

Orthopoxvirus. In some embodiments, the virus is Zaire Ebolavirus, Reston Ebolavirus, Sudan Ebolavirus, Ivory Coast Ebolavirus, Bundibugyo Ebolavirus, Marburgvirus, Lassa virus, Influenzavirus A, Cowpox virus, or Monkeypox virus. In some embodiments, the virus is not a reverse transcribing diploid single-stranded RNA virus or a reverse transcribing circular double-stranded DNA virus. In some embodiments, if the virus is an oncornavirus, the compound is an excluded compound.

[0021] In some embodiments, the present invention provides compounds having a structural formula falling within one of the general structural formulas described herein and compositions thereof. The compositions may have one or more compounds of the present invention. The compositions may further comprise pharmaceutically acceptable carriers, supplementarily active compounds, and the like as disclosed herein.

[0022] Both the foregoing general description and the following detailed description are exemplary and explanatory only and are intended to provide further explanation of the invention as claimed. The accompanying drawings are included to provide a further understanding of the invention and are incorporated in and constitute part of this specification, illustrate several embodiments of the invention, and together with the description, serve to explain the principles of the invention.

DESCRIPTION OF THE DRAWINGS

[0023] This invention is further understood by reference to the drawings wherein:

[0024] FIG. 1 shows cells emitting green fluorescent light (light spots) in the control sample (left panel) and a sample treated with a compound.

[0025] FIG. 2 shows the structural formulas for NSC 369723, NSC 294202, and NSC 128981.

[0026] FIG. 3 shows that mice treated with either NSC 369723 or NSC 294202 were completely protected from lethal challenge, whereas the control mice showed only 40% survival.

[0027] FIG. 4A shows that NSC 369723 exhibits dose dependent antiviral activity toward EBOV-GFP. Data are summary of about 3 to about 20 individual experiments.

[0028] FIG. 4B shows that NSC 294202 exhibits dose dependent antiviral activity toward EBOV-GFP. Data are summary of about 3 to about 20 individual experiments.

[0029] FIG. 4C shows that NSC 306365 exhibits dose dependent antiviral activity toward EBOV-GFP. Data are summary of about 3 to about 20 individual experiments.

[0030] FIG. 4D shows that NSC 300510 exhibits dose dependent antiviral activity toward EBOV-GFP. Data are summary of about 3 to about 20 individual experiments.

[0031] FIG. 4E shows that NSC 240893 exhibits dose dependent antiviral activity toward EBOV-GFP. Data are summary of about 3 to about 20 individual experiments.

[0032] FIG. 4F shows that NSC 294206 exhibits dose dependent antiviral activity toward EBOV-GFP. Data are summary of about 3 to about 20 individual experiments.

[0033] FIG. 5A shows that NSC 306365 at 4 μ M and NSC 294202 at a concentration of 10 μ M inhibit the replication of the ZH501 strain of Rift Valley fever virus (RVFV) in Vero-E6 cells.

[0034] FIG. 5B shows that NSC 306365 exhibits dose dependent antiviral activity toward the ZH501 strain of Rift Valley fever virus (RVFV) in Vero-E6 cells.

[0035] FIG. 5C shows that NSC 306365 at 4 μ M and NSC 294202 at a concentration of 10 μ M inhibit the replication of influenza virus (H1N1 A/Texas) in Vero-E6 cells.

[0036] FIG. 5D shows that NSC 306365 at 4 μ M and 2 μ M inhibit the replication of Lassa virus (Josiah strain) in Vero-E6 cells.

[0037] FIG. 6 shows NSC 369723 and NSC 294202 provided 100% protection and 90% of the control mice died from infection.

[0038] FIG. 7 shows the post-exposure dose-response efficacy of NSC 306365.

[0039] FIG. 8 shows that NSC 369723, NSC 294202, and NSC 300510 provided 100% protection against m-MARV in mice.

[0040] FIG. 9 shows that two injections of NSC300510, NSC294199, and NSC369723 on days 1 and 5 after infection of C57BL/6 mice with EBOV (1000 pfu) confers protection against death.

[0041] FIG. 10A shows that cells pretreated with NSC 369723 for 24 hours (and its removal during and after infection) is more effective than treatment during and after infection.

[0042] FIG. 10B shows the % inhibition of infection determined after 48 hours in cells that were treated with NSC 369723 for 24 hours or 48 hours and washed away before infection or kept in culture during infection.

[0043] FIG. 10C shows the % inhibition of infection determined after 48 hours in cells after challenge with virus that was pre-incubated with NSC 369723 or NSC

[0044] 294202. The resulting MOI and the concentration of the drug that was carried over to the cells are shown.

[0045] FIG. 11 shows that NSC 306365 prolongs the mean time to death in mouse model of Cowpox virus.

DETAILED DESCRIPTION OF THE INVENTION

[0046] The present invention relates to compounds and a pharmacophore model for compounds which exhibit antiviral activity. As used herein, "antiviral activity" refers to the activity of an agent that prevents, inhibits, or reduces the viral activity of a virus or the activity of a compound which destroys a virus. As used herein, "viral activity" refers to the ability of a virus to replicate, multiply, reproduce or infect a cell or a subject.

1. High Throughput Screening (HTS) Assays

[0047] For high throughput screening assays, a recombinant Ebola Zaire virus expressing green fluorescence protein (EBOV-GFP) was used. See Towner et al. (2005) *Virology* 332(1):20-27, which is herein incorporated by reference. Productive infection of cells with EBOV-GFP results in the cells emitting green fluorescent light when excited at 488 nm. In initial studies, the number of cells and multiplicity of infection (MOI) for EBOV-GFP and Vero-E6 cells to be used were optimized. Specifically, all possible combinations of different number of cells (about 10000 to about 50000 cells per well) and different MOIs (0.1, 1, 5, and 20) were tested in 24 well plates. 48 hours after infection cells were fixed in formalin and the percent infection (% GFP positive cells) was determined to identify standard conditions that results in about 50 to about 70% infection.

[0048] Then the assay format was adopted to a 96 well format and the MOI was adjusted to achieve about 50 to about 70% infection within about 48 hours. Specifically, cell num-