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(54) Titre : COMPOSES ANTIVIRAUX
(54) Title: PYRIMIDINEDIONE ANTI-VIRAL COMPOUNDS

Figure 2A

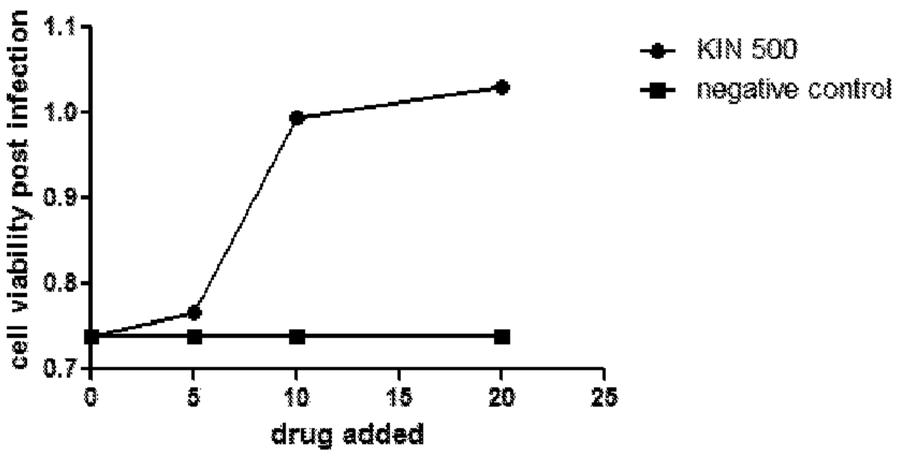
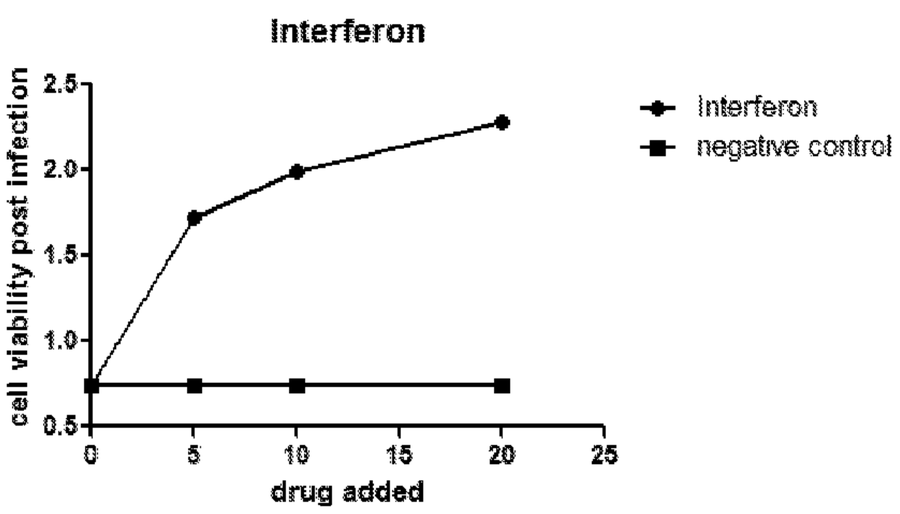


Figure 2B



(57) Abrégé/Abstract:
Disclosed herein are compounds and related compositions for the treatment of viral infection, including RNA viral infection, and compounds that can modulate the RIG- I pathway in vertebrate cells, including compounds that can activate the RIG-I pathway.

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ,

[Continued on next page]

(54) Title: ANTI-VIRAL COMPOUNDS

(57) Abstract: Disclosed herein are compounds and related compositions for the treatment of viral infection, including RNA viral infection, and compounds that can modulate the RIG- I pathway in vertebrate cells, including compounds that can activate the RIG-I pathway.

Figure 2A

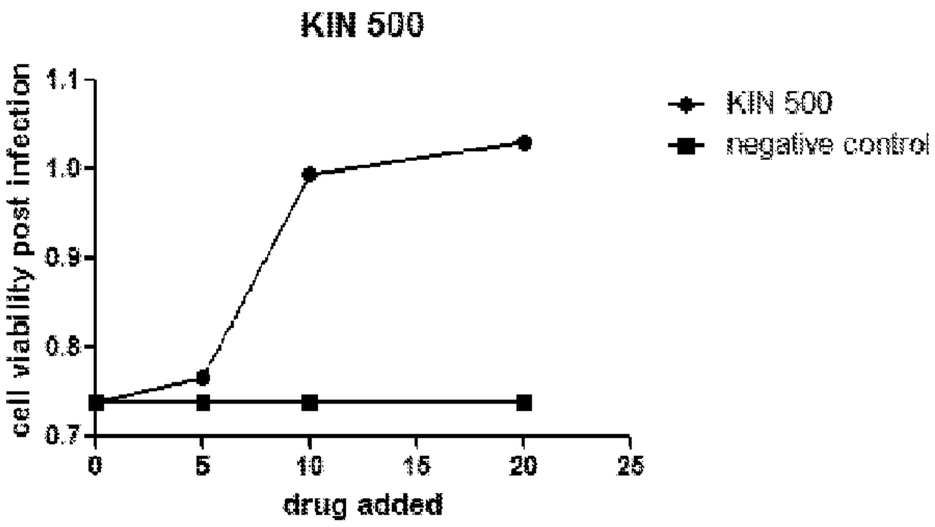
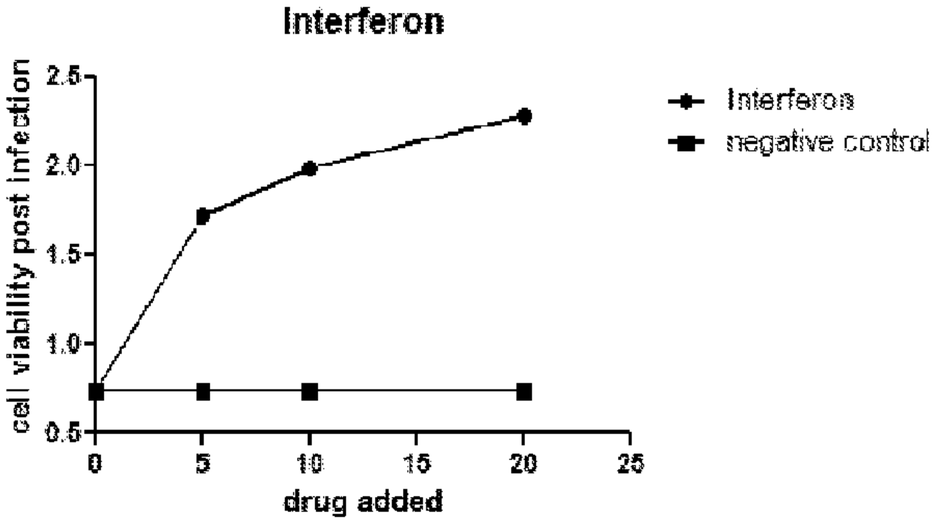


Figure 2B



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TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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PYRIMIDINEDIONE ANTI-VIRAL COMPOUNDS

FIELD OF THE DISCLOSURE

[0001] Compounds and methods disclosed herein are useful for treating viral infection in vertebrates, including RNA viral infections.

BACKGROUND OF THE DISCLOSURE

[0002] As a group, RNA viruses represent an enormous public health problem in the U.S. and worldwide. Well-known RNA viruses include influenza virus (including the avian and swine isolates), hepatitis C virus (HCV), West Nile virus, SARS-coronavirus, respiratory syncytial virus (RSV), and human immunodeficiency virus (HIV).

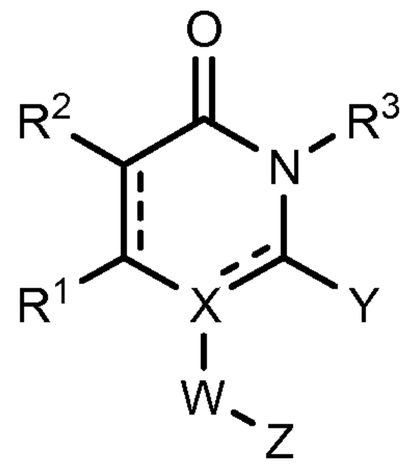
[0003] More than 170 million people worldwide are infected by HCV, and 130 million of those are chronic carriers at risk of developing chronic liver diseases (cirrhosis, carcinoma, and liver failure). As such, HCV is responsible for two thirds of all liver transplants in the developed world. Recent studies show that the death rate from HCV infection is rising due to the increasing age of chronically infected patients. Likewise seasonal flu infects 5 – 20% of the population resulting in 200,000 hospitalizations and 36,000 deaths each year.

[0004] Compared to influenza and HCV, West Nile virus causes the lowest number of infections, 981 in the United States in 2010. Twenty percent of infected patients develop a severe form of the disease, resulting in a 4.5% mortality rate. Unlike influenza and HCV, there are no approved therapies for the treatment of West Nile virus infection, and it is a high-priority pathogen for drug development due to its potential as a bioterrorist agent.

[0005] Among the RNA viruses listed, vaccines exist only for influenza virus. Accordingly, drug therapy is essential to mitigate the significant morbidity and mortality associated with these viruses. Unfortunately, the number of antiviral drugs is limited, many are poorly effective, and nearly all are plagued by the rapid evolution of viral resistance and a limited spectrum of action. Moreover, treatments for acute influenza and HCV infections are only moderately effective. The standard of care for HCV infection, PEGylated interferon and ribavirin, is effective in only 50% of patients, and there are a number of dose-limiting side effects associated with the combined therapy.

CLAIMS

1. A pharmaceutical composition comprising a compound having a structure



wherein R^1 and R^2 are each independently selected from H, lower alkyl, aryl, alkenyl, alkynyl, alkylaryl, arylalkyl, alkoxy, aryloxy, arylalkoxy, alkoxyalkylaryl, alkylamino, dialkylamino, arylamino, heteroalkyl, heteroaryl, cyclic heteroalkyl, acyl, CN, OCF_3, CF_3, Br, Cl, F, alkylcarbonyl, furanyl, thiophenyl, oxazole, SR^4, SOR^4, SO_2R^4, CO_2R^4, COR^4, $CONR^4R^5$, $CSNR^4R^5$, $SO_nNR^4R^5$ or if taken together form a cyclic group including, but not limited to, furan, thiophene, pyrrole, isoxazole, oxazole, thiazole, isothiazole, pyridinyl, pyrimidinyl, pyrazinyl, piperazine, piperadine, dioxane, quinoline, isoquinoline, quinazoline, benzene, naphthalene or the corresponding benzo derivatives;

R^3 is H, lower alkyl, aryl, alkenyl, alkynyl, alkylaryl, arylalkyl, alkoxy, aryloxy, arylalkoxy, heteroalkyl, heteroaryl, heteroarylalkyl or cyclic heteroalkyl;

R^4 and R^5 are each independently selected from H, lower alkyl, aryl, alkenyl, alkynyl, alkylaryl, arylalkyl, alkoxy, aryloxy, arylalkoxy, alkoxyalkylaryl, alkylamino, dialkylamino, arylamino, heteroalkyl, heteroaryl, heteroarylalkyl, cyclic heteroalkyl, cyclicheteroalkylalkyl, alkylcarbonyl, heteroalkylcarbonyl, furan, thiophene, oxazole, thiazole, isothiazole, pyridinyl, pyrimidinyl, pyrazinyl, piperazine, piperadine, dioxane, quinoline, isoquinoline, quinazoline, benzene or naphthalene or two can be taken together forming a cyclic constituent including, but not limited to, piperazine, piperadine, morpholine, thiomorpholine, thiomorpholine, S,S-dioxide, azapine or diazapine;

W is lower alkyl, aryl, alkenyl, alkynyl, alkylaryl, arylalkyl, alkoxy, aryloxy, arylalkoxy, alkoxyalkylaryl, alkylamino, arylamino, heteroalkyl, heteroaryl, cyclic heteroalkyl, C=O, alkylcarbonyl, O, S, NH, NR^6, $(CR^6R^7)_n$ or $(C=O)R^6$;

X is C or N;

Y is H, alkyl, OR^6, or C=O;

Z is H, alkyl, aryl, heteroalkyl, heteroaryl, OH, OR^6, NR^6R^7, $NR^6CO_2R^7$, $NR^6(C=O)NR^7R^8$, CO_2H, CO_2R^6, $CONH_2$, $CONR^6R^7$, 1-amidine, 2-amidine, guanidine, sulfonylamidine, sulfonylguanidine, N-cyanoamidine, N-cyanoguanidine, tetrazole, aminosquaric acid, aminosquaric acid amide, CO_2H, $CS(OR^6)$, SO_2R^6, COR^6, $CONR^6R^7$, $(SO)_nNR^6R^7$, $NR^6(SO)_nNR^7R^8$, NR^6 or SO_2R^6;

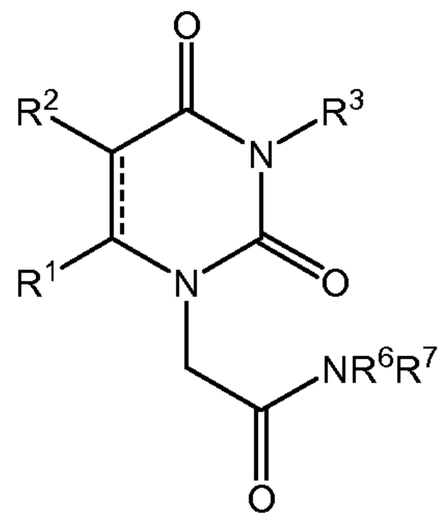
n is 0, 1 or 2;

wherein the dashed lines represent the presence or absence of a double bond; and

R^6, R^7 and R^8 are each independently selected from H, lower alkyl, aryl, alkenyl, alkynyl, alkylaryl, arylalkyl, alkoxy, aryloxy, arylalkoxy, alkoxyalkylaryl, alkylamino, arylamino, heteroalkyl, heteroaryl, heteroarylalkyl, cyclic heteroalkyl or cyclicheteroalkylalkyl or two can be taken together forming a cyclic constituent including, but not limited to, piperazine, piperadine, morpholine, thiomorpholine, thiomorpholine, S,S-dioxide, azapine or diazapine.

2. A pharmaceutical composition of claim 1 comprising a compound of claim 1 or a pharmaceutically acceptable salt, tautomer, isomer and/or prodrug thereof.

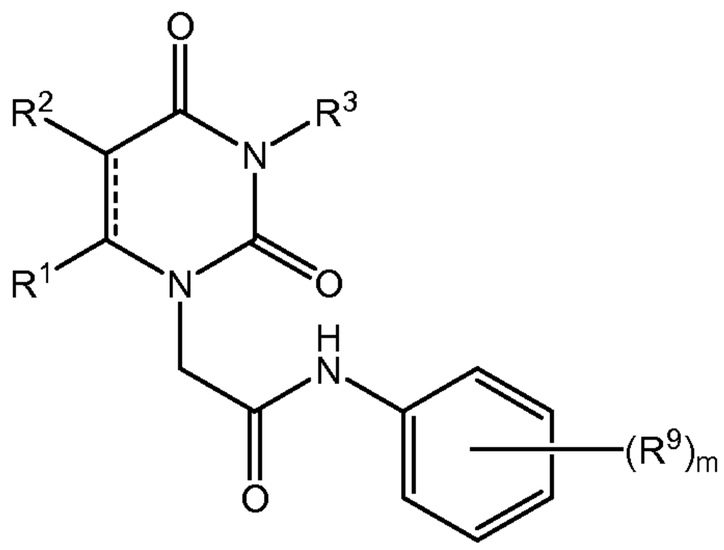
3. A pharmaceutical composition of claim 2 wherein the compound has a structure



wherein R^4 and R^5 are each independently selected from H, lower alkyl, aryl, alkenyl, alkynyl, alkylaryl, arylalkyl, alkoxy, aryloxy, arylalkoxy, alkoxyalkylaryl, heteroalkyl, heteroaryl or cyclic heteroalkyl or two can be taken together forming a cyclic constituent including, but not limited to, piperazine, piperadine, morpholine, thiomorpholine, thiomorpholine, S,S-dioxide, azapine or diazapine; and

R^6 and R^7 are each independently selected from H, lower alkyl, aryl, alkenyl, alkynyl, alkylaryl, arylalkyl, alkoxy, aryloxy, arylalkoxy, alkoxyalkylaryl, heteroalkyl, heteroaryl or cyclic heteroalkyl.

4. A pharmaceutical composition of claim 2 wherein the compound has a structure

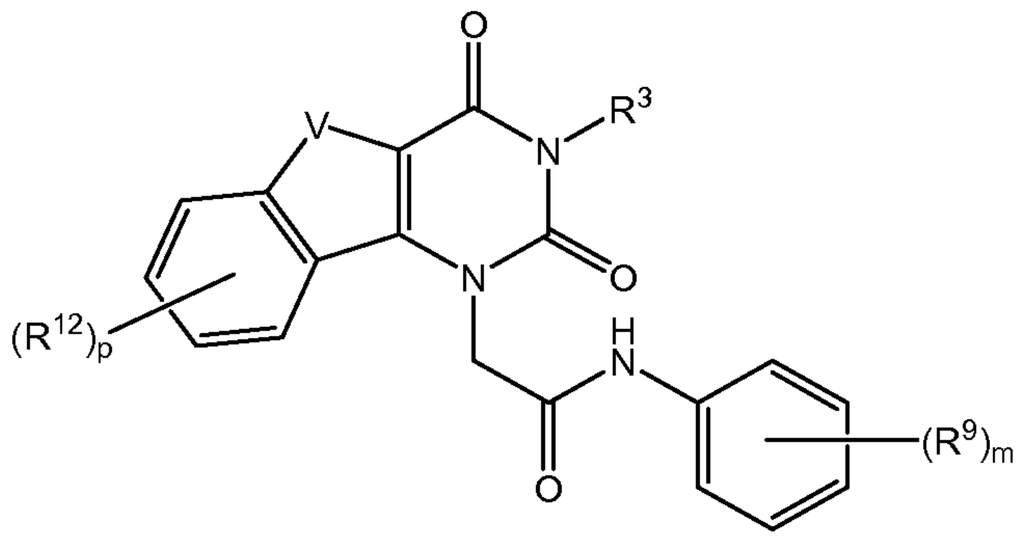


wherein R^9 is H, lower alkyl, aryl, alkenyl, alkynyl, alkylaryl, arylalkyl, alkoxy, aryloxy, arylalkoxy, alkoxyalkylaryl, alkylamino, dialkylamino, arylamino, heteroalkyl, heteroaryl, cyclic heteroalkyl, acyl, NH_2, OH, CN, NO_2, OCF_3, CF_3, Br, Cl, F, 1-amidino, 2-amidino, alkylcarbonyl, morpholino, piperidinyl, dioxanyl, pyranyl, heteroaryl, furanyl, thiophenyl, tetrazole, thiazole, isothiazole, imidazole, thiadiazole, thiadiazole S-oxide, thiadiazole S,S-dioxide,pyrazole, oxazole, isoxazole, pyridinyl, pyrimidinyl, piperazine, quinoline, isoquinoline, SR^{10}, SOR^{10}, SO_2R^{10}, CO_2R^{10}, COR^{10}, $CONR^{10}R^{11}$, $CSNR^{10}R^{11}$, $SO_nNR^{10}R^{11}$ or two adjacent R^9 are taken together to form a cyclic structre selected from furan, thiophene, pyrrole, isoxazole, oxazole, thiazole, isothiazole, pyridinyl, pyrimidinyl, pyrazinyl, piperazine, piperadine, dioxane, quinoline, isoquinoline, quinazoline, benzene, naphthalene or the corresponding benzo derivatives;

m is 0, 1, 2, 3, 4 or 5; and

R^{10} and R^{11} are each independently selected from H, lower alkyl, aryl, alkenyl, alkynyl, alkylaryl, arylalkyl, alkoxy, aryloxy, arylalkoxy, heteroalkyl, heteroaryl, heteroarylalkyl or cyclic heteroalkyl.

5. A pharmaceutical composition of claim 2 wherein the compound has a structure



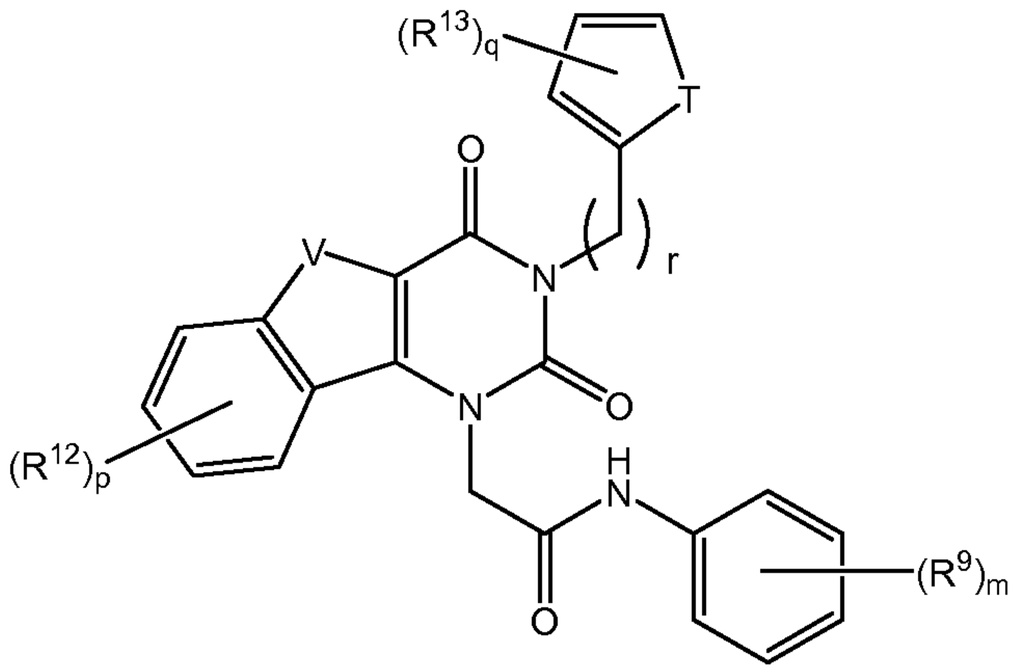
wherein R^{12} is H, lower alkyl, aryl, alkenyl, alkynyl, alkylaryl, arylalkyl, alkoxy, aryloxy, arylalkoxy, alkoxyalkylaryl, alkylamino, dialkylamino, arylamino, heteroalkyl, heteroaryl, cyclic heteroalkyl, acyl, NH_2, OH, CN, NO_2, OCF_3, CF_3, Br, Cl, F, 1-amidino, 2-amidino, alkylcarbonyl, morpholino, piperidinyl, dioxanyl, pyranyl, heteroaryl, furanyl, thiophenyl, tetrazole, thiazole, isothiazole, imidazole, thiadiazole, thiadiazole S-oxide, thiadiazole S,S-dioxide,pyrazole, oxazole, isoxazole, pyridinyl, pyrimidinyl, piperazine, quinoline, isoquinoline, SR^4, SOR^4, SO_2R^4, CO_2R^4, COR^4, $CONR^4R^5$, $CSNR^4R^5$, $SO_nNR^4R^5$ or if two adjacent R^{12} are together form a cyclic group including, but not limited to, furan, thiophene, pyrrole, isoxazole, oxazole, thiazole, isothiazole, pyridinyl, pyrimidinyl, pyrazinyl, piperazine, piperadine, dioxane, quinoline, isoquinoline, quinazoline, benzene, naphthalene or the corresponding benzo derivatives;

R^4R^5 are H, lower alkyl, aryl, alkenyl, alkynyl, alkylaryl, arylalkyl, alkoxy, aryloxy, arylalkoxy, heteroalkyl, heteroaryl, heteroarylalkyl or cyclic heteroalkyl;

V is O or S; and

p is 0, 1, 2, 3, 4 or 5.

6. A pharmaceutical composition of claim 2 wherein the compound has a structure



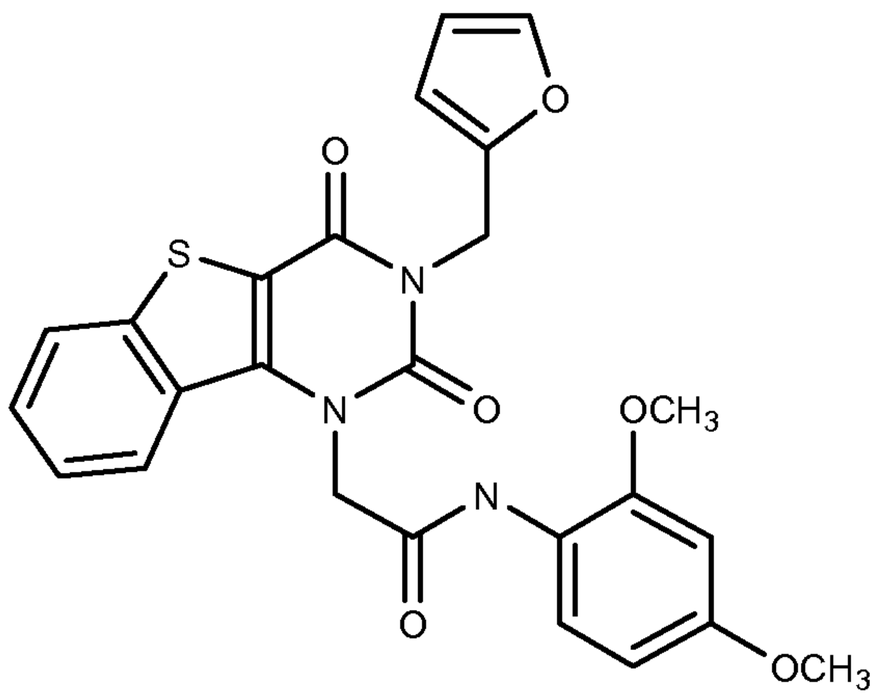
wherein R^{13} is H, lower alkyl, aryl, alkenyl, alkynyl, alkylaryl, arylalkyl, alkoxy, aryloxy, arylalkoxy, alkoxyalkylaryl, alkylamino, dialkylamino, arylamino, heteroalkyl, heteroaryl, cyclic heteroalkyl, acyl, NH_2, OH, CN, NO_2, OCF_3, CF_3, Br, Cl, F, 1-amidino, 2-amidino, alkylcarbonyl, morpholino, piperidinyl, dioxanyl, pyranyl, heteroaryl, furanyl, thiophenyl, tetrazole, thiazole, isothiazole, imidazole, thiadiazole, thiadiazole S-oxide, thiadiazole S,S-dioxide,pyrazole, oxazole, isoxazole, pyridinyl, pyrimidinyl, piperazine, quinoline, isoquinoline, SR^4, SOR^4, SO_2R^4, CO_2R^4, COR^4, $CONR^4R^5$, $CSNR^4R^5$, $SO_nNR^4R^5$ or if

two adjacent R^{13} are together form a cyclic group including, but not limited to, furan, thiophene, pyrrole, isoxazole, oxazole, thiazole, isothiazole, pyridinyl, pyrimidinyl, pyrazinyl, piperazine, piperadine, dioxane, quinoline, isoquinoline, quinazoline, benzene, naphthalene or the corresponding benzo derivatives;

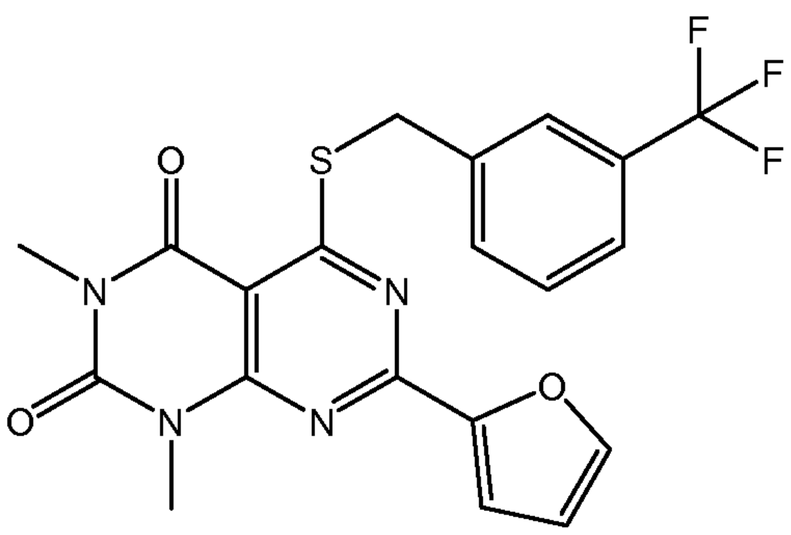
r is 1 to 5; and

t is O or S.

7. A pharmaceutical composition of claim 2 wherein the compound has a structure



or



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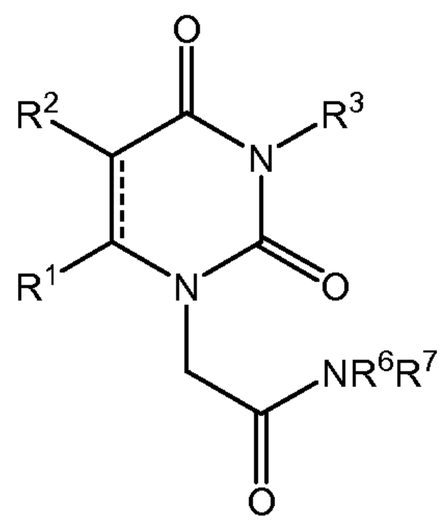
8. A method of treating or preventing a viral infection in a vertebrate comprising administering to the vertebrate a pharmaceutical composition of claim 2.

9. A method of claim 8 wherein the viral infection is caused by a virus from one or more of the following families: Arenaviridae, Astroviridae, Birnaviridae, Bromoviridae, Bunyaviridae, Caliciviridae, Closteroviridae, Comoviridae, Cystoviridae, Flaviviridae, Flexiviridae, Hepevirus, Leviviridae, Luteoviridae, Mononegavirales, Mosaic Viruses, Nidovirales, Nodaviridae, Orthomyxoviridae, Picobirnavirus, Picornaviridae, Potyviridae, Reoviridae, Retroviridae, Sequiviridae, Tenuivirus, Togaviridae, Tombusviridae, Totiviridae, Tymoviridae, Hepadnaviridae, Herpesviridae, Paramyxoviridae or Papillomaviridae.

10. A method of claim 8 wherein the viral infection is influenza virus, Hepatitis C virus, West Nile virus, SARS-coronavirus, poliovirus, measles virus, Dengue virus, yellow fever virus, tick-borne encephalitis virus, Japanese encephalitis virus, St. Louis encephalitis virus, Murray Valley virus, Powassan virus, Rocio virus, louping-ill virus,

Banzi virus, Ilheus virus, Kokobera virus, Kunjin virus, Alfuy virus, bovine diarrhea virus, Kyasanur forest disease virus or human immunodeficiency virus (HIV).

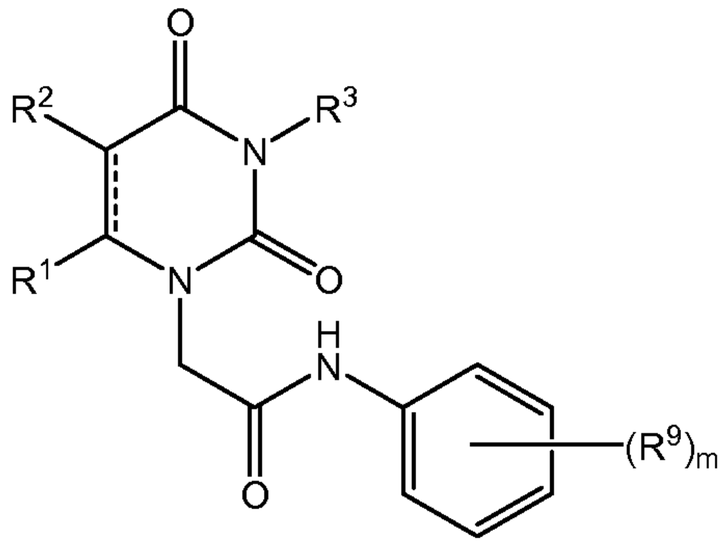
11. A method of claim 8 wherein the compound has a structure



wherein R^4 and R^5 are each independently selected from H, lower alkyl, aryl, alkenyl, alkynyl, alkylaryl, arylalkyl, alkoxy, aryloxy, arylalkoxy, alkoxyalkylaryl, heteroalkyl, heteroaryl or cyclic heteroalkyl or two can be taken together forming a cyclic constituent including, but not limited to, piperazine, piperadine, morpholine, thiomorpholine, thiomorpholine, S,S-dioxide, azapine or diazapine; and

R^6, R^7 and R^8 are each independently selected from H, lower alkyl, aryl, alkenyl, alkynyl, alkylaryl, arylalkyl, alkoxy, aryloxy, arylalkoxy, alkoxyalkylaryl, heteroalkyl, heteroaryl or cyclic heteroalkyl.

12. A method of claim 8 wherein the compound has a structure



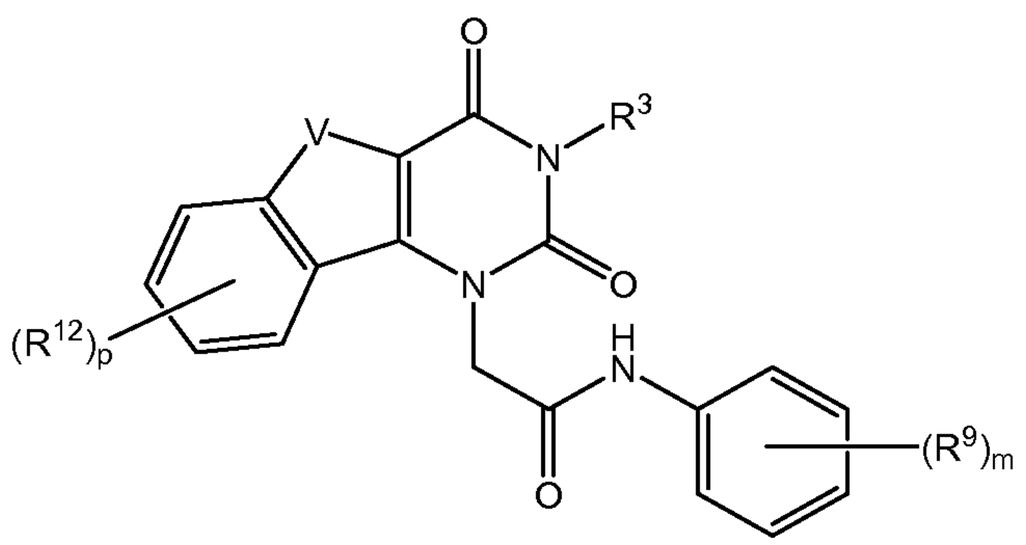
wherein R^9 is H, lower alkyl, aryl, alkenyl, alkynyl, alkylaryl, arylalkyl, alkoxy, aryloxy, arylalkoxy, alkoxyalkylaryl, alkylamino, dialkylamino, arylamino, heteroalkyl, heteroaryl, cyclic heteroalkyl, acyl, NH_2, OH, CN, NO_2, OCF_3, CF_3, Br, Cl, F, 1-amidino, 2-amidino, alkylcarbonyl, morpholino, piperidinyl, dioxanyl, pyranyl, heteroaryl, furanyl, thiophenyl, tetrazole, thiazole, isothiazole, imidazole, thiadiazole, thiadiazole S-oxide, thiadiazole S,S-dioxide,pyrazole, oxazole, isoxazole, pyridinyl, pyrimidinyl, piperazine, quinoline,

isoquinoline, SR^{10}, SOR^{10}, SO_2R^{10}, CO_2R^{10}, COR^{10}, $CONR^{10}R^{11}$, $CSNR^{10}R^{11}$, $SO_nNR^{10}R^{11}$ or two adjacent R^9 are taken together to form a cyclic structre selected from furan, thiophene, pyrrole, isoxazole, oxazole, thiazole, isothiazole, pyridinyl, pyrimidinyl, pyrazinyl, piperazine, piperadine, dioxane, quinoline, isoquinoline, quinazoline, benzene, naphthalene or the corresponding benzo derivatives;

m is 0, 1, 2, 3, 4 or 5; and

R^{10} and R^{11} are each independently selected from H, lower alkyl, aryl, alkenyl, alkynyl, alkylaryl, arylalkyl, alkoxy, aryloxy, arylalkoxy, heteroalkyl, heteroaryl, heteroarylalkyl or cyclic heteroalkyl.

13. A method of claim 8 wherein the compound has a structure



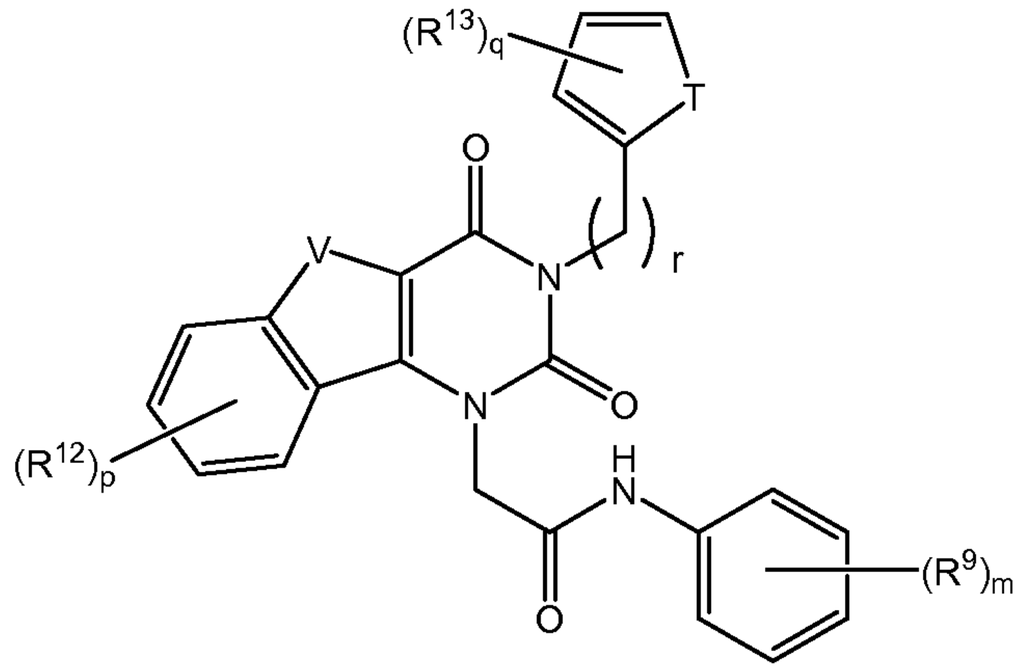
wherein R^{12} is H, lower alkyl, aryl, alkenyl, alkynyl, alkylaryl, arylalkyl, alkoxy, aryloxy, arylalkoxy, alkoxyalkylaryl, alkylamino, dialkylamino, arylamino, heteroalkyl, heteroaryl, cyclic heteroalkyl, acyl, NH_2, OH, CN, NO_2, OCF_3, CF_3, Br, Cl, F, 1-amidino, 2-amidino, alkylcarbonyl, morpholino, piperidinyl, dioxanyl, pyranyl, heteroaryl, furanyl, thiophenyl, tetrazole, thiazole, isothiazole, imidazole, thiadiazole, thiadiazole S-oxide, thiadiazole S,S-dioxide,pyrazole, oxazole, isoxazole, pyridinyl, pyrimidinyl, piperazine, quinoline, isoquinoline, SR^4, SOR^4, SO_2R^4, CO_2R^4, COR^4, $CONR^4R^5$, $CSNR^4R^5$, $SO_nNR^4R^5$ or if two adjacent R^{12} are together form a cyclic group including, but not limited to, furan, thiophene, pyrrole, isoxazole, oxazole, thiazole, isothiazole, pyridinyl, pyrimidinyl, pyrazinyl, piperazine, piperadine, dioxane, quinoline, isoquinoline, quinazoline, benzene, naphthalene or the corresponding benzo derivatives;

R^4R^5 are H, lower alkyl, aryl, alkenyl, alkynyl, alkylaryl, arylalkyl, alkoxy, aryloxy, arylalkoxy, heteroalkyl, heteroaryl, heteroarylalkyl or cyclic heteroalkyl;

V is O or S; and

p is 0, 1, 2, 3, 4 or 5.

14. A method of claim 8 wherein the compound has a structure

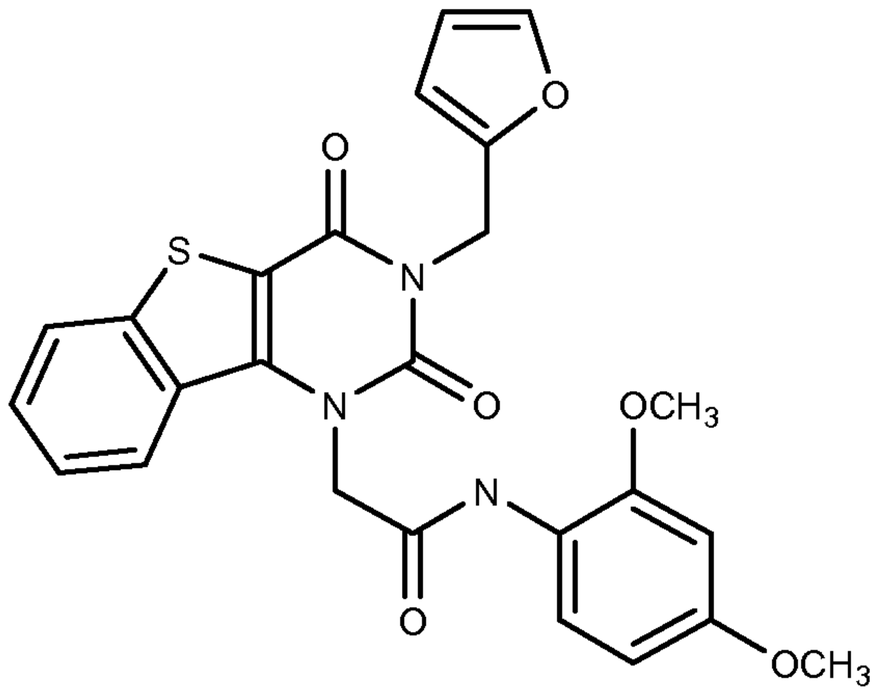


wherein R^{13} is H, lower alkyl, aryl, alkenyl, alkynyl, alkylaryl, arylalkyl, alkoxy, aryloxy, arylalkoxy, alkoxyalkylaryl, alkylamino, dialkylamino, arylamino, heteroalkyl, heteroaryl, cyclic heteroalkyl, acyl, NH_2, OH, CN, NO_2, OCF_3, CF_3, Br, Cl, F, 1-amidino, 2-amidino, alkylcarbonyl, morpholino, piperidinyl, dioxanyl, pyranyl, heteroaryl, furanyl, thiophenyl, tetrazole, thiazole, isothiazole, imidazole, thiadiazole, thiadiazole S-oxide, thiadiazole S,S-dioxide,pyrazole, oxazole, isoxazole, pyridinyl, pyrimidinyl, piperazine, quinoline, isoquinoline, SR^4, SOR^4, SO_2R^4, CO_2R^4, COR^4, $CONR^4R^5$, $CSNR^4R^5$, $SO_nNR^4R^5$ or if two adjacent R^{13} are together form a cyclic group including, but not limited to, furan, thiophene, pyrrole, isoxazole, oxazole, thiazole, isothiazole, pyridinyl, pyrimidinyl, pyrazinyl, piperazine, piperadine, dioxane, quinoline, isoquinoline, quinazoline, benzene, naphthalene or the corresponding benzo derivatives;

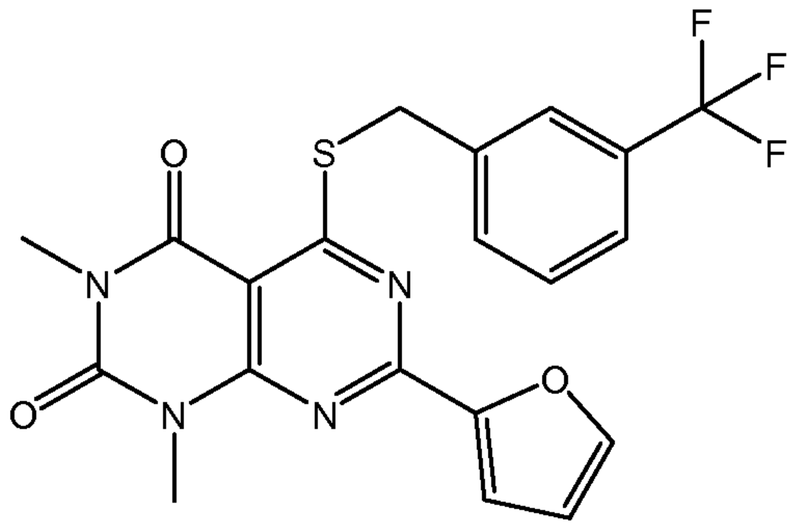
r is 1 to 5; and

T is O or S.

15. A method of claim 8 wherein the compound has a structure



or



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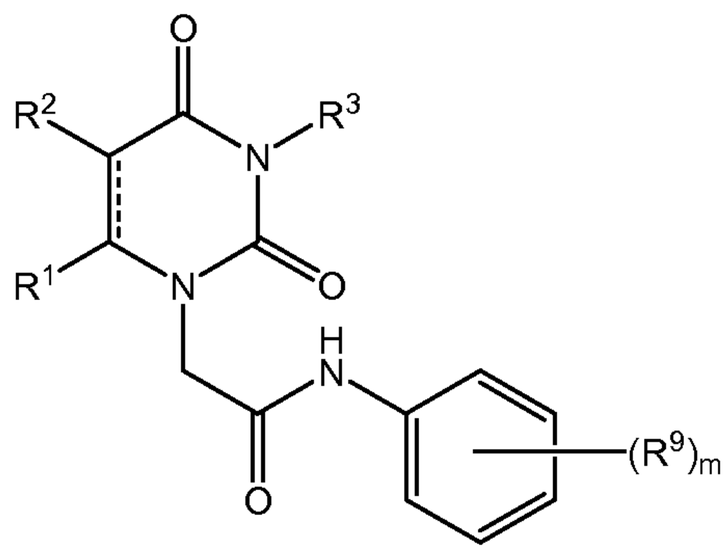
16. A method of claim 8 wherein said method comprises vaccinating a vertebrate by additionally administering a vaccine against influenza virus, Hepatitis C virus, West Nile virus, SARS-coronavirus, poliovirus, measles virus, Dengue virus, yellow fever virus, tick-borne encephalitis virus, Japanese encephalitis virus, St. Louis encephalitis virus, Murray Valley virus, Powassan virus, Rocio virus, louping-ill virus, Banzi virus, Ilheus virus, Kokobera virus, Kunjin virus, Alfuy virus, bovine diarrhea virus, Kyasanur forest disease virus or human immunodeficiency virus (HIV).

17. A method of modulating the innate immune response in a eukaryotic cell, comprising administering to the cell a compound of claim 2.

18. A method of claim 17 wherein the compound has a structure



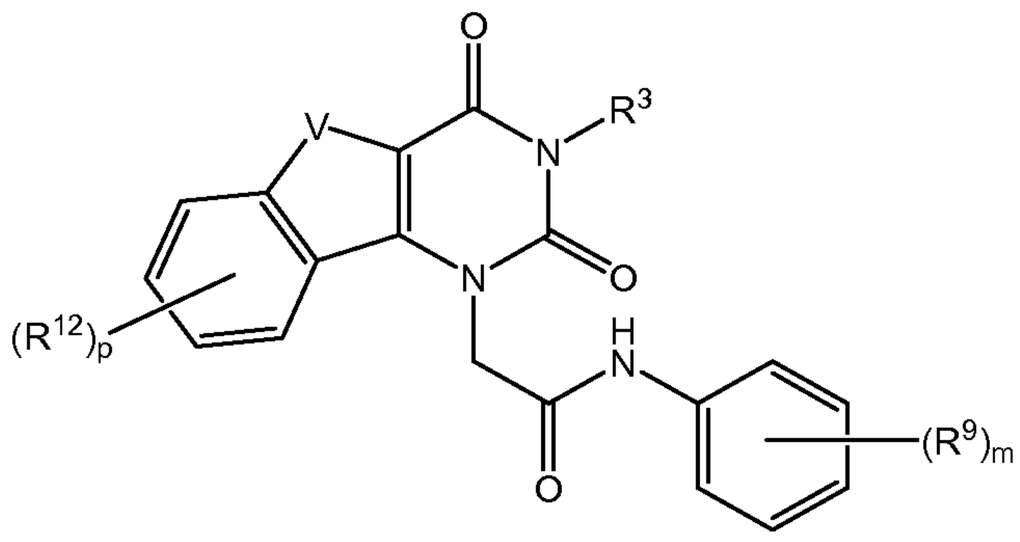
wherein R^9 is H, lower alkyl, aryl, alkenyl, alkynyl, alkylaryl, arylalkyl, alkoxy, aryloxy, arylalkoxy, alkoxyalkylaryl, alkylamino, dialkylamino, arylamino, heteroalkyl, heteroaryl, cyclic heteroalkyl, acyl, NH_2, OH, CN, NO_2, OCF_3, CF_3, Br, Cl, F, 1-amidino, 2-amidino, alkylcarbonyl, morpholino, piperidinyl, dioxanyl, pyranyl, heteroaryl, furanyl, thiophenyl,

tetrazole, thiazole, isothiazole, imidazole, thiadiazole, thiadiazole S-oxide, thiadiazole S,S-dioxide,pyrazole, oxazole, isoxazole, pyridinyl, pyrimidinyl, piperazine, quinoline, isoquinoline, SR^{10}, SOR^{10}, SO_2R^{10}, CO_2R^{10}, COR^{10}, $CONR^{10}R^{11}$, $CSNR^{10}R^{11}$, $SO_nNR^{10}R^{11}$ or two adjacent R^9 are taken together to form a cyclic structre selected from furan, thiophene, pyrrole, isoxazole, oxazole, thiazole, isothiazole, pyridinyl, pyrimidinyl, pyrazinyl, piperazine, piperadine, dioxane, quinoline, isoquinoline, quinazoline, benzene, naphthalene or the corresponding benzo derivatives;

m is 0, 1, 2, 3, 4 or 5; and

R^{10} and R^{11} are each independently selected from H, lower alkyl, aryl, alkenyl, alkynyl, alkylaryl, arylalkyl, alkoxy, aryloxy, arylalkoxy, heteroalkyl, heteroaryl, heteroarylalkyl or cyclic heteroalkyl.

19. A method of claim 17 wherein the compound has a structure



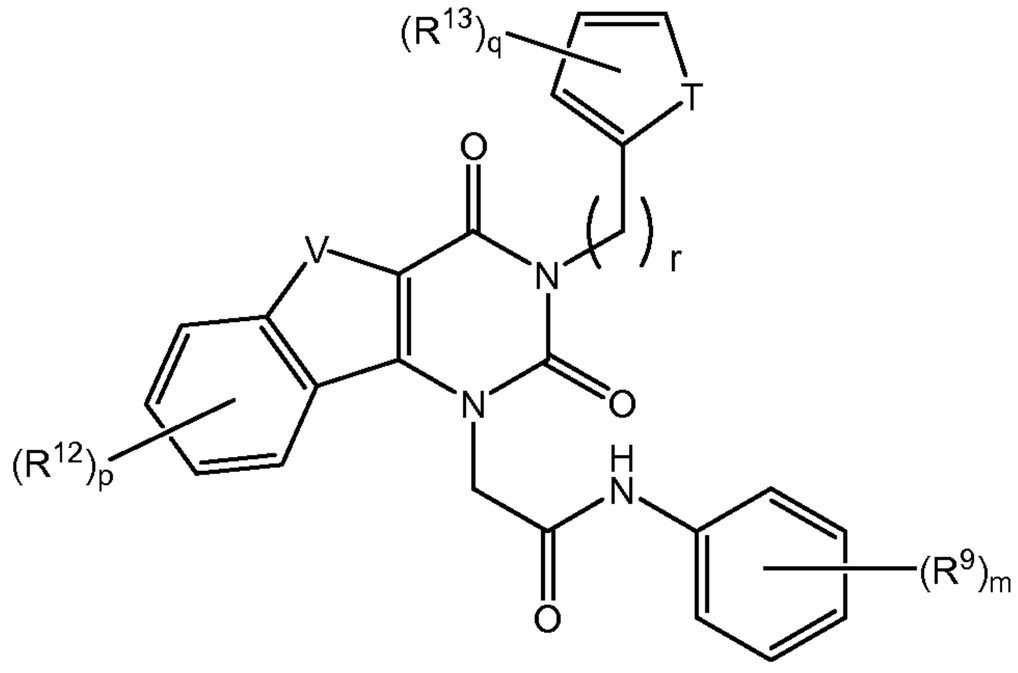
wherein R^{12} is H, lower alkyl, aryl, alkenyl, alkynyl, alkylaryl, arylalkyl, alkoxy, aryloxy, arylalkoxy, alkoxyalkylaryl, alkylamino, dialkylamino, arylamino, heteroalkyl, heteroaryl, cyclic heteroalkyl, acyl, NH_2, OH, CN, NO_2, OCF_3, CF_3, Br, Cl, F, 1-amidino, 2-amidino, alkylcarbonyl, morpholino, piperidinyl, dioxanyl, pyranyl, heteroaryl, furanyl, thiophenyl, tetrazole, thiazole, isothiazole, imidazole, thiadiazole, thiadiazole S-oxide, thiadiazole S,S-dioxide,pyrazole, oxazole, isoxazole, pyridinyl, pyrimidinyl, piperazine, quinoline, isoquinoline, SR^4, SOR^4, SO_2R^4, CO_2R^4, COR^4, $CONR^4R^5$, $CSNR^4R^5$, $SO_nNR^4R^5$ or if two adjacent R^{12} are together form a cyclic group including, but not limited to, furan, thiophene, pyrrole, isoxazole, oxazole, thiazole, isothiazole, pyridinyl, pyrimidinyl, pyrazinyl, piperazine, piperadine, dioxane, quinoline, isoquinoline, quinazoline, benzene, naphthalene or the corresponding benzo derivatives;

R^4R^5 are H, lower alkyl, aryl, alkenyl, alkynyl, alkylaryl, arylalkyl, alkoxy, aryloxy, arylalkoxy, heteroalkyl, heteroaryl, heteroarylalkyl or cyclic heteroalkyl;

V is O or S; and

p is 0, 1, 2, 3, 4 or 5.

20. A method of claim 17 wherein the compound has a structure



wherein R^{13} is H, lower alkyl, aryl, alkenyl, alkynyl, alkylaryl, arylalkyl, alkoxy, aryloxy, arylalkoxy, alkoxyalkylaryl, alkylamino, dialkylamino, arylamino, heteroalkyl, heteroaryl, cyclic heteroalkyl, acyl, NH_2, OH, CN, NO_2, OCF_3, CF_3, Br, Cl, F, 1-amidino, 2-amidino, alkylcarbonyl, morpholino, piperidinyl, dioxanyl, pyranyl, heteroaryl, furanyl, thiophenyl, tetrazole, thiazole, isothiazole, imidazole, thiadiazole, thiadiazole S-oxide, thiadiazole S,S-dioxide,pyrazole, oxazole, isoxazole, pyridinyl, pyrimidinyl, piperazine, quinoline, isoquinoline, SR^4, SOR^4, SO_2R^4, CO_2R^4, COR^4, $CONR^4R^5$, $CSNR^4R^5$, $SO_nNR^4R^5$ or if two adjacent R^{13} are together form a cyclic group including, but not limited to, furan, thiophene, pyrrole, isoxazole, oxazole, thiazole, isothiazole, pyridinyl, pyrimidinyl, pyrazinyl, piperazine, piperadine, dioxane, quinoline, isoquinoline, quinazoline, benzene, naphthalene or the corresponding benzo derivatives;

r is 1 to 5; and

T is O or S.

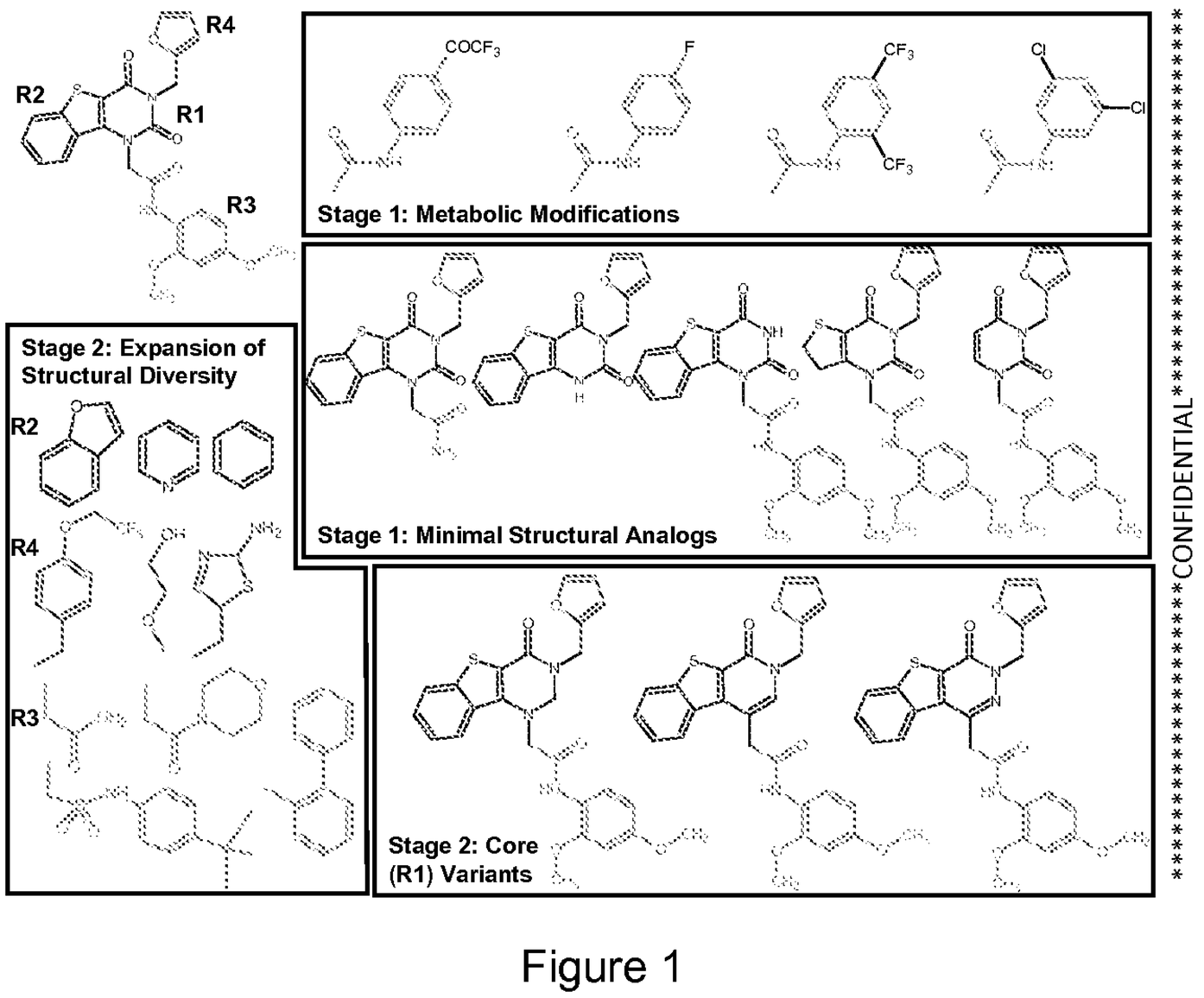

R4
R2
R1
R3
COCF3
F
CF3
CF3
Cl
Cl
Stage 1: Metabolic Modifications
Stage 1: Minimal Structural Analogs
Stage 2: Expansion of Structural Diversity
R2
R4
R3
Stage 2: Core (R1) Variants
CONFIDENTIAL

Figure 1

Figure 2A

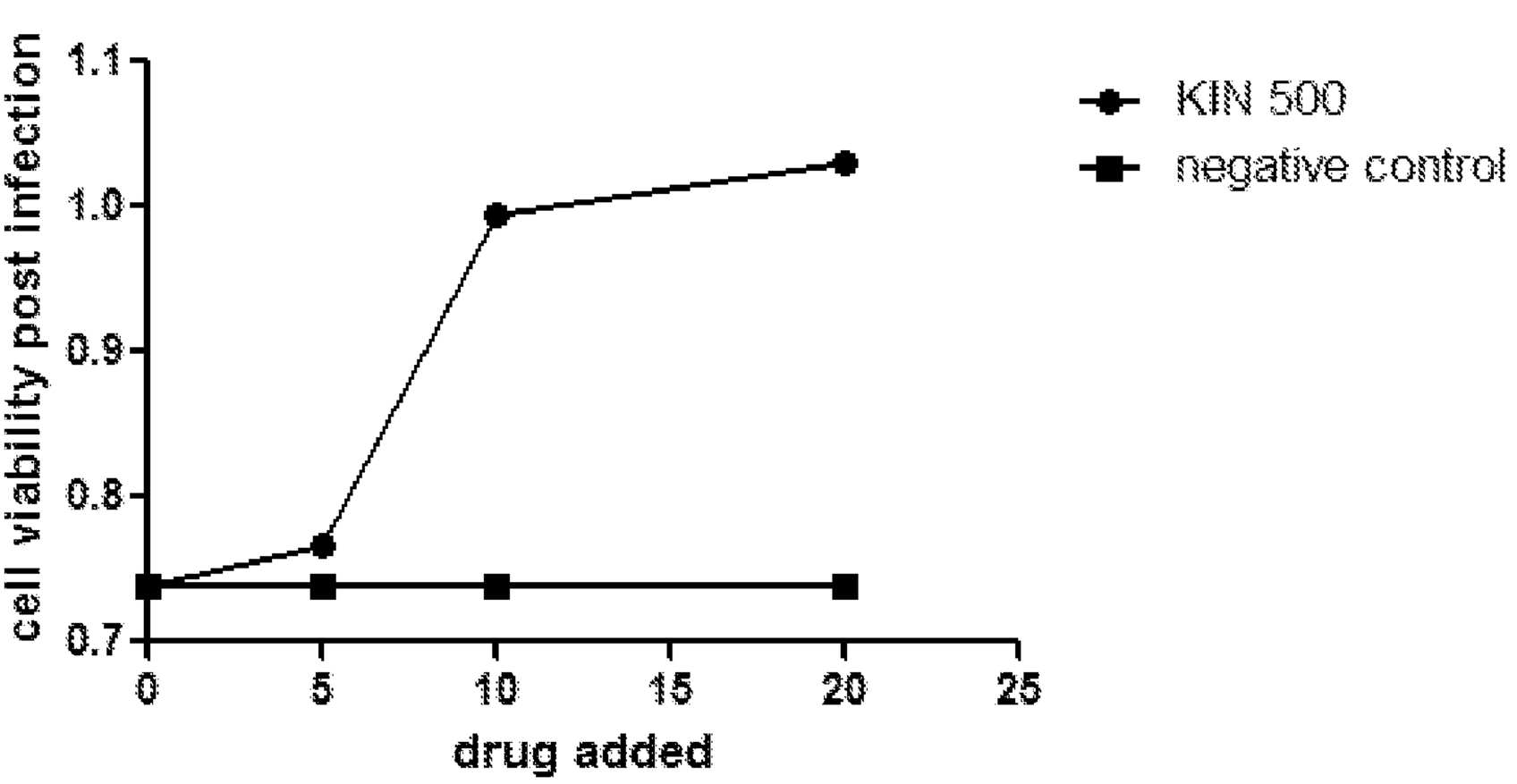


Figure 2B

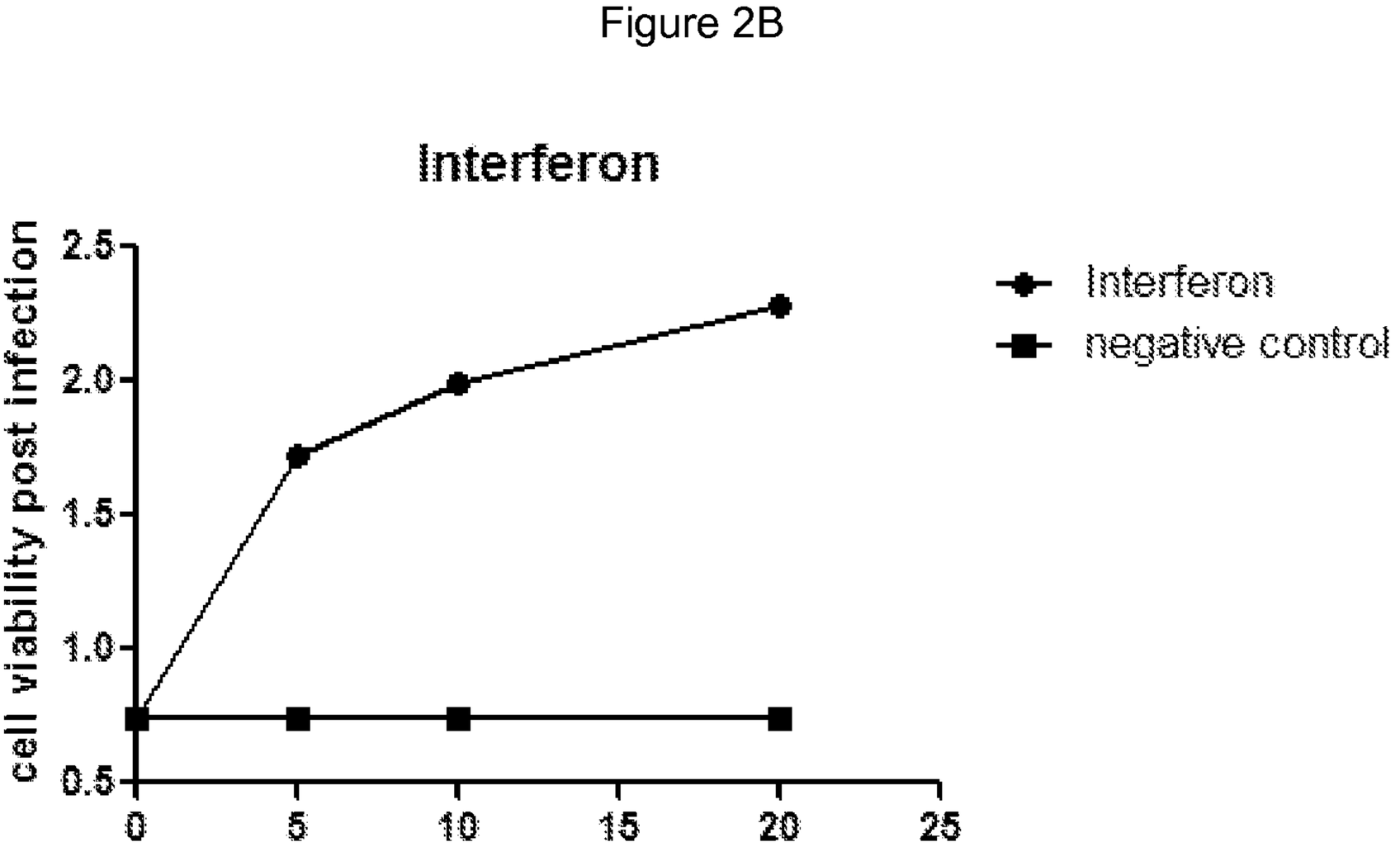


Figure 2A

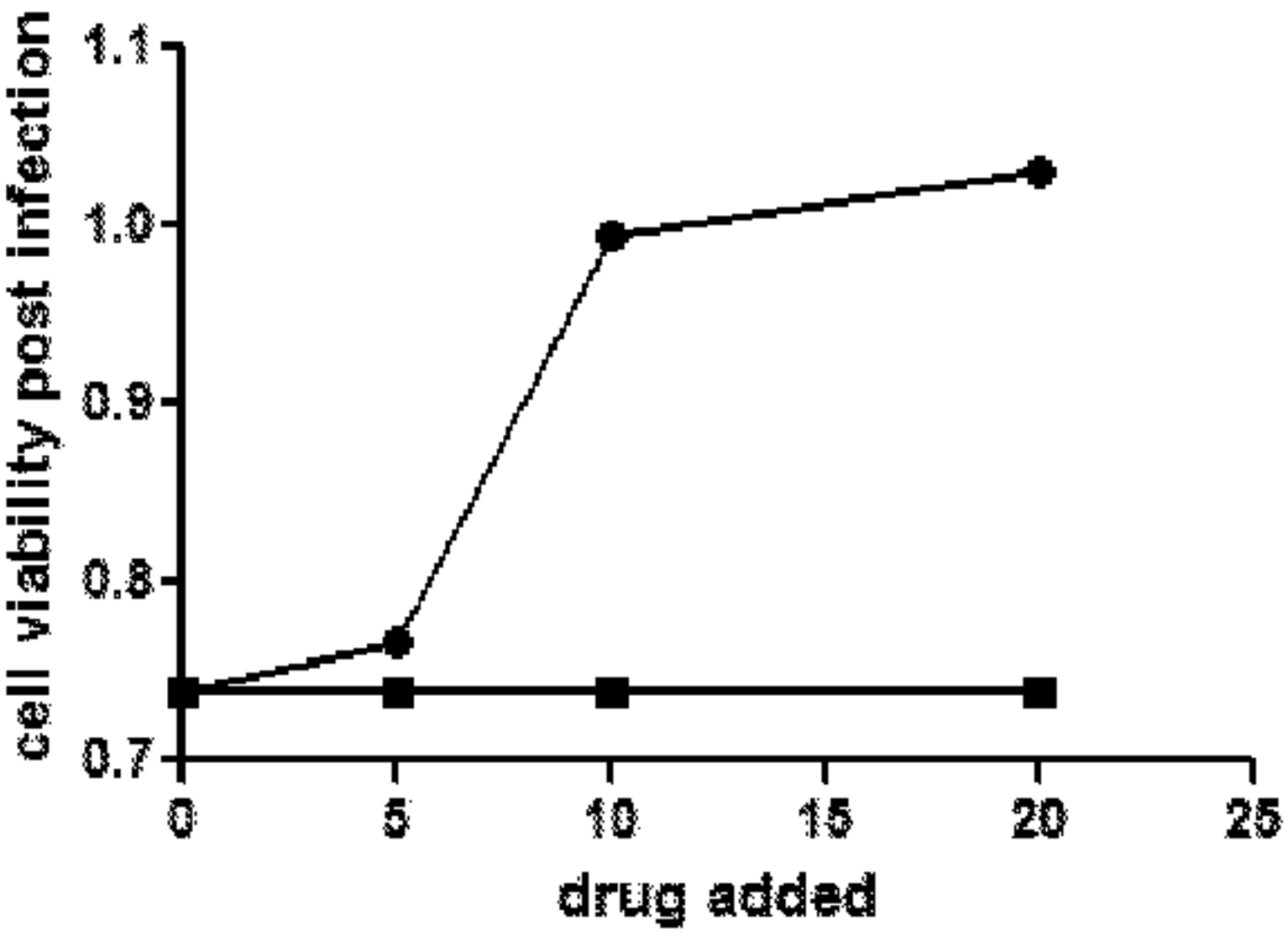


Figure 2B