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(54) Title: ENSEMBLE-BASED VIRTUAL SCREENING REVEALS NOVEL ANTIVIRAL COMPOUNDS FOR AVIAN INFLUENZA NEURAMINIDASE

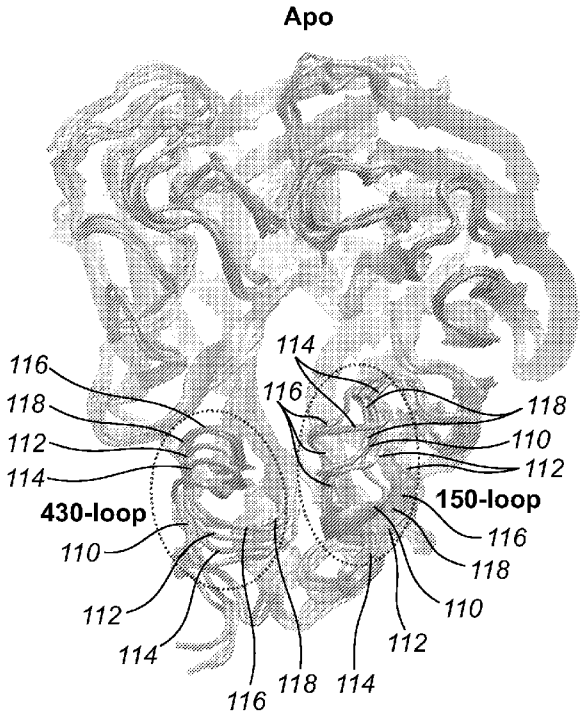

FIG. 1A

(57) Abstract: The embodiments provide compound that can bind to the avian influenza virus subtype H5N1 neuraminidase protein, as well as compositions, including pharmaceutical compositions comprising a subject compound. The embodiments further provide treatment methods, including methods of treating avian influenza.

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ENSEMBLE-BASED VIRTUAL SCREENING REVEALS NOVEL ANTIVIRAL COMPOUNDS FOR AVIAN INFLUENZA NEURAMINIDASE

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application No. 61/062,215, filed January 23, 2008 which is incorporated herein by reference in its entirety.

STATEMENT OF GOVERNMENT SUPPORT

[0002] This invention was made with government support under W81XWH-07-02-0014 awarded by the Army, GM031749 awarded by the National Institutes of Health, GM077729 awarded by the National Institutes of Health, RR008605 awarded by the National Institutes of Health, INT-0314015 awarded by the National Science Foundation, INT-0407508 awarded by the National Science Foundation, MCB-0506593 awarded by the National Science Foundation, and OCI-0627026 awarded by the National Science Foundation. The government has certain rights in the invention.

BACKGROUND OF THE INVENTION

Field of the Invention

[0003] The present invention relates to ensemble-based virtual screening of compound libraries, analogs of initial lead compounds obtained from screening methods and compounds for treatment of avian influenza.

Description of the Related Art

[0004] Avian influenza has recently received worldwide attention due to its rapid global spread and the growing number of human cases [1]. The highly pathogenic avian virus that the World Health Organization fears may also become highly contagious in humans is an influenza A virus of the subtype H5N1 [1]. The subtype name is derived from the membrane glycoproteins hemagglutinin (HA) and neuraminidase (NA); there are 16 known types of HA and nine types of NA [2]. The antiviral drugs Tamiflu (oseltamivir) and Relenza (zanamivir) target the NA and have been used to successfully

treat several human cases [3], but drug-resistant strains of the virus have already begun to emerge [4].

[0005] Neuraminidase (NA) is a transmembrane homotetramer that cleaves terminal sialic residues on the host cell surface [4]. The sialidase activity of NA prevents viral aggregation by cleaving terminal sialic acid residues on host cell surface receptors, thus facilitating the release of viral progeny from infected cells [4]. As the NA active site is relatively well-conserved, NA has become a popular target for antiviral drugs [5]. Currently available NA inhibitors such as Tamiflu and Relenza are sialic acid analogs that competitively inhibit the protein's sialidase function and, consequentially, stall the viral infectious cycle [4].

[0006] The first crystal structures of NA-1 (N1) revealed the existence of a so-called flexible "150-loop" near the active site [7]. These crystal structures revealed a new cavity adjacent to the active site that was conjectured to present novel opportunities for drug design. With Tamiflu bound, the 150-loop was crystallized in both open and closed conformations, suggesting that a slow conformational change may occur upon inhibitor binding [7].

[0007] To further probe the structure and dynamics of N1, explicitly solvated molecular dynamics (MD) simulations were carried out for both the apo and holo (i.e. Tamiflu bound) tetramer N1 systems [6]. These simulations revealed that the flexibility of the 150-loop may be even greater than previously anticipated. In addition, the neighboring 430-loop also adopted more open conformations, which was an insight not observed in crystal studies. Evaluation of the crystal structure alone did not show these additional open conformations. These open positions presented novel areas for further study.

[0008] The coupled motions of the 150- and 430-loops caused significant changes in the side chain positions of several important active site residues that are known to stabilize inhibitor binding [6, 8]. In a separate study, representative conformations of the N1 binding region that were extracted from a clustering analysis of the MD simulations were used for computational solvent mapping (CS-Map). CS-Map assessed the binding affinity of small, solvent-sized probe molecules within the N1 binding site [7]. The mapping analyses of the representative MD conformations revealed the presence of novel druggable hot spots in the 150- and 430-loop regions, providing further support for the feasibility of developing high-affinity inhibitors capable of binding these areas.

[0009] High-throughput virtual screening is a fast, efficient method of finding novel inhibitors, but typical screens use only one crystal structure and assume the receptor is rigid. Due to the variable nature of the NA active site, however, the traditional method may fail to find inhibitors of the protein that have the greatest potential as drug candidates or drug candidate leads. Accommodating receptor flexibility in computer-aided drug design has been a longstanding challenge (reviewed in [8]) and only in the last decade have methods able to treat it been developed [11-18]. Treating protein backbone and side chain flexibility simultaneously has typically involved computationally intensive physically-based MD simulations in order to generate viable receptor conformations. A particularly relevant example of the importance of accommodating receptor flexibility in drug design is the novel HIV integrase inhibitor Isentress (raltegravir), which has recently been approved by the FDA [9]. During MD simulations of the integrase enzyme in complex with the known inhibitor 5CITEP, a new pocket adjacent to the binding site was revealed, and the virtual docking of ligands into this new area indicated favorable binding [10]. The development of compounds capable of binding to both the original binding site and the new cavity, so-called "butterfly" compounds, formed the basis for a new class of integrase inhibitors.

[0010] In this work, we employ a related strategy for the discovery of compounds active against the potentially pandemic N1. In a novel, ensemble-based approach to virtual screening, the three most dominant clusters from the MD simulations of the apo and holo ensembles are used in a virtual screen against the National Cancer Institute Diversity Set I using AutoDock 4. Top hits are selected based on membrane permeability, solubility, toxicity, and druglikeness.

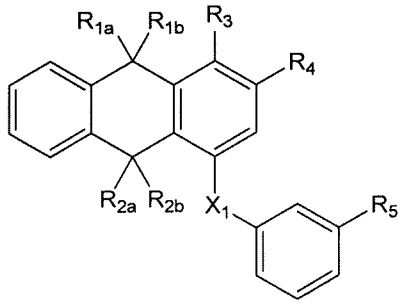
[0011] A comparison of the ensemble-based screening results to virtual screens performed against the open and closed N1 crystal structures clearly indicates a number of available compounds that bind with higher affinity than Tamiflu and other known antivirals to the sialic acid binding site and, more interestingly, to the new 150- and 430-loop regions. The relaxed complex scheme (RCS), a promising hybrid computational methodology that combines the advantages of docking algorithms with dynamic structural information provided by molecular dynamics (MD) simulations [11-13], is used to redock the top compounds into the entire non-redundant and representative holo ensemble from the MD trajectories. The RCS application results in a reordering of

the compounds, which can be used to make final ranked recommendations. Ultimately, a set of compounds identified as binding the avian influenza N1 can be identified.

[0012] In vitro screening can identify compounds that show inhibitory activity to the neuraminidase protein of Influenza A virus subtype H5N1. However, in vitro activity alone may not provide information for the rational design of further optimized compounds. The novel conformations of the known binding sites of neuraminidase protein of Influenza A virus subtype H5N1 can provide information for designing drug candidates, especially if correlated to in vitro activity. Further, newly identified binding sites provide additional information for rational drug design. Ranking of *in vitro* and computational results can provide correlation of the in vitro activity to a binding site and potentially the conformation of the compound in the binding site. The final rank recommendations provided by the current method are valuable in correlating binding site and conformation of compound in the binding site to in vitro activity.

SUMMARY OF THE INVENTION

[0013] One embodiment is the pharmaceutical composition comprising an agent and a pharmaceutically acceptable carrier, wherein the agent is a compound having the formula (**I**):



(**I**)

or a pharmaceutically acceptable salt or prodrug thereof wherein:

(a) $\mathbf{R^{1a}}$ and $\mathbf{R^{1b}}$ are each separately selected from the group consisting of H (hydrogen), -C(O)N$\mathbf{R^{1c}R^{1d}}$, –C(O)O$\mathbf{R^{1e}}$, –C(S)N$\mathbf{R^{1c}R^{1d}}$, –C(S)O$\mathbf{R^{1e}}$, –NHC(O)$\mathbf{R^{1e}}$, -NHC(O)N$\mathbf{R^{1c}R^{1d}}$, –NHC(O)O$\mathbf{R^{1e}}$, -NHC(S)N$\mathbf{R^{1c}R^{1d}}$, –NHC(S)O$\mathbf{R^{1e}}$, -OC(O)N$\mathbf{R^{1c}R^{1d}}$, -OC(O)O$\mathbf{R^{1e}}$, –OC(S)N$\mathbf{R^{1c}R^{1d}}$, -O$\mathbf{R^{1f}}$, and -N$\mathbf{R^{1c}R^{1d}}$; or $\mathbf{R^{1a}}$ and $\mathbf{R^{1b}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

each $\mathbf{R^{1c}}$ and $\mathbf{R^{1d}}$ is independently selected from the group consisting of H (hydrogen), C_{1-6} alkyl, heteroaryl, and aryl, or $\mathbf{R^{1c}}$ and $\mathbf{R^{1d}}$ are optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

each $\mathbf{R^{1e}}$ is independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

each $\mathbf{R^{1f}}$ is independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(b) $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are each separately selected from the group consisting of H (hydrogen), -C(O)N$\mathbf{R^{2c}R^{2d}}$, –C(O)O$\mathbf{R^{2e}}$, –C(S)N$\mathbf{R^{2c}R^{2d}}$, –C(S)O$\mathbf{R^{2e}}$, –NHC(O)$\mathbf{R^{2e}}$, -NHC(O)N$\mathbf{R^{2c}R^{2d}}$, –NHC(O)O$\mathbf{R^{2e}}$, -NHC(S)N$\mathbf{R^{2c}R^{2d}}$, –NHC(S)O$\mathbf{R^{2e}}$, -OC(O)N$\mathbf{R^{2c}R^{2d}}$, -OC(O)O$\mathbf{R^{2e}}$, –OC(S)N$\mathbf{R^{2c}R^{2d}}$, -O$\mathbf{R^{2f}}$, and -N$\mathbf{R^{1c}R^{1d}}$; or $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

each $\mathbf{R^{2c}}$ and $\mathbf{R^{2d}}$ is independently selected from the group consisting of H (hydrogen), C_{1-6} alkyl, and aryl, or $\mathbf{R^{2c}}$ and $\mathbf{R^{2d}}$ are optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

each $\mathbf{R^{2e}}$ is independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

each $\mathbf{R^{2f}}$ is independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) $\mathbf{R^3}$ is selected from the group consisting of H (hydrogen), –NHC(O)$\mathbf{R^{3a}}$, -NHC(O)N$\mathbf{R^{3b}R^{3c}}$, –NHC(O)O$\mathbf{R^{3d}}$, -NHC(S)N$\mathbf{R^{3b}R^{3c}}$, –NHC(S)O$\mathbf{R^{3d}}$, -OC(S)N$\mathbf{R^{3b}R^{3c}}$, -O$\mathbf{R^{3e}}$, -S$\mathbf{R^{3e}}$, -N$\mathbf{R^{3b}R^{3c}}$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

$\mathbf{R^{3a}}$ is selected from the group consisting of aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

$\mathbf{R^{3b}}$ and $\mathbf{R^{3c}}$ are each separately selected from the group consisting of H (hydrogen), C_{1-6} alkyl, heteroaryl, and aryl, or $\mathbf{R^{3b}}$ and $\mathbf{R^{3c}}$ are optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

R^{3d} is selected from the group consisting of aryl, heteroaryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

R^{3e} is selected from the group consisting of H (hydrogen), aryl, heteroaryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(d) R^4 is selected from the group consisting of H (hydrogen), $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, $-OP(O)(OR^{4a})_2$, $-SR^{4b}$, halo, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

each R^{4a} is independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

R^{4b} is selected from the group consisting of H (hydrogen), heteroaryl, aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

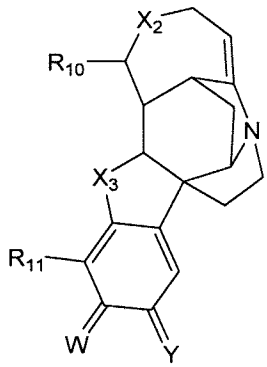
(e) R^5 is selected from the group consisting of $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, $-OP(O)(OR^{5a})_2$, $-SR^{5b}$, and halo;

each R^{5a} is independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

R^{5b} is selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro; and

(f) X_1 is selected from the group consisting of O (oxygen), S (sulfur) and $-NR^6$; where R^6 is H (hydrogen) or C_{1-6} alkyl. In one aspect of the embodiment R^{1a} and R^{1b} are taken together with the carbon to which they are attached to form keto; and R^{2a} and R^{2b} are taken together with the carbon to which they are attached to form keto. In another aspect of the embodiment R^3 is $-NH_2$; and R^4 is $-S(O)_2OH$. In another aspect of the embodiment R^5 is selected from the group consisting of $-S(O)_2OH$, and $-S(O)_2NH_2$; and X_1 is $-NR^6$; where R^6 is H (hydrogen) or C_{1-6} alkyl.

[0014] Another embodiment is the pharmaceutical composition comprising an agent and a pharmaceutically acceptable carrier, wherein the agent is a compound having the formula (**II**):



(II)

or a pharmaceutically acceptable salt or prodrug thereof wherein:

(a) $\mathbf{R^{10}}$ is selected from the group consisting of $-(CH_2)_n\mathbf{R^{10a}}$;

(b) $\mathbf{R^{10a}}$ is selected from the group consisting of tetrazole, $-C(O)\mathbf{R^{10b}}$, and $-C(S)\mathbf{R^{10b}}$;

(c) $\mathbf{R^{10b}}$ is selected from the group consisting of H (hydrogen), $-S\mathbf{R^{10c}}$, $-O\mathbf{R^{10c}}$, $-NH\mathbf{R^{10c}}$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(d) $\mathbf{R^{10c}}$ is selected from the group consisting of H (hydrogen) and C_{1-6} alkyl;

(e) **n** is 0, 1, or 2;

(f) $\mathbf{R^{11}}$ is selected from the group consisting of tetrazole, $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, nitro, $-OP(O)(O\mathbf{R^{11a}})_2$, and $-C(O)O\mathbf{R^{11b}}$;

$\mathbf{R^{11a}}$ is selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

$\mathbf{R^{11b}}$ is selected from the group consisting of H (hydrogen), and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

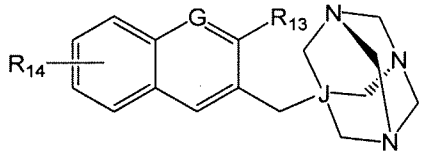
(g) **W** is O (oxygen) or S (sulfur);

(h) **Y** is O (oxygen) or S (sulfur); and

(i) $\mathbf{X_2}$ and $\mathbf{X_3}$ are each individually selected from the group consisting of O (oxygen), S (sulfur) and -NH. In one aspect of the embodiment $\mathbf{R^{10a}}$ is $-CH_2C(O)\mathbf{R^{10b}}$. In another aspect of the embodiment $\mathbf{X_2}$ is O (oxygen) and $\mathbf{X_3}$ is -NH. In another aspect of the embodiment $\mathbf{R^{10a}}$ is $-CH_2C(O)O\mathbf{R^{10c}}$; and $\mathbf{R^{11}}$ is selected from the group consisting of $-S(O)_2NH_2$, $-P(O)(OH)_2$, nitro, $-OP(O)(O\mathbf{R^{11a}})_2$, and $-C(O)O\mathbf{R^{11b}}$. In another aspect of the embodiment $\mathbf{R^{10c}}$ is H (hydrogen); $\mathbf{R^{11}}$ is selected from the group consisting of nitro, $-OP(O)(O\mathbf{R^{11a}})_2$,

and -C(O)O$\mathbf{R^{11b}}$; $\mathbf{R^{11a}}$ is selected from the group consisting of H (hydrogen), and C_{1-6} alkyl; $\mathbf{R^{11b}}$ is H (hydrogen); **W** is O (oxygen); and **Y** is O (oxygen).

[0015] Another embodiment is the pharmaceutical composition comprising an agent and a pharmaceutically acceptable carrier, wherein the agent is a compound having the formula (**III**):



(III)

or a pharmaceutically acceptable salt or prodrug thereof wherein:

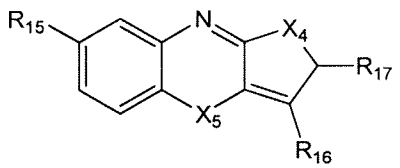
(a) $\mathbf{R^{13}}$ is selected from the group consisting of H (hydrogen), C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(b) $\mathbf{R^{14}}$ is one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) G is selected from the group consisting of CH and N (nitrogen); and

(d) J is selected from the group consisting of N^+ (nitrogen) and P^+ (phosphorous). In one aspect of the embodiment **G** is N (nitrogen). In another aspect of the embodiment $\mathbf{R^{13}}$ is selected from the group consisting of H (hydrogen) and C_{1-6} alkyl optionally substituted with up to 5 fluoro; and **J** is N^+ (nitrogen).

[0016] Another embodiment is the pharmaceutical composition comprising an agent and a pharmaceutically acceptable carrier, wherein the agent is a compound having the formula (**IV**):



(IV)

or tautomer thereof, or their pharmaceutically acceptable salts or prodrugs, wherein:

(a) $\mathbf{R^{15}}$ is selected from the group consisting of nitro, and -C(O)$\mathbf{R^{15a}}$;

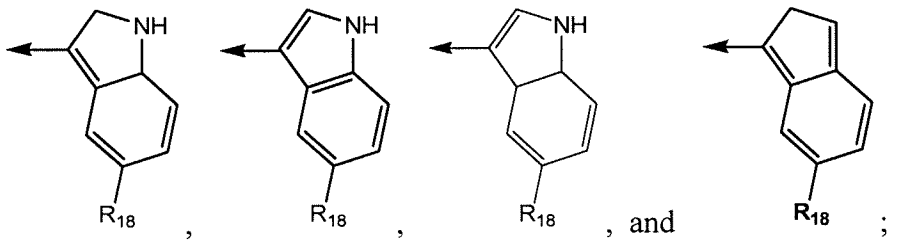
(b) $\mathbf{R^{15a}}$ is selected from the group consisting of H (hydrogen), -S$\mathbf{R^{15b}}$, and -O$\mathbf{R^{15b}}$;

(c) $\mathbf{R^{15b}}$ is selected from the group consisting of H (hydrogen) and C_{1-6} alkyl;

(d) $\mathbf{R^{16}}$ is selected from the group consisting of H (hydrogen) and -O$\mathbf{R^{16a}}$;

(e) $\mathbf{R^{16a}}$ is selected from the group consisting of H (hydrogen), and C_{1-6} alkyl;

(f) $\mathbf{R^{17}}$ is selected from the group consisting of:



, , , and ;

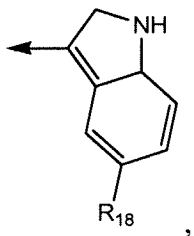
(g) $\mathbf{R^{18}}$ is selected from the group consisting of $-(CH_2)_n\mathbf{R^{18a}}$ and -CH=CH$\mathbf{R^{18a}}$;

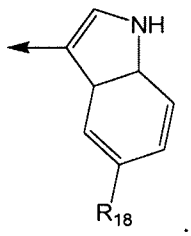
(h) **n** is 0, 1, or 2;

(i) $\mathbf{R^{18a}}$ is selected from the group consisting of -S$\mathbf{R^{18b}}$, -O$\mathbf{R^{18b}}$, aryl optionally substituted with one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro, and heteroaryl optionally substituted with one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(j) $\mathbf{R^{18b}}$ is selected from the group consisting of aryl and heteroaryl, each optionally substituted with one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro; and

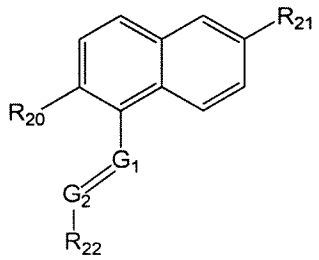
(k) $\mathbf{X_4}$ and $\mathbf{X_5}$ are each individually selected from the group consisting of O (oxygen), S (sulfur) and -NH. In one aspect of the embodiment $\mathbf{R^{17}}$ is selected from the group consisting of:



, and


. In another aspect of the embodiment $\mathbf{X_4}$ is O (oxygen) and $\mathbf{X_5}$ is -NH. In another aspect of the embodiment $\mathbf{R^{18}}$ is $-(CH_2)_n\mathbf{R^{18a}}$; **n** is 1; and $\mathbf{R^{18a}}$ is $-O\mathbf{R^{18b}}$. In another aspect of the embodiment $\mathbf{R^{16}}$ is $-O\mathbf{R^{16a}}$; and $\mathbf{R^{18b}}$ is aryl optionally substituted with one or more substituents each individually selected from the group consisting of OH, halo, cyano, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro.

[0017] Another embodiment is the pharmaceutical composition comprising an agent and a pharmaceutically acceptable carrier, wherein the agent is a compound having the formula (**V**):



(**V**)

or tautomer thereof, or their pharmaceutically acceptable salts or prodrugs, wherein:

(a) $\mathbf{R^{20}}$ is selected from the group consisting of H (hydrogen), $-O\mathbf{R^{20a}}$, $-S\mathbf{R^{20a}}$, $-C(O)N\mathbf{R^{20c}}\mathbf{R^{20d}}$, $-NHC(O)\mathbf{R^{20e}}$;

(b) $\mathbf{R^{20a}}$ is selected from the group consisting of H (hydrogen), and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) $\mathbf{R^{20c}}$ and $\mathbf{R^{20d}}$ are each separately selected from the group consisting of H (hydrogen), C_{1-6} alkyl, heteroaryl, and aryl, or $\mathbf{R^{20c}}$ and $\mathbf{R^{20d}}$ are optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

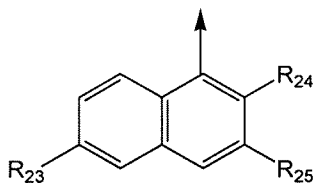
(d) $\mathbf{R^{20e}}$ is selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

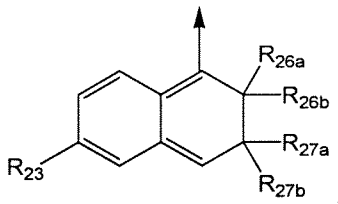
(e) $\mathbf{R^{21}}$ is selected from the group consisting of H (hydrogen), $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, halo, $-C(O)\mathbf{R^{21a}}$, and $-C(S)\mathbf{R^{21a}}$;

(f) $\mathbf{R^{21a}}$ is selected from the group consisting of H (hydrogen), $-\mathbf{SR^{21b}}$, $-\mathbf{OR^{21b}}$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(g) $\mathbf{R^{21b}}$ is selected from the group consisting of H (hydrogen), and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(h) $\mathbf{R^{22}}$ is selected from the group consisting of:



and


;

(i) $\mathbf{R^{23}}$ is selected from the group consisting of H (hydrogen), $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -OH and C_{1-6} alkoxy optionally substituted with up to 5 fluoro;

(j) $\mathbf{R^{24}}$ is -OH or C_{1-6} alkoxy optionally substituted with up to 5 fluoro;

(k) $\mathbf{R^{25}}$ is selected from the group consisting of H (hydrogen), $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -OH and C_{1-6} alkoxy optionally substituted with up to 5 fluoro;

(l) $\mathbf{R^{26a}}$ and $\mathbf{R^{26b}}$ are each separately selected from the group consisting of H (hydrogen), -OH, C_{1-6} alkyl optionally substituted with up to 5 fluoro, and C_{1-6} alkoxy optionally substituted with up to 5 fluoro; or $\mathbf{R^{26a}}$ and $\mathbf{R^{26b}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

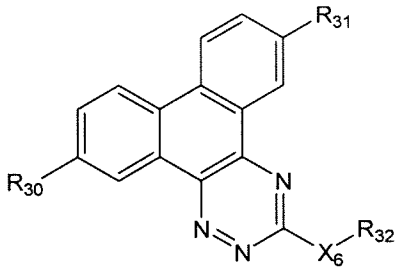
(m) $\mathbf{R^{27a}}$ and $\mathbf{R^{27b}}$ are each separately selected from the group consisting of H (hydrogen), -OH, C_{1-6} alkyl optionally substituted with up to 5 fluoro, and C_{1-6} alkoxy optionally substituted with up to 5 fluoro; or $\mathbf{R^{27a}}$ and $\mathbf{R^{27b}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

(n) $\mathbf{G_1}$ is selected from the group consisting of CH and N (nitrogen); and

(o) $\mathbf{G_2}$ is selected from the group consisting of CH and N (nitrogen). In one aspect of the embodiment $\mathbf{R^{20}}$ is H (hydrogen); and $\mathbf{R^{21}}$ is H (hydrogen) or $-S(O)_2OH$. In another aspect of the embodiment $\mathbf{R^{23}}$ is H (hydrogen) or $-S(O)_2OH$; $\mathbf{R^{24}}$ is –OH; and $\mathbf{R^{25}}$ is H (hydrogen), or $-S(O)_2OH$. In another aspect of the embodiment $\mathbf{G_1}$ is N (nitrogen); and $\mathbf{G_2}$ is N (nitrogen). In another aspect of

the embodiment $\mathbf{R^{26a}}$ and $\mathbf{R^{26b}}$ are optionally taken together with the carbon to which they are attached to form a keto group; and $\mathbf{R^{27a}}$ and $\mathbf{R^{27b}}$ are optionally taken together with the carbon to which they are attached to form a keto group.

[0018] Another embodiment is the pharmaceutical composition comprising an agent and a pharmaceutically acceptable carrier, wherein the agent is a compound having the formula (**VI**):



(**VI**)

or tautomer thereof, or their pharmaceutically acceptable salts or prodrugs, wherein:

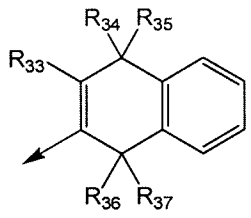
(a) $\mathbf{R^{30}}$ is selected from the group consisting of H (hydrogen), $-O\mathbf{R^{30a}}$, $-S\mathbf{R^{30a}}$, $-N\mathbf{R^{30b}}\mathbf{R^{30c}}$, $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, $-C(O)OH$, $-CH_2C(O)OH$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(b) $\mathbf{R^{30a}}$ is selected from the group consisting of H (hydrogen) and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) $\mathbf{R^{30b}}$ and $\mathbf{R^{30c}}$ are each separately selected from the group consisting of H (hydrogen) and C_{1-6} alkyl, or $\mathbf{R^{30b}}$ and $\mathbf{R^{30c}}$ are optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

(d) $\mathbf{R^{31}}$ is selected from the group consisting of H (hydrogen), -OH, –SH, $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, $-C(O)OH$, $-CH_2C(O)OH$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(e) $\mathbf{R^{32}}$ is selected from the group consisting of $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, $-C(O)OH$, and $-CH_2C(O)OH$; or $\mathbf{R^{32}}$ is :



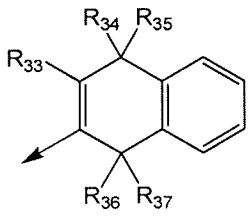
;

(f) $\mathbf{R^{33}}$ is selected from the group consisting of H (hydrogen), -OH, halo, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(g) $\mathbf{R^{34}}$ and $\mathbf{R^{35}}$ are each separately selected from the group consisting of H (hydrogen), -OH, halo, and C_{1-6} alkyl optionally substituted with up to 5 fluoro; or $\mathbf{R^{34}}$ and $\mathbf{R^{35}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

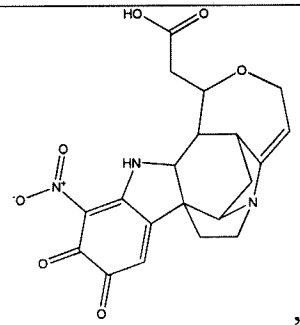
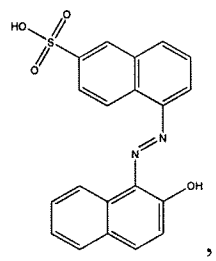
(h) $\mathbf{R^{36}}$ and $\mathbf{R^{37}}$ are each separately selected from the group consisting of H (hydrogen), -OH, -SH, and halo; or $\mathbf{R^{36}}$ and $\mathbf{R^{37}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group; and

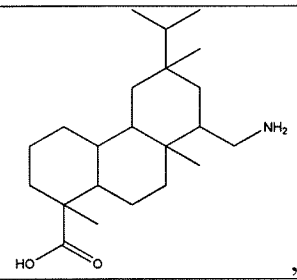
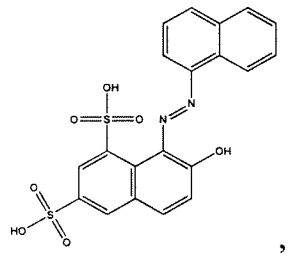
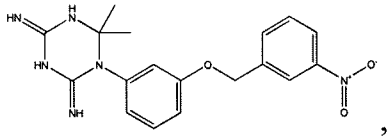
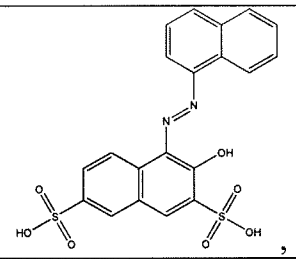
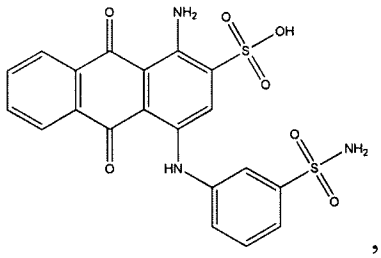
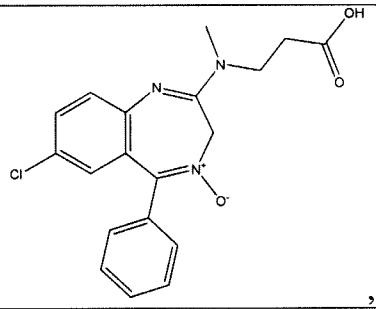
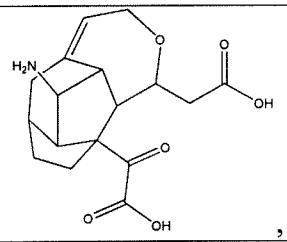
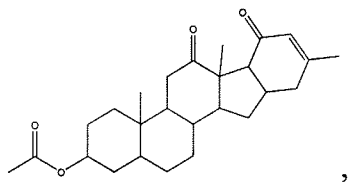
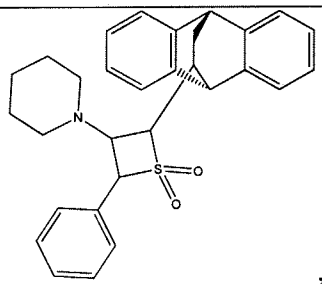
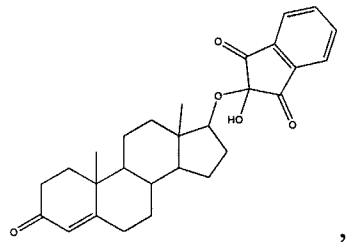
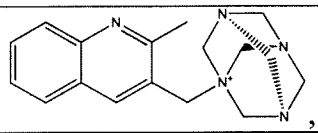
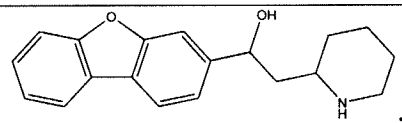
(i) $\mathbf{X_6}$ is selected from the group consisting of O (oxygen), S (sulfur) and -NH. In one aspect of the embodiment $\mathbf{R^{30}}$ and $\mathbf{R^{31}}$ are H (hydrogen); and $\mathbf{R^{32}}$ is

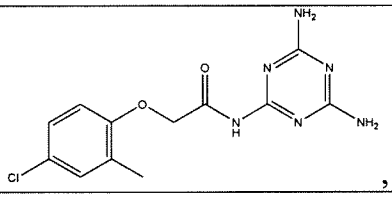
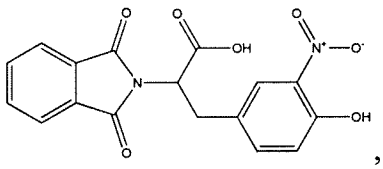
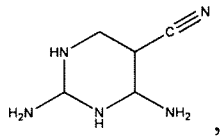
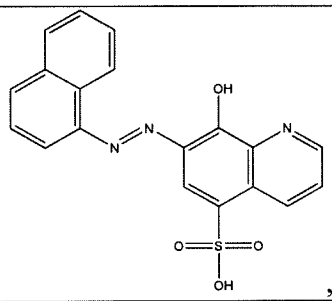
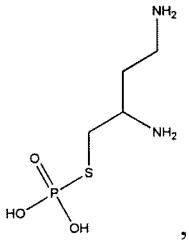
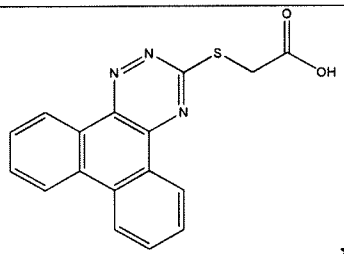
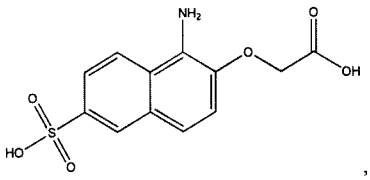
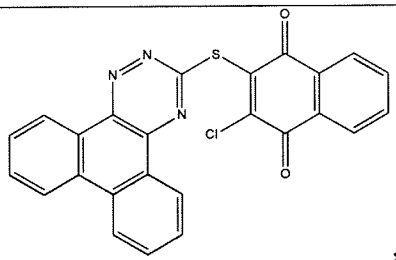
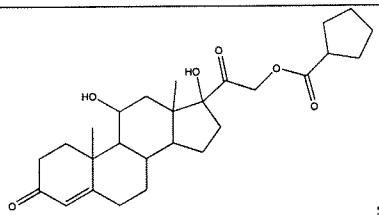
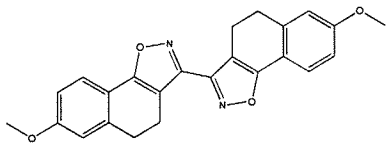
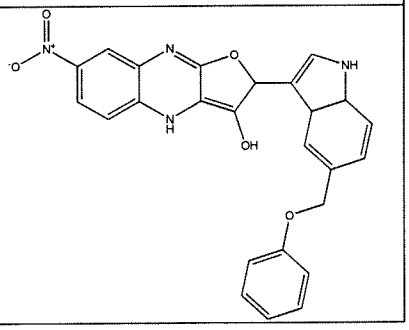


. In another aspect of the embodiment $\mathbf{X_6}$ is S (sulfur). In another aspect of the embodiment $\mathbf{R^{34}}$ and $\mathbf{R^{35}}$ are optionally taken together with the carbon to which they are attached to form a keto group; and $\mathbf{R^{36}}$ and $\mathbf{R^{37}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group. In another aspect of the embodiment $\mathbf{R^{33}}$ is halo. In another aspect of the embodiment $\mathbf{R^{30}}$ is H (hydrogen); and $\mathbf{R^{32}}$ is selected from the group consisting of $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -C(O)OH, and $-CH_2C(O)OH$. In another aspect of the embodiment $\mathbf{R^{31}}$ is H (hydrogen); and $\mathbf{R^{32}}$ is selected from the group consisting of $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -C(O)OH, and $-CH_2C(O)OH$.

[0019] Another embodiment is the pharmaceutical composition comprising an agent and a pharmaceutically acceptable carrier, wherein the agent is selected from the group consisting of:

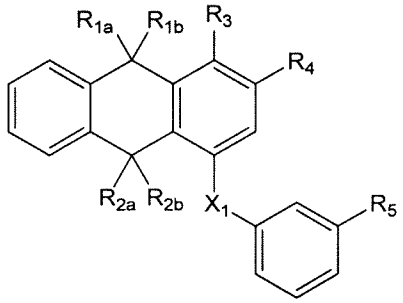
5069	 ,		45576	 ,

70194			45582	
109836			45583	
117079			46080	
131612			59620	
135371			72254	
141562			90630	

164640		106920	
211332		148354	
350191		327704	
16163		327705	
17245		371688	
	and	372294	

or a pharmaceutically acceptable salt or prodrug thereof.

[0020] Another embodiment is the compound having the formula (**I**):



(I)

or a pharmaceutically acceptable salt or prodrug thereof wherein:

(a) $\mathbf{R^{1a}}$ and $\mathbf{R^{1b}}$ are each separately selected from the group consisting of H (hydrogen), -C(O)N$\mathbf{R^{1c}R^{1d}}$, –C(O)O$\mathbf{R^{1e}}$, –C(S)N$\mathbf{R^{1c}R^{1d}}$, –C(S)O$\mathbf{R^{1e}}$, –NHC(O)$\mathbf{R^{1e}}$, -NHC(O)N$\mathbf{R^{1c}R^{1d}}$, –NHC(O)O$\mathbf{R^{1e}}$, -NHC(S)N$\mathbf{R^{1c}R^{1d}}$, –NHC(S)O$\mathbf{R^{1c}}$, -OC(O)N$\mathbf{R^{1c}R^{1d}}$, -OC(O)O$\mathbf{R^{1e}}$, –OC(S)N$\mathbf{R^{1c}R^{1d}}$, -O$\mathbf{R^{1f}}$, and -N$\mathbf{R^{1c}R^{1d}}$; or $\mathbf{R^{1a}}$ and $\mathbf{R^{1b}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

each $\mathbf{R^{1c}}$ and $\mathbf{R^{1d}}$ is independently selected from the group consisting of H (hydrogen), $C_{1\text{-}6}$ alkyl, heteroaryl, and aryl, or $\mathbf{R^{1c}}$ and $\mathbf{R^{1d}}$ are optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

each $\mathbf{R^{1e}}$ is independently selected from the group consisting of H (hydrogen), aryl, and $C_{1\text{-}6}$ alkyl optionally substituted with up to 5 fluoro;

each $\mathbf{R^{1f}}$ is independently selected from the group consisting of H (hydrogen), aryl, and $C_{1\text{-}6}$ alkyl optionally substituted with up to 5 fluoro;

(b) $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are each separately selected from the group consisting of H (hydrogen), -C(O)N$\mathbf{R^{2c}R^{2d}}$, –C(O)O$\mathbf{R^{2e}}$, –C(S)N$\mathbf{R^{2c}R^{2d}}$, –C(S)O$\mathbf{R^{2e}}$, –NHC(O)$\mathbf{R^{2e}}$, -NHC(O)N$\mathbf{R^{2c}R^{2d}}$, –NHC(O)O$\mathbf{R^{2e}}$, -NHC(S)N$\mathbf{R^{2c}R^{2d}}$, –NHC(S)O$\mathbf{R^{2e}}$, -OC(O)N$\mathbf{R^{2c}R^{2d}}$, -OC(O)O$\mathbf{R^{2e}}$, –OC(S)N$\mathbf{R^{2c}R^{2d}}$, -O$\mathbf{R^{2f}}$, and -N$\mathbf{R^{1c}R^{1d}}$; or $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

each $\mathbf{R^{2c}}$ and $\mathbf{R^{2d}}$ is independently selected from the group consisting of H (hydrogen), $C_{1\text{-}6}$ alkyl, and aryl, or $\mathbf{R^{2c}}$ and $\mathbf{R^{2d}}$ are optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

each $\mathbf{R^{2e}}$ is independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

each $\mathbf{R^{2f}}$ is independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) $\mathbf{R^3}$ is selected from the group consisting of H (hydrogen), –NHC(O)$\mathbf{R^{3a}}$, -NHC(O)N$\mathbf{R^{3b}R^{3c}}$, –NHC(O)O$\mathbf{R^{3d}}$, -NHC(S)N$\mathbf{R^{3b}R^{3c}}$, –NHC(S)O$\mathbf{R^{3d}}$, -OC(S)N$\mathbf{R^{3b}R^{3c}}$, -O$\mathbf{R^{3e}}$, -S$\mathbf{R^{3e}}$, -N$\mathbf{R^{3b}R^{3c}}$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

$\mathbf{R^{3a}}$ is selected from the group consisting of aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

$\mathbf{R^{3b}}$ and $\mathbf{R^{3c}}$ are each separately selected from the group consisting of H (hydrogen), C_{1-6} alkyl, heteroaryl, and aryl, or $\mathbf{R^{3b}}$ and $\mathbf{R^{3c}}$ are optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

$\mathbf{R^{3d}}$ is selected from the group consisting of aryl, heteroaryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

$\mathbf{R^{3e}}$ is selected from the group consisting of H (hydrogen), aryl, heteroaryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(d) $\mathbf{R^4}$ is selected from the group consisting of H (hydrogen), -$S(O)_2OH$, -$S(O)_2NH_2$, -$P(O)(OH)_2$, -$OP(O)(OR^{4a})_2$, -S$\mathbf{R^{4b}}$, halo, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

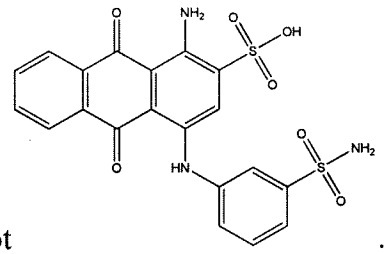
each $\mathbf{R^{4a}}$ is independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

$\mathbf{R^{4b}}$ is selected from the group consisting of H (hydrogen), heteroaryl, aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

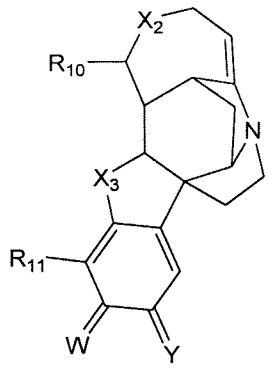
(e) $\mathbf{R^5}$ is selected from the group consisting of -$S(O)_2OH$, -$S(O)_2NH_2$, -$P(O)(OH)_2$, -$OP(O)(OR^{5a})_2$, -S$\mathbf{R^{5b}}$, and halo;

each $\mathbf{R^{5a}}$ is independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

$\mathbf{R^{5b}}$ is selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro; and

(f) $\mathbf{X_1}$ is selected from the group consisting of O (oxygen), S (sulfur) and -N$\mathbf{R^6}$; where $\mathbf{R^6}$ is H (hydrogen) or C_{1-6} alkyl. In one aspect of the embodiment the compound of formula (**I**) is not  . In another aspect of the embodiment $\mathbf{R^{1a}}$ and $\mathbf{R^{1b}}$ are taken together with the carbon to which they are attached to form keto; and $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are taken together with the carbon to which they are attached to form keto. In another aspect of the embodiment $\mathbf{R^3}$ is $-NH_2$; and $\mathbf{R^4}$ is $-S(O)_2OH$. In another aspect of the embodiment $\mathbf{R^5}$ is selected from the group consisting of $-S(O)_2OH$, and $-S(O)_2NH_2$; and $\mathbf{X_1}$ is -N$\mathbf{R^6}$; where $\mathbf{R^6}$ is H (hydrogen) or C_{1-6} alkyl.

[0021] Another embodiment is the compound having the formula (**II**):



(**II**)

or a pharmaceutically acceptable salt or prodrug thereof wherein:

(a) $\mathbf{R^{10}}$ is selected from the group consisting of $-(CH_2)_n\mathbf{R^{10a}}$;

(b) $\mathbf{R^{10a}}$ is selected from the group consisting of tetrazole, -C(O)$\mathbf{R^{10b}}$, and -C(S)$\mathbf{R^{10b}}$;

(c) $\mathbf{R^{10b}}$ is selected from the group consisting of H (hydrogen), -S$\mathbf{R^{10c}}$, -O$\mathbf{R^{10c}}$, -NH$\mathbf{R^{10c}}$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(d) $\mathbf{R^{10c}}$ is selected from the group consisting of H (hydrogen) and C_{1-6} alkyl;

(e) **n** is 0, 1, or 2;

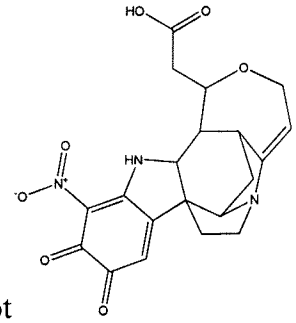
(f) $\mathbf{R^{11}}$ is selected from the group consisting of tetrazole, $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, nitro, $-OP(O)(O\mathbf{R^{11a}})_2$, and -C(O)O$\mathbf{R^{11b}}$;

$\mathbf{R^{11a}}$ is selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

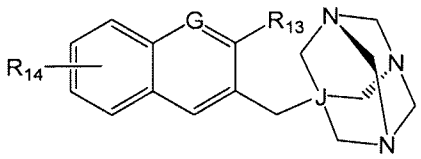
$\mathbf{R^{11b}}$ is selected from the group consisting of H (hydrogen), and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(g) **W** is O (oxygen) or S (sulfur);

(h) **Y** is O (oxygen) or S (sulfur); and

(i) $\mathbf{X_2}$ and $\mathbf{X_3}$ are each individually selected from the group consisting of O (oxygen), S (sulfur) and -NH. In one aspect of the embodiment the compound of formula (**II**) is not  . In another aspect of the embodiment $\mathbf{X_2}$ is O (oxygen) and $\mathbf{X_3}$ is -NH. In another aspect of the embodiment $\mathbf{R^{10a}}$ is $-CH_2C(O)\mathbf{R^{10b}}$. In another aspect of the embodiment $\mathbf{R^{10a}}$ is $-CH_2C(O)O\mathbf{R^{10c}}$; and $\mathbf{R^{11}}$ is selected from the group consisting of $-S(O)_2NH_2$, $-P(O)(OH)_2$, nitro, $-OP(O)(O\mathbf{R^{11a}})_2$, and $-C(O)O\mathbf{R^{11b}}$. In another aspect of the embodiment $\mathbf{R^{10c}}$ is H (hydrogen); $\mathbf{R^{11}}$ is selected from the group consisting of nitro, $-OP(O)(O\mathbf{R^{11a}})_2$, and $-C(O)O\mathbf{R^{11b}}$; $\mathbf{R^{11a}}$ is selected from the group consisting of H (hydrogen), and C_{1-6} alkyl; $\mathbf{R^{11b}}$ is H (hydrogen); **W** is O (oxygen); and **Y** is O (oxygen).

[0022] Another embodiment is the compound having the formula (**III**):



(**III**)

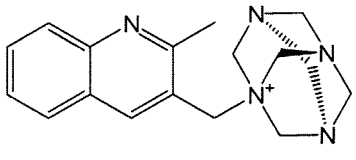
or a pharmaceutically acceptable salt or prodrug thereof wherein:

(a) $\mathbf{R^{13}}$ is selected from the group consisting of H (hydrogen), C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

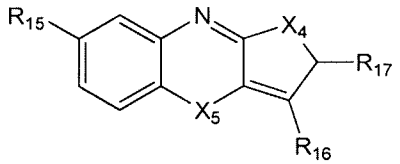
(b) $\mathbf{R^{14}}$ is one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally

substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) G is selected from the group consisting of CH and N (nitrogen); and

(d) J is selected from the group consisting of N^+ (nitrogen) and P^+ (phosphorous). In one aspect of the embodiment the compound of formula (**III**) is not  . In another aspect of the embodiment **G** is N (nitrogen). In another aspect of the embodiment $\mathbf{R^{13}}$ is selected from the group consisting of H (hydrogen) and C_{1-6} alkyl optionally substituted with up to 5 fluoro; and **J** is N^+ (nitrogen).

[0023] Another embodiment is the compound having the formula (**IV**):



(**IV**)

or tautomer thereof, or their pharmaceutically acceptable salts or prodrugs, wherein:

(a) $\mathbf{R^{15}}$ is selected from the group consisting of nitro, and -C(O)$\mathbf{R^{15a}}$;

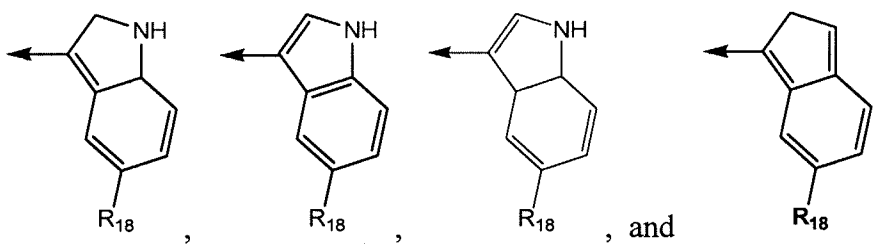
(b) $\mathbf{R^{15a}}$ is selected from the group consisting of H (hydrogen), -S$\mathbf{R^{15b}}$, and -O$\mathbf{R^{15b}}$;

(c) $\mathbf{R^{15b}}$ is selected from the group consisting of H (hydrogen) and C_{1-6} alkyl;

(d) $\mathbf{R^{16}}$ is selected from the group consisting of H (hydrogen) and -O$\mathbf{R^{16a}}$;

(e) $\mathbf{R^{16a}}$ is selected from the group consisting of H (hydrogen), and C_{1-6} alkyl;

(f) $\mathbf{R^{17}}$ is selected from the group consisting of:

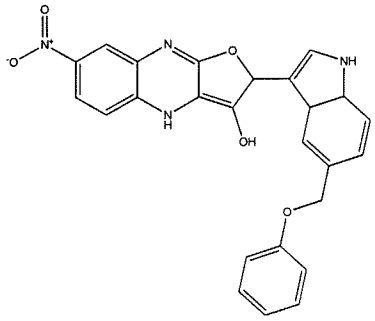
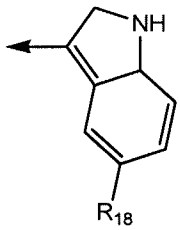
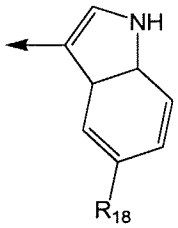


(g) $\mathbf{R^{18}}$ is selected from the group consisting of $-(CH_2)_n\mathbf{R^{18a}}$ and $-CH=CH\mathbf{R^{18a}}$;

(h) **n** is 0, 1, or 2;

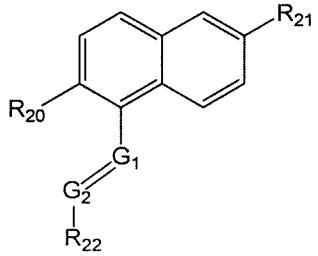
(i) $\mathbf{R^{18a}}$ is selected from the group consisting of $-S\mathbf{R^{18b}}$, $-O\mathbf{R^{18b}}$, aryl optionally substituted with one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro, and heteroaryl optionally substituted with one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(j) $\mathbf{R^{18b}}$ is selected from the group consisting of aryl and heteroaryl, each optionally substituted with one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro; and

(k) $\mathbf{X_4}$ and $\mathbf{X_5}$ are each individually selected from the group consisting of O (oxygen), S (sulfur) and -NH. In one aspect of the embodiment the compound of formula (**IV**) is not  . In another aspect of the embodiment $\mathbf{R^{17}}$ is selected from the group consisting of  , and  . In another aspect of the embodiment $\mathbf{X_4}$ is O (oxygen) and $\mathbf{X_5}$ is

-NH. In another aspect of the embodiment $\mathbf{R^{18}}$ is–$(CH_2)_n\mathbf{R^{18a}}$; **n** is 1; and $\mathbf{R^{18a}}$ is -$\mathbf{OR^{18b}}$. In another aspect of the embodiment $\mathbf{R^{16}}$ is -$\mathbf{OR^{16a}}$; and $\mathbf{R^{18b}}$ is aryl optionally substituted with one or more substituents each individually selected from the group consisting of OH, halo, cyano, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro.

[0024] Another embodiment is the compound having the formula (**V**):



(**V**)

or tautomer thereof, or their pharmaceutically acceptable salts or prodrugs, wherein:

(a) $\mathbf{R^{20}}$ is selected from the group consisting of H (hydrogen), -$\mathbf{OR^{20a}}$, -$\mathbf{SR^{20a}}$, -C(O)N$\mathbf{R^{20c}R^{20d}}$, –NHC(O)$\mathbf{R^{20e}}$;

(b) $\mathbf{R^{20a}}$ is selected from the group consisting of H (hydrogen), and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) $\mathbf{R^{20c}}$ and $\mathbf{R^{20d}}$ are each separately selected from the group consisting of H (hydrogen), C_{1-6} alkyl, heteroaryl, and aryl, or $\mathbf{R^{20c}}$ and $\mathbf{R^{20d}}$ are optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

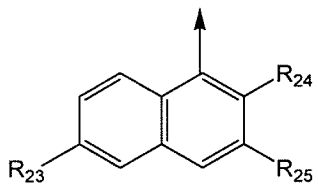
(d) $\mathbf{R^{20e}}$ is selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

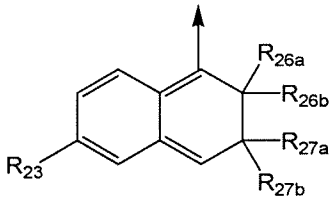
(e) $\mathbf{R^{21}}$ is selected from the group consisting of H (hydrogen), -$S(O)_2OH$, -$S(O)_2NH_2$, -$P(O)(OH)_2$, halo, -C(O)$\mathbf{R^{21a}}$, and -C(S)$\mathbf{R^{21a}}$;

(f) $\mathbf{R^{21a}}$ is selected from the group consisting of H (hydrogen), -$\mathbf{SR^{21b}}$, -$\mathbf{OR^{21b}}$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(g) $\mathbf{R^{21b}}$ is selected from the group consisting of H (hydrogen), and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(h) $\mathbf{R^{22}}$ is selected from the group consisting of:



and


;

(i) $\mathbf{R^{23}}$ is selected from the group consisting of H (hydrogen), $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -OH and C_{1-6} alkoxy optionally substituted with up to 5 fluoro;

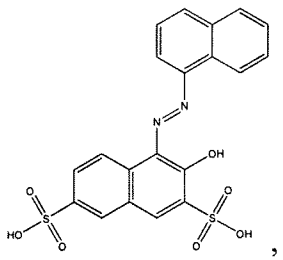
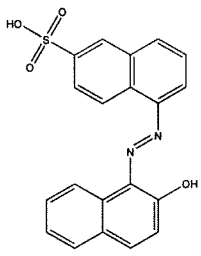
(j) $\mathbf{R^{24}}$ is -OH or C_{1-6} alkoxy optionally substituted with up to 5 fluoro;

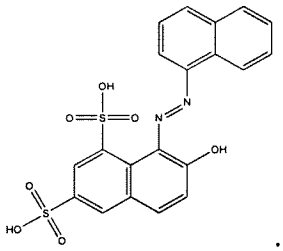
(k) $\mathbf{R^{25}}$ is selected from the group consisting of H (hydrogen), $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -OH and C_{1-6} alkoxy optionally substituted with up to 5 fluoro;

(l) $\mathbf{R^{26a}}$ and $\mathbf{R^{26b}}$ are each separately selected from the group consisting of H (hydrogen), -OH, C_{1-6} alkyl optionally substituted with up to 5 fluoro, and C_{1-6} alkoxy optionally substituted with up to 5 fluoro; or $\mathbf{R^{26a}}$ and $\mathbf{R^{26b}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

(m) $\mathbf{R^{27a}}$ and $\mathbf{R^{27b}}$ are each separately selected from the group consisting of H (hydrogen), -OH, C_{1-6} alkyl optionally substituted with up to 5 fluoro, and C_{1-6} alkoxy optionally substituted with up to 5 fluoro; or $\mathbf{R^{27a}}$ and $\mathbf{R^{27b}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group; and

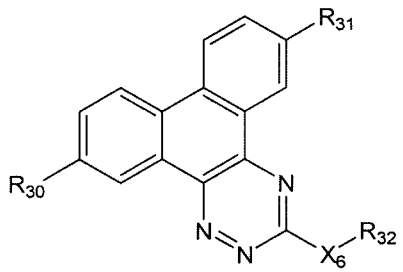
(n) $\mathbf{G_1}$ is selected from the group consisting of CH and N (nitrogen); and

(o) $\mathbf{G_2}$ is selected from the group consisting of CH and N (nitrogen). In one aspect of the embodiment the compound of formula (**V**) is not selected from the group consisting of

,

, and



. In another aspect of the embodiment $\mathbf{R^{20}}$ is H (hydrogen); and $\mathbf{R^{21}}$ is H (hydrogen) or -$S(O)_2OH$. In another aspect of the embodiment $\mathbf{R^{23}}$ is H (hydrogen) or -$S(O)_2OH$; $\mathbf{R^{24}}$ is –OH; and $\mathbf{R^{25}}$ is H (hydrogen), or -$S(O)_2OH$. In another aspect of the embodiment $\mathbf{G_1}$ is N (nitrogen); and $\mathbf{G_2}$ is N (nitrogen). In another aspect of the embodiment $\mathbf{R^{26a}}$ and $\mathbf{R^{26b}}$ are optionally taken together with the carbon to which they are attached to form a keto group; and $\mathbf{R^{27a}}$ and $\mathbf{R^{27b}}$ are optionally taken together with the carbon to which they are attached to form a keto group.

[0025] Another embodiment is the compound having the formula (**VI**):



(**VI**)

or tautomer thereof, or their pharmaceutically acceptable salts or prodrugs, wherein:

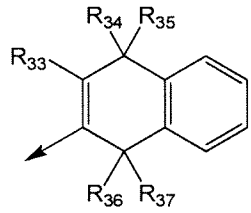
(a) $\mathbf{R^{30}}$ is selected from the group consisting of H (hydrogen), -OR^{30a}, -SR^{30a}, -$NR^{30b}R^{30c}$, -$S(O)_2OH$, -$S(O)_2NH_2$, -$P(O)(OH)_2$, -C(O)OH, -$CH_2C(O)OH$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(b) $\mathbf{R^{30a}}$ is selected from the group consisting of H (hydrogen) and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) $\mathbf{R^{30b}}$ and $\mathbf{R^{30c}}$ are each separately selected from the group consisting of H (hydrogen) and C_{1-6} alkyl, or $\mathbf{R^{30b}}$ and $\mathbf{R^{30c}}$ are optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

(d) $\mathbf{R^{31}}$ is selected from the group consisting of H (hydrogen), -OH, –SH, -$S(O)_2OH$, -$S(O)_2NH_2$, -$P(O)(OH)_2$, -C(O)OH, -$CH_2C(O)OH$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(e) $\mathbf{R^{32}}$ is selected from the group consisting of $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -C(O)OH, and $-CH_2C(O)OH$; or $\mathbf{R^{32}}$ is :



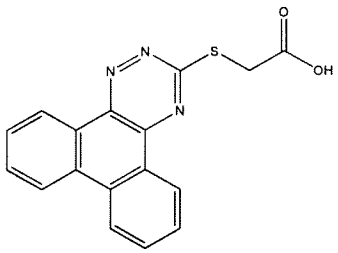
;

(f) $\mathbf{R^{33}}$ is selected from the group consisting of H (hydrogen), -OH, halo, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

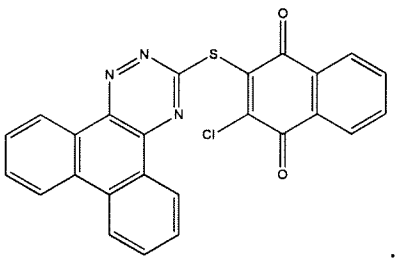
(g) $\mathbf{R^{34}}$ and $\mathbf{R^{35}}$ are each separately selected from the group consisting of H (hydrogen), -OH, halo, and C_{1-6} alkyl optionally substituted with up to 5 fluoro; or $\mathbf{R^{34}}$ and $\mathbf{R^{35}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

(h) $\mathbf{R^{36}}$ and $\mathbf{R^{37}}$ are each separately selected from the group consisting of H (hydrogen), -OH, -SH, and halo; or $\mathbf{R^{36}}$ and $\mathbf{R^{37}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group; and

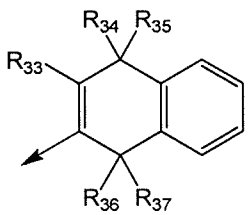
(i) $\mathbf{X_6}$ is selected from the group consisting of O (oxygen), S (sulfur) and -NH. In one aspect of the embodiment the compound of formula (**VI**) is not selected from the group consisting of



and



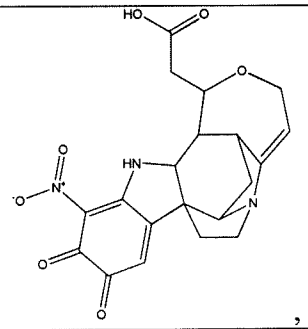
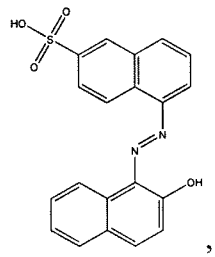
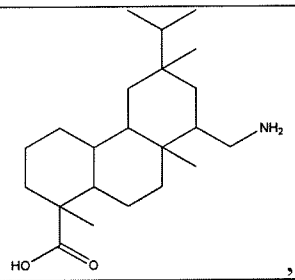
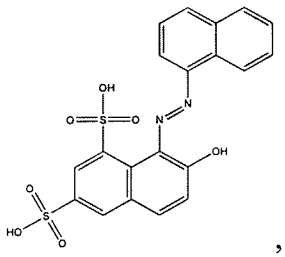
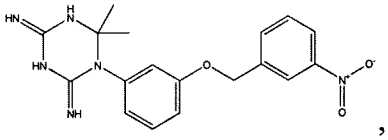
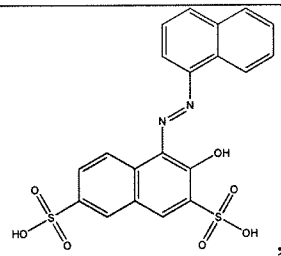
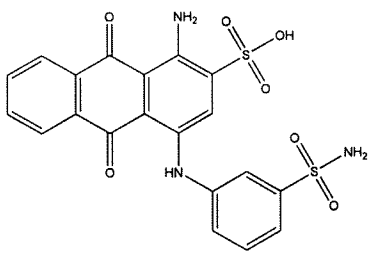
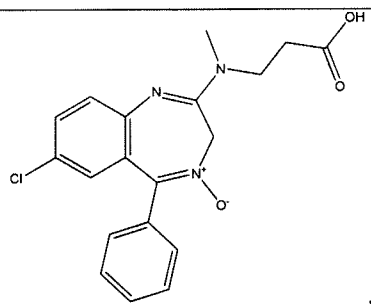
. In another aspect of the embodiment $\mathbf{R^{30}}$ and $\mathbf{R^{31}}$ are H (hydrogen); and $\mathbf{R^{32}}$ is

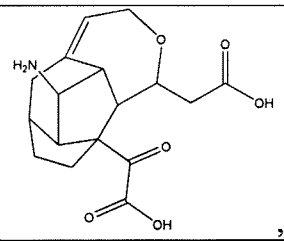
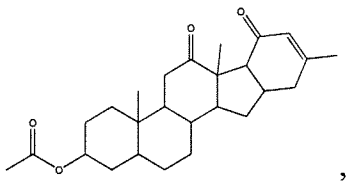
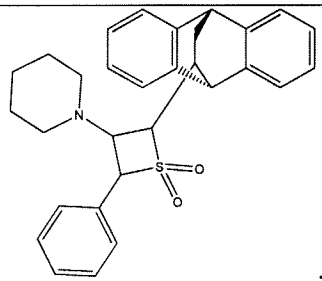
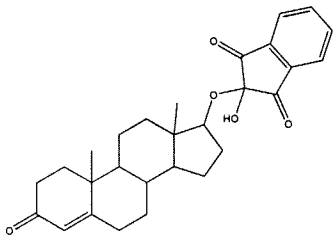
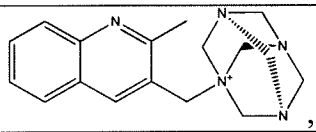
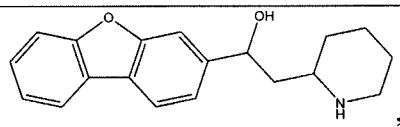
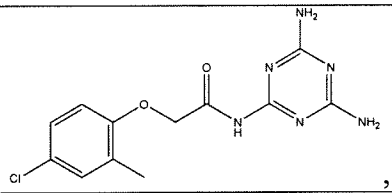
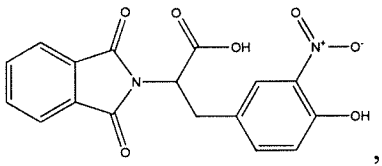
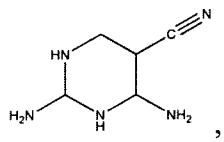
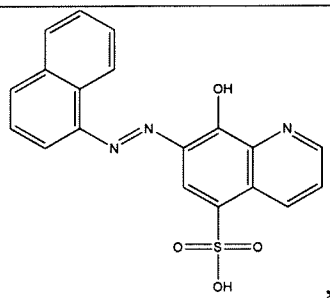
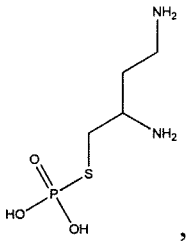
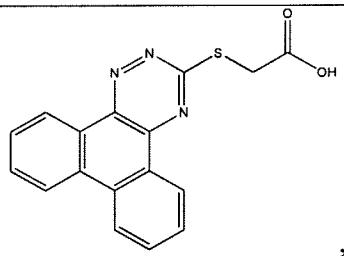


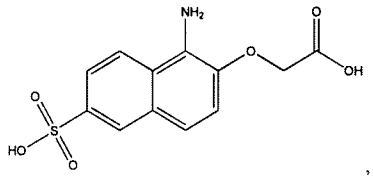
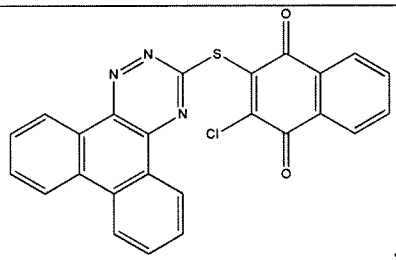
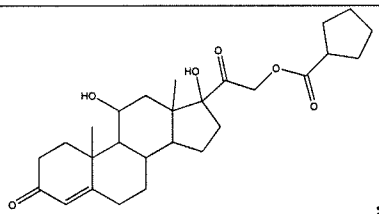
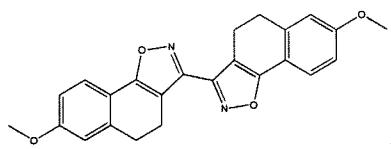
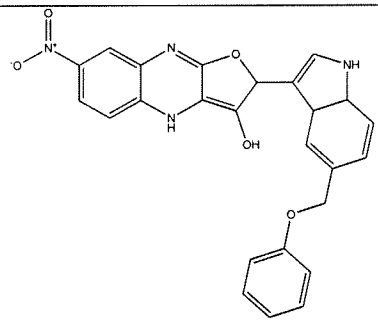
. In another aspect of the embodiment $\mathbf{X_6}$ is S (sulfur). In another aspect of the embodiment $\mathbf{R^{34}}$ and $\mathbf{R^{35}}$ are

optionally taken together with the carbon to which they are attached to form a keto group; and $\mathbf{R^{36}}$ and $\mathbf{R^{37}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group. In another aspect of the embodiment $\mathbf{R^{33}}$ is halo. In another aspect of the embodiment $\mathbf{R^{30}}$ is H (hydrogen); and $\mathbf{R^{32}}$ is selected from the group consisting of $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -C(O)OH, and $-CH_2C(O)OH$. In another aspect of the embodiment $\mathbf{R^{31}}$ is H (hydrogen); and $\mathbf{R^{32}}$ is selected from the group consisting of $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -C(O)OH, and $-CH_2C(O)OH$.

[0026] Another embodiment is the compound selected from the group consisting of:

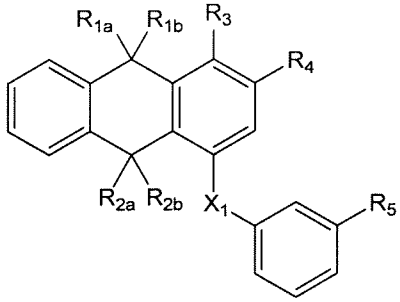
5069		45576	
70194		45582	
109836		45583	
117079		46080	

131612			59620	
135371			72254	
141562			90630	
164640			106920	
211332			148354	
350191			327704	

16163			327705	
17245			371688	
	and		372294	

or a pharmaceutically acceptable salt or prodrug thereof for use in the treatment of an avian influenza infection in an individual.

[0027] Another embodiment is the compound having the formula (**I**):



(**I**)

or a pharmaceutically acceptable salt or prodrug thereof for use in the treatment of an avian influenza infection in an individual,

wherein:

(a) $\mathbf{R^{1a}}$ and $\mathbf{R^{1b}}$ are each separately selected from the group consisting of H (hydrogen), -C(O)N$\mathbf{R^{1c}R^{1d}}$, –C(O)O$\mathbf{R^{1e}}$, –C(S)N$\mathbf{R^{1c}R^{1d}}$, –C(S)O$\mathbf{R^{1e}}$, –NHC(O)$\mathbf{R^{1e}}$, -NHC(O)N$\mathbf{R^{1c}R^{1d}}$, –NHC(O)O$\mathbf{R^{1e}}$, -NHC(S)N$\mathbf{R^{1c}R^{1d}}$, –NHC(S)O$\mathbf{R^{1e}}$, -OC(O)N$\mathbf{R^{1c}R^{1d}}$, -OC(O)O$\mathbf{R^{1e}}$, –OC(S)N$\mathbf{R^{1c}R^{1d}}$, -O$\mathbf{R^{1f}}$, and

-$NR^{1c}R^{1d}$; or R^{1a} and R^{1b} are optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

each R^{1c} and R^{1d} is independently selected from the group consisting of H (hydrogen), C_{1-6} alkyl, heteroaryl, and aryl, or R^{1c} and R^{1d} are optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

each R^{1e} is independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

each R^{1f} is independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(b) R^{2a} and R^{2b} are each separately selected from the group consisting of H (hydrogen), -$C(O)NR^{2c}R^{2d}$, –$C(O)OR^{2e}$, –$C(S)NR^{2c}R^{2d}$, –$C(S)OR^{2e}$, –$NHC(O)R^{2e}$, -$NHC(O)NR^{2c}R^{2d}$, –$NHC(O)OR^{2e}$, -$NHC(S)NR^{2c}R^{2d}$, –$NHC(S)OR^{2e}$, -$OC(O)NR^{2c}R^{2d}$, -$OC(O)OR^{2e}$, –$OC(S)NR^{2c}R^{2d}$, -OR^{2f}, and -$NR^{1c}R^{1d}$; or R^{2a} and R^{2b} are optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

each R^{2c} and R^{2d} is independently selected from the group consisting of H (hydrogen), C_{1-6} alkyl, and aryl, or R^{2c} and R^{2d} are optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

each R^{2e} is independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

each R^{2f} is independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) R^3 is selected from the group consisting of H (hydrogen), –$NHC(O)R^{3a}$, -$NHC(O)NR^{3b}R^{3c}$, –$NHC(O)OR^{3d}$, -$NHC(S)NR^{3b}R^{3c}$, –$NHC(S)OR^{3d}$, -$OC(S)NR^{3b}R^{3c}$, -OR^{3e}, -SR^{3e}, -$NR^{3b}R^{3c}$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

R^{3a} is selected from the group consisting of aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

R^{3b} and R^{3c} are each separately selected from the group consisting of H (hydrogen), C_{1-6} alkyl, heteroaryl, and aryl, or R^{3b} and R^{3c} are optionally taken

together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

R^{3d} is selected from the group consisting of aryl, heteroaryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

R^{3e} is selected from the group consisting of H (hydrogen), aryl, heteroaryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(d) R^4 is selected from the group consisting of H (hydrogen), $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, $-OP(O)(OR^{4a})_2$, $-SR^{4b}$, halo, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

each R^{4a} is independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

R^{4b} is selected from the group consisting of H (hydrogen), heteroaryl, aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

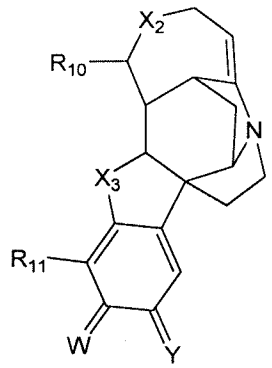
(e) R^5 is selected from the group consisting of $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, $-OP(O)(OR^{5a})_2$, $-SR^{5b}$, and halo;

each R^{5a} is independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

R^{5b} is selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro; and

(f) X_1 is selected from the group consisting of O (oxygen), S (sulfur) and $-NR^6$; where R^6 is H (hydrogen) or C_{1-6} alkyl.

[0028] Another embodiment is the compound having the formula (**II**):



(**II**)

or a pharmaceutically acceptable salt or prodrug thereof for use in the treatment of an avian influenza infection in an individual,

wherein:

(a) $\mathbf{R^{10}}$ is selected from the group consisting of $-(CH_2)_n\mathbf{R^{10a}}$;

(b) $\mathbf{R^{10a}}$ is selected from the group consisting of tetrazole, $-C(O)\mathbf{R^{10b}}$, and $-C(S)\mathbf{R^{10b}}$;

(c) $\mathbf{R^{10b}}$ is selected from the group consisting of H (hydrogen), $-S\mathbf{R^{10c}}$, $-O\mathbf{R^{10c}}$, $-NH\mathbf{R^{10c}}$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(d) $\mathbf{R^{10c}}$ is selected from the group consisting of H (hydrogen) and C_{1-6} alkyl;

(e) **n** is 0, 1, or 2;

(f) $\mathbf{R^{11}}$ is selected from the group consisting of tetrazole, $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, nitro, $-OP(O)(O\mathbf{R^{11a}})_2$, and $-C(O)O\mathbf{R^{11b}}$;

$\mathbf{R^{11a}}$ is selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

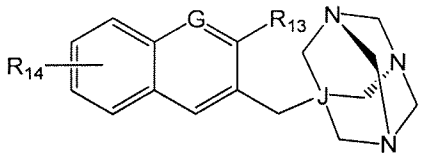
$\mathbf{R^{11b}}$ is selected from the group consisting of H (hydrogen), and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(g) **W** is O (oxygen) or S (sulfur);

(h) **Y** is O (oxygen) or S (sulfur); and

(i) $\mathbf{X_2}$ and $\mathbf{X_3}$ are each individually selected from the group consisting of O (oxygen), S (sulfur) and -NH.

[0029] Another embodiment is the compound having the formula (**III**):



(III)

or a pharmaceutically acceptable salt or prodrug thereof for use in the treatment of an avian influenza infection in an individual,

wherein:

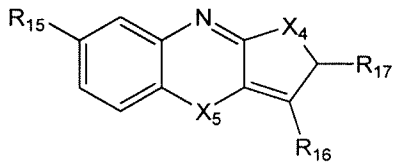
(a) $\mathbf{R^{13}}$ is selected from the group consisting of H (hydrogen), C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(b) $\mathbf{R^{14}}$ is one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) G is selected from the group consisting of CH and N (nitrogen); and

(d) J is selected from the group consisting of N^+ (nitrogen) and P^+ (phosphorous).

[0030] Another embodiment is the compound having the formula **(IV)**:



(IV)

or tautomer thereof, or their pharmaceutically acceptable salts or prodrugs, for use in the treatment of an avian influenza infection in an individual,

wherein:

(a) $\mathbf{R^{15}}$ is selected from the group consisting of nitro, and $-C(O)\mathbf{R^{15a}}$;

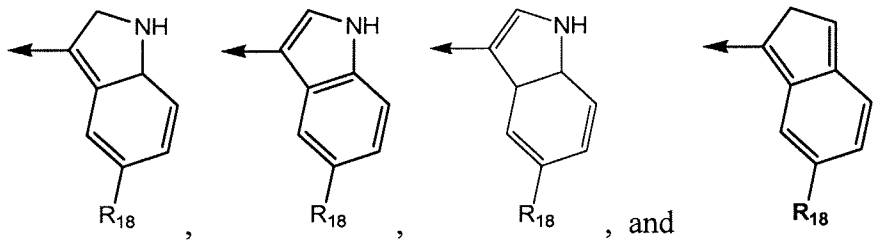
(b) $\mathbf{R^{15a}}$ is selected from the group consisting of H (hydrogen), $-S\mathbf{R^{15b}}$, and $-O\mathbf{R^{15b}}$;

(c) $\mathbf{R^{15b}}$ is selected from the group consisting of H (hydrogen) and C_{1-6} alkyl;

(d) $\mathbf{R^{16}}$ is selected from the group consisting of H (hydrogen) and $-O\mathbf{R^{16a}}$;

(e) $\mathbf{R^{16a}}$ is selected from the group consisting of H (hydrogen), and C_{1-6} alkyl;

(f) $\mathbf{R^{17}}$ is selected from the group consisting of:



(g) $\mathbf{R^{18}}$ is selected from the group consisting of $-(CH_2)_n\mathbf{R^{18a}}$ and $-CH{=}CH\mathbf{R^{18a}}$;

(h) n is 0, 1, or 2;

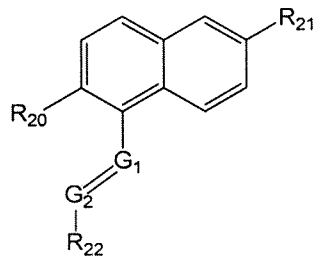
(i) $\mathbf{R^{18a}}$ is selected from the group consisting of $-S\mathbf{R^{18b}}$, $-O\mathbf{R^{18b}}$, aryl optionally substituted with one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro, and heteroaryl optionally substituted with one or more

substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(j) $\mathbf{R^{18b}}$ is selected from the group consisting of aryl and heteroaryl, each optionally substituted with one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro; and

(k) $\mathbf{X_4}$ and $\mathbf{X_5}$ are each individually selected from the group consisting of O (oxygen), S (sulfur) and -NH.

[0031] Another embodiment is the compound having the formula (**V**):



(**V**)

or tautomer thereof, or their pharmaceutically acceptable salts or prodrugs, for use in the treatment of an avian influenza infection in an individual,

wherein:

(a) $\mathbf{R^{20}}$ is selected from the group consisting of H (hydrogen), $-O\mathbf{R^{20a}}$, $-S\mathbf{R^{20a}}$, $-C(O)N\mathbf{R^{20c}R^{20d}}$, $-NHC(O)\mathbf{R^{20e}}$;

(b) $\mathbf{R^{20a}}$ is selected from the group consisting of H (hydrogen), and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) $\mathbf{R^{20c}}$ and $\mathbf{R^{20d}}$ are each separately selected from the group consisting of H (hydrogen), C_{1-6} alkyl, heteroaryl, and aryl, or $\mathbf{R^{20c}}$ and $\mathbf{R^{20d}}$ are optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

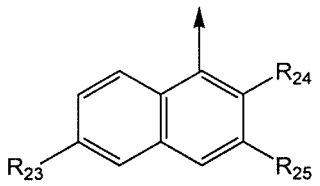
(d) $\mathbf{R^{20e}}$ is selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(e) $\mathbf{R^{21}}$ is selected from the group consisting of H (hydrogen), $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, halo, $-C(O)\mathbf{R^{21a}}$, and $-C(S)\mathbf{R^{21a}}$;

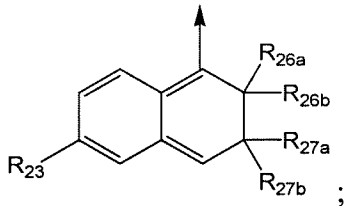
(f) $\mathbf{R^{21a}}$ is selected from the group consisting of H (hydrogen), $-S\mathbf{R^{21b}}$, $-O\mathbf{R^{21b}}$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(g) $\mathbf{R^{21b}}$ is selected from the group consisting of H (hydrogen), and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(h) $\mathbf{R^{22}}$ is selected from the group consisting of:



and



;

(i) $\mathbf{R^{23}}$ is selected from the group consisting of H (hydrogen), $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -OH and C_{1-6} alkoxy optionally substituted with up to 5 fluoro;

(j) $\mathbf{R^{24}}$ is -OH or C_{1-6} alkoxy optionally substituted with up to 5 fluoro;

(k) $\mathbf{R^{25}}$ is selected from the group consisting of H (hydrogen), $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -OH and C_{1-6} alkoxy optionally substituted with up to 5 fluoro;

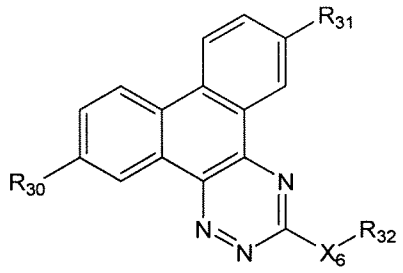
(l) $\mathbf{R^{26a}}$ and $\mathbf{R^{26b}}$ are each separately selected from the group consisting of H (hydrogen), -OH, C_{1-6} alkyl optionally substituted with up to 5 fluoro, and C_{1-6} alkoxy optionally substituted with up to 5 fluoro; or $\mathbf{R^{26a}}$ and $\mathbf{R^{26b}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

(m) $\mathbf{R^{27a}}$ and $\mathbf{R^{27b}}$ are each separately selected from the group consisting of H (hydrogen), -OH, C_{1-6} alkyl optionally substituted with up to 5 fluoro, and C_{1-6} alkoxy optionally substituted with up to 5 fluoro; or $\mathbf{R^{27a}}$ and $\mathbf{R^{27b}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group; and

(n) $\mathbf{G_1}$ is selected from the group consisting of CH and N (nitrogen); and

(o) $\mathbf{G_2}$ is selected from the group consisting of CH and N (nitrogen).

[0032] Another embodiment is the compound having the formula (**VI**):



(VI)

or tautomer thereof, or their pharmaceutically acceptable salts or prodrugs, for use in the treatment of an avian influenza infection in an individual,

wherein:

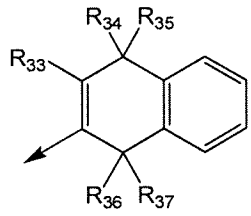
(a) $\mathbf{R^{30}}$ is selected from the group consisting of H (hydrogen), $-O\mathbf{R^{30a}}$, $-S\mathbf{R^{30a}}$, $-N\mathbf{R^{30b}}\mathbf{R^{30c}}$, $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, $-C(O)OH$, $-CH_2C(O)OH$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(b) $\mathbf{R^{30a}}$ is selected from the group consisting of H (hydrogen) and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) $\mathbf{R^{30b}}$ and $\mathbf{R^{30c}}$ are each separately selected from the group consisting of H (hydrogen) and C_{1-6} alkyl, or $\mathbf{R^{30b}}$ and $\mathbf{R^{30c}}$ are optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

(d) $\mathbf{R^{31}}$ is selected from the group consisting of H (hydrogen), -OH, –SH, $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, $-C(O)OH$, $-CH_2C(O)OH$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(e) $\mathbf{R^{32}}$ is selected from the group consisting of $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, $-C(O)OH$, and $-CH_2C(O)OH$; or $\mathbf{R^{32}}$ is :



;

(f) $\mathbf{R^{33}}$ is selected from the group consisting of H (hydrogen), -OH, halo, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

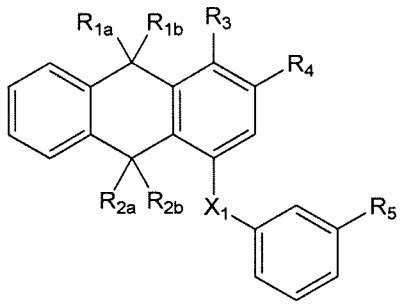
(g) $\mathbf{R^{34}}$ and $\mathbf{R^{35}}$ are each separately selected from the group consisting of H (hydrogen), -OH, halo, and C_{1-6} alkyl optionally substituted with up to 5 fluoro; or

R^{34} and R^{35} are optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

(h) R^{36} and R^{37} are each separately selected from the group consisting of H (hydrogen), -OH, -SH, and halo; or R^{36} and R^{37} are optionally taken together with the carbon to which they are attached to form a keto or thioketo group; and

(i) X_6 is selected from the group consisting of O (oxygen), S (sulfur) and -NH.

[0033] Another embodiment is the method of ameliorating an avian influenza infection in an individual, the method comprising administering to the individual an effective amount of a compound having the formula (**I**):



(**I**)

or a pharmaceutically acceptable salt or prodrug thereof,

wherein:

(a) R^{1a} and R^{1b} are each separately selected from the group consisting of H (hydrogen), -C(O)N$R^{1c}R^{1d}$, –C(O)OR^{1e}, –C(S)N$R^{1c}R^{1d}$, –C(S)OR^{1e}, –NHC(O)R^{1e}, -NHC(O)N$R^{1c}R^{1d}$, –NHC(O)OR^{1e}, -NHC(S)N$R^{1c}R^{1d}$, –NHC(S)OR^{1e}, -OC(O)N$R^{1c}R^{1d}$, -OC(O)OR^{1e}, –OC(S)N$R^{1c}R^{1d}$, -OR^{1f}, and -N$R^{1c}R^{1d}$; or R^{1a} and R^{1b} are optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

each R^{1c} and R^{1d} is independently selected from the group consisting of H (hydrogen), C_{1-6} alkyl, heteroaryl, and aryl, or R^{1c} and R^{1d} are optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

each R^{1e} is independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

each R^{1f} is independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(b) $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are each separately selected from the group consisting of H (hydrogen), -C(O)N$\mathbf{R^{2c}R^{2d}}$, –C(O)O$\mathbf{R^{2e}}$, –C(S)N$\mathbf{R^{2c}R^{2d}}$, –C(S)O$\mathbf{R^{2e}}$, –NHC(O)$\mathbf{R^{2e}}$, -NHC(O)N$\mathbf{R^{2c}R^{2d}}$, –NHC(O)O$\mathbf{R^{2e}}$, -NHC(S)N$\mathbf{R^{2c}R^{2d}}$, –NHC(S)O$\mathbf{R^{2e}}$, -OC(O)N$\mathbf{R^{2c}R^{2d}}$, -OC(O)O$\mathbf{R^{2e}}$, –OC(S)N$\mathbf{R^{2c}R^{2d}}$, -O$\mathbf{R^{2f}}$, and -N$\mathbf{R^{1c}R^{1d}}$; or $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

each $\mathbf{R^{2c}}$ and $\mathbf{R^{2d}}$ is independently selected from the group consisting of H (hydrogen), $C_{1\text{-}6}$ alkyl, and aryl, or $\mathbf{R^{2c}}$ and $\mathbf{R^{2d}}$ are optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

each $\mathbf{R^{2e}}$ is independently selected from the group consisting of H (hydrogen), aryl, and $C_{1\text{-}6}$ alkyl optionally substituted with up to 5 fluoro;

each $\mathbf{R^{2f}}$ is independently selected from the group consisting of H (hydrogen), aryl, and $C_{1\text{-}6}$ alkyl optionally substituted with up to 5 fluoro;

(c) $\mathbf{R^3}$ is selected from the group consisting of H (hydrogen), –NHC(O)$\mathbf{R^{3a}}$, -NHC(O)N$\mathbf{R^{3b}R^{3c}}$, –NHC(O)O$\mathbf{R^{3d}}$, -NHC(S)N$\mathbf{R^{3b}R^{3c}}$, –NHC(S)O$\mathbf{R^{3d}}$, -OC(S)N$\mathbf{R^{3b}R^{3c}}$, -O$\mathbf{R^{3e}}$, -S$\mathbf{R^{3e}}$, -N$\mathbf{R^{3b}R^{3c}}$, and $C_{1\text{-}6}$ alkyl optionally substituted with up to 5 fluoro;

$\mathbf{R^{3a}}$ is selected from the group consisting of aryl, and $C_{1\text{-}6}$ alkyl optionally substituted with up to 5 fluoro;

$\mathbf{R^{3b}}$ and $\mathbf{R^{3c}}$ are each separately selected from the group consisting of H (hydrogen), $C_{1\text{-}6}$ alkyl, heteroaryl, and aryl, or $\mathbf{R^{3b}}$ and $\mathbf{R^{3c}}$ are optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

$\mathbf{R^{3d}}$ is selected from the group consisting of aryl, heteroaryl, and $C_{1\text{-}6}$ alkyl optionally substituted with up to 5 fluoro;

$\mathbf{R^{3e}}$ is selected from the group consisting of H (hydrogen), aryl, heteroaryl, and $C_{1\text{-}6}$ alkyl optionally substituted with up to 5 fluoro;

(d) $\mathbf{R^4}$ is selected from the group consisting of H (hydrogen), -$S(O)_2OH$, -$S(O)_2NH_2$, -$P(O)(OH)_2$, -OP(O)(O$\mathbf{R^{4a}}$)$_2$, -S$\mathbf{R^{4b}}$, halo, and $C_{1\text{-}6}$ alkyl optionally substituted with up to 5 fluoro;

each $\mathbf{R^{4a}}$ is independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

$\mathbf{R^{4b}}$ is selected from the group consisting of H (hydrogen), heteroaryl, aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

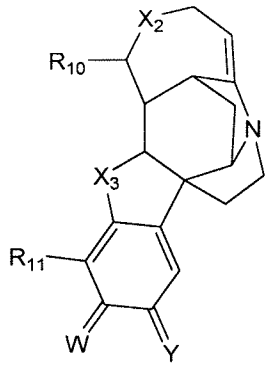
(e) $\mathbf{R^5}$ is selected from the group consisting of $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, $-OP(O)(OR^{5a})_2$, $-SR^{5b}$, and halo;

each $\mathbf{R^{5a}}$ is independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

$\mathbf{R^{5b}}$ is selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro; and

(f) $\mathbf{X_1}$ is selected from the group consisting of O (oxygen), S (sulfur) and $-NR^6$; where $\mathbf{R^6}$ is H (hydrogen) or C_{1-6} alkyl.

[0034] Another embodiment is the method of ameliorating an avian influenza infection in an individual, the method comprising administering to the individual an effective amount of a compound having the formula (**II**):



(II)

or a pharmaceutically acceptable salt or prodrug thereof,

wherein:

(a) $\mathbf{R^{10}}$ is selected from the group consisting of $-(CH_2)_nR^{10a}$;

(b) $\mathbf{R^{10a}}$ is selected from the group consisting of tetrazole, $-C(O)R^{10b}$, and $-C(S)R^{10b}$;

(c) $\mathbf{R^{10b}}$ is selected from the group consisting of H (hydrogen), $-SR^{10c}$, $-OR^{10c}$, $-NHR^{10c}$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(d) $\mathbf{R^{10c}}$ is selected from the group consisting of H (hydrogen) and C_{1-6} alkyl;

(e) n is 0, 1, or 2;

(f) $\mathbf{R^{11}}$ is selected from the group consisting of tetrazole, $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, nitro, $-OP(O)(OR^{11a})_2$, and $-C(O)OR^{11b}$;

$\mathbf{R^{11a}}$ is selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

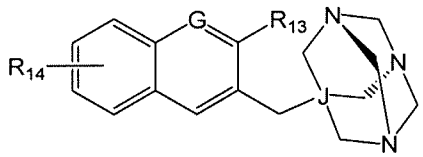
$\mathbf{R^{11b}}$ is selected from the group consisting of H (hydrogen), and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(g) W is O (oxygen) or S (sulfur);

(h) Y is O (oxygen) or S (sulfur); and

(i) $\mathbf{X_2}$ and $\mathbf{X_3}$ are each individually selected from the group consisting of O (oxygen), S (sulfur) and -NH.

[0035] Another embodiment is the method of ameliorating an avian influenza infection in an individual, the method comprising administering to the individual an effective amount of a compound having the formula (**III**):



(III)

or a pharmaceutically acceptable salt or prodrug thereof,

wherein:

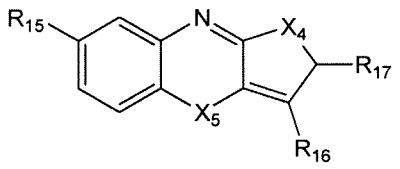
(a) $\mathbf{R^{13}}$ is selected from the group consisting of H (hydrogen), C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(b) $\mathbf{R^{14}}$ is one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) G is selected from the group consisting of CH and N (nitrogen); and

(d) J is selected from the group consisting of N^+ (nitrogen) and P^+ (phosphorous).

[0036] Another embodiment is the method of ameliorating an avian influenza infection in an individual, the method comprising administering to the individual an effective amount of a compound having the formula (**IV**):



(IV)

or tautomer thereof, or their pharmaceutically acceptable salts or prodrugs, wherein:

(a) $\mathbf{R^{15}}$ is selected from the group consisting of nitro, and -C(O)$\mathbf{R^{15a}}$;

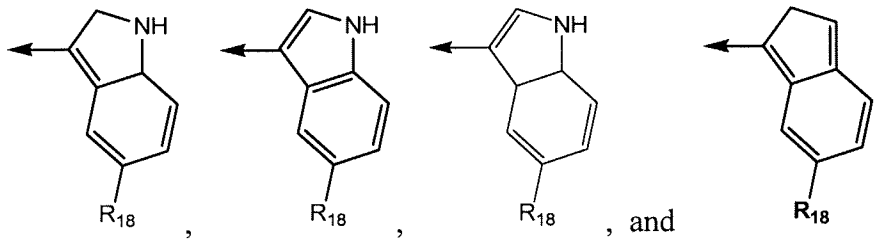
(b) $\mathbf{R^{15a}}$ is selected from the group consisting of H (hydrogen), -S$\mathbf{R^{15b}}$, and -O$\mathbf{R^{15b}}$;

(c) $\mathbf{R^{15b}}$ is selected from the group consisting of H (hydrogen) and C_{1-6} alkyl;

(d) $\mathbf{R^{16}}$ is selected from the group consisting of H (hydrogen) and -O$\mathbf{R^{16a}}$;

(e) $\mathbf{R^{16a}}$ is selected from the group consisting of H (hydrogen), and C_{1-6} alkyl;

(f) $\mathbf{R^{17}}$ is selected from the group consisting of:



;

(g) $\mathbf{R^{18}}$ is selected from the group consisting of $-(CH_2)_n\mathbf{R^{18a}}$ and -CH=CH$\mathbf{R^{18a}}$;

(h) **n** is 0, 1, or 2;

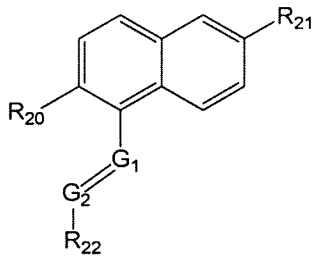
(i) $\mathbf{R^{18a}}$ is selected from the group consisting of -S$\mathbf{R^{18b}}$, -O$\mathbf{R^{18b}}$, aryl optionally substituted with one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro, and heteroaryl optionally substituted with one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(j) $\mathbf{R^{18b}}$ is selected from the group consisting of aryl and heteroaryl, each optionally substituted with one or more substituents each individually selected

from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro; and

(k) $\mathbf{X_4}$ and $\mathbf{X_5}$ are each individually selected from the group consisting of O (oxygen), S (sulfur) and -NH.

[0037] Another embodiment is the method of ameliorating an avian influenza infection in an individual, the method comprising administering to the individual an effective amount of a compound having the formula (**V**):



(**V**)

or tautomer thereof, or their pharmaceutically acceptable salts or prodrugs, wherein:

(a) $\mathbf{R^{20}}$ is selected from the group consisting of H (hydrogen), $-O\mathbf{R^{20a}}$, $-S\mathbf{R^{20a}}$, $-C(O)N\mathbf{R^{20c}R^{20d}}$, $-NHC(O)\mathbf{R^{20e}}$;

(b) $\mathbf{R^{20a}}$ is selected from the group consisting of H (hydrogen), and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) $\mathbf{R^{20c}}$ and $\mathbf{R^{20d}}$ are each separately selected from the group consisting of H (hydrogen), C_{1-6} alkyl, heteroaryl, and aryl, or $\mathbf{R^{20c}}$ and $\mathbf{R^{20d}}$ are optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

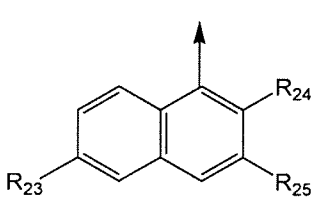
(d) $\mathbf{R^{20e}}$ is selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

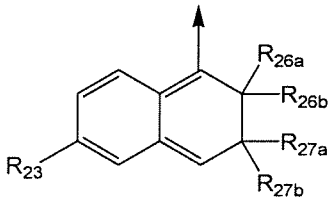
(e) $\mathbf{R^{21}}$ is selected from the group consisting of H (hydrogen), $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, halo, $-C(O)\mathbf{R^{21a}}$, and $-C(S)\mathbf{R^{21a}}$;

(f) $\mathbf{R^{21a}}$ is selected from the group consisting of H (hydrogen), $-S\mathbf{R^{21b}}$, $-O\mathbf{R^{21b}}$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(g) $\mathbf{R^{21b}}$ is selected from the group consisting of H (hydrogen), and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(h) $\mathbf{R^{22}}$ is selected from the group consisting of:



and


;

(i) $\mathbf{R^{23}}$ is selected from the group consisting of H (hydrogen), $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -OH and C_{1-6} alkoxy optionally substituted with up to 5 fluoro;

(j) $\mathbf{R^{24}}$ is -OH or C_{1-6} alkoxy optionally substituted with up to 5 fluoro;

(k) $\mathbf{R^{25}}$ is selected from the group consisting of H (hydrogen), $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -OH and C_{1-6} alkoxy optionally substituted with up to 5 fluoro;

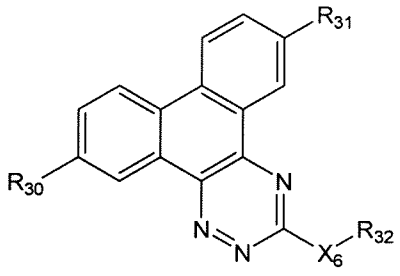
(l) $\mathbf{R^{26a}}$ and $\mathbf{R^{26b}}$ are each separately selected from the group consisting of H (hydrogen), -OH, C_{1-6} alkyl optionally substituted with up to 5 fluoro, and C_{1-6} alkoxy optionally substituted with up to 5 fluoro; or $\mathbf{R^{26a}}$ and $\mathbf{R^{26b}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

(m) $\mathbf{R^{27a}}$ and $\mathbf{R^{27b}}$ are each separately selected from the group consisting of H (hydrogen), -OH, C_{1-6} alkyl optionally substituted with up to 5 fluoro, and C_{1-6} alkoxy optionally substituted with up to 5 fluoro; or $\mathbf{R^{27a}}$ and $\mathbf{R^{27b}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group; and

(n) $\mathbf{G_1}$ is selected from the group consisting of CH and N (nitrogen); and

(o) $\mathbf{G_2}$ is selected from the group consisting of CH and N (nitrogen).

[0038] Another embodiment is the method of ameliorating an avian influenza infection in an individual, the method comprising administering to the individual an effective amount of a compound having the formula (**VI**):



(VI)

or tautomer thereof, or their pharmaceutically acceptable salts or prodrugs, wherein:

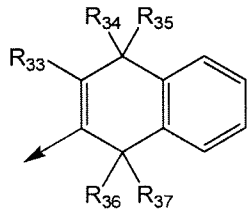
(a) $\mathbf{R^{30}}$ is selected from the group consisting of H (hydrogen), $-O\mathbf{R^{30a}}$, $-S\mathbf{R^{30a}}$, $-N\mathbf{R^{30b}R^{30c}}$, $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, $-C(O)OH$, $-CH_2C(O)OH$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(b) $\mathbf{R^{30a}}$ is selected from the group consisting of H (hydrogen) and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) $\mathbf{R^{30b}}$ and $\mathbf{R^{30c}}$ are each separately selected from the group consisting of H (hydrogen) and C_{1-6} alkyl, or $\mathbf{R^{30b}}$ and $\mathbf{R^{30c}}$ are optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

(d) $\mathbf{R^{31}}$ is selected from the group consisting of H (hydrogen), -OH, –SH, $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, $-C(O)OH$, $-CH_2C(O)OH$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(e) $\mathbf{R^{32}}$ is selected from the group consisting of $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, $-C(O)OH$, and $-CH_2C(O)OH$; or $\mathbf{R^{32}}$ is :



;

(f) $\mathbf{R^{33}}$ is selected from the group consisting of H (hydrogen), -OH, halo, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(g) $\mathbf{R^{34}}$ and $\mathbf{R^{35}}$ are each separately selected from the group consisting of H (hydrogen), -OH, halo, and C_{1-6} alkyl optionally substituted with up to 5 fluoro; or $\mathbf{R^{34}}$ and $\mathbf{R^{35}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

(h) $\mathbf{R^{36}}$ and $\mathbf{R^{37}}$ are each separately selected from the group consisting of H (hydrogen), -OH, -SH, and halo; or $\mathbf{R^{36}}$ and $\mathbf{R^{37}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group; and

(i) $\mathbf{X_6}$ is selected from the group consisting of O (oxygen), S (sulfur) and -NH.

[0039] Another embodiment is the method of identifying compounds which bind to the neuraminidase protein of Influenza A virus subtype H5N1, comprising:

(a) performing molecular dynamic simulations on an Influenza A virus subtype H5N1 neuraminidase protein crystal structure;

(b) generating an Influenza A virus subtype H5N1 protein structure using RMSD (root-mean-square-difference) clustering of related residues from the molecular dynamic simulations;

(c) docking compounds to the 150-loop of the generated Influenza A virus subtype H5N1 neuraminidase protein structure; and

(d) identifying the binding affinity of the docked compounds

wherein the MD simulations are performed on 2 or more Influenza A virus subtype H5N1 neuraminidase protein crystal structures. In one aspect of the embodiment the method further comprises docking the compounds to sialic acid cavity.

[0040] Another embodiment is the method of identifying compounds which bind to the neuraminidase protein of Influenza A virus subtype H5N1, comprising:

(a) performing molecular dynamic simulations on an Influenza A virus subtype H5N1 crystal structure;

(b) generating an Influenza A virus subtype H5N1 protein structure using RMSD (root-mean-square-difference) clustering of related residues from the molecular dynamic (MD) simulations;

(c) docking compounds to the 430-loop of the generated Influenza A virus subtype H5N1 neuraminidase protein structure; and

(d) identifying the binding affinity of the docked compounds

wherein the MD simulations are performed on 2 or more Influenza A virus subtype H5N1 neuraminidase protein crystal structures. In one aspect of the embodiment the method further comprises docking the compounds to sialic acid cavity. In another aspect of the embodiment the method further comprises docking the compounds to the 150-loop. In another aspect of the embodiment the method further comprises docking the compounds to the sialic acid cavity and the 150-loop.

[0041] Another embodiment is the method of identifying an agent that interacts with Influenza A virus subtype H5N1 neuraminidase protein comprising:

(a) using a crystal structure of a complex comprising Influenza A virus subtype H5N1 neuraminidase protein;

(b) obtaining the atomic coordinates of the crystal structure; and

(c) using the atomic coordinates and one or more molecular modeling techniques to identify a ligand that interacts with Influenza A virus subtype H5N1 neuraminidase protein.

[0042] Another embodiment is the method of identifying a compound which binds to the an Influenza A virus subtype H5N1 neuraminidase protein with a desired affinity comprising:

identifying one or more interactions between a ligand and a sub-unit of the Influenza A virus subtype H5N1 neuraminidase protein; and

changing a substituent on the ligand in order to modify the interaction between the ligand the neuraminidase protein subunit to provide said compound.

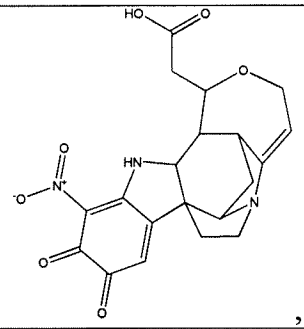
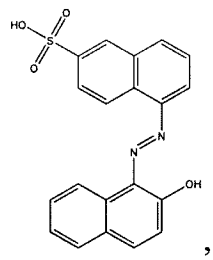
[0043] Another embodiment is the composition comprising an agent and a pharmaceutically-acceptable carrier wherein the agent is identified by

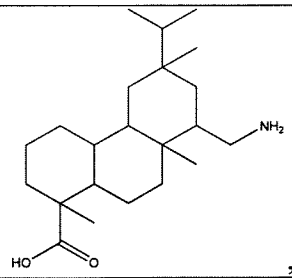
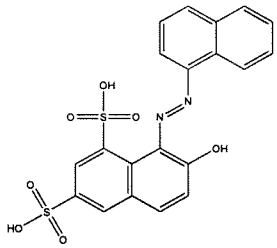
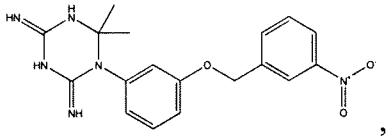
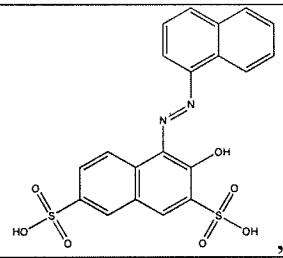
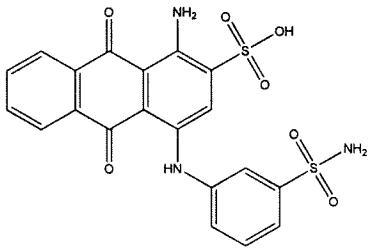
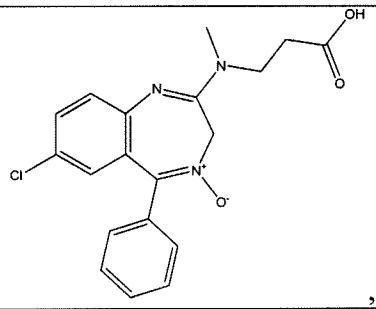
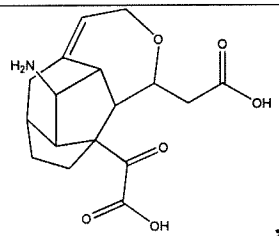
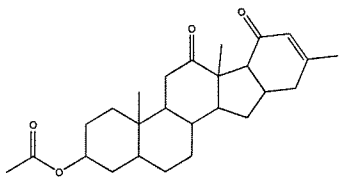
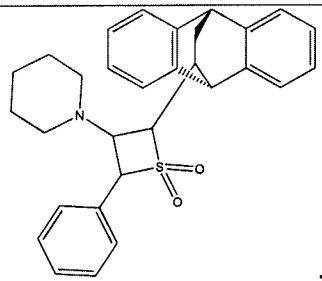
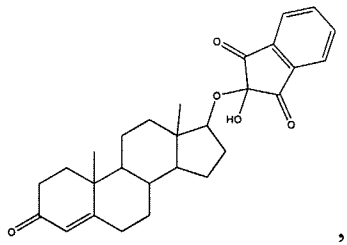
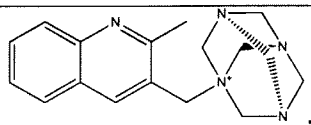
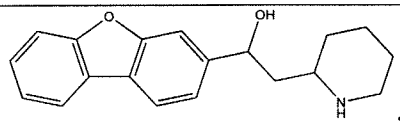
(a) using a crystal structure of a complex comprising Influenza A virus subtype H5N1 neuraminidase protein;

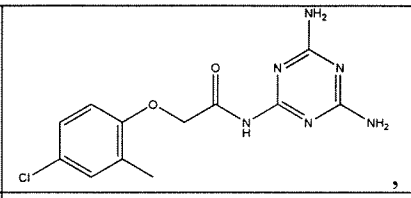
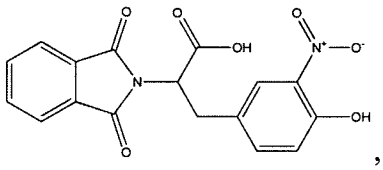
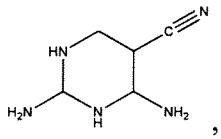
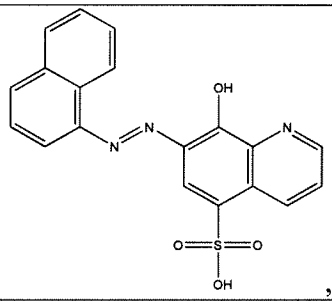
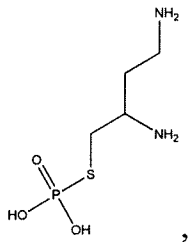
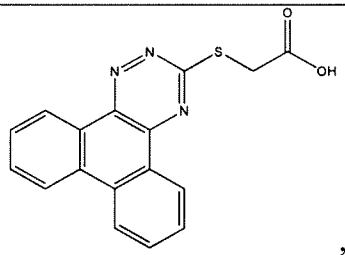
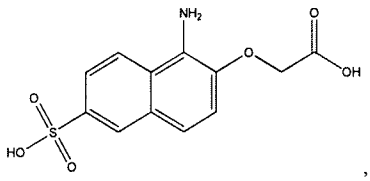
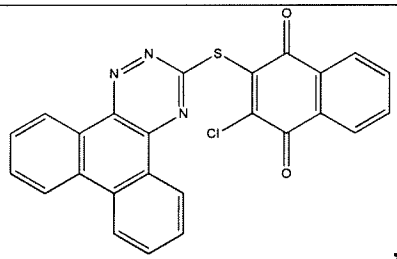
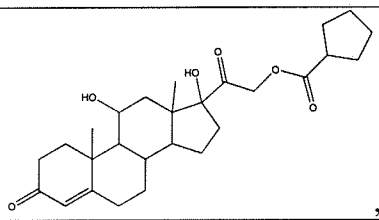
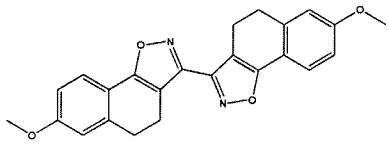
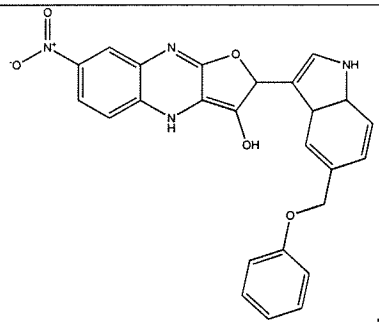
(b) obtaining the atomic coordinates of the crystal structure;

(c) using the atomic coordinates and one or more molecular modeling techniques to identify a ligand that interacts with Influenza A virus subtype H5N1.

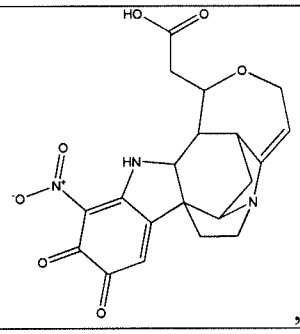
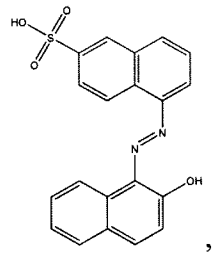
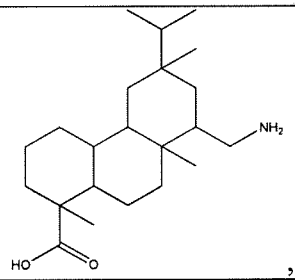
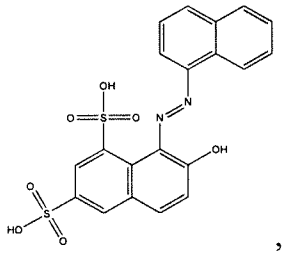
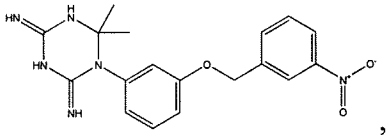
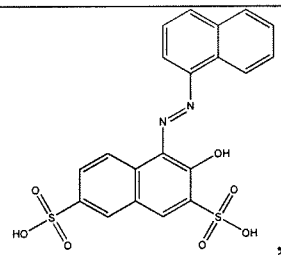
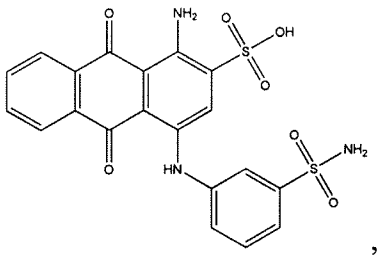
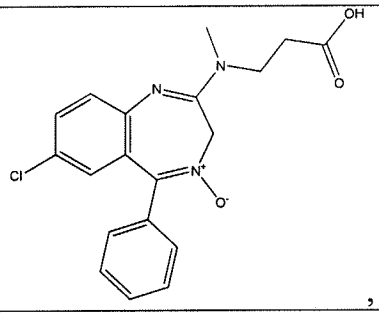
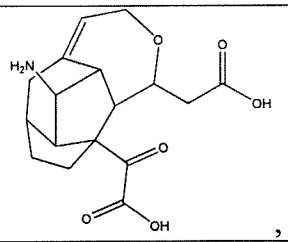
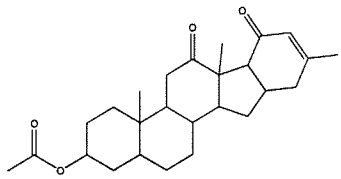
[0044] Another embodiment is the pill comprising a compound selected from the group consisting of:

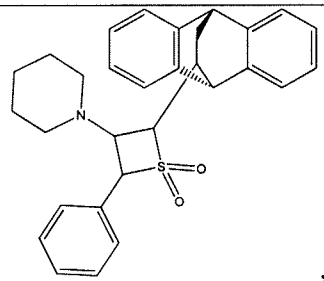
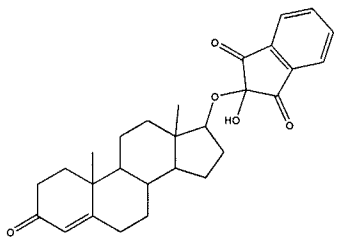
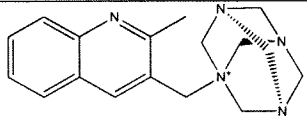
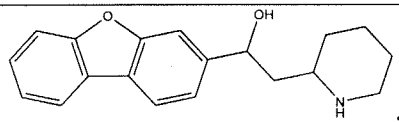
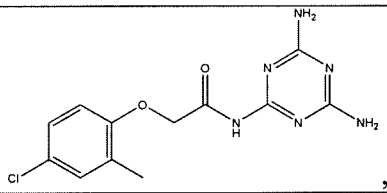
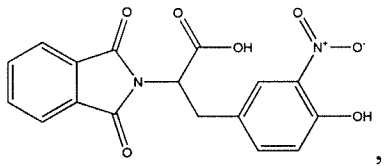
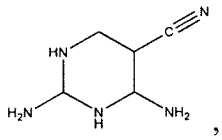
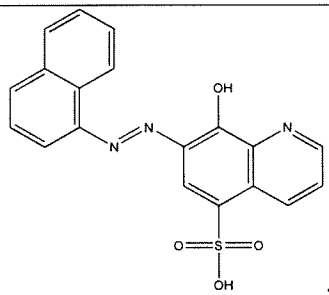
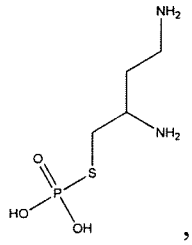
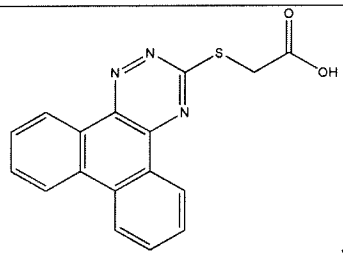
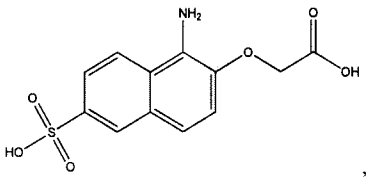
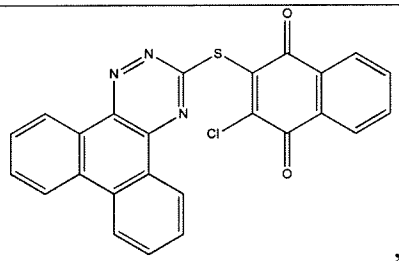
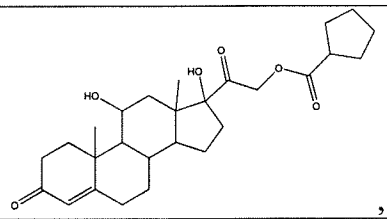
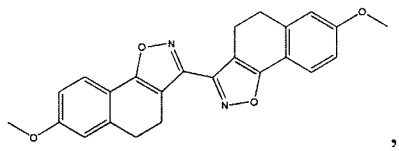
5069	 ,		45576	 ,

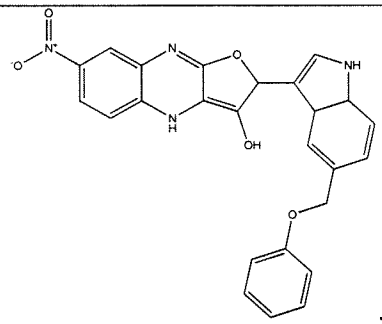
70194		45582	
109836		45583	
117079		46080	
131612		59620	
135371		72254	
141562		90630	

164640			106920	
211332			148354	
350191			327704	
16163			327705	
17245			371688	
	and		372294	

[0045] Another embodiment is the injectable pharmaceutical composition comprising a compound selected from the group consisting of:

5069		45576	
70194		45582	
109836		45583	
117079		46080	
131612		59620	

135371		72254	
141562		90630	
164640		106920	
211332		148354	
350191		327704	
16163		327705	
17245		371688	

	and		372294	

[0046] Another embodiment is the method of ameliorating an avian influenza infection in an individual, the method comprising administering to the individual an effective amount of a compound identified by any of the above methods.

[0047] Another embodiment is the method of screening a compound library to identify compounds which bind to an Influenza A virus subtype H5N1 neuraminidase protein comprising:

(a) obtaining a library comprising a plurality of compound structures;

(b) performing molecular dynamic simulations on an Influenza A virus subtype H5N1 neuraminidase protein crystal structure;

(c) generating an Influenza A virus subtype H5N1 protein structure using RMSD (root-mean-square-difference) clustering of related residues from the molecular dynamic simulations;

(d) docking compounds to the 150-loop of the generated Influenza A virus subtype H5N1 neuraminidase protein structure; and

(e) identifying compounds which bind to said Influenza A virus subtype H5N1 neuraminidase protein with a desired affinity. In one aspect of the embodiment the method further comprises docking the compounds to sialic acid cavity. In another aspect of the embodiment the method further comprises docking the compounds to the 430-loop. In another aspect of the embodiment the method further comprises docking the compounds to the sialic acid cavity and the 430-loop.

[0048] Another embodiment is the method of screening a compound library comprising:

(a) obtaining a library comprising a plurality of compound structures;

(b) performing molecular dynamic simulations on an Influenza A virus subtype H5N1 neuraminidase protein crystal structure;

(c) generating an Influenza A virus subtype H5N1 protein structure using RMSD (root-mean-square-difference) clustering of related residues from the molecular dynamic simulations;

(d) docking compounds to the 430-loop of the generated Influenza A virus subtype H5N1 neuraminidase protein structure; and

(e) identifying compounds which bind to said Influenza A virus subtype H5N1 neuraminidase protein with a desired affinity. In one aspect of the embodiment the method further comprises docking the compounds to the sialic acid cavity. In another aspect of the embodiment the method further comprises docking the compounds to the 150-loop. In another aspect of the embodiment the method further comprises docking the compounds to the sialic acid cavity and the 150-loop.

[0049] Another embodiment is the method of identifying compounds which bind to a target protein, comprising:

(a) performing molecular dynamic simulations on the target protein crystal structure;

(b) generating a target protein structure using RMSD (root-mean-square-difference) clustering of related residues from the molecular dynamic simulations;

(c) docking compounds to a binding pocket of the generated target protein structure;

(d) identifying the binding affinity of the docked compounds;

(e) ranking the compounds using relaxed complex scheme (RCS) computational methodology

[0050] wherein the MD simulations are performed on one or more target protein crystal structures.

[0051] Another embodiment is the injection device comprising the pharmaceutical composition comprising an agent and a pharmaceutically acceptable carrier, wherein the agent is a compound having the formulae (**I**), (**II**), (**III**), (**IV**), (**V**), or (**VI**). In one aspect of the embodiment the injection device is a syringe.

BRIEF DESCRIPTION OF THE DRAWINGS

[0052] Figure 1. The three central member structures for the most dominant clusters from the apo and holo simulations are represented above in (a) and (b), respectively, each shown in comparison to the open and closed 150-loop crystal structure.

[0053] Figure 2. Selected compounds are shown clustered in apo protein binding sites.

[0054] Figure 3. Selected compounds are shown clustered in holo protein binding sites.

[0055] Figure 4A. The open 150-loop crystal structure (2HTY) is shown with compounds NSC46080 and NSC109836.

[0056] Figure 4B. NSC16163 is shown bound to the wide-open 150-cavity in Apo-1.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

Definitions

[0057] The term "pharmaceutical composition" refers to a mixture of a compound disclosed herein with other chemical components, such as diluents or carriers. The pharmaceutical composition facilitates administration of the compound to an organism. Multiple techniques of administering a compound exist in the art including, but not limited to, oral, injection, aerosol, parenteral, and topical administration. Pharmaceutical compositions can also be obtained by reacting compounds with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

[0058] The term "carrier" defines a chemical compound that facilitates the incorporation of a compound into cells or tissues. For example dimethyl sulfoxide (DMSO) is a commonly utilized carrier as it facilitates the uptake of many organic compounds into the cells or tissues of an organism.

[0059] The term "diluent" defines chemical compounds diluted in water that will dissolve the compound of interest as well as stabilize the biologically active form of the compound. Salts dissolved in buffered solutions are utilized as diluents in the art. One commonly used buffered solution is phosphate buffered saline because it mimics the

salt conditions of human blood. Since buffer salts can control the pH of a solution at low concentrations, a buffered diluent rarely modifies the biological activity of a compound.

[0060] The term "physiologically acceptable" defines a carrier or diluent that does not abrogate the biological activity and properties of the compound.

[0061] The term "halo" as used herein refers to fluoro, chloro, bromo, or iodo.

[0062] The term "keto," and "carbonyl" as used herein refers to a C=O group.

[0063] The term "thioketo" as used herein refers to a C=S group. The thioketo moiety has a sulfur in place of where an oxygen is present in a keto group. The thioketo moiety is covalently bonded to the parent molecule through the carbon atom.

[0064] The term "cyano" as used herein refers to a -CN group.

[0065] The term "nitro" as used herein refers to a $-NO_2$ group.

[0066] The term "carboxy" used herein refers to a –COOH group or pharmaceutically acceptable salt thereof.

[0067] The term "alkyl," as used herein, means any unbranched or branched, saturated hydrocarbon. The alkyl moiety, may be branched or straight chain. The alkyl group may have 1 to 20 carbon atoms (whenever it appears herein, a numerical range such as "1 to 20" refers to each integer in the given range; *e.g.*, "1 to 20 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 20 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated). The alkyl group may also be a medium size alkyl having 1 to 10 carbon atoms. The alkyl group could also be a lower alkyl having 1 to 5 carbon atoms. The alkyl group may be designated as "C_1-C_6 alkyl" or similar designations. By way of example only, "C_1-C_6 alkyl" indicates that there are one to six carbon atoms in the alkyl chain, i.e., the alkyl chain is selected from the group consisting of methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, pentyl, and hexyl.

[0068] The term "alkoxy" used herein refers to straight or branched chain alkyl radical covalently bonded to the parent molecule through an --O-- linkage. Examples of alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, butoxy, n-butoxy, sec-butoxy, t-butoxy and the like. By way of example only, "C_{1-6} alkoxy" indicates that there are one to six carbon atoms in the alkyl chain and the alkyl radical is covalently bonded to the parent molecule through an --O—linkage.

[0069] The term "aryl" used herein refers to homocyclic aromatic radical whether one ring or multiple fused rings. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, biphenyl, phenanthrenyl, naphthacenyl, and the like. In some embodiments, the aryl group can be optionally substituted with one or more substituents each independently selected from the group consisting of halo, cyano, nitro, hydroxy, carboxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl optionally substituted with up to 5 fluoro, and C_{1-6} alkoxy optionally substituted with up to 5 fluoro.

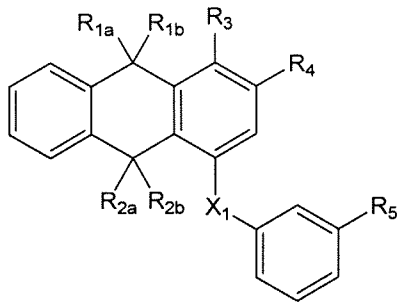
[0070] The term "heteroaryl" used herein refers to an aromatic heterocyclic group, whether one ring or multiple fused rings. In fused ring systems, the one or more heteroatoms may be present in only one of the rings. Examples of heteroaryl groups include, but are not limited to, benzothiazyl, benzoxazyl, quinazolinyl, quinolinyl, isoquinolinyl, quinoxalinyl, pyridinyl, pyrimidinyl, thiazolyl, thienyl, pyrrolyl, oxazolyl, indolyl, imidazolyl, tetrazolyl and the like. In some embodiments, the heteroaryl group can be optionally substituted with one or more substituents each independently selected from the group consisting of halo, cyano, nitro, hydroxy, carboxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl optionally substituted with up to 5 fluoro, and C_{1-6} alkoxy optionally substituted with up to 5 fluoro.

[0071] The term "pharmaceutically acceptable salt" refers to a salt of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In some embodiments, the salt is an acid addition salt of the compound. Pharmaceutical salts can be obtained by reacting a compound with inorganic acids such as hydrohalic acid (e.g., hydrochloric acid or hydrobromic acid), sulfuric acid, nitric acid, phosphoric acid and the like. Pharmaceutical salts can also be obtained by reacting a compound with an organic acid such as aliphatic or aromatic carboxylic or sulfonic acids, for example acetic, succinic, lactic, malic, tartaric, citric, ascorbic, nicotinic, methanesulfonic, ethanesulfonic, p-toluensulfonic, salicylic or naphthalenesulfonic acid. Pharmaceutical salts can also be obtained by reacting a compound with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)methylamine, C_1-C_7 alkylamine, cyclohexylamine, triethanolamine, ethylenediamine, and salts with amino acids such as arginine, lysine, and the like.

[0072] As used herein, the terms "treatment," "treating," "ameliorating" and the like, refer to obtaining a desired pharmacologic and/or physiologic effect. The effect may be prophylactic in terms of completely or partially preventing a disease or symptom thereof and/or may be therapeutic in terms of a partial or complete cure for a disease and/or adverse affect attributable to the disease. "Treatment," as used herein, covers any treatment of a disease in a mammal, particularly in a human, and includes: (a) preventing the disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it; (b) inhibiting the disease, i.e., arresting its development; and (c) relieving the disease, i.e., causing regression of the disease.

[0073] The terms "individual," "host," "subject," and "patient" are used interchangeably herein, and refer to a mammal, including, but not limited to, primates, including simians and humans.

[0074] Some embodiments provide a pharmaceutical composition comprising an agent and a pharmaceutically acceptable carrier, wherein the agent can be a compound having the formula (**I**):



(**I**)

or a pharmaceutically acceptable salt or prodrug thereof wherein:

(a) $\mathbf{R^{1a}}$ and $\mathbf{R^{1b}}$ can each be separately selected from the group consisting of H (hydrogen), -C(O)N$\mathbf{R^{1c}R^{1d}}$, –C(O)O$\mathbf{R^{1e}}$, –C(S)N$\mathbf{R^{1c}R^{1d}}$, –C(S)O$\mathbf{R^{1e}}$, –NHC(O)$\mathbf{R^{1e}}$, -NHC(O)N$\mathbf{R^{1c}R^{1d}}$, –NHC(O)O$\mathbf{R^{1e}}$, -NHC(S)N$\mathbf{R^{1c}R^{1d}}$, –NHC(S)O$\mathbf{R^{1e}}$, -OC(O)N$\mathbf{R^{1c}R^{1d}}$, -OC(O)O$\mathbf{R^{1e}}$, –OC(S)N$\mathbf{R^{1c}R^{1d}}$, -O$\mathbf{R^{1f}}$, and -N$\mathbf{R^{1c}R^{1d}}$; or $\mathbf{R^{1a}}$ and $\mathbf{R^{1b}}$ can be optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

each $\mathbf{R^{1c}}$ and $\mathbf{R^{1d}}$ can be independently selected from the group consisting of H (hydrogen), $C_{1\text{-}6}$ alkyl, heteroaryl, and aryl, or $\mathbf{R^{1c}}$ and $\mathbf{R^{1d}}$ optionally can be

taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

each $\mathbf{R^{1e}}$ can be independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

each $\mathbf{R^{1f}}$ can be independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(b) $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ can each be separately selected from the group consisting of H (hydrogen), -C(O)N$\mathbf{R^{2c}R^{2d}}$, –C(O)O$\mathbf{R^{2e}}$, –C(S)N$\mathbf{R^{2c}R^{2d}}$, –NHC(O)O$\mathbf{R^{2e}}$, -NHC(O)N$\mathbf{R^{2c}R^{2d}}$, –NHC(O)O$\mathbf{R^{2e}}$, -NHC(S)N$\mathbf{R^{2c}R^{2d}}$, –NHC(S)O$\mathbf{R^{2e}}$, -OC(O)N$\mathbf{R^{2c}R^{2d}}$, -OC(O)O$\mathbf{R^{2e}}$, –OC(S)N$\mathbf{R^{2c}R^{2d}}$, -O$\mathbf{R^{2f}}$, and -N$\mathbf{R^{1c}R^{1d}}$; or $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ can be optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

each $\mathbf{R^{2c}}$ and $\mathbf{R^{2d}}$ can be independently selected from the group consisting of H (hydrogen), C_{1-6} alkyl, and aryl, or $\mathbf{R^{2c}}$ and $\mathbf{R^{2d}}$ can be optionally are taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

each $\mathbf{R^{2e}}$ can be independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

each $\mathbf{R^{2f}}$ can be independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) $\mathbf{R^{3}}$ can be selected from the group consisting of H (hydrogen), –NHC(O)$\mathbf{R^{3a}}$, -NHC(O)N$\mathbf{R^{3b}R^{3c}}$, –NHC(O)O$\mathbf{R^{3d}}$, -NHC(S)N$\mathbf{R^{3b}R^{3c}}$, –NHC(S)O$\mathbf{R^{3d}}$, -OC(S)N$\mathbf{R^{3b}R^{3c}}$, -O$\mathbf{R^{3e}}$, -S$\mathbf{R^{3e}}$, -N$\mathbf{R^{3b}R^{3c}}$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

$\mathbf{R^{3a}}$ can be selected from the group consisting of aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

$\mathbf{R^{3b}}$ and $\mathbf{R^{3c}}$ can each be separately selected from the group consisting of H (hydrogen), C_{1-6} alkyl, heteroaryl, and aryl, or $\mathbf{R^{3b}}$ and $\mathbf{R^{3c}}$ optionally can be taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

$\mathbf{R^{3d}}$ can be selected from the group consisting of aryl, heteroaryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

R^{3c} can be selected from the group consisting of H (hydrogen), aryl, heteroaryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(d) R^4 can be selected from the group consisting of H (hydrogen), $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, $-OP(O)(OR^{4a})_2$, $-SR^{4b}$, halo, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

each R^{4a} can be independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

R^{4b} can be selected from the group consisting of H (hydrogen), heteroaryl, aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

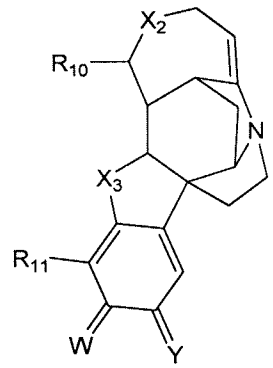
(e) R^5 can be selected from the group consisting of $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, $-OP(O)(OR^{5a})_2$, $-SR^{5b}$, and halo;

each R^{5a} can be independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

R^{5b} can be selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro; and

(f) X_1 can be selected from the group consisting of O (oxygen), S (sulfur) and $-NR^6$; where R^6 is H (hydrogen) or C_{1-6} alkyl. In some embodiments R^{1a} and R^{1b} can be taken together with the carbon to which they are attached to form keto; and R^{2a} and R^{2b} can be taken together with the carbon to which they are attached to form keto. In some embodiments R^3 can be $-NH_2$; and R^4 can be $-S(O)_2OH$. In some embodiments R^5 can be selected from the group consisting of $-S(O)_2OH$, and $-S(O)_2NH_2$; and X_1 can be $-NR^6$; where R^6 can be H (hydrogen) or C_{1-6} alkyl.

[0075] Some embodiments provide a pharmaceutical composition comprising an agent and a pharmaceutically acceptable carrier, wherein the agent canbe a compound having the formula (**II**):



(**II**)

or a pharmaceutically acceptable salt or prodrug thereof wherein:

(a) $\mathbf{R^{10}}$ is selected from the group consisting of $-(CH_2)_n\mathbf{R^{10a}}$;

(b) $\mathbf{R^{10a}}$ is selected from the group consisting of tetrazole, $-C(O)\mathbf{R^{10b}}$, and $-C(S)\mathbf{R^{10b}}$;

(c) $\mathbf{R^{10b}}$ is selected from the group consisting of H (hydrogen), $-S\mathbf{R^{10c}}$, $-O\mathbf{R^{10c}}$, $-NH\mathbf{R^{10c}}$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(d) $\mathbf{R^{10c}}$ is selected from the group consisting of H (hydrogen) and C_{1-6} alkyl;

(e) n is 0, 1, or 2;

(f) $\mathbf{R^{11}}$ is selected from the group consisting of tetrazole, $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, nitro, $-OP(O)(O\mathbf{R^{11a}})_2$, and $-C(O)O\mathbf{R^{11b}}$;

$\mathbf{R^{11a}}$ is selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

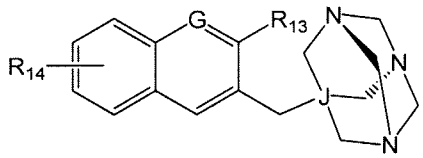
$\mathbf{R^{11b}}$ is selected from the group consisting of H (hydrogen), and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(g) W is O (oxygen) or S (sulfur);

(h) Y is O (oxygen) or S (sulfur); and

(i) $\mathbf{X_2}$ and $\mathbf{X_3}$ are each individually selected from the group consisting of O (oxygen), S (sulfur) and -NH. In some embodiments $\mathbf{X_2}$ can be O (oxygen) and $\mathbf{X_3}$ can be –NH. In some embodiments $\mathbf{R^{10a}}$ can be $-CH_2C(O)\mathbf{R^{10b}}$. In some embodiments $\mathbf{R^{10a}}$ can be $-CH_2C(O)O\mathbf{R^{10c}}$; and $\mathbf{R^{11}}$ can be selected from the group consisting of $-S(O)_2NH_2$, $-P(O)(OH)_2$, nitro, $-OP(O)(O\mathbf{R^{11a}})_2$, and $-C(O)O\mathbf{R^{11b}}$. In some embodiments $\mathbf{R^{10c}}$ can be H (hydrogen); $\mathbf{R^{11}}$ can be selected from the group consisting of nitro, $-OP(O)(O\mathbf{R^{11a}})_2$, and $-C(O)O\mathbf{R^{11b}}$; $\mathbf{R^{11a}}$ can be selected from the group consisting of H (hydrogen), and C_{1-6} alkyl; $\mathbf{R^{11b}}$ can be H (hydrogen); **W** can be O (oxygen); and **Y** can be O (oxygen).

[0076] Some embodiments provide a pharmaceutical composition comprising an agent and a pharmaceutically acceptable carrier, wherein the agent can be a compound having the formula (**III**):



(**III**)

or a pharmaceutically acceptable salt or prodrug thereof wherein:

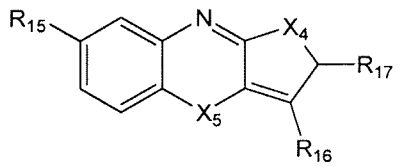
(a) $\mathbf{R^{13}}$ can be selected from the group consisting of H (hydrogen), C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(b) $\mathbf{R^{14}}$ can be one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) G can be selected from the group consisting of CH and N (nitrogen); and

(d) J can be selected from the group consisting of N^+ (nitrogen) and P^+ (phosphorous). In some embodiments **G** can be N (nitrogen). In some embodiments $\mathbf{R^{13}}$ can be selected from the group consisting of H (hydrogen) and C_{1-6} alkyl optionally substituted with up to 5 fluoro; and **J** can be N^+ (nitrogen).

[0077] Some embodiments provide a pharmaceutical composition comprising an agent and a pharmaceutically acceptable carrier, wherein the agent can be a compound having the formula (**IV**):



(**IV**)

or tautomer thereof, or their pharmaceutically acceptable salts or prodrugs, wherein:

(a) $\mathbf{R^{15}}$ can be selected from the group consisting of nitro, and -C(O)$\mathbf{R^{15a}}$;

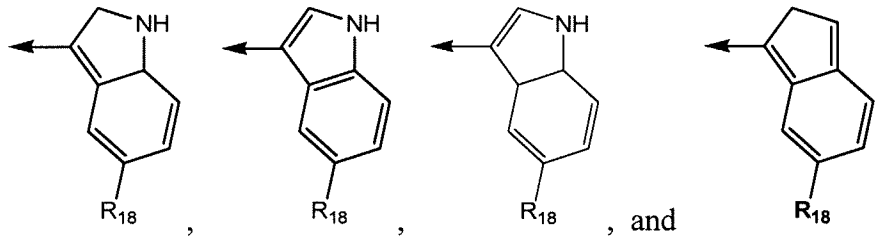
(b) $\mathbf{R^{15a}}$ can be selected from the group consisting of H (hydrogen), -S$\mathbf{R^{15b}}$, and -O$\mathbf{R^{15b}}$;

(c) $\mathbf{R^{15b}}$ can be selected from the group consisting of H (hydrogen) and C_{1-6} alkyl;

(d) $\mathbf{R^{16}}$ can be selected from the group consisting of H (hydrogen) and -O$\mathbf{R^{16a}}$;

(e) $\mathbf{R^{16a}}$ can be selected from the group consisting of H (hydrogen), and C_{1-6} alkyl;

(f) $\mathbf{R^{17}}$ can be selected from the group consisting of:



;

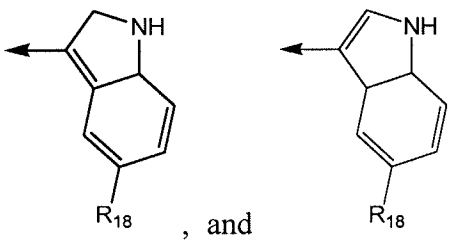
(g) $\mathbf{R^{18}}$ can be selected from the group consisting of $-(CH_2)_n\mathbf{R^{18a}}$ and $-CH=CH\mathbf{R^{18a}}$;

(h) **n** can be 0, 1, or 2;

(i) $\mathbf{R^{18a}}$ can be selected from the group consisting of $-S\mathbf{R^{18b}}$, $-O\mathbf{R^{18b}}$, aryl optionally substituted with one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro, and heteroaryl optionally substituted with one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(j) $\mathbf{R^{18b}}$ can be selected from the group consisting of aryl and heteroaryl, each optionally substituted with one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro; and

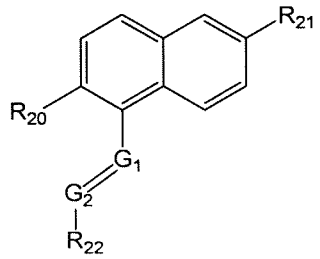
(k) $\mathbf{X_4}$ and $\mathbf{X_5}$ can each be individually selected from the group consisting of O (oxygen), S (sulfur) and -NH. In one aspect of the embodiments $\mathbf{R^{17}}$ can be selected from the group consisting of:



. In some embodiments $\mathbf{X_4}$ can be O (oxygen) and $\mathbf{X_5}$ can be –NH. In some embodiments $\mathbf{R^{18}}$ can be $-(CH_2)_n\mathbf{R^{18a}}$; **n** can be 1; and $\mathbf{R^{18a}}$ can be $-O\mathbf{R^{18b}}$. In some embodiments $\mathbf{R^{16}}$ can be $-O\mathbf{R^{16a}}$; and $\mathbf{R^{18b}}$ can be aryl optionally substituted with one or more substituents each individually selected from the group

consisting of OH, halo, cyano, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro.

[0078] Some embodiments provide a pharmaceutical composition comprising an agent and a pharmaceutically acceptable carrier, wherein the agent can be a compound having the formula (**V**):



(**V**)

or tautomer thereof, or their pharmaceutically acceptable salts or prodrugs, wherein:

(a) $\mathbf{R^{20}}$ can be selected from the group consisting of H (hydrogen), -O$\mathbf{R^{20a}}$, -S$\mathbf{R^{20a}}$, -C(O)N$\mathbf{R^{20c}R^{20d}}$, –NHC(O)$\mathbf{R^{20e}}$;

(b) $\mathbf{R^{20a}}$ can be selected from the group consisting of H (hydrogen), and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) $\mathbf{R^{20c}}$ and $\mathbf{R^{20d}}$ can each be separately selected from the group consisting of H (hydrogen), C_{1-6} alkyl, heteroaryl, and aryl, or $\mathbf{R^{20c}}$ and $\mathbf{R^{20d}}$ can be optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

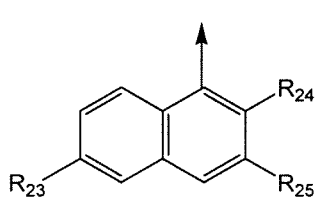
(d) $\mathbf{R^{20e}}$ can be selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

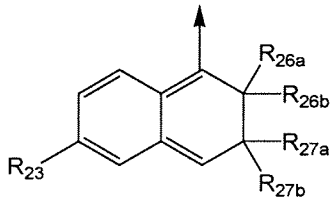
(e) $\mathbf{R^{21}}$ can be selected from the group consisting of H (hydrogen), -$S(O)_2OH$, -$S(O)_2NH_2$, -$P(O)(OH)_2$, halo, -C(O)$\mathbf{R^{21a}}$, and -C(S)$\mathbf{R^{21a}}$;

(f) $\mathbf{R^{21a}}$ can be selected from the group consisting of H (hydrogen), -S$\mathbf{R^{21b}}$, -O$\mathbf{R^{21b}}$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(g) $\mathbf{R^{21b}}$ can be selected from the group consisting of H (hydrogen), and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(h) $\mathbf{R^{22}}$ can be selected from the group consisting of:



and


;

(i) $\mathbf{R^{23}}$ can be selected from the group consisting of H (hydrogen), $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -OH and C_{1-6} alkoxy optionally substituted with up to 5 fluoro;

(j) $\mathbf{R^{24}}$ can be -OH or C_{1-6} alkoxy optionally substituted with up to 5 fluoro;

(k) $\mathbf{R^{25}}$ can be selected from the group consisting of H (hydrogen), $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -OH and C_{1-6} alkoxy optionally substituted with up to 5 fluoro;

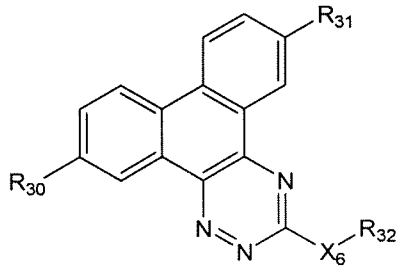
(l) $\mathbf{R^{26a}}$ and $\mathbf{R^{26b}}$ can each be separately selected from the group consisting of H (hydrogen), -OH, C_{1-6} alkyl optionally substituted with up to 5 fluoro, and C_{1-6} alkoxy optionally substituted with up to 5 fluoro; or $\mathbf{R^{26a}}$ and $\mathbf{R^{26b}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

(m) $\mathbf{R^{27a}}$ and $\mathbf{R^{27b}}$ can each be separately selected from the group consisting of H (hydrogen), -OH, C_{1-6} alkyl optionally substituted with up to 5 fluoro, and C_{1-6} alkoxy optionally substituted with up to 5 fluoro; or $\mathbf{R^{27a}}$ and $\mathbf{R^{27b}}$ can be optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

(n) $\mathbf{G_1}$ can be selected from the group consisting of CH and N (nitrogen); and

(o) $\mathbf{G_2}$ can be selected from the group consisting of CH and N (nitrogen). In some embodiments $\mathbf{R^{20}}$ can be H (hydrogen); and $\mathbf{R^{21}}$ can be H (hydrogen) or $-S(O)_2OH$. In some embodiments $\mathbf{R^{23}}$ can be H (hydrogen) or $-S(O)_2OH$; $\mathbf{R^{24}}$ can be –OH; and $\mathbf{R^{25}}$ can be H (hydrogen), or $-S(O)_2OH$. In some embodiments $\mathbf{G_1}$ can be N (nitrogen); and $\mathbf{G_2}$ can be N (nitrogen). In some embodiments $\mathbf{R^{26a}}$ and $\mathbf{R^{26b}}$ can be optionally taken together with the carbon to which they are attached to form a keto group; and $\mathbf{R^{27a}}$ and $\mathbf{R^{27b}}$ can be optionally taken together with the carbon to which they are attached to form a keto group.

[0079] Some embodiments provide a pharmaceutical composition comprising an agent and a pharmaceutically acceptable carrier, wherein the agent can be a compound having the formula (**VI**):



(**VI**)

or tautomer thereof, or their pharmaceutically acceptable salts or prodrugs, wherein:

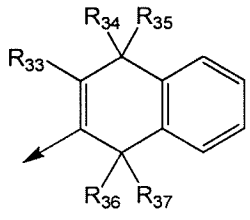
(a) $\mathbf{R^{30}}$ can be selected from the group consisting of H (hydrogen), -$\mathbf{OR^{30a}}$, -$\mathbf{SR^{30a}}$, -$\mathbf{NR^{30b}R^{30c}}$, -$S(O)_2OH$, -$S(O)_2NH_2$, -$P(O)(OH)_2$, -C(O)OH, -$CH_2C(O)OH$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(b) $\mathbf{R^{30a}}$ can be selected from the group consisting of H (hydrogen) and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) $\mathbf{R^{30b}}$ and $\mathbf{R^{30c}}$ can each be separately selected from the group consisting of H (hydrogen) and C_{1-6} alkyl, or $\mathbf{R^{30b}}$ and $\mathbf{R^{30c}}$ can be optionally are taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

(d) $\mathbf{R^{31}}$ can be selected from the group consisting of H (hydrogen), -OH, –SH, -$S(O)_2OH$, -$S(O)_2NH_2$, -$P(O)(OH)_2$, -C(O)OH, -$CH_2C(O)OH$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(e) $\mathbf{R^{32}}$ can be selected from the group consisting of -$S(O)_2OH$, -$S(O)_2NH_2$, -$P(O)(OH)_2$, -C(O)OH, and -$CH_2C(O)OH$; or $\mathbf{R^{32}}$ can be:



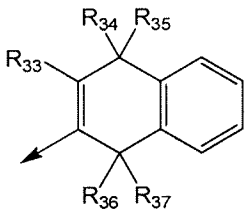
;

(f) $\mathbf{R^{33}}$ can be selected from the group consisting of H (hydrogen), -OH, halo, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(g) R^{34} and R^{35} can each be separately selected from the group consisting of H (hydrogen), -OH, halo, and C_{1-6} alkyl optionally substituted with up to 5 fluoro; or R^{34} and R^{35} can be optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

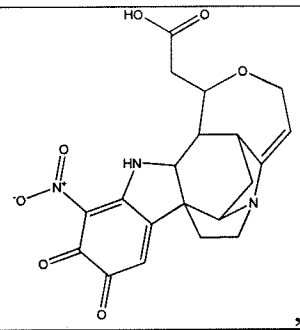
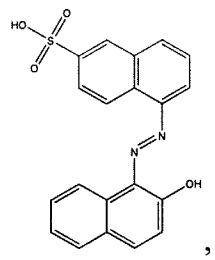
(h) R^{36} and R^{37} can each be separately selected from the group consisting of H (hydrogen), -OH, -SH, and halo; or R^{36} and R^{37} can be optionally taken together with the carbon to which they are attached to form a keto or thioketo group; and

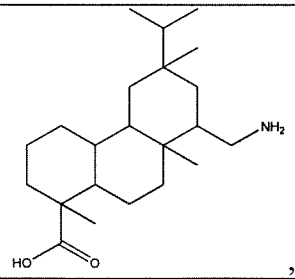
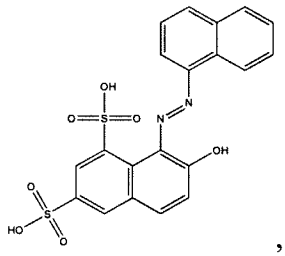
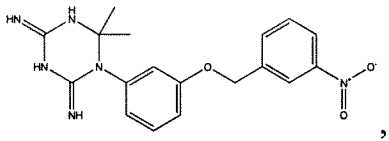
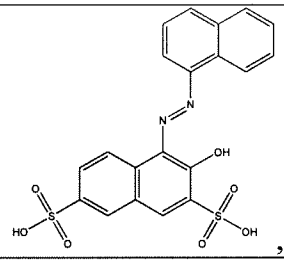
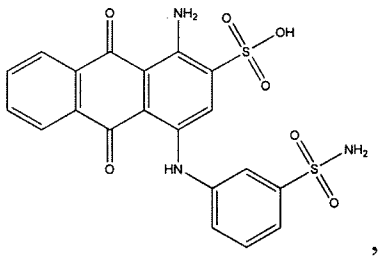
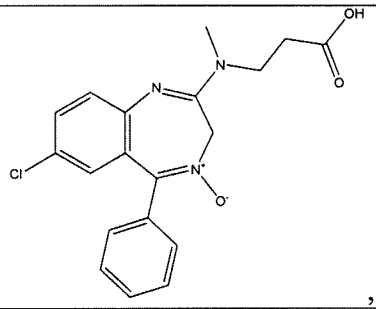
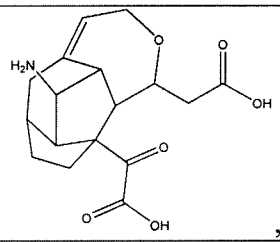
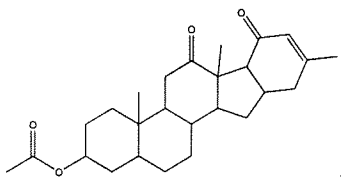
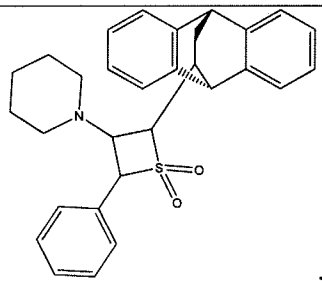
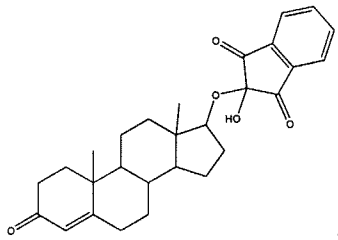
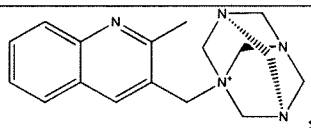
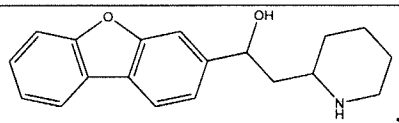
(i) X_6 can be selected from the group consisting of O (oxygen), S (sulfur) and -NH. In some embodiments R^{30} and R^{31} can be H (hydrogen); and R^{32} can be

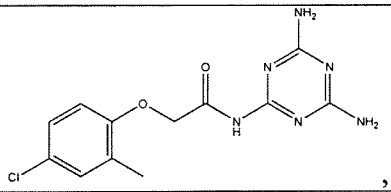
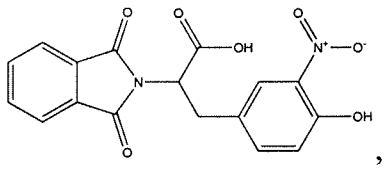
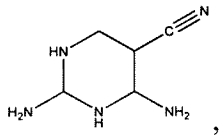
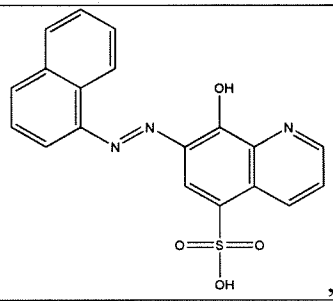
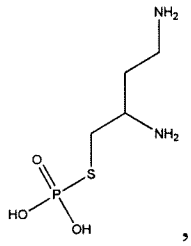
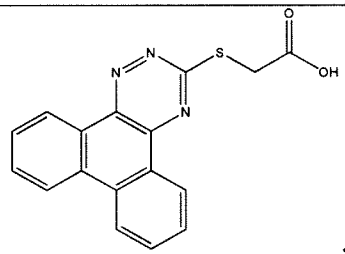
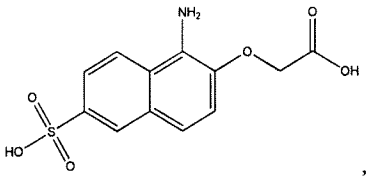
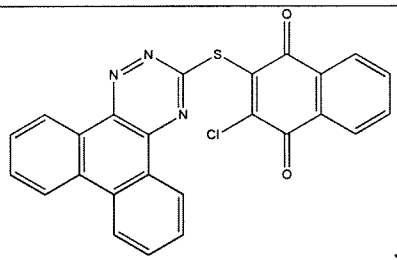
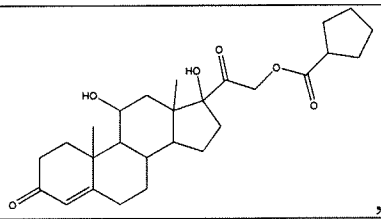
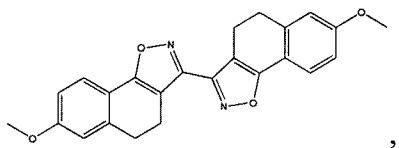
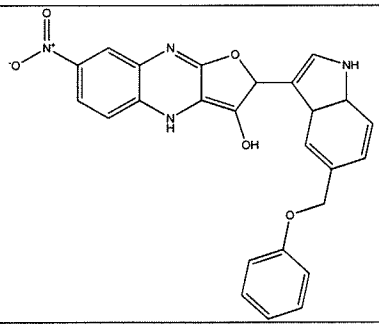


. In some embodiments X_6 can be S (sulfur). In some embodiments R^{34} and R^{35} can be optionally taken together with the carbon to which they are attached to form a keto group; and R^{36} and R^{37} can be optionally taken together with the carbon to which they are attached to form a keto or thioketo group. In some embodiments R^{33} can be halo. In some embodiments R^{30} can be H (hydrogen); and R^{32} can be selected from the group consisting of $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -C(O)OH, and $-CH_2C(O)OH$. In some embodiments R^{31} can be H (hydrogen); and R^{32} can be selected from the group consisting of $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -C(O)OH, and $-CH_2C(O)OH$.

[0080] Some embodiments provide a pharmaceutical composition comprising an agent and a pharmaceutically acceptable carrier, wherein the agent can be selected from the group consisting of:

5069	 ,		45576	 ,

70194			45582	
109836			45583	
117079			46080	
131612			59620	
135371			72254	
141562			90630	

164640	 ,	106920	 ,
211332	 ,	148354	 ,
350191	 ,	327704	 ,
16163	 ,	327705	 ,
17245	 ,	371688	 ,
	and	372294	

[0081] or a pharmaceutically acceptable salt or prodrug thereof.

[0082] The present disclosure provides a pharmaceutical composition comprising an agent and a pharmaceutically acceptable carrier, the agent can be selected from one or more of the preceding compounds.

[0083] In some embodiments, the pharmaceutical composition can comprise physiologically acceptable surface active agents, carriers, diluents, excipients, smoothing agents, suspension agents, film forming substances, and coating assistants, or a combination thereof; and a compound disclosed herein. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical art, and are described, for example, in Remington's Pharmaceutical Sciences, 18th Ed., Mack Publishing Co., Easton, PA (1990), which is incorporated herein by reference in its entirety. Preservatives, stabilizers, dyes, sweeteners, fragrances, flavoring agents, and the like may be provided in the pharmaceutical composition. For example, sodium benzoate, ascorbic acid and esters of p-hydroxybenzoic acid may be added as preservatives. In addition, antioxidants and suspending agents may be used. In various embodiments, alcohols, esters, sulfated aliphatic alcohols, and the like may be used as surface active agents; sucrose, glucose, lactose, starch, crystallized cellulose, mannitol, light anhydrous silicate, magnesium aluminate, magnesium methasilicate aluminate, synthetic aluminum silicate, calcium carbonate, sodium acid carbonate, calcium hydrogen phosphate, calcium carboxymethyl cellulose, and the like may be used as excipients; magnesium stearate, talc, hardened oil and the like may be used as smoothing agents; coconut oil, olive oil, sesame oil, peanut oil, soya may be used as suspension agents or lubricants; cellulose acetate phthalate as a derivative of a carbohydrate such as cellulose or sugar, or methylacetate-methacrylate copolymer as a derivative of polyvinyl may be used as suspension agents; and plasticizers such as ester phthalates and the like may be used as suspension agents.

[0084] The pharmaceutical compositions described herein can be administered to a human patient *per se*, or in pharmaceutical compositions where they are mixed with other active ingredients, as in combination therapy, or suitable carriers or excipient(s). Techniques for formulation and administration of the compounds of the instant application may be found in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA, 18th edition, 1990.

[0085] Suitable routes of administration may, for example, include oral, rectal, transmucosal, topical, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal,

direct intraventricular, intraperitoneal, intranasal, or intraocular injections. The compounds can also be administered in sustained or controlled release dosage forms, including depot injections, osmotic pumps, pills, transdermal (including electrotransport) patches, and the like, for prolonged and/or timed, pulsed administration at a predetermined rate.

[0086] The pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or tabletting processes.

[0087] Pharmaceutical compositions for use in accordance with the present invention thus may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art; *e.g.*, in Remington's Pharmaceutical Sciences, above.

[0088] Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Suitable excipients are, for example, water, saline, dextrose, mannitol, lactose, lecithin, albumin, sodium glutamate, cysteine hydrochloride, and the like. In addition, if desired, the injectable pharmaceutical compositions may contain minor amounts of nontoxic auxiliary substances, such as wetting agents, pH buffering agents, and the like. Physiologically compatible buffers include, but are not limited to, Hanks's solution, Ringer's solution, or physiological saline buffer. If desired, absorption enhancing preparations (for example, liposomes), may be utilized.

[0089] For transmucosal administration, penetrants appropriate to the barrier to be permeated may be used in the formulation.

[0090] Pharmaceutical formulations for parenteral administration, *e.g.*, by bolus injection or continuous infusion, include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or other organic oils such as soybean, grapefruit or almond oils, or synthetic fatty acid esters, such as ethyl oleate or

triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

[0091] For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or

pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0092] Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration.

[0093] For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

[0094] For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, *e.g.*, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[0095] Further disclosed herein are various pharmaceutical compositions well known in the pharmaceutical art for uses that include intraocular, intranasal, and intraauricular delivery. Suitable penetrants for these uses are generally known in the art. Pharmaceutical compositions for intraocular delivery include aqueous ophthalmic solutions of the active compounds in water-soluble form, such as eyedrops, or in gellan gum (Shedden et al., *Clin. Ther.*, 23(3):440-50 (2001)) or hydrogels (Mayer et al., *Ophthalmologica*, 210(2):101-3 (1996)); ophthalmic ointments; ophthalmic suspensions, such as microparticulates, drug-containing small polymeric particles that are suspended in a liquid carrier medium (Joshi, A., *J. Ocul. Pharmacol.*, 10(1):29-45 (1994)), lipid-soluble formulations (Alm et al., *Prog. Clin. Biol. Res.*, 312:447-58 (1989)), and microspheres (Mordenti, *Toxicol. Sci.*, 52(1):101-6 (1999)); and ocular inserts. All of the above-mentioned references, are incorporated herein by reference in their entireties. Such suitable pharmaceutical formulations are most often and preferably formulated to be

sterile, isotonic and buffered for stability and comfort. Pharmaceutical compositions for intranasal delviery may also include drops and sprays often prepared to simulate in many respects nasal secretions to ensure maintenance of normal ciliary action. As disclosed in Remington's Pharmaceutical Sciences, 18th Ed., Mack Publishing Co., Easton, PA (1990), which is incorporated herein by reference in its entirety, and well-known to those skilled in the art, suitable formulations are most often and preferably isotonic, slightly buffered to maintain a pH of 5.5 to 6.5, and most often and preferably include antimicrobial preservatives and appropriate drug stabilizers. Pharmaceutical formulations for intraauricular delivery include suspensions and ointments for topical application in the ear. Common solvents for such aural formulations include glycerin and water.

[0096] The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

[0097] In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

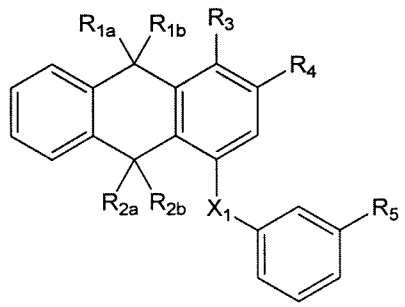
[0098] For hydrophobic compounds, a suitable pharmaceutical carrier may be a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. A common cosolvent system used is the VPD co-solvent system, which is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant Polysorbate 80™, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. Naturally, the proportions of a co-solvent system may be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of POLYSORBATE 80™; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, *e.g.*, polyvinyl pyrrolidone; and other sugars or polysaccharides may substitute for dextrose.

[0099] Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethylsulfoxide also may be employed, although usually at the cost of greater toxicity. Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

[0100] Agents intended to be administered intracellularly may be administered using techniques well known to those of ordinary skill in the art. For example, such agents may be encapsulated into liposomes. All molecules present in an aqueous solution at the time of liposome formation are incorporated into the aqueous interior. The liposomal contents are both protected from the external micro-environment and, because liposomes fuse with cell membranes, are efficiently delivered into the cell cytoplasm. The liposome may be coated with a tissue-specific antibody. The liposomes will be targeted to and taken up selectively by the desired organ. Alternatively, small hydrophobic organic molecules may be directly administered intracellularly.

[0101] Additional therapeutic or diagnostic agents may be incorporated into the pharmaceutical compositions. Alternatively or additionally, pharmaceutical compositions may be combined with other compositions that contain other therapeutic or diagnostic agents.

[0102] Some embodiments provide a compound having the formula (**I**):



(**I**)

or a pharmaceutically acceptable salt or prodrug thereof wherein:

(a) $\mathbf{R^{1a}}$ and $\mathbf{R^{1b}}$ can each be separately selected from the group consisting of H (hydrogen), -C(O)N$\mathbf{R^{1c}R^{1d}}$, –C(O)O$\mathbf{R^{1e}}$, –C(S)N$\mathbf{R^{1c}R^{1d}}$, –C(S)O$\mathbf{R^{1e}}$, –NHC(O)$\mathbf{R^{1e}}$, -NHC(O)N$\mathbf{R^{1c}R^{1d}}$, –NHC(O)O$\mathbf{R^{1e}}$, -NHC(S)N$\mathbf{R^{1c}R^{1d}}$, –NHC(S)O$\mathbf{R^{1e}}$, -OC(O)N$\mathbf{R^{1c}R^{1d}}$, -OC(O)O$\mathbf{R^{1e}}$, –OC(S)N$\mathbf{R^{1c}R^{1d}}$, -O$\mathbf{R^{1f}}$, and -N$\mathbf{R^{1c}R^{1d}}$; or $\mathbf{R^{1a}}$ and $\mathbf{R^{1b}}$ can be optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

each $\mathbf{R^{1c}}$ and $\mathbf{R^{1d}}$ can be independently selected from the group consisting of H (hydrogen), $C_{1\text{-}6}$ alkyl, heteroaryl, and aryl, or $\mathbf{R^{1c}}$ and $\mathbf{R^{1d}}$ can be optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

each $\mathbf{R^{1e}}$ can be independently selected from the group consisting of H (hydrogen), aryl, and $C_{1\text{-}6}$ alkyl optionally substituted with up to 5 fluoro;

each $\mathbf{R^{1f}}$ can be independently selected from the group consisting of H (hydrogen), aryl, and $C_{1\text{-}6}$ alkyl optionally substituted with up to 5 fluoro;

(b) $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ can each be separately selected from the group consisting of H (hydrogen), -C(O)N$\mathbf{R^{2c}R^{2d}}$, –C(O)O$\mathbf{R^{2e}}$, –C(S)N$\mathbf{R^{2c}R^{2d}}$, –C(S)O$\mathbf{R^{2e}}$, –NHC(O)$\mathbf{R^{2e}}$, -NHC(O)N$\mathbf{R^{2c}R^{2d}}$, –NHC(O)O$\mathbf{R^{2e}}$, -NHC(S)N$\mathbf{R^{2c}R^{2d}}$, –NHC(S)O$\mathbf{R^{2e}}$, -OC(O)N$\mathbf{R^{2c}R^{2d}}$, -OC(O)O$\mathbf{R^{2e}}$, –OC(S)N$\mathbf{R^{2c}R^{2d}}$, -O$\mathbf{R^{2f}}$, and -N$\mathbf{R^{1c}R^{1d}}$; or $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ can be optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

each $\mathbf{R^{2c}}$ and $\mathbf{R^{2d}}$ can be independently selected from the group consisting of H (hydrogen), $C_{1\text{-}6}$ alkyl, and aryl, or $\mathbf{R^{2c}}$ and $\mathbf{R^{2d}}$ can be optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

each $\mathbf{R^{2e}}$ can be independently selected from the group consisting of H (hydrogen), aryl, and $C_{1\text{-}6}$ alkyl optionally substituted with up to 5 fluoro;

each $\mathbf{R^{2f}}$ can be independently selected from the group consisting of H (hydrogen), aryl, and $C_{1\text{-}6}$ alkyl optionally substituted with up to 5 fluoro;

(c) $\mathbf{R^{3}}$ can be selected from the group consisting of H (hydrogen), -NHC(O)$\mathbf{R^{3a}}$, -NHC(O)N$\mathbf{R^{3b}R^{3c}}$, –NHC(O)O$\mathbf{R^{3d}}$, -NHC(S)N$\mathbf{R^{3b}R^{3c}}$, –NHC(S)O$\mathbf{R^{3d}}$, -OC(S)N$\mathbf{R^{3b}R^{3c}}$, -O$\mathbf{R^{3e}}$, -S$\mathbf{R^{3e}}$, -N$\mathbf{R^{3b}R^{3c}}$, and $C_{1\text{-}6}$ alkyl optionally substituted with up to 5 fluoro;

R^{3a} can be selected from the group consisting of aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

R^{3b} and R^{3c} can each be separately selected from the group consisting of H (hydrogen), C_{1-6} alkyl, heteroaryl, and aryl, or R^{3b} and R^{3c} can be optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

R^{3d} can be selected from the group consisting of aryl, heteroaryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

R^{3e} can be selected from the group consisting of H (hydrogen), aryl, heteroaryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(d) R^4 can be selected from the group consisting of H (hydrogen), $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, $-OP(O)(OR^{4a})_2$, $-SR^{4b}$, halo, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

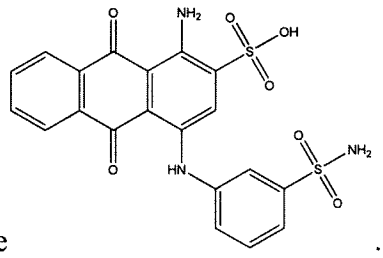
each R^{4a} can be independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

R^{4b} can be selected from the group consisting of H (hydrogen), heteroaryl, aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(e) R^5 can be selected from the group consisting of $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, $-OP(O)(OR^{5a})_2$, $-SR^{5b}$, and halo;

each R^{5a} can be independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

R^{5b} can be selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro; and

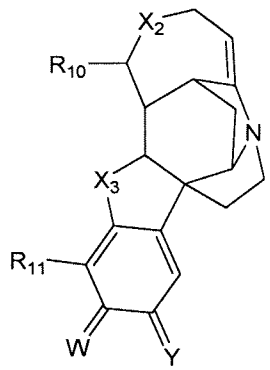
(f) X_1 can be selected from the group consisting of O (oxygen), S (sulfur) and $-NR^6$; where R^6 can be H (hydrogen) or C_{1-6} alkyl. In some embodiments the compound of formula (**I**) may not be 

. In some embodiments R^{1a} and R^{1b} can be taken together with the carbon to which they are attached to form keto; and R^{2a} and R^{2b} can be taken together with the carbon to which they are attached to form keto. In some embodiments R^3 can be $-NH_2$; and

$\mathbf{R^4}$ can be $-S(O)_2OH$. In some embodiments $\mathbf{R^5}$ can be selected from the group consisting of $-S(O)_2OH$, and $-S(O)_2NH_2$; and $\mathbf{X_1}$ can be $-N\mathbf{R^6}$; where $\mathbf{R^6}$ can be H (hydrogen) or C_{1-6} alkyl.

[0103] The compounds of formula (**I**) can be synthesized by methods known in the art. In some embodiments, the compounds of formula (**I**) can be synthesized by condensing an appropriately substituted halo-anthraquinone, such as bromamine acid (1-amino-4-bromo anthraquinone-2-sulfonic acid), and an appropriately substituted aniline using a copper catalyst. For example, certain compounds of formula (**I**) can be synthesized using an Ullmann Condensation in a manner similar to that disclosed in Tuong *et al.* "Mechanism of the Ullmann Condensation. I. Kinetic and Thermodynamic Studies," Bulletin of the Chemical Society of Japan; 43; 1970; pp. 1763-68, incorporated herein in its entirety and in a manner similar to that disclosed in Naik *et al.*, "Synthesis of [2,4-Diarylureido-6-yl-aminoceramidone]-*s*-triazine Derivatives"; J. Indian Chem. Soc.; 64; 1987; pp. 760-761, incorporated herein in its entirety. In some embodiments, the compounds of formula (**I**) can be synthesized by condensing an appropriately substituted diazoanthraquinone with an appropriately substituted aniline in a manner similar to that disclosed in Lynas-Gray et al., "The Action of Bases on 1-Diazoanthraquinone-2-sulphonate and its Derivatives," Journal of the Chemical Society; 1943; 45, incorporated herein in its entirety.

[0104] Some embodiments provide a compound having the formula (**II**):



(**II**)

or a pharmaceutically acceptable salt or prodrug thereof wherein:

(a) $\mathbf{R^{10}}$ can be selected from the group consisting of $-(CH_2)_n\mathbf{R^{10a}}$;

(b) $\mathbf{R^{10a}}$ can be selected from the group consisting of tetrazole, $-C(O)\mathbf{R^{10b}}$, and $-C(S)\mathbf{R^{10b}}$;

(c) $\mathbf{R^{10b}}$ can be selected from the group consisting of H (hydrogen), -$\mathbf{SR^{10c}}$, -$\mathbf{OR^{10c}}$, -$\mathbf{NHR^{10c}}$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(d) $\mathbf{R^{10c}}$ can be selected from the group consisting of H (hydrogen) and C_{1-6} alkyl;

(e) **n** can be 0, 1, or 2;

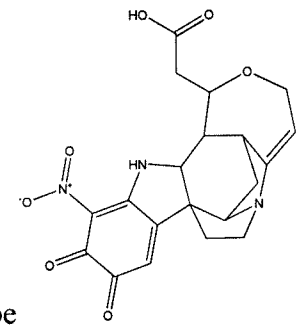
(f) $\mathbf{R^{11}}$ can be selected from the group consisting of tetrazole, -$S(O)_2OH$, -$S(O)_2NH_2$, -$P(O)(OH)_2$, nitro, -$OP(O)(OR^{11a})_2$, and -$C(O)OR^{11b}$;

$\mathbf{R^{11a}}$ can be selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

$\mathbf{R^{11b}}$ can be selected from the group consisting of H (hydrogen), and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(g) **W** is O (oxygen) or S (sulfur);

(h) **Y** can be O (oxygen) or S (sulfur); and

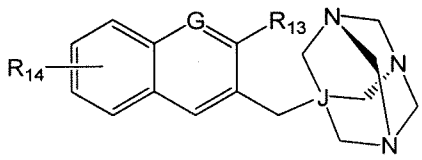
(i) $\mathbf{X_2}$ and $\mathbf{X_3}$ are each individually selected from the group consisting of O (oxygen), S (sulfur) and -NH. In some embodiments the compound of formula (**II**) may not be 

. In some embodiments $\mathbf{X_2}$ can be O (oxygen) and $\mathbf{X_3}$ can be –NH. In some embodiments $\mathbf{R^{10a}}$ can be $-CH_2C(O)\mathbf{R^{10b}}$. In some embodiments $\mathbf{R^{10a}}$ can be $-CH_2C(O)O\mathbf{R^{10c}}$; and $\mathbf{R^{11}}$ can be selected from the group consisting of -$S(O)_2NH_2$, -$P(O)(OH)_2$, nitro, -$OP(O)(OR^{11a})_2$, and -$C(O)OR^{11b}$. In some embodiments $\mathbf{R^{10c}}$ can be H (hydrogen); $\mathbf{R^{11}}$ can be selected from the group consisting of nitro, -$OP(O)(OR^{11a})_2$, and -$C(O)OR^{11b}$; $\mathbf{R^{11a}}$ can be selected from the group consisting of H (hydrogen), and C_{1-6} alkyl; $\mathbf{R^{11b}}$ can be H (hydrogen); **W** can be O (oxygen); and **Y** can be O (oxygen).

[0105] The compounds of formula (**II**) can be synthesized by methods known in the art. In some embodiments, the compounds of formula (**II**) can be synthesized derivatization of brucine. For example, certain compounds of formula (**II**) can be synthesized by nitration of brucine in a manner similar to that disclosed in Leuchs et al.,

"Über farbige isomere Säureverbindungen der Base des Kakothelins," Ber. 43, 1042 (1910), incorporated herein in its entirety.

[0106] Some embodiments provide a compound having the formula (**III**):



(**III**)

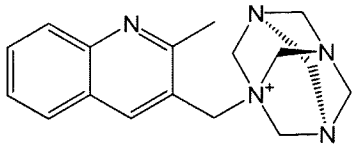
or a pharmaceutically acceptable salt or prodrug thereof wherein:

(a) $\mathbf{R^{13}}$ can be selected from the group consisting of H (hydrogen), C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(b) $\mathbf{R^{14}}$ can be one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

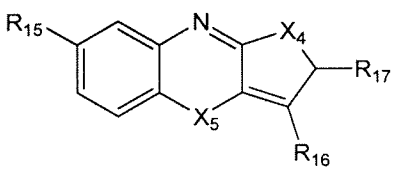
(c) G can be selected from the group consisting of CH and N (nitrogen); and

(d) J can be selected from the group consisting of N^+ (nitrogen) and P^+ (phosphorous). In some embodiments the compound of formula (**III**) may not be



. In some embodiments **G** can be N (nitrogen). In some embodiments $\mathbf{R^{13}}$ can be selected from the group consisting of H (hydrogen) and C_{1-6} alkyl optionally substituted with up to 5 fluoro; and **J** can be N^+ (nitrogen).

[0107] Some embodiments provide a compound having the formula (**IV**):



(**IV**)

or tautomer thereof, or their pharmaceutically acceptable salts or prodrugs, wherein:

(a) $\mathbf{R^{15}}$ can be selected from the group consisting of nitro, and -C(O)$\mathbf{R^{15a}}$;

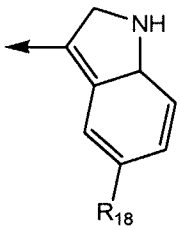
(b) $\mathbf{R^{15a}}$ can be selected from the group consisting of H (hydrogen), -S$\mathbf{R^{15b}}$, and -O$\mathbf{R^{15b}}$;

(c) $\mathbf{R^{15b}}$ can be selected from the group consisting of H (hydrogen) and C_{1-6} alkyl;

(d) $\mathbf{R^{16}}$ can be selected from the group consisting of H (hydrogen) and -O$\mathbf{R^{16a}}$;

(e) $\mathbf{R^{16a}}$ can be selected from the group consisting of H (hydrogen), and C_{1-6} alkyl;

(f) $\mathbf{R^{17}}$ can be selected from the group consisting of:



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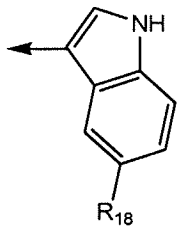

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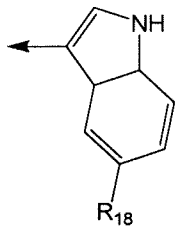
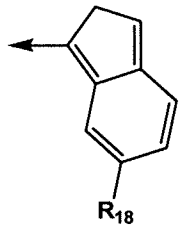


, and


;

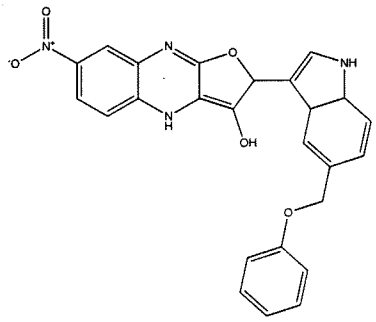
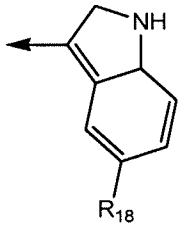
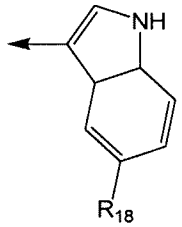
(g) $\mathbf{R^{18}}$ can be selected from the group consisting of $-(CH_2)_n\mathbf{R^{18a}}$ and -CH=CH$\mathbf{R^{18a}}$;

(h) **n** can be 0, 1, or 2;

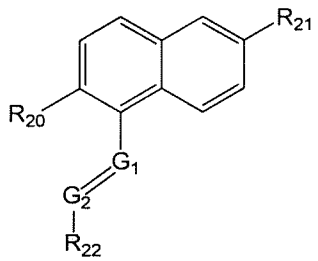
(i) $\mathbf{R^{18a}}$ can be selected from the group consisting of -S$\mathbf{R^{18b}}$, -O$\mathbf{R^{18b}}$, aryl optionally substituted with one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro, and heteroaryl optionally substituted with one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(j) $\mathbf{R^{18b}}$ can be selected from the group consisting of aryl and heteroaryl, each optionally substituted with one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro; and

(k) $\mathbf{X_4}$ and $\mathbf{X_5}$ can each be individually selected from the group consisting of O (oxygen), S (sulfur) and -NH. In some embodiments the compound of

formula (**IV**) may not be  . In some embodiments $\mathbf{R^{17}}$ can be selected from the group consisting of  , and  . In some embodiments $\mathbf{X_4}$ can be O (oxygen) and $\mathbf{X_5}$ can be –NH. In some embodiments $\mathbf{R^{18}}$ can be $-(CH_2)_n\mathbf{R^{18a}}$; **n** can be 1; and $\mathbf{R^{18a}}$ can be $-O\mathbf{R^{18b}}$. In some embodiments $\mathbf{R^{16}}$ can be $-O\mathbf{R^{16a}}$; and $\mathbf{R^{18b}}$ can be aryl optionally substituted with one or more substituents each individually selected from the group consisting of OH, halo, cyano, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro.

[0108] Some embodiments provide a compound having the formula (**V**):



(**V**)

or tautomer thereof, or their pharmaceutically acceptable salts or prodrugs, wherein:

(a) $\mathbf{R^{20}}$ can be selected from the group consisting of H (hydrogen), $-O\mathbf{R^{20a}}$, $-S\mathbf{R^{20a}}$, $-C(O)N\mathbf{R^{20c}}\mathbf{R^{20d}}$, $-NHC(O)\mathbf{R^{20e}}$;

(b) $\mathbf{R^{20a}}$ can be selected from the group consisting of H (hydrogen), and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) $\mathbf{R^{20c}}$ and $\mathbf{R^{20d}}$ can each be separately selected from the group consisting of H (hydrogen), C_{1-6} alkyl, heteroaryl, and aryl, or $\mathbf{R^{20c}}$ and $\mathbf{R^{20d}}$ can be optionally

taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

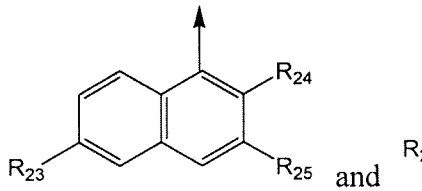
(d) $\mathbf{R^{20e}}$ can be selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

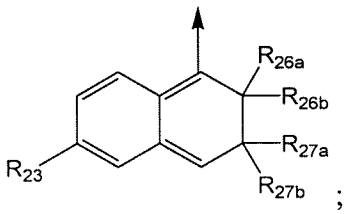
(e) $\mathbf{R^{21}}$ can be selected from the group consisting of H (hydrogen), $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, halo, $-C(O)\mathbf{R^{21a}}$, and $-C(S)\mathbf{R^{21a}}$;

(f) $\mathbf{R^{21a}}$ can be selected from the group consisting of H (hydrogen), $-S\mathbf{R^{21b}}$, $-O\mathbf{R^{21b}}$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(g) $\mathbf{R^{21b}}$ can be selected from the group consisting of H (hydrogen), and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(h) $\mathbf{R^{22}}$ can be selected from the group consisting of:



and


;

(i) $\mathbf{R^{23}}$ can be selected from the group consisting of H (hydrogen), $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -OH and C_{1-6} alkoxy optionally substituted with up to 5 fluoro;

(j) $\mathbf{R^{24}}$ can be -OH or C_{1-6} alkoxy optionally substituted with up to 5 fluoro;

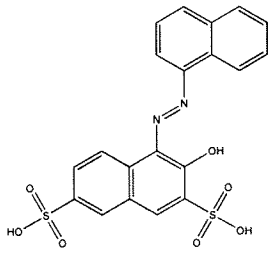
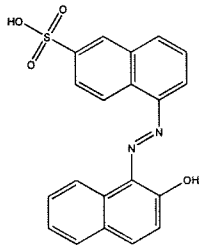
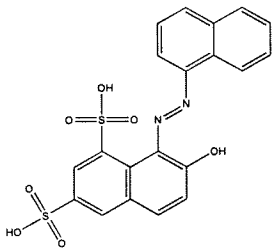
(k) $\mathbf{R^{25}}$ can be selected from the group consisting of H (hydrogen), $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -OH and C_{1-6} alkoxy optionally substituted with up to 5 fluoro;

(l) $\mathbf{R^{26a}}$ and $\mathbf{R^{26b}}$ can each be separately selected from the group consisting of H (hydrogen), -OH, C_{1-6} alkyl optionally substituted with up to 5 fluoro, and C_{1-6} alkoxy optionally substituted with up to 5 fluoro; or $\mathbf{R^{26a}}$ and $\mathbf{R^{26b}}$ can be optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

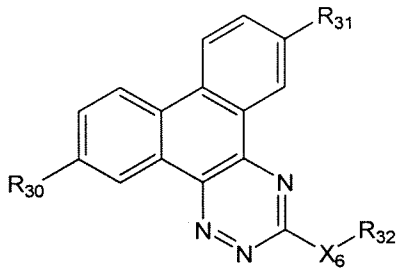
(m) $\mathbf{R^{27a}}$ and $\mathbf{R^{27b}}$ can each be separately selected from the group consisting of H (hydrogen), -OH, C_{1-6} alkyl optionally substituted with up to 5 fluoro, and C_{1-6} alkoxy optionally substituted with up to 5 fluoro; or $\mathbf{R^{27a}}$ and $\mathbf{R^{27b}}$

can be optionally taken together with the carbon to which they are attached to form a keto or thioketo group; and

(n) G_1 can be selected from the group consisting of CH and N (nitrogen); and

(o) G_2 can be selected from the group consisting of CH and N (nitrogen). In some embodiments the compound of formula (**V**) may not be selected from the group consisting of  ,  , and  . In some embodiments R^{20} can be H (hydrogen); and R^{21} can be H (hydrogen) or -$S(O)_2OH$. In some embodiments R^{23} can be H (hydrogen) or -$S(O)_2OH$; R^{24} can be –OH; and R^{25} can be H (hydrogen), or -$S(O)_2OH$. In some embodiments G_1 can be N (nitrogen); and G_2 can be N (nitrogen). In some embodiments R^{26a} and R^{26b} can be optionally taken together with the carbon to which they are attached to form a keto group; and R^{27a} and R^{27b} can be optionally taken together with the carbon to which they are attached to form a keto group.

[0109] Some embodiments provide a compound having the formula (**VI**):



(VI)

or tautomer thereof, or their pharmaceutically acceptable salts or prodrugs, wherein:

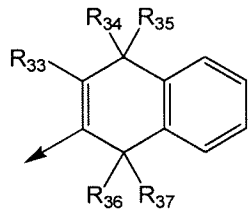
(a) $\mathbf{R^{30}}$ can be selected from the group consisting of H (hydrogen), $-O\mathbf{R^{30a}}$, $-S\mathbf{R^{30a}}$, $-N\mathbf{R^{30b}}\mathbf{R^{30c}}$, $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, $-C(O)OH$, $-CH_2C(O)OH$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(b) $\mathbf{R^{30a}}$ can be selected from the group consisting of H (hydrogen) and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) $\mathbf{R^{30b}}$ and $\mathbf{R^{30c}}$ can each be separately selected from the group consisting of H (hydrogen) and C_{1-6} alkyl, or $\mathbf{R^{30b}}$ and $\mathbf{R^{30c}}$ can be optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

(d) $\mathbf{R^{31}}$ can be selected from the group consisting of H (hydrogen), -OH, –SH, $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, $-C(O)OH$, $-CH_2C(O)OH$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(e) $\mathbf{R^{32}}$ can be selected from the group consisting of $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, $-C(O)OH$, and $-CH_2C(O)OH$; or $\mathbf{R^{32}}$ is :



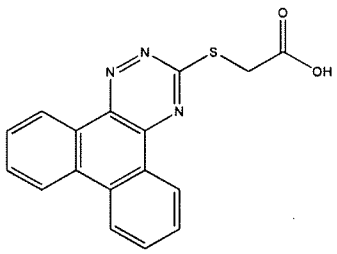
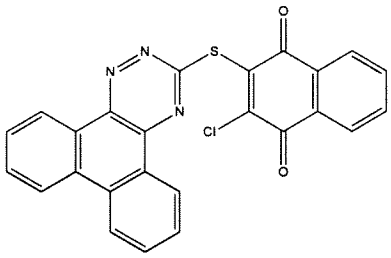
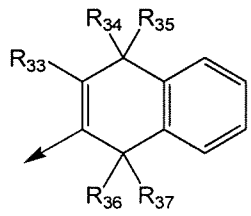
;

(f) $\mathbf{R^{33}}$ can be selected from the group consisting of H (hydrogen), -OH, halo, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(g) $\mathbf{R^{34}}$ and $\mathbf{R^{35}}$ can each be separately selected from the group consisting of H (hydrogen), -OH, halo, and C_{1-6} alkyl optionally substituted with up to 5 fluoro; or $\mathbf{R^{34}}$ and $\mathbf{R^{35}}$ can be optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

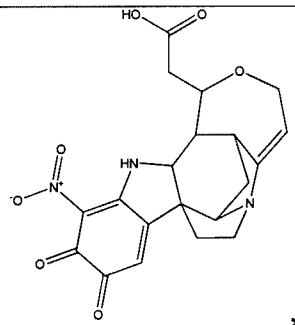
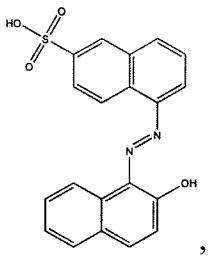
(h) $\mathbf{R^{36}}$ and $\mathbf{R^{37}}$ can each be separately selected from the group consisting of H (hydrogen), -OH, -SH, and halo; or $\mathbf{R^{36}}$ and $\mathbf{R^{37}}$ can be optionally taken together with the carbon to which they are attached to form a keto or thioketo group; and

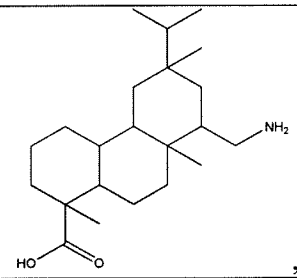
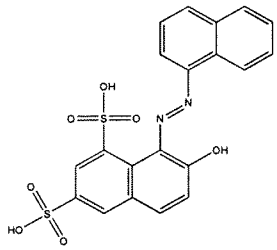
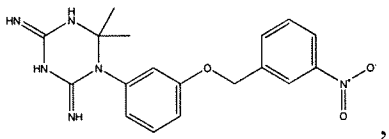
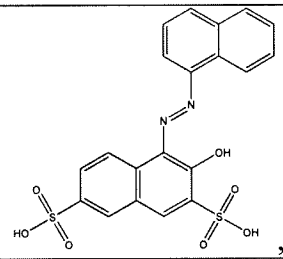
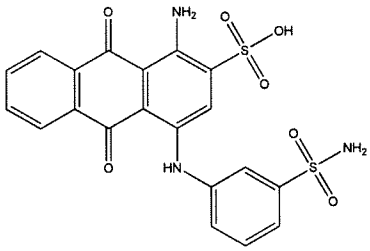
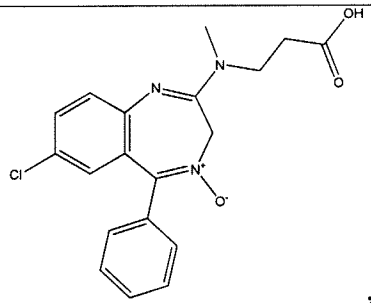
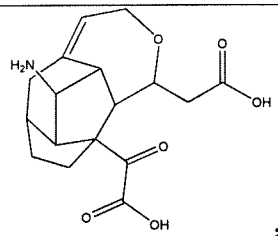
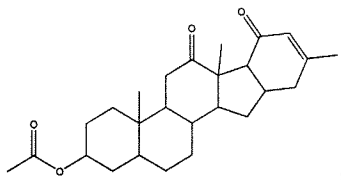
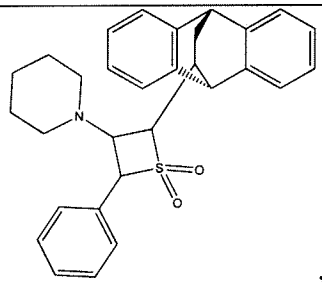
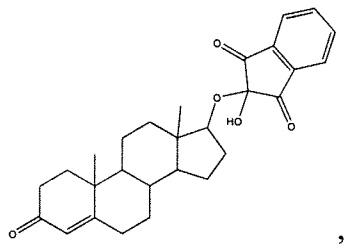
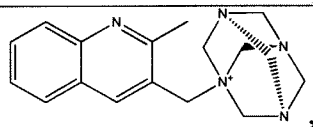
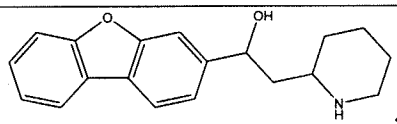
(i) $\mathbf{X_6}$ can be selected from the group consisting of O (oxygen), S (sulfur) and -NH. In some embodiments the compound of formula (**VI**) may not be selected from the

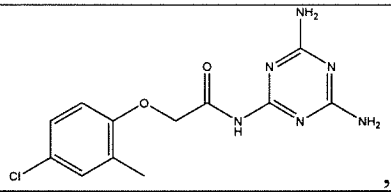
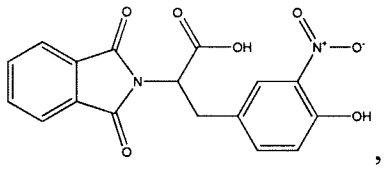
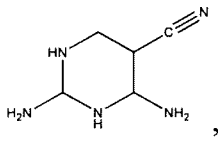
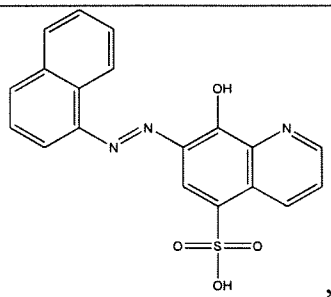
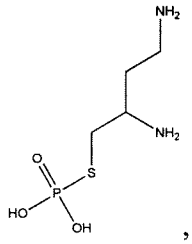
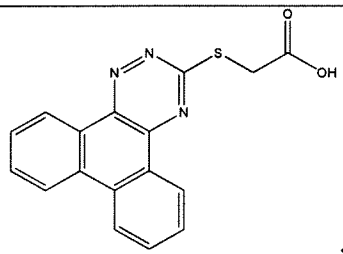
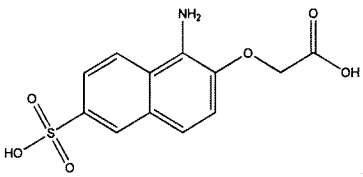
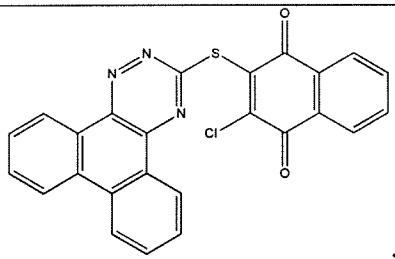
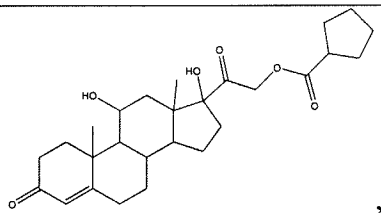
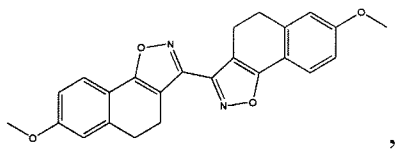
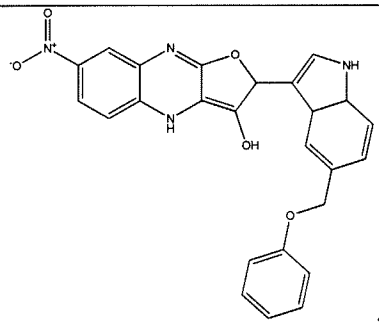
group consisting of  and  . In some embodiments $\mathbf{R^{30}}$ and $\mathbf{R^{31}}$ can be H (hydrogen); and $\mathbf{R^{32}}$ can be  . In some embodiments $\mathbf{X_6}$ can be S (sulfur). In some embodiments $\mathbf{R^{34}}$ and $\mathbf{R^{35}}$ can be optionally taken together with the carbon to which they are attached to form a keto group; and $\mathbf{R^{36}}$ and $\mathbf{R^{37}}$ can be optionally taken together with the carbon to which they are attached to form a keto or thioketo group. In some embodiments $\mathbf{R^{33}}$ can be halo. In some embodiments $\mathbf{R^{30}}$ can be H (hydrogen); and $\mathbf{R^{32}}$ can be selected from the group consisting of $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -C(O)OH, and $-CH_2C(O)OH$. In some embodiments $\mathbf{R^{31}}$ can be H (hydrogen); and $\mathbf{R^{32}}$ can be selected from the group consisting of $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -C(O)OH, and $-CH_2C(O)OH$.

[0110] In various embodiments, the compounds disclosed herein can be used alone, in combination with other compounds disclosed herein, or in combination with one or more other agents active in the therapeutic areas described herein.

[0111] Some embodiments provide a compound selected from the group consisting of:

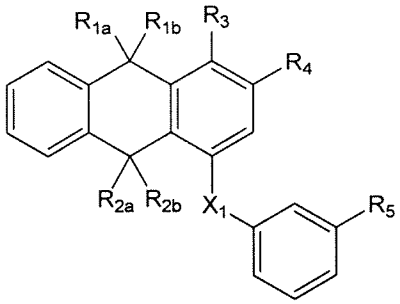
5069			45576	

70194		45582	
109836		45583	
117079		46080	
131612		59620	
135371		72254	
141562		90630	

164640		106920	
211332		148354	
350191		327704	
16163		327705	
17245		371688	
	and	372294	

or a pharmaceutically acceptable salt or prodrug thereof for use in the treatment of an avian influenza infection in an individual.

[0112] Some embodiments provide a compound having the formula (I):



(I)

or a pharmaceutically acceptable salt or prodrug thereof for use in the treatment of an avian influenza infection in an individual,

wherein:

(a) R^{1a} and R^{1b} can each be separately selected from the group consisting of H (hydrogen), -C(O)N$R^{1c}R^{1d}$, –C(O)OR^{1e}, –C(S)N$R^{1c}R^{1d}$, –C(S)OR^{1e}, –NHC(O)R^{1e}, -NHC(O)N$R^{1c}R^{1d}$, –NHC(O)OR^{1e}, -NHC(S)N$R^{1c}R^{1d}$, –NHC(S)OR^{1e}, -OC(O)N$R^{1c}R^{1d}$, -OC(O)OR^{1e}, –OC(S)N$R^{1c}R^{1d}$, -OR^{1f}, and -N$R^{1c}R^{1d}$; or R^{1a} and R^{1b} can be optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

each R^{1c} and R^{1d} can be independently selected from the group consisting of H (hydrogen), C_{1-6} alkyl, heteroaryl, and aryl, or R^{1c} and R^{1d} can be optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

each R^{1e} can be independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

each R^{1f} can be independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(b) R^{2a} and R^{2b} can each be separately selected from the group consisting of H (hydrogen), -C(O)N$R^{2c}R^{2d}$, –C(O)OR^{2e}, –C(S)N$R^{2c}R^{2d}$, –C(S)OR^{2e}, –NHC(O)R^{2e}, -NHC(O)N$R^{2c}R^{2d}$, –NHC(O)OR^{2e}, -NHC(S)N$R^{2c}R^{2d}$, –NHC(S)OR^{2e}, -OC(O)N$R^{2c}R^{2d}$, -OC(O)OR^{2e}, –OC(S)N$R^{2c}R^{2d}$, -OR^{2f}, and -N$R^{1c}R^{1d}$; or R^{2a} and R^{2b} can be optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

each R^{2c} and R^{2d} can be independently selected from the group consisting of H (hydrogen), C_{1-6} alkyl, and aryl, or R^{2c} and R^{2d} can be optionally taken

together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

each $\mathbf{R^{2e}}$ can be independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

each $\mathbf{R^{2f}}$ can be independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) $\mathbf{R^3}$ can be selected from the group consisting of H (hydrogen), -NHC(O)$\mathbf{R^{3a}}$, -NHC(O)N$\mathbf{R^{3b}R^{3c}}$, –NHC(O)O$\mathbf{R^{3d}}$, -NHC(S)N$\mathbf{R^{3b}R^{3c}}$, –NHC(S)O$\mathbf{R^{3d}}$, -OC(S)N$\mathbf{R^{3b}R^{3c}}$, -O$\mathbf{R^{3e}}$, -S$\mathbf{R^{3e}}$, -N$\mathbf{R^{3b}R^{3c}}$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

$\mathbf{R^{3a}}$ can be selected from the group consisting of aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

$\mathbf{R^{3b}}$ and $\mathbf{R^{3c}}$ can each be separately selected from the group consisting of H (hydrogen), C_{1-6} alkyl, heteroaryl, and aryl, or $\mathbf{R^{3b}}$ and $\mathbf{R^{3c}}$ can be optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

$\mathbf{R^{3d}}$ can be selected from the group consisting of aryl, heteroaryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

$\mathbf{R^{3e}}$ can be selected from the group consisting of H (hydrogen), aryl, heteroaryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(d) $\mathbf{R^4}$ can be selected from the group consisting of H (hydrogen), -S(O)$_2$OH, -S(O)$_2$NH$_2$, -P(O)(OH)$_2$, -OP(O)(O$\mathbf{R^{4a}}$)$_2$, -S$\mathbf{R^{4b}}$, halo, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

each $\mathbf{R^{4a}}$ can be independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

$\mathbf{R^{4b}}$ can be selected from the group consisting of H (hydrogen), heteroaryl, aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

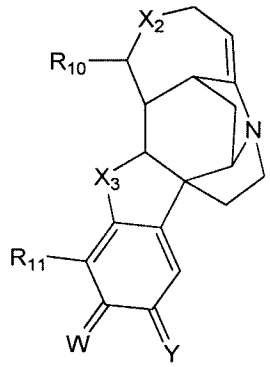
(e) $\mathbf{R^5}$ can be selected from the group consisting of -S(O)$_2$OH, -S(O)$_2$NH$_2$, -P(O)(OH)$_2$, -OP(O)(O$\mathbf{R^{5a}}$)$_2$, -S$\mathbf{R^{5b}}$, and halo;

each $\mathbf{R^{5a}}$ can be independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

R^{5b} can be selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro; and

(f) X_1 can be selected from the group consisting of O (oxygen), S (sulfur) and -NR^6; where R^6 is H (hydrogen) or C_{1-6} alkyl.

[0113] Some embodiments provide a compound having the formula (**II**):



(**II**)

or a pharmaceutically acceptable salt or prodrug thereof for use in the treatment of an avian influenza infection in an individual,

wherein:

(a) R^{10} can be selected from the group consisting of $-(CH_2)_nR^{10a}$;

(b) R^{10a} can be selected from the group consisting of tetrazole, -$C(O)R^{10b}$, and -$C(S)R^{10b}$;

(c) R^{10b} can be selected from the group consisting of H (hydrogen), -SR^{10c}, -OR^{10c}, -NHR^{10c}, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(d) R^{10c} can be selected from the group consisting of H (hydrogen) and C_{1-6} alkyl;

(e) **n** can be 0, 1, or 2;

(f) R^{11} can be selected from the group consisting of tetrazole, -$S(O)_2OH$, -$S(O)_2NH_2$, -$P(O)(OH)_2$, nitro, -$OP(O)(OR^{11a})_2$, and -$C(O)OR^{11b}$;

R^{11a} can be selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

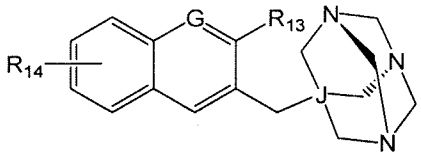
R^{11b} can be selected from the group consisting of H (hydrogen), and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(g) **W** can be O (oxygen) or S (sulfur);

(h) **Y** can be O (oxygen) or S (sulfur); and

(i) X_2 and X_3 are each individually selected from the group consisting of O (oxygen), S (sulfur) and -NH.

[0114] Some embodiments provide a compound having the formula (**III**):



(**III**)

or a pharmaceutically acceptable salt or prodrug thereof for use in the treatment of an avian influenza infection in an individual,

wherein:

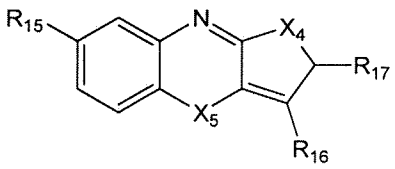
(a) R^{13} can be selected from the group consisting of H (hydrogen), C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(b) R^{14} can be one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) **G** can be selected from the group consisting of CH and N (nitrogen); and

(d) **J** can be selected from the group consisting of N^+ (nitrogen) and P^+ (phosphorous).

[0115] Some embodiments provide a compound having the formula (**IV**):



(**IV**)

or tautomer thereof, or their pharmaceutically acceptable salts or prodrugs, for use in the treatment of an avian influenza infection in an individual,

wherein:

(a) R^{15} can be selected from the group consisting of nitro, and -C(O)R^{15a};

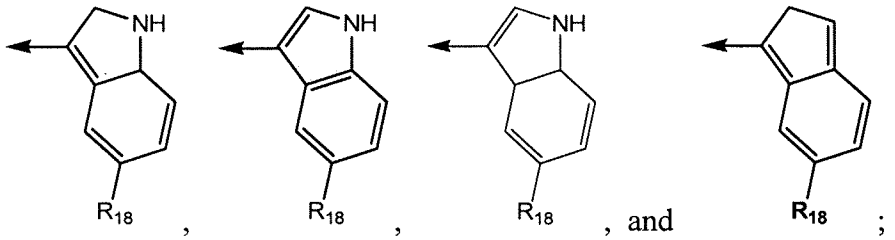
(b) R^{15a} can be selected from the group consisting of H (hydrogen), -SR^{15b}, and -OR^{15b};

(c) $\mathbf{R^{15b}}$ can be selected from the group consisting of H (hydrogen) and C_{1-6} alkyl;

(d) $\mathbf{R^{16}}$ can be selected from the group consisting of H (hydrogen) and $-OR^{16a}$;

(e) $\mathbf{R^{16a}}$ can be selected from the group consisting of H (hydrogen), and C_{1-6} alkyl;

(f) $\mathbf{R^{17}}$ can be selected from the group consisting of:



, , , and ;

(g) $\mathbf{R^{18}}$ can be selected from the group consisting of $-(CH_2)_nR^{18a}$ and $-CH=CHR^{18a}$;

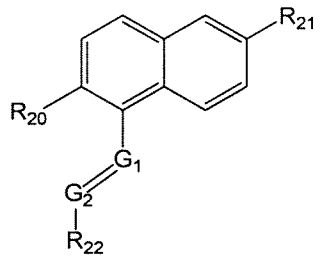
(h) **n** can be 0, 1, or 2;

(i) $\mathbf{R^{18a}}$ can be selected from the group consisting of $-SR^{18b}$, $-OR^{18b}$, aryl optionally substituted with one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro, and heteroaryl optionally substituted with one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(j) $\mathbf{R^{18b}}$ can be selected from the group consisting of aryl and heteroaryl, each optionally substituted with one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro; and

(k) $\mathbf{X_4}$ and $\mathbf{X_5}$ can each be individually selected from the group consisting of O (oxygen), S (sulfur) and -NH.

[0116] Some embodiments provide a compound having the formula (**V**):



(V)

or tautomer thereof, or their pharmaceutically acceptable salts or prodrugs, for use in the treatment of an avian influenza infection in an individual,

wherein:

(a) $\mathbf{R^{20}}$ can be selected from the group consisting of H (hydrogen), -O$\mathbf{R^{20a}}$, -S$\mathbf{R^{20a}}$, -C(O)N$\mathbf{R^{20c}R^{20d}}$, –NHC(O)$\mathbf{R^{20e}}$;

(b) $\mathbf{R^{20a}}$ can be selected from the group consisting of H (hydrogen), and $C_{1\text{-}6}$ alkyl optionally substituted with up to 5 fluoro;

(c) $\mathbf{R^{20c}}$ and $\mathbf{R^{20d}}$ can each be separately selected from the group consisting of H (hydrogen), $C_{1\text{-}6}$ alkyl, heteroaryl, and aryl, or $\mathbf{R^{20c}}$ and $\mathbf{R^{20d}}$ can be optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

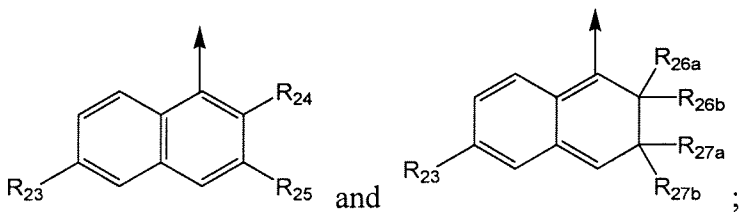
(d) $\mathbf{R^{20e}}$ can be selected from the group consisting of H (hydrogen), aryl, and $C_{1\text{-}6}$ alkyl optionally substituted with up to 5 fluoro;

(e) $\mathbf{R^{21}}$ can be selected from the group consisting of H (hydrogen), -$S(O)_2OH$, -$S(O)_2NH_2$, -$P(O)(OH)_2$, halo, -C(O)$\mathbf{R^{21a}}$, and -C(S)$\mathbf{R^{21a}}$;

(f) $\mathbf{R^{21a}}$ can be selected from the group consisting of H (hydrogen), -S$\mathbf{R^{21b}}$, -O$\mathbf{R^{21b}}$, and $C_{1\text{-}6}$ alkyl optionally substituted with up to 5 fluoro;

(g) $\mathbf{R^{21b}}$ can be selected from the group consisting of H (hydrogen), and $C_{1\text{-}6}$ alkyl optionally substituted with up to 5 fluoro;

(h) $\mathbf{R^{22}}$ can be selected from the group consisting of:



and

;

(i) $\mathbf{R^{23}}$ can be selected from the group consisting of H (hydrogen), -$S(O)_2OH$, -$S(O)_2NH_2$, -$P(O)(OH)_2$, -OH and $C_{1\text{-}6}$ alkoxy optionally substituted with up to 5 fluoro;

(j) $\mathbf{R^{24}}$ canbe -OH or C_{1-6} alkoxy optionally substituted with up to 5 fluoro;

(k) $\mathbf{R^{25}}$ can be selected from the group consisting of H (hydrogen), $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -OH and C_{1-6} alkoxy optionally substituted with up to 5 fluoro;

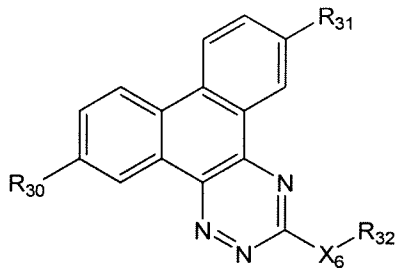
(l) $\mathbf{R^{26a}}$ and $\mathbf{R^{26b}}$ can each be separately selected from the group consisting of H (hydrogen), -OH, C_{1-6} alkyl optionally substituted with up to 5 fluoro, and C_{1-6} alkoxy optionally substituted with up to 5 fluoro; or $\mathbf{R^{26a}}$ and $\mathbf{R^{26b}}$ can be optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

(m) $\mathbf{R^{27a}}$ and $\mathbf{R^{27b}}$ can each be separately selected from the group consisting of H (hydrogen), -OH, C_{1-6} alkyl optionally substituted with up to 5 fluoro, and C_{1-6} alkoxy optionally substituted with up to 5 fluoro; or $\mathbf{R^{27a}}$ and $\mathbf{R^{27b}}$ can be optionally taken together with the carbon to which they are attached to form a keto or thioketo group; and

(n) $\mathbf{G_1}$ can be selected from the group consisting of CH and N (nitrogen); and

(o) $\mathbf{G_2}$ can be selected from the group consisting of CH and N (nitrogen).

[0117] Some embodiments provide a compound having the formula (**VI**):



(**VI**)

or tautomer thereof, or their pharmaceutically acceptable salts or prodrugs, for use in the treatment of an avian influenza infection in an individual,

wherein:

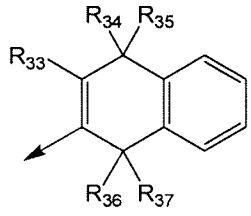
(a) $\mathbf{R^{30}}$ can be selected from the group consisting of H (hydrogen), $-OR^{30a}$, $-SR^{30a}$, $-NR^{30b}R^{30c}$, $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -C(O)OH, $-CH_2C(O)OH$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(b) $\mathbf{R^{30a}}$ can be selected from the group consisting of H (hydrogen) and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) $\mathbf{R^{30b}}$ and $\mathbf{R^{30c}}$ can each be separately selected from the group consisting of H (hydrogen) and C_{1-6} alkyl, or $\mathbf{R^{30b}}$ and $\mathbf{R^{30c}}$ can be optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

(d) $\mathbf{R^{31}}$ can be selected from the group consisting of H (hydrogen), -OH, –SH, $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -C(O)OH, $-CH_2C(O)OH$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(e) $\mathbf{R^{32}}$ can be selected from the group consisting of $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -C(O)OH, and $-CH_2C(O)OH$; or $\mathbf{R^{32}}$ can be :



;

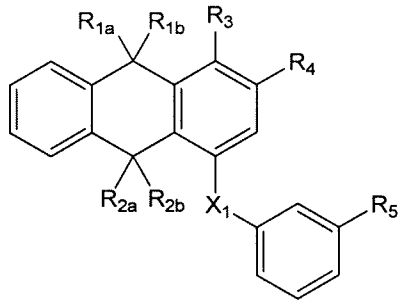
(f) $\mathbf{R^{33}}$ can be selected from the group consisting of H (hydrogen), -OH, halo, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(g) $\mathbf{R^{34}}$ and $\mathbf{R^{35}}$ can each be separately selected from the group consisting of H (hydrogen), -OH, halo, and C_{1-6} alkyl optionally substituted with up to 5 fluoro; or $\mathbf{R^{34}}$ and $\mathbf{R^{35}}$ can be optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

(h) $\mathbf{R^{36}}$ and $\mathbf{R^{37}}$ can each be separately selected from the group consisting of H (hydrogen), -OH, -SH, and halo; or $\mathbf{R^{36}}$ and $\mathbf{R^{37}}$ can be optionally taken together with the carbon to which they are attached to form a keto or thioketo group; and

(i) $\mathbf{X_6}$ can be selected from the group consisting of O (oxygen), S (sulfur) and -NH.

[0118] Some embodiments provide a method of ameliorating an avian influenza infection in an individual, the method comprising administering to the individual an effective amount of a compound having the formula (**I**):



(I)

or a pharmaceutically acceptable salt or prodrug thereof,

wherein:

(a) $\mathbf{R^{1a}}$ and $\mathbf{R^{1b}}$ can each be separately selected from the group consisting of H (hydrogen), -C(O)N$\mathbf{R^{1c}R^{1d}}$, –C(O)O$\mathbf{R^{1e}}$, –C(S)N$\mathbf{R^{1c}R^{1d}}$, –C(S)O$\mathbf{R^{1e}}$, –NHC(O)$\mathbf{R^{1e}}$, -NHC(O)N$\mathbf{R^{1c}R^{1d}}$, –NHC(O)O$\mathbf{R^{1e}}$, -NHC(S)N$\mathbf{R^{1c}R^{1d}}$, –NHC(S)O$\mathbf{R^{1e}}$, -OC(O)N$\mathbf{R^{1c}R^{1d}}$, -OC(O)O$\mathbf{R^{1e}}$, –OC(S)N$\mathbf{R^{1c}R^{1d}}$, -O$\mathbf{R^{1f}}$, and -N$\mathbf{R^{1c}R^{1d}}$; or $\mathbf{R^{1a}}$ and $\mathbf{R^{1b}}$ can be optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

each $\mathbf{R^{1c}}$ and $\mathbf{R^{1d}}$ can be independently selected from the group consisting of H (hydrogen), $C_{1\text{-}6}$ alkyl, heteroaryl, and aryl, or $\mathbf{R^{1c}}$ and $\mathbf{R^{1d}}$ can be optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

each $\mathbf{R^{1e}}$ can be independently selected from the group consisting of H (hydrogen), aryl, and $C_{1\text{-}6}$ alkyl optionally substituted with up to 5 fluoro;

each $\mathbf{R^{1f}}$ can be independently selected from the group consisting of H (hydrogen), aryl, and $C_{1\text{-}6}$ alkyl optionally substituted with up to 5 fluoro;

(b) $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ can each be separately selected from the group consisting of H (hydrogen), -C(O)N$\mathbf{R^{2c}R^{2d}}$, –C(O)O$\mathbf{R^{2e}}$, –C(S)N$\mathbf{R^{2c}R^{2d}}$, –C(S)O$\mathbf{R^{2e}}$, –NHC(O)$\mathbf{R^{2e}}$, -NHC(O)N$\mathbf{R^{2c}R^{2d}}$, –NHC(O)O$\mathbf{R^{2e}}$, -NHC(S)N$\mathbf{R^{2c}R^{2d}}$, –NHC(S)O$\mathbf{R^{2e}}$, -OC(O)N$\mathbf{R^{2c}R^{2d}}$, -OC(O)O$\mathbf{R^{2e}}$, –OC(S)N$\mathbf{R^{2c}R^{2d}}$, -O$\mathbf{R^{2f}}$, and -N$\mathbf{R^{1c}R^{1d}}$; or $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ can be optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

each $\mathbf{R^{2c}}$ and $\mathbf{R^{2d}}$ can be independently selected from the group consisting of H (hydrogen), $C_{1\text{-}6}$ alkyl, and aryl, or $\mathbf{R^{2c}}$ and $\mathbf{R^{2d}}$ can be optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

each $\mathbf{R^{2e}}$ can be independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

each $\mathbf{R^{2f}}$ can be independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) $\mathbf{R^3}$ can be selected from the group consisting of H (hydrogen), –NHC(O)$\mathbf{R^{3a}}$, -NHC(O)N$\mathbf{R^{3b}R^{3c}}$, –NHC(O)O$\mathbf{R^{3d}}$, -NHC(S)N$\mathbf{R^{3b}R^{3c}}$, –NHC(S)O$\mathbf{R^{3d}}$, -OC(S)N$\mathbf{R^{3b}R^{3c}}$, -O$\mathbf{R^{3e}}$, -S$\mathbf{R^{3e}}$, -N$\mathbf{R^{3b}R^{3c}}$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

$\mathbf{R^{3a}}$ can be selected from the group consisting of aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

$\mathbf{R^{3b}}$ and $\mathbf{R^{3c}}$ can each be separately selected from the group consisting of H (hydrogen), C_{1-6} alkyl, heteroaryl, and aryl, or $\mathbf{R^{3b}}$ and $\mathbf{R^{3c}}$ can be optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

$\mathbf{R^{3d}}$ can be selected from the group consisting of aryl, heteroaryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

$\mathbf{R^{3e}}$ can be selected from the group consisting of H (hydrogen), aryl, heteroaryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(d) $\mathbf{R^4}$ can be selected from the group consisting of H (hydrogen), -S(O)$_2$OH, -S(O)$_2$NH$_2$, -P(O)(OH)$_2$, -OP(O)(O$\mathbf{R^{4a}}$)$_2$, -S$\mathbf{R^{4b}}$, halo, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

each $\mathbf{R^{4a}}$ can be independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

$\mathbf{R^{4b}}$ can be selected from the group consisting of H (hydrogen), heteroaryl, aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

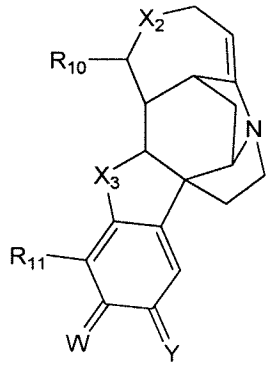
(e) $\mathbf{R^5}$ can be selected from the group consisting of -S(O)$_2$OH, -S(O)$_2$NH$_2$, -P(O)(OH)$_2$, -OP(O)(O$\mathbf{R^{5a}}$)$_2$, -S$\mathbf{R^{5b}}$, and halo;

each $\mathbf{R^{5a}}$ can be independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

$\mathbf{R^{5b}}$ can be selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro; and

(f) $\mathbf{X_1}$ can be selected from the group consisting of O (oxygen), S (sulfur) and -N$\mathbf{R^6}$; where $\mathbf{R^6}$ is H (hydrogen) or C_{1-6} alkyl.

[0119] Some embodiments provide a method of ameliorating an avian influenza infection in an individual, the method comprising administering to the individual an effective amount of a compound having the formula (**II**):



(**II**)

or a pharmaceutically acceptable salt or prodrug thereof,

wherein:

(a) $\mathbf{R^{10}}$ can be selected from the group consisting of $-(CH_2)_n\mathbf{R^{10a}}$;

(b) $\mathbf{R^{10a}}$ can be selected from the group consisting of tetrazole, -C(O)$\mathbf{R^{10b}}$, and -C(S)$\mathbf{R^{10b}}$;

(c) $\mathbf{R^{10b}}$ can be selected from the group consisting of H (hydrogen), -S$\mathbf{R^{10c}}$, -O$\mathbf{R^{10c}}$, -NH$\mathbf{R^{10c}}$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(d) $\mathbf{R^{10c}}$ can be selected from the group consisting of H (hydrogen) and C_{1-6} alkyl;

(e) n can be 0, 1, or 2;

(f) $\mathbf{R^{11}}$ can be selected from the group consisting of tetrazole, $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, nitro, $-OP(O)(O\mathbf{R^{11a}})_2$, and -C(O)O$\mathbf{R^{11b}}$;

$\mathbf{R^{11a}}$ can be selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

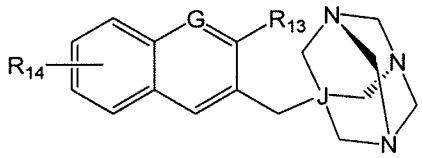
$\mathbf{R^{11b}}$ can be selected from the group consisting of H (hydrogen), and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(g) W can be O (oxygen) or S (sulfur);

(h) Y can be O (oxygen) or S (sulfur); and

(i) $\mathbf{X_2}$ and $\mathbf{X_3}$ are each individually selected from the group consisting of O (oxygen), S (sulfur) and -NH.

[0120] Some embodiments provide a method of ameliorating an avian influenza infection in an individual, the method comprising administering to the individual an effective amount of a compound having the formula (**III**):



(**III**)

or a pharmaceutically acceptable salt or prodrug thereof,

wherein:

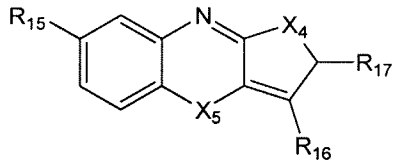
(a) $\mathbf{R^{13}}$ can be selected from the group consisting of H (hydrogen), C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(b) $\mathbf{R^{14}}$ can be one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) G can be selected from the group consisting of CH and N (nitrogen); and

(d) J can be selected from the group consisting of N^+ (nitrogen) and P^+ (phosphorous).

[0121] Some embodiments provide a method of ameliorating an avian influenza infection in an individual, the method comprising administering to the individual an effective amount of a compound having the formula (**IV**):



(**IV**)

or tautomer thereof, or their pharmaceutically acceptable salts or prodrugs, wherein:

(a) $\mathbf{R^{15}}$ can be selected from the group consisting of nitro, and $-C(O)\mathbf{R^{15a}}$;

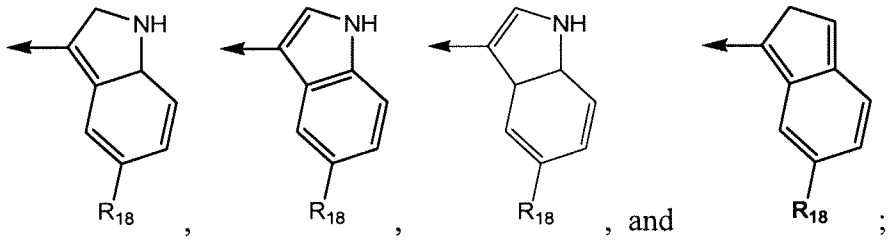
(b) $\mathbf{R^{15a}}$ can be selected from the group consisting of H (hydrogen), $-S\mathbf{R^{15b}}$, and $-O\mathbf{R^{15b}}$;

(c) $\mathbf{R^{15b}}$ can be selected from the group consisting of H (hydrogen) and C_{1-6} alkyl;

(d) $\mathbf{R^{16}}$ can be selected from the group consisting of H (hydrogen) and $-OR^{16a}$;

(e) $\mathbf{R^{16a}}$ can be selected from the group consisting of H (hydrogen), and C_{1-6} alkyl;

(f) $\mathbf{R^{17}}$ can be selected from the group consisting of:



, , , and ;

(g) $\mathbf{R^{18}}$ can be selected from the group consisting of $-(CH_2)_nR^{18a}$ and $-CH=CHR^{18a}$;

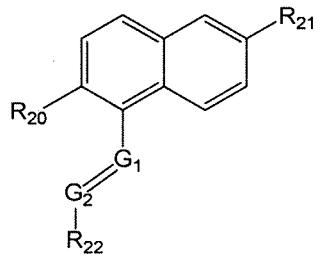
(h) **n** can be 0, 1, or 2;

(i) $\mathbf{R^{18a}}$ can be selected from the group consisting of $-SR^{18b}$, $-OR^{18b}$, aryl optionally substituted with one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro, and heteroaryl optionally substituted with one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(j) $\mathbf{R^{18b}}$ can be selected from the group consisting of aryl and heteroaryl, each optionally substituted with one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro; and

(k) $\mathbf{X_4}$ and $\mathbf{X_5}$ can each be individually selected from the group consisting of O (oxygen), S (sulfur) and -NH.

[0122] Some embodiments provide a method of ameliorating an avian influenza infection in an individual, the method comprising administering to the individual an effective amount of a compound having the formula (**V**):



(V)

or tautomer thereof, or their pharmaceutically acceptable salts or prodrugs, wherein:

(a) $\mathbf{R^{20}}$ can be selected from the group consisting of H (hydrogen), -$\mathbf{OR^{20a}}$, -$\mathbf{SR^{20a}}$, -C(O)N$\mathbf{R^{20c}R^{20d}}$, –NHC(O)$\mathbf{R^{20e}}$;

(b) $\mathbf{R^{20a}}$ can be selected from the group consisting of H (hydrogen), and $C_{1\text{-}6}$ alkyl optionally substituted with up to 5 fluoro;

(c) $\mathbf{R^{20c}}$ and $\mathbf{R^{20d}}$ can each be separately selected from the group consisting of H (hydrogen), $C_{1\text{-}6}$ alkyl, heteroaryl, and aryl, or $\mathbf{R^{20c}}$ and $\mathbf{R^{20d}}$ can be optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

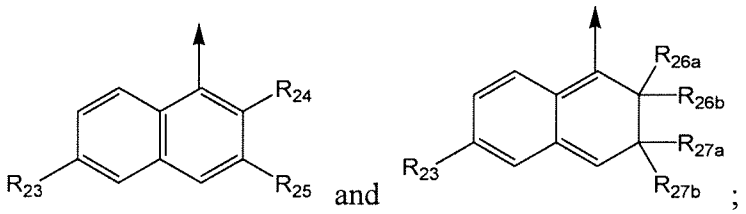
(d) $\mathbf{R^{20e}}$ can be selected from the group consisting of H (hydrogen), aryl, and $C_{1\text{-}6}$ alkyl optionally substituted with up to 5 fluoro;

(e) $\mathbf{R^{21}}$ can be selected from the group consisting of H (hydrogen), -$S(O)_2OH$, -$S(O)_2NH_2$, -$P(O)(OH)_2$, halo, -C(O)$\mathbf{R^{21a}}$, and -C(S)$\mathbf{R^{21a}}$;

(f) $\mathbf{R^{21a}}$ can be selected from the group consisting of H (hydrogen), -$\mathbf{SR^{21b}}$, -$\mathbf{OR^{21b}}$, and $C_{1\text{-}6}$ alkyl optionally substituted with up to 5 fluoro;

(g) $\mathbf{R^{21b}}$ can be selected from the group consisting of H (hydrogen), and $C_{1\text{-}6}$ alkyl optionally substituted with up to 5 fluoro;

(h) $\mathbf{R^{22}}$ can be selected from the group consisting of:



and ;

(i) $\mathbf{R^{23}}$ can be selected from the group consisting of H (hydrogen), -$S(O)_2OH$, -$S(O)_2NH_2$, -$P(O)(OH)_2$, -OH and $C_{1\text{-}6}$ alkoxy optionally substituted with up to 5 fluoro;

(j) $\mathbf{R^{24}}$ can be -OH or C_{1-6} alkoxy optionally substituted with up to 5 fluoro;

(k) $\mathbf{R^{25}}$ can be selected from the group consisting of H (hydrogen), $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -OH and C_{1-6} alkoxy optionally substituted with up to 5 fluoro;

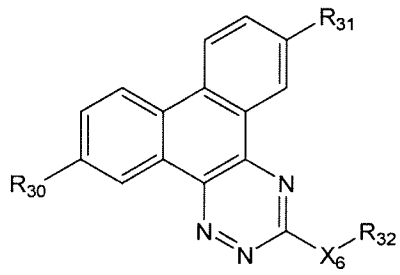
(l) $\mathbf{R^{26a}}$ and $\mathbf{R^{26b}}$ can each be separately selected from the group consisting of H (hydrogen), -OH, C_{1-6} alkyl optionally substituted with up to 5 fluoro, and C_{1-6} alkoxy optionally substituted with up to 5 fluoro; or $\mathbf{R^{26a}}$ and $\mathbf{R^{26b}}$ can be optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

(m) $\mathbf{R^{27a}}$ and $\mathbf{R^{27b}}$ can each be separately selected from the group consisting of H (hydrogen), -OH, C_{1-6} alkyl optionally substituted with up to 5 fluoro, and C_{1-6} alkoxy optionally substituted with up to 5 fluoro; or $\mathbf{R^{27a}}$ and $\mathbf{R^{27b}}$ can be optionally taken together with the carbon to which they are attached to form a keto or thioketo group; and

(n) $\mathbf{G_1}$ can be selected from the group consisting of CH and N (nitrogen); and

(o) $\mathbf{G_2}$ can be selected from the group consisting of CH and N (nitrogen).

[0123] Some embodiments provide a method of ameliorating an avian influenza infection in an individual, the method comprising administering to the individual an effective amount of a compound having the formula (**VI**):



(**VI**)

or tautomer thereof, or their pharmaceutically acceptable salts or prodrugs, wherein:

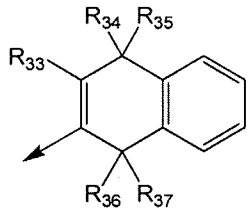
(a) $\mathbf{R^{30}}$ can be selected from the group consisting of H (hydrogen), $-O\mathbf{R^{30a}}$, $-S\mathbf{R^{30a}}$, $-N\mathbf{R^{30b}R^{30c}}$, $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -C(O)OH, $-CH_2C(O)OH$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(b) $\mathbf{R^{30a}}$ can be selected from the group consisting of H (hydrogen) and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) $\mathbf{R^{30b}}$ and $\mathbf{R^{30c}}$ can each be separately selected from the group consisting of H (hydrogen) and C_{1-6} alkyl, or $\mathbf{R^{30b}}$ and $\mathbf{R^{30c}}$ can be optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

(d) $\mathbf{R^{31}}$ can be selected from the group consisting of H (hydrogen), -OH, –SH, $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -C(O)OH, $-CH_2C(O)OH$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(e) $\mathbf{R^{32}}$ can be selected from the group consisting of $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -C(O)OH, and $-CH_2C(O)OH$; or $\mathbf{R^{32}}$ can be :



;

(f) $\mathbf{R^{33}}$ can be selected from the group consisting of H (hydrogen), -OH, halo, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(g) $\mathbf{R^{34}}$ and $\mathbf{R^{35}}$ can each be separately selected from the group consisting of H (hydrogen), -OH, halo, and C_{1-6} alkyl optionally substituted with up to 5 fluoro; or $\mathbf{R^{34}}$ and $\mathbf{R^{35}}$ can be optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

(h) $\mathbf{R^{36}}$ and $\mathbf{R^{37}}$ can each be separately selected from the group consisting of H (hydrogen), -OH, -SH, and halo; or $\mathbf{R^{36}}$ and $\mathbf{R^{37}}$ can be optionally taken together with the carbon to which they are attached to form a keto or thioketo group; and

(i) $\mathbf{X_6}$ can be selected from the group consisting of O (oxygen), S (sulfur) and -NH.

[0124] The present disclosure provides a method of ameliorating an avian influenza infection in an individual, the method comprising administering to the individual an effective amount of a compound identified by the methods described herein.

[0125] The compounds or pharmaceutical compositions may be administered to the patient by any suitable means. Non-limiting examples of methods of administration

include, among others, (a) administration though oral pathways, which administration includes administration in capsule, tablet, granule, spray, syrup, or other such forms; (b) administration through non-oral pathways such as rectal, vaginal, intraurethral, intraocular, intranasal, or intraauricular, which administration includes administration as an aqueous suspension, an oily preparation or the like or as a drip, spray, suppository, salve, ointment or the like; (c) administration via injection, subcutaneously, intraperitoneally, intravenously, intramuscularly, intradermally, intraorbitally, intracapsularly, intraspinally, intrasternally, or the like, including infusion pump delivery; (d) administration locally such as by injection directly in the renal or cardiac area, e.g., by depot implantation; as well as (e) administration topically; as deemed appropriate by those of skill in the art for bringing the compound of the invention into contact with living tissue.

[0126] Pharmaceutical compositions suitable for administration include compositions where the active ingredients are contained in an amount effective to achieve its intended purpose. The therapeutically effective amount of the compounds disclosed herein required as a dose will depend on the route of administration, the type of animal, including human, being treated, and the physical characteristics of the specific animal under consideration. The dose can be tailored to achieve a desired effect, but will depend on such factors as weight, diet, concurrent medication and other factors which those skilled in the medical arts will recognize. More specifically, a therapeutically effective amount means an amount of compound effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated. Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

[0127] As will be readily apparent to one skilled in the art, the useful *in vivo* dosage to be administered and the particular mode of administration will vary depending upon the age, weight and mammalian species treated, the particular compounds employed, and the specific use for which these compounds are employed. The determination of effective dosage levels, that is the dosage levels necessary to achieve the desired result, can be accomplished by one skilled in the art using routine pharmacological methods. Typically, human clinical applications of products are commenced at lower dosage levels, with dosage level being increased until the desired effect is achieved. Alternatively, acceptable *in vitro* studies can be used to establish useful doses and routes of

administration of the compositions identified by the present methods using established pharmacological methods.

[0128] In non-human animal studies, applications of potential products are commenced at higher dosage levels, with dosage being decreased until the desired effect is no longer achieved or adverse side effects disappear. The dosage may range broadly, depending upon the desired affects and the therapeutic indication. Typically, dosages may be between about 10 microgram/kg and 100 mg/kg body weight, preferably between about 100 microgram/kg and 10 mg/kg body weight. Alternatively dosages may be based and calculated upon the surface area of the patient, as understood by those of skill in the art.

[0129] The exact formulation, route of administration and dosage for the pharmaceutical compositions of the present invention can be chosen by the individual physician in view of the patient's condition. (See *e.g.*, Fingl *et al.* 1975, in "The Pharmacological Basis of Therapeutics", which is hereby incorporated herein by reference in its entirety, with particular reference to Ch. 1, p. 1). Typically, the dose range of the composition administered to the patient can be from about 0.5 to 1000 mg/kg of the patient's body weight. The dosage may be a single one or a series of two or more given in the course of one or more days, as is needed by the patient. In instances where human dosages for compounds have been established for at least some condition, the present invention will use those same dosages, or dosages that are between about 0.1% and 500%, more preferably between about 25% and 250% of the established human dosage. Where no human dosage is established, as will be the case for newly-discovered pharmaceutical compounds, a suitable human dosage can be inferred from ED_{50} or ID_{50} values, or other appropriate values derived from *in vitro* or *in vivo* studies, as qualified by toxicity studies and efficacy studies in animals.

[0130] It should be noted that the attending physician would know how to and when to terminate, interrupt, or adjust administration due to toxicity or organ dysfunctions. Conversely, the attending physician would also know to adjust treatment to higher levels if the clinical response were not adequate (precluding toxicity). The magnitude of an administrated dose in the management of the disorder of interest will vary with the severity of the condition to be treated and to the route of administration. The severity of the condition may, for example, be evaluated, in part, by standard prognostic evaluation methods. Further, the dose and perhaps dose frequency, will also

vary according to the age, body weight, and response of the individual patient. A program comparable to that discussed above may be used in veterinary medicine.

[0131] Although the exact dosage will be determined on a drug-by-drug basis, in most cases, some generalizations regarding the dosage can be made. The daily dosage regimen for an adult human patient may be, for example, an oral dose of between 0.1 mg and 2000 mg of each active ingredient, preferably between 1 mg and 500 mg, e.g. 5 to 200 mg. In other embodiments, an intravenous, subcutaneous, or intramuscular dose of each active ingredient of between 0.01 mg and 100 mg, preferably between 0.1 mg and 60 mg, e.g. 1 to 40 mg is used. In cases of administration of a pharmaceutically acceptable salt, dosages may be calculated as the free base. In some embodiments, the composition is administered 1 to 4 times per day. Alternatively the compositions of the invention may be administered by continuous intravenous infusion, preferably at a dose of each active ingredient up to 1000 mg per day. As will be understood by those of skill in the art, in certain situations it may be necessary to administer the compounds disclosed herein in amounts that exceed, or even far exceed, the above-stated, preferred dosage range in order to effectively and aggressively treat particularly aggressive diseases or infections. In some embodiments, the compounds will be administered for a period of continuous therapy, for example for a week or more, or for months or years.

[0132] Dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the modulating effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from in vitro data. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. However, HPLC assays or bioassays can be used to determine plasma concentrations.

[0133] Dosage intervals can also be determined using MEC value. Compositions should be administered using a regimen which maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%.

[0134] The selected dosage level can depend upon, for example, the route of administration, the severity of the infection being treated, and the condition and prior medical history of the patient being treated. It will be understood, however, that the specific dose level for any particular patient can depend upon a variety of factors including the genetic makeup, body weight, general health, diet, time and route of

administration, combination with other drugs and the particular condition being treated, and its severity.

[0135] An oral composition described herein may be administered or prescribed in a dosage less than, for example, about 750 mg/kg, about 500 mg/kg, about 300 mg/kg, or about 150 mg/kg. An intravenous composition described herein may be administered or prescribed in a dosage less than, for example, about 25 mg/kg and greater than, for example, 5 mg/kg.

[0136] A composition described herein can be prescribed or administered at a constant dose, or the dosage can change as a function of treatment time. For example, dosages may increase or decrease with time in a step-wise or continuous manner. The dosage may vary depending on the effect of the dosage on a condition being treated and the occurrence of adverse side effects. For example, the patient may be instructed to continue to lower the dosage until a side effect is reduced to an acceptable level. As another example, the patient may be instructed to continue to lower the dosage until the dosage is no longer effective and then slightly increase the dosage.

[0137] In some embodiments, a composition described herein can be prescribed or administered at a specific dosage per day.

[0138] In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration.

[0139] The amount of composition administered will, of course, be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration and the judgment of the prescribing physician.

[0140] Compounds disclosed herein can be evaluated for efficacy and toxicity using known methods. For example, the toxicology of a particular compound, or of a subset of the compounds, sharing certain chemical moieties, may be established by determining *in vitro* toxicity towards a cell line, such as a mammalian, and preferably human, cell line. The results of such studies are often predictive of toxicity in animals, such as mammals, or more specifically, humans. Alternatively, the toxicity of particular compounds in an animal model, such as mice, rats, rabbits, or monkeys, may be determined using known methods. The efficacy of a particular compound may be established using several recognized methods, such as *in vitro* methods, animal models, or human clinical trials. Recognized *in vitro* models exist for nearly every class of condition, including but not limited to cancer, cardiovascular disease, and various

immune dysfunction. Similarly, acceptable animal models may be used to establish efficacy of chemicals to treat such conditions. When selecting a model to determine efficacy, the skilled artisan can be guided by the state of the art to choose an appropriate model, dose, and route of administration, and regime. Of course, human clinical trials can also be used to determine the efficacy of a compound in humans.

[0141] The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, may be the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. Compositions comprising a compound of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

[0142] Compounds according to the invention may be formulated into pharmaceutical compositions for administration according to well known methodologies. Pharmaceutical compositions may, for example, comprise one or more of the above-identified compounds, in combination with a pharmaceutically acceptable carrier, excipient or diluent. Such carriers will be nontoxic to recipients at the dosages and concentrations employed. A suitable dosage may be from about 0.01 μg/kg to about 1 g/kg body weight, typically by the intraocular, intravenous, intradermal, subcutaneous, intramuscular, or by other routes. A more typical dosage is about 1 μg/kg to about 500 mg/kg, with about 10 μg/kg, 100 μg/kg, 1 mg/kg, 10 mg/kg, 20 mg/kg, 50 mg/kg, 100 mg/kg, 200 mg/kg, 300 mg/kg, 400 mg/kg, and various ranges within these amount being still more typical for administration. It will be evident to those skilled in the art that the number and frequency of administration will be dependent upon the response of the host. "Pharmaceutically acceptable carriers" for therapeutic use are well known in the pharmaceutical art, and are described, for example, in *Remingtons Pharmaceutical Sciences*, Mack Publishing Co. (A.R. Gennaro edit. 1985). For example, sterile saline and phosphate-buffered saline at physiological pH may be used. Preservatives, stabilizers,

dyes and even flavoring agents may be provided in the pharmaceutical composition. For example, sodium benzoate, sorbic acid and esters of *p*-hydroxybenzoic acid may be added as preservatives. In addition, antioxidants and suspending agents may be used.

[0143] The compositions as described herein can be in a unit dosage form. Unit dosage form can refer to a product form in which premeasured dosages of the drug are packaged, in contrast to bulk preparations. Examples of unit dosage forms are described herein, but several non limiting examples, include, a pill, a tablet, a capsule, a gel cap, a small liquid drug, an ampoule, a fast melt formulation, and the like.

[0144] In performing the methods, a composition described herein can be administered using any suitable route or method of delivery. For example, the composition may be in the form of a solid, liquid or gas (aerosol). Also, a composition described herein can be administered alone or in combination with other substances. Suitable routes of administration include oral; buccal; sublingual; pulmonary; transdermal; rectal; vaginal; topical; transmucosal; intestinal administration; intraspinally; ocular; parenteral delivery (*e.g.* sublingually or buccally), including intramuscular, subcutaneous, intrasternal, intracavernous intrameatal, intraurethral, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular; intraperitoneal; intranasal; through infusion techniques; or intraocular injections. The route of administration may be determined by a condition to be treated. Preferred routes of administration include oral administration.

[0145] The pharmaceutical composition is formulated so as to allow the active ingredients contained therein to be bioavailable upon administration of the composition to a patient. Compositions that will be administered to a patient take the form of one or more dosage units, where for example, a tablet may be a single dosage unit, and a container of one or more compounds of the invention in aerosol form may hold a plurality of dosage units.

[0146] For oral administration, the compositions may be formulated as pills, tablets, powders, granules, dragees, capsules, liquids, sprays, gels, syrups, slurries, suspensions and the like, in bulk or unit dosage forms, for oral ingestion by a patient to be treated. The composition may be an oral dosage form, and the oral dosage form may be a solid oral dosage form. The compositions can be formulated readily, for example, by combining the active compound with any suitable pharmaceutically acceptable carrier or excipient.

[0147] Pharmaceutical preparations for oral use can be obtained by mixing one or more solid excipients with a pharmaceutical composition as described herein, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are listed below, while others are listed in incorporated references. Some examples include fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[0148] The compounds may be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

[0149] Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[0150] One can also administer the compounds of the invention in sustained release forms or from sustained release drug delivery systems. A description of representative sustained release materials can be found in the incorporated materials in *Remington: The Science and Practice of Pharmacy* (20th ed, Lippincott Williams & Wilkens Publishers (2003)), which is incorporated herein by reference in its entirety. A variety of techniques for formulation and administration can be found in *Remington: The Science and Practice of Pharmacy* (20th ed, Lippincott Williams & Wilkens Publishers (2003)), which is incorporated herein by reference in its entirety.

[0151] If the manufacture of pharmaceutical formulations involves intimate mixing of the pharmaceutical excipients and the active ingredient in its salt form, then it

may be desirable to use pharmaceutical excipients which are non-basic, that is, either acidic or neutral excipients.

[0152] As mentioned above, the compositions and formulations disclosed herein also can include one or more pharmaceutically acceptable carrier materials or excipients. Such compositions can be prepared for storage and for subsequent administration. Acceptable carriers or diluents for therapeutic use are described, for example, in the incorporated material of *Remington: The Science and Practice of Pharmacy* (2003). The term "carrier" material or "excipient" herein can mean any substance, not itself a therapeutic agent, used as a carrier and/or diluent and/or adjuvant, or vehicle for delivery of a therapeutic agent to a subject or added to a pharmaceutical composition to improve its handling or storage properties or to permit or facilitate formation of a dose unit of the composition into a discrete article such as a capsule or tablet suitable for oral administration. Excipients can include, by way of illustration and not limitation, diluents, disintegrants, binding agents, adhesives, wetting agents, polymers, lubricants, glidants, substances added to mask or counteract a disagreeable taste or odor, flavors, dyes, fragrances, and substances added to improve appearance of the composition. Acceptable excipients include lactose, sucrose, starch powder, maize starch or derivatives thereof, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinyl-pyrrolidone, and/or polyvinyl alcohol, saline, dextrose, mannitol, lactose, lecithin, albumin, sodium glutamate, cysteine hydrochloride, and the like. Examples of suitable excipients for soft gelatin capsules include vegetable oils, waxes, fats, semisolid and liquid polyols. Suitable excipients for the preparation of solutions and syrups include, without limitation, water, polyols, sucrose, invert sugar and glucose. Suitable excipients for injectable solutions include, without limitation, water, alcohols, polyols, glycerol, and vegetable oils. The pharmaceutical compositions can additionally include preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorings, buffers, coating agents, or antioxidants. Sterile compositions for injection can be formulated according to conventional pharmaceutical practice as described in the incorporated material in *Remington: The Science and Practice of Pharmacy* (2003). For example, dissolution or suspension of the active compound in a vehicle such as water or naturally occurring vegetable oil like sesame, peanut, or cottonseed oil or a synthetic fatty vehicle like ethyl

oleate or the like may be desired. Buffers, preservatives, antioxidants and the like can be incorporated according to accepted pharmaceutical practice. The compound can also be made in microencapsulated form. In addition, if desired, the injectable pharmaceutical compositions may contain minor amounts of nontoxic auxiliary substances, such as wetting agents, pH buffering agents, and the like.

[0153] The compositions and formulations can include any other agents that provide improved transfer, delivery, tolerance, and the like. These compositions and formulations can include, for example, powders, pastes, ointments, jellies, waxes, oils, lipids, DNA conjugates, anhydrous absorption pastes, oil-in-water and water-in-oil emulsions, emulsions carbowax (polyethylene glycols of various molecular weights), semi-solid gels, and semi-solid mixtures containing carbowax. Any of the foregoing mixtures may be appropriate in treatments and therapies in accordance with the present invention, provided that the at least one active ingredient in the formulation is not inactivated by the formulation and the formulation is physiologically compatible and tolerable with the route of administration. *See also* Baldrick P. "Pharmaceutical excipient development: the need for preclinical guidance." *Regul. Toxicol. Pharmacol.* 32(2):210-8 (2000), Charman WN "Lipids, lipophilic drugs, and oral drug delivery-some emerging concepts." *J Pharm Sci* .89(8):967-78 (2000), Powell *et al.* "Compendium of excipients for parenteral formulations" *PDA J Pharm Sci Technol.* 52:238-311 (1998) and the citations therein for additional information related to formulations, excipients and carriers well known to pharmaceutical chemists.

[0154] Some embodiments provide a method of identifying compounds which bind to the neuraminidase protein of Influenza A virus subtype H5N1, comprising:

(a) performing molecular dynamic simulations on an Influenza A virus subtype H5N1 neuraminidase protein crystal structure;

(b) generating an Influenza A virus subtype H5N1 protein structure using RMSD (root-mean-square-difference) clustering of related residues from the molecular dynamic simulations;

(c) docking compounds to the 150-loop of the generated Influenza A virus subtype H5N1 neuraminidase protein structure; and

(d) identifying the binding affinity of the docked compounds

wherein the MD simulations are performed on 2 or more Influenza A virus subtype H5N1 neuraminidase protein crystal structures. In some embodiments, the method further comprises docking compounds to sialic acid cavity.

[0155] Some embodiments provide a method of identifying compounds which bind to the neuraminidase protein of Influenza A virus subtype H5N1, comprising:

(a) performing molecular dynamic simulations on an Influenza A virus subtype H5N1 crystal structure;

(b) generating an Influenza A virus subtype H5N1 protein structure using RMSD (root-mean-square-difference) clustering of related residues from the molecular dynamic (MD) simulations;

(c) docking compounds to the 430-loop of the generated Influenza A virus subtype H5N1 neuraminidase protein structure; and

(d) identifying the binding affinity of the docked compounds

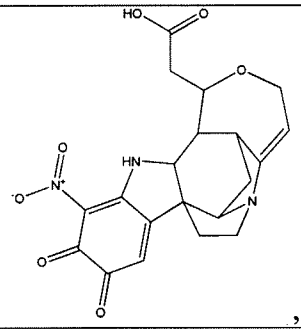
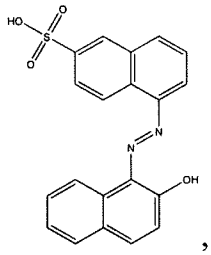
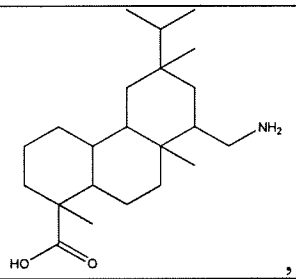
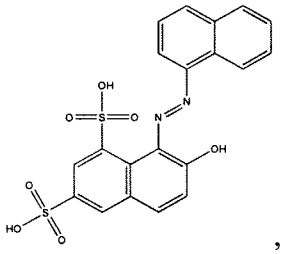
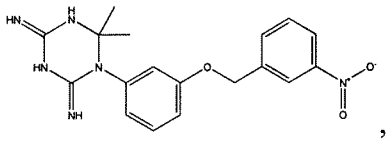
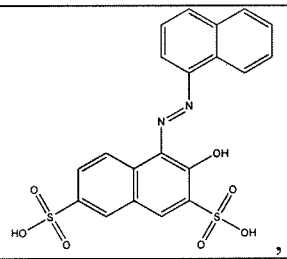
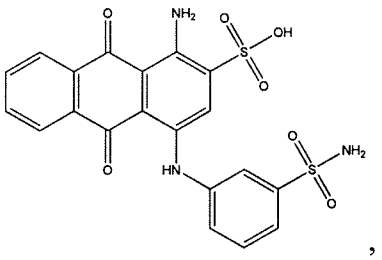
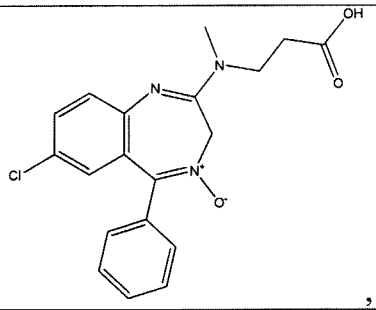
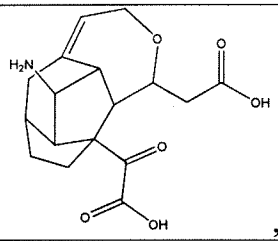
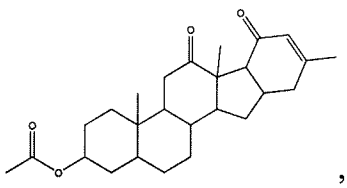
wherein the MD simulations are performed on 2 or more Influenza A virus subtype H5N1 neuraminidase protein crystal structures. In some embodiments, the method further comprises docking the compounds to sialic acid cavity. In some embodiments, the method further comprises docking the compounds to the 150-loop. In some embodiments, the method further comprises docking the compounds to the sialic acid cavity and the 150-loop.

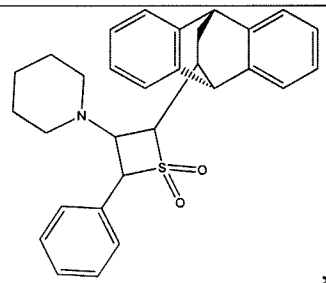
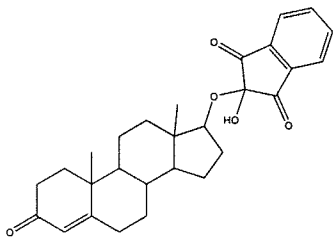
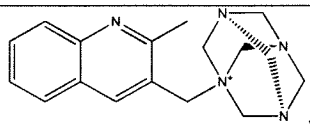
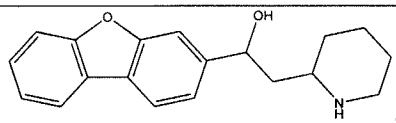
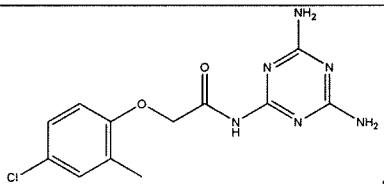
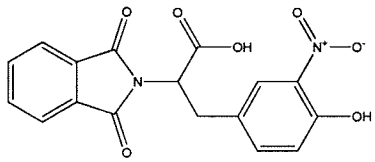
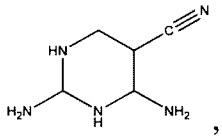
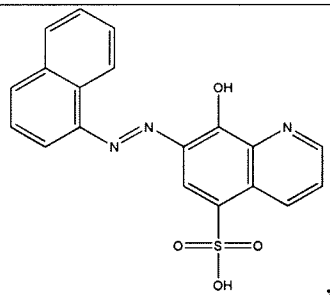
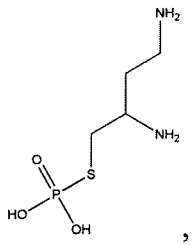
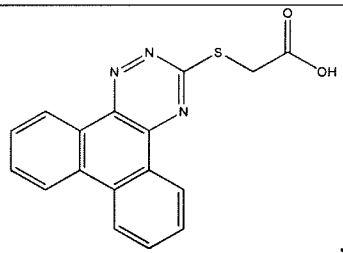
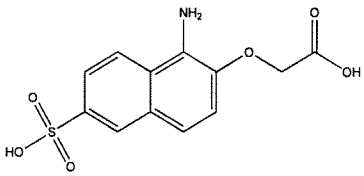
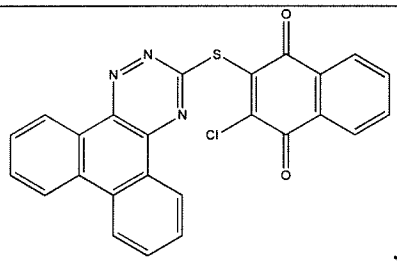
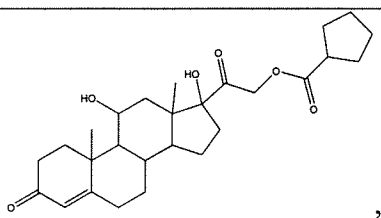
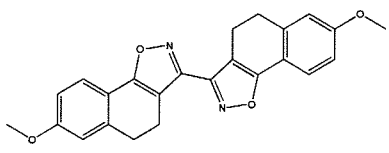
[0156] Some embodiments provide a method of identifying an agent that interacts with Influenza A virus subtype H5N1 neuraminidase protein comprising:

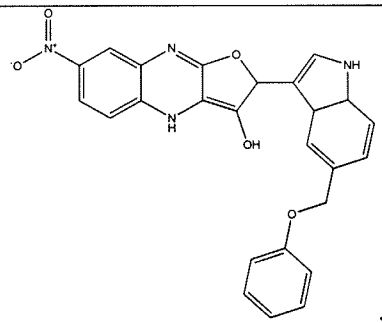
(a) using a crystal structure of a complex comprising Influenza A virus subtype H5N1 neuraminidase protein;

(b) obtaining the atomic coordinates of the crystal structure; and

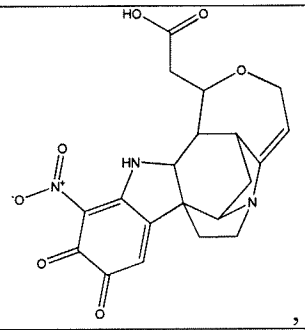
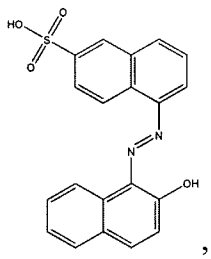
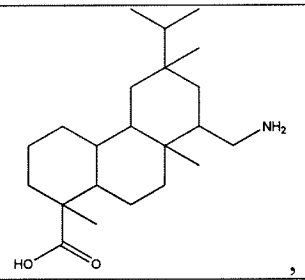
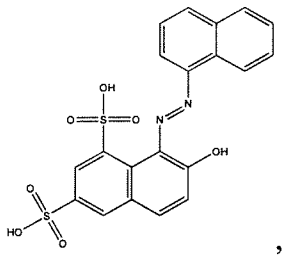
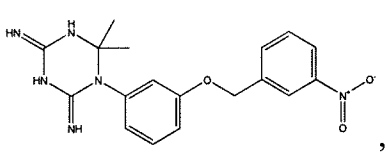
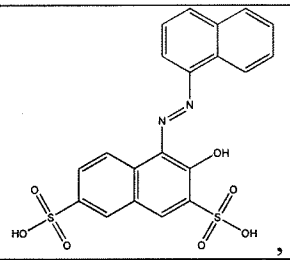
(c) using the atomic coordinates and one or more molecular modeling techniques to identify a ligand that interacts with Influenza A virus subtype H5N1 neuraminidase protein. For example, in some embodiments, the agent that interacts with Influenza A virus subtype H5N1 neuraminidase protein can be selected from the group consisting of:

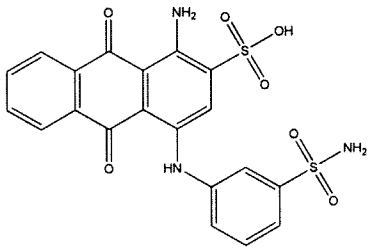
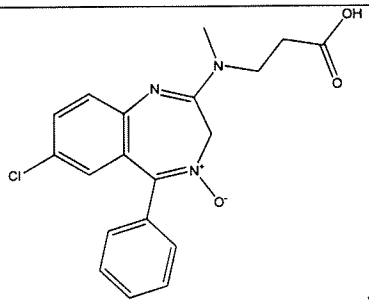
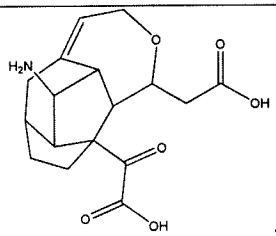
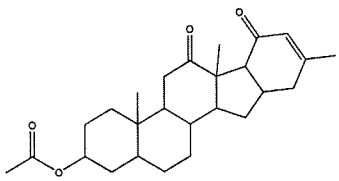
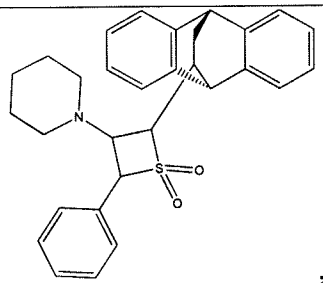
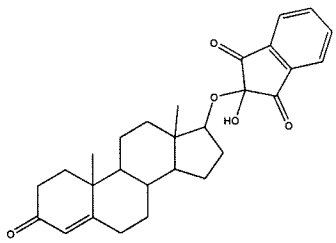
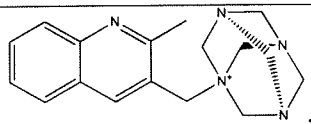
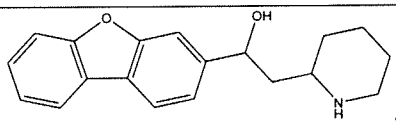
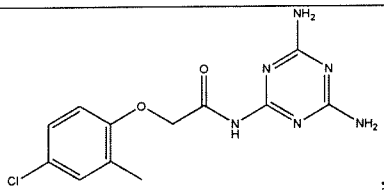
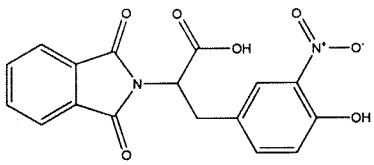
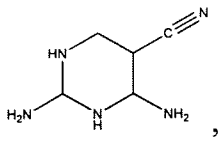
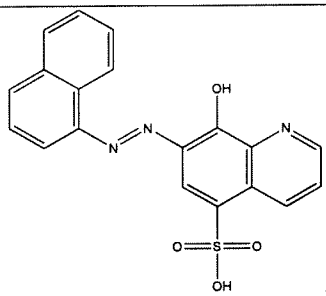
5069		45576	
70194		45582	
109836		45583	
117079		46080	
131612		59620	

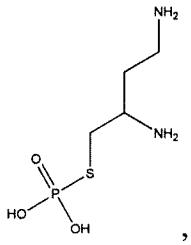
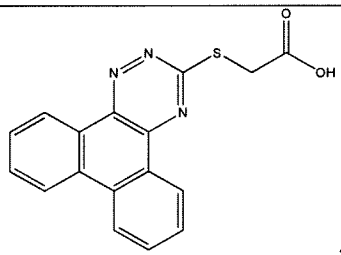
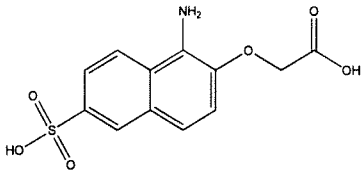
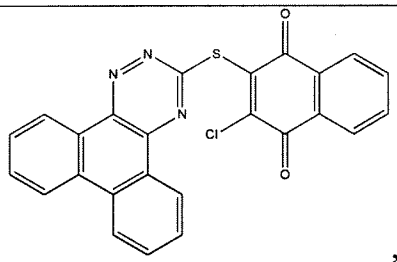
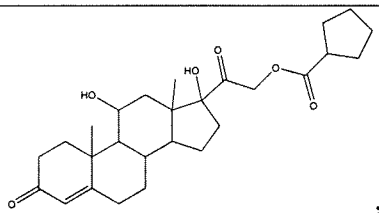
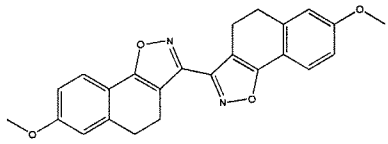
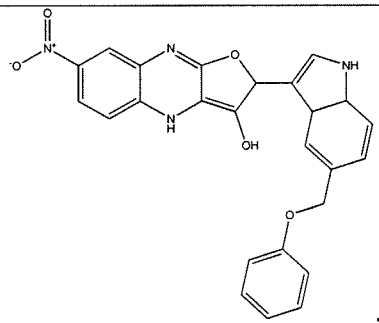
135371		72254	
141562		90630	
164640		106920	
211332		148354	
350191		327704	
16163		327705	
17245		371688	

	and		372294	

[0157] Some embodiments provide a method of identifying a compound which binds to an Influenza A virus subtype H5N1 neuraminidase protein with a desired affinity comprising identifying one or more interactions between a ligand and a sub-unit of the Influenza A virus subtype H5N1 neuraminidase protein; and changing a substituent on the ligand in order to modify the interaction between the ligand the neuraminidase protein subunit to provide said compound. For example, in some embodiments, the ligand can be selected from the group consisting of:

5069			45576	
70194			45582	
109836			45583	

117079		46080	
131612		59620	
135371		72254	
141562		90630	
164640		106920	
211332		148354	

350191			327704	
16163			327705	
17245			371688	
	and		372294	

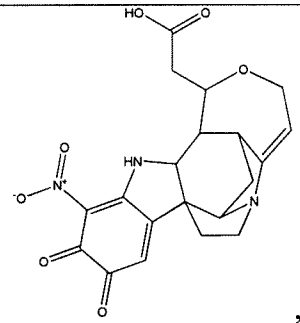
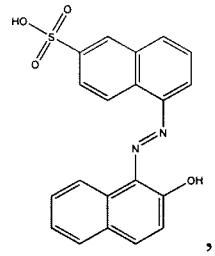
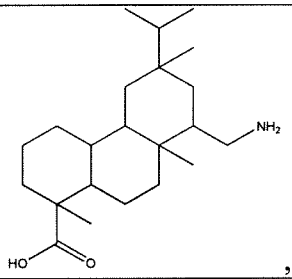
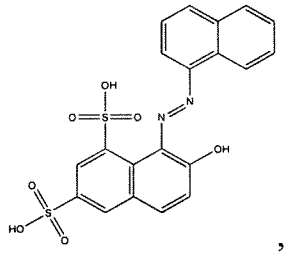
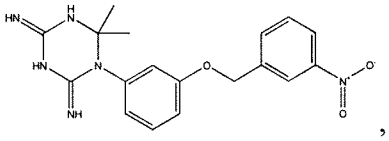
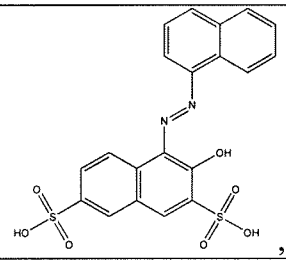
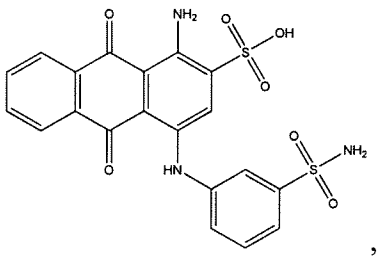
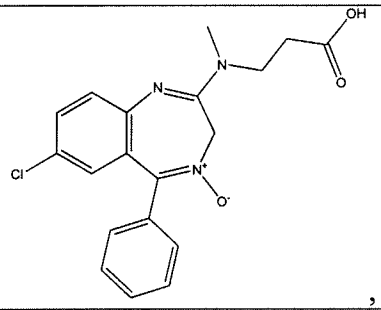
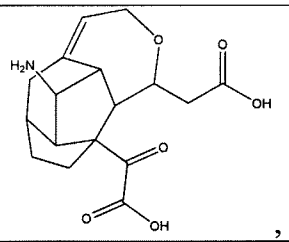
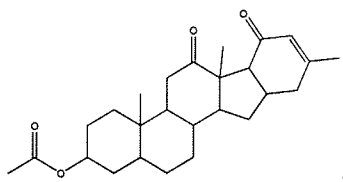
[0158] Some embodiments provide a composition comprising an agent and a pharmaceutically-acceptable carrier wherein the agent is identified by

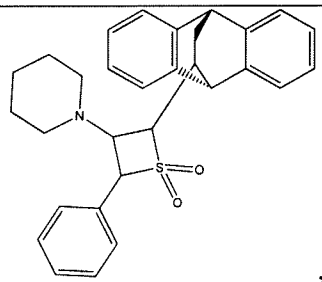
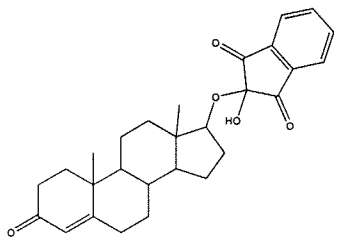
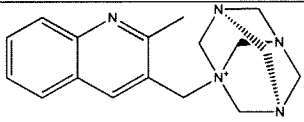
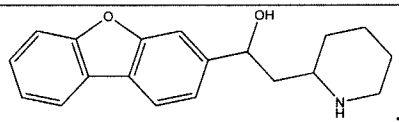
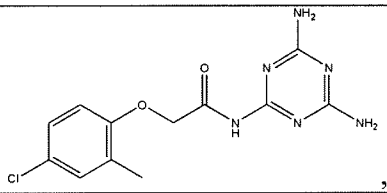
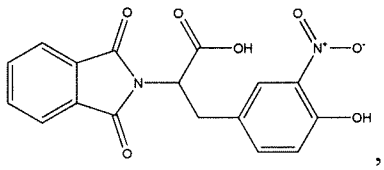
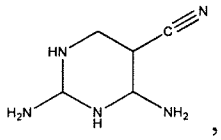
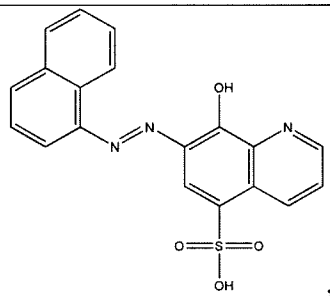
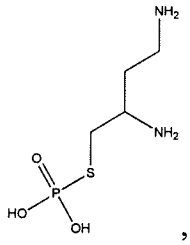
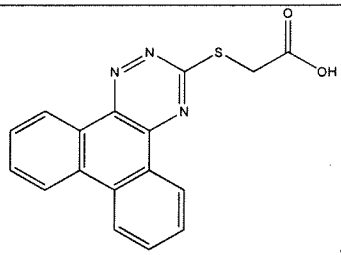
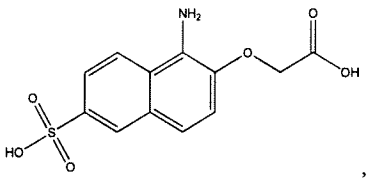
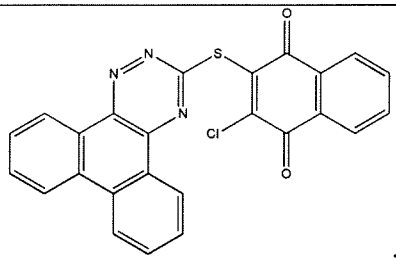
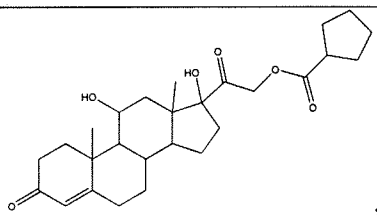
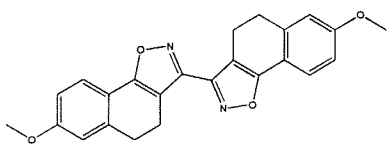
(a) using a crystal structure of a complex comprising Influenza A virus subtype H5N1 neuraminidase protein;

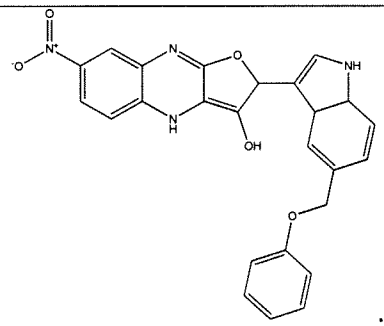
(b) obtaining the atomic coordinates of the crystal structure;

(c) using the atomic coordinates and one or more molecular modeling techniques to identify a ligand that interacts with Influenza A virus subtype H5N1.

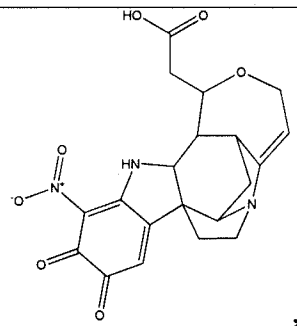
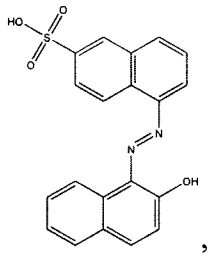
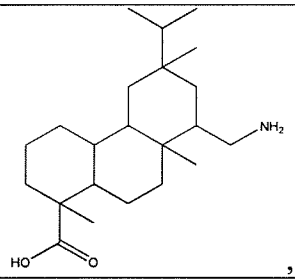
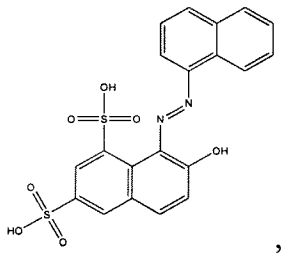
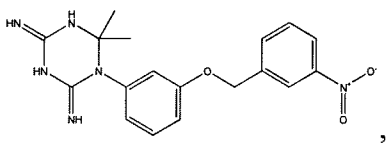
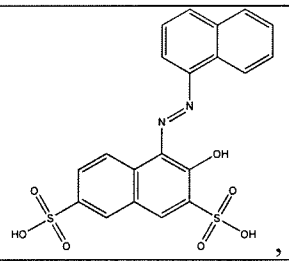
[0159] The present disclosure provides a pill comprising a compound selected from the group consisting of:

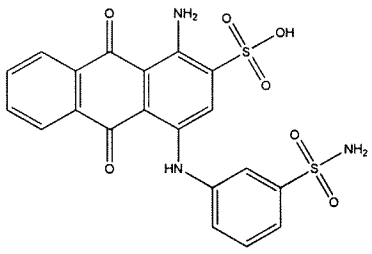
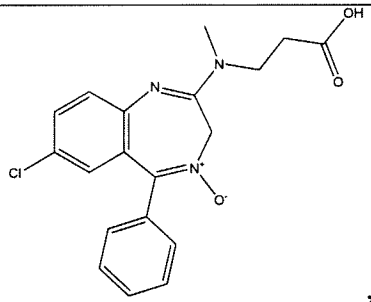
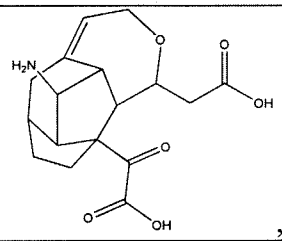
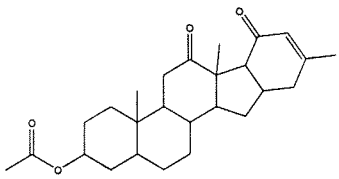
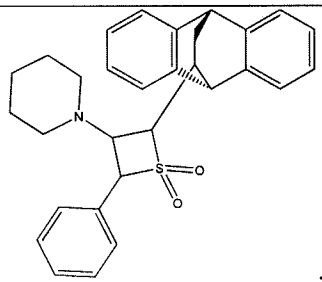
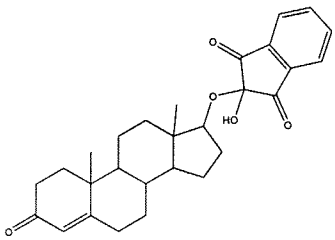
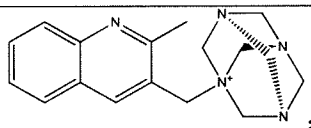
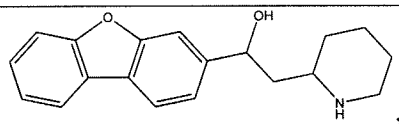
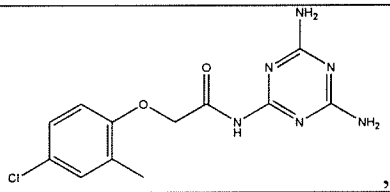
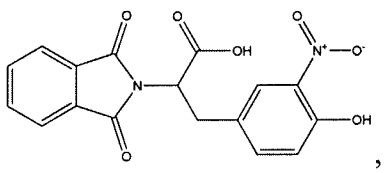
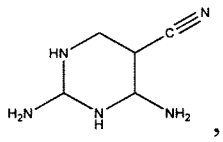
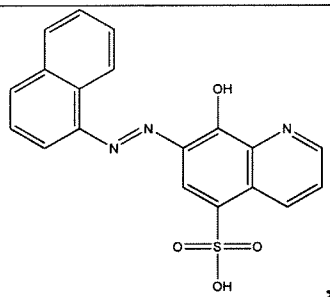
5069			45576	
70194			45582	
109836			45583	
117079			46080	
131612			59620	

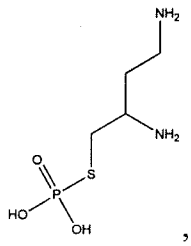
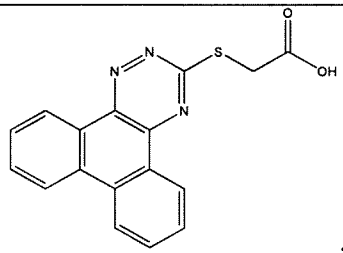
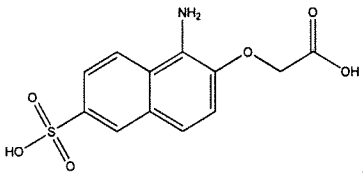
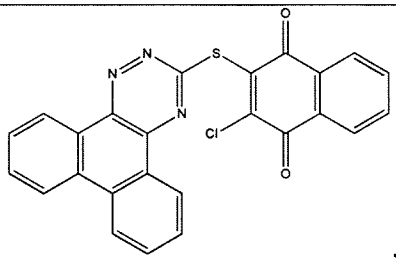
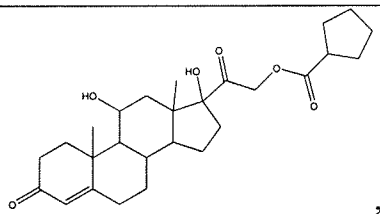
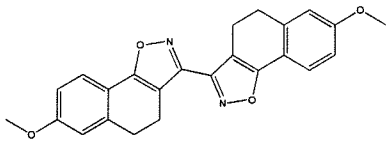
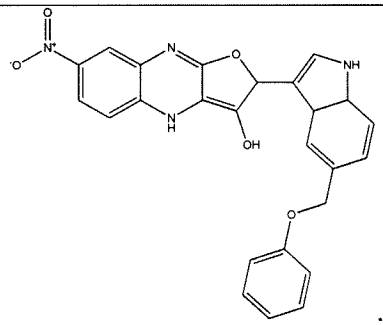
135371		72254	
141562		90630	
164640		106920	
211332		148354	
350191		327704	
16163		327705	
17245		371688	

	and		372294	

[0160] The present disclosure provides an injectable pharmaceutical composition comprising a compound selected from the group consisting of:

5069			45576	
70194			45582	
109836			45583	

117079		46080	
131612		59620	
135371		72254	
141562		90630	
164640		106920	
211332		148354	

350191			327704	
16163			327705	
17245			371688	
	and		372294	

[0161] The present disclosure provides a method of screening a compound library to identify compounds which bind to an Influenza A virus subtype H5N1 neuraminidase protein comprising:

(a) obtaining a library comprising a plurality of compound structure;

(b) performing molecular dynamic simulations on an Influenza A virus subtype H5N1 neuraminidase protein crystal structure;

(c) generating an Influenza A virus subtype H5N1 protein structure using RMSD (root-mean-square-difference) clustering of related residues from the molecular dynamic simulations;

(d) docking compounds to the 150-loop of the generated Influenza A virus subtype H5N1 neuraminidase protein structure; and

(e) identifying compounds which bind to said Influenza A virus subtype H5N1 neuraminidase protein with a desired affinity. In some embodiments, the method further comprises docking compounds to sialic acid cavity. In some embodiments, the method further comprises docking compounds to the 430-loop. In some embodiments, the method further comprises docking compounds to sialic acid cavity and the 430-loop.

[0162] The present disclosure provides a method of screening a compound library comprising:

(a) obtaining a library comprising a plurality of compound structure;

(b) performing molecular dynamic simulations on an Influenza A virus subtype H5N1 neuraminidase protein crystal structure;

(c) generating an Influenza A virus subtype H5N1 protein structure using RMSD (root-mean-square-difference) clustering of related residues from the molecular dynamic simulations;

(d) docking compounds to the 430-loop of the generated Influenza A virus subtype H5N1 neuraminidase protein structure; and

(e) identifying compounds which bind to said Influenza A virus subtype H5N1 neuraminidase protein with a desired affinity. In some embodiments, the library can contain in the range of from about 1000 to about 2000 individual compounds, in the range of from about 2000 to about 10,000 individual compounds, in the range of from about 10,000 to about 50,000 compounds, in the range of from about 50,000 to about 150,000, in the range of from about 150,000 to about 500,000 compounds. In one embodiment, the library can be the National Cancer Institute First Diversity Set I which contains 1990 individual compounds. In another embodiment, the library can be the National Cancer Institute Second Diversity Set II which contains 1364 individual compounds.

[0163] In some embodiments, virtual screening can identify the compounds which bind to the Influenza A virus subtype H5N1 neuraminidase protein with a desired binding affinity. In some embodiements, the binding affinity can be represented by comparison of the energy of the holo protein structure with the energy of the apo protein structure.

[0164] The present disclosure provides a method of screening a compound library comprising:

(a) obtaining a library comprising a plurality of compound structure;

(b) performing molecular dynamic simulations on an Influenza A virus subtype H5N1 neuraminidase protein crystal structure;

(c) generating an Influenza A virus subtype H5N1 protein structure using RMSD (root-mean-square-difference) clustering of related residues from the molecular dynamic simulations;

(d) docking compounds to the 430-loop of the generated Influenza A virus subtype H5N1 neuraminidase protein structure; and

(e) identifying compounds which inhibit Neuramidase from H5N1. In some embodiments, *in vitro* screening can identify compounds which inhibit Neuramidase from H5N1 with greater than 50% inhibition from about 10 mg/mL to about 200 mg/L. For example, the amount of compound providing greater than 50% inhibition can be in the range of from about 10 mg/mL to about 50 mg/mL, from 50 mg/mL to 100 mg/mL or from 100 mg/mL to about 200 mg/mL. In one embodiment, the amount of compound providing greater than 50% inhibition can be 200 mg/mL. In some embodiments, *in vitro* screening can identify compounds which inhibit Neuramidase from H5N1 with greater than 5% inhibition from about 5 μg/mL to about 200 μg/L. For example, the amount of compound providing greater than 5% inhibition can be in the range of from about 5 μg/mL to about 50 μg/mL, from 50 μg/mL to 100 μg/mL or from 100 μg/mL to about 200 μg/mL. In one embodiment, the amount of compound providing greater than 5% inhibition can be 20 μg/mL. In some embodiments, the method further comprises docking compounds to sialic acid cavity. In some embodiments, the method further comprises docking compounds to the 150-loop. In some embodiments, the method further comprises docking compounds to sialic acid cavity and the 150-loop.

[0165] It will be understood that there is no intent in the use of terms and expressions herein to exclude any equivalent of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the

scope of the invention as claimed. It will also be understood that each of the narrower species and subgeneric groupings falling within the generic disclosure also form part of the invention. This includes the generic description of the invention with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

[0166] From the foregoing, it will be obvious to those skilled in the art that various modifications in the above-described methods, and compositions can be made without departing from the spirit and scope of the invention. Accordingly, the invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. Present embodiments and examples, therefore, are to be considered in all respects as illustrative and not restrictive, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

Example 1-1

Experimentals

Apo system setup

[0167] The apo system was built with the 2HTY crystal structure [7]. Protonation states for histidine residues were defined at an apparent pH 6.5 using the PDB2PQR web server [14]. All crystallographically resolved water oxygen positions were retained in the apo system, as well as Ca^{2+} ions, which are required for optimal NA function [15]. In order to mimic future experimental inhibition assay conditions, a 20 mM NaCl salt bath was introduced. The simulated system contained 112,311 atoms. Additional details for the of the simulation set-up is known in the art as exemplified in Amaro, R.E., et al., *Remarkable loop flexibility in avian influenza N1 and its implications for antiviral drug design. J Am Chem Soc*, 2007. **129**(25): p. 7764-7765 [6].

Holo (*i.e.* Tamiflu-bound) system setup

[0168] The 2HU0 structure used for the holo system initially had a single Tamiflu molecule bound in the active site of chain B [7]. In order to introduce Tamiflu within each of the other chains, chain B was aligned to chain A, C, and D by superimposition of the backbone C_α-atoms and the resulting transformation matrix was applied to the Tamiflu molecule. Amber9 was used to set up the Tamiflu-bound system

using an identical protocol to the apo system, with the exception of the additional Tamiflu parameters. Tamiflu was parameterized as described in Ref. [6]. Full details for the holo-system setup can be found in References [8, 9]. The composite tetrameric Tamiflu-bound system, comprising one Tamiflu molecule in each of the four active sites and calcium ions in 20 mM NaCl salt bath, contained 112,457 atoms.

Molecular dynamics simulations

[0169] The apo and holo systems were energy minimized for $5x10^4$ steps using NAMD version 2.6b1 (http://www.ks.uiuc.edu/Research/namd/) [16]. The MD methods have been previously described in References [8, 9]. Free dynamics were subsequently performed using a 2-fs timestep, for a total of 40 ns, for each system. Trajectories were generated on the San Diego Supercomputing Center's DataStar machine (benchmark time of 0.3 days/nanosecond using 112 parallel processors).

RMSD-clustering to extract representative MD structures

[0170] In order to generate a reduced, representative set of N1 structures for the CS-Map calculations, RMSD conformational clustering was performed as previously described in Ref. [7]. Clustering was performed with the GROMOS++ analysis software [17], part of the GROMOS05 software for biomolecular simulation (http://www.igc.ethz.ch/GROMOS).

[0171] Briefly, for the apo and holo simulations, each chain of the tetramer was extracted at 10 ps intervals over the 40 ns simulation. The resulting $1.6x10^4$ trajectory structures for each simulation were superimposed using all C_α atoms to remove overall rotation and translation. The RMSD-clustering was performed on the subset of 62 residues that line the entire binding-site area, which we define here as the binding-site residues: 117-119, 133-138, 146-152, 156, 179, 180, 196-200, 223-228, 243-247, 277, 278, 293, 295, 344-347, 368, 401, 402, and 426-441. These residues were clustered into batches of similar configurations using the atom-positional root-mean-square difference (RMSD) of all atoms (including side chains and hydrogens) as the similarity criterion. A cutoff of 1.3 Å was chosen after evaluation of the dependence of cluster populations against the total number of clusters found for each simulation using a cutoff in the range 1.0-1.5 Å. A full discussion of the clustering results can be found in Ref. [7].

[0172] The three most dominant configurations from the apo and holo ensembles were used in the virtual screening experiments. These structures represented 20%, 20%, 20% and 40%, 20%, 15% of the apo and holo ensembles, respectively [7].

Virtual screening with AutoDock

[0173] AutoDockTools version 1.4.5 [18] was used to add polar hydrogens and assign Gastieger charges to each of the eight NA structures. The PDB2PQR web server (http://nbcr.net/pdb2pqr) was used to simulate a biological assay pH of 6.5 [14]. For each of the eight NA structures, AutoGrid version 4.0 was used to create affinity grids centered on the active site. Each grid enclosed an area of 64 by 72 by 66 Å with 0.375 Å spacing and affinity grids were calculated for all of the following atom types: A (aromatic carbon), C, F, I, N, NA (hydrogen-bond-accepting N) Cl, O, OA (hydrogen-bond-accepting O), P, S, SA (hydrogen-bond-accepting S), Br, H and e (electrostatic). All NA structures from simulation were aligned with the closed 150-loop crystal structure (2HU4, chain B) to maintain consistent grid location.

[0174] The National Cancer Institute Diversity Set (NCIDS) is a collection of approximately two thousand compounds that are structurally representative of a wide range of pharmacophores [19]. AutoDockTools version 1.4.5 was used to merge non-polar hydrogens, add Gastieger charges to each ligand and set up rotatable bonds through AutoTors. A number of ligands containing rare earth elements could not be processed and were excluded. A total of 1,883 compounds from the NCIDS were included in the screen. Five additional compounds experimentally known to bind avian influenza N1 were also included in the screen: sialic acid, 2,3-didehydro-2-deoxy-N-acetyl neuraminic acid (DANA), Tamiflu, Relenza and peramivir (an experimental inhibitor in Phase II clinical trials [28]).

[0175] AutoDock version 4.0.1 with the Lamarckian genetic algorithm was used to simulate ligand-receptor docking [20]. Docking parameters were optimized for the positive control docking of Tamiflu to the closed 150-loop conformation of NA (2HU4) and were as follows: trials of 100 dockings, population size of 200, random starting position and conformation, translation step ranges of 2.0 Å, rotation step ranges of 50°, elitism of 1, mutation rate of 0.02, crossover rate of 0.8, local search rate of 0.06, and 5 million energy evaluations. A total of 15,104 docking jobs were run on the National Biomedical Computation Resource (NBCR) Kryptonite cluster. Docked conformations

were clustered using a tolerance of 2.0 Å root-mean-square deviation (RMSD) using the external clustering script provided with AutoDockTools version 1.4.5.

[0176] Docking results were sorted by the energy of the most populated cluster using AutoDockTools version 1.4.5 and the top 27 hits from each of the eight systems were chosen for further analysis. The top hits from each screen were initially filtered for druglikeness by their adherence to Lipinski's Rule of Five. Only compounds having: no more than five hydrogen bond donors, no more than ten hydrogen bond acceptors, a molecular weight under 500 g/mol, and a partition coefficient (log P) under five were considered [21]. The remaining hits were further filtered based on clustering criteria in AutoDock: a compound was considered a top hit only if the most populated cluster included at least 25 percent of all docked conformations. Receptor-ligand interactions, including hydrogen-bonding interactions and molecular surfaces, were calculated in AutoDockTools version 1.4.5 [26, 31].

Relaxed complex (RC) scheme

[0177] To validate and refine the virtual screening results, re-docking experiments were performed on the top 30 hits (including Tamiflu, Relenza, peramivir and DANA). Each compound was re-docked into the 27 central member cluster structures, which accounts for 100% of the ensemble variance from the holo simulation. Following the same docking procedure and parameter set described in the previous section, 756 re-docking calculations were carried out on NBCR's Kryptonite computing cluster as well as the Pacific Rim Application and Grid Middleware Assembly (PRAGMA, http://www.pragma-grid.net/) grid computing resource using NBCR's Community Scheduler Framework (CSF4, http://sourceforge.net/projects/gcsf/), a grid computing job scheduler. The binding free energies were extracted with AutoDockTools 1.4.5 scripts and the ligand binding spectra were plotted for further analysis.

On the structural variability of N1

[0178] Two crystal structures of N1 were used in this study, the "open-loop" structure (PDB 2HTY) and the "closed-loop" structure (PDB 2HU4) published in Ref. [7] with "open" and "closed" referring to the conformation of the 150-loop, and six computationally-derived structures, the three most dominant central-member structures from both the apo and holo ensembles, for virtual screening. In comparison to the crystal

structures, the configurations from the MD simulations exhibit a much greater degree of flexibility, especially in the 150- and 430-loop regions (Fig. 1) [6, 22]. The three central member structures for the most dominant clusters from the apo and holo MD simulations are represented Fig 1. (a) and (b), respectively, each shown in comparison to the open and closed 150-loop crystal structure. In the 430-loop and the 150-loop region, the central member structure of the most dominant cluster is indicated by label 110, the second most dominant cluster is indicated by label 112 and the third most dominant cluster is indicated by label 114. In the 430-loop and 150-loop regions, the closed 150-loop crystal structure (2HU4) is indicated by label 116 while the open 150-loop crystal structure (2HTY) is indicated by label 118. In the simulations, the 150-loop exhibited a remarkable degree of flexibility, but the 430-loop seems to be constrained by the presence of Tamiflu in the holo-ensemble relative to the apo ensemble.

[0179] In some instances, the topological changes within the N1 binding site influence the electrostatic potential of the binding site cavity surfaces, as shown in Figures 2 and 3. Figure 2a shows selected hits clustered in Apo crystal structure. Figure 2b shows selected hits clustered in the Apo-1 simulation structure. Figure 2c shows selected hits clustered in the Apo-2 simulation structure. Figure 2d shows selected hits clustered in the Apo-3 simulation structure.

[0180] In the apo simulations, the central member structure of the most dominant cluster for the apo simulations, Apo-1, is significantly more open in the 150-loop region than in the open-loop crystal structure. A comparison of the alpha-carbon atoms for the 62 residues lining the binding site results in an RMSD between the open crystal structure and Apo-1 of 2.05 Å (Fig. 1). The so-called "wide-open" structure [6] appears to be energetically and structurally stabilized by locally-formed hydrogen bonds, as noted in [7]. Structurally, the central member configuration for the second most dominant apo cluster, Apo-2, is similar to the open-loop crystal structure, exhibiting a binding site alpha-carbon RMSD of 0.95 Å. The central member structure of third most dominant apo cluster, Apo-3, is similar to the closed-loop crystal structure; alignment of Apo-3 to the closed-loop crystal structure yields an alpha-carbon RMSD over the 62 binding site residues of 1.73 Å.

[0181] In the holo simulations, the central member structure of the most dominant cluster, Holo-1, is similar to the open-loop crystal structure, and exhibits an alpha-carbon RMSD over the binding site region of 0.95 Å. The central member structure

of the second cluster, Holo-2, is intermediary to the open-loop crystal structure and the closed-loop crystal structure with an alpha-carbon RMSD of 1.18 Å and 1.27 Å, respectively. The third central member cluster structure, Holo-3, is similar to the open-loop crystal structure in the 150-loop region, and the two structures exhibit an alpha-carbon RMSD of 1.54 Å over the entire binding site.

[0182] Overall, the apo ensemble exhibits a greater degree of flexibility in the 150- and 430-loop regions than the holo ensemble. A comparison of the total number of structures representing each ensemble at the employed cutoff of 1.3 Å, 51 clusters for the apo simulation and 27 clusters for the holo simulation, illustrates the increased flexibility of the apo system [7]. The presence of Tamiflu in the active site constrained the motion of the protein during the holo trajectory, through contacts formed between D151 and R152 in the 150-loop and Tamiflu [6]. The holo ensemble was predisposed to have higher-affinity for Tamiflu than the apo-ensemble. This preference is reflected in the binding energies and relative rankings calculated in automated docking (Tables S1, S2).

Table S1: Hits to the receptor active site (sialic acid binding site)

Ligand	Apo Crystal	Apo-1	Apo-2	Apo-3	Holo Crystal	Holo-1	Holo 2	Holo-3
211332	-7.99 (63)	**-9.74 (94)**	-8.91 (100)	**-11.6 (100)**	**-9.96 (100)**	**-10.89 (74)**	**-9.96 (100)**	**-9.35 (98)**
109836	**-9.83 (31)**	[-9.50 (19)]	[-8.99 (18)]	[-9.92 (17)]	**-11.14 (43)**	[-9.17 (12)]	-10.41 (22)]	**-9.89 (32)**
Tamiflu	[-7.91 (14)]	-7.22 (28)	-7.82 (39)	-7.88 (28)	**-10.20 (43)**	**-10.24 (53)**	**-10.06 (60)**	-8.57 (41)
350191	[-7.54 (8)]	[-8.24 (15)]	[-6.89 (20)]	[-8.70 (20)]	-8.52 (26)	**-10.0 (34)**	-8.73 (35)	-6.79 (33)
117079	[-8.29 (11)]	[-10.6 (22)]	**-9.81 (25)**	[-9.99 (10)]	[-7.99 (11)]	[-9.17 (7)]	-10.89 (7)]	[-9.29 (6)]
Relenza	[-7.93 (12)]	[-6.71 (6)]	[-5.49 (8)]	[-8.35 (6)]	**-9.79 (29)**	**-9.41 (26)**	[-8.45 (23)]	[-6.66 (7)]
141562	-6.98 (35)	-8.23 (52)	-8.90 (77)	-9.05 (32)	[-8.28 (20)]	**-9.71 (46)**	-7.81 (29)	[-7.77 (23)]
5069	-8.35 (30)	-7.31 (25)	**-9.60 (63)**	[-6.39 (18)]	-8.60 (28)	-7.21 (39)	-8.97 (25)	-7.50 (29)
131612	**-9.54 (34)**	[-8.05 (10)]	-8.11 (30)	[-7.90 (15)]	**-9.31 (29)**	[-8.36 (19)]	-9.33 (32)	-8.09 (49)
70194	-7.55 (29)	-8.73 (36)	**-9.43 (50)**	-7.97 (26)	[-6.40 (18)]	[-7.61 (19)]	-7.86 (41)	-7.36 (34)
135371	-7.28 (27)	[-7.81 (16)]	-6.65 (25)	-8.69 (66)	**-9.24 (62)**	-8.22 (48)	-8.15 (22)]	[-7.77 (20)]
164640	[-6.60 (16)]	[-7.42 (12)]	[-7.04 (19)]	[-8.21 (24)]	-8.66 (25)	[-8.69 (21)]	-7.38 (30)	**-9.06 (34)**
Peramivir	[-6.11 (23)]	[-5.09 (18)]	[-5.77 (16)]	[-7.81 (15)]	[-9.00 (16)]	[-8.08 (17)]	-7.04 (9)]	[-6.98 (10)]
DANA	[-6.77 (9)]	[-6.66 (19)]	[-6.86 (9)]	[-7.15 (12)]	[-7.85 (12)]	[-7.00 (11)]	-7.69 (15)]	[-7.77 (20)]

[0183] Table S1 shows hits sorted by lowest binding energy. Each compound is identified by its NSC classification number. Tamiflu is included for reference. Table S1 expresses the binding affinity of each ligand as the Gibbs free energy (kcal/mol) of the most populated cluster followed by the percentage of docked conformations in that energy in parenthesis. Bold font denotes that the compound is among the top 27 lowest energy hits for the given receptor. Brackets denote that the clustering of the docking did not meet

the 25 percent cutoff. Ligands identified from the ensemble screens that were not identified by the crystal structure screens are underlined.

Table S2: Hits to other locales in the receptor binding site

Ligand	Apo Crystal	Apo-1	Apo-2	Apo-3	Holo Crystal	Holo-1	Holo 2	Holo-3
46080	**-10.60 (35)**	[-6.34 (8)]	-8.98 (40)	[-7.98 (13)]	**-10.35 (29)**	[-8.70 (23)]	[-7.56 (14)]	[-7.24 (14)]
45583	**-10.57 (32)**	**-10.24 (25)**	[-9.36 (18)]	[-8.46 (19)]	[-9.57 (14)]	**-9.55 (34)**	**-9.95 (37)**	[-10.53 (13)]
18312	-8.49 (47)	**-10.56 (63)**	-8.29 (76)	-7.44 (50)	-7.79 (29)	-7.43 (49)	-7.88 (49)	-7.48 (30)
106920	[-8.62 (10)]	[-7.03 (11)]	[-9.13 (19)]	**-10.08 (45)**	[-8.80 (11)]	[-7.83 (18)]	-9.32 (34)	[-8.02 (9)]
17245	**-10.07 (33)**	**-9.60 (33)**	[-9.76 (20)]	[-8.34 (13)]	[-8.83 (8)]	[-9.53 (16)]	[-9.58 (11)]	[-8.15 (8)]
45576	**-9.79 (29)**	**-10.05 (54)**	-9.20 (42)	[-9.00 (20)]	[-7.63 (13)]	[-7.43 (20)]	[-8.33 (18)]	-8.12 (26)
327704	**-9.52 (27)**	-8.52 (28)	**-9.75 (69)**	-9.01 (66)	**-9.97 (48)**	-8.96 (84)	-8.39 (64)	-7.98 (38)
37245	**-9.80 (28)**	[-7.20 (8)]	[-7.47 (7)]	[-7.98 (17)]	[-7.83 (24)]	[-8.31 (11)]	[-8.84 (14)]	[-7.20 (5)]
59620	-8.41 (72)	**-9.79 (60)**	-8.18 (52)	-7.45 (62)	-7.88 (70)	-7.87 (34)	-8.25 (51)	-7.33 (69)
16163	[-7.15 (12)]	**-9.72 (28)**	[-8.45 (14)]	[-7.23 (10)]	-7.06 (26)	[-5.79 (9)]	-6.25 (26)	[-7.16 (15)]
90630	**-7.53 (25)**	[-7.92 (19)]	-8.56 (36)	[-8.33 (14)]	[-7.86 (16)]	[-7.27 (22)]	**-9.71 (42)**	[-7.74 (14)]
148354	[-7.95 (11)]	[-8.78 (7)]	[-8.48 (9)]	[-9.49 (23)]	[-8.15 (7)]	[-7.82 (11)]	**-9.70 (29)**	[-8.73 (22)]
327705	**-9.53 (36)**	[-7.32 (17)]	-8.82 (26)	-8.37 (37)	[-9.76 (24)]	-9.30 (44)	-9.39 (30)	[-7.69 (15)]
372294	[-8.09 (12)]	[-7.17 (22)]	[-8.86 (7)]	**-9.45 (31)**	[-9.02 (17)]	[-8.36 (21)]	-7.54 (36)	[-8.01 (17)]
45582	[-7.44 (8)]	[-8.03 (9)]	**-9.37 (28)**	[-8.27 (9)]	[-7.62 (10)]	[-8.50 (17)]	[-7.44 (9)]	[-7.79 (14)]
371688	[-7.87 (22)]	[-8.94 (21)]	[-8.94 (17)]	[-7.74 (18)]	**-9.35 (26)**	[-8.71 (19)]	[-7.72 (10)]	[-7.28 (14)]
72254	[-8.30 (13)]	-8.59 (41)	**-9.25 (25)**	-8.48 (37)	[-8.76 (14)]	[-8.43 (17)]	-8.61 (28)	[-7.88 (17)]

[0184] Table S2 shows hits sorted by lowest binding energy. Each compound is identified by its NSC classification number. The binding affinity is expressed as the Gibbs free energy (kcal/mol) of the most populated cluster followed by the percentage of docked conformations in that energy in parenthesis. Bold font denotes that the compound is among the top 27 lowest energy hits for the given receptor. The values in brackets denote that the clustering of the docking did not meet the 25 percent cutoff. Underlined hits are those identified from the ensemble screens that were not identified by the crystal structure screens.

[0185] The three most dominant clusters used in the virtual screens for the apo and holo simulations accounted for approximately 60% and 75% of the overall MD ensembles, respectively. In total, the four concatenated monomer trajectories (extracted from the tetramer simulation) are equivalent to 160 ns of MD simulation. Thus the use of 60% of the apo simulation and 75% of the holo simulation accounts for a generous sampling of configurational space, given current computing standards.

[0186] The clustering of top hits in each system reveals three distinct cavities (Fig. 2, 3) within the NA active site. The sialic acid cavity is the locality in which the endogenous ligand binds and it is lined with important residues that facilitate the sialidase

activity of NA (Table1). Tamiflu was correctly predicted to bind within sialic acid cavity in seven of the eight structures, providing a positive control for the docking studies (Fig. S1); the exception was the predicted binding pose of Tamiflu to the central member structure of the most dominant apo cluster. The opening of the 150-loop in reveals a second cavity to which a number of docked hits clustered. The 150-cavity is a variable binding region adjacent to the sialic acid cavity that opens and closes with the motion of the 150-loop (Table1). Finally, a third cavity of high ligand affinity is uncovered by hits clustering to the region near the flexible 430-loop. The 430-cavity varies in size with the motion of the 430-loop (Table1). The existence of these high affinity regions in the 150-cavity and the 430-cavity, which are disparate from the sialic acid cavity, correlate with the location of several hot spots indicated by the CS-Map analysis of the same NA receptor-ensembles [7].

Table1

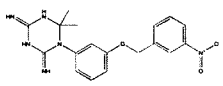
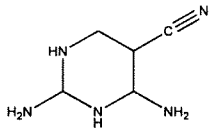
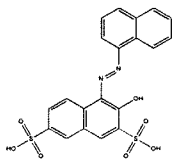
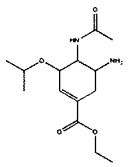
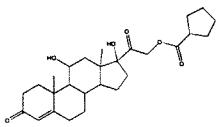
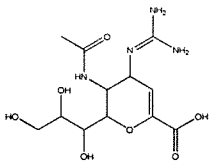
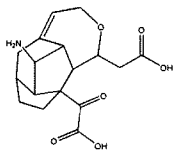
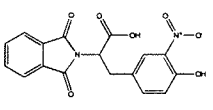
	Residues Lining the Binding Cavities
Sialic Acid Cavity	**R118, E119,** L134, **V149*,** K150*, **D151, R152, S153, P154, R156, W178, S179, S195, G196,** I222, **R224, E227, S246,** E276, **E277,** R292, N294, Y347, **R371, Y406**
150-loop Cavity	**V116,** I117, **R118,** L134, T135, Q136, S145, G147, T148, **V149,** K150, **D151, R156, R430, P431,** I437, W438, **T439**
430-loop Cavity	N325, P326, Y347, N369, S370, **R371,** W403, **S404, Y406, I427, R428,** G429, **R430, P431, K432,** E433, I437, W438, **T439**
Italicized residues are those also identified by CS-Map analysis [7]. Underlined residues define the borders between cavities. An asterix indicates the residues that line the sialic acid cavity only when the 150-loop assumes a closed conformation	

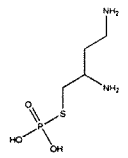
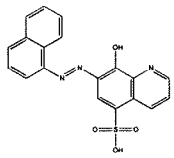
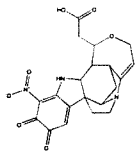
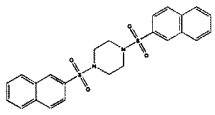
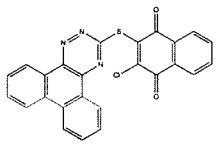
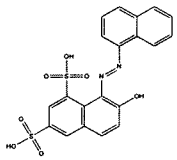
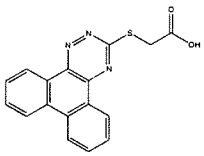
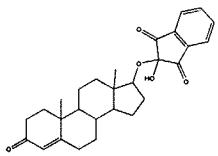
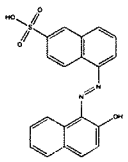
Results from the crystal structure screens

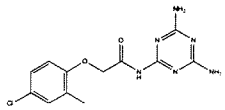
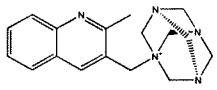
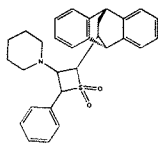
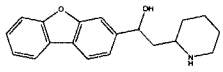
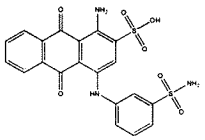
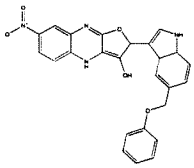
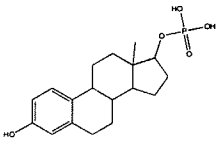
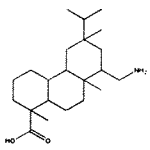
[0187] Tamiflu docks to both open- and closed-loop crystal structures in a manner consistent with its crystallized conformation. The overall RMSD (all-atoms) of the predicted binding pose compared to the crystal structure pose is 1.8 Å for the closed-loop structure and 2.1 Å for the open-loop structure. In the re-docking of Tamiflu to the closed N1 structure, the differences between docked and crystal poses lie primarily in the orientation of the pentyl ether group, which interacts with the protein through variable hydrophobic interactions. The negatively charged carboxylate group is anchored through electrostatic interactions to the arginine trio (R118, R292 and R371) and its position does not differ significantly between the docked and crystal poses. The successful re-docking of Tamiflu confirms that AutoDock 4.0.1 is able to emulate experimental binding with an excellent degree of accuracy and precision, serving as a positive control to validate the virtual screening hits.

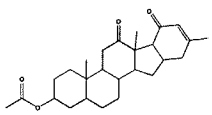
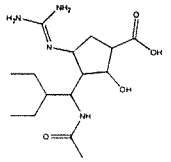
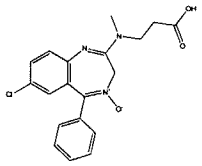
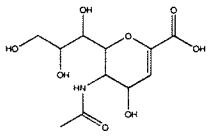
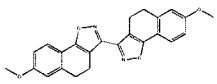
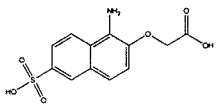
[0188] In the open-loop crystal structure, the conformation of the 150-loop reveals the presence of the so-called "open" 150-cavity . In the screen of the open-loop crystal structure, two of the 11 selected hits for this structure (selection criteria delineated in the Methods section) dock in the sialic acid cavity, three dock in the open 150-cavity and two dock in the 430-cavity (Fig. 2a). Two other hits bind simultaneously to both the 150-cavity and the 430-cavity. These two compounds are note-worthy for their ability to span two cavities. Another notable compound docks primarily in the 430-cavity but extends a carboxylic acid functional group into the sialic acid cavity. Overall, the results indicate that residues in the 150- and 430-cavities are able to mediate binding interactions that are as favorable as, or more favorable than, interactions within the active site (Table 2). The clustering of top hits to these adjacent cavities support findings from the CS-Map analysis, which uncovered several new binding hot spots in the open 150-cavity and 430-cavity in the open crystal structure [7].

Table 2: Final set of identified compounds

Rank	NSC	Mean Energy	K_i (μM)	Chemical Structure	Binding Site	Open-loop Crystal Rank	Closed-loop Crystal Rank
1	109836	-10.42	0.023		SA-cavity	15	1
2	211332	-10.13	0.037		SA-cavity	212	10
3	45583	-9.78	0.067		SA-cavity 150-cavity 430-cavity	6	18
-	Tamiflu	-9.60	0.091 (0.3 – 1.0)		SA-cavity	238	5
4	17245	-8.92	0.29		150-cavity	10	65
-	Relenza	-8.89	0.30 (0.5 – 2.5)		SA-cavity	230	12
5	131612	-8.82	0.34		SA-cavity	26	29
6	106920	-8.82	0.34		430-cavity	99	71

7	350191	-8.80	0.35		SA-cavity	336	113
8	148354	-8.74	0.39		430-cavity	225	184
9	5069	-8.73	0.40		SA-cavity	143	101
10	37245	-8.61	0.48		150-cavity 430-cavity	16	285
11	327705	-8.59	0.50		150-cavity 430-cavity	29	13
12	45582	-8.45	0.63		430-cavity	370	376
13	327704	-8.29	0.83		SA-cavity 430-cavity	30	9
14	72254	-8.17	1.02		430-cavity	152	74
15	45576	-8.16	1.04		150-cavity	17	370

16	164640	-8.14	1.07		SA-cavity 150-cavity	884	90
17	141562	-8.12	1.11		SA-cavity	633	161
18	135371	-8.05	1.25		SA-cavity	459	31
19	90630	-7.97	1.43		150-cavity 430-cavity	337	277
20	117079	-7.90	1.61		SA-cavity 430-cavity	154	232
21	372294	-7.81	1.87		430-cavity	200	46
22	18312	-7.69	2.29		150-cavity	117	303
23	70194	-7.62	2.58		SA-cavity	328	1091

24	59620	-7.55	2.9		150-cavity	131	267
-	Peramivir	-7.43	3.55 (0.2 – 1.4)		SA-cavity	1210	49
25	46080	-7.43	3.55		430-cavity	5	3
-	DANA	-7.27	4.65		SA-cavity	763	279
26	371688	-7.18	5.42		430-cavity	246	27
27	16163	-6.56	15.43		150-cavity	518	675

[0189] Table 2 shows the 27 identified compounds ranked by their weighted mean energy (kcal/mol) from the Relaxed Complex Scheme. Also listed in Table 2 are the predicted Ki (μM) as calculated from the weighted mean binding energy, the chemical structure, and the predicted binding site. Experimental IC_{50} values (nM/L) for Tamiflu, Relenza and peramivir are denoted with parenthesis [38]. For comparison, the last two columns indicate the compounds' relative rank (among all 1883 NCI Diversity Set I compounds and the four control compounds screened) in the crystal structure screenings. Underlined hits are those identified from the ensemble screens that were not identified by the crystal structure screens.

[0190] In the screen of the closed-loop crystal structure, four of the seven selected hits dock in the sialic acid cavity and the other three dock in the 430-cavity (Fig. 3a). The 150-loop is in the closed conformation in this crystal structure, therefore no ligands are able to bind in the area as there is no 150-cavity. The results show that compounds exhibit greater affinity for the sialic acid cavity in the closed-loop structure

than in the open-loop structure; more compounds dock to the sialic acid cavity in the closed-loop structure and these compounds possess lower binding energies on average than the compounds docked to the sialic acid cavity of the open-loop structure (Tables S2, S3). With Tamiflu as an example, it appears that ligand-binding to the sialic acid cavity is better stabilized when the 150-loop is in the closed conformation.

Results from the apo-ensemble screens

[0191] Apo-1 is characterized by the wide-open conformations of both the 150-loop and the 430-loop (Fig. 1a), revealing the presence of the so-called "wide-open" 150-cavity and "wide-open" 430-cavity, respectively. This degree of loop flexibility is not observed in the crystal structures and the large outward shift of the 150-loop in particular has a profound effect on ligand binding. Six out of seven selected hits for this structure—and Tamiflu, notably—dock in the wide-open 150-cavity (Fig. 2b). Only one of the selected hits docks in the sialic acid cavity and none in the wide-open 430-cavity (Fig. 2b). As the 150-loop contains several important residues experimentally known to stabilize Tamiflu binding, the wide-open 150-loop conformation may cause Tamiflu to dock irregularly in this structure. The fact that no hits dock in the wide-open 430-cavity agrees with findings from the CS-Map analysis that hot spots in the 430-cavity disappear when the 430-loop opens past a certain point [7].

[0192] As previously discussed, Apo-2 is structurally similar to the open-loop crystal structure with the notable exception of a more open 430-loop conformation, which is still less open than the wide-open 430-loop conformation in Apo-1 (Fig. 1a). The open 430-loop conformation defines the presence of a corresponding "open" 430-cavity. Four of the six selected hits for this structure dock in the open 430-cavity and two hits dock in the sialic acid cavity (Fig. 2c). One potential butterfly compound docks primarily in the open 430-cavity, but also extends into the sialic acid cavity with a primary amide functional group. Despite its structural similarity to the open 150-loop crystal structure, no hits dock to the open 150-cavity in Apo-2 (Fig. 2c). Based on this analysis, it seems that the open 430-cavity may be a region of higher affinity than the open 150-cavity. This conclusion substantiates findings from the CS-Map analysis, which found more favorable hot spots in the open 430-cavity than in the open 150-cavity in this structure [7].

[0193] Apo-3 is structurally similar to the closed-loop crystal structure in the 150-loop region, but differs in the open conformation of the 430-loop and the subsequent

presence of the open 430-cavity (Fig. 1a). Two of the three selected hits for this structure dock in the open 430-cavity and one hit docks in the sialic acid cavity (Fig. 2d). As the 150-loop is in the closed conformation, the 150-cavity is absent in Apo-3. Fewer hits were selected from the virtual screen of Apo-3 than from other apo-ensemble screens because fewer compounds met the clustering and druglikeness selection criteria. This may be due to the binding opportunities excluded by the closed 150-cavity and may suggest that the opening of the 150-loop has an allosteric affect on ligand-receptor interactions in the sialic acid cavity and 430-cavity.

[0194] Many compounds are identified that exhibit high affinity for 150- and 430-cavities in the apo-ensemble structures. The wide-open 150-cavity and the open 430-cavity are regions of particularly high affinity that are notably not present in the crystal structures (Fig. 1a). A number of hits that dock in these two cavities might reasonably be linked to known inhibitors or to hits that dock in the sialic acid cavity to form the framework for a novel, bridged inhibitor.

Results from the holo-ensemble screens

[0195] Holo-1 is structurally similar to the open-loop crystal structure (Fig. 1b). Holo-1 possesses an open 150-loop conformation and an open 430-loop conformation that corresponds to an open 150 cavity and an open 430-cavity, respectively. Three of the four selected hits for this structure dock in the sialic acid cavity. One hit docks primarily in the 430-cavity but extends into the sialic acid cavity with a sulfate functional group (Fig. 3b). This latter compound is notable for its possible bridging interactions. No hits dock to the open 150-cavity. This pattern is similar to the clustering observed in the screen Apo-2, which is structurally similar to the open-loop crystal structure and Holo-1; Holo-1 and Apo-2 have an alpha-carbon binding site RMSD of 0.83 Å. It appears that the open 430-cavity is a region of higher affinity than the open 150-cavity. This conclusion is also supported by findings from the CS-Map analysis, which found more favorable hot spots in the open 430-cavity than in the open 150-cavity [7].

[0196] In the Holo-2 structure, the conformation of the 150-loop is in-between the open and closed positions seen in the two crystal structures (Fig. 1b). This so-called "half-open" 150-loop conformation and the subsequent "half-open" 150-cavity represent a distinct conformation not observed in the crystal structures or in the apo-ensemble. The conformation of the 430-loop in Holo-2 is open, corresponding to an open 430-cavity.

One of the four selected hits for this structure docks to the sialic acid cavity and two hits dock to the 430-cavity (Fig. 3b). One hit docks simultaneously to the 430-cavity and the half-open 150-cavity and its bridging possibilities. Perhaps due to the reduced 150-cavity size, fewer hits dock to the half-open 150-cavity than to the open 150-cavity.

[0197] Holo-3 possesses another unique intermediary conformation in which the 150-loop is more open in comparison to the open-loop crystal structure but less open in comparison to the wide-open 150-loop conformation seen in Apo-1 (Fig. 1b). The conformation the 430-loop in Holo-2 is open, corresponding to an open 430-cavity (Fig 3d). All of the three selected for this structure hits dock in the active site. One of these hits extends into the 150-cavity with a methyl-chlorobenzene functional group. This latter compound possesses bridging potential. Notably, no hits dock into the open 430-loop in Holo-3. Again, fewer hits were selected from the Holo-3 screen due to the fact that they did not meet the clustering and druglikeness criteria. The average ligand-binding affinity for Holo-3 is also reduced in comparison to the other seven structures (Table S2, S3).

Table S3

Ligand	Weighted RC Mean	RC Mean	RC Min.	RC STD	Ensemble Mean	Ensemble Min.
109836	-10.42	-10.00	-11.08	0.71	-9.82	-10.41
211332	-10.13	-10.05	-12.34	0.88	-10.07	-10.89
45583	-9.78	-9.09	-10.58	0.85	-10.01	-10.53
Tamiflu	-9.60	-9.05	-10.63	1.06	-9.62	-10.24
17245	-8.92	-8.64	-9.74	0.62	-9.09	-9.58
Relenza	-8.89	-8.00	-10.22	1.41	-8.17	-9.41
131612	-8.82	-8.44	-10.00	0.92	-8.59	-9.33
106920	-8.82	-7.11	-10.23	0.96	-8.39	-9.32
350191	-8.80	-8.36	-10.29	0.89	-8.51	-10.00
148354	-8.74	-8.00	-9.62	0.83	-8.75	-9.70
5069	-8.73	-8.31	-9.85	0.83	-7.89	-8.97
37245	-8.61	-8.34	-9.61	0.77	-8.12	-8.84
327705	-8.59	-8.27	-9.44	0.80	-8.79	-9.39
45582	-8.45	-8.07	-9.77	0.81	-7.91	-8.50
327704	-8.29	-7.86	-10.04	0.95	-8.44	-8.96
72254	-8.17	-8.13	-9.40	0.70	-8.31	-8.61
45576	-8.16	-8.33	-9.32	0.49	-7.96	-8.33
164640	-8.14	-8.05	-9.54	0.76	-8.38	-9.06
141562	-8.12	-8.44	-10.65	0.93	-8.43	-9.71
135371	-8.05	-7.87	-9.80	0.76	-8.05	-8.22
90630	-7.97	-7.70	-9.73	0.63	-8.24	-9.71
117079	-7.90	-8.67	-10.41	0.91	-9.78	-10.89
372294	-7.81	-7.86	-9.32	0.50	-7.97	-8.36
18312	-7.69	-7.66	-9.88	0.73	-7.60	-7.88
70194	-7.62	-8.00	-9.92	0.77	-7.61	-7.86
59620	-7.55	-7.76	-9.42	0.62	-7.82	-8.25
Peramivir	-7.43	-6.99	-8.74	1.17	-7.37	-8.08

46080	-7.43	-7.02	-9.92	1.09	-7.83	-8.70
DANA	-7.27	-7.11	-8.54	0.63	-7.49	-7.77
371688	-7.18	-7.53	-9.21	0.80	-7.90	-8.71
16163	-6.56	-6.84	-8.28	0.81	-6.40	-7.16

[0198] Table S3 shows 27 hits, the hits are re-ranked by their weighted RC mean. The weighted RC mean is the mean energy (kcal/mol) of each ligand to each of the 27 clusters of the non-redundant set, weighted by the percentage of time the receptor spends in each cluster. This value is shown in comparison to the energy predicted from the holo crystal structure alone, the average predicted energy from the three most dominant holo clusters, and the unweighted RC mean.

[0199] In general, fewer compounds met the cut-off criteria in the holo-ensemble screens than in the apo-ensemble screen. As a result, the holo-ensemble contributed fewer compounds to the final recommended set than the apo-ensemble (Tables S2, S3). Many of the hits identified by the holo-ensemble screens contain small, six-member rings similar to the structure of Tamiflu. The binding of Tamiflu in the active site may also allosterically reduce the protein's affinity for other compounds. The holo-ensemble also exhibited less 150- and 430-loop flexibility than the apo-ensemble, most likely due to interactions between residues in the 150-loop and Tamiflu. Despite the reduced flexibility, several new compounds are identified that bind in the sialic acid cavity, 150-cavity and 430-cavity.

Results from the relaxed complex scheme

[0200] The redocking of ligands into the 27 non-redundant structures representing the entire holo MD ensemble attempts to account for receptor flexibility and provides a corresponding "binding spectrum" for each compound. The ligand-binding spectra demonstrate remarkably similar trends between the minimum, mean and weighted binding free energies obtained from virtual screening against the three dominant holo-ensemble receptor structures (75% variance) and re-docking against the full holo-receptor ensemble (27 cluster representative structures, 100% variance) (Table S3). Some minor deviations are expected due to the 25% information loss using the three most dominant structures, compared to docking against the complete 27 cluster representatives. The comparison of binding spectra provides clear statistical support and justification for the RC virtual screening approach in terms of employing the dominant holo- and apo-ensembles. With a small number of representative structures as determined by the RMSD-

based clustering technique, the majority of the sampled conformational space is captured. The subsequent screening of large compound libraries against the reduced set of receptor structures is then possible without sacrificing binding energy accuracy. Ultimately, the mean weighted binding free energy is used to provide the final ranking for the top 27 hits and four control compounds presented in Table 2.

Refinement based on the relaxed complex scheme (RCS)

[0201] The RCS combines the advantages of docking algorithms with dynamic structural information provided by MD simulations, explicitly accounting for the flexibility of both the receptor and docked ligands. The development of computational tools for computer-aided drug design depends on the critical compromise between accuracy and computational costs. Ideally, the most reliable prediction of molecular affinity can be obtained through rigorous free energy calculations of the ligand-binding process [23-34]. The goal of the RCS has been to account for receptor flexibility in a relatively computationally inexpensive manner.

[0202] The top compounds were redocked into the entire, non-redundant holo-ensemble. The rationale for using the holo-ensemble for the re-dockings is two-fold. First, biologically, the neuraminidase receptor may be interacting with its natural sialic acid substrate before any other ligand gains access to the active site. Therefore the Tamiflu-bound holo-ensemble may be considered a better approximation to the receptor structures *in vivo* because of the ligand-induced effect on the binding site. Additionally the use of the holo-ensemble has been supported by recent work on RC methodology [13] and the application of the method to the discovery of inhibitors against an RNA editing ligase in *Trypanosoma brucei*, the parasite responsible for African sleeping sickness [35].

[0203] The inclusion of Tamiflu, Relenza, peramivir, and DANA as positive controls indicates that this method may be able to properly rank the controls relative to one another, given the ± 2 kcal/mol standard error of AutoDock (Table 2). The ranking of the four control ligands is correct, with the exception of peramivir, which is ranked lower than what is expected based on its experimental IC_{50} values. One possible explanation may be that the Tamiflu-bound holo-ensemble, though it represents a more realistic receptor than the apo-ensemble, may be biased towards Tamiflu-like compounds (a six-member ring scaffold) over others such as peramivir (a cyclopentane scaffold). The correct rank-order prediction of Tamiflu, Relenza, and DANA supports this rationale.

Identified compounds that bind in the sialic acid cavity

[0204] Sixteen hits were isolated that bind within the sialic acid cavity in one or more of the eight N1 structures (Table 2). Of these sixteen compounds, three exhibit mean weighted binding energies lower than that of Tamiflu: NSC109836, NSC211332 and NSC45583. NSC45583 also cross-binds to the 150-cavity and the 430-cavity. NSC109836 and NSC211332 are two similar structures that both contain a nitrogen-heavy six-member ring. Both compounds interact heavily with catalytic and framework residues known to be important in cleaving sialic acid [36]. These two hits represent promising starting points for the development of new sialic acid cavity inhibitors.

[0205] NSC109836 consistently binds in the sialic acid cavity and may not be affected by the motion of the 150- and 430-loops (Fig. 4a). In its lowest energy conformation, docking to the closed-loop crystal structure, the diimino-triazinane functional group forms hydrogen bonds to framework residues E119 and S179 and the hydoxy(oxido)amino functional group forms hydrogen bonds to the catalytic arginine trio (R118, R292 and R371) in the same manner as the carboxylate functional group of Tamiflu [36]. Importantly, residues R118, S179, and R371 were also identified as important hydrogen-bond mediators by CS-Map analysis [7]. NSC109836 also forms non-hydrogen-bonding interactions with known catalytic residues D151, R224, E276, and Y406 and framework residues R156, W178, E227 and E277 [36]. Of these residues, all except E276 and Y406 are also predicted to mediate non-bonded interactions by the CS-Map analysis [7].

[0206] NSC211332 also binds consistently in the sialic acid cavity regardless of 150- or 430-loop motion. It is a diaminohexahydro-carbonitrile that in its lowest energy pose, docking to Apo-3, forms hydrogen bonds to framework residues E119 and E227 [36]. NSC211332 also forms non-hydrogen bonding interactions with catalytic residues D151, R152 and Y406 and with framework residue W178 [36]. Residue E227 is predicted to be an important hydrogen-bond mediator by the CS-Map analysis and D151, R152 and W178 are recognized as important non-bonded interaction mediators [7].

Identified compounds that bind in the 150-cavity

[0207] As the open 150-loop conformation appears to be unique to N1, the 150-cavity may be a promising target for novel, selective inhibitors against the pandemic

strain. Compounds may inhibit N1 by binding to this area alone or when bridged to active site binders. Ten compounds exhibit high affinity for open or wide-open 150-cavity in one or more of the eight N1 structures (Table 2). Six compounds exhibit high affinity the wide-open 150-cavity in Apo-1 (Table S2), these compounds were identified using the receptor-ensemble as described herein.

[0208] NSC16163 is one of the six compounds that bind the wide-open 150-cavity in Apo-1 (Fig. 4b). NSC16163 surprisingly binds with high affinity in the wide-open 150-cavity and does not bind favorably in the open 150-cavity, which may explain its relatively low ranking despite its many strong interactions with the protein. It is an acidic naphthalene-based structure that forms hydrogen bonds with Q136, L134, D151, R156 and R430; all except L134 are also predicted to be important hydrogen-bond mediators by CS-Map analysis [7]. NSC16163 also interacts with V149 and T439 through non-hydrogen-bonding interactions in agreement with the CS-Map analysis. Though NSC16163 does not bind directly in the sialic acid cavity, it interacts with catalytic residue D151 and framework residue R156, suggesting that it may inhibit NA activity [36].

[0209] Several other naphthalene-based compounds also bind with high affinity in the 150-cavity, interacting through hydrophobic interactions to the hydrophobic naphthalene group and through hydrogen-bonding interactions to polar functional groups on the naphthalene base (Table 2). These compounds include NSC45576, NSC45583, NSC37245 and NSC327705.

[0210] Some of the highest affinity hits to the open and wide-open 150-cavity are steroids such as NSC17245, NSC18312 and NSC59620. These compounds interact with the 150-cavity primarily through hydrophobic interactions, specifically to hydrophobic residues V116, I117, L134, T135, S145, T148, V149, P431, I437, W438 and T439. Of these residues, V116, V149, P431 and T439 are also predicted to be important non-bonded interaction mediators by CS-Map analysis [7]. These compounds also interact with catalytic and framework residues—most notably R118, D151 and R156—known to be important in cleaving sialic acid [36].

Identified Compounds that bind in the 430-cavity

[0211] Similar to the wide-open 150-cavity, the open 430-cavity is seen only in MD simulations and not observed in the crystal structures. Thus hits to the open 430-

cavity from the apo- and holo-ensemble screens are found only through the utilization of the representative receptor-ensemble. Thirteen hits to the 430-cavity were identified among the top 27 hits (Table 2).

[0212] Similar to the 150-cavity, the 430-cavity may favor naphthalene-based compounds, namely NSC148354, NSC45582, NSC37245 and NSC327705. These compounds interact through hydrophobic interactions to hydrophobic residues P326, Y347, S370, W403, S404, Y406, I427, G429, P431, I437, W438 and T439 in the 430-cavity. Residues S404, Y406, I427, P431 and T439 are also indicted by CS-Map analysis to be important in mediating non-bonded interactions [7].

[0213] NSC148354 is one example of a naphthalene-based compound that binds with high affinity to the open 430-cavity seen only in MD simulations. In its lowest energy conformation, docking to Holo-2, NSC148354 forms hydrogen bonds to residues N369 and R371; R371 is predicted by CS-Map analysis to be a hydrogen bond mediator [7]. NSC148354 also interacts through non-bonded interactions to Y347, S370, W403, S404, I427, R428, P431 and K432; S404, I427, R428, P431 and K432 are predicted to mediate non-bonded interactions by CS-Map analysis [7]. Of these residues, R371 is identified as a catalytic residue [36]; though NSC148354 does not bind in the sialic acid cavity, it may still inhibit NA sialidase activity through hydrogen bonding with R371.

[0214] Other compounds with hydrophobic benzene rings, similar to naphthalene, also bind in the open 430-cavity with high affinity. For example, NSC90630, NSC106920, NSC327704, NSC371688, NSC372294 and NSC46080 all bind in the 430-cavity with strong interactions to the same hydrophobic residues listed previously. NSC46080 is an interesting benzodiazepine that is highly ranked in the crystal structure screens but poorly ranked in the apo- and holo-ensemble screens and the RCS redocking (Table 2). Figure 4a shows the open 150-loop crystal structure (2HTY) with NSC46080 and NSC109836 bound. NSC46080 docks similarly in both crystal structures, its overlapping position is shown in Fig. 4a. NSC109836 also docks similarly in both crystal structures, and its overlapping position is shown in Fig. 4a.

Identified Compounds that bind across cavities

[0215] Of the identified compounds, seven compounds dock simultaneously to more than one cavity (Table 2). Four compounds dock in the sialic acid cavity and either the 150-cavity or the 430-cavity. These compounds are of particular interest because they

may be linked to known inhibitors to form a novel, bridged inhibitor that may bind with higher affinity than un-bridged compounds alone.

[0216] Three hits-- NSC45583, NSC327704 and NSC117079-- dock primarily with hydrophobic interactions in the 430-cavity and extend a polar function group into the sialic acid cavity. Of these three compounds, NSC327704 and NSC117079 may be candidates for bridging to Tamiflu with a distance of 1.47 Å and 2.19 Å, respectively, between the carboxylate group of Tamiflu and the closest possible linker atom. NSC45583 has a distance of 5.20 between the carboxylate group and the closest linker atom. Though NSC45583 binds with high affinity to four out of eight N1 structures, it binds very differently to each structure.

[0217] NSC16460 may be a promising cavity-bridging compound. NSC16460 finds its lowest energy pose when docking to Holo-3. NSC16460 contains a diamino-triazine group that binds in the sialic acid cavity and forms hydrogen bonds to catalytic residue R118 and to framework residues S179 and E277 [36]. Of these three residues, S179 and E277 are also predicted to mediate hydrogen-bonding by the CS-Map analysis [7]. NSC16460 also interacts through non-bonded interactions to catalytic residues D151 and Y406 and framework residues E119, R156, W178 and E227 [36]. All of the above mentioned residues are predicted to mediate non-bonded interactions by the CS-Map analysis [7]. NSC16460 binds simultaneously to the open 150-cavity through hydrophobic contacts to residues I117, T135, Q136 and T439, which are mediated by a methyl-chlorobenzene group on the ligand. The CS-Map analysis predicted that Q136 and T439 are important mediators of non-bonded interactions [7]. Unlike the other three hits that bind in the sialic acid cavity, NSC16460 may not need to be linked to sialic acid. NSC16460 may naturally bridge the catalytic residues in the sialic acid cavity to the high-affinity open 150-cavity.

Identifying Possible Aggregators

[0218] Table 2compounds were compared to a list of 263 known false-positives [37]. These so-called "promiscuous inhibitors" are irregular compounds that inhibit non-specifically by forming aggregates onto which the protein will adsorb and thus block activity [34, 35]. A similarity search (Tanimoto index 98%) was performed to identify false-positives within the Table 2compounds and no false-positives were identified.

Identification of 27 drug like compounds

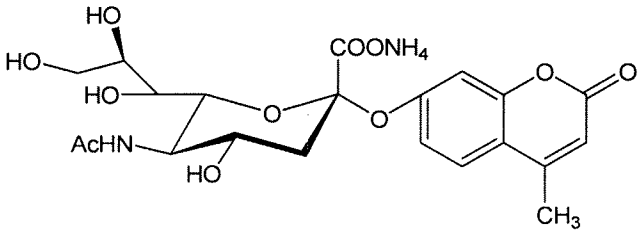
[0219] Through eight different virtual screens of the NCI diversity set I, which employed structures taken from crystallographic studies as well as representative structures from apo and holo MD simulations, 27 drug-like compounds have been identified that bind with high affinity to avian influenza N1. Fourteen of these compounds are unique hits that were not identified by the crystal structure screens alone, and they include compounds that bind to flexible loop regions unseen in the crystal structures. The docking of thousands of compounds to the N1 binding site elucidated specific regions of high ligand-binding affinity in the flexible 150- and 430-loop cavities. These cavities and the residue contacts observed among the top hits strongly agree with the location of hot spots and residues predicted to mediate receptor-ligand interactions by a recent CS-Map analysis. The compounds of interest are validated and ranked through re-docking experiments into a set of structures representing the holo ensemble within the RCS framework. The method described herein identified 27 drug-like compounds available from the NCI diversity set that may yield viable new compounds and scaffolds for future antiviral development against N1.

Example 1-2

Experimental

In-vitro Test for Recombinant Neuraminidase from H5N1

[0220] Fluorescence based neuraminidase assay was determined as previously described (Potier *et al.*, "Fluorometric assay of neuraminidase with a sodium (4-methylumbelliferyl-alpha-D-N-acetylneuraminate) substrate," Anal. Biochem., 1979, 94:287-96). Recombinant N1 influenza enzyme was incubated in a reaction buffer containing 33 mM MES, pH 6.5, and 4 mM calcium chloride, with or without inhibitors. Two inhibitor concentrations were used: 200 mM in the first round and 20 μM in the second round. After 30 min at 37 °C, the fluorescent substrate 4-Methylumbeliferyl-*N*-acetyl-a-*D*-neuramininic acid ammonium salt (4MU-NANA) was added to a final concentration of 50 μM. Reactions were stopped after 1, 15, and 30 minutes at 37 °C with the addition of 0.014 mM sodium hydroxide in 83% ethanol. Fluorescence was quantified with a Spectrofluorometric detector (RF-551), using an excitation wavelength of 362 nm and emission wavelength of 448 nm.



4-Methylumbeliferyl-N-acetyl-α-D-neuramininic acid Ammonium salt

Example 1-5

In-Vitro Test Results

[0221] Table 3 shows the in vitro results from testing 26 ligands with one reference compound. The reference compound was oseltamivir and was purified from Tamiflu by using HPLC. Two kinds of concentration were used: 200 mg/L for 26 compounds; and then 20 μg/L for the 6 compounds with the highest inhibition. The MW of the 26 ligands were considered to all be similar and the in vitro testing was blinded. Thus, the same concentration for each compound was used in the assay, about 400 μM and about 40 nM), respectively. The percent inhibition for each ligand was compared at different reaction times. After 30 min 23 compounds from among 26 compounds showed some inhibition at 200 mg/L. The inhibition ranged from 6.3% to 89.8% at 200 mg/L. The oseltamivir (reference compound) showed 62% inhibition at 200 mg/L. The 6 compounds that had the highest percent inhibition at 200 mg/L were chosen for the 20 μg/L in vitro test. The percent inhibition ranged from 6 to 21% for these 6 compounds. Oseltamivir showed very low inhibition at this concentration.

Table 3: Invitro Screening

Screening					
		First		Second	
sample		200 mg/L		20 μg/L	
No.	Ligands	Inhibition %	Ranking from In-vitro	Inhibition %	Ranking from In-vitro
1	59620	6.3	22		
2	106920	69	9		
3	45576	59	12		
4	37245	2.2	23		
5	16163	26.5	17		
6	350191		NA		

7	46080	49.9	14		
8	90630		NA		
9	109836	63.9	11		
10	17245	14.2	20		
11	371688	34.9	16		
12	135371	53.4	13		
13	164640	42.6	15		
14	117079	89.8	1	21	1
15	70194		NA		
16	327705	73.4	7		
17	372294	88.3	2	17	4
18	18312	20.1	18		
19	327704	72	8	6	6
20	148354	78	5		
21	72254	7.3	21		
22	5069	81	4	19	2
23	131612	16.2	19		
24	45583	85.9	3	8	5
25	211332	70.2	10		
26	141562	75.6	6	18	3
	Oseltamivir	62			

[0222] Table 4 shows that by screening only 26 compounds out of the NCI diversity set I, six compounds were identified that showed inhibition ranging from about 6% to about 21% at 20 μg/L.

Table 4: Comparison of In vitro and Simulation Results

	Simulation Ranking		20 ug/L	
Ligands	RCS hit	RC Mean	Inhibition	Ranking from In-vitro
59620				
106920	6	-9.2		
45576	22	-8.2		
37245	11	-9.02		
16163	31	-7.07		
350191	8	-9.14		
46080	23	-8.5		
90630	13	-8.89		
109836	1	-10.63		
17245	7	-8.92		
371688	29	-7344		
135371	21	-8.28		
164640	20	-8.37		

117079	**17**	**-8.72**	**21%**	**1**
70194	26	-7.74		
327705	15	-8.83		
372294	**24**	**-7.92**	**17%**	**4**
18312	27	-7.72		
327704	**18**	**-8.6**	**6%**	**6**
148354	9	-9.12		
72254	19	-8.47		
5069	**14**	**-8.83**	**19%**	**2**
131612	10	-9.1		
45583	**3**	**-10.09**	**8%**	**5**
211332	**2**	**-10.34**		
141562	**16**	**-8.78**	**18%**	**3**
Oseltamivir	4	-9.82		
Zanamivir	5	-9.38		
45582	12	-8.6		
Peramivir	25	-7.79		
SA	28	-7.47		
DANA	30	-7.41		

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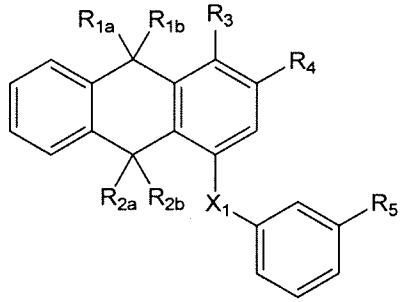
WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising an agent and a pharmaceutically acceptable carrier, wherein the agent is a compound having the formula (**I**):



(**I**)

or a pharmaceutically acceptable salt or prodrug thereof wherein:

(a) $\mathbf{R^{1a}}$ and $\mathbf{R^{1b}}$ are each separately selected from the group consisting of H (hydrogen), -C(O)N$\mathbf{R^{1c}R^{1d}}$, –C(O)O$\mathbf{R^{1e}}$, –C(S)N$\mathbf{R^{1c}R^{1d}}$, –C(S)O$\mathbf{R^{1e}}$, –NHC(O)$\mathbf{R^{1e}}$, -NHC(O)N$\mathbf{R^{1c}R^{1d}}$, –NHC(O)O$\mathbf{R^{1e}}$, -NHC(S)N$\mathbf{R^{1c}R^{1d}}$, –NHC(S)O$\mathbf{R^{1e}}$, -OC(O)N$\mathbf{R^{1c}R^{1d}}$, -OC(O)O$\mathbf{R^{1e}}$, –OC(S)N$\mathbf{R^{1c}R^{1d}}$, -O$\mathbf{R^{1f}}$, and -N$\mathbf{R^{1c}R^{1d}}$; or $\mathbf{R^{1a}}$ and $\mathbf{R^{1b}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

each $\mathbf{R^{1c}}$ and $\mathbf{R^{1d}}$ is independently selected from the group consisting of H (hydrogen), $C_{1\text{-}6}$ alkyl, heteroaryl, and aryl, or $\mathbf{R^{1c}}$ and $\mathbf{R^{1d}}$ are optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

each $\mathbf{R^{1e}}$ is independently selected from the group consisting of H (hydrogen), aryl, and $C_{1\text{-}6}$ alkyl optionally substituted with up to 5 fluoro;

each $\mathbf{R^{1f}}$ is independently selected from the group consisting of H (hydrogen), aryl, and $C_{1\text{-}6}$ alkyl optionally substituted with up to 5 fluoro;

(b) $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are each separately selected from the group consisting of H (hydrogen), -C(O)N$\mathbf{R^{2c}R^{2d}}$, –C(O)O$\mathbf{R^{2e}}$, –C(S)N$\mathbf{R^{2c}R^{2d}}$, –C(S)O$\mathbf{R^{2e}}$, –NHC(O)$\mathbf{R^{2e}}$, -NHC(O)N$\mathbf{R^{2c}R^{2d}}$, –NHC(O)O$\mathbf{R^{2e}}$, -NHC(S)N$\mathbf{R^{2c}R^{2d}}$, –NHC(S)O$\mathbf{R^{2e}}$, -OC(O)N$\mathbf{R^{2c}R^{2d}}$, -OC(O)O$\mathbf{R^{2e}}$, –OC(S)N$\mathbf{R^{2c}R^{2d}}$, -O$\mathbf{R^{2f}}$, and -N$\mathbf{R^{1c}R^{1d}}$; or $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

each $\mathbf{R^{2c}}$ and $\mathbf{R^{2d}}$ is independently selected from the group consisting of H (hydrogen), $C_{1\text{-}6}$ alkyl, and aryl, or $\mathbf{R^{2c}}$ and $\mathbf{R^{2d}}$ are optionally taken together with

the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

each $\mathbf{R^{2e}}$ is independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

each $\mathbf{R^{2f}}$ is independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) $\mathbf{R^3}$ is selected from the group consisting of H (hydrogen), –NHC(O)$\mathbf{R^{3a}}$, -NHC(O)N$\mathbf{R^{3b}R^{3c}}$, –NHC(O)O$\mathbf{R^{3d}}$, -NHC(S)N$\mathbf{R^{3b}R^{3c}}$, –NHC(S)O$\mathbf{R^{3d}}$, -OC(S)N$\mathbf{R^{3b}R^{3c}}$, -O$\mathbf{R^{3e}}$, -S$\mathbf{R^{3e}}$, -N$\mathbf{R^{3b}R^{3c}}$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

$\mathbf{R^{3a}}$ is selected from the group consisting of aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

$\mathbf{R^{3b}}$ and $\mathbf{R^{3c}}$ are each separately selected from the group consisting of H (hydrogen), C_{1-6} alkyl, heteroaryl, and aryl, or $\mathbf{R^{3b}}$ and $\mathbf{R^{3c}}$ are optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

$\mathbf{R^{3d}}$ is selected from the group consisting of aryl, heteroaryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

$\mathbf{R^{3e}}$ is selected from the group consisting of H (hydrogen), aryl, heteroaryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(d) $\mathbf{R^4}$ is selected from the group consisting of H (hydrogen), -S(O)$_2$OH, -S(O)$_2$NH$_2$, -P(O)(OH)$_2$, -OP(O)(O$\mathbf{R^{4a}}$)$_2$, -S$\mathbf{R^{4b}}$, halo, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

each $\mathbf{R^{4a}}$ is independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

$\mathbf{R^{4b}}$ is selected from the group consisting of H (hydrogen), heteroaryl, aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(e) $\mathbf{R^5}$ is selected from the group consisting of -S(O)$_2$OH, -S(O)$_2$NH$_2$, -P(O)(OH)$_2$, -OP(O)(O$\mathbf{R^{5a}}$)$_2$, -S$\mathbf{R^{5b}}$, and halo;

each $\mathbf{R^{5a}}$ is independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

R^{5b} is selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro; and

(f) X_1 is selected from the group consisting of O (oxygen), S (sulfur) and $-NR^6$; where R^6 is H (hydrogen) or C_{1-6} alkyl.

2. The pharmaceutical composition of Claim 1, wherein:

R^{1a} and R^{1b} are taken together with the carbon to which they are attached to form keto; and

R^{2a} and R^{2b} are taken together with the carbon to which they are attached to form keto.

3. The pharmaceutical composition of any of Claims 1 to 2, wherein:

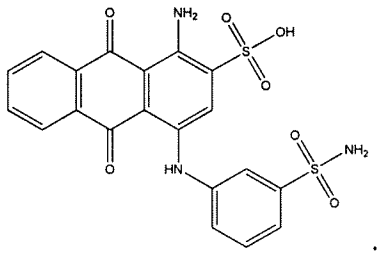
R^3 is $-NH_2$; and R^4 is $-S(O)_2OH$.

4. The pharmaceutical composition of any of Claims 1 to 3, wherein:

R^5 is selected from the group consisting of $-S(O)_2OH$, and $-S(O)_2NH_2$; and

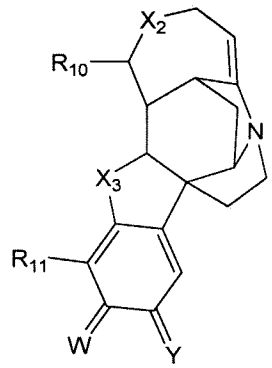
X_1 is $-NR^6$; where R^6 is H (hydrogen) or C_{1-6} alkyl.

5. The pharmaceutical composition of Claim 1, wherein the agent is:



6. The pharmaceutical composition of any of Claims 1 to 5, comprising a pill.

7. A pharmaceutical composition comprising an agent and a pharmaceutically acceptable carrier, wherein the agent is a compound having the formula **(II)**:



(II)

or a pharmaceutically acceptable salt or prodrug thereof wherein:

(a) R^{10} is selected from the group consisting of $-(CH_2)_nR^{10a}$;

(b) $\mathbf{R^{10a}}$ is selected from the group consisting of tetrazole, -C(O)$\mathbf{R^{10b}}$, and -C(S)$\mathbf{R^{10b}}$;

(c) $\mathbf{R^{10b}}$ is selected from the group consisting of H (hydrogen), -S$\mathbf{R^{10c}}$, -O$\mathbf{R^{10c}}$, -NH$\mathbf{R^{10c}}$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(d) $\mathbf{R^{10c}}$ is selected from the group consisting of H (hydrogen) and C_{1-6} alkyl;

(e) n is 0, 1, or 2;

(f) $\mathbf{R^{11}}$ is selected from the group consisting of tetrazole, -$S(O)_2OH$, -$S(O)_2NH_2$, -$P(O)(OH)_2$, nitro, -OP(O)(O$\mathbf{R^{11a}}$)$_2$, and -C(O)O$\mathbf{R^{11b}}$;

$\mathbf{R^{11a}}$ is selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

$\mathbf{R^{11b}}$ is selected from the group consisting of H (hydrogen), and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(g) W is O (oxygen) or S (sulfur);

(h) Y is O (oxygen) or S (sulfur); and

(i) $\mathbf{X_2}$ and $\mathbf{X_3}$ are each individually selected from the group consisting of O (oxygen), S (sulfur) and -NH.

8. The pharmaceutical composition of Claim 7, wherein:

$\mathbf{R^{10a}}$ is $-CH_2C(O)\mathbf{R^{10b}}$.

9. The pharmaceutical composition of any of Claims 7 to 8, wherein:

$\mathbf{R^{10a}}$ is $-CH_2C(O)O\mathbf{R^{10c}}$; and

$\mathbf{R^{11}}$ is selected from the group consisting of -$S(O)_2NH_2$, -$P(O)(OH)_2$, nitro, -OP(O)(O$\mathbf{R^{11a}}$)$_2$, and -C(O)O$\mathbf{R^{11b}}$.

10. The pharmaceutical composition of any of Claims 7 to 9, wherein:

$\mathbf{R^{10c}}$ is H (hydrogen);

$\mathbf{R^{11}}$ is selected from the group consisting of nitro, -OP(O)(O$\mathbf{R^{11a}}$)$_2$, and -C(O)O$\mathbf{R^{11b}}$;

$\mathbf{R^{11a}}$ is selected from the group consisting of H (hydrogen), and C_{1-6} alkyl;

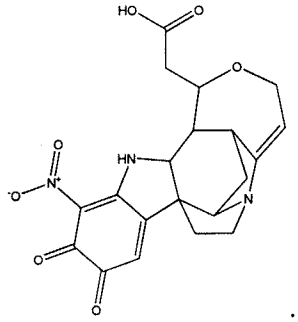
$\mathbf{R^{11b}}$ is H (hydrogen);

W is O (oxygen); and

Y is O (oxygen).

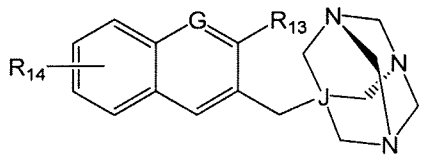
11. The pharmaceutical composition of Claim 7, wherein $\mathbf{X_2}$ is O (oxygen) and $\mathbf{X_3}$ is -NH..

12. The pharmaceutical composition of Claim 7, wherein the agent is:



13. The pharmaceutical composition of any of Claims 7 to 12, comprising a pill.

14. A pharmaceutical composition comprising an agent and a pharmaceutically acceptable carrier, wherein the agent is a compound having the formula (**III**):



(**III**)

or a pharmaceutically acceptable salt or prodrug thereof wherein:

(a) $\mathbf{R^{13}}$ is selected from the group consisting of H (hydrogen), $C_{1\text{-}6}$ alkoxy optionally substituted with up to 5 fluoro, and $C_{1\text{-}6}$ alkyl optionally substituted with up to 5 fluoro;

(b) $\mathbf{R^{14}}$ is one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, $C_{1\text{-}6}$ alkoxy optionally substituted with up to 5 fluoro, and $C_{1\text{-}6}$ alkyl optionally substituted with up to 5 fluoro;

(c) G is selected from the group consisting of CH and N (nitrogen); and

(d) J is selected from the group consisting of N^+ (nitrogen) and P^+ (phosphorous).

15. The pharmaceutical composition of Claim 14, wherein:

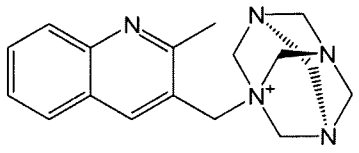
G is N (nitrogen).

16. The pharmaceutical composition of any of Claims 14 to 15, wherein:

$\mathbf{R^{13}}$ is selected from the group consisting of H (hydrogen) and $C_{1\text{-}6}$ alkyl optionally substituted with up to 5 fluoro; and

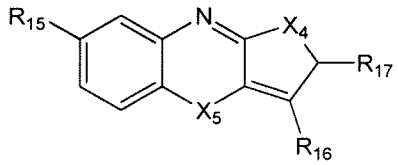
J is N^+ (nitrogen).

17. The pharmaceutical composition of Claim 14, wherein the agent is:



18. The pharmaceutical composition of any of Claims 14 to 17, comprising a pill.

19. A pharmaceutical composition comprising an agent and a pharmaceutically acceptable carrier, wherein the agent is a compound having the formula (**IV**):



(**IV**)

or tautomer thereof, or their pharmaceutically acceptable salts or prodrugs, wherein:

(a) $\mathbf{R^{15}}$ is selected from the group consisting of nitro, and -C(O)$\mathbf{R^{15a}}$;

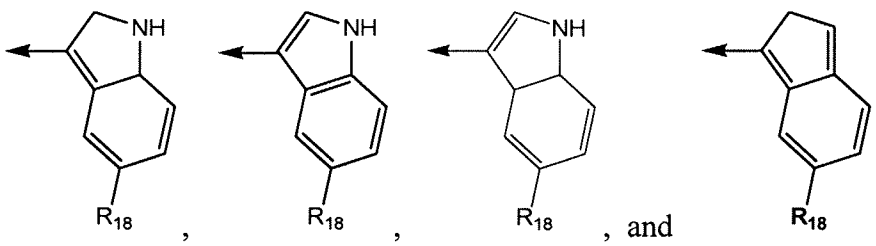
(b) $\mathbf{R^{15a}}$ is selected from the group consisting of H (hydrogen), -S$\mathbf{R^{15b}}$, and -O$\mathbf{R^{15b}}$;

(c) $\mathbf{R^{15b}}$ is selected from the group consisting of H (hydrogen) and $C_{1\text{-}6}$ alkyl;

(d) $\mathbf{R^{16}}$ is selected from the group consisting of H (hydrogen) and -O$\mathbf{R^{16a}}$;

(e) $\mathbf{R^{16a}}$ is selected from the group consisting of H (hydrogen), and $C_{1\text{-}6}$ alkyl;

(f) $\mathbf{R^{17}}$ is selected from the group consisting of:



(g) $\mathbf{R^{18}}$ is selected from the group consisting of $-(CH_2)_n\mathbf{R^{18a}}$ and -CH=CH$\mathbf{R^{18a}}$;

(h) **n** is 0, 1, or 2;

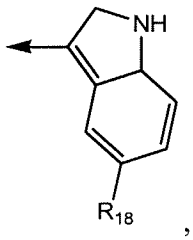
(i) $\mathbf{R^{18a}}$ is selected from the group consisting of -$\mathbf{SR^{18b}}$, -$\mathbf{OR^{18b}}$, aryl optionally substituted with one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro, and heteroaryl optionally substituted with one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

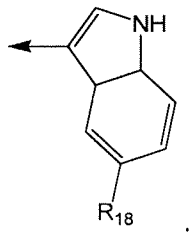
(j) $\mathbf{R^{18b}}$ is selected from the group consisting of aryl and heteroaryl, each optionally substituted with one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro; and

(k) $\mathbf{X_4}$ and $\mathbf{X_5}$ are each individually selected from the group consisting of O (oxygen), S (sulfur) and -NH.

20. The pharmaceutical composition of Claim 19, wherein:

$\mathbf{R^{17}}$ is selected from the group consisting of:



, and


.

21. The pharmaceutical composition of any of Claims 19 to 20, wherein:

$\mathbf{R^{18}}$ is–$(CH_2)_n\mathbf{R^{18a}}$;

n is 1; and

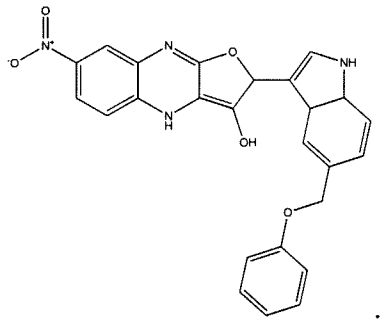
$\mathbf{R^{18a}}$ is -$\mathbf{OR^{18b}}$.

22. The pharmaceutical composition of any of Claims 19 to 21, wherein:

$\mathbf{R^{16}}$ is -$\mathbf{OR^{16a}}$; and

$\mathbf{R^{18b}}$ is aryl optionally substituted with one or more substituents each individually selected from the group consisting of OH, halo, cyano, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro.

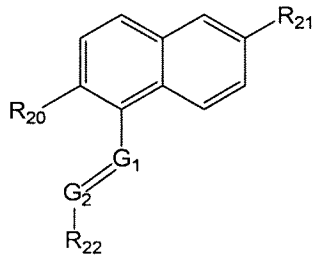
23. The pharmaceutical composition of Claim 19, wherein the agent is:



24. The pharmaceutical composition of Claim 19, wherein $\mathbf{X_4}$ is O (oxygen) and $\mathbf{X_5}$ is –NH.

25. The pharmaceutical composition of any of Claims 19 to 24, comprising a pill.

26. A pharmaceutical composition comprising an agent and a pharmaceutically acceptable carrier, wherein the agent is a compound having the formula (**V**):



(**V**)

or tautomer thereof, or their pharmaceutically acceptable salts or prodrugs, wherein:

(a) $\mathbf{R^{20}}$ is selected from the group consisting of H (hydrogen), -O$\mathbf{R^{20a}}$, -S$\mathbf{R^{20a}}$, -C(O)N$\mathbf{R^{20c}R^{20d}}$, –NHC(O)$\mathbf{R^{20e}}$;

(b) $\mathbf{R^{20a}}$ is selected from the group consisting of H (hydrogen), and $C_{1\text{-}6}$ alkyl optionally substituted with up to 5 fluoro;

(c) $\mathbf{R^{20c}}$ and $\mathbf{R^{20d}}$ are each separately selected from the group consisting of H (hydrogen), $C_{1\text{-}6}$ alkyl, heteroaryl, and aryl, or $\mathbf{R^{20c}}$ and $\mathbf{R^{20d}}$ are optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

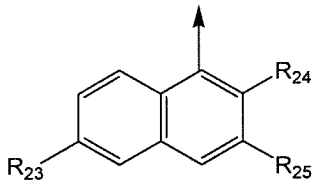
(d) $\mathbf{R^{20e}}$ is selected from the group consisting of H (hydrogen), aryl, and $C_{1\text{-}6}$ alkyl optionally substituted with up to 5 fluoro;

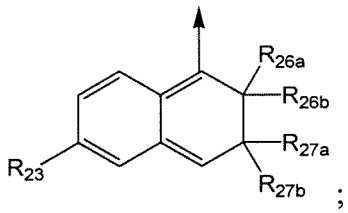
(e) $\mathbf{R^{21}}$ is selected from the group consisting of H (hydrogen), -$S(O)_2OH$, -$S(O)_2NH_2$, -$P(O)(OH)_2$, halo, -C(O)$\mathbf{R^{21a}}$, and -C(S)$\mathbf{R^{21a}}$;

(f) $\mathbf{R^{21a}}$ is selected from the group consisting of H (hydrogen), $-S\mathbf{R^{21b}}$, $-O\mathbf{R^{21b}}$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(g) $\mathbf{R^{21b}}$ is selected from the group consisting of H (hydrogen), and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(h) $\mathbf{R^{22}}$ is selected from the group consisting of:



and


;

(i) $\mathbf{R^{23}}$ is selected from the group consisting of H (hydrogen), $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -OH and C_{1-6} alkoxy optionally substituted with up to 5 fluoro;

(j) $\mathbf{R^{24}}$ is -OH or C_{1-6} alkoxy optionally substituted with up to 5 fluoro;

(k) $\mathbf{R^{25}}$ is selected from the group consisting of H (hydrogen), $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -OH and C_{1-6} alkoxy optionally substituted with up to 5 fluoro;

(l) $\mathbf{R^{26a}}$ and $\mathbf{R^{26b}}$ are each separately selected from the group consisting of H (hydrogen), -OH, C_{1-6} alkyl optionally substituted with up to 5 fluoro, and C_{1-6} alkoxy optionally substituted with up to 5 fluoro; or $\mathbf{R^{26a}}$ and $\mathbf{R^{26b}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

(m) $\mathbf{R^{27a}}$ and $\mathbf{R^{27b}}$ are each separately selected from the group consisting of H (hydrogen), -OH, C_{1-6} alkyl optionally substituted with up to 5 fluoro, and C_{1-6} alkoxy optionally substituted with up to 5 fluoro; or $\mathbf{R^{27a}}$ and $\mathbf{R^{27b}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

(n) $\mathbf{G_1}$ is selected from the group consisting of CH and N (nitrogen); and

(o) $\mathbf{G_2}$ is selected from the group consisting of CH and N (nitrogen).

27. The pharmaceutical composition of Claim 26, wherein:

$\mathbf{R^{20}}$ is H (hydrogen); and

$\mathbf{R^{21}}$ is H (hydrogen) or $-S(O)_2OH$.

28. The pharmaceutical composition of any of Claims 26 to 27, wherein:

R^{23} is H (hydrogen) or -$S(O)_2OH$;

R^{24} is –OH; and

R^{25} is H (hydrogen), or -$S(O)_2OH$.

29. The pharmaceutical composition of any of Claims 26 to 28, wherein:

G_1 is N (nitrogen); and

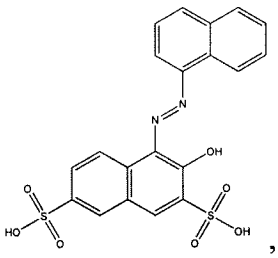
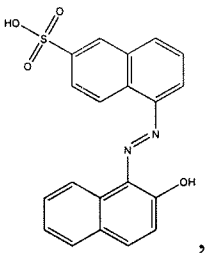
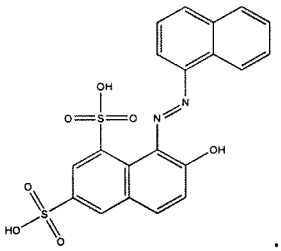
G_2 is N (nitrogen).

30. The pharmaceutical composition of any of Claims 26 to 29, wherein:

R^{26a} and R^{26b} are optionally taken together with the carbon to which they are attached to form a keto group; and

R^{27a} and R^{27b} are optionally taken together with the carbon to which they are attached to form a keto group.

31. The pharmaceutical composition of Claim 26, wherein the agent is selected from the group consisting of:


,

, and

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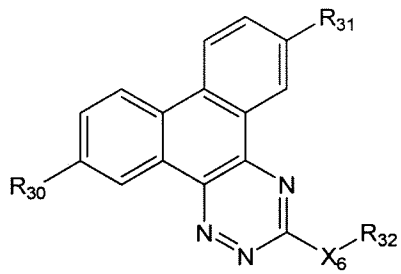
32. The pharmaceutical composition of any of Claims 26 to 31, comprising a pill.

33. A pharmaceutical composition comprising an agent and a pharmaceutically acceptable carrier, wherein the agent is a compound having the formula (**VI**):



(**VI**)

or tautomer thereof, or their pharmaceutically acceptable salts or prodrugs, wherein:

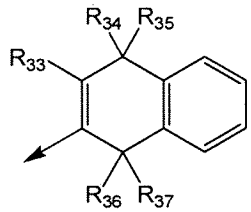
(a) R^{30} is selected from the group consisting of H (hydrogen), -OR^{30a}, -SR^{30a}, -$NR^{30b}R^{30c}$, -$S(O)_2OH$, -$S(O)_2NH_2$, -$P(O)(OH)_2$, -C(O)OH, -$CH_2C(O)OH$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(b) $\mathbf{R^{30a}}$ is selected from the group consisting of H (hydrogen) and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) $\mathbf{R^{30b}}$ and $\mathbf{R^{30c}}$ are each separately selected from the group consisting of H (hydrogen) and C_{1-6} alkyl, or $\mathbf{R^{30b}}$ and $\mathbf{R^{30c}}$ are optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

(d) $\mathbf{R^{31}}$ is selected from the group consisting of H (hydrogen), -OH, –SH, $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -C(O)OH, $-CH_2C(O)OH$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(e) $\mathbf{R^{32}}$ is selected from the group consisting of $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -C(O)OH, and $-CH_2C(O)OH$; or $\mathbf{R^{32}}$ is :



;

(f) $\mathbf{R^{33}}$ is selected from the group consisting of H (hydrogen), -OH, halo, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(g) $\mathbf{R^{34}}$ and $\mathbf{R^{35}}$ are each separately selected from the group consisting of H (hydrogen), -OH, halo, and C_{1-6} alkyl optionally substituted with up to 5 fluoro; or $\mathbf{R^{34}}$ and $\mathbf{R^{35}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

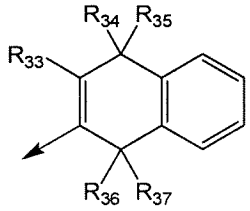
(h) $\mathbf{R^{36}}$ and $\mathbf{R^{37}}$ are each separately selected from the group consisting of H (hydrogen), -OH, -SH, and halo; or $\mathbf{R^{36}}$ and $\mathbf{R^{37}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group; and

(i) $\mathbf{X_6}$ is selected from the group consisting of O (oxygen), S (sulfur) and -NH.

34. The pharmaceutical composition of Claim 33, wherein:

$\mathbf{R^{30}}$ and $\mathbf{R^{31}}$ are H (hydrogen); and

$\mathbf{R^{32}}$ is :



35. The pharmaceutical composition of any of Claims 33 to 34, wherein:

$\mathbf{R^{34}}$ and $\mathbf{R^{35}}$ are optionally taken together with the carbon to which they are attached to form a keto group; and

$\mathbf{R^{36}}$ and $\mathbf{R^{37}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group.

36. The pharmaceutical composition of any of Claims 33 to 35, wherein $\mathbf{R^{33}}$ is halo.

37. The pharmaceutical composition of Claim 33, wherein:

$\mathbf{R^{30}}$ is H (hydrogen); and

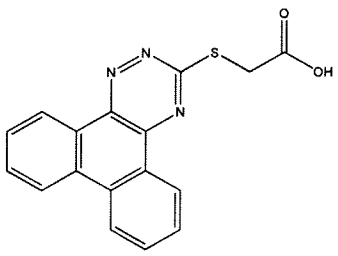
$\mathbf{R^{32}}$ is selected from the group consisting of $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -C(O)OH, and $-CH_2C(O)OH$.

38. The pharmaceutical composition of Claim 33, wherein:

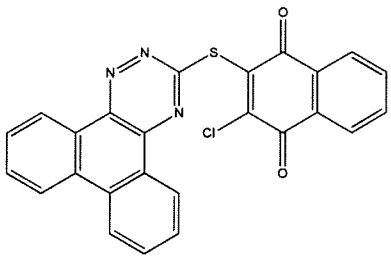
$\mathbf{R^{31}}$ is H (hydrogen); and

$\mathbf{R^{32}}$ is selected from the group consisting of $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -C(O)OH, and $-CH_2C(O)OH$.

39. The pharmaceutical composition of Claim 33, wherein the agent is selected from the group consisting of:



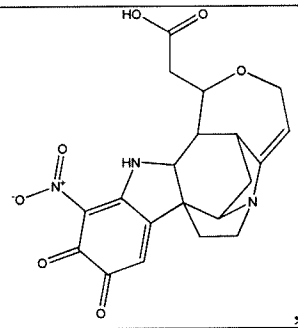
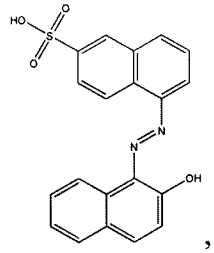
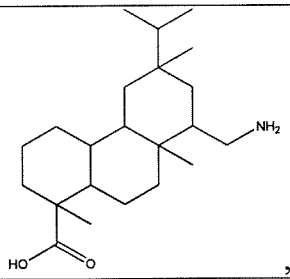
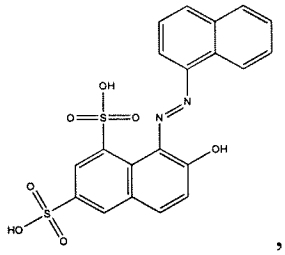
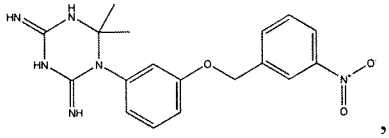
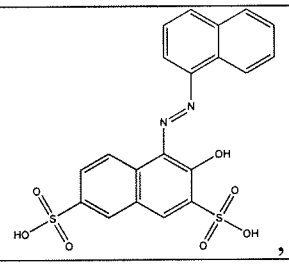
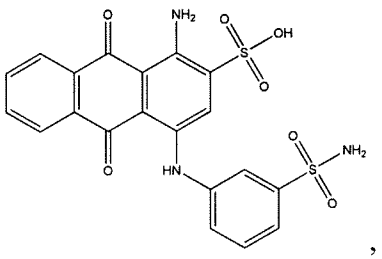
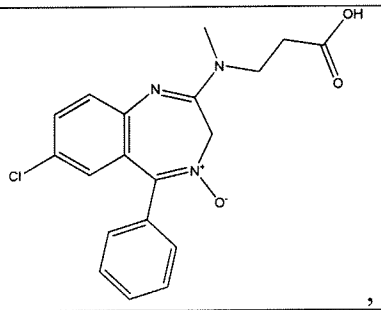
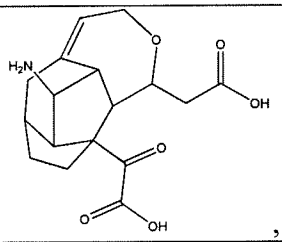
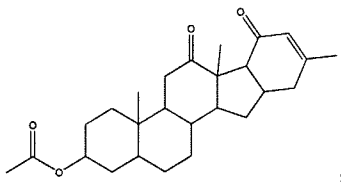
and

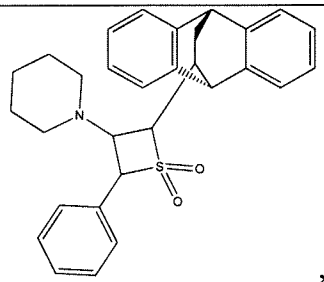
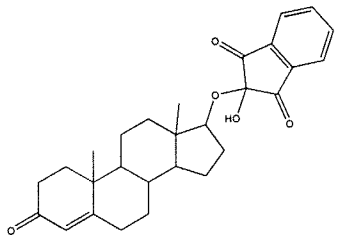
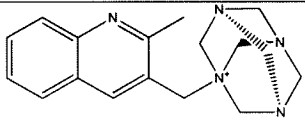
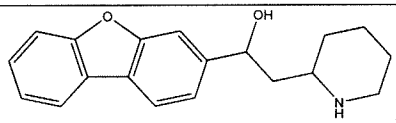
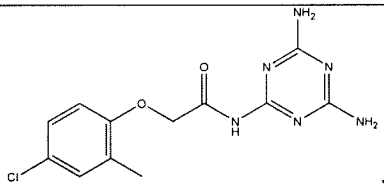
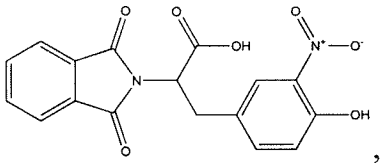
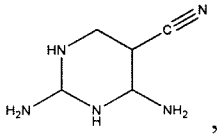
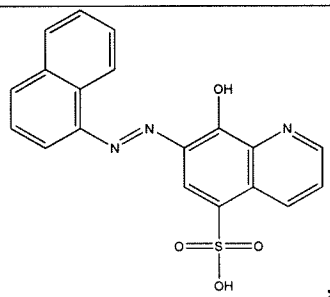
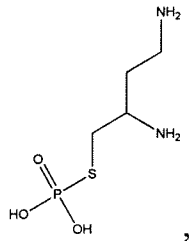
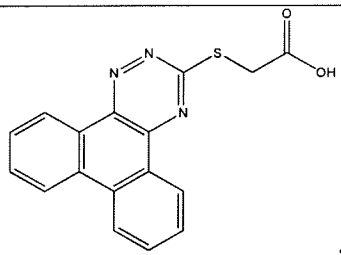
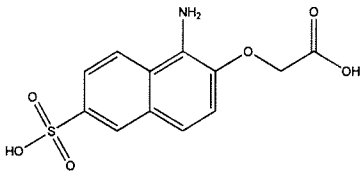
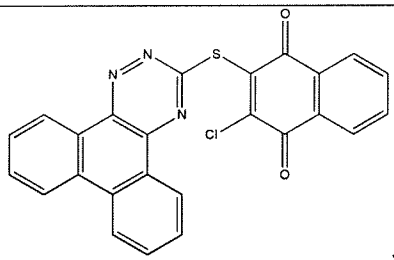
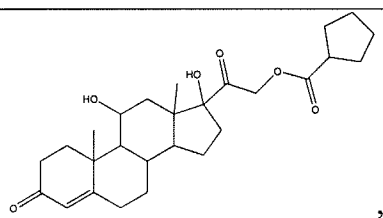
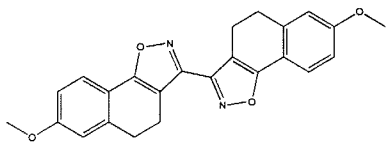


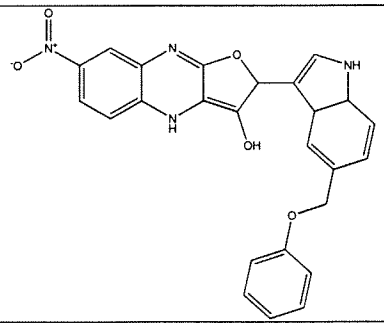
40. The pharmaceutical composition of Claim 33, wherein $\mathbf{X_6}$ is S (sulfur).

41. The pharmaceutical composition of any of Claims 33 to 41, comprising a pill.

42. A pharmaceutical composition comprising an agent and a pharmaceutically acceptable carrier, wherein the agent is selected from the group consisting of:

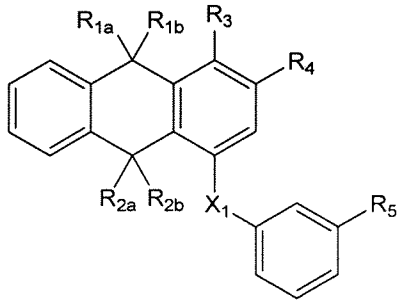
5069		45576	
70194		45582	
109836		45583	
117079		46080	
131612		59620	

135371		72254	
141562		90630	
164640		106920	
211332		148354	
350191		327704	
16163		327705	
17245		371688	

	and		372294	

or a pharmaceutically acceptable salt or prodrug thereof.

43. A compound having the formula (**I**):



(**I**)

or a pharmaceutically acceptable salt or prodrug thereof wherein:

(a) $\mathbf{R^{1a}}$ and $\mathbf{R^{1b}}$ are each separately selected from the group consisting of H (hydrogen), -C(O)N$\mathbf{R^{1c}R^{1d}}$, –C(O)O$\mathbf{R^{1e}}$, –C(S)N$\mathbf{R^{1c}R^{1d}}$, –C(S)O$\mathbf{R^{1e}}$, –NHC(O)$\mathbf{R^{1e}}$, -NHC(O)N$\mathbf{R^{1c}R^{1d}}$, –NHC(O)O$\mathbf{R^{1e}}$, -NHC(S)N$\mathbf{R^{1c}R^{1d}}$, –NHC(S)O$\mathbf{R^{1e}}$, -OC(O)N$\mathbf{R^{1c}R^{1d}}$, -OC(O)O$\mathbf{R^{1e}}$, –OC(S)N$\mathbf{R^{1c}R^{1d}}$, -O$\mathbf{R^{1f}}$, and -N$\mathbf{R^{1c}R^{1d}}$; or $\mathbf{R^{1a}}$ and $\mathbf{R^{1b}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

each $\mathbf{R^{1c}}$ and $\mathbf{R^{1d}}$ is independently selected from the group consisting of H (hydrogen), $C_{1\text{-}6}$ alkyl, heteroaryl, and aryl, or $\mathbf{R^{1c}}$ and $\mathbf{R^{1d}}$ are optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

each $\mathbf{R^{1e}}$ is independently selected from the group consisting of H (hydrogen), aryl, and $C_{1\text{-}6}$ alkyl optionally substituted with up to 5 fluoro;

each $\mathbf{R^{1f}}$ is independently selected from the group consisting of H (hydrogen), aryl, and $C_{1\text{-}6}$ alkyl optionally substituted with up to 5 fluoro;

(b) $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are each separately selected from the group consisting of H (hydrogen), -C(O)N$\mathbf{R^{2c}R^{2d}}$, –C(O)O$\mathbf{R^{2e}}$, –C(S)N$\mathbf{R^{2c}R^{2d}}$, –C(S)O$\mathbf{R^{2e}}$, –NHC(O)$\mathbf{R^{2e}}$, -NHC(O)N$\mathbf{R^{2c}R^{2d}}$, –NHC(O)O$\mathbf{R^{2e}}$, -NHC(S)N$\mathbf{R^{2c}R^{2d}}$, –

$NHC(S)OR^{2e}$, $-OC(O)NR^{2c}R^{2d}$, $-OC(O)OR^{2e}$, $-OC(S)NR^{2c}R^{2d}$, $-OR^{2f}$, and $-NR^{1c}R^{1d}$; or R^{2a} and R^{2b} are optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

each R^{2c} and R^{2d} is independently selected from the group consisting of H (hydrogen), C_{1-6} alkyl, and aryl, or R^{2c} and R^{2d} are optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

each R^{2e} is independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

each R^{2f} is independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) R^3 is selected from the group consisting of H (hydrogen), $-NHC(O)R^{3a}$, $-NHC(O)NR^{3b}R^{3c}$, $-NHC(O)OR^{3d}$, $-NHC(S)NR^{3b}R^{3c}$, $-NHC(S)OR^{3d}$, $-OC(S)NR^{3b}R^{3c}$, $-OR^{3e}$, $-SR^{3e}$, $-NR^{3b}R^{3c}$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

R^{3a} is selected from the group consisting of aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

R^{3b} and R^{3c} are each separately selected from the group consisting of H (hydrogen), C_{1-6} alkyl, heteroaryl, and aryl, or R^{3b} and R^{3c} are optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

R^{3d} is selected from the group consisting of aryl, heteroaryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

R^{3e} is selected from the group consisting of H (hydrogen), aryl, heteroaryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(d) R^4 is selected from the group consisting of H (hydrogen), $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, $-OP(O)(OR^{4a})_2$, $-SR^{4b}$, halo, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

each R^{4a} is independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

R^{4b} is selected from the group consisting of H (hydrogen), heteroaryl, aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

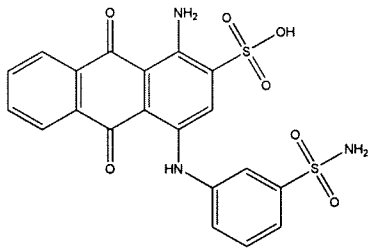
(e) $\mathbf{R^5}$ is selected from the group consisting of $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, $-OP(O)(OR^{5a})_2$, $-SR^{5b}$, and halo;

each $\mathbf{R^{5a}}$ is independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

$\mathbf{R^{5b}}$ is selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro; and

(f) $\mathbf{X_1}$ is selected from the group consisting of O (oxygen), S (sulfur) and $-NR^6$; where $\mathbf{R^6}$ is H (hydrogen) or C_{1-6} alkyl.

44. The compound of Claim 43, with the proviso the compound of formula (**I**) is not:



45. The compound of any of Claims 43 to 44, wherein:

$\mathbf{R^{1a}}$ and $\mathbf{R^{1b}}$ are taken together with the carbon to which they are attached to form keto; and

$\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are taken together with the carbon to which they are attached to form keto.

46. The compound of any of Claims 43 to 45, wherein:

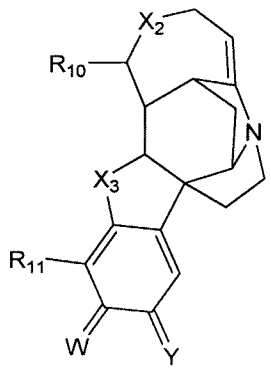
$\mathbf{R^3}$ is $-NH_2$; and $\mathbf{R^4}$ is $-S(O)_2OH$.

47. The compound of any of Claims 43 to 46, wherein:

$\mathbf{R^5}$ is selected from the group consisting of $-S(O)_2OH$, and $-S(O)_2NH_2$; and

$\mathbf{X_1}$ is $-NR^6$; where $\mathbf{R^6}$ is H (hydrogen) or C_{1-6} alkyl.

48. A compound having the formula (**II**):



(II)

or a pharmaceutically acceptable salt or prodrug thereof wherein:

(a) $\mathbf{R^{10}}$ is selected from the group consisting of $-(CH_2)_n\mathbf{R^{10a}}$;

(b) $\mathbf{R^{10a}}$ is selected from the group consisting of tetrazole, $-C(O)\mathbf{R^{10b}}$, and $-C(S)\mathbf{R^{10b}}$;

(c) $\mathbf{R^{10b}}$ is selected from the group consisting of H (hydrogen), $-S\mathbf{R^{10c}}$, $-O\mathbf{R^{10c}}$, $-NH\mathbf{R^{10c}}$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(d) $\mathbf{R^{10c}}$ is selected from the group consisting of H (hydrogen) and C_{1-6} alkyl;

(e) n is 0, 1, or 2;

(f) $\mathbf{R^{11}}$ is selected from the group consisting of tetrazole, $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, nitro, $-OP(O)(O\mathbf{R^{11a}})_2$, and $-C(O)O\mathbf{R^{11b}}$;

$\mathbf{R^{11a}}$ is selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

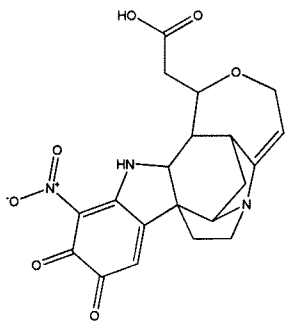
$\mathbf{R^{11b}}$ is selected from the group consisting of H (hydrogen), and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(g) W is O (oxygen) or S (sulfur);

(h) Y is O (oxygen) or S (sulfur); and

(i) $\mathbf{X_2}$ and $\mathbf{X_3}$ are each individually selected from the group consisting of O (oxygen), S (sulfur) and -NH.

49. The compound of Claim 48, with the proviso the compound of formula (II) is not:



50. The compound of any of Claims 48 to 49, wherein:

$\mathbf{R^{10a}}$ is $-CH_2C(O)\mathbf{R^{10b}}$.

51. The compound of any of Claims 48 to 50, wherein:

$\mathbf{R^{10a}}$ is $-CH_2C(O)O\mathbf{R^{10c}}$; and

$\mathbf{R^{11}}$ is selected from the group consisting of $-S(O)_2NH_2$, $-P(O)(OH)_2$, nitro, $-OP(O)(OR^{11a})_2$, and $-C(O)OR^{11b}$.

52. The compound of any of Claims 48 to 51, wherein:

$\mathbf{R^{10c}}$ is H (hydrogen);

$\mathbf{R^{11}}$ is selected from the group consisting of nitro, $-OP(O)(OR^{11a})_2$, and $-C(O)OR^{11b}$;

$\mathbf{R^{11a}}$ is selected from the group consisting of H (hydrogen), and C_{1-6} alkyl;

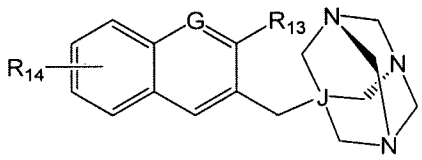
$\mathbf{R^{11b}}$ is H (hydrogen);

W is O (oxygen); and

Y is O (oxygen).

53. The compound of Claim 48, wherein $\mathbf{X_2}$ is O (oxygen) and $\mathbf{X_3}$ is -NH.

54. A compound having the formula (**III**):



(**III**)

or a pharmaceutically acceptable salt or prodrug thereof wherein:

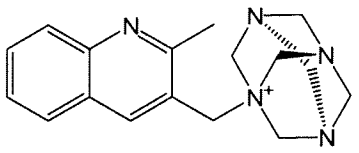
(a) $\mathbf{R^{13}}$ is selected from the group consisting of H (hydrogen), C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(b) $\mathbf{R^{14}}$ is one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) G is selected from the group consisting of CH and N (nitrogen); and

(d) J is selected from the group consisting of N^+ (nitrogen) and P^+ (phosphorous).

55. The compound of Claim 54, with the proviso the compound of formula (**III**) is not:



56. The compound of any of Claims 54 to 55, wherein:

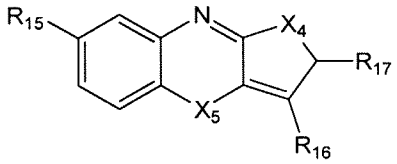
G is N (nitrogen).

57. The compound of any of Claims 54 to 56, wherein:

$\mathbf{R^{13}}$ is selected from the group consisting of H (hydrogen) and C_{1-6} alkyl optionally substituted with up to 5 fluoro; and

J is N^+ (nitrogen).

58. A compound having the formula (**IV**):



(**IV**)

or tautomer thereof, or their pharmaceutically acceptable salts or prodrugs, wherein:

(a) $\mathbf{R^{15}}$ is selected from the group consisting of nitro, and $-C(O)\mathbf{R^{15a}}$;

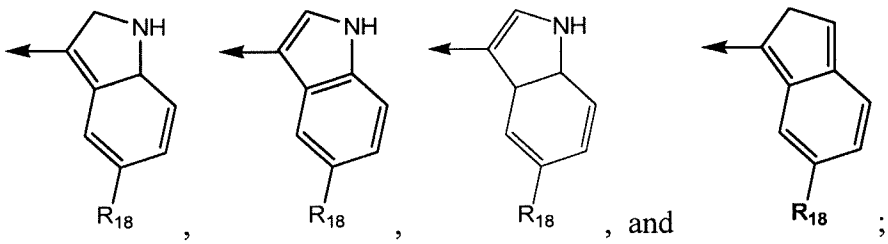
(b) $\mathbf{R^{15a}}$ is selected from the group consisting of H (hydrogen), $-S\mathbf{R^{15b}}$, and $-O\mathbf{R^{15b}}$;

(c) $\mathbf{R^{15b}}$ is selected from the group consisting of H (hydrogen) and C_{1-6} alkyl;

(d) $\mathbf{R^{16}}$ is selected from the group consisting of H (hydrogen) and $-O\mathbf{R^{16a}}$;

(e) $\mathbf{R^{16a}}$ is selected from the group consisting of H (hydrogen), and C_{1-6} alkyl;

(f) $\mathbf{R^{17}}$ is selected from the group consisting of:



, , , and ;

(g) $\mathbf{R^{18}}$ is selected from the group consisting of $-(CH_2)_n\mathbf{R^{18a}}$ and $-CH{=}CH\mathbf{R^{18a}}$;

(h) **n** is 0, 1, or 2;

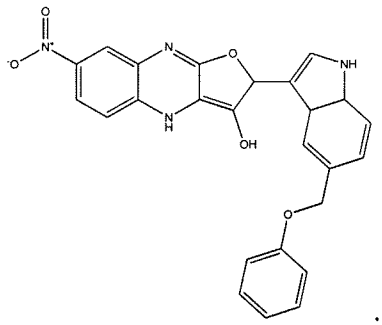
(i) $\mathbf{R^{18a}}$ is selected from the group consisting of $-S\mathbf{R^{18b}}$, $-O\mathbf{R^{18b}}$, aryl optionally substituted with one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted

with up to 5 fluoro, and heteroaryl optionally substituted with one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(j) $\mathbf{R^{18b}}$ is selected from the group consisting of aryl and heteroaryl, each optionally substituted with one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro; and

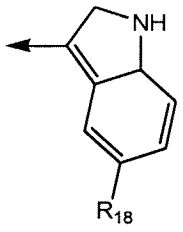
(k) $\mathbf{X_4}$ and $\mathbf{X_5}$ are each individually selected from the group consisting of O (oxygen), S (sulfur) and -NH.

59. The compound of Claim 58, with the proviso the compound of formula (**IV**) is not:

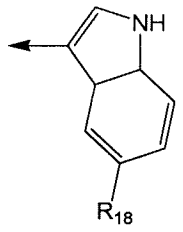


60. The compound of any of Claims 58 to 59, wherein:

$\mathbf{R^{17}}$ is selected from the group consisting of:



, and



.

61. The compound of any of Claims 58 to 60, wherein:

$\mathbf{R^{18}}$ is–$(CH_2)_n\mathbf{R^{18a}}$;

n is 1; and

$\mathbf{R^{18a}}$ is -$\mathbf{OR^{18b}}$.

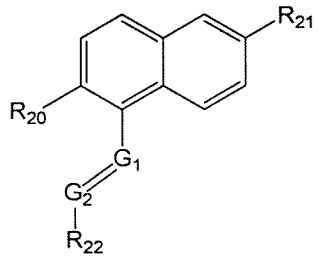
62. The compound of any of Claims 58 to 61, wherein:

$\mathbf{R^{16}}$ is -$\mathbf{OR^{16a}}$; and

R^{18b} is aryl optionally substituted with one or more substituents each individually selected from the group consisting of OH, halo, cyano, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro.

63. The compound of Claim 58, wherein X_4 is O (oxygen) and X_5 is –NH.

64. A compound having the formula (V):



(V)

or tautomer thereof, or their pharmaceutically acceptable salts or prodrugs, wherein:

(a) R^{20} is selected from the group consisting of H (hydrogen), -OR^{20a}, -SR^{20a}, -C(O)N$R^{20c}R^{20d}$, –NHC(O)R^{20e};

(b) R^{20a} is selected from the group consisting of H (hydrogen), and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) R^{20c} and R^{20d} are each separately selected from the group consisting of H (hydrogen), C_{1-6} alkyl, heteroaryl, and aryl, or R^{20c} and R^{20d} are optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

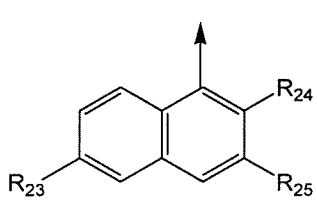
(d) R^{20e} is selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

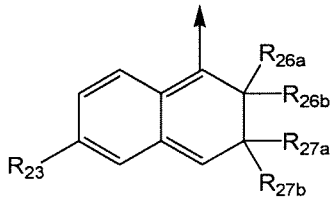
(e) R^{21} is selected from the group consisting of H (hydrogen), -$S(O)_2OH$, -$S(O)_2NH_2$, -$P(O)(OH)_2$, halo, -C(O)R^{21a}, and -C(S)R^{21a};

(f) R^{21a} is selected from the group consisting of H (hydrogen), -SR^{21b}, -OR^{21b}, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(g) R^{21b} is selected from the group consisting of H (hydrogen), and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(h) R^{22} is selected from the group consisting of:



and


;

(i) $\mathbf{R^{23}}$ is selected from the group consisting of H (hydrogen), $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -OH and C_{1-6} alkoxy optionally substituted with up to 5 fluoro;

(j) $\mathbf{R^{24}}$ is -OH or C_{1-6} alkoxy optionally substituted with up to 5 fluoro;

(k) $\mathbf{R^{25}}$ is selected from the group consisting of H (hydrogen), $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -OH and C_{1-6} alkoxy optionally substituted with up to 5 fluoro;

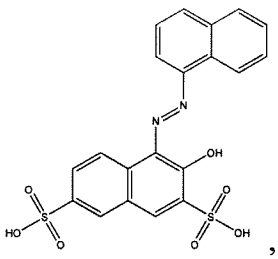
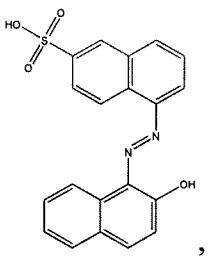
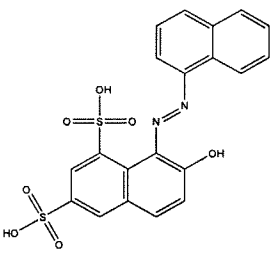
(l) $\mathbf{R^{26a}}$ and $\mathbf{R^{26b}}$ are each separately selected from the group consisting of H (hydrogen), -OH, C_{1-6} alkyl optionally substituted with up to 5 fluoro, and C_{1-6} alkoxy optionally substituted with up to 5 fluoro; or $\mathbf{R^{26a}}$ and $\mathbf{R^{26b}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

(m) $\mathbf{R^{27a}}$ and $\mathbf{R^{27b}}$ are each separately selected from the group consisting of H (hydrogen), -OH, C_{1-6} alkyl optionally substituted with up to 5 fluoro, and C_{1-6} alkoxy optionally substituted with up to 5 fluoro; or $\mathbf{R^{27a}}$ and $\mathbf{R^{27b}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

(n) $\mathbf{G_1}$ is selected from the group consisting of CH and N (nitrogen); and

(o) $\mathbf{G_2}$ is selected from the group consisting of CH and N (nitrogen).

65. The compound of Claim 64 with the proviso the compound of formula (**V**) is not selected from the group consisting of:


,

, and

.

66. The compound of any of Claims 64 to 65, wherein:

$\mathbf{R^{20}}$ is H (hydrogen); and

$\mathbf{R^{21}}$ is H (hydrogen) or $-S(O)_2OH$.

67. The compound of any of Claims 64 to 66, wherein:

$\mathbf{R^{23}}$ is H (hydrogen) or -$S(O)_2OH$;

$\mathbf{R^{24}}$ is –OH; and

$\mathbf{R^{25}}$ is H (hydrogen), or -$S(O)_2OH$.

68. The compound of any of Claims 64 to 67, wherein:

$\mathbf{G_1}$ is N (nitrogen); and

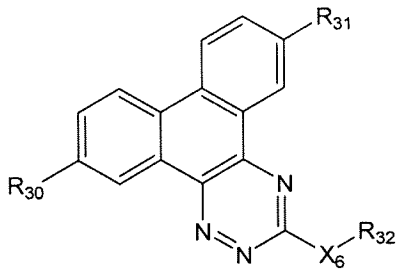
$\mathbf{G_2}$ is N (nitrogen).

69. The compound of any of Claims 64 to 66, wherein:

$\mathbf{R^{26a}}$ and $\mathbf{R^{26b}}$ are optionally taken together with the carbon to which they are attached to form a keto group; and

$\mathbf{R^{27a}}$ and $\mathbf{R^{27b}}$ are optionally taken together with the carbon to which they are attached to form a keto group.

70. A compound having the formula (**VI**):



(**VI**)

or tautomer thereof, or their pharmaceutically acceptable salts or prodrugs, wherein:

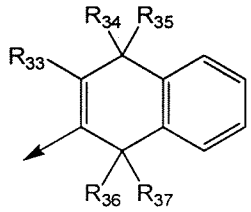
(a) $\mathbf{R^{30}}$ is selected from the group consisting of H (hydrogen), -$\mathbf{OR^{30a}}$, -$\mathbf{SR^{30a}}$, -$\mathbf{NR^{30b}R^{30c}}$, -$S(O)_2OH$, -$S(O)_2NH_2$, -$P(O)(OH)_2$, -C(O)OH, -$CH_2C(O)OH$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(b) $\mathbf{R^{30a}}$ is selected from the group consisting of H (hydrogen) and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) $\mathbf{R^{30b}}$ and $\mathbf{R^{30c}}$ are each separately selected from the group consisting of H (hydrogen) and C_{1-6} alkyl, or $\mathbf{R^{30b}}$ and $\mathbf{R^{30c}}$ are optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

(d) $\mathbf{R^{31}}$ is selected from the group consisting of H (hydrogen), -OH, –SH, $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -C(O)OH, $-CH_2C(O)OH$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(e) $\mathbf{R^{32}}$ is selected from the group consisting of $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -C(O)OH, and $-CH_2C(O)OH$; or $\mathbf{R^{32}}$ is :



;

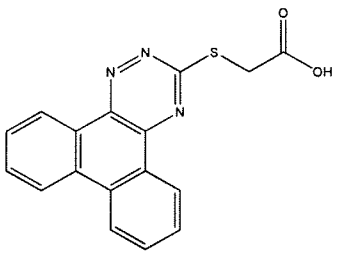
(f) $\mathbf{R^{33}}$ is selected from the group consisting of H (hydrogen), -OH, halo, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

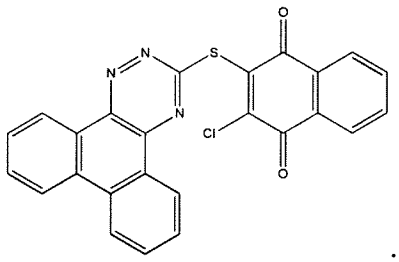
(g) $\mathbf{R^{34}}$ and $\mathbf{R^{35}}$ are each separately selected from the group consisting of H (hydrogen), -OH, halo, and C_{1-6} alkyl optionally substituted with up to 5 fluoro; or $\mathbf{R^{34}}$ and $\mathbf{R^{35}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

(h) $\mathbf{R^{36}}$ and $\mathbf{R^{37}}$ are each separately selected from the group consisting of H (hydrogen), -OH, -SH, and halo; or $\mathbf{R^{36}}$ and $\mathbf{R^{37}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group; and

(i) $\mathbf{X_6}$ is selected from the group consisting of O (oxygen), S (sulfur) and -NH.

71. The compound of Claim 70 with the proviso the compound of formula (**VI**) is not selected from the group consisting of:



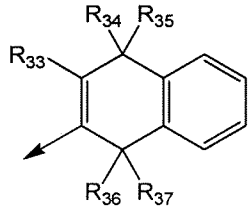
and


.

72. The compound of any of Claims 70 to 71, wherein:

$\mathbf{R^{30}}$ and $\mathbf{R^{31}}$ are H (hydrogen); and

$\mathbf{R^{32}}$ is :



73. The compound of any of Claims 70 to 72, wherein:

$\mathbf{R^{34}}$ and $\mathbf{R^{35}}$ are optionally taken together with the carbon to which they are attached to form a keto group; and

$\mathbf{R^{36}}$ and $\mathbf{R^{37}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group.

74. The compound of any of Claims 70 to 72, wherein $\mathbf{R^{33}}$ is halo.

75. The compound of any of Claims 70 to 71, wherein:

$\mathbf{R^{30}}$ is H (hydrogen); and

$\mathbf{R^{32}}$ is selected from the group consisting of $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, $-C(O)OH$, and $-CH_2C(O)OH$.

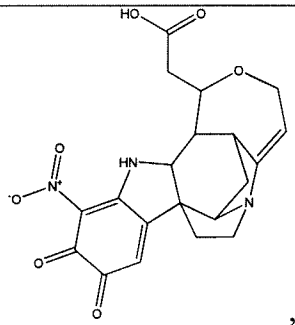
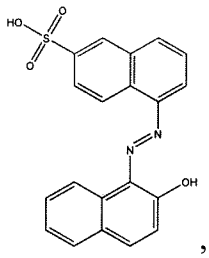
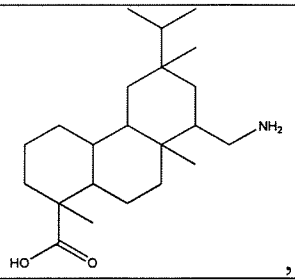
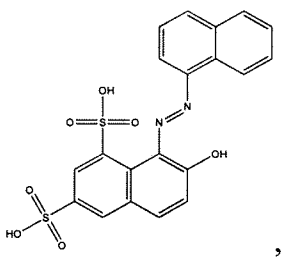
76. The compound of any of Claims 70 to 71, wherein:

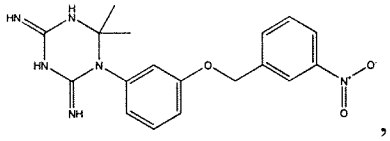
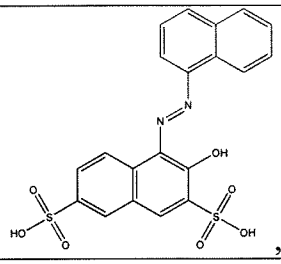
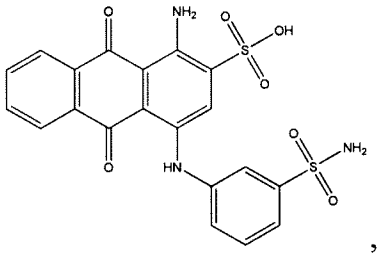
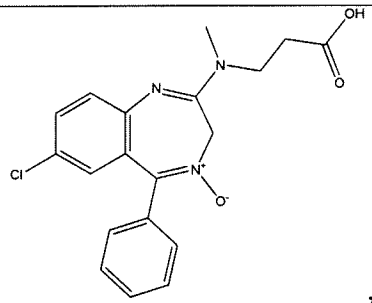
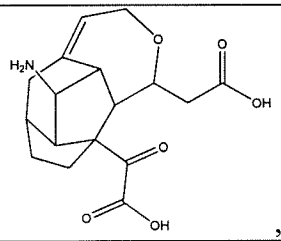
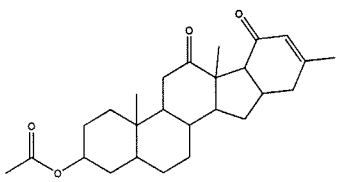
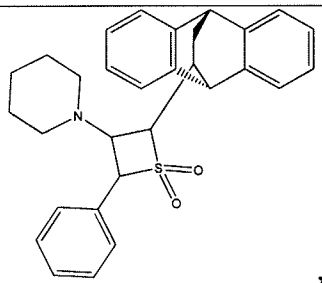
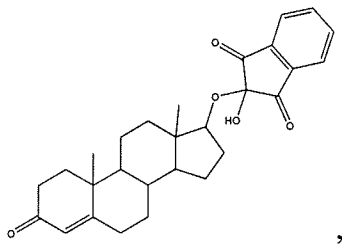
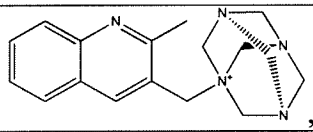
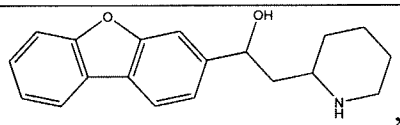
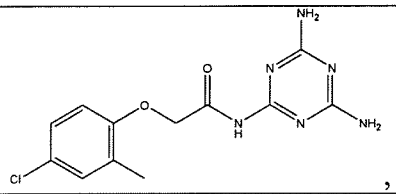
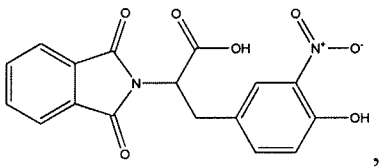
$\mathbf{R^{31}}$ is H (hydrogen); and

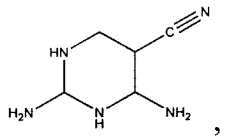
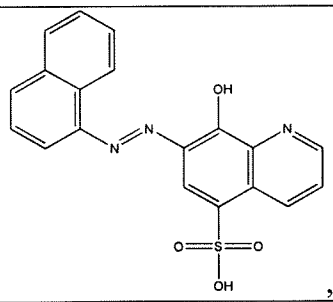
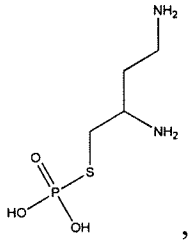
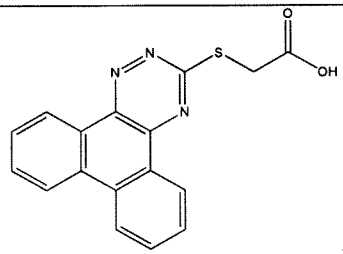
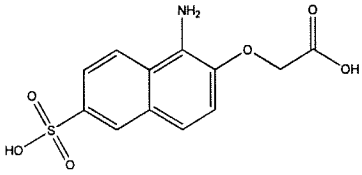
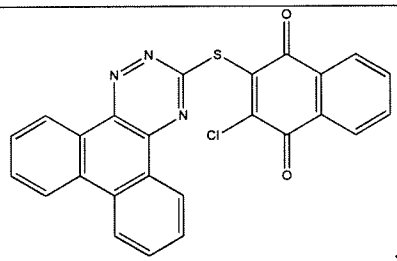
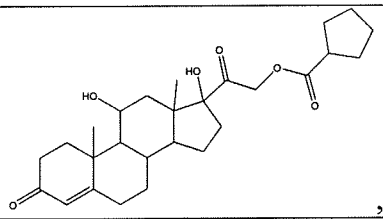
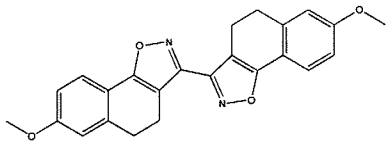
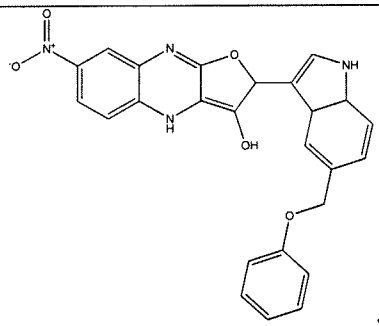
$\mathbf{R^{32}}$ is selected from the group consisting of $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, $-C(O)OH$, and $-CH_2C(O)OH$.

77. The compound of Claim 70, wherein $\mathbf{X_6}$ is S (sulfur).

78. A compound selected from the group consisting of:

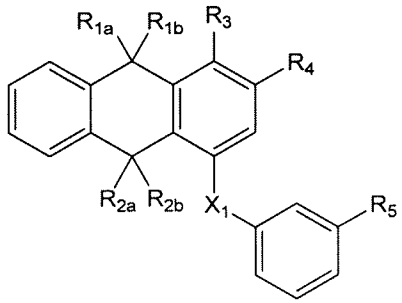
5069			45576	
70194			45582	

109836			45583		
117079			46080		
131612			59620		
135371			72254		
141562			90630		
164640			106920		

211332		148354	
350191		327704	
16163		327705	
17245		371688	
	and	372294	

or a pharmaceutically acceptable salt or prodrug thereof for use in the treatment of an avian influenza infection in an individual.

79. A compound having the formula (**I**):



(I)

or a pharmaceutically acceptable salt or prodrug thereof for use in the treatment of an avian influenza infection in an individual,

wherein:

(a) $\mathbf{R^{1a}}$ and $\mathbf{R^{1b}}$ are each separately selected from the group consisting of H (hydrogen), -C(O)N$\mathbf{R^{1c}R^{1d}}$, –C(O)O$\mathbf{R^{1e}}$, –C(S)N$\mathbf{R^{1c}R^{1d}}$, –C(S)O$\mathbf{R^{1e}}$, –NHC(O)$\mathbf{R^{1e}}$, -NHC(O)N$\mathbf{R^{1c}R^{1d}}$, –NHC(O)O$\mathbf{R^{1e}}$, -NHC(S)N$\mathbf{R^{1c}R^{1d}}$, –NHC(S)O$\mathbf{R^{1e}}$, -OC(O)N$\mathbf{R^{1c}R^{1d}}$, -OC(O)O$\mathbf{R^{1e}}$, –OC(S)N$\mathbf{R^{1c}R^{1d}}$, -O$\mathbf{R^{1f}}$, and -N$\mathbf{R^{1c}R^{1d}}$; or $\mathbf{R^{1a}}$ and $\mathbf{R^{1b}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

each $\mathbf{R^{1c}}$ and $\mathbf{R^{1d}}$ is independently selected from the group consisting of H (hydrogen), $C_{1\text{-}6}$ alkyl, heteroaryl, and aryl, or $\mathbf{R^{1c}}$ and $\mathbf{R^{1d}}$ are optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

each $\mathbf{R^{1e}}$ is independently selected from the group consisting of H (hydrogen), aryl, and $C_{1\text{-}6}$ alkyl optionally substituted with up to 5 fluoro;

each $\mathbf{R^{1f}}$ is independently selected from the group consisting of H (hydrogen), aryl, and $C_{1\text{-}6}$ alkyl optionally substituted with up to 5 fluoro;

(b) $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are each separately selected from the group consisting of H (hydrogen), -C(O)N$\mathbf{R^{2c}R^{2d}}$, –C(O)O$\mathbf{R^{2e}}$, –C(S)N$\mathbf{R^{2c}R^{2d}}$, –C(S)O$\mathbf{R^{2e}}$, –NHC(O)$\mathbf{R^{2e}}$, -NHC(O)N$\mathbf{R^{2c}R^{2d}}$, –NHC(O)O$\mathbf{R^{2e}}$, -NHC(S)N$\mathbf{R^{2c}R^{2d}}$, –NHC(S)O$\mathbf{R^{2e}}$, -OC(O)N$\mathbf{R^{2c}R^{2d}}$, -OC(O)O$\mathbf{R^{2e}}$, –OC(S)N$\mathbf{R^{2c}R^{2d}}$, -O$\mathbf{R^{2f}}$, and -N$\mathbf{R^{1c}R^{1d}}$; or $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

each $\mathbf{R^{2c}}$ and $\mathbf{R^{2d}}$ is independently selected from the group consisting of H (hydrogen), $C_{1\text{-}6}$ alkyl, and aryl, or $\mathbf{R^{2c}}$ and $\mathbf{R^{2d}}$ are optionally taken together with

the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

each $\mathbf{R^{2e}}$ is independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

each $\mathbf{R^{2f}}$ is independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) $\mathbf{R^3}$ is selected from the group consisting of H (hydrogen), –NHC(O)$\mathbf{R^{3a}}$, -NHC(O)N$\mathbf{R^{3b}R^{3c}}$, –NHC(O)O$\mathbf{R^{3d}}$, -NHC(S)N$\mathbf{R^{3b}R^{3c}}$, –NHC(S)O$\mathbf{R^{3d}}$, -OC(S)N$\mathbf{R^{3b}R^{3c}}$, -O$\mathbf{R^{3e}}$, -S$\mathbf{R^{3e}}$, -N$\mathbf{R^{3b}R^{3c}}$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

$\mathbf{R^{3a}}$ is selected from the group consisting of aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

$\mathbf{R^{3b}}$ and $\mathbf{R^{3c}}$ are each separately selected from the group consisting of H (hydrogen), C_{1-6} alkyl, heteroaryl, and aryl, or $\mathbf{R^{3b}}$ and $\mathbf{R^{3c}}$ are optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

$\mathbf{R^{3d}}$ is selected from the group consisting of aryl, heteroaryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

$\mathbf{R^{3e}}$ is selected from the group consisting of H (hydrogen), aryl, heteroaryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(d) $\mathbf{R^4}$ is selected from the group consisting of H (hydrogen), -S(O)$_2$OH, -S(O)$_2$NH$_2$, -P(O)(OH)$_2$, -OP(O)(O$\mathbf{R^{4a}}$)$_2$, -S$\mathbf{R^{4b}}$, halo, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

each $\mathbf{R^{4a}}$ is independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

$\mathbf{R^{4b}}$ is selected from the group consisting of H (hydrogen), heteroaryl, aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

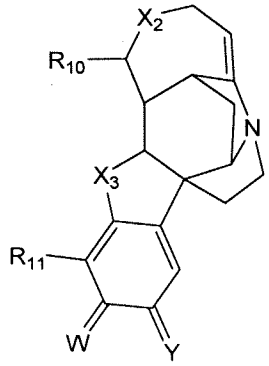
(e) $\mathbf{R^5}$ is selected from the group consisting of -S(O)$_2$OH, -S(O)$_2$NH$_2$, -P(O)(OH)$_2$, -OP(O)(O$\mathbf{R^{5a}}$)$_2$, -S$\mathbf{R^{5b}}$, and halo;

each $\mathbf{R^{5a}}$ is independently selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

$\mathbf{R^{5b}}$ is selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro; and

(f) $\mathbf{X_1}$ is selected from the group consisting of O (oxygen), S (sulfur) and $-NR^6$; where $\mathbf{R^6}$ is H (hydrogen) or C_{1-6} alkyl.

80. A compound having the formula (**II**):



(**II**)

or a pharmaceutically acceptable salt or prodrug thereof for use in the treatment of an avian influenza infection in an individual,

wherein:

(a) $\mathbf{R^{10}}$ is selected from the group consisting of $-(CH_2)_n\mathbf{R^{10a}}$;

(b) $\mathbf{R^{10a}}$ is selected from the group consisting of tetrazole, $-C(O)\mathbf{R^{10b}}$, and $-C(S)\mathbf{R^{10b}}$;

(c) $\mathbf{R^{10b}}$ is selected from the group consisting of H (hydrogen), $-S\mathbf{R^{10c}}$, $-O\mathbf{R^{10c}}$, $-NH\mathbf{R^{10c}}$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(d) $\mathbf{R^{10c}}$ is selected from the group consisting of H (hydrogen) and C_{1-6} alkyl;

(e) n is 0, 1, or 2;

(f) $\mathbf{R^{11}}$ is selected from the group consisting of tetrazole, $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, nitro, $-OP(O)(O\mathbf{R^{11a}})_2$, and $-C(O)O\mathbf{R^{11b}}$;

$\mathbf{R^{11a}}$ is selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

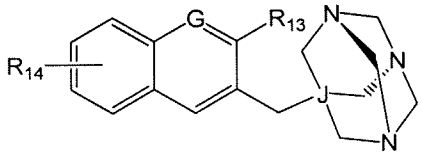
$\mathbf{R^{11b}}$ is selected from the group consisting of H (hydrogen), and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(g) W is O (oxygen) or S (sulfur)

(h) Y is O (oxygen) or S (sulfur); and

(i) X_2 and X_3 are each individually selected from the group consisting of O (oxygen), S (sulfur) and -NH.

81. A compound having the formula (**III**):



(**III**)

or a pharmaceutically acceptable salt or prodrug thereof for use in the treatment of an avian influenza infection in an individual,

wherein:

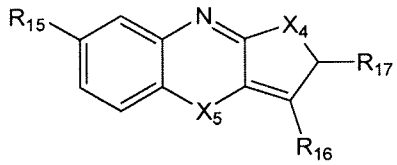
(a) R^{13} is selected from the group consisting of H (hydrogen), C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(b) R^{14} is one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) G is selected from the group consisting of CH and N (nitrogen); and

(d) J is selected from the group consisting of N^+ (nitrogen) and P^+ (phosphorous).

82. A compound having the formula (**IV**):



(**IV**)

or tautomer thereof, or their pharmaceutically acceptable salts or prodrugs, for use in the treatment of an avian influenza infection in an individual,

wherein:

(a) R^{15} is selected from the group consisting of nitro, and -C(O)R^{15a};

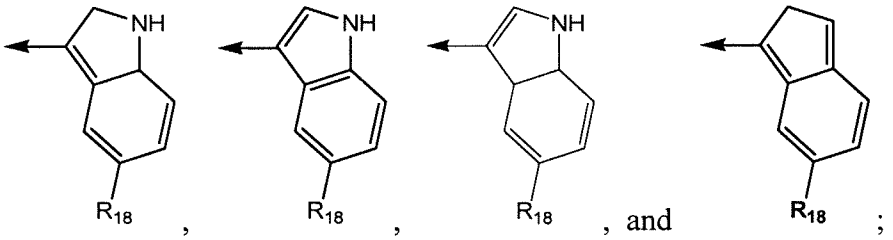
(b) R^{15a} is selected from the group consisting of H (hydrogen), -SR^{15b}, and -OR^{15b};

(c) $\mathbf{R^{15b}}$ is selected from the group consisting of H (hydrogen) and C_{1-6} alkyl;

(d) $\mathbf{R^{16}}$ is selected from the group consisting of H (hydrogen) and -$\mathbf{OR^{16a}}$;

(e) $\mathbf{R^{16a}}$ is selected from the group consisting of H (hydrogen), and C_{1-6} alkyl;

(f) $\mathbf{R^{17}}$ is selected from the group consisting of:



, , , and ;

(g) $\mathbf{R^{18}}$ is selected from the group consisting of $-(CH_2)_n\mathbf{R^{18a}}$ and -CH=CH$\mathbf{R^{18a}}$;

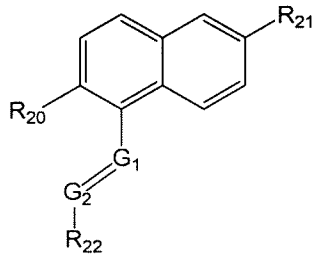
(h) n is 0, 1, or 2;

(i) $\mathbf{R^{18a}}$ is selected from the group consisting of -$\mathbf{SR^{18b}}$, -$\mathbf{OR^{18b}}$, aryl optionally substituted with one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro, and heteroaryl optionally substituted with one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(j) $\mathbf{R^{18b}}$ is selected from the group consisting of aryl and heteroaryl, each optionally substituted with one or more substituents each individually selected from the group consisting of OH, halo, cyano, nitro, aryl, heteroaryl, C_{1-6} alkoxy optionally substituted with up to 5 fluoro, and C_{1-6} alkyl optionally substituted with up to 5 fluoro; and

(k) $\mathbf{X_4}$ and $\mathbf{X_5}$ are each individually selected from the group consisting of O (oxygen), S (sulfur) and -NH.

83. A compound having the formula (**V**):



(V)

or tautomer thereof, or their pharmaceutically acceptable salts or prodrugs, for use in the treatment of an avian influenza infection in an individual,

wherein:

(a) $\mathbf{R^{20}}$ is selected from the group consisting of H (hydrogen), $-O\mathbf{R^{20a}}$, $-S\mathbf{R^{20a}}$, $-C(O)N\mathbf{R^{20c}R^{20d}}$, $-NHC(O)\mathbf{R^{20e}}$;

(b) $\mathbf{R^{20a}}$ is selected from the group consisting of H (hydrogen), and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) $\mathbf{R^{20c}}$ and $\mathbf{R^{20d}}$ are each separately selected from the group consisting of H (hydrogen), C_{1-6} alkyl, heteroaryl, and aryl, or $\mathbf{R^{20c}}$ and $\mathbf{R^{20d}}$ are optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

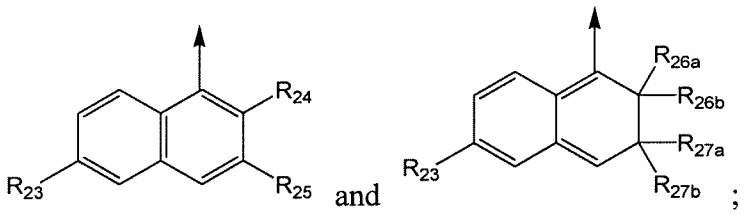
(d) $\mathbf{R^{20e}}$ is selected from the group consisting of H (hydrogen), aryl, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(e) $\mathbf{R^{21}}$ is selected from the group consisting of H (hydrogen), $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, halo, $-C(O)\mathbf{R^{21a}}$, and $-C(S)\mathbf{R^{21a}}$;

(f) $\mathbf{R^{21a}}$ is selected from the group consisting of H (hydrogen), $-S\mathbf{R^{21b}}$, $-O\mathbf{R^{21b}}$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(g) $\mathbf{R^{21b}}$ is selected from the group consisting of H (hydrogen), and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(h) $\mathbf{R^{22}}$ is selected from the group consisting of:



;

(i) $\mathbf{R^{23}}$ is selected from the group consisting of H (hydrogen), $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -OH and C_{1-6} alkoxy optionally substituted with up to 5 fluoro;

(j) $\mathbf{R^{24}}$ is -OH or C_{1-6} alkoxy optionally substituted with up to 5 fluoro;

(k) $\mathbf{R^{25}}$ is selected from the group consisting of H (hydrogen), $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -OH and C_{1-6} alkoxy optionally substituted with up to 5 fluoro;

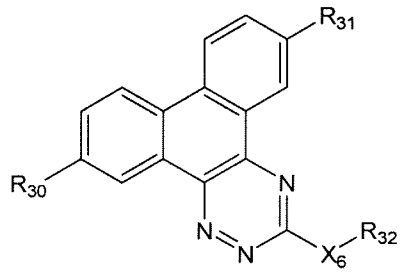
(l) $\mathbf{R^{26a}}$ and $\mathbf{R^{26b}}$ are each separately selected from the group consisting of H (hydrogen), -OH, C_{1-6} alkyl optionally substituted with up to 5 fluoro, and C_{1-6} alkoxy optionally substituted with up to 5 fluoro; or $\mathbf{R^{26a}}$ and $\mathbf{R^{26b}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

(m) $\mathbf{R^{27a}}$ and $\mathbf{R^{27b}}$ are each separately selected from the group consisting of H (hydrogen), -OH, C_{1-6} alkyl optionally substituted with up to 5 fluoro, and C_{1-6} alkoxy optionally substituted with up to 5 fluoro; or $\mathbf{R^{27a}}$ and $\mathbf{R^{27b}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group; and

(n) $\mathbf{G_1}$ is selected from the group consisting of CH and N (nitrogen); and

(o) $\mathbf{G_2}$ is selected from the group consisting of CH and N (nitrogen).

84. A compound having the formula (**VI**):



(**VI**)

or tautomer thereof, or their pharmaceutically acceptable salts or prodrugs, for use in the treatment of an avian influenza infection in an individual,

wherein:

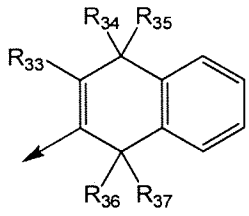
(a) $\mathbf{R^{30}}$ is selected from the group consisting of H (hydrogen), $-OR^{30a}$, $-SR^{30a}$, $-NR^{30b}R^{30c}$, $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -C(O)OH, $-CH_2C(O)OH$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(b) $\mathbf{R^{30a}}$ is selected from the group consisting of H (hydrogen) and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(c) $\mathbf{R^{30b}}$ and $\mathbf{R^{30c}}$ are each separately selected from the group consisting of H (hydrogen) and C_{1-6} alkyl, or $\mathbf{R^{30b}}$ and $\mathbf{R^{30c}}$ are optionally taken together with the nitrogen to which they are attached to form indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl;

(d) $\mathbf{R^{31}}$ is selected from the group consisting of H (hydrogen), -OH, –SH, $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -C(O)OH, $-CH_2C(O)OH$, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(e) $\mathbf{R^{32}}$ is selected from the group consisting of $-S(O)_2OH$, $-S(O)_2NH_2$, $-P(O)(OH)_2$, -C(O)OH, and $-CH_2C(O)OH$; or $\mathbf{R^{32}}$ is :



;

(f) $\mathbf{R^{33}}$ is selected from the group consisting of H (hydrogen), -OH, halo, and C_{1-6} alkyl optionally substituted with up to 5 fluoro;

(g) $\mathbf{R^{34}}$ and $\mathbf{R^{35}}$ are each separately selected from the group consisting of H (hydrogen), -OH, halo, and C_{1-6} alkyl optionally substituted with up to 5 fluoro; or $\mathbf{R^{34}}$ and $\mathbf{R^{35}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group;

(h) $\mathbf{R^{36}}$ and $\mathbf{R^{37}}$ are each separately selected from the group consisting of H (hydrogen), -OH, -SH, and halo; or $\mathbf{R^{36}}$ and $\mathbf{R^{37}}$ are optionally taken together with the carbon to which they are attached to form a keto or thioketo group; and

(i) $\mathbf{X_6}$ is selected from the group consisting of O (oxygen), S (sulfur) and -NH.

85. A method of ameliorating an avian influenza infection in an individual, the method comprising administering to the individual an effective amount of a compound of Claim 43.

86. A method of ameliorating an avian influenza infection in an individual, the method comprising administering to the individual an effective amount of a compound of Claim 48.

87. A method of ameliorating an avian influenza infection in an individual, the method comprising administering to the individual an effective amount of a compound of Claim 54.

88. A method of ameliorating an avian influenza infection in an individual, the method comprising administering to the individual an effective amount of a compound of Claim 58.

89. A method of ameliorating an avian influenza infection in an individual, the method comprising administering to the individual an effective amount of a compound of Claim 64.

90. A method of ameliorating an avian influenza infection in an individual, the method comprising administering to the individual an effective amount of a compound of Claim 70.

91. A method of identifying compounds which bind to the neuraminidase protein of Influenza A virus subtype H5N1, comprising:

(a) performing molecular dynamic simulations on an Influenza A virus subtype H5N1 neuraminidase protein crystal structure;

(b) generating an Influenza A virus subtype H5N1 protein structure using RMSD (root-mean-square-difference) clustering of related residues from the molecular dynamic simulations;

(c) docking compounds to the 150-loop of the generated Influenza A virus subtype H5N1 neuraminidase protein structure; and

(d) identifying the binding affinity of the docked compounds

wherein the MD simulations are performed on 2 or more Influenza A virus subtype H5N1 neuraminidase protein crystal structures.

92. The method of Claim 91 further comprising docking compounds to sialic acid cavity.

93. A method of identifying compounds which bind to the neuraminidase protein of Influenza A virus subtype H5N1, comprising:

(a) performing molecular dynamic simulations on an Influenza A virus subtype H5N1 crystal structure;

(b) generating an Influenza A virus subtype H5N1 protein structure using RMSD (root-mean-square-difference) clustering of related residues from the molecular dynamic (MD) simulations;

(c) docking compounds to the 430-loop of the generated Influenza A virus subtype H5N1 neuraminidase protein structure; and

(d) identifying the binding affinity of the docked compounds

wherein the MD simulations are performed on 2 or more Influenza A virus subtype H5N1 neuraminidase protein crystal structures.

94. The method of Claim 93 further comprising docking compounds to sialic acid cavity.

95. The method of Claim 93 further comprising docking compounds to the 150-loop.

96. The method of Claim 93 further comprising docking compounds to sialic acid cavity and the 150-loop.

97. A method of identifying an agent that interacts with Influenza A virus subtype H5N1 neuraminidase protein comprising:

(a) using a crystal structure of a complex comprising Influenza A virus subtype H5N1 neuraminidase protein;

(b) obtaining the atomic coordinates of the crystal structure; and

(c) using the atomic coordinates and one or more molecular modeling techniques to identify a ligand that interacts with Influenza A virus subtype H5N1 neuraminidase protein.

98. A method of identifying a compound which binds to the an Influenza A virus subtype H5N1 neuraminidase protein with a desired affinity comprising:

identifying one or more interactions between a ligand and a sub-unit of the Influenza A virus subtype H5N1 neuraminidase protein; and

changing a substituent on the ligand in order to modify the interaction between the ligand the neuraminidase protein subunit to provide said compound.

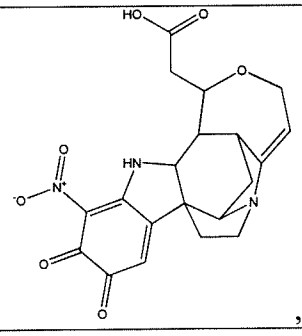
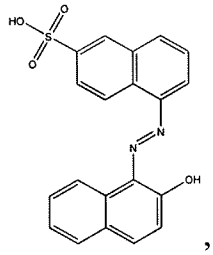
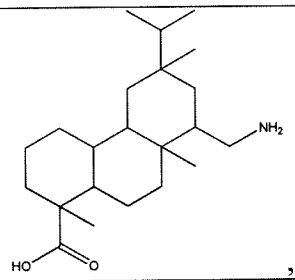
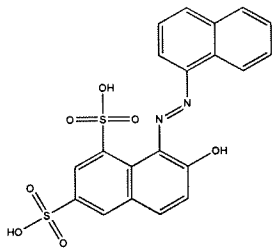
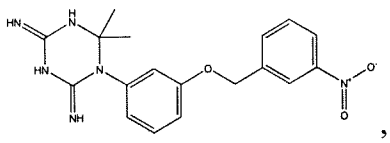
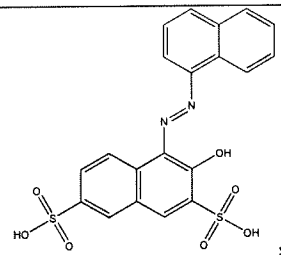
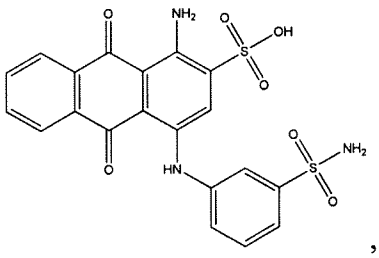
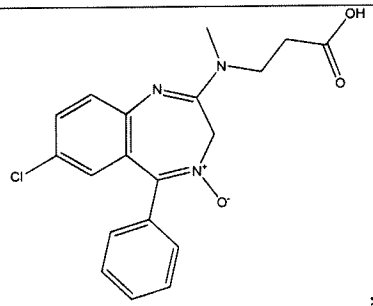
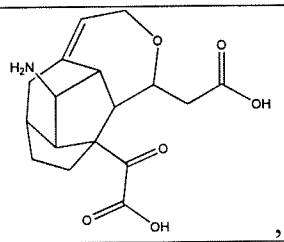
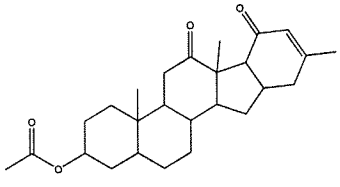
99. A composition comprising an agent and a pharmaceutically-acceptable carrier wherein the agent is identified by

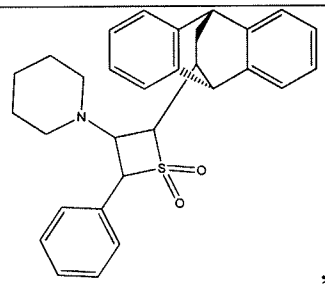
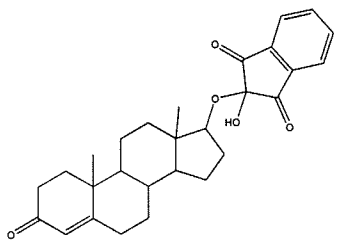
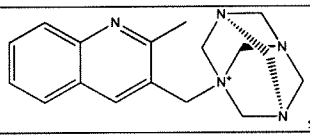
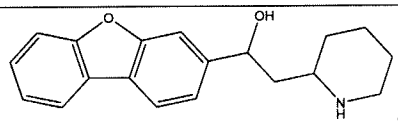
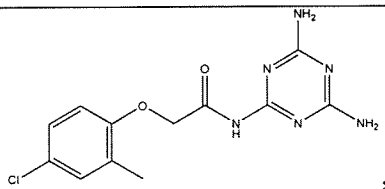
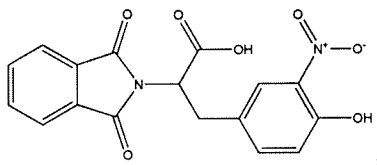
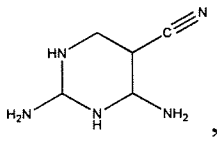
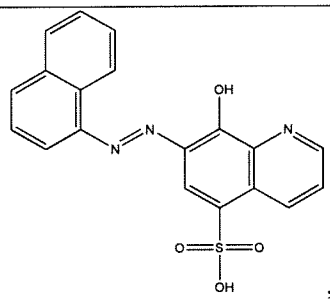
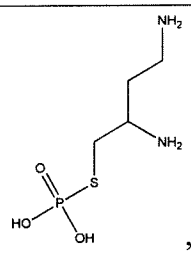
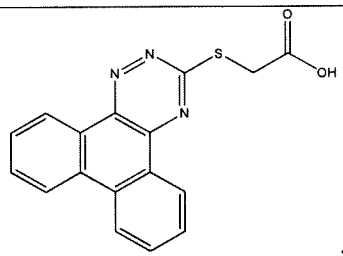
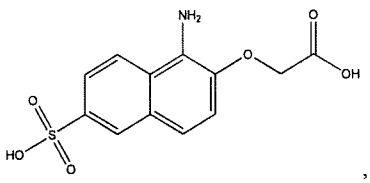
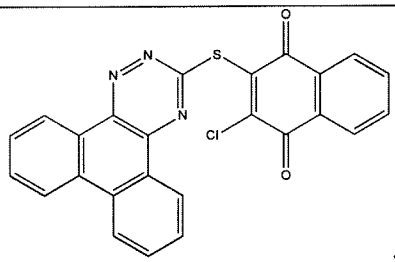
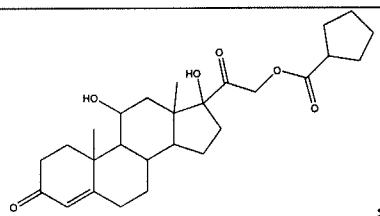
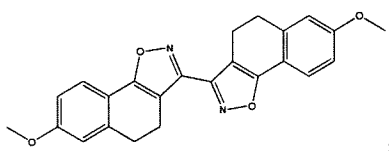
(a) using a crystal structure of a complex comprising Influenza A virus subtype H5N1 neuraminidase protein;

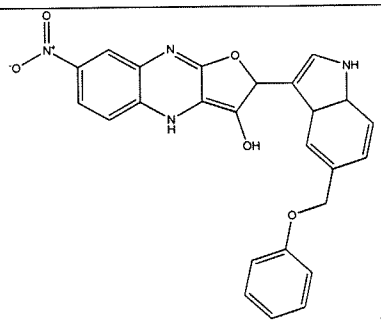
(b) obtaining the atomic coordinates of the crystal structure;

(c) using the atomic coordinates and one or more molecular modeling techniques to identify a ligand that interacts with Influenza A virus subtype H5N1.

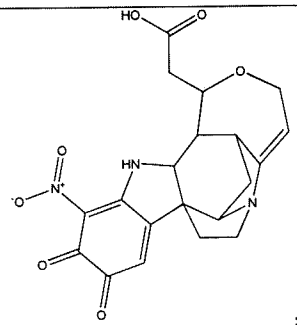
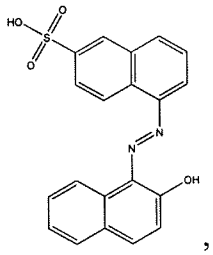
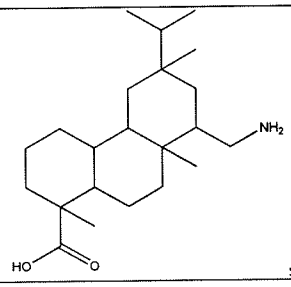
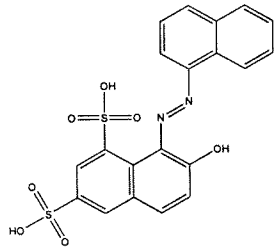
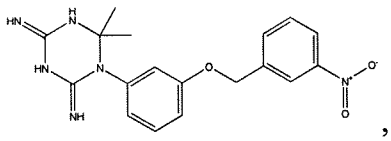
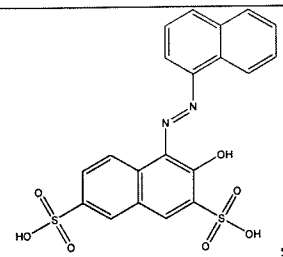
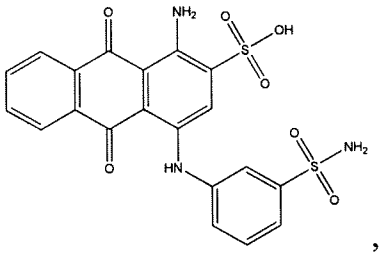
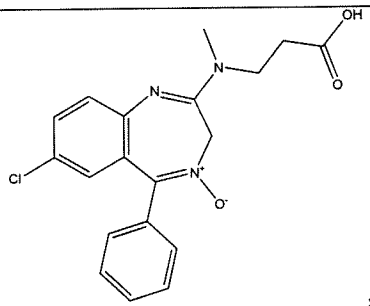
100. A pill comprising a compound selected from the group consisting of:

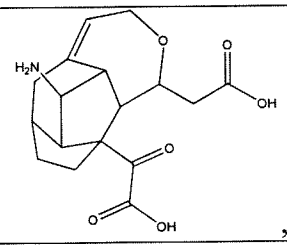
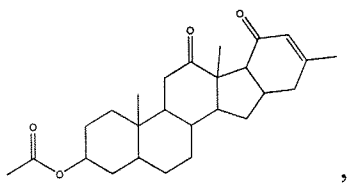
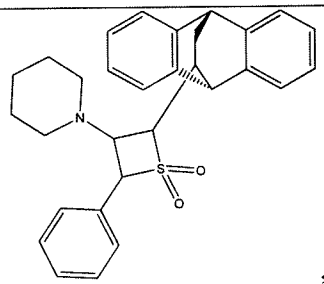
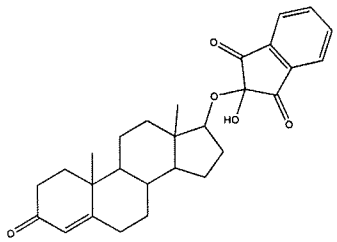
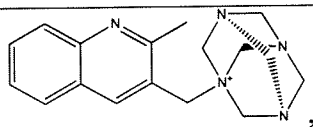
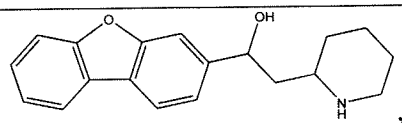
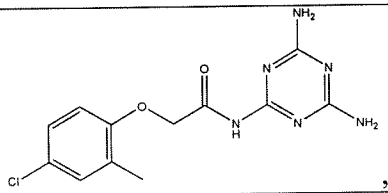
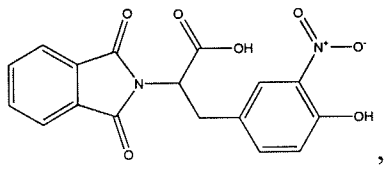
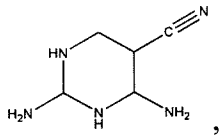
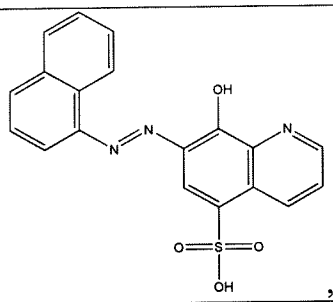
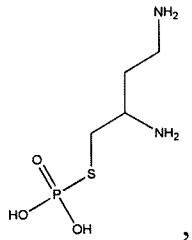
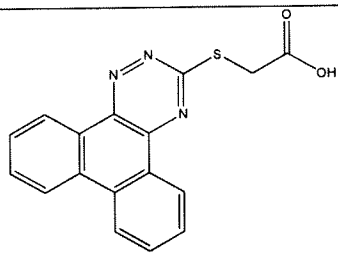
5069		45576	
70194		45582	
109836		45583	
117079		46080	
131612		59620	

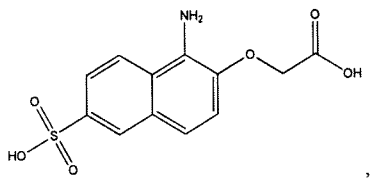
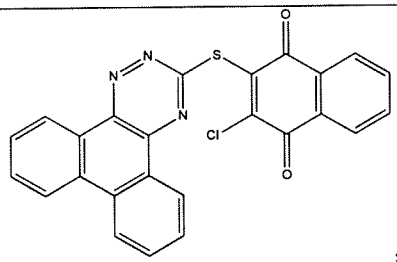
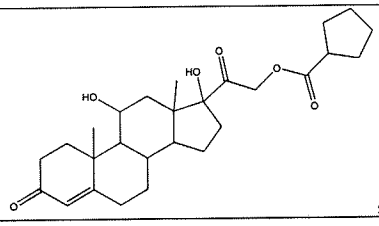
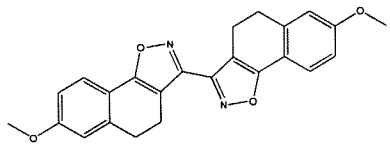
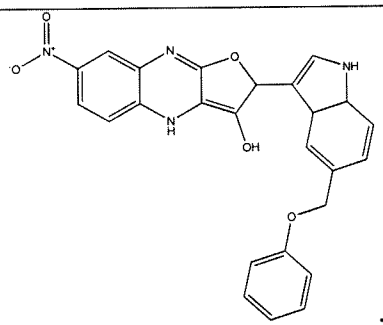
135371		72254	
141562		90630	
164640		106920	
211332		148354	
350191		327704	
16163		327705	
17245		371688	

	and		372294	

101. An injectable pharmaceutical composition comprising a compound selected from the group consisting of:

5069			45576	
70194			45582	
109836			45583	
117079			46080	

131612		59620	
135371		72254	
141562		90630	
164640		106920	
211332		148354	
350191		327704	

16163		327705	
17245		371688	
	and	372294	

102. A method of ameliorating an avian influenza infection in an individual, the method comprising administering to the individual an effective amount of a compound identified by the method of Claim 91.

103. A method of ameliorating an avian influenza infection in an individual, the method comprising administering to the individual an effective amount of a compound identified by the method of Claim 98.

104. A method of screening a compound library to identify compounds which bind to an Influenza A virus subtype H5N1 neuraminidase protein comprising:

(a) obtaining a library comprising a plurality of compound structures;

(b) performing molecular dynamic simulations on an Influenza A virus subtype H5N1 neuraminidase protein crystal structure;

(c) generating an Influenza A virus subtype H5N1 protein structure using RMSD (root-mean-square-difference) clustering of related residues from the molecular dynamic simulations;

(d) docking compounds to the 150-loop of the generated Influenza A virus subtype H5N1 neuraminidase protein structure; and

(e) identifying compounds which bind to said Influenza A virus subtype H5N1 neuraminidase protein with a desired affinity.

105. The method of Claim 104 further comprising docking compounds to sialic acid cavity.

106. The method of Claim 104 further comprising docking compounds to the 430-loop.

107. The method of Claim 104 further comprising docking compounds to sialic acid cavity and the 430-loop.

108. A method of screening a compound library comprising:

(a) obtaining a library comprising a plurality of compound structures;

(b) performing molecular dynamic simulations on an Influenza A virus subtype H5N1 neuraminidase protein crystal structure;

(c) generating an Influenza A virus subtype H5N1 protein structure using RMSD (root-mean-square-difference) clustering of related residues from the molecular dynamic simulations;

(d) docking compounds to the 430-loop of the generated Influenza A virus subtype H5N1 neuraminidase protein structure; and

(e) identifying compounds which bind to said Influenza A virus subtype H5N1 neuraminidase protein with a desired affinity.

109. The method of Claim 108 further comprising docking compounds to sialic acid cavity.

110. The method of Claim 108 further comprising docking compounds to the 150-loop.

111. The method of Claim 108 further comprising docking compounds to sialic acid cavity and the 150-loop.

112. An injection device comprising the pharmaceutical composition of Claim 1.

113. The injection device of Claim 112, wherin the injection device is a syringe.

114. An injection device comprising the pharmaceutical composition of Claim 7.

115. The injection device of Claim 114, wherin the injection device is a syringe.

116. An injection device comprising the pharmaceutical composition of Claim 14.

117. The injection device of Claim 116, wherin the injection device is a syringe.

118. An injection device comprising the pharmaceutical composition of Claim 19.

119. The injection device of Claim 118, wherin the injection device is a syringe.

120. An injection device comprising the pharmaceutical composition of Claim 26.

121. The injection device of Claim 120, wherin the injection device is a syringe.

122. An injection device comprising the pharmaceutical composition of Claim 33.

123. The injection device of Claim 122, wherin the injection device is a syringe.

124. An injection device comprising the pharmaceutical composition of Claim 42.

125. The injection device of Claim 124, wherin the injection device is a syringe.

126. A method of identifying compounds which bind to a target protein, comprising:

(a) performing molecular dynamic simulations on the target protein crystal structure;

(b) generating a target protein structure using RMSD (root-mean-square-difference) clustering of related residues from the molecular dynamic simulations;

(c) docking compounds to a binding pocket of the generated target protein structure;

(d) identifying the binding affinity of the docked compounds;

(e) ranking the compounds using relaxed complex scheme (RCS) computational methodology,

wherein the MD simulations are performed on one or more target protein crystal structures.

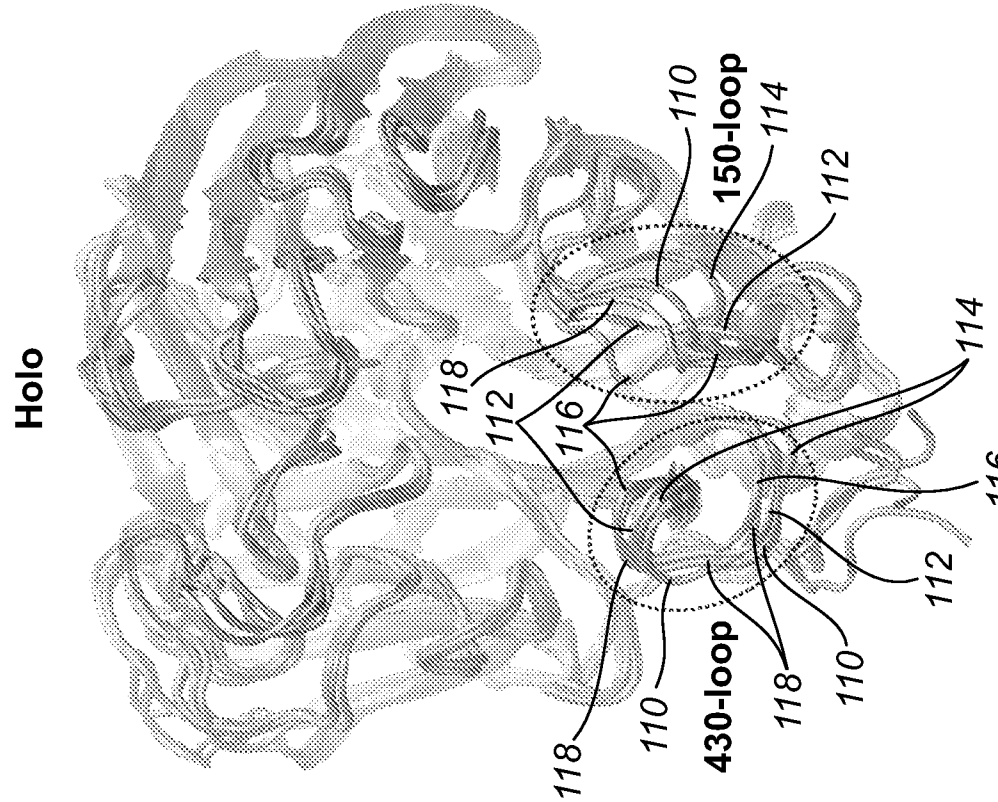

Holo
150-loop
430-loop
110
112
114
116
118

FIG. 1B

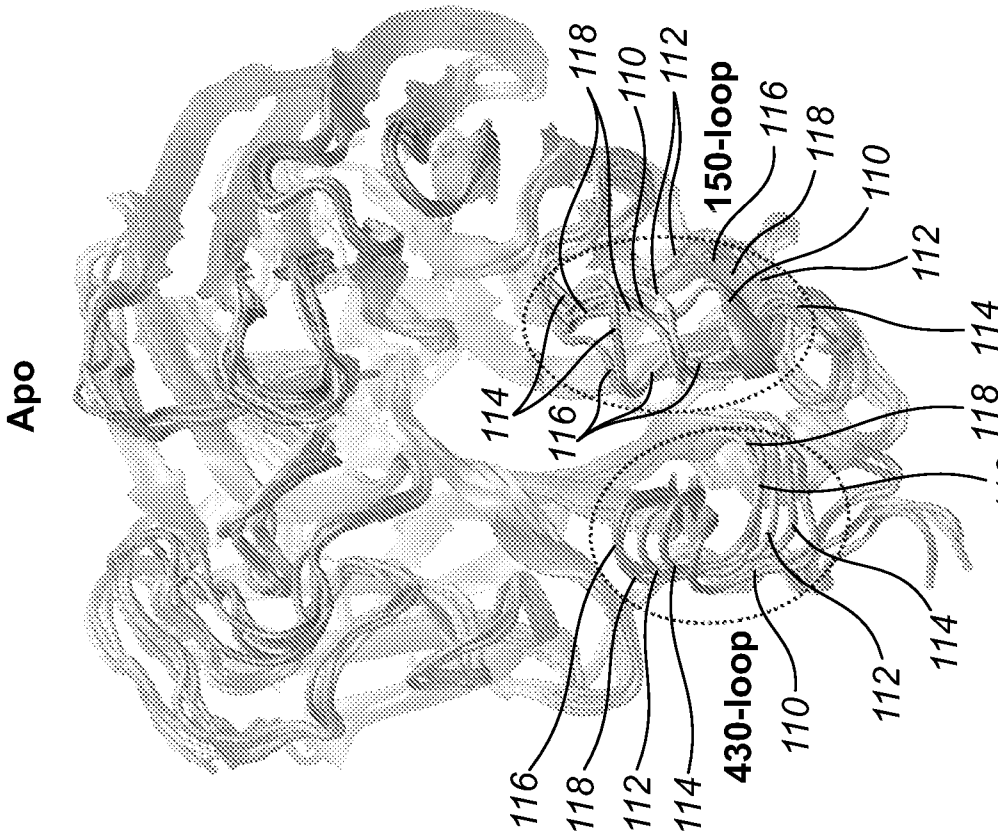

Apo
150-loop
430-loop
110
112
114
116
118

FIG. 1A

FIG. 2A

FIG. 2B

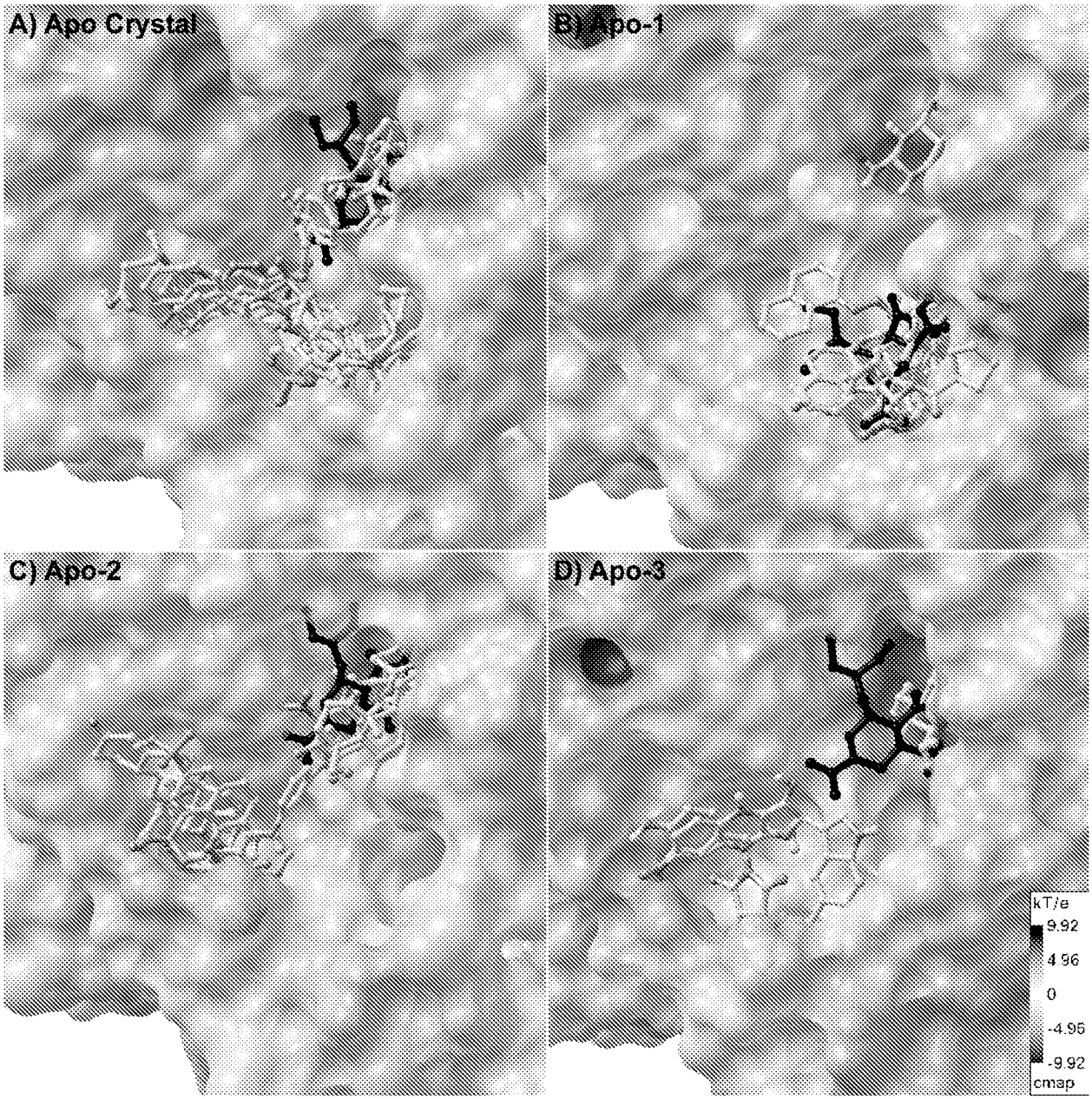


FIG. 2C

FIG. 2D

FIG. 3A

FIG. 3B

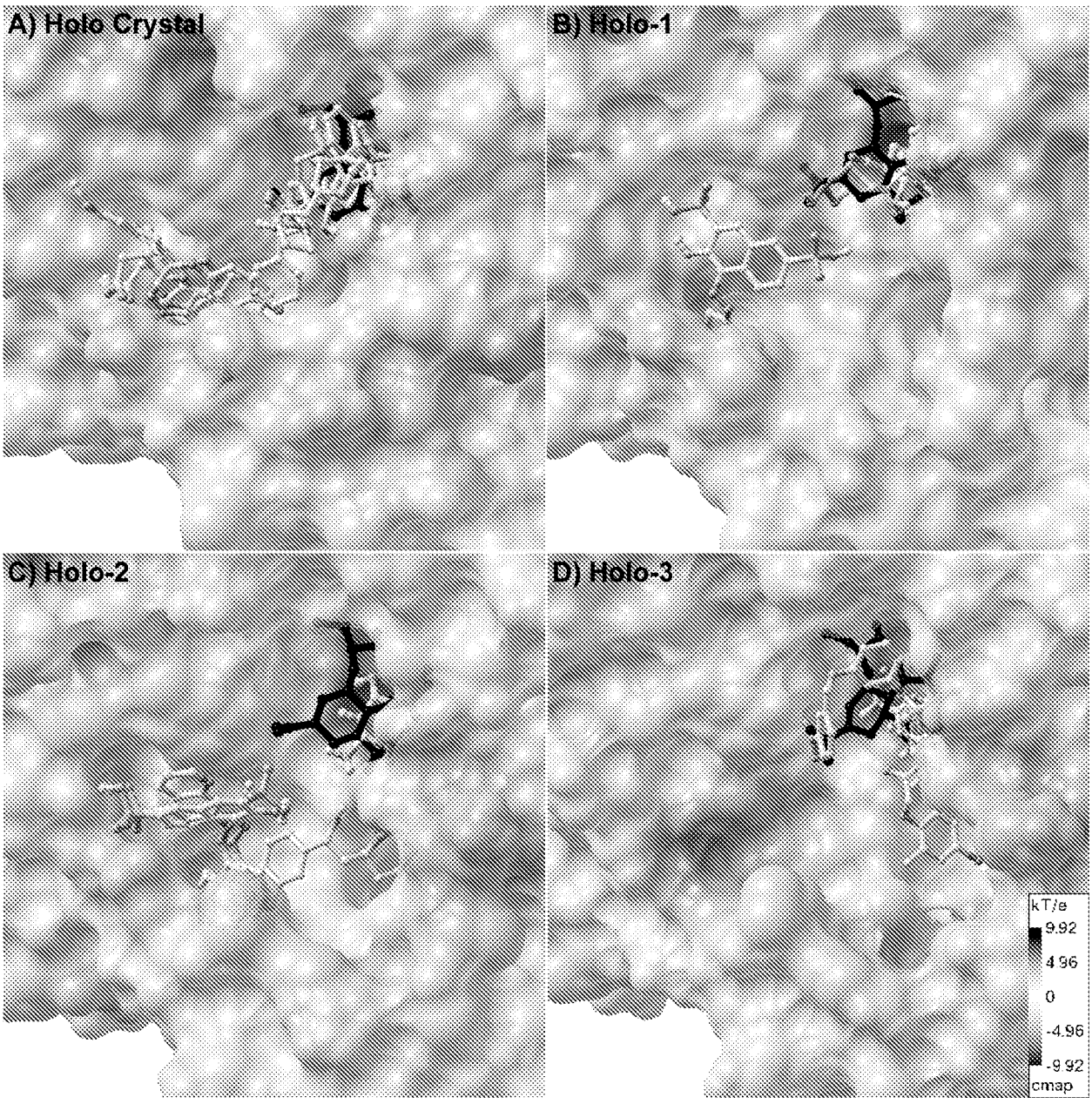


FIG. 3C

FIG. 3D

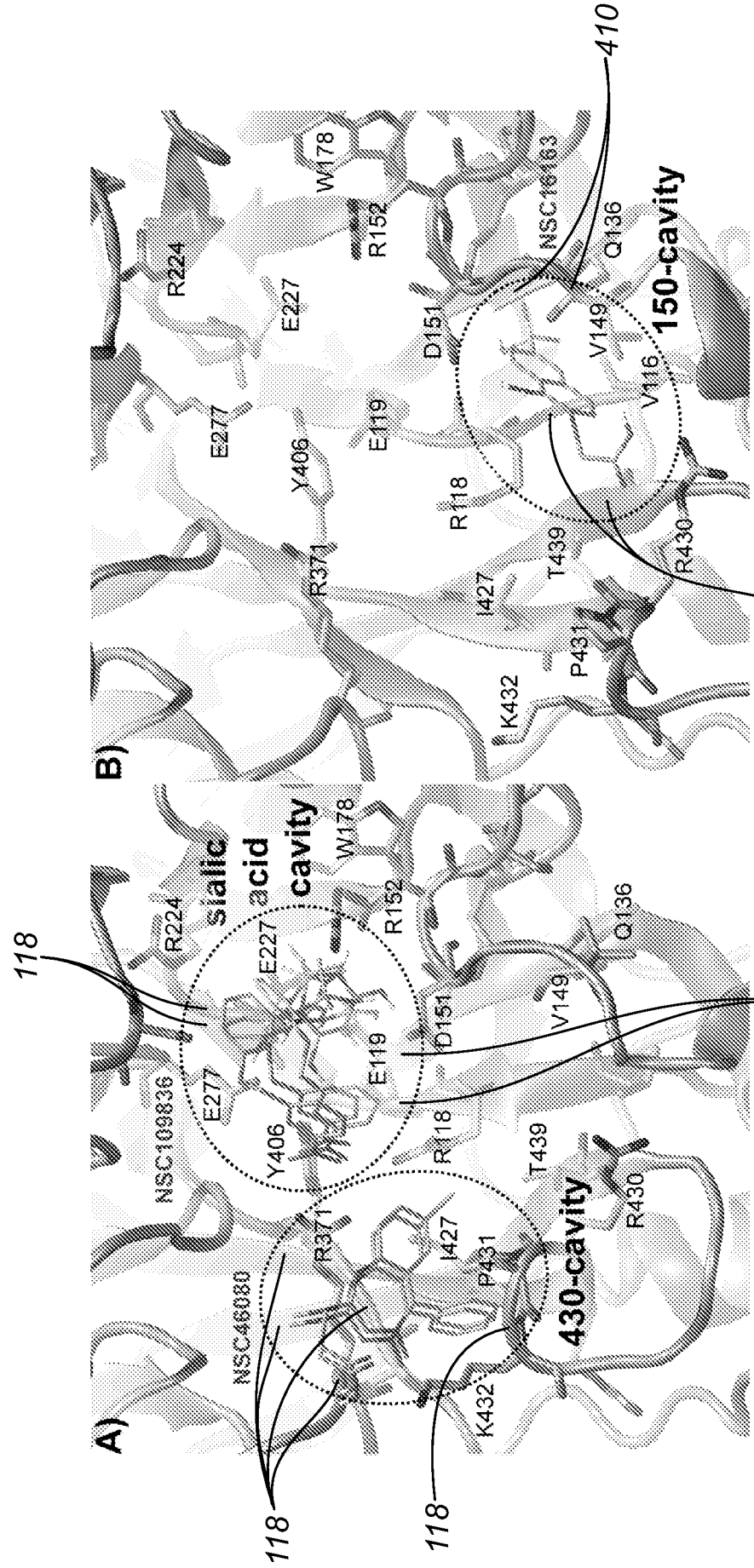

A)
B)
Sialic acid cavity
430-cavity
150-cavity
NSC109836
NSC46080
NSC16183
R224
E227
E277
W178
R152
D151
E119
Y406
R118
R371
I427
T439
P431
R430
K432
Q136
V149
V116
118
110
410

FIG. 4A

FIG. 4B