-N-(2-(2-(3,4-dihydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- 25 (E)-N-(2-(2-(2,4-dihydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- (E)-N-(2-(2-(2,6-dihydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- (E)-N-(2-oxo-2-(2-(pyrimidin-4-ylmethylene)hydrazinyl)ethyl)-1-naphthamide;
- 30 (E)-N-(2-oxo-2-(2-(pyridin-2-ylmethylene)hydrazinyl)ethyl)-1-naphthamide;
- (E)-N-(2-oxo-2-(2-(pyridin-4-ylmethylene)hydrazinyl)ethyl)-1-naphthamide;
- (E)-N-(2-oxo-2-(2-(pyridin-3-ylmethylene)hydrazinyl)ethyl)-1-naphthamide;

- (E)-N-(2-oxo-2-(2-(pyrimidin-2-ylmethylene)hydrazinyl)ethyl)-1-naphthamide;
- (E)-N-(2-(2-((3-hydroxypyridin-2-yl)methylene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- 5 (E)-N-(2-(2-((3-hydroxypyridin-4-yl)methylene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- (E)-N-(2-(2-((2-hydroxypyridin-3-yl)methylene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- (E)-N-(2-(2-(2-aminobenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- 10 (E)-N-(2-(2-(3-aminobenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- (E)-N-(2-(2-(4-aminobenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- (E)-N-(2-(2-(2-fluorobenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- (E)-N-(2-(2-(3-fluorobenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- (E)-N-(2-(2-(4-fluorobenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- 15 (E)-N-(2-(2-(5-fluoro-2-hydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide, and;
- (E)-N-(2-(2-(2-hydroxy-5-methoxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide.

- In another aspect, the present invention relates to a method for interfering with
- 20 herpesviruses replication from (in) a cell. The method may comprise contacting a cell infected by the herpesvirus with a compound of formula IA or IB or a compound selected from the group consisting of:

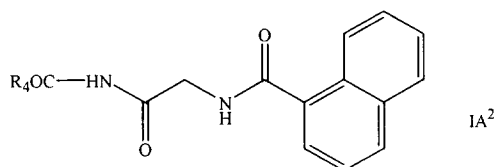
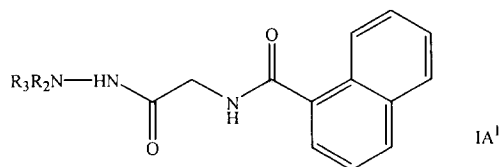
- N-(2-(2-(2-hydroxy-5-methoxybenzylidene) hydrazino)-2-oxoethyl)-3-methylbenzamide;
- 25 N-(2-(2-(2-hydroxybenzylidene) hydrazino)-2-oxoethyl)-1-naphthamide;
- N-(2-(2-(3-allyl-2-hydroxybenzylidene) hydrazino)-2-oxoethyl)-3-chlorobenzamide;
- N-[2-(4-methoxyphenyl)ethyl]-2-[(1-phenyl-1H-tetrazol-5-yl)thio]acetamide;
- 1-(2-chloro-5-nitrophenyliminomethyl)-2-naphthol;
- N-1H-tetrazol-5-yl-4-biphenylcarboxamide;
- 30 9-anthracenecarbaldehyde 1H-tetrazol-5-ylhydrazone;

- N-{[(2-methyl-2H-tetrazol-5-yl) amino]carbonothioyl}-2-thiophenecarboxamide;
- N-(2-(2-(2-hydroxy-5-methoxybenzylidene)hydrazino)-2-oxoethyl)-1-naphthamide;
- 5 N-(2-(2-(3- allyl -2- hydroxybenzylidene) hydrazino)-2-oxoethyl)-2-chlorobenzamide;
- N-(2-(2-(3- allyl -2- hydroxybenzylidene) hydrazino)-2-oxoethyl)-4-chlorobenzamide;
- 10 N-(2-(2-(3- allyl -2- hydroxybenzylidene) hydrazino)-2- oxoethyl)-1-naphthamide;
- (E)-N-(2-(2-(2-hydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- (E)-N-(2-(2-(3-hydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- (E)-N-(2-(2-(4-hydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- 15 (E)-N-(2-(2-(3,4-dihydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- (E)-N-(2-(2-(2,4-dihydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- (E)-N-(2-(2-(2,6-dihydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- 20 (E)-N-(2-oxo-2-(2-(pyrimidin-4-ylmethylene)hydrazinyl)ethyl)-1-naphthamide;
- (E)-N-(2-oxo-2-(2-(pyridin-2-ylmethylene)hydrazinyl)ethyl)-1-naphthamide;
- (E)-N-(2-oxo-2-(2-(pyridin-4-ylmethylene)hydrazinyl)ethyl)-1-naphthamide;
- (E)-N-(2-oxo-2-(2-(pyridin-3-ylmethylene)hydrazinyl)ethyl)-1-naphthamide;
- 25 (E)-N-(2-oxo-2-(2-(pyrimidin-2-ylmethylene)hydrazinyl)ethyl)-1-naphthamide;
- (E)-N-(2-(2-((3-hydroxypyridin-2-yl)methylene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- 30 (E)-N-(2-(2-((3-hydroxypyridin-4-yl)methylene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- (E)-N-(2-(2-((2-hydroxypyridin-3-yl)methylene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- (E)-N-(2-(2-(2-aminobenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;

- (E)-N-(2-(2-(3-aminobenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
 (E)-N-(2-(2-(4-aminobenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
 (E)-N-(2-(2-(2-fluorobenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
 (E)-N-(2-(2-(3-fluorobenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
 5 (E)-N-(2-(2-(4-fluorobenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
 (E)-N-(2-(2-(5-fluoro-2-hydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide, and;
 (E)-N-(2-(2-(2-hydroxy-5-methoxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide.
- 10 In yet another aspect, the present invention provides a method of treating herpesvirus infection. The method may comprise administering a compound or a pharmaceutically acceptable salt thereof to a mammal in need. The compound or salt may comprise formula IA or IB or may be selected from the group consisting of :
- 15 N-(2-(2-(2-hydroxy-5-methoxybenzylidene) hydrazino)-2-oxoethyl)-3-methylbenzamide;
 N-(2-(2-(2-hydroxybenzylidene) hydrazino)-2-oxoethyl)-1-naphthamide;
 N-(2-(2-(3-allyl-2-hydroxybenzylidene) hydrazino)-2-oxoethyl)-3-chlorobenzamide;
 N-[2-(4-methoxyphenyl)ethyl]-2-[(1-phenyl-1H-tetrazol-5-yl)thio]acetamide;
 1-(2-chloro-5-nitrophenyl)iminomethyl)-2-naphthol;
 20 N-1H-tetrazol-5-yl-4-biphenylcarboxamide;
 9-anthracenecarbaldehyde 1H-tetrazol-5-ylhydrazone;
 N-[(2-methyl-2H-tetrazol-5-yl) amino]carbonothioyl)-2-thiophenecarboxamide;
 25 N-(2-(2-(2-hydroxy-5-methoxybenzylidene)hydrazino)-2-oxoethyl)-1-naphthamide;
 N-(2-(2-(3-allyl-2-hydroxybenzylidene) hydrazino)-2-oxoethyl)-2-chlorobenzamide;
 N-(2-(2-(3-allyl-2-hydroxybenzylidene) hydrazino)-2-oxoethyl)-4-chlorobenzamide;
 30 N-(2-(2-(3-allyl-2-hydroxybenzylidene) hydrazino)-2-oxoethyl)-1-naphthamide;

- (E)-N-(2-(2-(2-hydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
(E)-N-(2-(2-(3-hydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
(E)-N-(2-(2-(4-hydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
5 (E)-N-(2-(2-(3,4-dihydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
(E)-N-(2-(2-(2,4-dihydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
(E)-N-(2-(2-(2,6-dihydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
10 (E)-N-(2-oxo-2-(2-(pyrimidin-4-ylmethylene)hydrazinyl)ethyl)-1-naphthamide;
(E)-N-(2-oxo-2-(2-(pyridin-2-ylmethylene)hydrazinyl)ethyl)-1-naphthamide;
(E)-N-(2-oxo-2-(2-(pyridin-4-ylmethylene)hydrazinyl)ethyl)-1-naphthamide;
(E)-N-(2-oxo-2-(2-(pyridin-3-ylmethylene)hydrazinyl)ethyl)-1-naphthamide;
15 (E)-N-(2-oxo-2-(2-(pyrimidin-2-ylmethylene)hydrazinyl)ethyl)-1-naphthamide;
(E)-N-(2-(2-((3-hydroxypyridin-2-yl)methylene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
(E)-N-(2-(2-((3-hydroxypyridin-4-yl)methylene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
20 (E)-N-(2-(2-((2-hydroxypyridin-3-yl)methylene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
(E)-N-(2-(2-(2-aminobenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
(E)-N-(2-(2-(3-aminobenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
25 (E)-N-(2-(2-(4-aminobenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
(E)-N-(2-(2-(2-fluorobenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
(E)-N-(2-(2-(3-fluorobenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
(E)-N-(2-(2-(4-fluorobenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
(E)-N-(2-(2-(5-fluoro-2-hydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide, and;
30 (E)-N-(2-(2-(2-hydroxy-5-methoxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide.

Further aspects of the invention relates to compounds that may be useful in the manufacture of the compounds of formula IA described herein. Such compounds may have, for example, formula IA¹ or IA² :

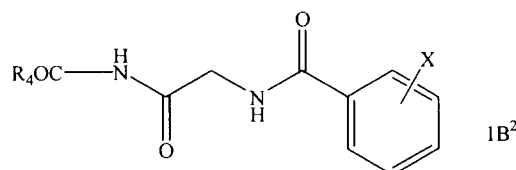
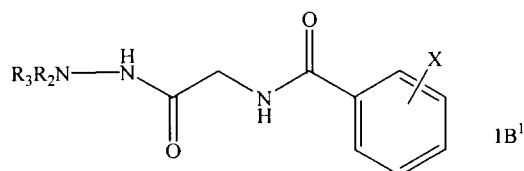


- 5 where R₂ and R₃ may independently be H or an alkyl group of 1 to 6 carbon atoms and;

where R₄ may be, for example H or an alkyl group of 1 to 6 carbon atoms.

- Yet further aspects of the invention encompass the use of the compounds of formula IA¹ and IA² in the manufacture of a herpesvirus DNA polymerase ligand or in the manufacture of a herpesvirus inhibitor, especially inhibitors of herpes simplex 1, herpes simplex 2, varicella zoster virus or cytomegalovirus. Compounds of formulas IA¹ or IA² may be used for the manufacture of a compound of formula IA.
- 10

- Further aspects of the invention relates to compounds that may be useful in the manufacture of the compounds of formula IB. Such compounds may have, for example, formula IB¹ or IB² :
- 15



where R₂ and R₃ may independently be H or an alkyl group of 1 to 6 carbon atoms;

wherein R₄ may be, for example H or an alkyl group of 1 to 6 carbon atoms;

where X may be selected, for example, from the group consisting of H, -OR₁, NH₂, F,
5 Cl, Br, I, an alkyl group of 1 to 3 carbon atoms and an allyl group and;

where R₁ may be selected from the group consisting of H or an alkyl group of 1 to 3 carbon atoms.

Yet further aspects of the invention encompass the use of the compounds of formula IB¹ and IB² in the manufacture of a herpesvirus DNA polymerase ligand or in the
10 manufacture of a herpesvirus inhibitor, especially inhibitors of herpes simplex 1, herpes simplex 2, varicella zoster virus or cytomegalovirus. Compounds of formulas IB¹ or IB² may be used for the manufacture of a compound of formula IB.

In an additional aspect, the present invention relates to the use of a compound of formula IA or IB in the manufacture of a herpesvirus DNA polymerase ligand or a
15 herpesvirus inhibitor.

As used herein, the term “lower alkyl” can be straight-chain or branched having from 1 to 6 carbon atoms.

It is to be understood herein that a “straight alkyl group of 1 to 6 carbon atoms” includes for example, methyl, ethyl, propyl, butyl, pentyl, hexyl.

20 It is to be understood herein that a “branched alkyl group of 3 to 6 carbon atoms” includes for example, without limitation, *iso*-butyl, *tert*-butyl, 2-pentyl, 3-pentyl, etc.

It is to be understood herein, that a "cycloalkyl group having 3 to 6 carbon" includes for example, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl (i.e., C₆H₁₁).

Salts derived from appropriate bases include alkali metal (e.g., sodium), alkaline earth metal (e.g., magnesium), ammonium and N - (C₁₋₄ alkyl)₄⁺ salts.

The compounds of this invention contain one or more asymmetric carbon atoms and thus may occur as racemates and racemic mixtures, single enantiomer, diastereomeric mixtures and individual diastereoisomers. All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic carbon may be of the *R* or *S* configuration.

Pharmaceutically acceptable salts of the compounds of this invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of such acid salts include: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylhydrogensulfate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycollate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, malonate, methanesulfonate, 2-naphthylsulfonate, nicotinate, nitrate, oxalate, pamoate, pectinate, perchlorate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, thiocyanate, tosylate, and undecanoate.

Examples of base addition salts include but are not limited to alkali metal salts and alkaline earth metal salts. Non-limiting examples of alkali metal salts include lithium, sodium and potassium salts. Non-limiting examples of alkaline earth metal salts include magnesium and calcium salts.

This invention also envisions the quaternization of any basic nitrogen containing groups of the compounds disclosed herein. The basic nitrogen may be quaternized with any agents known to those of ordinary skill in the art including, for example, lower alkyl halides, such as methyl, ethyl, propyl and butyl chlorides, bromides and iodides; dialkyl sulfates including dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and

iodides, and aralkyl halides including benzyl and phenethyl bromides. Water or oil-soluble or dispersible products may be obtained by such quaternization.

Pharmaceutically acceptable carrier includes for example and without limitation alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, 5 buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethyleneglycol, sodium carboxymethylcellulose, polyacrylates, waxes, 10 polyoxyethylene-polyoxypropylene-block copolymers, and polyethylene glycol.

EXAMPLE 1

Materials and Methods

To discover new viral DNA polymerase inhibitors, we used a rational approach called structure-based inhibitor design.

15 *Docking site selection and pre-docking preparation:* The recently-determined 3D model of CMV DNA pol determined by our group [8] and the recent crystal structure of HSV-1 DNA polymerase (pdb id 2GV9) [9] served as receptors for docking. Hydrophobic pockets on the crystal structure of the HSV-1 DNA polymerase in non-replicating state (pdb 2GV9) [9] were calculated with the Site Finder application 20 under Molecular Application Environment (MOE) program (Chemical Computing Group, Montreal, Canada), and ranked according to their hydrophobic contacts and their location. Two magnesium atoms that were missing in the crystal structure coordinates of HSV1 DNA polymerase (2GV9) were modeled in the catalytic site. Water molecules were removed and hydrogen atoms were added, and the protein was 25 inspected visually for accuracy in the χ_2 dihedral angle of Asn and His residues and the χ_3 angle of Gln, and rotated by 180 degree when needed to maximize hydrogen bonding. The proper His tautomer was also manually selected to maximize hydrogen bonding. All Asp, Glu, Arg and Lys were usually left in their charged state.

Ligand docking in the DNA pol selected docking site was carried out with the GOLD 30 version 3.2 [10]. Ligand and side-chain flexibility was allowed during docking. The

ChemScore function estimates the free energy of ligand binding to a protein as follows: $\text{ChemScore} = \Delta G_{\text{binding}} + P_{\text{clash}} + c_{\text{internal}} P_{\text{internal}} + (P_{\text{covalent}} C_{\text{covalent}} + P_{\text{constraint}})$ with $\Delta G_{\text{binding}} = \Delta G_o + \Delta G_{\text{hbond}} S_{\text{hbond}} + \Delta G_{\text{metal}} S_{\text{metal}} + \Delta G_{\text{lipo}} S_{\text{lipo}} + \Delta G_{\text{rot}} H_{\text{rot}}$, where S_{hbond} , S_{metal} , and S_{lipo} are scores for hydrogen bonding, acceptor-metal, and lipophilic interactions, respectively. H_{rot} represents the loss of conformational entropy of the ligand upon binding to the protein [11].

Virtual Screening: A free public database “ZINC 6” [12] was selected for virtual screening. A subset of 128 000 compounds with drug-like properties satisfying the Lipinski rules of 5 [13] was selected. The database was used for virtual screening into the selected docking site and the compounds were scored according to ChemScore function [11]. In the docking simulation with HSV-1 DNA pol, compounds were ranked according to the ChemScore and hydrogen bonding potential.

Antiviral compounds: Top leading compounds were purchased from Sigma-Aldrich or ChemBridge for *in vitro* testing. On the day of the assay, compounds were prepared in DMSO at a concentration of 10 mM. Stock solutions were then diluted in Eagle’s minimal essential medium (MEM) to the appropriate concentrations. ACV, GCV and FOS (prepared in MEM) were used as comparators for susceptible and resistant recombinant viruses and clinical isolates.

Cells and viruses: Human foreskin fibroblasts (HFFs) and African green monkey kidney cells (Vero) were grown in MEM supplemented with 10% fetal bovine serum. Cells were maintained at 37°C in a humidified 5% CO₂ atmosphere. Vero cells and HFFs were used for propagation of viral strains and susceptibility assays for HSV-1/HSV-2 and VZV/CMV, respectively. Clinical strains H25 (HSV-1), HSV22 (HSV-2) as well as laboratory strains KOS (HSV-1), Ellen (VZV) and AD169 (CMV) were used as wild-type susceptible reference isolates. Clinical strains C119629 (HSV-1), C114093 (HSV-1), C80249 (HSV-1), L920062 (HSV-1), MS2 (HSV-2), C75134 (HSV-2), W-940012 (HSV-2), C72984 (HSV-2), D-900180 (HSV-2), M-890546 (HSV-2), P-920056 (HSV-2) and GB2000VZV (VZV) as well as laboratory strains Xbaf (CMV) and VQA3 (CMV) were used as drug (ACV/GCV/FOS)- resistant isolates [14-16]. All clinical strains starting with the letter C originated from the Quebec City clinical virology laboratory.

Cytotoxicity assays: Toxicity of compounds 1 to 8 as well as derivatives of compounds 2 and 3 was assessed on Vero cells and HFFs using the CellTiter 96 Aqueous Non-Radioactive Cell Proliferation Assay protocol (Promega, Madison, Wis). This assay is based on the use of solutions of a tetrazolium salt (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulphophenyl)-2H-tetrazolium, inner salt; MTS) and an electron coupling reagent (phenazine methosulfate; PMS). The tetrazolium salt is reduced by living cells to yield a formazan product that can be assayed colorimetrically. Briefly, HFFs and Vero cells were seeded in 96-well plates. After 24 h, media was aspirated and 100 µl of compounds diluted in MEM at concentrations up to 100 µM were added to wells in quadruplicate. After incubation at 37°C for 3 days, 10 µl of a solution of MTS and PMS were added to each well. The plates were incubated at 37°C for 2 h. The absorbance of the supernatant was read at a wavelength of 492 nm to measure cell viability compared to no-drug control wells. The drug concentration was plotted against the optical density of each sample and cellular toxicity (CC₅₀) was calculated using GraphPad Prism version 5.0 (GraphPad Inc., La Jolla, CA, USA).

Antiviral assays: Antiviral activity of compounds 1 to 8 was first tested at two concentrations, i.e. 1 µM and 10 µM, along with currently-available first-line drugs (ACV for HSV/VZV and GCV for CMV). Then, 50% inhibitory concentration (IC₅₀) values were determined for the top leading compounds in comparison with ACV, GCV and FOS using a standard plaque reduction assay (PRA) [17]. Briefly, Vero cells or HFFs seeded in 24-well plates were inoculated with 40 plaque forming units (PFUs) of recombinant viruses or clinical isolates. Infected cells were incubated with serial drug concentrations for appropriate periods of time. Cells were fixed and stained. The number of plaques was counted in each well and expressed in percentage of the PFUs in no-drug control wells. Recombinant and clinical viral strains were considered resistant to a drug if their IC₅₀ values were at least 2.5 times greater than that of the representative wild-type strains.

Microsomal stability: Sprague-Dawley rat liver microsomes (concentration 1 mg/ml) were incubated at 37°C with 2 µM of compounds 2 or 3 in PBS containing 5 mM MgCl₂ and 1 mM NADPH. The antihypertensive drug reserpine was used as a reference compound. Aliquots of 50 µl were withdrawn at different time intervals and

- placed in 96-well plates containing 50 μL of acetonitrile on ice. Samples were then mixed and centrifuged at 3000 rpm and 10 μL were injected in a liquid chromatography system (Agilent 1100 Binary Pumps). The aliquots from liquid chromatography were subjected to mass spectrometry analysis on SCIEX API4000
- 5 with TurboIonSpray ionization source to determine the remaining percentage of the parent compound. Intrinsic clearance (Cl_{int}) estimates were determined using the rate of parent compound disappearance. The slope ($-k$) was determined by linear regression analysis from the linear portion of the natural logarithm of the test compound concentration *versus* time plot. The elimination rate constant ($t_{1/2}$) was
- 10 calculated according to $k = \ln 2/t_{1/2}$. The microsomal Cl_{int} can be derived from the equation $\text{Cl}_{\text{int}} = kV/f_u$ (mL/min/mg protein) where f_u is the unbound fraction and V is the volume of the incubation expressed in milliliters per mg of microsomal protein. As f_u is not known for the tested compounds, the calculation was performed with $f_u=1$ (V). The Cl_{int} was also extrapolated to the whole liver protein.
- 15 *Membrane permeability measurement:* Passive membrane permeability was determined using Parallel Artificial Membrane Permeability Assay (PAMPA) [18]. Initial concentrations of compounds 2 and 3 used for this assay were 37 and 2.5 μM , respectively. Membrane area was 0.3 cm^2 . After a 5 h incubation, fractions were taken on both sides of the membrane and compound concentrations were determined by LC-
- 20 MS/MS. The apparent permeability coefficient (P_{app}) was calculated using the equation $P_{\text{app}} = (dQ/dtAc_0)$, where dQ/dt is the appearance rate of compound in the acceptor compartment, A is the surface area of the transwell membrane, and c_0 is the initial concentration in the donor compartment.

EXAMPLE 2

- 25 **Virtual screening and molecular modeling:** To discover new viral DNA pol inhibitors, we used a rational approach called structure-based inhibitor design. The recently-determined 3D model of CMV DNA pol determined by our group and the recent crystal structure of HSV-1 DNA pol (pdb id 2GV9) served as receptors for docking. Two Mg^{2+} atoms were modeled in the active site of the HSV-1 crystal
- 30 structure to complete the catalytic site. A docking site, was selected from a number of potential sites suggested by the Site Finder utility of the program MOE. Other potential sites were not considered because they were too far ($> 15 \text{ \AA}$) from the DNA

binding site. The selected site is located in the vicinity of the active site in a pocket close to the Mg^{2+} atoms and delimited by residues Val715, Asp717, Ser720, Arg785, Lys811, Asn815, Tyr884, Lys939 (Figure 1). Virtual screening of a large database of commercially-available compounds was performed inside a sphere delimited by 10 Å radius around Val715 CB atom, which is located near the center of the selected pocket. The top 50 ranking compounds were selected and their location in the active site was inspected. Further selection left only 12 compounds that have a predicted binding location close to the Mg^{2+} atoms. Selected compounds were purchased and tested for antiviral activity (see Figure 2 for list of compounds and Figure 3 for chemical structure of lead compounds). Twenty new chemical entity derivatives of lead compound 2 with substitution on the hydroxyl benzyldiene group were also designed (Figure 4A and 4B) and docked to evaluate their binding energy. Many compound derivatives have better predicted binding energy than lead compound 2 (Figure 4C). New derivatives of compound 2 (i.e. compounds C2.05, C2.11 and C2.20) and two derivatives of compound 3 (i.e. compounds C3-1 and C3-2) (Figure 5), which are all new chemical entities, were selected for chemical synthesis.

Toxicity of compounds: Toxicity of compounds 1 to 8 was evaluated on HFFs and Vero cells using a MTS assay. Compounds 1 to 8 were not toxic on both cell lines at the highest concentration tested (i.e. 100 μ M) after an incubation period of 3 days (see Figure 6 for cell toxicity of lead compounds 2 and 3).

Activity of compounds: Antiviral activity of compounds 1 to 8 was first tested at two concentrations (1 μ M and 10 μ M) along with currently-available first-line drugs (ACV for HSV/VZV and GCV for CMV) using a standard PRA. The relative activity (% viral plaques relative to control with no antiviral) for compounds 1 to 8 against HSV-1, HSV-2, VZV and CMV representative strains is presented in Figures 7A and 7B.

IC₅₀ values were determined for compounds 2, 3 and 9 (most active drugs) along with commercial compounds against a panel of wild-type HSV-1, HSV-2, VZV and CMV strains (Figure 8). Compound 2 was slightly less active than ACV (by a factor of 2 to 3-fold) against representative strains of HSV and VZV while compound 3 was also slightly less active than GCV (by a factor of 2-fold) against CMV reference strain. Compound 9 was also less active than ACV (by a factor of 3 to 4-fold) against

representative strains of HSV.

Antiviral activity of compound 2 against drug-resistant HSV-1 and HSV-2 strains: A more detailed evaluation of the activity of compound 2 against a series of wild-type as well as ACV- and/or FOS- resistant HSV clinical isolates and recombinant strains was performed in Vero cells using a standard PRA (see Figures 9 and 10 for HSV-1 and HSV-2, respectively). Compound 2 retained full antiviral activity against ACV- and/or FOS- resistant HSV-1 and HSV-2 strains with IC₅₀ value increases of 0.7 to 1.7-fold compared to the representative wild-type strains.

Antiviral activity of compound 2 against wild-type and drug-resistant VZV strains: Antiviral activity of compound 2 against a wild-type VZV strain and an ACV-resistant clinical isolate was evaluated in HFF cells using a standard PRA (Figure 11). This compound retained full antiviral activity against ACV-resistant VZV strain with an IC₅₀ value increase of 0.6 compared to the reference drug-susceptible strain.

Antiviral activity of compound 3 against drug-resistant CMV strains: Evaluation of antiviral activity of compound 3 against wild-type as well as GCV- and/or FOS-resistant CMV clinical isolates and recombinant strains was also performed in HFF cells using a standard PRA (Figure 12). Compound 3 retained activity against GCV- and/or FOS- resistant CMV strains with IC₅₀ value increases of 1 to 2-fold compared to the representative wild-type strain.

Membrane permeability: PAMPA assesses passive diffusion of a molecule, the most common pathway for drug absorption and uptake by target tissues. In this assay, permeability of compounds can be classified as low ($P_{app} (\times 10^{-6} \text{ cm/s}) < 1$), intermediate ($1 < P_{app} < 10$), or high ($P_{app} > 10$). PAMPA was used to predict membrane permeability for lead compounds 2 and 3. Compound 2 shows high permeability with $P_{app} = 11.3 \pm 1.17 \times 10^{-6} \text{ cm/s}$ ($n = 4$) while compound 3 has intermediate permeability with $P_{app} = 3.4 \pm 0.45 \times 10^{-6} \text{ cm/s}$ ($n = 4$) (Figure 13).

Microsomal stability: Metabolic stability of compounds 2 and 3 was evaluated using rat liver microsomes. Samples were taken at defined time points and the percentage of unmetabolized parent compound was determined by LC-MS/MS. Half-life and intrinsic clearance were evaluated and compared to the reference compound reserpine

(Figure 14). Half-life ($t_{1/2}$) values of 33 and 22 min as well as intrinsic clearance (Cl_{int}) extrapolated to whole rat liver of 37 and 62 ml/min/kg proteins were obtained for compounds 2 and 3, respectively. In comparison, $t_{1/2}$ and Cl_{int} were 43 min and 28 ml/min/kg for reserpine.

- 5 **Antiviral activity of compounds 2 and 3 derivatives against herpesviruses strains:** Three derivatives of compound 2 (i.e., compounds C2.05, C2.11 and C2.20) and two derivatives of compound 3 (C3-1 and C3-2), which are new chemical entities selected for synthesis, were evaluated against HSV-1, HSV-2, VZV and CMV strains by PRA (Figure 15). Derivative C2.20 was as active against wild-type HSV-1 and
10 HSV-2 as well as ACV-resistant VZV strains as compound 2. Derivative C2.11 was also active against wild-type HSV-2 and ACV-resistant VZV strains, but not against HSV-1. Derivative C2.05 was active against wild-type HSV-2 only. Compound 2 derivatives C2.05, C2.11 and C2.20 were not active against the wild-type CMV isolate. Compound 3 derivatives C3-1 and C3-2 were not active against any
15 herpesvirus strains at the concentrations tested.

- Cellular toxicity of compounds 2 and 3 and their derivatives:** Toxicity of compound 2, compound 3 and their derivatives along with ACV, GCV and FOS was assessed on Vero cells and HFFs using a MTS cell proliferation assay and the concentration which inhibited 50% of cell viability (CC_{50}) was calculated (Figure 16).
20 In both cell lines, compound 2, compound 3 and their derivatives were somewhat more toxic than ACV, GCV and FOS. Nevertheless, the therapeutic index values (CC_{50}/IC_{50}) of compound 2 and C2.20 were 19.3 and 9.6, respectively, for Vero cells using the IC_{50} values of the HSV-1 reference strain (H25) whereas the therapeutic index of compound 3 was 6.6 for HFFs using the IC_{50} value of the CMV reference
25 strain (AD169).

- Infections by herpesviruses such as HSV, VZV and CMV are associated with significant morbidity in immunocompetent subjects and even mortality in severely immunocompromised hosts. Except for VZV, there are currently no vaccines commercially-available for preventing herpesvirus infections. Furthermore, because
30 of the establishment of viral latency in immune-preserved sites, infected individuals are subjected to lifelong recurrent infections. Antiviral agents remain the best strategy to treat and also prevent clinical viral reactivations. However, as for all antivirals,

drug resistance is now a significant problem in immunocompromised patients exposed to prolonged antiviral therapy. Thus, there is an urgent and unmet need for developing anti-herpesvirus agents with different mechanisms of action.

In the present study, virtual screening of a drug-like compound library was done against a newly-described HSV-1 DNA polymerase pocket near the active site. Twelve non-nucleoside compounds were selected from screening and tested *in vitro*. Compound 2 was identified as a highly active inhibitor against HSV-1, -2 and VZV and to a lesser extent against CMV. Compound 3 was also highly active against CMV. The *in vitro* activity of these two compounds was almost comparable (2 to 3-fold higher IC₅₀ values) than conventional drugs, such as ACV and GCV against wild-type isolates. Remarkably, these two compounds were also active against drug-resistant strains isolated from patients or generated *in vitro*. Of note, both compounds displayed good cell permeability, low cell toxicity and good metabolic stability. New chemical entity derivatives of compounds 2 and 3 with binding potential to the HSV-1 DNA polymerase pocket (based on ChemScore) were synthesized and tested for antiviral activity in cell cultures. Compound C2.20 retained excellent activity against HSV-1, HSV-2 and VZV like the parental compound, including against strains resistant to current antiviral agents. Compound 2 derivatives listed in Figure 4C having a Chemscore rank closed to that of compound 2 are likely to have a similar or better activity than the parent compound. This suggests that the new compounds bind to the viral DNA pol at a different site than nucleoside or pyrophosphate analogues probably through interactions with residues Tyr884, Val715, Lys939, Tyr722 and the two Mg²⁺ atoms.

EXAMPLE 3

25 *Chemical synthesis:*

The method of preparation of compounds 2 and 3 and selected derivatives is illustrated in Figures 17 and 18 respectively.

Procedures for the preparation of naphthalene-hydrazide derivatives (Scheme synthesis of compound 2 and derivatives)

30 **Step a: Preparation of methyl-N-(naphthalen-1-ylcarbonyl)glycinate (2a)**

To a suspension of methylglycinate hydrochloride (3.3 g, 26 mmol) in THF (100 mL) was added at 0°C triethylamine (11 mL, 78 mmol). After stirring for 5 min, 1-naphthaloylchloride (4.5 mL, 31.5 mmol) was added dropwise and the resulting mixture was stirred overnight at room temperature. 10% HCl was added and the aqueous phase extracted with EtOAc. The combined organic phases were washed with 10% NaOH, brine and concentrated under vacuum. The crude compound was purified by flash chromatography using DCM/EtOAc (98:2) as eluent to give the compound **2a** (5 g, 79%). ¹H NMR (acetone-d₆) δ 3.76 (s, 3H, **OMe**), 4.24 (d, *J* = 6.0 Hz, 2H, **CH₂**), 7.52-7.58 (m, 3H, **Ar**), 7.72 (dd, *J* = 1.1 and 7.0 Hz, 1H, **Ar**), 7.90 (m, 1H, **Ar**), 8.01 (d, *J* = 8.3 Hz, 2H, **Ar**), 8.46 (m, 1H, **NH**); ¹³C NMR (acetone-d₆) δ 41.91 (**CH₂**), 52.22 (**OMe**), 125.67, 126.07, 126.66, 127.09, 127.49, 128.99, 131.09, 131.22, 134.57, 135.36, 170.12 (**CO**), 171.13 (**CO**).

Step b: Preparation of N-(2-hydrazinyl-2-oxoethyl)naphthalene-1-carboxamide (3a)

The above compound **2a** (3.3 g, 13.1 mmol) was heated at 60°C with hydrazine hydrate (3.5 mL, 65 mmol) in EtOH (30 mL) for 2 hours. After cooling at room temperature, water (10 mL) was added. The resulting white precipitate was filtered and dried under vacuum to give hydrazide derivative **3a** (2.6 g, 79%). ¹H NMR (acetone-d₆) δ 3.91 (d, *J* = 5.9 Hz, 2H, **CH₂**), 7.55-7.58 (m, 3H, **Ar**), 7.68 (dd, *J* = 1.1 and 7.0 Hz, 1H, **Ar**), 7.98 (d, *J* = 8.0 Hz, 1H, **Ar**), 8.02 (d, *J* = 8.3 Hz, 2H, **Ar**), 8.35 (m, 1H, **NH**), 8.74 (t, *J* = 6.3 Hz, 1H, **NH**), 9.31 (bs, 1H, **NH**); ¹³C NMR (acetone-d₆) δ 41.08 (**CH₂**), 124.88, 124.92, 125.13, 125.72, 126.12, 126.56, 128.07, 129.67, 129.80, 129.83, 133.08, 134.46, 168.34 (**CO**), 168.91 (**CO**).

Step c: General Procedure for preparation of benzylidene-hydrazides

Aldehyde (1 mmol) was added to a stirred suspension of hydrazide **3a** (1 mmol) in ethanol (10 mL) and refluxed for 1 hour. For compound **C2.20**, the resulting white solid was filtered and recrystallized from EtOH (50 mL). For compounds **C2.11** and **C2.05**, the crude mixture was concentrated under vacuum and triturated in acetone.

N-(2-((2*E*)-2-[(3-hydroxypyridin-2-yl)methylidene]hydrazinyl)-2-

oxoethyl)naphthalene-1-carboxamide (C2.11)

Compound **C2.11** was obtained as a yellow solid (237 mg, 64%) from 3-hydroxypyridine-2-carboxaldehyde. HPLC (Luna Phenyl-Hexyl column 75 x 4.6 mm, 3 μ m) t_r 4.84 min, purity 100%; IR (KBr) ν 3485, 3119, 3031, 1702, 1644, 1601, 1580, 1544; ^1H NMR (DMSO- d_6) (mixture of conformers) δ 4.12 and 4.47 (2d, J = 5.5 Hz, 2H, **CH₂**), 7.34-7.49 (m, 2H, **Ar**), 7.59 (m, 3H, **Ar**), 7.70 (d, J = 6.6 Hz, 1H, **Ar**), 7.99 (d, J = 6.5 Hz, 1H, **Ar**), 8.04 (d, J = 8.0 Hz, 1H, **Ar**), 8.21 (s, 1H, **Ar**), 8.35 and 8.45 (2s, 1H, **CH=NH**), 8.36 (d, J = 7.9 Hz, 1H, **Ar**), 8.77 and 8.97 (2bt, 1H, **NH**) 10.30 and 11.50 (2s, 1H, **OH**), 11.76 and 12.22 (2s, 1H, **NH**); ^{13}C NMR (DMSO- d_6) (mixture of conformers) δ 41.07, 42.15, 124.28, 124.56, 125.44, 125.79, 125.88, 125.98, 126.08, 126.16, 126.74, 127.12, 127.20, 128.62, 130.28, 130.37, 130.51, 133.59, 134.62, 134.98, 137.12, 138.26, 141.67, 144.82, 149.49, 154.02, 154.99, 166.32, 169.63, 169.71, 170.37; HRMS (ESI) m/z calcd for $\text{C}_{19}\text{H}_{17}\text{N}_4\text{O}_3[\text{M} + \text{H}]^+$: 349.1295; found: 349.1301.

N-{2-[(2E)-2-(2,6-dihydroxybenzylidene)hydrazinyl]-2-oxoethyl)naphthalene-1-carboxamide (C2.05)

Compound **C2.05** was obtained as a white solid (181 mg, 50%) from 2,6-hydroxybenzaldehyde¹. HPLC (Luna Phenyl-Hexyl column 75 x 4.6 mm, 3 μ m) t_r 6.64 min, purity 99.7%; IR (KBr) ν 3317, 3313, 3051, 1634, 1601, 1535; ^1H NMR (DMSO- d_6) (mixture of conformers) δ 4.07 and 4.37 (2d, J = 5.7 Hz, 2H, **CH₂**), 6.36-6.41 (m, 2H, **Ar**), 7.10 (t, J = 8.2 Hz, 1H, **Ar**), 7.56-7.59 (m, 3H, **Ar**), 7.70 (d, J = 6.5 Hz, 1H, **Ar**), 7.98 (d, J = 5.9 Hz, 1H, **Ar**), 8.03 (d, J = 8.2 Hz, 1H, **Ar**), 8.36 (m, 1H, **Ar**), 8.58 and 8.75 (2s, 1H, **CH=N**), 8.79 and 8.91 (2t, J = 5.7 Hz, 1H, **NH**), 10.47 and 11.02 (2s, 2H, **2OH**), 11.62 and 11.88 (2s, 1H, **NH**); ^{13}C NMR (DMSO- d_6) (mixture of conformers) δ 41.62, 106.03, 106.12, 106.53, 106.66, 124.97, 125.32, 125.43, 125.67, 126.27, 126.66, 126.72, 128.15, 129.83, 129.92, 130.02, 132.23, 132.31, 133.13, 134.22, 134.51, 138.99, 143.42, 145.30, 157.98, 158.29, 165.17, 168.84, 169.19; HRMS (ESI) m/z calcd for $\text{C}_{20}\text{H}_{18}\text{N}_3\text{O}_4[\text{M} + \text{H}]^+$: 364.1292; found: 364.1295.

N-{2-[(2E)-2-(4-fluoro-2-hydroxybenzylidene)hydrazinyl]-2-oxoethyl)naphthalene-1-carboxamide (C2.20)

Compound **C2.20** was obtained as a white solid (264 mg, 72%) from 5-fluoro-2-hydroxybenzaldehyde. HPLC (Luna Phenyl-Hexyl column 75 x 4.6 mm, 3 μ m) t_r 6.94 min, purity 99.1%; IR (KBr) ν 3264, 3062, 1685, 1636, 1541, 1282; ^1H NMR (DMSO- d_6) (mixture of conformers) δ 4.09 and 4.49 (2d, J = 5.8 Hz, 2H, CH_2), 6.92-6.96 (m, 1H, **Ar**), 7.08-7.15 (m, 1H, **Ar**), 7.45-7.59 (m, 4H, **Ar**), 7.69 (d, J = 6.3 Hz, 1H, **Ar**), 7.98-8.04 (m, 2H, **Ar**), 8.32 and 8.45 (2s, 1H, $\text{CH}=\text{N}$), 8.36-8.42 (m, 1H, **Ar**), 8.75 and 8.93 (2t, J = 5.8 Hz, 1H, **NH**), 10.09 and 10.88 (2s, 1H, **OH**), 11.57 and 11.93 (2s, 1H, **NH**); ^{13}C NMR (DMSO- d_6) (mixture of conformers) δ 41.28, 42.15, 111.49, 111.73, 114.07, 114.30, 117.83, 117.91, 118.00, 118.07, 118.24, 118.30, 118.53, 120.23, 120.31, 121.82, 121.90, 125.46, 125.69, 125.82, 126.13, 126.21, 126.69, 126.72, 127.07, 127.16, 128.58, 130.30, 130.44, 133.59, 134.76, 135.18, 139.80, 145.41, 153.13, 153.91, 154.65, 154.94, 156.98, 157.27, 166.08, 169.60, 169.67, 170.65; HRMS (ESI) m/z calcd for $\text{C}_{20}\text{H}_{17}\text{FN}_3\text{O}_3$ $[\text{M} + \text{H}]^+$: 366.1250; found: 366.1248.

15 N-{2-[(2E)-2-(2-hydroxybenzylidene)hydrazinyl]-2-oxoethyl}naphthalene-1-carboxamide (compound 2)

Compound 2 was obtained starting with 2-hydroxybenzaldehyde giving a solid (g, %). The crude compound was purified by flash chromatography using EtOAc/hexanes as eluent to give pure **compound 2** (g, %). IR (film); ^1H NMR (CDCl_3); ^{13}C NMR (CDCl_3); LRMS for $\text{C}_x\text{H}_y\text{ON}$ $[\text{M} + \text{H}]^+$: m/z .

Procedures for the preparation of 3-chlorobenzene-hydrazide derivatives (Scheme synthesis of compound 3 and derivatives)

Step a: Preparation of methyl-N-(3-chlorophenyl-1-ylcarbonyl)glycinate (6a)

Compound **6a** was obtained using procedure described for preparation of amide **2a** starting with methylglycinate hydrochloride (5 g, 39 mmol) and 3-chlorobenzoyl chloride reagent (5.6 mL, 44 mmol). The crude compound was purified by flash chromatography using DCM/EtOAc (98:2) as eluent to give pure compound **6a** (4.1 g, 54%). ^1H NMR (acetone- d_6) δ 3.70 (s, 3H, **OMe**), 4.15 (d, J = 6 Hz, 2H, CH_2), 7.52 (t, J = 7.8 Hz, 1H, **Ar**), 7.59 (d, J = 8.0 Hz, 1H, **Ar**), 7.87 (d, J = 7.7 Hz, 1H, **Ar**), 7.92 (s, 1H, **Ar**), 7.93 (bs, 1H, **NH**); ^{13}C NMR (acetone- d_6) δ 41.99 (CH_2), 52.17

(OMe), 126.54, 128.15, 131.09, 132.17, 134.85, 137.07, 166.38 (CO), 170.10 (CO).

Step b: Preparation of N-(2-hydrazinyl-2-oxoethyl)-3-chlorophenyl-1-carboxamide (7a)

Following the procedure described for the preparation of naphthyl analog **3a**, we
5 obtained hydrazide **7a** (2.6 g, 87%) from ester **6a** (3 g, 12.5 mmol). ¹H NMR (acetone-d₆) δ 3.84 (d, *J* = 6.0 Hz, 2H, CH₂), 7.51 (t, *J* = 7.8 Hz, 1H, Ar), 7.61 (d, *J* = 8 Hz, 1H, Ar), 7.82 (d, *J* = 7.7 Hz, 1H, Ar), 7.94 (s, 1H, Ar), 7.93 (t, *J* = 5.8 Hz, 1H, NH), 9.16 (bs, 1H, NH); ¹³C NMR (acetone-d₆) δ 41.49 (CH₂), 125.96, 126.13, 127.10, 130.25, 131.10, 133.09, 136.08, 165.13 (CO), 168.08 (CO)..

10 Step c: General procedure for preparation of benzylidene-hydrazides C3.1-2

Hydrazide **7a** (1 mmol) was converted by condensation with aldehyde (1 mmol) into the corresponding derivatives **C3.1-2** as described for the preparation of the naphthyl analogs **C2-#**.

15 3-chloro-N-(2-{2-[(E)-2-(2-hydroxy-3-methylphenyl)ethenyl]hydrazinyl}-2-oxoethyl)benzamide (C3-1)

Compound **3-1** was obtained as a white solid (338 mg, 76 %) from 2-hydroxy-3-methylbenzaldehyde. HPLC (Luna Phenyl-Hexyl column 75 x 4.6 mm, 3 μm) *t*_r 8.36 min, purity 100%; IR (KBr) ν 3420, 3215, 3068, 1716, 1630, 1568, 1527; ¹H NMR (DMSO-d₆) (mixture of conformers) δ 2.19 and 2.20 (2s, 3H, Me), 4.03 and 4.38 (2d, *J* = 6.2 Hz, 2H, CH₂), 6.82-6.88 (m, 1H, Ar), 7.20 (d, *J* = 7.9 Hz, 1H, Ar), 7.27 and 7.34 (d, *J* = 7.4 Hz, 1H, Ar), 7.55 (t, *J* = 7.9 Hz, 1H, Ar), 7.65 (d, *J* = 8 Hz, 1H, Ar), 7.87 (d, *J* = 7.8 Hz, Ar), 7.97 (s, 1H, Ar), 8.24 and 8.39 (s, 1H, CH=N), 8.93 and 9.10 (t, *J* = 5.6 Hz, 1H, NH), 10.16 and 11.72 (2s, 1H, OH), 11.64 and 11.86 (2s, 1H, NH); ¹³C NMR (DMSO-d₆) (mixture of conformers) δ 15.89, 16.12, 40.37, 117.55,
20 118.74, 119.34, 119.96, 125.41, 125.56, 126.53, 126.61, 127.63, 127.73, 129.11, 130.85, 131.78, 132.86, 133.69, 136.21, 136.41, 146.08, 149.78, 155.32, 156.31, 165.80, 169.63; HRMS (ESI) *m/z* calcd for C₁₇H₁₇ClN₃O₃ [M + H]⁺: 346.0953; found: 346.0954.

3-chloro-N-(2-{2-[(E)-2-(1-hydroxynaphthalen-2-yl)ethenyl]hydrazinyl}-2-oxoethyl)benzamide (C3-2)

Compound **C3-2** was obtained as a yellow solid (327 mg, 82%) from 1-hydroxy-2-naphthaldehyde. HPLC (Luna Phenyl-Hexyl column 75 x 4.6 mm, 3 μ m) t_r 10.81 min, purity 99.9%; IR (KBr) ν 3260, 3064, 1675, 1634, 1564, 1537; ^1H NMR (DMSO- d_6) (mixture of conformers) δ 4.06 and 4.47 (2d, J = 5.7 Hz, 2H, **CH**₂), 7.44-7.68 (m, 6H, **Ar**), 7.88 (t, J = 6.80 Hz, 2H, **Ar**), 7.98 (s, 1H, **Ar**), 8.28 (d, J = 8.0 Hz, 1H) 8.46 and 8.55 (s, 1H, **CH=N**), 8.95 and 9.12 (t, J = 5.6 Hz, 1H, **NH**), 10.80 and 12.71 (2s, 1H, **OH**), 11.68 and 11.96 (2s, 1H, **NH**); ^{13}C NMR (DMSO- d_6) (mixture of conformers) δ 41.18, 42.44, 111.79, 114.08, 119.24, 120.15, 122.88, 123.05, 124.75, 125.20, 125.48, 126.16, 126.24, 126.54, 126.63, 127.15, 127.63, 127.73, 128.02, 128.11, 128.21, 128.42, 130.89, 131.72, 131.80, 133.69, 134.93, 135.08, 136.24, 136.46, 144.85, 149.64, 153.63, 155.24, 165.73, 165.81, 169.79; HRMS (ESI) m/z calcd for $\text{C}_{20}\text{H}_{17}\text{ClN}_3\text{O}_3$ $[\text{M} + \text{H}]^+$: 382.0956; found: 382.0953.

3-chloro-N-(2-{(2E)-2-[2-hydroxy-3-(prop-2-en-1-yl)benzylidene]hydrazinyl}-2-oxoethyl)benzamide (compound 3)

Compound 3 was obtained starting with 2-hydroxy-3-(prop-2-en-1-yl)benzaldehyde. The crude compound was purified by flash chromatography using EtOAc/hexanes as eluent to give pure **compound 3** (g, %). IR (film); ^1H NMR (CDCl_3); ^{13}C NMR (CDCl_3); LRMS for $\text{C}_x\text{H}_y\text{ON}$ $[\text{M} + \text{H}]^+$: m/z .

The present description refers to a number of documents, the content of which is herein incorporated by reference in their entirety.

It is to be understood that the invention is not limited in its application to the details of construction and parts as described hereinabove. The invention is capable of other embodiments and of being practiced in various ways. It is also understood that the phraseology or terminology used herein is for the purpose of description and not limitation. Hence, although the present invention has been described hereinabove by way of illustrative embodiments thereof, it can be modified, without departing from the spirit, scope and nature of the subject invention as defined in the appended claims.

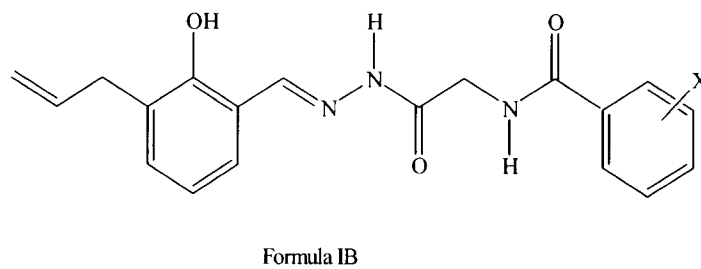
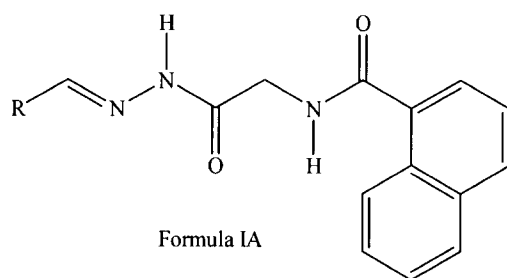
REFERENCES

1. Gilbert C, Bestman-Smith J and Boivin G. Resistance of herpesvirus to antiviral drugs: clinical impacts and molecular mechanisms. *Drug Resist Updat.* 2002 Apr;5(2):88-114.
- 5 2. Boivin G, Gilbert C, Gaudreau A *et al.* Rate of emergence of cytomegalovirus (CMV) mutations in leukocytes of patients with acquired immunodeficiency syndrome who are receiving valganciclovir as induction and maintenance therapy for CMV retinitis. *J Infect Dis.* 2001 Dec 15;184(12):1598-602.
- 10 3. Limaye AP, Corey L and Koelle DM *et al.* Emergence of ganciclovir-resistant cytomegalovirus disease among recipients of solid-organ transplants. *Lancet.* 2000 Aug 19;356(9230):645-9.
- 15 4. Jabs DA, Enger C, Forman M *et al.* Incidence of foscarnet resistance and cidofovir resistance in patients treated for cytomegalovirus retinitis. The Cytomegalovirus Retinitis and Viral Resistance Study Group. *Antimicrob Agents Chemother.* 1998 Sep;42(9):2240-4.
5. Weinberg A, Jabs DA, Chou S *et al.* Mutations conferring foscarnet resistance in a cohort of patients with acquired immunodeficiency syndrome and cytomegalovirus retinitis. *J Infect Dis.* 2003 Mar 1;187(5):777-84.
- 20 6. Cihlar T, Fuller MD, Mulato AS *et al.* A point mutation in the human cytomegalovirus DNA polymerase gene selected in vitro by cidofovir confers a slow replication phenotype in cell culture. *Virology.* 1998 Sep 1;248(2):382-93.
7. Chou S, Lurain NS, Thompson KD *et al.* Viral DNA polymerase mutations associated with drug resistance in human cytomegalovirus. *J Infect Dis.* 2003 Jul 1;188(1):32-9.
- 25 8. Shi R, Azzi A, Gilbert C *et al.* Three-dimensional modeling of cytomegalovirus DNA polymerase and preliminary analysis of drug resistance. *Proteins.* 2006 Aug 1;64(2):301-7.
9. Liu S, Knafels JD, Chang JS *et al.* Crystal structure of the herpes simplex virus 1 DNA polymerase. *J Biol Chem.* 2006 Jun 30;281(26):18193-200.

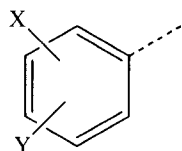
10. Jones G, Willett P and Glen RC. Molecular recognition of receptor sites using a genetic algorithm with a description of desolvation J. Mol. Biol. 1995;245:43-53.
11. Eldridge MD, Murray CD, Auton TR *et al.* Empirical scoring functions: I. The development of a fast empirical scoring function to estimate the binding affinity
5 of ligands in receptor complexes. Journal of Computer-Aided Molecular Design 1997;11:425-445.
12. Irwin and Shoichet. ZINC--a free database of commercially available compounds for virtual screening. J. Chem. Inf. Model. 2005;45(1):177-82.
13. Lipinski A, Lombardo F, Dominy BW *et al.* Experimental and computational
10 approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Del Rev. 1997;23:3-25.
14. Schmit I and Boivin G. Characterization of the DNA polymerase and thymidine kinase genes of herpes simplex virus isolates from AIDS patients in whom acyclovir and foscarnet therapy sequentially failed. J Infect Dis. 1999
15 Aug;180(2):487-90.
15. McSharry JJ, Lurain NS, Drusano GL *et al.* Rapid ganciclovir susceptibility assay using flow cytometry for human cytomegalovirus clinical isolates. Antimicrob Agents Chemother. 1998 Sep;42(9):2326-31.
16. Talarico CL, Burnette TC, Miller WH *et al.* Acyclovir is phosphorylated by the
20 human cytomegalovirus UL97 protein. Antimicrob Agents Chemother. 1999 Aug;43(8):1941-6.
17. Landry ML, Stanat S, Biron K *et al.* A standardized plaque reduction assay for determination of drug susceptibilities of cytomegalovirus clinical isolates. Antimicrob Agents Chemother. 2000 Mar;44(3):688-92.
- 25 18. Avdeef A, Strafford M, Block E *et al.* Drug absorption in vitro model: filter-immobilized artificial membranes. 2. Studies of the permeability properties of lactones in Piper methysticum Forst. Eur J Pharm Sci 2001;14:271-80.

CLAIMS:

1. A pharmaceutical composition comprising a compound of formula IA or formula IB or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier:

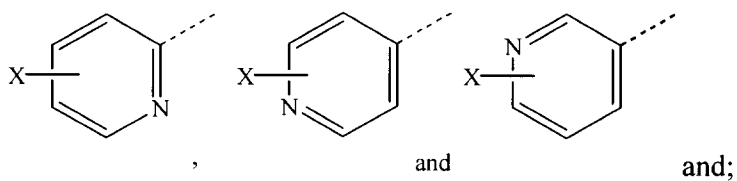


wherein R is selected from the group consisting of unsubstituted benzyl or a substituted benzyl of formula II:

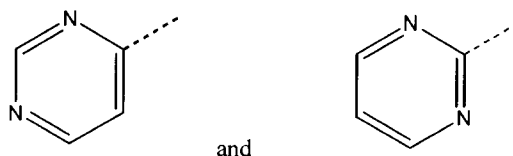


II;

- 10 an unsubstituted pyridine or a substituted pyridine selected from the group consisting of:



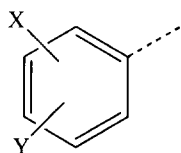
a pyrimidine selected from the group consisting of :



wherein X and Y each are independently selected from the group consisting of H, $-OR_1$, NH_2 , F, Cl, Br, I, an alkyl group of 1 to 3 carbon atoms and an allyl group;

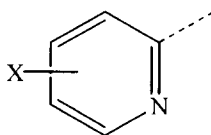
5 and wherein R_1 is selected from the group consisting of H and an alkyl group of 1 to 3 carbon atoms.

2. The pharmaceutical composition of claim 1, wherein R is selected from the group consisting of unsubstituted benzyl or a substituted benzyl of formula II:



II; and,

10 an unsubstituted pyridine or a substituted pyridine of formula:

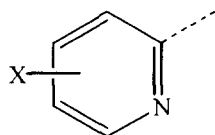


wherein X and Y each are independently selected from the group consisting of H, $-OR_1$, NH_2 , F, Cl, Br, I, an alkyl group of 1 to 3 carbon atoms and an allyl group;

15 and wherein R_1 is selected from the group consisting of H and an alkyl group of 1 to 3 carbon atoms.

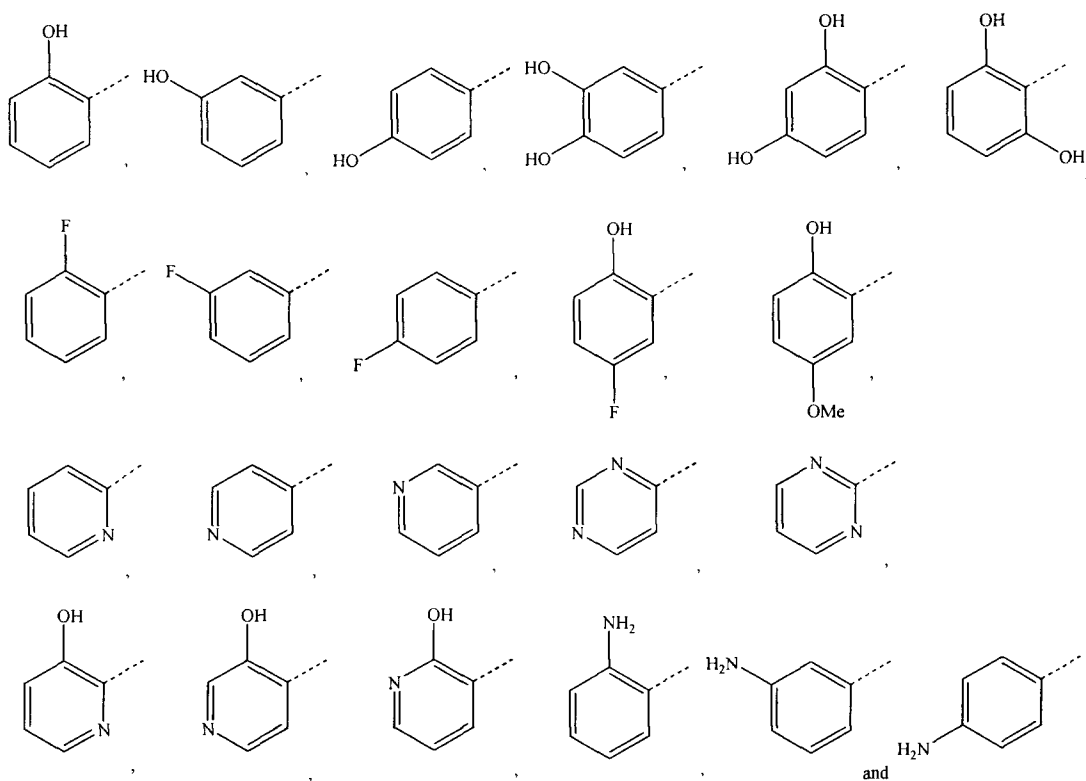
3. The pharmaceutical composition of claim 2, wherein R is a substituted benzyl of formula II and wherein X is OR_1 and Y is F, OR_1 or H.
4. The pharmaceutical composition of claim 3, wherein X is OH and Y is F.
5. The pharmaceutical composition of claim 3, wherein X is OH and Y is H.

6. The pharmaceutical composition of claim 3, wherein X is OR₁ and Y is OH.
7. The pharmaceutical composition of claim 6, wherein R₁ is H.
8. The pharmaceutical composition of claim 6, wherein R₁ is methyl.
9. The pharmaceutical composition of claim 2, wherein R is a substituted pyridine of
5 formula

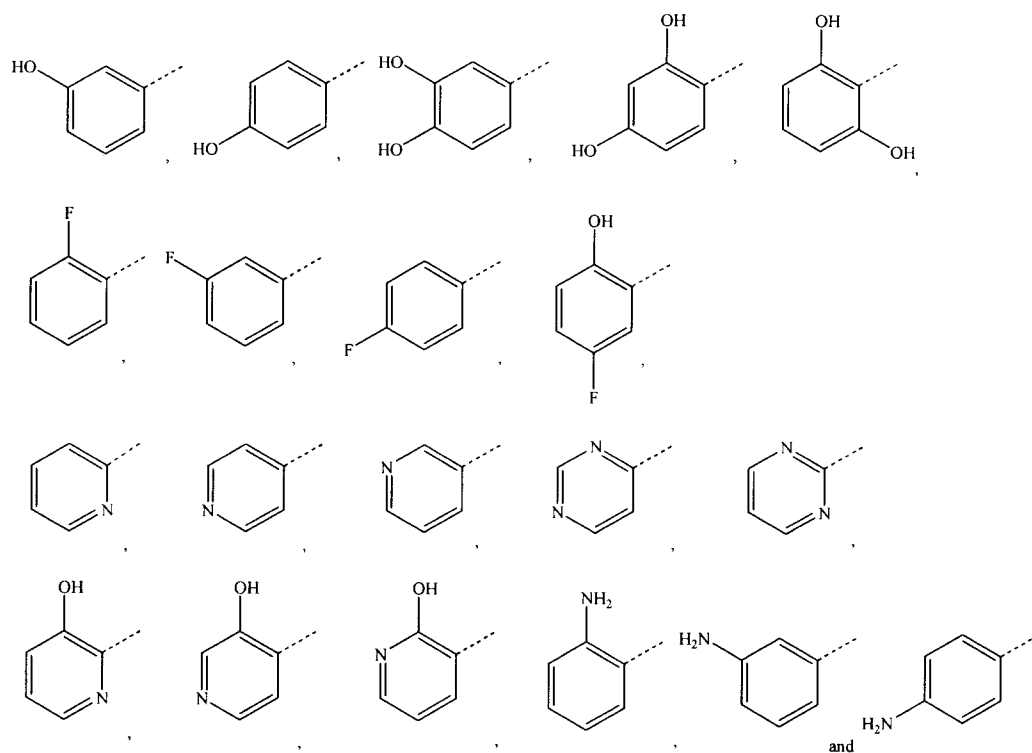


and wherein X is OR₁.

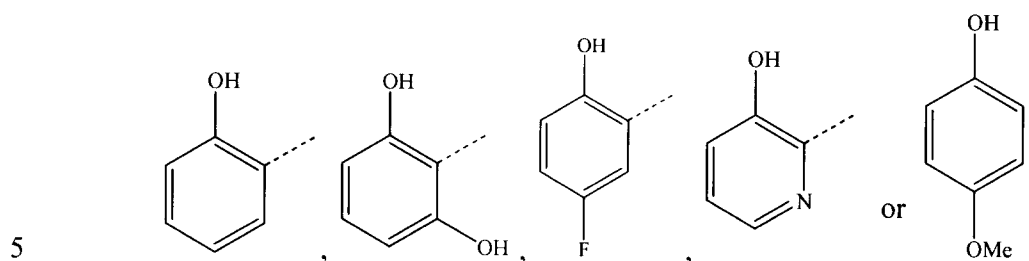
10. The pharmaceutical composition of claim 9, wherein R₁ is H.
11. The pharmaceutical composition as defined in claim 1,
10 wherein R is selected from the group consisting of:



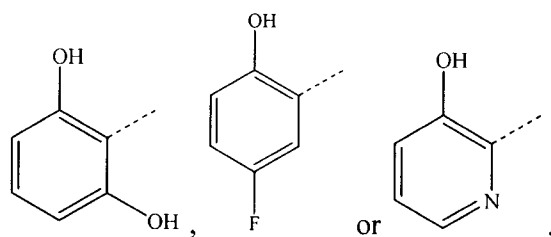
12. The pharmaceutical composition of claim 11, wherein R is selected from the group consisting of:



13. The pharmaceutical composition of claim 11, wherein R is

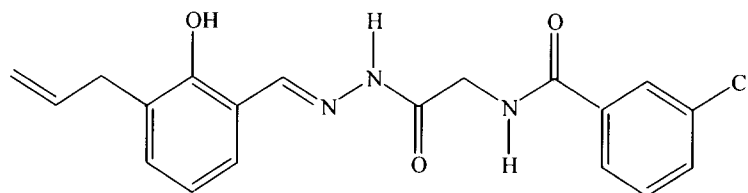


14. The pharmaceutical composition of claim 13, wherein R is



15. The pharmaceutical composition of claim 1, wherein the compound is a compound of formula IB and wherein X is Cl.

16. The pharmaceutical composition of claim 15, wherein the compound is a compound of formula:



17. A pharmaceutical composition comprising:

a. a compound selected from the group consisting of:

- i. N-(2-(2-(2-hydroxy-5-methoxybenzylidene) hydrazino)-2-oxoethyl)-3-methyl-benzamide;
- ii. N-(2-(2-(2-hydroxybenzylidene) hydrazino)-2-oxoethyl)-1-naphthamide;
- iii. N-(2-(2-(3-allyl-2-hydroxybenzylidene) hydrazino)-2-oxoethyl)-3-chlorobenzamide;
- iv. N-[2-(4-methoxyphenyl)ethyl]-2-[(1-phenyl-1H-tetrazol-5-yl)thio]acetamide;
- v. 1-(2-chloro-5-nitrophenyliminomethyl)-2-naphthol;
- vi. N-1H-tetrazol-5-yl-4-biphenylcarboxamide;
- vii. 9-anthracenecarbaldehyde 1H-tetrazol-5-ylhydrazone;
- viii. N-{[(2-methyl-2H-tetrazol-5-yl) amino]carbonothioyl} -2-thiophenecarboxamide;
- ix. N-(2-(2-(2-hydroxy-5-methoxybenzylidene) hydrazino)-2-oxoethyl)-1-naphthamide;
- x. N-(2-(2-(3-allyl-2-hydroxybenzylidene) hydrazino)-2-oxoethyl)-2-chlorobenzamide;
- xi. N-(2-(2-(3-allyl-2-hydroxybenzylidene) hydrazino)-2-oxoethyl)-4-chlorobenzamide;
- xii. N-(2-(2-(3-allyl-2-hydroxybenzylidene) hydrazino)-2-oxoethyl)-1-naphthamide;
- xiii. (E)-N-(2-(2-(3-hydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- xiv. (E)-N-(2-(2-(4-hydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- xv. (E)-N-(2-(2-(3,4-dihydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;

- xvi. (E)-N-(2-(2-(2,4-dihydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- xvii. (E)-N-(2-(2-(2,6-dihydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- 5 xviii. (E)-N-(2-oxo-2-(2-(pyrimidin-4-ylmethylene)hydrazinyl)ethyl)-1-naphthamide;
- xix. (E)-N-(2-oxo-2-(2-(pyridin-2-ylmethylene)hydrazinyl)ethyl)-1-naphthamide;
- 10 xx. (E)-N-(2-oxo-2-(2-(pyridin-4-ylmethylene)hydrazinyl)ethyl)-1-naphthamide;
- xxi. (E)-N-(2-oxo-2-(2-(pyridin-3-ylmethylene)hydrazinyl)ethyl)-1-naphthamide;
- xxii. (E)-N-(2-oxo-2-(2-(pyrimidin-2-ylmethylene)hydrazinyl)ethyl)-1-naphthamide;
- 15 xxiii. (E)-N-(2-(2-((3-hydroxypyridin-2-yl)methylene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- xxiv. (E)-N-(2-(2-((3-hydroxypyridin-4-yl)methylene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- 20 xxv. (E)-N-(2-(2-((2-hydroxypyridin-3-yl)methylene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- xxvi. (E)-N-(2-(2-(2-aminobenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- xxvii. (E)-N-(2-(2-(3-aminobenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- 25 xxviii. (E)-N-(2-(2-(4-aminobenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- xxix. (E)-N-(2-(2-(2-fluorobenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- 30 xxx. (E)-N-(2-(2-(3-fluorobenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide;
- xxxi. (E)-N-(2-(2-(4-fluorobenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide, and;
- xxxii. (E)-N-(2-(2-(5-fluoro-2-hydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide,
- 35 b. and a pharmaceutically acceptable carrier.

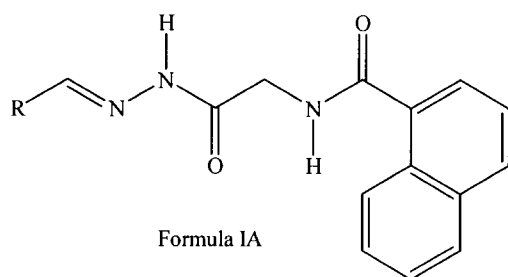
18. The pharmaceutical composition of any one of claims 1 to 17, for use in interfering with herpesvirus replication.

19. The pharmaceutical composition of claim 18, wherein the herpesvirus is selected from the group consisting of herpes simplex 1, herpes simplex 2, cytomegalovirus and varicella zoster virus.

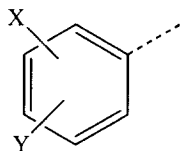
20. The pharmaceutical composition of claim 19, wherein the herpesvirus is characterized as being resistant to a pyrophosphate analogue, to a nucleoside analogue or to a prodrug or derivative thereof.

21. The pharmaceutical composition of claim 19, wherein the herpesvirus is characterized as being resistant to acyclovir, ganciclovir and/or foscarnet.

22. A compound of formula IA or a pharmaceutically acceptable salt thereof:

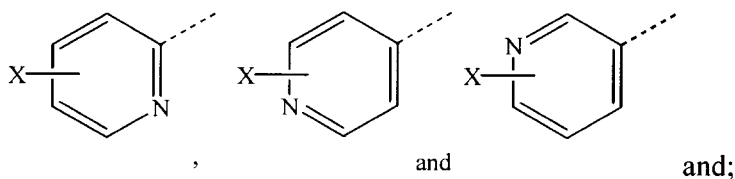


wherein R is selected from the group consisting of unsubstituted benzyl or a substituted benzyl of formula II:

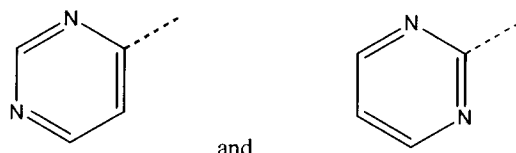


II;

an unsubstituted pyridine or a substituted pyridine selected from the group consisting of:



a pyrimidine selected from the group consisting of :



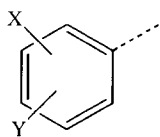
wherein X and Y each are independently selected from the group consisting of H, –OR₁, NH₂, F, Cl, Br, I, an alkyl group of 1 to 3 carbon atoms and an allyl group;

and wherein R₁ is selected from the group consisting of H and an alkyl group of 1 to 3 carbon atoms

provided that the compound is not:

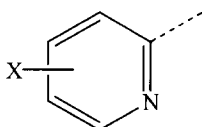
- i. N-(2-(2-(2-hydroxybenzylidene) hydrazino)-2-oxoethyl)-1-naphthamide;
- ii. N-(2-(2-(2-hydroxy-5-methoxybenzylidene) hydrazino)-2-oxoethyl)-1-naphthamide, or
- iii. N-(2-(2-(3-allyl-2-hydroxybenzylidene) hydrazino)-2-oxoethyl)-1-naphthamide.

23. The compound of claim 22, wherein R is selected from the group consisting of unsubstituted benzyl or a substituted benzyl of formula II:



II; and,

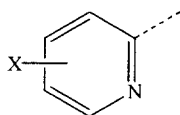
an unsubstituted pyridine or a substituted pyridine of formula:



wherein X and Y each are independently selected from the group consisting of H, –OR₁, NH₂, F, Cl, Br, I, an alkyl group of 1 to 3 carbon atoms and an allyl group;

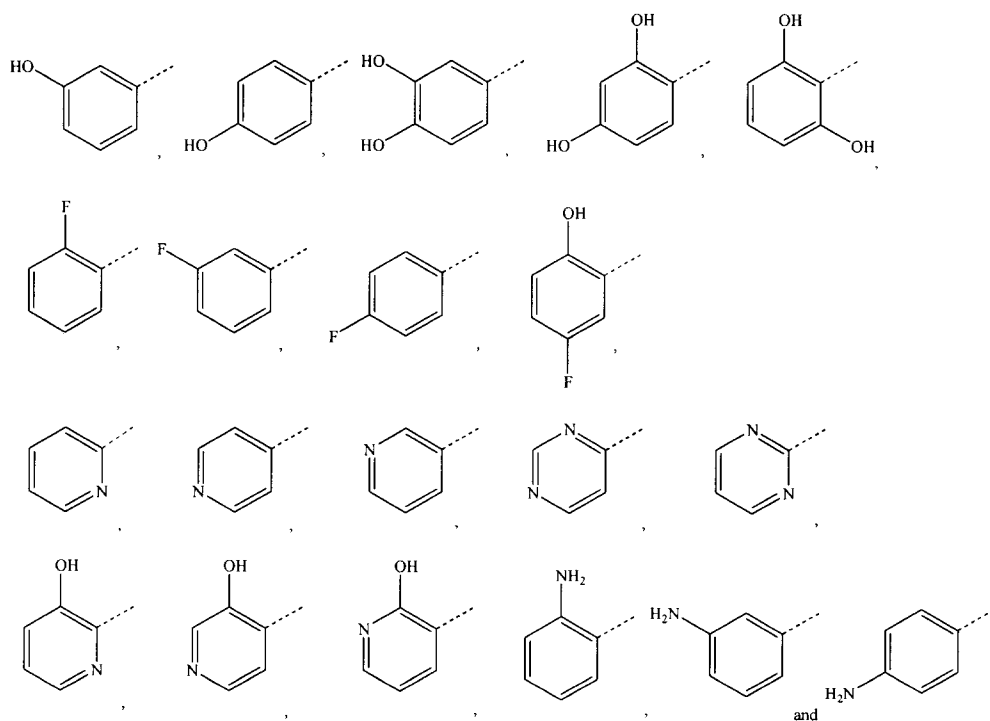
and wherein R₁ is selected from the group consisting of H and an alkyl group of 1 to 3 carbon atoms.

24. The compound of claim 23, wherein R is a substituted benzyl of formula II and wherein X is OR₁ and Y is F, OR₁ or H.
25. The compound of claim 24, wherein X is OH and Y is F.
26. The compound of claim 24, wherein X is OH and Y is H.
27. The compound of claim 24, wherein X is OR₁ and Y is OH.
28. The compound of claim 27, wherein R₁ is H.
29. The compound of claim 27, wherein R₁ is methyl.
30. The compound of claim 23, wherein R is a substituted pyridine of formula

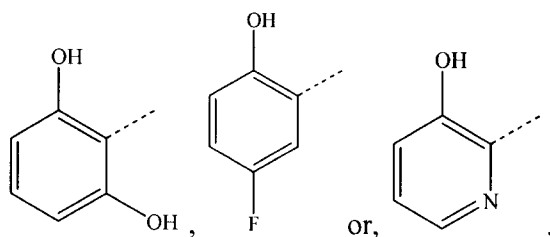


- and wherein X is OR₁.

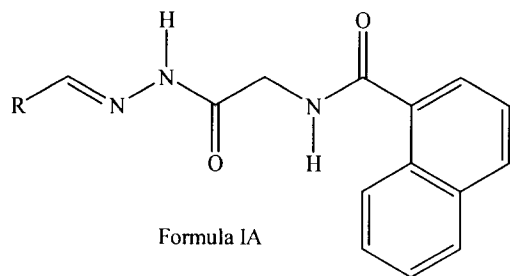
31. The compound of claim 30, wherein R₁ is H.
32. The compound of claim 22, wherein R is selected from the group consisting of:



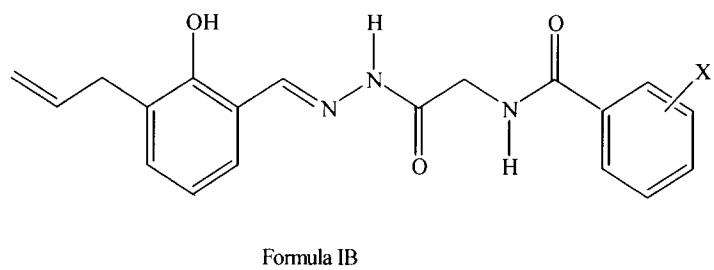
33. The compound of claim 32, wherein R is



34. Use of a compound of formula IA or formula IB for interfering with herpesvirus replication:

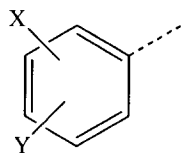


5



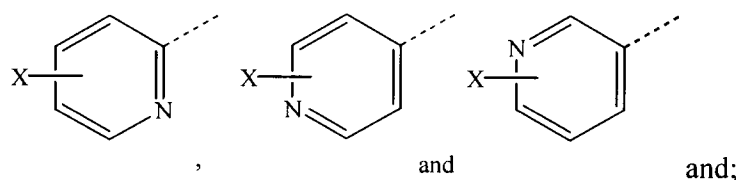
;

wherein R is selected from the group consisting of unsubstituted benzyl or a substituted benzyl of formula II:

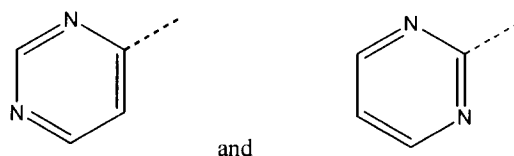


II;

10 an unsubstituted pyridine or a substituted pyridine selected from the group consisting of:



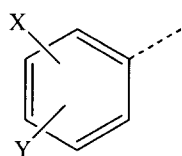
a pyrimidine selected from the group consisting of :



wherein X and Y each are independently selected from the group consisting of H, –
 5 OR₁, NH₂, F, Cl, Br, I, an alkyl group of 1 to 3 carbon atoms and an allyl group;

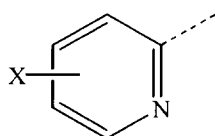
and wherein R₁ is selected from the group consisting of H and an alkyl group of 1 to 3 carbon atoms.

35. The use as defined in claim 34, wherein R is selected from the group consisting of unsubstituted benzyl or a substituted benzyl of formula II:



10 II; and,

an unsubstituted pyridine or a substituted pyridine of formula:



wherein X and Y each are independently selected from the group consisting of H, –
 OR₁, NH₂, F, Cl, Br, I, an alkyl group of 1 to 3 carbon atoms and an allyl group;

15 and wherein R₁ is selected from the group consisting of H and an alkyl group of 1 to 3 carbon atoms.

36. The use as defined in claim 35, wherein R is a substituted benzyl of formula II and wherein X is OR₁ and Y is F, OR₁ or H.

37. The use as defined in claim 36, wherein X is OH and Y is F.

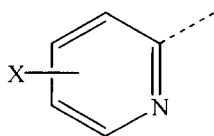
38. The use as defined in claim 36, wherein X is OH and Y is H.

5 39. The use as defined in claim 36, wherein X is OR₁ and Y is OH.

40. The use as defined in claim 39, wherein R₁ is H.

41. The use as defined in claim 39 wherein R₁ is methyl.

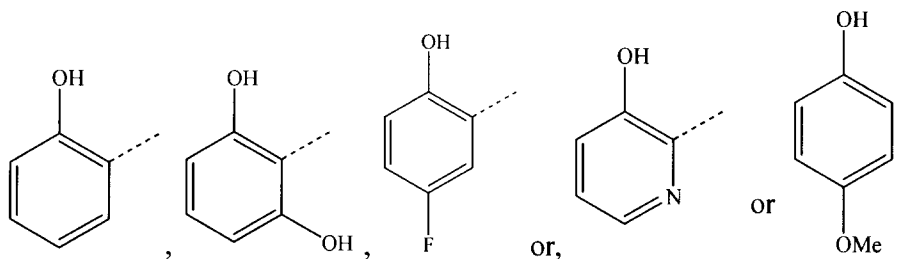
42. The use as defined in claim 35, wherein R is a substituted pyridine of formula



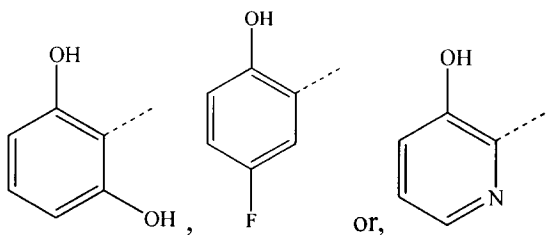
10 and wherein X is OR₁.

43. The use as defined in claim 42, wherein R₁ is H.

44. The use as defined in claim 34, wherein R is



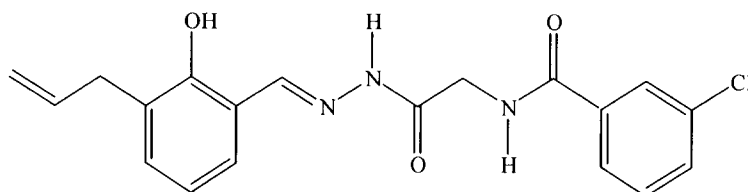
45. The use as defined in claim 44, wherein R is



15

46. The use as defined in claim 34, wherein the compound is a compound of formula IB and wherein X is Cl.

47. The use as defined in claim 46, wherein the compound is a compound of formula:



48. The use as defined in any one of claims 34 to 47, wherein the herpesvirus is selected from the group consisting of herpes simplex 1, herpes simplex 2, cytomegalovirus and varicella zoster virus.

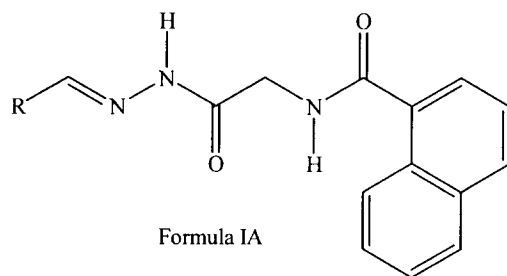
49. The use as defined in claim 48, wherein the herpesvirus is characterized as being resistant to a pyrophosphate analogue, a nucleoside analogue or to a prodrug or derivative thereof.

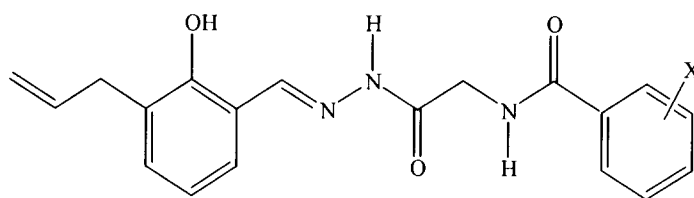
50. The use as defined in claim 48, wherein the herpesvirus is characterized as being resistant to acyclovir, ganciclovir and/or foscarnet.

51. The use as defined in claim 50, wherein the herpesvirus is a herpes simplex 1, herpes simplex 2 or varicella zoster virus that is characterized as being resistant to acyclovir and/or foscarnet.

52. The use as defined in claim 50, wherein the herpesvirus is a cytomegalovirus that is characterized as being resistant to ganciclovir and/or foscarnet.

53. A method of treating or preventing a herpesvirus infection, the method comprising administering a compound of formula IA or formula IB to a mammal in need:

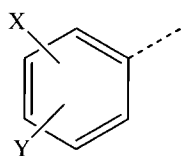




Formula IB

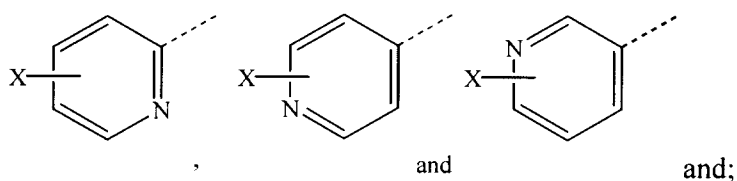
;

wherein R is selected from the group consisting of unsubstituted benzyl or a substituted benzyl of formula II:

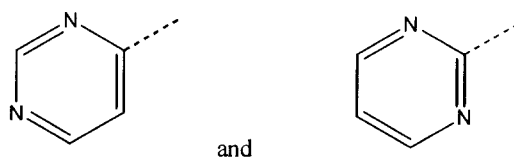


II;

- 5 an unsubstituted pyridine or a substituted pyridine selected from the group consisting of:



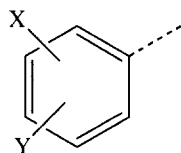
a pyrimidine selected from the group consisting of :



- 10 wherein X and Y each are independently selected from the group consisting of H, –OR₁, NH₂, F, Cl, Br, I, an alkyl group of 1 to 3 carbon atoms and an allyl group;

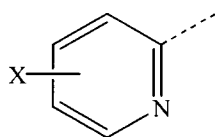
and wherein R₁ is selected from the group consisting of H and an alkyl group of 1 to 3 carbon atoms.

54. The method of claim 53, wherein R is selected from the group consisting of
15 unsubstituted benzyl or a substituted benzyl of formula II:



II; and,

an unsubstituted pyridine or a substituted pyridine of formula:



wherein X and Y each are independently selected from the group consisting of H, –

- 5 OR₁, NH₂, F, Cl, Br, I, an alkyl group of 1 to 3 carbon atoms and an allyl group;

and wherein R₁ is selected from the group consisting of H and an alkyl group of 1 to 3 carbon atoms.

55. The method of claim 54, wherein R is a substituted benzyl of formula II and wherein X is OR₁ and Y is F, OR₁ or H.

- 10 56. The method of claim 55, wherein X is OH and Y is F.

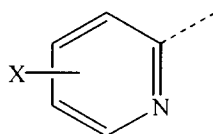
57. The method of claim 55, wherein X is OH and Y is H.

58. The method of claim 55, wherein X is OR₁ and Y is OH.

59. The method of claim 58, wherein R₁ is H.

60. The method of claim 58, wherein R₁ is methyl.

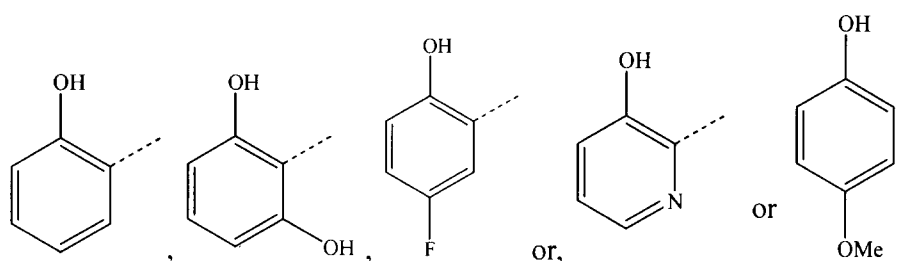
- 15 61. The method of claim 54, wherein R is a substituted pyridine of formula



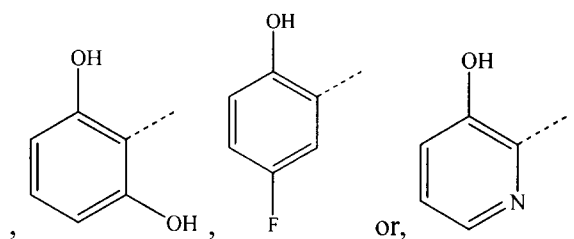
and wherein X is OR₁.

62. The method of claim 61, wherein R₁ is H.

63. The method of claim 53, wherein R is

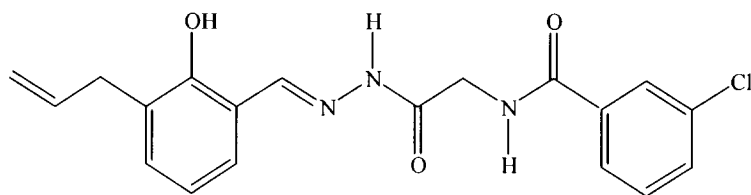


64. The method of claim 63, wherein R is



5 65. The method of claim 53, wherein the compound is a compound of formula IB and wherein X is Cl.

66. The method of claim 65, wherein the compound is a compound of formula:



67. The method of any one of claims 53 to 66, wherein the mammal in need is
10 immunocompetent.

68. The method of any one of claims 53 to 66, wherein the mammal in need is an immunocompromised individual.

69. The method of claim 68, wherein the immunocompromised individual suffers from HIV-infection or neoplasia.

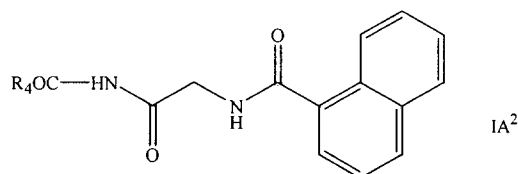
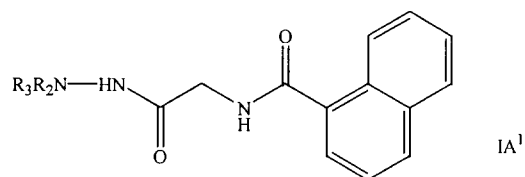
15 70. The method of claim 68, wherein the immunocompromised individual is a transplant recipient.

71. The method of any one of claims 53 to 70, wherein the mammal in need suffers from chickenpox or shingles associated with varicella zoster virus.
72. The method of any one of claims 53 to 70, wherein the mammal in need has an oro-labial or genital infection associated with HSV-1 or HSV-2.
- 5 73. The method of any one of claims 53 to 70, wherein the mammal in need suffers from pneumonitis, colitis or retinitis associated with cytomegalovirus.
74. The method of any one of claims 53 to 70, wherein the herpesvirus infection is associated with a herpesvirus selected from the group consisting of herpes simplex 1, herpes simplex 2, cytomegalovirus and varicella zoster.
- 10 75. The method of claim 74, wherein the herpesvirus is characterized as being resistant to a pyrophosphate analogue, a nucleoside analogue or to a prodrug or derivative thereof.
76. The method of claim 74, wherein the herpesvirus is characterized as being resistant to acyclovir, ganciclovir and/or foscarnet.
- 15 77. The method of claim 76, wherein the herpesvirus is a herpes simplex 1, herpes simplex 2 or varicella zoster virus that is characterized as being resistant to acyclovir and/or foscarnet.
78. The method of claim 76, wherein the herpesvirus is a cytomegalovirus that is characterized as being resistant to ganciclovir and/or foscarnet
- 20 79. A method for identifying a ligand capable of interfering with the replication of herpesvirus, the method comprising, selection of a pocket near the active site, docking a computer-generated model of a putative ligand onto a computer-generated model of a pocket located near the active site of a HSV-1 DNA polymerase in a non-replicating state, and selecting compounds according to an
- 25 estimation of the free energy of ligand binding to the polymerase and hydrogen bonding potential of the ligand with the polymerase.
80. The method of claim 79, wherein said pocket is delimited by residues Val715, Asp717, Ser720, Arg785, Lys811, Asn815, Tyr884 and Lys939.

81. The method of claims 79 or 80, wherein the putative ligand is obtained and tested for *in vitro* inhibition of replication of herpesvirus.

82. A ligand obtained by the method of any one of claims 79 to 81, wherein said ligand is capable of inhibiting the replication of herpesvirus.

5 83. A compound of formula IA¹ or IA²:

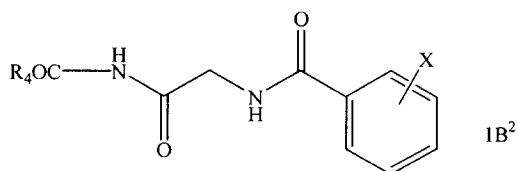
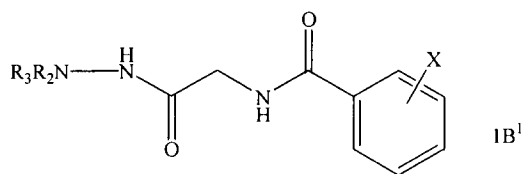


wherein R₂ and R₃ are independently H or an alkyl group of 1 to 6 carbon atoms and;

wherein R₄ is H or an alkyl group of 1 to 6 carbon atoms.

10 84. The use of at least one of the compound of claim 83, in the manufacture of a herpesvirus DNA polymerase ligand or a herpesvirus inhibitor.

85. A compound of formula IB¹ or IB²:



wherein R_2 and R_3 are independently H or an alkyl group of 1 to 6 carbon atoms;

wherein R_4 is H or an alkyl group of 1 to 6 carbon atoms;

wherein X is selected from the group consisting of H, $-OR_1$, NH_2 , F, Cl, Br, I, an alkyl group of 1 to 3 carbon atoms and an allyl group and;

5 wherein R_1 is selected from the group consisting of H and an alkyl group of 1 to 3 carbon atoms.

86. The use of at least one of the compound of claim 85, in the manufacture of a herpesvirus DNA polymerase ligand or a herpesvirus inhibitor.

87. The use of at least one of the compound of claim 22, in the manufacture of a
10 herpesvirus DNA polymerase ligand or a herpesvirus inhibitor.

Figure 1

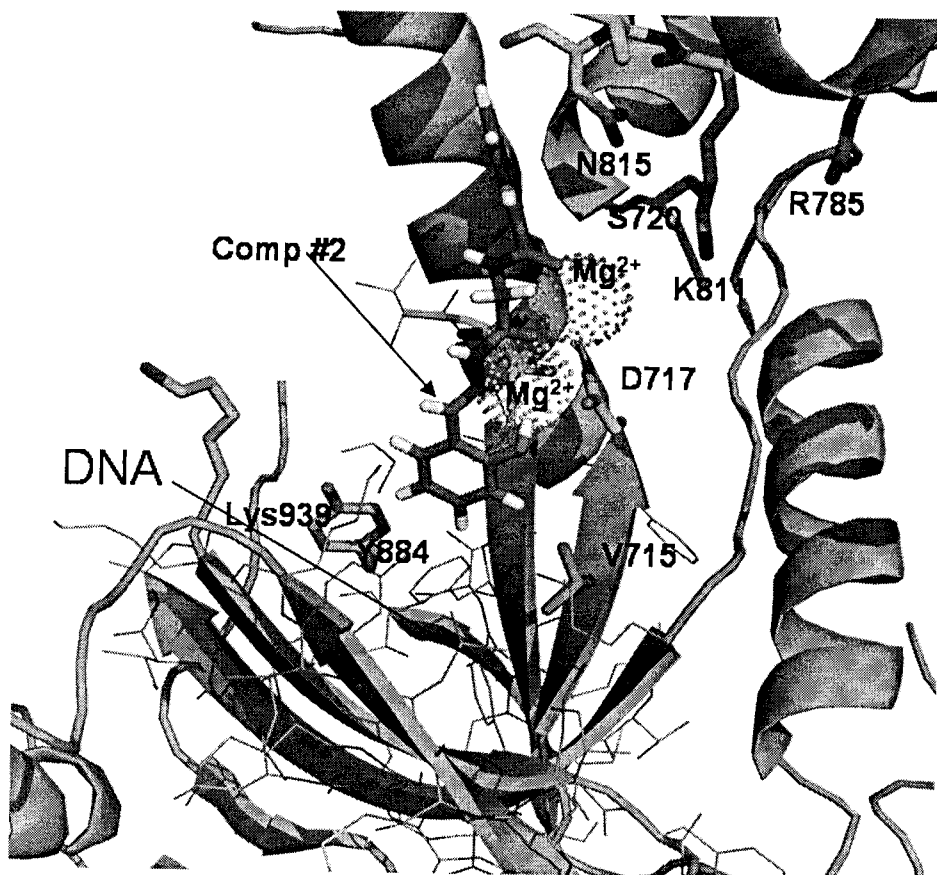


Figure 2

#	Compound name	Catalogue number/supplier
1	N-(2-(2-(2-HYDROXY-5-METHOXYBENZYLIDENE) HYDRAZINO)-2-OXOETHYL)-3-METHYL-BENZAMIDE	R981133/Sigma
2	N-(2-(2-(2-HYDROXYBENZYLIDENE) HYDRAZINO)-2-OXOETHYL)-1-NAPHTHAMIDE	R122629/Sigma
3	N-(2-(2-(3-ALLYL-2-HYDROXYBENZYLIDENE)HYDRAZINO)-2-OXOETHYL)-3-CHLOROBENZAMIDE	R941719/Sigma
4	N-[2-(4-METHOXYPHENYL)ETHYL]-2-[(1-PHENYL-1H-TETRAZOL-5-YL)THIO]ACETAMIDE	7213912/ChemBridge
5	1-(2-CHLORO-5-NITROPHENYLIMINOMETHYL)-2-NAPHTHOL	S698814/Sigma
6	N-1H-TETRAZOL-5-YL-4-BIPHENYLCARBOXAMIDE	7246306/Chembridge
7	9-ANTHRACENECARBALDEHYDE 1H-TETRAZOL-5-YLHYDRAZONE	5482924/ChemBridge
8	N-{[(2-METHYL-2H-TETRAZOL-5-YL) AMINO]CARBONOTHIOYL} -2-THIOPHENECARBOXAMIDE	7726183/ChemBridge
9	N-(2-(2-(2-HYDROXY-5-METHOXYBENZYLIDENE) HYDRAZINO)-2-OXOETHYL)-1-NAPHTHAMIDE	R124397/Sigma
10	N-(2-(2-(3-ALLYL-2-HYDROXYBENZYLIDENE)HYDRAZINO)-2-OXOETHYL)-2-CHLOROBENZAMIDE	R123803/Sigma
11	N-(2-(2-(3-ALLYL-2-HYDROXYBENZYLIDENE)HYDRAZINO)-2-OXOETHYL)-4-CHLOROBENZAMIDE	R115428/Sigma
12	N-(2-(2-(3-ALLYL-2-HYDROXYBENZYLIDENE) HYDRAZINO)-2-OXOETHYL)-1-NAPHTHAMIDE	R122726/Sigma

Figure 3

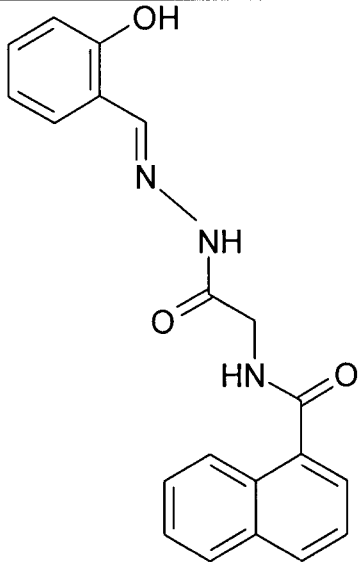
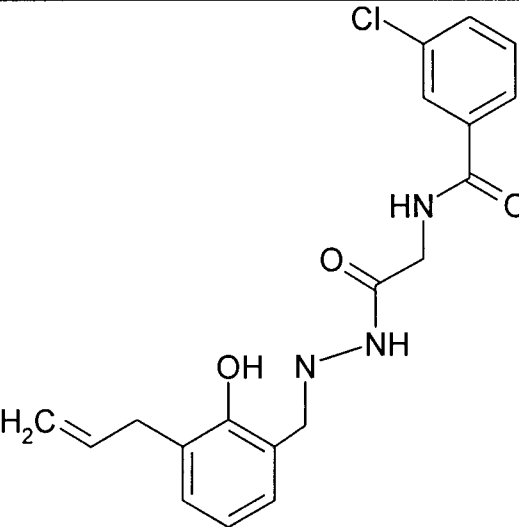
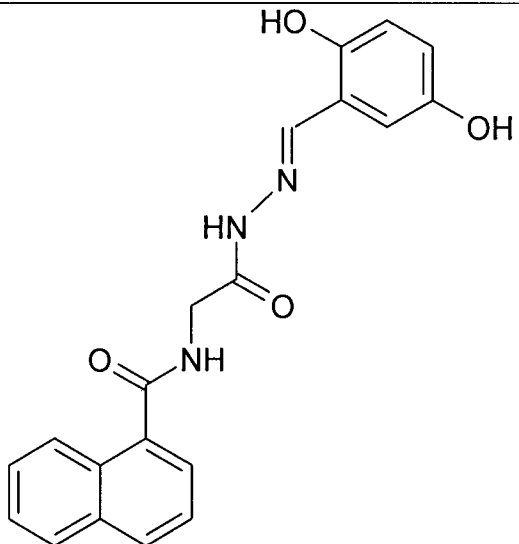
Compound 2 N-(2-(2-(2-HYDROXYBENZYLIDENE)HYDRAZINO)-2-OXOETHYL)-1-NAPHTHAMIDE	
Compound 3 N-(2-(2-(3-ALLYL-2-HYDROXYBENZYLIDENE)HYDRAZINO)-2-OXOETHYL)-3-CHLOROBENZAMIDE	
Compound 9 N-(2-(2-(2-HYDROXY-5-METHOXYBENZYLIDENE)HYDRAZINO)-2-OXOETHYL)-1-NAPHTHAMIDE	

Figure 4A

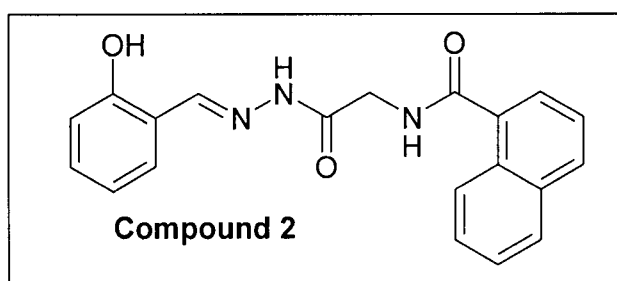
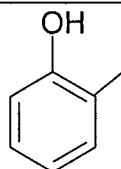
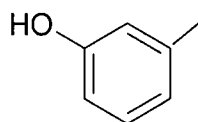
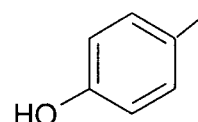
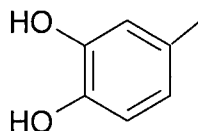
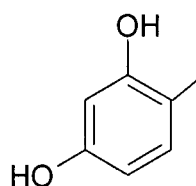
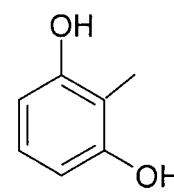
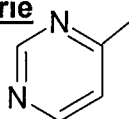
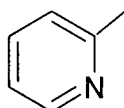
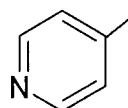
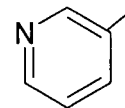
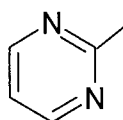
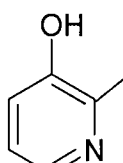
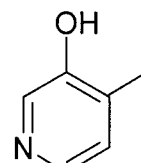
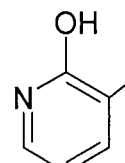
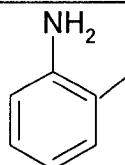
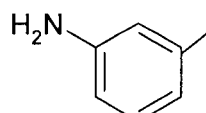
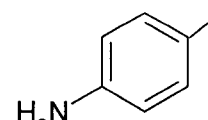
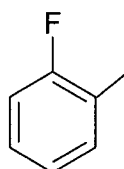
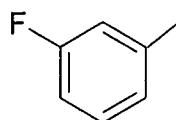
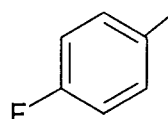
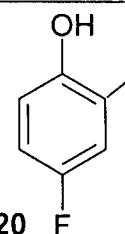
**Hydroxy serie****C2****C2.01****C2.02****C2.03****C2.04****C2.05****Pyridine serie****C2.06****C2.07****C2.08****C2.09****C2.10****C2.11****C2.12****C2.13****Anilline serie****C2.14****C2.15****C2.16****Fluoro serie****C2.17****C2.18****C2.19****C2.20**

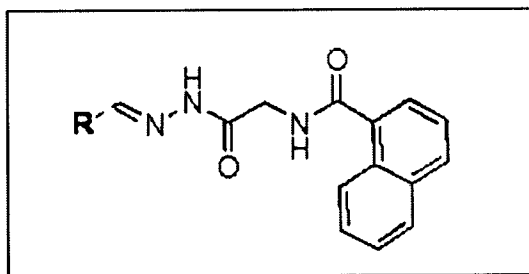
Figure 4B

- C2. (E)-N-(2-(2-(2-hydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide.
C2.01 (E)-N-(2-(2-(3-hydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide
C2.02 (E)-N-(2-(2-(4-hydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide
5 C2.03 (E)-N-(2-(2-(3,4-dihydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide
C2.04 (E)-N-(2-(2-(2,4-dihydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide
C2.05 (E)-N-(2-(2-(2,6-dihydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide
C2.06 (E)-N-(2-oxo-2-(2-(pyrimidin-4-ylmethylene)hydrazinyl)ethyl)-1-naphthamide
C2.07 (E)-N-(2-oxo-2-(2-(pyridin-2-ylmethylene)hydrazinyl)ethyl)-1-naphthamide
10 C2.08 (E)-N-(2-oxo-2-(2-(pyridin-4-ylmethylene)hydrazinyl)ethyl)-1-naphthamide
C2.09 (E)-N-(2-oxo-2-(2-(pyridin-3-ylmethylene)hydrazinyl)ethyl)-1-naphthamide
C2.10 (E)-N-(2-oxo-2-(2-(pyrimidin-2-ylmethylene)hydrazinyl)ethyl)-1-naphthamide
C2.11 (E)-N-(2-(2-((3-hydroxypyridin-2-yl)methylene)hydrazinyl)-2-oxoethyl)-1-naphthamide
15 C2.12 (E)-N-(2-(2-((3-hydroxypyridin-4-yl)methylene)hydrazinyl)-2-oxoethyl)-1-naphthamide
C2.13 (E)-N-(2-(2-((2-hydroxypyridin-3-yl)methylene)hydrazinyl)-2-oxoethyl)-1-naphthamide
C2.14 (E)-N-(2-(2-(2-aminobenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide
20 C2.15 (E)-N-(2-(2-(3-aminobenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide
C2.16 (E)-N-(2-(2-(4-aminobenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide
C2.17 (E)-N-(2-(2-(2-fluorobenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide
C2.18 (E)-N-(2-(2-(3-fluorobenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide
C2.19 (E)-N-(2-(2-(4-fluorobenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide
25 C2.20 (E)-N-(2-(2-(5-fluoro-2-hydroxybenzylidene)hydrazinyl)-2-oxoethyl)-1-naphthamide.

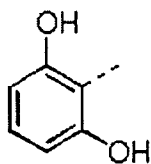
Figure 4C

ChemScore	Compound
42.54	C2.04
40.86	C2.11
40.82	C2.05
40.53	C2.08
40.27	C2.10
40.08	C2.20
40.05	C2
38.98	C2.12
38.53	C2.13
37.71	C2.01
36.98	C2.16
36.71	C2.09
36.07	C2.17
35.82	C2.06
35.65	C2.14
34.24	C2.07
33.33	C2.15
32.32	C2.18
30.53	C2.19
30.52	C2.03
26.99	C2.02

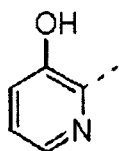
Figure 5

**Compound 2
derivatives**

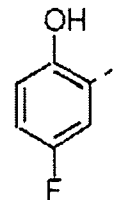
R =



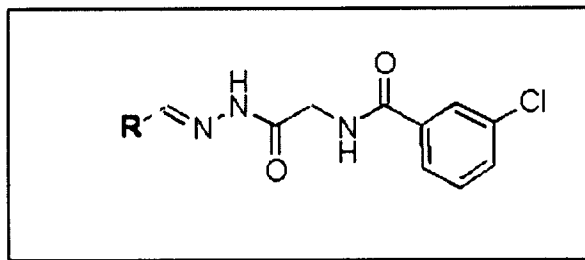
C2.5



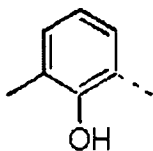
C2.11



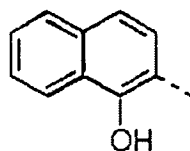
C2.20

**Compound 3
derivatives**

R =



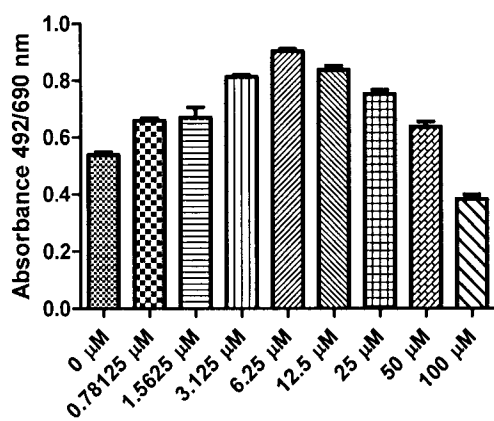
C3-1



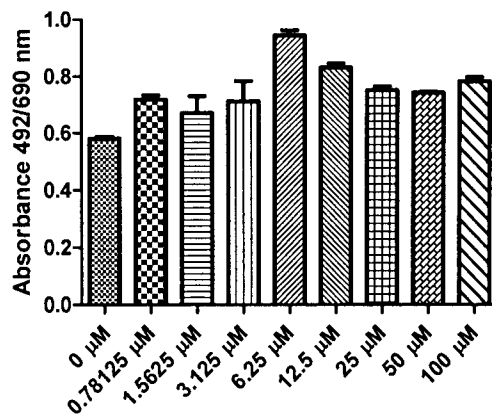
C3-2

Figure 6

A

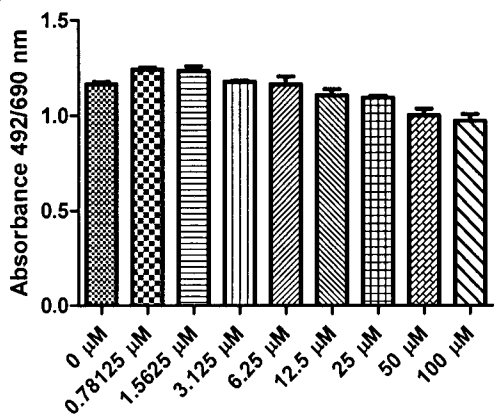


Compound 2

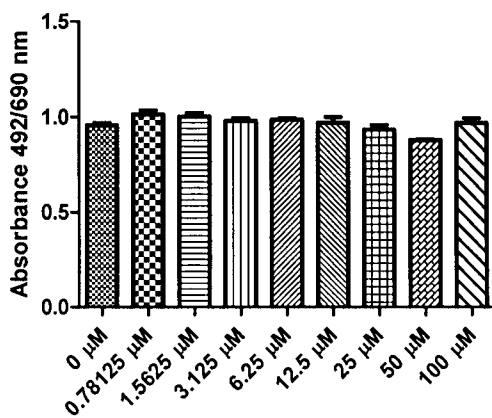


Compound 3

B



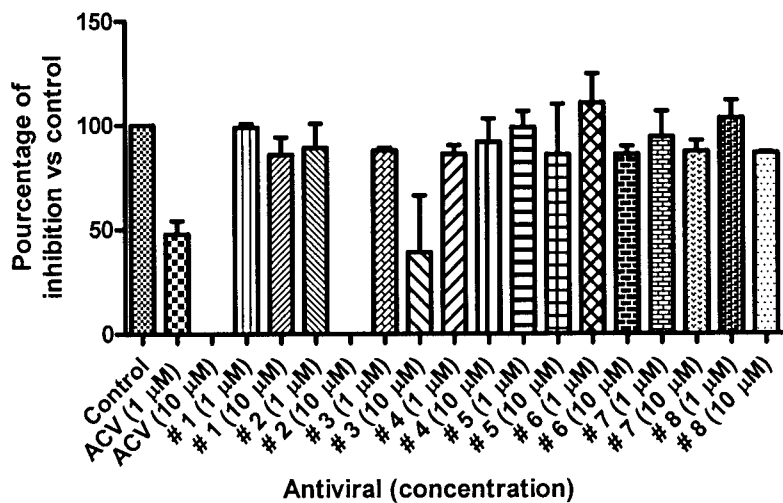
Compound 2



Compound 3

Figure 7A

HSV-1



HSV-2

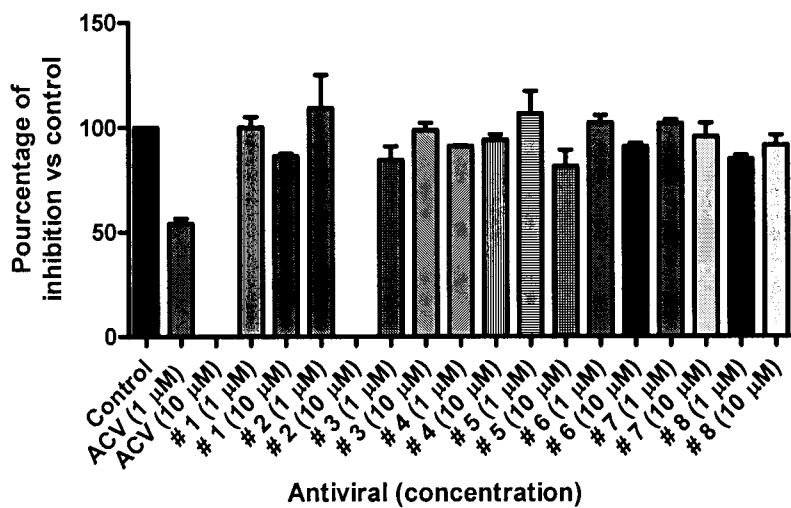
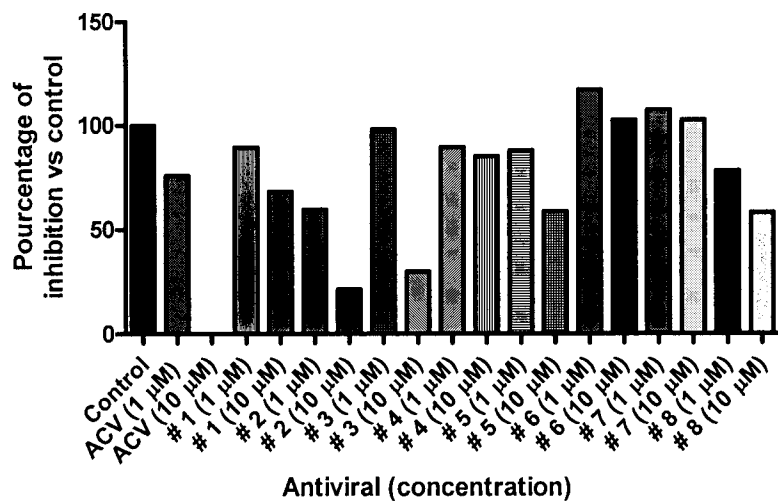


Figure 7B

VZV



CMV

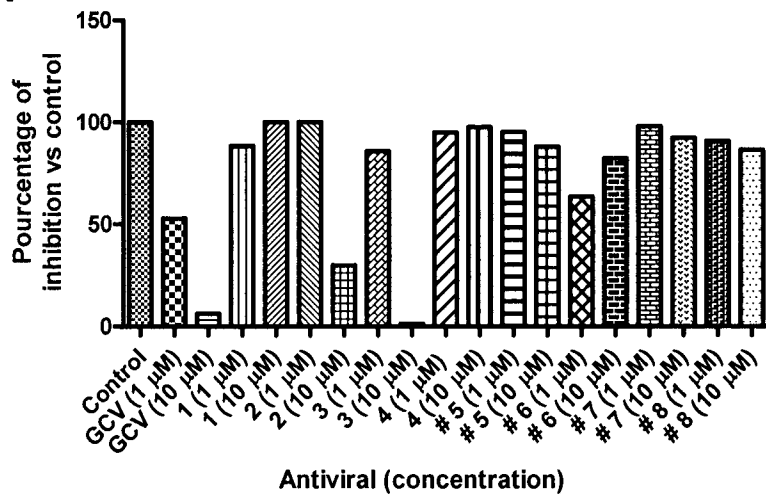


Figure 8

Viral strains	50% inhibitory concentration (IC ₅₀) values (μM)					
	ACV	GCV	FOS	Compound 2	Compound 3	Compound 9
HSV-1						
(H25)	1.2 ± 0.2	nd	38,9	4.2 ± 0.5	9.3 ± 0.8	4.2 ± 0.5
HSV-2						
(HSV22)	1.5 ± 0.3	nd	83,3	4.5 ± 0.6	8.2 ± 0.7	6.6 ± 0.2
VZV						
(Ellen)	4.8	nd	nd	9.6 ± 1.6	8.8 ± 1.6	nd
CMV						
(AD169)	nd	1.6 ± 0.2	27.8 ± 0.7	> 16	4.1 ± 1.6	> 16

Abbreviations: ACV, acyclovir; GCV, ganciclovir; FOS, foscarnet; nd, not determined.

Figure 9

HSV-1 strains	50% inhibitory concentration (IC ₅₀) values (μM)		
	ACV (Fold)*	FOS (Fold)*	Compound 2 (Fold)*
H25 (WT)	1.22 (1)	38.9 (1)	4.24 ± 0.48 (1)
KOS	0.4 (0.3)	44.06 (1.1)	4.05 ± 0.22 (1)
C119629	0.42 (0.3)	14.89 (0.4)	4.39 ± 0.26 (1)
C114093 (ACV-Res) ^a	17.74 (14.5)	27.22 (0.7)	4.72 ± 1.20 (1.1)
C80249 (ACV-Res) ^b	8.51 (7.0)	28.95 (0.7)	3.09 ± 0.45 (0.7)
L-920062 (FOS-Res) ^c	1.5 (1.2)	390.4 (10.0)	3.49 ± 0.65 (0.8)

* Fold change compared to the HSV-1 strain H25 (wild-type).

5 Abbreviations: ACV, acyclovir; FOS, foscarnet; Res, resistant.

^a, The ACV-resistant C114093 carries a truncated version of the thymidine kinase (stop codon leading to a truncated protein of 281 amino acids)

^b, The ACV-resistant C80249 carries a truncated version of the thymidine kinase (stop codon leading to a truncated protein of 225 amino acids) and a DNA polymerase mutation (E756Q)

10 ^c, The FOS-resistant L-920062 carries two DNA polymerase mutations (S724N and P920S)

Figure 10

HSV-2 strains	50% inhibitory concentration (IC ₅₀) values (μM)		
	ACV (Fold)*	FOS (Fold)*	Compound 2 (Fold)*
HSV22 (WT)	1.51 (1)	83.3 (1)	4.52 ± 0.63 (1)
MS2	3.22 (2.1)	89.55 (1.1)	6.62 ± 0.68 (1.5)
C75134	1.65 (1.1)	42.86 (0.5)	6.33 ± 0.39 (1.4)
W-940012 (ACV-Res) ^a	27.01 (17.9)	91.1 (1.1)	7.03 ± 0.52 (1.6)
C72984 (ACV-Res) ^b	27.54 (18.2)	36.88 (0.4)	6.09 ± 1.08 (1.4)
D-900180 (FOS-Res) ^c	1.99 (1.32)	367.1 (4.4)	4.97 ± 0.30 (1.1)
M-890546 (ACV/FOS-Res) ^d	10.73 (7.1)	234 (2.8)	7.9 ± 0.57 (1.7)
P-920056 (ACV/FOS-Res) ^e	276.1 (182.8)	521.1 (6.2)	5.63 ± 1.31 (1.3)

* Fold change compared to the HSV-2 strain HSV22 (wild-type).

Abbreviations: ACV, acyclovir; FOS, foscarnet; Res, resistant.

^a, The ACV-resistant W-940012 carries a truncated version of the thymidine kinase (stop codon leading to a truncated protein of 228 amino acids)

5 ^b, The ACV-resistant C72984 carries three mutations in the thymidine kinase (R272V, P273S and N274R)

^c, The FOS-resistant D-900180 carries a DNA polymerase mutation (L850I)

^d, The ACV/FOS-resistant M-890546 carries a DNA polymerase mutation (S729N)

10 ^e, The ACV/FOS-resistant P-920056 carries a truncated version of the thymidine kinase (stop codon leading to a truncated protein of 184 amino acids) and a DNA polymerase mutation (D912V)

Figure 11

VZV		50% inhibitory concentration (IC ₅₀) values (μM)		
strains		ACV (Fold)*	FOS	Compound 2 (Fold)*
Ellen (WT)		4.8 (1)	nd	9.6 ± 1.6 (1)
GB2000VZV (ACV-Res) ^a		41 (8.5)	86.7	6.0 ± 2.2 (0.6)

*, Fold-change compared to the VZV strain Ellen (wild-type)

Abbreviations: ACV, acyclovir; FOS, foscarnet; Res, resistant; nd, not determined

^a, The ACV-resistant GB2000VZV carries a thymidine kinase mutation (C138R)

5

Figure 12

CMV		50% inhibitory concentration (IC ₅₀) values (μM)		
strains		GCV (Fold)*	FOS (Fold)*	Compound 3 (Fold)*
AD169 (WT)		1.61 ± 0.23 (1)	27.79 ± 0.68 (1)	4.06 ± 1.61 (1)
VQA3 (GCV/FOS-Res) ^a		27.48 (17.1)	335.8 (12.1)	6.12 ± 1.52 (1.5)
Xbaf (GCV-Res) ^b		6.10 (3.8)	21.29 (0.8)	8.1 ± 0.70 (2)

* Fold change compared to the CMV strain AD169 (wild-type).

Abbreviations: GCV, ganciclovir; FOS, foscarnet; Res, resistant.

^a, The GCV/FOS-resistant VQA3 carries two mutations in the DNA polymerase (UL54; F412C and L802M) and one mutation in the UL97 gene (C603W)

^b, The GCV-resistant Xbaf has amino acid deletions at positions 590-593

10

Figure 13

	Permeability coefficient (10^{-6} cm/s) (P_{app})
Compound 2	11,4
Compound 3	3,4

Figure 14

Compound ID	Microsomal Cl_{int} (ml/min/mg microsomal protein)	Half-life $t_{1/2}$ (min)	Cl_{int} extrapolated to the whole liver (ml/min/kg protein)
Compound 2	0.02105	32.93	37.26
Compound 3	0.0318	21.94	61.92
Reserpine	0.0163	42.59	28.08

5 Figure 15

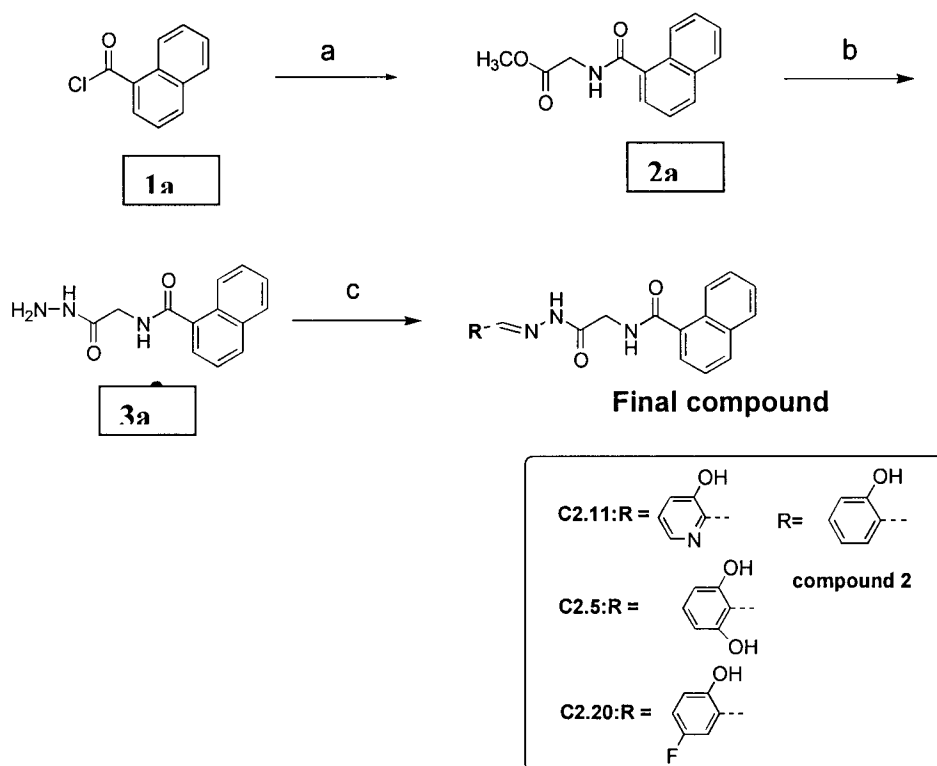
Viral strains	50% inhibitory concentration (IC_{50}) values (μ M)				
	C2.05	C2.11	C2.20	C3-1	C3-2
HSV-1 (H25)	> 16	> 16	8.27 ± 1.70	> 16	> 16
HSV-2 (HSV22)	9.85 ± 3.60	8.60 ± 3.50	6.50 ± 2.80	> 16	> 16
VZV (GB2000VZV)	> 16	11.70 ± 2.50	5.00 ± 0.80	> 16	> 16
CMV (AD169)	> 16	> 16	> 16	> 16	> 16

Figure 16

Compounds	50% cytotoxicity (CC ₅₀) values (μM)	
	Vero cells	HFFs
C2	82.1	56.2
C2.05	> 100	67.1
C2.11	> 100	52.4
C2.20	79.5	43.3
C3	53.1	27
C3-1	76.6	28.5
C3-2	49.1	27.2
ACV	> 100	---
GCV	---	> 100
FOS	> 100	> 100

Abbreviations: HFFs, human foreskin fibroblasts; ACV, acyclovir; GCV, ganciclovir; FOS, foscarnet

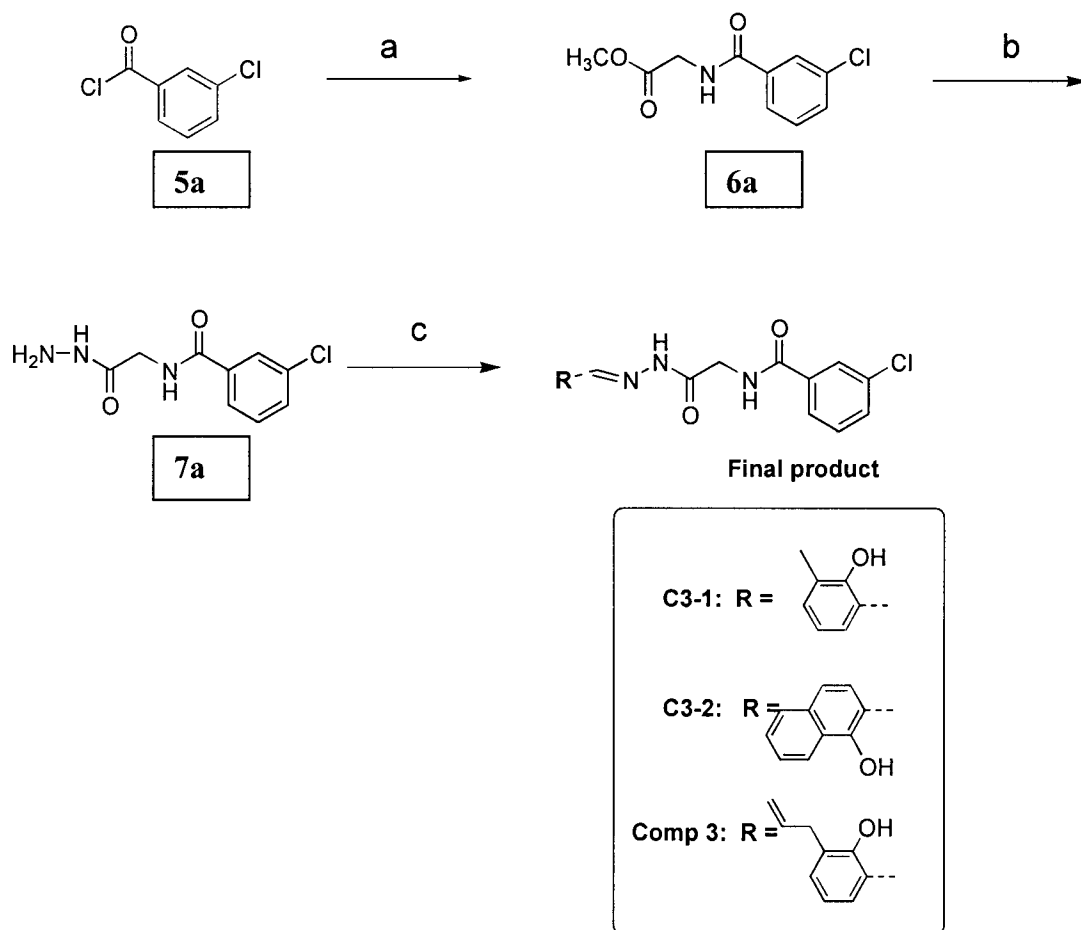
Figure 17



Reagents and conditions: (a) methyl glycinate, triethylamine, THF, rt; (b) Hydrazine, MeOH, t.p; (c) corresponding aldehyde (**C2.11**: 3-hydroxypyridine-2-carboxaldehyde; **C2.5**: 2,6 dihydroxybenzaldehyde; **C2.20**: 5-Fluoro-2-hydroxybenzaldehyde); **compound 2** : 2-hydroxybenzaldehyde), EtOH, rt.

Figure 18

5



Reagents and conditions: (a) methyl glycinate, triethylamine, THF, rt; (b) Hydrazine, MeOH, t.p; (c) corresponding aldehyde (**C3-1**: 2-hydroxy-3-methylbenzaldehyde; **C3-2**: 1-Hydroxy-2-naphtaldehyde; **Compound 3**: 2-hydroxy-3-(prop-2-en-1-yl)benzaldehyde), EtOH, rt.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2010/000762

A. CLASSIFICATION OF SUBJECT MATTER IPC: <i>C07C 251/86</i> (2006.01) , <i>A61K 31/166</i> (2006.01) , <i>A61K 31/41</i> (2006.01) , <i>A61K 31/44</i> (2006.01) , <i>A61K 31/505</i> (2006.01) , <i>A61P 31/22</i> (2006.01) (more IPCs on the last page) According to International Patent Classification (IPC) or to both national classification and IPC														
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) <i>C07C 251/86</i> (2006.01), <i>A61P 31/22</i> (2006.01), <i>C07D 213/53</i> (2006.01) , <i>C07D 239/26</i> (2006.01), <i>A61K 31/166</i> (2006.01), <i>A61K 31/41</i> (2006.01), <i>A61K 31/44</i> (2006.01), <i>A61K 31/505</i> (2006.01) Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used) Chemical Abstracts Database (STN): structure search; EPOQUE (EPODOC, NPL): IPC, keywords (DNA, polymerase, herpesvirus, cytomegalovirus, varicella-zoster), applicant, inventors; Canadian Patent Database: IPC.														
C. DOCUMENTS CONSIDERED TO BE RELEVANT <table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>P,X</td> <td>WO 2009/088975 A2 (SOUMYA et al.) 16 July 2009 (16-07-2009) * Figure 12/3, molecule_0074 * * Claim 27 *</td> <td>1-3, 6, 7, 11, 12, 17, 22-24, 27, 28, 32</td> </tr> <tr> <td>X</td> <td>STN, Chemical Abstract Service: Columbus, OH, 2010 RN 391893-54-2, 391893-51-9, 391893-50-8, 391893-49-5, 391893-48-4, 391893-47-3, 391883-69-5, 391883-67-3, 391883-65-1, 391883-64-0, 391883-63-9, 391883-62-8, 391883-61-7, 391883-60-6, 391883-59-3, 391883-57-1, 391883-55-9, 391883-53-7, 391883-49-1: all entered 13 February 2002 (13-02-2002) RN 765273-27-6: entered 19 October 2004 (19-10-2004) RN 880069-85-2, 880064-70-0, 880048-87-3, 880046-14-0, 880044-10-0, 880042-27-3, 880030-97-7, 880029-42-5: all entered 11 April 2006 (11-04-2006) RN 883790-72-5 : entered 11 May 2006 (11-05-2006)</td> <td>22-33</td> </tr> <tr> <td>X</td> <td>STN, Chemical Abstract Service: Columbus, OH, 2010 RN 392247-16-4: entered 14 February 2002 (14-02-2002)</td> <td>83</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	P,X	WO 2009/088975 A2 (SOUMYA et al.) 16 July 2009 (16-07-2009) * Figure 12/3, molecule_0074 * * Claim 27 *	1-3, 6, 7, 11, 12, 17, 22-24, 27, 28, 32	X	STN, Chemical Abstract Service: Columbus, OH, 2010 RN 391893-54-2, 391893-51-9, 391893-50-8, 391893-49-5, 391893-48-4, 391893-47-3, 391883-69-5, 391883-67-3, 391883-65-1, 391883-64-0, 391883-63-9, 391883-62-8, 391883-61-7, 391883-60-6, 391883-59-3, 391883-57-1, 391883-55-9, 391883-53-7, 391883-49-1: all entered 13 February 2002 (13-02-2002) RN 765273-27-6: entered 19 October 2004 (19-10-2004) RN 880069-85-2, 880064-70-0, 880048-87-3, 880046-14-0, 880044-10-0, 880042-27-3, 880030-97-7, 880029-42-5: all entered 11 April 2006 (11-04-2006) RN 883790-72-5 : entered 11 May 2006 (11-05-2006)	22-33	X	STN, Chemical Abstract Service: Columbus, OH, 2010 RN 392247-16-4: entered 14 February 2002 (14-02-2002)	83
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.												
P,X	WO 2009/088975 A2 (SOUMYA et al.) 16 July 2009 (16-07-2009) * Figure 12/3, molecule_0074 * * Claim 27 *	1-3, 6, 7, 11, 12, 17, 22-24, 27, 28, 32												
X	STN, Chemical Abstract Service: Columbus, OH, 2010 RN 391893-54-2, 391893-51-9, 391893-50-8, 391893-49-5, 391893-48-4, 391893-47-3, 391883-69-5, 391883-67-3, 391883-65-1, 391883-64-0, 391883-63-9, 391883-62-8, 391883-61-7, 391883-60-6, 391883-59-3, 391883-57-1, 391883-55-9, 391883-53-7, 391883-49-1: all entered 13 February 2002 (13-02-2002) RN 765273-27-6: entered 19 October 2004 (19-10-2004) RN 880069-85-2, 880064-70-0, 880048-87-3, 880046-14-0, 880044-10-0, 880042-27-3, 880030-97-7, 880029-42-5: all entered 11 April 2006 (11-04-2006) RN 883790-72-5 : entered 11 May 2006 (11-05-2006)	22-33												
X	STN, Chemical Abstract Service: Columbus, OH, 2010 RN 392247-16-4: entered 14 February 2002 (14-02-2002)	83												
[X] Further documents are listed in the continuation of Box C. [X] See patent family annex. <table border="1"> <tbody> <tr> <td>* Special categories of cited documents :</td> <td>"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</td> </tr> <tr> <td>"A" document defining the general state of the art which is not considered to be of particular relevance</td> <td>"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</td> </tr> <tr> <td>"E" earlier application or patent but published on or after the international filing date</td> <td>"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</td> </tr> <tr> <td>"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)</td> <td>"&" document member of the same patent family</td> </tr> <tr> <td>"O" document referring to an oral disclosure, use, exhibition or other means</td> <td></td> </tr> <tr> <td>"P" document published prior to the international filing date but later than the priority date claimed</td> <td></td> </tr> </tbody> </table>			* Special categories of cited documents :	"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	"A" document defining the general state of the art which is not considered to be of particular relevance	"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	"E" earlier application or patent but published on or after the international filing date	"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	"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)	"&" document member of the same patent family	"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	
* Special categories of cited documents :	"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													
"A" document defining the general state of the art which is not considered to be of particular relevance	"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													
"E" earlier application or patent but published on or after the international filing date	"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													
"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)	"&" document member of the same patent family													
"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														
Date of the actual completion of the international search 21 July 2010 (21-07-2010)		Date of mailing of the international search report 19 August 2010 (19-08-2010)												
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001-819-953-2476		Authorized officer Philippe Couture (819) 934-9089												

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/CA2010/000762**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the 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. ☒ Claim Nos. : 53-78

because they relate to subject matter not required to be searched by this Authority, namely :

Although claims 53-78 are directed to methods of medical treatment which this Authority is not required to search in accordance with Rule 39.1 (iv) of the PCT, the search has been carried out based on the use of the compounds defined therein.

2. ☐ Claim 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. ☐ Claim Nos. :

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

Box No. III 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 :

Group A: Claims 1-16, 17-21 (in part), 22-78 and 83-87

A pharmaceutical composition comprising a compound of formula IA or IB and its use in impairing the replication of herpesviruses and in treating or preventing a herpesvirus infection; a compound of formula IA; and intermediates used in the synthesis of IA or IB.

Group B: Claims 17-21 (in part)

A pharmaceutical composition comprising the compound (i) as defined in claim 17 and its use in interfering with herpesvirus replication.
[continued on extra 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 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 claim 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 claim Nos. : 1-16, 17-21 (in part), 22-78 and 83-87

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.

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/CA2010/000762

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STN, Chemical Abstract Service: Columbus, OH, 2010 RN 737773-98-7: entered 02 September 2002 (02-09-2002) RN 330470-70-7, 330470-69-4, 330470-60-5: all entered 06 April 2001 (06-04-2001) RN 140181-28-8: entered 03 April 1992 (03-04-1992) RN 90872-07-4, 6063-98-5, 2443-68-7, 21568-89-8: all entered 16 November 1984 (16-11-1984)	85

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2010/000762

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
WO2009088975	16-07-2009	US20090233845A1	17-09-2009

Continuation of: Box 3

Group C: Claims 17-21 (in part)

A pharmaceutical composition comprising the compound (iv) as defined in claim 17 and its use in interfering with herpesvirus replication.

Group D: Claims 17-21 (in part)

A pharmaceutical composition comprising the compound (v) as defined in claim 17 and its use in interfering with herpesvirus replication.

Group E: Claims 17-21 (in part)

A pharmaceutical composition comprising the compound (vi) as defined in claim 17 and its use in interfering with herpesvirus replication.

Group F: Claims 17-21 (in part)

A pharmaceutical composition comprising the compound (vii) as defined in claim 17 and its use in interfering with herpesvirus replication.

Group G: Claims 17-21 (in part)

A pharmaceutical composition comprising the compound (viii) as defined in claim 17 and its use in interfering with herpesvirus replication.

Group H: Claims 79-82

A method for identifying a ligand capable of interfering with the replication of herpesvirus.

There is no novel common structural feature linking the compounds of Groups B-G, or linking the compounds of any one of Groups B-G with those of Group A. It is noted that the compounds of Groups B-G do not fall within formula IA or IB as defined in claim 1; furthermore, they cannot serve as intermediates in the preparation of compound IA or IB. In the case of Group H, the ligands which can be identified using the claimed method would not necessarily share the structural features of compounds of formula IA or IB, or of the compounds of Groups B-G.

Continuation of: Item A, page 5

C07D 213/53 (2006.01) , *C07D 239/26* (2006.01) , *C07D 257/04* (2006.01) , *C12Q 1/70* (2006.01) ,
G01N 33/571 (2006.01) , *G06F 17/50* (2006.01) , *G06F 19/00* (2006.01)